The Dissertation Committee for Wandi Zhang Certifies that this is the approved version of the following Dissertation:

Transition-Metal Catalyzed Redox Triggered C-C Bond Forming Reactions *via* Carbonyl Addition

Committee:

Michael J. Krische, Supervisor

Stephen F. Martin

Hung-Wen (Ben) Liu

Emily L. Que

Simon M. Humphrey

Transition-Metal Catalyzed Redox Triggered C-C Bond Forming Reactions *via* Carbonyl Addition

by

Wandi Zhang

Dissertation

Presented to the Faculty of the Graduate School of

The University of Texas at Austin

in Partial Fulfillment

of the Requirements

for the Degree of

Doctor of Philosophy

The University of Texas at Austin

May 2019

Dedication

To my parents

Acknowledgements

First, I must thank Prof. Krische for the guidance and mentorship during my graduate studies. Thank you for creating such a thriving research environment which allow me to develop skills to be a chemist.

The work included in this dissertation won't be done without the collaboration of many talented and hardworking Krische group members and UT chemistry department staff. I am grateful for the opportunity to work with Tao, and Khao when I just joined the group for their mentorship and instruction on projects. I also must thank Weijie, Hongde, Johannes, James, Ming, Rob, Will, Brian for their support and collaboration on projects. Thanks are also due to Steve, Angela, and Vincent for their assistant with NMR studies and solving X-ray crystal structures.

Finally, I would like to thank my friends and family for their encouragement and support. To my parents: Your unconditional love and understanding has carried me through both good times and bad. Cannot wait to see you in the commencement. To Tom, Ryan, Hiroki: I'm so grateful for our friendship both in and out of lab. So lucky for working in the same lab/office with you and I really enjoyed it. To Xue and Mengxuan, my BFF: Thank you girls for always being there for me even though we are far apart.

Abstract

Transition-Metal Catalyzed Redox Triggered C-C Bond Forming Reactions *via* Carbonyl Addition

Wandi Zhang, Ph.D.

The University of Texas at Austin, 2019

Supervisor: Michael J. Krische

Carbon-carbon (C–C) bonds construct the skeleton of all organic molecules. Hence, the development of new efficient methods of C–C bond formation is of great significance in organic chemistry. Since the discovery of the Grignard reaction, carbonyl addition has been an established method for C–C bond formation. In classical carbonyl additions, premetalated reagents or stoichiometric metallic reductants are required. By taking advantage of the native reducing capability of alcohols, our lab has developed methods that exploit alcohols and π-unsaturates to generate transient electrophile-nucleophile pairs to directly convert lower alcohols to higher alcohol. Efforts have been focused on the development of transition metal-catalyzed redox-triggered coupling reactions of primary alcohols and aldehydes to π-unsaturates as well as aryl iodides. Modern methods to construct new C-C bonds in highly selective manner via carbonyl addition were undertaken.

Table of Contents

List of Tables

List of Figures

List of Schemes

Chapter 1: Metal-Catalyzed Reductive Coupling of Aryl Halides and Carbonyl Compounds beyond Nozaki-Hiyama-Kishi Reaction

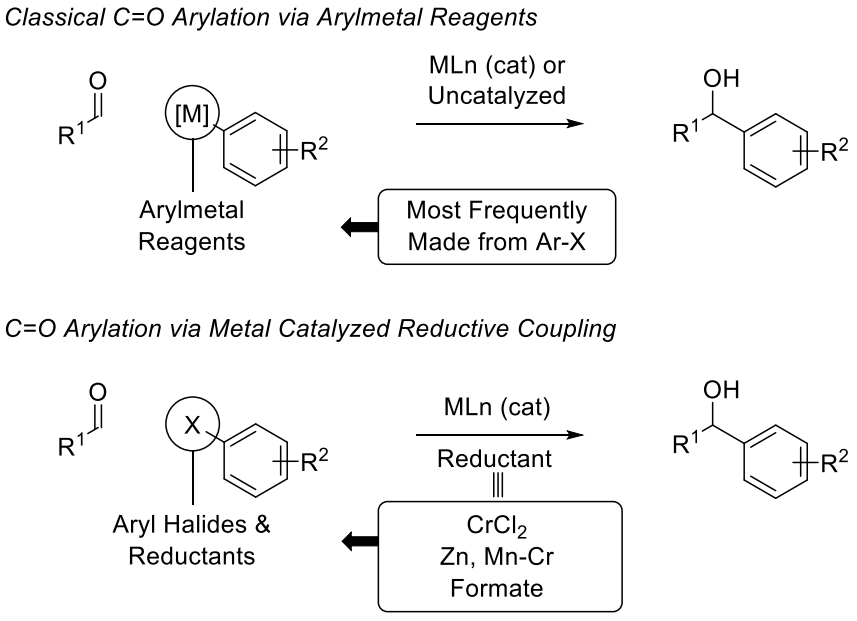
1.1 Introduction and Historical Perspective

Constructing new carbon-carbon(C-C) bonds is one of the most important tasks for organic chemists since the skeleton of organic molecules is constructed of C-C bonds. Among the C-C bond forming methods, carbonyl addition reactions, especially carbonyl allylation, have been broadly used currently in organic synthesis.[1-8] Carbonyl addition reactions mediated by pre-formed organometallic reagents became a milestone in organic synthesis since the seminal work of Butlerov[9,10] (1863), Reformatsky[11] (1887), and Grignard[12] (1900). Nevertheless, the issues of safety, requirement of cryogenic conditions, disposal of stoichiometric metal byproducts, low chemoselectivity and tolerance of functional groups, as well as the low accessibility of the premetalated nucleophiles complicate their applications in large-scale synthesis. Notably, the organometallic reagents are usually prepared from the corresponding organic halides,[13] which are much more readily available. Therefore, the metal-catalyzed reductive coupling of organic halides with carbonyl compounds is more desirable when contrasted with the use of premetalated nucleophiles in carbonyl addition. The reductive coupling of organic halides with carbonyl compounds also represents a class of cross-electrophile coupling reactions[14], which depict the deviation from traditional nucleophilic carbonyl addition with organometallic reagents and allow people to explore more chemical space.

In 1977, Nozaki and Hiyama reported the chromium(II)-mediated Barbier-type coupling of allyl halides with aldehydes to form homoallylic alcohols,[15] which was the initial report of Nozaki-Hiyama-Kishi (NHK) reaction. In 1986, Nozaki[16] and Kishi[17] independently found that nickel(II) chloride functioned as a catalyst in the NHK reaction.

The discovery of this reaction has had a huge impact on organic synthesis strategy,[18,19] but also revealed the feasibility of metal-catalyzed reductive coupling of organic halides with carbonyl compounds without employing pre-formed nucleophiles. The requirement of stoichiometric amounts of the toxic chromium(II) salts limits the application of NHK reaction on a practical scale. Consequently the metal-catalyzed reductive coupling of organic halides with carbonyl compounds utilizing cheaper and more benign reductants has been explored in recent years. However, when compared with metal-catalyzed redox-neutral couplings of aryl halides and aldehydes to form ketone products, which has been extensively studied by many research groups and can be conducted under different metal catalyst systems (palladium,[20-29] rhodium, [30,31] nickel, [32,33] photo-redox, [34] and cobalt [35]), metal-catalyzed reductive coupling is more challenging due to the choice of reductants (Scheme 1.1).

Scheme 1.1 Carbonyl Arylation via Arylmetal Reagents and Metal Catalyzed Reductive Coupling Strategies.



In this review, the metal-catalyzed reductive coupling of aryl halides with carbonyl compounds, including aldehydes, ketones, carbon dioxide, acid chlorides, anhydrides, isocyanates and other carbonyl sources, are surveyed and organized on the basis of metal catalysts. Related reductive coupling to gaseous carbon monoxide to produce aldehydes[36-47], which is also referred as carbonylation or formylation, is not discussed here, and the reader is referred to the provided literature.

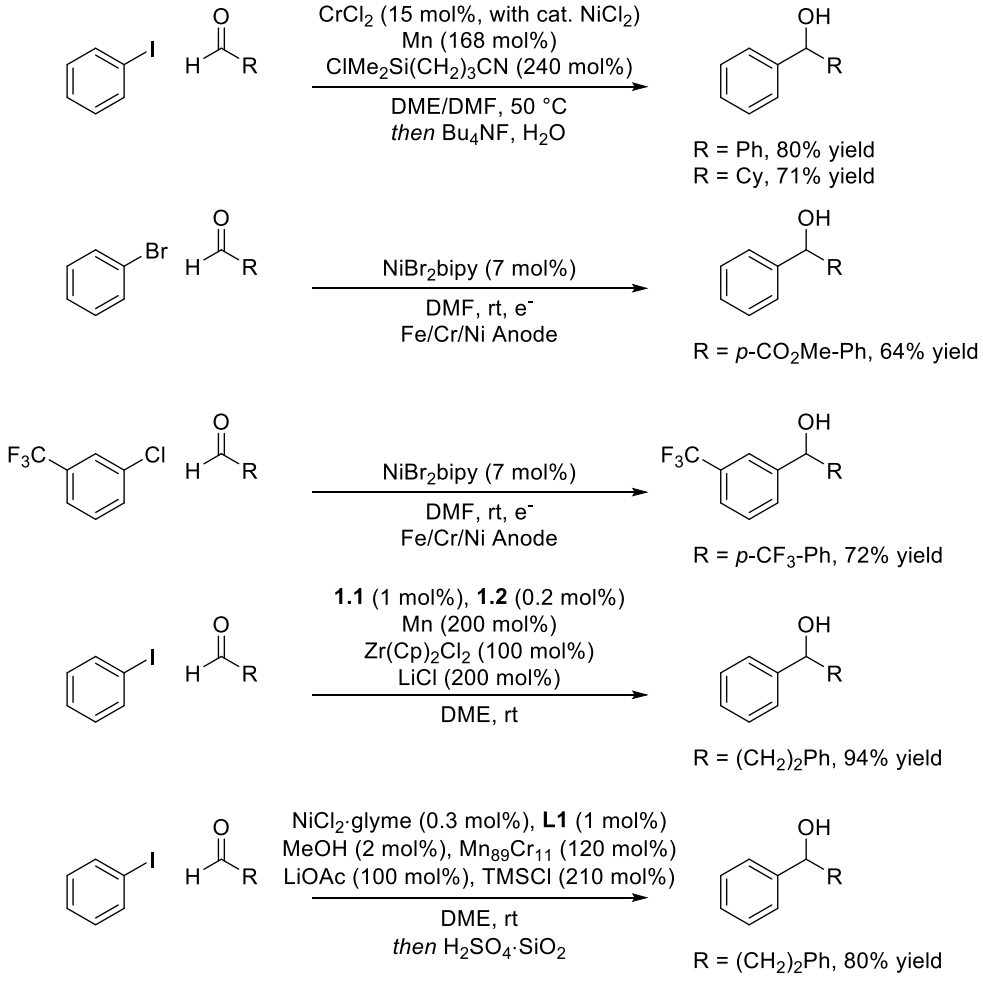
1.2 Reductive Coupling with Aldehydes

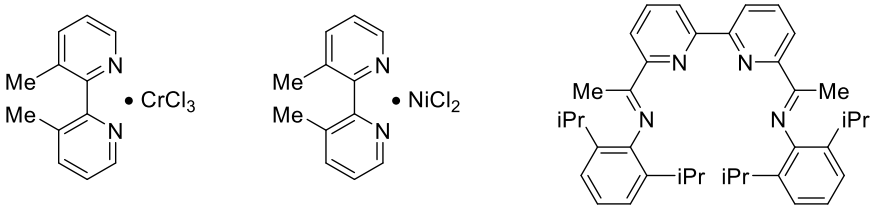
1.2.1 Nickel

Following the original report of the NHK coupling of aryl halides and aldehydes,[15] catalytic NHK reactions had been studied by several research groups due to usage of the toxicity of divalent chromium salts (Scheme 1.2). Related NHK reaction catalytic in nickel/chromium was first developed by Fürstner and co-workers [48,49] in 1996 using manganese as reducing agent to reduce Cr(III) to Cr(II) and chlorosilane as oxophile to cleave the stable O-Cr(III) bond and release Cr(III). Upon aqueous workup with Bu_4NF, alcohol adducts were obtained by coupling of aryl iodides and aldehydes. Later in 1999 and 2001, electroreductive coupling of aryl bromides/chlorides and aldehydes with iron anode in the presence of nickel and chromium catalysts was reported by Durrandetti and co-workers[50,51]. Further studies by Kishi and co-workers[52], Ni/Cr-mediated reductive coupling of iodobenzene with aldehyde was reported by using manganese as reductant together with $Zr(Cp)_2Cl_2$ to dissociate the chromium alkoxide and regenerate chromium catalyst. The loading of nickel and chromium was 0.2 mol% and 1 mol% respectively, and excellent isolated yields were obtained. In 2015, Berkessel and co-workers reported an efficient protocol for coupling of aryl iodides with aldehydes under nickel catalysis.[53]

Mn/Cr alloy was used as terminal reductant instead of the classical combination of manganese powder and chromium salt, and TMSCl was used as dissociating agent.

Scheme 1.2 Ni/Cr-Catalyzed Aryl Halide-Aldehyde Reductive Coupling.

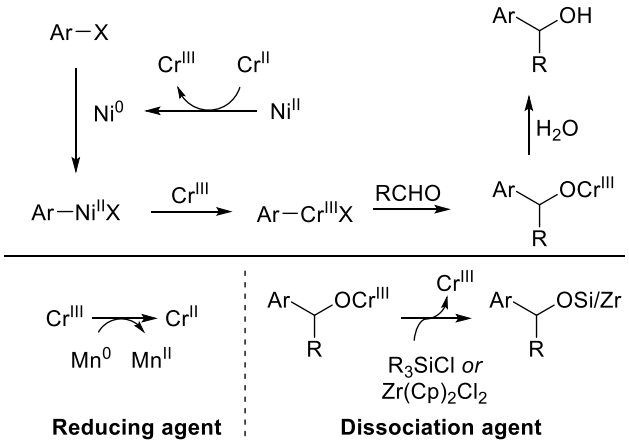




1.1 **1.2** **L1**

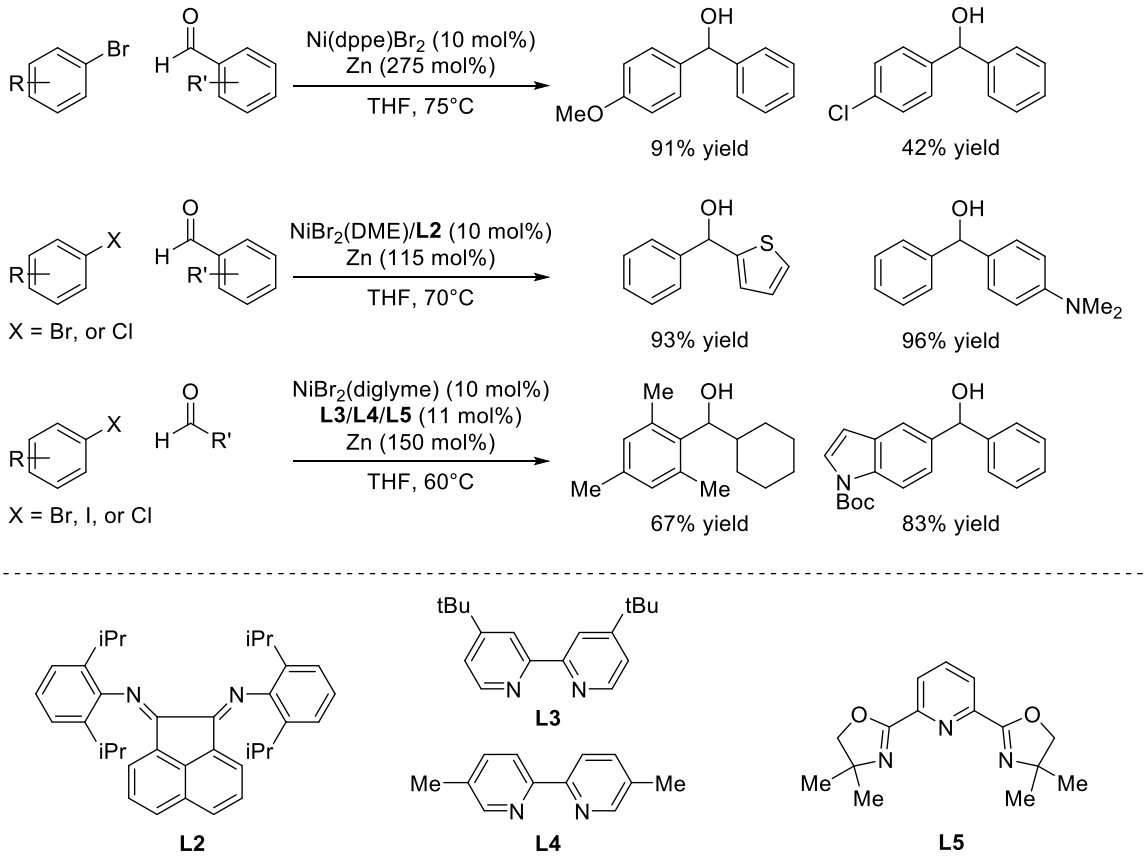
A General mechanism for Ni/Cr-catalyzed aryl halide-aldehyde reductive coupling has been proposed (Scheme 1.3). Oxidative addition of aryl halide to nickel(0) to form arylnickel(II) intermediate, which underwent transmetalation with chromium(III) to generate arylchromium(III) intermediate. Nucleophilic carbonyl addition afforded the chromium(III) alkoxide, which was converted to the final alcohol adduct and release chromium(III) with the help of dissociation agents. Reducing agents converted chromium(III) back to chromium(II), which reentered the catalytic cycle.

Scheme 1.3 Catalytic Mechanism for Ni/Cr-Catalyzed Aryl Halide-Aldehyde Reductive Coupling.



In 2000, the first chromium-free (diphenylphosphino)ethane-modified nickel catalyzed zinc mediated direct arylation of benzaldehydes was reported by Cheng and co-workers (Scheme 1.4).[54] The chelating ligands was found crucial in promoting the coupling, and monodentate phosphine ligands were ineffective. A catalytic mechanism was proposed (Scheme 1.5). First, reduction of Ni(II) to Ni(0) by zinc followed by oxidative addition of aryl bromide provided arylnickel(II) species. Substitution of bromide ligand on nickel center with aldehyde and subsequent carbonyl insertion to the Ni-Ar bond generated

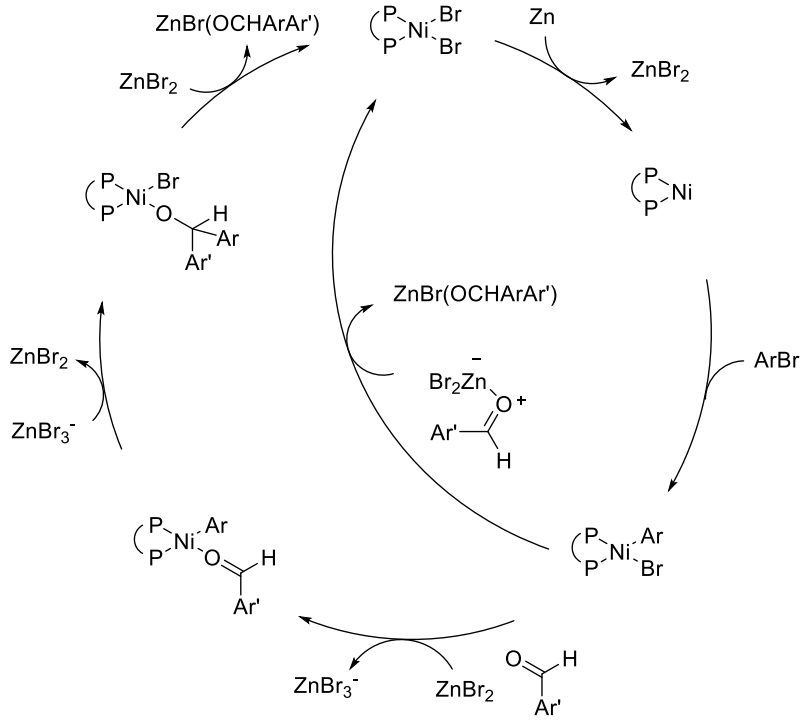
Scheme 1.4 Ni-Catalyzed Aryl Halide-Aldehyde Reductive Coupling for Form Alcohol Adducts.



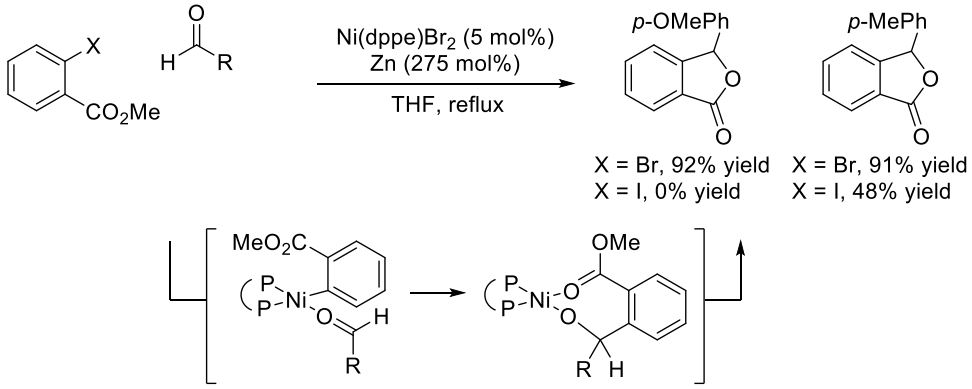
nickel alkoxide intermediate. Transmetalation with zinc bromides released the zinc alkoxide and regenerated Ni(II) catalyst. In 2015, diazabutadiene ligands were found to be effectively promoting the nickel catalyzed reductive coupling of aryl bromides and chlorides with benzaldehydes in good to excellent yields by Voskoboynikov and co-workers.[55] Recently, Weix and co-workers reported nickel complexes of bipyridine and Pybox catalyzed addition of aryl bromides to aromatic and aliphatic aldehydes with zinc metal as reducing agent.[56] Less reactive and more steric hindered aldehyes, as well as bulky aryl bromide were able to form the resesponding couping adducts with good to excellent

yields. Not only aryl bromies, aryl iodide could give comparable efficiency in the reaction. While when aryl chloride was used instead, couping adduct was isolated but with much

Scheme 1.5 Catalytic Mechanism for Ni-Catalyzed Aryl Halide-Aldehyde Reductive Coupling.



Scheme 1.6 Ni-Catalyzed Reductive Coupling of o-Haloesters with Aldehydes to Form Phthalide Derivatives.



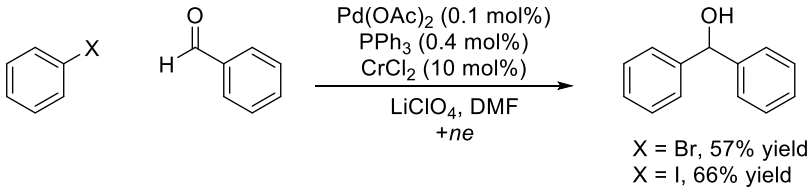
lower yield even at hight temperature; aryl triflate could not engage in the coupling under the standard conditions. Also a very broad substrate scope was demonstrated in this work.

In 2004, Cheng and co-workers reported reductive coupling of o-Haloesters with aldehydes in the presence of $Ni(dppe)Br_2$, and phthalide derivatives were obtained with moderate to good yields (Scheme 1.6).[57] When 2-iodobenzoate was subjected to the same reaction conditions, much lower yields were obtained, which was due to more homocoupling byproducts of both reactants were generated.

1.2.2 Palladium

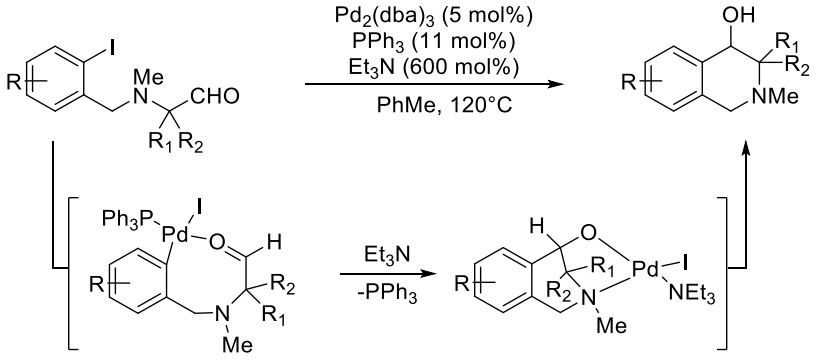
The first palladium(0) catalyzed chromium mediated electroreductive coupling of aryl halides and benzaldehydes was reported by Grigg and co-workers in 1997 (Scheme 1.7).[58] Catalytic amount of $CrCl_2$ (10 mol%) was required and $LiClO_4$ was used as oxophile to cleave O-Cr bond. Similar yields were obtained from coupling with aryl bromide and aryl iodide

Scheme 1.7 Pd/Cr-Catalyzed Reductive Coupling of Aryl Halides with Benzaldehydes.



In 2014, palladium catalyzed intramolecular addition of aryl iodides to aldehyde reported by Solé, Fernández and co-workers (Scheme 1.8).[59] Simple PPh_3-modefied palladium enabled the formation of diverse tetrahydroisoquinolin-4-ols with triethylamine as reducing agent. Notably, lower halide was demonstrated to be compatible under the

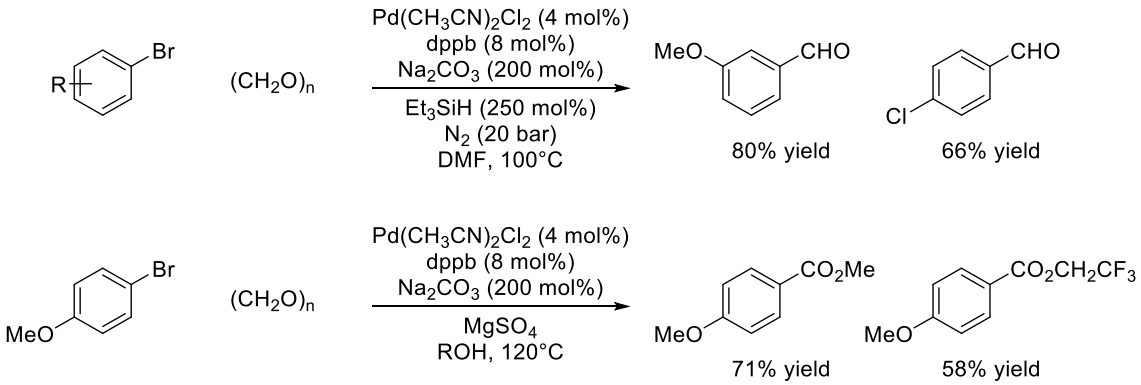
Scheme 1.8 Pd-Catalyzed Intramolecular Reductive Coupling of Aryl Iodides with Aldehydes.



standard conditions. According to DFT calculations, reaction mechanism was proposed through oxidative addition of aryl iodide to Pd(0) followed by the nucleophilic addition to aldehyde. Due to the coordination of palladium with nitrogen atom in the palladium alkoxide intermediate, β-hydride elimination was not sterically favored, which explained why ketone products were not observed.

In the same year, Beller and co-workers reported palladium catalyzed carbonylation of aryl bromides with paraformaldehyde to form aldehydes and esters[60]. Paraformaldehyde was used as a carbon monoxide surrogate and subjected to the aryl bromide with $Pd(CH_3CN)_2Cl_2$, dppb, Na_2CO_3 and Et_3SiH as reducing agent in DMF at 100℃ to deliver benzaldehydes. Introduction of N_2 gas was to avoid the evaporation of paraformaldehyde from the reaction mixture to increase the reaction efficiency. When alcohols were used as the solvent instead of DMF, the corresponding esters were obtained under the same catalytic system without Et_3SiH.

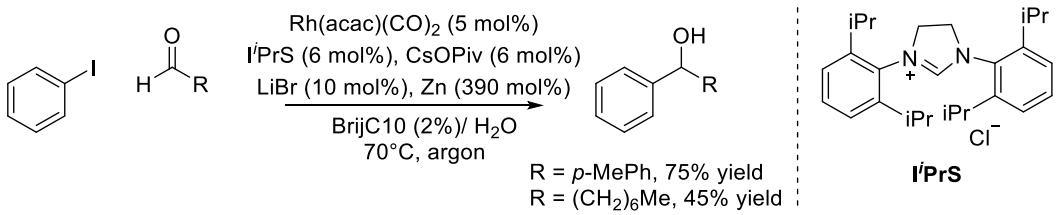
Scheme 1.9 Pd-Catalyzed Reductive Coupling of Aryl Bromides with Paraformaldehyde.



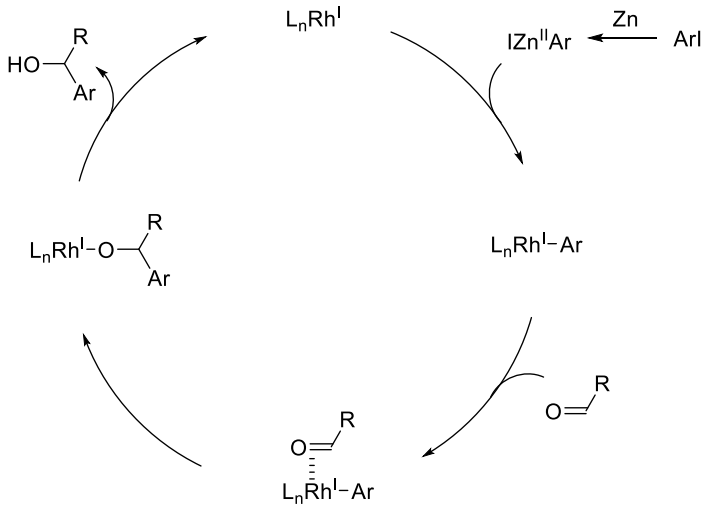
1.2.3 Rhodium

Insertion of aldehyde carbonyl group to rhodium-aryl complex to form rhodium alkoxide was reported to by Hartwig and co-workers in 2002.[61] The first rhodium catalyzed arylation of aldehydes by coupling with aryl iodides was reported by Li and co-workers in 2014 (Scheme 1.10).[62] NHC ligands showed unique high efficiency in the coupling, and the reaction was carried out in water. The mechanism for this method was proposed to proceed through transmetalation of arylzinc intermediate, which was generated *in situ*, to rhodium (I) to form arylrhoium (I) species (Scheme 1.11). Coordination of reactant

Scheme 1.10 Rh-Catalyzed Reductive Coupling of Aryl Iodides with Aldehydes in Water.

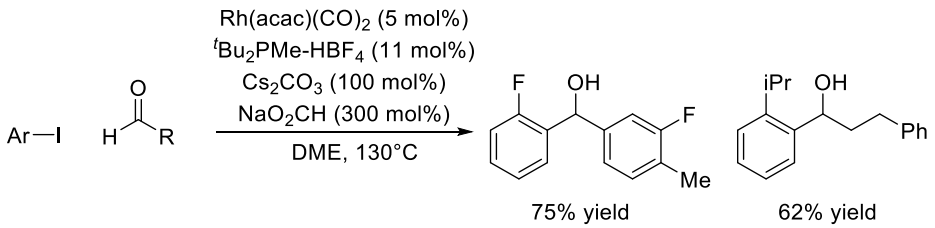


Scheme 1.11 Catalytic Mechanism of Rh-Catalyzed Reductive Coupling of Aryl Iodides with Aldehydes in Water.

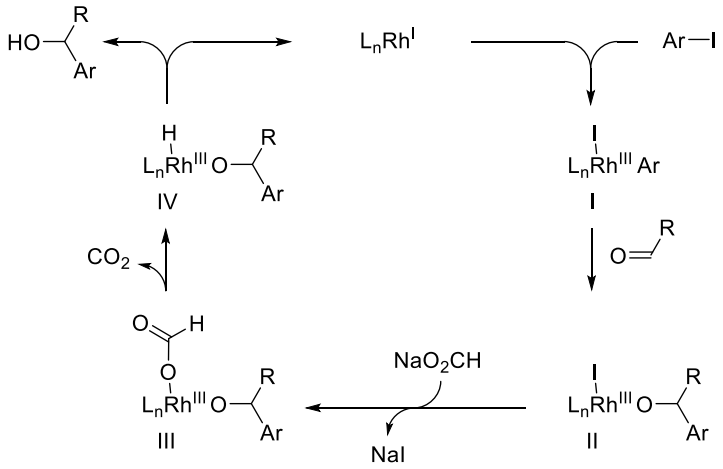


aldehyde followed by carbonyl insertion into the Rh-Ar bond generated rhodium alkoxide, which upon protonolysis, secondary alcohols was released and regenerate the active catalyst Rh(I). Another rhodium catalyzed reductive coupling of aryl iodide with aldehydes was recently reported by Krische and co-workers by using sodium formate as terminal reductant, which represented the first example of intermolecular carbonyl arylation via transfer hydrogenative reductive coupling (Scheme 1.12).[63] A very broad range of alcohol adducts were obtained, and the reaction was not sensitive to the substituted on the benzaldehydes. Notably, lower halides and protic functional groups were tolerated under the standard conditions. The catalytic mechanism was proposed based on the results of deuterium study (Scheme 1.13). Oxidative addition of aryl iodide to rhodium(I) to form arylrhodium(III) intermediate. Coordination of aldehyde to Rh(III) followed by carbonyl insertion afforded the rhodium alkoxide intermediate. Ligand exchange with formate followed by β-hydride elimination and further reductive elimination to release the coupling adduct, as well as close the catalytic cycle.

Scheme 1.12 Rh-Catalyzed Formate Mediated Reductive Coupling of Aryl Iodides with Aldehydes.



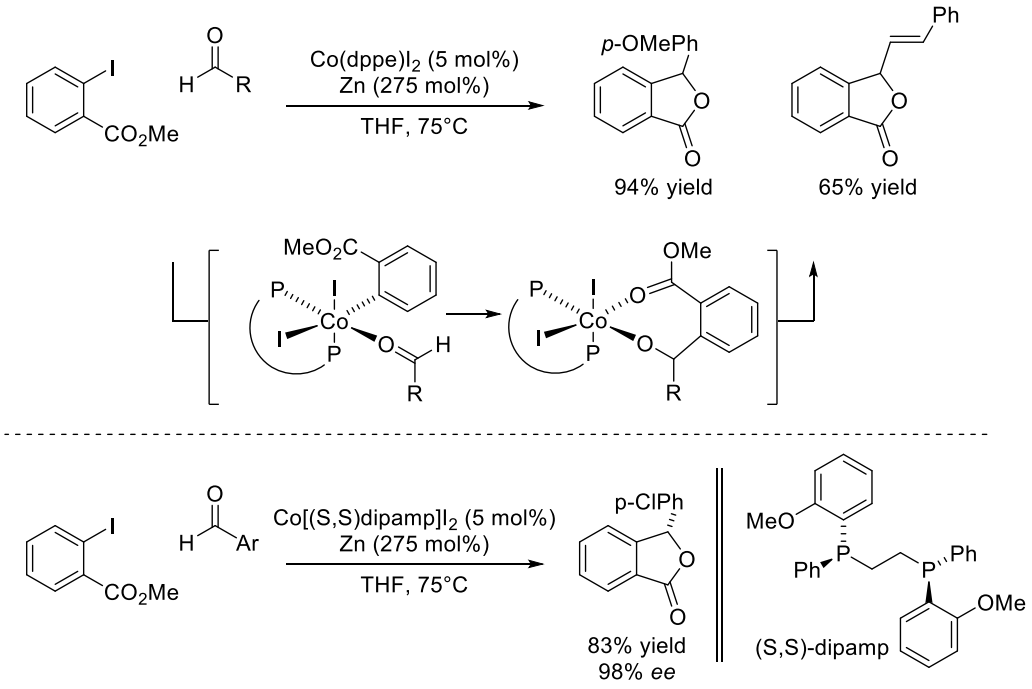
Scheme 1.13 Catalytic Mechanism of Rh-Catalyzed Formate Mediated Reductive Coupling of Aryl Iodides with Aldehydes in Water.



1.2.4 Cobalt

There's only one report on cobalt catalyzed reductive coupling of *o*-iodobenzoates with benzaldehydes to form phthalides with good yields in 2007 by Cheng and co-workers (Scheme 1.14).[64] Enantiomeric enriched phthalides up to 98% *ee* were obtained when (S,S)-dipamp was used. Notably, when cinnamyl aldehyde was subjected to the coupling condition with 2-iodobenzoate, coupling adduct was isolated in 65% yield, which indicated

Scheme 1.14 Co-Catalyzed Reductive Coupling of o-Haloesters with Aldehydes to Form Phthalide Derivatives.



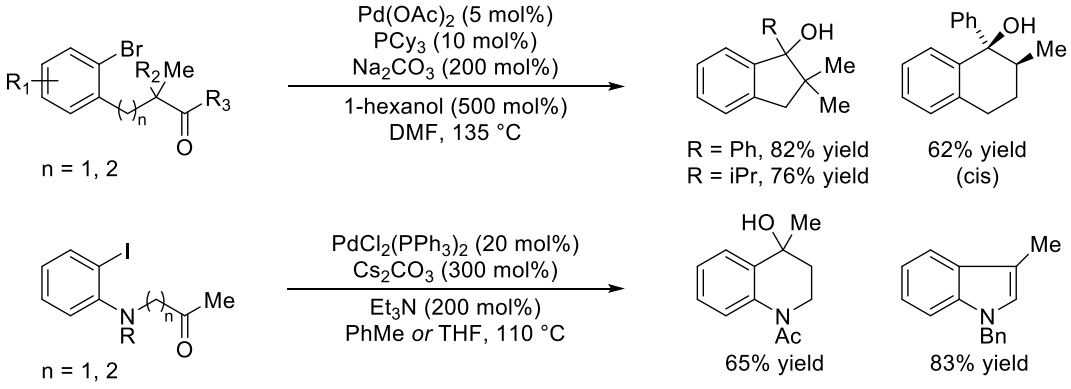
that aldehyde carbonyl group competed effectively with the double bond in the insertion step. The reaction was proposed undergo a Co(I)/Co(III) catalytic cycle.

1.3 REDUCTIVE COUPLING WITH KETONES

1.3.1 Palladium

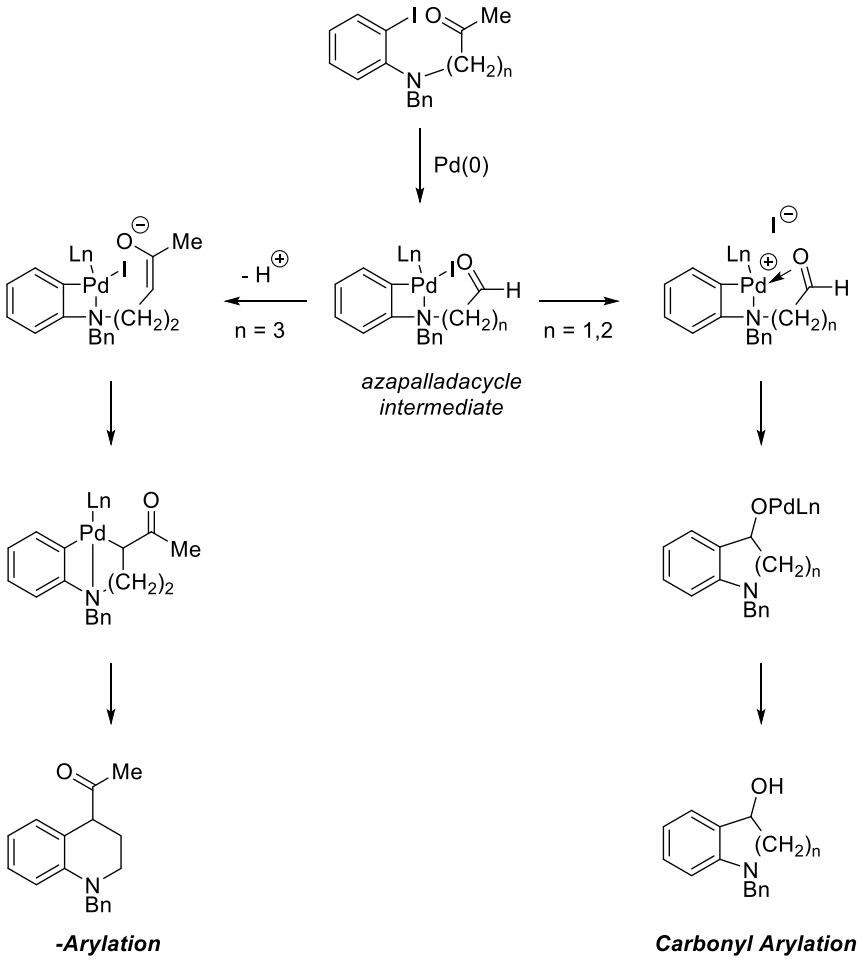
Palladium catalyzed reductive coupling of aryl halides with ketones are all intramolecular cyclization. The first example of Grignard-type nucleophilic addition of aryl bromides to ketones was reported by Yamamoto and co-workers in 2000 (Scheme 1.15)[65]. In the presence of $Pd(OAc)_2$ and PCy_3, *o*-bromophenyl ketones were converted to the cyclization adducts with 1-hexanol as reductant. Other alcohols, such as 1-pentanol and 1-propanol gave equally efficiency in the reaction as reductant. Both aromatic and aliphatic

Scheme 1.15 Pd-Catalyzed Intramolecular Reductive Coupling of Aryl Halides with Aldehydes to Form the Cyclization Adducts.



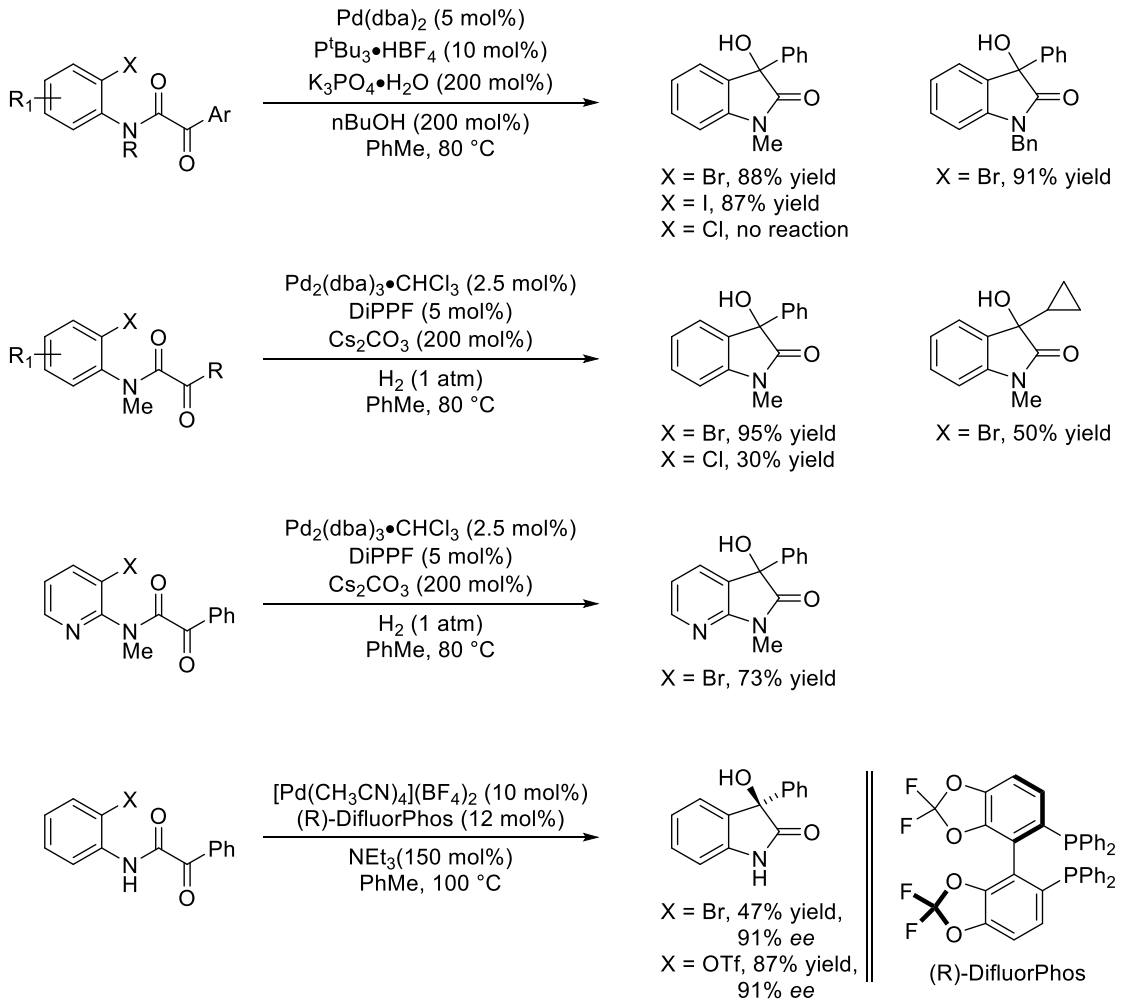
ketones underwent the arylation, which could get access to five- and six-member ring containing products. In 2001, Solé, Bonjoch and co-workers reported triethylamine mediated intramolecular annulation of 2-haloanilines and ketones[66]. From the carbonyl addition adducts, which were further subjected to trifluoroacetic acid, indole derivatives were obtained in good yields. In the course of studies, a competing cyclization pathway, which is enolate arylation, was observed and found to be depending on the structure of the starting amino-ketone. Through further studies[67], the catalytic mechanism for the intramolecular cyclization was proposed (Scheme 1.16). Oxidative addition of aryl halide to palladium(0) to form the four-membered azapalladacycle, which could undergo facile addition to the carbonyl group. The carbonyl addition is a consequence of the coordination of amino group to palladium, which facilitated the chelation between carbonyl and palladium and further triggered the carbonyl addition to for the palladium alkoxide intermediate.

Scheme 1.16 Proposed Mechanism for α-Arylation and Carbonyl Addition of 2-Haloanilino Ketones.



In 2010, Kündig and co-workers reported the synthesis of 3-hydroxyindoles via palladium catalyzed intramolecular cyclization of aryl halides to α-ketoamides in the presence of *n*BuOH as terminal reductant with good yields (Scheme 1.17)[68]. Aryl bromide and iodide could both engage in the reductive cyclization with similar isolated yields obtained. In 2015, Krische and co-workers reported the hydrogen-mediated reductive cyclization of haloketones to form 3-hydroxy-2-oxindoles[69]. By using DiPPF-modified palladium, in combination with hydrogen gas as reductant, not only aryl substituted

Scheme 1.17 Pd-Catalyzed Intramolecular Reductive Coupling of Aryl Halides with Aldehydes to Form 3-Hydroxy-2-Oxindoles.



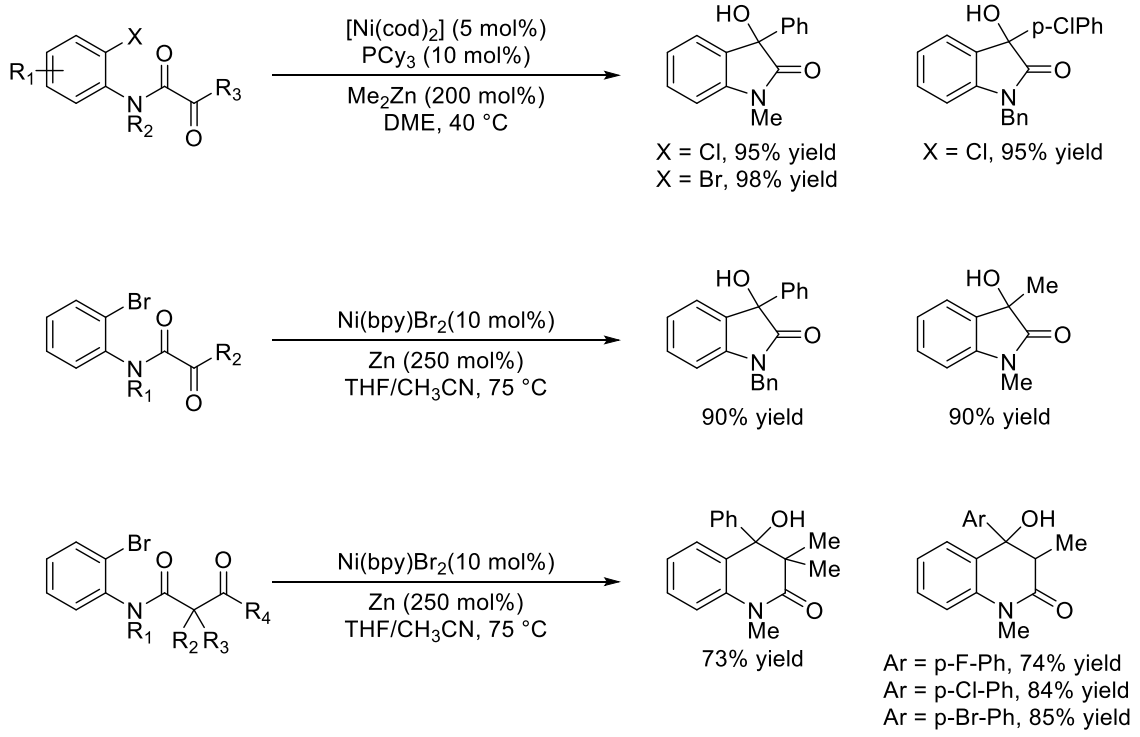
hydroxy oxindoles could be obtained with good yield, heteroaryl and alkyl substituted adducts were isolated with moderate to good yields. Notably, α-ketoamide derived from 2-amino-3-bromopyridine gave good yield under the standard conditions. The asymmetric version of the synthesis of 3-hydroxyindoles with (R)-DifluorPhos-modified palladium complex was reported by Shibasaki, Kanai and co-workers in 2011[70]. When aryl iodide was used, moderate yield and excellent enantioselectivity was obtained. To improve the

reaction efficiency, aryl triflate was used instead of aryl iodide and good yield and high level of enantioselectivity was obtained.

1.3.2 Nickel

In 2011, nickel catalyzed intramolecular reductive coupling of aryl chloride and α-ketoamides mediated by Me_2Zn in DME was reported by Jia, Gao and co-workers (Scheme 1.18)[71]. C-Cl bond was successfully activated by electron-rich, bulky phosphine ligand PCy_3-modified nickel complex. When Et_3B and Zn dust were applied as reductant in the coupling, no desired product was observed. Both aryl chloride and bromides could engage in the carbonyl arylation under standard conditions and comparable yields were obtained.

Scheme 1.18 Ni-Catalyzed Intramolecular Reductive Coupling of Aryl Halides with Ketones.



Notably, chlorine substituents on the aromatic rings remain untouched during the nickel catalyzed reductive coupling, which could be utilized in cross-coupling reaction for further functionalization. Further studies by Jia and co-workers demonstrated the formation of 3-hydroxyoxindole and dihydroquinolinone via nickel-catalyzed zinc mediated intramolecular reductive nucleophilic addition of aryl bromides to ketoamides[72]. In this transformation, monodentate phosphine ligand, such as PCy_3, was not as effective as bidentate chelating ligands, for example, 2,2'-bipyridine(bpy). When α-ketoamides were subjected to the standard conditions, excellent yields of the desired adduct 3-hydroxyoxindoles were obtained. When β-ketoamides were subjected to the standard conditions, dihydroquinolinones were isolated with good yields when at least one methyl group at α-position due to Thorpe-Ingold effect. Also, bromine, chlorine, and fluorine substituents on the aromatic rings were tolerated.

1.4 Reductive Coupling with Acid Chlorides and Anhydrides

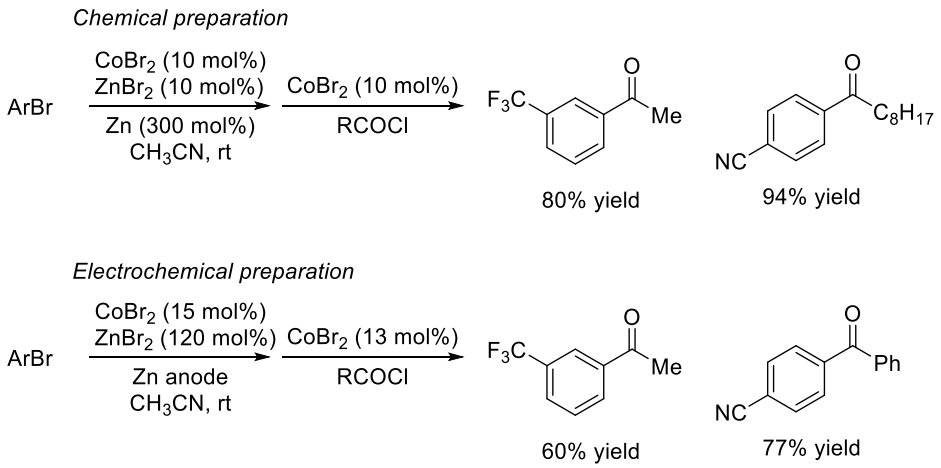
1.4.1 Cobalt

Acid Chlorides are considered ideal carbonyl compounds for reductive coupling reaction due to the higher reactivity. In 2003, Gosmini and co-workers reported the first example of cobalt catalyzed zinc mediated reductive coupling of aryl bromides with acid chloride, which could be used for preparation of aromatic ketones (Scheme 1.19)[73]. This 2-stpes protocol could be conducted in two different manner for the preparation of aryl zinc intermediate, electrochemical and chemical preparations. The mechanism of the reaction was proposed via oxidative addition of acid chloride to Co(I) complex to form the Co(III), which was further converted to arylcobalt(III) via transmetalation with arylzinc reagent

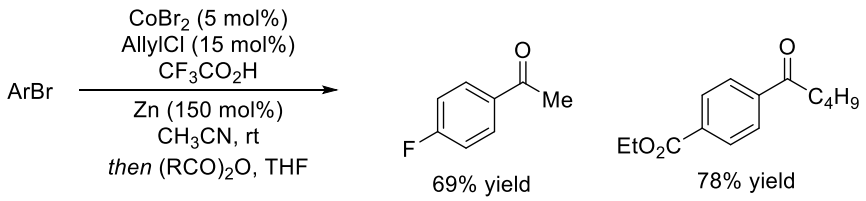
formed in the first step. Final reductive elimination released the aromatic ketones and regenerated Co(I) to close the catalytic cycle.

Related cobalt catalyzed reductive coupling of aryl bromides with acid anhydrides were discovered by Gosmini and co-workers in 2004 (Scheme 1.20)[74]. Aromatic ketones could be obtained in on step due to the lower reactivity of acid anhydride comparing with acid chlorides. Arylzinc was prepared *in situ* under the presence of $CoBr_2$, allyl chloride and trifluoroacetic acid from aryl bromides and zinc dust. Catalytic amount of allyl chloride was need in order to enhance the yield of arylzinc species and suppress the formation of reductive dehalogenation adducts. Trifluoroacetic acid was added to activate zinc dust.

Scheme 1.19 Co-Catalyzed Reductive Coupling of Aryl Bromides with Acid Chloride to Form Aromatic Ketones.



Scheme 1.20 Co-Catalyzed Reductive Coupling of Aryl Bromides with Acid Anhydrides to Form Aromatic Ketones.

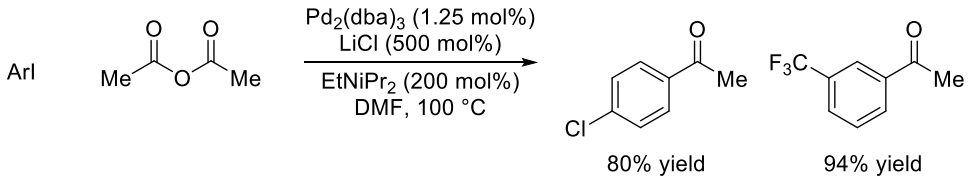


1.4.2 Palladium

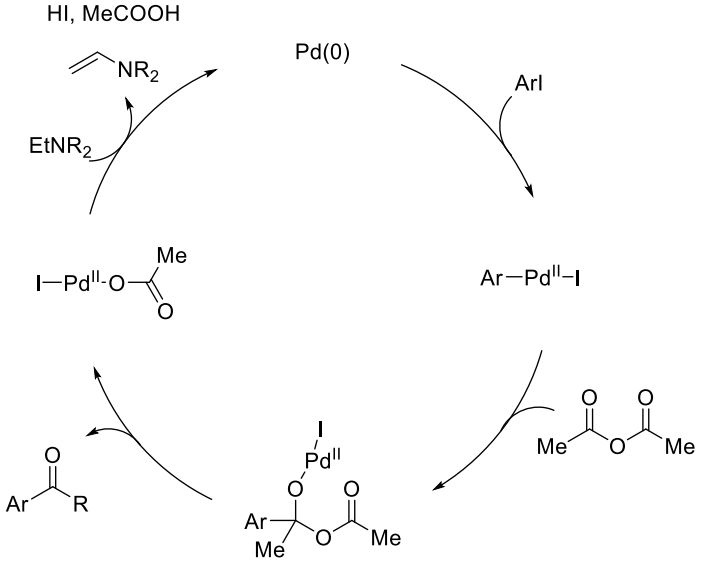
In 2003, Cacchi and co-workers reported the first palladium catalyzed reductive coupling of aryl iodide with acetic anhydride to synthesize acetophenones(Scheme 1.21)[75]. The use of $Pd_2(dba)_3$ in combination with Hünig's base as reductant, and LiCl in DMF at 100℃ led to the reductive coupling of acetic anhydride with a wide range of aryl iodides. With LiCl added in the reaction mixture, formation of homocoupling adducts from aryl iodides was suppressed. For the aryl iodides with strong electron-withdrawing substituents, biaryl byproducts from the homocoupling of aryl iodides were isolated in significant yield, even with LiCl in presence. The catalytic mechanism was proposed (Scheme 1.22). Oxidative addition of aryl iodides to palladium(0) followed by carbonyl insertion to the aryl-Pd bond delivered alkoxy-palladium intermediate. Acetophenone adduct was released via β-elimination and palladium(0) was regenerated by tertiary amine mediated reduction.

In 2004, Cacchi and co-workers reported palladium catalyzed reductive coupling of aryl iodides with a mixed anhydride, acetic formic anhydride, which could be readily prepared from acetyl chloride and sodium formate (Scheme 1.23)[76]. In the presence of $Pd_2(dba)_3$, dppe, Hünig's base and Et_3SiH as reducing agent in MeCN at 60℃, diverse aryl iodides with various functional groups, including, ether, ester, amide, carboxylic acid and keton, were converted to aldehydes with good yields. For electron pool aryl iodides, LiCl was added to obtain higher yields. This protocol demonstrated the palladium catalyzed carbonylation of aryl halides could be achieved by coupling with acetic formic anhydride instead of using pressurized toxic carbon monoxide gas.

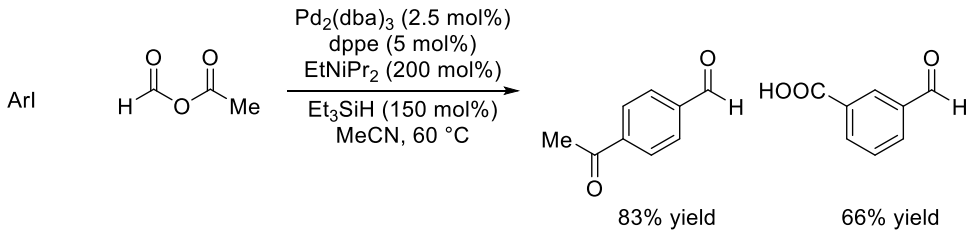
Scheme 1.21 Pd-Catalyzed Reductive Coupling of Aryl Iodides and Acetic Anhydride to Form Acetophenones.



Scheme 1.22 Proposed Mechanism for Pd-Catalyzed Reductive Coupling of Aryl Iodides and Acetic Anhydride to Form Acetophenones.



Scheme 1.23 Pd-Catalyzed Reductive Coupling of Aryl Iodides and Acetic Formic Anhydride to Form Aldehydes.

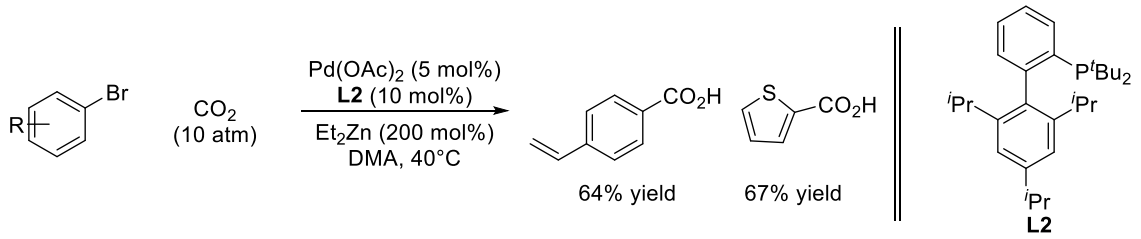


1.5 Reductive Coupling with Carbon Dioxide

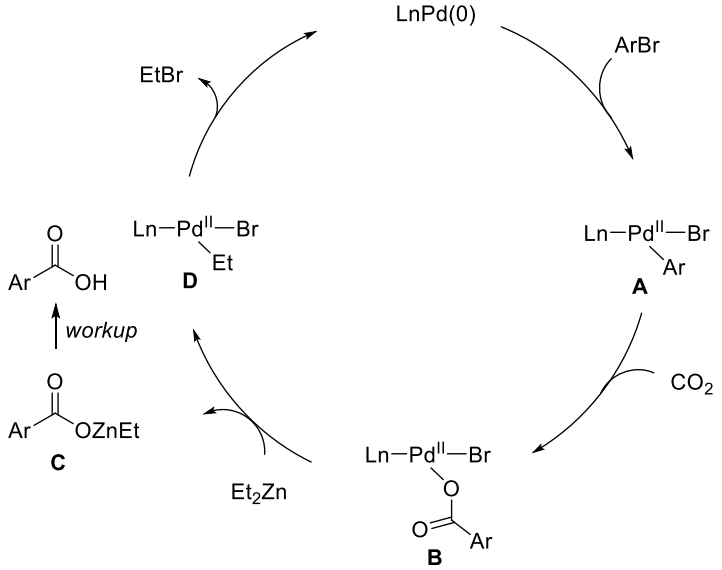
1.5.1 Palladium

In 2009, Martin and co-workers discovered the first palladium catalyzed reductive carboxylation of aryl bromides with carbon dioxide to form benzoic acids (Scheme 1.24)[77]. In this catalytic process, diethylzinc was used as reducing agent. The choice of ligand is crucial in promoting the efficient nucleophilic addition to carbon dioxide. The use of DMA favored the carboxylation over other byproducts. The best isolation yield (64%) of carboxylic acid adduct was obtained when the reaction was conducted under higher pressure of carbon dioxide (10 atm). Aryl bromides with diverse substituents were subjected to the optimal conditions and the desired reductive coupling adducts were delivered smoothly with moderate to good yields. Various functional groups, including amine, ether, thioether, olefin, ester, ketone, aldehyde, epoxide, and heterocycle, were tolerated. Notably, aryl chloride remained untouched under the standard conditions. The palladium catalyzed mechanism for the reductive coupling of aryl bromides with carbon dioxide was proposed based on the experimental results (Scheme 1.25). Initially, oxidative addition of aryl bromides to palladium(0) followed by carbon dioxide carbonyl insertion into the aryl-Pd bond delivered palladium carboxylate B. Subsequent transmetalation with diethyl zinc released the zinc carboxylate C, which was further converted to the carboxylic acid via workup, and palladium(II) complex D. Final reductive elimination regenerated the palladium(0) catalyst and closed the catalytic cycle.

Scheme 1.24 Pd-Catalyzed Reductive Coupling of Aryl Bromides and Carbon Dioxide to Form Carboxylic Acids.



Scheme 1.25 Proposed Mechanism for Pd-Catalyzed Reductive Coupling of Aryl Bromides and Carbon Dioxide to Form Carboxylic Acids.

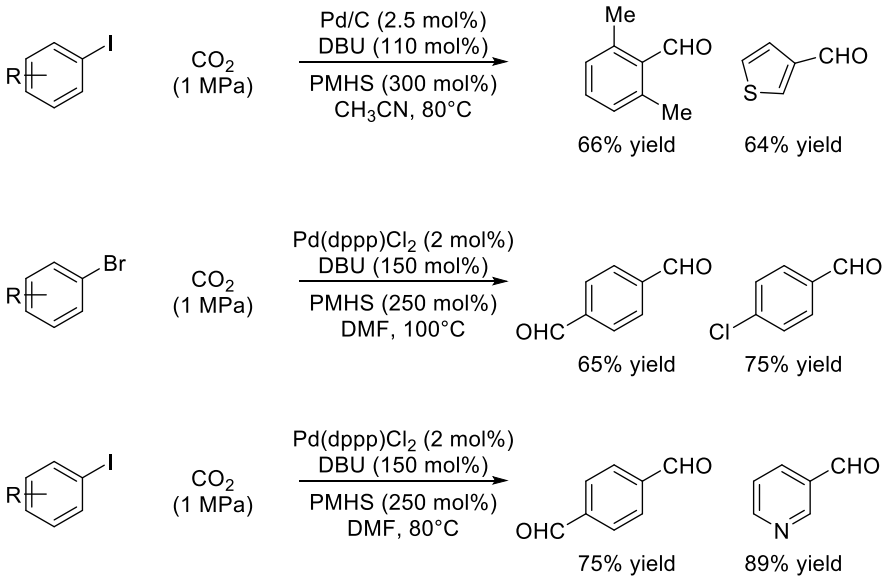


In 2014, Liu and co-workers reported the Pd/C-catalyzed direct formylation of aryl iodides by reductive coupling with carbon dioxide (Scheme 1.26)[78]. Due to the thermodynamic stability of carbon dioxide, direct functionalization is usually not easy. While it was found that hydrosilylation of carbon dioxide made it could be functionalized under relative milder conditions. In the presence of Pd/C, poly(methylhydrosiloxane) (PMHS), and DBU, reductive coupling of aryl iodides with carbon dioxide in acetonitrile under 80℃delivered the desired aldehydes with moderate to good isolation yields. The use of DBU as base is important for the formation of aldehydes. When inorganic carbonates

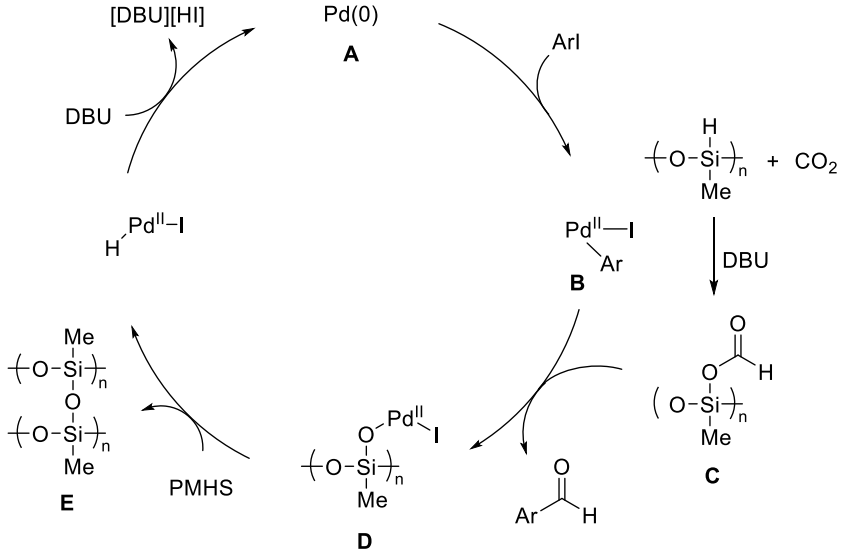
were used as base in the reaction, no aldehydes were obtained and biaryl compounds were isolated with high yields, which formed via homocoupling of aryl iodides. A wide range of aryl iodides were subjected to the reaction condition and aldehydes were obtained with moderate to good yields. Ortho-substituents didn't affect the reaction efficiency. Notably, electron-poor aryl iodides didn't engage in the coupling effectively due to the competing dehalogenation pathway. The catalytic mechanism for the silane mediated formation of aldehydes by coupling of aryl iodide and carbon dioxide was proposed (Scheme 1.27). Initially, oxidative addition of aryl iodide to palladium(0) led to the formation arylpalladium(II) complex B. Formation of silyl formate C from carbon dioxide and PMHS in the presence of DBU was confirmed by ^{1}H NMR analysis. Addition of aryl group to silyl formate C generated aldehyde together with silyloxylpalladium complex D, which further reacted with PMHS to form polysiloxane E and palladium(II) hydride. Upon DBU facilitated reductive elimination of HI, palladium(0) was regenerated.

Later in 2016, further studies by Liu and co-workers discovered a more general and efficient palladium catalytic system for formylation of aryl halides with carbon dioxides mediated by PMHS[79]. In the presence of 1,3-bis(diphenylphosphino)propane-modified palladium dichloride complex with DBU, less reactive aryl bromides were converted to aromatic aldehydes with good yields in DMF at 100℃. Aryl iodides were also successfully converted to the corresponding adducts under same reaction conditions at slightly lower temperature (80℃).

Scheme 1.26 Pd-Catalyzed Reductive Coupling of Aryl Halides and Carbon Dioxide to Form Aldehydes.

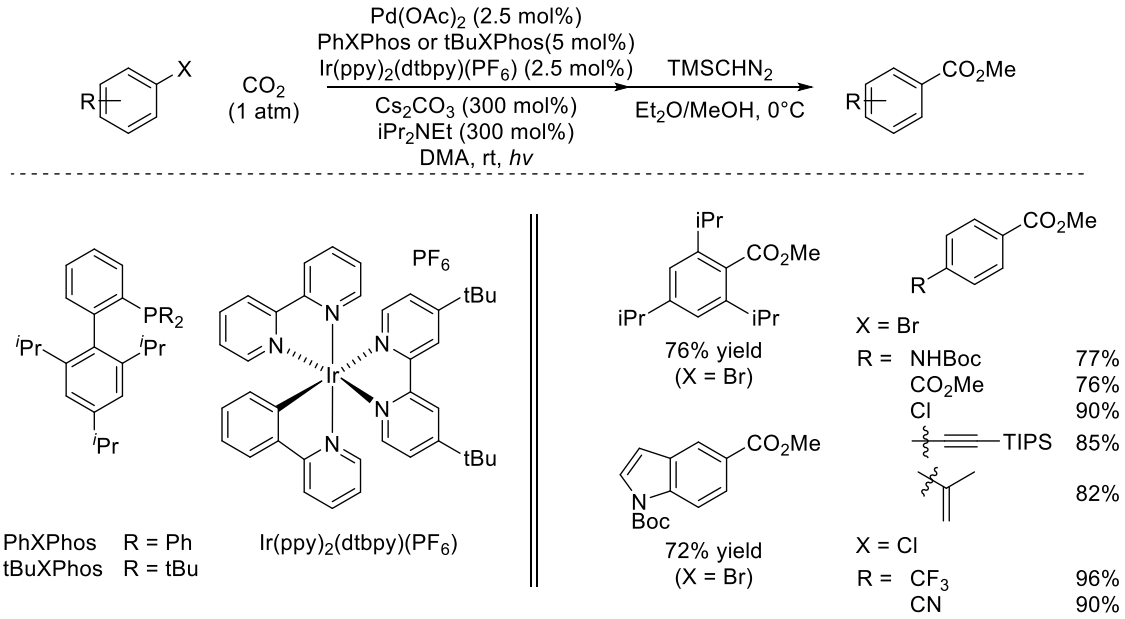


Scheme 1.27 Proposed Mechanism for Pd-Catalyzed PMHS Mediated Reductive Coupling of Aryl Halides and Carbon Dioxide to Form Aldehydes

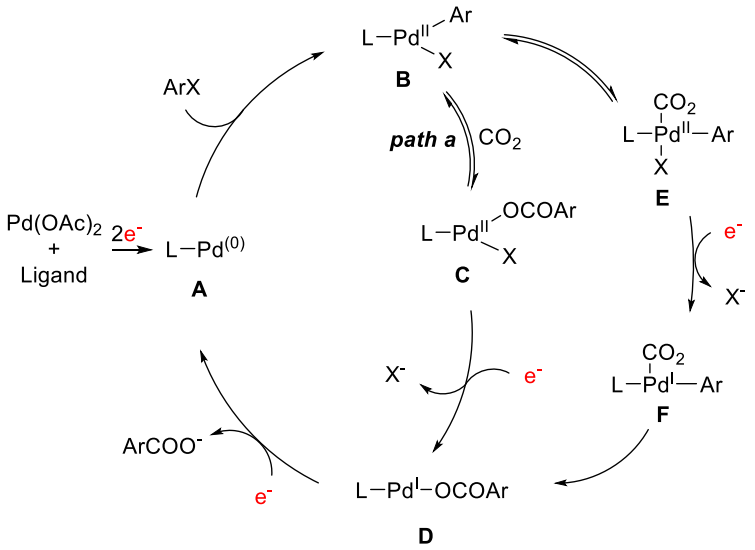


In 2017, visible-light-driven carboxylation of aryl halides with carbon dioxide was reported by Iwasawa and co-workers using palladium and photoredox dual catalysis (Scheme 1.28)[80]. Notably, the reaction was conducted under 1 atm carbon dioxide and light irradiation in the presence of $Pd(OAc)_2$, PhXPhos, $Ir(ppy)_2(dtbpy)(PF_6)$, Cs_2CO_3 as base, and Hünig's base as reductant in DMA at rt, which were very mild conditions. A wide range of aryl bromides and chlorides were converted to carboxylic acids, which were further treated with trimethylsilyldiazomethane ($TMSCHN_2$) to give the corresponding methyl esters. Steric hindered aryl halide 2,4,6-triisopropylbromobenzene was converted to the corresponding methyl ester with 76% yield. The activation of C-Br bond was achieved selectively in the presence of C-Cl bond, which was demonstrated with formation of 4-chlorobenzoate from 4-chlorobromobenzene. The mechanism for this transformation was proposed with two major possible pathways (Scheme 1.29). After the oxidative addition of aryl halide to palladium(0) to form arylpalladium(II) complex B, two possible palladium species were proposed. One was palladium(II) carboxylate species formed by direct insertion of carbon dioxide into Ar-Pd bond (pathway a), which underwent photoredox-catalyzed one-electron reduction to form palladium(I) carboxylate species D. Subsequent one-electron reduction of complex D released the coupling adduct and regenerated palladium(0). Another possible pathway was via coordination of carbon dioxide to form palladium(II) complex E, which underwent one-electron reduction first to form arylpalladium(I) complex F (pathway b). Subsequent addition of aryl group to carbon dioxide gave the palladium(I) carboxylate intermediate D, which underwent same process to close the catalytic cycle.

Scheme 1.28 Pd- and Photoredox-Catalyzed Reductive Coupling of Aryl Halides and Carbon Dioxide to Form the Corresponding Methyl Esters.



Scheme 1.29 Proposed Mechanism for Pd- and Photoredox-Catalyzed Reductive Coupling of Aryl Halides and Carbon Dioxide to Form the Corresponding Methyl Ester.



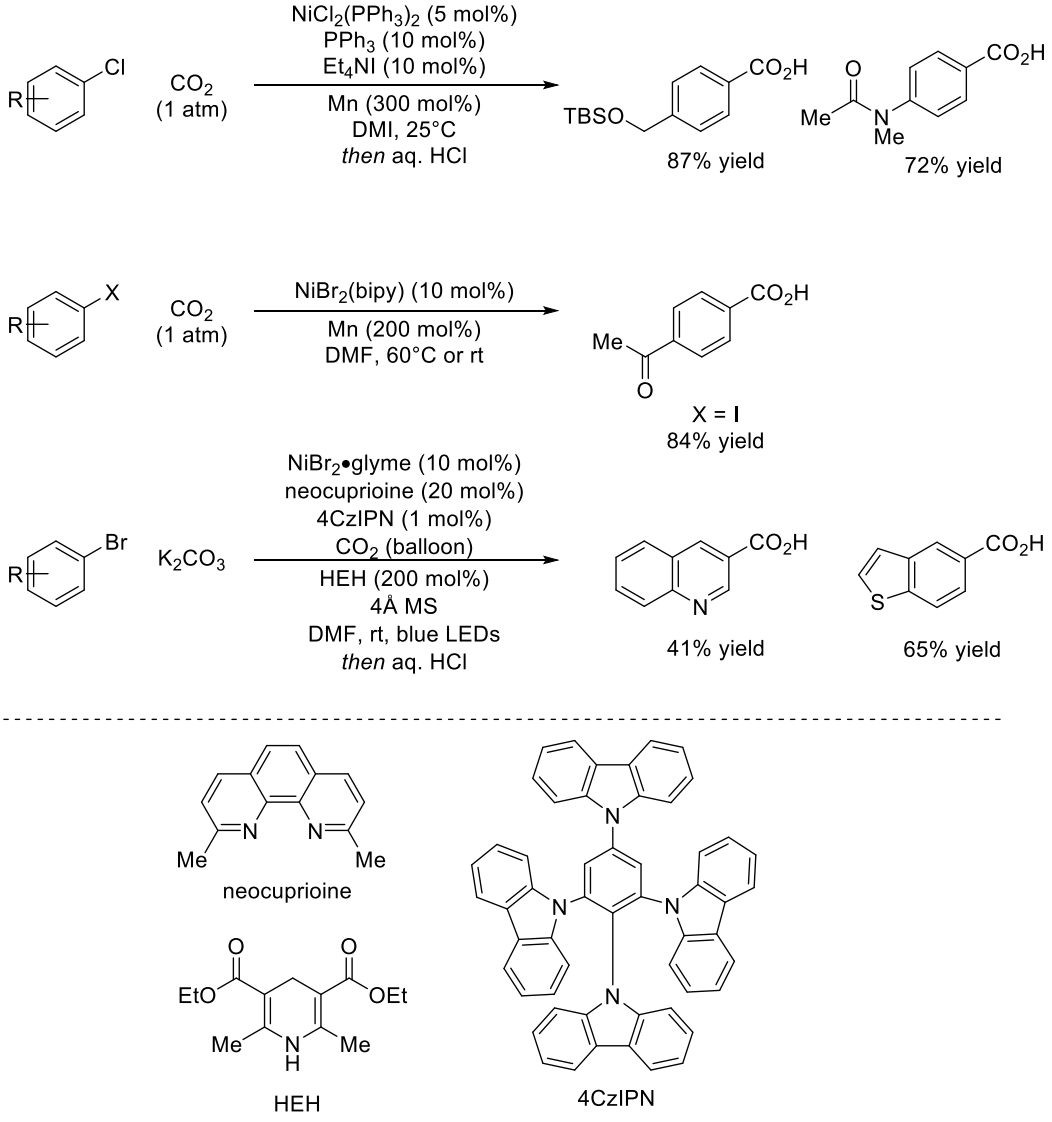
1.5.2 Nickel

In 2012, Tsuji and co-workers reported the first nickel catalyzed reductive carboxylation of aryl chlorides to form benzoic acids under mild conditions (Scheme 1.30)[81]. It was found that in the presence of $NiCl_2(PPh_3)_2$, PPh_3, Et_4NI, manganese powder aryl chlorides were converted to benzoic acids with good to excellent yield in 1,3-dimethyl-2-imidazolidinone (DMI) at room temperature under 1 atm carbon dioxide. Addition of PPh_3 was found to enhance the reaction efficiency by improving yield and suppressing formation of byproduct. When Et_4NI was omitted, desired coupling product was obtained only in trace amount. The role of catalytic amount of Et_4NI was believed to assist the electron transfer from manganese metal to nickel via the bridging of the iodide ion. Diverse aryl chlorides were evaluated under the standard conditions, and various functional groups, including silyl ether, ester, amide, boronic ester and ketone, were tolerant. Aryl bromide, tosylate and triflate were converted to the same carboxylation products under similar reaction conditions. A possible catalytic mechanism was proposed (Scheme 1.31). Zero valent nickel was generated in situ from nickel(II) through reduction. Oxidative addition of aryl chloride to nickel(0) gave arylnickel(II) species, which was reduced to arylnickel(I) by manganese metal. Subsequent insertion of carbon dioxide to aryl-Ni bond to delivere nickel carboxylate intermediate followed by reduction regenerated zero valent nickel and released coupling adduct. Later in 2013, DFT studies on the nickel catalyzed carboxylation of aryl chloride with carbon dioxide were conducted by Sakaki and co-workers[82]. Formation of arylnickel(I) intermediate was proved to be the key intermediate for the carboxylation reaction.

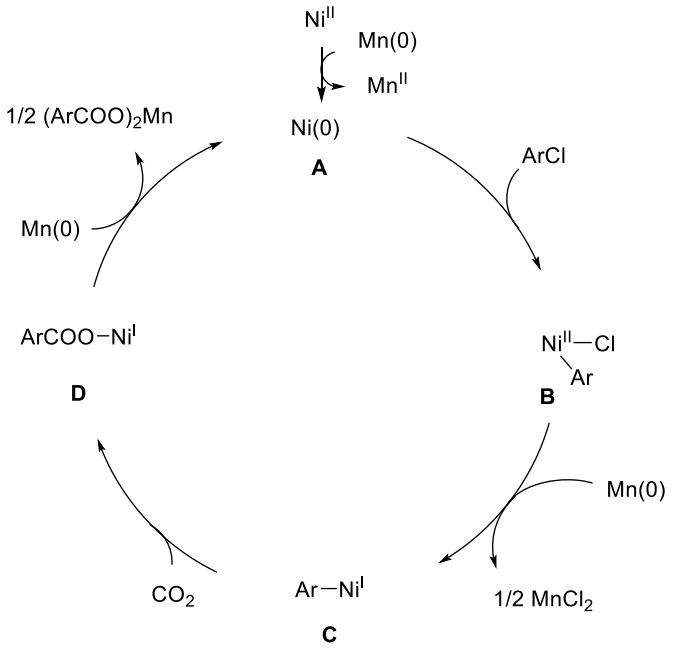
In 2016, Durandetti and co-workers reported the direct carbonylation of aryl tosylates with carbon dioxide by nickel catalysis[83]. It was found that in the presence of $NiBr_2$(bipy), and manganese powder, aryl tosylates could be converted to carboxylic acids

in DMF under 1 atm carbon dioxide at 60℃. When aryl iodide was subjected to the standard conditions at room temperature, benzoic acid was obtained with good yield.

Scheme 1.30 Nickel Catalyzed Reductive Coupling of Aryl Halides and Carbon Dioxide to Form Carboxylic Acids.

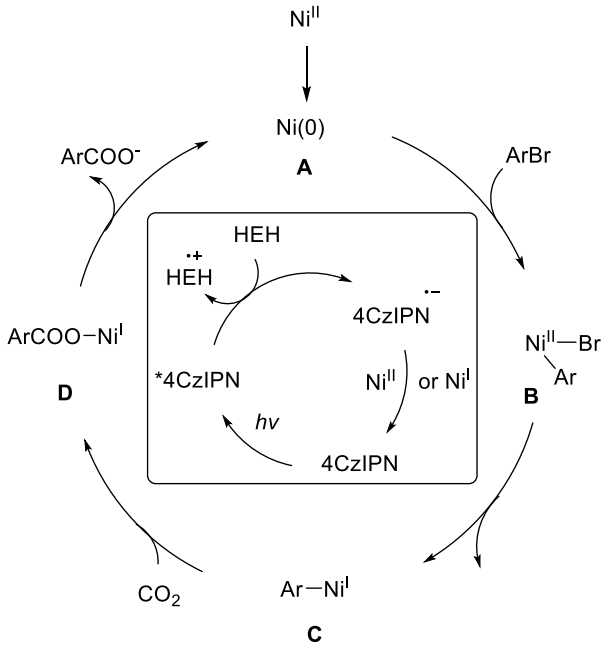


Scheme 1.31 Proposed Mechanism for Nickel Catalyzed Reductive Coupling of Aryl Halides and Carbon Dioxide to Form Carboxylic Acids.



In 2017, carboxylation of aryl bromides and triflates with carbon dioxide by nickel-photo dual catalysis, whereas K_2CO_3 was used as the source of carbon dioxide, was reported by König and co-workers[84]. In the combination of $NiBr_2$·glyme, neocuprioine, organic photosensitizer and Hantzsch ester (HEH) as reducing agent, carboxylation adducts of aryl bromides were obtained in moderate to good yield under room temperature with visible-light irradiation. A broad range of functional groups, including free alcohol, ether, ester, ketone, Boc-protected aniline, and cyano group, were tolerant under the standard conditions. Heteroaromatic bromides were also successfully converted to the corresponding heteroaromatic carboxylic acids with moderate yields. Catalytic mechanism was also proposed through insertion of carbon dioxide into arylnikel(I) intermediate (Scheme 1.32).

Scheme 1.32 Proposed Mechanism for Nickel-Photo Dual Catalyzed Reductive Coupling of Aryl Bromides and Carbon Dioxide to Form Carboxylic Acids.

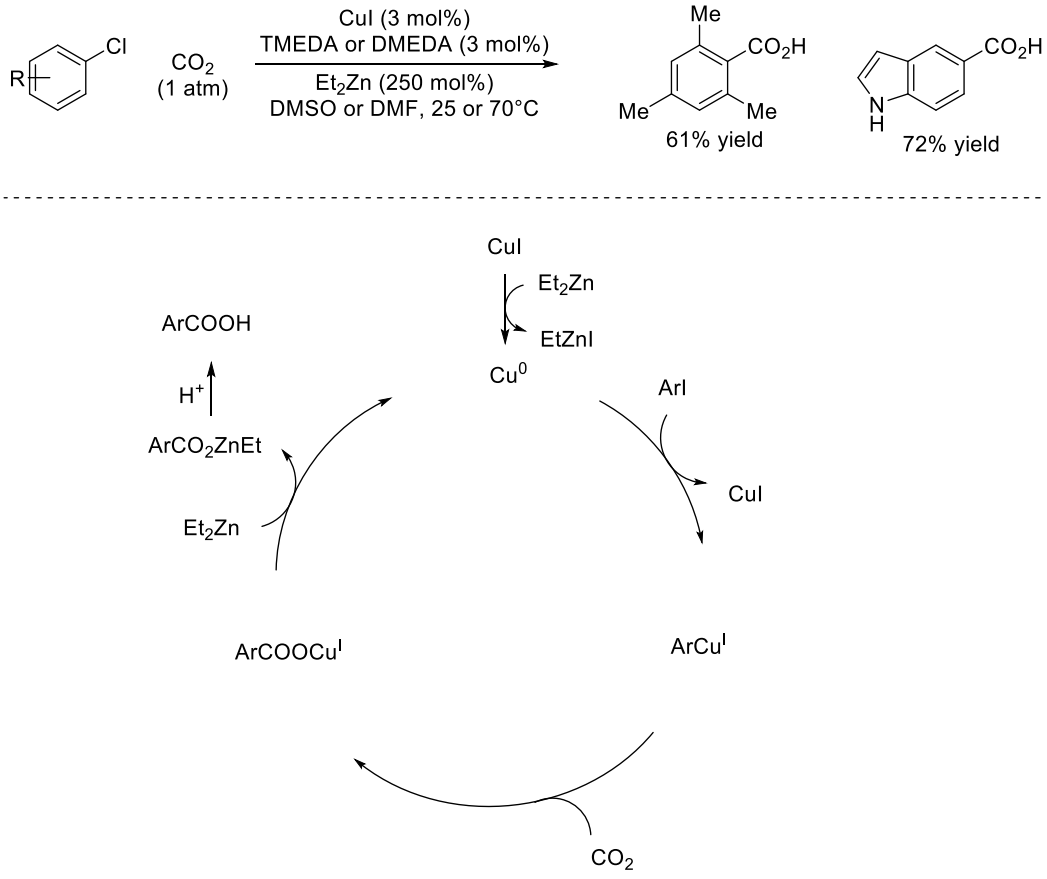


1.5.3 Copper

There's only one report on copper catalyzed carboxylation of aryl iodide with carbon dioxide by Daugulis and co-workers in 2013 (Scheme 1.33)[85]. It was found that with CuI, DMEDA or TMEDA and Et_2Zn as reductant, aryl iodides were converted to the corresponding carboxylic acid with 1 atm carbon dioxide at 25 or 70℃. Diverse aryl bromides were evaluated under the standard conditions, and carboxylic acids with various functional groups, such as ketone, ester, and hydroxy group, were obtained with moderate to good yields. Steric hindered substrate iodomesitylene engaged in the reductive coupling effectively. Aryl iodides could be selectively activated by copper catalyst in the presence of lower halides. The possible reaction mechanism was proposed by starting with reduction of copper(I) to zero valent copper by Et_2Zn. Oxidative addition of aryl iodide to zero valent copper afforded arylcopper(I) species, which reacted with carbon dioxide to form copper(I)

carboxylate intermediate. Reduction of copper(I) carboxylate with Et_2Zn regenerated the zero valent copper and released the coupling adduct.

Scheme 1.33 Copper Catalyzed Reductive Coupling of Aryl Iodides and Carbon Dioxide to Form Carboxylic Acids.



1.6 Reductive Coupling with Isocyanates and Other Carbonyl Sources

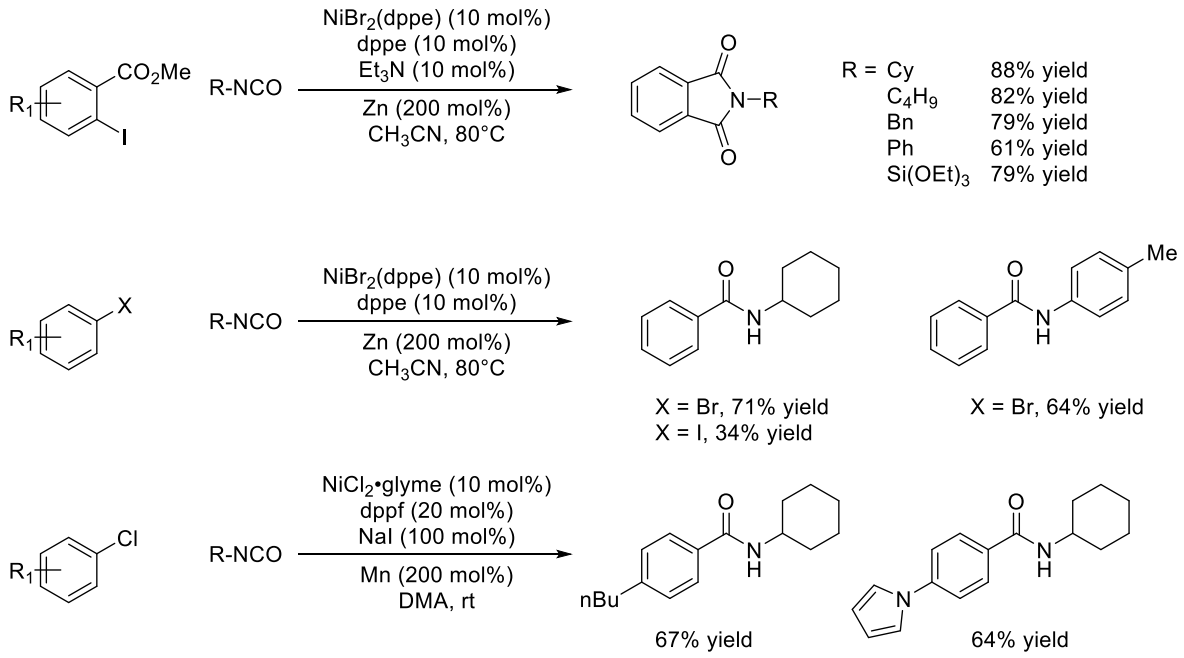
1.6.1 Nickel

Isocyanate derivatives are very reactive species, which are potential good electrophiles for reductive coupling reactions[86]. The first nickel catalyzed reductive coupling of aryl iodides with isocyanates was reported by Cheng and co-worker in 2005

(Scheme 1.34)[87]. Treatment of methyl ortho-iodobenzoate with aryl iodides in combination with $NiBr_2$(dppe), dppe, Et_3N, and zinc as reductant in acetonitrile at 80℃, led to formation of isoindoline-1,3-dione with moderate to excellent yields. The catalytic system could be applied to simple aryl iodides and bromides for the reductive coupling with isocyanates to form amides. It was observed that aryl bromides led to higher yields comparing with aryl iodides, which was due to more dimerization products of aryl halides were obtained when aryl iodides were used.

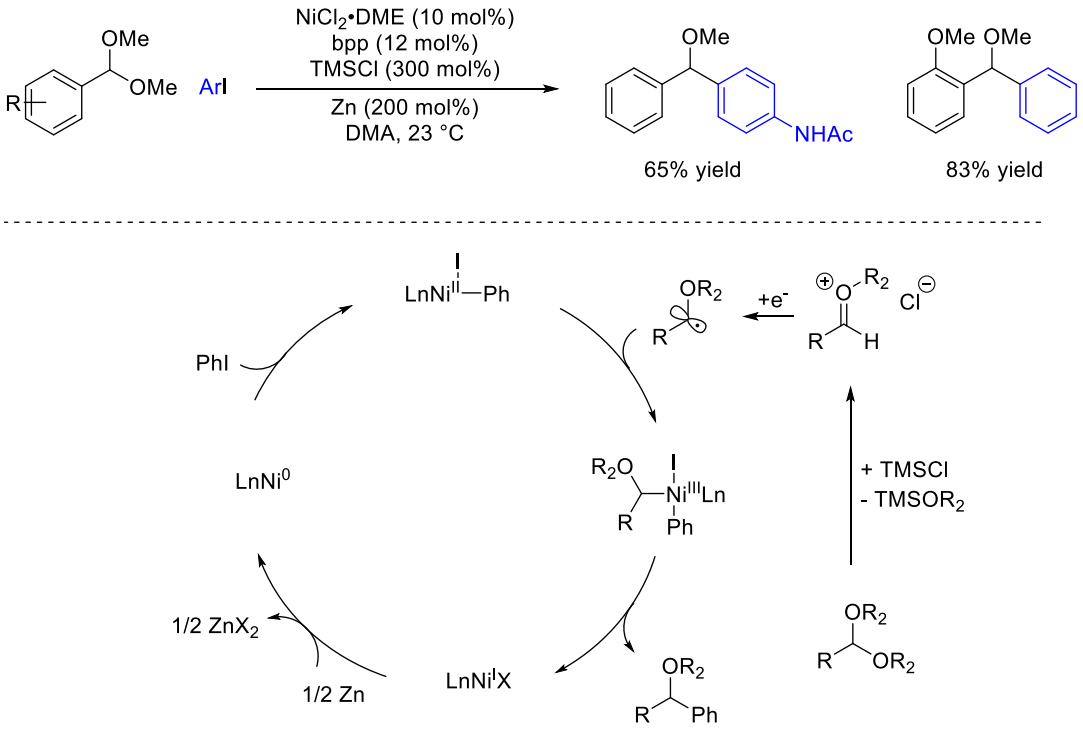
In 2014, Martin and co-workers reported a nickel catalyzed reductive amidation by coupling of pivalates or tosylates with isocyanates[88]. Limited aryl chlorides were also evaluated under reductive coupling conditions, and good yields were obtained in the presence of $NiCl_2$·glyme, dppf, NaI, and Mn powder as reductant at room temperature. Addition of NaI suppressed the competing dimerization, which was observed in other literature.

Scheme 1.34 Nickel Catalyzed Reductive Coupling of Aryl Halides and Isocyanates.



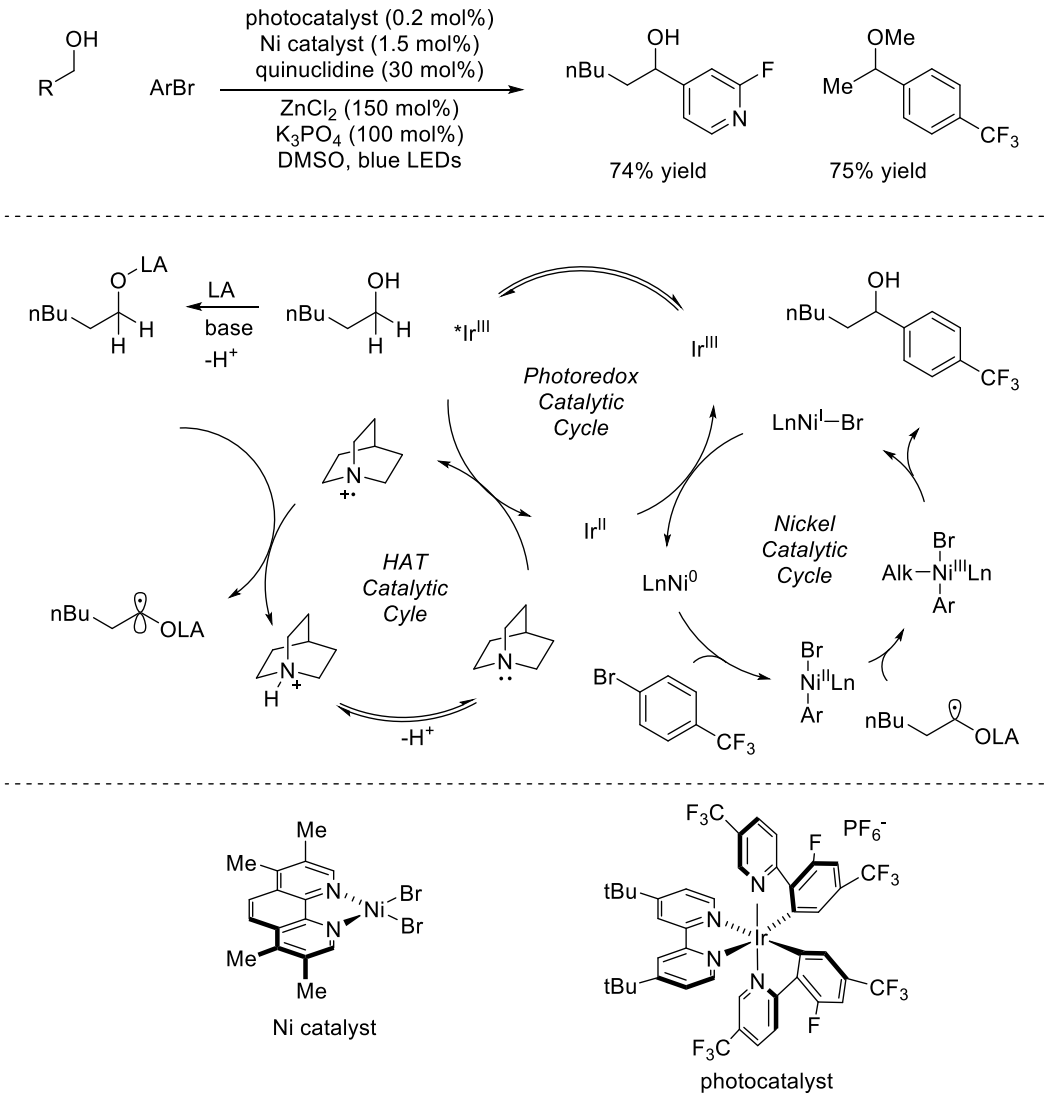
Other than the carbonyl compounds mentioned above, acetals used as carbonyl equivalent in the nickel catalyzed reductive coupling with aryl iodides was reported by Doyle and co-workers in 2015(Scheme 1.35)[89]. Diaryl ethers bearing diverse functional groups were obtained in the presence of $NiCl_2$·DME, bpp, TMSCl, and Zn as reductant in DMA at room temperature. The catalytic mechanism was proposed initiated by oxidative addition of aryl iodide to Ni(0) to form arylnickel(II) intermediate. Addition of α-oxy radical generated from acetel to arylnickel(II) delivered nickel(III) species. Subsequent reductive elimination released the diaryl ether and regenerated nickel(I), which was reduced back to zero valent form by metal zinc.

Scheme 1.35 Nickel Catalyzed Reductive Coupling of Aryl Iodides and Acetals to Form Diaryl Ethers.



In 2018, MacMillan and co-workers reported photoredox, HAT, and nickel catalyzed direct coupling of aryl bromides with primary alcohols to for benzylic alcohols(Scheme 1.36)[90]. The reaction mechanism began with photoexcitation of

Scheme 1.36 Photoredox, HAT, and Nickel Catalyzed Reductive Coupling of Aryl Bromides and Alcohols to Form Benzylic Alcohols.

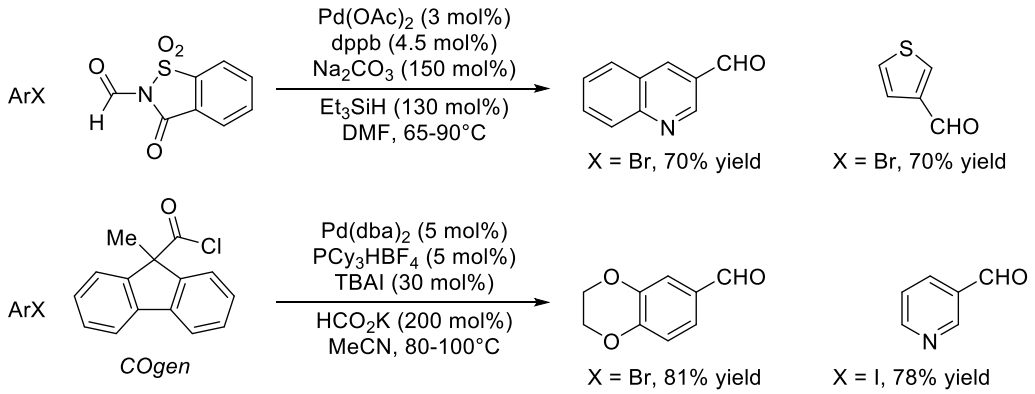


iridium(III) photocatalyst, which could oxidize HAT catalyst quinuclidine to deliver the radical cation and iridium(II) complex. Lewis acid facilitated deprotonation followed by hydrogen atom abstraction afforded α-alkoxy radical, which could combine with arylnickel(II) generated through oxidative addition of aryl bromide to nickel(0). Subsequent reductive elimination furnished benzylic alcohol and nickel(I) species, which was reduced to zero valent form by iridium(II) via single-electron transfer.

1.6.2 Palladium

In 2013, Manabe and co-workers reported a palladium catalyzed reductive carbonylation of aryl halides with N-formylsaccharin as carbon monoxide surrogate (Scheme 1.37)[91]. N-formylsaccharin was first developed by Cossy and co-workers and used as formylating agent of amines[92]. In the same year, Skrydstrup and co-workers reported a protocol to synthesize aryl aldehydes by reductive coupling of aryl halides with 9-methylfluorene-9-carbonyl chloride (COgen)[93]. In the presence of $Pd(dba)_2$, PCy_3HBF_4, TBAI, and HCO_2K as reductant, diverse aryl bromide and iodides were converted to aryl aldehydes with good to excellent yields. Notably, isotope labeled aryl aldehydes could be obtained when DCO_2K or ^{13}COgen were used in the coupling.

Scheme 1.37 Palladium Catalyzed Reductive Coupling of Aryl Halides and Carbon Monoxide Surrogates.



1.7 CONCLUSION

Metal-catalyzed reductive coupling of aryl halides with carbonyl compounds were developed as an alternative to addition of organometallic reagents but challenges remain. For example, enantioselective reductive coupling of aryl halides with carbonyl compounds has not been exploited much and only one example showed above. Also, reductive coupling via hydrogen autotransfer will be a more ideal protocol considering about reaction economy.

Chapter 2: Enantioselective Ruthenium Catalyzed Redox-Triggered Carbonyl Allylation Using Alkynes as Chiral Allylmetal Equivalents via Allene Hydrometalation*

2.1 INTRODUCTION

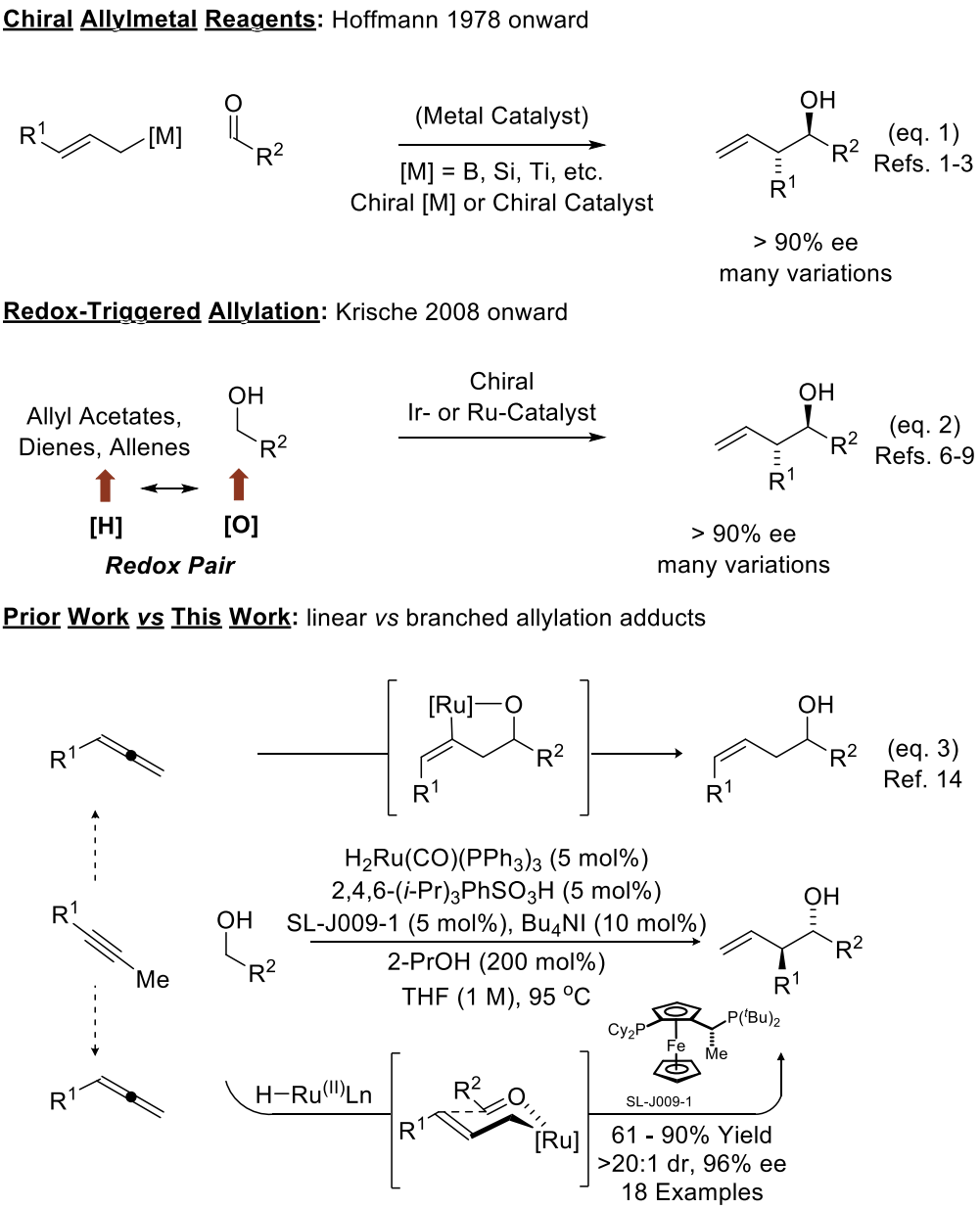
Carbonyl addition reactions are one of the most important methods to construct new carbon-carbon (C-C) bond, and especially carbonyl allylation has been widely used in organic synthesis.[1] In enantioselective carbonyl allylation, preformed allylmetal reagents modified by chiral auxiliaries were first proved to be efficient.[2] Achiral allylmetal reagents used together with chiral catalysts became an alternative to chiral allylmetal reagents.[3] Nozaki-Hiyama-Kishi type allylation[4] by direct coupling of aldehydes with allylic halides was developed, which allows people to form the new C-C bond without intervening preformed metal reagents, but the use of toxic chromium(II) salts was not ideal. Also metal catalyzed umpoled reactions[5] coupling with allylic carboxylates usually require stoichiometric metallic reductants. In recent years, Krische group has developed transition metal catalyzed redox-neutral enantioselective carbonyl allylations[6] by exploiting the reductive property of alcohols, which enable direct conversion of primary alcohols to secondary alcohols, and different pronucleophiles (allylic carboxylates,[7] dienes,[8] and allenes[9]) were able to engage in carbonyl allylation reactions (Scheme 2.1).

In 2009, Obora and Ishii reported iridium catalyzed carbonyl aryl allylation by coupling of 1-aryl-1-propynes and alcohols, where alkynes was proposed to go through iridium catalyzed isomerization to allenes followed by hydrometalation to form iridium allyl intermediate.[10] In 2014, Krische group reported the ruthenium catalyzed formation of (Z)-homoallylic alcohols by coupling of primary alcohol and 2-alkynes via alkyne to allene isomerization followed by allene carbonyl oxidative coupling.[11] So in this chapter,

*This chapter is based on the published work:
Liang, T.; Nguyen, K. D.; Zhang, W.; Krische, M. J. *J. Am. Chem. Soc.* **2015**, *137*, 3161.

enantioselective and diastereoselective carbonyl allylation was described by suppressing oxidative coupling to favor hydrometalation pathway in coupling of alkynes and alcohols.

Scheme 2.1 Enantioselective Carbonyl Allylation Strategies.



2.2 Reaction Development and Scope

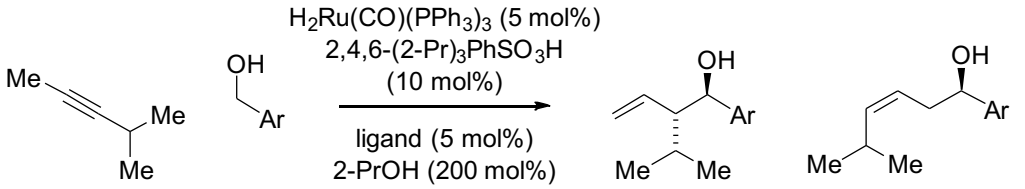
Starting from the established condition for the formation of linear (Z)-homoallylic alcohol **2.4a** by coupling of 4-methyl-2-pentyne **2.1a** and *p*-bromobenzyl alcohol **2.2a**, it was found that addition of catalytic amount of Bu_4NI suppressed the formation of linear homoallylic alcohol **2.4a** (Table 2.1, entry 2). By introducing of bidentate phosphine ligand dppf, a mixture of both linear adduct **2.4a** and desired branched adduct **2.3a** was obtained (Table 2.1, entry 3). Combination of catalytic Bu_4NI and dppf gave only branched homoallylic alcohol **2.3a** in 83% yield as a 15:1 (*anti:syn*) diastereomeric mixture (Table 2.1, entry 4). By screening of different bidentate phosphine ligands, single *anti*-diastereomer of branched adduct **2.3a** could be obtained with more electron rich ligands, like dippf and dCypb (Table 2.1, entry 5 and 7).

With these promising results, diverse chiral chelating phosphine ligands were examined. Good level of enantioselectivity was obtained with utilizing the Josiphos ligands SL-J009-1 and SL-J002-1 (Table 2.1, entry 8 and 9). By lowering the loading of additive 2,4,6-tri(2-propyl)-phenylsulfonic acid (5 mol%), desired branched allylation product **2.3a** was obtained in excellent yield and enantiomeric excess using both SL-J009-1 and SL-J002-1 (Table 2.1, entry 10 and 11).

SL-J009-1 was used as the optimal ligand in this transformation due to the generality in substrate scope. Catalytic amount of the 2,4,6-tri(2-propyl)-phenylsulfonic acid was necessary in the reaction because it suppressed the formation of over-oxidation ketone product. Also, in the absence of 2-PrOH, lower yield of desired product **2.3a** was obtained due to the accumulation of unreacted aldehyde, which formed from oxidation of the primary alcohol **2.2a** *in situ*.

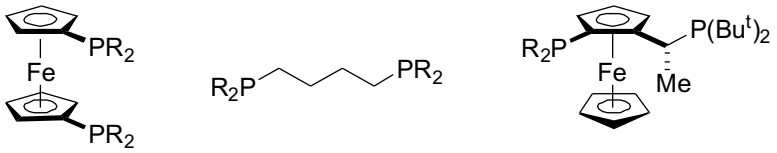
With the optimized condition in hand, a variety range of alcohols **2.2a**-**2.2l** were

Table 2.1 Selective Optimizations of Formation of Branched Adduct **2.3a** by Partitioning of Hydrometalation and Oxidative Pathways.



2.1a (300 mol %) | **2.2a** (100 mol %) Ar = *p*-BrPh | **2.3a**, *via* allene hydrometallation | **2.4a,** *via* allene-C=O oxidative coupling

Entry	Bu_4NI	ligand	**2.3a** (yield, dr)	**2.4a** (yield, *Z*:*E*)
1[b]	-	-	-	70%, >20:1
2	(10 mol%)	-	-	24%, 10:1
3	-	dppf	21%, 7:1	16%, 5:1
4	(10 mol%)	dppf	83%, 15:1	-
5	(10 mol%)	dippf	57%, >20:1	-
6	(10 mol%)	dppb	36%, 13:1	-
7	(10 mol%)	dCypb	49%, >20:1	-
8	(10 mol%)	SL-J009-1	59%, >20:1, 84% ee	-
9	(10 mol%)	SL-J002-1	86%, >20:1, 80% ee	-
10[c]	(10 mol%)	SL-J002-1	86%, >20:1, 94% ee	-
11[c,d]	(10 mol%)	SL-J009-1	79%, >20:1, 94% ee	-



dppf, R = Ph
dippf, R = 2-Pr

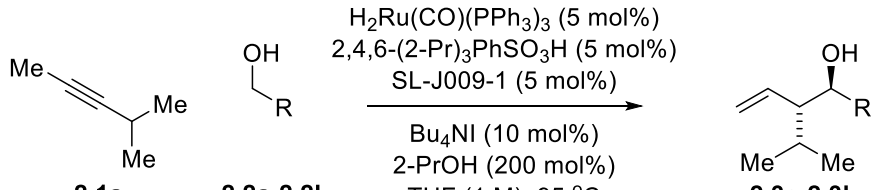
dppb, R = Ph
dCypb, R = Cy

SL-J002-1, R = Ph
SL-J009-1, R = Cy

[a]Yields are material isolated by silica gel chromatography. See supporting Information for further experimental details. [b]2,4,6-(2-Pr)$_3$PhSO$_3$H (14 mol%). [c]2,4,6-(2-Pr)$_3$PhSO$_3$H (5 mol%). [d]THF (1.0 M).

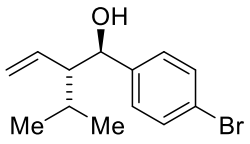
evaluated and were able to engage in the formation of branched homoallylic alcohols (Table 2.2). Benzylic alcohols **2.2a**-**2.2f** were converted to the allylation adducts **2.3a**-**2.3f**

Table 2.2 Diastereoselective and Enantioselective Formation of Branched Homoallylic Alcohol **2.3a**-**2.3l**.

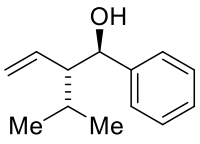


2.1a (300 mol %) | **2.2a-2.2l** (100 mol%) | **2.3a-2.3l**

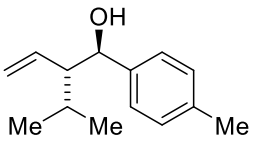
2.2a, R = 4-BrPh	**2.2b**, R = Ph	**2.2c**, R = 4-MePh	**2.2d**, R = 4-MeOPh
2.2e, R = 4-piperonyl	**2.2f**, R = 2-MeOPh	**2.2g**, R = HC=CMe$_2$	**2.2h**, geraniol
2.2i, R = HC=CH(Ph)	**2.2j**, R = (CH$_2$)$_7$Me	**2.2k**, R = (CH$_2$)$_2$Ph	**2.2l**, R = (CH$_2$)$_2$OBn



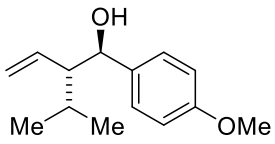
2.3a, 79% Yield
>20:1 dr, 94% ee



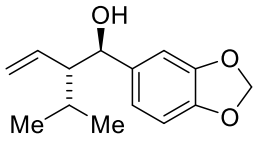
2.3b, 82% Yield
>20:1 dr, 95% ee



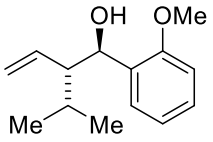
2.3c, 76% Yield
>20:1 dr, 95% ee



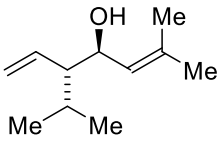
2.3d, 73% Yield
>20:1 dr, 95% ee



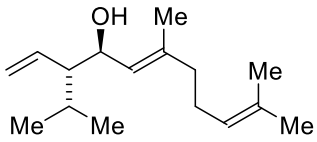
2.3e, 75% Yield
>20:1 dr, 96% ee



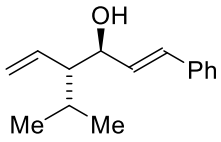
2.3f, 76% Yield
>20:1 dr, 95% ee



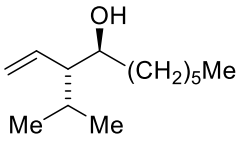
2.3g, 76% Yield
>20:1 dr, 95% ee



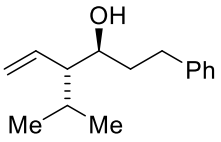
2.3h, 90% Yield
>20:1 dr, 96% ee



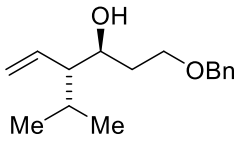
2.3i, 67% Yield
>20:1 dr, 96% ee



2.3j, 72% Yield[b,c,d]
>20:1 dr, 93% ee



2.3k, 65% Yield[b,c]
>20:1 dr, 94% ee

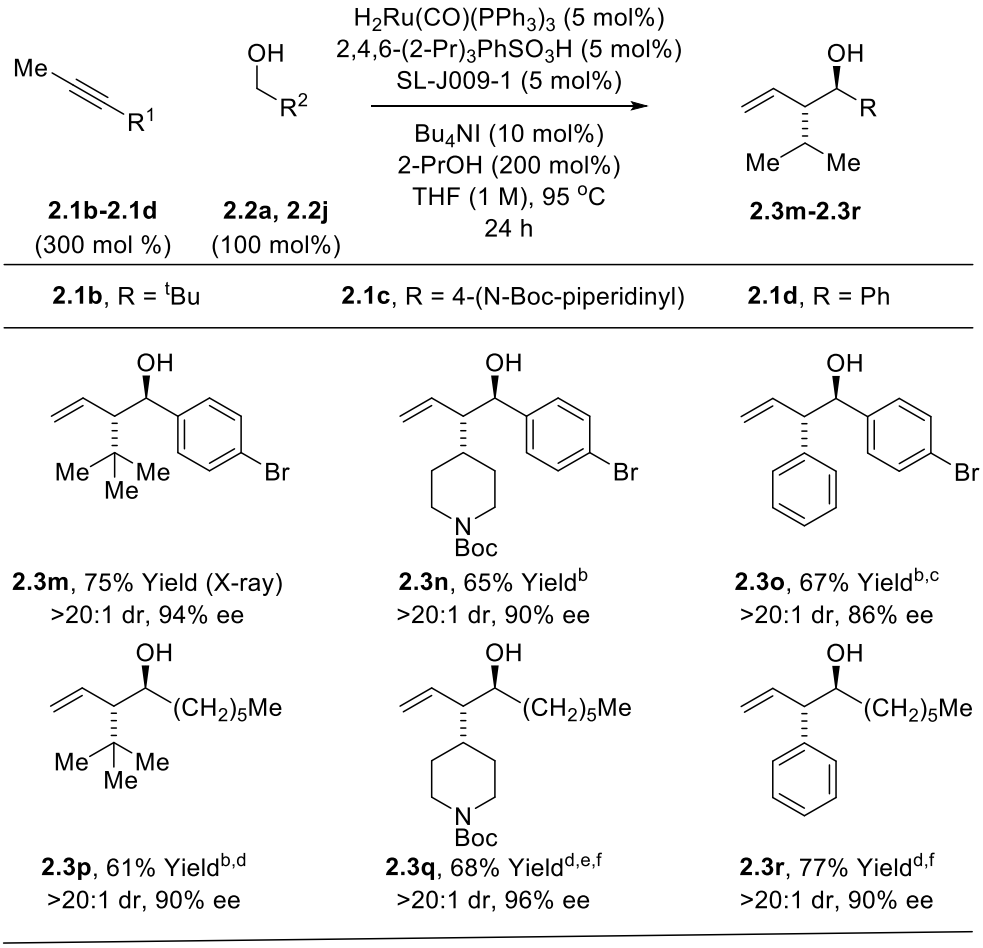


2.3l, 66% Yield[b,c]
>20:1 dr, 91% ee

[a]Yields are material isolated by silica gel chromatography. Diastereoselectivities were determined by ^{1}H NMR analysis of crude reaction mixtures. See supporting Information for further experimental details. [b]2-PrOH was omitted. [c]125 ℃. [d]48 h.

in good yields with complete *anti*-diastereoselectivity and excellent enantioselectivity. Notably, bromine was tolerable under our condition without formation of dehalogenative

Table 2.3 Diastereoselective and Enantioselective Formation of Branched Homoallylic Alcohol **2.3m**-**2.3r**.



[a]Yields are material isolated by silica gel chromatography. Diastereoselectivities were determined by ^{1}H NMR analysis of crude reaction mixtures. See supporting Information for further experimental details. [b]72 h. [c]75 °C. [d]2-PrOH was omitted. [e]7.5 mol% of $H_2Ru(CO)(PPh_3)_3$, $ArSO_3H$, SL-J009-1, and 15 mol% Bu_4NI. [f]48 h.

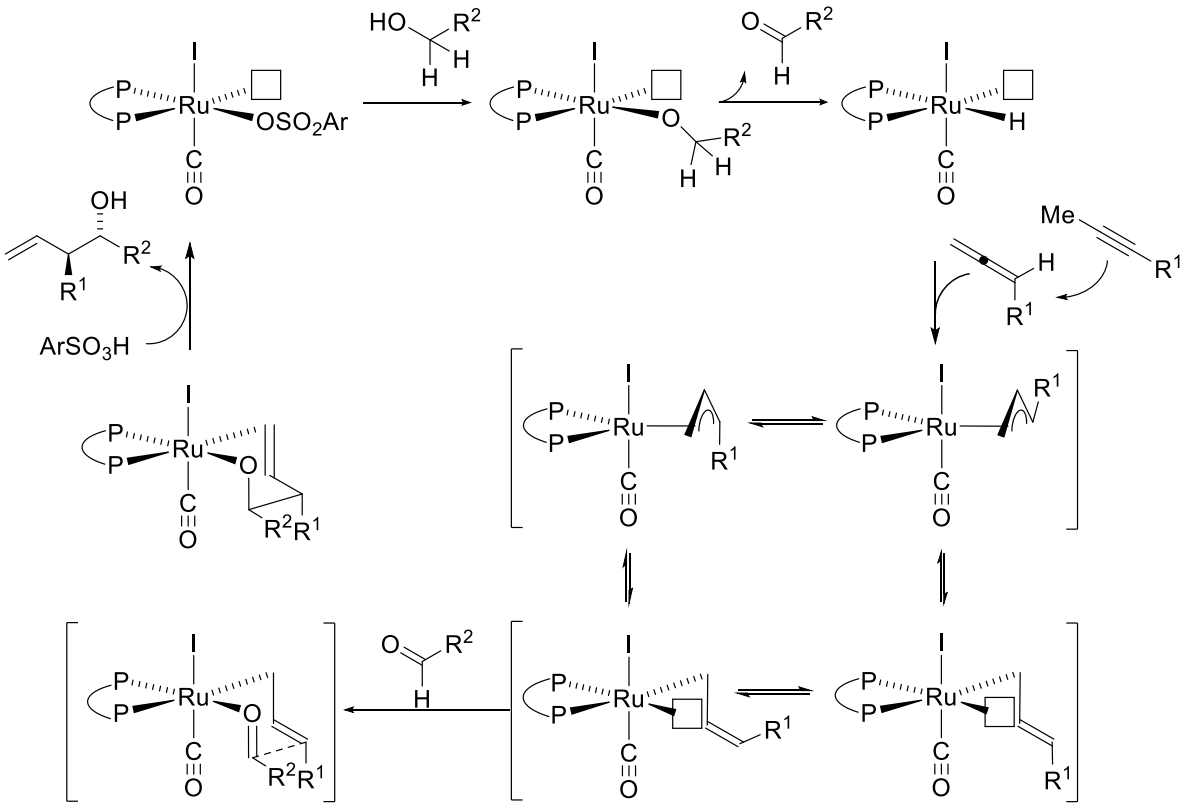
adduct. *Para*-, *meta*-, and *ortho*-substituents containing alcohols provided adducts **2.3a**, **2.3c**-**2.3f**. For allylic alcohols **2.2g**-**2.2i**, which could be converted to the corresponding aldehydes catalyzed by transition metal through internal redox isomerization, adducts **2.3g**-**2.3i** were also formed in highly stereoselective manner. Also, aliphatic alcohols **2.3j**-**2.3l** gave slightly lower yields but still excellent level of diastereo- and enantioselectivity.

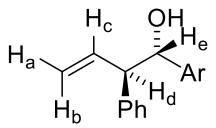
To further explore the scope for this transformation, a series of 2-propynes bearing tert-butyl (**2.1b**), 4-(N-Boc-piperidinyl) (**2.1c**) and phenyl (**2.1d**) moieties were evaluated under the optimal condition by coupling with both benzylic and aliphatic alcohol **2.2a** and **2.2j,** respectively. Desired allylation products **2.3m**-**2.3r** were obtained with moderate to good yields and good to excellent enantioselectivity.

2.3 MECHANISM AND DISCUSSION

The reaction was proposed to proceed through the catalytic cycle below (Scheme 2.2). Ruthenium catalyst, derived from acid-base reaction of $H_2Ru(CO)(PPh_3)_3$ and sulfonic acid, was converted to ruthenium alkoxide through ligand exchange. Subsequent β-hydride elimination released aldehyde and ruthenium hydride. Allylruthenium species were formed via hydrometalation of transient allene[12], which formed by isomerization 2-propyne. Such allylruthenium species were undergoing rapid isomerization between σ-allyl and π-allyl haptomers. Coordination of aldehyde to the (E)-σ-allylruthenium species triggered the carbonyl addition to form the homoallylic ruthenium alkoxide through a closed transition structure. Protonolysis facilitated by the sulfonic acid released the homoallylic alcohol and closed the catalytic cycle. The proposed mechanism was supported by the deuterium labeling studies. Bu_4NI in the reaction helped to suppressed oxidative coupling pathway due to the strong σ-donicity of iodide ligand on ruthenium, which may destabilize ruthenium(0).

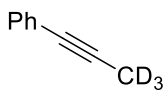
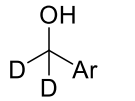
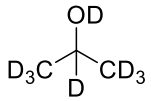
Scheme 2.2 Proposed General Catalytic Mechanism and Deuterium Labeling Experiment Results.





deuterio-**2.3a** (Ar = 4-BrPh)

Experiment I: 72% Yield, >20:1 dr
Experiment II: 83% Yield, >20:1 dr
Experiment III: 65% Yield, >20:1 dr

Experiment I	**Experiment II**	**Experiment III**
$H_{a,b}$ (>95% ^2H)	$H_{a,b}$ (0% ^2H)	$H_{a,b}$ (0% ^2H)
H_c (64% ^2H)	H_c (36% ^2H)	H_c (0% ^2H)
H_d (27% ^2H)	H_d (44% ^2H)	H_d (0% ^2H)
H_e (0% ^2H)	H_e (>95% ^2H)	H_e (0% ^2H)
		
deuterio-**2.1d** (300 mol%) (no 2-PrOH)	*deuterio*-**2.2a** (100 mol%) (no 2-PrOH)	d_8-2-PrOH (200 mol%)

2.4 CONCLUSION

In summary, a ruthenium-catalyzed formation of enantiomeric enriched homoallylic alcohols was reported, where 2-alkynes were used as reservoir for allenes. It's noticed that subtle changes in the reaction could lead to the partition of different mechanism pathways-oxidative coupling vs hydrometalation. And this process further expanded the scope for π-unsaturated compounds engaging in transition metal catalyzed redox-triggered carbonyl allylation reactions.

2.5 EXPERIMENTAL DETAILS

General Information

All reactions were run under an atmosphere of argon, unless otherwise indicated. Resealable pressure tubes (13x100 mm) were purchased from Fischer Scientific (catalog number 14–959–35C) and were flame dried followed by cooling in a desiccator or under a stream of argon prior to use. Tetrahydrofuran (THF) was dried over sodium metal, benzophenone, and distilled immediately prior to use. $RuH_2(PPh_3)_3$ were prepared according to literature procedure.1 All ligands were used as received from Strem Chemicals Inc. Alcohols were purified by distillation or recrystallization immediately prior to use. Preparative column chromatography employing Silicycle silica gel (40-63 μm) was performed according to the method of Still.2 Analytical thin-layer chromatography (TLC) was carried out using 0.25 mm commercial silica gel plates (Dynamic Absorbents F254). Visualization was accomplished with UV light followed by dipping in Seebach's stain solution then heating. Purification of reactions was carried out by flash chromatography using Silicycle silica gel (40–63 μm).

Spectroscopy, Spectrometry, and Data Collection

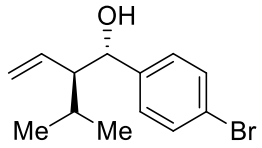
Infrared spectra were recorded on a Perkin-Elmer 1600 spectrometer. Low-resolution mass spectra (LRMS) were obtained on a Karatos MS9 and are reported as m/z (relative intensity). Accurate masses are reported for the molecular ion (M+H, M+Na), or a suitable fragment ion. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded with a Varian Gemini (400 MHz) spectrometer. Chemical shifts are reported in delta (δ) units, parts per million (ppm) downfield from tetramethylsilane or ppm relative to the center of the singlet at 7.26 ppm for deuteriochloroform. Data reported as multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). Integration and coupling constants were reported in Hertz (Hz). Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded with a Varian Gemini (100 MHz) spectrometer and were routinely run with broadband decoupling. Chemical shifts are reported in delta (δ) units, ppm relative to the center of the triplet at 77.16 ppm for deuteriochloroform.

Experimental Details and Spectral Data

General Procedure for the Couplings of Alcohols 2.2a-2.2l and Alkynes

To a resealable pressure tube (ca. 13 x 100) was added $H_2Ru(CO)(PPh_3)_3$ (9.2 mg, 0.010 mmol, 5 mol%), SL-J009-1 ligand (5.6 mg, 0.010 mmol, 5 mol%), Bu_4NI (7.4 mg, 0.020 mmol, 10 mol%) and 2,4,6-tri(2-propyl)phenylsulfonic acid (2.9 mg, 0.010 mmol, 5 mol%). At this stage solid alcohol coupling partners (0.20 mmol, 100 mol%) were added. The tube was then sealed with a rubber septum and purged with argon. THF (0.20 mL, 1 M concentration with respect to alcohols) was then added. At this stage, liquid alcohol coupling partners (0.20 mmol, 100 mol%) were added. 2-propylalcohol (31 μL, 0.40 mmol, 200 mol%) was then added. Alkynes (0.60 mmol, 300 mol%) was added via syringe and the rubber septum was quickly replaced with a screw cap. The mixture was then heated at 95 °C for the time stated. After cooling to room temperature, the mixture was concentrated in vacuo. The residue was subjected to flash column chromatography (SiO_2), under the conditions noted, to afford the corresponding branched homoallylic alcohols.

(1S,2S)-1-(4-bromophenyl)-2-isopropylbut-3-en-1-ol (2.3a).



The residue was subjected to flash column chromatography for purification (SiO_2, 300 mL of EtOAc: Hexanes = 1:5) to furnish the title compound (42.5 mg, 79%, *dr* = >20:1) as a yellow oil.

R_f=0.37 (Hexanes: Et_2O = 4:1).

Spectral data is reported for the major isomer.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 – 7.44 (m, 2H), 7.25 – 7.19 (m, 2H), 5.84 – 5.72 (m, 1H), 5.31 (dd, *J* = 10.3, 2.1 Hz, 1H), 5.14 (ddd, *J* = 17.1, 2.1, 0.6 Hz, 1H), 4.59 (dd, *J* = 8.2, 2.3 Hz, 1H), 2.12 – 2.04 (m, 2H), 1.52 – 1.41 (m, 1H), 0.86 (d, *J* = 6.8 Hz, 3H), 0.84 (d, *J* = 6.8 Hz, 3H).

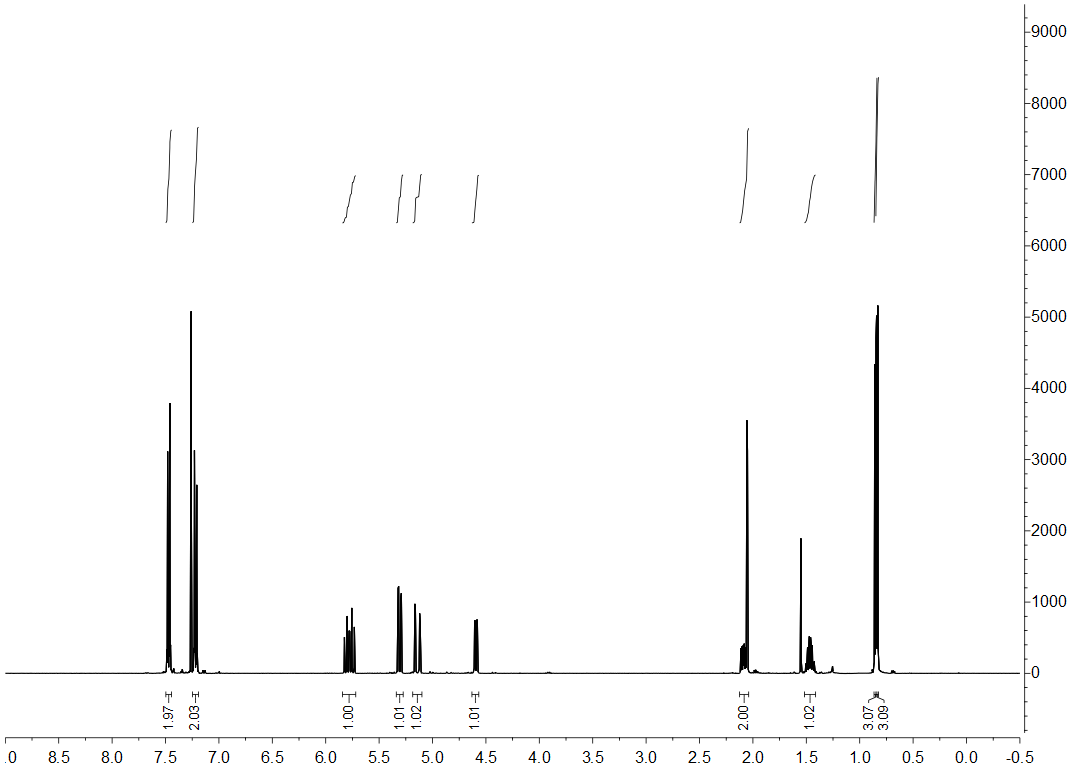
^{13}C NMR (100 MHz, $CDCl_3$): δ 142.0, 135.4, 131.6, 128.7, 121.5, 120.8, 74.1, 59.1, 27.7, 22.0, 17.6.

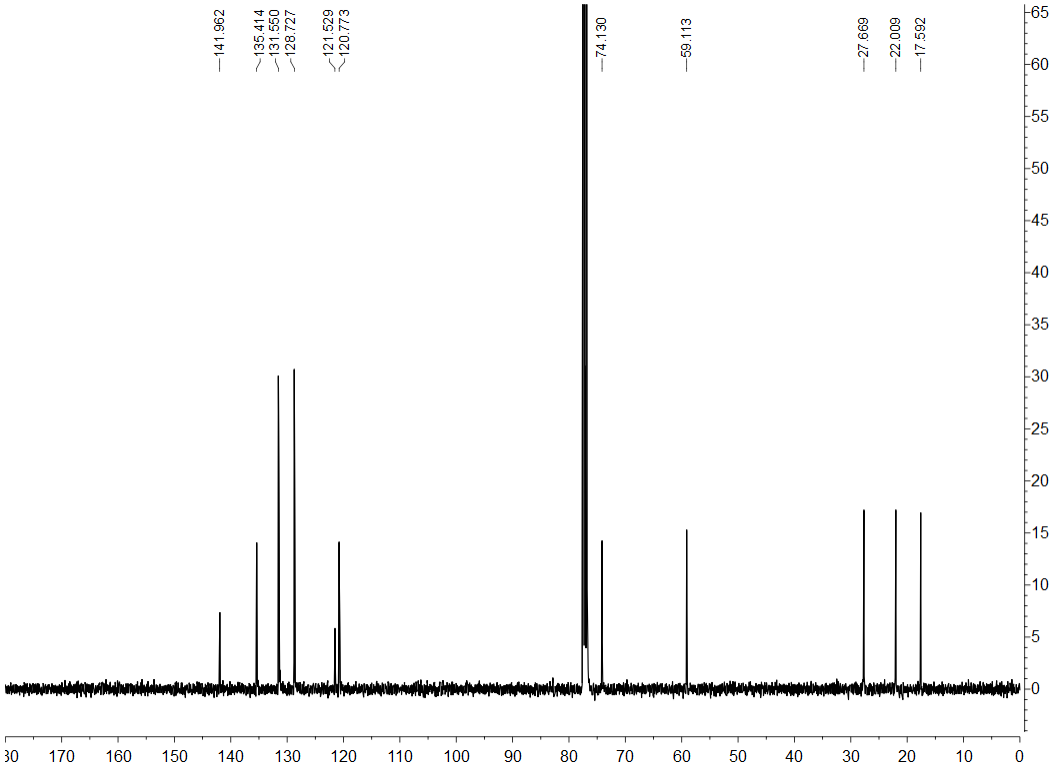
LRMS (CI) Calcd. for $C_{13}H_{17}BrO$ $[M+H]^+$: 269/271, Found: 269/271.

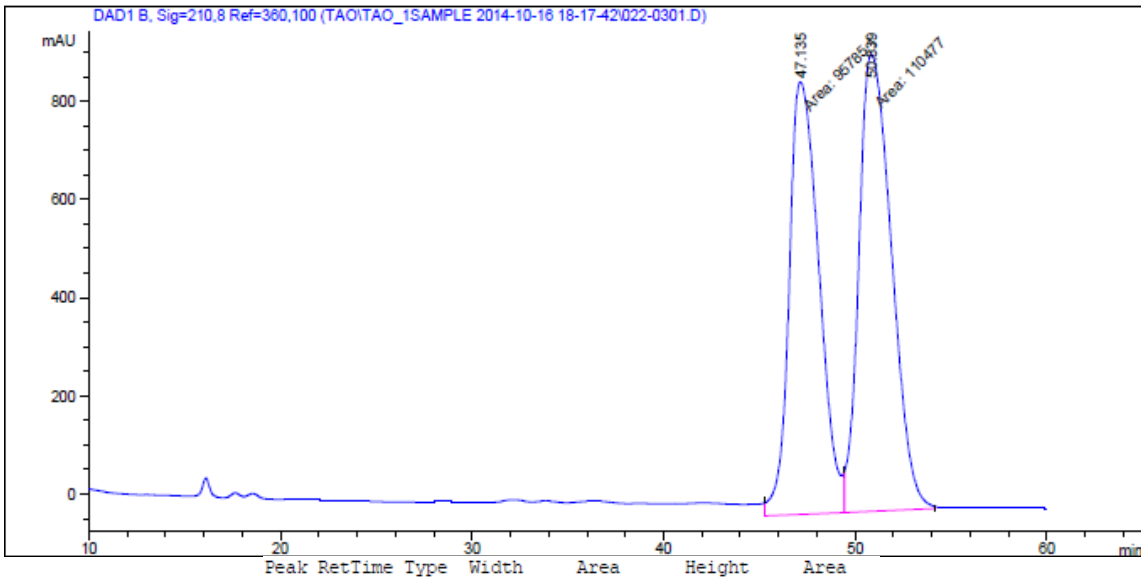
FTIR (neat): 3432, 3388, 2959, 2904, 1638, 1592, 1486, 1190, 1070, 1009, 915, 818 cm^{-1}.

HPLC (Chiralcel AD-H column, hexanes:*i*-PrOH = 99.5:0.5, 0.50 mL/min, 210 nm), ee = 94%.

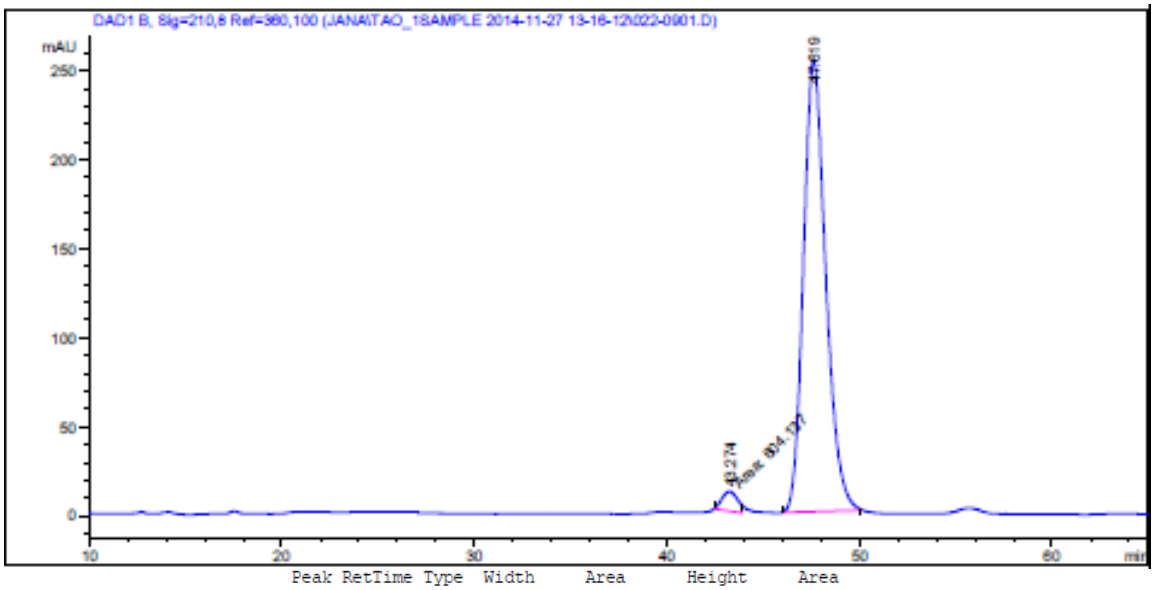
$[\alpha]^{25}_D$ = - 41.3 (c = 0.5, $CHCl_3$)


1.97
2.03
1.00
1.01
1.02
1.01
2.00
1.02
3.07
3.09


141.962
135.414
131.550
128.727
121.529
120.773
74.130
59.113
27.669
22.009
17.592

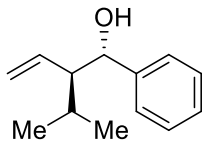


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	47.135	MF	1.8097	9.57851e4	882.16333	46.4386
2	50.839	FM	1.9773	1.10477e5	931.20276	53.5614



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	43.274	MM	0.9201	604.13654	10.94374	2.8772
2	47.619	BB	1.2175	2.03932e4	253.79462	97.1228

(1S,2S)-2-isopropyl-1-phenylbut-3-en-1-ol (2.3b).



The residue was subjected to flash column chromatography for purification (SiO_2, 300 mL of EtOAc: Hexanes = 1:12) to furnish the title compound (31.2 mg, 82%, *dr* = >20:1) as a yellow oil.

R_f = 0.56 (20% EtOAc/Hexanes).

Spectral data is reported for the major isomer.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 – 7.26 (m, 5H), 5.81 (dt, *J* = 17.1, 10.0 Hz, 1H), 5.31 (dd, *J* = 10.3, 2.0 Hz, 1H), 5.16 (dd, *J* = 17.1, 2.1 Hz, 1H), 4.61 (dd, *J* = 8.5, 1.5 Hz, 1H), 2.16 (td, *J* = 9.1, 4.1 Hz, 1H), 2.05 (d, *J* = 2.0 Hz, 1H), 1.52 – 1.40 (m, 1H), 0.85 (d, *J* = 6.8 Hz, 3H), 0.82 (d, *J* = 6.8 Hz, 3H).

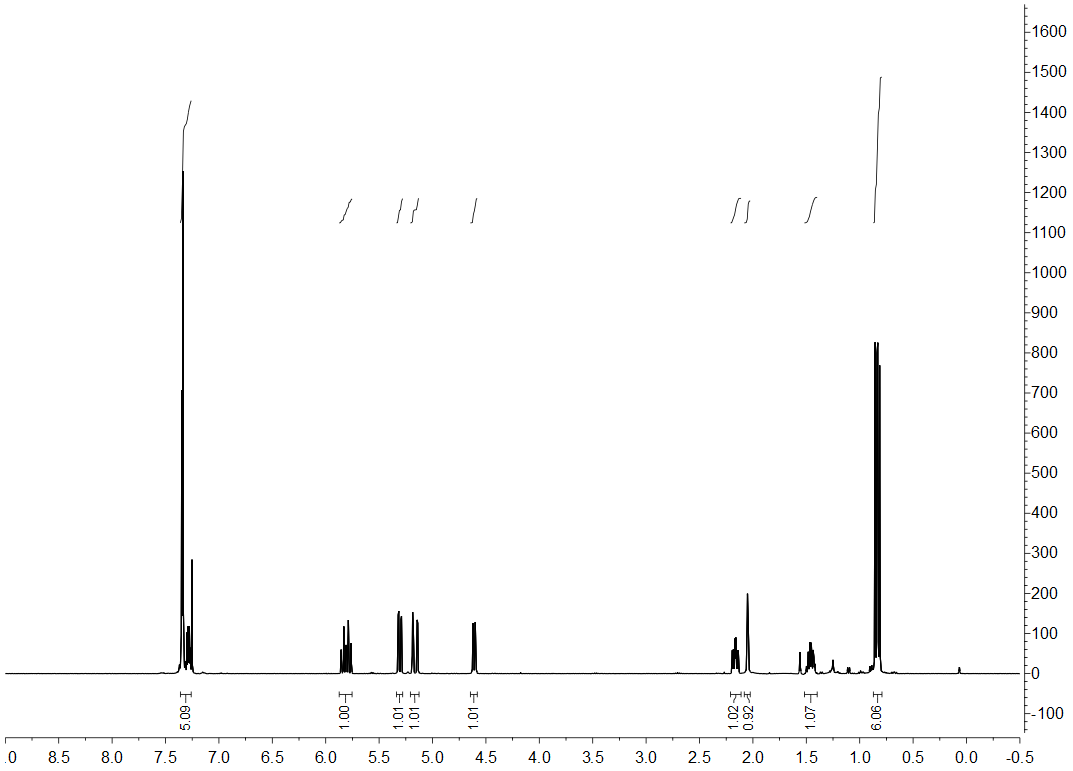
^{13}C NMR (100 MHz, $CDCl_3$): δ 142.9, 135.9, 128.5, 127.8, 127.0, 120.4, 74.8, 59.0, 27.7, 22.1, 17.4.

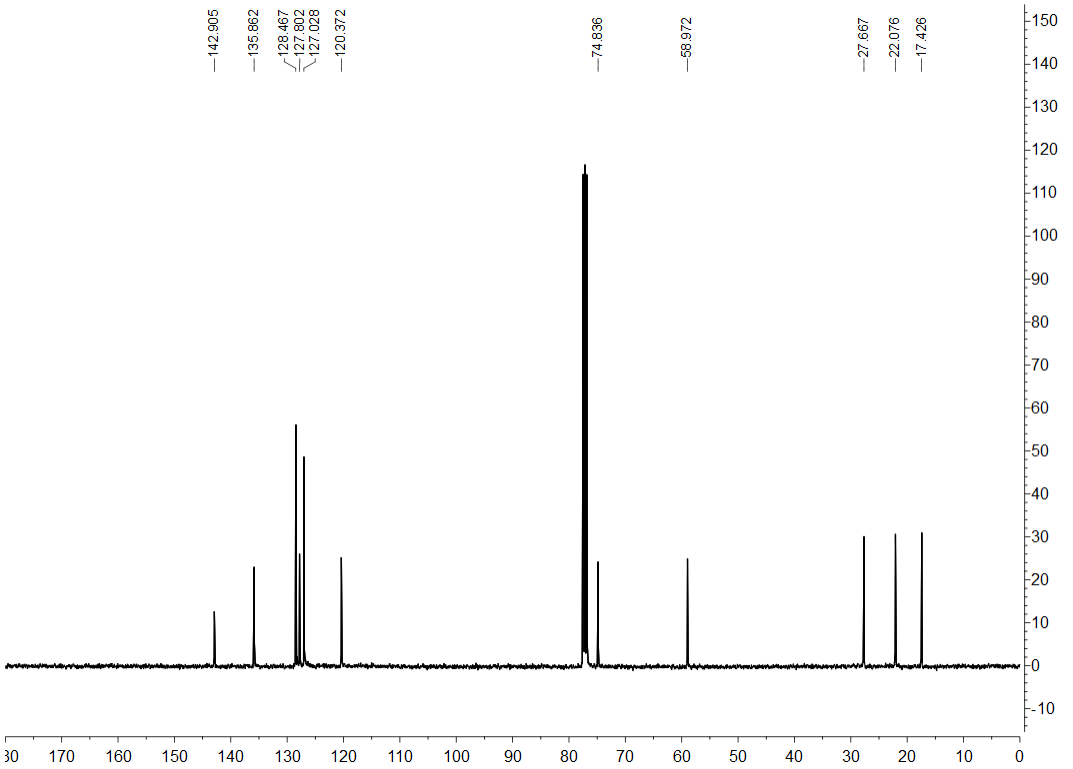
LRMS (CI) Calcd. for $C_{13}H_{18}O$ $[M\text{-}OH]^+$: 173, Found: 173.

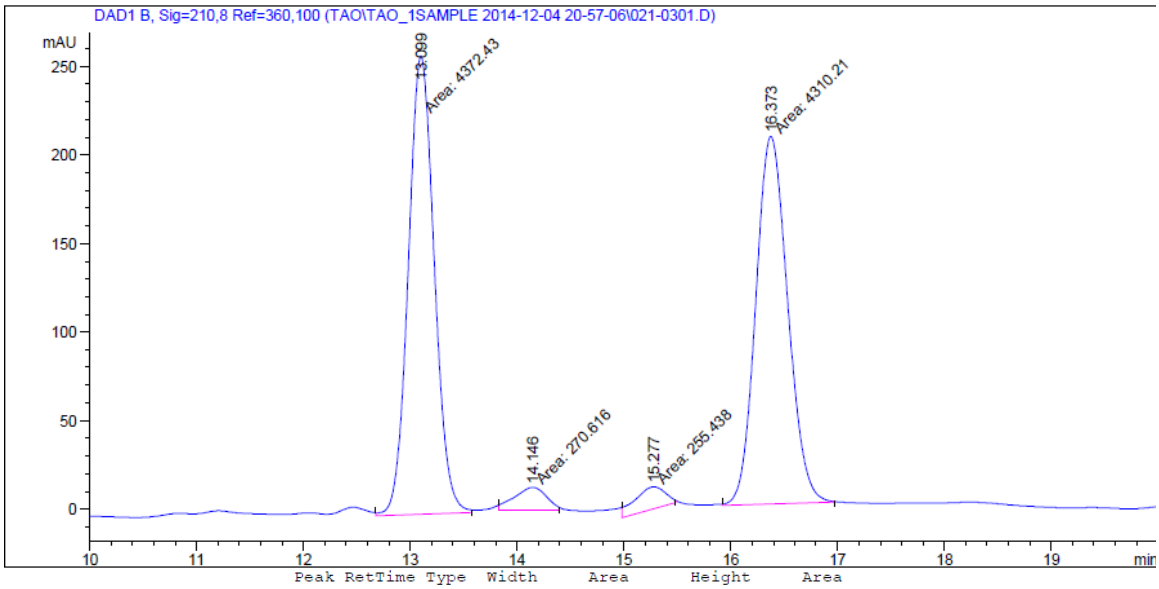
FTIR (neat): 3439, 3071, 3028, 2929, 1612, 1591, 1454, 1368, 1194, 1001, 913, 764, 700 cm^{-1}.

HPLC (Chiralcel AD-H column, hexanes:*i*-PrOH = 99:1, 1 mL/min, 210 nm), ee = 95%.

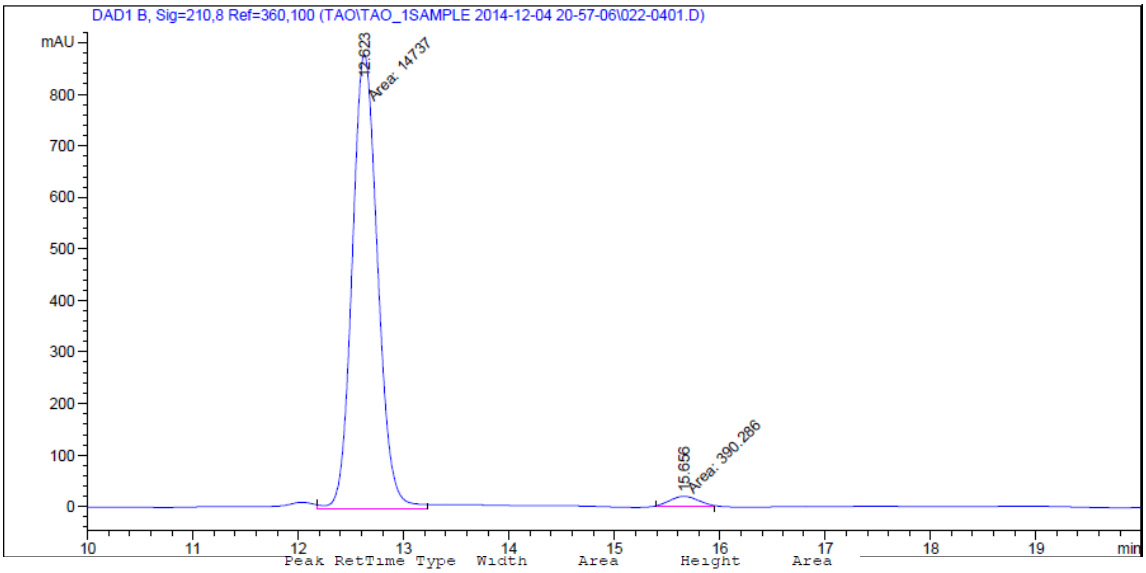
$[\alpha]^{25}_D$ = - 83.4 (c = 0.5, $CHCl_3$)


5.09
1.00
1.01
1.01
1.01
1.02
0.92
1.07
6.06


142.905
135.862
128.467
127.802
127.028
120.372
74.836
58.972
27.667
22.076
17.426

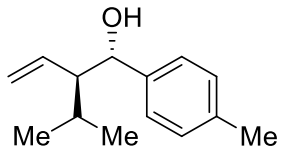


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.099	MM	0.2817	4372.42871	258.73590	47.4815
2	14.146	MM	0.3465	270.61618	13.01561	2.9387
3	15.277	MM	0.3394	255.43791	12.54517	2.7739
4	16.373	MM	0.3461	4310.21045	207.58981	46.8059



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.623	MM	0.2790	1.47370e4	880.28857	97.4200
2	15.656	MM	0.3220	390.28595	20.20200	2.5800

(1S,2S)-2-isopropyl-1-(p-tolyl)but-3-en-1-ol (2.3c).



The residue was subjected to flash column chromatography for purification (SiO_2, 300 mL of EtOAc: Hexanes = 1:12) to furnish the title compound (31.1 mg, 76%, *dr* = >20:1) as a yellow oil.

R_f = 0.56 (20% EtOAc/Hexanes).

Spectral data is reported for the major isomer.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 – 7.21 (m, 2H), 7.19 – 7.13 (m, 2H), 5.81 (dt, *J* = 17.1, 10.0 Hz, 1H), 5.31 (dd, *J* = 10.3, 2.2 Hz, 1H), 5.18 (ddd, *J* = 17.1, 2.2, 0.6 Hz, 1H), 4.57 (dd, *J* = 8.7, 2.1 Hz, 1H), 2.34 (d, *J* = 7.2 Hz, 3H), 2.17 (td, *J* = 9.2, 3.9 Hz, 1H), 2.02 (d, *J* = 2.3 Hz, 1H), 1.52 – 1.39 (m, 1H), 0.89 – 0.84 (d, *J* = 6.8 Hz, 3H), 0.82 (d, *J* = 6.8 Hz, 3H).

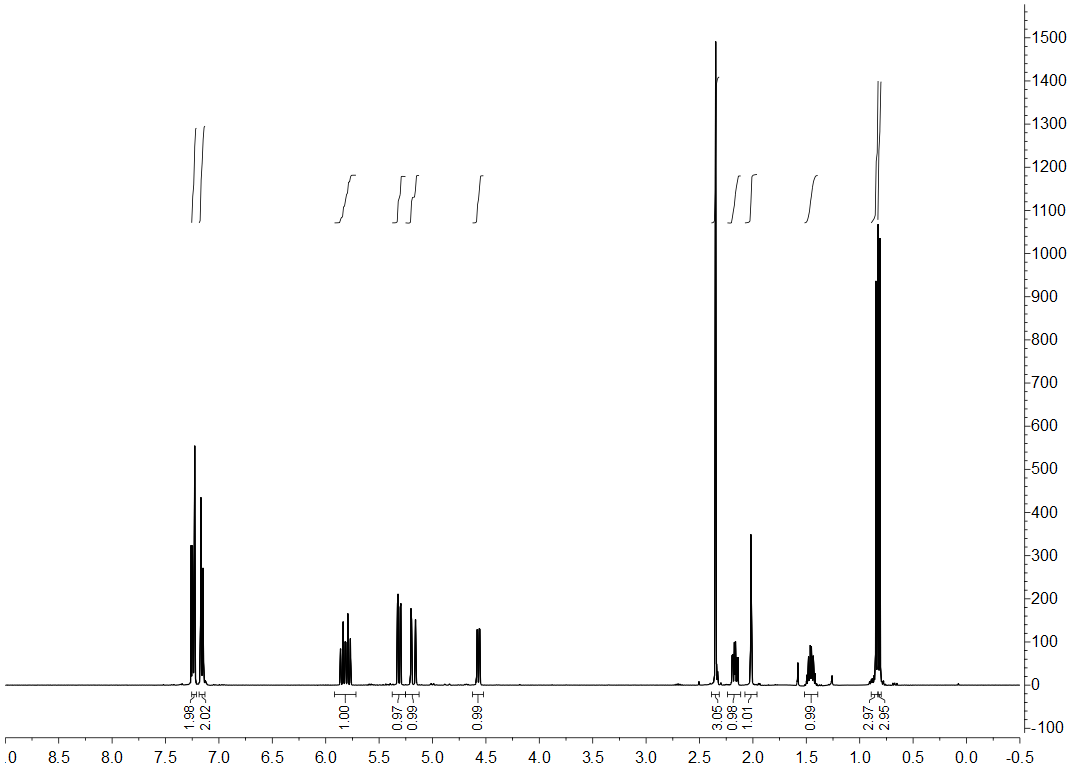
^{13}C NMR (100 MHz, $CDCl_3$): δ 139.9, 137.5, 136.0, 129.2, 127.0, 120.3, 74.7, 58.9, 27.7, 22.1, 21.3, 17.3.

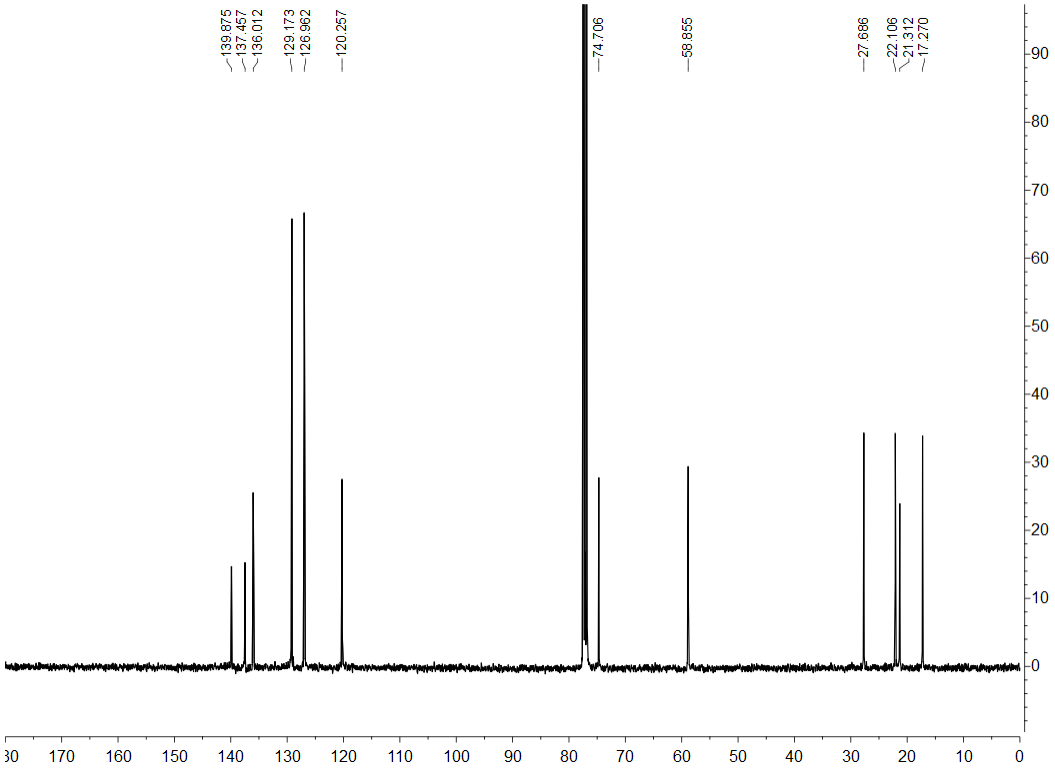
LRMS (CI) Calcd. for $C_{14}H_{20}O$ $[M\text{-}OH]^+$: 187, Found: 187.

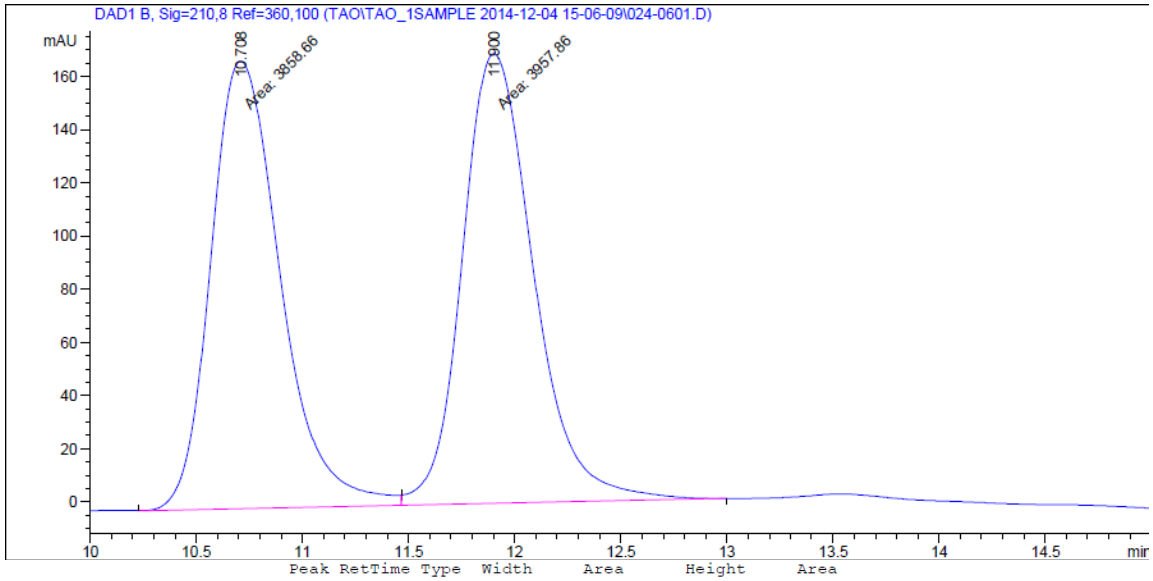
FTIR (neat): 3452, 2957, 2925, 2871, 1637, 1514, 1194, 1000, 911, 814, 675 cm^{-1}.

HPLC (Chiralcel AD-H column, hexanes:*i*-PrOH = 99:1, 1 mL/min, 210 nm), ee = 95%.

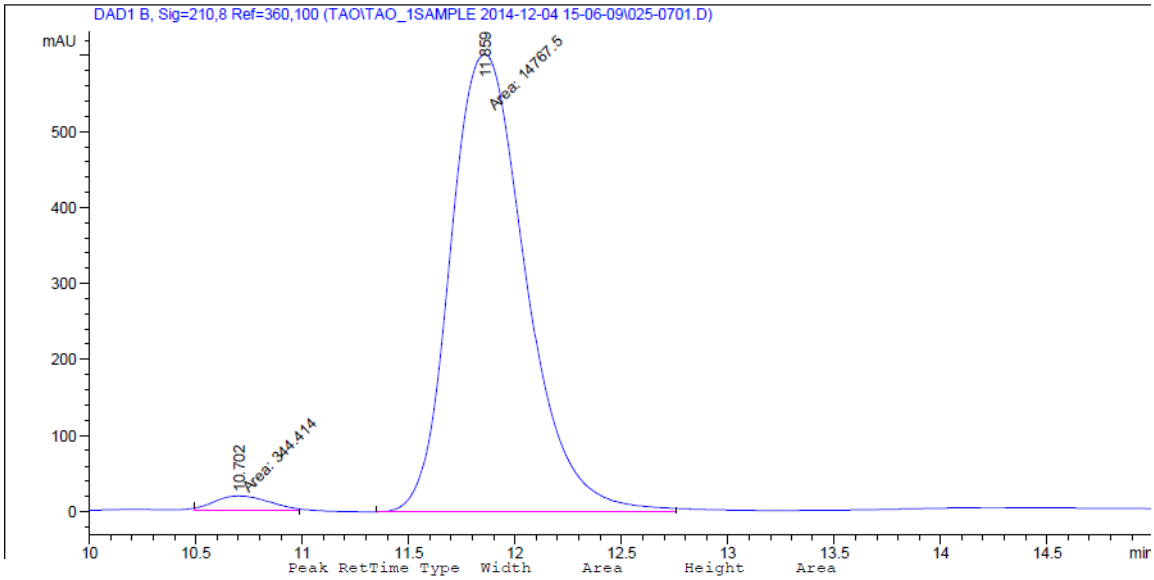
$[\alpha]^{25}_D$ = - 105.3 (c = 0.5, $CHCl_3$)


1.98
2.02
1.00
0.97
0.99
0.99
3.05
0.98
1.01
0.99
2.97
2.95


139.875
137.457
136.012
129.173
126.962
120.257
74.706
58.855
27.686
22.106
21.312
17.270

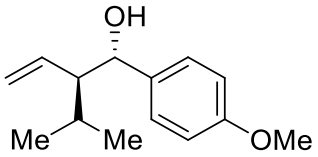


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.708	MF	0.3814	3858.65918	168.61931	49.3655
2	11.900	FM	0.3898	3957.85645	169.24431	50.6345



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.702	MM	0.2997	344.41418	19.15584	2.2791
2	11.859	MM	0.4088	1.47675e4	602.06384	97.7209

(1S,2S)-2-isopropyl-1-(4-methoxyphenyl)but-3-en-1-ol (2.3d).



The residue was subjected to flash column chromatography for purification (SiO_2, 300 mL of EtOAc: Hexanes = 1:7) to furnish the title compound (32.2 mg, 73%, *dr* = >20:1) as a yellow oil.

R_f = 0.39 (20% EtOAc/Hexanes).

Spectral data is reported for the major isomer.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 – 7.24 (m, 2H), 6.92 – 6.85 (m, 2H), 5.81 (dt, *J* = 17.1, 10.0 Hz, 1H), 5.31 (dd, *J* = 10.3, 2.1 Hz, 1H), 5.18 (ddd, *J* = 17.1, 2.1, 0.7 Hz, 1H), 4.55 (dd, *J* = 8.8, 1.5 Hz, 1H), 3.81 (s, 3H), 2.15 (td, *J* = 9.2, 3.8 Hz, 1H), 2.03 (d, *J* = 2.1 Hz, 1H), 1.53 – 1.38 (m, 1H), 0.82 (t, *J* = 6.5 Hz, 6H).

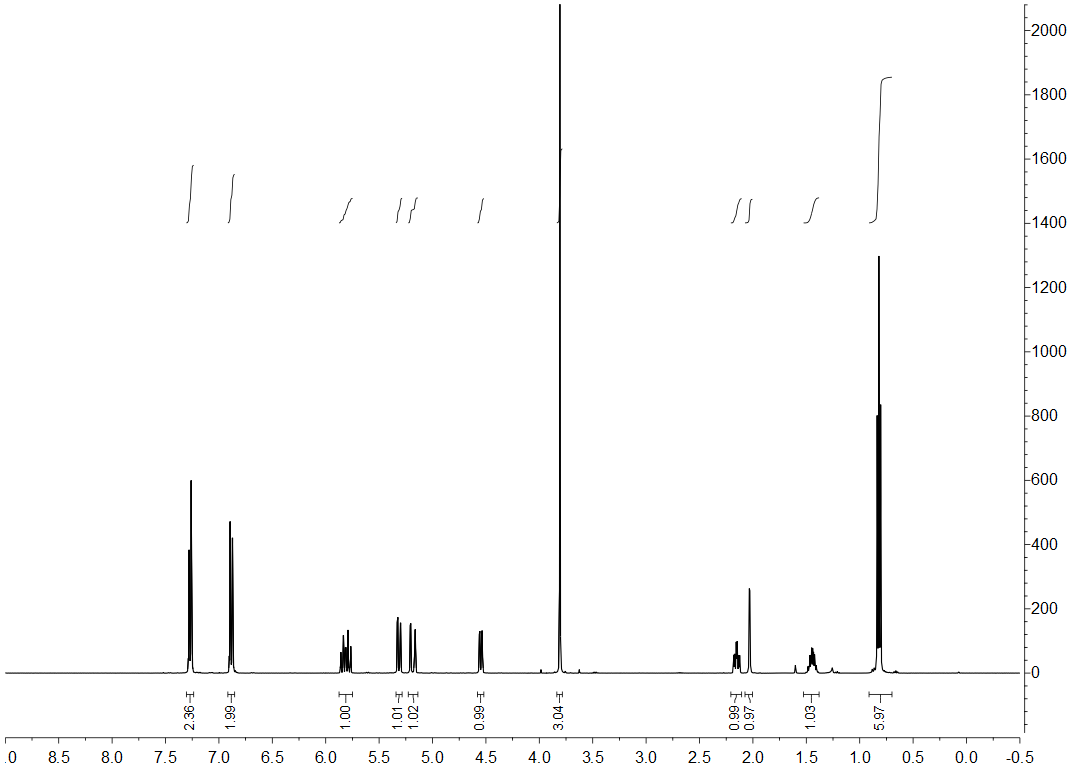
^{13}C NMR (100 MHz, $CDCl_3$): δ 159.2, 136.0, 135.0, 128.2, 120.3, 113.9, 74.4, 58.9, 55.4, 27.7, 22.1, 17.2.

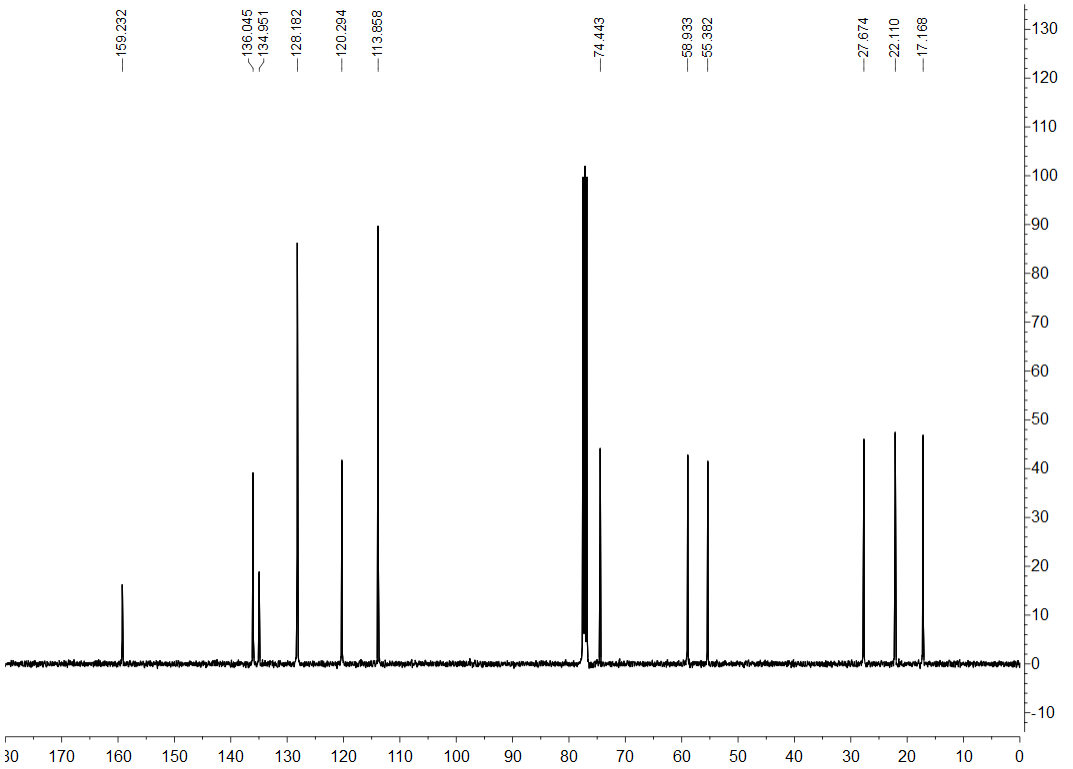
LRMS (CI) Calcd. for $C_{14}H_{20}O_2$ $[M+H]^+$: 221, Found: 221.

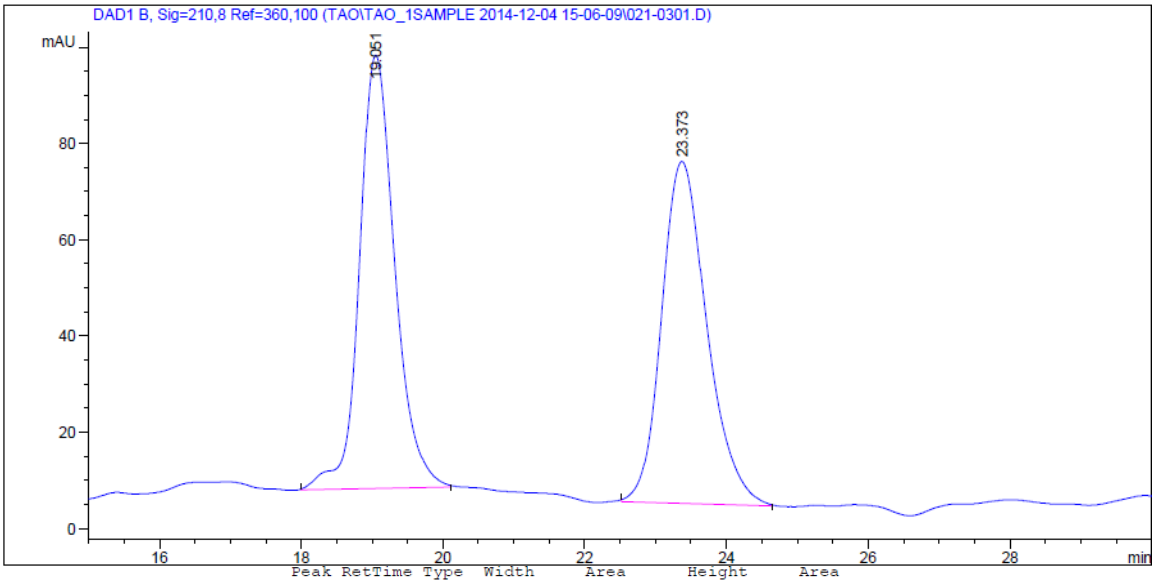
FTIR (neat): 3446, 3072, 2999, 2873, 1612, 1586, 1512, 1367, 1246, 1174, 1035, 833 cm^{-1}.

HPLC (Chiralcel AD-H column, hexanes:*i*-PrOH = 99:1, 1 mL/min, 210 nm), ee = 95%.

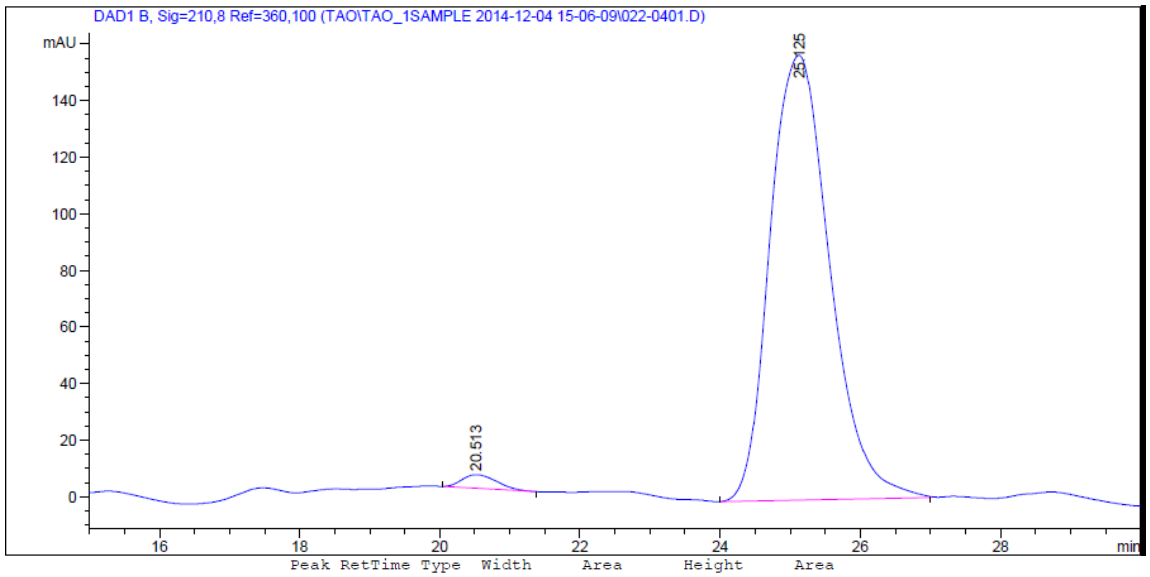
$[\alpha]^{25}_D$ = - 92.3 (c = 0.5, $CHCl_3$)


2.36
1.99
1.00
1.01
1.02
0.99
3.04
0.99
0.97
1.03
5.97


159.232
136.045
134.951
128.182
120.294
113.858
74.443
58.933
55.382
27.674
22.110
17.168

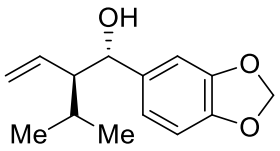


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.051	BB	0.5279	3131.21509	89.99529	49.7731
2	23.373	BB	0.6810	3159.76660	71.02366	50.2269



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.513	BB	0.4651	164.00195	4.74670	1.7292
2	25.125	BB	0.9238	9320.48828	157.18344	98.2708

(1S,2S)-1-(benzo[d][1,3]dioxol-5-yl)-2-isopropylbut-3-en-1-ol (2.3e).



The residue was subjected to flash column chromatography for purification (SiO_2, 300 mL of EtOAc: Hexanes = 1:7) to furnish the title compound (35.1 mg, 75%, *dr* = >20:1) as a yellow oil.

R_f = 0.31 (20% EtOAc/Hexanes).

Spectral data is reported for the major isomer.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.85 (s, 1H), 6.81 – 6.71 (m, 2H), 5.94 (s, 2H), 5.86 – 5.71 (m, 1H), 5.31 (dd, *J* = 10.3, 2.1 Hz, 1H), 5.16 (dd, *J* = 17.2, 2.0 Hz, 1H), 4.50 (d, *J* = 8.7 Hz, 1H), 2.16 – 2.05 (m, 2H), 1.56 – 1.38 (m, 1H), 0.83 (d, *J* = 2.4 Hz, 3H), 0.81 (d, *J* = 2.4 Hz, 3H).

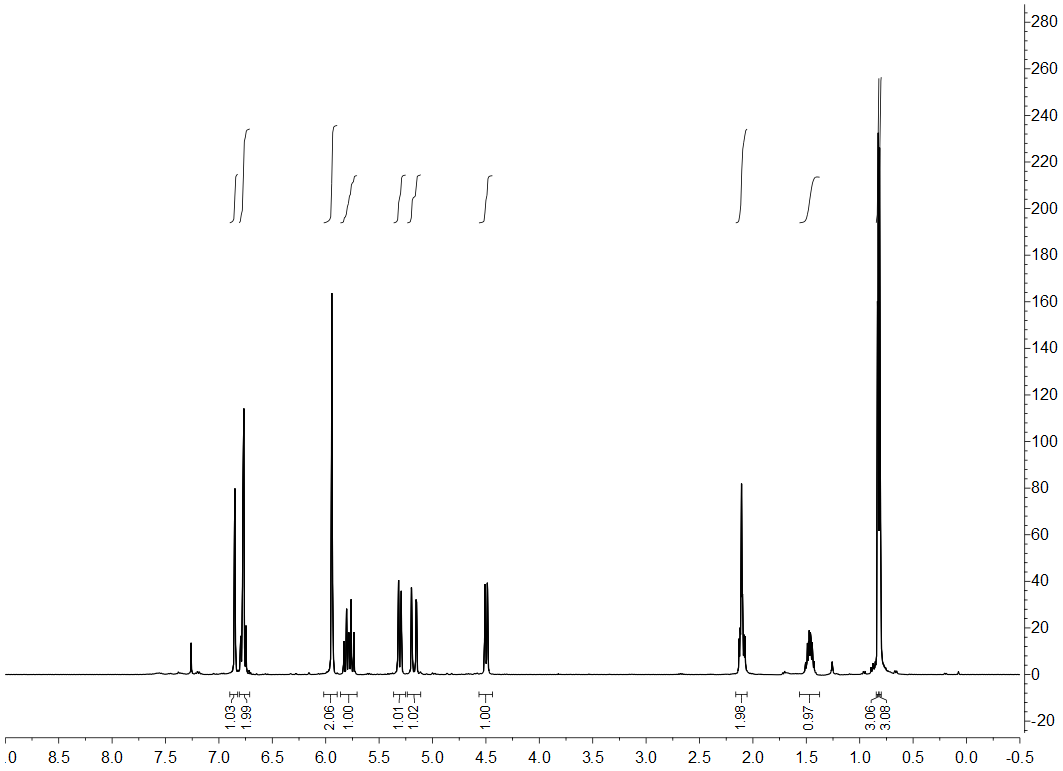
^{13}C NMR (100 MHz, $CDCl_3$): δ 147.8, 147.1, 136.8, 135.8, 120.6, 120.4, 108.0, 107.1, 101.1, 74.6, 58.9, 27.6, 22.0, 17.2.

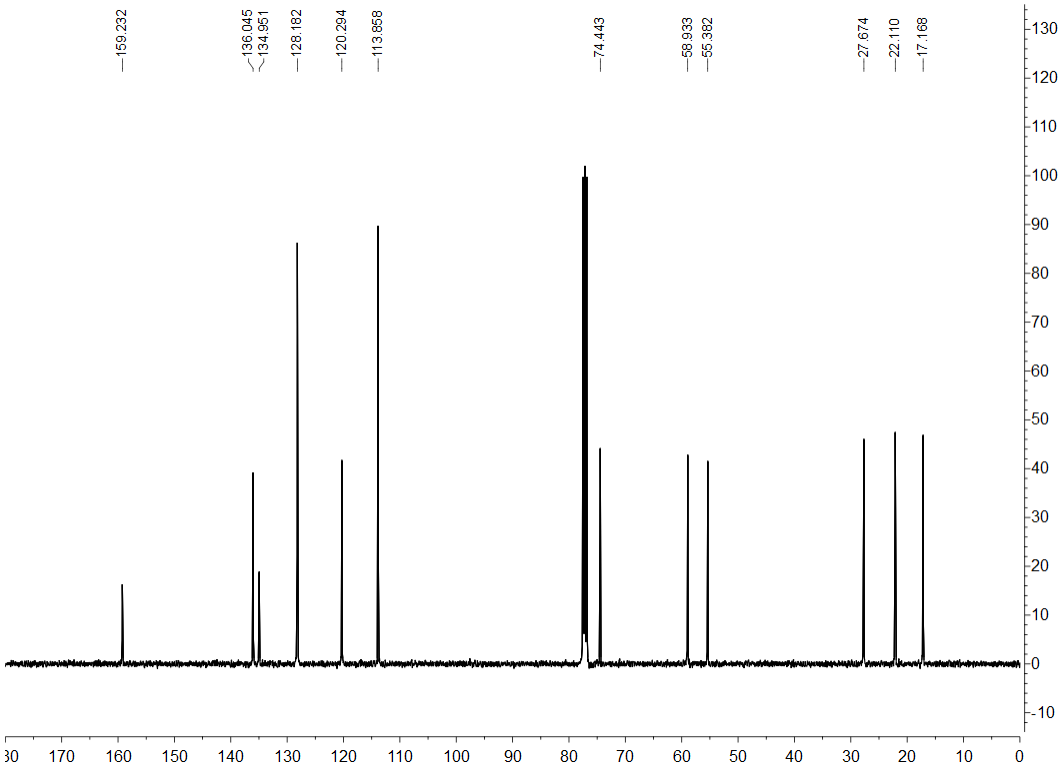
LRMS (CI) Calcd. for $C_{14}H_{18}O_3$ $[M+H]^+$: 235, Found: 235.

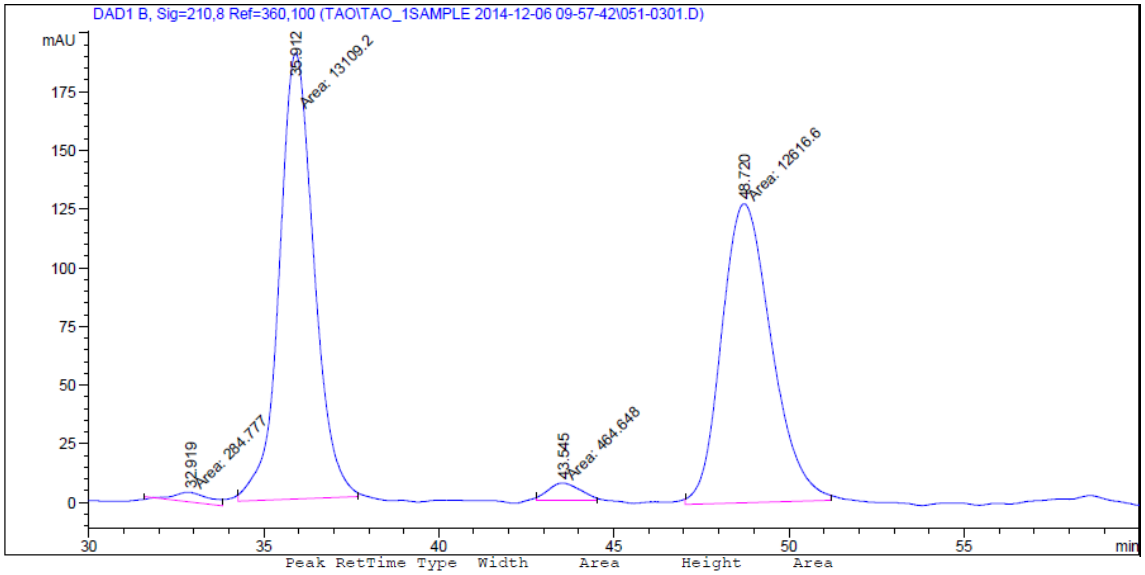
FTIR (neat): 3446, 3073, 2958, 2874, 1638, 1610, 1503, 1441, 1243, 1038, 916, 810 cm^{-1}.

HPLC (Chiralcel OD-H column, hexanes:*i*-PrOH = 99:1, 1 mL/min, 210 nm), ee = 96%.

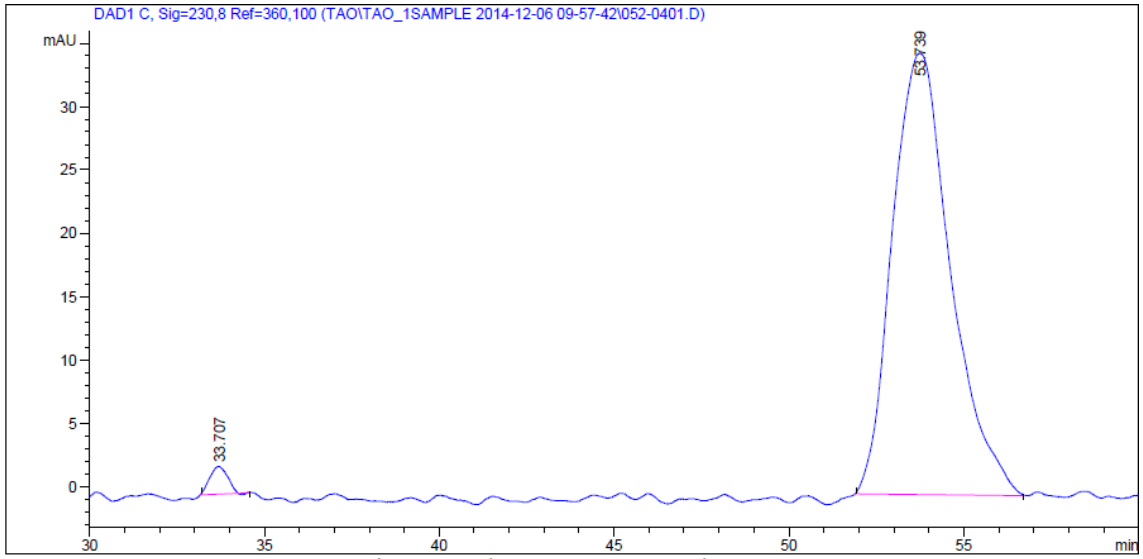
$[\alpha]^{25}_D$ = - 77.1 (c = 1.72, $CHCl_3$)


1.03
1.99
2.06
1.00
1.01
1.02
1.00
1.98
0.97
3.06
3.08


159.232
136.045
134.951
128.182
120.294
113.858
74.443
59.933
55.382
27.674
22.110
17.168

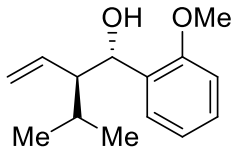


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	32.919	MM	1.1377	284.77719	4.17166	1.0756
2	35.912	MM	1.1510	1.31092e4	189.82373	49.5149
3	43.545	MM	1.0546	464.64780	7.34331	1.7550
4	48.720	MM	1.6523	1.26166e4	127.26545	47.6544



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	33.707	BB	0.4233	76.27319	2.17407	1.8565
2	53.739	BB	1.3670	4032.19458	34.82101	98.1435

(1S,2S)-2-isopropyl-1-(2-methoxyphenyl)but-3-en-1-ol (2.3f).



The residue was subjected to flash column chromatography for purification (SiO_2, 300 mL of EtOAc: Hexanes = 1:5) to furnish the title compound (33.5 mg, 76%, *dr* = >20:1) as a yellow oil.

R_f = 0.28 (20% EtOAc/Hexanes).

Spectral data is reported for the major isomer.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.27 – 7.22 (m, 1H), 6.96 (td, *J* = 7.5, 1.0 Hz, 1H), 6.88 (dd, *J* = 8.3, 0.7 Hz, 1H), 5.82 (dt, *J* = 17.1, 10.0 Hz, 1H), 5.22 (dd, *J* = 10.3, 2.2 Hz, 1H), 5.08 – 4.97 (m, 2H), 3.84 (s, 3H), 2.31 (d, *J* = 5.4 Hz, 1H), 2.29 – 2.23 (m, 1H), 1.55 – 1.49 (m, 1H), 0.87 (d, *J* = 4.8 Hz, 3H), 0.85 (d, *J* = 4.8 Hz, 3H).

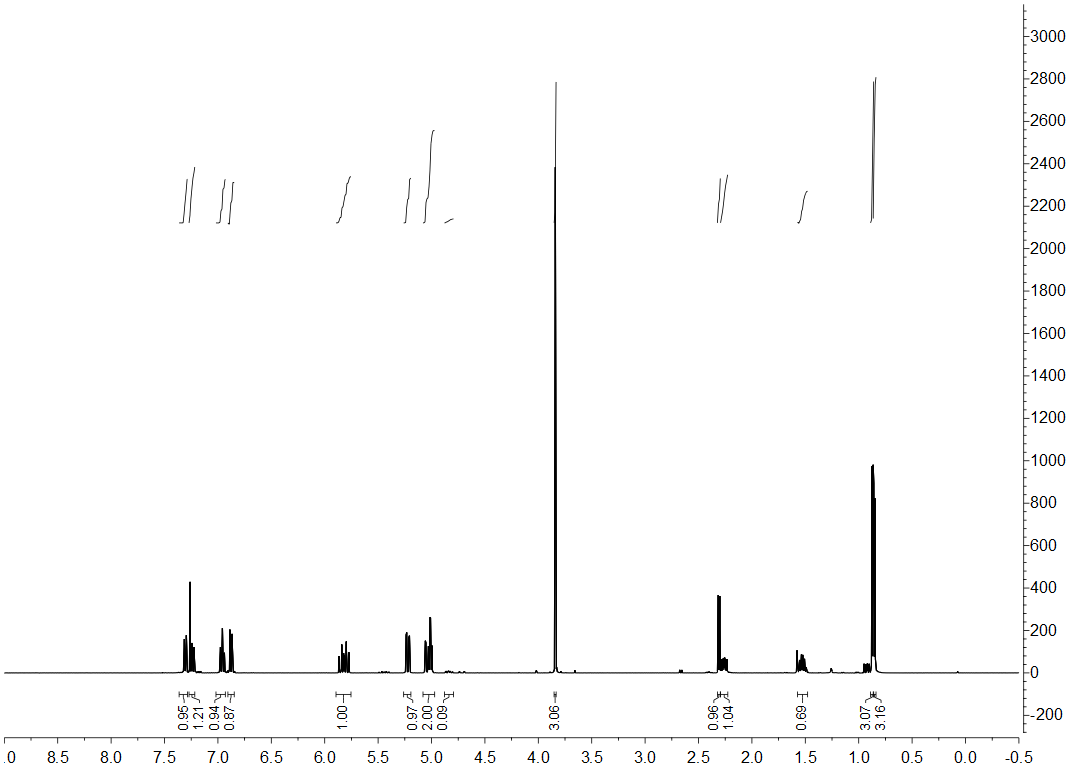
^{13}C NMR (100 MHz, $CDCl_3$): δ 156.9, 136.7, 131.3, 128.4, 128.1, 120.8, 119.1, 110.7, 70.5, 57.6, 55.4, 28.2, 22.0, 18.1.

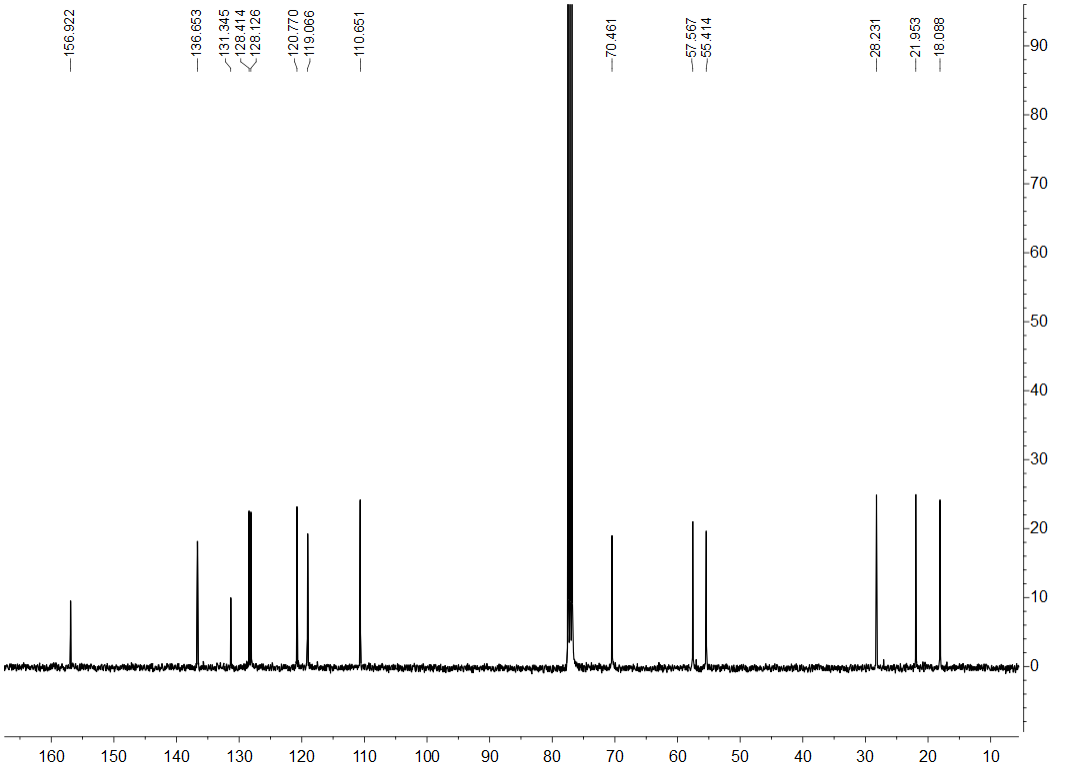
LRMS (CI) Calcd. for $C_{14}H_{20}O_2$ $[M+H]^+$: 221, Found: 221.

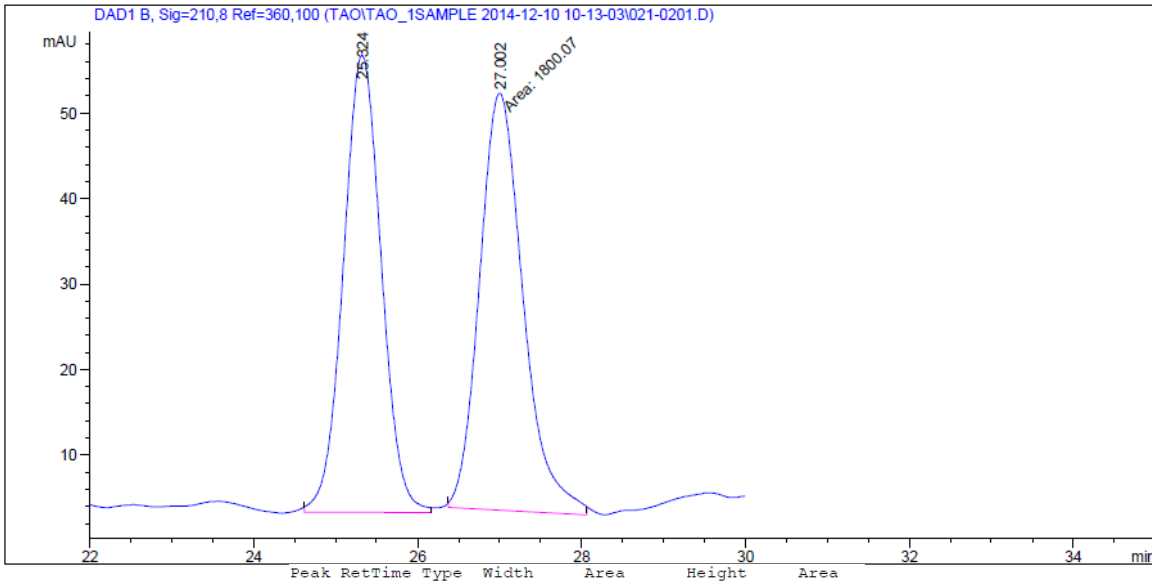
FTIR (neat): 3452, 2956, 2871, 1601, 1588, 1490, 1464, 1237, 1049, 1030, 912, 753 cm^{-1}.

HPLC (Chiralcel OD-H column, hexanes:*i*-PrOH = 99:1, 1 mL/min, 210 nm), ee = 95%.

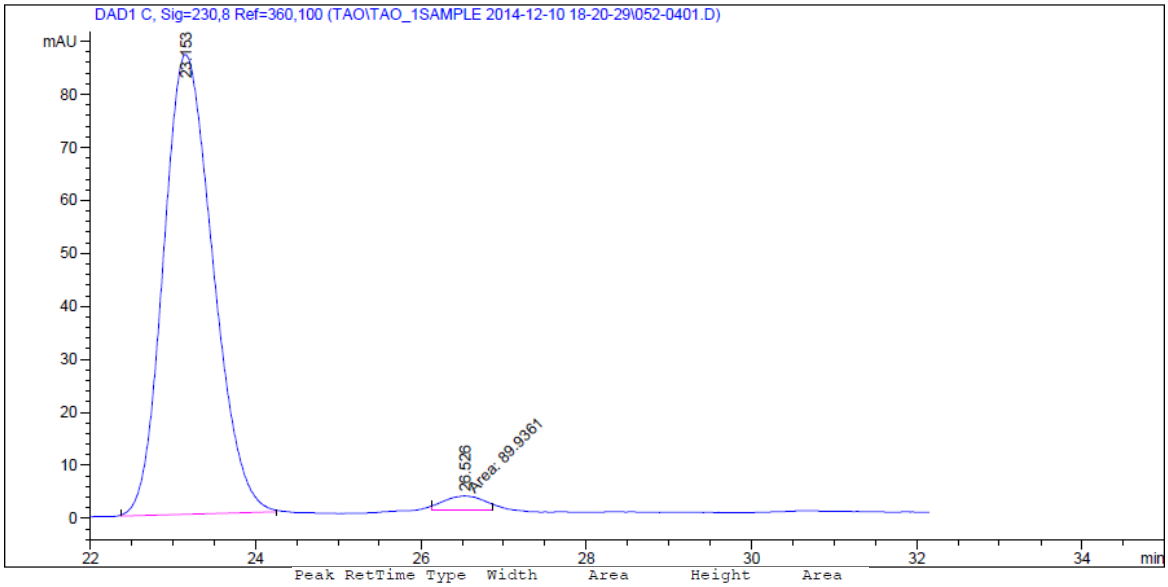
$[\alpha]^{25}_D$ = - 60.4(c = 1.57, $CHCl_3$)


0.95
1.21
0.94
0.87
1.00
0.97
2.00
0.09
3.06
0.96
1.04
0.69
3.07
3.16


156.922
136.653
131.345
128.414
128.126
120.770
119.066
110.651
70.461
57.567
55.414
28.231
21.953
18.088

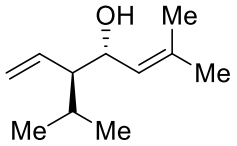


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	25.324	BB	0.5012	1717.31079	53.40089	48.8235
2	27.002	MM	0.6156	1800.07227	48.73238	51.1765



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	23.153	BB	0.6445	3598.44604	86.64355	97.5616
2	26.526	MM	0.5479	89.93610	2.73595	2.4384

(3S,4S)-3-isopropyl-6-methylhepta-1,5-dien-4-ol (2.3g).



The residue was subjected to flash column chromatography for purification (SiO_2, 250 mL of Et_2O: Pentane = 1:7) to furnish the title compound (25.6 mg, 76%, *dr* = >20:1) as a colorless oil.

R_f = 0.32 (5:1 Hexanes : Et_2O).

Spectral data is reported for the major isomer.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.74 (td, *J* = 17.1, 10.0 Hz, 1H), 5.27 (dt, *J* = 10.3, 2.1 Hz, 1H), 5.18 – 5.05 (m, 2H), 4.30 (t, *J* = 8.6 Hz, 1H), 1.89 – 1.77 (m, 3H), 1.76 (s, 3H), 1.72 (s, 3H), 1.54 (t, *J* = 2.2 Hz, 1H), 0.88 (dd, *J* = 6.8, 1.8 Hz, 3H), 0.79 (dd, *J* = 6.8, 1.7 Hz, 3H)

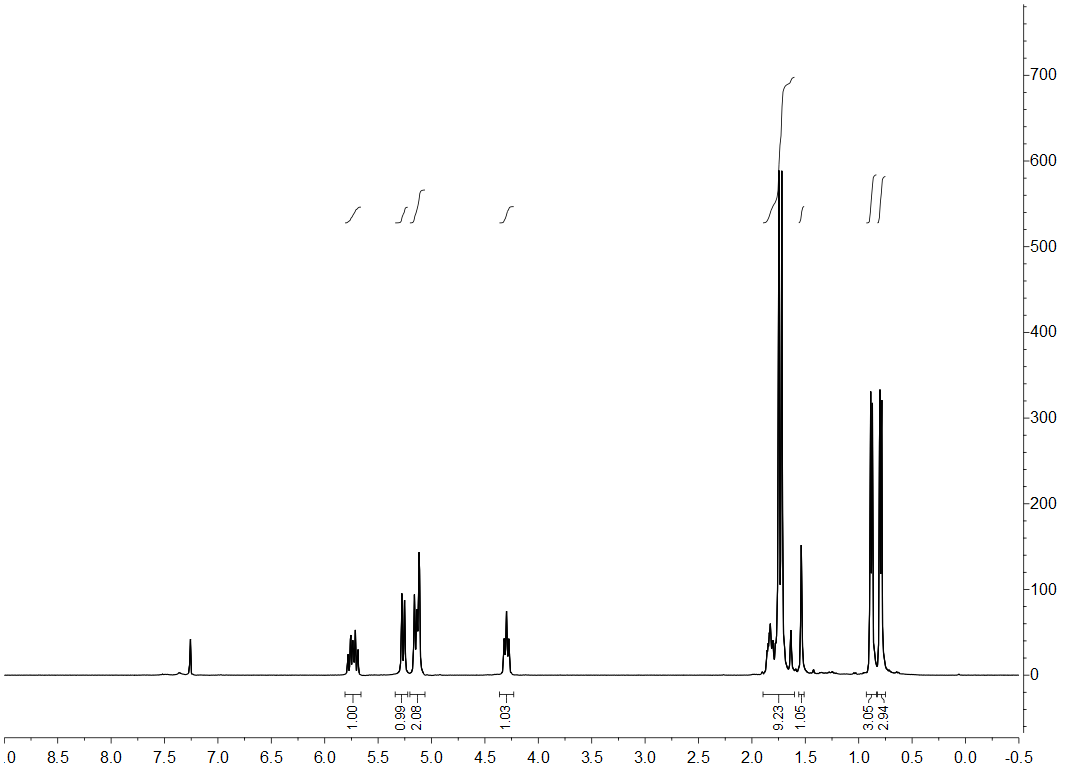
^{13}C NMR (100 MHz, $CDCl_3$): δ 136.43, 136.25, 126.52, 119.83, 68.55, 57.72, 27.97, 26.10, 22.05, 18.50, 17.79.

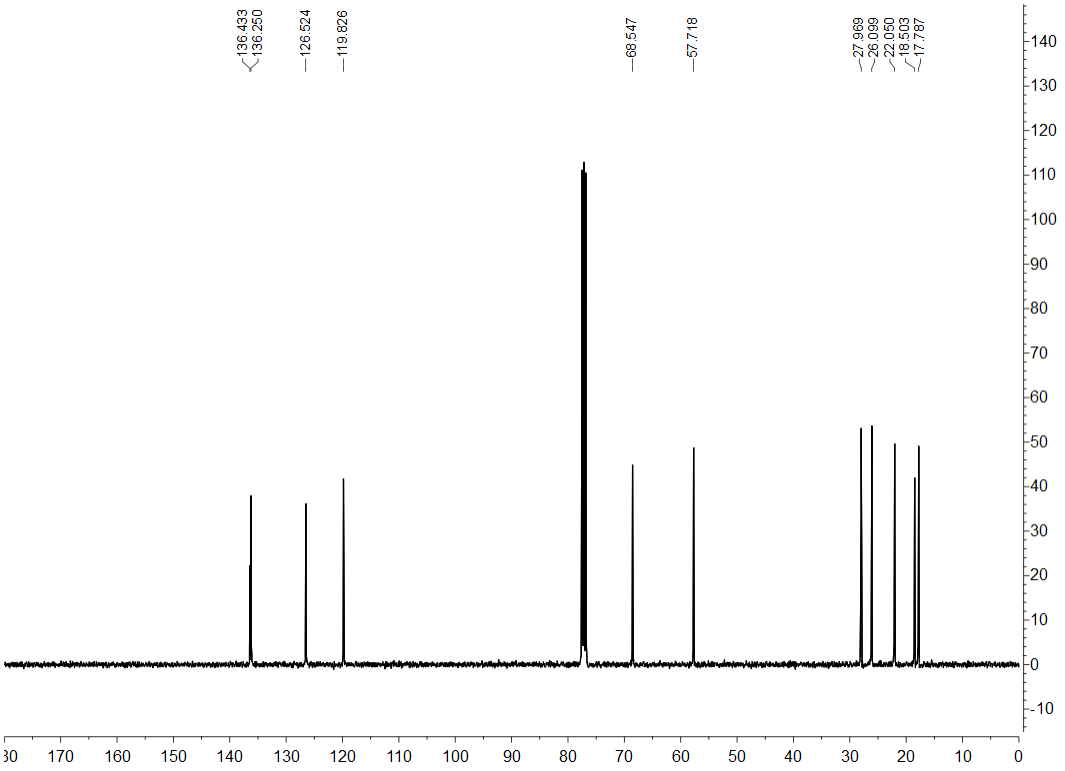
LRMS (CI) Calcd. for $C_{11}H_{20}O$ $[M+H]^+$: 169, Found: 169.

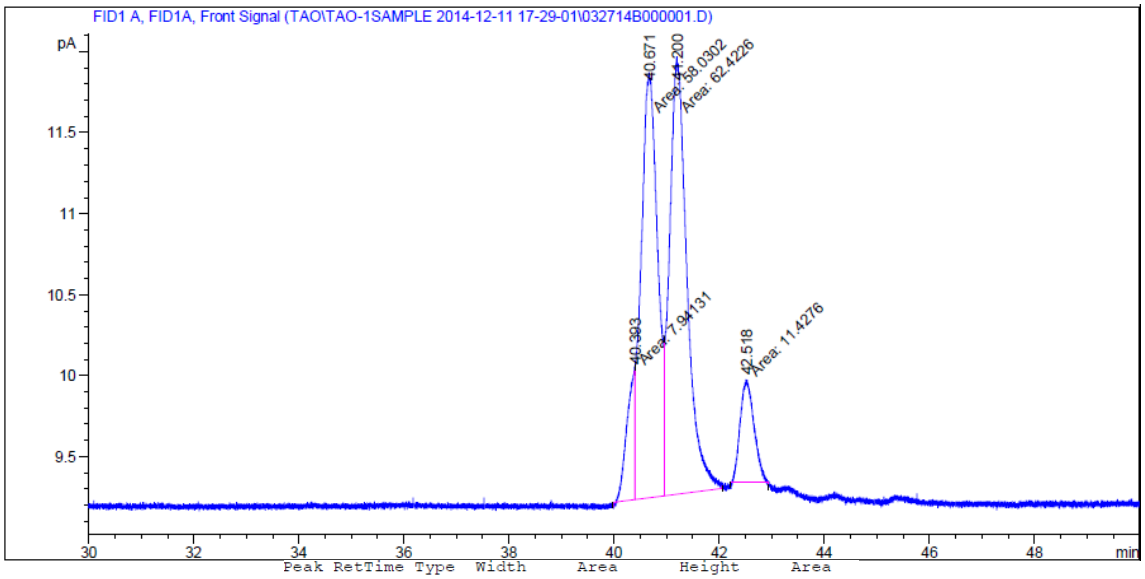
FTIR (neat): 3390, 2959, 2928, 1676, 1638, 1449, 1385, 1026, 913, 743 cm^{-1}.

GC (cyclosil-B: Initial temperature: 50°C; 130 °C, rate: 1 °C /min), ee = 95%.

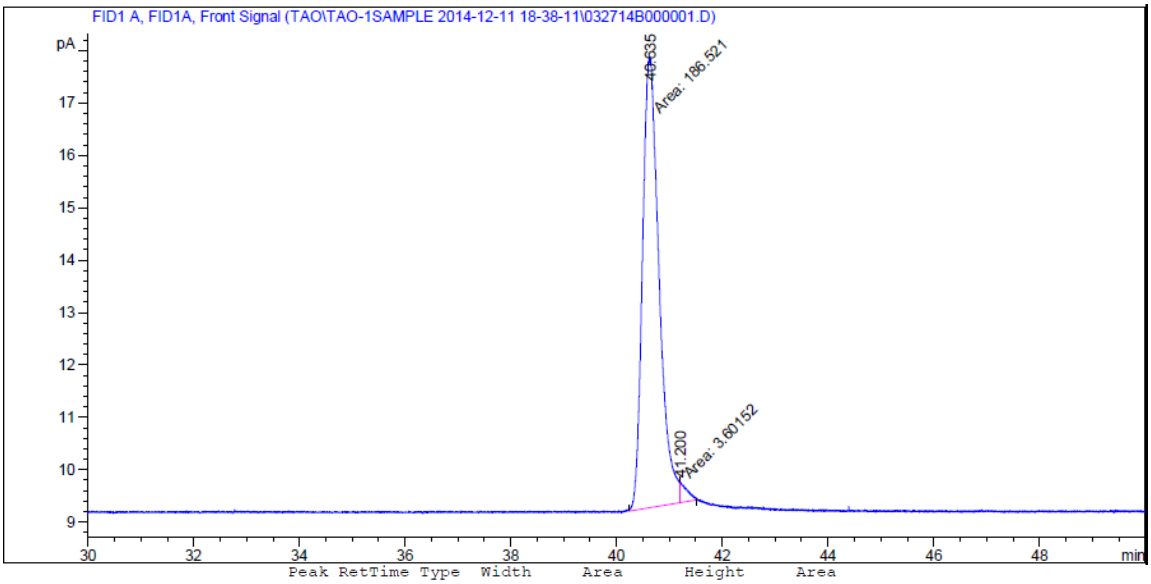
$[\alpha]^{25}_D$ = - 3.2(c = 0.73, $CHCl_3$)


1.00
0.99
2.08
1.03
9.23
1.05
3.05
2.94


136.433
136.250
126.524
119.826
68.547
57.718
27.969
26.099
22.050
18.503
17.787

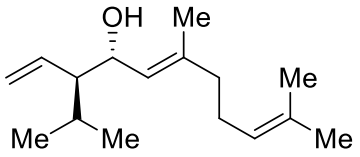


Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	40.393	MF	0.1631	7.94131	8.11470e-1	5.67960
2	40.671	MF	0.3691	58.03016	2.62011	41.50301
3	41.200	FM	0.3864	62.42256	2.69232	44.64444
4	42.518	MM	0.2999	11.42756	6.34987e-1	8.17296



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	40.635	MF	0.3613	186.52057	8.60528	98.10568
2	41.200	FM	0.1494	3.60152	4.01855e-1	1.89432

(3S,4S,E)-3-isopropyl-6,10-dimethylundeca-1,5,9-trien-4-ol (2.3h).



The residue was subjected to flash column chromatography for purification (SiO_2, 200 mL of 10% EtOAc/Hexanes) to furnish the title compound (42.6 mg, 90%, *dr* = >20:1) as a colorless oil.

R_f = 0.50 (20% EtOAc/Hexanes).

Spectral data is reported for the major isomer.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.74 (dt, *J* = 17.1, 10.0 Hz, 1H), 5.27 (dd, *J* = 10.3, 2.3 Hz, 1H), 5.18 – 5.10 (m, 2H), 5.07 (tt, *J* = 6.9, 1.5 Hz, 1H), 4.31 (ddd, *J* = 9.1, 8.0, 2.6 Hz, 1H), 2.22 – 2.00 (m, 4H), 1.90 – 1.74 (m, 2H), 1.71 (d, *J* = 1.4 Hz, 3H), 1.67 (d, *J* = 1.3 Hz, 3H), 1.60 (s, 3H), 1.52 (d, *J* = 2.6 Hz, 1H), 0.89 (d, *J* = 6.8 Hz, 3H), 0.79 (d, *J* = 6.8 Hz, 3H).

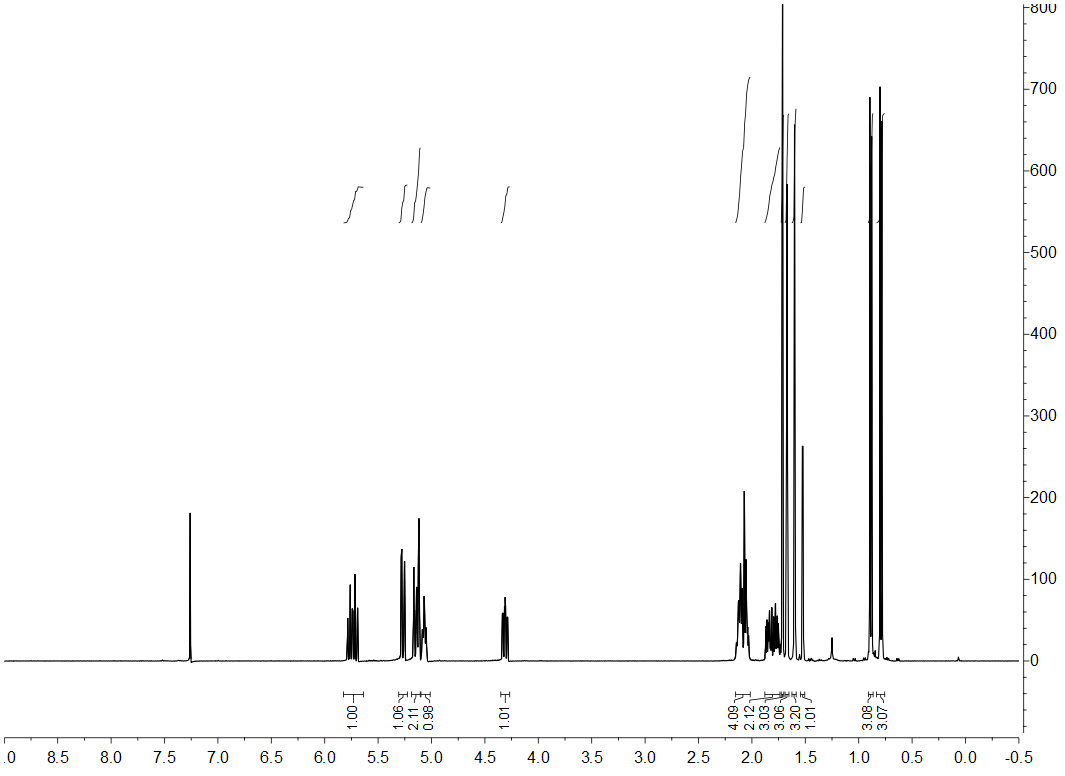
^{13}C NMR (100 MHz, $CDCl_3$): δ 139.70, 136.28, 131.77, 126.45, 124.11, 119.81, 68.49, 57.77, 39.90, 27.98, 26.36, 25.83, 22.11, 17.84, 17.77, 16.81.

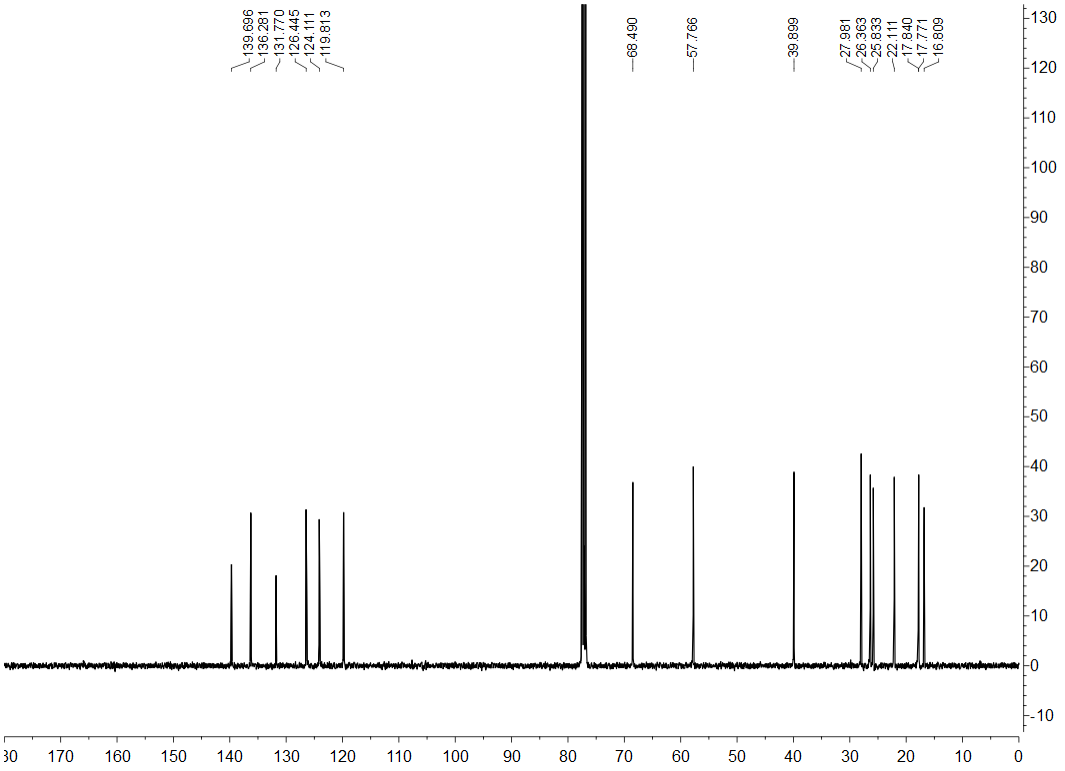
LRMS (CI) Calcd. for $C_{16}H_{28}O$ $[M+H]^+$: 237, Found: 237.

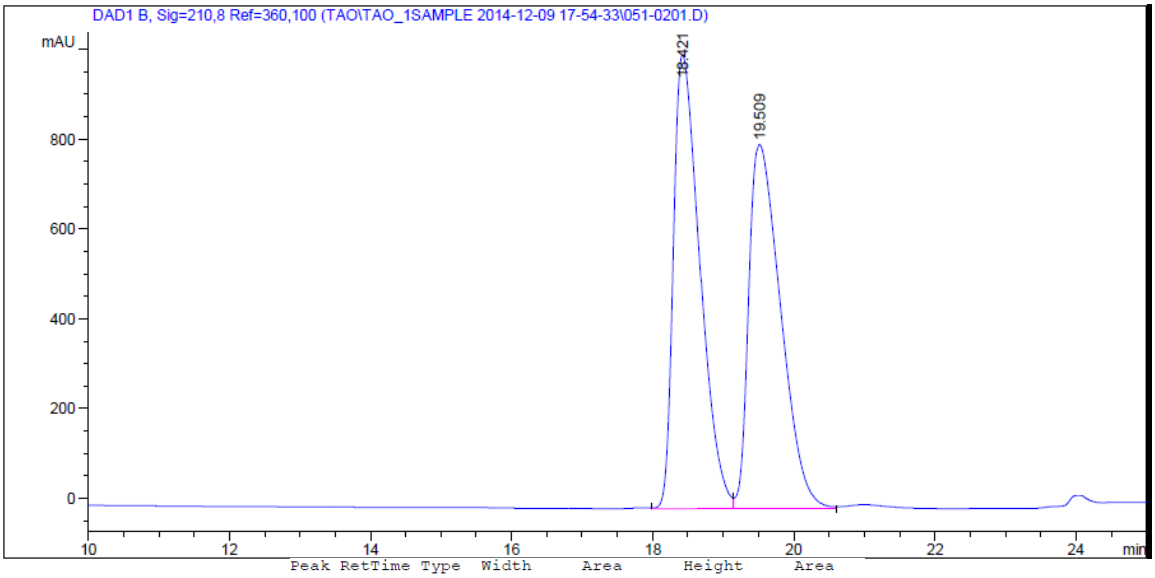
FTIR (neat): 3423, 3073, 2958, 2927, 2870, 1669, 1638, 1446, 1383, 1027, 1001, 909, 684 cm^{-1}.

HPLC (Chiralcel OD-H column, hexanes:*i*-PrOH = 99.5:0.5, 0.50 mL/min, 210 nm), ee = 96%.

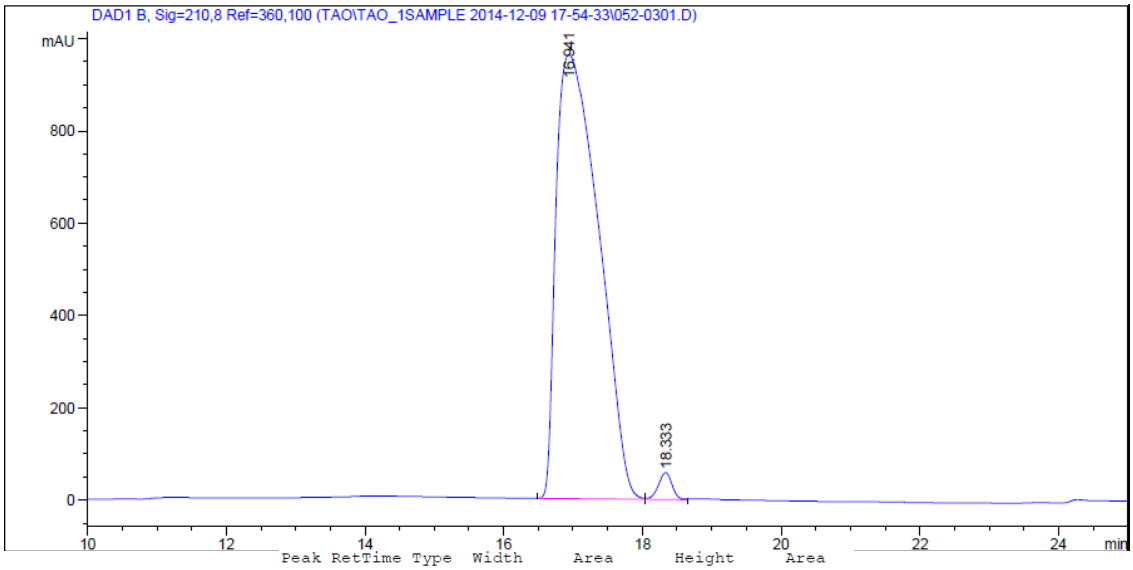
$[\alpha]^{25}_D$ = - 15.9 (c = 1.33, $CHCl_3$)


1.00
1.06
2.11
0.98
1.01
4.09
2.12
3.03
3.06
3.20
1.01
3.08
3.07


139.696
136.281
131.770
126.445
124.111
119.813
68.490
57.766
39.899
27.981
26.363
25.833
22.111
17.840
17.771
16.809

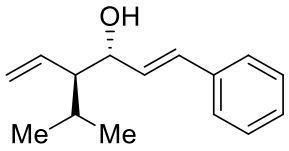


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.421	VV	0.4048	2.64146e4	1011.03748	50.9964
2	19.509	VB	0.4951	2.53824e4	811.12073	49.0036



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.941	BV	0.7571	4.09813e4	961.87451	98.0713
2	18.333	VV	0.2149	805.94647	58.42590	1.9287

(3R,4S,E)-4-isopropyl-1-phenylhexa-1,5-dien-3-ol (2.3i).



The residue was subjected to flash column chromatography for purification (SiO_2, 250 mL of 1:9 Et_2OAc: Hexanes) to furnish the title compound (29.0 mg, 67%, *dr* = >20:1) as a colorless oil.

R_f = 0.50 (20% EtOAc/Hexanes).

Spectral data is reported for the major isomer.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 – 7.37 (m, 2H), 7.35 – 7.29 (m, 2H), 7.27 – 7.20 (m, 1H), 6.61 (d, *J* = 15.9 Hz, 1H), 6.20 (dd, *J* = 15.9, 7.5 Hz, 1H), 5.78 (dt, *J* = 17.1, 10.0 Hz, 1H), 5.30 (dd, *J* = 10.3, 2.2 Hz, 1H), 5.17 (ddd, *J* = 17.1, 2.2, 0.7 Hz, 1H), 4.26 (td, *J* = 7.5, 1.8 Hz, 1H), 1.97 (ddd, *J* = 9.7, 7.4, 4.9 Hz, 1H), 1.92 – 1.82 (m, 1H), 1.76 (d, *J* = 2.8 Hz, 1H), 0.93 (d, *J* = 6.8 Hz, 3H), 0.88 (d, *J* = 6.8 Hz, 3H).

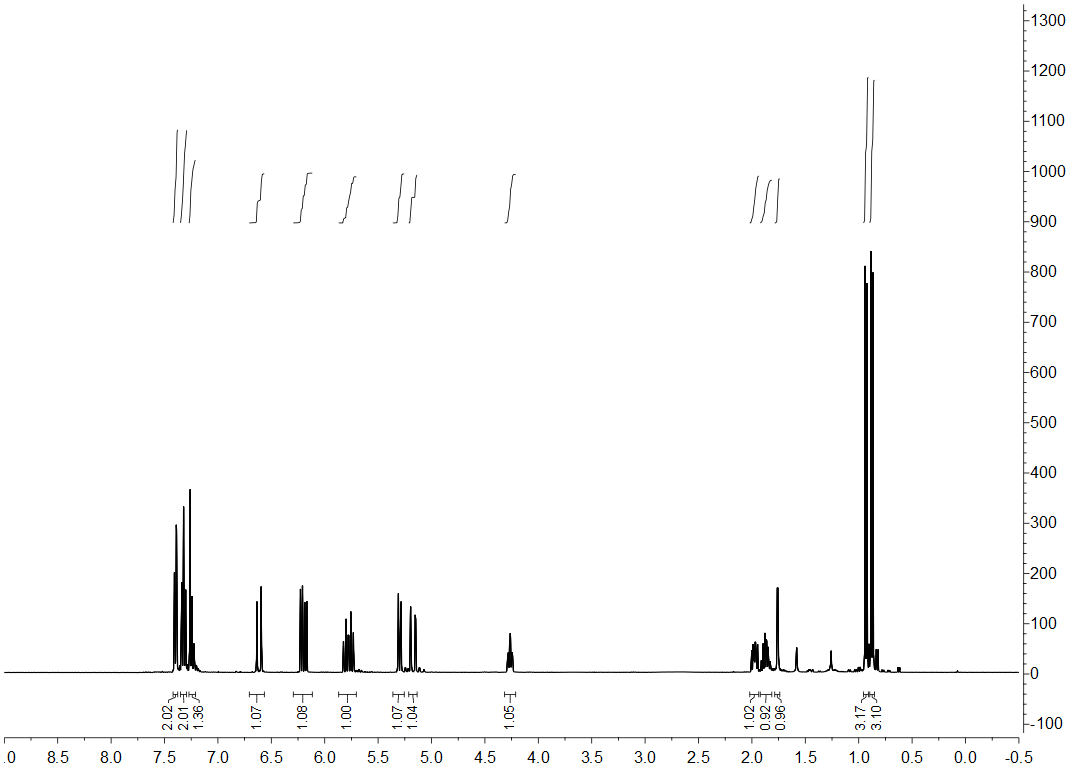
^{13}C NMR (100 MHz, $CDCl_3$): δ 136.88, 135.92, 131.82, 130.98, 128.69, 127.81, 126.66, 119.96, 73.32, 57.63, 27.96, 21.88, 17.97.

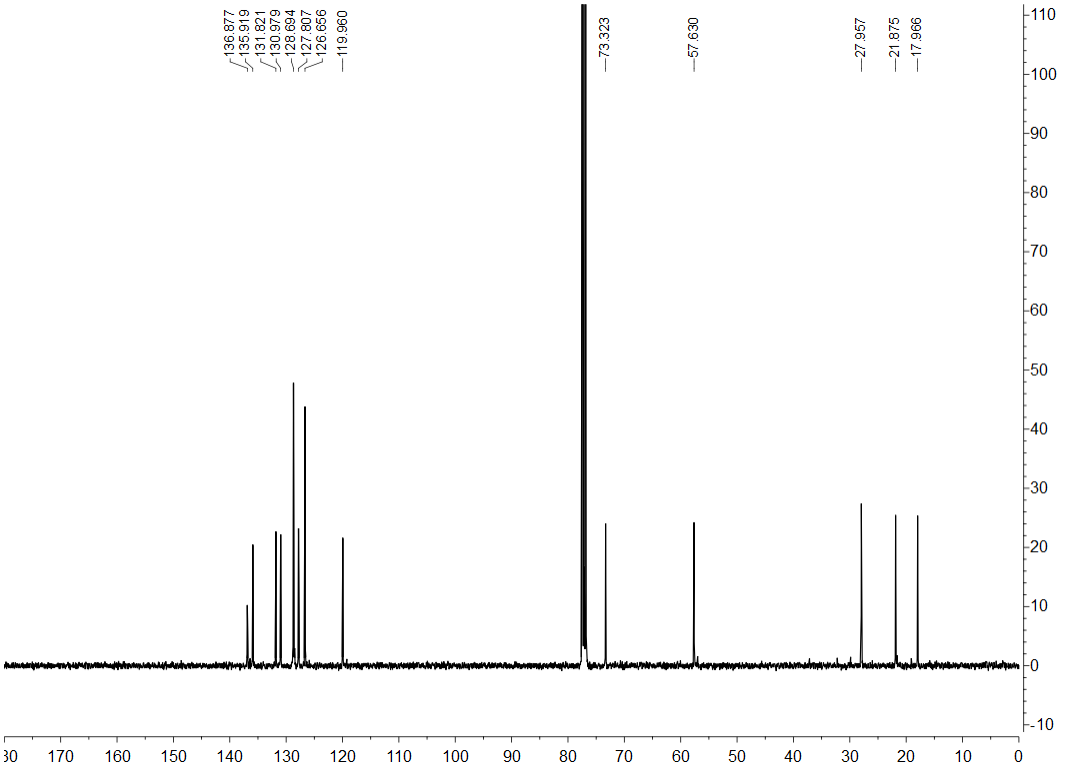
LRMS (CI) Calcd. for $C_{15}H_{20}O$ $[M+H]^+$: 217, Found: 217.

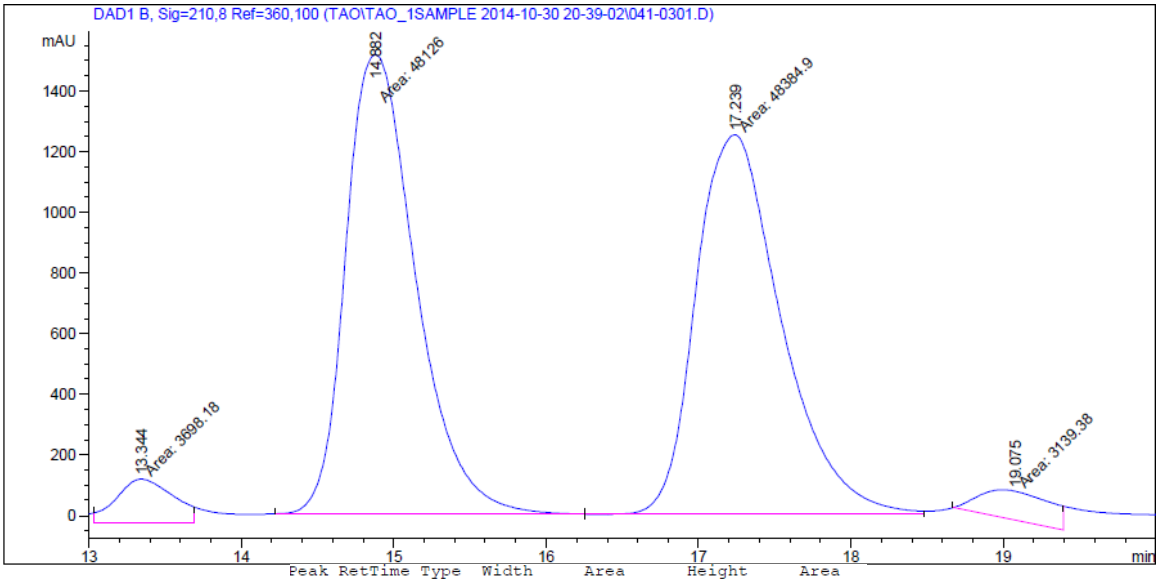
FTIR (neat): 3422, 3073, 2957, 2870, 1637, 1494, 1449, 1386, 1002, 966, 751, 693 cm^{-1}.

HPLC (Chiralcel AD-H column, hexanes:*i*-PrOH = 99:1, 1 mL/min, 210 nm), ee = 96%.

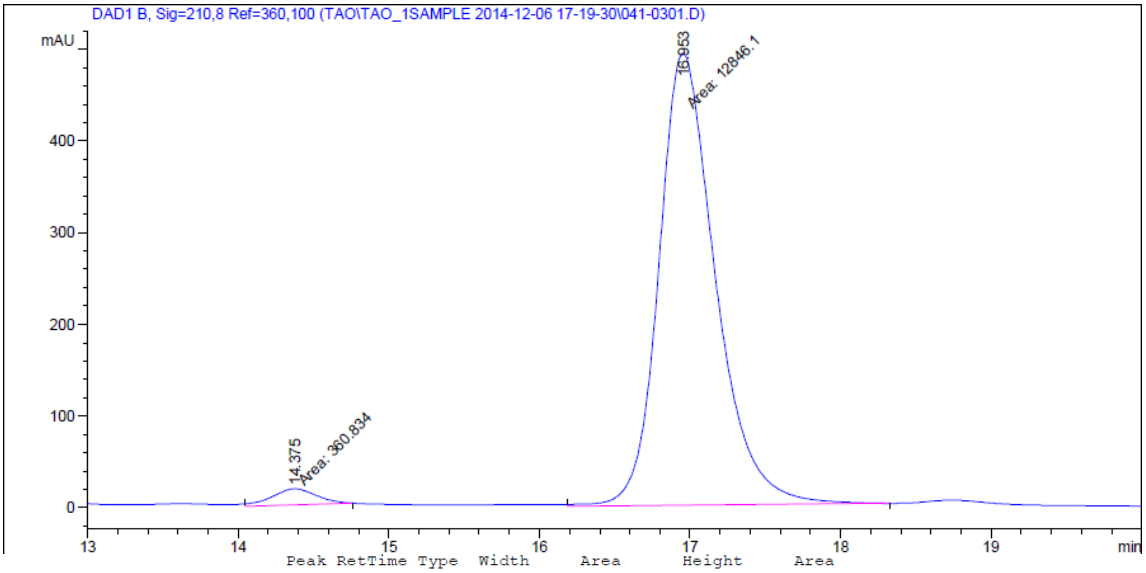
$[\alpha]^{25}_D$ = + 10.0 (c = 0.5, $CHCl_3$)


2.02
2.01
1.36
1.07
1.08
1.00
1.07
1.04
1.05
1.02
0.92
0.96
3.17
3.10


136.877
135.919
131.821
130.979
128.694
127.807
126.656
119.960
73.323
57.630
27.957
21.875
17.966

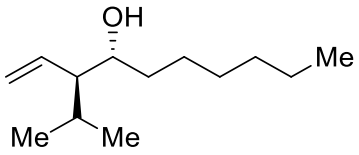


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.344	MM	0.4296	3698.17773	143.48155	3.5784
2	14.882	MF	0.5302	4.81260e4	1512.79456	46.5667
3	17.239	FM	0.6457	4.83849e4	1248.97717	46.8172
4	19.075	MM	0.5455	3139.38403	95.91157	3.0377



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.375	MM	0.3428	360.83444	17.54486	2.7322
2	16.953	MM	0.4346	1.28461e4	492.61343	97.2678

(3S,4R)-3-isopropyldec-1-en-4-ol (2.3j).



In modification to the general procedure, 2-PrOH was omitted. The reaction was heated for 48 hours at 125 ^{o}C, concentrated *in vacuo.* The residue was subjected to flash column chromatography (SiO_2, 250 mL of 1:15 Et_2O: Hexanes) to furnish the title compound (28.6 mg, 72%, *dr* = >20:1) as a pale yellow liquid.

R_f = 0.74 (1:5 of Et_2O: Hexanes).

Spectral data is reported for the major isomer.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.69 (dt, *J* = 17.2, 10.0 Hz, 1H), 5.21 (dd, *J* = 10.3, 2.3 Hz, 1H), 5.06 (dd, *J* = 17.1, 2.3 Hz, 1H), 3.66 (s, 1H), 1.81 (dt, *J* = 13.4, 6.7 Hz, 1H), 1.76 – 1.64 (m, 1H), 1.53 – 1.21 (m, 11H), 0.92 (d, *J* = 6.7 Hz, 3H), 0.91 – 0.87 (m, 3H), 0.85 (d, *J* = 6.8 Hz, 3H).

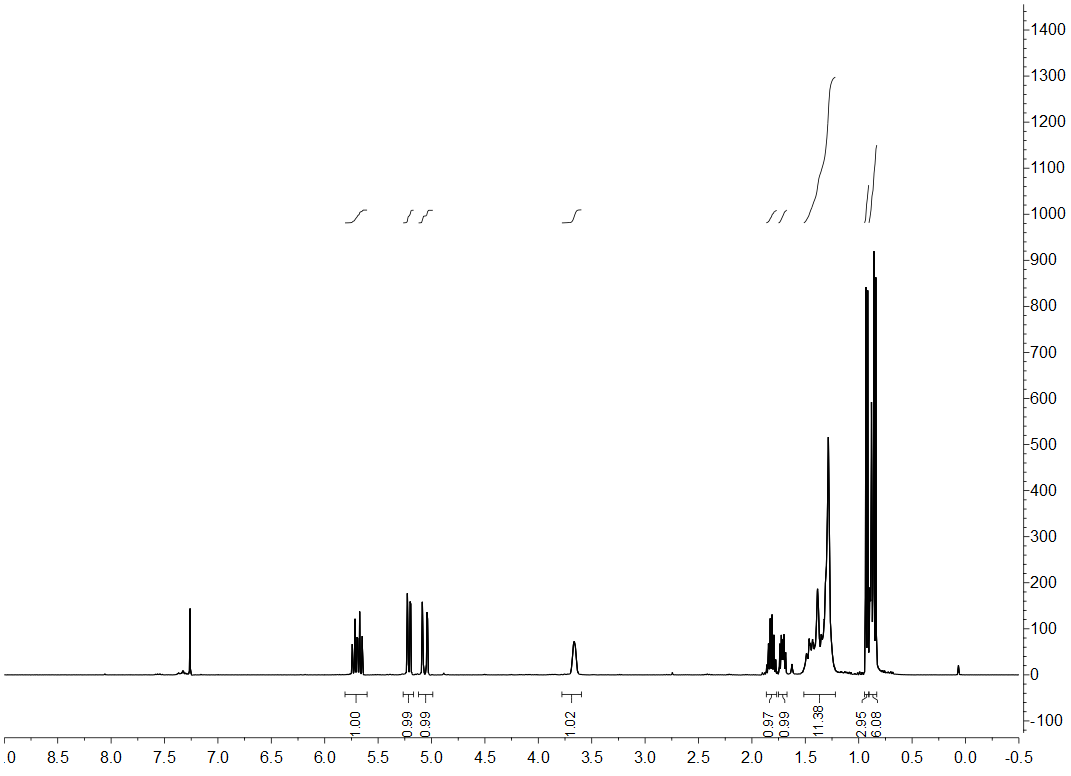
^{13}C NMR (100 MHz, $CDCl_3$): δ 136.66, 118.88, 71.26, 56.86, 35.35, 32.02, 29.57, 27.89, 25.73, 22.79, 21.62, 19.29, 14.24.

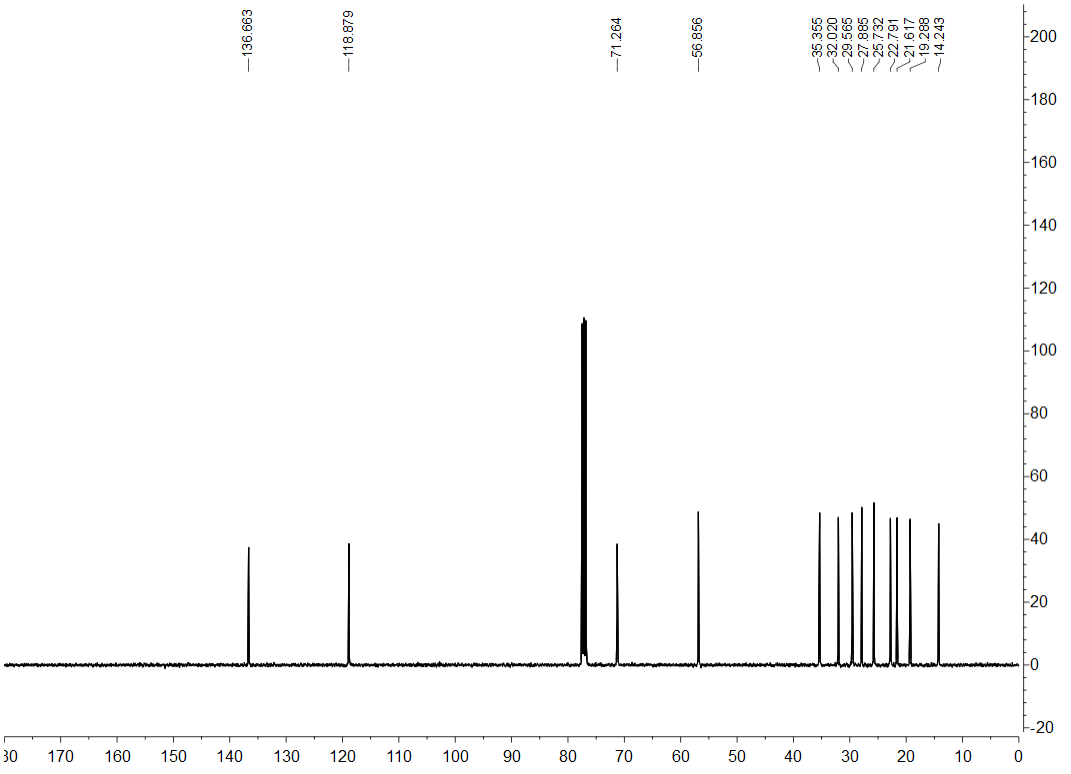
LRMS (CI) Calcd. for $C_{13}H_{26}O$ $[M+H]^+$: 199, Found: 199.

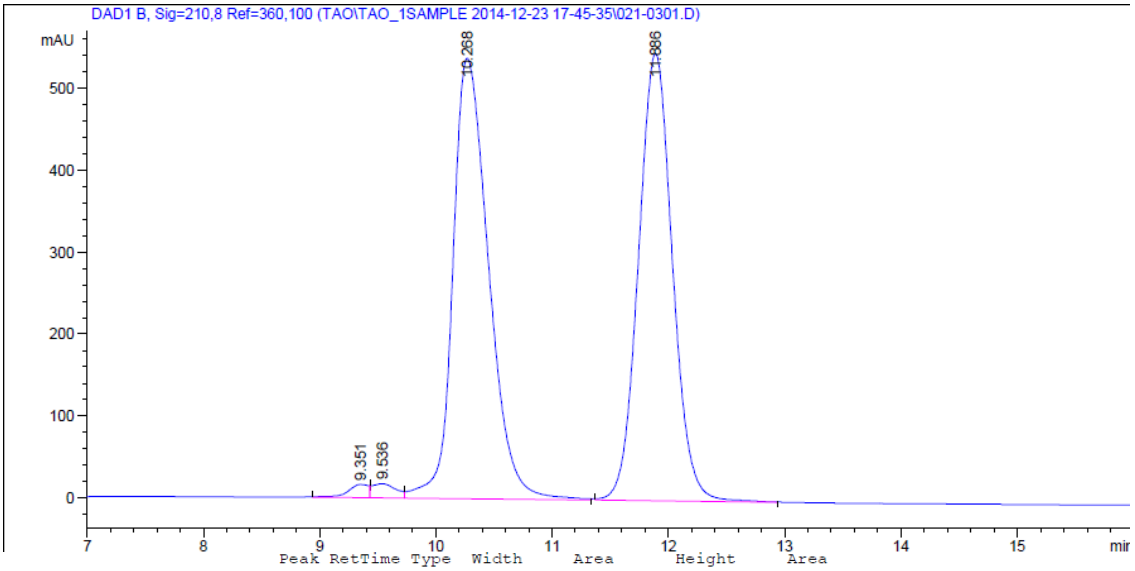
FTIR (neat): 3389, 2956, 2928, 1638, 1467, 1368, 1144, 1038, 1003, 911, 725 cm^{-1}.

HPLC Enantiomeric excess was determined by HPLC analysis of the 4-nitro-benzoate of product (Chiralcel AD-H column, hexanes:*i*-PrOH = 99:1, 0.50 mL/min, 210 nm), ee = 93%.

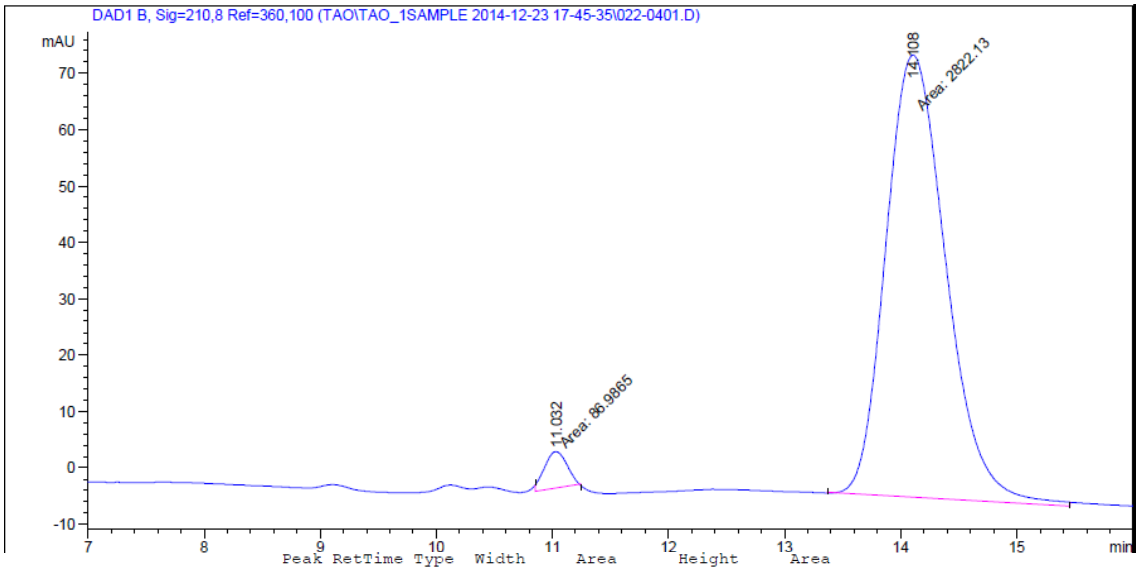
$[\alpha]^{25}_D$ = + 15.0 (c = 0.5, $CHCl_3$)


1.00
0.99
0.99
1.02
0.97
0.99
11.38
2.95
6.08


136.663
118.879
71.264
56.856
35.355
32.020
29.565
27.885
25.732
22.791
21.617
19.288
14.243

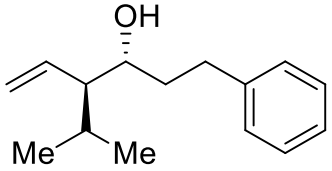


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.351	BV	0.1842	203.32397	16.22901	0.8821
2	9.536	VV	0.2064	245.42508	17.42006	1.0648
3	10.268	VB	0.3337	1.15174e4	538.02423	49.9670
4	11.886	BB	0.3168	1.10839e4	546.01355	48.0861



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.032	MM	0.2234	86.98645	6.48899	2.9901
2	14.108	MM	0.5997	2822.13110	78.42963	97.0099

(3R,4S)-4-isopropyl-1-phenylhex-5-en-3-ol (2.3k).



In modification to the general procedure, 2-PrOH was omitted and the reaction was heated at 125 ^{o}C. The residue was subjected to flash column chromatography (SiO_2, 250 mL of 1:16 Et_2O: Hexanes) to furnish the title compound (28.4 mg, 65%, *dr* = >20:1) as a yellow liquid.

R_f = 0.46 (20% EtOAc/Hexanes).

Spectral data is reported for the major isomer.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (t, *J* = 7.4 Hz, 2H), 7.24 – 7.14 (m, 3H), 5.71 (dt, *J* = 17.2, 10.0 Hz, 1H), 5.23 (dd, *J* = 10.3, 2.3 Hz, 1H), 5.09 (dd, *J* = 17.2, 2.3 Hz, 1H), 3.76 – 3.61 (m, 1H), 2.81 (ddd, *J* = 13.7, 10.1, 5.5 Hz, 1H), 2.68 (ddd, *J* = 13.7, 9.9, 6.5 Hz, 1H), 1.89 – 1.67 (m, 4H), 1.47 (d, *J* = 4.2 Hz, 1H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.83 (d, *J* = 6.6 Hz, 3H).

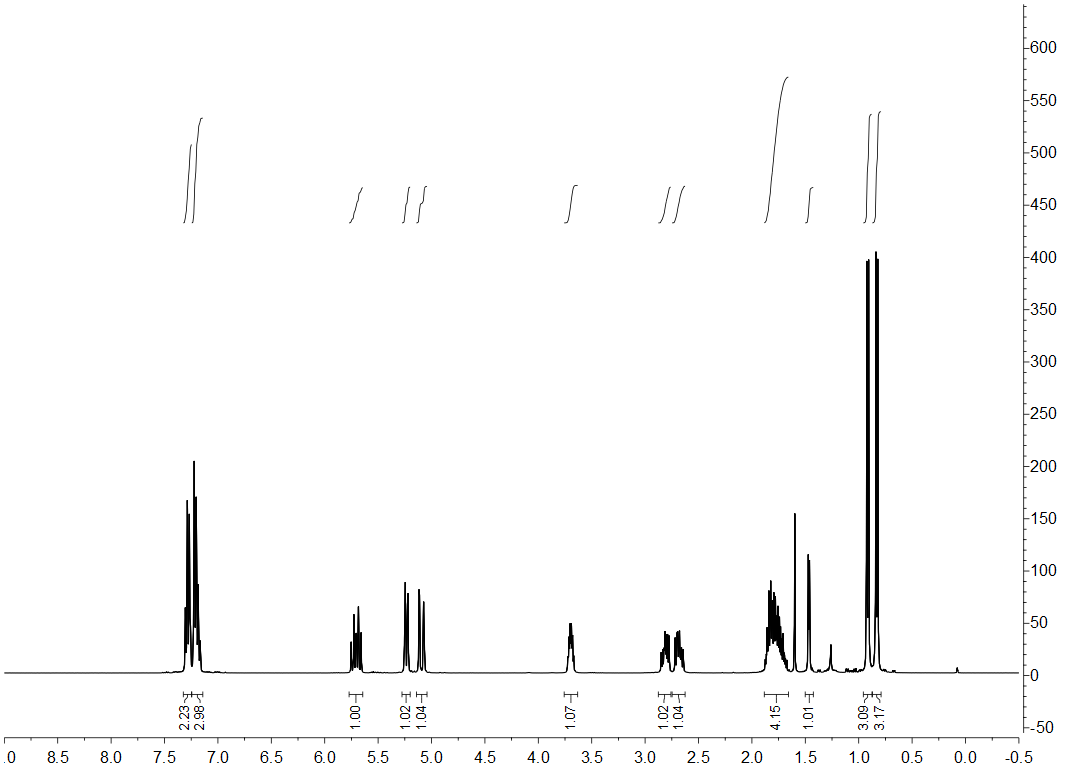
^{13}C NMR (100 MHz, $CDCl_3$): δ 142.46, 136.42, 128.58, 128.50, 125.90, 119.18, 70.72, 57.00, 37.17, 32.24, 27.89, 21.61, 19.12.

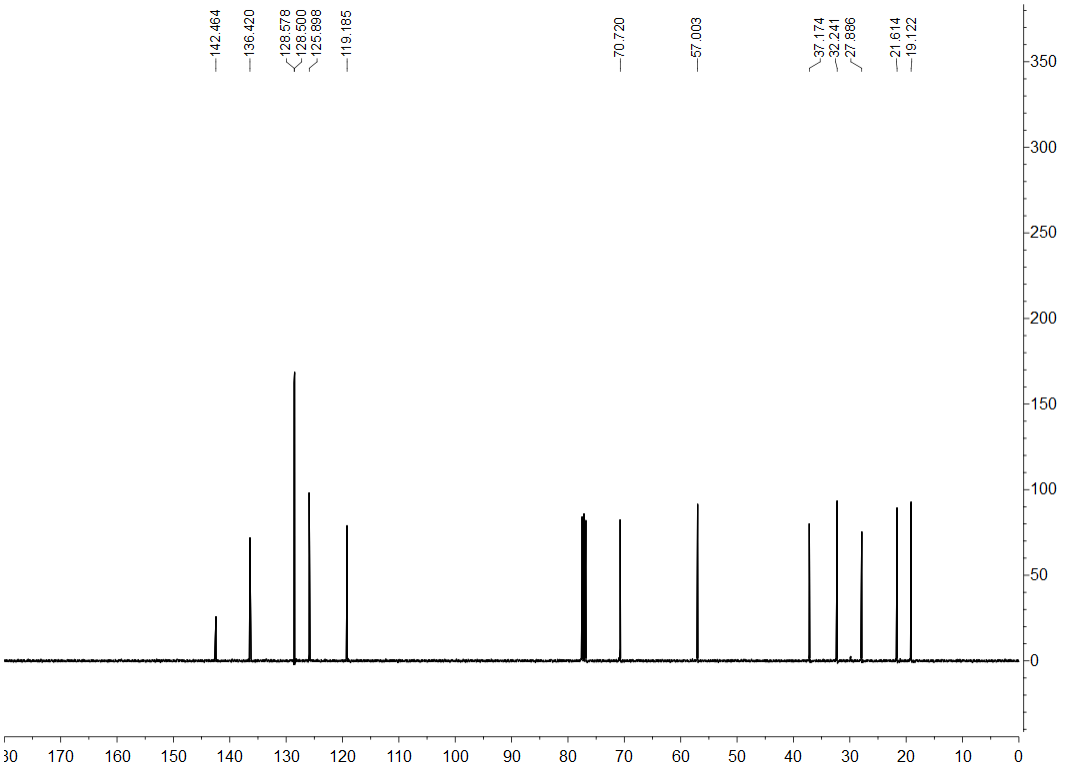
LRMS (CI) Calcd. for $C_{15}H_{22}O$ $[M\text{-}OH]^+$: 201, Found: 201.

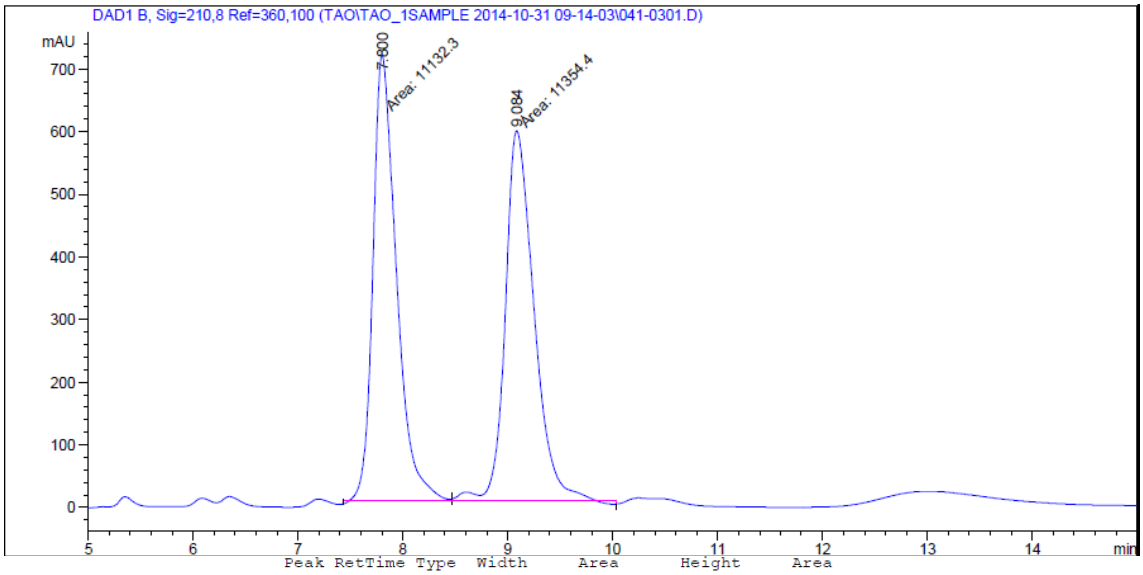
FTIR (neat): 3363, 3067, 2955, 2926, 1637, 1603, 1455, 1385, 1044, 1003, 914, 699 cm^{-1}.

