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Catalytic Diastereo- and Enantioselective Formation of All-Carbon Quaternary Centers: Ir-Catalyzed *tert*-(Hydroxy)prenylation of Alcohols and its Application to Modular Syntheses of Terpenoids

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by

Jiajie Feng, B.S.

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 2017

Dedication

To my family

and

my fiancée, and best friend – Yawei

Acknowledgements

First of all, I would like to thank my parents, Min and Danhua, for continuous understanding and support for my oversea study. As my very first teachers, you have sparked my curiosity towards natural science. Influence has lasted, as I have decided to pursue my career in chemistry. I would also like to thank my grandparents for your endless love and encouragement all over the time.

I must thank my supervisor, Professor Mike Krische for admitting me to UT for graduate study – it is a valuable experience. You have educated me a lot both inside and outside the lab. Your dedication to chemistry and expectations towards students have made me understand what a real professor should be like.

I am indebted to my fellow labmates and friends, Tom Luong and Victoria Garza, for the joys and tears we shared together. Your encouragement always lifts me up, and supports me through these years.

I would also like to say thanks to my committee members and other professors whom I have met: your generous help and inspiring discussion between us will be always appreciated. To my coworkers, Thomas, Binit, Florian, Kim, Yian, Yousef, and Ron: working with you is always educating and delightful, and I cannot achieve that much without your help. To other lab members, Eiji, Aakarsh, Inji, Xinqi, Zhaobin, Laina, Ian, John, Susumu, Suckchang, Wonchul, Julian, Michael, Xin (Sunny), Emma, Brannon, Patrick, Te-Yu (Ryan), Boyoung, Gang, Zach, Khoa, Wandi, Hiroki, Hongde, James, Seung Wook (Louis), Yuk-Ming, Leyah to name a few: you all make my lab life colorful, and I have spent wonderful time with you! To people in chemistry department, Betsy, Angela, Steve, Ian, Jordan, Roger to name a few: without your support, my projects

cannot even be finished. To my other dear friends: getting to know you all is my greatest fortune.

Last but not least, I would like to express my greatest appreciation to my significant one, confidant, and whole life partner – Yawei Liang. Thank you for your precious love that brings me endless power. Thank you for your kind understanding of my numerous nights and weekends I spent in lab. Thank you for taking the adventure with me. Without you, I cannot imagine that I can go that far.

Catalytic Diastereo- and Enantioselective Formation of All-Carbon Quaternary Centers: Ir-Catalyzed *tert*-(Hydroxy)prenylation of Alcohols and its Application to Modular Syntheses of Terpenoids

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The University of Texas at Austin, 2017

Supervisor: Michael J. Krische

All-carbon quaternary stereocenters are ubiquitous in bioactive natural products as well as pharmaceutical molecules. However, stereoselective access of these structural motifs is still a challenge in synthetic chemistry. Therefore, a general method that can construct quaternary carbon centers diastereo- and enantioselectively is in high demand. Redox-triggered stereoselective C-C bond forming reactions via metal-catalyzed transfer hydrogenation are able to avoid usage of sensitive preformed organometallic reagents and formation of stoichiometric metal waste. Efforts have been focused on the development of efficient methods for diastereo- and enantioselective generation of quaternary centers via iridium-catalyzed *tert*-(hydroxy)prenylation of alcohols and aldehydes. Applying this methodology to modular syntheses of terpenoid natural products oridamycin A, triptoquinones B and C, isoiresin and andrographolide in the most concise routes is described.

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Chapter 1: Transition-Metal-Catalyzed Enantioselective Formation of Acyclic All-Carbon Quaternary Stereocenters

1.1 HISTORY

A quaternary stereocenter, which is defined as a carbon atom connected to four different carbon substituents, is a scaffold commonly seen in natural products. As natural products and their derivatives/mimics are one of the major sources of new pharmaceuticals and agrochemicals,[1] it is not surprising that all-carbon quaternary centers are also frequently found in these drugs and insecticides (Figure 1.1).

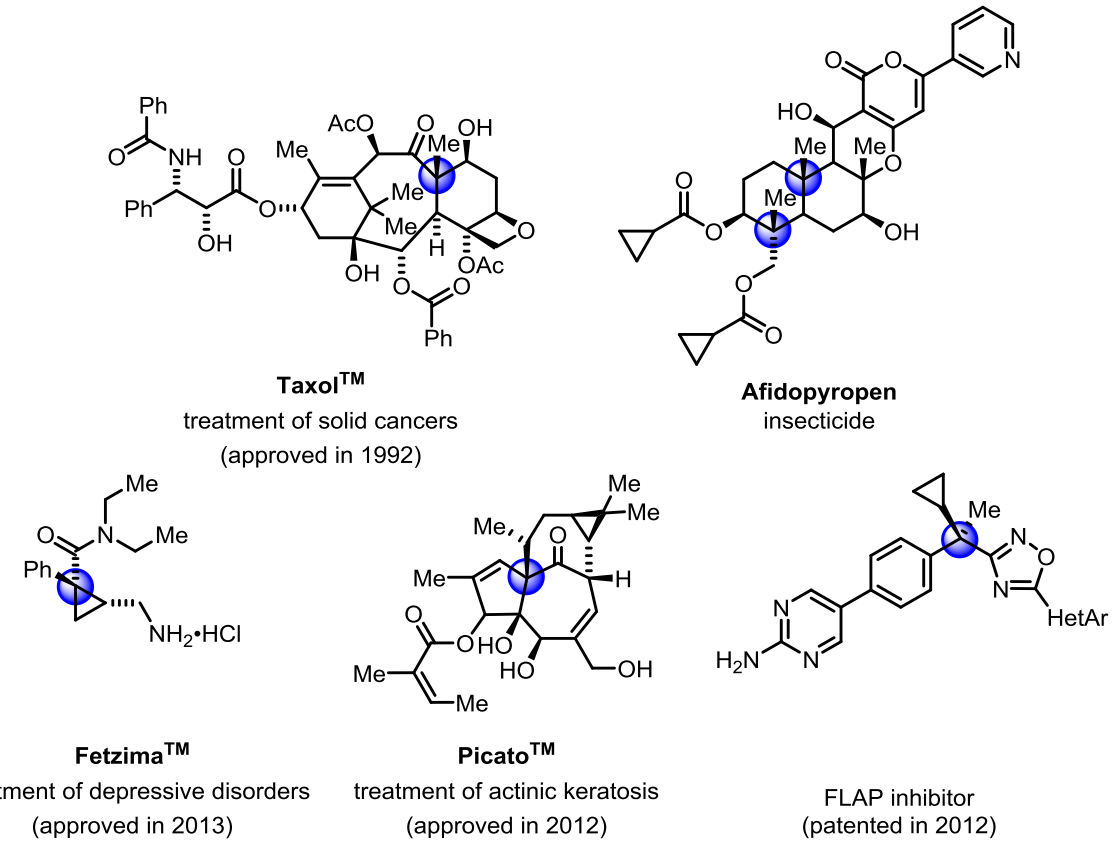
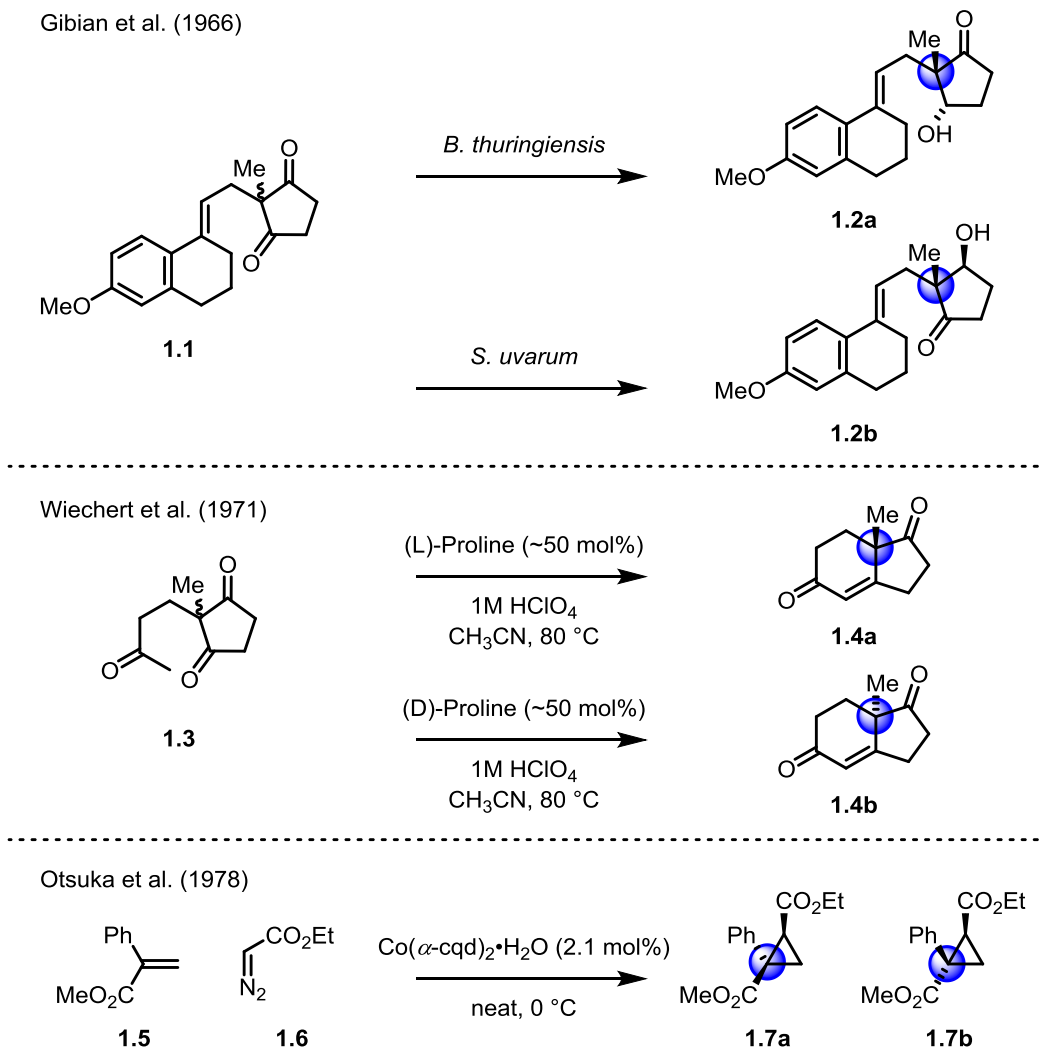


Figure 1.1 Examples of bioactive molecules with all-carbon quaternary stereocenters.

However, almost every stereogenic quaternary center in commercialized pharmaceutical drugs inherits directly from the chiral pool, with only a few exceptions, where they are formed via diastereoselective transformations controlled by the chirality of substrates.[2,3] This explicitly illustrates that enantioselective construction of such stereocenters[4–13] is still being considered as an unmet challenge. The difficulty of forming all-carbon quaternary centers efficiently and stereoselectively mainly arises from the congested environment around the targeted carbon atoms,[5] rendering them usually inaccessible to reactants and/or chiral reagents.

Fundamental interest and strong desire in industrial application has triggered intensive research in this area. The first report of enantioselective formation of all-carbon quaternary stereocenters from prochiral starting material was discovered in 1966, when chemists in Schering AG successfully applied microorganisms to obtain optically active products via selective reduction of diketone **1.1** (Scheme 1.1, top).[14] A few years later, Wiechert and coworkers published the first chemical catalytic method for enantioselective formation of quaternary centers via desymmetrizing Robinson annulation of **1.3** catalyzed by natural amino acids (Scheme 1.1, middle).[15] Since then reports regarding to construction of this motif became numerous in literature, and reactions beyond desymmetrization were also used. The emergence of asymmetric transition metal catalysis has brought in yet another powerful tool for organic chemists, as it has led to the discovery of more novel transformations with the possibility of introducing quaternary stereocenters. The first transition-metal-catalyzed enantioselective formation of quaternary center was reported by Nakamura and Otsuka in 1978. The chiral cobalt complex derived from camphor facilitated cyclopropanation of 1,1-disubstituted olefins in moderate enantiomeric excess (Scheme 1.1, bottom).[16,17] Significant progress has been made in the past 20 years[5,9] by numerous chemists towards this area of research.



Scheme 1.1 Early examples of enantioselective formation of all-carbon quaternary centers.

While formation of stereogenic quaternary centers in a ring becomes more accessible, similar chemistry in an acyclic system remains formidable. This is due to the larger degrees of freedom in molecules,[6,18] making it difficult for precise stereochemical control. Fortunately, organic chemists start to tackle this problem as a result of remarkable advance in metal catalysis during recent years.[4]

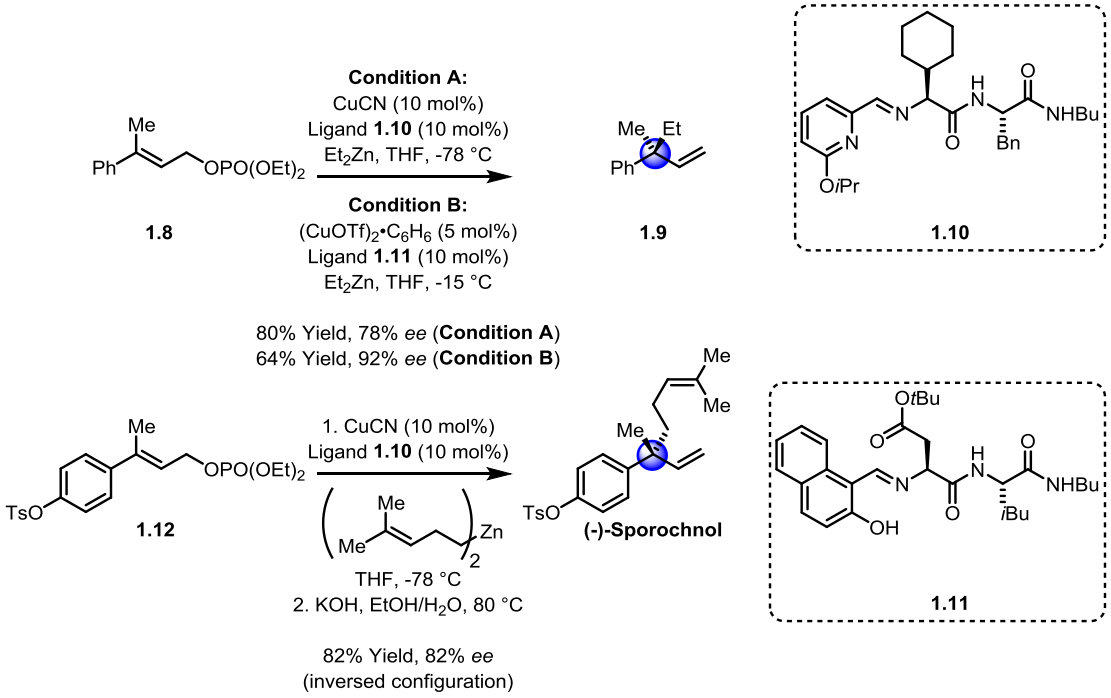
In this review, transition-metal-catalyzed reactions which enantioselectively form acyclic all-carbon quaternary stereocenters will be categorized by types of reactions. Desymmetrization of prochiral stereocenters,[19] which in theory can be applied through any reaction type, will be introduced in an individual section. The review will mainly focus on enantioselective synthesis of quaternary centers from achiral/prochiral substrates, and diastereoselective formation of these stereocenters based on preinstalled chiral centers in molecules[6,7,18] will not be discussed.

1.2 ALLYLIC SUBSTITUTION

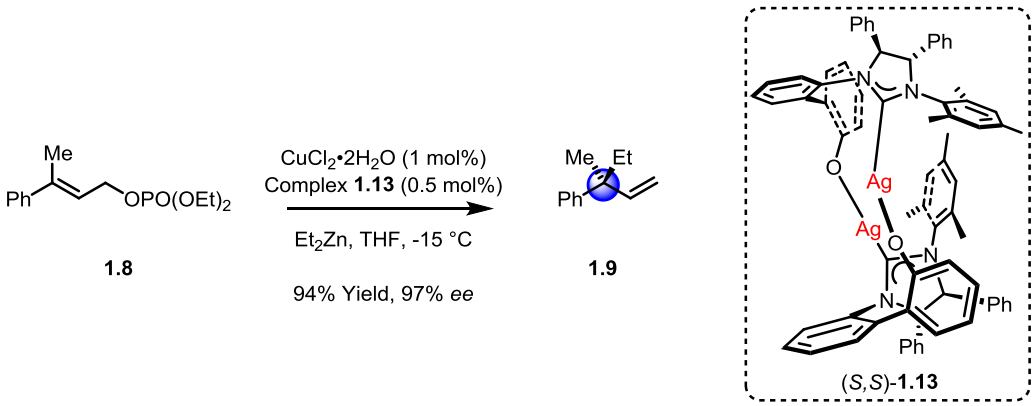
Enantioselective allylic substitution (EAS)[20,21] of γ,γ-disubstituted allyl compounds is one of the earliest methods that have been utilized for construction of acyclic all-carbon quaternary stereocenters. A formal S_N2' mechanism allows functionalization to occur at the more substituted carbons which will lead to the formation of quaternary centers. One of the advantages of utilizing EAS is the resulting terminal olefin in the product can be easily used for further derivatization. Copper catalysis have played a very important role in the development of these methodologies, and both sp^3- and sp^2- nucleophiles are successfully applied to these reactions.

In 2001, Hoveyda and coworkers reported an enantioselective Cu-catalyzed alkylation of *γ,γ*-disubstituted allylic phosphates with diethylzinc.[22] By using synthetic peptide-based ligands, good *ee*s (78%-90%) were achieved (Scheme 1.2). Interestingly, when the alkyl chain on zinc reagent became longer, the opposite enantioselectivity was observed. A more selective ligand **1.11** was discovered later, which led to both an improvement in enantioselectivities and a broader substrate scope (*e.g.*, trialkyl-substituted alkenes also obtained promising results) (Scheme 1.2).[23] The same research group developed a second-generation catalytic system in 2004. Utilizing Ag-NHC

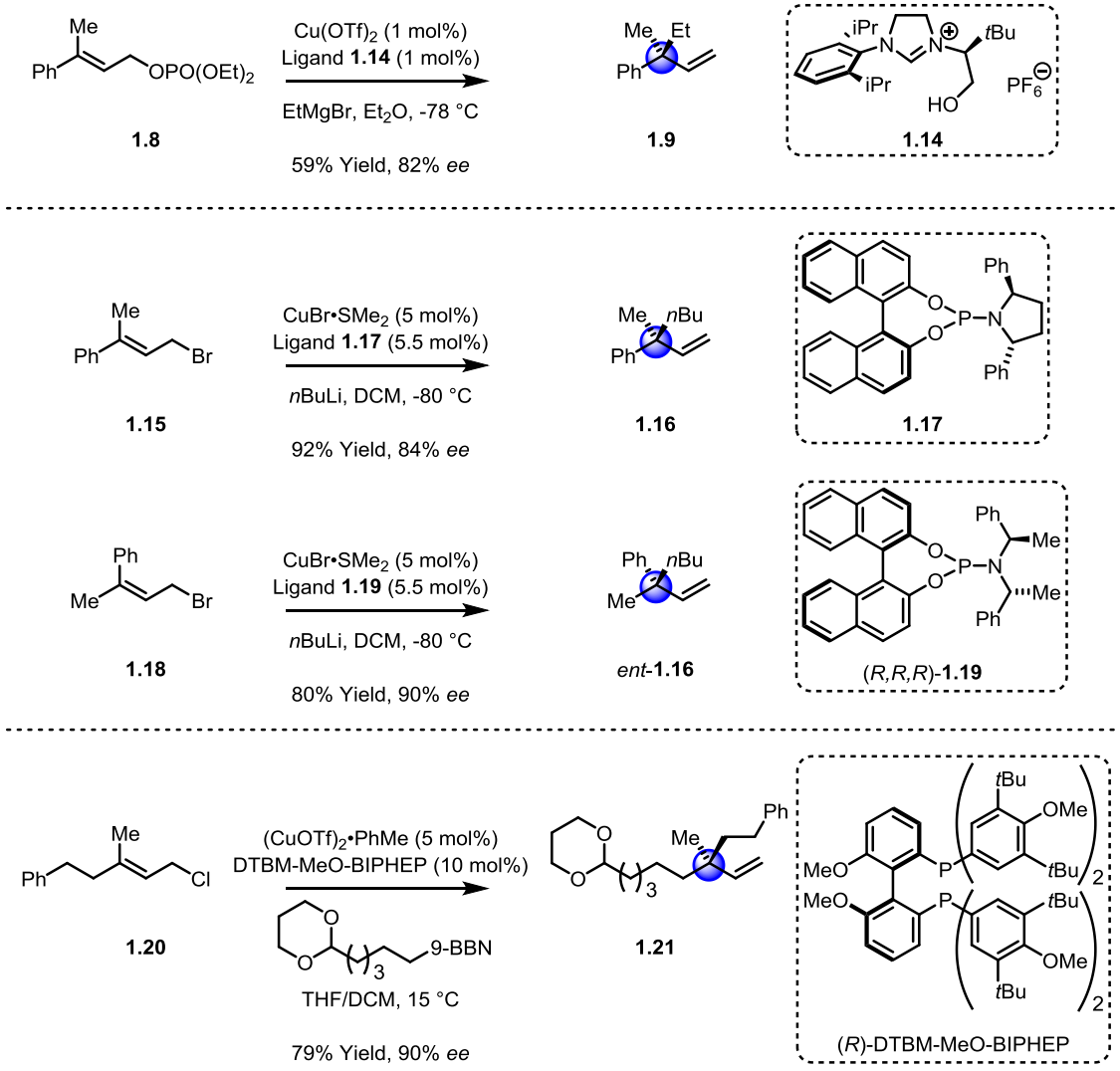
complexes as precursors permitted a much lower loading of copper catalyst (1 mol% vs. 10 mol%), and continued to enhance the enantioselectivities of reactions (Scheme 1.3).[24,25]



Scheme 1.2 Cu-catalyzed alkylation of trisubstituted alkenes with peptide-based ligands.



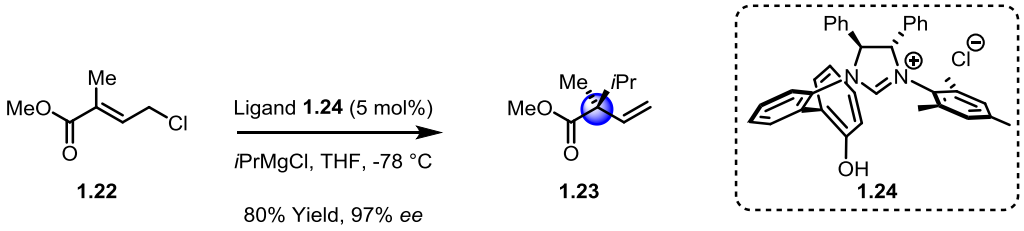
Scheme 1.3 Cu-catalyzed alkylation of trisubstituted alkenes with NHC-based ligands.



Scheme 1.4 Cu-catalyzed alkylation of trisubstituted alkenes with various organometallic reagents.

Besides air and moisture sensitive dialkylzinc reagent, Grignard reagents,[26–28] organolithiums,[29,30] and even the more stable alkyl boron reagents[31] were also used for the formation of quaternary stereocenters via Cu-catalyzed allylic substitution. Mauduit and coworkers applied a hydroxyalkyl NHC-ligand for reaction between Grignard reagents and allylic phosphates, leading to good to excellent regioselectivity (S_N2':S_N2)

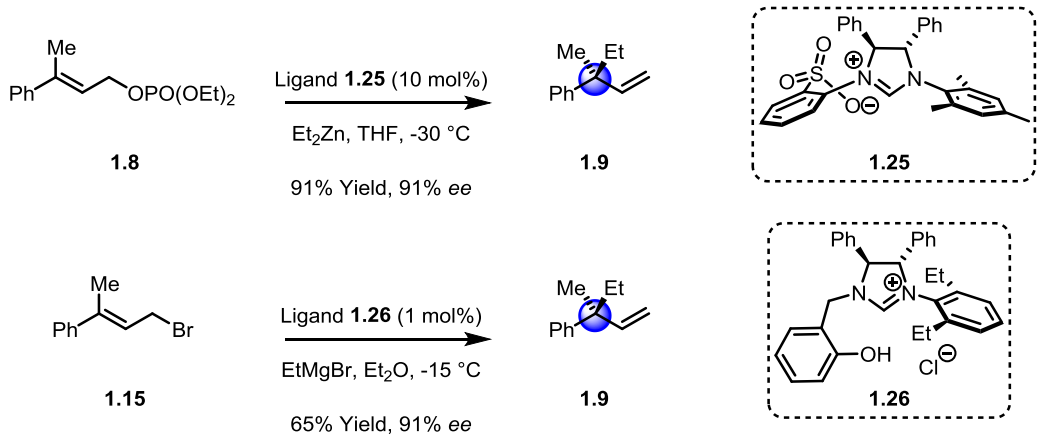
as well as good enantioselectivity (82%-87% *ee*) (Scheme 1.4, top).[28] Feringa and coworkers found that the phosphoramidites could be used as ligands for highly regio- and enantioselective alkylation of (*E*)-[29] and (*Z*)-allyl bromides[30] with alkyllithium (Scheme 1.4, middle). It should be noted that previously allylic substitution of (*Z*)-olefins usually suffered from slow reaction rate and inferior enantioselectivity.[25,31] In 2014, Sawamura and coworkers managed to utilize 9-alkyl-9-BBN (prepared from terminal olefins *in situ*) in copper-catalyzed alkylation of *γ,γ*-dialkyl substituted allylic chlorides.[31] With bidentate phosphine ligand DTBM-MeO-BIPHEP, good to excellent enantioselectivity (71%-90% *ee*) was able to be achieved (Scheme 1.4, bottom).



Scheme 1.5 Cu-free alkylation of *α,β*-unsaturated ester with Grignard reagents.

Copper-free asymmetric alkylation of trisubstituted olefins with dialkylzinc[32] and Grignard reagents[33–35] was also reported. Hoveyda and coworkers found that *α*-alkyl-*γ*-chloro-*α,β*-unsaturated ester could be alkylated at the α-position in the presence of a bidentate NHC-ligand (Scheme 1.5).[33] A few years later, the same research group discovered that the previously explored *γ*-alkyl-*γ*-aryl substituted allylic phosphate could also be alkylated by zinc reagents without copper salt, via switching to a different NHC-ligand (Scheme 1.6, top).[32] Alexakis and coworkers reported a similar transformation, yet using the more readily available Grignard reagents and allyl bromide instead (Scheme 1.6, bottom). The optimal NHC-ligand **1.26** which could provide high regio- and enantioselectivity at relatively low loading was identified after a thorough screening.[34,35]

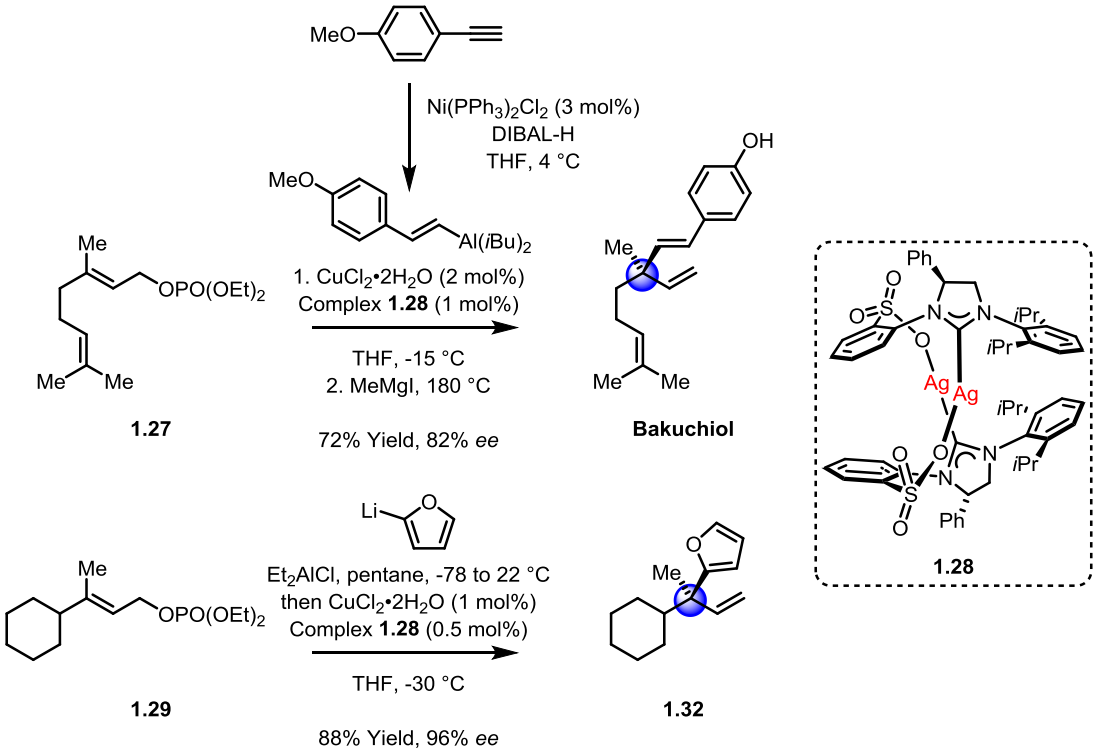
Remarkably, the selectivities of these copper-free conditions are comparable to those with Cu catalysts. Mechanistic study suggested that the Mg/Zn-NHC complex is the active catalyst in these Cu-free processes.[32]



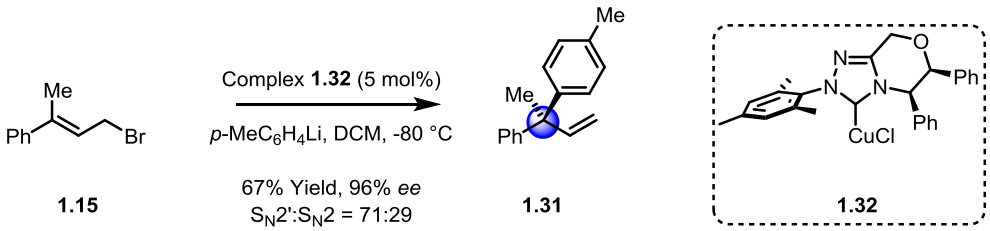
Scheme 1.6 Cu-free alkylation of trisubstituted olefins with NHC-ligands.

Copper-catalyzed alkenylation and arylation of *γ,γ*-disubstituted allylic compounds via S_N2' substitution was also achieved in the last decade. Hoveyda and coworkers reported that vinyl-[36] and arylaluminum[37] reagents (*in situ* prepared from hydroalumination of activated terminal alkynes and transmetallation from aryllithium reagents, respectively) were able to proceed highly enantioselective allylic substitution to generate quaternary stereocenters catalyzed by copper-NHC complex (Scheme 1.7). It is suggested that vinyl- and aryl- groups are favored over alkyl units in transmetallation from aluminum to copper. Aryllithium itself was later proved to be useful for Cu-catalyzed allylic substitution of allyl bromide using a triazolium derived NHC ligand by Feringa and coworkers, though in certain cases unsatisfactory regioselectivity was observed (Scheme 1.8).[38] Recently the Hoveyda[39] and Hayashi[40,41] groups also successfully applied organoboronates to asymmetric vinyl- and arylation of *γ,γ*-

disubstituted allylic phosphates (Scheme 1.9), in which cryogenic conditions were not required.



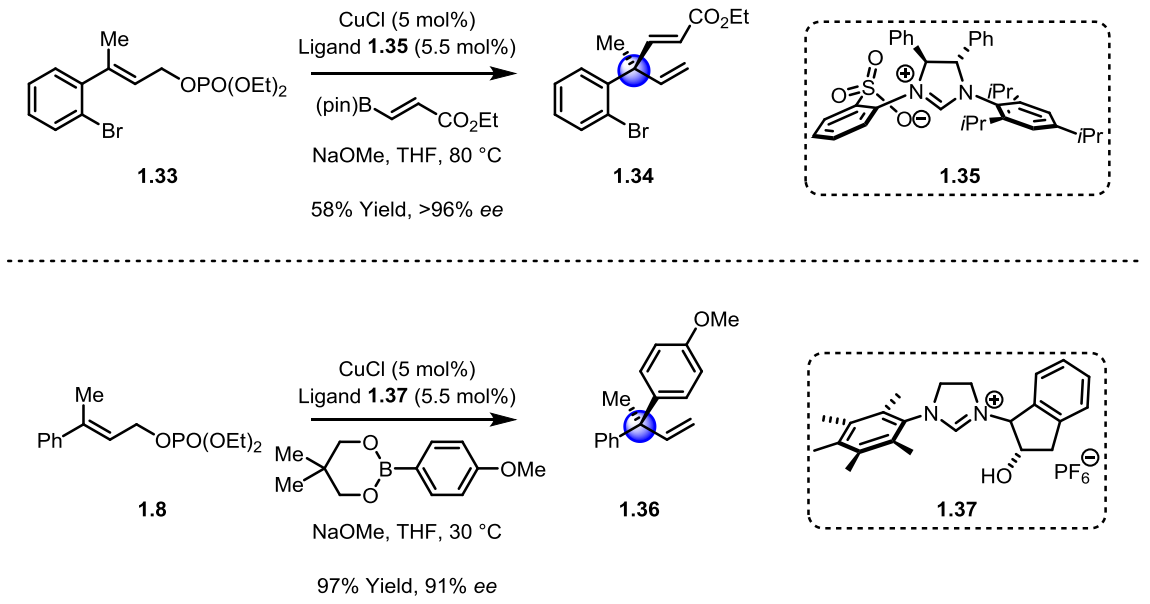
Scheme 1.7 Enantioselective vinyl- and arylation of trisubstituted olefins with aluminum reagents.



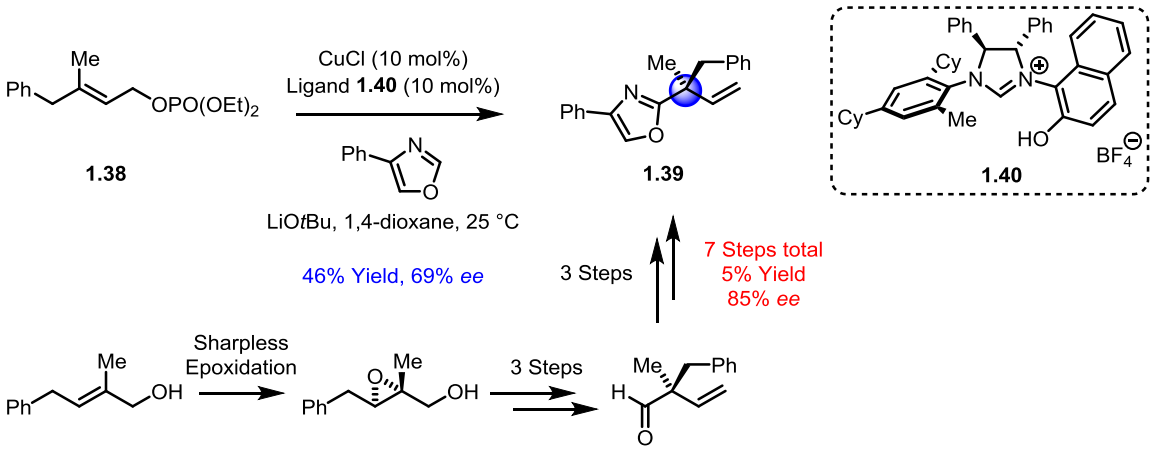
Scheme 1.8 Enantioselective arylation of trisubstituted olefins with lithium reagents.

In another case, heterocycles were also enantioselectively incorporated onto allylic phosphates via copper catalyzed C-H activation.[42] Substituted thiazoles and oxazoles were used to form quaternary stereocenters at the α-position of heteroarenes.

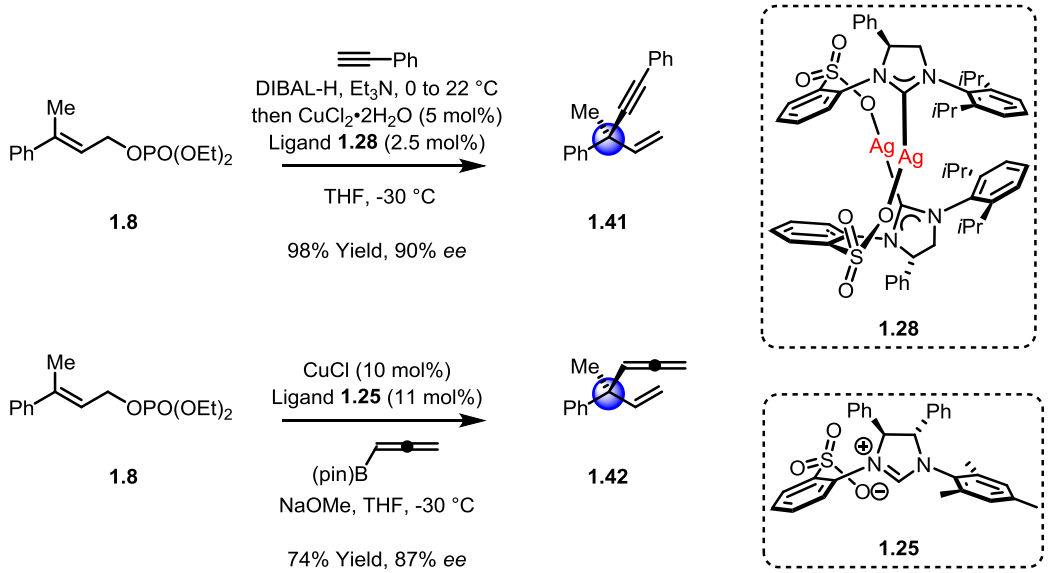
The authors demonstrated quick access to an otherwise difficult to synthesize compound by this newly developed methodology (Scheme 1.10).



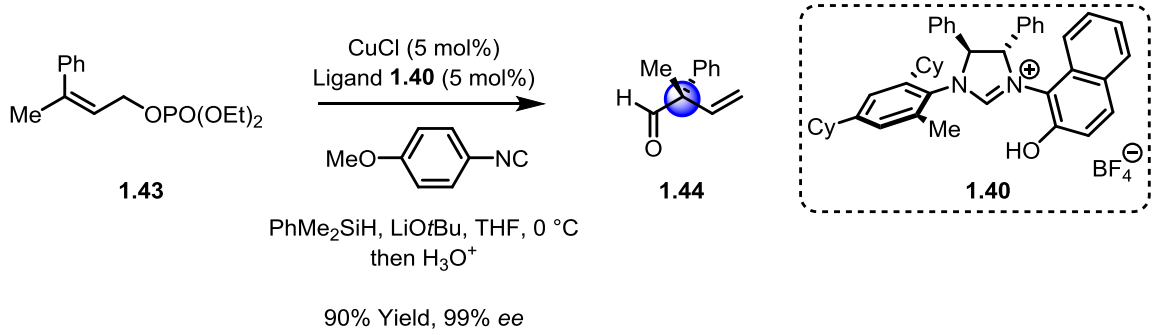
Scheme 1.9 Hoveyda (top) and Hayashi's (bottom) protocols for vinyl- and arylation of trisubstituted olefins with organoboronates.



Scheme 1.10 Sawamura's protocol to introduce quaternary stereocenters at α-position of heterocycles.



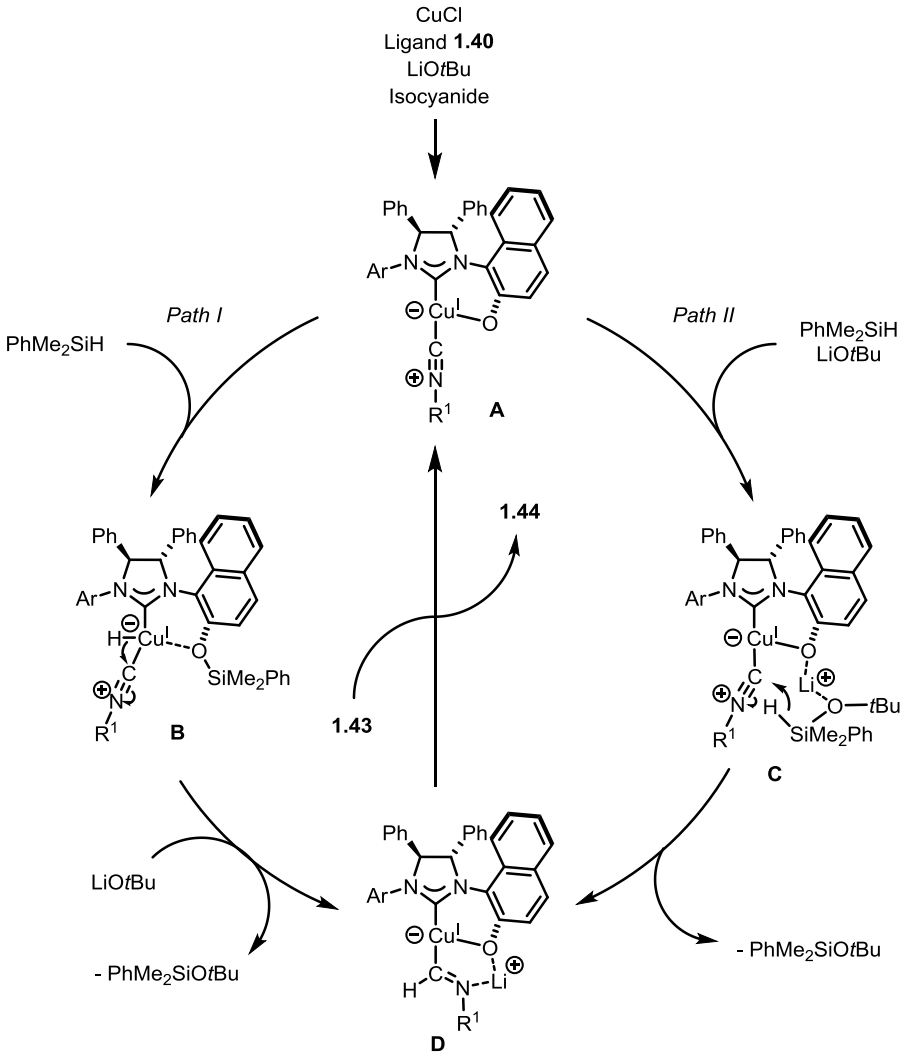
Scheme 1.11 Cu-catalyzed alkynylation and allenylation of trisubstituted olefins.



Scheme 1.12 Enantioselective formylation of trisubstituted olefins with isocyanides.

Alkynylation[43] and allenylation[44] of trisubstituted olefins via copper-catalyzed EAS were also reported in literature (Scheme 1.11). Sawamura and coworkers have recently developed a method for formylation of (*Z*)-allylic phosphate with isocyanides and dimethylphenylsilane (Scheme 1.12).[45] The authors proposed two possible pathways for the formation of formimidoylcopper(I) species (Scheme 1.13, **D**): Path I involves a copper-hydride intermediate (Scheme 1.13, **B**) followed by a 1,1-insertion of isocyanide;

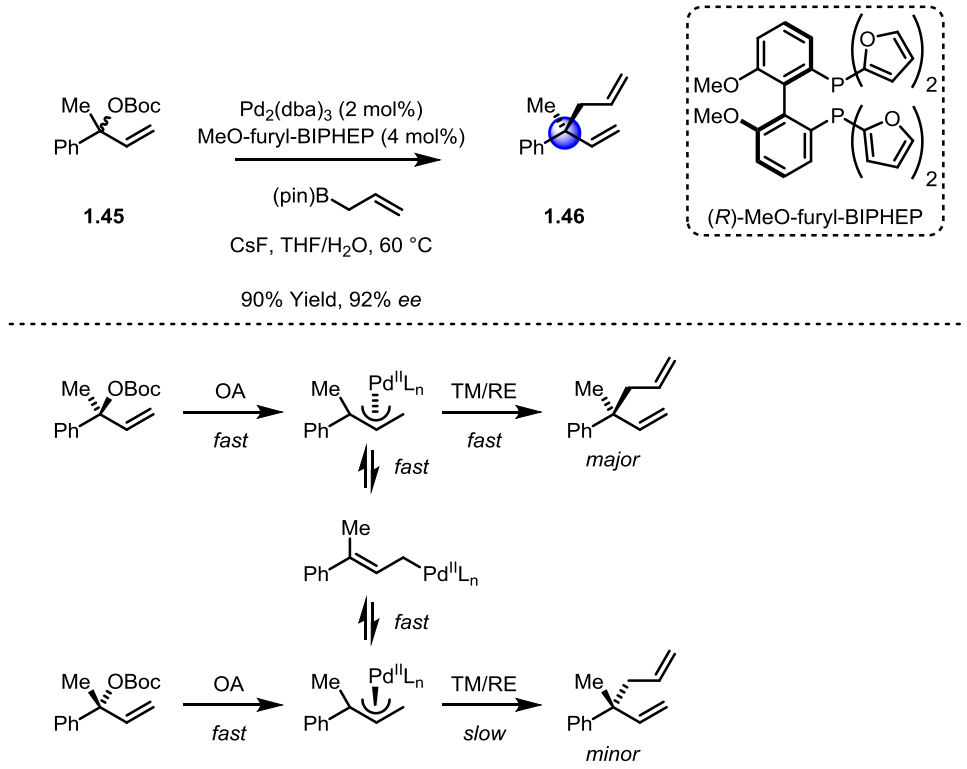
Path II suggests a direct hydride transfer from silane to isocyanide via base activation (Scheme 1.13, **C** to **D**). Then the new C-C bond forms via S_N2' attack from the imidoyl carbon or oxidative addition/reductive elimination pathway (Scheme 1.13, **D** to **A**).



Scheme 1.13 Plausible mechanisms of formylation of trisubstituted olefins with isocyanides.

Morken and coworkers reported a palladium-catalyzed allylation of allylic carbamates to generate all-carbon quaternary centers.[46] Racemic tertiary allylic

carbamates could be used and good enantioselectivity was achieved through a DyKAT (Dynamic Kinetic Asymmetric Transformation) process[47] (Scheme 1.14).

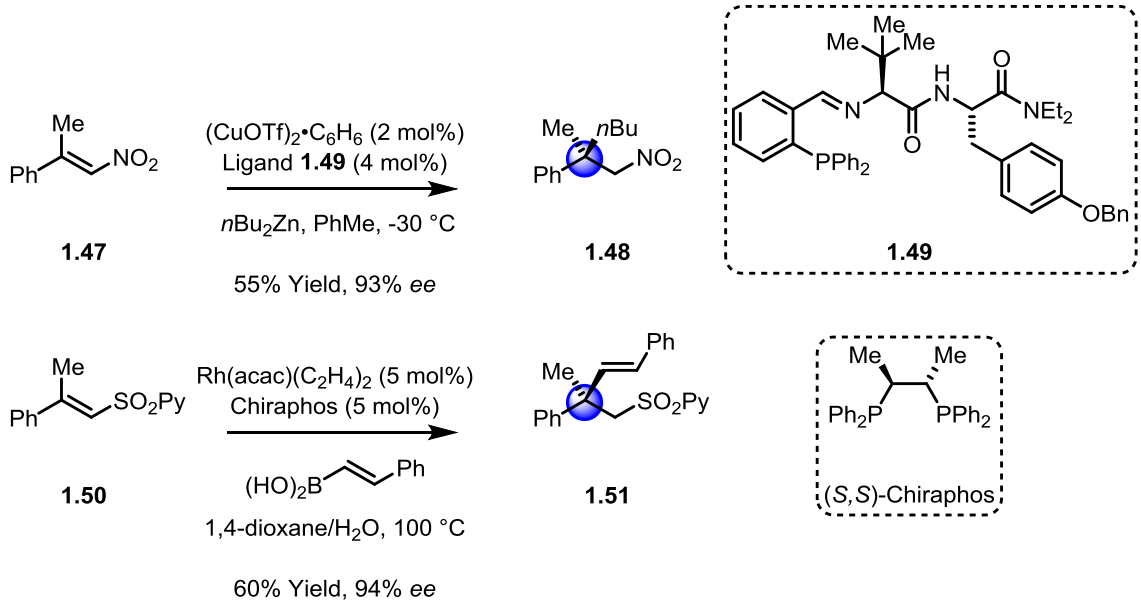


Scheme 1.14 Pd-catalyzed enantioselective allylation of allyl carbamates (top) and DyKAT mechanism of reaction (bottom).

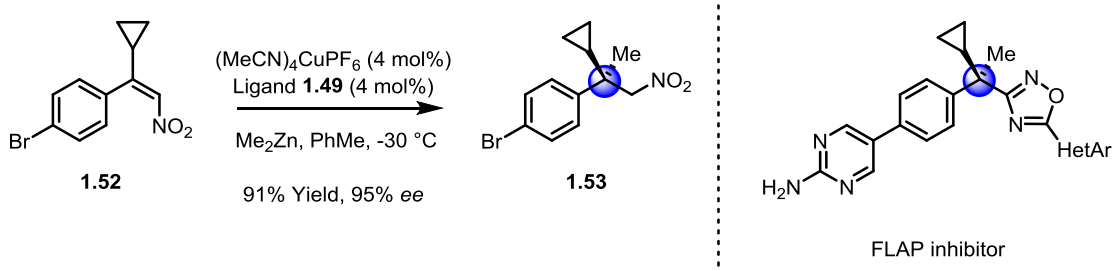
1.3 CONJUGATE ADDITION

Similar to allylic substitution, conjugate addition[48] to *β,β*-disubstituted enones (enoates, nitroalkenes, etc.) was also widely utilized to construct acyclic quaternary centers.[49] Initially, however, transition metal complexes (for example, Rh,[50–54] Pd,[55–57] Pt,[58] La[59], Ni,[60] Ir,[61] etc.) was used as chiral Lewis acid catalysts to promote reactions between *α,β*-unsaturated carbonyl compounds and enolates/enamines. It was not until 2005 that metal catalysis started playing more roles in the formation of acyclic all-carbon quaternary stereocenters. Hoveyda and coworkers reported copper-catalyzed conjugate

addition of dialkylzinc to (*E*)-nitroalkenes with peptide-based ligands,[62] while in the same year Carretero group published a communication about rhodium-catalyzed addition of alkenylboronic acids to unsaturated sulfones with bidentate Chiraphos (Scheme 1.15).[63] The former chemistry gained attention from process chemists from Boehringer Ingelheim, due to its potential use in synthesizing an active pharmaceutical ingredient (API). After a detailed study, previously retarded methylation of trisubstituted (*Z*)-nitroalkenes was optimized to excellent yield and enantioselectivity (Scheme 1.16).[64]

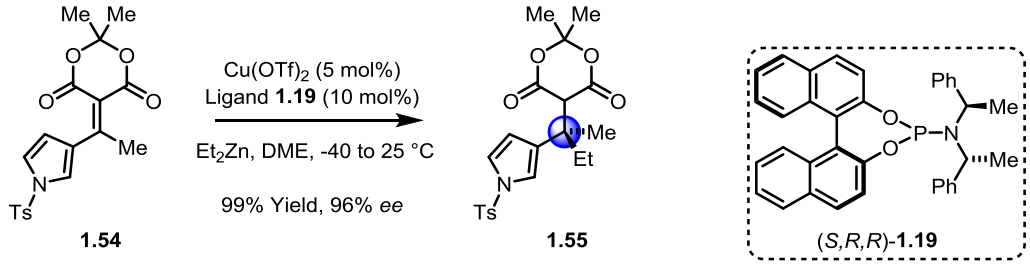


Scheme 1.15 Asymmetric conjugate addition to nitroalkenes (top) and vinyl sulfones (bottom) to generate quaternary stereocenters.



Scheme 1.16 Improved condition for conjugate addition to nitroalkenes.

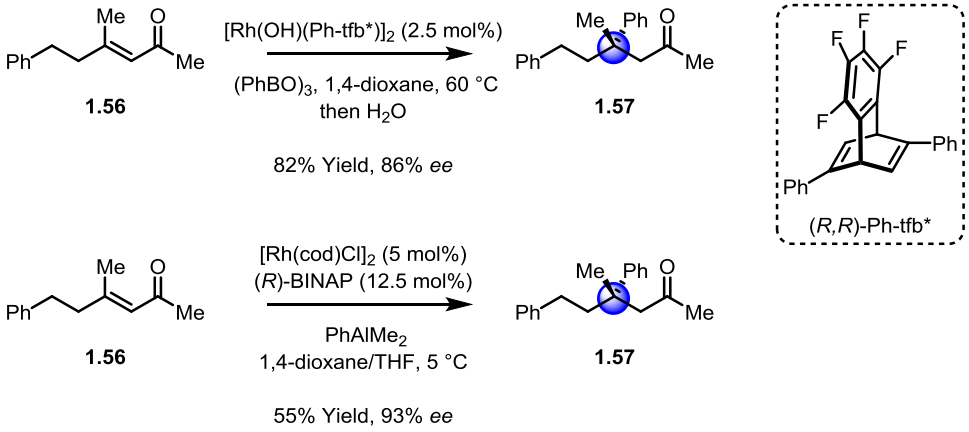
The highly reactive alkylidene Meldrum's acids were also used as substrates for enantioselective conjugate addition. Fillion and coworkers have developed a protocol for enantioselective alkylation of arylalkylidene Meldrum's acids with dialkylzinc under copper-catalyzed condition (Scheme 1.17).[65–68] However, the substrate scope was very limited.



Scheme 1.17 Cu-catalyzed asymmetric alkylation of alkylidene Meldrum's acids.

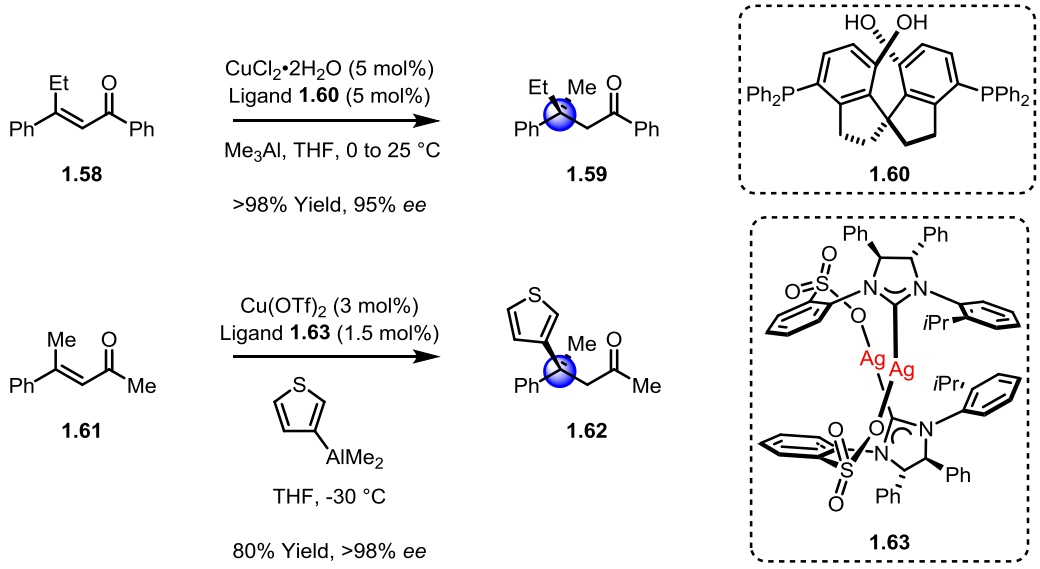
The more flexible and less reactive acyclic *α,β*-unsaturated carbonyl compounds turn out to be very challenging targets for asymmetric conjugate addition to generate all-carbon quaternary centers. Unlike in cyclic systems, release of ring strain cannot become the driving force of all reactions. In addition, chiral ligands used in cyclic enones/enoates (usually in (*Z*)-configuration) might not be effective in acyclic systems (more often with (*E*)-configuration) and need to be reinvestigated.

Breakthrough was first obtained from rhodium catalysis with chiral diene ligands. Shintani and Hayashi reported arylation of *β,β*-disubstituted unsaturated ketones and esters with tetraarylborates[69,70] as well as the more readily available and atom-economic reagent arylboroxines (Scheme 1.18, top).[71] Woodward and Alexakis also found that the more active aryldimethylaluminum could be applied to similar Rh-catalyzed transformation by using the more common ligand BINAP (Scheme 1.18, bottom).[72]

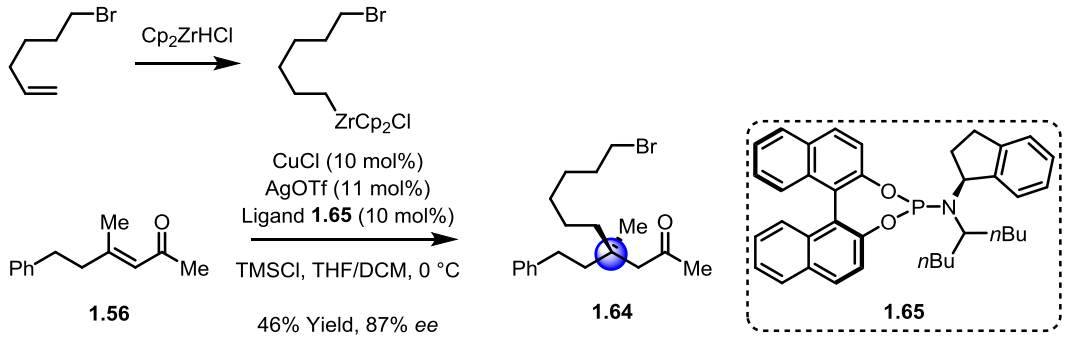


Scheme 1.18 Rh-catalyzed enantioselective arylation of acyclic unsaturated ketones.

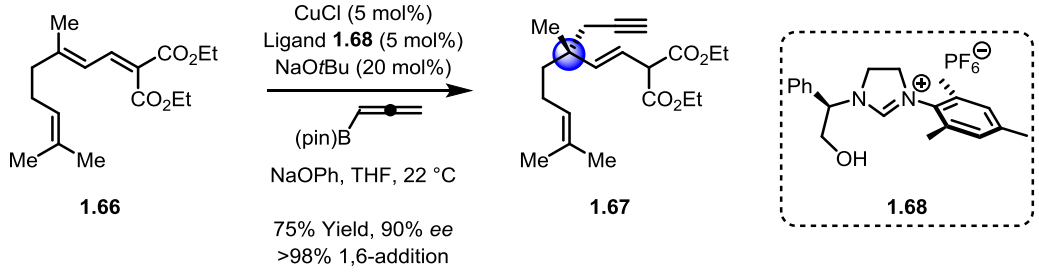
Highly enantioselective copper-catalyzed conjugate addition to acyclic *β,β*-disubstituted enones was developed as well. Endo and Shibata disclosed methylation of various *α,β*-unsaturated ketones using trimethylaluminum with ligands bearing phosphine and hydroxyl moieties (Scheme 1.19, top).[73] Later, Hoveyda and coworkers generalized the nucleophiles to vinyl,[74] aryl- and more alkylaluminum reagents[75] with their NHC ligands (Scheme 1.19, bottom). Recently, Fletcher and coworkers used Schwartz reagent to generate alkylzirconium *in situ* from terminal alkenes and added them to enones in good to excellent *ee*s (Scheme 1.20).[76] It has significantly expanded the scope of introduced alkyl functionality which used to be limited by the availability of aluminum reagents.



Scheme 1.19 Cu-catalyzed enantioselective functionalization of acyclic *β,β*-disubstituted enones with aluminum reagents.

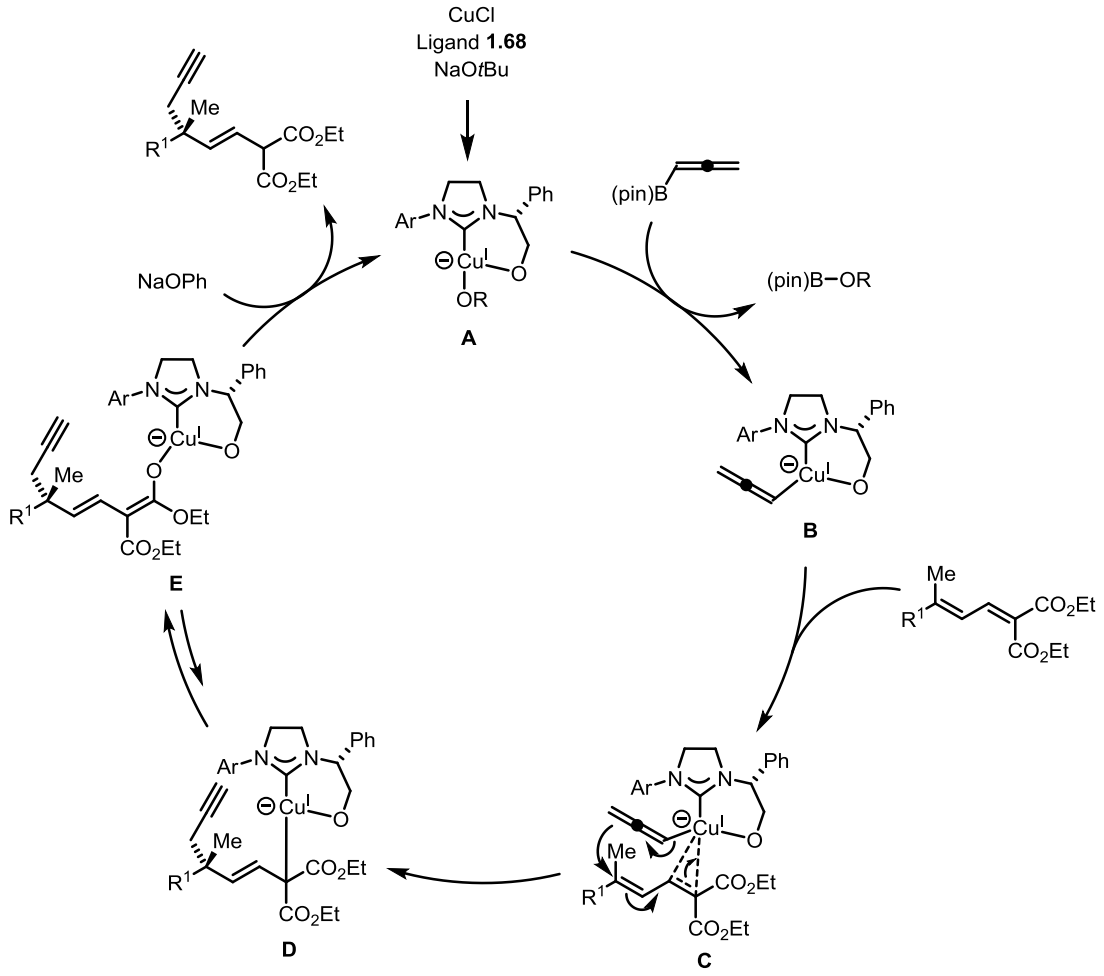


Scheme 1.20 Cu-catalyzed alkylation acyclic *β,β*-disubstituted enones with terminal olefins.



Scheme 1.21 Cu-catalyzed asymmetric propargylation of dienoates by 1,6-addition.

Hoveyda and coworkers recently reported an enantioselective 1,6-addition of propargyl groups to *α,β,γ,δ*-unsaturated esters.[77] By using NHC instead of phosphine ligands, 1,6-adducts were exclusively obtained over 1,4-addition byproduct, despite the fact that *β*-position of dienoates has the largest LUMO coefficient (Scheme 1.21).



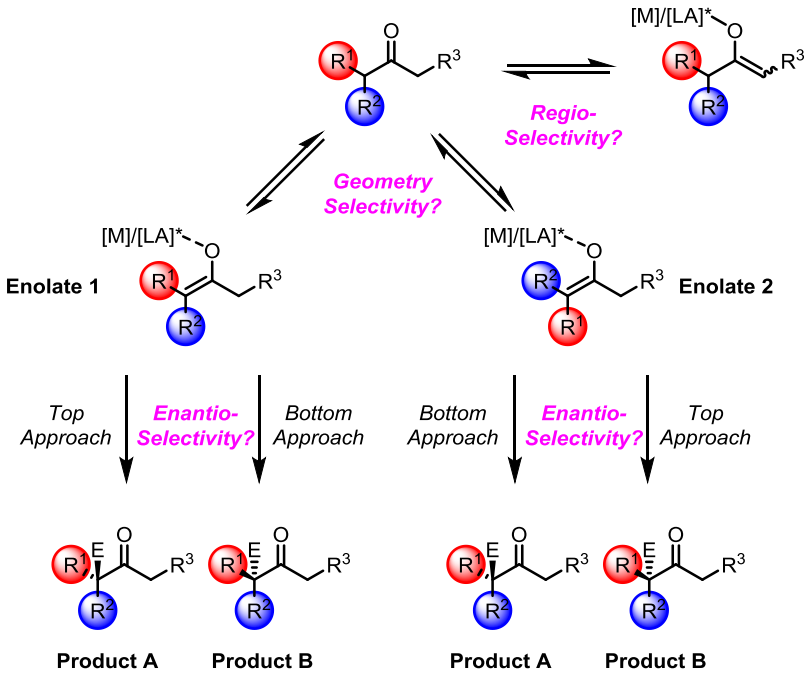
Scheme 1.22 Proposed mechanism for Cu-catalyzed asymmetric propargylation of dienoates by 1,6-addition.

The authors accounted for this selectivity by a mechanism that allenylcopper species coordinates to the *α,β*-π bond due to the strong σ-donating NHC ligand, followed

by a 3,3'-addition which will form the C-C bond at δ-position (Scheme 1.22). Interestingly, using the same allenylboronate in reaction with allylic phosphates under a copper-NHC catalytic condition, allenylation products were obtained instead.[44]

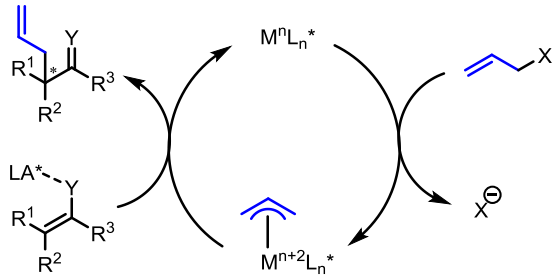
1.4 *ALPHA*-FUNCTIONALIZATION OF CARBONYL COMPOUNDS/IMINES

The α-position of carbonyl compounds (imines, nitriles, etc.) is nucleophilic under basic conditions or via activation by Lewis acids. When α,α-disubstituted substrates attack carbon-electrophiles, all-carbon quaternary centers will form. The major obstacle to developing a catalytic enantioselective protocol is that the catalysts not only need to differentiate the enantiotopic faces of enolates/enamines, but also should be able to preferentially react with one of the two possible geometrical isomers and avoid forming the less substituted regiomer during enolate formation step (Scheme 1.23).[78]

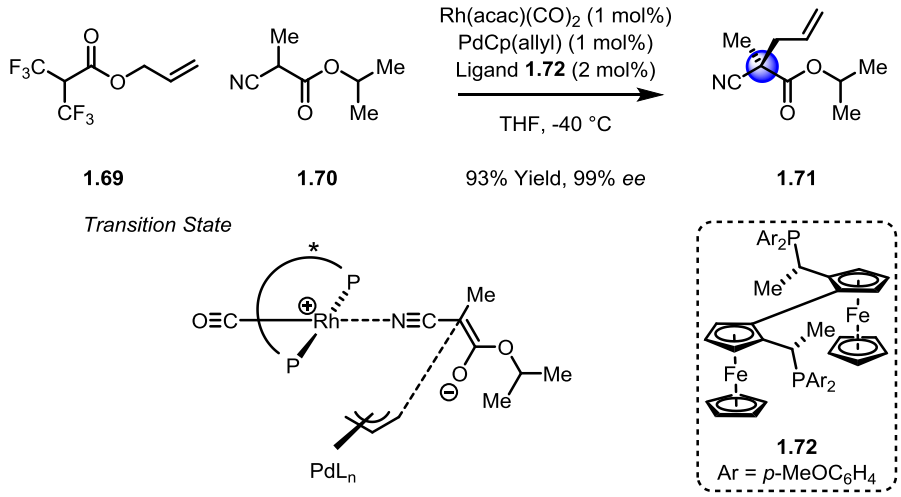


Scheme 1.23 Multiple selectivity issues in stereoselective α-functionalization of carbonyl compounds.

Similar to conjugate addition, transition metal complexes are only acting as a Lewis acid in some cases,[79,80] while metal catalysis is playing a more crucial role at other times. α-Allylation of carbonyl compounds via Tsuji-Trost reaction[81] is one of the most common methods for quaternary stereocenter formation. A general reaction mechanism is shown below (Scheme 1.24): metal catalysts oxidatively add to the allylic substrates to form allyl-metal species, which are attacked by enolate/enamine nucleophiles to form the C-C bonds. Enantioselectivity of reactions can be controlled by chiral ligands on metals, chiral Lewis acids on enolates, or both synergistically. Besides that, branch/linear selectivity can be an issue sometimes when unsymmetrical allylic substrates are used.

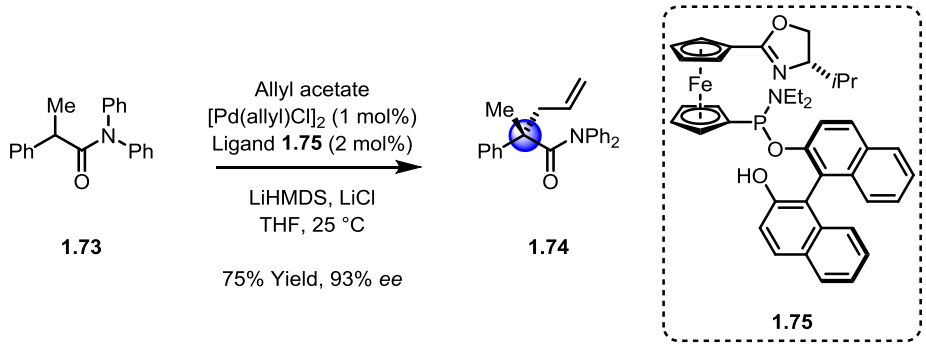


Scheme 1.24 General mechanism for α-allylation of carbonyl compounds.



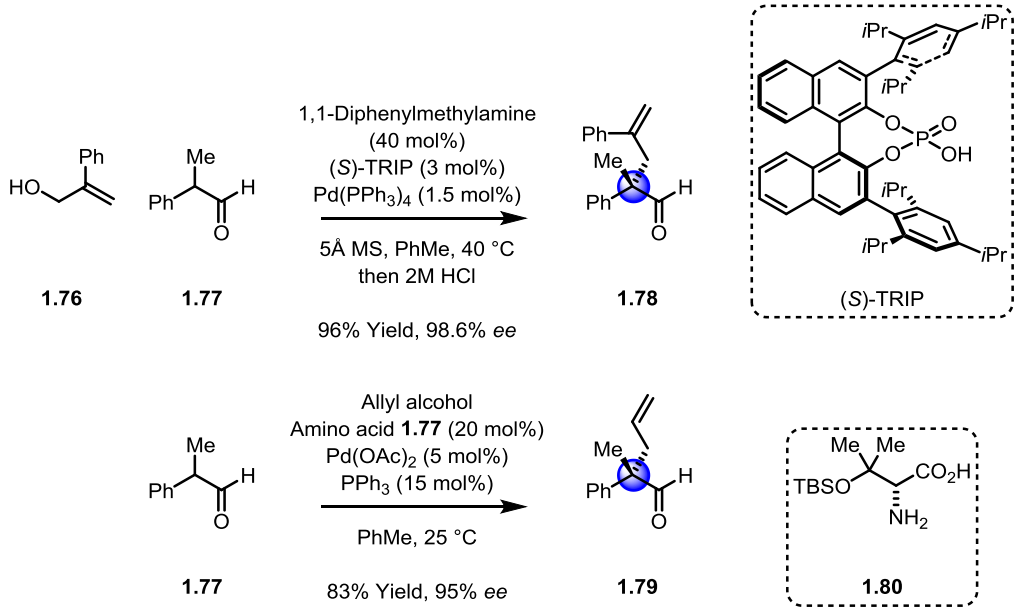
Scheme 1.25 Two-component catalyzed asymmetric α-allylation of cyanoesters.