HPLC (Chiralcel AD-H column, hexanes:*i*-PrOH = 99:1, 1 mL/min, 210 nm), ee = 94%.

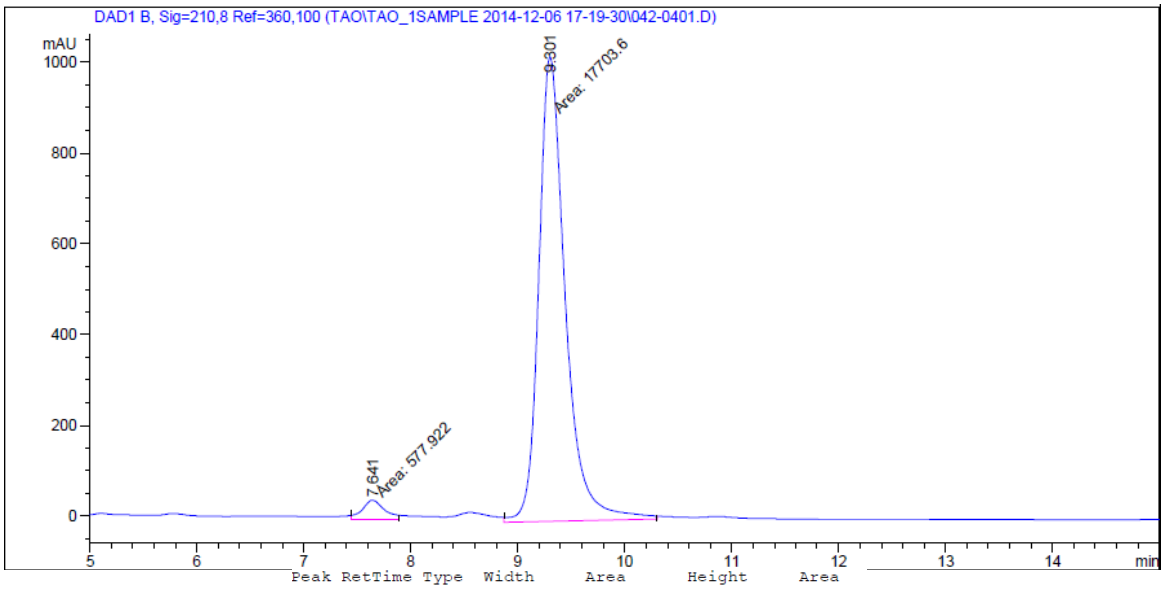
$[\alpha]^{25}_D$ = + 26.4 (c = 1.1, $CHCl_3$)


2.23
2.98
1.00
1.02
1.04
1.07
1.02
1.04
4.15
1.01
3.09
3.17


142.464
136.420
128.578
128.500
125.898
119.185
70.720
57.003
37.174
32.241
27.886
21.614
19.122

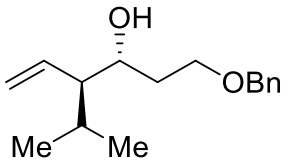


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.800	MF	0.2605	1.11323e4	712.26514	49.5063
2	9.084	FM	0.3200	1.13544e4	591.43671	50.4937



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.641	MM	0.2349	577.92224	41.00342	3.1612
2	9.301	MM	0.2883	1.77036e4	1023.32373	96.8388

(3R,4S)-1-(benzyloxy)-4-isopropylhex-5-en-3-ol (2.3l).



In modification to the general procedure, 2-PrOH was omitted and the reaction was heated at 125 ^{o}C. The residue was subjected to flash column chromatography (SiO_2, 250 mL of 1:16 Et_2O: Hexanes) to furnish the title compound (32.7 mg, 66%, *dr* = >20:1) as a yellow liquid.

R_f = 0.40 (20% EtOAc/Hexanes).

Spectral data is reported for the major isomer.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 – 7.27 (m, 5H), 5.74 (dt, *J* = 17.2, 10.1 Hz, 1H), 5.17 (dd, *J* = 10.3, 2.3 Hz, 1H), 5.00 (ddd, *J* = 17.2, 2.3, 0.7 Hz, 1H), 4.52 (s, 2H), 3.99 – 3.92 (m, 1H), 3.76 – 3.60 (m, 2H), 2.53 (d, *J* = 2.7 Hz, 1H), 1.89 – 1.73 (m, 2H), 1.71 – 1.60 (m, 2H), 0.95 (d, *J* = 6.7 Hz, 3H), 0.85 (d, *J* = 6.8 Hz, 3H).

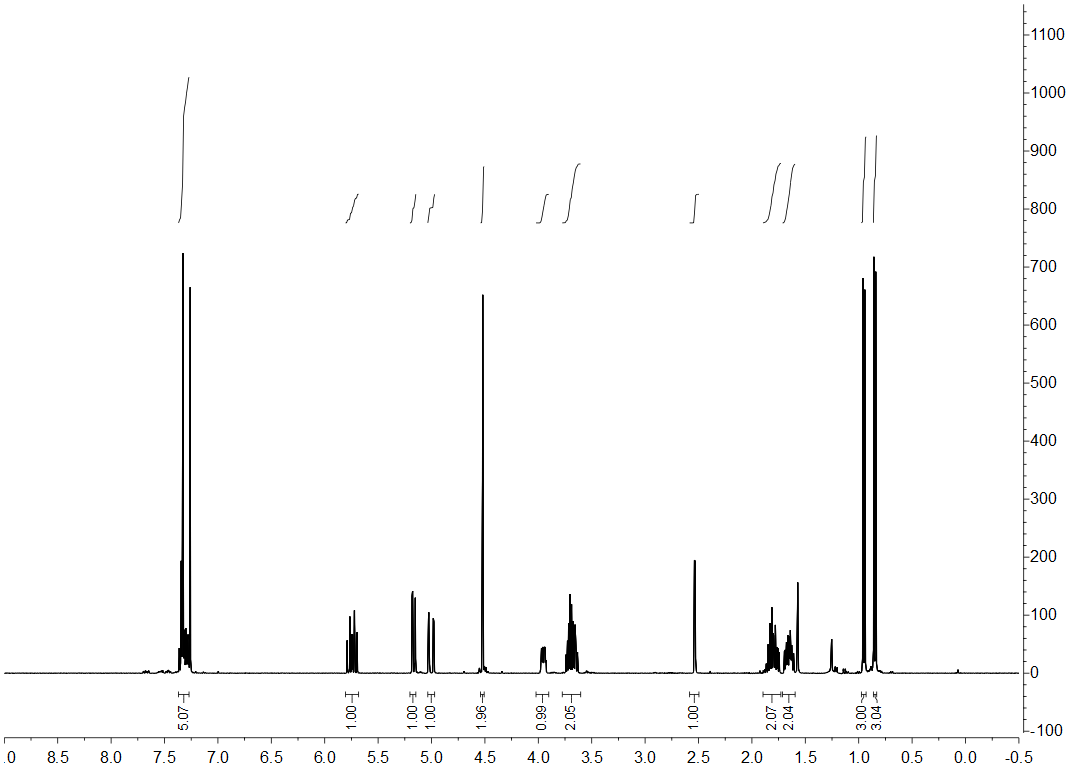
^{13}C NMR (100 MHz, $CDCl_3$): δ 138.19, 137.17, 128.57, 127.82, 118.09, 73.44, 70.76, 69.36, 57.48, 35.34, 28.01, 21.41, 19.91.

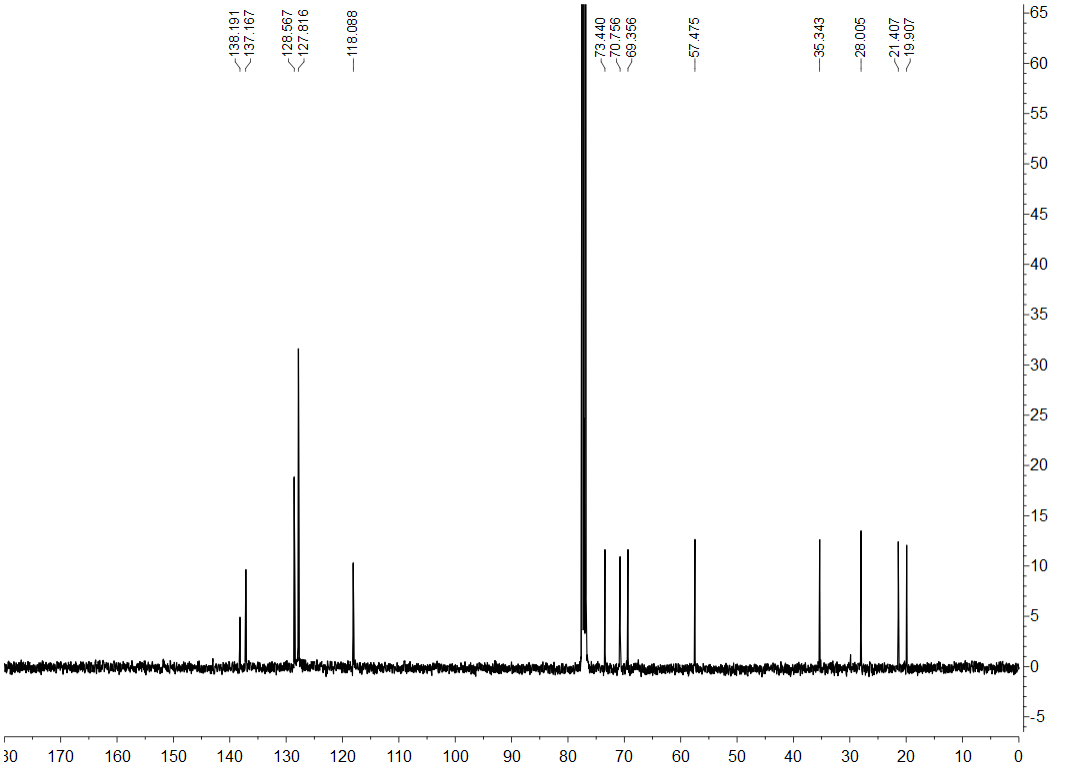
LRMS (CI) Calcd. for $C_{16}H_{24}O_2$ $[M+H]^+$: 249, Found: 249.

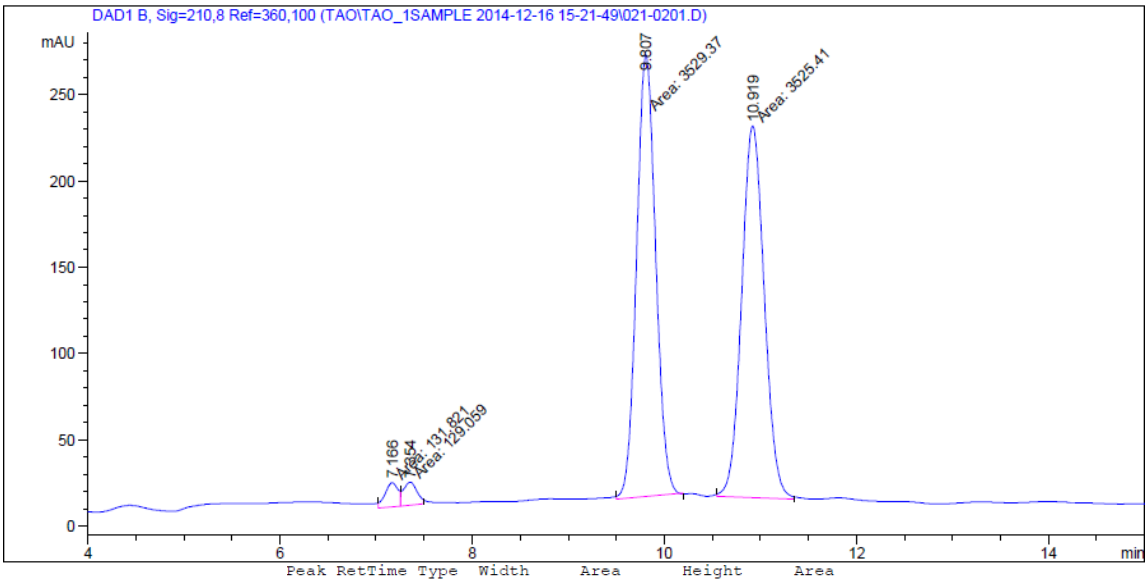
FTIR (neat): 3491, 3067, 2954, 2926, 1496, 1386, 1095, 1028, 913, 737, 697 cm^{-1}.

HPLC (Chiralcel OD-H column, hexanes:*i*-PrOH = 99:1, 1 mL/min, 210 nm), ee = 96%.

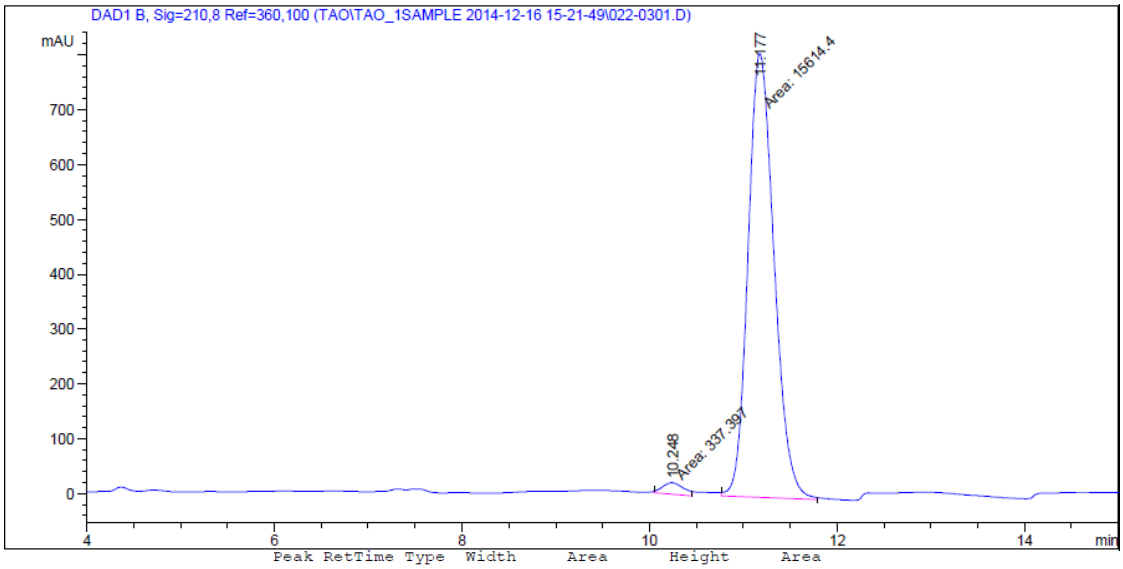
$[\alpha]^{25}_D$ = + 21.6 (c = 0.5, $CHCl_3$)


5.07
1.00
1.00
1.00
1.96
0.99
2.05
1.00
2.07
2.04
3.00
3.04


138.191
137.167
128.567
127.816
118.088
73.440
70.756
69.356
57.475
35.343
28.005
21.407
19.907

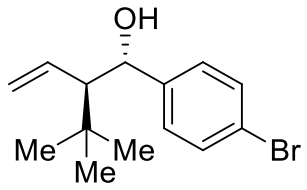


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.166	MF	0.1585	131.82112	13.86100	1.8019
2	7.354	FM	0.1605	129.05884	13.39918	1.7641
3	9.807	MM	0.2298	3529.37378	255.92351	48.2441
4	10.919	MM	0.2727	3525.40820	215.44110	48.1899



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.248	MM	0.2650	337.39709	21.21904	2.1151
2	11.177	MM	0.3217	1.56144e4	808.87964	97.8849

(1S,2R)-1-(4-bromophenyl)-2-(tert-butyl)but-3-en-1-ol (2.3m).



The residue was subjected to flash column chromatography for purification (SiO_2, 200 mL of 10% EtOAc/Hexanes) to furnish the title compound (42.5 mg, 75%, *dr* = >20:1) as a pale white solid.

R_f = 0.49 (20% EtOAc/Hexanes).

Spectral data is reported for the major isomer.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 – 7.40 (m, 2H), 7.16 – 7.11 (m, 2H), 5.89 (dt, *J* = 17.2, 10.2 Hz, 1H), 5.10 (dd, *J* = 10.3, 2.3 Hz, 1H), 5.05 – 5.01 (m, 1H), 4.65 (dd, *J* = 17.2, 2.2 Hz, 1H), 1.90 (dd, *J* = 10.1, 2.6 Hz, 1H), 1.74 (d, *J* = 4.2 Hz, 1H), 1.00 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 144.5, 133.8, 131.2, 128.0, 120.8, 119.7, 72.9, 62.3, 33.2, 28.9.

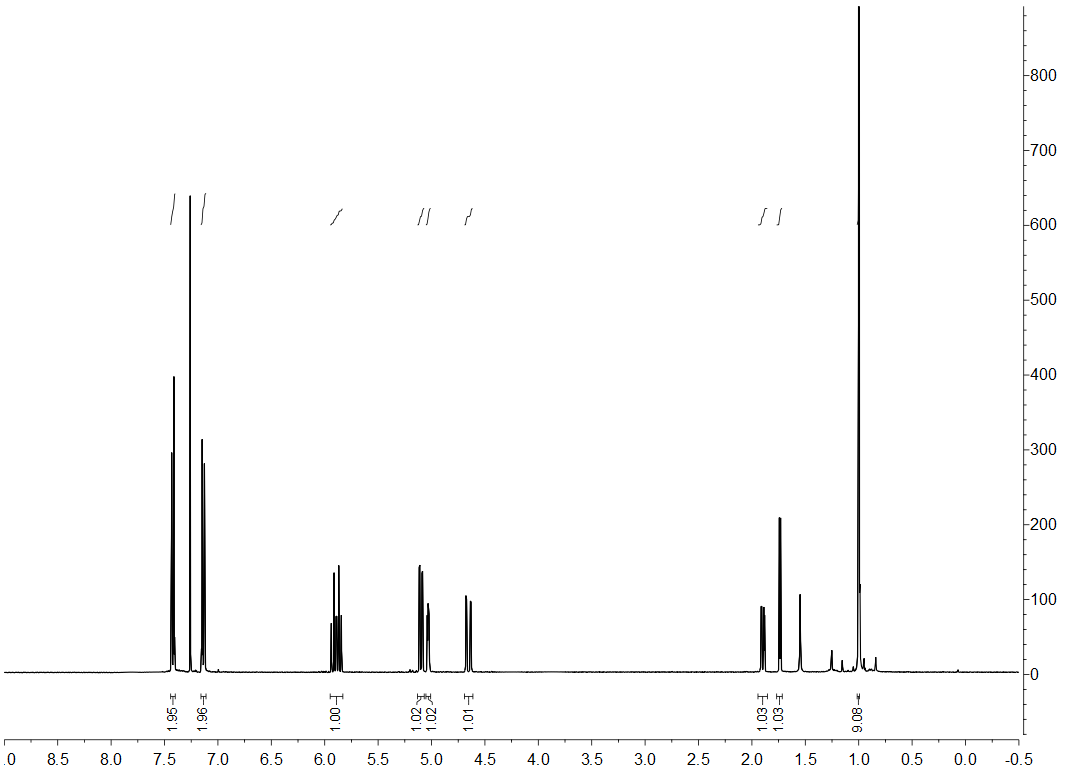
LRMS (CI) Calcd. for C14H19BrO $[M+H]^+$: 283/285, Found: 283/285.

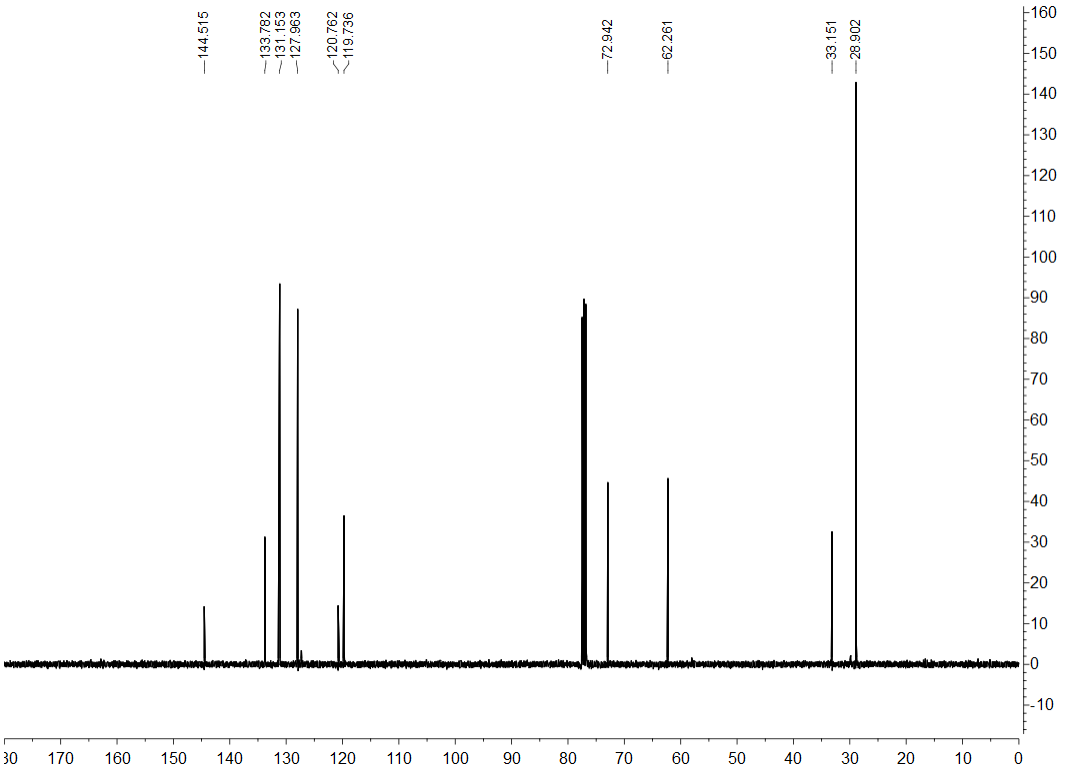
FTIR (neat): 3459, 3073, 2955, 2905, 1636, 1592, 1487, 1366, 1230, 1072, 1010, 917, 776 cm^{-1}.

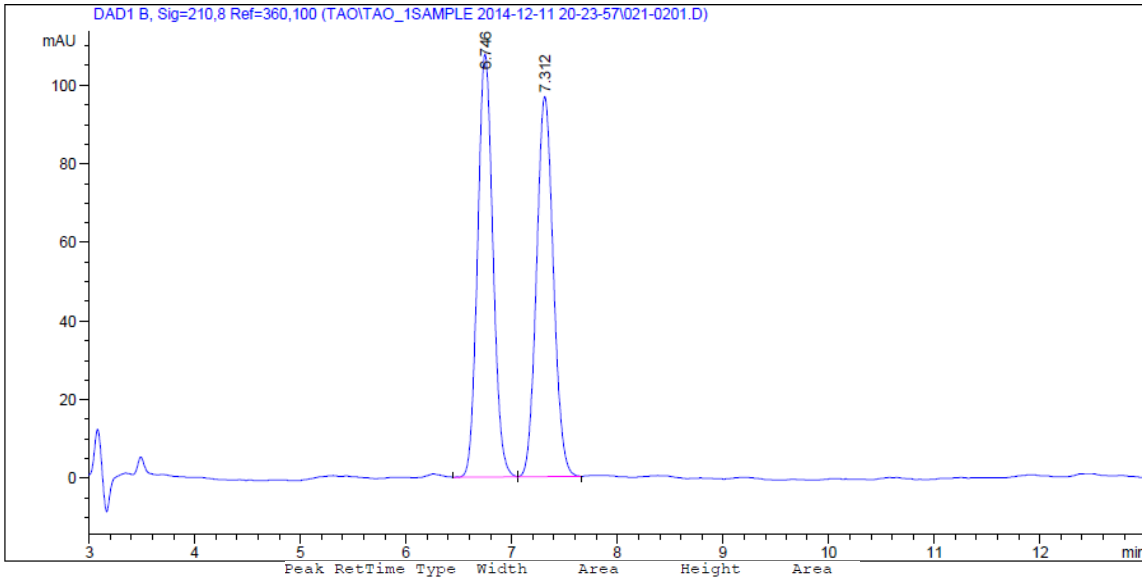
MP 55.6-56.2 ˚C

HPLC (Chiralcel OD-H column, hexanes:*i*-PrOH = 95:5, 1 mL/min, 210 nm), ee = 94%.

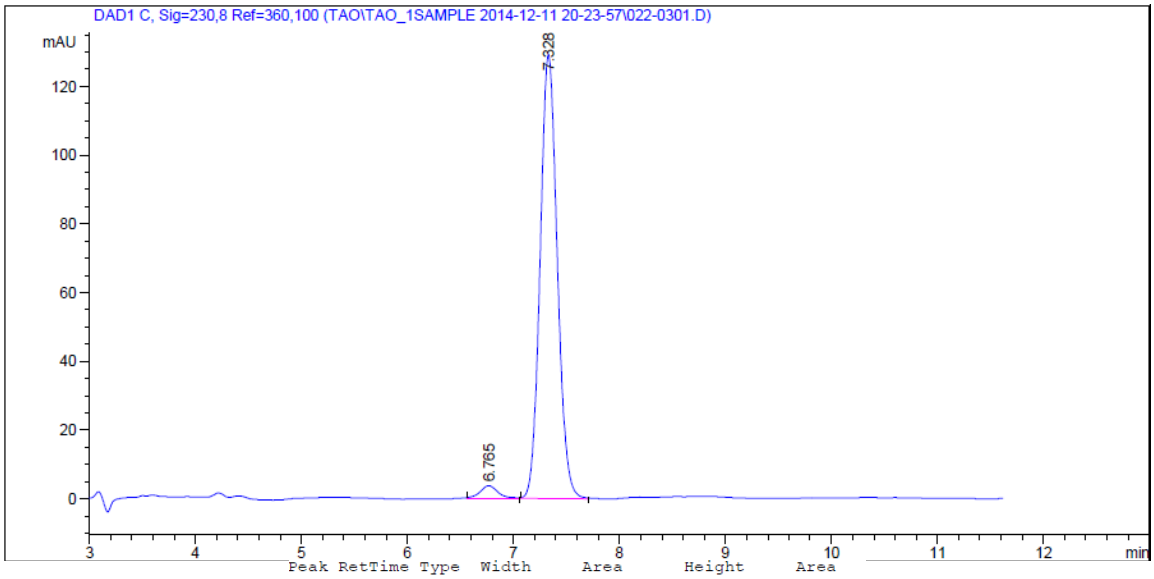
$[\alpha]^{25}_D$ = -10.5 (c = 0.5, $CHCl_3$)


1.95
1.96
1.00
1.02
1.02
1.01
1.03
1.03
9.08


144.515
133.782
131.153
127.963
120.762
119.736
72.942
62.261
33.151
28.902

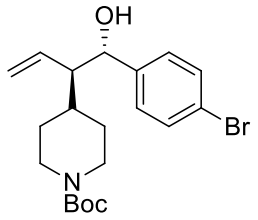


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.746	VV	0.1560	1089.00806	107.66858	50.3218
2	7.312	VB	0.1718	1075.08191	96.65478	49.6782



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.765	BB	0.1788	43.82901	3.73701	2.9257
2	7.328	BB	0.1755	1454.21802	129.04500	97.0743

tert-butyl 4-((1S,2R)-1-(4-bromophenyl)-1-hydroxybut-3-en-2-yl)piperidine-1-carboxylate (2.3n).



In modification to the general procedure, the reaction was extended for 72 hours. The residue was subjected to flash column chromatography (SiO_2, 200 mL of 30% Et_2O/Hexanes followed by 150 mL of 40% Et_2O/Hexanes) to furnish the title compound (53.3 mg, 65%, *dr* = >20:1) as a yellow liquid.

R_f = 0.30 (50% Et_2O/Hexanes).

Spectral data is reported for the major isomer.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 – 7.44 (m, 2H), 7.20 – 7.15 (m, 2H), 5.73 (dt, *J* = 17.1, 10.1 Hz, 1H), 5.22 (dd, *J* = 10.3, 1.7 Hz, 1H), 4.99 (d, *J* = 17.5 Hz, 1H), 4.72 (dd, *J* = 6.7, 2.5 Hz, 1H), 4.07 (s, 2H), 2.63 – 2.41 (m, 2H), 2.11 – 2.03 (m, 2H), 1.63 – 1.13 (m, 14H).

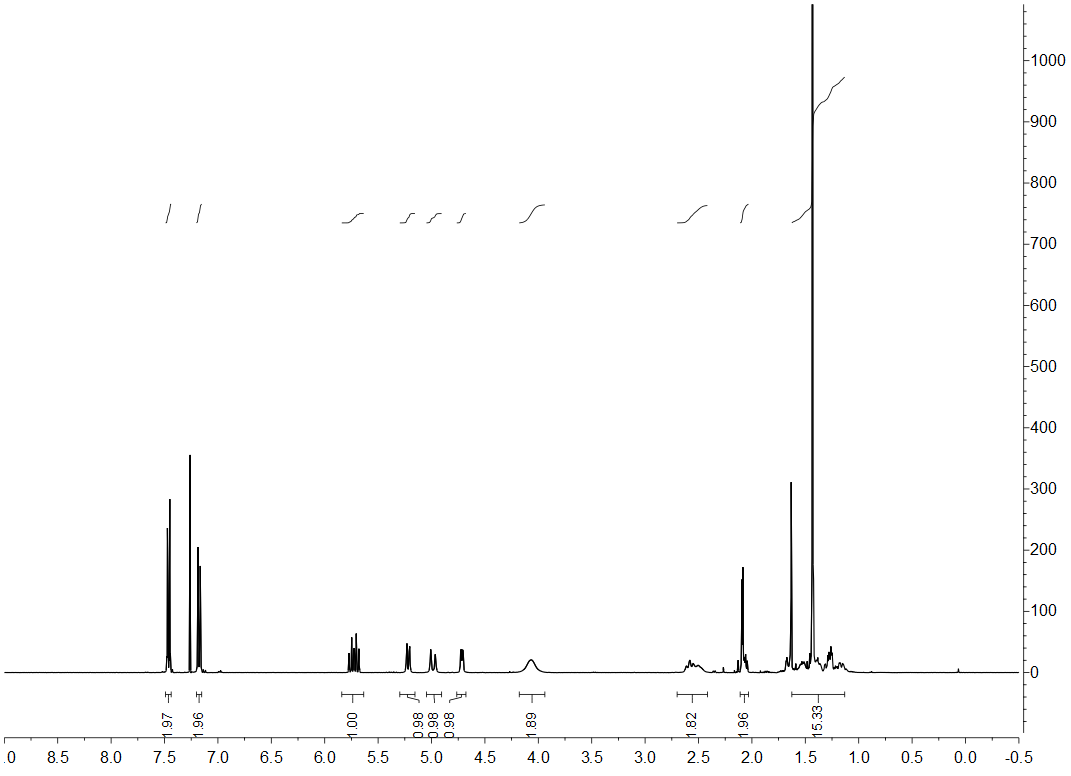
^{13}C NMR (100 MHz, $CDCl_3$): δ 154.88, 142.07, 135.24, 131.56, 128.41, 121.51, 120.53, 79.47, 73.19, 57.80, 36.50, 34.82, 28.59, 25.43.

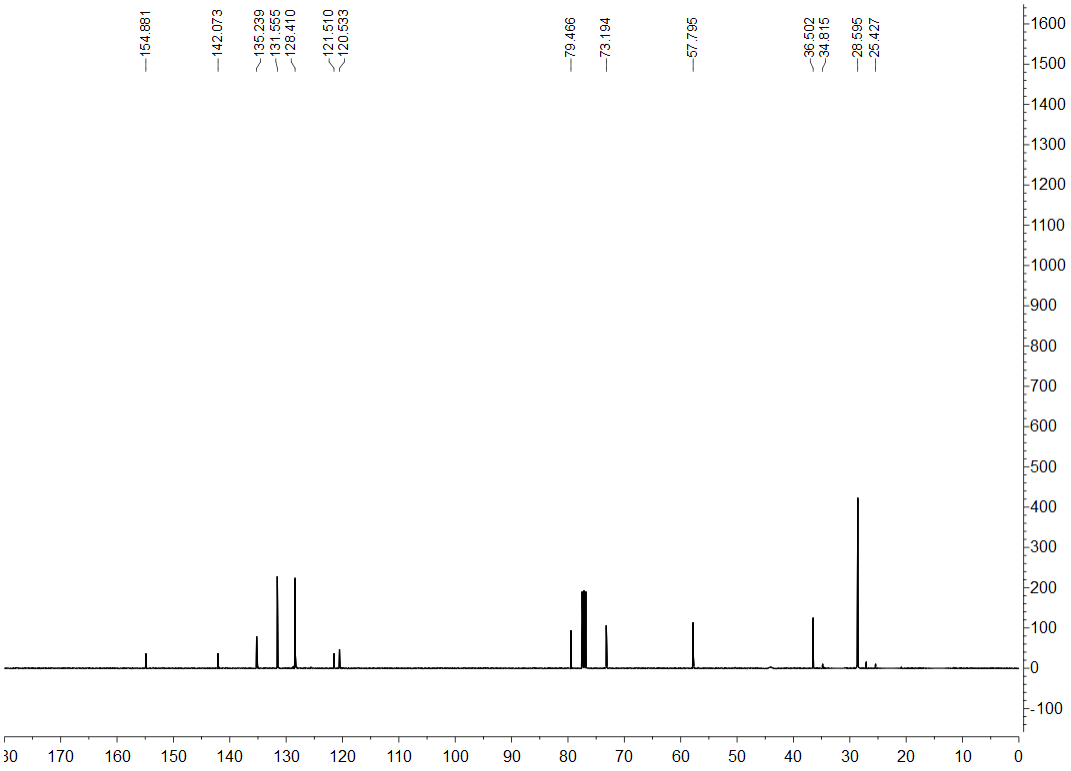
LRMS (ESI) Calcd. for $C_{20}H_{28}BrNO_3$ $[M+Na]^+$: 434, Found: 434.

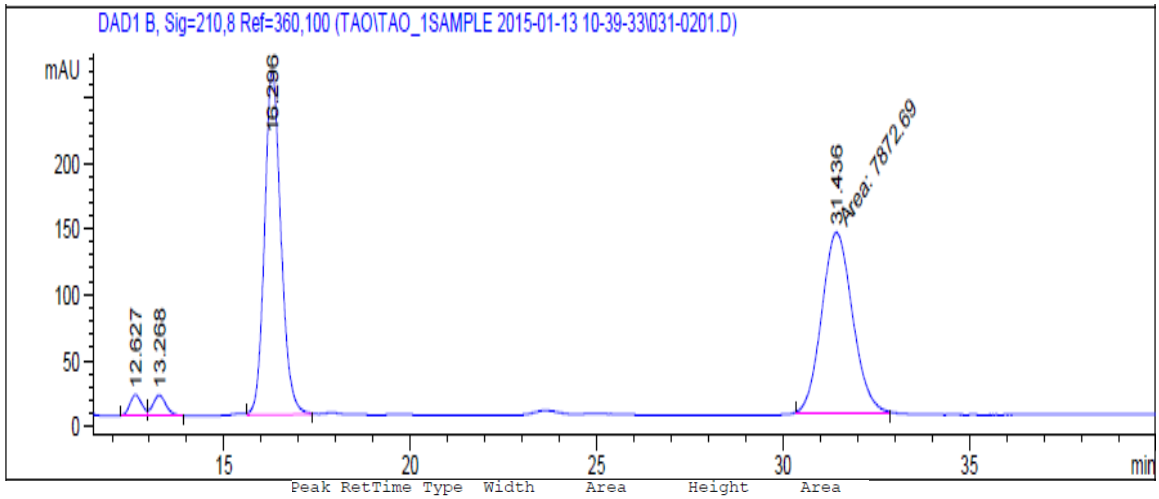
FTIR (neat): 3424, 2976, 2930, 1667, 1485, 1428, 1366, 1166, 1071, 751 cm^{-1}.

HPLC (Chiralcel AD-H column, hexanes:*i*-PrOH = 95:5, 1 mL/min, 210 nm), ee = 90%.

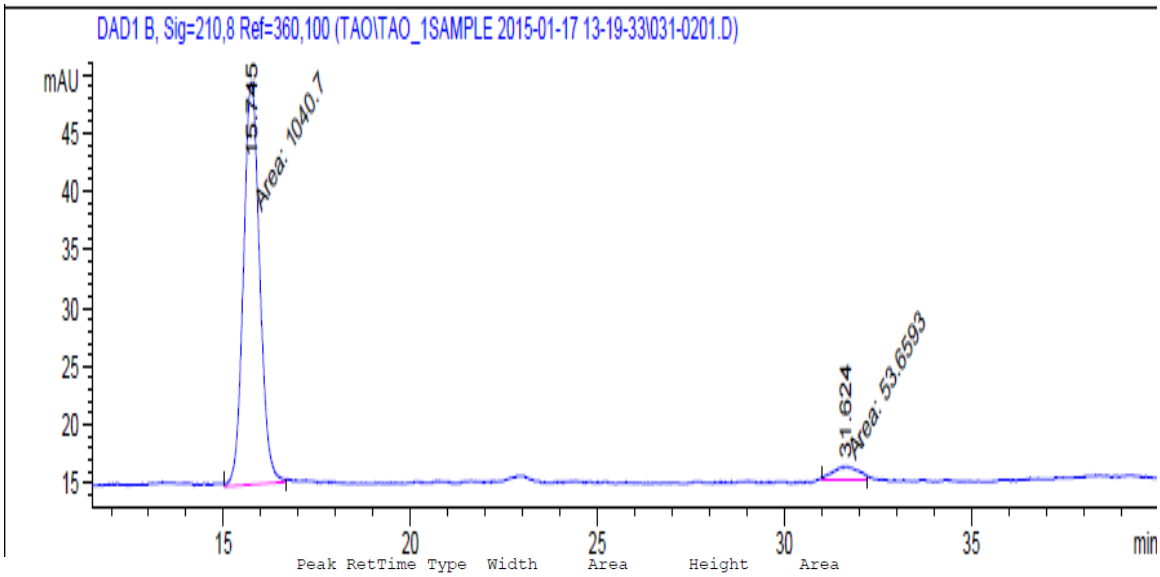
$[\alpha]^{25}_D$ = - 5.66 (c = 0.5, $CHCl_3$)


1.97
1.96
1.00
0.98
0.98
0.98
1.89
1.82
1.96
15.33


154.881
142.073
135.239
131.555
128.410
121.510
120.533
79.466
73.194
57.795
36.502
34.815
28.595
25.427

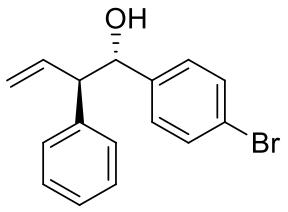


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.627	BV	0.3425	358.53976	16.18220	2.1605
2	13.268	VB	0.3656	381.12958	15.46133	2.2966
3	16.296	BB	0.4708	7982.87793	261.05267	48.1034
4	31.436	MM	0.9598	7872.69043	136.71358	47.4395



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.745	MM	0.5031	1040.70325	34.47526	95.0968
2	31.624	MM	0.8027	53.65927	1.11415	4.9032

(1S,2R)-1-(4-bromophenyl)-2-phenylbut-3-en-1-ol (2.3o).



In modification to the general procedure, the reaction was heated at 75 ^{o}C for 72 hours. The residue was subjected to flash column chromatography (SiO_2, 300 mL of 5% EtOAc/Hexanes) to furnish the title compound (40.6 mg, 67%, *dr* = >20:1) as a yellow liquid.

R_f = 0.56 (20% EtOAc/Hexanes).

Spectral data is reported for the major isomer.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 – 7.29 (m, 2H), 7.25 – 7.14 (m, 3H), 7.06 – 6.98 (m, 4H), 6.27 – 6.18 (m, 1H), 5.36 – 5.18 (m, 2H), 4.80 (d, *J* = 7.9 Hz, 1H), 3.47 (t, *J* = 8.4 Hz, 1H), 2.35 (s, 1H).

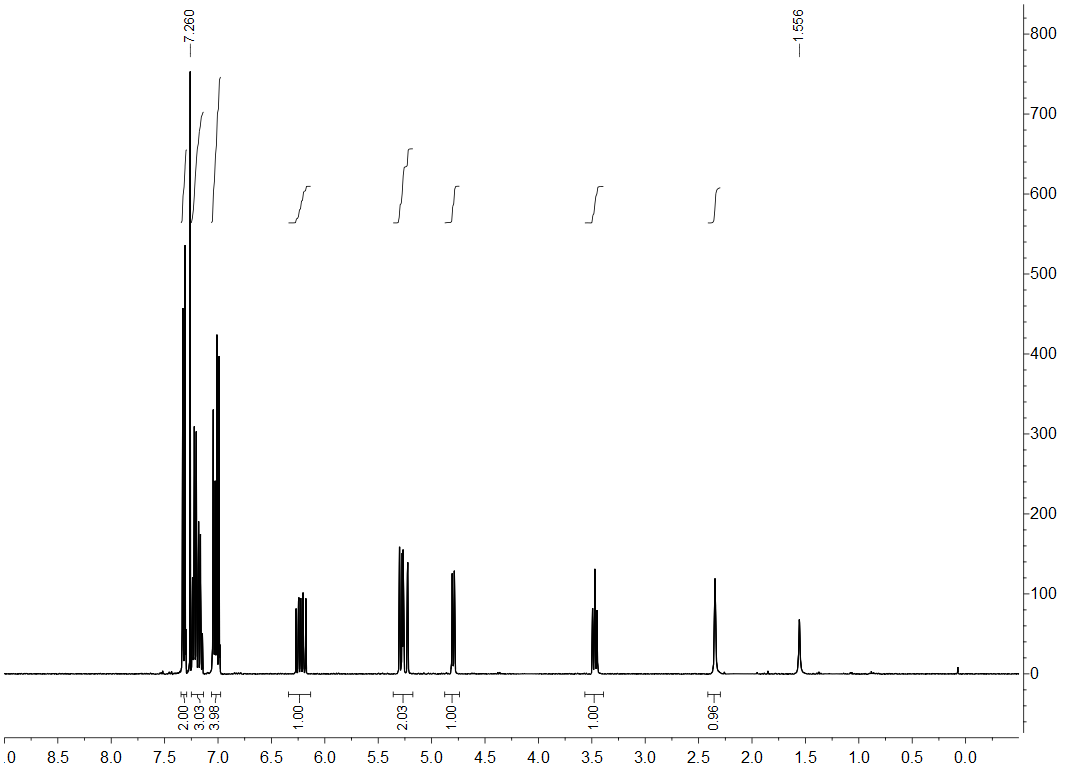
^{13}C NMR (100 MHz, $CDCl_3$): δ 140.9, 140.3, 137.6, 131.1, 128.7, 128.5, 128.4, 127.0, 121.4, 119.0, 76.7, 59.5.

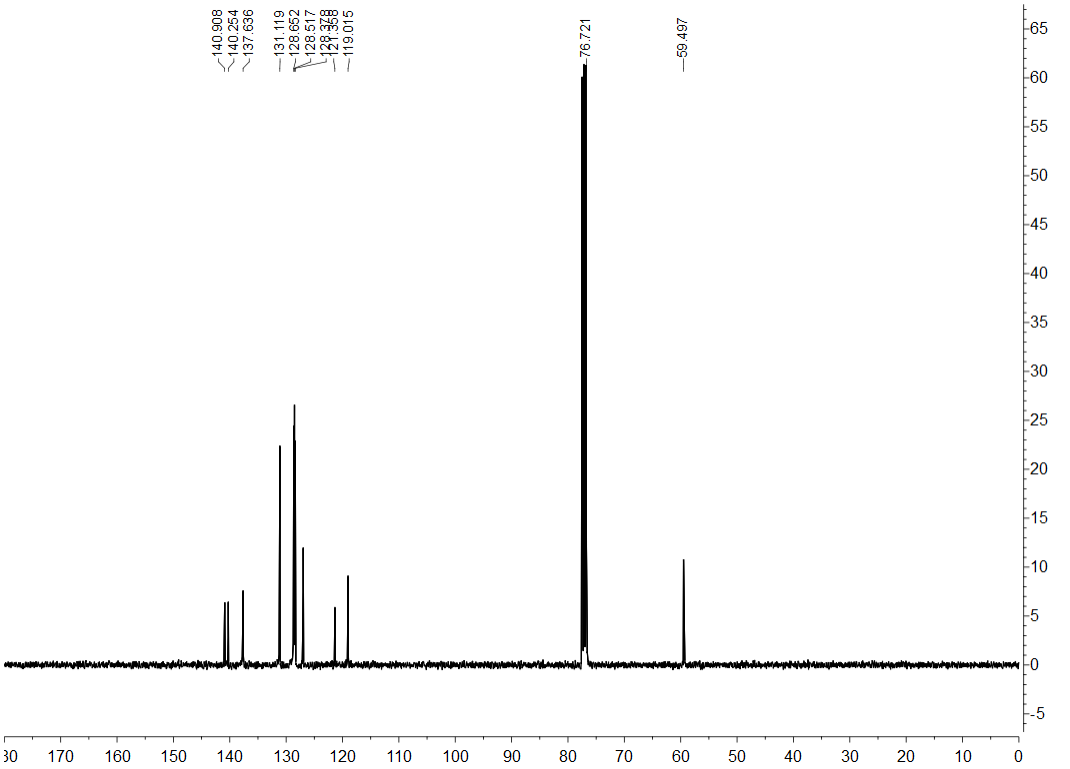
LRMS (CI) Calcd. for $C_{16}H_{15}BrO$ $[M+H]^+$: 303/305, Found: 303/305.

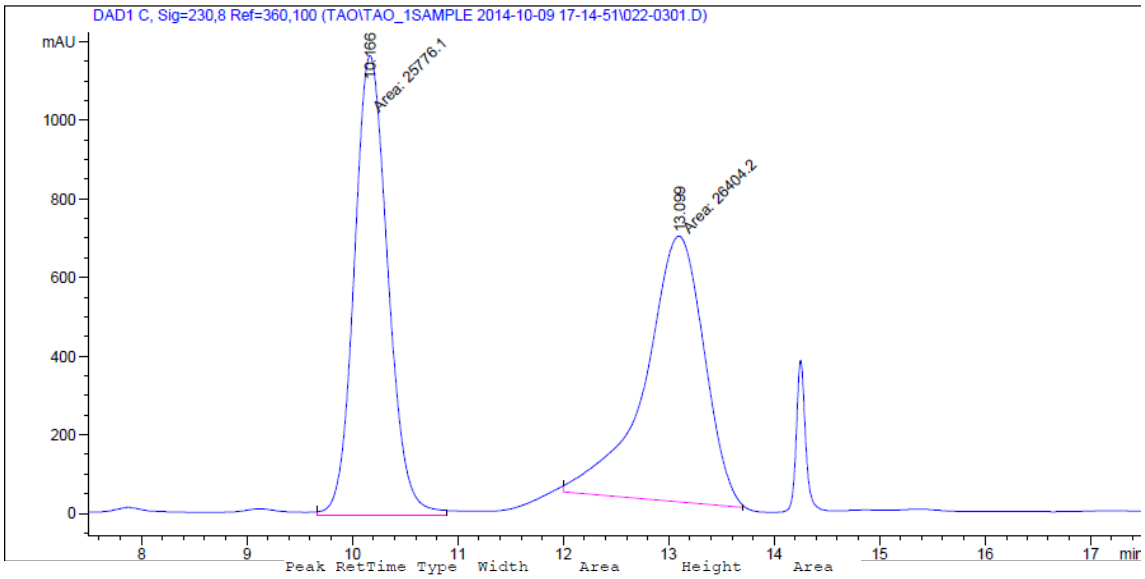
FTIR (neat): 3402, 3082, 2974, 2904, 1636, 1559, 1405, 1226, 1071, 1010, 819, 700 cm^{-1}.

HPLC (Chiralcel OD-H column, hexanes:*i*-PrOH = 95:5, 1 mL/min, 210 nm), ee = 86%.

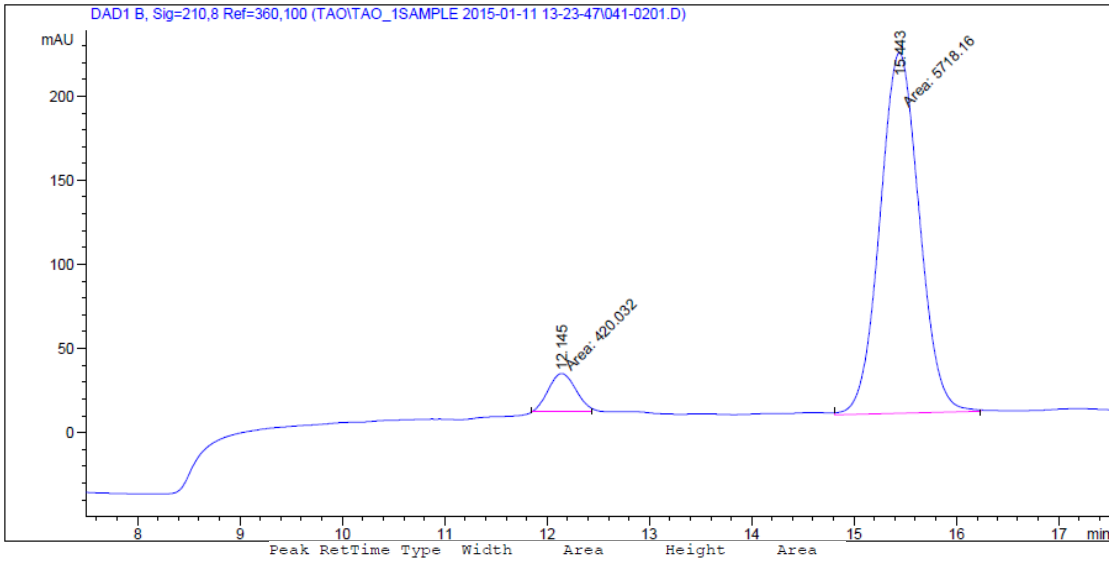
$[\alpha]^{25}_D$ = +19.8 (c = 0.5, $CHCl_3$)


7.260
1.556
2.00
3.03
3.98
1.00
2.03
1.00
1.00
0.96


140.908
140.254
137.636
131.119
128.652
128.517
119.015
76.721
59.497

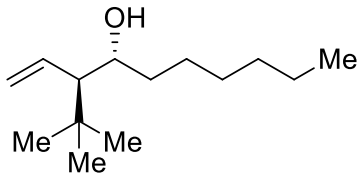


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.166	MM	0.3681	2.57761e4	1167.06567	49.3981
2	13.099	MM	0.6516	2.64042e4	675.38287	50.6019



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.145	MM	0.3095	420.03214	22.61896	6.8429
2	15.443	MM	0.4445	5718.16113	214.40942	93.1571

(3R,4R)-3-(tert-butyl)dec-1-en-4-ol (2.3p).



In modification to the general procedure, 2-PrOH was omitted and the reaction was heated for 72 hours, concentrated *in vacuo*. The residue was subjected to flash column chromatography (SiO_2, 250 mL of 1:9 Et_2O: Hexanes) to furnish the title compound (25.9 mg, 61%, *dr* = >20:1) as a pale yellow liquid.

R_f = 0.50 (1:5 of Et_2O: Hexanes).

Spectral data is reported for the major isomer.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.85 (dt, *J* = 17.2, 10.2 Hz, 1H), 5.19 (dd, *J* = 10.3, 2.5 Hz, 1H), 4.99 (dd, *J* = 17.2, 2.5 Hz, 1H), 3.89 (s, 1H), 1.65 (dd, *J* = 10.2, 0.8 Hz, 1H), 1.45 – 1.23 (m, 10H), 1.09 – 1.00 (m, 1H), 0.95 (s, 9H), 0.88 (t, *J* = 6.8 Hz, 3H).

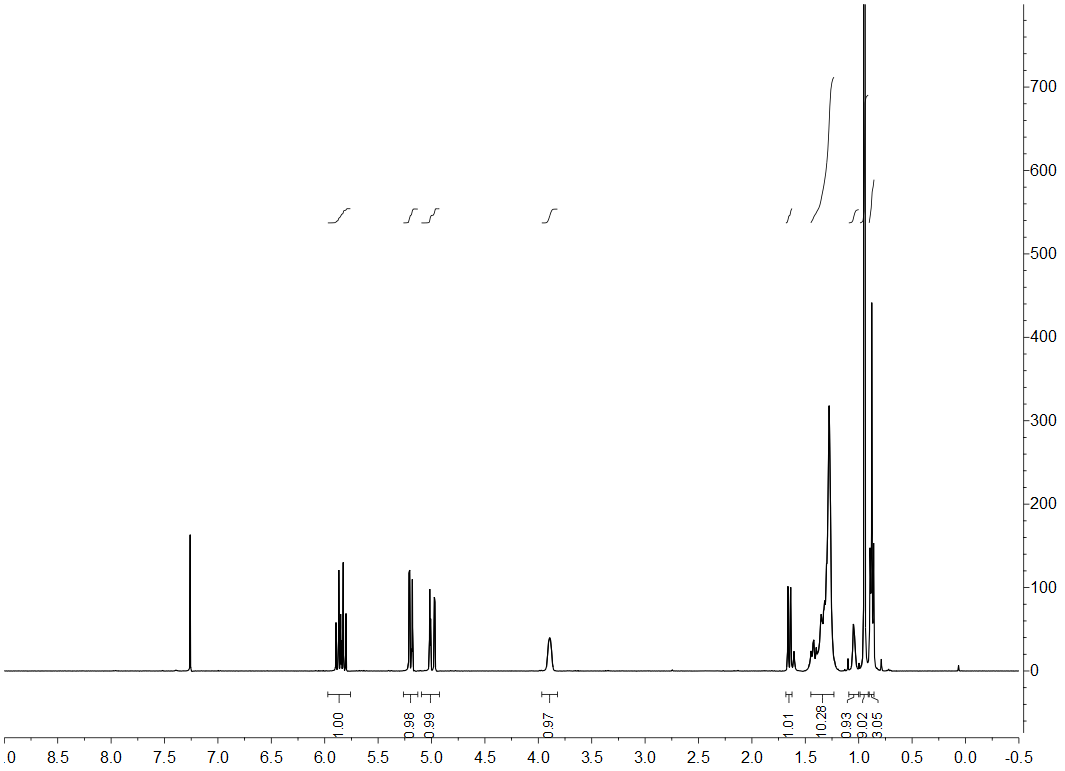
^{13}C NMR (100 MHz, $CDCl_3$): δ 135.4, 118.7, 71.0, 59.2, 37.9, 32.8, 32.0, 29.4, 28.7, 26.1, 22.8, 14.2.

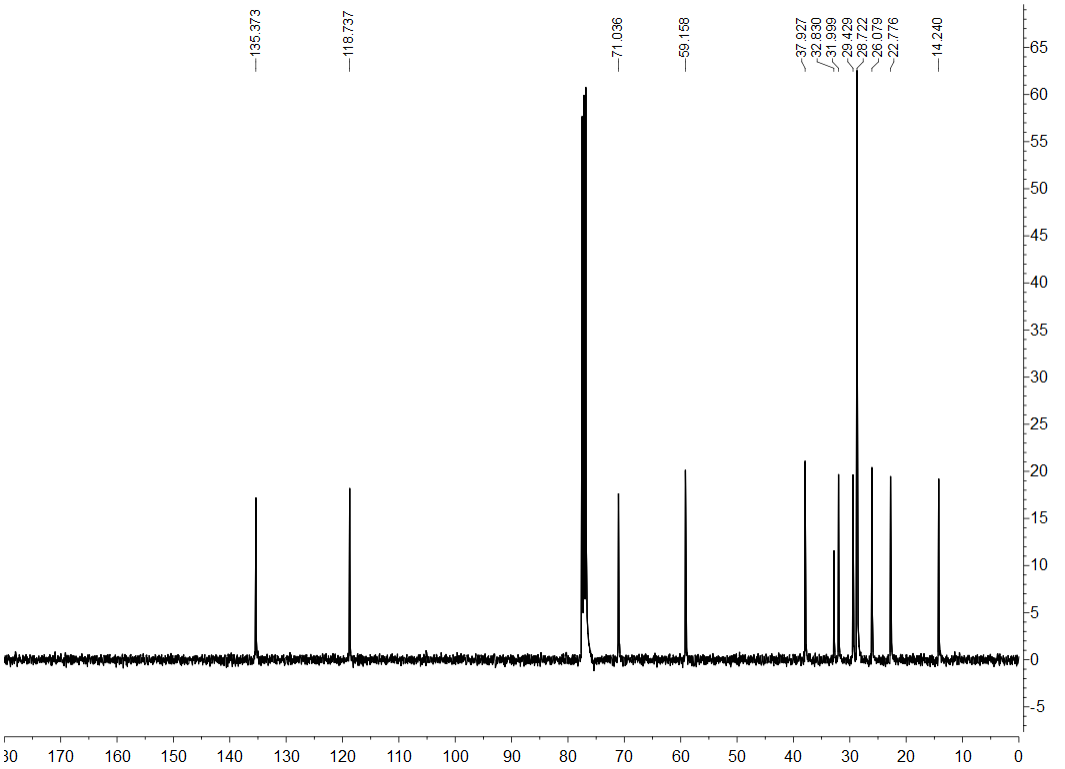
LRMS (ESI) Calcd. for $C_{14}H_{28}O$ $[M+H]^+$: 213, Found: 213.

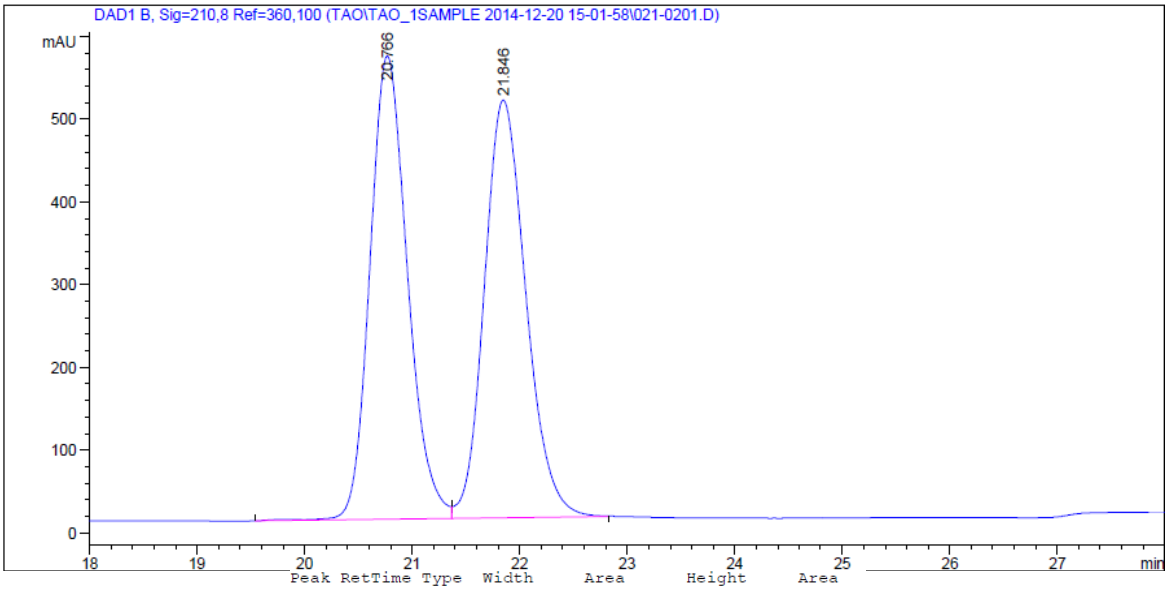
FTIR (neat): 3415, 2954, 2930, 2858, 1637, 1466, 1364, 1006, 913, 727 cm^{-1}.

HPLC Enantiomeric excess was determined by HPLC analysis of the 4-nitro-benzoate of product (Chiralcel OD-H column, hexanes:*i*-PrOH = 99:1, 0.50 mL/min, 210 nm), ee = 90%.

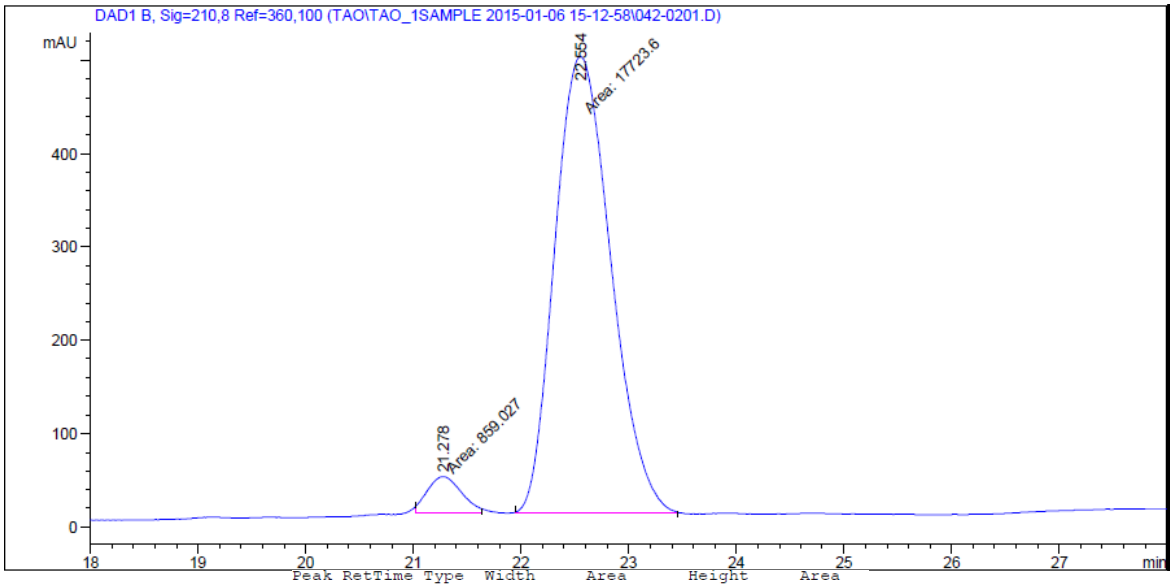
$[\alpha]^{25}_D$ = +21.8 (c = 0.57, $CHCl_3$)


1.00
0.98
0.99
0.97
1.01
10.28
0.93
9.02
3.05


135.373
118.737
71.036
59.158
37.927
32.830
31.999
29.429
28.722
26.079
22.776
14.240

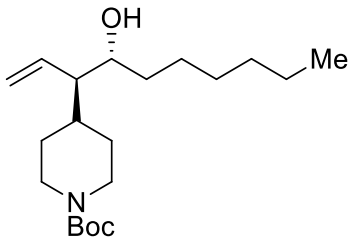


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.766	BV	0.3755	1.36185e4	560.37512	50.0198
2	21.846	VB	0.4142	1.36076e4	505.27417	49.9802



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.278	MM	0.3661	859.02740	39.10651	4.6228
2	22.554	MM	0.6037	1.77236e4	489.30823	95.3772

tert-butyl 4-((3R,4R)-4-hydroxydec-1-en-3-yl)piperidine-1-carboxylate (2.3q).



In modification to the general procedure, the loading of Ruthenium catalyst was 7.5%. The reaction was omitted 2-PrOH and heated for 48 hours, concentrated *in vacuo*. The residue was subjected to flash column chromatography (SiO_2, 200 mL of 30% Et_2O/Hexanes followed by 150 mL of 40% Et_2O/Hexanes) to furnish the title compound (46.1 mg, 68%, *dr* = >20:1) as a yellow oil.

R_f = 0.33 (50% Et_2O/Hexanes).

Spectral data is reported for the major isomer.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.68 (dt, *J* = 17.2, 10.1 Hz, 1H), 5.20 (dd, *J* = 10.3, 2.2 Hz, 1H), 5.03 (dd, *J* = 17.2, 2.2 Hz, 1H), 4.09 (s, 2H), 3.73 (dd, *J* = 10.0, 5.9 Hz, 1H), 2.78 – 2.57 (m, 2H), 1.82 – 1.60 (m, 4H), 1.46 – 1.07 (m, 22H), 0.88 (t, *J* = 6.9 Hz, 3H).

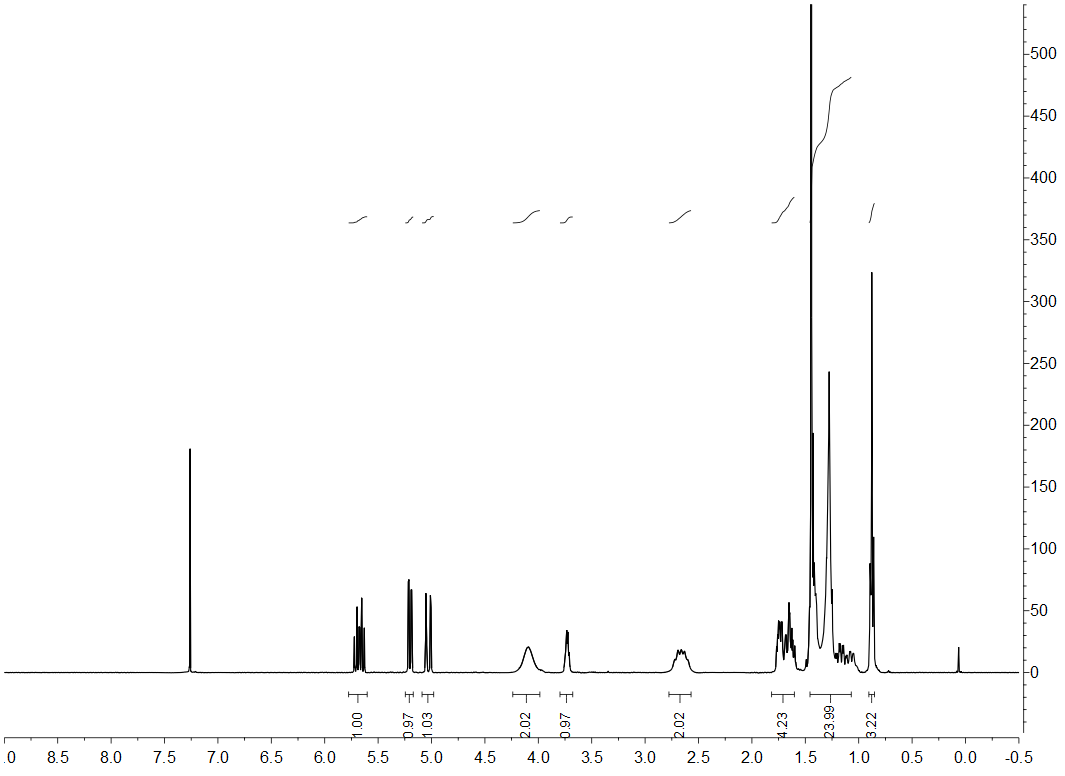
^{13}C NMR (100 MHz, $CDCl_3$): δ 154.9, 136.1, 119.0, 79.4, 70.4, 55.1, 36.2, 35.9, 32.0, 30.5, 30.0, 29.5, 28.6, 26.3, 25.9, 25.3, 22.8, 14.2.

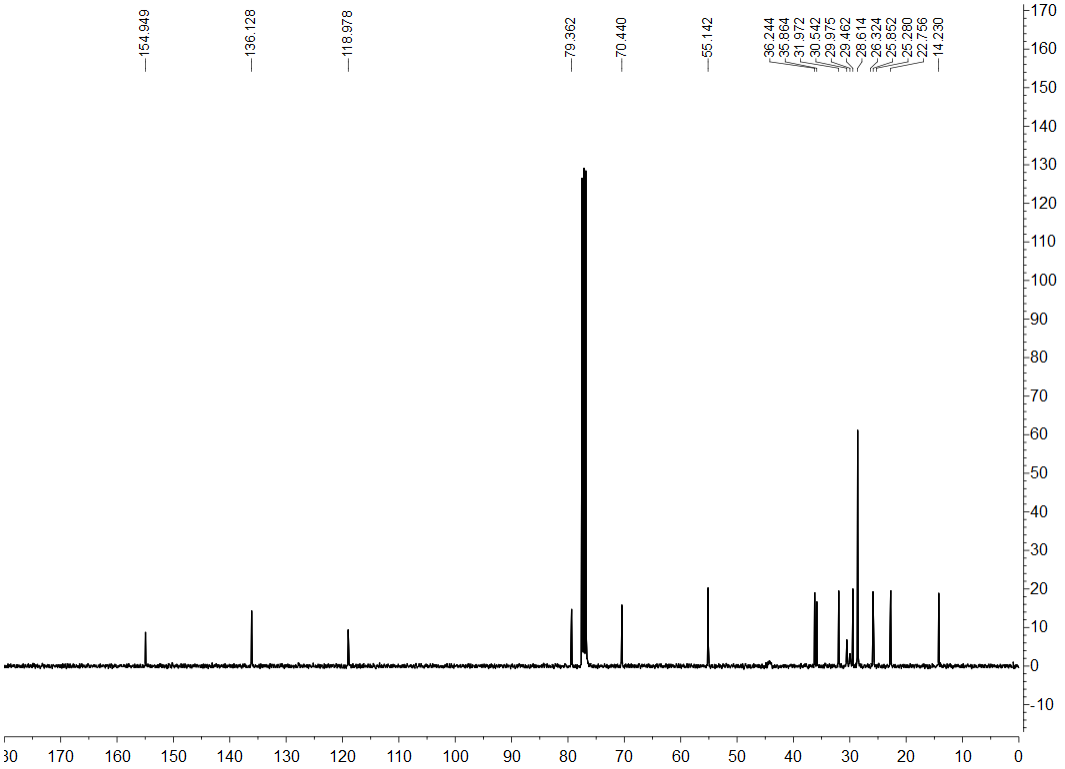
LRMS (ESI) Calcd. for $C_{20}H_{37}NO_3$ $[M+Na]^+$: 362, Found: 362.

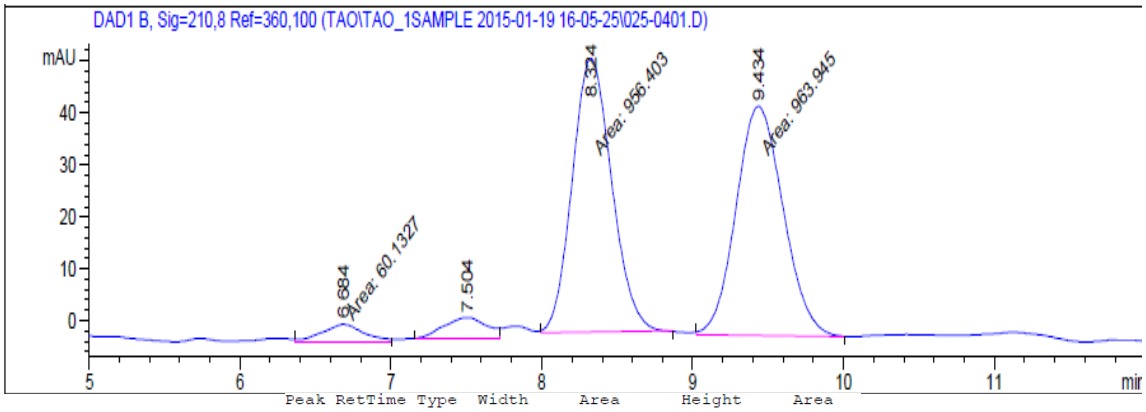
FTIR (neat): 3471, 2952, 2853, 1673, 1427, 1366, 1172, 1073, 911, 669 cm^{-1}.

HPLC (Chiralcel OD-H column, hexanes:*i*-PrOH = 97:3, 1 mL/min, 210 nm), ee = 96%.

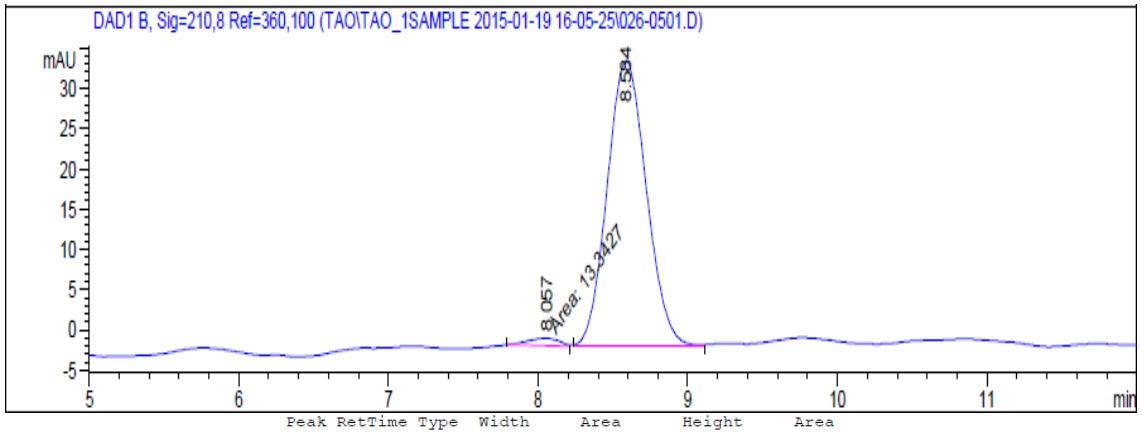
$[\alpha]^{25}_D$ = +5.7 (c = 0.5, $CHCl_3$)


1.00
0.97
1.03
2.02
0.97
2.02
4.23
23.99
3.22


154.949
136.128
118.978
79.362
70.440
55.142
36.244
35.864
31.972
30.542
29.975
29.462
28.614
26.324
25.852
25.280
22.756
14.230

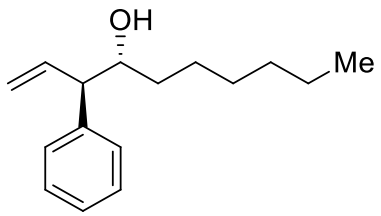


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.684	MM	0.3099	60.13270	3.23438	2.9186
2	7.504	BV	0.2693	79.86040	4.06245	3.8761
3	8.324	MM	0.3027	956.40344	52.65660	46.4196
4	9.434	MM	0.3638	963.94550	44.15833	46.7857



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.057	MM	0.2371	13.34268	9.37873e-1	2.0553
2	8.584	BB	0.2825	635.84479	35.24606	97.9447

(3R,4R)-3-phenyldec-1-en-4-ol (2.3r).



In modification to the general procedure, the reaction was omitted 2-PrOH and heated for 48 hours, concentrated *in vacuo*. The residue was subjected to flash column chromatography (SiO_2, 300 mL of 5% EtOAc/Hexanes) to furnish the title compound (40.1 mg, 77%, *dr* = >20:1) as a yellow oil.

R_f = 0.65 (20% EtOAc/Hexanes).

Spectral data is reported for the major isomer.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 – 7.29 (m, 2H), 7.25 – 7.17 (m, 3H), 6.12 (ddd, *J* = 17.0, 10.3, 9.2 Hz, 1H), 5.23 (ddd, *J* = 10.4, 1.6, 0.4 Hz, 1H), 5.20 (ddd, *J* = 17.0, 1.7, 0.8 Hz, 1H), 3.82 – 3.73 (m, 1H), 3.24 (dd, *J* = 9.1, 7.2 Hz, 1H), 1.78 (d, *J* = 3.4 Hz, 1H), 1.52 – 1.12 (m, 10H), 0.85 (d, *J* = 7.2 Hz, 3H).

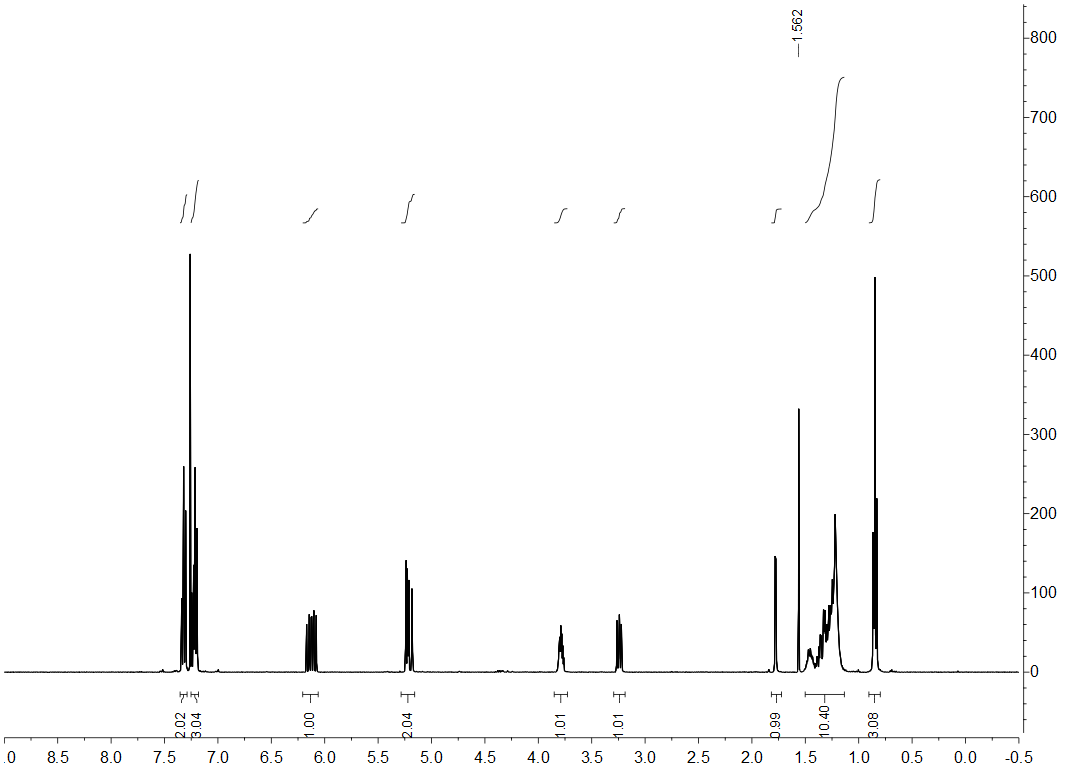
^{13}C NMR (100 MHz, $CDCl_3$): δ 141.85, 138.51, 128.83, 128.13, 126.77, 118.00, 74.10, 57.57, 34.54, 31.94, 29.37, 25.82, 22.73, 14.22.

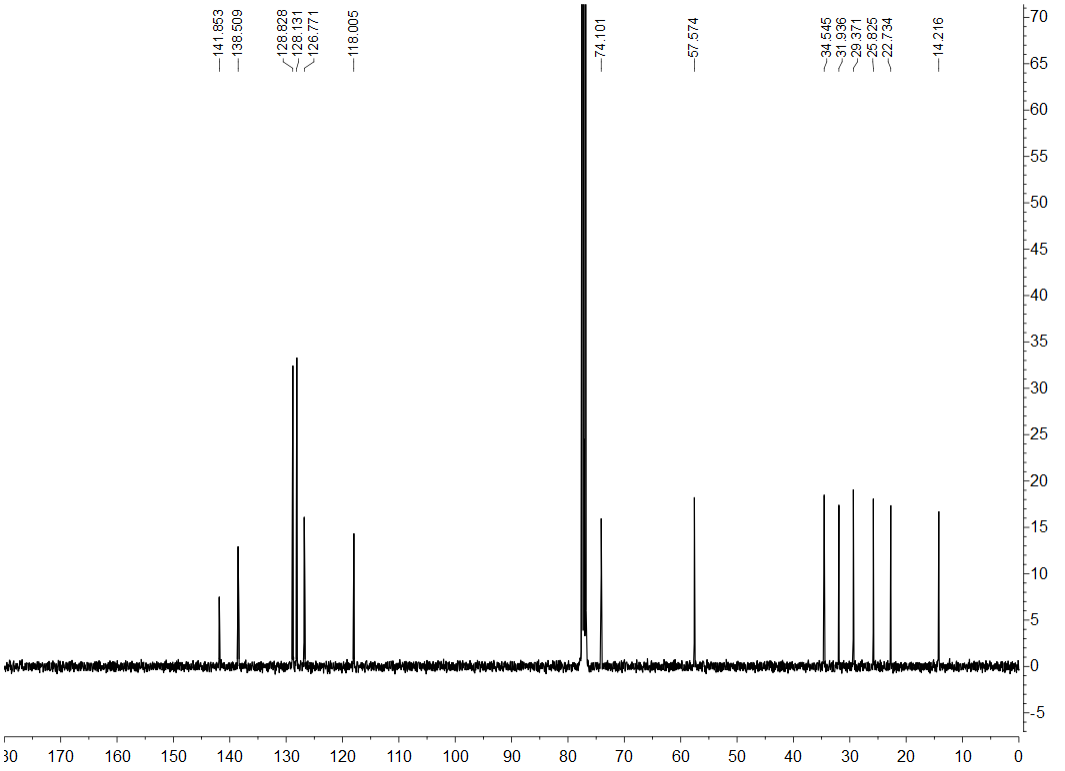
LRMS (ESI) Calcd. for $C_{16}H_{24}O$ $[M+H]^+$: 233, Found: 233.

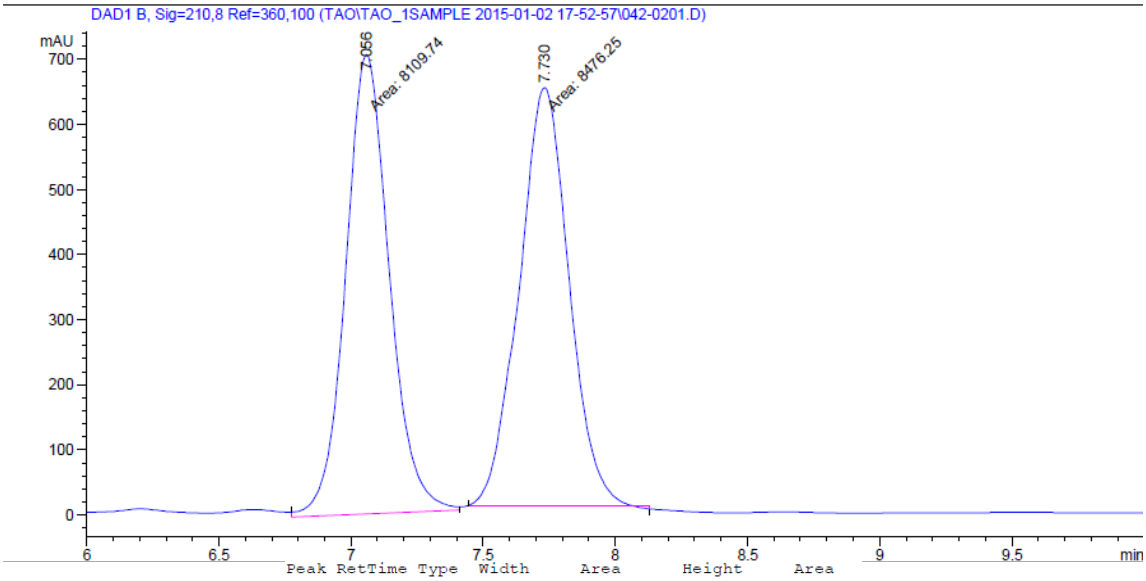
FTIR (neat): 3430, 2926, 2856, 1637, 1493, 1453, 1066, 995, 916, 678 cm^{-1}.

HPLC (Chiralcel AD-H column, hexanes:*i*-PrOH = 99:1, 1 mL/min, 210 nm), ee = 90%.

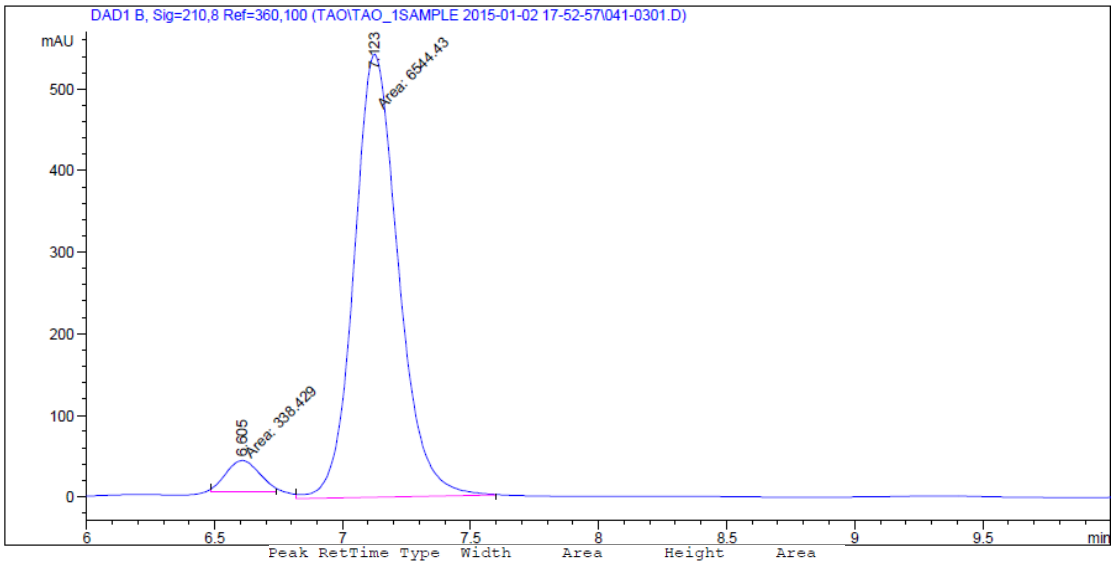
$[\alpha]^{25}_D$ = - 44.9 (c = 0.5, $CHCl_3$)


1.562
2.02
3.04
1.00
2.04
1.01
1.01
0.99
10.40
3.08


141.853
138.509
128.828
128.131
126.771
118.005
74.101
57.574
34.545
31.936
29.371
25.825
22.734
14.216



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.056	MM	0.1915	8109.74121	705.67908	48.8951
2	7.730	MM	0.2194	8476.24902	643.90448	51.1049



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.605	MM	0.1490	338.42938	37.84349	4.9170
2	7.123	MM	0.2006	6544.42969	543.64313	95.0830

Crystallographic Material for Coupling product 2.3m

X-ray Experimental for $C_{14}H_{19}OBr$ (2.3m)

Crystals grew as clusters of clear, colorless prisms by slow evaporation from hexane and pentane. The data crystal was cut from a larger crystal and had approximate dimensions; 0.31 x 0.30 x 0.14 mm. The data were collected at -140 °C on a Nonius Kappa CCD diffractometer using a Bruker AXS Apex II detector and a graphite monochromator with MoK α radiation (λ = 0.71073Å). Reduced temperatures were maintained by use of an Oxford Cryosystems 600 low-temperature device. A total of 1280 frames of data were collected using ω and ϕ-scans with a scan range of 1° and a counting time of 51 seconds per frame. Details of crystal data, data collection and structure refinement are listed in Table 1. Data reduction were performed using SAINT V8.27B.[13] The structure was solved by direct methods using SUPERFLIP [14] and refined by full-matrix least-squares on F^2 with anisotropic displacement parameters for the non-H atoms using SHELXL-2013.[15] Structure analysis was aided by use of the programs PLATON98 [16] and WinGX.[17] The hydrogen atoms were calculated in idealized positions. The absolute configuration was determined by anomalous dispersion effects.

The function, $\Sigma w(|F_O|^2 - |F_c|^2)^2$, was minimized, where $w = 1/[(\sigma(F_O))^2 + (0.021*P)^2 + (2.4901*P)]$ and $P = (|F_O|^2 + 2|F_c|^2)/3$. $R_W(F^2)$ refined to 0.0614, with R(F) equal to 0.0318 and a goodness of fit, S, = 1.01. Definitions used for calculating R(F),$R_W(F^2)$ and the goodness of fit, S, are given below.[18] The data were checked for secondary extinction but no correction was necessary. Neutral atom scattering factors and values used to calculate the linear absorption coefficient are from the International Tables for X-ray Crystallography (1992).[19] All figures were generated using SHELXTL/PC.[20] Tables of positional and thermal parameters, bond lengths and angles, torsion angles and figures are found elsewhere.

Table 2.4 Crystal data and structure refinement for **2.3m.**

Empirical formula	C_{14} H_{19} Br O	
Formula weight	283.20	
Temperature	133(2) K	
Wavelength	0.71073 Å	
Crystal system	orthorhombic	
Space group	*C 2 2 2₁*	
Unit cell dimensions	a = 14.3605(7) Å	α= 90°.
	b = 16.2960(7) Å	β= 90°.
	c = 24.0795(10) Å	γ = 90°.
Volume	5635.1(4) $Å^3$	
Z	16	
Density (calculated)	1.335 Mg/m^3	
Absorption coefficient	2.898 mm^{-1}	
F(000)	2336	
Crystal size	0.310 x 0.300 x 0.140 mm	
Theta range for data collection	2.500 to 27.623°.	
Index ranges	-18<=h<=18, -21<=k<=21, -30<=l<=31	
Reflections collected	71234	
Independent reflections	6493 [R(int) = 0.0720]	
Completeness to theta = 25.242°	99.8 %	
Absorption correction	Numerical	
Max. and min. transmission	0.742 and 0.595	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6493 / 0 / 298	
Goodness-of-fit on F^2	1.011	
Final R indices [I>2sigma(I)]	R_1 = 0.0318, wR_2 = 0.0560	
R indices (all data)	R_1 = 0.0542, wR_2 = 0.0614	
Absolute structure parameter	0.006(8)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.307 and -0.335 e.$Å^{-3}$	

Table 2.5 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for **2.3m**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Br1	2739(1)	2598(1)	7154(1)	47(1)
O1	6106(2)	4599(1)	5695(1)	31(1)
C1	5455(2)	3750(2)	6424(1)	24(1)
C2	4633(2)	4199(2)	6454(2)	31(1)
C3	3833(3)	3865(2)	6675(1)	34(1)
C4	3849(3)	3068(2)	6865(1)	32(1)
C5	4649(3)	2603(2)	6841(1)	33(1)
C6	5444(3)	2949(2)	6625(1)	28(1)
C7	6323(3)	4096(2)	6169(1)	26(1)
C8	6916(2)	4608(2)	6578(1)	24(1)
C9	6496(2)	5440(2)	6672(1)	27(1)
C10	6054(2)	5670(2)	7121(2)	39(1)
C11	7969(2)	4650(2)	6432(2)	34(1)
C12	8462(3)	5155(3)	6881(2)	63(1)
C13	8395(3)	3794(2)	6441(2)	47(1)
C14	8157(3)	5028(3)	5864(2)	60(1)
Br2	1269(1)	5391(1)	6468(1)	48(1)
O2	5572(2)	6114(1)	5317(1)	31(1)
C15	4153(2)	6349(2)	5855(1)	23(1)
C16	3647(3)	5801(2)	5541(1)	29(1)
C17	2801(3)	5500(2)	5721(1)	31(1)
C18	2449(2)	5771(2)	6226(1)	30(1)
C19	2939(2)	6316(2)	6545(1)	32(1)
C20	3795(2)	6598(2)	6361(1)	29(1)
C21	5087(2)	6684(2)	5666(1)	24(1)
C22	4974(2)	7502(2)	5356(1)	22(1)
C23	4463(2)	7389(2)	4818(1)	25(1)
C24	3748(3)	7823(2)	4657(2)	34(1)
C25	5890(2)	8008(2)	5279(2)	27(1)
C26	6447(3)	8036(2)	5819(2)	41(1)

Table 2.5 Continued

C27	5620(3)	8881(2)	5117(2)	36(1)
C28	6517(2)	7658(2)	4818(1)	32(1)

Table 2.6 Bond lengths [Å] and angles [°] for **2.3m**.

Br1-C4	1.900(4)	C13-H13C	0.98
O1-C7	1.438(4)	C14-H14A	0.98
O1-H1	0.84	C14-H14B	0.98
C1-C2	1.389(5)	C14-H14C	0.98
C1-C6	1.392(4)	Br2-C18	1.897(3)
C1-C7	1.500(5)	O2-C21	1.433(4)
C2-C3	1.379(5)	O2-H2A	0.84
C2-H2	0.95	C15-C16	1.377(5)
C3-C4	1.377(5)	C15-C20	1.384(4)
C3-H3	0.95	C15-C21	1.518(5)
C4-C5	1.378(5)	C16-C17	1.380(5)
C5-C6	1.375(5)	C16-H16	0.95
C5-H5	0.95	C17-C18	1.387(5)
C6-H6	0.95	C17-H17	0.95
C7-C8	1.548(5)	C18-C19	1.370(5)
C7-H7	1.00	C19-C20	1.385(5)
C8-C9	1.500(5)	C19-H19	0.95
C8-C11	1.553(5)	C20-H20	0.95
C8-H8	1.00	C21-C22	1.537(4)
C9-C10	1.307(5)	C21-H21	1.00
C9-H9	0.95	C22-C23	1.498(4)
C10-H10A	0.95	C22-C25	1.564(5)
C10-H10B	0.95	C22-H22	1.00
C11-C13	1.524(5)	C23-C24	1.306(5)
C11-C14	1.525(5)	C23-H23	0.95
C11-C12	1.532(5)	C24-H24A	0.95
C12-H12A	0.98	C24-H24B	0.95
C12-H12B	0.98	C25-C27	1.525(5)
C12-H12C	0.98	C25-C26	1.529(5)
C13-H13A	0.98	C25-C28	1.538(5)
C13-H13B	0.98	C26-H26A	0.98

Table 2.6 Continued

C26-H26B	0.98	C9-C8-C11	112.7(3)
C26-H26C	0.98	C7-C8-C11	114.5(3)
C27-H27A	0.98	C9-C8-H8	105.9
C27-H27B	0.98	C7-C8-H8	105.9
C27-H27C	0.98	C11-C8-H8	105.9
C28-H28A	0.98	C10-C9-C8	125.3(3)
C28-H28B	0.98	C10-C9-H9	117.3
C28-H28C	0.98	C8-C9-H9	117.3
C7-O1-H1	109.5	C9-C10-H10A	120.0
C2-C1-C6	117.8(3)	C9-C10-H10B	120.0
C2-C1-C7	121.9(3)	H10A-C10-H10B	120.0
C6-C1-C7	120.2(3)	C13-C11-C14	108.1(3)
C3-C2-C1	121.3(3)	C13-C11-C12	107.2(3)
C3-C2-H2	119.3	C14-C11-C12	109.6(4)
C1-C2-H2	119.3	C13-C11-C8	110.3(3)
C4-C3-C2	119.1(4)	C14-C11-C8	113.1(3)
C4-C3-H3	120.4	C12-C11-C8	108.3(3)
C2-C3-H3	120.4	C11-C12-H12A	109.5
C3-C4-C5	121.2(3)	C11-C12-H12B	109.5
C3-C4-Br1	119.2(3)	H12A-C12-H12B	109.5
C5-C4-Br1	119.6(3)	C11-C12-H12C	109.5
C6-C5-C4	118.9(3)	H12A-C12-H12C	109.5
C6-C5-H5	120.5	H12B-C12-H12C	109.5
C4-C5-H5	120.5	C11-C13-H13A	109.5
C5-C6-C1	121.6(3)	C11-C13-H13B	109.5
C5-C6-H6	119.2	H13A-C13-H13B	109.5
C1-C6-H6	119.2	C11-C13-H13C	109.5
O1-C7-C1	111.1(3)	H13A-C13-H13C	109.5
O1-C7-C8	108.5(2)	H13B-C13-H13C	109.5
C1-C7-C8	113.5(3)	C11-C14-H14A	109.5
O1-C7-H7	107.9	C11-C14-H14B	109.5
C1-C7-H7	107.9	H14A-C14-H14B	109.5
C8-C7-H7	107.9	C11-C14-H14C	109.5
C9-C8-C7	111.2(3)	H14A-C14-H14C	109.5

Table 2.6 Continued

H14B-C14-H14C	109.5	C25-C22-H22	105.8
C21-O2-H2A	109.5	C24-C23-C22	125.1(3)
C16-C15-C20	118.6(3)	C24-C23-H23	117.5
C16-C15-C21	122.4(3)	C22-C23-H23	117.5
C20-C15-C21	119.1(3)	C23-C24-H24A	120.0
C15-C16-C17	121.4(3)	C23-C24-H24B	120.0
C15-C16-H16	119.3	H24A-C24-H24B	120.0
C17-C16-H16	119.3	C27-C25-C26	108.8(3)
C16-C17-C18	118.9(3)	C27-C25-C28	108.2(3)
C16-C17-H17	120.5	C26-C25-C28	108.6(3)
C18-C17-H17	120.5	C27-C25-C22	107.9(3)
C19-C18-C17	120.7(3)	C26-C25-C22	110.8(3)
C19-C18-Br2	119.9(3)	C28-C25-C22	112.5(3)
C17-C18-Br2	119.4(3)	C25-C26-H26A	109.5
C18-C19-C20	119.4(3)	C25-C26-H26B	109.5
C18-C19-H19	120.3	H26A-C26-H26B	109.5
C20-C19-H19	120.3	C25-C26-H26C	109.5
C15-C20-C19	121.0(3)	H26A-C26-H26C	109.5
C15-C20-H20	119.5	H26B-C26-H26C	109.5
C19-C20-H20	119.5	C25-C27-H27A	109.5
O2-C21-C15	111.8(3)	C25-C27-H27B	109.5
O2-C21-C22	109.2(2)	H27A-C27-H27B	109.5
C15-C21-C22	111.4(3)	C25-C27-H27C	109.5
O2-C21-H21	108.1	H27A-C27-H27C	109.5
C15-C21-H21	108.1	H27B-C27-H27C	109.5
C22-C21-H21	108.1	C25-C28-H28A	109.5
C23-C22-C21	111.4(3)	C25-C28-H28B	109.5
C23-C22-C25	112.0(3)	H28A-C28-H28B	109.5
C21-C22-C25	115.2(3)	C25-C28-H28C	109.5
C23-C22-H22	105.8	H28A-C28-H28C	109.5
C21-C22-H22	105.8	H28B-C28-H28C	109.5

Table 2.7 Anisotropic displacement parameters ($Å^2$ x 10^3) for **2.3m**. The anisotropic displacement factor exponent takes the form: $-2p^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Br1	50(1)	50(1)	40(1)	11(1)	1(1)	-18(1)
O1	57(2)	17(1)	18(1)	2(1)	-2(1)	-3(1)
C1	39(2)	16(2)	18(2)	-2(1)	-4(2)	-2(1)
C2	42(2)	19(2)	31(2)	5(2)	-3(2)	-4(2)
C3	42(2)	26(2)	35(2)	2(2)	-5(2)	-1(2)
C4	42(2)	30(2)	24(2)	4(2)	-4(2)	-10(2)
C5	57(2)	22(2)	22(2)	10(2)	-5(2)	-7(2)
C6	43(2)	21(2)	22(2)	4(1)	-3(2)	1(2)
C7	44(2)	15(2)	19(2)	2(1)	4(2)	2(2)
C8	31(2)	19(2)	22(2)	0(1)	3(1)	2(1)
C9	29(2)	21(2)	32(2)	-5(2)	-4(1)	-1(2)
C10	38(2)	34(2)	44(2)	-12(2)	0(2)	5(2)
C11	33(2)	30(2)	40(2)	3(2)	9(2)	4(2)
C12	25(2)	74(4)	91(4)	-34(3)	-1(2)	3(2)
C13	38(2)	41(2)	62(3)	3(2)	14(2)	12(2)
C14	49(3)	63(3)	69(3)	26(3)	24(2)	-4(2)
Br2	47(1)	54(1)	44(1)	2(1)	8(1)	-16(1)
O2	47(2)	19(1)	27(1)	3(1)	10(1)	13(1)
C15	32(2)	14(2)	21(2)	1(1)	-2(1)	6(1)
C16	44(2)	21(2)	22(2)	-4(1)	3(2)	3(2)
C17	46(2)	21(2)	27(2)	-4(2)	-3(2)	-8(2)
C18	37(2)	23(2)	29(2)	6(2)	2(2)	1(2)
C19	43(2)	31(2)	21(2)	-5(2)	7(2)	1(2)
C20	38(2)	23(2)	24(2)	-5(1)	-1(2)	-1(2)
C21	33(2)	21(2)	18(2)	-3(1)	0(1)	8(2)
C22	26(2)	18(2)	23(2)	-3(1)	2(1)	5(1)
C23	27(2)	21(2)	26(2)	2(2)	3(1)	-1(2)
C24	32(2)	33(2)	36(2)	4(2)	-2(2)	2(2)
C25	28(2)	21(2)	32(2)	-4(2)	1(2)	1(2)
C26	38(2)	40(2)	44(2)	-13(2)	-6(2)	-3(2)
C27	35(2)	20(2)	55(3)	-2(2)	6(2)	-4(2)
C28	28(2)	28(2)	39(2)	-4(2)	1(2)	2(2)

Table 2.8 Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for **2.3m.**

	x	y	z	U(eq)
H1	5956	4297	5427	46
H2	4623	4746	6319	37
H3	3278	4180	6695	41
H5	4651	2053	6970	40
H6	6000	2633	6612	34
H7	6712	3626	6038	31
H8	6878	4317	6943	29
H9	6557	5832	6382	33
H10A	5978	5296	7420	46
H10B	5809	6210	7147	46
H12A	9132	5168	6805	95
H12B	8353	4904	7245	95
H12C	8216	5716	6880	95
H13A	9075	3838	6418	70
H13B	8162	3478	6124	70
H13C	8223	3517	6787	70
H14A	7913	5589	5855	91
H14B	7849	4699	5576	91
H14C	8829	5038	5795	91
H2A	5705	5692	5501	46
H16	3885	5627	5192	35
H17	2465	5114	5504	38
H19	2694	6500	6890	38
H20	4141	6968	6585	34
H21	5477	6785	6003	29
H22	4559	7848	5594	27
H23	4676	6969	4576	30
H24A	3514	8249	4887	40
H24B	3462	7713	4309	40
H26A	6994	8387	5770	61
H26B	6648	7480	5918	61
H26C	6056	8257	6117	61
H27A	5235	9122	5411	55
H27B	5267	8871	4769	55
H27C	6184	9212	5068	55

Table 2.8 Continued

H28A	7104	7964	4808	47
H28B	6201	7708	4459	47
H28C	6646	7078	4894	47

Table 2.9 Torsion angles [°] for **2.3m.**

C6-C1-C2-C3	0.1(5)	C20-C15-C16-C17	-0.2(5)
C7-C1-C2-C3	178.0(3)	C21-C15-C16-C17	179.6(3)
C1-C2-C3-C4	-0.6(5)	C15-C16-C17-C18	1.3(5)
C2-C3-C4-C5	0.3(5)	C16-C17-C18-C19	-1.2(5)
C2-C3-C4-Br1	-178.5(3)	C16-C17-C18-Br2	177.9(3)
C3-C4-C5-C6	0.5(5)	C17-C18-C19-C20	0.0(5)
Br1-C4-C5-C6	179.3(3)	Br2-C18-C19-C20	-179.2(3)
C4-C5-C6-C1	-1.0(5)	C16-C15-C20-C19	-1.1(5)
C2-C1-C6-C5	0.7(5)	C21-C15-C20-C19	179.1(3)
C7-C1-C6-C5	-177.3(3)	C18-C19-C20-C15	1.2(5)
C2-C1-C7-O1	-37.0(4)	C16-C15-C21-O2	-29.2(4)
C6-C1-C7-O1	140.9(3)	C20-C15-C21-O2	150.6(3)
C2-C1-C7-C8	85.6(4)	C16-C15-C21-C22	93.2(4)
C6-C1-C7-C8	-96.5(4)	C20-C15-C21-C22	-87.0(3)
O1-C7-C8-C9	47.6(3)	O2-C21-C22-C23	57.8(4)
C1-C7-C8-C9	-76.4(3)	C15-C21-C22-C23	-66.1(3)
O1-C7-C8-C11	-81.6(3)	O2-C21-C22-C25	-71.1(3)
C1-C7-C8-C11	154.4(3)	C15-C21-C22-C25	164.9(3)
C7-C8-C9-C10	105.5(4)	C21-C22-C23-C24	129.8(4)
C11-C8-C9-C10	-124.3(4)	C25-C22-C23-C24	-99.5(4)
C9-C8-C11-C13	170.1(3)	C23-C22-C25-C27	67.0(4)
C7-C8-C11-C13	-61.4(4)	C21-C22-C25-C27	-164.3(3)
C9-C8-C11-C14	-68.6(4)	C23-C22-C25-C26	-174.0(3)
C7-C8-C11-C14	59.9(4)	C21-C22-C25-C26	-45.3(4)
C9-C8-C11-C12	53.0(4)	C23-C22-C25-C28	-52.2(4)
C7-C8-C11-C12	-178.5(3)	C21-C22-C25-C28	76.4(3)

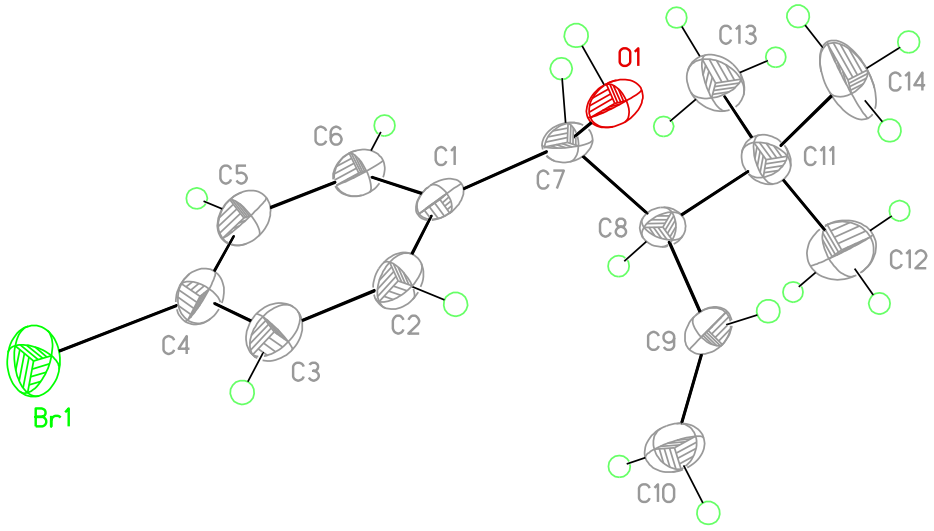
Table 2.10 Hydrogen bonds for **2.3m** [Å and °]**.**

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O1-H1...O2#1	0.84	1.99	2.807(3)	163.9
O2-H2A...O1	0.84	1.93	2.742(3)	162.2

Symmetry transformations used to generate equivalent atoms:

#1 x,-y+1,-z+1

Figure 2.1 View of **2.3m** showing the atom labeling scheme. Displacement ellipsoids are scaled to the 50% probability level.



Chapter 3: Siloxy-Crotylation of Primary Alcohols by Coupling with Propargyl Ethers via Novel Hydride Shift Enabled Formation of Allylruthenium from Alkynes*

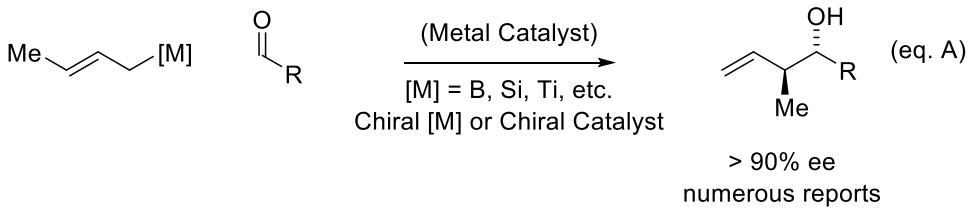
3.1 INTRODUCTION

Polyketides are important sources for discovery of medicine due to their bioactivities.[1] In the present, all polyketide drugs, except one, are prepared through fermentation or modification of fermentation products.[2] Only very small portion (less than 5%) of the bacteria are able to culture, which limit the further study on the polyketides.[3] Chemical synthesis for the polyketides synthesis is still in demand for more efficient and economic routes. Carbonyl crotylation has been used broadly in the construction of polyketides.[4] While most of the enantioselective carbonyl crotylation protocols require chiral auxiliaries or preformed crotylmetal nucleophiles (Figure 3.1, eq A).[5] Krische group has introduced the redox-triggered carbonyl addition, by which primary alcohols can be directly converted to secondary alcohols by coupling with π-unsaturated compounds in diastereoselective and enantioselective manner[6] (Figure 3.1, eq B).

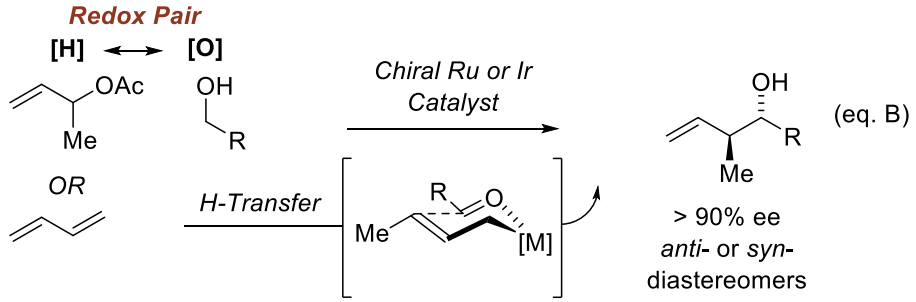
Recently, our group published ruthenium catalyzed coupling of alcohols and 2-alkynes to furnish the formation of both linear[7] and branched homoallylic alcohols[8] (Scheme 3.1). Both protocols went through the alkyne-to-allene isomerization facilitated by ruthenium catalysis. Inspired by these results, in this chapter, the first enantioselective and diastereoselective alkynes mediated carbonyl crotylation (Figure 3.1, eq C) was described and a novel mechanism for the formation of π-allylmetal species from alkyne without intervening allene intermediate was proposed (Figure 3.1, eq D).

*This chapter is based on the published work:
Liang, T.; Zhang, W.; Chen, T,-Y.; Nguyen, K. D.; Krische, M. J. *J. Am. Chem. Soc.* **2015**, *137*, 13066.

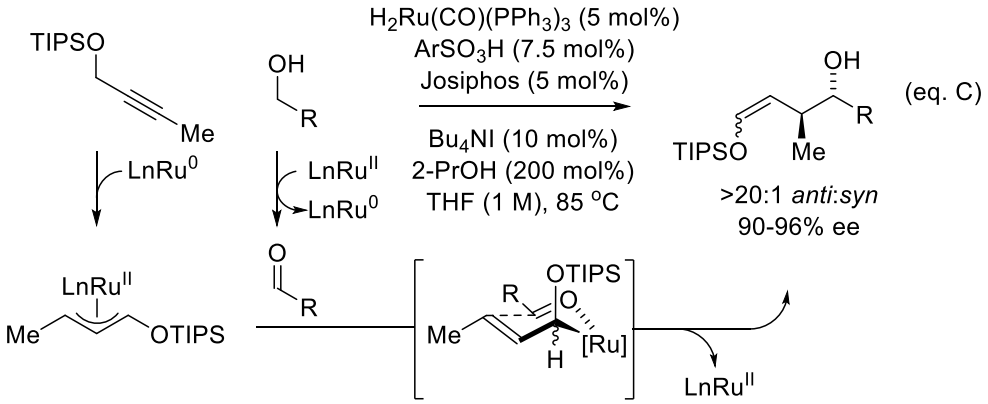
Chiral Allylmetal Reagents: Hoffmann 1978 onward



Prior Work: Diastereo- and Enantioselective Redox-Triggered Carbonyl Crotylation



This Work: Diastereo- Enantioselective Alkyne-Mediated Carbonyl Crotylation



Novel Mechanism: Direct Conversion of Alkyne to π-Allyl wihtout Intervening Allenes

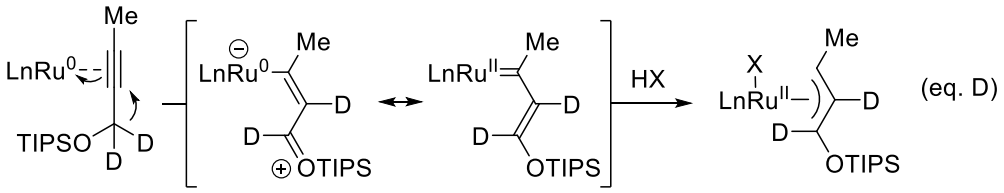
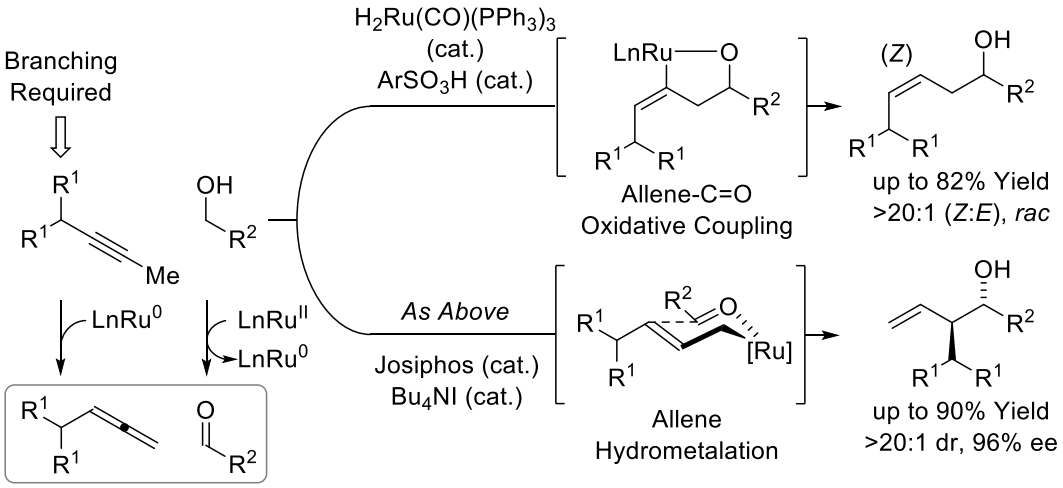


Figure 3.1 Enantioselective Carbonyl Crotylation Strategies.

Scheme 3.1 Redox-Triggered Formation of Linear and Branched Homoallylic Alcohols via Alkyne-to-Allene Isomerization.



3.2 Reaction Development and Scope

Treatment of propargyl ether **3.1a** and p-bromobenzyl alcohol **3.2c** under the condition used in asymmetric formation of branched homoallylic alcohols,[8] carbonyl siloxy-crotylation product **3.3c** was obtained with 70% yield and complete region- and diastereoselectivity as a 3:1 (Z:E) mixture of olefin geometrical isomers. Notably, both Z- and E-olefin isomers showed good enantiomeric enrichment, 87% ee and 94% ee, respectively. Further optimization was conducted, and it's found that slightly higher loading of the sulfonic acid additive (7.5 mol%) at lower temperature (85 ℃) was optimal (Scheme 3.2). Due to the not complete olefin geometry selectivity, treatment of the C-C coupling adduct **3.3c** with TBAF to cleave the TIPS silyl protecting group followed by reduction with $NaBH_4$ provided diol **3.5c**. The absolute stereochemistry was determined in analogy to **3.5c** by X-ray diffraction analysis.

With the optimized condition in hand, a variety range of alcohols **3.2a**-**3.2o** were

Scheme 3.2 Redox-Triggered Siloxyl Crotylation by Coupling of Proparyl Ether **3.1a** and p-Bromobenzyl Alcohol **3.2c**.

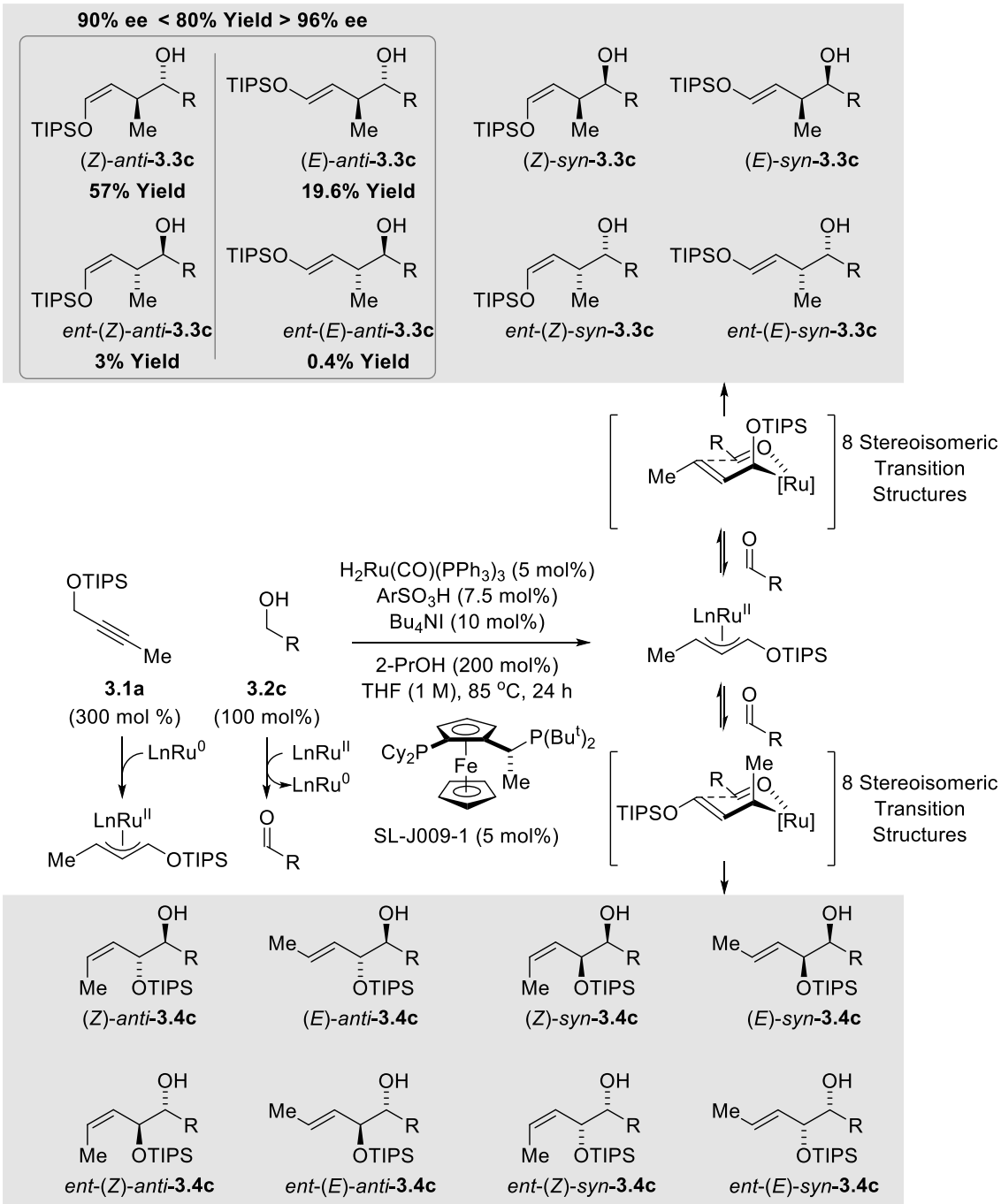
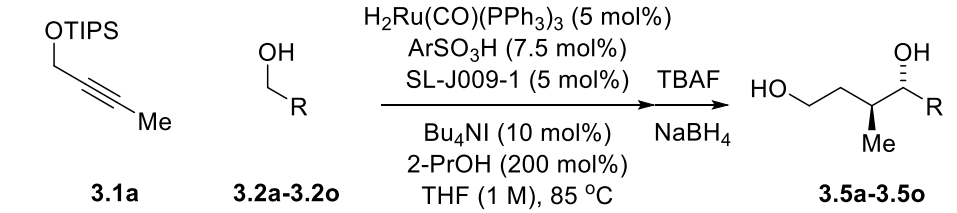
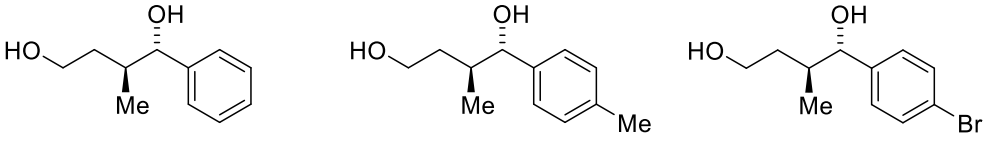


Table 3.1 Diastereoselective and Enantioselective Formation of 1,4-Diols **3.1a-3.5o**.



3.1a (300 mol %) | **3.2a-3.2o** (100 mol%) | **3.5a-3.5o**

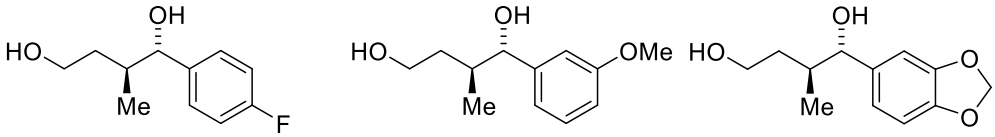
3.2a, R = Ph	**3.2b**, R = 4-Me-Ph	**3.2c**, R = 4-Br-Ph
3.2d, R = 4-F-Ph	**3.2e**, R = 3-MeO-Ph	**3.2f**, R = benzodioxole
3.2g, R = 2-Me-Ph	**3.2h**, R = 2-Cl-Ph	**3.2i**, R = (*Z*)-CH=CHCH$_2$OBn
3.2j, R = CH=CMe$_2$	**3.2k**, geraniol	**3.2l**, R = CH=CHPh
3.2m, R = (CH$_2$)$_2$Ph	**3.2n**, R = (CH$_2$)$_5$Me	**3.2o**, R = (CH$_2$)$_2$CF$_3$



3.5a, 70% Yield[b]
>20:1 dr, 91% ee

3.5b, 64% Yield[b,c]
>20:1 dr, 93% ee

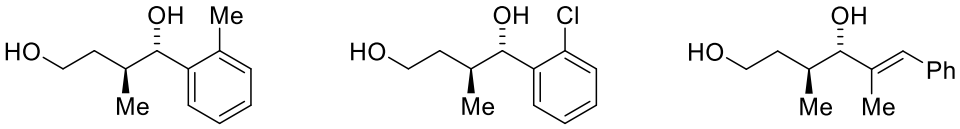
3.5c, 77% Yield
>20:1 dr, 92% ee



3.5d, 70% Yield
>20:1 dr, 92% ee

3.5e, 75% Yield
>20:1 dr, 92% ee

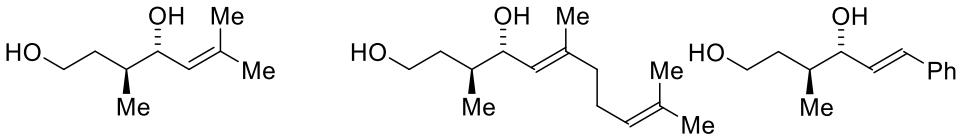
3.5f, 63% Yield[b,c]
>20:1 dr, 94% ee



3.5g, 69% Yield[b,c]
>20:1 dr, 87% ee

3.5h, 68% Yield[b]
>20:1 dr, 91% ee

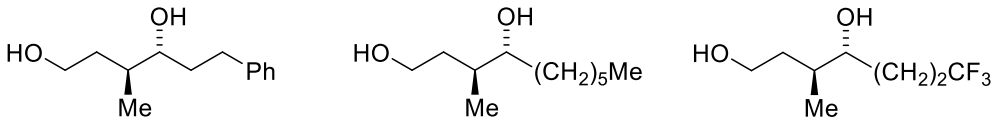
3.5i, 63% Yield[c]
>20:1 dr, 90% ee



3.5j, 73% Yield[b]
>20:1 dr, 94% ee

3.5k, 72% Yield[b]
>20:1 dr, 96% ee

3.5l, 73% Yield
>20:1 dr, 94% ee

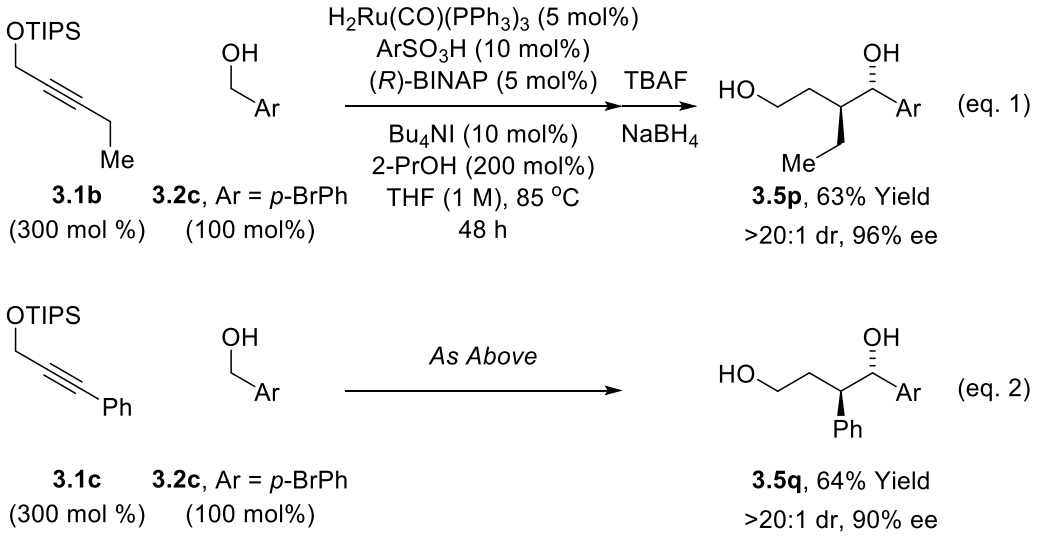


3.5m, 70% Yield[b,d] >20:1 dr, 90% ee | **3.5n**, 81% Yield[b,d] >20:1 dr, 90% ee | **3.5o**, 67% Yield[b,d] >20:1 dr, 90% ee

[a]Yields are material isolated by silica gel chromatography. Diastereoselectivities were determined by ^{1}H NMR analysis of crude reaction mixtures. See supporting Information for further experimental details. [b]48 h. [c]$H_2Ru(CO)(PPh_3)_3$ (6 mol%), SL-J009-1 (6 mol%), $ArSO_3H$ (9 mol%), and Bu_4NI (12 mol%). [d]2-PrOH was omitted.

tested coupling with propargyl ether **3.1a**, and converted to diols **3.5a**-**3.5o** with complete regio and *anti*-diastereoselectivity and uniformly good enantioselectivity. And not only methyl substituted propargyl ether **3.1a**, ehtyl- and phenyl-substituted propargyl ether, **3.1b** and **3.1c**, also gave the desired diol adducts **3.5p** and **3.5q** with BINAP modified ruthenium catalyst in good enantioselective manner (Scheme 3.3, eq 1 and eq 2).

Scheme 3.3 Coupling of Propargyl Ether **3.1b** and **3.1c** with **3.2c** to Form Diols

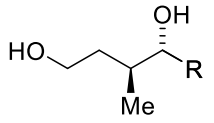


3.1b (300 mol %) **3.2c**, Ar = *p*-BrPh (100 mol%) → **3.5p**, 63% Yield, >20:1 dr, 96% ee

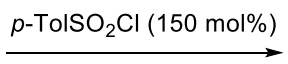
3.1c (300 mol %) **3.2c**, Ar = *p*-BrPh (100 mol%) → **3.5q**, 64% Yield, >20:1 dr, 90% ee

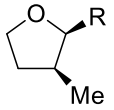
To demonstrate the utility of this transformation, diols **3.5a**, **3.5c**, **3.5e**, **3.5f**, **3.5k**, and **3.5m**, were treated with p-toluenesulfonyl chloride in pyridine resulting in mono-tosylation of the primary alcohol, which spontatneously cyclized to form the *trans*-2,3-disubstituted furans **3.6a**, **3.6c**, **3.6e**, **3.6f**, **3.6k**, and **3.6m** (Table 3.2). In type I polyketide natural products, 2,3-disubstituted furans with 3-methyl substituents were frequently found as as substructures.[9]

Table 3.2 Formation of *trans*-2,3-Disubstituted Furans **3.6a, 3.6c, 3.6e, 3.6f, 3.6k, 3.6m** from Diol Adducts.

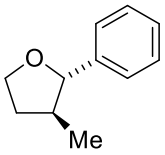


3.5a, 3.5c, 3.5e, 3.5f, 3.5k, 3.5m (100 mol%)

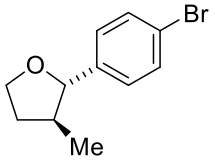




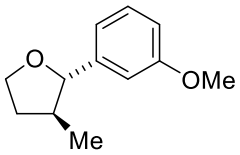
3.6a, 3.6c, 3.6e, 3.6f, 3.6k, 3.6m



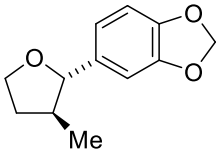
3.6a, 73% Yield
>20:1 dr, 91% ee



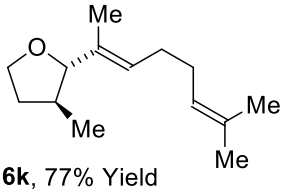
3.6c, 78% Yield
>20:1 dr, 92% ee



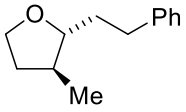
3.6e, 80% Yield
>20:1 dr, 92% ee



3.6f, 82% Yield
>20:1 dr, 92% ee



3.6k, 77% Yield
>20:1 dr, 96% ee



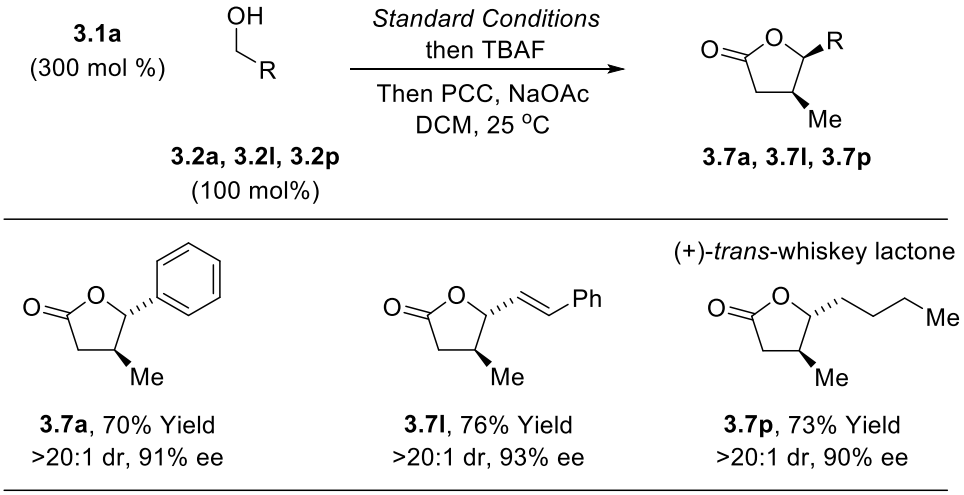
3.6m, 72% Yield
>20:1 dr, 90% ee

[a]Yields are material isolated by silica gel chromatography. See supporting Information for further experimental details.

Also, coupling of alcohols **3.2a**, **3.2l**, and **3.2p** with propargyl ether **3.1a** under the standard condition followed by removal of TIPS protecting group resulted in the crude hemiacetals, which were treated with PCC gave the *trans*-4,5-disubstituted γ-butyrolactones **3.7a, 3.7l,** and **3.7p**. The formation of **3.7p** represents a total synthesis of (+)-*trans*-whiskey lactone from simple starting material pentanol.[10]

The crude hemiacetal, obtained under standard condition followed by the TBAF treatment, can be converted to *trans*-4,5-disubstituted-2,3-dehydrofuran **3.8a** by treated with mesyl chloride in trimethylamine (Scheme 3.4, eq 3). Finally, the crude hemiacetal can be converted to enoate **3.9a** with complete *E*-olefin selectivity by treated with Wittig reagent (Scheme 3.4, eq 4).

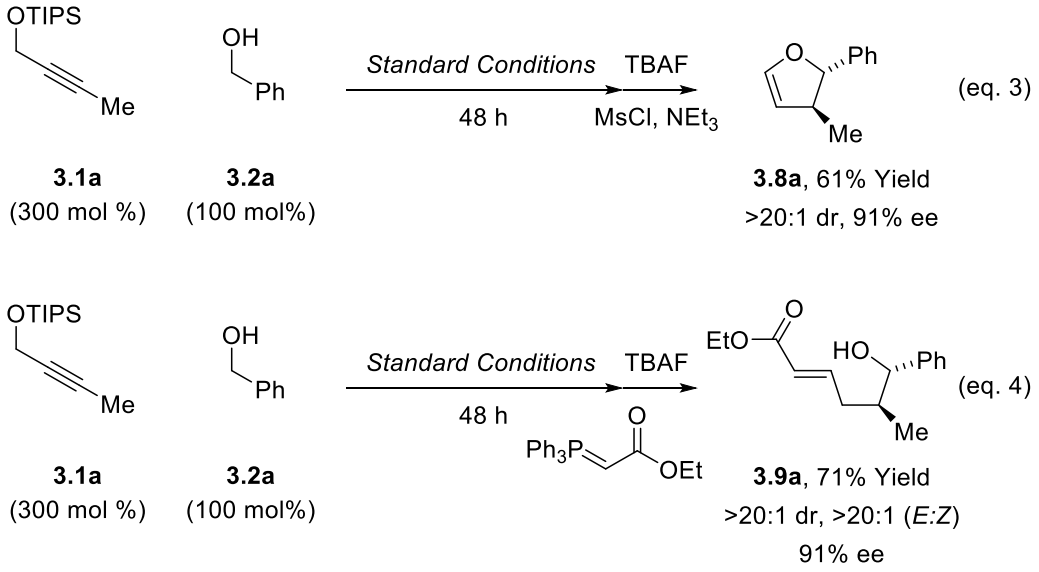
Table 3.3 Formation of *trans*-4,5-Disubstituted γ-Butyrolactones **3.7a, 3.7l, and 3.7p** from C-C Coupling Adducts.



3.7a, 70% Yield	**3.7l**, 76% Yield	**3.7p**, 73% Yield
>20:1 dr, 91% ee	>20:1 dr, 93% ee	>20:1 dr, 90% ee

[a]Yields are material isolated by silica gel chromatography. See supporting Information for further experimental details.

Scheme 3.4 Elaboration of Coupling Adducts.

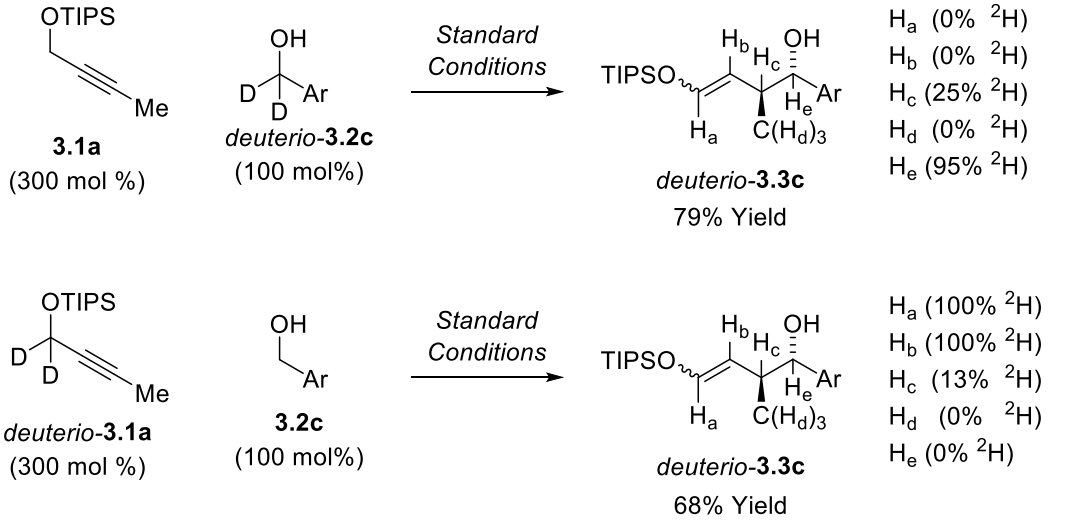


3.3 MECHANISM AND DISCUSSION

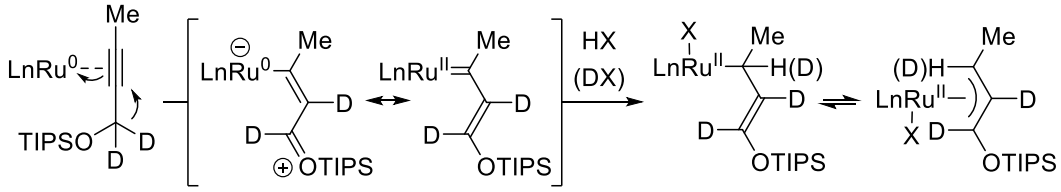
By comparing with the formation of branched homoallylic alcohol[8], coupling of propargyl ether **3.1a** with primary alcohols didn't go through the mono-substituted allene **3.1d** intermediate. Initially, the mechanism of this transformation was assumed to proceed through alkyne **3.1a** to disubstituted allene **3.1e** or diene **3.1f** isomerization under ruthenium catalysis. However, the deuterium labeling experiment results didn't support for allene **3.1e** and **3.1f** intermediates. When *deuterio*-**3.2c** was used in the coupling with **3.1a** under standard conditions, H_b and H_d should get deuterium incorporation if allene or diene intermediates were involved. And when *deuterio*-**3.1a** and **3.2c** were subjected to the standard conditions, deuterium was transferred to H_a and H_b. These data clearly indicated 1,2-hydride shift mechanism (Scheme 3.5).[11,12,13]

A general catalytic mechanism for this asymmetric carbonyl siloxy-crotylation was proposed (Scheme 3.6). The ruthenium (II) complex $LnRu(II)X_2$ was converted to ruthenium alkoxide via ligand exchange with the primary alcohol, which was followed by β-hydride elimination to generate aldehyde and LnRu(II)HX. Reductive elimination of HX gave Ru(0) complex. The strong π-backbonding between Ru(0) and bound alkyne **3.1a**

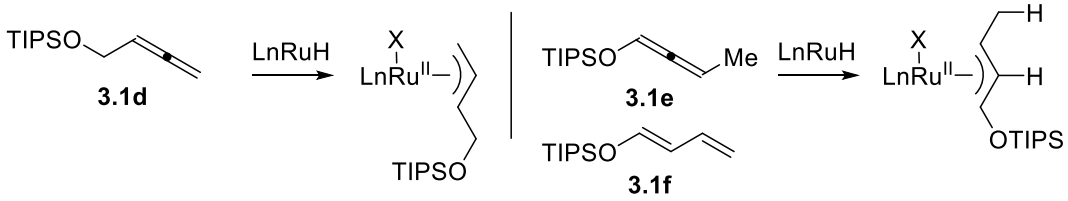
Scheme 3.5 Deuterium Labelling Experiments and Proposed Hydride Shift Mechanism.



Proposed Hydride Shift Mechanism

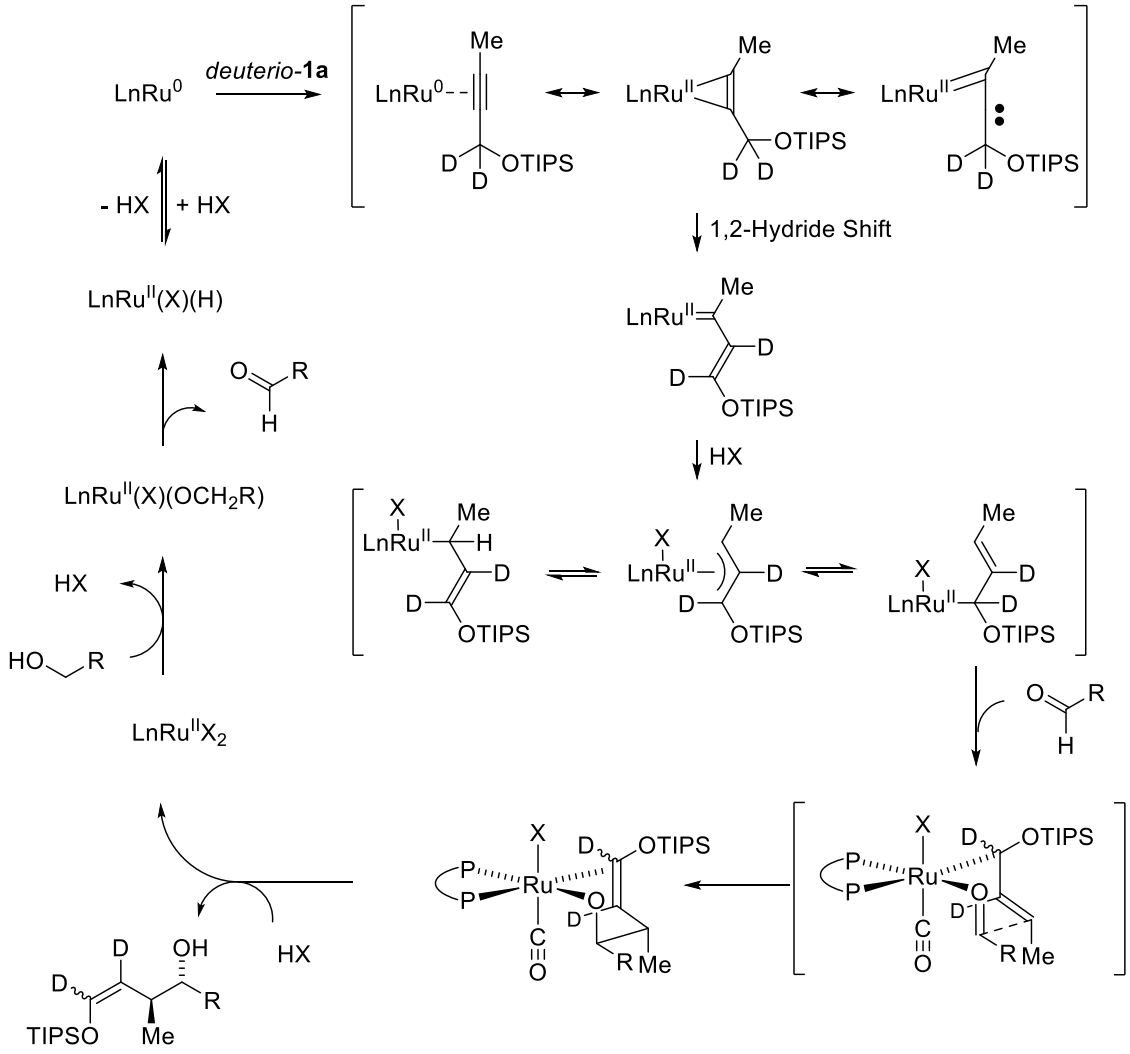


Allenes 3.1b, 3.1c and Diene 3.1d Inconsistent with Product Structure or ^{2}H-Labelling Results



induced 1,2-hydride shift, which delivered the vinyl ruthenium(II) carbene species. Also the n → σ* interaction between the oxygen lone pair and the propargylic C-H bond played an important role in the 1,2-hydride shift. The vinyl ruthenium(II) carbene species was converted to nucleophilic siloxy-substituted allylruthenium(II) complex by protonation. The σ-allylruthenium haptomer, where ruthenium resided on the carbon adjacent to oxygen, was added to aldehyde through a Zimmerman-Traxler transition structure to form

Scheme 3.6 Proposed Ruthenium Catalyzed Carbonyl Siloxy-Crotylation Catalytic Cycle.



homoallylic ruthenium(II) alkoxide. Protonolysis cleavage released the carbonyl addition product and closed the catalytic cycle.

3.4 CONCLUSION

In summary, a ruthenium catalyzed redox-triggered carbonyl siloxy-crotylation mediated by alkyne through novel 1,2-hydride shift mechanism was reported. Complete regio- and diastereoselectivity, as well as high enantioselectivity, were achieved. From the coupling adducts, enantiomeric enriched diols, furans, and lactones were able to be accessed.

3.5 EXPERIMENTAL DETAILS

General Information

All reactions were run under an atmosphere of argon, unless otherwise indicated. Resealable pressure tubes (13x100 mm) were purchased from Fischer Scientific (catalog number 14–959–35C) and were flame dried followed by cooling in a desiccator or under a stream of argon prior to use. Tetrahydrofuran (THF) was dried over sodium metal, benzophenone, and distilled immediately prior to use. $RuH_2(PPh_3)_3$ were prepared according to literature procedure.1 All ligands were used as received from Strem Chemicals Inc. Alcohols were purified by distillation or recrystallization immediately prior to use. Preparative column chromatography employing Silicycle silica gel (40-63 μm) was performed according to the method of Still.2 Analytical thin-layer chromatography (TLC) was carried out using 0.25 mm commercial silica gel plates (Dynamic Absorbents F254). Visualization was accomplished with UV light followed by dipping in Seebach's stain solution then heating. Purification of reactions was carried out by flash chromatography using Silicycle silica gel (40–63 μm).

Spectroscopy, Spectrometry, and Data Collection

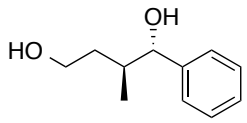
Infrared spectra were recorded on a Perkin-Elmer 1600 spectrometer. Low-resolution mass spectra (LRMS) were obtained on a Karatos MS9 and are reported as m/z (relative intensity). Accurate masses are reported for the molecular ion (M+H, M+Na), or a suitable fragment ion. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded with a Varian Gemini (400 MHz) spectrometer. Chemical shifts are reported in delta (δ) units, parts per million (ppm) downfield from tetramethylsilane or ppm relative to the center of the singlet at 7.26 ppm for deuteriochloroform. Data reported as multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). Integration and coupling constants were reported in Hertz (Hz). Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded with a Varian Gemini (100 MHz) spectrometer and were routinely run with broadband decoupling. Chemical shifts are reported in delta (δ) units, ppm relative to the center of the triplet at 77.16 ppm for deuteriochloroform.

Experimental Details and Spectral Data

General Procedure for the Couplings of Alcohols 2.2a-2.2l and Alkynes

To a resealable pressure tube (ca. 13 x 100) was added $H_2Ru(CO)(PPh_3)_3$ (9.2 mg, 0.010 mmol, 5 mol%), SL-J009-1 ligand (5.6 mg, 0.010 mmol, 5 mol%), Bu_4NI (7.4 mg, 0.020 mmol, 10 mol%) and 2,4,6-tri(2-propyl)phenylsulfonic acid (4.2 mg, 0.015 mmol, 7.5 mol%). At this stage solid alcohol coupling partners (0.20 mmol, 100 mol%) were added. The tube was then sealed with a rubber septum and purged with argon. THF (0.20 mL, 1 M concentration with respect to alcohols) was then added. At this stage, liquid alcohol coupling partners (0.20 mmol, 100 mol%) were added. 2-propylalcohol (31 μL, 0.40 mmol, 200 mol%) was then added. Alkyne 1a (0.60 mmol, 300 mol%) was added *via* syringe and the rubber septum was quickly replaced with a screw cap. The mixture was then heated at 85 °C for the time stated. After cooling to room temperature, the mixture was passed through a short silica pad, washed the pad with EA, and concentrated *in vacuo*. The residue was dissolved in THF (2.0 mL) and TBAF (1.0 M in THF, 0.2 mL) was added at 0ºC. The mixture was stirred at r.t for 30 min, then $NaBH_4$ (14.8 mg, 0.4 mmol), EtOH (1.0 mL) were added. After 1 h, the reaction was quenched by NH_4Cl (aq), and extracted by EA. Organic layer was washed by water, brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was subjected to flash column chromatography (SiO_2, eluent Hexanes:EA = 2:1) to afford the corresponding crotylation products.

(1*S*,2*S*)-2-methyl-1-phenylbutane-1,4-diol (3.5a).



The residue was subjected to flash column chromatography for purification to furnish the title compound (37.8 mg, 70%, *dr* = >20:1) as a white solid.

R_f=0.3 (50% EtOAc/Hexanes).

Spectral data is reported for the major isomer.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 – 7.24 (m, 5H), 4.41 (d, J = 7.6 Hz, 1H), 3.83 – 3.74 (m, 1H), 3.71 – 3.61 (m, 1H), 2.68 (m, 2H), 2.00 (d, J = 6.0 Hz, 1H), 1.86 – 1.75 (m, 1H), 1.67 – 1.55 (m, 1H), 0.78 (d, J = 6.9 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.75, 128.46, 127.70, 126.79, 79.40, 61.10, 38.54, 36.34, 17.48.

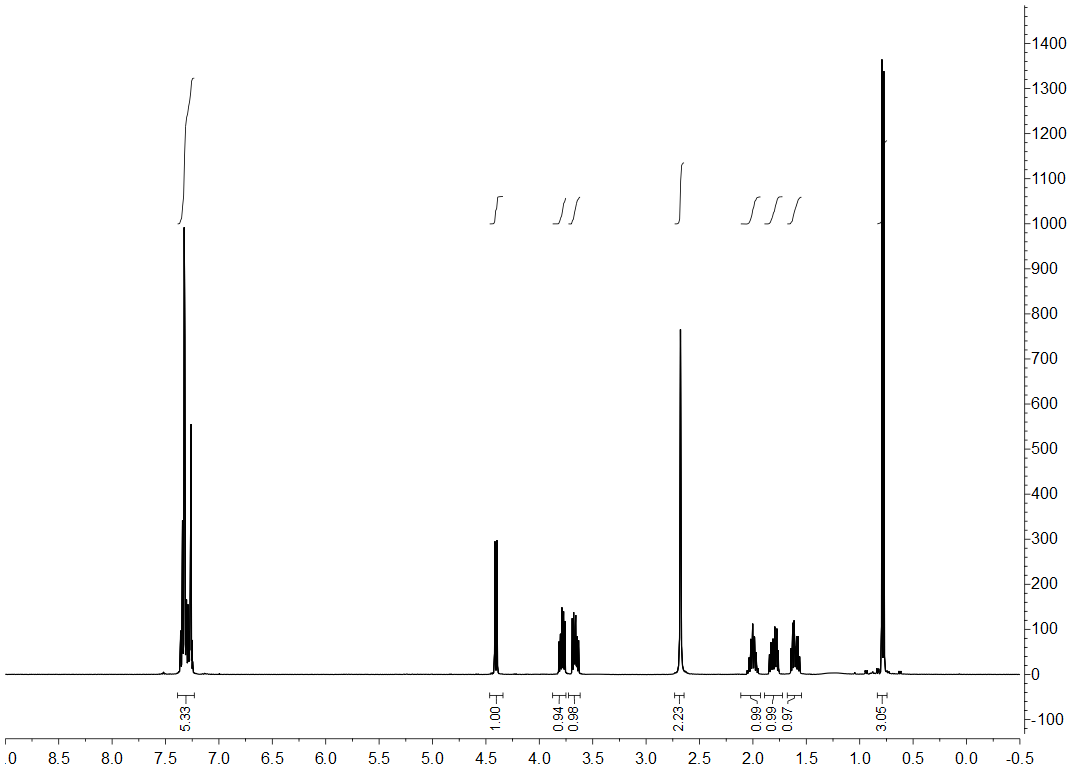
LRMS (CI) Calcd. for $C_{11}H_{16}NaO_2$ $[M+Na]^+$: 203, Found: 203.

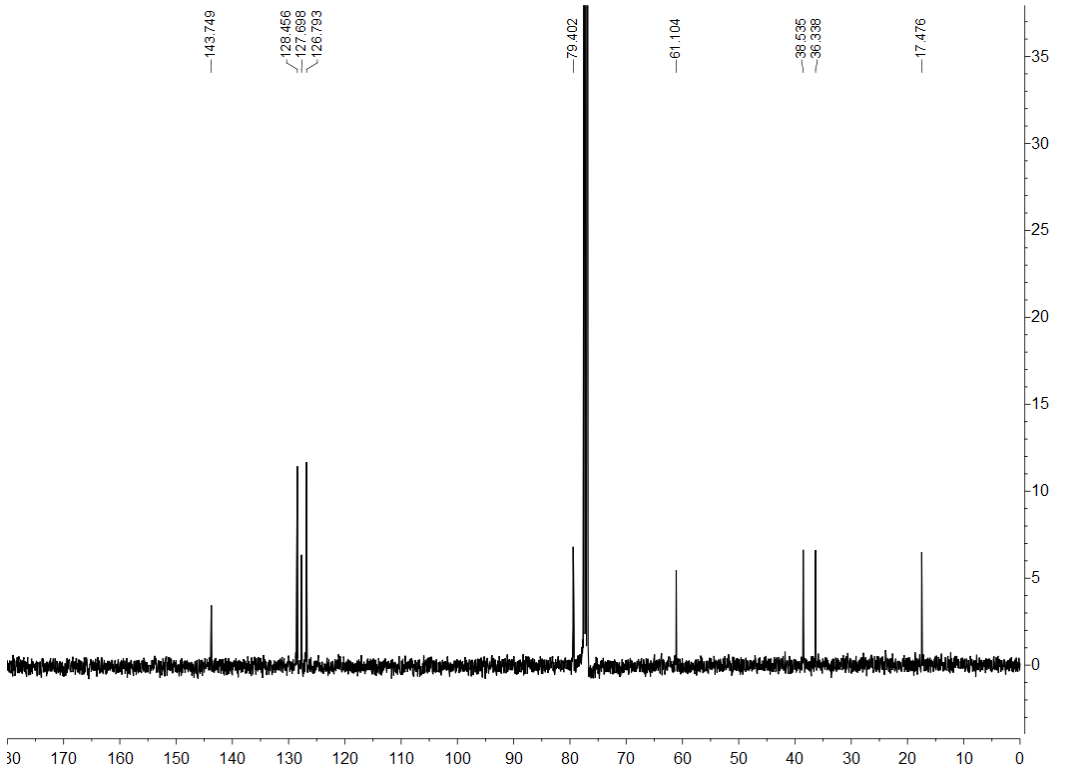
FTIR (neat): 3355, 3288, 2874, 1456, 1052, 1021, 1000, 768, 700 cm^{-1}.

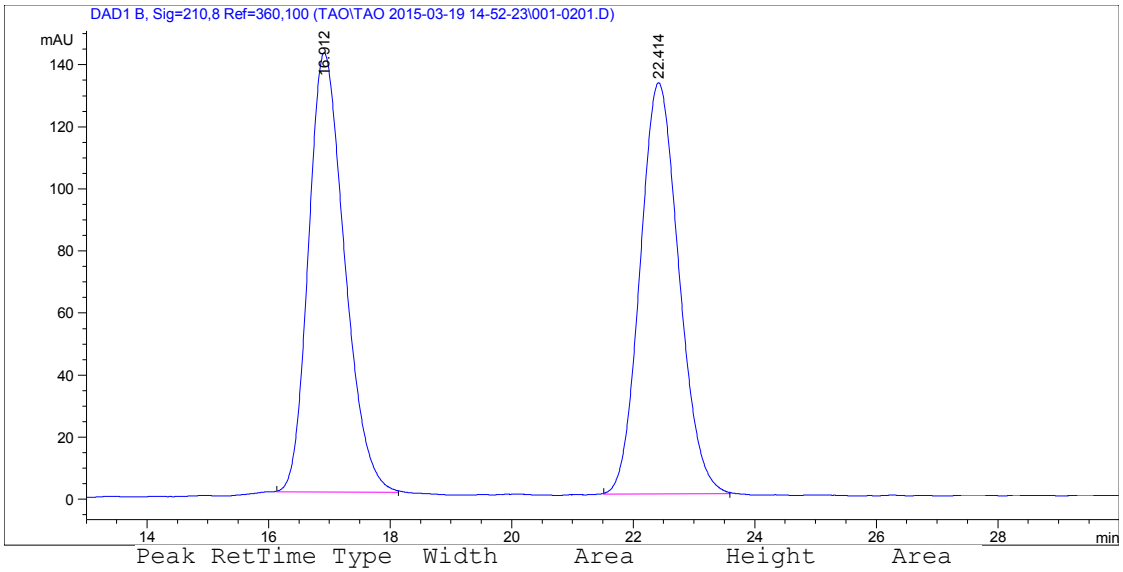
HPLC (Chiralcel OD-H column, hexanes:*i*-PrOH = 95:5, 1 mL/min, 210 nm), ee = 91%.

$[\alpha]^{25}_D$ = - 41.3 (c = 0.75, $CHCl_3$)

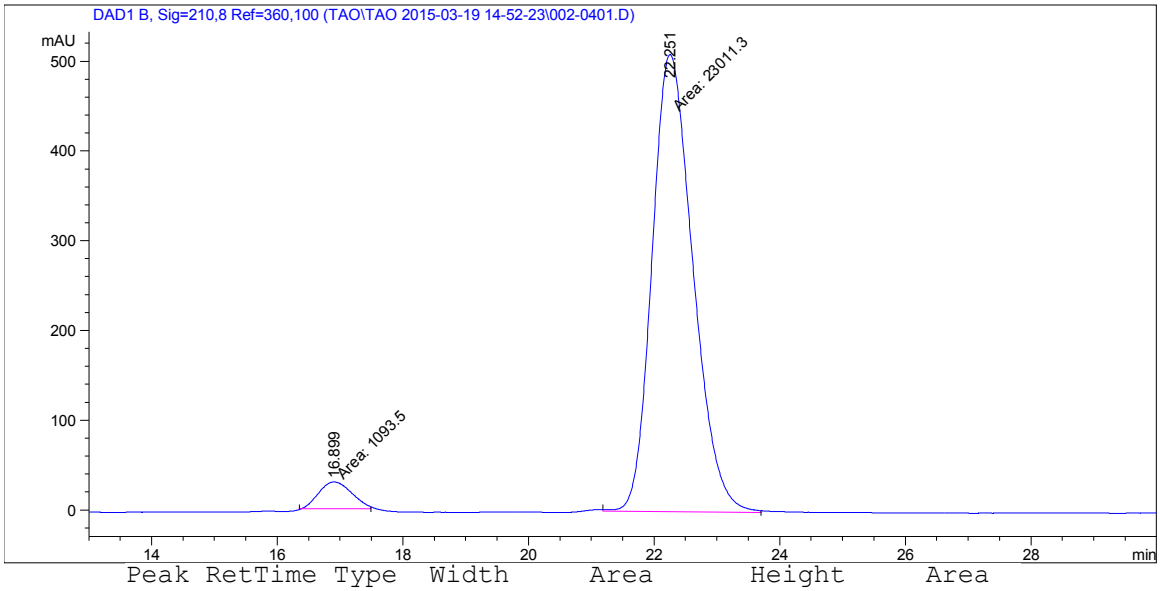
M.P. 91.3-92.3 °C


5.33
1.00
0.94
0.98
2.23
0.99
0.99
0.97
3.05


143.749
128.456
127.698
126.793
79.402
61.104
38.535
36.338
17.476

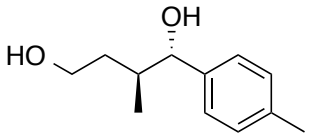


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.912	BB	0.6339	5844.65186	141.50946	49.8516
2	22.414	BB	0.6877	5879.45801	132.49396	50.1484



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.899	MM	0.6081	1093.50195	29.96907	4.5364
2	22.251	MM	0.7528	2.30113e4	509.44580	95.4636

(1*S*,2*S*)-2-methyl-1-(*p*-tolyl)butane-1,4-diol (3.5b).



The residue was subjected to flash column chromatography for purification to furnish the title compound (24.8mg, 64%, *dr* = >20:1) as a white solid.

R_f = 0.3 (50% EtOAc/Hexanes).

Spectral data is reported for the major isomer.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21 (d, J = 8.1 Hz, 2H), 7.15 (d, J = 7.9 Hz, 2H), 4.39 (d, J = 7.6 Hz, 1H), 3.86 – 3.76 (m, 1H), 3.74 – 3.61 (m, 1H), 2.34 (s, 3H), 2.26 (s, 2H), 1.99 (d, J = 6.4 Hz, 1H), 1.88 – 1.76 (m, 1H), 1.67 – 1.55 (m, 1H), 0.78 (d, J = 7.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 140.77, 137.42, 129.18, 126.71, 79.34, 61.27, 38.43, 36.52, 21.26, 17.49.

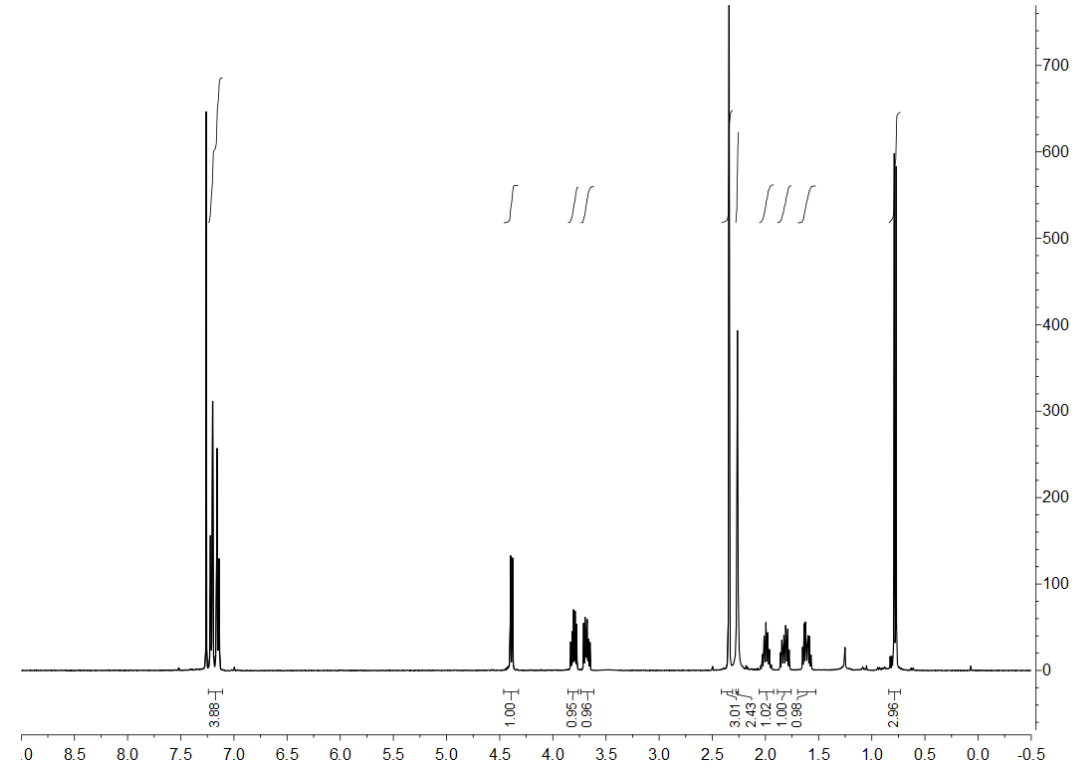
LRMS (CI) Calcd. for $C_{12}H_{18}NaO_2$ $[M+Na]^+$: 217, Found: 217.

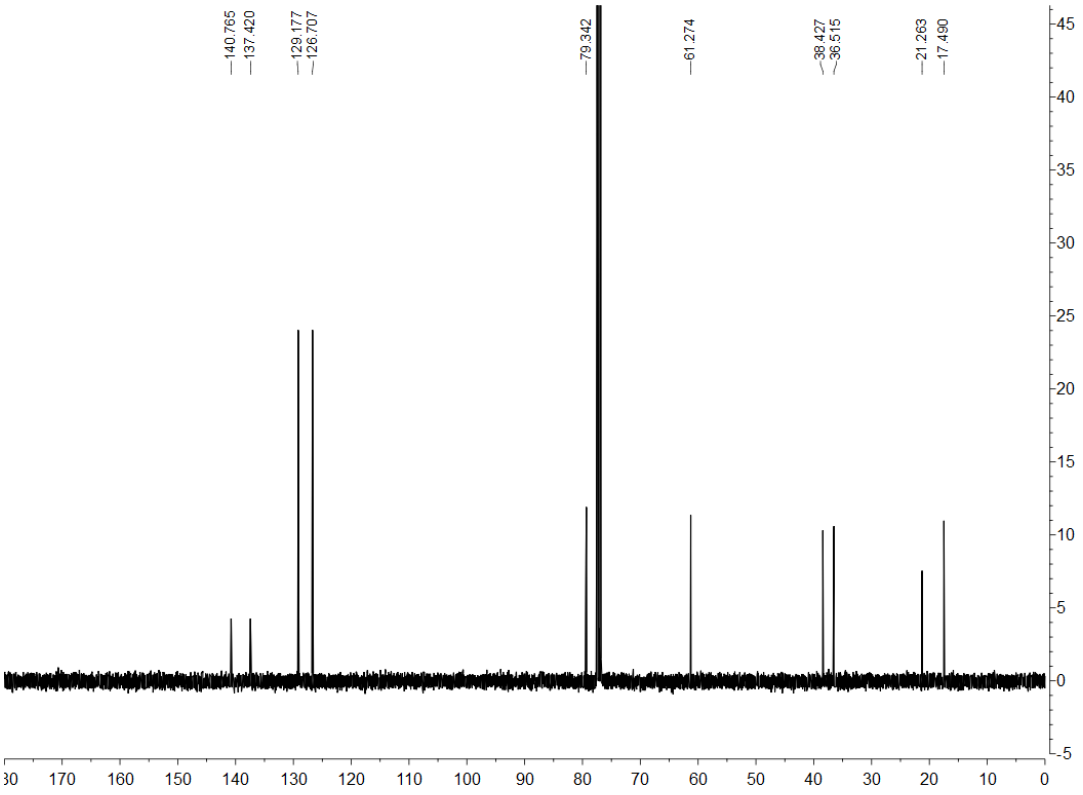
FTIR (neat): 3314, 3016, 2970, 1739, 1365, 1229, 1217cm^{-1}.

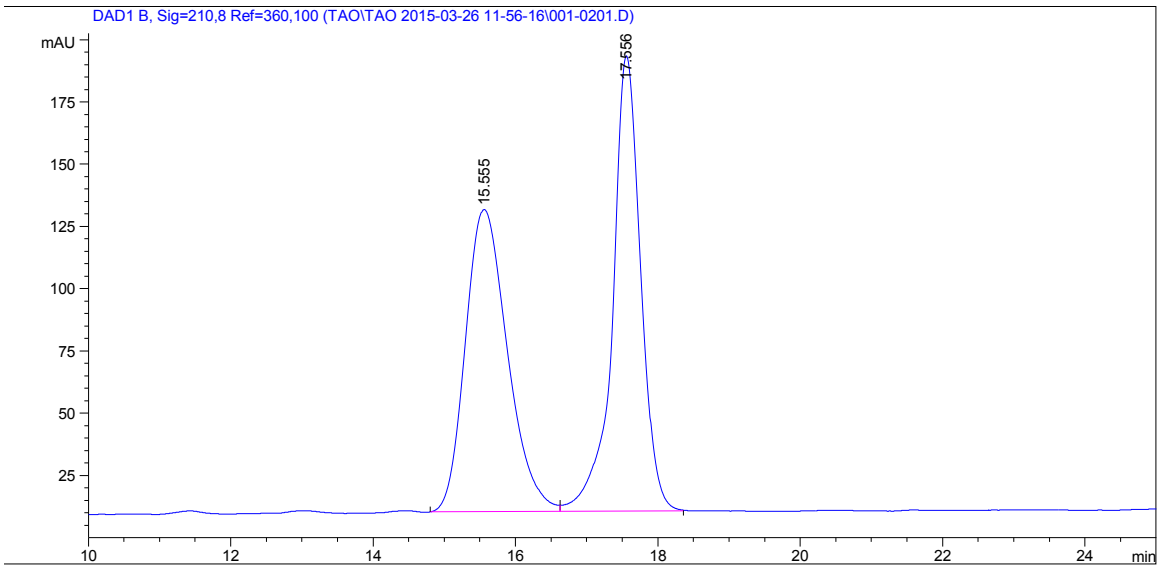
HPLC (Chiralcel OD-H column, hexanes:*i*-PrOH = 95:5, 1 mL/min, 210 nm), ee = 93%.

$[\alpha]^{25}_D$ = - 51.8 (c = 0.65, $CHCl_3$)

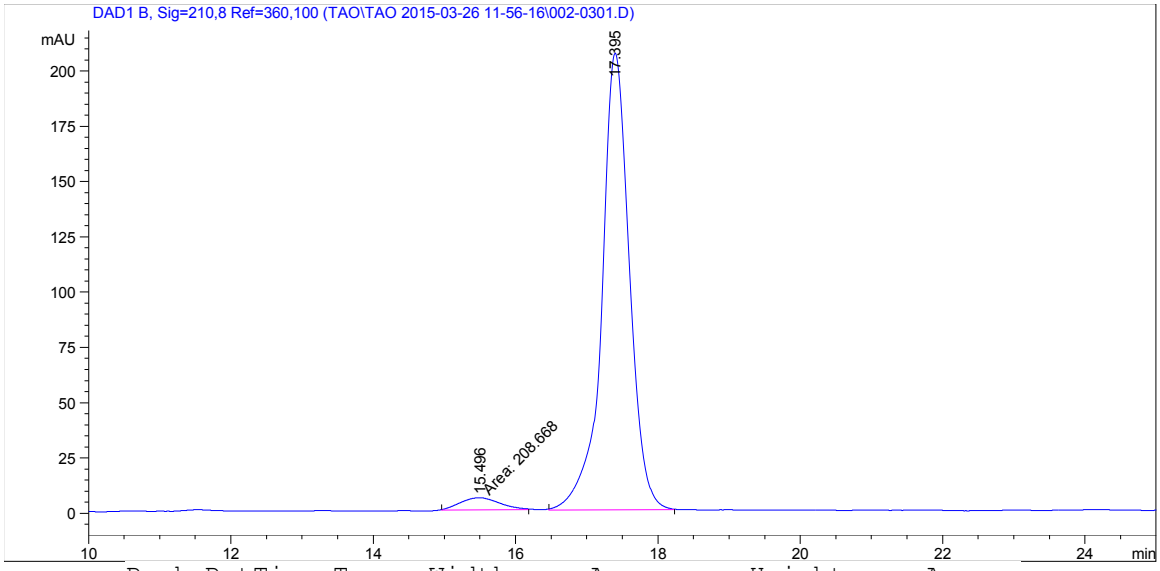
M.P. 117-118.6 °C


3.88
1.00
0.95
0.98
3.01
2.43
1.02
1.00
0.98
2.96


140.765
137.420
129.177
126.707
79.342
61.274
38.427
36.515
21.263
17.490

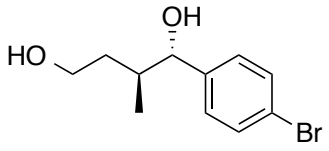


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.555	BV	0.6318	4969.22900	121.32995	49.7294
2	17.556	VB	0.4167	5023.30176	182.76692	50.2706



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.496	MM	0.6357	208.66779	5.47067	3.5911
2	17.395	BB	0.4124	5601.99072	206.54958	96.4089

(1*S*,2*S*)-1-(4-bromophenyl)-2-methylbutane-1,4-diol (3.5c).



The residue was subjected to flash column chromatography for purification to furnish the title compound (39.8 mg, 76%, *dr* = >20:1) as a white solid.

R_f = 0.3 (50% EtOAc/Hexanes).

Spectral data is reported for the major isomer.

^{1}H NMR (400 MHz, Methanol-d_4): δ 7.47 (d, *J* = 8.5 Hz, 2H), 7.25 (d, *J* = 8.2 Hz, 2H), 4.40 (d, *J* = 6.5 Hz, 1H), 3.69 – 3.61 (m, 1H), 3.59 – 3.51 (m, 1H), 1.97 – 1.78 (m, 2H), 1.39 – 1.26 (m, 1H), 0.81 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, Methanol-d_4): δ 144.57, 132.02, 129.74, 121.62, 78.81, 61.13, 38.41, 36.07, 16.54.

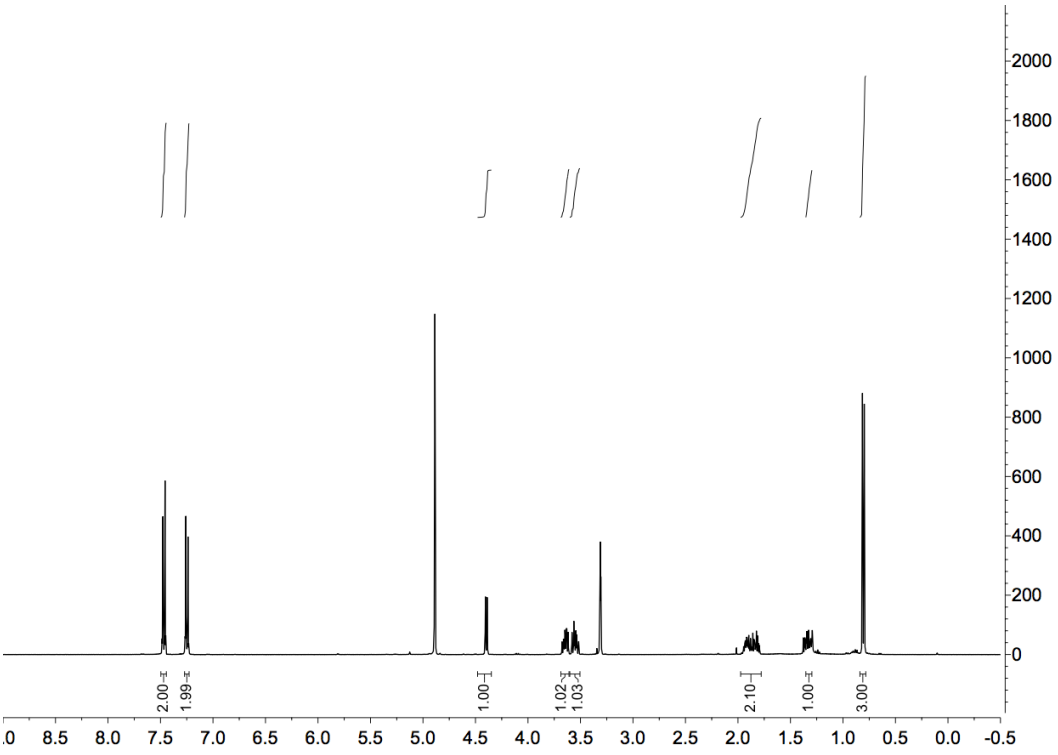
LRMS (CI) Calcd. for $C_{11}H_{15}BrNaO_2$ $[M+Na]^+$: 281, Found: 281.

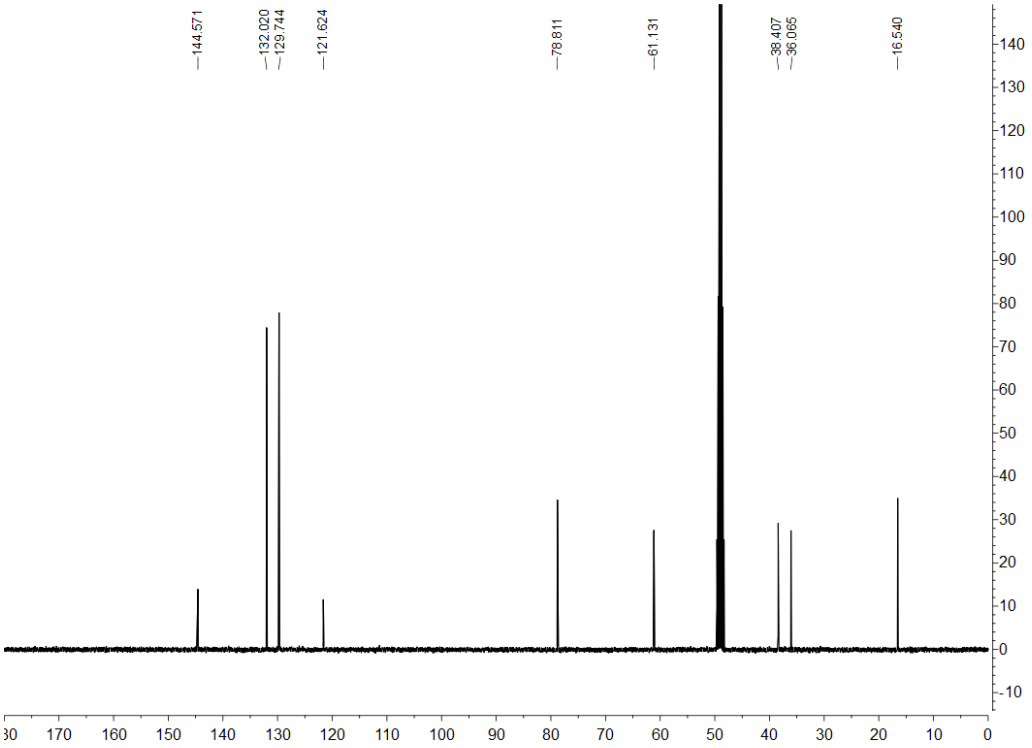
FTIR (neat): 2959, 2929, 2856, 1484, 1050, 1011, 825 cm^{-1}.

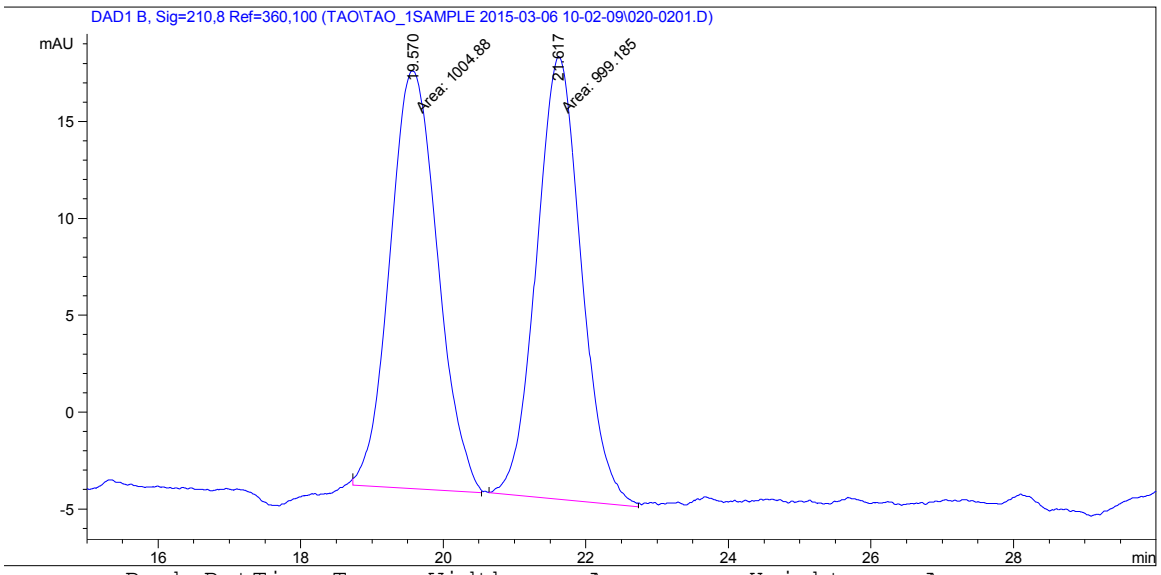
HPLC (Chiralcel OD-H column, hexanes:*i*-PrOH = 95:5, 1 mL/min, 210 nm), ee = 92%.

$[\alpha]^{25}_D$ = - 6.4 (c = 0.7, $CHCl_3$)

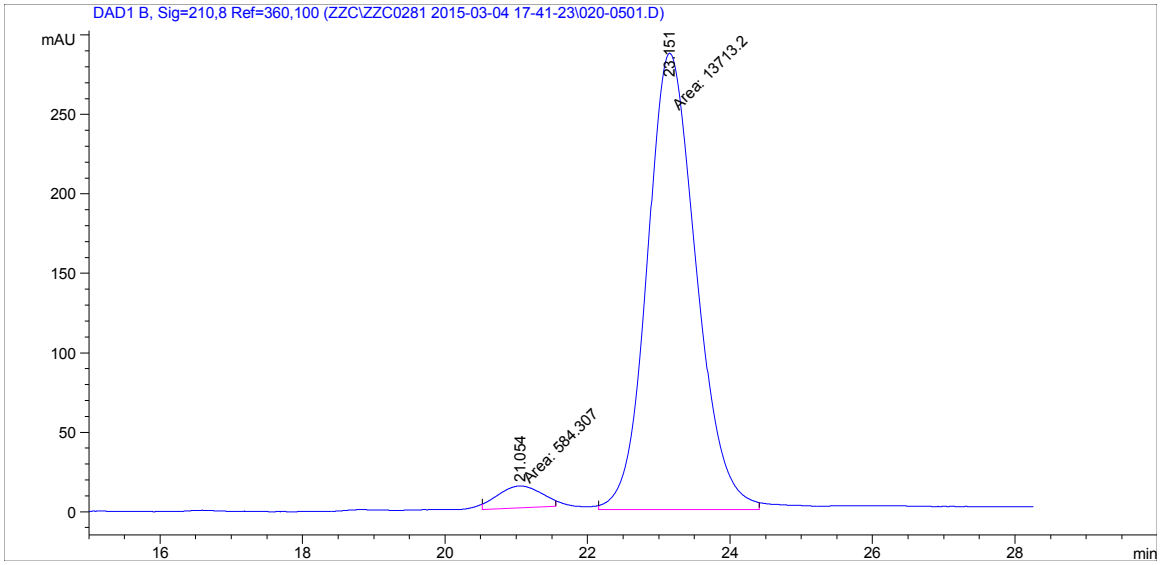
M.P. 146.1-147.4 °C


2.00
1.99
1.00
1.02
1.03
2.10
1.00
3.00


144.571
132.020
129.744
121.624
78.811
61.131
38.407
36.065
16.540

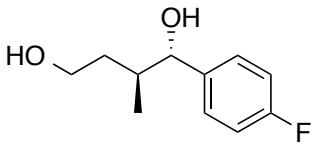


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.570	MM	0.7770	1004.88214	21.55487	50.1421
2	21.617	MM	0.7291	999.18536	22.84135	49.8579



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.054	MM	0.7062	584.30731	13.79014	4.0868
2	23.151	MM	0.7959	1.37132e4	287.16132	95.9132

(1*S*,2*S*)-1-(4-fluorophenyl)-2-methylbutane-1,4-diol (3.5d).



The residue was subjected to flash column chromatography for purification to furnish the title compound (27.7 mg, 75%, *dr* = >20:1) as a white solid.

R_f = 0.3 (50% EtOAc/Hexanes).

Spectral data is reported for the major isomer.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 – 7.26 (m, 2H), 7.06 – 6.99 (m, 2H), 4.41 (d, *J* = 7.5 Hz, 1H), 3.81 (ddd, *J* = 10.6, 6.3, 5.1 Hz, 1H), 3.68 (ddd, *J* = 10.7, 7.8, 4.8 Hz, 1H), 2.03 – 1.91 (m, 1H), 1.85 – 1.75 (m, 1H), 1.65 – 1.56 (m, 1H), 0.78 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 163.37, 160.93, 139.40, 139.37, 128.22, 128.14, 115.21, 115.00, 78.56, 60.91, 38.49, 36.03, 17.20.

^{19}F NMR (100 MHz, $CDCl_3$): δ -115.17.

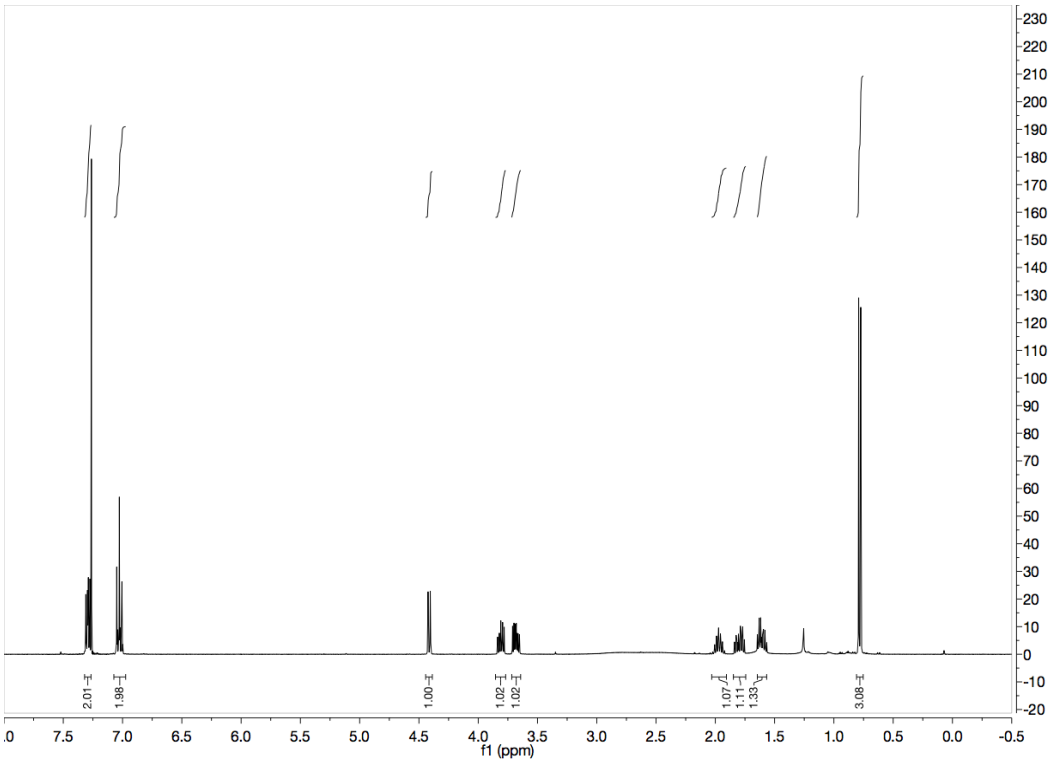
LRMS (CI) Calcd. for $C_{11}H_{15}FNaO_2$ $[M+Na]^+$: 221, Found: 221.

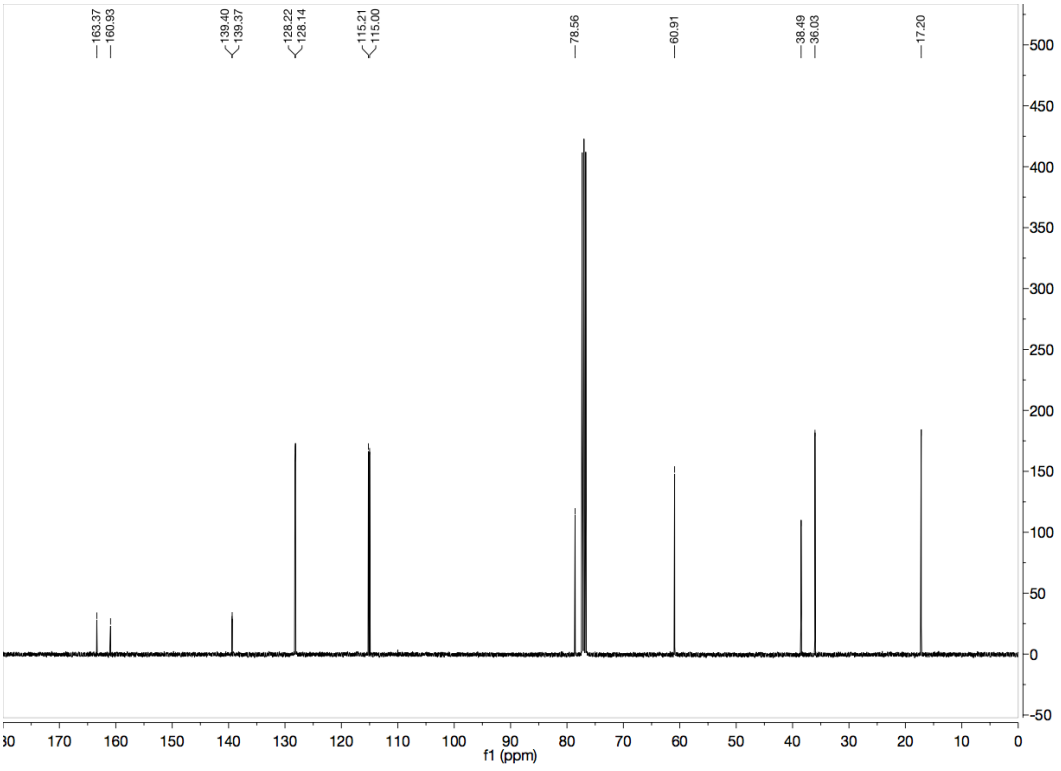
FTIR (neat): 3336, 1604, 1509, 1222, 1056, 1033, 1013, 836 cm^{-1}.

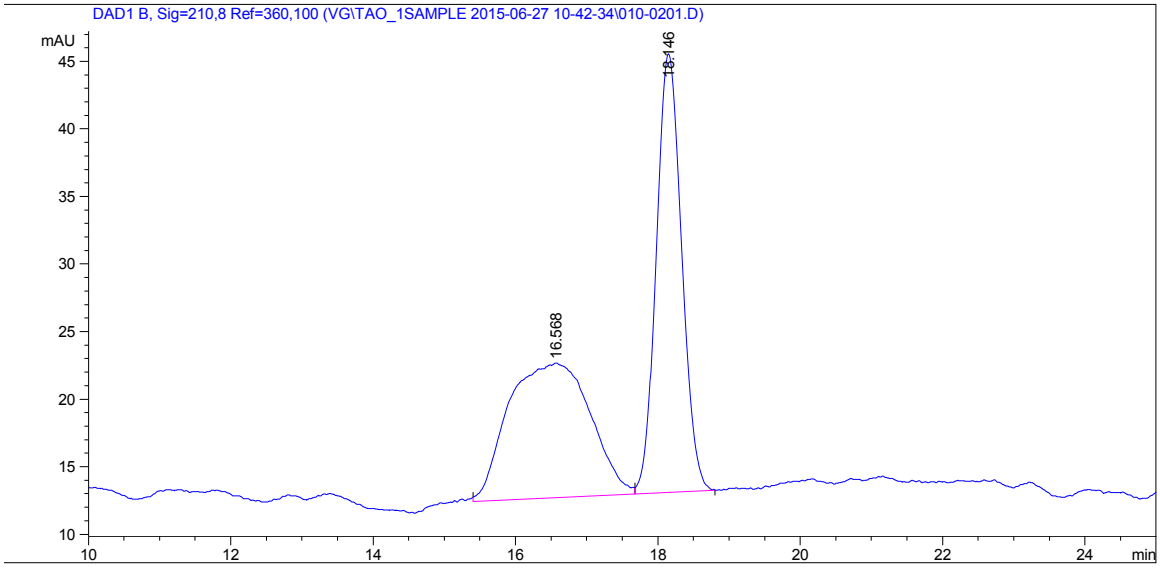
HPLC (Chiralcel OD-H column, hexanes:*i*-PrOH = 95:5, 1 mL/min, 210 nm), ee = 92%.

$[\alpha]^{25}_D$ = + 10.0 (c = 0.32, $CHCl_3$)

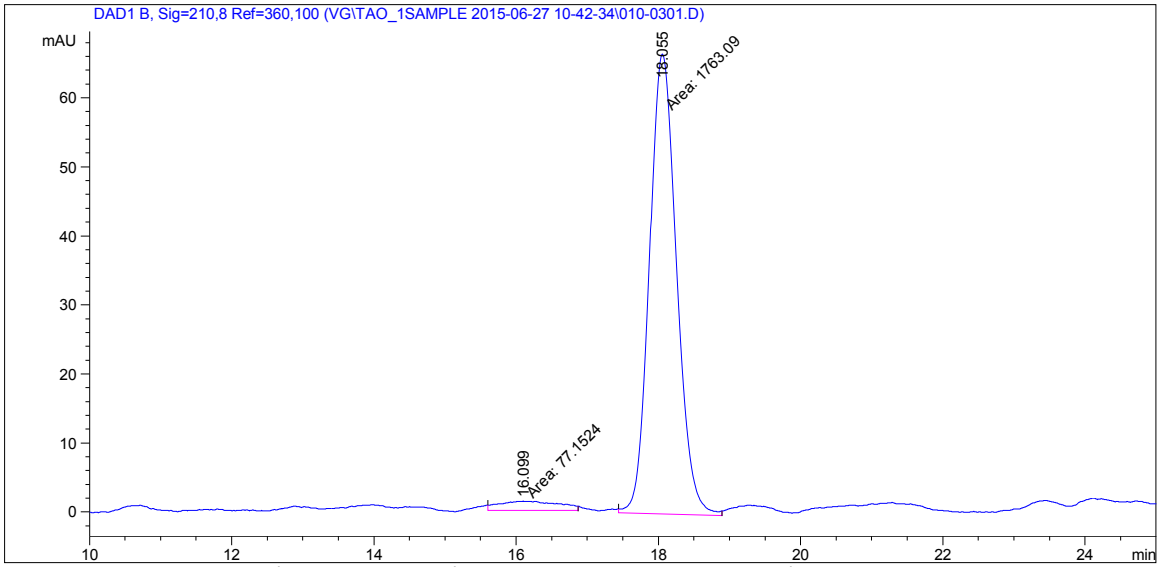
M.P. 114.7-115.9 °C


2.01
1.98
1.00
1.02
1.02
1.07
1.11
1.33
3.08
f1 (ppm)


163.37
160.93
139.40
139.37
128.22
128.14
115.21
115.00
78.56
60.91
38.49
36.03
17.20
f1 (ppm)

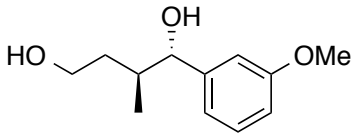


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.568	BV	0.9456	794.74628	9.95268	49.6548
2	18.146	VB	0.3818	805.79523	32.44131	50.3452



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.099	MM	0.9821	77.15244	1.30927	4.1925
2	18.055	MM	0.4412	1763.08777	66.59743	95.8075

(1*S*,2*S*)-1-(3-methoxyphenyl)-2-methylbutane-1,4-diol (3.5e).



The residue was subjected to flash column chromatography for purification to furnish the title compound (31.5 mg, 75%, *dr* = >20:1) as a colorless oil.

R_f = 0.3 (50% EtOAc/Hexanes).

Spectral data is reported for the major isomer.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24 (t, *J* = 8.1 Hz, 1H), 6.90 – 6.86 (m, 2H), 6.83 – 6.78 (m, 1H), 4.35 (d, *J* = 7.6 Hz, 1H), 3.79 (s, 3H), 3.78 – 3.72 (m, 1H), 3.68 – 3.59 (m, 1H), 3.01 – 2.87 (m, 2H), 1.97 (p, *J* = 6.5 Hz, 1H), 1.83 – 1.72 (m, 1H), 1.65 – 1.53 (m, 1H), 0.78 (d, *J* = 6.9 Hz, 3H).

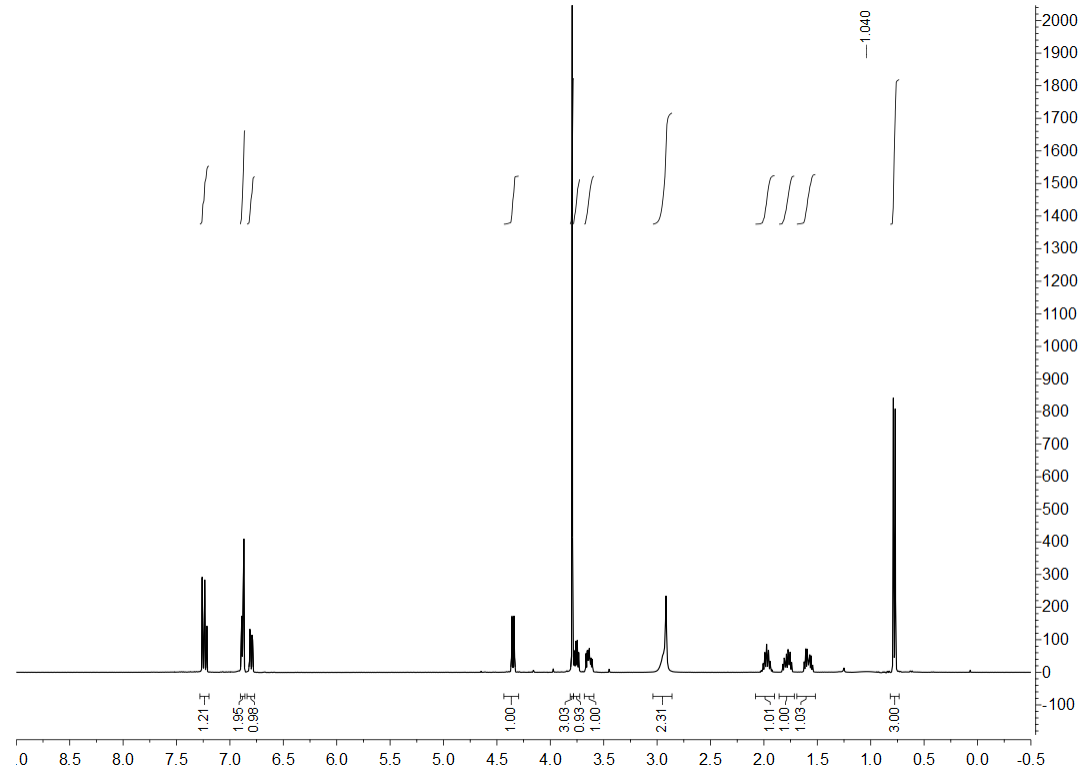
^{13}C NMR (100 MHz, $CDCl_3$): δ 159.71, 145.53, 129.39, 119.23, 112.99, 112.30, 79.26, 60.99, 55.34, 38.50, 36.32, 17.50.

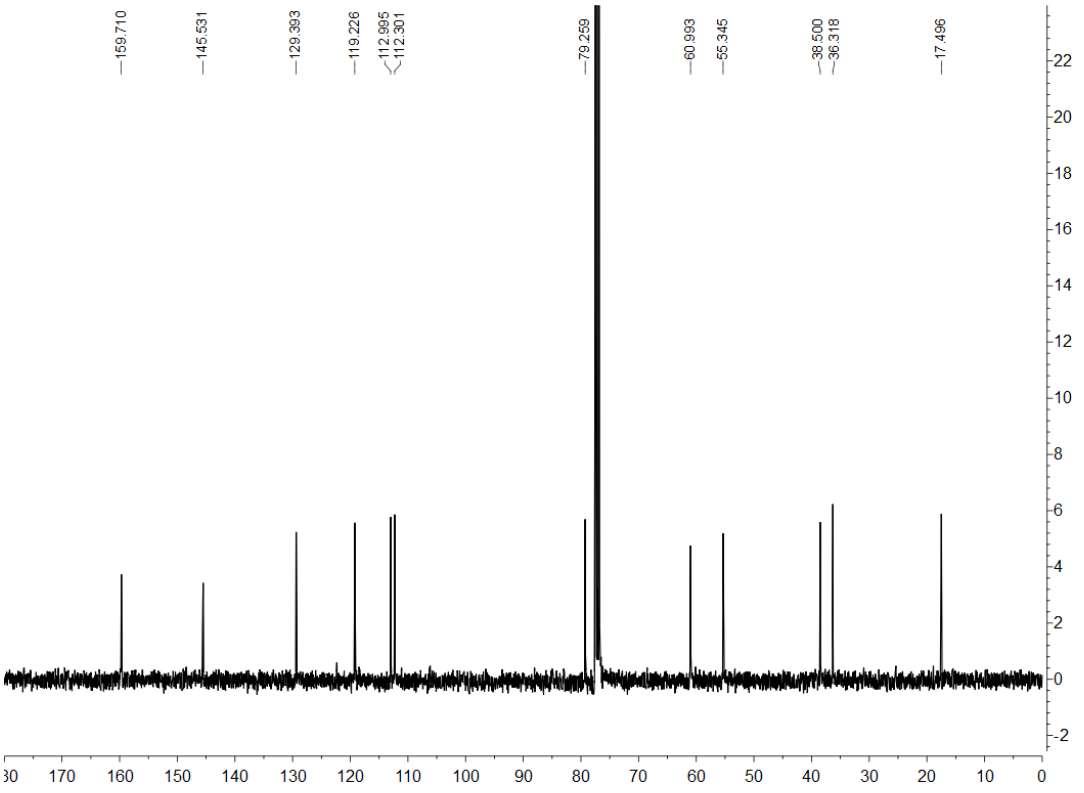
LRMS (CI) Calcd. for $C_{12}H_{18}NaO_3$ $[M+Na]^+$: 233, Found: 233.

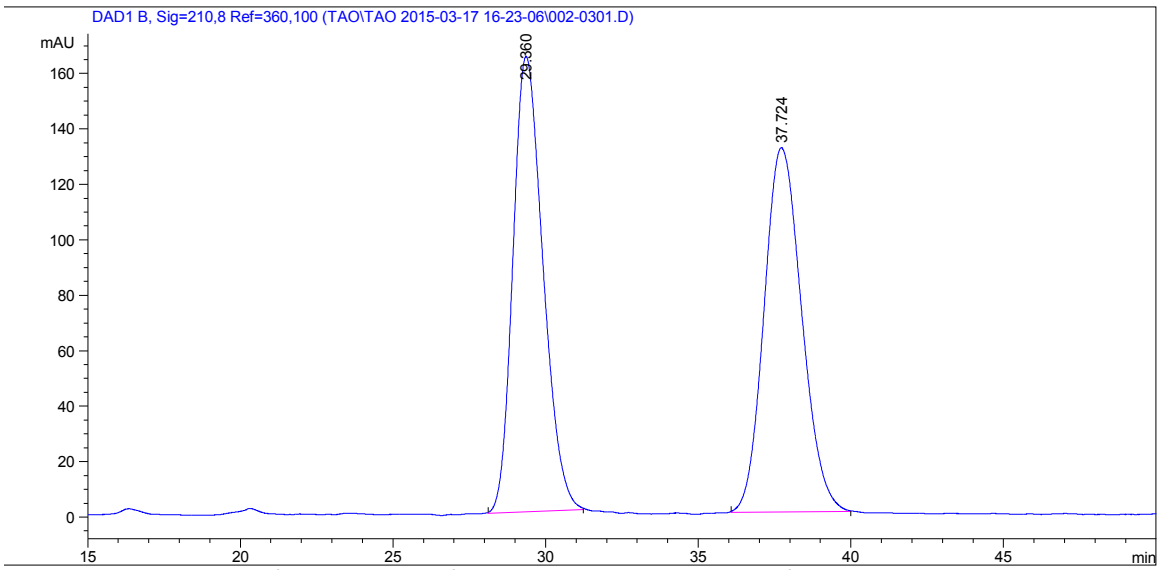
FTIR (neat): 3448, 3016, 2970,1739, 1435, 1366, 1229, 1216 cm^{-1}.

HPLC (Chiralcel OD-H column, hexanes:*i*-PrOH = 95:5, 1 mL/min, 210 nm), ee = 92%.

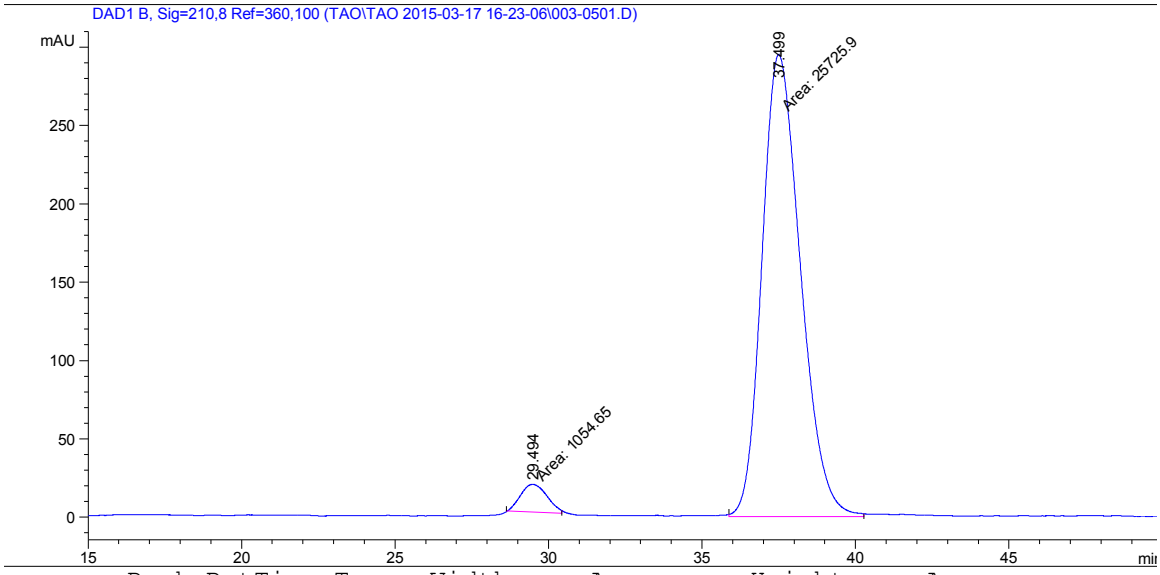
$[\alpha]^{25}_D$ = - 29.0 (c = 0.76, $CHCl_3$)


1.040
1.21
1.95
0.98
1.00
3.03
0.93
1.00
2.31
1.01
1.00
1.03
3.00


159.710
145.531
129.393
119.226
112.995
112.301
79.259
60.993
55.345
38.500
36.318
17.496

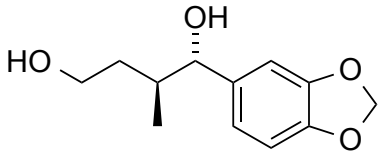


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	29.360	BB	1.0488	1.12134e4	164.18495	49.8926
2	37.724	BB	1.2898	1.12617e4	131.41185	50.1074



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	29.494	MM	0.9963	1054.65125	17.64229	3.9381
2	37.499	MM	1.4534	2.57259e4	295.01712	96.0619

(1*S*,2*S*)-1-(benzo[*d*][1,3]dioxol-5-yl)-2-methylbutane-1,4-diol (3.5f).



The residue was subjected to flash column chromatography for purification to furnish the title compound (23.7 mg, 63%, *dr* = >20:1) as a white solid.

R_f = 0.3 (50% EtOAc/Hexanes).

Spectral data is reported for the major isomer.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.84 (s, 1H), 6.76 (d, *J* = 1.0 Hz, 2H), 5.95 (s, 2H), 4.32 (d, *J* = 7.8 Hz, 1H), 3.84 – 3.76 (m, 1H), 3.72 – 3.64 (m, 1H), 2.61 (s, 2H), 1.94 (hept, *J* = 6.7 Hz, 1H), 1.85 – 1.76 (m, 1H), 1.65 – 1.57 (m, 1H), 0.77 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 147.71, 146.90, 137.73, 120.11, 107.90, 106.88, 100.96, 79.17, 61.07, 38.48, 36.41, 17.38.

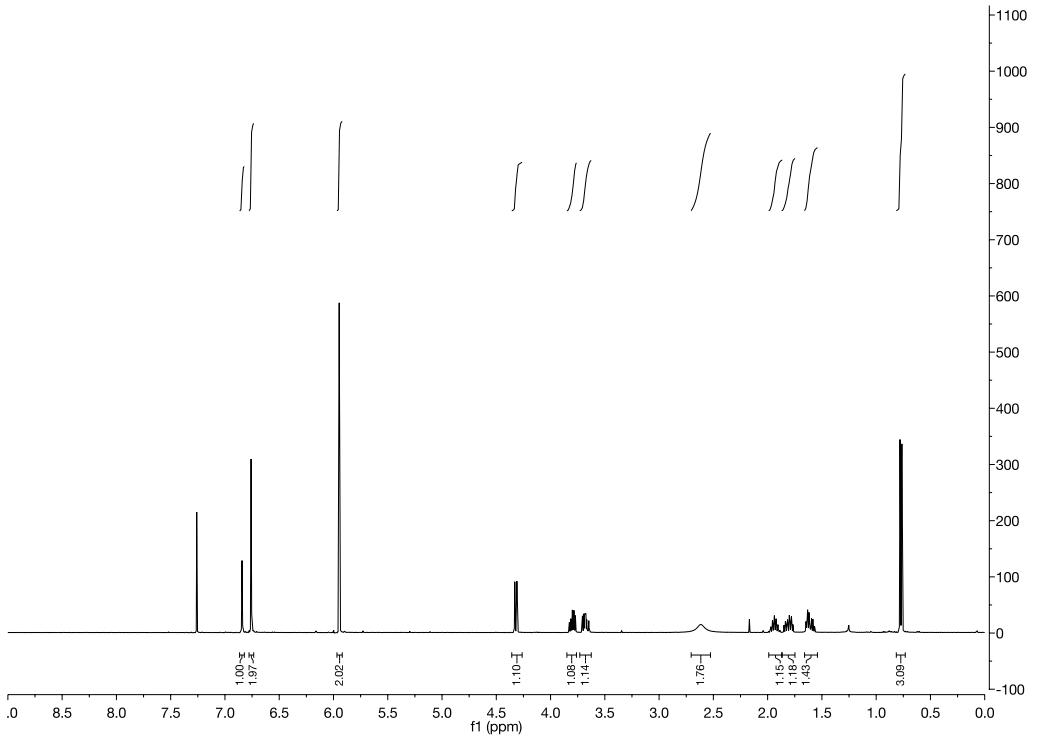
LRMS (CI) Calcd. for $C_{12}H_{16}NaO_4$ $[M+Na]^+$: 247, Found: 247.

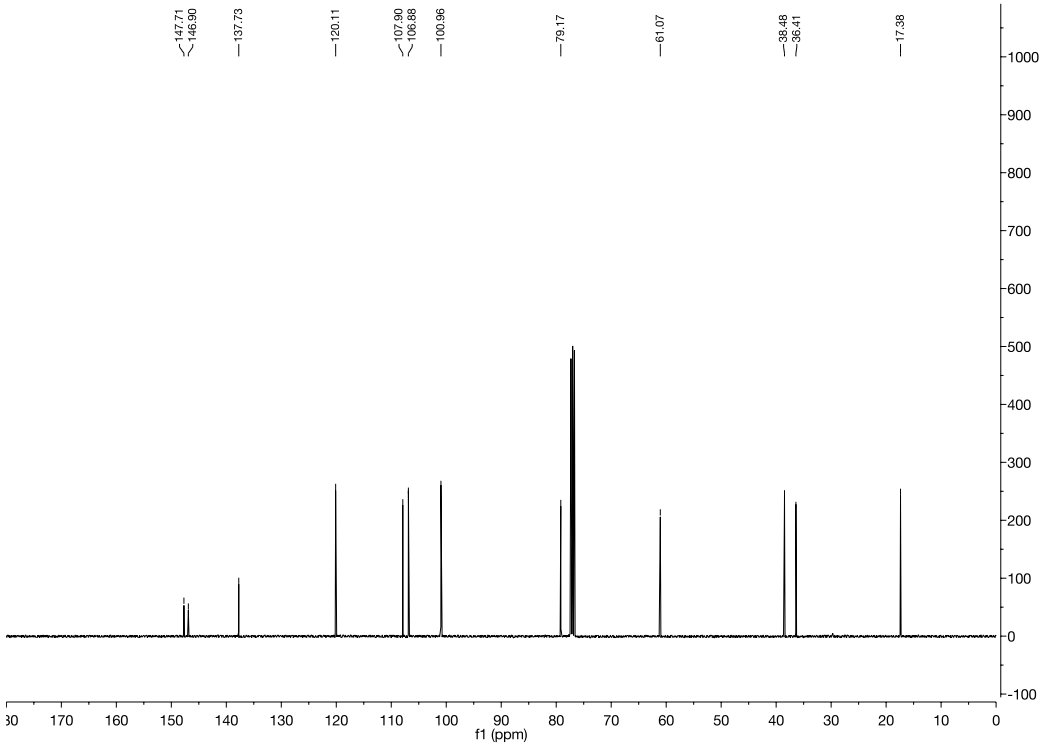
FTIR (neat): 3323, 2890, 1488,1246, 1037, 1006, 932, 823 cm^{-1}.

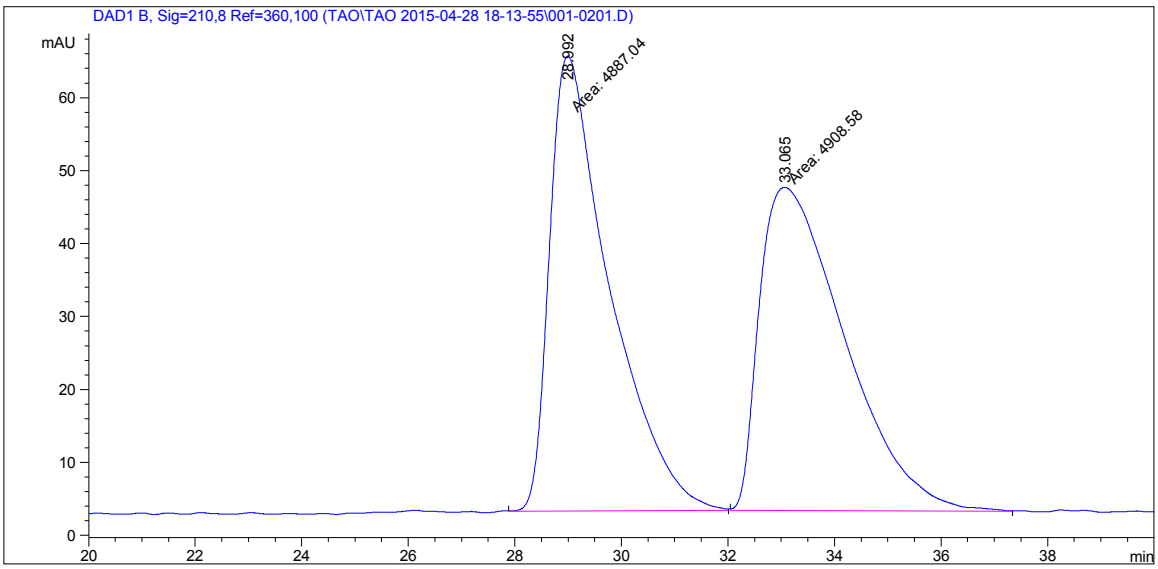
HPLC (Chiralcel AS-H column, hexanes:*i*-PrOH = 95:5, 1 mL/min, 210 nm), ee = 94%.

$[\alpha]^{25}_D$ = - 58.7 (c = 0.48, $CHCl_3$)

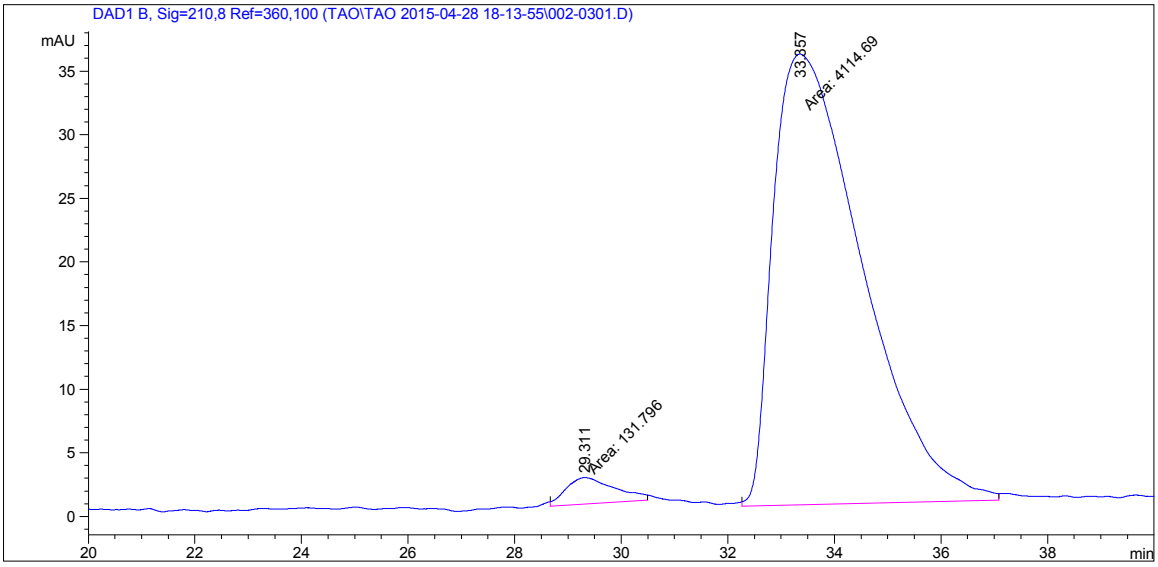
M.P. 97.3-98.6 °C


1.00
1.97
2.02
1.10
1.08
1.14
1.76
1.15
1.18
1.43
3.09
f1 (ppm)


147.71
146.90
137.73
120.11
107.90
106.88
100.96
79.17
61.07
38.48
36.41
17.38
f1 (ppm)

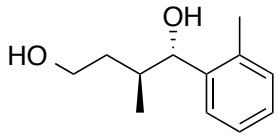


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	28.992	MM	1.3066	4887.03564	62.33603	49.8900
2	33.065	MM	1.8481	4908.57764	44.26786	50.1100



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	29.311	MM	1.0546	131.79645	2.08292	3.1037
2	33.357	MM	1.9357	4114.68604	35.42754	96.8963

(1*S*,2*S*)-2-methyl-1-(o-tolyl)butane-1,4-diol (3.5g)



The residue was subjected to flash column chromatography for purification to furnish the title compound (23.6 mg, 61%, *dr* = >20:1) as a white solid.

R_f = 0.4 (50% EtOAc/Hexanes).

Spectral data is reported for the major isomer.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.22 (td, *J* = 7.3, 1.8 Hz, 1H), 7.16 (td, *J* = 7.3, 1.5 Hz, 1H), 7.13 (dd, *J* = 7.5, 1.8 Hz, 1H), 4.69 (d, *J* = 7.8 Hz, 1H), 3.84 – 3.73 (m, 1H), 3.66 (ddd, *J* = 10.8, 7.9, 4.7 Hz, 1H), 2.86 (s, 2H), 2.34 (s, 3H), 2.02 (hept, *J* = 7.0 Hz, 1H), 1.90 – 1.76 (m, 1H), 1.74 – 1.61 (m, 1H), 0.81 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 141.99, 135.06, 130.37, 127.18, 126.30, 126.22, 75.18, 61.06, 38.02, 36.22, 19.49, 17.40.

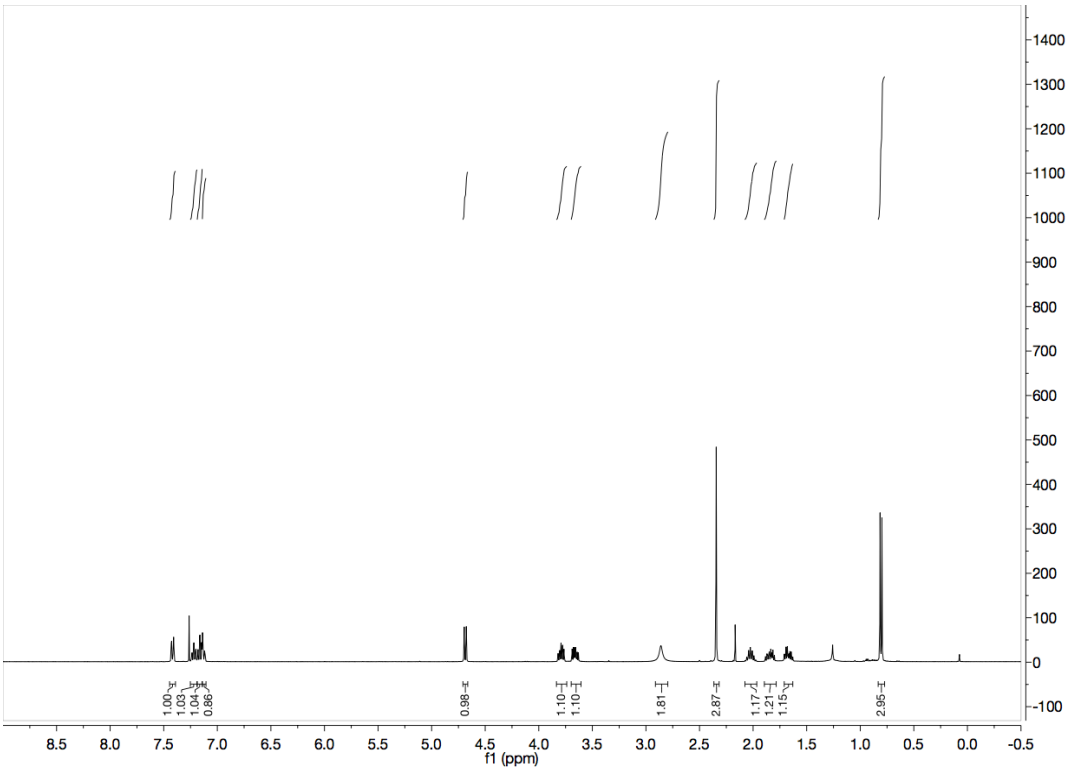
LRMS (CI) Calcd. for $C_{12}H_{18}NaO_2$ $[M+Na]^+$: 217, Found: 217.

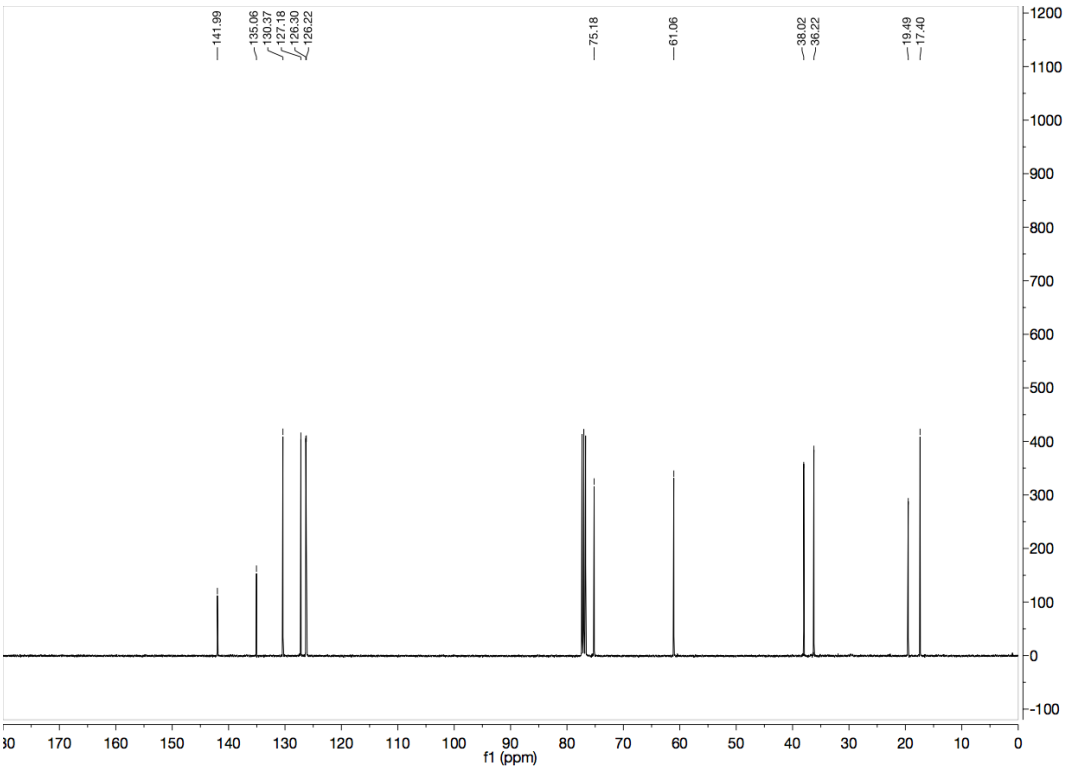
FTIR (neat): 2958, 2923, 1460, 1378, 1054, 1012, 756, 729 cm^{-1}.

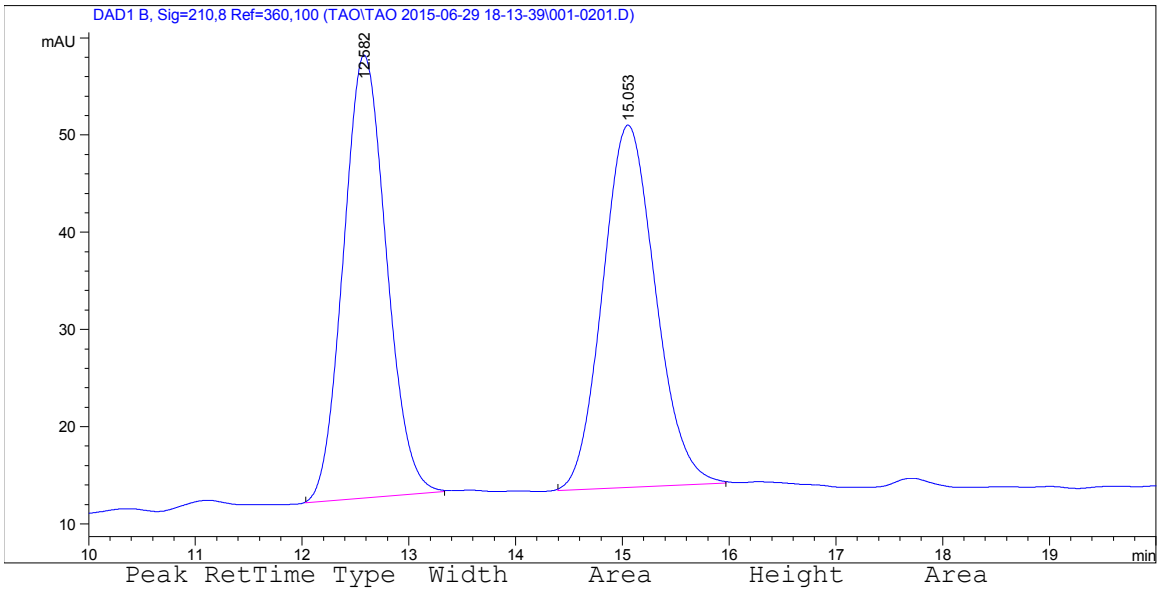
HPLC (Chiralcel OD-H column, hexanes:*i*-PrOH = 95:5, 1 mL/min, 210 nm), ee = 87%.

$[\alpha]^{25}_D$ = - 37.9 (c = 0.44, $CHCl_3$)

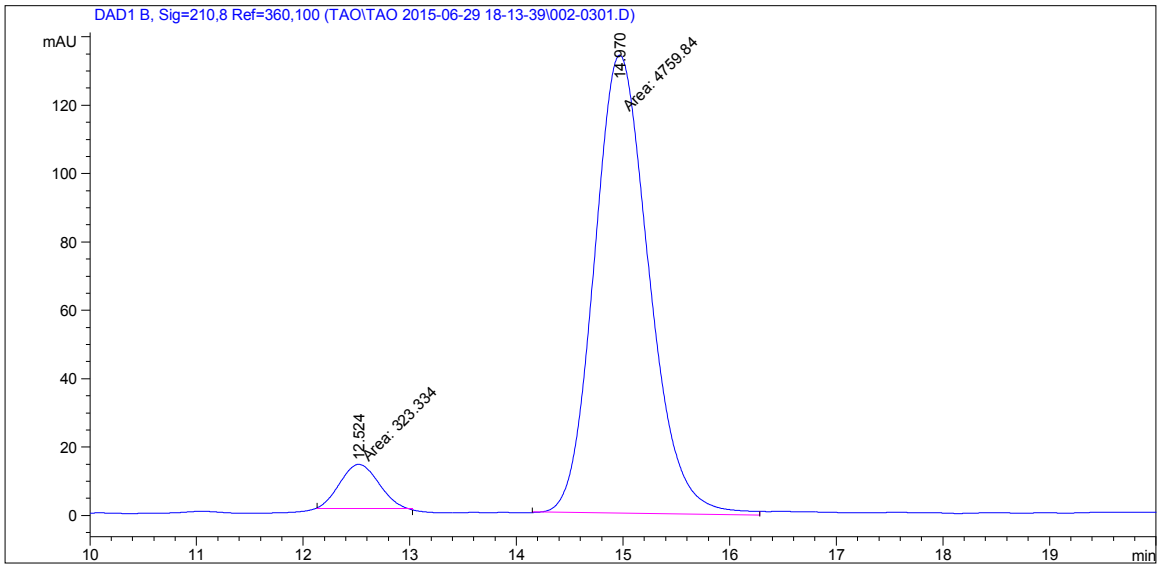
M.P. 84.6-86.7 °C


1.00
1.03
1.04
0.86
0.98
1.10
1.10
1.81
2.87
1.17
1.21
1.15
2.95
f1 (ppm)


141.99
135.06
130.37
127.18
126.30
126.22
75.18
61.06
38.02
36.22
19.49
17.40
f1 (ppm)

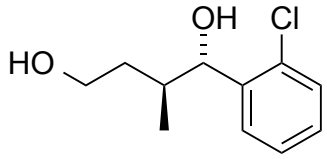


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.582	BB	0.4370	1277.60510	45.58098	49.9202
2	15.053	BB	0.5332	1281.68738	37.27221	50.0798



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.524	MM	0.4181	323.33398	12.88840	6.3609
2	14.970	MM	0.5924	4759.83838	133.90485	93.6391

(1*S*,2*S*)-1-(2-chlorophenyl)-2-methylbutane-1,4-diol (3.5h).



The residue was subjected to flash column chromatography for purification to furnish the title compound (29.1 mg, 68%, *dr* = >20:1) as a colorless oil.

R_f = 0.5 (50% EtOAc/Hexanes).

Spectral data is reported for the major isomer.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.32 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.28 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.19 (dd, *J* = 7.7, 1.8 Hz, 1H), 4.95 (d, *J* = 6.8 Hz, 1H), 3.83 – 3.74 (m, 1H), 3.68 – 3.58 (m, 1H), 3.26 (bs, 1H), 2.69 (bs, 1H), 2.09 (hept, *J* = 6.5 Hz, 1H), 1.83 – 1.69 (m, 1H), 1.68 – 1.56 (m, 1H), 0.90 (d, *J* = 7.0 Hz, 3H).

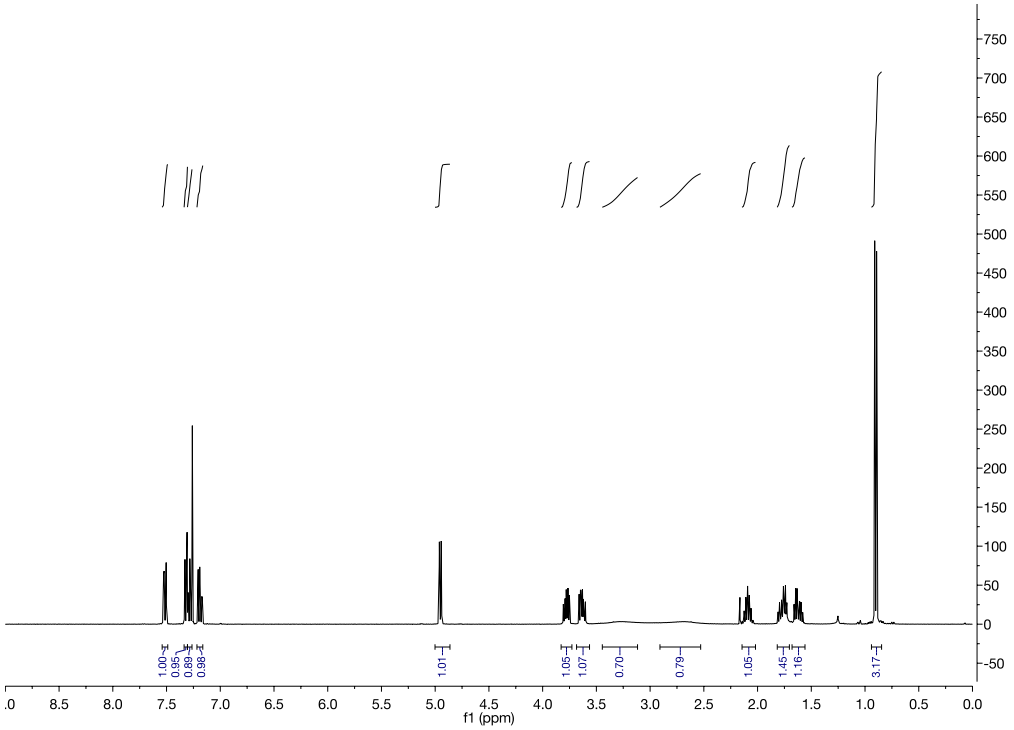
^{13}C NMR (100 MHz, $CDCl_3$): δ 141.23, 132.45, 129.33, 128.38, 128.19, 126.95, 74.73, 60.67, 37.38, 35.01, 16.92.

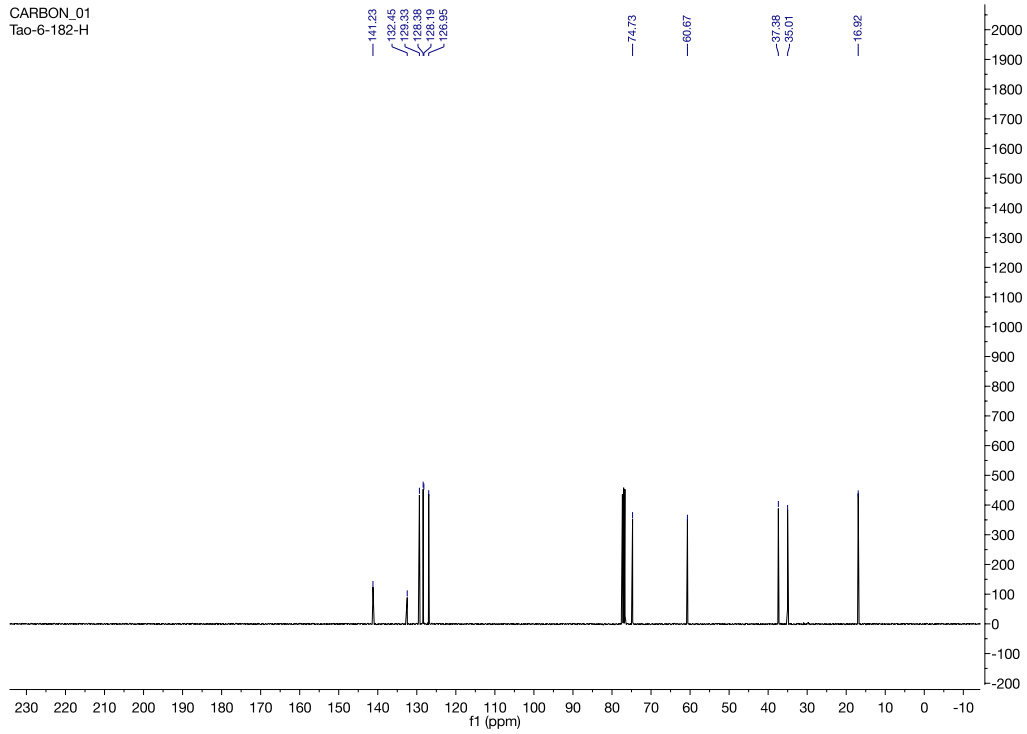
LRMS (CI) Calcd. for $C_{11}H_{15}NaClO_2$ $[M+Na]^+$: 237, Found: 237.

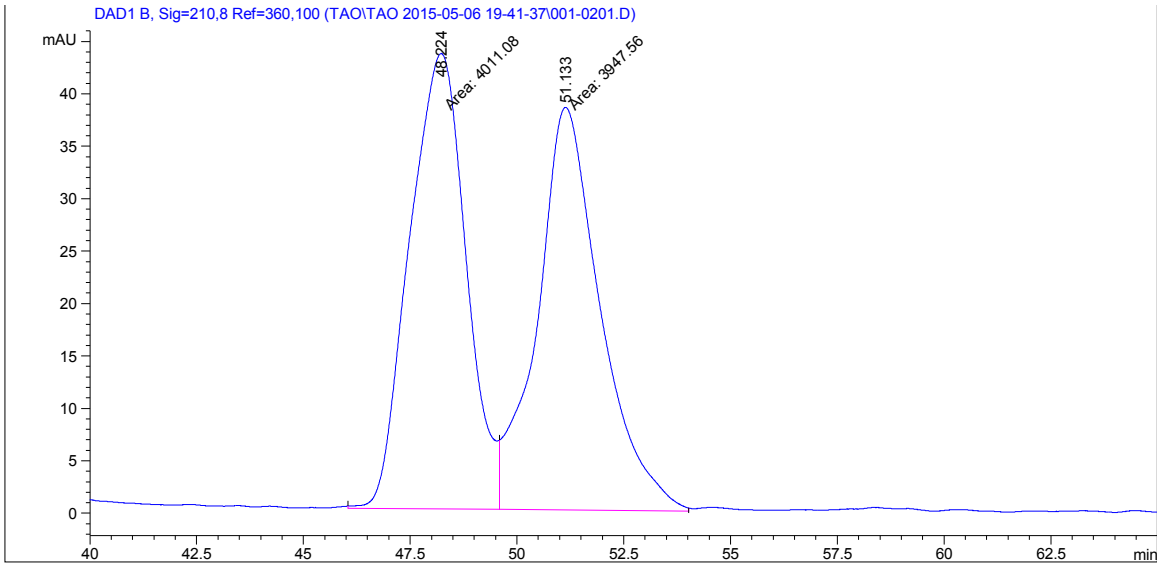
FTIR (neat): 3315, 2958, 2922,2850, 1438, 1049, 1023, 735 cm^{-1}.

HPLC (Chiralcel AS-H/AS-H column, hexanes:*i*-PrOH = 95:5, 0.5 mL/min, 210 nm), ee = 91%.

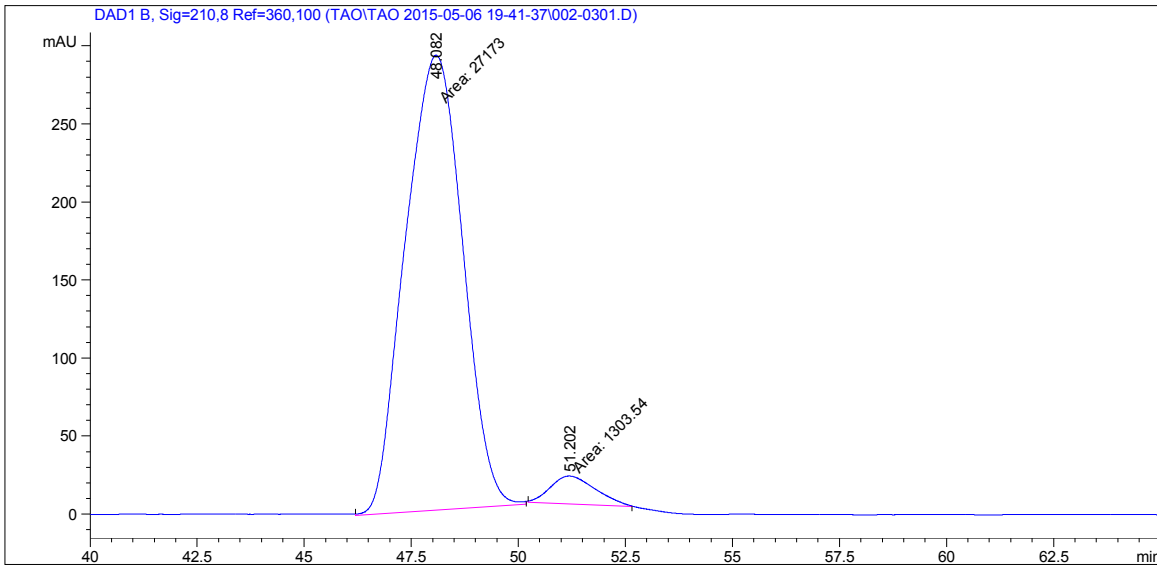
$[\alpha]^{25}_D$ = - 19.2 (c = 0.53, $CHCl_3$)


1.00
0.95
0.89
0.98
1.01
1.05
1.07
0.70
0.79
1.05
1.45
1.16
3.17
f1 (ppm)


CARBON_01
Tao-6-182-H
141.23
132.45
129.33
128.38
128.19
126.95
74.73
60.67
37.38
35.01
16.92
f1 (ppm)

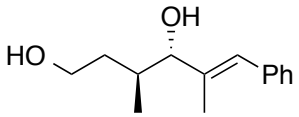


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	48.224	MF	1.5389	4011.08301	43.44012	50.3991
2	51.133	FM	1.7133	3947.55981	38.40157	49.6009



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	48.082	MM	1.5540	2.71730e4	291.42899	95.4224
2	51.202	MM	1.2196	1303.53503	17.81412	4.5776

(3*S*,4*S*,*E*)-3,5-dimethyl-6-phenylhex-5-ene-1,4-diol (3.5i).



The residue was subjected to flash column chromatography for purification to furnish the title compound (29.7 mg, 72%, *dr* = >20:1) as a colorless liquid.

R_f = 0.3 (50% EtOAc/Hexanes).

Spectral data is reported for the major isomer.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 – 7.31 (m, 2H), 7.30 – 7.27 (m, 2H), 7.27 – 7.18 (m, 1H), 6.47 (s, 1H), 3.88 (d, *J* = 8.3 Hz, 1H), 3.85 – 3.78 (m, 1H), 3.69 (ddd, *J* = 10.8, 8.1, 4.5 Hz, 1H), 2.76 (s, 2H), 1.97 – 1.88 (m, 1H), 1.87 (d, *J* = 1.4 Hz, 3H), 1.86 – 1.79 (m, 1H), 1.68 – 1.58 (m, 1H), 0.90 (d, *J* = 6.8 Hz, 3H).

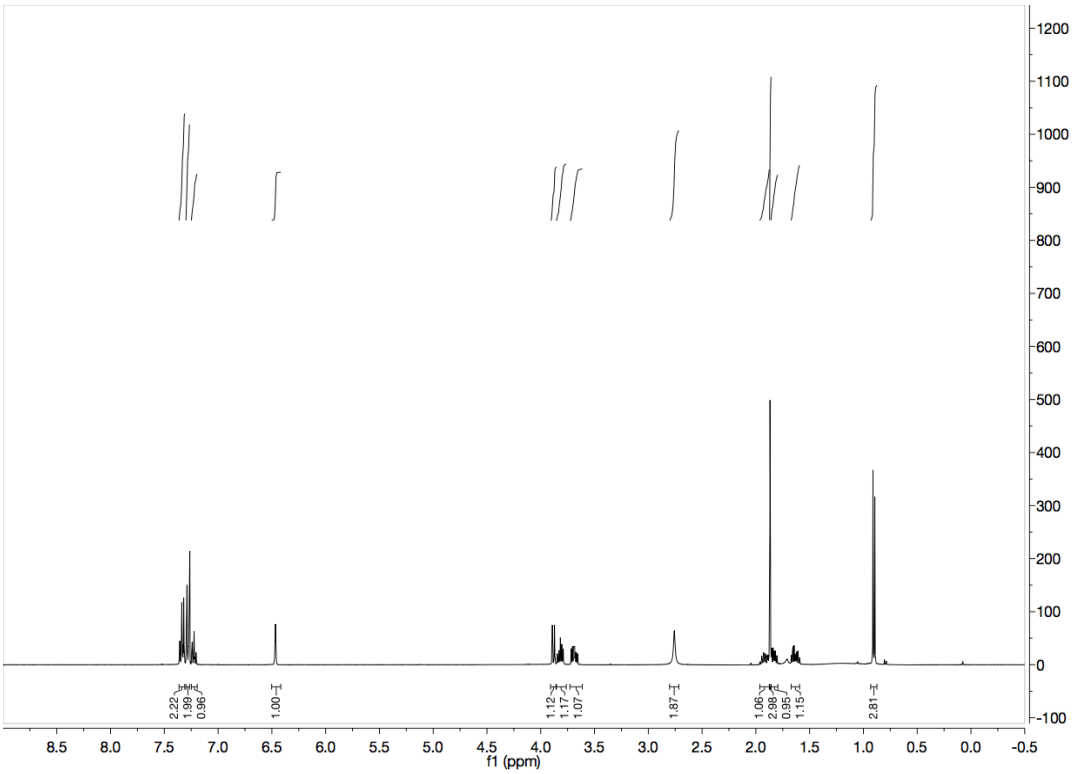
^{13}C NMR (100 MHz, $CDCl_3$): δ 139.37, 137.42, 128.97, 128.12, 127.52, 126.51, 83.42, 61.24, 36.78, 34.64, 17.82, 12.98.

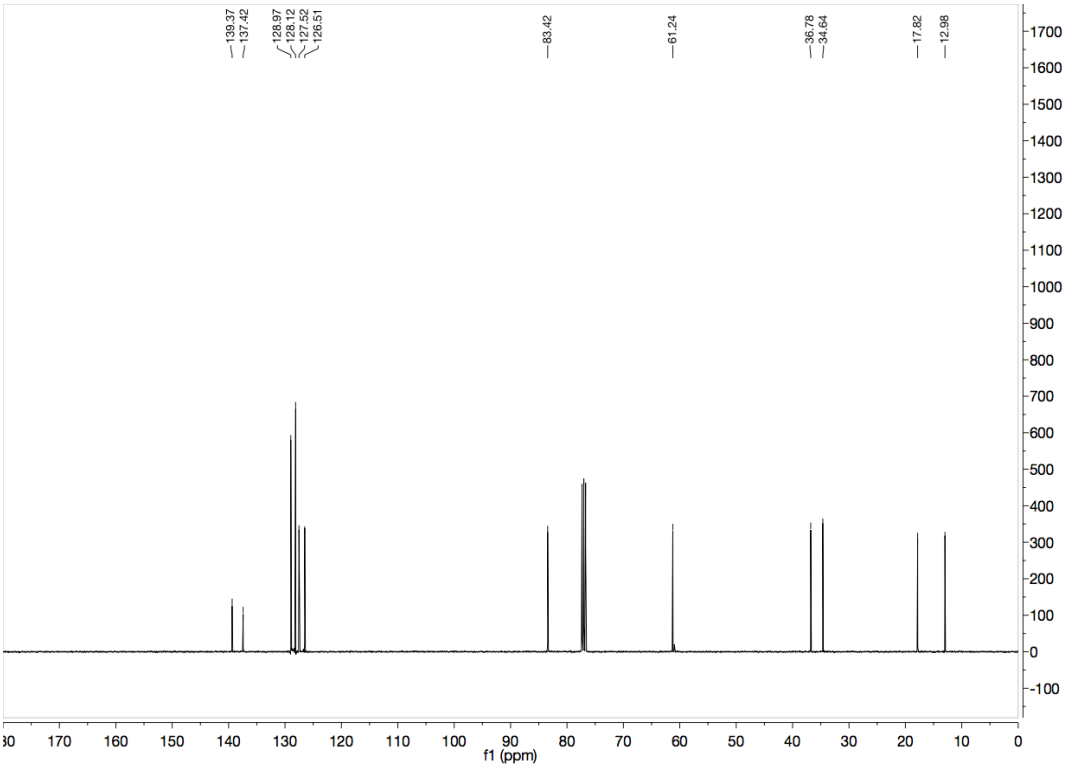
LRMS (CI) Calcd. for $C_{14}H_{20}NaO_2$ $[M+Na]^+$: 243, Found: 243.

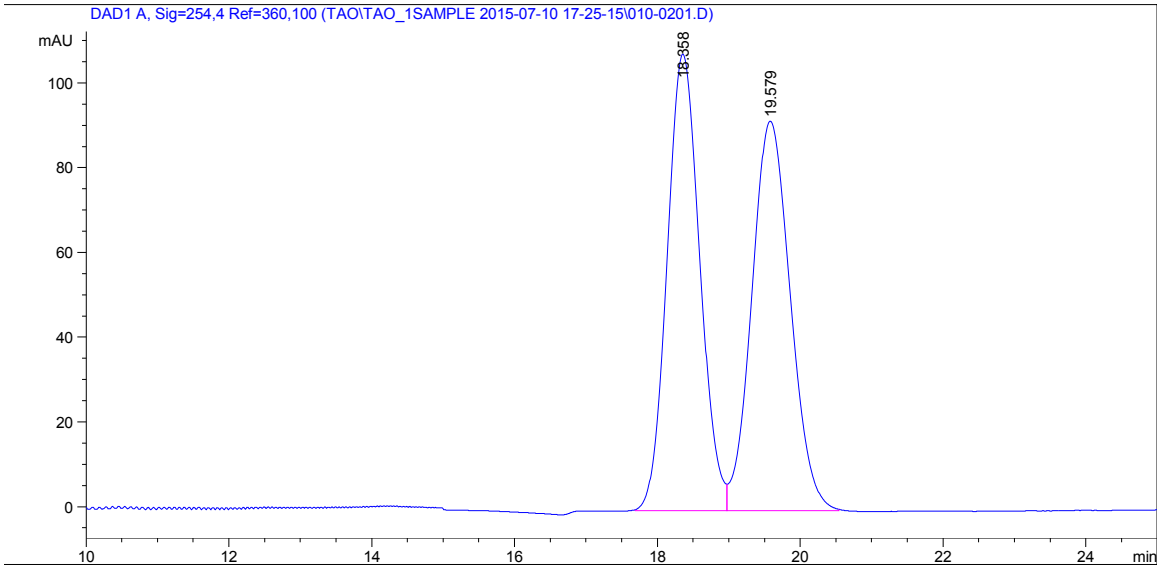
FTIR (neat): 2959, 2923, 1147, 1378, 1057, 1008, 750, 699 cm^{-1}.

HPLC (Chiralcel OD-H column, hexanes:*i*-PrOH = 95:05, 1 mL/min, 254 nm), ee = 90%.

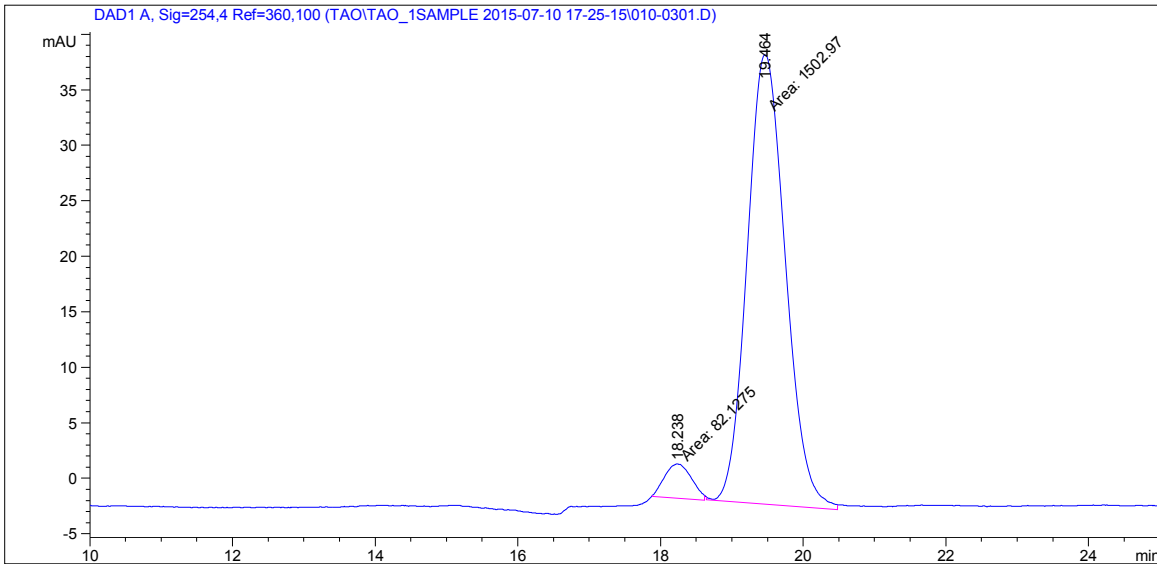
$[\alpha]^{25}_D$ = + 42.4 (c = 0.11, $CHCl_3$)


2.22
1.99
0.96
1.00
1.12
1.17
1.07
1.87
1.06
2.98
0.95
1.15
2.81
f1 (ppm)


139.37
137.42
128.97
128.12
127.52
126.51
83.42
61.24
36.78
34.64
17.82
12.98
f1 (ppm)

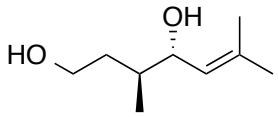


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.358	BV	0.5027	3442.22559	107.74624	49.9694
2	19.579	VB	0.5774	3446.44556	91.92495	50.0306



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.238	MM	0.4430	82.12747	3.08987	5.1812
2	19.464	MM	0.6189	1502.96655	40.47425	94.8188

(3*S*,4*S*)-3,6-dimethylhept-5-ene-1,4-diol (3.5j).



The residue was subjected to flash column chromatography for purification to furnish the title compound (23.1 mg, 73%, *dr* = >20:1) as a colorless oil.

R_f = 0.3 (50% EtOAc/Hexanes).

Spectral data is reported for the major isomer.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.19 (dp, *J* = 9.0, 1.4 Hz, 1H), 4.12 (dd, *J* = 9.0, 7.2 Hz, 1H), 3.83 – 3.71 (m, 1H), 3.69 – 3.57 (m, 1H), 2.40 (s, 2H), 1.79 – 1.65 (m, 8H), 1.62 – 1.51 (m, 1H), 0.86 (d, *J* = 6.7 Hz, 3H).

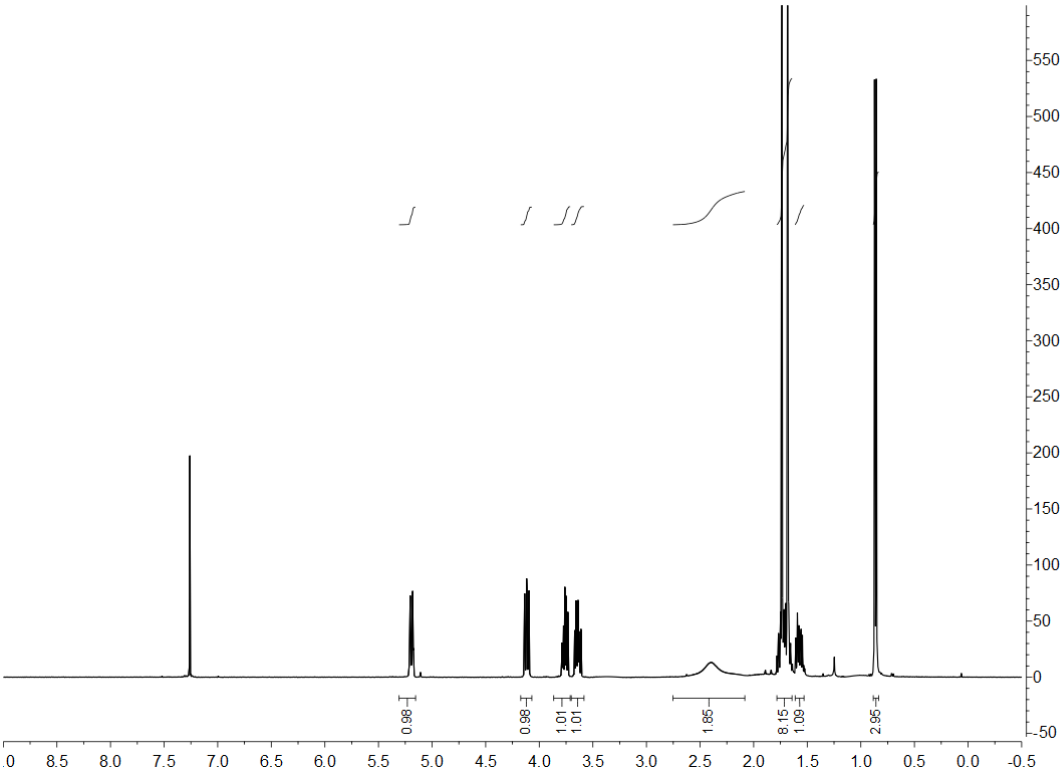
^{13}C NMR (100 MHz, $CDCl_3$): δ 136.01, 126.76, 73.00, 61.23, 37.63, 36.76, 26.04, 18.52, 16.66.

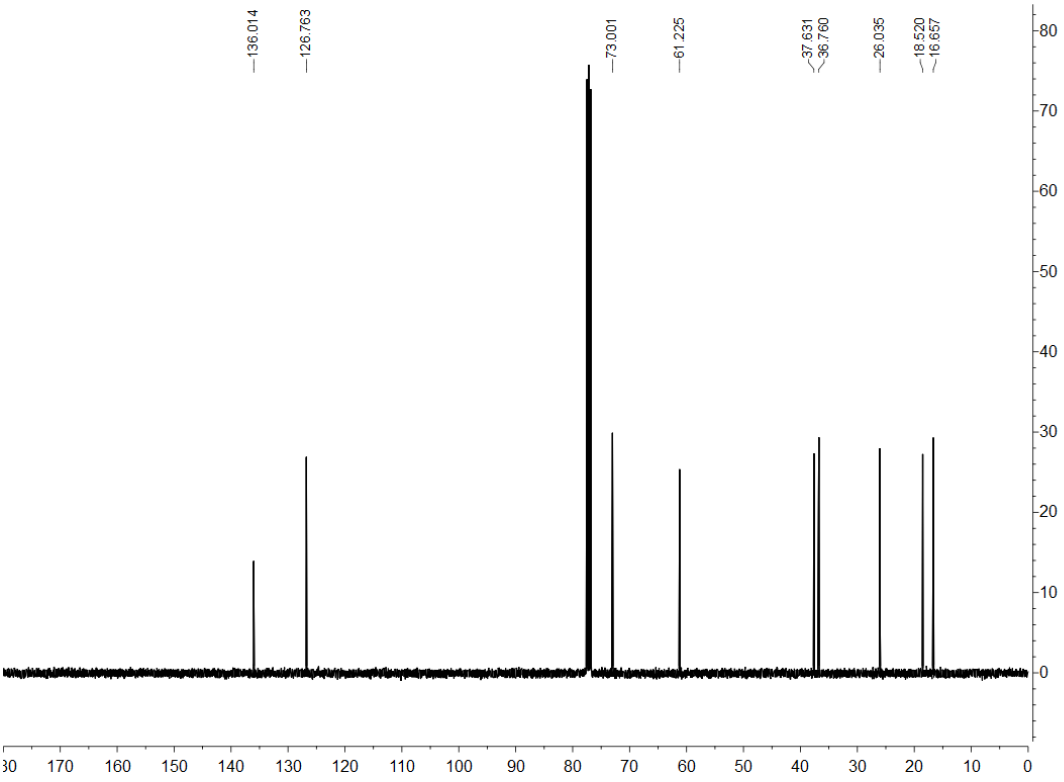
LRMS (CI) Calcd. for $C_9H_{18}NaO_2$ $[M+Na]^+$: 181, Found: 181.

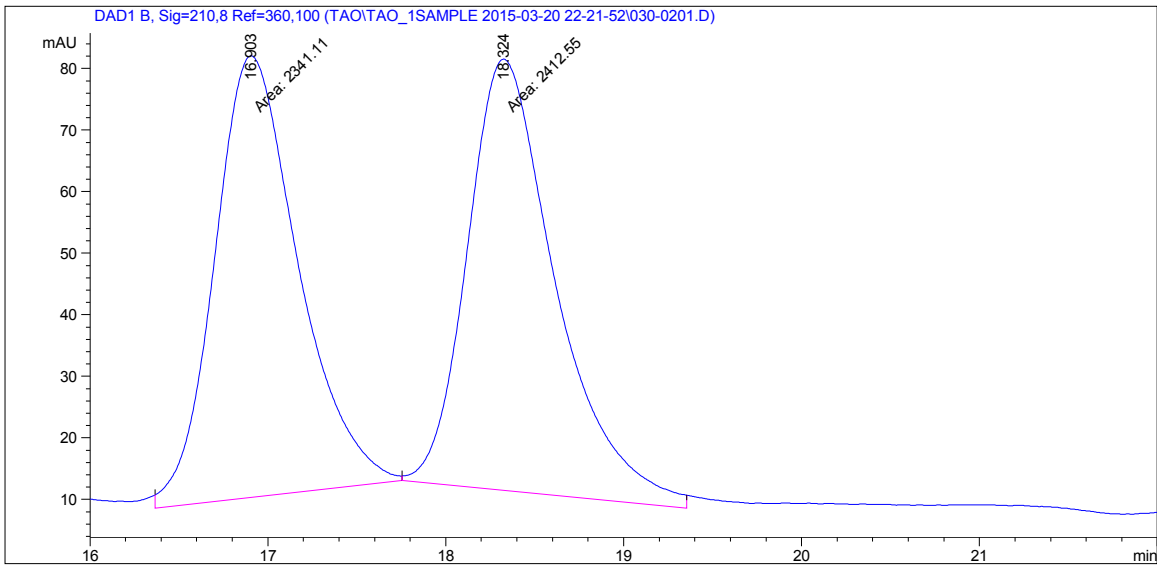
FTIR (neat): 3016, 2970, 1739, 1366, 1229, 1217 cm^{-1}.

HPLC (Chiralcel AD-H column, hexanes:*i*-PrOH = 95:5, 1 mL/min, 210 nm), ee = 94%.

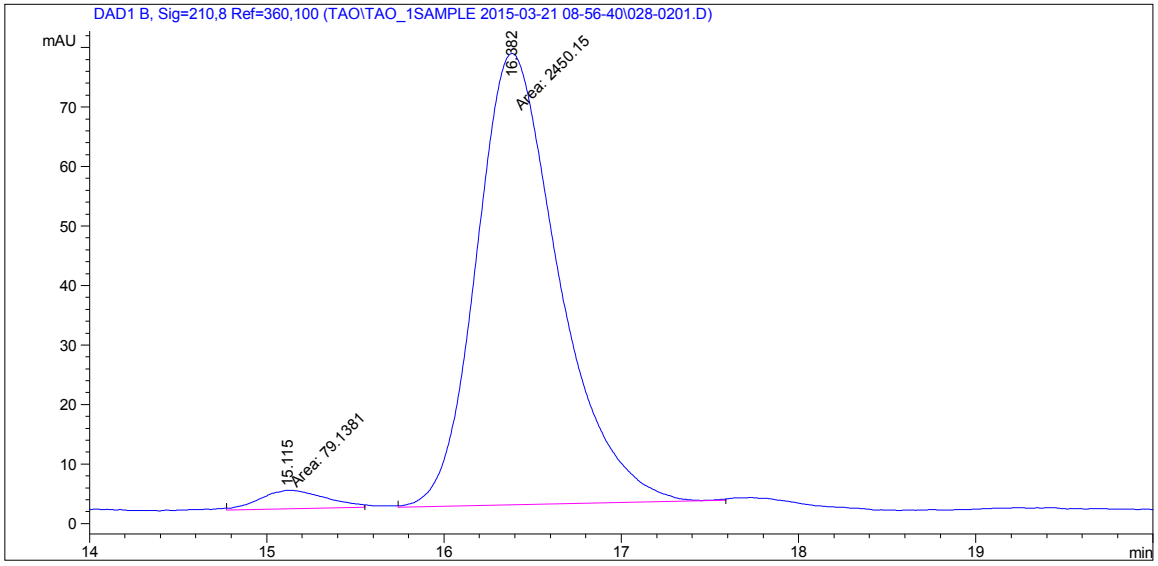
$[\alpha]^{25}_D$ = + 3.8 (c = 0.61, $CHCl_3$)


0.98
0.98
1.01
1.01
1.85
8.15
1.09
2.95


136.014
126.763
73.001
61.225
37.631
36.760
26.035
18.520
16.657

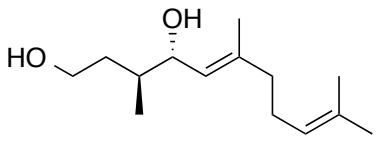


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.903	MM	0.5440	2341.11060	71.72882	49.2486
2	18.324	MM	0.5742	2412.55249	70.02545	50.7514



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.115	MM	0.4262	79.13813	3.09482	3.1289
2	16.382	MM	0.5384	2450.14819	75.85360	96.8711

(3*S*,4*S*,*E*)-3,6,10-trimethylundeca-5,9-diene-1,4-diol (3.5k).



The residue was subjected to flash column chromatography for purification to furnish the title compound (42.3 mg, 72%, *dr* = >20:1) as a colorless oil.

R_f = 0.3 (50% EtOAc/Hexanes).

Spectral data is reported for the major isomer.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.19 (dq, *J* = 9.1, 1.3 Hz, 1H), 5.10 – 5.03 (m, 1H), 4.13 (dd, *J* = 9.0, 7.3 Hz, 1H), 3.76 (ddd, *J* = 11.0, 6.1, 5.0 Hz, 1H), 3.70 – 3.60 (m, 1H), 2.14 – 2.00 (m, 4H), 1.81 – 1.69 (m, 2H), 1.68 – 1.66 (m, 6H), 1.60 (s, 3H), 1.58 – 1.54 (m, 1H), 0.86 (d, *J* = 6.7 Hz, 3H).

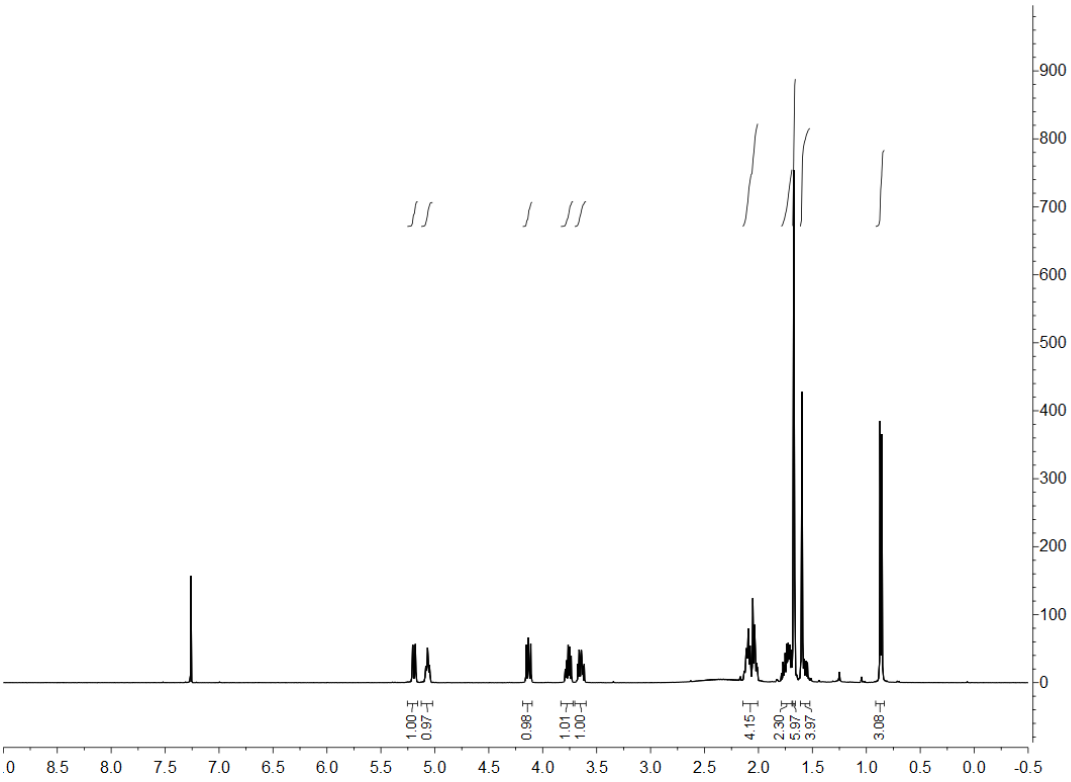
^{13}C NMR (100 MHz, $CDCl_3$): δ 139.39, 131.85, 126.69, 124.07, 72.92, 61.27, 39.86, 37.69, 36.85, 26.48, 25.83, 17.84, 16.86, 16.62.

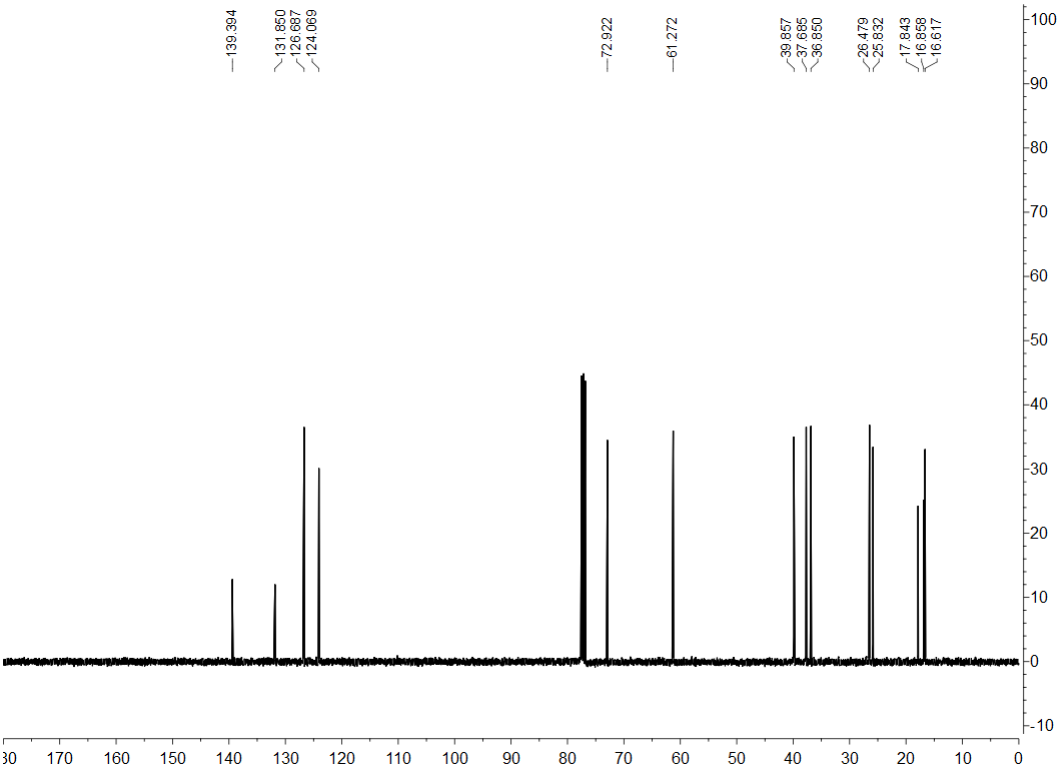
LRMS (CI) Calcd. for $C_{14}H_{26}NaO_2$ $[M+Na]^+$: 249, Found: 249.

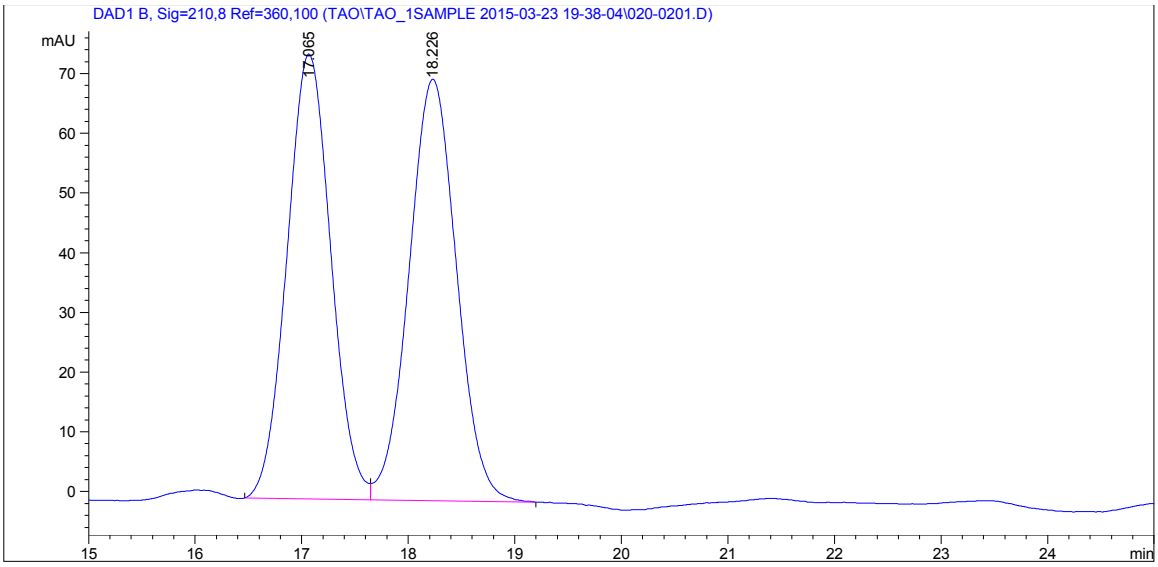
FTIR (neat): 2970, 1739, 1448, 1366, 1229, 1217 cm^{-1}.

HPLC (Chiralcel OD-H column/OD-H column, hexanes:*i*-PrOH = 95:5, 1 mL/min, 210 nm), ee = 96%.

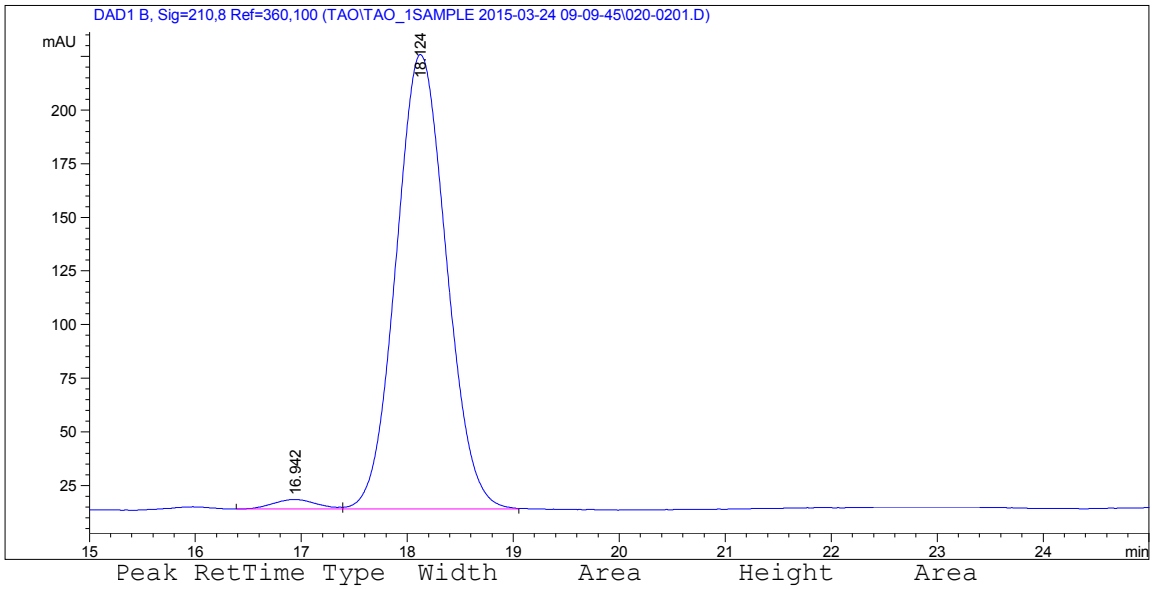
$[\alpha]^{25}_D$ = - 6.8(c = 0.54, $CHCl_3$)


1.00
0.97
0.98
1.01
1.00
4.15
2.30
5.97
3.97
3.08


139.394
131.850
126.687
124.069
72.922
61.272
39.857
37.685
36.850
26.479
25.832
17.843
16.858
16.617

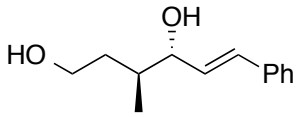


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.065	BV	0.4444	2136.06885	74.53375	49.3446
2	18.226	VB	0.4783	2192.80786	70.60277	50.6554



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.942	BV	0.3495	126.60713	4.42887	1.7824
2	18.124	VB	0.5183	6976.73682	211.78230	98.2176

(3*S*,4*S*,*E*)-3-methyl-6-phenylhex-5-ene-1,4-diol (3.5l).



The residue was subjected to flash column chromatography for purification to furnish the title compound (29.7 mg, 72%, *dr* = >20:1) as a white solid.

R_f = 0.3 (50% EtOAc/Hexanes).

Spectral data is reported for the major isomer.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.20 (m, 5H), 6.57 (d, *J* = 15.9 Hz, 1H), 6.22 (dd, *J* = 15.9, 7.1 Hz, 1H), 4.08 (t, *J* = 6.9 Hz, 1H), 3.83 – 3.75 (m, 1H), 3.71 – 3.63 (m, 1H), 2.59 (s, 2H), 1.91 – 1.71 (m, 2H), 1.68 – 1.55 (m, 1H), 0.97 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 136.81, 131.54, 131.15, 128.71, 127.80, 126.59, 60.87, 37.18, 36.17, 16.79.

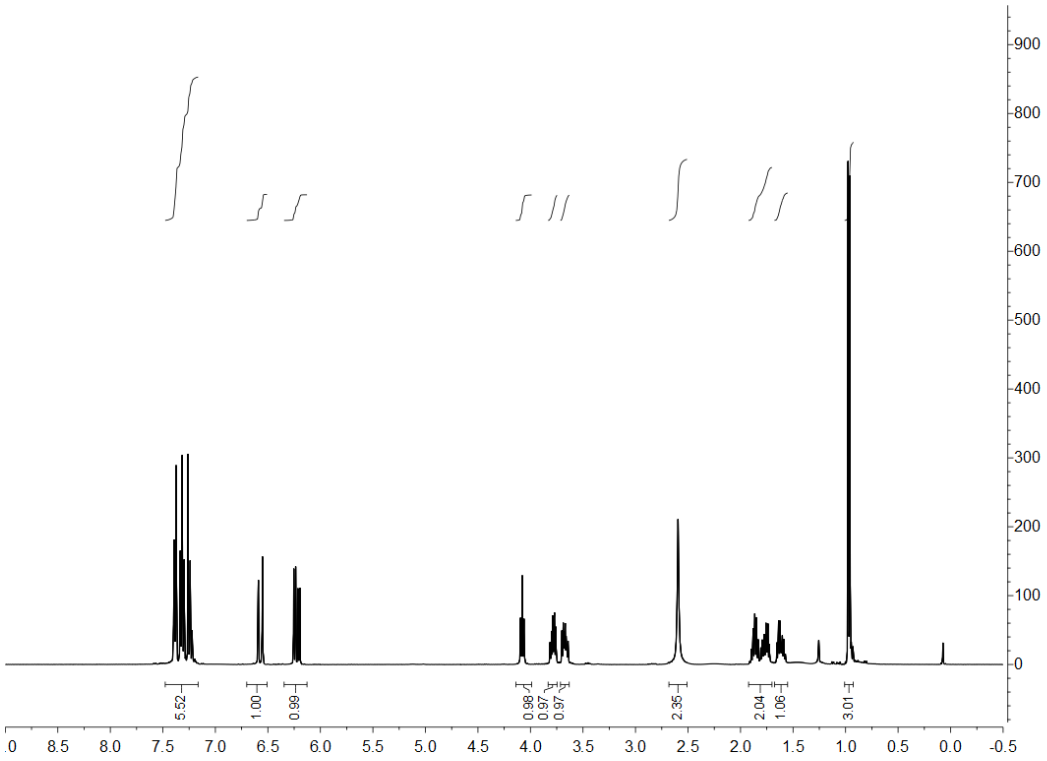
LRMS (CI) Calcd. for $C_{13}H_{18}NaO_2$ $[M+Na]^+$: 229, Found: 229.

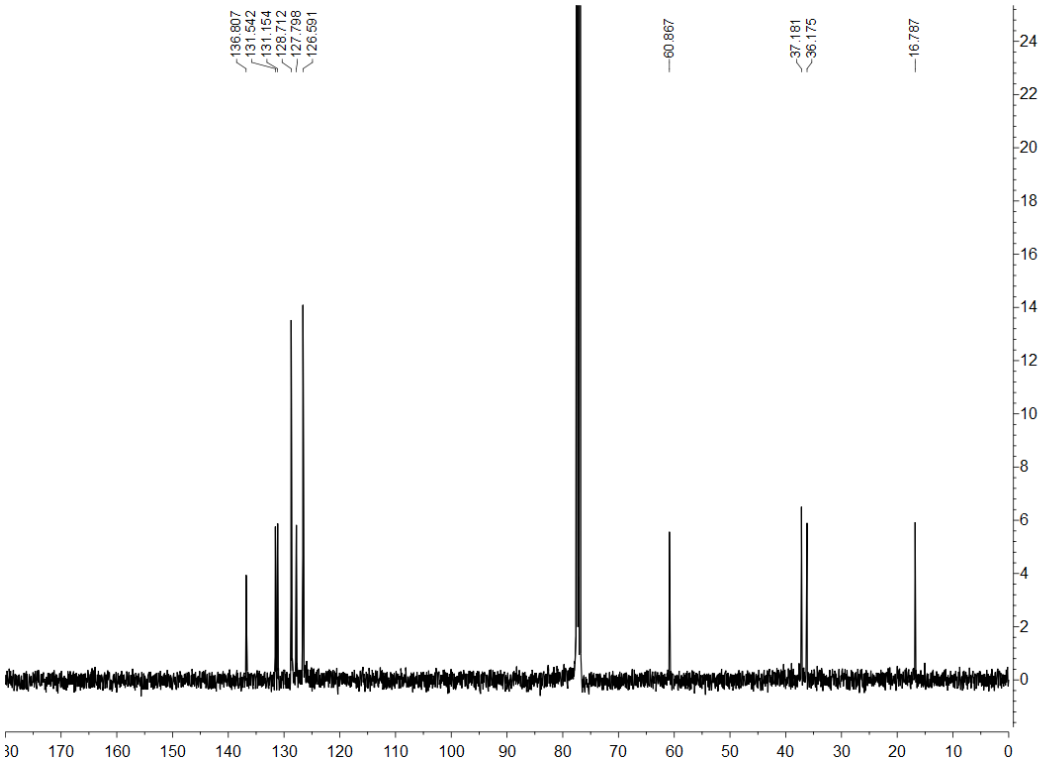
FTIR (neat): 3260, 3025, 2970, 2944, 1739, 1449, 1366, 1228, 1217, 1011, 970, 693 cm^{-1}.

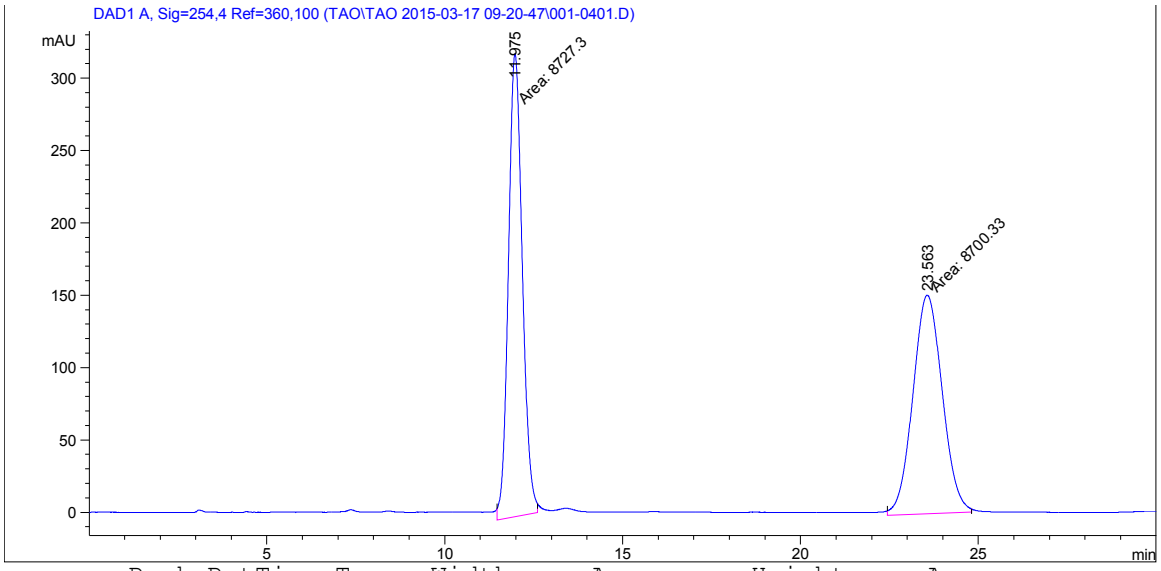
HPLC (Chiralcel OD-H column, hexanes:*i*-PrOH = 90:10, 1 mL/min, 254 nm), ee = 93%.

$[\alpha]^{25}_D$ = + 8.2 (c = 0.65, $CHCl_3$)

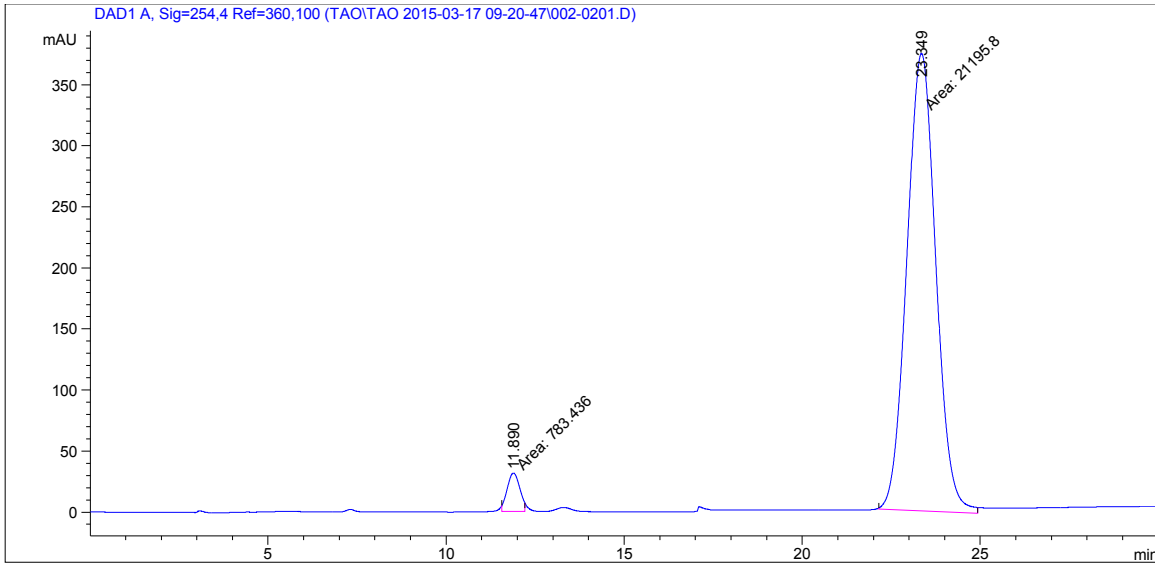
M.P. 84.5-86 ºC


5.52
1.00
0.99
0.98
0.97
0.97
2.35
2.04
1.06
3.01


136.807
131.542
131.154
128.712
127.798
126.591
60.867
37.181
36.175
16.787

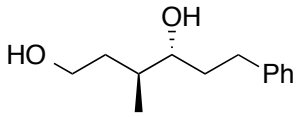


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.975	MM	0.4547	8727.30273	319.92133	50.0774
2	23.563	MM	0.9592	8700.32813	151.16803	49.9226



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.890	MM	0.4136	783.43585	31.57117	3.5644
2	23.349	MM	0.9433	2.11958e4	374.49902	96.4356

(3*S*,4*R*)-3-methyl-6-phenylhexane-1,4-diol (3.5m).



The residue was subjected to flash column chromatography for purification to furnish the title compound (14.5 mg, 0.1 mmol scale, 70%, *dr* = >20:1) as a colorless oil.

R_f = 0.3 (50% EtOAc/Hexanes).

Spectral data is reported for the major isomer.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 – 7.26 (m, 2H), 7.24 – 7.15 (m, 3H), 3.76 (ddd, *J* = 10.6, 6.6, 5.0 Hz, 1H), 3.63 (ddd, *J* = 10.6, 7.0, 5.0 Hz, 1H), 3.52 – 3.40 (m, 1H), 2.85 (ddd, *J* = 13.7, 9.9, 5.5 Hz, 1H), 2.72 – 2.56 (m, 3H), 1.92 – 1.51 (m, 5H), 0.95 (d, *J* = 6.8 Hz, 3H).

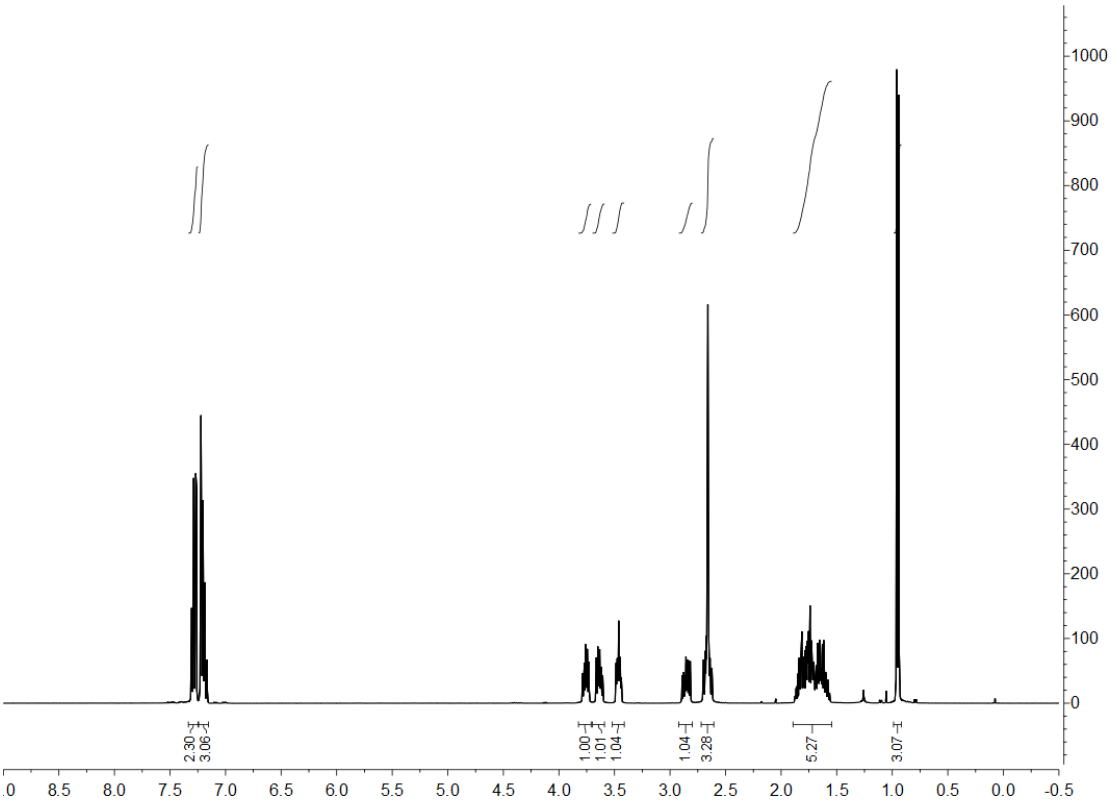
^{13}C NMR (100 MHz, $CDCl_3$): δ 142.40, 128.57, 128.53, 125.93, 75.34, 60.50, 36.76, 36.39, 35.34, 32.45, 16.62.

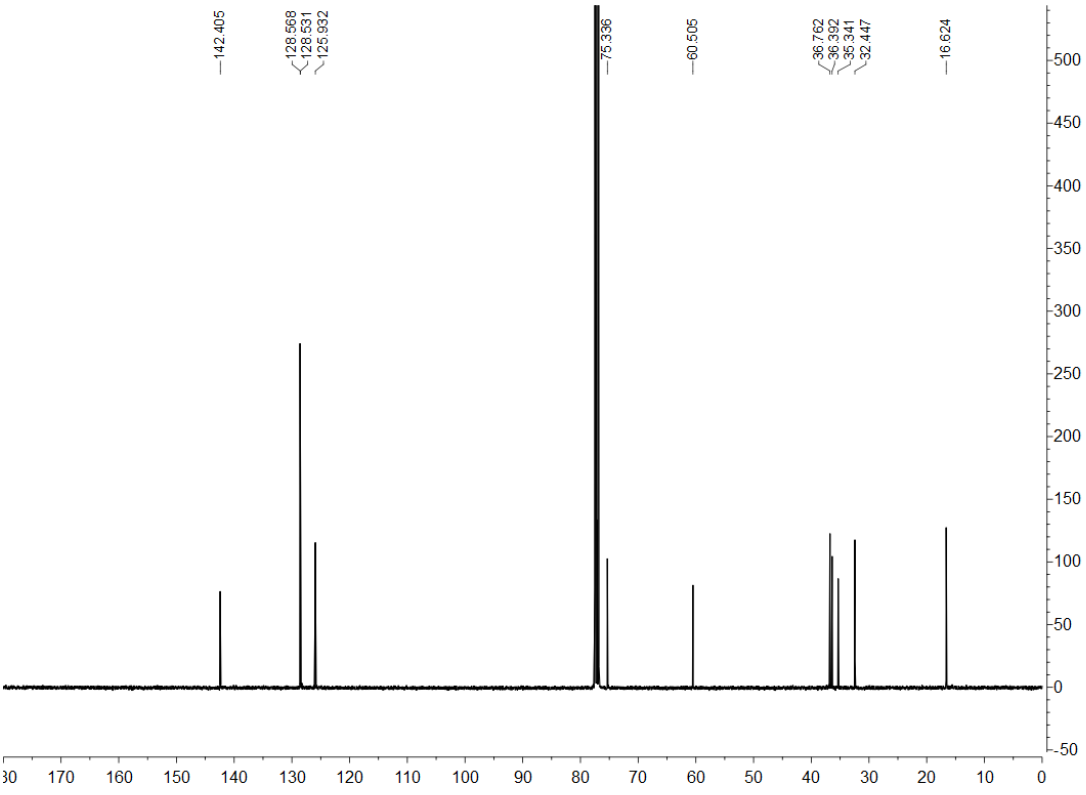
LRMS (CI) Calcd. for $C_{13}H_{20}NaO_2$ $[M+Na]^+$: 231, Found: 231.

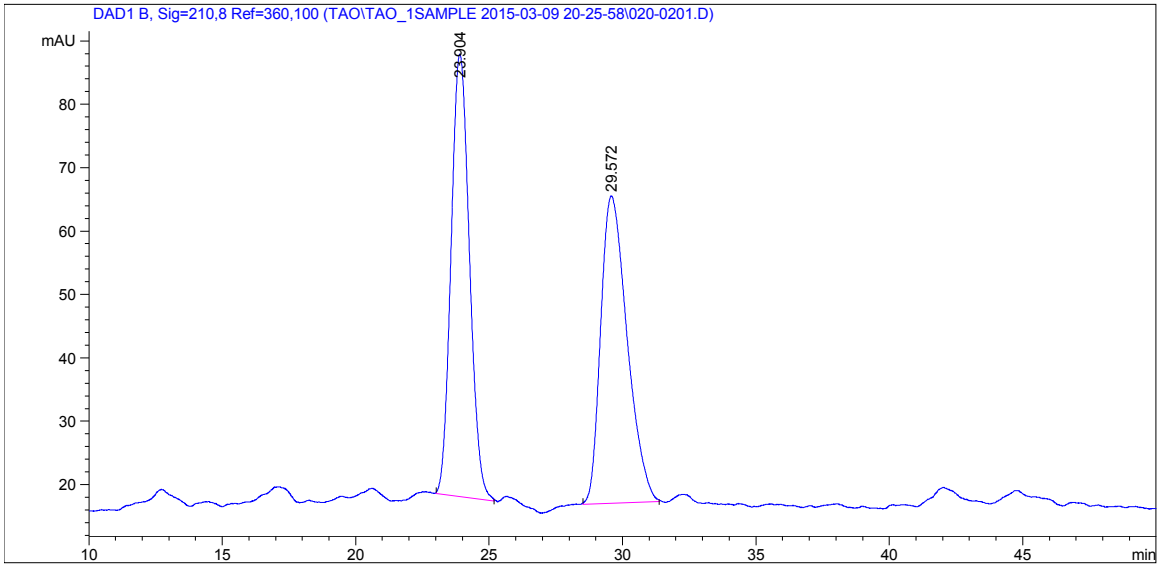
FTIR (neat): 3026, 2970, 2946, 1739, 1454, 1366, 1229, 1217, 1052, 698 cm^{-1}.

HPLC (Chiralcel OD-H column, hexanes:*i*-PrOH = 95:5, 1.0 mL/min, 210 nm), ee = 90%.

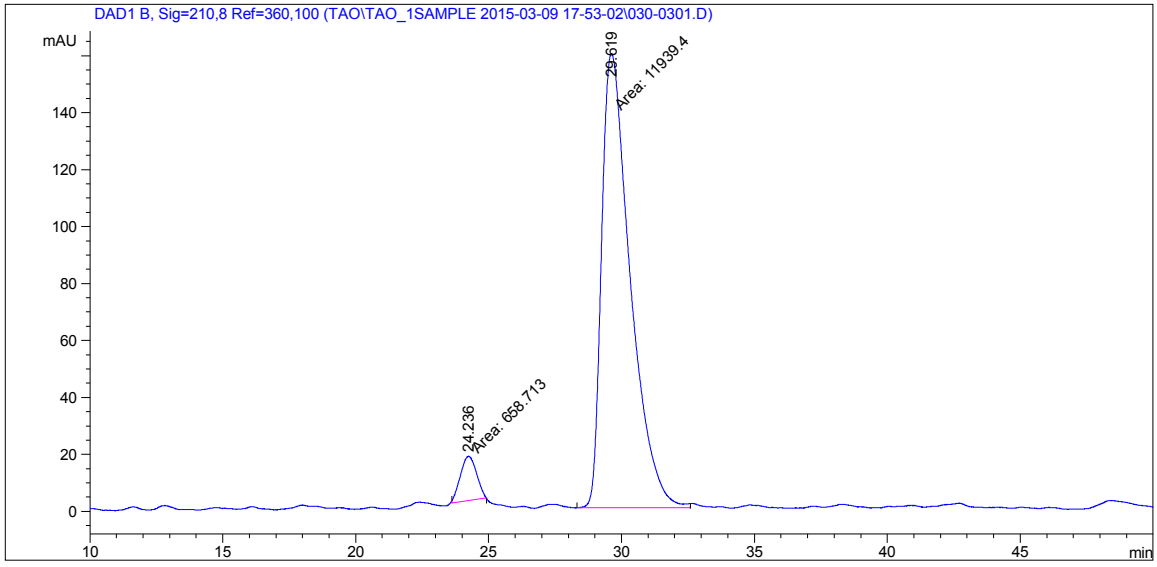
$[\alpha]^{25}_D$ = + 17.8 (c = 0.73, $CHCl_3$)


2.30
3.06
1.00
1.01
1.04
1.04
3.28
5.27
3.07


142.405
128.568
128.531
125.932
75.336
60.505
36.762
36.392
35.341
32.447
16.624

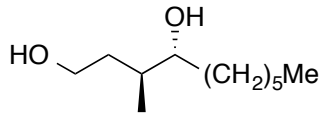


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	23.904	BB	0.6953	3334.83179	69.80979	50.0286
2	29.572	BB	0.8201	3331.01636	48.44849	49.9714



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	24.236	MM	0.7041	658.71326	15.59339	5.2287
2	29.619	MM	1.2478	1.19394e4	159.47311	94.7713

(3*S*,4*R*)-3-methyldecane-1,4-diol (3.5n).



The residue was subjected to flash column chromatography for purification to furnish the title compound (30.5 mg, 81%, *dr* = >20:1) as a colorless oil.

R_f = 0.3 (50% EtOAc/Hexanes).

Spectral data is reported for the major isomer.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.75 (ddd, *J* = 11.3, 6.7, 4.9 Hz, 1H), 3.62 (ddd, *J* = 10.7, 7.0, 5.0 Hz, 1H), 3.44 – 3.35 (m, 1H), 2.73 (s, 2H), 1.75 – 1.17 (m, 14H), 0.93 (d, *J* = 6.7 Hz, 3H), 0.90 – 0.85 (m, 3H).

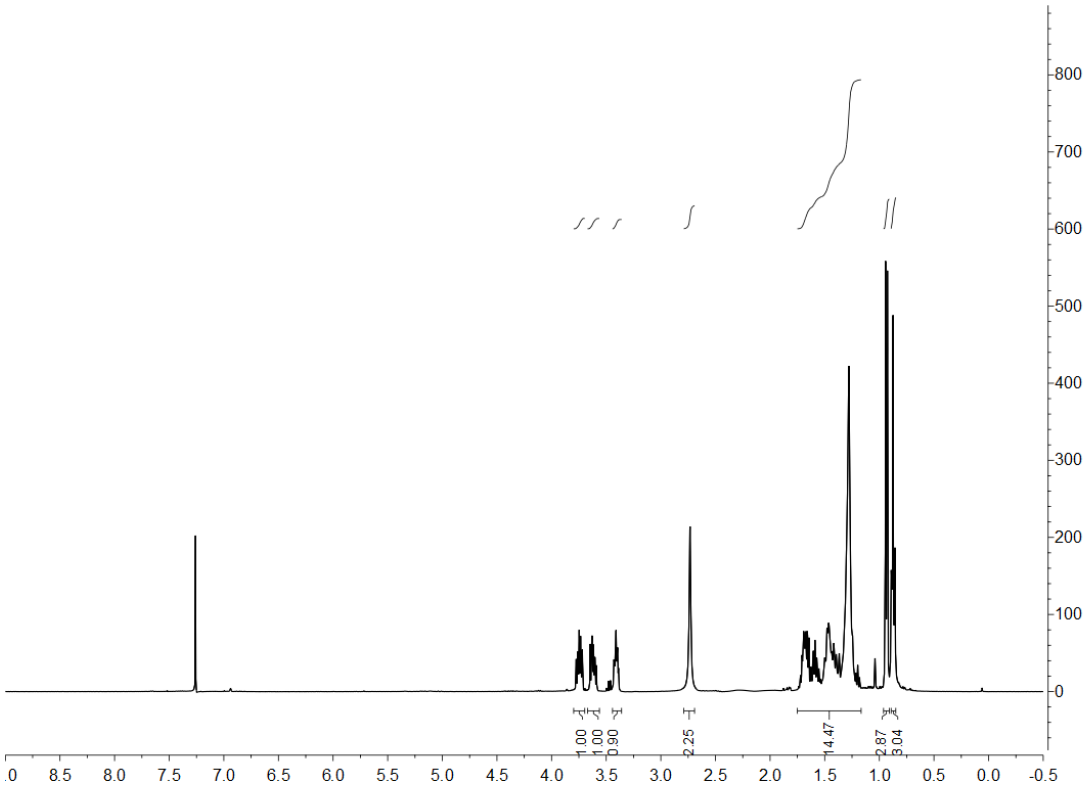
^{13}C NMR (100 MHz, $CDCl_3$): δ 76.03, 60.54, 36.53, 35.36, 34.59, 32.00, 29.55, 25.97, 22.78, 16.73, 14.23.

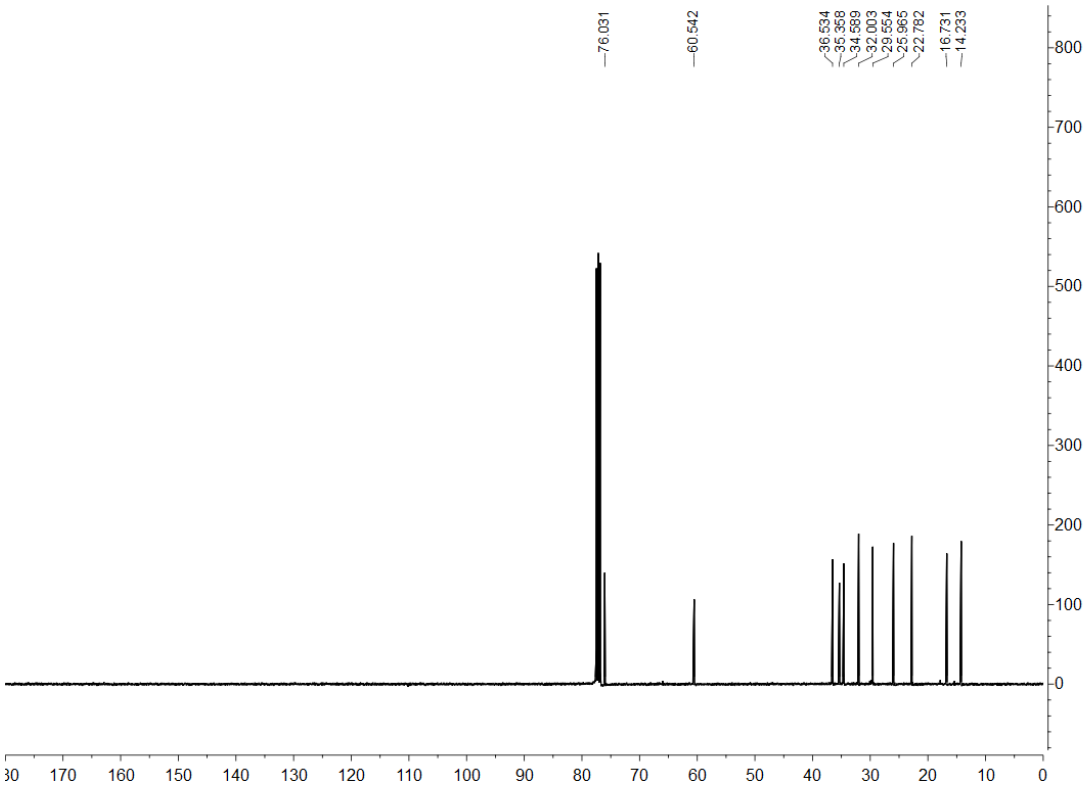
LRMS (CI) Calcd. for $C_{11}H_{24}NaO_2$ $[M+Na]^+$: 211, Found: 211.

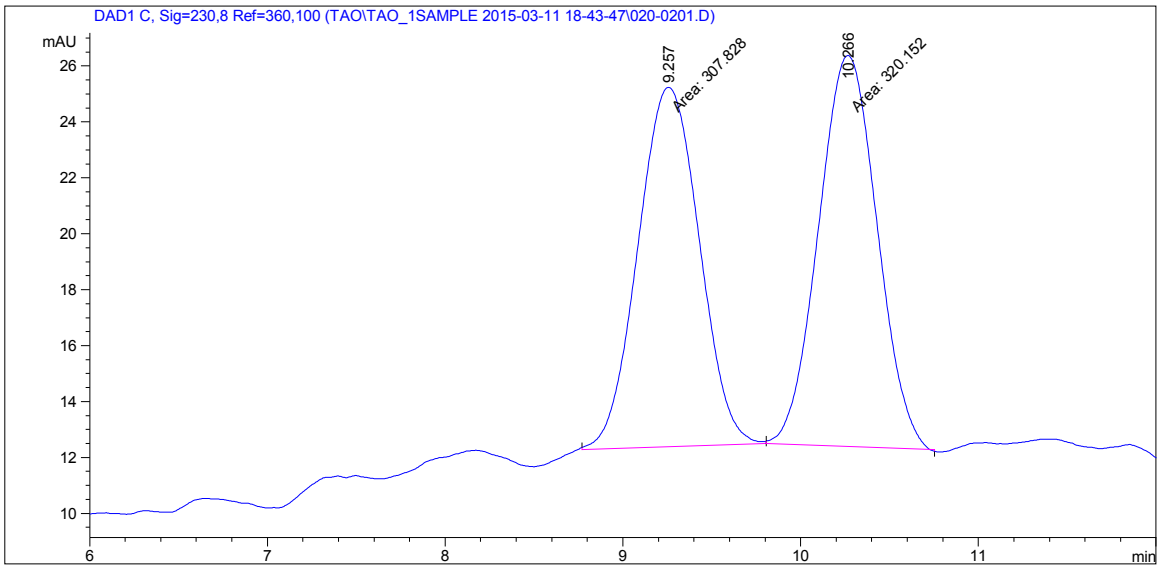
FTIR (neat): 2970, 2928, 1739, 1456, 1366, 1229, 1217 cm^{-1}.

HPLC (Chiralcel OD-H column, hexanes:*i*-PrOH = 95:5, 1 mL/min, 230 nm), ee = 90%.

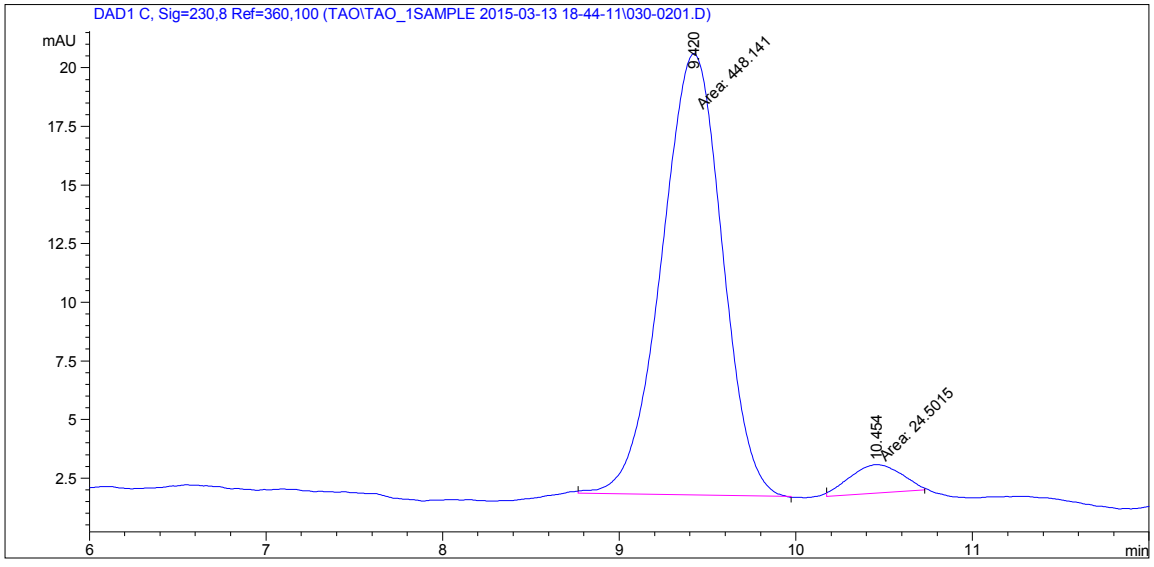
$[\alpha]^{25}_D$ = -2.1 (c = 0.62, $CHCl_3$)


1.00
1.00
0.90
2.25
14.47
2.87
3.04


76.031
60.542
36.534
35.358
34.589
32.003
29.554
25.965
22.782
16.731
14.233

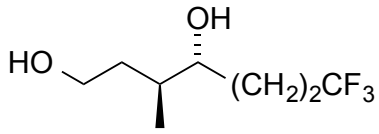


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.257	MM	0.3991	307.82849	12.85460	49.0188
2	10.266	MM	0.3816	320.15195	13.98154	50.9812



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.420	MM	0.3969	448.14063	18.81815	94.8160
2	10.454	MM	0.3367	24.50155	1.21290	5.1840

(3*S*,4*R*)-7,7,7-trifluoro-3-methylheptane-1,4-diol (3.5o).



The residue was subjected to flash column chromatography for purification to furnish the title compound (26.8 mg, 67%, *dr* = >20:1) as a colorless oil.

R_f = 0.3 (50% EtOAc/Hexanes).

Spectral data is reported for the major isomer.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.86 – 3.75 (m, 1H), 3.73 – 3.63 (m, 1H), 3.43 (ddd, *J* = 9.3, 6.1, 3.0 Hz, 1H), 2.54 (s, 2H), 2.47 – 2.27 (m, 1H), 2.25 – 2.03 (m, 1H), 1.84 – 1.55 (m, 5H), 0.97 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 74.47, 60.40, 37.10, 35.29, 31.12, 30.83, 30.55, 30.26, 27.02, 26.99, 16.60.

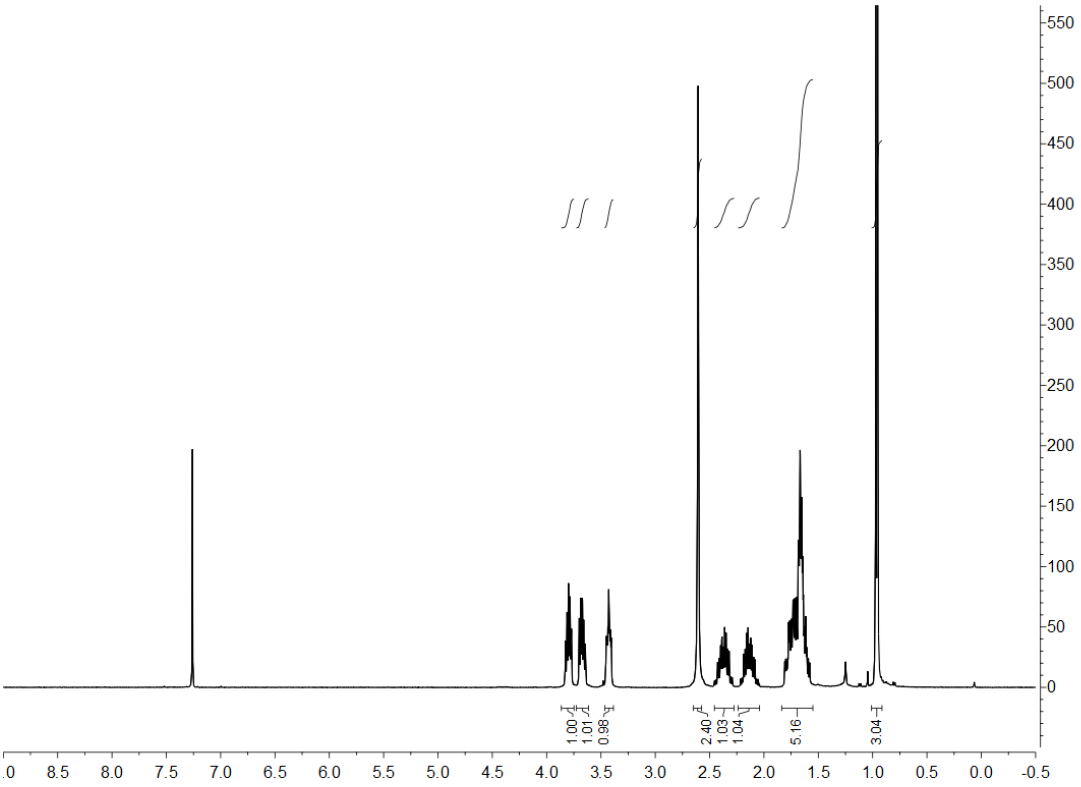
^{19}F NMR (378 MHz, $CDCl_3$): δ 66.34.

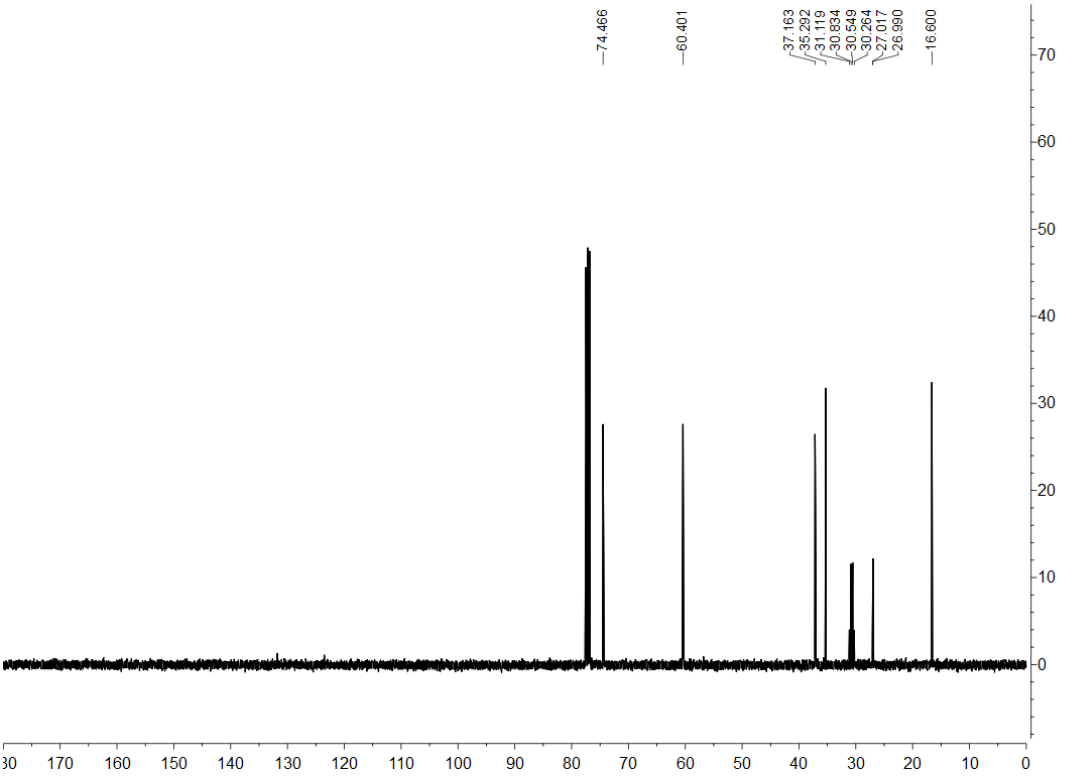
LRMS (CI) Calcd. for $C_8H_{15}NaF_3O_2$ $[M+Na]^+$: 223, Found: 223.

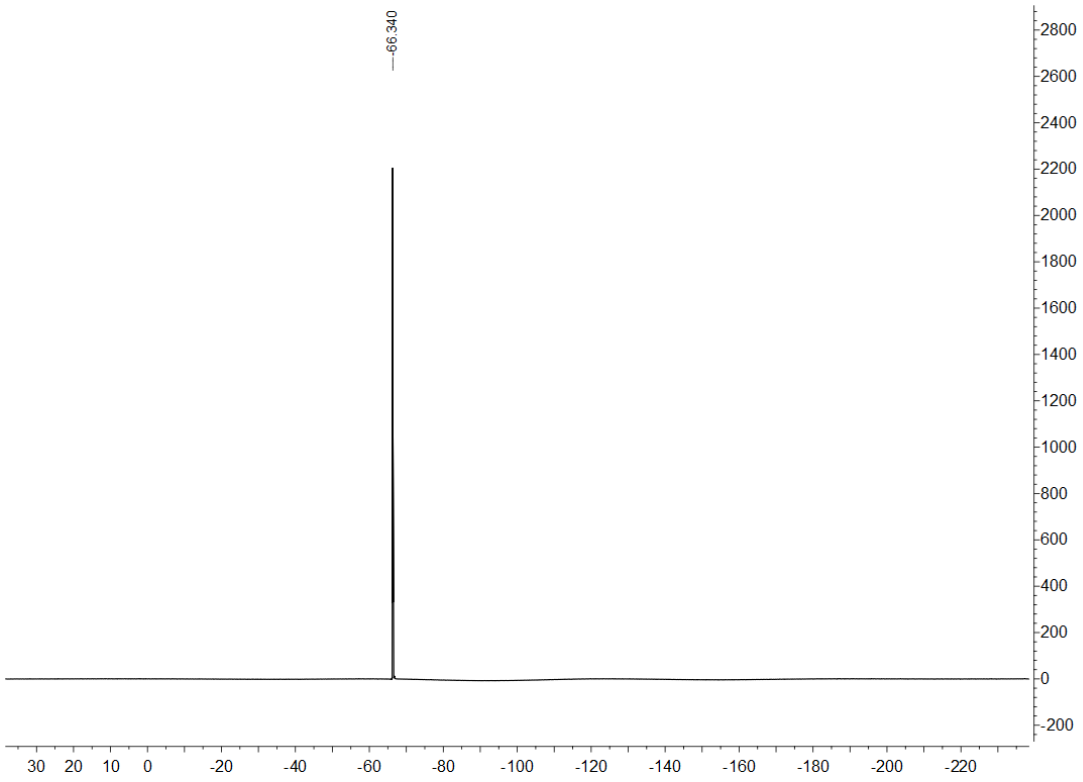
FTIR (neat): 2970, 1739, 1366, 1252, 1229, 1217, 1138, 1031 cm^{-1}.

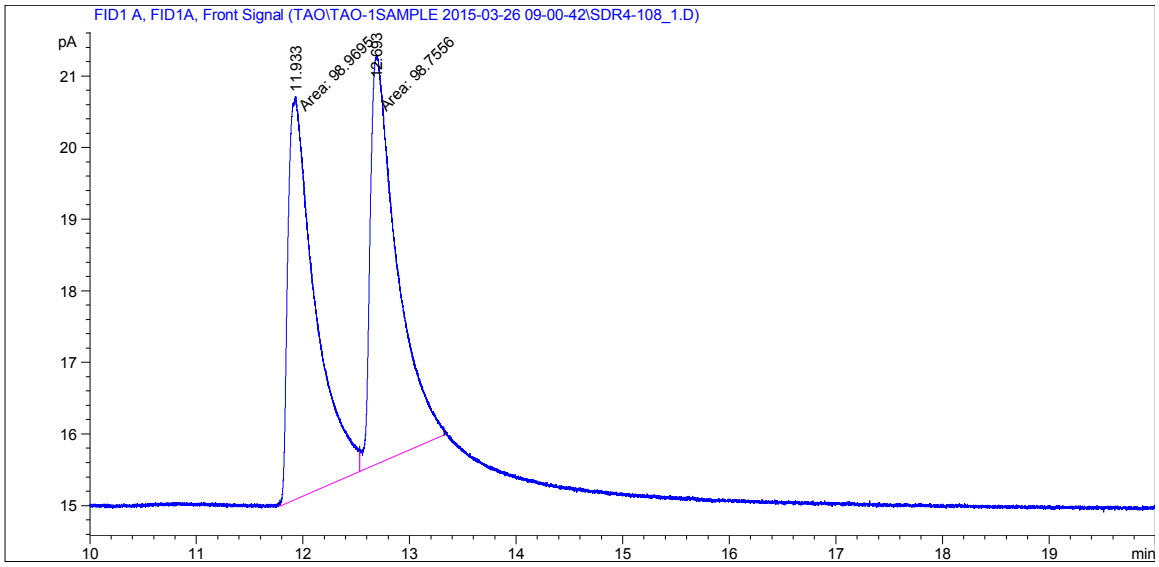
GC (cyclosil-B: Initial temperature: 110℃, rate: 1℃ /min, End temperature: 150℃), ee = 90%.

$[\alpha]^{25}_D$ = -4.7 (c = 0.63, $CHCl_3$)

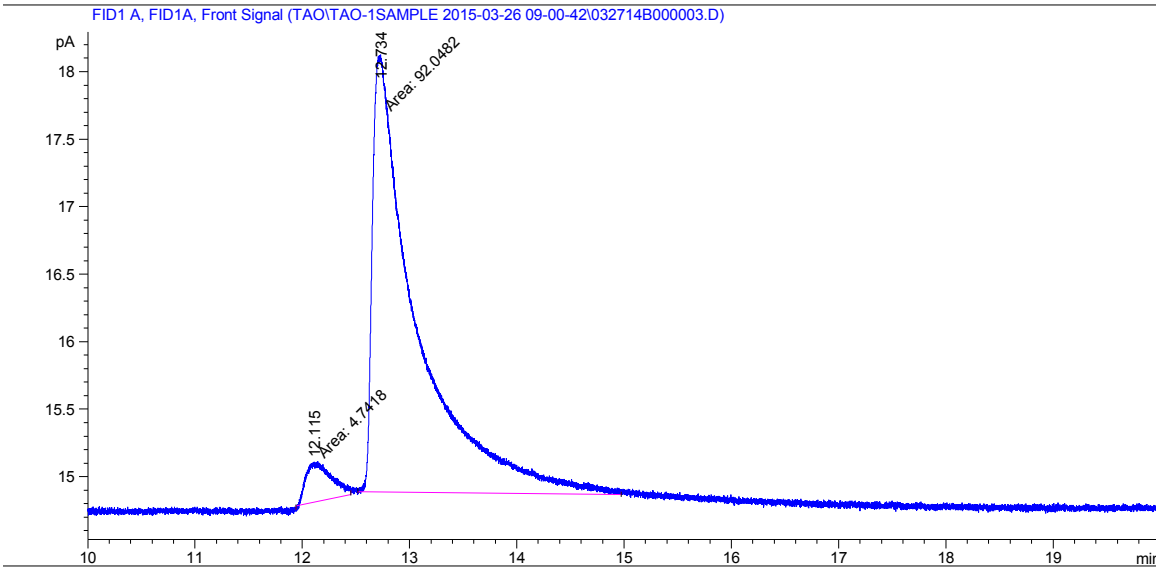

1.00
1.01
0.98
2.40
1.03
1.04
5.16
3.04


74.466
60.401
37.163
35.292
31.119
30.834
30.549
30.264
27.017
26.990
16.600


-66.340
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
30
20
10
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220

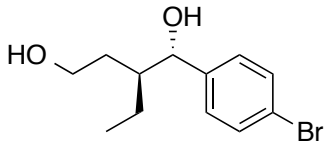


Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	11.933	MF	0.2926	98.96948	5.63673	50.05408
2	12.693	FM	0.2884	98.75562	5.70641	49.94592



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	12.115	MM	0.2619	4.74180	3.01749e-1	4.89906
2	12.734	MM	0.4743	92.04816	3.23429	95.10094

(1*S*,2*S*)-1-(4-bromophenyl)-2-ethylbutane-1,4-diol (3.5p).



The residue was subjected to flash column chromatography for purification to furnish the title compound (34.3 mg, 63%, *dr* = >20:1) as a white solid.

R_f = 0.3 (50% EtOAc/Hexanes).

Spectral data is reported for the major isomer.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (d, *J* = 8.4 Hz, 2H), 7.20 (d, *J* = 8.1 Hz, 2H), 4.54 (d, *J* = 6.5 Hz, 1H), 3.74 (ddd, *J* = 10.6, 6.8, 4.7 Hz, 1H), 3.58 (ddd, *J* = 10.6, 6.8, 4.7 Hz, 1H), 3.35 (s, 1H), 1.78 – 1.60 (m, 3H), 1.40 – 1.14 (m, 3H), 0.88 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.08, 131.35, 128.20, 121.01, 76.00, 60.69, 45.26, 31.68, 23.66, 11.43.

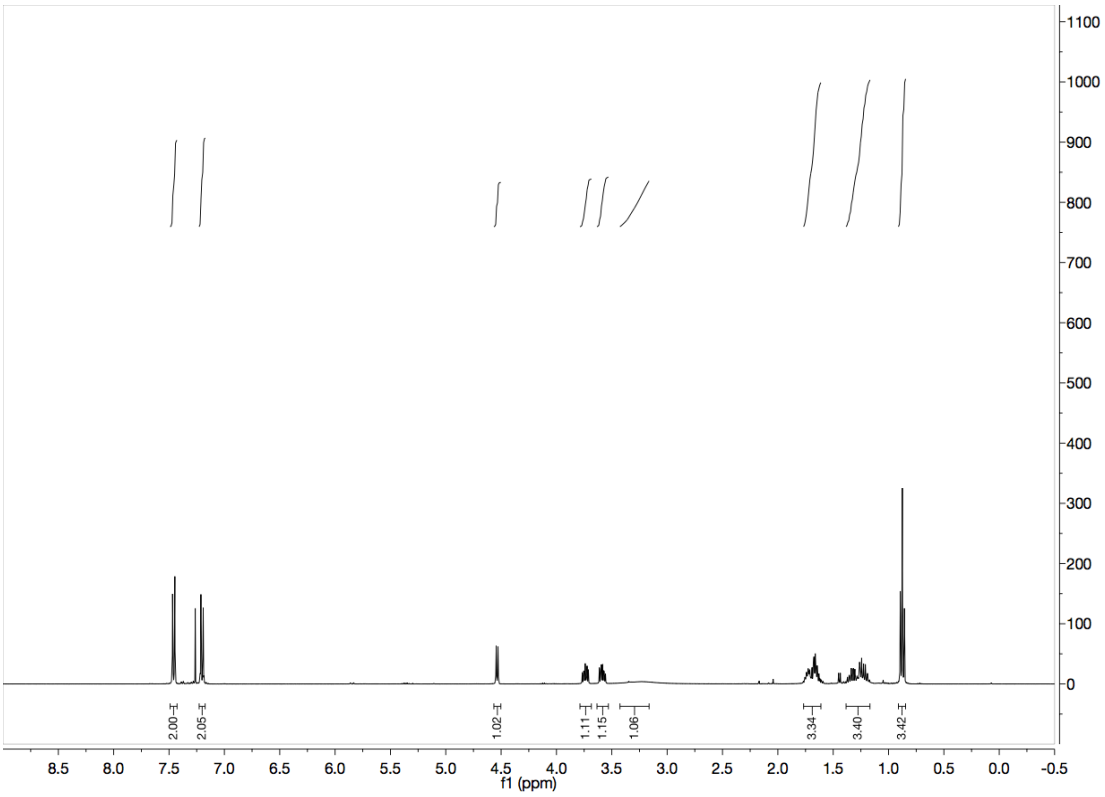
LRMS (CI) Calcd. for $C_{12}H_{17}BrNaO_2$ $[M+Na]^+$: 295, Found: 295.

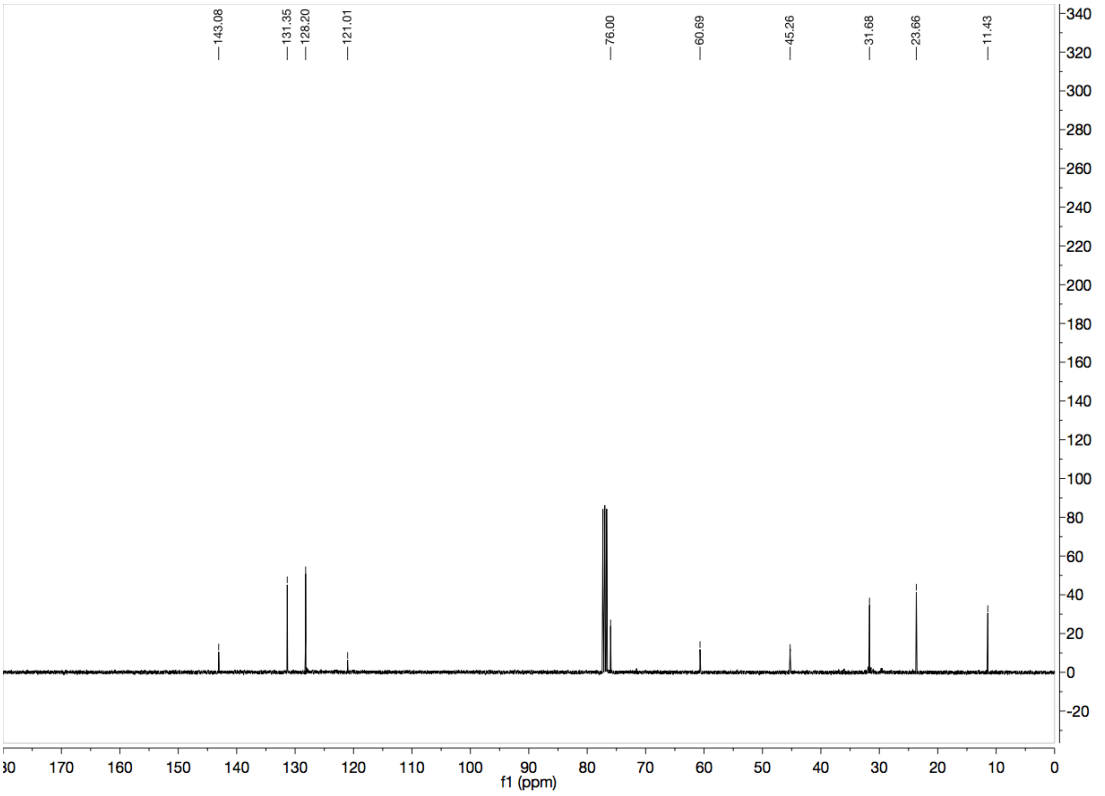
FTIR (neat): 3299, 2886, 1070, 1057, 1008, 838, 686, 669 cm^{-1}.

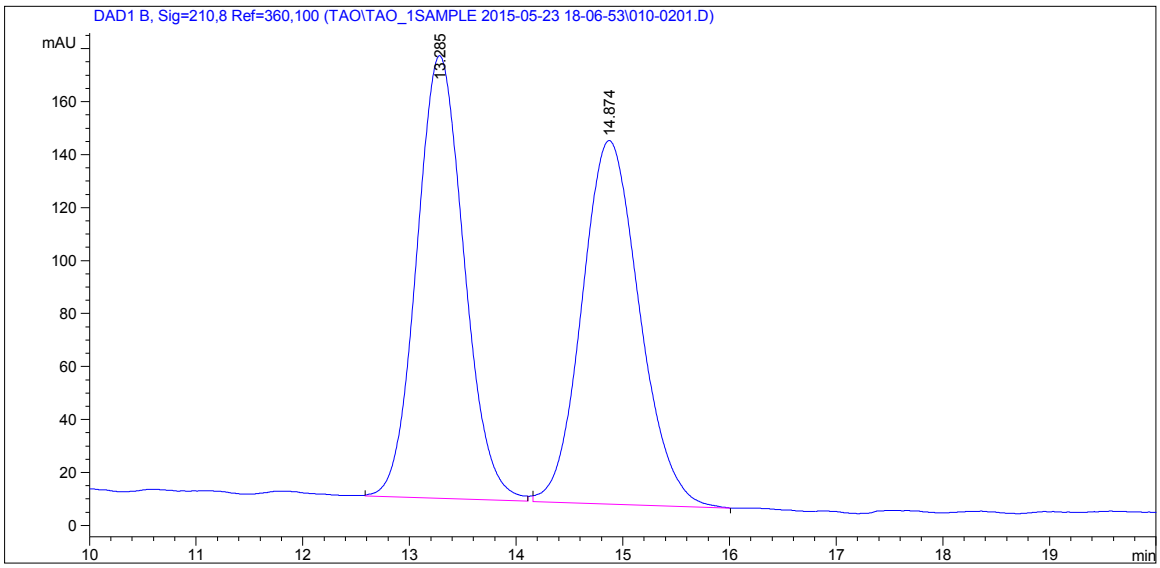
HPLC (Chiralcel OD-H column, hexanes:*i*-PrOH = 95:5, 1 mL/min, 230 nm), ee = 96%.

$[\alpha]^{25}_D$ = -30.0 (c = 0.45, $CHCl_3$)

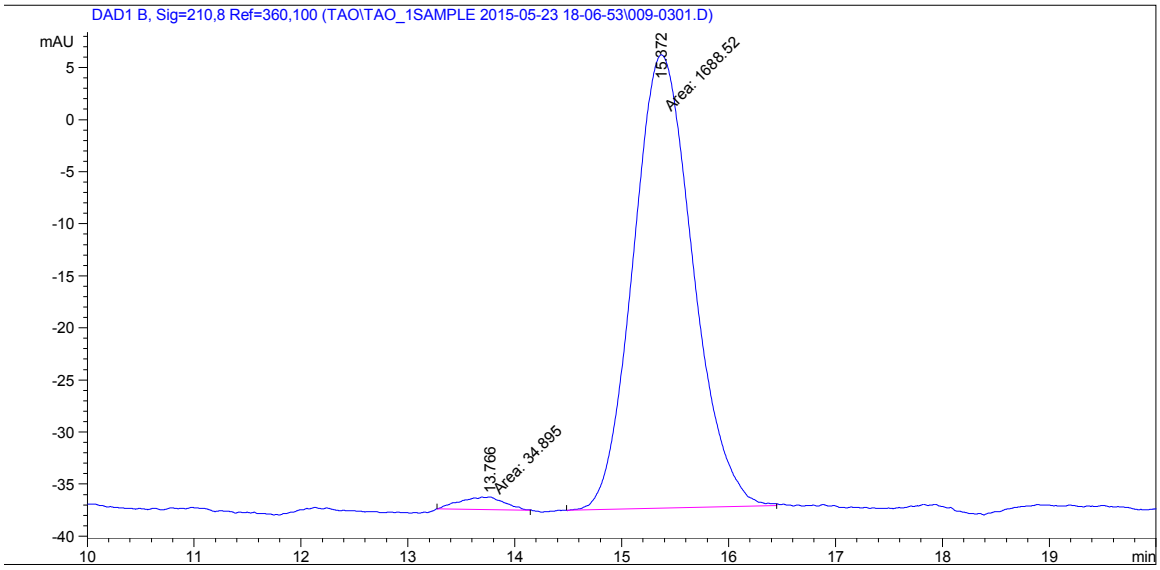
M.P. 134.9-135.9 ºC


2.00
2.05
1.02
1.11
1.15
1.06
3.34
3.40
3.42
f1 (ppm)


143.08
131.35
128.20
121.01
76.00
60.69
45.26
31.68
23.66
11.43
f1 (ppm)

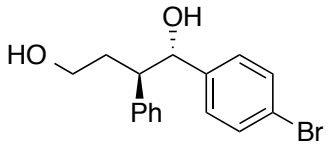


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.285	BB	0.4783	5161.87988	167.12447	50.0902
2	14.874	BB	0.5751	5143.28369	137.27925	49.9098



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.766	MM	0.4741	34.89495	1.22664	2.0248
2	15.372	MM	0.6464	1688.51941	43.53523	97.9752

(1*S*,2*R*)-1-(4-bromophenyl)-2-phenylbutane-1,4-diol (3.5q).



The residue was subjected to flash column chromatography for purification to furnish the title compound (41 mg, 64%, *dr* = >20:1).

R_f = 0.3 (50% EtOAc/Hexanes).

Spectral data is reported for the major isomer.

^{1}H NMR (400 MHz, Methanol-d_4) δ 7.22 – 7.14 (m, 2H), 7.09 – 7.02 (m, 2H), 7.01 – 6.96 (m, 1H), 6.95 – 6.89 (m, 4H), 4.58 (d, *J* = 8.1 Hz, 1H), 3.30 (ddd, *J* = 10.6, 8.0, 4.5 Hz, 1H), 3.26 – 3.15 (m, 3H), 2.87 (ddd, *J* = 11.5, 8.1, 3.7 Hz, 1H), 2.33 – 2.17 (m, 1H), 1.93 – 1.75 (m, 1H).

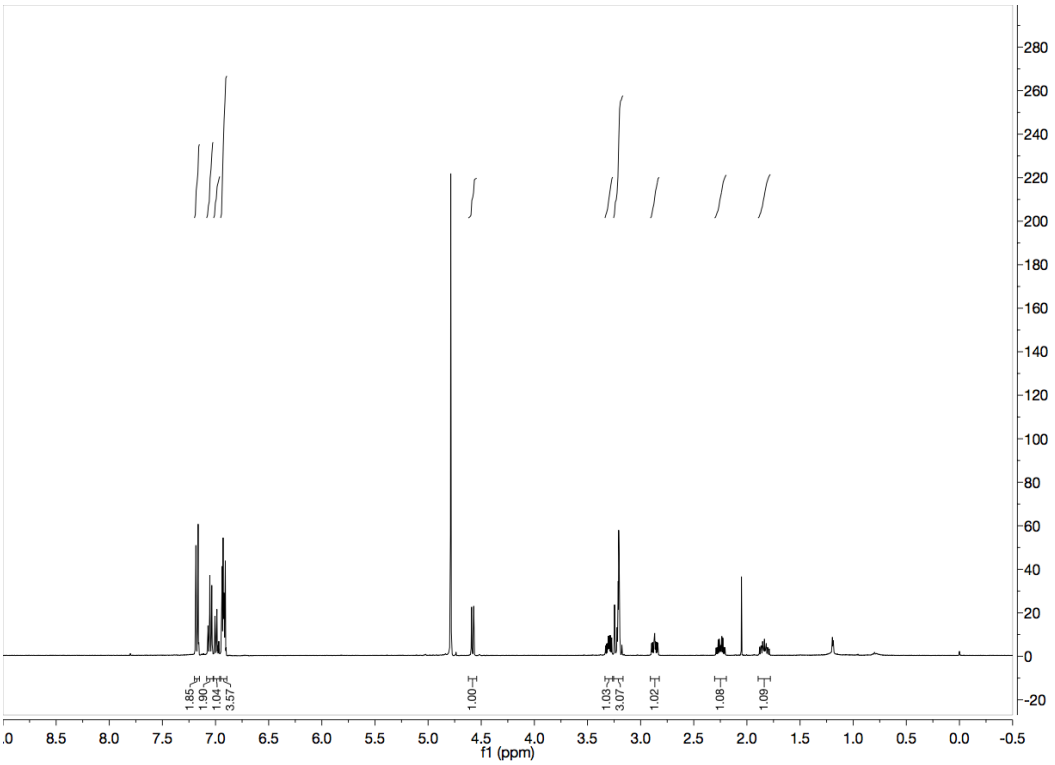
^{13}C NMR (100 MHz, Methanol-d_4): δ 144.57, 142.79, 131.71, 129.89, 129.84, 129.12, 127.39, 121.47, 78.79, 61.27, 51.78, 35.43.

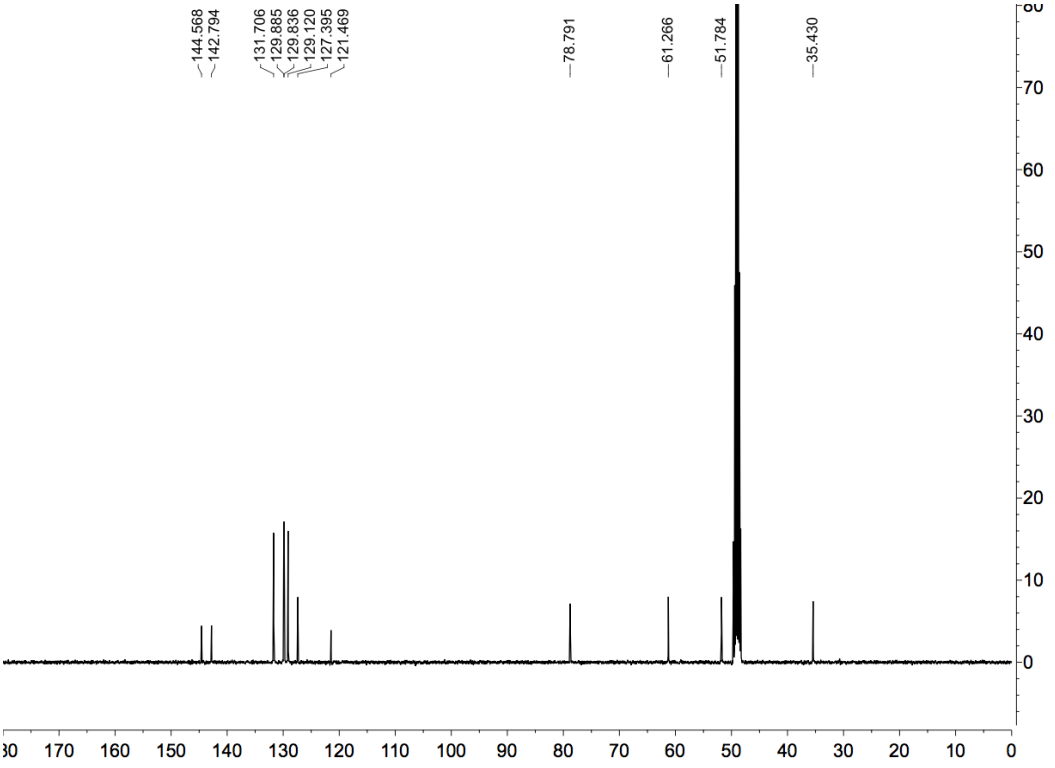
LRMS (CI) Calcd. for $C_{16}H_{17}BrNaO_2$ $[M+Na]^+$: 343, Found: 343.

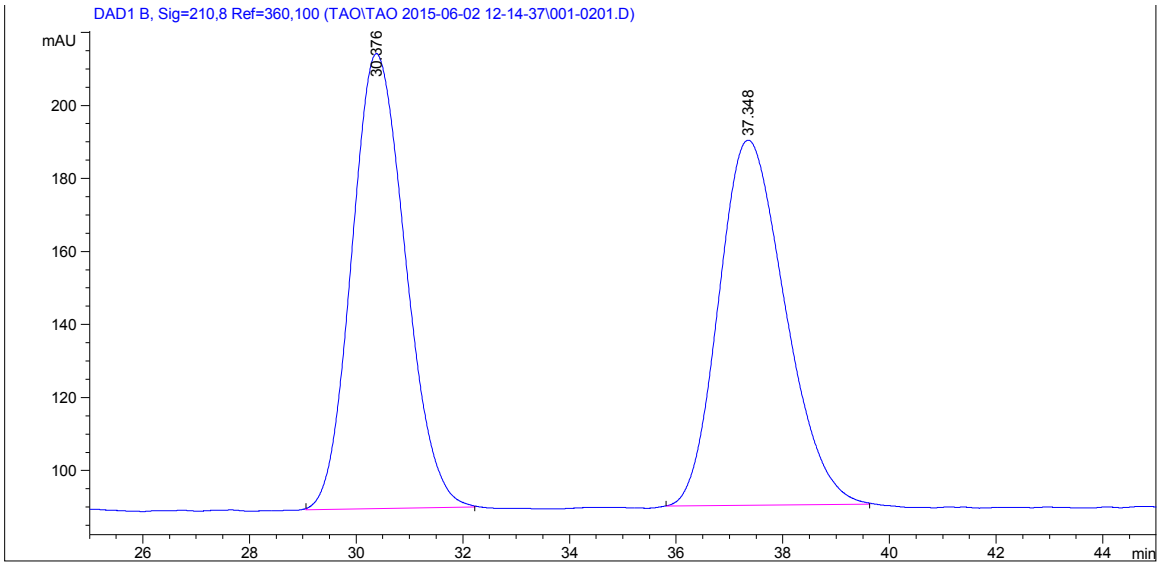
FTIR (neat): 2362, 1486, 1070, 1037, 1008, 818, 756, 700 cm^{-1}.

HPLC (Chiralcel OD-H column, hexanes:*i*-PrOH = 95:5, 1 mL/min, 210 nm), ee = 90%.

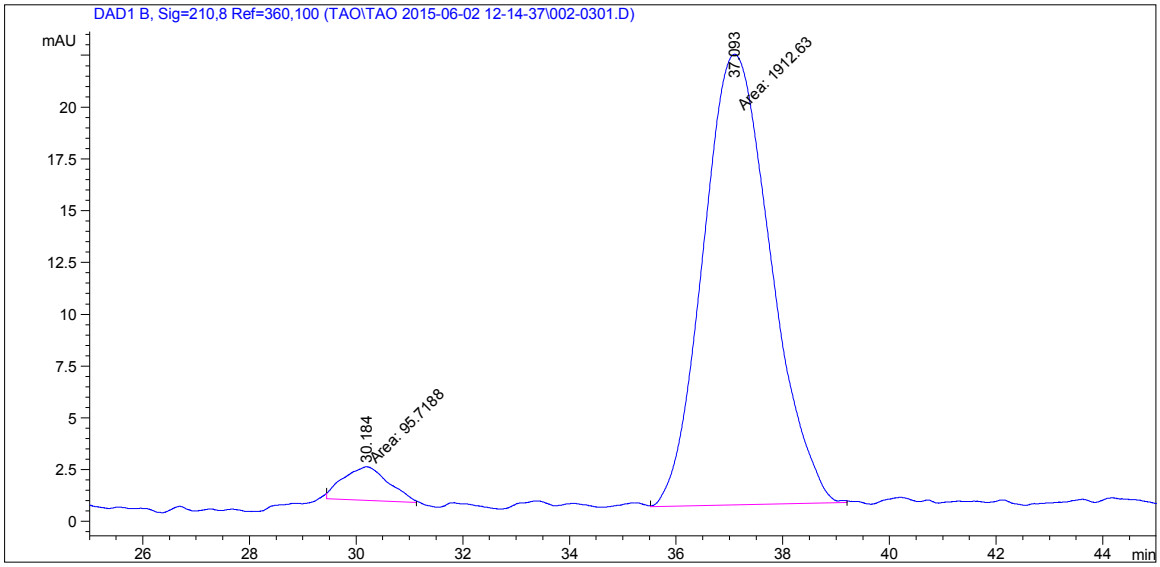
$[\alpha]^{25}_D$ = -1.3 (c = 1.0, Methanol)


1.85
1.80
1.04
3.57
1.00
1.03
3.07
1.02
1.08
1.09
f1 (ppm)


144.568
142.794
131.706
129.885
129.836
129.120
127.395
121.469
78.791
61.266
51.784
35.430



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	30.376	BB	1.0911	8726.72266	124.59850	50.2329
2	37.348	BB	1.3323	8645.80469	100.04136	49.7671

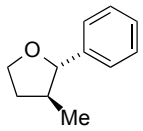


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	30.184	MM	0.9871	95.71881	1.61612	4.7660
2	37.093	MM	1.4656	1912.62830	21.75019	95.2340

General Procedure for Conversion of Alcohols 3.5a, 3.5c, 3.5e, 3.5f, 3.5k and 3.5m to *trans*-2,3-disubstituted furans 3.6a, 3.6c, 3.6e, 3.6f, 3.6k and 3.6m

To a solution of alcohol in pyridine (0.4 M) at 0 °C was added TsCl (1.5 eq) in one portion. The mixture was stirred at 0 °C for 5 hours and was allowed to warm to room temperature overnight. Once TLC indicated no alcohol left, pyridine was removed by vacuo and the residue was subjected to flash column chromatography (Alumina, basic, 60-325 Mesh, eluent Hexanes:EA = 20:1) to afford the corresponding disubstituted furan products.

(2*S*,3*S*)-3-methyl-2-phenyltetrahydrofuran (3.6a).



The residue was subjected to flash column chromatography for purification to furnish the title compound (81%, *dr* = >20:1) as a colorless liquid.

R_f = 0.7 (20% EtOAc/Hexanes).

Spectral data is reported for the major isomer.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.21 (m, 5H), 4.28 (d, *J* = 8.3 Hz, 1H), 4.10 (td, *J* = 8.3, 7.0 Hz, 1H), 4.03 (td, *J* = 8.4, 4.2 Hz, 1H), 2.27 – 2.15 (m, 1H), 2.15 – 1.99 (m, 1H), 1.71 (dq, *J* = 12.0, 8.5 Hz, 1H), 1.08 (d, *J* = 6.6 Hz, 3H).

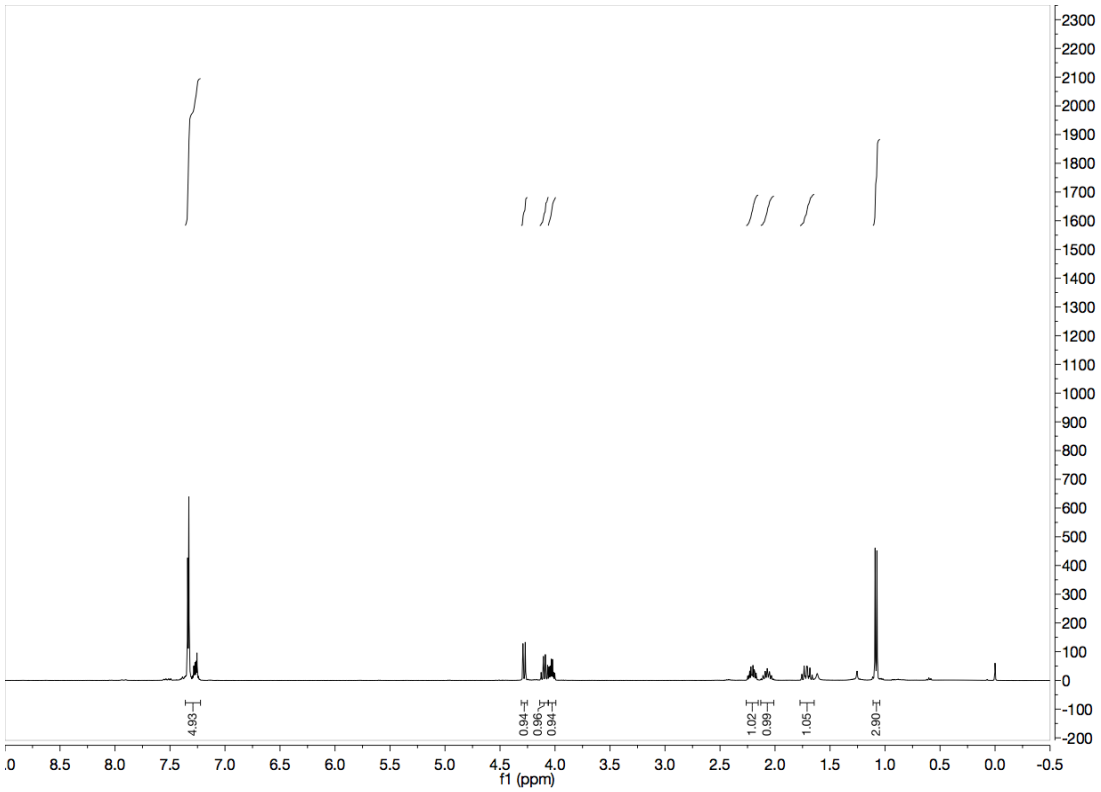
^{13}C NMR (100 MHz, $CDCl_3$): δ 142.21, 128.27, 127.40, 126.08, 87.91, 67.90, 42.87, 34.95, 16.38.

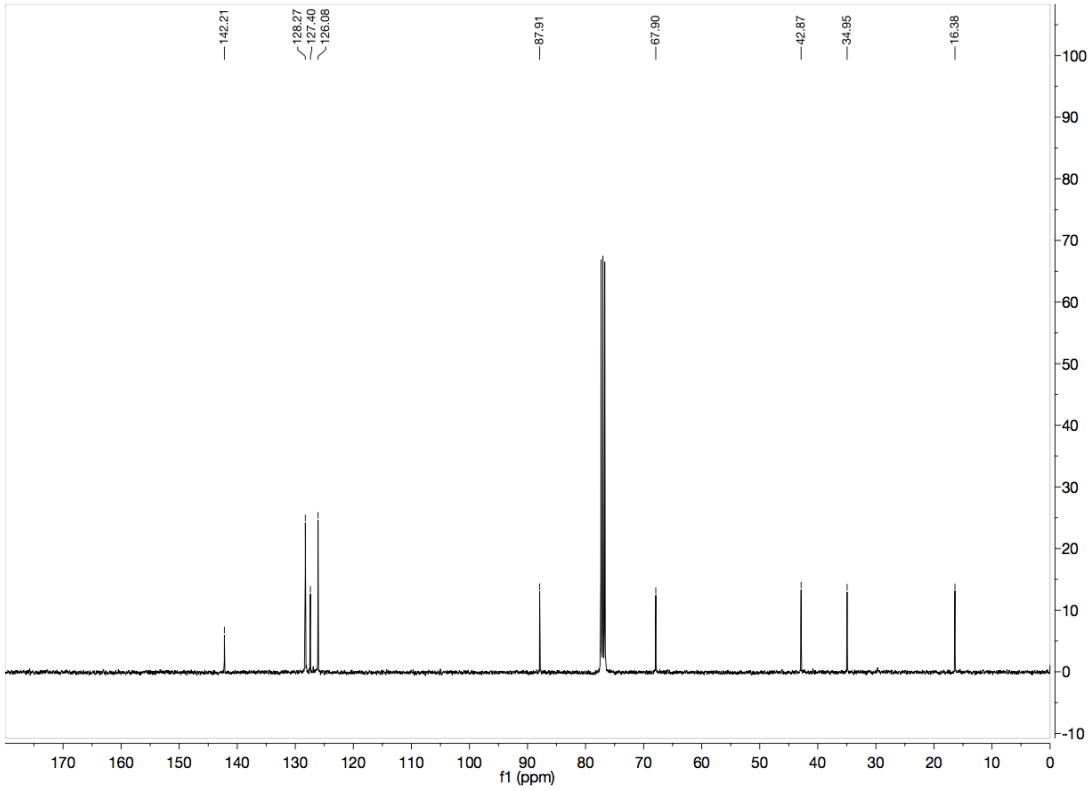
LRMS (CI) Calcd. for $C_{11}H_{15}O$ $[M+H]^+$: 163, Found: 163.

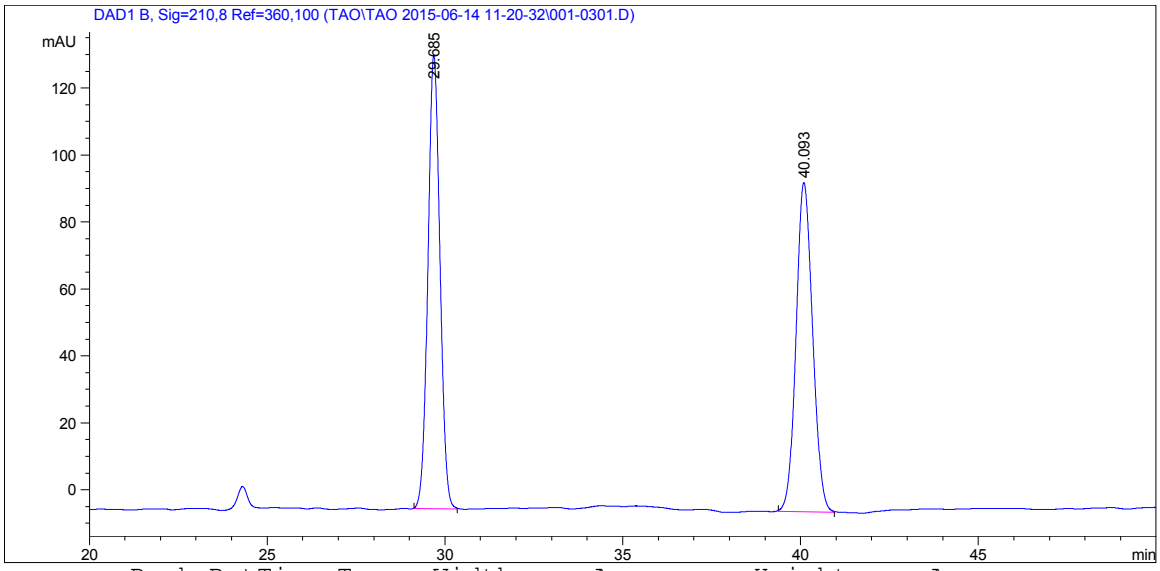
FTIR (neat): 1453, 1097, 1044, 1026, 995, 926, 751, 699 cm^{-1}.

HPLC (Chiralcel OJ-H/OJ-H column, hexanes:*i*-PrOH = 99:1, 1 mL/min, 210 nm), ee = 91%.

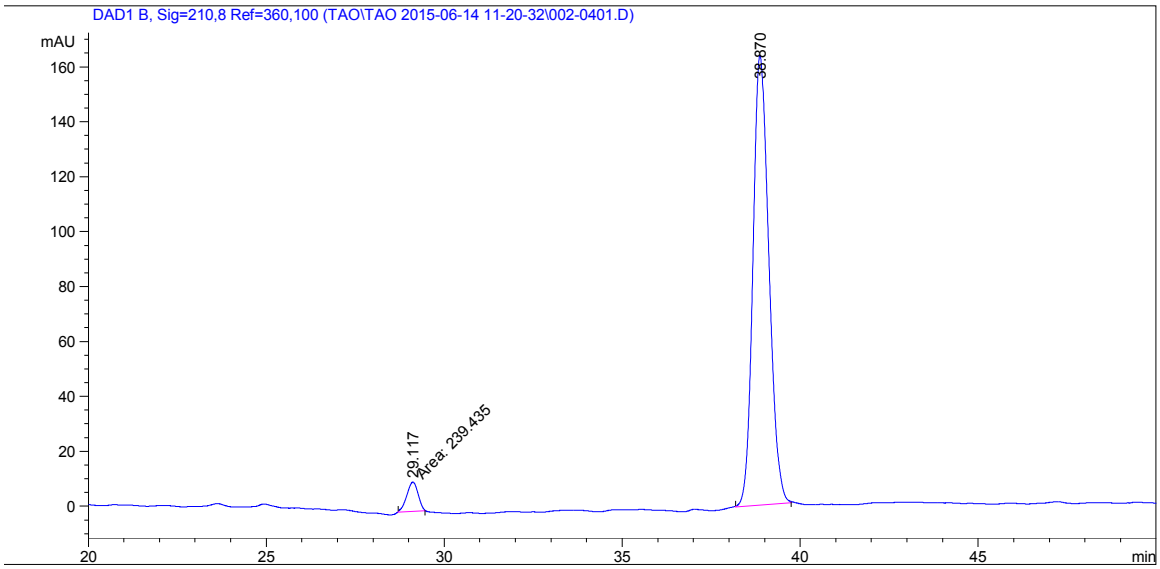
$[\alpha]^{25}_D$ = -9.7 (c = 0.52, $CHCl_3$)


4.93
0.94
0.96
0.94
1.02
0.99
1.05
2.90
f1 (ppm)


142.21
128.27
127.40
126.08
87.91
67.90
42.87
34.95
16.38
f1 (ppm)

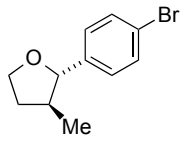


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	29.685	BB	0.3669	3197.04639	135.66116	50.0370
2	40.093	BB	0.5027	3192.31348	98.35523	49.9630



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	29.117	MM	0.3720	239.43546	10.72619	4.4972
2	38.870	BB	0.4801	5084.62305	163.82202	95.5028

(2*S*,3*S*)-2-(4-bromophenyl)-3-methyltetrahydrofuran (3.6c).



The residue was subjected to flash column chromatography for purification to furnish the title compound (78%, *dr* = >20:1) as a colorless liquid.

R_f = 0.7 (20% EtOAc/Hexanes).

Spectral data is reported for the major isomer.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.44 (m, 2H), 7.23 – 7.19 (m, 2H), 4.24 (d, *J* = 8.2 Hz, 1H), 4.08 (td, *J* = 8.3, 7.0 Hz, 1H), 4.02 (td, *J* = 8.4, 4.3 Hz, 1H), 2.25 – 2.16 (m, 1H), 2.07 – 1.94 (m, 1H), 1.77 – 1.66 (m, 1H), 1.07 (d, *J* = 6.6 Hz, 3H).

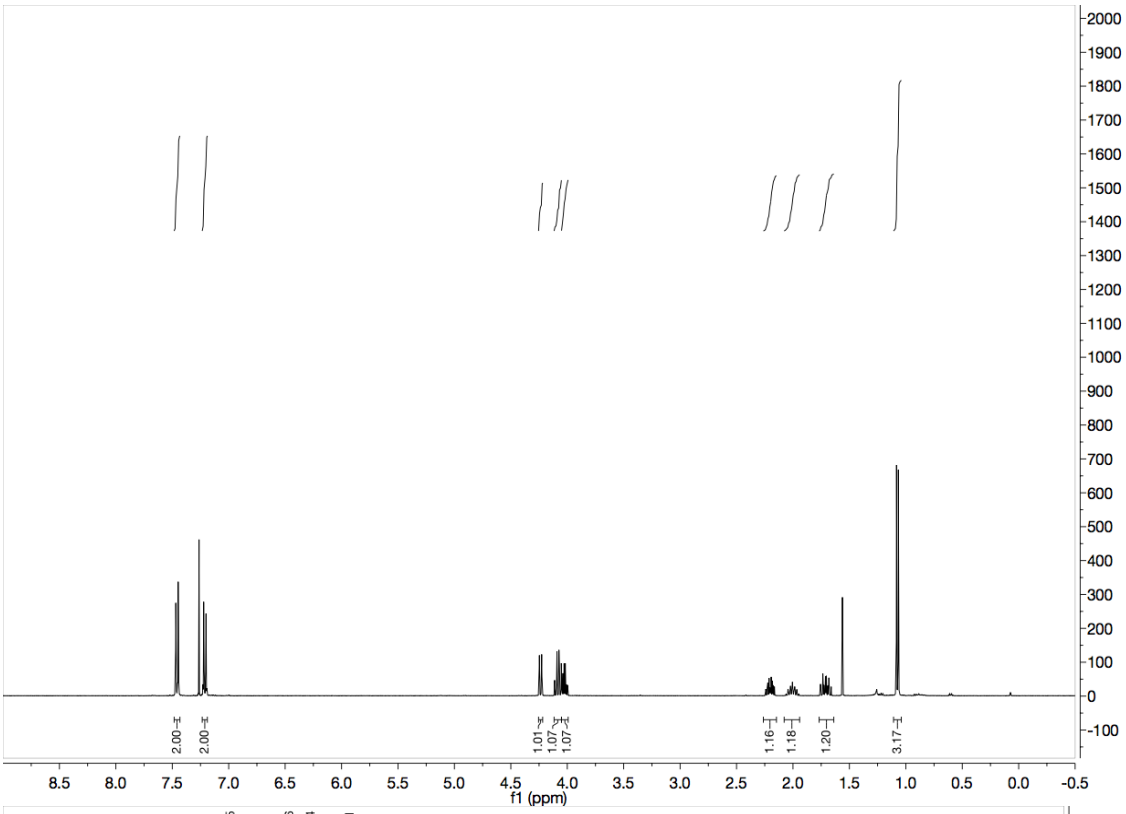
^{13}C NMR (100 MHz, $CDCl_3$): δ 141.35, 131.36, 127.74, 121.11, 87.21, 67.92, 43.02, 34.85, 16.25.

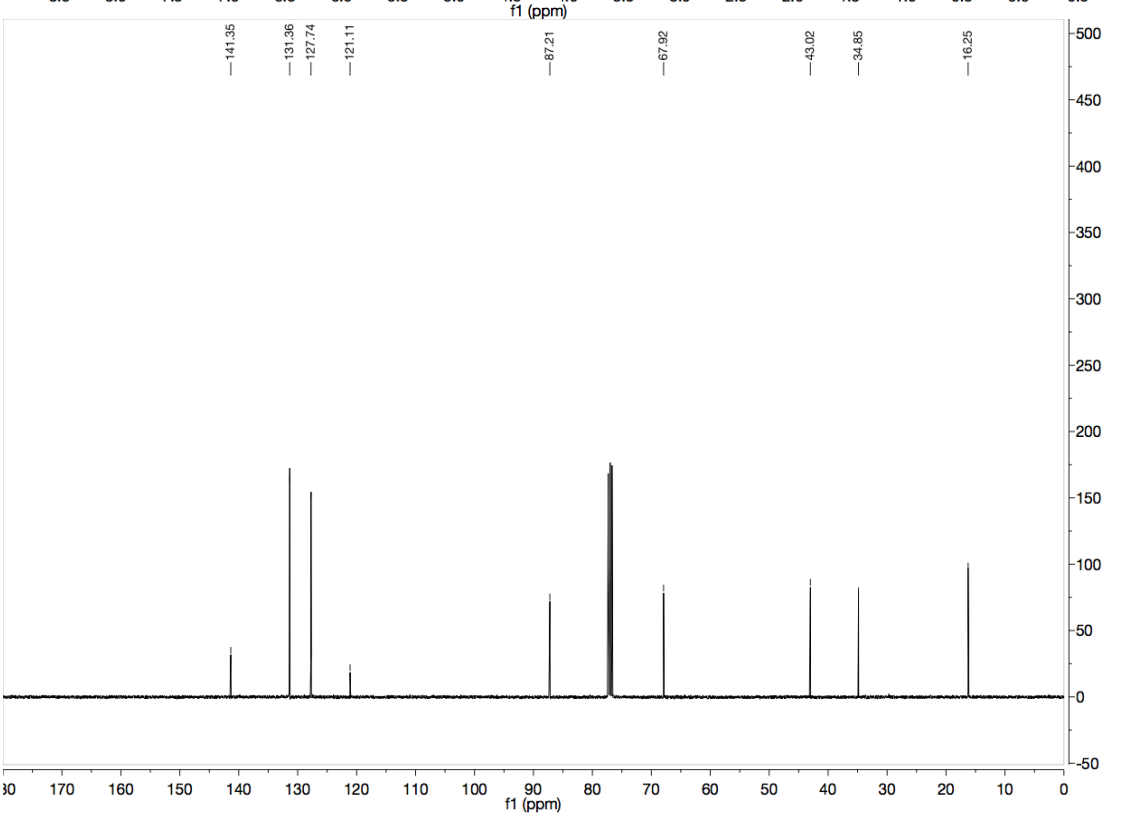
LRMS (CI) Calcd. for $C_{11}H_{14}BrO$ $[M+H]^+$: 241, Found: 241.

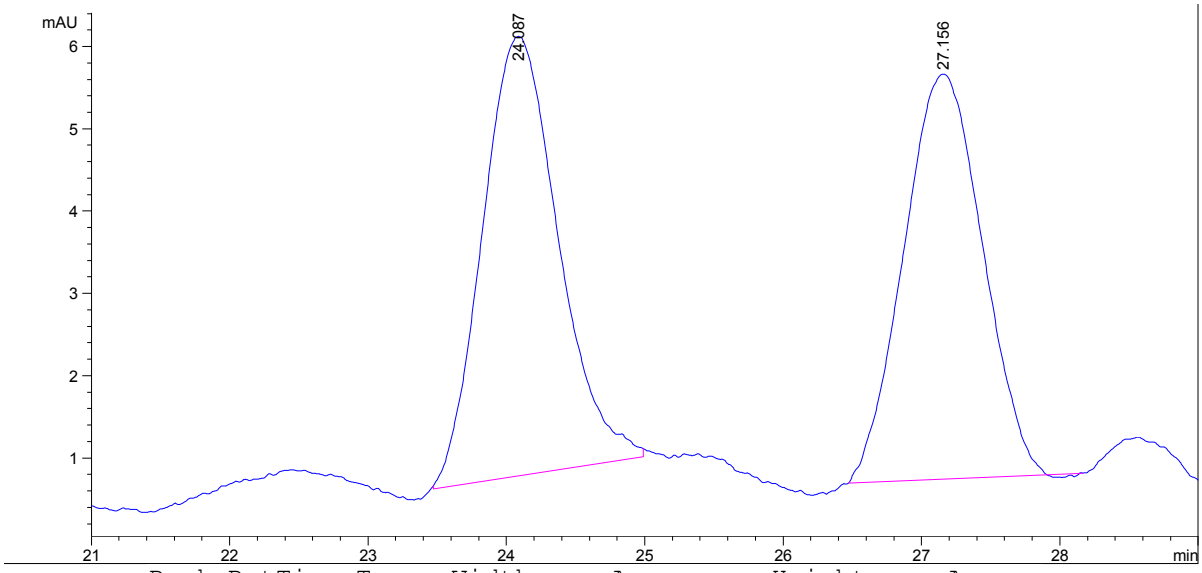
FTIR (neat): 2960, 2871, 1486, 1069, 1046, 1010, 819, 800 cm^{-1}.

HPLC (Chiralcel AD-H/AD-H column, hexanes:*i*-PrOH = 99:1, 0.5 mL/min, 210 nm), ee = 92%.

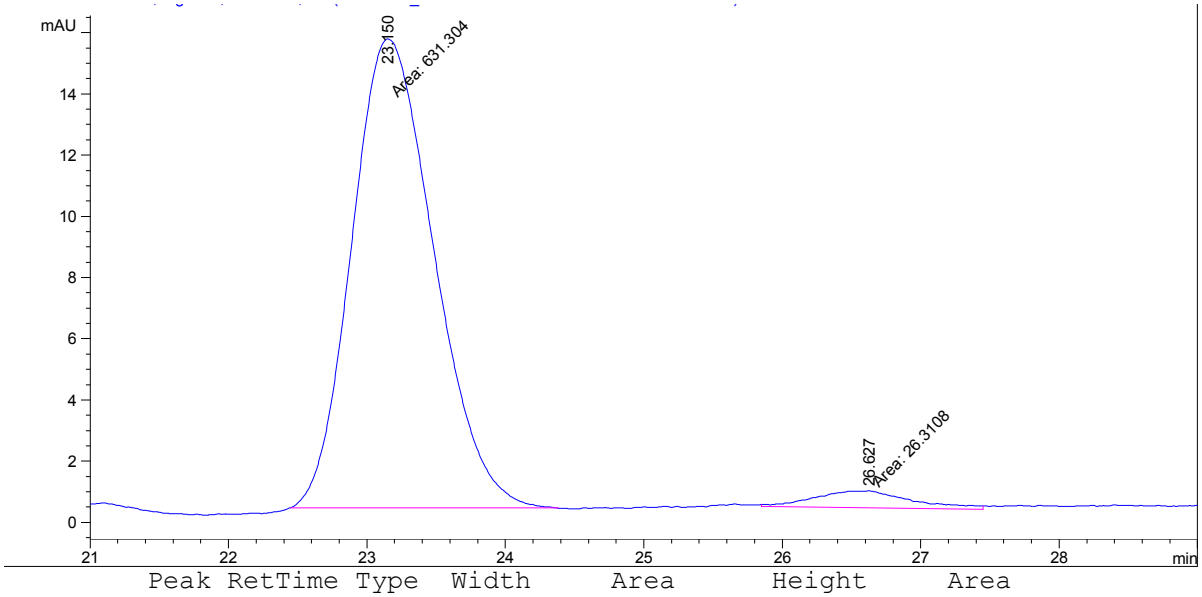
$[\alpha]^{25}_D$ = -1.8 (c = 1.15, $CHCl_3$)


2.00
2.00
1.01
1.07
1.07
1.16
1.18
1.20
3.17
f1 (ppm)


141.35
131.36
127.74
121.11
87.21
67.92
43.02
34.85
16.25
f1 (ppm)

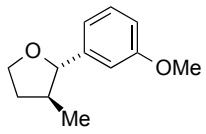


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	24.081	BB	0.5451	592.29285	15.95542	49.1568
2	27.161	MM	0.6626	612.61224	15.40874	50.8432



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	23.150	MM	0.6870	631.30402	15.31611	95.9991
2	26.627	MM	0.7998	26.31081	5.48276e-1	4.0009

(2*S*,3*S*)-2-(3-methoxyphenyl)-3-methyltetrahydrofuran (3.6e).



The residue was subjected to flash column chromatography for purification to furnish the title compound (80%, *dr* = >20:1) as a colorless liquid.

R_f = 0.7 (20% EtOAc/Hexanes).

Spectral data is reported for the major isomer.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.23 (m, 1H), 6.93 – 6.89 (m, 2H), 6.83 – 6.79 (m, 1H), 4.27 (d, *J* = 8.1 Hz, 1H), 4.09 (td, *J* = 8.2, 7.0 Hz, 1H), 4.03 (td, *J* = 8.4, 4.3 Hz, 1H), 3.82 (s, 3H), 2.25 – 2.15 (m, 1H), 2.13 – 2.01 (m, 1H), 1.76 – 1.64 (m, 1H), 1.10 (d, *J* = 6.6 Hz, 3H).

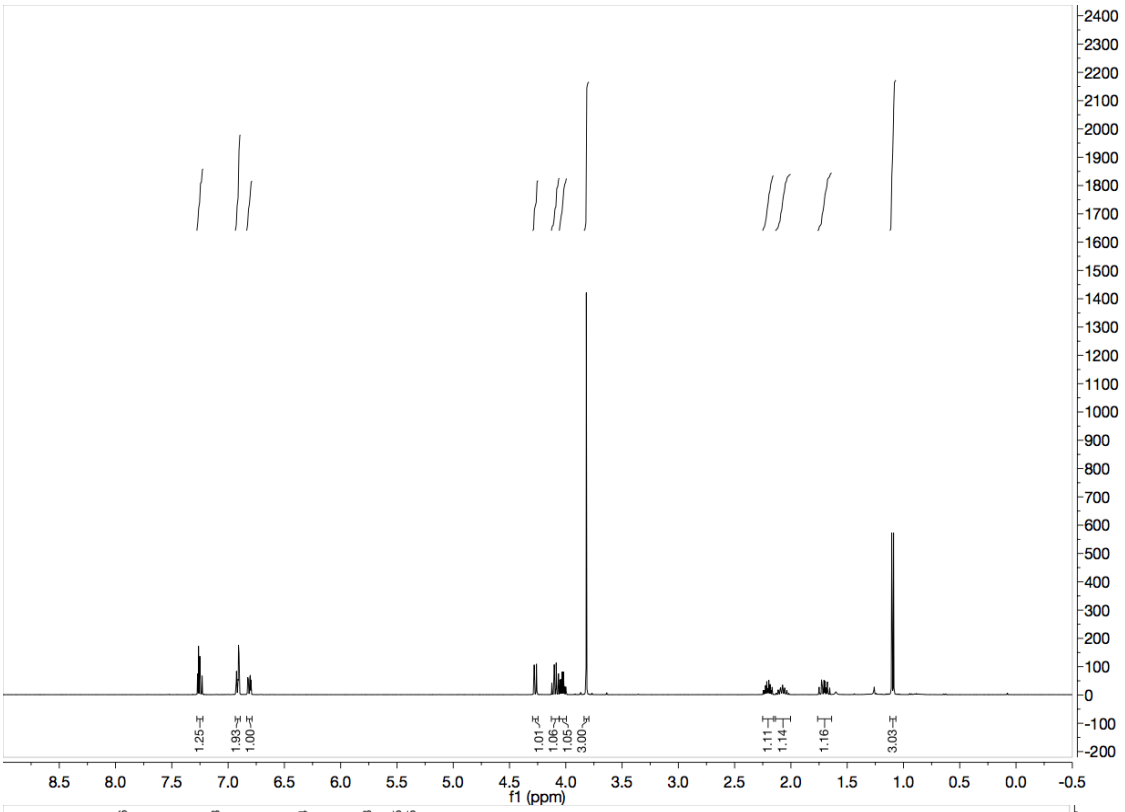
^{13}C NMR (100 MHz, $CDCl_3$): δ 159.66, 144.03, 129.24, 118.43, 112.85, 111.45, 87.75, 67.90, 55.19, 42.79, 34.91, 16.53.

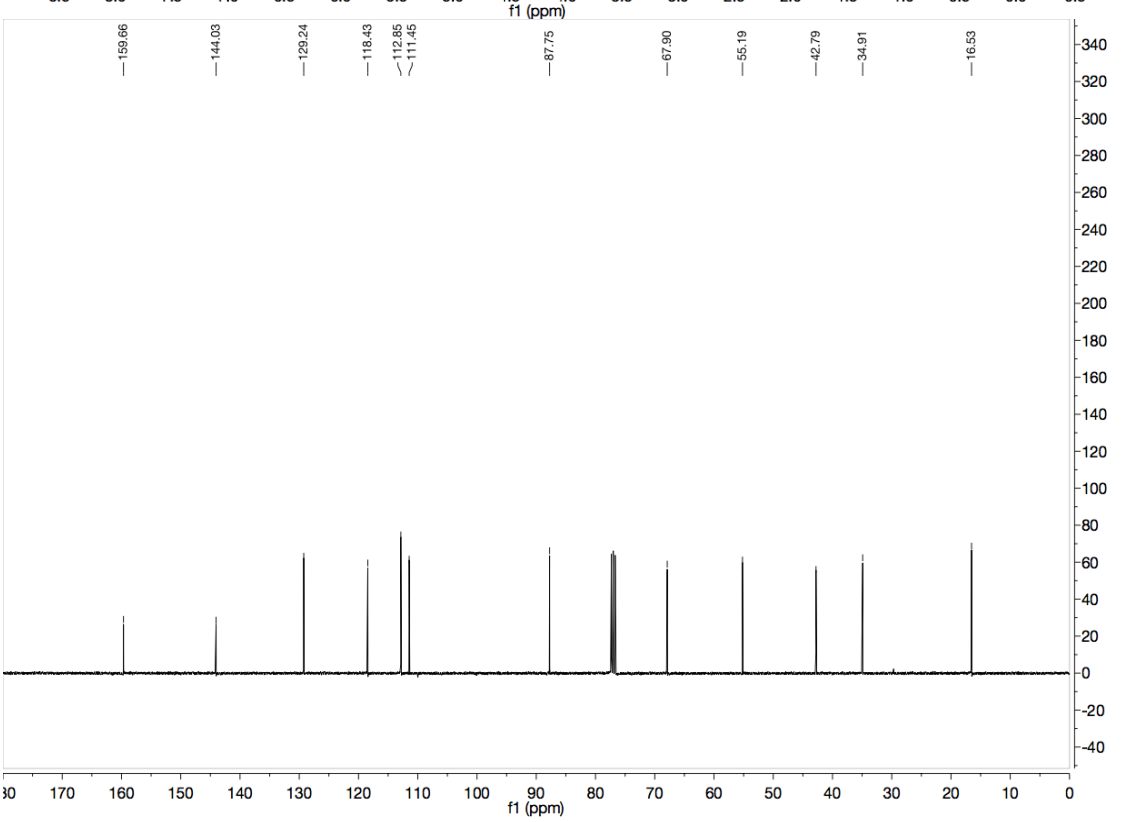
LRMS (ESI) Calcd. for $C_{12}H_{17}O_2$ $[M+H]^+$: 193, Found: 193.

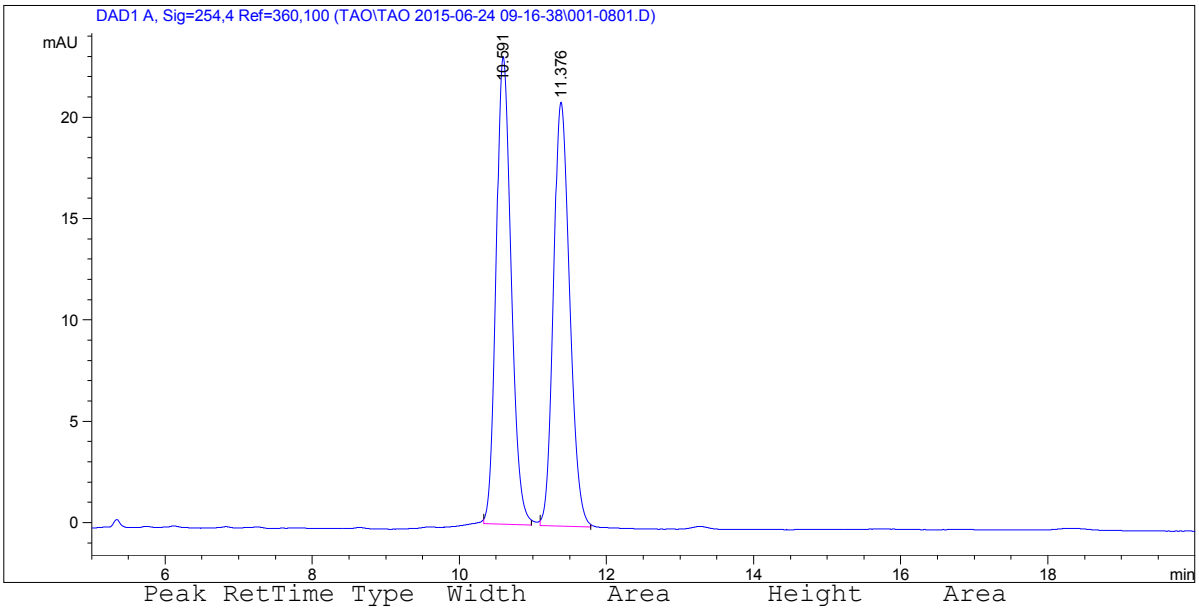
FTIR (neat): 1602, 1585, 1488, 1455, 1267, 1158, 1040, 782 cm^{-1}.

HPLC (Chiralcel OD-H column, hexanes:*i*-PrOH = 99:1, 1 mL/min, 210 nm), ee = 92%.

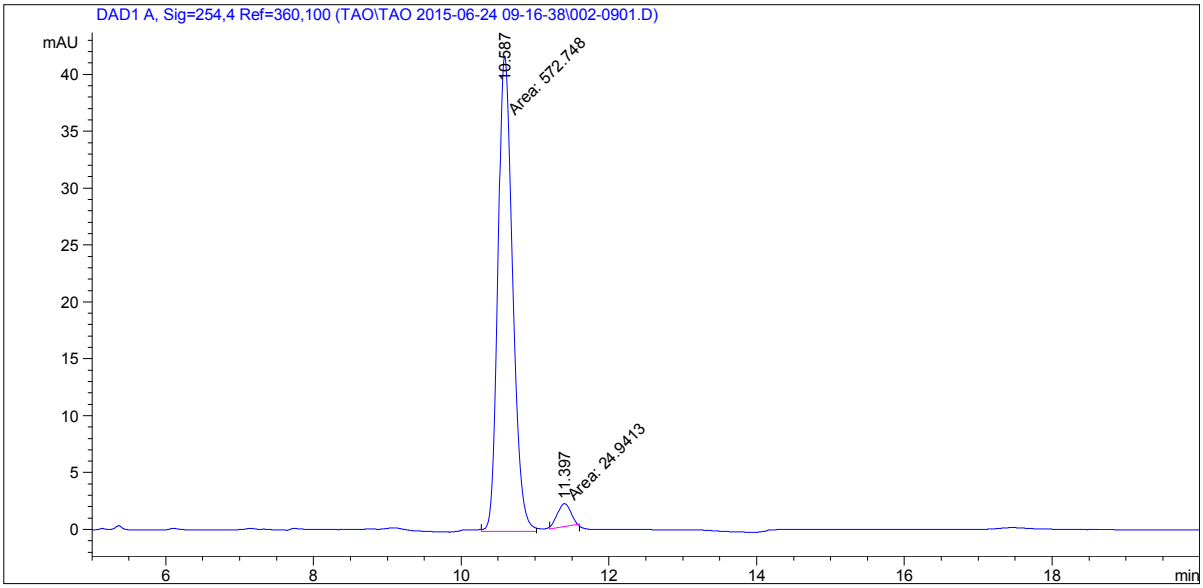
$[\alpha]^{25}_D$ = +1.9 (c = 0.52, $CHCl_3$)


1.25
1.93
1.00
1.01
1.06
1.05
3.00
1.11
1.14
1.16
3.03
f1 (ppm)


159.66
144.03
129.24
118.43
112.85
111.45
87.75
67.90
55.19
42.79
34.91
16.53
f1 (ppm)

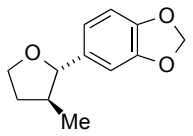


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.591	BB	0.2184	324.96088	23.06670	50.5531
2	11.376	BB	0.2353	317.84952	20.91154	49.4469



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.587	MM	0.2284	572.74780	41.79500	95.8270
2	11.397	MM	0.2063	24.94130	2.01465	4.1730

5-((2*S*,3*S*)-3-methyltetrahydrofuran-2-yl)benzo[*d*][1,3]dioxole (3.6f).



The residue was subjected to flash column chromatography for purification to furnish the title compound (82%, *dr* = >20:1) as a colorless liquid.

R_f = 0.7 (20% EtOAc/Hexanes).

Spectral data is reported for the major isomer.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.86 – 6.84 (m, 1H), 6.80 – 6.75 (m, 2H), 5.94 (s, 2H), 4.18 (d, *J* = 8.4 Hz, 1H), 4.06 (td, *J* = 8.3, 7.0 Hz, 1H), 3.99 (td, *J* = 8.4, 4.2 Hz, 1H), 2.25 – 2.15 (m, 1H), 2.08 – 1.94 (m, 1H), 1.75 – 1.62 (m, 1H), 1.05 (d, *J* = 6.6 Hz, 3H).

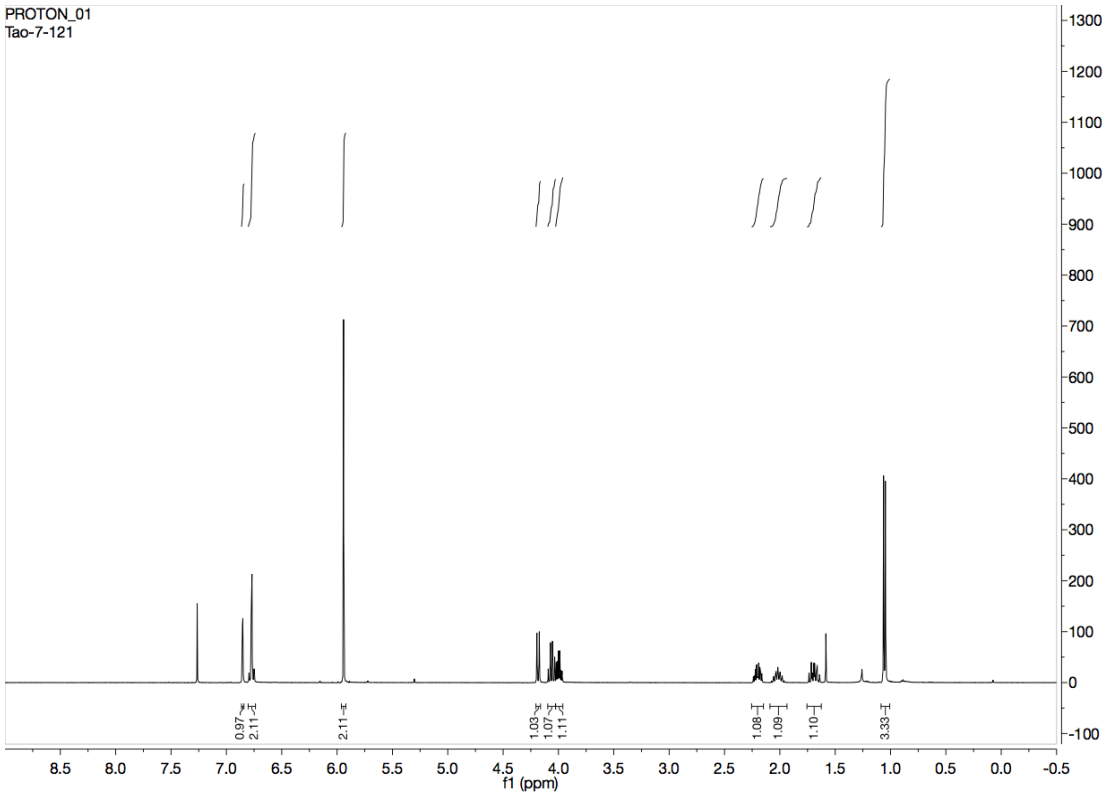
^{13}C NMR (100 MHz, $CDCl_3$): δ 147.70, 146.89, 136.04, 119.65, 107.91, 106.52, 100.89, 87.85, 67.73, 42.73, 34.87, 16.22.

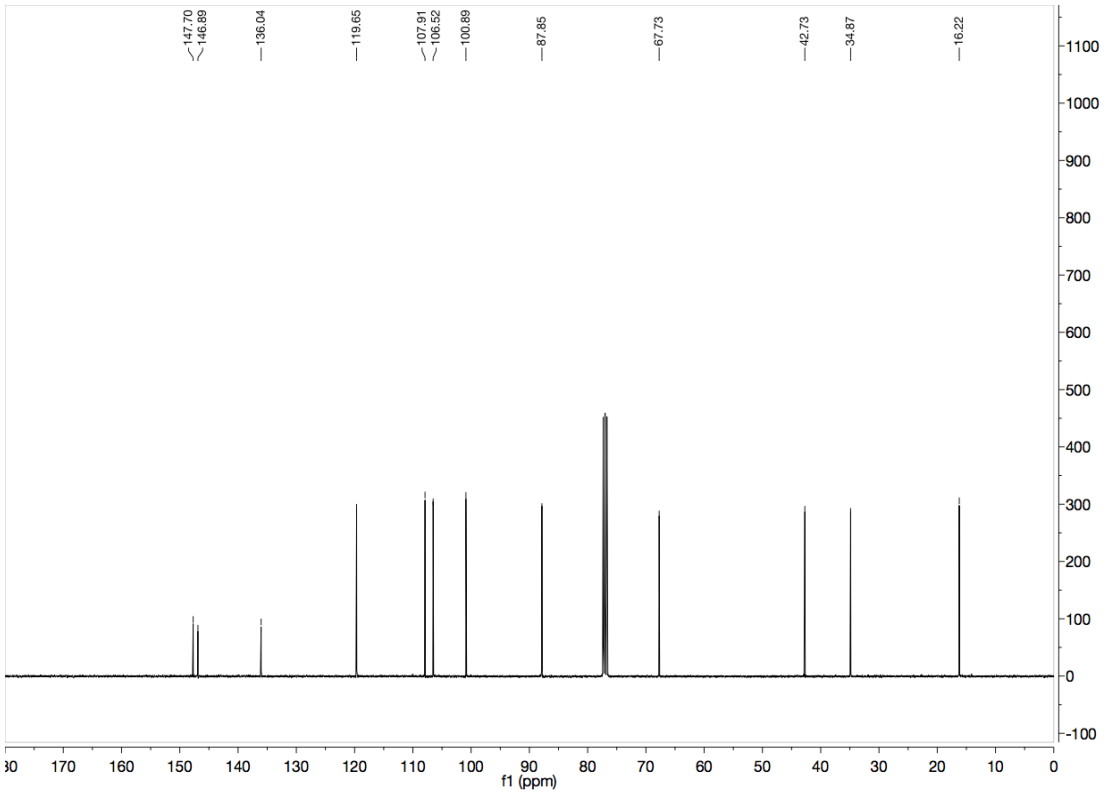
LRMS (ESI) Calcd. for $C_{12}H_{15}O_3$ $[M+H]^+$: 207, Found: 207.

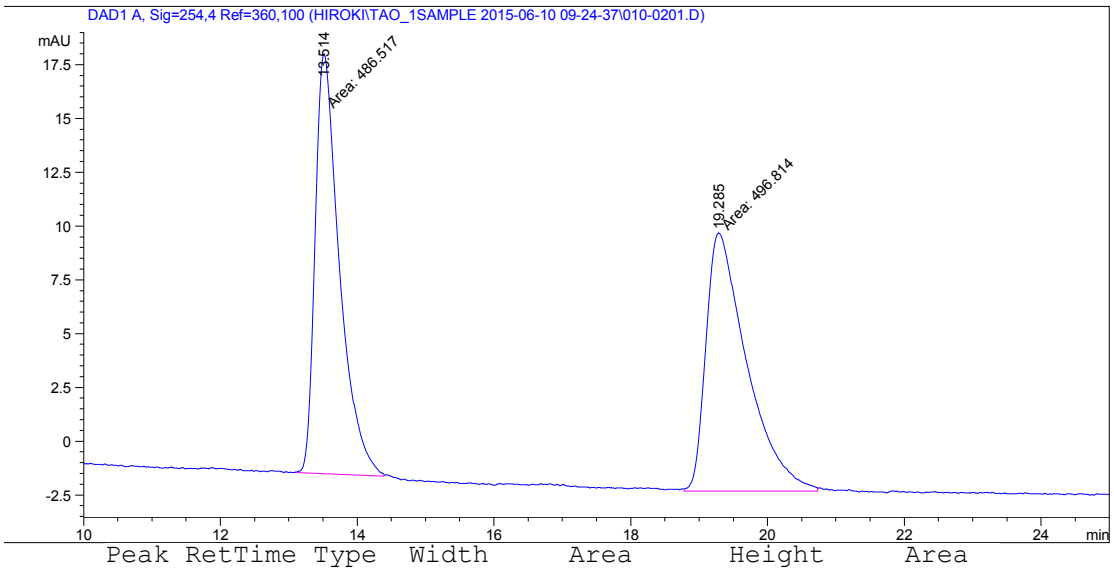
FTIR (neat): 1504, 1487, 1243, 1096, 1036, 934, 808, 784 cm^{-1}.

HPLC (Chiralcel AD-H column, hexanes:*i*-PrOH = 99:1, 1 mL/min, 254 nm), ee = 92%.

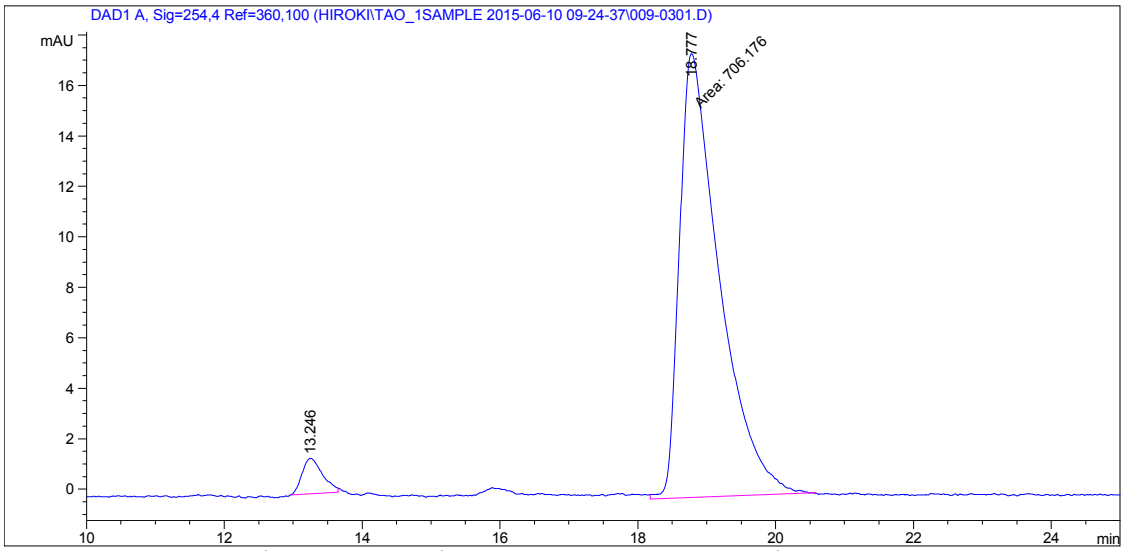
$[\alpha]^{25}_D$ = +5.2 (c = 0.58, $CHCl_3$)


PROTON_01
Tao-7-121
f1 (ppm)


147.70
146.89
136.04
119.65
107.91
106.52
100.89
87.85
67.73
42.73
34.87
16.22
f1 (ppm)

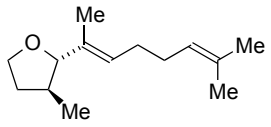


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.514	MM	0.4154	486.51660	19.51870	49.4764
2	19.285	MM	0.6902	496.81357	11.99724	50.5236



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.246	BB	0.2576	28.69911	1.39728	3.9053
2	18.777	MM	0.6696	706.17615	17.57615	96.0947

(2*S*,3*S*)-3-methyl-2-((*E*)-7-methylocta-2,6-dien-2-yl)tetrahydrofuran (3.6k).



The residue was subjected to flash column chromatography for purification to furnish the title compound (77%, *dr* = >20:1) as a colorless liquid.

R_f = 0.7 (20% EtOAc/Hexanes).

Spectral data is reported for the major isomer.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.15 (dq, *J* = 8.8, 1.3 Hz, 1H), 5.12 – 5.06 (m, 1H), 4.00 (t, *J* = 8.7 Hz, 1H), 3.93 – 3.81 (m, 2H), 2.16 – 2.07 (m, 3H), 2.07 – 2.00 (m, 2H), 1.91 – 1.77 (m, 1H), 1.70 (d, *J* = 1.4 Hz, 3H), 1.68 (d, *J* = 1.3 Hz, 3H), 1.62 – 1.53 (m, 4H), 0.99 (d, *J* = 6.6 Hz, 3H).

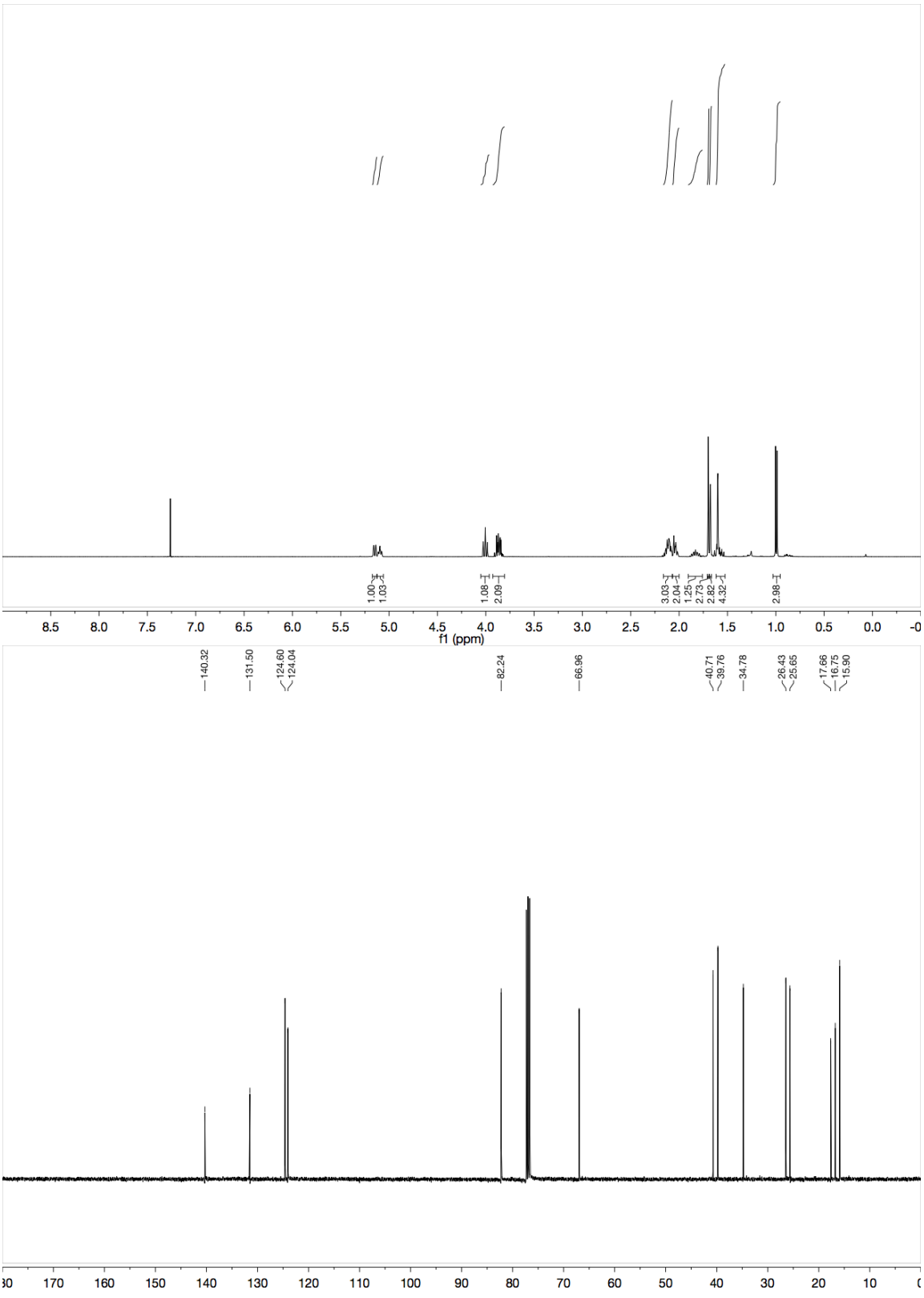
^{13}C NMR (100 MHz, $CDCl_3$): δ 140.32, 131.50, 124.60, 124.04, 82.24, 66.96, 40.71, 39.76, 34.78, 26.43, 25.65, 17.66, 16.75, 15.90.

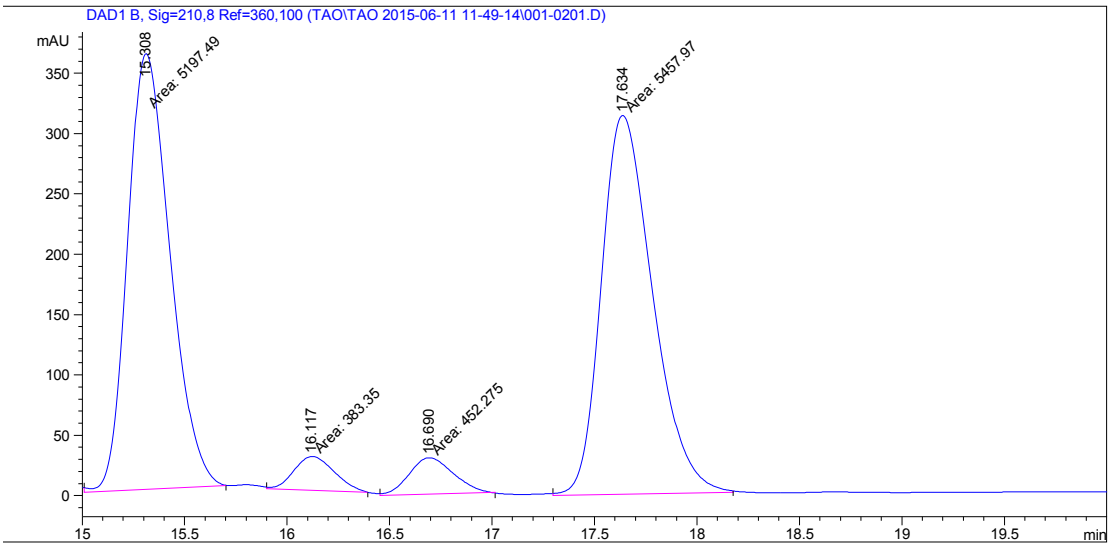
LRMS (ESI) Calcd. for $C_{14}H_{25}O$ $[M+H]^+$: 209, Found: 209.

FTIR (neat): 2958, 2926, 2871, 1452, 1376, 1101, 1032, 987, 913 cm^{-1}.

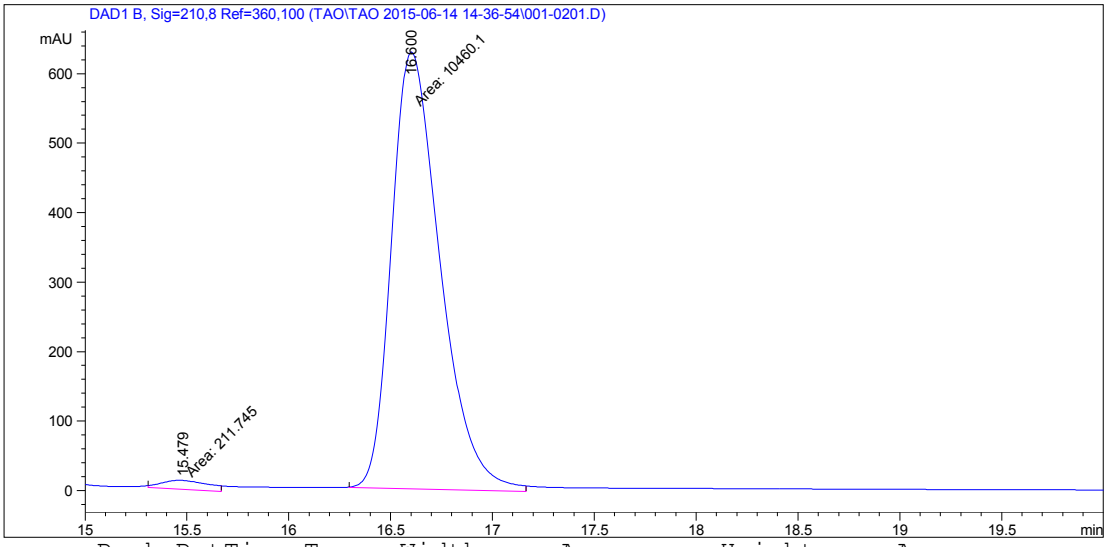
HPLC (Chiralcel AD-H/AD-H column, hexanes:*i*-PrOH = 99:1, 0.5 mL/min, 254 nm), ee = 96%.

$[\alpha]^{25}_D$ = +3.9 (c = 0.30, $CHCl_3$)


1.00
1.03
1.08
2.09
3.03
2.04
1.25
2.73
2.82
4.32
2.98
f1 (ppm)
140.32
131.50
124.60
124.04
82.24
66.96
40.71
39.76
34.78
26.43
25.65
17.66
16.75
15.90

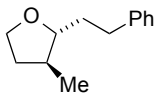


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.308	MM	0.2399	5197.48584	361.13022	45.2306
2	16.117	MM	0.2279	383.35046	28.03022	3.3361



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.479	MM	0.2695	211.74541	13.09471	1.9842
2	16.600	MM	0.2771	1.04601e4	629.16864	98.0158

(2*R*,3*S*)-3-methyl-2-phenethyltetrahydrofuran (3.6m).



The residue was subjected to flash column chromatography for purification to furnish the title compound (72%, *dr* = >20:1) as a colorless liquid.

R_f = 0.7 (20% EtOAc/Hexanes).

Spectral data is reported for the major isomer.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.26 (m, 2H), 7.24 – 7.16 (m, 3H), 3.90 – 3.80 (m, 2H), 3.34 (td, *J* = 8.2, 3.5 Hz, 1H), 2.85 (ddd, *J* = 13.7, 10.8, 5.1 Hz, 1H), 2.67 (ddd, *J* = 13.7, 10.5, 6.2 Hz, 1H), 2.15 – 2.04 (m, 1H), 1.92 – 1.69 (m, 3H), 1.59 – 1.48 (m, 1H), 1.03 (d, *J* = 6.7 Hz, 3H).

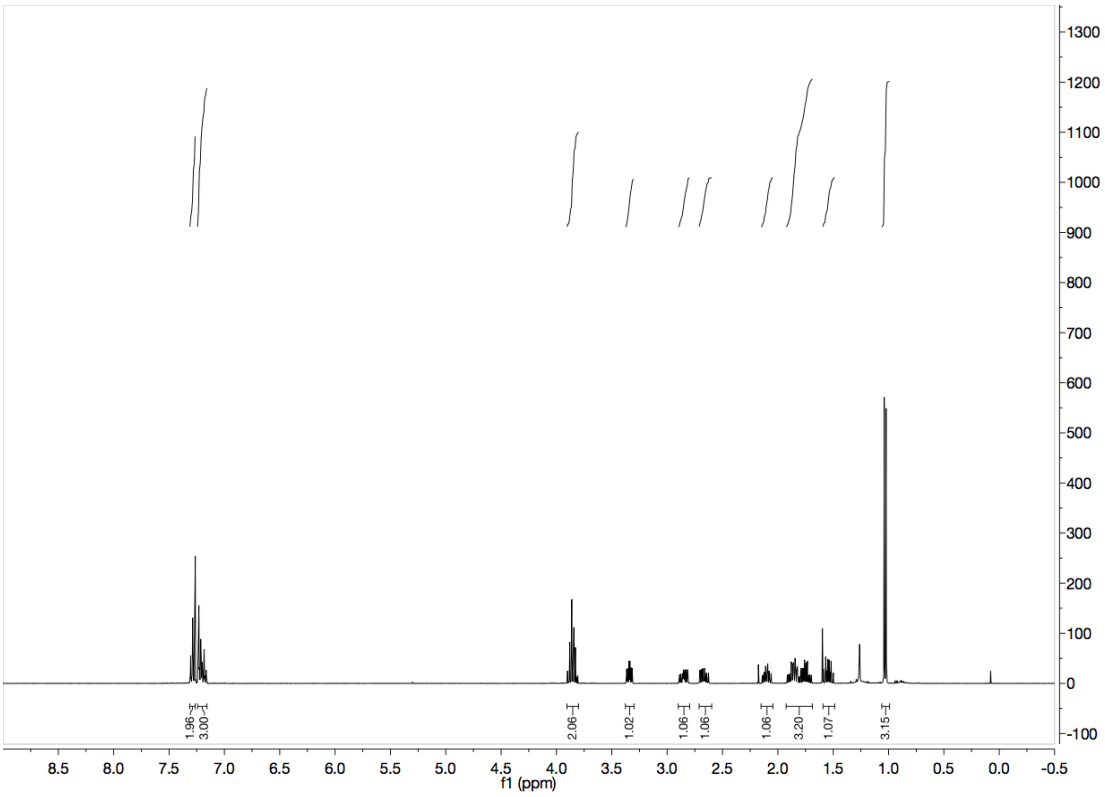
^{13}C NMR (100 MHz, $CDCl_3$): δ 142.43, 128.38, 128.29, 125.66, 85.24, 66.74, 39.05, 36.23, 34.72, 32.84, 17.23.

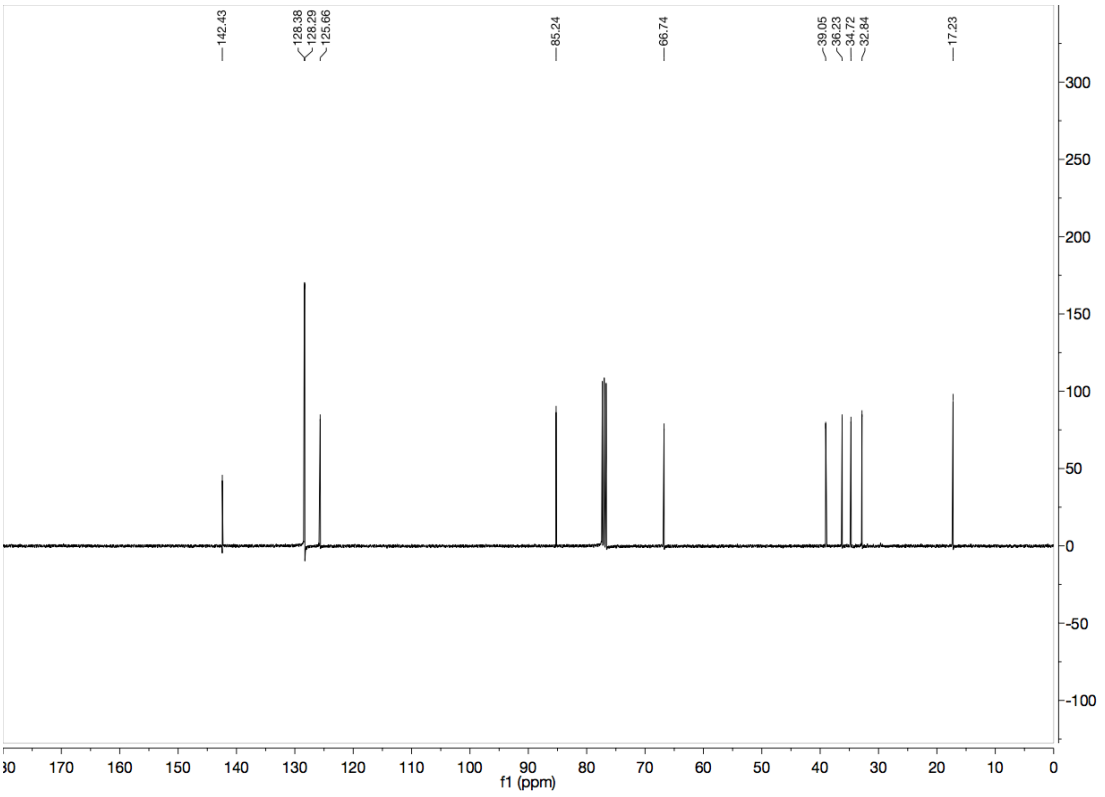
LRMS (ESI) Calcd. for $C_{13}H_{19}O$ $[M+H]^+$: 191, Found: 191.

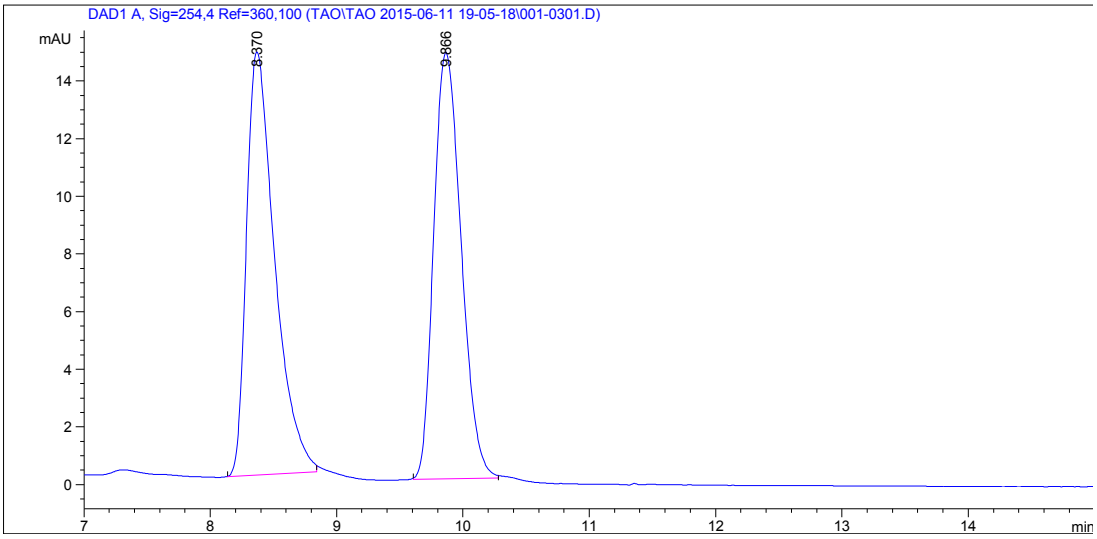
FTIR (neat): 2957, 2927, 1454, 1106, 1039, 1013, 745, 699 cm^{-1}.

HPLC (Chiralcel AD-H column, hexanes:*i*-PrOH = 99:1, 0.5 mL/min, 254 nm), ee = 90%.

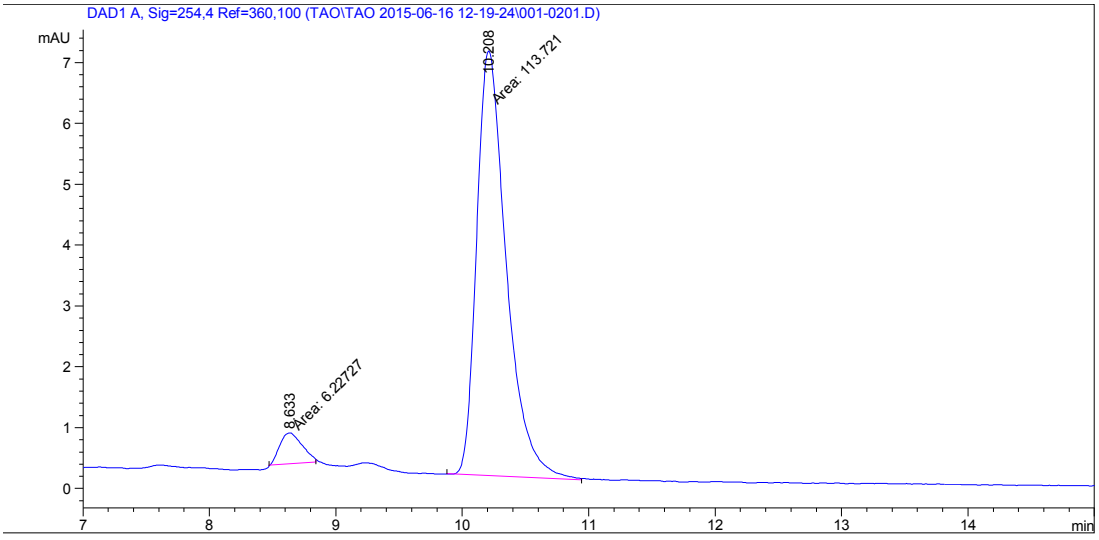
$[\alpha]^{25}_D$ = +39.2 (c = 0.31, $CHCl_3$)


1.96
3.00
2.06
1.02
1.06
1.06
1.06
3.20
1.07
3.15
f1 (ppm)


142.43
128.38
128.29
125.66
85.24
66.74
39.05
36.23
34.72
32.84
17.23
f1 (ppm)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.370	BB	0.2329	227.55005	14.67808	50.5338
2	9.866	BB	0.2376	222.74254	14.79539	49.4662

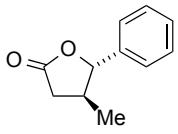


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.633	MM	0.2052	6.22727	5.05894e-1	5.1916
2	10.208	MM	0.2717	113.72086	6.97588	94.8084

General Procedure for Conversion of Alcohols 3.2a, 3.2l, 3.2p to *trans*-4,5-disubstituted lactones 3.7a, 3.7l and 3.7p

To a resealable pressure tube (ca. 13 x 100) was added $H_2Ru(CO)(PPh_3)_3$ (9.2 mg, 0.010 mmol, 5 mol%), SL-J009-1 ligand (5.6 mg, 0.010 mmol, 5 mol%), Bu_4NI (7.4 mg, 0.020 mmol, 10 mol%) and 2,4,6-tri(2-propyl)phenylsulfonic acid (4.2 mg, 0.015 mmol, 7.5 mol%). At this stage solid alcohol coupling partners (0.20 mmol, 100 mol%) were added. The tube was then sealed with a rubber septum and purged with argon. THF (0.20 mL, 1 M concentration with respect to alcohols) was then added. At this stage, liquid alcohol coupling partners (0.20 mmol, 100 mol%) were added. 2-propylalcohol (31 μL, 0.40 mmol, 200 mol%) was then added. Alkyne 1a (0.60 mmol, 300 mol%) was added *via* syringe and the rubber septum was quickly replaced with a screw cap. The mixture was then heated at 85 °C for the time stated. After cooling to room temperature, the mixture was passed through a short silica pad, washed the pad with EA, and concentrated *in vacuo*. The residue was dissolved in THF (2.0 mL) and TBAF (1.0 M in THF, 0.2 mL) was added at 0ºC. The mixture was stirred at r.t for 30 min, and then quenched by water, extracted by DCM (3 x 1 mL). The organic layer was washed by brine, dried over Na_2SO_4. The organic solvent was evaporated down to 2 mL and 4 Å MS (100 mg), NaOAc (8.2 mg, 0.10 mmol) and PCC (129 mg, 0.60 mmol) were added, and the mixture was stirred at room temperature for 24 hours. The solvent was removed by *vacuo*, and the residue was subjected to flash column chromatography (SiO_2, eluent Hexanes:EA = 5:1) to afford the corresponding lactone products.

(4*S*,5*S*)-4-methyl-5-phenyldihydrofuran-2(3*H*)-one (3.7a).



The residue was subjected to flash column chromatography for purification to furnish the title compound (70%, *dr* = >20:1) as a colorless liquid.

R_f = 0.2 (20% EtOAc/Hexanes).

Spectral data is reported for the major isomer.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.31 (m, 5H), 4.94 (d, *J* = 8.3 Hz, 1H), 2.79 (dd, *J* = 16.9, 7.7 Hz, 1H), 2.55 – 2.42 (m, 1H), 2.34 (dd, *J* = 16.9, 10.5 Hz, 1H), 1.19 (d, *J* = 6.6 Hz, 3H).

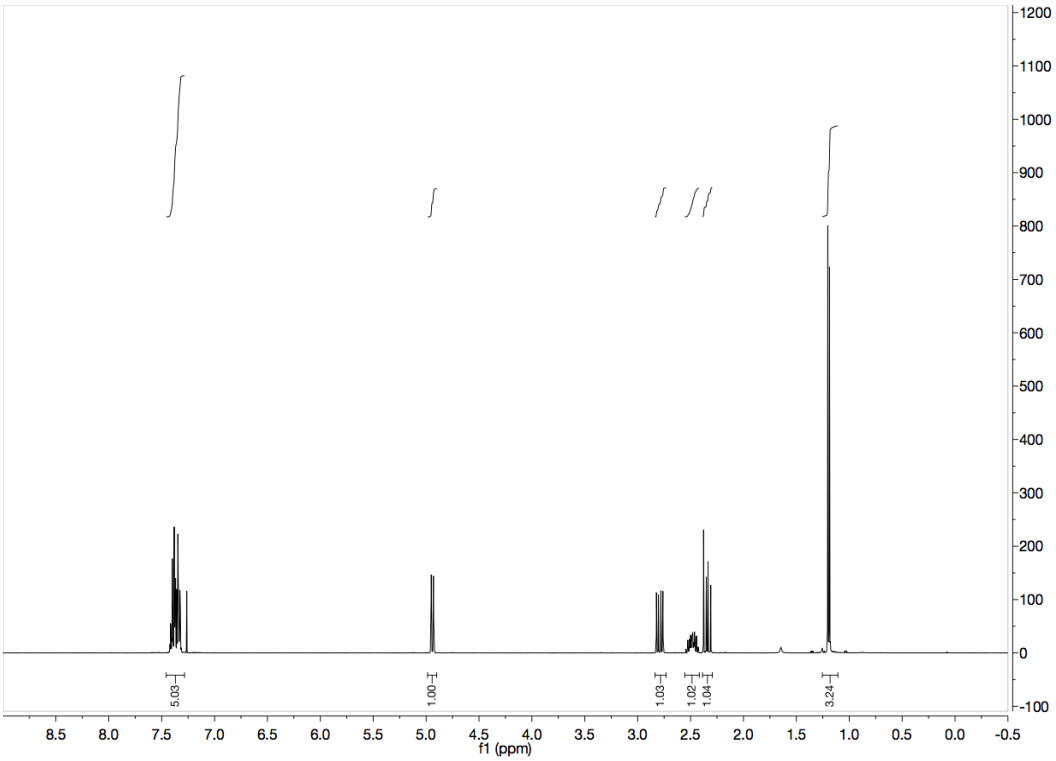
^{13}C NMR (100 MHz, $CDCl_3$): δ 176.07, 137.93, 128.69, 125.90, 88.13, 39.81, 37.21, 16.49.

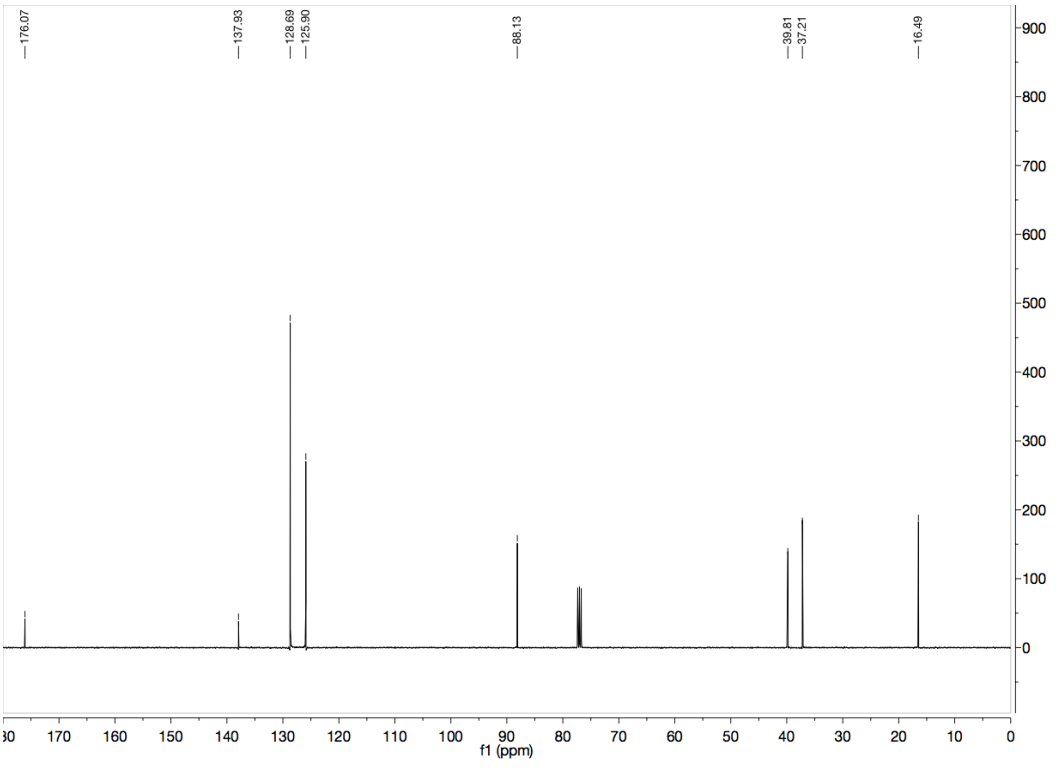
LRMS (ESI) Calcd. for $C_{11}H_{13}O_2$ $[M+H]^+$: 177, Found: 177.

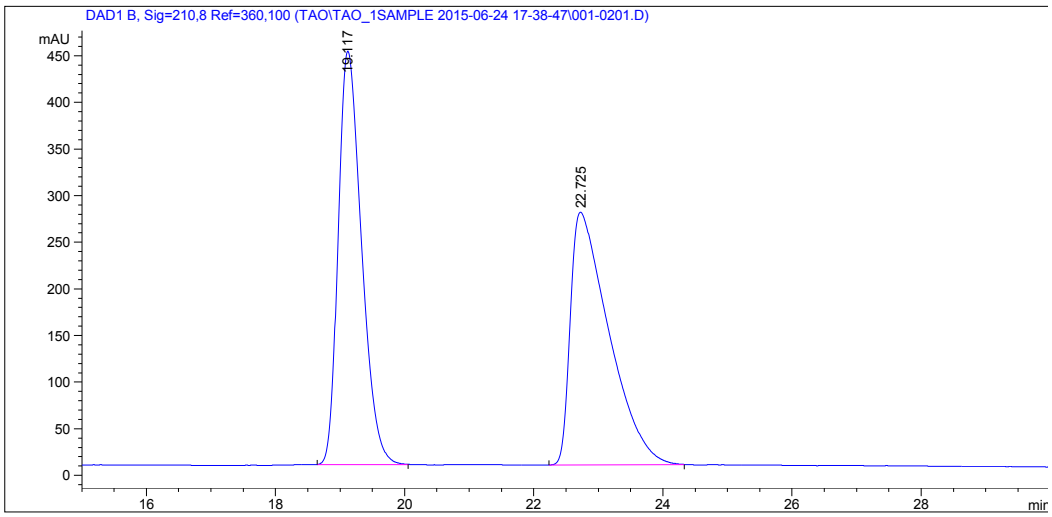
FTIR (neat): 1778, 1278, 1210, 1140, 998, 946, 756, 699 cm^{-1}.

HPLC (Chiralcel OD-H column, hexanes:*i*-PrOH = 95:5, 1 mL/min, 210 nm), ee = 91%.

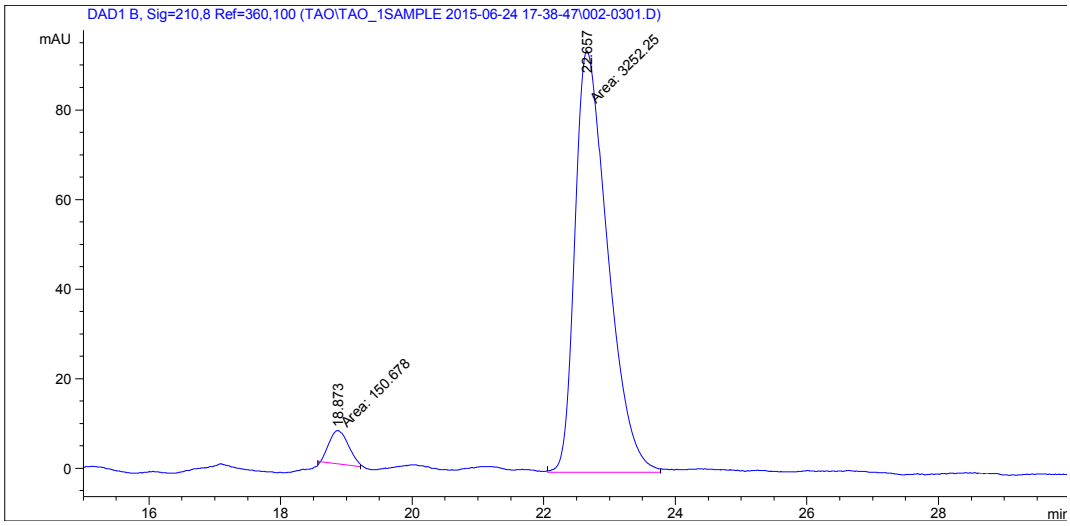
$[\alpha]^{25}_D$ = +1.1 (c = 0.9, $CHCl_3$)


5.03
1.00
1.03
1.02
1.04
3.24
f1 (ppm)


176.07
137.93
128.69
125.90
88.13
39.81
37.21
16.49
f1 (ppm)

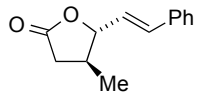


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.117	BB	0.3870	1.11370e4	443.40332	49.8286
2	22.725	BB	0.5887	1.12136e4	271.02835	50.1714



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.873	MM	0.3384	150.67789	7.42006	4.4279
2	22.657	MM	0.5766	3252.25488	94.00772	95.5721

(4*S*,5*S*)-4-methyl-5-((*E*)-styryl)dihydrofuran-2(3*H*)-one (3.7l).



The residue was subjected to flash column chromatography for purification to furnish the title compound (76%, *dr* = >20:1) as a colorless liquid.

R_f = 0.2 (20% EtOAc/Hexanes).

Spectral data is reported for the major isomer.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.27 (m, 5H), 6.70 (d, *J* = 16.3 Hz, 1H), 6.17 (dd, *J* = 15.9, 7.2 Hz, 1H), 4.58 (ddd, *J* = 8.1, 7.2, 1.1 Hz, 1H), 2.74 (dd, *J* = 16.9, 7.7 Hz, 1H), 2.46 – 2.33 (m, 1H), 2.27 (dd, *J* = 16.9, 10.2 Hz, 1H), 1.20 (d, *J* = 6.6 Hz, 3H).

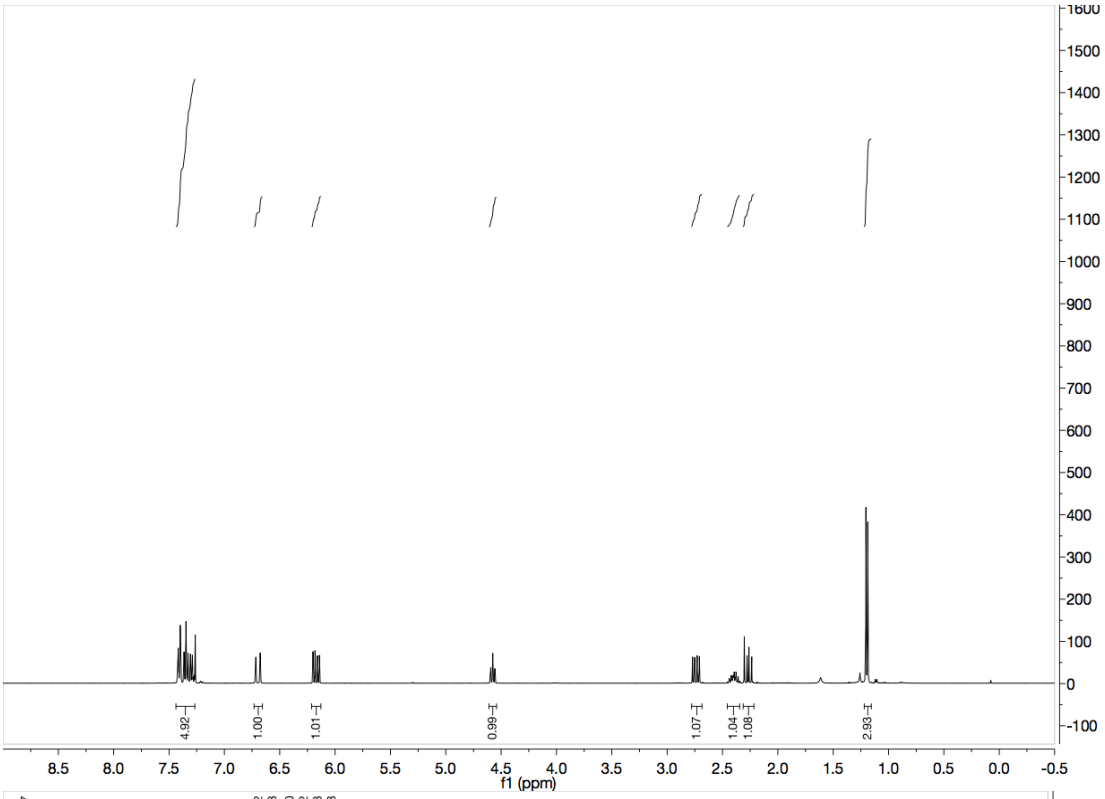
^{13}C NMR (100 MHz, $CDCl_3$): δ 176.07, 135.62, 133.88, 128.70, 128.42, 126.73, 125.18, 87.46, 37.32, 36.78, 16.50.

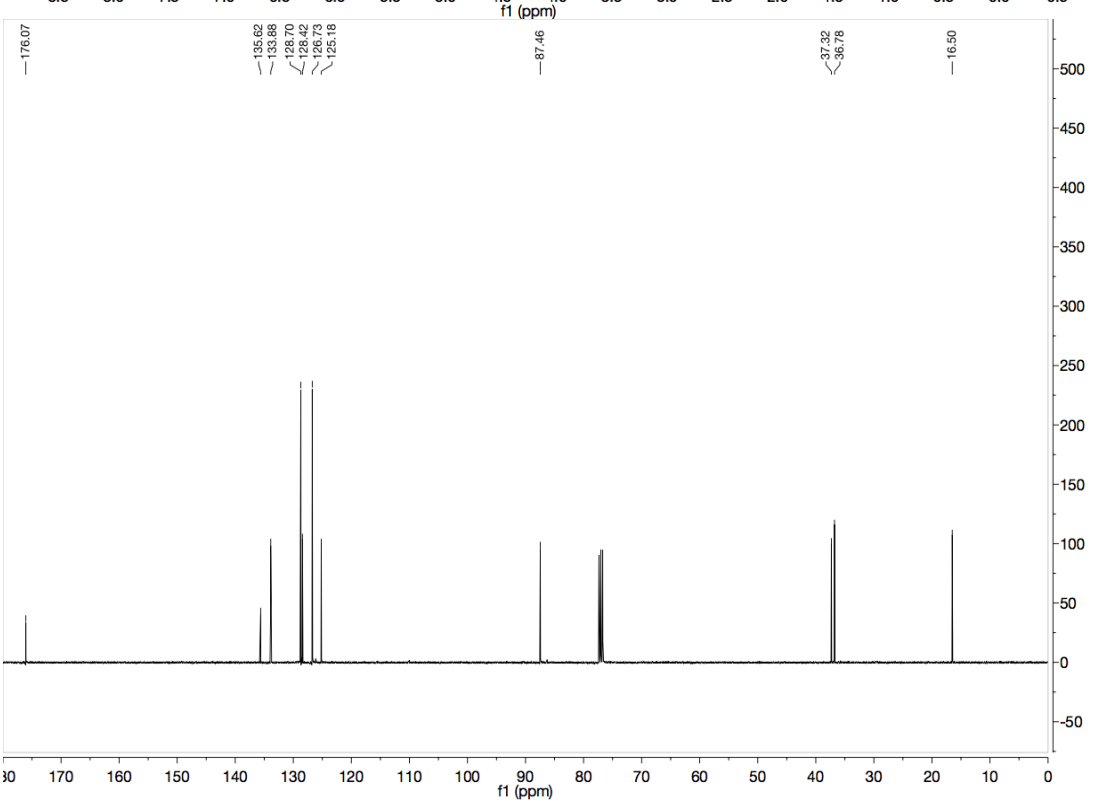
LRMS (ESI) Calcd. for $C_{13}H_{15}O_2$ $[M+H]^+$: 203, Found: 203.

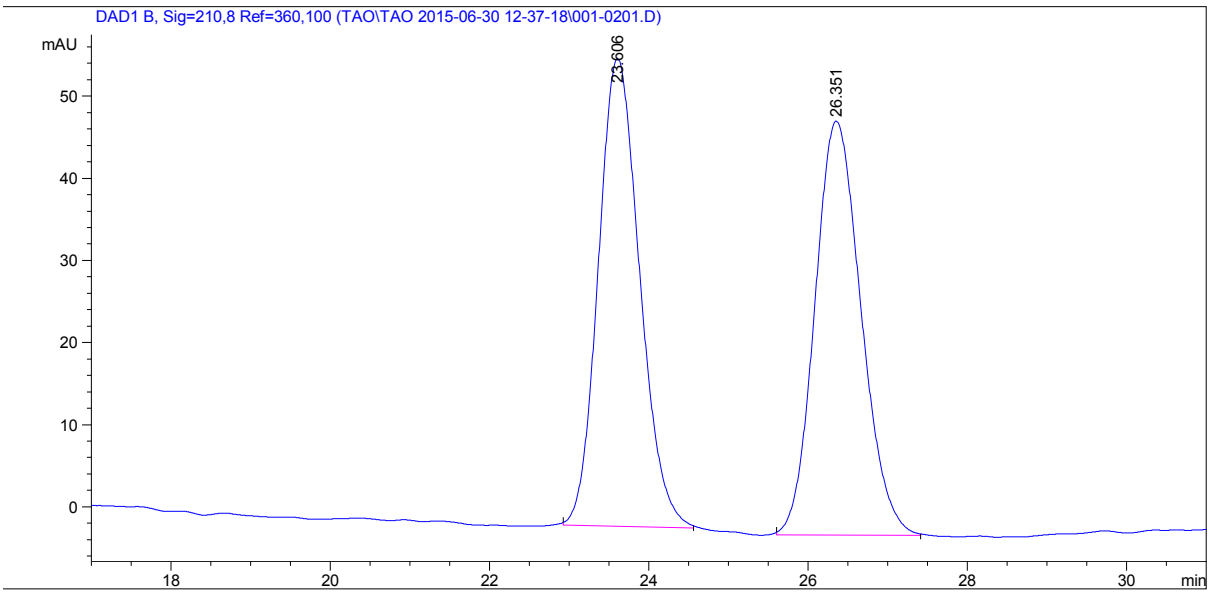
FTIR (neat): 1775, 1209, 1156, 986, 968, 939, 750, 693 cm^{-1}.

HPLC (Chiralcel OD-H column, hexanes:*i*-PrOH = 95:5, 1 mL/min, 210 nm), ee = 93%.

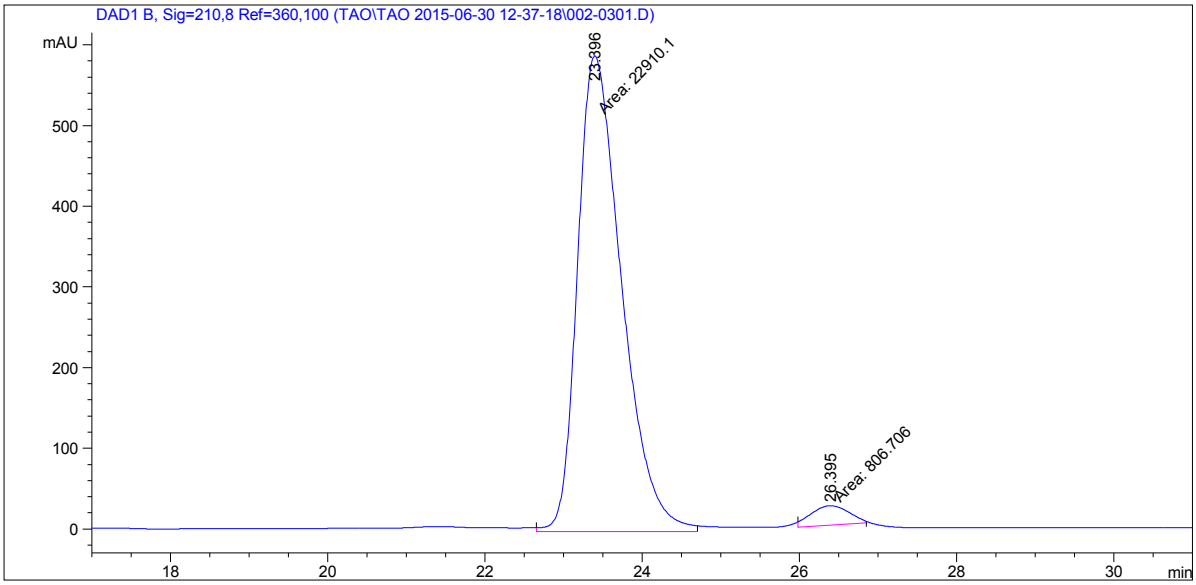
$[\alpha]^{25}_D$ = +47.5 (c = 0.4, $CHCl_3$)


4.92
1.00
1.01
0.99
1.07
1.04
1.08
2.93
f1 (ppm)


176.07
135.62
133.88
128.70
128.42
126.73
125.18
87.46
37.32
36.78
16.50
f1 (ppm)

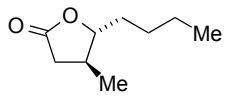


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	23.606	BB	0.5565	2052.90649	56.96287	50.3022
2	26.351	BB	0.6218	2028.24023	50.36858	49.6978



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	23.396	MM	0.6482	2.29101e4	589.07062	96.5986
2	26.395	MM	0.5590	806.70642	24.05120	3.4014

(4*S*,5*R*)-5-butyl-4-methyldihydrofuran-2(3*H*)-one (3.7p).



The residue was subjected to flash column chromatography for purification to furnish the title compound (72%, *dr* = >20:1) as a colorless liquid.

R_f = 0.2 (20% EtOAc/Hexanes).

Spectral data is reported for the major isomer.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.00 (td, *J* = 8.0, 4.1 Hz, 1H), 2.72 – 2.60 (m, 1H), 2.26 – 2.13 (m, 2H), 1.72 – 1.56 (m, 2H), 1.55 – 1.44 (m, 1H), 1.42 – 1.30 (m, 3H), 1.13 (d, *J* = 6.4 Hz, 3H), 0.91 (t, *J* = 7.1 Hz, 3H).

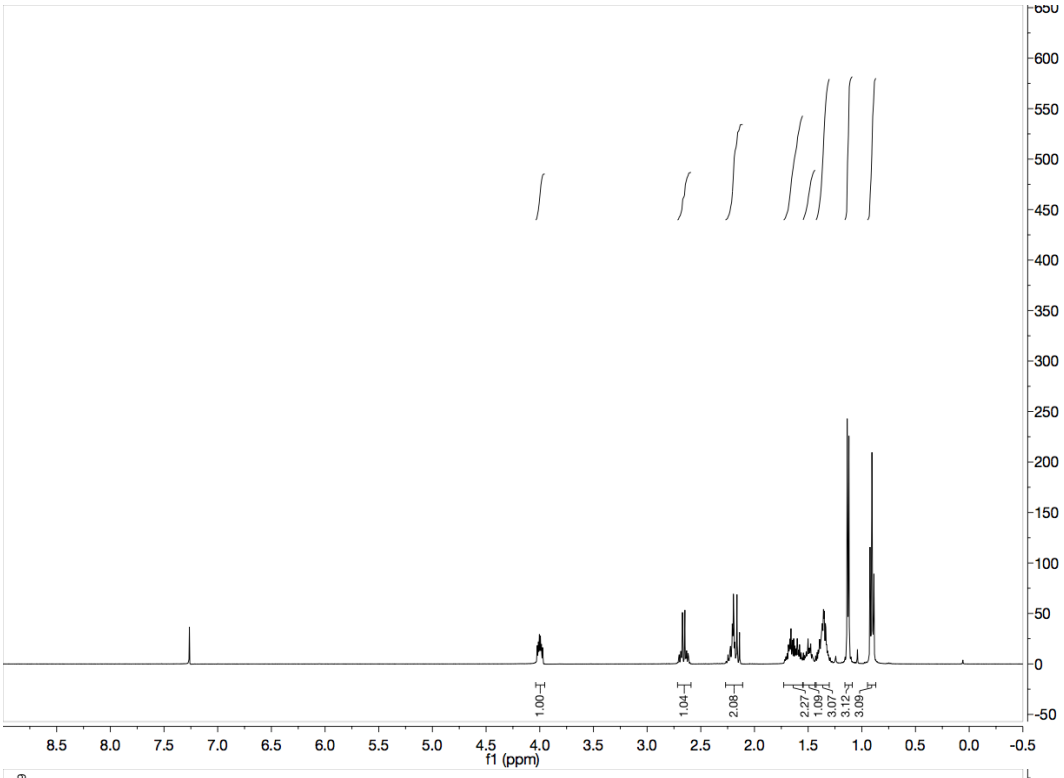
^{13}C NMR (100 MHz, $CDCl_3$): δ 176.59, 87.44, 37.11, 36.06, 33.68, 27.83, 22.46, 17.47, 13.88.

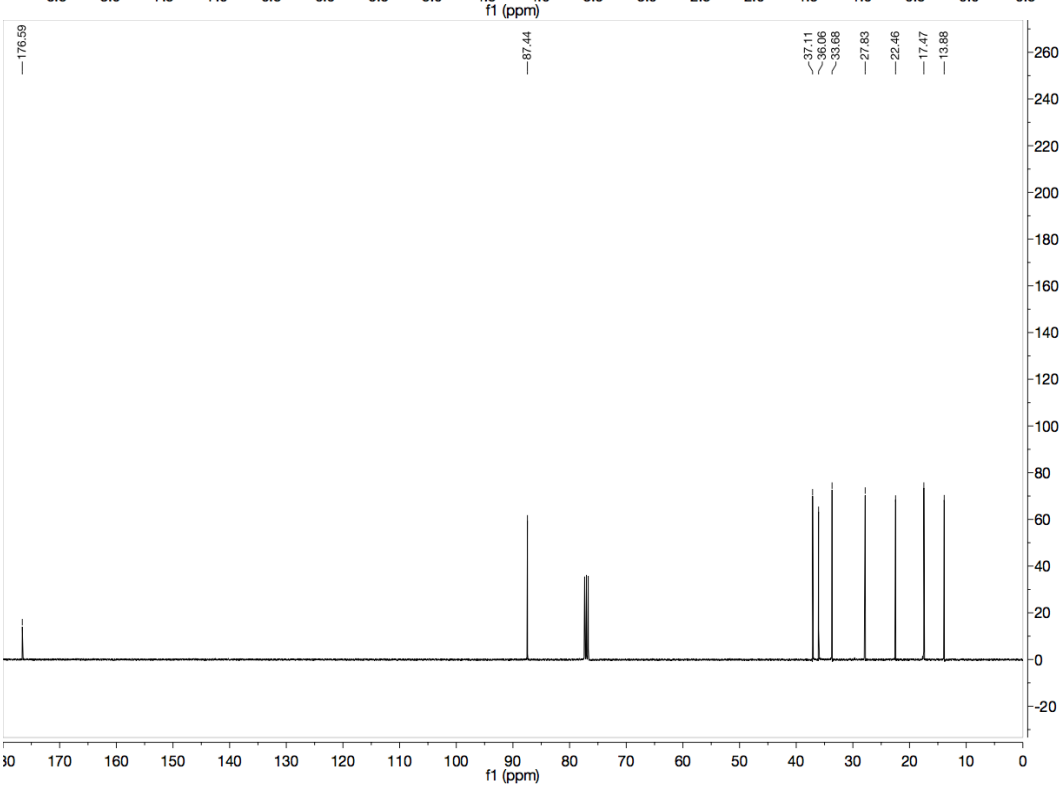
LRMS (ESI) Calcd. for $C_9H_{17}O_2$ $[M+H]^+$: 157, Found: 157.

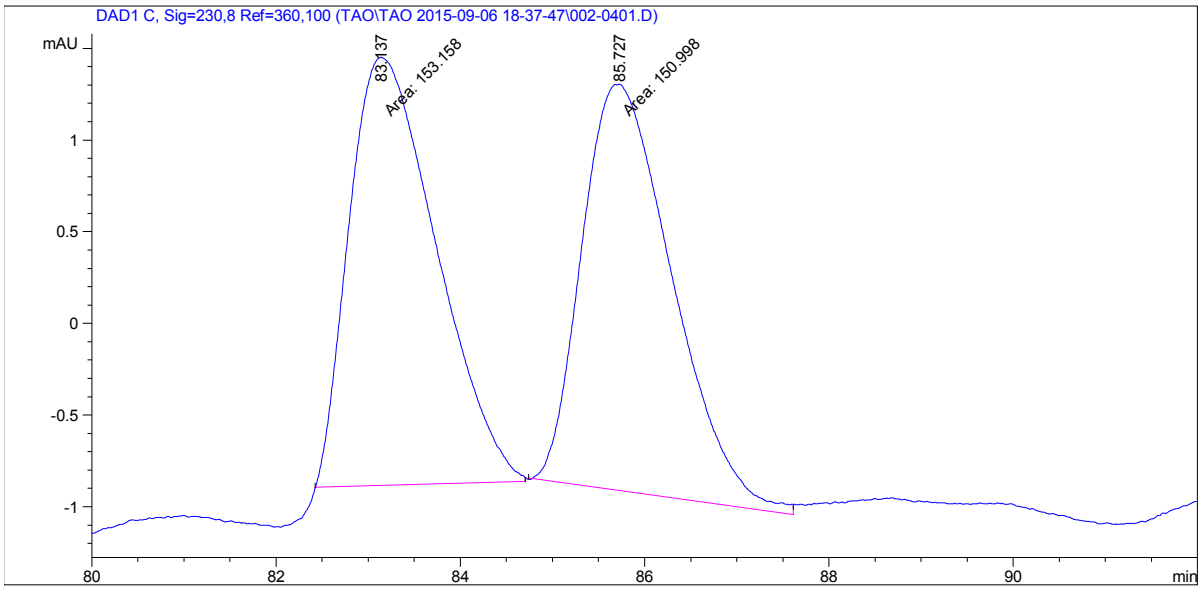
FTIR (neat): 1775, 1210, 1170, 1124, 1077, 984, 942, 926 cm^{-1}.

HPLC (Chiralcel OD-H/OD-H/OD-H column, hexanes:*i*-PrOH = 99:1, 0.5 mL/min, 230 nm), ee = 90%.

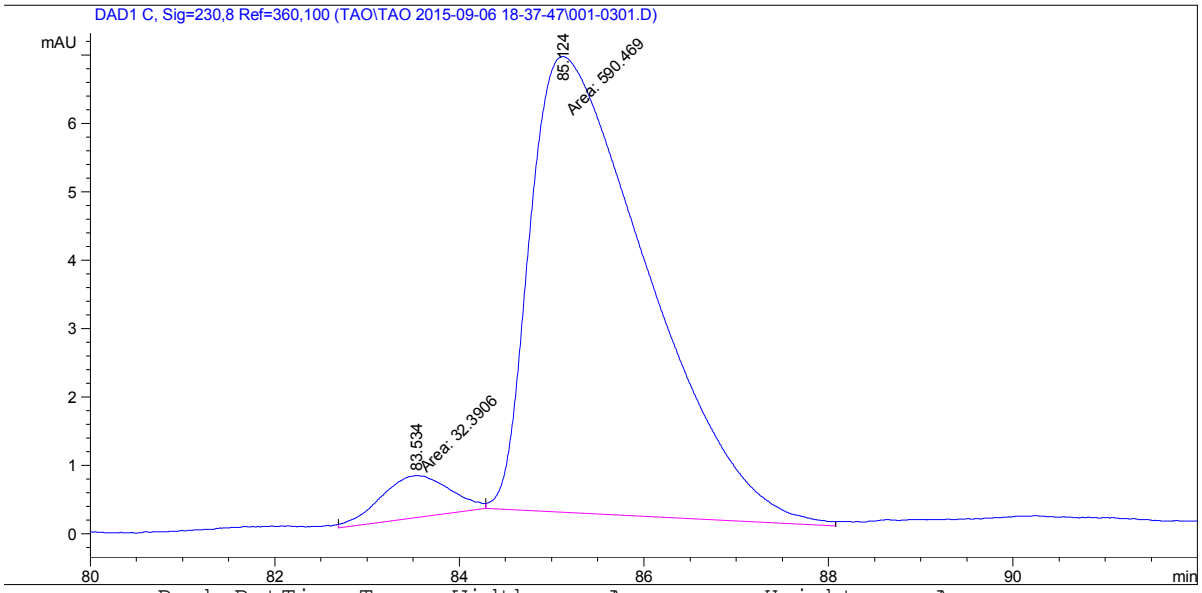
$[\alpha]^{25}_D$ = +59.6 (c = 0.71, $CHCl_3$)


1.00
1.04
2.08
2.27
1.09
3.07
3.12
3.09
f1 (ppm)


176.59
87.44
37.11
36.06
33.68
27.83
22.46
17.47
13.88
f1 (ppm)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	83.137	MM	1.0936	153.15843	2.33419	50.3552
2	85.727	MM	1.1356	150.99785	2.21610	49.6448

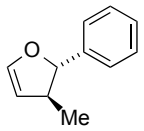


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	83.534	MM	0.6246	32.39059	6.15862e-1	5.2003
2	85.124	MM	1.4763	590.46930	6.66621	94.7997

Formation of trans-4,5-disubstituted-2,3-dehydrofuran 3.8a

To a resealable pressure tube (ca. 13 x 100) was added $H_2Ru(CO)(PPh_3)_3$ (9.2 mg, 0.010 mmol, 5 mol%), SL-J009-1 ligand (5.6 mg, 0.010 mmol, 5 mol%), Bu_4NI (7.4 mg, 0.020 mmol, 10 mol%) and 2,4,6-tri(2-propyl)phenylsulfonic acid (4.2 mg, 0.015 mmol, 7.5 mol%). THF (0.20 mL, 1 M concentration with respect to alcohols) was then added, followed by benzyl alcohol (0.20 mmol, 100 mol%), 2-propylalcohol (31 μL, 0.40 mmol, 200 mol%). Alkyne 1a (0.60 mmol, 300 mol%) was added *via* syringe and the rubber septum was quickly replaced with a screw cap. The mixture was then heated at 85 °C for 48 hours. After cooling to room temperature, the mixture was passed through a short silica pad, washed the pad with EA, and concentrated *in vacuo*. The residue was dissolved in THF (2.0 mL) and TBAF (1.0 M in THF, 0.2 mL) was added at 0ºC. The mixture was stirred at r.t for 30 min, and then quenched by water, extracted by DCM (3 x 1 mL). The organic layer was washed by brine, dried over Na_2SO_4. The organic solvent was evaporated and THF (2 mL) was added, followed by MsCl (45.6 mg, 0.4 mmol) and triethyl amine (121 mg, 1.2 mmol). The mixture was refluxed for 1 hour and then quenched by NH_4Cl, extracted by ether (3 x 1 mL). The organic layer was washed by water, brine, dried over Na_2SO_4. The solvent was removed by *vacuo*, and the residue was subjected to flash column chromatography (SiO_2, eluent Pentane:Et_2O = 9:1) to afford the dehydrofuran 8a (61%, *dr* = >20:1) as colorless liquid.

(2*S*,3*S*)-3-methyl-2-phenyl-2,3-dihydrofuran (3.8a).



R_f = 0.3 (20% EtOAc/Hexanes).

Spectral data is reported for the major isomer.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 5H), 6.45 (dd, *J* = 2.8, 2.1 Hz, 1H), 4.97 – 4.90 (m, 2H), 3.04 – 2.90 (m, 1H), 1.23 (d, *J* = 6.7 Hz, 3H).

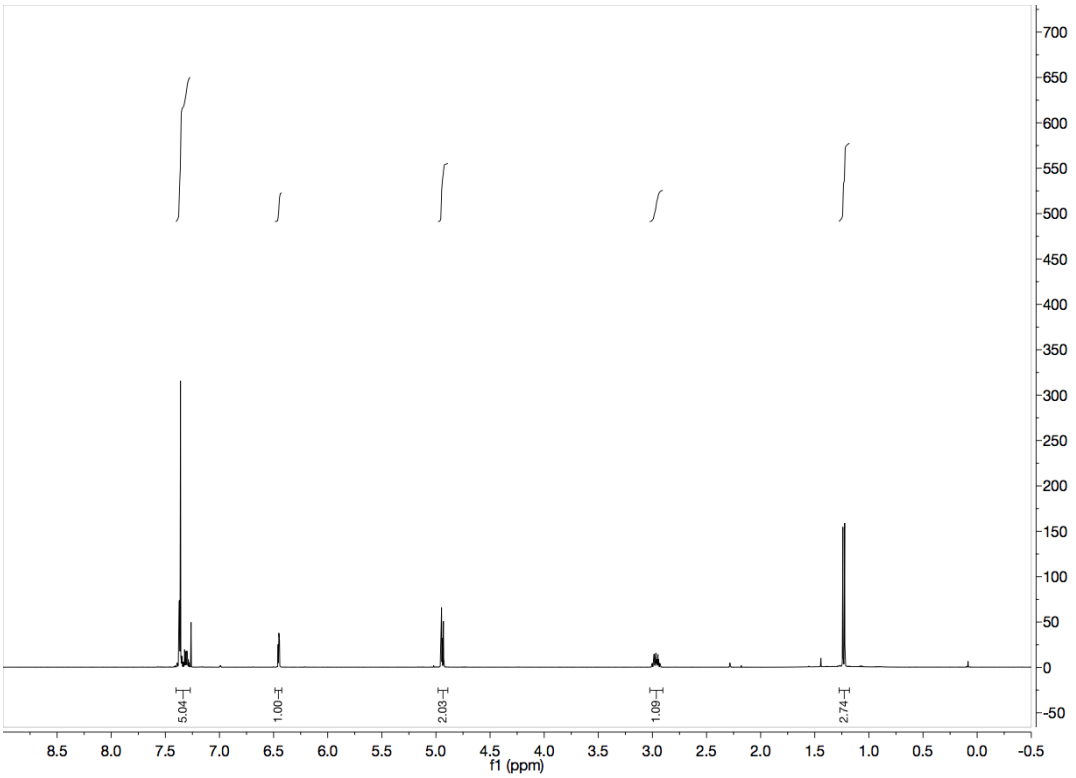
^{13}C NMR (100 MHz, $CDCl_3$): δ 144.74, 142.41, 128.51, 127.70, 125.46, 105.78, 90.15, 45.93, 20.78.

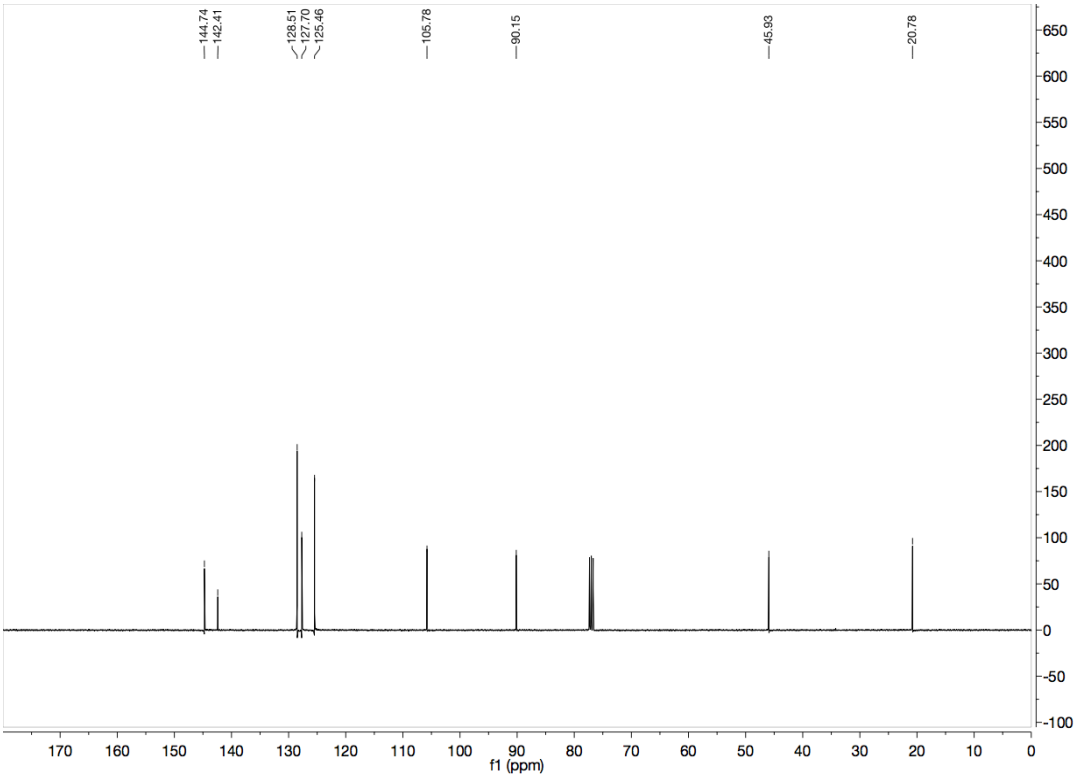
LRMS (ESI) Calcd. for $C_{11}H_{13}O$ $[M+H]^+$: 161, Found: 161.

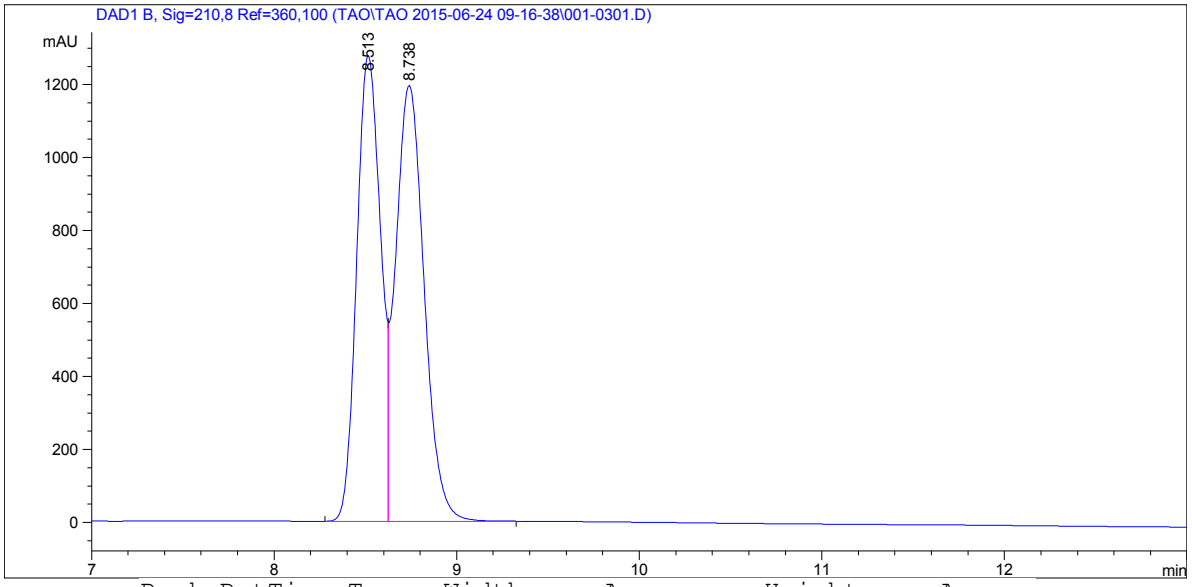
FTIR (neat): 2359, 2341, 1140, 1095, 1011, 721, 697, 669 cm^{-1}.

HPLC (Chiralcel OD-H column, hexanes:*i*-PrOH = 99:1, 0.5 mL/min, 210 nm), ee = 91%.

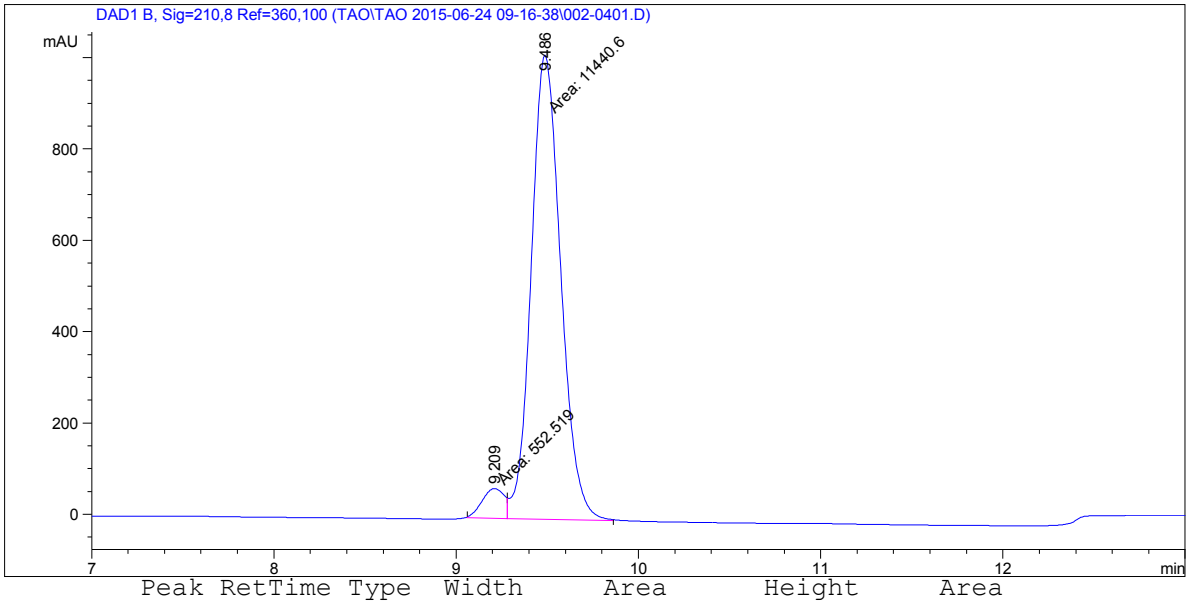
$[\alpha]^{25}_D$ = +171.4 (c = 0.34, $CHCl_3$)


5.04
1.00
2.03
1.09
2.74
f1 (ppm)


144.74
142.41
128.51
127.70
125.46
105.78
90.15
45.93
20.78
f1 (ppm)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.513	BV	0.1425	1.16507e4	1276.80237	47.5093
2	8.738	VB	0.1637	1.28723e4	1194.92786	52.4907

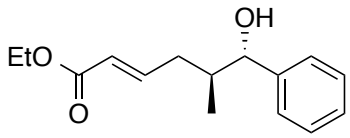


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.209	MF	0.1417	552.51855	64.98923	4.6070
2	9.486	FM	0.1877	1.14406e4	1016.07440	95.3930

Formation of 3.9a

To a resealable pressure tube (ca. 13 x 100) was added $H_2Ru(CO)(PPh_3)_3$ (9.2 mg, 0.010 mmol, 5 mol%), SL-J009-1 ligand (5.6 mg, 0.010 mmol, 5 mol%), Bu_4NI (7.4 mg, 0.020 mmol, 10 mol%) and 2,4,6-tri(2-propyl)phenylsulfonic acid (4.2 mg, 0.015 mmol, 7.5 mol%). THF (0.20 mL, 1 M concentration with respect to alcohols) was then added, followed by benzyl alcohol (0.20 mmol, 100 mol%), 2-propylalcohol (31 μL, 0.40 mmol, 200 mol%). Alkyne 1a (0.60 mmol, 300 mol%) was added *via* syringe and the rubber septum was quickly replaced with a screw cap. The mixture was then heated at 85 °C for 48 hours. After cooling to room temperature, the mixture was passed through a short silica pad, washed the pad with EA, and concentrated *in vacuo*. The residue was dissolved in THF (4.0 mL, 0.05 M) and TBAF (1.0 M in THF, 0.2 mL) was added at 0ºC. The mixture was stirred at r.t for 30 min, and then (Carbethoxymethylene)triphenylphosphorane (208 mg, 0.6 mmol) was added. The mixture was stirred at room temperature for 36 hours. The solvent was removed by *vacuo*, and the residue was subjected to flash column chromatography (SiO_2, eluent Hexanes:EA = 6:1) to afford 9a (71%, *dr* = >20:1, *E/Z* = >20:1) as colorless liquid.

Ethyl (5*S*,6*S*,*E*)-6-hydroxy-5-methyl-6-phenylhex-2-enoate (3.9a).



R_f = 0.2 (20% EtOAc/Hexanes).

Spectral data is reported for the major isomer.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.27 (m, 5H), 6.97 (ddd, *J* = 15.6, 8.4, 6.6 Hz, 1H), 5.85 (dd, *J* = 15.6, 1.7 Hz, 1H), 4.43 (d, *J* = 7.3 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 2.61 – 2.51 (m, 1H), 2.15 (ddd, *J* = 14.2, 8.6, 1.3 Hz, 1H), 2.06 – 1.95 (m, 2H), 1.28 (t, *J* = 7.1 Hz, 3H), 0.77 (d, *J* = 6.8 Hz, 3H).

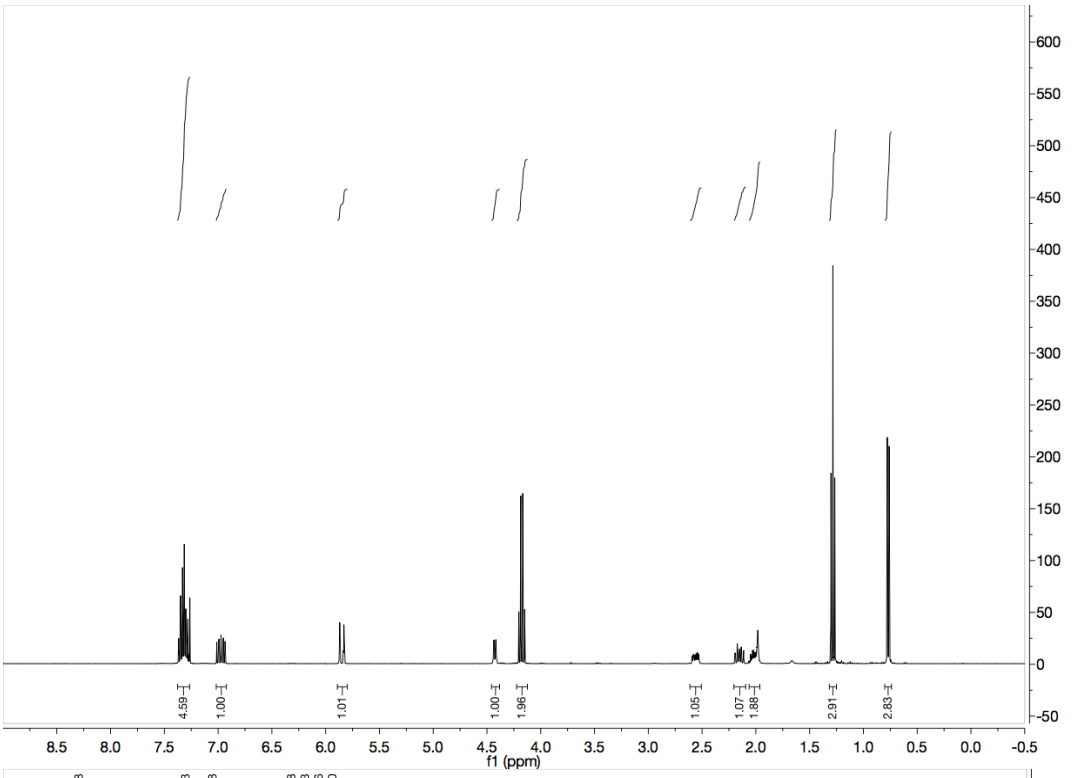
^{13}C NMR (100 MHz, $CDCl_3$): δ 166.58, 147.83, 143.08, 128.38, 128.36, 127.73, 126.56, 122.80, 78.34, 60.17, 39.68, 35.13, 15.98, 14.27.

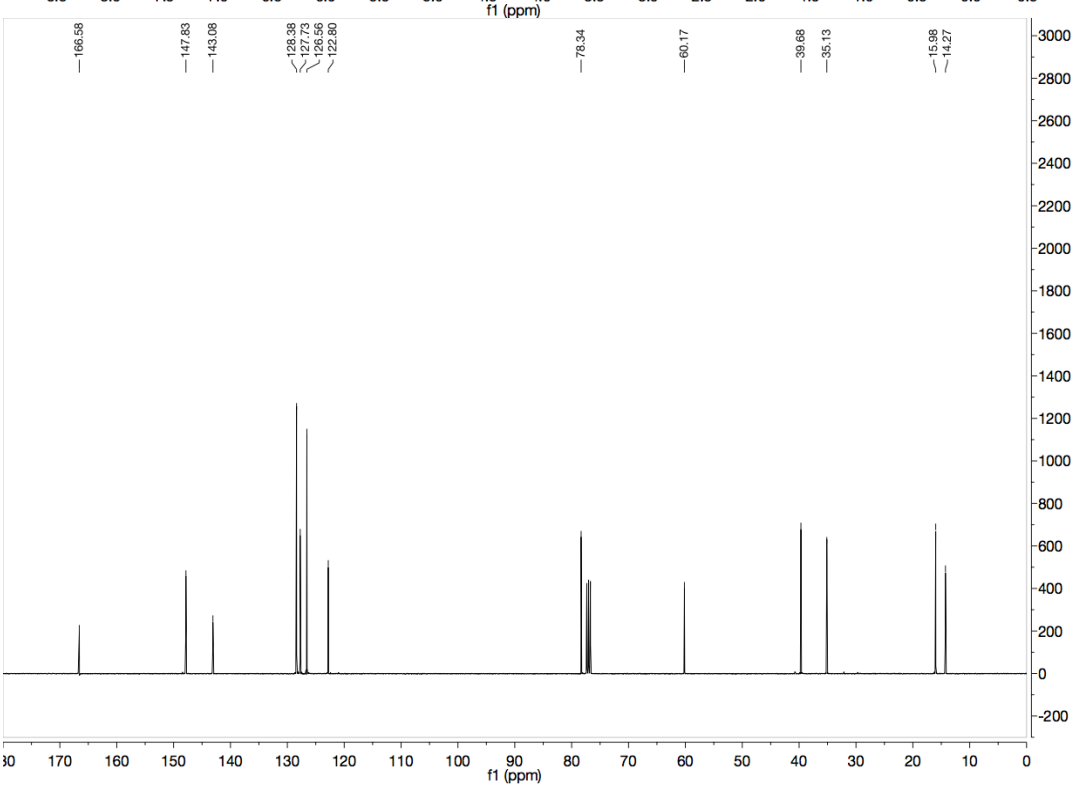
LRMS (ESI) Calcd. for $C_{15}H_{21}O_3$ $[M+H]^+$: 249, Found: 249.

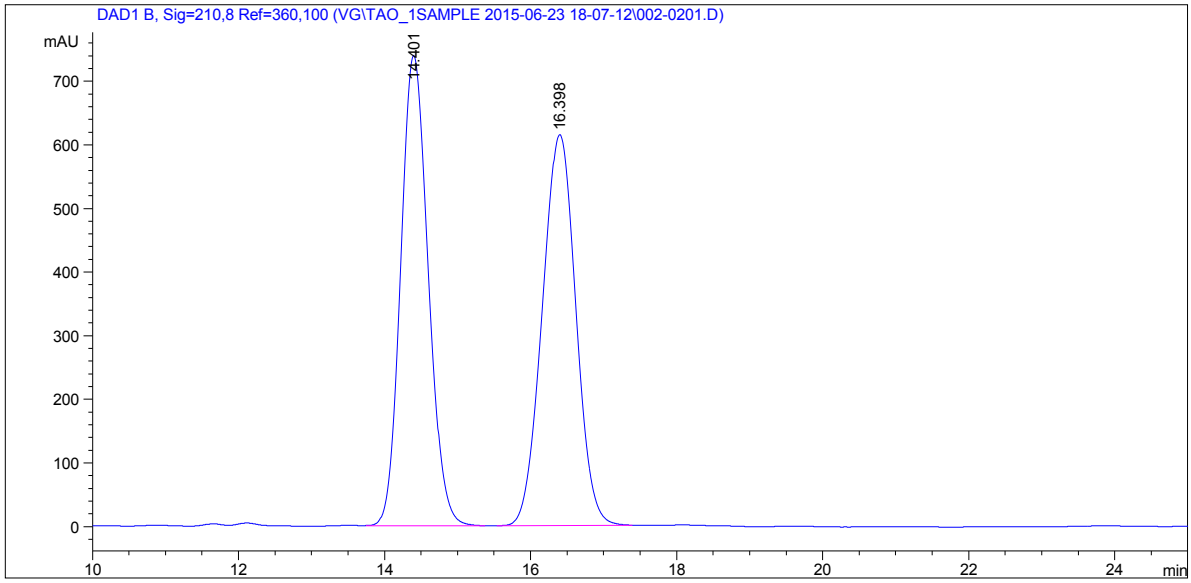
FTIR (neat): 1699, 1651, 1311, 1270, 1172, 1041, 982, 762, 701 cm^{-1}.

HPLC (Chiralcel OD-H column, hexanes:*i*-PrOH = 95:5, 1 mL/min, 210 nm), ee = 91%.

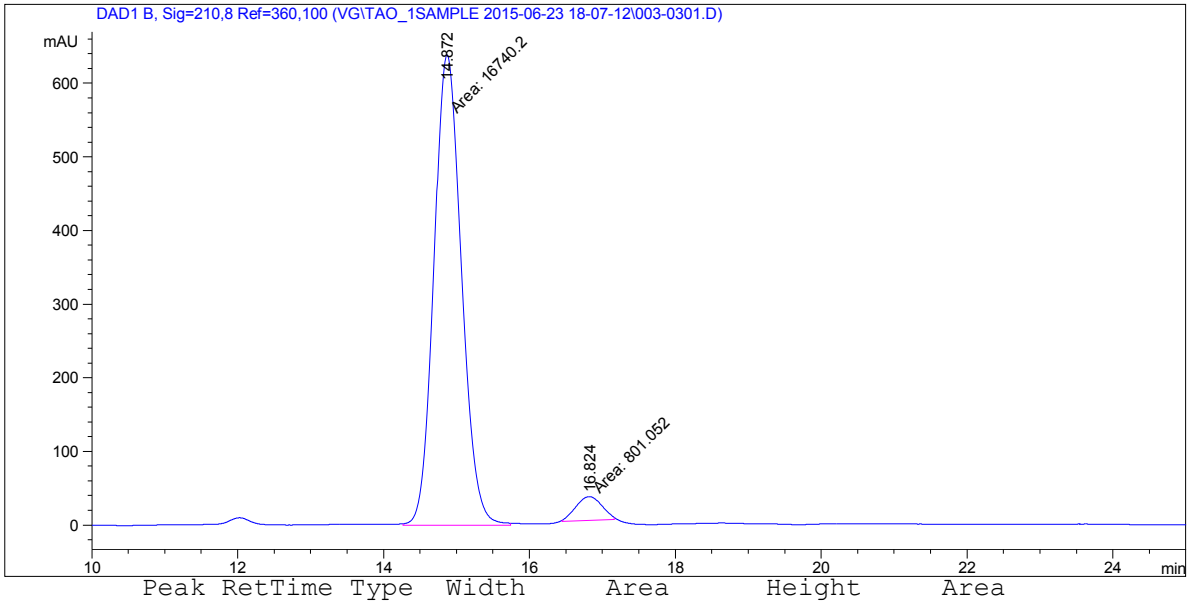
$[\alpha]^{25}_D$ = -11.3 (c = 1.2, $CHCl_3$)


4.59
1.00
1.01
1.00
1.96
1.05
1.07
1.88
2.91
2.83
f1 (ppm)


166.58
147.83
143.08
128.38
127.73
126.56
122.80
78.34
60.17
39.68
35.13
15.98
14.27
f1 (ppm)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.401	BB	0.4108	1.94268e4	738.85236	49.7849
2	16.398	BB	0.5020	1.95947e4	614.55487	50.2151



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.872	MM	0.4368	1.67402e4	638.75323	95.4333
2	16.824	MM	0.4139	801.05170	32.25486	4.5667

Crystallographic Material for Coupling product 3.5c

X-ray Experimental for $C_{11}H_{15}O_2Br$ (3.5c)

Crystals grew as clusters of clear, colorless prisms by slow evaporation from Ethyl Acetate and DCM. The data crystal was cut from a larger crystal and had approximate dimensions; 0.38 x 0.27 x 0.08 mm. The data were collected at -140 °C on a Nonius Kappa CCD diffractometer using a Bruker AXS Apex II detector and a graphite monochromator with MoKα radiation (λ = 0.71073Å). Reduced temperatures were maintained by use of an Oxford Cryosystems 600 low-temperature device. A total of 1011 frames of data were collected using ω and φ-scans with a scan range of 2° and a counting time of 48 seconds per frame. Details of crystal data, data collection and structure refinement are listed in Table 1. Data reduction were performed using SAINT V8.27B.[14] The structure was solved by direct methods using SUPERFLIP[15] and refined by full-matrix least-squares on F2 with anisotropic displacement parameters for the non-H atoms using SHELXL-2013.[16] Structure analysis was aided by use of the programs PLATON98[17] and WinGX.[18] The hydrogen atoms bound to carbon atoms were calculated in idealized positions. The hydrogen atoms on the hydroxyl oxygen atoms were observed in a ΔF map and refined with isotropic displacement parameters. The absolute structure was determined by the method of Flack.[19] The Flack x parameter refined to 0.006(9). This assignment was confirmed by use of the Hooft y-parameter[20], which refined to 0.013(5).

The function, Σw(|Fo|2 - |Fc|2)2, was minimized, where w = 1/[(σ(Fo))2 + (0.0221*P)2] and P = (|Fo|2 + 2|Fc|2)/3. $R_w(F^2)$ refined to 0.0506, with R(F) equal to 0.0271 and a goodness of fit, S, = 1.01. Definitions used for calculating R(F),$R_w(F^2)$ and the goodness of fit, S, are given below.[21] The data were checked for secondary extinction but no correction was necessary. Neutral atom scattering factors and values used to calculate the linear absorption coefficient are from the International Tables for X-ray Crystallography (1992).[22] All figures were generated using SHELXTL/PC.[5] Tables of positional and thermal parameters, bond lengths and angles, torsion angles and figures are found elsewhere.

Table 3.4. Crystal data and structure refinement for **3.5c**.

Empirical formula	C_{11} H_{15} Br O_2	
Formula weight	259.14	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	monoclinic	
Space group	*P* 2_1	
Unit cell dimensions	a = 5.7323(12) Å	α= 90°.
	b = 7.920(2) Å	β= 98.524(6)°.
	c = 12.149(2) Å	γ = 90°.
Volume	545.5(2) Å3	
Z	2	
Density (calculated)	1.578 Mg/m^3	
Absorption coefficient	3.740 mm^{-1}	
F(000)	264	
Crystal size	0.384 x 0.272 x 0.084 mm	
Theta range for data collection	3.081 to 33.184°.	
Index ranges	-8<=h<=8, -12<=k<=12, -17<=l<=18	
Reflections collected	24040	
Independent reflections	3850 [R(int) = 0.0432]	
Completeness to theta = 25.242°	99.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00 and 0.700	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3850 / 1 / 137	
Goodness-of-fit on F2	1.006	
Final R indices [I>2sigma(I)]	R_1 = 0.0271, wR_2 = 0.0487	
R indices (all data)	R_1 = 0.0366, wR_2 = 0.0506	
Absolute structure parameter	0.006(9)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.666 and -0.452 e.$Å^{-3}$	

Table 3.5. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **3.5c**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor**.**

	x	y	z	U(eq)
C1	8039(4)	5546(3)	3656(2)	14(1)
C2	8445(4)	4948(3)	2624(2)	15(1)
C3	6838(4)	3832(3)	2054(2)	14(1)
C4	4841(4)	3314(3)	2492(2)	12(1)
C5	4472(4)	3944(3)	3523(2)	14(1)
C6	6072(4)	5061(3)	4110(2)	15(1)
C7	3115(3)	2064(5)	1870(1)	13(1)
C8	4239(4)	335(3)	1754(2)	14(1)
C9	2425(4)	-909(3)	1157(2)	14(1)
C10	3389(4)	-2686(3)	1082(2)	16(1)
C11	5293(6)	-338(3)	2897(2)	33(1)
O1	2288(3)	2826(2)	807(1)	18(1)
O2	1669(3)	-3674(2)	387(1)	19(1)
Br1	10228(1)	7057(1)	4472(1)	21(1)

Table 3.6. Bond lengths [Å] and angles [°] for **3.5c**.

C1-C6	1.382(3)
C1-C2	1.391(3)
C1-Br1	1.903(2)
C2-C3	1.386(3)
C2-H2	0.95
C3-C4	1.394(3)
C3-H3	0.95
C4-C5	1.393(3)
C4-C7	1.519(3)
C5-C6	1.392(3)
C5-H5	0.95
C6-H6	0.95
C7-O1	1.441(3)
C7-C8	1.529(4)
C7-H7	1.00
C8-C11	1.526(3)
C8-C9	1.534(3)
C8-H8	1.00
C9-C10	1.520(3)
C9-H9A	0.99
C9-H9B	0.99
C10-O2	1.432(3)
C10-H10A	0.99
C10-H10B	0.99
C11-H11A	0.98
C11-H11B	0.98
C11-H11C	0.98
O1-H1O	0.81(3)
O2-H5O	0.78(3)
C6-C1-C2	121.36(19)
C6-C1-Br1	118.75(16)
C2-C1-Br1	119.89(17)
C3-C2-C1	118.7(2)

Table 3.6 Continued

C3-C2-H2	120.7
C1-C2-H2	120.7
C2-C3-C4	121.31(19)
C2-C3-H3	119.3
C4-C3-H3	119.3
C5-C4-C3	118.72(19)
C5-C4-C7	120.38(19)
C3-C4-C7	120.89(17)
C6-C5-C4	120.8(2)
C6-C5-H5	119.6
C4-C5-H5	119.6
C1-C6-C5	119.1(2)
C1-C6-H6	120.4
C5-C6-H6	120.4
O1-C7-C4	106.0(2)
O1-C7-C8	112.30(18)
C4-C7-C8	112.18(17)
O1-C7-H7	108.7
C4-C7-H7	108.7
C8-C7-H7	108.7
C11-C8-C7	110.12(17)
C11-C8-C9	110.78(18)
C7-C8-C9	110.71(17)
C11-C8-H8	108.4
C7-C8-H8	108.4
C9-C8-H8	108.4
C10-C9-C8	113.33(17)
C10-C9-H9A	108.9
C8-C9-H9A	108.9
C10-C9-H9B	108.9
C8-C9-H9B	108.9
H9A-C9-H9B	107.7
O2-C10-C9	108.45(17)
O2-C10-H10A	110.0

Table 3.6 Continued

C9-C10-H10A	110.0
O2-C10-H10B	110.0
C9-C10-H10B	110.0
H10A-C10-H10B	108.4
C8-C11-H11A	109.5
C8-C11-H11B	109.5
H11A-C11-H11B	109.5
C8-C11-H11C	109.5
H11A-C11-H11C	109.5
H11B-C11-H11C	109.5
C7-O1-H1O	110(2)
C10-O2-H5O	111(2)

Table 3.7. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **3.5c**. The anisotropic displacement factor exponent takes the form: $-2p^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C1	12(1)	9(1)	17(1)	-2(1)	-6(1)	0(1)
C2	11(1)	16(1)	18(1)	0(1)	1(1)	0(1)
C3	17(1)	13(1)	12(1)	-3(1)	2(1)	2(1)
C4	11(1)	9(1)	14(1)	0(1)	-2(1)	2(1)
C5	14(1)	12(1)	16(1)	1(1)	2(1)	1(1)
C6	16(1)	16(1)	11(1)	-2(1)	0(1)	3(1)
C7	13(1)	11(1)	14(1)	-2(1)	-2(1)	-2(1)
C8	15(1)	9(1)	15(1)	0(1)	-4(1)	1(1)
C9	15(1)	10(1)	17(1)	-2(1)	-3(1)	0(1)
C10	15(1)	14(2)	19(1)	0(1)	-4(1)	-1(1)
C11	51(2)	14(1)	26(1)	1(1)	-23(1)	-2(1)
O1	20(1)	10(1)	20(1)	3(1)	-11(1)	-2(1)
O2	21(1)	7(1)	25(1)	-2(1)	-9(1)	0(1)
Br1	16(1)	18(1)	26(1)	-8(1)	-6(1)	-2(1)

Table 3.8. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2 x 10^3) for **3.5c**.

	x	y	z	U(eq)
H2	9796	5298	2317	18
H3	7103	3412	1351	17
H5	3113	3607	3829	17
H6	5813	5484	4814	18
H7	1748	1925	2287	16
H8	5541	470	1297	16
H9A	1043	-950	1558	17
H9B	1876	-487	396	17
H10A	4880	-2653	762	20
H10B	3718	-3194	1833	20
H11A	4023	-570	3334	50
H11B	6367	506	3283	50
H11C	6164	-1381	2807	50
H1O	1210(50)	2280(50)	490(20)	33(8)
H5O	1900(60)	-4640(40)	480(30)	32(9)

Table 3.9. Torsion angles [°] for **3.5c.**

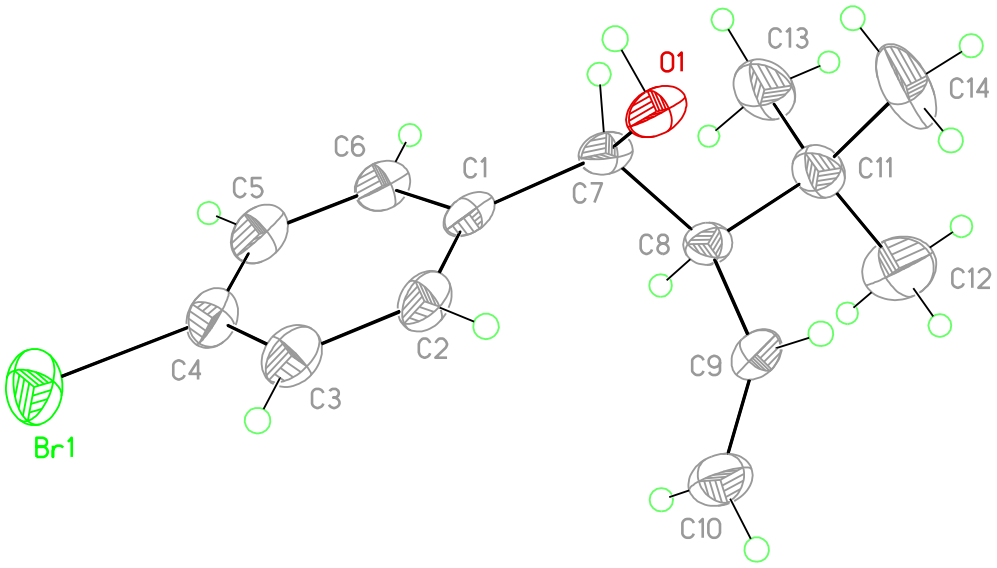
C6-C1-C2-C3	-0.6(3)
Br1-C1-C2-C3	179.19(16)
C1-C2-C3-C4	0.3(3)
C2-C3-C4-C5	0.1(3)
C2-C3-C4-C7	-178.8(2)
C3-C4-C5-C6	-0.4(3)
C7-C4-C5-C6	178.6(2)
C2-C1-C6-C5	0.3(3)
Br1-C1-C6-C5	-179.43(16)
C4-C5-C6-C1	0.2(3)
C5-C4-C7-O1	122.3(2)
C3-C4-C7-O1	-58.8(3)
C5-C4-C7-C8	-114.8(2)
C3-C4-C7-C8	64.1(3)
O1-C7-C8-C11	174.6(2)
C4-C7-C8-C11	55.3(3)
O1-C7-C8-C9	-62.6(2)
C4-C7-C8-C9	178.12(17)
C11-C8-C9-C10	-53.8(3)
C7-C8-C9-C10	-176.23(19)
C8-C9-C10-O2	-172.37(17)

Table 3.10. Hydrogen bonds for **3.5c** [Å and °].

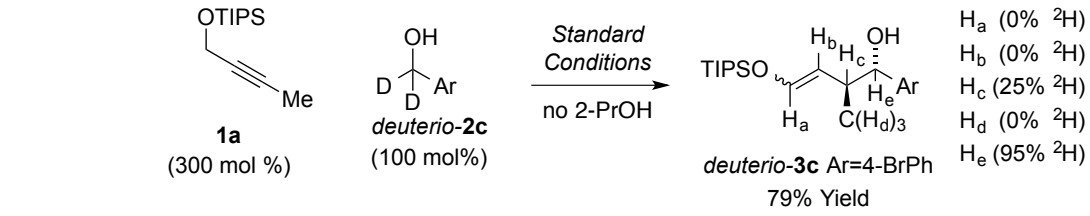
D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O1-H1O...O2#1	0.81(3)	1.98(3)	2.772(2)	170(4)
O2-H5O...O1#2	0.78(3)	2.05(3)	2.832(2)	175(3)

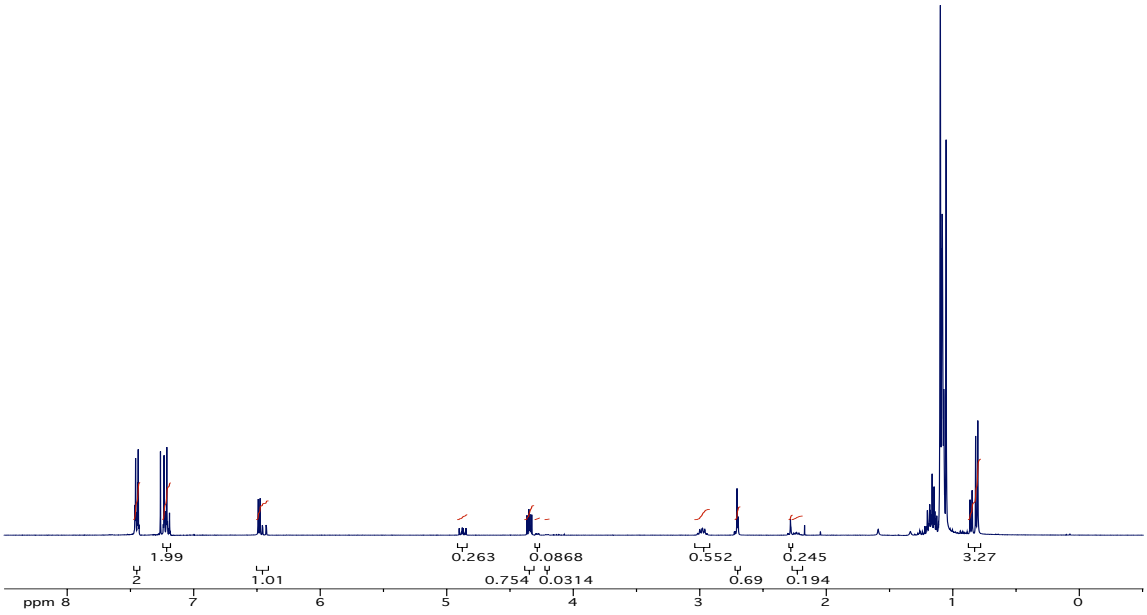
Symmetry transformations used to generate equivalent atoms:
#1 -x,y+1/2,-z #2 x,y-1,z

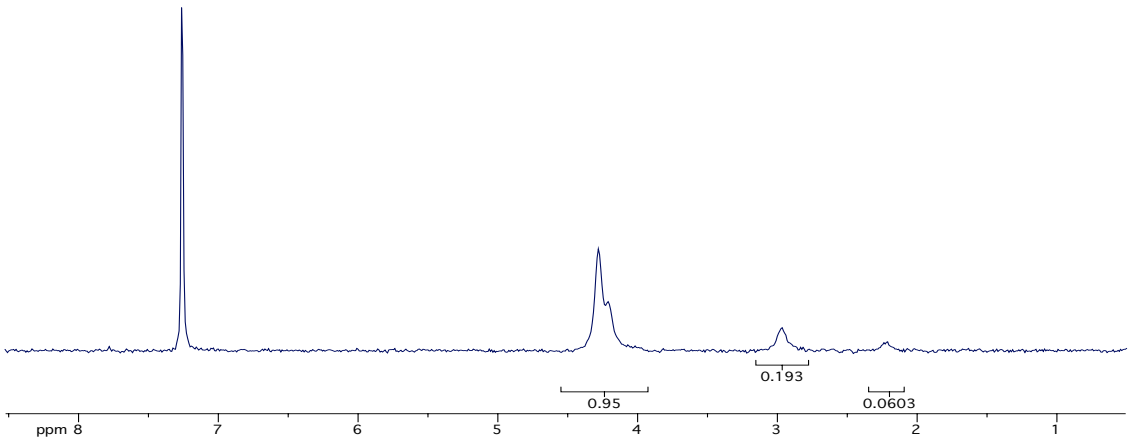
Figure 3.2. View of **3.5c** showing the atom labeling scheme. Displacement ellipsoids are scaled to the 50% probability level.

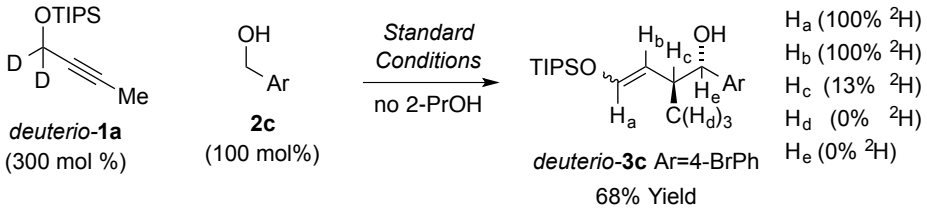


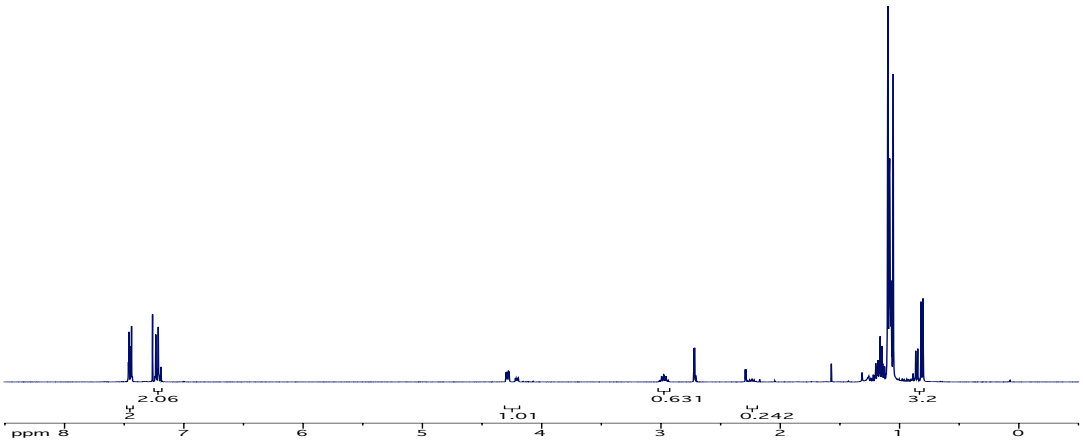
Isotopic Labeling Studies

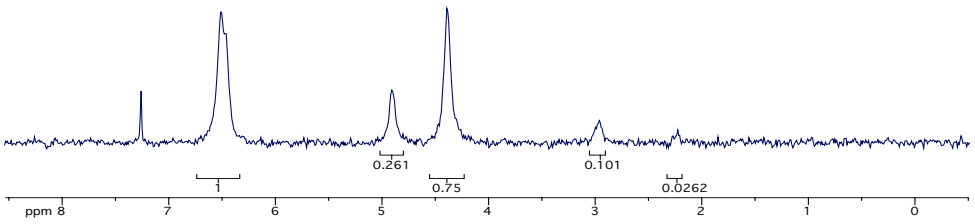







OTIPS
D
D
Me
deuterio-1a
(300 mol %)
OH
Ar
2c
(100 mol%)
Standard
Conditions
no 2-PrOH
TIPSO
Hb
Hc
OH
He
Ar
Ha
C(Hd)3
deuterio-3c Ar=4-BrPh
68% Yield
Ha (100% 2H)
Hb (100% 2H)
Hc (13% 2H)
Hd (0% 2H)
He (0% 2H)


2.06
1.01
0.631
0.242
3.2
ppm 8
7
6
5
4
3
2
1
0


1
0.261
0.75
0.101
0.0262
ppm 8
7
6
5
4
3
2
1
0

Chapter 4: Iridium Catalyzed (*Z*) - Selective Siloxy-Allylation of Primary Alcohols by Coupling with Terminal Propargyl Ether via 1,2 - Hydride Shift Mechanism*

4.1 INTRODUCTION

Carbonyl addition is broadly used in chemical synthesis to construct new C-C bonds.[1] To come up with an alternative way of using organometallic reagents and metallic reductants, Krische group has developed a broad system of redox-triggered carbonyl addition reactions by merging carbonyl addition and transfer hydrogenation, which allows the direct conversion of primary alcohols to secondary alcohols. [2] Different π-unsaturated compounds were proved to be able to engage the carbonyl addition reactions, and many of them are abundant chemical feedstocks, such as butadiene[3] and allyl acetate.[4]

In recent work from the group, internal alkynes were found to engage in the carbonyl allylation reactions serving as pronucleophiles by different mechanisms.[5,6,7] One possible mechanism was proceeding through alkyne-to-allen isomerization followed by either oxidative coupling[5] or hydrometalation[6] pathways. The other possible mechanism was involving 1,2-hydride shift enabled formation of π-allylmetal species directly from alkynes.[7] In this chapter, we reported that terminal alkyne, unsubstituted proparyl ether **4.1a**, mediated (*Z*)-selective carbonyl siloxy-allylation via 1,2-hydride shift mechanism. This protocol represented the divergence from the classical acetylide carbonyl addition reactions[8,9], and allowed formation of homoenolate equivalents[10,11] from propargyl ethers; also demonstrated the generality of 1,2-hydride shift mechanism for the formation of π-allylmetal species in the context of transition metal catalysis (Figure 4.1).

*This chapter is based on the published work:
Liang, T.; Zhang, W.; Krische, M. J. *J. Am. Chem. Soc.* **2015**, *137*, 16024.

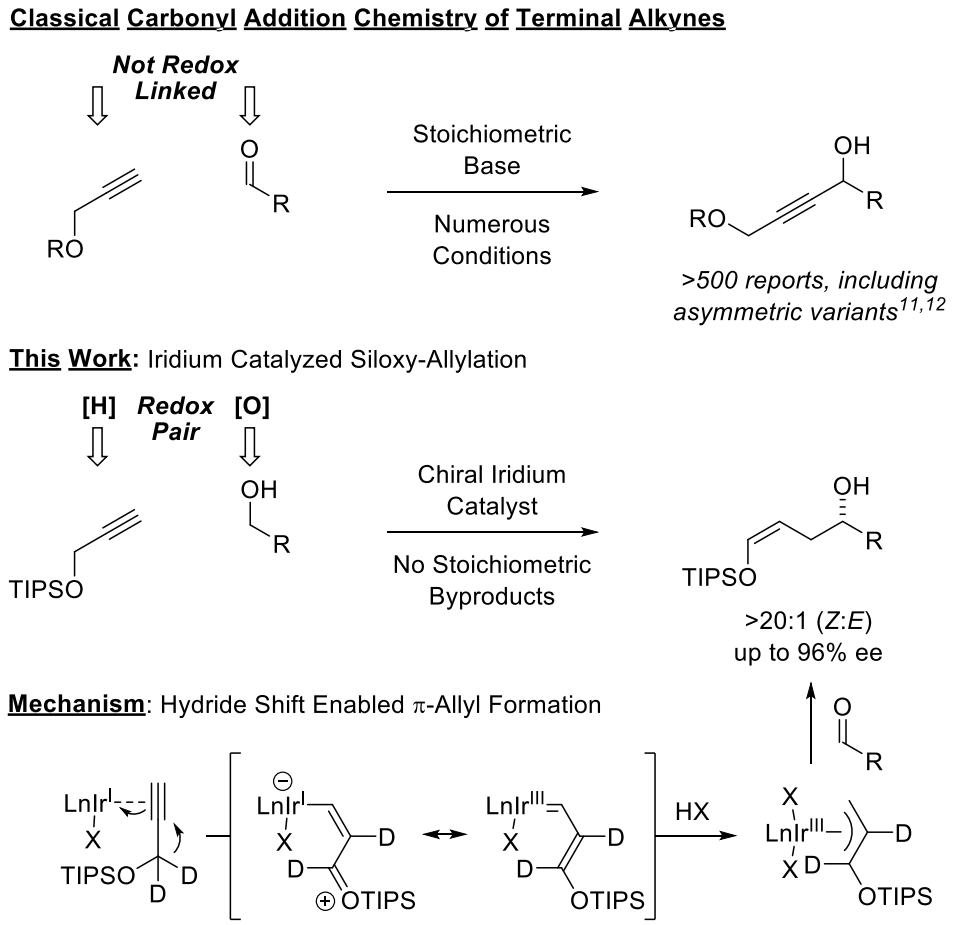
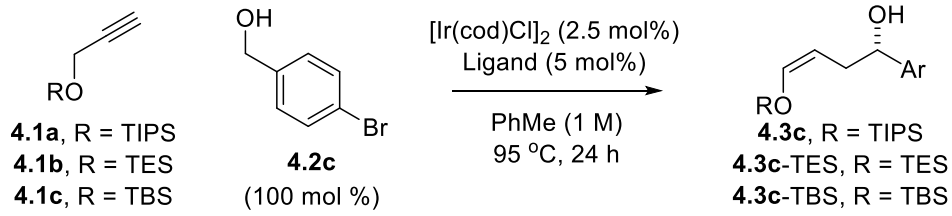


Figure 4.1 Enantioselective Carbonyl Crotylation Strategies.

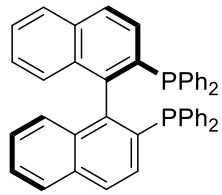
4.2 Reaction Development and Scope

Exposure of propargyl ether **4.1a** to p-bromobenzyl alcohol **4.2c** with 2.5 mol% $[Ir(cod)Cl]_2$ and 5 mol% (R)-BINAP in toluene at 95°C gave the desired γ-hydroxy enol silane **4.3c** with complete (*Z*)-selectivity in 14% yield and 87% enantiomeric excess (Table 4.1, entry 1). Introduction of catalytic amount of Bu_4NI was found to be helpful in improving both yield and ee (Table 4.1, entry 2). Catalytic amount of Ph_3CCO_2H was found to have a beneficial effect on the conversion (Table 4.1, entry 3). By combining Bu_4NI and Ph_3CCO_2H, 47% yield and 90% ee was obtained (Table 4.1, entry 4). The conversion was further improved to 86% yield with 91% ee by

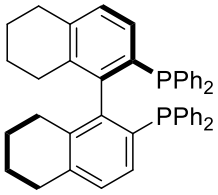
Table 4.1 Selective Optimization for Formation of γ-Hydroxy Enol Silane **4.3c**.



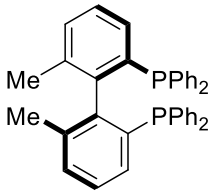
Entry	4.1	Ligand	Bu_4NI	Ph_3CCO_2H	3c (Yield, *Z*:*E*)	ee%
1	**4.1a**, 300 mol%	(*R*)-BINAP	-	-	14%, >20:1	87
2	**4.1a**, 300 mol%	(*R*)-BINAP	10 mol%	-	21%, >20:1	92
3	**4.1a**, 300 mol%	(*R*)-BINAP	-	5 mol%	23%, >20:1	87
4	**4.1a**, 300 mol%	(*R*)-BINAP	10 mol%	5 mol%	47%, >20:1	90
5	**4.1a**, 300 mol%	(*R*)-H_8-BINAP	10 mol%	5 mol%	55%, >20:1	91
6	**4.1a**, 400 mol%	(*R*)-BINAP	10 mol%	5 mol%	64%, >20:1	93
⇨ **7**	**4.1a**, **400 mol%**	**(*R*)-H_8-BINAP**	**10 mol%**	**5 mol%**	**86%, >20:1**	**91**
8	**4.1a**, 400 mol%	(*R*)-H_8-BINAP	10 mol%	-	38%, >20:1	88
9	**4.1a**, 400 mol%	(*R*)-H_8-BINAP	-	5 mol%	58%, >20:1	85
10	**4.1a**, 400 mol%	(*R*)-SEGPHOS	10 mol%	5 mol%	30%, >20:1	96
11	**4.1a**, 400 mol%	(*R*)-MeO-BIPHEP	10 mol%	5 mol%	47%, >20:1	94
12	**4.1a**, 400 mol%	(*R*)-C3-TUNEPHOS	10 mol%	5 mol%	32%, >20:1	91
13	**4.1a**, 400 mol%	(*R*)-BIPHEMP	10 mol%	5 mol%	48%, >20:1	86
14[b]	**4.1a**, 400 mol%	(*R*)-H_8-BINAP	-	5 mol%	83%, >20:1	84
15	**4.1b**, 400 mol%	(*R*)-H_8-BINAP	10 mol%	5 mol%	36%, >20:1	90
16	**4.1c**, 400 mol%	(*R*)-H_8-BINAP	10 mol%	5 mol%	56%, >20:1	91



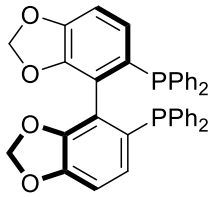
(*R*)-BINAP



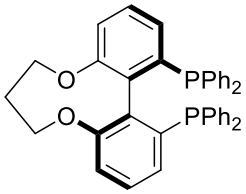
(*R*)-H8-BINAP



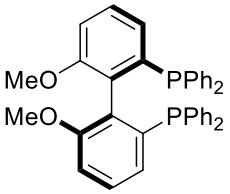
(*R*)-BIPHEMP



(*R*)-SEGPHOS



(*R*)-C3-TUNEPHOS



(*R*)-MeO-BIPHEP

[a]Yields are of material isolated by silica gel chromatography. See supporting Information for further details. [b]$[Ir(cod)I]_2$

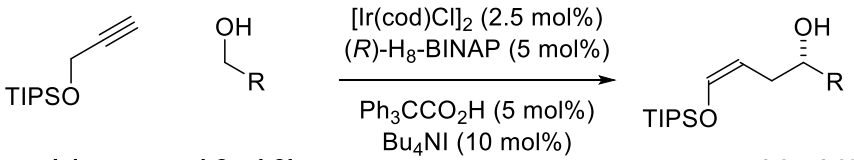
using (R)-H_8-BINAP and higher loading of propargyl ether **4.1a** (Table 4.1, entry 7). Other chiral ligands within structural neighborhood were also evaluated (Table 4.1, entries 10-13), even though in some cases higher enantioselectivity was obtained but the yield was not relatively low comparing with (R)-H_8-BINAP. Notably, when $[Ir(cod)I]_2$ was used in the absence of Bu_4NI, similar isolation yield was obtained, which suggested the role of Bu_4NI involved in the formation of iodide modified iridium catalyst (Table 4.1, entry 14).

With the optimal conditions in hand, different primary alcohols were subjected to coupling with propargyl ether **4.1a**. Benzyl alcohols **4.2a-4.2f** were converted to (*Z*)-γ-hydroxy enol silane **4.3a-4.3f** in excellent yield and uniformly high level of enantioselectivity. Different substituents positions were tolerated in the transformation. Allylic alcohols **4.2g-4.2i** were able to engage in the coupling with propargyl ether **4.1a** with good isolation yield and excellent enantioselectivity. Also, aliphatic alcohols **4.2j-4.2l** were successfully converted to the adduct **4.3j-4.3l** with slightly lower yields but still complete (*Z*)-selectivity and high enantioselectivity.

The absolute stereochemical structure of adduct **4.3a-4.3l** was confirmed by subjecting **4.3a** to silyl group cleavage followed by reduction to form (*S*)-1-phenylbutane-1,4-diol, which is a previous reported compound.

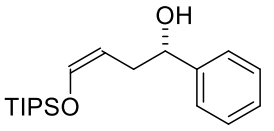
To demonstrate the utility of this protocol, the coupling adducts γ-hydroxy enol silanes **4.3a**, **4.3c**, **4.3e**, **4.3h**, and **4.3j** were converted to enantiomeric enriched γ-lactones **4.4a**, **4.4c**, **4.4e**, **4.4h**, and **4.4j** by treatment of TBAF to remove the TIPS group followed by PCC mediated oxidation (Scheme 4.1, eq 1). Additionally, *m*-CPBA mediated epoxidation of adducts **4.3a**, **4.3c**, **4.3e**, **4.3f**, **4.3j**, and **4.3k** occurred in a highly diastereoselective manner and delivered the trisubstituted furans **4.5a**, **4.5c**, **4.5e**, **4.5f**, **4.5j**, and **4.5k** (Scheme 4.1, eq 2).

Table 4.2 Iridium Catalyzed Formation of γ-Hydroxy Enol Silanes **4.3a-4.3l**.

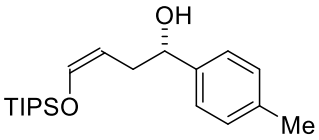


4.1a (400 mol %) **4.2a-4.2l** (100 mol%) **4.3a-4.3l**

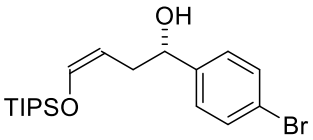
4.2a, R = Ph	**4.2b**, R = 4-MePh	**4.2c**, R = 4-BrPh
4.2d, R = 2-MePh	**4.2e**, R = 3-MeOPh	**4.2f**, R = 5-benzodioxole
4.2g, R = HC=CHPh	**4.2h**, R = $HC=CMe_2$	**4.2i**, R = $HC=CCH_2OBn$
4.2j, R = $(CH_2)_2OBn$	**4.2k**, R = $(CH_2)_5Me$	**4.2l**, R = *c*-Pr



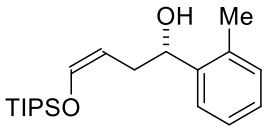
4.3a, 93% Yield
>20:1 (*Z*:*E*), 94% ee



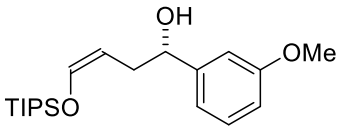
4.3b, 84% Yield
>20:1 (*Z*:*E*), 95% ee



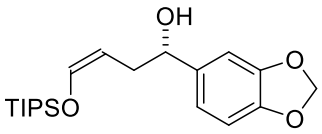
4.3c, 86% Yield
>20:1 (*Z*:*E*), 91% ee



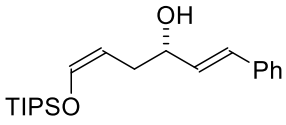
4.3d, 85% Yield
>20:1 (*Z*:*E*), 95% ee



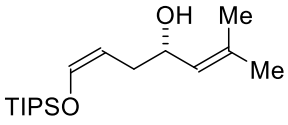
4.3e, 94% Yield
>20:1 (*Z*:*E*), 95% ee



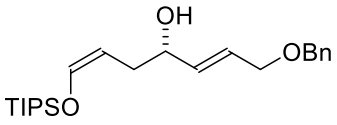
4.3f, 91% Yield
>20:1 (*Z*:*E*), 94% ee



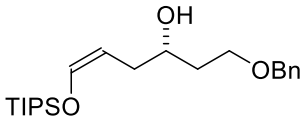
4.3g, 78% Yield
>20:1 (*Z*:*E*), 94% ee



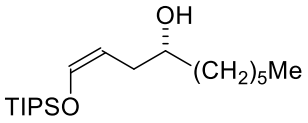
4.3h, 67% Yield
>20:1 (*Z*:*E*), 96% ee



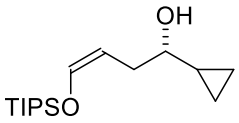
4.3i, 75% Yield
>20:1 (*Z*:*E*), 92% ee



4.3j, 68% Yield[b]
>20:1 (*Z*:*E*), 85% ee



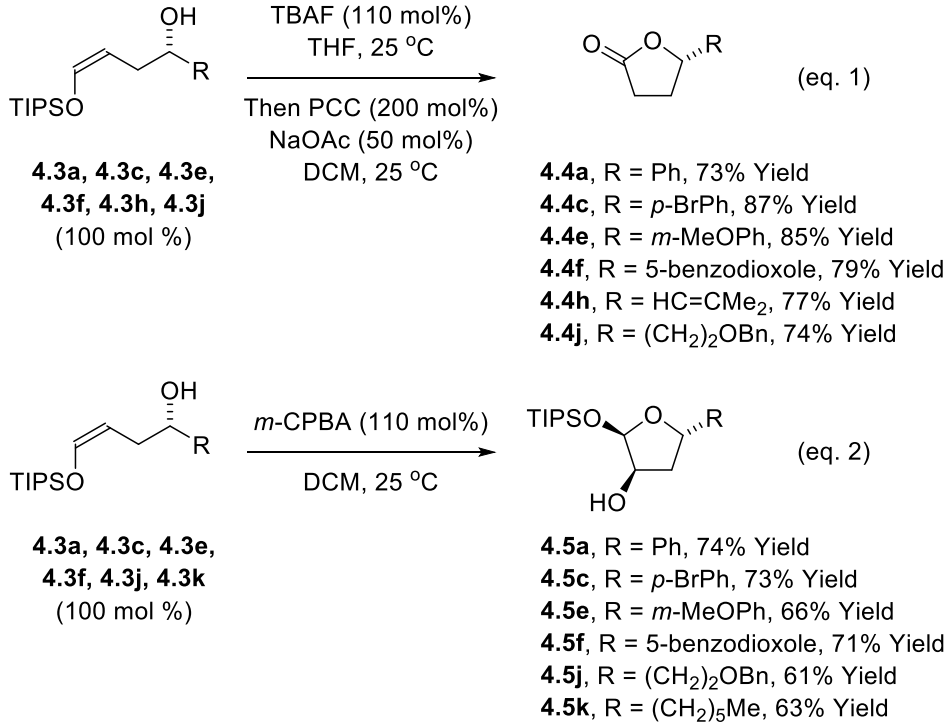
4.3k, 64% Yield[b]
>20:1 (*Z*:*E*), 90% ee



4.3l, 63% Yield[b]
>20:1 (*Z*:*E*), 95% ee

[a]Yields are material isolated by silica gel chromatography. See supporting Information for further experimental details. [b]Adamantane carboxylic aicd was used instead of Ph_3CCO_2H.

Scheme 4.1 Elaboration of Coupling Adducts to Form γ-Lactones and Furans.