Palladium catalysts are widely used in this type of transformations. Sawamura and Ito reported a Pd-Rh dual-catalyzed allylation of α-cyanoester with their TRAP ligands in 1996.[82] While palladium participated in the formation of allyl species, rhodium-TRAP complex was coordinated to the cyano group of (*Z*)-enolate and controlled the stereochemical outcome (Scheme 1.25). Hou and coworkers successfully introduced an allyl group to an α,α-disubstituted amide enantioselectively with a ferrocene derived ligand (Scheme 1.26).[83] Similar transformation with using α-aryl-β-hydroxyacrylates as substrates was also reported by Hossain and coworkers.[84]

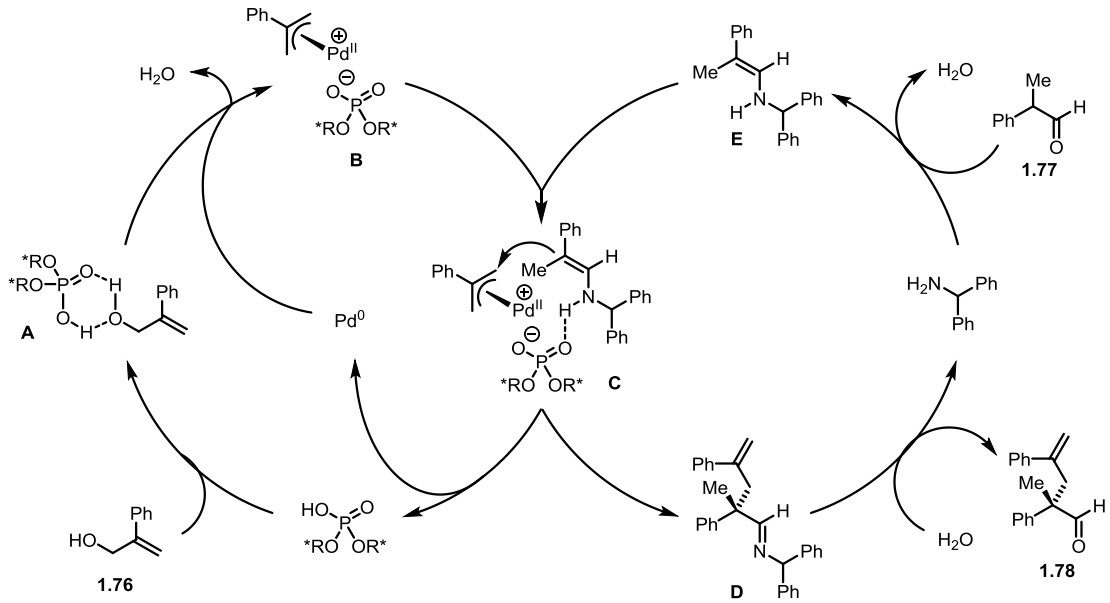


Scheme 1.26 Enantioselective allylation of an α,α-disubstituted amide.

The corresponding enolates/enols of α,α-disubstituted aldehydes are usually formed as a mixture of (*E*)- and (*Z*)- isomers, which makes the stereochemical control even more difficult (Scheme 1.23). This challenge was first overcome by forming more stereodefined enamines stoichiometrically or catalytically in the reactions. List and coworkers described a strategy of generating single-configuration enamines *in situ* (Scheme 1.28, **E**), and delivering the allyl group to α-carbon via a locked transition state (Scheme 1.28, **C**) involving a chiral phosphoric acid (Scheme 1.27, top).[85,86] A similar strategy was also applied by Yoshida and coworkers with chiral amino acids (Scheme 1.27, bottom).[87,88]

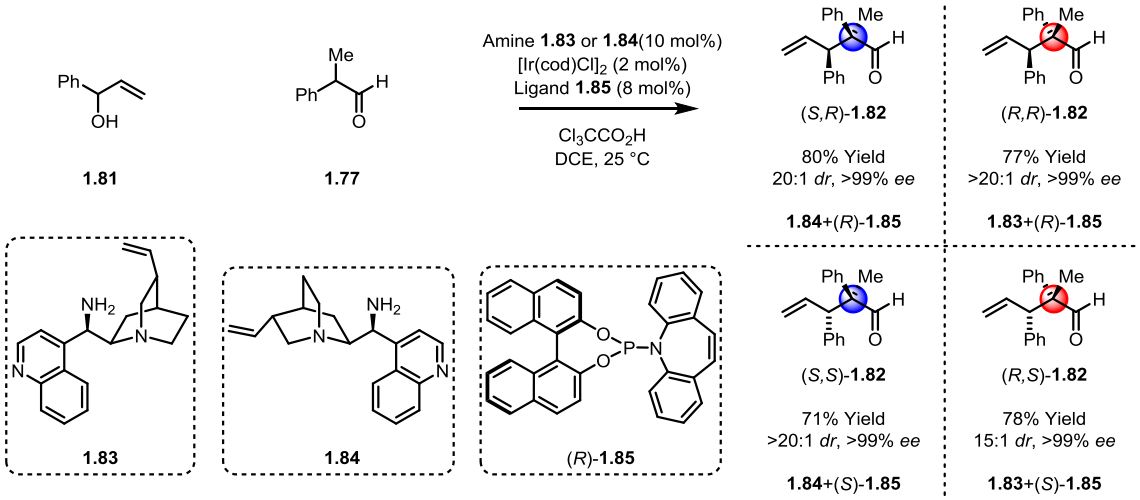


Scheme 1.27 Enantioselective allylation of α,α-disubstituted aldehydes with allyl alcohols and amine/acid catalysts.

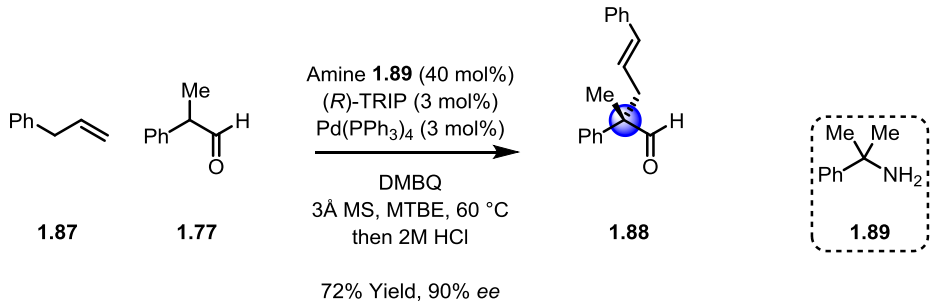


Scheme 1.28 Proposed mechanism for allylation of α,α-disubstituted aldehydes via dual catalysis.

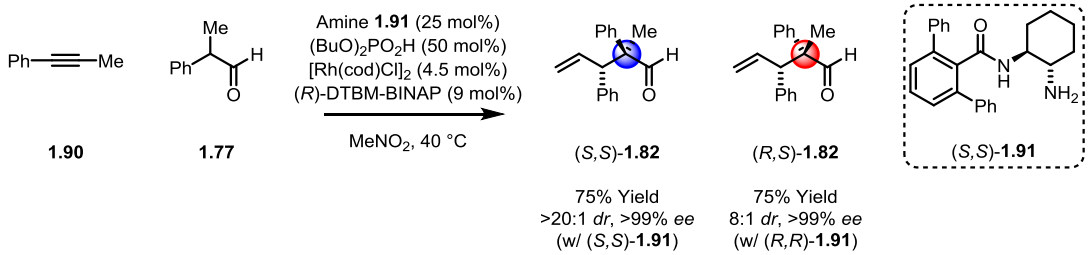
Later, Carreira and coworkers moved one step forward: an iridium/amine-catalyzed system was used in asymmetric allylation of α,α-disubstituted aldehydes. Absolute configurations of the two stereocenters generated in this reaction could be controlled by the chiral ligands on the metal center and the optically active amine catalysts, respectively (Scheme 1.29).[89] Gong and coworkers reported an oxidative coupling between α-branched aldehydes and 3-phenylpropyl-1-ene via palladium/amine-catalyzed allylic C-H activation, which offered an alternative method for allylating the α-position of aldehydes (Scheme 1.30).[90] Recently, Dong and coworkers discovered that 4-aryl-2-butynes could be also transformed into allyl species (Scheme 1.31, **D**) under rhodium-catalyzed condition via isomerization/hydrometallation mechanism, and added to chiral enamines (Scheme 1.31, **E**) from α,α-disubstituted aldehydes in high enantioselectivity and in a stereodivergent manner (Scheme 1.31).[91] It provided a complementary strategy of Carreira's methodology using alkynes instead of allyl alcohols as starting material.

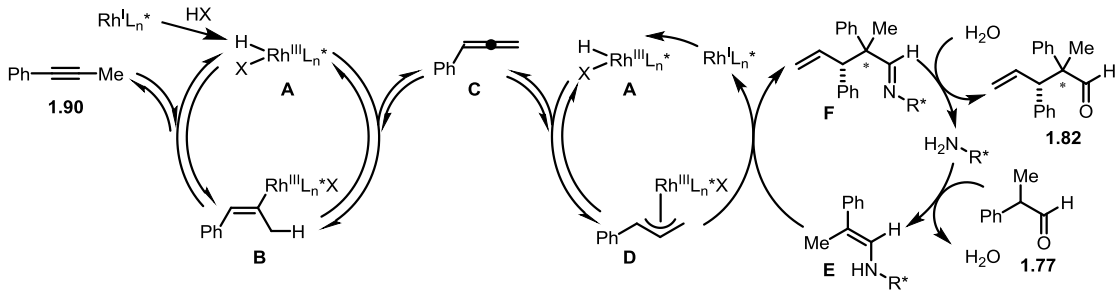


Scheme 1.29 Stereodivergent synthesis of allylated α,α,α-trisubstituted aldehydes.



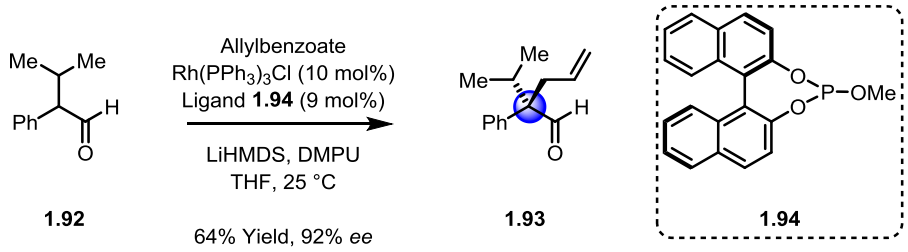
Scheme 1.30 Enantioselective allylation of α,α-disubstituted aldehydes via C-H activation.





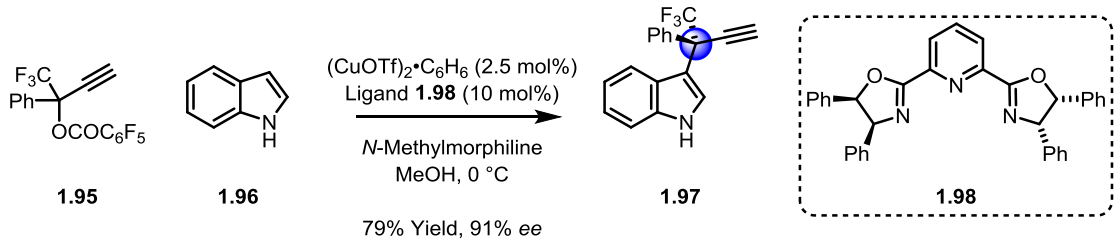
Scheme 1.31 Rh-catalyzed allylation of α-branched aldehydes with alkynes and the proposed mechanism.

Based upon previous study on allylation of α-substituted benzyl nitriles,[92] Evans and coworker recently observed that α-branched aldehydes were allylated in good enantioselectivity under rhodium-catalyzed condition without forming enamines during reaction.[93] LiHMDS was used as base, and substrate scope was expanded to aldehydes with longer alkyl chain (Scheme 1.32). Mechanistic studies indicated both (*E*)- and (*Z*)-enolates are generated in the reaction, but the origin of selectivity was still unclear.

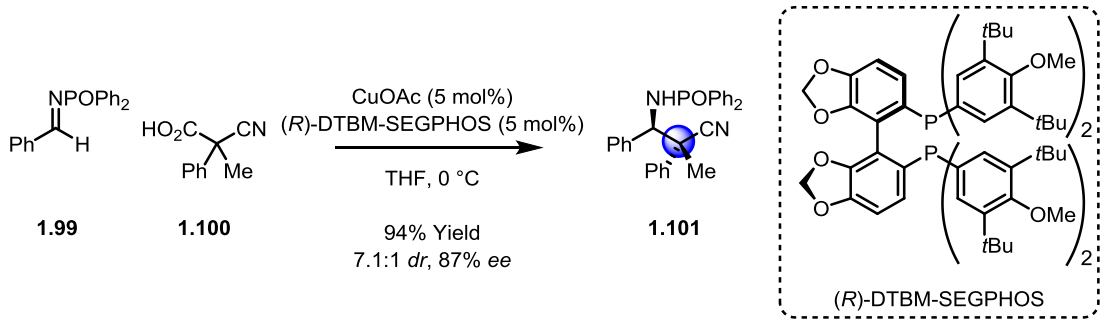


Scheme 1.32 Enantioselective allylation of α,α -disubstituted aldehydes without enamine formation.

A related study regarding to propargylation of indoles under copper-catalyzed condition was reported by Nishibayashi and coworkers.[94] α-Phenyl-α-trifluoromethyl substituted propargylic esters were used as substrates, but compounds with some other electron-withdrawing substituents which do not contain any β-H also displayed similar reactivity in the transformation (Scheme 1.33).



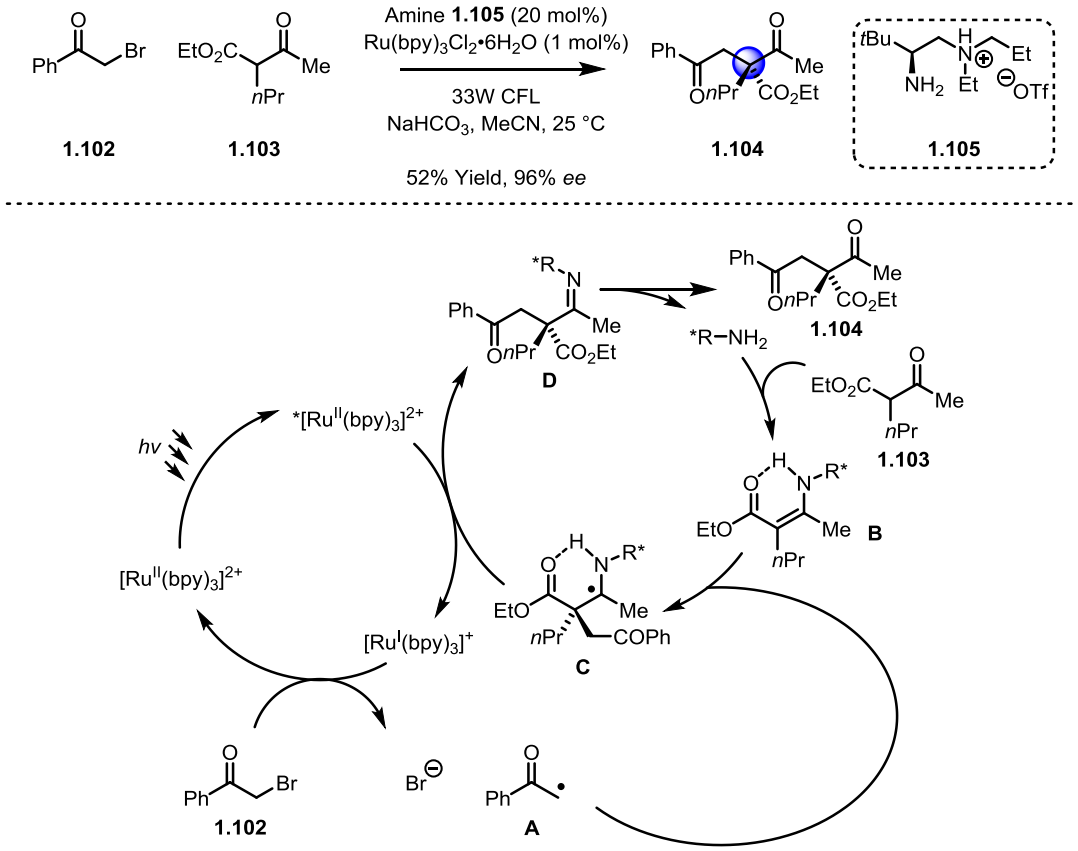
Scheme 1.33 Cu-catalyzed enantioselective propargylation of indoles.



Scheme 1.34 Cu-catalyzed stereoselective decarboxylative Mannich-type reaction.

Kanai and Shibasaki reported a copper-catalyzed asymmetric decarboxylative Mannich reaction between substituted 2-cyanoacetic acids and imines (Scheme 1.34).[95] Good diastereo- and enantioselectivity could be obtained, but using alkyl aldimines as substrates gave inferior selectivity.

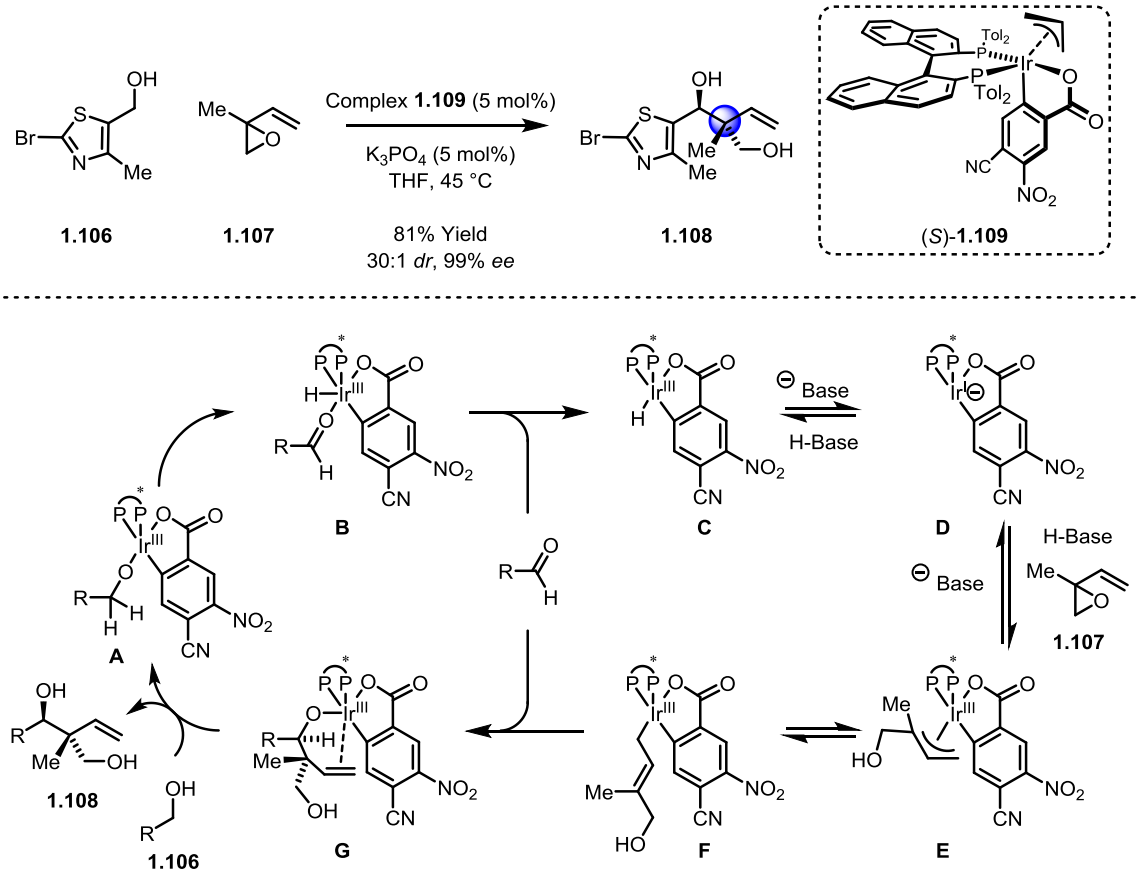
Recently, Luo and coworkers described a method of synthesizing γ-keto carbonyl compounds from α-bromoketones and β-ketocarbonyls via photocatalytic radical addition.[96] Phenacyl radical (Scheme 1.35, **A**) was generated upon homolytic cleavage of C-Br bond by photocatalyst, and added to chiral enamines to form the all-carbon quaternary centers in a stereocontrolled pathway (Scheme 1.35).



Scheme 1.35 Photocatalytic asymmetric alkylation and proposed mechanism.

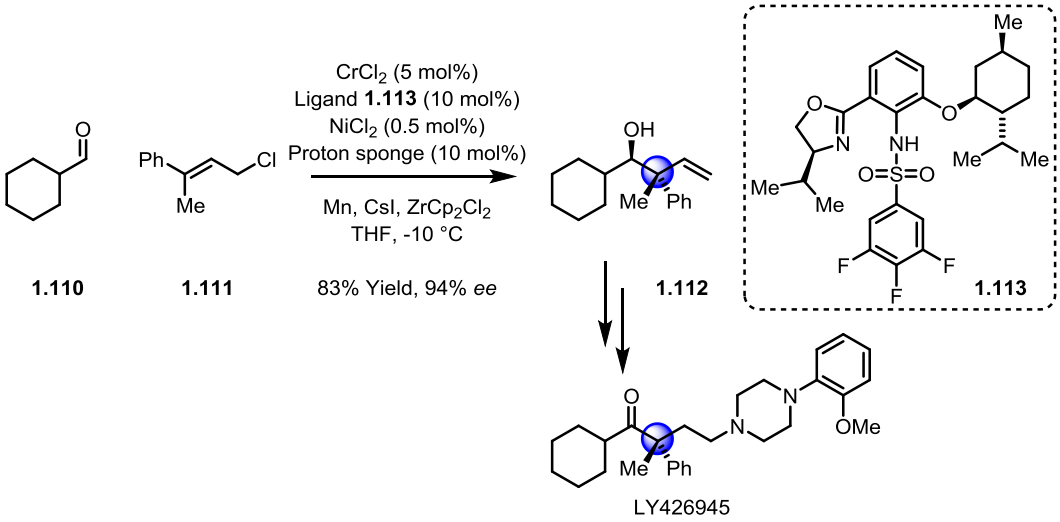
1.5 NUCLEOPHILIC ALLYLATION

Allylmetal reagents are also widely used in stereoselective carbonyl addition.[97–99] Since 1990s, configurational stable *γ,γ*-disubstituted allylic organometallic reagents (boron, silicon, tin, etc.) started being applied to construction of quaternary stereocenters.[7] Despite its success in controlling the absolute and relative stereochemistry in products, stoichiometric usage of metals (and chiral ligands in some cases) does not align with the concepts of atom-economic[100,101] and green chemistry.[102] Catalytic methods that can achieve similar efficiency and selectivity are highly desirable.



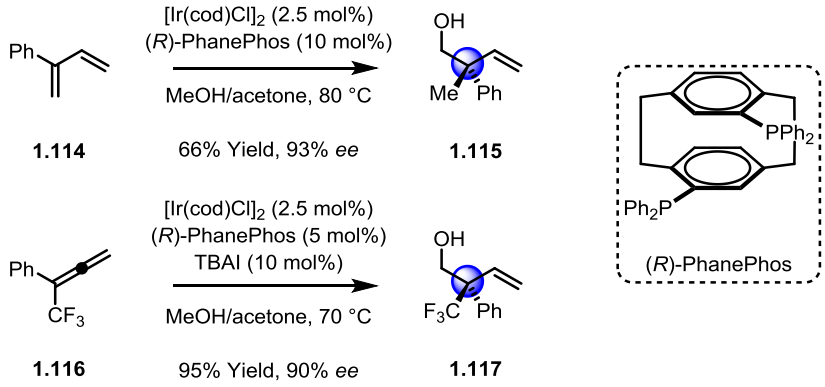
Scheme 1.36 Ir-catalyzed enantioselective *tert*-(hydroxy)prenylation of primary alcohols.

In 2008, Krische and coworkers discovered that allyliridium species generated catalytically under transfer hydrogenative condition from allyl acetate exhibited "umpolung" reactivity and added to aldehydes enantioselectively.[103–105] This novel reacting pattern indicated that catalytic stereoselective carbonyl allylation could now be attained with feedstock starting material (departure from preformed organometallic reagents) and circumvent producing stoichiometric amount of metal waste in the reactions. In 2014, the same research group disclosed the first catalytic protocol for generating acyclic quaternary stereocenters via carbonyl allylation.[106,107] The redox-linked reactant isoprene monoxide and primary alcohols were transformed to Ir-allyl species (Scheme 1.36, **E**) and aldehydes *in situ*, and formed the new C-C bonds in high level of diastereo- and enantioselectivity with wide functional groups tolerance (Scheme 1.36). The atom-economic methodology was later successfully applied to construction of vicinal stereocenters[108,109] in a concise synthesis of terpenoid natural products.[110]



Scheme 1.37 Cr-catalyzed coupling of aldehydes and γ,γ-disubstituted allyl chloride.

Following that, Zhang and coworkers reported a chromium-catalyzed (or nickel-catalzyed, see condition) asymmetric reductive coupling of γ,γ-disubstituted allyl chloride and aldehydes (Scheme 1.37).[111] Mn metal was used as terminal reductant and $ZrCp_2Cl_2$ was added for catalyst turnover. Substituents on the formed quaternary stereocenters could vary from alkyl to aryl groups. Recently, Krische and coworkers used 2-arylbuta-1,3-dienes[112] and 1-phenyl-1-trifluoromethylallene[113] as precursors to generate allylmetal species and coupled with methanol (also as terminal reductant) enantioselectively (Scheme 1.38). Remarkably, the iridium catalytic system completely deviated the reactivity from traditional electrophilic hydromethoxylation of olefins to new C-C bond formation.



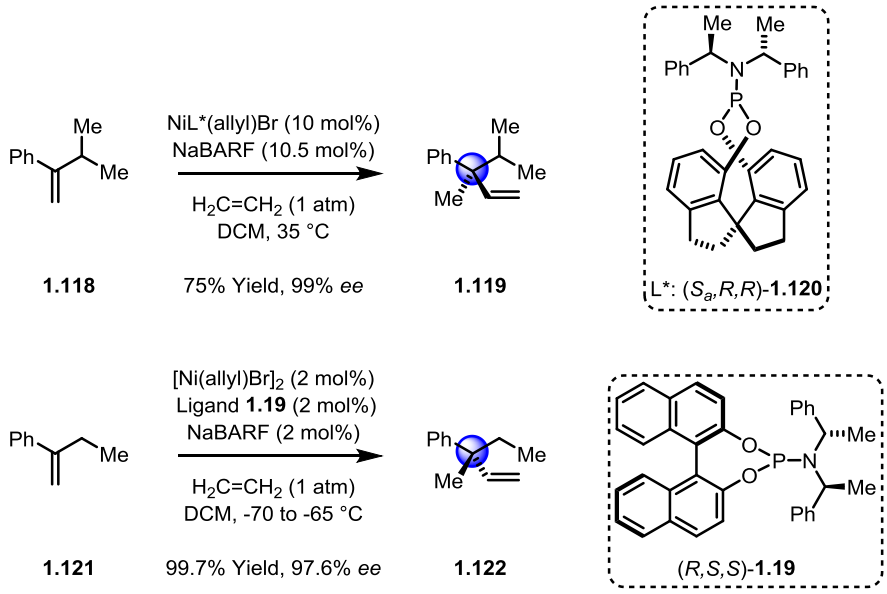
1.114 **1.115** **1.116** **1.117**

Scheme 1.38 Ir-catalyzed enantioselective hydrohydroxymethylation of dienes and allenes.

1.6 OLEFIN FUNCTIONALIZATION

As numerous organic reactions occur at C=C double bonds, olefins are among the most commonly used substrates for constructing all-carbon quaternary stereocenters. Indeed, activated alkenes have been utilized for forming quaternary centers via transformations like allylic substitution, conjugate addition, and nucleophilic allylation, as mentioned earlier in this review. Unactivated double bonds, or mildly activated olefins

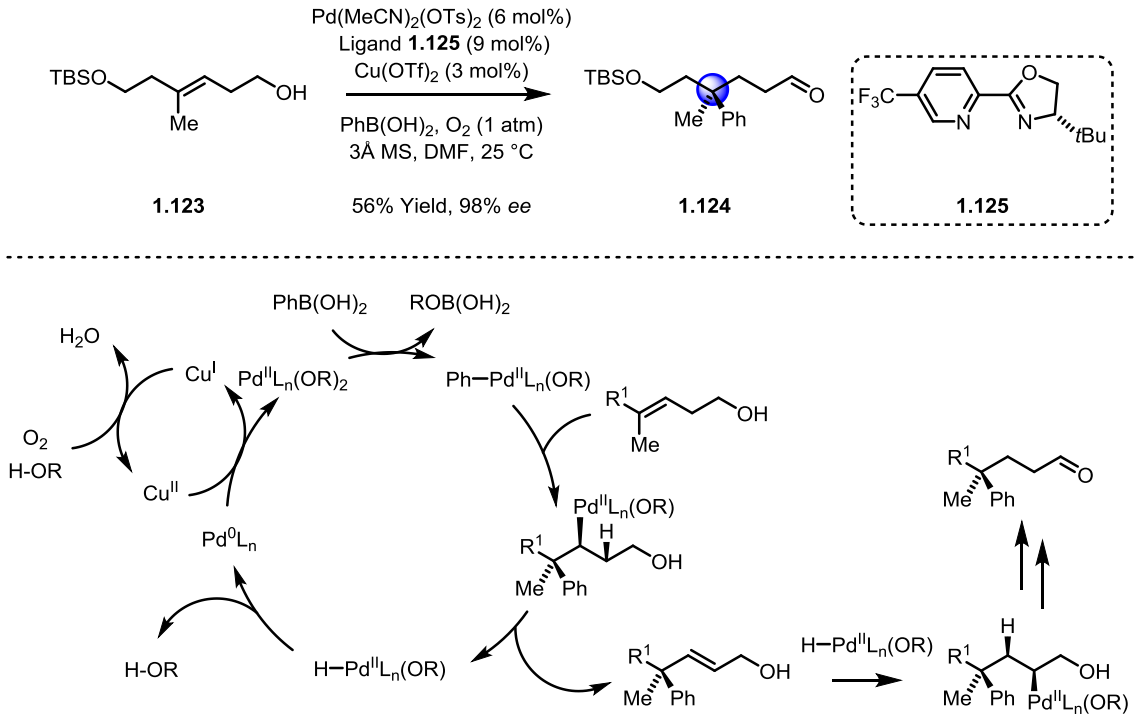
(such as styrenes) are less well-documented in reactions creating acyclic quaternary stereocenters.



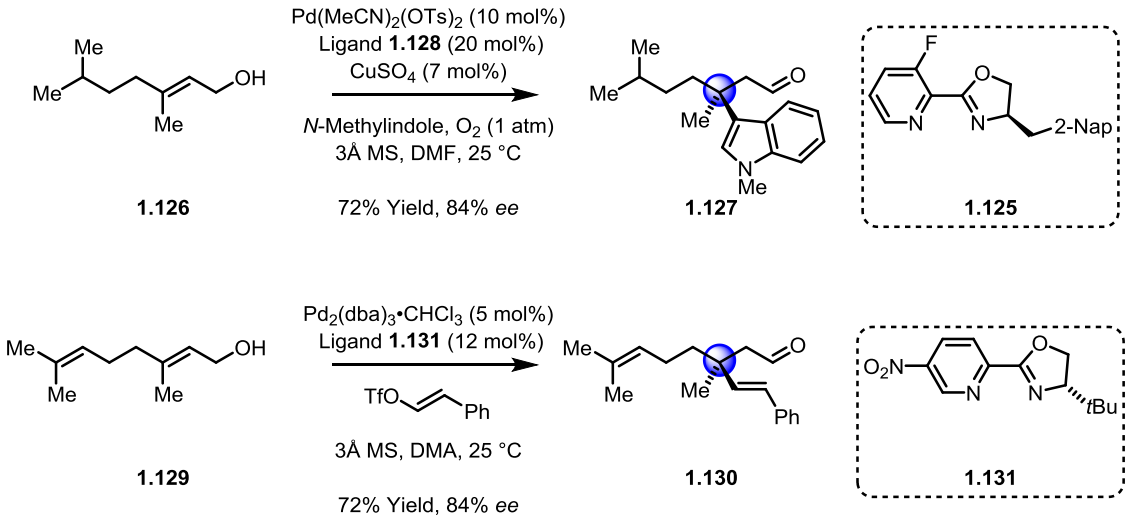
Scheme 1.39 Ni-catalyzed asymmetric hydrovinylation of α-alkylstyrenes with ethylene.

Asymmetric hydrovinylation of α-substituted styrenes is one of these methods that fall to this category. Synthesis of stereogenic quaternary centers directly from feedstocks like ethylene and styrene derivatives is valuable because it minimizes the waste production and time costs during the process. Zhou reported the first enantioselective hydrovinylation of α-substituted styrenes with ethylene gas in 2006.[114] The combination of nickel catalyst and chiral spiro-phosphoramidite ligands has led to excellent enantioselectivity for substrates with secondary alkyl substituents (Scheme 1.39, top). RajanBabu and coworkers published their results concurrently, and by using binaphthyl phosphoramidite ligands α-ethylstyrenes were hydrovinylated in high *ee*s (Scheme 1.39, bottom).[115–117]

Intramolecular Heck reaction has been utilized as one of the earliest methods to form cyclic quaternary stereocenters. Intermolecular coupling of trisubstituted olefins, however, was less known because of problems like sluggish reactivity and low regioselectivity. Sigman and coworkers developed an intermolecular oxidative Heck coupling protocol with arylboronic acids to construct quaternary stereocenters in 2014.[118] The resulted double bond would migrate along alkyl chain via palladium-catalyzed chain-walking mechanism until it formed aldehyde or ketone, and therefore all-carbon quaternary centers could be located remotely from any functional groups (Scheme 1.40). The methodology was later extended to indole addition,[119] and intermolecular Heck reaction between trisubstituted olefins and vinyl triflates was also reported (Scheme 1.41).[120]



Scheme 1.40 Pd-catalyzed redox-relay asymmetric Heck-type coupling to construct remote quaternary centers and proposed mechanism.



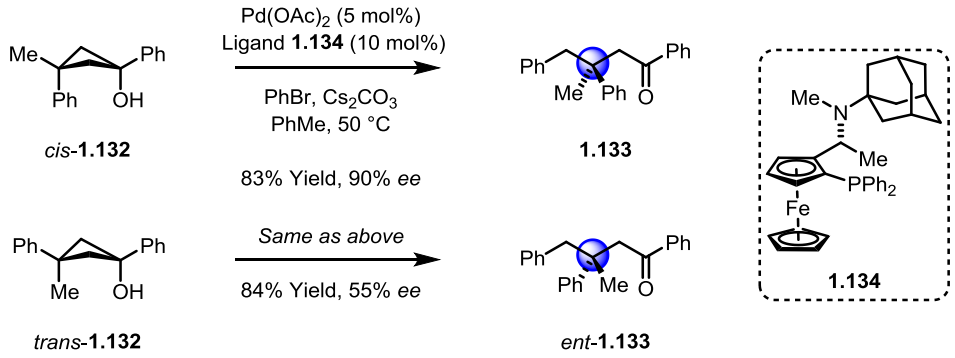
Scheme 1.41 Asymmetric Pd-catalyzed indole addition (top) and alkenylation (bottom) of trisubstituted olefins.

1.7 DESYMMETRIZATION REACTIONS

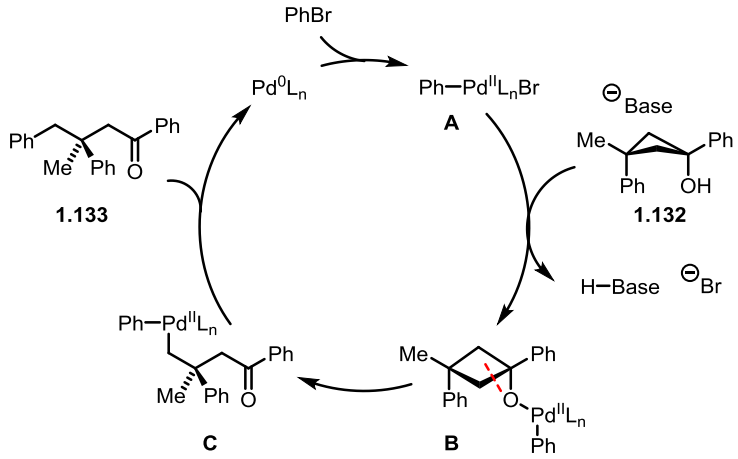
Desymmetrization, referring to reactions that transform substrates with prochiral centers into asymmetric compounds by breaking the symmetry element(s) in the molecules, can be used for synthesis of optically active compounds if such conversions are enantioselective.[121–123] Utilizing this type of transformations in stereoselective construction of quaternary centers has its own advantages, since it can separate the events of creating quaternary centers and inducing chirality into different steps. Unlike the widely recognized desymmetrizing cyclizations,[124] forming acyclic quaternary stereocenters via transition-metal catalyzed desymmetrization is scarcely reported.

Enantioselective ring-opening of strained cyclic systems is one common strategy, because it still has a relatively rigid transition state in the stereo-determining step. Uemura and coworkers reported a palladium-catalyzed ring-opening arylation of prochiral 3,3-disubstituted cyclobutanols in 2003 (Scheme 1.42).[125] During reaction, Pd(II) alkoxide (Scheme 1.43, **B**) went through a stereoselective *β*-C elimination to

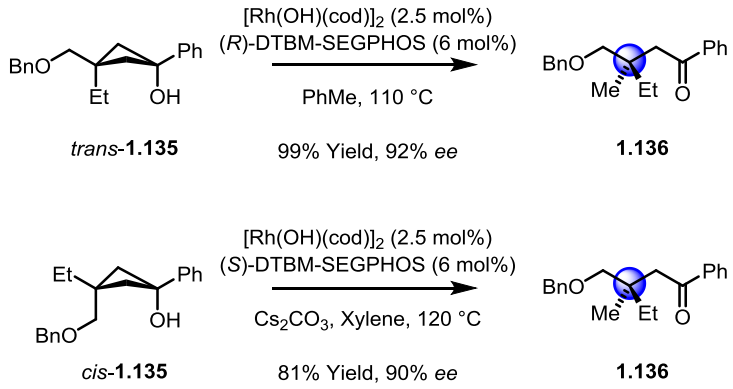
generate an optically active alkylpalladium species (Scheme 1.43, **C**), followed by reductive elimination to form the coupling product containing a quaternary stereocenter. A strong match/mismatch effect was observed: while *cis*-butanol **1.132** gave an excellent 90% *ee* (Scheme 1.42, top), its epimer *trans*-**1.132** only led to moderate enantioselectivity (55% *ee*) (Scheme 1.42, bottom). Cramer and coworker later discovered a rhodium-catalyzed desymmetrizing ring-opening of cyclobutanols.[126] Unlike the former report, the chiral catalyst was able to dominate the stereochemical outcome of this reaction (Scheme 1.44).



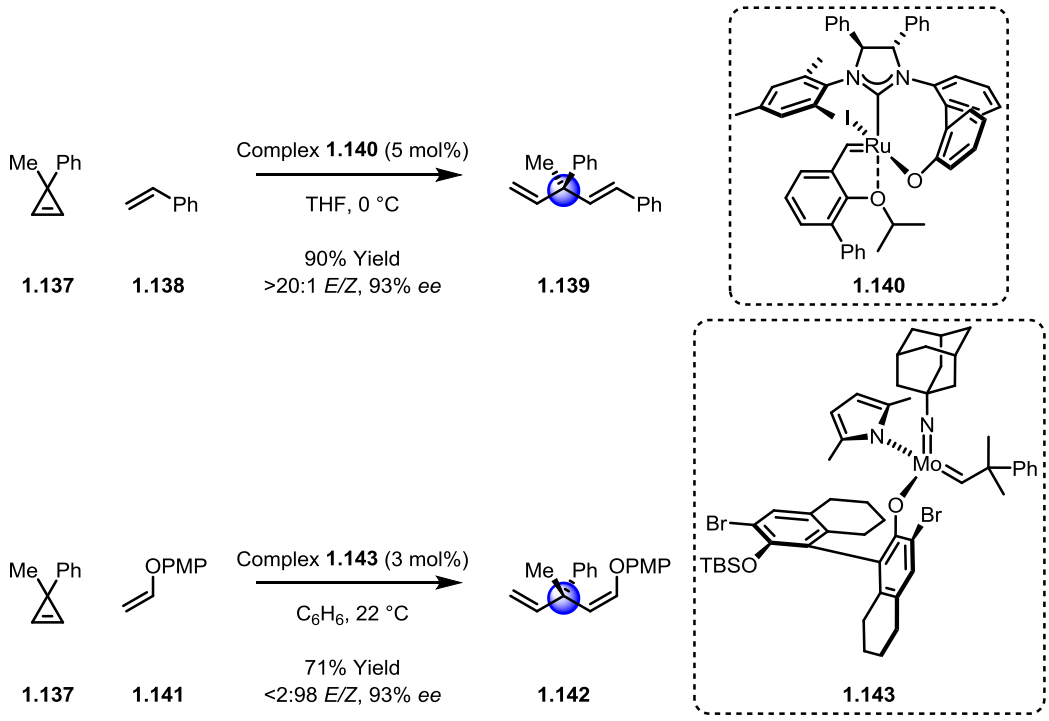
Scheme 1.42 Pd-catalyzed desymmetrizing arylation of cyclobutanols.



Scheme 1.43 Plausible mechanism for Pd-catalyzed desymmetrizing arylation of cyclobutanols.



Scheme 1.44 Rh-catalyzed enantioselective ring-opening of 3,3-disubstituted cyclobutanols

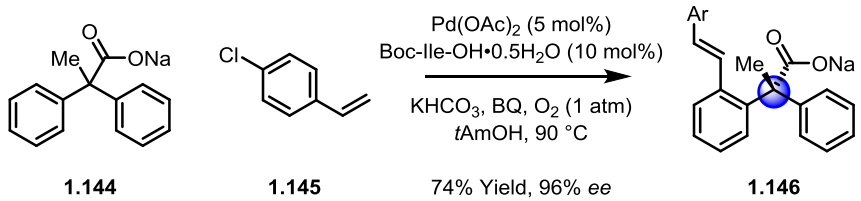


Scheme 1.45 *E*- (top) and *Z*-selective (bottom) AROM of cyclopropenes.

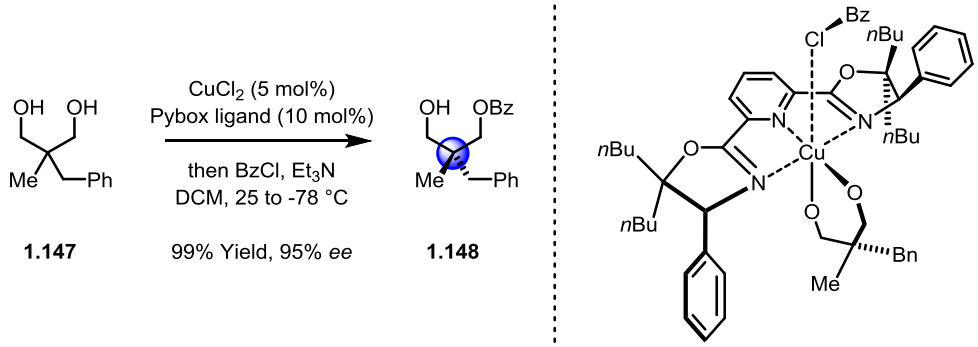
AROM (Asymmetric Ring-Opening Metathesis) was also applied to this type of desymmetrization. Hoveyda and coworker disclosed an enantioselective ring-opening of 3,3-disubstituted cyclopropenes through a chiral NHC-ligand modified Hoveyda-Grubbs

catalyst to create acyclic all-carbon quaternary centers.[127] The reaction had moderate to excellent control over *E*/*Z* selectivity of olefin products, and the major *E*-product was obtained in good to excellent enantioselectivity (Scheme 1.45, top). A few years later, a highly *Z*-selective molybdenum-based metathesis catalyst was developed by the same research group, allowing access of enantiopure *Z*-olefins with quaternary stereocenters (Scheme 1.45, bottom).[128]

Desymmetrization from acyclic prochiral substrates is even less known. Yu and coworkers reported a desymmetrizing oxidative Heck-type C-H functionalization of arenes.[129] A vinyl group was introduced at the *ortho*-position through the carboxylate directing group, and Boc-protected isoleucine was used to discriminate the enantiotopic C-H bonds (Scheme 1.46).



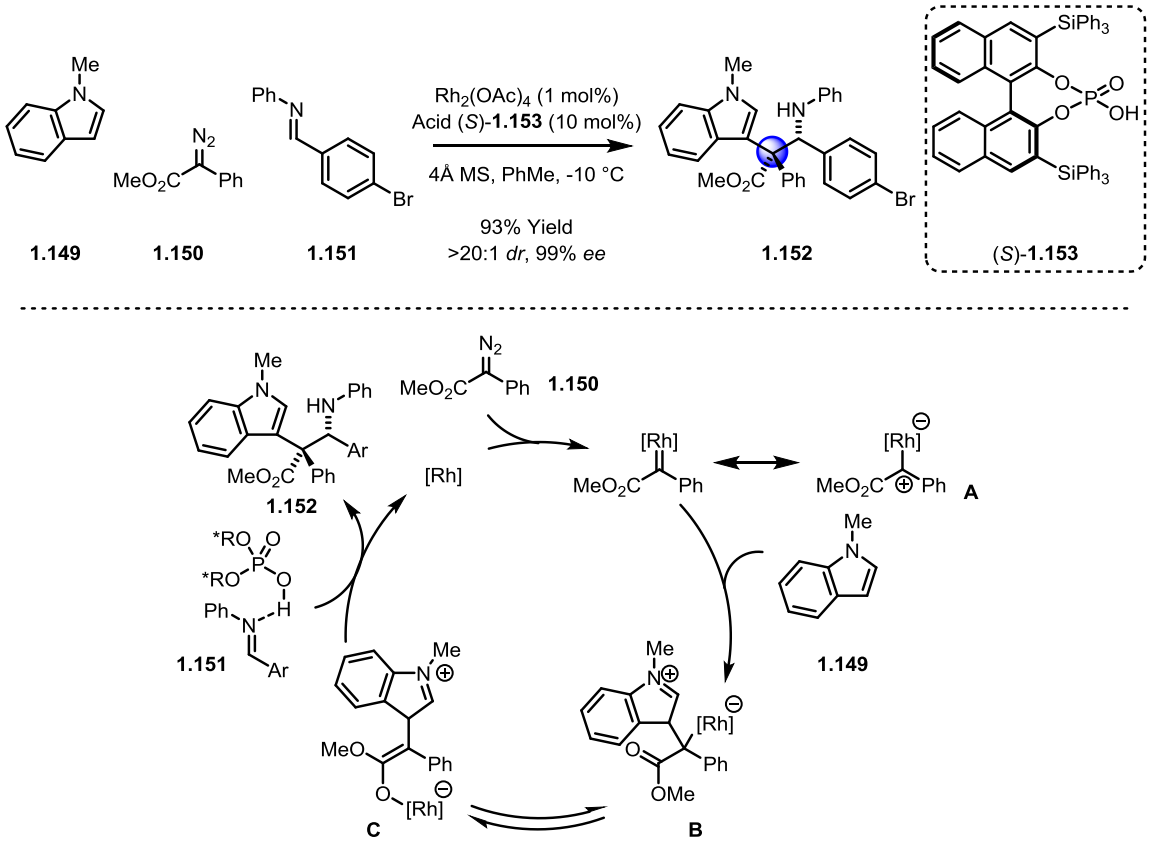
Scheme 1.46 Pd-catalyzed desymmetrizing Heck-type C-H functionalization.



Scheme 1.47 Cu-catalyzed desymmetrizing mono-benzylation (left) and the proposed transition state (right).

Kang and coworkers established a copper-Pybox complex for enantioselective mono-benzylation of prochiral 2,2-disubstituted 1,3-propanediols.[130] The authors proposed a rigid transition state involving copper binding to both hydroxyl groups and the two substituents on C-2 being arranged to avoid steric interaction (Scheme 1.47).

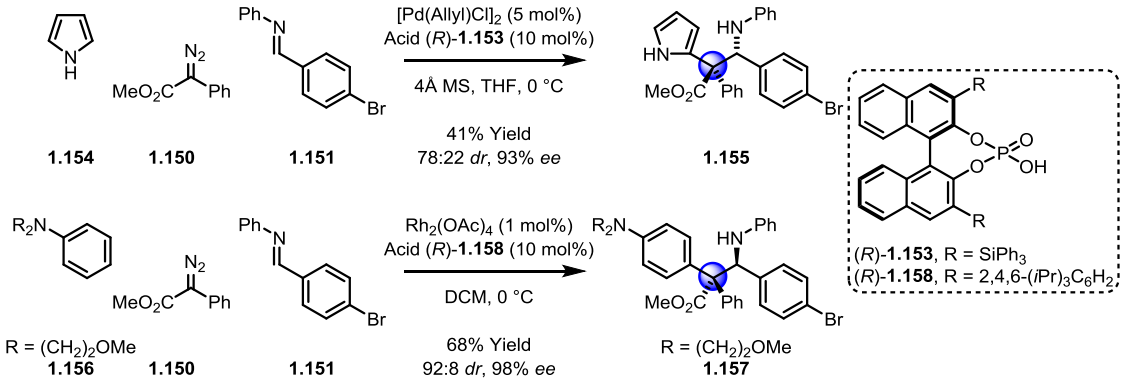
1.8 Miscellaneous Reactions



Scheme 1.48 Asymmetric three-component reaction with indoles to form all-carbon quaternary centers.

Hu and coworkers reported an asymmetric three-component reaction to generate acyclic quaternary stereocenters in 2012.[131] Rhodium carbenoids formed from diazo compounds are attacked by indoles to generate metal enolate intermediates (Scheme 1.48,

C), which undergo further asymmetric Mannich reaction with imines to form quaternary stereocenters. With the help of a BINOL-derived chiral phosphoric acid, high diastereo- and enantioselectivity could be obtained. The authors have later expanded the substrate scope to some other electron-rich aromatic compounds (pyrroles,[132] anilines,[133] etc.) through palladium or rhodium catalysis, but different diastereoselectivity was observed (Scheme 1.49).



Scheme 1.49 Asymmetric three-component reactions with pyrroles (top) and anilines (bottom).

1.9 Conclusion and Outlook

This review summarizes transition-metal-catalyzed asymmetric construction of acyclic all-carbon quaternary stereocenters. The area has been thriving over the last decade, as demonstrated by the number of related publications during this period. Compared to before, more diverse transformations (see chapter 1.5-1.8) were applied to formation of quaternary centers. Even for the well-documented reaction types (see chapter 1.2-1.4), catalytic systems with much higher efficiency and selectivity were developed in recent years. Some of the chiral ligands/catalysts are modified from the ones which have been used for corresponding cyclic systems, while there are also reagents specifically designed for acyclic substrates.

More asymmetric processes will be discovered in the future with no doubt, as chemists delve deeper into metal catalysis and stereochemical control. However, attention should be paid to aspects beyond reactivity and selectivity: for example, improvement of atom-efficiency to avoid generating stoichiometric amount of wastes, application of stereodivergent transformations to increase synthetic efficacy, using feedstock as starting materials to maximize the added value of reactions, high-turnover/recyclable catalysts to lower costs, etc. Gratifyingly, organic chemists have already started solving these problems: a few proof-of-concept reports has already been collected in this review. Advancement in this area will provide powerful tools to overcome hurdles in asymmetric natural products/derivatives synthesis.

Chapter 2: Diastereo- and Enantioselective Formation of All-Carbon Quaternary Centers via *tert*-(Hydroxy)prenylation: Redox-Triggered C-C Coupling of Alcohols and Vinyl Epoxides*

2.1 INTRODUCTION

Stereoselective carbonyl allylation[1–3] has been intensely studied since late 1970s due to the need of accessing the complex structures of polyketide natural products.[4–6] Numerous methods have been developed majorly based on the use of organometallic reagents (*e.g.*, boron,[7–10] silicon,[8] tin,[11] titanium,[12,13] etc.) with chiral auxiliaries/ligands. Despite their large success in controlling the absolute and relative stereochemistry during nucleophilic allylation, application of these methods mostly remains in laboratory research. What prohibits their broader utilization in industry is the requirement of stoichiometric use of allylmetal reagents, which usually need multi-step synthesis from commercially available material and produce stoichiometric amount of metallic waste when reactions complete. In addition, protecting groups are always necessary for these transformations, and therefore add up more steps between feedstock and the desired products. All of the problems have made these processes too costly to commercialize.

Guided by the concept of synthetic efficacy[14] and green chemistry,[15] Krische and coworkers have developed a series of stereoselective redox-neutral alcohol C-H functionalization reactions[6] (allylation,[16–21] crotylation,[22–27] propargylation,[28,29] prenylation,[30,31] etc.) which can access the same products as carbonyl allylation. The reductive C-C coupling between allyl donors and *in situ* generated aldehydes/ketones is triggered by iridium- or ruthenium-catalyzed alcohol dehydrogenation. The merge of

* This chapter is partially based on the previously published work:
Feng, J.; Garza, V. J.; Krische, M. J. *J. Am. Chem. Soc.* **2014**, *136*, 8911–8914.
J. F. contributed to reaction discovery and optimization (Table 2.1), alcohol substrate scope table (Table 2.2 and Scheme 2.2), other oxirane substrate scheme (Scheme 2.3), mechanistic study (Table 2.4), and preparation of manuscript and supporting information.

redox reactions and C-C bond forming events allows to simplify the synthesis of complex molecules, as demonstrated by several concise syntheses of polyketide natural products.[32]

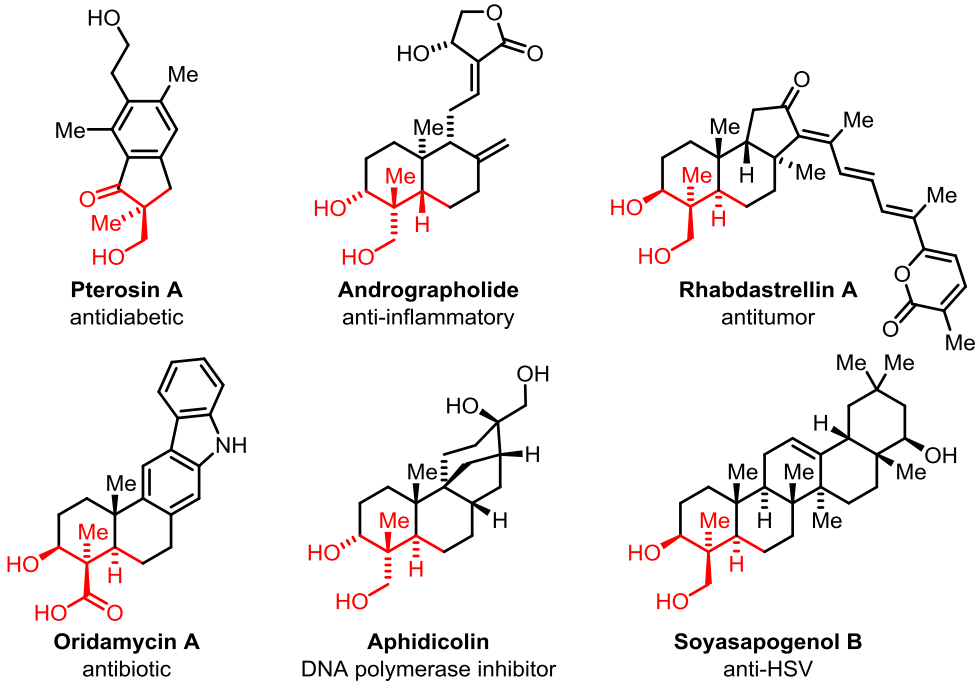
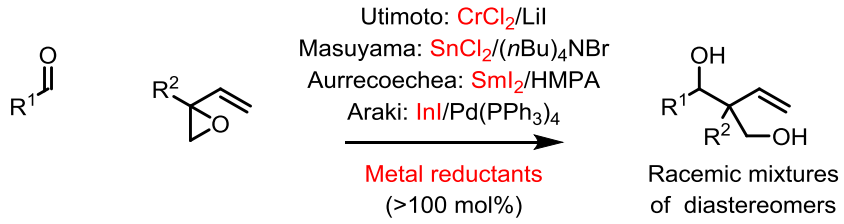


Figure 2.1 Terpenoid natural products containing *tert*-(hydroxy)prenyl and related motif.

Terpenoids represent another important class of natural products with attractive bioactivities.[33,34] The complicated multicyclic backbones along with contiguous stereocenters (including all-carbon quaternary centers) pose a big challenge in *de novo* synthesis of these compounds.[35,36] Among them, the *tert*-(hydroxy)prenyl motif and other related substructures (highlighted in red) are found in over 2000 terpenoid natural products (Figure 2.1). Retrosynthetically, this unique structure can be constructed via stereoselective carbonyl *tert*-(hydroxy)prenylation. However, only a paucity of reports[37–42] on related transformation are known in literatures: none of them were enantioselective, let alone limited substrate scope, unsatisfactory diastereoselectivity and use of

stoichiometric metal reagents (Scheme 2.1). Therefore, a catalytic protocol for stereoselective carbonyl *tert*-(hydroxy)prenylation is highly desirable.



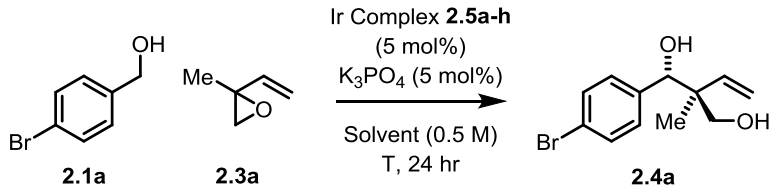
Scheme 2.1 Previous reports on metal-mediated racemic *tert*-(hydroxy)prenylation.

2.2 Reaction Development and Scope

Having re-inspected the alcohol C-H functionalization strategy, we envisioned that a direct carbonyl *tert*-(hydroxy)prenylation may be achieved by utilizing commercially available isoprene monoxide[43] as coupling partner. There was concern, however, that electrophilic *O*-allylation[44–46] or other side reactions[47–51] may compete with the desired pathway. Gratifyingly, treating 4-bromobenzyl alcohol (**2.1a**) with isoprene monoxide (**2.3a**) in the presence of preformed iridium catalyst (*R*)-**2.5b** modified by (*R*)-SEGPHOS and 4-cyano-3-nitrobenzoic acid at 60 °C in THF did give the desired *tert*-(hydroxy)prenylation product in 37% yield as a single regioisomer with a moderate diastereomeric ratio (2:1, *anti*:*syn*) and excellent enantiomeric excess (93%, Table 2.1, entry 1). After obtaining this promising result, a series of optimization experiments were performed. Upon the addition of catalytic amount of base, excellent yield was obtained along with slightly improved diastereoselectivity (Table 2.1, entry 2). It is believed that inorganic base can facilitate ionization of the vinyl epoxide with iridium catalysts to generate allyl species. Though prenylation did not proceed at room temperature, it went smoothly at 45 °C to furnish 95% yield with 2.5:1 *dr* and 93% *ee*. Higher reaction temperature led to diminished isolated yield and enantioselectivity due to side reactions[52]

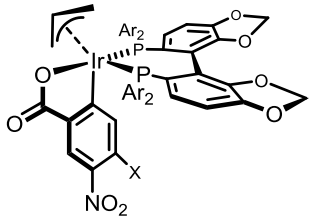
(Table 2.1, entry 3-5). Catalyst (*R*)-**2.5h** modified by (*R*)-TolBINAP and 4-cyano-3-nitrobenzoic acid proved to be superior in terms of diastereoselectivity (30:1 vs. 2.5:1 *dr*),

Table 2.1 Optimizations for iridium-catalyzed *tert*-(hydroxy)prenylation of **2.1a** with **2.3a**.[a]

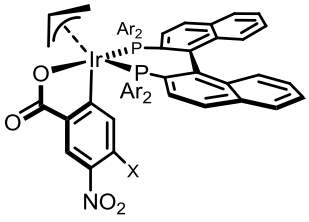


2.1a (100 mol%) **2.3a** **2.4a**

Entry	**2.3a** (mol%)	T (°C)	Ir Complex	Solvent	**2.4a** Yield (*dr*, *ee*%)
1[b]	200	60	(*R*)-**2.5b**	THF	37% (2:1, 93)
2	200	60	(*R*)-**2.5b**	THF	90% (4:1, 93)
3[c]	200	25	(*R*)-**2.5b**	THF	trace
4	200	45	(*R*)-**2.5b**	THF	95% (2.5:1, 93)
5	200	90	(*R*)-**2.5b**	THF	60% (4:1, 75)
6	200	45	(*R*)-**2.5h**	THF	71% (30:1, 93)
7	**300**	**45**	(*R*)-**2.5h**	**THF**	**91% (40:1, 94)**
8	300	45	(*R*)-**2.5a**	THF	72% (17:1, 94)
9	300	45	(*R*)-**2.5b**	THF	98% (4:1, 89)
10	300	45	(*R*)-**2.5c**	THF	17% (17:1, 94)
11	300	45	(*R*)-**2.5d**	THF	71% (8:1, 94)
12	300	45	(*R*)-**2.5e**	THF	81% (30:1, 91)
13	300	45	(*R*)-**2.5f**	THF	84% (30:1, 91)
14	300	45	(*R*)-**2.5g**	THF	66% (30:1, 92)
15	300	45	(*R*)-**2.5h**	PhMe	45% (12:1, 95)
16	300	45	(*R*)-**2.5h**	1,4-dioxane	91% (20:1, 93)
17	300	45	(*R*)-**2.5h**	EtOAc	81% (30:1, 95)



(*R*)-**2.5a**, Ar = Ph, X = H
(*R*)-**2.5b**, Ar = Ph, X = CN
(*R*)-**2.5c**, Ar = 3,5-Me_2Ph, X = H
(*R*)-**2.5d**, Ar = 3,5-Me_2Ph, X = CN



(*R*)-**2.5e**, Ar = Ph, X = H
(*R*)-**2.5f**, Ar = Ph, X = CN
(*R*)-**2.5g**, Ar = 4-MePh, X = H
(*R*)-**2.5h**, Ar = 4-MePh, X = CN

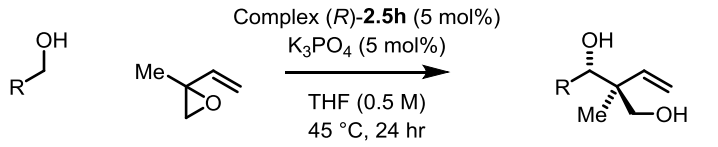
[a]Yields are of material isolated by silica gel chromatography. [b]K_3PO_4 was omitted. [c]48 hr.

although the reaction was slightly retarded (Table 2.1, entry 6). Later we were delighted to find that excellent yield could be achieved again by simply increasing the stoichiometry of **2.3a**, without any erosion to stereoselectivity (Table 2.1, entry 7). An extensive screening of iridium catalysts was also conducted (Table 2.1, entry 7-14): among the eight complexes which were modified by four different bidentate phosphine ligands and two representative nitrobenzoic acids (3-nitrobenzoic acid and 4-cyano-3-nitrobenzoic acid), we observed a trend that higher yields were obtained when employing iridium complex coordinated with a more electron-deficient acid (4-CN-3-NO_2BzOH), and better diastereoselectivity was achieved by ligands with larger dihedral angle in the biaryl backbone (73.49˚ for BINAP vs. 64.99˚ for SEGPHOS).[53] The fact that catalyst (*R*)-**2.5h** gave the best result matched this observation pretty well. The reaction was equally efficient, albeit with a slightly lower diastereoselectivity when performed in 1,4-dioxane, while lower conversion was observed with toluene or ethyl acetate as solvent (Table 2.1, entry 15-17). Therefore, the optimal condition was identified as with catalyst (*R*)-**2.5h** at 45 ˚C in tetrahydrofuran.

With this optimal condition in hand, we started to test the scope of *tert*-(hydroxy)prenylation (Table 2.1). Benzylic alcohols **2.1a-c** and allylic alcohols **2.1d-f** reacted smoothly with isoprene monoxide at 45 °C to give **2.4a-f** in good to excellent isolated yields, while alkyl alcohols **2.1g-i** required slightly higher temperature (60 °C) in order to achieve good conversions. Remarkably, all products were obtained with uniformly excellent *anti*-diastereo- and enantioselectivity (*dr* > 20:1, > 90% *ee*). The corresponding aldehydes **2.2a-h** also coupled with isoprene monoxide in good yields by using 2-propanol as terminal reductant (Table 2.3). Generally, higher levels of enantioselectivity were observed under the more concentrated conditions, probably because ligand dissociation from *C,O*-benzoate complex in low concentration would lead

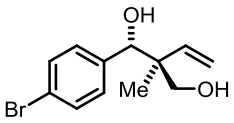
to a less rigid transition state. In addition, diminished diastereoselectivity was usually observed in reactions from aldehyde oxidation state. The selectivity could be improved by diluting the reaction mixtures. Detailed discussion of this observation will be in the next section. The absolute stereochemistry of *tert*-(hydroxy)prenylation products was assigned according to the structure of **2.4a**-acetonide, determined by single-crystal X-ray diffraction analysis using the abnormal dispersion method.

Table 2.2 Regio-, diastereo- and enantioselective iridium-catalyzed *tert*-(hydroxy)prenylation of alcohols **2.1a-i** employing vinyl epoxide **2.3a**.[a]

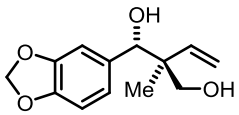


2.1a-i (100 mol%) **2.3a** (300 mol%) **2.4a-i**

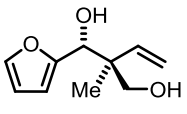
2.1a, R = 4-Br-Ph; **2.1b**, R = piperonyl; **2.1c**, R = 2-furyl
2.1d, geraniol; **2.1e**, prenyl alcohol; **2.1f**, cinnamyl alcohol
2.1g, R = *n*-hexyl; **2.1h**, R = 2-phenylethyl; **2.1i**, R = *c*-hexylmethyl



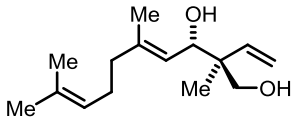
2.4a, 91% Yield
40:1 *dr*, 94% *ee*



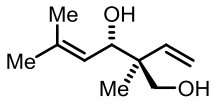
2.4b, 89% Yield
60:1 *dr*, 91% *ee*[b]



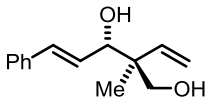
2.4c, 91% Yield
30:1 *dr*, 98% *ee*



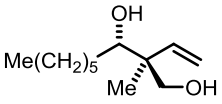
2.4d, 73% Yield
30:1 *dr*, 91% *ee*[c,d]



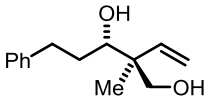
2.4e, 85% Yield
>99:1 *dr*, 93% *ee*[b,c]



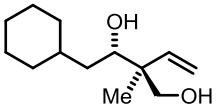
2.4f, 85% Yield
40:1 *dr*, 93% *ee*[d]



2.4g, 74% Yield
40:1 *dr*, 93% *ee*[c,e]



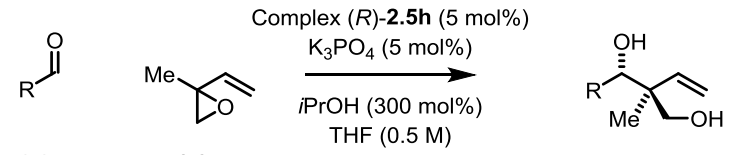
2.4h, 76% Yield
30:1 *dr*, 93% *ee*[e]



2.4i, 76% Yield
30:1 *dr*, 99% *ee*[c,e]

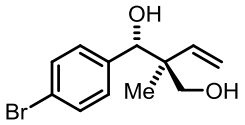
[a]Yields are of material isolated by silica gel chromatography. [b]THF (1.0 M). [c]**2.3a** (400 mol%). [d]THF (0.33 M). [e]60 °C.