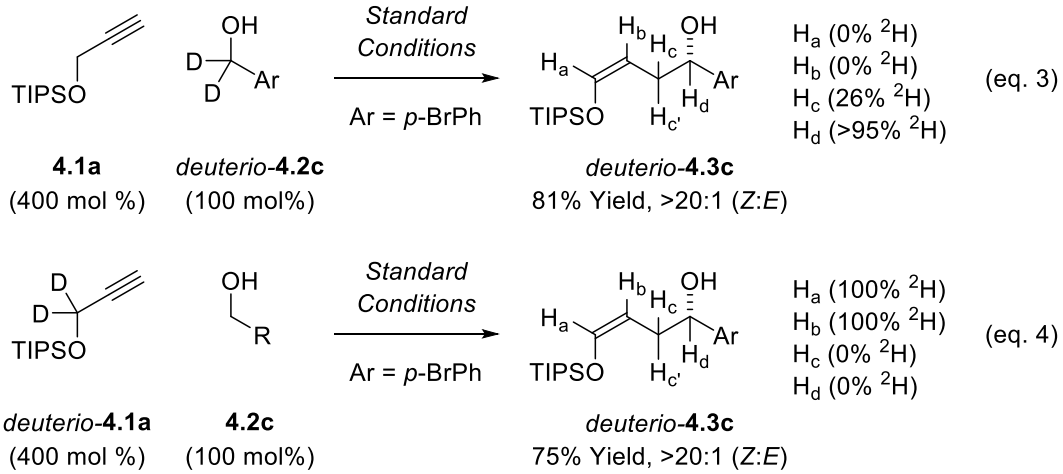


4.3 Mechanism and Discussion

Deuterium labeling experiments were conducted to confirm the reaction mechanism. When propargyl ether **4.1a** was treated with *deuterio*-**4.2c** under the standard conditions, deuterium was observed at the allylic (H_c) and carbinol (H_d) positions (Scheme 4.2, eq 3). When *deuterio*-**4.1a** was treated with p-bromobenzyl alcohol **4.2c** under standard conditions, complete deuterium incorporation was observed at both vinylic (H_a and H_b) positions (Scheme 4.2, eq 4).

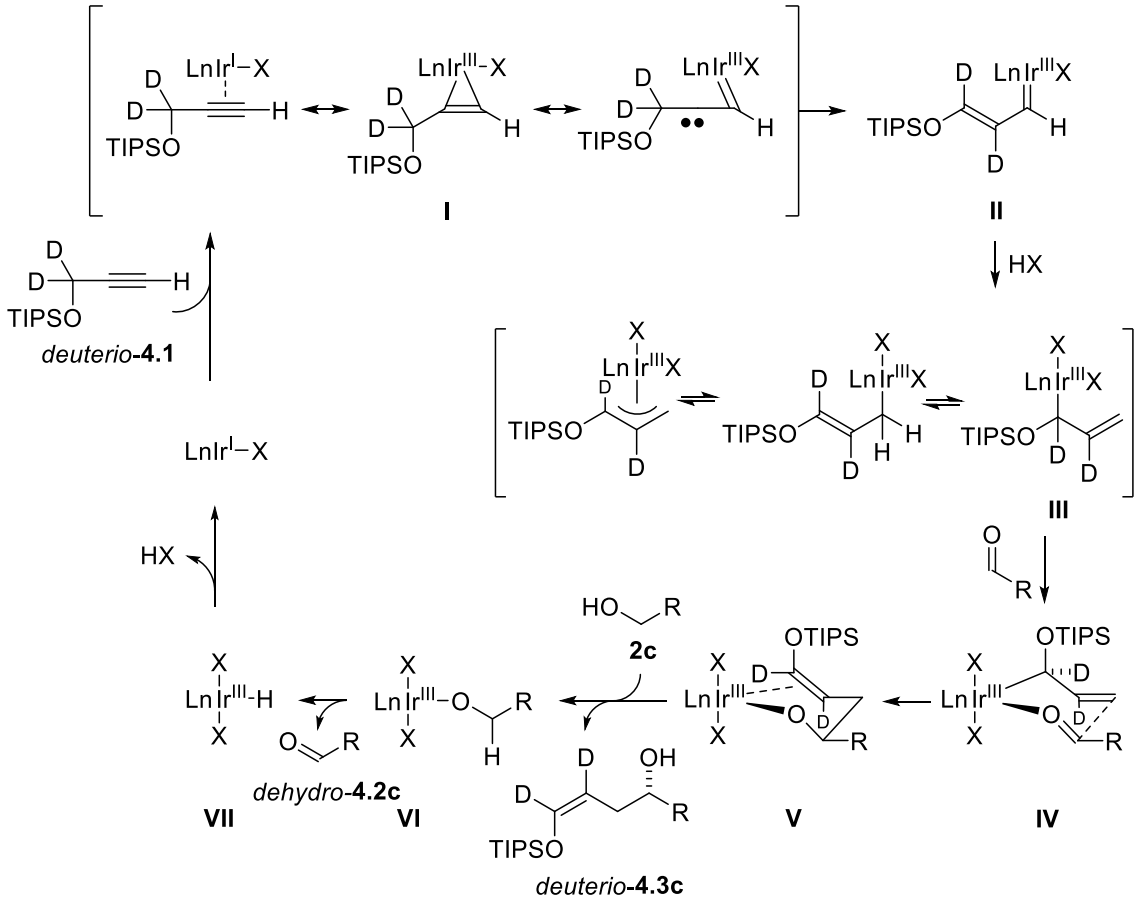
These data clearly indicated the catalytic mechanism via 1,2-hydride shift to form π-allyliridium species (Scheme 4.3). Coordination of alkyne to the low-valent iridium(I) induced 1,2-hydride shift to form vinylcarbene **II**. It is worth mentioning that the n → σ* interaction between oxygen lone pair with the propargylic C-H bond is crucial in promoting

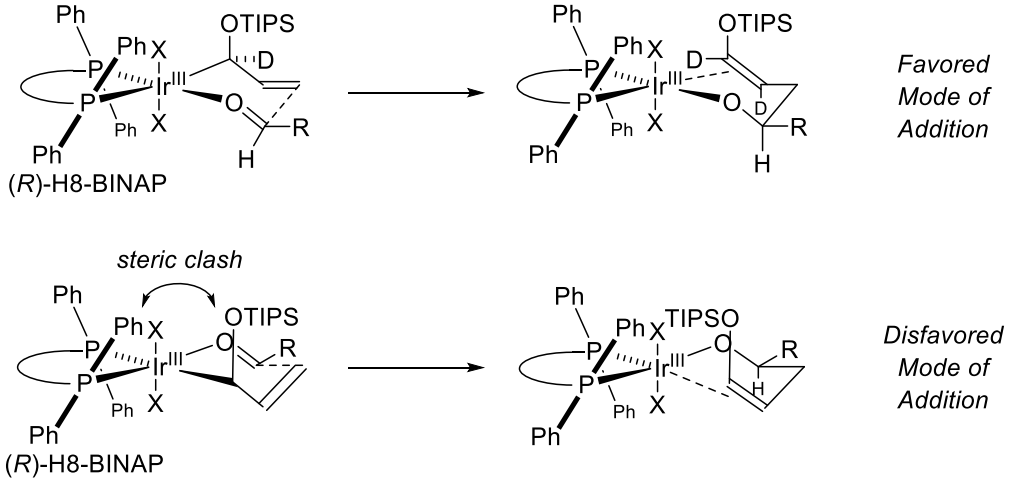
Scheme 4.2 Deuterium Labelling Experiments to Probe Reaction Mechanism.



1,2-hydride shift. Protonation of vinylcarbene **II** gave the siloxyallyliridium intermediate **III**. Coordination of aldehyde, formed *in situ*, to siloxyallylridium **III** triggered the carbonyl addition via closed transition structure to form homoallylic iridium alkoxide **V**. Protonolysis of iridium alkoxide **V** by reactant alcohol released the λ-hydroxyl enol silane and formed iridium alkoxide **VI**, which went through β–hydride elimination to generate aldehyde and iridium hydride species **VII**. Finally, reductive elimination of HX closed the catalytic cycle. A stereochemical model was proposed to rationalize the absolute stereoselective (Scheme 4.3).

Scheme 4.3 Proposed Iridium Catalyzed Carbonyl Siloxy-Crotylation Catalytical Cycle.





4.4 CONCLUSION

In summary, iridium catalyzed coupling of terminal propargyl ether **4.1a** with primary alcohols to form γ-hydroxyl enol silanes with complete (Z)-selectivity and high enantioselectivity was reported. According to the deuterium labeling studies, 1,2-hydride shift mechanism was proposed in the catalytic cycle. This protocol expanded the scope for the π-unsaturated compounds in redox-triggered carbonyl allylation reactions, as well as represented the departure from classic carbonyl addition of terminal alkynes.

4.5 EXPERIMENTAL DETAILS

General Information

All reactions were run under an atmosphere of argon, unless otherwise indicated. Resealable pressure tubes (13x100 mm) were purchased from Fischer Scientific (catalog number 14–959–35C) and were flame dried followed by cooling in a desiccator or under a stream of argon prior to use. Tetrahydrofuran (THF) was dried over sodium metal, benzophenone, and distilled immediately prior to use. $RuH_2(PPh_3)_3$ were prepared according to literature procedure.1 All ligands were used as received from Strem Chemicals Inc. Alcohols were purified by distillation or recrystallization immediately prior to use. Preparative column chromatography employing Silicycle silica gel (40-63 μm) was performed according to the method of Still.2 Analytical thin-layer chromatography (TLC) was carried out using 0.25 mm commercial silica gel plates (Dynamic Absorbents F254). Visualization was accomplished with UV light followed by dipping in Seebach's stain solution then heating. Purification of reactions was carried out by flash chromatography using Silicycle silica gel (40–63 μm).

Spectroscopy, Spectrometry, and Data Collection

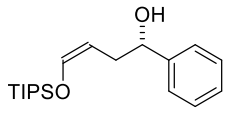
Infrared spectra were recorded on a Perkin-Elmer 1600 spectrometer. Low-resolution mass spectra (LRMS) were obtained on a Karatos MS9 and are reported as m/z (relative intensity). Accurate masses are reported for the molecular ion (M+H, M+Na), or a suitable fragment ion. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded with a Varian Gemini (400 MHz) spectrometer. Chemical shifts are reported in delta (δ) units, parts per million (ppm) downfield from tetramethylsilane or ppm relative to the center of the singlet at 7.26 ppm for deuteriochloroform. Data reported as multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). Integration and coupling constants were reported in Hertz (Hz). Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded with a Varian Gemini (100 MHz) spectrometer and were routinely run with broadband decoupling. Chemical shifts are reported in delta (δ) units, ppm relative to the center of the triplet at 77.16 ppm for deuteriochloroform.

Experimental Details and Spectral Data

General Procedure for the Couplings of Alcohols **4.2a-4.2l** and **4.1a**

To a resealable pressure tube (13x100) was added $[Ir(cod)Cl]_2$ (3.4mg, 0.005 mmol, 2.5 mol%), (*R*)-H_8BINAP (6.3 mg, 0.010 mmol, 5 mol%), Bu_4NI (7.4 mg, 0.020 mmol, 10 mol%), triphenylacetic acid (2.9 mg, 0.010 mmol, 5 mol%). At this stage solid alcohol coupling partners (0.20 mmol, 100 mol%) were added. The tube was sealed with a rubber septum and purged with argon. Toluene (0.20 mL, 1 M) was added to the reaction vessel. At this stage, liquid alcohol coupling partners (0.20 mmol, 100 mol%) were added. Propargyl ether **4.1a** (0.80 mmol, 400 mol%) was added to the reaction vessel and the rubber septum was replaced with a screw cap. The mixture was heated at 95 °C for 24 hours, at which point the reaction mixture was allowed to cool to room temperature. The solvents were removed *in vacuo* and the residue was subjected to column chromatography (SiO_2).

(*S*,*Z*)-1-phenyl-4-((triisopropylsilyl)oxy)but-3-en-1-ol (4.3a).



In accordance with the general procedure, the title compound was obtained in 93% yield (59.5 mg, 0.186 mmol, *Z:E* = >20:1) as a yellow liquid after column chromatography (SiO_2; 6% EtOAc/hexanes).

R_f=0.6 (20% EtOAc/Hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.30 (m, 4H), 7.28 – 7.23 (m, 1H), 6.45 (dt, *J* = 5.8, 1.3 Hz, 1H), 4.78 – 4.72 (m, 1H), 4.47 (td, *J* = 7.5, 5.8 Hz, 1H), 2.67 – 2.49 (m, 2H), 2.46 (d, *J* = 3.4 Hz, 1H), 1.20 – 1.12 (m, 3H), 1.09 (d, *J* = 5.6 Hz, 18H).

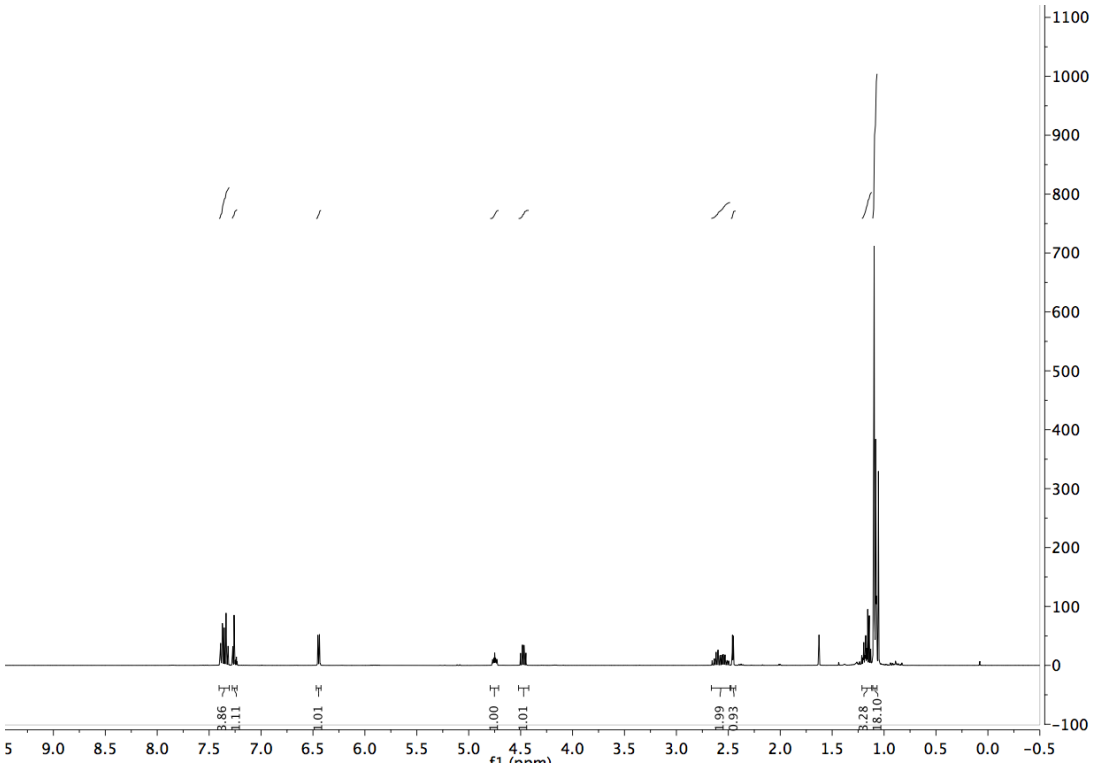
^{13}C NMR (100 MHz, $CDCl_3$): δ 144.5, 141.8, 128.2, 127.2, 125.8, 104.6, 74.2, 34.1, 17.7, 11.9.

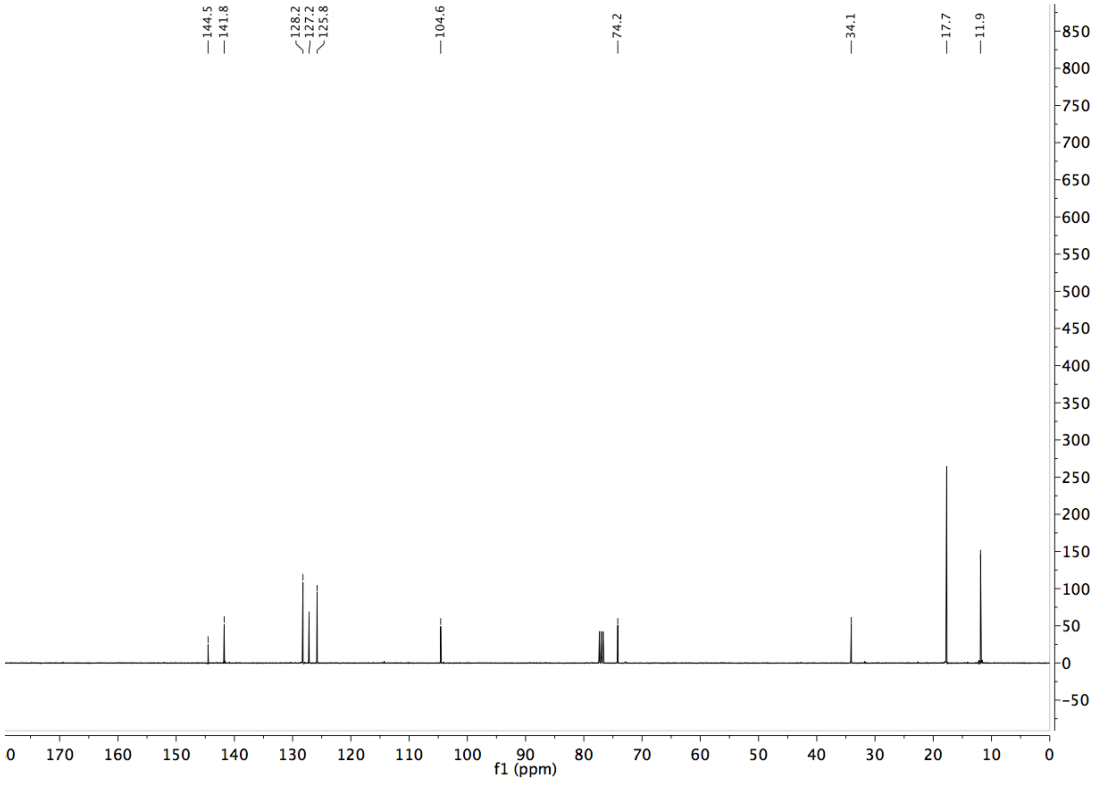
LRMS (ESI) Calcd. for $C_{19}H_{32}NaO_2Si$ $[M+Na]^+$: 343, Found: 343

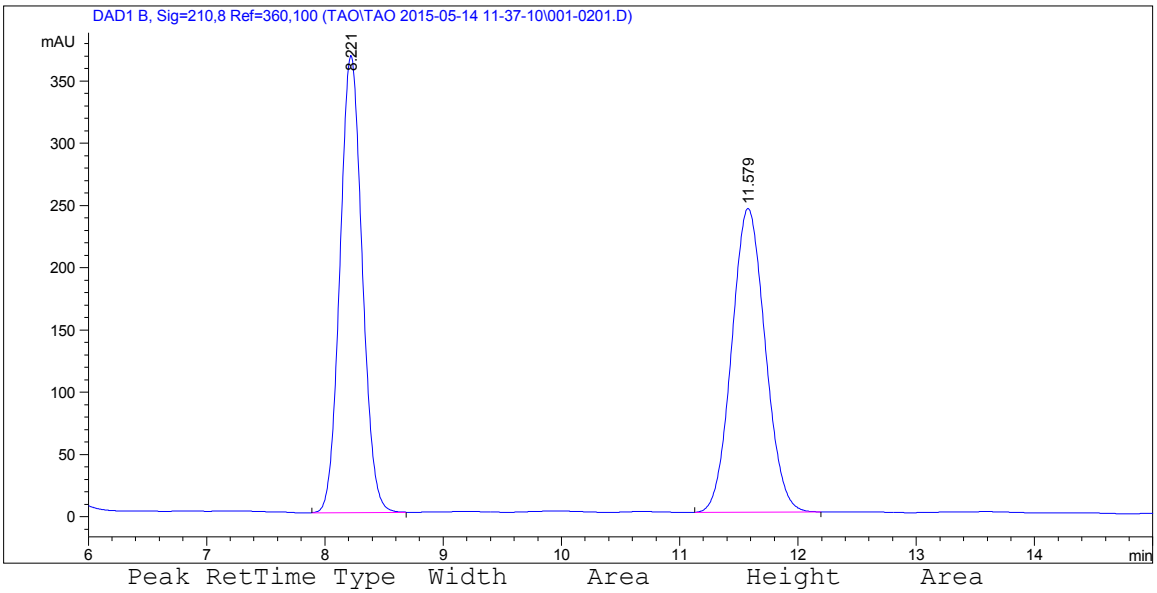
FTIR (neat): 2943, 2866, 2874, 1463, 1116, 1050, 882, 684, 665 cm^{-1}.

HPLC (Chiralcel OD-H column, hexanes:*i*-PrOH = 99:1, 1 mL/min, 210 nm), ee = 94%.

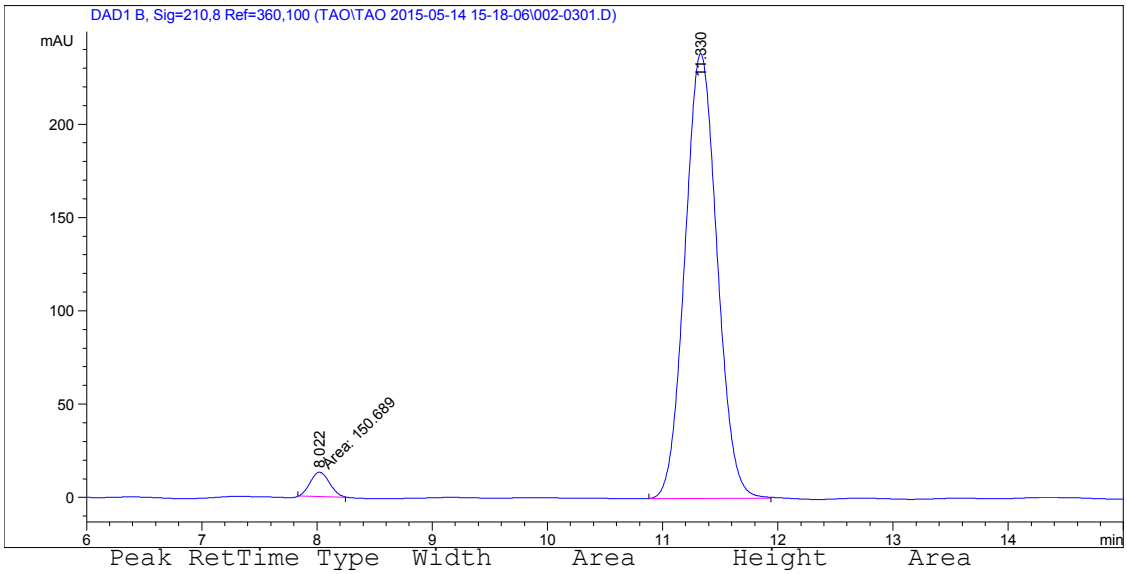
$[\alpha]^{28}_D$ = 25.7 (c = 0.92, $CHCl_3$)


3.86
1.11
1.01
1.00
1.01
1.99
0.93
3.28
18.10
f1 (ppm)


144.5
141.8
128.2
127.2
125.8
104.6
74.2
34.1
17.7
11.9
f1 (ppm)

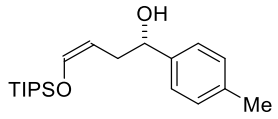


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.221	BB	0.2023	4792.19092	367.16394	50.0134
2	11.579	BB	0.3049	4789.62354	244.08528	49.9866



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.022	MM	0.1924	150.68938	13.05360	3.1547
2	11.330	BB	0.3024	4626.01172	238.38820	96.8453

(*S*,*Z*)-1-(p-tolyl)-4-((triisopropylsilyl)oxy)but-3-en-1-ol (4.3b).



In accordance with the general procedure, the title compound was obtained in 84% yield (56.1 mg, 0.168 mmol, *Z:E* = >20:1) as a yellow liquid after column chromatography (SiO_2; 7% EtOAc/hexanes).

R_f = 0.6 (20% EtOAc/Hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 (d, *J* = 7.4 Hz, 2H), 7.15 (d, *J* = 7.5 Hz, 2H), 6.43 (dt, *J* = 5.8, 1.3 Hz, 1H), 4.74 – 4.69 (m, 1H), 4.47 (td, *J* = 7.5, 5.8 Hz, 1H), 2.67 – 2.56 (m, 1H), 2.56 – 2.47 (m, 1H), 2.35 (s, 1H), 2.34 (s, 3H), 1.20 – 1.12 (m, 3H), 1.09 (d, *J* = 5.9 Hz, 18H).

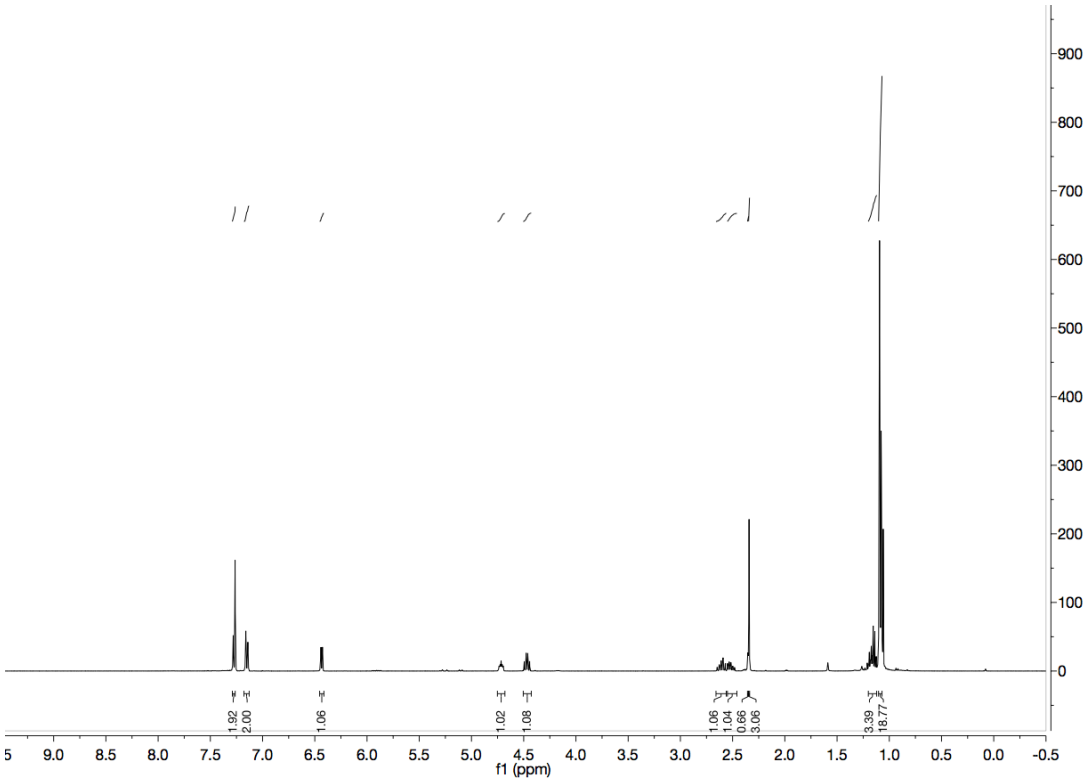
^{13}C NMR (100 MHz, $CDCl_3$): δ 141.7, 141.6, 136.8, 128.9, 125.7, 104.7, 74.0, 34.0, 21.1, 17.7, 11.9.

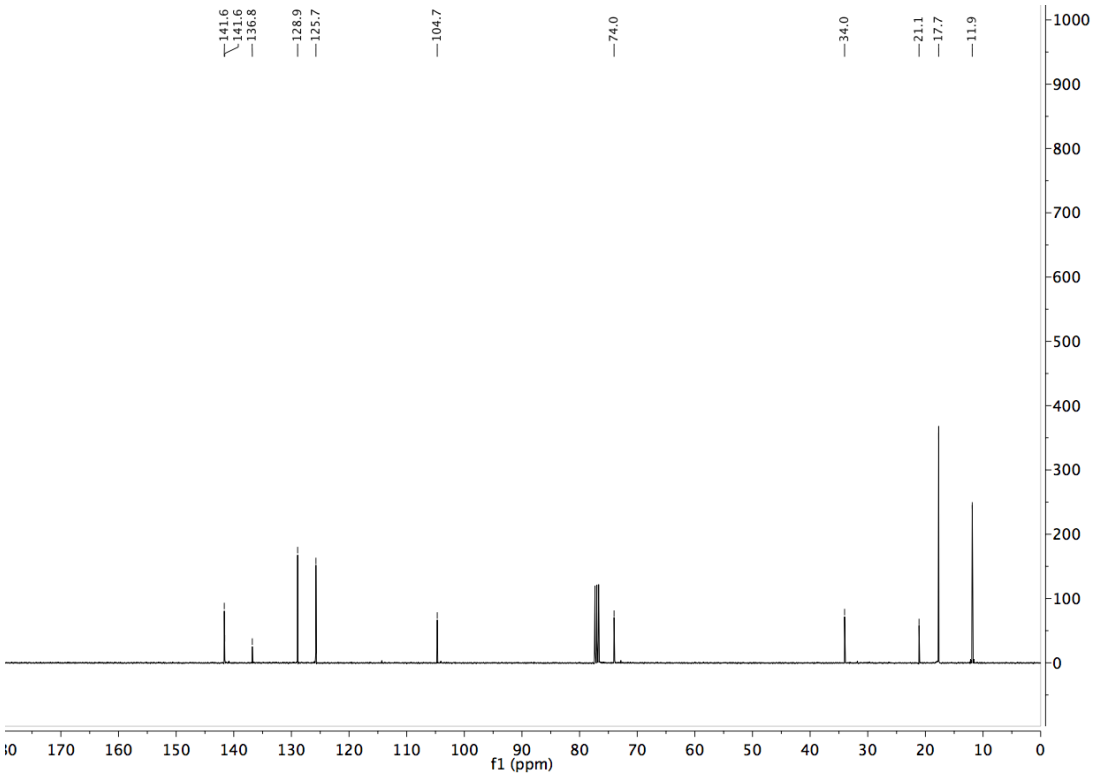
LRMS (ESI) Calcd. for $C_{20}H_{34}NaO_2Si$ $[M+Na]^+$: 357, Found: 357.

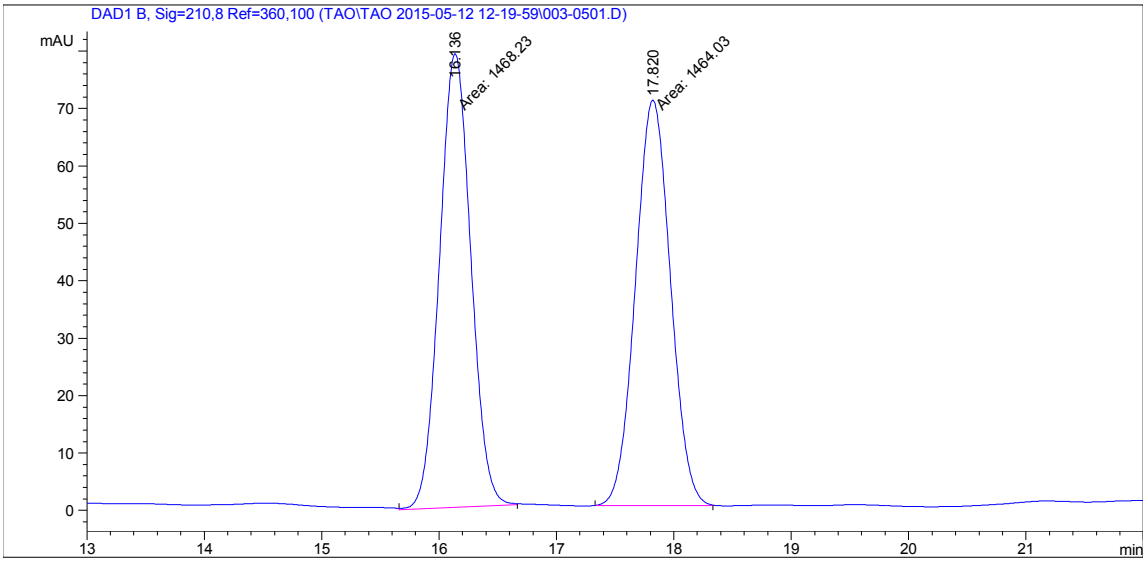
FTIR (neat): 2943, 2866, 1654, 1463, 1248, 1162, 1052, 881, 817, 683, 666 cm^{-1}.

HPLC (Chiralcel OD-H/OD-H column, hexanes:*i*-PrOH = 99:1, 1 mL/min, 210 nm), ee = 95%.

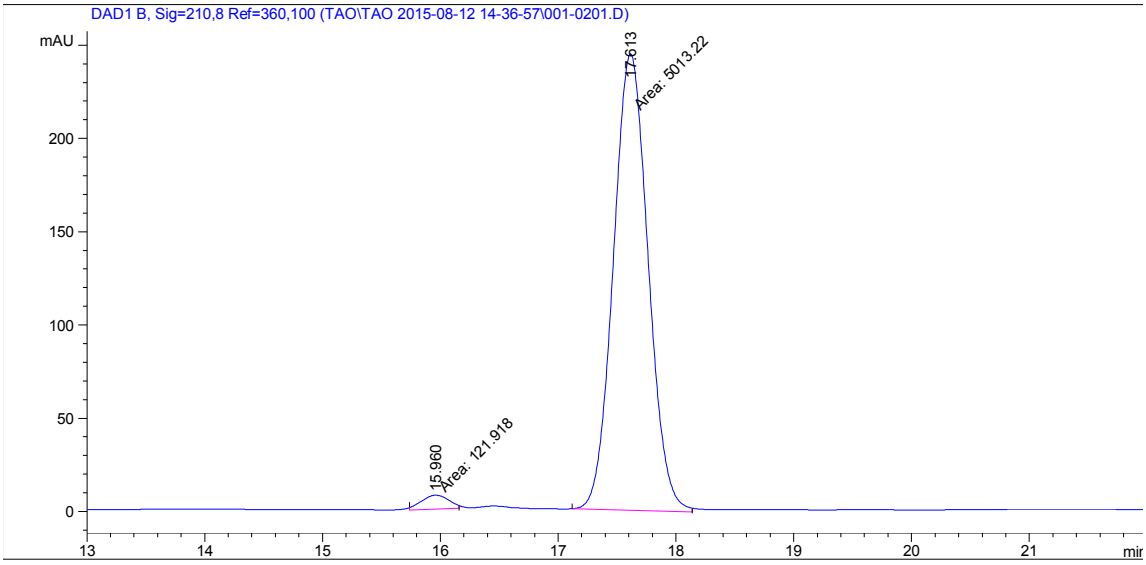
$[\alpha]^{29}_D$ = - 35.8 (c = 0.80, $CHCl_3$)


1.92
2.00
1.06
1.02
1.08
1.06
1.04
0.66
3.06
3.39
18.77
f1 (ppm)


141.6
141.6
136.8
128.9
125.7
104.7
74.0
34.0
21.1
17.7
11.9
f1 (ppm)

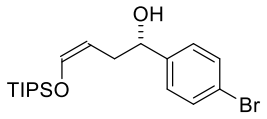


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.136	MM	0.3097	1468.23145	79.00329	50.0716
2	17.820	MM	0.3454	1464.03186	70.64793	49.9284



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.960	MM	0.2703	121.91837	7.51688	2.3742
2	17.613	MM	0.3414	5013.22412	244.76976	97.6258

(*S*,*Z*)-1-(4-bromophenyl)-4-((triisopropylsilyl)oxy)but-3-en-1-ol (4.3c).



In accordance with the general procedure, the title compound was obtained in 86% yield (68.5 mg, 0.172 mmol, *Z:E* = >20:1) as a yellow liquid after column chromatography (SiO_2; 7% EtOAc/hexanes).

R_f = 0.55 (20% EtOAc/Hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 – 7.43 (m, 2H), 7.27 – 7.23 (m, 2H), 6.44 (dt, *J* = 5.8, 1.2 Hz, 1H), 4.75 – 4.68 (m, 1H), 4.44 (td, *J* = 7.5, 5.8 Hz, 1H), 2.60 – 2.45 (m, 3H), 1.23 – 1.11 (m, 3H), 1.08 (d, *J* = 5.8 Hz, 18H).

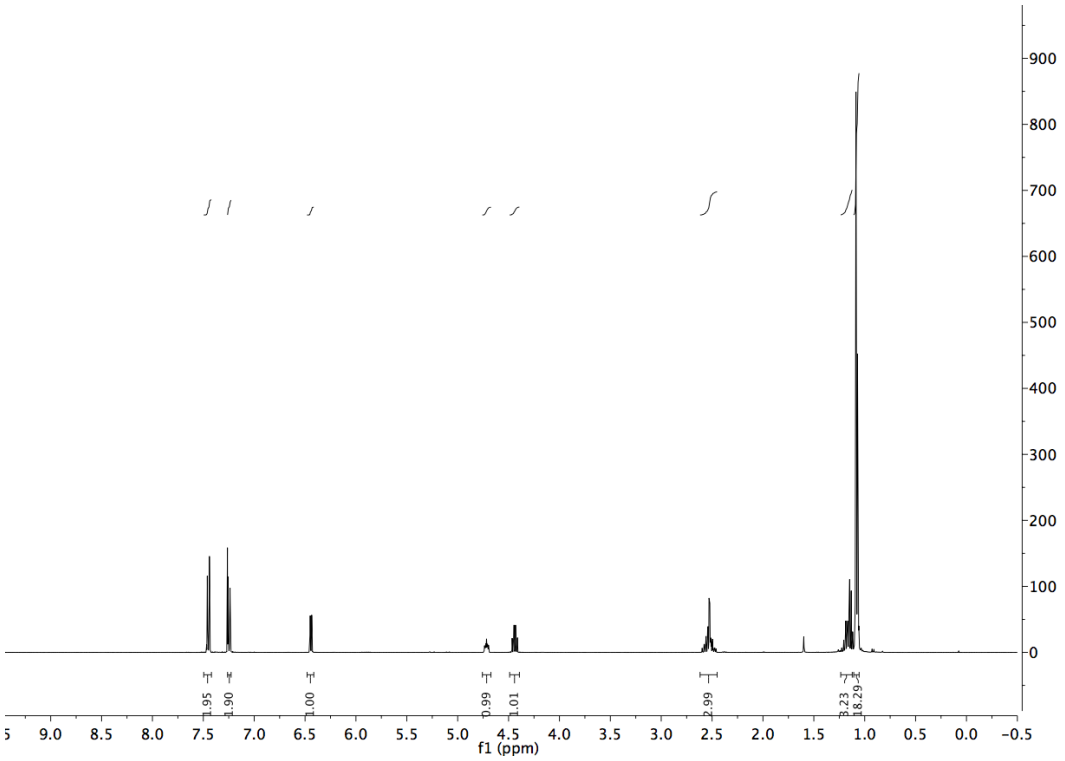
^{13}C NMR (100 MHz, $CDCl_3$): δ 143.5, 142.1, 131.3, 127.6, 120.9, 104. 0, 73.5, 34.1, 17.7, 11.8.

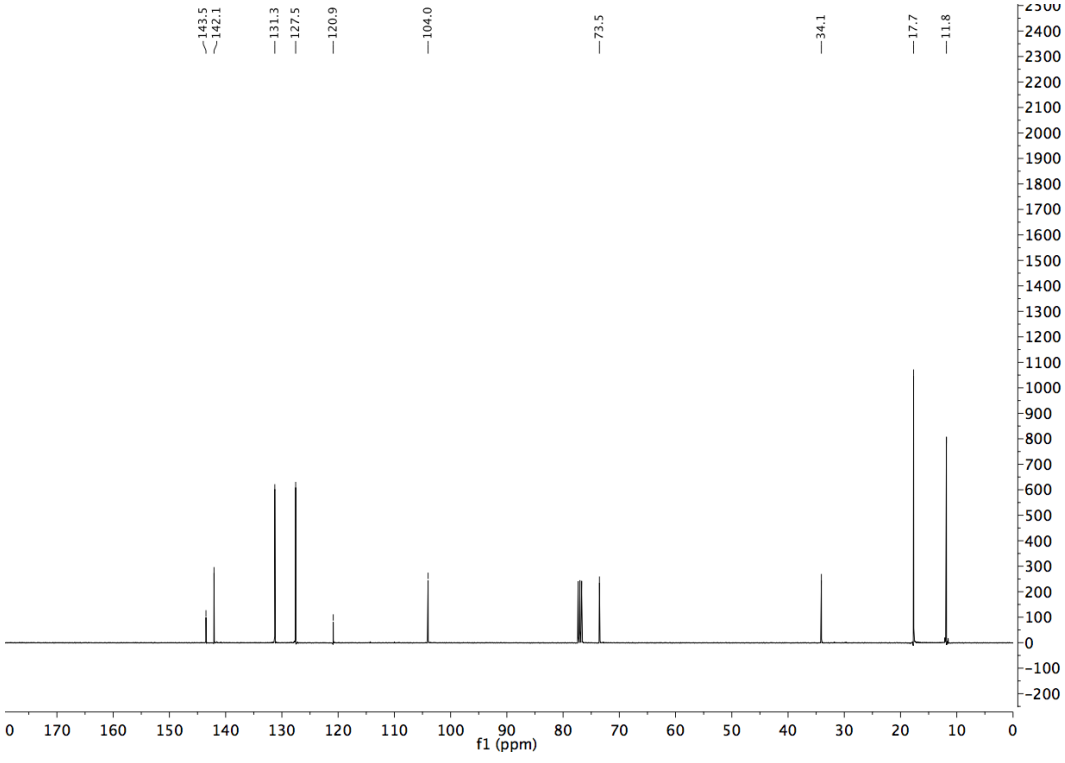
LRMS (ESI) Calcd. for $C_{19}H_{31}BrNaO_2Si$ $[M+Na]^+$: 421, Found: 421.

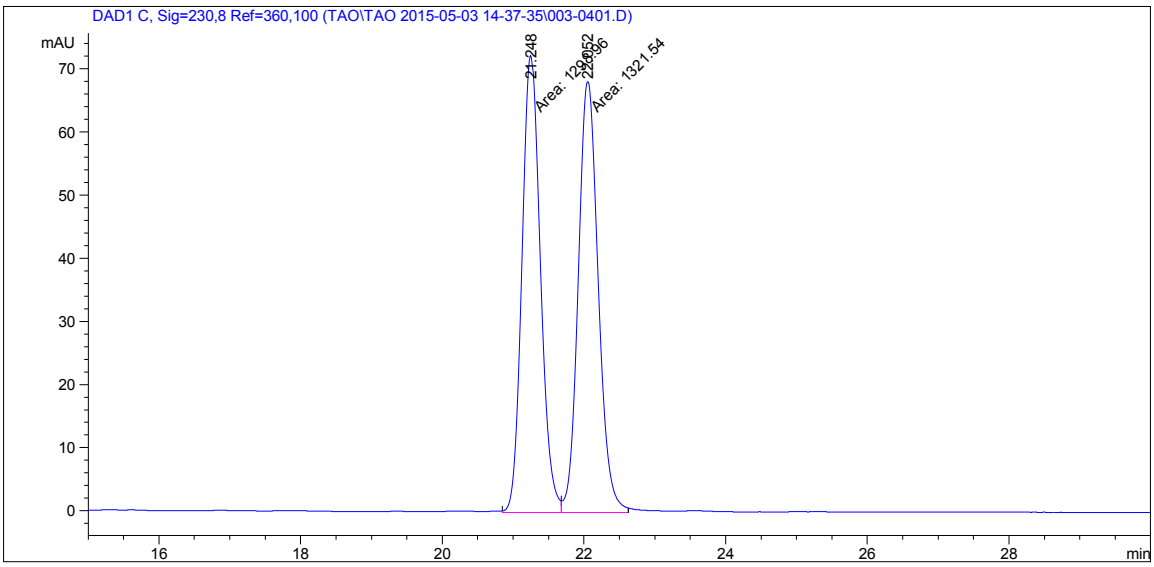
FTIR (neat): 2943, 2866, 1653, 1463, 1118, 1059, 1010, 882, 828, 685 cm^{-1}.

HPLC (Chiralcel AS-H/AS-H column, hexanes:*i*-PrOH = 99:1, 0.5 mL/min, 210 nm), ee = 91%.

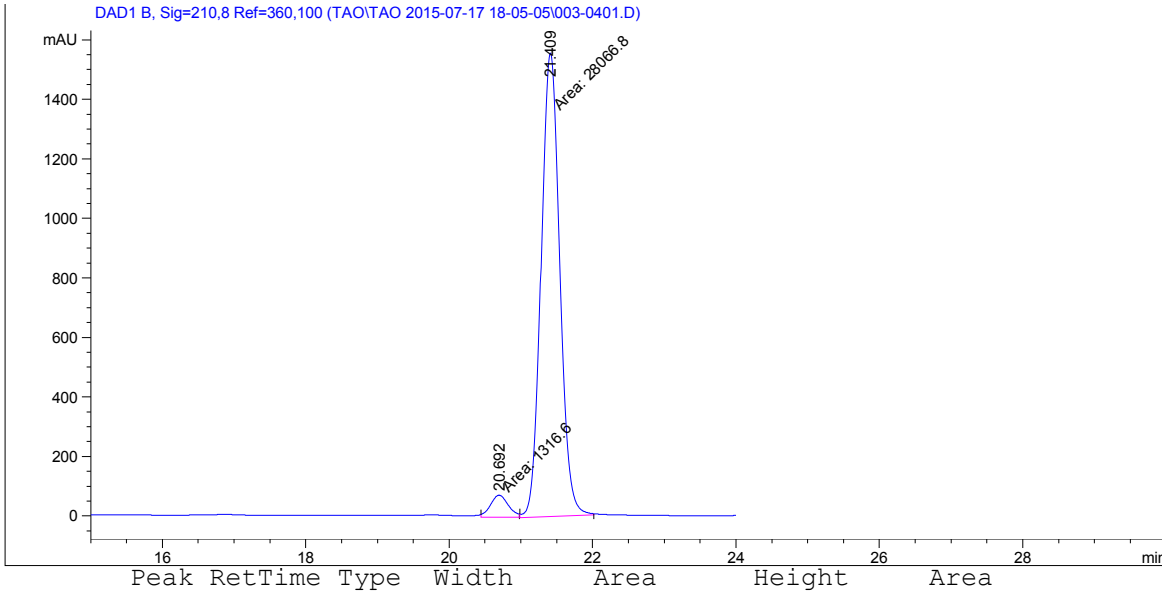
$[\alpha]^{30}_D$ = - 24.1 (c = 1.08, $CHCl_3$)


1.95
1.90
1.00
0.99
1.01
2.99
3.23
18.29
f1 (ppm)


143.5
142.1
131.3
127.5
120.9
104.0
73.5
34.1
17.7
11.8
f1 (ppm)

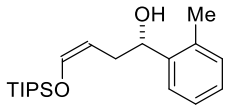


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.248	MF	0.2993	1298.96252	72.33195	49.5692
2	22.052	FM	0.3229	1321.53833	68.20992	50.4308



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.692	MM	0.2935	1316.60364	74.75982	4.4808
2	21.409	MM	0.3004	2.80668e4	1557.28015	95.5192

(*S*,*Z*)-1-(o-tolyl)-4-((triisopropylsilyl)oxy)but-3-en-1-ol (4.3d).



In accordance with the general procedure, the title compound was obtained in 85% yield (56.8 mg, 0.17 mmol, *Z:E* = >20:1) as a yellow liquid after column chromatography (SiO_2; 5% EtOAc/hexanes).

R_f = 0.5 (20% EtOAc/Hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.23 (td, *J* = 7.4, 1.8 Hz, 1H), 7.16 (td, *J* = 7.3, 1.5 Hz, 1H), 7.14 – 7.10 (m, 1H), 6.46 (dt, *J* = 5.8, 1.3 Hz, 1H), 5.00 – 4.94 (m, 1H), 4.52 (td, *J* = 7.5, 5.8 Hz, 1H), 2.60 – 2.49 (m, 2H), 2.37 (d, *J* = 3.2 Hz, 1H), 2.35 (s, 3H), 1.20 – 1.13 (m, 3H), 1.09 (d, *J* = 6.4 Hz, 18H).

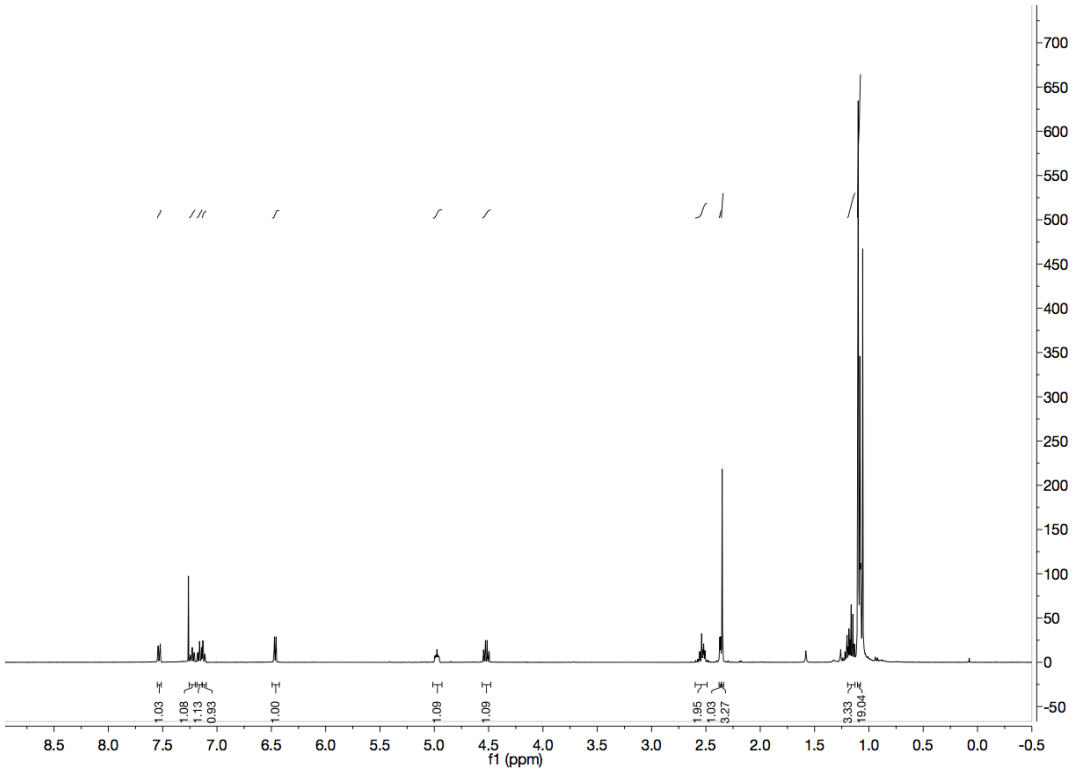
^{13}C NMR (100 MHz, $CDCl_3$): δ 142.5, 141.7, 134.4, 130.2, 126.9, 126.1, 125.2, 104.8, 70.7, 32.8, 19.0, 17.7, 12.3, 11.9.

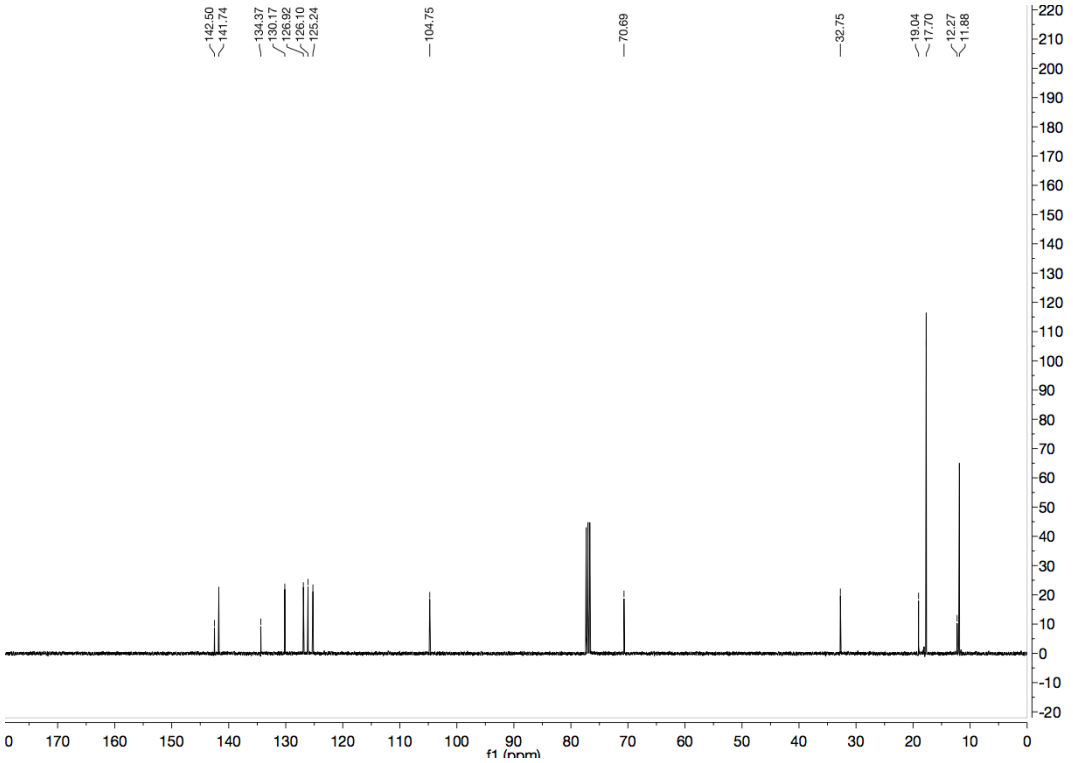
LRMS (ESI) Calcd. for $C_{20}H_{34}NaO_2Si$ $[M+Na]^+$: 357, Found: 357.

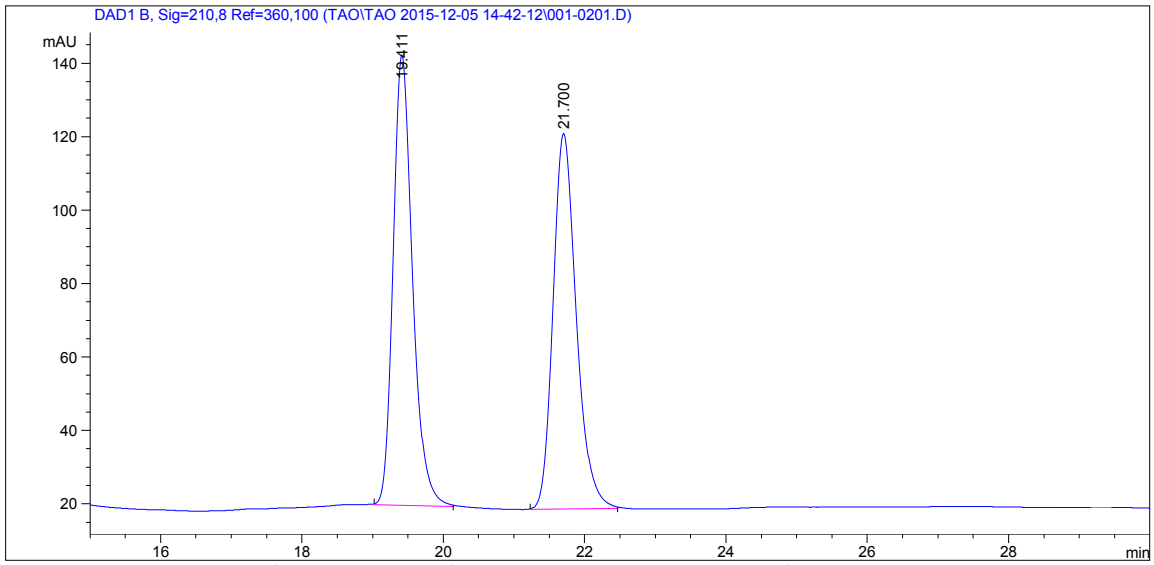
FTIR (neat): 2944, 2866, 1654, 1463, 1121, 1104, 1047, 882, 745, 684 cm^{-1}.

HPLC (Chiralcel AD-H/AD-H column, hexanes:*i*-PrOH = 99:1, 1 mL/min, 210 nm), ee = 95%.

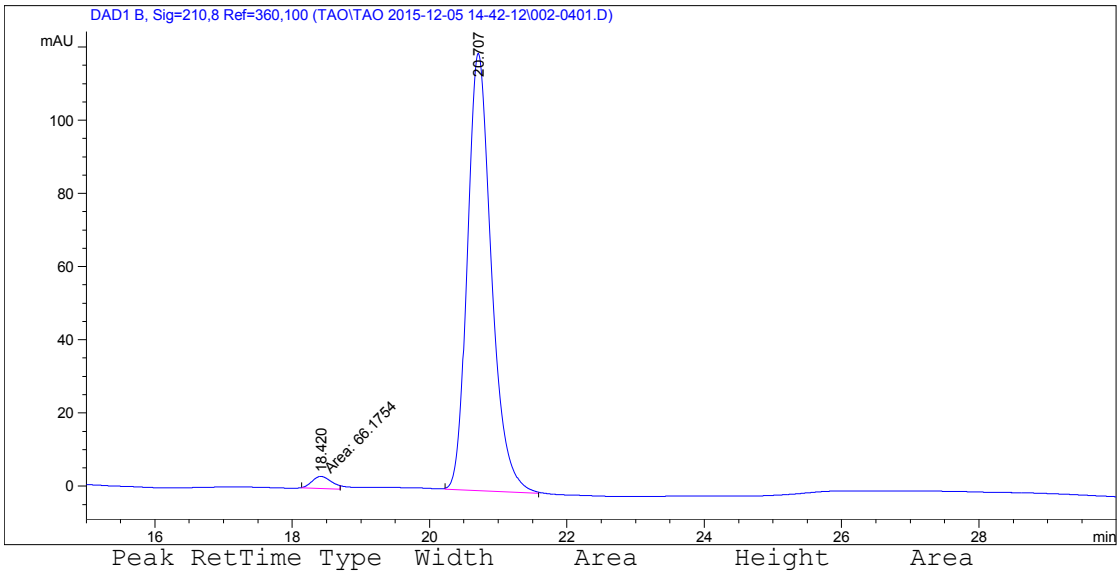
$[\alpha]^{30}_D$ = - 45.3 (c = 1.14, $CHCl_3$)


1.03
1.08
1.13
0.93
1.00
1.09
1.09
1.95
1.03
3.27
3.33
19.04
f1 (ppm)


142.50
141.74
134.37
130.17
126.92
126.10
125.24
104.75
70.69
32.75
19.04
17.70
12.27
11.88
f1 (ppm)

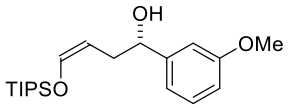


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.411	BB	0.2936	2349.12549	122.59051	50.0210
2	21.700	BB	0.3499	2347.15088	102.22230	49.9790



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.420	MM	0.3313	66.17539	3.32879	2.2265
2	20.707	BB	0.3719	2906.04346	119.41266	97.7735

(*S*,*Z*)-1-(3-methoxyphenyl)-4-((triisopropylsilyl)oxy)but-3-en-1-ol (4.3e).



In accordance with the general procedure, the title compound was obtained in 94% yield (65.8 mg, 0.188 mmol, *Z:E* = >20:1) as a yellow liquid after column chromatography (SiO_2; 8% EtOAc/hexanes).

R_f = 0.45 (20% EtOAc/Hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 – 7.21 (m, 1H), 6.97 – 6.92 (m, 2H), 6.80 (ddd, *J* = 8.2, 2.4, 1.2 Hz, 1H), 6.45 (dt, *J* = 5.8, 1.3 Hz, 1H), 4.72 (dd, *J* = 8.1, 4.8 Hz, 1H), 4.48 (td, *J* = 7.5, 5.8 Hz, 1H), 3.81 (s, 3H), 2.65 – 2.39 (m, 3H), 1.21 – 1.12 (m, 3H), 1.08 (d, *J* = 6.3 Hz, 18H).

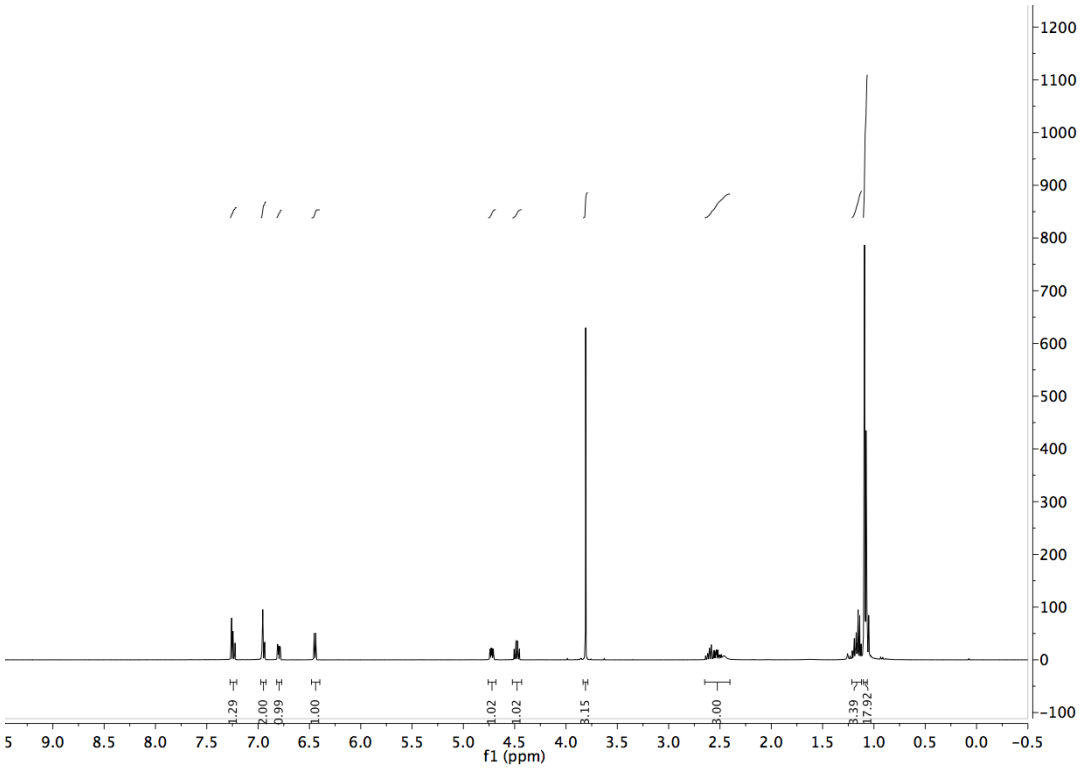
^{13}C NMR (100 MHz, $CDCl_3$): δ 159.60, 146.29, 141.80, 129.22, 118.13, 112.78, 111.15, 104.56, 74.08, 55.14, 34.08, 17.70, 11.86.

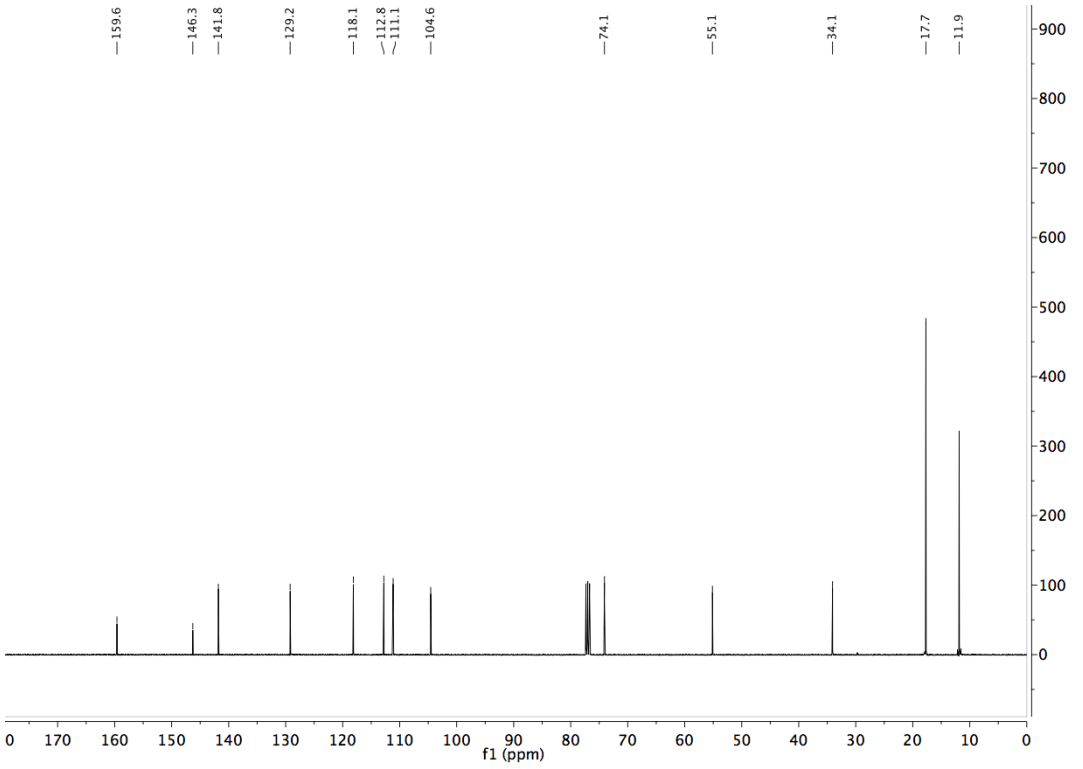
LRMS (ESI) Calcd. for $C_{20}H_{34}NaO_3Si$ $[M+Na]^+$: 373, Found: 373.

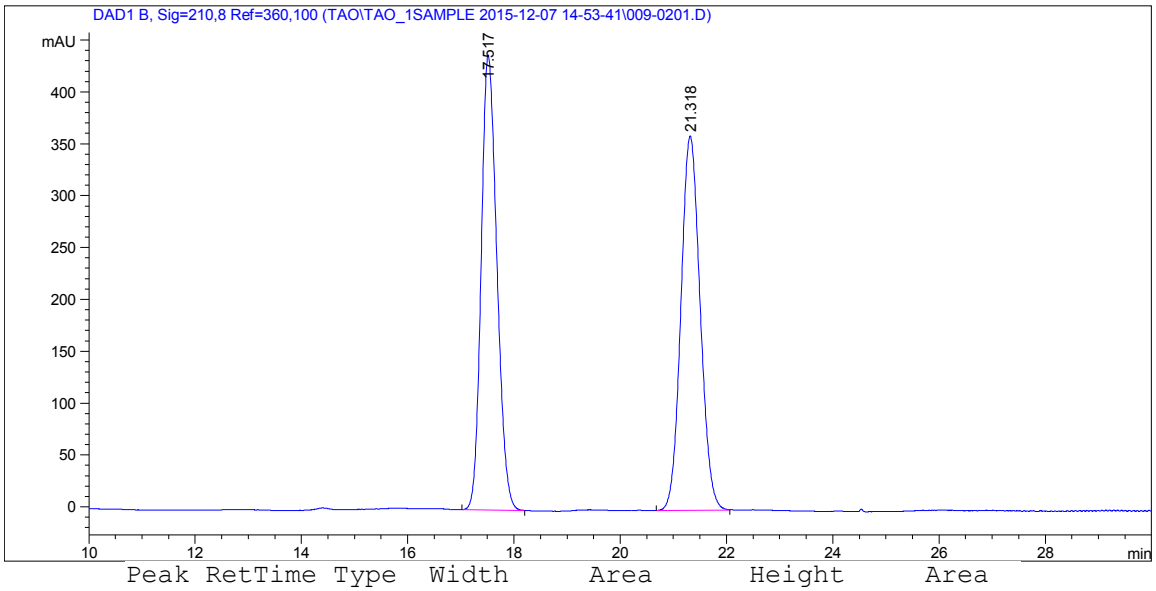
FTIR (neat): 3443, 2943, 2866,1738, 1653, 1258, 1115, 1044, 881, 684 cm^{-1}.

HPLC (Chiralpak IB column, hexanes:*i*-PrOH = 99:1, 1 mL/min, 210 nm), ee = 95%.

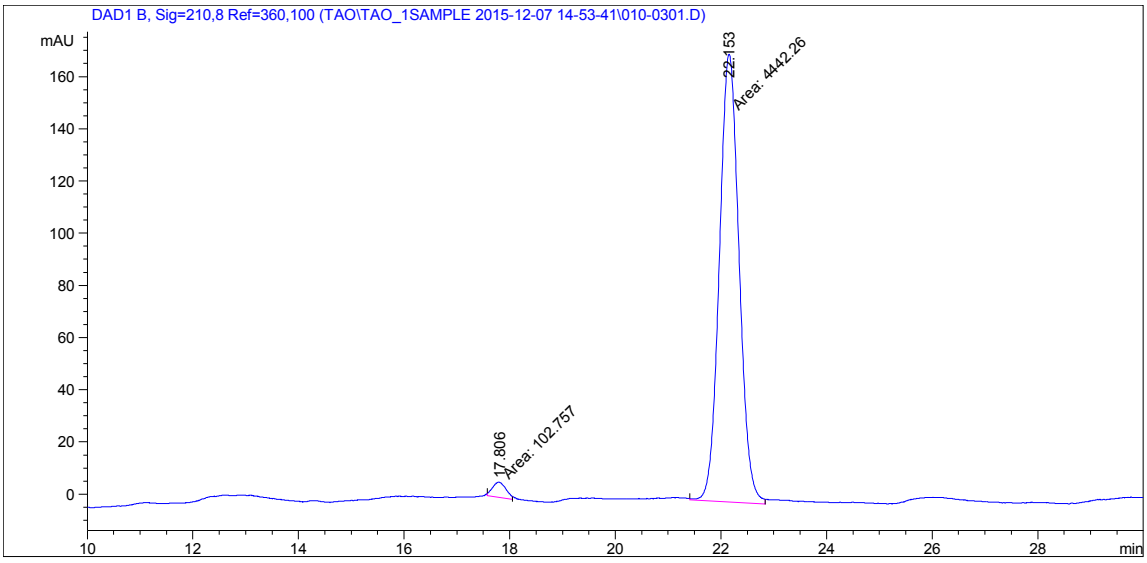
$[\alpha]^{30}_D$ = - 30.6 (c = 1.17, $CHCl_3$)


1.29
2.00
0.99
1.00
1.02
1.02
3.15
3.00
3.39
17.92
f1 (ppm)


159.6
146.3
141.8
129.2
118.1
112.8
111.1
104.6
74.1
55.1
34.1
17.7
11.9
f1 (ppm)

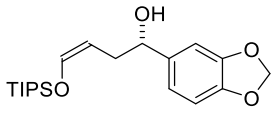


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.517	BB	0.3197	9010.00000	438.58646	49.8306
2	21.318	BB	0.3913	9071.25293	360.80719	50.1694



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.806	MM	0.2970	102.75671	5.76684	2.2609
2	22.153	MM	0.4315	4442.26123	171.60025	97.7391

(*S*,*Z*)-1-(benzo[d][1,3]dioxol-5-yl)-4-((triisopropylsilyl)oxy)but-3-en-1-ol (4.3f).



In accordance with the general procedure, the title compound was obtained in 91% yield (66.2 mg, 0.182, *Z:E* = >20:1) as a yellow liquid after column chromatography (SiO_2; 8% EtOAc/hexanes).

R_f = 0.45 (20% EtOAc/Hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.90 (d, *J* = 1.6 Hz, 1H), 6.81 (ddd, *J* = 7.9, 1.7, 0.6 Hz, 1H), 6.75 (d, *J* = 7.9 Hz, 1H), 6.42 (dt, *J* = 5.8, 1.3 Hz, 1H), 5.93 (s, 2H), 4.70 – 4.61 (m, 1H), 4.44 (td, *J* = 7.5, 5.8 Hz, 1H), 2.62 – 2.52 (m, 1H), 2.51 – 2.43 (m, 1H), 2.39 (s, 1H), 1.19 – 1.11 (m, 3H), 1.08 (d, *J* = 6.8 Hz, 18H).

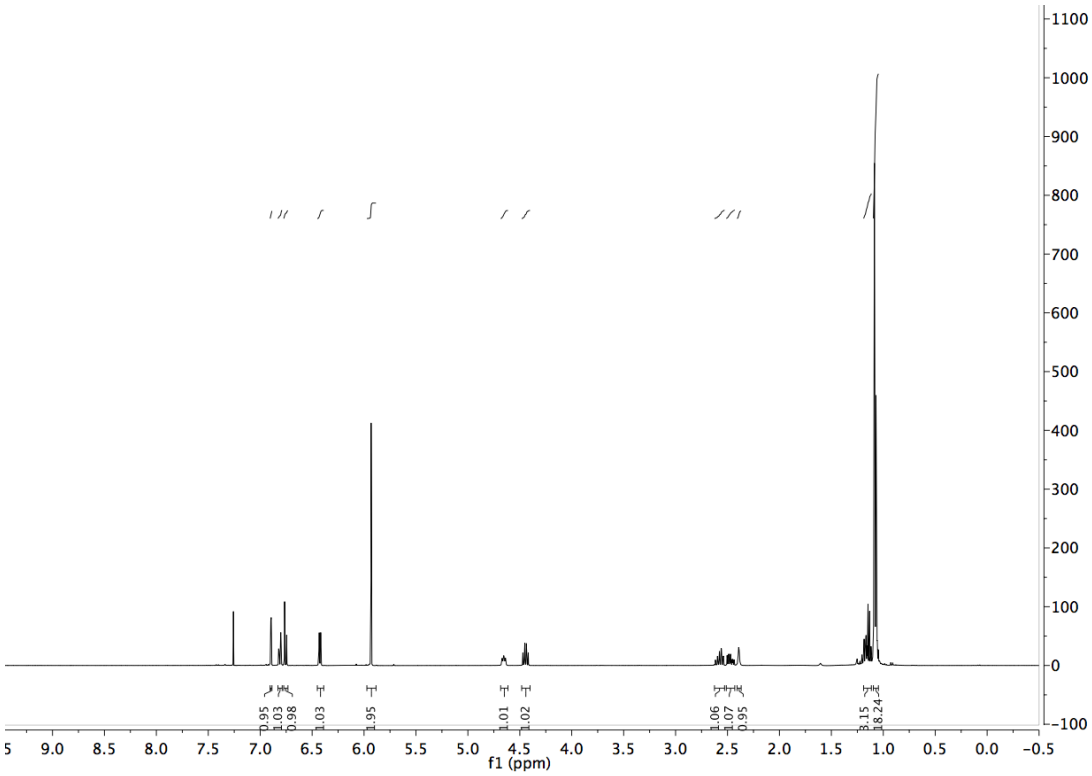
^{13}C NMR (100 MHz, $CDCl_3$): δ 147.6, 146.6, 141.7, 138.7, 119.1, 107.9, 106.4, 104.5, 100.8, 74.0, 34.1, 17.7, 11.9.

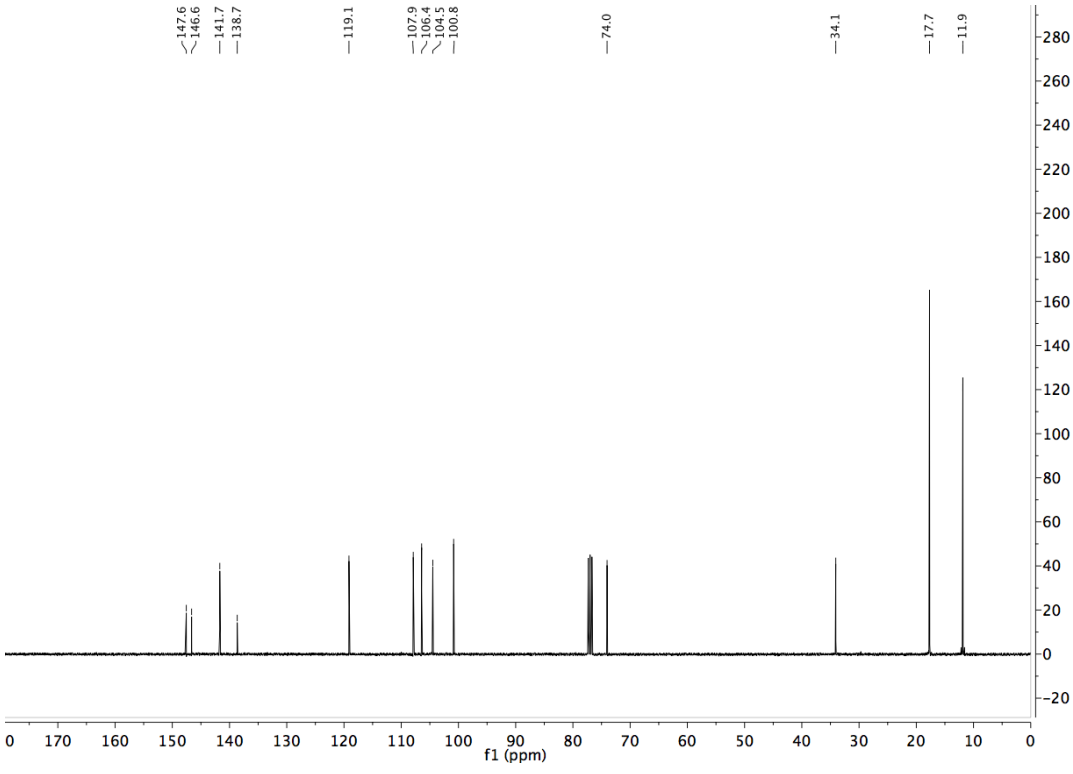
LRMS (ESI) Calcd. for $C_{20}H_{32}NaO_4Si$ $[M+Na]^+$: 387, Found: 387.

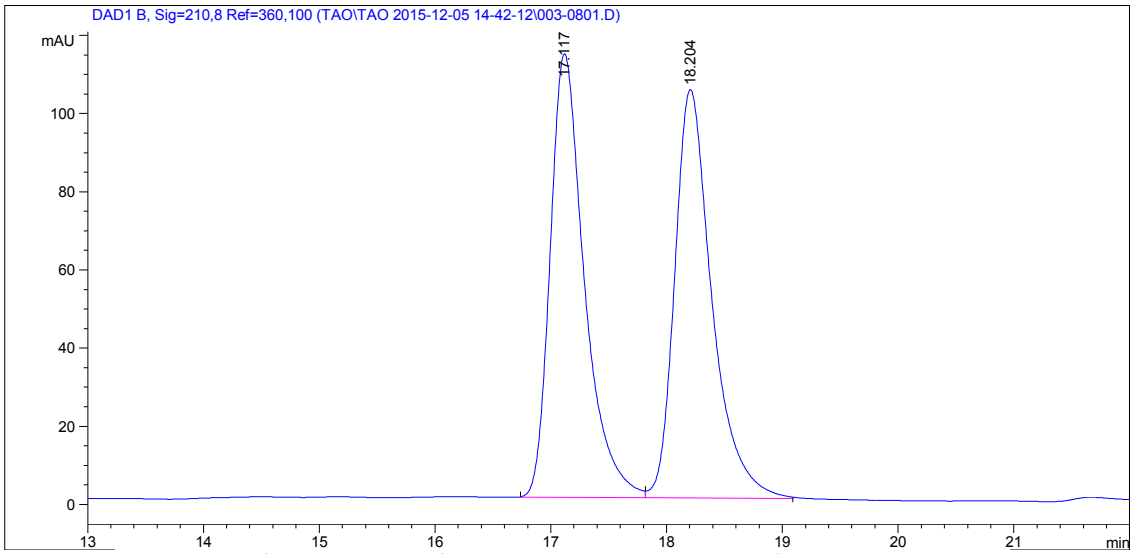
FTIR (neat): 3402, 2943, 1738,1488, 1241, 1113, 882, 810, 684 cm^{-1}.

HPLC (Chiralcel AD-H/AD-H column, hexanes:*i*-PrOH = 97:3, 1 mL/min, 210 nm), ee = 94%.

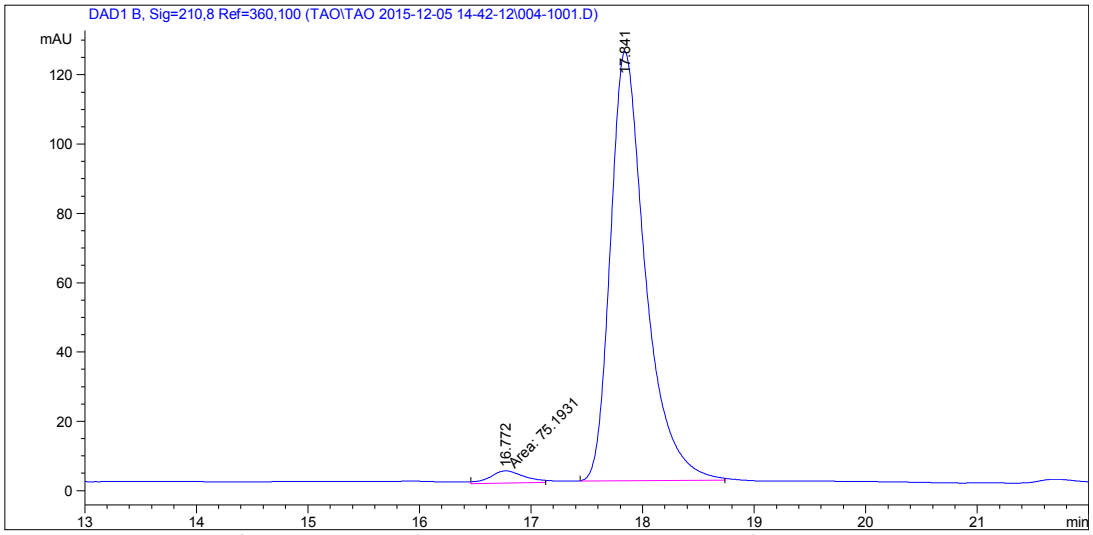
$[\alpha]^{30}_D$ = - 20.1 (c = 1.99, $CHCl_3$)


0.95
1.03
0.98
1.03
1.95
1.01
1.02
1.06
1.07
0.95
3.15
18.24
f1 (ppm)


147.6
146.6
141.7
138.7
119.1
107.9
106.4
104.5
100.8
74.0
34.1
17.7
11.9
f1 (ppm)

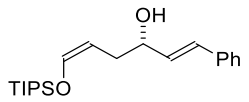


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.117	BV	0.3096	2330.78101	113.50340	49.9588
2	18.204	VB	0.3367	2334.62402	104.49120	50.0412



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.772	MM	0.3545	75.19310	3.53555	2.7092
2	17.841	BB	0.3265	2700.32568	123.79351	97.2908

(*S*,1E,5Z)-1-phenyl-6-((triisopropylsilyl)oxy)hexa-1,5-dien-3-ol (4.3g)



In accordance with the general procedure, the title compound was obtained in 78% yield (54.0 mg, 0.156 mmol, *Z:E* = >20:1) as a yellow liquid after column chromatography (SiO_2; 6% EtOAc/hexanes).

R_f = 0.55 (20% EtOAc/Hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 – 7.37 (m, 2H), 7.31 (t, *J* = 7.5 Hz, 2H), 7.22 (tt, *J* = 7.3, 1.4 Hz, 1H), 6.61 (dd, *J* = 15.9, 1.2 Hz, 1H), 6.45 (dt, *J* = 5.8, 1.3 Hz, 1H), 6.26 (dd, *J* = 15.9, 6.3 Hz, 1H), 4.52 (td, *J* = 7.4, 5.8 Hz, 1H), 4.40 – 4.31 (m, 1H), 2.47 (ddd, *J* = 7.5, 6.2, 1.4 Hz, 2H), 2.12 (d, *J* = 4.0 Hz, 1H), 1.21 – 1.11 (m, 3H), 1.10 – 1.06 (m, 18H).

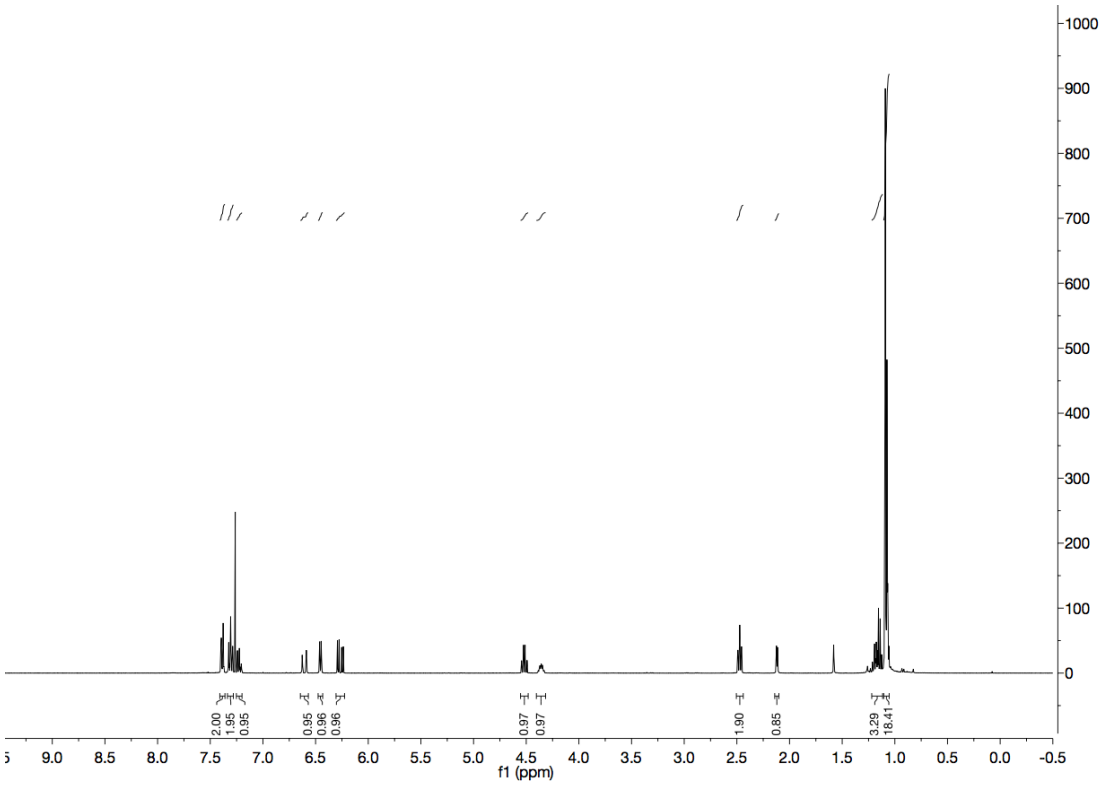
^{13}C NMR (100 MHz, $CDCl_3$): δ 141.7, 136.9, 132.3, 129.8, 128.5, 127.4, 126.5, 104.1, 72.7, 32.2, 17.7, 11.9.

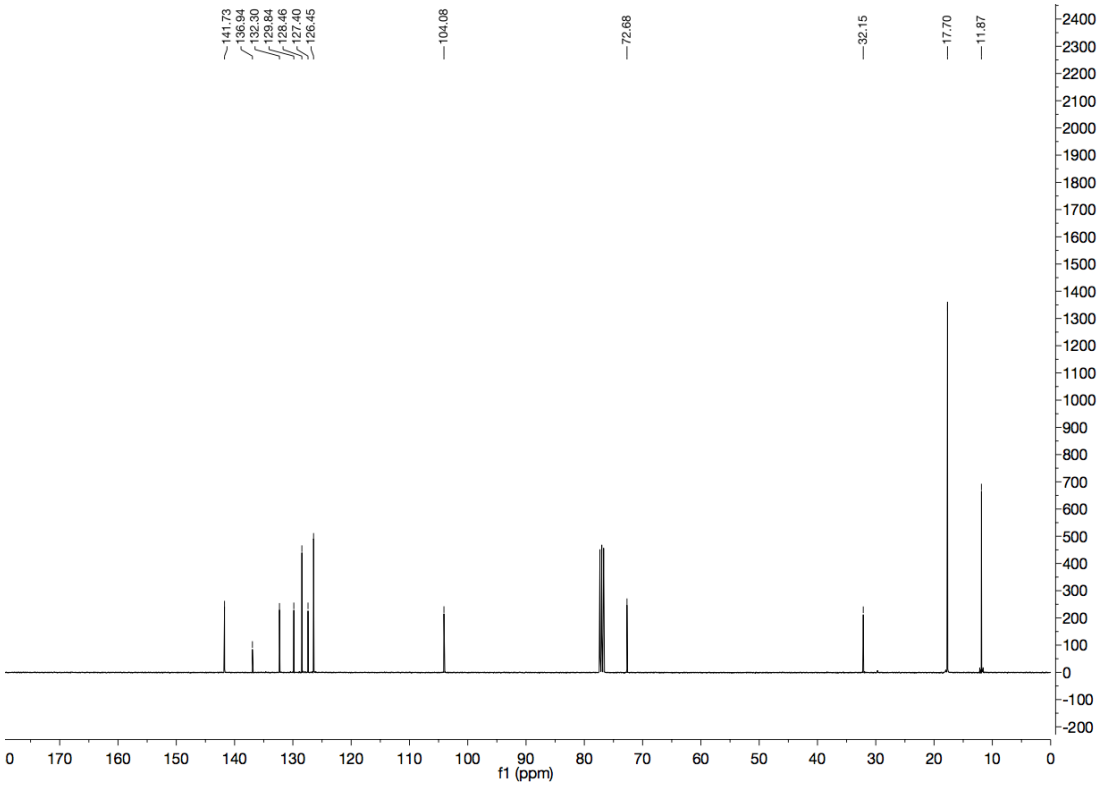
LRMS (ESI) Calcd. for $C_{21}H_{34}NaO_2Si$ $[M+Na]^+$: 369, Found: 369.

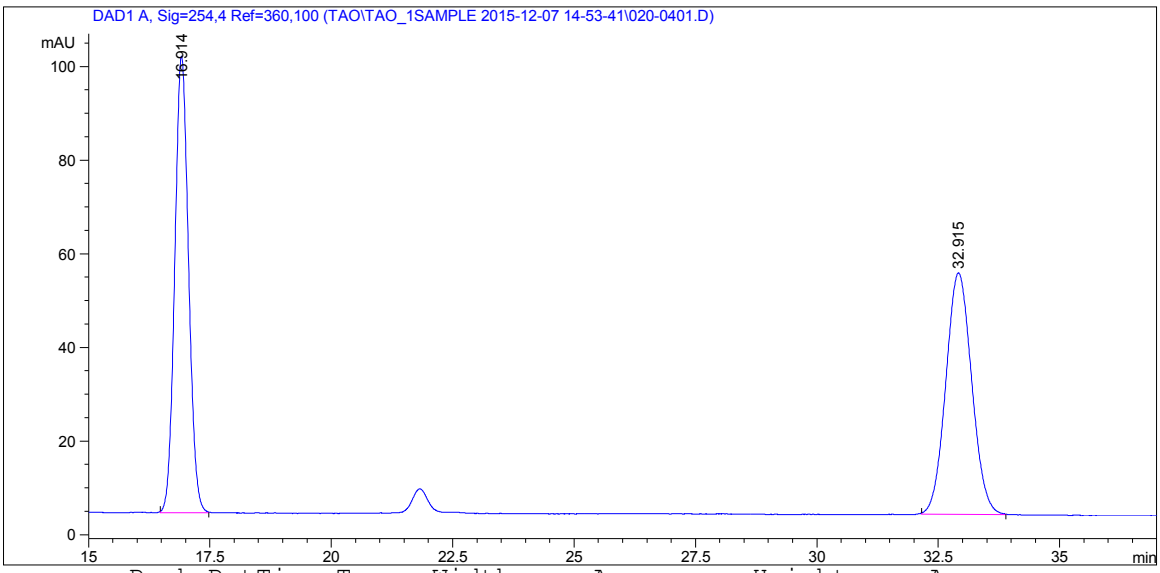
FTIR (neat): 2943, 2866, 1460, 1654, 1463, 1249, 1120, 1093, 1045, 882, 747, 688, 666 cm^{-1}.

HPLC (Chiralpak IB column, hexanes:*i*-PrOH = 99:1, 1 mL/min, 254 nm), ee = 94%.

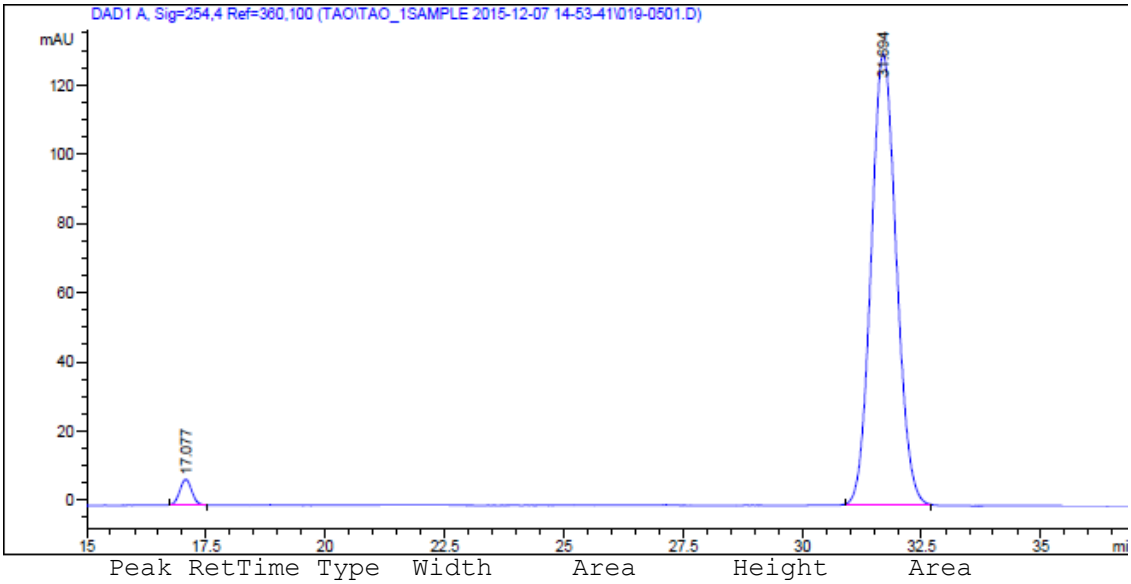
$[\alpha]^{30}_D$ = - 7.2 (c = 0.83, $CHCl_3$)


2.00
1.95
0.95
0.95
0.96
0.96
0.97
0.97
1.90
0.85
3.29
18.41
f1 (ppm)


141.73
136.94
132.30
129.84
128.46
127.40
126.45
104.08
72.68
32.15
17.70
11.87
f1 (ppm)

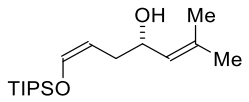


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.914	BB	0.3038	1918.98425	97.43860	50.0762
2	32.915	BB	0.5747	1913.14270	51.58790	49.9238



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.077	BB	0.2707	132.74297	7.49196	2.6963
2	31.694	BB	0.5682	4790.32129	130.51765	97.3037

(*S*,*Z*)-6-methyl-1-((triisopropylsilyl)oxy)hepta-1,5-dien-4-ol (4.3h).



In accordance with the general procedure, the title compound was obtained in 67% yield (39.9 mg, 0.134 mmol, *Z:E* = >20:1) as a yellow liquid after column chromatography (SiO_2; 6% EtOAc/hexanes).

R_f = 0.55 (20% EtOAc/Hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.41 (dt, *J* = 5.9, 1.4 Hz, 1H), 5.23 (dp, *J* = 8.6, 1.4 Hz, 1H), 4.45 (ddd, *J* = 7.7, 7.2, 5.8 Hz, 1H), 4.42 – 4.35 (m, 1H), 2.44 – 2.34 (m, 1H), 2.31 – 2.22 (m, 1H), 1.79 (d, *J* = 3.2 Hz, 1H), 1.72 (d, *J* = 1.4 Hz, 3H), 1.69 (d, *J* = 1.4 Hz, 3H), 1.19 – 1.11 (m, 3H), 1.10 – 1.07 (m, 18H).

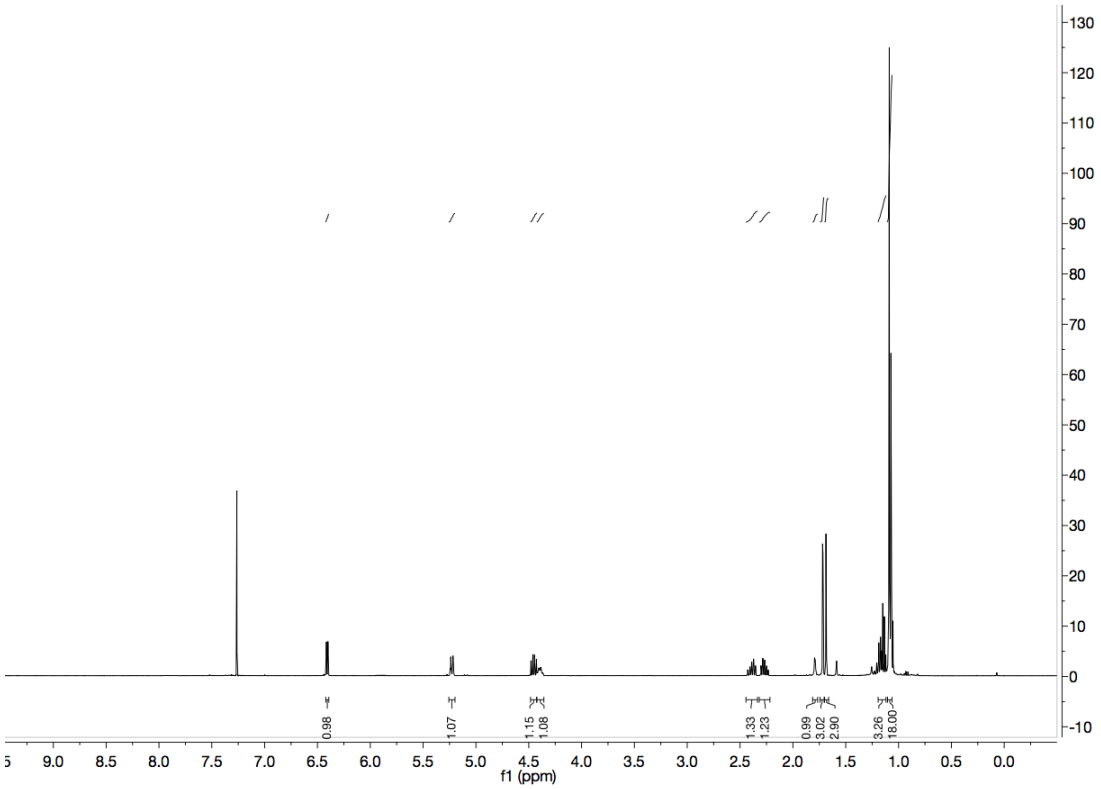
^{13}C NMR (100 MHz, $CDCl_3$): δ 141.3, 134.8, 127.8, 104.6, 68.6, 32.2, 25.8, 18.2, 17.7, 11.9.

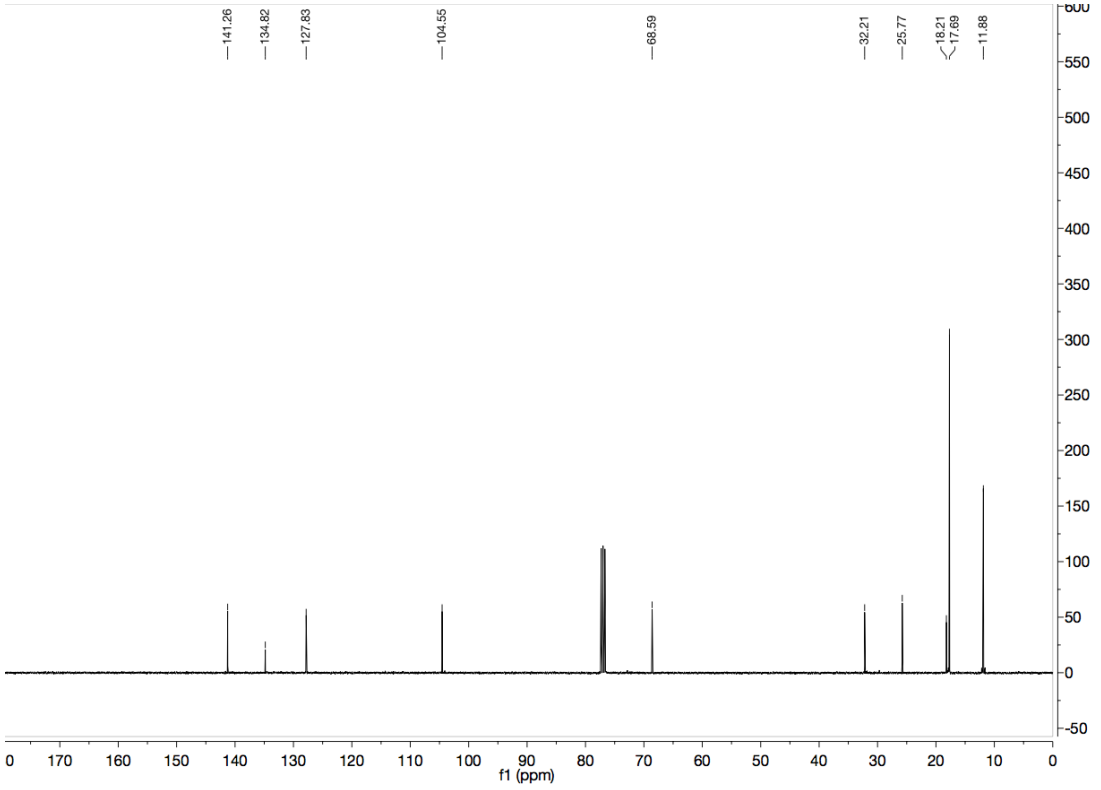
LRMS (ESI) Calcd. for $C_{17}H_{34}NaO_2Si$ $[M+Na]^+$: 321, Found: 321.

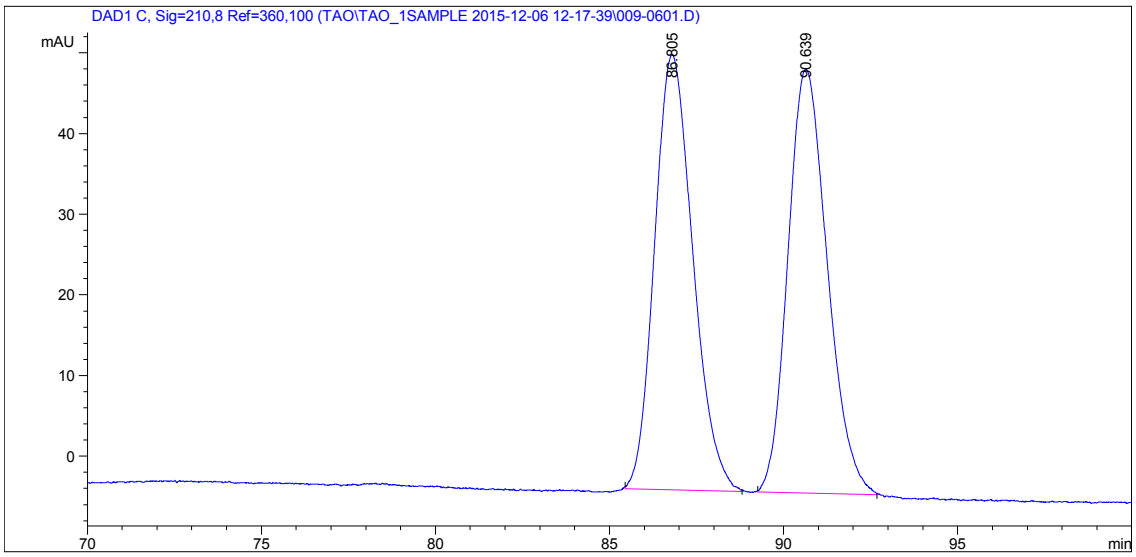
FTIR (neat): 2943, 2866, 1654, 1463, 1248, 1106, 1046, 882, 800, 684, 665 cm^{-1}.

HPLC (Chiralcel OD-H/OD-H/OD-H column, hexanes:*i*-PrOH = 99:1, 0.5 mL/min, 210 nm), ee = 96%.

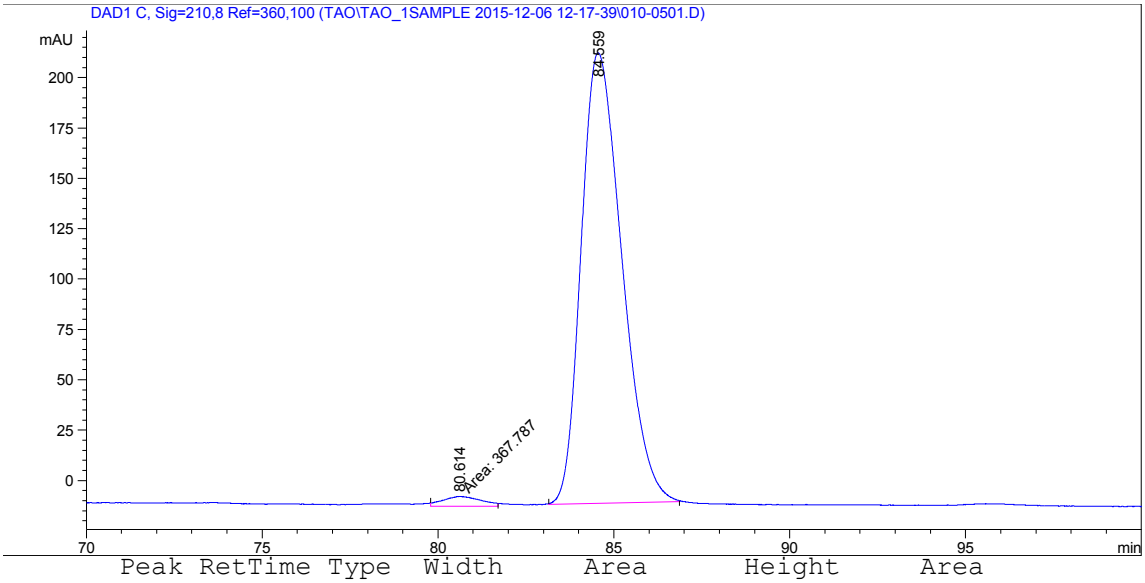
$[\alpha]^{22}_D$ = - 14.7 (c = 0.34, $CHCl_3$)


0.98
1.07
1.15
1.08
1.33
1.23
0.99
3.02
2.90
3.26
18.00
f1 (ppm)


141.26
134.82
127.83
104.55
68.59
32.21
25.77
18.21
17.69
11.88
f1 (ppm)

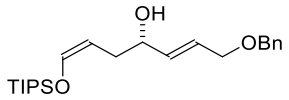


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	86.805	BB	0.9105	4125.79297	53.93298	49.9627
2	90.639	BB	0.9316	4131.96094	52.53322	50.0373



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	80.614	MM	1.2822	367.78705	4.78063	2.0068
2	84.559	BB	1.1233	1.79596e4	223.53833	97.9932

(*S*,1Z,5E)-7-(benzyloxy)-1-((triisopropylsilyl)oxy)hepta-1,5-dien-4-ol (4.3i).



In accordance with the general procedure, the title compound was obtained in 75% yield (58.5 mg, 0.15 mmol, *Z:E* = >20:1) as a yellow liquid after column chromatography (SiO_2; 7% EtOAc/hexanes).

R_f = 0.3 (50% EtOAc/Hexanes).

Spectral data is reported for the major isomer.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (d, *J* = 4.4 Hz, 4H), 7.31 – 7.27 (m, 1H), 6.43 (dt, *J* = 5.8, 1.3 Hz, 1H), 5.84 – 5.80 (m, 2H), 4.52 (s, 2H), 4.47 (td, *J* = 7.4, 5.8 Hz, 1H), 4.24 – 4.17 (m, 1H), 4.03 (dd, *J* = 4.2, 0.9 Hz, 2H), 2.38 (ddd, *J* = 7.5, 6.3, 1.4 Hz, 2H), 2.02 (d, *J* = 4.1 Hz, 1H), 1.19 – 1.11 (m, 3H), 1.08 (d, *J* = 6.4 Hz, 18H).

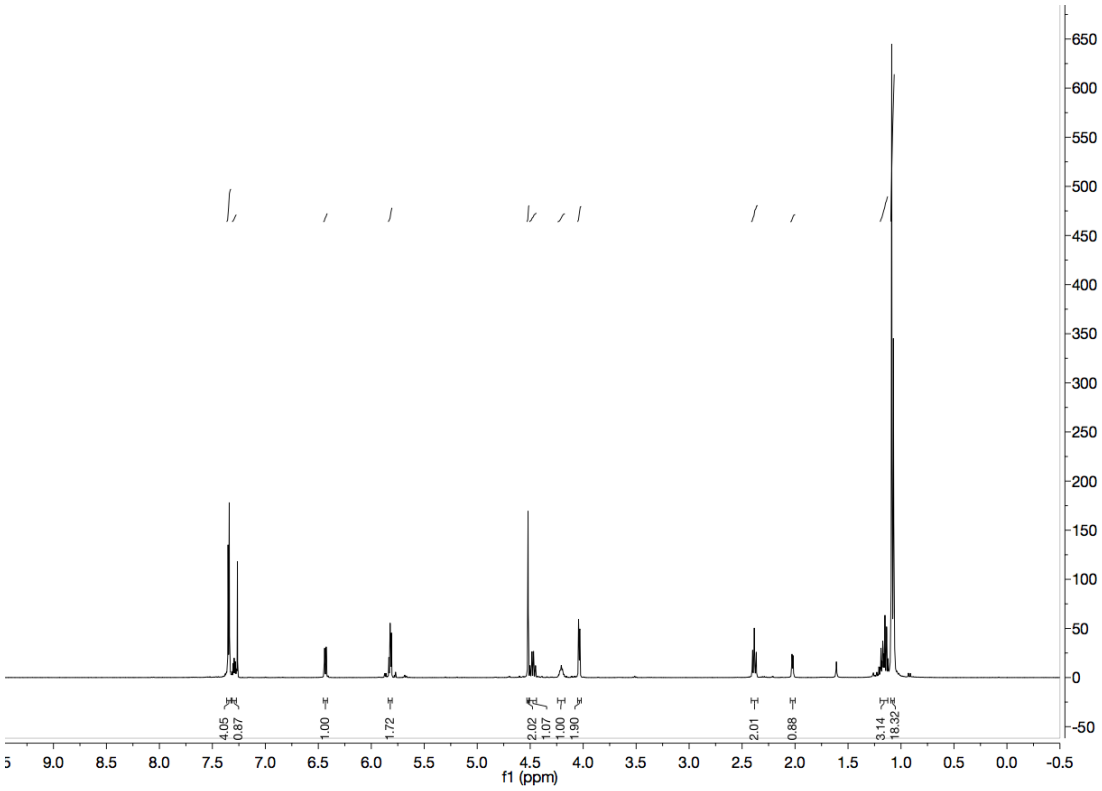
^{13}C NMR (100 MHz, $CDCl_3$): δ 141.6, 138.3, 135.8, 128.3, 127.8, 127.6, 126.8, 104.1, 72.1, 72.0, 70.3, 31.9, 17.7, 11.9.

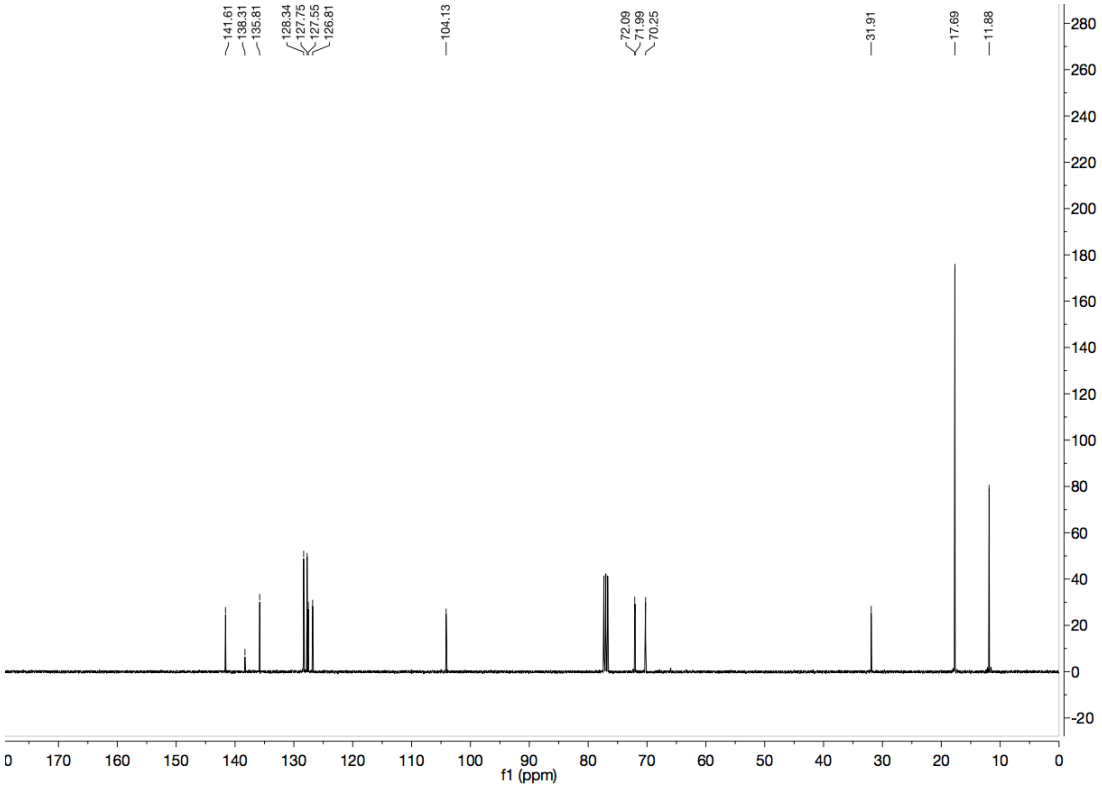
LRMS (ESI) Calcd. for $C_{23}H_{38}NaO_3Si$ $[M+Na]^+$: 413, Found: 413.

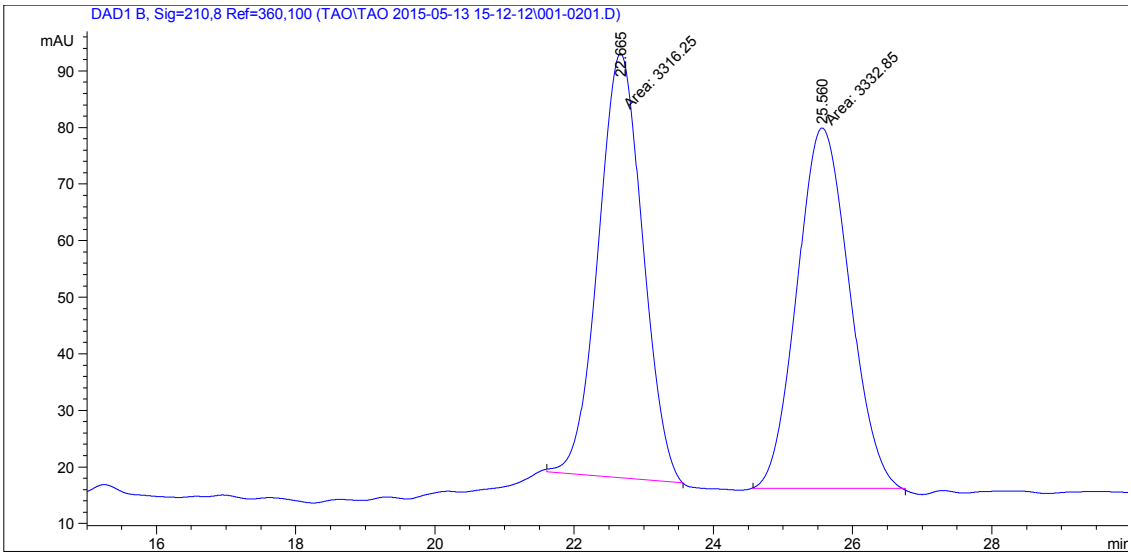
FTIR (neat): 2943, 2866, 1653, 1463, 1248, 1095, 1066, 882, 735, 685, 666 cm^{-1}.

HPLC (Chiralcel OD-H column, hexanes:*i*-PrOH = 99:1, 1 mL/min, 254 nm), ee = 92%.

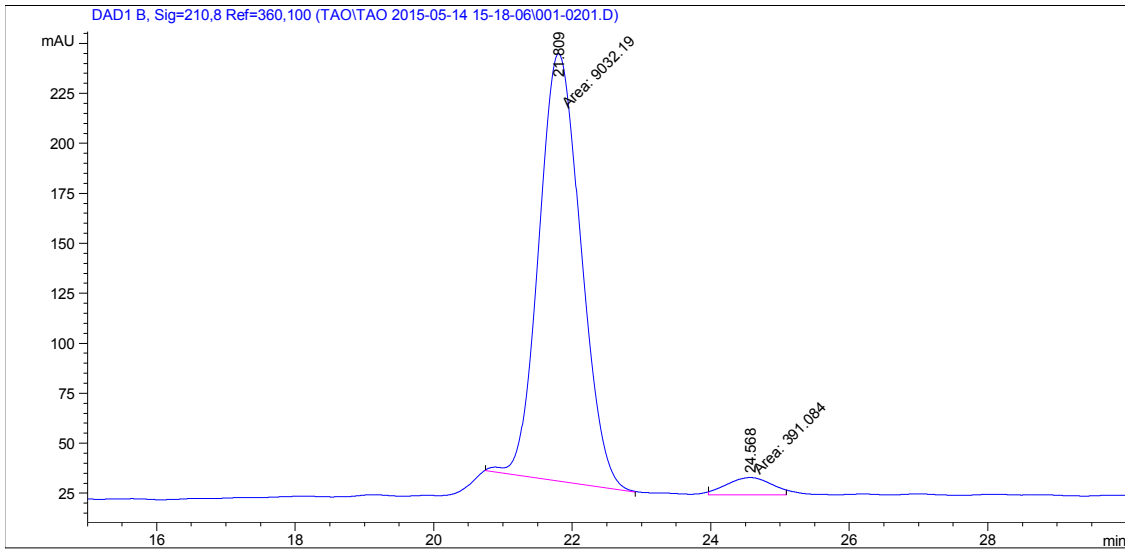
$[\alpha]^{24}_D$ = + 1.3 (c = 0.77, $CHCl_3$)


4.05
0.87
1.00
1.72
2.02
1.07
1.00
1.90
2.01
0.88
3.14
18.32
f1 (ppm)


141.61
138.31
135.81
128.34
127.75
127.55
126.81
104.13
72.09
71.99
70.25
31.91
17.69
11.88
f1 (ppm)

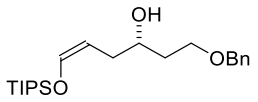


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.665	MM	0.7374	3316.25366	74.95737	49.8752
2	25.560	MM	0.8720	3332.84961	63.69908	50.1248



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.809	MM	0.7037	9032.18750	213.91315	95.8498
2	24.568	MM	0.7473	391.08380	8.72204	4.1502

(*S*,*Z*)-1-(benzyloxy)-6-((triisopropylsilyl)oxy)hex-5-en-3-ol (4.3j).



In accordance with the general procedure, the title compound was obtained in 68% yield (51.4 mg, 0.136 mmol, *Z:E* = >20:1) as a yellow liquid after column chromatography (SiO_2; 8% EtOAc/hexanes).

R_f = 0.35 (20% EtOAc/Hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.35 – 7.27 (m, 5H), 6.40 (dt, *J* = 5.9, 1.4 Hz, 1H), 4.54 – 4.51 (m, 2H), 4.47 (td, *J* = 7.4, 5.8 Hz, 1H), 3.89 – 3.82 (m, 1H), 3.75 – 3.69 (m, 1H), 3.68 – 3.61 (m, 1H), 2.84 (d, *J* = 3.2 Hz, 1H), 2.38 – 2.27 (m, 2H), 1.84 – 1.74 (m, 2H), 1.19 – 1.11 (m, 3H), 1.07 (d, *J* = 6.4 Hz, 18H).

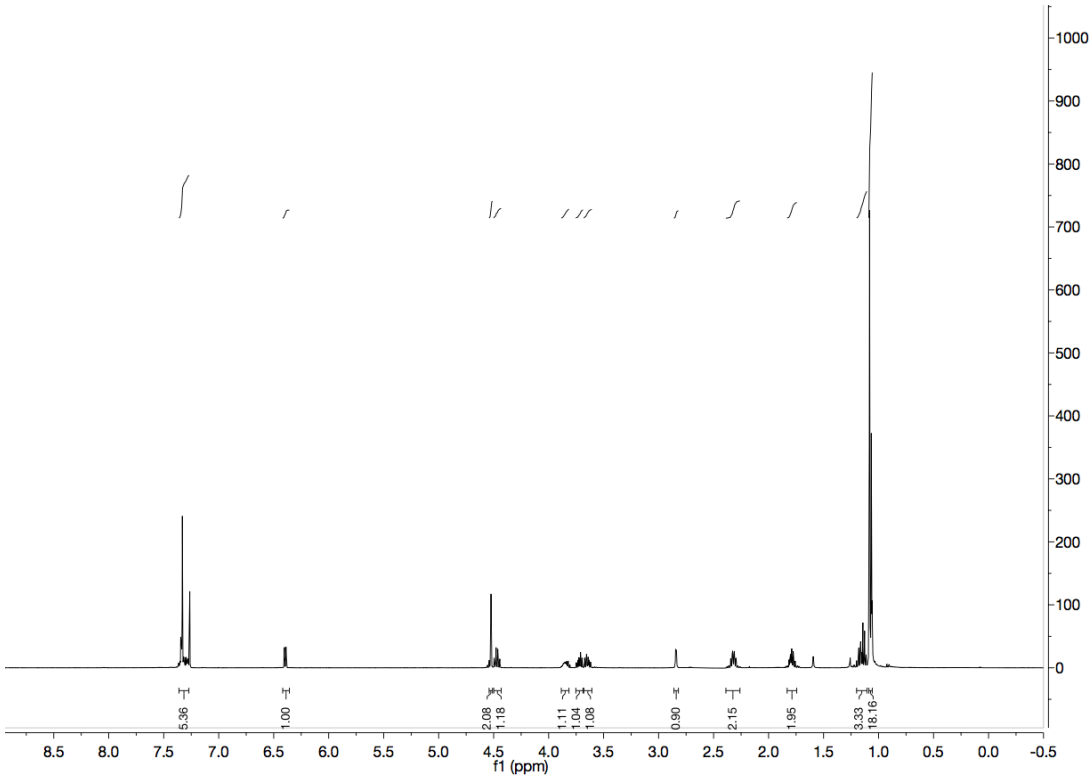
^{13}C NMR (100 MHz, $CDCl_3$): δ 141.02, 138.14, 128.39, 127.62, 127.61, 104.91, 73.23, 71.02, 69.00, 36.02, 31.73, 17.71, 11.88.

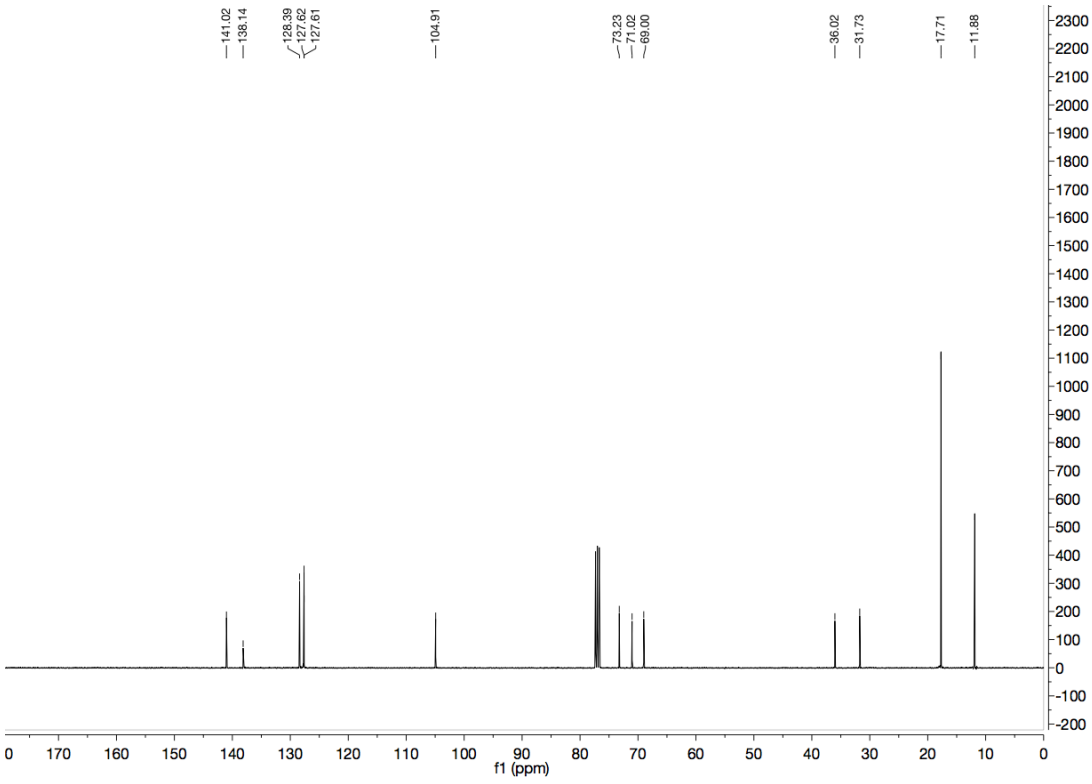
LRMS (ESI) Calcd. for $C_{22}H_{38}NaO_3Si$ $[M+Na]^+$: 401, Found: 401.

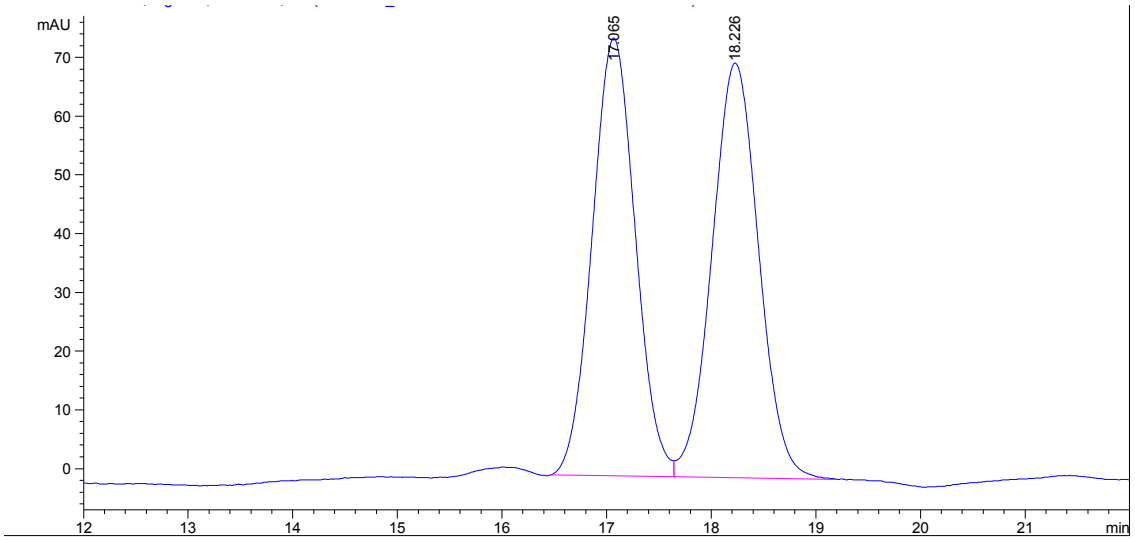
FTIR (neat): 2943, 2866, 1654, 1085, 882, 735, 687, 669 cm^{-1}.

HPLC (Chiralcel AD-H/AD-H column, hexanes:*i*-PrOH = 99:1, 1 mL/min, 210 nm), ee = 85%.

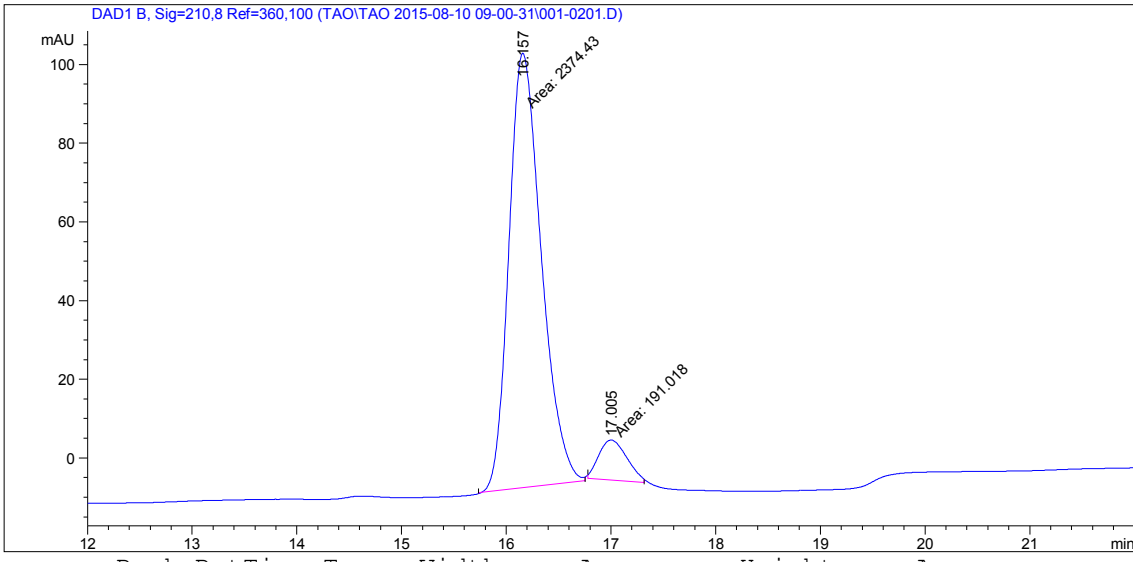
$[\alpha]^{25}_D$ = + 3.5 (c = 0.51, $CHCl_3$)


5.36
1.00
2.08
1.18
1.11
1.04
1.08
0.90
2.15
1.95
3.33
18.16
f1 (ppm)


141.02
138.14
128.39
127.62
127.61
104.91
73.23
71.02
69.00
36.02
31.73
17.71
11.88
f1 (ppm)

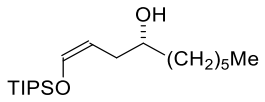


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.065	BV	0.4444	2136.06885	74.53375	49.3446
2	18.226	VB	0.4783	2192.80786	70.60277	50.6554



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.157	MM	0.3582	2374.43384	110.47179	92.5542
2	17.005	MM	0.3118	191.01845	10.21050	7.4458

(*R*,Z)-1-((triisopropylsilyl)oxy)dec-1-en-4-ol (4.3k).



In accordance with the general procedure, the title compound was obtained in 64% yield (42.0 mg, 0.128 mmol, *Z:E* = >20:1) as a yellow liquid after column chromatography (SiO_2; 4% EtOAc/hexanes).

R_f = 0.6 (20% EtOAc/Hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.43 (dt, *J* = 5.8, 1.3 Hz, 1H), 4.48 (td, *J* = 7.5, 5.8 Hz, 1H), 3.69 – 3.59 (m, 1H), 2.34 – 2.20 (m, 2H), 1.84 (d, *J* = 4.0 Hz, 1H), 1.49 – 1.40 (m, 3H), 1.36 – 1.24 (m, 7H), 1.20 – 1.12 (m, 3H), 1.08 (d, *J* = 6.4 Hz, 18H), 0.91 – 0.84 (m, 3H).

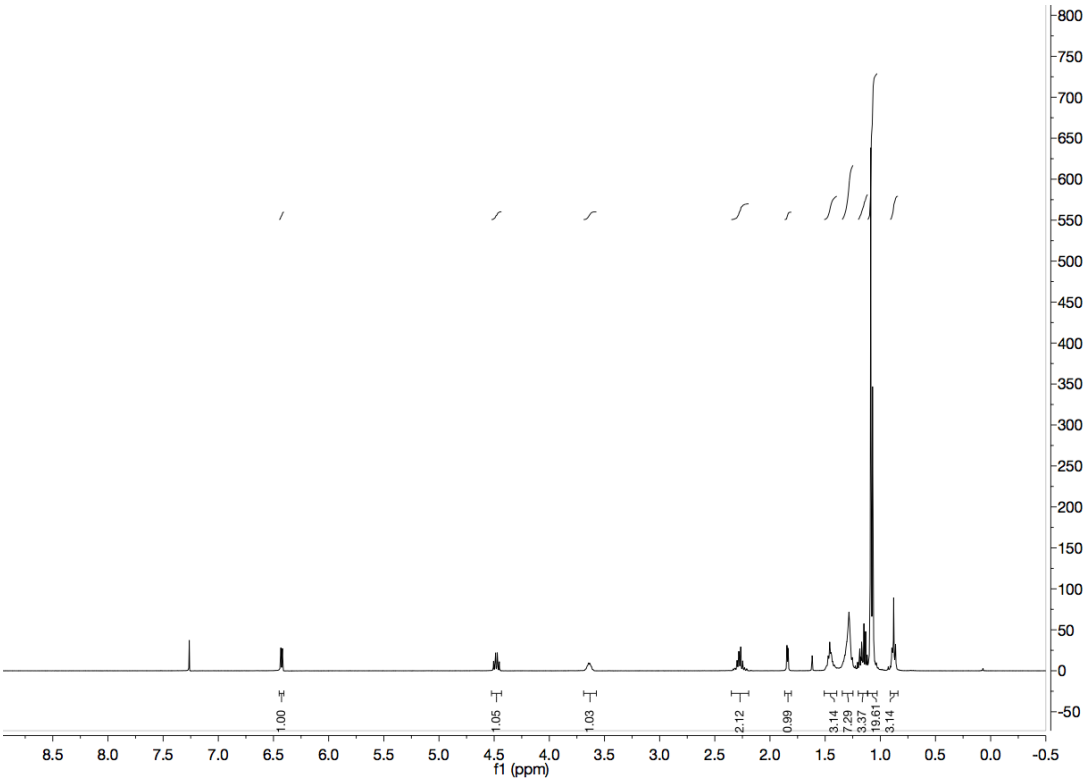
^{13}C NMR (100 MHz, $CDCl_3$): δ 141.3, 104.9, 71.9, 37.0, 31.9, 31.8, 29.4, 25.7, 22.6, 17.7, 14.1, 11.9.

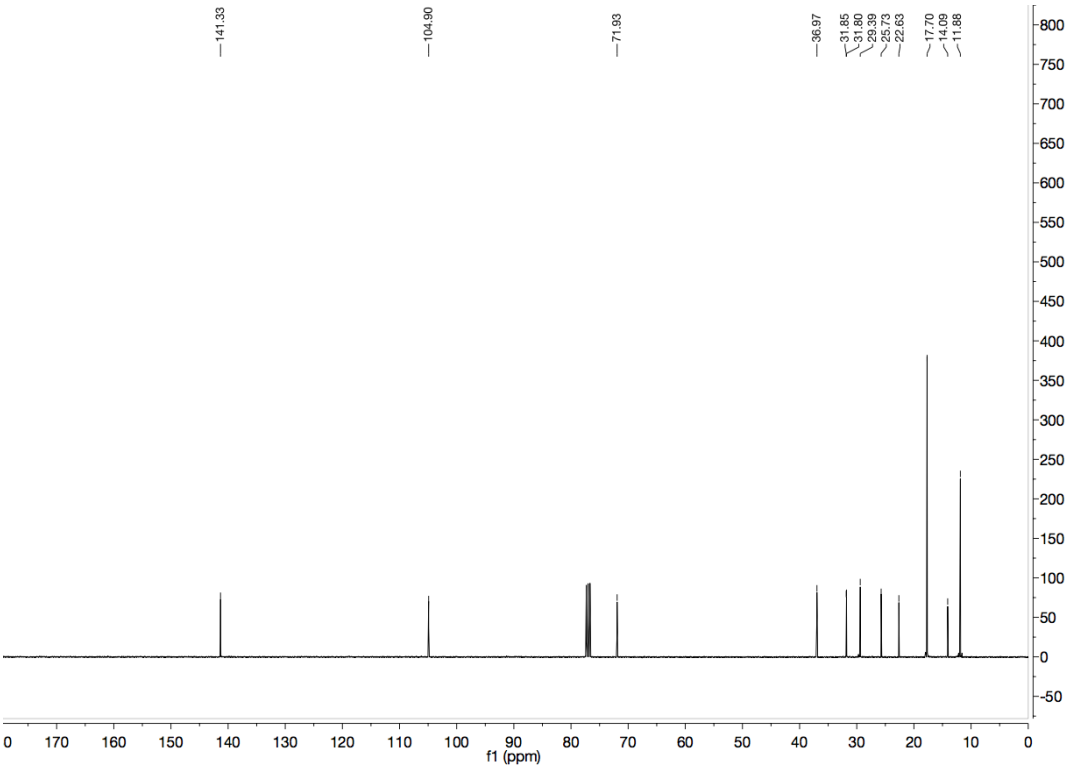
LRMS (ESI) Calcd. for $C_{19}H_{40}NaO_2Si$ $[M+Na]^+$: 351.3, Found: 351.3.

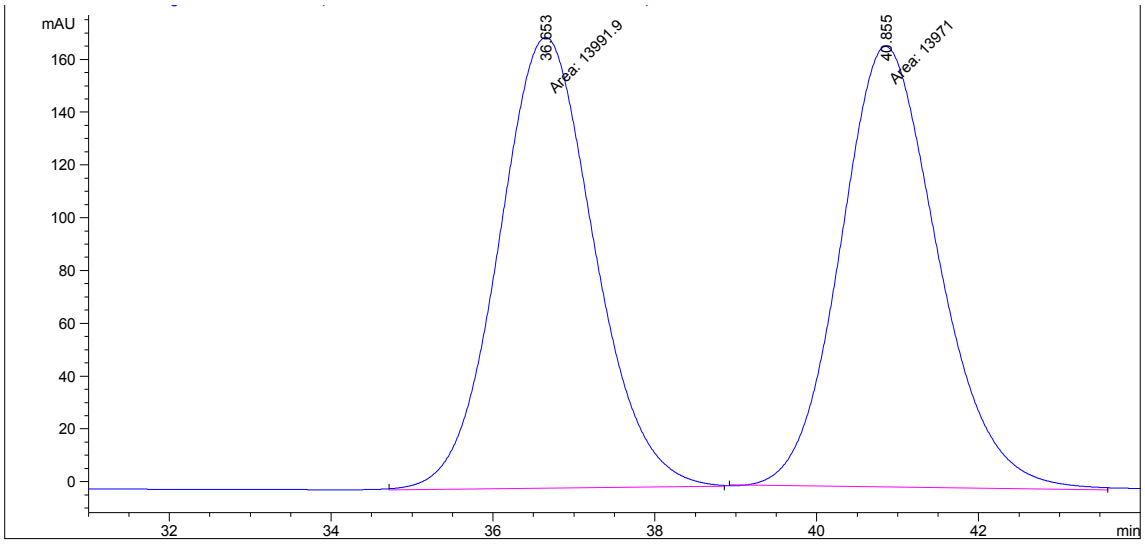
FTIR (neat): 2928, 2867, 1654, 1464, 1258, 1104, 1055, 882, 684, 666 cm^{-1}.

HPLC (Chiralcel AD-H column/AD-H column/AD-H column, hexanes:*i*-PrOH = 99.7:0.3, 0.5 mL/min, 210 nm), ee = 90%.

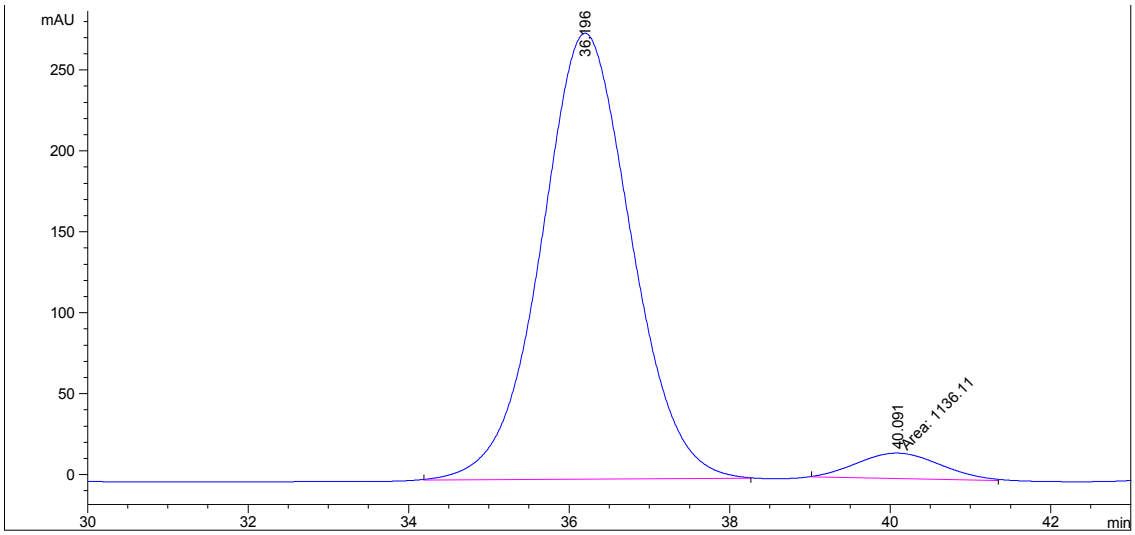
$[\alpha]^{25}_D$ = + 1.0 (c = 0.99, $CHCl_3$)


1.00
1.05
1.03
2.12
0.99
3.14
7.29
3.37
19.61
3.14
f1 (ppm)


141.33
104.90
71.93
36.97
31.85
31.80
29.39
25.73
22.63
17.70
14.09
11.88
f1 (ppm)

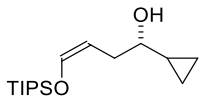


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	36.653	MM	1.3654	1.39919e4	170.78845	50.0372
2	40.855	MM	1.3957	1.39710e4	166.83641	49.9628



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	36.196	BB	1.1955	2.14855e4	275.60040	94.9778
2	40.091	MM	1.2029	1136.10657	15.74072	5.0222

(*S*,*Z*)-1-cyclopropyl-4-((triisopropylsilyl)oxy)but-3-en-1-ol (4.3l).



In accordance with the general procedure, the title compound was obtained in 63% yield (35.8 mg, 0.126 mmol, *Z:E* = >20:1) as a yellow liquid after column chromatography (SiO_2; 5% EtOAc/hexanes).

R_f = 0.55 (20% EtOAc/Hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.42 (dt, *J* = 5.8, 1.3 Hz, 1H), 4.55 (td, *J* = 7.5, 5.8 Hz, 1H), 2.98 – 2.89 (m, 1H), 2.45 – 2.40 (m, 2H), 1.98 (d, *J* = 3.3 Hz, 1H), 1.20 – 1.13 (m, 3H), 1.10 – 1.07 (m, 18H), 0.98 – 0.89 (m, 1H), 0.53 – 0.44 (m, 2H), 0.36 – 0.28 (m, 1H), 0.24 – 0.17 (m, 1H).

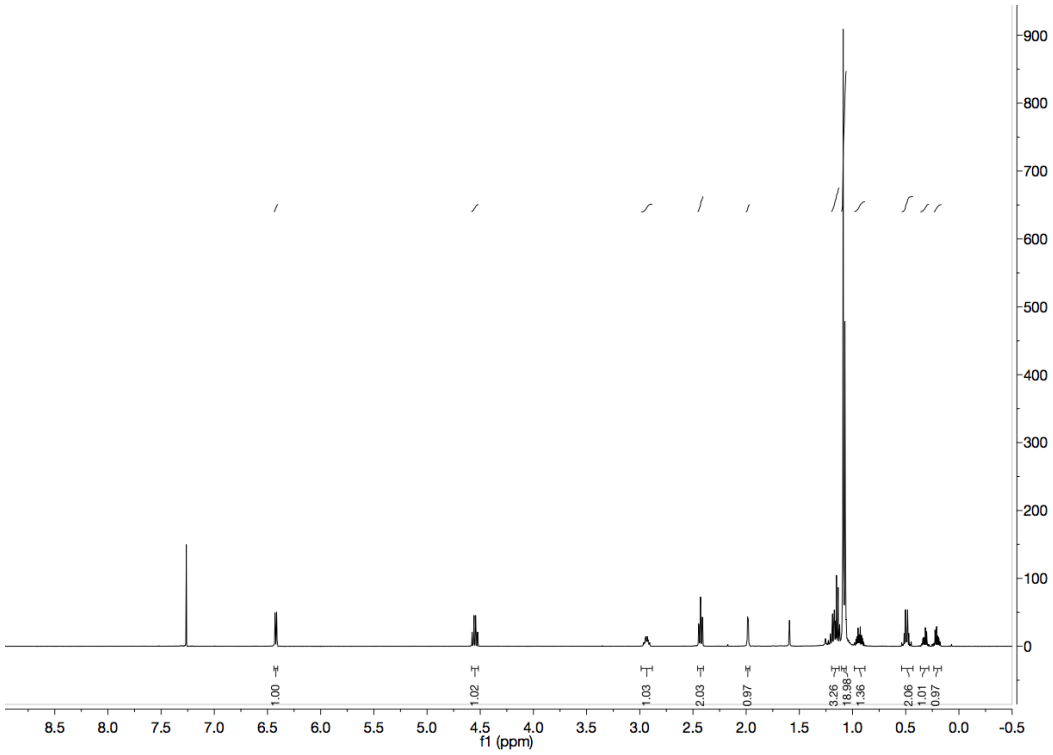
^{13}C NMR (100 MHz, $CDCl_3$): δ 141.2, 105.0, 31.7, 17.7, 17.3, 11.9, 2.7, 2.3.

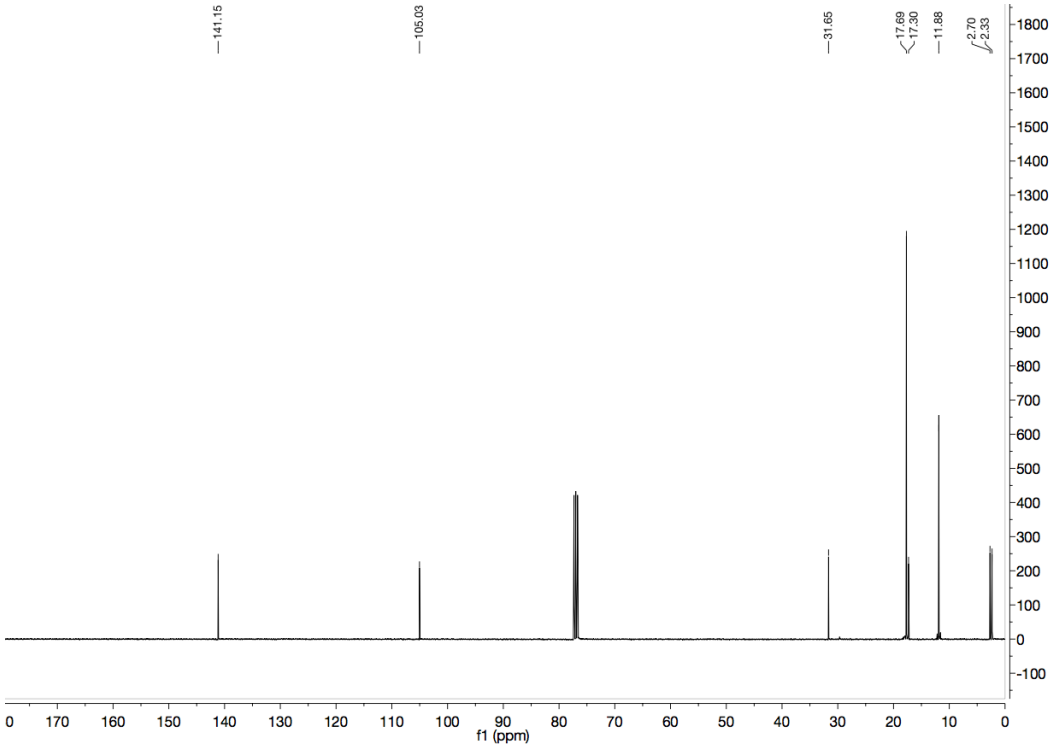
LRMS (ESI) Calcd. for $C_{16}H_{32}NaO_2Si$ $[M+Na]^+$: 307.2, Found: 307.2.

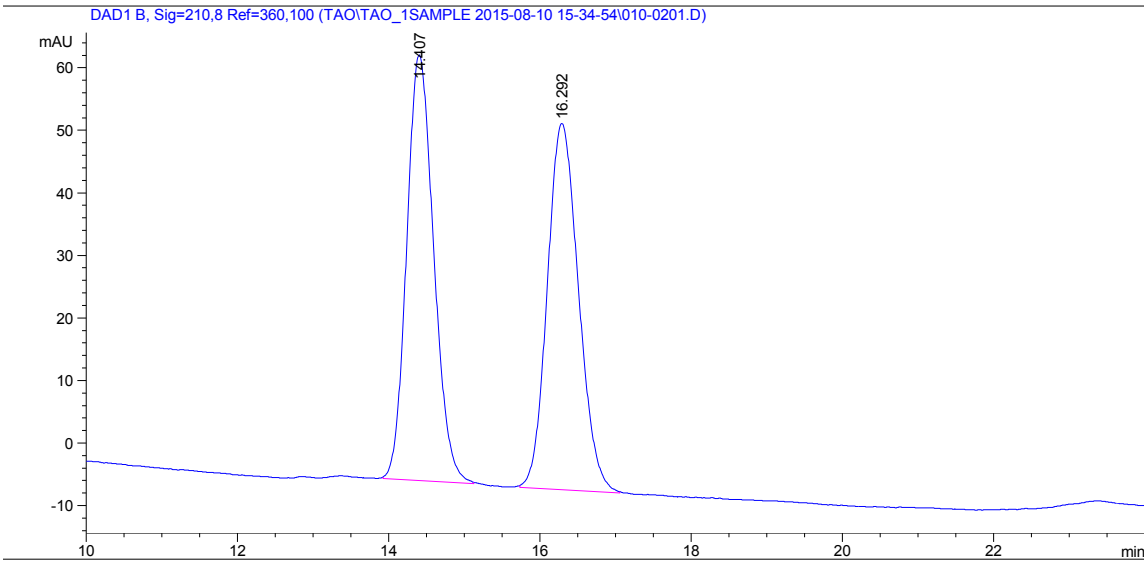
FTIR (neat): 2944, 2867, 1655, 1464, 1252, 1113, 1058, 882, 683, 669 cm^{-1}.

HPLC (Chiralcel OD-H column, hexanes:*i*-PrOH = 99:1, 1 mL/min, 210 nm), ee = 95%.

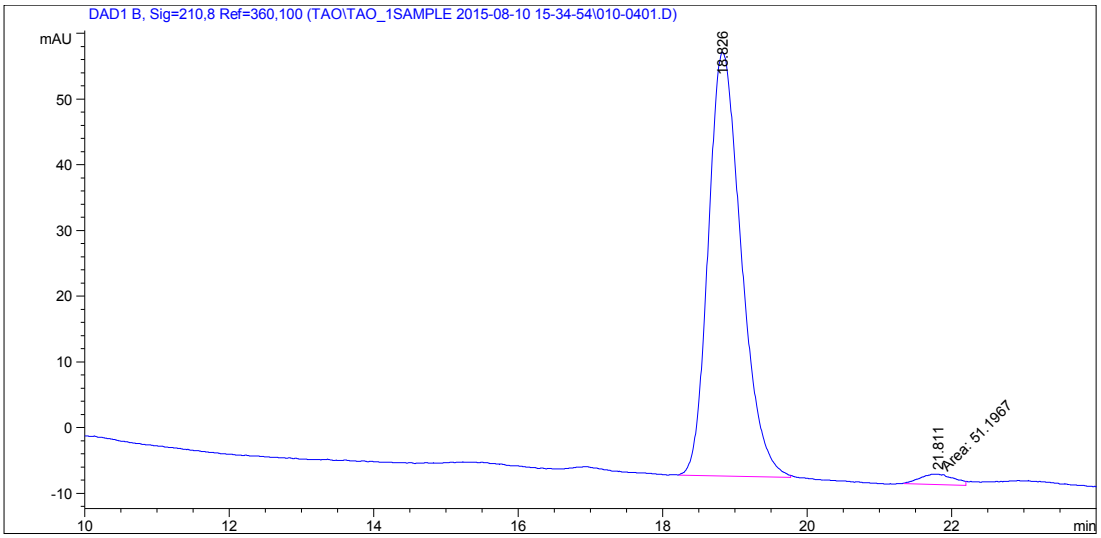
$[\alpha]^{25}_D$ = + 2.4 (c = 0.41, $CHCl_3$)


1.00
1.02
1.03
2.03
0.97
3.26
18.98
1.36
2.06
1.01
0.97
f1 (ppm)


141.15
105.03
31.65
17.69
17.30
11.88
2.70
2.33
f1 (ppm)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.407	BB	0.3855	1688.31445	68.03547	50.1816
2	16.292	BB	0.4481	1676.09619	58.52392	49.8184

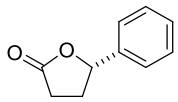


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.826	BB	0.4891	2040.42163	64.50284	97.5523
2	21.811	MM	0.5485	51.19666	1.55563	2.4477

General Procedure and Preparation of 4.4a, 4.4c, 4.4e, 4.4f, 4.4h, 4.4j

To a solution of adduct **4.3** (0.20 mmol) in THF (1 mL) at 0 °C was added TBAF (0.22 mL, 110 mol%, 1M in THF) via syringe. The mixture was stirred at 0 °C for 30 min, at which point water was added and the mixture was extracted by DCM (3 x 1 mL). The organic layer was washed by brine, dried (Na_2SO_4) and filtered with the aid of DCM. The filtrate was evaporated to 2 mL and 4 Å MS (100 mg), NaOAc (8.2 mg, 0.10 mmol) and PCC (86.2 mg, 0.40 mmol) were added, and the mixture was stirred at room temperature for 24 hours. The solvents were removed *in vacuo* and the residue was subjected to column chromatography (SiO_2) to afford the corresponding lactone products.

(*S*)-5-phenyldihydrofuran-2(3H)-one (4.4a).



In accordance with the general procedure, the title compound was obtained in 73% yield (23.7 mg, 0.146 mmol) as a colorless liquid after column chromatography (SiO_2; 12% EtOAc/hexanes).

R_f = 0.2 (20% EtOAc/Hexanes).

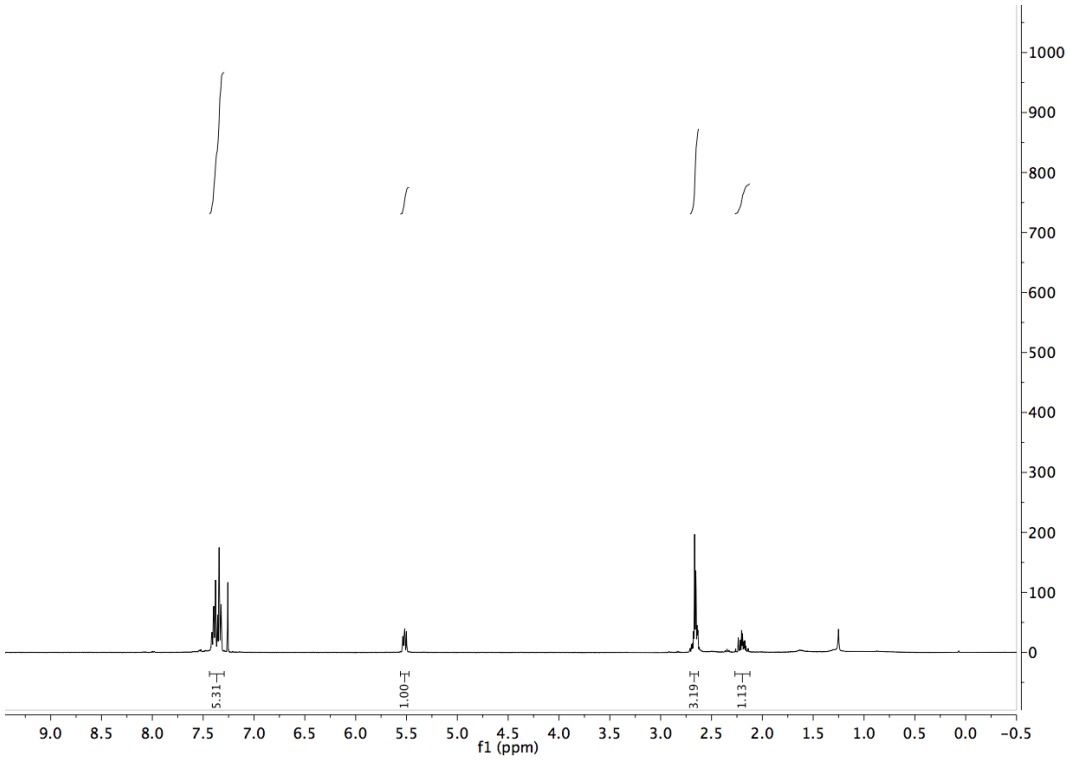
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.30 (m, 5H), 5.52 (t, *J* = 6.8 Hz, 1H), 2.71 – 2.62 (m, 3H), 2.27 – 2.13 (m, 1H).

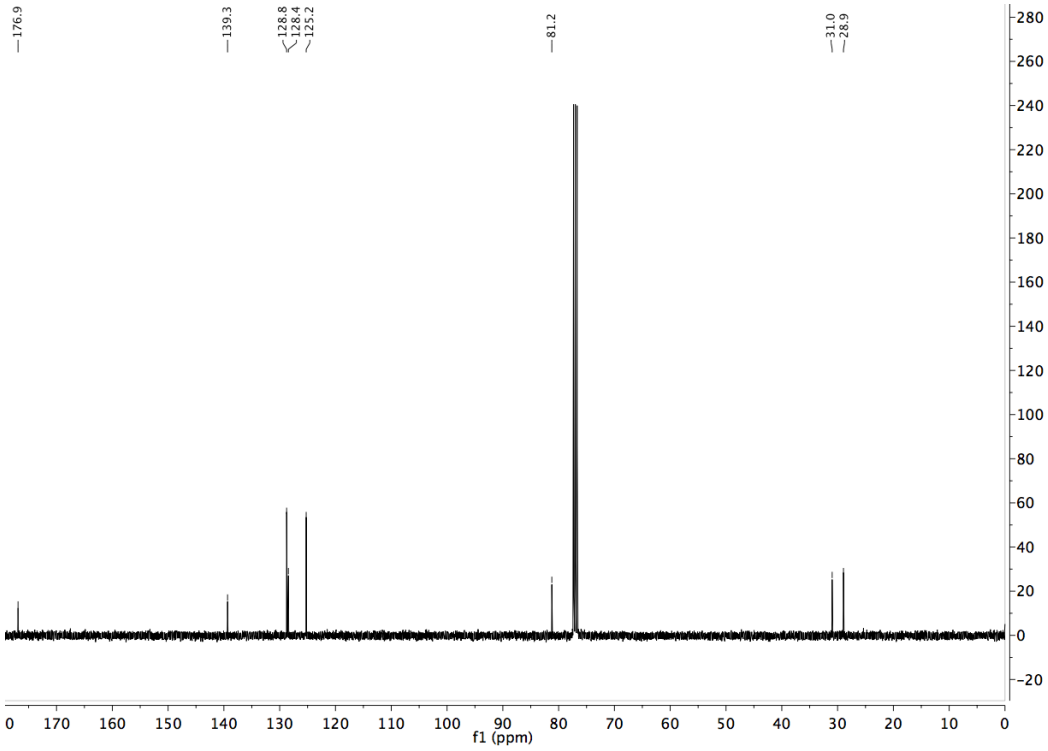
^{13}C NMR (100 MHz, $CDCl_3$): δ 176.9, 139.3, 128.8, 128.4, 125.3, 81.2, 31.0, 29.0.

LRMS (CI) Calcd. for $C_{10}H_{11}O_2$ $[M+H]^+$: 163, Found: 163.

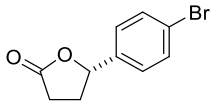
FTIR (neat): 1770, 1365, 1216, 1176, 1141, 1019, 940, 759, 700 cm^{-1}.

$[\alpha]^{25}_D$ = -48.9 (c = 0.3, $CHCl_3$)


5.31
1.00
3.19
1.13
f1 (ppm)


176.9
139.3
128.8
128.4
125.2
81.2
31.0
28.9
f1 (ppm)

(*S*)-5-(4-bromophenyl)dihydrofuran-2(3H)-one (4.4c).



In accordance with the general procedure, the title compound was obtained in 87% yield (41.8 mg, 0.174 mmol) after column chromatography (SiO_2; 12% EtOAc/hexanes).

R_f = 0.2 (20% EtOAc/Hexanes).

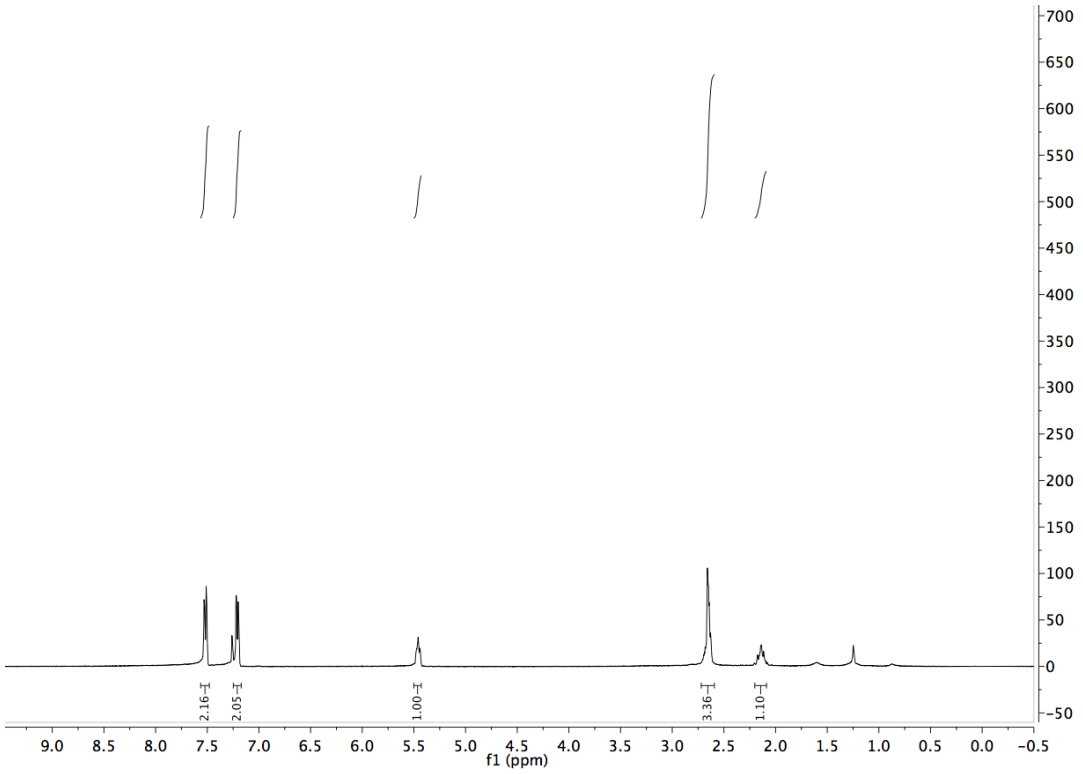
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.49 (m, 2H), 7.24 – 7.18 (m, 2H), 5.46 (t, *J* = 6.3 Hz, 1H), 2.72 – 2.61 (m, 3H), 2.21 – 2.06 (m, 1H).

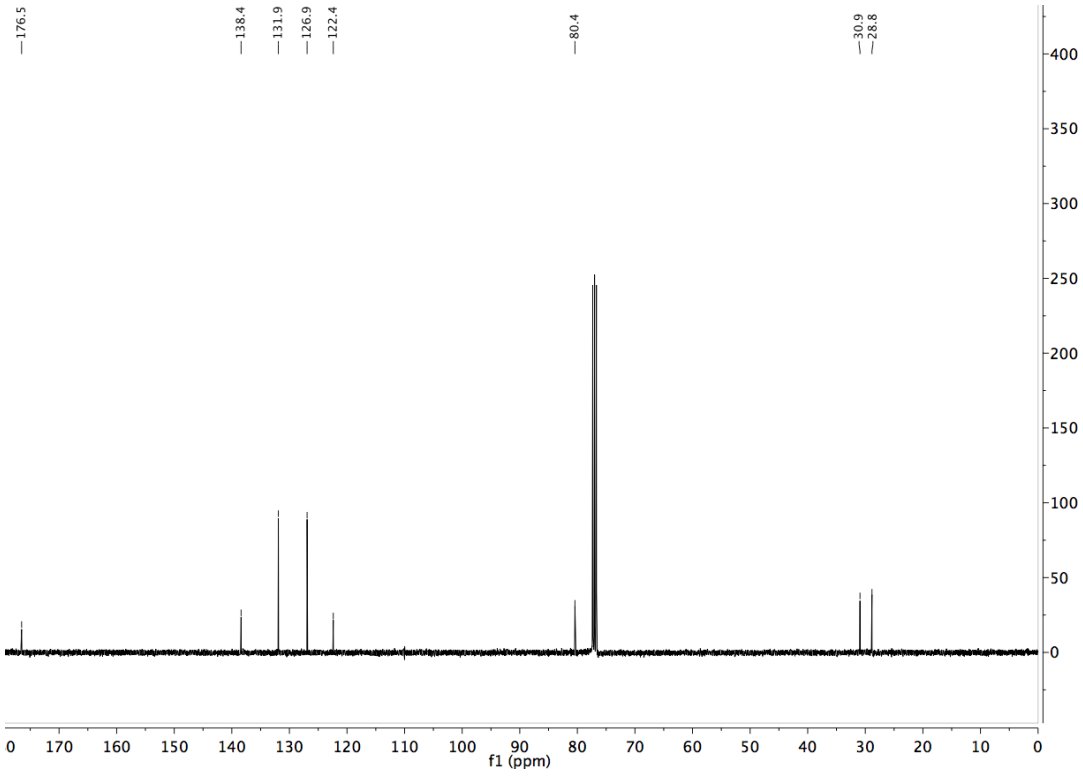
^{13}C NMR (100 MHz, $CDCl_3$): δ 176.5, 138.4, 131.9, 126.9, 122.4, 80.4, 30.9, 28.8.

LRMS (ESI) Calcd. for $C_{10}H_{10}BrO_2$ $[M+H]^+$: 241, Found: 241.

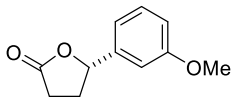
FTIR (neat): 1771, 1365, 1216, 1173, 1140, 1010, 938, 806 cm^{-1}.

$[\alpha]^{25}_D$ = -32.0 (c = 0.5, $CHCl_3$)


2.16
2.05
1.00
3.36
1.10
f1 (ppm)


176.5
138.4
131.9
126.9
122.4
80.4
30.9
28.8
f1 (ppm)

(*S*)-5-(3-methoxyphenyl)dihydrofuran-2(3H)-one (4.4e).



In accordance with the general procedure, the title compound was obtained in 85% yield (32.6 mg, 0.17 mmol) as a colorless liquid after column chromatography (SiO_2; 14% EtOAc/hexanes).

R_f = 0.15 (20% EtOAc/Hexanes).

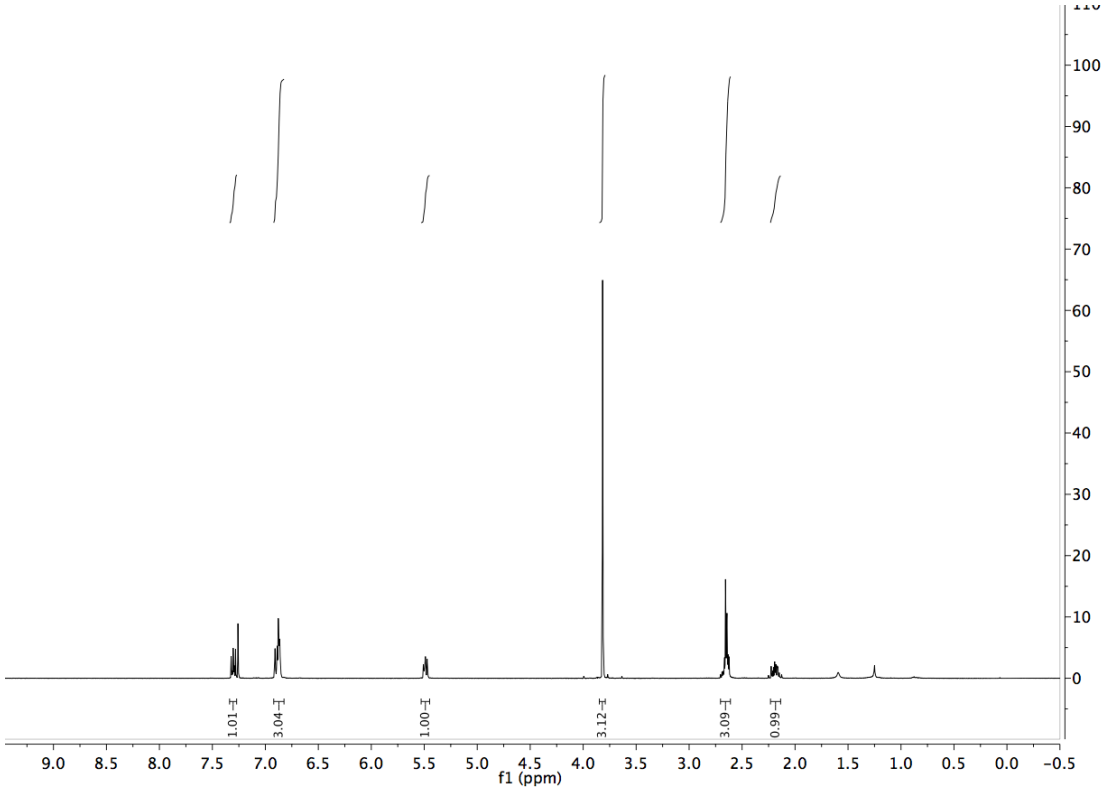
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.27 (m, 1H), 6.92 – 6.83 (m, 3H), 5.49 (dd, *J* = 8.0, 6.1 Hz, 1H), 3.82 (s, 3H), 2.71 – 2.60 (m, 3H), 2.24 – 2.13 (m, 1H).

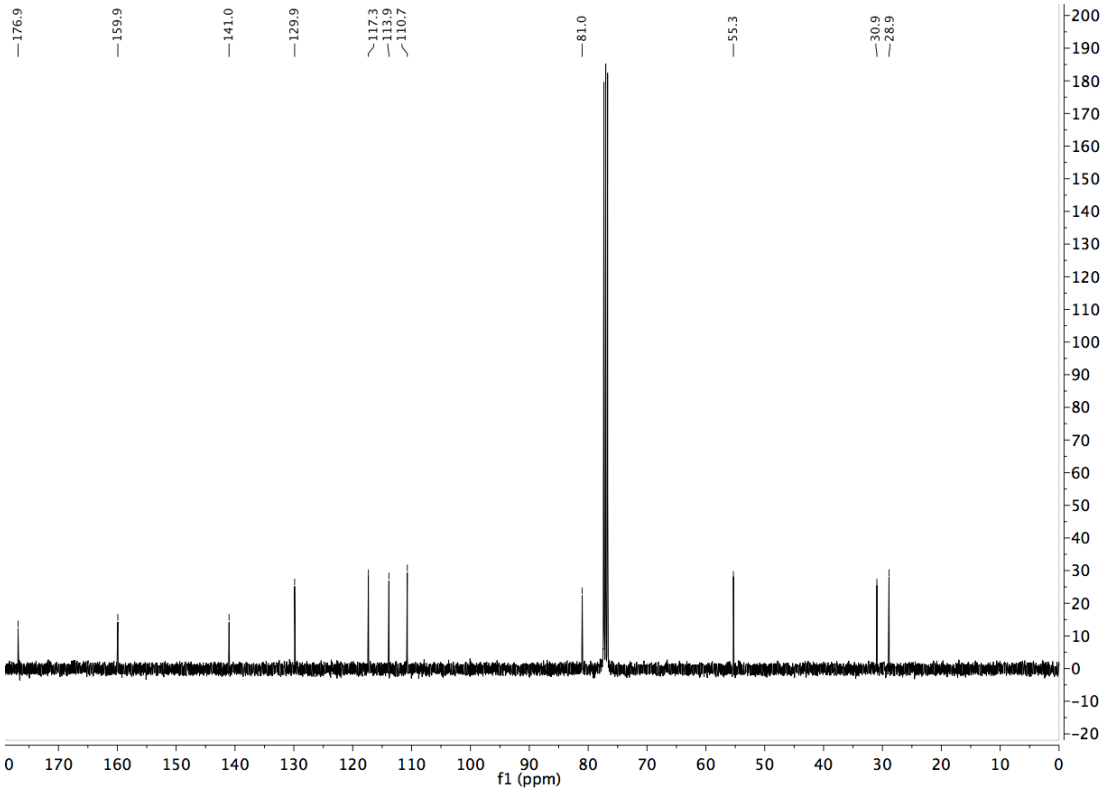
^{13}C NMR (100 MHz, $CDCl_3$): δ 176.9, 159.9, 141.0, 129.9, 117.3, 113.9, 110.7, 81.0, 55.3, 31.0, 28.9.

LRMS (ESI) Calcd. for $C_{11}H_{13}O_3$ $[M+H]^+$: 193, Found: 193.

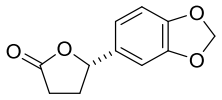
FTIR (neat): 1772, 1262, 1157, 1140, 1031, 909, 789, 698 cm^{-1}.

$[\alpha]^{25}_D$ = -32.3 (c = 0.35, $CHCl_3$)


1.01
3.04
1.00
3.12
3.09
0.99
f1 (ppm)


176.9
159.9
141.0
129.9
117.3
113.9
110.7
81.0
55.3
30.9
28.9
f1 (ppm)

(*S*)-5-(benzo[d][1,3]dioxol-5-yl)dihydrofuran-2(3H)-one (4.4f).



In accordance with the general procedure, the title compound was obtained in 79% yield (32.5 mg, 0.158 mmol) as a colorless liquid after column chromatography (SiO_2; 14% EtOAc/hexanes).

R_f = 0.15 (20% EtOAc/Hexanes).

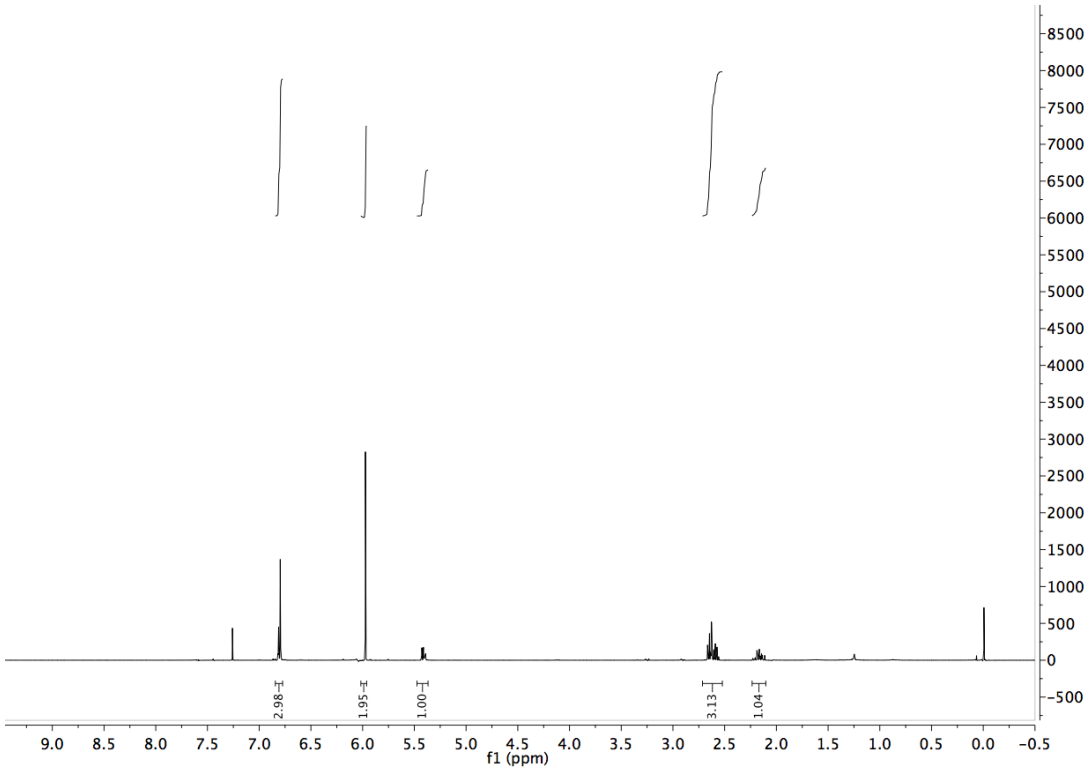
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 – 6.78 (m, 3H), 5.97 (s, 2H), 5.41 (dd, *J* = 8.5, 6.3 Hz, 1H), 2.67 – 2.55 (m, 3H), 2.24 – 2.10 (m, 1H).

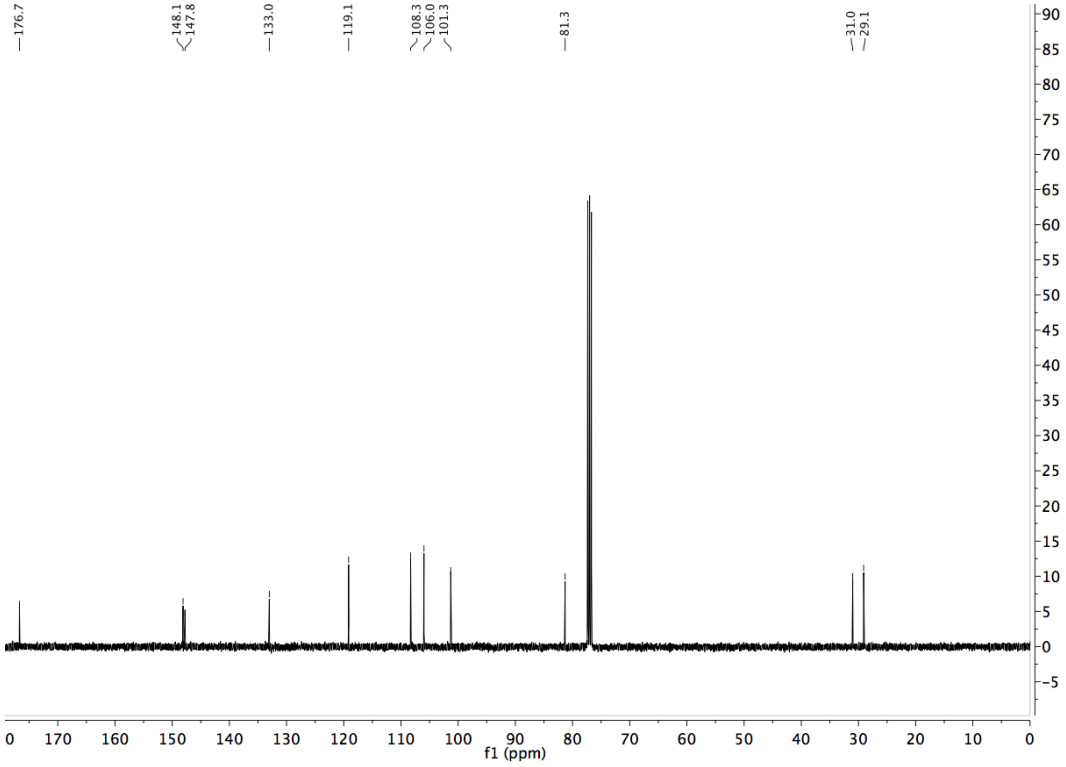
^{13}C NMR (100 MHz, $CDCl_3$): δ 176.7, 148.1, 147.8, 133.0, 119.2, 108.3, 106.0, 101.3, 81.3, 31.0, 29.1.

LRMS (ESI) Calcd. for $C_{11}H_{10}NaO_4$ $[M+Na]^+$: 229, Found: 229.

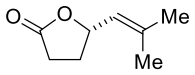
FTIR (neat): 1767, 1504, 1491, 1446, 1248, 1176, 1141, 1035, 931, 910, 805 cm^{-1}.

$[\alpha]^{25}_D$ = -21.7 (c = 0.6, $CHCl_3$)


2.98
1.95
1.00
3.13
1.04
f1 (ppm)


176.7
148.1
147.8
133.0
119.1
108.3
106.0
101.3
81.3
31.0
29.1
f1 (ppm)

(*S*)-5-(2-methylprop-1-en-1-yl)dihydrofuran-2(3H)-one (4.4h).



In accordance with the general procedure, the title compound was obtained in 77% yield (21.6 mg, 0.154 mmol) as a colorless liquid after column chromatography (SiO_2; 10% EtOAc/hexanes).

R_f = 0.25 (20% EtOAc/Hexanes).

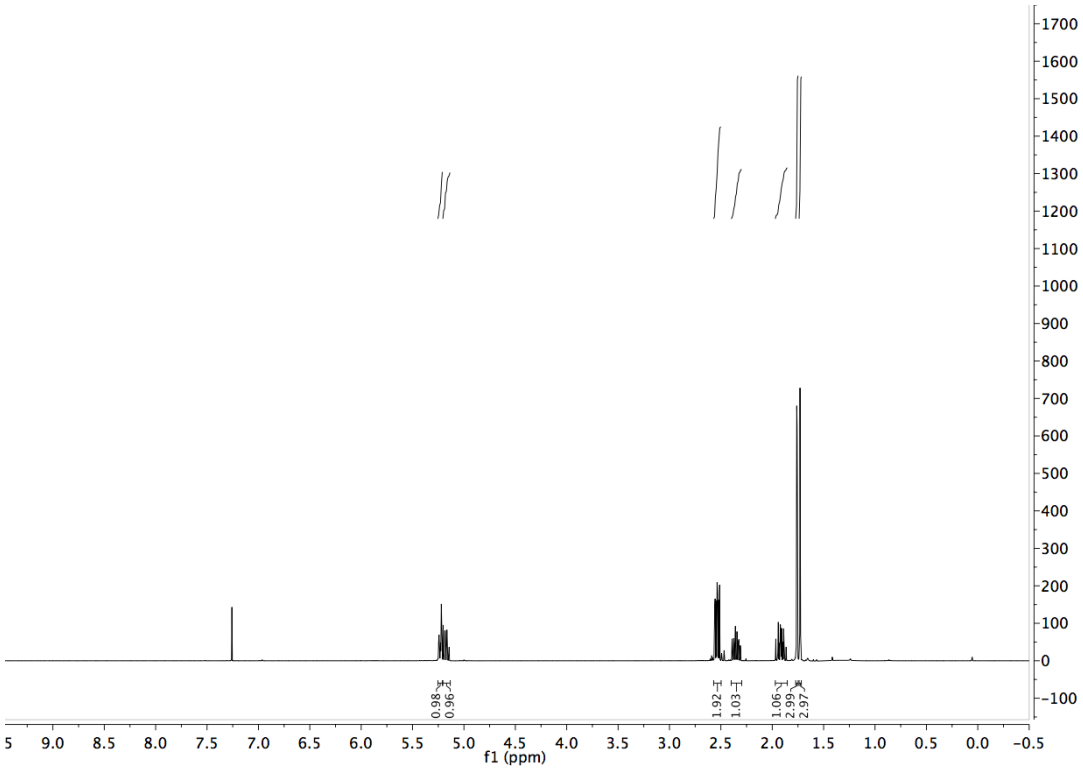
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.23 (dp, *J* = 8.7, 1.3 Hz, 1H), 5.23 – 5.12 (m, 1H), 2.57 – 2.50 (m, 2H), 2.40 – 2.30 (m, 1H), 1.97 – 1.85 (m, 1H), 1.76 (d, *J* = 1.4 Hz, 3H), 1.73 (d, *J* = 1.4 Hz, 3H).

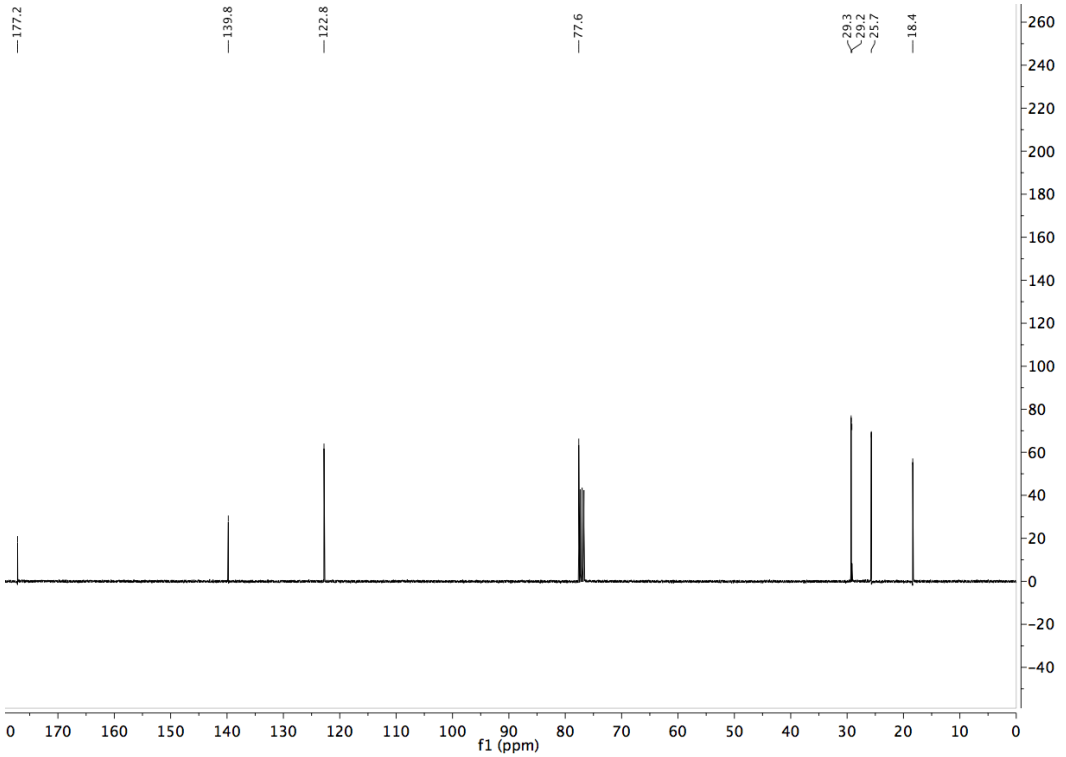
^{13}C NMR (100 MHz, $CDCl_3$): δ 177.2, 139.8, 122.8, 77.6, 29.3, 29.2, 25.7, 18.4.

LRMS (ESI) Calcd. for $C_8H_{12}NaO_2$ $[M+Na]^+$: 163, Found: 163.

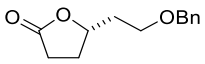
FTIR (neat): 1772, 1376, 1228, 1217, 1177, 1007, 913 cm^{-1}.

$[\alpha]^{25}_D$ = +57.1 (c = 1.25, $CHCl_3$)


0.98
0.96
1.92
1.03
1.06
2.99
2.97
f1 (ppm)


177.2
139.8
122.8
77.6
29.3
29.2
25.7
18.4
f1 (ppm)

(*S*)-5-(2-(benzyloxy)ethyl)dihydrofuran-2(3H)-one (4.4j).



In accordance with the general procedure, the title compound was obtained in 74% yield (32.6 mg, 0.148 mmol) as a colorless liquid after column chromatography (SiO_2; 20% EtOAc/hexanes).

R_f = 0.1 (20% EtOAc/Hexanes).

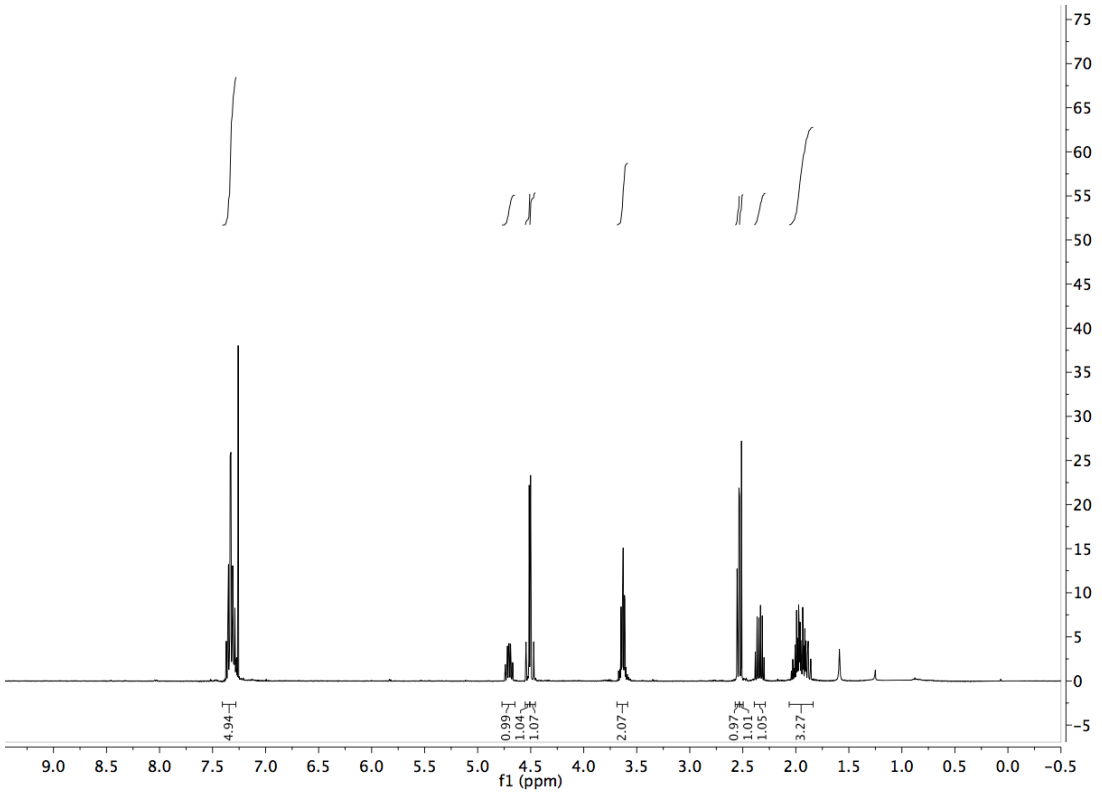
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.26 (m, 5H), 4.77 – 4.64 (m, 1H), 4.53 (d, *J* = 11.9 Hz, 1H), 4.49 (d, *J* = 11.8 Hz, 1H), 3.68 – 3.58 (m, 2H), 2.55 (d, *J* = 7.1 Hz, 1H), 2.52 (d, *J* = 6.8 Hz, 1H), 2.41 – 2.27 (m, 1H), 2.05 – 1.85 (m, 3H).

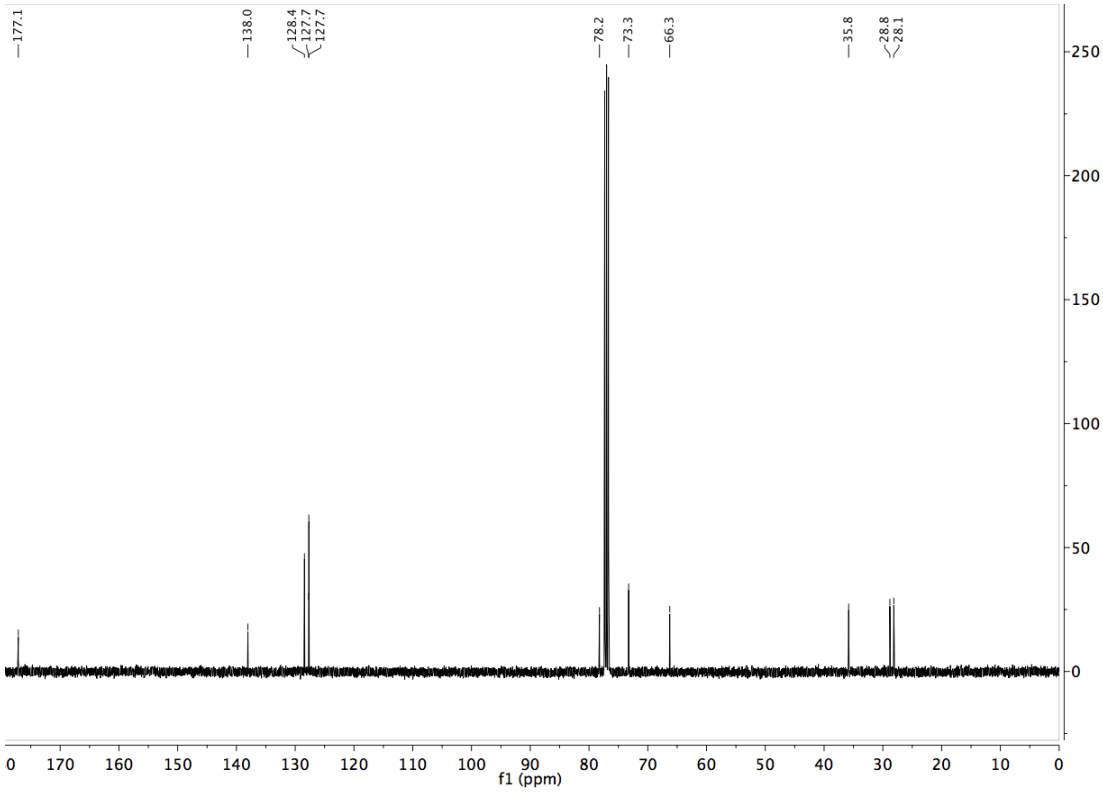
^{13}C NMR (100 MHz, $CDCl_3$): δ 177.1, 138.1, 128.4, 127.7, 127.7, 78.2, 73.3, 66.3, 35.8, 28.8, 28.1.

LRMS (ESI) Calcd. for $C_{13}H_{16}NaO_3$ $[M+Na]^+$: 243, Found: 243.

FTIR (neat): 1739, 1365, 1229, 1217, 1093, 905, 742 cm^{-1}.

$[\alpha]^{25}_D$ = +15.8 (c = 0.4, $CHCl_3$)

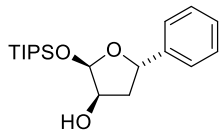

4.94
0.99
1.04
1.07
2.07
0.97
1.01
1.05
3.27
f1 (ppm)


177.1
138.0
128.4
127.7
127.7
78.2
73.3
66.3
35.8
28.8
28.1
f1 (ppm)

General Procedure and Preparation of 4.5a, 4.5c, 4.5e, 4.5f, 4.5j, 4.5k

To a solution of adduct **4.3** (0.20 mmol) in DCM (1.7 mL) at -20 °C was added a solution of *m*-CPBA (0.22 mmol, 110 mol%) in DCM (1.0 mL) over one hour via syringe pump. The reaction mixture was allowed to stir at -20 °C for 1h, and then was allowed to stir at 0 °C for 24 hours. To the reaction mixture was added saturated $NaHCO_3$ (aq). The reaction mixture was transferred to a separatory funnel and the organic layer was washed with saturated $NaHCO_3$(aq), water, and brine. The organic layer was collected, dried (Na_2SO_4) and filtered. The solvents were removed *in vacuo* and the residue was subjected to column chromatography (SiO_2).

(2*R*,3*R*,5*S*)-5-phenyl-2-((triisopropylsilyl)oxy)tetrahydrofuran-3-ol (4.5a).



In accordance with the general procedure, the title compound was obtained in 74% yield (49.7 mg, 0.148 mmol) as a colorless liquid after column chromatography (SiO_2; 16% EtOAc/hexanes).

R_f = 0.5 (20% EtOAc/Hexanes).

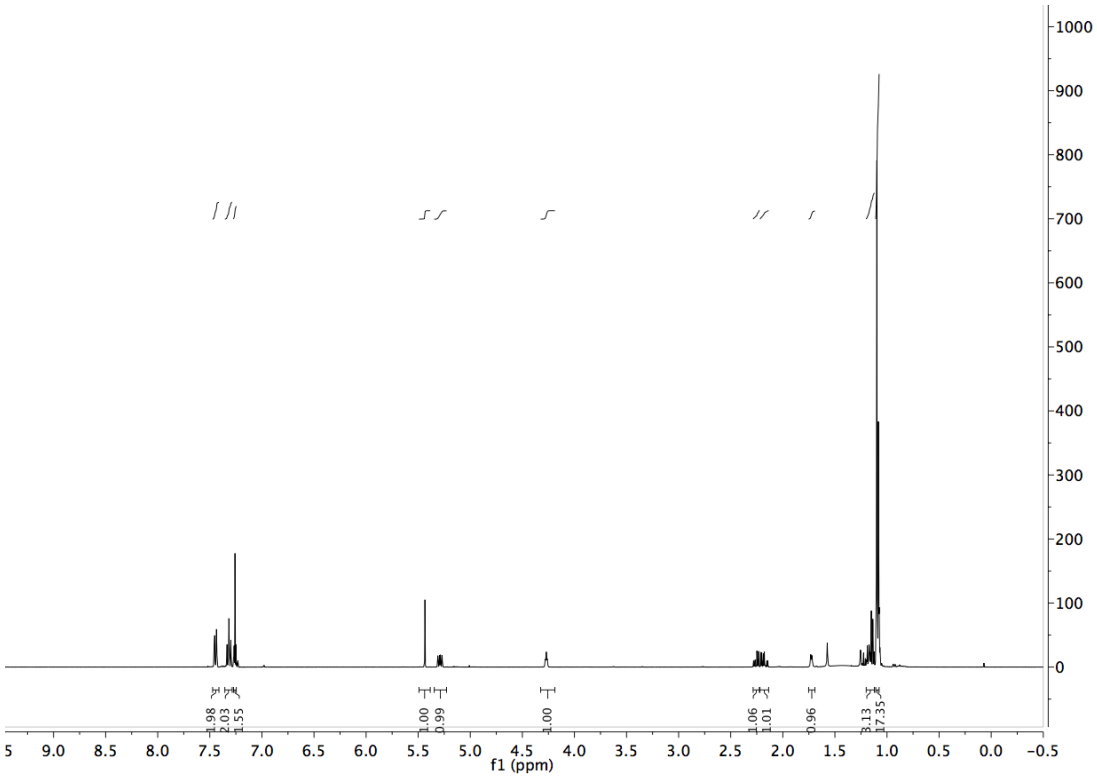
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.41 (m, 2H), 7.35 – 7.28 (m, 2H), 7.27 – 7.22 (m, 1H), 5.44 (s, 1H), 5.29 (dd, *J* = 10.1, 6.1 Hz, 1H), 4.30 – 4.24 (m, 1H), 2.26 (ddd, *J* = 13.3, 6.2, 1.0 Hz, 1H), 2.18 (ddd, *J* = 13.4, 10.1, 4.0 Hz, 1H), 1.73 (d, *J* = 4.7 Hz, 1H), 1.20 – 1.12 (m, 3H), 1.09 (d, *J* = 5.8 Hz, 18H).

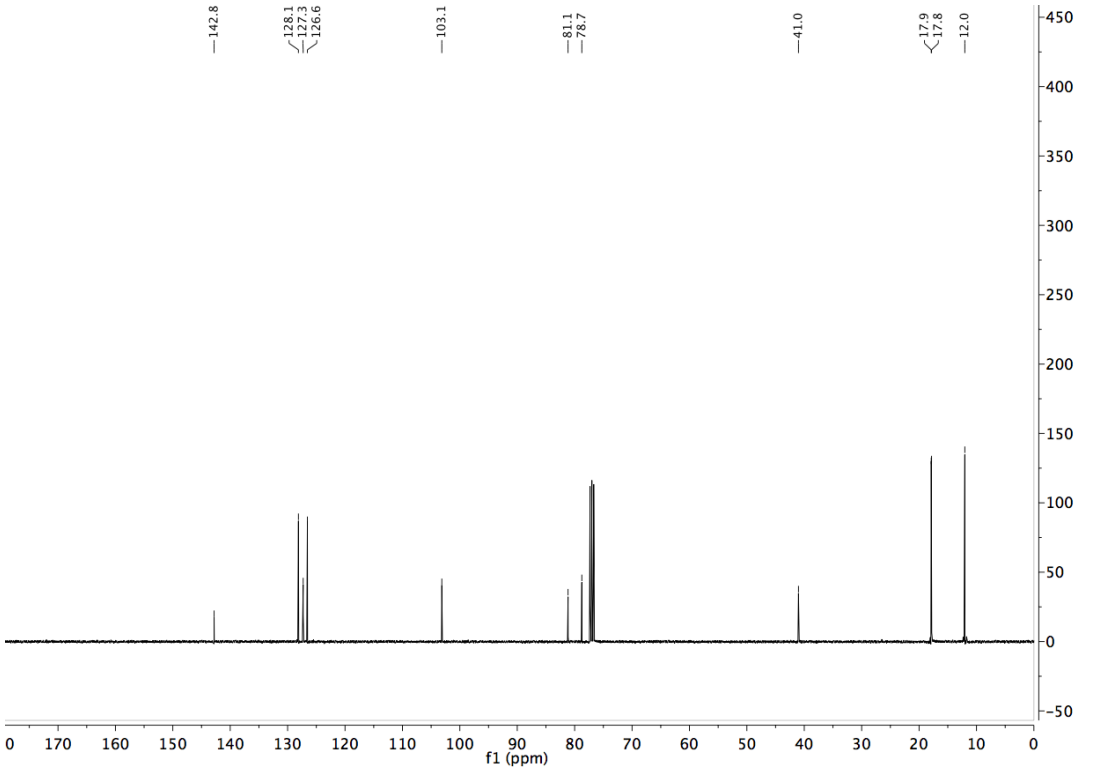
^{13}C NMR (100 MHz, $CDCl_3$): δ 142.8, 128.1, 127.3, 126.6, 103.1, 81.2, 78.8, 41.0, 17.9, 17.8, 12.0.

LRMS (ESI) Calcd. for $C_{19}H_{33}O_3Si$ $[M+H]^+$: 337, Found: 337.

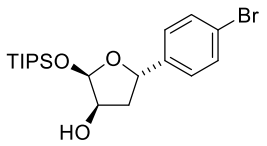
FTIR (neat): 2943, 2866, 1463, 1085, 1065, 1025, 996, 882, 755, 699, 682 cm^{-1}.

$[\alpha]^{25}_D$ = -53.3 (c = 0.4, $CHCl_3$)


1.98
2.03
1.55
1.00
0.99
1.00
1.06
1.01
0.96
3.13
17.35
f1 (ppm)


142.8
128.1
127.3
126.6
103.1
81.1
78.7
41.0
17.9
17.8
12.0
f1 (ppm)

(2*R*,3*R*,5*S*)-5-(4-bromophenyl)-2-((triisopropylsilyl)oxy)tetrahydrofuran-3-ol (4.5c).



In accordance with the general procedure, the title compound was obtained in 73% yield (60.4 mg, 0.146 mmol) as a colorless liquid after column chromatography (SiO_2; 15% EtOAc/hexanes).

R_f = 0.3 (20% EtOAc/Hexanes).

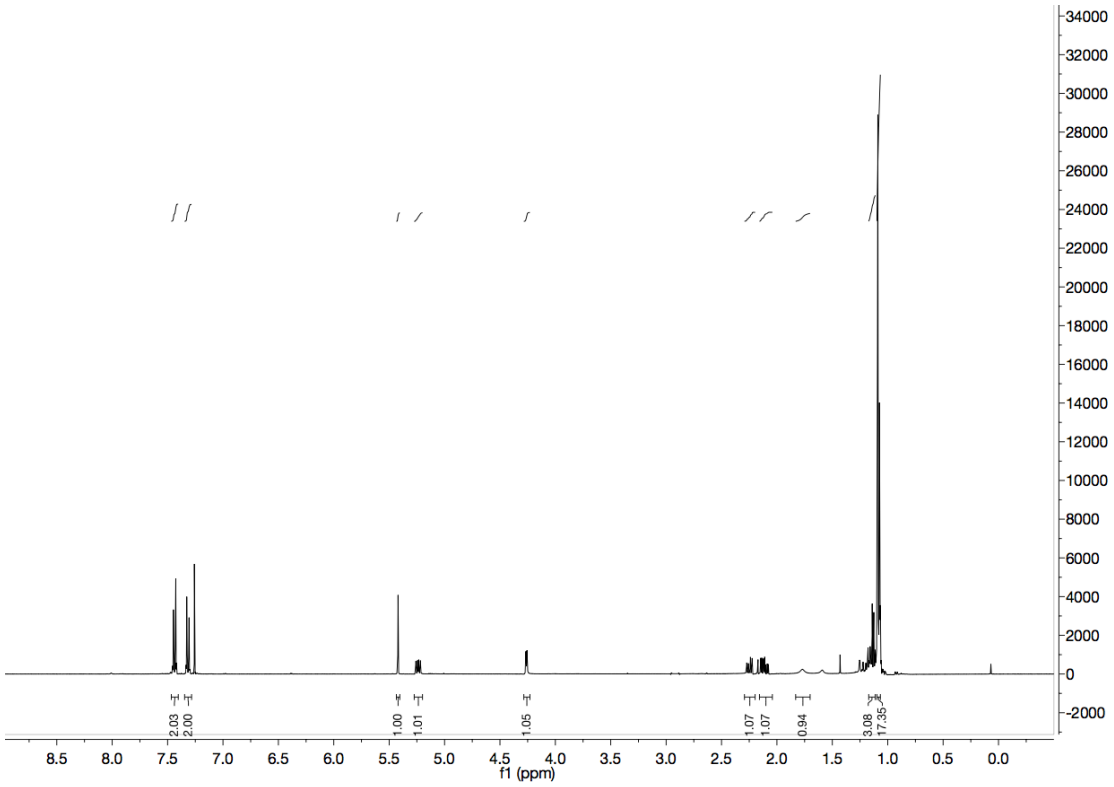
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.41 (m, 2H), 7.34 – 7.28 (m, 2H), 5.42 (s, 1H), 5.24 (dd, *J* = 10.2, 6.0 Hz, 1H), 4.26 (d, *J* = 4.0 Hz, 1H), 2.25 (dd, *J* = 13.3, 6.1 Hz, 1H), 2.11 (ddd, *J* = 13.4, 10.2, 4.1 Hz, 1H), 1.77 (s, 1H), 1.17 – 1.12 (m, 3H), 1.08 (d, *J* = 5.6 Hz, 18H).

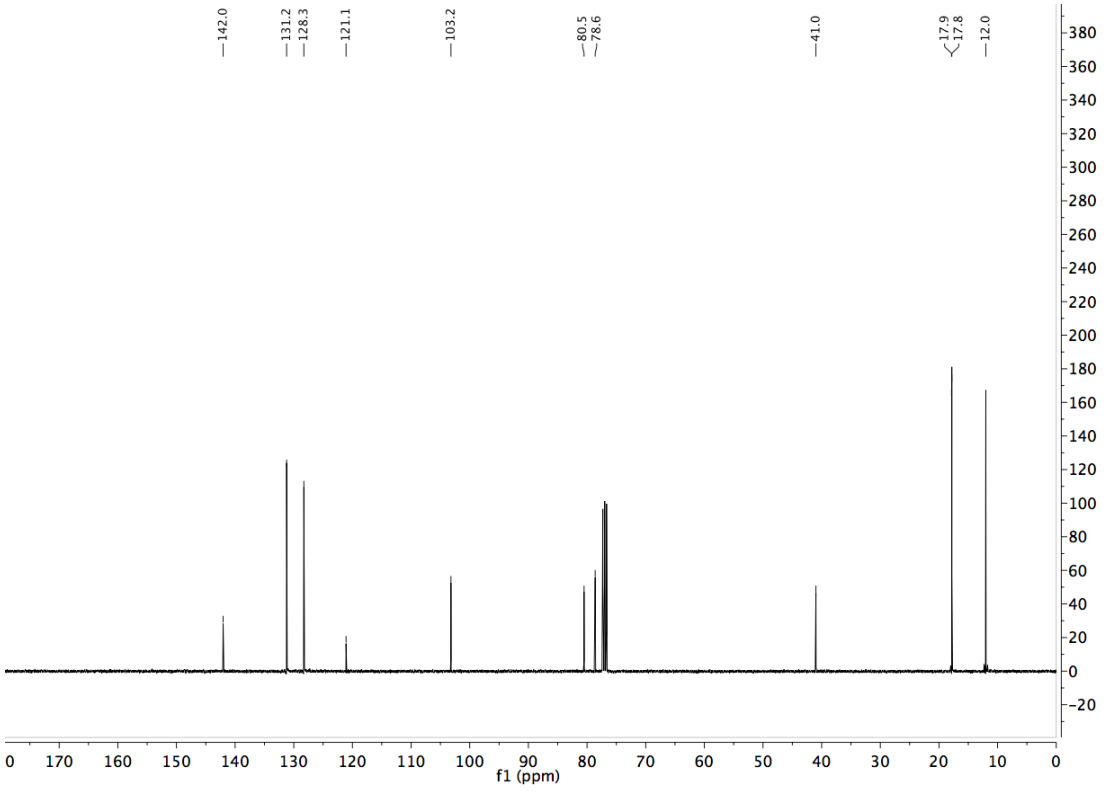
^{13}C NMR (100 MHz, $CDCl_3$): δ 142.0, 131.2, 128.3, 121.1, 103.2, 80.5, 78.6, 41.0, 17.9, 17.8, 12.0.

LRMS (ESI) Calcd. for $C_{19}H_{32}BrO_3Si$ $[M+H]^+$: 415, Found: 415.

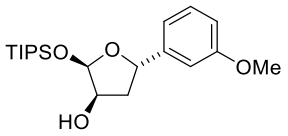
FTIR (neat): 2942, 2866, 1176, 1026, 1009, 995, 881, 816, 683, 661 cm^{-1}.

$[\alpha]^{25}_D$ = +37.8 (c = 0.68, $CHCl_3$)


2.03
2.00
1.00
1.01
1.05
1.07
1.07
0.94
3.08
17.35
f1 (ppm)


142.0
131.2
128.3
121.1
103.2
80.5
78.6
41.0
17.9
17.8
12.0
f1 (ppm)

(2*R*,3*R*,5*S*)-5-(3-methoxyphenyl)-2-((triisopropylsilyl)oxy)tetrahydrofuran-3-ol (4.5e).



In accordance with the general procedure, the title compound was obtained in 66% yield (48.3 mg, 0.132 mmol) as a colorless liquid after column chromatography (SiO_2; 15% EtOAc/hexanes).

R_f = 0.3 (20% EtOAc/Hexanes).

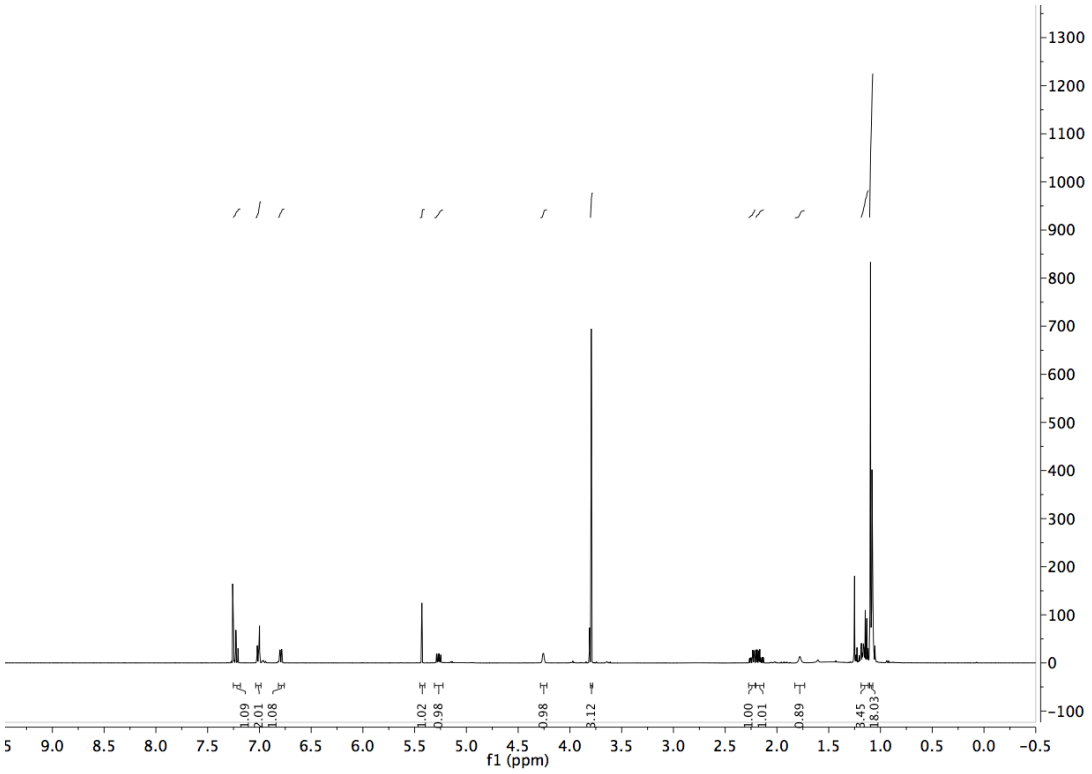
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.19 (m, 1H), 7.04 – 6.97 (m, 2H), 6.81 – 6.76 (m, 1H), 5.43 (s, 1H), 5.27 (dd, *J* = 10.1, 6.1 Hz, 1H), 4.29 – 4.22 (m, 1H), 3.79 (s, 3H), 2.24 (ddd, *J* = 13.3, 6.1, 1.0 Hz, 1H), 2.17 (ddd, *J* = 13.3, 10.2, 4.0 Hz, 1H), 1.78 (s, 1H), 1.18 – 1.12 (m, 3H), 1.11 – 1.07 (m, 18H).

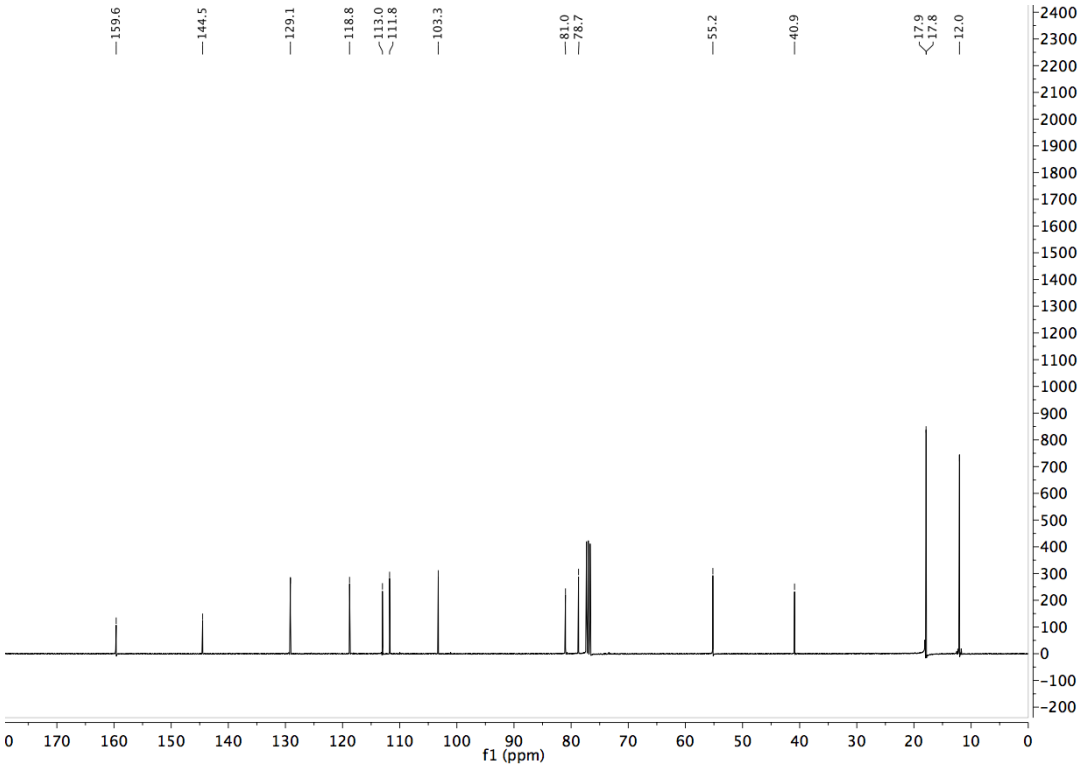
^{13}C NMR (100 MHz, $CDCl_3$): δ 159.6, 144.5, 129.1, 118.8, 113.0, 111.8, 103.3, 81.0, 78.7, 55.2, 40.9, 17.9, 17.8, 12.0.

LRMS (ESI) Calcd. for $C_{20}H_{35}O_4Si$ $[M+H]^+$: 367, Found: 367.

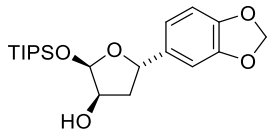
FTIR (neat): 2944, 2866, 1464, 1263, 1078, 1027, 995, 882, 788, 683 cm^{-1}.

$[\alpha]^{25}_D$ = - 29.4 (c = 0.85, $CHCl_3$)


1.09
2.01
1.08
1.02
0.98
0.98
3.12
1.00
1.01
0.89
3.45
18.03
f1 (ppm)


159.6
144.5
129.1
118.8
113.0
111.8
103.3
81.0
78.7
55.2
40.9
17.9
17.8
12.0
f1 (ppm)

(2*R*,3*R*,5*S*)-5-(benzo[d][1,3]dioxol-5-yl)-2-((triisopropylsilyl)oxy)tetrahydrofuran-3-ol (4.5f).



In accordance with the general procedure, the title compound was obtained in 71% yield (54.0 mg, 0.142 mmol) as a colorless liquid after column chromatography (SiO_2; 15% EtOAc/hexanes).

R_f = 0.4 (20% EtOAc/Hexanes).

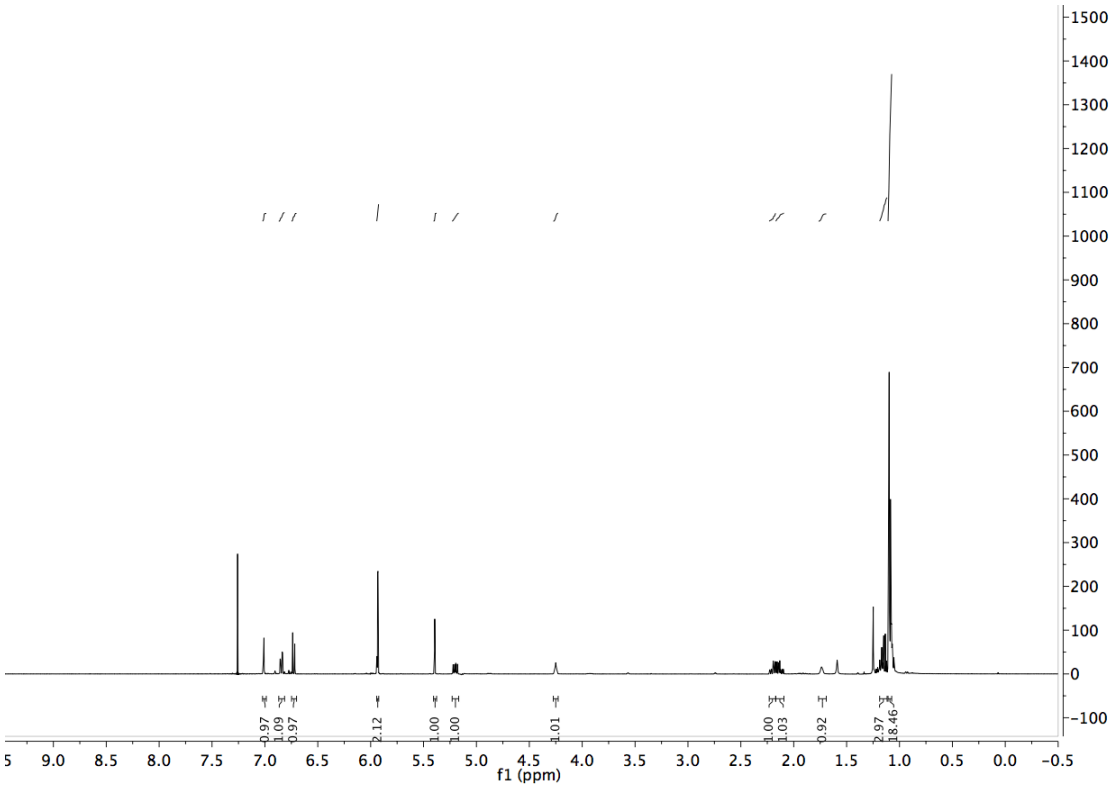
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (d, *J* = 1.7 Hz, 1H), 6.84 (ddd, *J* = 8.0, 1.7, 0.6 Hz, 1H), 6.73 (dd, *J* = 7.9, 0.4 Hz, 1H), 5.94 – 5.92 (m, 2H), 5.39 (s, 1H), 5.20 (dd, *J* = 10.0, 6.2 Hz, 1H), 4.27 – 4.21 (m, 1H), 2.20 (ddd, *J* = 13.4, 6.2, 1.0 Hz, 1H), 2.13 (ddd, *J* = 13.5, 10.0, 3.9 Hz, 1H), 1.74 (s, 1H), 1.19 – 1.12 (m, 3H), 1.11 – 1.07 (m, 18H).

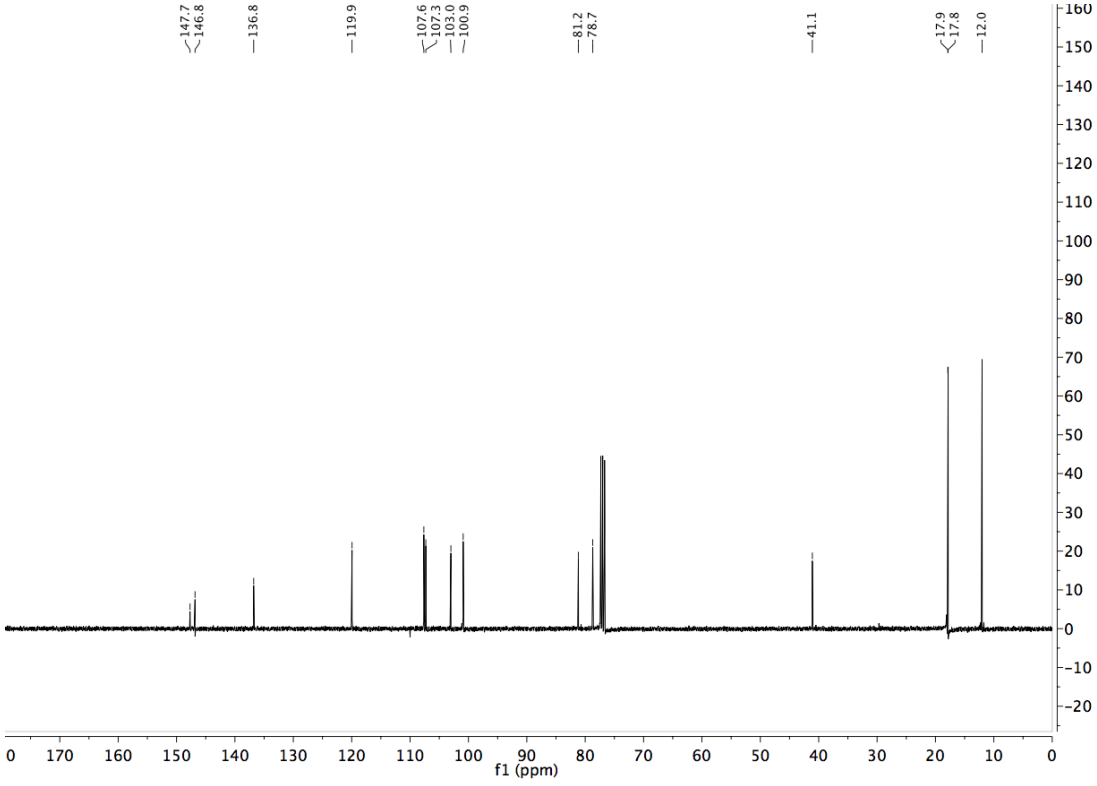
^{13}C NMR (100 MHz, $CDCl_3$): δ 147.7, 146.8, 136.8, 120.0, 107.7, 107.3, 103.0, 100.9, 81.2, 78.7, 41.09, 17.9, 17.8, 12.0.

LRMS (ESI) Calcd. for $C_{20}H_{33}O_5Si$ $[M+H]^+$: 381, Found: 381.

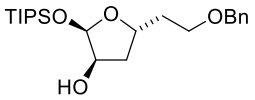
FTIR (neat): 2943, 2866, 1488, 1446, 1247, 1080, 1025, 937, 882, 804, 682 cm^{-1}.

$[\alpha]^{25}_D$ = - 42.1 (c = 0.87, $CHCl_3$)


0.97
1.09
0.97
2.12
1.00
1.00
1.01
1.00
1.03
0.92
2.97
18.46
f1 (ppm)


147.7
146.8
136.8
119.9
107.6
107.3
103.0
100.9
81.2
78.7
41.1
17.9
17.8
12.0
f1 (ppm)

(2*R*,3*R*,5*S*)-5-(2-(benzyloxy)ethyl)-2-((triisopropylsilyl)oxy)tetrahydrofuran-3-ol (4.5j).



In accordance with the general procedure, the title compound was obtained in 61% yield (48.1 mg, 0.122 mmol) as a colorless liquid after column chromatography (SiO_2; 14% EtOAc/hexanes).

R_f = 0.3 (20% EtOAc/Hexanes).

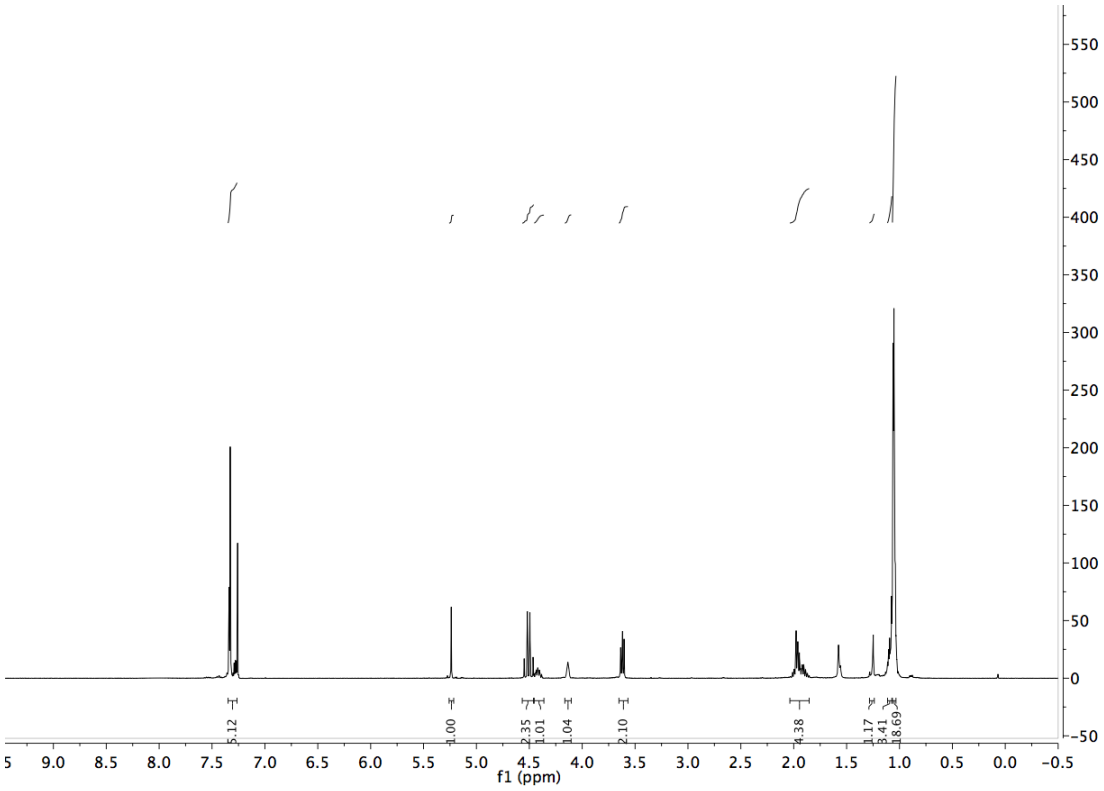
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.26 (m, 5H), 5.24 (s, 1H), 4.53 (d, *J* = 12.0 Hz, 1H), 4.48 (d, *J* = 11.9 Hz, 1H), 4.46 – 4.37 (m, 1H), 4.16 – 4.10 (m, 1H), 3.62 (dd, *J* = 7.2, 5.8 Hz, 2H), 2.03 – 1.86 (m, 4H), 1.27 – 1.23 (m, 1H), 1.11 – 1.07 (m, 3H), 1.07 – 1.03 (m, 18H).

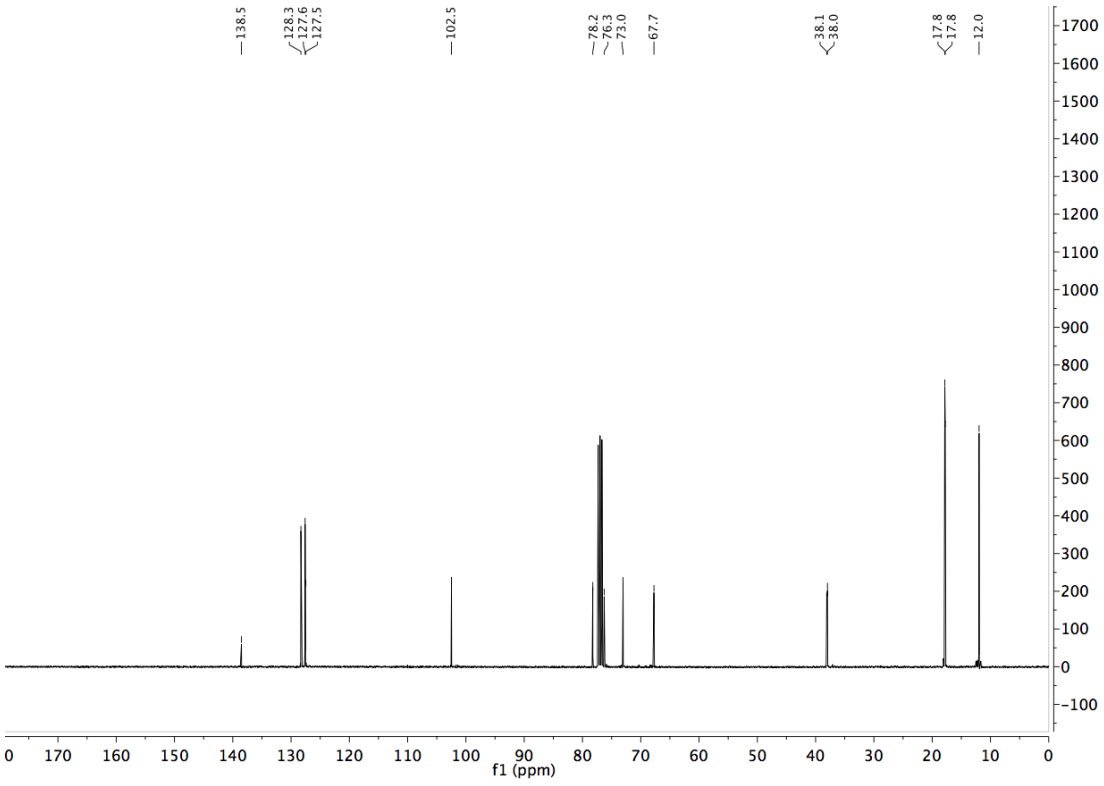
^{13}C NMR (100 MHz, $CDCl_3$): δ 138.5, 128.3, 127.6, 127.5, 102.5, 78.2, 76.3, 73.03, 67.7, 38.1, 38.0, 17.8(3), 17.7(7), 12.0.

LRMS (ESI) Calcd. for $C_{22}H_{39}O_4Si$ $[M+H]^+$: 395, Found: 395.

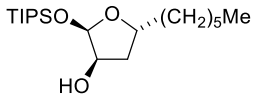
FTIR (neat): 2942, 2866, 1101, 1046, 1009, 994, 882, 832, 736, 683, 659 cm^{-1}.

$[\alpha]^{25}_D$ = - 34.9 (c = 0.43, $CHCl_3$)


5.12
1.00
2.35
1.01
1.04
2.10
4.38
1.17
3.41
18.69
f1 (ppm)


138.5
128.3
127.6
127.5
102.5
78.2
76.3
73.0
67.7
38.1
38.0
17.8
17.8
12.0
f1 (ppm)

(2*R*,3*R*,5*S*)-5-hexyl-2-((triisopropylsilyl)oxy)tetrahydrofuran-3-ol (4.5k).



In accordance with the general procedure, the title compound was obtained in 63% yield (43.3 mg, 0.126 mmol) as a colorless liquid after column chromatography (SiO_2; 12% EtOAc/hexanes).

R_f = 0.5 (20% EtOAc/Hexanes).

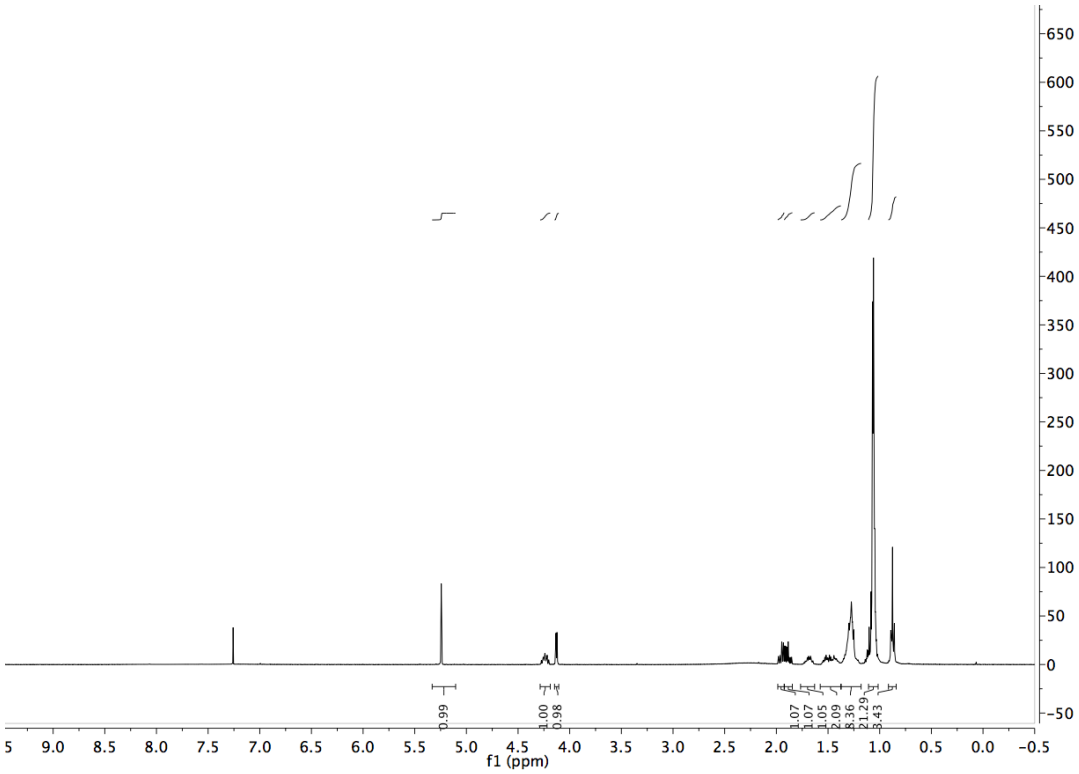
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.24 (s, 1H), 4.28 – 4.19 (m, 1H), 4.13 (d, *J* = 3.7 Hz, 1H), 1.96 (ddd, *J* = 13.2, 6.3, 0.9 Hz, 1H), 1.89 (ddd, *J* = 13.3, 9.2, 4.1 Hz, 1H), 1.76 – 1.63 (m, 1H), 1.57 – 1.39 (m, 2H), 1.36 – 1.19 (m, 8H), 1.11 – 1.01 (m, 21H), 0.88 (t, *J* = 6.8 Hz, 3H).

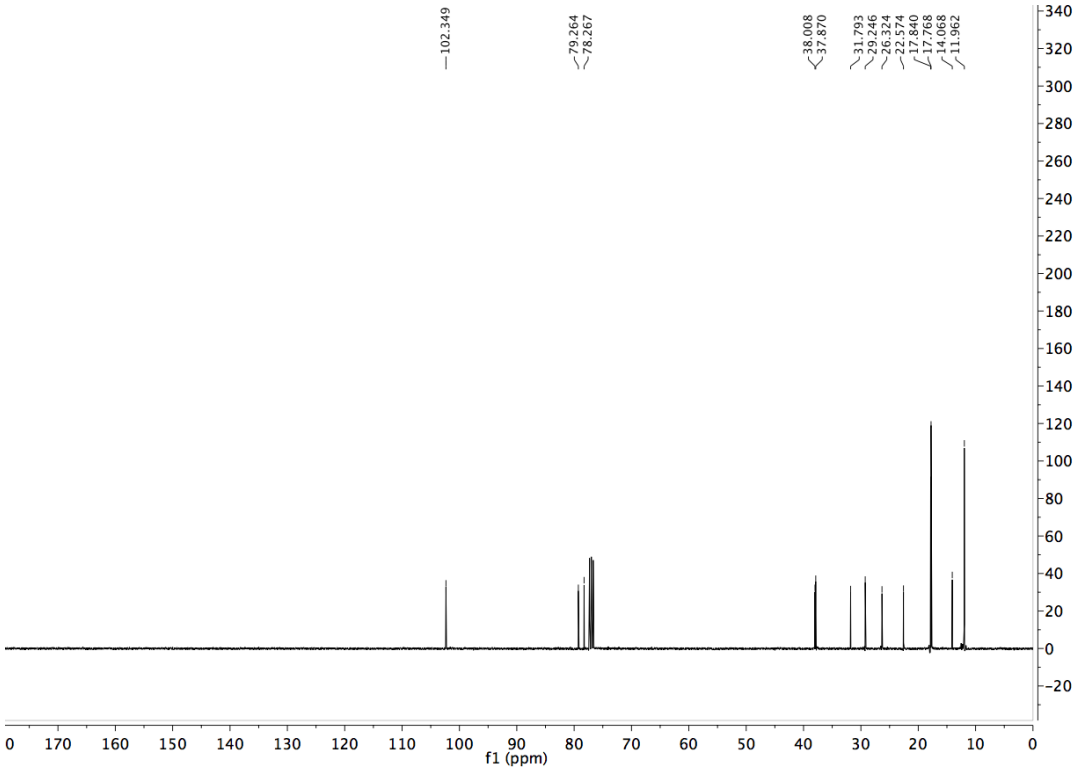
^{13}C NMR (100 MHz, $CDCl_3$): δ 102.4, 79.3, 78.3, 38.0, 37.9, 31.8, 29.3, 26.3, 22.6, 17.8(4), 17.7(7), 14.1, 12.0.

LRMS (ESI) Calcd. for $C_{19}H_{41}O_3Si$ $[M+H]^+$: 345, Found: 345.

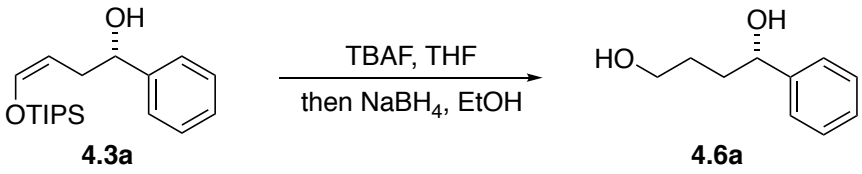
FTIR (neat): 2929, 2866, 1464, 1107, 1029, 1010, 994, 882, 683, 657 cm^{-1}.

$[\alpha]^{25}_D$ = - 32.0 (c = 0.75, $CHCl_3$)


0.99
1.00
0.98
1.07
1.07
1.05
2.09
8.36
21.29
3.43
f1 (ppm)


102.349
79.264
78.267
38.008
37.870
31.793
29.246
26.324
22.574
17.840
17.768
14.068
11.962
f1 (ppm)

Absolute Stereochemical Assignment of 4.3a



4.3a **4.6a**

To a solution of **4.3a** (0.2 mmol) in THF (2.0 mL) was added TBAF (1.0 M in THF, 0.2 mL, 100 mol%) dropwise at 0ºC. The mixture was stirred at r.t for 30 min, then $NaBH_4$ (14.8 mg, 0.4 mmol), EtOH (1.0 mL) were added. After 1 h, the reaction was quenched by NH_4Cl (aq), and extracted by EA. Organic layer was washed by water, brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was subjected to flash column chromatography (SiO_2, eluent Hexanes:EA = 2:1) to afford diol **4.6a** (95%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.23 (m, 5H), 4.70 (t, J = 6.2 Hz, 1H), 3.68 – 3.58 (m, 2H), 3.10 (bs. 2H), 1.89 – 1.83 (m, 2H), 1.74 – 1.61 (m, 2H).

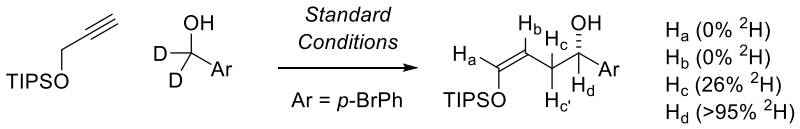
^{13}C NMR (100 MHz, $CDCl_3$): δ 144.7, 128.4, 127.4, 125.8, 74.2, 62.6, 36.3, 29.1.

The spectroscopy data (^{1}H, ^{13}C NMR) matched the literature data[1]

Optical rotation of **4.6a**: $[\alpha]^{25}_D$ = - 31.0 (c = 1.0, MeOH) (94% *ee*). Literature[1] optical rotation for (*S*)-1-phenylbutane-1,4-diol: $[\alpha]^{20}_D$ = - 33.5 (c = 1.0, MeOH) (98.7% *ee*)

4.6a was assigned to be (*S*)-1-phenylbutane-1,4-diol, therefor **4.3a** was assigned to be (*S*,*Z*)-1-phenyl-4-((triisopropylsilyl)oxy)but-3-en-1-ol.

Isotopic Labeling Studies

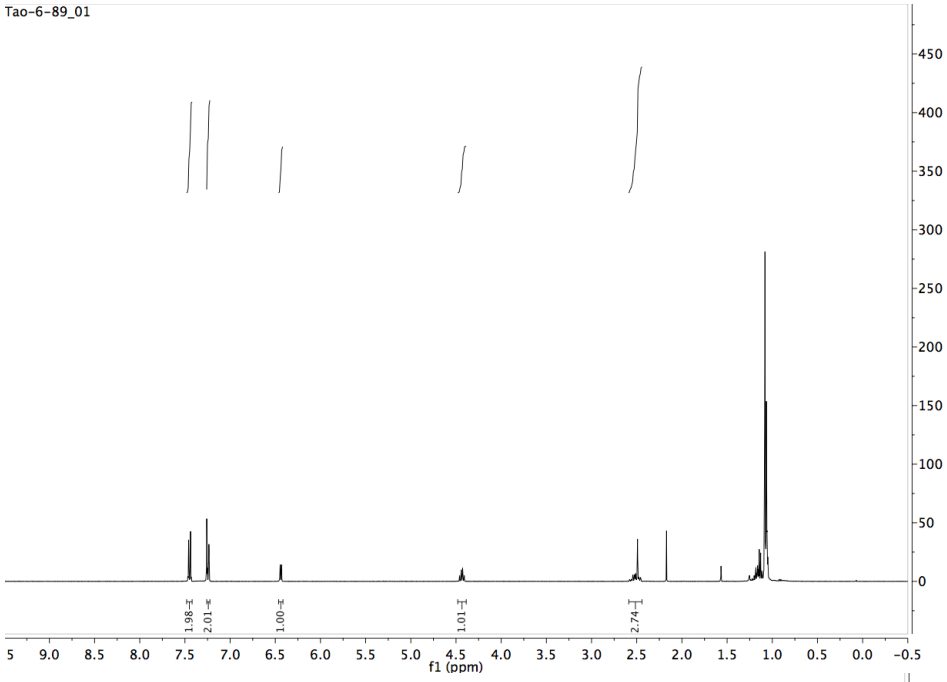


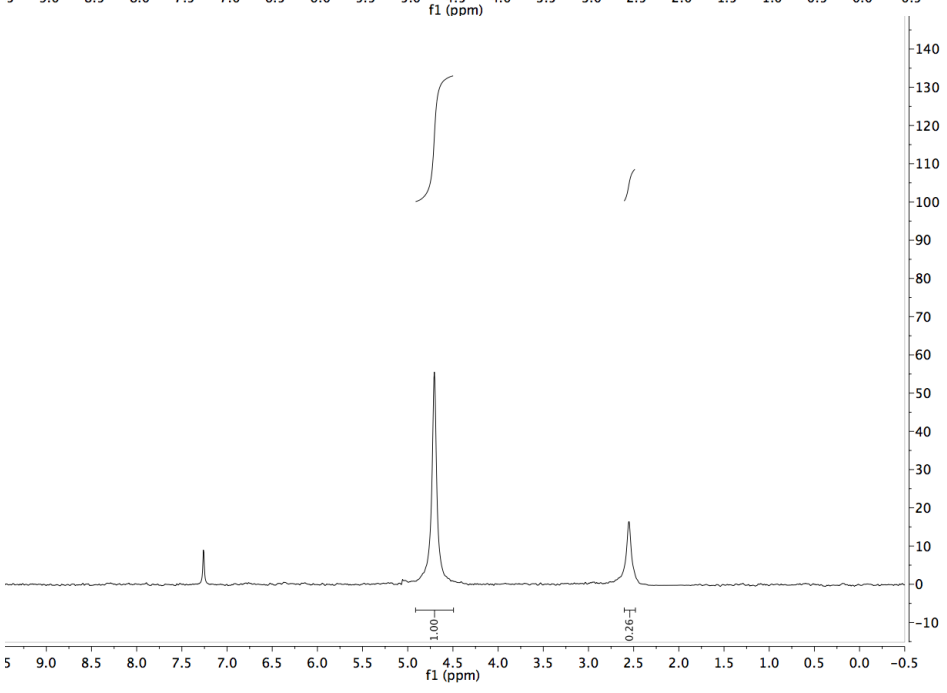
H_a (0% ^2H)
H_b (0% ^2H)
H_c (26% ^2H)
H_d (>95% ^2H)

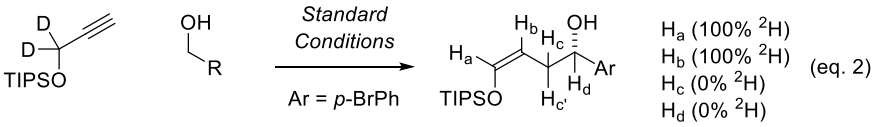
1 (400 mol %)

deuterio-**2c** (100 mol%)

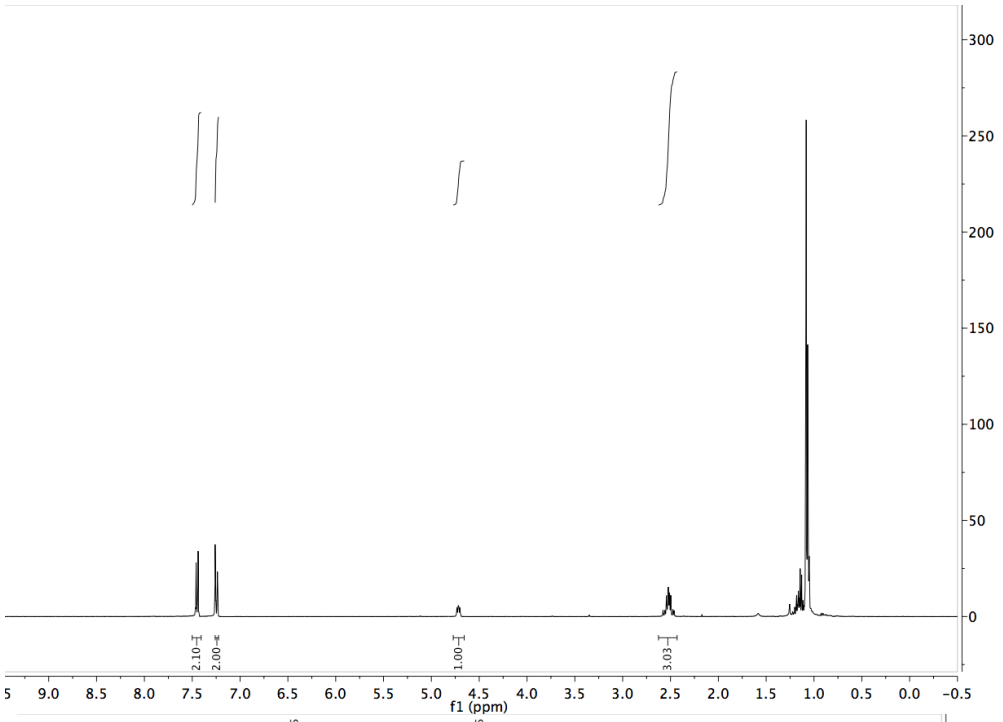
deuterio-**3c**
81% Yield, >20:1 (*Z*:*E*)

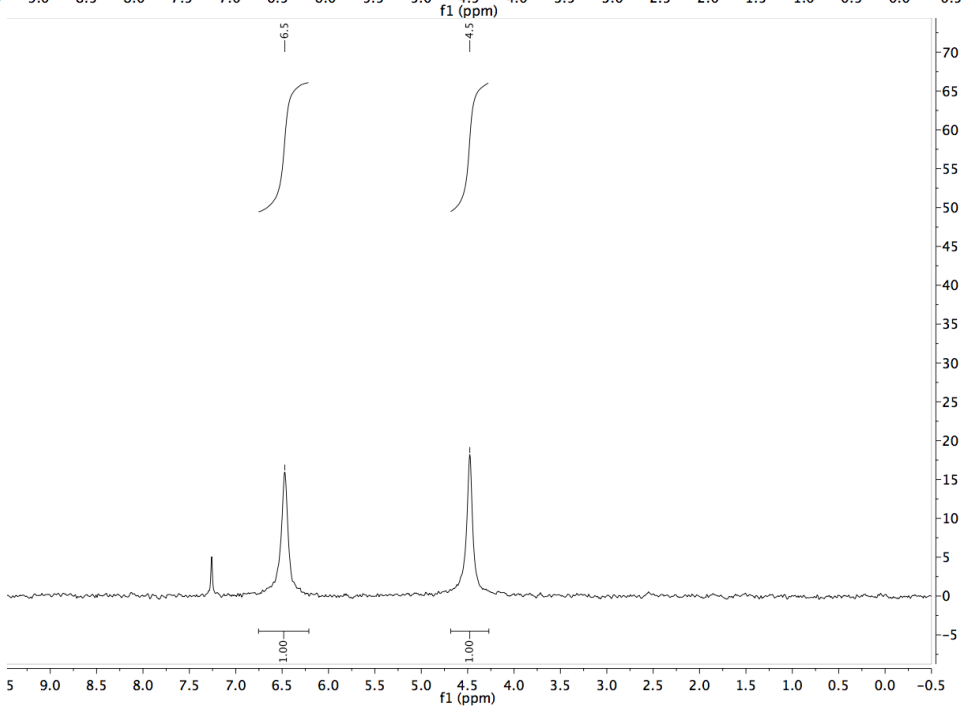






deuterio-**1** (400 mol %) | **2c** (100 mol%) | *deuterio*-**3c** 75% Yield, >20:1 (*Z*:*E*)





Chapter 5: Ruthenium Catalyzed Redox-Triggered Carbonyl *anti*-(α-Amino)allylation by Coupling with Acetylenic Pyrrole*

5.1 INTRODUCTION

2-Amino alcohols are common moieties found in natural products and fine chemicals.[1] While there are very few reports on the construction of 2-amino alcohol moieties. Barrett reported asymmetric syntheses of anti-β-amino alcohols by coupling of allylborane with aldehydes (Figure 5.1).[2] To come up with an alternative to nonstabilized carbanion addition to carbonyl compounds, Krische group has developed a broad system of catalytic carbonyl addition reactions by coupling of carbonyl compounds with different π-unsaturated compounds, which allowed the direct conversion of primary alcohols to secondary alcohol. [3]

In 2009, Krische group reported the carbonyl anti-(α-amino)allylation by coupling of N-substituted allenes with aldehyde under ruthenium catalysis via 2-propanol mediated reductive coupling.[4] Later, Krische group also reported the redox-neutral coupling between N-substituted allenes and primary alcohols under ruthenium catalysis, which also represented a byproduct free protocol.[5] However, to achieve a good *anti*-diastereoselectivity, the protecting groups on the nitrogen atom are very crucial. Both p-nitrobenzenesulfonyl and 2,4-dimethyloxybenzyl protecting groups were required, so the elaboration of the coupling products was limited. A more desirable protecting group for amines was found, by which the amines was protect as 2,5-dimethylpyrrole and could be removed easily by treatment with hydroxylamine hydrochloride.[6] Also, we found alkynes could be a precursor to allenes[7,8] under ruthenium catalysis via isomerization, and then allenes were converted to π-allylruthenium species through hydrometalation. [8]

In this chapter, a more desirable allyl donor for carbonyl *anti*-(α-amino)allylation was reported, N-propynyl-2,5-dimethylpyrrole **5.1**, which served as a pronucleophiles in carbonyl anti-(α-amino)allylation (Scheme 5.1).

---

*This chapter is based on the published work:
Zhang, W.†; Chen, W. †; Xiao, H.; Krische, M. J. *Org. Lett.* **2017**, *19*, 4876.

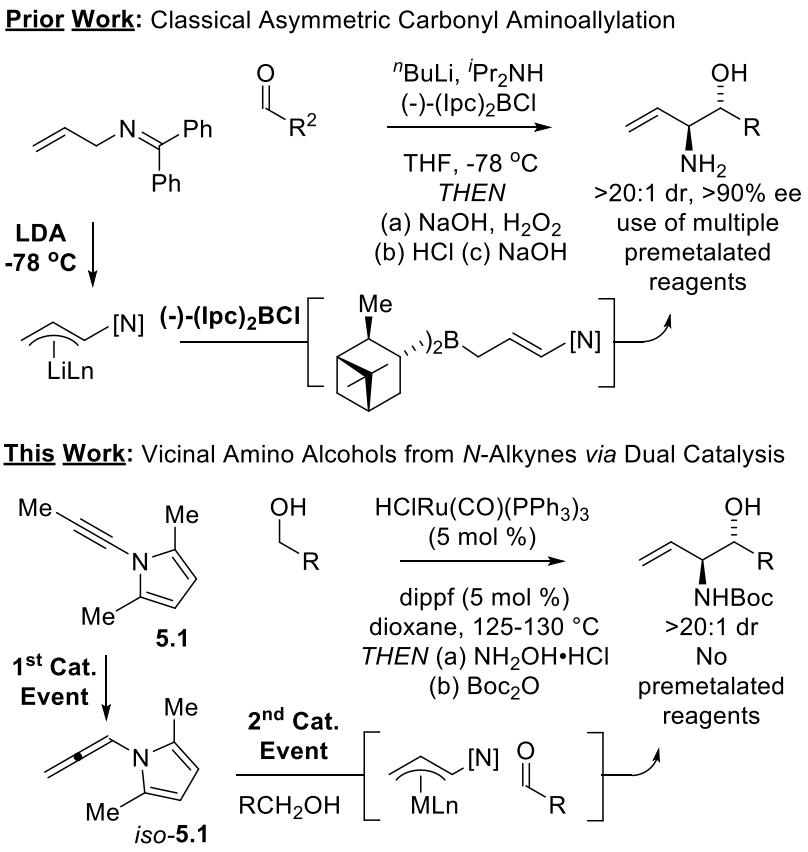
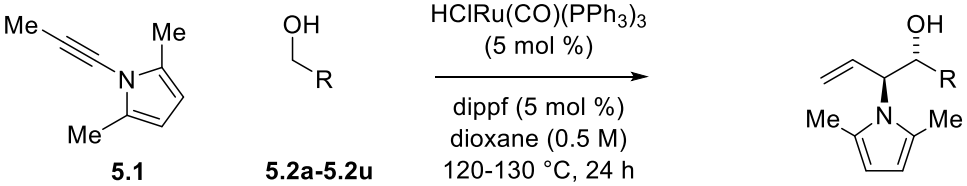


Figure 5.1 Classical Carbonyl (α-Amino)allylation and Catalytic Carbonyl (α-Amino)allylation via Coupling of Alcohols with Alkyne.

5.2 Reaction Development and Scope

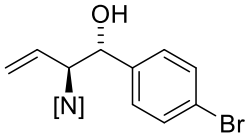
Initially *p*-bromobenzyl alcohol **5.2a** was subjected to acetylenic pyrrole **5.1** with $HClRu(CO)(PPh_3)_3$ and bidentate phosphine ligands, and dippf was found to be the optimal ligand for this transformation. Further optimization of solvents and temperature, carbonyl (α-amino)allylation product **5.3a** was obtained with 83% yield and complete *anti*-diastereoselectivity.

Table 5.1 Diastereoselective and Enantioselective Formation of 1,4-Diols **3.1a-3.5o**.