Table 2.3 Regio-, diastereo- and enantioselective iridium-catalyzed *tert*-(hydroxy)prenylation of aldehydes **2.2a-i** employing vinyl epoxide **2.3a**.[a]

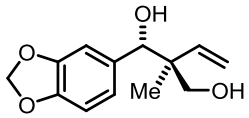


2.2a-i (100 mol%) **2.3a** (300 mol%) **2.4a-i**

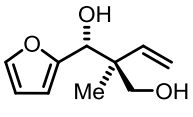
2.2a, R = 4-Br-Ph	**2.2b**, R = piperonyl	**2.2c**, R = 2-furyl
2.2d, geranial	**2.2e**, prenal	**2.2f**, cinnamaldehyde
2.2g, R = *n*-hexyl	**2.2h**, R = 2-phenylethyl	**2.2i**, R = *c*-hexylmethyl



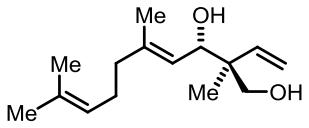
2.4a, 87% Yield
10:1 *dr*, 94% *ee*



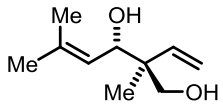
2.4b, 90% Yield
50:1 *dr*, 90% *ee*[b]



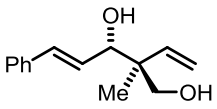
2.4c, 91% Yield
5:1 *dr*, 94% *ee*[c,d]



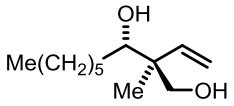
2.4d, 77% Yield
20:1 *dr*, 94% *ee*



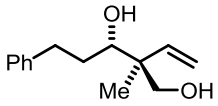
2.4e, 81% Yield
20:1 *dr*, 86% *ee*



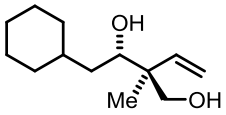
2.4f, 76% Yield
10:1 *dr*, 91% *ee*[e]



2.4g, 73% Yield
12:1 *dr*, 93% *ee*[f]



2.4h, 91% Yield
5:1 *dr*, 85% *ee*[f]

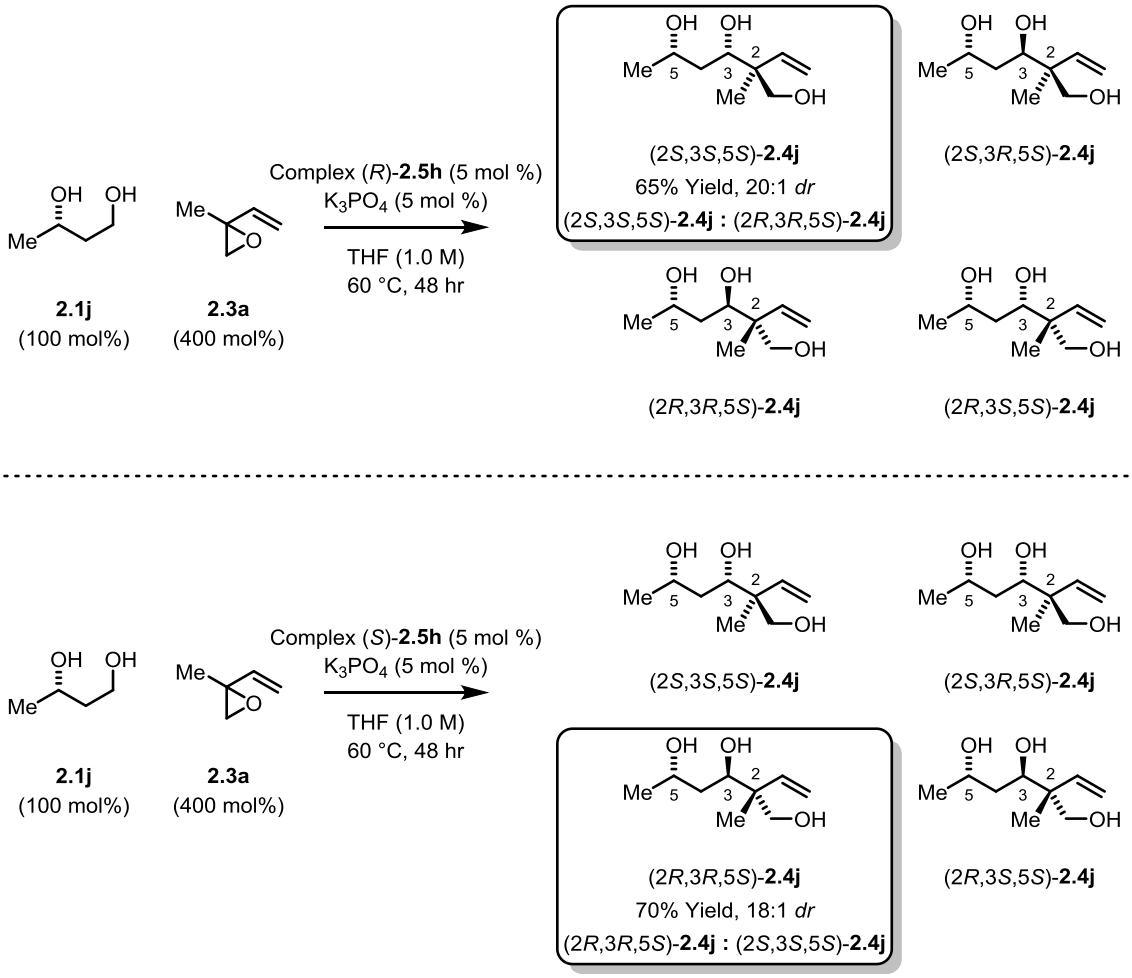


2.4i, 65% Yield
20:1 *dr*, 95% *ee*[g]

[a]Yields are of material isolated by silica gel chromatography. [b]THF (1.0 M). [c]THF (0.33 M). [d]35 °C. [e]THF (0.1 M). [f]60 °C. [g]70 °C.

Unprotected (*S*)-butane-1,3-diol (**2.1j**) was coupled to isoprene monoxide with (*R*)-**2.5h** catalyst under slightly varied condition, and gave the triol product (2*S*,3*S*,5*S*)-**2.4j** as single regioisomer (C-C bond forming at primary carbon) in good yield with excellent diastereoselectivity out of the four possible isomers (Scheme 2.2, top). It perfectly exemplified a site-specific functionalization without using protecting group. (*S*)-**2.5h** catalyst modified by (*S*)-TolBINAP was also applied to the same substrate, and good

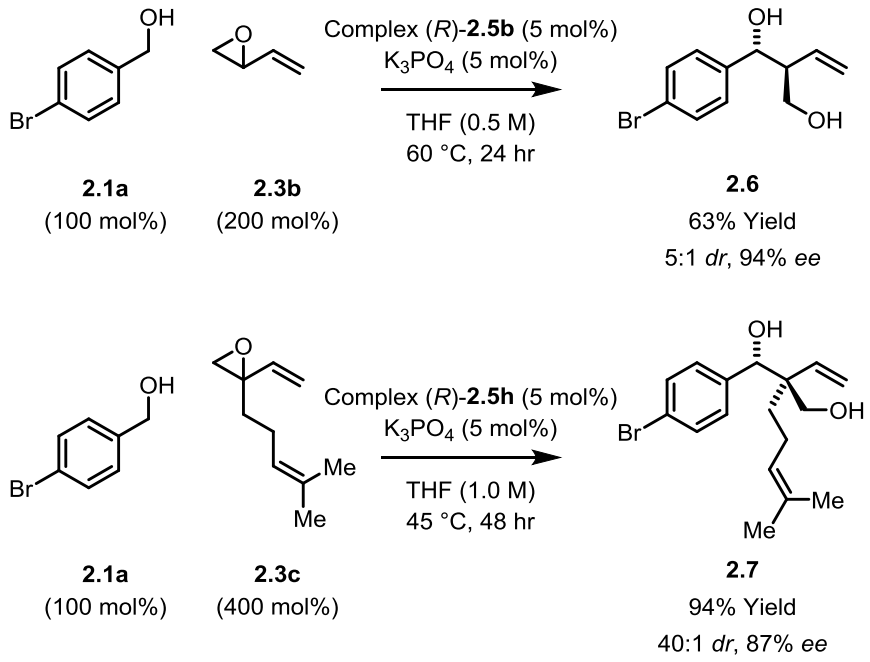
isolated yield of (2*R*,3*R*,5*S*)-**2.4j** with high level of selectivity was achieved. No apparent match/mismatch effect was observed, which indicated that stereoselectivity of this reaction was under catalyst control.



Scheme 2.2 Catalyst-controlled stereoselective *tert*-(hydroxy)prenylation of unprotected diols.

Other vinyl epoxides, such as butadiene monoxide (**2.3b**) and myrcene oxide (**2.3c**),[54,55] were also tested for this tranformation. The corresponding (hydroxymethyl)allylation and (hydroxy)linalylation products were isolated in good to

excellent yield with high stereoselectivity (Scheme 2.3). The moderate diastereoselectivity observed in hydroxymethylallylation may be due to the use of (*R*)-**2.5b,** a more reactive but less selective iridium catalyst.

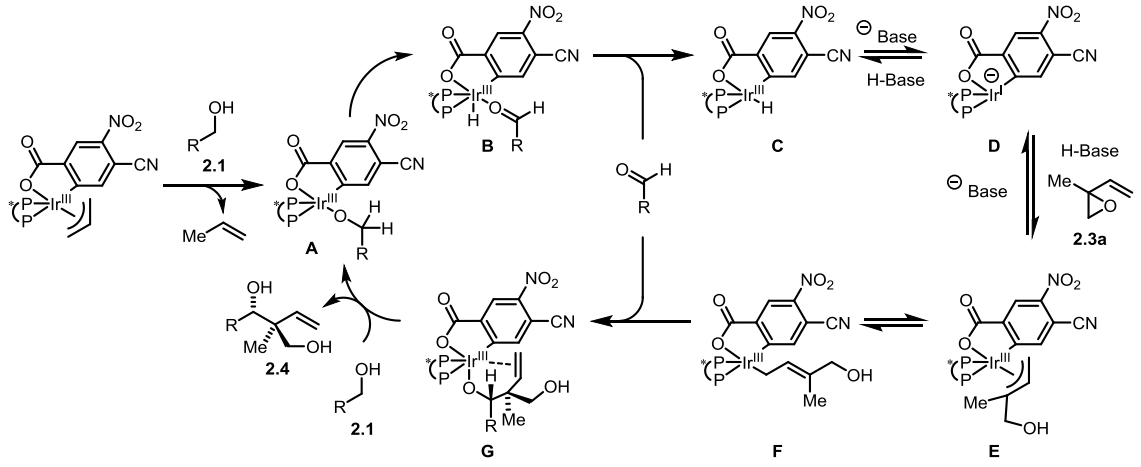


Scheme 2.3 (Hydroxymethyl)allylation and (hydroxy)linalylation of 4-bromobenzyl alcohol (**2.1a**) with butadiene monoxide (**2.3b**) and myrcene Oxide (**2.3c**).

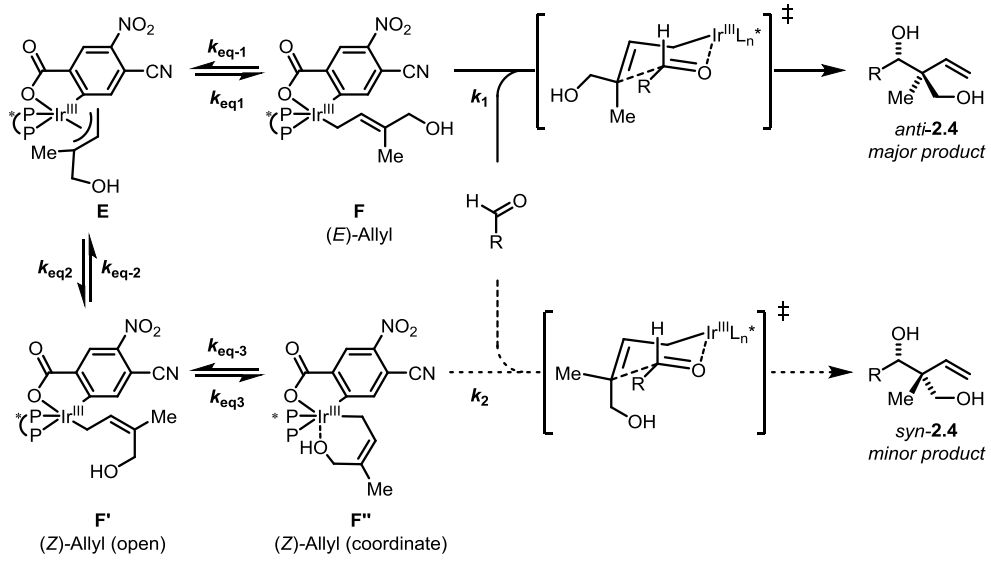
2.3 MECHANISM AND DISCUSSION

A plausible mechanism was proposed based upon our observation and previously developed similar transformations (Scheme 2.4): an iridium alkoxide complex (**A**) is formed via protonation of allyl group. Dehydrogenation then occurs to deliver the metal-hydride (**C**) as well as an aldehyde. An anionic iridium(I) species (**D**) is formed via deprotonation by base, and undergoes oxidative addition to isoprene monoxide generating the allyliridium(III) complex (**E**). The σ-allyl and π-allyl haptomer (**E** and **F**) exists in an equilibrium, while primary σ-allyliridium intermediate (**F**) reacts readily with

the aldehyde in a chair-like transition state to give *tert*-(hydroxy)prenylation product. The double bond in product occupies the last coordination site on metal, and therefore prevents further dehydrogenation on the homoallylic alcohol. The catalytic cycle is closed by ligand exchange to release the product.



Scheme 2.4 Plausible mechanism for *tert*-(hydroxy)prenylation of primary alcohols with isoprene monoxide.



Scheme 2.5 Curtin-Hammett scenario at the carbonyl addition step.

It is suggested that the excellent *anti*-diastereoselectivity of *tert*-(hydroxy)prenylation is the result of Curtin-Hammett control.[56–58] According to the proposed mechanism (Scheme 2.4), the new C-C bond is formed between aldehyde and primary σ-allyliridium intermediate. As Scheme 2.5 shows, there are two possible geometric isomers for the primary σ-allyliridium species (Scheme 2.5, **F** and **F'**). Assuming carbonyl addition proceeds via chair-like transition state, (*E*)-allyliridium will eventually deliver *anti*-product while (*Z*)-allyl intermediate will give *syn*-adduct.

According to Curtin-Hammett postulate, when interconversions between the (*E*)- and (*Z*)-allyl complex is much faster than carbonyl addition (k_{eq1}[E], k_{eq-1}[F], k_{eq2}[E], k_{eq-2} [F'], k_{eq3}[F'], k_{eq-3}[F''] >> k_1[F][aldehyde], k_2[F''][aldehyde]), the relative rate of nucleophilic addition can dominate the diastereomeric ratio of reaction. In *tert*-(hydroxy)prenylation, the rate constant of carbonyl addition from (*E*)-allyl species is thought to be significantly larger than one from (*Z*)-allyl complex ($k_1 > k_2$), which leads to favorable formation of *anti*-diastereomer. Under this scenario, as (*E*)-allyliridium is getting consumed in reaction with aldehyde, it can immediately be replenished by (*Z*)-isomer via the fast interconversions. As a result, the rate of *anti*-product formation will not be effected by concentration change of substrate, and will be always faster than the one forming *syn*-adduct.

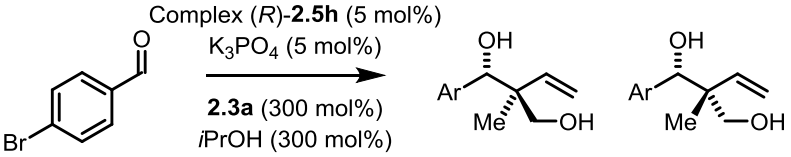
There are two explanations for the rate difference: (1) Hydroxymethyl group is slightly larger than methyl group, which tends to reside at equatorial position in the chair-like transition state to avoid large diaxial interaction. The transition state from (*E*)-allyl is therefore more stable, leading to a larger k_1. (2) A six-membered-ring oxametallacycle is formed in the (*Z*)-allylmetal complex.[39] This relatively stable 18-electron structure significantly retards further interaction between metal center and aldehyde in the solution, which is necessary for forming the transition state of carbonyl addition, and therefore

results in a much smaller k_2. The second explanation seems more reasonable, as the same selectivity was still observed in reaction between alcohol and myrcene oxide (**2.3c**), where the size between hydroxymethyl group and the long alkyl chain is hard to compare.

The Curtin-Hammett scenario also supports the fact that diminished diastereomeric ratios were sometimes observed for reactions from aldehyde oxidation level. Since there is stoichiometric amount of carbonyl compound in reaction, the rate of nucleophilic addition can now be comparable to those of allyl complex interconversions (k_{eq1}[E], k_{eq-1}[F], k_{eq2}[E], k_{eq-2} [F'], k_{eq3}[F'], k_{eq-3}[F''] $\approx$ k_1[F][aldehyde], k_2[F''][aldehyde]). It means that (*E*)- and (*Z*)-allyl species cannot equilibrate fast enough to compensate the consumed material in carbonyl addition. The forming rate of *anti*-adduct is still much faster than *syn*-product at the beginning of reaction, but it may not be true as the concentration of (*E*)-allyliridium becomes lower than that of (*Z*)-isomer. Therefore, the diastereomeric ratio will corrode as reaction continues.

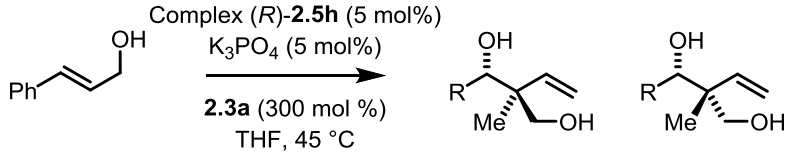
It is not surprising now to learn that lowering concentration of reaction mixtures can improve diastereoselectivity of *tert*-(hydroxy)prenylation. Since interconversions between isomers are first order reactions, while carbonyl addition is second order, diluting reaction will make the nucleophilic addition even slower. As a result, "fast" equilibrium between geometric isomers of allyliridium will be established again, and high stereoselectivity is retained. A series of reactions between 4-bromobenzaldehyde and isoprene monoxide under different concentrations were conducted (Table 2.4, top). Diastereoselectivity of reactions increased as expected when concentration of substrates became lower. The same effect could also be observed in reactions from alcohol oxidation level (Table 2.4, bottom).

Table 2.4 Concentration dependent diastereoselectivity in iridium-catalyzed *tert*-(hydroxy)prenylation of alcohols or aldehydes.



2.2a (100 mol%) | *anti*-**2.4a** (major) | *syn*-**2.4a** (minor)

Entry	THF (conc.)	Yield	*anti*:*syn* (ee%)
1	1.0 M	92%	6:1 (92)
2	0.5 M	87%	10:1 (94)
3	0.33 M	84%	14:1 (90)
4	0.1 M	79%	17:1 (90)



2.1f (100 mol%) | *anti*-**2.4f** (major) | *syn*-**2.4f** (minor)

Entry	THF (conc.)	Yield	*anti*:*syn* (ee%)
1	1.0 M	90%	9:1 (95)
2	0.5 M	88%	11:1 (95)
3	0.33 M	85%	40:1 (93)
4	0.1 M	trace	n.d.

2.4 CONCLUSION

The first diastereo- and enantioselective *tert*-(hydroxy)prenylation of primary alcohols and aldehydes has been developed. With chromatographically purified iridium complex (*R*)-**2.5h**, various types of alcohols and aldehydes readily coupled with isoprene monoxide (**2.3a**) to form products in good to excellent yield with high level of stereoselectivity. Furthermore, other vinyl epoxides such as butadiene monoxide (**2.3b**) and myrcene oxide (**2.3c**) reacted in similar fashion. The excellent diastereoselectivity observed in reactions is due to Curtin-Hammett control during the rate determining step. This methodology opened up a new way to access acyclic all-carbon quaternary centers, and it would be applied to total synthesis of terpenoid natural products with *tert*-(hydroxy)prenyl motif.

2.5 EXPERIMENTAL DETAILS

General Information

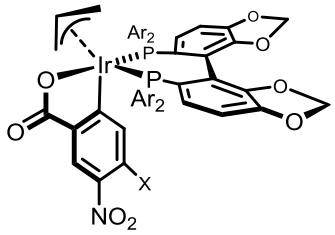
All reactions were run under an atmosphere of argon. Sealed tubes (13x100 mm) were purchased from Fischer Scientific (catalog number 14-959-35C) and were flame dried followed by cooling in a desiccator. Tetrahydrofuran, toluene, and dioxanes were distilled from sodium-benzophenone immediately prior to use. Ethyl Acetate was dried over potassium carbonate and distilled immediately prior to use. Anhydrous solvents were transferred by oven-dried syringes. Analytical thin-layer chromatography (TLC) was carried out using 0.25 mm commercial silica gel plates (Dynanmic Absorbents F_{254}). Visualization was accomplished with UV light followed by dipping in *p*-anisaldehyde stain solution then heating. Purification of reactions was carried out by flash chromatography using Silacycle silica gel (40-63 μm, unless indicated specifically). Potassium phosphate was purchased through Acros Organics, flame dried prior to use, and stored in a desiccator. All alcohol substrates were purchased from commercially available sources and purified prior to use. Cyclohexylacetaldehyde **2.2i** and geranial **2.2d** were prepared through known procedures with NMR spectra comparable to that in the literatures.[59,60] All other aldehydes were used from commercially available sources, and purified via distillation in a Hickman still or column chromatography prior to use.

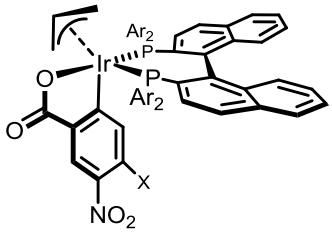
Spectroscopy, Spectrometry, and Data Collection

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, M+H, or M-H), or a suitable fragment ion. ^{1}H Nuclear magnetic resonance spectra were recorded using a 400 MHz spectrometer. Coupling constants are reported in Hertz (Hz) for $CDCl_3$ solutions, and chemical shifts are reported as parts per million (ppm) relative to residual

$CHCl_3$ δ_H (7.26 ppm). ^{13}C Nuclear magnetic resonance spectra were recorded using a 100 MHz spectrometer for $CDCl_3$ solutions, and chemical shifts are reported as parts per million (ppm) relative to residual $CDCl_3$ δ_C (77.0 ppm). The products formed through C-C coupling from the alcohol and aldehyde oxidation levels are identical in all respects outside of diastereomeric ratios and enantiomeric excess. Melting points were taken on a Stuart SMP3 melting point apparatus.

General Procedures for Preparation of Preformed Iridium Catalysts





(*R*)-**2.5a**, Ar = Ph, X = H
(*R*)-**2.5b**, Ar = Ph, X = CN
(*R*)-**2.5c**, Ar = 3,5-Me_2Ph, X = H
(*R*)-**2.5d**, Ar = 3,5-Me_2Ph, X = CN
(*R*)-**2.5e**, Ar = Ph, X = H
(*R*)-**2.5f**, Ar = Ph, X = CN
(*R*)-**2.5g**, Ar = 4-MePh, X = H
(*R*)-**2.5h**, Ar = 4-MePh, X = CN

A sealed tube equipped with a magnetic stir bar was added Cs_2CO_3 (169 mg, 0.52 mmol, 200 mol%), corresponding benzoic acid (0.52 mmol, 200 mol%), bidentate phosphine ligand (0.26 mmol, 100 mol%), $[Ir(cod)Cl]_2$ (87.3 mg, 0.13 mmol, 50 mol%). The mixture was purged with argon, and THF (2.6 mL, 0.1 M) was added, followed by addition of allyl acetate (0.070 mL, 0.65 mmol, 250 mol%). The resulted mixture was stirred at room temperature for 30 min, and then was stirred at 80 ˚C for another 90 min. After cooled to ambient temperature, the mixture was filtered through a celite plug and washed by DCM (50 mL) until all yellow residue was dissolved. The combined filtrate was concentrated *in vacuo* and purified by column chromatography on silica gel (DCM:THF = 15:1). The obtained gum-like product was dissolved in THF (0.6 mL), and precipitated upon rapid addition of HPLC grade hexanes (6 mL). The product was filtered

and washed by small amount of HPLC grade hexanes, followed by removal of trace amount of solvent *in vacuo*.

(*R*)-**2.5a**: 3-nitrobenzoic acid (87 mg) and (*R*)-SEGPHOS (159 mg) was used. The title complex was obtained as light yellow powder in 63% yield (166 mg).

(*R*)-**2.5b**: 4-cyano-3-nitrobenzoic acid (100 mg) and (*R*)-SEGPHOS (159 mg) was used. The title complex was obtained as yellow powder in 62% yield (167 mg).

(*R*)-**2.5c**: 3-nitrobenzoic acid (87 mg) and (*R*)-DM-SEGPHOS (188 mg) was used. The title complex was obtained as yellow powder in 47% yield (110 mg).

(*R*)-**2.5d**: 4-cyano-3-nitrobenzoic acid (100 mg) and (*R*)-DM-SEGPHOS (188 mg) was used. The title complex was obtained as bright yellow powder in 82% yield (243 mg).

(*R*)-**2.5e**: 3-nitrobenzoic acid (87 mg) and (*R*)-BINAP (162 mg) was used. After chromatography purification, the title complex was obtained as light yellow powder in 83% yield (221 mg) without any further precipitation.

(*R*)-**2.5f**: 4-cyano-3-nitrobenzoic acid (100 mg) and (*R*)-BINAP (162 mg) was used. The title complex was obtained as yellow powder in 63% yield (171 mg).

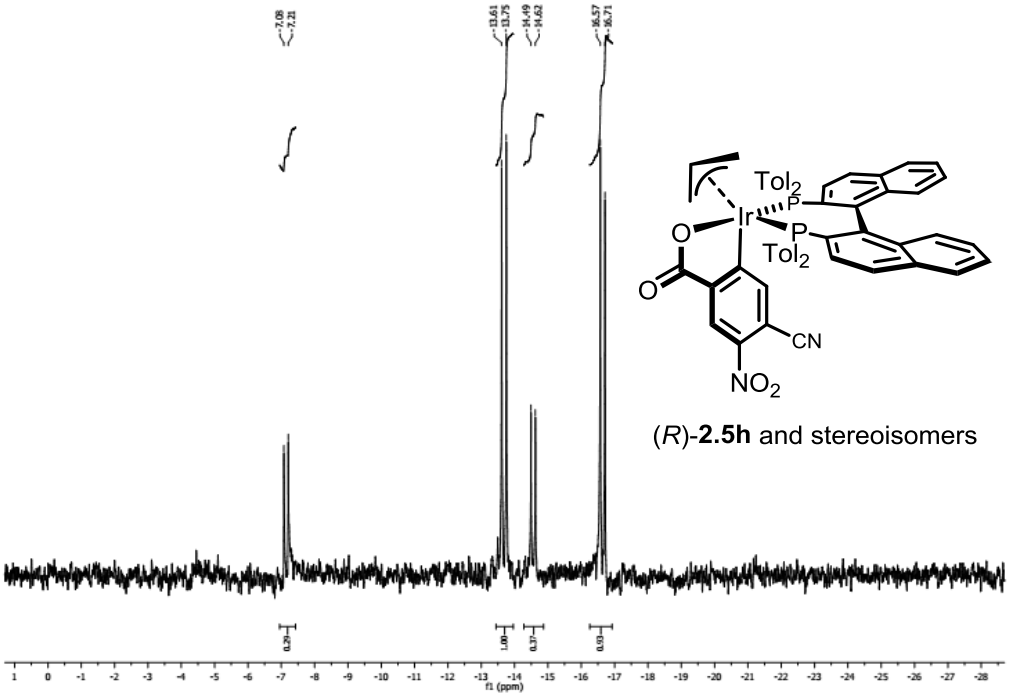
(*R*)-**2.5g**: 3-nitrobenzoic acid (87 mg) and (*R*)-TolBINAP (176 mg) was used. The title complex was obtained as yellow powder in 73% yield (205 mg).

(*R*)-**2.5h**: 4-cyano-3-nitrobenzoic acid (100 mg) and (*R*)-TolBINAP (176 mg) was used. The title complex was obtained as yellow powder in 70% yield (202 mg).

^{31}P NMR (162 MHz, $CDCl_3$) δ -7.14* (d, J = 21.2 Hz, 0.3H), -13.68 (d, J = 22.7 Hz, 1H), -14.56* (d, J = 21.2 Hz, 0.3H), -16.64 (d, J = 22.7 Hz, 1H).

HRMS (ESI) Calcd. for $C_{59}H_{47}IrN_2O_4P_2Na$ $[M+Na]^+$: 1125.2537, Found: 1125.2525.

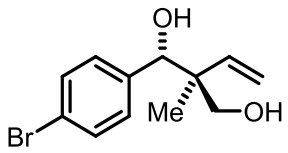
MP 228.3-229.9 ˚C (decomposed)



(*R*)-**2.5h** and stereoisomers

Detailed Procedures and Spectral Data for *tert*-(Hydroxy)Prenylation of Alcohols (2.1a-j) and Aldehydes (2.2a-i)

(1*S*,2*S*)-1-(4-bromophenyl)-2-methyl-2-vinylpropane-1,3-diol (2.4a)



Detailed Procedures

From alcohol oxidation level: An oven-dried pressure tube equipped with a magnetic stir bar was charged with K_3PO_4 (2.2 mg, 0.01 mmol, 5 mol%), (*R*)-**2.5h** (11.0 mg, 0.01 mmol, 5 mol%), and 4-bromobenzyl alcohol (37.4 mg, 0.2 mmol, 100 mol%). The reaction vessel was placed under an atmosphere of argon, and THF (0.4 mL, 0.5 M) and isoprene monoxide (59 μL, 0.6 mmol, 300 mol%) were added by syringe. The reaction vessel was sealed and the reaction mixture was allowed to stir at 45 ˚C for 1 day. The reaction was allowed to reach ambient temperature and concentrated *in vacuo*. The residue was subjected to column chromatography (SiO_2: hexanes:ethyl acetate, 5:1) to furnish the title compound as a white solid (49.5 mg, *anti*:*syn* > 20:1) in 91% yield.

From aldehyde oxidation level: An oven-dried pressure tube equipped with a magnetic stir bar was charged with K_3PO_4 (2.2 mg, 0.01 mmol, 5 mol%), (*R*)-**2.5h** (11.0 mg, 0.01 mmol, 5 mol%), and 4-bromobenzaldehyde (37.0 mg, 0.2 mmol, 100 mol%). The reaction vessel was placed under an atmosphere of argon, and THF (0.4 mL, 0.5 M), 2-propanol (46 μL, 0.6 mmol, 300 mol%) and isoprene monoxide (59 μL, 0.6 mmol, 300 mol%) were added by syringe. The reaction vessel was sealed and the reaction mixture was allowed to stir at 45 ˚C for 1 day. The reaction was allowed to reach ambient temperature and concentrated *in vacuo*. The residue was subjected to column chromatography (SiO_2: hexanes:ethyl acetate, 5:1) to furnish the title compound as a white solid (46.9 mg, *anti*:*syn* = 10:1) in 87% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.5 Hz, 2H), 7.16 (d, *J* = 8.4 Hz, 2H), 6.02 (dd, *J* = 17.7, 11.0 Hz, 1H), 5.22 (dd, *J* = 11.0, 1.1 Hz, 1H), 5.01 (dd, *J* = 17.7, 1.2 Hz, 1H), 4.65 (s, 1H), 3.60 (d, *J* = 10.7 Hz, 1H), 3.52 (d, *J* = 10.7 Hz, 1H), 3.28 (br, 1H), 2.62 (br, 1H), 0.87 (s, 3H).

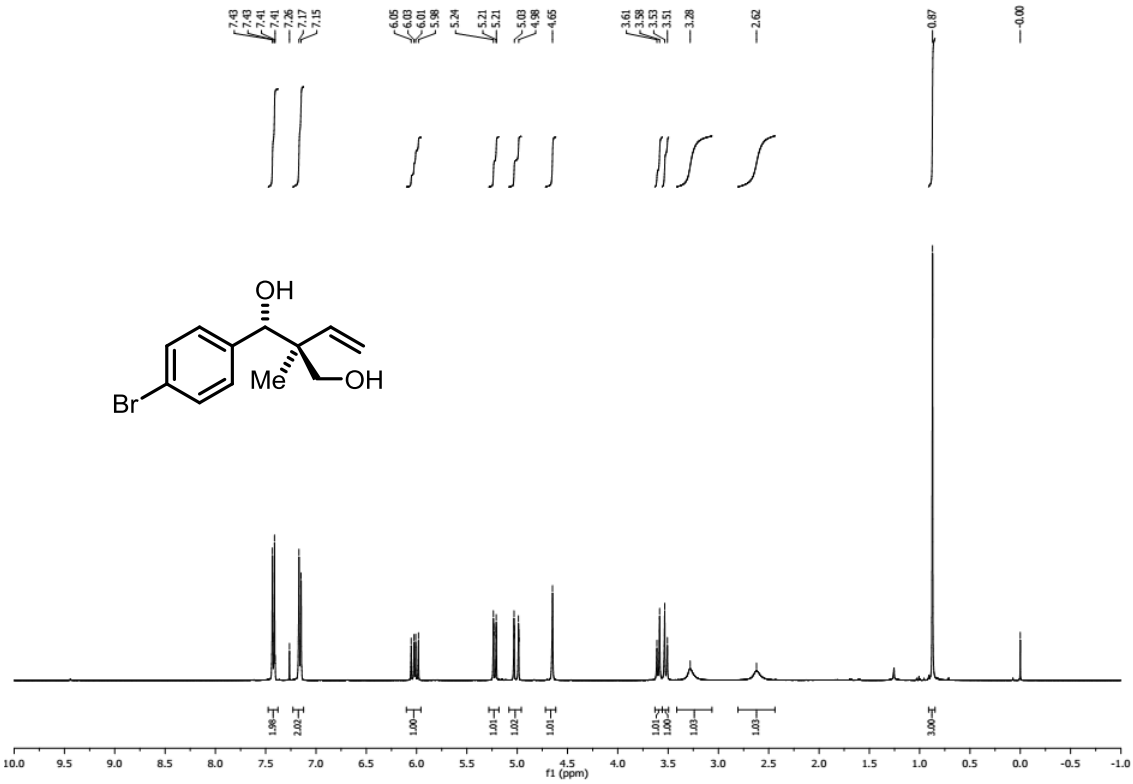
^{13}C NMR (100 MHz, $CDCl_3$) δ 139.7, 139.1, 130.8, 129.4, 121.5, 116.6, 79.2, 69.8, 46.3, 17.6.

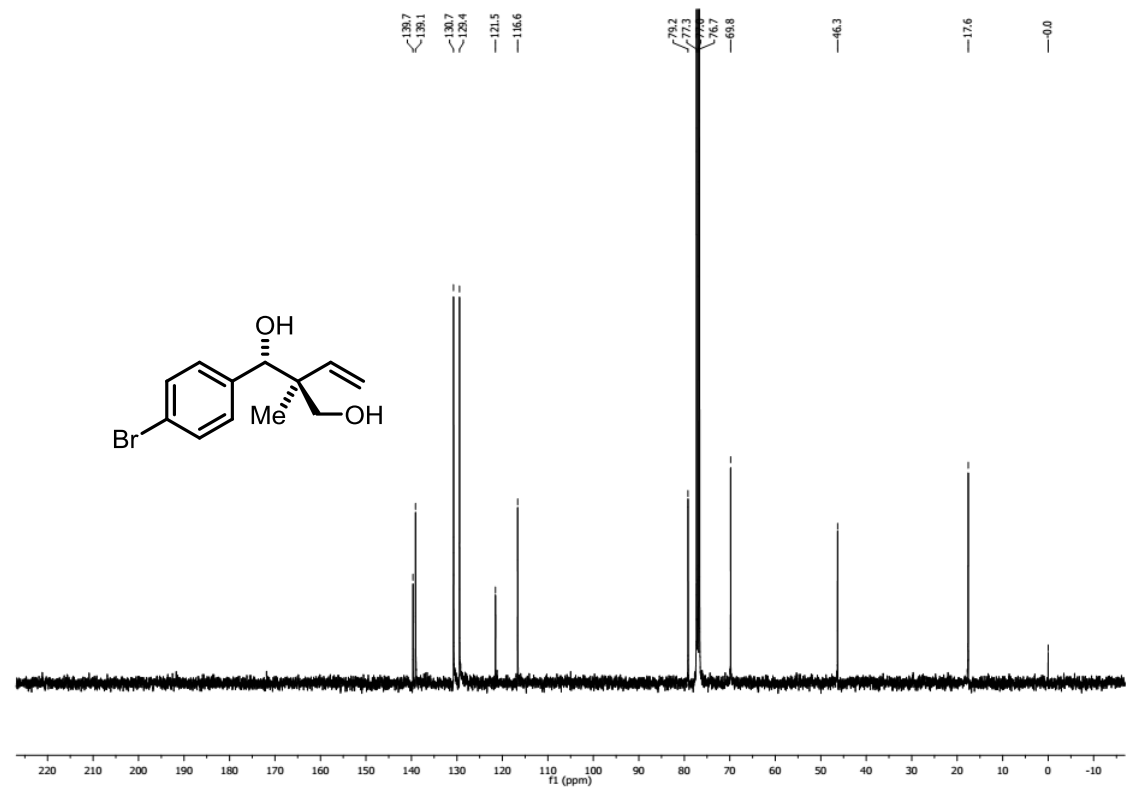
LRMS (ESI) Calcd. for $C_{12}H_{15}BrO_2Na$ $[M+Na]^+$: 293.0, Found: 293.0.

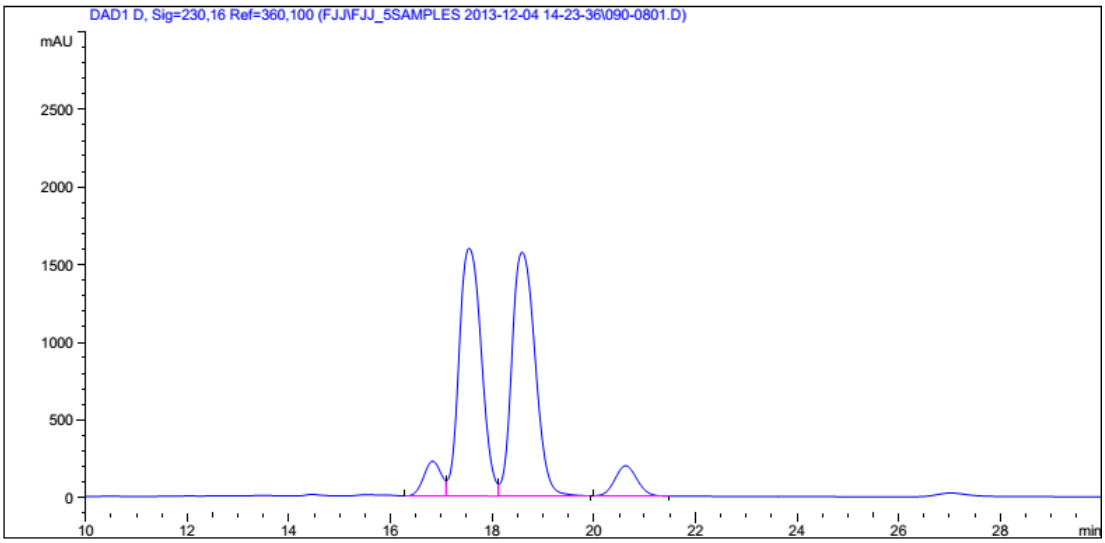
FTIR (neat): 3343, 2926, 1637, 1592, 1486, 1404, 1200, 1104, 1070, 1036, 1009, 921, 826, 755, 698 cm^{-1}.

MP 51.1-51.7 ˚C

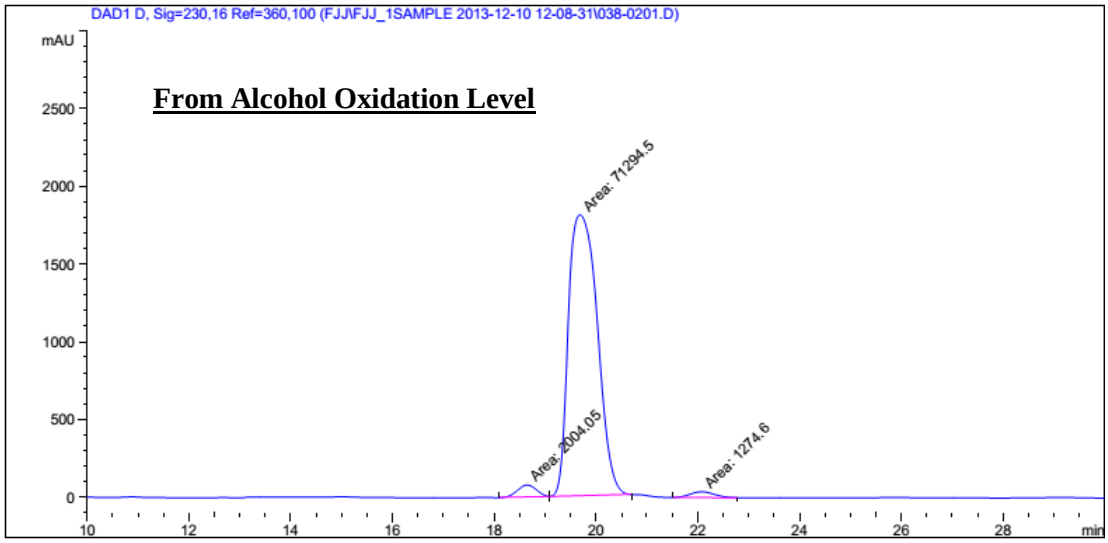
HPLC (Chiralcel OD-H column, hexanes:*i*-PrOH = 90:10, 0.50 mL/min, 230 nm), *anti*:*syn* = 40:1, *ee* = 94% from 4-bromobenzyl alcohol; *ee* = 94% from 4-bromobenzaldehyde.


OH
Me
OH
Br
f1 (ppm)

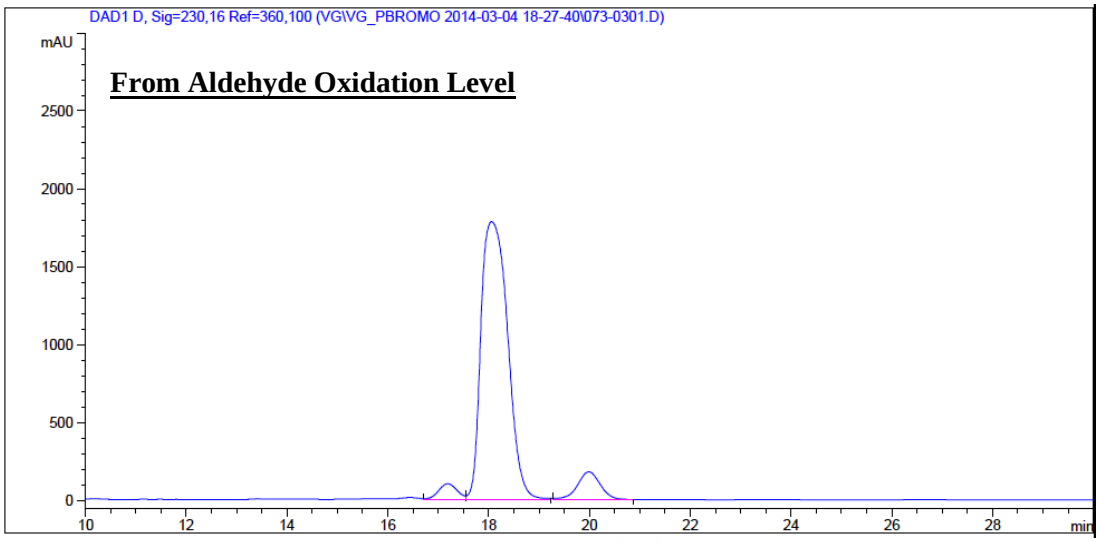

OH
Me
OH
Br
f1 (ppm)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.824	VV	0.3739	5373.34814	223.97386	4.8940
2	17.542	VV	0.4869	4.85357e4	1595.49243	44.2062
3	18.583	VB	0.5048	4.99210e4	1570.89380	45.4679
4	20.622	BB	0.4736	5963.83789	195.68607	5.4319

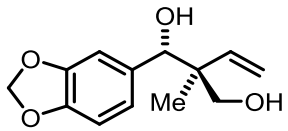


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.642	MM	0.4320	2004.05054	77.31152	2.6874
2	19.680	MM	0.6576	7.12945e4	1807.01978	95.6034
3	22.074	MM	0.5602	1274.59680	37.91838	1.7092



Peak #	Time [min]	Type	Area [mAU*s]	Height [mAU]	Width [min]	Start [min]	End [min]
1	17.183	VV	2589.09790	101.23418	0.3984	16.715	17.536
2	18.055	VB	6.55493e4	1783.26868	0.5968	17.536	19.244
3	19.983	BB	5596.25928	177.88858	0.4830	19.270	20.864

(1*S*,2*S*)-1-(benzo[d][1,3]dioxol-5-yl)-2-methyl-2-vinylpropane-1,3-diol (2.4b)



Detailed Procedures

From alcohol oxidation level: An oven-dried pressure tube equipped with a magnetic stir bar was charged with K_3PO_4 (2.2 mg, 0.01 mmol, 5 mol%), (*R*)-**2.5h** (11.0 mg, 0.01 mmol, 5 mol%), and piperonyl alcohol (30.4 mg, 0.2 mmol, 100 mol%). The reaction vessel was placed under an atmosphere of argon, and THF (0.2 mL, 1 M) and isoprene monoxide (59 μL, 0.6 mmol, 300 mol%) were added by syringe. The reaction vessel was sealed and the reaction mixture was allowed to stir at 45 ˚C for 1 day. The reaction was allowed to reach ambient temperature and concentrated *in vacuo*. The residue was subjected to column chromatography (SiO_2: hexanes:ethyl acetate, 4:1) to furnish the title compound as a colorless oil (42.1 mg, *anti*:*syn* > 20:1) in 89% yield.

From aldehyde oxidation level: An oven-dried pressure tube equipped with a magnetic stir bar was charged with K_3PO_4 (2.2 mg, 0.01 mmol, 5 mol%), (*R*)-**2.5h** (11.0 mg, 0.01 mmol, 5 mol%), and piperonal (30.0 mg, 0.2 mmol, 100 mol%). The reaction vessel was placed under an atmosphere of argon, and THF (0.2 mL, 1 M), 2-propanol (46 μL, 0.6 mmol, 300 mol%), and isoprene monoxide (59 μL, 0.6 mmol, 300 mol%) were added by syringe. The reaction vessel was sealed and the reaction mixture was allowed to stir at 45 ˚C for 1 day. The reaction was allowed to reach ambient temperature and concentrated *in vacuo*. The residue was subjected to column chromatography (SiO_2: hexanes:ethyl acetate, 4:1) to furnish the title compound as a colorless oil (42.5 mg, *anti*:*syn* > 20:1) in 90% yield.

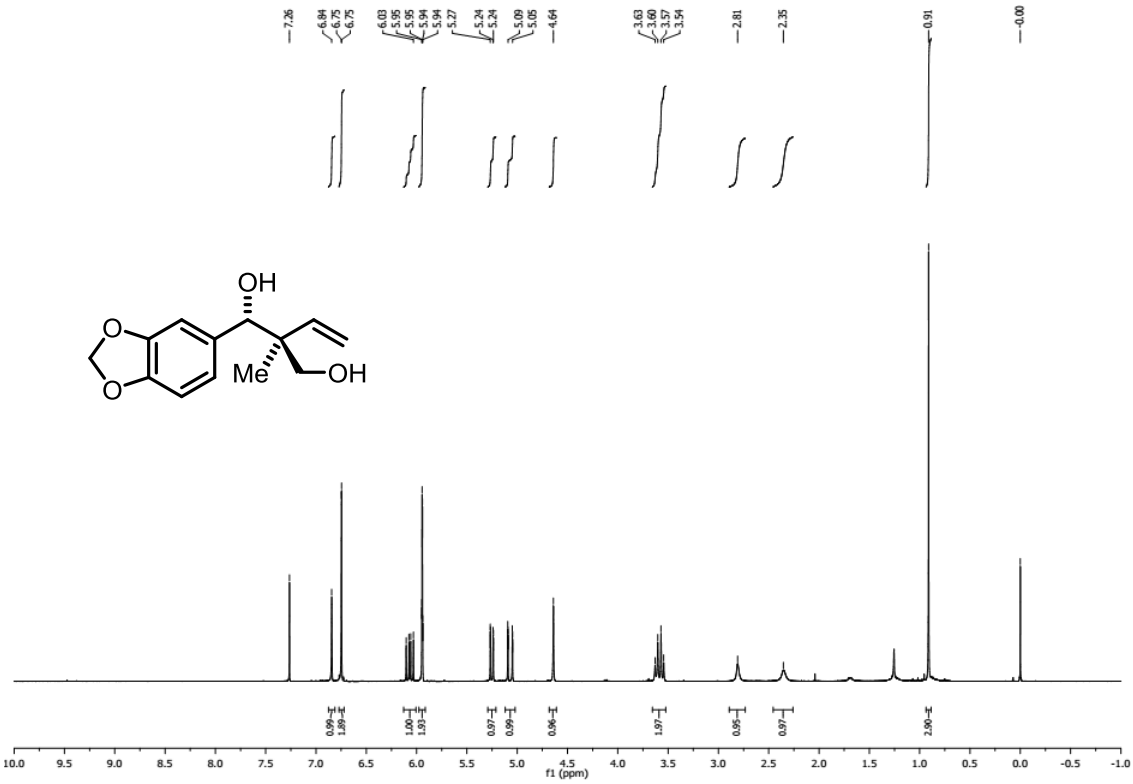
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84 (s, 1H), 6.75 (d, *J* = 0.5 Hz, 2H), 6.07 (dd, *J* = 17.8, 11.0 Hz, 1H), 5.96-5.93 (m, 2H), 5.25 (dd, *J* = 11.0, 1.3 Hz, 1H), 5.07 (dd, *J* = 17.8, 1.3 Hz, 1H), 4.64 (s, 1H), 3.62 (d, *J* = 10.7 Hz, 1H), 3.56 (d, *J* = 10.7 Hz, 1H), 2.81 (br, 1H), 2.35 (br, 1H), 0.91 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 147.1, 146.9, 139.6, 134.7, 121.1, 116.3, 108.2, 107.4, 100.9, 79.8, 69.9, 46.5, 17.7.

LRMS (ESI) Calcd. for $C_{13}H_{16}O_4Na$ $[M+Na]^+$: 259.1, Found: 259.1.

FTIR (neat): 3362, 2922, 1739, 1504, 1487, 1442, 1372, 1241, 1124, 1094, 1038, 929, 866, 816, 757 cm^{-1}.

HPLC (Chiralcel OJ-H column, hexanes:*i*-PrOH = 95:5, 0.50 mL/min, 280 nm), *anti*:*syn* = 60:1, *ee* = 91% from piperonyl alcohol; *anti*:*syn* = 50:1, *ee* = 90% from piperonal.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6.75
6.03
5.95
5.95
5.94
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5.27
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5.24
5.09
5.05
4.64
3.63
3.60
3.57
3.54
2.81
2.35
0.91
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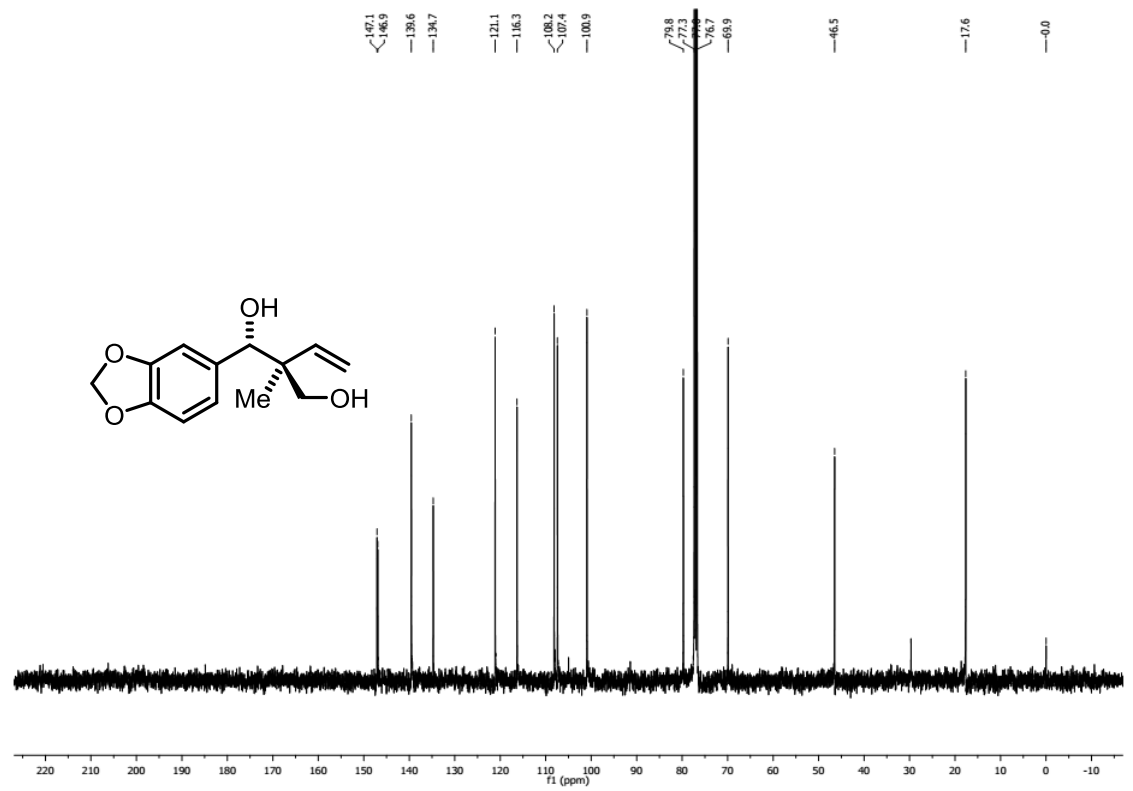
OH
O
O
Me
OH
0.99
1.89
1.00
1.93
0.97
0.99
0.96
1.97
0.95
0.97
2.90
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)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134.7
121.1
116.3
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107.4
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76.7
69.9
46.5
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OH
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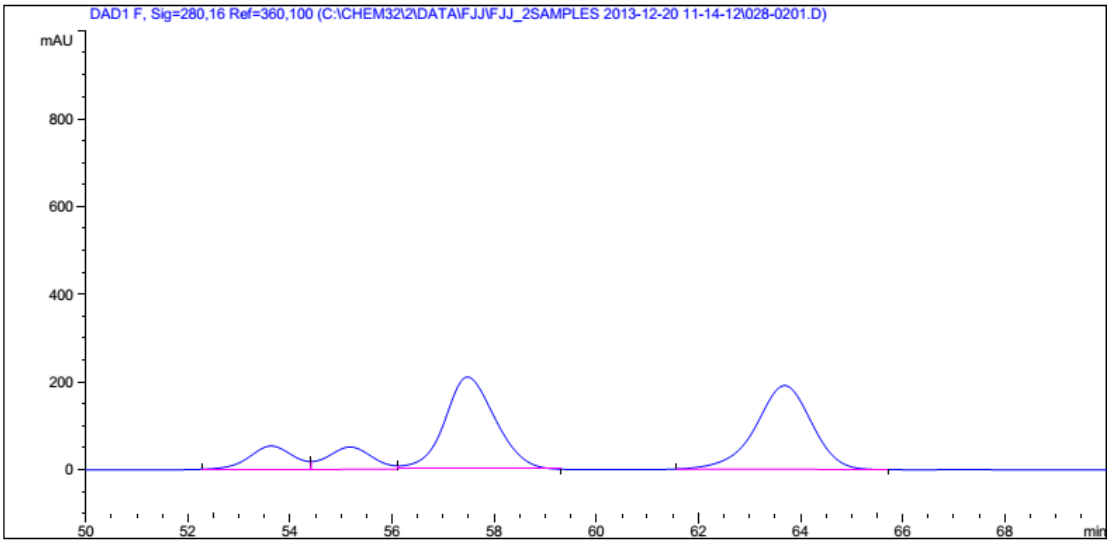
f1 (ppm)



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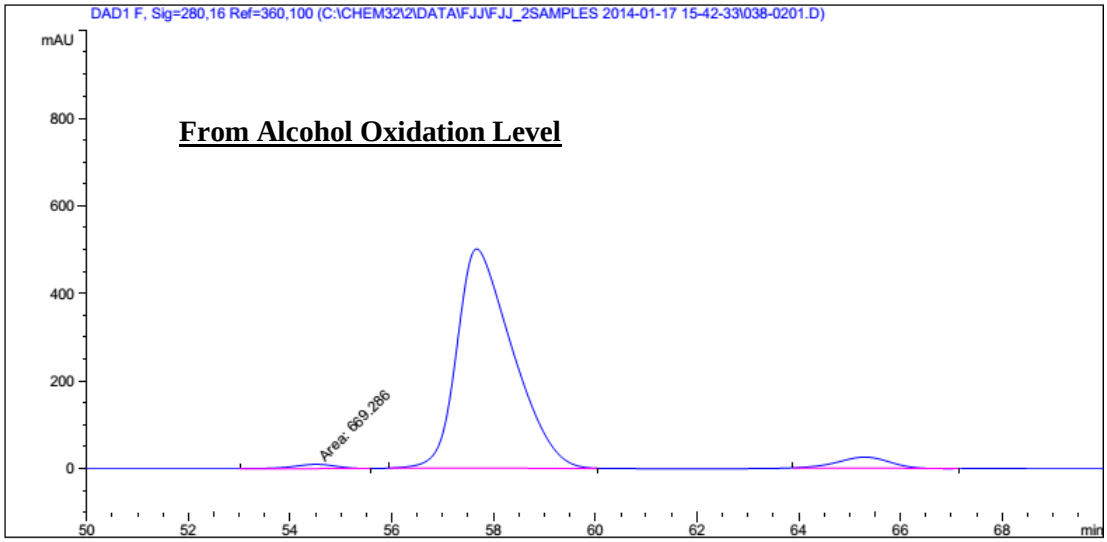
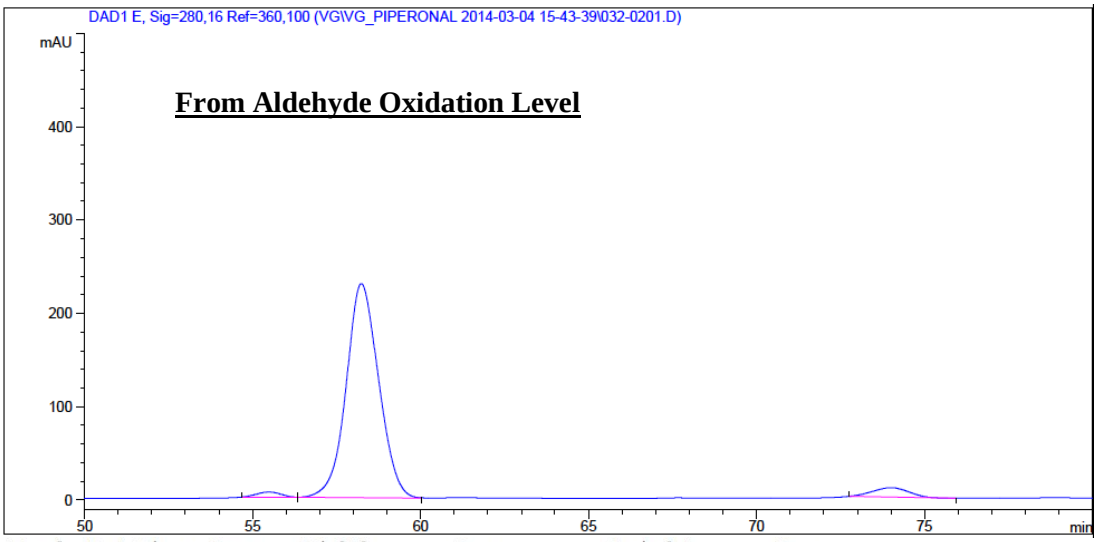
1	53.625	BV	0.9198	3254.34741	53.49318	9.1137
2	55.171	VV	0.9244	3139.77246	51.27665	8.7928
3	57.471	VB	1.0593	1.46131e4	210.66290	40.9235
4	63.683	BB	1.1709	1.47012e4	191.22240	41.1700



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	54.510	MM	1.0710	669.28601	10.41562	1.6446
2	57.661	BB	1.1436	3.81921e4	500.85275	93.8448
3	65.293	BB	1.0882	1835.71179	25.55136	4.5107



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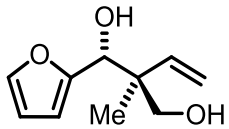
1	55.486	BV	0.7324	286.49448	5.60444	1.7399
2	58.236	VB	1.0328	1.54241e4	229.30447	93.6717
3	73.997	BB	0.9421	755.52783	10.06055	4.5884

(1*R*,2*S*)-1-(furan-2-yl)-2-methyl-2-vinylpropane-1,3-diol (4c)



Detailed Procedures

From alcohol oxidation level: An oven-dried pressure tube equipped with a magnetic stir bar was charged with K_3PO_4 (2.2 mg, 0.01 mmol, 5 mol%), (*R*)-**2.5h** (11.0 mg, 0.01 mmol, 5 mol%), and furfuryl alcohol (19.6 mg, 0.2 mmol, 100 mol%). The reaction vessel was placed under an atmosphere of argon, and THF (0.4 mL, 0.5 M) and isoprene monoxide (59 µL, 0.6 mmol, 300 mol%) were added by syringe. The reaction vessel was sealed and the reaction mixture was allowed to stir at 45 ˚C for 1 day. The reaction was allowed to reach ambient temperature and concentrated *in vacuo*. The residue was subjected to column chromatography (SiO_2: hexanes:ethyl acetate, 5:1) to furnish the title compound as a colorless oil (33.3 mg, *anti*:*syn* > 20:1) in 91% yield.

From aldehyde oxidation level: An oven-dried pressure tube equipped with a magnetic stir bar was charged with K_3PO_4 (2.2 mg, 0.01 mmol, 5 mol%), (*R*)-**2.5h** (11.0 mg, 0.01 mmol, 5 mol%), and furfural (19.2 mg, 0.2 mmol, 100 mol%). The reaction vessel was placed under an atmosphere of argon, and THF (0.6 mL, 0.33 M), 2-propanol (46 µL, 0.6 mmol, 300 mol%), and isoprene monoxide (59 µL, 0.6 mmol, 300 mol%) were added by syringe. The reaction vessel was sealed and the reaction mixture was allowed to stir at 45 ˚C for 1 day. The reaction was allowed to reach ambient temperature and concentrated *in vacuo*. The residue was subjected to column chromatography (SiO_2: hexanes:ethyl acetate, 5:1) to furnish the title compound as a colorless oil (33.1 mg, *anti*:*syn* = 5:1) in 91% yield.

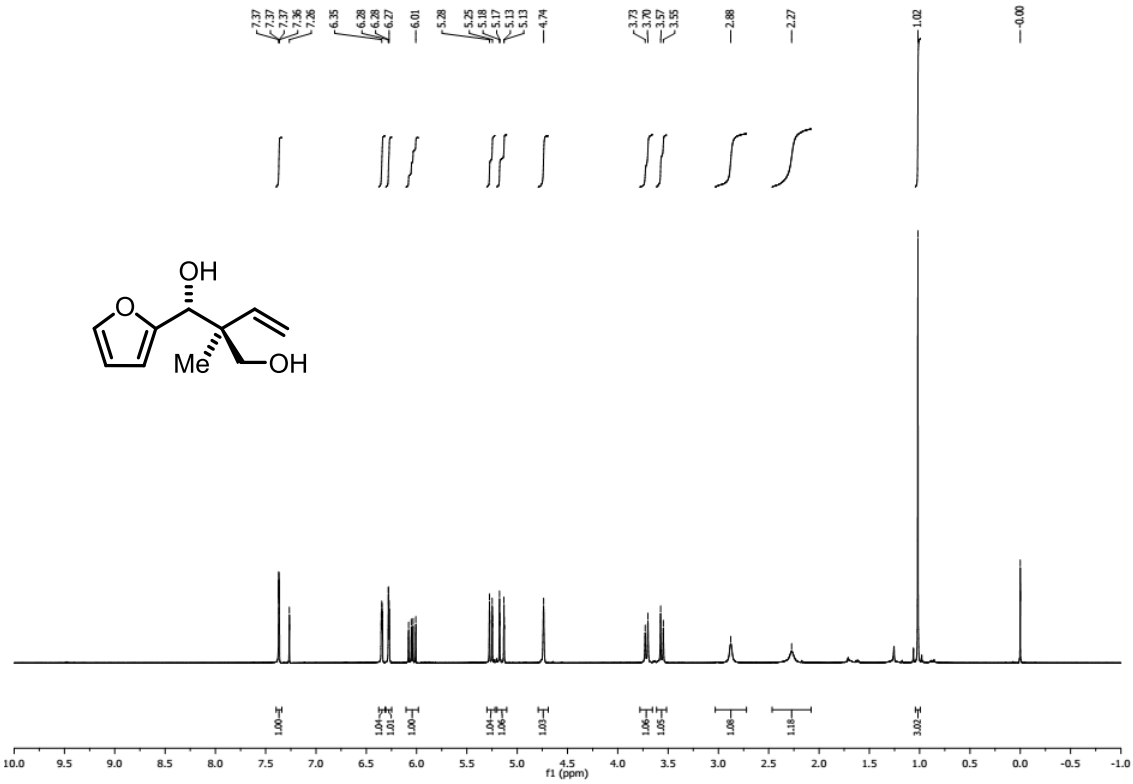
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (dd, *J* = 1.8, 0.8 Hz, 1H), 6.34 (dd, *J* = 3.1, 2.0 Hz, 1H), 6.30-6.26 (m, 1H), 6.04 (dd, *J* = 17.7, 11.0 Hz, 1H), 5.26 (dd, *J* = 11.0, 1.1 Hz, 1H), 5.15 (dd, *J* = 17.8, 1.1 Hz, 1H), 4.74 (s, 1H), 3.71 (d, *J* = 10.8 Hz, 1H), 3.56 (d, *J* = 10.9 Hz, 1H), 2.88 (br, 1H), 2.27 (br, 1H), 1.02 (s, 3H).

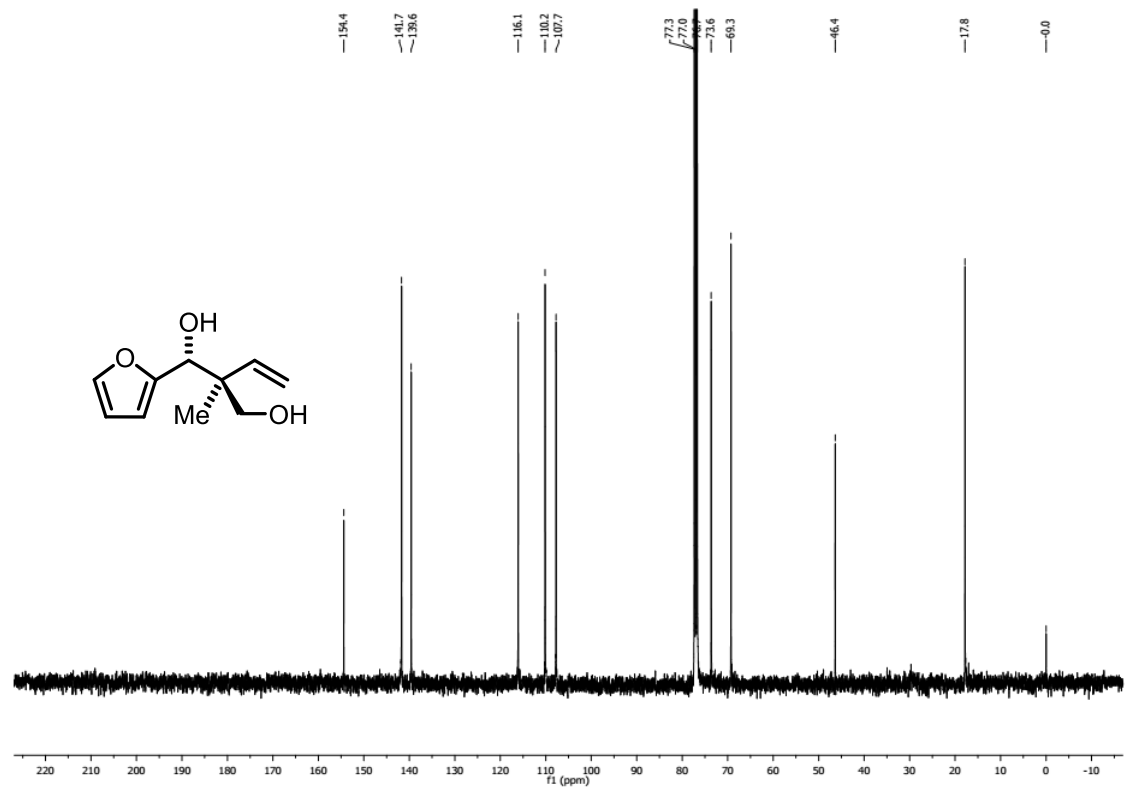
^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4, 141.7, 139.6 116.1, 110.2, 107.7, 73.6, 69.3, 46.4, 17.8.

LRMS (ESI) Calcd. for $C_{10}H_{14}O_3Na$ $[M+Na]^+$: 205.1, Found: 205.1.

FTIR (neat): 3363, 2923, 1637, 1503, 1459, 1416, 1259, 1148, 1007, 921, 884, 813, 734, 669 cm^{-1}.

HPLC (two connected Chiralcel OC-H columns, hexanes:*i*-PrOH = 88:12, 0.20 mL/min, 210 nm), *anti*:*syn* = 30:1, *ee* = 91% from furfuryl alcohol; *ee* = 94% from furfural.