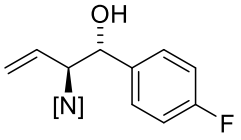


5.1 (300 mol%) **5.2a-5.2u** (100 mol%) **5.3a-5.3u**

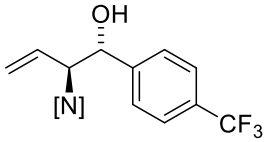
5.2a, R = 4-Br-Phenyl	**5.2b**, R = 4-F-Phenyl	**5.2c**, R = 4-CF_3-Phenyl
5.2d, R = 4-MeO-Phenyl	**5.2e**, R = 3-MeO-Phenyl	**5.2f**, R = 2-Cl-Phenyl
5.2g, R = 4-CO_2Me-Phenyl	**5.2h**, R = 4-Br-3-NO_2-Phenyl	**5.2i**, R = 2-Furyl
5.2j, R = 2-Benzothienyl	**5.2k**, R = 5-(2-MeO-Pyridyl)	**5.2l**, R = 5-(2-Ph-Pyrimidyl)
5.2m, R = 5-(2-Ph-Oxazolyl)	**5.2n**, R = (*trans*)-CH=CHPh	**5.2o**, R = CH=CMe_2
5.2p, R = $(CH_2)_5$Me	**5.2q**, R = $CH_2CH_2CF_3$	**5.2r**, R = CH_2CH_2NHBoc
5.2s, R = CH_2CH_2OBn	**5.2t**, R = CH_2(c-Hexyl)	**5.2u**, R = *c*-Propyl



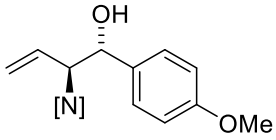
5.3a, 83% yield, >20:1 dr
74% yield (1 mmol scale)



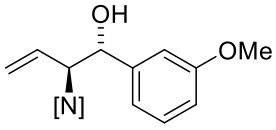
5.3b, 75% yield
>20:1 dr



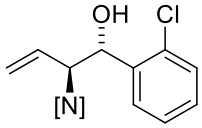
5.3c, 96% yield
>20:1 dr



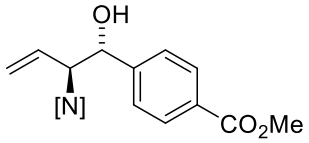
5.3d, 50% yield
>20:1 dr



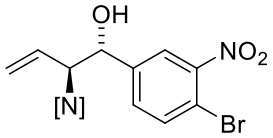
5.3e, 71% yield
>20:1 dr



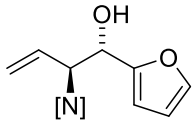
5.3f, 86% yield
>20:1 dr



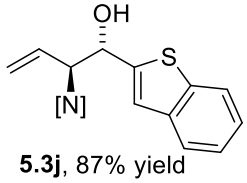
5.3g, 73% yield
>20:1 dr



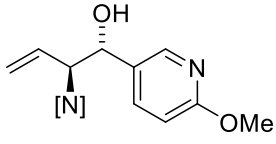
5.3h, 73% yield
>20:1 dr



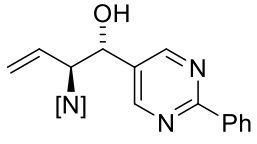
5.3i, 71% yield[b]
>20:1 dr



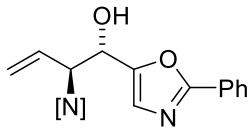
5.3j, 87% yield
>20:1 dr



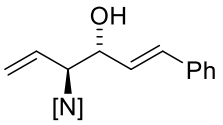
5.3k, 70% yield[b]
>20:1 dr



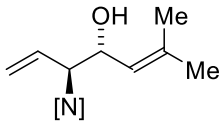
5.3l, 94% yield
>20:1 dr



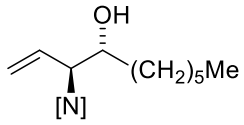
5.3m, 77% yield
>20:1 dr



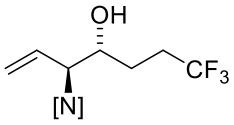
5.3n, 72% yield[b]
>20:1 dr



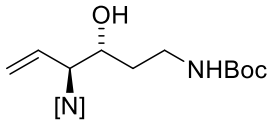
5.3o, 73% yield
>20:1 dr



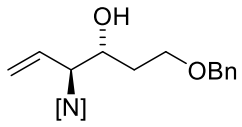
5.3p, 62% yield
>20:1 dr



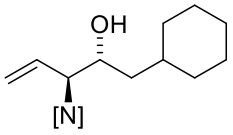
5.3q, 73% yield
>20:1 dr



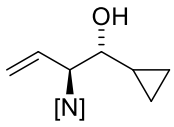
5.3r, 63% yield
>20:1 dr



5.3s, 61% yield[c]
>20:1 dr



5.3t, 75% yield[c]
>20:1 dr

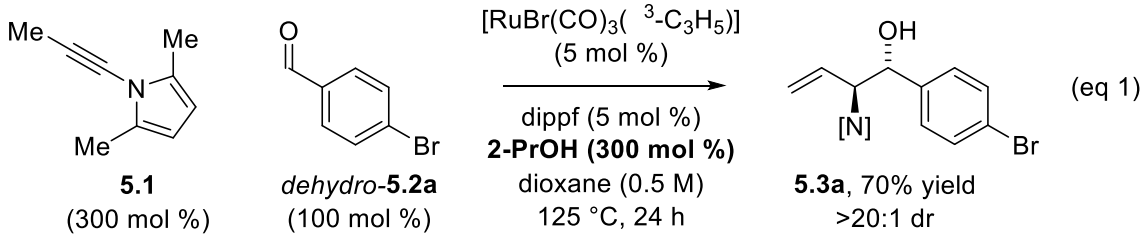


5.3u, 63% yield[c,d]
>20:1 dr

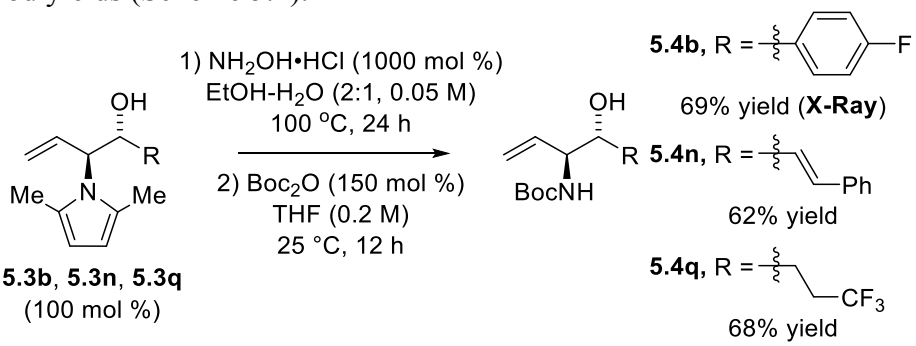
[a]Yields are material isolated by silica gel chromatography. See supporting Information for further experimental details. [b]2-PrOH (200 mol%). [c]48 h. [d]Dioxane (1.0 M).

The optimal condition was applied to coupling of **5.1** with diverse primary alcohols (Table 5.1). Benzylic alcohols 5.2a-5.2h and heterobenzylic alcohols 5.2i-5.2m were converted to addition adduct with good to excellent yields. To our delight, different substituents on the aromatic rings were tolerable. Notably, different heterocycles, such as furan, benzothiophene, pyridine, pyrimidine, and oxazole, were tolerant under the standard condition. Allylic alcohols **5.2n**-**5.2o** and aliphatic alcohols **5.2p**-**5.2u** were also engaged in the coupling with good yields. The 1 mmol scale was conducted with p-bromobenzyl alcohol, and 74% yield was obtained.

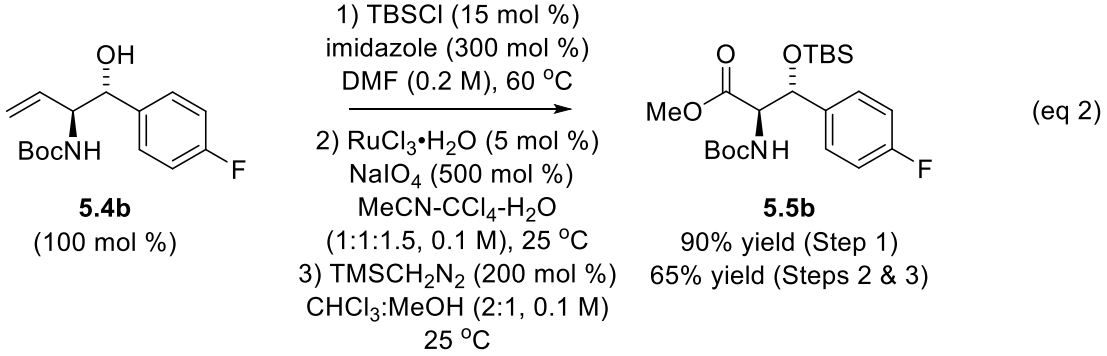
A side reaction was found during the formation of **5.3i**, **5.3k** and **5.3n**, which was formation of α, β-unsaturated ketones. By introduction of 2-propanol, the side reaction was suppressed. The reaction could proceed not only in redox-neutral manner, but also reductive coupling mediated by 2-propanol. Exposure of acetylenic pyrrole **5.1** to *p*-bromobenzaldehyde with ruthenium catalyst, dippf and 2-propanol, comparable coupling yield was obtained (eq 1).



Deprotection of the coupling adducts were explored for **5.3b**, **5.3n**, and **5.3q** derived from aromatic, allylic, and aliphatic alcohols **5.2b**, **5.2n**, and **5.2q**. The coupling adducts were treated with hydroxylamine hydrochloride in aqueous ethanol under heating, followed by *N*-Boc-protection of the resulting 2-amino alochols. Vicinal amino alcohols **5.4b**, **5.4n**, and **5.4q** were isolated in good yields (Scheme 5.1).



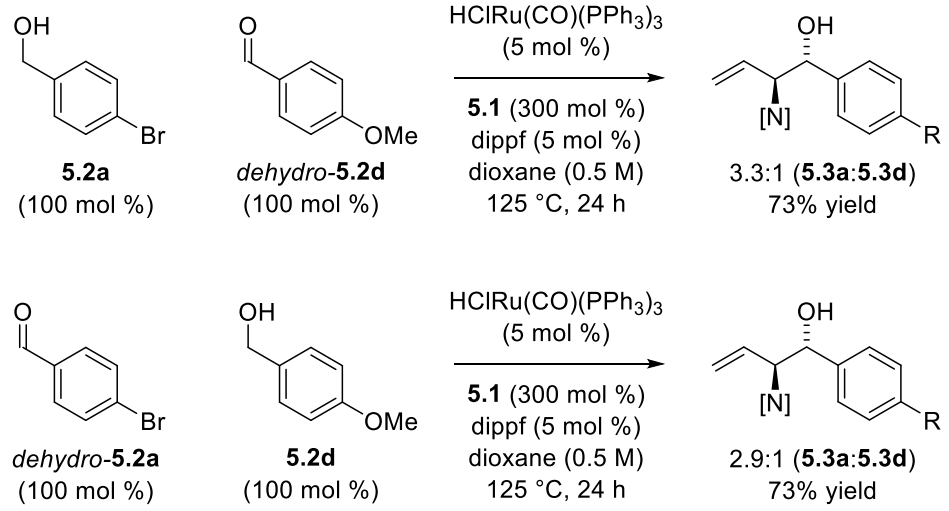
Scheme 5.1 Deprotection of Coupling Adducts to the Corresponding *N*-Boc-Protected Amino Alcohols.



Finally, to demonstrate the utility of this transformation, Boc-protected amino alcohol **5.4b** was converted to α-amino-β-hydroxyl amino ester **5.5b** via oxidative cleavage of alkene[9] followed by treatment with TMS diazomethane (eq 2).

5.3 Mechanism and Discussion

To obtain further insight in this transformation, the competition experiments were conducted (Scheme 5.2). When equimolar quantities of alcohol **5.2a** and aldehyde *dehydro*-**5.2d** were subjected to the standard reaction conditions, the coupling adducts **5.3a** and **5.3d** were produced with roughly 3:1 ratio. When the oxidation level of alcohol and aldehyde was inversed, similar coupling adduct ratio was obtained under the same reaction conditions. These data indicated that dehydrogenation of primary alcohols was rapid and reversible and carbonyl addition was the turnover limiting step.



Scheme 5.2 Competition Experiments Corroborating Rapid Reversible Dehydrogenation with Respect to Carbonyl Addition.

5.4 CONCLUSION

In summary, *anti*-diastereoselective carbonyl (α-amino)allylation by coupling of primary alcohols and acetylenic pyrrole **5.1** under ruthenium catalysis was reported. The coupling proceeded through two discrete catalytic cycle: alkyne-to-allene isomerization and allene-carbonyl coupling via transfer hydrogenation. This process also represented a byproduct free protocol.

5.5 EXPERIMENTAL DETAILS

General Information

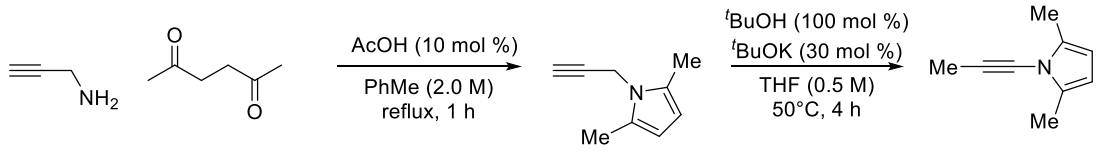
All reactions were run under an atmosphere of argon, unless otherwise indicated. Resealable pressure tubes (13x100 mm) were purchased from Fischer Scientific (catalog number 14–959–35C) and were flame dried followed by cooling in a desiccator or under a stream of argon prior to use. Tetrahydrofuran (THF) was dried over sodium metal, benzophenone, and distilled immediately prior to use. $RuH_2(PPh_3)_3$ were prepared according to literature procedure.1 All ligands were used as received from Strem Chemicals Inc. Alcohols were purified by distillation or recrystallization immediately prior to use. Preparative column chromatography employing Silicycle silica gel (40-63 μm) was performed according to the method of Still.2 Analytical thin-layer chromatography (TLC) was carried out using 0.25 mm commercial silica gel plates (Dynamic Absorbents F254). Visualization was accomplished with UV light followed by dipping in Seebach's stain solution then heating. Purification of reactions was carried out by flash chromatography using Silicycle silica gel (40–63 μm).

Spectroscopy, Spectrometry, and Data Collection

Infrared spectra were recorded on a Perkin-Elmer 1600 spectrometer. Low-resolution mass spectra (LRMS) were obtained on a Karatos MS9 and are reported as m/z (relative intensity). Accurate masses are reported for the molecular ion (M+H, M+Na), or a suitable fragment ion. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded with a Varian Gemini (400 MHz) spectrometer. Chemical shifts are reported in delta (δ) units, parts per million (ppm) downfield from tetramethylsilane or ppm relative to the center of the singlet at 7.26 ppm for deuteriochloroform. Data reported as multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). Integration and coupling constants were reported in Hertz (Hz). Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded with a Varian Gemini (100 MHz) spectrometer and were routinely run with broadband decoupling. Chemical shifts are reported in delta (δ) units, ppm relative to the center of the triplet at 77.16 ppm for deuteriochloroform.

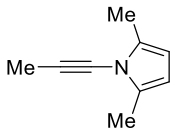
Experimental Details and Spectral Data

Preparation of Acetylenic Pyrrole 5.1



To a solution of propargyl amine (2.75 g, 50 mmol, 100 mol %) and 2,5-hexanedione (7.1 g, 50 mmol, 100 mol %) in toluene (25 mL, 2.0 M) was added acetic acid (0.29 mL, 5 mmol, 10 mol %) dropwise. The reaction mixture was allowed to reflux for 1 hour and then cooled to room temperature. The reaction mixture was washed with saturated aqueous NH_4Cl, $NaHCO_3$, and brine. The solvent was removed *in vacuo* and afforded crude product as a brown solid.[2] To the crude product dissolved in THF (100 mL, 0.5 M) under argon was added *tert*-BuOH (4.74 mL, 50 mmol, 100 mol %) and *tert*-BuOK (1.68 g, 15 mmol, 30 mol %). The reaction was stirred at 50°C for 4 hours until complete consumption of starting material as monitored by TLC. The reaction mixture was filtered through a short pad of celite and then washed with EtOAc. The filtrate was then washed with H_2O. The solvent was removed *in vacuo* and the residue was subjected to column chromatography (SiO_2; hexanes). The title compound was obtained in 41% yield (2.73 g, 20 mmol) as a colorless liquid.

2,5-dimethyl-1-(prop-1-yn-1-yl)-1H-pyrrole (5.1).



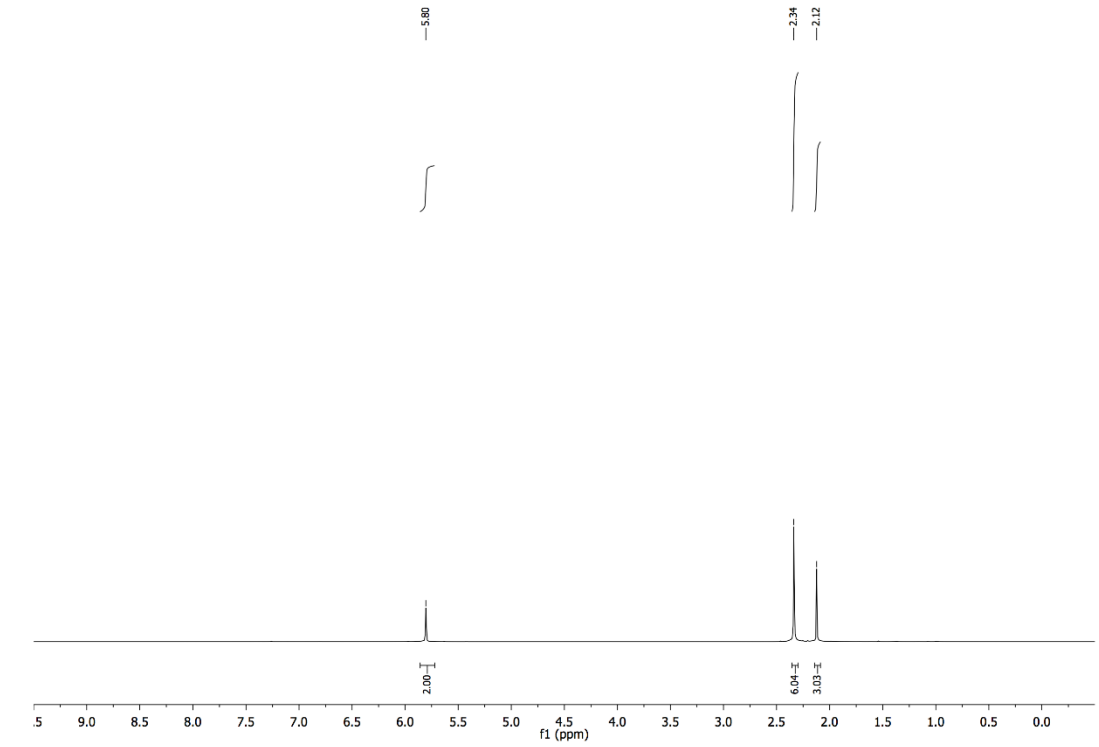
Rf=0.4 (100% Hexanes).

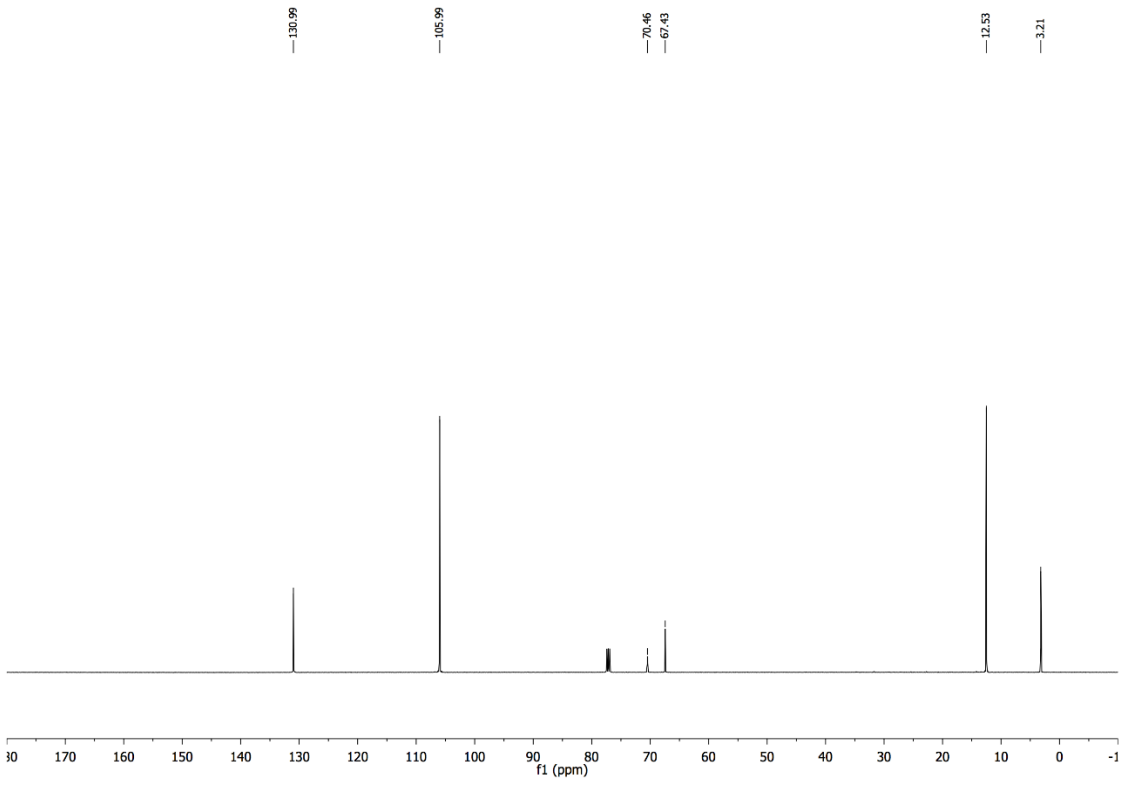
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.80 (s, 2H), 2.34 (s, 6H), 2.12 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 131.0, 106.0, 70.5, 67.4, 12.5, 3.2.

HRMS (ESI) Calcd. for $C_9H_{12}N$ $[M+H]^+$: 134.0964, Found: 134.0962.

FTIR (neat): 2919, 2265, 1537, 1412, 1372, 1325, 1210, 1023, 980, 954, 759 cm^{-1}.


5.80
2.34
2.12
2.00
6.04
3.03
f1 (ppm)


130.99
105.99
70.46
67.43
12.53
3.21
f1 (ppm)

General Procedure for the Couplings of Alcohols 5.2a-5.2u and 5.1

To a resealable pressure tube (13x100) were added $HClRu(CO)(PPh_3)_3$ (9.5 mg, 0.010 mmol, 5 mol %) and dippf (4.2 mg, 0.010 mmol, 5 mol %). At this stage the solid alcohol coupling partners (0.20 mmol, 100 mol %) were added. The tube was sealed with a rubber septum and purged with argon. Dioxane (0.40 mL, 0.5 M) was added to the reaction vessel. At this stage, the liquid alcohol coupling partners (0.20 mmol, 100 mol %) were added. Acetylenic pyrrole **5.1** (0.60 mmol, 300 mol %) was added to the reaction vessel and the rubber septum was quickly replaced with a screw cap. The mixture was allowed to stir at the indicated temperature for the indicated time. The reaction mixture was then allowed to cool to room temperature. The solvents were removed *in vacuo* and the residue was subjected to column chromatography (SiO_2).

1 mmol Scale Procedure

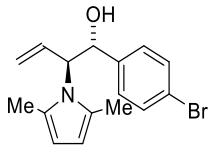
To a resealable pressure tube were added $HClRu(CO)(PPh_3)_3$ (47.6 mg, 0.050 mmol, 5 mol %) and dippf (20.9 mg, 0.050 mmol, 5 mol %). At this stage the solid alcohol coupling partners (1.0 mmol, 100 mol %) were added. The tube was sealed with a rubber septum and purged with argon. Dioxane (2.0 mL, 0.5 M) was added to the reaction vessel. At this stage, the liquid alcohol coupling partners (1.0 mmol, 100 mol %) were added. Acetylenic pyrrole **5.1** (3.0 mmol, 300 mol %) was added to the reaction vessel and the rubber septum was quickly replaced with a screw cap. The mixture was allowed to stir at the indicated temperature for the indicated time. The reaction mixture was then allowed to cool to room temperature. The solvents were removed *in vacuo* and the residue was subjected to column chromatography (SiO_2).

From Aldehyde Oxidation Level

To a resealable pressure tube (13x100) were added $RuBr(CO)_3(\eta^3\text{-}C_3H_5)$ (3.1 mg, 0.010 mmol, 5 mol %) and dippf (4.2 mg, 0.010 mmol, 5 mol %). At this stage the coupling partner aldehyde (0.2

mmol, 100 mol %) was added. The tube was sealed with a rubber septum and purged with argon. Dioxane (0.4 mL, 0.5 M) was added to the reaction vessel. Acetylenic pyrrole **5.1** (0.6 mmol, 300 mol %) was added to the reaction vessel followed by 2-propanol (0.6 mmol, 300 mol %) and the rubber septum was quickly replaced with a screw cap. The mixture was allowed to stir at the indicated temperature for the indicated time. The reaction mixture was then allowed to cool to room temperature. The solvents were removed *in vacuo* and the residue was subjected to column chromatography (SiO_2).

1-(4-bromophenyl)-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)but-3-en-1-ol (5.3a).



In accordance with the general procedure at 125°C for 24 hours, the title compound was obtained in 83% yield (53.2 mg, *dr* = >20:1) as a yellow liquid after column chromatography (SiO_2; 10% EtOAc/hexanes).
Comparable yield and equivalent diastereoselectivity was observed when the reaction was conducted on 1 mmol scale (74% yield, dr = > 20:1) and from aldehyde oxidation level (70% yield, dr = > 20:1).

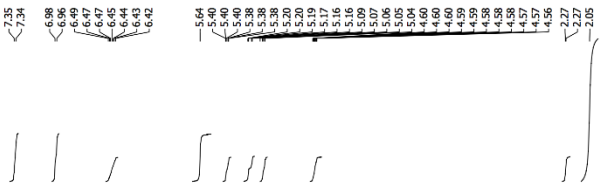
R_f=0.6 (20% EtOAc/Hexanes).

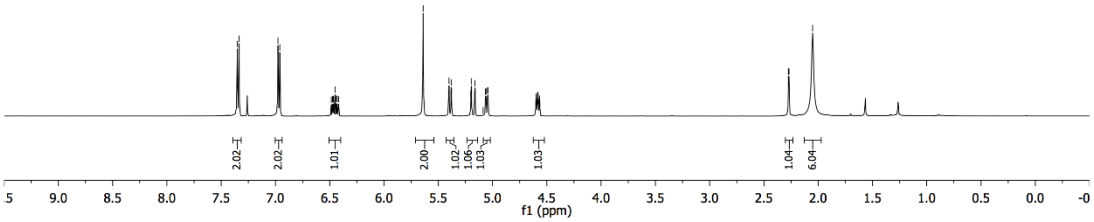
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.32 (m, 2H), 7.00 – 6.94 (m, 2H), 6.45 (ddd, *J* = 16.9, 10.5, 6.2 Hz, 1H), 5.64 (s, 2H), 5.39 (dt, *J* = 10.5, 1.5 Hz, 1H), 5.18 (dt, *J* = 17.2, 1.5 Hz, 1H), 5.05 (dd, *J* = 9.5, 2.5 Hz, 1H), 4.58 (ddt, *J* = 9.6, 6.3, 1.7 Hz, 1H), 2.27 (d, *J* = 2.8 Hz, 1H), 2.05 (s, 6H).

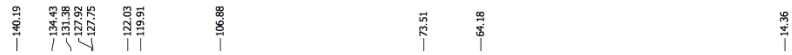
^{13}C NMR (100 MHz, $CDCl_3$): δ 140.19, 134.43, 131.38, 127.92, 127.75, 122.03, 119.91, 106.88, 73.51, 64.18, 14.36.

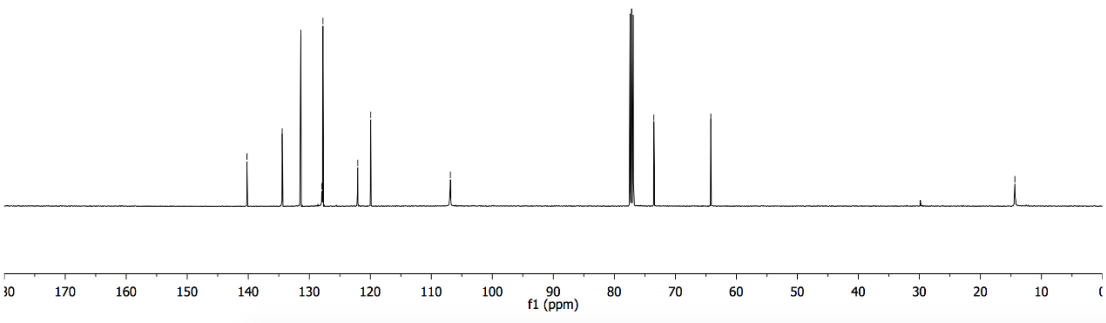
HRMS (ESI) Calcd. for $C_{16}H_{19}BrNO$ $[M+H]^+$: 320.0645, Found: 320.0643.

FTIR (neat): 3462, 2921, 2360, 1486, 1395, 1292, 1072, 1010, 929, 816, 757 cm^{-1}.

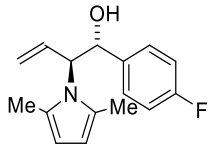

7.35
7.34
6.98
6.96
6.49
6.47
6.47
6.45
6.44
6.43
6.42
5.64
5.40
5.40
5.40
5.38
5.38
5.20
5.20
5.19
5.17
5.16
5.16
5.09
5.07
5.06
5.05
5.04
4.60
4.60
4.59
4.59
4.58
4.58
4.58
4.57
4.57
4.56
2.27
2.27
2.05


2.02
2.02
1.01
2.00
1.02
1.06
1.03
1.03
1.04
6.04
f1 (ppm)


140.19
134.43
131.38
127.92
127.75
122.03
119.91
106.88
73.51
64.18
14.36


f1 (ppm)

2-(2,5-dimethyl-1*H*-pyrrol-1-yl)- 1-(4-fluorophenyl)but-3-en-1-ol (5.3b).



In accordance with the general procedure at 125°C for 24 hours, the title compound was obtained in 75% yield (38.9 mg, *dr* = >20:1) as a yellow liquid after column chromatography (SiO_2; 10% EtOAc/hexanes).

R_f=0.41 (20% EtOAc/Hexanes)

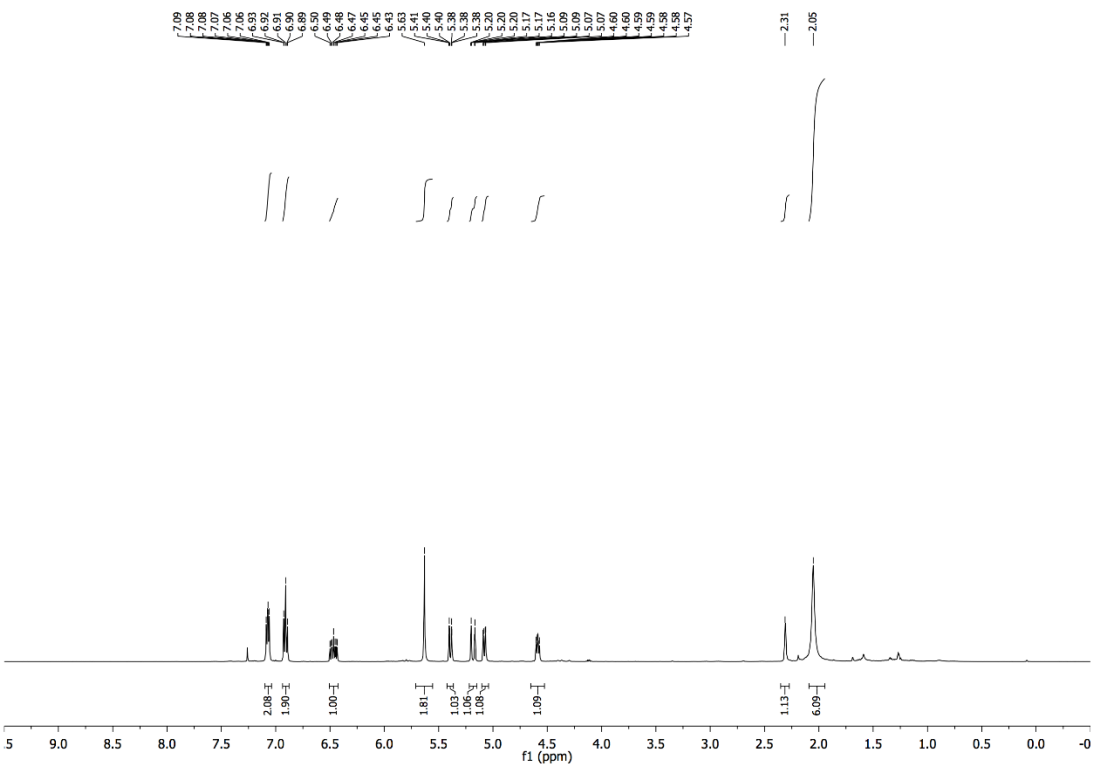
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 – 7.03 (m, 2H), 6.91 (t, *J* = 8.7 Hz, 2H), 6.47 (ddd, *J* = 16.9, 10.4, 6.1 Hz, 1H), 5.63 (s, 2H), 5.39 (dd, *J* = 10.4, 1.5 Hz, 1H), 5.18 (dd, *J* = 17.2, 1.5 Hz, 1H), 5.08 (dd, *J* = 9.5, 2.1 Hz, 1H), 4.62 – 4.54 (m, 1H), 2.31 (d, *J* = 2.7 Hz, 1H), 2.05 (s, 6H).

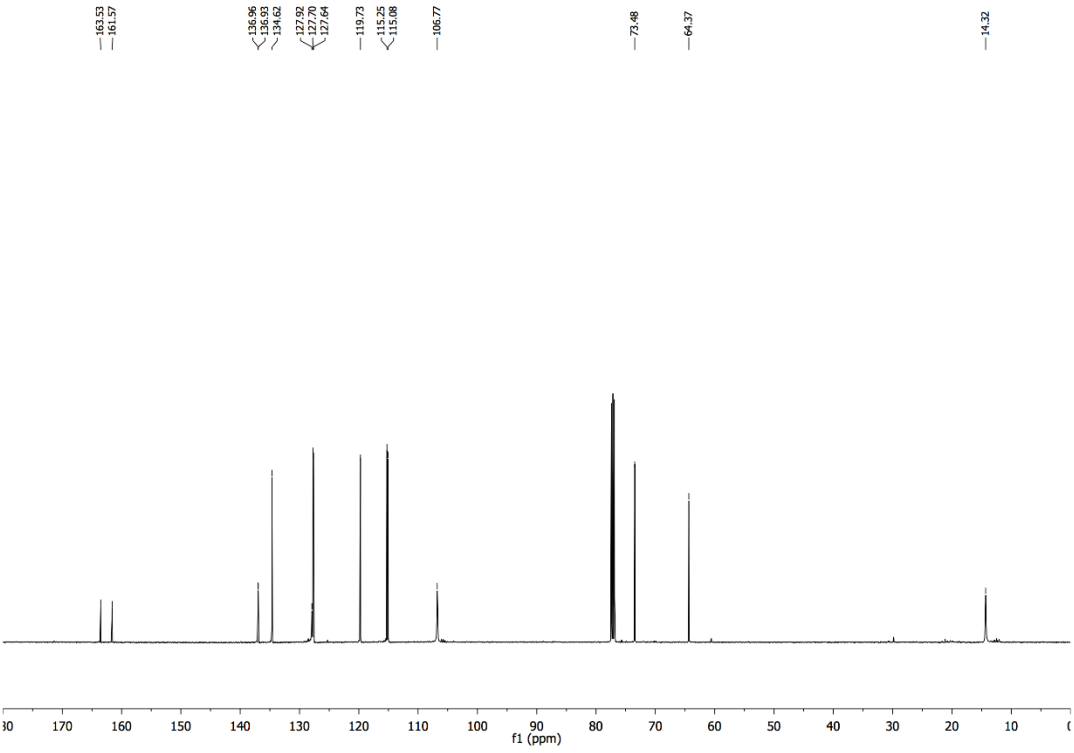
^{19}F NMR (100 MHz, $CDCl_3$) δ -114.2.

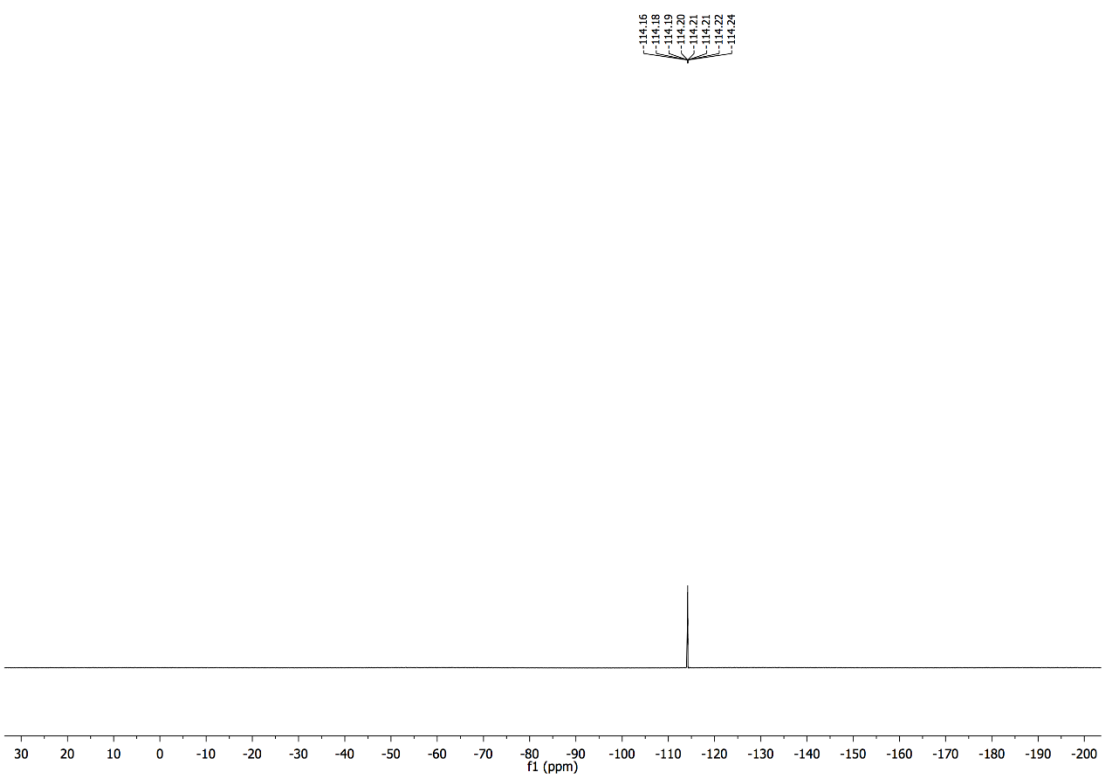
^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6 (d, $J_{C\text{-}F}$ = 246.2 Hz), 136.9 (d, $J_{C\text{-}F}$ = 3.2 Hz), 134.6, 127.9, 127.7 (d, $J_{C\text{-}F}$ = 8.0 Hz), 119.7, 115.2 (d, $J_{C\text{-}F}$ = 21.4 Hz), 106.8, 73.5, 64.4, 14.3.

HRMS (ESI) Calcd. for $C_{16}H_{19}FNO^+$ $[M+H]^+$: 260.1451, Found: 260.1445.

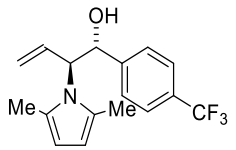
FTIR (neat): 3439, 2970, 2929, 1739, 1604, 1509, 1395, 1292, 1221, 1043, 854, 834, 752 cm^{-1}.


7.09
7.08
7.08
7.07
7.07
7.06
7.06
6.93
6.92
6.91
6.90
6.89
6.50
6.49
6.48
6.47
6.45
6.45
6.43
5.63
5.41
5.40
5.40
5.38
5.38
5.20
5.20
5.20
5.17
5.15
5.09
5.09
5.07
5.07
4.60
4.60
4.59
4.59
4.58
4.58
4.57
2.31
2.05
2.08
1.90
1.00
1.81
1.03
1.06
1.08
1.09
1.13
6.09
f1 (ppm)


163.53
161.57
136.96
136.93
134.62
127.92
127.70
127.64
119.73
115.25
115.08
106.77
73.48
64.37
14.32
f1 (ppm)


-114.16
-114.18
-114.19
-114.20
-114.21
-114.21
-114.22
-114.24
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

2-(2,5-dimethyl-1H-pyrrol-1-yl)-1-(4-(trifluoromethyl)phenyl)but-3-en-1-ol (5.3c).



In accordance with the general procedure at 125°C for 24 hours, the title compound was obtained in 96% yield (59.4 mg, *dr* = >20:1) as a yellow liquid after column chromatography (SiO_2; 10% EtOAc/hexanes).

R_f=0.40 (20% EtOAc/Hexanes)

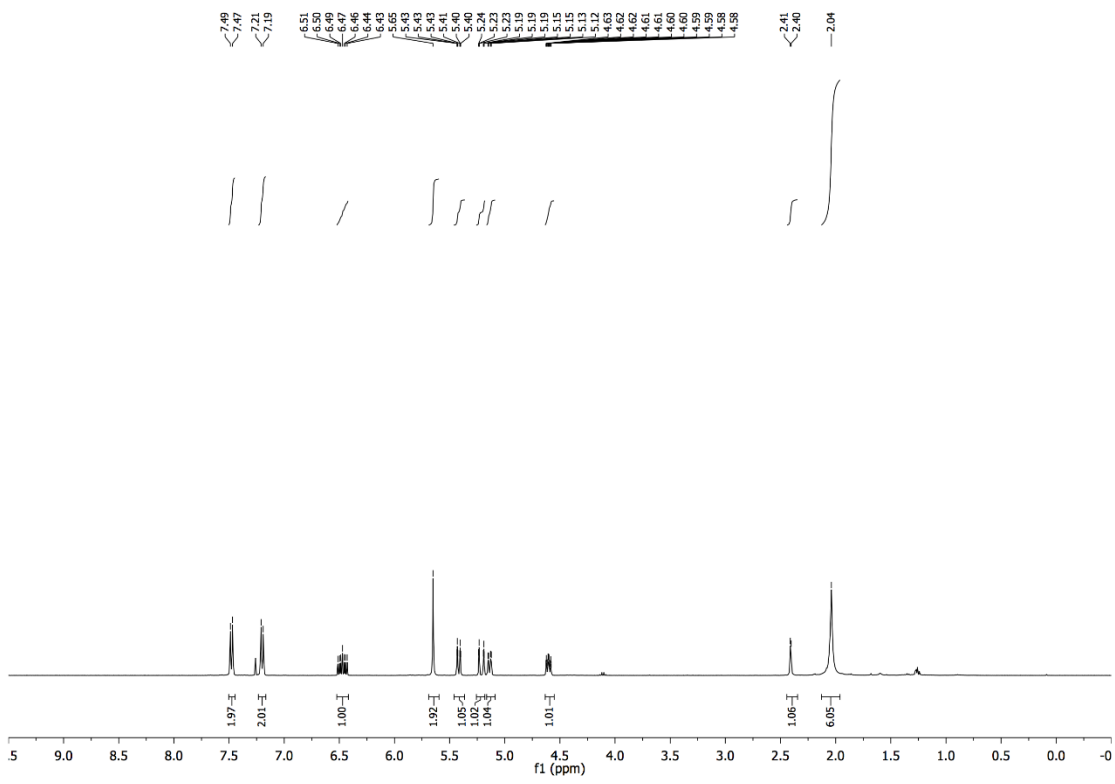
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.1 Hz, 2H), 7.20 (d, *J* = 8.1 Hz, 2H), 6.47 (ddd, *J* = 17.0, 10.4, 6.3 Hz, 1H), 5.65 (s, 2H), 5.42 (dt, *J* = 10.5, 1.4 Hz, 1H), 5.21 (dt, *J* = 17.2, 1.5 Hz, 1H), 5.14 (dd, *J* = 9.5, 2.3 Hz, 1H), 4.64 – 4.57 (m, 1H), 2.41 (d, *J* = 2.8 Hz, 1H), 2.04 (s, 6H).

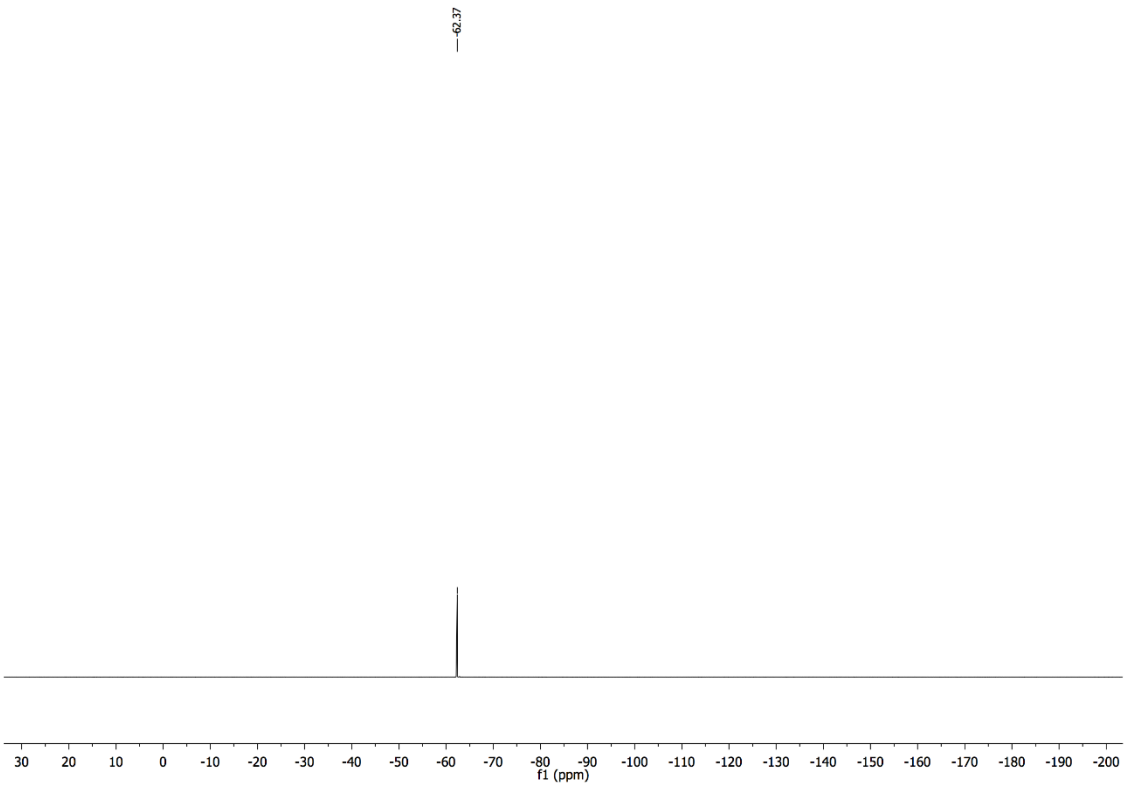
^{19}F NMR (100 MHz, $CDCl_3$) δ -62.5.

^{13}C NMR (100 MHz, $CDCl_3$) δ 145.1, 134.2, 130.2 (q, J_{C-F} = 32.4 Hz), 128.0, 126.4, 125.2 (q, J_{C-F} = 3.8 Hz), 124.2 (q, J_{C-F} = 272.0 Hz), 120.2, 107.0, 73.5, 64.2, 14.3.

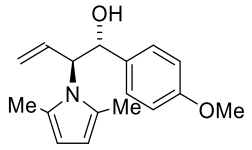
HRMS (ESI) Calcd. for $C_{17}H_{19}F_3NO^+$ $[M+H]^+$: 310.1419, Found: 310.1415.

FTIR (neat): 3462, 2970, 1739, 1395, 1324, 1164, 1123, 1068, 928, 836, 759 cm^{-1}.


7.49
7.47
7.21
7.19
6.51
6.50
6.49
6.47
6.46
6.44
6.43
5.65
5.43
5.43
5.41
5.40
5.40
5.24
5.23
5.23
5.19
5.19
5.19
5.15
5.15
5.13
5.12
4.63
4.62
4.62
4.61
4.61
4.60
4.60
4.59
4.59
4.58
4.58
2.41
2.40
2.04
1.97
2.01
1.00
1.92
1.05
1.02
1.04
1.01
1.06
6.05
f1 (ppm)
145.13
134.21
130.62
130.36
130.10
129.85
127.95
126.40
125.27
125.22
125.19
125.16
125.13
123.10
120.21
107.02
73.51
64.21
14.30
f1 (ppm)


-62.37
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

2-(2,5-dimethyl-1H-pyrrol-1-yl)-1-(4-methoxyphenyl)but-3-en-1-ol (5.3d).



In accordance with the general procedure at 125°C for 24 hours, the title compound was obtained in 50% yield (27.1 mg, *dr* = >20:1) as a yellow liquid after column chromatography (SiO_2; 10% EtOAc/hexanes).

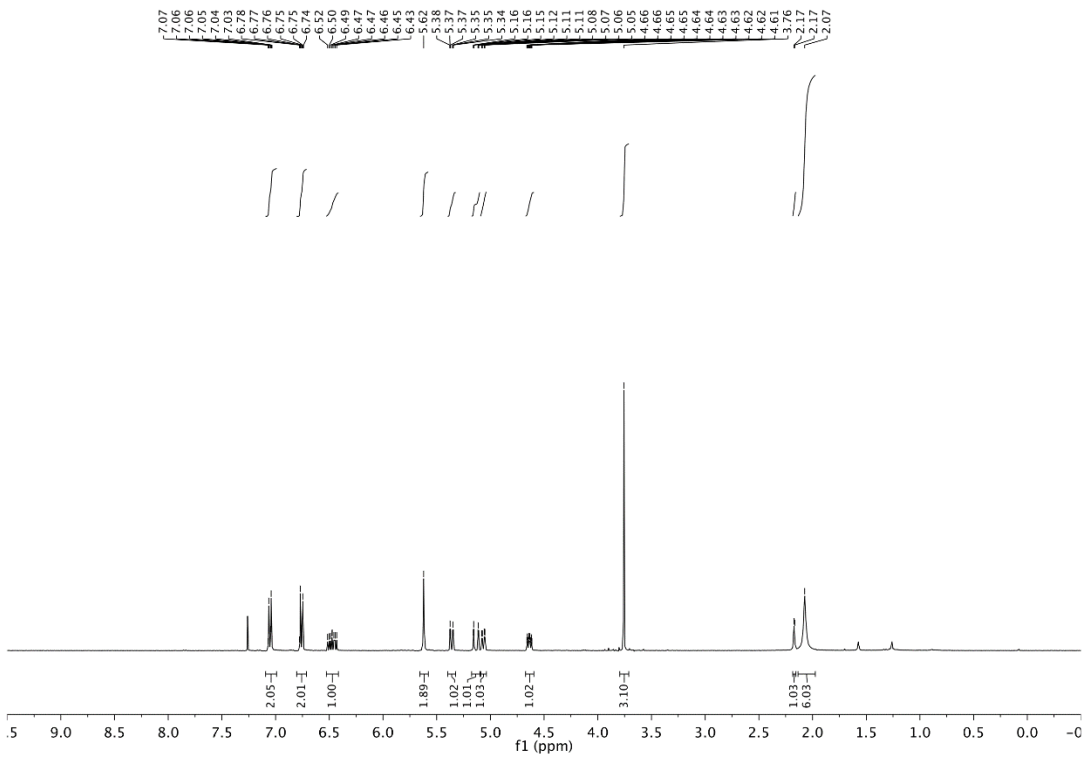
R_f=0.29 (20% EtOAc/Hexanes)

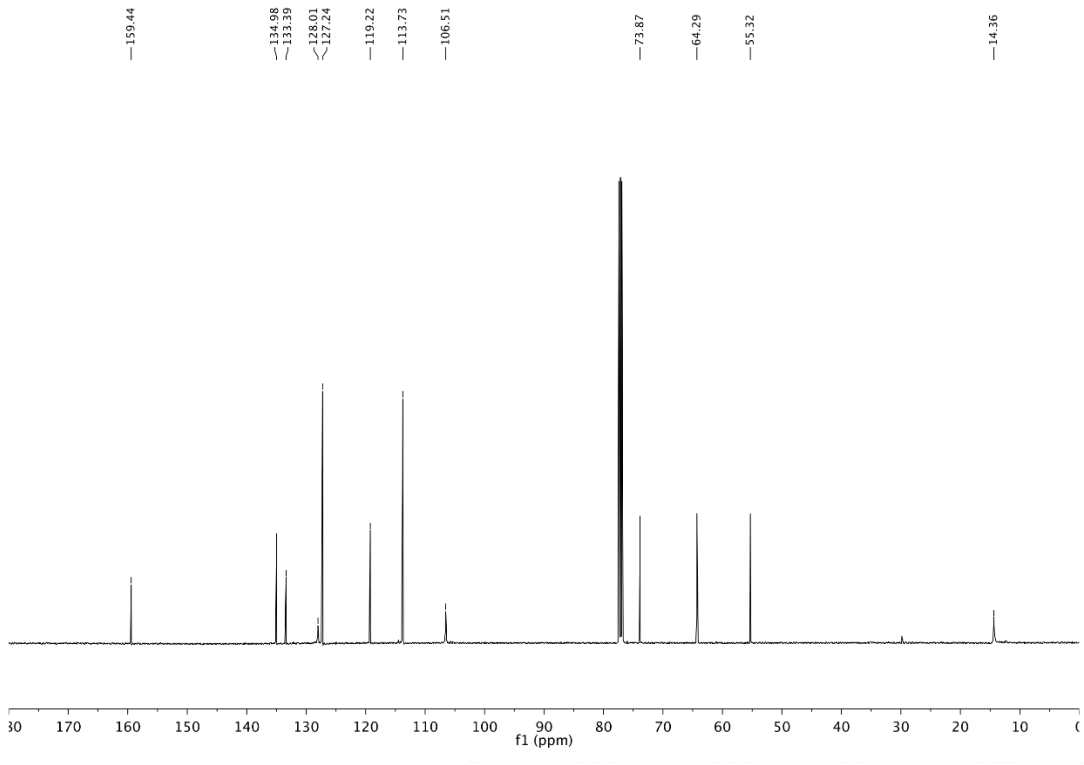
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 – 7.02 (m, 2H), 6.79 – 6.73 (m, 2H), 6.47 (ddd, *J* = 17.2, 10.4, 6.0 Hz, 1H), 5.62 (s, 2H), 5.36 (dt, *J* = 10.4, 1.5 Hz, 1H), 5.13 (dt, *J* = 17.2, 1.5 Hz, 1H), 5.07 (dd, *J* = 9.4, 2.2 Hz, 1H), 4.64 (ddt, *J* = 9.4, 5.9, 1.7 Hz, 1H), 3.76 (s, 3H), 2.17 (d, *J* = 2.6 Hz, 1H), 2.07 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 135.0, 133.4, 128.0, 127.2, 119.2, 113.7, 106.5, 73.9, 64.3, 55.3, 14.4.

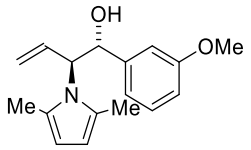
HRMS (ESI) Calcd. for $C_{17}H_{21}NO_2Na^+$ $[M+Na]^+$: 294.1470, Found: 294.1452.

FTIR (neat): 3458, 2970, 1738, 1612, 1512, 1396, 1373, 1243, 1036, 925, 828, 750 cm^{-1}.


7.07
7.06
7.06
7.05
7.04
7.03
6.78
6.77
6.76
6.75
6.75
6.74
6.52
6.50
6.49
6.47
6.47
6.46
6.45
6.43
5.62
5.38
5.37
5.37
5.35
5.35
5.34
5.16
5.16
5.15
5.12
5.11
5.11
5.08
5.07
5.06
5.05
4.66
4.66
4.65
4.65
4.64
4.64
4.63
4.62
4.62
4.61
3.76
2.17
2.17
2.07
2.05
2.01
1.00
1.89
1.02
1.01
1.03
1.02
3.10
1.03
6.03
f1 (ppm)


159.44
134.98
133.39
128.01
127.24
119.22
113.73
106.51
73.87
64.29
55.32
14.36
f1 (ppm)

2-(2,5-dimethyl-1H-pyrrol-1-yl)-1-(3-methoxyphenyl)but-3-en-1-ol (5.3e).



In accordance with the general procedure at 125°C for 24 hours, the title compound was obtained in 71% yield (38.5 mg, *dr* = >20:1) as a yellow liquid after column chromatography (SiO_2; 7.5-10% EtOAc/hexanes).

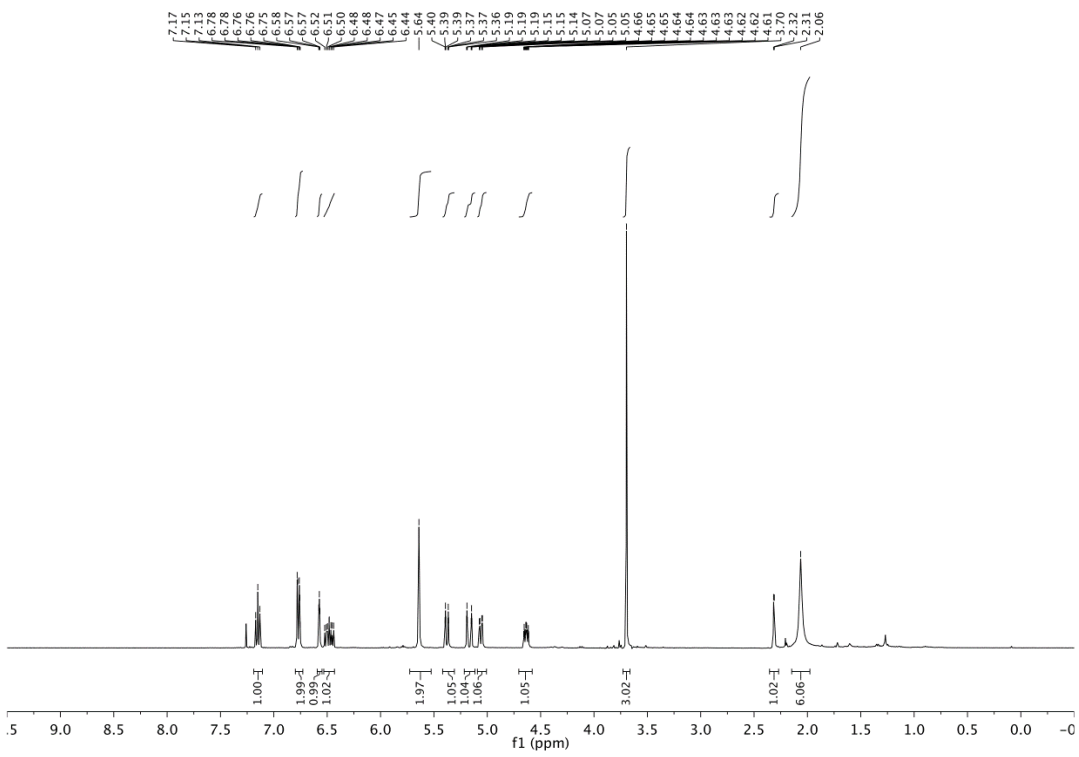
R_f=0.37 (20% EtOAc/Hexanes)

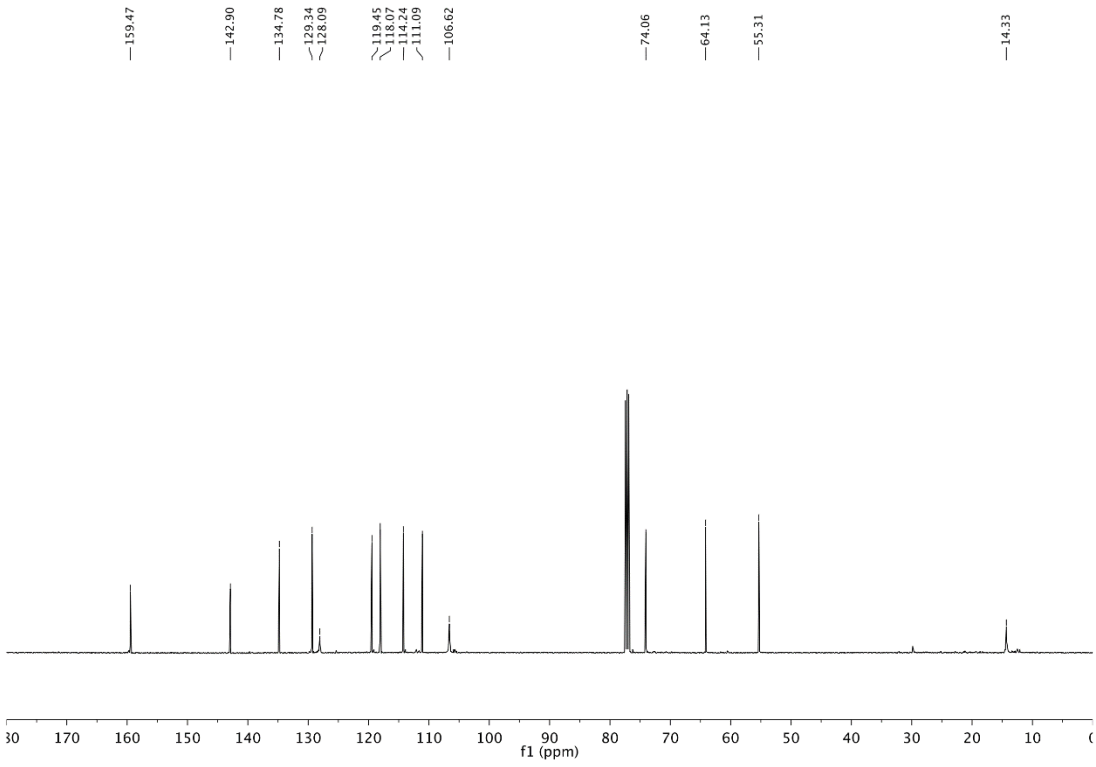
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (t, *J* = 7.9 Hz, 1H), 6.77 (dd, *J* = 8.0, 2,2 Hz, 2H), 6.57 (t, *J* = 2.1 Hz, 1H), 6.48 (ddd, *J* = 17.3, 10.5, 6.0 Hz, 1H), 5.64 (s, 2H), 5.38 (dt, *J* = 10.5, 1.5 Hz, 1H), 5.17 (dt, *J* = 17.2, 1.5 Hz, 1H), 5.06 (dd, *J* = 9.4, 2.5 Hz, 1H), 4.63 (ddt, *J* = 9.4, 6.1, 1.7 Hz, 1H), 3.70 (s, 3H), 2.31 (d, *J* = 2.8 Hz, 1H), 2.06 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 142.9, 134.8, 129.3, 128.1, 119.5, 118.1, 114.2, 111.1, 106.6, 74.1, 64.1, 55.3, 14.3.

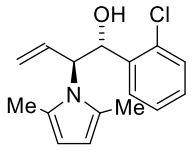
HRMS (ESI) Calcd. for $C_{17}H_{21}NO_2Na^+$ $[M+Na]^+$: 294.1470, Found: 294.1457.

FTIR (neat): 3464, 2934, 1739, 1602, 1455, 1395, 1290, 1256, 1156, 1038, 925, 750, 698 cm^{-1}.


7.17
7.15
7.13
6.78
6.78
6.76
6.76
6.75
6.58
6.57
6.52
6.51
6.50
6.48
6.48
6.47
6.45
6.44
5.64
5.40
5.39
5.39
5.37
5.37
5.36
5.19
5.19
5.19
5.15
5.15
5.14
5.07
5.07
5.05
5.05
4.66
4.65
4.65
4.64
4.64
4.63
4.63
4.63
4.62
4.62
4.61
3.70
2.32
2.31
2.06
1.00
1.99
0.99
1.02
1.97
1.05
1.04
1.06
1.05
3.02
1.02
6.06
f1 (ppm)


159.47
142.90
134.78
129.34
128.09
119.45
118.07
114.24
111.09
106.62
74.06
64.13
55.31
14.33
f1 (ppm)

1-(2-chlorophenyl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)but-3-en-1-ol (5.3f).



In accordance with the general procedure at 125°C for 24 hours, the title compound was obtained in 86% yield (47.4 mg, *dr* = >20:1) as a yellow liquid after column chromatography (SiO_2; 8% EtOAc/hexanes).

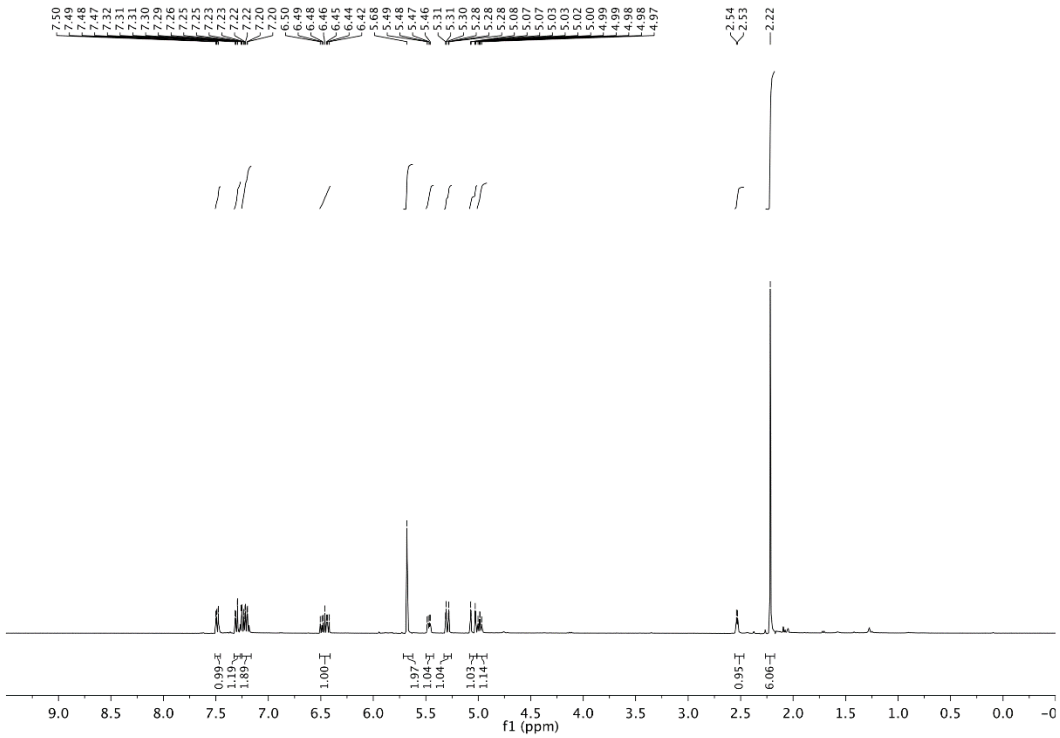
R_f=0.43 (20% EtOAc/Hexanes)

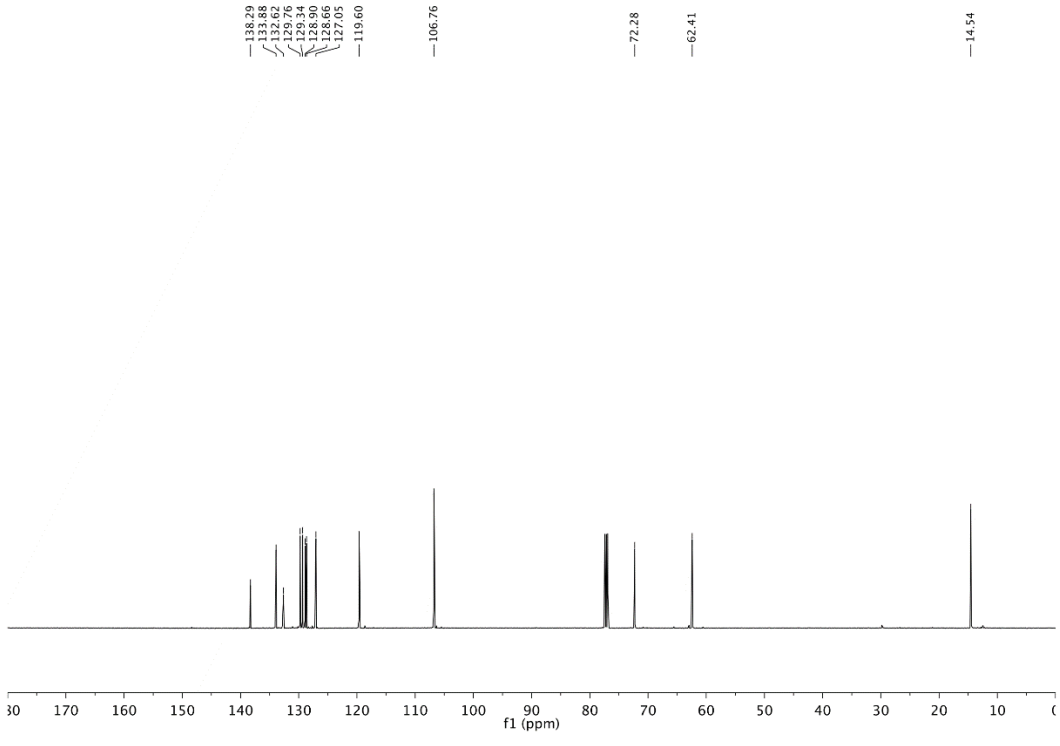
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.30 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.33 – 7.17 (m, 2H), 6.46 (ddd, *J* = 17.0, 10.4, 6.5 Hz, 1H), 5.67 (s, 2H), 5.47 (dd, *J* = 7.9, 3.7 Hz, 1H), 5.29 (dt, *J* = 10.4, 1.4 Hz, 1H), 5.05 (dt, *J* = 17.2, 1.4 Hz, 1H), 5.01 – 4.94 (m, 1H), 2.53 (d, *J* = 4.2 Hz, 1H), 2.22 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 133.9, 132.6, 129.8, 129.3, 128.9, 128.7, 127.1, 119.6, 106.8, 72.3, 62.4, 14.5.

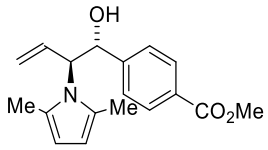
HRMS (ESI) Calcd. for $C_{16}H_{19}ClNO^+$ $[M+H]^+$: 276.1155, Found: 276.1147.

FTIR (neat): 3446, 2970, 1739, 1439, 1393, 1287, 1239, 1034, 927, 751 cm^{-1}.


7.50
7.49
7.48
7.47
7.32
7.31
7.31
7.30
7.29
7.26
7.25
7.25
7.23
7.23
7.22
7.22
7.20
7.20
6.50
6.49
6.48
6.46
6.45
6.44
6.42
5.50
5.49
5.48
5.47
5.46
5.31
5.31
5.30
5.28
5.28
5.28
5.08
5.07
5.07
5.03
5.03
5.02
5.00
4.99
4.99
4.98
4.98
4.97
2.54
2.53
2.22
0.99
1.19
1.89
1.00
1.97
1.04
1.04
1.03
1.14
0.95
6.06
f1 (ppm)


138.29
133.88
132.62
129.76
129.34
128.90
128.66
127.05
119.60
106.76
72.28
62.41
14.54
f1 (ppm)

methyl 4-(2-(2,5-dimethyl-1H-pyrrol-1-yl)-1-hydroxybut-3-en-1-yl)benzoate (5.3g)



In accordance with the general procedure at 125°C for 24 hours, the title compound was obtained in 73% yield (43.7 mg, *dr* = >20:1) as a yellow liquid after column chromatography (SiO_2; 7.5%-15% EtOAc/hexanes).

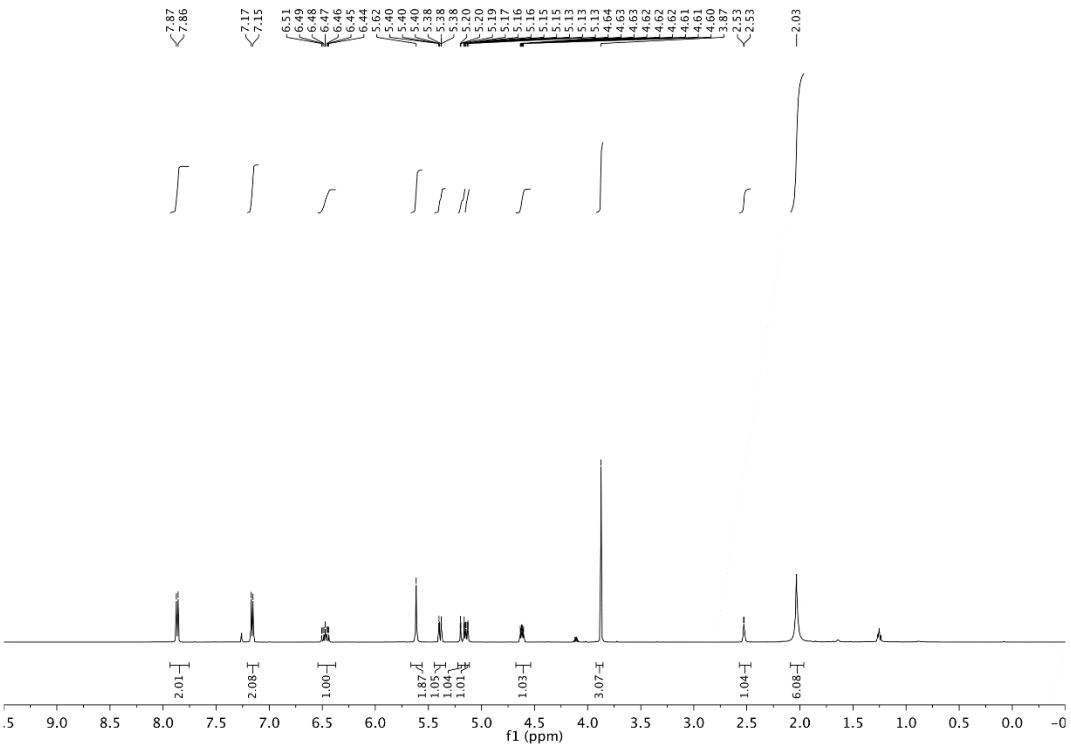
R_f=0.22 (20% EtOAc/Hexanes)

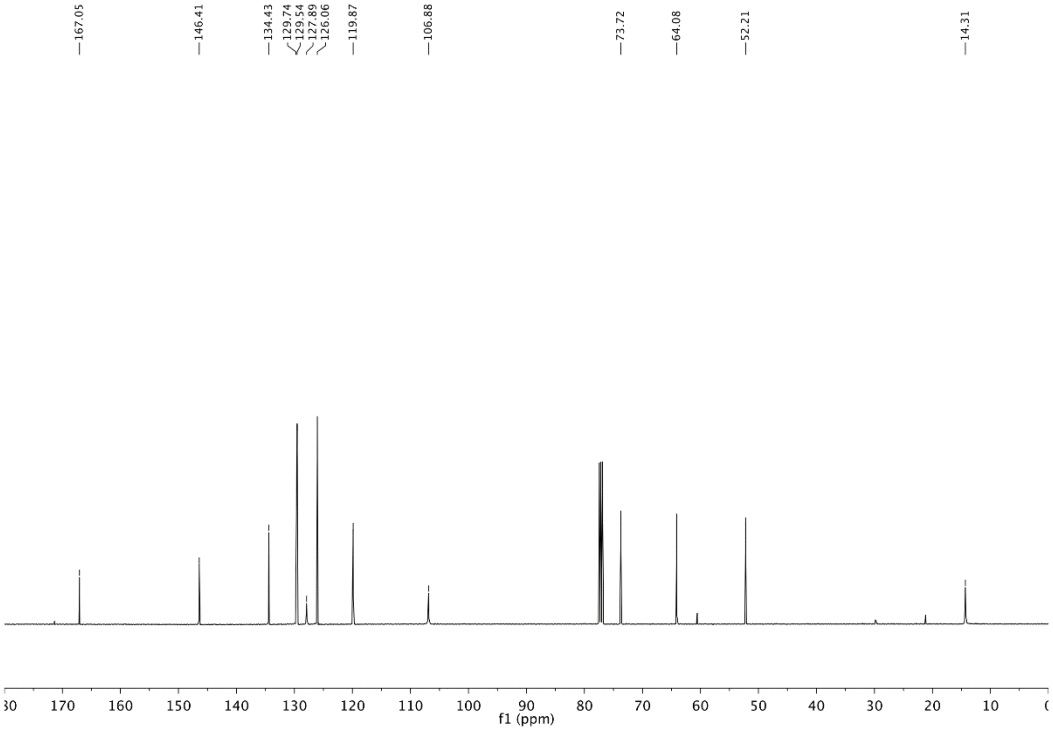
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 – 7.83 (m, 2H), 7.19 – 7.13 (m, 2H), 6.47 (ddd, *J* = 16.9, 10.5, 6.1 Hz, 1H), 5.62 (s, 2H), 5.39 (dt, *J* = 10.5, 1.4 Hz, 1H), 5.18 (dt, *J* = 17.2, 1.5 Hz, 1H), 5.14 (dd, *J* = 9.3, 2.1 Hz, 1H), 4.62 (ddt, *J* = 9.4, 6.2, 1.7 Hz, 1H), 3.87 (s, 3H), 2.53 (d, *J* = 2.9 Hz, 1H), 2.03 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 146.4, 134.4, 129.7, 129.5, 127.9, 126.1, 119.9, 106.9, 73.7, 64.1, 52.2, 14.3.

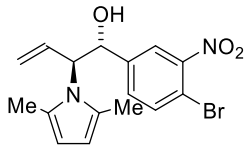
HRMS (ESI) Calcd. for $C_{18}H_{21}NO_3Na^+$ $[M+Na]^+$: 322.1419, Found: 322.1414.

FTIR (neat): 3461, 2952, 2359, 1738, 1707, 1697, 1395, 1281, 1111, 1040, 920, 760, 704 cm^{-1}.


7.87
7.86
7.17
7.15
6.51
6.49
6.48
6.47
6.46
6.45
6.44
5.62
5.40
5.40
5.40
5.38
5.38
5.20
5.20
5.19
5.17
5.16
5.16
5.15
5.15
5.13
5.13
4.64
4.63
4.63
4.62
4.62
4.62
4.61
4.61
4.60
3.87
2.53
2.53
2.03
2.01
2.08
1.00
1.87
1.05
1.04
1.01
1.03
3.07
1.04
6.08
f1 (ppm)


167.05
146.41
134.43
129.74
129.54
127.89
126.06
119.87
106.88
73.72
64.08
52.21
14.31
f1 (ppm)

1-(4-bromo-3-nitrophenyl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)but-3-en-1-ol (5.3h).



In accordance with the general procedure at 125°C for 24 hours, the title compound was obtained in 73% yield (53.3 mg, *dr* = >20:1) as a yellow liquid after column chromatography (SiO_2; 7.5%-12.5% EtOAc/hexanes).

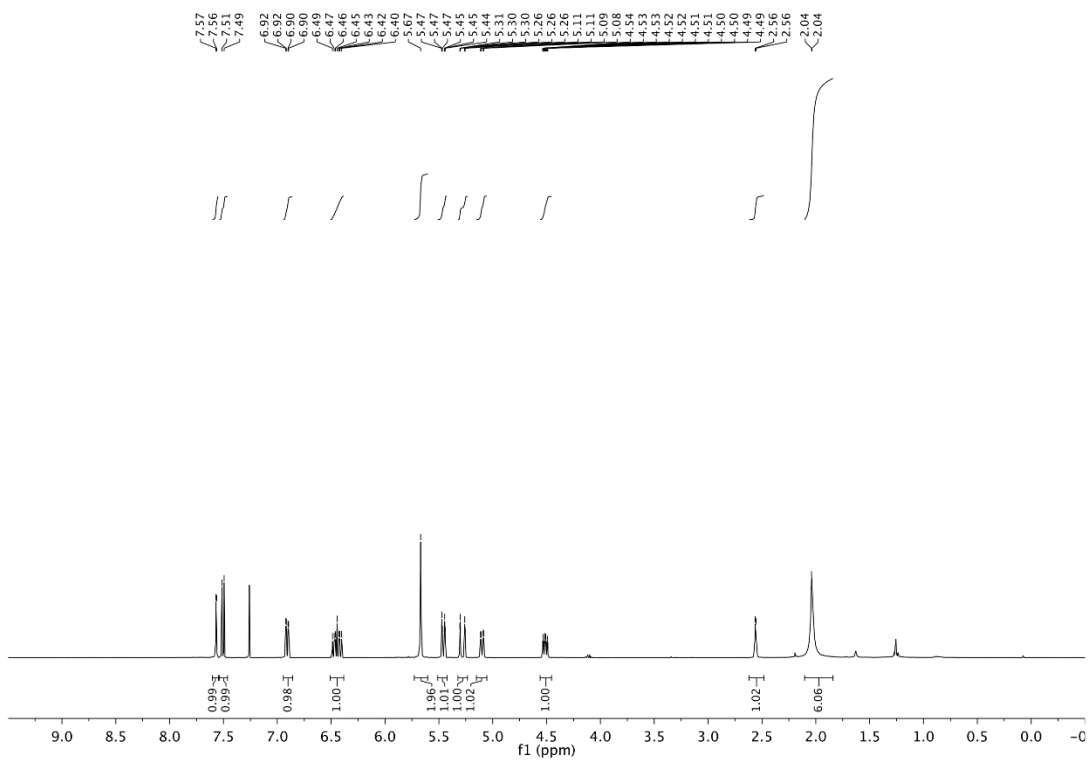
R_f =0.28 (20% EtOAc/Hexanes)

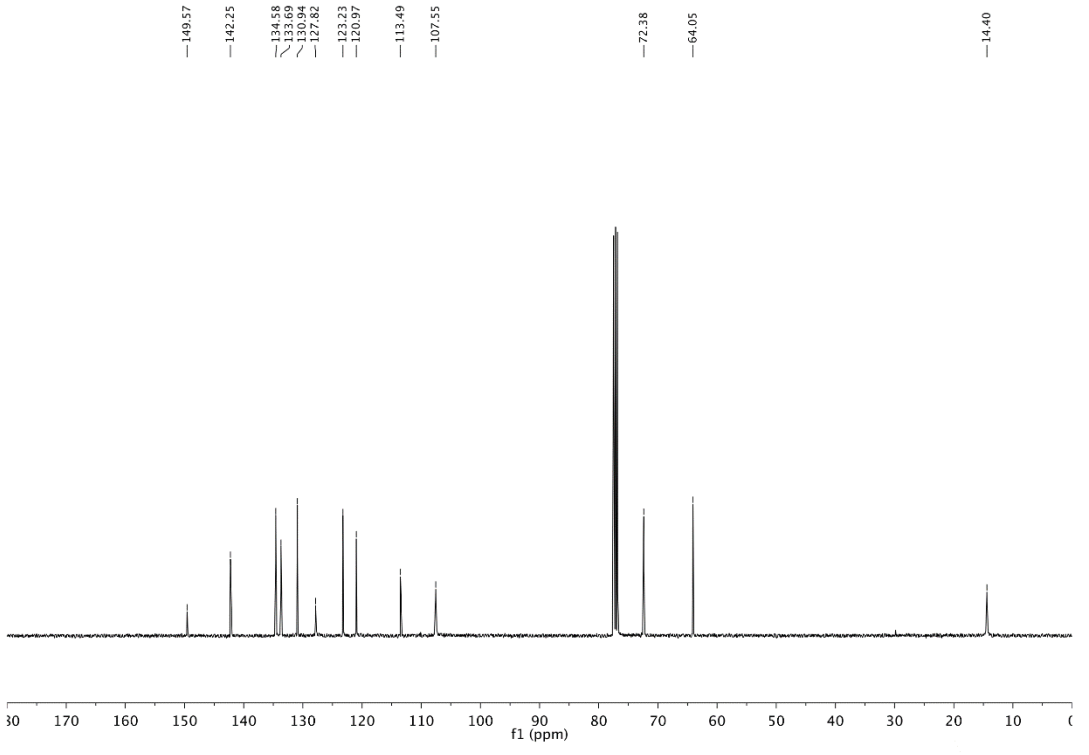
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 2.1 Hz, 1H), 7.50 (d, *J* = 8.3 Hz, 1H), 6.91 (dd, *J* = 8.3, 2.2 Hz, 1H), 6.45 (ddd, *J* = 17.1, 10.4, 6.5 Hz, 1H), 5.67 (s, 2H), 5.46 (dt, *J* = 10.4, 1.3 Hz, 1H), 5.28 (dt, *J* = 17.2, 1.4 Hz, 1H), 5.10 (dd, *J* = 9.7, 2.4 Hz, 1H), 4.51 (ddt, *J* = 9.6, 6.5, 1.6 Hz, 1H), 2.56 (d, *J* = 2.8 Hz, 1H), 2.04 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 149.6, 142.3, 134.6, 133.7, 130.9, 127.8, 123.2, 121.0, 113.5, 107.6, 72.4, 64.1, 14.4.

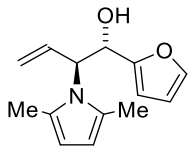
HRMS (ESI) Calcd. for $C_{16}H_{17}BrN_2O_3Na^+$ $[M+Na]^+$: 387.0320, Found: 387.0304.

FTIR (neat): 3458, 2978, 2928, 1736, 1707, 1536, 1393, 1373, 1357, 1291, 1243, 1044, 1031, 930, 823, 752 cm^{-1}.


7.57
7.56
7.51
7.49
6.92
6.92
6.90
6.90
6.49
6.47
6.46
6.45
6.43
6.42
6.40
5.67
5.47
5.47
5.47
5.45
5.45
5.44
5.31
5.30
5.30
5.26
5.26
5.26
5.11
5.11
5.09
5.08
4.54
4.53
4.53
4.52
4.52
4.51
4.51
4.50
4.50
4.49
4.49
2.56
2.56
2.04
2.04
0.99
0.99
0.98
1.00
1.96
1.01
1.06
1.02
1.00
1.02
6.06
f1 (ppm)


149.57
142.25
134.58
133.69
130.94
127.82
123.23
120.97
113.49
107.55
72.38
64.05
14.40
f1 (ppm)

2-(2,5-dimethyl-1H-pyrrol-1-yl)-1-(furan-2-yl)but-3-en-1-ol (5.3i).



In accordance with the general procedure at 125°C for 24 hours with 2-PrOH (200 mol%), the title compound was obtained in 71% yield (32.8 mg, *dr* = >20:1) as a yellow liquid after column chromatography (SiO_2; 10% EtOAc/hexanes).

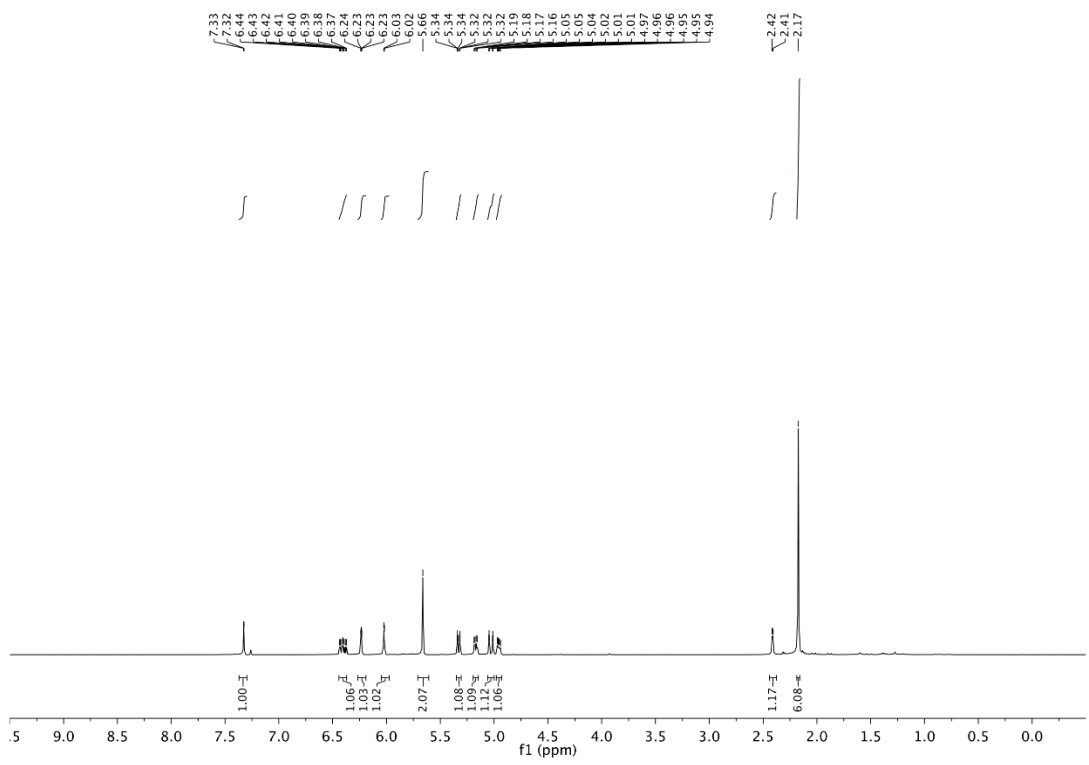
R_f = 0.4 (20% EtOAc/Hexanes).

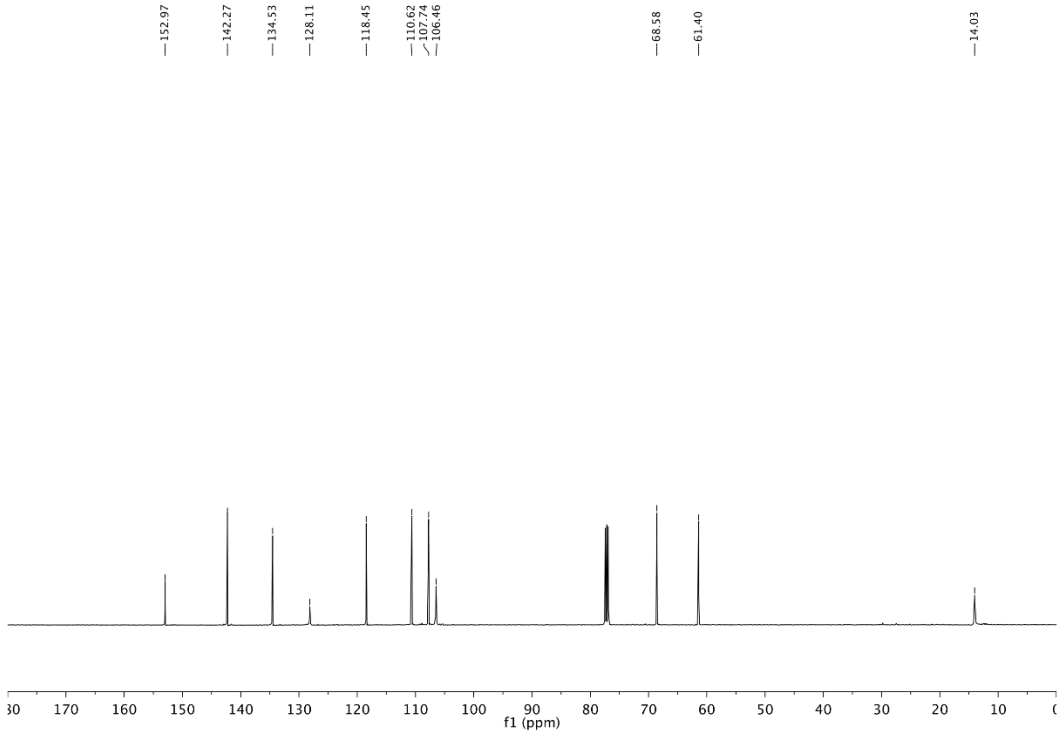
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (d, *J* = 1.8 Hz, 1H), 6.40 (ddd, *J* = 17.3, 10.5, 5.0 Hz, 1H), 6.23 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.02 (d, *J* = 3.3 Hz, 1H), 5.66 (s, 2H), 5.33 (dt, *J* = 10.5, 1.6 Hz, 1H), 5.17 (dd, *J* = 9.7, 4.5 Hz, 1H), 5.03 (dt, *J* = 17.2, 1.6 Hz, 1H), 4.95 (ddt, *J* = 9.4, 4.7, 2.0 Hz, 1H), 2.41 (d, *J* = 4.7 Hz, 1H), 2.17 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 153.0, 142.3, 134.5, 128.1, 118.4, 110.6, 107.7, 106.5, 68.6, 61.4, 14.0.

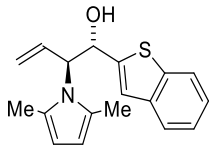
HRMS (ESI) Calcd. for $C_{14}H_{17}NaNO_2$ $[M+Na]^+$: 254.1151, Found: 254.1151.

FTIR (neat): 3429, 2926, 2360, 2342, 1934, 1397, 1292, 1150, 1011, 923, 822, 738 cm^{-1}.


7.33
7.32
6.44
6.43
6.42
6.41
6.40
6.39
6.38
6.37
6.24
6.23
6.23
6.23
6.03
6.02
5.66
5.34
5.34
5.34
5.32
5.32
5.32
5.19
5.18
5.17
5.16
5.05
5.05
5.04
5.02
5.01
5.01
4.97
4.96
4.96
4.95
4.95
4.94
2.42
2.41
2.17
1.00
1.06
1.03
1.02
2.07
1.08
1.09
1.12
1.06
1.17
6.08
f1 (ppm)


152.97
142.27
134.53
128.11
118.45
110.62
107.74
106.46
68.58
61.40
14.03
f1 (ppm)

1-(benzo[b]thiophen-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)but-3-en-1-ol (5.3j).



In accordance with the general procedure at 125°C for 24 hours, the title compound was obtained in 87% yield (51.8 mg, *dr* = >20:1) as a yellow liquid after column chromatography (SiO_2; 5%-10% EtOAc/hexanes).

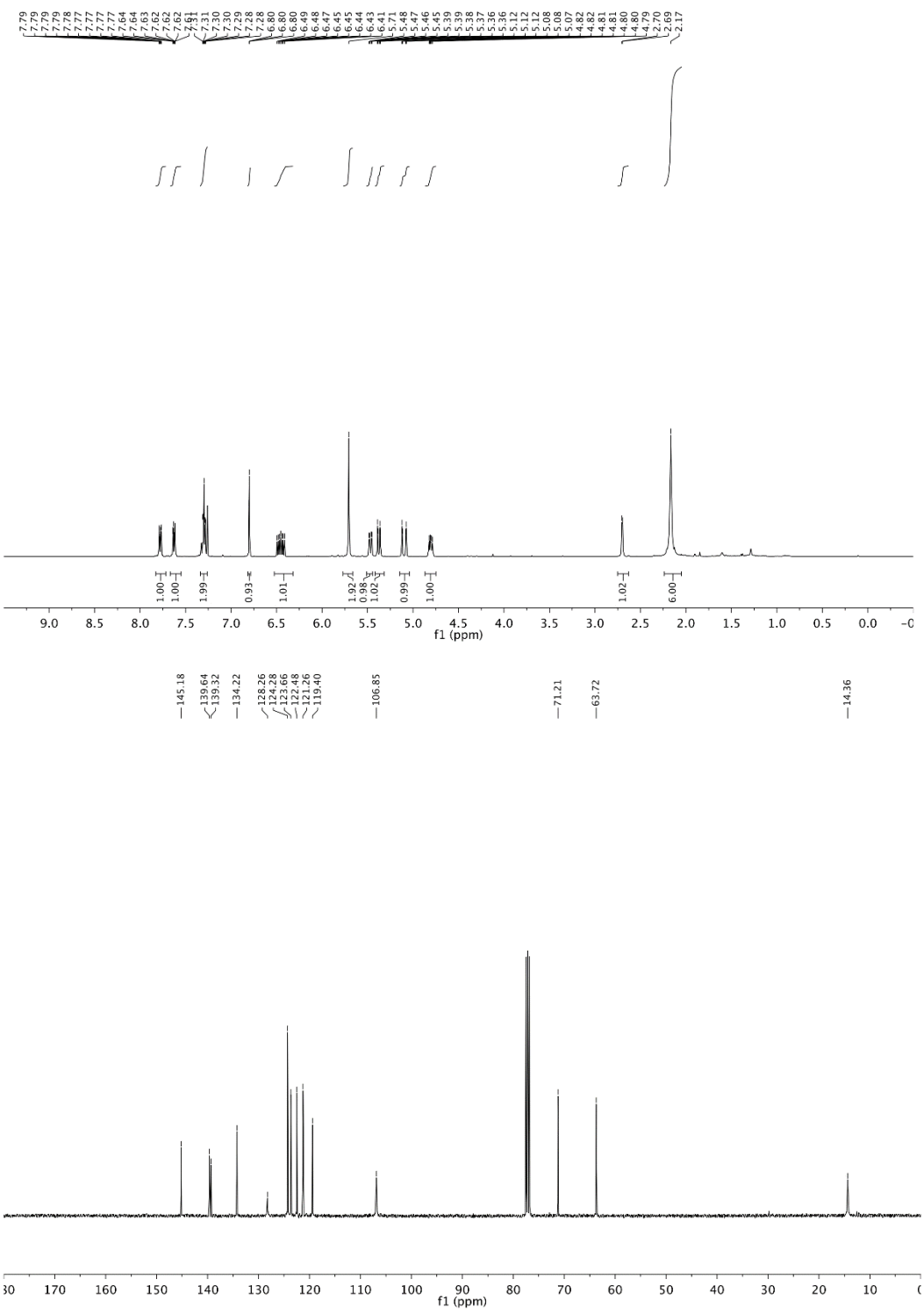
R_f=0.38 (20% EtOAc/Hexanes)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 – 7.75 (m, 1H), 7.67 – 7.59 (m, 1H), 7.34 – 7.25 (m, 2H), 6.80 (d, *J* = 0.9 Hz, 1H), 6.45 (ddd, *J* = 17.2, 10.5, 5.6 Hz, 1H), 5.71 (s, 2H), 5.47 (dd, *J* = 9.4, 3.1 Hz, 1H), 5.38 (dt, *J* = 10.5, 1.5 Hz, 1H), 5.10 (dt, *J* = 17.2, 1.5 Hz, 1H), 4.80 (ddt, *J* = 9.3, 5.6, 1.8 Hz, 1H), 2.70 (d, *J* = 3.4 Hz, 1H), 2.17 (s, 6H).

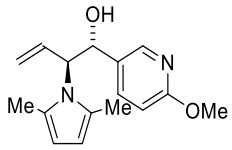
^{13}C NMR (100 MHz, $CDCl_3$) δ 145.2, 139.6, 139.3, 134.2, 128.3, 124.3, 123.7, 122.5, 121.3, 119.4, 106.9, 71.2, 63.7, 14.4.

HRMS (ESI) Calcd. for $C_{18}H_{20}NOS^+$ $[M+H]^+$: 298.1266, Found: 298.1255.

FTIR (neat): 3446, 2970, 1739, 1458, 1395, 1374, 1236, 1042, 928, 822, 745 cm^{-1}.



2-(2,5-dimethyl-1H-pyrrol-1-yl)-1-(6-methoxypyridin-3-yl)but-3-en-1-ol (5.3k).



In accordance with the general procedure at 125°C for 48 hours, the title compound was obtained in 70% yield (38.1 mg, *dr* = >20:1) as a yellow liquid after column chromatography (SiO_2; 20% EtOAc/hexanes).

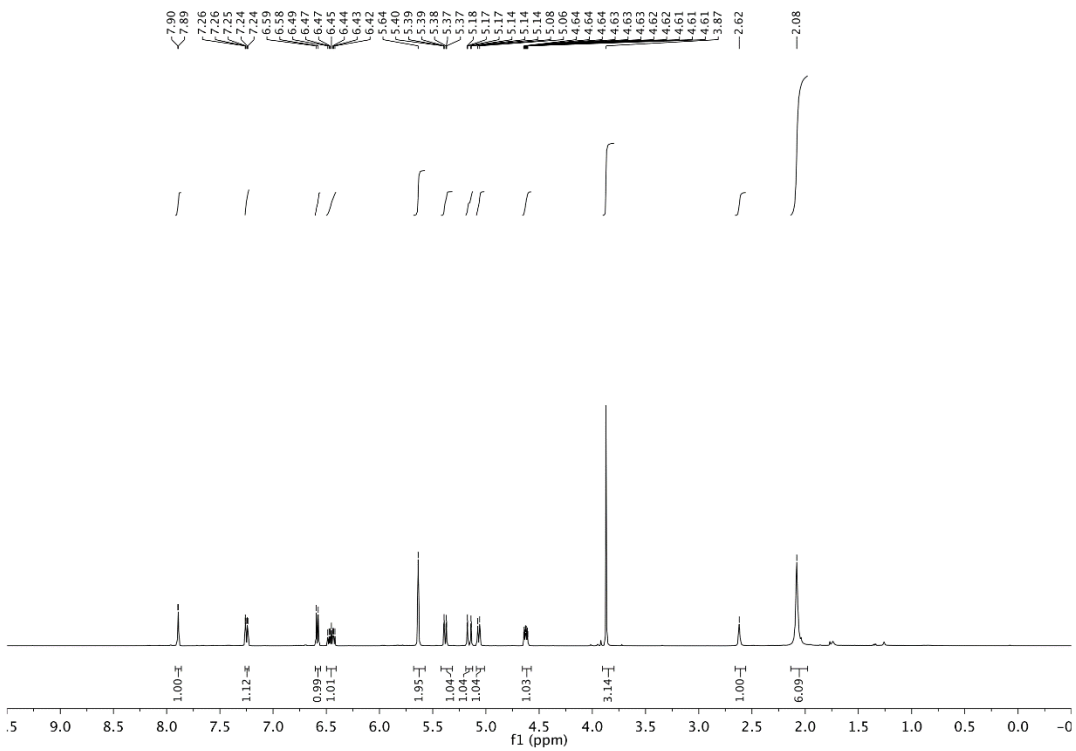
R_f = 0.13 (20% EtOAc/Hexanes).

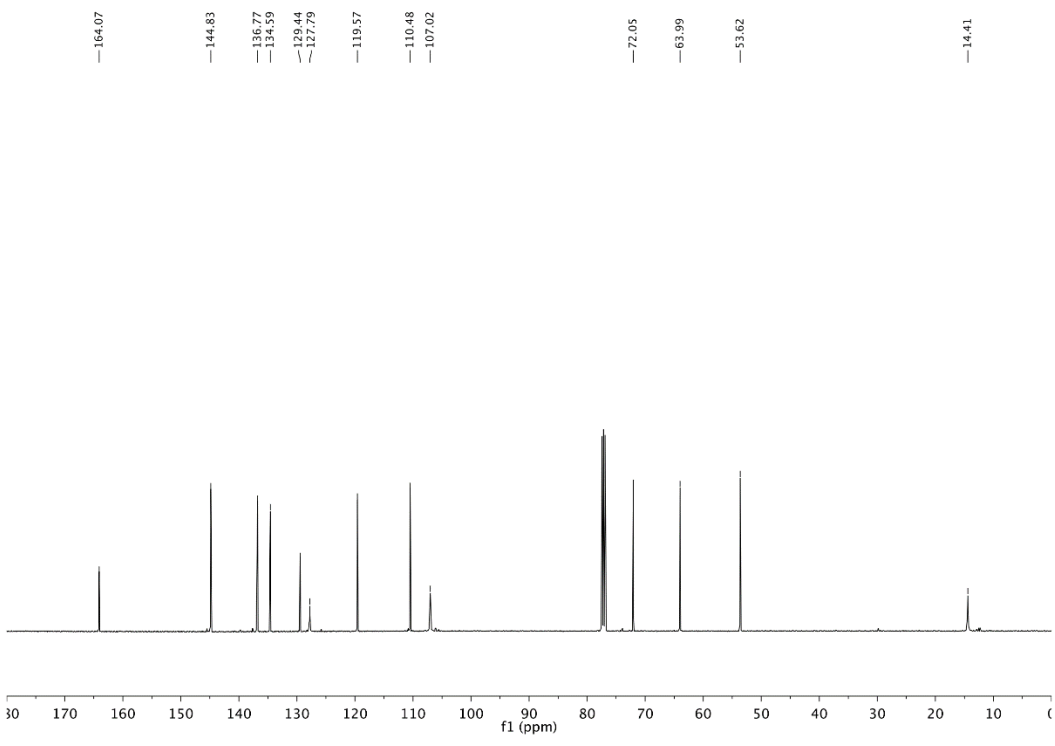
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (d, *J* = 2.4 Hz, 1H), 7.25 (dd, *J* = 8.6, 2.5 Hz, 1H), 6.58 (d, *J* = 8.6 Hz, 1H), 6.45 (ddd, *J* = 16.7, 10.5, 5.9 Hz, 1H), 5.64 (s, 2H), 5.38 (dt, *J* = 10.5, 1.5 Hz, 1H), 5.16 (dt, *J* = 17.2, 1.5 Hz, 1H), 5.07 (d, *J* = 9.5 Hz, 1H), 4.63 (ddt, *J* = 9.5, 5.9, 1.7 Hz, 1H), 3.87 (s, 3H), 2.62 (s, 1H), 2.08 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 164.1, 144.8, 136.8, 134.6, 129.4, 127.8, 119.6, 110.5, 107.0, 72.0, 64.0, 53.6, 14.4.

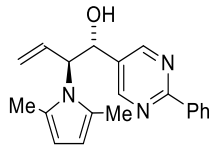
HRMS (ESI) Calcd. for $C_{16}H_{21}N_2O_2$ $[M+H]^+$: 273.1598, Found: 273.1603.

FTIR (neat): 3389, 2927, 2358, 1607, 1493, 1395, 1289, 1.24, 928, 829, 757 cm^{-1}.


7.90
7.89
7.26
7.26
7.25
7.24
7.24
6.59
6.58
6.49
6.47
6.47
6.45
6.44
6.43
6.42
5.64
5.40
5.39
5.39
5.38
5.37
5.37
5.18
5.17
5.17
5.14
5.14
5.14
5.08
5.06
4.64
4.64
4.64
4.63
4.63
4.63
4.62
4.62
4.61
4.61
4.61
3.87
2.62
2.08
1.00
1.12
0.99
1.01
1.95
1.04
1.04
1.04
1.03
3.14
1.00
6.09
f1 (ppm)


164.07
144.83
136.77
134.59
129.44
127.79
119.57
110.48
107.02
72.05
63.99
53.62
14.41
f1 (ppm)

2-(2,5-dimethyl-1H-pyrrol-1-yl)-1-(2-phenylpyrimidin-5-yl)but-3-en-1-ol (5.3l).



In accordance with the general procedure at 125°C for 24 hours, the title compound was obtained in 94% yield (60.0 mg, *dr* = >20:1) as a yellow liquid after column chromatography (SiO_2; 20% EtOAc/hexanes).

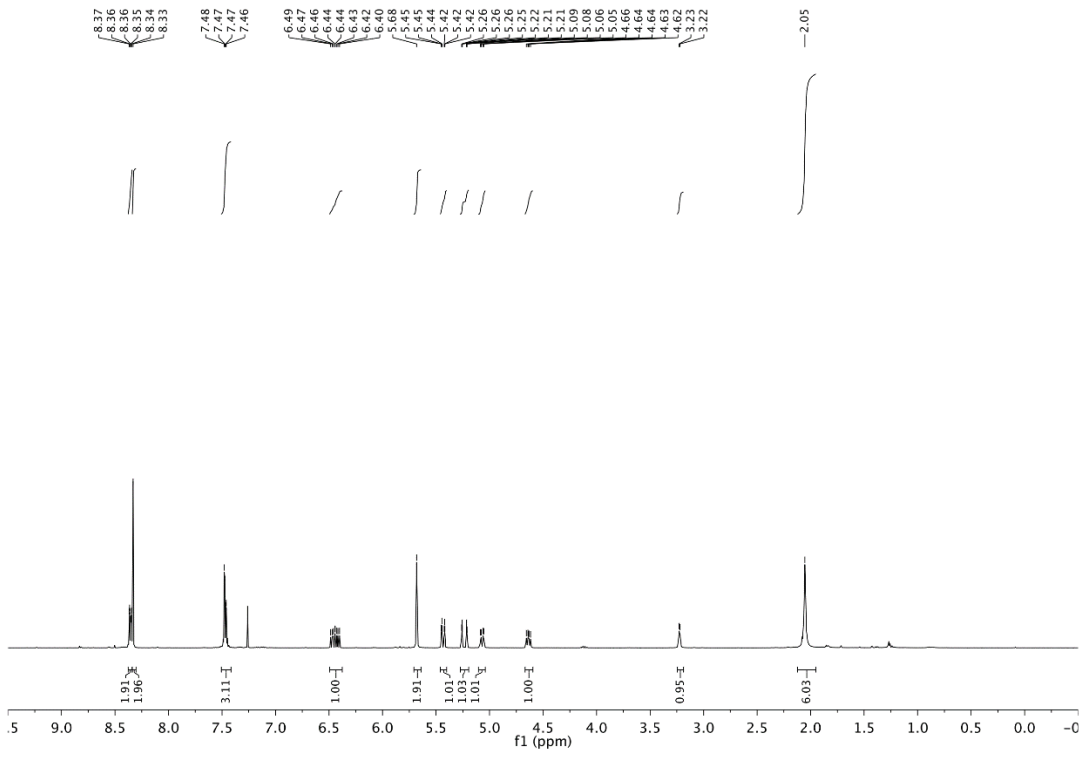
R_f = 0.14 (20% EtOAc/Hexanes).

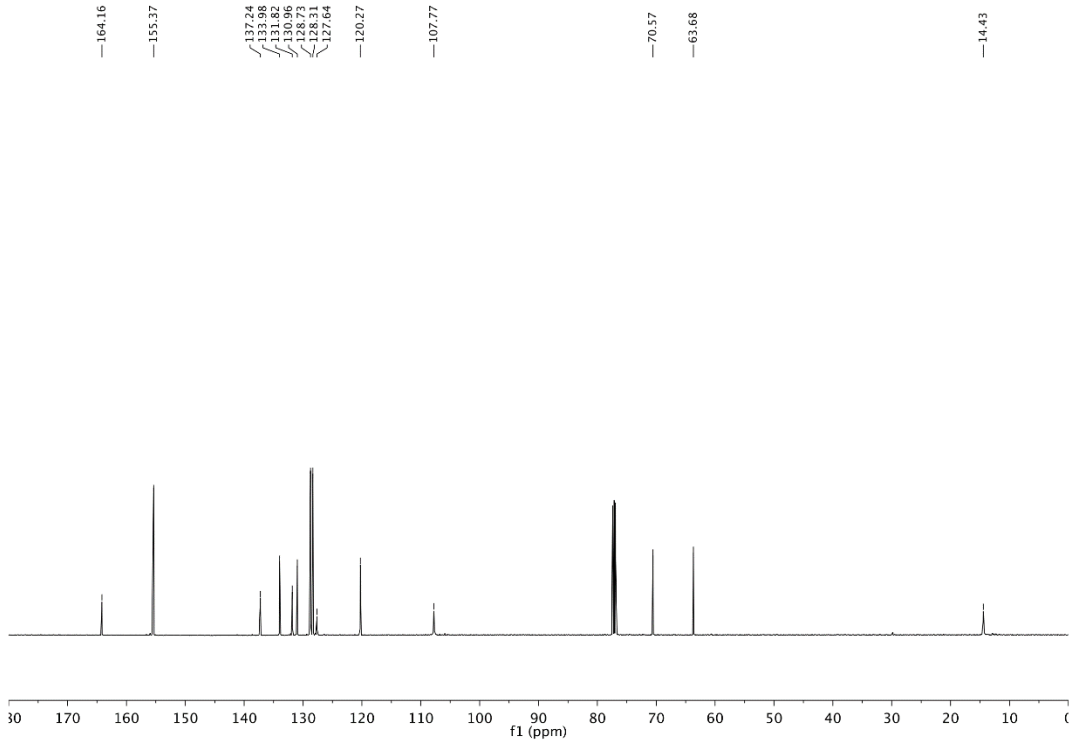
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38 – 8.34 (m, 2H), 8.33 (s, 2H), 7.51 – 7.42 (m, 3H), 6.44 (ddd, *J* = 17.2, 10.5, 5.9 Hz, 1H), 5.68 (s, 2H), 5.43 (dt, *J* = 10.5, 1.4 Hz, 1H), 5.27 – 5.19 (m, 1H), 5.07 (dd, *J* = 9.8, 2.6 Hz, 1H), 4.64 (ddt, *J* = 9.6, 5.9, 1.7 Hz, 1H), 3.23 (d, *J* = 3.3 Hz, 1H), 2.05 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 164.2, 155.4, 137.2, 134.0, 131.8, 131.0, 128.7, 128.3, 127.6, 120.3, 107.8, 70.6, 63.7, 14.4.

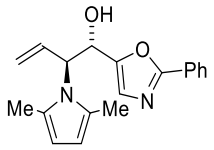
HRMS (ESI) Calcd. for $C_{20}H_{22}N_3O$ $[M+H]^+$: 320.1757, Found: 320.1757.

FTIR (neat): 3260, 2924, 1584, 1545, 1430, 1394, 1291, 1023, 929, 749, 694 cm^{-1}.


8.37
8.36
8.36
8.35
8.34
8.33
7.48
7.47
7.47
7.46
6.49
6.47
6.46
6.44
6.44
6.43
6.42
6.40
5.68
5.45
5.45
5.44
5.42
5.42
5.26
5.26
5.26
5.25
5.22
5.21
5.21
5.09
5.08
5.06
5.05
4.66
4.64
4.64
4.63
4.62
3.23
3.22
2.05
1.91
1.96
3.11
1.00
1.91
1.01
1.03
1.01
1.00
0.95
6.03
f1 (ppm)


164.16
155.37
137.24
133.98
131.82
130.96
128.73
128.31
127.64
120.27
107.77
70.57
63.68
14.43
f1 (ppm)

2-(2,5-dimethyl-1H-pyrrol-1-yl)-1-(2-phenyloxazol-5-yl)but-3-en-1-ol (5.3m).



In accordance with the general procedure at 125°C for 24 hours, the title compound was obtained in 77% yield (47.5 mg, *dr* = >20:1) as a yellow liquid after column chromatography (SiO_2; 20% EtOAc/hexanes).

R_f = 0.4 (50% EtOAc/Hexanes).

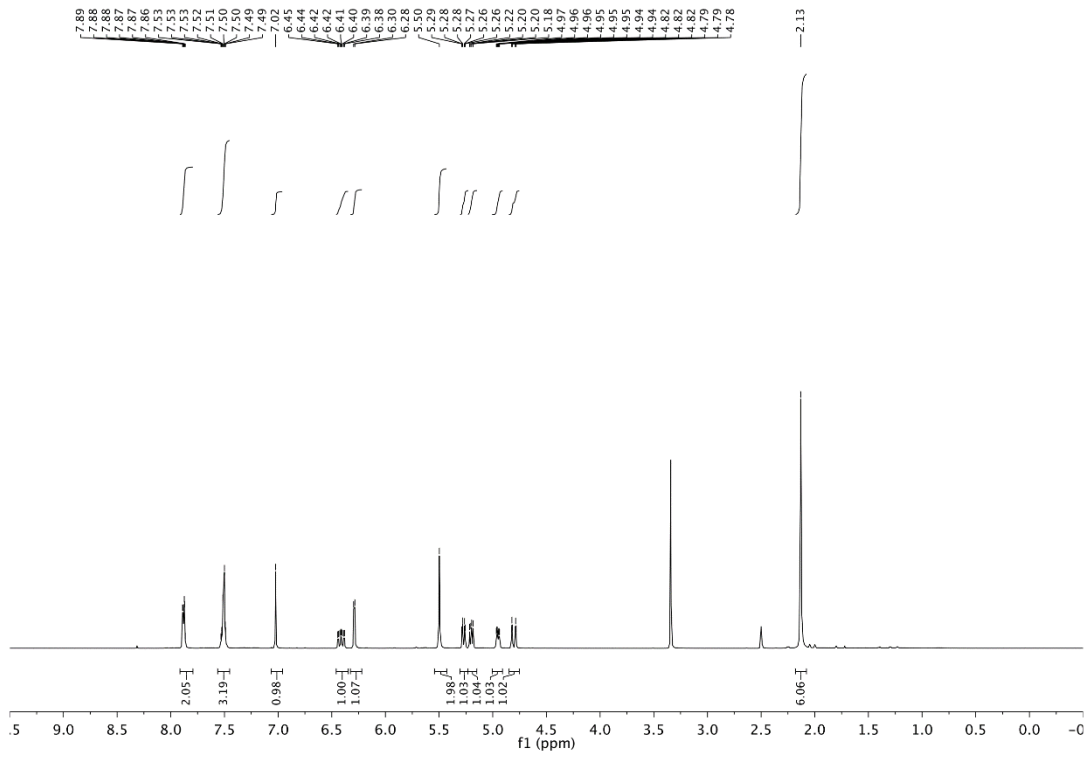
^{1}H NMR (400 MHz, DMSO-d_6): δ 7.91 – 7.79 (m, 2H), 7.56 – 7.45 (m, 3H), 7.02 (s, 1H), 6.41 (ddd, *J* = 17.3, 10.5, 4.2 Hz, 1H), 6.29 (d, *J* = 6.0 Hz, 1H), 5.50 (s, 2H), 5..27 (dt, *J* = 10.6, 1.9 Hz, 1H), 5.20 (dd, *J* = 10.0, 5.9 Hz, 1H), 4.95 (ddt, *J* = 10.1, 4.3, 2.1 Hz, 1H), 4.80 (dt, *J* = 17.3, 1.8 Hz, 1H), 2.13 (s, 6H).

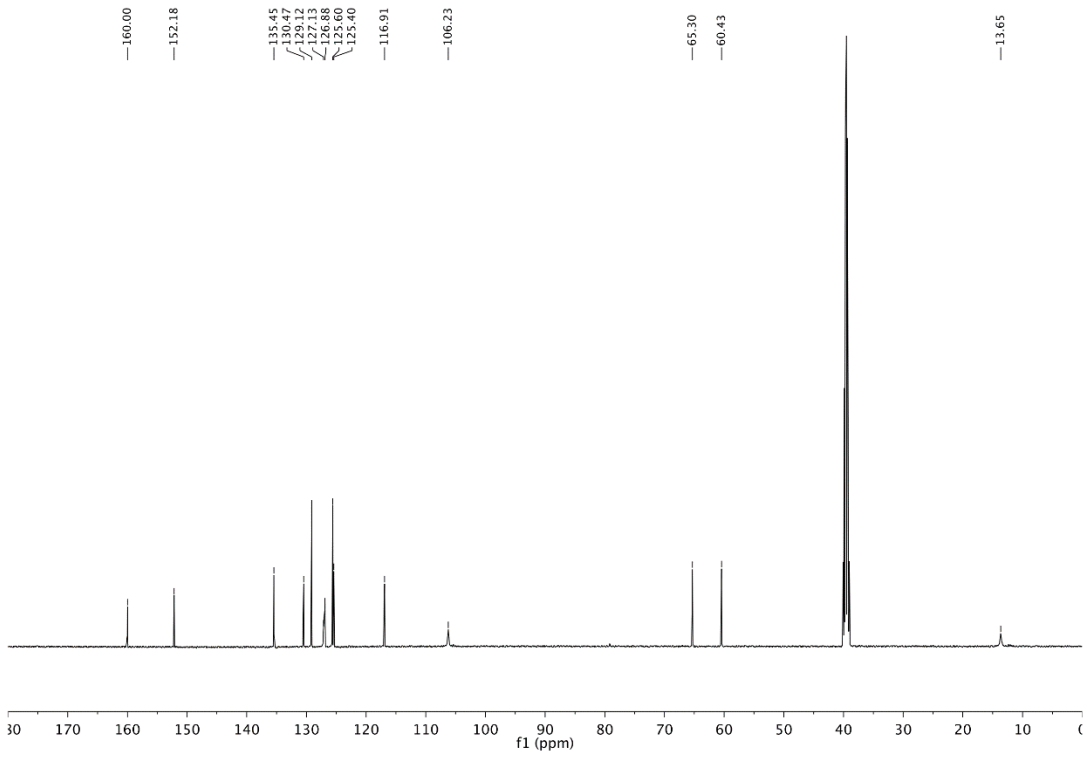
^{13}C NMR (100 MHz, DMSO-d_6): δ 160.0, 152.2, 135.4, 130.5, 129.1, 127.1, 126.9, 125.6, 125.4, 116.9, 106.2, 65.3, 60.4, 13.6.

HRMS (ESI) Calcd. for $C_{19}H_{21}N_2O_2$ $[M+H]^+$: 309.1598, Found: 309.1603.

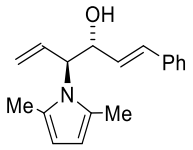
FTIR (neat): 3204, 3099, 2931, 1547, 1396, 1300, 1134, 1041, 977, 920, 824, 754, 713, 684 cm^{-1}.

MP: 183℃ (decomp.)


7.89
7.88
7.88
7.88
7.87
7.87
7.86
7.53
7.53
7.53
7.52
7.51
7.50
7.50
7.49
7.49
7.02
6.45
6.44
6.42
6.42
6.41
6.40
6.39
6.38
6.30
6.28
5.30
5.29
5.28
5.28
5.27
5.26
5.26
5.22
5.20
5.20
5.18
4.97
4.96
4.96
4.95
4.95
4.95
4.94
4.82
4.82
4.82
4.79
4.79
4.78
2.13
2.05
3.19
0.98
1.00
1.07
1.98
1.03
1.04
1.03
1.02
6.06
f1 (ppm)


160.00
152.18
135.45
130.47
129.12
127.13
126.88
125.60
125.40
116.91
106.23
65.30
60.43
13.65
f1 (ppm)

(E)-4-(2,5-dimethyl-1H-pyrrol-1-yl)-1-phenylhexa-1,5-dien-3-ol (5.3n).



In accordance with the general procedure at 125°C for 24 hours with 2-PrOH (200 mol%), the title compound was obtained in 72% yield (38.5 mg, *dr* = >20:1) as a yellow liquid after column chromatography (SiO_2; 10% EtOAc/hexanes).

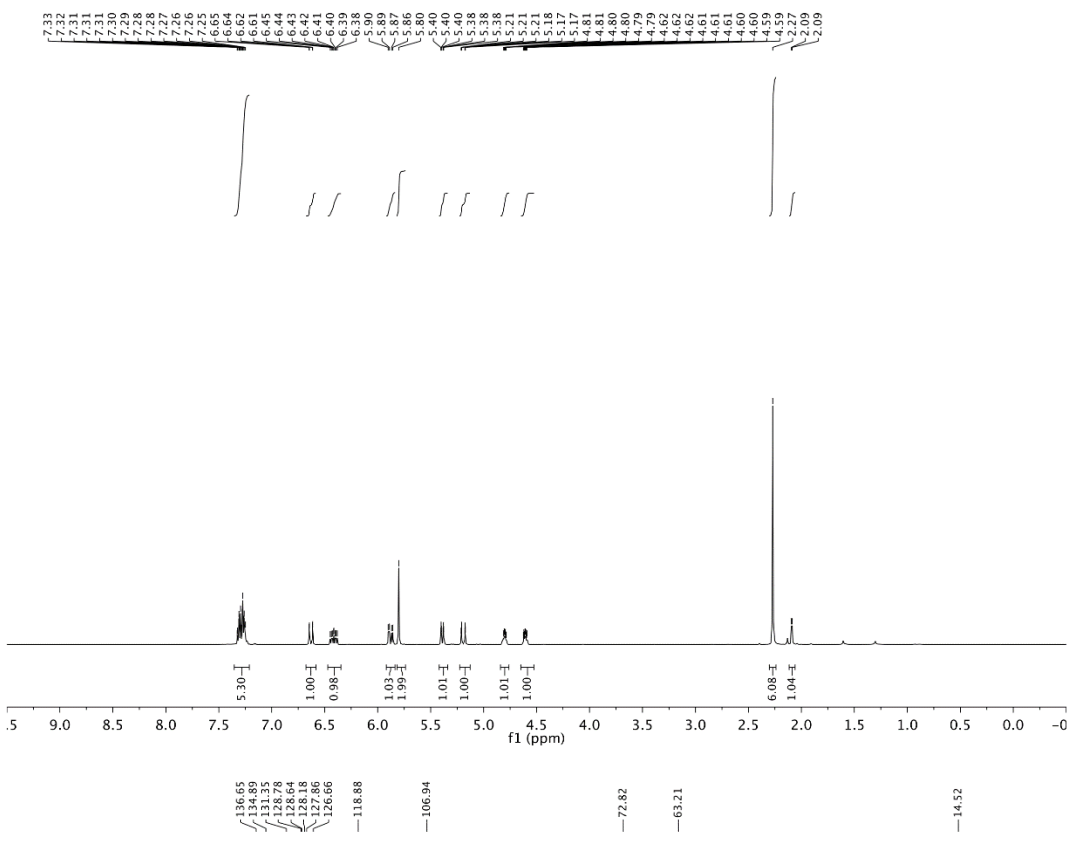
R_f = 0.38 (20% EtOAc/Hexanes).

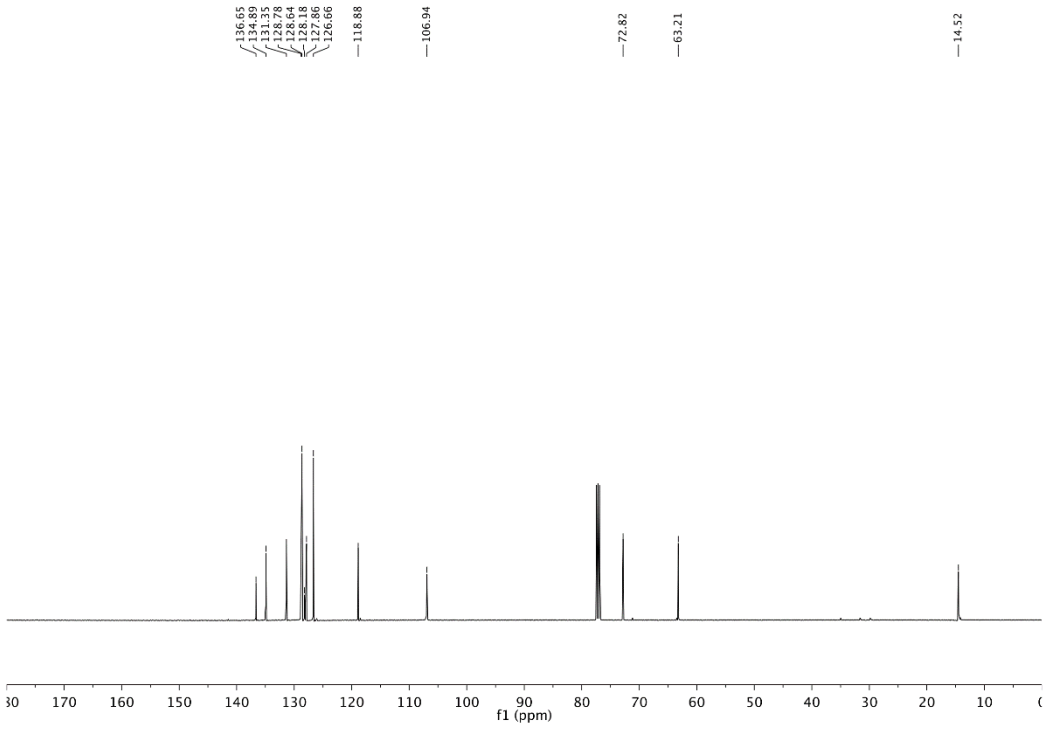
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 – 7.21 (m, 5H), 6.63 (dd, *J* = 16.0, 1.4 Hz, 1H), 6.41 (ddd, *J* = 17.3, 10.5, 5.6 Hz, 1H), 5.88 (dd, *J* = 16.0, 5.6 Hz, 1H), 5.80 (s, 2H), 5.39 (dt, *J* = 10.5, 1.5 Hz, 1H), 5.19 (dt, *J* = 17.2, 1.5 Hz, 1H), 4.84 – 4.76 (m, 1H), 4.61 (ddt, *J* = 7.2, 5.2, 2.6 Hz, 1H), 2.27 (s, 6H), 2.09 (d, *J* = 3.9 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 136.6, 134.9, 131.4, 128.8, 128.6, 128.2, 127.9, 126.7, 118.9, 106.9, 72.8, 63.2, 14.5.

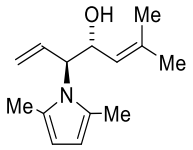
HRMS (ESI) Calcd. for $C_{18}H_{22}NO$ $[M+H]^+$: 268.1696, Found: 268.1700.

FTIR (neat): 3430, 2924, 1519, 1494, 1448, 1395, 1291, 1113, 1022, 973, 928, 747, 693 cm^{-1}.


5.30
1.00
0.98
1.03
1.99
1.01
1.00
1.01
1.00
6.08
1.04
f1 (ppm)


136.65
134.89
131.35
128.78
128.64
128.48
127.86
126.66
118.88
106.94
72.82
63.21
14.52
f1 (ppm)

3-(2,5-dimethyl-1H-pyrrol-1-yl)-6-methylhepta-1,5-dien-4-ol (5.3o).



In accordance with the general procedure at 125°C for 24 hours, the title compound was obtained in 73% yield (32.0 mg, *dr* = >20:1) as a yellow liquid after column chromatography (SiO_2; 7.5%-10% EtOAc/hexanes).

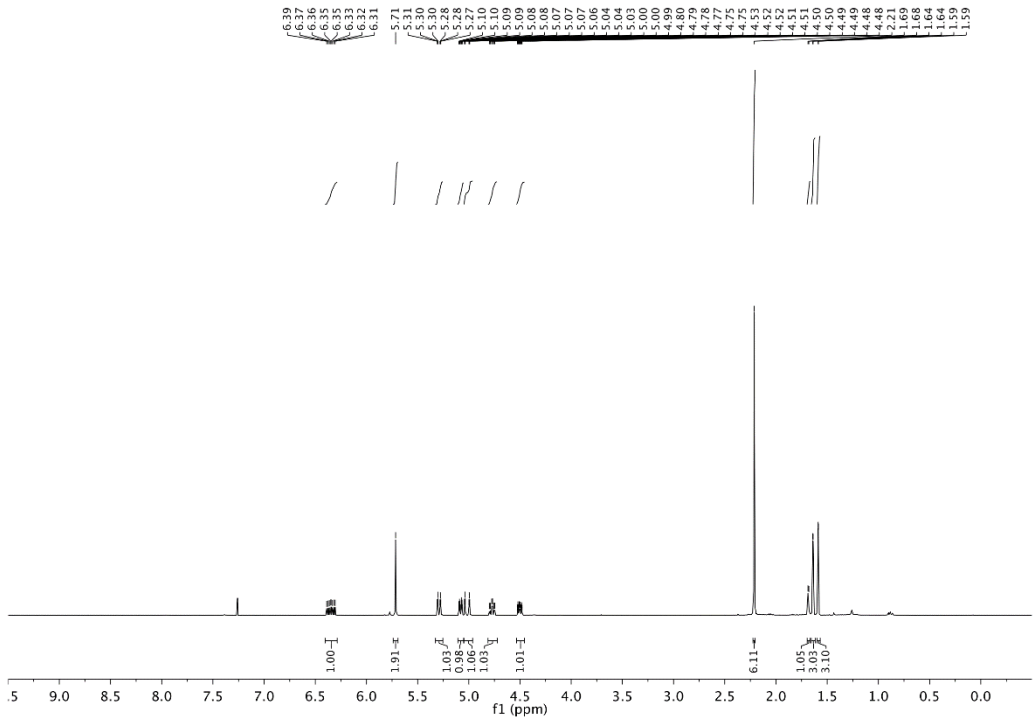
R_f =0.40 (20% EtOAc/Hexanes)

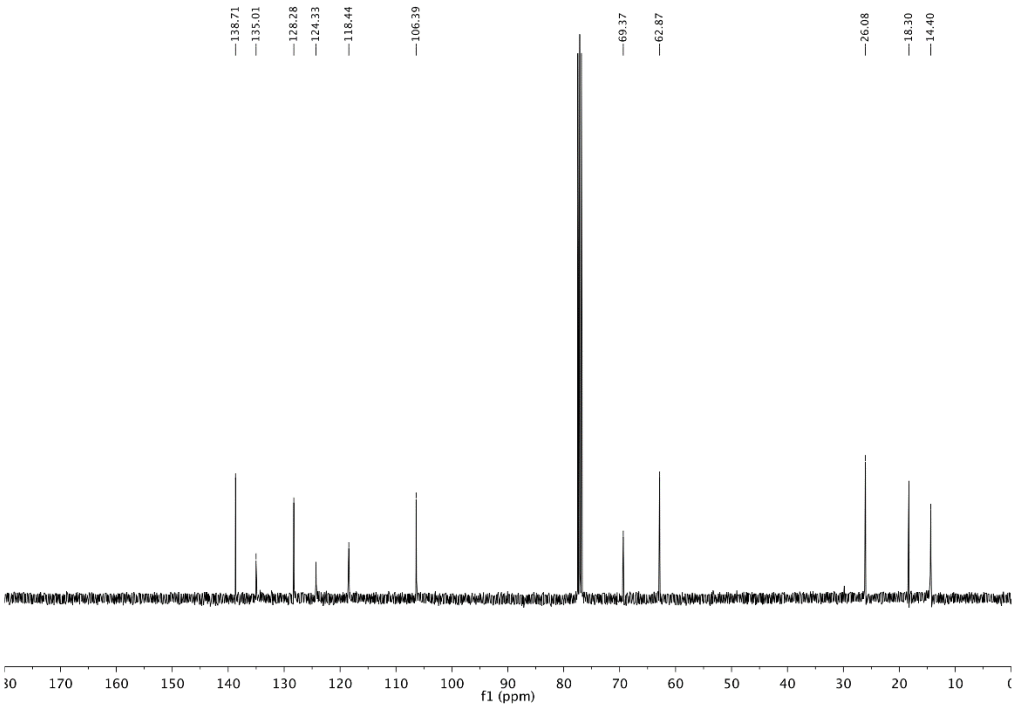
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.35 (ddd, *J* = 17.2, 10.5, 5.6 Hz, 1H), 5.71 (s, 2H), 5.29 (dt, *J* = 10.5, 1.6 Hz, 1H), 5.08 (ddq, *J* = 8.7, 2.8, 1.4 Hz, 1H), 5.02 (dt, *J* = 17.3, 1.6 Hz, 1H), 4.77 (td, *J* = 8.9, 3.5 Hz, 1H), 4.50 (ddt, *J* = 9.1, 5.6, 1.8 Hz, 1H), 2.21 (s, 6H), 1.68 (d, *J* = 3.6 Hz, 1H), 1.64 (d, *J* = 1.4 Hz, 3H), 1.59 (d, *J* = 1.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 135.0, 128.3, 124.3, 118.4, 106.4, 69.4, 62.9, 26.1, 18.3, 14.4.

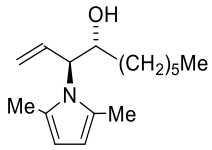
HRMS (ESI) Calcd. for $C_{14}H_{22}NO^+$ $[M+H]^+$: 220.1701, Found: 220.1693.

FTIR (neat): 3439, 2970, 2929, 1741, 1444, 1397, 1292, 1216, 1021, 992, 924, 827, 749 cm^{-1}.


6.39
6.37
6.36
6.35
6.35
6.33
6.32
6.31
5.71
5.31
5.30
5.30
5.28
5.28
5.27
5.10
5.10
5.09
5.09
5.08
5.08
5.07
5.07
5.07
5.06
5.04
5.04
5.03
5.00
5.00
4.80
4.79
4.78
4.77
4.75
4.75
4.53
4.52
4.52
4.51
4.51
4.50
4.50
4.49
4.49
4.48
4.48
2.21
1.69
1.68
1.64
1.64
1.59
1.59
1.00
1.91
1.03
0.98
1.06
1.03
1.01
6.11
1.05
3.03
3.10
f1 (ppm)


138.71
135.01
128.28
124.33
118.44
106.39
69.37
62.87
26.08
18.30
14.40
f1 (ppm)

3-(2,5-dimethyl-1H-pyrrol-1-yl)dec-1-en-4-ol (5.3p).



In accordance with the general procedure at 125°C for 48 hours, the title compound was obtained in 62% yield (30.9 mg, *dr* = >20:1) as a yellow liquid after column chromatography (SiO_2; 5% EtOAc/hexanes).

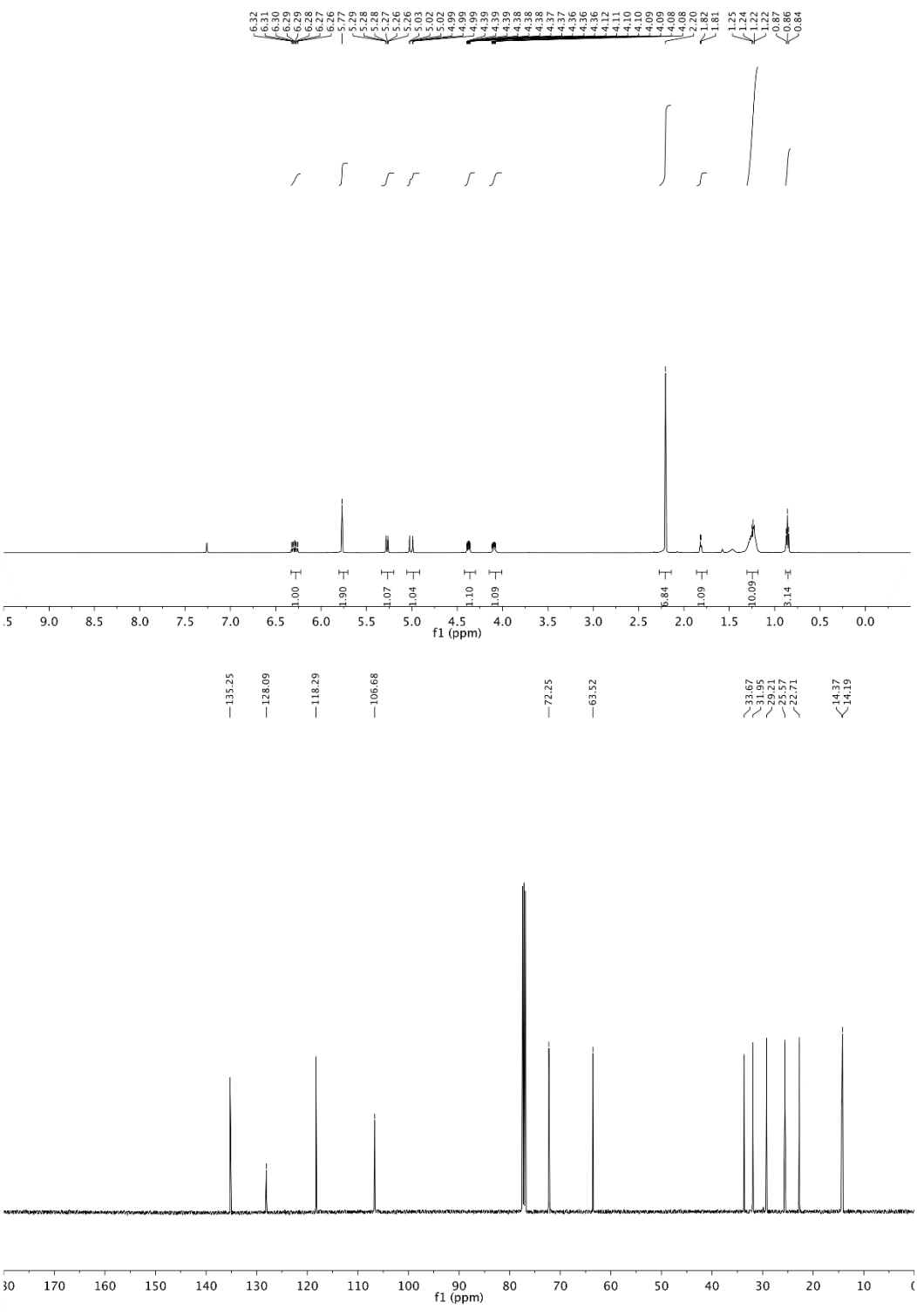
R_f = 0.55 (20% EtOAc/Hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.29 (ddd, *J* = 17.2, 10.4, 5.7 Hz, 1H), 5.77 (s, 2H), 5.27 (dt, *J* = 10.5, 1.5 Hz, 1H), 5.01 (dt, *J* = 17.2, 1.5 Hz, 1H), 4.38 (ddt, *J* = 9.2, 5.8, 1.7 Hz, 1H), 4.10 (tq, *J* = 9.5, 6.3, 4.9 Hz, 1H), 2.20 (s, 6H), 1.82 (d, *J* = 4.5 Hz, 1H), 1.31 – 1.18 (m, 10H), 0.86 (t, *J* = 6.9 Hz, 3H).

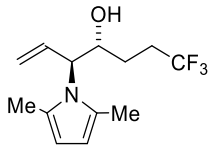
^{13}C NMR (100 MHz, $CDCl_3$): δ 135.2, 128.1, 118.3, 106.7, 72.2, 63.5, 33.7, 31.9, 29.2, 25.6, 22.7, 14.4, 14.2.

HRMS (ESI) Calcd. for $C_{16}H_{27}NaNO$ $[M+Na]^+$: 272.1985, Found: 272.1989.

FTIR (neat): 3402, 2926, 2857, 1519, 1456, 1397, 1292, 1022, 925, 821, 753 cm^{-1}.


6.32
6.31
6.30
6.29
6.29
6.28
6.27
6.26
5.77
5.29
5.28
5.28
5.27
5.26
5.26
5.03
5.02
5.02
4.99
4.99
4.99
4.39
4.39
4.39
4.38
4.38
4.38
4.37
4.37
4.36
4.36
4.36
4.12
4.11
4.10
4.10
4.09
4.09
4.08
4.08
2.20
1.82
1.81
1.25
1.24
1.22
1.22
0.87
0.86
0.84
1.00
1.90
1.07
1.04
1.10
1.09
6.84
1.09
10.09
3.14
f1 (ppm)
135.25
128.09
118.29
106.68
72.25
63.52
33.67
31.95
29.21
25.57
22.71
14.37
14.19
f1 (ppm)

3-(2,5-dimethyl-1H-pyrrol-1-yl)-7,7,7-trifluorohept-1-en-4-ol (5.3q).



In accordance with the general procedure at 125°C for 24 hours, the title compound was obtained in 73% yield (38.1 mg, *dr* = >20:1) as a yellow liquid after column chromatography (SiO_2; 7.5%-10% EtOAc/hexanes).

R_f =0.41 (20% EtOAc/Hexanes)

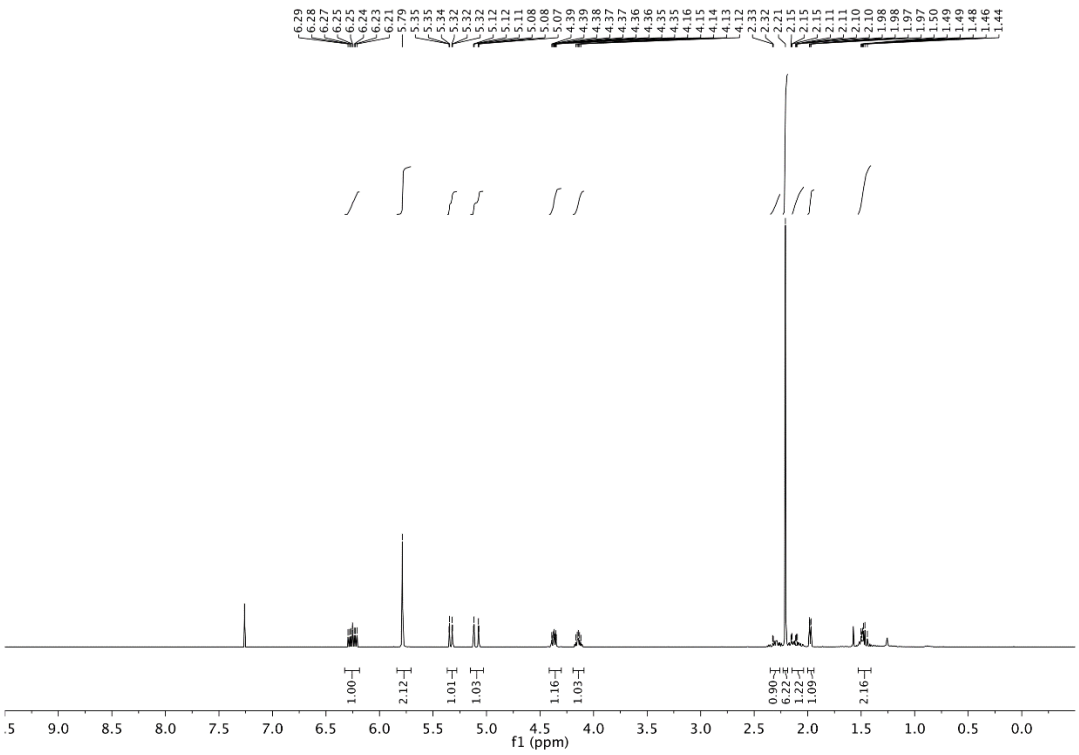
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.25 (ddd, *J* = 16.8, 10.4, 6.2 Hz, 1H), 5.79 (s, 2H), 5.33 (dt, *J* = 10.4, 1.4 Hz, 1H), 5.10 (dt, *J* = 17.1, 1.4 Hz, 1H), 4.37 (ddt, *J* = 9.4, 6.2, 1.6 Hz, 1H), 4.14 (tt, *J* = 9.0, 4.0 Hz, 1H), 2.30 (dddd, *J* = 20.4, 9.3, 4.5, 2.8 Hz, 1H), 2.21 (s, 6H), 2.17 – 2.02 (m, 1H), 1.97 (d, *J* = 4.6 Hz, 1H), 1.55 – 1.40 (m, 2H).

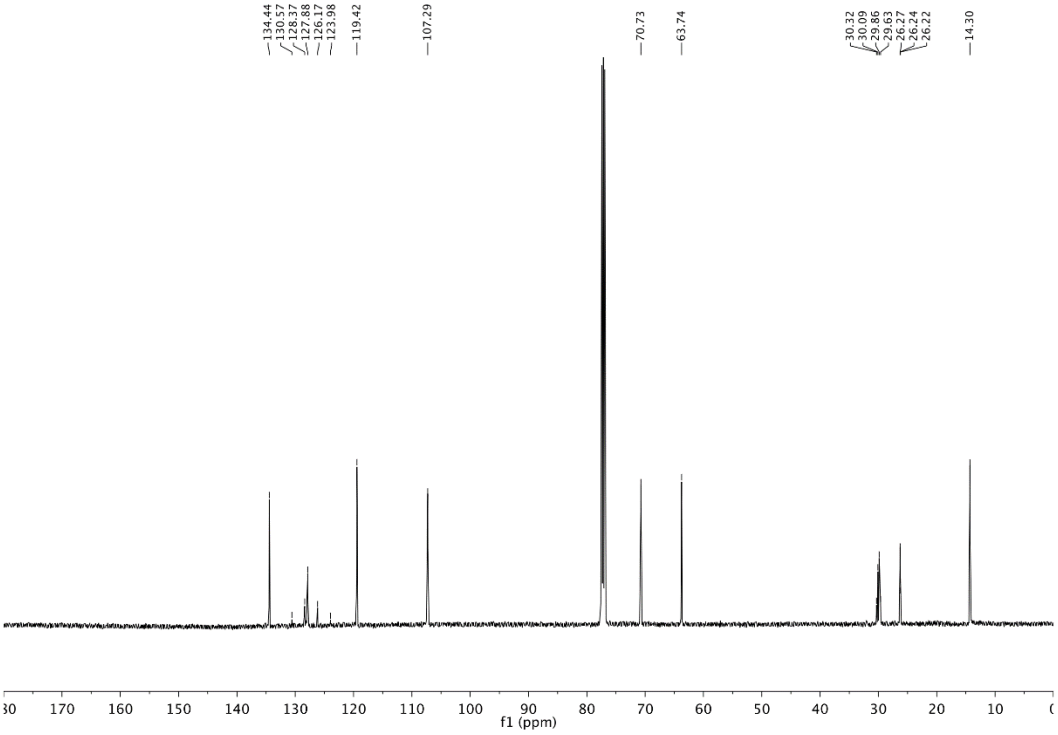
^{19}F NMR (100 MHz, $CDCl_3$) δ -66.0.

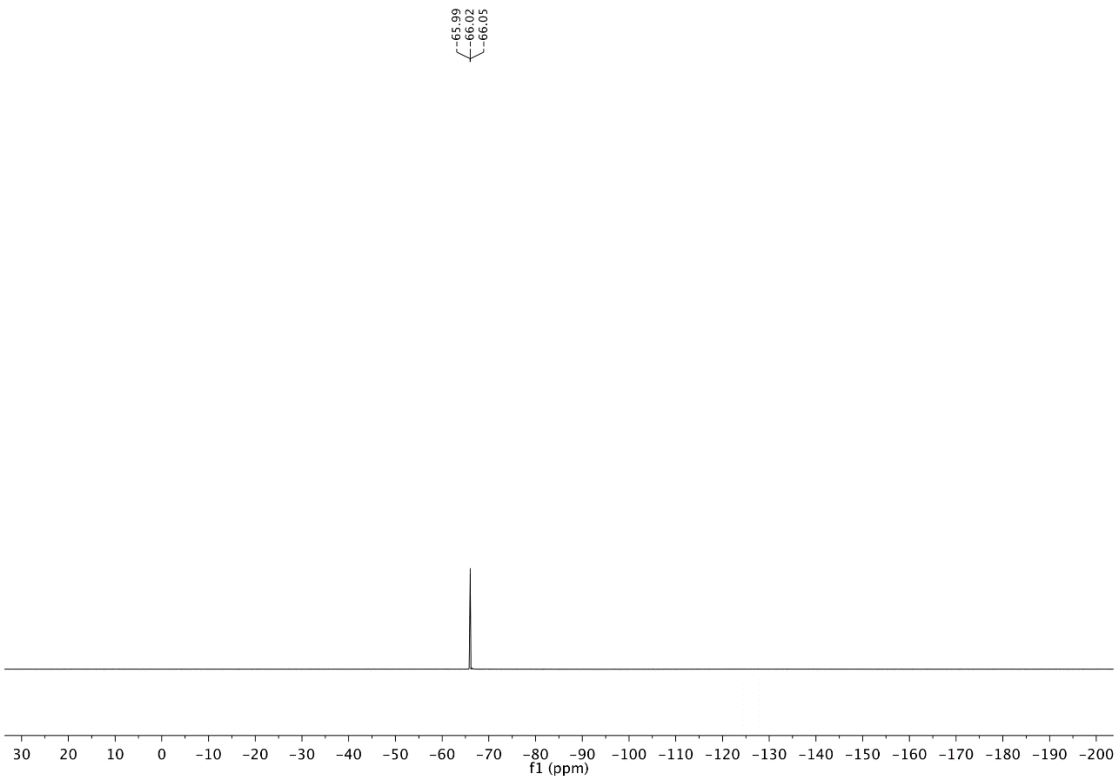
^{13}C NMR (100 MHz, $CDCl_3$) δ 134.4, 127.9, 127.3 (q, J_{C-F} = 276.4 Hz), 119.4, 107.3, 70.7, 63.7, 30.0 (q, J_{C-F} = 29.0 Hz), 26.3 (q, J_{C-F} = 3.3 Hz), 14.3.

HRMS (ESI) Calcd. for $C_{13}H_{19}F_3NO^+$ $[M+H]^+$: 262.1419, Found: 262.1416.

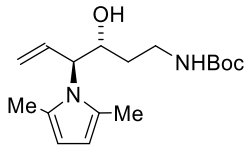
FTIR (neat): 3460, 2934, 1934, 1740, 1520, 1452, 1395, 1290, 1254, 1138, 1042, 928, 820, 755 cm^{-1}.


6.29 6.28 6.27 6.25 6.25 6.24 6.23 6.21 5.79 5.35 5.35 5.34 5.32 5.32 5.32 5.12 5.12 5.11 5.08 5.08 5.07 4.39 4.39 4.38 4.37 4.37 4.36 4.36 4.35 4.35 4.16 4.15 4.14 4.13 4.12 2.33 2.32 2.21 2.15 2.15 2.11 2.11 2.10 2.10 1.98 1.98 1.97 1.97 1.50 1.49 1.49 1.48 1.46 1.44
1.00 2.12 1.01 1.03 1.16 1.03 0.90 6.22 1.22 1.09 2.16
f1 (ppm)


134.44 130.57 128.37 127.88 126.17 123.98 119.42 107.29 70.73 63.74 30.32 30.09 29.86 29.63 26.27 26.24 26.22 14.30
f1 (ppm)


-65.99
-66.02
-66.05
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

tert-butyl (4-(2,5-dimethyl-1H-pyrrol-1-yl)-3-hydroxyhex-5-en-1-yl)carbamate (5.3r).



In accordance with the general procedure at 125°C for 24 hours, the title compound was obtained in 63% yield (38.9 mg, *dr* = >20:1) as a yellow liquid after column chromatography (SiO_2; 20% EtOAc/hexanes).

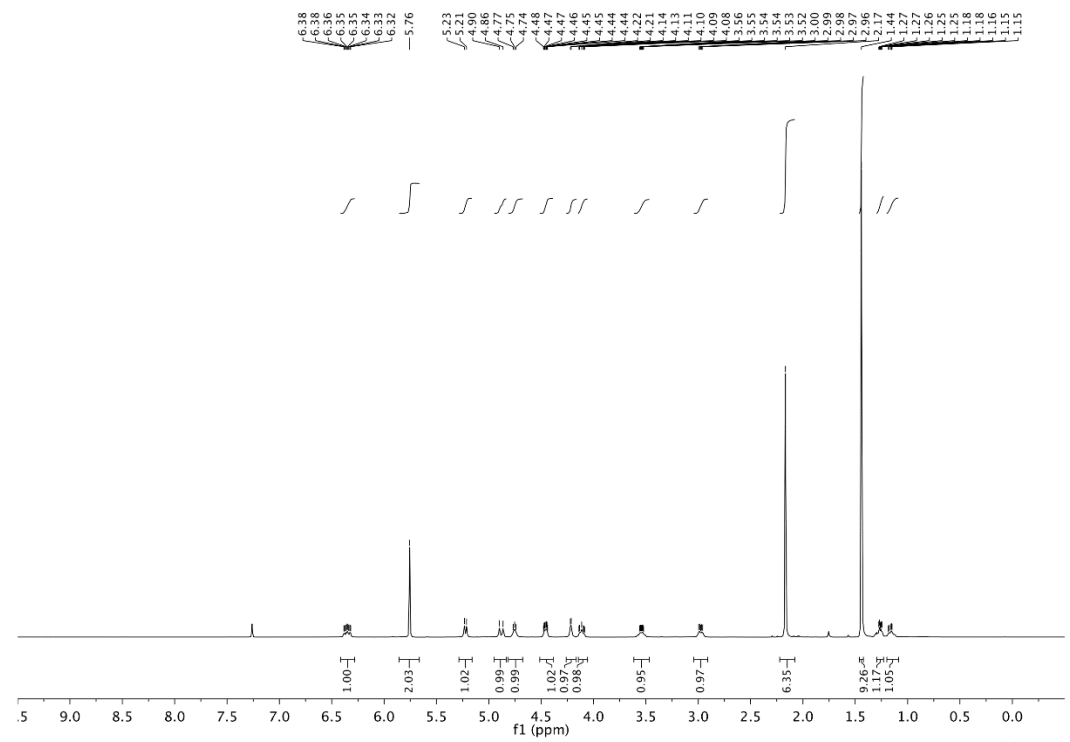
R_f = 0.17 (20% EtOAc/Hexanes).

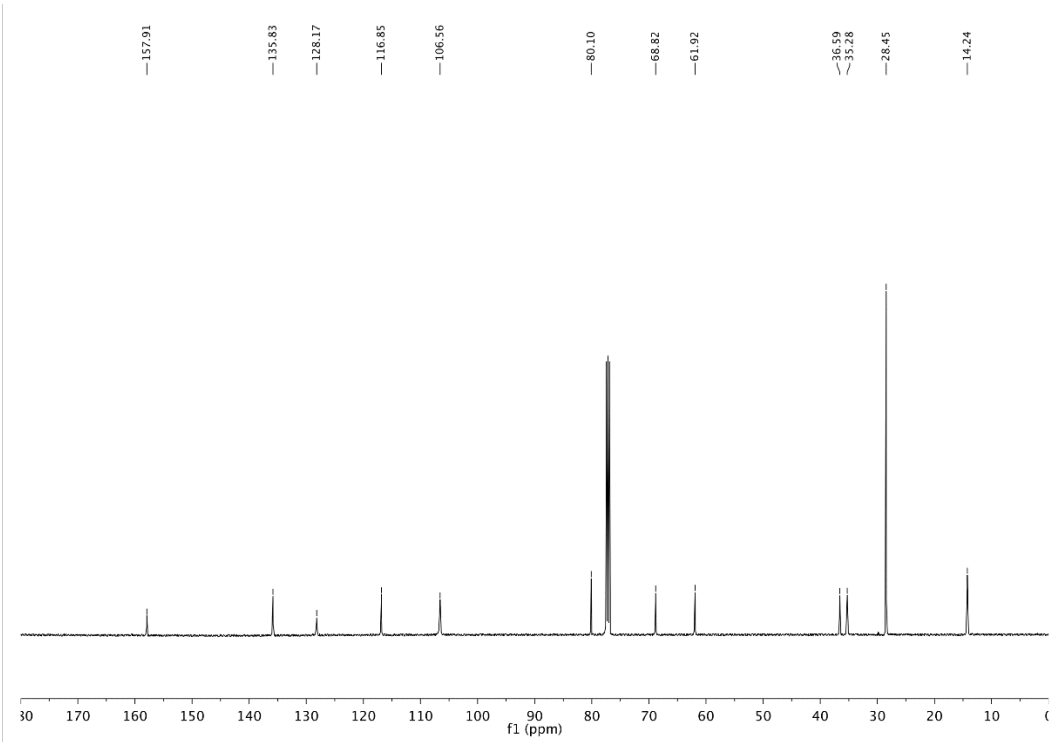
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.35 (ddd, *J* = 17.4, 10.6, 4.2 Hz, 1H), 5.76 (s, 2H), 5.22 (d, *J* = 10.5 Hz, 1H), 4.88 (d, *J* = 17.3 Hz, 1H), 4.75 (d, *J* = 6.7 Hz, 1H), 4.51 – 4.39 (m, 1H), 4.22 (d, *J* = 4.2 Hz, 1H), 4.15 – 4.06 (m, 1H), 3.61 – 3.47 (m, 1H), 2.98 (dq, *J* = 14.6, 4.6 Hz, 1H), 2.17 (s, 6H), 1.44 (s, 9H), 1.26 (dq, *J* = 7.9, 5.3, 3.8 Hz, 1H), 1.16 (td, *J* = 12.1, 11.7, 6.7 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 157.9, 135.8, 128.2, 116.8, 106.6, 80.1, 68.8, 61.9, 36.6, 35.3, 28.4, 14.2.

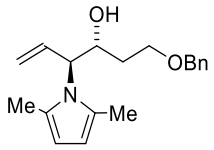
HRMS (ESI) Calcd. for $C_{17}H_{29}N_2O_3$ $[M+H]^+$: 309.2173, Found: 309.2171.

FTIR (neat): 3368, 2977, 2932, 2361, 1687, 1518, 1448, 1397, 1367, 1290, 1252, 1169, 1006, 923, 753 cm^{-1}.


6.38
6.38
6.36
6.35
6.35
6.34
6.33
6.32
5.76
5.23
5.21
4.90
4.86
4.77
4.75
4.74
4.48
4.47
4.47
4.46
4.45
4.45
4.44
4.44
4.22
4.21
4.14
4.13
4.11
4.10
4.09
4.08
3.56
3.55
3.54
3.54
3.53
3.52
3.00
2.99
2.98
2.97
2.96
2.17
1.44
1.27
1.27
1.26
1.25
1.25
1.18
1.18
1.16
1.15
1.15
1.15
1.00
2.03
1.02
0.99
0.99
1.02
0.97
0.98
0.95
0.97
6.35
9.26
1.17
1.05
f1 (ppm)


157.91
135.83
128.17
116.85
106.56
80.10
68.82
61.92
36.59
35.28
28.45
14.24
f1 (ppm)

1-(benzyloxy)-4-(2,5-dimethyl-1H-pyrrol-1-yl)hex-5-en-3-ol (5.3s).



In accordance with the general procedure at 125°C for 48 hours, the title compound was obtained in 61% yield (36.5 mg, *dr* = >20:1) as a yellow liquid after column chromatography (SiO_2; 5%-10% EtOAc/hexanes).

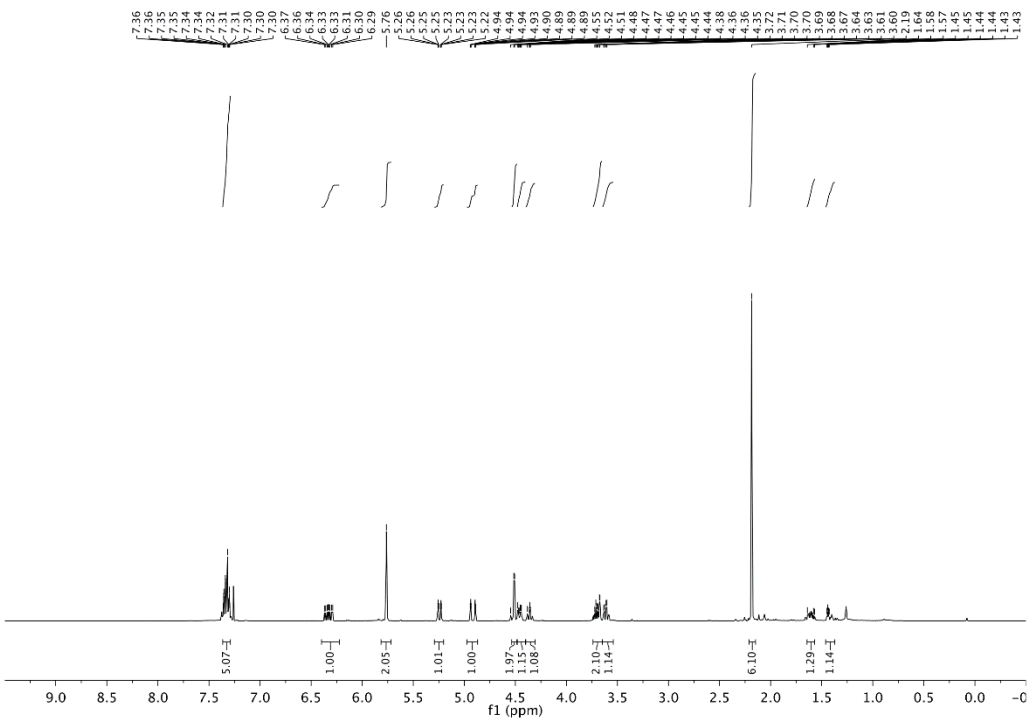
R_f=0.38 (20% EtOAc/Hexanes)

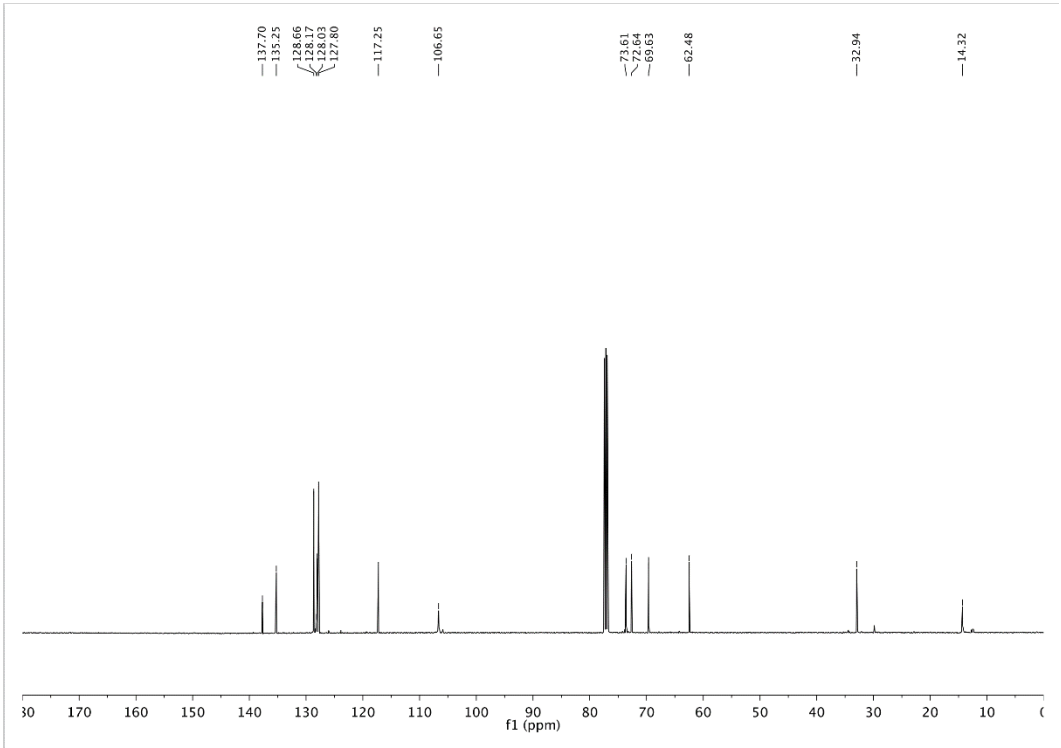
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 5H), 6.33 (ddd, *J* = 17.2, 10.5, 4.5 Hz, 1H), 5.76 (s, 2H), 5.24 (dt, *J* = 10.5, 1.7 Hz, 1H), 4.92 (dt, *J* = 17.3, 1.7 Hz, 1H), 4.51 (d, *J* = 5.2 Hz, 2H), 4.46 (ddt, *J* = 11.8, 4.4, 2.2 Hz, 1H), 4.36 (tt, *J* = 9.8, 2.1 Hz, 1H), 3.71 (ddd, *J* = 9.5, 5.4, 4.0 Hz, 1H), 3.66 – 3.57 (m, 2H), 2.19 (s, 6H), 1.61 (dtd, *J* = 14.9, 9.3, 4.0 Hz, 1H), 1.43 (dddd, *J* = 14.8, 5.5, 3.4, 2.0 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 137.7, 135.3, 128.7, 128.2, 128.0, 127.8, 117.3, 106.7, 73.6, 72.6, 69.6, 62.5, 32.9, 14.3.

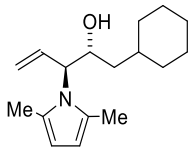
HRMS (ESI) Calcd. for $C_{19}H_{26}NO_2^+$ $[M+H]^+$: 300.1964, Found: 300.1960.

FTIR (neat): 3472, 2928, 2863, 1739, 1454, 1397, 1291, 1241, 1092, 923, 820, 747, 698 cm^{-1}.


7.36
7.36
7.35
7.35
7.34
7.34
7.32
7.31
7.31
7.30
7.30
7.30
6.37
6.36
6.34
6.33
6.33
6.31
6.30
6.29
5.76
5.26
5.26
5.25
5.25
5.23
5.23
5.22
4.94
4.94
4.94
4.93
4.90
4.89
4.89
4.89
4.55
4.52
4.51
4.48
4.47
4.47
4.46
4.45
4.45
4.44
4.38
4.36
4.35
3.72
3.71
3.70
3.70
3.69
3.68
3.67
3.64
3.63
3.61
3.60
2.19
1.64
1.58
1.57
1.45
1.45
1.44
1.44
1.43
1.43
5.07
1.00
2.05
1.01
1.00
1.97
1.35
1.08
2.10
1.14
6.10
1.29
1.14
f1 (ppm)


137.70
135.25
128.66
128.17
128.03
127.80
117.25
106.65
71.61
72.64
69.63
62.48
32.94
14.32
f1 (ppm)

1-cyclohexyl-3-(2,5-dimethyl-1H-pyrrol-1-yl)pent-4-en-2-ol (5.3t).



In accordance with the general procedure at 125°C for 48 hours, the title compound was obtained in 75% yield (39.2 mg, *dr* = >20:1) as a yellow liquid after column chromatography (SiO_2; 3%-5% EtOAc/hexanes).

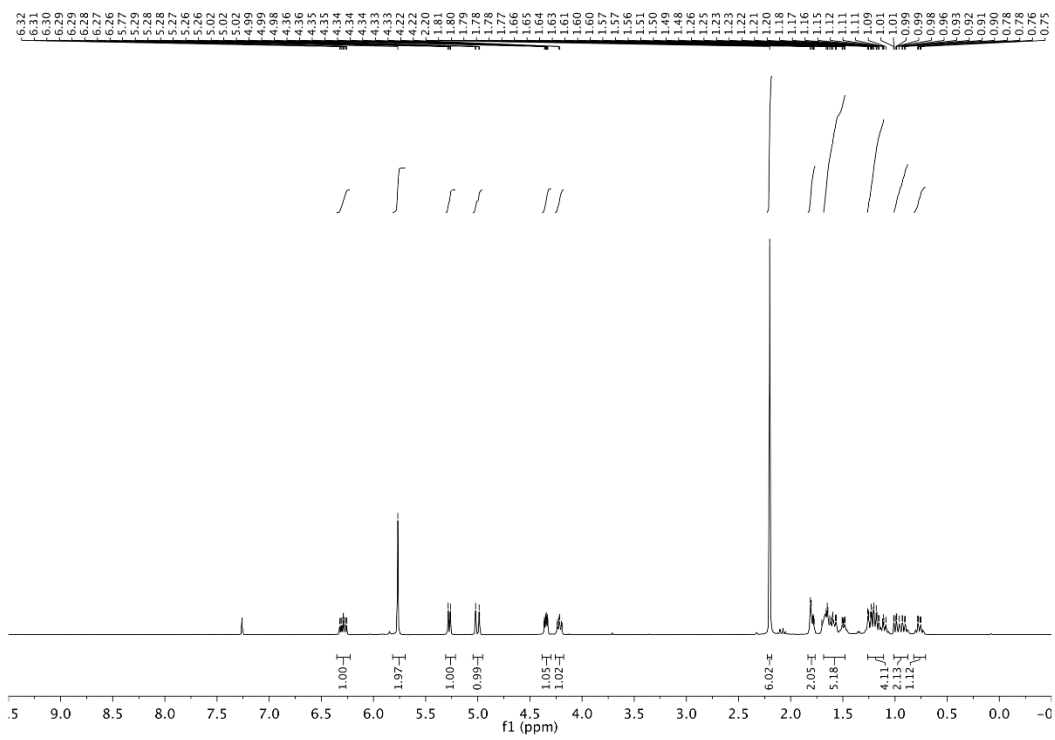
R_f=0.38 (10% EtOAc/Hexanes)

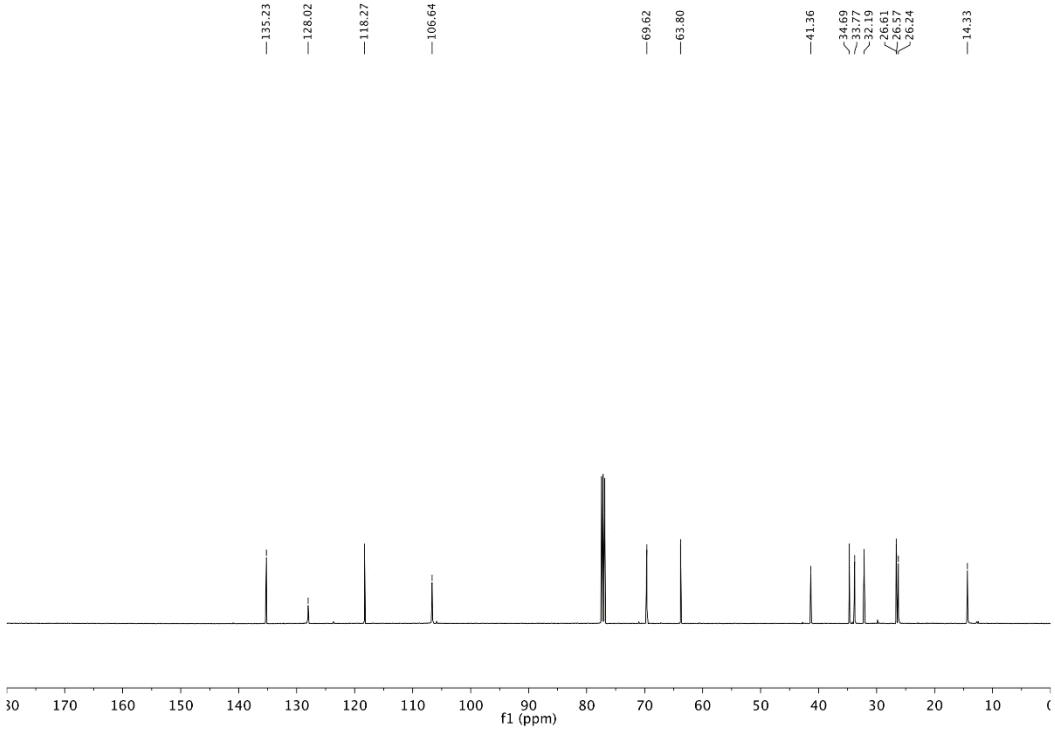
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.29 (ddd, *J* = 17.3, 10.5, 5.7 Hz, 1H), 5.77 (s, 2H), 5.27 (dt, *J* = 10.4, 1.6 Hz, 1H), 5.00 (dt, *J* = 17.2, 1.5 Hz, 1H), 4.35 (ddt, *J* = 9.3, 5.8, 1.7 Hz, 1H), 4.26 – 4.17 (m, 1H), 2.20 (s, 6H), 1.79 (dd, *J* = 12.9, 3.2 Hz, 2H), 1.73 – 1.44 (m, 4H), 1.31 – 1.04 (m, 4H), 1.04 – 0.85 (m, 3H), 0.77 (qd, *J* = 12.4, 3.5 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 135.2, 128.0, 118.3, 106.6, 69.6, 63.8, 41.4, 34.7, 33.8, 32.2, 26.6(1), 26.5(7), 26.2, 14.3.

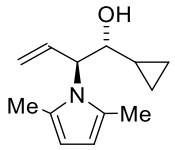
HRMS (ESI) Calcd. for $C_{17}H_{27}NONa^+$ $[M+Na]^+$: 284.1990, Found: 284.1985.

FTIR (neat): 3464, 2922, 2851, 1741, 1724, 1447, 1397, 1241, 1044, 988, 922, 751, 733 cm^{-1}.


f1 (ppm)


f1 (ppm)

1-cyclopropyl-2-(2,5-dimethyl-1H-pyrrol-1-yl)but-3-en-1-ol (5.3u).



In accordance with the general procedure at 125°C for 48 hours in dioxane (1.0 M), the title compound was obtained in 63% yield (25.9 mg, *dr* = >20:1) as a yellow liquid after column chromatography (SiO_2; 10% EtOAc/hexanes).

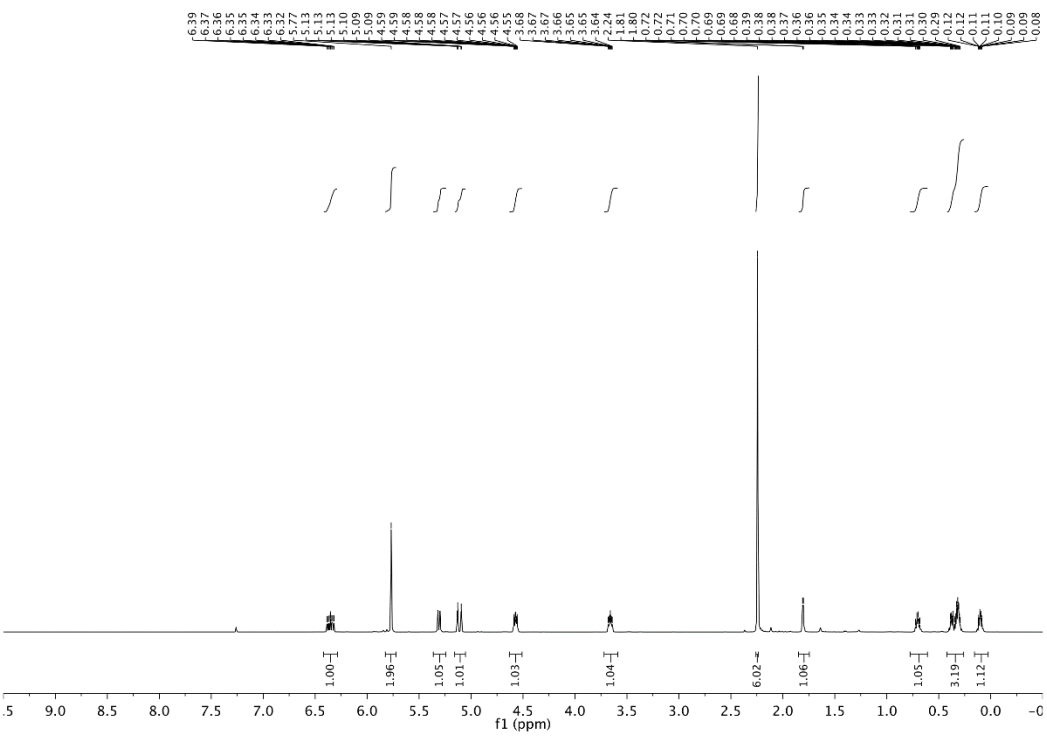
R_f = 0.42 (20% EtOAc/Hexanes).

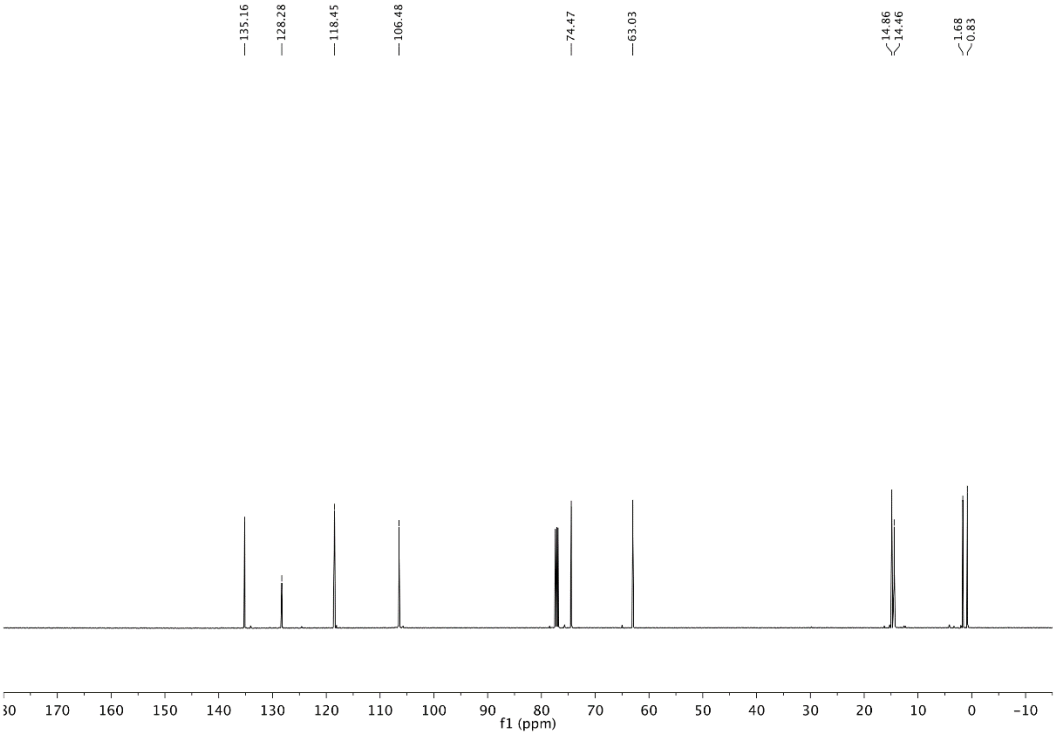
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.35 (ddd, *J* = 17.4, 10.5, 5.6 Hz, 1H), 5.77 (s, 2H), 5.31 (dt, *J* = 10.6, 1.6 Hz, 1H), 5.11 (dt, *J* = 17.3, 1.6 Hz, 1H), 4.57 (ddt, *J* = 9.2, 5.8, 1.8 Hz, 1H), 3.66 (ddd, *J* = 9.3, 6.5, 3.4 Hz, 1H), 2.24 (s, 6H), 1.81 (d, *J* = 3.6 Hz, 1H), 0.78 – 0.61 (m, 1H), 0.42 – 0.26 (m, 3H), 0.16 – 0.02 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 135.2, 128.3, 118.4, 106.5, 74.5, 63.0, 14.9, 14.5, 1.7, 0.8.

HRMS (ESI) Calcd. for $C_{13}H_{20}NO$ $[M+H]^+$: 206.1539, Found: 206.1539.

FTIR (neat): 3444, 3084, 2930, 1519, 1398, 1293, 1138, 1021, 926, 828, 753 cm^{-1}.

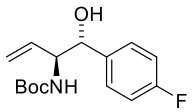

6.39 6.37 6.36 6.35 6.35 6.34 6.33 6.32 5.77 5.13 5.13 5.10 5.09 5.09 4.59 4.59 4.58 4.58 4.58 4.57 4.57 4.56 4.56 4.56 4.55 3.68 3.67 3.67 3.66 3.65 3.65 3.64 2.24 1.81 1.80 0.72 0.72 0.71 0.70 0.70 0.69 0.69 0.68 0.39 0.38 0.38 0.37 0.36 0.36 0.35 0.34 0.34 0.33 0.33 0.32 0.31 0.31 0.30 0.29 0.12 0.12 0.11 0.11 0.10 0.10 0.09 0.09 0.08
1.00 1.96 1.05 1.01 1.03 1.04 6.02 1.06 1.05 3.19 1.12
f1 (ppm)


135.16 128.28 118.45 106.48 74.47 63.03 14.86 14.46 1.68 0.83
f1 (ppm)

General Procedure and Preparation of 5.4b, 5.4n, 5.4q

To a solution of adduct **5.3** (0.2 mmol, 100 mol %) in EtOH (4 mL) was added hydroxylamine hydrochloride (139 mg, 2 mmol, 1000 mol %) followed by H_2O (2 mL). The mixture was allowed to stir at 100 °C for 24 hours. After cooled to room temperature, the reaction mixture was washed with 2N aqueous NaOH and extracted three times with Et_2O.The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo* and the crude amine was dissolved in THF (1 mL, 0.2 M). $(Boc)_2O$ (65.5 mg, 0.3 mmol, 150 mol %) was subsequently added and the reaction mixture was allowed to stir at room temperature overnight. Saturated aqueous NH_4Cl was added to the reaction mixture. The mixture was extracted three times with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was then removed *in vacuo*, and the residue was purified by flash chromatography (SiO_2: 20% EtOAc/Hexanes) to furnish the title compound.

tert-butyl (1-(4-fluorophenyl)-1-hydroxybut-3-en-2-yl)carbamate (5.4b).



In accordance with the general procedure, the title compound was obtained in 69% yield as a yellow solid after column chromatography (SiO_2; 20% EtOAc/hexanes).

R_f = 0.22 (20% EtOAc/Hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (dd, J = 8.5, 5.5 Hz, 2H), 7.02 (t, J = 8.7 Hz, 2H), 5.68 (ddd, J = 16.8, 10.5, 5.9 Hz, 1H), 5.23 – 5.06 (m, 2H), 4.93 – 4.79 (m, 2H), 4.43 (s, 1H), 3.14 (s, 1H), 1.44 (s, 9H).

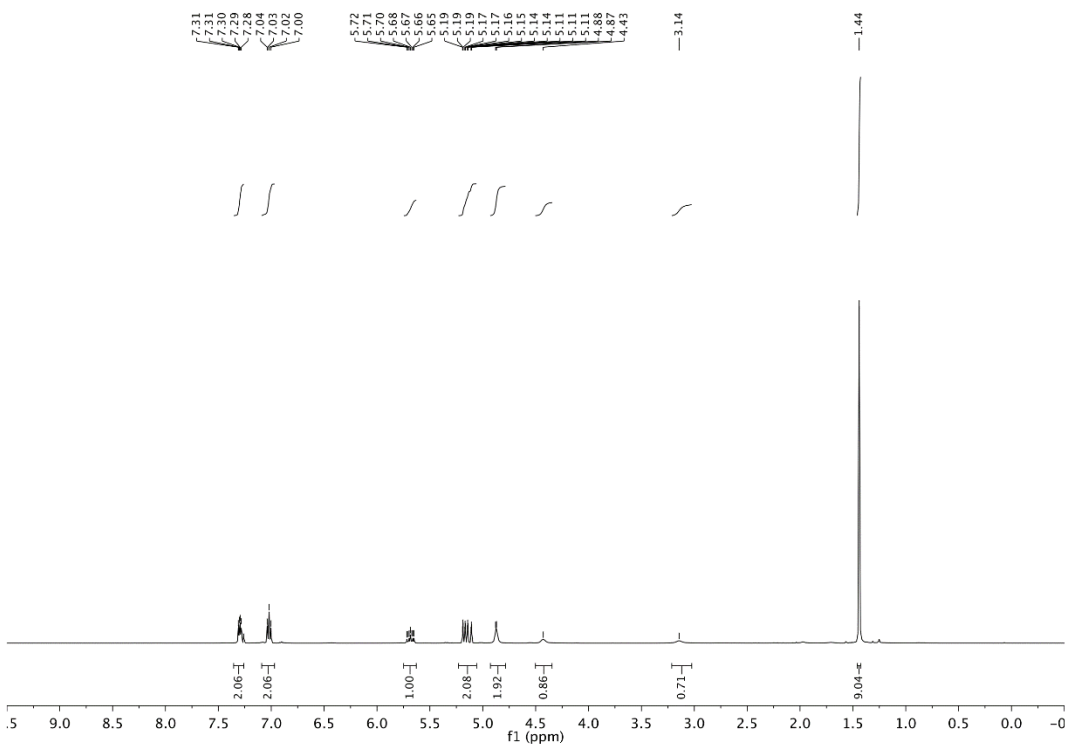
^{19}F NMR (100 MHz, $CDCl_3$): δ -115.06

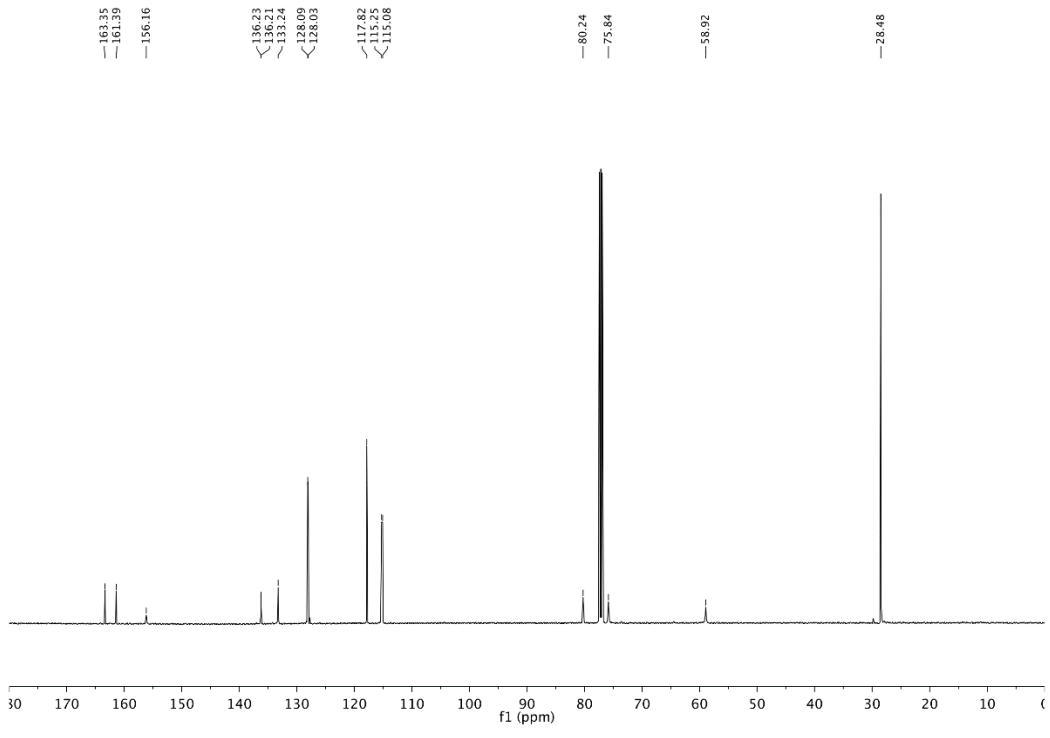
^{13}C NMR (100 MHz, $CDCl_3$): δ 162.4(d, $J_{C\text{-}F}$ = 245.7 Hz), 156.2, 136.2(d, $J_{C\text{-}F}$ = 3.1 Hz), 133.2, 128.1(d, $J_{C\text{-}F}$ = 8.0 Hz), 117.8, 115.2(d, $J_{C\text{-}F}$ = 21.3 Hz), 80.2, 75.8, 58.9, 28.5.

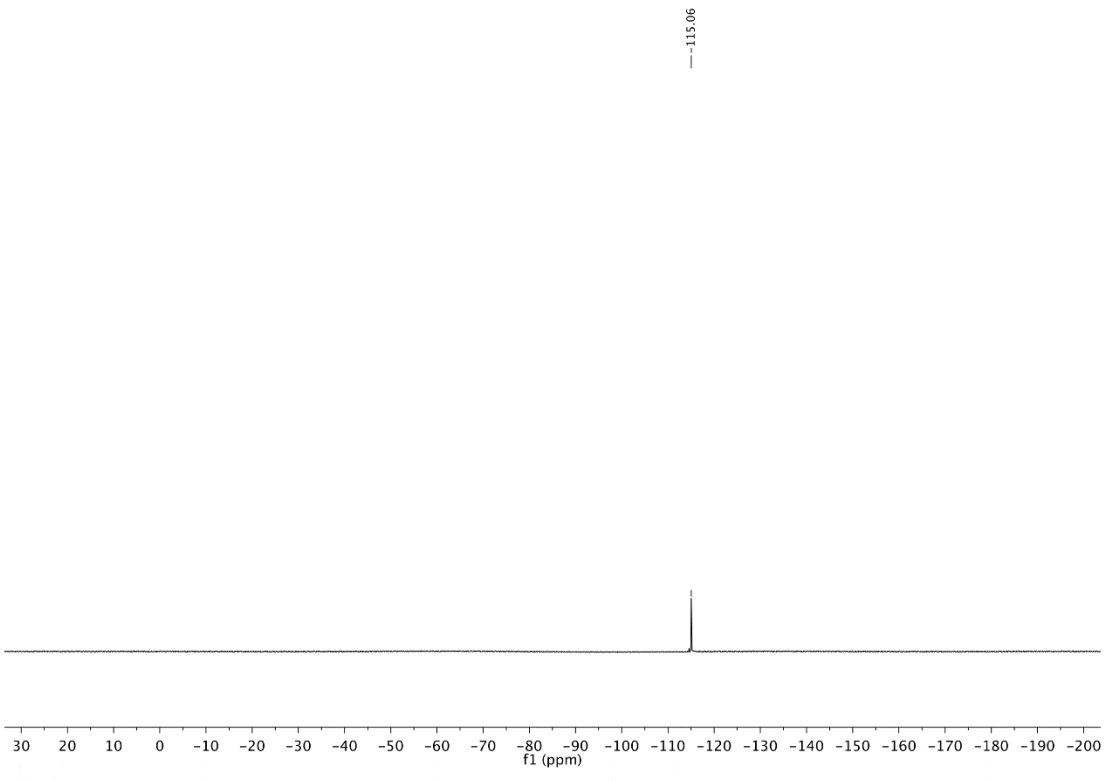
HRMS (ESI) Calcd. for $C_{15}H_{20}FNNaO_3$ $[M+Na]^+$: 304.1319, Found: 304.1328.

FTIR (neat): 3329, 2978, 2925, 1687, 1590, 1550, 1508, 1430, 1222, 1160, 1024, 837, 749, 694 cm^{-1}.

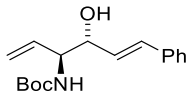
MP: 121-123℃


7.31
7.31
7.30
7.29
7.28
7.04
7.03
7.02
7.00
5.72
5.71
5.70
5.68
5.67
5.66
5.65
5.19
5.19
5.19
5.17
5.17
5.16
5.15
5.14
5.14
5.11
5.11
5.11
4.88
4.87
4.43
3.14
1.44
2.06
2.06
1.00
2.08
1.92
0.86
0.71
9.04
f1 (ppm)


163.35
161.39
156.16
136.23
136.21
133.24
128.09
128.03
117.82
115.55
115.68
80.24
75.84
58.92
28.48
f1 (ppm)


-115.06
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

tert-butyl (E)-(4-hydroxy-6-phenylhexa-1,5-dien-3-yl)carbamate (5.4n).



In accordance with the general procedure, the title compound was obtained in 62% over two steps (35.9 mg) as a yellow oil after column chromatography (SiO_2; 15%-20% EtOAc/hexanes).

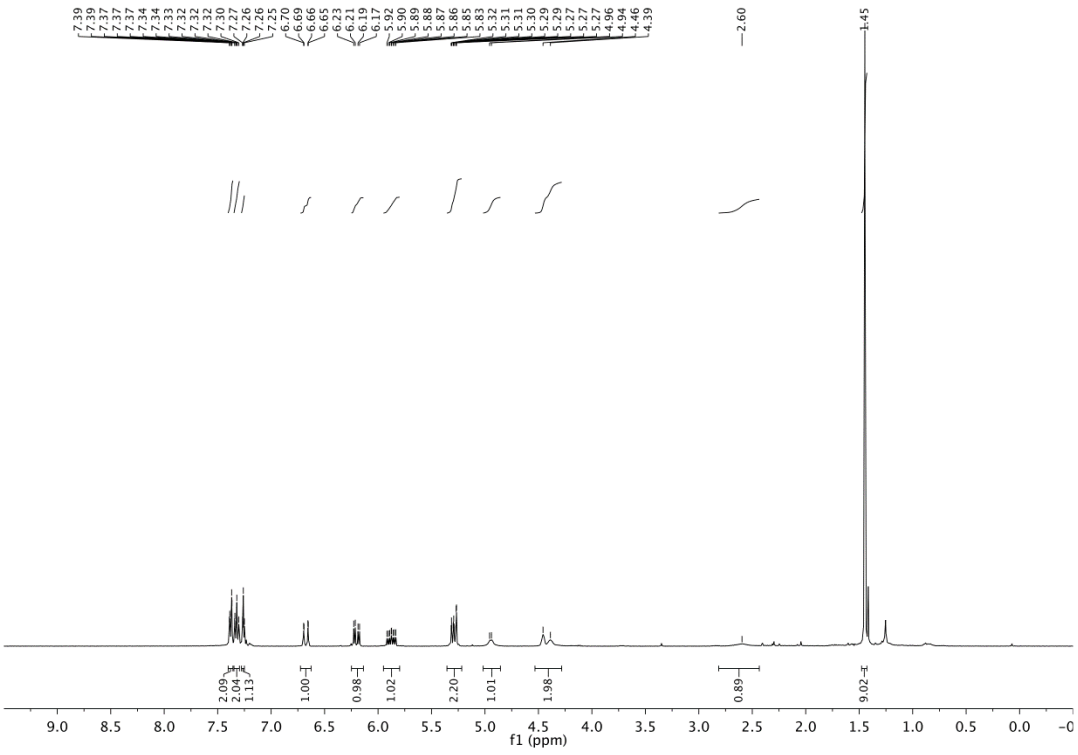
R_f=0.18 (20% EtOAc/Hexanes)

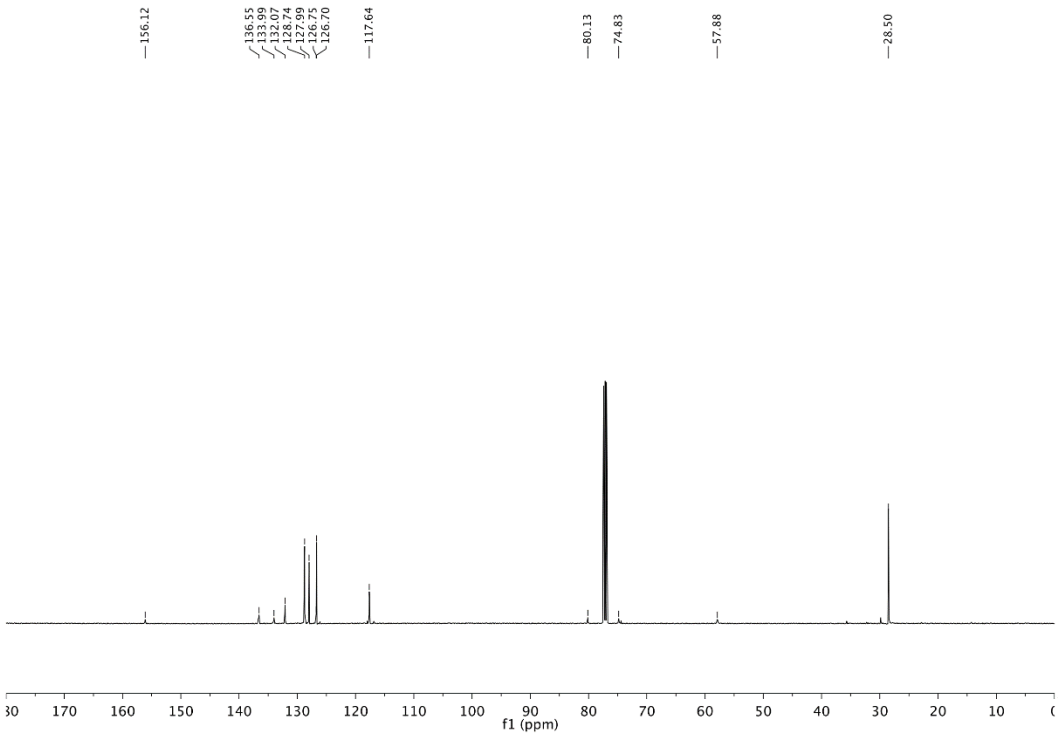
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.1 Hz, 2H), 7.32 (t, *J* = 7.5 Hz, 2H), 7.28 – 7.22 (m, 1H), 6.72 – 6.63 (m, 1H), 6.20 (dd, *J* = 16.0, 5.7 Hz, 1H), 5.88 (ddd, *J* = 16.7, 10.5, 5.6 Hz, 1H), 5.35 – 5.22 (m, 2H), 4.94 (d, *J* = 8.2 Hz, 1H), 4.51 – 4.27 (m, 2H), 2.64 (br s, 1H), 1.45 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 136.6, 134.0, 132.1, 128.7, 128.0, 126.8, 126.7, 117.7, 80.1, 74.8, 57.9, 28.5.

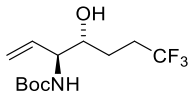
HRMS (ESI) Calcd. for $C_{17}H_{23}NO_3Na^+$ $[M+Na]^+$: 312.1576, Found: 312.1576.

FTIR (neat): 3350, 2982, 2927, 1740, 1682, 1524, 1447, 1367, 1250, 1166, 1000, 967, 922, 750 cm^{-1}.


7.39
7.39
7.37
7.37
7.37
7.34
7.34
7.33
7.32
7.32
7.32
7.30
7.27
7.26
7.26
7.25
6.70
6.69
6.66
6.65
6.23
6.21
6.19
6.17
5.92
5.90
5.89
5.88
5.87
5.86
5.85
5.83
5.32
5.31
5.31
5.30
5.29
5.29
5.27
5.27
5.27
4.96
4.94
4.46
4.39
2.60
1.45
2.09
2.04
1.13
1.00
0.98
1.02
2.20
1.01
1.98
0.89
9.02
f1 (ppm)


156.12
136.55
133.99
132.07
128.74
127.99
126.75
126.70
117.64
80.13
74.83
57.88
28.50
f1 (ppm)

tert-butyl (7,7,7-trifluoro-4-hydroxyhept-1-en-3-yl)carbamate (5.4q).



In accordance with the general procedure, the title compound was obtained in 68% over two steps as a yellow oil (38.5 mg) after column chromatography (SiO_2; 20%-25% EtOAc/hexanes).

R_f=0.20 (20% EtOAc/Hexanes)

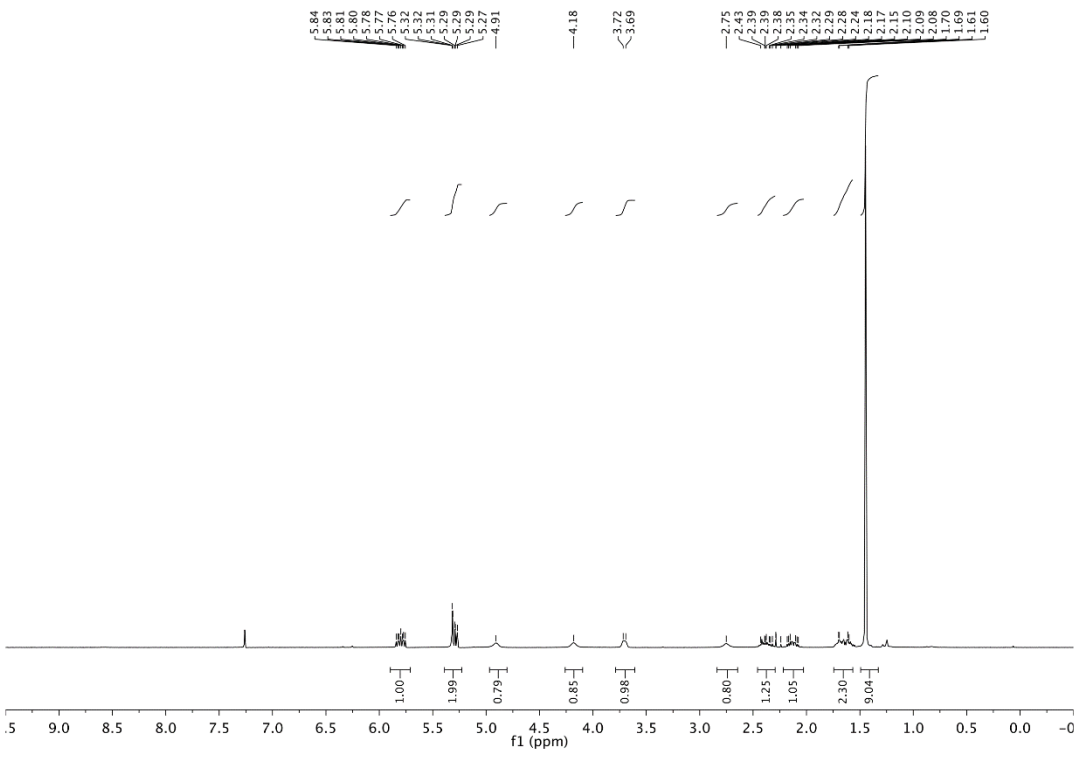
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80 (ddd, J = 17.1, 10.7, 6.5 Hz, 1H), 5.37 – 5.22 (m, 2H), 4.90 (br s, 1H), 4.18 (br s, 1H), 3.70 (dd, J = 9.9, 4.4 Hz, 1H), 2.73 (br s, 1H), 2.47 – 2.30 (m, 1H), 2.20 – 2.06 (m, 1H), 1.75 – 1.54 (m, 2H), 1.45 (s, 9H).

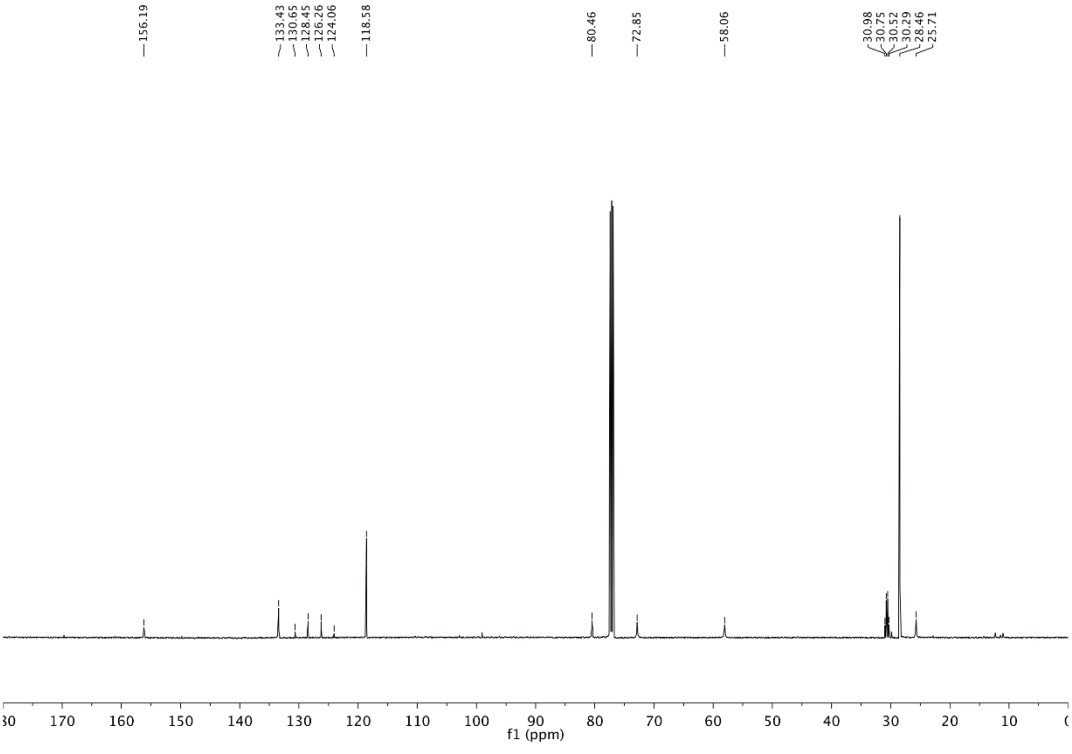
^{19}F NMR (100 MHz, $CDCl_3$) δ -66.4.

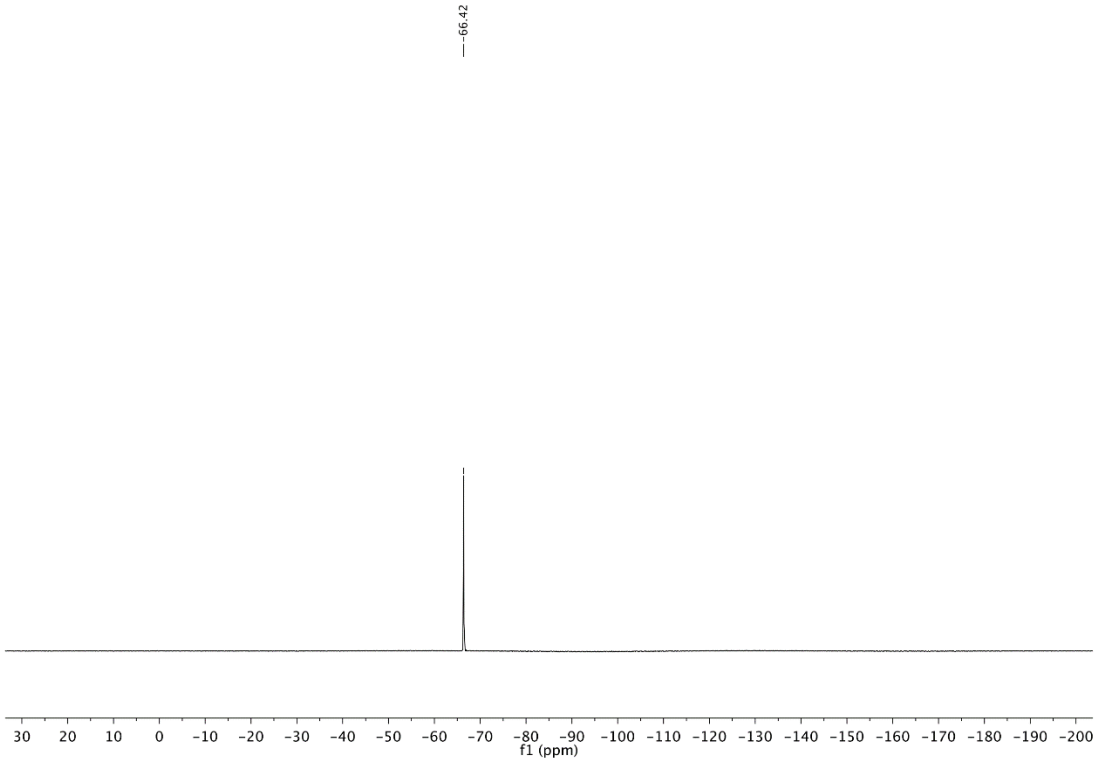
^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2, 133.4, 127.4 (q, $J_{C\text{-}F}$ = 276.0), 118.6, 80.5, 72.9, 58.1, 30.6 (q, $J_{C\text{-}F}$ = 29.0), 28.5, 25.7.

HRMS (ESI) Calcd. for $C_{12}H_{20}F_3NO_3Na^+$ $[M+Na]^+$: 306.1293, Found: 306.1292.

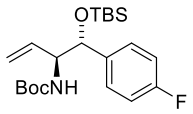
FTIR (neat): 3347, 2987, 2944, 1740, 1676, 1529, 1449, 1368, 1305, 1246, 1224, 1161, 1131, 1008, 935, 859, 769 cm^{-1}.


5.84
5.83
5.81
5.80
5.78
5.77
5.76
5.32
5.31
5.29
5.29
5.29
5.27
4.91
4.18
3.72
3.69
2.75
2.43
2.39
2.39
2.38
2.35
2.34
2.32
2.29
2.28
2.24
2.18
2.17
2.15
2.10
2.09
2.08
1.70
1.69
1.61
1.60
1.00
1.99
0.79
0.85
0.98
0.80
1.25
1.05
2.30
9.04
f1 (ppm)


156.19
133.43
130.65
128.45
126.26
124.06
118.58
80.46
72.85
58.06
30.98
30.75
30.52
30.29
28.46
25.71
f1 (ppm)


-66.42
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

Procedure and Preparation of S1



To a stirred solution of compound **5.4b** (0.2 mmol, 100 mol %) in anhydrous DMF (1 mL, 0.2 M) were added imidazole (0.6 mmol, 300 mol %) and TBSCl (0.3 mmol, 150 mol %). The mixture was allowed to stir at 60 °C for 15 hours. H_2O was then added after the mixture cooled to room temperature. The mixture was extracted three times with EtOAc, and the combined organic layers was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed in *vacuo* and the residue was subjected to column chromatography (SiO_2; 3%-5% EtOAc/Hexanes). The title compound was obtained as a colorless oil in 90% yield (71.3 mg).

R_f = 0.64 (20% EtOAc/Hexanes).

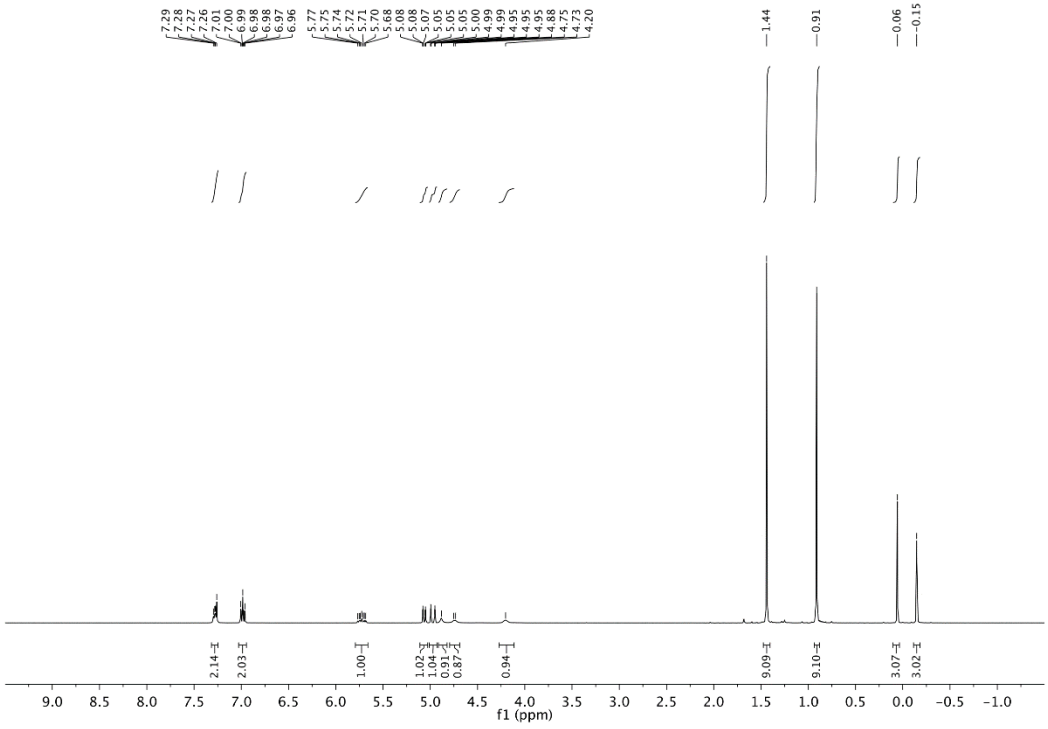
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.25 (m, 2H), 7.03 – 6.95 (m, 2H), 5.72 (ddd, J = 17.0, 10.5, 6.3 Hz, 1H), 5.06 (dt, J = 10.6, 1.3 Hz, 1H), 4.97 (dt, J = 17.3, 1.4 Hz, 1H), 4.88 (s, 1H), 4.74 (d, J = 8.6 Hz, 1H), 4.20 (s, 1H), 1.44 (s, 9H), 0.91 (s, 9H), 0.06 (s, 3H), -0.15 (s, 3H).

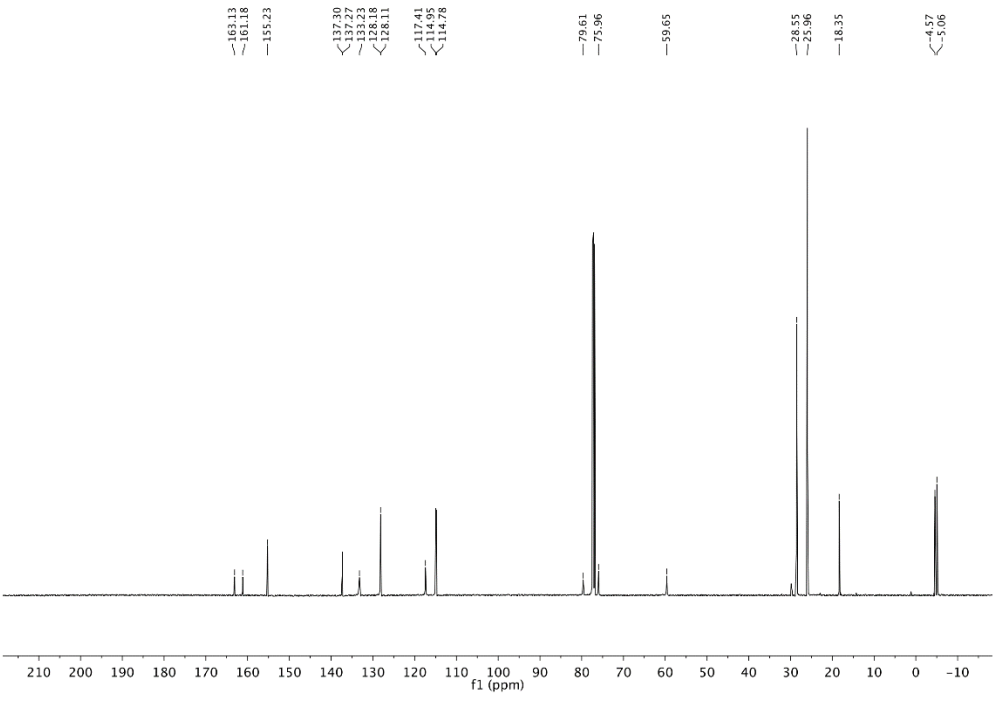
^{19}F HMR (100 MHz, $CDCl_3$) δ -115.6.

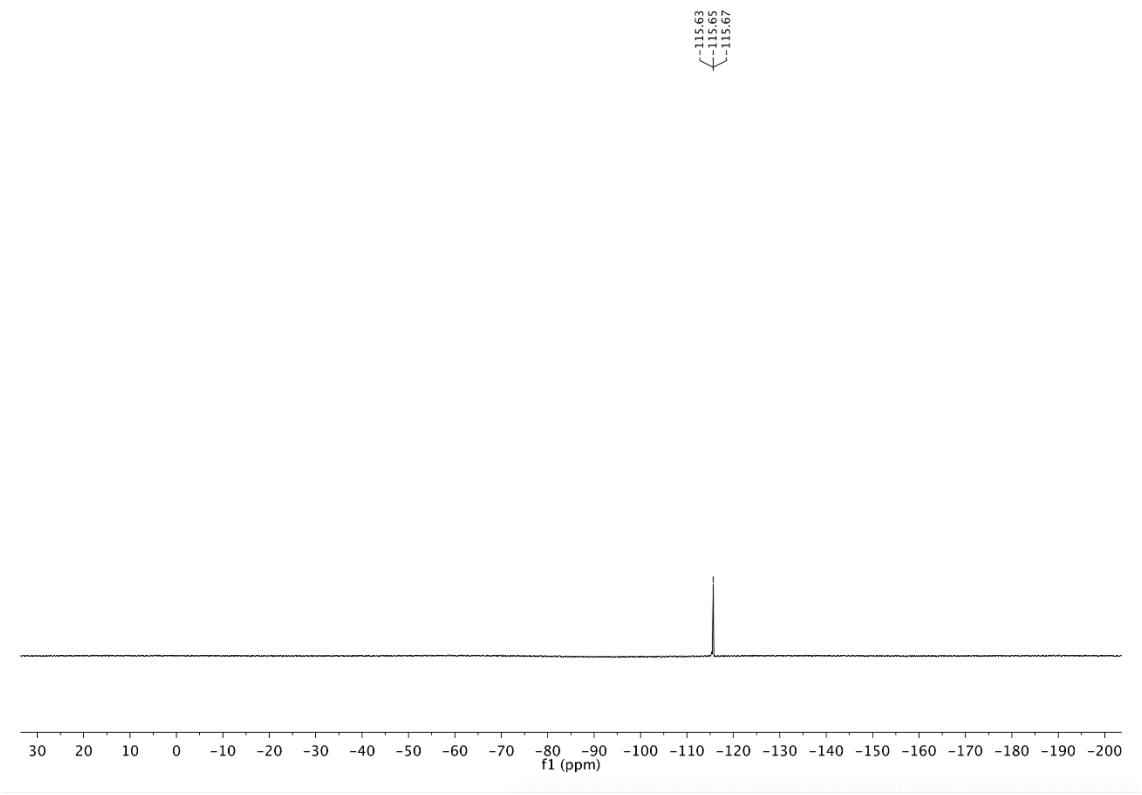
^{13}C NMR (100 MHz, $CDCl_3$): δ 162.2 (d, $J_{C\text{-}F}$ = 244.8 Hz), 155.2, 137.3 (d, $J_{C\text{-}F}$ = 3.1 Hz),, 133.23, 128.1 (d, $J_{C\text{-}F}$ = 8.0 Hz),, 117.41, 114.9 (d, $J_{C\text{-}F}$ = 21.3 Hz)., 79.61, 75.96, 59.65, 28.55, 25.96, 18.35, -4.57, -5.06.

HRMS (ESI) Calcd. for $C_{21}H_{34}FNaNO_3Si$ $[M+Na]^+$: 418.2192, Found: 418.2184.

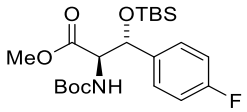
FTIR (neat): 2956, 2930, 2858, 1707, 1509, 1366, 1253, 1223, 1169, 1088, 992, 864, 837, 776, 669 cm^{-1}.


7.29
7.28
7.27
7.26
7.01
7.00
6.99
6.98
6.98
6.97
6.96
5.77
5.75
5.74
5.72
5.71
5.70
5.68
5.08
5.08
5.07
5.05
5.05
5.05
5.00
4.99
4.99
4.95
4.95
4.88
4.75
4.73
4.20
1.44
0.91
0.06
-0.15
2.14
2.03
1.00
1.02
1.04
0.91
0.87
0.94
9.09
9.10
3.07
3.02
f1 (ppm)


163.13
161.18
155.23
137.30
137.27
133.23
128.18
128.11
117.41
114.95
114.78
79.61
75.96
59.65
28.55
25.96
18.35
4.57
5.06
f1 (ppm)


-115.63
-115.65
-115.67
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

General Procedure and Preparation of 5.5b



To a stirred solution of compound **S1** (0.15 mmol, 100 mol%) in MeCN:CCl_4:H_2O (1.5 mL, 1:1:1.5, 0.1 M) were added $NaIO_4$ (0.75 mmol, 500 mol %) and $RuCl_3 \cdot xH_2O$ (0.0075 mmol, 5 mol %). The mixture was allowed to stir at room temperature for 12 hours until the complete consumption of the starting material as monitored by TLC. The mixture was diluted with DCM, filtered through a short pad of celite and washed with DCM. The filtrate was washed with H_2O and the aqueous phase was extracted three times with DCM. The combined organic layers was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed in *vacuo* and the residue was dissolved in $CHCl_3$:MeOH (1.5 mL, 2:1, 0.1 M). $TMSCH_2N_2$ in hexanes (0.15 mL, 0.3 mmol, 200 mol %) was then added dropwise. The mixture was allowed to stir at room temperature for 2 hours. The solvent was then removed in *vacuo* and the residue was subjected to column chromatography (SiO_2; 3%-5% EtOAc/Hexanes). The title compound was obtained as a colorless oil in 65% yield over two steps (41.7 mg).

R_f = 0.23 (10% EtOAc/Hexanes).

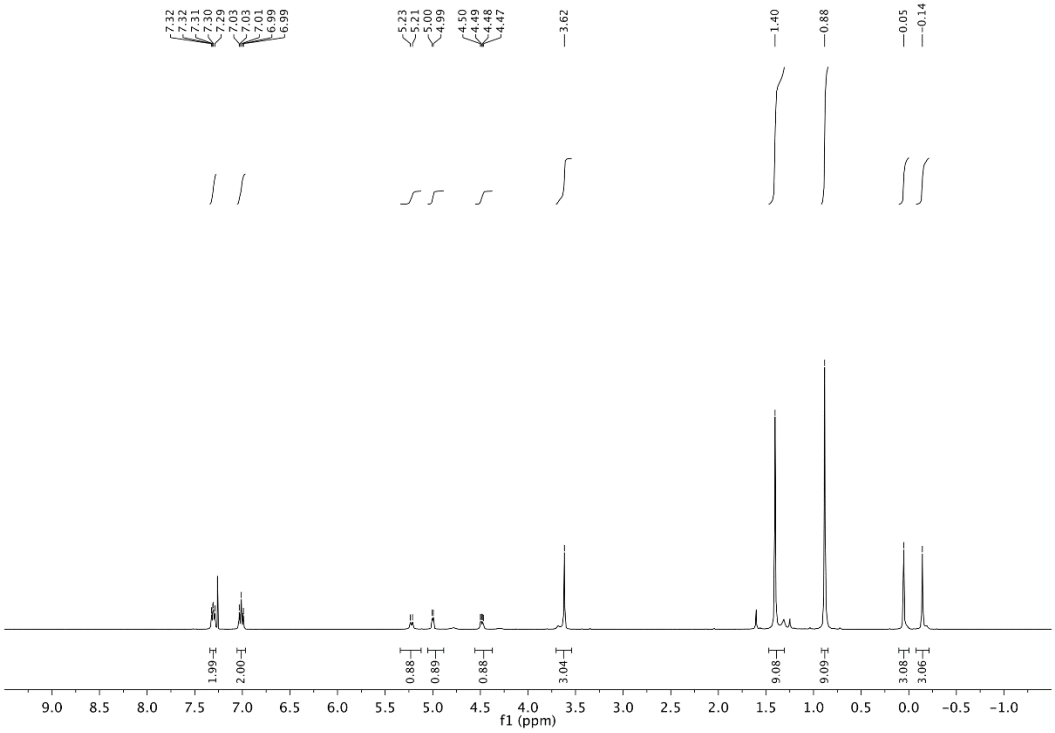
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (dd, J = 8.4, 5.4 Hz, 2H), 7.01 (t, J = 8.6 Hz, 2H), 5.22 (d, J = 8.4 Hz, 1H), 5.00 (d, J = 4.3 Hz, 1H), 4.49 (dd, J = 8.6, 4.4 Hz, 1H), 3.62 (s, 3H), 1.40 (s, 9H), 0.88 (s, 9H), 0.05 (s, 3H), -0.14 (s, 3H).

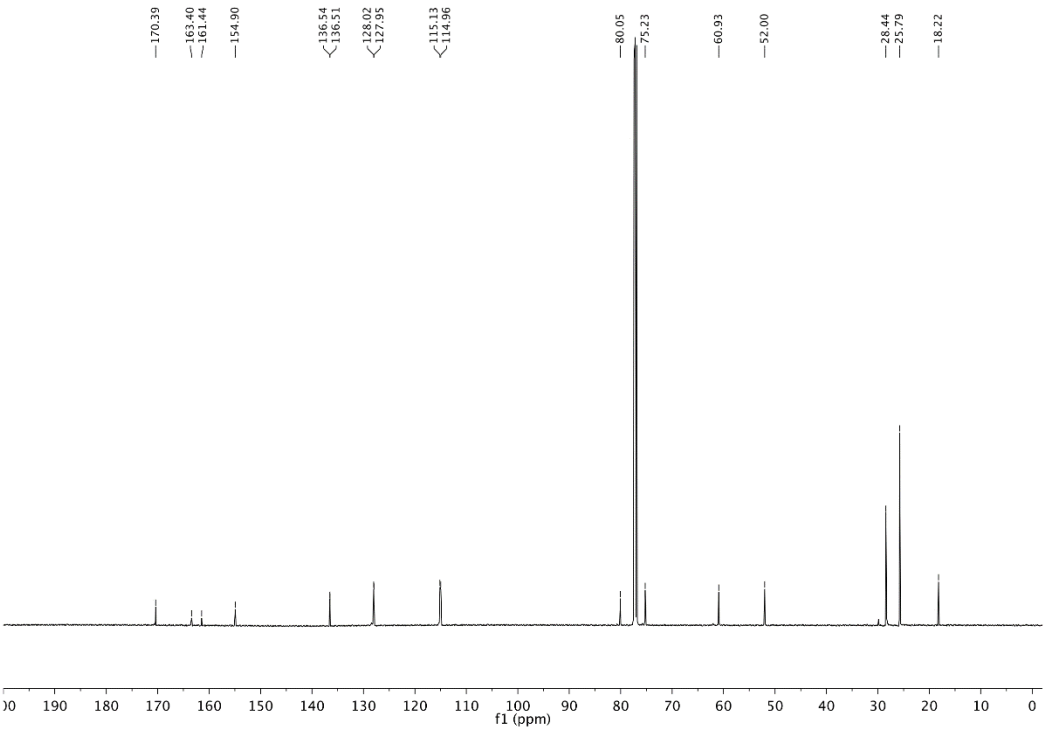
^{19}F NMR (125 MHz, $CDCl_3$) δ -115.0.

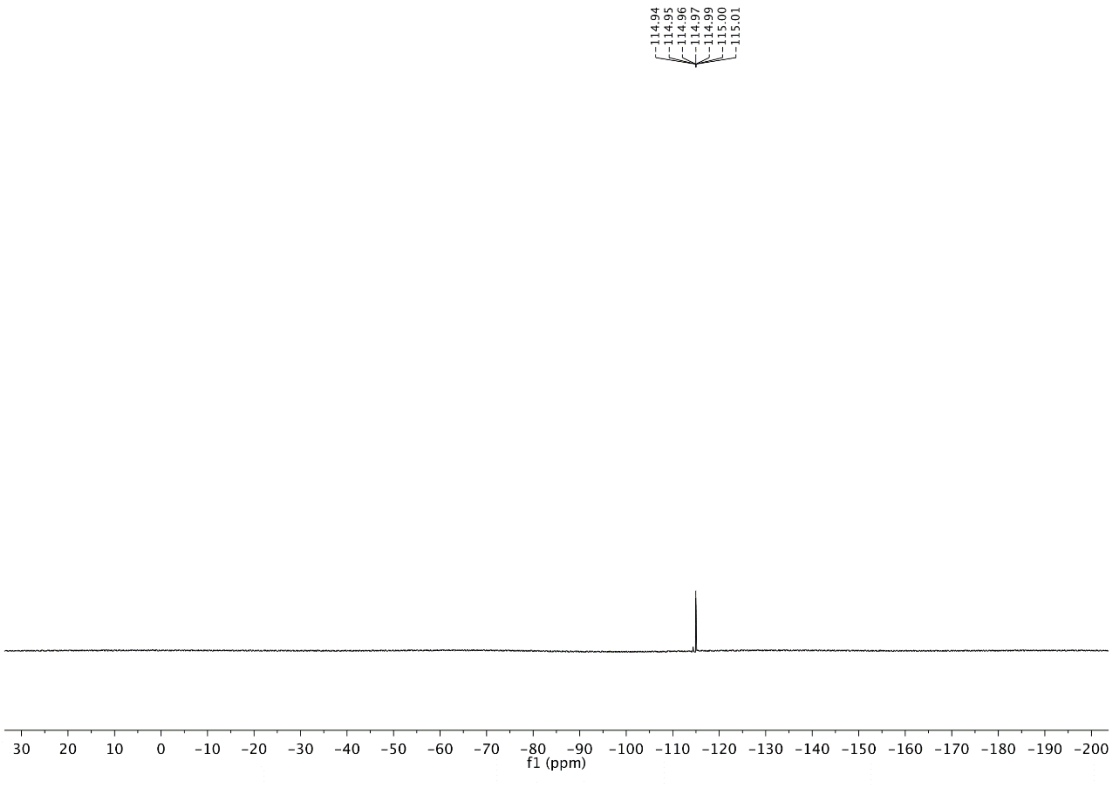
^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 162.4 (d, $J_{C\text{-}F}$ = 245.7 Hz), 154.9, 136.5 (d, $J_{C\text{-}F}$ = 3.1 Hz), 128.0 (d, $J_{C\text{-}F}$ = 8.1 Hz), 115.0 (d, $J_{C\text{-}F}$ = 21.7 Hz), 80.1, 75.2, 60.9, 52.0, 28.4, 25.8, 18.2, -4.7, -5.2.

HRMS (ESI) Calcd. for $C_{21}H_{34}FNO_5SiNa^+$ $[M+Na]^+$: 450.2088, Found: 450.2089.

FTIR (neat): 2954, 2928, 2852, 1712, 1606, 1509, 1365, 1253, 1222, 1156, 1088, 1015, 854, 837, 777,757, 699 cm^{-1}.


7.32
7.32
7.31
7.30
7.29
7.03
7.03
7.01
6.99
6.99
5.23
5.21
5.00
4.99
4.50
4.49
4.48
4.47
3.62
1.40
0.88
0.05
-0.14
1.99
2.00
0.88
0.89
0.88
3.04
9.08
9.09
3.08
3.06
f1 (ppm)


170.39
163.40
161.44
154.90
136.54
136.51
128.02
127.95
115.13
114.96
80.05
75.23
60.93
52.00
28.44
25.79
18.22
f1 (ppm)


-114.94
-114.95
-114.96
-114.97
-114.99
-115.00
-115.01
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

Crystallographic Material for 5.4b

X-ray Experimental for $C_{15}H_{20}FNO_3$ (5.4b)

X-ray Experimental for complex $C_{15}H_{20}NO_3F$: Crystals grew as long, very thin colorless needles by vapor diffusion of pentane into diethyl ether. The data crystal was cut from a longer crystal and had approximate dimensions; 0.32 x 0.03 x 0.02 mm. The data were collected on an Agilent Technologies SuperNova Dual Source diffractometer using a μ-focus Cu Kα radiation source (λ = 1.5418Å) with collimating mirror monochromators. A total of 364 frames of data were collected using ω-scans with a scan range of 1° and a counting time of 53 seconds per frame with a detector offset of +/- 42.4° and 120 seconds per frame with a detector offset of +/- 109.8°. The data were collected at 100 K using an Oxford 700 Cryostream low temperature device. Details of crystal data, data collection and structure refinement are listed in Table 1. Data collection, unit cell refinement and data reduction were performed using Agilent Technologies CrysAlisPro V 1.171.38.43f.[12] The structure was solved by direct methods using SHELXT[13] and refined by full-matrix least-squares on F2 with anisotropic displacement parameters for the non-H atoms using SHELXL-2016/6.[14] Structure analysis was aided by use of the programs PLATON[15] and WinGX.[16] The hydrogen atoms were calculated in ideal positions with isotropic displacement parameters set to 1.2xUeq of the attached atom (1.5xUeq for methyl hydrogen atoms). The hydrogen atoms bound to N1 atoms was located in a ΔF map and refined with an isotropic displacement parameter.

The function, $\Sigma w(|Fo|^2 - |Fc|^2)^2$, was minimized, where $w = 1/[(\sigma(Fo))^2 + (0.0829*P)^2 + (1.279*P)]$ and $P = (|Fo|^2 + 2|Fc|^2)/3$. $Rw(F^2)$ refined to 0.226, with R(F) equal to 0.0859 and a goodness of fit, S, = 1.12. Definitions used for calculating R(F), $Rw(F^2)$ and the goodness of fit, S, are given below.[17] The data were checked for secondary extinction effects but no correction was necessary. Neutral atom scattering factors and values used to calculate the linear absorption coefficient are from the International Tables for X-ray Crystallography (1992).[18] All figures were generated using SHELXTL/PC.[19] Tables of positional and thermal parameters, bond lengths and angles, torsion angles and figures are found elsewhere.

Table 5.2. Crystal data and structure refinement for **5.4b**.

Empirical formula	C_{15} H_{20} F N O_3	
Formula weight	281.32	
Temperature	100(2) K	
Wavelength	1.54184 Å	
Crystal system	orthorhombic	
Space group	*P* 2_1 2_1 2_1	
Unit cell dimensions	a = 5.0624(7) Å	α= 90°.
	b = 10.961(3) Å	β= 90°.
	c = 26.361(4) Å	γ = 90°.
Volume	1462.8(5) $Å^3$	
Z	4	
Density (calculated)	1.277 Mg/m^3	
Absorption coefficient	0.805 mm^{-1}	
F(000)	600	
Crystal size	0.320 x 0.030 x 0.020 mm^3	
Theta range for data collection	3.353 to 75.126°.	
Index ranges	-6<=h<=5, -13<=k<=13, -16<=l<=32	
Reflections collected	3095	
Independent reflections	2260 [R(int) = 0.0495]	
Completeness to theta = 67.684°	98.3 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00 and 0.602	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2260 / 120 / 189	
Goodness-of-fit on F^2	1.115	
Final R indices [I>2sigma(I)]	R_1 = 0.0859, wR_2 = 0.2060	
R indices (all data)	R_1 = 0.1075, wR_2 = 0.2259	
Absolute structure parameter	-0.1(5)	
Largest diff. peak and hole	0.410 and -0.349 e.$Å^{-3}$	

Table 5.3. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3) for **5.4b**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C1	7659(13)	4793(7)	4370(2)	29(1)
C2	8520(15)	5686(6)	4041(3)	32(2)
C3	7279(15)	6825(7)	4013(3)	38(2)
C4	5107(16)	7028(7)	4318(3)	40(2)
C5	4209(16)	6184(6)	4659(3)	36(2)
C6	5483(14)	5045(6)	4680(3)	31(2)
C7	8945(13)	3552(6)	4378(2)	29(1)
C8	7725(14)	2666(6)	3980(2)	29(1)
C9	9128(15)	1463(6)	3979(2)	31(2)
C10	8127(18)	409(7)	4112(3)	42(2)
C11	5661(13)	3694(6)	3247(2)	27(1)
C12	4442(13)	4878(7)	2485(3)	32(2)
C13	2766(15)	3897(7)	2236(3)	34(2)
C14	6199(16)	5491(9)	2093(3)	44(2)
C15	2845(15)	5817(7)	2768(3)	36(2)
N9	7818(11)	3209(6)	3479(2)	28(1)
O1	8915(9)	2984(5)	4867(2)	30(1)
O2	3408(8)	3610(5)	3397(2)	31(1)
O3	6425(9)	4295(5)	2824(2)	33(1)
F1	3859(11)	8130(4)	4290(2)	54(1)

Table 5.4. Bond lengths [Å] and angles [°] for **5.4b**.

C1-C2	1.379(10)	C14-H14B	0.98
C1-C6	1.399(10)	C14-H14C	0.98
C1-C7	1.508(10)	C15-H15A	0.98
C2-C3	1.399(10)	C15-H15B	0.98
C2-H2	0.95	C15-H15C	0.98
C3-C4	1.380(11)	N9-H9N	0.83(7)
C3-H3	0.95	O1-H1O	0.84
C4-F1	1.365(8)	C2-C1-C6	118.4(7)
C4-C5	1.366(11)	C2-C1-C7	120.8(6)
C5-C6	1.406(10)	C6-C1-C7	120.7(6)
C5-H5	0.95	C1-C2-C3	121.7(7)
C6-H6	0.95	C1-C2-H2	119.2
C7-O1	1.433(8)	C3-C2-H2	119.2
C7-C8	1.557(9)	C4-C3-C2	118.1(7)
C7-H7	1.0000	C4-C3-H3	121.0
C8-N9	1.450(9)	C2-C3-H3	121.0
C8-C9	1.497(9)	F1-C4-C5	118.8(7)
C8-H8	1.00	F1-C4-C3	118.7(7)
C9-C10	1.309(10)	C5-C4-C3	122.5(7)
C9-H9	0.95	C4-C5-C6	118.4(7)
C10-H10A	0.95	C4-C5-H5	120.8
C10-H10B	0.95	C6-C5-H5	120.8
C11-O2	1.210(8)	C5-C6-C1	120.9(7)
C11-O3	1.354(8)	C5-C6-H6	119.6
C11-N9	1.359(9)	C1-C6-H6	119.6
C12-O3	1.487(8)	O1-C7-C1	113.6(6)
C12-C15	1.507(11)	O1-C7-C8	109.3(6)
C12-C13	1.518(10)	C1-C7-C8	112.5(5)
C12-C14	1.522(10)	O1-C7-H7	107.0
C13-H13A	0.98	C1-C7-H7	107.0
C13-H13B	0.98	C8-C7-H7	107.0
C13-H13C	0.98	N9-C8-C9	110.2(6)
C14-H14A	0.98	N9-C8-C7	110.1(6)

Table 5.4 Continued

C9-C8-C7	111.2(5)	H13A-C13-H13B	109.5
N9-C8-H8	108.4	C12-C13-H13C	109.5
C9-C8-H8	108.4	H13A-C13-H13C	109.5
C7-C8-H8	108.4	H13B-C13-H13C	109.5
C10-C9-C8	126.4(7)	C12-C14-H14A	109.5
C10-C9-H9	116.8	C12-C14-H14B	109.5
C8-C9-H9	116.8	H14A-C14-H14B	109.5
C9-C10-H10A	120.0	C12-C14-H14C	109.5
C9-C10-H10B	120.0	H14A-C14-H14C	109.5
H10A-C10-H10B	120.0	H14B-C14-H14C	109.5
O2-C11-O3	125.2(6)	C12-C15-H15A	109.5
O2-C11-N9	125.5(6)	C12-C15-H15B	109.5
O3-C11-N9	109.4(6)	H15A-C15-H15B	109.5
O3-C12-C15	111.0(6)	C12-C15-H15C	109.5
O3-C12-C13	109.5(6)	H15A-C15-H15C	109.5
C15-C12-C13	113.5(6)	H15B-C15-H15C	109.5
O3-C12-C14	101.7(5)	C11-N9-C8	123.0(6)
C15-C12-C14	110.4(7)	C11-N9-H9N	128(4)
C13-C12-C14	110.2(6)	C8-N9-H9N	108(4)
C12-C13-H13A	109.5	C7-O1-H1O	109.5
C12-C13-H13B	109.5	C11-O3-C12	120.7(5)

Table 5.5. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **5.4b**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C1	25(3)	33(3)	29(3)	-2(3)	-6(3)	-3(3)
C2	30(3)	31(3)	35(3)	1(3)	-2(3)	-5(3)
C3	31(3)	34(4)	49(4)	7(3)	-3(3)	-7(3)
C4	40(4)	25(3)	53(4)	-4(3)	-5(3)	-3(3)
C5	36(4)	28(3)	43(4)	-8(3)	0(3)	2(3)
C6	24(3)	31(3)	37(3)	-1(3)	4(3)	-4(3)
C7	21(3)	33(3)	33(3)	2(3)	-1(3)	1(3)
C8	24(3)	31(3)	33(3)	4(3)	0(3)	1(3)
C9	36(4)	24(3)	33(3)	-4(3)	-7(3)	5(3)
C10	53(5)	31(4)	41(4)	2(3)	-2(4)	1(4)
C11	19(3)	25(3)	35(3)	-3(3)	-7(3)	1(3)
C12	16(3)	40(4)	40(3)	8(3)	-1(3)	0(3)
C13	29(4)	37(4)	37(3)	-1(3)	-7(3)	8(3)
C14	31(4)	61(5)	40(4)	20(4)	1(3)	0(4)
C15	31(4)	31(4)	45(4)	6(3)	-5(3)	-4(3)
N9	11(2)	36(3)	36(3)	0(2)	-3(2)	1(2)
O1	21(2)	39(3)	31(2)	3(2)	2(2)	3(2)
O2	13(2)	36(3)	43(3)	4(2)	1(2)	-1(2)
O3	18(2)	45(3)	34(2)	13(2)	0(2)	0(2)
F1	56(3)	23(2)	82(3)	3(2)	-2(3)	5(2)

Table 5.6. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2 x 10^3) for **5.4b**.

	x	y	z	U(eq)
H2	9992	5525	3828	38
H3	7913	7440	3791	45
H5	2759	6362	4875	43
H6	4858	4440	4908	37
H7	10839	3671	4283	35
H8	5834	2521	4072	35
H9	10919	1466	3872	37
H10A	6344	359	4222	50
H10B	9185	-306	4098	50
H13A	3920	3285	2080	52
H13B	1649	4268	1975	52
H13C	1649	3506	2492	52
H14A	7310	6104	2259	66
H14B	5096	5887	1835	66
H14C	7324	4877	1930	66
H15A	1414	5412	2954	54
H15B	2094	6402	2527	54
H15C	3989	6249	3008	54
H1O	7348	2834	4952	46
H9N	9390(140)	3320(60)	3400(20)	8(14)

Table 5.7. Torsion angles [°] for **5.4b**.

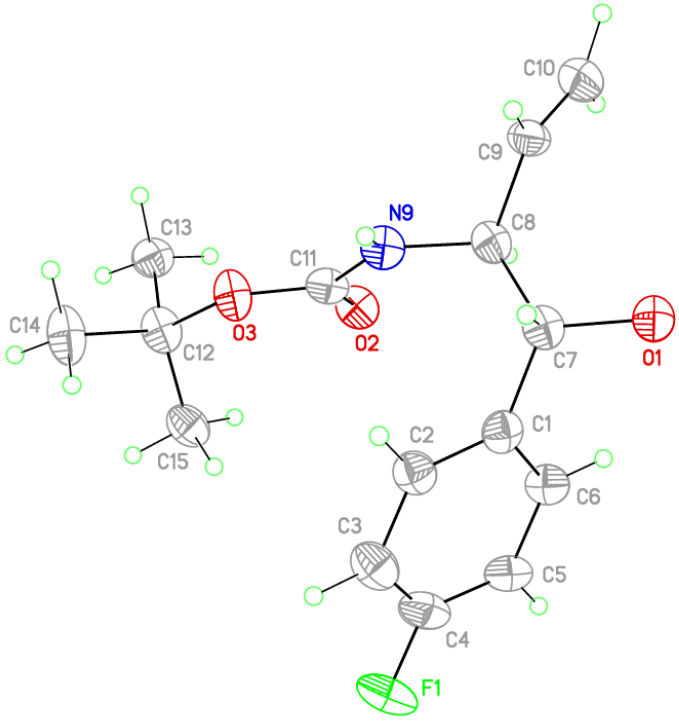
C6-C1-C2-C3	0.2(10)
C7-C1-C2-C3	177.2(6)
C1-C2-C3-C4	-1.4(11)
C2-C3-C4-F1	-179.2(7)
C2-C3-C4-C5	2.9(11)
F1-C4-C5-C6	179.1(7)
C3-C4-C5-C6	-2.9(11)
C4-C5-C6-C1	1.6(11)
C2-C1-C6-C5	-0.2(10)
C7-C1-C6-C5	-177.3(6)
C2-C1-C7-O1	148.9(6)
C6-C1-C7-O1	-34.2(8)
C2-C1-C7-C8	-86.3(7)
C6-C1-C7-C8	90.7(7)
O1-C7-C8-N9	-178.1(5)
C1-C7-C8-N9	54.7(7)
O1-C7-C8-C9	-55.6(7)
C1-C7-C8-C9	177.2(6)
N9-C8-C9-C10	-123.2(8)
C7-C8-C9-C10	114.3(8)
O2-C11-N9-C8	-8.9(11)
O3-C11-N9-C8	170.6(6)
C9-C8-N9-C11	132.9(7)
C7-C8-N9-C11	-104.0(7)
O2-C11-O3-C12	-2.8(11)
N9-C11-O3-C12	177.7(6)
C15-C12-O3-C11	59.1(8)
C13-C12-O3-C11	-66.9(8)
C14-C12-O3-C11	176.5(6)

Table 5.8. Hydrogen bonds for **5.4b** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C13-H13C...O2	0.98	2.55	3.094(9)	115.1
O1-H1O...O1#1	0.84	2.01	2.832(4)	164.8
N9-H9N...O2#2	0.83(7)	2.06(7)	2.872(7)	167(6)

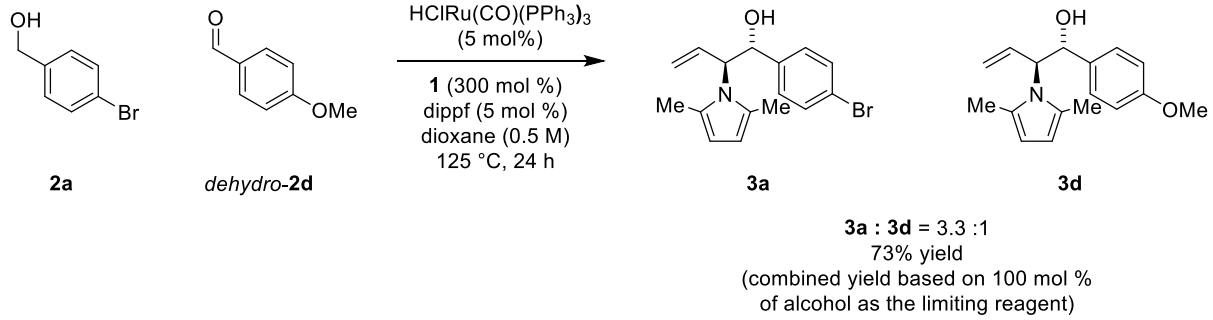
Symmetry transformations used to generate equivalent atoms:
#1 x-1/2,-y+1/2,-z+1 #2 x+1,y,z

Figure 5.2. View of **5.4b** showing the atom labeling scheme. Displacement ellipsoids are scaled to the 50% probability level.



Competition Experiment Establishing Rapid Redox Equilibrium

Reaction between Alcohol 5.2a and Aldehyde *dehydro*-5.2d

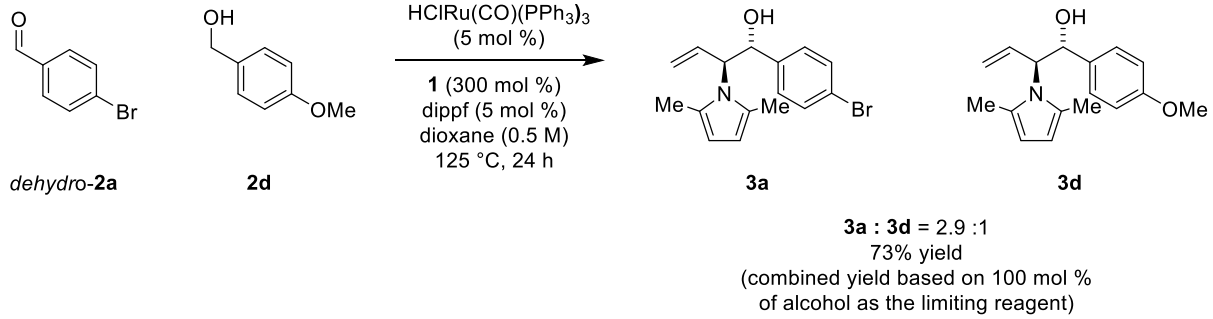


2a *dehydro*-**2d** **3a** **3d**

3a : 3d = 3.3 :1
73% yield
(combined yield based on 100 mol % of alcohol as the limiting reagent)

To a resealable pressure tube (13x100) were added $HClRu(CO)(PPh_3)_3$ (9.5 mg, 0.010 mmol, 5 mol %), dippf (4.2 mg, 0.010 mmol, 5 mol %) and alcohol **5.2a** (37.4 mg, 0.2 mmol, 100 mol %). The tube was sealed with a rubber septum and purged with argon for 20 minutes. Dioxane (0.40 mL, 0.5 M) was added to the reaction vessel. Aldehyde *dehydro*-**5.2d** (24.3 μL, 0.2 mmol, 100 mol %) and acetylenic pyrrole **5.1** (0.60 mmol, 300 mol %) were subsequently added to the reaction vessel and the rubber septum was quickly replaced with a screw cap. The mixture was allowed to stir at 125 °C for 24 hours. The mixture was then allowed to cool to room temperature and the solvent was removed *in vacuo*. The residue was subjected to column chromatography (SiO_2; 7.5%-10% EtOAc/Hexanes) and a 3.3:1 mixture of **5.3a** (35.9 mg, 56% yield) and **5.3d** (9.3 mg, 17% yield).

Reaction between Alcohol 5.2d and Aldehyde *dehydro*-5.2a



To a resealable pressure tube (13x100) were added $HClRu(CO)(PPh_3)_3$ (9.5 mg, 0.010 mmol, 5 mol %), dippf (4.2 mg, 0.010 mmol, 5 mol %) and aldehyde *dehydro*-**5.2a** (37.0 mg, 0.2 mmol, 100 mol %). The tube was sealed with a rubber septum and purged with argon for 20 minutes. Dioxane (0.40 mL, 0.5 M) was added to the reaction vessel. Alcohol **5.2d** (24.8 μL, 0.2 mmol, 100 mol %) and acetylenic pyrrole 1 (0.60 mmol, 300 mol %) were subsequently added to the reaction vessel and the rubber septum was quickly replaced with a screw cap. The mixture was allowed to stir at 125 °C for 24 hours. The mixture was then allowed to cool to room temperature and the solvent was removed *in vacuo*. The residue was subjected to column chromatography (SiO_2; 7.5%-10% EtOAc/Hexanes) and a 2.9:1 mixture of **5.3a** (34.5 mg, 54% yield) and **5.3d** (10.2 mg, 19% yield).

Chapter 6: Enantioselective Iridium Catalyzed *anti*-(α-Aryl)allylation of Fluoral Hydrate and Difluoroacetaldehyde Ethyl Hemiacetal*

6.1 INTRODUCTION

Alcohol mediated carbonyl reductive couplings has been developed broadly by Krische group, by which catalytic enantioselective carbonyl allylations and propargylations.[1] Branched aryl-substituted allylic acetates were explored in the coupling with paraformaldehyde mediated by 2-propanol to form primary homoallylic alcohols and high enantioselectivity was observed.[2] While when higher aldehyde was used in the reductive coupling with branched aryl-substituted allylic acetate, a correlation between enantioselectivity and aldehyde electrophilicity was found, which is with the increasing of carbonyl electrophilicity enantioselectivity increases.

There is no systematic study on catalytic enantioselective carbonyl (α-aryl)allylation in the literatures, and in many of the examples chiral auxiliaries were involved,[3] modest enantioselectivity were observed.[4] Enantioselective (α-aryl)allylation of fluoral and difluoroacetaldehyde, which are readily commercial available resources of fluorinated moieties, were not reported before.

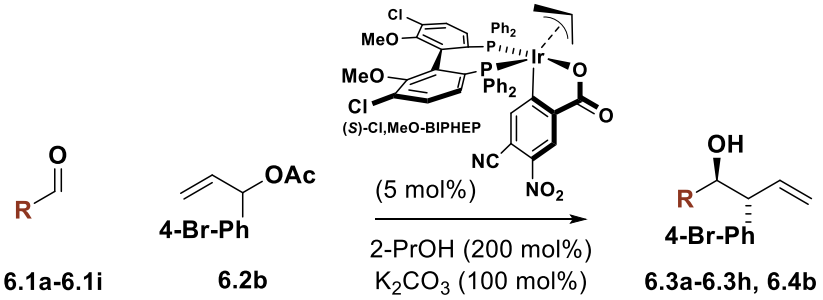
In this chapter, iridium catalyzed 2-propanol mediated enantioselective reductive coupling of branched aryl-substituted allylic acetates with fluoral and difluoroacetaldehyde was reported. The correlation between enantioselectivity and carbonyl electrophilicity was explained by different carbonyl binding modes: diastereomeric kinetic and thermodynamic coordination.

*This chapter is based on the published work:
Cabrera, J. M. †; Tauber, J. †; Zhang, W.; Xiang, M.; Krische, M. J. *J. Am. Chem. Soc.* **2018**, *140*, 9392.

6.2 Reaction Development and Scope

Initially, different *p*-substituted benzaldehydes **6.1a-6.1f** were exposed to 1-(4-bromophenyl)allyl acetate **6.2b** under 2-propanol mediated reductive coupling conditions, whereas iridium complex modified by (S)-Cl, MeO-BIPHEP was used (Table 6.1, entries 1-6). From the results of these experiments, a clear correlation between enantioselectivity and carbonyl electrophilicity σ was observed. For the electron-rich carbonyl, such as *p*-(dimethylamino)benzaldehyde **6.1a**, and *p*-methoxybenzaldehyde **6.1b**, carbonyl addition

Table 6.1 Correlation between Enantioselectivity with Carbonyl Electrophilicity in Carbonyl reductive (α-Aryl)allylation.



6.1a-6.1i (100 mol%) | **6.2b** (200 mol%) | **6.3a-6.3h, 6.4b**

Entry	R		6.1a-6.1i	6.3a-6.3h	Yield%	dr	ee%
1	4-Me_2N-Ph	-0.83	**6.1a**	**6.3a**	16	4:1	1
2	4-MeO-Ph	-0.27	**6.1b**	**6.3b**	54	9:1	5
3	4-Me-Ph	-0.17	**6.1c**	**6.3c**	69	4:1	12
4	Ph	0.00	**6.1d**	**6.3d**	74	4:1	15
5	4-F-Ph	0.06	**6.1e**	**6.3e**	88	3:1	16
6	4-Br-Ph	0.23	**6.1f**	**6.3f**	88	4:1	23
7	3-(6-Br-Pyr)	-	**6.1g**	**6.3g**	82	5:1	37
8	2-(6-Br-Pyr)	-	**6.1h**	**6.3h**	75	4:1	65
9[b]	CF_3	-	**6.1i**	**6.4b**	88	>20:1	94

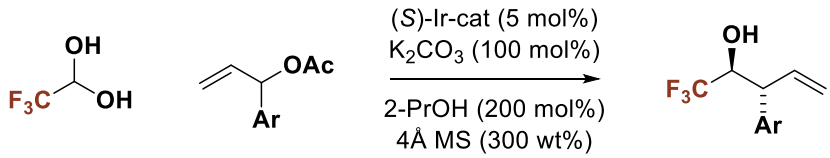
[a]Yields are material isolated by silica gel chromatography. See supporting Information for further experimental details. [b]4Å MS (300 wt %), and fluoral hydate in water (75 wt %)

products were obtained in nearly racemic form. When fluoral hydrate 6.1i was used with addition of 4Å molecular sieves, carbonyl (α-aryl)allylation product was isolated in 88% yield with complete *anti*-diastereoselecitivity and excellent enantioselectivity (Table 6.1, entry 9). Molecular sieves was crucial for this reaction, which is due to it helped with dehydration of fluoral hydrate.

The above conditions were applied to different branched aryl-substituted allylic acetates **6.2a**-**6.2l**, and the corresponding coupling adducts **6.4a**-**6.4l** were obtained in uniformly high enantioselectivity and complete diastereoselectivity and good to excellent yileds (Table 6.2). Not only mono-substituted aryl moieties on the allylic acetates could promote the C-C coupling, di-substituted aryl moieties could also engage in the coupling with fluoral hydrate under iridium catalysis. Notably, herteroarometic ring bearing allylic acetates **6.2i**-**6.2l** also gave the corresponding adducts **6.4i**-**6.4l**. The absolute stereochemical structure of **6.4l** was determined by single crystal X-ray diffraction analysis, and the absolute structure of other adducts were made in analogy to compound **6.4l**.

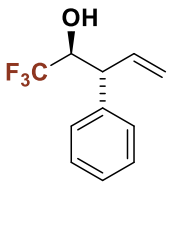
With the optimal conditions, difluoroacetaldehyde ethyl hemiacetal in ethanol (90 wt %), which is the only available source for difluoroacetaldehyde, was tested as an electrophile in the carbonyl (α-aryl)allylation. Ultilizing the same set of branched aryl-substituted allylic acetates, CHF_2-bearing β-aryl alcohols **6.5a**-**6.5l** were formed in good yields with complete *anti*-diastereoselectivity and high enantioselectivity as well. As we know that ethanol itself could engage in the reodx-triggered carbonyl addition reaction, small amount of (3-14% yield) ethanol coupling products were observed as side products. The absolute stereochemical structure of **6.5l** was determined by single crystal X-ray

Table 6.2 Iridium Catalyzed Enantioselective Reductive Coupling of Fluoral Hydrate **6.1i** to Form CF_3-Bearing Adducts **6.4a-6.4l**.

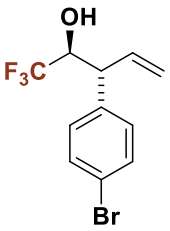


6.1i, 75 wt% in H_2O (100 mol%) | **6.2a-6.2l** (200 mol%) | **6.4a-6.4l**

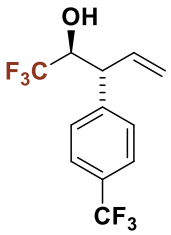
6.2a, Ar = Ph	**6.2b**, Ar = 4-Br-Ph	**6.2c**, Ar = 4-CF_3-Ph
6.2d, Ar = 4-Me-Ph	**6.2e**, Ar = 4-MeO-Ph	**6.2f**, Ar = 2-Cl-Ph
6.2g, Ar = 3,5-Cl_2-Ph	**6.2h**, Ar = 5-Benzodioxolyl	**6.2i**, Ar = 2-Furyl
6.2j, Ar = 2-Thienyl	**6.2k**, Ar = 5-(2-MeO-Pyr)	**6.2l**, Ar = 4-Quinolinyl



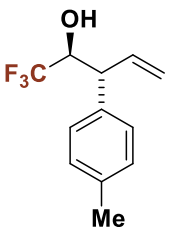
6.4a, 85% Yield, >20:1 dr, 93% ee



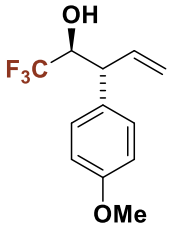
6.4b, 88% Yield, >20:1 dr, 94% ee



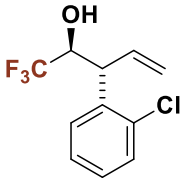
6.4c, 64% Yield, >20:1 dr, 93% ee



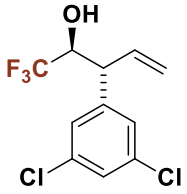
6.4d, 77% Yield, >20:1 dr, 92% ee



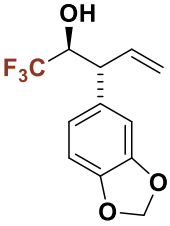
6.4e, 71% Yield, >20:1 dr, 92% ee



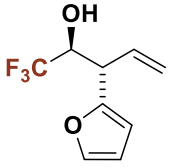
6.4f, 60% Yield, >20:1 dr, 89% ee



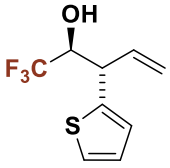
6.4g, 91% Yield, >20:1 dr, 94% ee



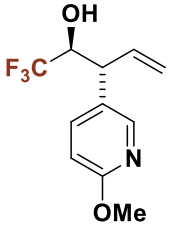
6.4h, 84% Yield, >20:1 dr, 92% ee



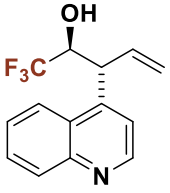
6.4i, 61% Yield, >20:1 dr, 94% ee



6.4j, 82% Yield, >20:1 dr, 94% ee

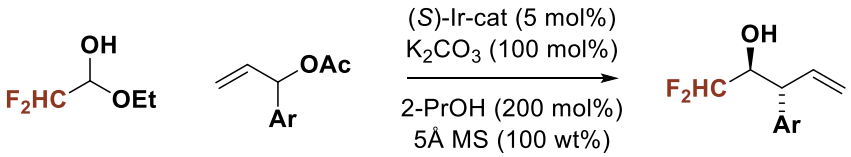


6.4k, 87% Yield, >20:1 dr, 91% ee



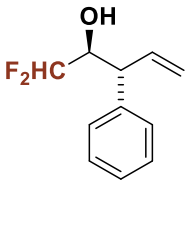
6.4l, 84% Yield, >20:1 dr, 93% ee (**X-Ray**)

Table 6.3 Iridium Catalyzed Enantioselective Reductive Coupling of Difluoroacetaldehyde Ethyl Hemiacetal **6.1j** to Form CHF_2-Bearing Adducts **6.5a-6.5l**.