OH
O
Me
OH
f1 (ppm)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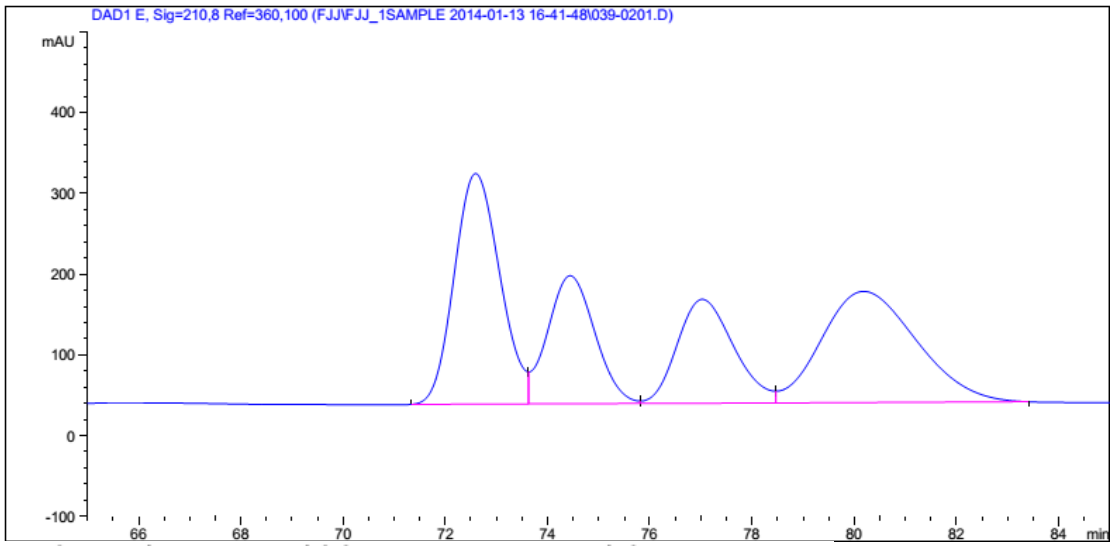
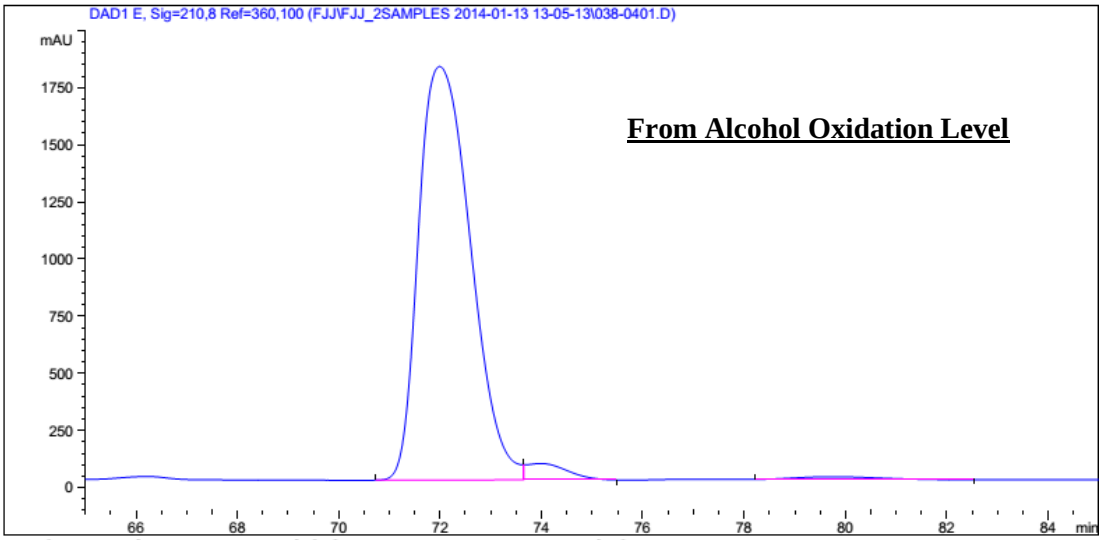
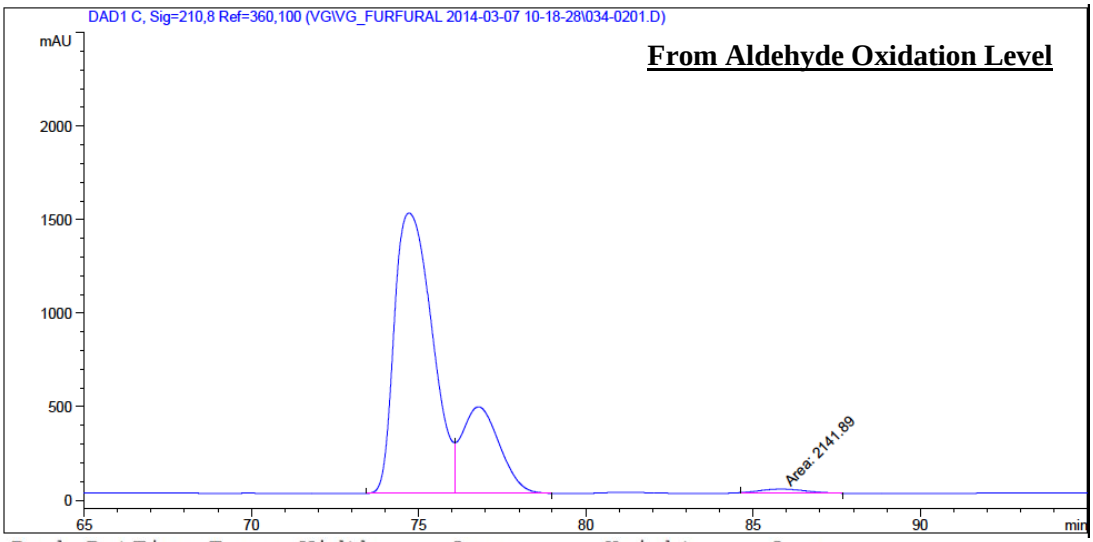


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	72.587	BV	0.9586	1.77582e4	285.93222	31.8576
2	74.436	VV	0.9860	1.02144e4	158.88849	18.3243
3	77.020	VV	1.1169	9909.42285	128.90489	17.7772
4	80.189	VB	1.7907	1.78604e4	137.93100	32.0409



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	71.984	BV	0.8527	1.29328e5	1811.90845	95.9316
2	73.980	VB	0.8027	4067.89795	72.71142	3.0175
3	79.761	BB	1.3577	1416.78125	12.22801	1.0509



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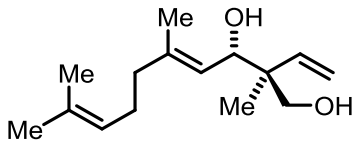
1	74.729	BV	0.9818	1.17614e5	1498.28320	75.3427
2	76.789	VB	1.1783	3.63492e4	462.78833	23.2852
3	85.848	MM	1.5995	2141.89429	22.31884	1.3721

(2*S*,3*S*,*E*)-2,5,9-trimethyl-2-vinyldeca-4,8-diene-1,3-diol (2.4d)



Detailed Procedures

From alcohol oxidation level: An oven-dried pressure tube equipped with a magnetic stir bar was charged with K_3PO_4 (2.2 mg, 0.01 mmol, 5 mol%), (*R*)-**2.5h** (11.0 mg, 0.01 mmol, 5 mol%), and geraniol (30.9 mg, 0.2 mmol, 100 mol%). The reaction vessel was placed under an atmosphere of argon, and THF (0.6 mL, 0.3 M) and isoprene monoxide (79 μL, 0.8 mmol, 400 mol%) were added by syringe. The reaction vessel was sealed and the reaction mixture was allowed to stir at 45 ˚C for 1 day. The reaction was allowed to reach ambient temperature and concentrated *in vacuo*. The residue was subjected to column chromatography (SiO_2: chloroform:methanol, 150:1) to furnish the title compound as a colorless oil (35.0 mg, *anti*:*syn* > 20:1) in 73% yield.

From aldehyde oxidation level: An oven-dried pressure tube equipped with a magnetic stir bar was charged with K_3PO_4 (2.2 mg, 0.01 mmol, 5 mol%), (*R*)-**2.5h** (11.0 mg, 0.01 mmol, 5 mol%), and geranial (30.4 mg, 0.2 mmol, 100 mol%). The reaction vessel was placed under an atmosphere of argon, and THF (0.4 mL, 0.5 M), 2-propanol (46 μL, 0.6 mmol, 300 mol%), and isoprene monoxide (59 μL, 0.6 mmol, 300 mol%) were added by syringe. The reaction vessel was sealed and the reaction mixture was allowed to stir at 45 ˚C for 1 day. The reaction was allowed to reach ambient temperature and concentrated *in vacuo*. The residue was subjected to column chromatography (SiO_2: chloroform:methanol, 50:1) to furnish the title compound as a colorless oil (36.7 mg, *anti*:*syn* = 20:1) in 77% yield.

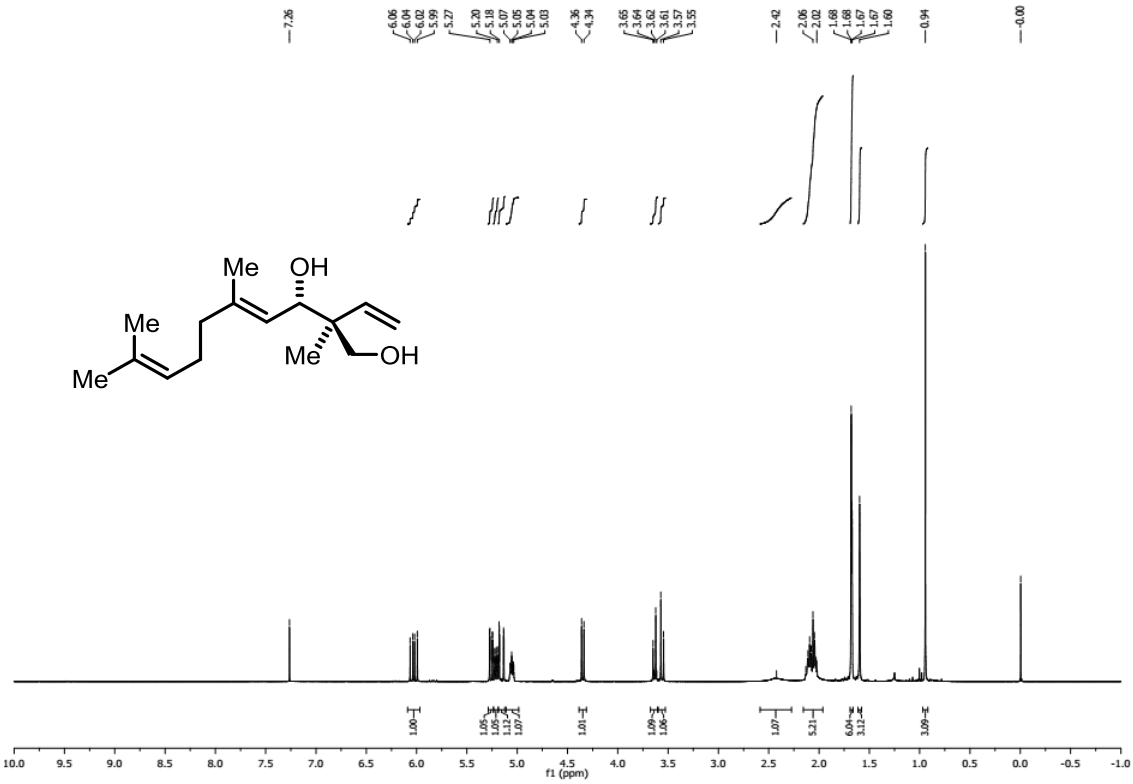
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.03 (dd, *J* = 17.7, 11.0 Hz, 1H), 5.26 (dd, *J* = 11.0, 1.4 Hz, 1H), 5.21 (dd, *J* = 9.4, 1.2 Hz, 1H), 5.16 (dd, *J* = 17.7, 1.4 Hz, 1H), 5.06 (ddd, *J* = 6.9, 4.1, 1.3 Hz, 1H), 4.35 (d, *J* = 9.4 Hz, 1H), 3.64 (d, *J* = 10.7 Hz, 1H), 3.56 (d, *J* = 10.8 Hz, 1H), 2.38 (br, 1H), 2.25-1.86 (m, 5H), 1.69 (d, *J* = 1.4 Hz, 3H), 1.68 (d, *J* = 1.0 Hz, 3H), 1.60 (s, 3H), 0.95 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 140.3, 139.8, 131.7, 123.9, 123.9, 116.0, 73.8, 69.9, 46.1, 39.8, 26.2, 25.7, 17.7, 17.2, 16.8.

LRMS (ESI) Calcd. $C_{15}H_{26}O_2Na$ for $[M+Na]^+$: 261.2, Found: 261.2.

FTIR (neat): 3340, 2966, 2922, 1669, 1637, 1439, 1415, 1377, 1260, 1097, 1035, 1009, 916, 818, 756, 668 cm^{-1}.

HPLC Diastereomeric ratio and enantiomeric excess was determined by HPLC analysis of the 1-benzoate of product (Chiralcel OD-H column, hexanes:*i*-PrOH = 99:1, 0.20 mL/min, 210 nm), *anti*:*syn* = 30:1, *ee* = 91% from geraniol; *ee* = 94% from geranial.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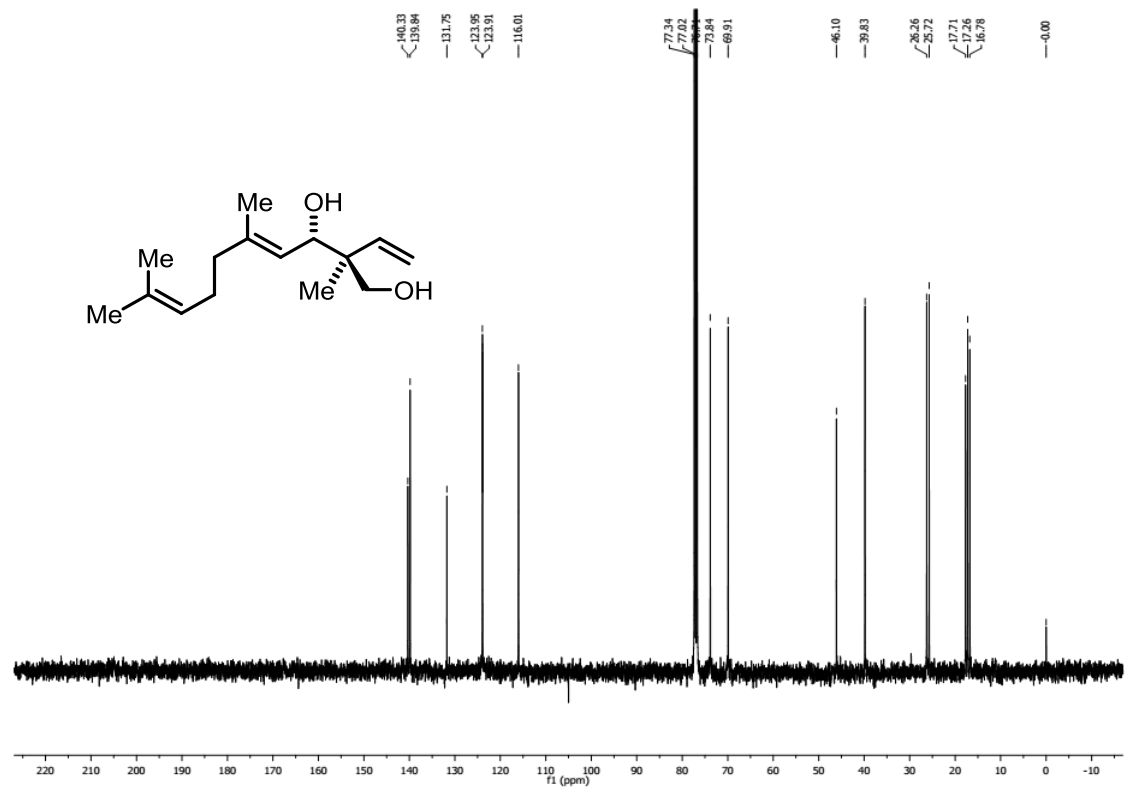
f1 (ppm)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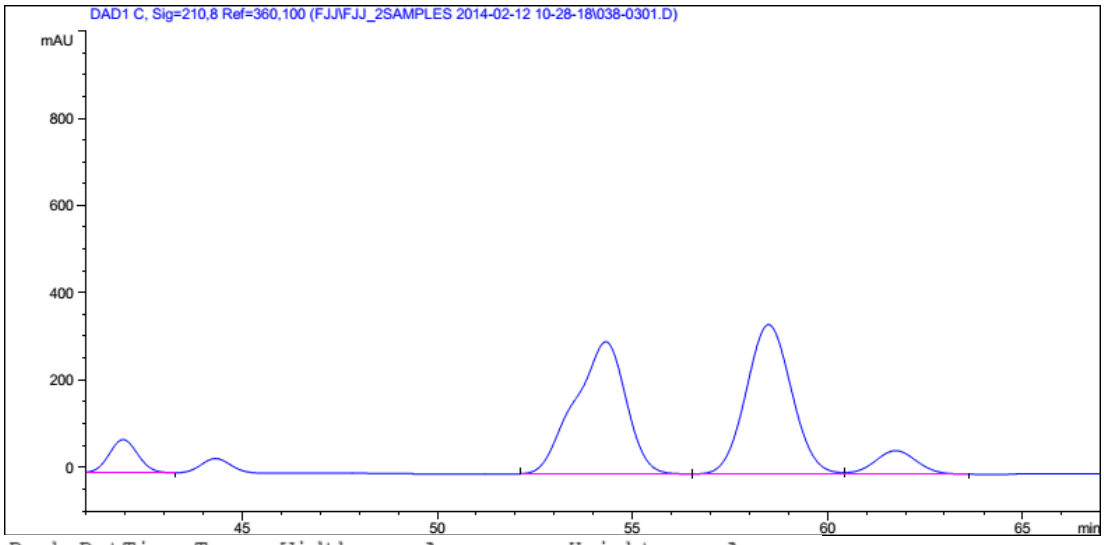

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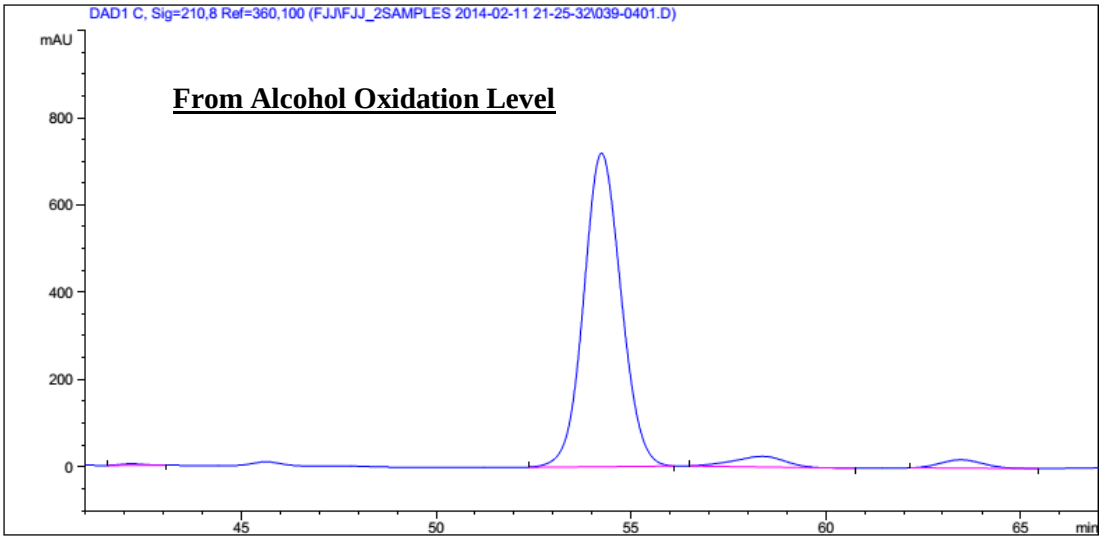
1	41.946	BB	0.7982	3878.34546	75.89896	6.1285
2	54.315	BV	1.3010	2.76214e4	303.16302	43.6467
3	58.485	VV	1.2532	2.77584e4	342.62363	43.8632
4	61.739	VB	1.1138	4025.89600	53.87474	6.3616



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
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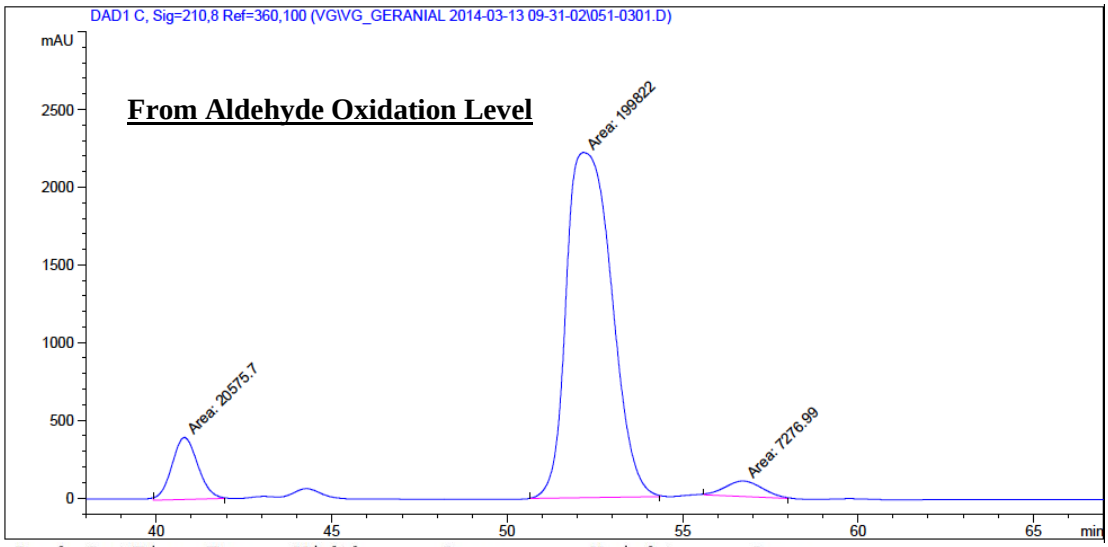
2	54.239	BB	1.0403	4.80523e4	718.49957	92.6957
3	58.361	BB	1.1394	2178.22876	24.16941	4.2019
4	63.462	BB	0.9835	1466.89954	19.06814	2.8297



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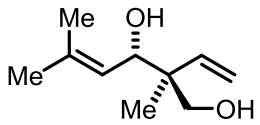
1	40.799	MM	0.8599	2.05757e4	398.80432	9.0374
2	52.176	MM	1.4991	1.99822e5	2221.62500	87.7664
3	56.739	MM	1.2249	7276.98828	99.01257	3.1962

(2*S*,3*S*)-2,5-dimethyl-2-vinylhex-4-ene-1,3-diol (2.4e)



Detailed Procedures

From alcohol oxidation level: An oven-dried pressure tube equipped with a magnetic stir bar was charged with K_3PO_4 (2.2 mg, 0.01 mmol, 5 mol%), (*R*)-**2.5h** (11.0 mg, 0.01 mmol, 5 mol%), and prenol (17.2 mg, 0.2 mmol, 100 mol%). The reaction vessel was placed under an atmosphere of argon, and THF (0.2 mL, 1 M) and isoprene monoxide (79 μL, 0.8 mmol, 400 mol%) were added by syringe. The reaction vessel was sealed and the reaction mixture was allowed to stir at 45 ˚C for 1 day. The reaction was allowed to reach ambient temperature and concentrated *in vacuo*. The residue was subjected to column chromatography (SiO_2: hexanes:ethyl acetate, 5:1) to furnish the title compound as a white solid (29.1 mg, *anti*:*syn* > 20:1) in 85% yield.

From aldehyde oxidation level: An oven-dried pressure tube equipped with a magnetic stir bar was charged with K_3PO_4 (2.2 mg, 0.01 mmol, 5 mol%), (*R*)-**2.5h** (11.0 mg, 0.01 mmol, 5 mol%), and prenal (16.8 mg, 0.2 mmol, 100 mol%). The reaction vessel was placed under an atmosphere of argon, and THF (0.4 mL, 0.5 M), 2-propanol (46 μL, 0.6 mmol, 300 mol%), and isoprene monoxide (59 μL, 0.6 mmol, 300 mol%) were added by syringe. The reaction vessel was sealed and the reaction mixture was allowed to stir at 45 ˚C for 1 day. The reaction was allowed to reach ambient temperature and concentrated *in vacuo*. The residue was subjected to column chromatography (SiO_2: hexanes:ethyl acetate, 5:1) to furnish the title compound as a white solid (27.6 mg, *anti*:*syn* = 20:1) in 81% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.04 (dd, *J* = 17.8, 11.0 Hz, 1H), 5.26 (dd, *J* = 11.0, 1.4 Hz, 1H), 5.22 (dq, *J* = 9.4, 1.4 Hz, 1H), 5.16 (dd, *J* = 17.8, 1.4 Hz, 1H), 4.34 (d, *J* = 9.4 Hz, 1H), 3.64 (d, *J* = 10.7 Hz, 1H), 3.56 (d, *J* = 10.7 Hz, 1H), 2.52 (br, 1H), 2.14 (br, 1H), 1.75 (d, *J* = 1.3 Hz, 3H), 1.70 (d, *J* = 1.3 Hz, 3H), 0.95 (s, 3H).

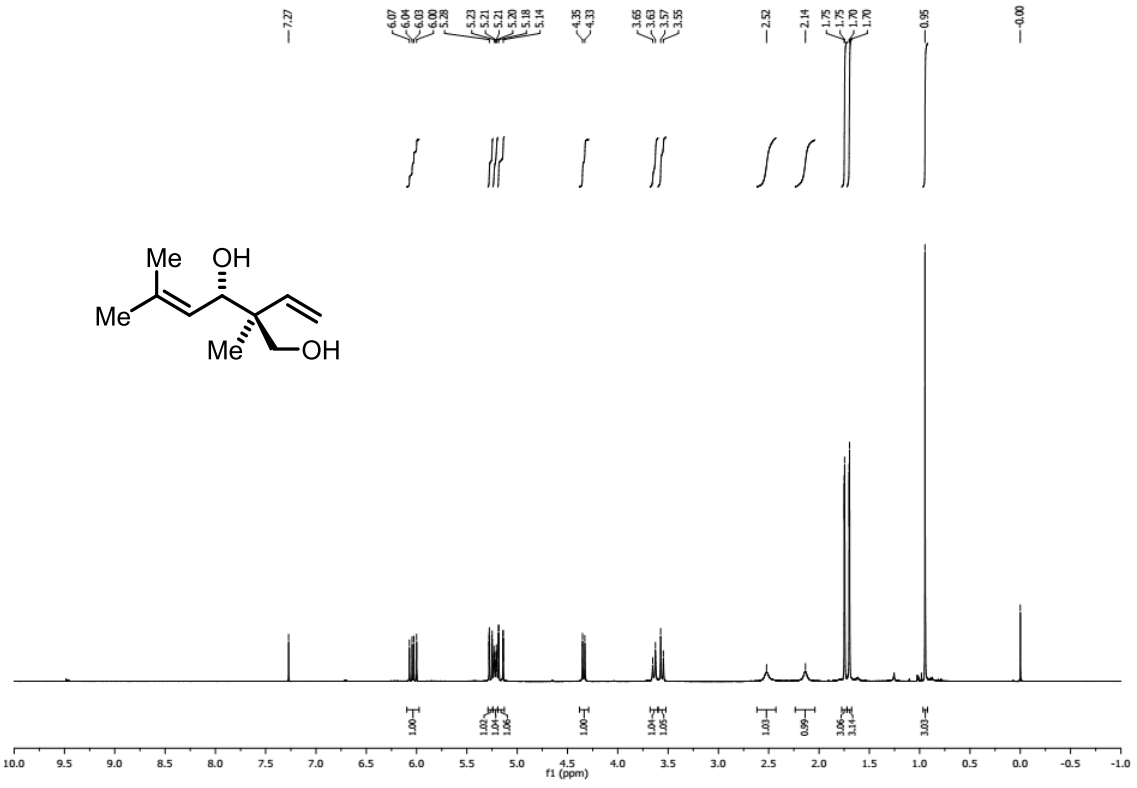
^{13}C NMR (100 MHz, $CDCl_3$) δ 139.8, 137.1, 123.9, 116.0, 73.9, 69.9, 46.0, 26.0, 18.4, 17.3.

LRMS (ESI) Calcd. $C_{10}H_{18}O_2Na$ for $[M+Na]^+$: 193.1, Found: 193.1.

FTIR (neat): 3361, 2969, 2923, 1675, 1637, 1445, 1416, 1376, 1005, 915, 846, 681 cm^{-1}.

MP 39.8-41.0 ˚C

HPLC Diastereomeric ratio and enantiomeric excess was determined by HPLC analysis of the 1-benzoate of product (two connected Chiralpak AD-H columns, hexanes:*i*-PrOH = 95:5, 0.20 mL/min, 210 nm), *anti*:*syn* > 99:1, *ee* = 93% from prenol; *ee* = 86% from prenal.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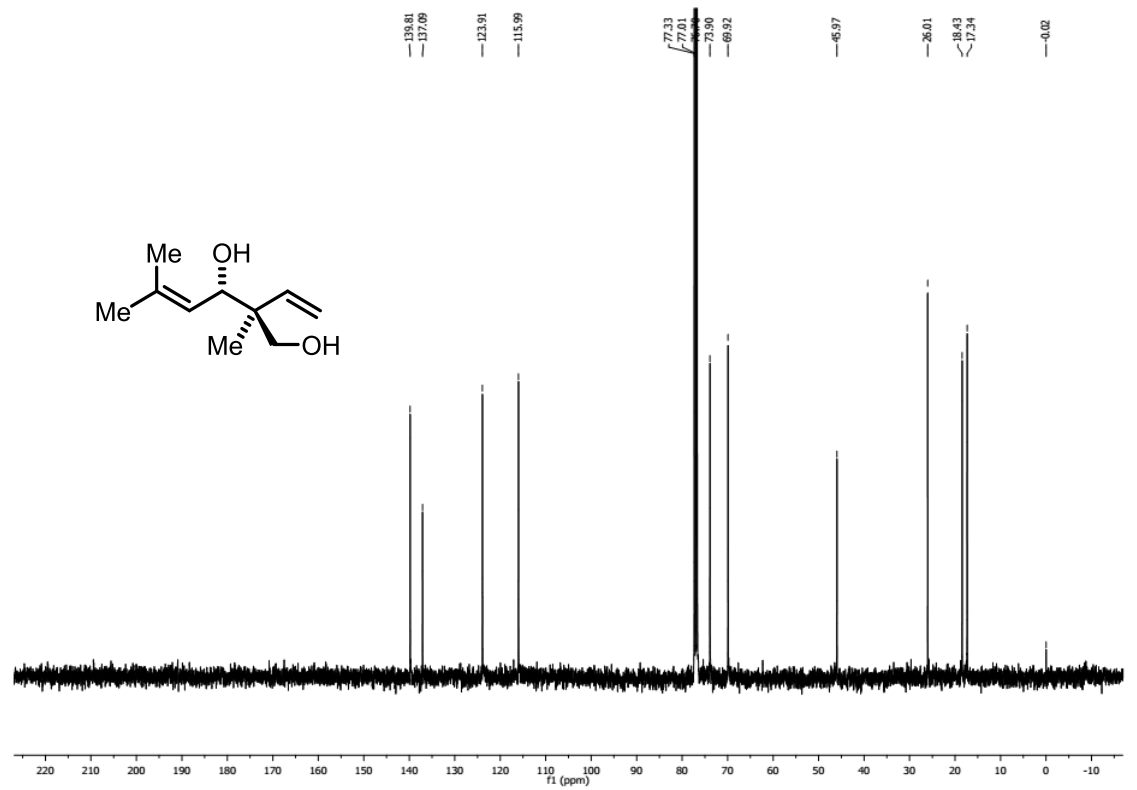
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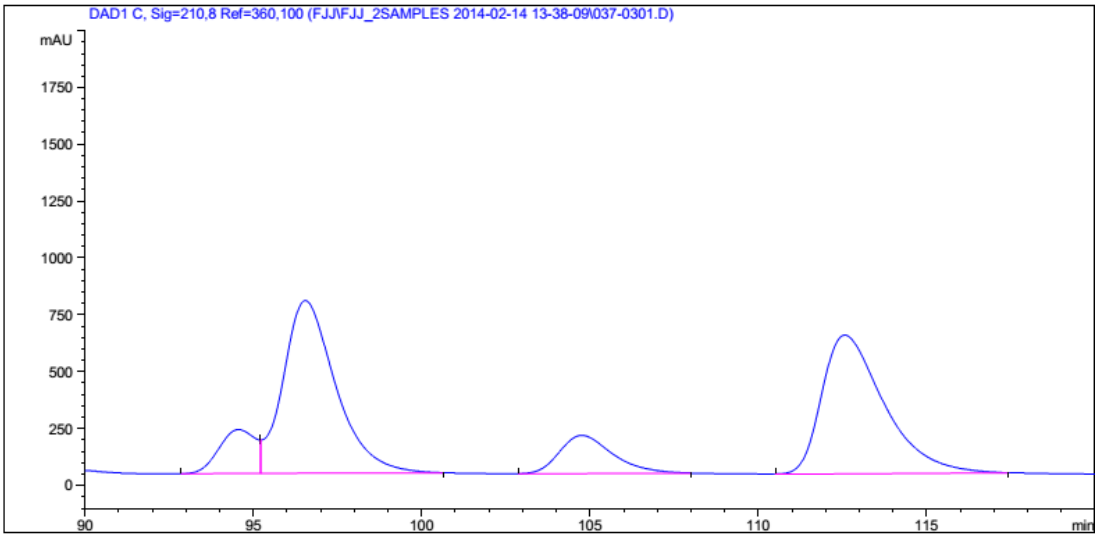

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1	94.556	BV	1.1457	1.45915e4	193.95432	7.5084
2	96.541	VB	1.6253	8.29694e4	760.21350	42.6943
3	104.758	BB	1.6311	1.84827e4	167.79832	9.5108
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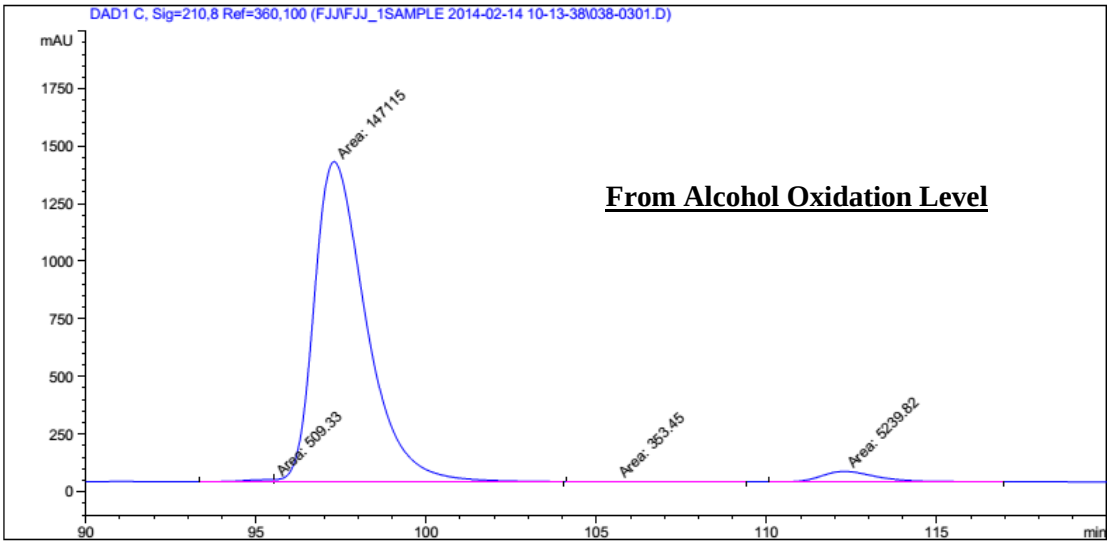
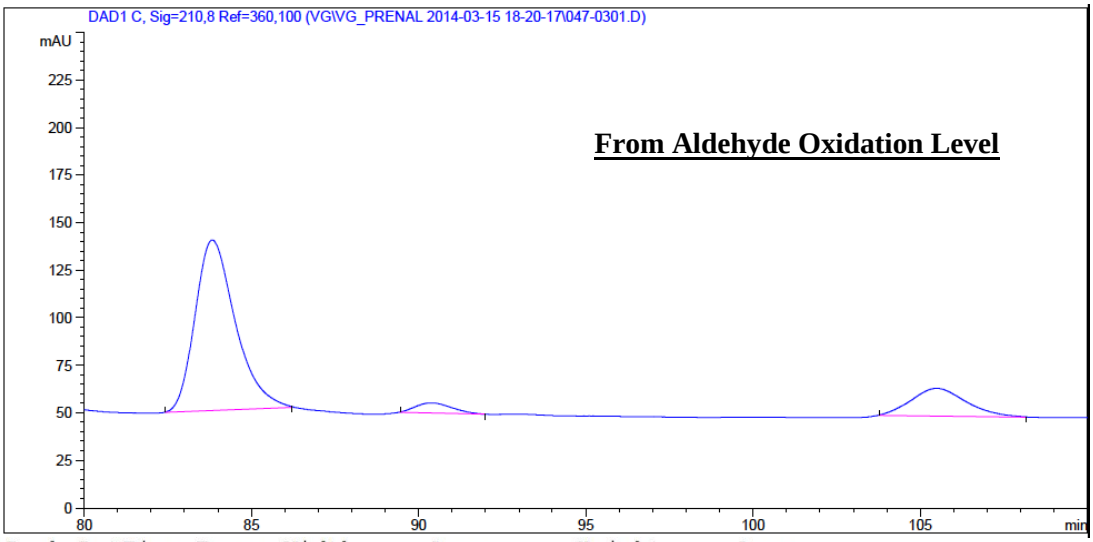


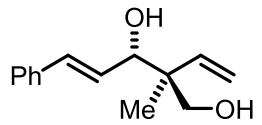
From Alcohol Oxidation Level

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	95.503	MF	0.9691	509.32959	8.75961	0.3324
2	97.292	FM	1.7649	1.47115e5	1389.27380	96.0170
3	105.569	MM	2.5649	353.45041	2.29672	0.2307
4	112.291	MM	1.9092	5239.81689	45.74290	3.4199



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	83.835	BB	1.2388	7536.07959	89.82337	78.5005
2	90.379	BB	0.8929	402.28818	5.31590	4.1905
3	105.492	BB	1.3433	1661.66968	14.58324	17.3090

(2*S*,3*S*,*E*)-2-methyl-5-phenyl-2-vinylpent-4-ene-1,3-diol (2.4f)



Detailed Procedures

From alcohol oxidation level: An oven-dried pressure tube equipped with a magnetic stir bar was charged with K_3PO_4 (2.2 mg, 0.01 mmol, 5 mol%), (*R*)-**2.5h** (11.0 mg, 0.01 mmol, 5 mol%), and cinnamyl alcohol (26.8 mg, 0.2 mmol, 100 mol%). The reaction vessel was placed under an atmosphere of argon, and THF (0.6 mL, 0.3 M) and isoprene monoxide (59 μL, 0.6 mmol, 300 mol%) were added by syringe. The reaction vessel was sealed and the reaction mixture was allowed to stir at 45 ˚C for 1 day. The reaction was allowed to reach ambient temperature and concentrated *in vacuo*. The residue was subjected to column chromatography (SiO_2: hexanes:ethyl acetate, 5:1) to furnish the title compound as a white solid (37.2 mg, *anti*:*syn* > 20:1) in 85% yield.

From aldehyde oxidation level: An oven-dried pressure tube equipped with a magnetic stir bar was charged with K_3PO_4 (2.2 mg, 0.01 mmol, 5 mol%), (*R*)-**2.5h** (11.0 mg, 0.01 mmol, 5 mol%), and cinnamaldehyde (26.4 mg, 0.2 mmol, 100 mol%). The reaction vessel was placed under an atmosphere of argon, and THF (2.0 mL, 0.1 M) 2-propanol (46 μL, 0.6 mmol, 300 mol%), and isoprene monoxide (59 μL, 0.6 mmol, 300 mol%) were added by syringe. The reaction vessel was sealed and the reaction mixture was allowed to stir at 45 ˚C for 1 day. The reaction was allowed to reach ambient temperature and concentrated *in vacuo*. The residue was subjected to column chromatography (SiO_2: hexanes:ethyl acetate, 5:1) to furnish the title compound as a white solid (33.2 mg, *anti*:*syn* = 10:1) in 76% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.20 (m, 5H), 6.59 (d, *J* = 15.8 Hz, 1H), 6.23 (dd, *J* = 15.9, 7.5 Hz, 1H), 6.07 (dd, *J* = 17.8, 11.0 Hz, 1H), 5.28 (dd, *J* = 11.0, 1.3 Hz, 1H), 5.17 (dd, *J* = 17.8, 1.3 Hz, 1H), 4.25 (d, *J* = 7.4 Hz, 1H), 3.71 (d, *J* = 10.8 Hz, 1H), 3.61 (d, *J* = 10.7 Hz, 1H), 2.69 (br, 1H), 2.51 (br, 1H), 1.05 (d, *J* = 8.4 Hz, 3H).

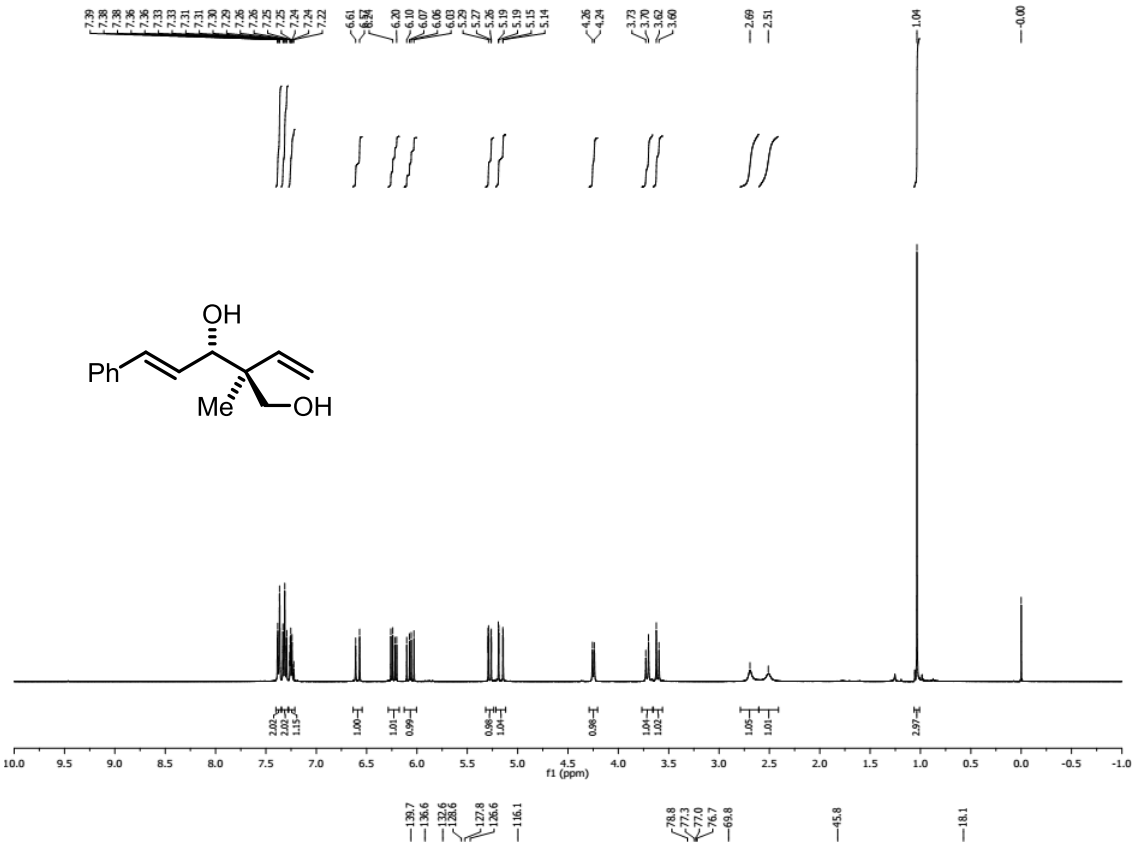
^{13}C NMR (100 MHz, $CDCl_3$) δ 139.7, 136.6, 132.6, 128.6, 128.4, 127.8, 126.6, 116.1, 78.8, 69.8, 45.8, 18.1.

LRMS (ESI) Calcd. $C_{14}H_{18}O_2Na$ for $[M+Na]^+$: 241.1, Found: 241.1.

FTIR (neat): 3357, 3081, 3025, 2965, 2926, 2875, 1637, 1494, 1449, 1416, 1300, 1156, 1095, 1070, 1028, 967, 919, 836, 757, 741, 692 cm^{-1}.

MP 87.0-87.6 ˚C

HPLC (two connected Chiralcel OJ-H columns, hexanes:*i*-PrOH = 92:8, 0.50 mL/min, 230 nm), *anti*:*syn* = 40:1, *ee* = 93% from cinnamyl alcohol; *ee* = 91% from cinnamaldehyde.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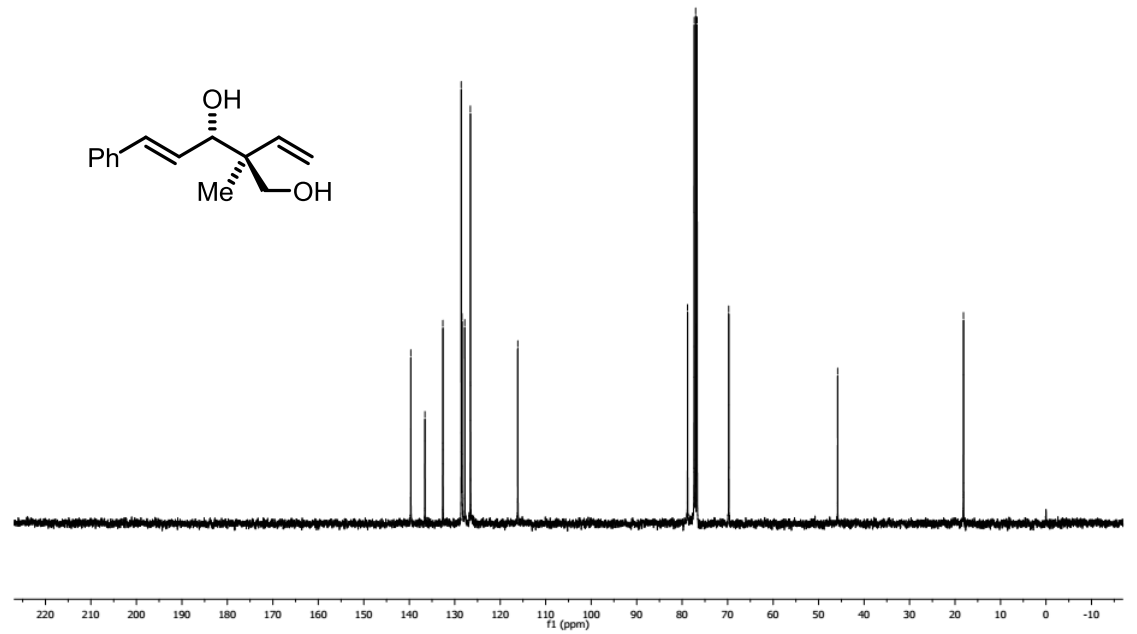
Ph
Me
OH
f1 (ppm)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Ph
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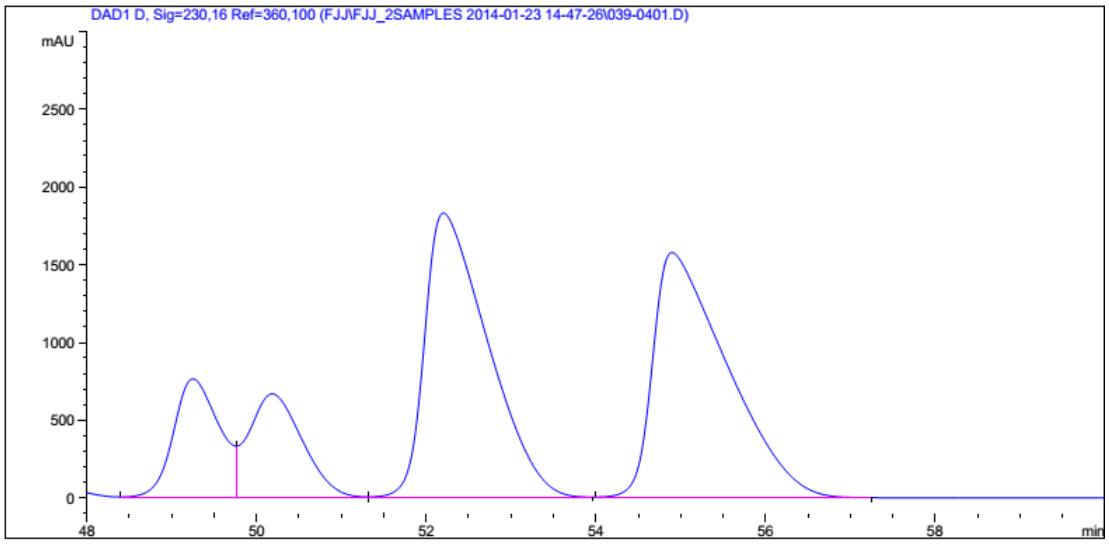
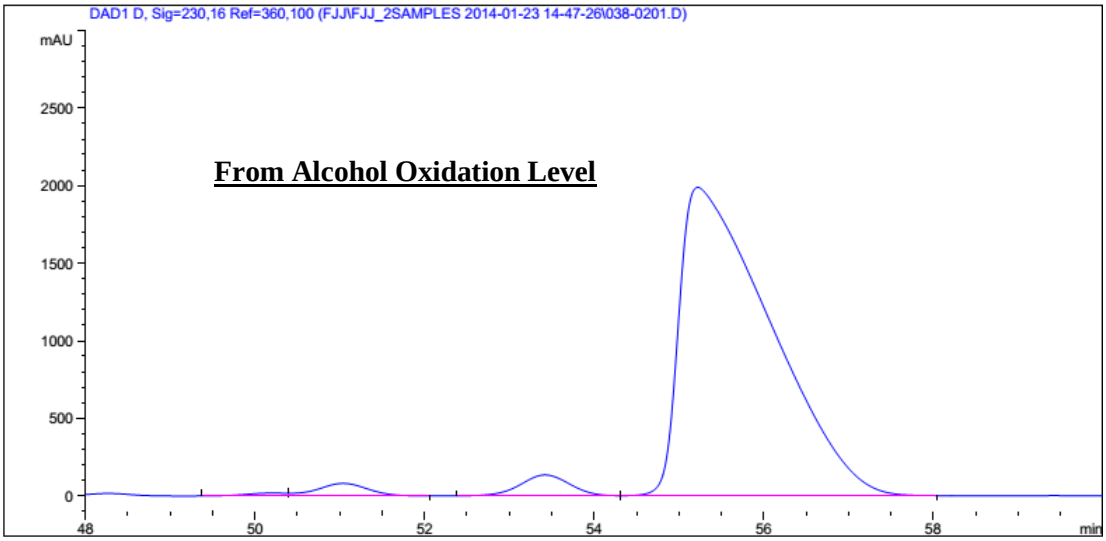
f1 (ppm)

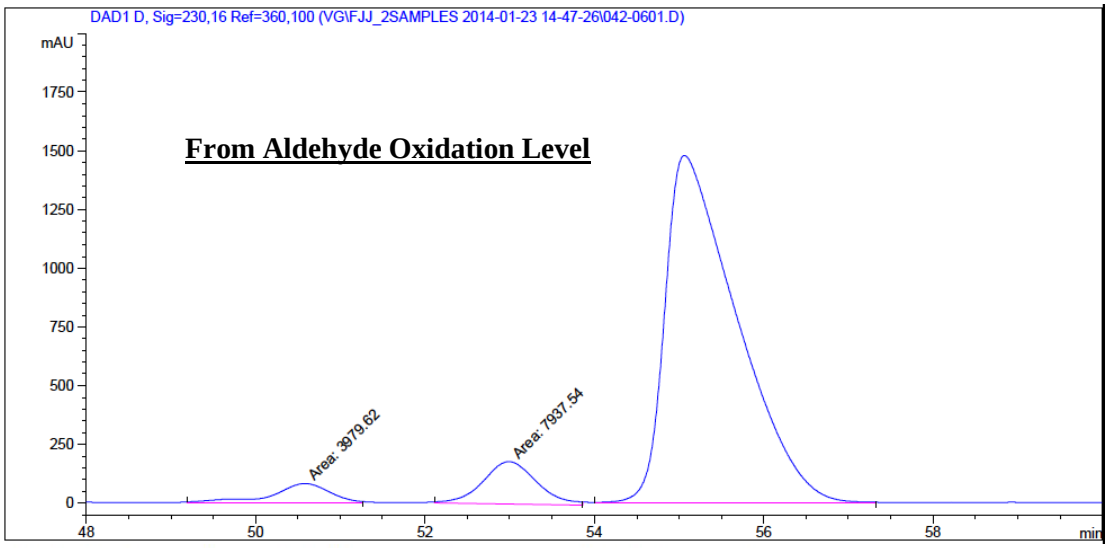


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	49.245	VV	0.5703	2.89010e4	765.79352	11.6025
2	50.181	VV	0.6663	2.93848e4	669.12909	11.7967
3	52.199	VB	0.7797	9.48030e4	1832.00684	38.0594
4	54.894	BB	0.8895	9.60035e4	1578.56946	38.5413



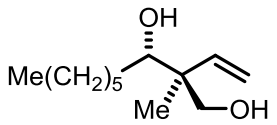
From Alcohol Oxidation Level

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	50.196	BV	0.4991	612.76685	18.66265	0.3878
2	51.035	VB	0.6355	3380.96704	81.23939	2.1398
3	53.418	BV	0.6328	5530.77246	135.33653	3.5004
4	55.220	VB	0.9970	1.48481e5	1988.94861	93.9720



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	50.586	MM	0.8034	3979.61768	82.55744	4.0357
2	52.995	MM	0.7323	7937.53613	180.65753	8.0494
3	55.066	VB	0.8548	8.66935e4	1477.02136	87.9149

(2*S*,3*S*)-2-methyl-2-vinylnonane-1,3-diol (2.4g)



Detailed Procedures

From alcohol oxidation level: An oven-dried pressure tube equipped with a magnetic stir bar was charged with K_3PO_4 (2.2 mg, 0.01 mmol, 5 mol%), (*R*)-**2.5h** (11.0 mg, 0.01 mmol, 5 mol%), and 1-heptanol (23.2 mg, 0.2 mmol, 100 mol%). The reaction vessel was placed under an atmosphere of argon, and THF (0.4 mL, 0.5 M) and isoprene monoxide (79 μL, 0.8 mmol, 400 mol%) were added by syringe. The reaction vessel was sealed and the reaction mixture was allowed to stir at 60 ˚C for 1 day. The reaction was allowed to reach ambient temperature and concentrated *in vacuo*. The residue was subjected to column chromatography (SiO_2: hexanes:ethyl acetate, 6:1) to furnish the title compound as a white solid (30.3 mg, *anti*:*syn* > 20:1) in 74% yield.

From aldehyde oxidation level: An oven-dried pressure tube equipped with a magnetic stir bar was charged with K_3PO_4 (2.2 mg, 0.01 mmol, 5 mol%), (*R*)-**2.5h** (11.0 mg, 0.01 mmol, 5 mol%), and heptanal (22.8 mg, 0.2 mmol, 100 mol%). The reaction vessel was placed under an atmosphere of argon, and THF (0.4 mL, 0.5 M) 2-propanol (46 μL, 0.6 mmol, 300 mol%), and isoprene monoxide (59 μL, 0.6 mmol, 300 mol%) were added by syringe. The reaction vessel was sealed and the reaction mixture was allowed to stir at 60 ˚C for 1 day. The reaction was allowed to reach ambient temperature and concentrated *in vacuo*. The residue was subjected to column chromatography (SiO_2: hexanes:ethyl acetate, 6:1) to furnish the title compound as a white solid (29.2 mg, *anti*:*syn* = 12:1) in 73% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.96 (dd, *J* = 17.8, 11.1 Hz, 1H), 5.23 (dd, *J* = 11.1, 1.3 Hz, 1H), 5.13 (dd, *J* = 17.8, 1.3 Hz, 1H), 3.69 (d, *J* = 10.7 Hz, 1H), 3.60-3.51 (m, 2H), 2.48 (br, 1H), 2.42 (br, 1H), 1.60-1.40 (m, 2H), 1.40-1.21 (m, 8H), 1.01 (s, 3H), 0.88 (t, *J* = 6.8 Hz, 3H).

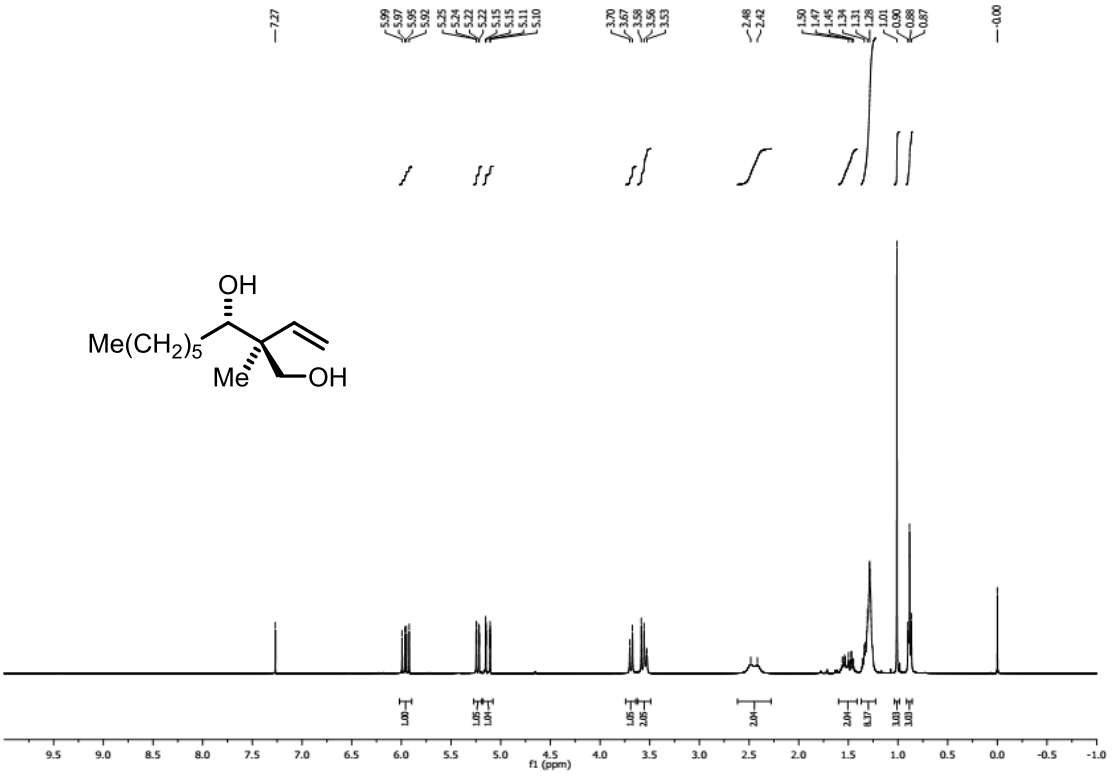
^{13}C NMR (100 MHz, $CDCl_3$) δ 140.2, 115.6, 77.8, 70.0, 45.6, 32.0, 31.8, 29.3, 26.5, 22.6, 18.2, 14.1.

LRMS (CI) Calcd. $C_{12}H_{25}O_2$ for $[M+H]^+$: 201, Found: 201.

FTIR (neat): 3348, 2955, 2923, 2872, 2857, 1459, 1417, 1377, 1028, 963, 915, 679 cm^{-1}.

MP 53.6-54.3 ˚C

HPLC Diastereomeric ratio and enantiomeric excess was determined by HPLC analysis of the 1-benzoate of product (Chiralcel OD-H column, hexanes:*i*-PrOH = 98:2, 0.25 mL/min, 254 nm), *anti*:*syn* = 40:1, *ee* = 93% from 1-heptanol; *ee* = 93% from heptanal.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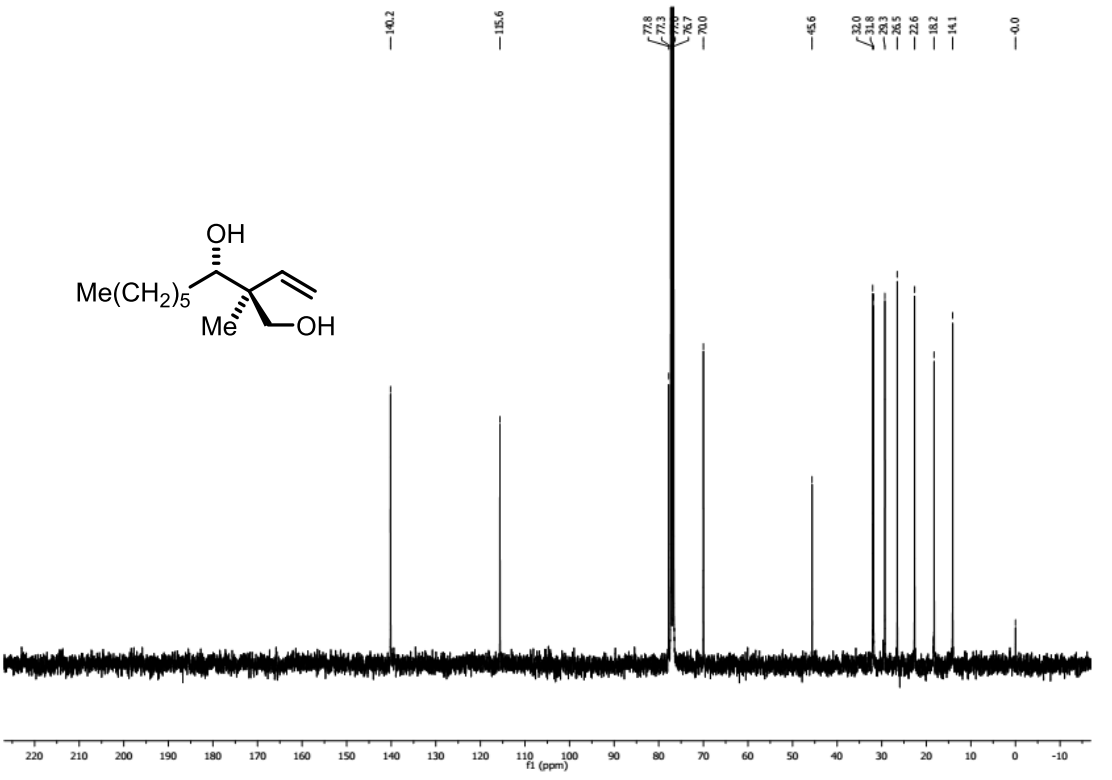
Me
OH
f1 (ppm)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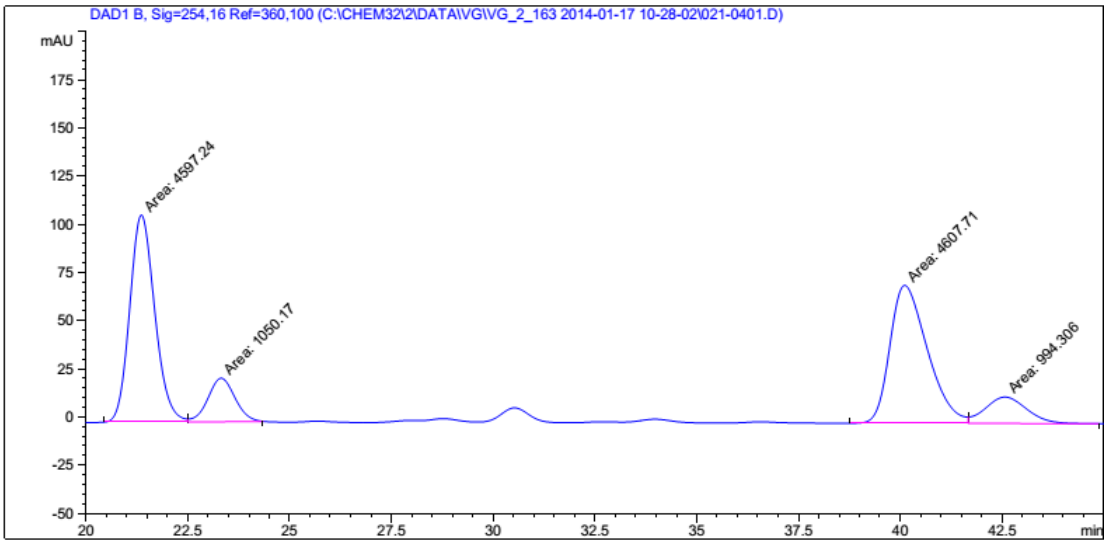
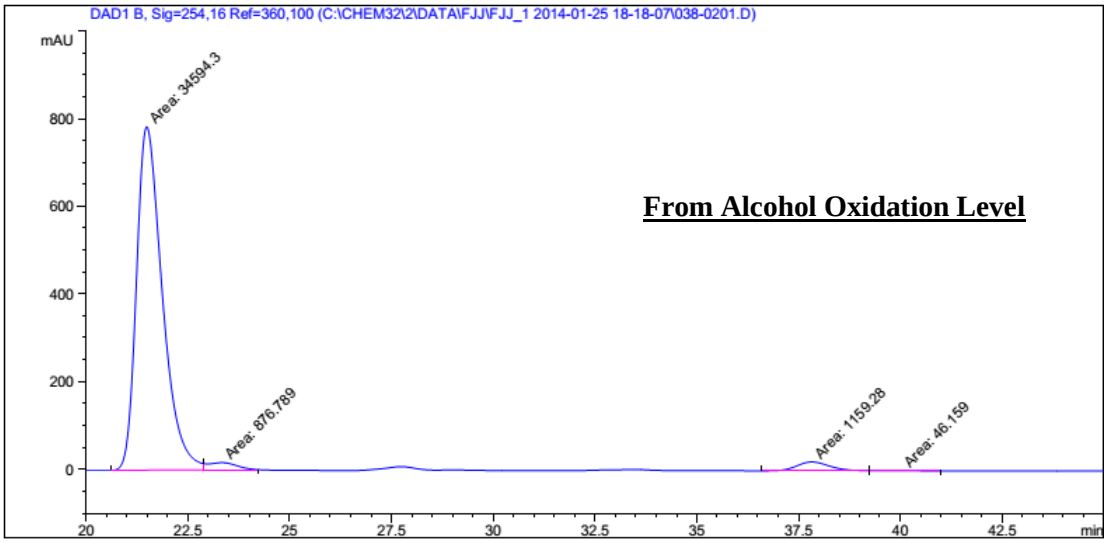
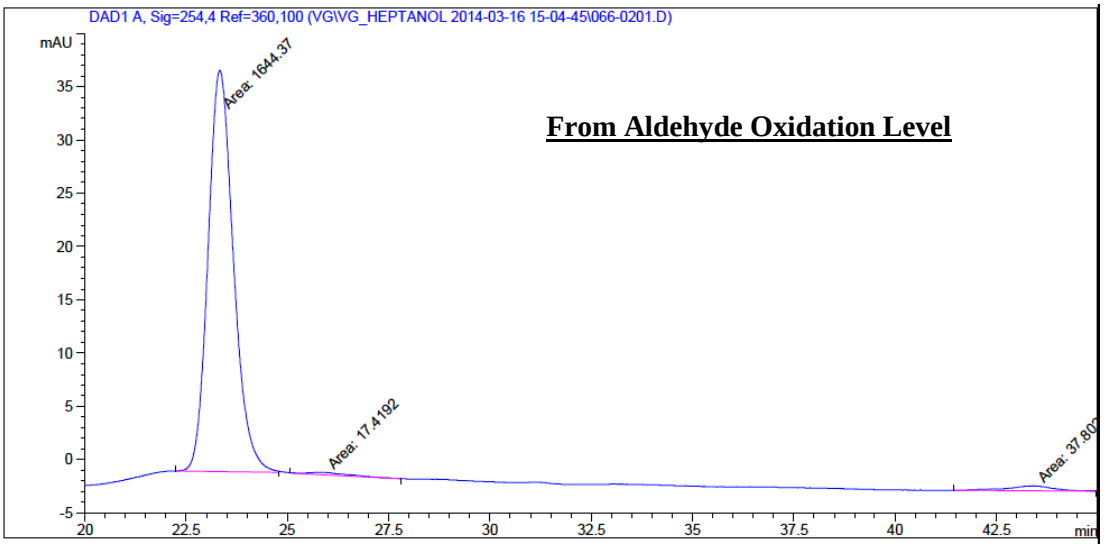


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.353	MF	0.7128	4597.23535	107.48956	40.8664
2	23.313	FM	0.7727	1050.16504	22.65009	9.3353
3	40.102	MF	1.0703	4607.71191	71.75194	40.9596
4	42.568	FM	1.1985	994.30566	13.82739	8.8387



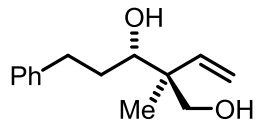
From Alcohol Oxidation Level

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.479	MF	0.7353	3.45943e4	784.07703	94.3227
2	23.332	FM	0.8452	876.78882	17.28872	2.3906
3	37.818	MF	0.9477	1159.28284	20.38825	3.1608
4	40.010	FM	1.2449	46.15897	6.17962e-1	0.1259



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	23.327	MM	0.7276	1644.37085	37.66661	96.7509
2	25.910	MM	1.1734	17.41916	2.47408e-1	1.0249
3	43.439	MM	1.3668	37.80240	4.60965e-1	2.2242

(2*S*,3*S*)-2-methyl-5-phenyl-2-vinylpentane-1,3-diol (2.4h)



Detailed Procedures

From alcohol oxidation level: An oven-dried pressure tube equipped with a magnetic stir bar was charged with K_3PO_4 (2.2 mg, 0.01 mmol, 5 mol%), (*R*)-**2.5h** (11.0 mg, 0.01 mmol, 5 mol%), and 3-phenyl-1-propanol (27.2 mg, 0.2 mmol, 100 mol%). The reaction vessel was placed under an atmosphere of argon, and THF (0.4 mL, 0.5 M) and isoprene monoxide (59 μL, 0.6 mmol, 300 mol%) were added by syringe. The reaction vessel was sealed and the reaction mixture was allowed to stir at 60 ˚C for 1 day. The reaction was allowed to reach ambient temperature and concentrated *in vacuo*. The residue was subjected to column chromatography (SiO_2: hexanes:ethyl acetate, 5:1) to furnish the title compound as a white solid (33.7 mg, *anti*:*syn* > 20:1) in 76% yield.

From aldehyde oxidation level: An oven-dried pressure tube equipped with a magnetic stir bar was charged with K_3PO_4 (2.2 mg, 0.01 mmol, 5 mol%), (*R*)-**2.5h** (11.0 mg, 0.01 mmol, 5 mol%), and 3-phenylpropionaldehyde (26.8 mg, 0.2 mmol, 100 mol%). The reaction vessel was placed under an atmosphere of argon, and THF (0.4 mL, 0.5 M), 2-propanol (46 μL, 0.6 mmol, 300 mol%), and isoprene monoxide (59 μL, 0.6 mmol, 300 mol%) were added by syringe. The reaction vessel was sealed and the reaction mixture was allowed to stir at 60 ˚C for 1 day. The reaction was allowed to reach ambient temperature and concentrated *in vacuo*. The residue was subjected to column chromatography (SiO_2: hexanes:ethyl acetate, 5:1) to furnish the title compound as a white solid (40.0 mg, *anti*:*syn* = 5:1) in 91% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.12 (m, 5H), 5.95 (dd, *J* = 17.8, 11.1 Hz, 1H), 5.22 (dd, *J* = 11.1, 1.2 Hz, 1H), 5.10 (dd, *J* = 17.8, 1.3 Hz, 1H), 3.69 (d, *J* = 10.7 Hz, 1H), 3.61-3.52 (m, 2H), 2.96-2.87 (m, 1H), 2.62 (ddd, *J* = 13.7, 9.6, 6.8 Hz, 1H), 2.79-2.38 (m, 2H), 1.86-1.75 (m, 1H), 1.74-1.58 (m, 1H), 1.00 (s, 3H).

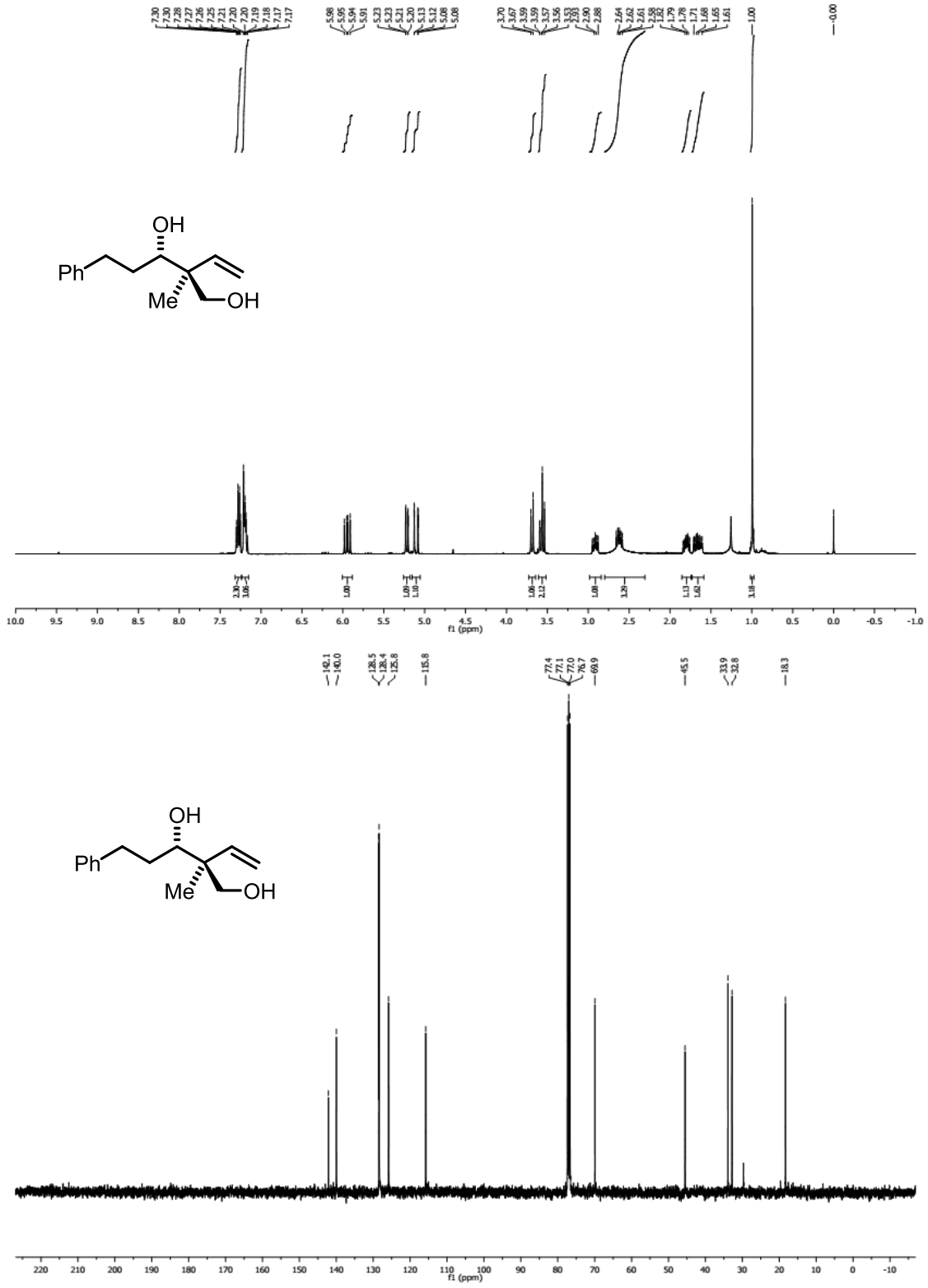
^{13}C NMR (100 MHz, $CDCl_3$) δ 142.2, 140.0, 128.5, 128.4, 125.9, 115.8, 77.1, 69.9, 45.5, 33.9, 32.8, 18.3.