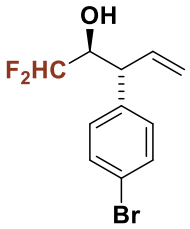


6.1j, 90 wt% in EtOH (100 mol%) | **6.2a-6.2l** (200 mol%) | **6.5a-6.5l**

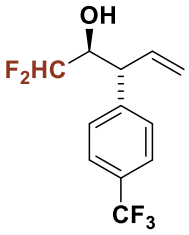
2a, Ar = Ph	**2b**, Ar = 4-Br-Ph	**2c**, Ar = 4-CF_3-Ph
2d, Ar = 4-Me-Ph	**2e**, Ar = 4-MeO-Ph	**2f**, Ar = 2-Cl-Ph
2g, Ar = 3,5-Cl_2-Ph	**2h**, Ar = 5-Benzodioxolyl	**2i**, Ar = 2-Furyl
2j, Ar = 2-Thienyl	**2k**, Ar = 5-(2-MeO-Pyr)	**2l**, Ar = 4-Quinolinyl



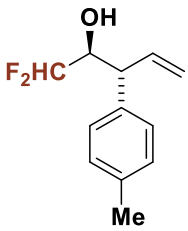
6.5a, 80% Yield, >20:1 dr, 94% ee



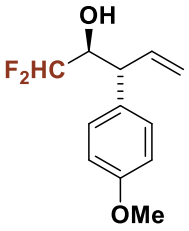
6.5b, 84% Yield, >20:1 dr, 94% ee



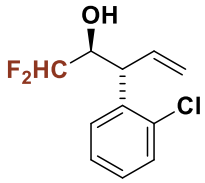
6.5c, 82% Yield, >20:1 dr, 94% ee



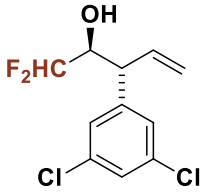
6.5d, 75% Yield, >20:1 dr, 95% ee



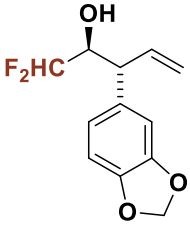
6.5e, 82% Yield, >20:1 dr, 93% ee



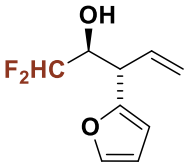
6.5f, 76% Yield, >20:1 dr, 92% ee



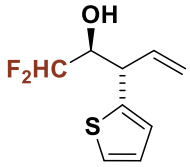
6.5g, 77% Yield, >20:1 dr, 95% ee



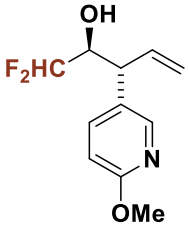
6.5h, 89% Yield, >20:1 dr, 93% ee



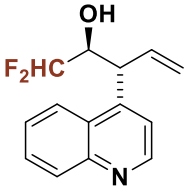
6.5i, 65% Yield, >20:1 dr, 91% ee



6.5j, 70% Yield, >20:1 dr, 88% ee



6.5k, 75% Yield, >20:1 dr, 93% ee

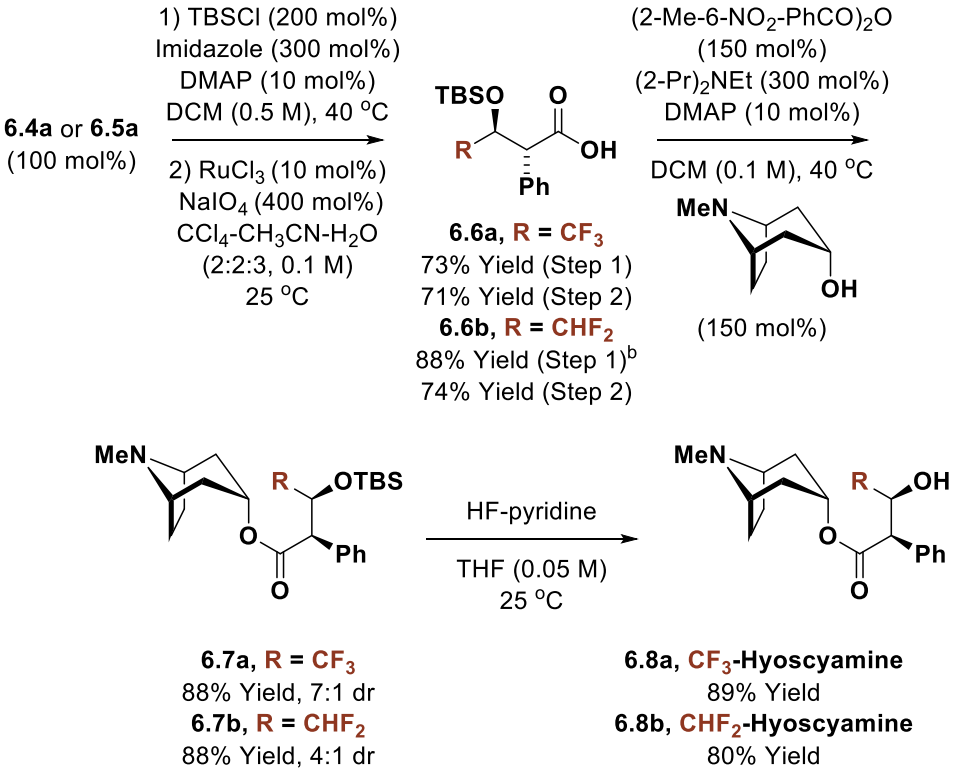


6.5l, 86% Yield, >20:1 dr, 97% ee (**X-Ray**)

diffraction analysis, and the absolute structure of other adducts were made in analogy to compound **6.5l**.

To demonstrate the utility of this transformation, it was successfuly applied to synthese of CF_3-bearing and CHF_2-bearing derivatives of *d*-hyoscyamine, which is a FDA approved alkaloid (Scheme 6.1). The TBS-protection of the free alcohol in the coupling adduct **6.4a** followed by alkene oxidative cleavage under Johnson-Lemieux conditions[5] delivered α,β-stereogenic carboxylic acid **6.6a**, which was treated with tropine under Shiina's esterification conditions[6] to form TBS-protected ester **6.7a** in good yield with some epimerization. Finally cleavage of silyl group with HF-pyridine provided CF_3-

Scheme 6.1 Synthesis of *d*-Hyoscyamine Derivatives **6.8a**, and **6.8b**.



hyoscyamine **6.8a**. The CHF_2-bearing derivative **6.8b** was synthesized in an analogous manner.

6.3 Mechanism and Discussion

The correlation between enantioselectivity with carbonyl electrophilicity was quite special (Figure 6.1).[7] In the earlier studies on enantioselective carbonyl allylation reactions, when the same chiral ligand was used, an inversion in the enantioselectivity was observed due to steric difference of the allyl donors. To be more specific, carbonyl allylation[8a,b] and crotylation[8c,d] have same enantiofacial preferences, while carbonyl *tert*-prenylation[9] has an inversion in the enantiofacial selectivity when the same chiral iridium catalyst in use. These observations suggested that when the allyl donors were small, the carbonyl additions

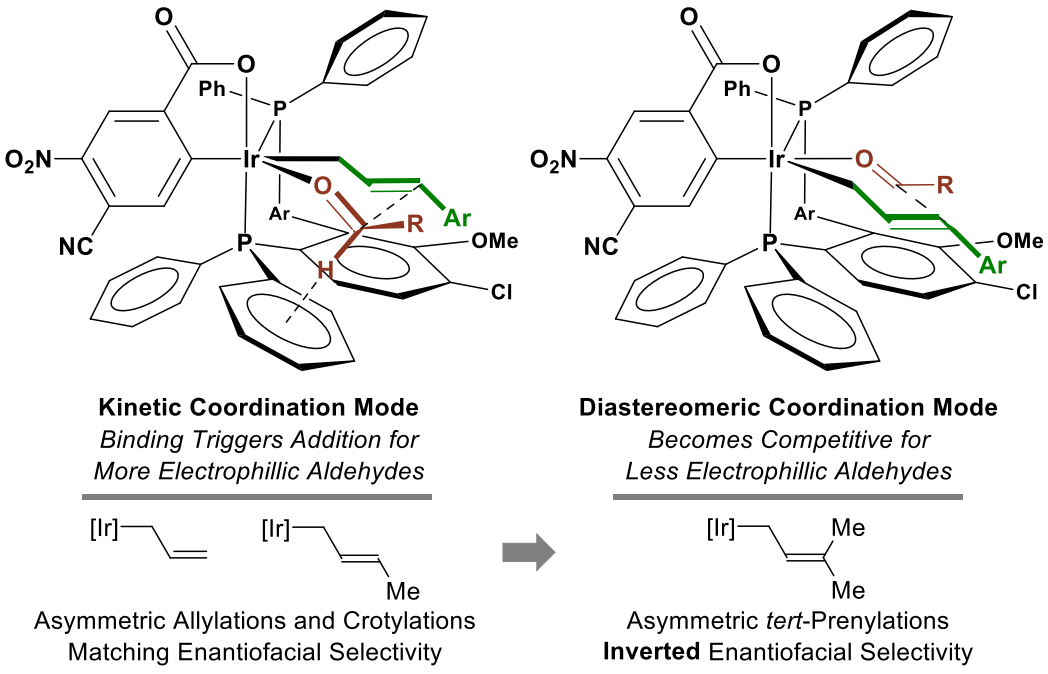


Figure 6.1 Proposed Stereochemical Model for Iridium Catalyzed Enantioselective Carbonyl *anti*-(α-aryl)allylation.

occurred via the transition structure where aldehyde approached from more open side (Figure 6.1, left), and when the allyl donor was big, the allyl group would reside on the more open side instead during the carbonyl addition (Figure 6.1, right). For the (aryl)allyl donor, which is between these two extreme coordination modes, kinetic coordination was preferred for sufficiently electrophilic aldehydes and as soon as the carbonyl coordinate to the iridium carbonyl addition would happen. However, for the less reactive aldehydes, carbonyl addition could proceed through either coordination mode, which caused the erosion in the enantioselectivity.

6.4 CONCLUSION

In summary, iridium catalyzed 2-propanol mediated enantioselective *anti*-(α-aryl)allylation of fluoral hydrate and difluoroacetaldehyde ethyl hemiacetal by coupling with various branched aryl-substituted allylic acetates. Two different coordination modes were proposed and rationalized the correlation between enantioselectivity with carbonyl electrophilicity in carbonyl allylation reactions. Also, two derivatives of *d*-hyoscyamine with CF_3 and CHF_2 group were synthesized from the coupling adducts **6.4a** and **6.5a**, respectively, to demonstrate the utility of this method.

6.5 EXPERIMENTAL DETAILS

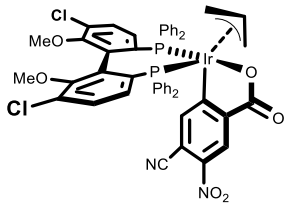
General Information

All reactions were run under an atmosphere of argon, unless otherwise indicated. Resealable pressure tubes (13x100 mm) were purchased from Fischer Scientific (catalog number 14–959–35C) and were flame dried followed by cooling in a desiccator or under a stream of argon prior to use. Tetrahydrofuran (THF) was dried over sodium metal, benzophenone, and distilled immediately prior to use. $RuH_2(PPh_3)_3$ were prepared according to literature procedure.1 All ligands were used as received from Strem Chemicals Inc. Alcohols were purified by distillation or recrystallization immediately prior to use. Preparative column chromatography employing Silicycle silica gel (40-63 μm) was performed according to the method of Still.2 Analytical thin-layer chromatography (TLC) was carried out using 0.25 mm commercial silica gel plates (Dynamic Absorbents F254). Visualization was accomplished with UV light followed by dipping in Seebach's stain solution then heating. Purification of reactions was carried out by flash chromatography using Silicycle silica gel (40–63 μm). Fluoral hydrate (75% in water) was purchased through Oakwood Chemical, difluoroacetaldehyde ethyl hemiacetal (90% in ethanol) through AstaTech, and potassium carbonate through Fisher Chemicals and used without further purification. Allylic acetates 2a[1] 2b–2c,[2] 2d,[3] 2e,[4] 2f–2l[2] were prepared according to previous literature.

Spectroscopy, Spectrometry, and Data Collection

Infrared spectra were recorded on a Perkin-Elmer 1600 spectrometer. Low-resolution mass spectra (LRMS) were obtained on a Karatos MS9 and are reported as m/z (relative intensity). Accurate masses are reported for the molecular ion (M+H, M+Na), or a suitable fragment ion. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded with a Varian Gemini (400 MHz) spectrometer. Chemical shifts are reported in delta (δ) units, parts per million (ppm) downfield from tetramethylsilane or ppm relative to the center of the singlet at 7.26 ppm for deuteriochloroform. Data reported as multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). Integration and coupling constants were reported in Hertz (Hz). Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded with a Varian Gemini (100 MHz) spectrometer and were routinely run with broadband decoupling. Chemical shifts are reported in delta (δ) units, ppm relative to the center of the triplet at 77.16 ppm for deuteriochloroform.

Detailed Procedure for Preparation of Preformed Iridium Catalyst



To a sealed tube equipped with a magnetic stir bar was added Cs_2CO_3 (501.8 mg, 1.54 mmol, 200 mol%), 4-cyano-3-nitrobenzoic acid (296.8 mg, 1.54 mmol, 200 mol%), (*S*)-Cl,MeO-BIPHEP (503.0 mg, 0.772 mmol, 100 mol%) and $[Ir(cod)Cl]_2$ (259.3 mg, 0.386 mmol, 50 mol%). The reaction vessel was purged with argon and THF (7.7 mL, 0.1 M) was added followed by allyl acetate (0.208 mL, 1.93 mmol, 250 mol%). The resulting mixture was stirred at room temperature for 30 min, and for another 90 min at 80 ˚C. After cooling to ambient temperature, the mixture was filtered through a celite plug with the aid of DCM (45 mL). The combined filtrate was concentrated *in vacuo* and subjected to flash column chromatography (DCM:THF = 10:1). The resulting gum-like residue was dissolved in THF (2.0 mL). Addition of HPLC grade hexanes (20 mL) led to formation of a precipitate. The product was filtered and washed with HPLC grade hexanes, followed by removal of trace amount of solvent *in vacuo,* to provide a light yellow powder (620.0 mg, 0.577 mmol) in 75% yield as a mixture of stereoisomers.

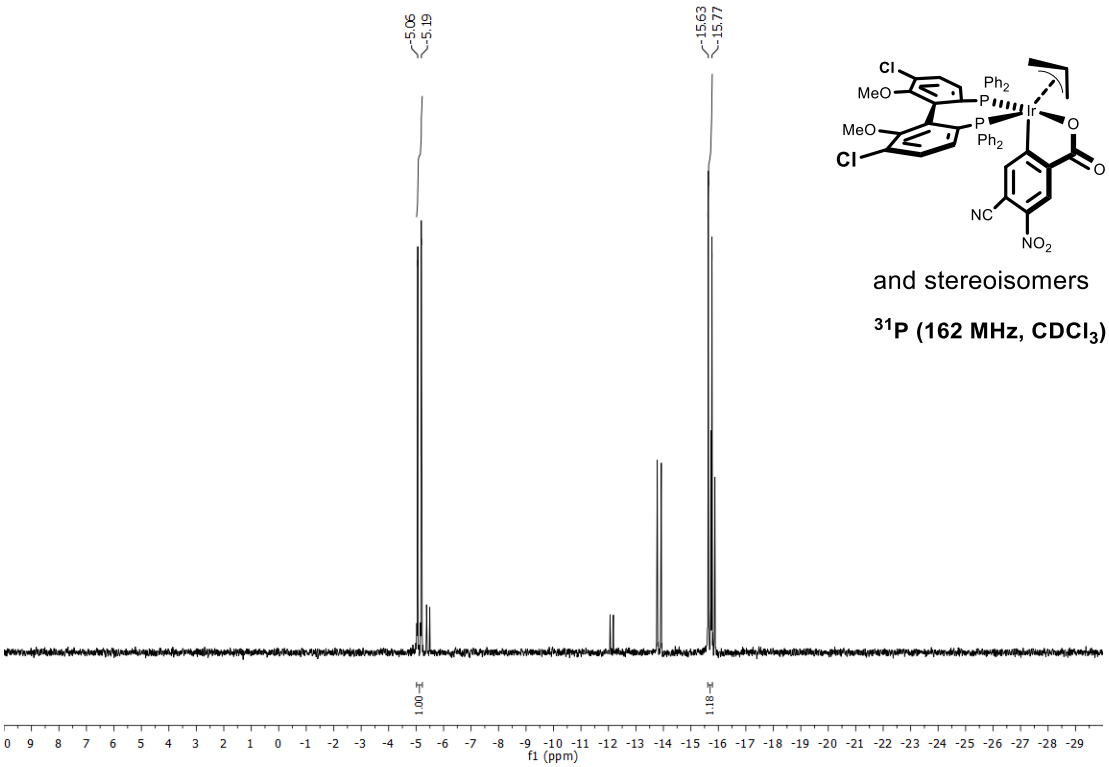
Spectral data is reported for the major isomer.

^{31}P NMR (162 MHz, $CDCl_3$): δ = -5.12 (d, *J* = 21.3 Hz), -15.70 (d, *J* = 21.4 Hz).

HRMS (ESI) Calculated for $C_{49}H_{37}Cl_2IrN_2O_6P_2$ $[M+H]^+$ = 1075.1195, Found 1075.1197.

$[\alpha]_D^{28}$: –4.0 (*c* = 1.0, $CHCl_3$)

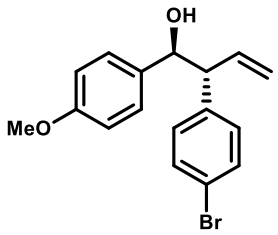
MP: 231-236 ˚C (decomposition)



General Procedure for Iridium Catalyzed Aryl Allylation of Aromatic Aldehydes

A pressure tube was equipped with a magnetic stir bar and charged with preformed iridium catalyst (10.7 mg, 10 μmol, 5 mol%), aldehyde (0.20 mmol, 100 mol%), K_2CO_3 (27.6 mg, 0.20 mmol, 100 mol%), 1-(4-bromophenyl)allyl acetate (0.40 mmol, 200 mol%). The pressure tube was purged with argon. Anhydrous THF (1.0 mL, 0.2 M) and 2-propanol (31 μL, 0.40 mmol, 200 mol%) were added via syringe. The sealed reaction vessel was stirred at 100 °C. After 24 h the solvent was removed *in vacuo* and the residue was subjected to flash column chromatography on silica.

(1S,2R)-2-(4-bromophenyl)-1-(4-methoxyphenyl)but-3-en-1-ol (6.3b)



The title compound was prepared according to the general procedure using 4-methoxybenzaldehyde (27.2 mg, 200 μmol) and 1-(4-bromophenyl)allyl acetate (102 mg, 0.40 mmol, 200 mol%). Flash chromatography on silica (Hex/EtOAc 6:1 → 3:1) provided the title compound (35.6 mg, 107 μmol, *anti:syn* = 9:1) in 54% yield as a yellow oil.

TLC (SiO_2) R_f = 0.37 (hexanes/ethyl acetate = 3:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.34 – 7.29 (m, 2H), 7.08 – 7.01 (m, 2H), 6.94 – 6.88 (m, 2H), 6.78 – 6.72 (m, 2H), 6.19 (ddd, *J* = 17.0, 10.2, 8.7 Hz, 1H), 5.28 (d, *J* = 10.1 Hz, 1H), 5.22 (dt, *J* = 17.2, 1.3 Hz, 1H), 4.76 (dd, *J* = 8.0, 1.7 Hz, 1H), 3.76 (s, 3H), 3.51 (t, *J* = 8.3 Hz, 1H), 2.22 (s, 1H).

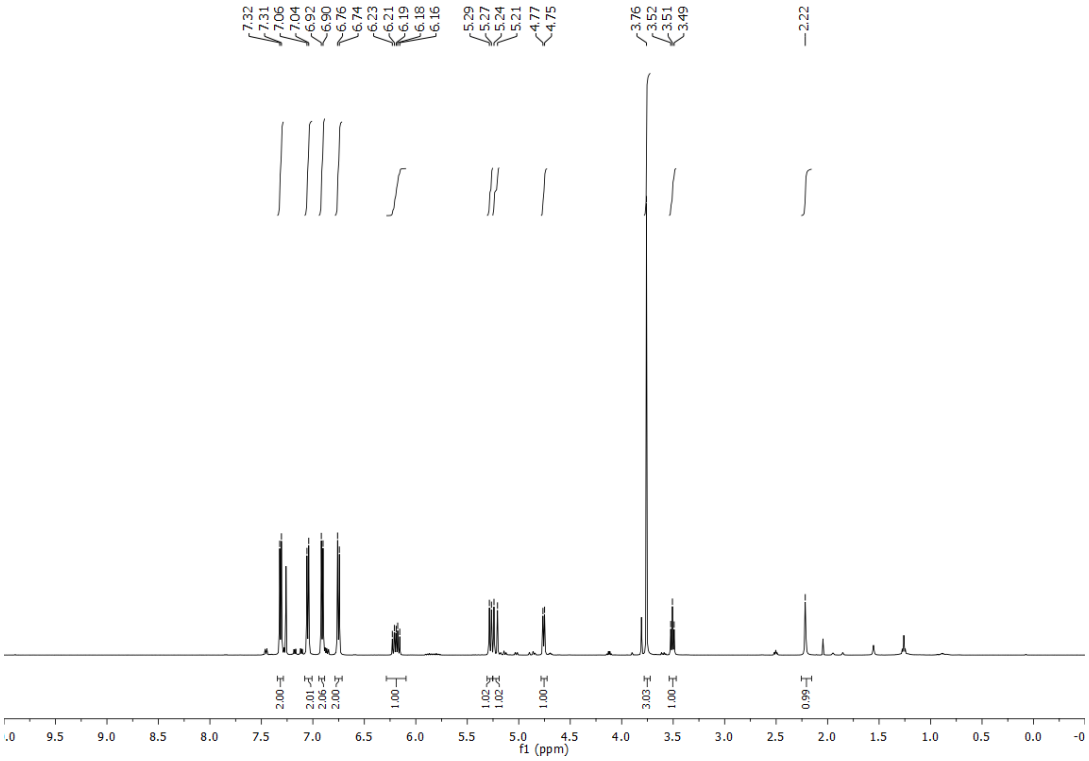
^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.1, 139.9, 137.8, 133.8, 131.5, 130.2, 128.0, 120.5, 118.7, 113.6, 76.8, 58.7, 55.3.

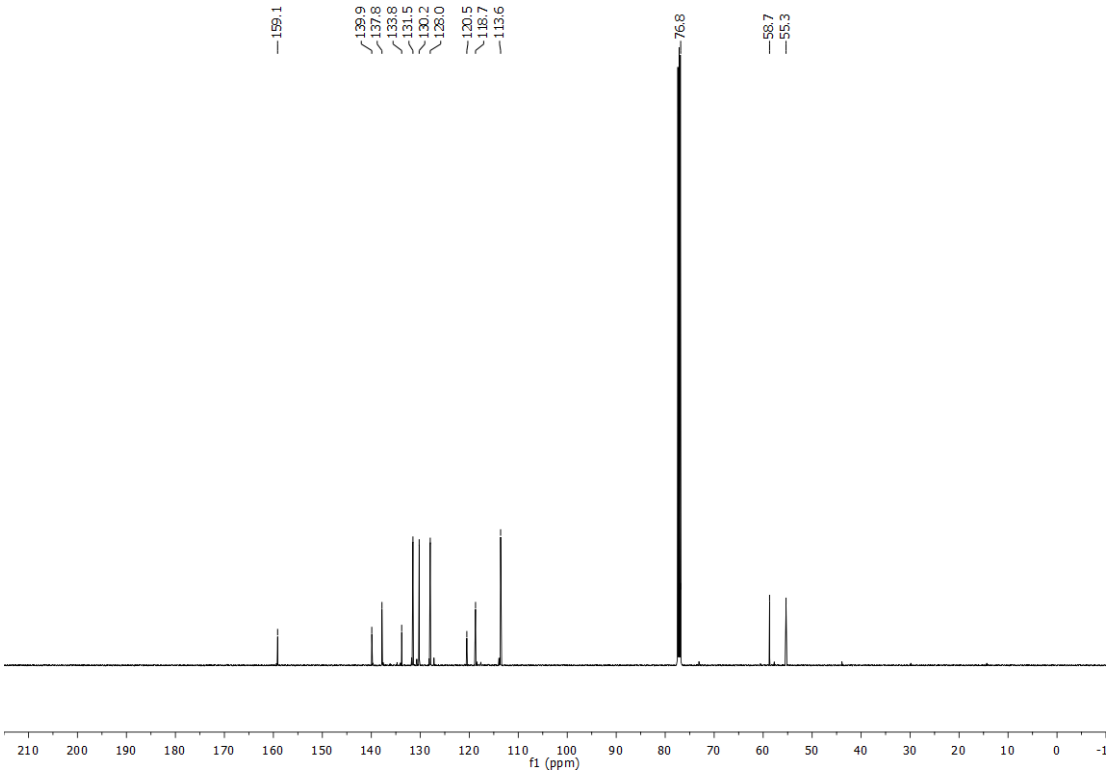
HRMS (ESI) Calculated for $C_{17}H_{17}{}^{79}BrO_2$ $[M+Na]^+$ = 355.0304, Found 355.0299.

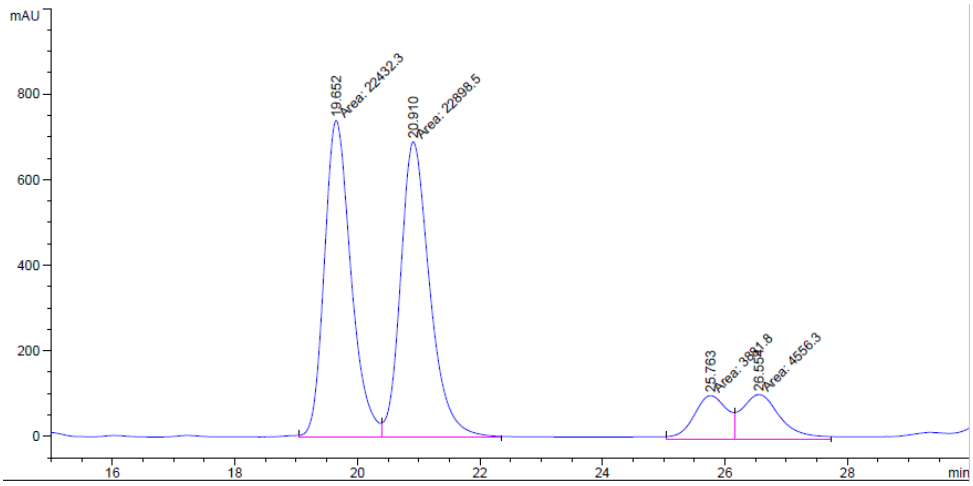
FTIR (neat) 3430, 2999, 2907, 2836, 1612, 1513, 1248, 1175, 1034, 1010, 921, 830 cm^{-1}.

$[\alpha]_D^{34}$: –9.0 (*c* = 1.0, $CHCl_3$)

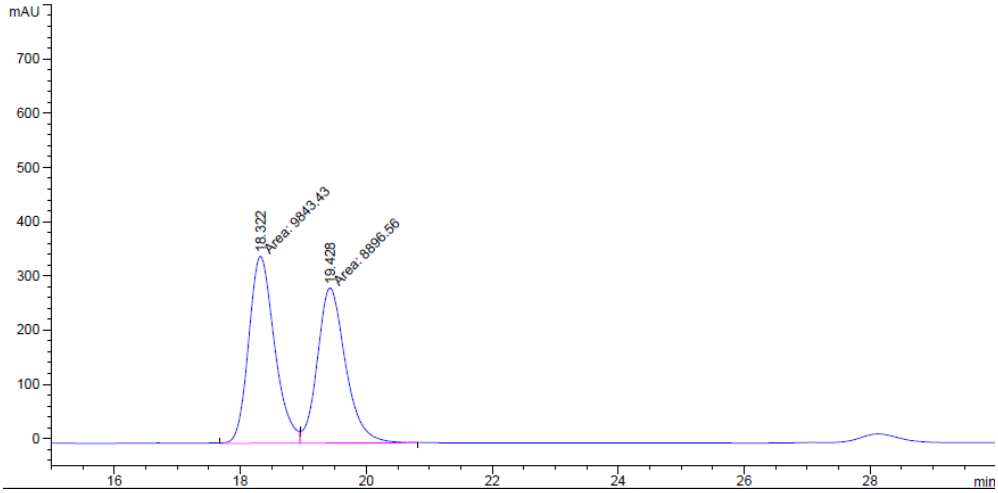
HPLC: (Chiralcel AD-H column, hexanes:*i*-PrOH = 95:5, 1.0 mL/min, 210 nm), *ee* = 5%.


7.32
7.31
7.06
7.04
6.92
6.90
6.76
6.74
6.23
6.21
6.19
6.18
6.16
5.29
5.27
5.24
5.21
4.77
4.75
3.76
3.52
3.51
3.49
2.22
2.00
2.01
2.06
2.00
1.00
1.02
1.02
1.00
3.03
1.00
0.99
f1 (ppm)


159.1
139.9
137.8
133.8
131.5
130.2
128.0
120.5
118.7
113.6
76.8
58.7
55.3
f1 (ppm)

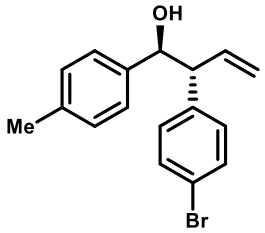


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.652	MF	0.5049	2.24323e4	740.49207	41.7198
2	20.910	FM	0.5525	2.28985e4	690.73303	42.5869
3	25.763	MF	0.6353	3881.79907	101.82919	7.2194
4	26.554	FM	0.7277	4556.29834	104.34978	8.4739



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.322	MF	0.4757	9843.43359	344.85089	52.5264
2	19.428	FM	0.5187	8896.55762	285.84869	47.4736

(1S,2R)-2-(4-bromophenyl)-1-(p-tolyl)but-3-en-1-ol (6.3c)



The title compound was prepared according to the general procedure using 4-methylbenzaldehyde (24.1 mg, 201 μmol) and 1-(4-bromophenyl)allyl acetate (102 mg, 0.40 mmol, 200 mol%). Flash chromatography on silica (Hex/EtOAc 10:1 → 5:1) provided the title compound (43.7 mg, 138 μmol, *anti:syn* = 4:1) in 69% yield as a yellow oil.

TLC (SiO_2) R_f = 0.43 (hexanes/ethyl acetate = 3:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36 – 7.29 (m, 2H), 7.03 (s, 4H), 6.97 – 6.90 (m, 2H), 6.19 (ddd, *J* = 17.1, 10.3, 8.6 Hz, 1H), 5.27 (dd, *J* = 10.3, 1.6 Hz, 1H), 5.20 (dt, *J* = 17.1, 1.3 Hz, 1H), 4.78 (d, *J* = 7.8 Hz, 1H), 3.53 (t, *J* = 8.2 Hz, 1H), 2.29 (s, 3H), 2.25 (s, 1H).

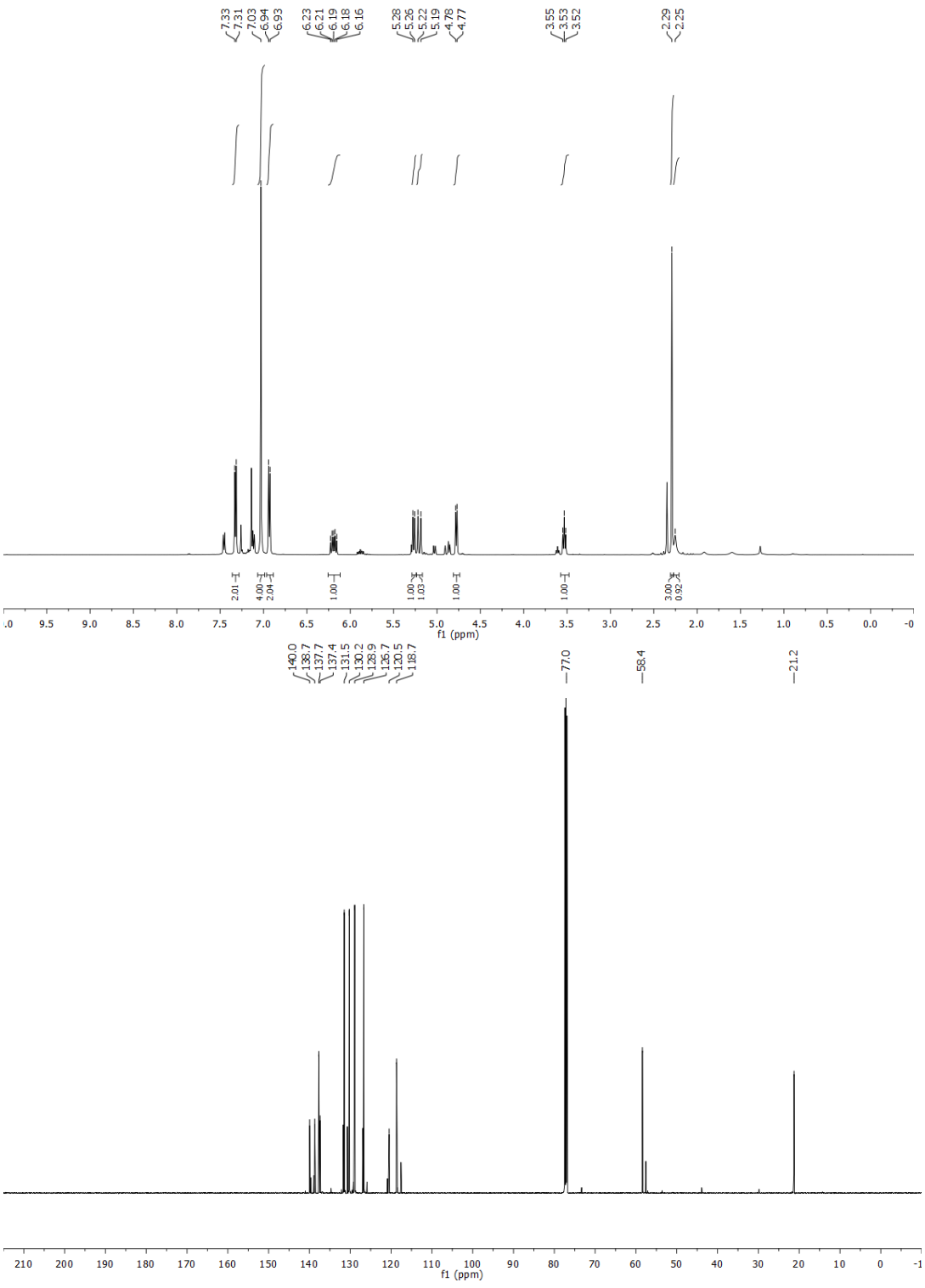
^{13}C NMR (125 MHz, $CDCl_3$): δ = 140.0, 138.7, 137.7, 137.4, 131.5, 130.2, 128.9, 126.7, 120.5, 118.7, 77.0, 58.4, 21.2.

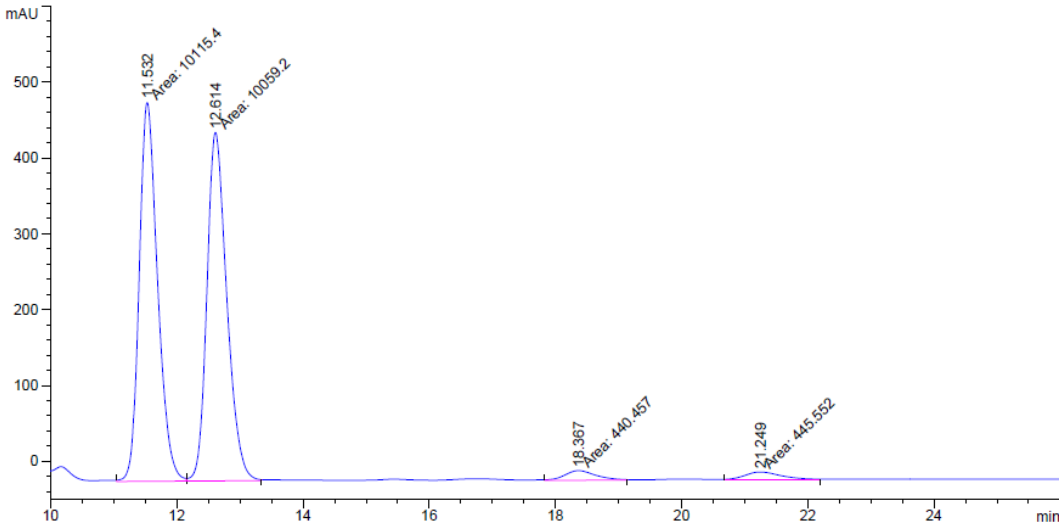
HRMS (CI) Calculated for $C_{17}H_{17}{}^{79}BrO$ $[M-H]^+$ = 315.0385, Found 315.0373.

FTIR (neat) 3439, 2918, 2861, 1487, 1402, 1179, 1073, 1010, 919, 816, 743 cm^{-1}.

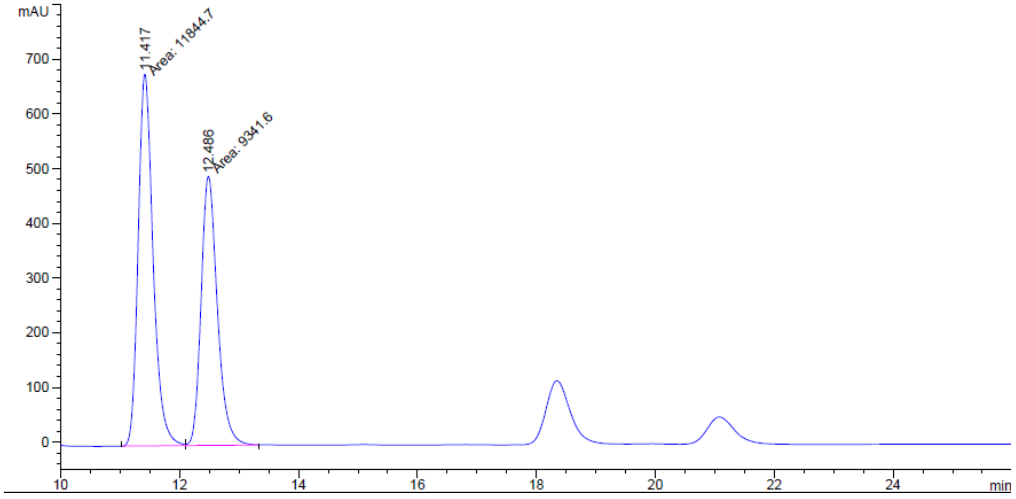
$[\alpha]_D^{32}$: –6.3 (*c* = 1.0, $CHCl_3$)

HPLC: (Chiralcel AD-H column, hexanes:*i*-PrOH = 95:5, 1.0 mL/min, 210 nm), *ee* = 12%.


7.33
7.31
7.03
6.94
6.93
6.23
6.21
6.19
6.18
6.16
5.28
5.26
5.22
5.19
4.78
4.77
3.55
3.53
3.52
2.29
2.25
2.01
4.00
2.04
1.00
1.00
1.03
1.00
1.00
3.00
0.92
f1 (ppm)
140.0
138.7
137.7
137.4
131.5
130.2
128.9
126.7
120.5
118.7
77.0
58.4
21.2
f1 (ppm)

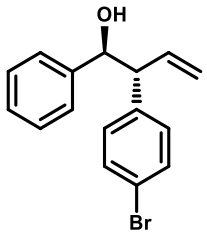


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.532	MF	0.3375	1.01154e4	499.51868	48.0300
2	12.614	FM	0.3648	1.00592e4	459.53488	47.7631
3	18.367	MM	0.5765	440.45721	12.73298	2.0914
4	21.249	MM	0.7047	445.55240	10.53725	2.1156



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.417	MF	0.2903	1.18447e4	680.00964	55.9073
2	12.486	FM	0.3163	9341.59961	492.20648	44.0927

(1*S*,2*R*)-2-(4-Bromophenyl)-1-phenylbut-3-en-1-ol (6.3d)



The title compound was prepared according to the general procedure using benzaldehyde (22.1 mg, 208 μmol) and 1-(4-bromophenyl)allyl acetate (102 mg, 0.40 mmol, 200 mol%). Flash chromatography on silica (Hex/EtOAc 6:1) provided the title compound (46.6 mg, 154 μmol, *anti:syn* = 4:1) in 74% yield as a yellow oil.

TLC (SiO_2) R_f = 0.36 (hexanes/ethyl acetate = 4:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.34–7.30 (m, 2H), 7.27–7.19 (m, 3H), 7.16–7.12 (m, 2H), 6.95–6.90 (m, 2H), 6.20 (ddd, *J* = 17.1, 10.3, 8.4 Hz, 1H), 5.28 (dd, *J* = 10.3, 1.5 Hz, 1H), 5.21 (d, *J* = 17.1 Hz, 1H), 4.80 (d, *J* = 7.7 Hz, 1H), 3.53 (t, *J* = 8.4 Hz, 1H), 2.29 (s, 1H).

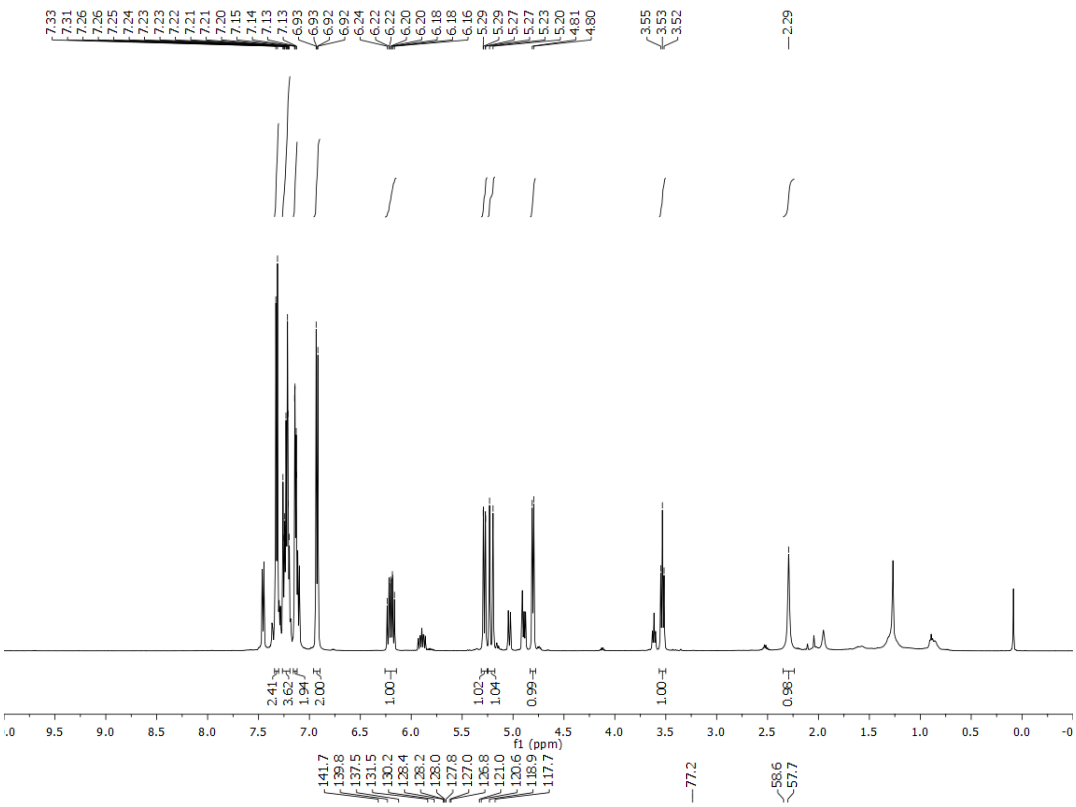
^{13}C NMR (125 MHz, $CDCl_3$): δ = 141.7, 139.8, 137.5, 131.5, 130.2, 128.2, 127.8, 126.8, 120.6, 118.9, 77.2, 58.6.

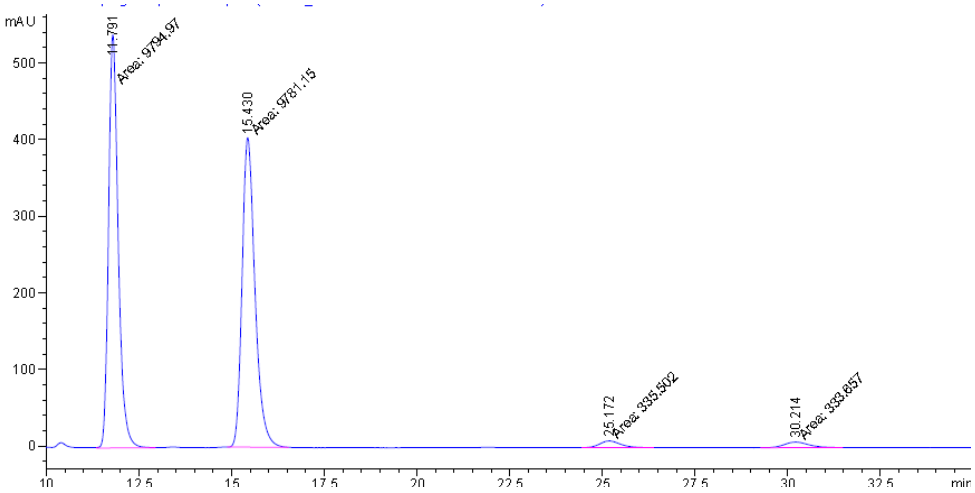
HRMS (CI) Calculated for $C_{16}H_{14}{}^{79}BrO$ $[M–H]^+$ = 301.0228, Found 301.0222.

FTIR (neat) 3434, 3062, 3029, 2920, 1487, 1074, 1010, 920, 814, 762, 726, 700 cm^{-1}.

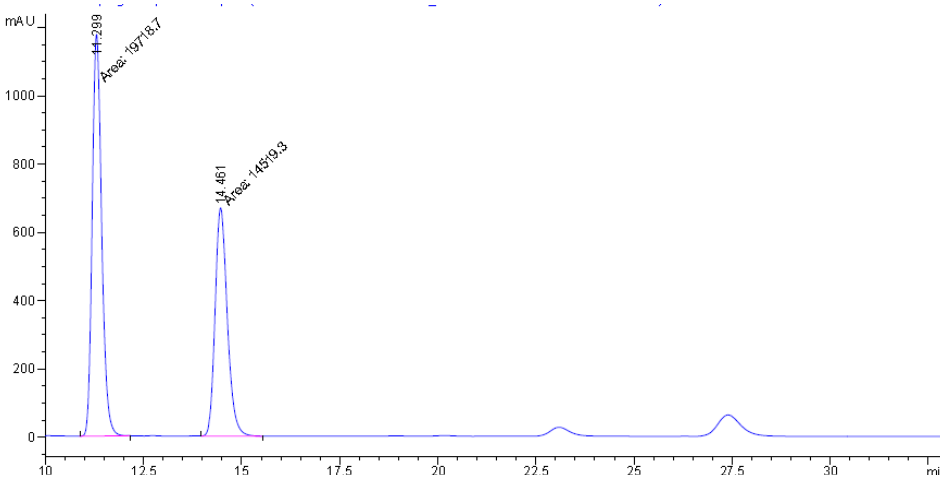
$[\alpha]_D^{34}$: –3.8 (*c* = 1.0, $CHCl_3$)

HPLC: (Chiralcel AD-H column, hexanes:*i*-PrOH = 95:5, 1.0 mL/min, 210 nm), *ee* = 15%.


7.33
7.31
7.26
7.26
7.25
7.24
7.23
7.23
7.22
7.21
7.21
7.21
7.20
7.15
7.14
7.13
7.13
6.93
6.93
6.92
6.92
6.24
6.22
6.22
6.20
6.20
6.18
6.18
6.16
5.29
5.29
5.27
5.27
5.23
5.20
4.81
4.80
3.55
3.53
3.52
2.29
2.41
3.62
1.94
2.00
1.00
1.02
1.04
0.99
1.00
0.98
f1 (ppm)
141.7
139.8
137.5
131.5
130.2
128.4
128.2
128.0
127.8
127.0
125.8
121.0
120.6
118.9
117.7
77.2
58.6
57.7
f1 (ppm)

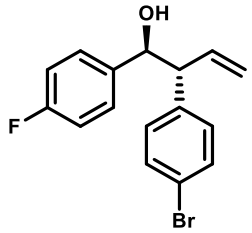


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.791	MM	0.3025	9794.96973	539.63959	48.3815
2	15.430	MM	0.4034	9781.14648	404.14508	48.3132
3	25.172	MM	0.6432	335.50162	8.69356	1.6572
4	30.214	MM	0.7663	333.65698	7.25710	1.6481



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.299	MM	0.2793	1.97187e4	1176.70996	57.5931
2	14.461	MM	0.3619	1.45193e4	668.66504	42.4069

(1S,2R)-2-(4-bromophenyl)-1-(4-fluorophenyl)but-3-en-1-ol (6.3e)



The title compound was prepared according to the general procedure using 4-fluorobenzaldehyde (24.8 mg, 200 μmol) and 1-(4-bromophenyl)allyl acetate (102 mg, 0.40 mmol, 200 mol%). Flash chromatography on silica (Hex/EtOAc 8:1 → 5:1) provided the title compound (56.5 mg, 176 μmol, *anti:syn* = 3:1) in 88% yield as a yellow oil.

TLC (SiO_2) R_f = 0.37 (hexanes/ethyl acetate = 3:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.37 – 7.29 (m, 2H), 7.12 – 7.06 (m, 2H), 6.94 – 6.87 (m, 4H), 6.18 (ddd, *J* = 17.0, 10.2, 8.8 Hz, 1H), 5.29 (d, *J* = 10.2 Hz, 1H), 5.23 (dt, *J* = 17.1, 1.2 Hz, 1H), 4.76 (d, *J* = 7.9 Hz, 1H), 3.46 (t, *J* = 8.4 Hz, 1H), 2.37 (s, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.2 (d, *J* = 245.7 Hz), 139.5, 137.4 (d, *J* = 3.1 Hz), 137.3, 131.6, 130.1, 128.4 (d, *J* = 8.1 Hz), 120.7, 119.1, 115.0 (d, *J* = 21.4 Hz), 76.6, 58.9.

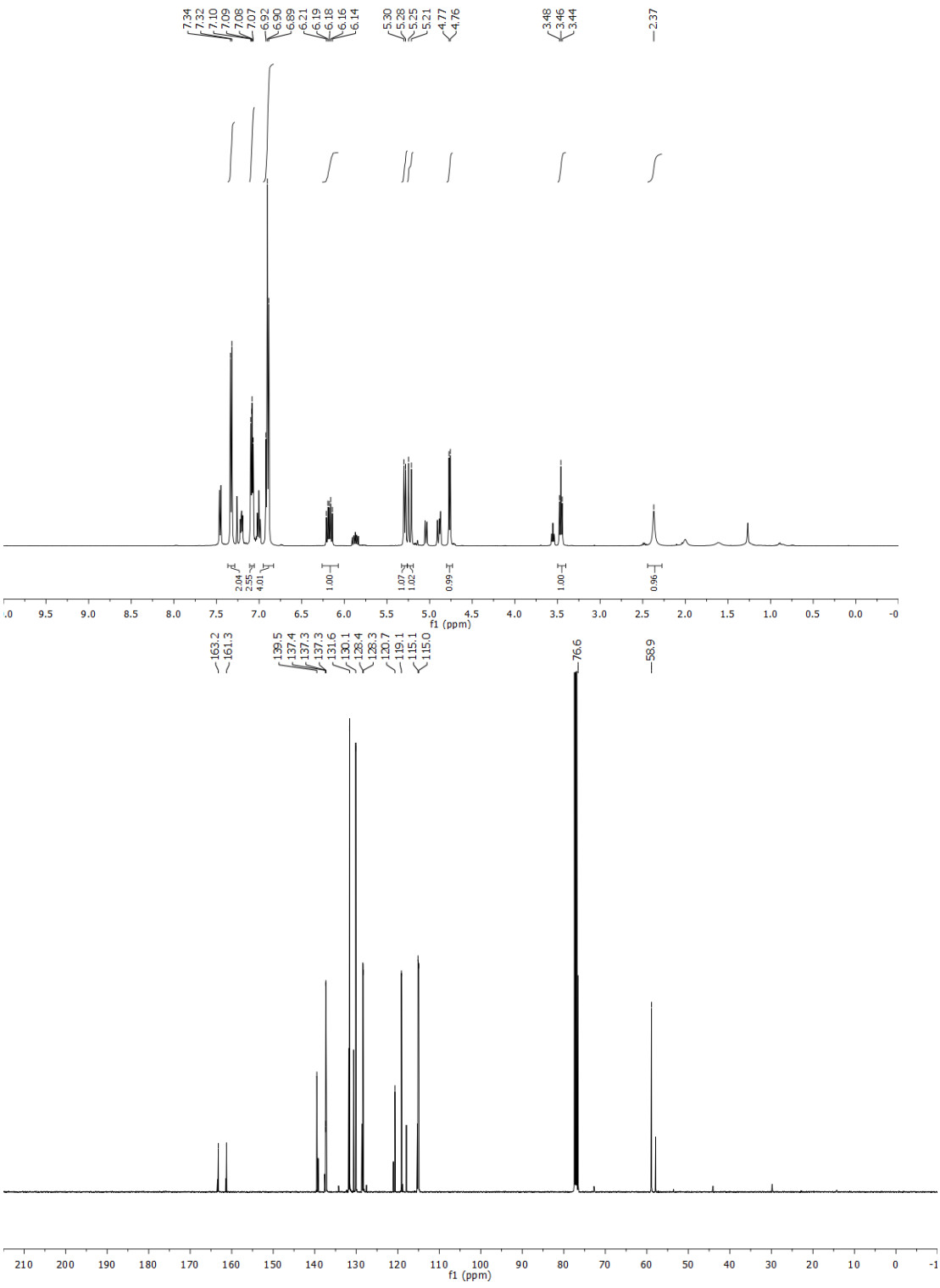
^{19}F NMR (471 MHz, $CDCl_3$): δ = -114.61 – -114.69 (m).

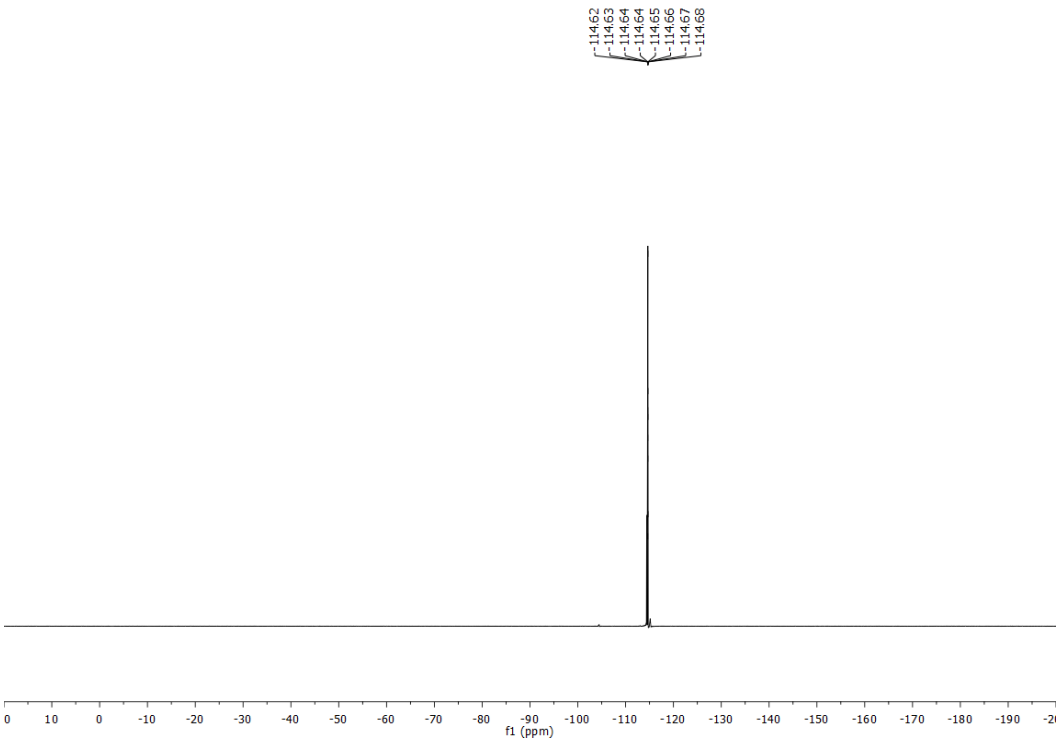
HRMS (CI) Calculated for $C_{16}H_{14}{}^{79}BrFO$ $[M-H]^+$ = 319.0134, Found 319.0133.

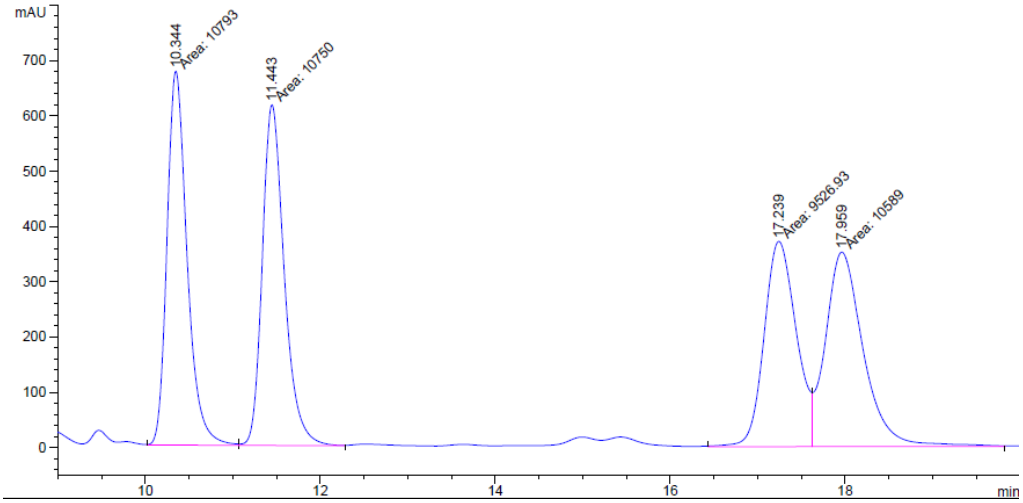
FTIR (neat) 3433, 3072, 2915, 1604, 1509, 1488, 1402, 1223, 1157, 1011, 924, 834 cm^{-1}.

$[\alpha]_D^{33}$: –6.5 (*c* = 1.0, $CHCl_3$)

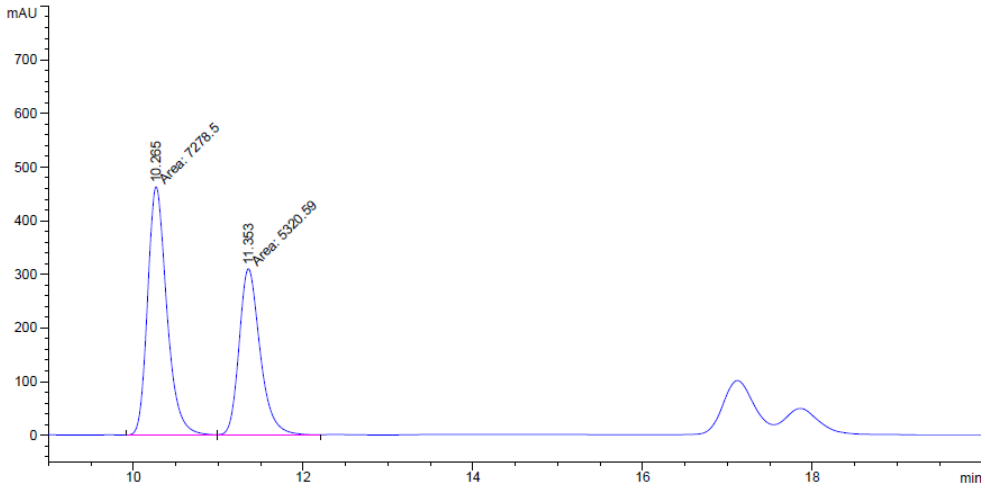
HPLC: (Chiralcel AD-H column, hexanes:*i*-PrOH = 95:5, 1.0 mL/min, 230 nm), *ee* = 16%.


7.34
7.32
7.10
7.09
7.08
7.07
6.92
6.90
6.89
6.21
6.19
6.18
6.16
6.14
5.30
5.28
5.25
5.21
4.77
4.76
3.48
3.46
3.44
2.37
2.04
2.55
4.01
1.00
1.07
1.02
0.99
1.00
0.96
f1 (ppm)
163.2
161.3
139.5
137.4
137.3
137.3
131.6
130.1
128.4
128.3
120.7
119.1
115.1
115.0
76.6
58.9
f1 (ppm)


-114.62
-114.63
-114.64
-114.64
-114.65
-114.66
-114.67
-114.68
0
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

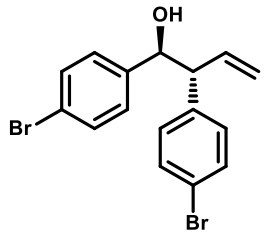


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.344	MF	0.2659	1.07930e4	676.44989	25.9080
2	11.443	FM	0.2908	1.07500e4	616.21399	25.8048
3	17.239	MF	0.4276	9526.93359	371.34500	22.8689
4	17.959	FM	0.5016	1.05890e4	351.85855	25.4183



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.265	MF	0.2619	7278.50488	463.13281	57.7701
2	11.353	FM	0.2861	5320.58691	309.96762	42.2299

(1*S*,2*R*)-1,2-Bis(4-bromophenyl)but-3-en-1-ol (6.3f)



The title compound was prepared according to the general procedure using 4-bromobenzaldehyde (37.1 mg, 201 μmol) and 1-(4-bromophenyl)allyl acetate (102 mg, 0.40 mmol, 200 mol%). Flash chromatography on silica (Hex/EtOAc 6:1) provided the title compound (67.5 mg, 177 μmol, *anti:syn* = 4:1) in 88% yield as a yellow oil.

TLC (SiO_2) R_f = 0.28 + 0.22 (hexanes/ethyl acetate = 4:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.37–7.31 (m, 4H), 7.02–6.96 (m, 2H), 6.94–6.88 (m, 2H), 6.16 (dt, *J* = 17.1, 9.9 Hz, 1H), 5.29 (d, *J* = 9.9 Hz, 1H), 5.22 (d, *J* = 17.1 Hz, 1H), 4.74 (d, *J* = 8.0 Hz, 1H), 3.45 (t, *J* = 8.0 Hz, 1H), 2.35 (s, 1H).

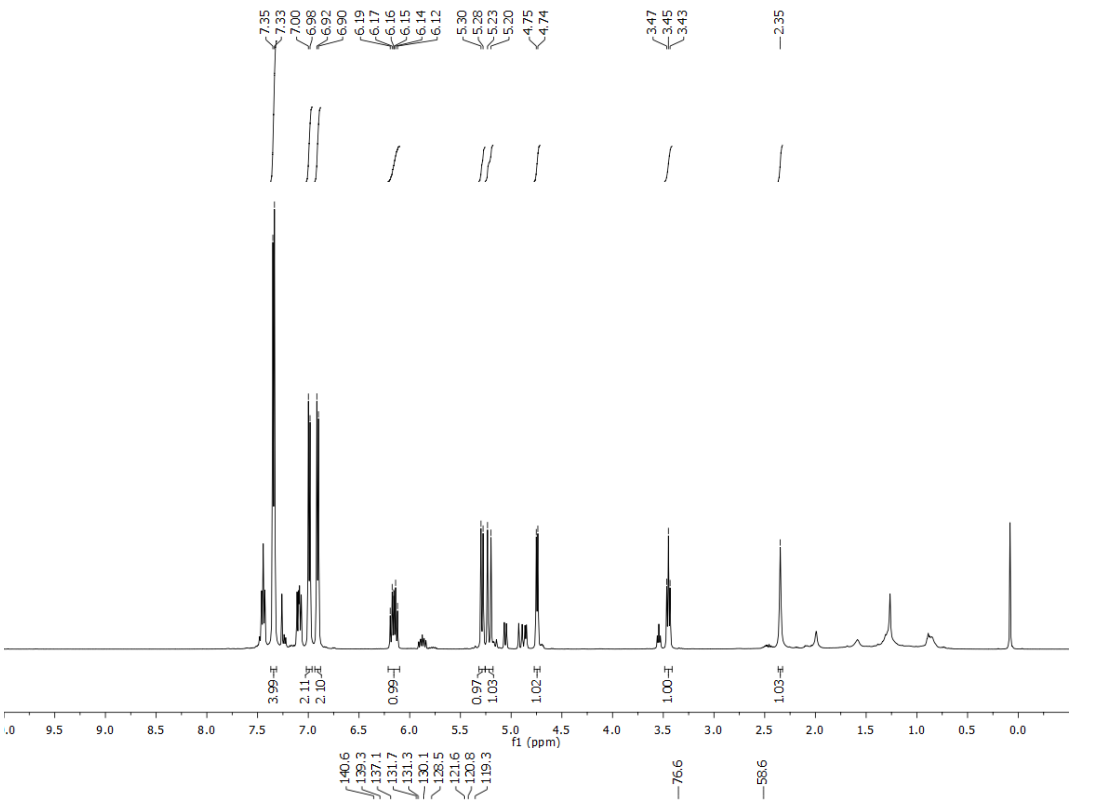
^{13}C NMR (125 MHz, $CDCl_3$): δ = 140.6, 139.3, 137.1, 131.7, 131.3, 130.1, 128.5, 121.6, 120.8, 119.3, 76.6, 58.6.

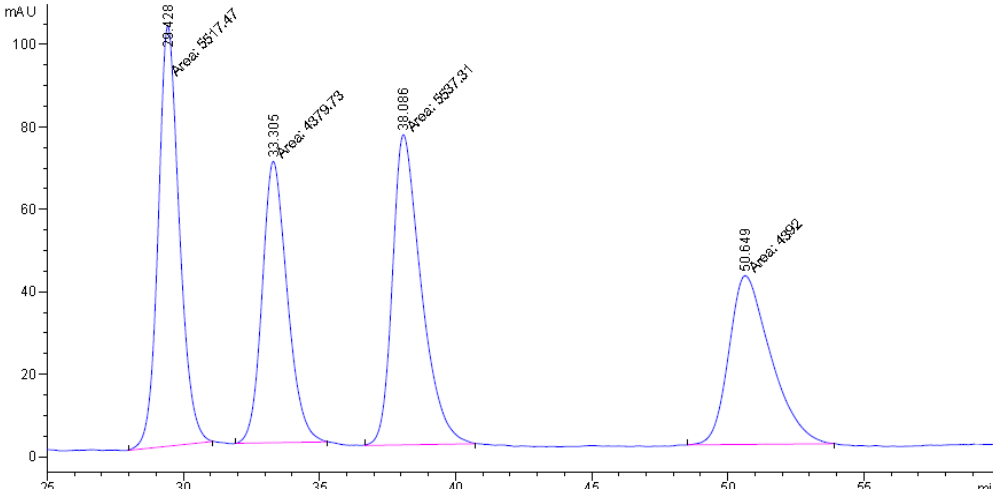
HRMS (CI) Calculated for $C_{16}H_{16}{}^{79}Br_2O$ $[M–H]^+$ = 378.9333, Found 378.9330.

FTIR (neat) 3434, 3078, 2919, 1487, 1403, 1072, 1010, 925, 819, 745 cm^{-1}.

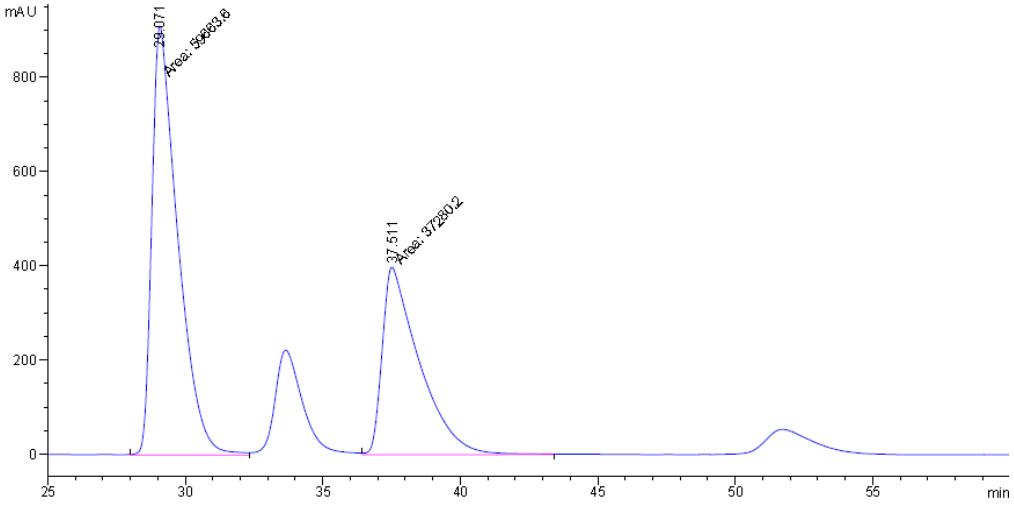
$[\alpha]_D^{34}$: +6.0 (*c* = 1.0, $CHCl_3$)

HPLC: (Chiralcel OJ-H column, hexanes:*i*-PrOH = 92:8, 1.0 mL/min, 210 nm), *ee* = 23%.


7.35
7.33
7.00
6.98
6.92
6.90
6.19
6.17
6.16
6.15
6.14
6.12
5.30
5.28
5.23
5.20
4.75
4.74
3.47
3.45
3.43
2.35
3.99
2.11
2.10
0.99
0.97
1.03
1.02
1.00
1.03
f1 (ppm)
140.6
139.3
137.1
131.7
131.3
130.1
128.5
121.6
120.8
119.3
76.6
58.6
f1 (ppm)

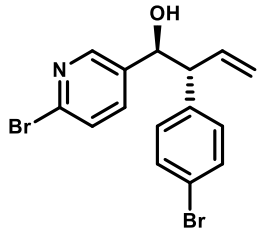


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	29.428	MM	0.9020	5517.47168	101.95429	27.8288
2	33.305	MM	1.0698	4379.72510	68.23000	22.0903
3	38.086	MM	1.2271	5537.31055	75.21107	27.9288
4	50.649	MM	1.7890	4391.99707	40.91771	22.1522



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	29.071	MF	1.0923	5.96636e4	910.36182	61.5445
2	37.511	FM	1.5622	3.72802e4	397.73111	38.4555

(1S,2R)-2-(4-bromophenyl)-1-(6-bromopyridin-3-yl)but-3-en-1-ol (6.3g)



The title compound was prepared according to the general procedure using 6-bromopyridine-3-carbaldehyde (37.1 mg, 199 μmol) and 1-(4-bromophenyl)allyl acetate (102 mg, 0.40 mmol, 200 mol%). Flash chromatography on silica (Hex/EtOAc 4:1) provided the title compound (62.5 mg, 163 μmol, *anti:syn* 5:1) in 82% yield as a yellow oil.

TLC (SiO_2) R_f = 0.21 (hexanes/ethyl acetate = 3:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.05 (s, 1H), 7.39 – 7.31 (m, 4H), 6.95 – 6.90 (m, 2H), 6.14 (ddd, *J* = 17.0, 10.3, 8.9 Hz, 1H), 5.32 (dd, *J* = 10.2, 1.4 Hz, 1H), 5.24 (dt, *J* = 17.0, 1.1 Hz, 1H), 4.81 (dd, *J* = 7.8, 2.2 Hz, 1H), 3.43 (t, *J* = 8.3 Hz, 1H), 2.60 (s, 1H).

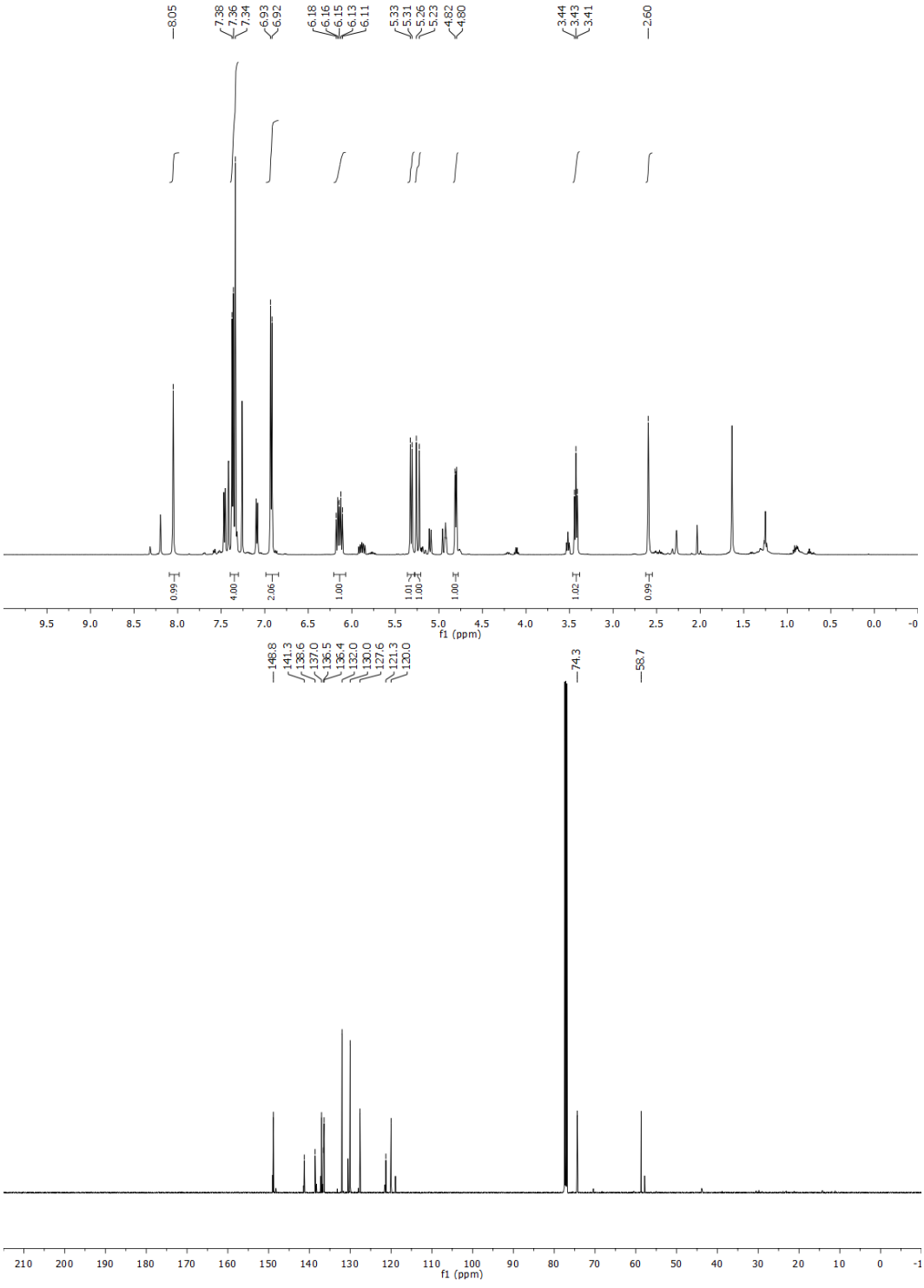
^{13}C NMR (125 MHz, $CDCl_3$): δ = 148.8, 141.3, 138.6, 137.0, 136.5, 136.4, 132.0, 130.0, 127.6, 121.3, 120.0, 74.3, 58.7.

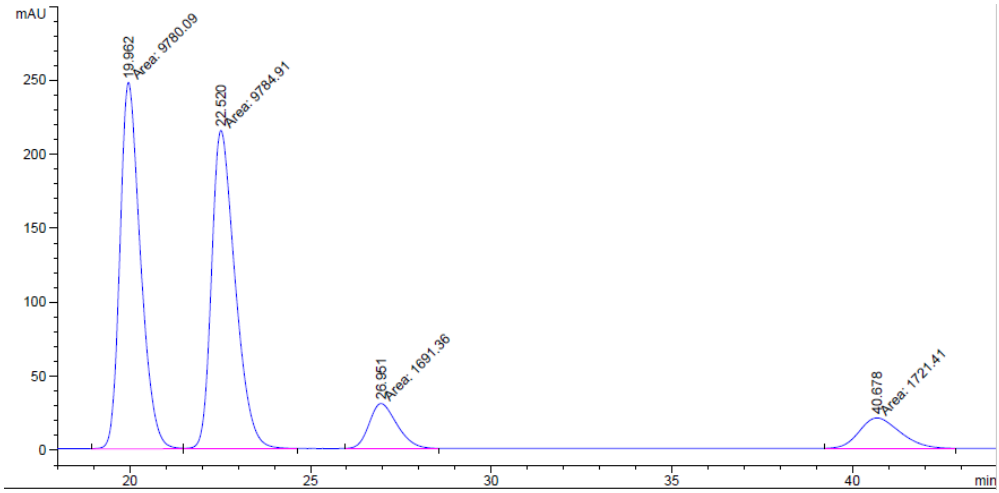
HRMS (ESI) Calculated for $C_{15}H_{13}{}^{79}Br_2NO$ $[M+Na]^+$ = 403.9256, Found 403.9260.

FTIR (neat) 3315, 3082, 2909, 1581, 1564, 1488, 1455, 1402, 1087, 1074, 101, 924, 831, 750 cm^{-1}.

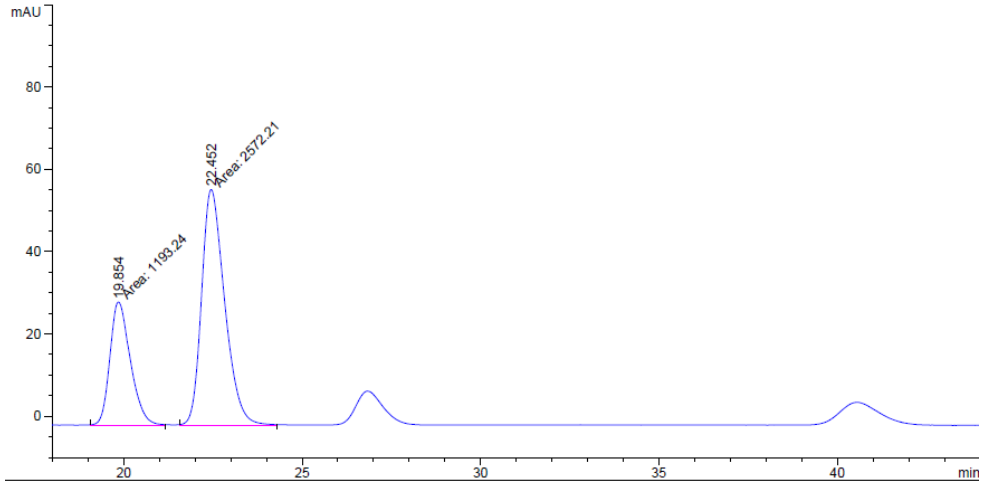
$[\alpha]_D^{30}$: +8.3 (*c* = 1.0, $CHCl_3$)

HPLC: (Chiralcel AD-H column, hexanes:*i*-PrOH = 95:5, 1.0 mL/min, 230 nm), *ee* = 37%.


8.05
7.38
7.36
7.34
6.93
6.92
6.18
6.16
6.15
6.13
6.11
5.33
5.31
5.26
5.23
4.82
4.80
3.44
3.43
3.41
2.60
0.99
4.00
2.06
1.00
1.01
1.00
1.00
1.02
0.99
f1 (ppm)
148.8
141.3
138.6
137.0
136.5
136.4
132.0
130.0
127.6
121.3
120.0
74.3
58.7
f1 (ppm)

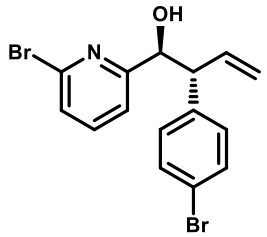


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.962	MF	0.6583	9780.09277	247.61111	42.5633
2	22.520	FM	0.7581	9784.91113	215.10538	42.5842
3	26.951	MM	0.9147	1691.35913	30.81730	7.3608
4	40.678	MM	1.3607	1721.40955	21.08541	7.4916



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.854	MM	0.6640	1193.23975	29.94984	31.6891
2	22.452	MM	0.7487	2572.21289	57.25787	68.3109

(1*S*,2*R*)-2-(4-Bromophenyl)-1-(6-bromopyridin-2-yl)but-3-en-1-ol (6.3h)



The title compound was prepared according to the general procedure using 6-bromopyridine-2-carbaldehyde (37.2 mg, 200 μmol) and 1-(4-bromophenyl)allyl acetate (102 mg, 0.40 mmol, 200 mol%). Flash chromatography on silica (Hex/EtOAc 6:1) provided the title compound (57.8 mg, 151 μmol, *anti:syn* 4:1) in 75% yield as a yellow oil.

TLC (SiO_2) R_f = 0.25 (hexanes/ethyl acetate = 4:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.41–7.37 (m, 3H), 7.33 (d, *J* = 7.8 Hz, 1H), 7.07 (d, *J* = 8.3 Hz, 2H), 6.96 (d, *J* = 7.5 Hz, 1H), 6.14 (ddd, *J* = 17.2, 10.5, 8.2 Hz, 1H), 5.16 (d, *J* = 10.5 Hz, 1H), 5.01 (d, *J* = 17.2 Hz, 1H), 4.88 (t, *J* = 6.2 Hz, 1H), 3.69 (t, *J* = 7.2 Hz, 1H), 3.45 (d, *J* = 6.5 Hz, 1H).

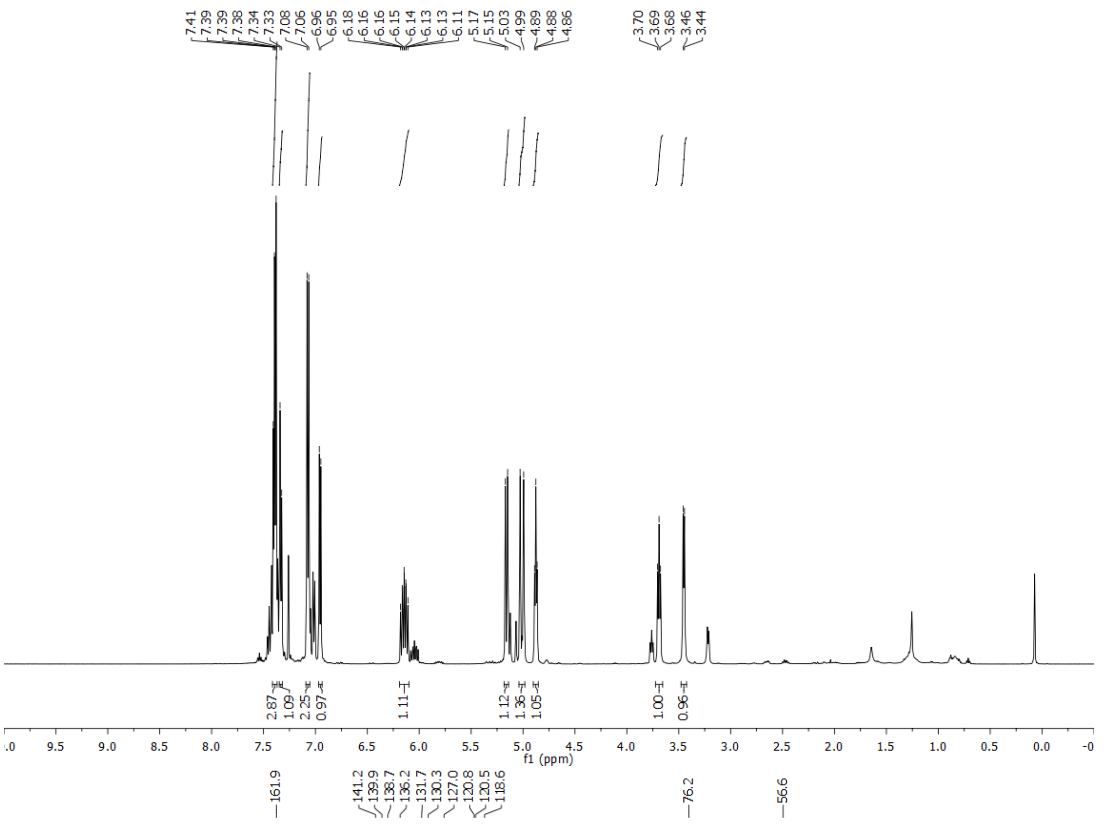
^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.9, 141.2, 139.9, 138.7, 136.2, 131.7, 130.3, 127.0, 120.8, 120.5, 118.6, 76.2, 56.6.

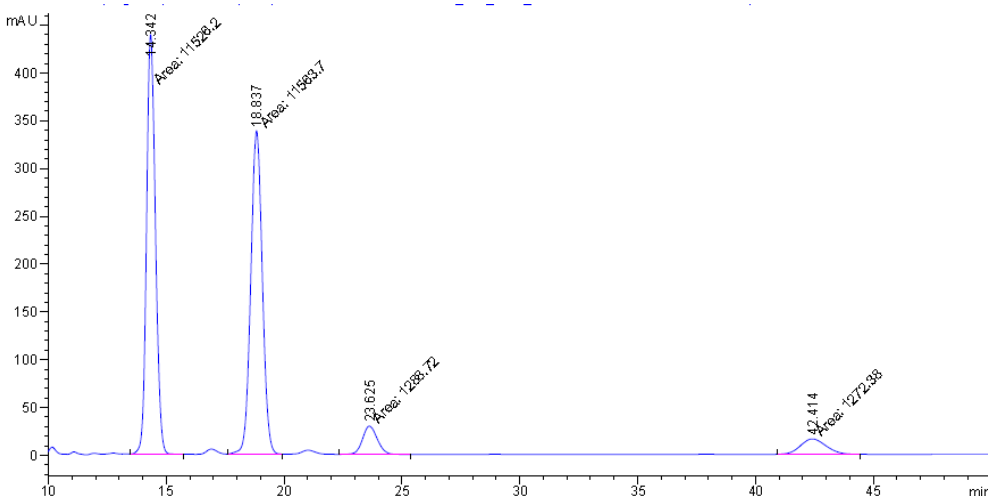
HRMS (APPI) Calculated for $C_{15}H_{14}{}^{79}Br_2NO$ $[M+H]^+$ = 381.9437, Found 381.9447.

FTIR (neat) 3411, 2923, 1582, 1556, 1488, 1437, 1406, 1125, 1072, 1011 cm^{-1}.

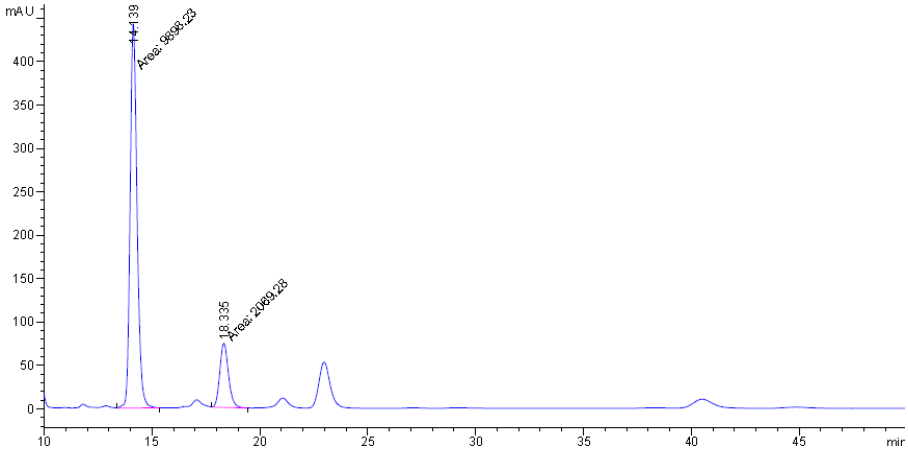
$[\alpha]_D^{33}$: –71.5 (*c* = 1.0, $CHCl_3$)

HPLC: (Chiralcel AD-H column, hexanes:*i*-PrOH = 95:5, 1.0 mL/min, 254 nm), *ee* = 65%.


7.41
7.39
7.39
7.38
7.34
7.33
7.08
7.06
6.96
6.95
6.18
6.16
6.16
6.15
6.14
6.13
6.11
5.17
5.15
5.03
4.99
4.89
4.88
4.86
3.70
3.69
3.68
3.46
3.44
2.87
1.09
2.25
0.97
1.11
1.12
1.36
1.05
1.00
0.96
f1 (ppm)
161.9
141.2
139.9
138.7
136.2
131.7
130.3
127.0
120.8
120.5
118.6
76.2
56.6
f1 (ppm)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.342	MM	0.4376	1.15262e4	438.95636	44.9348
2	18.837	MM	0.5693	1.15637e4	338.50641	45.0808
3	23.625	MM	0.7249	1288.72083	29.62928	5.0241
4	42.414	MM	1.2950	1272.38135	16.37522	4.9604

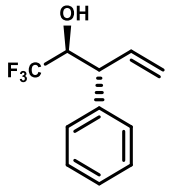


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.139	MM	0.3728	9898.23242	442.54211	82.7092
2	18.335	MM	0.4658	2069.27808	74.04234	17.2908

General Procedure and Spectral Data for Iridium Catalyzed *anti*-(α-Aryl)Allylation of Fluoral Hydrate 1i to form Products 6.4a-6.4l

A pressure tube was equipped with a magnetic stir bar and charged with preformed iridium catalyst (10.7 mg, 10 μmol, 5 mol%), K_2CO_3 (27.6 mg, 0.20 mmol, 100 mol%), allyl donor (0.40 mmol, 200 mol%) and 4A molecular sieves (90 mg, 300 wt%). The pressure tube was purged with argon. Anhydrous THF (1.0 mL, 0.2 M), 2-propanol (31 μL, 0.40 mmol, 200 mol%), and fluoral hydrate (75% in H_2O, 22 μL, 0.20 mmol, 100 mol%) were added via syringe. The sealed reaction vessel was stirred at 100 °C. After 24 h the solvent was removed *in vacuo* and the residue was subjected to flash column chromatography on silica.

(2S,3R)-1,1,1-trifluoro-3-phenylpent-4-en-2-ol (6.4a)



The title compound was prepared according to the general procedure using fluoral hydrate (75% in H_2O, 22 μL, 200 μmol) and 1-phenylallyl acetate (71 mg, 0.40 mmol, 200 mol%). Flash chromatography on silica (Hex/EtOAc 20:1 → 8:1) provided the title compound (36.7 mg, 170 μmol, *anti:syn* = >20:1) in 85% yield as a yellow oil.

TLC (SiO_2) R_f = 0.60 (hexanes/ethyl acetate = 3:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35 – 7.17 (m, 5H), 6.15 (ddd, *J* = 17.0, 10.1, 8.5 Hz, 1H), 5.27 (dt, *J* = 10.2, 0.9 Hz, 1H), 5.15 (dt, *J* = 17.1, 1.2 Hz, 1H), 4.20 (h, *J* = 6.4 Hz, 1H), 3.69 (dd, *J* = 8.5, 5.1 Hz, 1H), 2.35 (d, *J* = 5.6 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 139.8, 135.0, 128.9, 128.2, 127.4, 124.8 (d, *J* = 283.2 Hz), 119.9, 73.1 (q, *J* = 29.5 Hz), 50.2.

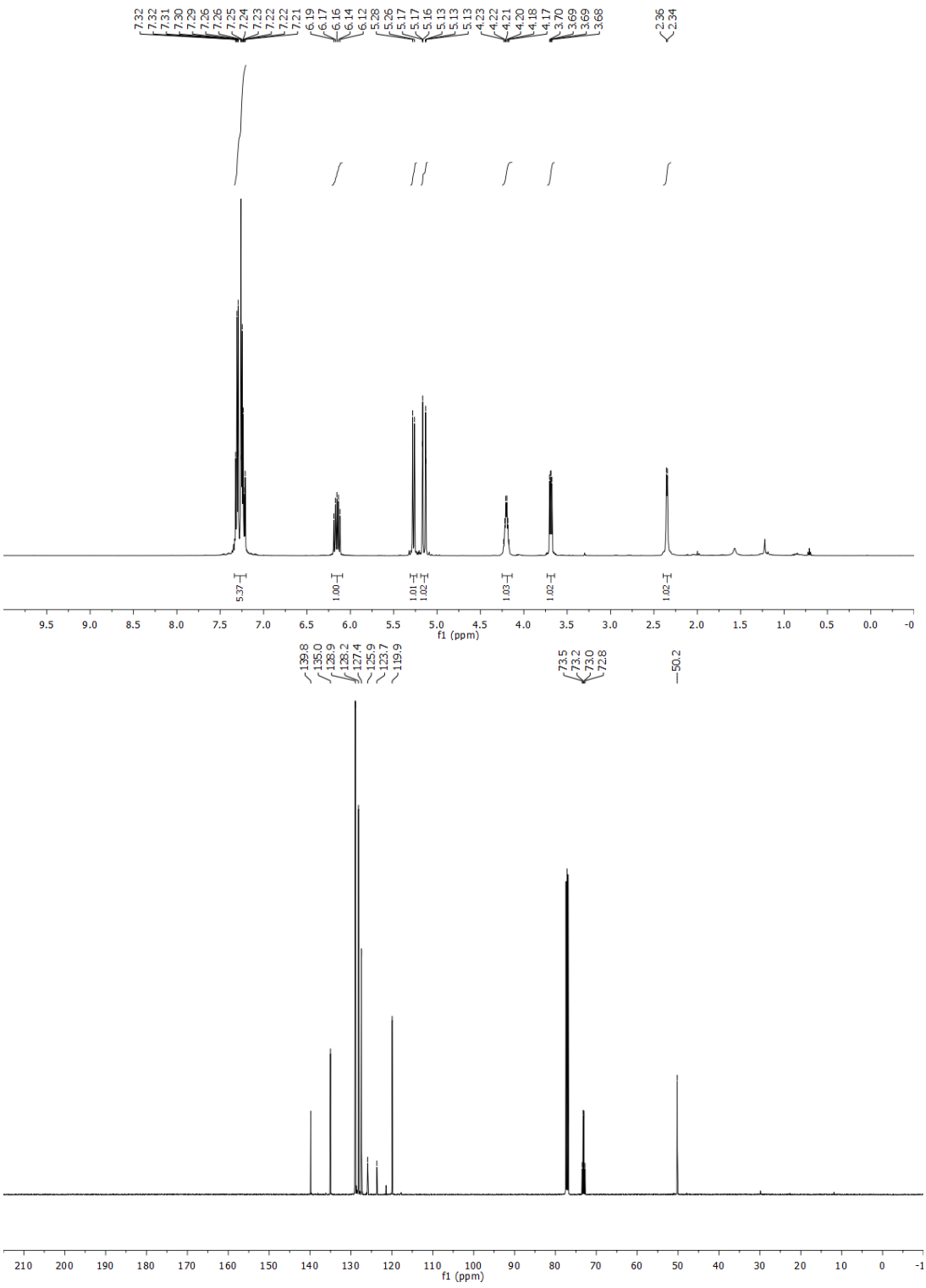
^{19}F NMR (471 MHz, $CDCl_3$): δ = –76.0 (d, *J* = 6.9 Hz).

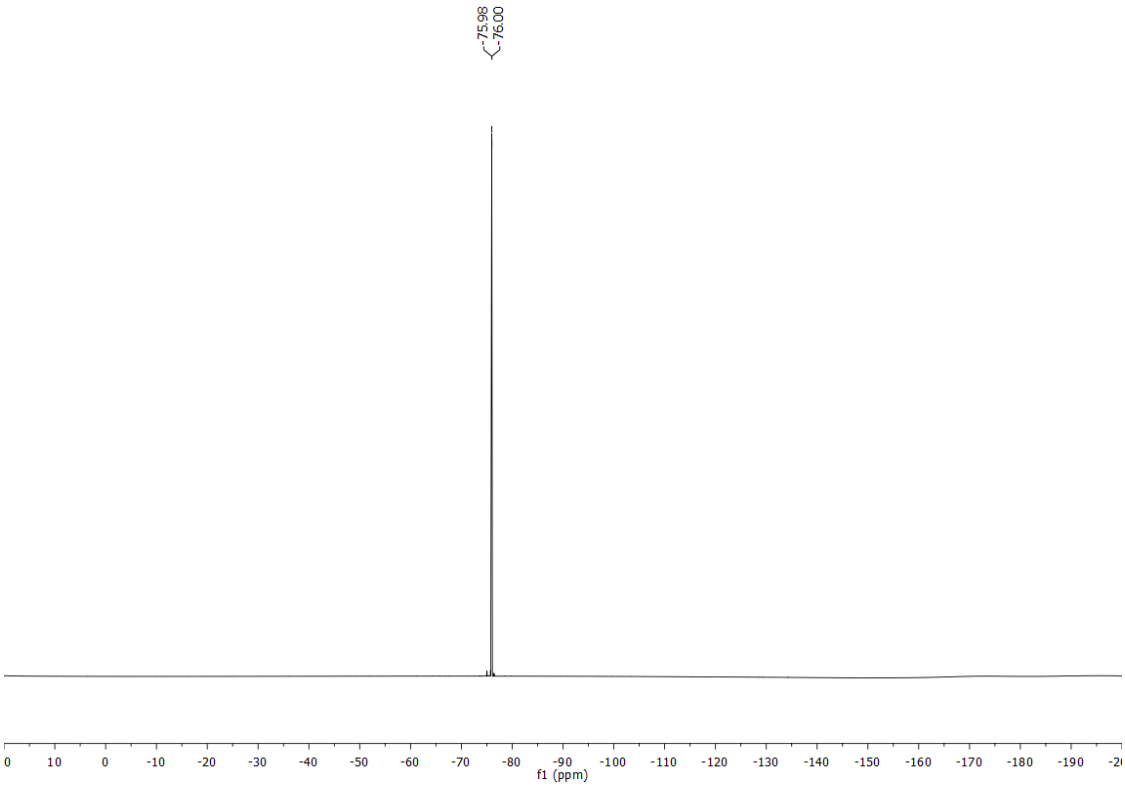
HRMS (CI) Calculated for $C_{11}H_{11}F_3O$ $[M]^+$ = 216.0762, Found 216.0766.

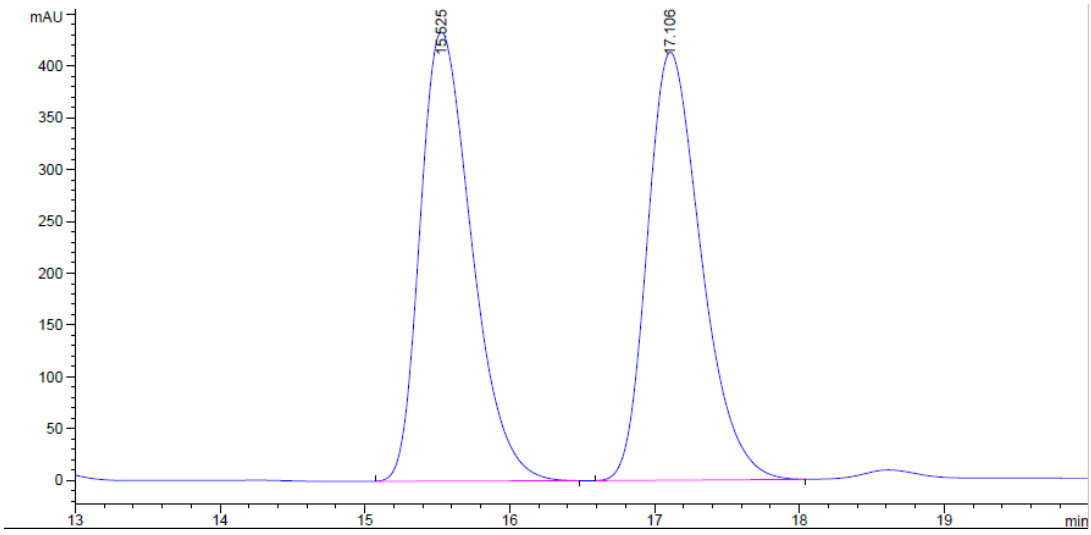
FTIR (neat) 3443, 2927, 1266, 1165, 1109, 925, 852, 761, 735, 701 cm^{-1}.

$[\alpha]_D^{34}$: –65.0 (*c* = 0.5, $CHCl_3$)

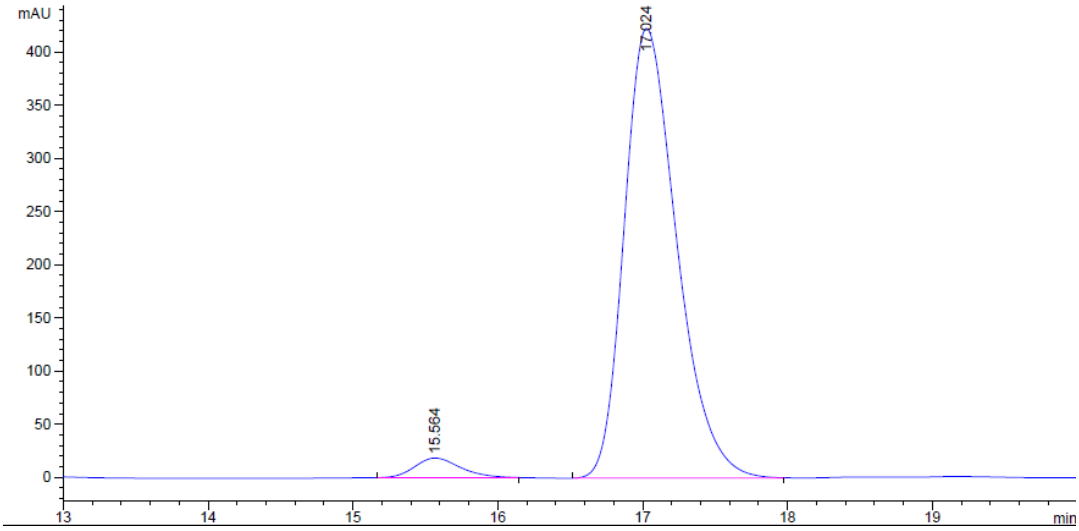
HPLC: (Chiralcel AS-H column, hexanes:*i*-PrOH = 99:1, 1.0 mL/min, 210 nm), *ee* = 93%.


7.32
7.32
7.31
7.30
7.29
7.26
7.26
7.25
7.24
7.23
7.22
7.22
7.21
6.19
6.17
6.16
6.14
6.12
5.28
5.26
5.17
5.17
5.16
5.13
5.13
5.13
4.23
4.22
4.21
4.20
4.18
4.17
3.70
3.69
3.69
3.68
2.36
2.34
5.37
1.00
1.01
1.02
1.03
1.02
1.02
f1 (ppm)
139.8
135.0
128.9
128.2
127.4
125.9
123.7
119.9
73.5
73.2
73.0
72.8
50.2
f1 (ppm)


-75.98
-76.00
0
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

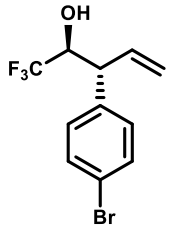


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.525	BB	0.3846	1.07149e4	433.17065	50.0908
2	17.106	BB	0.3998	1.06761e4	412.67371	49.9092



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.564	BB	0.3368	412.85068	18.60910	3.7250
2	17.024	BB	0.3904	1.06704e4	422.83902	96.2750

(2S,3R)-3-(4-bromophenyl)-1,1,1-trifluoropent-4-en-2-ol (6.4b)



The title compound was prepared according to the general procedure using fluoral hydrate (75% in H_2O, 22 μL, 200 μmol) and 1-(4-bromophenyl)allyl acetate (102 mg, 0.40 mmol, 200 mol%). Flash chromatography on silica (Hex/EtOAc 20:1 → 8:1) provided the title compound (51.8 mg, 176 μmol, *anti:syn* = >20:1) in 88% yield as a yellow oil.

TLC (SiO_2) R_f = 0.60 (hexanes/ethyl acetate = 3:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.51 – 7.41 (m, 2H), 7.21 – 7.13 (m, 2H), 6.22 – 6.08 (m, 1H), 5.32 (dt, *J* = 10.3, 1.0 Hz, 1H), 5.17 (dt, *J* = 17.1, 1.2 Hz, 1H), 4.20 (h, *J* = 6.5 Hz, 1H), 3.69 (dd, *J* = 8.3, 5.0 Hz, 1H), 2.43 (d, *J* = 5.9 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.9, 134.5, 132.0, 129.9, 124.7 (d, *J* = 283.3 Hz), 121.4, 120.3, 72.9 (q, *J* = 29.6 Hz), 49.5.

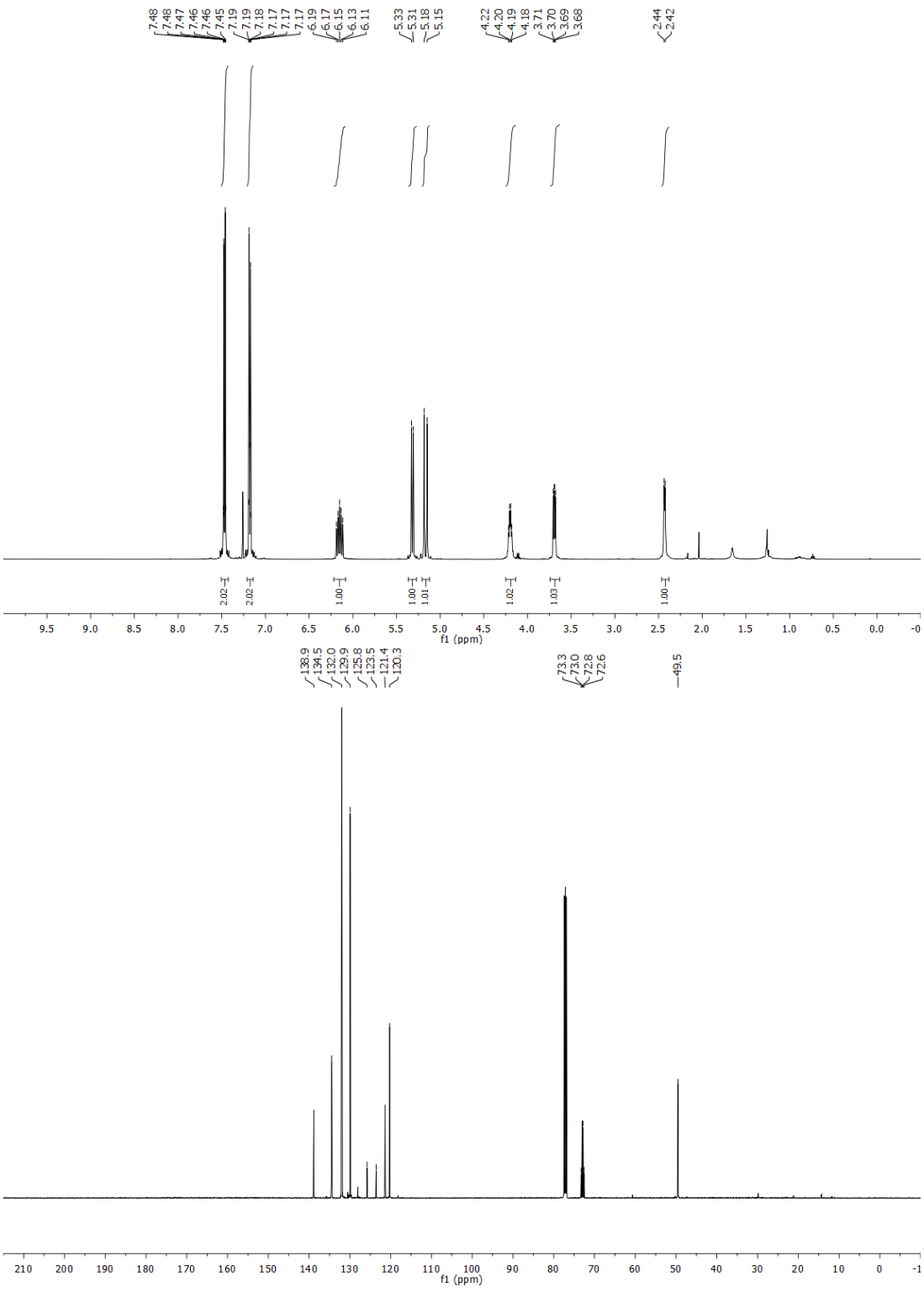
^{19}F NMR (471 MHz, $CDCl_3$): δ = –76.0 (d, *J* = 6.8 Hz)

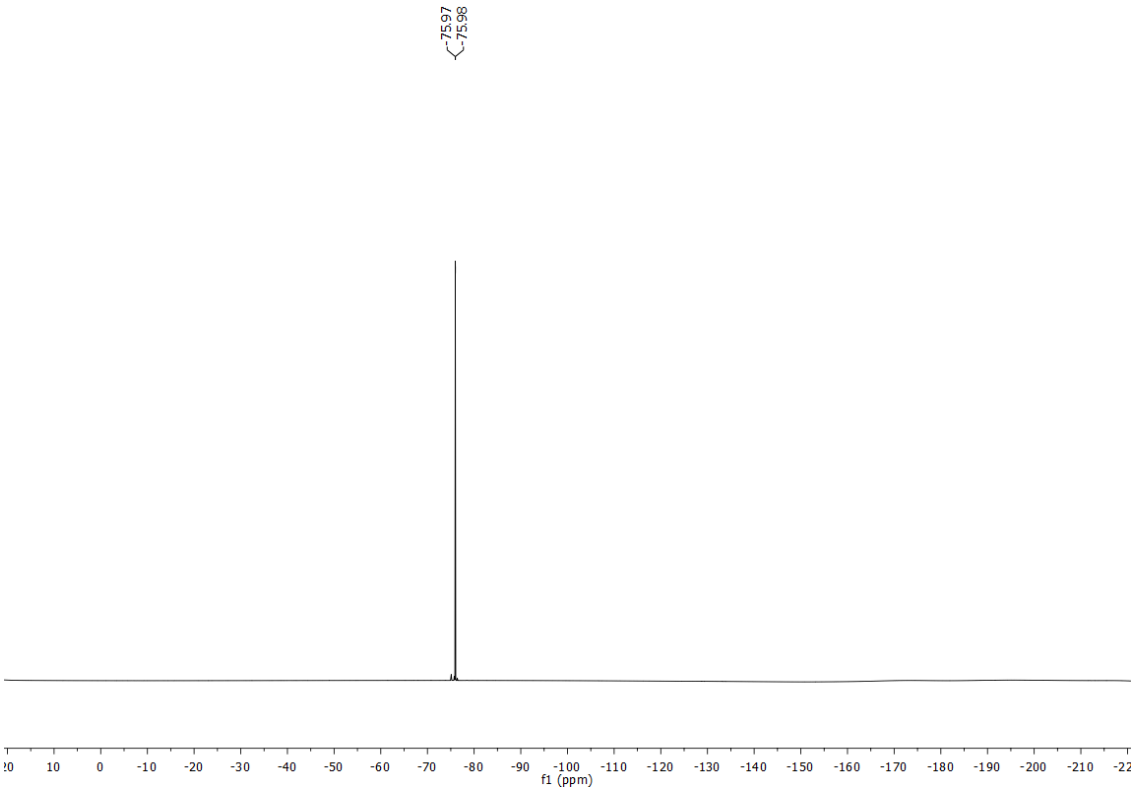
HRMS (CI) Calculated for $C_{11}H_{10}BrF_3O$ $[M]^+$ = 293.9867, Found 293.9868.

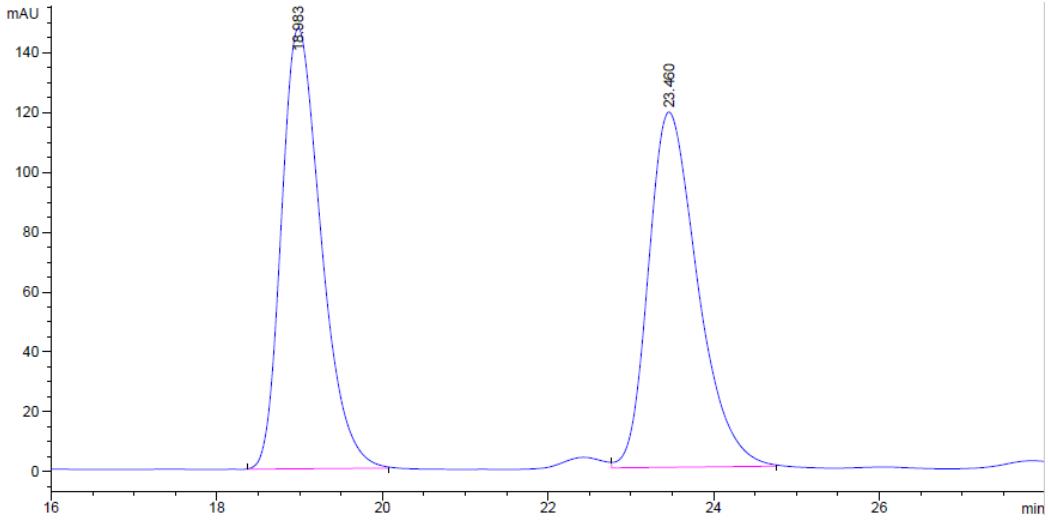
FTIR (neat) 3460, 2923, 1489, 1405, 1270, 1168, 1108, 1075, 1011, 928, 817, 720 cm^{-1}.

$[\alpha]_D^{27}$: –87.3 (*c* = 1.0, $CHCl_3$)

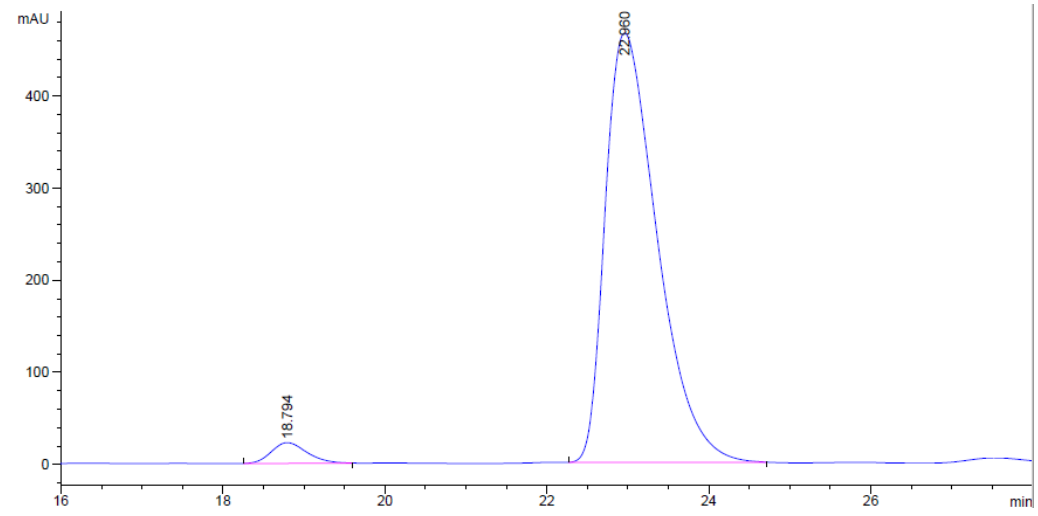
HPLC: (Chiralcel AS-H column, hexanes:*i*-PrOH = 99:1, 1.0 mL/min, 230 nm), *ee* = 94%.


7.48
7.48
7.47
7.46
7.46
7.45
7.19
7.19
7.18
7.17
7.17
7.17
6.19
6.17
6.15
6.13
6.11
5.33
5.31
5.18
5.15
4.22
4.20
4.19
4.18
3.71
3.70
3.69
3.68
2.44
2.42
2.02
2.02
1.00
1.00
1.01
1.02
1.03
1.00
f1 (ppm)
138.9
134.5
132.0
129.9
125.8
123.5
121.4
120.3
73.3
73.0
72.8
72.6
49.5
f1 (ppm)


-75.97
-75.98
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)

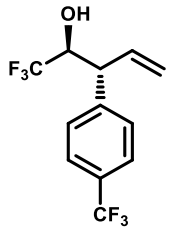


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.983	BB	0.5165	4904.00586	147.26453	50.0566
2	23.460	VB	0.6348	4892.91162	118.72536	49.9434



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.794	BB	0.4733	689.50726	22.51617	3.2090
2	22.960	BB	0.6906	2.07968e4	466.09949	96.7910

(2*S*,3*R*)-1,1,1-Trifluoro-3-(4-(trifluoromethyl)phenyl)pent-4-en-2-ol (6.4c)



The title compound was prepared according to the general procedure using fluoral hydrate (75% in H_2O, 22 μL, 200 μmol) and 1-(4-(trifluoromethyl)phenyl)allyl acetate (98 mg, 0.40 mmol, 200 mol%). Flash chromatography on silica (Hex/EtOAc 20:1 → 8:1) provided the title compound (36.3 mg, 128 μmol, *anti:syn* = >20:1) in 64% yield as a yellow oil.

TLC (SiO_2) R_f = 0.18 (hexanes/ethyl acetate = 10:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.63–7.58 (m, 2H), 7.46–7.41 (m, 2H), 6.19 (ddd, *J* = 17.6, 10.2, 8.4 Hz, 1H), 5.35 (d, *J* = 10.2 Hz, 1H), 5.18 (dt, *J* = 17.6, 1.0 Hz, 1H), 4.25 (pd, *J* = 6.5, 4.9 Hz, 1H), 3.80 (dd, *J* = 8.4, 4.9 Hz, 1H), 2.42 (d, *J* = 6.5 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 143.9, 134.2, 129.8 (q, *J* = 32.6 Hz), 128.6, 125.9 (q, *J* = 3.8 Hz), 124.6 (q, *J* = 284.0 Hz), 124.2 (q, *J* = 272.0 Hz), 120.6, 72.9 (q, *J* = 29.8 Hz), 49.9.

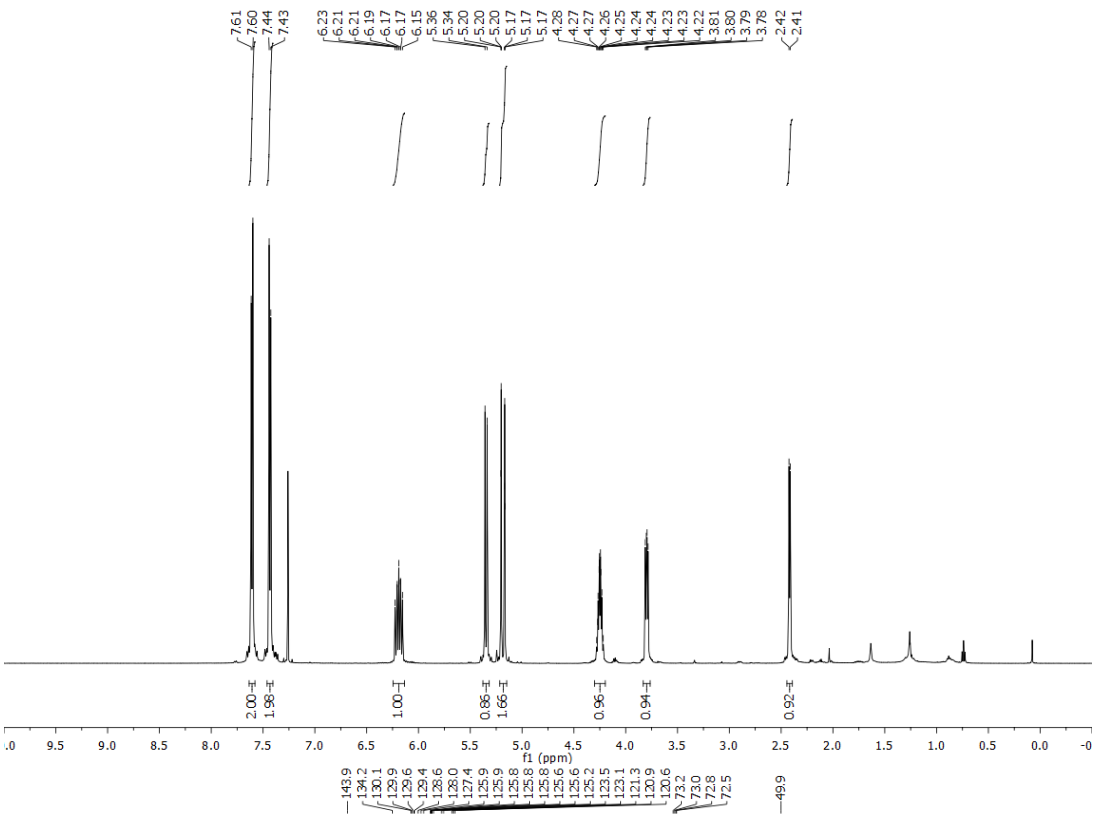
^{19}F NMR (471 MHz, $CDCl_3$): δ = –62.6, –76.1 (d, *J* = 6.5 Hz)

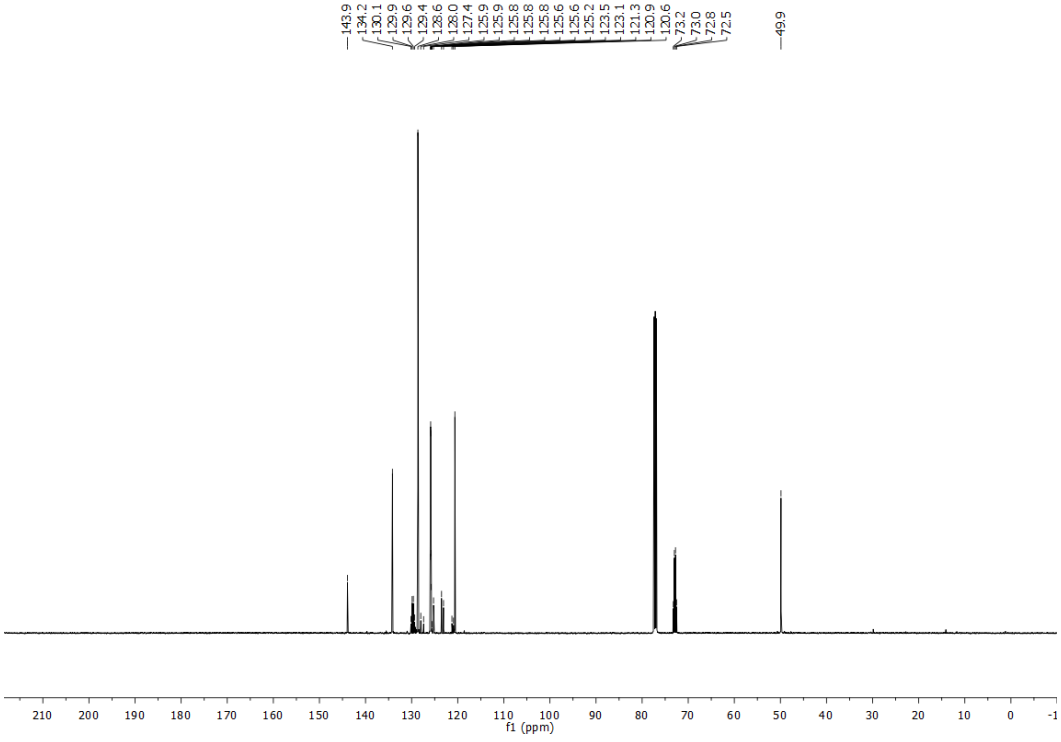
HRMS (CI) Calculated for $C_{12}H_{10}F_6O$ $[M]^+$ = 284.0636, Found 284.0636.

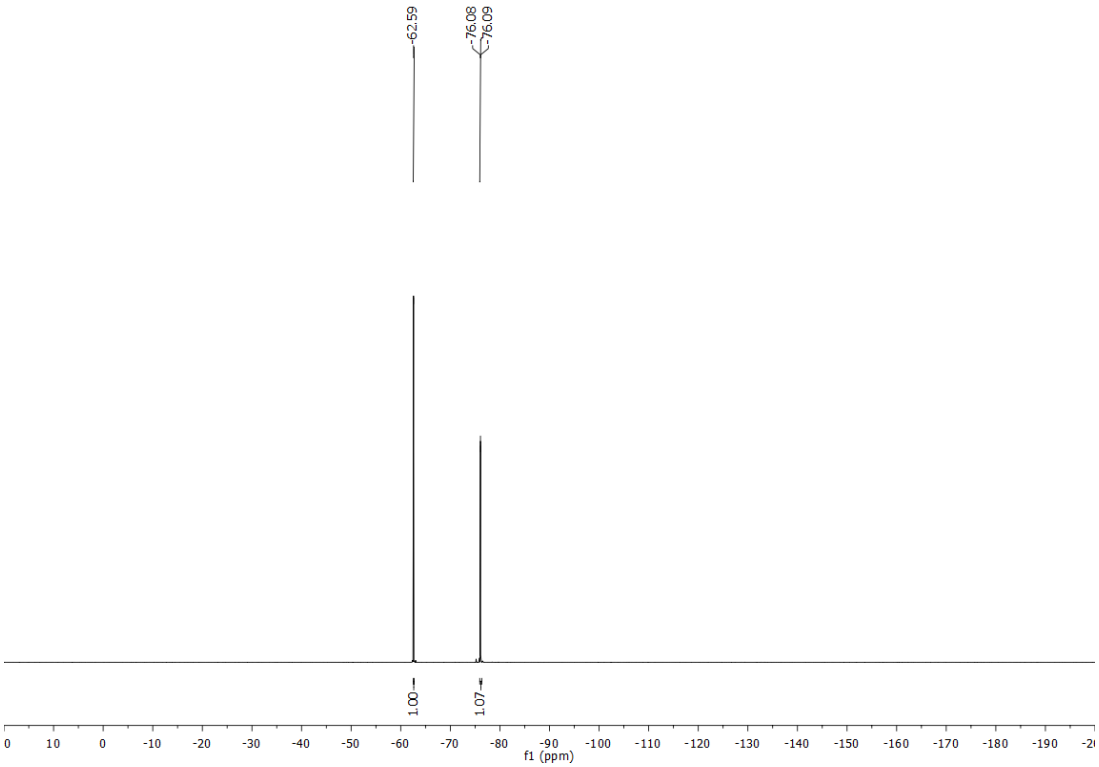
FTIR (neat) 3434, 2923, 1325, 1266, 1164, 1110, 1067, 1019, 832, 700 cm^{-1}.

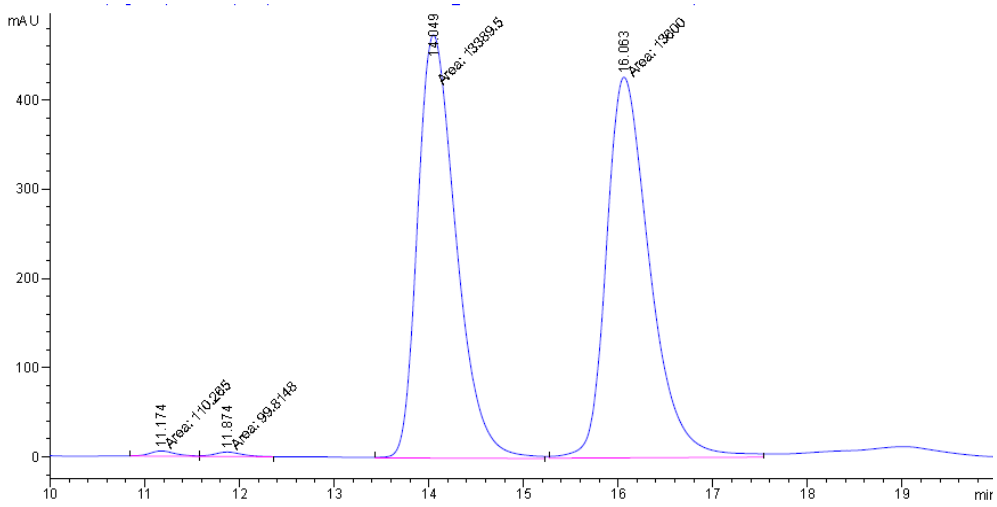
$[\alpha]_D^{33}$: –59.3 (*c* = 1.0, $CHCl_3$)

HPLC: (Chiralcel AS-H column, hexanes:*i*-PrOH = 99:1, 1.0 mL/min, 210 nm), *ee* = 93%.

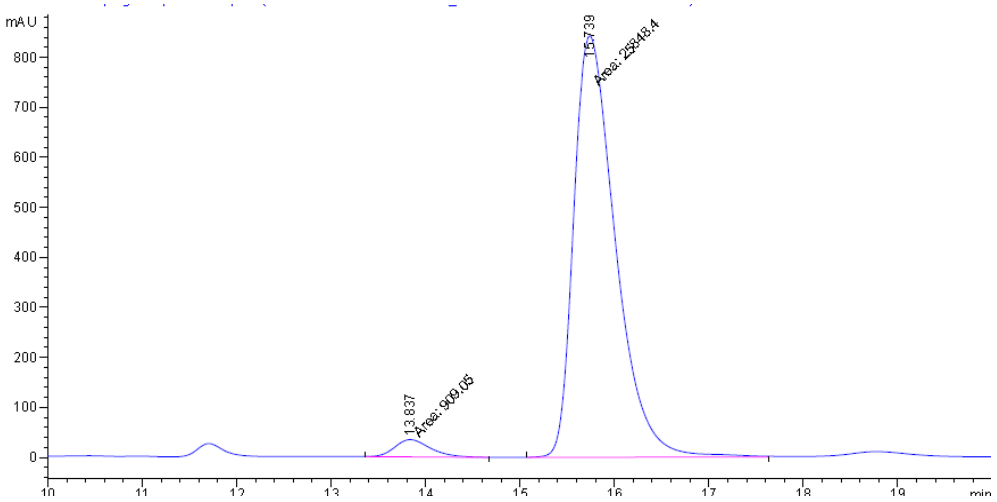

7.61
7.60
7.44
7.43
6.23
6.21
6.21
6.19
6.17
6.17
6.15
5.36
5.34
5.20
5.20
5.20
5.17
5.17
5.17
4.28
4.27
4.27
4.26
4.25
4.24
4.24
4.23
4.23
4.22
3.81
3.80
3.79
3.78
2.42
2.41
2.00
1.98
1.00
0.86
1.66
0.96
0.94
0.92
f1 (ppm)


143.9
134.2
130.1
129.9
129.6
129.4
128.6
128.0
127.4
125.9
125.9
125.8
125.8
125.8
125.6
125.6
125.2
123.5
123.1
121.3
120.9
120.6
73.2
73.0
72.8
72.5
49.9
f1 (ppm)


-62.59
-76.08
-76.09
1.00
1.07
0
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

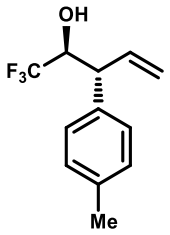


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.174	MF	0.3123	110.26528	5.88381	0.4054
2	11.874	FM	0.3321	99.81478	5.00884	0.3670
3	14.049	MM	0.4704	1.33895e4	474.37296	49.2268
4	16.063	MM	0.5313	1.36000e4	426.59085	50.0008



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.837	MM	0.4389	909.05029	34.52143	3.3974
2	15.739	MM	0.5114	2.58484e4	842.32935	96.6026

(2*S*,3*R*)-1,1,1-Trifluoro-3-(*p*-tolyl)pent-4-en-2-ol (6.4d)



The title compound was prepared according to the general procedure using fluoral hydrate (75% in H_2O, 22 μL, 200 μmol) and 1-(*p*-tolyl)allyl acetate (76 mg, 0.40 mmol, 200 mol%). Flash chromatography on silica (Hex/EtOAc 20:1 → 8:1) provided the title compound (35.5 mg, 154 μmol, *anti:syn* = >20:1) in 77% yield as a yellow oil.

TLC (SiO_2) R_f = 0.18 (hexanes/ethyl acetate = 10:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.23–7.12 (m, 4H), 6.18 (ddd, *J* = 17.6, 10.2, 8.6 Hz, 1H), 5.30 (dd, *J* = 10.2, 1.3 Hz, 1H), 5.19 (dt, *J* = 17.6, 1.3 Hz, 1H), 4.28–4.17 (m, 1H), 3.70 (dd, *J* = 8.6, 5.2 Hz, 1H), 2.35 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 137.1, 136.8, 135.2, 129.6, 128.0, 123.7 (d, *J* = 283.5 Hz), 119.7, 73.2 (q, *J* = 29.3 Hz), 49.9, 21.2.

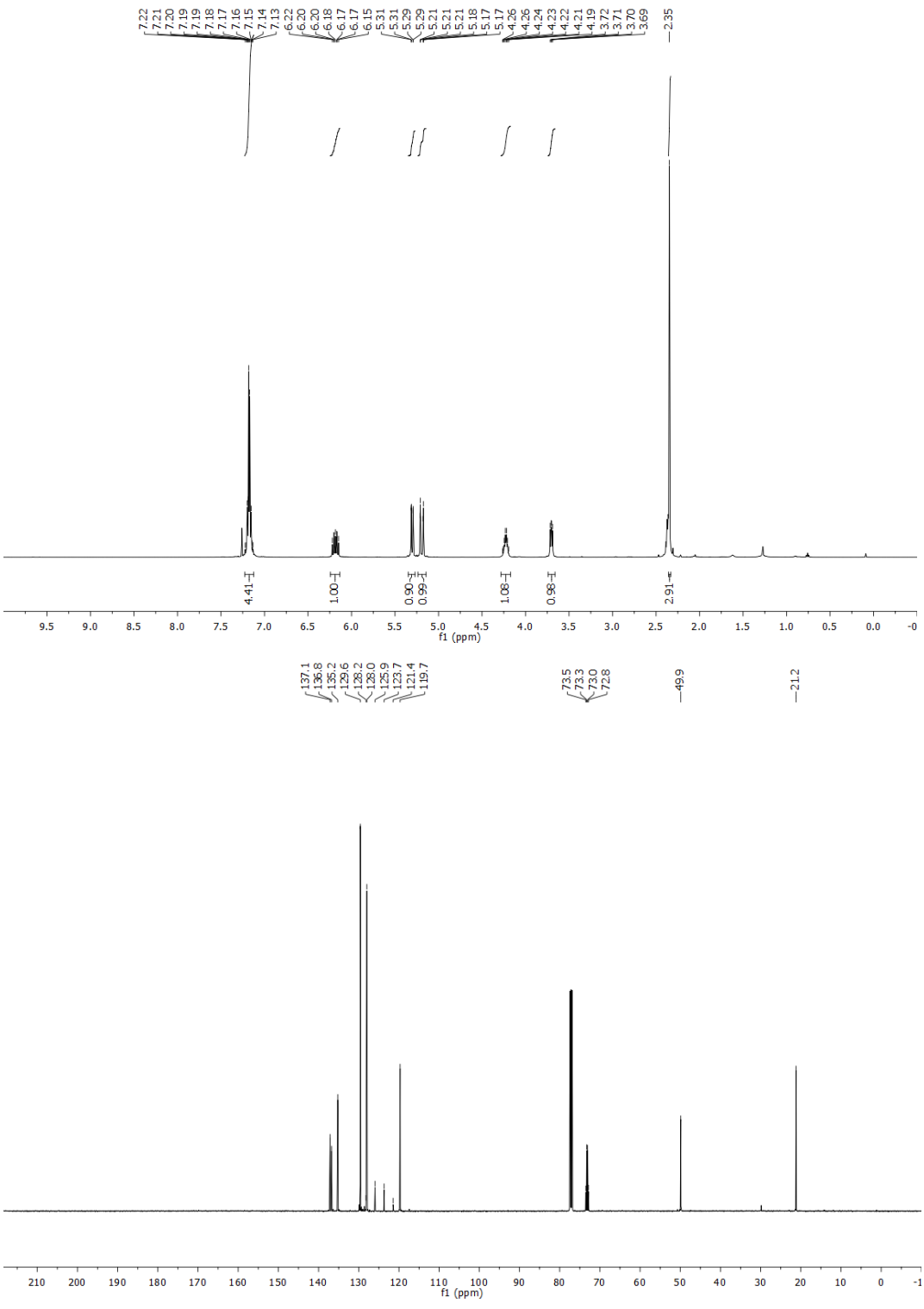
^{19}F NMR (471 MHz, $CDCl_3$): δ = –75.9 (d, *J* = 6.9 Hz)

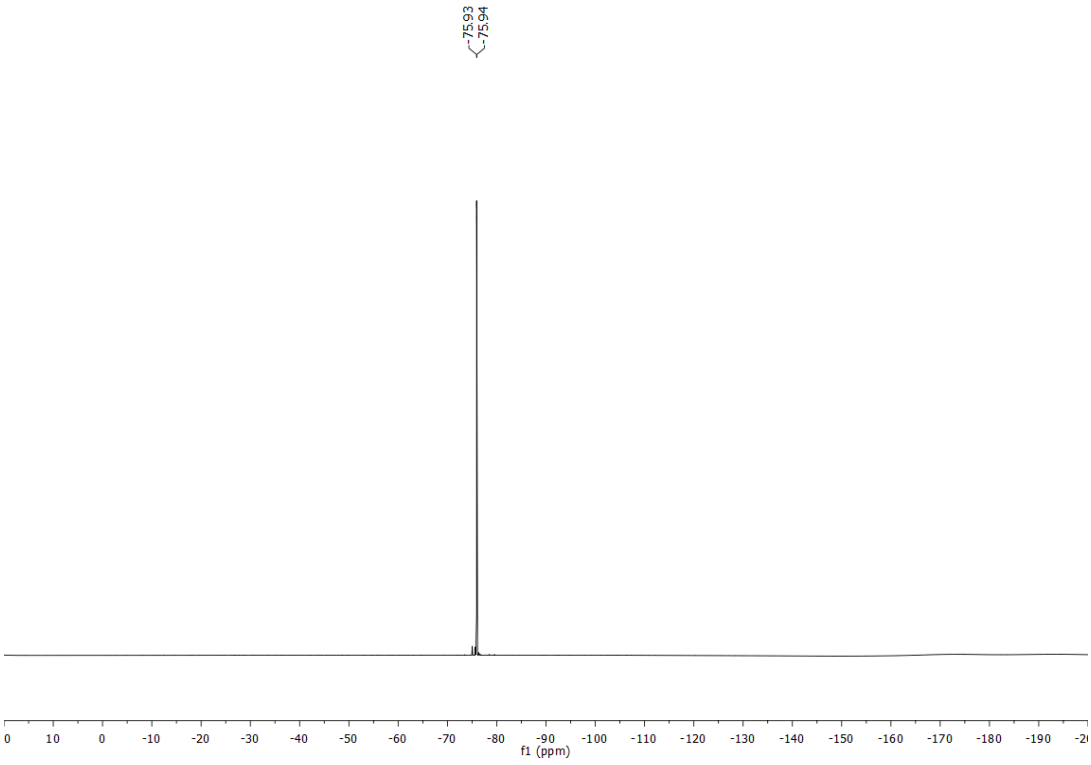
HRMS (CI) Calculated for $C_{12}H_{14}F_3O$ $[M+H]^+$ = 231.0997, Found 231.0999.

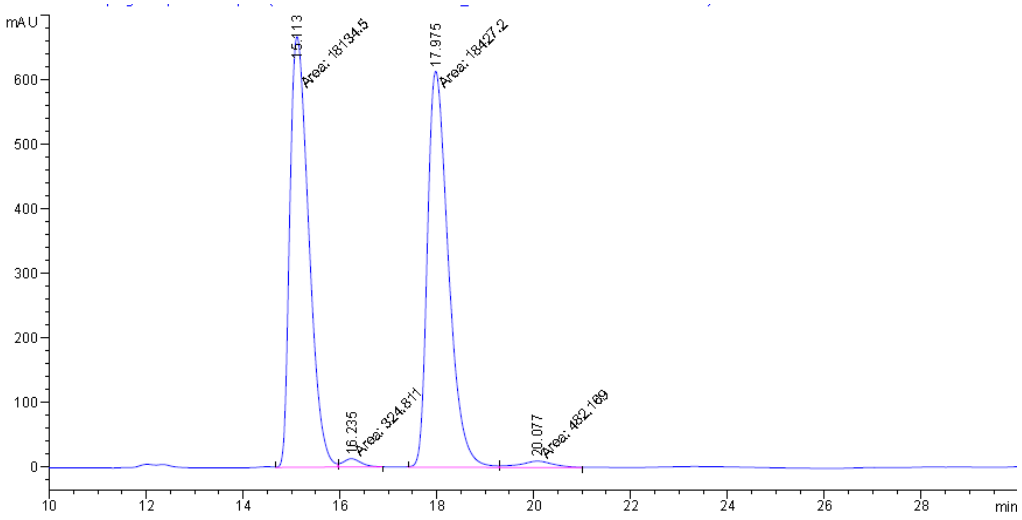
FTIR (neat) 3459, 2924, 1267, 1166, 1115, 924, 811, 783, 685, 669 cm^{-1}.

$[\alpha]_D^{33}$: –77.8 (*c* = 1.0, $CHCl_3$)

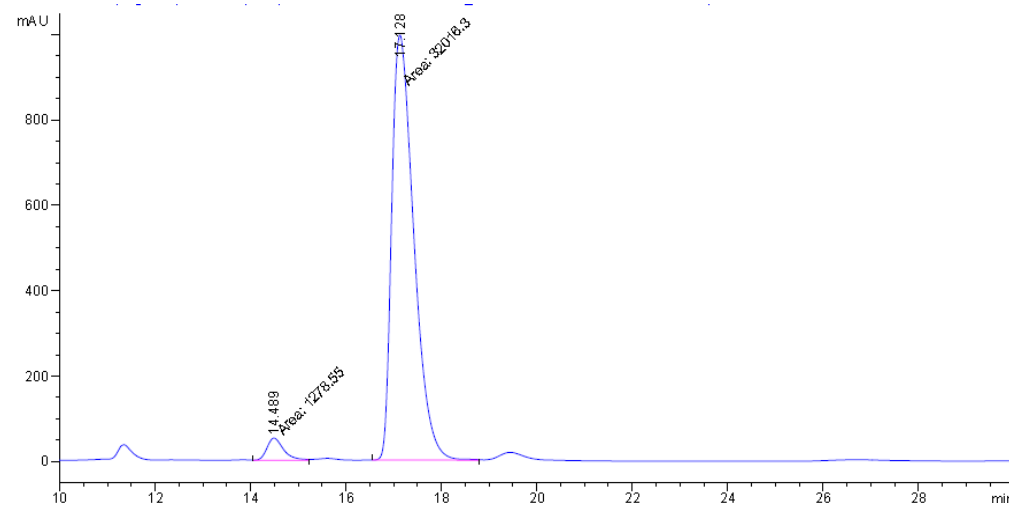
HPLC: (Chiralcel AS-H column, hexanes:*i*-PrOH = 99:1, 1.0 mL/min, 210 nm), *ee* = 92%.


7.22
7.21
7.20
7.19
7.19
7.19
7.18
7.17
7.16
7.15
7.14
7.13
6.22
6.20
6.20
6.18
6.17
6.17
6.15
5.31
5.31
5.29
5.29
5.21
5.21
5.21
5.18
5.17
5.17
4.26
4.26
4.24
4.23
4.22
4.21
4.19
3.72
3.71
3.70
3.69
2.35
4.41
1.00
0.90
0.99
1.08
0.98
2.91
f1 (ppm)
137.1
136.8
135.2
129.6
128.2
128.0
125.9
123.7
121.4
119.7
73.5
73.3
73.0
72.8
49.9
21.2
f1 (ppm)


-75.93
-75.94
0
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

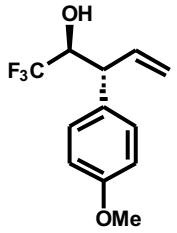


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.113	MF	0.4531	1.81345e4	667.04077	48.5286
2	16.235	FM	0.4216	324.81085	12.84072	0.8692
3	17.975	MF	0.5008	1.84272e4	613.20197	49.3119
4	20.077	FM	0.8083	482.16904	9.94247	1.2903



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.489	MF	0.4079	1278.54797	52.24576	3.8401
2	17.128	MF	0.5362	3.20163e4	995.22772	96.1599

(2*S*,3*R*)-1,1,1-Trifluoro-3-(4-methoxyphenyl)pent-4-en-2-ol (6.4e)



The title compound was prepared according to the general procedure using fluoral hydrate (75% in H_2O, 22 μL, 200 μmol) and 1-(4-methoxyphenyl)allyl acetate (82 mg, 0.40 mmol, 200 mol%). Flash chromatography on silica (Hex/EtOAc 20:1 → 8:1) provided the title compound (34.9 mg, 142 μmol, *anti:syn* = >20:1) in 71% yield as a yellow oil.

TLC (SiO_2) R_f = 0.36 (hexanes/ethyl acetate = 4:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.21 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 6.22 – 6.11 (m, 1H), 5.29 (dt, *J* = 10.2, 1.0 Hz, 1H), 5.17 (dt, *J* = 17.2, 1.3 Hz, 1H), 4.24 – 4.15 (m, 1H), 3.80 (s, 3H), 3.69 (dd, *J* = 8.4, 5.2 Hz, 1H), 2.42 (d, *J* = 6.2 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.8, 135.3, 131.8, 129.2, 124.8 (q, *J* = 283.3 Hz), 119.5, 114.3, 73.2 (q, *J* = 29.2 Hz), 55.4, 49.4.

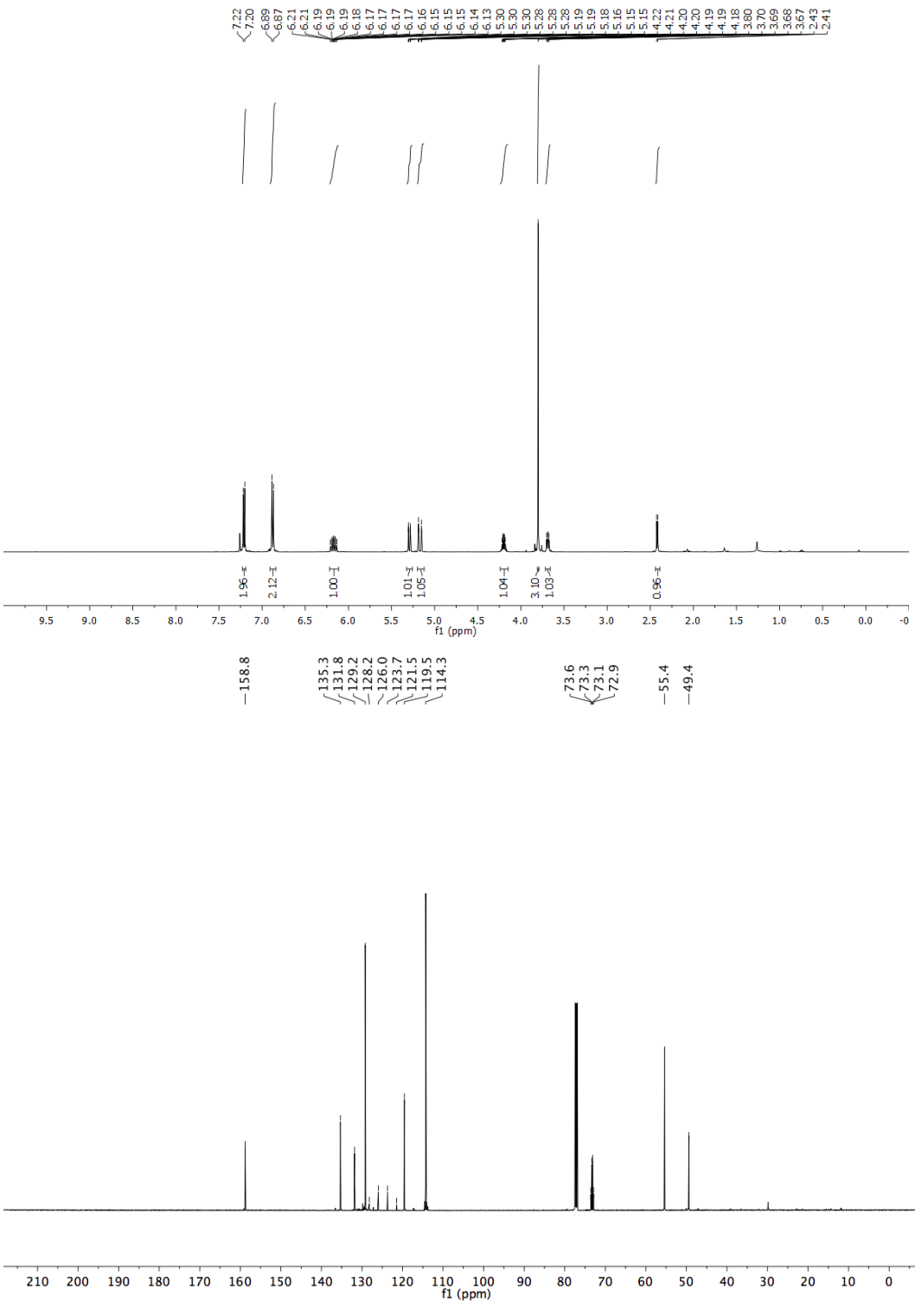
^{19}F NMR (471 MHz, $CDCl_3$): δ = -75.89 (d, *J* = 6.9 Hz).

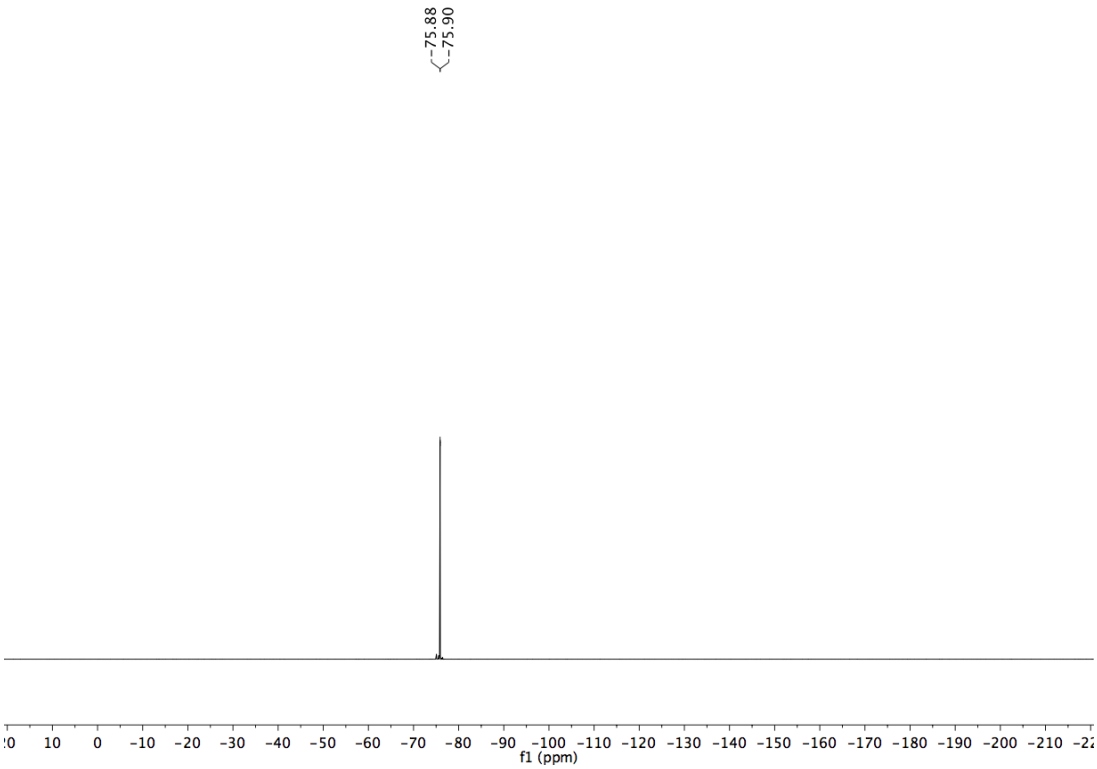
HRMS (CI) Calculated for $C_{12}H_{13}F_3O_2$ $[M]^+$ = 246.0868, Found 246.0866.

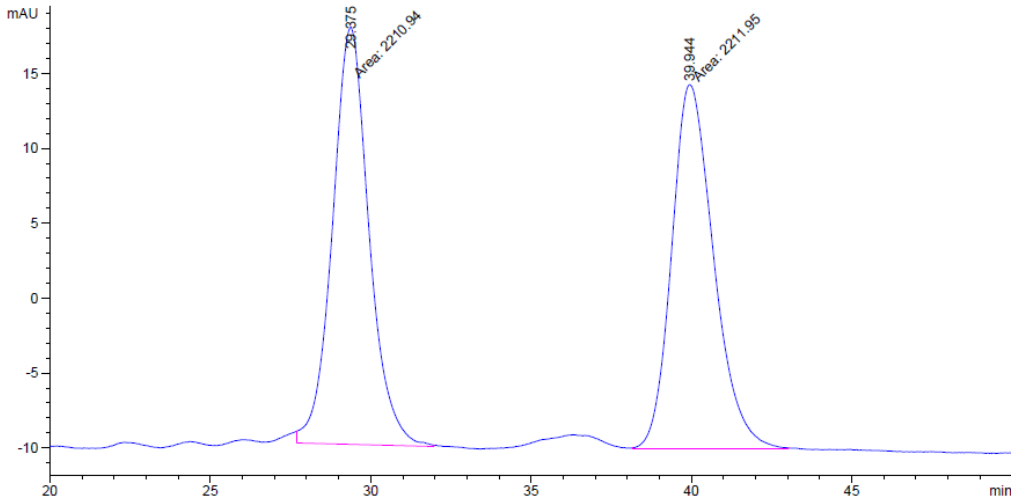
FTIR (neat) 3458, 3007, 2360, 1738, 1512, 1366, 1232, 1111, 1032, 826 cm^{-1}.

$[\alpha]_D^{33}$: –73.5 (*c* = 1.0, $CHCl_3$)

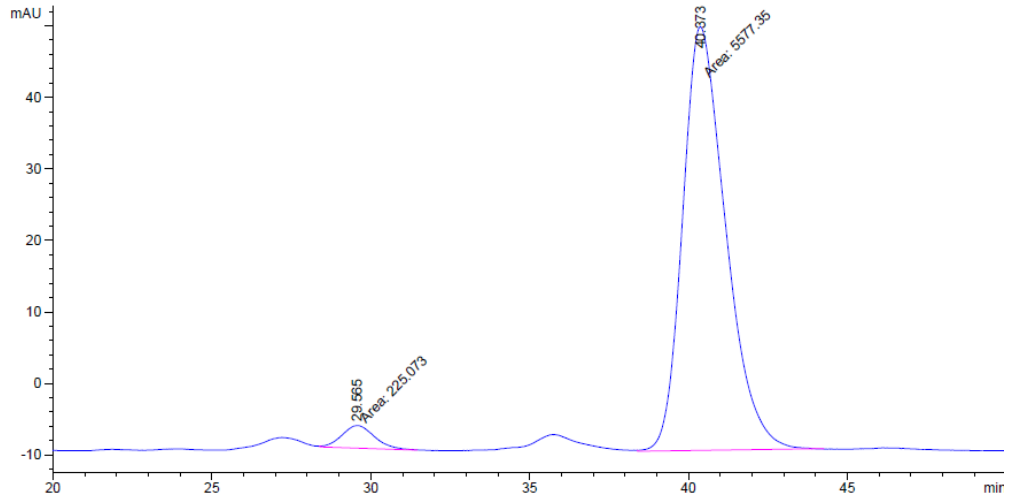
HPLC: (Chiralcel OD-H column, hexanes:*i*-PrOH = 99:1, 1.0 mL/min, 230 nm), *ee* = 92%.


7.22
7.20
6.89
6.87
6.21
6.19
6.19
6.18
6.17
6.17
6.17
6.16
6.15
6.15
6.15
6.14
6.13
5.30
5.30
5.30
5.28
5.28
5.28
5.19
5.19
5.18
5.16
5.15
5.15
4.22
4.21
4.20
4.20
4.19
4.19
4.18
3.80
3.70
3.69
3.68
3.67
2.43
2.41
1.96
2.12
1.00
1.01
1.05
1.04
3.10
1.03
0.96
f1 (ppm)
158.8
135.3
131.8
129.2
128.2
126.0
123.7
121.5
119.5
114.3
73.6
73.3
73.1
72.9
55.4
49.4
f1 (ppm)


-75.88
-75.90
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

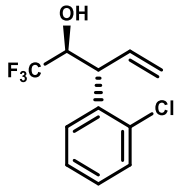


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	29.375	FM	1.3222	2210.93848	27.86860	49.9886
2	39.944	MM	1.5162	2211.94775	24.31518	50.0114



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	29.565	MM	1.1884	225.07312	3.15641	3.8790
2	40.373	MM	1.5699	5577.34863	59.21095	96.1210

(2S,3R)-3-(2-chlorophenyl)-1,1,1-trifluoropent-4-en-2-ol (6.4f)



The title compound was prepared according to the general procedure using fluoral hydrate (75% in H_2O, 22 μL, 200 μmol) and 1-(2-chlorophenyl)allyl acetate (84 mg, 0.40 mmol, 200 mol%). Flash chromatography on silica (Hex/EtOAc 20:1 → 8:1) provided the title compound (30.1 mg, 120 μmol, *anti:syn* = >20:1) in 60% yield as a yellow oil.

TLC (SiO_2) R_f = 0.57 (hexanes/ethyl acetate = 3:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.46 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.40 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.27 (td, *J* = 7.5, 1.4 Hz, 1H), 7.22 (td, *J* = 7.6, 1.7 Hz, 1H), 6.24 (dddt, *J* = 17.2, 10.1, 8.2, 1.0 Hz, 1H), 5.36 – 5.33 (m, 1H), 5.18 (dt, *J* = 17.2, 1.2 Hz, 1H), 4.40 – 4.22 (m, 2H), 2.40 (d, *J* = 6.6 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 137.7, 133.4, 133.3, 130.1, 129.8, 128.6, 127.2, 124.7 (d, *J* = 283.3 Hz), 120.7, 71.9 (q, *J* = 30.0 Hz), 45.6.

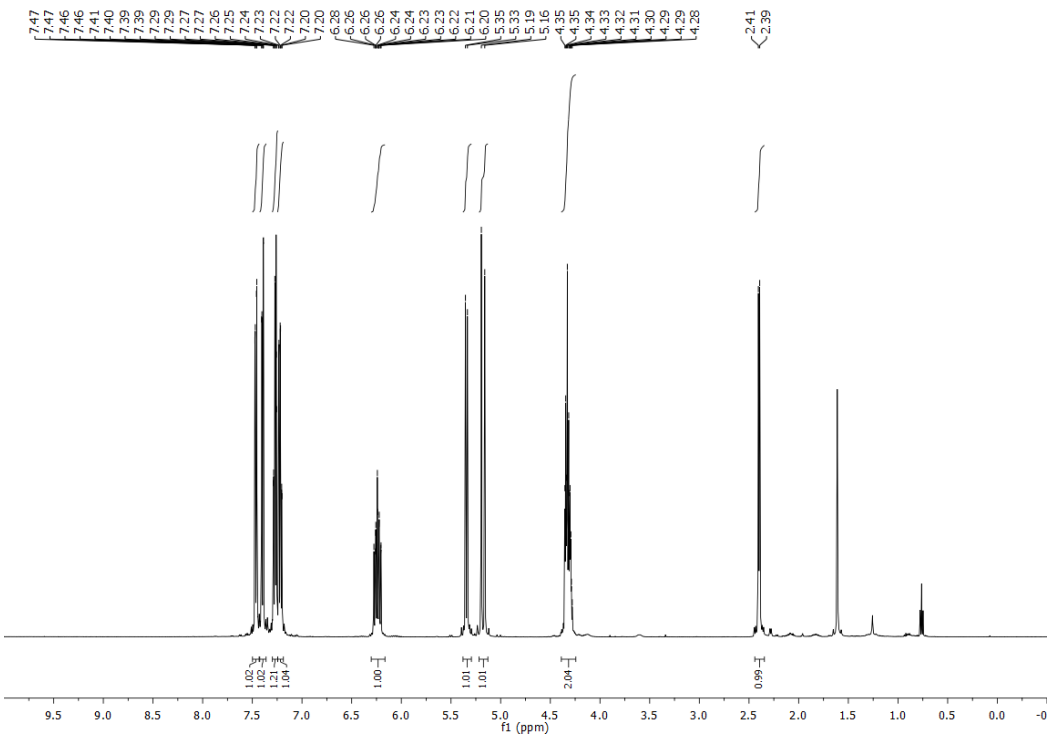
^{19}F NMR (471 MHz, $CDCl_3$): δ = –76.5 (d, *J* = 6.9 Hz).

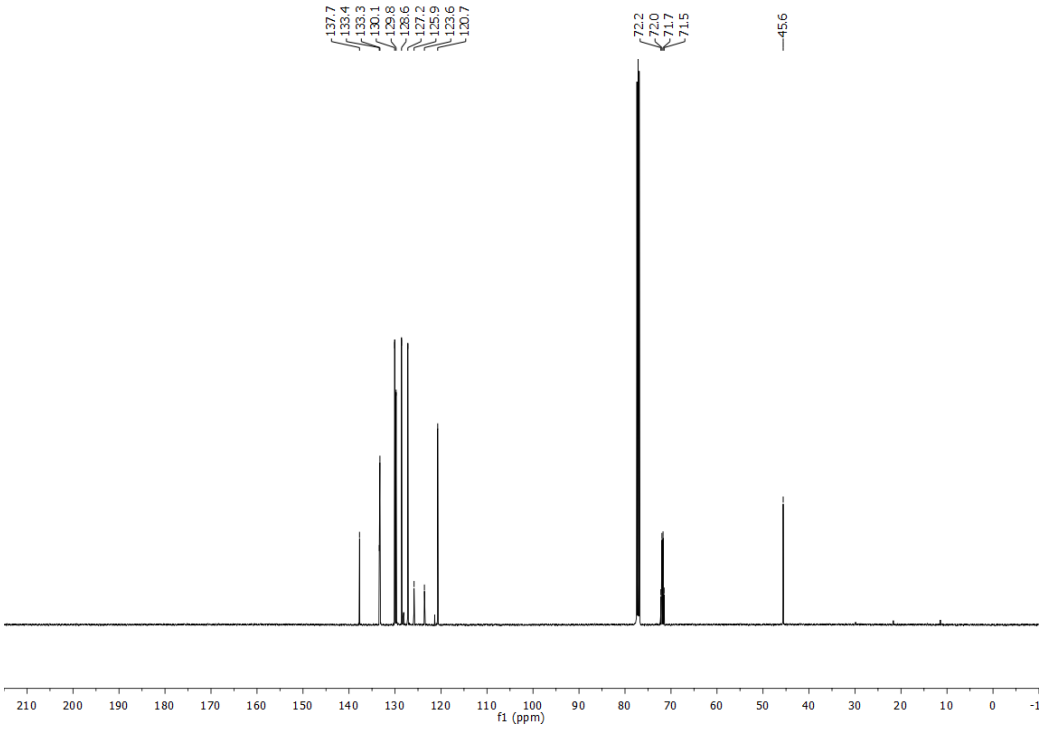
HRMS (CI) Calculated for $C_{11}H_{10}ClF_3O$ $[M]^+$ = 250.0372, Found 250.0367.

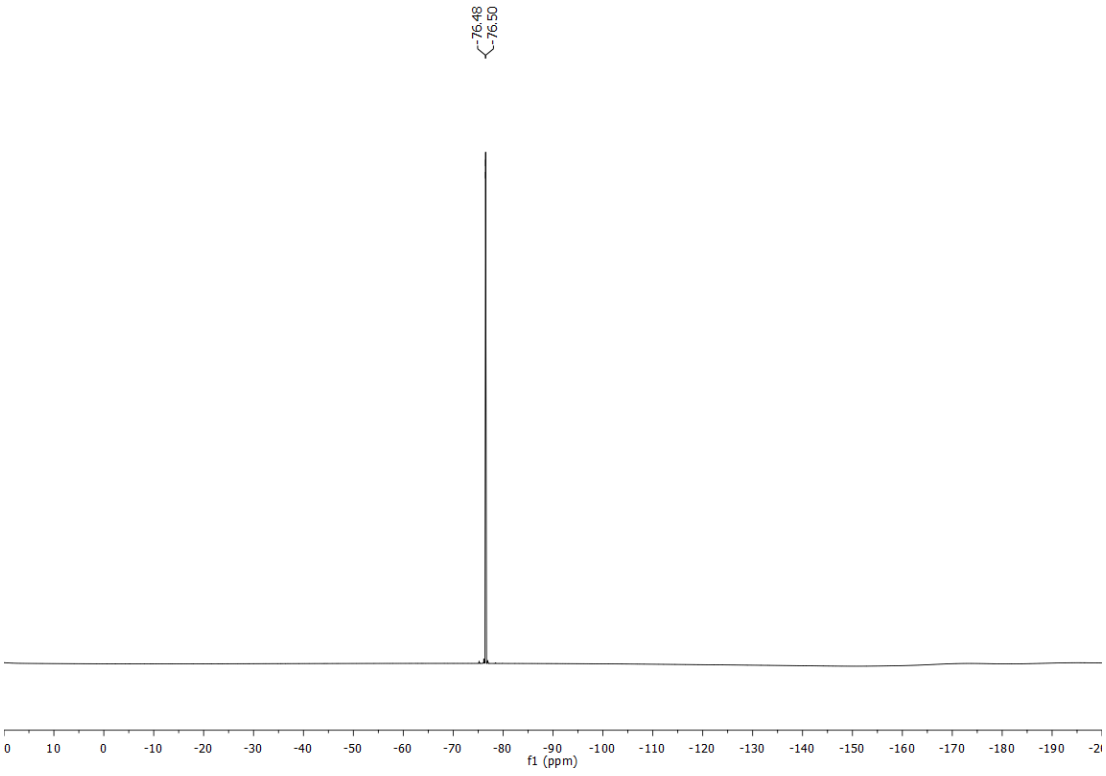
FTIR (neat) 3466, 2926, 1474, 1271, 1170, 1128, 1101, 928, 751, 680 cm^{-1}.

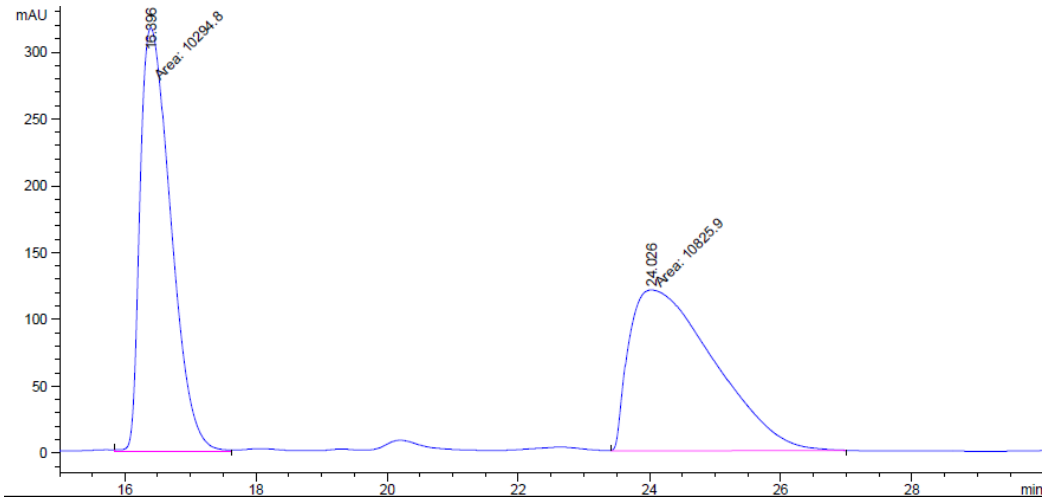
$[\alpha]_D^{30}$: –38.8 (*c* = 1.0, $CHCl_3$)

HPLC: (Chiralcel AS-H column, hexanes:*i*-PrOH = 99:1, 1.0 mL/min, 230 nm), *ee* = 89%.

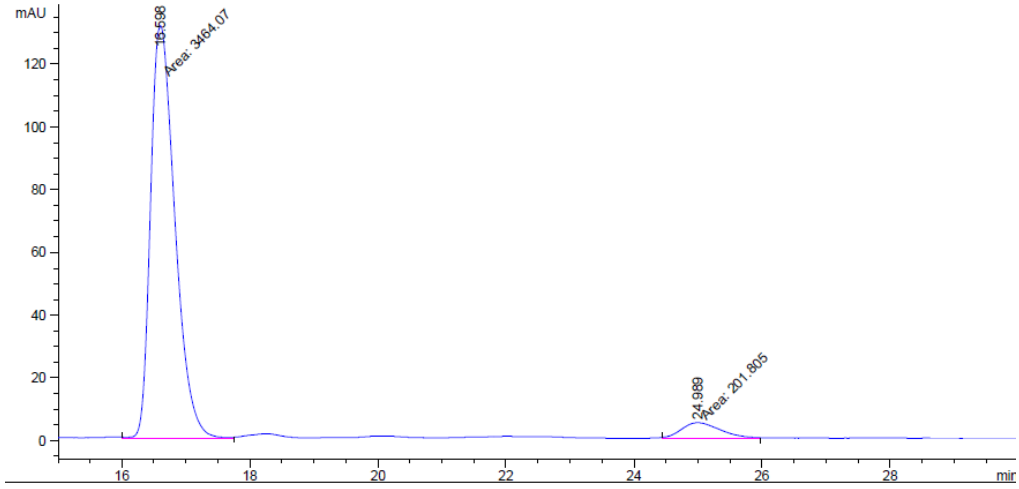

7.47
7.47
7.46
7.46
7.41
7.40
7.39
7.39
7.29
7.29
7.27
7.27
7.26
7.25
7.24
7.23
7.22
7.22
7.20
7.20
6.28
6.26
6.26
6.26
6.24
6.24
6.23
6.22
6.21
6.20
5.35
5.33
5.19
5.16
4.35
4.35
4.34
4.33
4.32
4.31
4.30
4.29
4.29
4.28
2.41
2.39
1.02
1.02
1.21
1.04
1.00
1.01
1.01
2.04
0.99
f1 (ppm)


137.7
133.4
133.3
130.1
129.8
128.6
127.2
125.9
123.6
120.7
72.2
72.0
71.7
71.5
45.6
f1 (ppm)


76.48
76.50
0
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

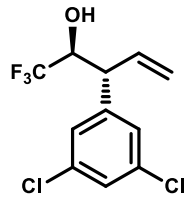


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.396	MM	0.5418	1.02948e4	316.68604	48.7426
2	24.026	MM	1.4987	1.08259e4	120.39088	51.2574



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.598	MM	0.4386	3464.07446	131.63419	94.4950
2	24.989	MM	0.6919	201.80528	4.86140	5.5050

(2S,3R)-3-(3,5-dichlorophenyl)-1,1,1-trifluoropent-4-en-2-ol (6.4g)



The title compound was prepared according to the general procedure using fluoral hydrate (75% in H_2O, 22 μL, 200 μmol) and 1-(3,5-dichlorophenyl)allyl acetate (98 mg, 0.40 mmol, 200 mol%). Flash chromatography on silica (Hex/EtOAc 20:1) provided the title compound (52 mg, 182 μmol, *anti:syn* = >20:1) in 91% yield as a yellow oil.

TLC (SiO_2) R_f = 0.34 (hexanes/ethyl acetate = 9:1).

^{1}H NMR (400 MHz, $CDCl_3$): 7.30 – 7.27 (m, 1H), 7.23 – 7.19 (m, 2H), 6.13 (dt, *J* = 17.8, 9.2 Hz, 1H), 5.35 (d, *J* = 10.2 Hz, 1H), 5.19 (d, *J* = 17.1 Hz, 1H), 4.21 (h, *J* = 6.4 Hz, 1H), 3.68 (dd, *J* = 8.1, 4.4 Hz, 1H), 2.43 (d, *J* = 6.1 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 143.30, 135.34, 133.52, 127.70, 126.83, 125.65, 123.39, 120.84, 72.76 (q, *J* = 30.0 Hz), 49.32.

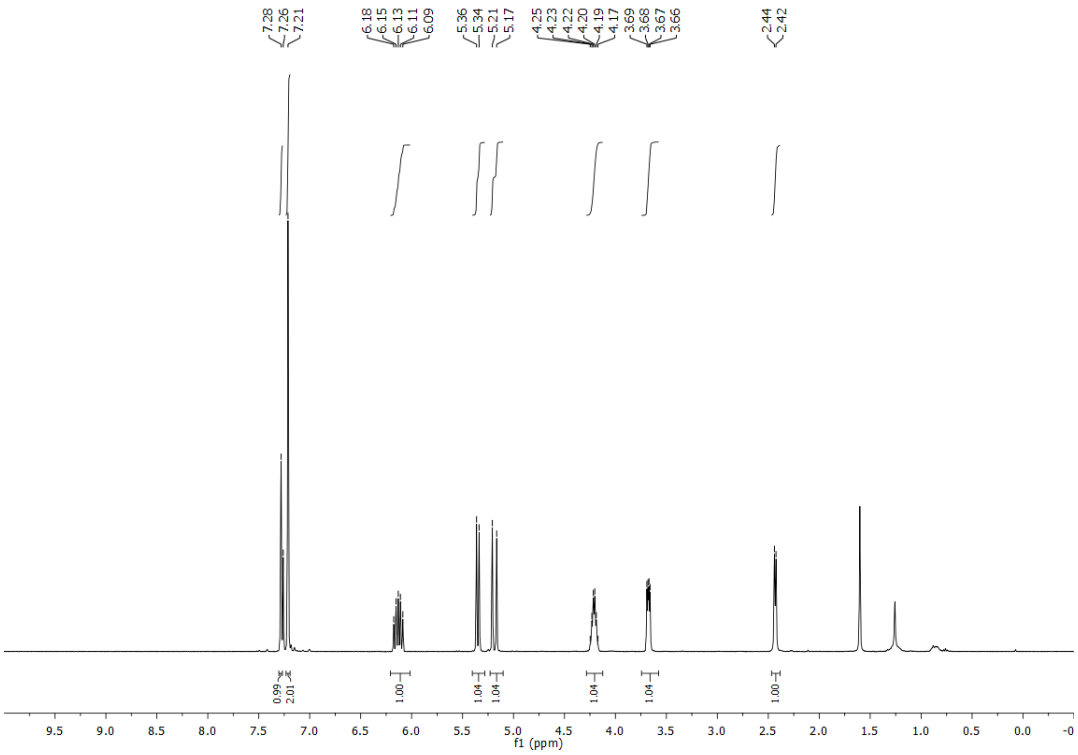
^{19}F NMR (471 MHz, $CDCl_3$): δ = -76.15 (d, *J* = 6.8 Hz).

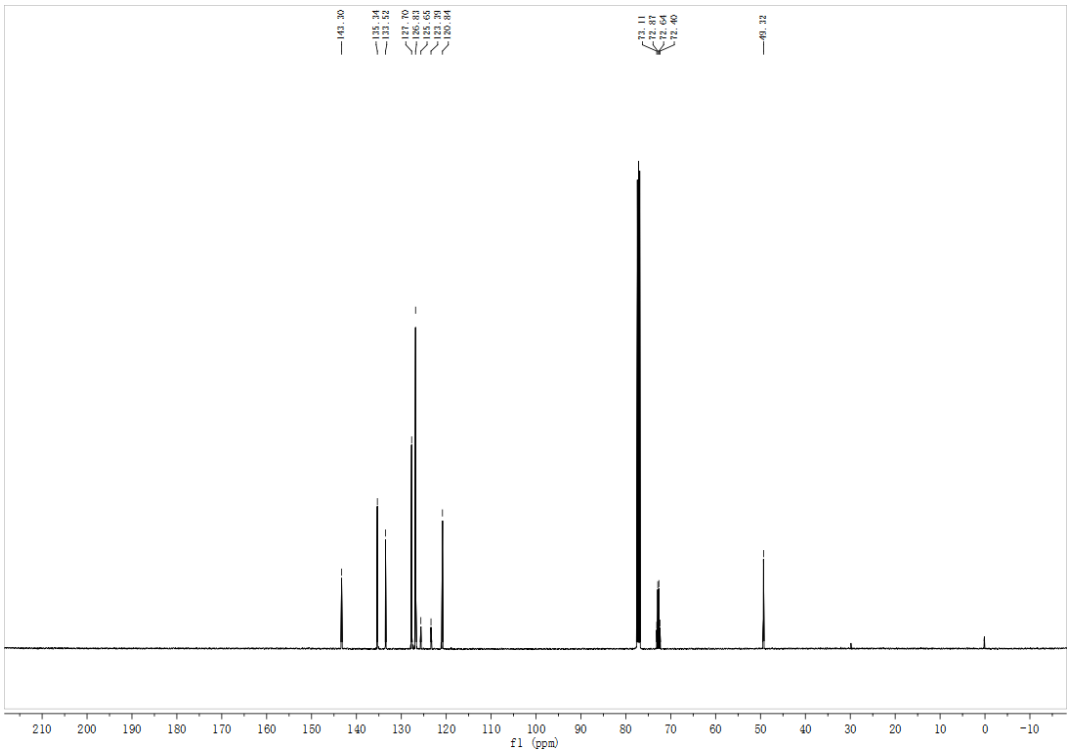
HRMS (CI) Calculated for $C_{11}H_9Cl_2F_3O$ $[M]^+$ = 283.9983, Found 283.9978.

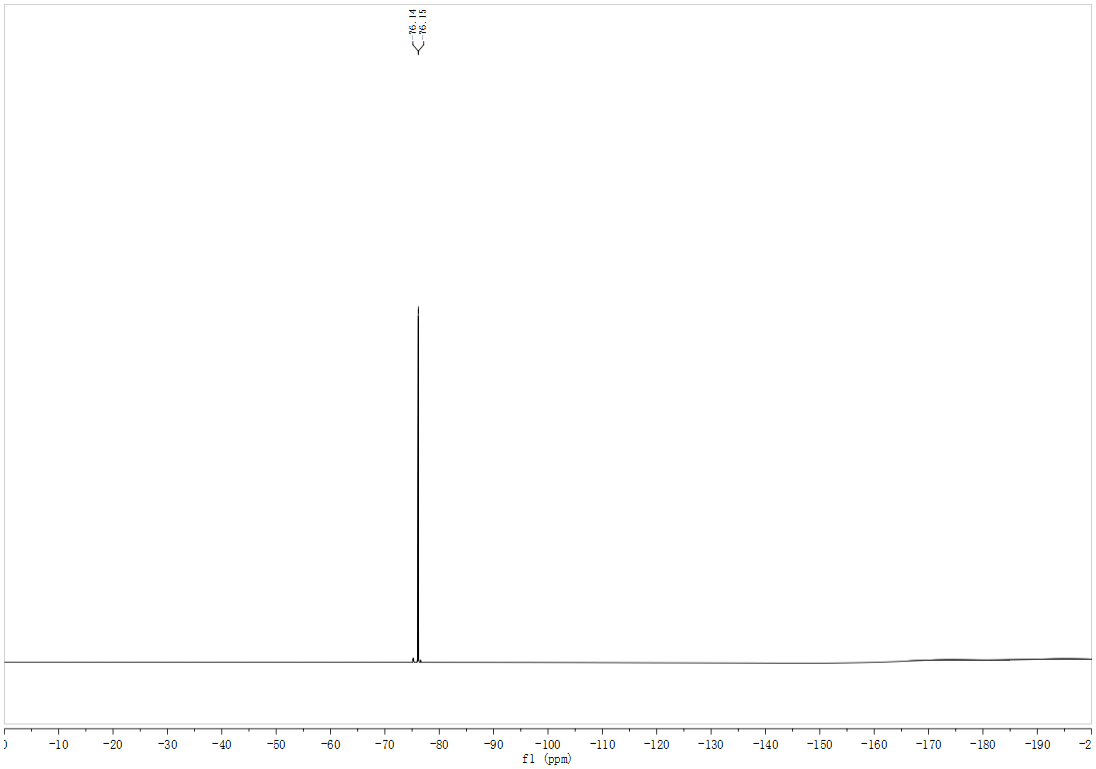
FTIR (neat) 3548, 2360, 1588, 1568, 1169, 1146, 738, 698 cm^{-1}.

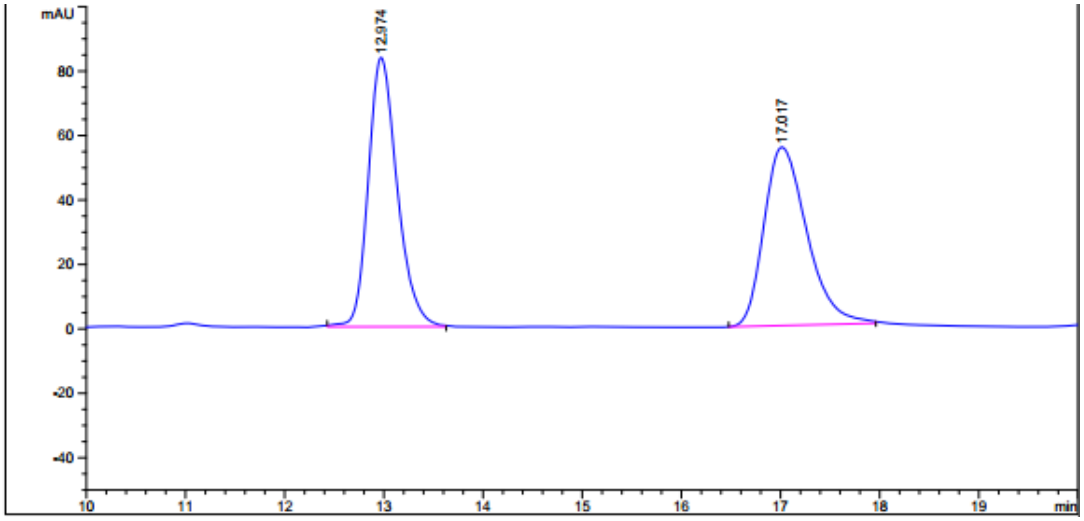
$[\alpha]_D^{33}$: –140.9 (*c* = 1.1, $CHCl_3$)

HPLC: (Chiralcel AS-H column, hexanes:*i*-PrOH = 99:1, 1.0 mL/min, 230 nm), *ee* = 94%.

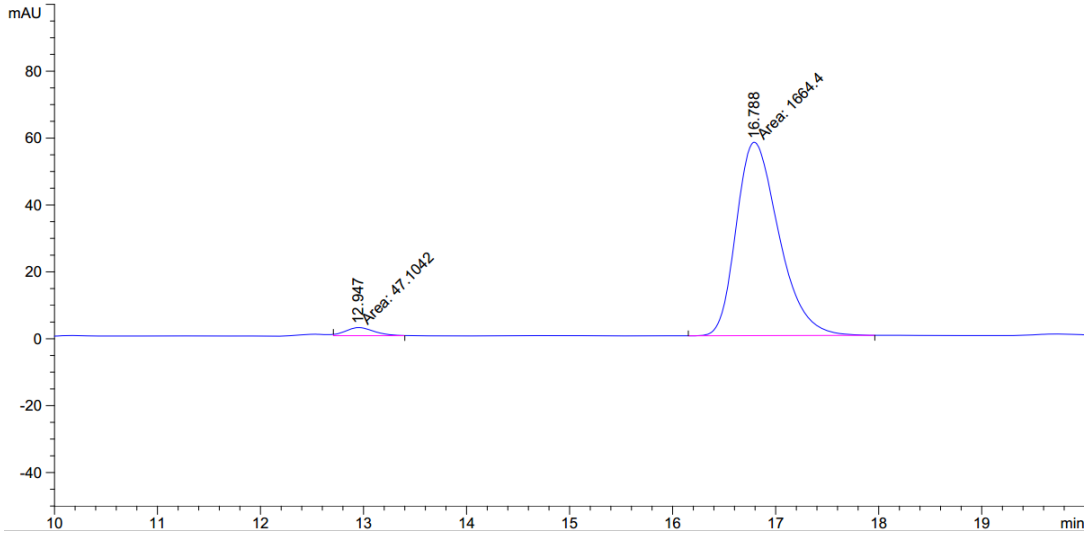

7.28
7.26
7.21
6.18
6.15
6.13
6.11
6.09
5.36
5.34
5.21
5.17
4.25
4.23
4.22
4.20
4.19
4.17
3.69
3.68
3.67
3.66
2.44
2.42
0.99
2.01
1.00
1.04
1.04
1.04
1.04
1.00
f1 (ppm)


143.30
135.24
133.52
127.70
126.83
125.65
123.39
120.84
73.11
72.87
72.64
72.40
69.32
f1 (ppm)


-76.14
-76.15
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-2
f1 (ppm)

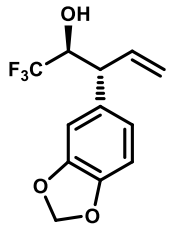


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.974	BB	0.3107	1694.64917	83.54061	50.4033
2	17.017	BB	0.4671	1667.53186	55.40837	49.5967



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.947	FM	0.3225	47.10421	2.43405	2.7522
2	16.788	MM	0.4797	1664.39624	57.82679	97.2478

(2*S*,3*R*)-3-(Benzo[d][1,3]dioxol-5-yl)-1,1,1-trifluoropent-4-en-2-ol (6.4h)



The title compound was prepared according to the general procedure using fluoral hydrate (75% in H_2O, 22 μL, 200 μmol) and 1-(benzo[d][1,3]dioxol-5-yl)allyl acetate (88 mg, 0.40 mmol, 200 mol%). Flash chromatography on silica (Hex/EtOAc 20:1 → 8:1) provided the title compound (43.7 mg, 168 μmol, *anti:syn* = >20:1) in 84% yield as a yellow oil.

TLC (SiO_2) R_f = 0.09 (hexanes/ethyl acetate = 10:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.82–6.76 (m, 2H), 6.74 (dd, *J* = 8.0, 1.8 Hz, 1H), 6.14 (ddd, *J* = 17.5, 10.3, 8.4 Hz, 1H), 5.95 (s, 2H), 5.29 (dt, *J* = 10.3, 1.0 Hz, 1H), 5.18 (dt, *J* = 17.5, 1.3 Hz, 1H), 4.22–4.13 (m, 1H), 3.64 (dd, *J* = 8.4, 5.1 Hz, 1H), 2.42 (d, *J* = 6.1 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 148.0, 146.8, 135.1, 133.6, 124.8 (d, *J* = 283.6 Hz), 121.3, 119.7, 108.6, 108.5, 101.2, 73.2 (q, *J* = 29.4 Hz), 49.8.

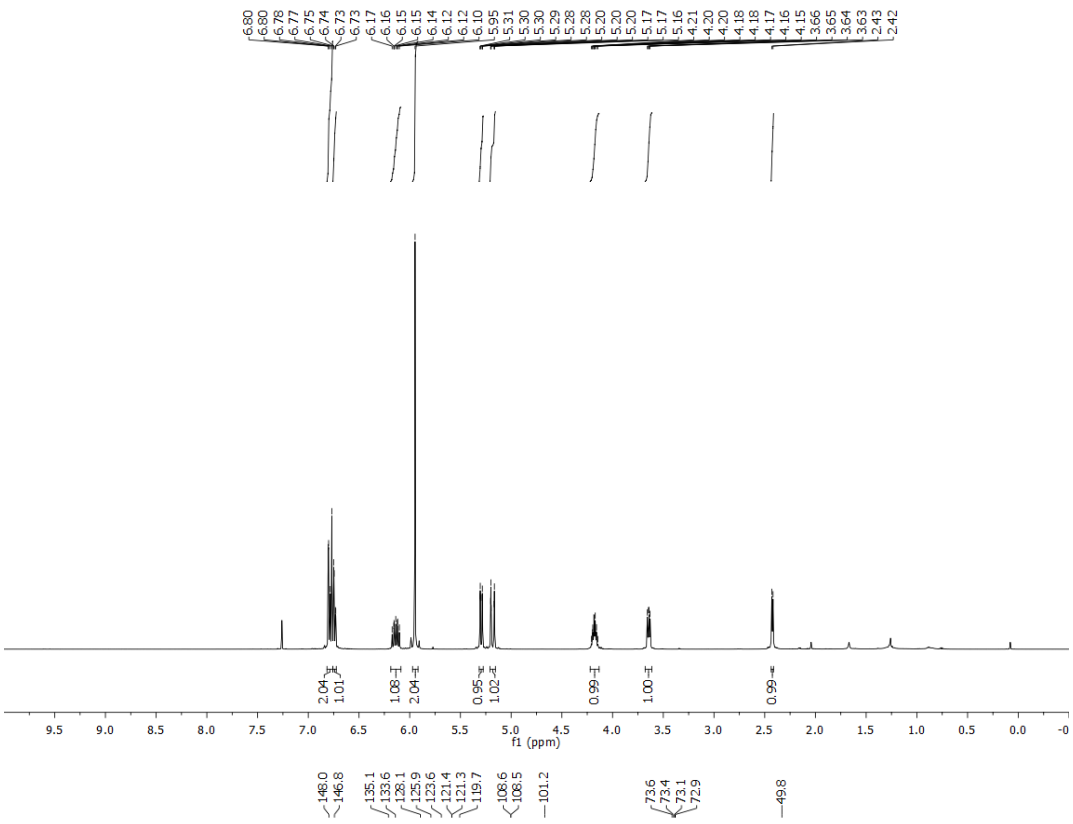
^{19}F NMR (471 MHz, $CDCl_3$): δ = –76.0 (d, *J* = 7.0 Hz)

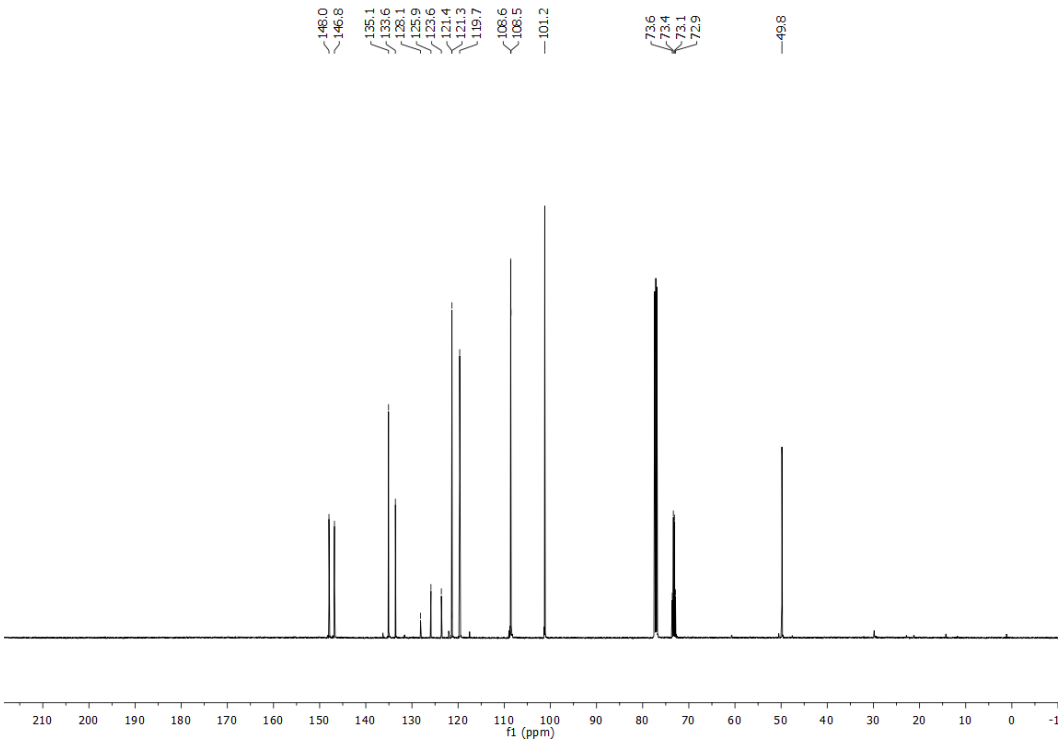
HRMS (CI) Calculated for $C_{12}H_{11}F_3O_3$ $[M]^+$ = 260.0660, Found 260.0658.

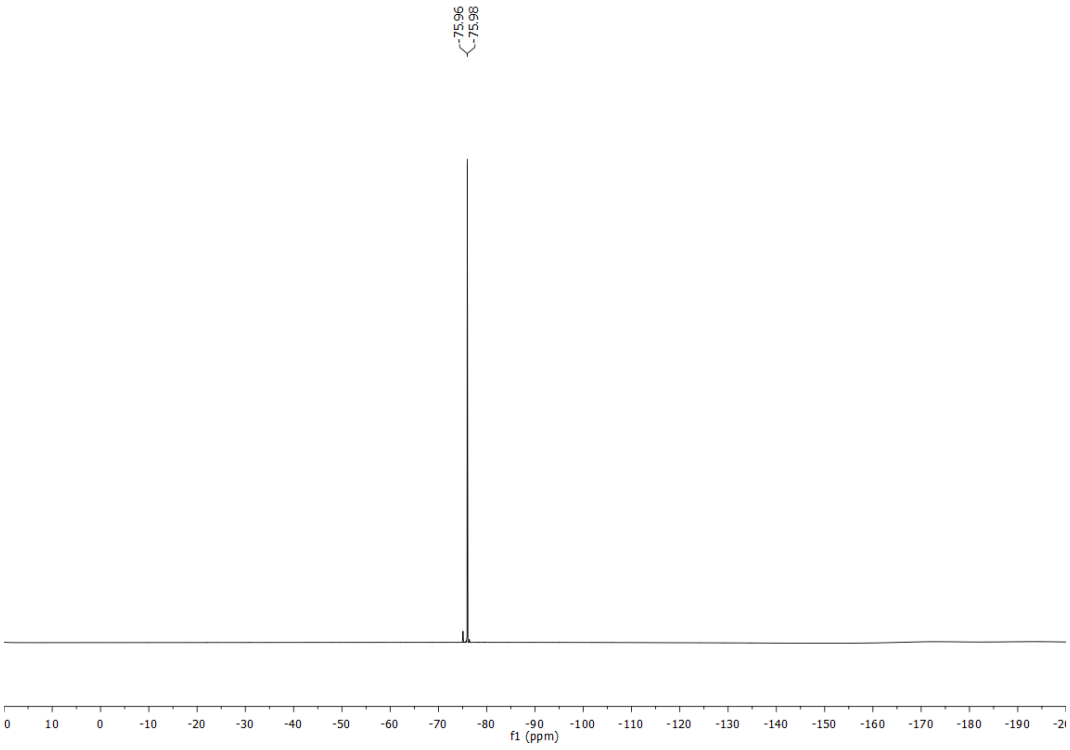
FTIR (neat) 3472, 2903, 1490, 1249, 1169, 1102, 1039, 931 cm^{-1}.

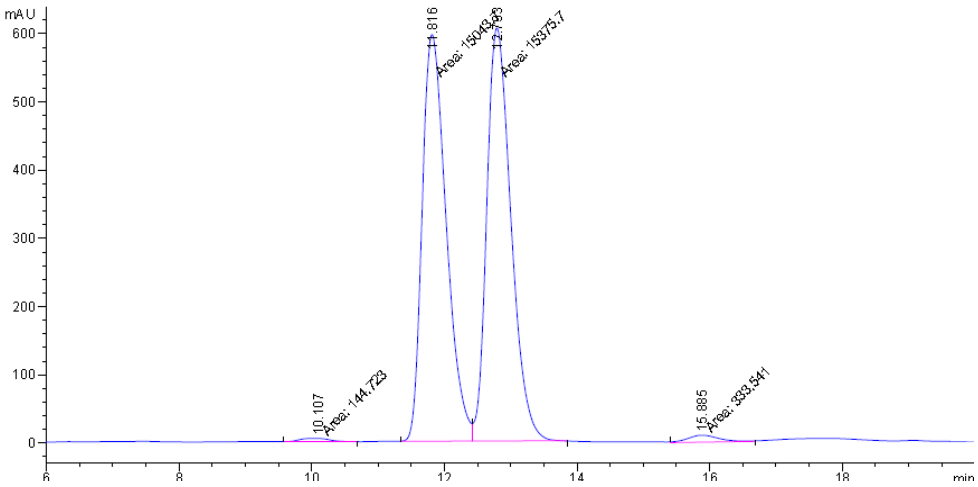
$[\alpha]_D^{32}$: –177.8 (*c* = 1.0, $CHCl_3$)

HPLC: (Chiralcel AS-H column, hexanes:*i*-PrOH = 95:5, 1.0 mL/min, 210 nm), *ee* = 92%.

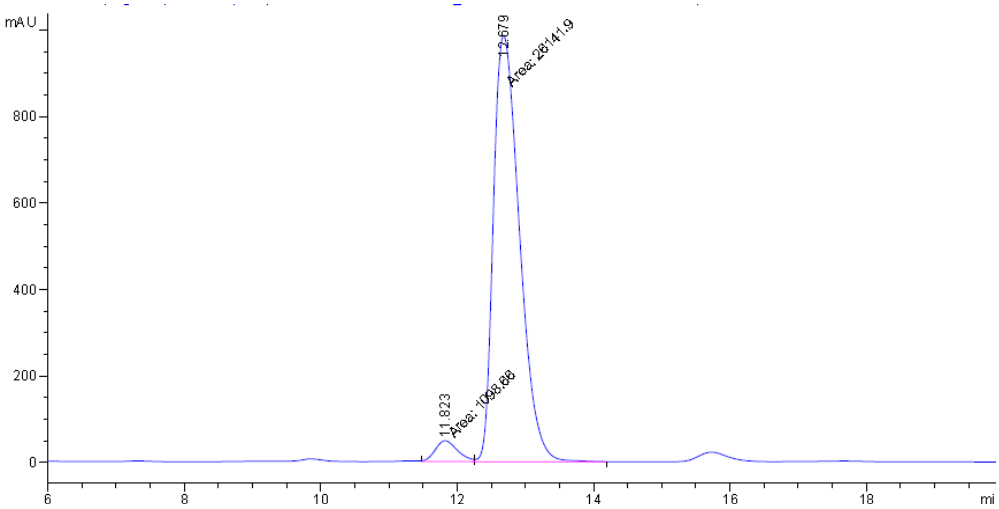

6.80
6.80
6.78
6.77
6.75
6.74
6.73
6.73
6.17
6.16
6.15
6.15
6.14
6.12
6.12
6.10
5.95
5.31
5.30
5.30
5.29
5.28
5.28
5.20
5.20
5.20
5.17
5.17
5.16
4.21
4.20
4.20
4.18
4.18
4.17
4.16
4.15
3.66
3.65
3.64
3.63
2.43
2.42
2.04
1.01
1.08
2.04
0.95
1.02
0.99
1.00
0.99
f1 (ppm)


148.0
146.8
135.1
133.6
128.1
125.9
123.6
121.4
121.3
119.7
108.6
108.5
101.2
73.6
73.4
73.1
72.9
49.8
f1 (ppm)


-75.96
-75.98
0
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

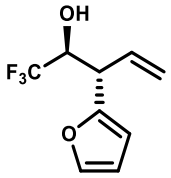


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.107	MM	0.5153	144.72284	4.68052	0.4684
2	11.816	MF	0.4204	1.50437e4	596.34747	48.6887
3	12.793	FM	0.4232	1.53757e4	605.56329	49.7634
4	15.885	MM	0.5463	333.54141	10.17532	1.0795



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.823	MF	0.3788	1098.65637	48.33823	4.0332
2	12.679	FM	0.4426	2.61419e4	984.48370	95.9668

(2S,3S)-1,1,1-trifluoro-3-(furan-2-yl)pent-4-en-2-ol (6.4i)



The title compound was prepared according to the general procedure using fluoral hydrate (75% in H_2O, 22 μL, 200 μmol) and 1-(furan-2-yl)allyl acetate (66.5 mg, 0.40 mmol, 200 mol%). Flash chromatography on silica (Hex/EtOAc 20:1) provided the title compound (25 mg, 120 μmol, *anti:syn* = >20:1) in 61% yield as a yellow oil.

TLC (SiO_2) R_f = 0.22 (hexanes/ethyl acetate = 9:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.38 (d, *J* = 1.2 Hz, 1H), 6.36 – 6.32 (m, 1H), 6.21 (d, *J* = 3.2 Hz, 1H), 6.14 – 6.04 (m, 1H), 5.36 (d, *J* = 10.2 Hz, 1H), 5.25 (d, *J* = 17.2 Hz, 1H), 4.40 (d, *J* = 5.4 Hz, 1H), 3.87 (dd, *J* = 8.3, 4.3 Hz, 1H), 2.50 (d, *J* = 5.4 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 143.30, 135.34, 133.52, 127.70, 126.83, 125.65, 123.39, 120.84, 71.43 (q, *J* = 30.0 Hz), 49.32.

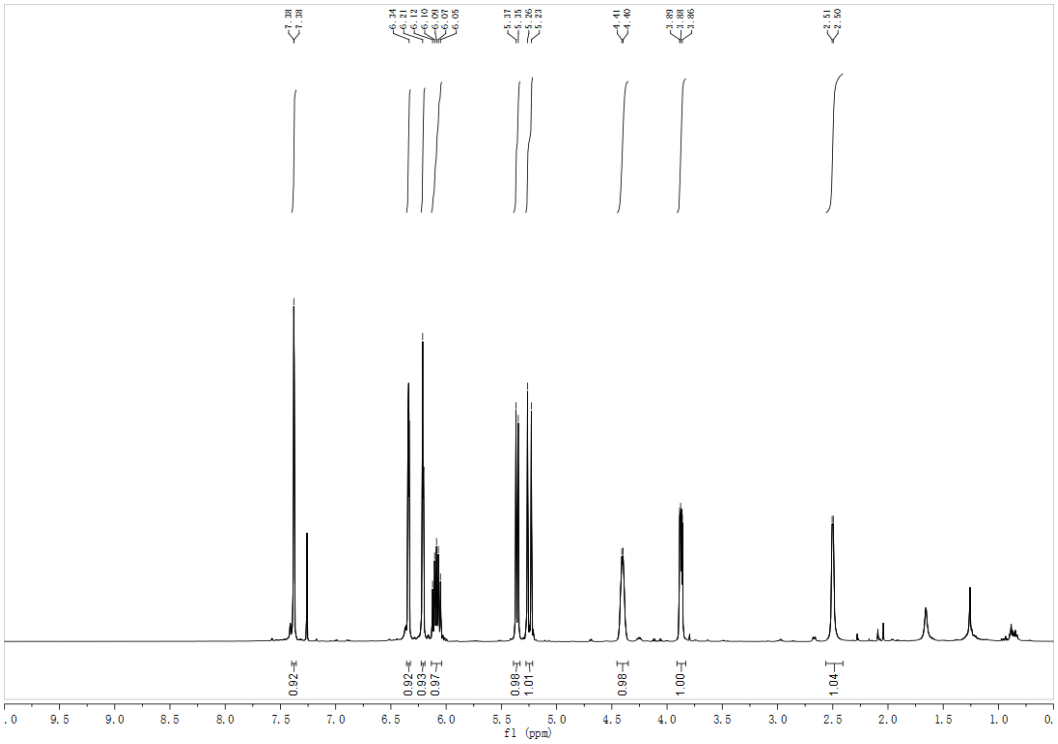
^{19}F NMR (471 MHz, $CDCl_3$): δ = -76.26 (d, *J* = 6.9 Hz).

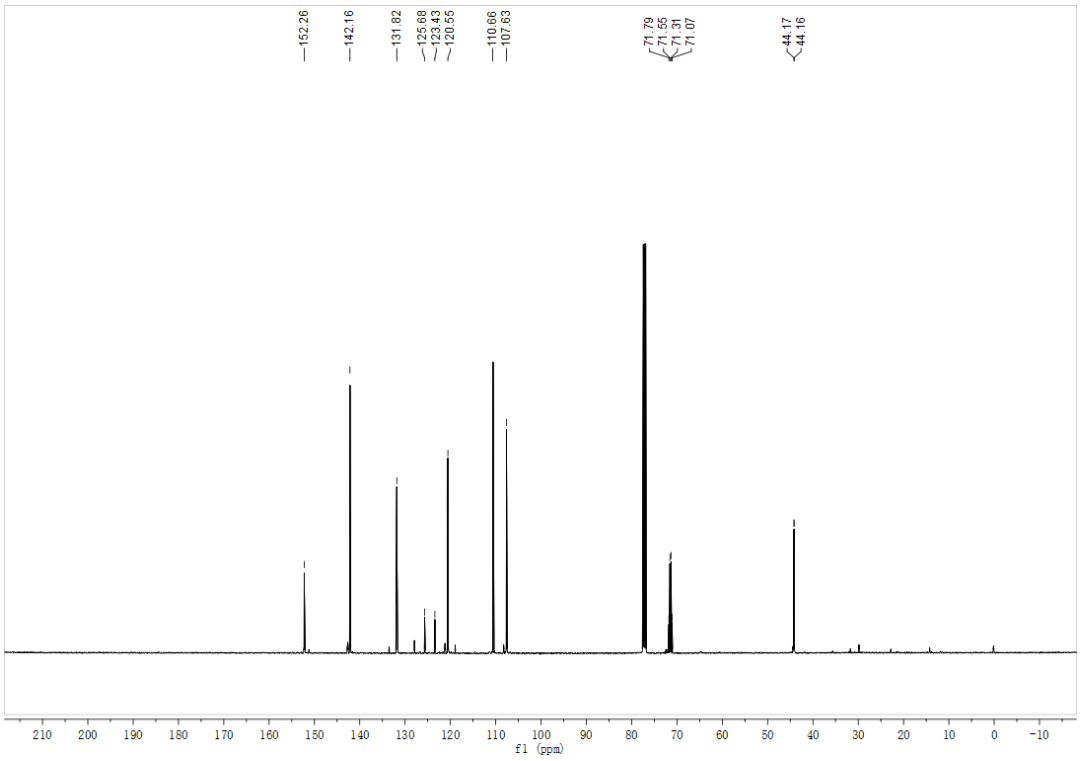
HRMS (CI) Calculated for $C_9H_9F_5O_2$ $[M]^+$ = 206.0555, Found 206.0554.

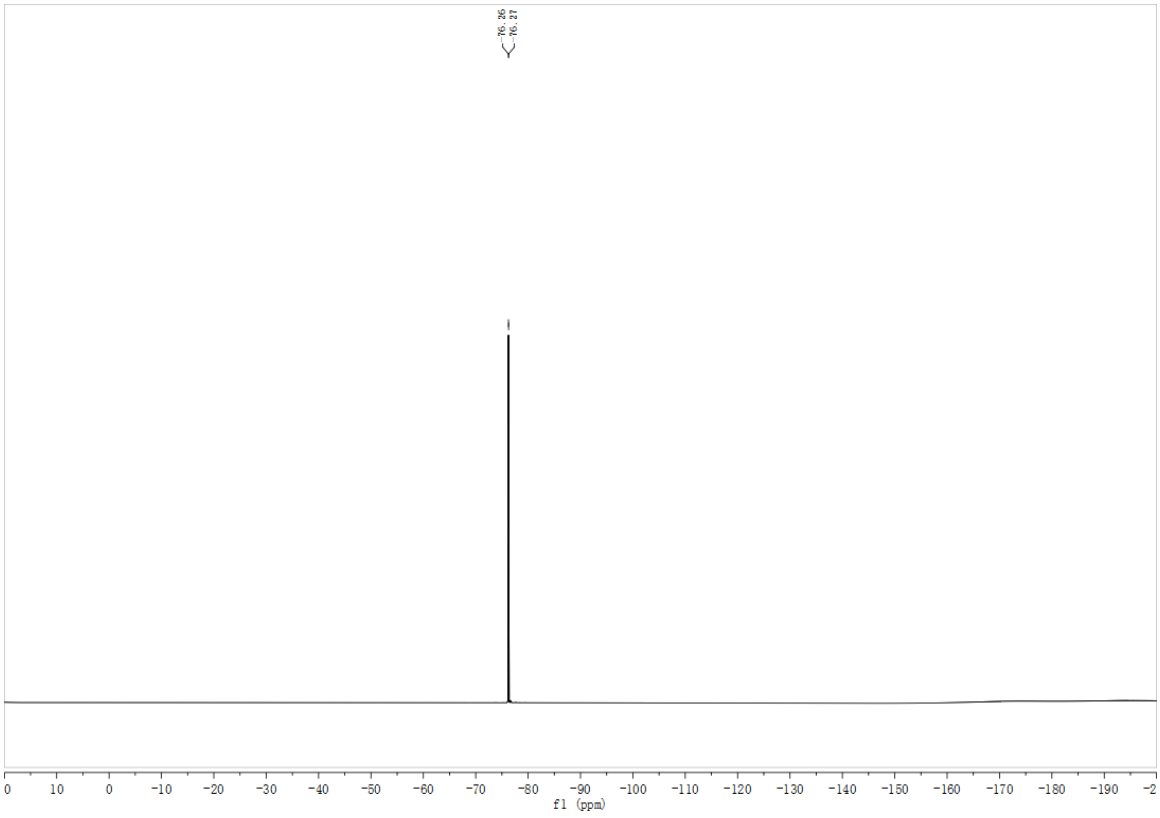
FTIR (neat) 3432, 2925, 1264, 1130, 895, 734, 703 cm^{-1}.

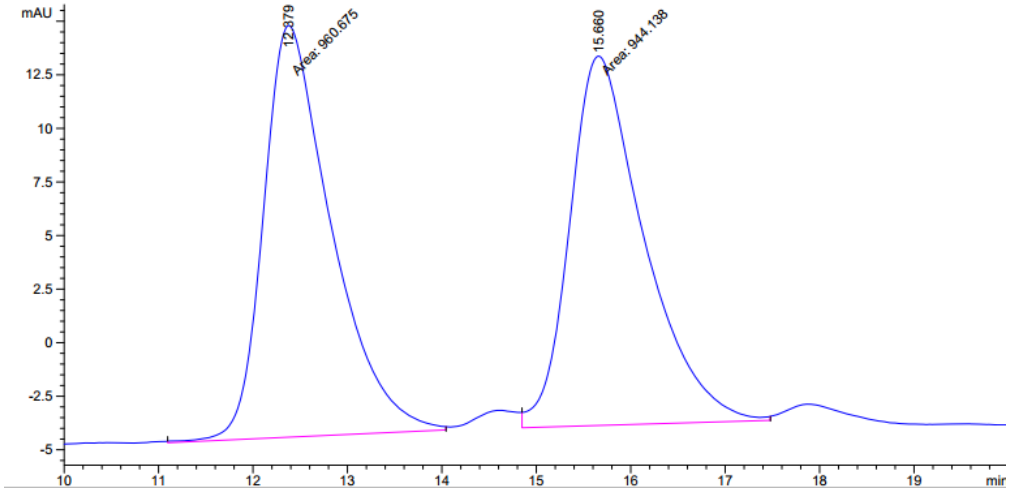
$[\alpha]_D^{33}$: –103 (*c* = 0.1, $CHCl_3$)

HPLC: (Chiralcel AD-H column, hexanes:*i*-PrOH = 99:1, 1.0 mL/min, 230 nm), *ee* = 94%.

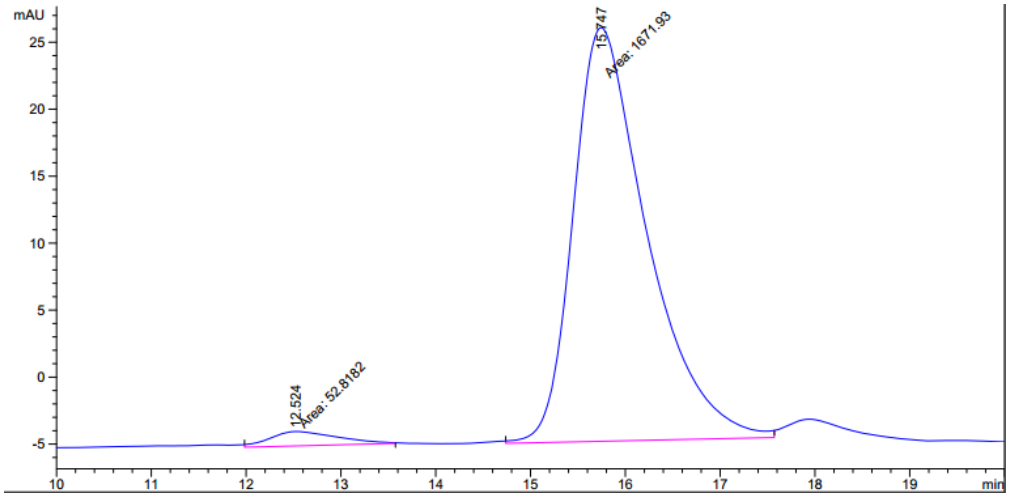

7.28
7.28
6.34
6.21
6.12
6.10
6.08
6.07
6.05
5.37
5.35
5.26
5.23
4.41
4.40
3.89
3.88
3.86
2.51
2.50
0.92
0.92
0.93
0.97
0.98
1.01
0.98
1.00
1.04
f1 (ppm)


152.26
142.16
131.82
125.68
123.43
120.55
110.66
107.63
71.79
71.55
71.31
71.07
44.17
44.16
f1 (ppm)


-76.26
-76.27
0
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-2
f1 (ppm)

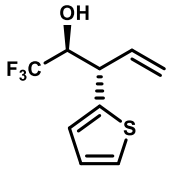


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.379	MM	0.8334	960.67517	19.21226	50.4341
2	15.660	FM	0.9129	944.13849	17.23668	49.5659



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.524	MM	0.8187	52.81821	1.07522	3.0624
2	15.747	MM	0.9024	1671.92981	30.88092	96.9376

(2*S*,3*S*)-1,1,1-trifluoro-3-(thiophen-2-yl)pent-4-en-2-ol (6.4j)



The title compound was prepared according to the general procedure using fluoral hydrate (75% in H_2O, 22 μL, 200 μmol) and 1-(thiophn-2-yl)allyl acetate (72.8 mg, 0.40 mmol, 200 mol%). Flash chromatography on silica (Hex/EtOAc 20:1) provided the title compound (36.2 mg, 164 μmol, *anti:syn* = >20:1) in 82% yield as a yellow oil.

TLC (SiO_2) R_f = 0.53 (hexanes/ethyl acetate = 4:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.24 (dd, *J* = 4.4, 2.0 Hz, 1H), 6.99 (d, *J* = 4.5 Hz, 2H), 6.21 – 6.09 (m, 1H), 5.34 (dt, *J* = 10.2, 0.9 Hz, 1H), 5.25 (dt, *J* = 17.1, 1.2 Hz, 1H), 4.29 (td, *J* = 6.9, 3.7 Hz, 1H), 4.09 (dd, *J* = 8.4, 3.7 Hz, 1H), 2.46 (d, *J* = 6.6 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 142.1, 133.9, 127.0, 125.5, 124.8, 124.5 (q, *J* = 283.3 Hz), 120.1, 73.5 (q, *J* = 29.9 Hz), 45.4.

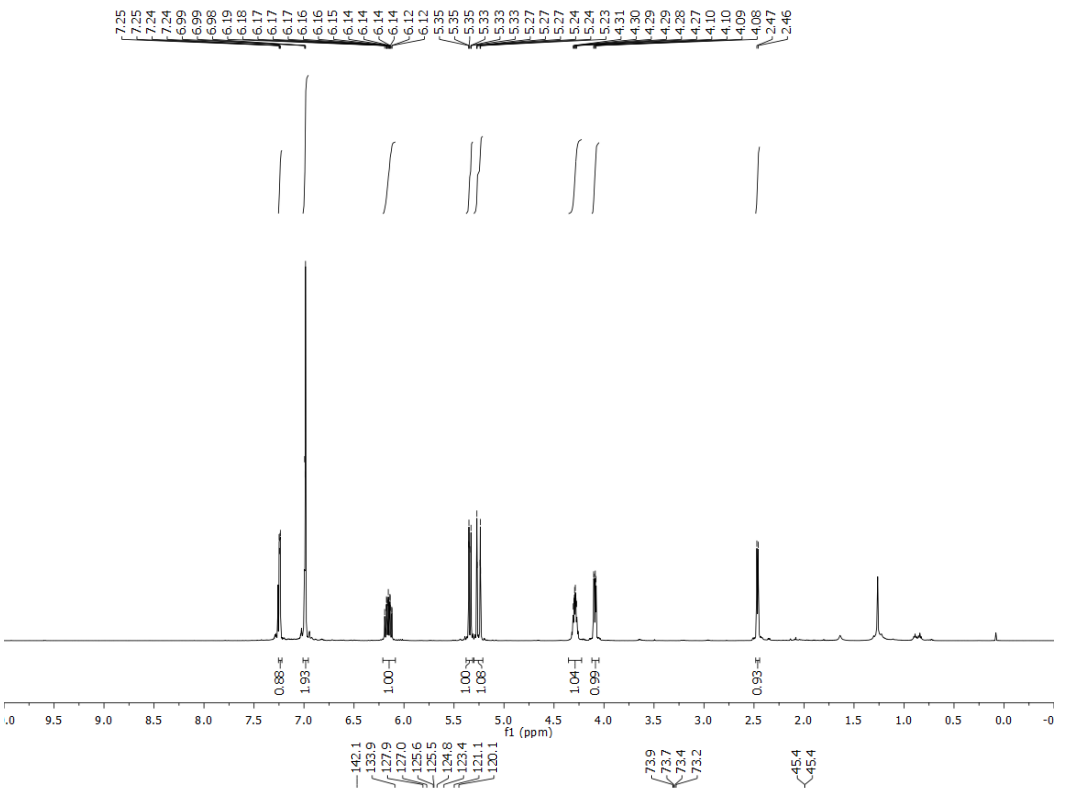
^{19}F NMR (471 MHz, $CDCl_3$): δ = -75.8 (d, *J* = 6.9 Hz).

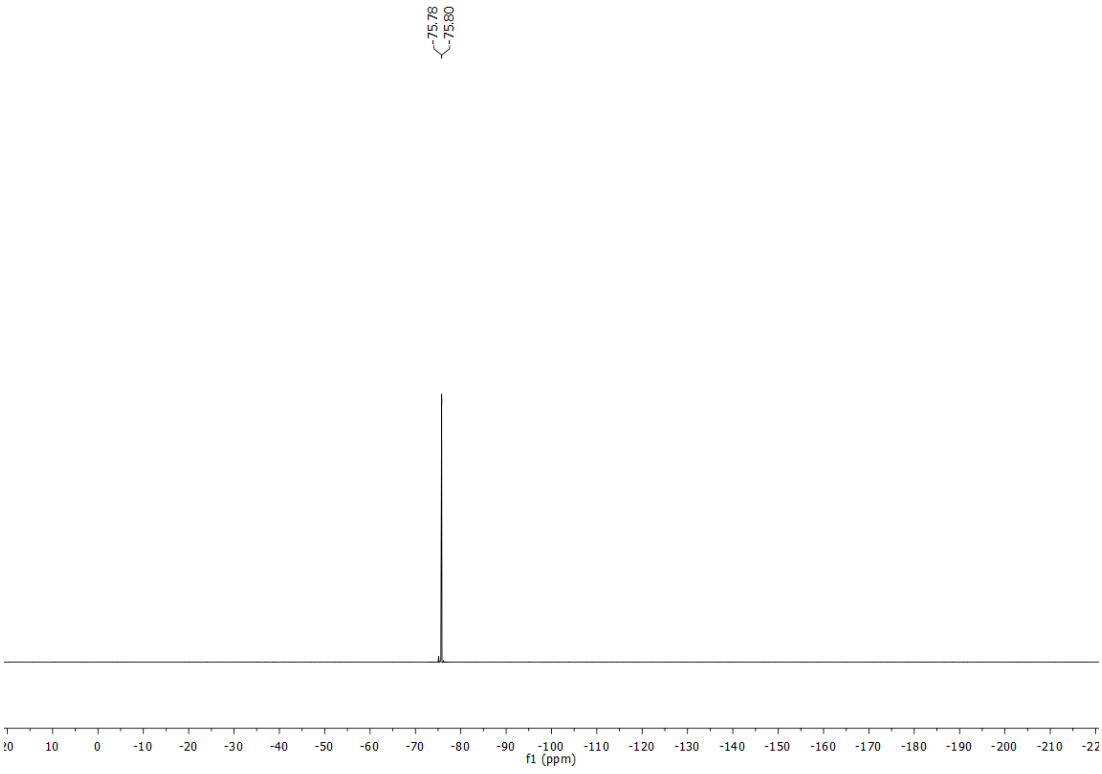
HRMS (CI) Calculated for $C_9H_9F_3OS$ $[M]^+$ = 222.0326, Found 222.0329.

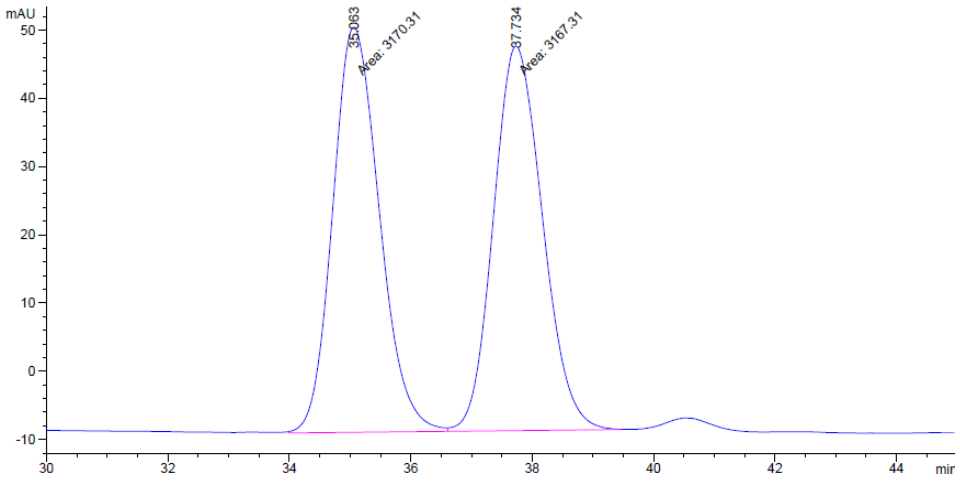
FTIR (neat) 3456, 2970, 2361, 1738, 1366, 1270, 1106, 927, 852, 695 cm^{-1}.

$[\alpha]_D^{33}$: –74.5 (*c* = 1.0, $CHCl_3$)

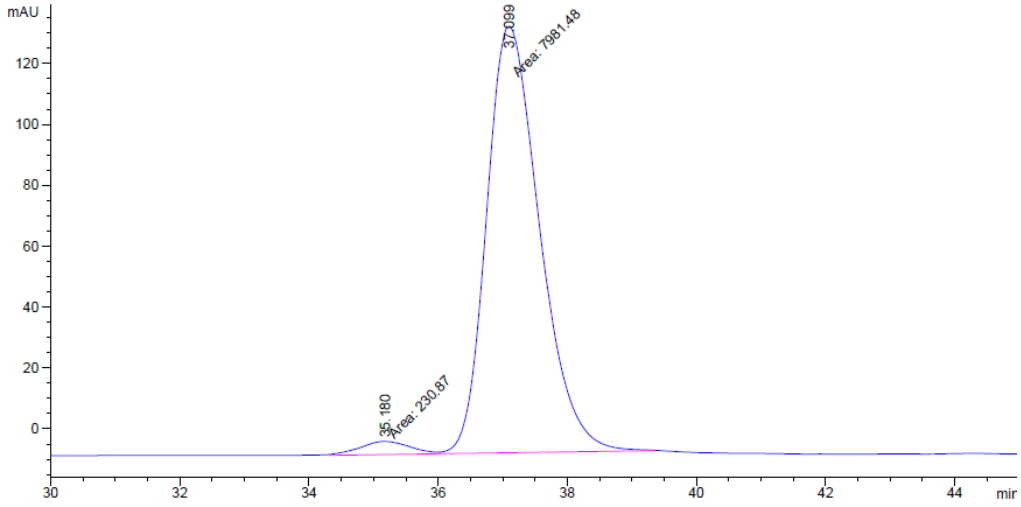
HPLC: (Chiralcel OJ-H column, hexanes:*i*-PrOH = 99:1, 1.0 mL/min, 230 nm), *ee* = 94%.


7.25
7.25
7.24
7.24
6.99
6.99
6.98
6.19
6.18
6.17
6.17
6.17
6.16
6.16
6.15
6.14
6.14
6.14
6.12
6.12
5.35
5.35
5.33
5.33
5.27
5.27
5.27
5.24
5.24
5.23
4.31
4.30
4.29
4.29
4.28
4.27
4.10
4.09
4.08
2.47
2.46
0.88
1.93
1.00
1.00
1.08
1.04
0.99
0.93
f1 (ppm)
142.1
133.9
127.9
127.0
125.6
125.5
124.8
123.4
121.1
120.1
73.9
73.7
73.4
73.2
45.4
45.4
f1 (ppm)


-75.78
-75.80
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)

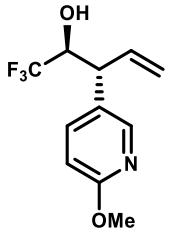


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	35.063	MF	0.8899	3170.31470	59.37821	50.0237
2	37.734	FM	0.9367	3167.30908	56.35373	49.9763



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	35.180	MF	0.6357	230.87035	4.27211	2.8113
2	37.099	FM	0.9494	7981.48096	140.11073	97.1887

(2S,3R)-1,1,1-trifluoro-3-(6-methoxypyridin-3-yl)pent-4-en-2-ol (6.4k)



The title compound was prepared according to the general procedure using fluoral hydrate (75% in H_2O, 22 μL, 200 μmol) and 1-(6-methoxypyridin-3-yl)allyl acetate (83 mg, 0.40 mmol, 200 mol%). Flash chromatography on silica (Hex/EtOAc 6:1) provided the title compound (42.8 mg, 173 μmol, *anti:syn* = >20:1) in 87% yield as a yellow oil.

TLC (SiO_2) R_f = 0.37 (hexanes/ethyl acetate = 3:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.04 (dt, *J* = 2.6, 0.6 Hz, 1H), 7.55 (dd, *J* = 8.6, 2.5 Hz, 1H), 6.72 (dd, *J* = 8.5, 0.7 Hz, 1H), 6.18 (dddd, *J* = 17.2, 10.2, 8.1, 0.9 Hz, 1H), 5.29 (dt, *J* = 10.3, 1.0 Hz, 1H), 5.15 (dt, *J* = 17.1, 1.2 Hz, 1H), 4.16 (h, *J* = 6.6 Hz, 1H), 3.89 (s, 3H), 3.68 (dd, *J* = 8.2, 4.8 Hz, 1H), 3.28 (d, *J* = 6.3 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.5, 146.2, 138.8, 134.6, 128.5, 124.8 (d, *J* = 283.5 Hz), 119.8, 111.0, 73.0 (q, *J* = 29.4 Hz), 53.7, 46.8.

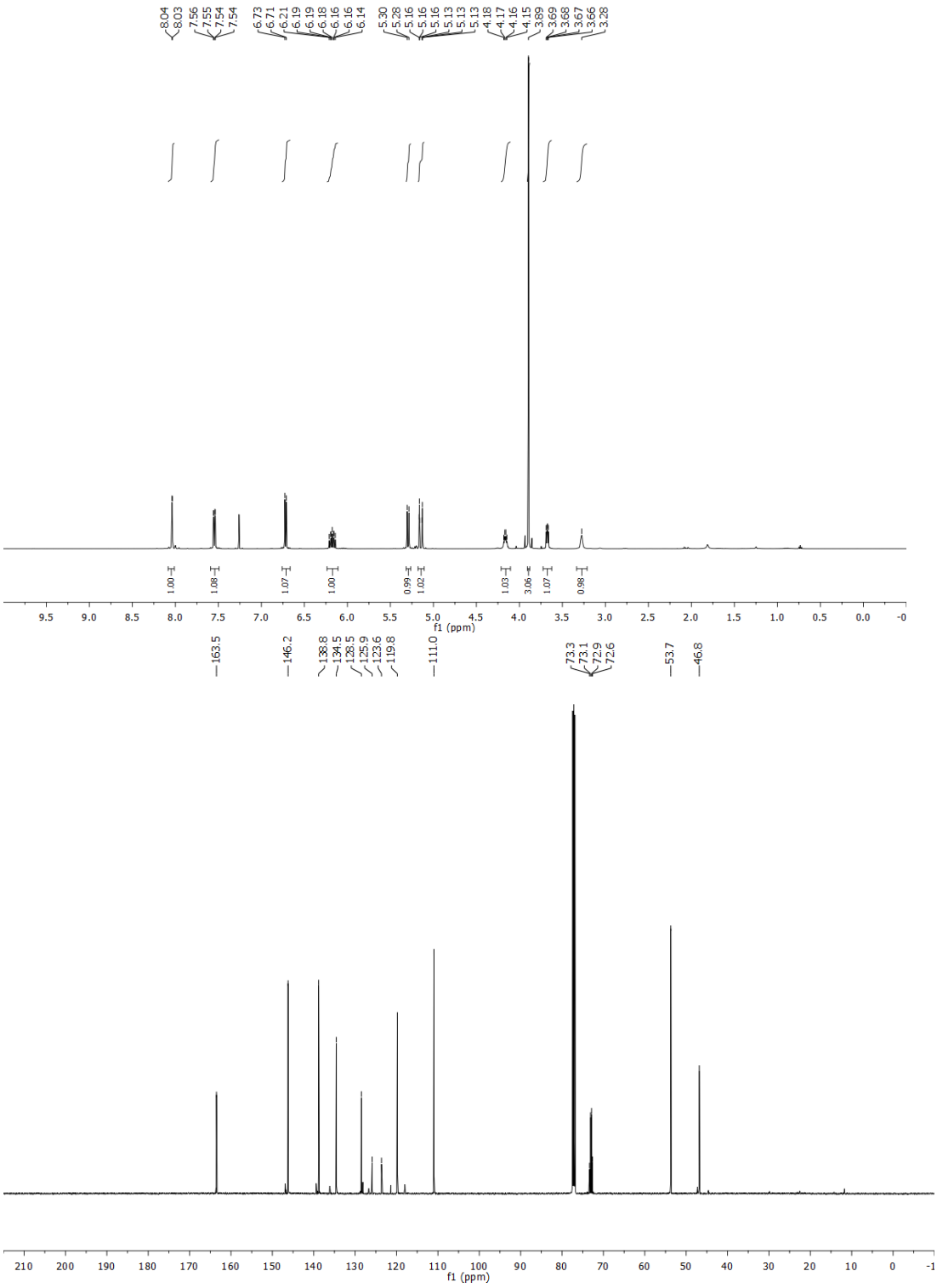
^{19}F NMR (471 MHz, $CDCl_3$): δ = –75.8 (d, *J* = 6.9 Hz)

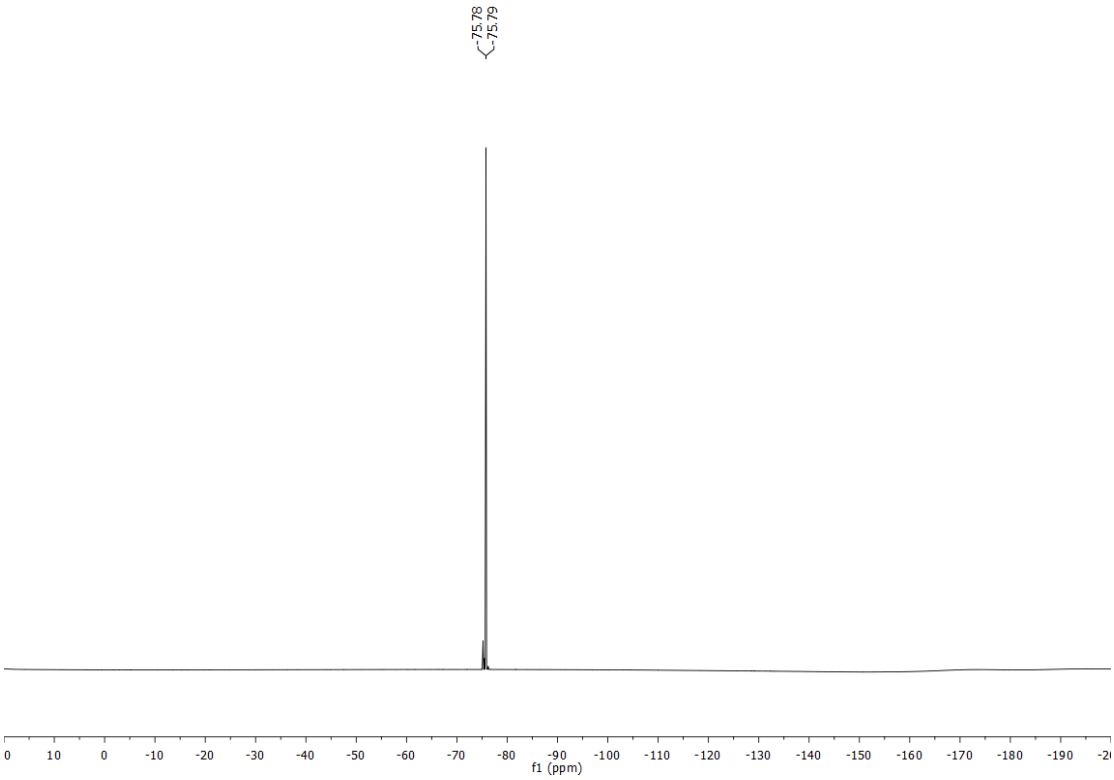
HRMS (CI) Calculated for $C_{11}H_{13}F_3NO_2$ $[M+H]^+$ = 248.0898, Found 248.0897.

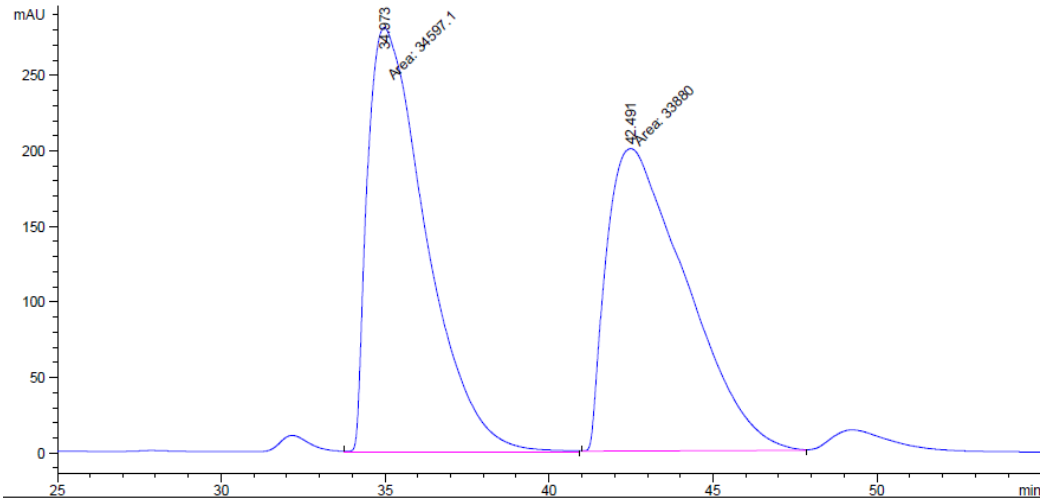
FTIR (neat) 3450, 2951, 1608, 1495, 1395, 1271, 1163, 1128, 1029, 927, 831, 693 cm^{-1}.

$[\alpha]_D^{33}$: –67.3 (*c* = 1.0, $CHCl_3$)

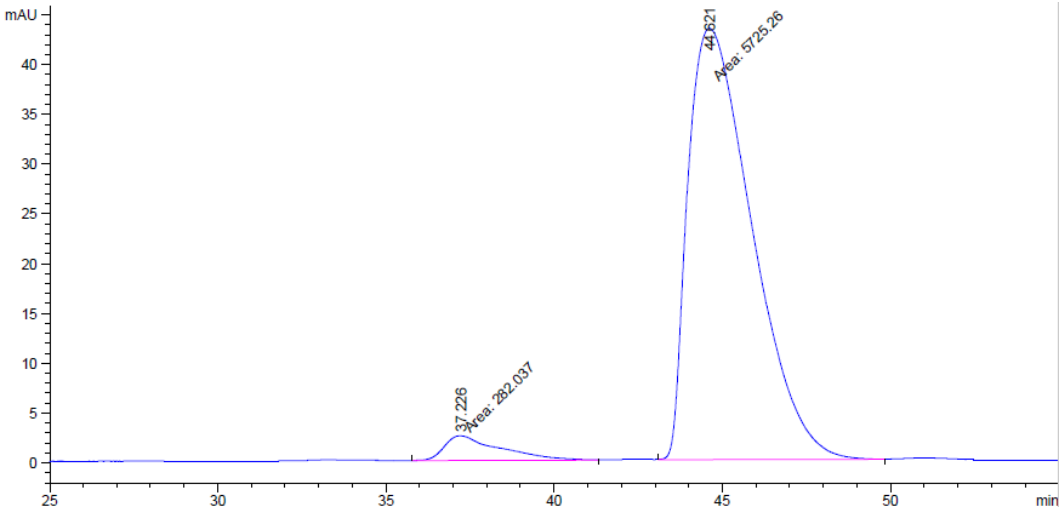
HPLC: (Chiralcel AS-H column, hexanes:*i*-PrOH = 99:1, 1.0 mL/min, 280 nm), *ee* = 91%.


8.04
8.03
7.56
7.55
7.54
7.54
6.73
6.71
6.21
6.19
6.18
6.16
6.16
6.14
5.30
5.28
5.16
5.16
5.13
5.13
5.13
4.18
4.17
4.16
4.15
3.89
3.69
3.68
3.67
3.66
3.28
1.00
1.08
1.07
1.00
0.99
1.02
1.03
3.06
1.07
0.88
f1 (ppm)
163.5
146.2
138.8
134.5
128.5
125.9
123.6
119.8
111.0
73.3
73.1
72.9
72.6
53.7
46.8
f1 (ppm)


75.78
75.79
0
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

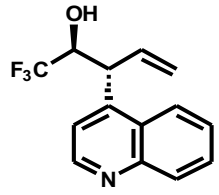


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	34.973	MM	2.0553	3.45971e4	280.54898	50.5236
2	42.491	MM	2.8224	3.38800e4	200.06589	49.4764



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	37.226	MM	1.9009	282.03705	2.47284	4.6949
2	44.621	MM	2.2037	5725.26025	43.30132	95.3051

(2*S*,3*R*)-1,1,1-trifluoro-3-(quinolin-4-yl)pent-4-en-2-ol (6.4l)



The title compound was prepared according to the general procedure using fluoral hydrate (75% in H_2O, 22 μL, 200 μmol) and 1-(quinolin-4-yl)allyl acetate (91 mg, 0.40 mmol, 200 mol%). Flash chromatography on silica (Hex/EtOAc 3:1 → 1:1) provided the title compound (44.7 mg, 168 μmol, *anti:syn* = >20:1) in 84% yield as a light yellow solid.

TLC (SiO_2) R_f = 0.21 (hexanes/ethyl acetate = 1:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.4 (d, *J* = 4.6 Hz, 1H), 7.9 – 7.9 (m, 1H), 7.6 – 7.5 (m, 1H), 7.5 – 7.4 (m, 2H), 7.4 (d, *J* = 4.6 Hz, 1H), 6.8 (s, 1H), 6.6 (dd, *J* = 17.7, 9.1 Hz, 1H), 5.4 (dd, *J* = 10.3, 1.1 Hz, 1H), 5.2 (dt, *J* = 17.3, 1.0 Hz, 1H), 4.6 (dd, *J* = 8.6, 2.4 Hz, 1H), 4.4 (dd, *J* = 7.1, 2.5 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 149.4, 147.9, 147.2, 132.8, 129.7, 129.1, 127.3, 125.8, 125.1 (q, *J* = 283.4 Hz), 122.4, 121.1, 120.3, 71.8 (q, *J* = 29.9 Hz), 44.3.

^{19}F NMR (471 MHz, $CDCl_3$): δ = –75.7 (d, *J* = 7.0 Hz).

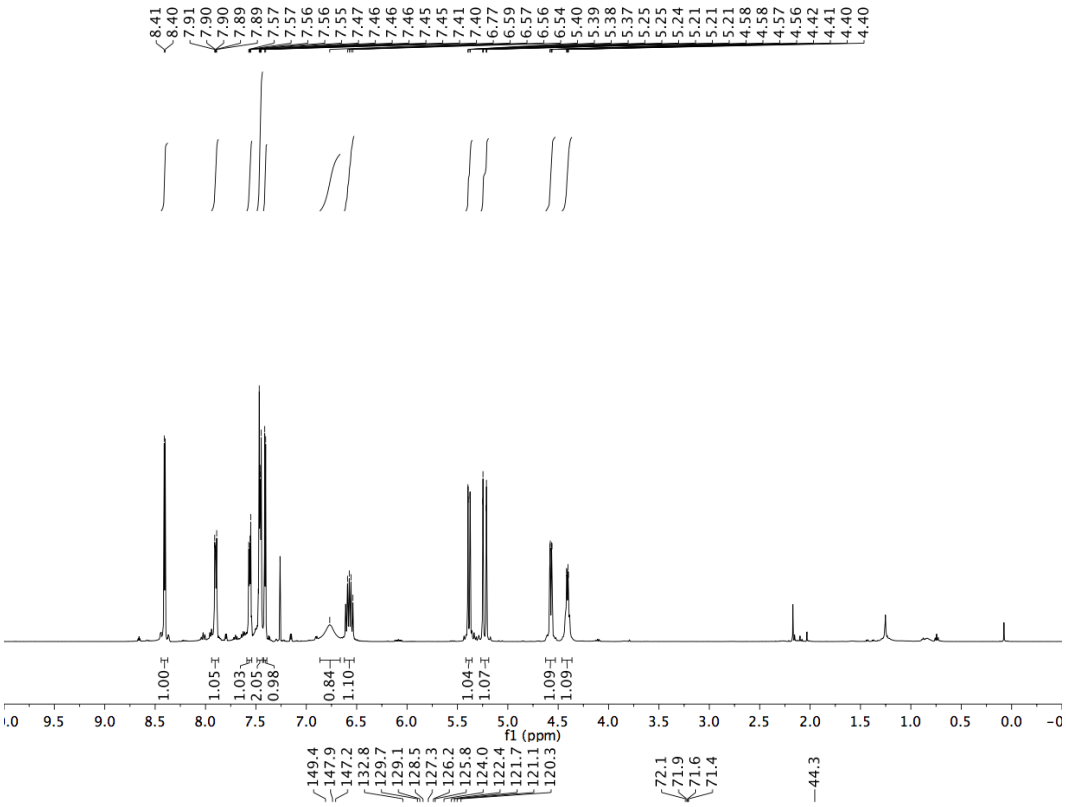
HRMS (ESI) Calculated for $C_{14}H_{12}F_3NO$ $[M+H]^+$ = 268.0944, Found 268.0947.

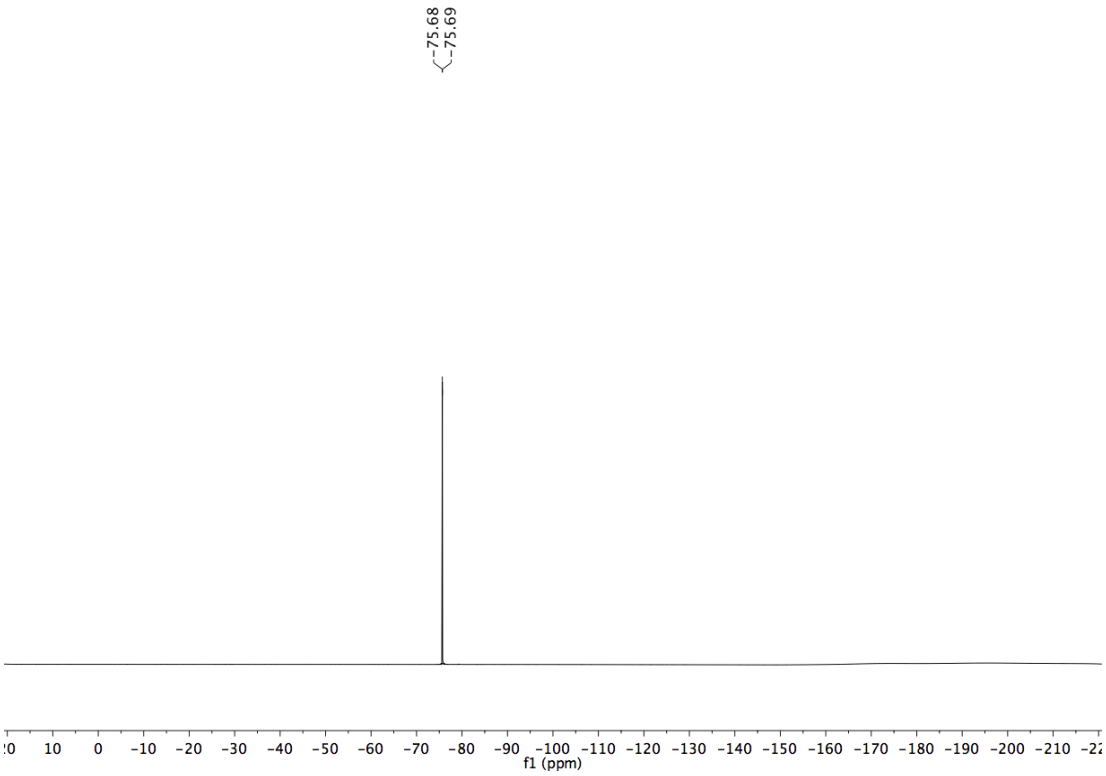
FTIR (neat) 3083, 2920, 2761, 1592, 1282, 1145, 1108, 980, 773 cm^{-1}.

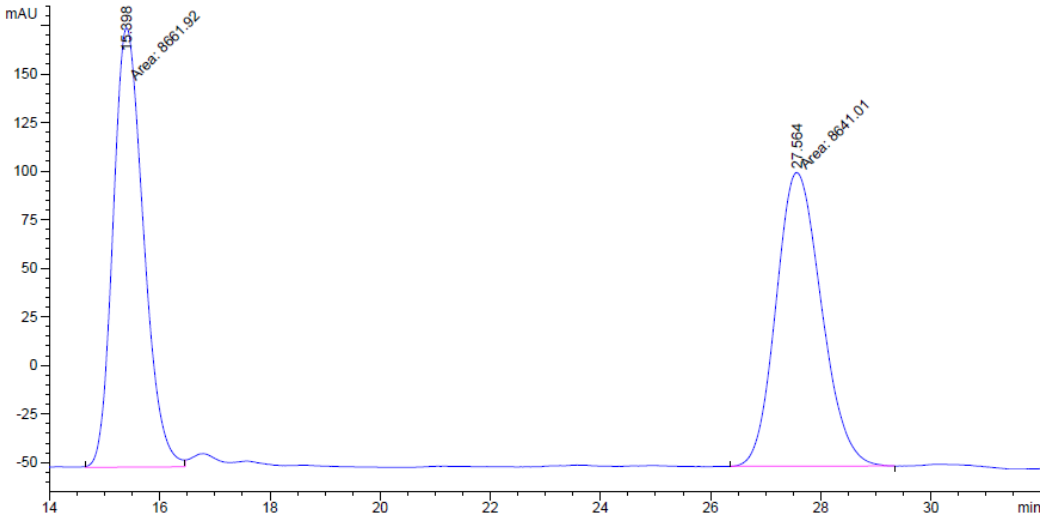
$[\alpha]_D^{33}$: –14.5 (*c* = 1.0, $CHCl_3$)

MP: 146˚C.

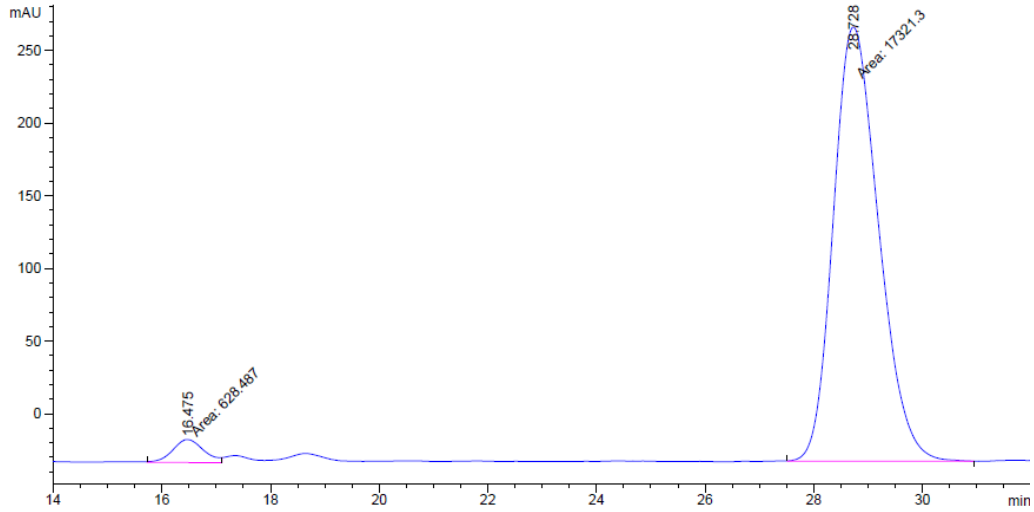
HPLC: (Chiralcel OD-H column, hexanes:*i*-PrOH = 95:5, 1.0 mL/min, 210 nm), *ee* = 93%.


8.41
8.40
7.91
7.90
7.90
7.89
7.89
7.57
7.57
7.56
7.56
7.55
7.47
7.46
7.46
7.46
7.45
7.45
7.41
7.40
6.77
6.59
6.57
6.56
6.54
5.40
5.39
5.38
5.37
5.25
5.24
5.21
5.21
5.21
4.58
4.58
4.57
4.56
4.42
4.41
4.40
4.40
1.00
1.05
1.03
2.05
0.98
0.84
1.10
1.04
1.07
1.09
1.09
f1 (ppm)
149.4
147.9
147.2
132.8
129.7
129.1
128.5
127.3
126.2
125.8
124.0
122.4
121.7
121.1
120.3
72.1
71.9
71.6
71.4
44.3
f1 (ppm)


-75.68
-75.69
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.398	MM	0.6387	8661.92383	226.02888	50.0604
2	27.564	MM	0.9531	8641.00684	151.09846	49.9396

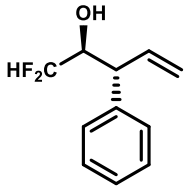


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.475	MM	0.6617	628.48694	15.82979	3.5014
2	28.728	MM	0.9663	1.73213e4	298.74704	96.4986

General Procedure and Spectral Data for Iridium Catalyzed *anti*-(α-Aryl)Allylation of Difluoroacetaldehyde Ethyl Hemiacetal 1j to form Products 6.5a-6.5l

A pressure tube was equipped with a magnetic stir bar and charged with preformed iridium catalyst (10.7 mg, 10 μmol, 5 mol%), K_2CO_3 (27.6 mg, 0.20 mmol, 100 mol%), allyl donor (0.40 mmol, 200 mol%) and 5A molecular sieves (28 mg, 100 wt%). The pressure tube was purged with argon. Anhydrous THF (1.0 mL, 0.2 M), 2-propanol (31 μL, 0.40 mmol, 200 mol%), and difluoroacetaldehyde ethyl hemiacetal (90% in EtOH, 28 mg, 200 μmol, 100 mol%) were added via syringe. The sealed reaction vessel was stirred at 100 °C. After 24 h the solvent was removed *in vacuo* and the residue was subjected to flash column chromatography on silica.

(2S,3R)-1,1-difluoro-3-phenylpent-4-en-2-ol (6.5a)



The title compound was prepared according to the general procedure using difluoroacetaldehyde ethyl hemiacetal (90%, 28 mg, 200 μmol) and 1-phenylallyl acetate (71 mg, 0.40 mmol, 200 mol%). Flash chromatography on silica (Hex/EtOAc 20:1 → 10:1) provided the title compound (31.5 mg, 159 μmol, *anti:syn* = >20:1) in 80% yield as a yellow oil.

TLC (SiO_2) R_f = 0.53 (hexanes/ethyl acetate = 3:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.37–7.34 (m, 2H), 7.29–7.28 (m, 3H), 6.20 (dt, *J* = 17.8, 9.5 Hz, 1H), 5.54 (td, *J* = 55.6, 3.7 Hz, 1H), 5.29 (d, *J* = 10.2 Hz, 1H), 5.23 (d, *J* = 17.2 Hz, 1H), 4.10 – 3.91 (m, 1H), 3.61 – 3.55 (m, 1H), 2.13 (s, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 139.6, 136.0, 129.1, 128.2, 127.5, 118.9, 115.2 (t, *J* = 243.2 Hz), 73.8 (dd, *J* = 23.1, 20.9 Hz), 51.0 (t, *J* = 3.6 Hz).

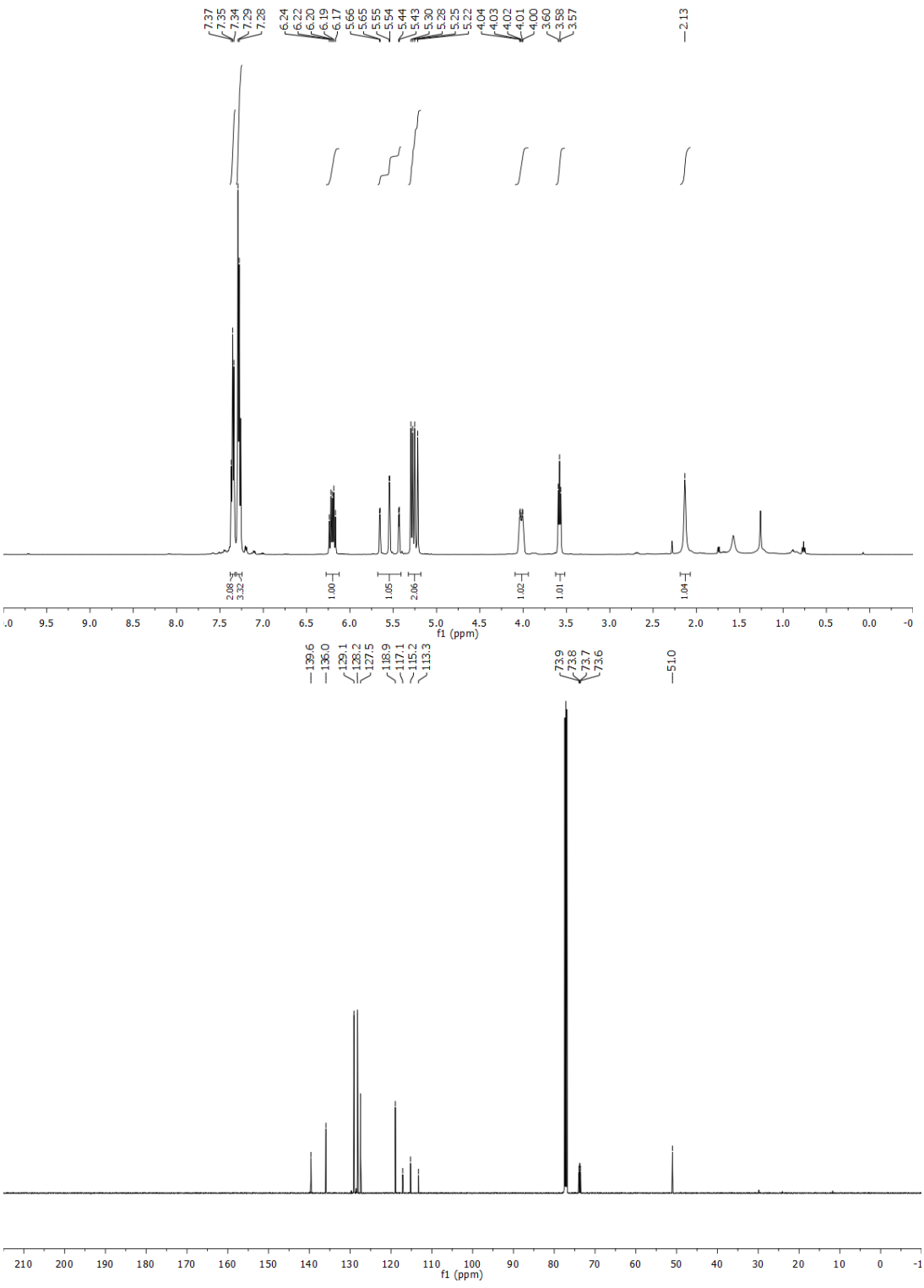
^{19}F NMR (471 MHz, $CDCl_3$): δ = -129.2 (ddd, *J* = 286.4, 54.9, 6.0 Hz), -134.4 (ddd, *J* = 286.4, 56.0, 15.7 Hz).

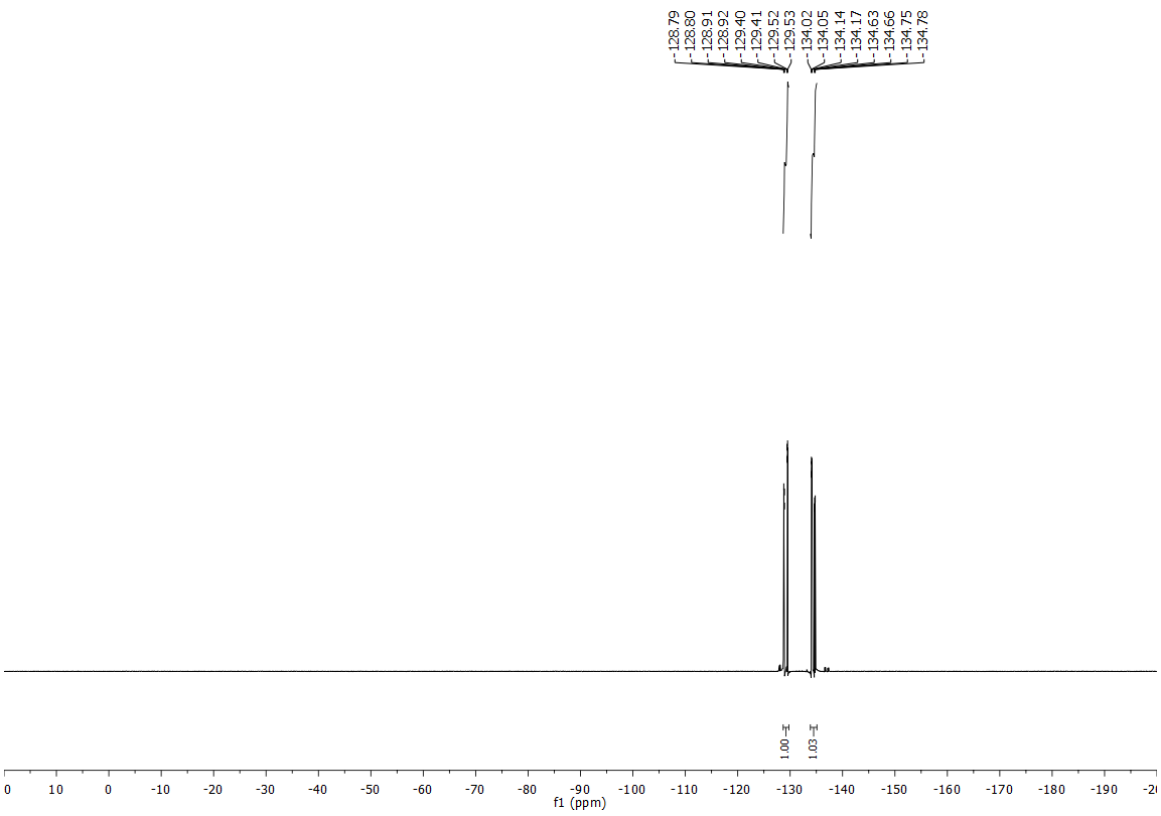
HRMS (CI) Calculated for $C_{11}H_{12}F_2O$ $[M]^+$ = 198.0856, Found 198.0852.

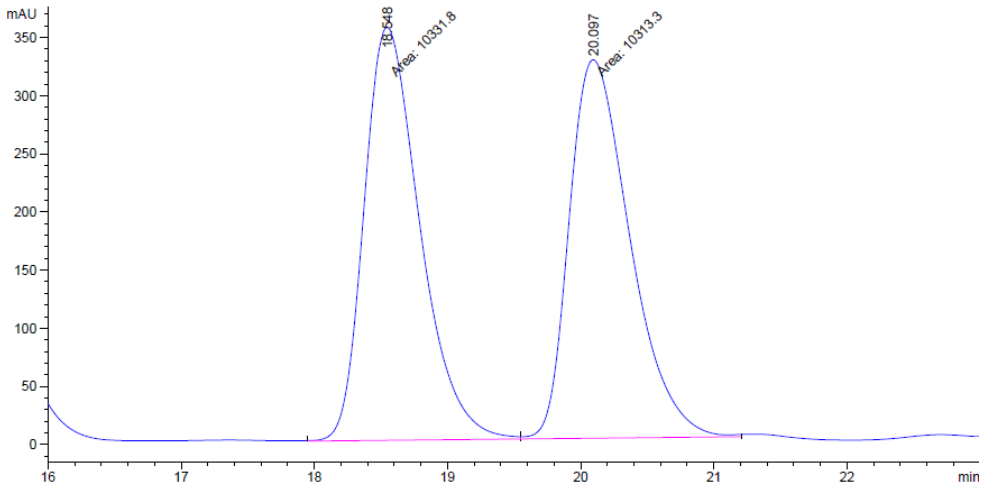
FTIR (neat) 3442, 3030, 2984, 2926, 1493, 1455, 1150, 1057, 926, 758, 701 cm^{-1}.

$[\alpha]_D^{33}$: –78.3 (*c* = 1.0, $CHCl_3$)

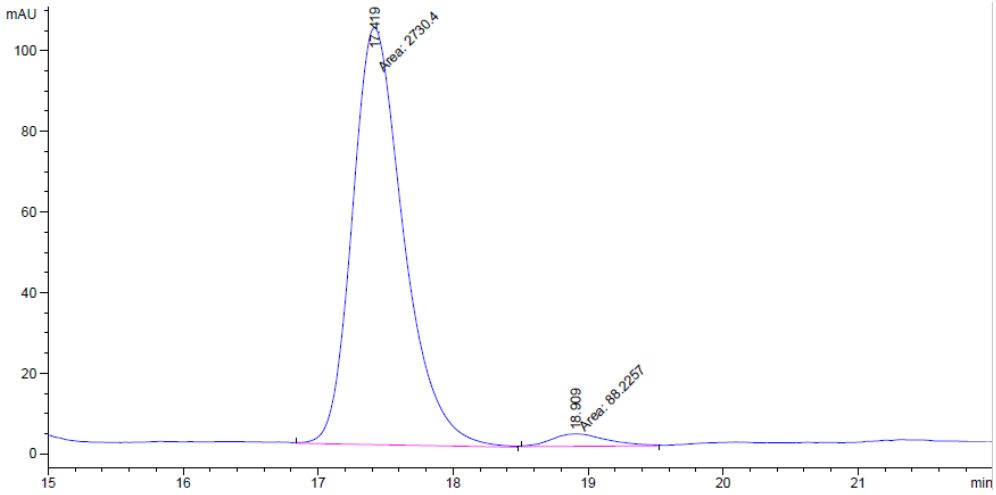
HPLC: (Chiralcel AS-H column, hexanes:*i*-PrOH = 99:1, 1.0 mL/min, 210 nm), *ee* = 94%.


7.37
7.35
7.34
7.29
7.28
6.24
6.22
6.20
6.19
6.17
5.66
5.65
5.55
5.54
5.44
5.43
5.30
5.28
5.25
5.22
4.04
4.03
4.02
4.01
4.00
3.60
3.58
3.57
2.13
2.08
3.32
1.00
1.05
2.06
1.02
1.01
1.04
f1 (ppm)
139.6
136.0
129.1
128.2
127.5
118.9
117.1
115.2
113.3
73.9
73.8
73.7
73.6
51.0
f1 (ppm)


128.79
128.80
128.91
128.92
129.40
129.41
129.52
129.53
134.02
134.05
134.14
134.17
134.63
134.66
134.75
134.78
1.00
1.03
0
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

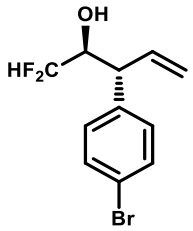


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.548	MF	0.4847	1.03318e4	355.27246	50.0450
2	20.097	FM	0.5282	1.03133e4	325.42999	49.9550



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.419	MM	0.4398	2730.39600	103.46590	96.8699
2	18.909	MM	0.4780	88.22573	3.07628	3.1301

(2*S*,3*R*)-3-(4-Bromophenyl)-1,1-difluoropent-4-en-2-ol (6.5b)



The title compound was prepared according to the general procedure using difluoroacetaldehyde ethyl hemiacetal (90%, 28 mg, 200 μmol) and 1-(4-bromophenyl)allyl acetate (102 mg, 0.40 mmol, 200 mol%). Flash chromatography on silica (Hex/EtOAc 20:1) provided the title compound (46.6 mg, 168 μmol, *anti:syn* = >20:1) in 84% yield as a yellow oil.

TLC (SiO_2) R_f = 0.17 (hexanes/ethyl acetate = 10:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.50–7.45 (m, 2H), 7.20–7.16 (m, 2H), 6.16 (ddd, *J* = 17.1, 10.2, 8.7 Hz, 1H), 5.56 (ddd, *J* = 56.2, 54.9, 4.3 Hz, 1H), 5.29 (dd, *J* = 10.2, 1.3 Hz, 1H), 5.22 (dt, *J* = 17.1, 1.3 Hz, 1H), 4.03–3.92 (m, 1H), 3.55 (dd, *J* = 8.7, 5.8 Hz, 1H), 2.20 (d, *J* = 4.5 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.8, 135.2, 132.1, 130.0, 121.3, 119.4, 115.2 (t, *J* = 243.6 Hz), 73.5 (dd, *J* = 23.7, 21.3 Hz), 50.1 (dd, *J* = 4.0, 3.1 Hz).

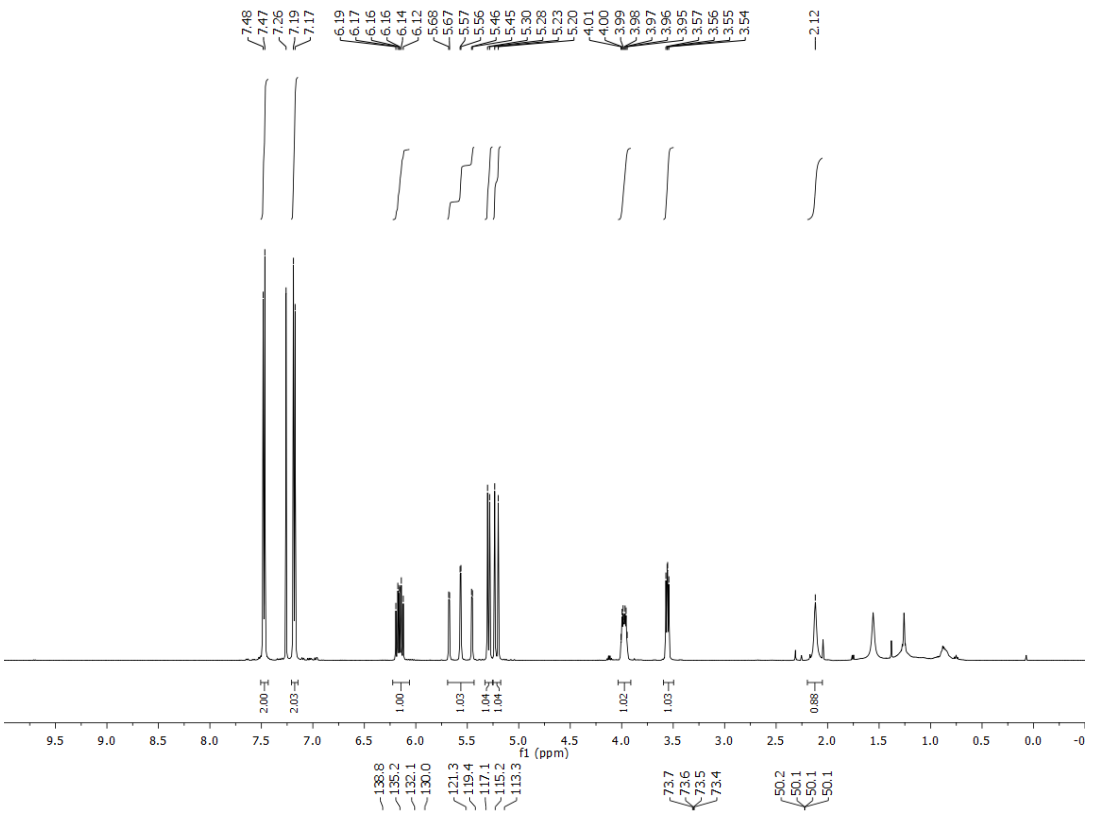
^{19}F NMR (471 MHz, $CDCl_3$): δ = –129.1 (ddd, *J* = 286.5, 55.0, 6.2 Hz), –133.5 (ddd, *J* = 287.6, 56.1, 14.7 Hz).

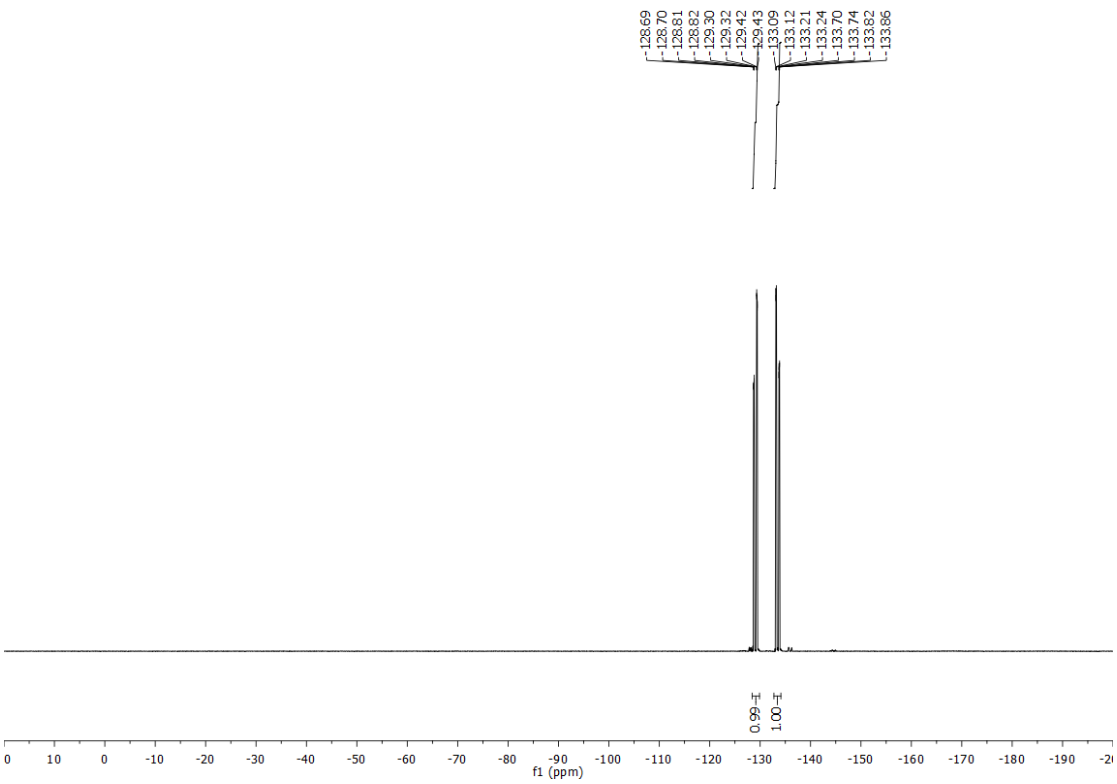
HRMS (CI) Calculated for $C_{11}H_{11}{}^{79}BrF_2O$ $[M]^+$ = 275.9961, Found 275.9954.

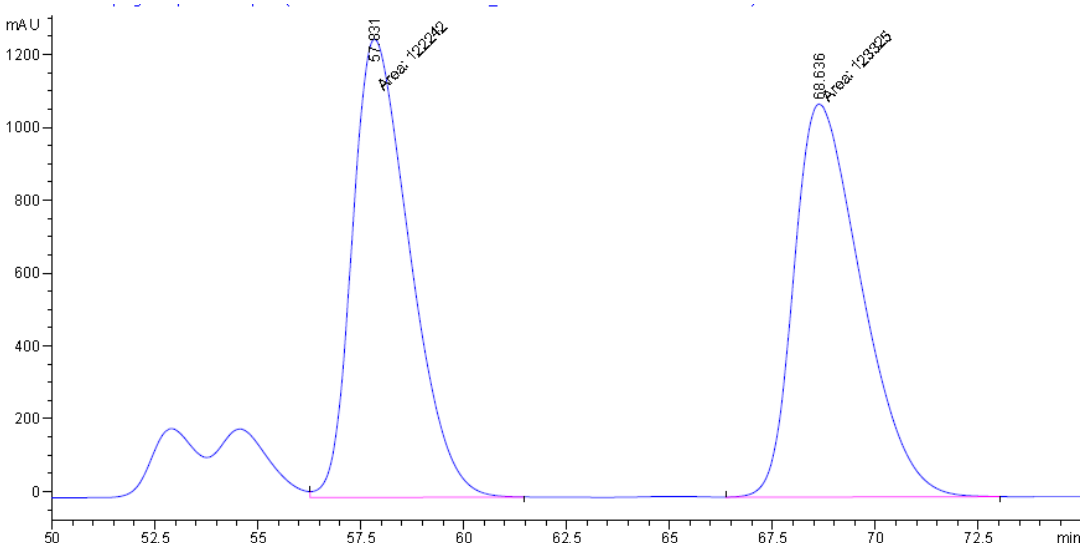
FTIR (neat) 3411, 2982, 2924, 1489, 1150, 1129, 1070, 1011, 929, 821, 760 cm^{-1}.

$[\alpha]_D^{33}$: –72.0 (*c* = 1.0, $CHCl_3$)

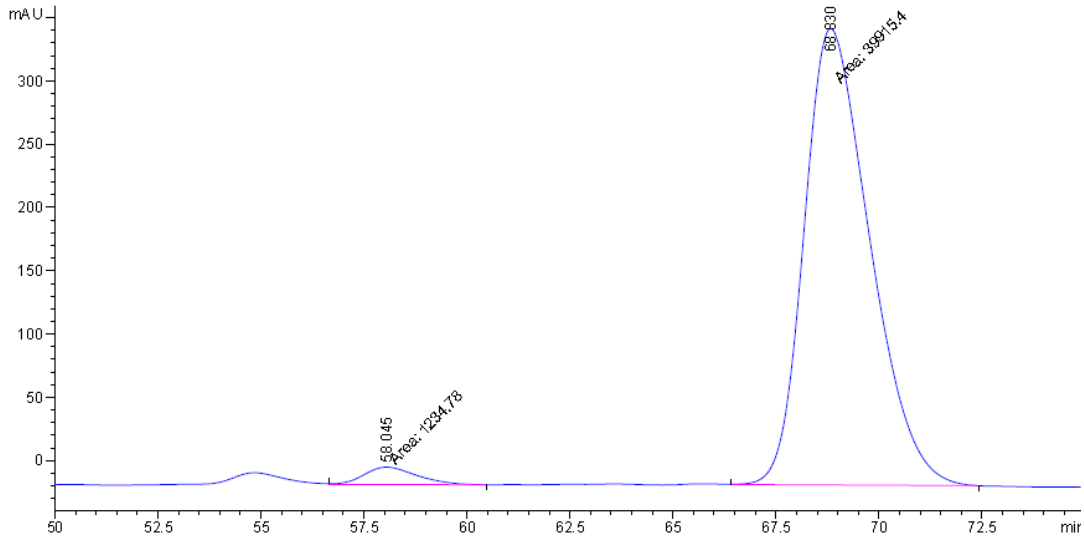
HPLC: (Chiralcel AD-H column, hexanes:*i*-PrOH = 99:1, 0.5 mL/min, 210 nm), *ee* = 94%.


7.48
7.47
7.26
7.19
7.17
6.19
6.17
6.16
6.16
6.14
6.12
5.68
5.67
5.57
5.56
5.46
5.45
5.30
5.28
5.23
5.20
4.01
4.00
3.99
3.98
3.97
3.96
3.95
3.57
3.56
3.55
3.54
2.12
2.00
2.03
1.00
1.03
1.04
1.04
1.02
1.03
0.88
f1 (ppm)
138.8
135.2
132.1
130.0
121.3
119.4
117.1
115.2
113.3
73.7
73.6
73.5
73.4
50.2
50.1
50.1
50.1
f1 (ppm)


-128.69
-128.70
-128.81
-128.82
-129.30
-129.32
-129.42
-129.43
-133.09
-133.12
-133.21
-133.24
-133.70
-133.74
-133.82
-133.86
0.99
1.00
0
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

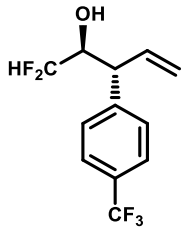


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	57.831	FM	1.6192	1.22242e5	1258.27502	49.7795
2	68.636	MM	1.9040	1.23325e5	1079.52051	50.2205



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	58.045	FM	1.4910	1234.77869	13.80225	3.0007
2	68.830	MM	1.8454	3.99154e4	360.48853	96.9993

(2*S*,3*R*)-1,1-Difluoro-3-(4-(trifluoromethyl)phenyl)pent-4-en-2-ol (6.5c)



The title compound was prepared according to the general procedure using difluoroacetaldehyde ethyl hemiacetal (90%, 28 mg, 200 μmol) and 1-(4-(trifluoromethyl)phenyl)allyl acetate (98 mg, 0.40 mmol, 200 mol%). Flash chromatography on silica (Hex/EtOAc 10:1) provided the title compound (43.7 mg, 164 μmol, *anti:syn* = >20:1) in 82% yield as a yellow oil.

TLC (SiO_2) R_f = 0.09 (hexanes/ethyl acetate = 10:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.63–7.59 (m, 2H), 7.46–7.42 (m, 2H), 6.20 (ddd, *J* = 17.1, 10.2, 8.8 Hz, 1H), 5.59 (ddd, *J* = 56.3, 55.0, 4.5 Hz, 1H), 5.33 (dd, *J* = 10.2, 1.2 Hz, 1H), 5.24 (dt, *J* = 17.1, 1.1 Hz, 1H), 4.02 (ddq, *J* = 14.1, 6.2, 4.6 Hz, 1H), 3.67 (dd, *J* = 8.8, 5.3 Hz, 1H), 2.20 (d, *J* = 4.6 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 144.0, 134.8, 129.7 (q, *J* = 32.5 Hz), 128.7, 125.9 (q, *J* = 3.7 Hz), 124.2 (q, *J* = 272.1 Hz), 119.8, 115.2 (t, *J* = 243.7 Hz), 73.5 (dd, *J* = 24.3, 21.6 Hz), 50.4 (dd, *J* = 4.6, 2.6 Hz).

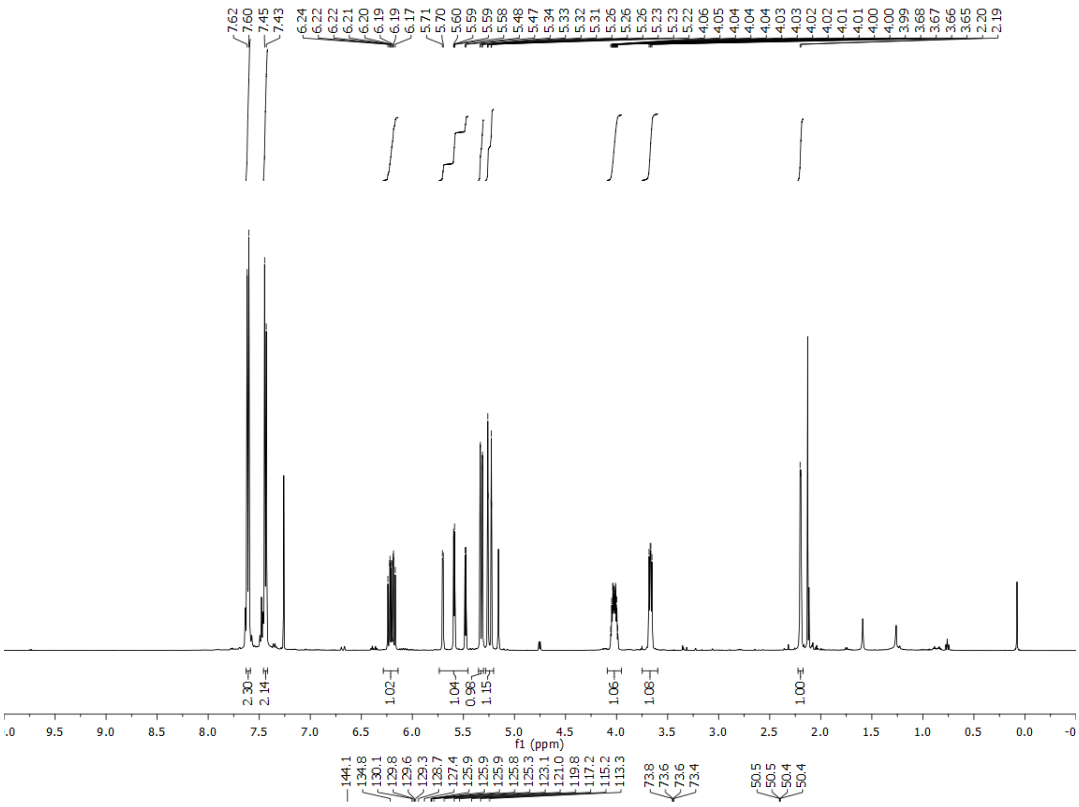
^{19}F NMR (471 MHz, $CDCl_3$): δ = –62.6, –129.0 (ddd, *J* = 288.7, 55.1, 6.4 Hz), –133.0 (ddd, *J* = 288.7, 56.3, 13.9 Hz).

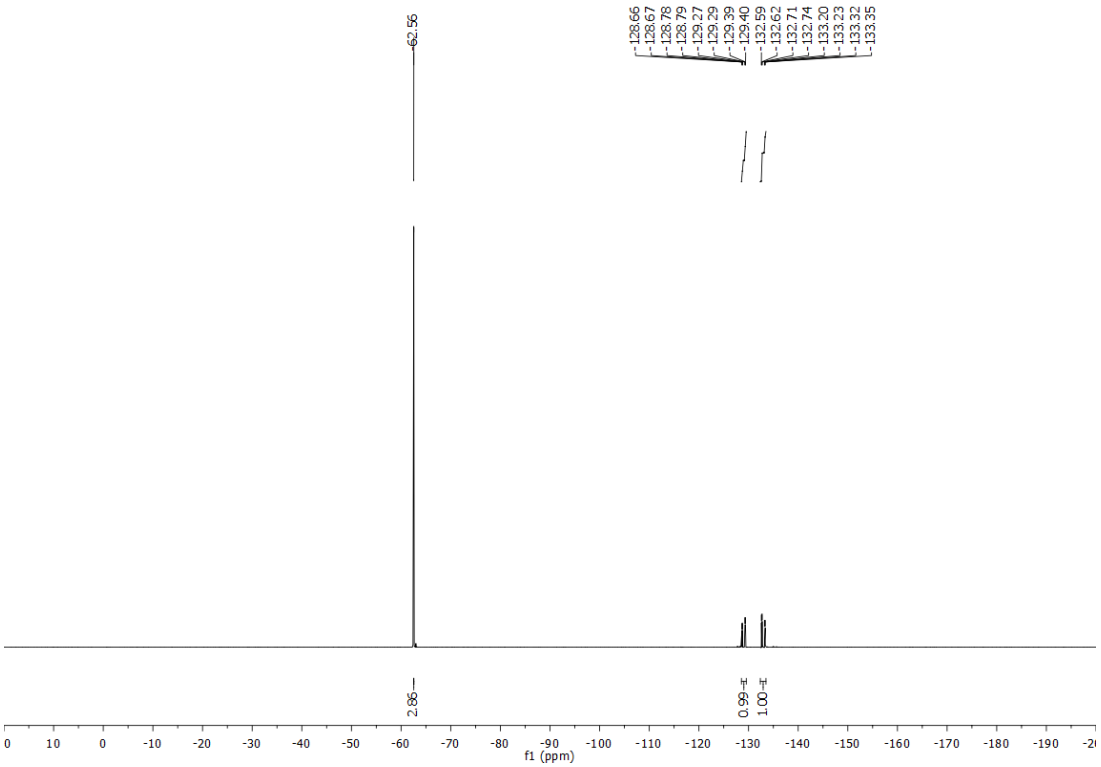
HRMS (CI) Calculated for $C_{12}H_{11}F_5O$ $[M]^+$ = 266.0730, Found 266.0726.

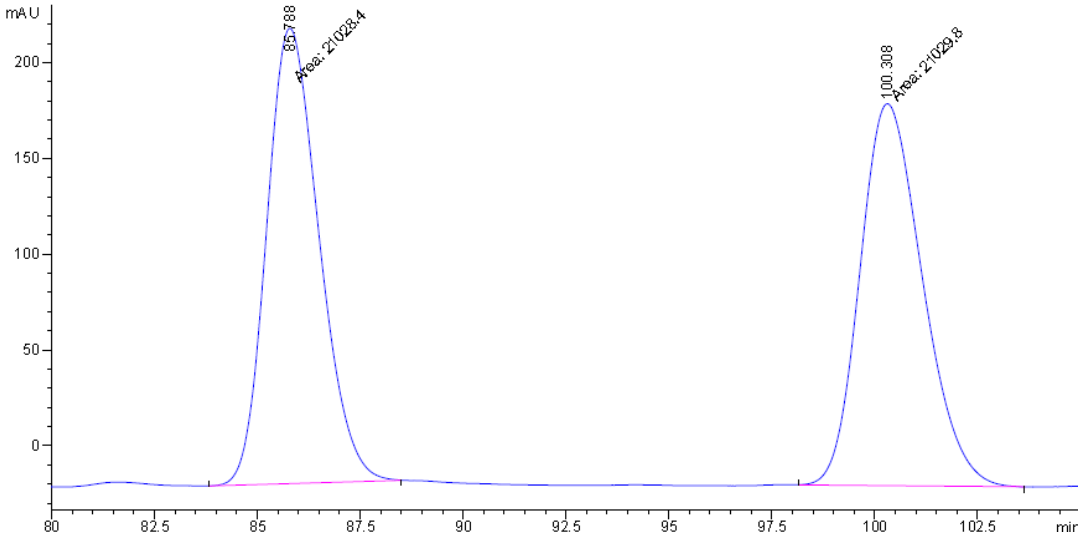
FTIR (neat) 3446, 2924, 1327, 1166, 1125, 1068, 1019, 931, 837, 771 cm^{-1}.

$[\alpha]_D^{33}$: –54.0 (*c* = 1.0, $CHCl_3$)

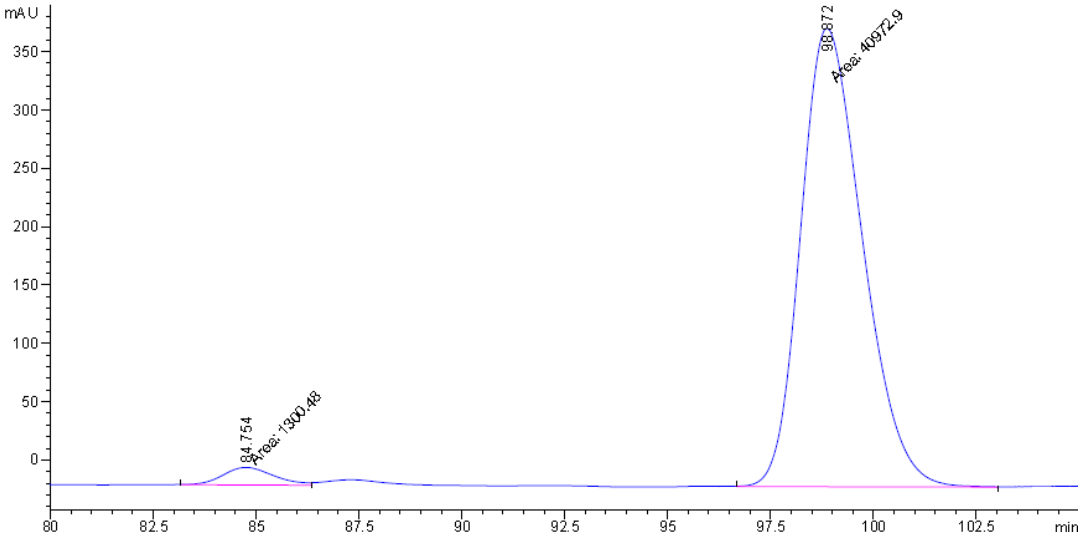
HPLC: (2× Chiralcel AD-H column, hexanes:*i*-PrOH = 99:1, 0.5 mL/min, 210 nm), *ee* = 94%.


7.62
7.60
7.45
7.43
6.24
6.22
6.22
6.21
6.20
6.19
6.19
6.17
5.71
5.70
5.60
5.59
5.59
5.58
5.48
5.47
5.34
5.33
5.32
5.31
5.26
5.26
5.26
5.23
5.23
5.22
4.06
4.05
4.04
4.04
4.04
4.03
4.03
4.02
4.02
4.01
4.01
4.00
4.00
3.99
3.68
3.67
3.66
3.65
2.20
2.19
2.30
2.14
1.02
1.04
0.98
1.15
1.06
1.08
1.00
f1 (ppm)
144.1
134.8
130.1
129.8
129.6
129.3
128.7
127.4
125.9
125.9
125.9
125.8
125.3
123.1
121.0
119.8
117.2
115.2
113.3
73.8
73.6
73.6
73.4
50.5
50.5
50.4
50.4
f1 (ppm)


62.56
128.66
128.67
128.78
128.79
129.27
129.29
129.39
129.40
132.59
132.62
132.71
132.74
133.20
133.23
133.32
133.35
2.86
0.99
1.00
f1 (ppm)

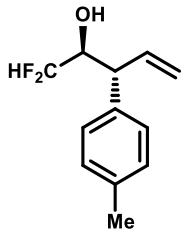


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	85.788	MM	1.4745	2.10284e4	237.68845	49.9984
2	100.308	MM	1.7586	2.10298e4	199.30756	50.0016



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	84.754	MF	1.4389	1300.47583	15.06372	3.0763
2	98.872	MM	1.7377	4.09729e4	392.98737	96.9237

(2*S*,3*R*)-1,1-Difluoro-3-(*p*-tolyl)pent-4-en-2-ol (6.5d)



The title compound was prepared according to the general procedure using difluoroacetaldehyde ethyl hemiacetal (90%, 28 mg, 200 μmol) and 1-(*p*-tolyl)allyl acetate (76 mg, 0.40 mmol, 200 mol%). Flash chromatography on silica (Hex/EtOAc 15:1) provided the title compound (31.7 mg, 149 μmol, *anti:syn* = >20:1) in 75% yield as a yellow oil.

TLC (SiO_2) R_f = 0.21 (hexanes/ethyl acetate = 10:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.17 (s, 4H), 6.18 (ddd, *J* = 17.2, 10.3, 8.7 Hz, 1H), 5.54 (ddd, *J* = 56.0, 54.8, 3.7 Hz, 1H), 5.27 (dd, *J* = 10.3, 1.5 Hz, 1H), 5.23 (dt, *J* = 17.2, 1.3 Hz, 1H), 4.05–3.95 (m, 1H), 3.57–3.51 (m, 1H), 2.34 (s, 3H), 2.11 (d, *J* = 4.6 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 137.2, 136.5, 136.2, 129.8, 128.0, 118.7, 115.2 (t, *J* = 243.1 Hz), 73.7 (dd, *J* = 22.9, 20.7 Hz), 50.7, 21.2.

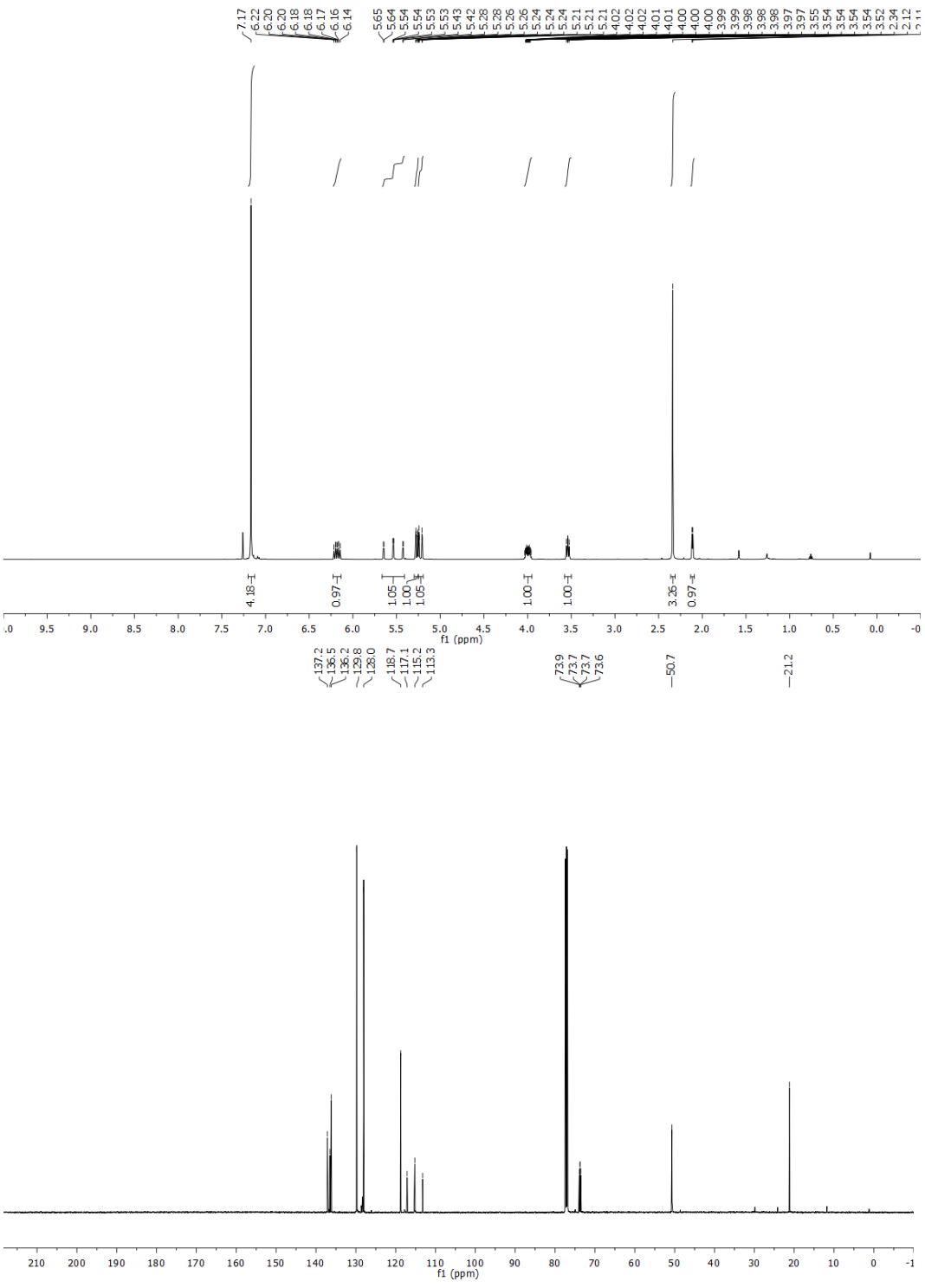
^{19}F NMR (471 MHz, $CDCl_3$): δ = –129.2 (ddd, *J* = 285.9, 54.9, 5.9 Hz), –134.7 (ddd, *J* = 286.0, 56.0, 16.1 Hz).

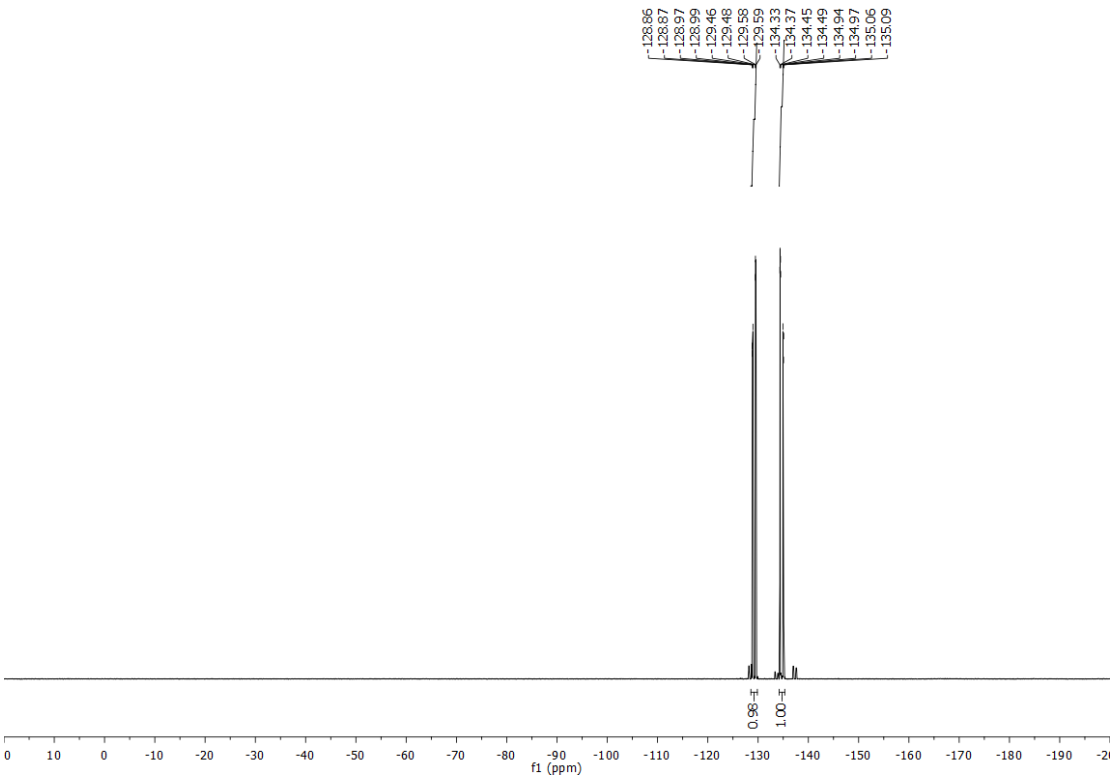
HRMS (CI) Calculated for $C_{12}H_{14}F_2O$ $[M]^+$ = 212.1013, Found 212.1010.

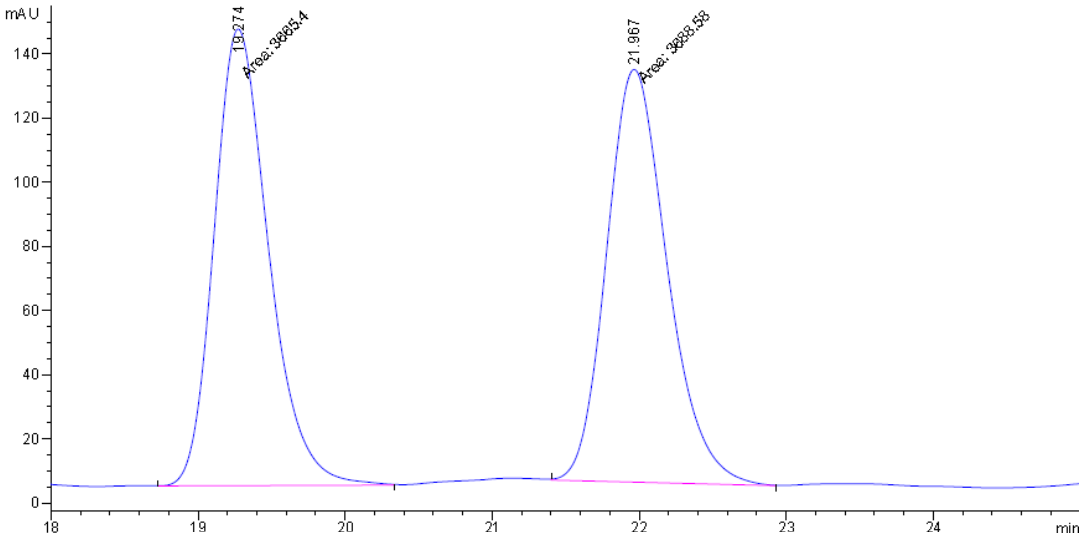
FTIR (neat) 3411, 2981, 2924, 1514, 1150, 1127, 1057, 1001, 925, 816, 760 cm^{-1}.

$[\alpha]_D^{33}$: –68.3 (*c* = 1.0, $CHCl_3$)

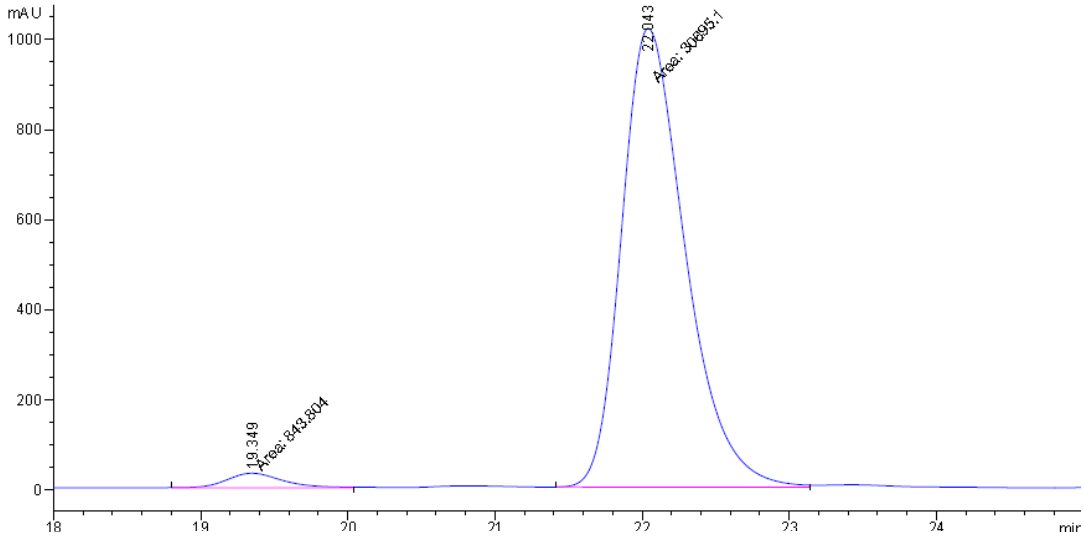
HPLC: (Chiralcel AD-H column, hexanes:*i*-PrOH = 99:1, 1.0 mL/min, 230 nm), *ee* = 95%.




-128.86
-128.87
-128.97
-128.99
-129.46
-129.48
-129.58
-129.59
-134.33
-134.37
-134.45
-134.49
-134.94
-134.97
-135.06
-135.09
0.98
1.00
f1 (ppm)

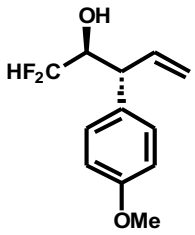


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.274	MM	0.4291	3665.40405	142.37234	49.8424
2	21.967	MM	0.4777	3688.58081	128.68335	50.1576



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.349	MM	0.4376	843.80371	32.13876	2.6754
2	22.043	MM	0.5019	3.06951e4	1019.36761	97.3246

(2*S*,3*R*)-1,1-difluoro-3-(4-methoxyphenyl)pent-4-en-2-ol (6.5e)



The title compound was prepared according to the general procedure using difluoroacetaldehyde ethyl hemiacetal (90%, 28 mg, 200 μmol) and 1-(4-methoxyphenyl)allyl acetate (82.4 mg, 0.40 mmol, 200 mol%). Flash chromatography on silica (Hex/EtOAc 20:1-10:1) provided the title compound (37.2 mg, 164 μmol, *anti:syn* = >20:1) in 82% yield as a white solid.

TLC (SiO_2) R_f = 0.26 (hexanes/ethyl acetate = 4:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.20 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 6.17 (ddd, *J* = 17.1, 10.2, 8.6 Hz, 1H), 5.53 (ddd, *J* = 55.9, 54.8, 3.7 Hz, 1H), 5.29 – 5.16 (m, 2H), 3.97 (dddt, *J* = 16.2, 8.3, 6.3, 3.9 Hz, 1H), 3.80 (s, 3H), 3.56 – 3.49 (m, 1H), 2.23 (d, *J* = 4.6 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.8, 136.3, 131.5, 129.2, 118.5 (dd, *J* = 243.5, 25.1 Hz), 115.2 (t, *J* = 243.3 Hz), 114.4, 73.8 (dd, *J* = 22.9, 20.7 Hz), 55.4, 50.2 (t, *J* = 3.7 Hz).

^{19}F NMR (471 MHz, $CDCl_3$): δ = -129.19 (ddd, *J* = 285.6, 55.0, 5.8 Hz), -134.65 (ddd, *J* = 286.0, 56.0, 16.3 Hz).

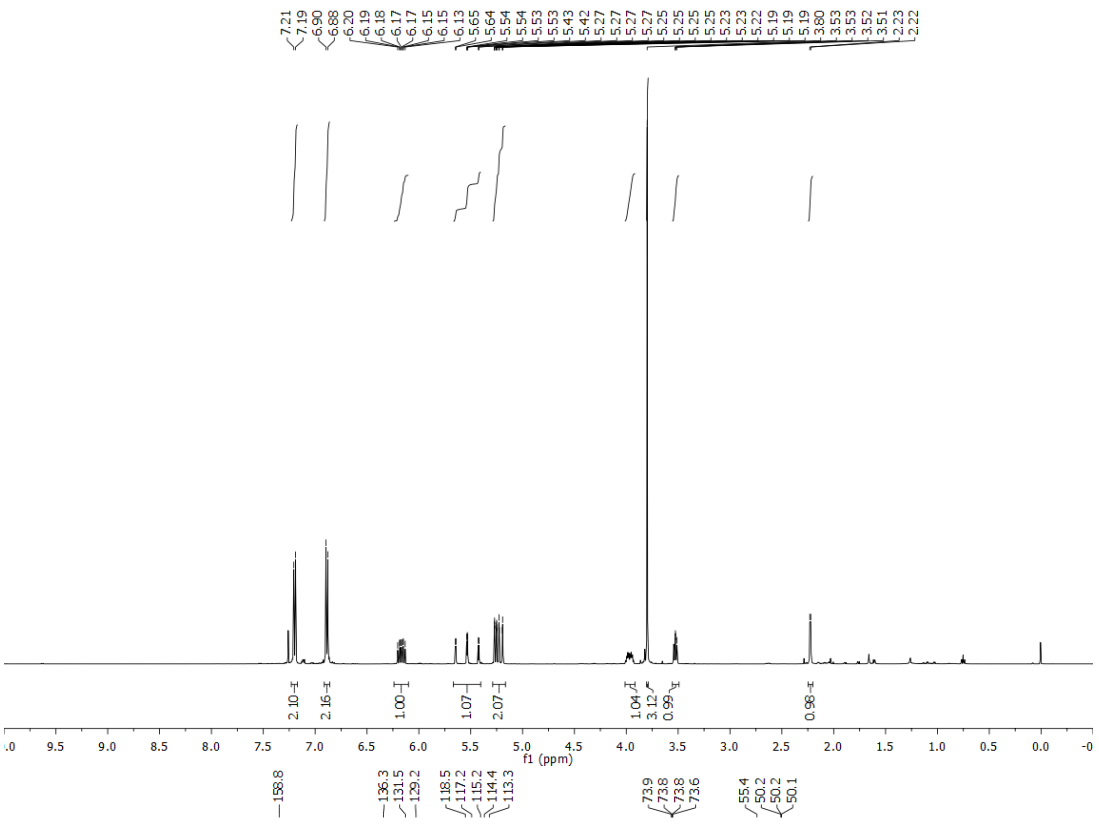
HRMS (CI) Calculated for $C_{12}H_{14}F_2O_2$ $[M]^+$ = 228.0962, Found 228.0960.

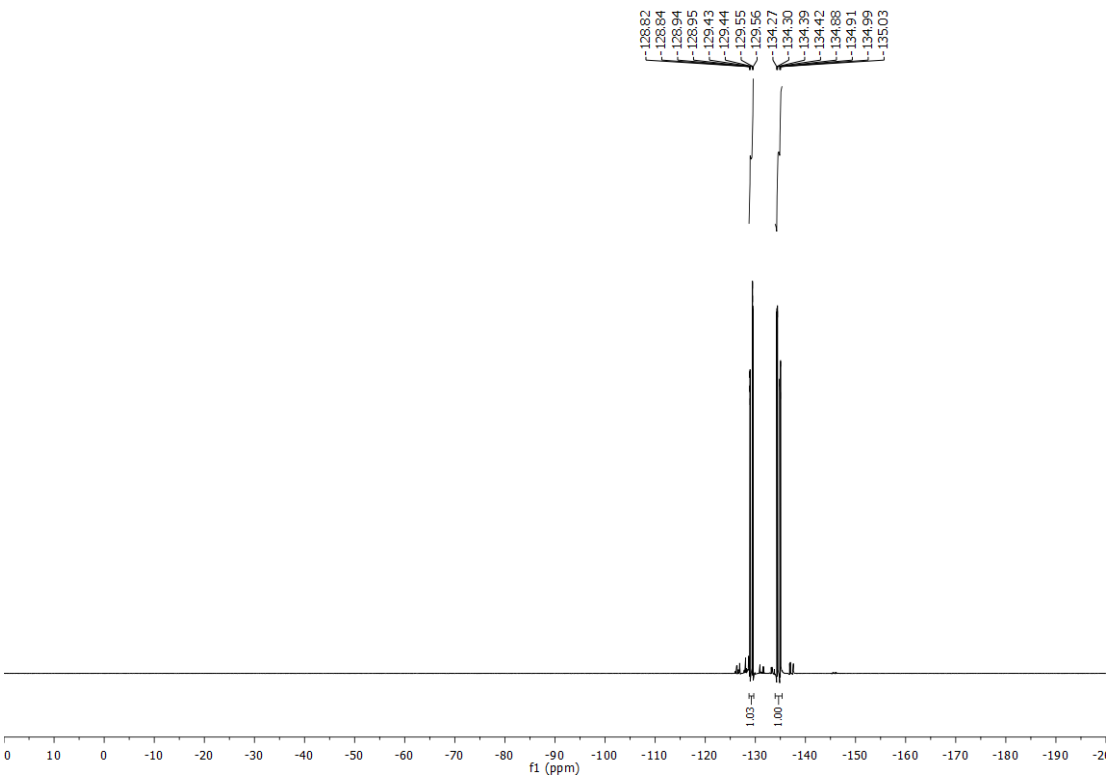
FTIR (neat) 3440, 2925, 2363, 1737, 1250, 1155, 1038, 1023, 817, 772 cm^{-1}.

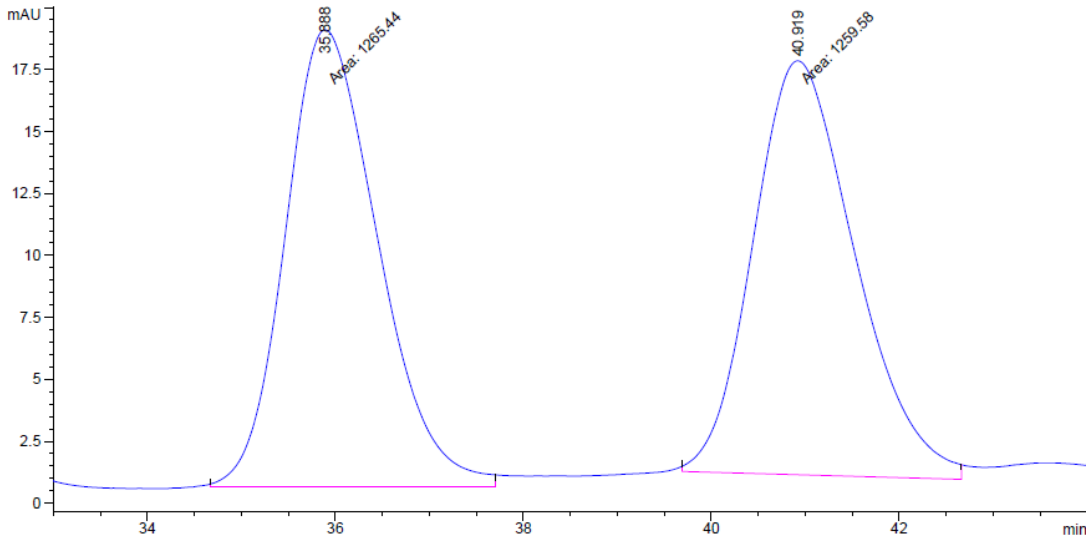
$[\alpha]_D^{33}$: –70.5 (*c* = 1.0, $CHCl_3$)

MP: 83-84˚C.

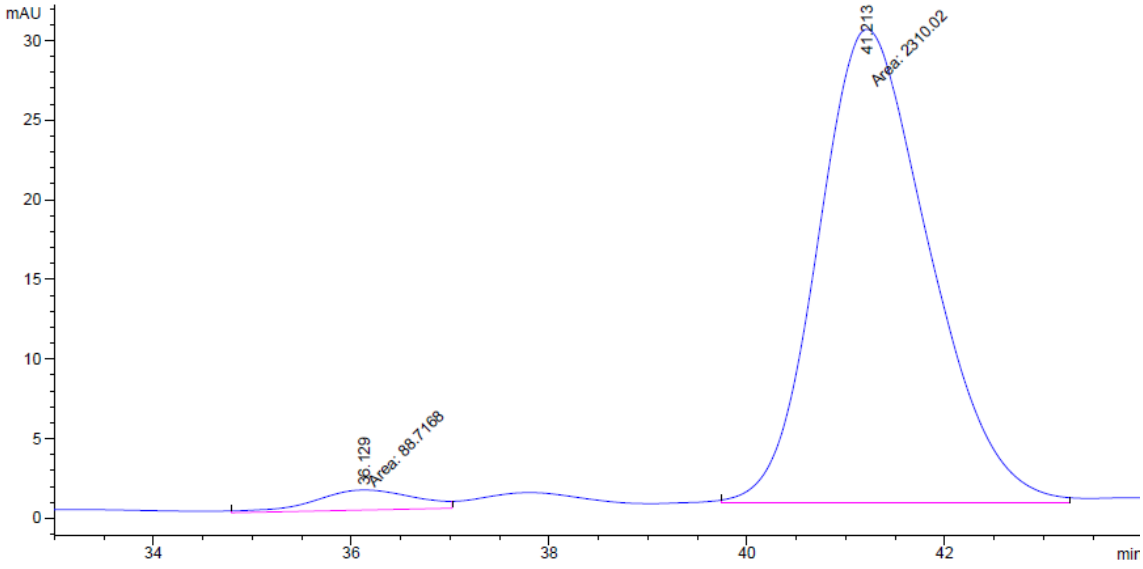
HPLC: (Chiralcel AD-H column, hexanes:*i*-PrOH = 99:1, 1.0 mL/min, 230 nm), *ee* = 93%.


7.21
7.19
6.90
6.88
6.20
6.19
6.18
6.17
6.17
6.15
6.15
6.13
5.65
5.64
5.54
5.54
5.53
5.53
5.43
5.42
5.27
5.27
5.27
5.27
5.25
5.25
5.25
5.25
5.23
5.23
5.22
5.19
5.19
5.19
3.80
3.53
3.53
3.52
3.51
2.23
2.22
2.10
2.16
1.00
1.07
2.07
1.04
3.12
0.99
0.98
f1 (ppm)
158.8
136.3
131.5
129.2
118.5
117.2
115.2
114.4
113.3
73.9
73.8
73.8
73.6
55.4
50.2
50.2
50.1
f1 (ppm)


-128.82
-128.84
-128.94
-128.95
-129.43
-129.44
-129.55
-129.56
-134.27
-134.30
-134.39
-134.42
-134.88
-134.91
-134.99
-135.03
1.03
1.00
f1 (ppm)

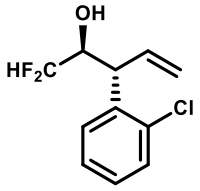


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	35.888	MM	1.1427	1265.43823	18.45711	50.1160
2	40.919	MM	1.2569	1259.57983	16.70190	49.8840



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	36.129	MF	1.1742	88.71684	1.25924	3.6985
2	41.213	MM	1.2962	2310.01831	29.70327	96.3015

(2S,3R)-3-(2-chlorophenyl)-1,1-difluoropent-4-en-2-ol (6.5f)



The title compound was prepared according to the general procedure using difluoroacetaldehyde ethyl hemiacetal (90%, 27.9 mg, 199 μmol) and 1-(2-chlorophenyl)allyl acetate (84 mg, 0.40 mmol, 200 mol%). Flash chromatography on silica (Hex/EtOAc 20:1 → 10:1) provided the title compound (35.1 mg, 151 μmol, *anti:syn* = >20:1) in 76% yield as a yellow oil.

TLC (SiO_2) R_f = 0.57 (hexanes/ethyl acetate = 3:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.43 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.40 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.29 – 7.25 (m, 1H), 7.21 (td, *J* = 7.6, 1.7 Hz, 1H), 6.23 (ddd, *J* = 17.1, 10.2, 8.7 Hz, 1H), 5.64 (ddd, *J* = 56.4, 55.0, 4.6 Hz, 1H), 5.32 (dd, *J* = 10.2, 1.4 Hz, 1H), 5.25 (dt, *J* = 17.0, 1.2 Hz, 1H), 4.20 (dd, *J* = 8.8, 4.8 Hz, 1H), 4.08 (ddq, *J* = 14.0, 6.6, 4.8 Hz, 1H), 2.16 (d, *J* = 4.9 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 137.6, 134.1, 133.5, 130.1, 129.9, 128.5, 127.2, 120.0, 115.4 (t, *J* = 243.8 Hz), 72.6 (dd, *J* = 24.7, 21.5 Hz), 46.3 (dd, *J* = 4.7, 2.7 Hz).

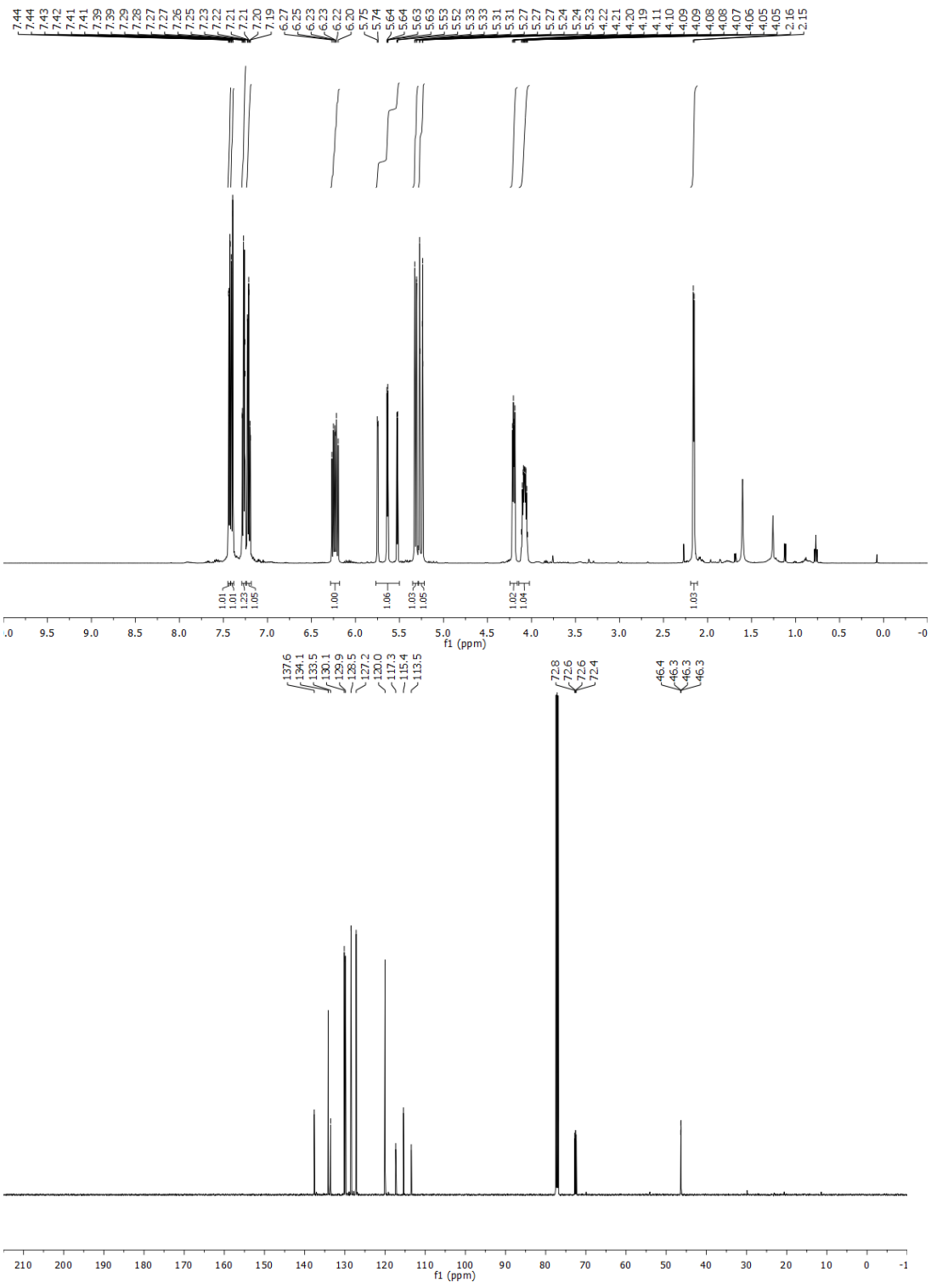
^{19}F NMR (471 MHz, $CDCl_3$): δ = -128.6 (ddd, *J* = 288.0, 55.0, 6.6 Hz), -132.0 (ddd, *J* = 288.0, 56.5, 13.5 Hz).

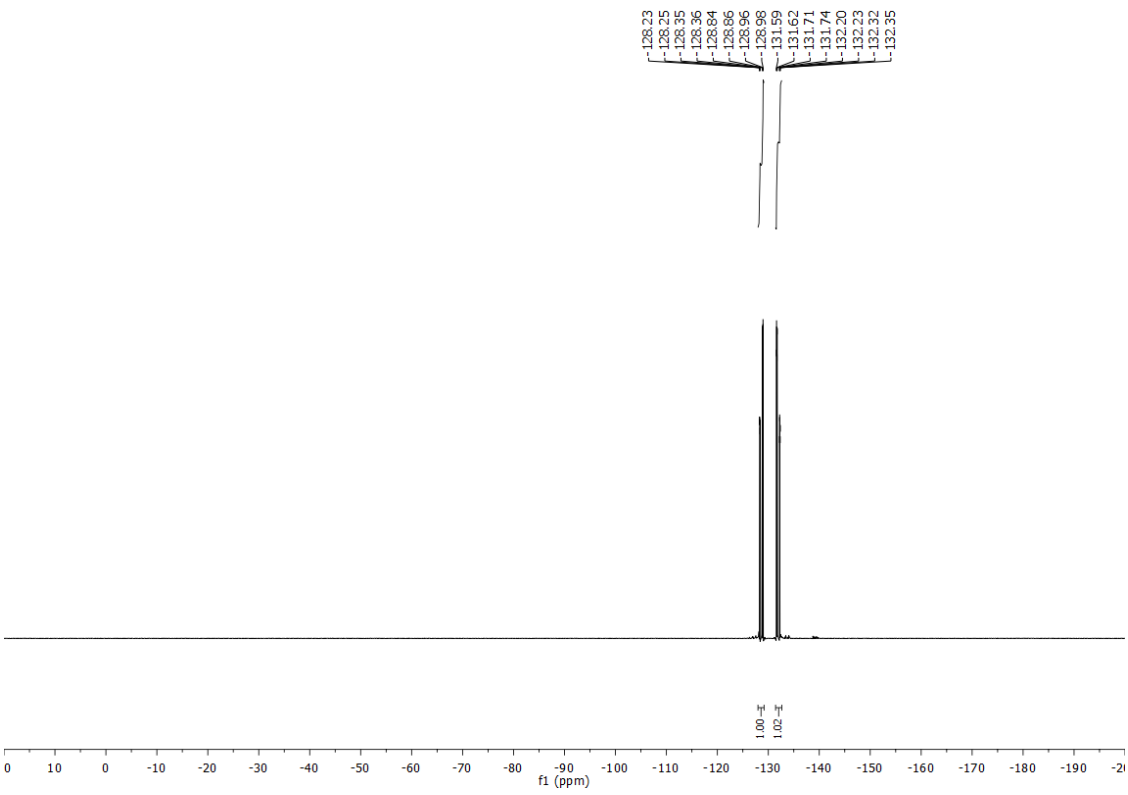
HRMS (CI) Calculated for $C_{11}H_{11}{}^{35}ClF_2O$ $[M]^+$ = 232.0466, Found 232.0465.

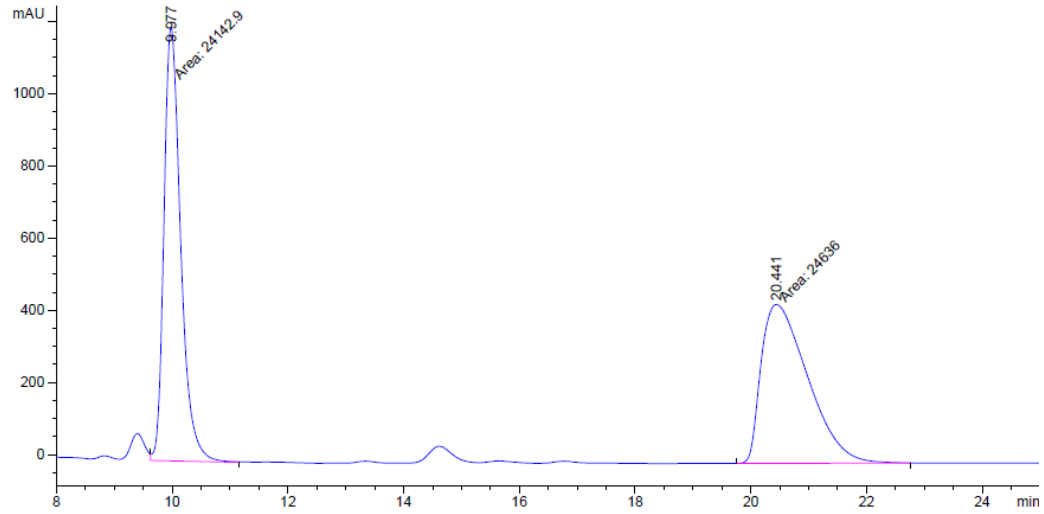
FTIR (neat) 3443, 3074, 2985, 2920, 1474, 1442, 1150, 1066, 1001, 930, 751 cm^{-1}.

$[\alpha]_D^{27}$: –44.3 (*c* = 1.0, $CHCl_3$)

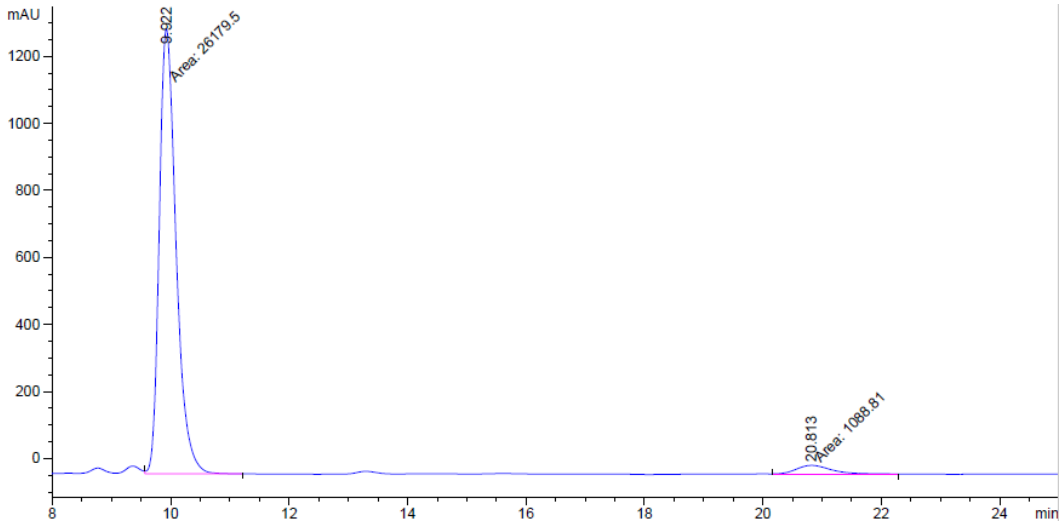
HPLC: (Chiralcel AS-H column, hexanes:*i*-PrOH = 97:3, 1.0 mL/min, 210 nm), *ee* = 92%.




-128.23
-128.25
-128.35
-128.36
-128.84
-128.86
-128.96
-128.98
-131.59
-131.62
-131.71
-131.74
-132.20
-132.23
-132.32
-132.35
1.00
1.02
0
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

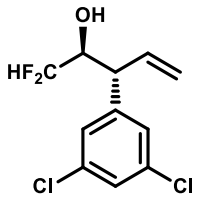


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.977	FM	0.3352	2.41429e4	1200.55249	49.4946
2	20.441	MM	0.9332	2.46360e4	439.98474	50.5054



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.922	FM	0.3286	2.61795e4	1327.65588	96.0070
2	20.813	MM	0.6958	1088.81360	26.08039	3.9930

(2S,3R)-3-(3,5-dichlorophenyl)-1,1-difluoropent-4-en-2-ol (6.5g)



The title compound was prepared according to the general procedure using difluoroacetaldehyde ethyl hemiacetal (90%, 28 mg, 200 μmol) and 1-(3,5-dichlorophenyl)allyl acetate (98 mg, 0.40 mmol, 200 mol%). Flash chromatography on silica (Hex/EtOAc 20:1) provided the title compound (43 mg, 160 μmol, *anti:syn* = >20:1) in 77% yield as a yellow oil.

TLC (SiO_2) R_f = 0.38 (hexanes/ethyl acetate = 9:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.28 (t, *J* = 1.7 Hz, 1H), 7.22 (d, *J* = 1.7 Hz, 2H), 6.13 (dt, *J* = 17.3, 9.6 Hz, 1H), 5.61 (ddd, *J* = 56.3, 55.3, 4.9 Hz, 1H), 5.29 (dd, *J* = 43.7, 13.7 Hz, 2H), 4.03 – 3.93 (m, 1H), 3.55 (dd, *J* = 8.8, 4.6 Hz, 1H), 2.21 (s, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 143.30, 135.34, 133.52, 127.70, 126.83, 125.65, 123.39, 120.84, 73.41 (dd, *J* = 24.8, 22.0 Hz), 49.90 (dd, *J* = 4.9, 2.3 Hz).

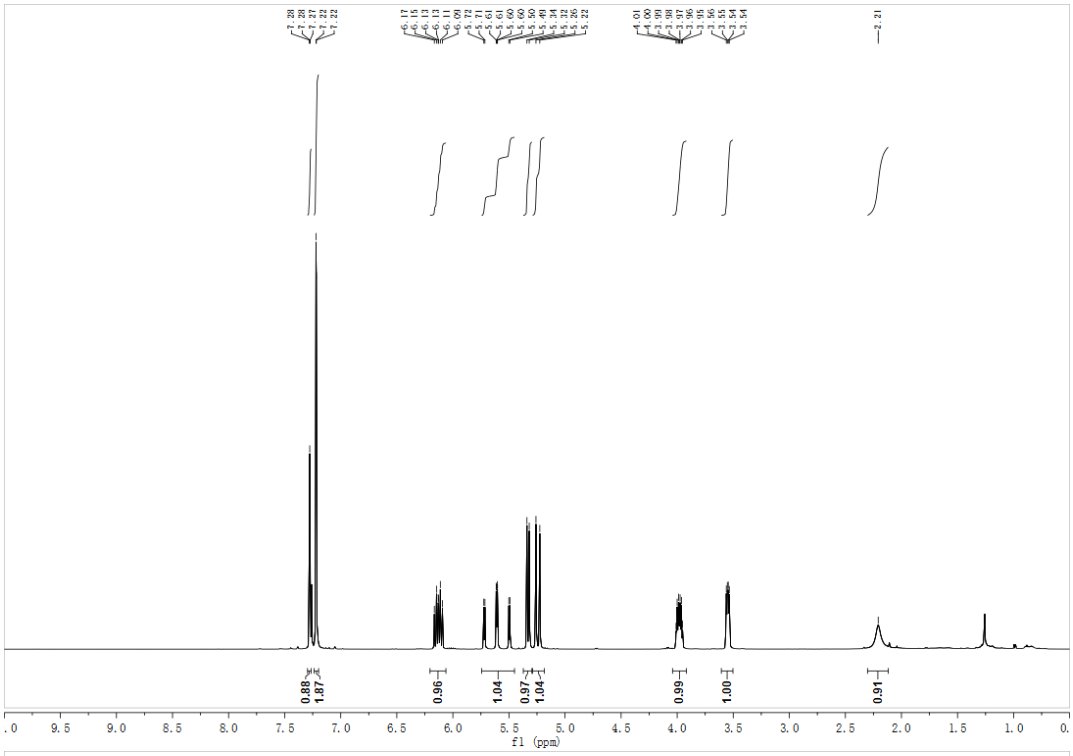
^{19}F NMR (471 MHz, $CDCl_3$): δ = -128.92 (ddd, *J* = 289.4, 55.1, 6.0 Hz), -132.45 (ddd, *J* = 289.4, 56.5, 13.4 Hz).

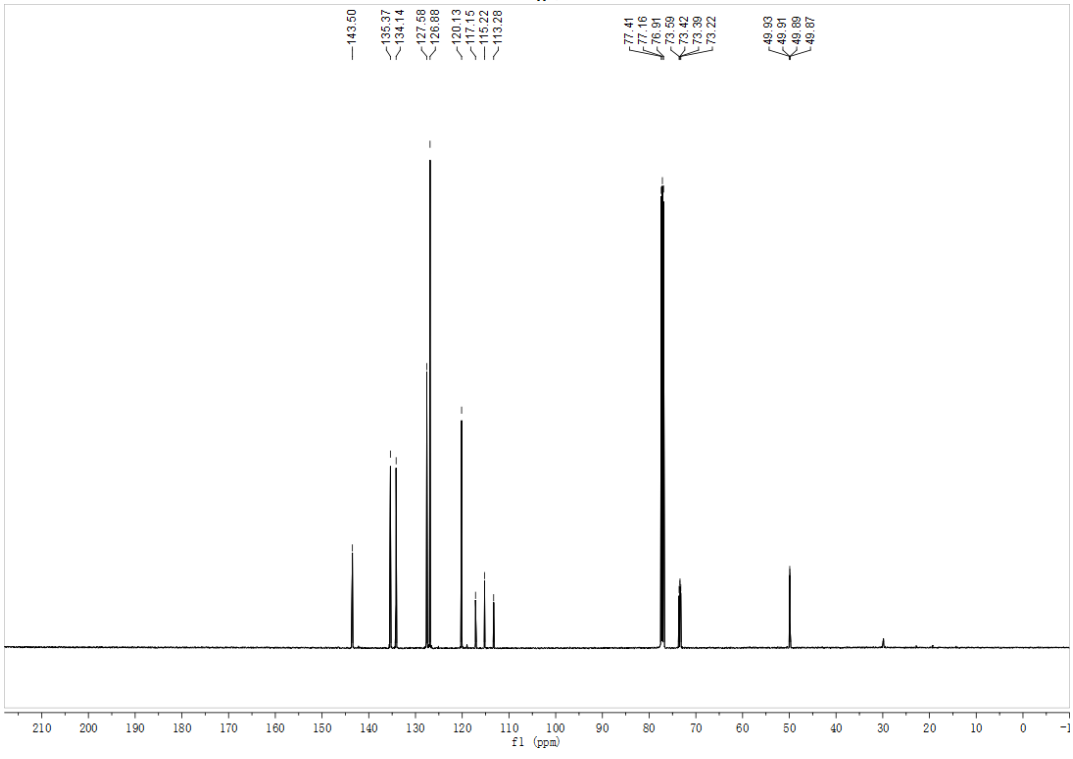
HRMS (CI) Calculated for $C_{11}H_{10}Cl_2F_2O$ $[M]^+$ = 266.0077, Found 266.0080.

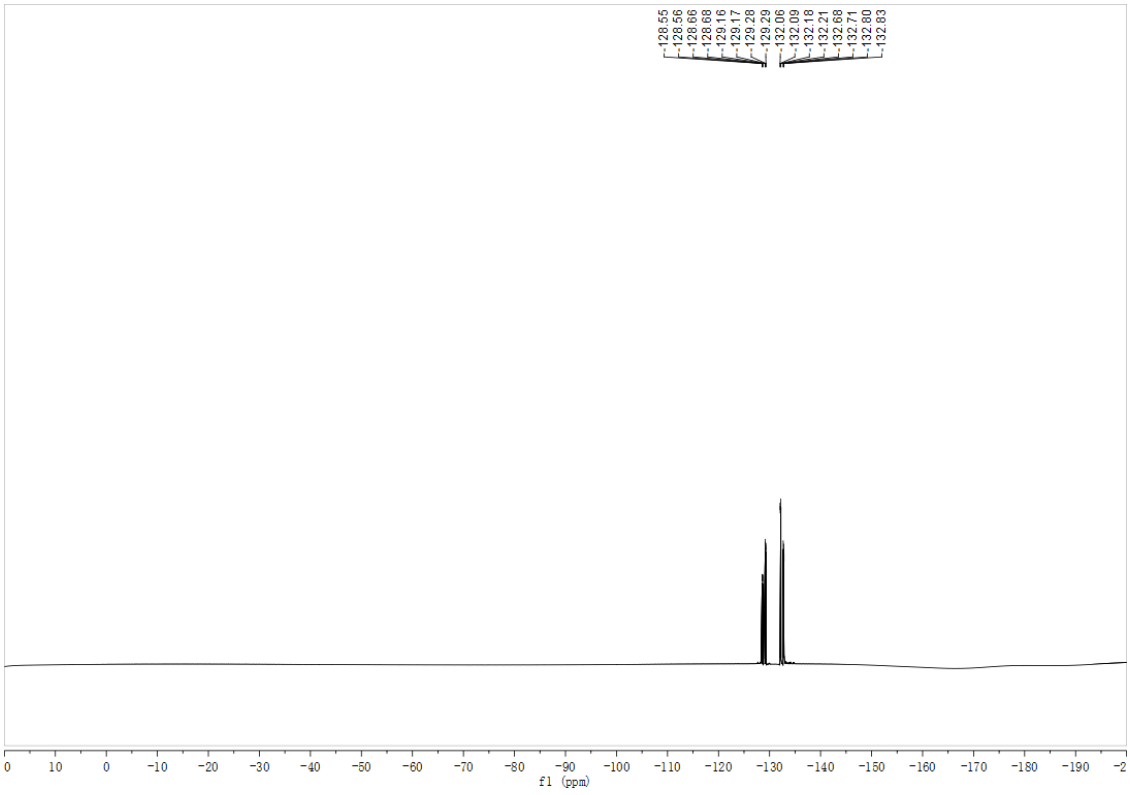
FTIR (neat) 3432, 3083, 2984, 1567, 1433, 1059, 858, 759, 681 cm^{-1}.

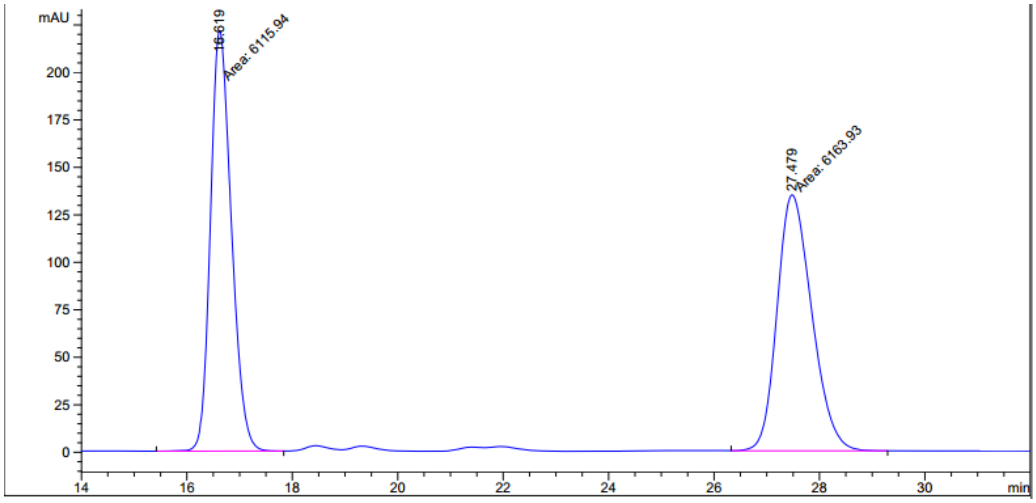
$[\alpha]_D^{33}$: –83.3 (*c* = 1.2, $CHCl_3$)

HPLC: (Chiralcel AS-H column, hexanes:*i*-PrOH = 99:1, 1.0 mL/min, 230 nm), *ee* = 95%.

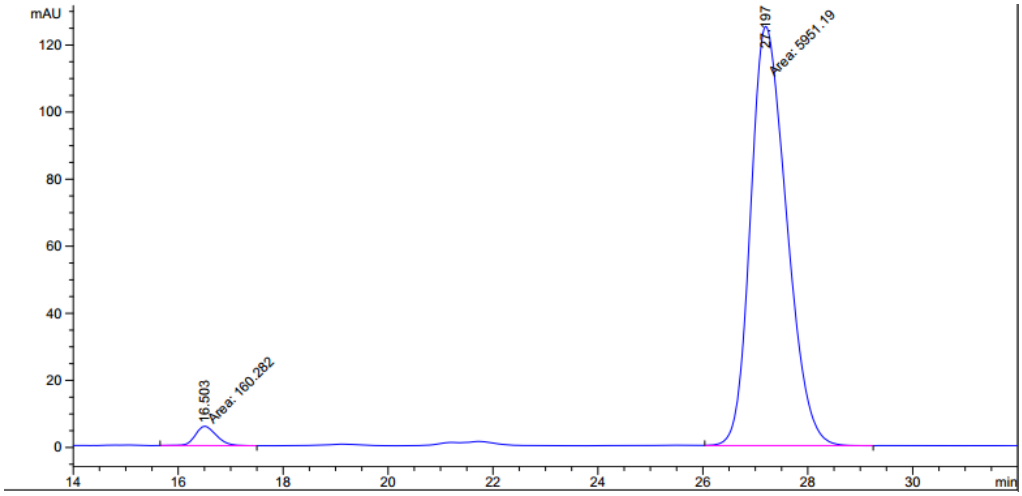

7.28
7.27
7.23
7.22
6.17
6.15
6.13
6.11
6.09
5.72
5.71
5.61
5.60
5.59
5.49
5.34
5.32
5.26
5.22
4.01
4.00
3.99
3.98
3.97
3.96
3.95
3.56
3.55
3.54
3.54
2.21
0.88
1.87
0.96
1.04
0.97
1.04
0.99
1.00
0.91
f1 (ppm)


143.50
135.37
134.14
127.58
126.88
120.13
117.15
115.22
113.28
77.41
77.16
76.91
73.59
73.42
73.39
73.22
49.93
49.91
49.89
49.87
f1 (ppm)


128.55
128.56
128.66
128.68
129.16
129.17
129.28
129.29
132.06
132.09
132.18
132.21
132.68
132.71
132.80
132.83
0 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -2
f1 (ppm)

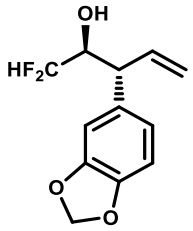


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.619	MM	0.4602	6115.94482	221.49268	49.8046
2	27.479	MM	0.7624	6163.93359	134.74940	50.1954



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.503	MM	0.4642	160.28223	5.75497	2.6226
2	27.197	MM	0.7938	5951.19092	124.95788	97.3774

(2*S*,3*R*)-3-(Benzo[d][1,3]dioxol-5-yl)-1,1-difluoropent-4-en-2-ol (6.5h)



The title compound was prepared according to the general procedure using difluoroacetaldehyde ethyl hemiacetal (90%, 28 mg, 200 μmol) and 1-(benzo[d][1,3]dioxol-5-yl)allyl acetate (88 mg, 0.40 mmol, 200 mol%). Flash chromatography on silica (Hex/EtOAc 10:1) provided the title compound (43.0 mg, 178 μmol, *anti:syn* = >20:1) in 89% yield as a yellow oil.

TLC (SiO_2) R_f = 0.13 (hexanes/ethyl acetate = 10:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.80–6.77 (m, 2H), 6.73 (dd, *J* = 8.0, 1.8 Hz, 1H), 6.13 (ddd, *J* = 17.1, 10.2, 8.6 Hz, 1H), 5.95 (s, 2H), 5.55 (ddd, *J* = 56.0, 54.8, 3.7 Hz, 1H), 5.28–5.25 (m, 1H), 5.22 (dt, *J* = 17.1, 1.3 Hz, 1H), 4.00–3.91 (m, 1H), 3.52–3.46 (m, 1H), 2.14 (d, *J* = 4.5 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 148.1, 146.8, 136.0, 133.3, 121.3, 118.7, 115.2 (t, *J* = 243.2 Hz), 108.8, 108.5, 101.3, 73.8 (dd, *J* = 23.1, 20.8 Hz), 50.6 (t, *J* = 3.7 Hz).

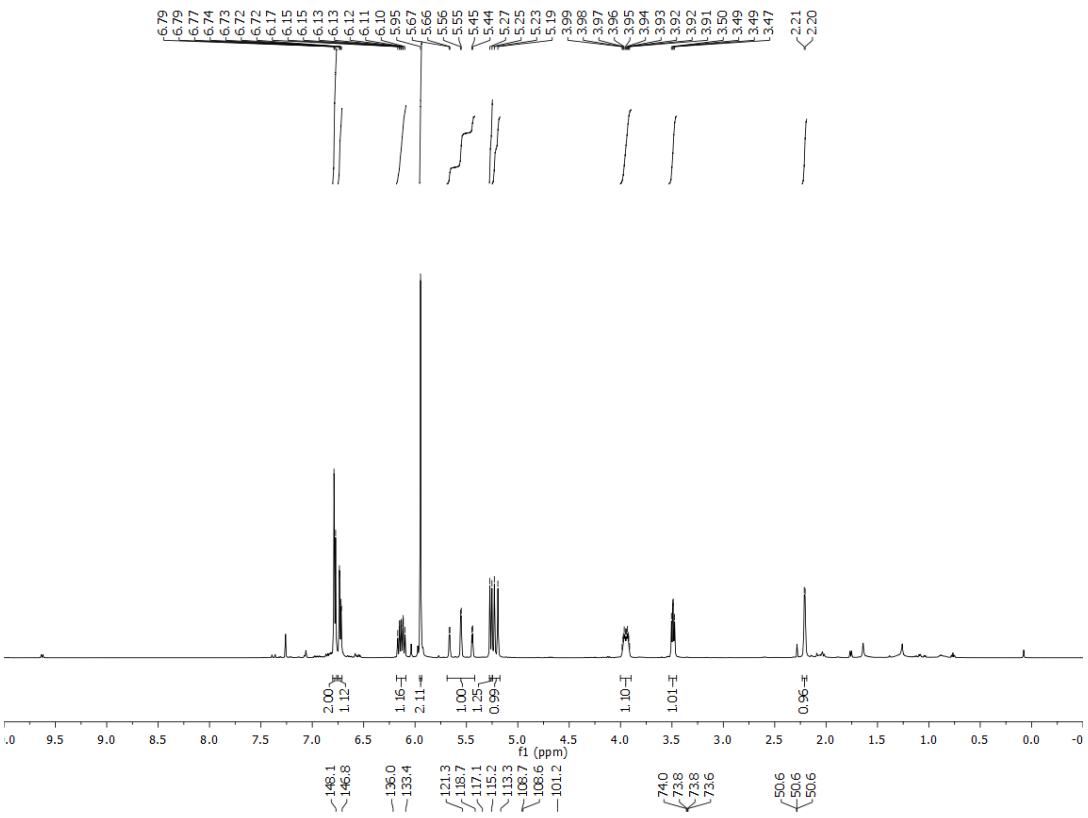
^{19}F NMR (471 MHz, $CDCl_3$): δ = –129.2 (ddd, *J* = 286.1, 54.7, 5.9 Hz), –134.6 (ddd, *J* = 286.2, 56.0, 15.8 Hz).

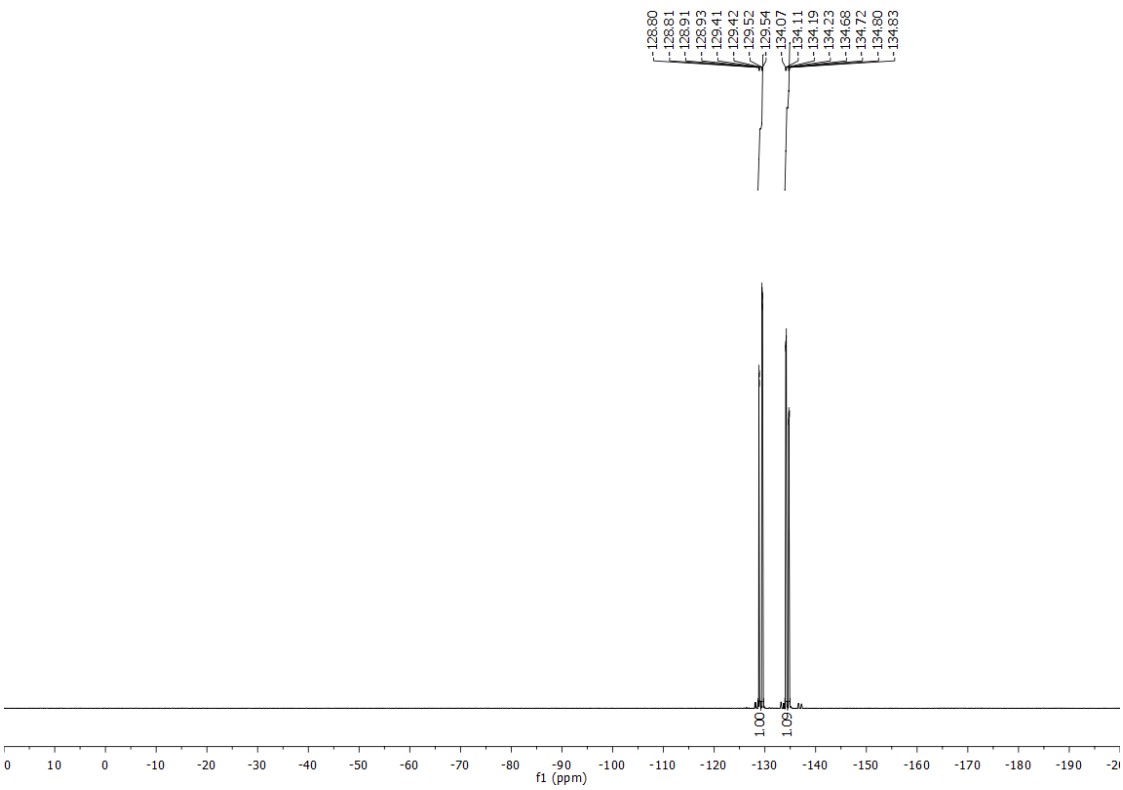
HRMS (CI) Calculated for $C_{12}H_{12}F_2O_3$ $[M]^+$ = 242.0755, Found 242.0758.

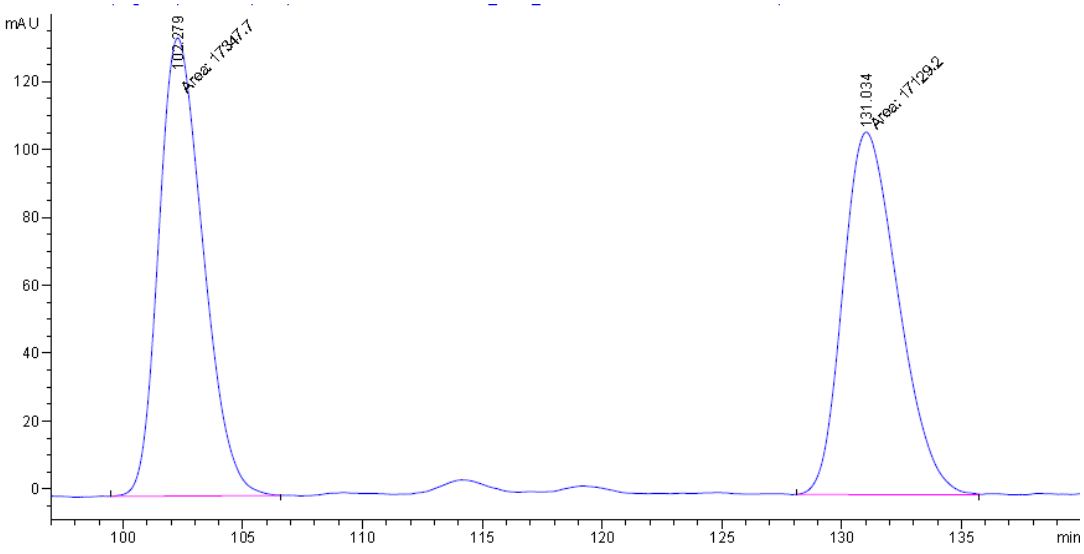
FTIR (neat) 3453, 2982, 2897, 1504, 1488, 1443, 1244, 1134, 1098, 1037, 929 cm^{-1}.

$[\alpha]_D^{32}$: –53.0 (*c* = 1.0, $CHCl_3$)

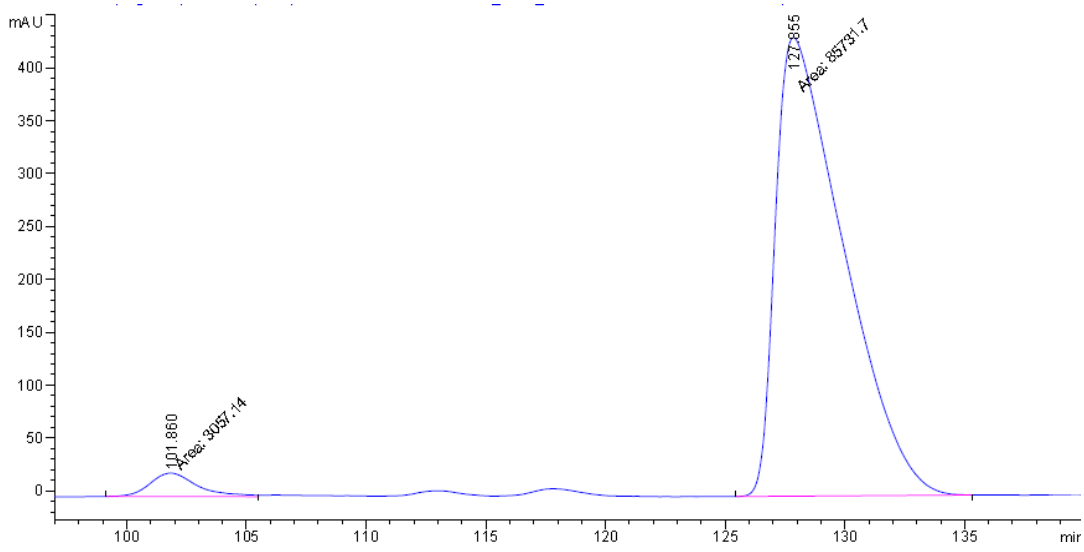
HPLC: (Chiralcel OJ-H column, hexanes:*i*-PrOH = 97:3, 0.5 mL/min, 210 nm), *ee* = 93%.


6.79
6.79
6.77
6.74
6.73
6.72
6.72
6.17
6.15
6.13
6.13
6.12
6.11
6.10
5.95
5.67
5.66
5.56
5.55
5.45
5.44
5.27
5.25
5.23
5.19
3.99
3.98
3.97
3.96
3.95
3.94
3.93
3.92
3.91
3.50
3.49
3.49
3.47
2.21
2.20
2.00
1.12
1.16
2.11
1.00
1.25
0.99
1.10
1.01
0.96
f1 (ppm)
148.1
146.8
136.0
133.4
121.3
118.7
117.1
115.2
113.3
108.7
108.6
101.2
74.0
73.8
73.8
73.6
50.6
50.6
50.6
f1 (ppm)


128.80
128.81
128.91
128.93
129.41
129.42
129.52
129.54
134.07
134.11
134.19
134.23
134.68
134.72
134.80
134.83
1.00
1.09
0
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

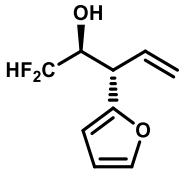


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	102.279	MM	2.1432	1.73477e4	134.90370	50.3169
2	131.034	MM	2.6742	1.71292e4	106.75617	49.6831



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	101.860	MM	2.2946	3057.13696	22.20513	3.4432
2	127.855	MM	3.2946	8.57317e4	433.70004	96.5568

(2S,3S)-1,1-difluoro-3-(furan-2-yl)pent-4-en-2-ol (6.5i)



The title compound was prepared according to the general procedure using using difluoroacetaldehyde ethyl hemiacetal (90%, 28 mg, 200 μmol) and 1-(furan-2-yl)allyl acetate (66.5 mg, 0.40 mmol, 200 mol%). Flash chromatography on silica (Hex/EtOAc 20:1) provided the title compound (25 mg, 120 μmol, *anti:syn* = >20:1) in 65% yield as a yellow oil.

TLC (SiO_2) R_f = 0.2 (hexanes/ethyl acetate = 9:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.39 – 7.37 (m, 1H), 6.35 (dd, *J* = 3.2, 1.9 Hz, 1H), 6.19 (d, *J* = 3.2 Hz, 1H), 6.12 – 6.03 (m, 1H), 5.63 (ddd, *J* = 56.3, 54.9, 4.6 Hz, 1H), 5.33 (dd, *J* = 10.1, 0.9 Hz, 1H), 5.27 (d, *J* = 17.2 Hz, 1H), 4.21 – 4.10 (m, 1H), 3.74 (dd, *J* = 8.7, 5.1 Hz, 1H), 2.27 (dd, *J* = 8.9, 3.7 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 152.69, 142.15, 132.73, 119.98, 117.23, 115.29, 113.36, 110.61, 107.44, 72.05 (dd, *J* = 24.6, 21.6 Hz), 44.86 (dd, *J* = 5.1, 2.9 Hz).

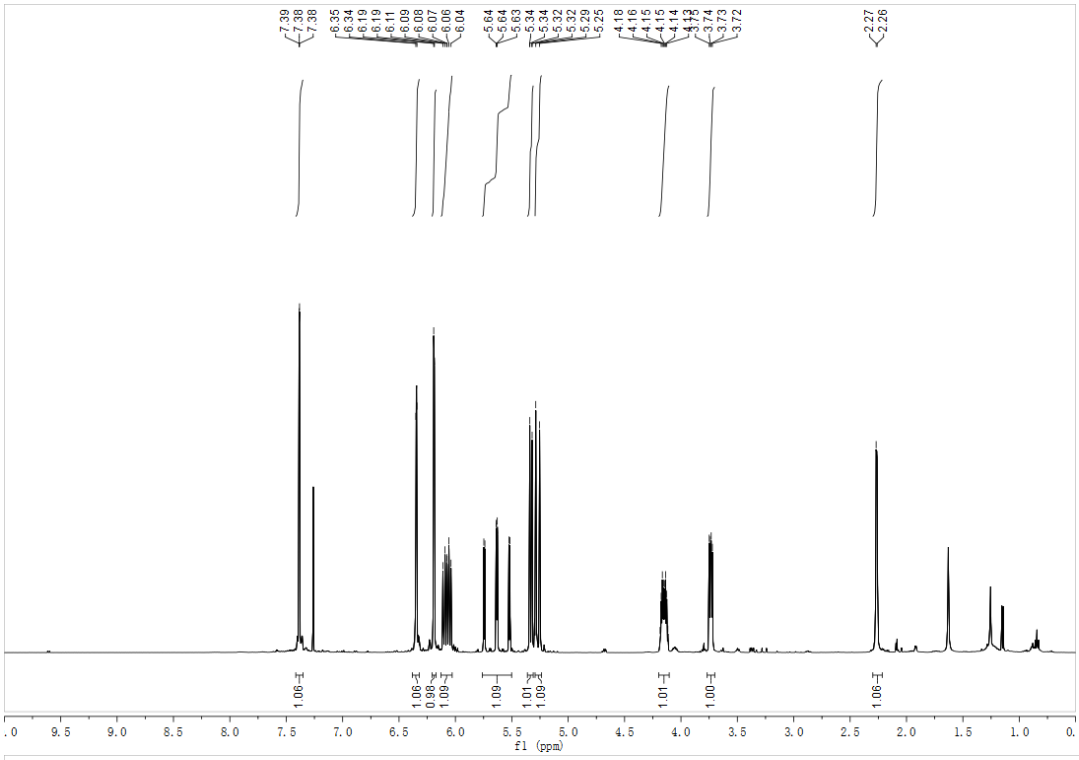
^{19}F NMR (471 MHz, $CDCl_3$): δ = -128.92 (ddd, *J* = 288.8, 54.8, 6.0 Hz), -132.79 (ddd, *J* = 288.8, 56.3, 14.2 Hz).

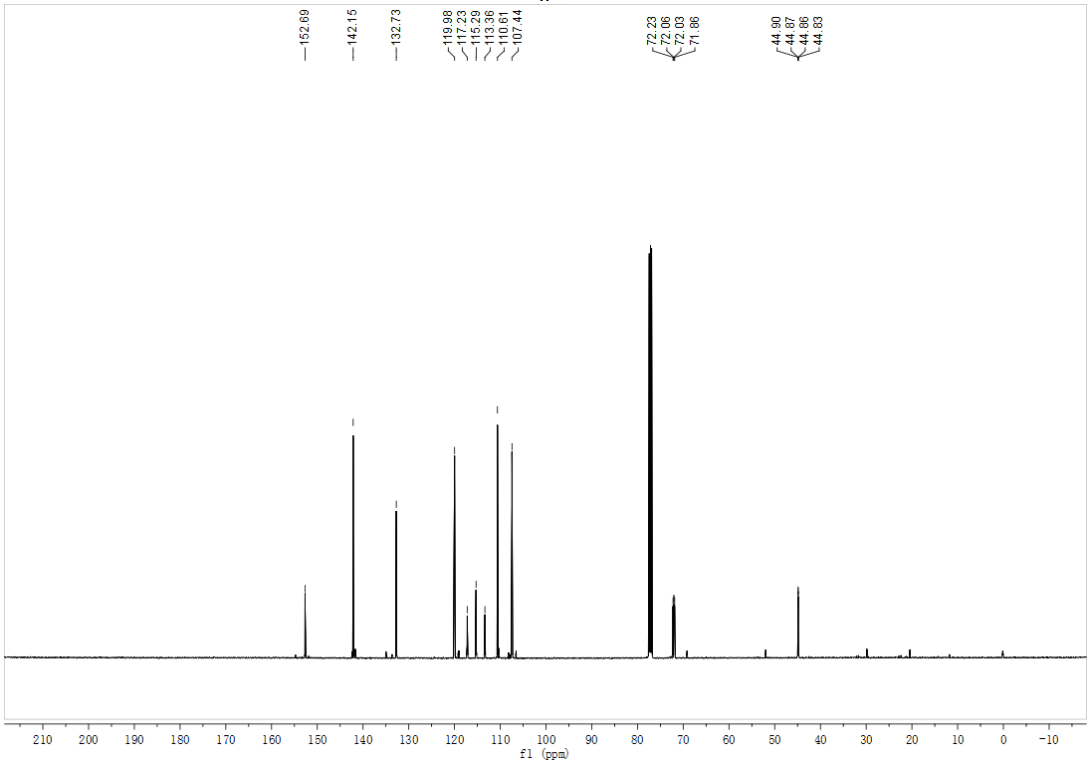
HRMS (CI) Calculated for $C_9H_{10}F_2O_2$ $[M]^+$ =188.0649, Found 188.0644.

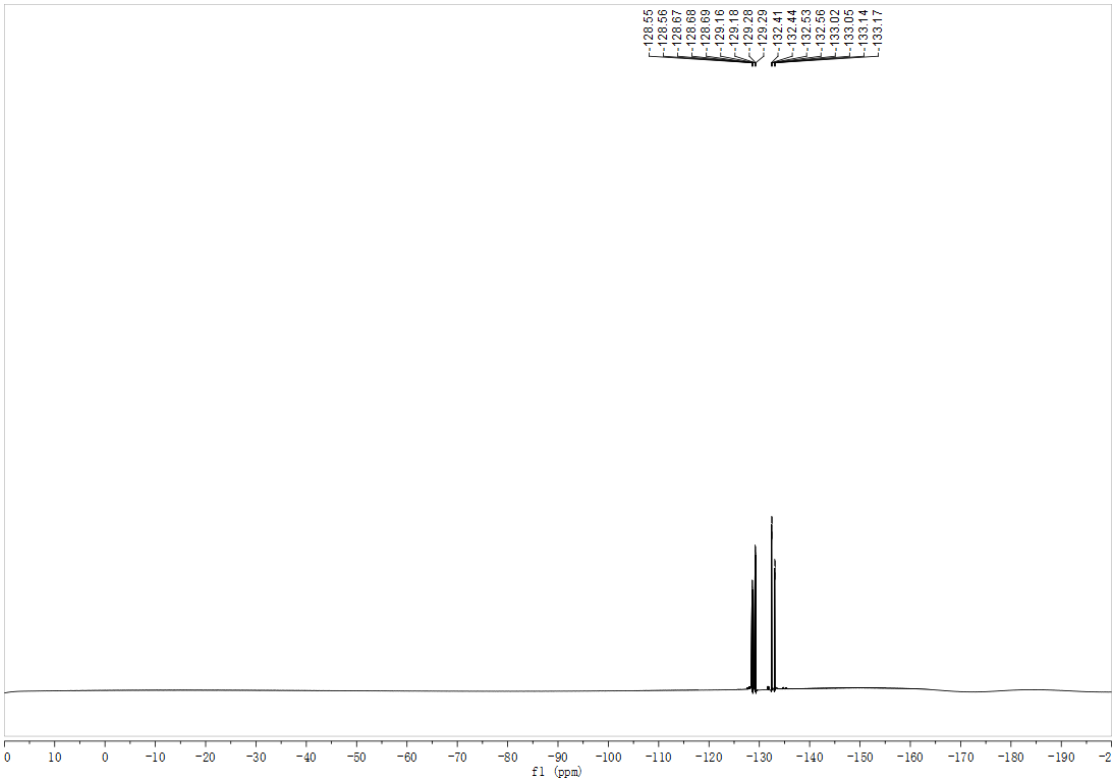
FTIR (neat) 3435, 2926, 1717, 1265, 1062, 935, 734, 703 cm^{-1}.

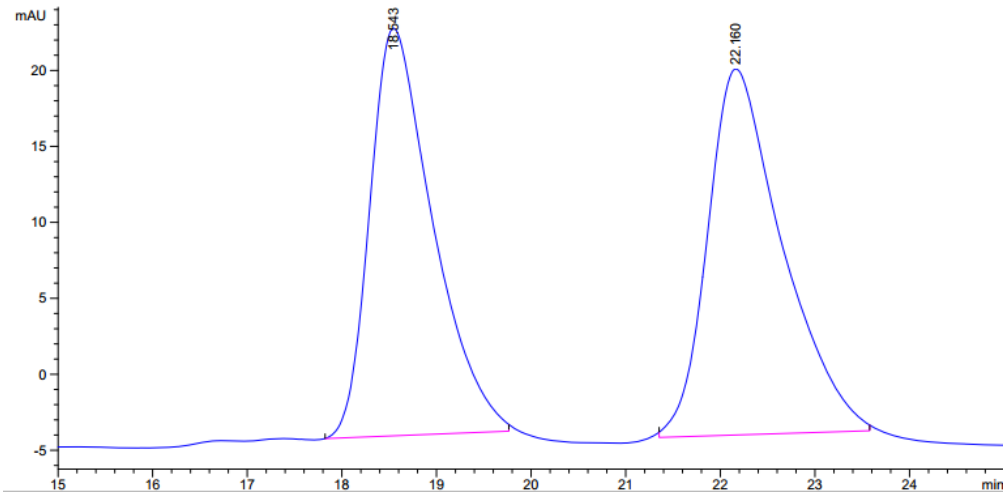
$[\alpha]_D^{33}$: –43.3 (*c* = 0.3, $CHCl_3$)

HPLC: (Chiralcel AD-H column, hexanes:*i*-PrOH = 99:1, 1.0 mL/min, 230 nm), *ee* = 91%.

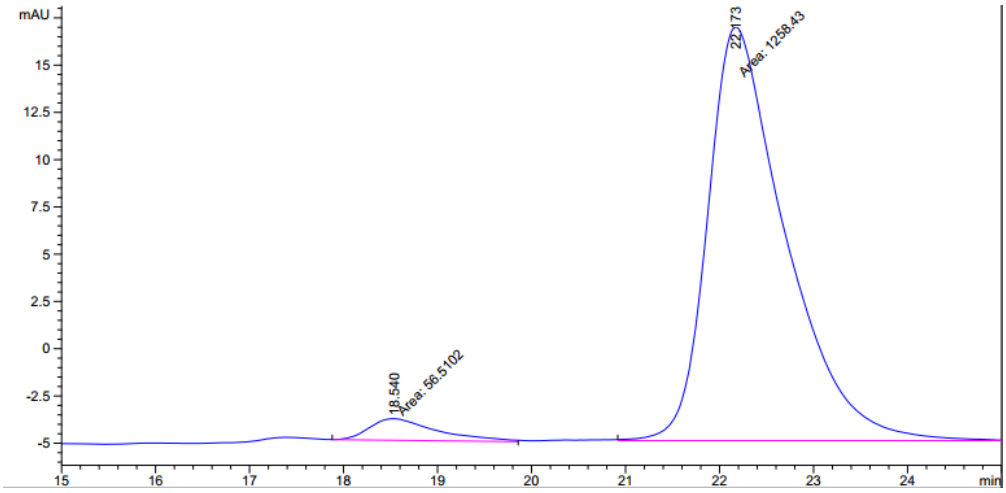

7.39
7.38
7.38
6.35
6.34
6.19
6.19
6.11
6.09
6.08
6.07
6.06
6.04
5.64
5.64
5.63
5.34
5.34
5.32
5.32
5.29
5.25
4.18
4.16
4.15
4.15
4.14
4.13
3.75
3.74
3.73
3.72
2.27
2.26
1.06
1.06
0.98
1.09
1.09
1.01
1.09
1.01
1.00
1.06
f1 (ppm)


152.69
142.15
132.73
119.98
117.23
115.29
113.36
110.61
107.44
72.23
72.06
72.03
71.86
44.90
44.87
44.86
44.83
f1 (ppm)


128.55
128.56
128.67
128.68
128.69
129.16
129.18
129.28
129.29
132.41
132.44
132.53
132.56
133.02
133.05
133.14
133.17
0
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-2
f1 (ppm)

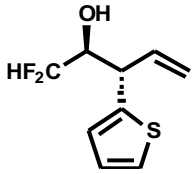


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.543	BB	0.6699	1241.43872	26.82661	48.4237
2	22.160	BB	0.7983	1322.26086	24.09177	51.5763



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.540	MM	0.8269	56.51017	1.13897	4.2975
2	22.173	MM	0.9590	1258.43079	21.87011	95.7025

(2*S*,3*S*)-1,1-difluoro-3-(thiophen-2-yl)pent-4-en-2-ol (6.5j)



The title compound was prepared according to the general procedure using difluoroacetaldehyde ethyl hemiacetal (90%, 28 mg, 200 μmol) and 1-(thiophen-2-yl)allyl acetate (73 mg, 0.40 mmol, 200 mol%). Flash chromatography on silica (Hex/EtOAc 20:1) provided the title compound (28.7 mg, 140 μmol, *anti:syn* = >20:1) in 70% yield as a yellow oil.

TLC (SiO_2) R_f = 0.54 (hexanes/ethyl acetate = 4:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.24 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.00 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.96 (s, 1H), 6.20 – 6.06 (m, 1H), 5.64 (ddd, *J* = 56.3, 54.9, 4.7 Hz, 1H), 5.34 – 5.24 (m, 2H), 4.03 (dt, *J* = 14.4, 4.8 Hz, 1H), 3.92 (dd, *J* = 8.9, 5.0 Hz, 1H), 2.30 (d, *J* = 4.3 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 142.3, 135.1, 127.2, 125.3, 124.8, 119.2, 115.3 (t, *J* = 243.3 Hz), 74.0 (dd, *J* = 24.6, 21.4 Hz), 46.3 (dd, *J* = 5.1, 2.7 Hz).

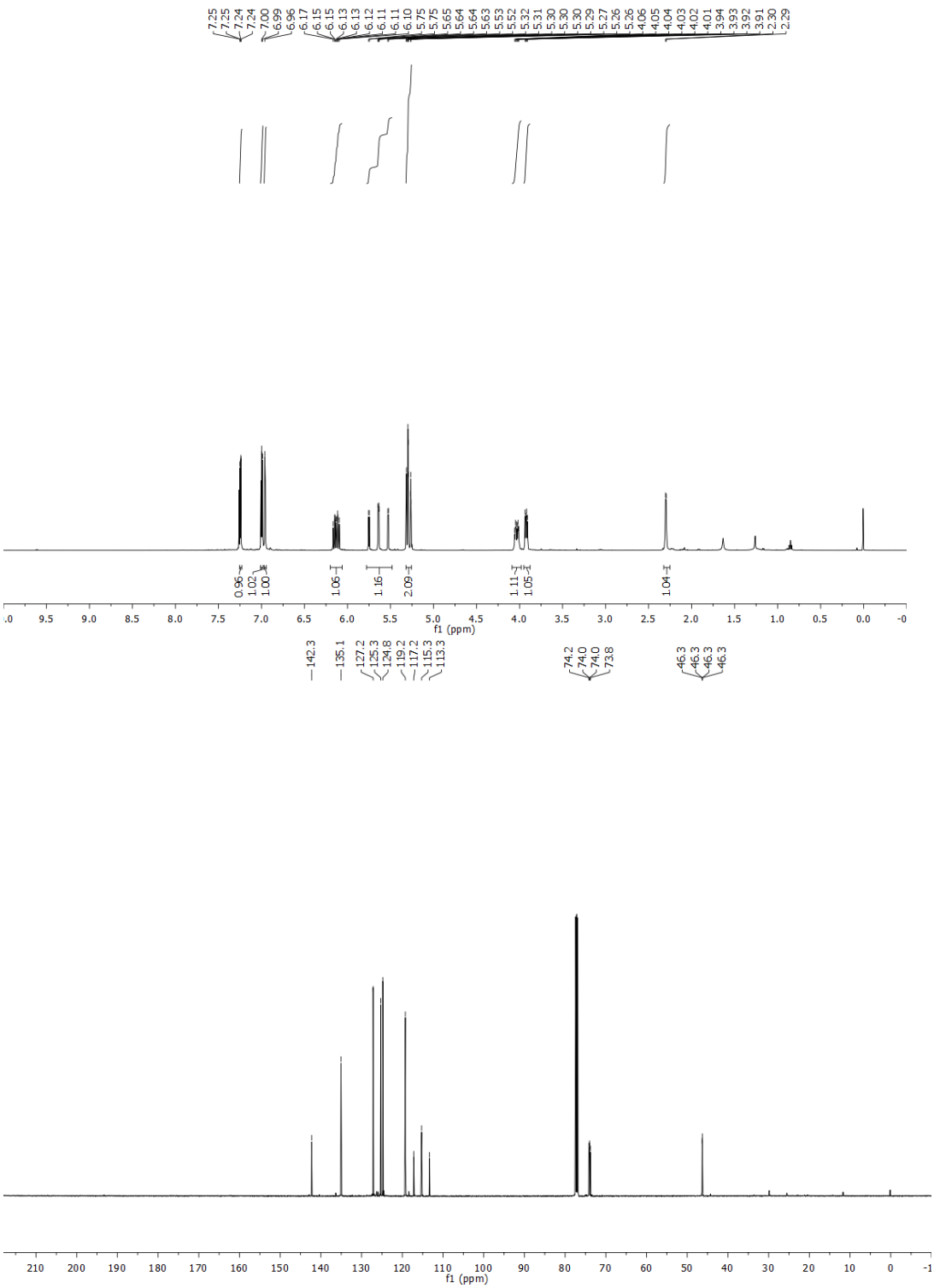
^{19}F NMR (471 MHz, $CDCl_3$): δ = -129.12 (ddd, *J* = 288.7, 54.9, 5.5 Hz), -133.10 (ddd, *J* = 288.6, 56.3, 14.3 Hz).

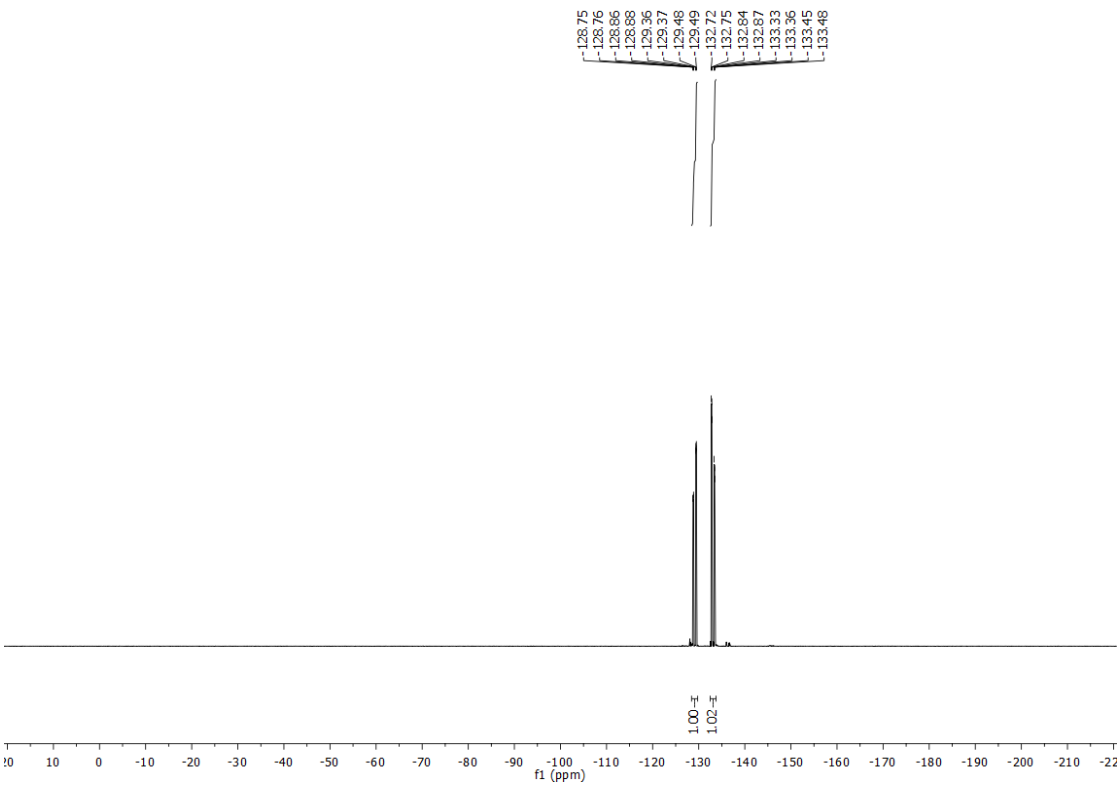
HRMS (CI) Calculated for $C_9H_{10}OF_2S$ $[M]^+$ = 204.0420, Found 204.0218.

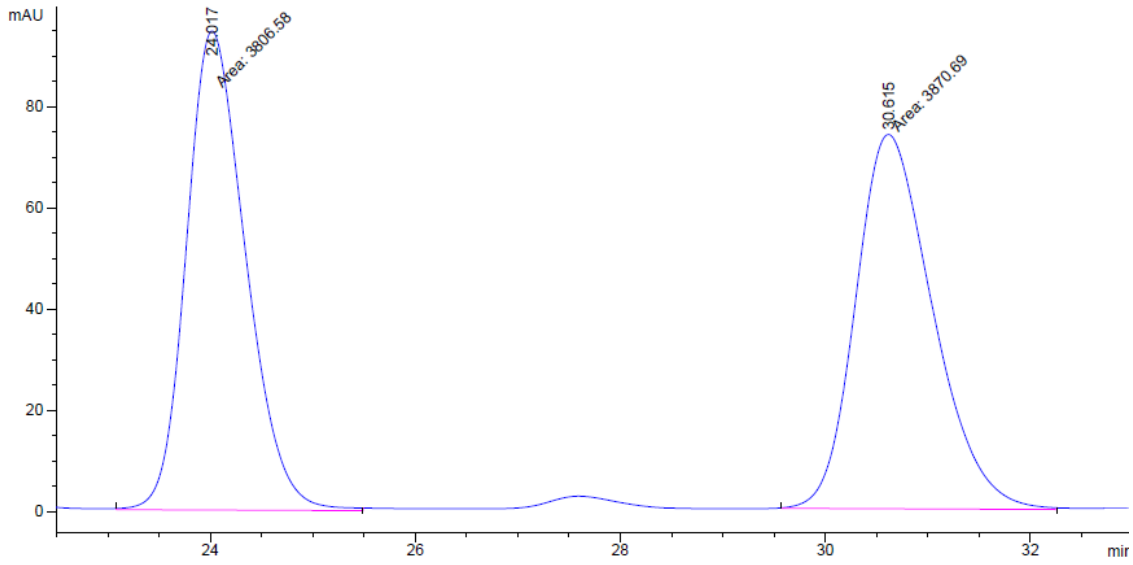
FTIR (neat) 3444, 1420, 1126, 1051, 928, 756, 697 cm^{-1}.

$[\alpha]_D^{33}$: –73.3 (*c* = 1.0, $CHCl_3$)

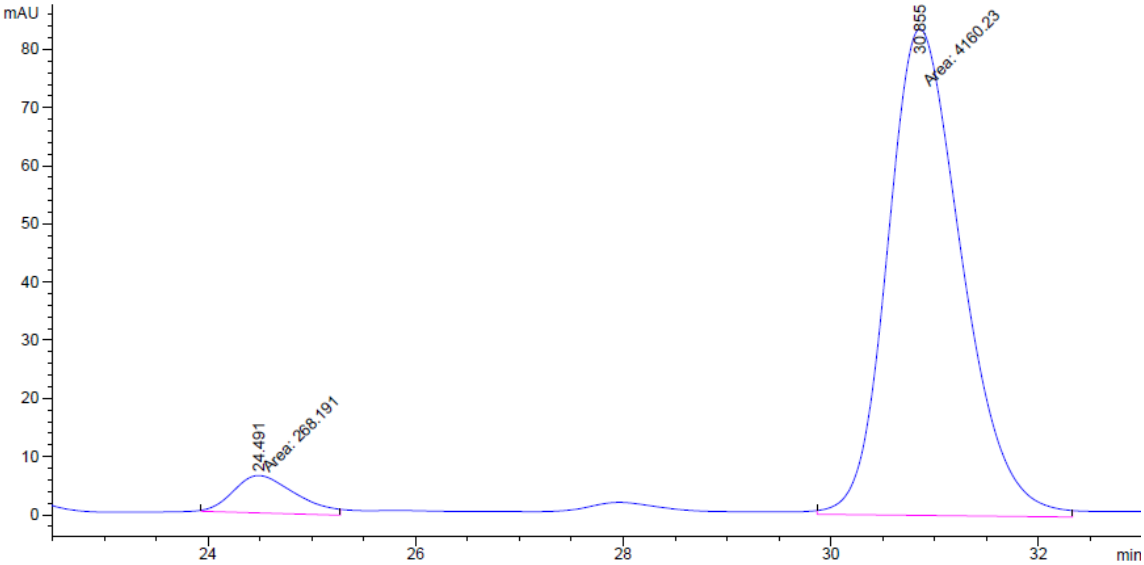
HPLC: (Chiralcel AD-H column, hexanes:*i*-PrOH = 99:1, 1.0 mL/min, 230 nm), *ee* = 88%.


7.25
7.25
7.24
7.24
7.00
6.99
6.96
6.17
6.15
6.15
6.13
6.13
6.12
6.11
6.11
6.10
5.75
5.75
5.65
5.64
5.64
5.63
5.53
5.52
5.32
5.31
5.30
5.30
5.30
5.29
5.27
5.26
5.26
4.06
4.05
4.04
4.03
4.02
4.01
3.94
3.93
3.92
3.91
2.30
2.29
0.96
1.02
1.00
1.06
1.16
2.09
1.11
1.05
1.04
f1 (ppm)
142.3
135.1
127.2
125.3
124.8
119.2
117.2
115.3
113.3
74.2
74.0
74.0
73.8
46.3
46.3
46.3
46.3
f1 (ppm)


128.75
128.76
128.86
128.88
129.36
129.37
129.48
129.49
132.72
132.75
132.84
132.87
133.33
133.36
133.45
133.48
1.00
1.02
f1 (ppm)

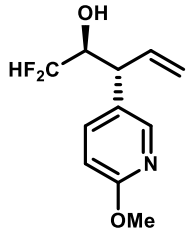


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	24.017	MM	0.6698	3806.58154	94.72547	49.5825
2	30.615	MM	0.8715	3870.68506	74.02729	50.4175



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	24.491	MM	0.6966	268.19061	6.41644	6.0561
2	30.855	MM	0.8292	4160.22949	83.61486	93.9439

(2S,3R)-1,1-difluoro-3-(6-methoxypyridin-3-yl)pent-4-en-2-ol (6.5k)



The title compound was prepared according to the general procedure using difluoroacetaldehyde ethyl hemiacetal (90%, 27.3 mg, 195 μmol) and 1-(6-methoxypyridin-3-yl)allyl acetate (83 mg, 0.40 mmol, 200 mol%). Flash chromatography on silica (Hex/EtOAc 6:1) provided the title compound (33.5 mg, 146 μmol, *anti:syn* = >20:1) in 75% yield as a yellow oil.

TLC (SiO_2) R_f = 0.37 (hexanes/ethyl acetate = 3:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.07 (d, *J* = 2.4 Hz, 1H), 7.54 (dd, *J* = 8.6, 2.4 Hz, 1H), 6.72 (d, *J* = 8.6 Hz, 1H), 6.21 – 6.11 (m, 1H), 5.60 (td, *J* = 55.7, 4.5 Hz, 1H), 5.28 (d, *J* = 10.2 Hz, 1H), 5.21 (d, *J* = 17.1 Hz, 1H), 3.97 – 3.92 (m, 1H), 3.91 (s, 3H), 3.55 (dd, *J* = 8.6, 5.4 Hz, 1H), 2.53 (s, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.5, 146.3, 138.7, 135.2, 128.3, 119.2, 115.4 (t, *J* = 243.6 Hz), 111.1, 73.7 (dd, *J* = 24.2, 21.4 Hz), 53.6, 47.4 (dd, *J* = 4.6, 2.5 Hz).

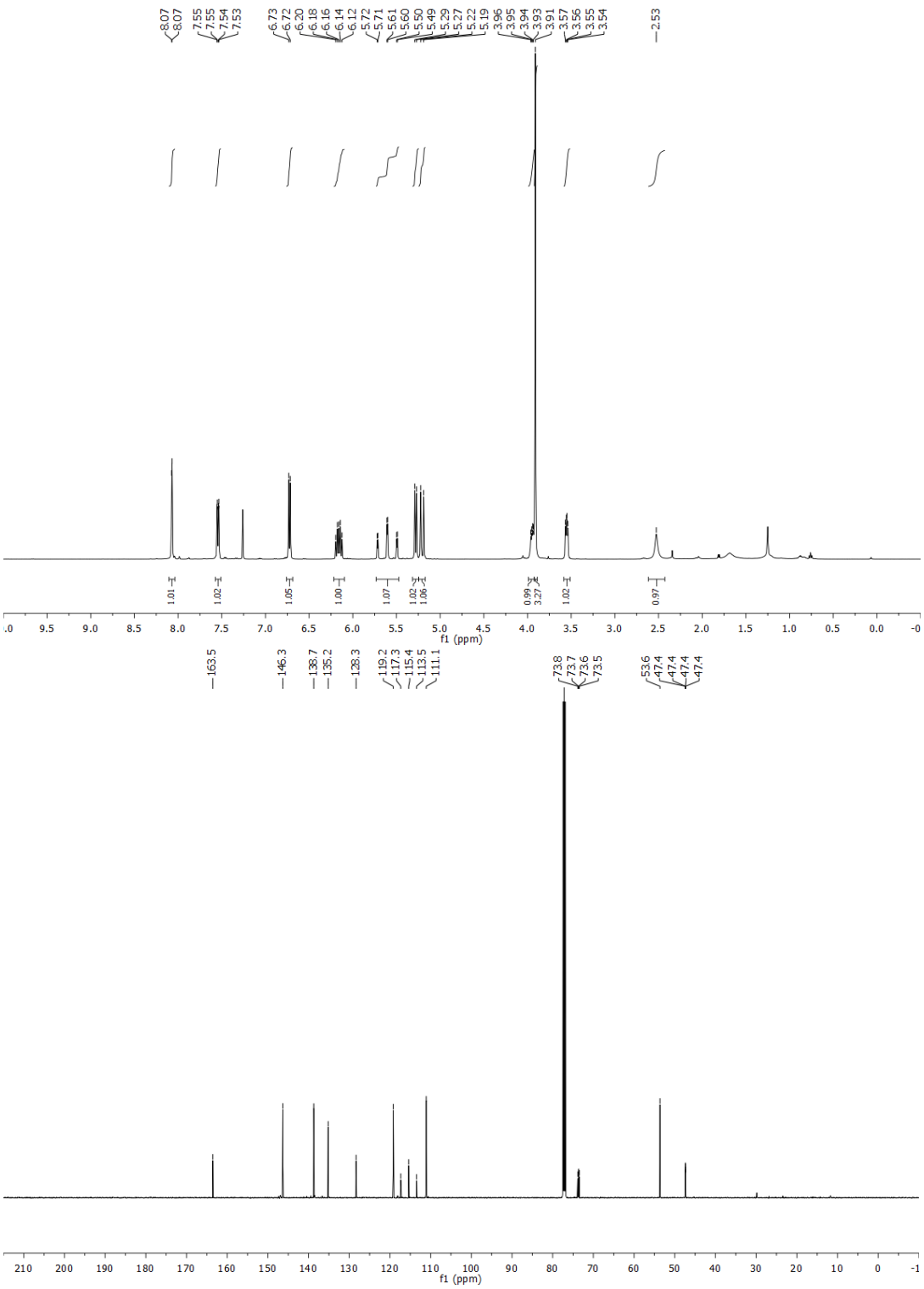
^{19}F NMR (471 MHz, $CDCl_3$): δ = -128.9 (ddd, *J* = 288.4, 55.1, 6.1 Hz), -132.8 (ddd, *J* = 288.5, 56.4, 14.0 Hz).

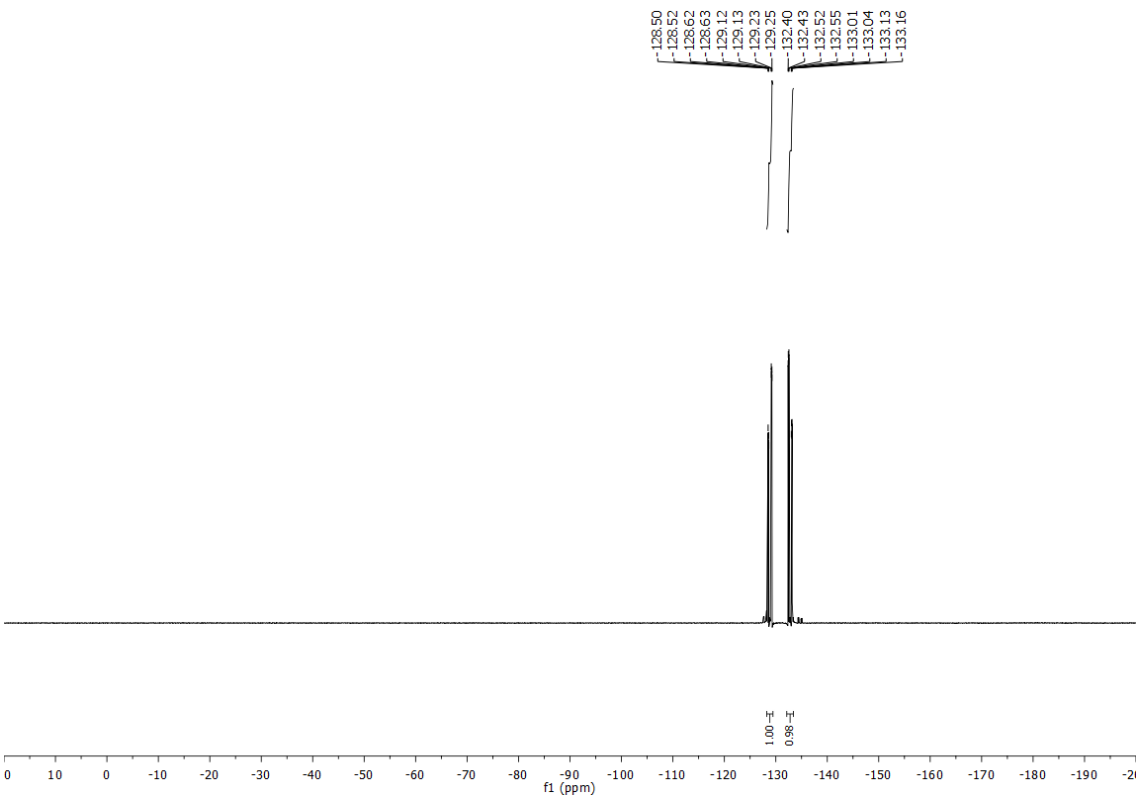
HRMS (ESI) Calculated for $C_{11}H_{13}F_2NO_2$ $[M+H]^+$ = 230.0987, Found 230.0994.

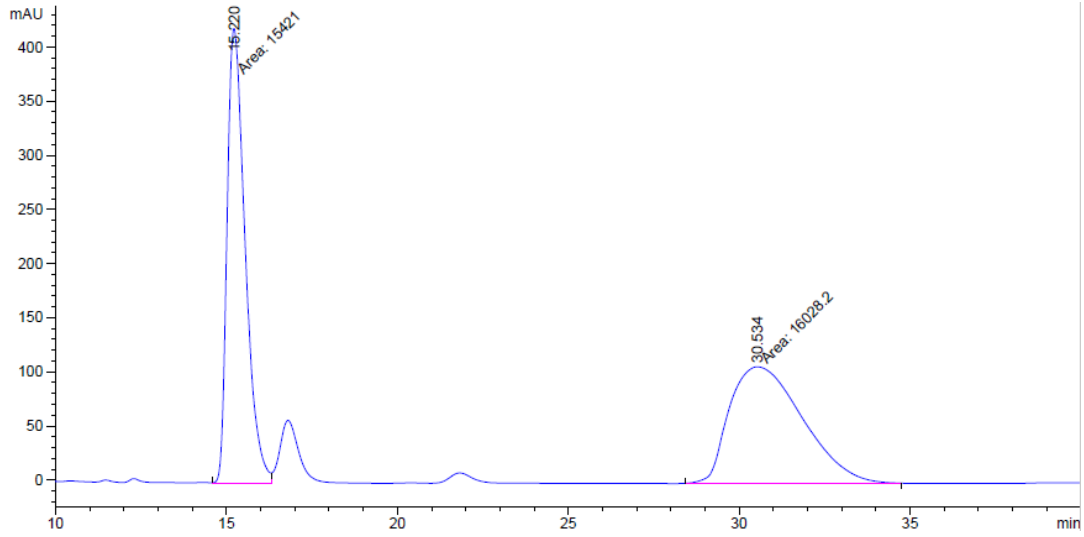
FTIR (neat) 3235, 2982, 2922, 1607, 1494, 1393, 1291, 1126, 1059, 1029, 928, 833, 774 cm^{-1}.

$[\alpha]_D^{29}$: –79.5 (*c* = 1.0, $CHCl_3$)

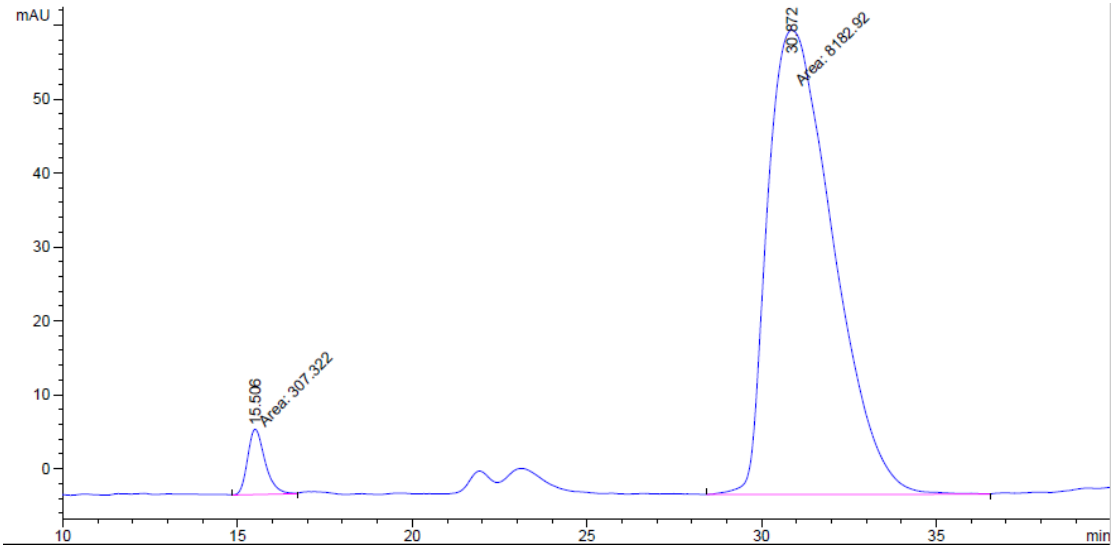
HPLC: (Chiralcel AS-H column, hexanes:*i*-PrOH = 97:3, 1.0 mL/min, 230 nm), *ee* = 93%.


8.07
8.07
7.55
7.55
7.54
7.53
6.73
6.72
6.20
6.18
6.16
6.14
6.12
5.72
5.71
5.61
5.60
5.50
5.49
5.29
5.27
5.22
5.19
3.96
3.95
3.94
3.93
3.91
3.57
3.56
3.55
3.54
2.53
1.01
1.02
1.05
1.00
1.07
1.02
1.06
0.99
3.27
1.02
0.97
f1 (ppm)
163.5
146.3
138.7
135.2
128.3
119.2
117.3
115.4
113.5
111.1
73.8
73.7
73.6
73.5
53.6
47.4
47.4
47.4
47.4
f1 (ppm)


128.50
128.52
128.62
128.63
129.12
129.13
129.23
129.25
132.40
132.43
132.52
132.55
133.01
133.04
133.13
133.16
1.00
0.98
0
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

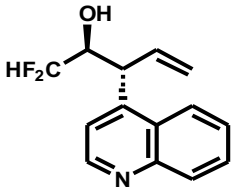


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.220	MF	0.6120	1.54210e4	419.95688	49.0348
2	30.534	MM	2.4809	1.60282e4	107.67802	50.9652



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.506	MM	0.5801	307.32208	8.82987	3.6197
2	30.872	MM	2.1719	8182.91895	62.79467	96.3803

(2*S*,3*R*)-1,1-difluoro-3-(quinolin-4-yl)pent-4-en-2-ol (6.5l)



The title compound was prepared according to the general procedure using difluoroacetaldehyde ethyl hemiacetal (90%, 28 mg, 200 μmol) and 1-(quinolin-4-yl)allyl acetate (91 mg, 0.40 mmol, 200 mol%). Flash chromatography on silica (Hex/EtOAc 3:1→ 1:1) provided the title compound (42.6 mg, 172 μmol, *anti:syn* = >20:1) in 86% yield as a white solid.

TLC (SiO_2) R_f = 0.26 (hexanes/ethyl acetate = 1:1).

^{1}H NMR (500 MHz, Acetone-d_6): δ = 8.81 (d, *J* = 4.5 Hz, 1H), 8.21 (ddt, *J* = 8.5, 1.3, 0.6 Hz, 1H), 8.04 (ddd, *J* = 8.4, 1.4, 0.6 Hz, 1H), 7.74 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.66 (dd, *J* = 8.4, 1.4 Hz, 1H), 7.62 – 7.60 (m, 1H), 6.51 (ddd, *J* = 17.2, 10.3, 8.8 Hz, 1H), 5.82 (ddd, *J* = 56.5, 55.3, 5.1 Hz, 1H), 5.35 – 5.27 (m, 2H), 4.56 (dd, *J* = 9.0, 4.0 Hz, 1H), 4.23 – 4.13 (m, 1H), 2.99 (s, 1H).

^{13}C NMR (125 MHz, Acetone-d_6): δ = 150.7, 149.3, 147.4, 135.8, 131.0, 129.7, 127.5, 127.0, 123.7, 121.7, 119.2, 117.1 (t, *J* = 243.6 Hz), 73.1 (dd, *J* = 24.9, 21.4 Hz), 45.3 (dd, *J* = 5.7, 2.5 Hz).

^{19}F NMR (471 MHz, Acetone-d_6): δ = -128.48 (ddd, *J* = 285.2, 55.3, 6.4 Hz), -131.12 (ddd, *J* = 285.0, 56.7, 14.0 Hz).

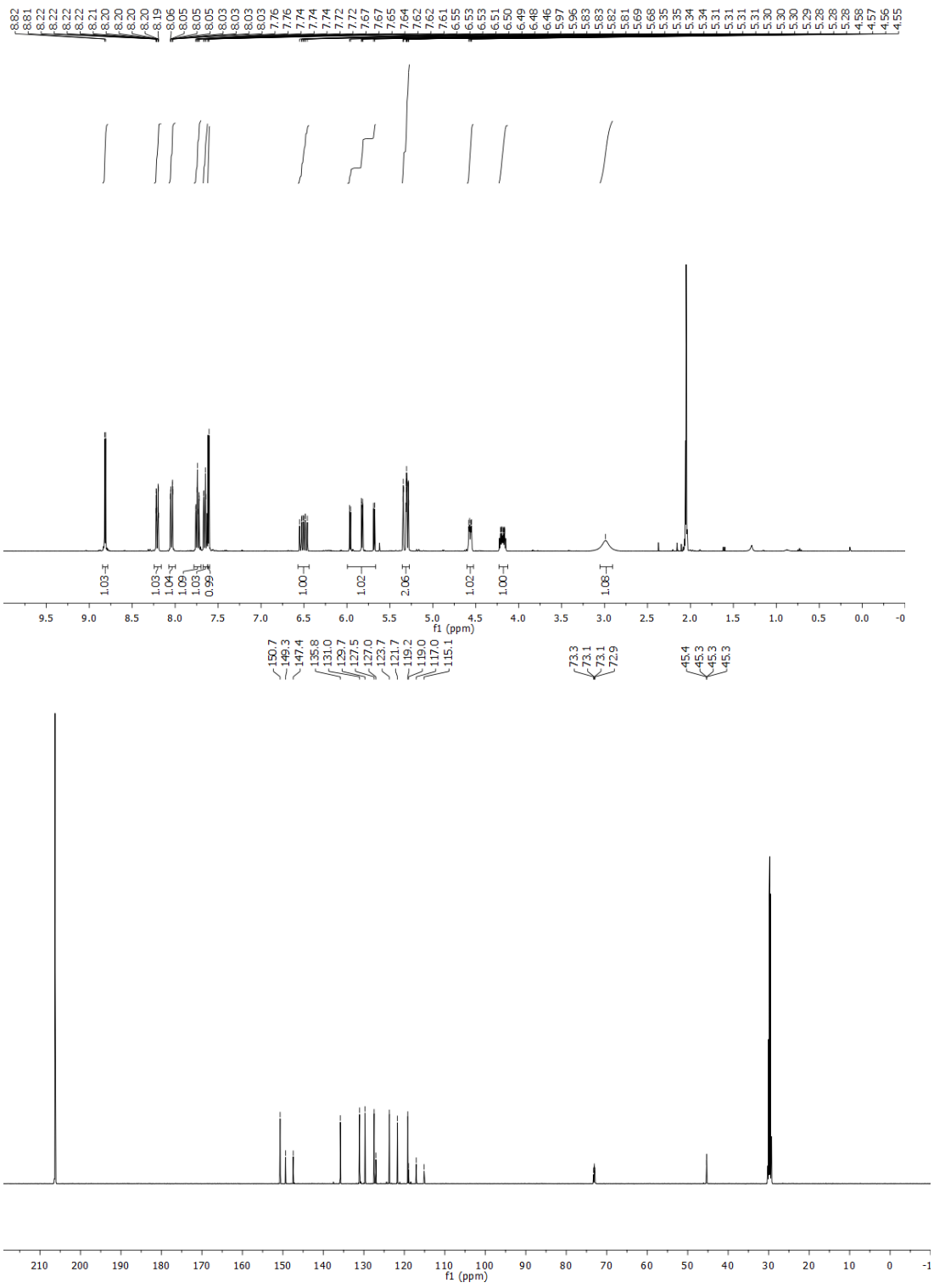
HRMS (ESI) Calculated for $C_{14}H_{13}F_2NO$ $[M+H]^+$ = 250.1038, Found 250.1036.

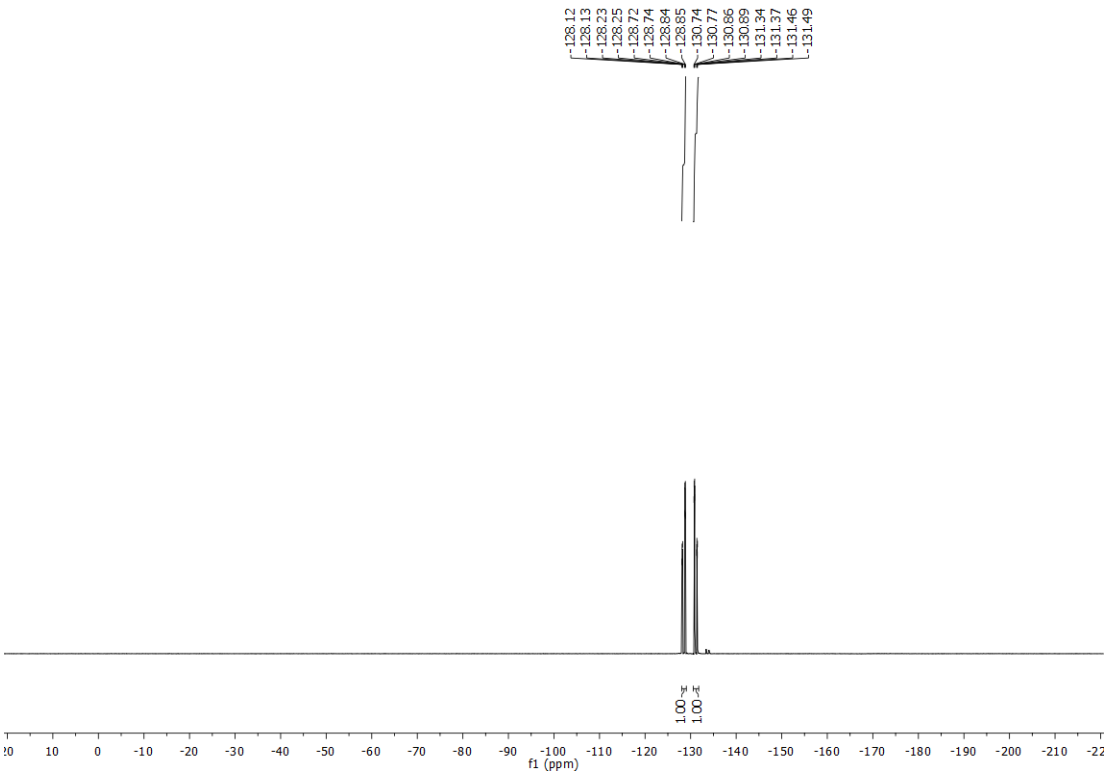
FTIR (neat) 3086, 2361, 1737, 1589, 1280, 1054, 927, 768, 660 cm^{-1}.

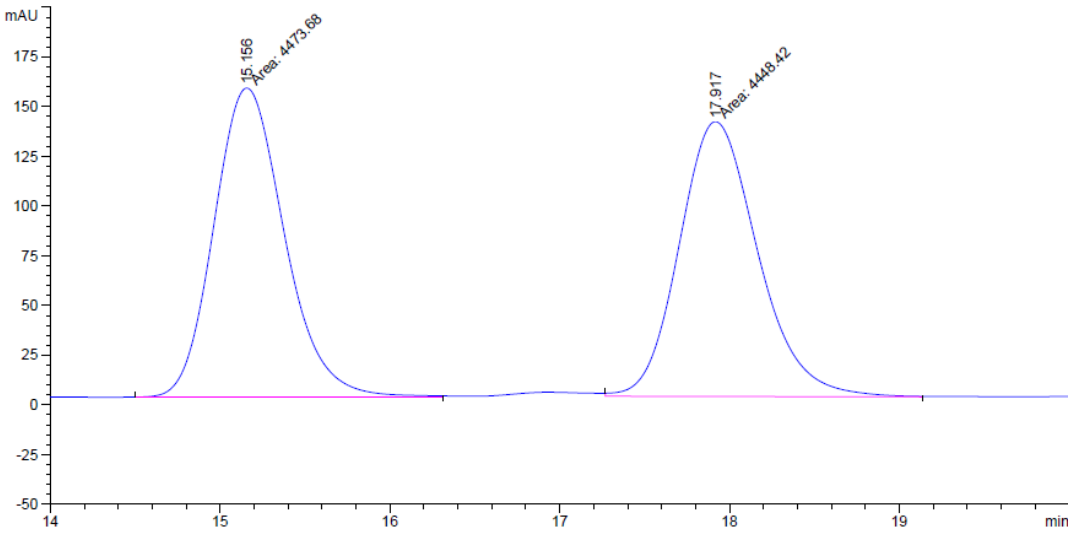
$[\alpha]_D^{33}$: –33.5 (*c* = 1.0, Acetone)

MP: 153-157˚C

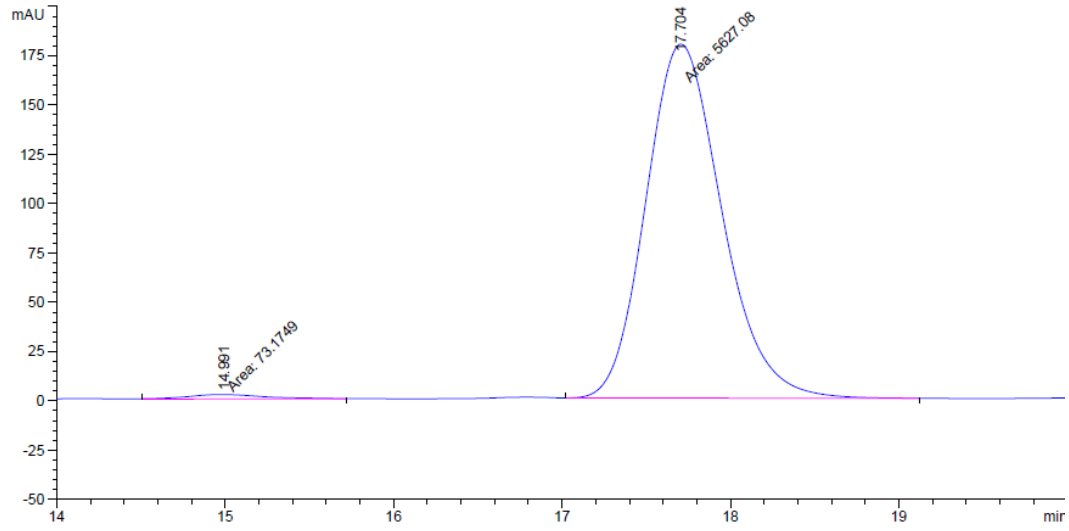
HPLC: (Chiralcel AD-H column, hexanes:*i*-PrOH = 95:5, 1.0 mL/min, 210 nm), *ee* = 97%.




-128.12
-128.13
-128.23
-128.25
-128.72
-128.74
-128.84
-128.85
-130.74
-130.77
-130.86
-130.89
-131.34
-131.37
-131.46
-131.49
1.00
1.00
f1 (ppm)



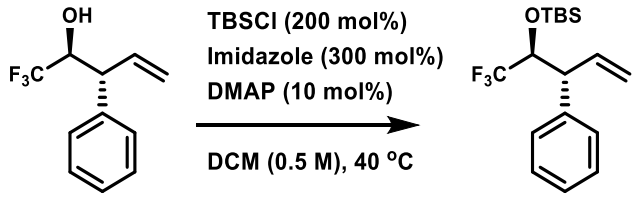
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.156	MM	0.4799	4473.67725	155.36191	50.1416
2	17.917	FM	0.5363	4448.41699	138.24548	49.8584



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.991	MM	0.5392	73.17490	2.26182	1.2837
2	17.704	MM	0.5226	5627.07617	179.45941	98.7163

Enantioselective Synthesis of Di- and Trifluoro-methylated Derivatives of *d*-Hyoscyamine 6.8a and 6.8b

tert-butyldimethyl(((2S,3R)-1,1,1-trifluoro-3-phenylpent-4-en-2-yl)oxy)silane (6.6a')



6.4a 6.6a'

To a solution of alcohol **6.4a** (216.2 mg, 1.000 mmol, 100 mol%) in CH_2Cl_2 (2 mL) was added imidazole (204.2 mg, 3.000 mmol, 300 mol%), TBSCl (301.5 mg, 2.000 mmol, 200 mol%) and 4-(dimethylamino)pyridine (12.2 mg, 0.100 mmol, 10 mol%). The reaction was heated to 40 °C for 24 h. The contents were diluted with CH_2Cl_2 (2 mL) and washed with H_2O (2 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 2 mL), and the combined organic phases were washed with brine (2 mL), dried (Na_2SO_4), filtered and the solvent was removed *in vacuo*. The residue was subjected to flash chromatography on silica (Hexanes) to furnish the title compound **6.6a'** (239.8 mg, 0.726 mmol) in 73% yield as a clear oil.

TLC (SiO_2) R_f = 0.43 (hexanes).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.34 – 7.29 (m, 2H), 7.25 – 7.21 (m, 3H), 6.41 – 6.24 (m, 1H), 5.25 (dd, *J* = 10.3, 1.6 Hz, 1H), 5.16 (d, *J* = 17.2 Hz, 1H), 4.23 (qd, *J* = 6.7, 3.7 Hz, 1H), 3.75 (dd, *J* = 9.1, 3.6 Hz, 1H), 0.85 (s, 9H), -0.02 (s, 3H), -0.36 (s, 3H).

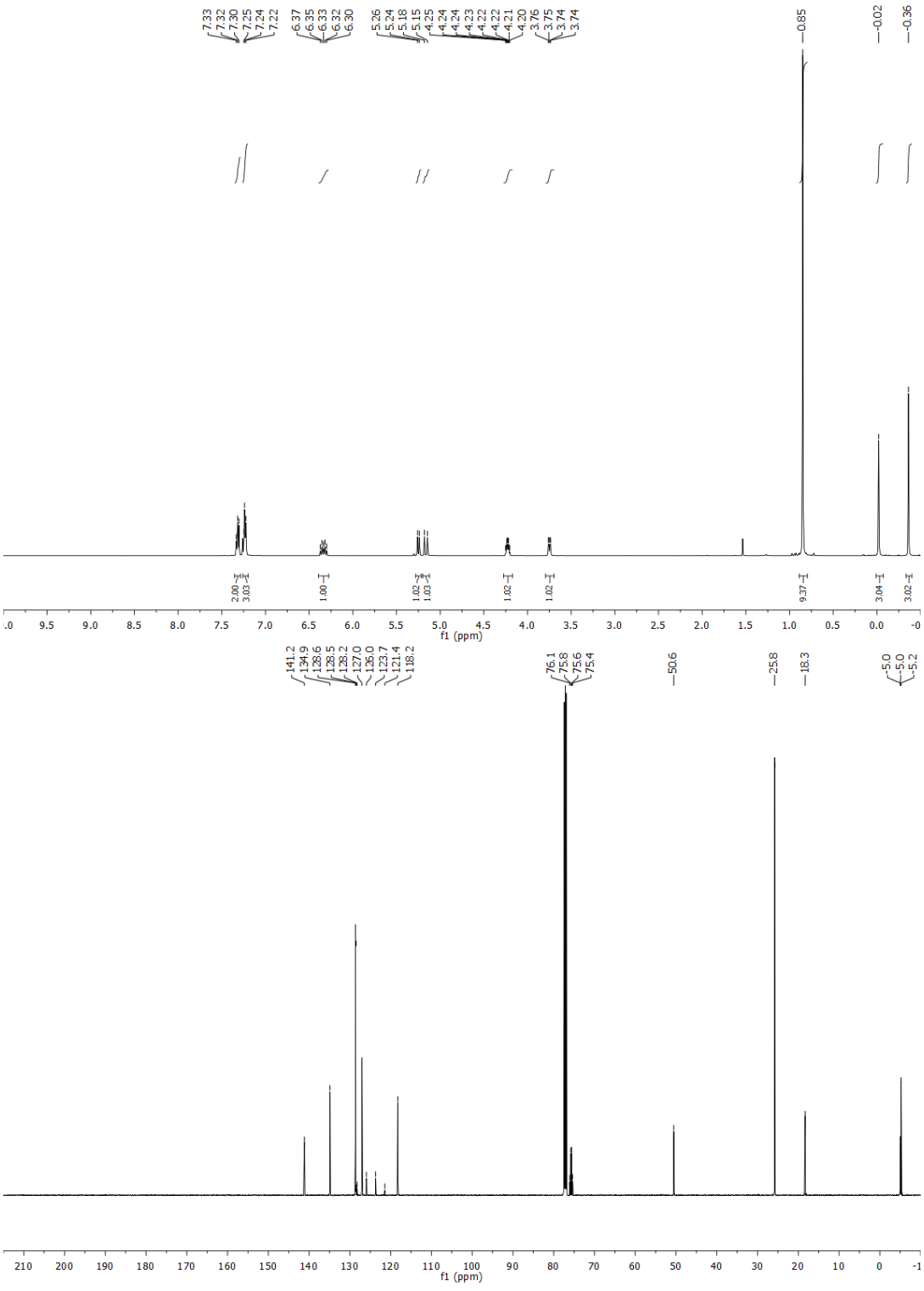
^{13}C NMR (125 MHz, $CDCl_3$): δ = 141.2, 134.9, 128.6, 128.5, 127.0, 124.8 (q, *J* = 284.9 Hz), 118.2, 75.7 (q, *J* = 29.0 Hz), 50.6, 25.8, 18.3, -5.0 (q, *J* = 1.9 Hz), -5.2.

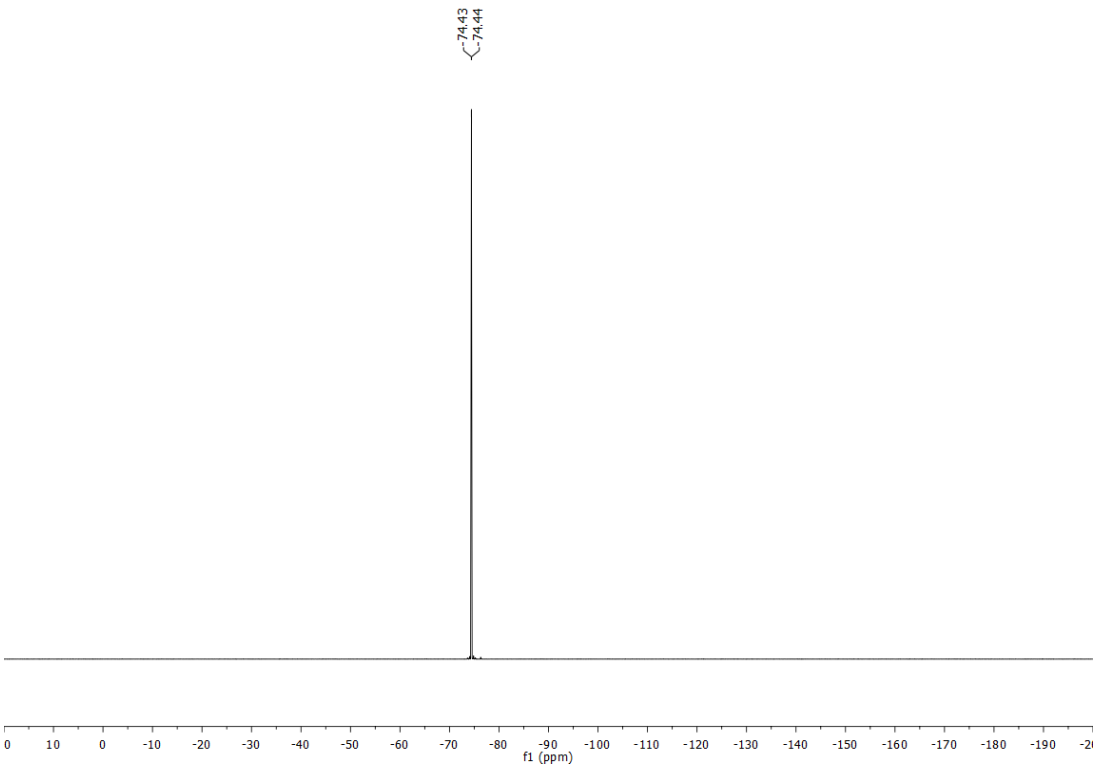
^{19}F NMR (471 MHz, $CDCl_3$): δ = -74.43 (d, *J* = 6.6 Hz).

HRMS (CI) Calculated for $C_{17}H_{25}F_3OSi$ $[M+H]^+$ = 331.1705, Found 331.1706.

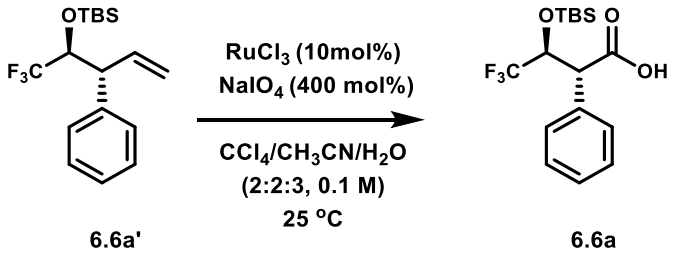
FTIR (neat) 2931, 2860, 1473, 1382, 1260, 1145, 1115, 1002, 927, 876, 829, 779, 700 cm^{-1}.

$[\alpha]_D^{26}$: –140.5 (*c* = 1.0, $CHCl_3$)


7.33
7.32
7.30
7.25
7.24
7.22
6.37
6.35
6.33
6.32
6.30
5.26
5.24
5.18
5.15
4.25
4.24
4.24
4.23
4.22
4.22
4.21
4.20
3.76
3.75
3.74
3.74
0.85
-0.02
-0.36
2.00
3.03
1.00
1.02
1.03
1.02
1.02
9.37
3.04
3.02
f1 (ppm)
141.2
134.9
128.6
128.5
128.2
127.0
126.0
123.7
121.4
118.2
76.1
75.8
75.6
75.4
50.6
25.8
18.3
-5.0
-5.0
-5.2
f1 (ppm)


-74.43
-74.44
0
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

(2R,3S)-3-((tert-butyldimethylsilyl)oxy)-4,4,4-trifluoro-2-phenylbutanoic acid (6.6a)



6.6a' 6.6a

To a stirred solution of **6.6a'** (195.0 mg, 0.590 mmol, 100 mol%), in 1.7 mL CCl_4, 1.7 mL CH_3CN, and 2.5 mL H_2O was added $NaIO_4$ (504.8 mg, 2.360 mmol, 400 mol%). After all the $NaIO_4$ had dissolved, $RuCl_3.2H_2O$ (14.4 mg, 0.059 mmol, 10 mol%) was added, and the reaction mixture was stirred vigorously for 24 h at 25 °C. The contents were diluted with EtOAc (5 mL) and washed with H_2O (5 mL). The aqueous layer was extracted with EtOAc (2 x 5 mL), and the combined organic phases were washed with brine (5 mL), dried (Na_2SO_4), filtered and the solvent was removed *in vacuo*. The residue was subjected to flash chromatography on silica (Hex/EtOAc 5:1) to furnish the title compound **6.6a** (145.2 mg, 0.417 mmol) in 71% yield as a white solid.

TLC (SiO_2) R_f = 0.43 (hexanes/ethyl acetate = 3:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.40 – 7.29 (m, 5H), 4.60 (dq, *J* = 9.4, 6.1 Hz, 1H), 3.97 (d, *J* = 9.5 Hz, 1H), 0.85 (s, 9H), 0.14 (s, 3H), 0.08 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.7, 132.7, 128.9, 128.6, 124.3 (q, *J* = 284.1 Hz), 73.1 (q, *J* = 29.7 Hz), 55.1, 25.7, 18.3, -4.8 – -4.9 (m), -5.0.

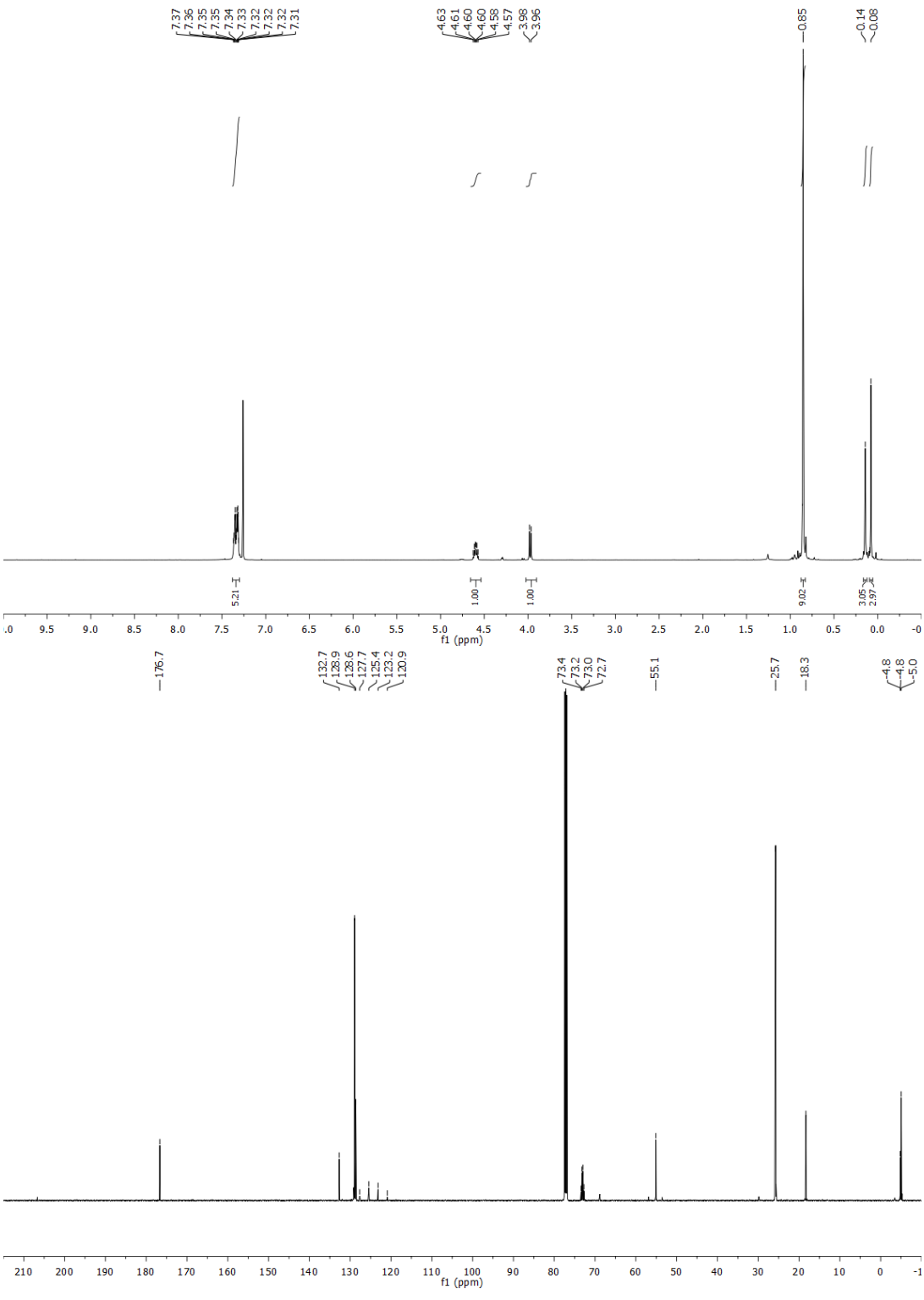
^{19}F NMR (471 MHz, $CDCl_3$): δ = -73.71 (d, *J* = 5.9 Hz).

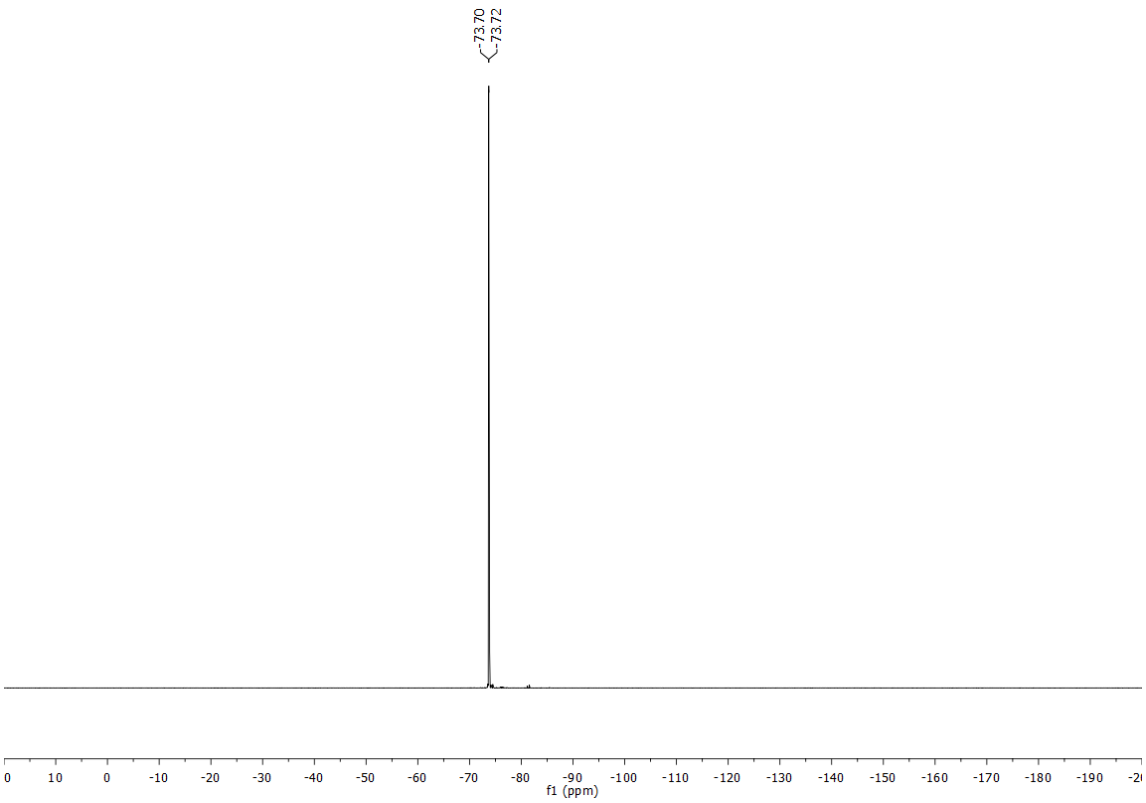
HRMS (CI) Calculated for $C_{16}H_{23}F_3O_3Si$ $[M+H]^+$ = 349.1447, Found 349.1449.

FTIR (neat) 2932, 2861, 1709, 1363, 1265, 1174, 1131, 892, 834, 784 cm^{-1}.

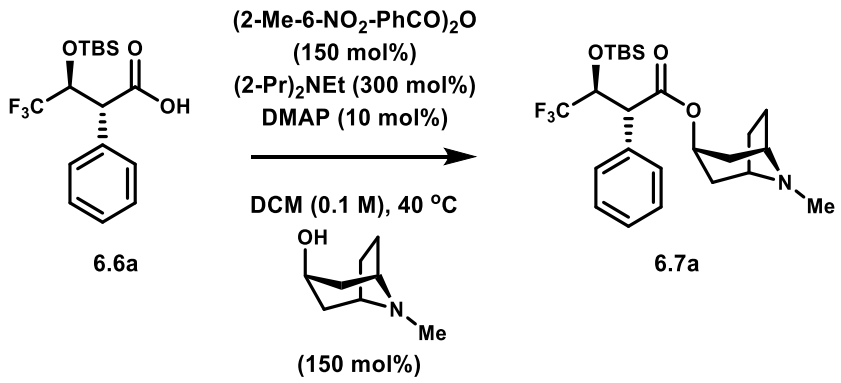
$[\alpha]_D^{28}$: –88.0 (*c* = 1.0, $CHCl_3$)

MP: 100-105˚C


7.37
7.36
7.35
7.35
7.34
7.33
7.32
7.32
7.32
7.31
4.63
4.61
4.60
4.60
4.58
4.57
3.98
3.96
0.85
0.14
0.08
5.21
1.00
1.00
9.02
3.05
2.97
f1 (ppm)
176.7
132.7
128.9
128.6
127.7
125.4
123.2
120.9
73.4
73.2
73.0
72.7
55.1
25.7
18.3
-4.8
-4.8
-5.0
f1 (ppm)


-73.70
-73.72
0
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

(1R,3r,5S)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl (2R,3S)-3-((tert-butyldimethylsilyl)oxy)-4,4,4-trifluoro-2-phenylbutanoate (6.7a)



A vial equipped with a magnetic stir bar was charged with **6.6a** (19.9 mg, 0.0571 mmol, 100 mol%), 2-methyl-6-nitrobenzoic anhydride (29.5 mg, 0.0857 mmol, 150 mol%), 4-(dimethylamino)pyridine (0.7 mg, 0.0057 mmol, 10 mol%) and purged with argon. Freshly distilled CH_2Cl_2 (570 μL) and *N,N*-diisopropylethylamine (29.3 μL, 0.1713 mmol, 300 mol%), were added sequentially via syringe. The resulting mixture was stirred at 25 °C for 10 minutes. Tropine (12.1 mg, 0.0857 mmol, 150 mol%) was added in a single portion at 25 °C. The reaction was stirred at 40 °C for 20 h. The reaction mixture was concentrated, and the residue was subjected to flash chromatography on basic alumina (DCM/MeOH 98:2) to furnish the title compound **6.7a** (23.7 mg, 0.0503 mmol, 7:1 dr) in 88% yield as a clear oil.

TLC (Basic Alumina) R_f = 0.50 (DCM/MeOH = 95:5).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.37 – 7.27 (m, 5H), 4.98 (t, *J* = 5.4 Hz, 1H), 4.70 (dq, *J* = 8.3, 5.8 Hz, 1H), 3.81 (d, *J* = 8.5 Hz, 1H), 3.05 (dt, *J* = 6.9, 3.2 Hz, 1H), 2.94 (dt, *J* = 6.8, 3.0 Hz, 1H), 2.21 (s, 3H), 2.10 (dt, *J* = 14.2, 4.2 Hz, 1H), 2.02 (dt, *J* = 15.1, 4.5 Hz, 1H), 1.91 (qdd, *J* = 10.6, 9.0, 7.3, 4.0 Hz, 1H), 1.81 – 1.72 (m, 2H), 1.70 – 1.65 (m, 1H), 1.50 – 1.41 (m, 1H), 1.40 – 1.33 (m, 1H), 0.68 (s, 9H), 0.03 (s, 3H), -0.41 (s, 3H).

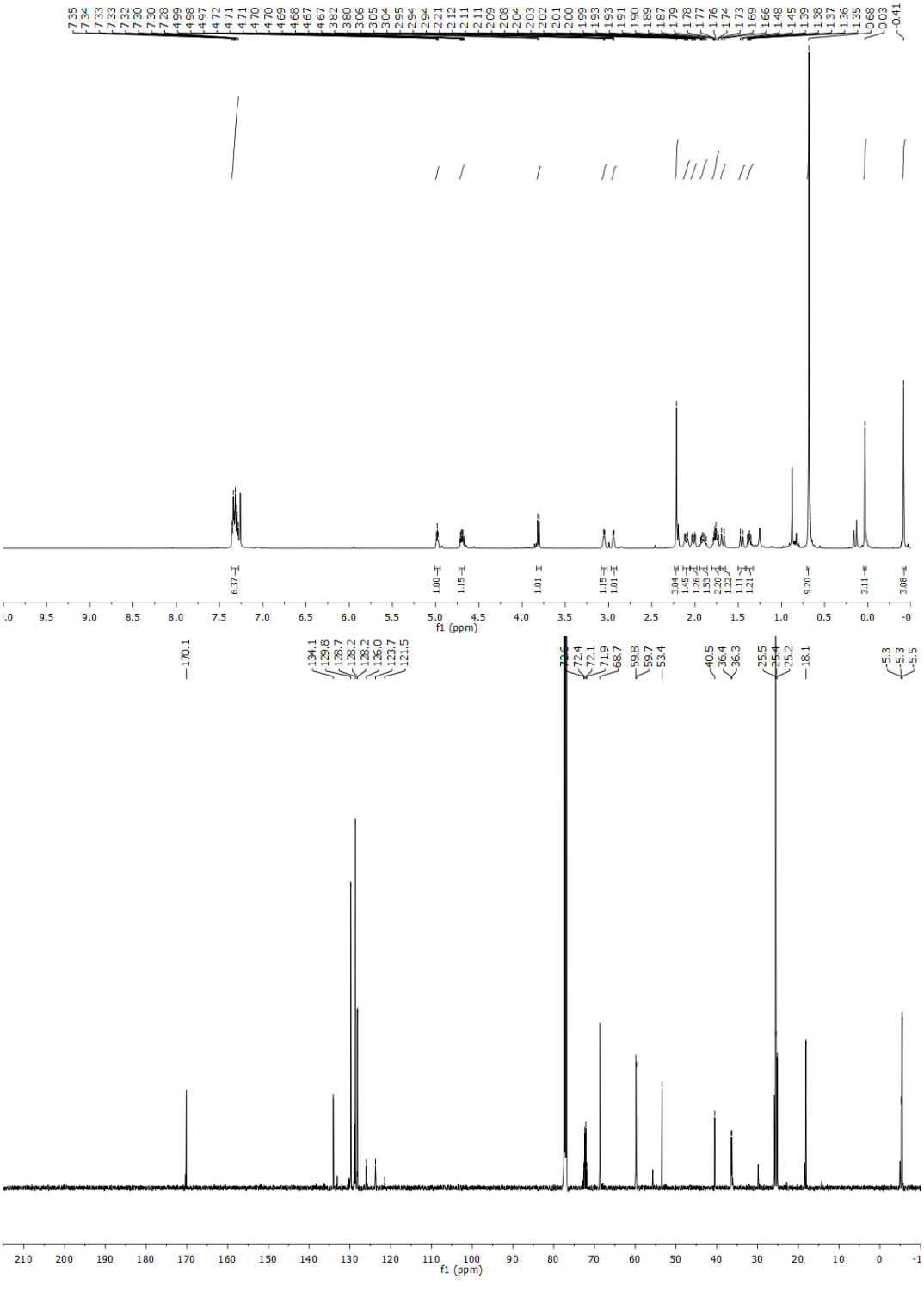
^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.1, 134.1, 129.8, 128.7, 128.2, 124.9 (q, *J* = 284.3 Hz), 72.3 (q, *J* = 30.3 Hz), 68.7, 59.8, 59.7, 53.4, 40.5, 36.4, 36.3, 25.5, 25.4, 25.2, 18.1, -5.2 – -5.4 (m), -5.5.

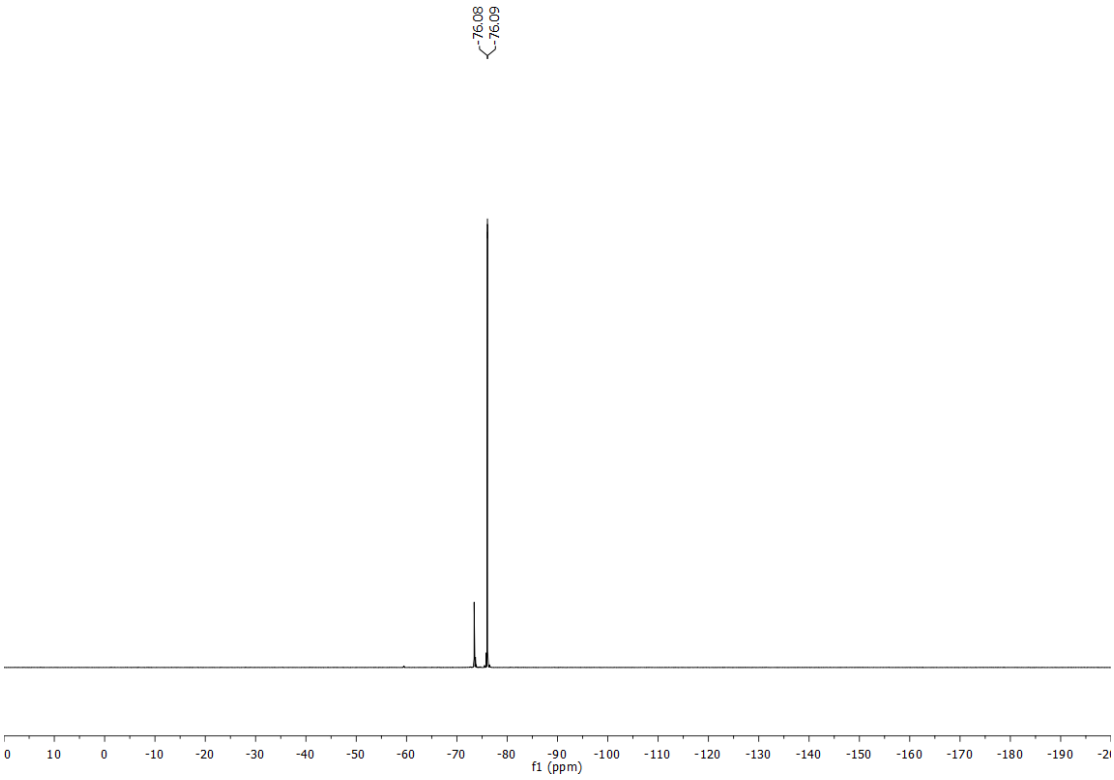
^{19}F NMR (471 MHz, $CDCl_3$): δ = -76.08 (d, *J* = 5.8 Hz).

HRMS (APPI) Calculated for $C_{24}H_{36}F_3NO_3Si$ $[M+H]^+$ = 472.2489, Found 472.2498.

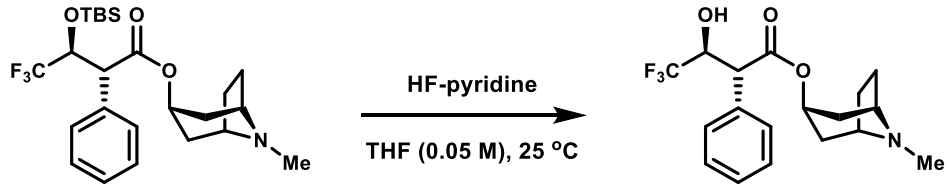
FTIR (neat) 2931, 2859, 1731, 1473, 1269, 1168, 1128, 1034, 840, 782, 700 cm^{-1}.

$[\alpha]_D^{26}$: –31.5 (*c* = 1.0, $CHCl_3$)




-76.08
-76.09
0
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

(1R,3r,5S)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl (2R,3S)-4,4,4-trifluoro-3-hydroxy-2-phenylbutanoate (6.8a)



6.7a 6.8a

To a polyethylene tube charged with **7a** (10.0 mg, 0.0212 mmol, 100 mol%) in THF (420 μL) was added HF-pyridine (100 μL) dropwise at 25 °C. The resulting mixture was stirred at 25 °C for 24 h. The reaction was diluted with CH_2Cl_2 (3 mL) and quenched by careful addition of saturated $NaHCO_3$ (2 mL). The reaction mixture was extracted with CH_2Cl_2 (2 x 2 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was subjected to flash chromatography on basic alumina (DCM/MeOH 95:5) to furnish the title compound **8a** (6.7 mg, 0.0188 mmol) in 89% yield as a clear oil.

TLC (Basic Alumina) R_f = 0.30 (DCM/MeOH = 95:5).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.40 – 7.32 (m, 5H), 4.99 (t, *J* = 5.3 Hz, 1H), 4.75 (p, *J* = 6.5 Hz, 1H), 3.87 (d, *J* = 6.9 Hz, 1H), 3.14 – 3.05 (m, 1H), 3.01 – 2.92 (m, 1H), 2.22 (s, 3H), 2.20 – 2.12 (m, 1H), 2.12 – 2.03 (m, 1H), 1.96 – 1.84 (m, 1H), 1.75 (dq, *J* = 10.4, 6.8, 5.0 Hz, 2H), 1.68 (d, *J* = 15.5 Hz, 1H), 1.46 (d, *J* = 15.1 Hz, 1H), 1.24 (ddd, *J* = 13.3, 9.3, 4.6 Hz, 1H).

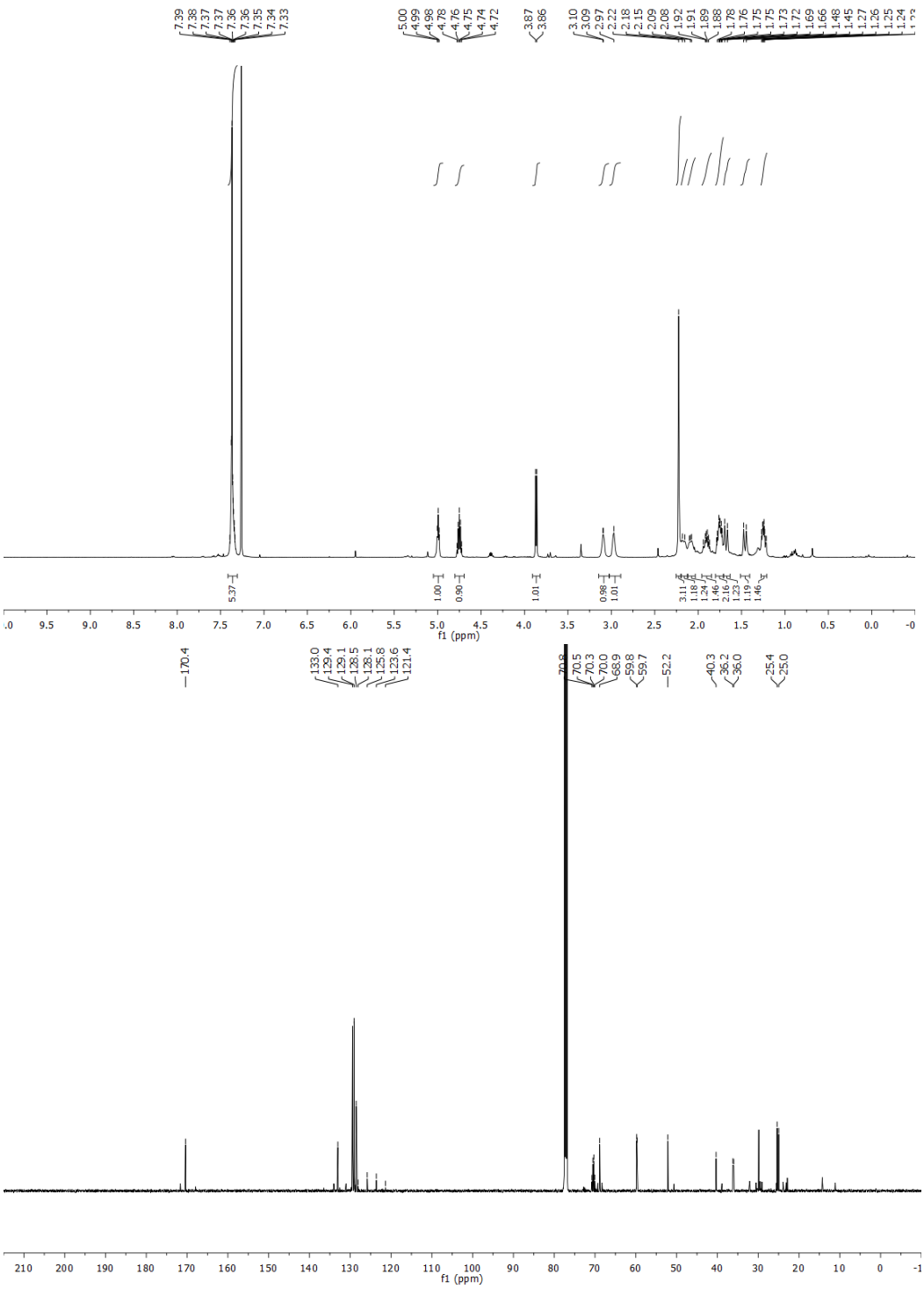
^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.4, 133.0, 129.4, 129.1, 128.5, 124.7 (q, *J* = 282.3 Hz), 70.4 (q, *J* = 30.7 Hz), 68.9, 59.8, 59.7, 52.2, 40.3, 36.2, 36.0, 25.4, 25.0.

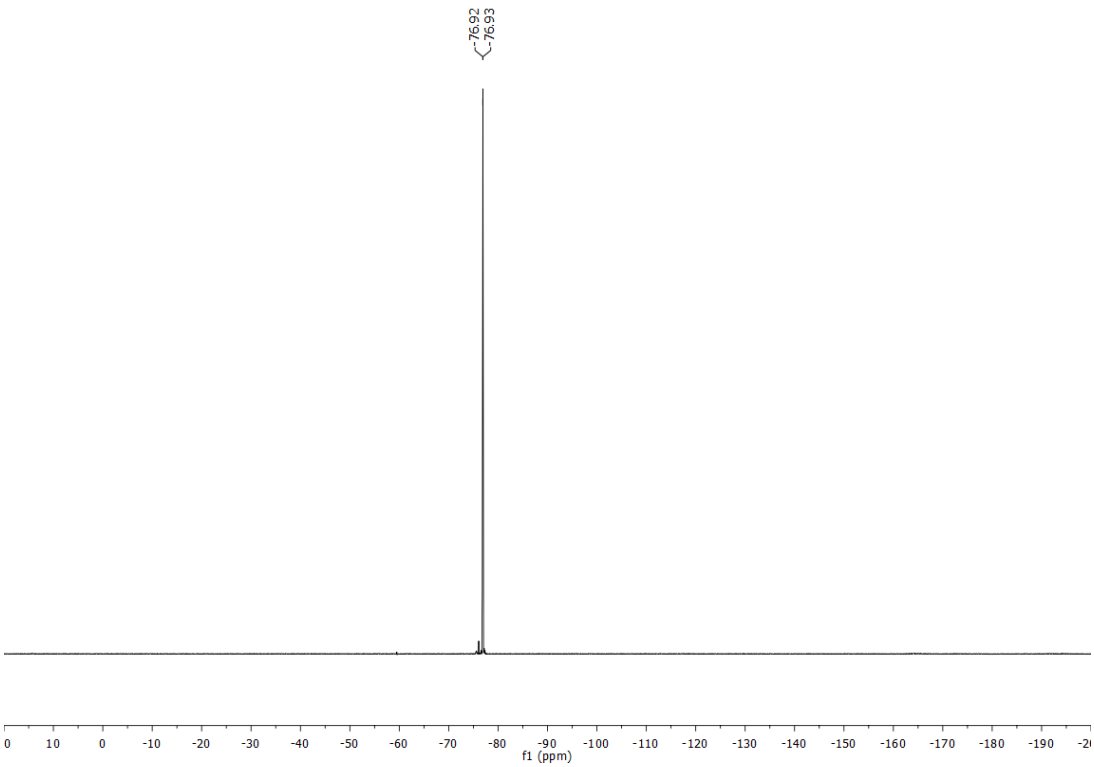
^{19}F NMR (471 MHz, $CDCl_3$): δ = -76.92 (d, *J* = 6.4 Hz).

HRMS (ESI) Calculated for $C_{18}H_{22}F_3NO_3$ $[M+H]^+$ = 358.1625, Found 358.1628.

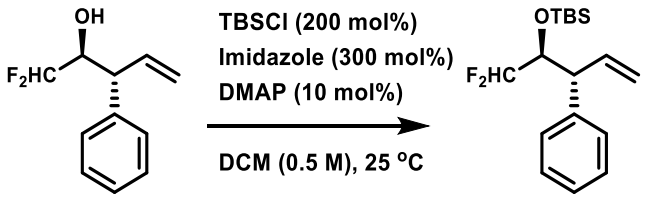
FTIR (neat) 2926, 2853, 1732, 1456, 1269, 1163, 1130, 1032, 700 cm^{-1}.

$[\alpha]_D^{35}$: –20.0 (*c* = 0.5, $CHCl_3$)




-76.92
-76.93
0
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

tert-butyldimethyl(((2S,3R)-1,1,1-trifluoro-3-phenylpent-4-en-2-yl)oxy)silane (6.6b')



6.5a 6.6b'

To a solution of alcohol **6.5a** (99.1 mg, 0.500 mmol, 100 mol%) in CH_2Cl_2 (1 mL) was added imidazole (102.1 mg, 1.500 mmol, 300 mol%), TBSCl (150.7 mg, 1.000 mmol, 200 mol%) and 4-(dimethylamino)pyridine (6.1 mg, 0.050 mmol, 10 mol%). The reaction was allowed to stir at 25 °C for 24 h. The contents were diluted with CH_2Cl_2 (1 mL) and washed with H_2O (1 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 1 mL), and the combined organic phases were washed with brine (1 mL), dried (Na_2SO_4), filtered and the solvent was removed *in vacuo*. The residue was subjected to flash chromatography on silica (Hexanes) to furnish the title compound **6.6b'** (137.0 mg, 0.438 mmol) in 88% yield as a clear oil.

TLC (SiO_2) R_f = 0.43 (hexanes).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35 – 7.27 (m, 2H), 7.25 – 7.20 (m, 3H), 6.29 (dt, *J* = 17.2, 9.8 Hz, 1H), 5.49 (ddd, *J* = 56.7, 55.1, 5.3 Hz, 1H), 5.27 (dd, *J* = 10.3, 1.7 Hz, 1H), 5.20 (ddd, *J* = 17.2, 1.8, 0.8 Hz, 1H), 3.98 (dq, *J* = 13.6, 4.6 Hz, 1H), 3.63 (dt, *J* = 9.0, 3.2 Hz, 1H), 0.82 (s, 9H), -0.03 (d, *J* = 1.9 Hz, 3H), -0.36 (s, 3H).

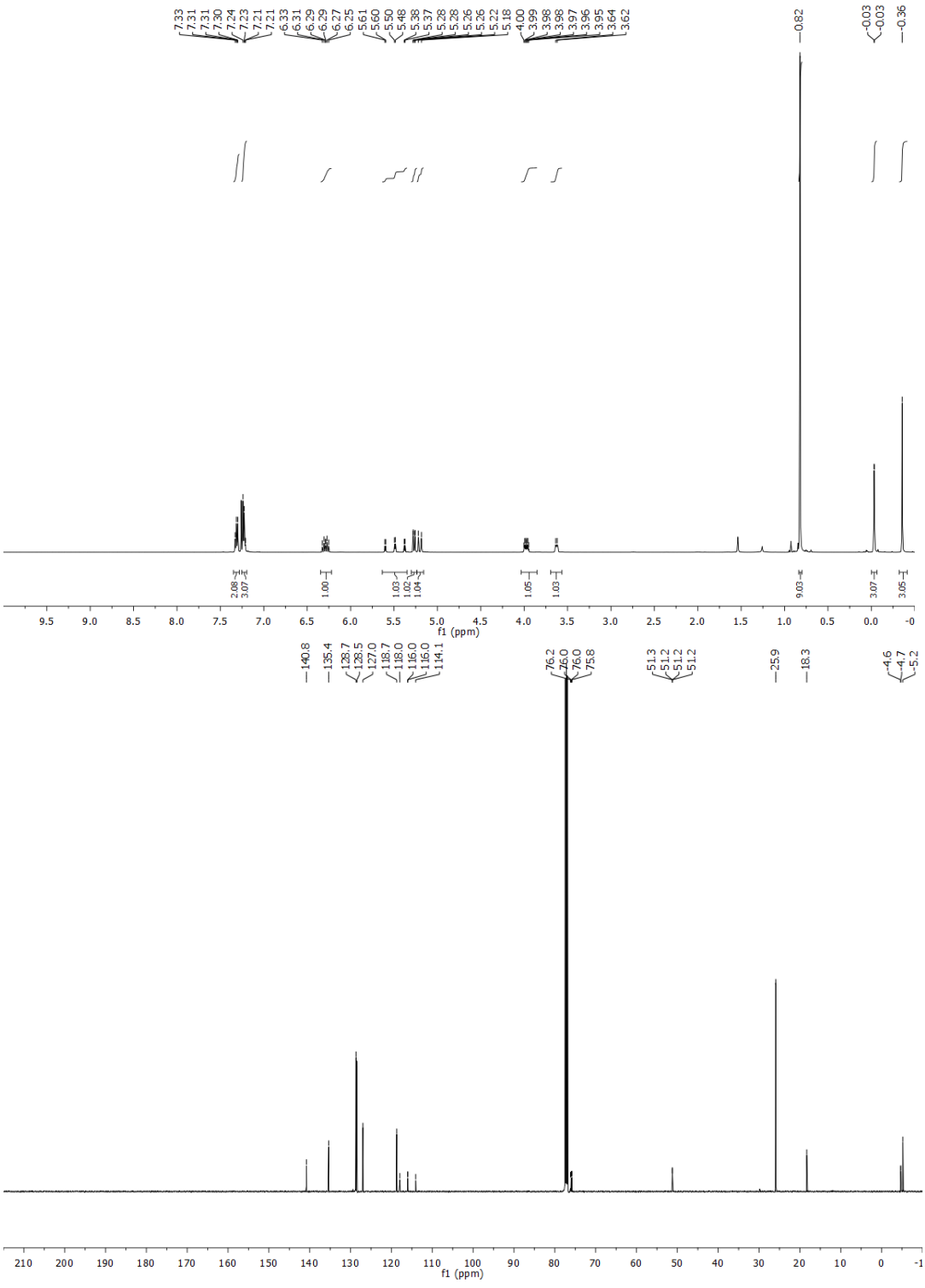
^{13}C NMR (125 MHz, $CDCl_3$): δ = 140.8, 135.4, 128.7, 128.5, 127.0, 118.7, 116.0 (dd, *J* = 245.7, 243.8 Hz), 76.0 (dd, *J* = 25.3, 20.3 Hz), 51.2 (dd, *J* = 5.6, 2.2 Hz), 25.9, 18.3, -4.7 (d, *J* = 3.6 Hz), -5.2.

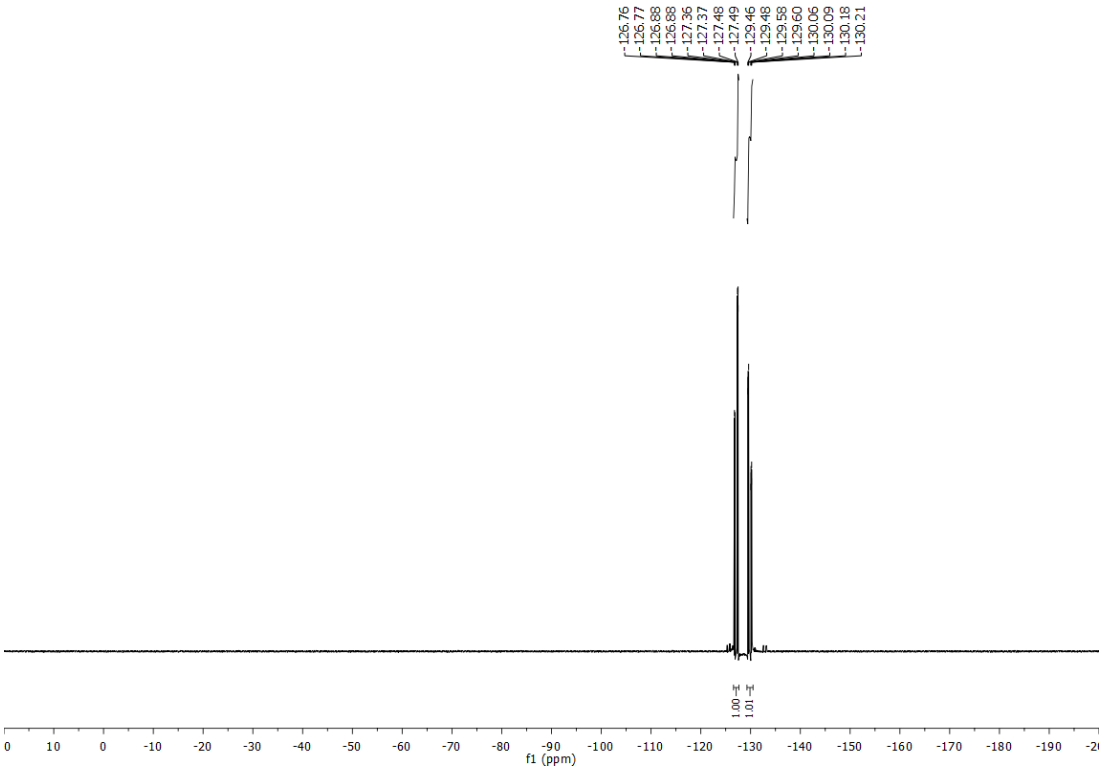
^{19}F NMR (471 MHz, $CDCl_3$): δ = -127.12 (ddd, *J* = 284.9, 55.5, 5.1 Hz), -129.83 (ddd, *J* = 283.5, 56.7, 13.5 Hz).

HRMS (ESI) Calculated for $C_{17}H_{26}F_2OSi$ $[M+H]^+$ = 313.1799, Found 313.1806.

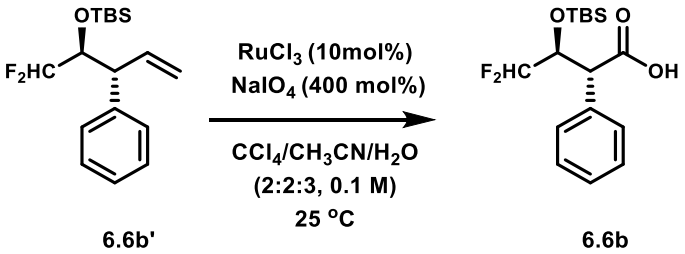
FTIR (neat) 2955, 2930, 2858, 1473, 1256, 1138, 1117, 1069, 1005, 927, 838, 779, 701 cm^{-1}.

$[\alpha]_D^{28}$: –133.3 (*c* = 1.0, $CHCl_3$)


7.33
7.31
7.31
7.30
7.24
7.23
7.21
7.21
6.33
6.31
6.29
6.29
6.27
6.25
5.61
5.60
5.50
5.48
5.38
5.37
5.28
5.28
5.26
5.26
5.22
5.18
4.00
3.99
3.98
3.98
3.97
3.96
3.95
3.64
3.62
0.82
-0.03
-0.03
-0.36
2.08
3.07
1.00
1.03
1.02
1.04
1.05
1.03
9.03
3.07
3.05
f1 (ppm)
140.8
135.4
128.7
128.5
127.0
118.7
118.0
116.0
116.0
114.1
76.2
76.0
76.0
75.8
51.3
51.2
51.2
51.2
25.9
18.3
-4.6
-4.7
-5.2
f1 (ppm)


126.76
126.77
126.88
126.88
127.36
127.37
127.48
127.49
129.46
129.48
129.58
129.60
130.06
130.09
130.18
130.21
1.00
1.01
0
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

(2R,3S)-3-((tert-butyldimethylsilyl)oxy)-4,4-difluoro-2-phenylbutanoic acid (6.6b)



6.6b' 6.6b

To a stirred solution of **6.6b'** (109.4 mg, 0.350 mmol, 100 mol%), in 1.0 mL CCl_4, 1.0 mL CH_3CN, and 1.5 mL H_2O was added $NaIO_4$ (299.5 mg, 1.400 mmol, 400 mol%). After all the $NaIO_4$ had dissolved, $RuCl_3.2H_2O$ (8.5 mg, 0.035 mmol, 10 mol%) was added, and the reaction mixture was stirred vigorously for 24 h at 25 °C. The contents were diluted with EtOAc (3 mL) and washed with H_2O (3 mL). The aqueous layer was extracted with EtOAc (2 x 3 mL), and the combined organic phases were washed with brine (3 mL), dried (Na_2SO_4), filtered and the solvent was removed *in vacuo*. The residue was subjected to flash chromatography on silica (Hex/EtOAc 5:1) to furnish the title compound **6.6b** (85.4 mg, 0.258 mmol) in 74% yield as a white solid.

TLC (SiO_2) R_f = 0.43 (hexanes/ethyl acetate = 3:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.40 – 7.28 (m, 5H), 5.30 (td, *J* = 54.4, 1.5 Hz, 1H), 4.43 (dddd, *J* = 19.1, 9.7, 6.0, 1.5 Hz, 1H), 3.88 (d, *J* = 9.6 Hz, 1H), 0.86 (s, 9H), 0.13 (s, 3H), 0.07 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.6, 133.1, 129.3, 128.8, 128.7, 114.2 (dd, *J* = 246.0, 242.6 Hz), 73.7 – 73.3 (m), 54.7, 25.9, 18.4, -4.5 (d, *J* = 3.7 Hz), -5.2.

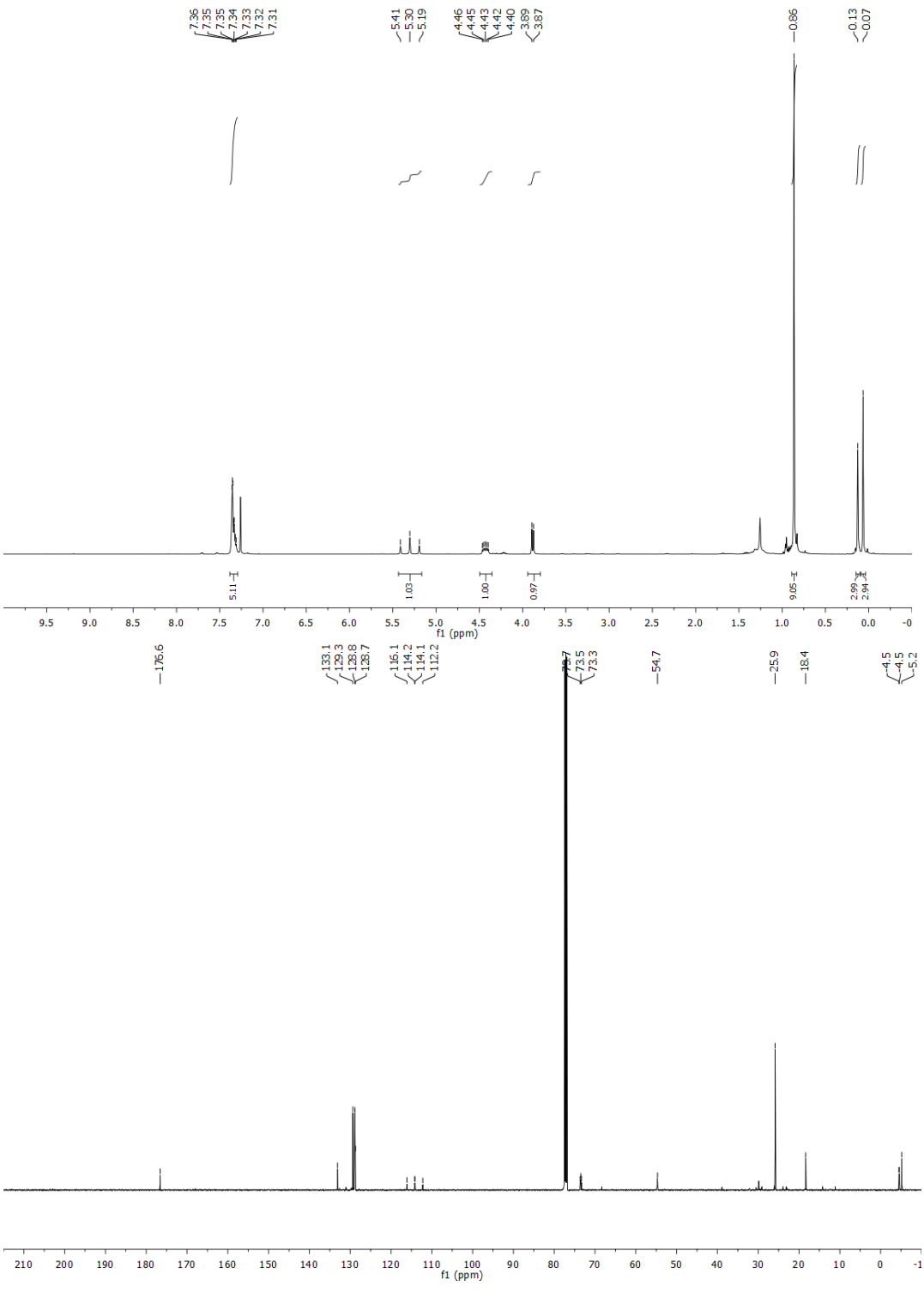
^{19}F NMR (471 MHz, $CDCl_3$): δ = -127.22 (ddd, *J* = 284.4, 54.5, 4.6 Hz), -135.17 (ddd, *J* = 284.2, 54.4, 19.1 Hz).

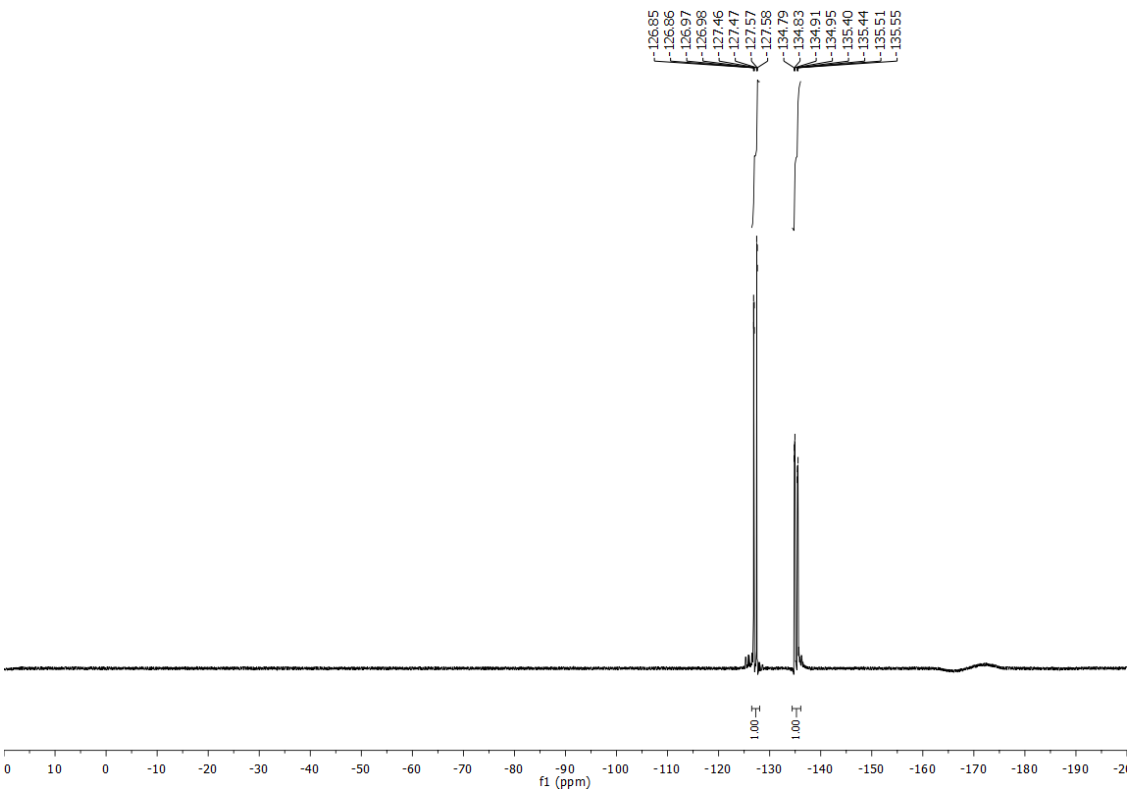
HRMS (ESI) Calculated for $C_{16}H_{24}F_2O_3Si$ $[M+Na]^+$ = 353.1355, Found 353.1361.

FTIR (neat) 2955, 2930, 2859, 1714, 1254, 1167,1115, 1065, 935, 837, 780, 699 cm^{-1}.

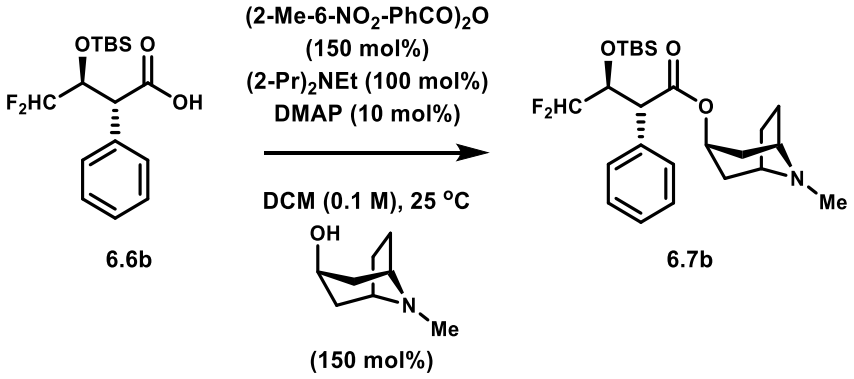
$[\alpha]_D^{29}$: –95.5 (*c* = 1.0, $CHCl_3$)

MP: 98-103˚C


7.36
7.35
7.35
7.34
7.33
7.32
7.31
5.41
5.30
5.19
4.46
4.45
4.43
4.42
4.40
3.89
3.87
0.86
0.13
0.07
5.11
1.03
1.00
0.97
9.05
2.99
2.94
f1 (ppm)
176.6
133.1
129.3
128.8
128.7
116.1
114.2
114.1
112.2
73.7
73.5
73.3
54.7
25.9
18.4
-4.5
-4.5
-5.2
f1 (ppm)


-126.85
-126.86
-126.97
-126.98
-127.46
-127.47
-127.57
-127.58
-134.79
-134.83
-134.91
-134.95
-135.40
-135.44
-135.51
-135.55
1.00
1.00
0
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

(1R,3r,5S)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl (2R,3S)-3-((tert-butyldimethylsilyl)oxy)-4,4-difluoro-2-phenylbutanoate (6.7b)



A vial equipped with a magnetic stir bar was charged with **6.6b** (10.0 mg, 0.0303 mmol, 100 mol%), 2-methyl-6-nitrobenzoic anhydride (15.7 mg, 0.0455 mmol, 150 mol%), 4-(dimethylamino)pyridine (0.4 mg, 0.0030 mmol, 10 mol%) and purged with argon. Freshly distilled CH_2Cl_2 (300 μL) and *N,N*-diisopropylethylamine (5.2 μL, 0.0303 mmol, 100 mol%), were added sequentially via syringe. The resulting mixture was stirred at 25 °C for 10 minutes. Tropine (6.4 mg, 0.0455 mmol, 150 mol%) was added in a single portion at 25 °C. The reaction was stirred at 25 °C for 20 h. The reaction mixture was concentrated, and the residue was subjected to flash chromatography on basic alumina (DCM/MeOH 98:2) to furnish the title compound **6.7b** (12.1 mg, 0.0267 mmol, 4:1 dr) in 88% yield as a clear oil.

TLC (Basic Alumina) R_f = 0.50 (DCM/MeOH = 95:5).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36 – 7.30 (m, 5H), 5.59 (td, *J* = 55.8, 4.0 Hz, 1H), 4.99 (t, *J* = 5.4 Hz, 1H), 4.53 – 4.43 (m, 1H), 3.75 (d, *J* = 7.4 Hz, 1H), 3.08 – 3.02 (m, 1H), 2.98 – 2.92 (m, 1H), 2.22 (s, 3H), 2.14 (d, *J* = 14.5 Hz, 1H), 2.05 (d, *J* = 15.6 Hz, 1H), 1.88 – 1.80 (m, 1H), 1.75 – 1.62 (m, 3H), 1.47 (d, *J* = 15.1 Hz, 1H), 1.23 – 1.17 (m, 1H), 0.73 (s, 9H), 0.03 (s, 3H), -0.29 (s, 3H).

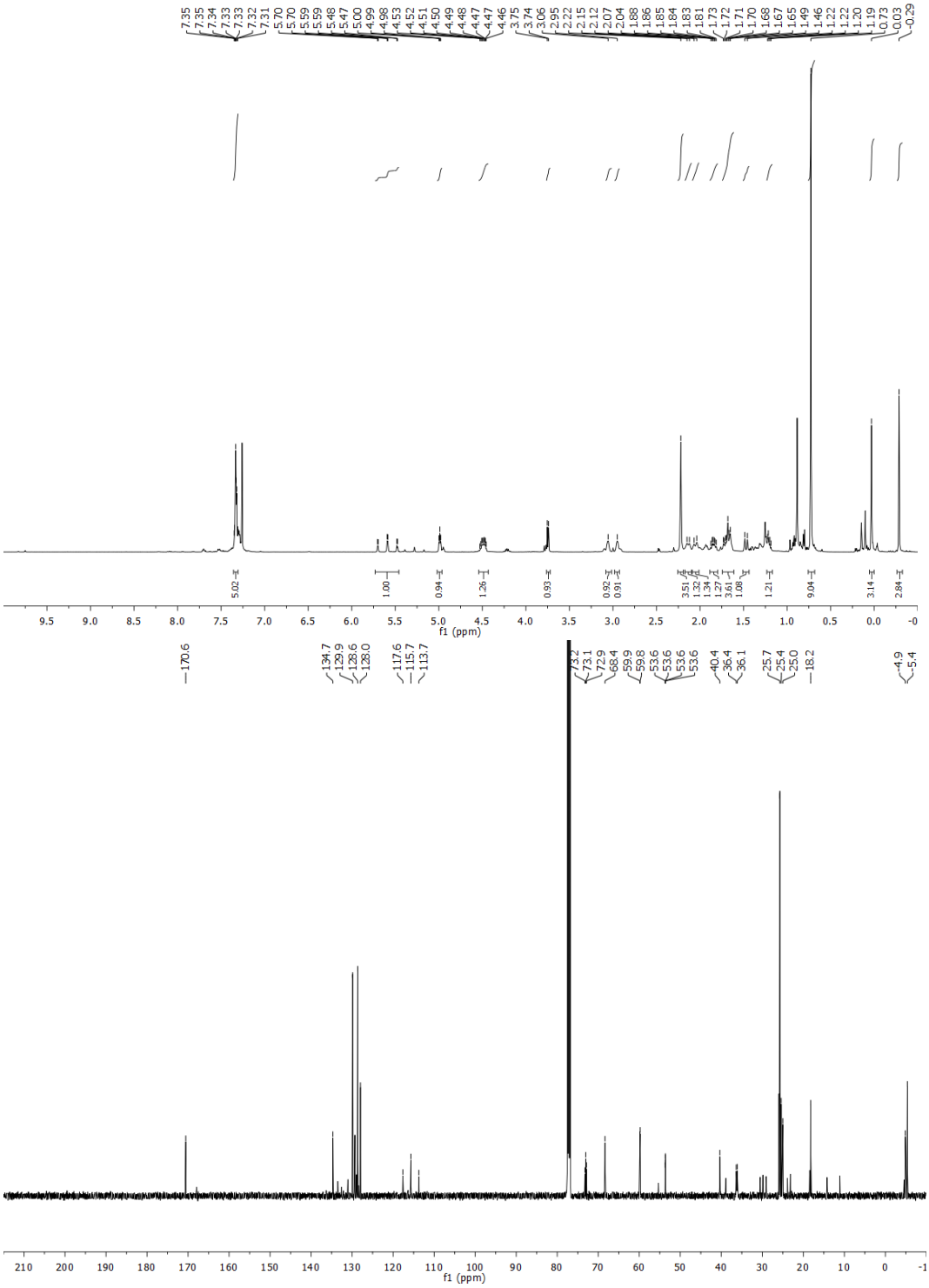
^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.6, 134.7, 129.9, 128.6, 128.0, 115.7 (t, *J* = 245.4 Hz), 73.1 (t, *J* = 22.9 Hz), 68.4, 59.9, 59.8, 53.7 – 53.5 (m), 40.4, 36.4, 36.1, 25.7, 25.4, 25.0, 18.2, -4.9, -5.4.

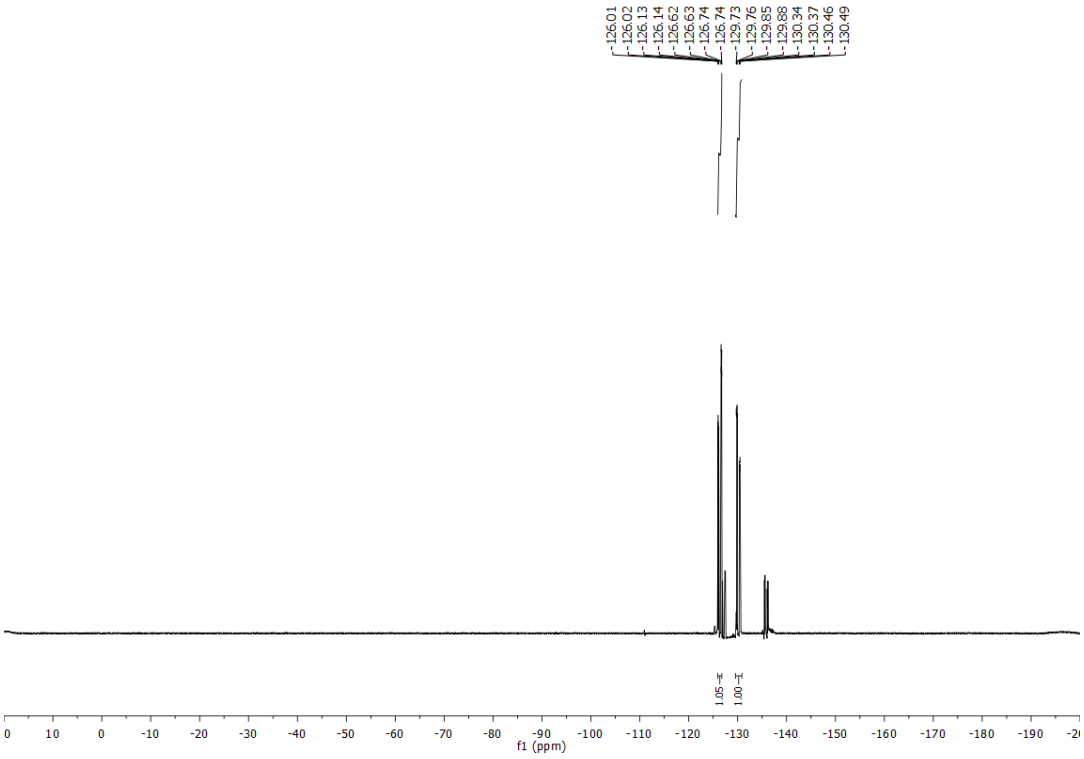
^{19}F NMR (471 MHz, $CDCl_3$): δ = -126.38 (ddd, *J* = 285.8, 55.2, 4.6 Hz), -130.11 (ddd, *J* = 285.7, 56.3, 14.4 Hz).

HRMS (APPI) Calculated for $C_{24}H_{37}F_2NO_3Si$ $[M+H]^+$ = 454.2584, Found 454.2588.

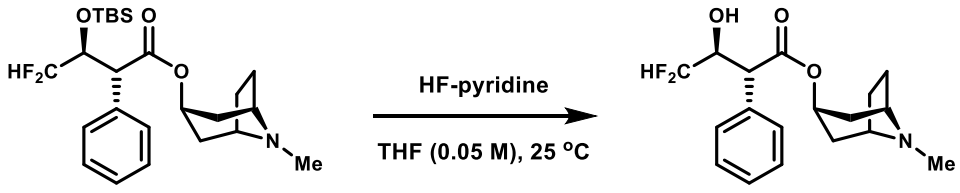
FTIR (neat) 2929, 2856, 1725, 1472, 1254, 1150, 1119, 1064, 1034, 934, 838, 780, 700 cm^{-1}.

$[\alpha]_D^{29}$: –20.5 (*c* = 1.0, $CHCl_3$)




126.01
126.02
126.13
126.14
126.62
126.63
126.74
126.74
129.73
129.76
129.85
129.88
130.34
130.37
130.46
130.49
1.05
1.00
0
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

(1R,3r,5S)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl (2R,3S)-4,4-difluoro-3-hydroxy-2-phenylbutanoate (6.8b)



6.7b 6.8b

To a polyethylene tube charged with **6.7b** (10.0 mg, 0.0220 mmol, 100 mol%) in THF (440 μL) was added HF-pyridine (100 μL) dropwise at 25 °C. The resulting mixture was stirred at 25 °C for 24 h. The reaction was diluted with CH_2Cl_2 (3 mL) and quenched by careful addition of saturated $NaHCO_3$ (2 mL). The reaction mixture was extracted with CH_2Cl_2 (2 x 2 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was subjected to flash chromatography on basic alumina (DCM/MeOH 95:5) to furnish the title compound **6.8b** (6.0 mg, 0.0177 mmol) in 80% yield as a clear oil.

TLC (Basic Alumina) R_f = 0.40 (DCM/MeOH = 95:5).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.42 – 7.30 (m, 5H), 5.57 (td, *J* = 55.7, 4.9 Hz, 1H), 5.04 (t, *J* = 5.4 Hz, 1H), 4.53 – 4.45 (m, 1H), 3.81 (d, *J* = 6.0 Hz, 1H), 3.17 – 3.09 (m, 1H), 3.05 – 2.96 (m, 1H), 2.26 (s, 3H), 2.22 – 2.14 (m, 1H), 2.31 – 2.23 (m, 1H), 1.93 – 1.84 (m, 1H), 1.78 – 1.63 (m, 3H), 1.49 (d, *J* = 15.2 Hz, 1H), 1.15 – 1.04 (m, 1H).

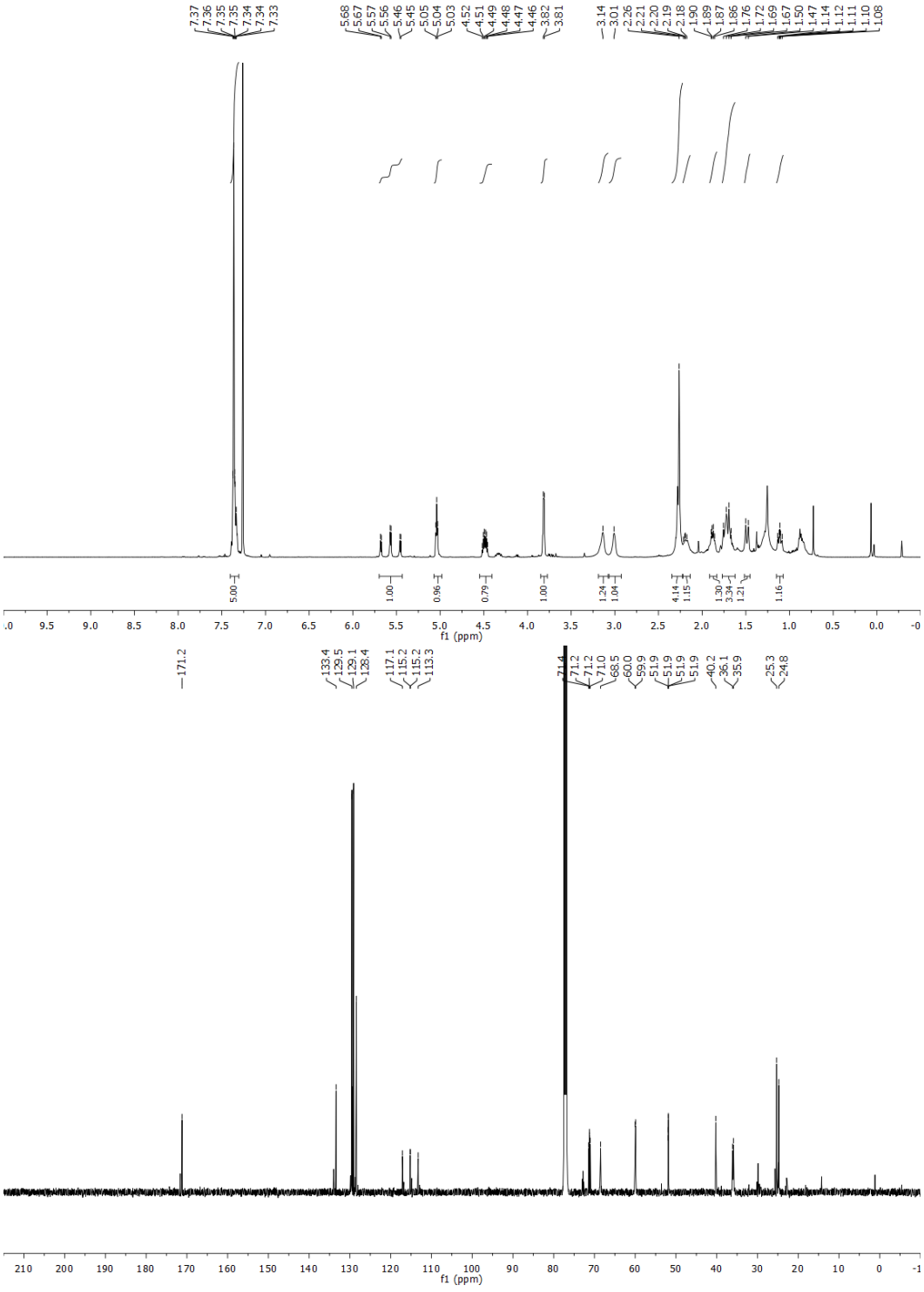
^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.2, 133.4, 129.5, 129.1, 128.4, 115.2 (dd, *J* = 244.8, 241.8 Hz), 71.2 (dd, *J* = 25.0, 23.3 Hz), 68.5, 60.0, 59.9, 51.9 (dd, *J* = 5.2, 1.9 Hz), 40.2, 36.1, 35.9, 25.3, 24.8.

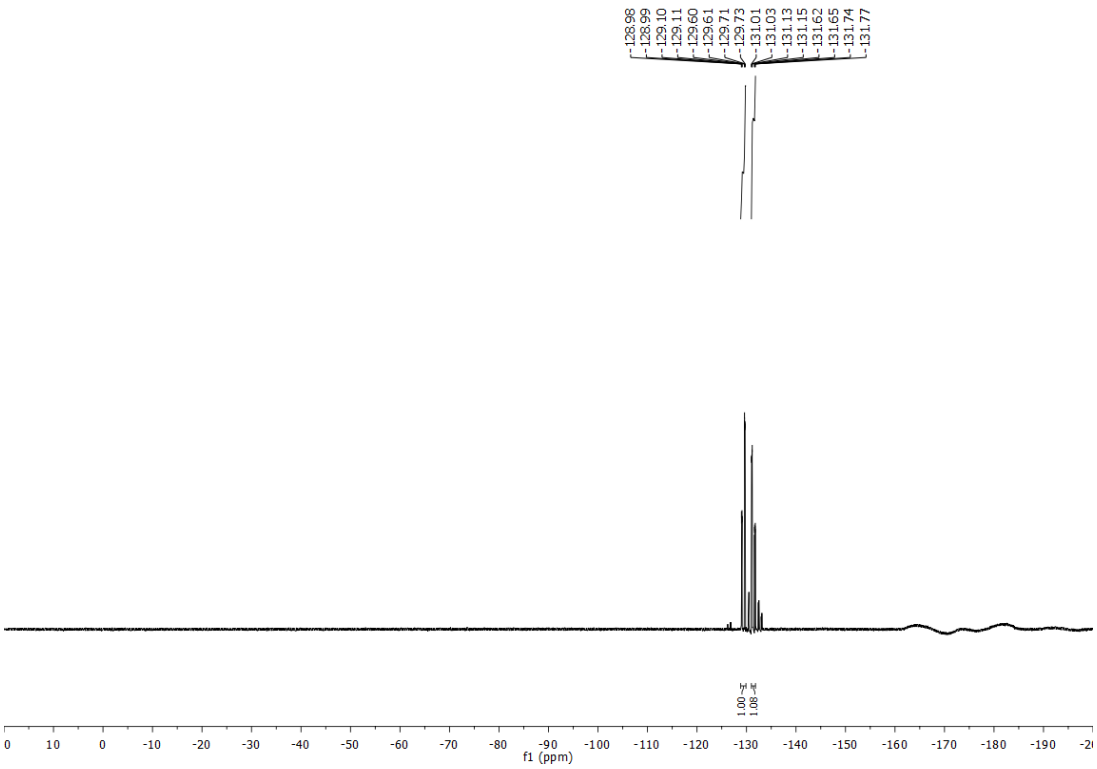
^{19}F NMR (471 MHz, $CDCl_3$): δ = -129.35 (ddd, *J* = 290.7, 54.9, 6.1 Hz), -131.39 (ddd, *J* = 290.6, 56.4, 13.1 Hz).

HRMS (ESI) Calculated for $C_{18}H_{23}F_2NO_3$ $[M+H]^+$ = 340.1719, Found 340.1722.

FTIR (neat) 2933, 2856, 1727, 1455, 1276, 1222, 1140, 1065, 1032, 705, 667 cm^{-1}.

$[\alpha]_D^{35}$: –18.5 (c = 0.5, $CHCl_3$)

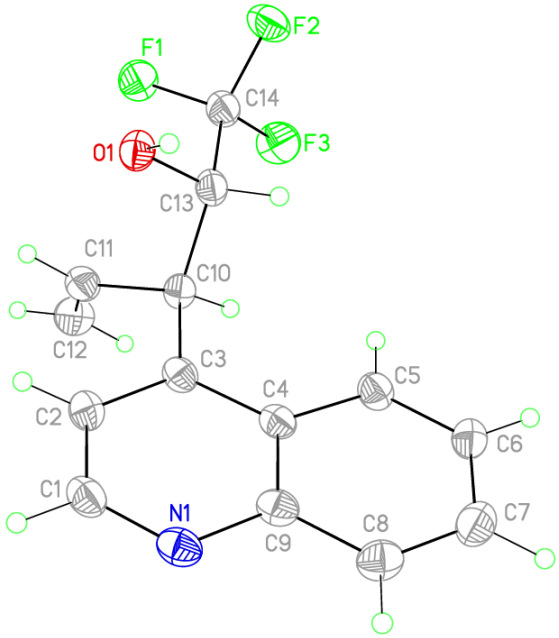

7.37
7.36
7.35
7.35
7.34
7.34
7.33
5.68
5.67
5.57
5.56
5.46
5.45
5.05
5.04
5.03
4.52
4.51
4.49
4.48
4.47
4.46
3.82
3.81
3.14
3.01
2.26
2.21
2.20
2.19
2.18
1.90
1.89
1.87
1.86
1.76
1.72
1.69
1.67
1.50
1.47
1.14
1.12
1.11
1.10
1.08
5.00
1.00
0.96
0.79
1.00
1.24
1.04
4.14
1.15
1.30
3.34
1.21
1.16
f1 (ppm)
171.2
133.4
129.5
129.1
128.4
117.1
115.2
115.2
113.3
71.4
71.2
71.2
71.0
68.5
60.0
59.9
51.9
51.9
51.9
51.9
40.2
36.1
35.9
25.3
24.8
f1 (ppm)


128.98
128.99
129.10
129.11
129.60
129.61
129.71
129.73
131.01
131.03
131.13
131.15
131.62
131.65
131.74
131.77
1.00
1.08
0
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

Single Crystal Diffraction Data for 6.4l

Empirical formula	$C_{14}\ H_{12}\ F_3\ N\ O$	
Formula weight	267.25	
Temperature	100(2) K	
Wavelength	1.54184 Å	
Crystal system	orthorhombic	
Space group	*P 2₁ 2₁ 2₁*	
Unit cell dimensions	a = 7.0471(10) Å	α= 90°.
	b = 9.5750(14) Å	β= 90°.
	c = 18.299(3) Å	γ = 90°.
Volume	1234.8(3) $Å^3$	
Z	4	
Density (calculated)	1.438 Mg/m^3	
Absorption coefficient	1.049 mm^{-1}	
F(000)	552	
Crystal size	0.260 x 0.150 x 0.060 mm^3	
Theta range for data collection	4.833 to 75.048°.	
Index ranges	-8<=h<=8, -11<=k<=11, -22<=l<=22	
Reflections collected	9466	
Independent reflections	2495 [R(int) = 0.0467]	
Completeness to theta = 67.684°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00 and 0.651	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2495 / 0 / 176	
Goodness-of-fit on F^2	1.133	
Final R indices [I>2sigma(I)]	R_1 = 0.0404, wR_2 = 0.1146	
R indices (all data)	R_1 = 0.0422, wR_2 = 0.1176	
Absolute structure parameter	-0.02(13)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.195 and -0.260 $e.Å^{-3}$	

View of **6.4l** showing the atom labeling scheme. Displacement ellipsoids are scaled to the 50% probability level.



Chapter 7: Rhodium Catalyzed Formate Mediated Reductive Coupling of Aldehydes and Aryl Iodides*

7.1 INTRODUCTION

Since the discovery of pre-formed organometallic reagents[1], the addition of organometallic reagents to carbonyl compounds and imines[2] to form new C-C bond has been a milestone in chemical synthesis.[3] While the requirement of cryogenic conditions and generation of stoichiometric metal byproducts complicate the applications of using organometallic reagents on practical scale. In most cases, the organometallic reagents were prepared from the corresponding organohalides, so metal catalyzed reductive coupling of organohalides with carbonyl compounds has become an alternative protocol to avoid organometallic reagents in carbonyl addition. The common reductants used in these reactions are metal reductants (Zn, Mn), toxic chromium(II) salts, pyrophoric organometallic reductants (BEt_3, $ZnEt_2$, $AlMe_3$), and expensive silane reductant.[4] Using relatively cheap, environment benign reductants, like hydrogen gas, 2-propanol and formic acid, which were used in the carbonyl and imine reductive coupling[5] by our group, are more desirable (Figure 7.1).

Except from Nozaki-Hiyama-Kishi reaction[6,7], there are very few intermolecular reductive couplings of aryl halide with aldehydes and all of those were utilizing zinc metal or Mn-Cr alloy[8] as terminal reductants or electrochemical reduction.[9] Recently in our lab, a hydrogen mediated intramolecular Grignard-type cyclization was reported,[10] while these conditions could not promote the intermolecular coupling reaction. Even though the related redox-neutral coupling of aryl halides with aldehydes to form ketone products have been

*This chapter is based on the published work:
Swyka, R. A. †; Zhang, W. †; Krische, M. J. *J. Am. Chem. Soc.* **2019**, *141*, 1828.

reported.[11] In this chapter, the first intermolecular metal catalyzed reductive coupling of aryl halide and aldehydes mediated by formate was discribed.

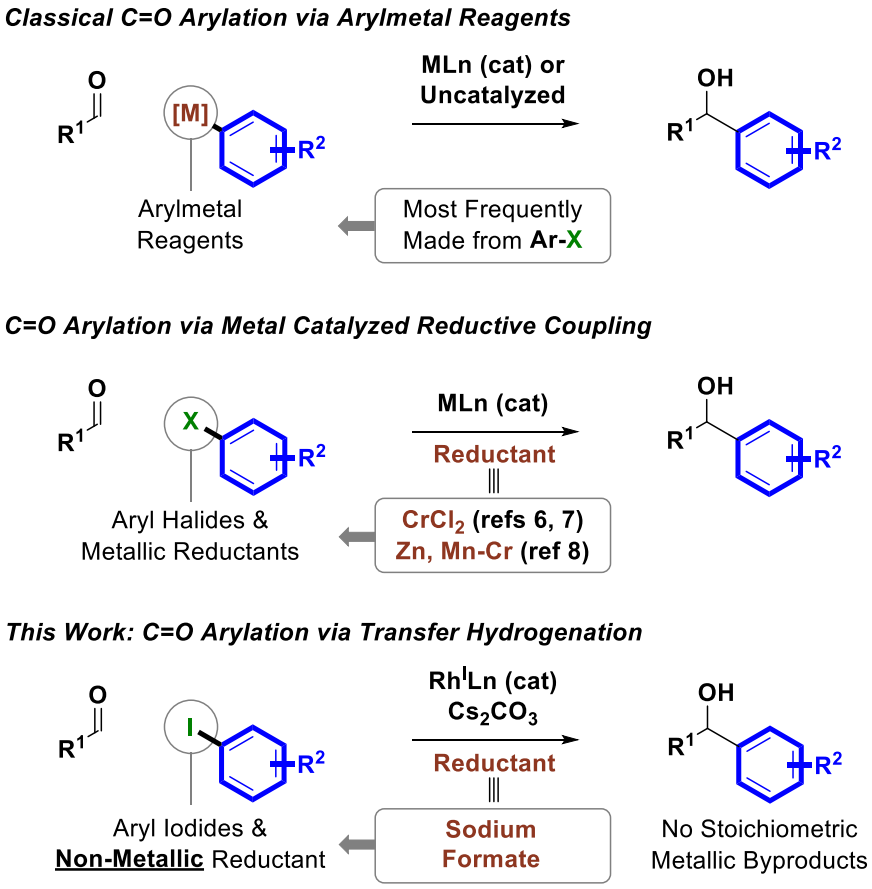
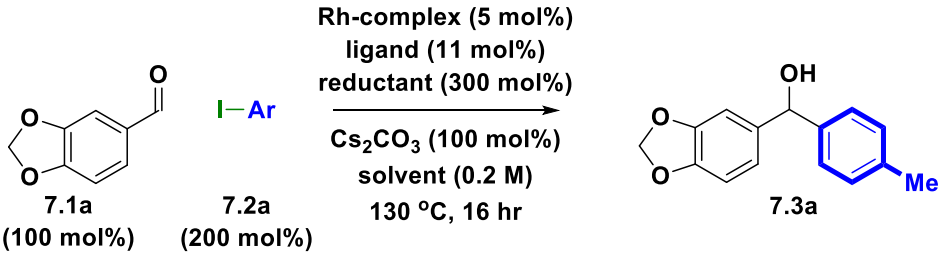


Figure 7.1 Carbonyl Arylation Strategies Comparison.

7.2 Reaction Development and Scope

Initial experiments started with exposing piperonal **7.1a** and iodotoluene **7.2a** to 2-propanol or sodium formate together with diverse rhodium and palladium complexes.

Table 7.1 Selected Optimization Experiments for Carbonyl Arylation to Form Adduct **7.3a**.



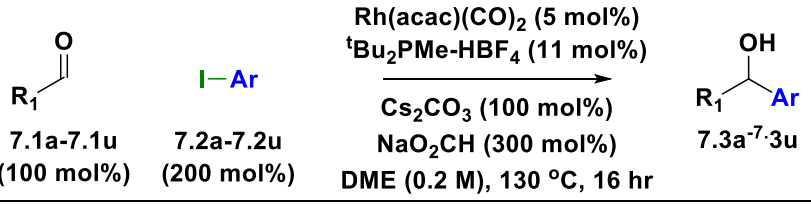
entry	catalyst	reductant	ligand	solvent	yield (%)
1	$Rh(acac)(CO)_2$	NaO_2CH	PCy_3	Dioxane	12
2	$Rh(acac)(CO)_2$	NaO_2CH	P^tBu_3	Dioxane	25
3	$Rh(acac)(CO)_2$	NaO_2CH	PPh_2Cy	Dioxane	8
4	$Rh(acac)(CO)_2$	NaO_2CH	dppe	Dioxane	trace
5	$Rh(acac)(CO)_2$	NaO_2CH	dCype	Dioxane	trace
6	$Rh(acac)(CO)_2$	NaO_2CH	dippf	Dioxane	trace
7	$Rh(acac)(CO)_2$	NaO_2CH	dppf	Dioxane	11
8	$Rh(acac)(CO)_2$	NaO_2CH	$^tBu_2PMe$	Dioxane	40
9	$Rh(acac)(CO)_2$	NaO_2CH	$^tBu_2PMe$	^{t}AmylOH	64
➡ 10	$Rh(acac)(CO)_2$	NaO_2CH	$^tBu_2PMe$	DME	72
11	$Rh(acac)(CO)_2$	NaO_2CH	$^tBu_2PMe$	DME	n.d.[b]
12	$Rh(acac)(CO)_2$	CsO_2CH	$^tBu_2PMe$	DME	17[b]
13	$Rh(acac)(CO)_2$	LiO_2CH	$^tBu_2PMe$	DME	44
14	$Rh(acac)(CO)_2$	NH_4O_2CH	$^tBu_2PMe$	DME	18
15	$Rh(acac)(CO)_2$	^{i}PrOH	$^tBu_2PMe$	DME	trace
16	$Rh(acac)(CO)_2$	H_2 (1 atm)	$^tBu_2PMe$	DME	trace[c]
17	$[RhCl(CO)_2]_2$	NaO_2CH	$^tBu_2PMe$	DME	47
18	$[Rh(cod)Cl]_2$	NaO_2CH	$^tBu_2PMe$	DME	27
19	$Rh(cod)_2BF_4$	NaO_2CH	$^tBu_2PMe$	DME	16
20	$Rh(acac)(CO)_2$	NaO_2CH	$^tBu_2PMe$	DME	56[d]

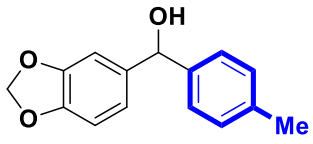
[a]Yields are material isolated by silica gel chromatography. $^tBu_2PMe{\cdot}HBF_4$ was emplyed as ligand precursor. P^tBu_3 was used as a 1.0 M solution in toluene. Lithium formate was used as the monohydrate. The loading of bidentate ligands was 5.5 mol%. The loading of dimeric rhodium pre-catalyst was 2.5 mol%. See supporting Information for further experimental details. [b]No Cs_2CO_3. [c]75 °C in DME or 130 °C in diglyme. [d]**7.2a** (150 mol%).

In the conditions when $Rh(acac)(CO)_2$ (5 mol%), PCy_3 (11 mol%), sodium formate (300 mol%), and Cs_2CO_3 (100 mol%) were used in dioxane under 130 ℃, the desired coupling product **7.3a** was obtained with 12% yield (Table 7.1, entry 1). Diverse ligands were tested under these conditions (Table 7.1, entries 2-8), and it was found that $^tBu_2PMe$ modified rhodium complex was relatively efficient in promoting the reductive coupling and provided adduct **7.3a** in 40% isolated yield (Table 7.1, entry 8). Different solvents were evaluated, and yields were improved to 64% and 72% by using *tert*-amyl alcohol (Table 7.1, entry 9) and dimethoxyethane (Table 7.1, entry 10), respectively. Later on, more formate salts, 2-propanol and hydrogen gas were also evaluated as terminal reductants, no improvement on the yield was observed. Other rhodium pre-catalysts could not provide the similar efficiency in the reaction. Lower loading of both aryl halide **7.2a** and sodium formate led to the decrease of isolation yield of adduct **7.3a**.

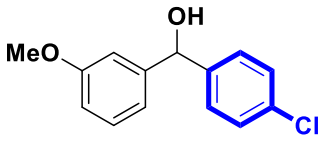
With the optimal conditions in hand, a wide range of substrates were applied to the reductive coupling to form secondary alcohols **7.3a**-**7.3u** (Table 7.2). Both aromatic **7.1a**-**7.1p** and aliphatic aldehydes **7.1q**-**7.1u** were engaged in the reductive coupling with aryl halides efficiently and diverse functional groups were tolerated. In the formation of **7.3b**, **7.3f**, **7.3j**, **7.3o**, and **7.3p**, lower halides (aryl chloride and aryl bromide) didn't disturb the activation of aryl halides to form the desired coupling adducts. Also, fluorine-containing functional groups were tolerated. Notably, 2-fluoroiodobenzene **7.2l** and 2-chloroiodobenzene **7.2o** were converted to adducts **7.3l** and **7.3o** without potential aryne formation.[12] Acidic hydrogens, like OH- and NH-groups, were also tolerated under our conditions, which was demonstrated by formation of **7.3g**, **7.3i**, and **7.3s**. Heterocyclic moiety containing secondary alcohols **7.3e**, **7.3h**, and **7.3o** were successfully obtained under reductive coupling. Steric hindered aryl iodide **7.2c** could engage in the coupling

Table 7.2 Formate Mediated Reductive Coupling of Aldehydes **7.1a-7.1u** to Aryl Iodides **7.2a-7.2u** to Form Adducts **7.3a-7.3u**.

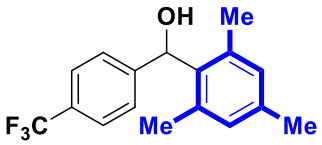




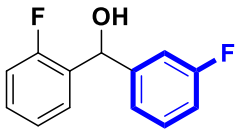
7.3a, 72% Yield



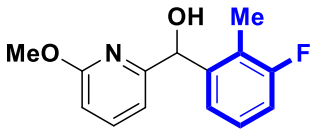
7.3b, 80% Yield



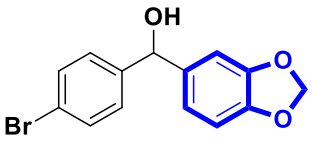
7.3c, 62% Yield[b]



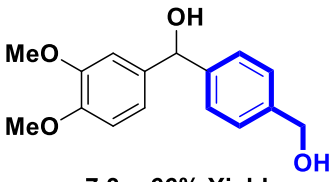
7.3d, 76% Yield[b]



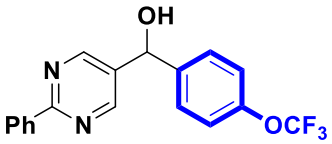
7.3e, 78% Yield[b]



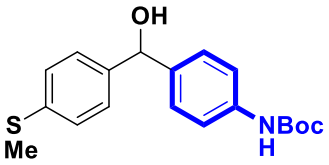
7.3f, 73% Yield



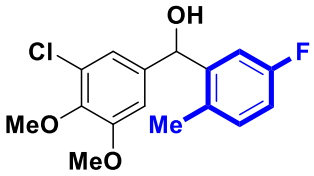
7.3g, 66% Yield



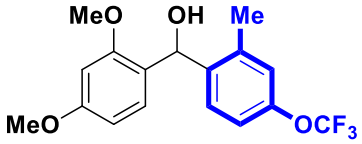
7.3h, 55% Yield



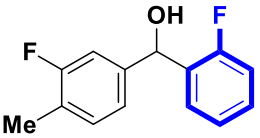
7.3i, 58% Yield



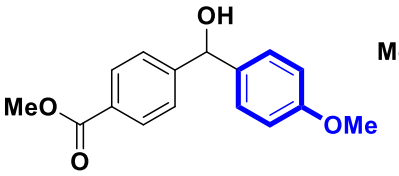
7.3j, 69% Yield



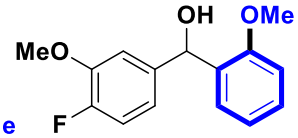
7.3k, 75% Yield



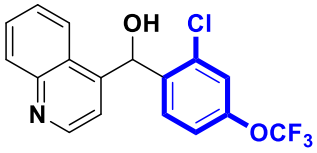
7.3l, 75% Yield



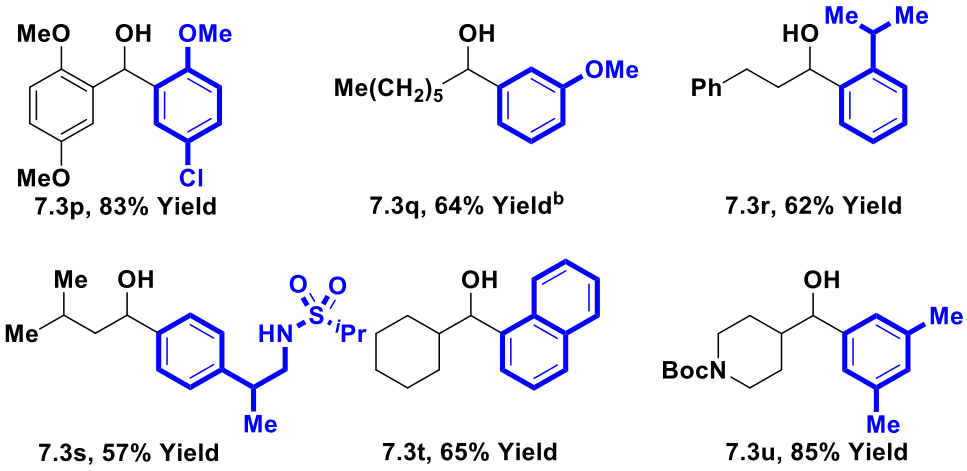
7.3m, 62% Yield



7.3n, 83% Yield



7.3o, 60% Yield



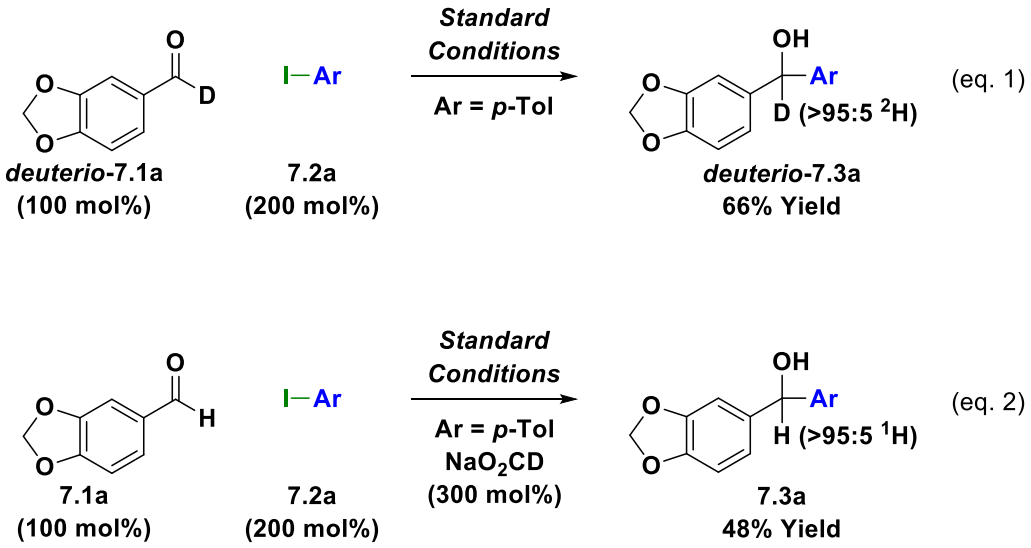
[a]Yields are material isolated by silica gel chromatography. See supporting Information for further experimental details. [b][$RhCl(CO)_2]_2$ (2.5 mol%) was used.

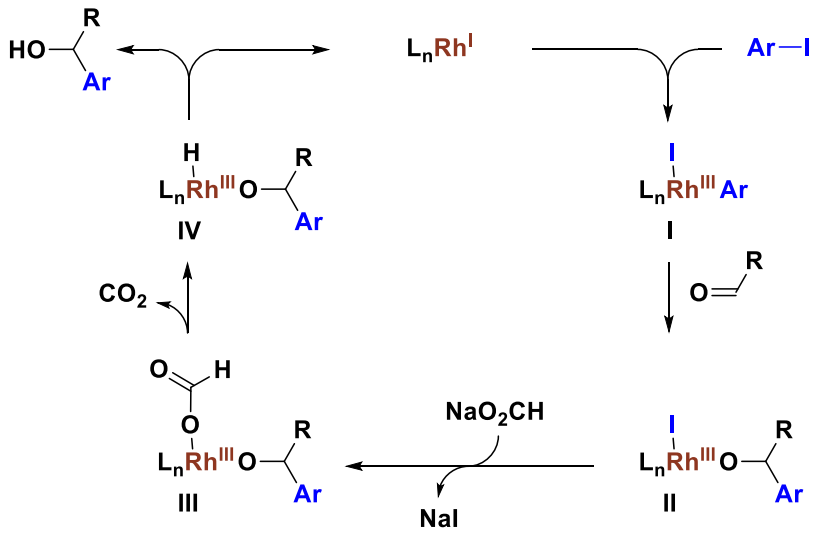
was very impressive. Finally, both linear and branched aliphatic aldehydes **7.1q**-**7.1u** were converted to the corresponding adducts **7.3q**-**7.3u** with good yields.

7.3 Mechanism and Discussion

Deuterium labelling experiments were conducted to help us to understand how the reaction proceeded (Scheme 7.1). When *deuterio*-**7.1a** and **7.2a** were used under the standard conditions, *dueterio*-**7.3a** was isolated with 77% yield and the carbinol position was fully deuterium incorporated. When NaO_2CD (300 mol%) was used instead under standard conditions, the isolated product did not have deuterium incorporated. These data suggested that the coupling adduct did not form via formate mediated reduction of ketones, which could derive from rhodium alkoxide via β-elimination. To further prove this, aryl ketones were subjected to the standard conditions and only trace carbonyl reduction

Scheme 7.1 Deuterium Labelling Experiments and Proposed Catalytic Mechanism for Formate Mediated Arylation.





product was observed.

Based on the deuterium study results, the catalytic mechanism for this rhodium catalyzed formate mediated reductive coupling of aryl halides and aldehydes was proposed (Scheme 7.1). Oxidative addition of aryl halide delivered rhodium(III) complex **I**. Coordination of aldehyde followed by carbonyl insertion into the rhodium-aryl bond to for the rhodium alkoxide **II**. Rhodium formate complex **III** was formed via ligand exchange with the sodium formate. Release of carbon dioxide gas via β-hydride elimination formed the rhodium hydride species **IV**. Final reductive elimination regenerated rhodium(I) and closed the catalytic cycle.

7.4 CONCLUSION

In summary, the first example of reductive carbonyl arylation using non-metallic reductant was reported here. This method was applied to a broad range of substrates with functional groups, for example, lower halides and protic functional groups, which were not compatible with traditional organometallic reagents. This work also expanded the scope of hydrogen transfer mediated C-C bond forming reactions.

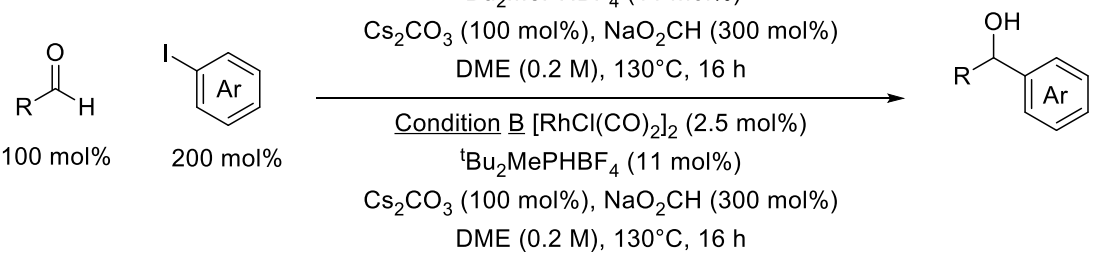
7.5 EXPERIMENTAL DETAILS

General Information

Unless otherwise noted, all reactions were performed using oven-dried glassware under an atmosphere of dry Ar. Rh-catalyzed cycloaddition reactions were conducted in pressure tubes (13 x 100 mm) sealed with PTFE-lined caps. Analytical thin-layer chromatography (TLC) was carried out using 0.25 mm commercial silica gel plates. Visualization was accomplished with UV light followed by dipping in a cerium ammonium molybdate, *p*-anisaldehyde, or potassium permanganate solution and heating. Purification of reaction products was carried out by flash column chromatography using 40-63 μm silica gel. Unless otherwise noted, reagents were purchased from commercial sources, and used as received. Deuterated substrate was prepared according to a previously reported protocol. 1,2 dimethoxyethane was obtained from Sigma-Aldrich in a septum sealed bottle. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on VARIAN INOVA, DirectDrive, or MR spectrometers (400 or 500 MHz) or on a Bruker AVANCE III 500 equipped with a BBFO Prodigy liquid nitrogen CryoProbe. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker AVANCE III 500. Chemical shifts (δ) for protons are reported in parts per million (ppm) downfield from tetramethylsilane, and are referenced to the proton resonance of residual $CHCl_3$ in the NMR solvent (δ = 7.26 ppm). Chemical shifts (δ) for carbon are reported in ppm downfield from tetramethylsilane, and are referenced to the carbon resonances of the solvent peak (δ = 77.16 ppm). NMR data are represented as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant in Hertz (Hz), and integration. Exact mass determinations were obtained by electrospray ionization (ESI) on an Agilent Technologies 6530 Accurate-Mass Q-TOF spectrometer or chemical

ionization (CI) on a Waters Micromass AutoSpec Ultima spectrometer. Infrared spectra were recorded on a Thermo Nicolet 380 spectrometer. Uncorrected melting points were measured on a Thomas Hoover Capillary Melting Point Apparatus.