LRMS (ESI) Calcd. $C_{14}H_{20}O_2Na$ for $[M+Na]^+$: 243.2, Found: 243.1.

FTIR (neat): 3326, 2923, 1496, 1454, 1417, 1313, 1155, 1071, 1029, 918, 748, 699, 669 cm^{-1}.

MP 72.1-73.4 ˚C

HPLC (two connected Chiralcel OJ-H columns, hexanes:*i*-PrOH = 98:2, 0.50 mL/min, 210 nm), *anti*:*syn* = 30:1, *ee* = 93% from 3-phenyl-1-propanol; *ee* = 85% from 3-phenylpropionaldehyde.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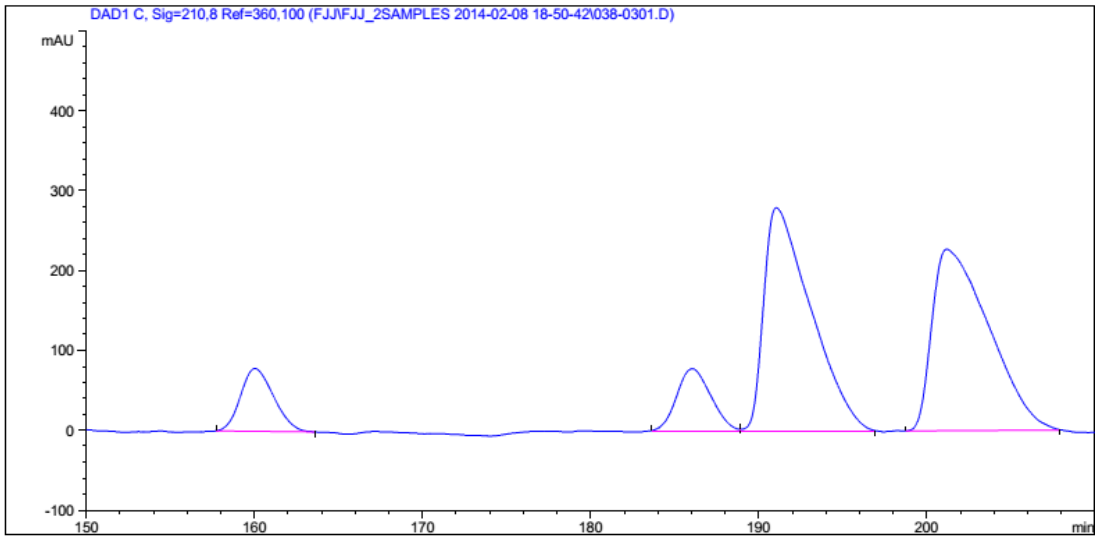
Ph
Me
OH
f1 (ppm)
OH
Ph
Me
OH
f1 (ppm)



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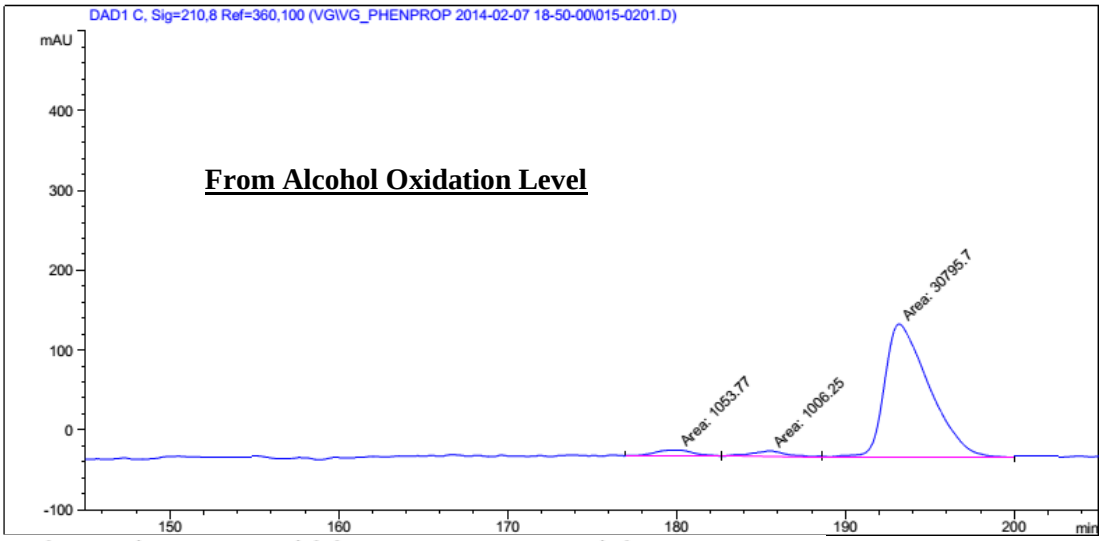
2	186.058	BV	1.6558	1.09341e4	77.69662	8.4315
3	191.048	VB	2.5492	5.44213e4	279.30661	41.9652
4	201.188	BB	2.7592	5.35188e4	227.44640	41.2693



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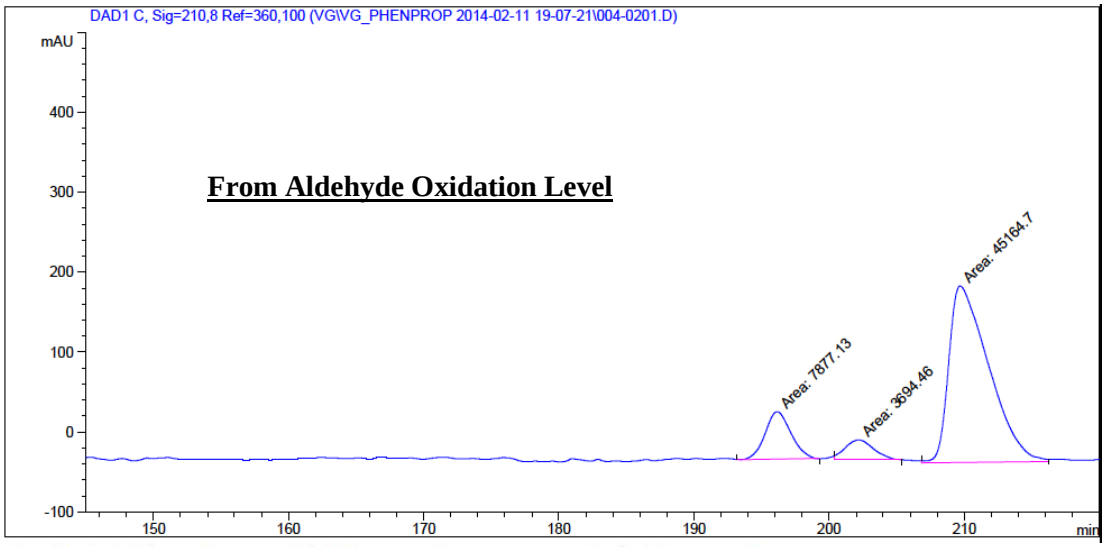
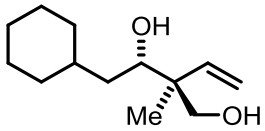
1	180.055	MM	2.4549	1053.76868	7.15417	3.2073
2	185.545	MM	2.3959	1006.25250	6.99975	3.0626
3	193.176	MM	3.0734	3.07957e4	166.99921	93.7301



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	196.154	MM	2.2134	7877.12500	59.31392	13.8838
2	202.192	MM	2.4781	3694.45679	24.84729	6.5116
3	209.675	MM	3.4103	4.51647e4	220.72470	79.6046

(2*S*,3*S*)-4-cyclohexyl-2-methyl-2-vinylbutane-1,3-diol (4i)



Detailed Procedures

From alcohol oxidation level: An oven-dried pressure tube equipped with a magnetic stir bar was charged with K_3PO_4 (2.2 mg, 0.01 mmol, 5 mol%), (*R*)-**2.5h** (11.0 mg, 0.01 mmol, 5 mol%), and 2-cyclohexyl-1-ethanol (25.6 mg, 0.2 mmol, 100 mol%). The reaction vessel was placed under an atmosphere of argon, and THF (0.4 mL, 0.5 M) and isoprene monoxide (79 μL, 0.8 mmol, 400 mol%) were added by syringe. The reaction vessel was sealed and the reaction mixture was allowed to stir at 60 ˚C for 1 day. The reaction was allowed to reach ambient temperature and concentrated *in vacuo*. The residue was subjected to column chromatography (SiO_2: hexanes:ethyl acetate, 6:1) to furnish the title compound as a white solid (32.3 mg, *anti*:*syn* > 20:1) in 76% yield.

From aldehyde oxidation level: An oven-dried pressure tube equipped with a magnetic stir bar was charged with K_3PO_4 (2.2 mg, 0.01 mmol, 5 mol%), (*R*)-**2.5h** (11.0 mg, 0.01 mmol, 5 mol%), and cyclohexylacetaldehyde (25.2 mg, 0.2 mmol, 100 mol%). The reaction vessel was placed under an atmosphere of argon, and THF (0.4 mL, 0.5 M), 2-propanol (46 μL, 0.6 mmol, 300 mol%), and isoprene monoxide (59 μL, 0.8 mmol, 300 mol%) were added by syringe. The reaction vessel was sealed and the reaction mixture was allowed to stir at 70 ˚C for 1 day. The reaction was allowed to reach ambient temperature and concentrated *in vacuo*. The residue was subjected to column chromatography (SiO_2: hexanes:ethyl acetate, 6:1) to furnish the title compound as a white solid (27.4 mg, *anti*:*syn* = 20:1) in 65% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.95 (dd, *J* = 17.8, 11.1 Hz, 1H), 5.23 (dd, *J* = 11.1, 1.3 Hz, 1H), 5.12 (dd, *J* = 17.8, 1.3 Hz, 1H), 3.72-3.65 (m, 2H), 3.57 (d, *J* = 10.7 Hz, 1H), 2.40 (br, 1H), 2.30 (br, 1H), 1.84 (d, *J* = 12.7 Hz, 1H), 1.75-1.59 (m, 4H), 1.55-1.40 (m, 1H), 1.35-1.11 (m, 5H), 1.04-0.89 (m, 4H), 0.86-0.73 (m, 1H).

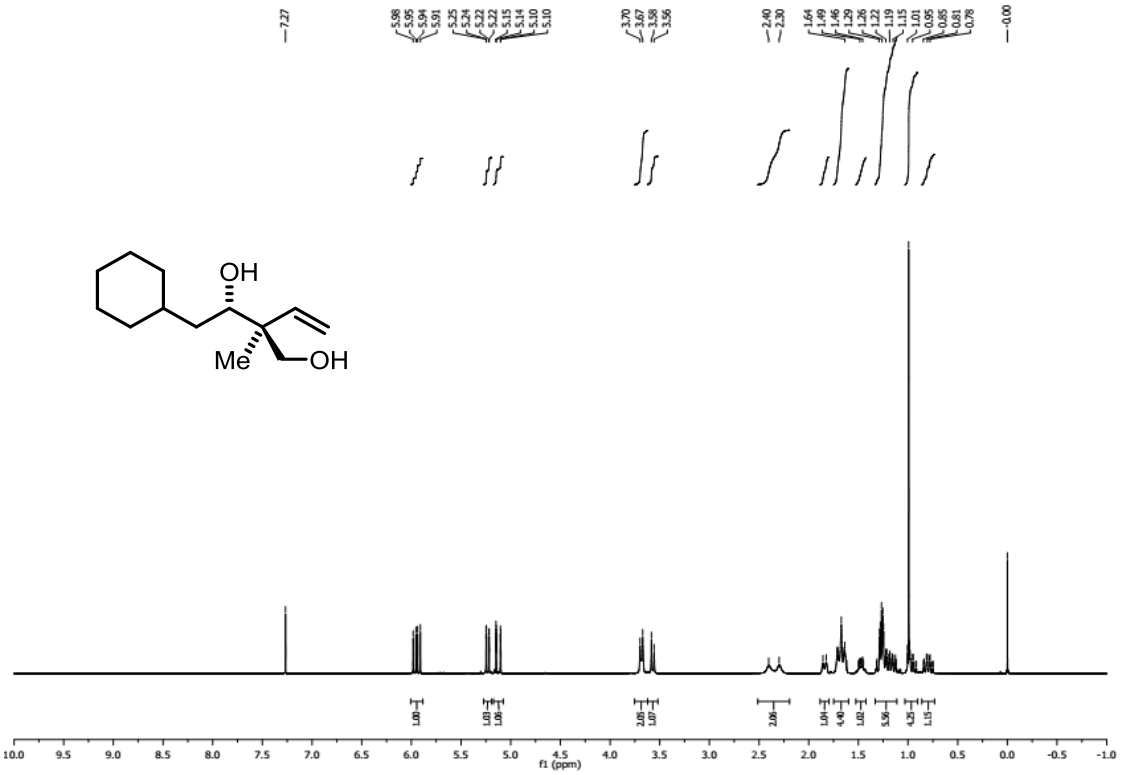
^{13}C NMR (100 MHz, $CDCl_3$) δ 140.2, 115.7, 74.8, 70.0, 45.5, 39.8, 34.8, 34.0, 32.2, 26.6, 26.4, 26.1, 18.2.

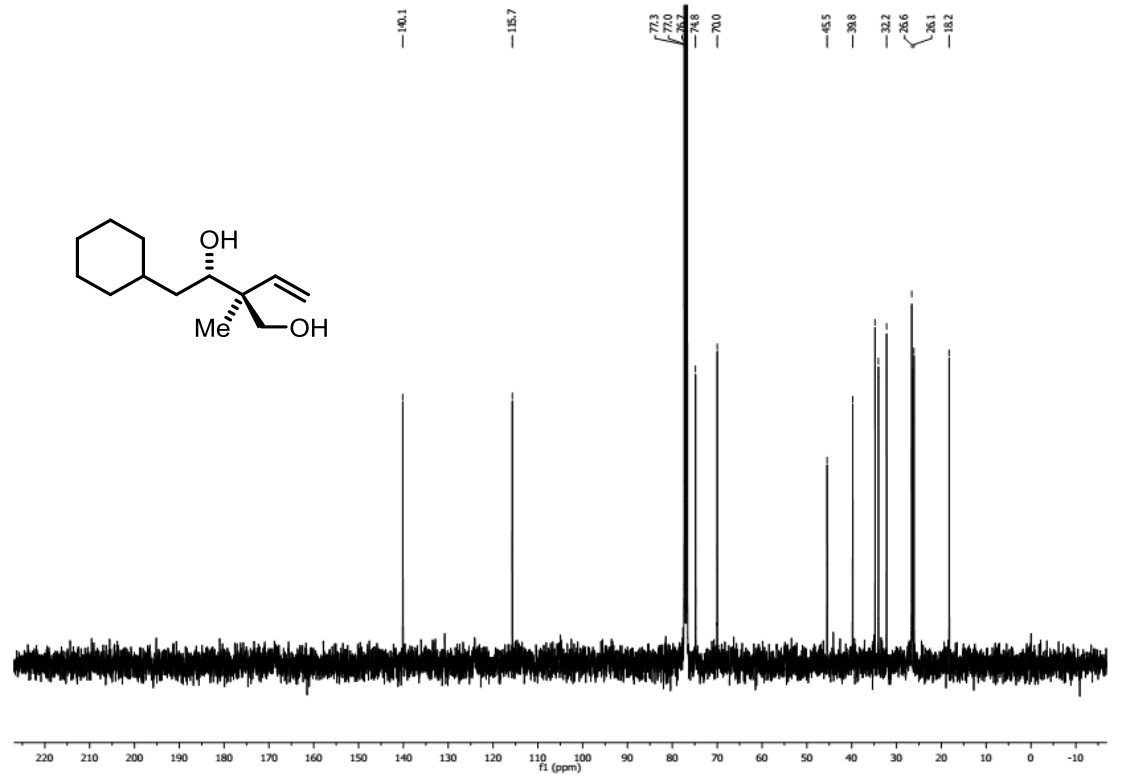
LRMS (ESI) Calcd. $C_{13}H_{24}O_2Na$ for $[M+Na]^+$: 235.2, Found: 235.2.

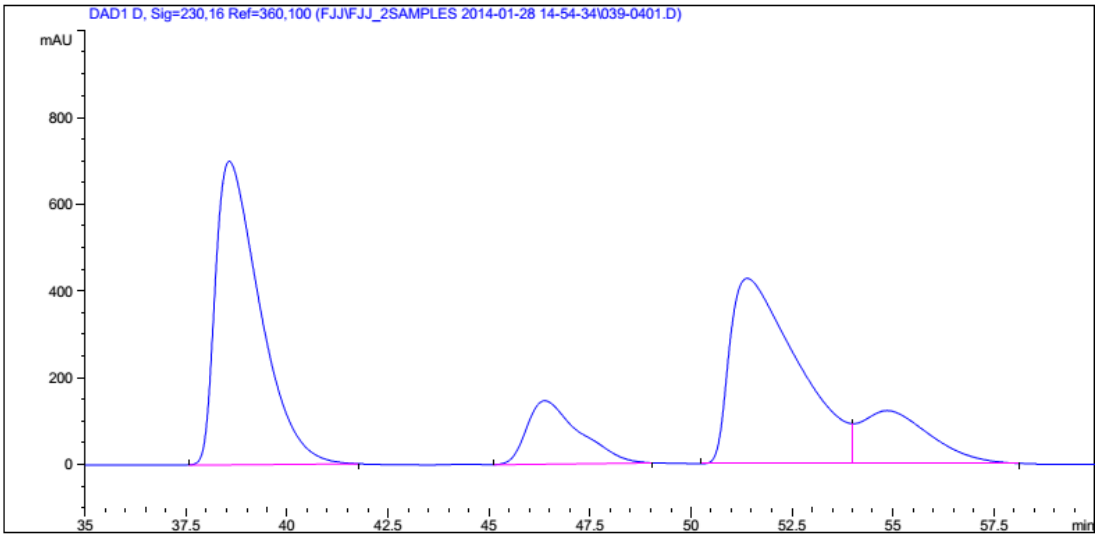
FTIR (neat): 3289, 2922, 2854, 1457, 1444, 1418, 1263, 1200, 1129, 1069, 1051, 1033, 992, 953, 916, 834, 759, 685 cm^{-1}.

MP 96.0-96.8 ˚C

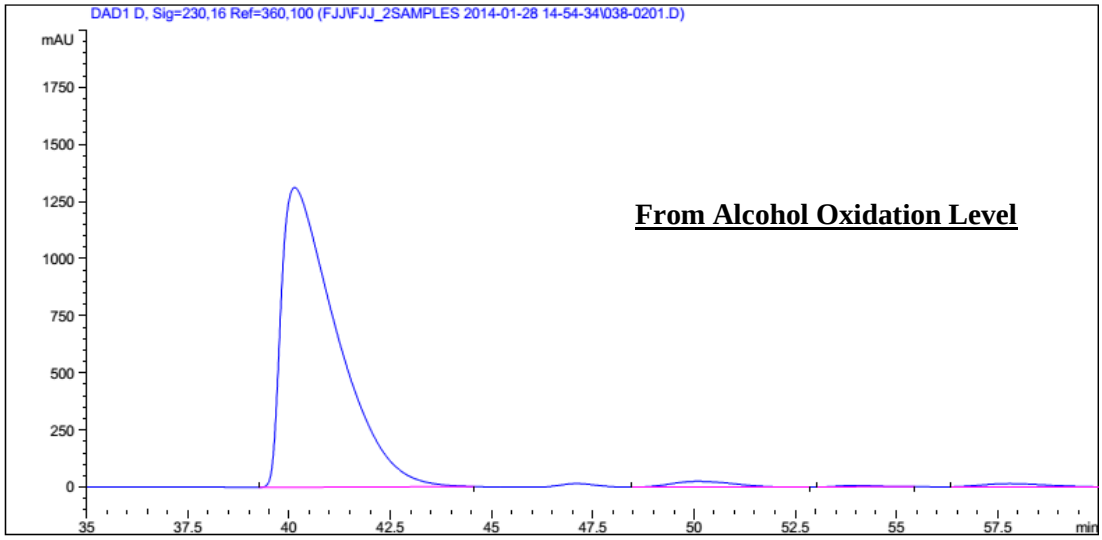
HPLC Diastereomeric ratio and enantiomeric excess was determined by HPLC analysis of the 1-benzoate of product (two connected Chiralcel OC-H columns, hexanes:*i*-PrOH = 98:2, 0.50 mL/min, 230 nm), *anti*:*syn* = 30:1, *ee* = 99% from 2-cyclohexyl-1-ethanol; *ee* = 95% from cyclohexylacetaldehyde.


OH
Me
OH
f1 (ppm)


OH
Me
OH
f1 (ppm)

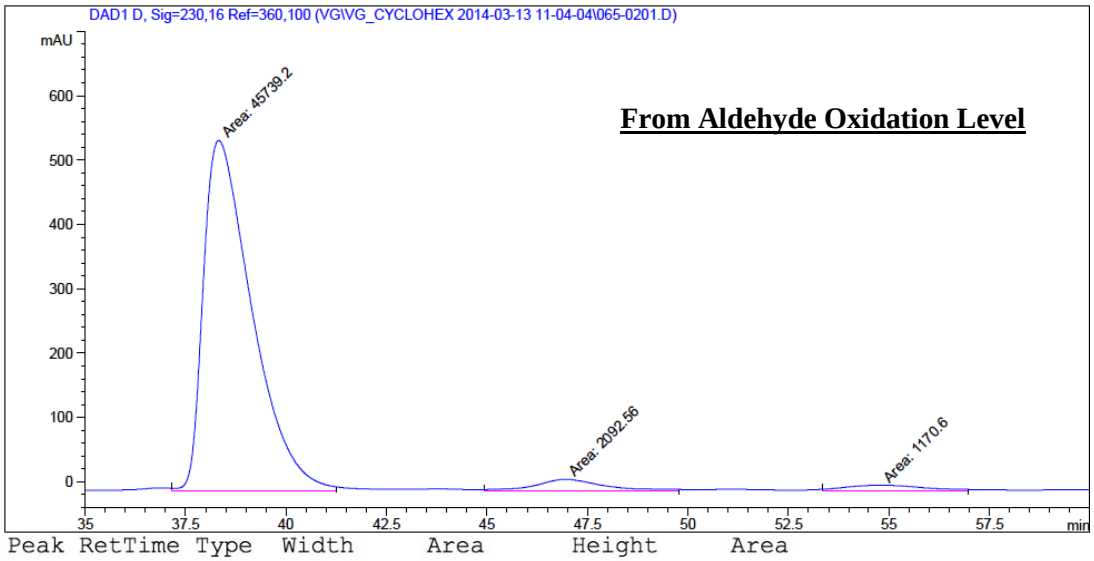


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	38.564	BB	1.1697	5.35729e4	699.39789	40.6564
2	46.378	BB	1.3130	1.31294e4	146.01938	9.9638
3	51.389	BV	1.7017	5.04832e4	427.49615	38.3116
4	54.851	VB	1.6986	1.45846e4	122.35559	11.0682



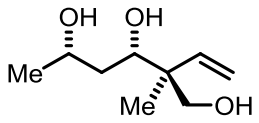
From Alcohol Oxidation Level

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	40.137	BB	1.3499	1.24632e5	1312.45300	96.3233
2	50.102	VB	1.3678	2722.18823	25.49278	2.1039
3	54.014	BB	0.7880	400.06882	6.01470	0.3092
4	57.795	BB	1.3488	1634.99207	14.41982	1.2636



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	38.324	MM	1.4002	4.57392e4	544.42340	93.3408
2	46.954	MM	1.9818	2092.56323	17.59784	4.2703
3	54.783	MM	2.2931	1170.60303	8.50797	2.3889

(2*S*,3*S*,5*S*)-2-methyl-2-vinylhexane-1,3,5-triol ((2*S*,3*S*,5*S*)-2.4j)



Detailed Procedures

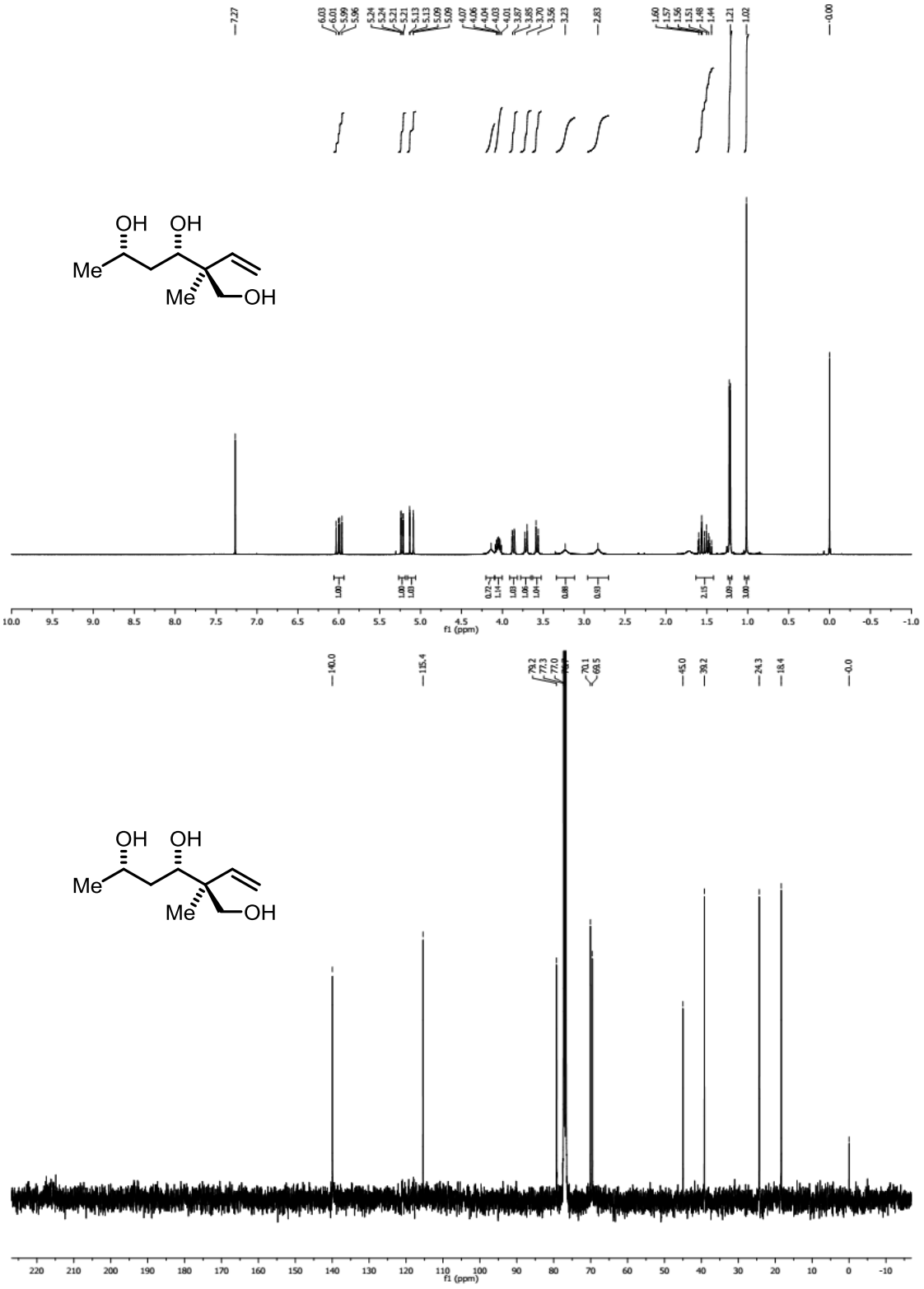
An oven-dried pressure tube equipped with a magnetic stir bar was charged with K_3PO_4 (2.2 mg, 0.01 mmol, 5 mol%), (*R*)-**2.5h** (11.0 mg, 0.01 mmol, 5 mol%), and (*S*)-butane-1,3-diol (18.0 mg, 0.2 mmol, 100 mol%). The reaction vessel was placed under an atmosphere of argon, and THF (0.2 mL, 1.0 M) and isoprene monoxide (79 μL, 0.8 mmol, 400 mol%) were added by syringe. The reaction vessel was sealed and the reaction mixture was allowed to stir at 60 ˚C for 2 days. The reaction was allowed to reach ambient temperature and concentrated *in vacuo*. The residue was subjected to column chromatography (SiO_2: DCM:*i*-PrOH, 10:1) to furnish the title compound ((2*S*,3*S*,5*S*)-**2.4j**) as a colorless oil (20.9 mg) in 60% yield. The (2*R*,3*R*)-diastereomer ((2*R*,3*R*,5*S*)-**2.4j**) was obtained as a colorless oil (1.0 mg) in 3% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.00 (dd, *J* = 17.8, 11.1 Hz, 1H), 5.23 (dd, *J* = 11.1, 1.3 Hz, 1H), 5.11 (dd, *J* = 17.8, 1.3 Hz, 1H), 4.14 (br, 1H), 4.10-3.99 (m, 1H), 3.86 (dd, *J* = 10.5, 2.0 Hz, 1H), 3.71 (d, *J* = 10.6 Hz, 1H), 3.58 (d, *J* = 10.7 Hz, 1H), 3.23 (br, 1H), 2.83 (br, 1H), 1.58 (dt, *J* = 14.4, 2.3 Hz, 1H), 1.55-1.43 (m, 1H), 1.22 (d, *J* = 6.2 Hz, 3H), 1.02 (s, 3H).

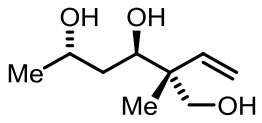
^{13}C NMR (100 MHz, $CDCl_3$) 140.0, 115.4, 79.2, 70.1, 69.5, 45.0, 39.2, 24.3, 18.4.

LRMS (ESI) Calcd. $C_9H_{18}O_3Na$ for $[M+Na]^+$: 197.1, Found: 197.1.

FTIR (neat): 3343, 2967, 2920, 2879, 1457, 1417, 1375, 1317, 1161, 1121, 1073, 1031, 982, 917, 836, 680 cm^{-1}.


OH
OH
Me
Me
OH
f1 (ppm)

(2*R*,3*R*,5*S*)-2-methyl-2-vinylhexane-1,3,5-triol ((2*R*,3*R*,5*S*)-2.4j)



Detailed Procedures

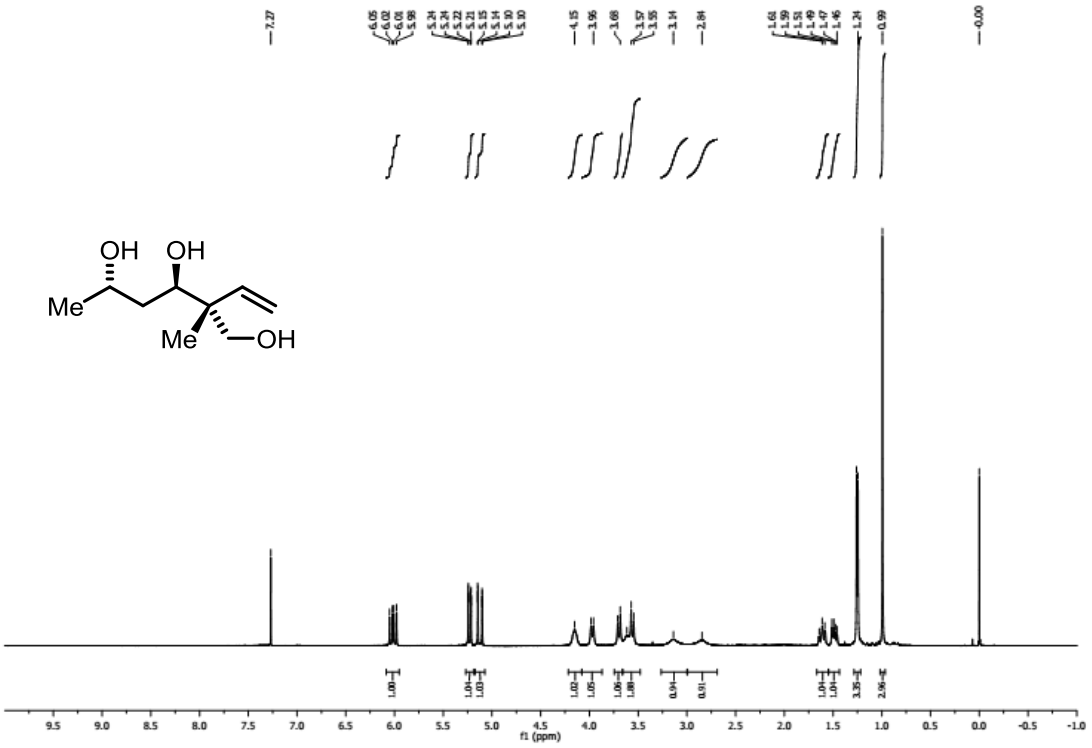
An oven-dried pressure tube equipped with a magnetic stir bar was charged with K_3PO_4 (2.2 mg, 0.01 mmol, 5 mol%), (*S*)-**2.5h** (11.0 mg, 0.01 mmol, 5 mol%), and (*S*)-butane-1,3-diol (18.0 mg, 0.2 mmol, 100 mol%). The reaction vessel was placed under an atmosphere of argon, and THF (0.2 mL, 1.0 M) and isoprene monoxide (79 μL, 0.8 mmol, 400 mol%) were added by syringe. The reaction vessel was sealed and the reaction mixture was allowed to stir at 60 ˚C for 2 days. The reaction was allowed to reach ambient temperature and concentrated *in vacuo*. The residue was subjected to column chromatography (SiO_2: DCM:*i*-PrOH, 10:1) to furnish the title compound ((2*R*,3*R*,5*S*)-**2.4j**) as a colorless oil (23.0 mg) in 66% yield. The (2*S*,3*S*)-diastereomer ((2*S*,3*S*,5*S*)-**2.4j**) was obtained as a colorless oil (1.3 mg) in 4% yield.

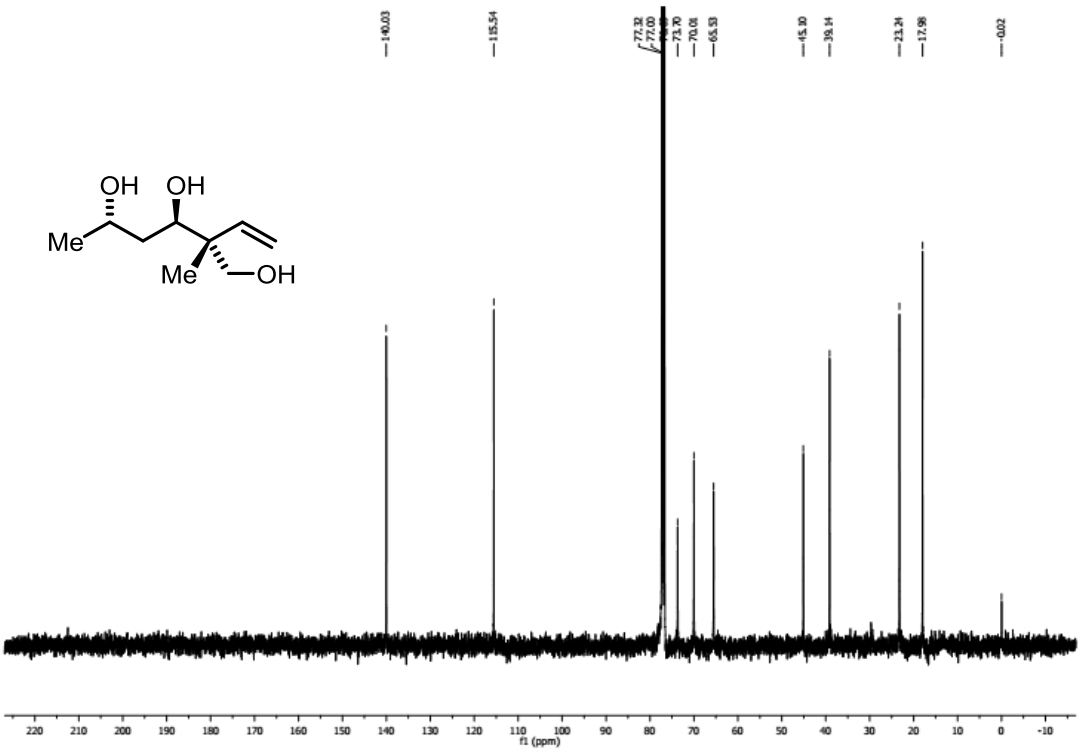
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.01 (dd, *J* = 17.8, 11.1 Hz, 1H), 5.23 (dd, *J* = 11.0, 1.2 Hz, 1H), 5.12 (dd, *J* = 17.8, 1.2 Hz, 1H), 4.23-4.07 (m, 1H), 3.97 (d, *J* = 10.1 Hz, 1H), 3.70 (d, *J* = 10.7 Hz, 1H), 3.66-3.50 (m, 2H), 3.14 (br, 1H), 2.84 (br, 1H), 1.68-1.55 (m, 1H), 1.49 (ddd, *J* = 14.9, 7.9, 1.8 Hz, 1H), 1.25 (d, *J* = 6.2 Hz, 3H), 0.99 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 140.0, 115.5, 73.7, 70.0, 65.5, 45.1, 39.1, 23.2, 18.0.

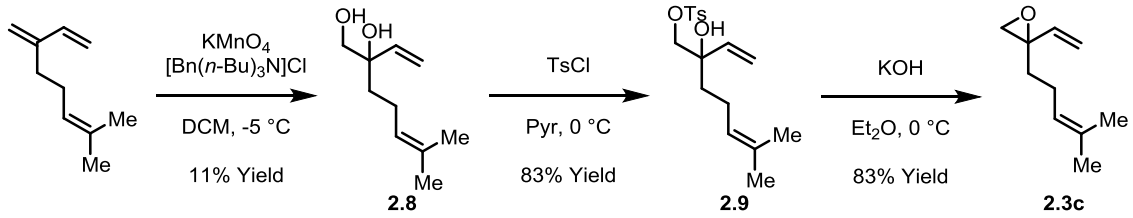
LRMS (ESI) Calcd. $C_9H_{18}O_3Na$ for $[M+Na]^+$: 197.1, Found: 197.1.

FTIR (neat): 3345, 2966, 2925, 1457, 1417, 1374, 1127, 1084, 1029, 984, 916, 855, 835, 811, 680 cm^{-1}.


OH
OH
Me
Me
OH
f1 (ppm)


OH
OH
Me
Me
OH
f1 (ppm)

Synthesis of Myrcene Oxide 3c[54,55]



6-methyl-2-vinylhept-5-ene-1,2-diol (2.8)

A solution of potassium permanganate (7.9 g, 50 mmol, 100 mol%) and benzyltri-*n*-butylammonium chloride (15.6 g, 50 mmol, 100 mol%) in DCM (500 mL) was stirred at ambient temperature for 3 h. It was then cooled to -5 ˚C, and myrcene (15.4 mL, 90 mmol, 180 mol%) was added to the solution. The resulted mixture was stirred at this temperature overnight. Aqueous NaOH solution (1.5 M, 160 mL), $NaHSO_3$ solution (0.6 M, 200 mL), and H_2SO_4 solution (1.0 M, 250 mL) was added in sequence to quench the reaction. The organic phase was separated and the aqueous phase was extracted with DCM (3 × 100 mL). The combined organic phases were washed with saturated $NaHCO_3$ solution (100 mL), and dried over anhydrous magnesium sulfate. The excessive myrcene was removed by a short plug of silica gel (hexanes:ethyl acetate, 5:1). The more polar residue was collected and subjected to column chromatography (SiO_2: hexanes:Et_2O, 2:1) to furnish the title compound as a colorless oil (0.95 g) in 11% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.34 (dd, *J* = 17.3, 1.4 Hz, 2H), 5.26 (dd, *J* = 10.8, 1.4 Hz, 1H), 5.10 (tq, *J* = 7.4, 1.4 Hz, 1H), 3.53-3.42 (m, 2H), 2.36 (br, 1H), 2.12-1.93 (m, 2H), 1.67 (d, *J* = 1.2 Hz, 3H), 1.65-1.57 (m, 4H), 1.50 (ddd, *J* = 13.8, 10.4, 5.5 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 140.6, 132.2, 124.1, 115.2, 76.2, 68.8, 36.7, 25.7, 22.0, 17.7.

2-hydroxy-6-methyl-2-vinylhept-5-en-1-yl 4-methylbenzenesulfonate (2.9)

A solution of **2.8** (0.95 g, 5.6 mmol, 100 mol%) in pyridine (7.5 mL) was cooled to 0 ˚C and TsCl (1.28 g, 6.7 mmol, 120 mmol%) was added. The resulted mixture was stirred at 0 ˚C for 5 h. Aqueous HCl solution (1.2 M, 5 mL) was then added, and the mixture was extracted with Et_2O (3 × 10 mL). The combined organic phase was washed with HCl (0.1 M, 10 mL) and brine (10 mL). It was dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was subjected to column chromatography (SiO_2: hexanes:ethyl acetate, 7:1) to furnish the title compound as a colorless oil (1.50 g) in 83% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81-7.76 (m, 2H), 7.35 (d, *J* = 8.6 Hz, 2H), 5.73 (dd, *J* = 17.3, 10.8 Hz, 1H), 5.33 (dd, *J* = 17.3, 1.1 Hz, 1H), 5.23 (dd, *J* = 10.8, 1.1 Hz, 1H), 5.05 (tq, *J* = 7.2, 1.3 Hz, 1H), 3.89 (s, 2H), 2.45 (s, 3H), 2.10 (s, 1H), 2.07-1.89 (m, 2H), 1.68-1.58 (m, 4H), 1.56 (s, 3H), 1.49 (ddd, *J* = 13.9, 10.4, 5.6 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 145.0, 138.7, 132.6, 132.6, 129.9, 128.0, 123.6, 116.0, 75.2, 74.3, 36.7, 25.7, 21.7, 21.7, 17.7.

2-(4-methylpent-3-en-1-yl)-2-vinyloxirane (2.3c)

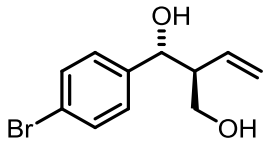
A solution of **2.9** (1.57 g, 4.8 mmol, 100 mol%) in Et_2O was cooled to 0 ˚C and KOH powder (0.54 g, 9.6 mmol, 200 mol%) was added. The resulted slurry was vigorously stirred at 0 ˚C for 3 h. The reaction mixture was then filtered through a short plug of celite and washed with excessive Et_2O. The filtrate was carefully concentrated *in vacuo* (185 mbar, 0 ˚C). The residue was subjected to column chromatography (SiO_2[61]: pentane:Et_2O, 200:1) to furnish the title compound (**3c**) as a colorless oil (0.63 g) in 83% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.77 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.35 (dd, *J* = 17.4, 1.3 Hz, 1H), 5.22 (dd, *J* = 10.8, 1.3 Hz, 1H), 5.11 (tq, *J* = 7.1, 1.4 Hz, 1H), 2.82 (d, *J* = 5.3 Hz, 1H), 2.67 (d, *J* = 5.3 Hz, 1H), 2.10 (dd, *J* = 15.6, 7.6 Hz, 2H), 1.80-1.66 (m, 5H), 1.60 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 137.5, 132.1, 123.5, 116.5, 58.5, 55.1, 33.6, 25.7, 23.7, 17.7.

Detailed Procedures and Spectral Data for Couplings between 4-Bromobenzyl Alcohol (2.1a) and Other Vinyl Epoxides: Butadiene Monoxide (2.3b) and Myrcene Oxide (2.3c)

(1*R*,2*S*)-1-(4-bromophenyl)-2-vinylpropane-1,3-diol (2.6)



Detailed Procedures

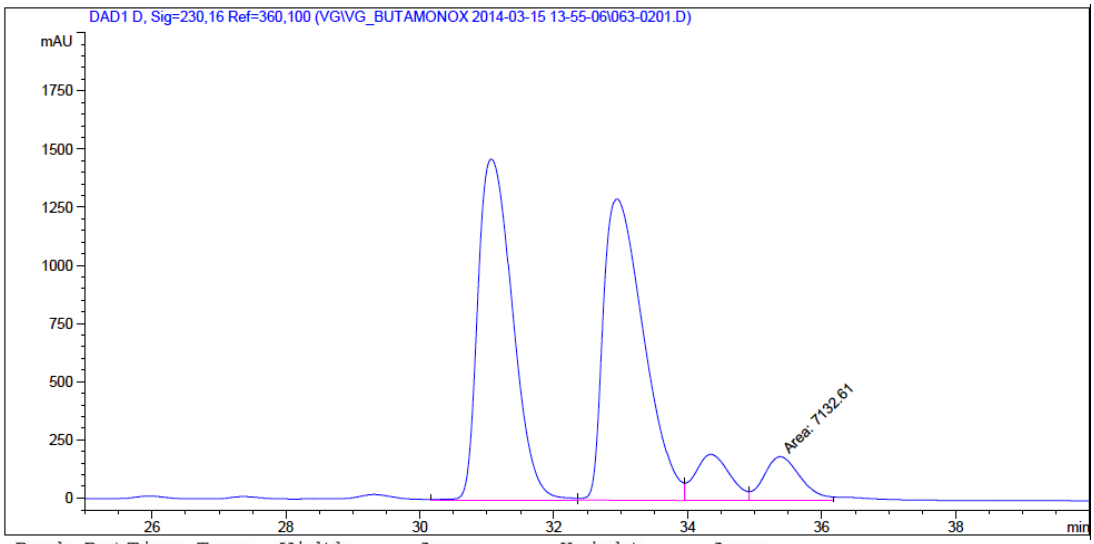
An oven-dried pressure tube equipped with a magnetic stir bar was charged with K_3PO_4 (2.2 mg, 0.01 mmol, 5 mol%), (*R*)-**2.5b** (10.3 mg, 0.01 mmol, 5 mol%), and 4-bromobenzyl alcohol (37.4 mg, 0.2 mmol, 100 mol%). The reaction vessel was placed under an atmosphere of argon, and THF (0.4 mL, 0.5 M) and butadiene monoxide **2.3b** (32 μL, 0.4 mmol, 200 mol%) were added by syringe. The reaction vessel was sealed and the reaction mixture was allowed to stir at 60 ˚C for 1 day. The reaction was allowed to reach ambient temperature and concentrated *in vacuo*. The residue was subjected to column chromatography (SiO_2: DCM:ethyl acetate, 10:1) to furnish the title compound as a yellow oil (32.3 mg, *anti*:*syn* = 5:1) in 63% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.4 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 5.78 (ddd, *J* = 17.2, 10.8, 8.4 Hz, 1H), 5.24 (dd, *J* = 10.8, 1.6 Hz, 1H), 5.13 (dd, *J* = 17.2, 1.6 Hz, 1H), 4.84 (d, *J* = 5.2 Hz, 1H), 3.66 (m, 2H), 2.73 (br, 1H), 2.58-2.51 (m, 1H), 1.90 (br, 1H).

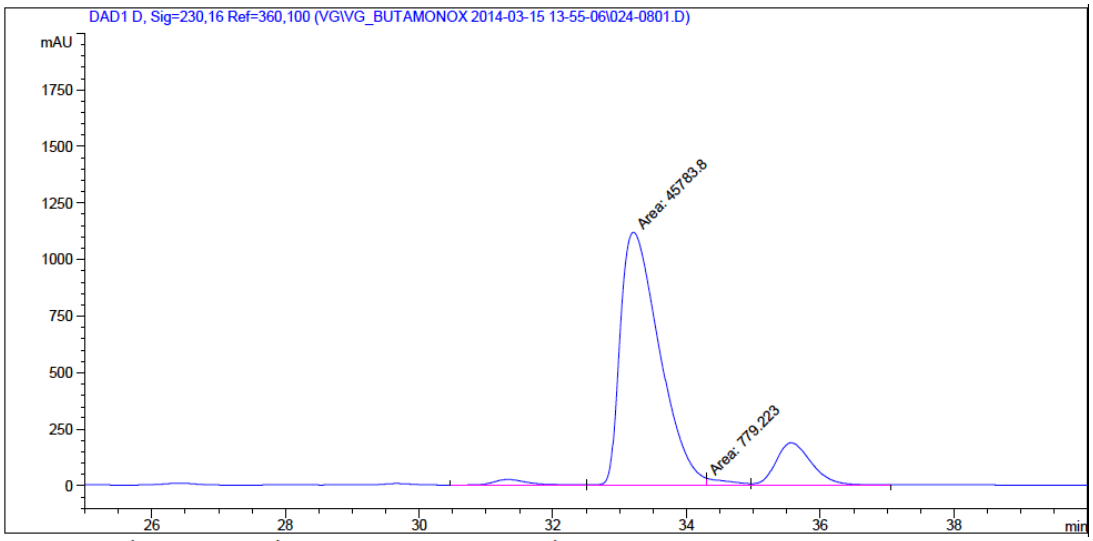
^{13}C NMR (100 MHz, $CDCl_3$) δ 141.1, 134.5, 131.3, 128.1, 121.4, 119.9, 74.3, 63.8, 53.1.

HPLC (two connected Chiralcel OC-H columns, hexanes:*i*-PrOH = 90:10, 0.50 mL/min, 230 nm), *anti*:*syn* = 5:1, *ee* = 94%.

The spectroscopic properties of this compound were consistent with the data available in the literature.[62]

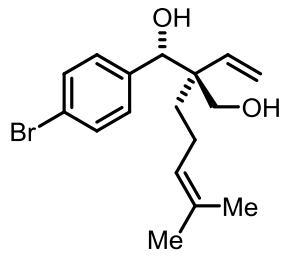


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	31.070	VV	0.5718	5.27088e4	1464.98840	43.5267
2	32.945	VV	0.6643	5.41713e4	1294.19458	44.7344
3	34.347	VV	0.5530	7082.66064	198.15199	5.8488
4	35.376	MF	0.6306	7132.60547	188.50462	5.8901



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	31.332	VV	0.6642	1289.96228	28.06549	2.3364
2	33.206	MF	0.6804	4.57838e4	1121.45105	82.9228
3	34.293	FM	0.3785	779.22272	34.31005	1.4113
4	35.570	VV	0.5953	7359.58105	190.23361	13.3295

(1*S*,2*S*)-1-(4-bromophenyl)-2-(4-methylpent-3-en-1-yl)-2-vinylpropane-1,3-diol (2.7)



Detailed Procedures

An oven-dried pressure tube equipped with a magnetic stir bar was charged with K_3PO_4 (1.1 mg, 0.005 mmol, 5 mol%), (*R*)-**2.5h** (5.5 mg, 0.005 mmol, 5 mol%), and 4-bromobenzyl alcohol (18.7 mg, 0.1 mmol, 100 mol%). The reaction vessel was placed under an atmosphere of argon, and THF (0.1 mL, 1.0 M) and myrcene oxide **3c** (60.9 mg, 0.4 mmol, 400 mol%) were added by syringe. The reaction vessel was sealed and the reaction mixture was allowed to stir at 45 ˚C for 2 day. The reaction was allowed to reach ambient temperature and concentrated *in vacuo*. The residue was subjected to column chromatography (SiO_2: DCM:*i*-PrOH, 200:1) to furnish the title compound as a colorless oil (32.0 mg, *anti*:*syn* > 20:1) in 94% yield.

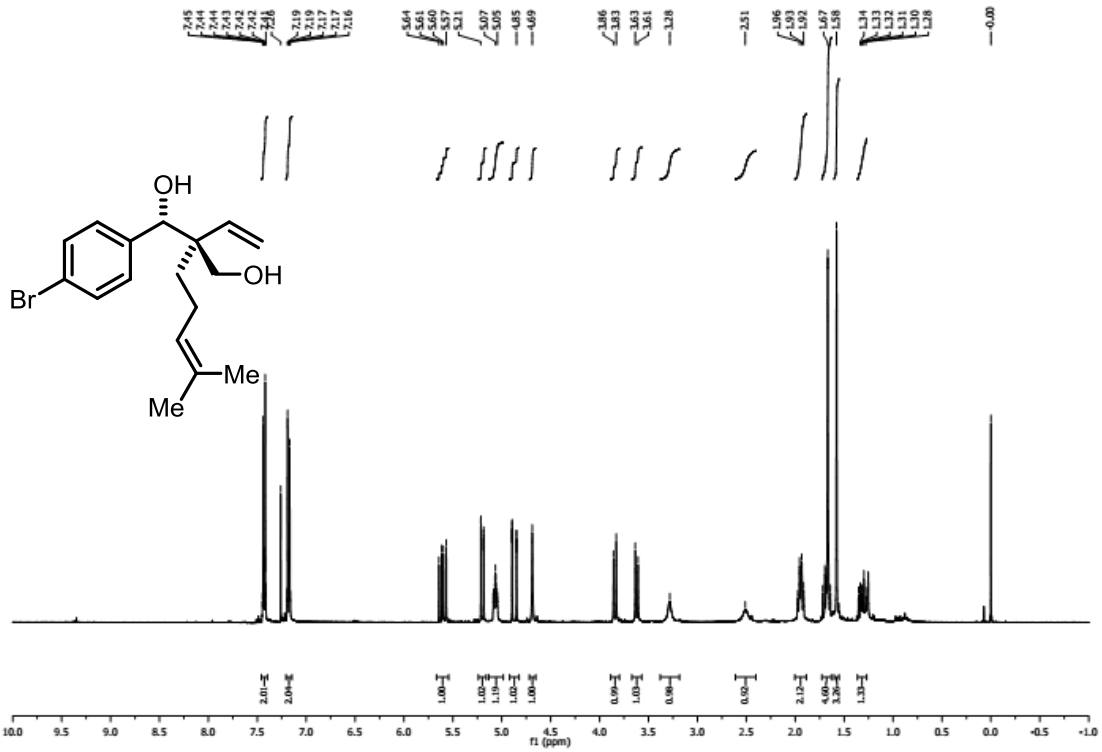
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-7.40 (m, 2H), 7.23-7.15 (m, 2H), 5.62 (dd, *J* = 18.0, 11.3 Hz, 1H), 5.21 (dd, *J* = 11.3, 1.0 Hz, 1H), 5.07 (ddq, *J* = 8.4, 5.6, 1.3 Hz, 1H), 4.89 (dd, *J* = 18.0, 1.0 Hz, 1H), 4.71 (s, 1H), 3.86 (d, *J* = 11.0 Hz, 1H), 3.64 (d, *J* = 11.0 Hz, 1H), 3.09 (br, 1H), 2.31 (br, 1H), 1.95 (dd, *J* = 16.0, 7.5 Hz, 2H), 1.73-1.63 (m, 4H), 1.58 (s, 3H), 1.37-1.28 (m, 1H).

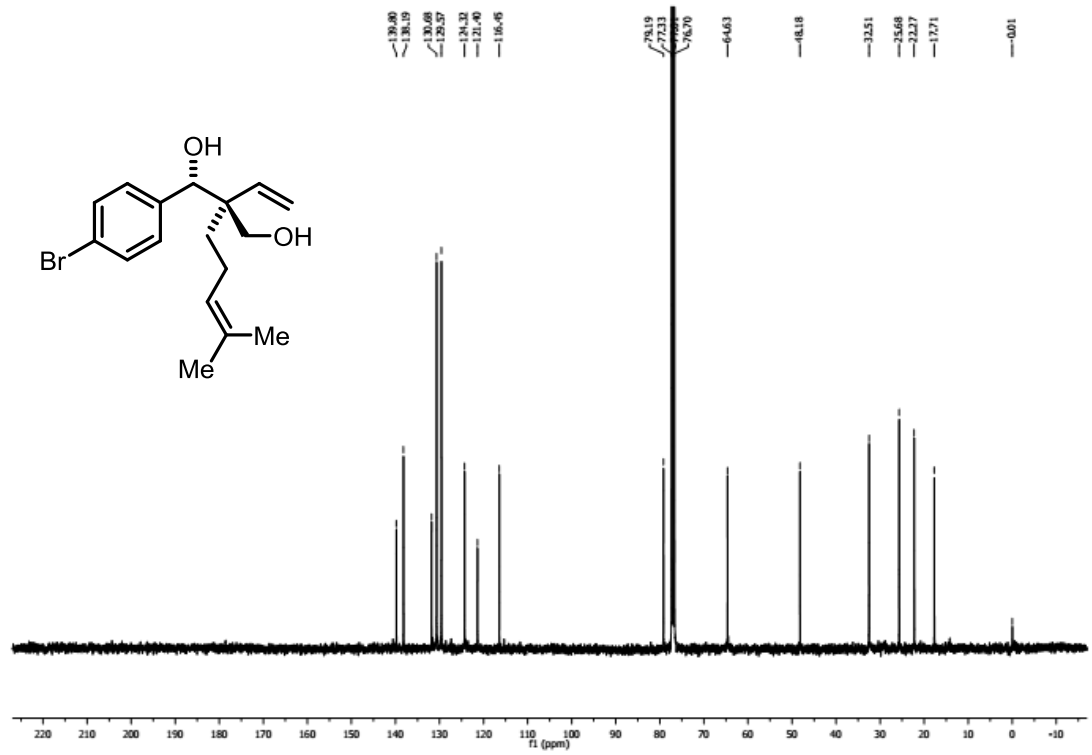
^{13}C NMR (100 MHz, $CDCl_3$) δ 139.8, 138.2, 131.8, 130.7, 129.6, 124.3, 121.4, 116.5, 79.2, 64.6, 48.2, 32.5, 25.7, 22.3, 17.7.

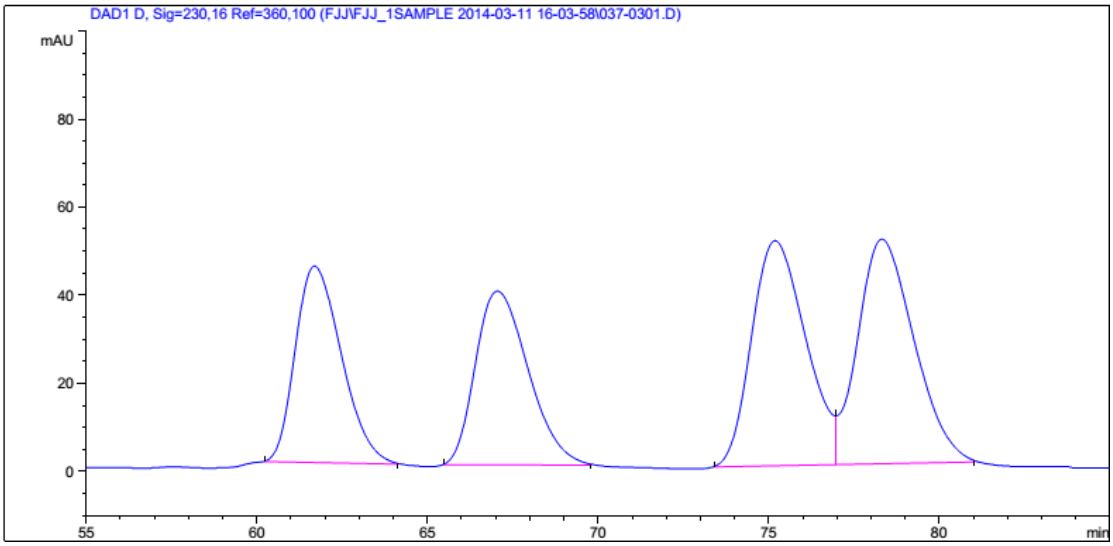
LRMS (ESI) Calcd. for $C_{17}H_{23}BrO_2Na$ $[M+Na]^+$: 361.1, Found: 361.1.

FTIR (neat): 3347, 2969, 2924, 1487, 1448, 1404, 1376, 1072, 1037, 1010, 919, 836, 760, 670 cm^{-1}.

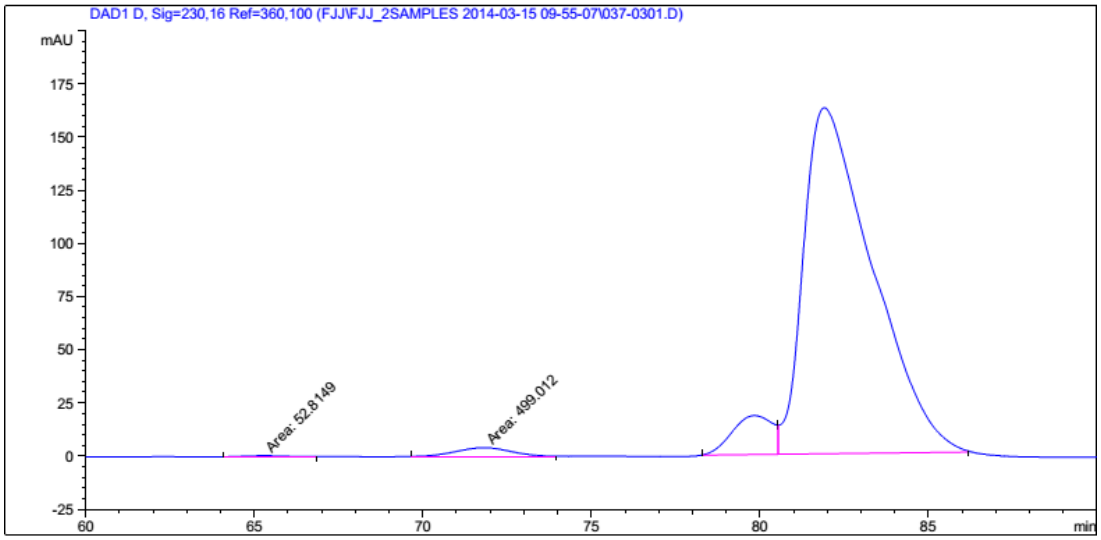
HPLC (two connected Chiralcel OC-H column, hexanes:*i*-PrOH = 98:2, 0.75 mL/min, 230 nm), *anti*:*syn* = 40:1, *ee* = 87%.


OH
OH
Br
Me
Me
f1 (ppm)


OH
OH
Br
Me
Me
f1 (ppm)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	61.687	BB	1.3520	4192.75195	44.63118	21.0426
2	67.045	BB	1.4602	4243.29102	39.47039	21.2963
3	75.186	BV	1.6168	5629.84229	51.12166	28.2551
4	78.319	VB	1.6522	5859.13916	51.00667	29.4059



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	65.248	MM	1.5639	52.81487	5.62856e-1	0.2087
2	71.795	MM	1.9859	499.01151	4.18788	1.9717
3	79.824	BV	0.9815	1521.01160	18.30414	6.0099
4	81.914	VB	1.9936	2.32358e4	162.75890	91.8098

Crystallographic Material for 2.4a-acetonide

X-ray Experimental for $C_{15}H_{19}O_2Br$ (2.4a-acetonide)

Crystals grew as colorless prisms by slow evaporation from n-hexanes. The data crystal had approximate dimensions; 0.35 x 0.13 x 0.05 mm. The data were collected on a Rigaku AFC12 diffractometer with a Saturn 724+ CCD using a graphite monochromator with MoKα radiation (λ = 0.71073 Å). A total of 1192 frames of data were collected using ω-scans with a scan range of 0.5° and a counting time of 45 seconds per frame. The data were collected at 100 K using a Rigaku XStream low temperature device. Details of crystal data, data collection and structure refinement are listed in Table 2.5. Data reduction were performed using the Rigaku Americas Corporation's Crystal Clear version 1.40.[63] The structure was solved by direct methods using SIR97[64] and refined by full-matrix least-squares on F^2 with anisotropic displacement parameters for the non-H atoms using SHELXL-97.[65] Structure analysis was aided by use of the programs PLATON98[66] and WinGX.[67] The hydrogen atoms on carbon were calculated in ideal positions with isotropic displacement parameters set to 1.2xUeq of the attached atom (1.5xUeq for methyl hydrogen atoms).

The absolute configuration of **2.4a**-acetonide was determined by the method of Flack.[68] The Flack x-parameter refined to 0.016(8). The assignment was corroborated by use of the Hooft y-parameter,[69] which refined to 0.020(6).

The function, $\Sigma w(|F_O|^2 - |F_C|^2)^2$, was minimized, where $w = 1/[(\sigma(F_O))^2 + (0.0234*P)^2 + (0.1828*P)]$ and $P = (|F_O|^2 + 2|F_C|^2)/3$. $R_W(F^2)$ refined to 0.0512, with R(F) equal to 0.0201 and a goodness of fit, S, = 1.08. Definitions used for calculating R(F), $R_W(F^2)$ and the goodness of fit, S, are given below.[70] 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).[71] All figures were generated using SHELXTL/PC.[72] Tables of positional and thermal parameters, bond lengths and angles, torsion angles and figures are found elsewhere.

Table 2.5 Crystal data and structure refinement for **2.4a**-acetonide.

Empirical formula	$C_{15}H_{19}BrO_2$	
Formula weight	311.21	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 7.051(3) Å	a= 90°.
	b = 12.646(5) Å	b= 90°.
	c = 16.338(5) Å	g = 90°.
Volume	1456.9(9) $Å^3$	
Z	4	
Density (calculated)	1.419 Mg/m^3	
Absorption coefficient	2.814 mm^{-1}	
F(000)	640	
Crystal size	0.350 x 0.130 x 0.050 mm	
Theta range for data collection	3.147 to 27.460°.	
Index ranges	-9<=h<=9, -16<=k<=15, -21<=l<=21	
Reflections collected	19873	
Independent reflections	3327 [R(int) = 0.0445]	
Completeness to theta = 25.242°	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00 and 0.770	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3327 / 0 / 167	
Goodness-of-fit on F^2	1.082	
Final R indices [I>2sigma(I)]	R1 = 0.0201, wR2 = 0.0508	
R indices (all data)	R1 = 0.0209, wR2 = 0.0512	
Absolute structure parameter	0.016(8)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.223 and -0.216 $e.Å^{-3}$	

Table 2.6 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **2.4a**-acetonide. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C1	6572(4)	4143(2)	1332(1)	19(1)
C2	8152(3)	5825(2)	1200(1)	16(1)
C3	9329(3)	5616(2)	1990(1)	18(1)
C4	9483(3)	4403(2)	2053(1)	21(1)
C5	4593(3)	3739(2)	1508(2)	26(1)
C6	7389(4)	3632(2)	565(2)	28(1)
C7	7697(3)	6980(2)	1063(1)	16(1)
C8	6091(3)	7444(2)	1413(1)	18(1)
C9	5729(3)	8518(2)	1313(1)	20(1)
C10	7005(3)	9117(2)	864(1)	20(1)
C11	8585(4)	8684(2)	498(1)	22(1)
C12	8925(3)	7604(2)	603(1)	20(1)
C13	8300(3)	6025(2)	2736(1)	22(1)
C14	8987(4)	6708(2)	3269(2)	30(1)
C15	11319(3)	6071(2)	1898(2)	25(1)
Br1	6540(1)	10594(1)	740(1)	28(1)
O1	6386(2)	5263(1)	1236(1)	18(1)
O2	7659(2)	3906(1)	2044(1)	20(1)

Table 2.7 Bond lengths [Å] and angles [°] for **2.4a**-acetonide.

C1-O2	1.425(3)	C6-H6C	0.98
C1-O1	1.432(2)	C7-C12	1.392(3)
C1-C5	1.513(3)	C7-C8	1.398(3)
C1-C6	1.523(3)	C8-C9	1.390(3)
C2-O1	1.434(2)	C8-H8	0.95
C2-C7	1.512(3)	C9-C10	1.386(3)
C2-C3	1.557(3)	C9-H9	0.95
C2-H2	1.00	C10-C11	1.378(3)
C3-C13	1.510(3)	C10-Br1	1.907(2)
C3-C15	1.523(3)	C11-C12	1.397(3)
C3-C4	1.542(3)	C11-H11	0.95
C4-O2	1.432(3)	C12-H12	0.95
C4-H4A	0.99	C13-C14	1.320(3)
C4-H4B	0.99	C13-H13	0.95
C5-H5A	0.98	C14-H14A	0.95
C5-H5B	0.98	C14-H14B	0.95
C5-H5C	0.98	C15-H15A	0.98
C6-H6A	0.98	C15-H15B	0.98
C6-H6B	0.98	C15-H15C	0.98
O2-C1-O1	110.33(17)	C7-C2-H2	108.5
O2-C1-C5	105.68(17)	C3-C2-H2	108.5
O1-C1-C5	105.71(19)	C13-C3-C15	113.13(19)
O2-C1-C6	112.3(2)	C13-C3-C4	108.68(18)
O1-C1-C6	111.36(17)	C15-C3-C4	108.51(17)
C5-C1-C6	111.17(19)	C13-C3-C2	110.76(17)
O1-C2-C7	107.48(16)	C15-C3-C2	110.24(17)
O1-C2-C3	110.13(16)	C4-C3-C2	105.17(17)
C7-C2-C3	113.55(17)	O2-C4-C3	111.93(16)
O1-C2-H2	108.5	O2-C4-H4A	109.2

Table 2.7 (cont'd)

C3-C4-H4A	109.2	O2-C4-H4B	109.2
C3-C4-H4B	109.2	C11-C10-C9	122.5(2)
H4A-C4-H4B	107.9	C11-C10-Br1	118.81(16)
C1-C5-H5A	109.5	C9-C10-Br1	118.71(17)
C1-C5-H5B	109.5	C10-C11-C12	118.3(2)
H5A-C5-H5B	109.5	C10-C11-H11	120.8
C1-C5-H5C	109.5	C12-C11-H11	120.8
H5A-C5-H5C	109.5	C7-C12-C11	120.9(2)
H5B-C5-H5C	109.5	C7-C12-H12	119.6
C1-C6-H6A	109.5	C11-C12-H12	119.6
C1-C6-H6B	109.5	C14-C13-C3	125.5(2)
H6A-C6-H6B	109.5	C14-C13-H13	117.3
C1-C6-H6C	109.5	C3-C13-H13	117.3
H6A-C6-H6C	109.5	C13-C14-H14A	120.0
H6B-C6-H6C	109.5	C13-C14-H14B	120.0
C12-C7-C8	119.1(2)	H14A-C14-H14B	120.0
C12-C7-C2	119.71(19)	C3-C15-H15A	109.5
C8-C7-C2	121.15(19)	C3-C15-H15B	109.5
C9-C8-C7	120.7(2)	H15A-C15-H15B	109.5
C9-C8-H8	119.6	C3-C15-H15C	109.5
C7-C8-H8	119.6	H15A-C15-H15C	109.5
C10-C9-C8	118.5(2)	H15B-C15-H15C	109.5
C10-C9-H9	120.8	C1-O1-C2	114.55(17)
C8-C9-H9	120.8	C1-O2-C4	113.51(16)

Table 2.8 Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **2.4a**-acetonide. 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	20(1)	15(1)	21(1)	3(1)	0(1)	-1(1)
C2	16(1)	16(1)	17(1)	0(1)	2(1)	-1(1)
C3	18(1)	17(1)	20(1)	2(1)	-1(1)	1(1)
C4	14(1)	18(1)	31(1)	3(1)	-2(1)	1(1)
C5	20(1)	26(1)	31(1)	9(1)	-2(1)	-5(1)
C6	37(1)	18(1)	28(1)	-2(1)	6(1)	-5(1)
C7	19(1)	16(1)	13(1)	0(1)	-1(1)	-1(1)
C8	19(1)	20(1)	16(1)	2(1)	1(1)	1(1)
C9	21(1)	22(1)	17(1)	-1(1)	-4(1)	3(1)
C10	26(1)	15(1)	19(1)	0(1)	-8(1)	0(1)
C11	26(1)	20(1)	21(1)	4(1)	1(1)	-5(1)
C12	22(1)	20(1)	18(1)	0(1)	5(1)	0(1)
C13	21(1)	24(1)	19(1)	4(1)	-2(1)	3(1)
C14	36(1)	28(1)	24(1)	-1(1)	-7(1)	10(1)
C15	18(1)	21(1)	36(1)	1(1)	-1(1)	0(1)
Br1	35(1)	14(1)	35(1)	1(1)	-13(1)	2(1)
O1	17(1)	16(1)	20(1)	2(1)	-1(1)	-2(1)
O2	18(1)	19(1)	24(1)	6(1)	-1(1)	-1(1)

Table 2.9 Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **2.4a**-acetonide.

	x	y	z	U(eq)
H2	8888	5560	719	20
H4A	10246	4133	1589	25
H4B	10149	4215	2566	25
H5A	4641	2976	1613	39
H5B	3775	3877	1035	39
H5C	4082	4102	1990	39
H6A	8687	3885	479	42
H6B	6605	3820	92	42
H6C	7400	2862	632	42
H8	5237	7022	1722	22
H9	4632	8833	1547	24
H11	9421	9109	183	27
H12	10010	7292	357	24
H13	7052	5769	2828	26
H14A	10230	6984	3199	36
H14B	8240	6924	3723	36
H15A	11250	6844	1885	37
H15B	11886	5813	1389	37
H15C	12100	5847	2363	37

Table 2.10 Torsion angles [°] for **2.4a**-acetonide.

O1-C2-C3-C13	-62.6(2)	C9-C10-C11-C12	-1.5(3)
C7-C2-C3-C13	57.9(2)	Br1-C10-C11-C12	179.15(17)
O1-C2-C3-C15	171.38(17)	C8-C7-C12-C11	0.9(3)
C7-C2-C3-C15	-68.0(2)	C2-C7-C12-C11	-177.0(2)
O1-C2-C3-C4	54.6(2)	C10-C11-C12-C7	0.2(3)
C7-C2-C3-C4	175.18(17)	C15-C3-C13-C14	0.3(3)
C13-C3-C4-O2	63.4(2)	C4-C3-C13-C14	120.9(2)
C15-C3-C4-O2	-173.18(17)	C2-C3-C13-C14	-124.1(2)
C2-C3-C4-O2	-55.2(2)	O2-C1-O1-C2	56.3(2)
O1-C2-C7-C12	-146.97(19)	C5-C1-O1-C2	170.15(17)
C3-C2-C7-C12	91.0(2)	C6-C1-O1-C2	-69.0(2)
O1-C2-C7-C8	35.2(3)	C7-C2-O1-C1	177.67(16)
C3-C2-C7-C8	-86.9(2)	C3-C2-O1-C1	-58.2(2)
C12-C7-C8-C9	-0.7(3)	O1-C1-O2-C4	-55.3(2)
C2-C7-C8-C9	177.14(19)	C5-C1-O2-C4	-169.07(17)
C7-C8-C9-C10	-0.5(3)	C6-C1-O2-C4	69.6(2)
C8-C9-C10-C11	1.7(3)	C3-C4-O2-C1	58.0(2)
C8-C9-C10-Br1	-179.02(16)		

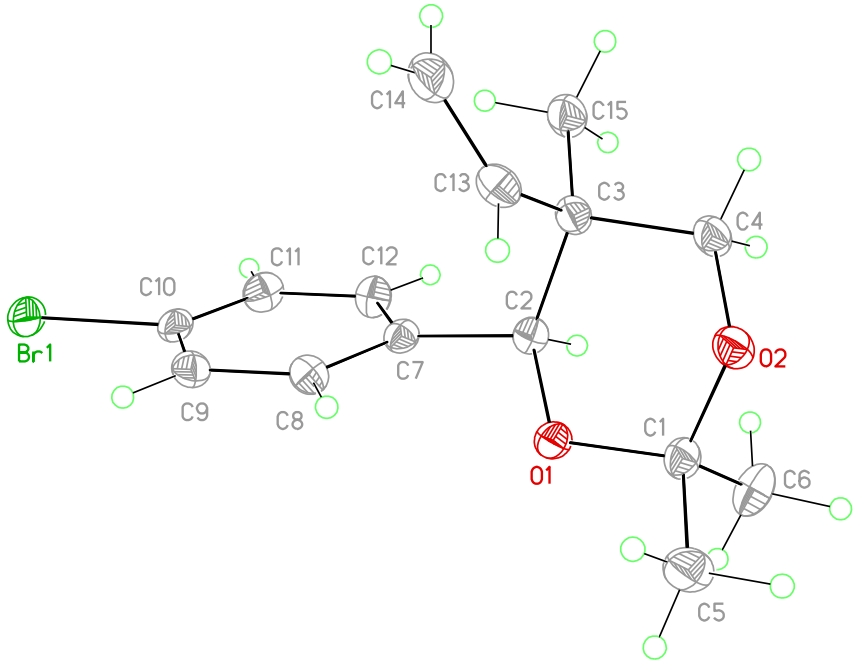


Figure 2.2 View of **2.4a**-acetonide showing the atom labeling scheme. Displacement ellipsoids are scaled to the 50% probability level.

Chapter 3: Total Synthesis of Oridamycin A, Triptoquinones B and C: Modular Terpenoid Construction via Ir-Catalyzed *tert*-(Hydroxy)prenylation and Lewis Acid Mediated Cyclization*

3.1 INTRODUCTION

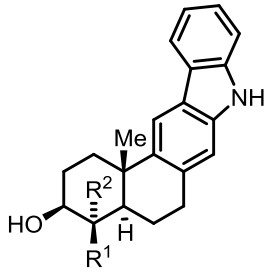
Terpenoids are regarded as the largest class of chemical compounds produced by nature.[1–3] These secondary metabolites are secreted by plants, animals, and even bacteria for their own good. For a long time, people have been utilizing terpenoid natural products in fragrance, food flavor and agriculture. More importantly, they are also found use in human medicines: quite a few pharmaceutical drugs and candidates are terpenoids, for example, paclitaxel, ingenol mebutate, phorbol, etc.

Terpenoids are also of interests from organic chemists because of their complex multicyclic strutures and dense functionalities. Biosynthetically, terpene backbone formation largely correlates to carbocationic cyclization and rearrangement catalyzed by cyclase and isomerase in organisms.[4–7] Therefore, biomimetic synthetic approaches which involve polyene cyclization are widely used strategies in terpenoid total synthesis.[8,9] These amazing ideas allow chemists to access structurally complicated terpenoids from relatively simple starting materials, but the synthetic routes are sometimes too long for practical use because of the lack of convergence. Alternatively, more convergent nonbiomimetic designs have come to chemists' mind as modern synthetic methodologies are developing.[10] Recently, my coworker and I have disclosed a highly stereoselective iridium-catalyzed *tert*-(hydroxy)prenylation of alcohols which allows us to access a motif existing in more than 2000 terpenoid natural products.[11] We

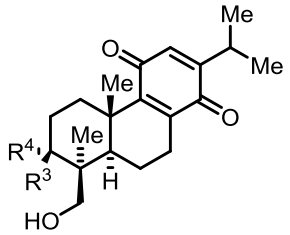
* This chapter is partially based on the previously published work:
Feng, J.; Noack, F.; Krische, M. J. *J. Am. Chem. Soc.* **2016**, *138*, 12364–12367.
J. F. contributed to route designs (Scheme 3.6), synthesis of oridamycin A (Table 3.2, Table 3.3, Scheme 3.7, Scheme 3.10, and Scheme 3.11), synthesis of triptoquinones B and C (Scheme 3.12), and preparation of manuscript and supporting information.

were then curious about whether this method could be really applied to synthesis of related terpenoids.

Oridamycin A (**3.1**) was first isolated in 2010 from the fermentation broth of *Streptomyces* sp. strain KS84 collected in Uji, Japan,[12] and is the first indolosesquiterpenoid natural product[13] from prokaryotic source. It exhibits a selective antibiotic activity towards *Saprolegnia parasitica*,[14] but other bioactivities are unknown due to limited accessible material. Oridamycin A contains a carbazole-fused *trans*-decalin ring structure with four contiguous stereocenters, two of which are all-carbon quaternary centers (Figure 3.1, left). Only two racemic syntheses were reported in literatures[15,16] since its discovery, suggesting the difficulty of installing all carbon centers in their correct stereochemistry. On the other hand, a close structural-related indolosesquiterpenoid, Xiamycin A and its dimer Dixiamycin A/B,[17–20] were also isolated from microorganism (Figure 3.1, left). These compounds have shown potent antiviral and antibacterial activities in bioassay, and more interesting properties were found when chemists have synthesized larger quantities of material *de novo*.[15,21]



Oridamycin A $R^1 = CO_2H$, R^2 = Me (**3.1**)
Xiamycin A R^1 = Me, $R^2 = CO_2H$

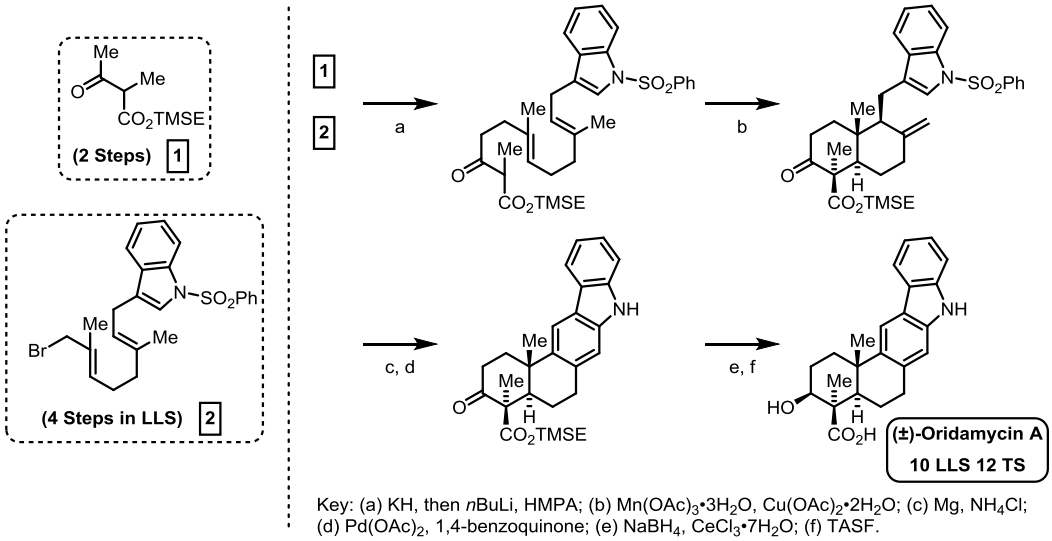


Triptoquinone B $R^3 = R^4$ = O (**3.2**)
Triptoquinone C R^3 = OH, R^4 = H (**3.3**)

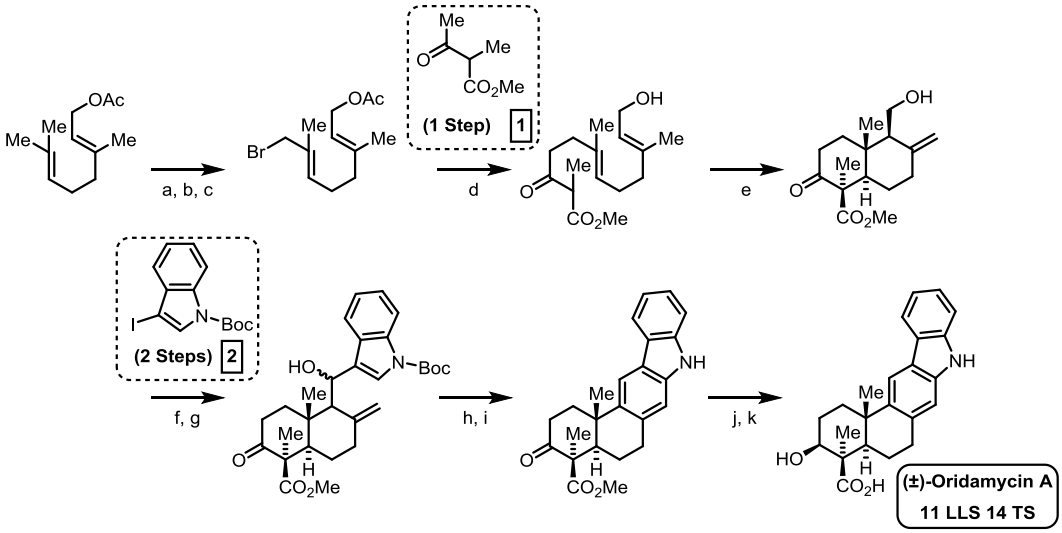
Figure 3.1 Structures of oridamycin A, xiamycin A, triptoquinones B and C.

Triptoquinones B (**3.2**) and C (**3.3**),[22–29] are diterpenoids first isolated from *Triptervgium wilfordii* var. *regelii*, a plant that is used in traditional Chinese medicines.

The two compounds exhibited potent inhibition to interleukin-1α (IL-1α) and -1β (IL-1β), cytokines that regulate immune response. These tricyclic terpenoids also have *trans*-decalin structure and two quaternary stereocenters (Figure 3.1, right). Two total syntheses of both compounds have been completed, including one asymmetric version.[30,31]

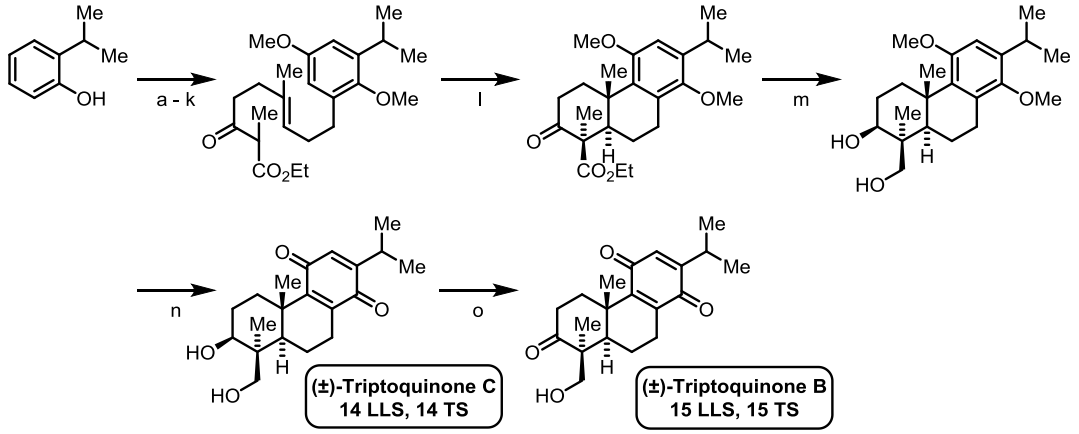


Scheme 3.1 Li's racemic synthesis of oridamycin A.



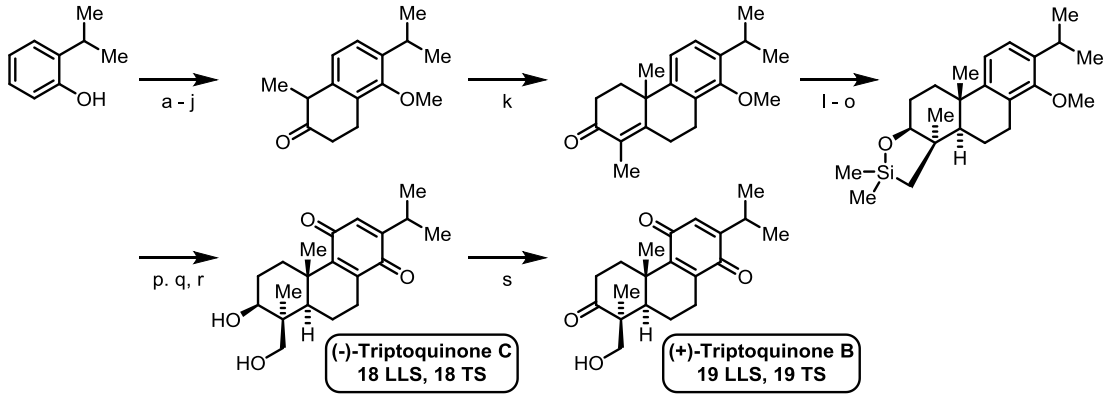
Scheme 3.2 Trotta's racemic synthesis of oridamycin A.

Most of the prior syntheses (Scheme 3.1-3.4) have utilized polyene cyclization as key transformation, which allowed them to access the stereocenters of molecules in one single step. However, quite a few steps were used in order to prepare the cyclizing precursors. In addition, the absolute stereochemistry could not be controlled in this process, thus leading to racemic syntheses only.



Key: (a) Br_2; (b) Allyl bromide, K_2CO_3; (c) NaOMe, CuI, MeOH; (d) 200 °C; (e) Me_2SO_4, K_2CO_3; (f) BH_3•SMe_2, then H_2O_2, NaOH; (g) $(COCl)_2$, DMSO, Et_3N; (h) PPh_3=C(Me)CO_2Et; (i) DIBAL; (j) PPh_3, CBr_4; (k) Ethyl methylacetoacetate, NaH, *n*BuLi, HMPA; (l) $Mn(OAc)_3$, AcOH; (m) $LiAlH_4$; (n) $(NH_4)_2Ce(NO_3)_6$; (o) 7% NaClO (aq.), AcOH.

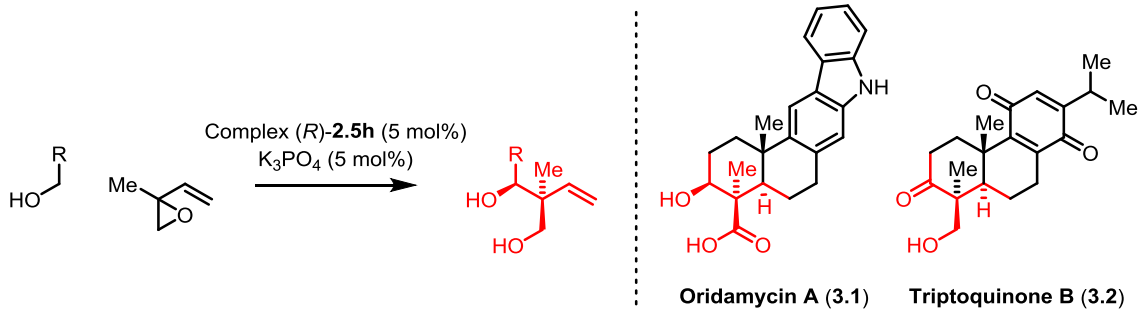
Scheme 3.3 Shishido's racemic synthesis of triptoquinones B and C.



Key: (a) Allyl bromide, K_2CO_3; (b) 200 °C; (c) Me_2SO_4, K_2CO_3; (d) 9-BBN, CO, $LiAlH(OtBu)_3$, then H_2O_2, NaH_2PO_4, K_2HPO_4•$2H_2O$; (e) H_2NSO_3H, $NaClO_2$; (f) PPA; (g) MeMgI; (h) *p*-TsOH; (i) BH_3•SMe_2, then H_2O_2, NaOH; (j) $(COCl)_2$, DMSO, Et_3N; (k) EVK, KOH; (l) $NaBH_4$, $CeCl_3$; (m) NOVOZYM 435, vinyl acetate; (n) $BrCH_2SiMe_2Cl$, Et_3N; (o) $NaBH_3CN$, Bu_3SnCl, AIBN; (p) Na_2CO_3, H_2O_2; (q) EtSH, $AlCl_3$; (r) $(KSO_3)_2NO$, KH_2PO_4; (s) 7% NaClO (aq.), AcOH.

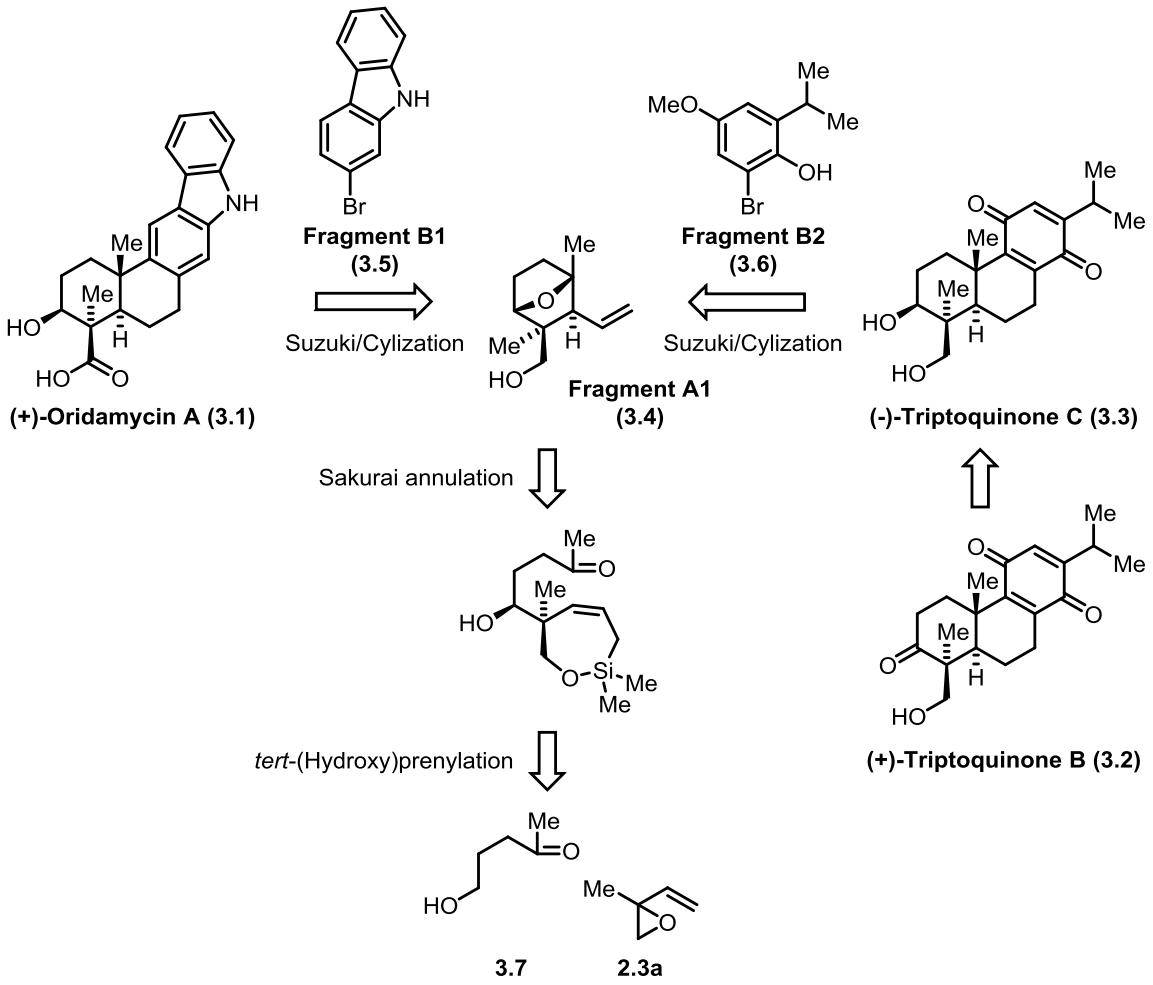
Scheme 3.4 Shishido's asymmetric synthesis of triptoquinones B and C.

3.2 RETROSYNTHETIC ANALYSIS



Scheme 3.5 Highly stereoselective *tert*-(hydroxy)prenylation is able to access moieties in terpenoid natural products.

We noticed that oridamycin A, triptoquinones B and C all have similar *trans*-decalin structures, and the southwestern moiety of molecules should be accessible by the newly developed Ir-catalyzed *tert*-(hydroxy)prenylation asymmetrically (Scheme 3.5). Based on this hypothesis and the idea to establish more convergent synthetic routes for terpenoids, a modular synthesis strategy was proposed (Scheme 3.6). Retrosynthetically, oridamycin A, triptoquinones B and C are constructed via Suzuki coupling of Fragment **A1** with Fragment **B1**/**B2**, followed by Friedel-Crafts cyclization. The common intermediate Fragment **A1** (**3.4**) is formed via Sakurai annulation from the cyclic allyl siloxane, and this precursor is prepared via Ir-catalyzed *tert*-(hydroxy)prenylation from hydroxyketone **3.7** and isoprene monoxide (**2.3a**). This proposal allows us to access all of the above mentioned natural products in a uniformed route, which shall be time- and cost-effective.



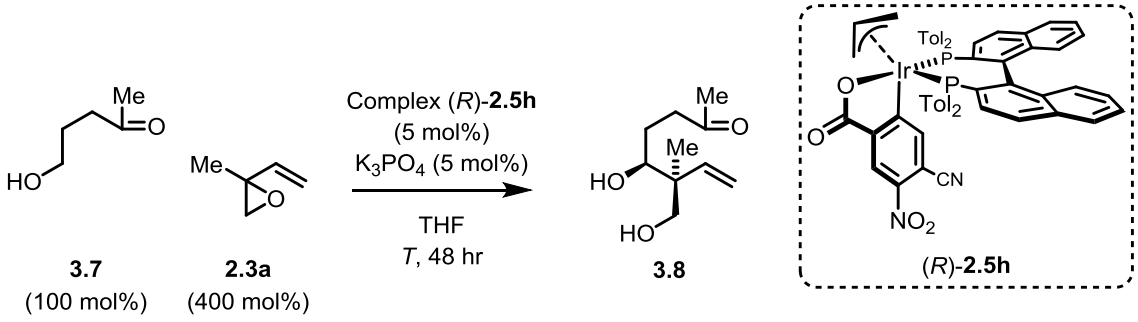
Scheme 3.6 Modular retrosynthetic analysis of oridamycin A and triptoquinone B.

3.3 SYNTHESIS OF COMMON INTERMEDIATE FRAGMENT A1

The synthesis of Fragment **A1** began at *tert*-(hydroxy)prenylation of hydroxyketone **3.7** with isoprene monoxide. The primary alcohol is commercially available, though purification will be needed to get reproducible yield if it starts dimerizing to form intermolecular ketal.[32] Using the previously developed condition for alkyl alcohols[11] led to a clean reaction and delivered the desired product **3.8** in 65% yield with satisfactory diastereo- and enantioselectivity, albeit conversion was not completed (Table 3.1, entry 1). Change of temperature or stoichiometry of isoprene monoxide did

not make a large difference (Table 3.1, entry 2 and 3), but altering the concentration of reaction had a significant impact on yield of product. While diluting the reaction mixtures resulted in very slow conversion, doubling the concentration to 1.0 M led to full conversion (90% isolated yield) in 2 days and still maintained high stereoselectivity (Table 3.1, entry 4 and 5). Remarkably, product could be obtained in good yield even with 2.5 mol% catalyst loading (Table 3.1, entry 7). It is also worthy to mention that **3.8** exists as a mixture of three equilibrating compounds (hydroxyketone and two diastereomeric lactols) in solution, and is not stable under acidic conditions (forming an intramolecular bicyclic ketal).

Table 3.1 Optimization of *tert*-(hydroxy)prenylation of hydroxyketone **3.7**.[a]



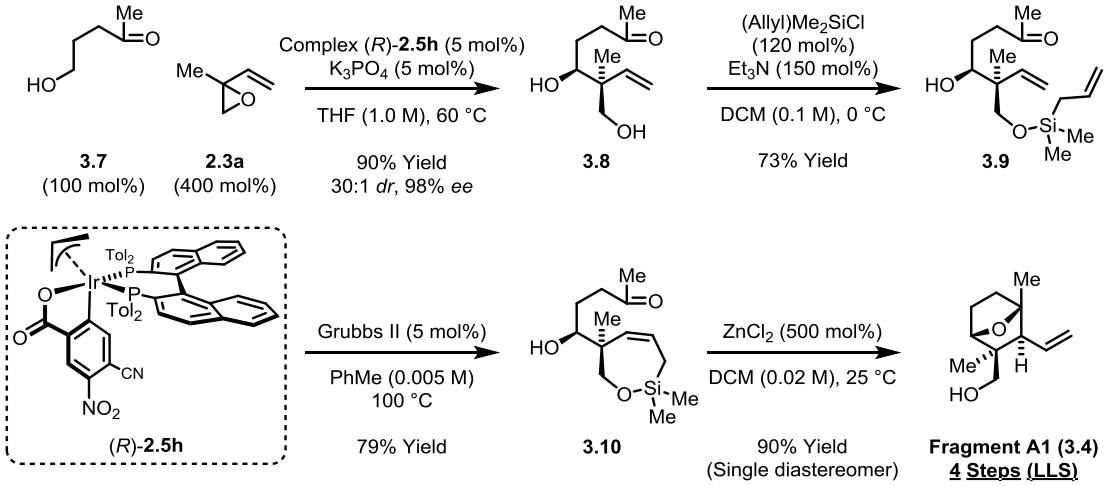
3.7 (100 mol%) **2.3a** (400 mol%) **3.8** (*R*)-**2.5h**

Entry	*T* (°C)	THF Conc. (M)	**3.8** Yield (*dr*, *ee*%)
1	60	0.5	65% (30:1, 96)
2	70	0.5	50% (n.d.)
3[b]	60	0.5	78% (35:1, 97)
4	60	0.25	trace (n.d.)
5	**60**	**1.0**	**90% (30:1, 98)**
6[c]	60	1.0	76% (30:1, 98)
7[d]	60	1.0	70% (30:1, 96)

[a]Yields are of material isolated by silica gel chromatography. [b]**2.3a** (500 mol%). [c]24 hr. [d]Ir complex (2.5 mol%).

With *tert*-(hydroxy)prenylation product **3.8** in hand, a regioselective silylation was performed with 1.2 equivalents of allyldimethylsilyl chloride at 0 ˚C. Ring-closing

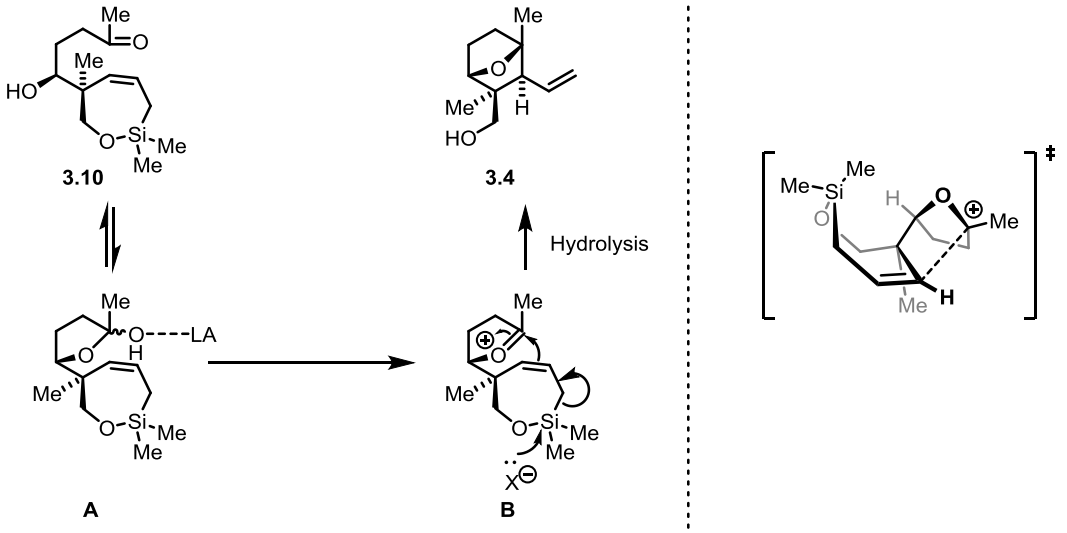
metathesis[33] of **3.9** catalyzed by Grubbs II catalyst successfully delivered the cyclic siloxane **3.10** in good yield. It should be noted that initial attempts on cross-metathesis of **3.8** and allylsilane did not succeed, probably due to steric hindrance of the adjacent quaternary center. Even under RCM condition, elevated temperature (100 ˚C) was required to ensure good conversion. Upon treating with Lewis acid, allylic siloxane underwent Sakurai annulation[34] to close the first ring in targeted natural products diastereoselectively, indicating Fragment **A1** was synthesized in only four steps from commercially available starting materials (Scheme 3.7).



Scheme 3.7 4-Step synthesis of Fragment **A1**.

A plausible mechanism for the formation of oxabyclic compound **3.4** is shown in Scheme 3.8: Similar to **3.8**, **3.10** also has an equilibrium between hydroxyketone form and lactols (Scheme 3.8, **A**). Upon binding to Lewis acid, an oxocarbenium ion is generated (Scheme 3.8, **B**) and attacked intramolecularly by allylic siloxane to form the new C-C bond. In order to illustrate the diastereoselectivity, a stereochemical model is also displayed: due to a conformational restriction, only the *Si* face of alkene was exposed to carbocation, and therefore forming a single isomer in the end (Scheme 3.8,

right). Several Lewis acids (BF_3•OEt_2, $ZrCl_4$, $SnCl_4$, TMSOTf, TFA, $ZnCl_2$, etc.) were screened for this transformation, and the milder reagent $ZnCl_2$ provided the highest yield under ambient condition.



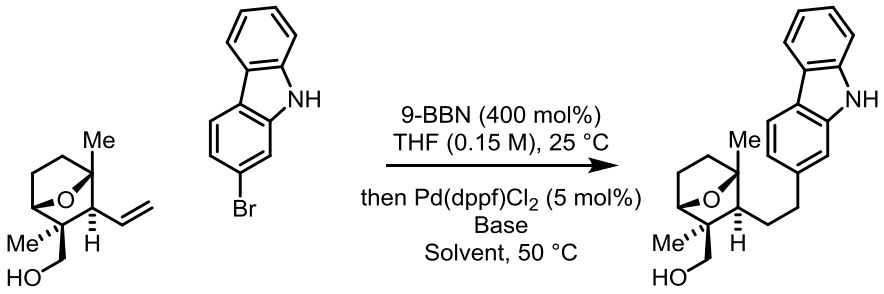
Scheme 3.8 Plausible mechanism and stereochemical model for Sakurai annulation.

3.4 COMPLETION OF SYNTHESIS OF ORIDAMYCIN A

The next stage of the synthesis was to couple Fragment **A1** with Fragment **B1**. Suzuki coupling of 2-bromocarbazole (**3.5**) and 9-alkyl-9-BBN reagent[35] (*in situ* generated from hydroboration of terminal olefin in **3.4**) delivered the union product **3.11**. The structure and stereochemistry of this compound was confirmed by single crystal X-ray diffraction analysis. It turns out that the amount of water and choice of base in reaction is crucial to the obtained yield. Using aqueous base solution did give some desired coupling product (Table 3.2, entry 1), but the low conversion could not be improved because the boron reagent was very water-soluble and got extracted to aqueous phase. Nonaqueous conditions boosted the yield up to 40%, and the use of potassium fluoride[36,37] led to a much more efficient reaction (Table 3.2, entry 2 and 3). Interestingly,

anhydrous KF did not facilitate the reaction at all, but corresponding dihydrate compound or addition of small amount of water to reaction mixture was equally effective (Table 3.2, entry 3-5).[38] The role of water may be ionizing KF to provide fluoride anion.

Table 3.2 Selected optimizations of Suzuki coupling between Fragment **A1** and **B1**.



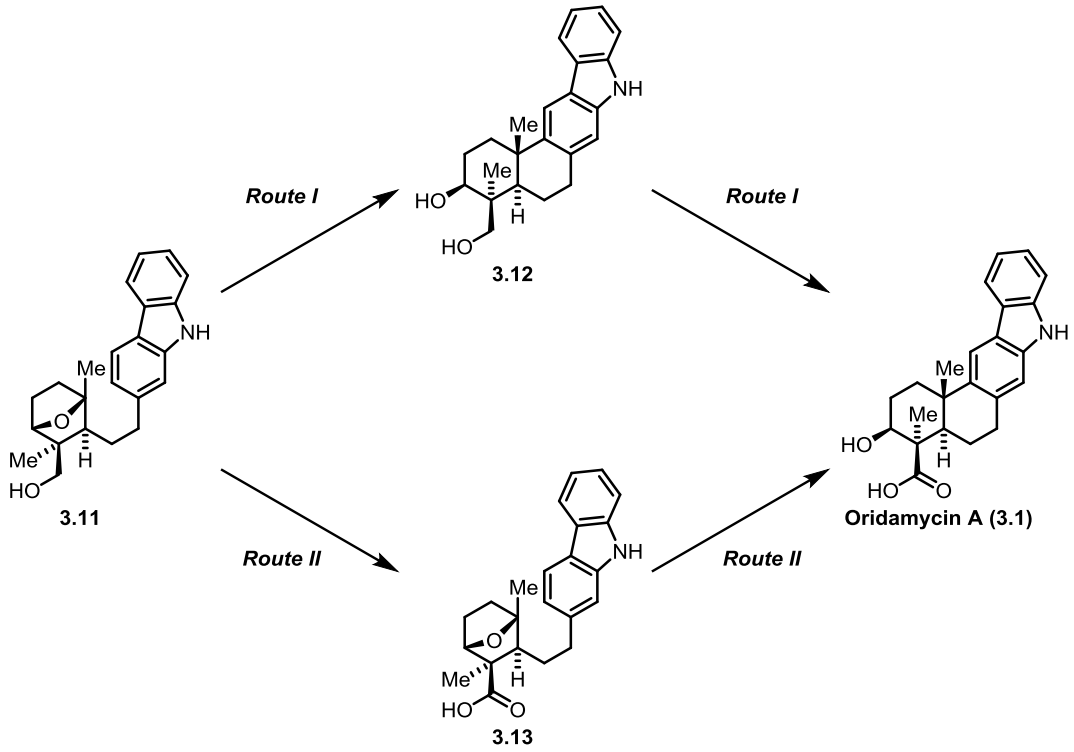
3.4 (100 mol%) **3.5** (150 mol%) **3.11**

Entry	Base (mol%)	Solvent	**3.11** Yield
1[b]	NaOH (600)	THF/H_2O	18%
2[c]	K_3PO_4 (480)	THF/DMF	40%
3	**KF•2H_2O (480)**	**THF/DMF**	**66%**
4	KF (480)	THF/DMF	n.p.
5[d]	**KF (600)**	**THF/DMF**	**66%**

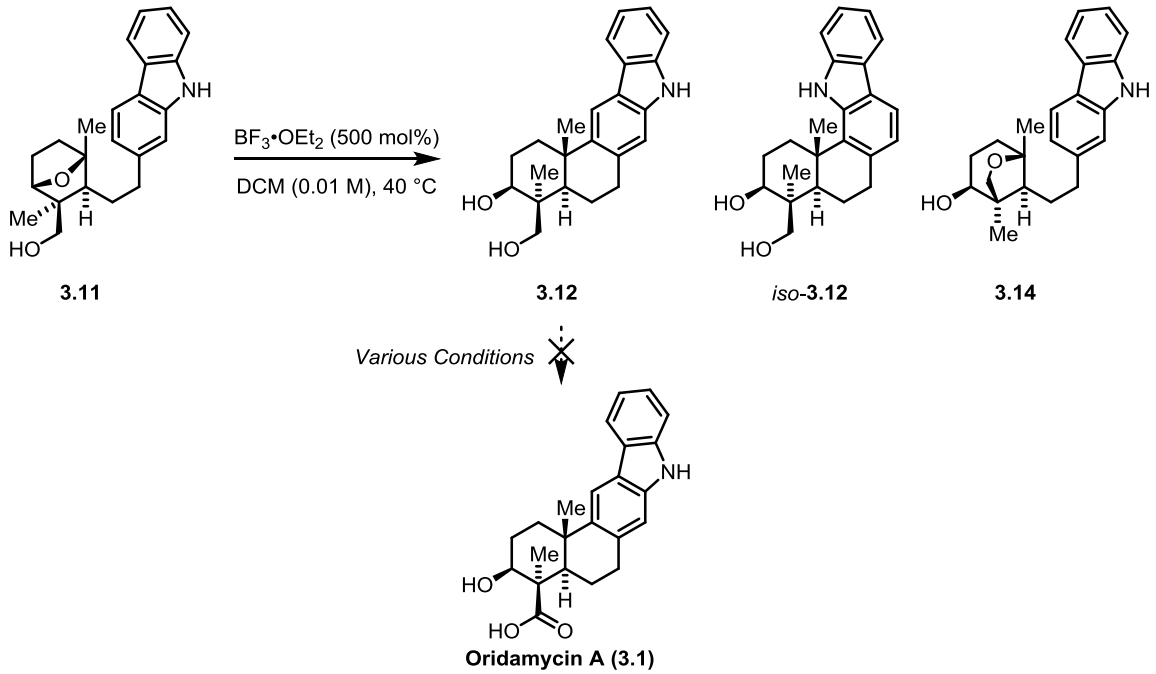
[a]Yields are of material isolated by silica gel chromatography. [b]9-BBN (600 mol%), Pd(dppf)Cl_2•DCM (10 mol%), 60 °C. [c]2-Bromocarbazole (135 mol%). [d]H_2O (1200 mol%) was added.

There were two possible strategies to furnish the synthesis after the fragment union step: close the ring, and then oxidize the primary alcohol to carboxylic acid (Scheme 3.9, Route **I**); or first perform an oxidation, and cyclize it afterwards (Scheme 3.9, Route **II**). Route **I** was tested first: even though tetrahydrofuran-type cyclic ethers are not common precursors for forming carbocation under acidic conditions,[39,40] the more strained [2.2.1]-bicyclic structure may increase the reactivity of **3.11** towards Friedel-Crafts chemistry. Indeed, treating coupling product **3.11** with BF_3•OEt_2 in reflux DCM led to formation of three different compounds, the desired ring-closing product **3.12**, its

C-1 regioisomer *iso*-**3.12**, and another oxabicycle **3.14** (Scheme 3.10). It seemed that **3.14** was the reaction intermediate in Friedel-Crafts cyclization, since exposure of the bicyclic compound to Lewis acid would also result in product formation. Single crystal X-ray analysis of confirmed the correct *trans*-decalin structure in **3.12**. However, further oxidation of cyclization product **3.12** to oridamycin A was not successful. Methods which have been reported to selectively oxidize primary alcohol to carboxylic acid were tested (Heyns oxidation,[41–47] Anelli's oxidation,[48] Zhao's modification,[49–51] etc.), but either returned starting material or gave an unidentified mixture.



Scheme 3.9 Two strategies for finishing the total synthesis of oridamycin A.

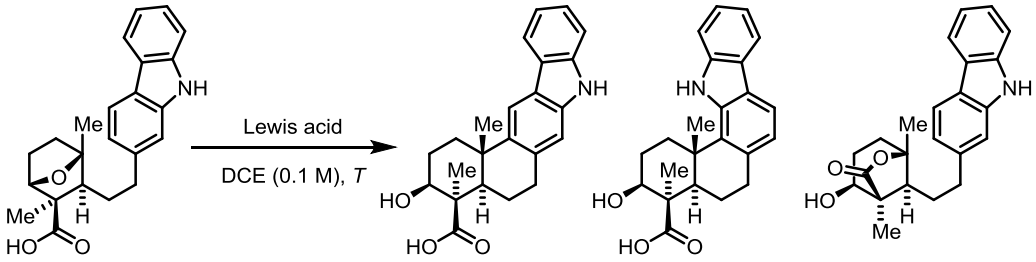


Scheme 3.10 Attempts to synthesize oridamycin A through cyclization/oxidation strategy.

The other strategy (Route **II**) was therefore pursued: the primary alcohol needed to be oxidized to carboxylic acid first. Surprisingly, most of the known methods did not work on this specific substrate, in which reactions would stop at the aldehyde stage. It might be because steric hindrance around the aldehyde hydrate intermediate (adjacent all-carbon quaternary center) impeded its interaction with oxidizing reagents. Fortunately, a one-pot procedure that applied IBX[52,53] (alcohol to aldehyde) and Pinnick oxidation[54–56] (aldehyde to acid) in DMSO achieved the desired product in 70% yield. We finally tested Friedel-Crafts cyclization on carboxylic acid **3.13**. The starting material was consumed quickly, again leading to isolation of three compounds, the desired oridamycin A, C-1 regioisomer *iso*-**3.1**, and lactone **3.15**. The lactone intermediate was converted to cyclization products mostly under more forcing conditions, which was observed by TLC. The C3-C1 regioselectivity was not effected by solvent, but strongly influenced by Lewis

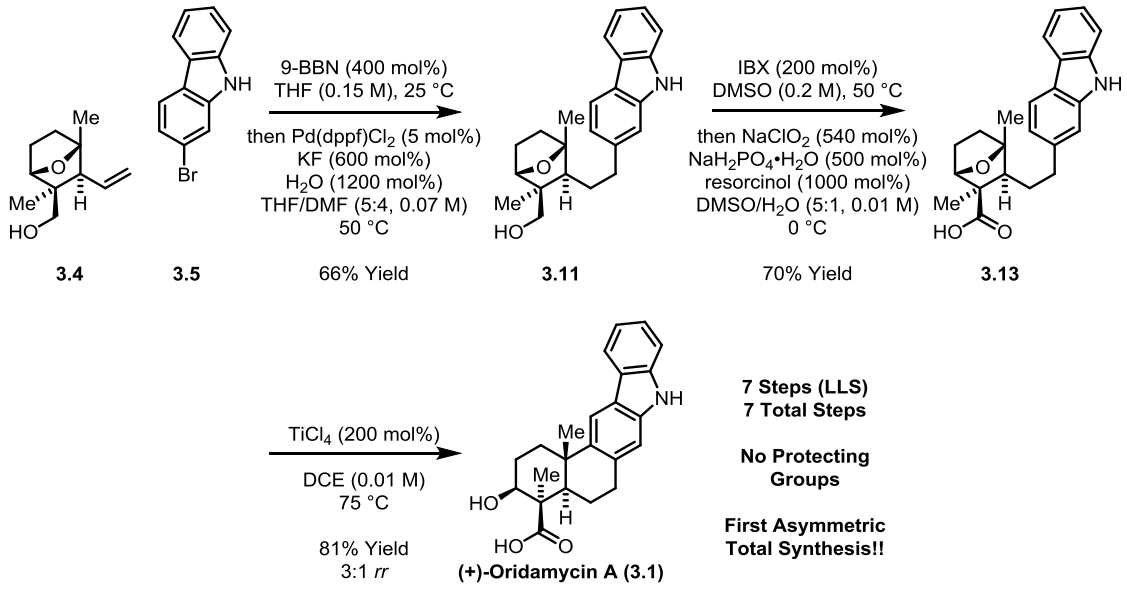
acids used in the reactions (Table 3.3): $TiCl_4$ gave the best 3:1 regiomeric ratio, while other reagents only resulted in inferior or even inversed selectivity. Elevated temperature facilitated a better conversion, but seemed to decompose products faster at the same time and not improving the yield. Therefore, less Lewis acid was added and a good yield was finally obtained! At this point, the first asymmetric total synthesis of oridamycin A was achieved in only seven longest linear steps (Scheme 3.11), even shorter than both known racemic syntheses.

Table 3.3 Optimizations of Lewis acid-mediated Friedel-Crafts cyclization of **3.13**.[a]



Entry	Lewis acid (mol%)	*T* (°C)	*rr* (**3.1**:*iso*-**3.1**)[b]	Yield
1	$AlCl_3$ (500)	65	2:1	n.d.
2	$FeCl_3$ (500)	25	n.d.	decomp.
3	$InCl_3$ (500)	65	<1:1	n.d.
4	$Sc(OTf)_3$ (500)	65	1:1	n.d.
5	TMSOTf (500)	25	<1:1	n.d.
6	TFA (2000)	65	<1:1	n.d.
7	$TiCl_4$ (500)	65	3:1	48
8[c]	$TiCl_4$ (500)	25	3:1	38
9	$TiCl_4$ (500)	40	3:1	48
10	$TiCl_4$ (500)	75	3:1	50
11	$TiCl_4$ (300)	75	3:1	58
⇨ **12**	**$TiCl_4$ (200)**	**75**	**3:1**	**81**
13	$TiCl_4$ (100)	75	n.d.	low conv.

[a]Yields are of material isolated by silica gel chromatography. [b]Regioselectivity was determined via intergral ratios of reaction crude ^{1}H-NMR. [c]DCM as solvent.

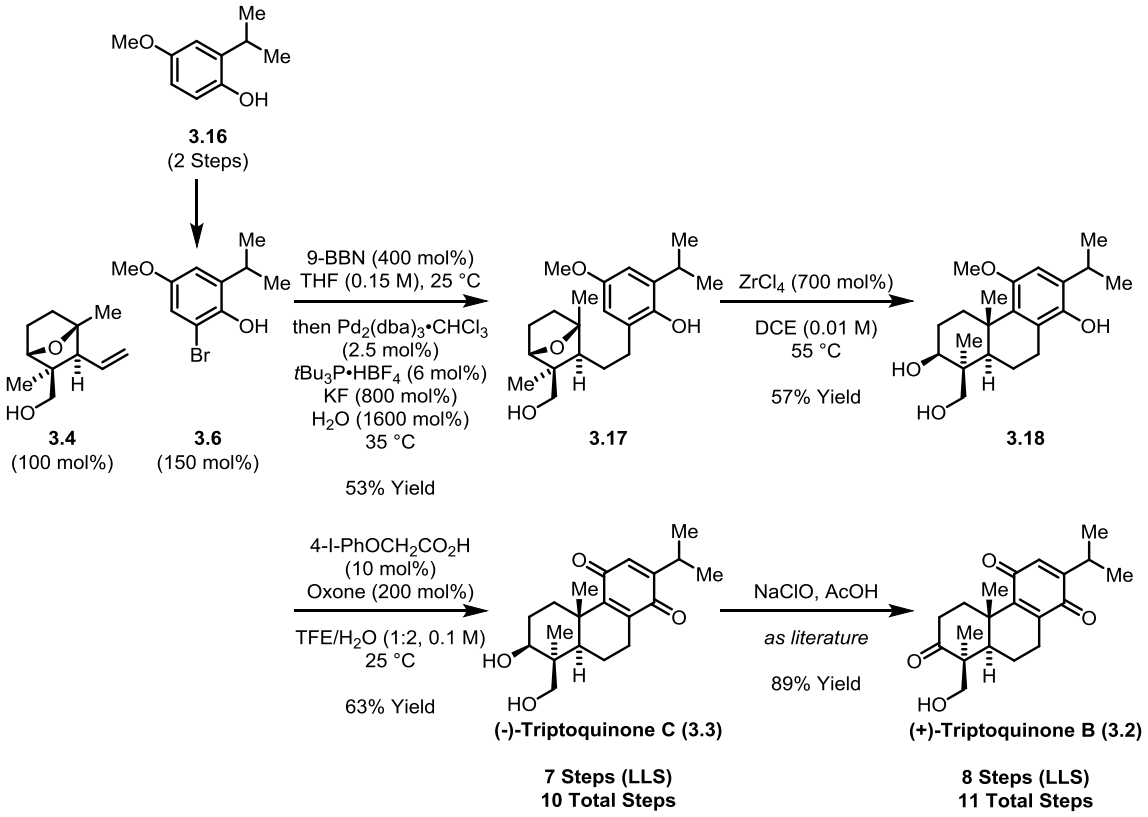


Scheme 3.11 Synthesis of oridamycin A (**3.1**) from Fragment A.

3.5 COMPLETION OF SYNTHESIS OF TRIPTOQUINONES B AND C

Since Suzuki coupling/Friedel-Crafts cyclization strategy was successfully applied to asymmetric synthesis of oridamycin A, synthesis of triptoquinones B and C was launched with similar approach (Scheme 3.12). Fragment **B2** (**3.6**) for Suzuki reaction was prepared from the known compound **3.16**[57] via chemo- and regioselective bromination (See experimental details). With readily available bromophenol **3.6**, Suzuki coupling between Fragment **A1** and **B2** was tested under the condition which was previously developed in synthesis of oridamycin A. Unfortunately, the more electron-donating **3.6** did not undergo C-X oxidative addition to palladium catalyst and therefore no coupling product was obtained. By switching to a more electron-donating and bulkier ligand P(*t*Bu)$_3$ which was reported to facilitate cross-couplings of traditionally unreactive aryl chlorides,[38,58,59] the desired product **3.17** was finally observed and isolated in moderate yield. Condition for Friedel-Crafts cyclization needed to be modified as well, because the more electron-rich intermediate/product seemed to be decomposed by $TiCl_4$

very quickly. A milder reagent $ZrCl_4$ was able to balance the reactivity and stability of substrate, leading to a much cleaner transformation to **3.18**. Final oxidation to quinone was achieved by a chemoselective catalyst, 4-iodophenoxyacetic acid, with Oxone® ($KHSO_5$•$0.5KHSO_4$•$0.5K_2SO_4$) as terminal oxidant.[60,61] The combination of reagents resulted in a smooth reaction, and therefore furnished a concise asymmetric synthesis of triptoquinone C (**3.3**) in seven longest linear steps. According to literature reports,[30,31] another step of chemoselective oxidation could be performed to obtain triptoquinone B (**3.2**) as well. Thus this route also represents a formal synthesis of triptoquinone B in eight steps.

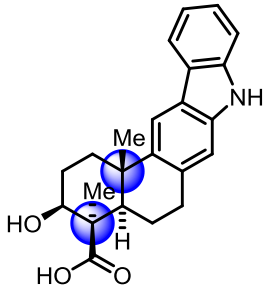


Scheme 3.12 Protecting-group free asymmetric synthesis of triptoquinones B and C with a similar strategy.

3.6 CONCLUSION

Oridamycin A
Li 2015, 10 Steps (LLS), 12 Total Steps (rac)
Trotta 2015, 11 Steps (LLS), 14 Total Steps (rac)

Now 7 Steps (LLS), 7 Steps (TS)



Triptoquinone B, $R^1 = R^2 = O$
Shishido 1993, 15 Steps (LLS), 15 Steps (TS) (rac)
Shishido 1997, 19 Steps (LLS), 19 Steps (TS)

Now 8 Steps (LLS), 11 Steps (TS)

Triptoquinone C, $R^1 = OH$, $R^2 = H$
Shishido 1993, 14 Steps (LLS), 14 Steps (TS) (rac)
Shishido 1997, 18 Steps (LLS), 18 Steps (TS)

Now 7 Steps (LLS), 10 Steps (TS)

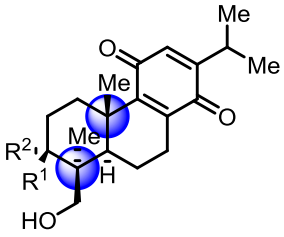


Figure 3.2 Summary of total synthesis of oridamycin A, triptoquinones B and C.

The first asymmetric synthesis of oridamycin A, and the synthesis of optically active triptoquinones B and C was achieved by a modular, convergent and concise route (Figure 3.2). The highly stereoselective iridium-catalyzed *tert*-(hydroxy)prenylation enabled efficient construction of the contiguous stereocenters in southwestern part of molecules, including all-carbon quaternary centers, which are otherwise difficult to access asymmetrically.[62] Careful strategy planning[63] and choice of reaction conditions allowed a protecting-group free[64,65] and thus very short synthesis of these terpenoid natural products. By altering the coupling partners and union strategies, more terpenoids shall become accessible.

3.7 EXPERIMENTAL DETAILS

General Information

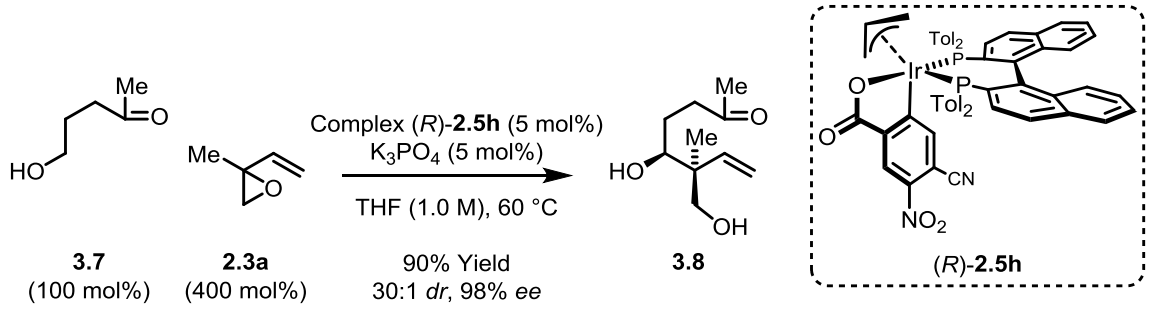
All reactions were performed under an atmosphere of argon, unless specifically noted in detailed procedures. Tetrahydrofuran, diethyl ether and toluene were distilled from sodium-benzophenone immediately prior to use. Dichloromethane, 1,2-dichloroethane were distilled from calcium hydride prior to use. Anhydrous solvents were transferred by oven-dried syringes and needles. Reagents purchased from commercial sources were used as received, or purified via Hickman distillation over appropriate drying agent. Analytical thin-layer chromatography (TLC) was carried out using 0.25 mm commercial silica gel plates (Dynanmic Absorbents F_{254}). Visualization was accomplished with UV light followed by dipping in appropriate stain solution then heating. Flash column chromatography was performed on Sorbent silica gel (40-63 μm, unless indicated specifically) or Sigma-Aldrich aluminum oxide (activated, neutral, Brockmann I, ~150 mesh, 58 Å pore size).

Spectroscopy, Spectrometry, and Data Collection

Infrared spectra were recorded on a Perkin-Elmer 1600 spectrometer. High-resolution mass spectra (HRMS) were obtained on an Agilent Technologies 6530 Accurate Mass Q-Tof LC/MS instrument for electrospray ionisation (ESI) or a Micromass Autospec Ultima instrument for chemical ionization (CI), and are reported as m/z (relative intensity). Accurate masses are reported for the molecular ion (M, M+H, M-H or M+Na), or a suitable fragment ion. ^{1}H Nuclear magnetic resonance spectra were recorded using an Agilent MR (400 MHz), Varian DirectDrive (400, 600 MHz), or Varian INOVA (500 MHz) spectrometer in $CDCl_3$ or CD_3OD solution. Coupling constants are reported in Hertz (Hz) with one decimal place, and chemical shifts are reported as parts per million (ppm) relative to residual solvent peaks ($CDCl_3$ δ_H 7.26 ppm; CD_3OD δ_H 3.31 ppm). ^{13}C Nuclear magnetic resonance spectra were recorded using an Agilent MR (400 MHz), Varian DirectDrive (400, 600 MHz), or Varian INOVA (500 MHz) spectrometer in $CDCl_3$ or CD_3OD solution, and chemical shifts are reported as parts per million (ppm) relative to solvent peaks ($CDCl_3$ δ_C 77.2 ppm; CD_3OD δ_C 49.0 ppm). Specific optical rotations ($[\alpha]_D$) were obtained on an Atago AP-300 automatic polarimeter at the sodium line (589.3 nm) in $CHCl_3$ or CH_3OH solution. Melting points were taken on a Stuart SMP3 melting point apparatus or SRS OptiMelt automated melting point system.

Detailed Procedures and Spectral Data for Asymmetric Synthesis of Oridamycin A

(5*S*,6*S*)-5-Hydroxy-6-(hydroxymethyl)-6-methyloct-7-en-2-one (3.8)



3.7 (100 mol%) **2.3a** (400 mol%) 90% Yield 30:1 *dr*, 98% *ee* **3.8** (*R*)-**2.5h**

Detailed Procedures

Catalyst (*R*)-**2.5h** (0.551 g, 0.5 mmol, 5 mol%) and K_3PO_4 (0.109 g, 0.5 mmol, 5 mol%) were added to a flame-dried seal tube and purged with argon. Anhydrous THF (10 mL) was added, followed by 5-hydroxypentan-2-one (1.02 g, 10 mmol, 100 mol%) and isoprene monoxide (3.9 mL, 40 mmol, 400 mol%) via syringe. (**Caution:** K_3PO_4 is hygroscopic. Please make sure all the base solid is placed at the bottom of reaction vial and submerged by solvent.) After sealed with cap, the resulting mixture was allowed to stir at 60 °C for 48 hours. The solution was cooled to ambient temperature and concentrated under reduced pressure. The residue was submitted to flash column chromatography on silica gel (pretreated with triethylamine, DCM/acetone = 10:1 to 5:1). (**Cautions:** product starts converting to ketal upon gently heating (>30 ˚C) under neutral or acidic condition!) The title compound was isolated as a brown oil (1.68 g, 9 mmol) in 90% yield. *Product exists as an equilibrating mixture between hydroxyl ketone and two diastereomeric lactols (equilibrated ratio 0.48:0.30:0.22).*

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.07* (dd, *J* = 17.8, 11.0 Hz, 1H (minor2)), 5.99 (dd, *J* = 17.7, 11.1 Hz, 1H, (major)), 5.93* (dd, *J* = 17.8, 11.0 Hz, 1H, (minor1)), 5.29-5.20 (m, 1H (major, minor1, minor2)), 5.18* (dd, *J* = 8.7, 1.5 Hz, 1H (minor1)), 5.14* (dd, *J* = 8.8, 1.5 Hz, 1H (minor2)), 5.13 (dd, *J* = 17.7, 1.4 Hz, 1H (major)), 4.20* (t, *J* = 7.0 Hz,

1H (minor1)), 4.00* (dd, *J* = 9.9, 5.7 Hz, 1H (minor2)), 3.69 (d, *J* = 10.8 Hz, 1H (major)), 3.61-3.49 (m, 2H (major, minor1, minor2)), 3.26 (br, 1H (major)), 2.99* (br, 2H (minor1, minor2)), 2.66 (td, *J* = 6.7, 4.0 Hz, 2H (major)), 2.18 (s, 3H (major)), 2.13-1.91 (m, 1H (major) + 2H (minor1, minor2)), 1.87-1.54 (m, 2H (major, minor1, minor2)), 1.52* (s, 3H (minor1, minor2)), 1.01 (s, 3H (major)), 0.99* (s, 3H (minor2)), 0.97* (s, 3H (minor1)).

^{13}C NMR (100 MHz, $CDCl_3$) δ 210.5 (major), 140.0 (major), 139.5* (minor2), 138.8* (minor1), 116.0* (minor1), 115.9* (minor2), 115.8 (major), 105.6* (minor1), 105.2* (minor2), 86.6* (minor2), 84.0* (minor1), 76.9 (major), 70.0 (major, minor1, minor2), 45.6 (major), 44.7* (minor1), 44.4* (minor2), 40.9 (major), 38.0* (minor2), 37.0* (minor1), 30.1 (major), 27.2* (minor2), 27.1* (minor1), 26.4* (minor2), 26.2* (minor1), 25.7 (major), 18.2* (minor2), 17.8 (major), 17.7* (minor1).

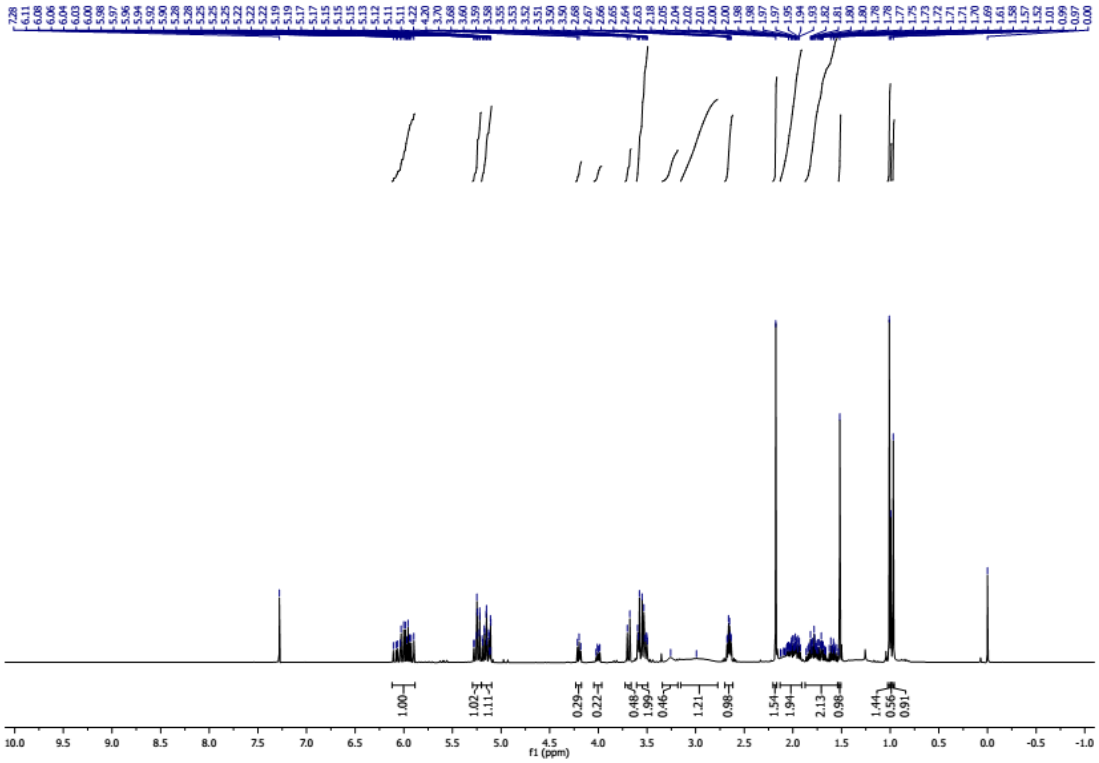
R_f 0.2 (DCM/acetone = 6:1, *p*-anisaldehyde)

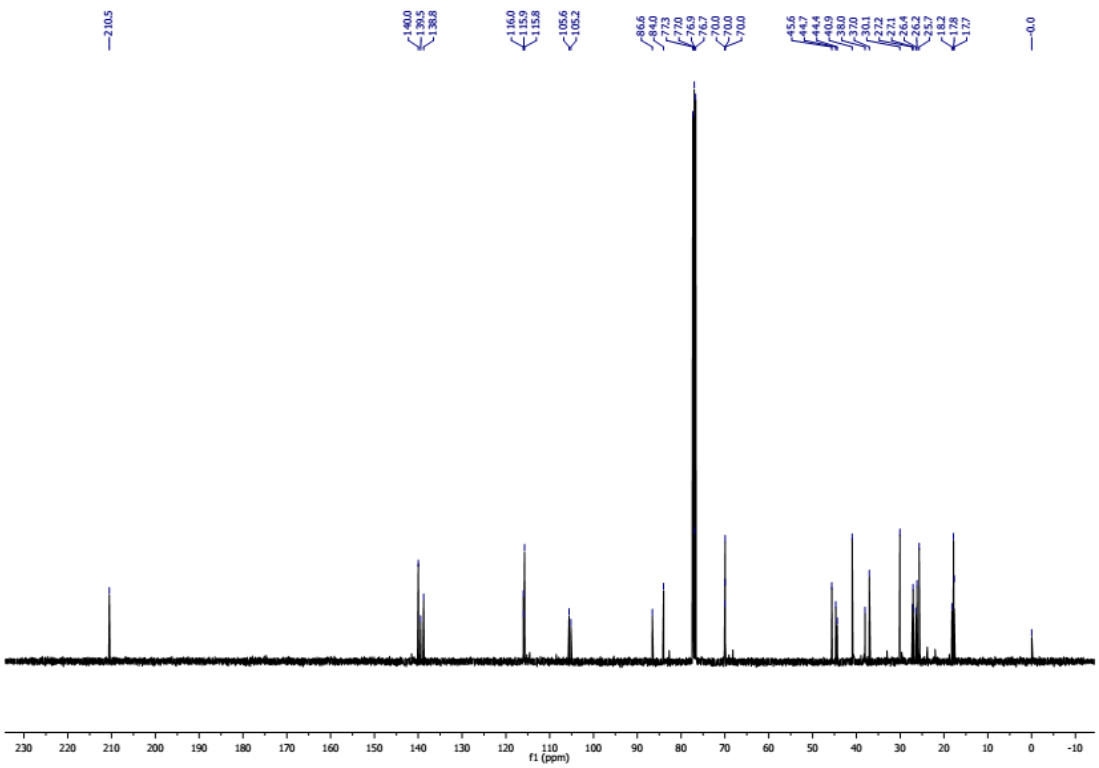
HRMS (ESI) Calcd. for $C_{10}H_{18}O_3$ $[M+Na]^+$: 209.1148, Found: 209.1149.

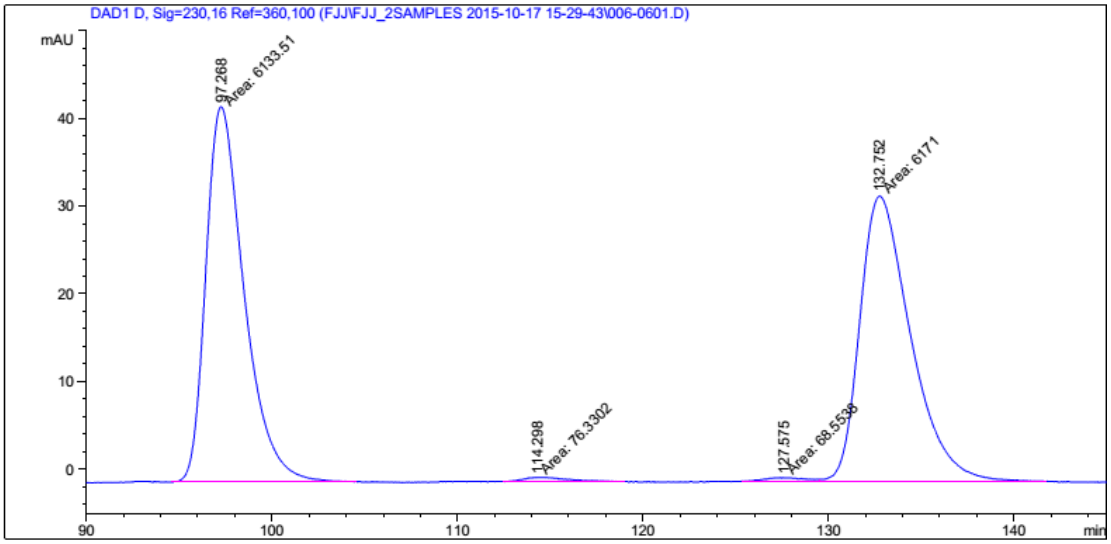
FTIR (neat): 3384, 2978, 2878, 1705, 1638, 1416, 1362, 1215, 1166, 1091, 1011, 917, 674 cm^{-1}.