General Procedure and Spectral Data for Arylation Reactions



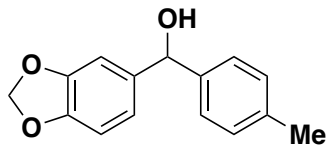
100 mol% 200 mol%

General procedure A: A resalable pressure tube (13 x 100 mm) was charged with $Rh(acac)(CO)_2$ (2.6 mg, 0.01 mmol, 5 mol%), Di-tert-butyl(methyl)phosphonium tetrafluoroborate (5.5 mg, 0.022 mmol, 11 mol%), reactant aldehyde (0.20 mmol, 100 mol%), and reactant aryl iodide (0.4 mmol, 200 mol%). The tube was sealed with a rubber septum and purged with Ar for 10 min. DME (1 mL, 0.2 M with respect to the aldehyde reactant) was injected, and the rubber septum was quickly replaced with a PTFE-lined screw cap. The tube was placed in a 130°C oil bath for 16 h. After cooling to room temperature, to the crude mixture was added a minimal amount of silica and concentrated *in vacuo*, the resultant powder was subjected to flash column chromatography (SiO_2) to afford the desired product.

General procedure B: A resalable pressure tube (13 x 100 mm) was charged with $[Rh(Cl)(CO)_2]_2$ (1.9 mg, 0.01 mmol, 2.5 mol%), Di-tert-butyl(methyl)phosphonium tetrafluoroborate (5.5 mg, 0.022 mmol, 11 mol%), reactant aldehyde (0.20 mmol, 100 mol%), and reactant aryl iodide (0.4 mmol, 200 mol%). The tube was sealed with a rubber septum and purged with Ar for 10 min. DME (1 mL, 0.2 M with respect to the aldehyde reactant) was injected, and the rubber septum was quickly replaced with a PTFE-lined screw cap. The tube was placed in a 130 °C oil bath for 16 h. After cooling to room

temperature, to the crude mixture was added a minimal amount of silica and concentrated *in vacuo*, the resultant powder was subjected to flash column chromatography (SiO_2) to afford the desired product.

benzo[d][1,3]dioxol-5-yl(p-tolyl)methanol (7.3a)



The title compound was prepared according to the general procedure A using piperonal (30.0 mg, 0.2 mmol, 100 mol%) and 4-iodotoluene (87.2 mg, 0.40 mmol, 200 mol%). Flash chromatography on silica (Hex/EtOAc 10:1) provided the title compound (34.8 mg, 144 μmol) in 72% yield as a white solid.

TLC (SiO_2) R_f = 0.33 (hexanes/ethyl acetate = 4:1).

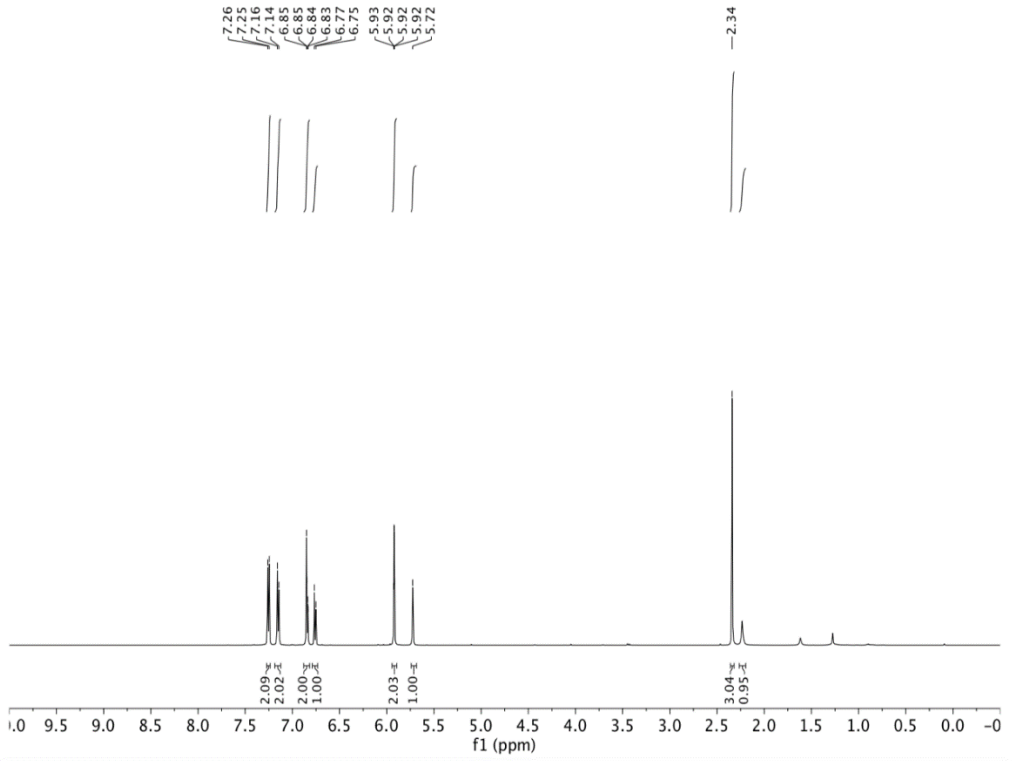
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 7.8 Hz, 2H), 7.15 (d, *J* = 7.8 Hz, 2H), 6.86 – 6.81 (m, 2H), 6.76 (d, *J* = 8.5 Hz, 1H), 5.92 (q, *J* = 1.4 Hz, 2H), 5.72 (s, 1H), 2.34 (s, 3H), 2.23 (s, 1H).

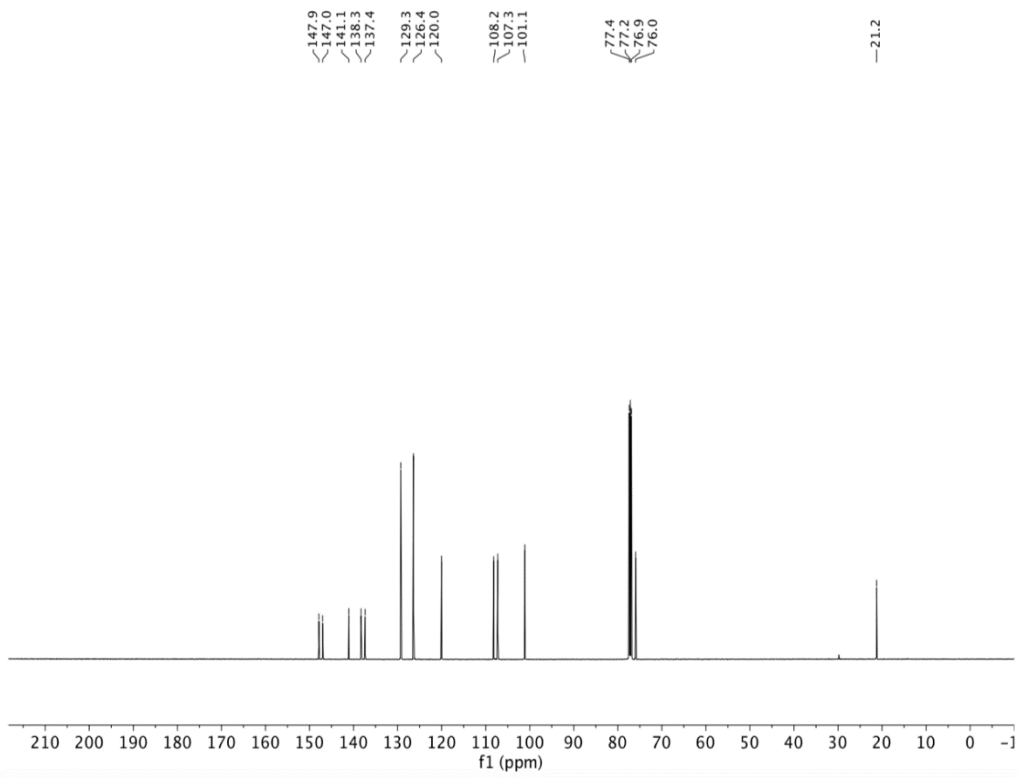
^{13}C NMR (125 MHz, $CDCl_3$): δ = 147.9, 147.0, 141.1, 138.3, 137.4, 129.3, 126.4, 120.0, 108.2, 107.3, 101.1, 76.0, 21.2.

HRMS (CI^+): mass calculated for $[M]^+$ (for $C_{15}H_{12}O_3$) requires *m/z* 242.0943, found *m/z* 242.0943

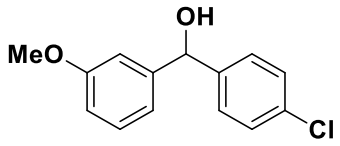
FTIR (neat) 3310, 2887, 2359, 1739, 1124, 1442, 1371, 1240, 1031, 928, 760 cm^{-1}.

MP 62-63°C


7.26
7.25
7.16
7.14
6.85
6.84
6.83
6.77
6.75
5.93
5.92
5.92
5.92
5.72
2.34
2.09
2.02
2.00
1.00
2.03
1.00
3.04
0.95
f1 (ppm)


147.9
147.0
141.1
138.3
137.4
129.3
126.4
120.0
108.2
107.3
101.1
77.4
77.2
76.9
76.0
21.2
f1 (ppm)

(4-chlorophenyl)(3-methoxyphenyl)methanol (7.3b)



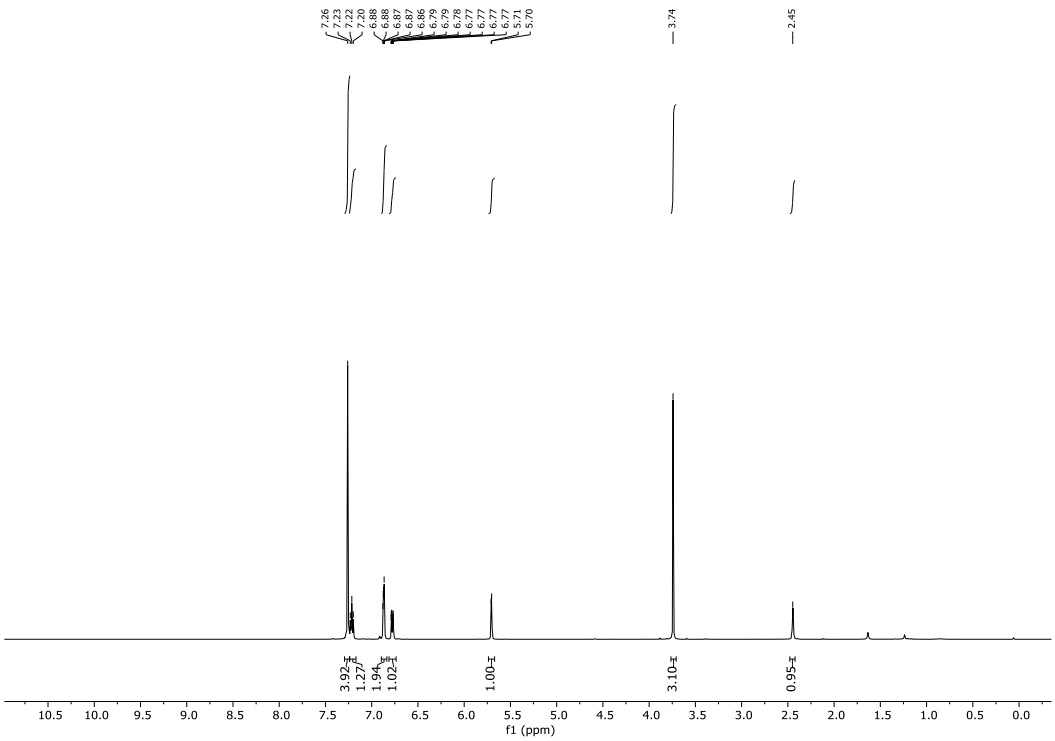
The reaction was conducted in accordance with general procedure A using *m*-anisaldehyde (24μL, 0.2 mmol, 100 mol%) and 4-chloroiodobenzene (95.2 mg, 0.4 mmol, 200 mol%). Flash column chromatography (SiO_2, hexanes/EtOAc = 10:1) provided 40 mg (80%, 0.161 mmol) of the title compound as a colorless oil.

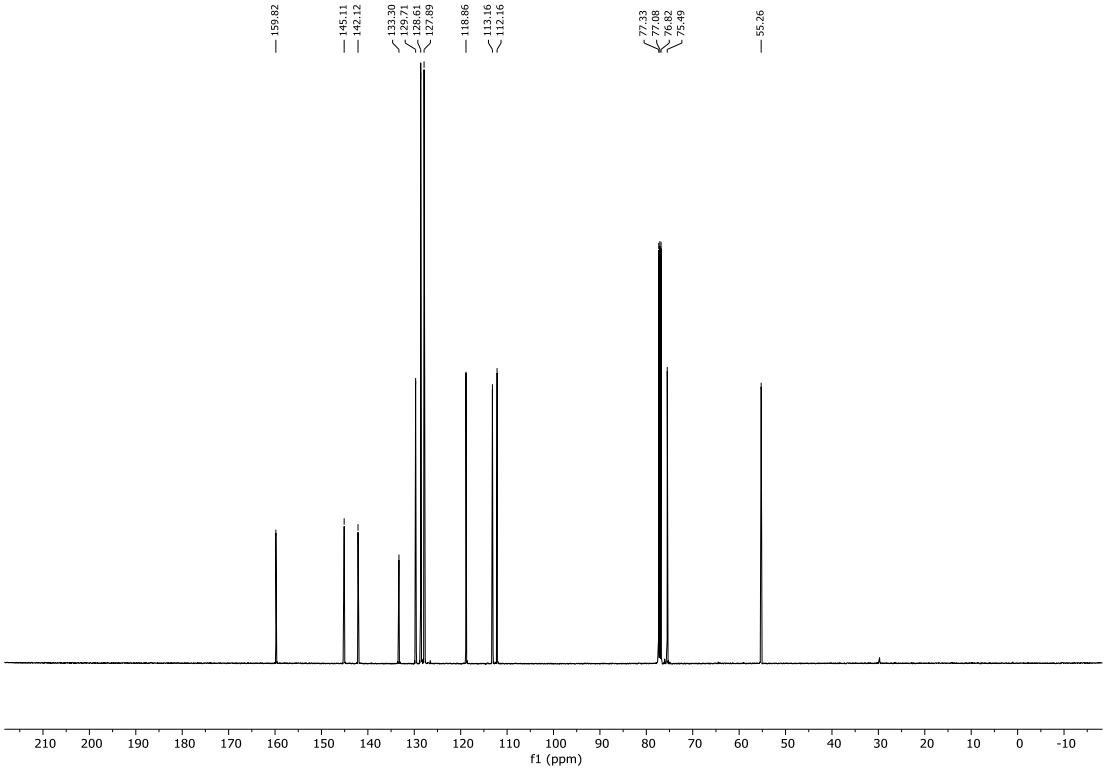
TLC (SiO_2) R_f = 0.43 (hexanes : EtOAc = 4:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26 (s, 3H), 7.22 (t, *J* = 8.1 Hz, 1H), 6.87 (dd, *J* = 4.4, 2.1 Hz, 2H), 6.81 – 6.70 (m, 1H), 5.70 (s, 1H), 3.74 (s, 3H), 2.45 (d, *J* = 3.1 Hz, 1H).

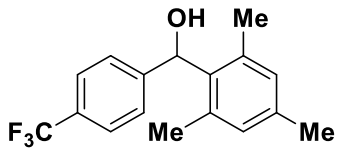
^{13}C NMR (125 MHz, $CDCl_3$): δ 159.8, 145.1, 142.1, 133.3, 129.7, 128.6, 127.9, 118.9, 113.2, 112.2, 75.5, 55.3.
HRMS (CI^+): mass calculated for $[M]^+$ ($C_{14}H_{13}O_2Cl$) requires *m/z* 248.0604, found *m/z* 248.0602.

FTIR (neat): 3386, 2939, 2835, 1738, 1488, 1454, 1256, 1035, 1013, 836, 783, 751, 699 cm^{-1}.


7.26
7.23
7.22
7.20
6.88
6.88
6.87
6.87
6.86
6.79
6.79
6.78
6.77
6.77
6.77
6.77
6.77
5.71
5.70
3.74
2.45
3.92
1.27
1.94
1.02
1.00
3.10
0.95
f1 (ppm)


159.82
145.11
142.12
133.30
129.71
128.61
127.89
118.86
113.16
112.16
77.33
77.08
76.82
75.49
55.26
f1 (ppm)

mesityl(4-(trifluoromethyl)phenyl)methanol (7.3c)



The reaction was conducted in accordance with general procedure B with 4-trifluoromethylbenzaldehyde (27μL, 0.2 mmol, 100mol%) and mesityl iodide (98.4 mg, 0.4 mmol, 200 mol%). Flash column chromatography (SiO_2, hexanes : EtOAc = 10:1) provided 36 mg (62%, 0.122 mmol) of the title compound as a white solid.

TLC (SiO_2): R_f = 0.6 (hexanes : EtOAc = 4:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.56 (d, *J* = 8.2 Hz, 1H), 7.41 (d, *J* = 8.1 Hz, 1H), 6.88 (s, 1H), 6.33 (s, 0H), 2.29 (s, 1H), 2.23 (s, 3H), 2.23 – 2.14 (m, 1H).

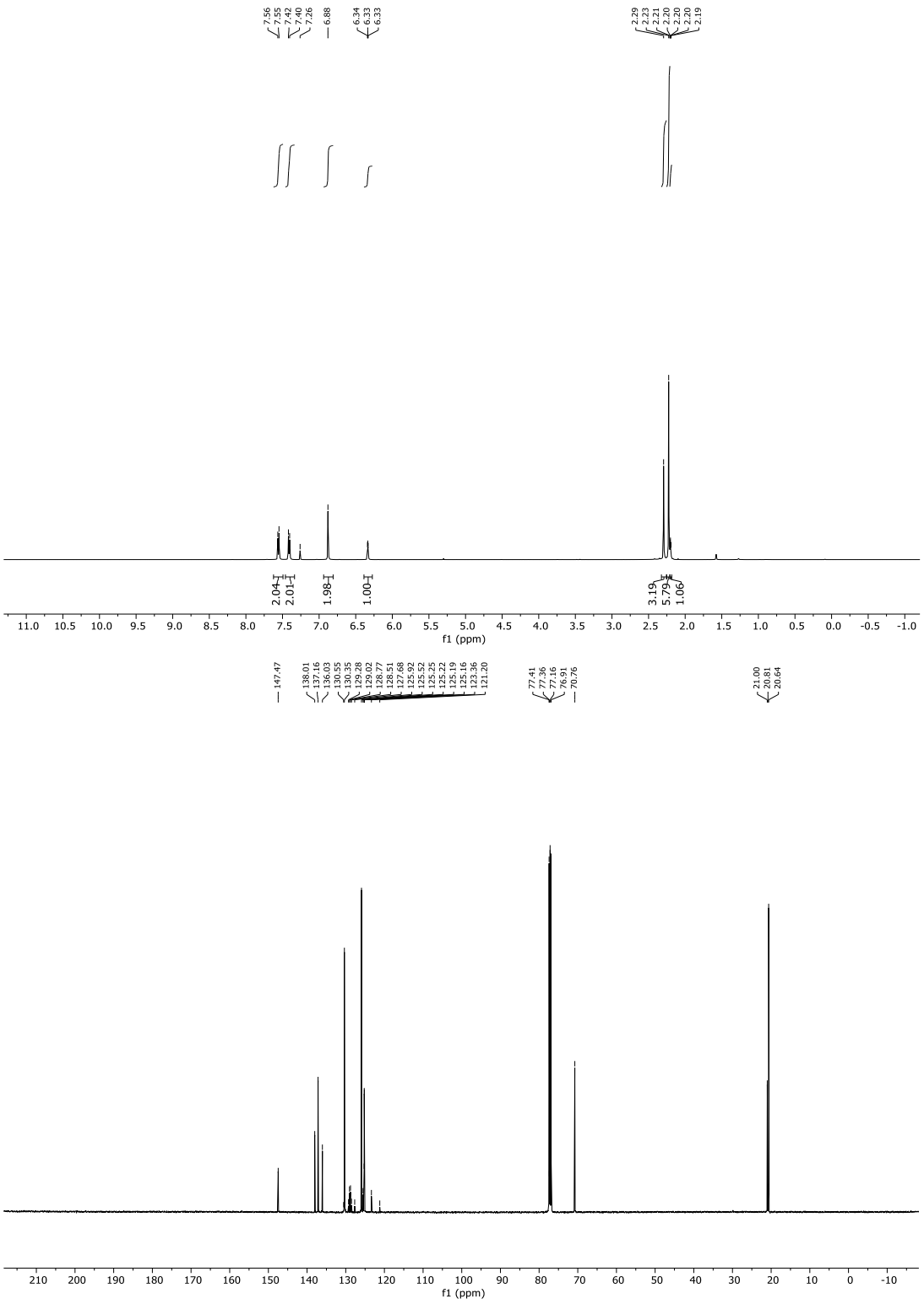
^{13}C NMR (125 MHz, $CDCl_3$ δ 147.5, 138.0, 137.2, 136.0, 130.4, 128.9 (q, *J* = 32.3 Hz), 125.9, 125.2 (q, *J* = 3.8 Hz), 124.4 (q, *J* = 271.8 Hz), 70.8, 21.0, 20.6.

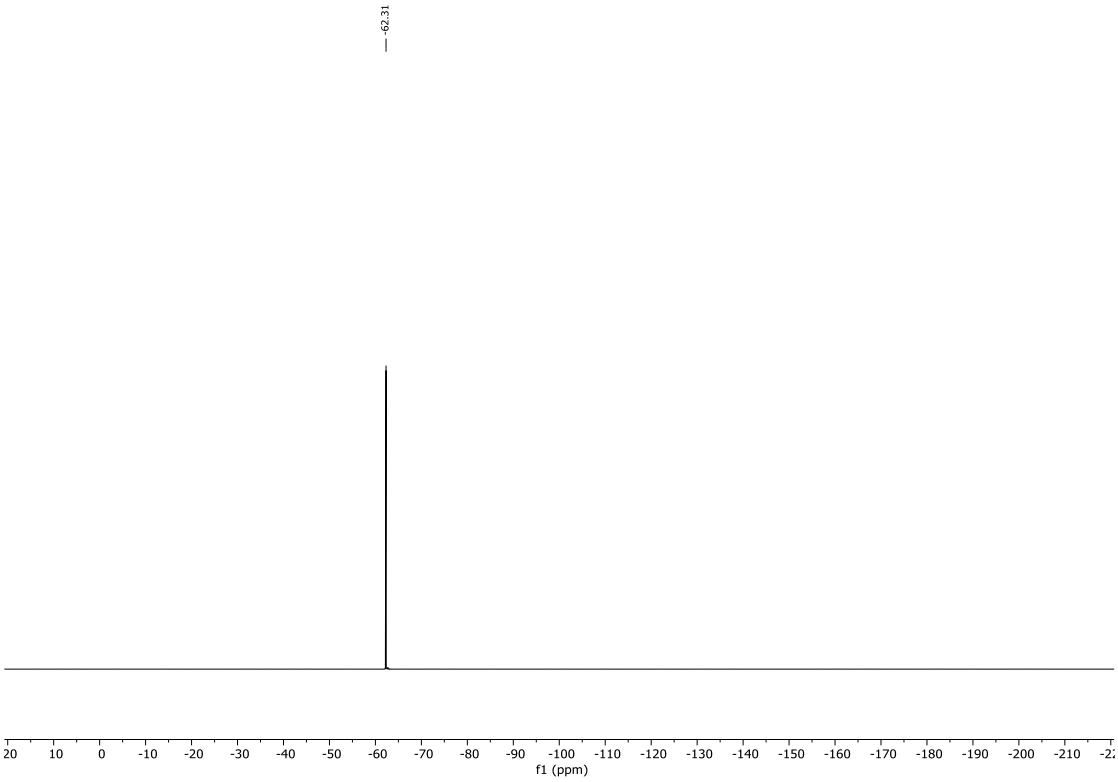
^{19}F NMR (471 MHz, $CDCl_3$) δ -62.31.

HRMS (CI^+): mass calculated for $[M]^+$ ($C_{17}H_{17}OF_3$) requires *m/z* 294.1232, found *m/z* 294.1235.

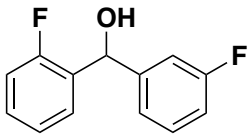
FTIR (neat): 3332, 2922, 1737, 1616, 1454, 1319, 1109, 1066, 1034, 859, 714 cm^{-1}.

MP 68 °C.


7.56
7.55
7.42
7.40
7.26
6.88
6.34
6.33
6.33
2.29
2.23
2.21
2.20
2.20
2.20
2.19
2.04
2.01
1.98
1.00
3.19
5.79
1.06
f1 (ppm)
147.47
138.01
137.16
136.03
130.55
130.35
129.28
129.02
128.77
128.51
127.68
125.92
125.52
125.25
125.22
125.19
123.16
123.06
121.20
77.41
77.36
77.16
76.91
70.76
21.00
20.81
20.64
f1 (ppm)


-62.31
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

(2-fluorophenyl)(3-fluorophenyl)methanol (7.3d)



The title compound was prepared according to the general procedure B using 2-fluorobenzaldehyde (24.8 mg, 0.2mmol, 100 mol%) and 3-fluoroiodobenzene (88.8 mg, 0.40 mmol, 200 mol%). Flash chromatography on silica (Hex/EtOAc 15:1 to 12:1) provided the title compound (33.5 mg, 152 μmol) in 76% yield as a light-yellow oil.

TLC (SiO_2) R_f = 0.38 (hexanes/ethyl acetate = 4:1).

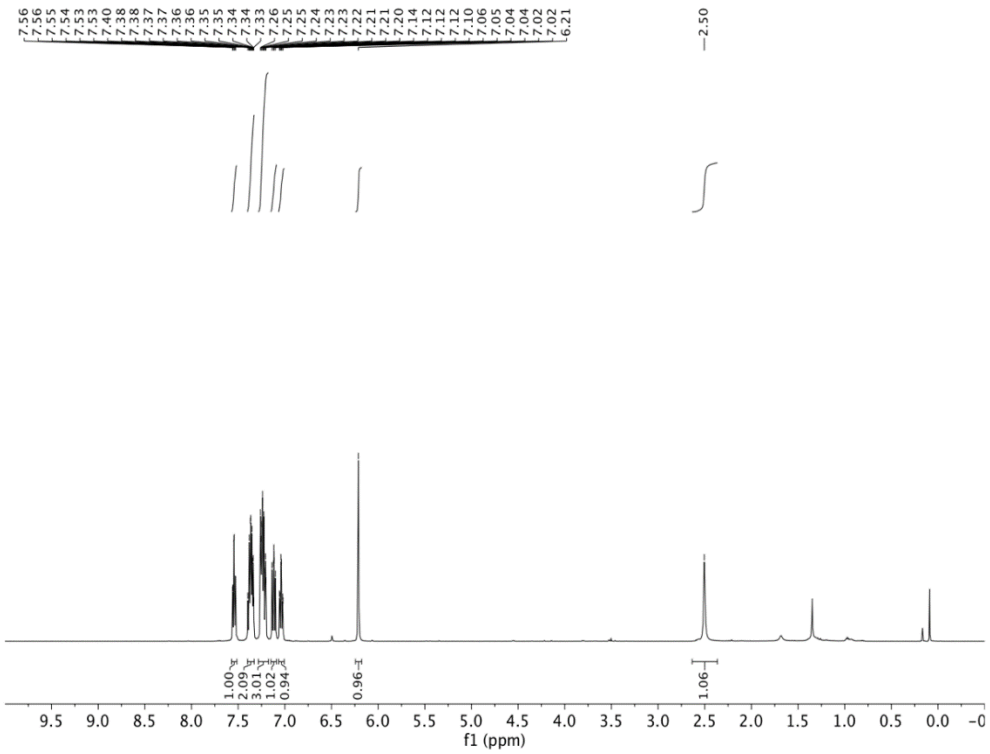
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.54 (td, *J* = 7.6, 1.7 Hz, 1H), 7.40 – 7.32 (m, 2H), 7.23 (ddd, *J* = 15.9, 8.0, 2.9 Hz, 3H), 7.15 – 7.09 (m, 1H), 7.04 (td, *J* = 8.4, 2.5 Hz, 1H), 6.21 (s, 1H), 2.50 (s, 1H).

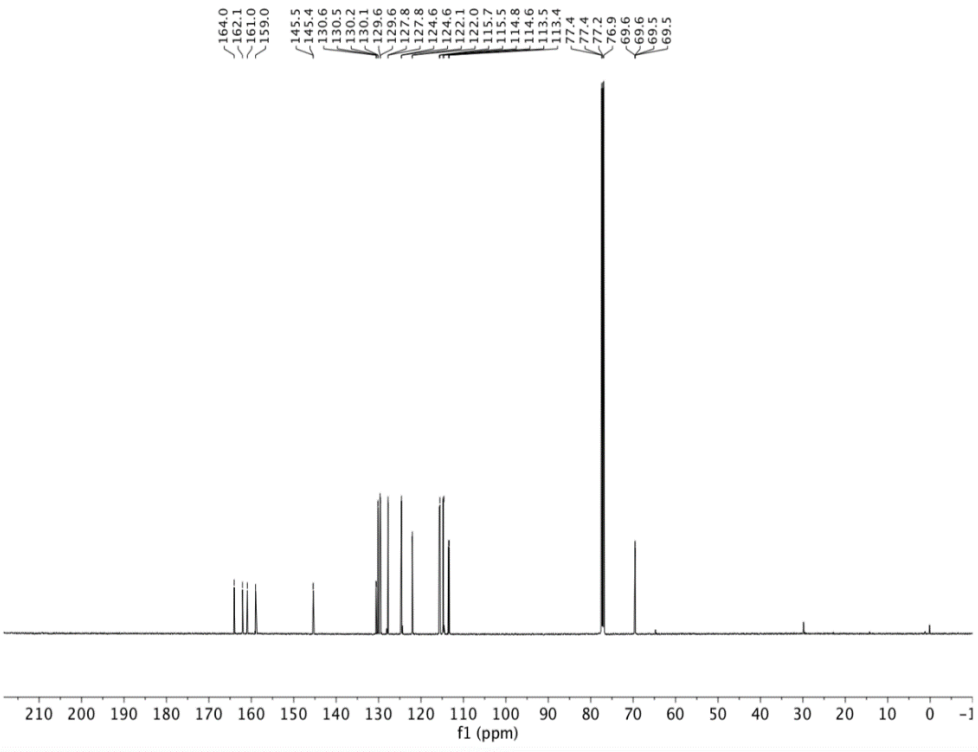
^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.1 (d, *J* = 246.1 Hz), 160.0 (d, *J* = 246.5 Hz), 145.4 (d, *J* = 6.8 Hz), 130.6 (d, *J* = 13.1 Hz), 130.1 (d, *J* = 8.2 Hz), 129.6 (d, *J* = 8.3 Hz), 127.8 (d, *J* = 4.0 Hz), 124.6 (d, *J* = 3.5 Hz), 122.0 (d, *J* = 2.9 Hz), 115.6 (d, *J* = 21.5 Hz), 114.7 (d, *J* = 21.1 Hz), 113.4 (d, *J* = 22.3 Hz), 69.5 (dd, *J* = 3.5, 1.9 Hz).

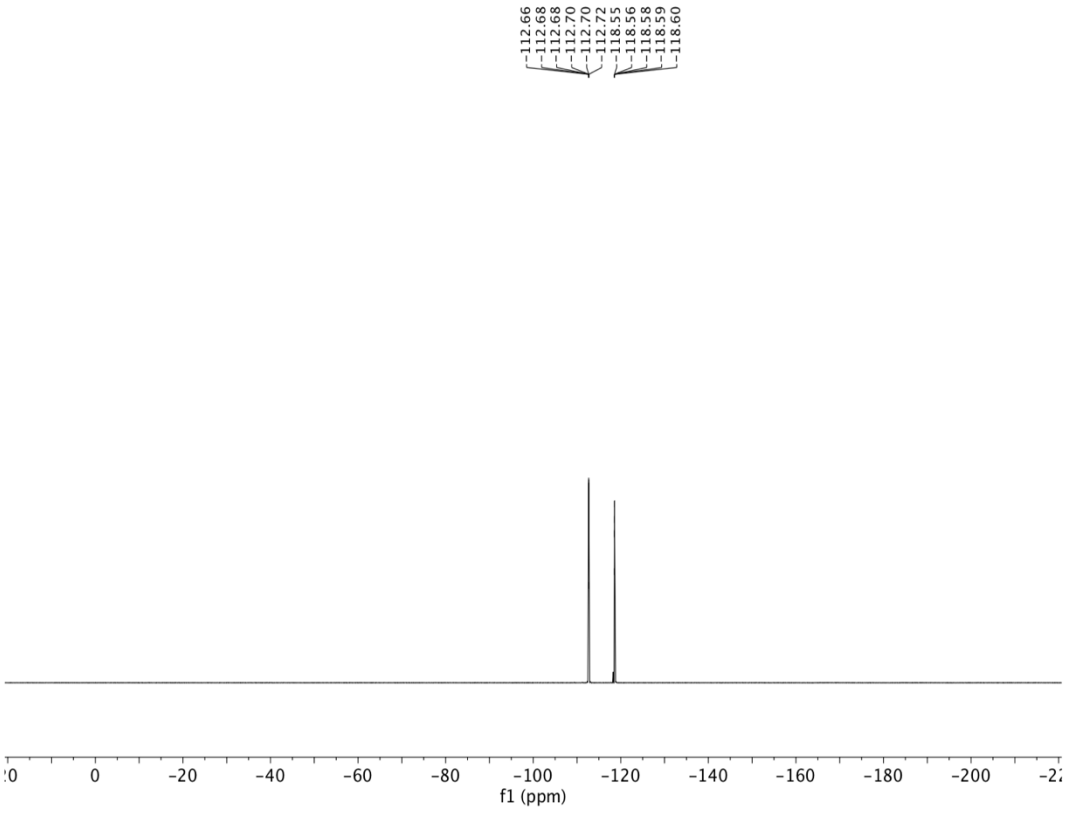
^{19}F NMR (471 MHz, $CDCl_3$): δ = -112.69 (td, *J* = 9.4, 5.6 Hz), -118.58 (m).

HRMS (CI^+): mass calculated for $[M]^+$ ($C_{13}H_{10}OF_2$) requires *m/z* 220.0700, found *m/z* 220.0700

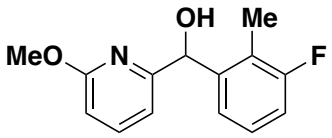
FTIR (neat) 3332, 2359, 1739, 1590, 1485, 1221, 1027, 839, 782, 752, 688 cm^{-1}.


7.56
7.56
7.55
7.54
7.53
7.53
7.40
7.38
7.38
7.37
7.37
7.36
7.36
7.35
7.35
7.34
7.34
7.33
7.26
7.25
7.25
7.24
7.23
7.23
7.22
7.21
7.21
7.20
7.14
7.12
7.12
7.10
7.06
7.05
7.04
7.04
7.02
7.02
6.21
2.50
1.00
2.09
3.01
1.02
0.94
0.96
1.06
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


164.0
162.1
161.0
159.0
145.5
145.4
130.6
130.5
130.2
130.1
129.6
129.6
127.8
127.8
124.6
124.6
122.1
122.0
115.7
115.5
114.8
114.6
113.5
113.4
77.4
77.4
77.2
76.9
69.6
69.6
69.5
69.5
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


-112.66
-112.68
-112.68
-112.70
-112.70
-112.72
-118.55
-118.56
-118.58
-118.59
-118.60
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
f1 (ppm)

(3-fluoro-2-methylphenyl)(6-methoxypyridin-2-yl)methanol (7.3e)



The title compound was prepared according to the general procedure B using 6-methoxypicolinaldehyde (27.4 mg, 0.2 mmol, 100 mol%) and 2-methyl-3-fluoroiodobenzene (94.4 mg, 0.40 mmol, 200 mol%). Flash chromatography on silica (Hex/EtOAc 12:1 to 10:1) provided the title compound (35.5 mg, 143 μmol) in 72% yield as a yellow oil.

TLC (SiO_2) R_f = 0.39 (hexanes/ethyl acetate = 4:1).

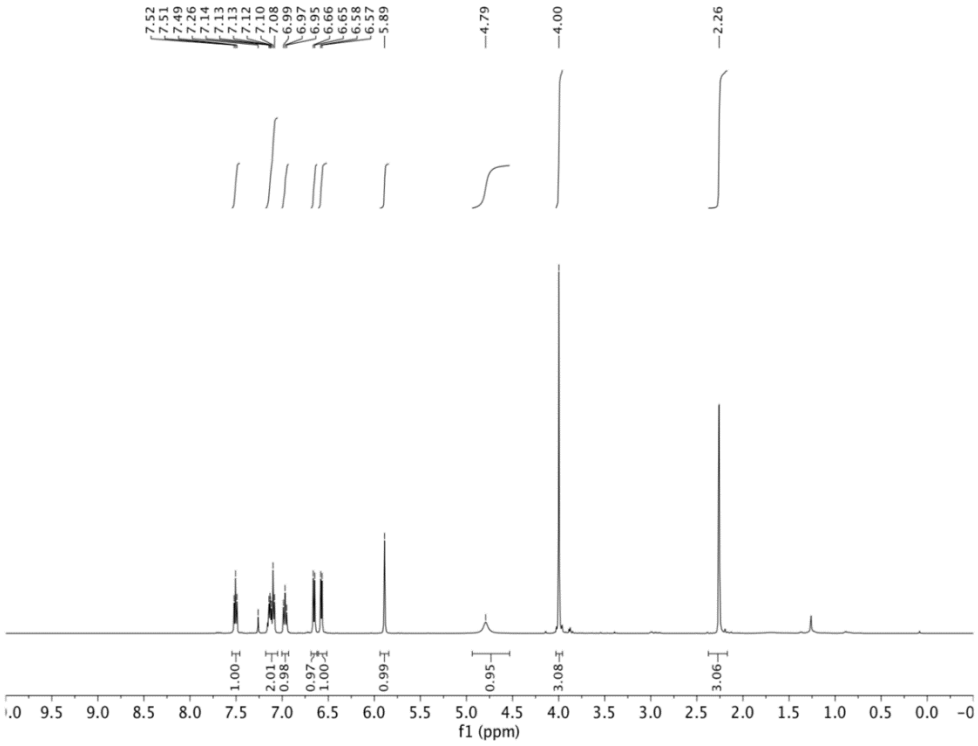
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.51 (t, *J* = 7.8 Hz, 1H), 7.18 – 7.02 (m, 2H), 6.97 (t, *J* = 8.8 Hz, 1H), 6.65 (d, *J* = 8.2 Hz, 1H), 6.57 (d, *J* = 7.3 Hz, 1H), 5.89 (s, 1H), 4.79 (s, 1H), 4.00 (s, 3H), 2.26 (s, 3H).

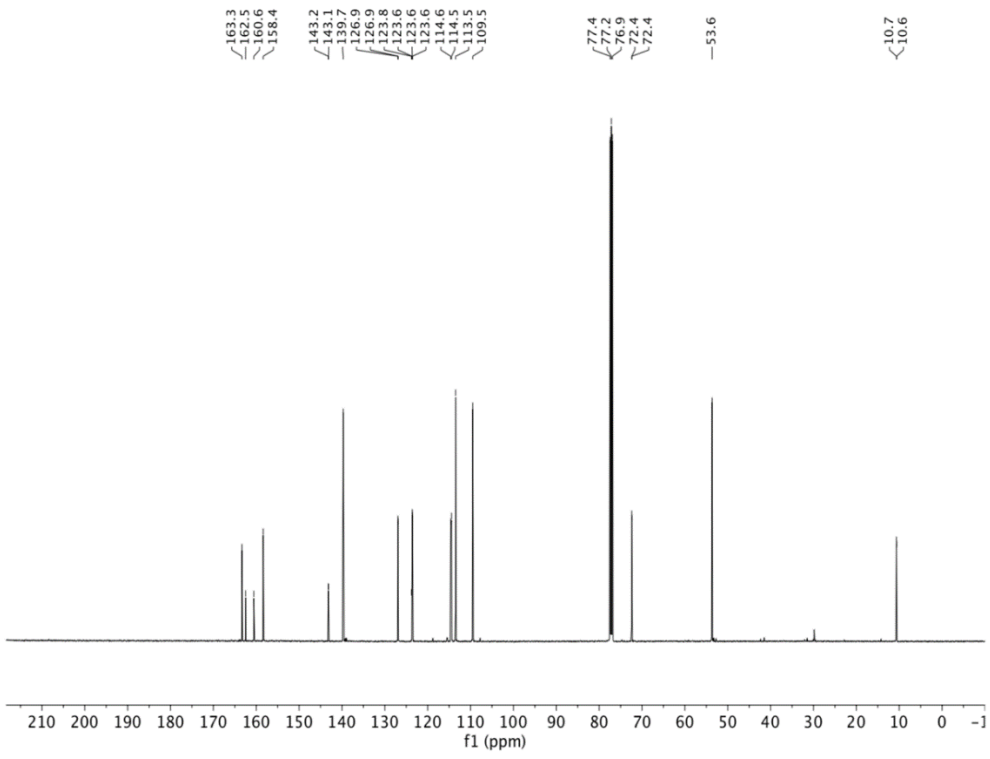
^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.3, 162.5, 160.6, 158.4, 143.2 (d, *J* = 3.7 Hz), 139.7, 126.9 (d, *J* = 8.9 Hz), 123.7 (d, *J* = 16.6 Hz), 123.6 (d, *J* = 3.1 Hz), 114.5 (d, *J* = 23.5 Hz), 113.5, 109.5, 72.4 (d, *J* = 3.1 Hz), 53.6, 10.6 (d, *J* = 6.2 Hz).

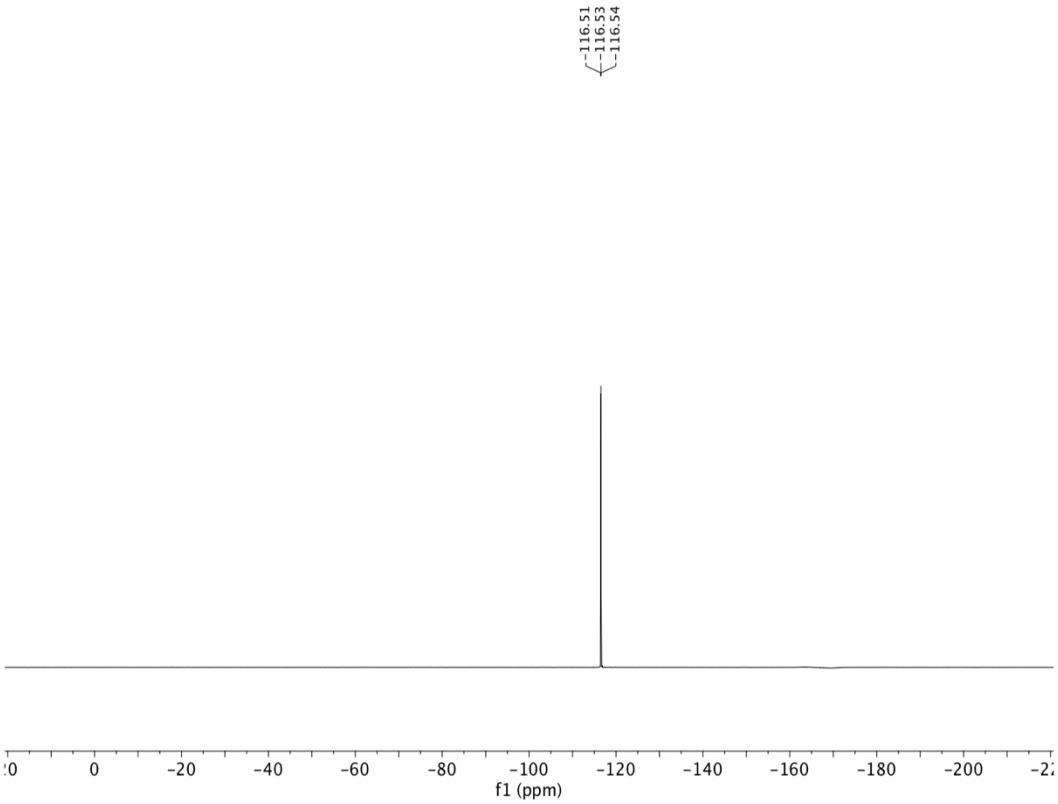
^{19}F NMR (471 MHz, $CDCl_3$): δ = -116.53 (t, *J* = 7.7 Hz).

HRMS (ESI+) Calculated for ($C_{14}H_{14}NO_2$) $[M+Na]^+$ requires 270.0901, found 270.0906.

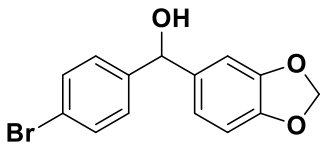
FTIR (neat) 3398, 2949, 2359, 2342, 1739, 1577, 1465, 1313, 1240, 1025, 769 cm^{-1}.


7.52
7.51
7.49
7.26
7.14
7.13
7.12
7.10
7.08
6.99
6.97
6.95
6.66
6.65
6.58
6.57
5.89
4.79
4.00
2.26
1.00
2.01
0.98
0.97
1.00
0.99
0.95
3.08
3.06
f1 (ppm)


163.3
162.5
160.6
158.4
143.2
143.1
139.7
126.9
126.9
123.8
123.6
123.6
123.6
114.6
114.5
113.5
109.5
77.4
77.2
76.9
72.4
72.4
53.6
10.7
10.6
f1 (ppm)


-116.51
-116.53
-116.54
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
f1 (ppm)

benzo[d][1,3]dioxol-5-yl(4-bromophenyl)methanol (7.3f)



The reaction was conducted in accordance with general procedure A with 4-bromobenzaldehyde (37 mg, 0.2 mmol, 100 mol%) and 5-Iodo-1,3-benzodioxole (99 mg, 0.4 mmol, 200 mol%). Flash column chromatography (SiO_2, hexanes : EtOAc = 10:1) provided 45 mg (74%, 0.147 mmol) of the title compound as a colorless oil.

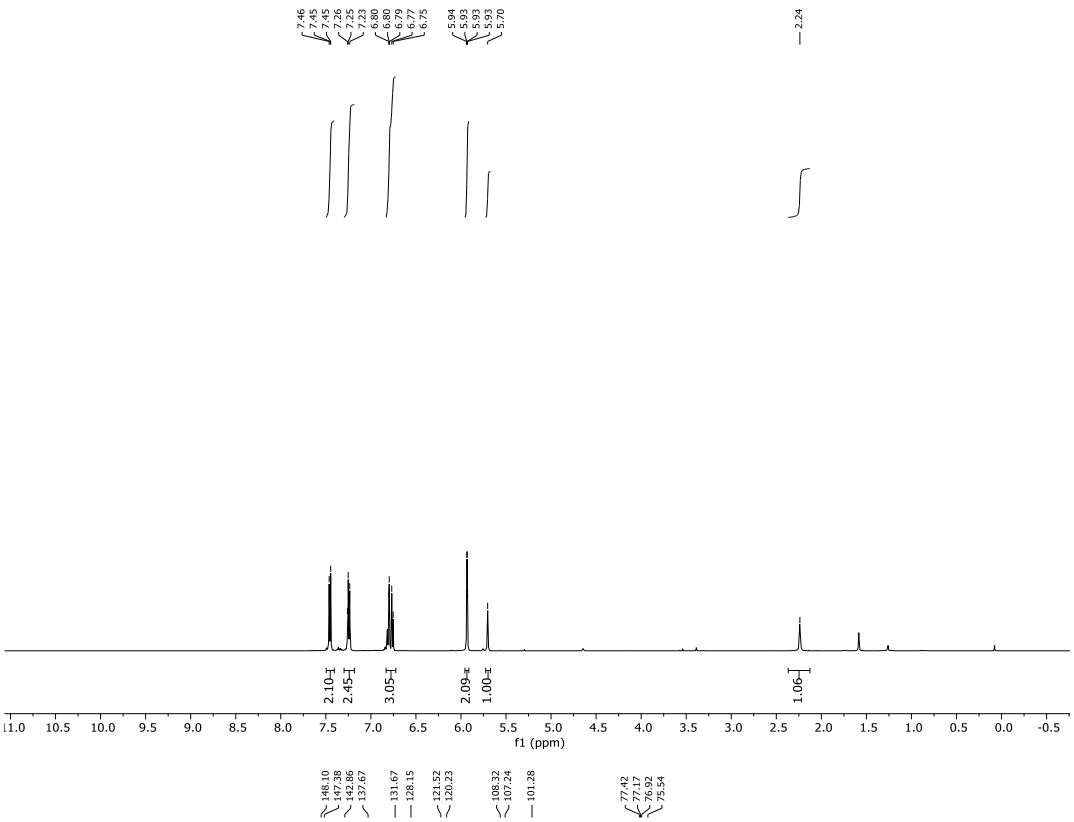
TLC (SiO_2) R_f = 0.33 (hexanes : EtOAc = 4:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45 (d, *J* = 8.5 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 6.85 – 6.78 (m, 2H), 6.76 (d, *J* = 7.9 Hz, 1H), 5.93 (d, *J* = 2.1 Hz, 2H), 5.71 (s, 1H), 2.24 (s, 1H).

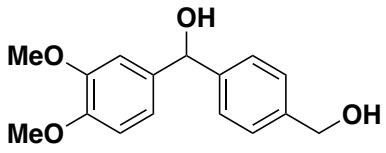
^{13}C NMR (125 MHz, $CDCl_3$): δ 148.1, 147.4, 142.9, 137.7, 131.7, 128.2, 121.5, 120.2, 108.3, 107.2, 101.3, 75.5.

HRMS (CI^+): mass calculated ($C_{14}H_{11}O_3{}^{79}Br$) requires *m/z* 305.9892, found *m/z* 305.9895. mass calculated ($C_{14}H_{11}O_3{}^{81}Br$) requires *m/z* 307.9871, found *m/z* 307.9893

FTIR (neat): 3344, 2893, 1738, 1500, 1484, 1092, 1036, 1008, 927, 802, 775, 670 cm^{-1}.


7.46
7.45
7.45
7.26
7.25
7.23
6.80
6.80
6.79
6.77
6.75
5.94
5.93
5.93
5.93
5.70
2.24
2.10
2.45
3.05
2.09
1.00
1.06
f1 (ppm)
149.10
147.38
142.86
137.67
131.67
128.15
121.52
120.23
108.32
107.24
101.28
77.42
77.17
76.92
75.54
f1 (ppm)

(3,4-dimethoxyphenyl)(4-(hydroxymethyl)phenyl)methanol (7.3g)



The title compound was prepared following general procedure A using 3,4-dimethylbenzaldehyde (33.2 mg, 0.2 mmol, 100 mol%) and (4-iodophenyl)methanol (93.6 mg, 0.40 mmol, 200 mol%). Flash chromatography on silica (Hex/EtOAc 1:1) provided the title compound (36.4 mg, 133 μmol) in 66% yield as a white solid.

TLC (SiO_2) R_f = 0.24 (hexanes/ethyl acetate = 1:3).

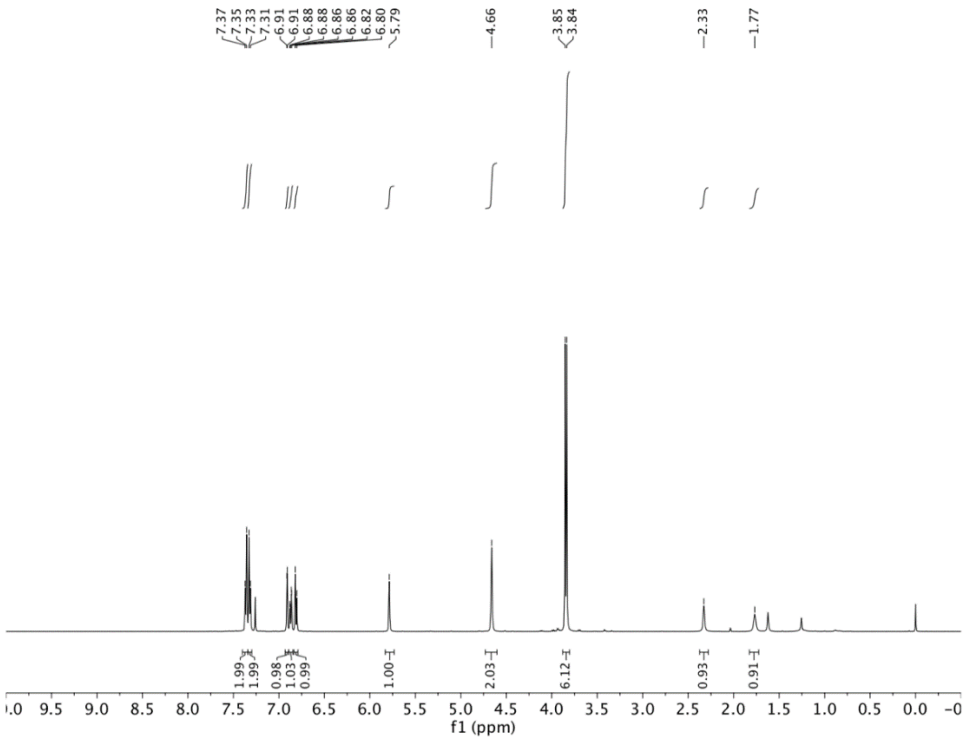
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 6.91 (d, *J* = 2.0 Hz, 1H), 6.87 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.81 (d, *J* = 8.2 Hz, 1H), 5.79 (s, 1H), 4.66 (s, 2H), 3.85 (s, 3H), 3.84 (s, 3H), 2.33 (s, 1H), 1.77 (s, 1H).

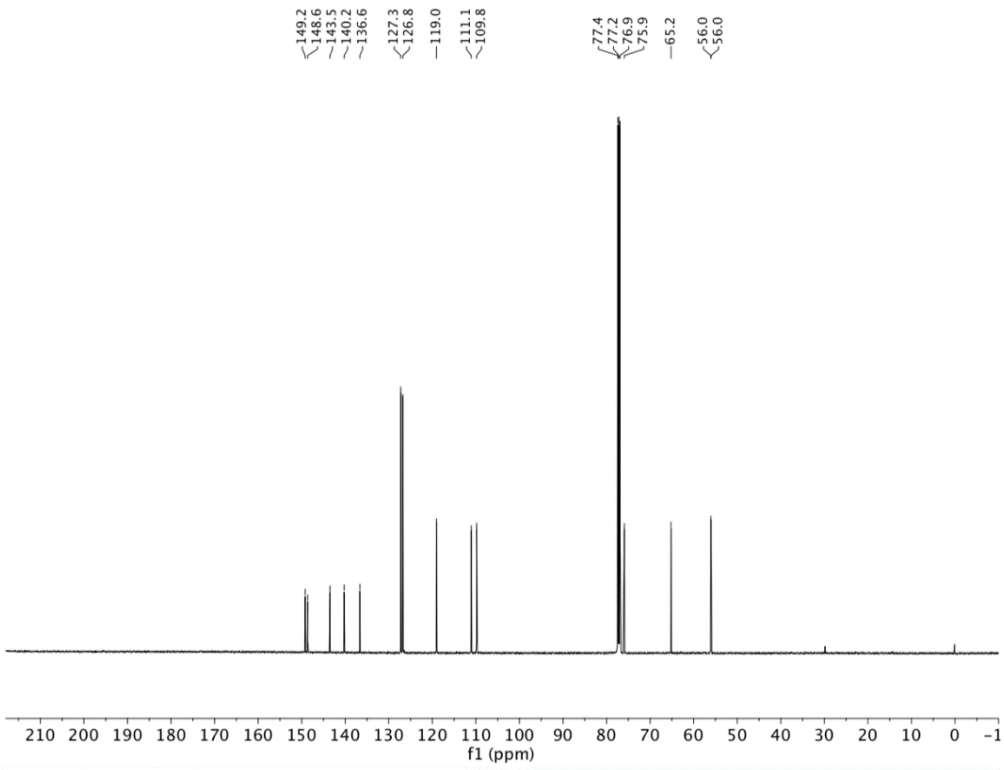
^{13}C NMR (125 MHz, $CDCl_3$): δ = 149.2, 148.6, 143.5, 140.2, 136.6, 127.3, 126.8, 119.0, 111.1, 109.8, 75.9, 65.2, 56.0, 56.0.

HRMS (ESI^+): mass calculated $[M+Na]^+$ ($C_{16}H_{18}O$) requires *m/z* 297.1097, found *m/z* 297.1099

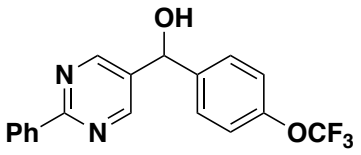
MP 131-133°C

FTIR (neat) 3332, 3219, 2919, 2839, 2360, 1739, 1595, 1558, 1419, 1360, 1258, 1231, 1137, 1012, 749 cm^{-1}.


7.37
7.35
7.33
7.31
6.91
6.88
6.88
6.86
6.86
6.82
6.80
5.79
4.66
3.85
3.84
2.33
1.77
1.99
1.99
0.98
1.03
0.99
1.00
2.03
6.12
0.93
0.91
f1 (ppm)


149.2
148.6
143.5
140.2
136.6
127.3
126.8
119.0
111.1
109.8
77.4
77.2
76.9
75.9
65.2
56.0
56.0
f1 (ppm)

(2-phenylpyrimidin-5-yl)(4-(trifluoromethoxy)phenyl)methanol (7.3h)



The title compound was prepared according to the general procedure A using 2-phenylpyrimidine-5-carbaldehyde (36.8 mg, 0.2 mmol, 100 mol%) and 1-iodo-4-(trifluoromethoxy)benzene (115.2 mg, 0.40 mmol, 200 mol%). Flash chromatography on silica (Hex/EtOAc 5:1) provided the title compound (38.2 mg, 111 μmol) in 55% yield as a yellow solid.

TLC (SiO_2) R_f = 0.19 (hexanes/ethyl acetate = 4:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.71 (s, 2H), 8.46 – 8.26 (m, 2H), 7.47 (dd, *J* = 5.2, 2.0 Hz, 3H), 7.42 – 7.36 (m, 2H), 7.21 (d, *J* = 8.2 Hz, 2H), 5.86 (s, 1H), 3.25 (s, 1H).

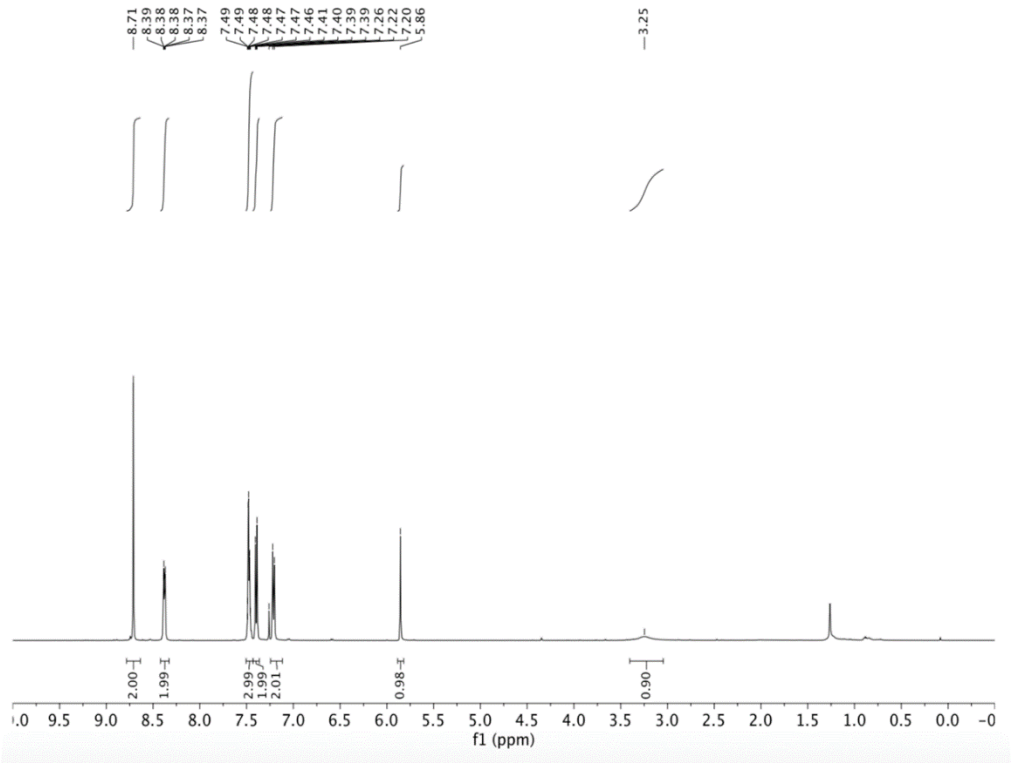
^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.2, 155.8, 149.2 (q, J = 2.0 Hz), 140.9, 137.1, 133.9, 131.1, 128.8, 128.3, 128.1, 121.5, 120.5 (q, J = 258.2 Hz), 71.8.

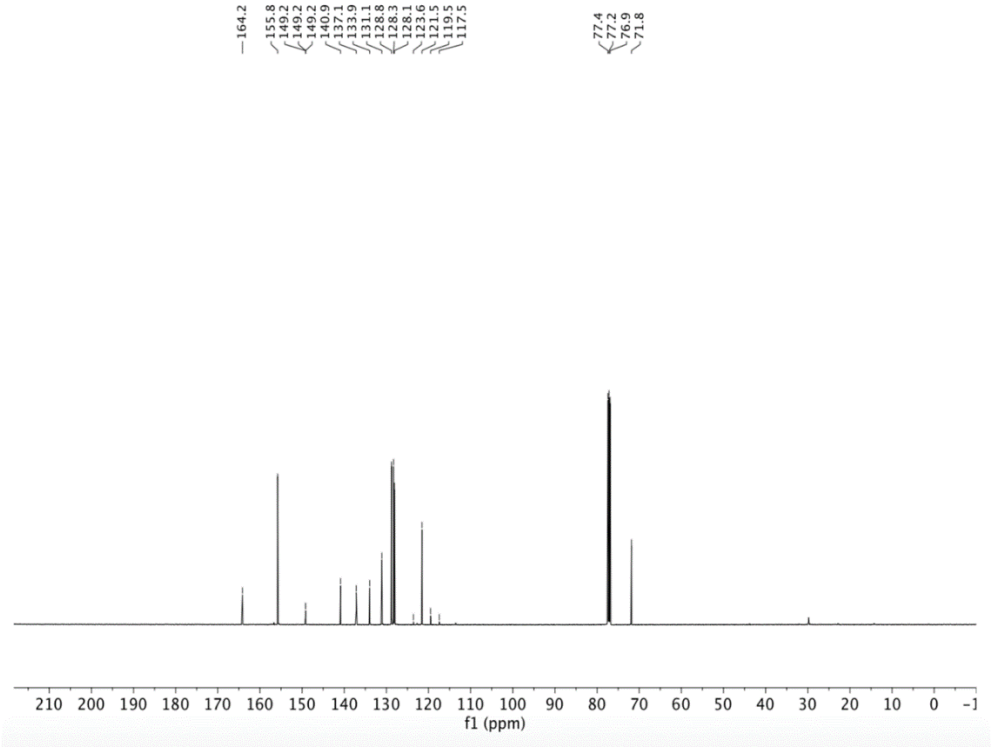
^{19}F NMR (471 MHz, $CDCl_3$): δ = -57.87

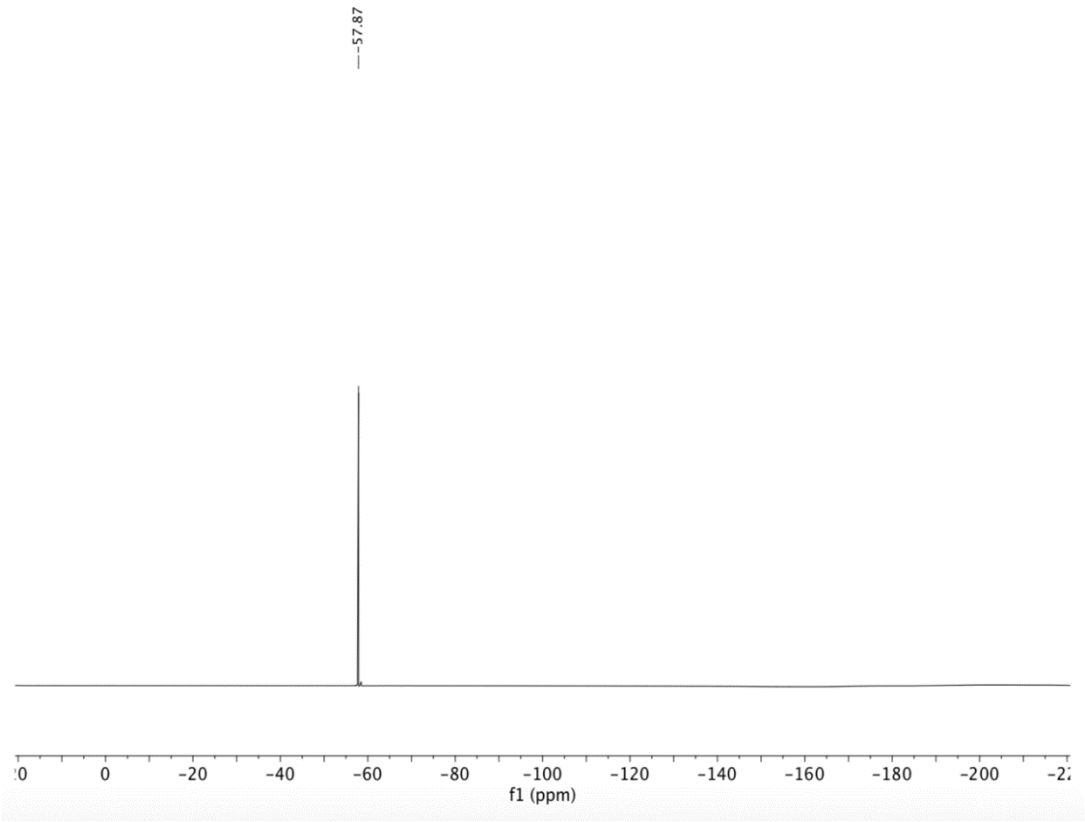
HRMS (ESI^+): mass calculated for $[M+H]^+$ ($C_{18}H_{13}F_3N_2O_2$) requires *m/z* 347.1002, found *m/z* 347.1011.

MP 110-112°C

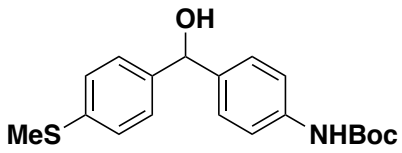
FTIR (neat) 3165, 2921, 2358, 1592, 1547, 1433, 1260, 1207, 1154, 863, 743, 688 cm^{-1}.


8.71
8.39
8.38
8.38
8.37
8.37
7.49
7.49
7.48
7.48
7.47
7.47
7.46
7.41
7.40
7.39
7.39
7.26
7.22
7.20
5.86
3.25
2.00
1.99
2.99
1.99
2.01
0.98
0.90
f1 (ppm)


164.2
155.8
149.2
149.2
149.2
140.9
137.1
133.9
131.1
128.8
128.3
128.1
123.6
121.5
119.5
117.5
77.4
77.2
76.9
71.8
f1 (ppm)


57.87
0
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
f1 (ppm)

***tert*-butyl (4-(hydroxy(4-(methylthio)phenyl)methyl)phenyl)carbamate (7.3i)**



The title compound was prepared according to the general procedure A using 4-(methylthio)benzaldehyde (30.4 mg, 0.2 mmol, 100 mol%) and *tert*-butyl (4-iodophenyl)carbamate[1] (127.6 mg, 0.40 mmol, 200 mol%). Flash chromatography on silica (Hex/EtOAc 4:1) provided the title compound (39.3 mg, 114 μmol) in 57% yield as a yellow solid.

TLC (SiO_2) R_f = 0.59 (hexanes/ethyl acetate = 1:1).

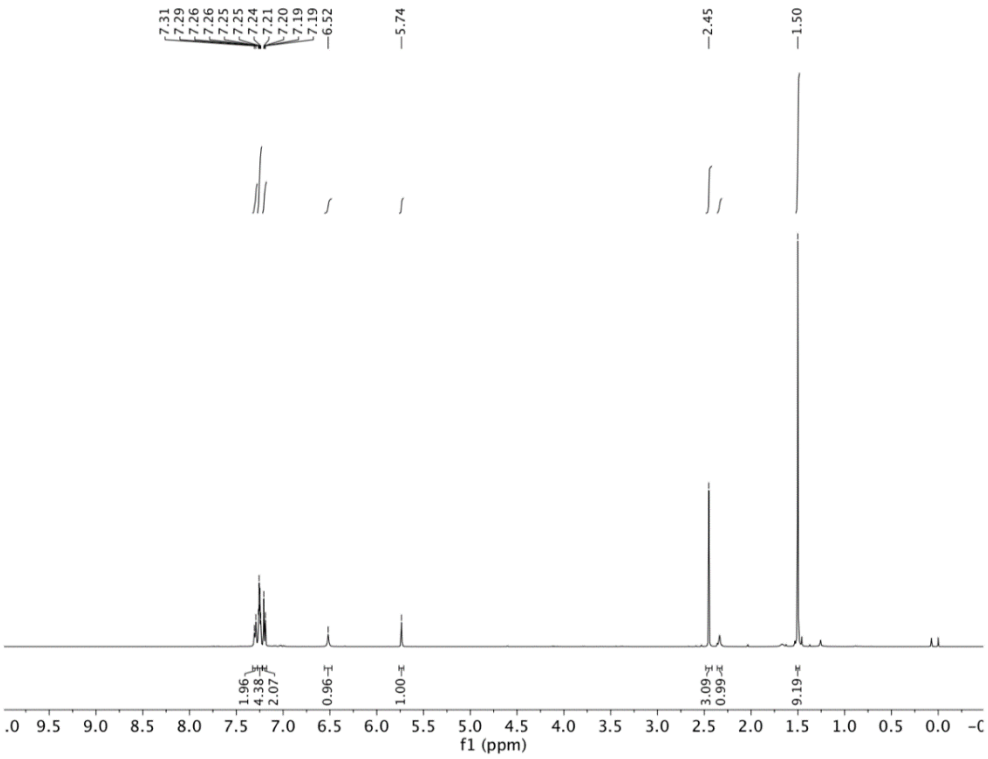
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.30 (d, *J* = 8.4 Hz, 2H), 7.26 (d, *J* = 3.9 Hz, 2H), 7.24 (d, *J* = 4.2 Hz, 2H), 7.20 (d, *J* = 8.5 Hz, 2H), 6.52 (s, 1H), 5.74 (s, 1H), 2.45 (s, 3H), 2.34 (s, 1H), 1.50 (s, 9H).

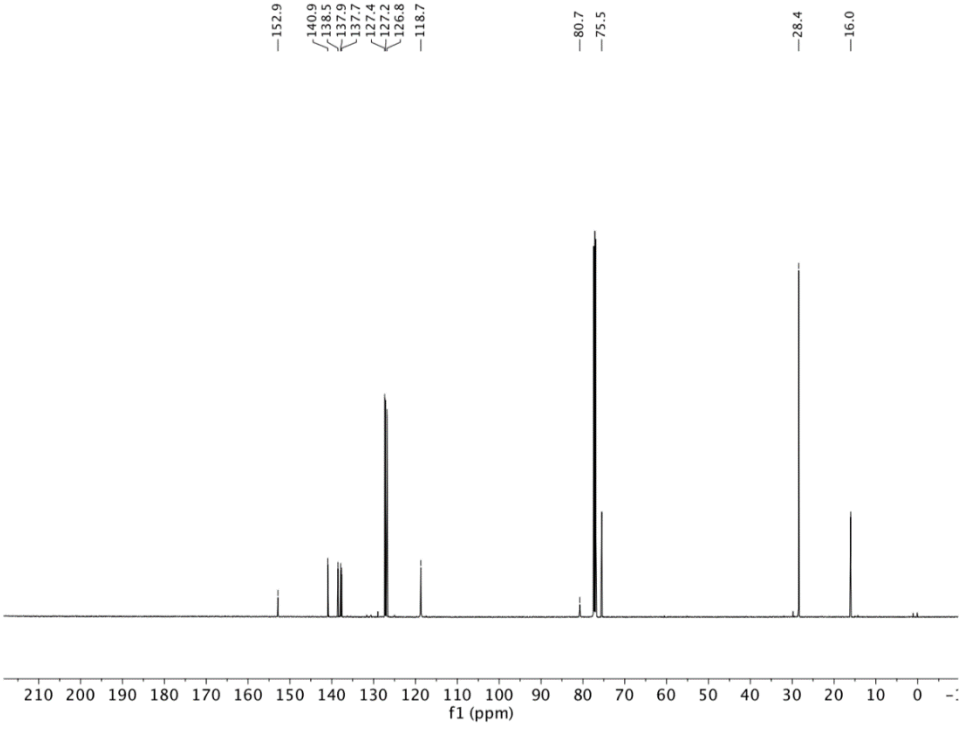
^{13}C NMR (125 MHz, $CDCl_3$): δ = 152.9, 140.9, 138.5, 137.9, 137.7, 127.4, 127.2, 126.8, 118.7, 80.7, 75.5, 28.4, 16.0.

HRMS (ESI^+): mass calculated for $[M+Na]^+$ ($C_{19}H_{23}NO_3S$) requires *m/z* 368.1291, found *m/z* 368.1294.

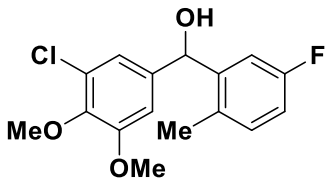
MP 121-123°C

FTIR (neat) 3368, 3250, 2972, 2914, 2359, 2342, 1699, 1522, 1412, 1309,1233, 1157, 1012, 858 cm^{-1}.


7.31
7.29
7.26
7.26
7.25
7.25
7.24
7.21
7.20
7.19
7.19
6.52
5.74
2.45
1.50
1.96
4.38
2.07
0.96
1.00
3.09
0.99
9.19
f1 (ppm)


152.9
140.9
138.5
137.9
137.7
127.4
127.2
126.8
118.7
80.7
75.5
28.4
16.0
f1 (ppm)

(3-chloro-4,5-dimethoxyphenyl)(5-fluoro-2-methylphenyl)methanol (7.3j)



The reaction was conducted in accordance with general procedure A using 3-chloro-4,5-dimethoxybenzaldehyde (40 mg, 0.2 mmol, 100 mol%) and 5-fluoro-2-methyliodobenzene (62μL, 0.4 mmol, 200 mol%). Flash column chromatography (SiO_2, hexanes : EtOAc = 5:1) provided 43 mg (75%, 0.138mmol) of the title compound as a colorless oil.

TLC (SiO_2) R_f = 0.22 (hexanes : EtOAc = 4:1).

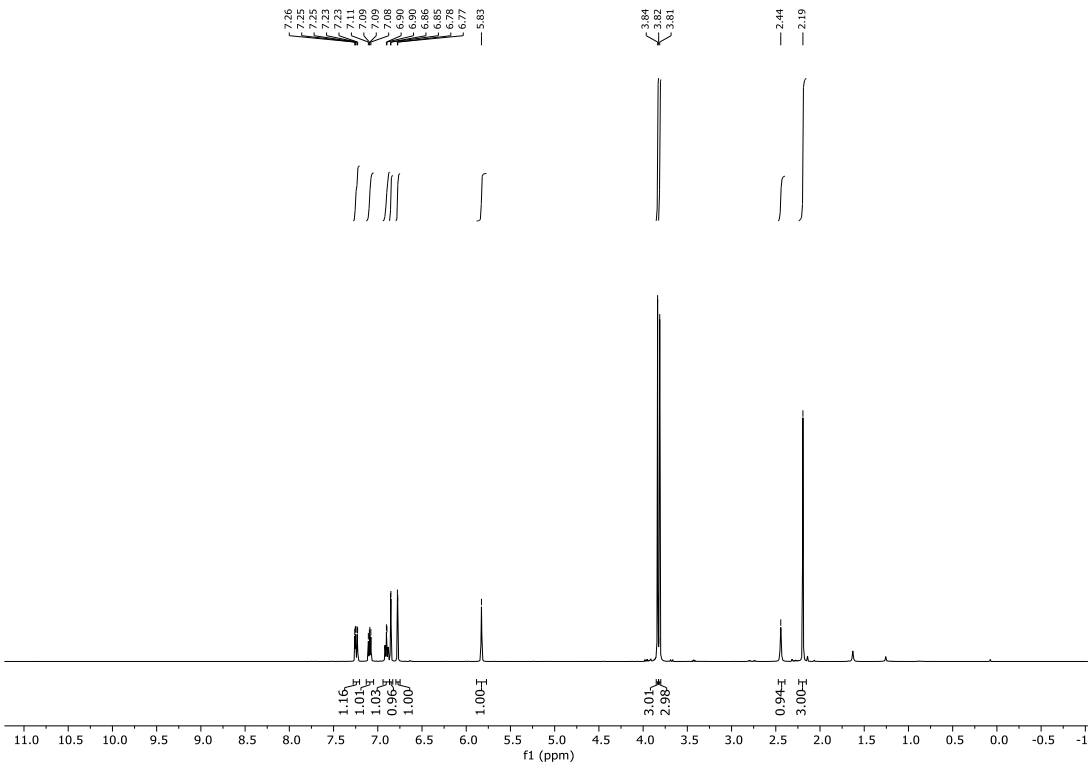
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24 (dd, *J* = 10.0, 2.8 Hz, 1H), 7.09 (dd, *J* = 8.3, 5.7 Hz, 1H), 6.90 (td, *J* = 8.3, 2.9 Hz, 1H), 6.85 (d, *J* = 1.9 Hz, 1H), 6.78 (d, *J* = 1.9 Hz, 1H), 5.83 (s, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 2.44 (s, 1H), 2.19 (s, 3H).

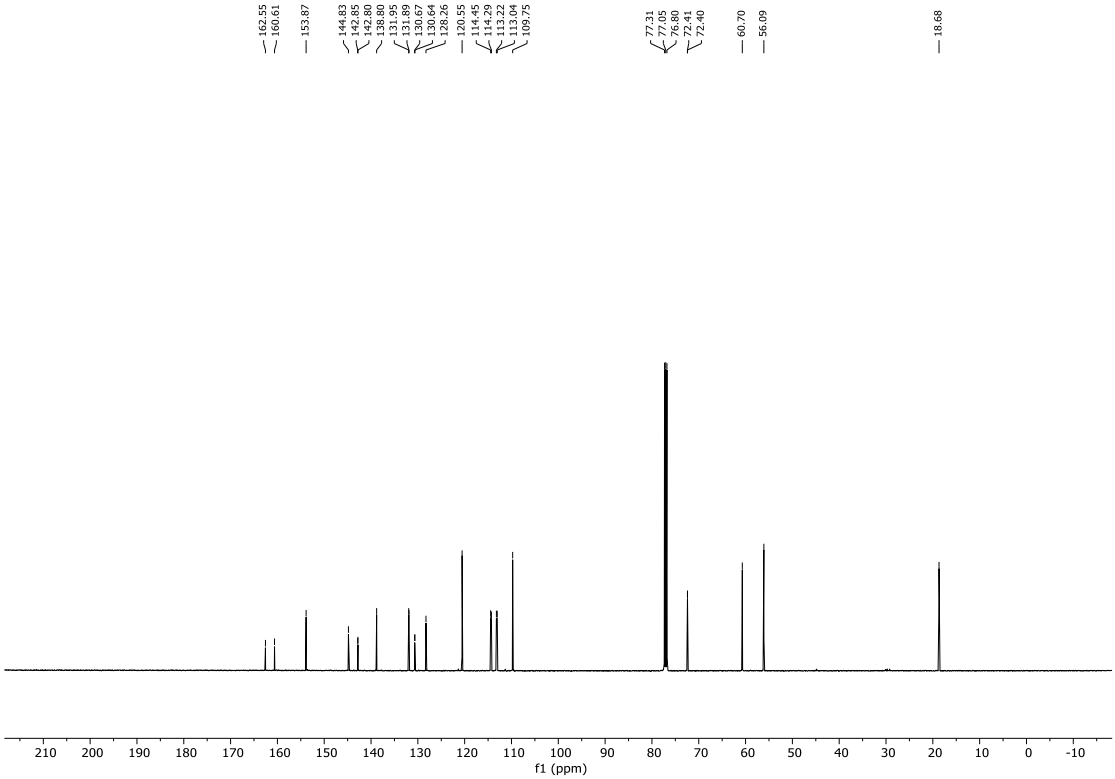
^{13}C NMR (125 MHz, $CDCl_3$): δ 162.6, 160.6, 153.9, 142.8 (d, *J* = 6.4 Hz), 131.9 (d, *J* = 7.6 Hz), 130.7 (d, *J* = 3.2 Hz), 128.2, 120.6, 114.4 (d, *J* = 20.9 Hz), 113.1 (d, *J* = 22.7 Hz), 109.8, 72.4 (d, *J* = 1.4 Hz), 60.7, 56.1, 18.7.

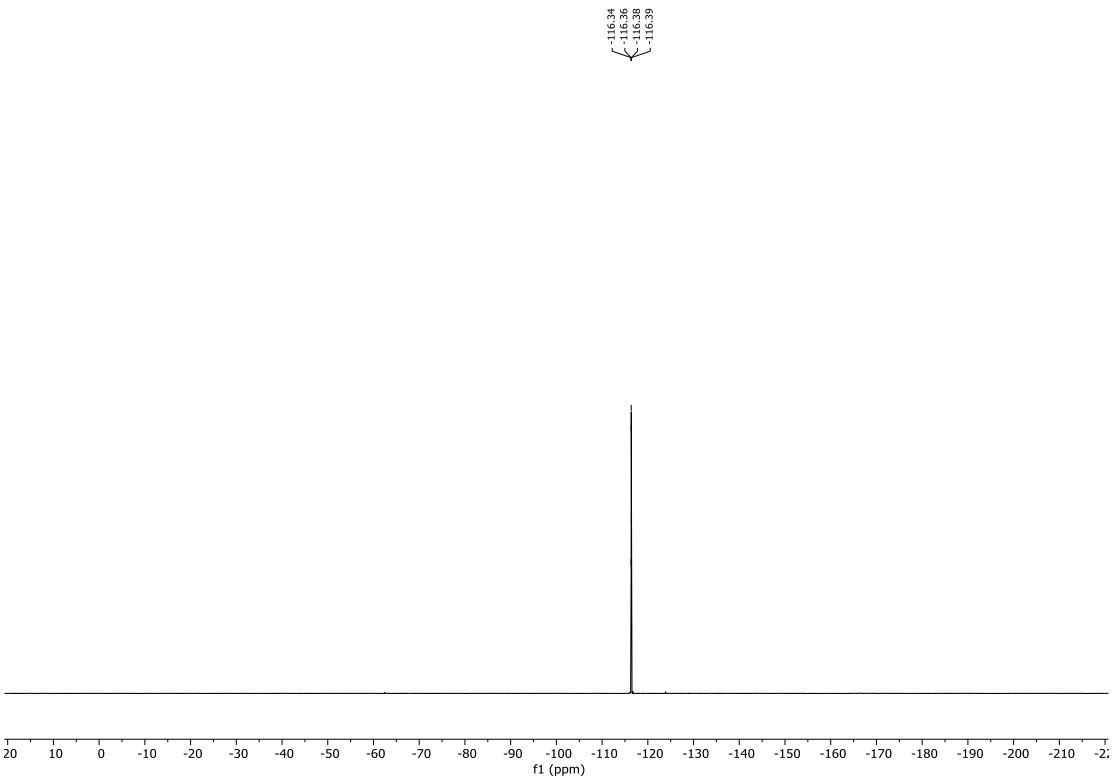
^{19}F NMR (470 MHz, $CDCl_3$): δ -116.37 (q, *J* = 8.3 Hz).

HRMS (CI^+): mass calculated for $[M]^+$ ($C_{16}H_{16}O_3FCl$) requires *m/z* 310.0772, found *m/z* 310.0766.

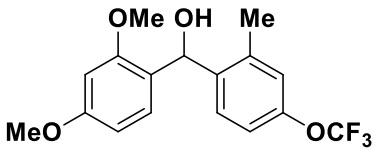
FTIR (neat): 3387, 2939, 2360, 1738, 1489, 1413, 1269, 1237, 1133, 1051, 999, 850, 687 cm^{-1}.


7.26
7.25
7.25
7.23
7.11
7.09
7.09
7.08
6.90
6.90
6.86
6.85
6.78
6.77
5.83
3.84
3.82
3.81
2.44
2.19
1.16
1.01
1.03
0.96
1.00
1.00
3.01
2.98
0.94
3.00
f1 (ppm)


162.55
160.61
153.87
144.83
142.85
142.80
138.80
131.95
131.89
130.67
130.64
128.26
120.55
114.45
114.29
113.22
113.04
109.75
77.31
77.05
76.80
72.44
72.40
60.70
56.09
18.68
f1 (ppm)


-116.34
-116.36
-116.38
-116.39
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

(2,4-dimethoxyphenyl)(2-methyl-4-(trifluoromethoxy)phenyl)methanol (7.3k)



The reaction was conducted in accordance with general procedure A using 2,4-dimethoxybenzaldehyde (33 mg, 0.2 mmol, 100 mol%) and 2-methyl-4-(trifluoromethoxy)iodobenzene (68μL, 0.4 mmol, 200 mol%). Flash column chromatography (SiO_2, hexanes : EtOAc = 5:1) provided 51 mg (75%, 0.149 mmol) of the title compound as a yellow oil.

TLC (SiO_2) R_f = 0.25 (hexanes : EtOAc = 4:1).

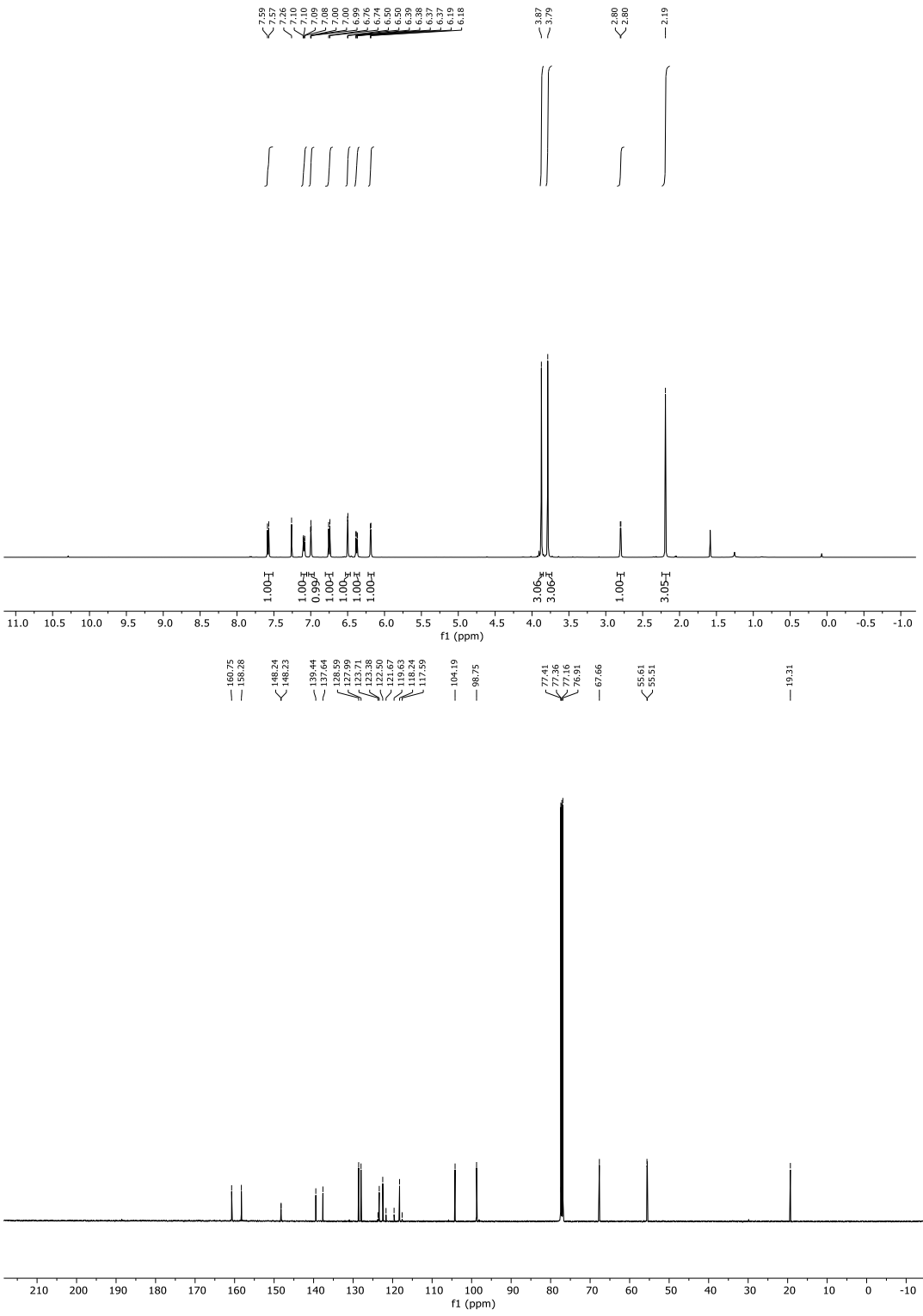
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.58 (d, *J* = 8.5 Hz, 1H), 7.09 (d, *J* = 10.7 Hz, 1H), 7.00 (s, 1H), 6.75 (d, *J* = 8.4 Hz, 1H), 6.50 (d, *J* = 2.4 Hz, 1H), 6.38 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.19 (d, *J* = 3.6 Hz, 1H), 3.87 (s, 3H), 3.79 (s, 3H), 2.80 (d, *J* = 3.8 Hz, 1H), 2.19 (s, 3H).

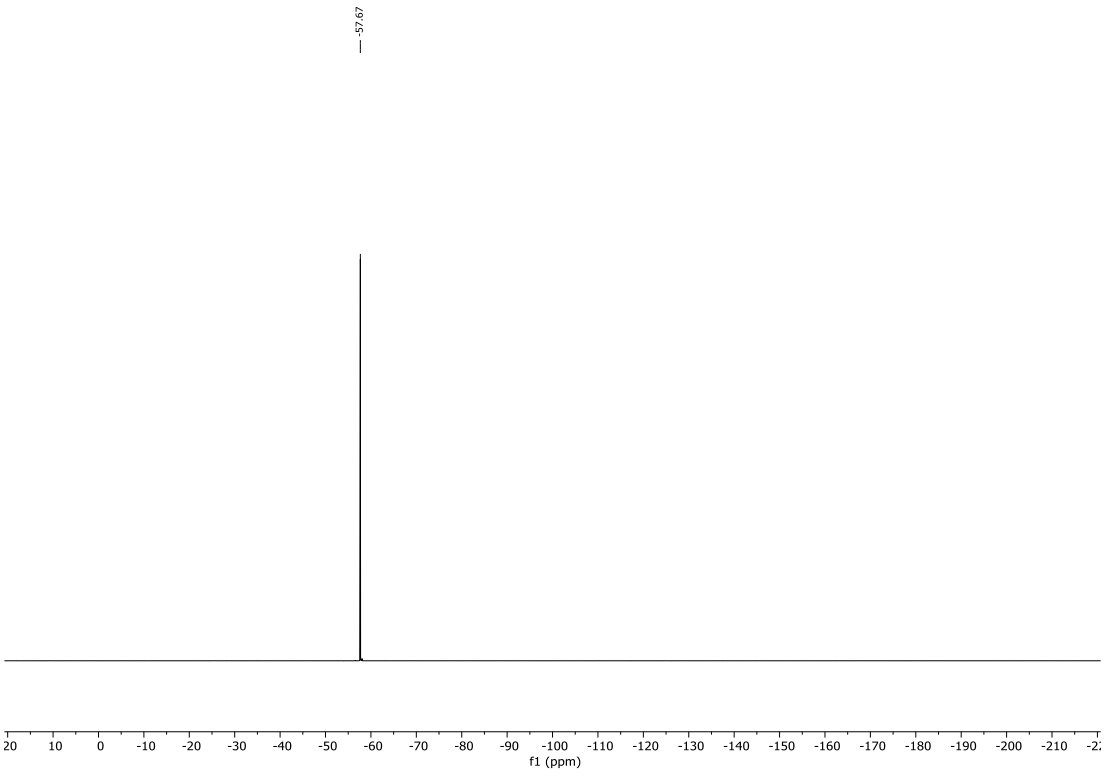
^{13}C NMR (125 MHz, $CDCl_3$): δ 160.75, 158.28, 148.23, 139.44, 137.64, 128.59, 127.99, 123.38, 122.50, 120.65 (q, *J* = 256.6 Hz), 118.24, 104.19, 98.75, 67.66, 55.61, 55.51, 19.31.

^{19}F NMR (470 MHz, $CDCl_3$): δ -57.67.

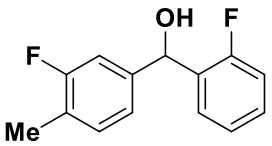
HRMS (ESI^+): mass calculated for $[M+Na]^+$ ($C_{17}H_{17}F_3O_4$) requires *m/z* 365.0971, found *m/z* 365.0969.

FTIR (neat): 3377, 2945, 1738, 1611, 1503, 1251, 1206, 1151, 1033, 869, 683 cm^{-1}.


7.59
7.57
7.26
7.10
7.10
7.09
7.08
7.00
7.00
6.99
6.76
6.74
6.50
6.50
6.39
6.38
6.37
6.37
6.19
6.18
3.87
3.79
2.80
2.80
2.19
1.00
1.00
0.99
1.00
1.00
1.00
3.06
3.06
1.00
3.05
f1 (ppm)
160.75
158.28
148.24
148.23
139.44
137.64
128.59
127.99
123.71
123.38
122.50
121.67
119.63
118.24
117.59
104.19
98.75
77.41
77.26
77.16
76.91
67.66
55.61
55.51
19.31
f1 (ppm)


-57.67
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

(3-fluoro-4-methylphenyl)(2-fluorophenyl)methanol (7.3l)



The reaction was conducted in accordance with general procedure A using 3-fluoro-4-methylbenzaldehyde (25 μL, 0.2 mmol, 100 mol%) and 2-fluoroiodobenzene (47 μL, 0.4 mmol, 200 mol%). Flash column chromatography (SiO_2, hexanes : EtOAc = 9:1) provided 35.1 mg (75%, 0.149 mmol) of the title compound as a colorless oil.

TLC (SiO_2) R_f = 0.5 (hexanes : EtOAc = 4:1).

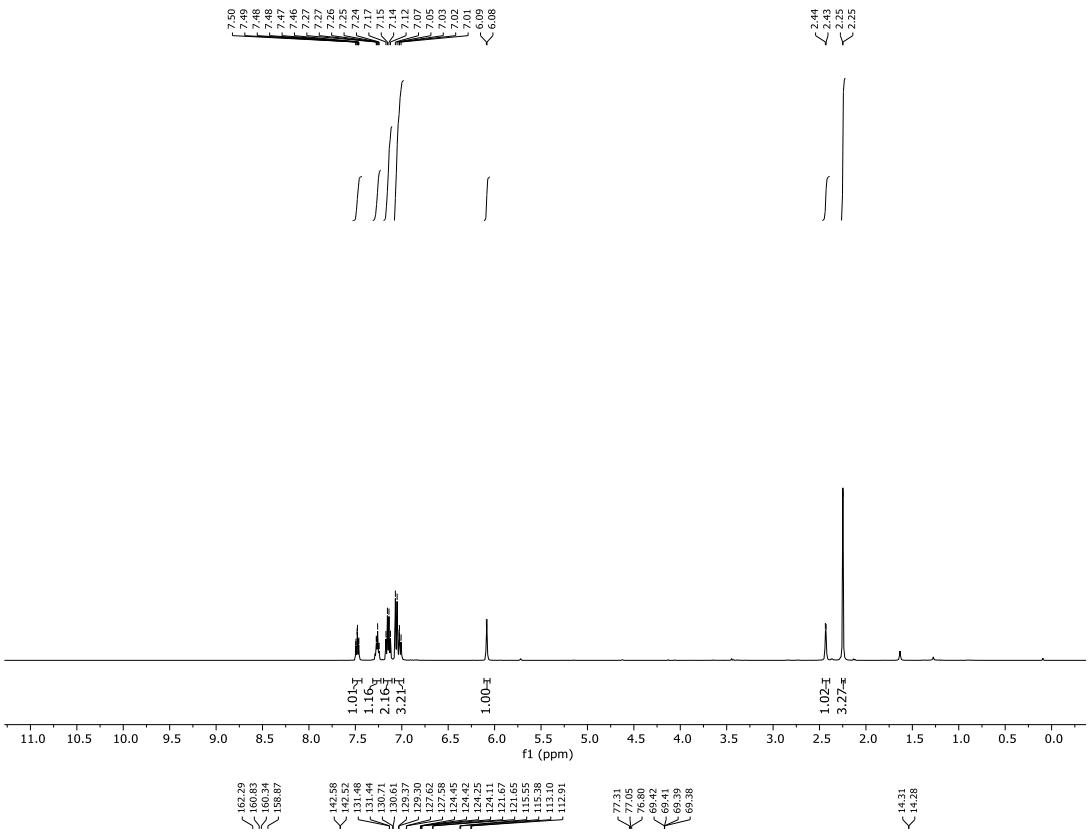
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48 (td, *J* = 7.6, 1.8 Hz, 1H), 7.32 – 7.22 (m, 1H), 7.15 (q, *J* = 8.0 Hz, 2H), 7.06 (d, *J* = 9.7 Hz, 2H), 7.04 – 6.94 (m, 1H), 6.09 (d, *J* = 3.4 Hz, 1H), 2.43 (d, *J* = 3.8 Hz, 1H), 2.25 (d, *J* = 1.9 Hz, 3H).

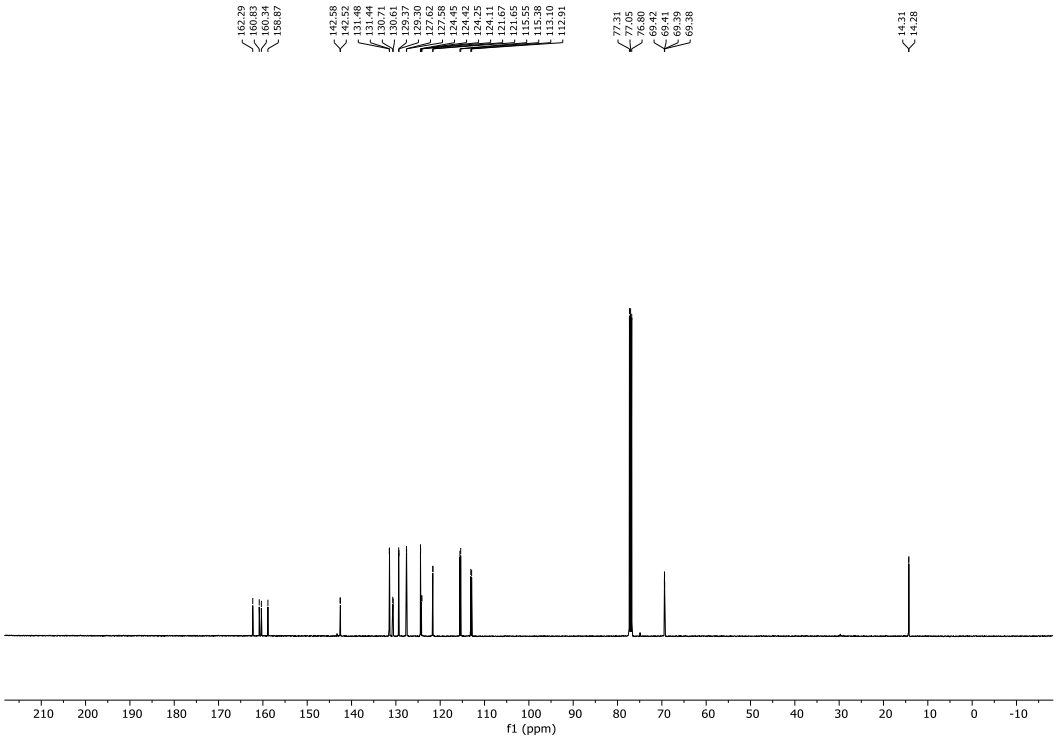
^{13}C NMR (125 MHz, $CDCl_3$): δ 161.6 (d, *J* = 183.9 Hz), 159.6 (d, *J* = 185.2 Hz), 142.6 (d, *J* = 6.8 Hz), 131.5 (d, *J* = 5.4 Hz), 130.7 (d, *J* = 13.0 Hz), 129.3 (d, *J* = 8.2 Hz), 127.6 (d, *J* = 4.0 Hz), 124.4 (d, *J* = 3.6 Hz), 124.2 (d, *J* = 17.3 Hz), 121.7 (d, *J* = 3.2 Hz), 115.5 (d, *J* = 21.4 Hz), 113.0 (d, *J* = 23.3 Hz), 69.4 (dd, *J* = 3.5, 1.8 Hz), 14.3 (d, *J* = 3.6 Hz).

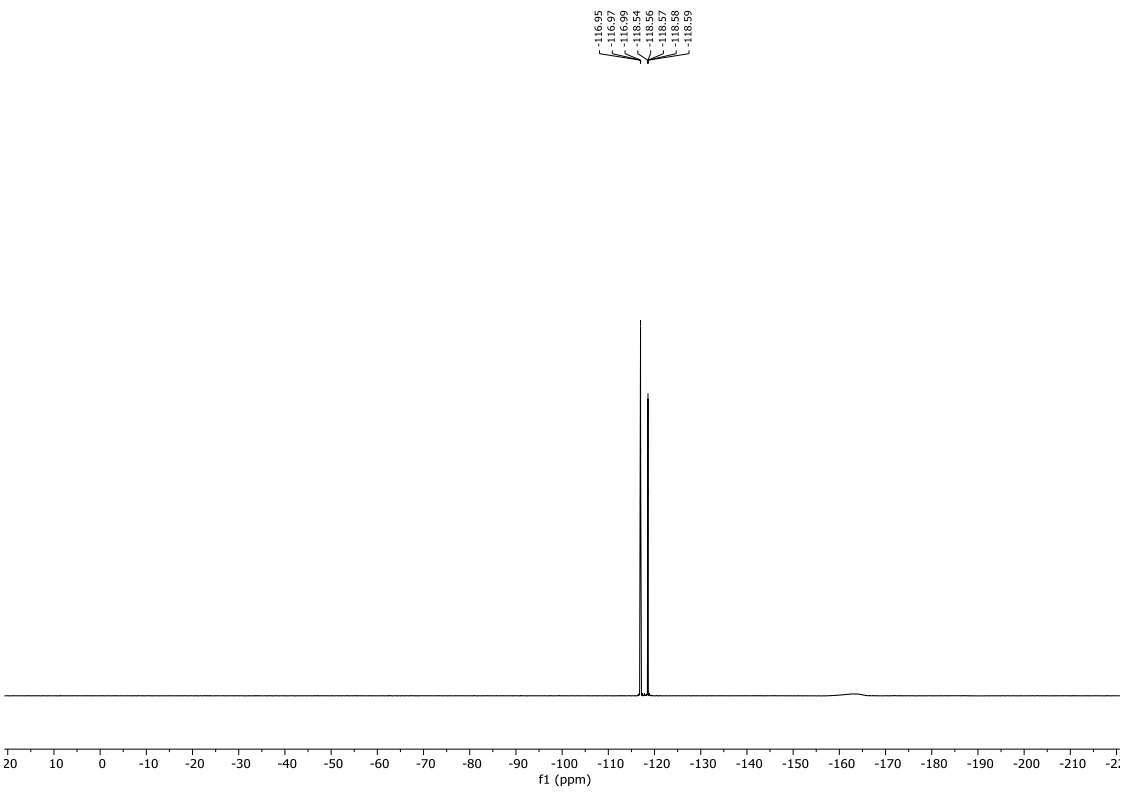
^{19}F NMR (470 MHz, $CDCl_3$): δ -116.97 (t, *J* = 9.3 Hz), -118.57 (dt, *J* = 12.2, 6.4 Hz).

HRMS (CI^+): mass calculated for $[M]^+$ ($C_{14}H_{12}OF_2$) requires *m/z* 234.0856, found *m/z* 234.0858.

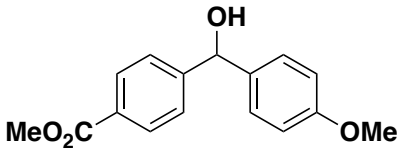
FTIR (neat): 3344, 2928, 1738, 1585, 1508, 1455, 1418, 1252, 1030, 824, 753 cm^{-1}.


7.50
7.49
7.48
7.48
7.47
7.46
7.27
7.27
7.26
7.25
7.24
7.17
7.15
7.14
7.12
7.07
7.05
7.03
7.02
7.01
6.09
6.08
2.44
2.43
2.25
2.25
1.01
1.16
2.16
3.21
1.00
1.02
3.27
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


162.29
160.83
160.34
158.87
142.58
142.52
131.44
130.71
130.61
129.37
129.30
127.62
127.58
124.45
124.42
124.25
124.11
121.67
121.65
115.55
115.38
113.10
112.91
77.31
77.05
76.80
69.42
69.41
69.39
69.38
14.31
14.28
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


-116.95
-116.97
-116.99
-118.54
-118.56
-118.57
-118.58
-118.59
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

methyl 4-(hydroxy(4-methoxyphenyl)methyl)benzoate (7.3m)



The title compound was prepared according to the general procedure A using methyl 4-formylbenzoate (32.8 mg, 0.2 mmol, 100 mol%) and 4-iodoanisole (93.6 mg, 0.40 mmol, 200 mol%). Flash chromatography on silica (Hex/EtOAc 4:1) provided the title compound (33.9 mg, 125 μmol) in 62% yield as a colorless oil.

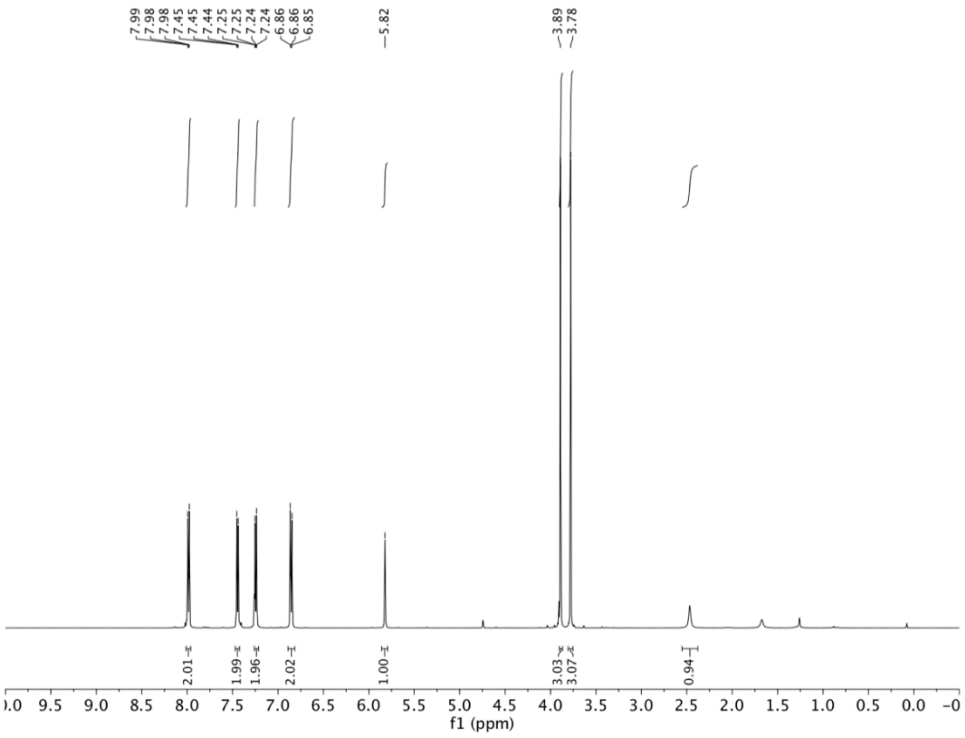
TLC (SiO_2) R_f = 0.18 (hexanes/ethyl acetate = 4:1).

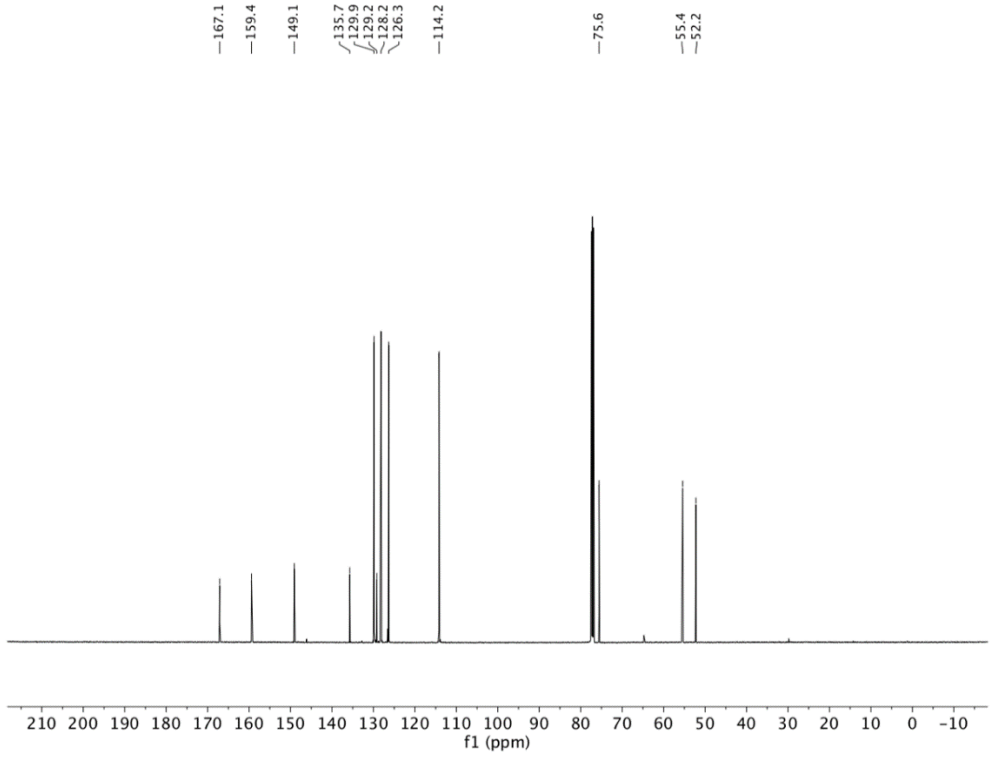
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 8.3 Hz, 2H), 7.45 (d, *J* = 8.3 Hz, 2H), 7.24 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 5.82 (s, 1H), 3.89 (s, 3H), 3.78 (s, 3H), 2.47 (s, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.1, 159.4, 149.1, 135.7, 129.9, 129.2, 128.2, 126.3, 114.2, 75.6, 55.4, 52.2.

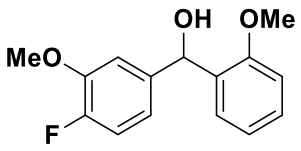
HRMS (ESI^+): mass calculated for $[M+Na]^+$ ($C_{16}H_{16}NO_4$) requires *m/z* 295.0941, found *m/z* 295.0942.

FTIR (neat) 3512, 3354, 2954, 2359, 1718, 1610, 1512, 1435, 1275, 1250, 1032, 835, 751 cm^{-1}.


7.99
7.98
7.98
7.45
7.45
7.44
7.25
7.25
7.24
7.24
6.86
6.86
6.85
5.82
3.89
3.78
2.01
1.99
1.96
2.02
1.00
3.03
3.07
0.94
f1 (ppm)


167.1
159.4
149.1
135.7
129.9
129.2
128.2
126.3
114.2
75.6
55.4
52.2
f1 (ppm)

(4-fluoro-3-methoxyphenyl)(2-methoxyphenyl)methanol (7.3n)



The title compound was prepared according to the general procedure A using 4-fluoro-3-methoxybenzaldehyde (30.8 mg, 0.2 mmol, 100 mol%) and 2-iodoanisole (107.4 mg, 0.40 mmol, 200 mol%). Flash column chromatography (SiO_2, hexanes/EtOAc 6:1) provided the title compound (43.4 mg, 166 μmol) in 83% yield as a colorless oil.

TLC (SiO_2) R_f = 0.22 (hexanes/ethyl acetate = 4:1).

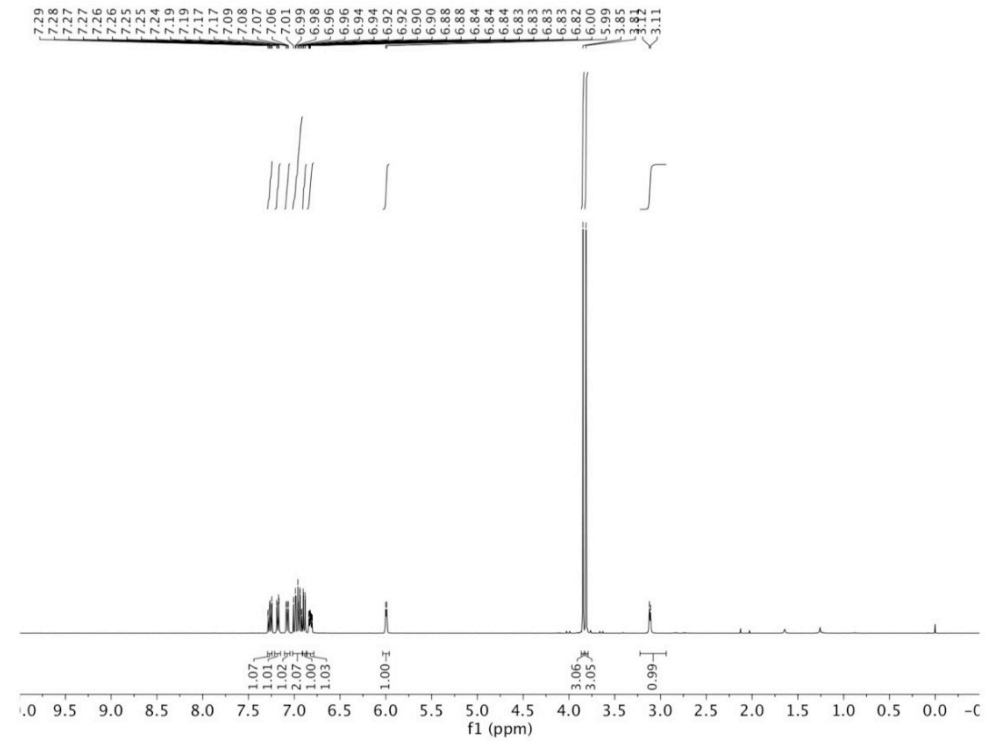
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.30 – 7.23 (m, 1H), 7.18 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.08 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.01 – 6.91 (m, 2H), 6.89 (dd, *J* = 8.2, 1.1 Hz, 1H), 6.82 (dddd, *J* = 8.4, 4.4, 2.1, 0.7 Hz, 1H), 6.00 (d, *J* = 4.3 Hz, 1H), 3.85 (s, 3H), 3.81 (s, 3H), 3.12 (d, *J* = 4.9 Hz, 1H).

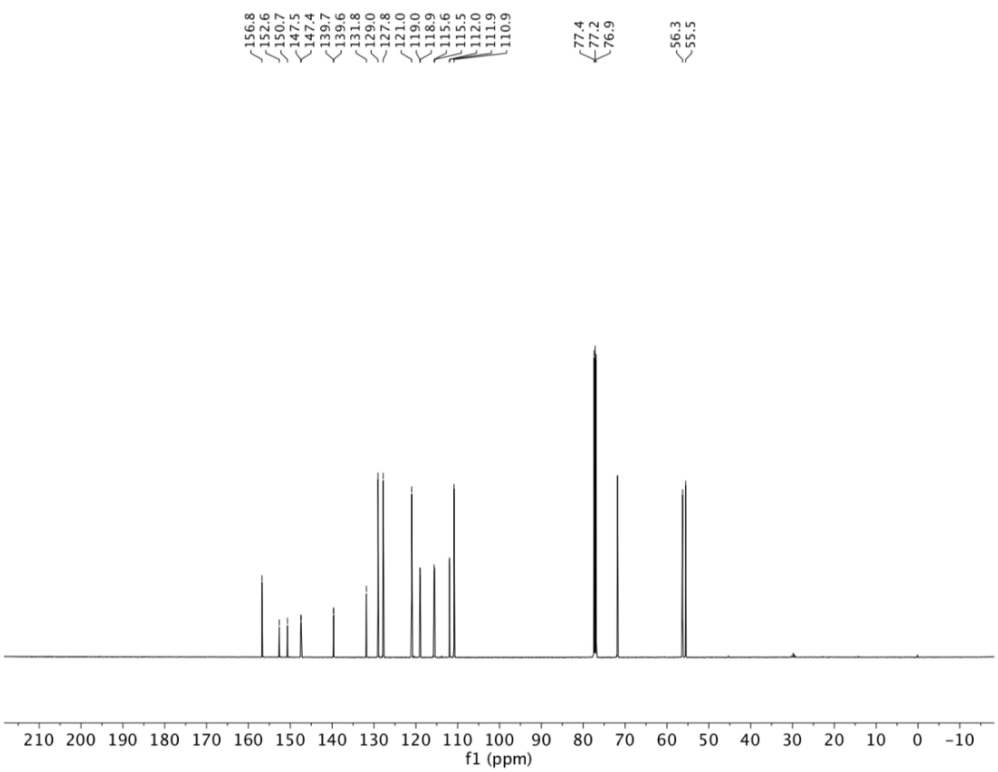
^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.8, 151.6 (d, *J* = 244.7 Hz), 147.4 (d, *J* = 10.9 Hz), 139.7 (d, *J* = 3.6 Hz), 131.8, 129.0, 127.8, 121.0, 119.0 (d, *J* = 6.9 Hz), 115.6 (d, *J* = 18.5 Hz), 112.0 (d, *J* = 1.9 Hz), 110.9, 71.8, 56.3, 55.5.

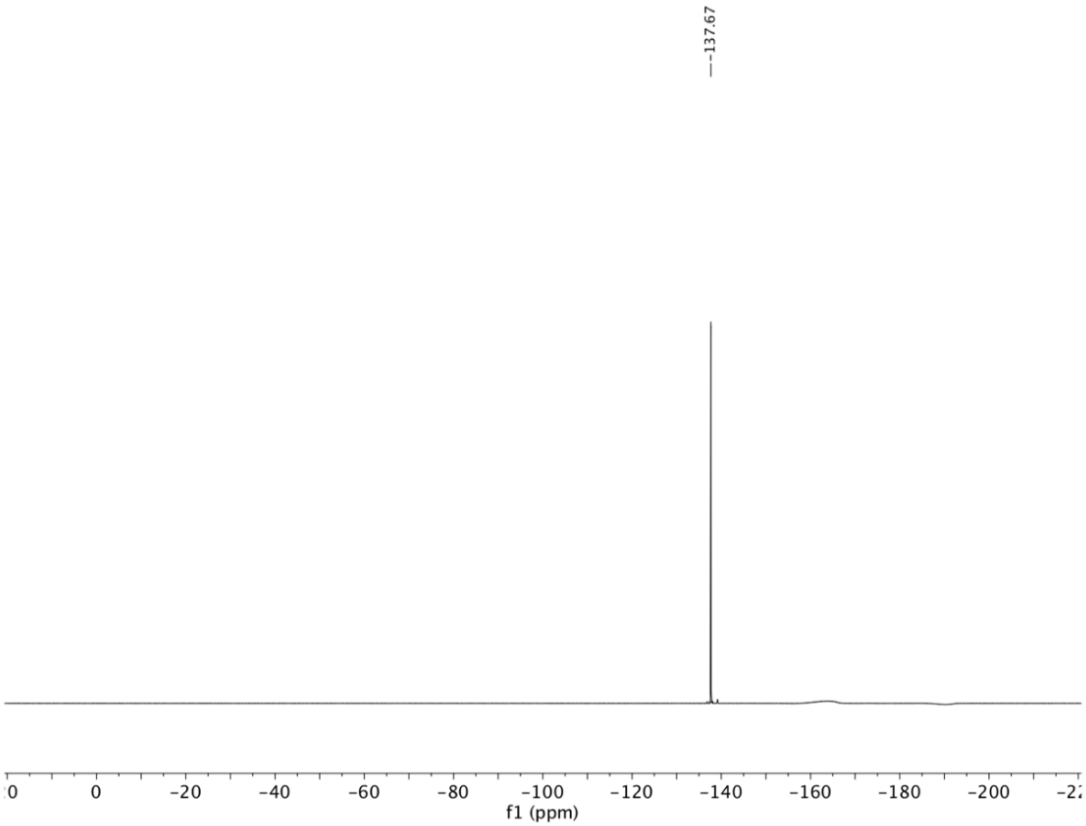
^{19}F NMR (471 MHz, CDCl3): δ = -137.67.

HRMS (CI^+): mass calculated for $[M]^+$ ($C_{15}H_{15}FO_3$) requires *m/z* 262.1005, found *m/z* 262.1010.

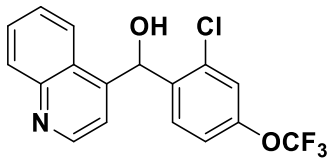
FTIR (neat) 3414, 2941, 2838, 1601, 1513, 1463, 1417, 1271, 1241, 1118, 1028, 909, 815, 755, 730 cm^{-1}.


7.29
7.28
7.27
7.27
7.26
7.26
7.25
7.25
7.24
7.19
7.19
7.17
7.17
7.09
7.08
7.07
7.06
7.01
6.99
6.98
6.96
6.96
6.94
6.94
6.92
6.92
6.90
6.90
6.88
6.88
6.84
6.84
6.83
6.83
6.83
6.82
6.00
5.99
3.85
3.81
3.12
3.11
1.07
1.01
1.02
2.07
1.00
1.03
1.00
3.06
3.05
0.99
f1 (ppm)


156.8
152.6
150.7
147.5
147.4
139.7
139.6
131.8
129.0
127.8
121.0
119.0
118.9
115.6
115.5
112.0
111.9
110.9
77.4
77.2
76.9
56.3
55.5
f1 (ppm)


-137.67
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
f1 (ppm)

(2-chloro-4-(trifluoromethoxy)phenyl)(quinolin-4-yl)methanol (7.3o)



The title compound was prepared according to the general procedure A using 4-formylquinoline (31.0 mg, 0.2 mmol, 100 mol%) and 2-chloro-1-iodo-4-(trifluoromethoxy)benzene (129 mg, 0.40 mmol, 200 mol%). Flash column chromatography (SiO_2, hexanes/EtOAc 4:1) provided the title compound (42 mg, 119 μmol) in 60% yield as a white solid.

TLC (SiO_2) R_f = 0.27 (hexanes/ethyl acetate = 1:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.90 (dd, *J* = 7.3, 4.4 Hz, 1H), 8.13 (d, *J* = 8.5 Hz, 1H), 7.83 (dd, *J* = 8.5, 1.3 Hz, 1H), 7.69 (ddd, *J* = 9.6, 6.4, 1.4 Hz, 1H), 7.58 (d, *J* = 4.5 Hz, 1H), 7.51 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H), 7.34 (d, *J* = 2.5 Hz, 1H), 7.27 – 7.24 (m, 1H), 7.06 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.92 (d, *J* = 3.3 Hz, 1H), 3.30 (d, *J* = 49.9 Hz, 1H).

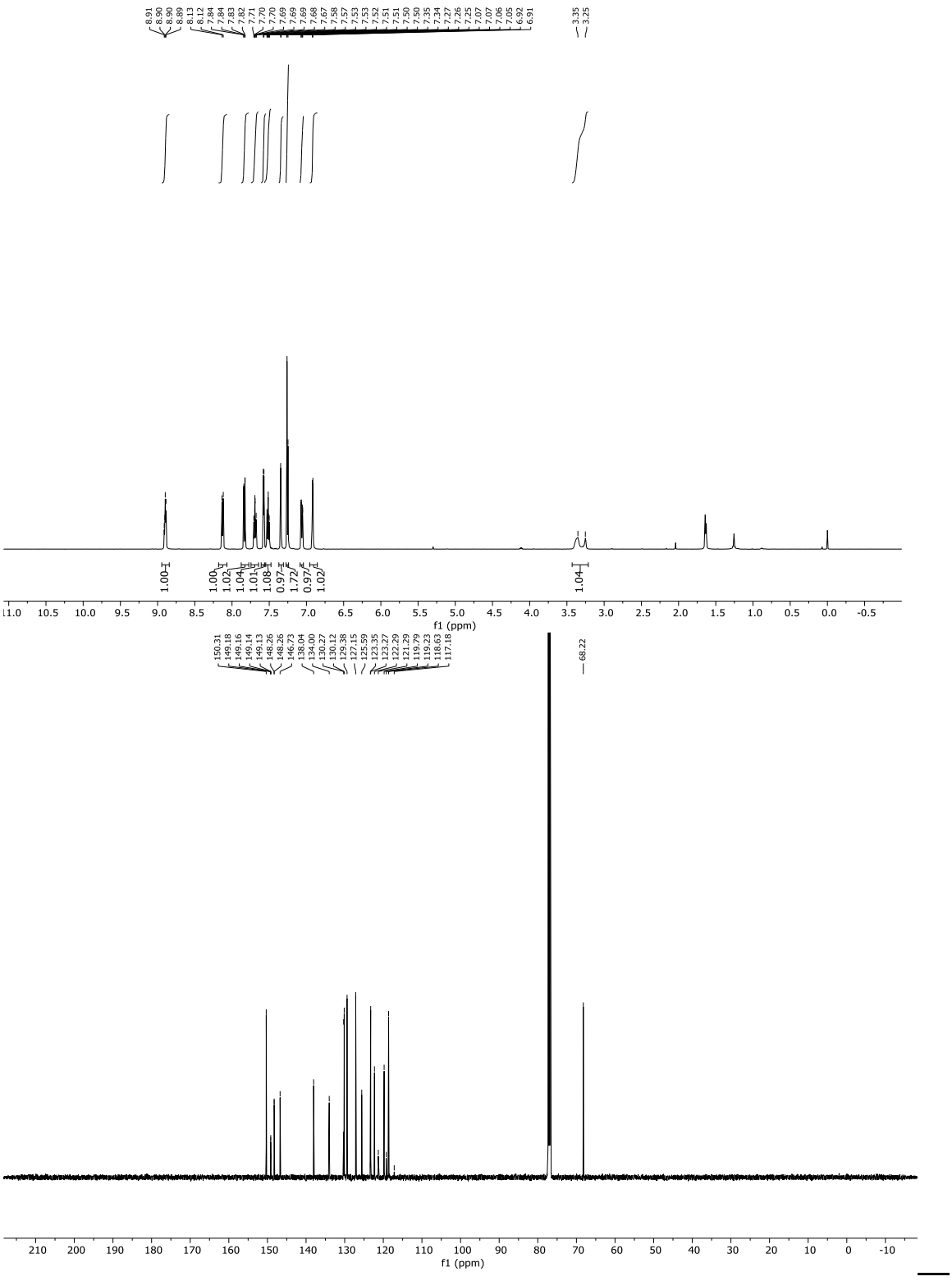
^{13}C NMR (125 MHz, $CDCl_3$): δ = 150.3, 149.1 (q, *J* = 2.1 Hz), 148.5, 146.7, 138.0, 134.0, 130.2, 130.1, 129.3, 127.1, 125.5, 123.3, 122.2, 120.3 (q, *J* = 258.7 Hz), 119.8, 118.6, 68.2.

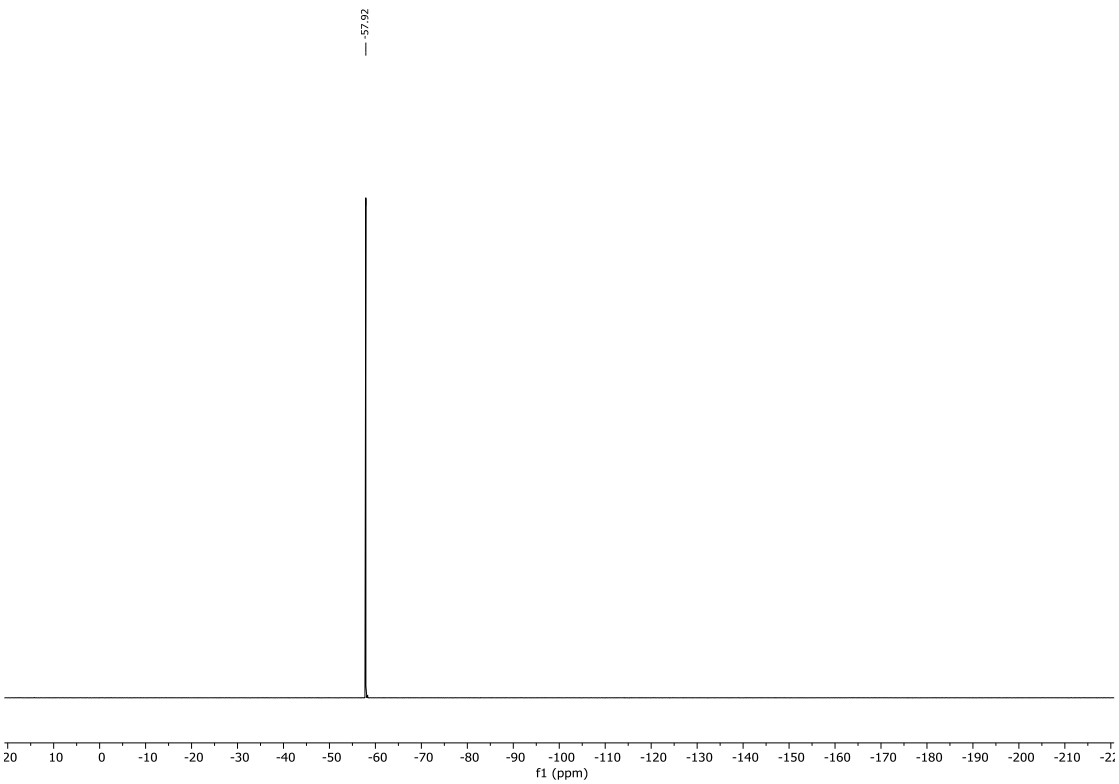
^{19}F NMR (471 MHz, $CDCl_3$) δ = -57.92.

HRMS (ESI^+): mass calculated for $[M+H]^+$ (for $C_{17}H_{12}ClF_3NO_2$) requires *m/z* 354.0503, found *m/z* 354.0508

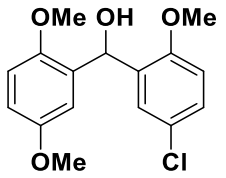
FTIR (neat) 3080, 2832, 2363,2341, 1736, 1509, 1392, 1313, 1256, 1214, 1143, 855 cm^{-1}.

MP 187-188°C


8.91
8.90
8.90
8.89
8.13
8.12
7.84
7.84
7.83
7.82
7.71
7.70
7.70
7.70
7.69
7.69
7.69
7.68
7.67
7.58
7.57
7.53
7.53
7.52
7.51
7.51
7.50
7.50
7.35
7.34
7.27
7.26
7.25
7.07
7.07
7.06
7.05
6.92
6.91
3.35
3.25
1.00
1.02
1.04
1.01
1.08
0.97
1.72
0.97
1.02
1.04
f1 (ppm)
150.31
149.18
149.16
149.14
149.13
148.26
148.26
146.73
138.04
134.00
130.27
130.12
129.38
127.15
125.59
123.35
123.27
122.29
121.29
119.79
119.23
118.63
117.18
68.22
f1 (ppm)


-57.92
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

(5-chloro-2-methoxyphenyl)(2,5-dimethoxyphenyl)methanol (7.3p)



The title compound was prepared according to the general procedure A using 2,5 dimethoxybenzaldehyde (33.2 mg, 0.2 mmol, 100 mol%) and 4-chloro-2-iodoanisole (107.4 mg, 0.40 mmol, 200 mol%). Flash column chromatography (SiO_2, hexanes/EtOAc 9:1) provided the title compound (51 mg, 166 μmol) in 83% yield as a colorless oil.

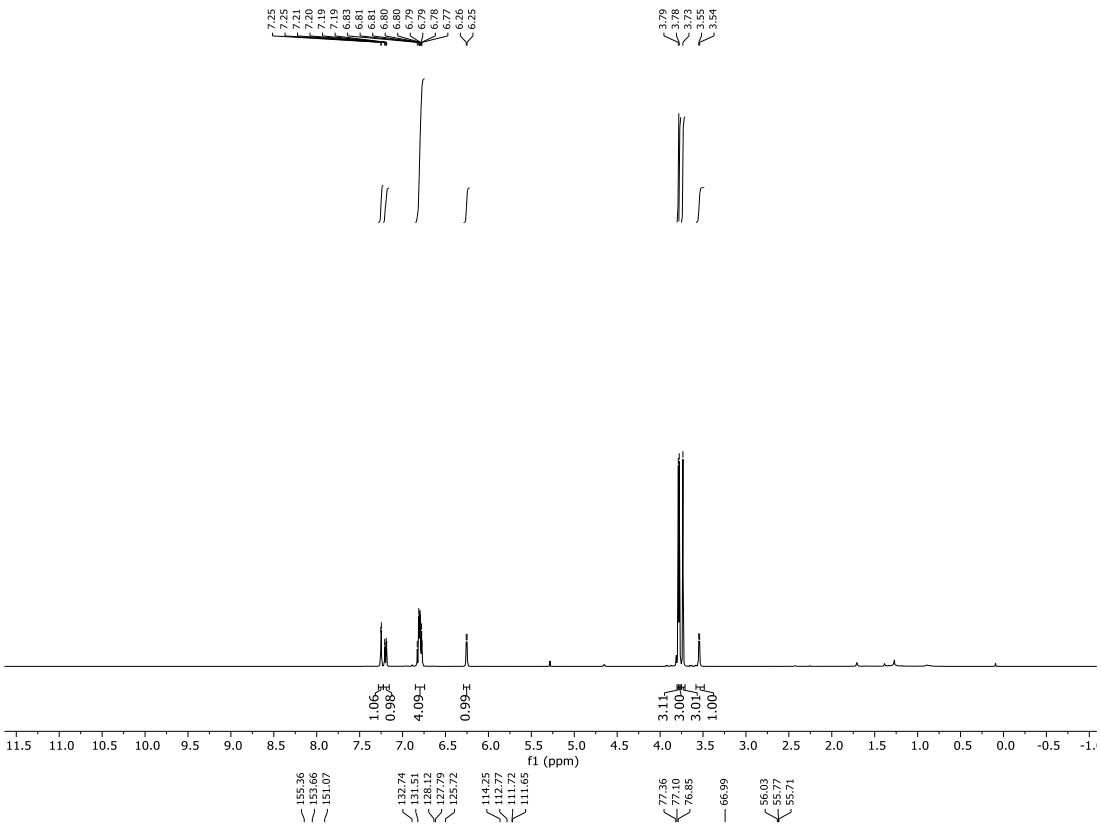
TLC (SiO_2) R_f = 0.17 (hexanes/ethyl acetate = 4:1).

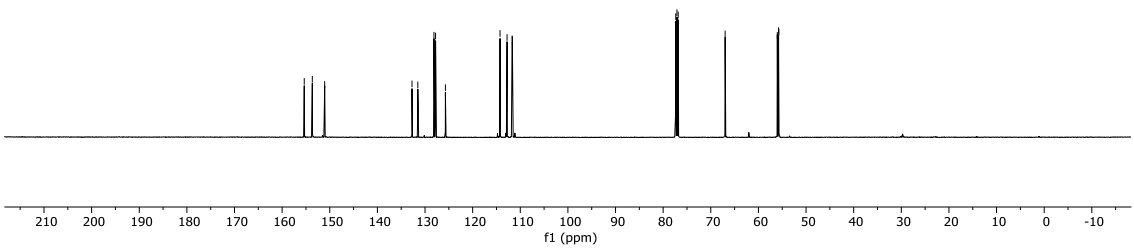
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 2.7 Hz, 1H), 7.20 (dd, *J* = 8.7, 2.7 Hz, 1H), 6.85 – 6.76 (m, 4H), 6.25 (d, *J* = 4.9 Hz, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 3.73 (s, 3H), 3.54 (d, *J* = 5.2 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.4, 153.7, 151.1, 132.7, 131.5, 128.1, 127.8, 125.7, 114.3, 112.8, 111.7, 111.7, 67.0, 56.0, 55.8, 55.7.

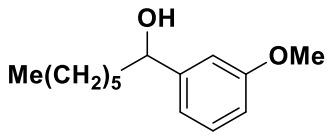
HRMS (CI^+): mass calculated for $[M]^+$ (for $C_{16}H_{17}O_4Cl$) requires *m/z* 308.0815, found *m/z* 308.0813

FTIR (neat) 3401, 2939, 2835, 1594, 1487, 1463, 1215, 1178, 1026, 908, 810, 731 cm^{-1}.


7.25
7.25
7.21
7.20
7.19
7.19
6.83
6.81
6.81
6.80
6.80
6.79
6.79
6.78
6.77
6.26
6.25
3.79
3.78
3.73
3.55
3.54
1.06
0.98
4.09
0.99
3.11
3.00
3.01
1.00
f1 (ppm)
155.36
153.66
151.07
132.74
131.51
128.12
127.79
125.72
114.25
112.77
111.72
111.65
77.36
77.10
76.85
66.99
56.03
55.77
55.71


f1 (ppm)

1-(3-methoxyphenyl)heptan-1-ol (7.3q)



The reaction was conducted in accordance with general procedure B using heptaldehyde (28 μL, 0.2 mmol, 100 mol%) and 3-methoxyiodobenzene (47 μL, 0.4 mmol, 200 mol%). Flash column chromatography (SiO_2, hexanes : EtOAc = 10:1) provided 29 mg (64%, 0.13 mmol) of the title compound as a colorless oil.

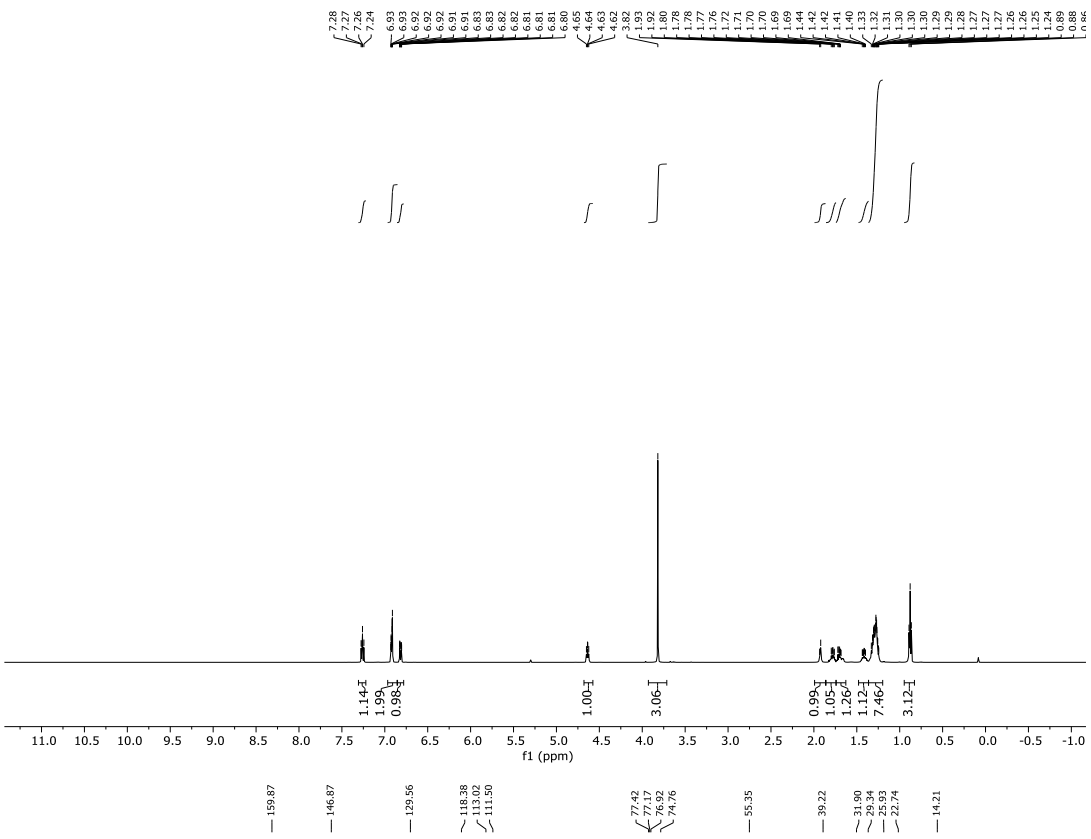
TLC (SiO_2) R_f = 0.48 (hexanes : EtOAc = 4:1).

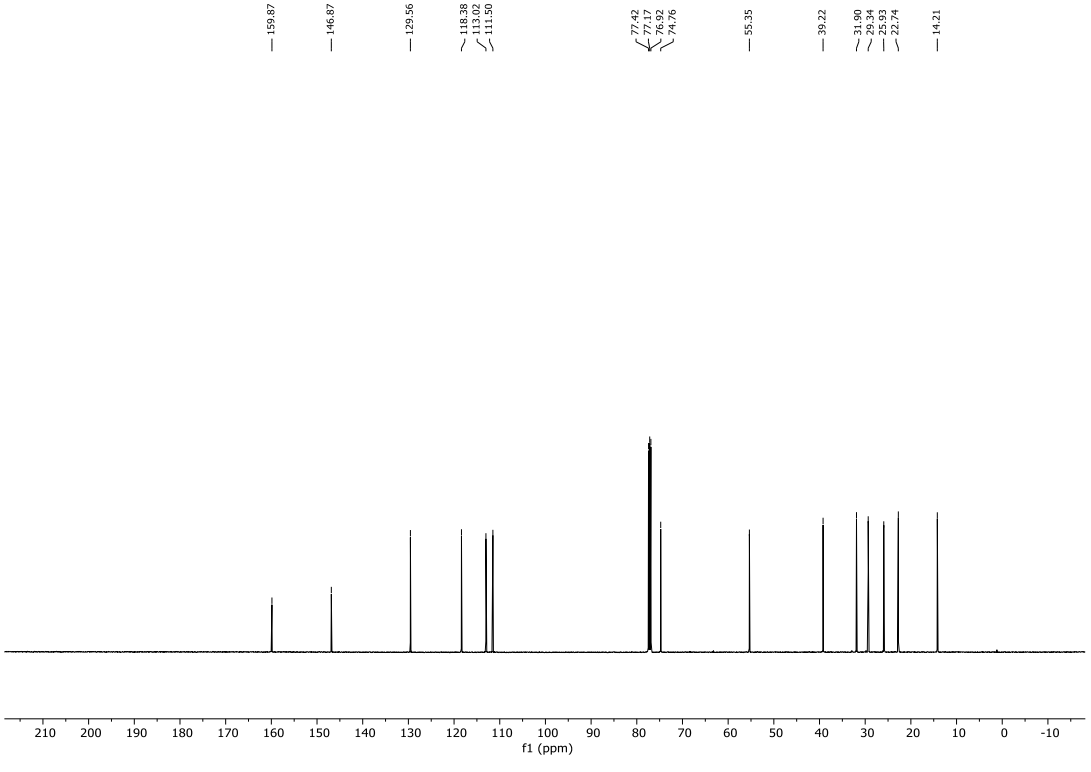
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31 – 7.22 (m, 1H), 6.95 – 6.88 (m, 2H), 6.82 (ddd, *J* = 8.3, 2.5, 1.1 Hz, 1H), 4.70 – 4.57 (m, 1H), 3.82 (s, 3H), 1.92 (s, 1H), 1.84 – 1.74 (m, 1H), 1.69 (ddt, *J* = 18.0, 9.8, 5.2 Hz, 1H), 1.42 (ddd, *J* = 13.0, 7.8, 3.3 Hz, 1H), 1.36 – 1.23 (m, 8H), 0.88 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 159.9, 146.9, 129.6, 118.4, 113.0, 111.5, 74.8, 55.4, 39.2, 31.9, 29.3, 25.9, 22.7, 14.2.

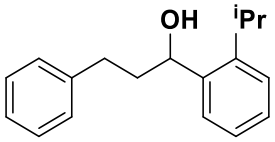
HRMS (CI^+): mass calculated for $[M]^+$ ($C_{14}H_{22}O_2$) requires *m/z* 222.1620, found *m/z* 222.1616.

FTIR (neat): 3344, 2928, 2856, 1739, 1600, 1257, 1043, 874, 781, 699 cm^{-1}.


7.28
7.27
7.26
7.24
6.93
6.93
6.92
6.92
6.92
6.91
6.91
6.83
6.82
6.82
6.81
6.81
6.80
4.65
4.64
4.63
4.62
3.82
1.93
1.92
1.80
1.78
1.78
1.77
1.76
1.72
1.71
1.70
1.70
1.69
1.69
1.44
1.42
1.42
1.41
1.40
1.33
1.32
1.31
1.30
1.30
1.30
1.29
1.29
1.28
1.27
1.27
1.27
1.26
1.26
1.25
1.24
0.89
0.88
1.14
1.99
0.98
1.00
3.06
0.99
1.05
1.26
1.12
7.46
3.12
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)


159.87
146.87
129.56
118.38
113.02
111.50
77.42
77.17
76.92
74.76
55.35
39.22
31.90
29.34
25.93
22.74
14.21
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

1-(2-isopropylphenyl)-3-phenylpropan-1-ol (7.3r)



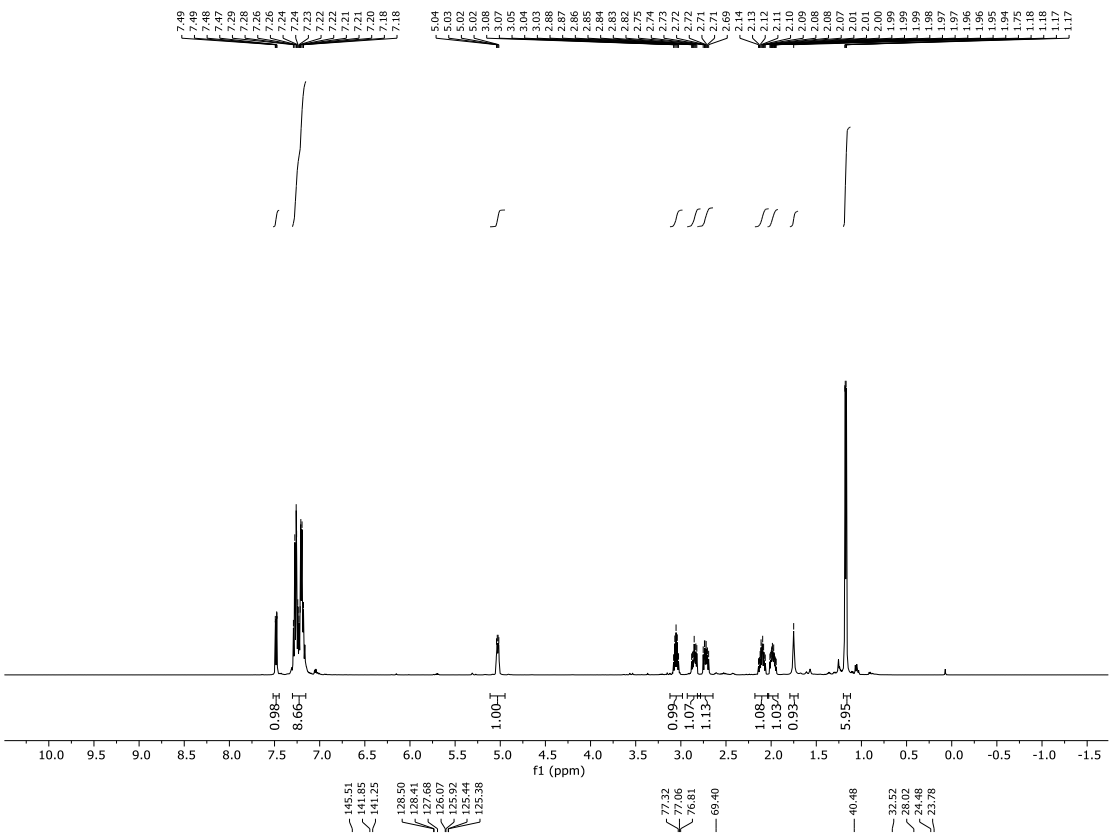
The title compound was prepared according to the general procedure A using 3-phenylpropionaldehyde (27 μL, 0.2 mmol, 100 mol%) and 2-iodocumene (64 μL, 0.40 mmol, 200 mol%). Flash column chromatography (SiO_2, hexanes/EtOAc 9:1) provided the title compound (31.4 mg, 123 μmol) in 62% yield as a colorless oil.

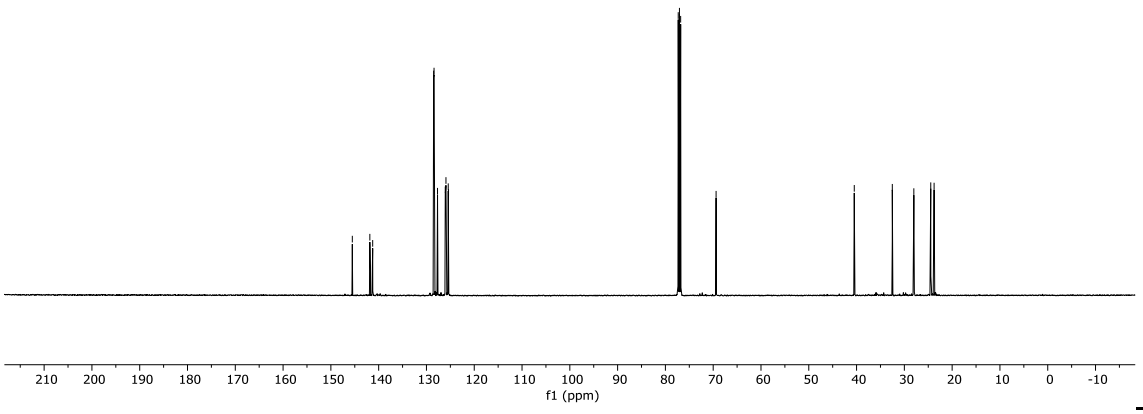
TLC (SiO_2) R_f = 0.49 (hexanes/ethyl acetate = 4:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.48 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.31 – 7.15 (m, 8H), 5.03 (dd, *J* = 8.6, 4.1 Hz, 1H), 3.05 (p, *J* = 6.9 Hz, 1H), 2.85 (ddd, *J* = 14.5, 9.6, 5.2 Hz, 1H), 2.72 (ddd, *J* = 13.8, 9.3, 7.0 Hz, 1H), 2.10 (ddt, *J* = 14.1, 9.0, 4.5 Hz, 1H), 1.98 (tdd, *J* = 13.9, 7.0, 4.1 Hz, 1H), 1.75 (s, 1H), 1.17 (dd, *J* = 6.9, 2.2 Hz, 6H).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 145.5, 141.9, 141.3, 128.5, 128.4, 127.7, 126.1 125.9, 125.4, 125.4, 69.4, 40.5, 32.5, 28.0, 24.5, 23.8.

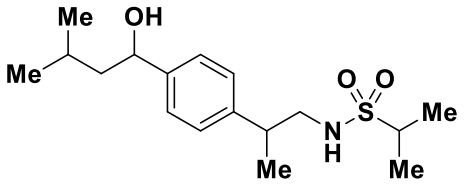
HRMS (CI^+): mass calculated for $[M]^+$ (for xx) requires *m/z* xx, found *m/z* xx

FTIR (neat) 3416, 3027, 2961, 1451, 1032, 907, 759. 698 cm^{-1}.


7.49 7.49 7.48 7.47 7.29 7.28 7.26 7.26 7.24 7.24 7.23 7.22 7.22 7.21 7.21 7.20 7.18 7.18
5.04 5.03 5.02 5.02 3.08 3.07 3.05 3.04 3.03 2.88 2.87 2.86 2.85 2.84 2.83 2.82 2.75 2.74 2.73 2.72 2.72 2.71 2.71 2.69 2.14 2.13 2.12 2.11 2.10 2.09 2.08 2.08 2.07 2.01 2.01 2.00 1.99 1.99 1.99 1.98 1.97 1.97 1.96 1.96 1.95 1.94 1.75 1.18 1.18 1.17 1.17
0.98 8.66 1.00 0.99 1.07 1.13 1.08 1.03 0.93 5.95
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5
f1 (ppm)
145.51 141.85 141.25 128.50 128.41 127.68 126.07 125.92 125.44 125.38 77.32 77.06 76.81 69.40 40.48 32.52 28.02 24.48 23.78


210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

N-(2-(4-(1-hydroxy-3-methylbutyl)phenyl)propyl)propane-2-sulfonamide (7.3s)



The reaction was conducted in accordance with general procedure A using isovaleraldehyde (22 μL, 0.2 mmol, 100 mol%) and N-(2-(4-iodophenyl)propyl)propane-2-sulfonamide (100.8 mg, 0.4 mmol, 200 mol%) . Flash column chromatography (SiO_2, hexanes : EtOAc = 7:3) provided 37.4 mg (57%, 0.114 mmol) of the title compound as a white solid.

TLC (SiO_2) R_f = 0.54 (hexanes : EtOAc = 1:1).

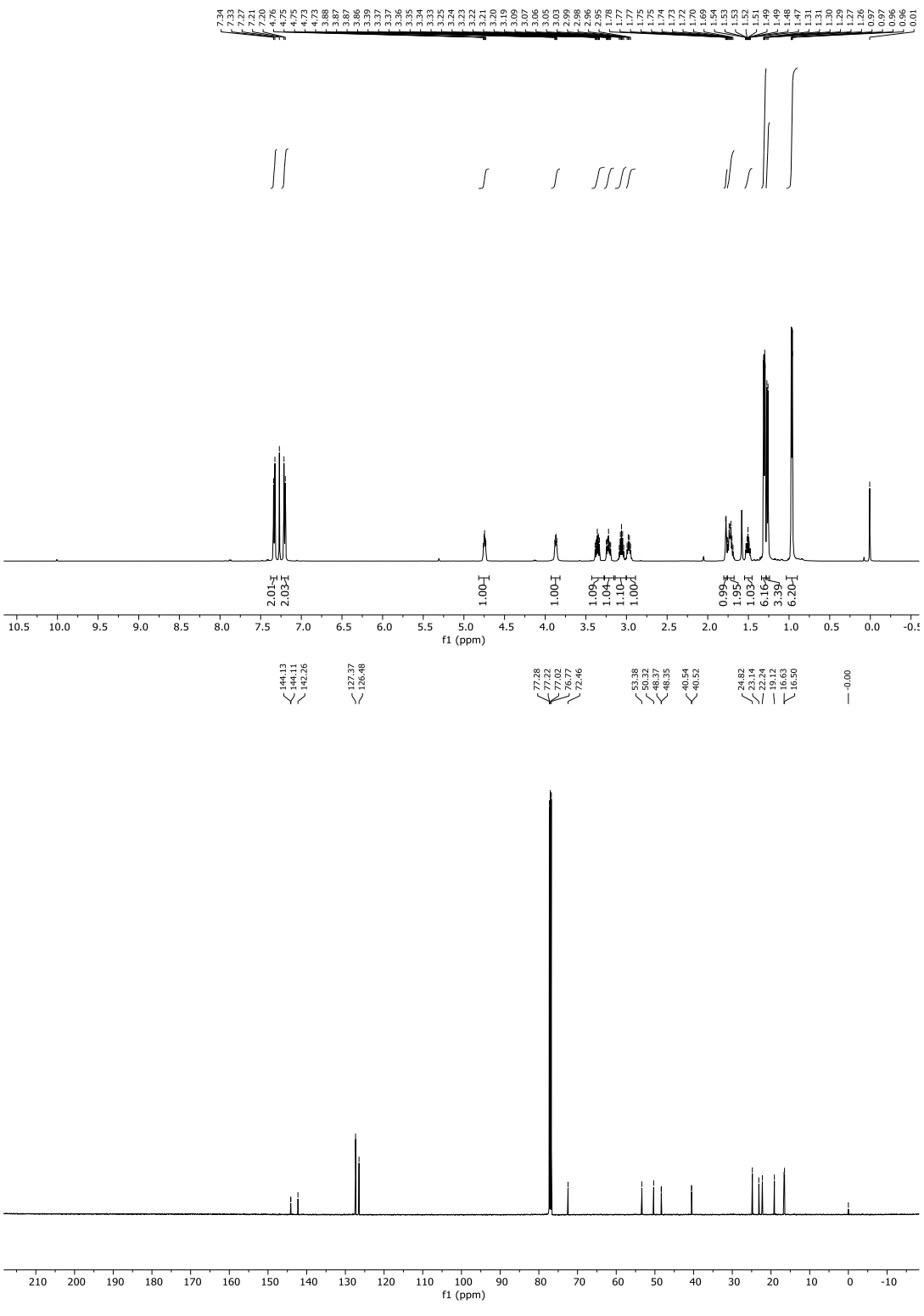
^{1}H NMR (500 MHz, $CDCl_3$δ 7.33 (d, *J* = 7.9 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 4.73 (dd, *J* = 8.4, 3.0 Hz, 1H), 3.86 (dd, *J* = 8.1, 4.7 Hz, 1H), 3.35 (ddd, *J* = 13.3, 7.9, 5.8 Hz, 1H), 3.21 (ddd, *J* = 13.1, 8.7, 4.7 Hz, 1H), 3.05 (p, *J* = 6.8 Hz, 1H), 2.96 (p, *J* = 7.0 Hz, 1H), 1.77 (d, *J* = 2.7 Hz, 1H), 1.71 (td, *J* = 13.2, 7.6 Hz, 2H), 1.54 – 1.43 (m, 1H), 1.30 (dd, *J* = 6.9, 2.4 Hz, 6H), 1.26 (d, *J* = 6.8 Hz, 3H), 0.97 (d, *J* = 6.2 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 144.1, 142.2, 127.4, 126.5, 72.5, 53.4, 50.3, 48.4, 48.4, 40.5, 40.5, 24.82, 23.1, 22.2, 19.1, 16.6, 16.5.

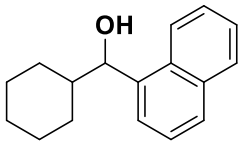
HRMS (ESI^+): mass calculated for $[M+Na]^+$ ($C_{17}H_{29}NO_3S$) requires *m/z* 350.1760, found *m/z* 350.1761.

FTIR (neat): 3246, 2956, 2867, 1738, 1385, 1311, 1132, 1061, 979, 691 cm^{-1}

MP 97-98 °C



cyclohexyl(naphthalen-1-yl)methanol (7.3t)



The reaction was conducted in accordance with general procedure A using cyclohexyl carboxaldehyde (22.4 mg, 0.2 mmol, 100 mol%) and 1-Iodonaphthalene (60 μL, 0.4 mmol, 200 mol%) Flash column chromatography (SiO_2, hexanes : EtOAc = 10:1) provided 31 mg (65%, 0.13 mmol) of the title compound as a pale yellow oil.

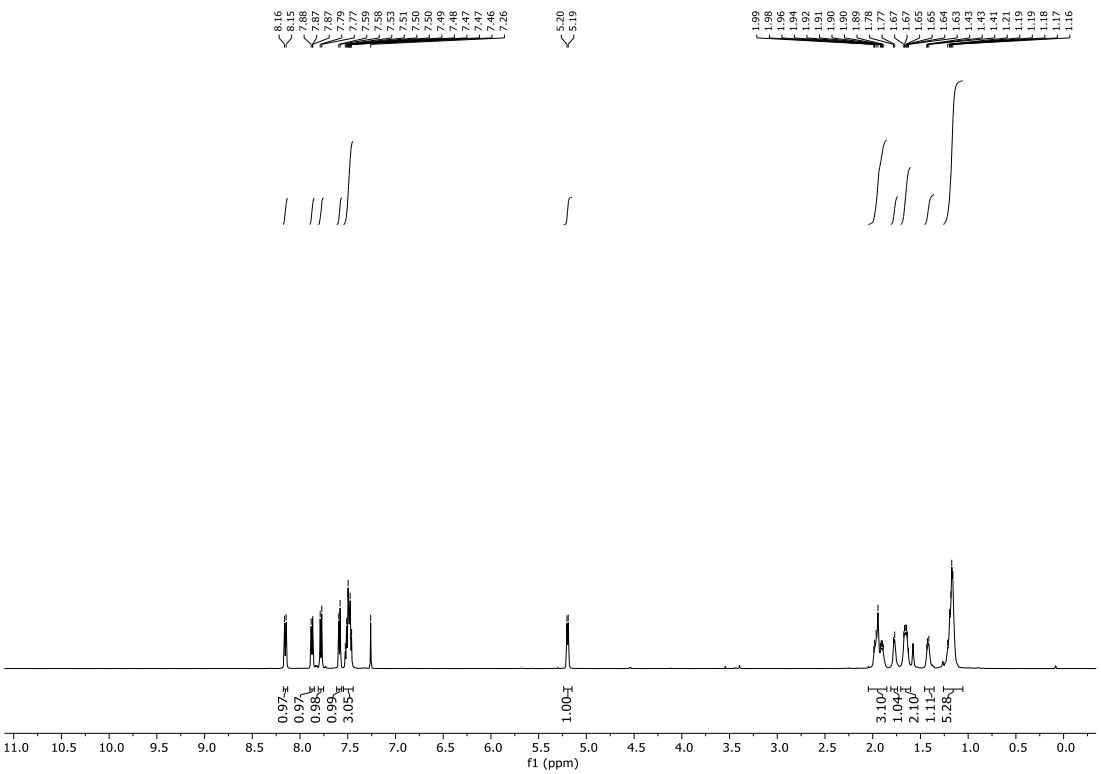
TLC (SiO_2) R_f = 0.63 (hexanes : EtOAc = 4:1).

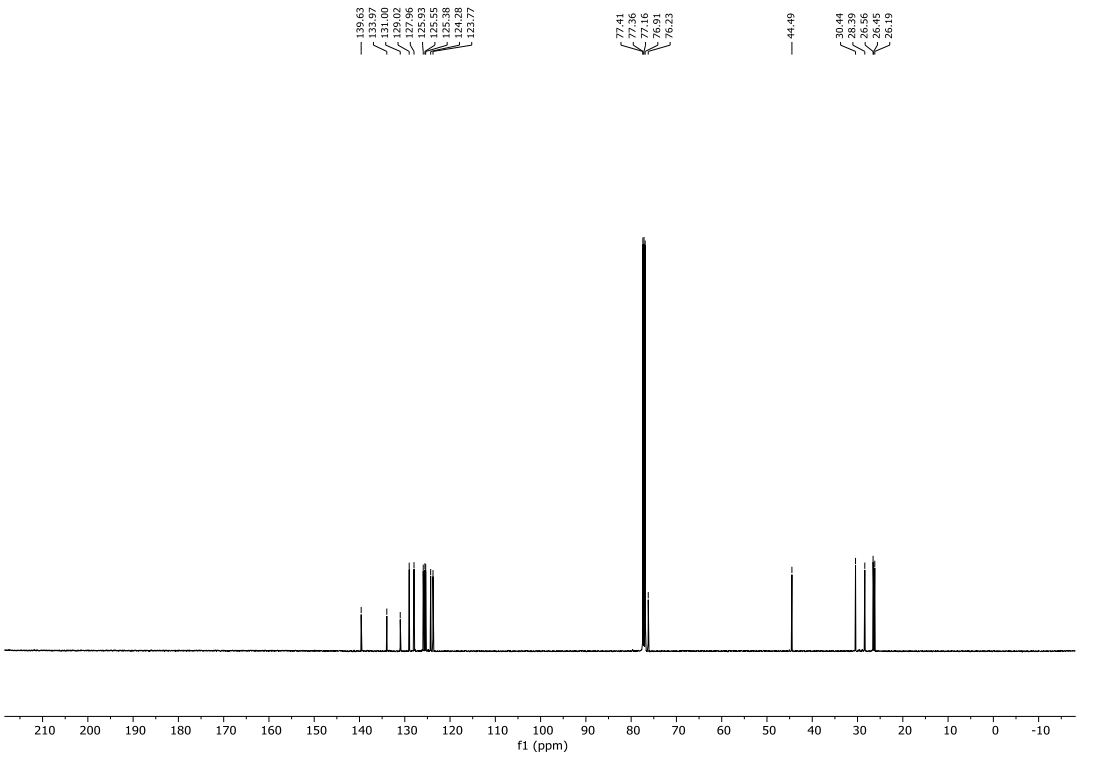
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.15 (d, *J* = 8.1 Hz, 1H), 7.90 – 7.84 (m, 1H), 7.78 (d, *J* = 8.1 Hz, 1H), 7.59 (d, *J* = 7.1 Hz, 1H), 7.53 – 7.44 (m, 3H), 5.20 (d, *J* = 6.4 Hz, 1H), 2.00 – 1.92 (m, 2H), 1.91 (s, 1H), 1.77 (s, 1H), 1.68 – 1.61 (m, 2H), 1.46 – 1.36 (m, 1H), 1.25 – 1.08 (m, 5H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 139.6, 134.0, 131.0, 129.0, 128.0, 125.9, 125.6, 125.4, 124.3, 123.8, 76.2, 44.5, 30.4, 28.4, 26.6, 26.5, 26.2.

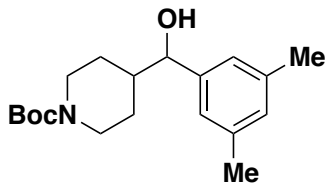
HRMS (CI^+): mass calculated for $[M]^+$ ($C_{17}H_{20}O$) requires *m/z* 240.1514, found *m/z* 240.1521.

FTIR (neat): 3404, 3046, 2921, 2849, 1738, 1449, 776 cm^{-1}.


8.16
8.15
7.88
7.87
7.87
7.79
7.77
7.59
7.58
7.53
7.51
7.50
7.50
7.49
7.48
7.47
7.47
7.46
7.26
5.20
5.19
1.99
1.98
1.96
1.94
1.92
1.91
1.90
1.90
1.88
1.78
1.77
1.67
1.67
1.65
1.65
1.64
1.63
1.43
1.43
1.41
1.21
1.19
1.19
1.18
1.17
1.16
0.97
0.97
0.98
0.99
3.05
1.00
3.10
1.04
2.10
1.11
5.28
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


139.63
133.97
131.00
129.02
127.96
125.83
125.55
125.38
124.28
123.77
77.41
77.16
77.16
76.91
76.23
44.49
30.44
28.39
26.56
26.45
26.19
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

***tert*-butyl 4-((3,5-dimethylphenyl)(hydroxy)methyl)piperidine-1-carboxylate (7.3u)**



The title compound was prepared according to the general procedure A using *tert*-butyl 4-formylpiperidine-1-carboxylate (42.6 mg, 0.2 mmol, 100 mol%) and 1-iodo-3,5-dimethylbenzene (92.8 mg, 0.40 mmol, 200 mol%). Flash chromatography on silica (Hex/EtOAc 5:1) provided the title compound (54.1 mg, 170 µmol) in 85% yield as a light-yellow oil.

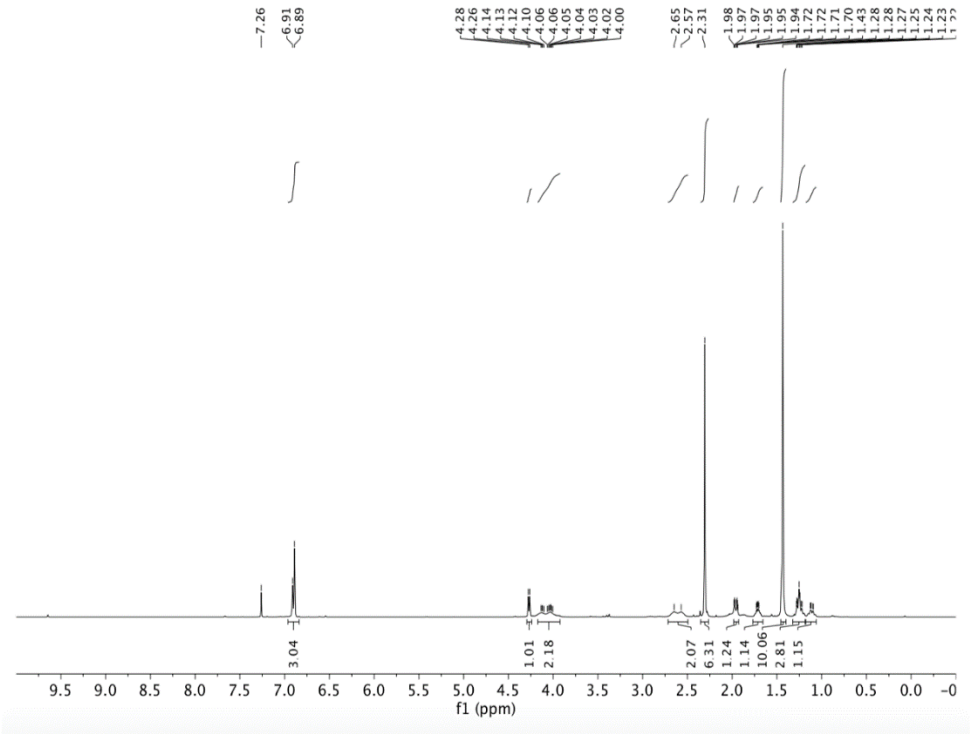
TLC (SiO_2) R_f = 0.50 (hexanes/ethyl acetate = 2:1).

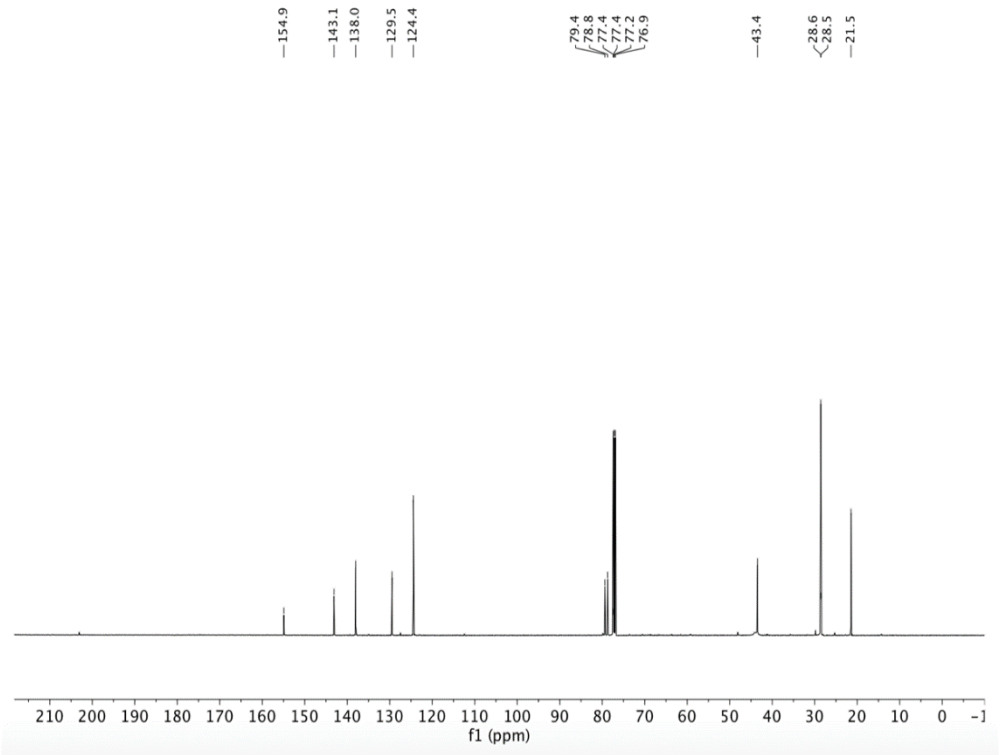
^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.90 (d, *J* = 10.0 Hz, 3H), 4.27 (d, *J* = 7.6 Hz, 1H), 4.19 – 3.89 (m, 2H), 2.61 (d, *J* = 39.7 Hz, 2H), 2.31 (s, 6H), 1.96 (dt, *J* = 13.2, 2.8 Hz, 1H), 1.72 (dt, *J* = 7.7, 3.7 Hz, 1H), 1.43 (s, 10H), 1.25 (td, *J* = 12.2, 3.9 Hz, 3H), 1.11 (dd, *J* = 12.7, 4.4 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.9, 143.1, 138.0, 129.5, 124.4, 79.4, 78.8, 43.4, 28.6, 21.5.

HRMS (ESI^+): mass calculated for $[M+Na]^+$ ($C_{19}H_{29}NO_3$) requires *m/z* 342.2040, found *m/z* 342.2045.

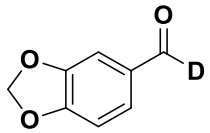
FTIR (neat) 2970, 2917, 2859, 2359, 1739, 1668, 1424, 1365, 1162, 1126, 847, 753 cm^{-1}.


7.26
6.91
6.89
4.28
4.26
4.14
4.13
4.12
4.10
4.06
4.06
4.05
4.04
4.03
4.02
4.00
2.65
2.57
2.31
1.98
1.97
1.97
1.95
1.95
1.94
1.72
1.72
1.71
1.70
1.43
1.28
1.28
1.27
1.25
1.24
1.23
3.04
1.01
2.18
2.07
6.31
1.24
1.14
10.06
2.81
1.15
f1 (ppm)


154.9
143.1
138.0
129.5
124.4
79.4
78.8
77.4
77.4
77.2
76.9
43.4
28.6
28.5
21.5
f1 (ppm)

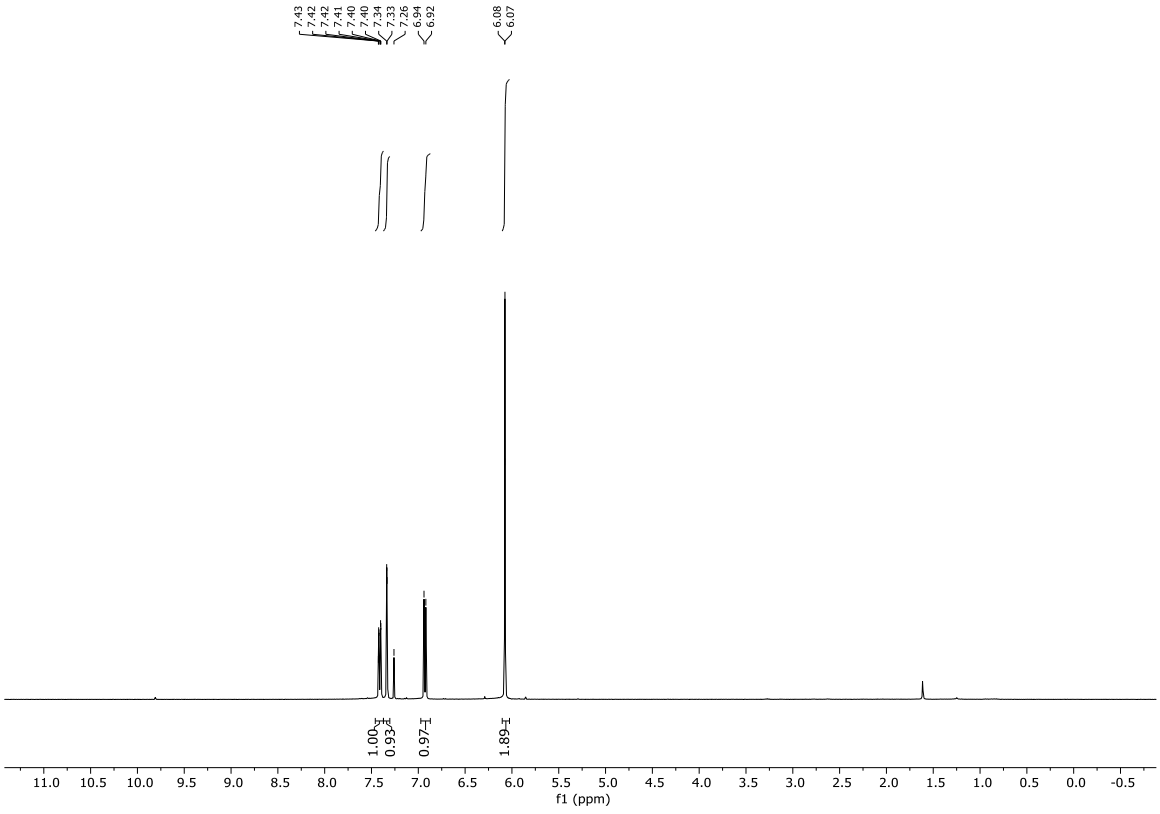
Preparation and Spectral Data for Deuterated Substrates:

benzo[d][1,3]dioxole-5-carbaldehyde-d (deutero-7.1a)

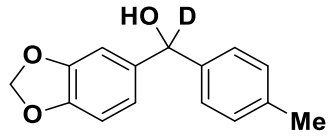


The title compound was synthesized over two steps from piperonal following literature procedures.[2]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 – 7.38 (m, 1H), 7.34 (s, 1H), 6.93 (d, J = 7.9 Hz, 1H), 6.07 (s, 2H).



benzo[d][1,3]dioxol-5-yl(p-tolyl)methan-d-ol (deutero- 7.3a)



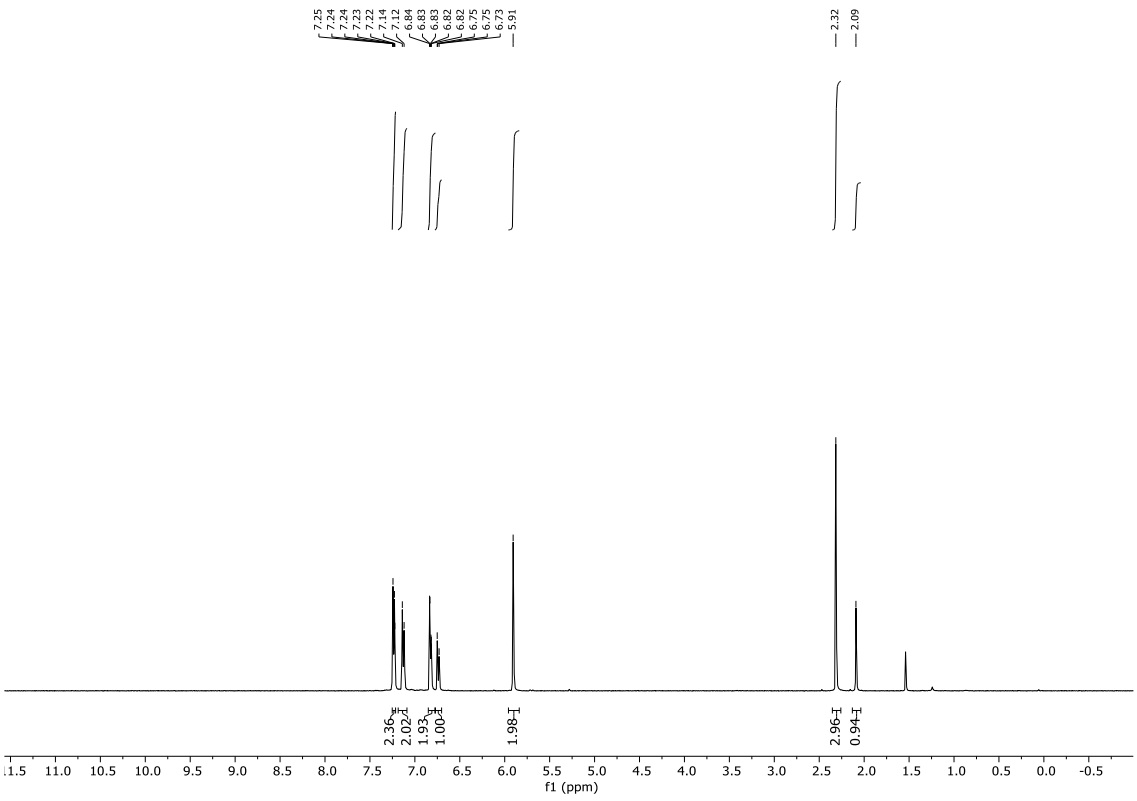
The reaction was conducted in accordance with general procedure A. Flash column chromatography (SiO_2, hexanes : EtOAc = 4:1) provided 32 mg (66%, 0.132 mmol) of the title compound as a white solid

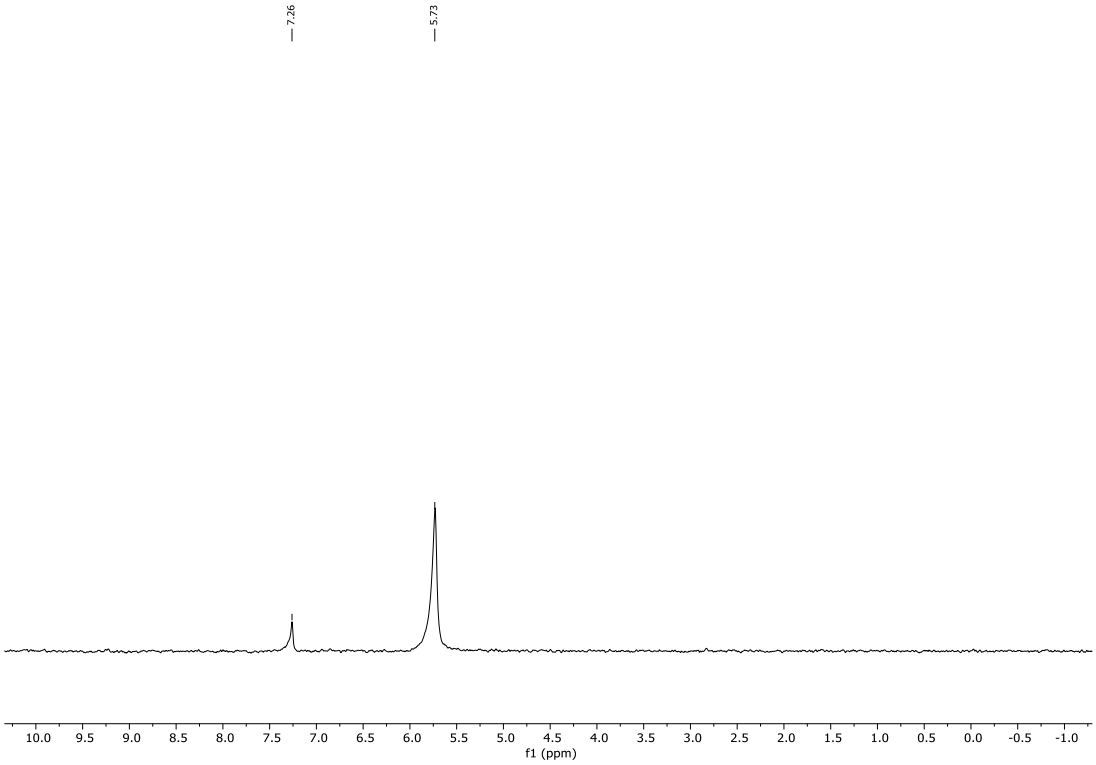
TLC (SiO_2) R_f = 0.33 (hexanes : EtOAc = 4:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.23 (d, *J* = 6.3 Hz, 2H), 7.13 (d, *J* = 7.8 Hz, 2H), 6.82 (dd, *J* = 6.1, 1.8 Hz, 2H), 6.77 – 6.68 (m, 1H), 5.90 (s, 2H), 2.31 (s, 3H), 2.09 (s, 1H).

^{2}H NMR (92 MHz, $CHCl_3$): δ 5.73 (s, 1H).

HRMS (CI^+): mass calculated for $[M]^+$ ($C_{15}O_3{}^1H_{12}{}^2H$) requires *m/z* 243.1006, found *m/z* 243.1005.


7.25
7.24
7.24
7.23
7.22
7.14
7.12
6.84
6.83
6.83
6.82
6.82
6.75
6.75
6.73
5.91
2.32
2.09
2.36
2.02
1.93
1.00
1.98
2.96
0.94
f1 (ppm)


7.26
5.73
f1 (ppm)

References

Chapter 1

(1) Ramachandran, P. V. Pinane-Based Versatile "Allyl"boranes. *Aldrichimica Acta* **2002**, *35*, 23-35.

(2) Denmark, S. E.; Fu, J. Catalytic Enantioselective Addition of Allylic Organometallic Reagents to Aldehydes and Ketones. *Chem. Rev.* **2003**, *103*, 2763-2794.

(3) Kennedy, J. W. J.; Hall, D. G. Recent Advances in the Activation and Stereochemistry of Boron and Silicon Allylation Reagents. *Angew. Chem. Int. Ed.* **2003**, *42*, 4732-4739.

(4) Yu, C.-M.; Youn, J.; Jung, H.-K. Regulation of Stereoselectivity and Reactivity in the Inter- and Intramolecular Allylic Transfer Reactions. *Bull. Korean Chem. Soc.* **2006**, *27*, 463-472.

(5) Marek, I.; Sklute, G. Creation of quaternary stereocenters in carbonyl allylation reactions. *Chem. Commun*. **2007**, *0*, 1683-1691.

(6) Hall, D. G. Lewis and Brønsted Acid Catalyzed Allylboration of Carbonyl Compounds: From Discovery to Mechanism and Applications. *Synlett* **2007**, 1644-1655.

(7) Lachance, H.; Hall, D. G. Allylboration of Carbonyl Compounds. *Org. React.* **2008**, *73*, 1-555.

(8) Yus, M.; González-Gómez, J. C.; Foubelo, F. Catalytic Enantioselective Allylation of Carbonyl Compounds and Imines. *Chem. Rev*. **2011**, *111*, 7774-7854.

(9) Butlerov, A. Studien über die Einfachsten Verbindungen der Organischen Chemie. Z. *Chem. Pharm*. **1863**, *6*, 484−497.

(10) Butlerov, A. Z. Sur l'Alcool Pseudobuylique Tertiare ou Alcool Méthylique triméthylé. *Bull. Soc. Chim. Fr*. **1864**, *2*, 106−116.

(11) Reformatsky, S. Neue Synthese Zweiatomiger Einbasischer Säuren aus den Ketonen. *Ber. Dtsch. Chem. Ges*. **1887**, *20*, 1210−1211.

(12) Grignard, V. Sur Quelques Nouvelles Combinaisons Organométalliques du Magnèsium et Leur Application àdes Synthèses d'alcools et d'hydrocarbures. *C R Hebd Seá nces Acad Sci, Ser C* **1900**, *130*, 1322−1324.

(13) Bew, S. P. *Comprehensive Organic Functional Group Transformations II*, 2nd ed.; Katritzky, A. R.; Taylor, R. J. K., Eds.; Elsevier: Oxford, 2005; 19-125.

(14) Weix, D. J. Methods and Mechanisms for Cross-Electrophile Coupling of Csp2 Halides with Alkyl Electrophiles. *Acc. Chem. Rev.* **2015**, *48*, 1767-1775.

(15) Okude, Y.; Hirano, S.; Hiyama, T.; Nozaki, H. Grignard-type Carbonyl Addition of Allyl Halides by Means of Chromous salt. A Chemospecific Synthesis of Homoallyl Alcohols. *J. Am. Chem. Soc.* **1977**, 99, 3179−3181.

(16) Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. Reactions of Alkenylchromium Reagents Prepared from Chloride under Nickel Catalysis. *J. Am. Chem. Soc.* **1986**, *108*, 6048-6050.

(17) Jin, H.; Uenishi, J.; Christ, W. J.; Kishi, Y. Catalytic Effect of Nickel(II) Chloride and Palladium(II) Acetate on Chlromium(II)-Mediated Coupling Reaction of Iodo Olefins with Aldehydes. *J. Am. Chem. Soc.* **1986**, *108*, 5644-5646.

(18) Fürstner, A. Carbon−Carbon Bond Formations Involving Organochromium(III) Reagents. *Chem. Rev.* **1999**, *99*, 991–1046.

(19) Gil, A.; Albericio, F.; Álvarez, M. Role of the Nozaki-Hiyama-Takai-Kishi Reaction in the Synthesis of Natural Products. *Chem. Rev.* **2017**, *117*, 8420-8446.

(20) Satoh, T.; Itaya, T.; Miura, M.; Nomura, M. Palladium-Catalyzed Coupling Reaction of Salicylaldehydes with Aryl Iodides via Cleavage of the Aldehyde C–H Bond. *Chem. Lett.* **1996**, *25*, 823–824.

(21) Ko, S.; Kang, B.; Chang, S. Cooperative Catalysis by Ru and Pd for the Direct Coupling of a Chelating Aldehyde with Iodoarenes or Organostannanes. *Angew. Chem. Int. Ed*. **2005**, *44*, 455–457.

(22) Takemiya, A.; Hartwig, J. F. Palladium-Catalyzed Synthesis of Aryl Ketones by Coupling of Aryl Bromides with an Acyl Anion Equivalent. *J. Am. Chem. Soc.* **2006**, *128*, 14800–14801.

(23) Ruan, J.; Saidi, O.; Iggo, J. A.; Xiao, J. Direct Acylation of Aryl Bromides with Aldehydes by Palladium Catalysis. *J. Am. Chem. Soc.* **2008**, *130*, 10510–10511.

(24) Zanardi, A.; Mata, J. A.; Peris, E. Palladium Complexes with Triazolyldiylidene. Structural Features and Catalytic Applications. *Organometallics* **2009**, *28*, 1480–1483.

(25) Adak, L.; Bhadra, S.; Ranu, B. C. Palladium(0) Nanoparticle-catalyzed sp^2 C–H Activation: A Convenient Route to alkyl–aryl Ketones by Direct Acylation of Aryl Bromides and Iodides with Aldehydes. *Tet. Lett.* **2010**, *51*, 3811–3814.

(26) Nowrouzi, N.; Motevalli, S.; Tarokh, D. Palladium-Catalyzed Direct C–H Arylation of 2-hydroxybenzaldehydes With Organic Halides in Neat Water. *J. Mol. Cat. A: Chem.* **2015**, *396*, 224–230.

(27) Nowrouzi, N.; Tarokh, D. $PdCl_2$/DABCO-Catalyzed Direct Arylation of 2-hydroxybenzaldehydes in H_2O. *J. Iran Chem. Soc.* **2016**, *13*, 1493–1497.

(28) Suchand, B.; Satyanarayana, G. Palladium-Catalyzed Environmentally Benign Acylation. *J. Org. Chem.* **2016**, *81*, 6409–6423.

(29) Wakaki, T.; Togo, T.; Yoshidome, D.; Kuninobu, Y.; Kanai, M. Palladium-Catalyzed Synthesis of Diaryl Ketones from Aldehydes and (Hetero)Aryl Halides via C–H Bond Activation. *ACS Catal.* **2018**, *8*, 3123–3128.

(30) Ishiyama, T.; Hartwig, J. F. A Heck-Type Reaction Involving Carbon−Heteroatom Double Bonds. Rhodium(I)-Catalyzed Coupling of Aryl Halides with *N*-Pyrazyl Aldimines. *J. Am. Chem. Soc.* **2000**, *122*, 12043–12044.

(31) Rao, M. L.; Ramakrishna, B. S. Rhodium- Catalyzed Directing- Group- Assisted Aldehydic C–H Arylations with Aryl Halides. *Eur. J. Org. Chem.* **2017**, *2017*, 5080–5093.

(32) Huang, Y.-C.; Majumdar, K. K.; Cheng, C.-H. Nickel-Catalyzed Coupling of Aryl Iodides with Aromatic Aldehydes: Chemoselective Synthesis of Ketones. *J. Org. Chem.* **2002**, *67*, 1682–1684.

(33) Nowrouzi, N.; Zarei, M.; Roozbin, F. First Direct Access to 2-hydroxybenzophenones *via* Nickel-Catalyzed Cross-Coupling of 2-Hydroxybenzaldehydes with Aryl Iodides. *RSC Adv.* **2015**, *5*, 102448–102453.

(34) Zhang, X.; MacMillan, D. W. C. Direct Aldehyde C–H Arylation and Alkylation *via* the Combination of Nickel, Hydrogen Atom Transfer, and Photoredox Catalysis. *J. Am. Chem. Soc.* **2017**, *139*, 11353–11356.

(35) Hu, Y. L.; Wu, Y. P.; Lu, M. Co (II)-C12 Alkyl Carbon Chain Multi- Functional Ionic Liquid Immobilized on Nano-SiO_2 Nano-SiO_2@$CoCl_3$-C12IL as an Efficient Cooperative Catalyst for C–H Activation by Direct Acylation of Aryl Halides with Aldehydes *Appl. Organomet. Chem.* **2018**, *32*, e4096.

(36) Schoenberg, A.; Heck, R. F. Palladium-Catalyzed Formylation of Aryl, Heterocyclic, and Vinylic Halides. *J. Am. Chem. Soc.* **1974**, *96*, 7761-7764.

(37) Pri-Bar, I.; Buchman, O. Reductive Formylation of Aromatic Halides under Low Carbon Monoxide Pressure Catalyzed by Transition-Metal Compounds. *J. Org. Chem.* **1984**, *49*, 4009-4011.

(38) Baillargeon, V. P.; Stille, J. K. Palladium-Catalyzed Formylation of Organic Halides with Carbon Monoxide and Tin Hydride. *J. Am. Chem. Soc.* **1986**, *108*, 452-461.

(39) Ben-David, Y.; Portnoy, M.; Milstein, D. Formylation of Aryl Chloride Catalysed by a Palladium Complex. *J. Chem. Soc. Chem. Commun.* **1989**, 1816-1817.

(40) Cai, M.-Z.; Zhao, H.; Zhou, J.; Song, C.-S. Formylation of Aryl Halides Catalyzed by a Silica-Supported Phosphine Palladium Complex. *Synth. Commun.* **2002**, *32*, 923-926.

(41) Klaus, S.; Neumann, H.; Zapf, A.; Strübing, D.; Hübner, S.; Almena, J.; Riemeier, T.; Groß, P.; Sarich, M.; Krahnert, W.-R.; Rossen, K.; Beller, M. A General and Efficient

Method for the Formylation of Aryl and Heteroaryl Bromides. *Angew. Chem. Int. Ed*. **2006**, *45*, 154-158.

(42) Ashfield, L.; Barnard, C. F. J. Reductive Carbonylation – an Efficient and Practical Catalytic Route for the Conversion of Aryl Halides to Aldehydes. *Org. Process Res. Dev.* **2007**, *11*, 39-43.

(43) Brennführer, A.; Neumann, H.; Klaus, S.; Riermeier, T.; Almena, J.; Beller, M. Palladium/di-1-Adamantyl-n-Butylphosphine-Catalyzed Reductive Carbonylation of Aryl and Vinyl Halides. *Tetrahedron* **2007**, *63*, 6252-6258.

(44) Singh, A. S.; Bhanage, B. M.; Nagarkar, J. M. Reductive Carbonylation of Aryl and Heteroaryl Iodides Using Pd(acac)2/dppm as an Efficient Catalyst. *Tetrahedron Lett*. **2011**, *52*, 2383-2386.

(45) Neumann, H.; Kadyrov, R.; Wu, X.-F.; Beller, M. Palladium-Catalyzed Reductive Carbonylation of Aryl Bromides with Phosphinite Ligands. *Chem. Asian J*. **2012**, *7*, 2213-2216.

(46) Hamasakk, A.; Yasutake, Y.; Norio, T.; Ishida, T.; Akita, T.; Ohashi, H.; Yokoyama, T.; Honma, T.; Tokunaga, M. Cooperative Catalysis of Palladium Nanoparticles and Cobalt Oxide Support for Formylation of Aryl Iodides under Syngas Atmosphere. *Appl. Catal. A* **2014**, *469*, 146-152.

(47) Ibrahim, M. Y. S.; Denmark, S. E. Palladium/Rhodium Cooperative Catalysis for the Production of Aryl Aldehydes and Their Deuterated Analogues Using the Water-Gas Shift Reaction. *Angew. Chem. Int. Ed.* **2018**, *57*, 10362-10367.

(48) Fürstner, A.; Shi, N. A Multicomponent Redox System Accounts for the First Nozaki-Hiyama-Kishi Reactions Catalytic in Chromium. *J. Am. Chem. Soc.* **1996**, *118*, 2533-2534.

(49) Fürstner, A.; Shi, N. Nozaki-Hiyama-Kishi Reactions Catalytic in Chromium. *J. Am. Chem. Soc*. **1996**, *118*, 12349-12357.

(50) Durandetti, M; Périchon, J.; Nédélec, J,-Y. Nickel- and Chromium-Catalysed Electrochemical Coupling of Aryl Halides with Arenecarboxaldehydes. *Tetrahedron Lett.* **1999**, *40*, 9009-9013.

(51) Durandetti, M.; Nédélec, J,-Y.; Périchon, J. An Electrochemical Coupling of Organic Halide with Aldehydes, Catalytic in Chromium and Nickel Salts. The Nozaki-Hiyama-Kishi Reaction. *Org. Lett.* **2001**, *3*, 2073-2076.

(52) Namba, K.; Wang, J.; Cui, S.; Kishi, Y. Surprisingly Efficient Catalytic Cr-Mediated Coupling Reactions. Org. Lett. 2005, 7, 5421-5424.

(53) Harnying, W.; Berkessel, A. Vinylation of Aldehydes Using Mn/Cr Alloy and a N_4-Ligand/Ni^{II}-Catalyst. *Chem. Eur. J.* **2015**, *21*, 6057-6061.

(54) Majumdar, K. K.; Cheng, C.-H. Ni(II)/Zn-Mediated Chemoselective Arylation of Aromatic Aldehydes: Facile Synthesis of Diaryl Carbinols. *Org. Lett.* **2000**, *2*, 2295-2298.

(55) Asachenko, A. F.; Valaeva, V. N.; Kudakina, V. A.; Uborsky, D. V.; Izmer, V. V.; Kononovich, D. S.; Voskoboynikov, A. Z. Coupling of Aromatic Aldehydes with Aryl Halides in the Presence of Nickel Catalysts with Diazabutadiene Ligands. *Russ. Chem. Bull. Int. Ed.* **2016**, *65*, 456-463.

(56) Garcia, K. J.; Gilbert, M. M.; Weix, D. J. Nickel-Catalyzed Addition of Aryl Bromides to Aldehydes to Form Hindered Secondary Alcohols. *J. Am. Chem. Soc.* **2019**, *141*, 1823-1827.

(57) Rayabarapu, D. K.; Chang, H,-T.; Cheng, C.-H. Synthesis of Phthalide Derivatives Using Nickel-Catalyzed Cyclization of o-Haloesters with Aldehydes. *Chem. Eur. J.* **2004**, *10*, 2991-2996.

(58) Grigg, R.; Putnikovic, B.; Urch, C. J. Electrochemically Driven Catalytic Pd(0)/Cr(II) Mediated Coupling of Organic Halides with Aldehydes. The Nozaki-Hiyama-Kishi Reaction. *Tetrahedron Lett*. **1997**, *38*, 6307-6308.

(59) Solé, D.; Mariani, F.; Fernández, I. Synthesis of Isoquinolin-4-ols by Palladium-Catalysed Intramolecular Nucleophilic Addition of Aryl Iodides to Aldehydes. *Adv. Synth. Catal.* **2014**, *356*, 3237-3243.

(60) Natte, K.; Dumrath, A.; Neumann, H.; Beller, M. Palladium-Catalyzed Carbonylations of Aryl Bromides Using Paraformaldehyde: Synthesis of Aldehydes and Esters. *Angew. Chem. Int. Ed*. **2014**, *53*, 10090-10094.

(61) Krug, C.; Hartwig, J. F. Direct Observation of Aldehyde Insertion into Rhodium−Aryl and −Alkoxide Complexes. *J. Am. Chem. Soc*. **2002**, *124*, 1674–1679.

(62) Zhou, F.; Li, C.-J. The Barbier–Grignard-Type Arylation of Aldehydes Using Unactivated Aryl Iodides in Water. *Nature Comm*. **2014**, *5*, 4254.

(63) Swyka, R. A.; Zhang, W.; Richardson, J.; Ruble, J. C.; Krische, M. J. *J. Am. Chem. Soc.* **2019**, *141*, 1828-1832.

(64) Chang, H,-T.; Jeganmohan, M.; Cheng, C.-H. Highly Efficient Cyclization of o-Iodobenzoates with Aldehydes Catalyzed by Cobalt Bidentate Phosphine Complexes: A Novel Entry to Chiral Phthalides. *Chem. Eur. J.* **2007**, *13*, 4356-4363.

(65) Quan, L. G.; Lamrani, M.; Yamamoto, Y. Intramolecular Nucleophilic Addition of Aryl Bromides to Ketones Catalyzed by Palladium. *J. Am. Chem. Soc*. **2000**, *122*, 4827-4828.

(66) Solé, D.; Vallverdú, L.; Peidró, E.; Bonjoch, J. Palladium-Catalysed Intramolecular Annulation of 2-Haloanilines and Ketones: Enolate Arylation vs. Nucleophilic Addition to the Carbonyl Group. *Chem. Commun*. **2001**, *37*, 1888-1889.

(67) Solé, D.; Vallverdú, L.; Solans, X.; Font-Bardía, M.; Bonjoch, J. Intramolecular Pd-Mediated Processes of Amino-Tethered Aryl Halides and Ketones: Insight into the Ketone r-Arylation and Carbonyl-Addition Dichotomy. A New Class of Four-Membered Azapalladacycles. *J. Am. Chem. Soc*. **2003***, 125*, 1587-1594.

(68) Jia, Y.-X.; Katayev, D.; Kündig, E. P. Synthesis of 3-Hydroxyoxindoles by Pd-Catalysed Intramolecular Nucleophilic Addition of Aryl Halides to α-Ketoamides. *Chem. Commun*. **2010**, *46*, 130-132.

(69) Shin, I.; Ramgren, S. D.; Krische, M. J. Reductive Cyclization of Halo-Ketones to Form 3-Hydroxy-2-Oxindoles via Palladium Catalyzed Hydrogenation: a Hydrogen-Mediated Grignard Addition *Tetrahedron* **2015**, *71*, 5776-5780.

(70) Yin, L.; Kanai, M.; Shibasaki, M. A Facile Pathway to Enantiomerically Enriched 3-Hydroxy-2-Oxindoles: Asymmetric Intramolecular Arylation of α-Keto Amides Catalyzed by a Palladium-DifluorPhos Coomplex. *Angew. Chem. Int. Ed.* **2011**, *50*, 7620-7623.

(71) Hu, J.-X.; Wu, H.; Li, C.-Y.; Sheng, W.-J.; Jia, Y.-X.; Gao, J.-R. Nickel-Catalyzed Intramolecular Nucleophilic Addition of Aryl or Vinyl Chlorides to a-Ketoamides Through C-Cl Bond Activation. *Chem. Eur. J.* **2011**, *17*, 5234-5237.

(72) He, J.-Q.; Chen, C.; Yu, W.-B.; Liu, R.-R.; Xu, M.; Li, Y.-J.; Gao, J.-R.; Jia, Y.-X. Nickel-Catalyzed Intramolecular Addition of Vinyl or Aryl Bromides to Ketoamides. *Tetrahedron Lett*. **2014**, *55*, 2805-2808.

(73) Fillon, H.; Gosmini, C.; Périchon, J. A Convenient Method for the Preparation of Aromatic Ketones form Acyl Chlorides and Arylzinc bromides Using a Cobalt Catalysis. *Tetrahedron* **2003**, *59*, 8199-9202.

(74) Kazmierski, I.; Bastienne, M.; Gosmini, C.; Paris, J.-M.; Périchon, J. Convenient Processes for the Synthesis of Aromatic Ketones from Aryl Bromides and Carboxylic Anhydrides Using a Cobalt Catalysis. *J. Org. Chem*. **2004**, *69*, 936-942.

(75) Cacchi, S.; Fabrizi, G.; Gavazza, F.; Goggiamani, A. Palladium-Catalyzed Reaction of Aryl Iodides with Acetic Anhydride. A Carbon Monoxide-Free Synthesis of Acetophenones. *Org. Lett*. **2003**, *5*, 289-291.

(76) Cacchi, S.; Fabrizi, G.; Goggiamani, A. Palladium-Catalyzed Synthesis of Aldehydes from Aryl Iodides and Acetic Formic Anhydride. *J. Comb. Chem.* **2004**, *6*, 692-694.

(77) Correa, A.; Martin, R. Palladium-Catalyzed Direct Carboxylation of Aryl Bromides with Carbon Dioxide. *J. Am. Chem. Soc*. **2009**, *131*, 15974-15975.

(78) Yu, B.; Zhao, Y.; Zhang, H.; Xu, J.; Hao, L.; Gao, X.; Liu, Z. Pd/C-Catalyzed Direct Formylation of Aromatic Iodides to Aryl Aldehydes Using Carbon Dioxide as a C1 Resource. *Chem. Commun*. **2014**, *50*, 2330-2333.

(79) Yu, B.; Yang, Z.; Zhao, Y.; Hao, L.; Zhang, H.; Gao, X.; Han, B.; Liu, Z. An Efficient and General Method for Formylation of Aryl Bromides with CO2 and Poly(methylhydrosiloxane). *Chem. Eur. J*. **2016**, *22*, 1097-1102.

(80) Shimomaki, K.; Murata, K.; Martin, R.; Iwasawa, N. Visible-Light-Driven Carboxylation of Aryl Halides by the Combined Use of Palladium and Photoredox Catalysts. *J. Am. Chem. Soc*. **2017**, *139*, 9467-9470.

(81) Fujihara, T.; Nogi, K.; Xu, T.; Terao, J.; Tsuji, Y. Nickel-Catalyzed Carboxylation of Aryl and Vinyl Chlorides Employing Carbon Dioxide. *J. Am. Chem. Soc*. **2012**, *134*, 9106-9109.

(82) Sayyed, F. B.; Tsuji, Y.; Sakaki, S. The Crucial Role of a Ni(I) Intermediate in Ni-Catalyzed Carboxylation of Aryl Chloride with CO2: a Theoretical Study. *Chem. Commun*. **2013**, *49*, 10715-10717.

(83) Rebih, F.; Andreini, M.; Moncomble, A.; Harrison-Marchand, A.; Maddaluno, J.; Durandetti, M. Direct Carboxylation of Aryl Tosylates by CO_2 Catalyzed by in situ-Generated Ni^0. *Chem. Eur. J*. **2016**, *22*, 3758-3763.

(84) Meng, Q.-Y.; Wang, S.; König, B. Carboxylation of Aromatic and Aliphatic Bromides and Triflates with CO2 by Dual Visible-Light-Nickel Catalysis. *Angew. Chem. Int. Ed*. **2017**, *56*, 13426-13430.

(85) Tran-Vu, H.; Daugulis, O. Copper-Catalyzed Carboxylation of Aryl Iodides with Carbon Dioxide. *ACS Catal*. **2013**, *3*, 2417-2420.

(86) Ozaki, S. Recent Advances in Isocyanate Chemistry. *Chem. Rev*. **1972**, *72*, 458-496.

(87) Hsieh, J.-C.; Cheng, C.-H. Nickel-Catalyzed Coupling of Isocyanates with 1,3-Iodoesters and Halobenzenes: A Novel Method for the Synthesis of Imide and Amide Derivatives. *Chem. Commun*. **2005**, 4554-4556.

(88) Correa, A.; Martin, R. Ni-Catalyzed Direct Reductive Amidation via C-O Bond Cleavage. *J. Am. Chem. Soc*. **2014**, *136*, 7253-7256.

(89) Arendt, K. M.; Doyle, A. G. Dialkyl Ether Formation by Nickel-Catalyzed Cross-Coupling of Acetals and Aryl Iodides. *Angew. Chem. Int. Ed*. **2015**, *54*, 9876-9880.

(90) Twilton, J.; Christensen, M.; DiRocco, D. A.; Ruck, R. T.; Davies, I. W.; MacMillan, D. W. C. Selective Hydrogen Atom Abstraction through Induced Bond Polarization: Direct α-Arylation of Alcohols through Photoredox, HAT, and Nickel Catalysis. *Angew. Chem. Int. Ed*. **2018**, *57*, 5369-5373.

(91) Ueda, T.; Konishi, H.; Manabe, K. Palladium-Catalyzed Reductive Carbonylation of Aryl Halides with N-Formylsaccharin as a CO Source. *Angew. Chem. Int. Ed*. **2013**, *52*, 8611-8615.

(92) Cocheta, T.; Bellostaa, V.; Greinerb, A.; Rocheb, D.; Cossy, J. N-Formylsaccharin: A New Formylation Agent. *Synlett* **2011**, 1920-1922.

(93) Korsager, S.; Taaning, R. H.; Lindhardt, A. T.; Skrydstrup, T. Reductive Carbonylation of Aryl Halides Employing a Two-Chamber Reactor: A Protocol for the Synthesis of Aryl Aldehydes Including 13C- and D-Isotope Labeling. *J. Org. Chem*. **2013**, *78*, 6112-6120.

Chapter 2

(1) For selected reviews on enantioselective carbonyl allylation, see: (a) Ramachandran, P. V. *Aldrichim. Acta* **2002**, *35*, 23. (b) Denmark, S. E.; Fu, J. *Chem. Rev*. **2003**, *103*, 2763. (c) Kennedy, Jason W. J.; Hall, Dennis G. *Angew. Chem Int. Ed*. **2003**, *42*, 473. (d) Yu, C.-M.; Youn, J.; Jung, H.-K. *Bull. Korean Chem. Soc*. **2006**, *27*, 463. (e) Marek, I.; Sklute, G. *Chem. Commun*. **2007**, 1683. (f) Hall, D. G. *Synlett* **2007**, 1644. (g) Lachance, H.; Hall, D. G. *Org. React*. **2008**, *73*, 1. (h) Yus, M.; González-Gómez, J. C.; Foubelo, F. *Chem. Rev. 2011*, **111**, 7774.

(2) For selected examples of enantioselective carbonyl allylation using chirally modified allyl metal reagents, see: (a) Herold, T.; Hoffmann, R. W. *Angew. Chem. Int. Ed*. **1978**, *17*, 768. (b) Hoffmann, R. W.; Herold, T. *Chem. Ber*. **1981**, *114*, 375. (c) Hayashi, T.; Konishi, M.; Kumada, M. *J. Am. Chem. Soc*. **1982**, *104*, 4963. (d) Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc*. **1983**, *105*, 2092. (e) Roush, W. R.; Walts, A. E.; Hoong, L. K. *J. Am. Chem. Soc*. **1985**, *107*, 8186. (f) Reetz, M. *Pure Appl. Chem*. **1988**, *60*, 1607. (g) Short, R. P.; Masamune, S. *J. Am. Chem. Soc.* **1989**, *111*, 1892. (h) Corey, E. J.; Yu, C.-M.; Kim, S. S. *J. Am. Chem. Soc*. **1989**, *111*, 5495. (i) See-bach, D.; Beck, A. K.; Imwinkeiried, R.; Roggo, S.; Wonnacott, A. *Helv. Chim. Acta* **1987**, *70*, 954. (j) Riediker, M.; Duthaler, R. O. *Angew. Chem. Int. Ed*. **1989**, *28*, 494. (k) Panek, J. S.; Yang, M. *J. Am. Chem. Soc*. **1991**, *113*, 6594. (l) Kinnaird, J. W. A.; Ng, P. Y.; Kubota, K.; Wang, X.; Leighton, J. L. *J. Am. Chem. Soc*. **2002**, *124*, 7920. (m) Hackman, B. M.; Lombardi, P. J.; Leighton, J. L. *Org. Lett*. **2004**, *6*, 4375. (n) Burgos, C. H.; Canales, E.; Matos, K.; Soderquist, J. A. *J. Am. Chem. Soc*. **2005**, *127*, 8044.

(3) For selected examples of enantioselective carbonyl allylation using achiral allylmetal reagents in combination with chiral catalysts, see: (a) Furuta, K.; Mouri, M.;

Yamamoto, H. *Synlett* **1991**, 561. (b) Cos-ta, A. L.; Piazza, M. G.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *J. Am. Chem Soc*. **1993**, *115*, 7001. (c) Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc*. **1993**, *115*, 8467. (d) Denmark, S. E.; Coe, D. M.; Pratt, N. E.; Griedel, B. D. *J. Org. Chem*. **1994**, *59*, 6161. (e) Denmark, S. E.; Fu, J. *J. Am. Chem. Soc*. **2001**, *123*, 9488. (f) Lachance, H.; Lu, X.; Gravel, M.; Hall, D. G. *J. Am. Chem. Soc*. **2003**, *125*, 10160. (g) Wada, R.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 8910. (h) Rauniyar, V.; Hall, D. G. *Angew. Chem. Int. Ed*. **2006**, *45*, 2426. (i) Rauniyar, V.; Zhai, H.; Hall, D. G. *J. Am. Chem. Soc.* **2006**, *130*, 8481. (j) Lou, S.; Moquist, P. N.; Schaus, S. E. *J. Am. Chem. Soc.* **2006**, *128*, 12660. (k) Bar-nett, D. S.; Moquist, P. N.; Schaus, S. E. *Angew. Chem. Int. Ed.* **2009**, *48*, 8679. (l) Jain, P.; Antilla, J. C. *J. Am. Chem. Soc*. **2010**, *132*, 11884.

(4) For selected reviews on enantioselective carbonyl allylation via Nozaki-Hiyama-Kishi coupling, see: (a) Avalos, M.; Babiano, R.; Cintas, P.; Jiménez, J. L.; Palacios, J. C. *Chem. Soc. Rev*. **1999**, *28*, 169. (b) Bandini, M.; Cozzi, P. G.; Umani-Ronchi, A. *Chem. Commun*. **2002**, 919. (c) Hargaden, G. C.; Guiry, P. J. *Adv. Synth. Catal*. **2007**, *349*, 2407.

(5) For selected reviews covering carbonyl allylation via umpolung of π-allyls, see: (a) Y. Masuyama, in Advances in Metal-Organic Chemis-try, ed. L. S. *Liebeskind, JAI Press*, Greenwich, **1994**, vol. *3*, p. 255. (b) Y. Tamaru, In Handbook of Organopalladium Chemistry for Organic Synthesis, (Eds. E.-i. Negishi, A. de Meijere), Wiley: New York, **2002**, Vol. *2*, pp. 1917. (c) Y. Tamaru, In Perspectives in Or-ganopalladium Chemistry for the XXI Century, (Ed. J. Tsuji), Else-vier: Amsterdam, **1999**, pp. 215. (d) Kondo, T.; Mitsudo, T.-a. *Curr. Org. Chem*. **2002**, *6*, 1163. (e) Tamaru, Y. Eur. *J.*

Org. Chem. **2005**, *13*, 2647. (f) Zanoni, G.; Pontiroli, A.; Marchetti, A.; Vidari, G. Eur. *J. Org. Chem*. **2007**, *22*, 3599.

(6) For a recent review, see: Ketcham, J. M.; Shin, I.; Montgomery, T. P., Krische, M. J. *Angew. Chem. Int. Ed*. **2014**, *53*, 9142.

(7) For catalytic enantioselective redox-triggered carbonyl allylations em-ploying allylic carboxylates as pronucleophiles, see: (a) Kim, I. S.; Ngai, M.-Y.; Krische, M. J. *J. Am. Chem. Soc*. **2008**, *130*, 6340. (b) Kim, I. S.; Ngai, M.-Y.; Krische, M. J. *J. Am. Chem. Soc*. **2008**, *130*, 14891. (c) Kim, I. S.; Han, S. B.; Krische, M. J. *J. Am. Chem. Soc.* **2009**, *131*, 2514. (d) Lu, Y.; Kim, I. S.; Hassan, A.; Del Valle, D. J.; Krische, M. J. *Angew. Chem. Int. Ed*. **2009**, *48*, 5018. (e) Hassan, A.; Lu, Y.; Krische, M. J. *Org. Lett*. **2009**, *11*, 3112. (f) Han, S. B.; Han, H.; Krische, M. J. *J. Am. Chem. Soc*. **2010**, *132*, 1760. (g) Zhang, Y. J.; Yang, J. H.; Kim, S. H.; Krische, M. J. *J. Am. Chem. Soc.* **2010**, *132*, 4562. (h) Han, S. B.; Gao, X.; Krische, M. J. *J. Am. Chem. Soc*. **2010**, *132*, 9153. (i) Hassan, A.; Zbieg, J. R.; Krische, M. J. *Angew. Chem. Int. Ed.* **2011**, *50*, 3493. (j) Gao, X.; Zhang, Y. J.; Krische, M. J. *Angew. Chem. Int. Ed.* **2011**, *50*, 4173. (j) Gao, X.; Han, H.; Krische, M. J. *J. Am. Chem. Soc.* **2011**, *133*, 12795. (k) Hassan, A.; Townsend, I. A.; Krische, M. J. *Chem. Comm.* **2011**, 10028. (l) Mo-ran, J.; Smith, A. G.; Carris, R. M.; Johnson, J. S.; Krische, M. J. *J. Am. Chem. Soc*. **2011**, *133*, 18618. (m) Hassan, A.; Montgomery, T. P.; Krische, M. J. *Chem. Comm*. **2012**, 4692. (n) Montgomery, T. P.; Hassan, A.; Park, B. Y.; Krische, M. J. *J. Am. Chem. Soc*. **2012**, *134*, 11100. (o) Schmitt, D. C.; Dechert-Schmitt, A.-M. R.; Krische, M. J. *Org. Lett*. **2012**, *14*, 6302. (p) Dechert-Schmitt, A.-M. R.; Schmitt, D. C.; Krische, M. J. *Angew. Chem. Int. Ed*. **2013**, *52*, 3195. (q) Feng, J.; Garza, V. J.; Krische, M. J. *J. Am. Chem. Soc.* **2014**, *136*, 8911. (r) Shin, I.; Wang, G.; Krische, M. J. *Chem. Eur. J*. **2014**, 13382.

(8) For catalytic enantioselective redox-triggered carbonyl allylations em-ploying dienes as pronucleophiles, see: (a) Zbieg, J. R.; Moran, J.; Krische, M. J. *J. Am. Chem. Soc*. **2011**, *133*, 10582. (b) Zbieg, J. R.; Yamaguchi, E.; McInturff, E. L.; Krische, M. J. *Science* **2012**, *336*, 324. (c) McInturff, E. L.; Yamaguchi, E.; Krische, M. J. *J. Am. Chem. Soc*. **2012**, *134*, 20628.

(9) For catalytic enantioselective redox-triggered carbonyl allylations em-ploying allenes as pronucleophiles, see: (a) Han, S. B.; Kim, I. S.; Han, H.; Krische, M. J. *J. Am. Chem. Soc*. **2009**, *131*, 6916. (b) Itoh, J.; Han, S. B.; Krische, M. J. *Angew. Chem. Int. Ed*. **2009**, *48*, 6313.

(10) Obora, Y.; Hatanaka, S; Ishii, Y. *Org. Lett.* **2009**, *11*, 3510.

(11) Park, B. Y.; Nguyen, K. D.; Chaulagain, M. R.; Komanduri, V.; Krische, M. J. *J. Am. Chem. Soc.* **2014**, *136*, 11902.

(12) For alkyne-to-allene isomerization followed by hydrometallation to form electrophilic allylpalladium or allylrhodium intermediates, see: (a) Trost, B. M.; Brieden, Baringhaus, K. H. *Angew. Chem. Int. Ed*. **1992**, *31*, 1335. (b) Gellrich, U.; Meißner, A.; Steffani, A.; Kähny, M.; Drexler, H.-J.; Heller, D.; Plattner, D. A.; Breit, B. *J. Am. Chem. Soc*. **2014**, *136*, 1097.

(13) SAINT V8.27B Bruker AXS Inc, (2012), Madison, WI.

(14) Palatinus, L.; Chapuis, G. *J. Appl. Cryst*. **2007**, *40*, 786.

(15) Sheldrick, G. M. SHELXL-2013. Program for the Refinement of Crystal Structures. *Acta Cryst*. **2008**, *64*, 112.

(16) Spek, A. L. (1998). PLATON, A Multipurpose Crystallographic Tool. Utrecht University,The Netherlands.

(17) Farrugia, L. J. WinGX 1.64. An Integrated System of Windows Programs for the Solution, Refinement and Analysis of Single Crystal X-ray Diffraction Data. *J. Appl. Cryst*.. **1999**, *32*. 837

(18) $R_w(F^2) = \{\Sigma w(|F_o|^2 - |F_c|^2)^2/\Sigma w(|F_o|)^4\}^{1/2}$ where w is the weight given each reflection. $R(F) = \Sigma(|F_o| - |F_c|)/\Sigma|F_o|\}$ for reflections with $F_o > 4(\sigma(F_o))$. $S = [\Sigma w(|F_o|^2 - |F_c|^2)^2/(n - p)]^{1/2}$, where n is the number of reflections and p is the number of refined parameters.

(19) Wilson, A. J. C. *International Tables for X-ray Crystallography*; Kluwer Academic Press: Boston, 1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4.

(20) Sheldrick, G. M. (1994). SHELXTL/PC (Version 5.03). Siemens Analytical X-ray Instruments, Inc., Madison, Wisconsin, USA.

Chapter 3

(1) Selected reviews: (a) D. O'Hagan, *The Polyketide Metabolites*, Ellis Horwood, Chichester, 1991. (b) Rohr, J. *Angew. Chem., Int. Ed*. **2000**, *39*, 2847. (c) Rimando, A. M.; Baerson, S. R. *ACS Symp. Ser.* **2007**, *955*, 1. (d) Itoh, T.; Dechert-Schmitt, A.-M. R.; Schmitt, D. C.; Gao, X.; Krische, M. J. *Nat. Prod. Rep.* **2014**, *31*, 504.

(2) Eribulin mesylate, a truncated derivative of the marine polyether macrolide halichondrin B, is the only commercial polyketide prepared through *de novo* chemical synthesis: Yu, M. J.; Zheng, W.; Seletsky, B. M. *Nat. Prod. Rep.* **2013**, *30*, 1158.

(3) Sait, M.; Hugenholtz, P.; Janssen, P. H. *Environ. Microbiol*. **2002**, *4*, 654 and references cited therein.

(4) For a review on the use of the aldol reaction in polyketide construction, see: Schetter, B.; Mahrwald, R. *Angew. Chem., Int. Ed.* **2006**, *45*, 7506.

(5) For selected reviews on enantioselective carbonyl allylation and crotylation, see: (a) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207. (b) Ramachandran, P. V. *Aldrichim. Acta* **2002**, *35*, 23. (c) Kennedy, J. W. J.; Hall, D. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4732. (d) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763. (e) Yu, C.-M.; Youn, J.; Jung, H.-K. *Bull. Korean Chem. Soc.* **2006**, *27*, 463. (f) Marek, I.; Sklute, G. *Chem. Commun.* **2007**, 1683. (g) Hall, D. G. *Synlett* **2007**, 1644. (h) Li, J.; Menche, D. *Synthesis* **2009**, 2293. (i) Leighton, J. L. *Aldrichim. Acta* **2010**, *43*, 3. (j) Yus, M.; González- Gómez, J. C.; Foubelo, F. *Chem. Rev.* **2011**, *111*, 7774. (k) Ketcham, J. M.; Shin, I.; Montgomery, T. P.; Krische, M. J. *Angew. Chem., Int. Ed.* **2014**, *53*, 9142.

(6) For catalytic diastereo- and enantioselective redox-triggered carbonyl crotylation using α-methyl allyl acetate or butadiene pronucleophiles, see: (a) Kim, I. S.; Han, S. B.;

Krische, M. J. *J. Am. Chem. Soc.* **2009**, *131*, 2514. (b) Gao, X.; Townsend, I. A.; Krische, M. J. *J. Org. Chem.* **2011**, *76*, 2350. (c) Gao, X.; Han, H.; Krische, M. J. *J. Am. Chem. Soc.* **2011**, *133*, 12795. (d) Zbieg, J. R.; Moran, J.; Krische, M. J. *J. Am. Chem. Soc.* **2011**, *133*, 10582. (e) Zbieg, J. R.; Yamaguchi, E.; McInturff, E. L.; Krische, M. J. *Science* **2012**, *336*, 324. (f) McInturff, E. L.; Yamaguchi, E.; Krische, M. J. *J. Am. Chem. Soc.* **2012**, *134*, 20628.

(7) Park, B. Y.; Nguyen, K. D.; Chaulagain, M. R.; Komanduri, V.; Krische, M. J. *J. Am. Chem. Soc.* **2014**, *136*, 11902

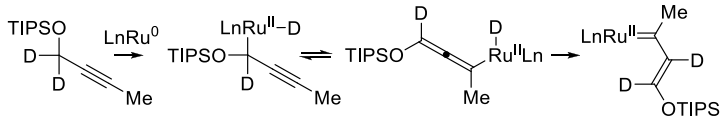
(8) Liang, T.; Nguyen, K. D.; Zhang, W.; Krische, M. J. *J. Am. Chem. Soc.* **2015**, *137*, 3161.

(9) Lorente, A.; Lamariano-Merketegi, J.; Alberico, F.; Álvarez, M. *Chem. Rev.* **2013**, *113*, 4567

(10) For reviews on the synthesis of γ-butyrolactones, see: (a) Seitz, M.; Reiser, O. *Curr. Opin. Chem. Biol.* **2005**, *9*, 285. (b) Burstein, C.; Tschan, S.; Xie, X.; Glorius, F. *Synthesis* **2006**, 2418. (c) Gil, S.; Parra, M.; Rodriguez, P.; Segura, J. *Mini-Rev. Org. Chem.* **2009**, *6*, 345.

(11) A related hydride shift was observed in the ruthenium catalyzed internal redox isomerization of propargyl alcohols to form conjugated enones: Trost, B. M.; Livingston, R. C. *J. Am. Chem. Soc.* **2008**, *130*, 11970.

(12) The indicated mechanism involving propargyl C-H oxidative addition followed by internal hydrometallation from the allenylruthenium haptomer was considered and cannot be excluded on the basis of the isotopic labelling studies. However, such internal hydrometallations of allenic species does not appear geometrically feasible.



(13) For rhodium catalyzed isomerization of 1-alkynes to allenes, which are then converted to electrophilic π-allyls, see: (a) Lumbroso, A.; Koschker, P.; Vautravers, N. R.; Breit, B. *J. Am. Chem. Soc.***2011**,*133*,2386. (b) Xu, K.; Khakyzadeh, V.; Bury, T.; Breit, B. *J. Am. Chem. Soc.***2014**,*136*,16124. (c) Koschker, P.; Kähny, M.; Breit, B. *J. Am. Chem. Soc.* **2015**, *137*, 3131.

(14)SAINT V8.27B Bruker AXS Inc, (2012), Madison, WI.

(15)Palatinus, L.; Chapuis, G. *J. Appl. Cryst*. **2007**, *40*, 786.

(16)Sheldrick, G. M. SHELXL-2013. Program for the Refinement of Crystal Structures. *Acta Cryst*. **2008**, *64*, 112.

(17)Spek, A. L. (1998). PLATON, A Multipurpose Crystallographic Tool. Utrecht University,The Netherlands.

(18)Farrugia, L. J. WinGX 1.64. An Integrated System of Windows Programs for the Solution, Refinement and Analysis of Single Crystal X-ray Diffraction Data. *J. Appl. Cryst*.. **1999**, *32*. 837

(19)Flack, H. D. *Acta Cryst A*. **1983**, *39*, 876.

(20)Hooft, R. W. W.; Straver, L. H.; Spek, A. L. *J. Appl. Cryst*. **2008**, *41*, 96.

(21)$R_W(F^2) = \{\Sigma w(|F_O|^2 - |F_C|^2)^2/\Sigma w(|F_O|)^4\}^{1/2}$ where w is the weight given each reflection. $R(F) = \Sigma(|F_O| - |F_C|)/\Sigma|F_O|\}$ for reflections with $F_O > 4(\sigma(F_O))$. $S = [\Sigma w(|F_O|^2 - |F_C|^2)^2/(n - p)]^{1/2}$, where n is the number of reflections and p is the number of refined parameters.

(22)Wilson, A. J. C. *International Tables for X-ray Crystallography*; Kluwer Academic Press: Boston, 1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4.

Chapter 4

(1) (a) Knochel, P.; Molander, G. A. *Comprehensive Organic Synthesis,* 2nd ed.; Elsevier, Oxford **2014,** Vols. 1 and Vol. 2; (b) Otera J. *Modern Carbonyl Chemistry*; Wiley-VCH, Weinheim, Germany, **2000**.

(2) Review: Ketcham, J. M.; Shin, I.; Montgomery, T. P.; Krische, M. J. *Angew. Chem., Int. Ed.* **2014**, *53*, 9142.

(3) For selected reviews on enantioselective carbonyl allylation and crotylation, see: (a) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207. (b) Ramachandran, P. V. *Aldrichim. Acta* **2002**, *35*, 23. (c) Kennedy, J. W. J.; Hall, D. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4732. (d) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763. (e) Yu, C.-M.; Youn, J.; Jung, H.-K. *Bull. Korean Chem. Soc.* **2006**, *27*, 463. (f) Marek, I.; Sklute, G. *Chem. Commun.* **2007**, 1683. (g) Hall, D. G. *Synlett* **2007**, 1644. (h) Li, J.; Menche, D. *Synthesis* **2009**, 2293. (i) Leighton, J. L. *Aldrichim. Acta* **2010**, *43*, 3. (j) Yus, M.; González- Gómez, J. C.; Foubelo, F. *Chem. Rev.* **2011**, *111*, 7774. (k) Pasco, M.; Gilboa, N.; Mejuch, T.; Marek, I. *Organometallics* **2013**, *32*, 942.

(4) For catalytic enantioselective carbonyl allylation *via* redox-triggered couplings of primary alcohols and allyl acetate, see: (a) Kim, I. S.; Ngai, M.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 6340. (b) Kim, I. S.; Ngai, M.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 14891. (c) Dechert-Schmitt, A.-M. R.; Schmitt, D. C.; Krische, M. J. *Angew. Chem. Int. Ed*. **2013**, *52*, 3195. (d) Shin, I.; Wang, G.; Krische, M. J. *Chem. Eur. J.* **2014**, *20*, 13382.

(5) Park, B. Y.; Nguyen, K. D.; Chaulagain, M. R.; Komanduri, V.; Krische, M. J. *J. Am. Chem. Soc.* **2014**, *136*, 11902.

(6) Liang, T.; Nguyen, K. D.; Zhang, W.; Krische, M. J. *J. Am. Chem. Soc.* **2015**, *137*, 3161.

(7) Liang, T.; Zhang, W.; Chen, T.-Y.; Nguyen, K. D.; Krische, M. J. *J. Am. Chem. Soc.* **2015**, *137*, 13066.

(8) Indirect use of 1-alkynes in carbonyl allylation is achieved through their conversion to allylboron reagents via tandem alkyne hydroboration−alkene isomerization, see: (a) Miura, T.; Nishida, Y.;Murakami, M. *J. Am. Chem. Soc*. **2014**, *136*, 6223. (b) Miura, T.;Nishida, Y.; Morimoto, M.; Murakami, M. *J. Am. Chem. Soc*. **2013**, *135*,11497.

(9) (a) Niwa, S.; Soai, K. J. Chem. Soc., Perkin Trans. 1 **1990**, 937.(b) Ramos Tombo, G. M.; Didier, E.; Loubinoux, B. *Synlett* **1990**,*1990*, 547. (c) Li, Z.; Upadhyay, V.; DeCamp, A. E.; DiMichele, L.;Reider, P. J. *Synthesis* **1999**, ***1999***, 1453. (d) Tan, L.; Chen, C.-y.;Tillyer, R. D.; Grabowski, E. J. J.; Reider, P. J. *Angew. Chem., Int. Ed.***1999**, *38*, 711. (e) Frantz, D. E.; Fässler, R.; Carreira, E. M. *J. Am.Chem. Soc.* **1999**, *121*, 11245.

(10) Review: Kimura, M. In Comprehensive Organic Synthesis, 2nd ed.;Knochel, P., Molander, G. A., Eds.; Elsevier: Oxford, **2014**; pp 606−628.

(11) Kang, J. Y.; Connell, B. T. *J. Am. Chem. Soc*. **2010**, 132, 7826.

Chapter 5

(1) Dictionary of Antibiotics and Related Substances, Bycroft, B. W., Ed.; Chapman and Hall: London, 1988.

(2) a) Barrett, A. G. M.; Seefeld, M. A. *J. Chem. Soc., Chem. Commun.* **1993**, 339; b) Barrett, A. G. M.; Seefeld, M. A. *Tetrahedron* **1993**, *49*, 7857; c) Barrett, A. G. M.; Seefeld, M. A.; Williams, D. J. *J. Chem. Soc., Chem. Commun.* **1994**, 1053; d) Barrett, A. G. M.; Seefeld, M. A.; White, A. J. P.; Williams, D. J. *J. Org. Chem.* **1996**, *61*, 2677.

(3) For recent reviews, see: a) Ketcham, J. M.; Shin, I.; Montgomery, T. P.; Krische, M. J. *Angew. Chem.* **2014**, *126*, 9294; *Angew. Chem., Int. Ed.* **2014**, *53*, 9142; b) Dechert-Schmitt, A.-M. R.; Schmitt, D. C.; Gao, X.; Itoh, T.; Krische, M. J. *Nat. Prod. Rep.* **2014**, *31*, 504; c) Perez, F.; Oda, S.; Geary, L. M.; Krische, M. J. *Top. Curr. Chem.* **2016**, *374*, 365; d) Nguyen, K. D.; Park, B. Y.; Luong, T.; Sato, H.; Garza, V. J.; Krische, M. J. *Science* **2016**, *354*, aah5133.

(4) Skucas, E.; Zbieg, J. R.; Krische, M. J. *J. Am. Chem. Soc.* **2009**, *131*, 5054

(5) Zbieg, J. R.; McInturff, E. L.; Krische, M. J. *Org. Lett.* **2010**, *12*, 2514.

(6) Walia, A.; Kang, S.; Silverman, R. B. *J. Org. Chem.* **2013**, *78*, 10931.

(7) Park, B. Y.; Nguyen, K. D.; Chaulagain, M. R.; Komanduri, V.; Krische, M. J. *J. Am. Chem. Soc.* **2014**, *136*, 11902.

(8) Liang, T.; Zhang, W.; Chen, T.-Y.; Nguyen, K. D.; Krische, M. J. *J. Am. Chem. Soc.* **2015**, *137*, 13066.

(9) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.

(10) Joseph, T.; Deshpande, S. S.; Halligudi, S. B.; Vinu, A.; Ernst, S.; Hartmann, M. *J. Mol. Catal. A: Chem.* **2003**, *206*, 13.

(11) Blickenstaff, R. T.; Forster, E.; Gerzon, K.; Young, P. *Steroids*, **1986**, *48*, 223.

(12) CrysAlisPro. Agilent Technologies (**2013**). Agilent Technologies UK Ltd., Oxford, UK, SuperNova CCD System, CrysAlicPro Software System, 1.171.38.43f.

(13) SHELXT. Sheldrick, G. M. (**2015**) *Acta. Cryst*. A71, 3-8.

(14) Sheldrick, G. M. (**2015**). SHELXL-2016/6. Program for the Refinement of Crystal Structures. *Acta Cryst*., C71, 9-18.

(15) Spek, A. L. (**2009**). PLATON, A Multipurpose Crystallographic Tool. Utrecht University, The Netherlands. *Acta Cryst*. D65, 148-155.

(16) WinGX 1.64. (**1999**). An Integrated System of Windows Programs for the Solution, Refinement and Analysis of Single Crystal X-ray Diffraction Data. Farrugia, L. *J. J. Appl. Cryst*. *32*. 837-838.

(17) Rw(F2) = {Σw(|Fo|2 - |Fc|2)2/Σw(|Fo|)4}1/2 where w is the weight given each reflection.

(18) R(F) = Σ|Fo| - |Fc|)/Σ|Fo|} for reflections with Fo > 4(σ (Fo)).

(19) S = [Σw(|Fo|2 - |Fc|2)2/(n - p)]1/2, where n is the number of reflections and p is the number of refined parameters..

(20) International Tables for X-ray Crystallography (**1992**). Vol. C, Tables 4.2.6.8 and 6.1.1.4, A. J. C. Wilson, editor, Boston: Kluwer Academic Press.

(21) Sheldrick, G. M. (**1994**). SHELXTL/PC (Version 5.03). Siemens Analytical X-ray Instruments, Inc., Madison, Wisconsin, USA.

Chapter 6

(1) For a recent review, see: Kim, S. W.; Zhang, W.; Krische, M. *Acc. Chem. Res*. **2017**, *50*, 2371.

(2) Garza, V. J.; Krische, M. J. *J. Am. Chem. Soc*. **2016**, *138*, 3655.

(3) (a) Riediker, M.; Duthaler, R. O. *Angew. Chem., Int. Ed. Engl*. **1989**, *28*, 494. (b) Hafner, A.; Duthaler, R. O.; Marti, R.; Rihs, G.;Rothe-Streit, P.; Schwarzenbach, F. *J. Am. Chem. Soc*. **1992**, *114*, 2321. (c) Sebelius, S.; Szabó, K. J. *Eur. J. Org. Chem*. **2005**, *2005*, 2539.(d) Vogt, M.; Ceylan, S.; Kirschning, A. *Tetrahedron* **2010**, *66*, 6450.(e) Haddad, T. D.; Hirayama, L. C.; Singaram, B. *J. Org. Chem*. **2010**,*75*, 642. (f) De Sio, V.; Massa, A.; Scettri, A. *Org. Biomol. Chem*. **2010**,*8*, 3055. (g) Li, L.-L.; Tao, Z.-L.; Han, Z.-Y.; Gong, L.-*Z. Org. Lett*.**2017**, *19*, 102. (h) Tekle-Smith, M. A.; Williamson, K. S.; Hughes, I. F.; Leighton, J. L. *Org. Lett*. **2017**, *19*, 6024.

(4) (a) Kanajima, M.; Saito, M.; Hashimoto, S. *Chem. Pharm. Bull*.**2000**, *48*, 306. (b) Zanoni, G.; Gladiali, S.; Marchetti, A.; Piccinini, P.;Tredici, I.; Vidari, G. *Angew. Chem., Int. Ed.* **2004**, *43*, 846. (c) Zhu,S.-F.; Yang, Y.; Wang, L.-X.; Liu, B.; Zhou, Q.-L. *Org. Lett*. **2005**, *7*,2333. (d) Hemelaere, R.; Carreaux, F.; Carboni, B. *Chem. - Eur. J*.**2014**, *20*, 14518. (e) Evans, D. A.; Aye, Y.; Wu, J. *Org. Lett*. **2006**, *8,*2071. (f) Bai, B.; Zhu, H.-J.; Pan, W. *Tetrahedron* **2012**, *68*, 6829.(g) Miura, T.; Nishida, Y.; Morimoto, M.; Murakami, M. *J. Am. Chem.Soc*. **2013**, *135*, 11497. (h) Tan, Z.; Wan, X.; Zang, Z.; Qian, Q.;Deng, W.; Gong, H. *Chem. Commun*. **2014**, *50*, 3827.

(5) Chen, Y. K.; Lurain, A. E.; Walsh, P. J. *J. Am. Chem. Soc*. **2002**,*124*, 12225.

(6) Shiina, I.; Ibuka, R.; Kubota, M. *Chem. Lett*. **2002**, *31*, 286.

(7) Unlike the present transformations, in chiral phosphoramidecatalyzedcross-aldol reactions, enantioselectivity increases as aldehydes become either more electron rich or more electron poor, indicative of a change in the stereodetermining event: Denmark, S. E.;Bui, T. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 5439.

(8) (a) Kim, I. S.; Ngai, M.-Y.; Krische, M. J. *J. Am. Chem. Soc*.**2008**, *130*, 6340. (b) Kim, I. S.; Ngai, M.-Y.; Krische, M. J. *J. Am.Chem. Soc.* **2008**, *130*, 14891. (c) Kim, I. S.; Han, S. B.; Krische, M. J.*J. Am. Chem. Soc*. **2009**, *131*, 2514. (d) Gao, X.; Townsend, I. A.;Krische, M. J. *J. Org. Chem*. **2011**, *76*, 2350.

(9) (a) Han, S. B.; Kim, I. S.; Han, H.; Krische, M. J. *J. Am. Chem.Soc*. **2009**, *131*, 6916. (b) Han, S. B.; Kim, I. S.; Han, H.; Krische, M.J. *J. Am. Chem. Soc.* **2010**, *132*, 12517.

Chapter 7

(1) Butlerov, A. Studien über die Einfachsten Verbindungen der Organischen Chemie,. *Z. Chem. Pharm*. **1863**, *6*, 484−497. (b) Butlerov, A. Z. Sur l'Alcool Pseudobuylique Tertiare ou Alcool Méthylique triméthylé. *Bull. Soc. Chim. Fr*. **1864**, *2*, 106−116. (c) Reformatsky, S. Neue Synthese Zweiatomiger Einbasischer Säuren aus den Ketonen. *Ber. Dtsch. Chem. Ges*. **1887**, *20*, 1210−1211. (d) Grignard, V. Sur Quelques Nouvelles Combinaisons Organométalliques du Magnèsium et Leur Application àdes Synthèses d'alcools et d'hydrocarbures. *C R Hebd Seá nces Acad Sci, Ser C* **1900**, *130*, 1322−1324.

(2) *Comprehensive Organic Synthesis, 2nd ed.*; Knochel, P.; Molander, G. A., Eds.; Elsevier: Oxford, 2014; Vols. 1 and 2.

(3) For selected reviews on catalytic enantioselective carbonyl addition, see: (a) Soai, K.; Shibata, T. Alkylation of Carbonyl Groups. In *Comprehensive Asymmetric Catalysis I-III*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag Berlin Heidelberg: Germany, 1999; Vol. 2, pp 911-922. (b) Kobayashi, S.; Ishitani, H. Catalytic Enantioselective Addition to Imines *Chem. Rev.* **1999**, *99*, 1069−1094. (c) Pu, L.; Yu, H.-B. Catalytic Asymmetric Organozinc Additions to Carbonyl Compounds. *Chem. Rev.* **2001**, *101*, 757–824. (d) Trost, B. M.; Weiss, A. H. The Enantioselective Addition of Alkyne Nucleophiles to Carbonyl Groups. *Adv. Synth. Catal.* **2009**, *351*, 963–983. (e) Garcia, C.; Martin, V. S. Asymmetric addition to ketones: enantioselective formation of tertiary alcohols. *Curr. Org. Chem.* **2006**, *10*, 1849–1889. (f) Miyaura, N. Celebrating 20 Years of SYNLETT-Special Account On Palladium (II)-Catalyzed Additions of Arylboronic Acids to Electron-Deficient Alkenes, Aldehydes, Imines, and Nitriles. *Synlett* **2009**, 2039–2050. (g)

Tian, P.; Dong, H.-Q.; Lin, G.-Q. Rhodium-Catalyzed Asymmetric Arylation. *ACS Catalysis* **2012**, 2, 95–119.

(4) For selected reviews on metal-catalyzed reductive coupling, see: (a) Montgomery, J. Nickel- Catalyzed Reductive Cyclizations and Couplings. *Angew. Chem. Int. Ed.* **2004**, *43*, 3890–3908. (b) Iida, H.; Krische, M. J. Catalytic Reductive Coupling of Alkenes and Alkynes to Carbonyl Compounds and Imines Mediated by Hydrogen. *Top. Curr. Chem.* **2007**, *279*, 77–104. (c) Jeganmohan, M.; Cheng, C.-H. Cobalt- and Nickel- Catalyzed Regio- and Stereoselective Reductive Coupling of Alkynes, Allenes, and Alkenes with Alkenes. *Chem. Eur. J.* **2008**, *14*, 10876–10886. (d) Hassan, A.; Krische, M. J. Unlocking Hydrogenation for C–C Bond Formation: A Brief Overview of Enantioselective Methods. *Org. Process Res. Devel.* **2011**, *15*, 1236–1242. (e) Moran, J.; Krische, M. J. Formation of C-C Bonds via Ruthenium Catalyzed Transfer Hydrogenation. *Pure Appl. Chem.* **2012**, *84*, 1729–1739. (f) Moragas, T.; Correa, A.; Martin. R. Metal-Catalyzed Reductive Coupling Reactions of Organic Halides with Carbonyl-Type Compounds. *Chem. Eur. J.* **2014**, *20*, 8242–8258. (g) Ketcham, J. M.; Shin, I.; Montgomery, T. P.; Krische, M. J. Catalytic Enantioselective C-H Functionalization of Alcohols by Redox-Triggered Carbonyl Addition: Borrowing Hydrogen, Returning Carbon. *Angew. Chem. Int. Ed.* **2014**, *53*, 9142–9150. (h) Everson, D. A.; Weix, D. J. Cross-Electrophile Coupling: Principles of Reactivity and Selectivity. *J. Org. Chem.* **2014**, 79, 4793–4798. (i) Nguyen, K. D.; Park, B. Y.; Luong, T.; Sato, H.; Garza, V. J.; Krische, M. J. Metal-catalyzed reductive coupling of olefin-derived nucleophiles: Reinventing carbonyl addition. *Science* **2016**, *354*, No. aah5133. (j) Wang, X.; Dai, Y.; Gong, H. Nickel-Catalyzed Reductive Couplings. *Top. Curr.*

Chem. **2016**, *374*, 1. (k) Kim, S. W.; Zhang, W.; Krische, M. J. Catalytic Enantioselective Carbonyl Allylation and Propargylation via Alcohol-Mediated Hydrogen Transfer: Merging the Chemistry of Grignard and Sabatier *Acc. Chem. Res.* **2017**, *50*, 2371–2380. (l) Holmes, M.; Schwartz, L. A.; Krische, M. J. Intermolecular Metal-Catalyzed Reductive Coupling of Dienes, Allenes, and Enynes with Carbonyl Compounds and Imines. *Chem. Rev.* **2018**, *118*, 6026–6052.

(5) For seminal examples of enantioselective hydrogenative and transfer hydrogenative aldol additions, vinylations, allylations and propargylations, see: (a) Bee, C.; Han, S. B.; Hassan, A.; Iida, H.; Krische, M. J. Diastereo- and Enantioselective Hydrogenative Aldol Coupling of Vinyl Ketones: Design of Effective Monodentate TADDOL-Like Phosphonite Ligands. *J. Am. Chem. Soc.* **2008**, *130*, 2746–2747. (b) Ngai, M.-Y.; Barchuk, A.; Krische, M. J. Enantioselective Iridium-Catalyzed Imine Vinylation: Optically Enriched Allylic Amines via Alkyne−Imine Reductive Coupling Mediated by Hydrogen. *J. Am. Chem. Soc.* **2007**, *129*, 12644–12645. (c) Kim, I. S.; Ngai, M.-Y.; Krische, M. J. Enantioselective Iridium-Catalyzed Carbonyl Allylation from the Alcohol or Aldehyde Oxidation Level Using Allyl Acetate as an Allyl Metal Surrogate. *J. Am. Chem. Soc.* **2008**, *130*, 6340–6341. (d) Kim, I. S.; Ngai, M.-Y.; Krische, M. J. Enantioselective Iridium-Catalyzed Carbonyl Allylation from the Alcohol or Aldehyde Oxidation Level via Transfer Hydrogenative Coupling of Allyl Acetate: Departure from Chirally Modified Allyl Metal Reagents in Carbonyl Addition. *J. Am. Chem. Soc.* **2008**, *130*, 14891–14899. (e) Kim, I. S.; Han, S. B.; Krische, M. J. *anti*-Diastereo- and Enantioselective Carbonyl Crotylation from the Alcohol or Aldehyde Oxidation Level Employing a Cyclometallated Iridium Catalyst: α-Methyl Allyl Acetate as a

Surrogate to Preformed Crotylmetal Reagents. *J. Am. Chem. Soc.* **2009**, *131*, 2514–2520. (f) Geary, L. M.; Woo, S. K.; Leung, J. C.; Krische, M. J. Diastereo- and Enantioselective Iridium- Catalyzed Carbonyl Propargylation from the Alcohol or Aldehyde Oxidation Level: 1,3- Enynes as Allenylmetal Equivalents. *Angew. Chem. Int. Ed*. **2012**, *51*, 2972–2976. (g) Woo, S. K.; Geary, L. M.; Krische, M. J. Enantioselective Carbonyl Propargylation by Iridium- Catalyzed Transfer Hydrogenative Coupling of Alcohols and Propargyl Chlorides. *Angew. Chem. Int. Ed*. **2012**, *51*, 7830–7834.

(6) For selected examples of intermolecular Nozaki-Hiyama-Kishi arylation, see: (a) Takai, K.; Kimura, K.; Kuroda, T.; Hiyama, T.; Nozaki, H. Selective Grignard-Type Carbonyl Addition of Alkenyl Halides Mediated by Chromium(II) Chloride. *Tet. Lett.* **1983**, *24*, 5281–5284. (b) Fürstner, A.; Shi, N. A Multicomponent Redox System Accounts for the First Nozaki−Hiyama−Kishi Reactions Catalytic in Chromium. *J. Am. Chem. Soc.* **1996**, *118*, 2533–2534. (c) Fürstner, A.; Shi, N. Nozaki−Hiyama−Kishi Reactions Catalytic in Chromium. *J. Am. Chem. Soc.* **1996**, *118*, 12349–12357. (d) Namba, K.; Wang, J.; Cui, S.; Kishi, Y. Surprisingly Efficient Catalytic Cr-Mediated Coupling Reactions. *Org. Lett.* **2005**, *7*, 5421–5424.

(7) For selected reviews on the Nozaki-Hiyama-Kishi reaction, see: (a) Fürstner, A. Carbon−Carbon Bond Formations Involving Organochromium(III) Reagents. *Chem. Rev.* **1999**, *99*, 991–1046. (b) Tian, Q.; Zhang, G. Recent Advances in the Asymmetric Nozaki–Hiyama–Kishi Reaction. *Synthesis* **2016,** *48*, 4038–4049.

(8) For intermolecular metal-catalyzed aryl halide-aldehyde reductive coupling employing metallic reductants, see: (a) **Nickel:** Majumdar, K. K.; Cheng, C.-H.

Ni(II)/Zn-Mediated Chemoselective Arylation of Aromatic Aldehydes: Facile Synthesis of Diaryl Carbinols. *Org. Lett.* **2000**, *2*, 2295–2298. (b) Rayabarapu, D. K.; Chang, H. T.; Cheng, C.-H. Synthesis of Phthalide Derivatives Using Nickel-Catalyzed Cyclization of *o*- Haloesters with Aldehydes *Chem. Eur. J.* **2004**, *10*, 2991–2996. (c) Harnying, W.; Berkessel, A. Vinylation of Aldehydes Using Mn/Cr Alloy and a N_4- Ligand/Ni^{II}- Catalyst *Chem. Eur. J.* **2015**, *21*, 6057–6061. (d) Arendt, K. M.; Doyle, A. G. Dialkyl Ether Formation by Nickel-Catalyzed Cross-Coupling of Acetals and Aryl Iodides. *Angew. Chem. Int. Ed.* **2015**, *54*, 9876-9880. (e) Asachenko, A. F.; Valaeva, V. N.; Kudakina, V. A.; Uborsky, D. V.; Izmer, V. V.; Kononovich, D. S.; Voskoboynikov, A. Z. Coupling of Aromatic Aldehydes with Aryl Halides in the Presence of Nickel Catalysts with Diazabutadiene Ligands. *Russ. Chem. Bull., Int. Ed.* **2016**, *65*, 456–463. (f) Garcia, K. J.; Gilbert, M. M.; Weix, D. J. Nickel Catalyzed Addition of Aryl Bromides to Aldehydes to Form Hindered 2° Alcohols. *J. Am. Chem. Soc.* **2019**, *141*, In Press - ja-2018-13709j. (g) **Rhodium:** Zhou, F.; Li, C.-J. The Barbier–Grignard-Type Arylation of Aldehydes Using Unactivated Aryl Iodides in Water. *Nature Comm.* **2014**, *5*, 4254.

(9) For electrochemical intermolecular aryl halide-aldehyde reductive couplings, see: (a) Durandetti, M.; Périchon, J.; Nédélec, J.-Y. Nickel- and Chromium-Catalyzed Electrochemical Coupling of Aryl Halides with Arenecarboxaldehydes. *Tet. Lett.* **1999**, *40*, 9009–9013. (b) Durandetti, M.; Nédélec, J.-Y.; Perichon, J. An Electrochemical Coupling of Organic Halide with Aldehydes, Catalytic in Chromium and Nickel Salts. The Nozaki−Hiyama−Kishi Reaction. *Org. Lett.* **2001**, *3*, 2073–2076.

(10) Shin, I.; Ramgren, S. D.; Krische, M. J. Reductive Cyclization of Halo-Ketones to form 3-hydroxy-2-oxindoles *via* Palladium Catalyzed Hydrogenation: a Hydrogen-mediated Grignard addition. *Tetrahedron* **2015**, *71*, 5776–5780.

(11) For redox-neutral catalytic aryl halide-aldehyde couplings to form ketone products, see: (a) **Palladium**: Satoh, T.; Itaya, T.; Miura, M.; Nomura, M. Palladium-Catalyzed Coupling Reaction of Salicylaldehydes with Aryl Iodides via Cleavage of the Aldehyde C–H Bond. *Chem. Lett.* **1996**, *25*, 823–824. (b) Ko, S.; Kang, B.; Chang, S. Cooperative Catalysis by Ru and Pd for the Direct Coupling of a Chelating Aldehyde with Iodoarenes or Organostannanes. *Angew. Chem. Int. Ed*. **2005**, *44*, 455–457. (c) Takemiya, A.; Hartwig, J. F. Palladium-Catalyzed Synthesis of Aryl Ketones by Coupling of Aryl Bromides with an Acyl Anion Equivalent. *J. Am. Chem. Soc.* **2006**, *128*, 14800–14801. (d) Ruan, J.; Saidi, O.; Iggo, J. A.; Xiao, J. Direct Acylation of Aryl Bromides with Aldehydes by Palladium Catalysis. *J. Am. Chem. Soc.* **2008**, *130*, 10510–10511. (e) Zanardi, A.; Mata, J. A.; Peris, E. Palladium Complexes with Triazolyldiylidene. Structural Features and Catalytic Applications. *Organometallics* **2009**, *28*, 1480–1483. (f) Adak, L.; Bhadra, S.; Ranu, B. C. Palladium(0) Nanoparticle-catalyzed sp^2 C–H Activation: A Convenient Route to alkyl–aryl Ketones by Direct Acylation of Aryl Bromides and Iodides with Aldehydes. *Tet. Lett.* **2010**, *51*, 3811–3814. (g) Nowrouzi, N.; Motevalli, S.; Tarokh, D. Palladium-Catalyzed Direct C–H Arylation of 2-hydroxybenzaldehydes With Organic Halides in Neat Water. *J. Mol. Cat. A: Chem.* **2015**, *396*, 224–230. (h) Nowrouzi, N.; Tarokh, D. $PdCl_2$/DABCO-Catalyzed Direct Arylation of 2-hydroxybenzaldehydes in H_2O. *J. Iran Chem. Soc.* **2016**, *13*, 1493–1497. (i) Suchand, B.; Satyanarayana, G. Palladium-Catalyzed

Environmentally Benign Acylation. *J. Org. Chem.* **2016**, *81*, 6409–6423. (j) Wakaki, T.; Togo, T.; Yoshidome, D.; Kuninobu, Y.; Kanai, M. Palladium-Catalyzed Synthesis of Diaryl Ketones from Aldehydes and (Hetero)Aryl Halides via C–H Bond Activation. *ACS Catal.* **2018**, *8*, 3123–3128. (k) **Rhodium**: Ishiyama, T.; Hartwig, J. F. A Heck-Type Reaction Involving Carbon−Heteroatom Double Bonds. Rhodium(I)-Catalyzed Coupling of Aryl Halides with *N*-Pyrazyl Aldimines. *J. Am. Chem. Soc.* **2000**, *122*, 12043–12044. (l) Rao, M. L.; Ramakrishna, B. S. Rhodium- Catalyzed Directing- Group- Assisted Aldehydic C–H Arylations with Aryl Halides. *Eur. J. Org. Chem.* **2017**, *2017*, 5080–5093. (m) **Nickel**: Huang, Y.-C.; Majumdar, K. K.; Cheng, C.-H. Nickel-Catalyzed Coupling of Aryl Iodides with Aromatic Aldehydes: Chemoselective Synthesis of Ketones. *J. Org. Chem.* **2002**, *67*, 1682–1684. (n) Nowrouzi, N.; Zarei, M.; Roozbin, F. First Direct Access to 2-hydroxybenzophenones *via* Nickel-Catalyzed Cross-Coupling of 2-Hydroxybenzaldehydes with Aryl Iodides. *RSC Adv.* **2015**, *5*, 102448–102453. (o) **Photoredox**: Zhang, X.; MacMillan, D. W. C. Direct Aldehyde C–H Arylation and Alkylation *via* the Combination of Nickel, Hydrogen Atom Transfer, and Photoredox Catalysis. *J. Am. Chem. Soc.* **2017**, *139*, 11353–11356. (p) **Cobalt**: Hu, Y. L.; Wu, Y. P.; Lu, M. Co (II)-C12 Alkyl Carbon Chain Multi- Functional Ionic Liquid Immobilized on Nano-SiO_2 Nano-SiO_2@$CoCl_3$-C12IL as an Efficient Cooperative Catalyst for C–H Activation by Direct Acylation of Aryl Halides with Aldehydes *Appl. Organomet. Chem.* **2018**, *32*, e4096.

(12) For the magnesium-mediated generation of benzyne from 1-bromo-2-fluorobenzene, see: Wittig G. Triptycene. *Org. Synth*. **1959**, *39*, 75.

(13) For studies on the oxidative addition of aryl halides to rhodium(I) complexes, see: (a) **Monophosphine Complexes**: Jiao, Y.; Brennessel, W. W.; Jones, W. D. Oxidative Addition of Chlorohydrocarbons to a Rhodium Tris(pyrazolyl)borate Complex. *Organometallics* **2015**, *34*, 1552–1566. (b) Townsend, N. S.; Chaplin, A. B.; Abu Naser, M.; Thompson, A. L.; Rees, N. H.; Macgregor, S. A.; Weller, A. S. Reactivity of the Latent 12- Electron Fragment $[Rh(PiBu_3)_2]^+$ with Aryl Bromides: Aryl–Br and Phosphine Ligand C–H Activation. *Chem. Eur. J.* **2010**, *16*, 8376–8389. (c) Chen, S.; Li, Y.; Zhao, J.; Li, X. Chelation-Assisted Carbon-Halogen Bond Activation by a Rhodium(I) Complex. *Inorg. Chem.* **2009**, *48*, 1198–1206. (d) Douglas, T. M.; Chaplin, A. B.; Weller, A. S. Dihydrogen Loss from a 14-Electron Rhodium(III) Bis-Phosphine Dihydride To Give a Rhodium(I) Complex That Undergoes Oxidative Addition with Aryl Chlorides. *Organometallics* **2008**, *27*, 2918–2921. (e) **Bisphosphine Complexes**: Pike, S. D.; Weller, A. S. C–Cl Activation of the Weakly Coordinating Anion $[B(3,5\text{-}Cl_2C_6H_3)_4]-$ at a Rh(I) Centre in Solution and the Solid-State *Dalton Trans.* **2013**, *42*, 12832–12835. (f) Koenig, A.; Fischer, C.; Alberico, E.; Selle, C.; Drexler, H.-J.; Baumann, W.; Heller, D. Oxidative Addition of Aryl Halides to Cationic Bis(phosphane)rhodium Complexes: Application in C–C Bond Formation. *Eur. J. Inorg. Chem.* **2017**, 2040–2047.

(14) For O-H reductive elimination of metal-bound alkoxides, see: (a) **Rhodium:** Milstein, D. Carbon-hydrogen vs. oxygen-hydrogen reductive elimination of methanol from a metal complex. Which is a more likely process? *J. Am. Chem. Soc*. **1986**, *108*, 3525–3526. (b) **Iridium:** Glueck, D. S.; Winslow, L. J. N.; Bergman, R. G. Iridium Alkoxide and Amide Hydride Complexes. Synthesis,

Reactivity, and the Mechanism of Oxygen-Hydrogen and Nitrogen-Hydrogen Reductive Elimination *Organometallics* **1991**, *10*, 1462–1479. (c) Blum, O.; Milstein, D. Direct Observation of O–H Reductive Elimination from Ir^{III} Complexes *Angew. Chem. Int Ed*. **1995**, *34*, 229–231.