Optical Rotation $[\alpha]_D^{30}$ = -4.5° (*c* = 1.0, $CHCl_3$)

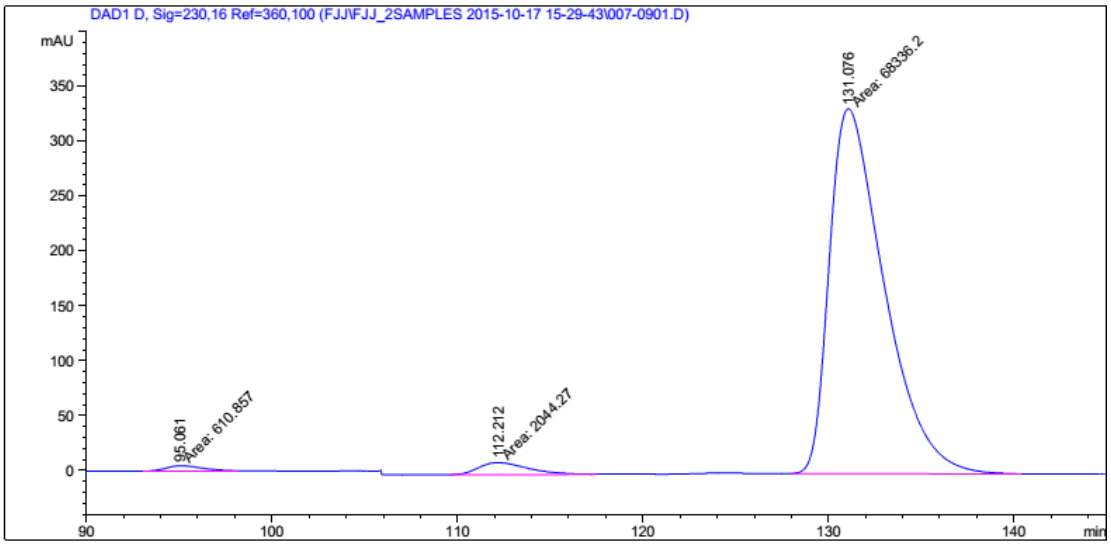
HPLC Diastereomeric ratio and enantiomeric excess was determined by HPLC analysis of the dibenzoate of product (Chiralcel AD-H column, hexanes/*i*-PrOH = 97:3, 0.50 mL/min, 230 nm), *anti*:*syn* = 30:1, *ee* = 98%.





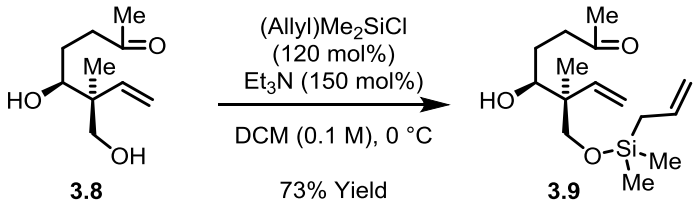


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	97.268	MM	2.3911	6133.50928	42.75188	49.2676
2	114.298	MM	2.6483	76.33024	4.80368e-1	0.6131
3	127.575	MF	2.6135	68.55382	4.37176e-1	0.5507
4	132.752	FM	3.1614	6170.99561	32.53297	49.5687



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	95.061	MM	2.2205	610.85699	4.58498	0.8605
2	112.212	MM	3.1221	2044.26855	10.91295	2.8796
3	131.076	MM	3.4238	6.83362e4	332.64838	96.2599

(5*S*,6*S*)-6-(((Allyldimethylsilyl)oxy)methyl)-5-hydroxy-6-methyloct-7-en-2-one (3.9)



Detailed Procedures

To a solution of **3.8** (1.32 g, 7.1 mmol, 100 mol%) in anhydrous DCM (71 mL), freshly distilled triethylamine (1.07 g, 10.6 mmol, 150 mol%) was added and the resulting mixture was cooled to 0 °C. Allyl(chloro)dimethylsilane (1.15 mL, 8.5 mmol, 120 mol%) was added dropwise via syringe. The mixture was allowed to stir for 1 hour at the same temperature and quenched by addition of saturated $NaHCO_3$ aqueous solution. The two layers were separated. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was submitted to flash column chromatography on silica gel (DCM/acetone = 100:1). The title compound was obtained as a light yellow liquid (1.48 g, 5.2 mmol) in 73% yield. *Product exists as an equilibrating mixture between hydroxyl ketone and two diastereomeric lactols (equilibrated ratio 0.70:0.18:0.12).*

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.98 (dd, *J* = 17.8, 11.1 Hz, 1H (major)), 5.95* (dd, *J* = 17.8, 11.0 Hz, 1H (minor1)), 5.88-5.76* (m, 1H (minor2)), 5.79* (dd, *J* = 16.9, 10.1 Hz, 1H (minor2)), 5.77 (dd, *J* = 16.9, 10.1 Hz, 1H (major)), 5.75* (dd, *J* = 17.0, 10.1 Hz, 1H (minor1)), 5.21* (dd, *J* = 11.0, 1.6 Hz, 1H (minor1)), 5.17 (dd, *J* = 11.1, 1.4 Hz, 1H (major)), 5.16* (dd, *J* = 11.0, 1.6 Hz, 1H (minor2)), 5.12* (dd, *J* = 17.8, 1.6 Hz, 1H (minor1)), 5.09* (dd, *J* = 17.7, 1.7 Hz, 1H (minor2)), 5.07 (dd, *J* = 17.8, 1.3 Hz, 1H (major)), 4.96-4.82 (m, 2H (major, minor1, minor2)), 4.23-4.16* (m, 1H (minor2)), 4.05-3.96* (m, 1H (minor1)), 3.71 (d, *J* = 9.7 Hz, 1H (major)), 3.61* (d, *J* = 9.7 Hz, 1H

(minor1)), 3.60* (d, J = 9.6 Hz, 1H (minor2)), 3.51 (d, J = 9.7 Hz, 1H (major)), 3.51-3.46 (m, 1H (major, minor2)), 3.48* (d, J = 9.6 Hz, 1H (minor1)), 3.43 (dd, J = 4.7, 1.0 Hz, 1H (major)), 3.38* (d, J = 9.6 Hz, 1H (minor2)), 2.72 (ddd, J = 17.7, 8.4, 5.7 Hz, 1H (major)), 2.58* (br, 1H (minor1)), 2.53 (ddd, J = 17.7, 8.3, 6.6 Hz, 1H (major)), 2.15 (s, 3H (major)), 2.11* (t, J = 0.9 Hz, 1H (minor2)), 2.07-1.88* (m, 2H (minor1, minor2)), 1.85-1.73 (m, 1H (major, minor1) + 2H (minor2)), 1.73-1.66* (m, 1H (minor1)), 1.65-1.60 (m, 2H (major, minor1, minor2)), 1.59-1.47 (m, 1H (major1)), 1.50 (s, 1H (minor2)), 1.49 (s, 1H (minor1)), 0.98 (s, 3H (major)), 0.97* (s, 3H (minor1)), 0.93* (s, 3H (minor2)), 0.13 (s, 6H (major)), 0.11* (s, 6H (minor1)), 0.10* (s, 6H (minor2)).

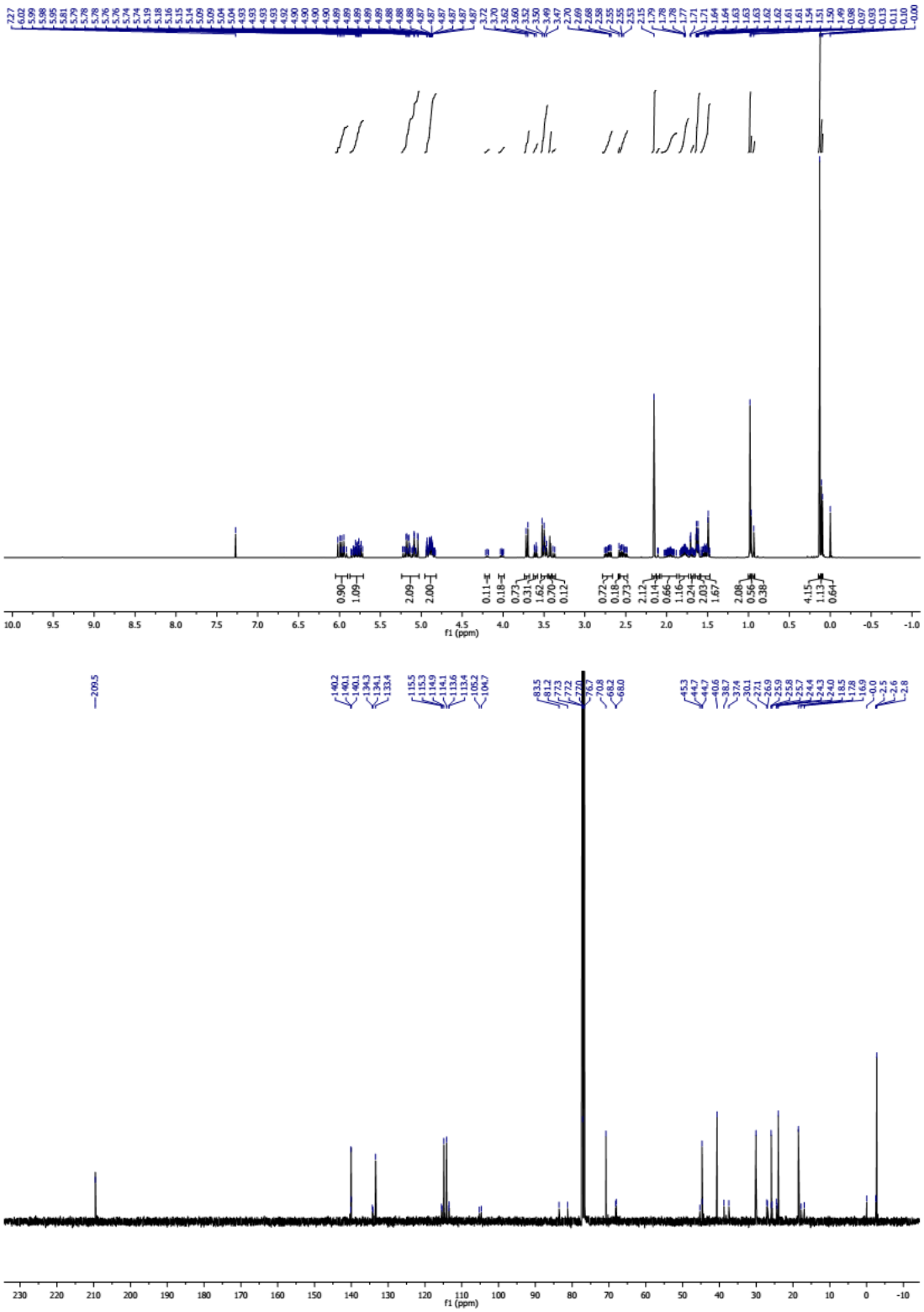
^{13}C NMR (100 MHz, $CDCl_3$) δ 209.6 (major), 140.2* (minor2), 140.1 (major), 140.1* (minor1), 134.3* (minor1), 134.1* (minor2), 133.4 (major), 115.5* (minor1), 115.3* (minor2), 114.9 (major), 114.1 (major), 113.6* (minor2), 113.4* (minor1), 105.2* (minor2), 104.7* (minor1), 83.6* (minor2), 81.2* (minor1), 77.2 (major), 70.8 (major), 68.2* (minor2), 68.0* (minor1), 45.3* (minor2), 44.7 (major), 44.7* (minor1), 40.6 (major), 38.7* (minor1), 37.4* (minor2), 30.1 (major), 27.1* (minor1), 26.9* (minor2), 25.9 (major), 25.8* (minor2), 25.7* (minor1), 24.4* (minor1), 24.3* (minor2), 24.0 (major), 18.5 (major), 17.8* (minor2), 16.95* (minor1), -2.5* (minor1), -2.6* (minor2), -2.8 (major).

R_f 0.3 (hexanes/acetone = 6:1, *p*-anisaldehyde)

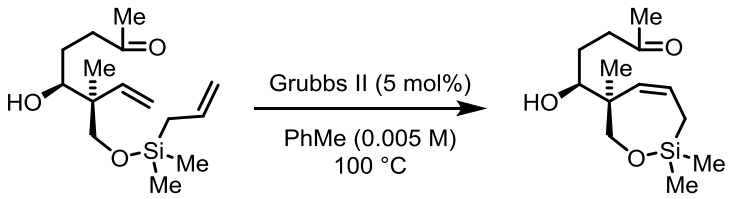
HRMS (ESI) Calcd. for $C_{15}H_{28}O_3Si$ $[M+Na]^+$: 307.1700, Found: 307.1704.

FTIR (neat): 3442, 2970, 1717, 1631, 1417, 1364, 1252, 1216, 1158, 1081, 893, 859, 834, 751 cm^{-1}.

Optical Rotation $[\alpha]_D^{30}$ = -8.0° (c = 1.0, $CHCl_3$)



(*S*)-5-Hydroxy-5-((*S*)-2,2,6-trimethyl-2,3,6,7-tetrahydro-1,2-oxasilepin-6-yl)pentan-2-one (3.10)



3.9 79% Yield **3.10**

Detailed Procedures

A solution of **3.9** (0.515 g, 1.8 mmol, 100 mol%) in toluene (350 mL) was degassed by freeze-pump-thaw cycle for three times. It was heated to 100 ˚C, and a freshly made solution of Grubbs-II catalyst (0.0768 g, 0.09 mmol, 5 mol%) in toluene (8 mL) was added via syringe pump in a period of 2 hours. The mixture was allowed to stir at the same temperature for 3 hours. It was cooled to ambient temperature and further cooled in an ice bath, when DMSO (0.32 mL, 4.5 mmol, 250 mol%) was added. After stirred for 12 hours, the solvent was removed under reduced pressure. The residue was submitted to flash column chromatography on silica gel (pretreated with triethylamine, hexanes/acetone = 15:1). The title compound was obtained as a brown oil (0.358 g, 1.4 mmol) in 79% yield, which solidified upon standing in -20 ˚C freezer. *Product exists as an equilibrating mixture between hydroxyl ketone and two diastereomeric lactols (equilibrated ratio 0.66:0.18:0.16).*

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78 (dt, *J* = 11.9, 7.3 Hz, 1H (major)), 5.73* (dt, *J* = 11.7, 7.2 Hz, 1H (minor2)), 5.66* (ddd, *J* = 11.8, 7.8, 6.8 Hz, 1H (minor1)), 5.22 (d, *J* = 11.9 Hz, 1H (major)), 5.17* (d, *J* = 12.0 Hz, 1H (minor2)), 5.15* (d, *J* = 11.8 Hz, 1H (minor1)), 4.23* (dd, *J* = 11.9, 0.8 Hz, 1H (minor1)), 4.08* (d, *J* = 11.7 Hz, 1H (minor2)), 4.05* (dd, *J* = 8.1, 5.6 Hz, 1H (minor1)), 4.00 (dd, *J* = 11.9, 1.0 Hz, 1H (major)), 3.89* (dd, *J* = 10.2, 6.4 Hz, 1H (minor2)), 3.82 (d, *J* = 11.9 Hz, 1H (major)),

3.65* (dd, *J* = 11.9, 0.7 Hz, 1H (minor1)), 3.58* (dd, *J* = 11.7, 1.0 Hz, 1H (minor2)), 3.40 (ddd, *J* = 11.1, 4.7, 2.2 Hz, 1H (major)), 3.32* (br, 1H (minor1)), 2.97 (dd, *J* = 4.7, 1.0 Hz, 1H (major)), 2.71 (ddd, *J* = 17.8, 7.9, 6.0 Hz, 1H (major)), 2.55 (dt, *J* = 17.9, 7.1 Hz, 1H (major)), 2.25-2.14* (m, 1H (minor1)), 2.16 (s, 3H (major)), 2.13-2.03* (m, 1H (minor2)), 2.01-1.74 (m, 1H (major) + 3H (minor1, minor2)), 1.70-1.56 (m, 3H (major) + 2H (minor1, minor2)), 1.54-1.44* (m, 1H (minor2)), 1.51* (s, 3H (minor2)), 1.50* (s, 3H (minor1)), 1.00* (s, 3H (minor1)), 0.99* (s, 3H (minor2)), 0.92 (s, 3H (major)), 0.16* (s, 3H (minor1)), 0.15 (s, 3H (major)), 0.14 (s, 3H (major)), 0.14* (s, 3H (minor1)), 0.13* (s, 3H (minor2)), 0.13* (s, 3H (minor2)).

^{13}C NMR (100 MHz, $CDCl_3$) δ 209.7 (major), 133.0* (minor1), 132.6* (minor2), 131.6 (major), 125.3 (major), 124.1* (minor2), 123.8* (minor1), 105.4* (minor1), 104.9* (minor2), 86.0* (minor2), 84.1* (minor1), 79.0 (major), 70.0 (major), 67.4* (minor1), 67.4* (minor2), 48.0 (major), 47.0* (minor1), 46.9* (minor2), 40.9 (major), 38.9* (minor1), 37.4* (minor2), 30.1 (major), 27.1* (minor1), 26.5* (minor2), 26.1* (minor1), 25.5 (major, minor2), 22.4* (minor2), 21.1 (major), 20.9* (minor1), 16.1* (minor1), 16.0 (major), 16.0* (minor2), -1.1* (minor1), -1.2* (minor1), -1.2* (minor2), -1.3 (major), -1.4 (major, minor2).

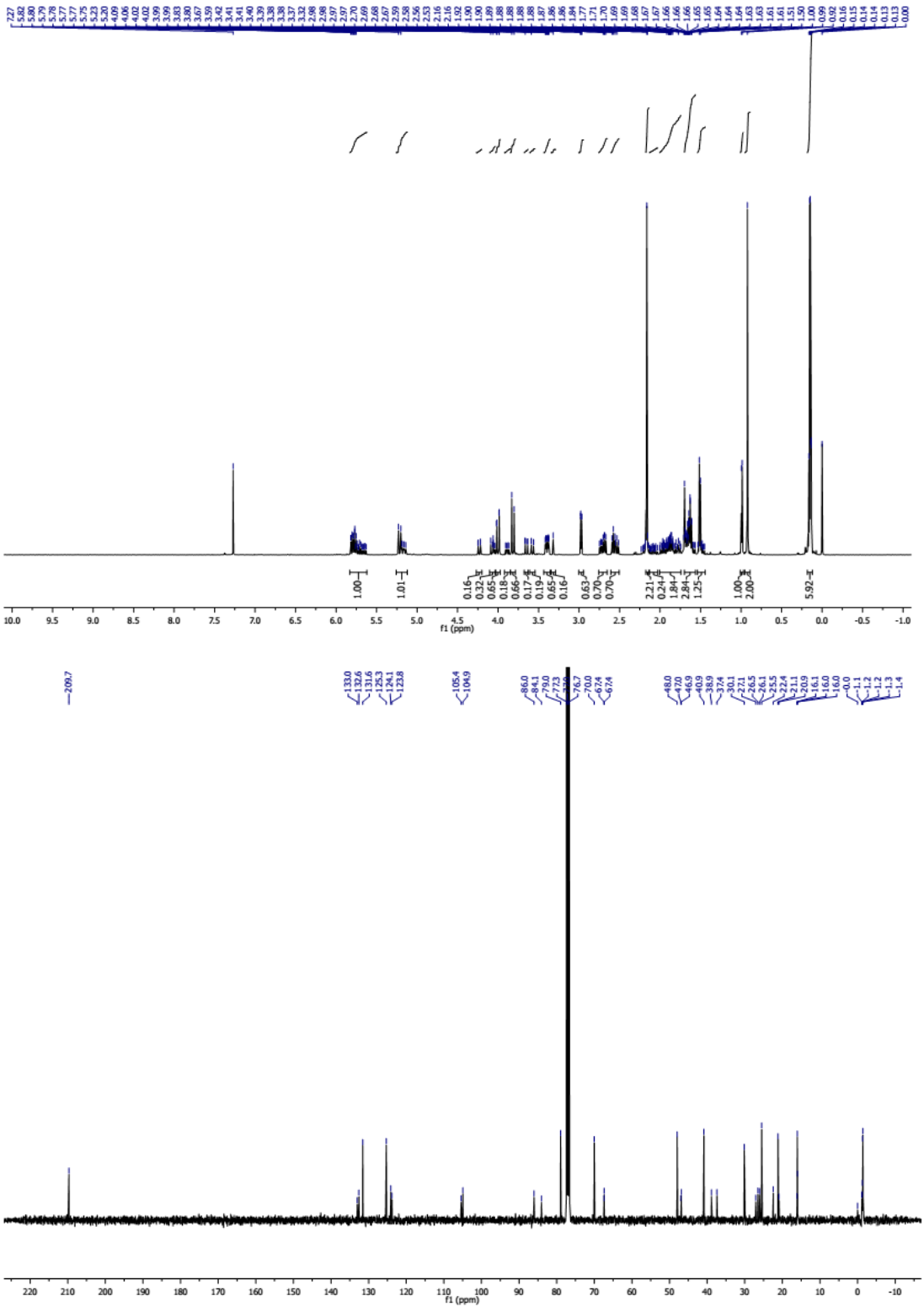
R_f 0.1 (DCM/acetone = 50:1, *p*-anisaldehyde)

HRMS (ESI) Calcd. for $C_{13}H_{24}O_3Si$ $[M+Na]^+$: 279.1387, Found: 279.1386.

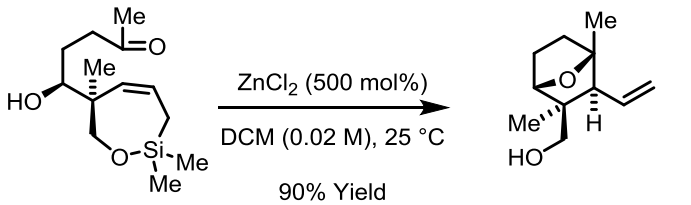
FTIR (neat): 3419, 2957, 2879, 1715, 1406, 1375, 1250, 1084, 859, 839, 809, 752, 730, 678 cm^{-1}.

MP 55.2-55.5 ˚C (CH_2Cl_2)

Optical Rotation $[\alpha]_D^{30}$ = +13.6˚ (*c* = 1.3, $CHCl_3$)



((1*S*,2*S*,3*S*,4*R*)-2,4-Dimethyl-3-vinyl-7-oxabicyclo[2.2.1]heptan-2-yl)methanol (Fragment A1, 3.4)



3.10 **Fragment A1 (3.4)**

Detailed Procedures

To a solution of **3.10** (0.128 g, 0.5 mmol, 100 mol%) in DCM (50 mL) at -78 ˚C, $ZnCl_2$ (1M solution in Et_2O, 2.5 mL, 2.5 mmol, 500 mol%) was added. The resulting mixture was allowed to warm to ambient temperature, and stirred for 2 hours. The reaction was quenched by addition of saturated $NaHCO_3$ (aq., 50 mL), and stirred for 10 min. The mixture was filtered through Celite, and the precipitate was washed with DCM. The filtrate was separated, and the aqueous layer was extracted with DCM (50 mL). The combined organic layers were dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was submitted to flash column chromatography on silica gel (hexanes/acetone = 15:1). The title compound was obtained as a light yellow oil (0.0843 g, 0.46 mmol) in 92% yield, which solidified upon standing in freezer.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.91 (ddd, *J* = 16.9, 10.8, 10.0 Hz, 1H), 5.11 (dd, *J* = 10.0, 2.3 Hz, 1H), 5.02 (ddd, *J* = 16.9, 2.3, 0.6 Hz, 1H), 4.23 (d, *J* = 5.4 Hz, 1H), 3.54-3.42 (m, 2H), 2.75 (dd, *J* = 6.6, 3.6 Hz, 1H), 2.02-1.92 (m, 2H), 1.80 (tt, *J* = 12.5, 5.3 Hz, 1H), 1.66-1.50 (m, 2H), 1.28 (s, 3H), 1.04 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 136.3, 117.8, 87.0, 82.5, 68.3, 63.1, 50.8, 37.7, 26.2, 20.3, 18.7.

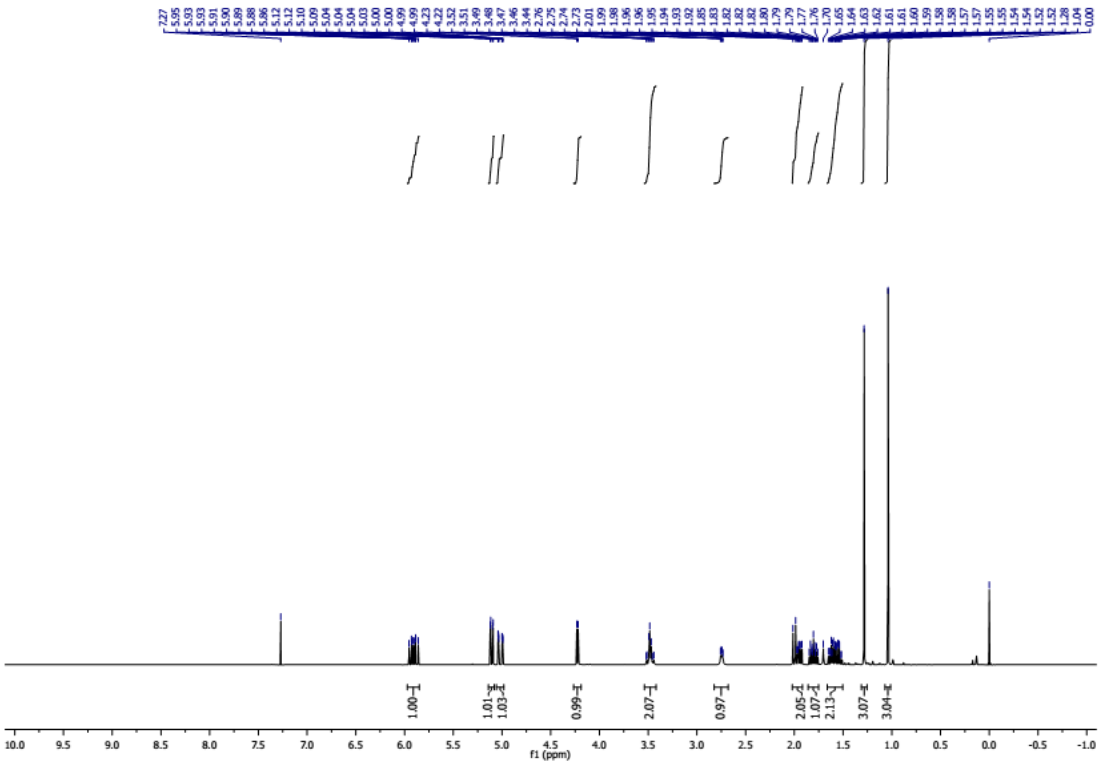
R_f 0.3 (hexanes/EA = 3:1, *p*-anisaldehyde)

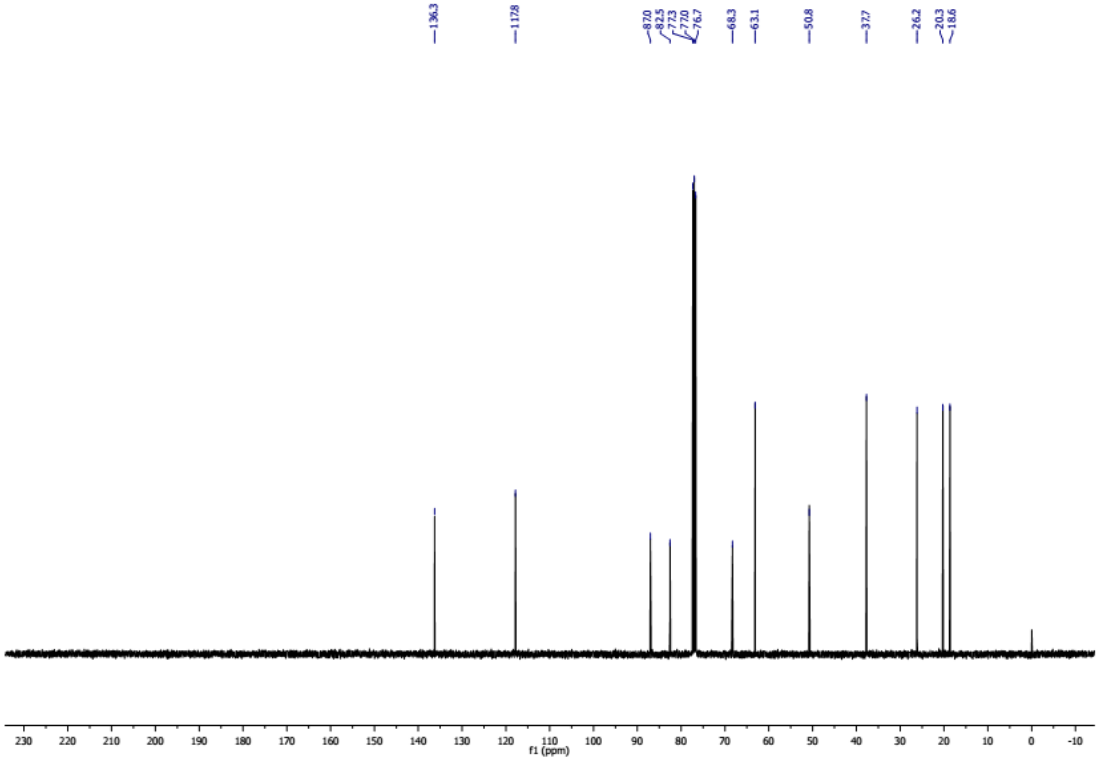
HRMS (CI) Calcd. for $C_{11}H_{18}O_2$ $[M+H]^+$: 183.1380, Found: 183.1383.

FTIR (neat): 3375, 2975, 2914, 1633, 1381, 1187, 1073, 1020, 1015, 1001, 991, 914, 908, 873, 826, 804, 682 cm^{-1}.

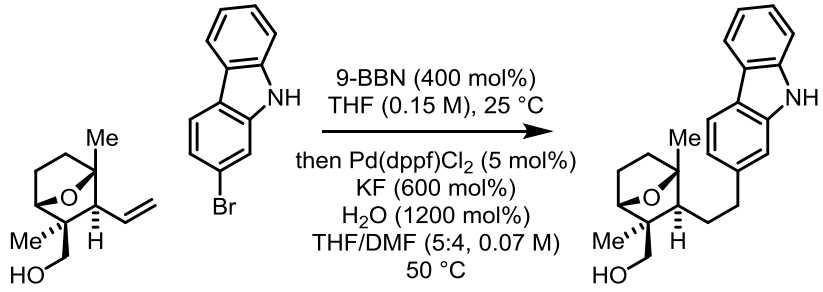
MP 60.9-61.5 ˚C (CH_2Cl_2)

Optical Rotation $[\alpha]_D^{30}$ = +40.0˚ (*c* = 1.0, $CHCl_3$)


1.00
1.01
1.03
0.99
2.07
0.97
2.05
1.07
2.13
3.07
3.04
f1 (ppm)


136.3
117.8
87.0
82.5
77.3
77.0
76.7
68.3
63.1
50.8
31.7
26.2
20.3
18.6
f1 (ppm)

((1*S*,2*S*,3*S*,4*R*)-3-(2-(9*H*-Carbazol-2-yl)ethyl)-2,4-dimethyl-7-oxabicyclo[2.2.1]heptan-2-yl)methanol (3.11)



3.4 **3.5** 66% Yield **3.11**

Detailed Procedures

To a solution of alkene **3.4** (0.150 g, 0.82 mmol, 100 mol%) in THF (0.8 mL), a solution of 9-BBN (0.403 g, 3.3 mmol, 400 mol%) in THF (4.4 mL) was added slowly at ambient temperature. The mixture was stirred at the same temperature until TLC indicated all the starting alkene was consumed (about an hour). The resulting clear solution was mixed with anhydrous KF (0.286 g, 4.9 mmol, 600 mol%), $Pd(dppf)Cl_2$ (0.0300 g, 0.041 mmol, 5 mol%) and 2-bromocarbazole **3.5** (0.303 g, 1.23 mmol, 150 mol%), followed by addition of DMF (4 mL) and water (0.18 mL, 9.8 mmol, 1200 mol%). The degassed heterogeneous mixture was heated to 50 ˚C and vigorously stirred overnight. After cooled to ambient temperature, the reaction mixture was diluted with ethyl acetate (5 mL) and water (5 mL). The separated organic layer was washed with 1 M NaOH (3 mL × 2) and brine (3 mL), and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was submitted to flash column chromatography on silica gel (hexanes/acetone = 10:1 to 5:1). The title compound was obtained as a pale yellow solid (0.191 g, 0.55 mmol) in 66% yield.

^{1}H NMR (400 MHz, CD_3OD) δ 7.98 (dt, *J* = 7.8, 1.1 Hz, 1H), 7.93 (dd, *J* = 8.0, 0.7 Hz, 1H), 7.40 (dt, *J* = 8.1, 1.0 Hz, 1H), 7.31 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H), 7.25 (dd, *J* = 1.5, 0.7 Hz, 1H), 7.11 (ddd, *J* = 8.0, 7.1, 1.1 Hz, 1H), 6.99 (dd, *J* = 8.0, 1.5 Hz, 1H), 4.26 (d, *J*

= 5.4 Hz, 1H), 3.72 (d, *J* = 10.3 Hz, 1H), 3.54 (d, *J* = 10.4 Hz, 1H), 2.86-2.70 (m, 2H), 1.94 (ddd, *J* = 12.5, 9.1, 4.6 Hz, 1H), 1.79-1.58 (m, 4H), 1.55-1.45 (m, 2H), 1.39 (s, 3H), 1.16 (s, 3H).

^{13}C NMR (100 MHz, CD_3OD) δ 141.9, 141.6, 141.4, 126.1, 124.4, 122.5, 120.8, 120.6, 120.4, 119.6, 111.6, 111.1, 88.4, 82.1, 66.3, 56.7, 50.8, 40.1, 38.0, 29.7, 26.6, 21.5, 19.1.

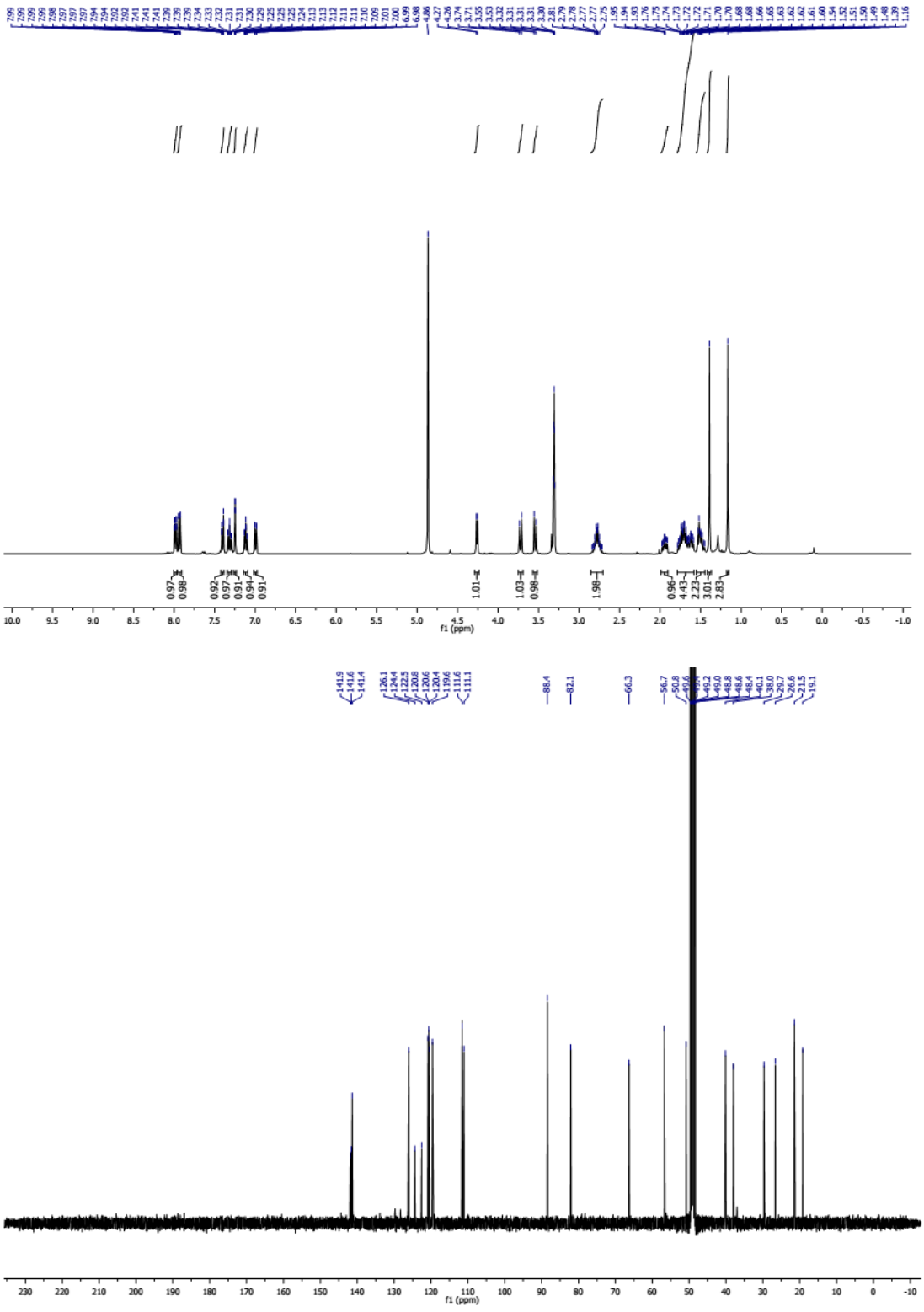
R_f 0.1 (hexanes/acetone = 5:1, UV/*p*-anisaldehyde)

HRMS (CI) Calcd. for $C_{23}H_{27}NO_2$ $[M]^+$: 349.2042, Found: 349.2036.

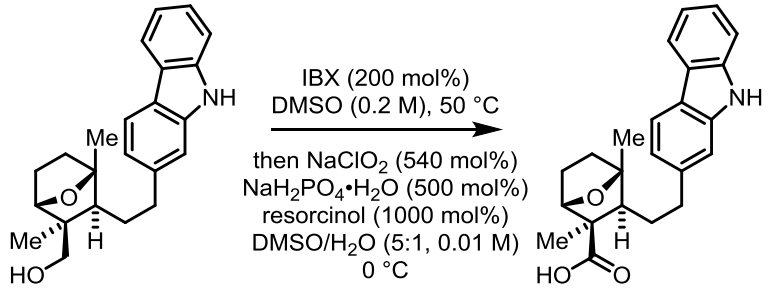
FTIR (neat): 3462, 3416, 2955, 2872, 1608, 1460, 1438, 1380, 1327, 1241, 1040, 1007, 984, 976, 828, 744, 726 cm^{-1}.

MP 215.4-217.0 ˚C ($CHCl_3$)

Optical Rotation $[\alpha]_D^{30}$ = +33.3˚ (*c* = 0.1, CH_3OH)



(1*S*,2*R*,3*S*,4*R*)-3-(2-(9H-Carbazol-2-yl)ethyl)-2,4-dimethyl-7-oxabicyclo[2.2.1]heptane-2-carboxylic acid (3.13)



3.11 70% Yield **3.13**

Detailed Procedures

A suspension of alcohol **3.11** (0.0175 g, 0.05 mmol, 100 mol%) and IBX (0.0280 g, 0.1 mmol, 200 mol%) in DMSO (0.25 mL) was heated to 50 ˚C. The mixture became homogeneous eventually and was stirred at the same temperature for 2 hours. After cooled to ambient temperature, a solution of resorcinol (0.0551 g, 0.5 mmol, 1000 mol%) in DMSO (3.5 mL) was added, followed by dropwise addition of an ice-cooled solution of $NaClO_2$ (80 wt% pure, 0.0305 g, 0.27 mmol, 540 mol%) and $NaH_2PO_4 \cdot H_2O$ (0.0345 g, 0.25 mmol, 500 mol%) in water (0.75 mL). The resulting mixture was allowed to stir at 0 ˚C for 30 min until all the aldehyde intermediate was consumed. The reaction was quenched by addition of saturated NH_4Cl (aq., 5 mL), and extracted with ethyl acetate (5 mL × 2). The combined organic layers were washed with water (5 mL × 2), and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure, and the residue was submitted to flash column chromatography on silica gel (hexanes/acetone/AcOH = 100:20:0.05). The product-containing fractions were concentrated and repurified by column chromatography on silica gel (hexanes/EA/AcOH = 100:30:0.05). The title compound was obtained as a white solid (0.0126 g, 0.035 mmol) in 70% yield.

^{1}H NMR (400 MHz, CD_3OD) δ 7.97 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.91 (dd, *J* = 8.0, 0.6 Hz, 1H), 7.39 (dt, *J* = 8.1, 0.9 Hz, 1H), 7.30 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H), 7.23 (dd, *J* = 1.5, 0.7 Hz, 1H), 7.10 (ddd, *J* = 8.0, 7.1, 1.1 Hz, 1H), 6.98 (dd, *J* = 8.0, 1.5 Hz, 1H), 4.46 (d, *J* = 5.2 Hz, 1H), 2.85 (ddd, *J* = 13.5, 10.3, 5.6 Hz, 1H), 2.71 (ddd, *J* = 13.5, 10.0, 6.0 Hz, 1H), 2.00 (ddd, *J* = 12.9, 9.0, 4.0 Hz, 1H), 1.94-1.83 (m, 1H), 1.83-1.63 (m, 4H), 1.56 (td, *J* = 12.1, 4.0 Hz, 1H), 1.44 (s, 3H), 1.36 (s, 3H).

^{13}C NMR (100 MHz, CD_3OD) δ 177.0, 140.5, 140.1, 139.9, 124.6, 122.9, 121.0, 119.3, 119.2, 119.1, 118.1, 110.1, 109.7, 86.5, 82.6, 57.8, 56.8, 37.7, 35.1, 31.7, 26.2, 20.8, 17.6.

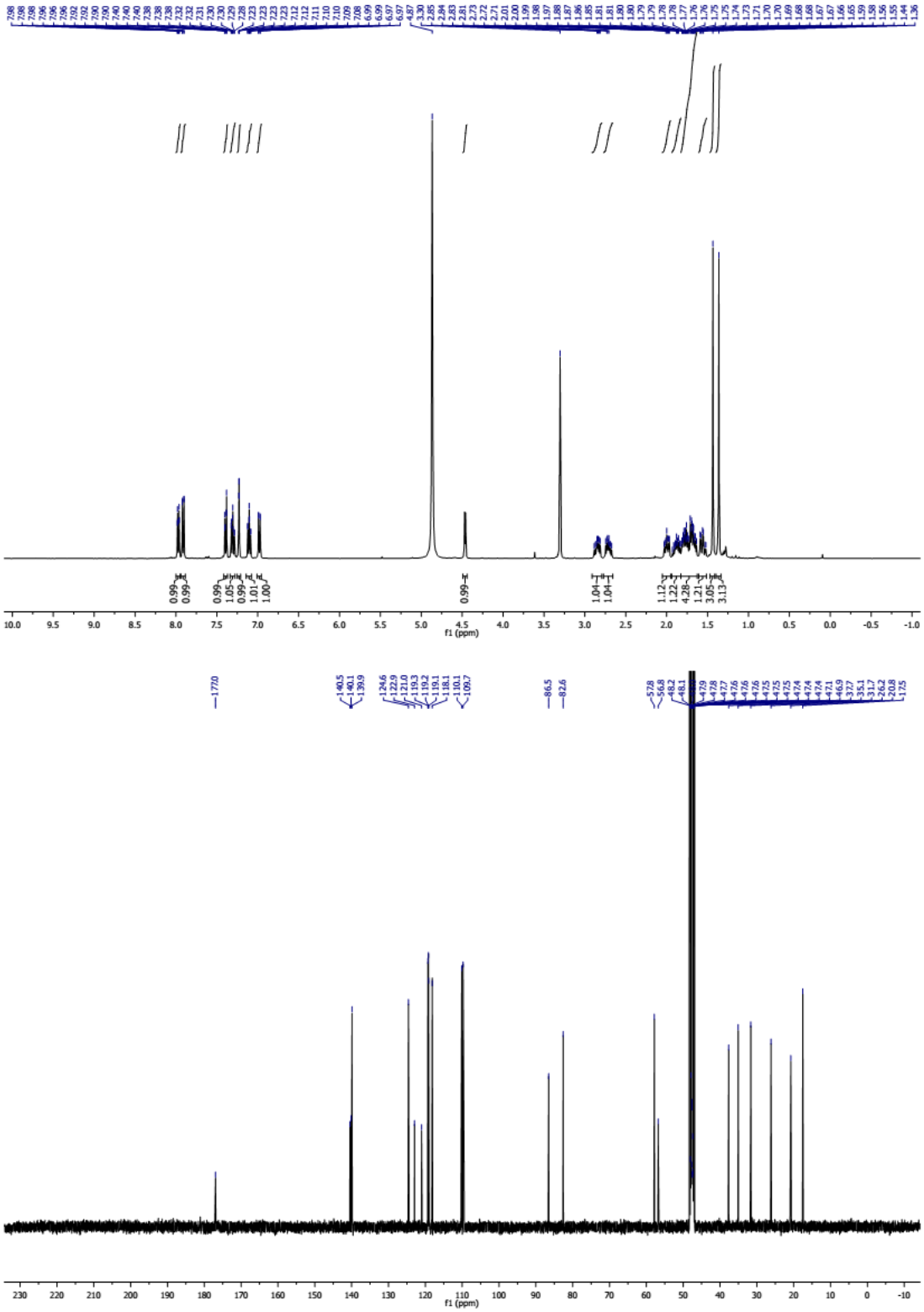
R_f 0.15 (hexanes/acetone/AcOH = 100:40:0.05, UV/*p*-anisaldehyde)

HRMS (ESI) Calcd. for $C_{23}H_{25}NO_3$ $[M+Na]^+$: 386.1727, Found: 386.1732.

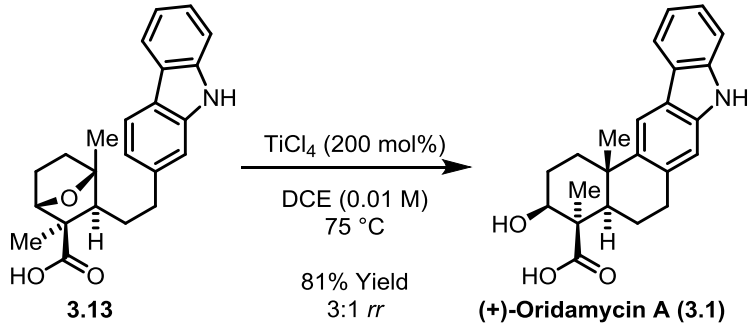
FTIR (neat): 3357, 2933, 2871, 2496, 1731, 1607, 1460, 1441, 1401, 1383, 1326, 1240, 1109, 1001, 976, 865, 819, 769, 750, 731 cm^{-1}.

MP 194.3-196.4 ˚C (CH_3OH)

Optical Rotation $[\alpha]_D^{30}$ = +5.4˚ (*c* = 0.6, CH_3OH)



(3*S*,4*R*,4a*R*,13b*S*)-3-Hydroxy-4,13b-dimethyl-2,3,4,4a,5,6,8,13b-octahydro-1H-naphtho[2,1-b]carbazole-4-carboxylic acid ((+)-Oridamycin A, 3.1)



Detailed Procedures

To a solution of acid **3.13** (0.0109 g, 0.03 mmol, 100 mol%) in DCE (2.8 mL), a solution of $TiCl_4$ in DCE (0.25 M, freshly prepared, 0.24 mL, 0.06 mmol, 200 mol%) was added dropwise. The mixture was heated to 75 ˚C and allowed to stir for 15 hours. After cooled to ambient temperature, the reaction was poured into saturated $NaHCO_3$ (aq., 20 mL) and allowed to stir for 15 min. Solid $KHSO_4$ was added until the pH was adjusted to 2. The mixture was extracted by DCM (10 mL × 2). The combined organic layers were washed with brine (10 mL), and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was submitted to flash column chromatography on silica gel (DCM/MeOH/AcOH = 100:1:0 to 100:1:0.05). The title compound **3.1** was obtained as a pale yellow solid (0.0068 g, 0.019 mmol) in 62% yield, and its regioisomer *iso*-**3.1** was obtained as a yellow solid (0.0023 g, 0.006 mmol) in 21% yield.

^{1}H NMR (500 MHz, CD_3OD) δ 7.96 (dt, *J* = 8.1, 1.0 Hz, 1H), 7.96 (s, 1H), 7.34 (dt, *J* = 8.1, 0.9 Hz, 1H), 7.28 (ddd, *J* = 8.1, 7.1, 1.2 Hz, 1H), 7.08 (ddd, *J* = 8.1, 7.1, 1.2 Hz, 1H), 7.06 (s, 1H), 3.25 (dd, *J* = 12.2, 4.4 Hz, 1H), 3.08 (ddd, *J* = 17.2, 5.6, 1.9 Hz, 1H), 2.97 (dddd, *J* = 16.5, 12.7, 6.2, 1.3 Hz, 1H), 2.60 (dt, *J* = 13.2, 3.7 Hz, 1H), 2.32 (qd, *J* = 13.3, 3.8 Hz, 1H), 2.28-2.19 (m, 1H), 2.20-2.07 (m, 1H), 1.93 (dq, *J* = 13.1, 3.9 Hz, 1H), 1.61 (td, *J* = 13.5, 3.9 Hz, 1H), 1.52 (dd, *J* = 12.2, 2.1 Hz, 1H), 1.50 (s, 3H), 1.28 (s, 3H).

^{13}C NMR (125 MHz, CD_3OD) δ 181.0, 142.1, 140.4, 140.1, 134.5, 126.1, 124.6, 123.3, 120.6, 119.3, 117.5, 111.4, 110.7, 79.1, 54.1, 49.8, 40.0, 39.6, 34.0, 30.3, 24.8, 24.6, 22.5.

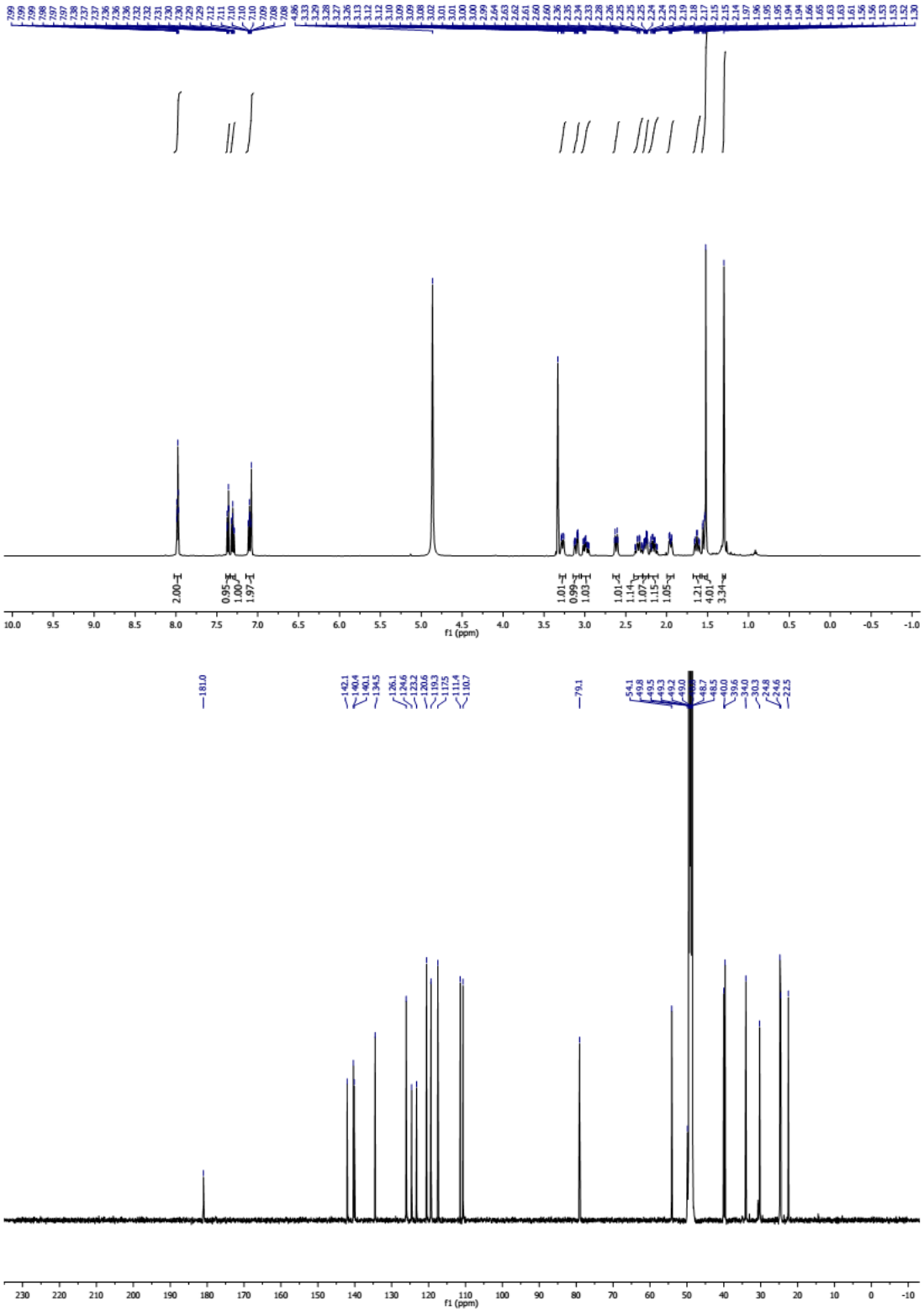
R_f 0.25 (DCM/MeOH = 50:1 (twice), UV/*p*-anisaldehyde)

HRMS (ESI) Calcd. for $C_{23}H_{25}NO_3$ $[M+Na]^+$: 386.1727, Found: 386.1725.

FTIR (neat): 3406, 2918, 2851, 1702, 1612, 1466, 1439, 1319, 1240, 1186, 1088, 1071, 1025, 889, 859, 749, 736 cm^{-1}.

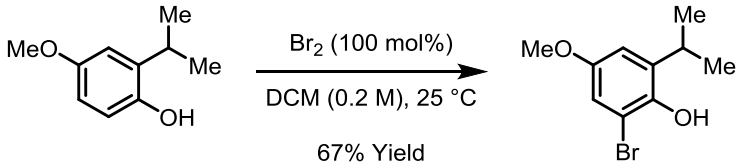
MP 183 ˚C (decomp.)

Optical Rotation $[\alpha]_D^{30}$ = +93.3˚ (*c* = 0.2, CH_3OH)



Detailed Procedures and Spectral Data for Synthesis of Triptoquinone C

2-Bromo-6-isopropyl-4-methoxyphenol (Fragment B2, 3.6)



3.16
(100 mol%)

Fragment B2 (3.6)

Detailed Procedures

To a solution of phenol **3.16**[66] (3.11 g, 18.7 mmol, 100 mol%) in DCM (73.5 mL) at 0 ˚C, a solution of Br_2 (0.96 mL, 18.7 mmol, 100 mol%) in DCM (20 mL) was added dropwise in a period of 10 min. The resulting mixture was allowed to warm to ambient temperature and stirred overnight. The reaction was quenched by addition of saturated $NaHCO_3$ (aq., 100 mL), and kept stirring until the solution turned yellow (about 10 min). The organic layer was separated, washed with brine (100 mL), and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was submitted to flash column chromatography on silica gel (hexanes/EA = 50:1). The title compound was obtained as a yellow to red-brown oil (3.08 g, 12.6 mmol) in 67% yield.

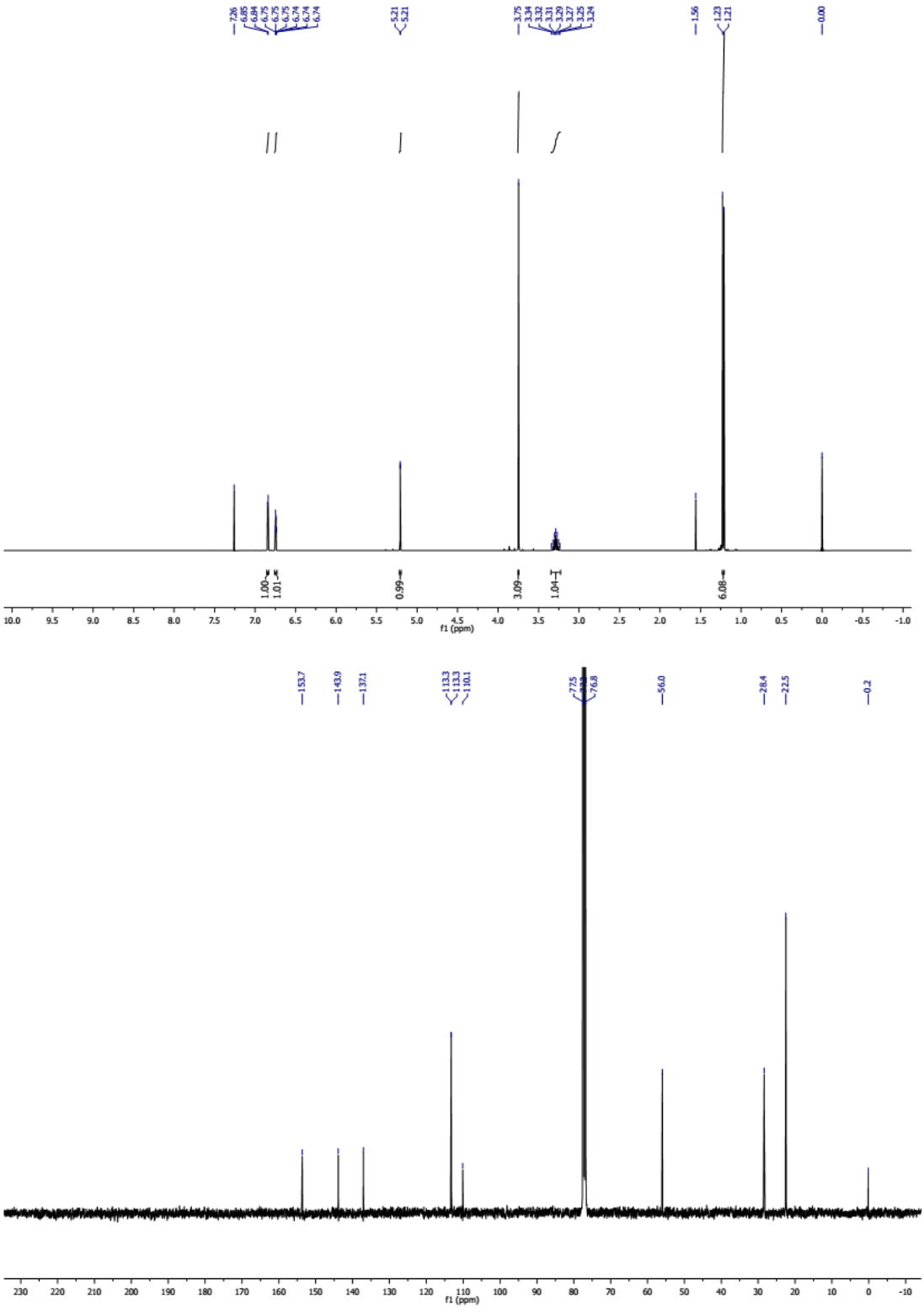
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84 (d, *J* = 2.9 Hz, 1H), 6.74 (dt, *J* = 2.9, 0.6 Hz, 1H), 5.21 (d, *J* = 0.5 Hz, 1H), 3.75 (s, 3H), 3.29 (hept, *J* = 6.9 Hz, 1H), 1.22 (d, *J* = 6.9 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 153.7, 143.9, 137.1, 113.3, 113.3, 110.1, 56.0, 28.4, 22.5.

R_f 0.6 (hexanes/EA = 10:1, UV)

HRMS (ESI) Calcd. for $C_{10}H_{13}BrO_2$ $[M+Na]^+$: 243.0026, Found: 243.0022.

FTIR (neat): 3516, 2961, 1606, 1576, 1474, 1425, 1330, 1292, 1198, 1175, 1157, 1092, 1039, 938, 877, 849, 824, 764, 733 cm^{-1}.


7.26
6.85
6.84
6.75
6.75
6.75
6.74
6.74
6.74
5.21
5.21
3.75
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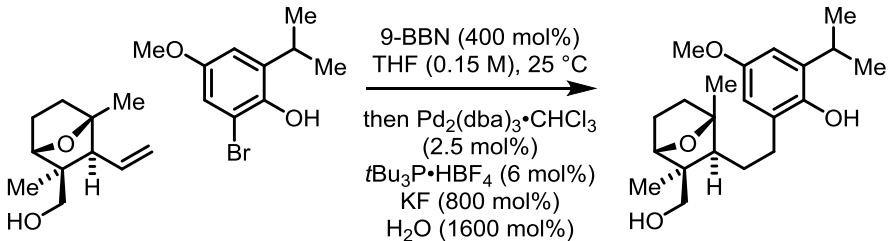
3.32
3.31
3.29
3.27
3.25
3.24
1.56
1.23
1.21
0.00
1.00
1.01
0.99
3.09
1.04
6.08
f1 (ppm)
153.7
143.9
137.1
113.3
113.3
110.1
77.5
77.3
76.8
56.0
28.4
22.5
-0.2
f1 (ppm)

2-(2-((1*R*,2*S*,3*S*,4*S*)-3-(Hydroxymethyl)-1,3-dimethyl-7-oxabicyclo[2.2.1]heptan-2-yl)ethyl)-6-isopropyl-4-methoxyphenol (3.17)



3.4 (100 mol%) **3.6** (150 mol%) **3.17**

53% Yield

Detailed Procedures

To a solution of alkene **3.4** (0.0547 g, 0.3 mmol, 100 mol%) in THF (0.3 mL), a solution of 9-BBN (0.146 g, 1.2 mmol, 400 mol%) in THF (1.6 mL) was added slowly at ambient temperature. The mixture was stirred at the same temperature until TLC indicated all the starting alkene was consumed (about an hour). The resulting clear solution was mixed with anhydrous KF (0.139 g, 2.4 mmol, 800 mol%), $Pd_2(dba)_3 \cdot CHCl_3$ (0.0078 g, 0.0075 mmol, 2.5 mol%) and $^tBu_3P \cdot HBF_4$ (0.0052 g, 0.018 mmol, 6 mol%), followed by addition of water (0.086 mL, 4.8 mmol, 1600 mol%) and the bromophenol **3.6** (0.110 g, 0.45 mmol, 150 mol%). The degassed heterogeneous mixture was heated to 35 ˚C and vigorously stirred overnight. After cooled to ambient temperature, the reaction mixture was diluted with ethyl acetate (2 mL) and water (2 mL). The separated organic layer was washed with 1 M NaOH (1 mL × 2) and brine (1 mL), and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was submitted to flash column chromatography on silica gel (hexanes/EA = 4:1). The title compound was obtained as a colorless oil (0.0550 g, 0.16 mmol) in 53% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.63 (d, *J* = 3.1 Hz, 1H), 6.50 (d, *J* = 3.1 Hz, 1H), 5.96 (br, 1H), 4.01 (d, *J* = 5.5 Hz, 1H), 3.90 (d, *J* = 11.2 Hz, 1H), 3.76 (s, 3H), 3.70 (d, *J* = 11.2 Hz, 1H), 3.20 (hept, *J* = 6.8 Hz, 1H), 3.07 (br, 1H), 2.93 (td, *J* = 12.9, 4.6 Hz, 1H),

2.37 (ddd, J = 13.5, 11.8, 5.5 Hz, 1H), 1.95 (ddd, J = 12.8, 9.0, 4.9 Hz, 1H), 1.86-1.65 (m, 3H), 1.60 (ddd, J = 11.5, 9.0, 4.4 Hz, 1H), 1.54-1.44 (m, 2H), 1.36 (s, 3H), 1.23 (d, J = 7.0 Hz, 3H), 1.21 (d, J = 7.0 Hz, 3H), 1.13 (s, 3H).

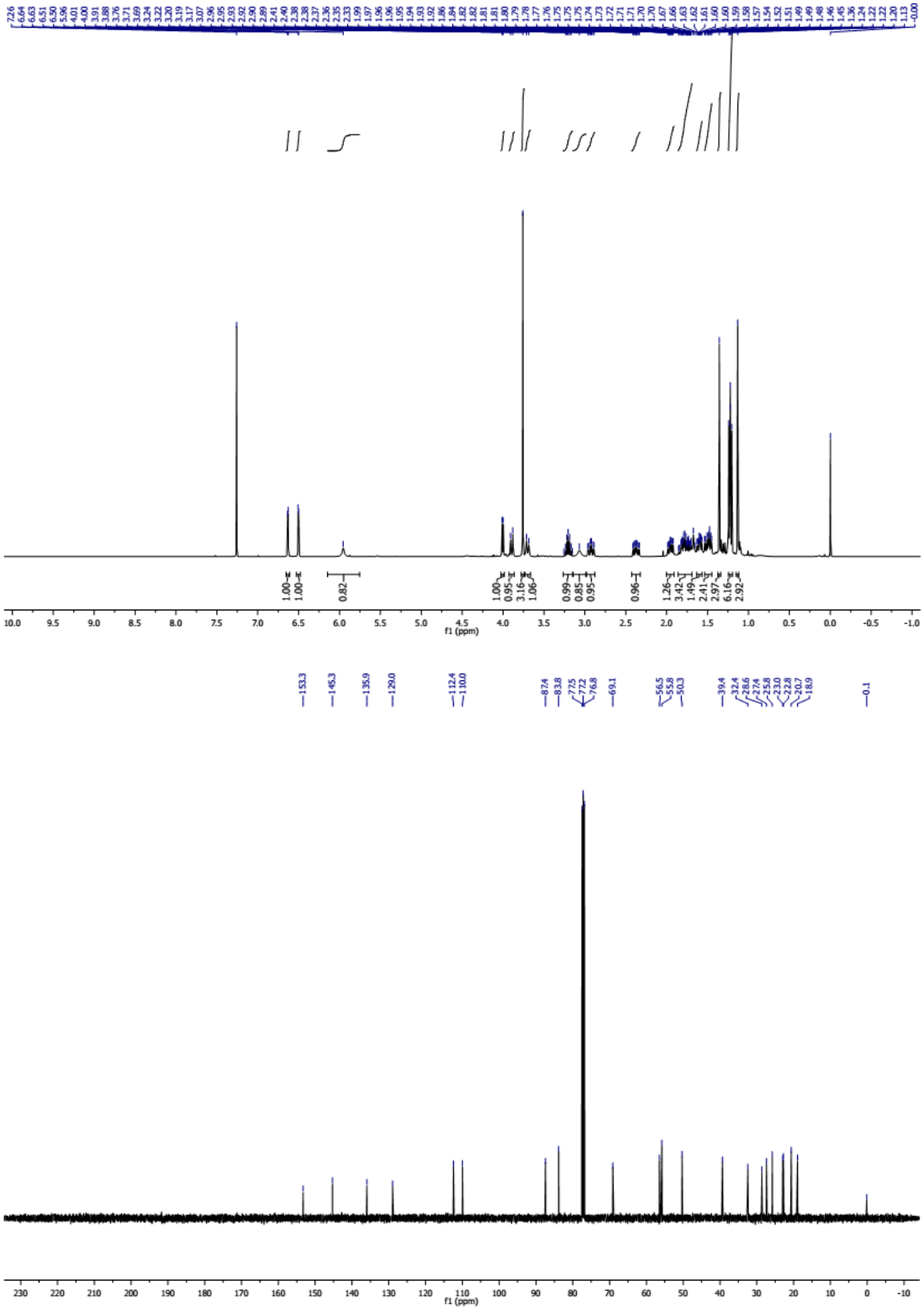
^{13}C NMR (100 MHz, $CDCl_3$) δ 153.3, 145.3, 136.0, 129.0, 112.4, 110.0, 87.4, 83.8, 69.1, 56.5, 55.8, 50.3, 39.4, 32.4, 28.6, 27.4, 25.8, 23.0, 22.8, 20.7, 18.9.

R_f 0.15 (hexanes/acetone = 5:1, *p*-anisaldehyde)

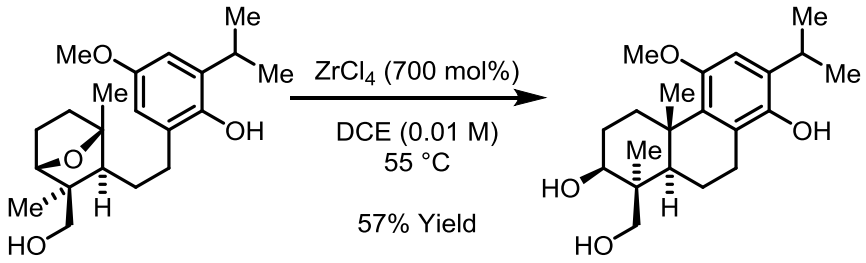
HRMS (ESI) Calcd. for $C_{21}H_{32}O_4$ $[M+Na]^+$: 371.2193, Found: 371.2195.

FTIR (neat): 3350, 2960, 2872, 1604, 1467, 1439, 1381, 1310, 1205, 1046, 1005, 988, 868, 828, 757 cm^{-1}.

Optical Rotation $[\alpha]_D^{30}$ = +55.7° (c = 0.3, $CHCl_3$)



(4b*S*,7*S*,8*S*,8a*R*)-8-(Hydroxymethyl)-2-isopropyl-4-methoxy-4b,8-dimethyl-4b,5,6,7,8,8a,9,10-octahydrophenanthrene-1,7-diol (3.18)



3.17 **3.18**

Detailed Procedures

To a vigorously stirred suspension of $ZrCl_4$ (0.197 g, 0.84 mmol, 700 mol%) in DCE (10 mL), a solution of **3.17** (0.0422 g, 0.12 mmol, 100 mol%) in DCE (2 mL) was added in one portion. The mixture was heated to 55 ˚C and allowed to stir for 11 hours. After cooled to ambient temperature, the reaction was poured into saturated $NaHCO_3$ (aq., 20 mL) and allowed to stir for 15 min. The mixture was extracted by DCM (10 mL × 2). The combined organic layers were washed with brine (10 mL), and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was submitted to flash column chromatography on silica gel (DCM/acetone = 10:1). The title compound was obtained as a white solid (0.0239 g, 0.069 mmol) in 57% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.62 (s, 1H), 4.35 (d, *J* = 11.3 Hz, 1H), 4.29 (s, 1H), 3.78 (s, 3H), 3.54 (dd, *J* = 11.8, 4.6 Hz, 1H), 3.41 (d, *J* = 11.3 Hz, 1H), 3.23-3.11 (m, 2H), 2.83 (ddd, *J* = 16.6, 5.6, 1.3 Hz, 1H), 2.56 (ddd, *J* = 16.6, 12.3, 6.9 Hz, 1H), 2.09-1.92 (m, 2H), 1.86-1.77 (m, 1H), 1.55 (qd, *J* = 12.3, 5.5 Hz, 1H), 1.37 (d, *J* = 12.1 Hz, 1H), 1.34 (s, 3H), 1.34-1.28 (m, 1H), 1.28 (s, 3H), 1.27 (d, *J* = 6.9 Hz, 3H), 1.25 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 152.5, 144.6, 135.0, 131.2, 123.7, 108.2, 80.7, 64.4, 55.9, 52.9, 43.6, 38.9, 34.7, 28.9, 27.5, 27.3, 23.0, 22.8, 22.6, 20.7, 18.4.

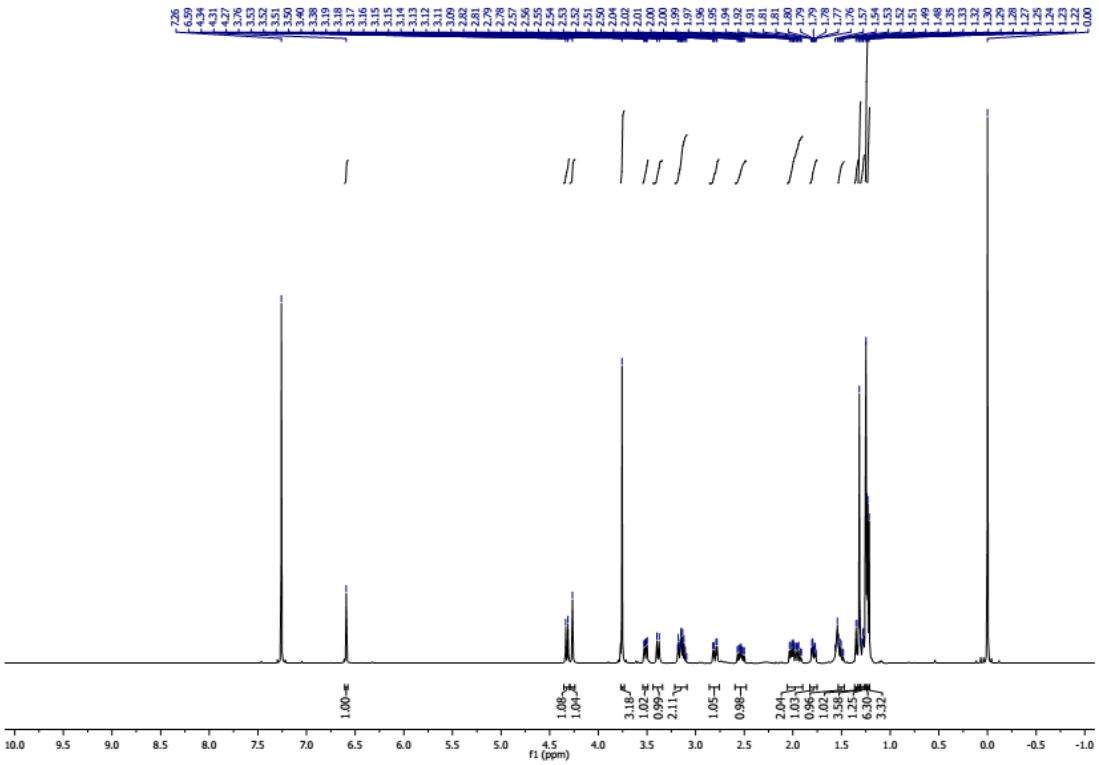
R_f 0.3 (DCM/acetone = 5:1, *p*-anisaldehyde)

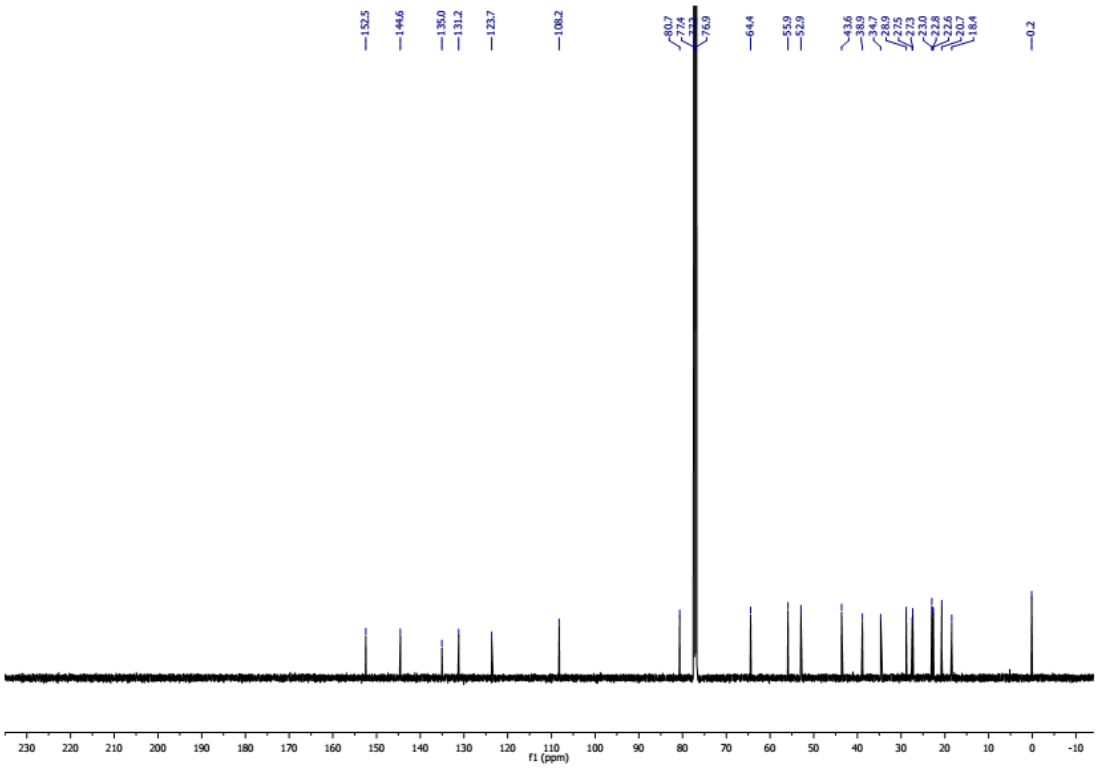
HRMS (ESI) Calcd. for $C_{21}H_{32}O_4$ $[M+Na]^+$: 371.2193, Found: 371.2201.

FTIR (neat): 3381, 2954, 2928, 2868, 1649, 1462, 1413, 1286, 1235, 1101, 1071, 1034, 992, 976, 919, 907, 817, 755 cm^{-1}.

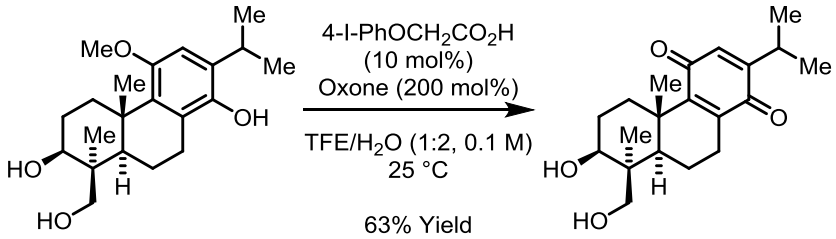
MP 206.4-208.1 ˚C ($CHCl_3$)

Optical Rotation $[\alpha]_D^{30}$ = +75.3˚ (*c* = 0.17, $CHCl_3$)





(4b*S*,7*S*,8*S*,8a*R*)-7-Hydroxy-8-(hydroxymethyl)-2-isopropyl-4b,8-dimethyl-4b,5,6,7,8,8a,9,10-octahydrophenanthrene-1,4-dione ((-)-Triptoquinone C, 3.3)



3.18 **(-)-Triptoquinone C (3.3)**

Detailed Procedures

To a mixture of **3.18** (0.0151 g, 0.043 mmol, 100 mol%) and *p*-iodo-phenoxyacetic acid[3] (0.0012 g, 0.0043 mmol, 10 mol%) in 2,2,2-trifluoroethanol (0.14 mL) and water (0.29 mL), Oxone® (0.0533 g, 0.087 mmol, 200 mol%) was added in one portion. The reaction turned yellow slowly, and was allowed to stir at ambient temperature for 2 hours. The mixture was diluted with ethyl acetate (2 mL), washed with water (2 mL) and saturated $NaHCO_3$ (aq., 2 mL), and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was submitted to flash column chromatography on silica gel (hexanes/EA = 3:2). The title compound was obtained as a yellow solid (0.0091 g, 0.027 mmol) in 63% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.32 (d, *J* = 1.3 Hz, 1H), 4.26 (d, *J* = 11.2 Hz, 1H), 3.49 (d, *J* = 11.8 Hz, 1H), 3.35 (t, *J* = 9.6 Hz, 1H), 2.98 (heptd, *J* = 6.9, 1.2 Hz, 1H), 2.81 (dt, *J* = 13.6, 3.6 Hz, 1H), 2.78 (br, 1H), 2.73 (ddd, *J* = 20.3, 5.7, 1.2 Hz, 1H), 2.39 (br, 1H), 2.31 (ddd, *J* = 20.3, 11.6, 7.3 Hz, 1H), 2.03-1.90 (m, 2H), 1.81 (dq, *J* = 13.5, 3.9 Hz, 1H), 1.39 (ddd, *J* = 25.0, 12.5, 5.6 Hz, 1H), 1.29 (s, 3H), 1.28-1.19 (m, 1H), 1.23 (s, 3H), 1.19 (dd, *J* = 12.5, 1.5 Hz, 1H), 1.10 (d, *J* = 6.8 Hz, 3H), 1.09 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 187.9, 187.8, 153.2, 149.7, 142.8, 132.1, 80.3, 64.1, 51.9, 43.3, 38.0, 34.3, 28.3, 26.6, 26.5, 22.8, 21.5, 21.5, 21.0, 17.5.

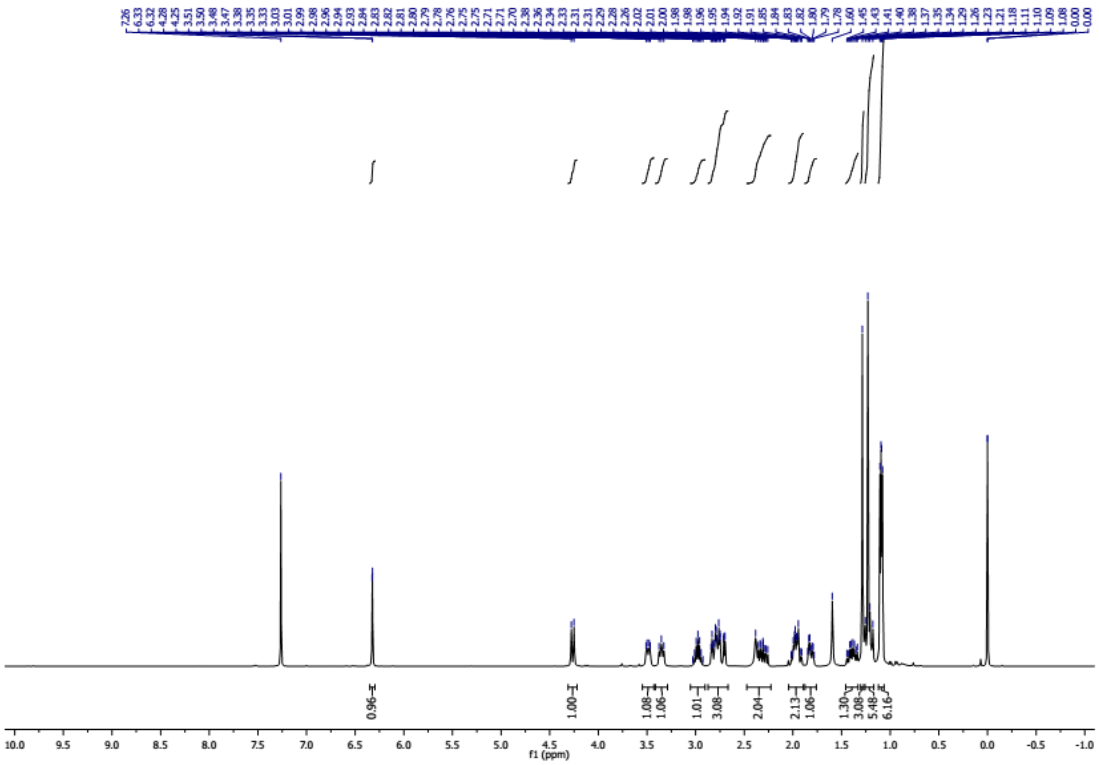
R_f 0.2 (hexanes/EA = 3:2, UV)

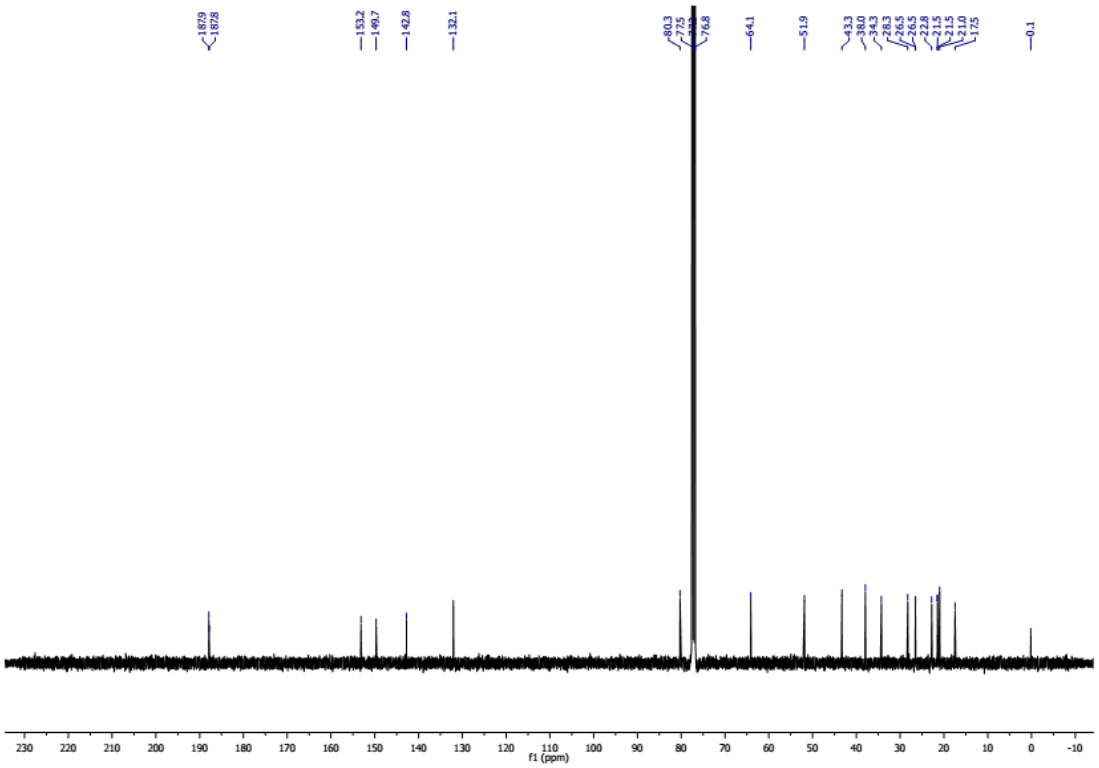
HRMS (ESI) Calcd. for $C_{20}H_{28}O_4$ $[M+Na]^+$: 355.1880, Found: 355.1880.

FTIR (neat): 3382, 2963, 2932, 2873, 1647, 1599, 1460, 1291, 1265, 1230, 1080, 1037, 907, 738 cm^{-1}.

MP 161.0-162.0 ˚C ($CHCl_3$)

Optical Rotation $[\alpha]_D^{30}$ = -43.0˚ (c = 0.3, $CHCl_3$)





Comparison of NMR Data between Natural and Synthetic Oridamycin A and Triptoquinone C

Table 3.4 ^{13}C NMR data of natural and synthetic oridamycin A (**3.1**).

Natural[12]	**Synthetic 1**[15]	**Synthetic 2**[16]	**Synthetic 3 (This Work)**
δ_C (ppm)	δ_C (ppm)	δ_C (ppm)	δ_C (ppm)
181.0	181.0	181.0	181.0
142.0	142.1	142.0	142.1
140.3	140.4	140.3	140.4
140.1	140.1	140.1	140.1
134.5	134.5	134.5	134.5
126.1	126.1	126.1	126.1
124.6	124.6	124.6	124.6
123.2	123.3	123.2	123.3
120.6	120.6	120.6	120.6
119.3	119.4	119.3	119.3
117.5	117.5	117.5	117.5
111.4	111.4	111.4	111.4
110.7	110.7	110.7	110.7
79.1	79.1	79.1	79.1
54.1	54.1	54.1	54.1
48.7*	49.8	48.7*	49.8
40.0	40.0	40.0	40.0
39.6	39.6	39.6	39.6
34.0	34.0	34.0	34.0
30.3	30.3	30.3	30.3
24.8	24.8	24.8	24.8
24.6	24.6	24.6	24.6
22.5	22.5	22.5	22.5

***** The peak at 48.7 ppm is buried under the solvent peaks, and there is no other evidence (such as HMBC data) to support this assignment. On the other hand, the peak at 49.8 ppm can be seen in ^{13}C NMR spectra of all three synthetic oridamycin A, but the author of synthetic 2 did not assign this peak to any carbon.

Table 3.5 ^{13}C NMR data of natural and synthetic triptoquinone C (**3.3**).

Natural[23]	**Synthetic (This Work)**
δ_C (ppm)	δ_C (ppm)
187.8	187.9
187.7	187.8
153.1	153.2
149.6	149.7
142.7	142.8
131.9	132.1
80.0	80.3
64.0	64.1
51.8	51.9
43.1	43.3
37.8	38.0
34.2	34.3
28.1	28.3
26.4	26.6
26.3	26.5
22.3	22.8
21.3	21.5
21.3	21.5
20.9	21.0
17.4	17.5

Crystallographic Material for 3.11

X-ray Experimental for $C_{17}H_{15}NO_2$ (3.11)

Crystals grew as thin, colorless plates by slow evaporation from chloroform. The data crystal was cut from a larger crystal and had approximate dimensions: 0.29 x 0.20 x 0.03 mm. The data were collected on an Agilent Technologies SuperNova Dual Source diffractometer using a μ-focus Cu Kα radiation source (λ = 1.5418 Å) with collimating mirror monochromators. A total of 990 frames of data were collected using ω-scans with a scan range of 1° and a counting time of 10 seconds per frame with a detector offset of +/- 40.6° and 40 seconds per frame with a detector offset of +/- 108.3°. The data were collected at 100 K using an Oxford Cryostream low temperature device. Details of crystal data, data collection and structure refinement are listed in Table 3.6. Data reduction were performed using Agilent Technologies CrysAlisPro V 1.171.37.31.[67] The structure was solved by direct methods using SuperFlip[68] and refined by full-matrix least-squares on F^2 with anisotropic displacement parameters for the non-H atoms using SHELXL-2013.[69] Structure analysis was aided by use of the programs PLATON98[70] and WinGX.[71] 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).

For six of the eight molecules in the unit cell, the carbazole moiety was disordered by rotation about the bond from the carbazole to a methylene carbon atom. The rings were disordered to differing degrees but were all modeled in the same fashion. The site occupancy factors for one component of the disordered carbazole were assigned to the variable x. The site occupancy factors for the alternate component were set to (1-x). A common isotropic displacement parameter was refined for the non-H atoms of both components while refining x. The geometry of the two components were restrained to be equivalent throughout the refinement process. The non-H atoms of the two components

were refined anisotropically with their displacement parameters restrained to be approximately isotropic.

The function, $\Sigma w(|F_o|^2 - |F_c|^2)^2$, was minimized, where $w = 1/[(\sigma(F_o))^2 + (0.01064*P)^2 + (1.475*P)]$ and $P = (|F_o|^2 + 2|F_c|^2)/3$. $R_W(F^2)$ refined to 0.212, with R(F) equal to 0.0786 and a goodness of fit, S, = 1.07. Definitions used for calculating R(F), $R_W(F^2)$ and the goodness of fit, S, are given below.[72] 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).[73] All figures were generated using SHELXTL/PC.[74] Tables of positional and thermal parameters, bond lengths and angles, torsion angles and figures are found elsewhere.

Table 3.6 Crystal data and structure refinement for **3.11**.

Empirical formula	$C_{23}H_{27}NO_2$	
Formula weight	349.45	
Temperature	100(2) K	
Wavelength	1.54184 Å	
Crystal system	triclinic	
Space group	P 1	
Unit cell dimensions	a = 11.7783(4) Å	α = 79.911(3)°.
	b = 14.8717(5) Å	β = 84.025(3)°.
	c = 21.5048(11) Å	γ = 89.908(3)°.
Volume	3687.9(3) $Å^3$	
Z	8	
Density (calculated)	1.259 Mg/m^3	
Absorption coefficient	0.622 mm^{-1}	
F(000)	1504	
Crystal size	0.29 x 0.20 x 0.03 mm	
Theta range for data collection	3.019 to 74.573°.	
Index ranges	-14<=h<=14, -18<=k<=16, -26<=l<=26	
Reflections collected	22860	
Independent reflections	22860 [R(int) = ?]	
Completeness to theta = 67.684°	99.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00 and 0.851	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	22860 / 7267 / 2566	
Goodness-of-fit on F^2	1.068	
Final R indices [I>2sigma(I)]	R1 = 0.0786, wR2 = 0.2037	
R indices (all data)	R1 = 0.0843, wR2 = 0.2115	
Absolute structure parameter	0.10(16)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.658 and -0.502 $e.Å^{-3}$	

Table 3.7 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **3.11**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O1	-1733(6)	9117(4)	8745(4)	45(1)
O2	-390(5)	11392(4)	8522(4)	40(1)
N1	2564(8)	9402(5)	4899(5)	32(2)
C12	872(13)	8579(6)	6500(18)	35(2)
C13	-12(12)	8243(6)	6245(7)	34(2)
C14	-96(10)	8268(6)	5587(6)	28(2)
C15	838(10)	8682(5)	5168(7)	24(2)
C16	1770(11)	9039(6)	5397(7)	27(2)
C17	1849(11)	9011(6)	6068(8)	31(2)
C18	1031(11)	8817(5)	4498(7)	26(2)
C19	521(10)	8654(6)	3983(8)	24(2)
C20	984(13)	8894(7)	3369(7)	28(2)
C21	2057(14)	9342(7)	3234(7)	33(2)
C22	2625(11)	9527(6)	3738(10)	30(2)
C23	2161(14)	9289(7)	4328(8)	31(2)
N1D	56(12)	8347(7)	4923(8)	29(2)
C12D	849(19)	8480(8)	6500(30)	35(2)
C13D	1884(15)	8918(8)	6388(12)	32(3)
C14D	2231(16)	9141(9)	5732(11)	28(3)
C15D	1620(20)	8951(10)	5248(12)	28(2)
C16D	552(19)	8486(9)	5448(12)	27(2)
C17D	110(20)	8230(10)	6060(12)	29(3)
C18D	1800(18)	9107(9)	4558(12)	28(2)
C19D	2628(19)	9503(10)	4102(14)	28(3)

Table 3.7 (Cont'd)

C20D	2500(20)	9528(11)	3458(14)	30(3)
C21D	1510(30)	9147(13)	3283(11)	30(3)
C22D	669(18)	8747(10)	3709(15)	26(3)
C23D	785(18)	8717(9)	4348(13)	26(2)
C1	73(7)	9770(6)	8596(4)	32(2)
C2	-927(7)	9471(5)	9101(5)	37(2)
C3	-697(10)	8624(6)	9581(5)	50(2)
C4	-737(9)	7853(6)	9196(5)	46(2)
C5	-991(8)	8394(6)	8550(5)	43(2)
C6	123(8)	8914(6)	8239(5)	38(2)
C7	1203(10)	9924(9)	8842(6)	54(3)
C8	-258(7)	10652(5)	8171(5)	37(2)
C9	-1658(12)	7861(7)	8164(6)	66(3)
C10	278(9)	9145(7)	7512(5)	46(2)
C11	835(14)	8373(10)	7198(6)	74(3)
O3	4270(5)	5589(4)	8978(3)	31(1)
O4	1658(5)	6833(4)	8546(4)	41(1)
N2	4939(6)	8319(5)	5127(4)	34(1)
C24	3637(6)	7066(5)	8771(4)	28(1)
C25	3614(6)	6220(5)	9302(4)	28(1)
C26	4328(7)	6332(6)	9842(4)	37(2)
C27	5542(7)	6253(6)	9521(4)	37(2)
C28	5334(6)	6144(5)	8839(4)	29(1)
C29	4922(6)	7072(5)	8493(4)	25(1)
C30	3280(7)	7940(5)	9005(4)	37(2)
C31	2840(6)	6875(5)	8289(4)	32(1)
C32	6216(7)	5617(6)	8500(5)	39(2)

Table 3.7 (Cont'd)

C33	5197(7)	7262(5)	7772(4)	29(1)
C34	4996(8)	8258(5)	7470(4)	33(2)
C35	5473(7)	8487(5)	6782(4)	30(1)
C36	6560(7)	8904(5)	6615(4)	32(2)
C37	7073(7)	9113(5)	6004(4)	29(1)
C38	6464(6)	8869(5)	5528(4)	28(1)
C39	5381(7)	8458(5)	5680(4)	30(2)
C40	4882(8)	8241(5)	6314(4)	32(2)
C41	6698(7)	9015(5)	4844(4)	28(1)
C42	7603(7)	9388(5)	4394(4)	31(2)
C43	7528(8)	9425(6)	3767(5)	37(2)
C44	6553(9)	9083(6)	3550(5)	39(2)
C45	5656(8)	8697(6)	3985(5)	36(2)
C46	5736(6)	8651(5)	4612(4)	26(1)
O5	1132(6)	4989(4)	8938(3)	32(1)
O6	3923(5)	3980(4)	8520(4)	40(1)
N3	2512(7)	4353(5)	5097(5)	30(2)
C58	914(11)	3448(6)	6664(12)	32(2)
C59	-31(10)	3079(6)	6432(6)	33(2)
C60	-104(9)	3143(5)	5792(6)	32(2)
C61	818(9)	3598(5)	5356(6)	27(2)
C62	1721(9)	3946(5)	5602(6)	28(2)
C63	1828(11)	3893(6)	6259(7)	32(2)
C64	1013(11)	3776(5)	4684(7)	30(2)
C65	482(10)	3621(6)	4170(8)	31(2)
C66	930(13)	3898(7)	3559(7)	32(2)
C67	1985(12)	4368(7)	3406(7)	31(2)

Table 3.7 (Cont'd)

C68	2566(12)	4544(6)	3922(7)	31(2)
C69	2108(11)	4261(6)	4544(6)	31(2)
N1E	26(14)	3312(8)	5079(10)	31(2)
C12E	1060(20)	3478(9)	6610(20)	32(2)
C13E	2127(17)	3934(9)	6371(13)	29(3)
C14E	2395(18)	4141(10)	5738(11)	30(3)
C15E	1681(19)	3932(9)	5279(14)	28(2)
C16E	610(20)	3471(11)	5541(14)	29(2)
C17E	280(20)	3227(12)	6239(14)	32(3)
C18E	1700(20)	4046(11)	4606(13)	30(2)
C19E	2500(20)	4436(13)	4134(15)	28(3)
C20E	2280(20)	4446(14)	3505(16)	29(3)
C21E	1200(20)	4044(13)	3366(15)	30(3)
C22E	510(20)	3694(12)	3848(18)	30(3)
C23E	700(20)	3671(10)	4474(17)	30(2)
C47	1870(7)	3630(5)	8701(4)	33(1)
C48	1685(6)	4174(5)	9243(4)	29(1)
C49	752(7)	3763(6)	9770(4)	35(2)
C50	-340(7)	4020(6)	9447(4)	36(2)
C51	146(7)	4523(5)	8784(4)	31(2)
C52	692(7)	3791(5)	8410(4)	31(1)
C53	2117(8)	2617(6)	8915(5)	41(2)
C54	2865(6)	4074(5)	8239(4)	32(1)
C55	-616(7)	5230(6)	8454(4)	37(2)
C56	714(6)	4018(5)	7696(4)	29(1)
C57	984(8)	3200(5)	7358(4)	35(2)
O7	-2743(5)	11528(4)	8856(3)	31(1)

Table 3.7 (Cont'd)

O8	-3998(6)	9407(4)	8605(4)	50(2)
N4	-5044(8)	13320(5)	4988(5)	27(2)
C81	-4370(14)	13384(7)	6610(15)	34(2)
C82	-3305(11)	13827(6)	6453(8)	36(2)
C83	-2824(10)	14097(6)	5827(6)	30(2)
C84	-3478(11)	13898(5)	5336(7)	25(2)
C85	-4556(11)	13446(6)	5525(7)	24(2)
C86	-5006(14)	13189(7)	6151(8)	32(2)
C87	-3316(12)	14047(6)	4667(7)	26(2)
C88	-2454(11)	14446(6)	4220(9)	27(2)
C89	-2551(12)	14488(6)	3575(9)	33(2)
C90	-3534(12)	14122(7)	3376(7)	32(2)
C91	-4397(11)	13723(6)	3817(8)	29(2)
C92	-4295(11)	13685(5)	4450(7)	26(2)
N1B	-2496(11)	14291(6)	5046(7)	26(2)
C12B	-2917(15)	14419(7)	3356(10)	30(3)
C13B	-4026(16)	13995(8)	3470(11)	32(3)
C14B	-4518(17)	13713(8)	4080(13)	29(3)
C15B	-3988(19)	13821(8)	4594(10)	26(2)
C16B	-2850(20)	14257(10)	4478(12)	26(2)
C17B	-2364(16)	14536(8)	3865(14)	28(3)
C18B	-4228(15)	13624(7)	5253(10)	26(2)
C19B	-5192(15)	13208(9)	5647(9)	28(2)
C20B	-5150(20)	13115(11)	6298(13)	32(3)
C21B	-4200(20)	13413(12)	6590(20)	34(2)
C22B	-3243(18)	13827(10)	6194(12)	30(3)
C23B	-3366(18)	13889(8)	5552(11)	26(2)

Table 3.7 (Cont'd)

C70	-4498(7)	10981(6)	8674(4)	34(2)
C71	-3706(6)	10998(5)	9198(4)	33(1)
C72	-4135(8)	11591(6)	9686(4)	41(2)
C73	-3865(8)	12560(6)	9301(4)	40(2)
C74	-3375(7)	12347(5)	8659(4)	33(1)
C75	-4358(7)	12019(6)	8328(4)	36(2)
C76	-5748(9)	10712(8)	8908(7)	58(3)
C77	-4008(8)	10319(6)	8255(5)	42(2)
C78	-2551(9)	13085(6)	8284(5)	48(2)
C79	-4224(9)	12180(6)	7607(5)	43(2)
C80	-4555(12)	13147(8)	7309(5)	68(3)
O9	6692(5)	8488(4)	1278(3)	34(1)
O10	5335(6)	10634(4)	1493(4)	42(1)
C93	4877(7)	9035(5)	1431(4)	32(2)
C94	5880(7)	9013(6)	913(4)	36(2)
C95	5620(9)	8391(6)	445(4)	45(2)
C96	5761(9)	7426(6)	845(4)	43(2)
C97	5990(7)	7656(5)	1489(4)	33(1)
C98	4865(7)	8023(5)	1795(4)	32(1)
C99	3734(9)	9331(7)	1191(6)	50(2)
C100	5211(7)	9726(5)	1846(4)	36(2)
C101	6675(8)	6946(6)	1879(5)	45(2)
C102	4703(7)	7884(5)	2513(4)	33(2)
C103	4276(10)	6911(7)	2827(5)	52(2)
N5	2468(8)	6882(5)	5070(5)	30(2)
C104	4115(12)	6776(6)	3551(9)	29(2)
C105	5083(12)	6278(7)	3800(7)	33(2)

Table 3.7 (Cont'd)

C106	5104(11)	6028(6)	4437(6)	27(2)
C107	4203(11)	6248(5)	4844(7)	26(2)
C108	3289(11)	6727(6)	4583(7)	28(2)
C109	3211(12)	6996(7)	3958(7)	29(2)
C110	3895(15)	6108(7)	5541(7)	29(2)
C111	4484(13)	5673(7)	6038(8)	33(2)
C112	3929(13)	5662(8)	6670(9)	35(2)
C113	2846(13)	6081(7)	6754(7)	32(2)
C114	2308(13)	6495(7)	6260(8)	31(2)
C115	2832(13)	6508(6)	5655(7)	29(2)
N1A	5062(13)	5832(7)	5114(8)	30(2)
C12A	4203(18)	6680(8)	3484(15)	29(2)
C13A	3107(17)	7013(8)	3769(11)	28(3)
C14A	2711(17)	6961(9)	4414(10)	30(3)
C15A	3450(18)	6546(9)	4828(12)	28(2)
C16A	4550(20)	6201(9)	4578(12)	27(2)
C17A	4870(20)	6272(11)	3953(12)	28(3)
C18A	3360(30)	6365(11)	5503(11)	30(2)
C19A	2500(20)	6542(10)	5993(15)	31(3)
C20A	2700(20)	6288(12)	6552(14)	36(3)
C21A	3680(20)	5846(12)	6748(14)	36(3)
C22A	4590(20)	5646(11)	6280(12)	33(3)
C23A	4390(20)	5925(10)	5645(12)	30(2)
O11	646(5)	5074(4)	1126(3)	28(1)
O12	3281(5)	6020(4)	1581(3)	38(1)
N6	59(7)	5838(6)	5038(4)	40(2)
C116	1312(6)	6413(5)	1375(4)	30(1)

Table 3.7 (Cont'd)

C117	1343(7)	5869(5)	823(4)	30(1)
C118	607(7)	6302(6)	303(4)	35(2)
C119	-626(7)	6052(6)	613(4)	33(1)
C120	-386(7)	5569(5)	1281(4)	30(1)
C121	12(6)	6287(5)	1652(4)	26(1)
C122	1668(8)	7428(6)	1160(5)	44(2)
C123	2121(6)	5935(5)	1845(4)	30(1)
C124	-1280(7)	4860(5)	1611(4)	33(2)
C125	-269(6)	6077(5)	2371(4)	27(1)
C126	-58(7)	6890(5)	2693(4)	35(2)
C127	-507(7)	6743(5)	3377(4)	30(1)
C128	-1597(8)	7084(6)	3555(5)	38(2)
C129	-2042(8)	7001(6)	4163(5)	36(2)
C130	-1483(7)	6585(5)	4644(5)	34(2)
C131	-375(8)	6212(5)	4496(5)	36(2)
C132	111(8)	6288(5)	3858(4)	34(2)
C133	-1682(8)	6396(6)	5330(5)	38(2)
C134	-2581(9)	6583(6)	5783(6)	46(2)
C135	-2479(10)	6320(7)	6408(5)	52(2)
C136	-1504(10)	5851(8)	6615(5)	53(2)
C137	-597(9)	5660(7)	6178(5)	46(2)
C138	-712(9)	5954(6)	5555(5)	42(2)
O13	3832(5)	4395(4)	1124(3)	29(1)
O14	1027(5)	3239(4)	1558(4)	42(1)
N7	2458(7)	1851(4)	5026(5)	34(2)
C150	4027(10)	1727(5)	3448(10)	30(1)
C151	4994(9)	1251(5)	3702(6)	32(2)

Table 3.7 (Cont'd)

C152	5069(9)	1018(5)	4337(6)	31(2)
C153	4199(9)	1234(4)	4757(6)	29(2)
C154	3211(9)	1713(5)	4517(6)	29(2)
C155	3153(10)	1935(5)	3898(6)	31(2)
C156	3970(12)	1098(5)	5457(6)	28(2)
C157	4567(10)	690(5)	5951(6)	30(2)
C158	4054(11)	690(6)	6586(6)	34(2)
C159	3002(13)	1085(7)	6690(7)	37(2)
C160	2413(10)	1484(6)	6207(8)	34(2)
C161	2903(12)	1495(5)	5567(7)	31(2)
N1F	5050(20)	850(11)	4990(13)	32(3)
C12F	3890(20)	1684(10)	3430(30)	30(1)
C13F	2970(20)	1929(10)	3751(17)	28(3)
C14F	2430(30)	1956(13)	4374(16)	34(3)
C15F	3360(30)	1526(13)	4730(20)	30(2)
C16F	4440(30)	1208(13)	4472(19)	30(3)
C17F	4690(30)	1293(15)	3820(20)	31(3)
C18F	3420(40)	1321(15)	5425(17)	29(2)
C19F	2590(30)	1504(14)	5860(30)	30(3)
C20F	2680(30)	1302(19)	6480(20)	32(3)
C21F	3600(40)	929(17)	6653(17)	33(3)
C22F	4610(30)	690(15)	6190(20)	31(3)
C23F	4370(30)	942(15)	5560(20)	30(3)
C139	3078(6)	2925(5)	1394(4)	30(1)
C140	3267(7)	3748(5)	833(4)	31(1)
C141	4171(7)	3562(6)	314(4)	37(2)
C142	5276(7)	3643(6)	624(4)	35(2)

Table 3.7 (Cont'd)

C143	4813(7)	3834(5)	1286(4)	30(1)
C144	4265(6)	2935(5)	1681(4)	28(1)
C145	2809(7)	2028(6)	1191(5)	42(2)
C146	2080(7)	3177(6)	1842(4)	36(2)
C147	5609(7)	4367(6)	1591(5)	38(2)
C148	4241(7)	2814(5)	2396(4)	32(1)
C149	3944(8)	1822(6)	2746(5)	40(2)
O15	-2333(5)	859(4)	1120(3)	34(1)
O16	-977(6)	-1378(4)	1319(4)	54(2)
N8	44(8)	864(7)	4930(5)	29(2)
C173	-584(15)	1618(17)	3261(11)	28(2)
C174	-1676(10)	1996(8)	3421(7)	30(2)
C175	-2077(11)	1977(8)	4029(7)	30(2)
C176	-1505(12)	1577(9)	4536(7)	28(2)
C177	-386(12)	1199(8)	4360(7)	27(2)
C178	20(14)	1195(11)	3758(7)	29(2)
C179	-1675(11)	1426(8)	5190(7)	26(2)
C180	-2620(11)	1615(8)	5624(6)	29(2)
C181	-2505(12)	1377(10)	6271(7)	32(2)
C182	-1562(13)	953(10)	6493(6)	34(2)
C183	-618(13)	743(9)	6085(8)	34(2)
C184	-711(12)	1005(10)	5436(7)	31(2)
N1C	-2480(16)	1831(12)	4839(9)	32(2)
C12C	-760(30)	1660(40)	3310(20)	28(2)
C13C	200(30)	1260(20)	3618(14)	29(3)
C14C	210(20)	1059(14)	4218(11)	27(3)
C15C	-700(20)	1295(16)	4594(13)	30(2)

Table 3.7 (Cont'd)

C16C	-1690(20)	1746(18)	4364(14)	28(2)
C17C	-1720(20)	1902(16)	3723(16)	28(3)
C18C	-970(30)	1163(18)	5308(13)	29(2)
C19C	-370(20)	833(16)	5821(15)	31(3)
C20C	-870(20)	849(17)	6444(13)	36(3)
C21C	-1950(30)	1224(19)	6523(13)	34(3)
C22C	-2560(20)	1545(18)	6042(16)	31(3)
C23C	-2070(30)	1514(16)	5392(14)	29(2)
C162	-536(7)	255(6)	1225(4)	36(2)
C163	-1384(7)	529(5)	742(4)	36(2)
C164	-1024(8)	1379(6)	249(4)	43(2)
C165	-1291(9)	2147(6)	641(4)	46(2)
C166	-1683(8)	1590(5)	1294(4)	39(2)
C167	-642(7)	1090(5)	1582(4)	37(2)
C168	668(9)	118(9)	955(7)	61(3)
C169	-950(8)	-639(6)	1667(5)	48(2)
C170	-2506(10)	2114(7)	1703(5)	55(2)
C171	-723(8)	888(6)	2305(4)	41(2)
C172	-260(10)	1656(7)	2589(5)	57(2)

Table 3.8 Bond lengths [Å] and angles [°] for **3.11**.

O1-C2	1.435(9)	C12D-C13D	1.36(3)
O1-C5	1.475(11)	C12D-C17D	1.44(6)
O2-C8	1.439(9)	C12D-C11	1.48(7)
O2-H2O	0.84	C13D-C14D	1.41(3)
N1-C16	1.379(18)	C13D-H13D	0.95
N1-C23	1.399(17)	C14D-C15D	1.39(3)
N1-H1	0.88	C14D-H14D	0.95
C12-C13	1.36(3)	C15D-C16D	1.43(4)
C12-C17	1.47(3)	C15D-C18D	1.45(4)
C12-C11	1.47(4)	C16D-C17D	1.35(4)
C13-C14	1.422(19)	C17D-H17D	0.95
C13-H13	0.95	C18D-C19D	1.36(3)
C14-C15	1.415(17)	C18D-C23D	1.48(3)
C14-H14	0.95	C19D-C20D	1.40(3)
C15-C16	1.391(17)	C19D-H19D	0.95
C15-C18	1.41(2)	C20D-C21D	1.40(4)
C16-C17	1.45(2)	C20D-H20D	0.95
C17-H17	0.95	C21D-C22D	1.34(4)
C18-C19	1.371(19)	C21D-H21D	0.95
C18-C23	1.49(2)	C22D-C23D	1.39(4)
C19-C20	1.362(19)	C22D-H22D	0.95
C19-H19	0.95	C1-C7	1.515(12)
C20-C21	1.408(19)	C1-C2	1.527(11)
C20-H20	0.95	C1-C8	1.537(11)
C21-C22	1.40(2)	C1-C6	1.596(11)
C21-H21	0.95	C2-C3	1.526(12)
C22-C23	1.32(2)	C2-H2	1.00
C22-H22	0.95	C3-C4	1.532(12)
N1D-C16D	1.37(3)	C3-H3A	0.99
N1D-C23D	1.45(3)	C3-H3B	0.99
N1D-H1D	0.88	C4-C5	1.537(12)

Table 3.8 (Cont'd)

C4-H4A	0.99	C25-C26	1.534(10)
C4-H4B	0.99	C25-H25	1.00
C5-C9	1.518(12)	C26-C27	1.535(11)
C5-C6	1.552(12)	C26-H26A	0.99
C6-C10	1.532(13)	C26-H26B	0.99
C6-H6	1.00	C27-C28	1.547(11)
C7-H7A	0.98	C27-H27A	0.99
C7-H7B	0.98	C27-H27B	0.99
C7-H7C	0.98	C28-C32	1.505(11)
C8-H8A	0.99	C28-C29	1.551(10)
C8-H8B	0.99	C29-C33	1.527(10)
C9-H9A	0.98	C29-H29	1.00
C9-H9B	0.98	C30-H30A	0.98
C9-H9C	0.98	C30-H30B	0.98
C10-C11	1.545(14)	C30-H30C	0.98
C10-H10F	0.99	C31-H31A	0.99
C10-H10G	0.99	C31-H31B	0.99
C11-H11E	0.99	C32-H32A	0.98
C11-H11F	0.99	C32-H32B	0.98
O3-C25	1.441(9)	C32-H32C	0.98
O3-C28	1.476(8)	C33-C34	1.539(10)
O4-C31	1.441(8)	C33-H33A	0.99
O4-H4O	0.84	C33-H33B	0.99
N2-C39	1.393(10)	C34-C35	1.507(11)
N2-C46	1.395(10)	C34-H34A	0.99
N2-H2N	0.88	C34-H34B	0.99
C24-C30	1.519(10)	C35-C40	1.381(11)
C24-C31	1.531(9)	C35-C36	1.408(11)
C24-C25	1.542(10)	C36-C37	1.370(11)
C24-C29	1.567(9)	C36-H36	0.95

Table 3.8 (Cont'd)

C37-C38	1.407(10)	C61-C62	1.376(17)
C37-H37	0.95	C61-C64	1.417(18)
C38-C39	1.397(9)	C62-C63	1.419(19)
C38-C41	1.446(11)	C63-H63	0.95
C39-C40	1.410(12)	C64-C65	1.378(17)
C40-H40	0.95	C64-C69	1.457(18)
C41-C42	1.408(11)	C65-C66	1.36(2)
C41-C46	1.428(10)	C65-H65	0.95
C42-C43	1.351(12)	C66-C67	1.41(2)
C42-H42	0.95	C66-H66	0.95
C43-C44	1.410(12)	C67-C68	1.423(17)
C43-H43	0.95	C67-H67	0.95
C44-C45	1.389(13)	C68-C69	1.382(18)
C44-H44	0.95	C68-H68	0.95
C45-C46	1.352(12)	N1E-C16E	1.32(3)
C45-H45	0.95	N1E-C23E	1.46(4)
O5-C51	1.450(9)	N1E-H1EN	0.88
O5-C48	1.459(9)	C12E-C17E	1.38(5)
O6-C54	1.436(9)	C12E-C13E	1.43(3)
O6-H6O	0.84	C12E-C57	1.58(5)
N3-C69	1.355(15)	C13E-C14E	1.35(4)
N3-C62	1.405(14)	C13E-H13E	0.95
N3-H3N	0.88	C14E-C15E	1.43(3)
C58-C63	1.40(2)	C14E-H14E	0.95
C58-C59	1.42(2)	C15E-C18E	1.43(4)
C58-C57	1.48(3)	C15E-C16E	1.45(4)
C59-C60	1.375(18)	C16E-C17E	1.49(4)
C59-H59	0.95	C17E-H17E	0.95
C60-C61	1.444(16)	C18E-C19E	1.36(4)
C60-H60	0.95	C18E-C23E	1.39(4)

Table 3.8 (Cont'd)

C19E-C20E	1.40(4)	C55-H55B	0.98
C19E-H19E	0.95	C55-H55C	0.98
C20E-C21E	1.48(4)	C56-C57	1.540(10)
C20E-H20E	0.95	C56-H56A	0.99
C21E-C22E	1.29(4)	C56-H56B	0.99
C21E-H21E	0.95	C57-H57A	0.99
C22E-C23E	1.38(4)	C57-H57B	0.99
C22E-H22E	0.95	O7-C71	1.441(8)
C47-C54	1.526(9)	O7-C74	1.449(9)
C47-C48	1.528(10)	O8-C77	1.432(11)
C47-C53	1.533(11)	O8-H8O	0.84
C47-C52	1.582(10)	N4-C85	1.384(16)
C48-C49	1.538(9)	N4-C92	1.407(16)
C48-H48	1.00	N4-H4N	0.88
C49-C50	1.541(11)	C81-C86	1.37(3)
C49-H49A	0.99	C81-C82	1.40(2)
C49-H49B	0.99	C81-C80	1.48(3)
C50-C51	1.541(11)	C82-C83	1.39(2)
C50-H50A	0.99	C82-H82	0.95
C50-H50B	0.99	C83-C84	1.441(18)
C51-C55	1.511(11)	C83-H83	0.95
C51-C52	1.564(10)	C84-C87	1.410(19)
C52-C56	1.510(11)	C84-C85	1.425(19)
C52-H52	1.00	C85-C86	1.38(2)
C53-H53A	0.98	C86-H86	0.95
C53-H53B	0.98	C87-C88	1.381(18)
C53-H53C	0.98	C87-C92	1.428(19)
C54-H54A	0.99	C88-C89	1.39(2)
C54-H54B	0.99	C88-H88	0.95
C55-H55A	0.98	C89-C90	1.42(2)

Table 3.8 (Cont'd)

C89-H89	0.95	C70-C76	1.535(12)
C90-C91	1.375(19)	C70-C71	1.540(10)
C90-H90	0.95	C70-C75	1.591(11)
C91-C92	1.37(2)	C71-C72	1.532(11)
C91-H91	0.95	C71-H71	1.00
N1B-C16B	1.34(2)	C72-C73	1.546(12)
N1B-C23B	1.46(3)	C72-H72A	0.99
N1B-H1BN	0.88	C72-H72B	0.99
C12B-C17B	1.37(3)	C73-C74	1.527(10)
C12B-C13B	1.43(2)	C73-H73A	0.99
C12B-H12B	0.95	C73-H73B	0.99
C13B-C14B	1.37(3)	C74-C78	1.525(11)
C13B-H13B	0.95	C74-C75	1.543(10)
C14B-C15B	1.36(3)	C75-C79	1.519(11)
C14B-H14B	0.95	C75-H75	1.00
C15B-C18B	1.40(3)	C76-H76A	0.98
C15B-C16B	1.47(3)	C76-H76B	0.98
C16B-C17B	1.37(3)	C76-H76C	0.98
C17B-H17B	0.95	C77-H77A	0.99
C18B-C23B	1.35(3)	C77-H77B	0.99
C18B-C19B	1.42(3)	C78-H78A	0.98
C19B-C20B	1.39(3)	C78-H78B	0.98
C19B-H19B	0.95	C78-H78C	0.98
C20B-C21B	1.45(5)	C79-C80	1.536(13)
C20B-H20B	0.95	C79-H79A	0.99
C21B-C22B	1.41(4)	C79-H79B	0.99
C21B-C80	1.53(5)	C80-H80A	0.99
C22B-C23B	1.39(3)	C80-H80B	0.99
C22B-H22B	0.95	O9-C94	1.442(10)
C70-C77	1.522(11)	O9-C97	1.466(8)

Table 3.8 (Cont'd)

O10-C100	1.429(10)	C103-C104	1.53(2)
O10-H10O	0.84	C103-H10J	0.99
C93-C99	1.528(13)	C103-H10K	0.99
C93-C94	1.541(11)	N5-C108	1.398(16)
C93-C100	1.551(10)	N5-C115	1.394(17)
C93-C98	1.569(10)	N5-H5N	0.88
C94-C95	1.536(11)	C104-C109	1.38(2)
C94-H94	1.00	C104-C105	1.46(2)
C95-C96	1.556(12)	C105-C106	1.36(2)
C95-H95A	0.99	C105-H105	0.95
C95-H95B	0.99	C106-C107	1.381(17)
C96-C97	1.534(11)	C106-H106	0.95
C96-H96A	0.99	C107-C108	1.40(2)
C96-H96B	0.99	C107-C110	1.48(2)
C97-C101	1.515(11)	C108-C109	1.35(2)
C97-C98	1.559(11)	C109-H109	0.95
C98-C102	1.513(11)	C110-C111	1.40(2)
C98-H98	1.00	C110-C115	1.40(2)
C99-H99A	0.98	C111-C112	1.44(2)
C99-H99B	0.98	C111-H111	0.95
C99-H99C	0.98	C112-C113	1.43(2)
C100-H10A	0.99	C112-H112	0.95
C100-H10B	0.99	C113-C114	1.349(19)
C101-H10C	0.98	C113-H113	0.95
C101-H10D	0.98	C114-C115	1.38(2)
C101-H10E	0.98	C114-H114	0.95
C102-C103	1.547(11)	N1A-C23A	1.35(3)
C102-H10H	0.99	N1A-C16A	1.38(3)
C102-H10I	0.99	N1A-H1AN	0.88
C103-C12A	1.39(3)	C12A-C17A	1.40(4)

Table 3.8 (Cont'd)

C12A-C13A	1.49(3)	C117-C118	1.538(10)
C13A-C14A	1.41(3)	C117-H117	1.00
C13A-H13A	0.95	C118-C119	1.551(10)
C14A-C15A	1.38(3)	C118-H11A	0.99
C14A-H14A	0.95	C118-H11B	0.99
C15A-C18A	1.42(3)	C119-C120	1.543(11)
C15A-C16A	1.47(3)	C119-H11C	0.99
C16A-C17A	1.35(4)	C119-H11D	0.99
C17A-H17A	0.95	C120-C124	1.519(9)
C18A-C23A	1.41(3)	C120-C121	1.541(9)
C18A-C19A	1.44(4)	C121-C125	1.525(10)
C19A-C20A	1.24(4)	C121-H121	1.00
C19A-H19A	0.95	C122-H12Q	0.98
C20A-C21A	1.40(4)	C122-H12R	0.98
C20A-H20A	0.95	C122-H12S	0.98
C21A-C22A	1.45(3)	C123-H12D	0.99
C21A-H21A	0.95	C123-H12E	0.99
C22A-C23A	1.40(3)	C124-H12F	0.98
C22A-H22A	0.95	C124-H12G	0.98
O11-C117	1.455(9)	C124-H12H	0.98
O11-C120	1.460(10)	C125-C126	1.529(9)
O12-C123	1.421(8)	C125-H12I	0.99
O12-H12O	0.84	C125-H12J	0.99
N6-C131	1.352(12)	C126-C127	1.488(11)
N6-C138	1.397(12)	C126-H12K	0.99
N6-H6N	0.88	C126-H12L	0.99
C116-C123	1.543(10)	C127-C132	1.402(11)
C116-C122	1.545(10)	C127-C128	1.420(12)
C116-C117	1.546(10)	C128-C129	1.343(13)
C116-C121	1.582(9)	C128-H128	0.95

Table 3.8 (Cont'd)

C129-C130	1.343(13)	C153-C154	1.457(15)
C129-H129	0.95	C153-C156	1.478(17)
C130-C131	1.443(13)	C154-C155	1.324(17)
C130-C133	1.448(13)	C155-H155	0.95
C131-C132	1.417(13)	C156-C157	1.386(16)
C132-H132	0.95	C156-C161	1.403(17)
C133-C138	1.404(14)	C157-C158	1.435(17)
C133-C134	1.423(14)	C157-H157	0.95
C134-C135	1.350(15)	C158-C159	1.385(18)
C134-H134	0.95	C158-H158	0.95
C135-C136	1.414(17)	C159-C160	1.357(17)
C135-H135	0.95	C159-H159	0.95
C136-C137	1.411(16)	C160-C161	1.434(18)
C136-H136	0.95	C160-H160	0.95
C137-C138	1.356(15)	N1F-C16F	1.41(4)
C137-H137	0.95	N1F-C23F	1.43(5)
O13-C140	1.436(8)	N1F-H1FN	0.88
O13-C143	1.460(10)	C12F-C13F	1.31(5)
O14-C146	1.434(9)	C12F-C17F	1.38(6)
O14-H14O	0.84	C12F-C149	1.44(6)
N7-C161	1.349(14)	C13F-C14F	1.43(5)
N7-C154	1.379(14)	C13F-H13F	0.95
N7-H7N	0.88	C14F-C15F	1.49(5)
C150-C155	1.41(2)	C14F-H14F	0.95
C150-C151	1.445(17)	C15F-C16F	1.45(6)
C150-C149	1.51(2)	C15F-C18F	1.47(5)
C151-C152	1.360(17)	C16F-C17F	1.39(6)
C151-H151	0.95	C17F-H17F	0.95
C152-C153	1.370(16)	C18F-C23F	1.29(5)
C152-H152	0.95	C18F-C19F	1.34(6)

Table 3.8 (Cont'd)

C19F-C20F	1.35(6)	C147-H14K	0.98
C19F-H19F	0.95	C147-H14L	0.98
C20F-C21F	1.27(6)	C148-C149	1.557(10)
C20F-H20F	0.95	C148-H14M	0.99
C21F-C22F	1.56(6)	C148-H14N	0.99
C21F-H21F	0.95	C149-H201	0.99
C22F-C23F	1.38(5)	C149-H202	0.99
C22F-H22F	0.95	O15-C163	1.450(10)
C139-C145	1.518(10)	O15-C166	1.454(9)
C139-C146	1.529(11)	O16-C169	1.434(12)
C139-C140	1.560(10)	O16-H16O	0.84
C139-C144	1.586(9)	N8-C184	1.377(18)
C140-C141	1.521(11)	N8-C177	1.387(16)
C140-H140	1.00	N8-H8N	0.88
C141-C142	1.537(10)	C173-C178	1.40(3)
C141-H14T	0.99	C173-C174	1.44(2)
C141-H14X	0.99	C173-C172	1.45(2)
C142-C143	1.545(11)	C174-C175	1.338(17)
C142-H14Y	0.99	C174-H174	0.95
C142-H14Z	0.99	C175-C176	1.385(17)
C143-C147	1.500(9)	C175-H175	0.95
C143-C144	1.554(9)	C176-C179	1.378(19)
C144-C148	1.515(11)	C176-C177	1.47(2)
C144-H144	1.00	C177-C178	1.33(2)
C145-H14Q	0.98	C178-H178	0.95
C145-H14R	0.98	C179-C184	1.402(18)
C145-H14S	0.98	C179-C180	1.436(16)
C146-H14H	0.99	C180-C181	1.395(18)
C146-H14I	0.99	C180-H180	0.95
C147-H14J	0.98	C181-C182	1.36(2)

Table 3.8 (Cont'd)

C181-H181	0.95	C162-C168	1.504(14)
C182-C183	1.41(2)	C162-C163	1.519(11)
C182-H182	0.95	C162-C169	1.540(11)
C183-C184	1.40(2)	C162-C167	1.569(11)
C183-H183	0.95	C163-C164	1.530(11)
N1C-C16C	1.33(3)	C163-H163	1.00
N1C-C23C	1.34(3)	C164-C165	1.548(12)
N1C-H1CN	0.88	C164-H16A	0.99
C12C-C13C	1.45(6)	C164-H16B	0.99
C12C-C17C	1.45(5)	C165-C166	1.527(11)
C12C-C172	1.60(5)	C165-H16C	0.99
C13C-C14C	1.27(4)	C165-H16D	0.99
C13C-H13C	0.95	C166-C170	1.542(14)
C14C-C15C	1.36(3)	C166-C167	1.559(12)
C14C-H203	0.95	C167-C171	1.524(11)
C15C-C16C	1.43(4)	C167-H167	1.00
C15C-C18C	1.51(4)	C168-H16E	0.98
C16C-C17C	1.36(4)	C168-H16F	0.98
C17C-H17C	0.95	C168-H16G	0.98
C18C-C19C	1.38(4)	C169-H16H	0.99
C18C-C23C	1.41(4)	C169-H16I	0.99
C19C-C20C	1.41(4)	C170-H17X	0.98
C19C-H19C	0.95	C170-H17Y	0.98
C20C-C21C	1.40(4)	C170-H17Z	0.98
C20C-H20C	0.95	C171-C172	1.514(11)
C21C-C22C	1.34(4)	C171-H17G	0.99
C21C-H21C	0.95	C171-H17H	0.99
C22C-C23C	1.46(4)	C172-H17I	0.99
C22C-H22C	0.95	C172-H17J	0.99

Table 3.8 (Cont'd)

C2-O1-C5	95.8(6)	C19-C20-H20	120.2
C8-O2-H2O	109.5	C21-C20-H20	120.2
C16-N1-C23	109.0(12)	C22-C21-C20	118.9(13)
C16-N1-H1	125.5	C22-C21-H21	120.6
C23-N1-H1	125.5	C20-C21-H21	120.6
C13-C12-C17	118(3)	C23-C22-C21	120.4(13)
C13-C12-C11	116.3(17)	C23-C22-H22	119.8
C17-C12-C11	125(2)	C21-C22-H22	119.8
C12-C13-C14	126.1(19)	C22-C23-N1	130.5(16)
C12-C13-H13	116.9	C22-C23-C18	123.0(13)
C14-C13-H13	116.9	N1-C23-C18	106.6(14)
C15-C14-C13	115.8(12)	C16D-N1D-C23D	110.3(18)
C15-C14-H14	122.1	C16D-N1D-H1D	124.8
C13-C14-H14	122.1	C23D-N1D-H1D	124.8
C16-C15-C18	108.4(12)	C13D-C12D-C17D	130(5)
C16-C15-C14	121.1(13)	C13D-C12D-C11	93(3)
C18-C15-C14	130.5(11)	C17D-C12D-C11	136(3)
N1-C16-C15	110.2(12)	C12D-C13D-C14D	111(3)
N1-C16-C17	127.1(12)	C12D-C13D-H13D	124.5
C15-C16-C17	122.7(13)	C14D-C13D-H13D	124.6
C16-C17-C12	115.8(17)	C15D-C14D-C13D	126(2)
C16-C17-H17	122.1	C15D-C14D-H14D	117.0
C12-C17-H17	122.1	C13D-C14D-H14D	117.0
C19-C18-C15	140.5(13)	C14D-C15D-C16D	116(2)
C19-C18-C23	113.6(12)	C14D-C15D-C18D	136(2)
C15-C18-C23	105.8(12)	C16D-C15D-C18D	109(2)
C20-C19-C18	124.4(12)	C17D-C16D-N1D	126(2)
C20-C19-H19	117.8	C17D-C16D-C15D	125(2)
C18-C19-H19	117.8	N1D-C16D-C15D	109(2)
C19-C20-C21	119.7(12)	C16D-C17D-C12D	112(3)

Table 3.8 (Cont'd)

C16D-C17D-H17D	124.0	C3-C2-H2	112.7
C12D-C17D-H17D	124.0	C1-C2-H2	112.7
C19D-C18D-C15D	136(2)	C2-C3-C4	102.9(7)
C19D-C18D-C23D	118(2)	C2-C3-H3A	111.2
C15D-C18D-C23D	106(2)	C4-C3-H3A	111.2
C18D-C19D-C20D	120(2)	C2-C3-H3B	111.2
C18D-C19D-H19D	120.0	C4-C3-H3B	111.2
C20D-C19D-H19D	120.0	H3A-C3-H3B	109.1
C19D-C20D-C21D	120(2)	C3-C4-C5	100.7(7)
C19D-C20D-H20D	120.0	C3-C4-H4A	111.6
C21D-C20D-H20D	120.0	C5-C4-H4A	111.6
C22D-C21D-C20D	123(2)	C3-C4-H4B	111.6
C22D-C21D-H21D	118.6	C5-C4-H4B	111.6
C20D-C21D-H21D	118.5	H4A-C4-H4B	109.4
C21D-C22D-C23D	118(2)	O1-C5-C9	107.9(8)
C21D-C22D-H22D	121.1	O1-C5-C4	101.5(7)
C23D-C22D-H22D	121.1	C9-C5-C4	114.4(7)
C22D-C23D-N1D	132(2)	O1-C5-C6	103.8(6)
C22D-C23D-C18D	122(2)	C9-C5-C6	119.8(9)
N1D-C23D-C18D	106(2)	C4-C5-C6	107.3(7)
C7-C1-C2	115.9(8)	C10-C6-C5	116.8(7)
C7-C1-C8	109.1(7)	C10-C6-C1	115.5(7)
C2-C1-C8	108.1(6)	C5-C6-C1	100.7(6)
C7-C1-C6	111.2(7)	C10-C6-H6	107.8
C2-C1-C6	99.9(6)	C5-C6-H6	107.8
C8-C1-C6	112.5(6)	C1-C6-H6	107.8
O1-C2-C3	101.4(6)	C1-C7-H7A	109.5
O1-C2-C1	102.4(7)	C1-C7-H7B	109.5
C3-C2-C1	114.0(7)	H7A-C7-H7B	109.5
O1-C2-H2	112.7	C1-C7-H7C	109.5

Table 3.8 (Cont'd)

H7A-C7-H7C	109.5	C39-N2-H2N	125.9
H7B-C7-H7C	109.5	C46-N2-H2N	125.9
O2-C8-C1	111.1(7)	C30-C24-C31	109.2(6)
O2-C8-H8A	109.4	C30-C24-C25	114.0(6)
C1-C8-H8A	109.4	C31-C24-C25	108.2(5)
O2-C8-H8B	109.4	C30-C24-C29	113.6(5)
C1-C8-H8B	109.4	C31-C24-C29	111.6(6)
H8A-C8-H8B	108.0	C25-C24-C29	100.1(5)
C5-C9-H9A	109.5	O3-C25-C26	103.0(6)
C5-C9-H9B	109.5	O3-C25-C24	101.0(5)
H9A-C9-H9B	109.5	C26-C25-C24	114.1(5)
C5-C9-H9C	109.5	O3-C25-H25	112.6
H9A-C9-H9C	109.5	C26-C25-H25	112.6
H9B-C9-H9C	109.5	C24-C25-H25	112.6
C6-C10-C11	113.3(8)	C25-C26-C27	101.0(6)
C6-C10-H10F	108.9	C25-C26-H26A	111.6
C11-C10-H10F	108.9	C27-C26-H26A	111.6
C6-C10-H10G	108.9	C25-C26-H26B	111.6
C11-C10-H10G	108.9	C27-C26-H26B	111.6
H10F-C10-H10G	107.7	H26A-C26-H26B	109.4
C12-C11-C10	111.9(9)	C26-C27-C28	102.8(6)
C12D-C11-C10	116.6(10)	C26-C27-H27A	111.2
C12-C11-H11E	109.2	C28-C27-H27A	111.2
C10-C11-H11E	109.2	C26-C27-H27B	111.2
C12-C11-H11F	109.2	C28-C27-H27B	111.2
C10-C11-H11F	109.2	H27A-C27-H27B	109.1
H11E-C11-H11F	107.9	O3-C28-C32	107.8(6)
C25-O3-C28	96.3(5)	O3-C28-C27	99.9(6)
C31-O4-H4O	109.5	C32-C28-C27	116.0(7)
C39-N2-C46	108.1(6)	O3-C28-C29	102.5(5)

Table 3.8 (Cont'd)

C32-C28-C29	119.8(7)	C34-C33-H33B	108.9
C27-C28-C29	108.1(6)	H33A-C33-H33B	107.7
C33-C29-C28	115.7(6)	C35-C34-C33	113.1(6)
C33-C29-C24	118.0(6)	C35-C34-H34A	109.0
C28-C29-C24	102.0(5)	C33-C34-H34A	109.0
C33-C29-H29	106.8	C35-C34-H34B	109.0
C28-C29-H29	106.8	C33-C34-H34B	109.0
C24-C29-H29	106.8	H34A-C34-H34B	107.8
C24-C30-H30A	109.5	C40-C35-C36	119.3(7)
C24-C30-H30B	109.5	C40-C35-C34	120.5(7)
H30A-C30-H30B	109.5	C36-C35-C34	120.1(7)
C24-C30-H30C	109.5	C37-C36-C35	124.1(7)
H30A-C30-H30C	109.5	C37-C36-H36	118.0
H30B-C30-H30C	109.5	C35-C36-H36	118.0
O4-C31-C24	112.2(6)	C36-C37-C38	116.4(7)
O4-C31-H31A	109.2	C36-C37-H37	121.8
C24-C31-H31A	109.2	C38-C37-H37	121.8
O4-C31-H31B	109.2	C39-C38-C37	120.8(7)
C24-C31-H31B	109.2	C39-C38-C41	107.0(6)
H31A-C31-H31B	107.9	C37-C38-C41	132.1(6)
C28-C32-H32A	109.5	N2-C39-C38	109.8(7)
C28-C32-H32B	109.5	N2-C39-C40	128.7(7)
H32A-C32-H32B	109.5	C38-C39-C40	121.4(7)
C28-C32-H32C	109.5	C35-C40-C39	117.9(7)
H32A-C32-H32C	109.5	C35-C40-H40	121.0
H32B-C32-H32C	109.5	C39-C40-H40	121.0
C29-C33-C34	113.3(6)	C42-C41-C46	117.4(7)
C29-C33-H33A	108.9	C42-C41-C38	136.2(7)
C34-C33-H33A	108.9	C46-C41-C38	106.4(6)
C29-C33-H33B	108.9	C43-C42-C41	120.3(7)

Table 3.8 (Cont'd)

C43-C42-H42	119.8	C64-C61-C60	132.5(12)
C41-C42-H42	119.8	C61-C62-N3	108.7(11)
C42-C43-C44	121.0(8)	C61-C62-C63	125.2(11)
C42-C43-H43	119.5	N3-C62-C63	126.1(11)
C44-C43-H43	119.5	C58-C63-C62	114.5(14)
C45-C44-C43	119.9(8)	C58-C63-H63	122.7
C45-C44-H44	120.1	C62-C63-H63	122.7
C43-C44-H44	120.1	C65-C64-C61	138.7(13)
C46-C45-C44	119.1(8)	C65-C64-C69	116.6(11)
C46-C45-H45	120.5	C61-C64-C69	104.8(12)
C44-C45-H45	120.5	C66-C65-C64	123.2(12)
C45-C46-N2	129.0(7)	C66-C65-H65	118.4
C45-C46-C41	122.2(7)	C64-C65-H65	118.4
N2-C46-C41	108.6(7)	C65-C66-C67	121.7(13)
C51-O5-C48	96.6(5)	C65-C66-H66	119.1
C54-O6-H6O	109.5	C67-C66-H66	119.1
C69-N3-C62	108.5(10)	C66-C67-C68	117.1(14)
C69-N3-H3N	125.8	C66-C67-H67	121.5
C62-N3-H3N	125.8	C68-C67-H67	121.5
C63-C58-C59	122.2(19)	C69-C68-C67	121.1(14)
C63-C58-C57	120.9(14)	C69-C68-H68	119.5
C59-C58-C57	116.0(11)	C67-C68-H68	119.5
C60-C59-C58	121.5(13)	N3-C69-C68	130.7(13)
C60-C59-H59	119.2	N3-C69-C64	109.0(11)
C58-C59-H59	119.2	C68-C69-C64	120.3(12)
C59-C60-C61	118.1(11)	C16E-N1E-C23E	108(2)
C59-C60-H60	120.9	C16E-N1E-H1EN	126.1
C61-C60-H60	120.9	C23E-N1E-H1EN	126.1
C62-C61-C64	109.1(11)	C17E-C12E-C13E	124(4)
C62-C61-C60	118.4(11)	C17E-C12E-C57	125(2)

Table 3.8 (Cont'd)

C13E-C12E-C57	110(3)	C23E-C22E-H22E	117.7
C14E-C13E-C12E	119(3)	C18E-C23E-C22E	119(3)
C14E-C13E-H13E	120.6	C18E-C23E-N1E	108(3)
C12E-C13E-H13E	120.6	C22E-C23E-N1E	133(3)
C13E-C14E-C15E	124(2)	C54-C47-C48	108.0(6)
C13E-C14E-H14E	117.8	C54-C47-C53	109.3(7)
C15E-C14E-H14E	117.9	C48-C47-C53	114.3(7)
C18E-C15E-C14E	138(2)	C54-C47-C52	111.7(6)
C18E-C15E-C16E	106(2)	C48-C47-C52	100.2(6)
C14E-C15E-C16E	115(2)	C53-C47-C52	113.0(6)
N1E-C16E-C15E	110(2)	O5-C48-C47	101.6(6)
N1E-C16E-C17E	127(3)	O5-C48-C49	101.9(6)
C15E-C16E-C17E	122(3)	C47-C48-C49	113.6(6)
C12E-C17E-C16E	115(3)	O5-C48-H48	112.9
C12E-C17E-H17E	122.7	C47-C48-H48	112.9
C16E-C17E-H17E	122.7	C49-C48-H48	112.9
C19E-C18E-C23E	121(3)	C48-C49-C50	101.4(6)
C19E-C18E-C15E	131(3)	C48-C49-H49A	111.5
C23E-C18E-C15E	108(3)	C50-C49-H49A	111.5
C18E-C19E-C20E	118(3)	C48-C49-H49B	111.5
C18E-C19E-H19E	121.1	C50-C49-H49B	111.5
C20E-C19E-H19E	121.2	H49A-C49-H49B	109.3
C19E-C20E-C21E	121(3)	C51-C50-C49	102.2(6)
C19E-C20E-H20E	119.7	C51-C50-H50A	111.3
C21E-C20E-H20E	119.7	C49-C50-H50A	111.3
C22E-C21E-C20E	116(3)	C51-C50-H50B	111.3
C22E-C21E-H21E	121.8	C49-C50-H50B	111.3
C20E-C21E-H21E	121.8	H50A-C50-H50B	109.2
C21E-C22E-C23E	125(3)	O5-C51-C55	108.3(6)
C21E-C22E-H22E	117.7	O5-C51-C50	101.1(6)

Table 3.8 (Cont'd)

C55-C51-C50	115.9(7)	C57-C56-H56A	108.7
O5-C51-C52	103.0(6)	C52-C56-H56B	108.8
C55-C51-C52	118.7(7)	C57-C56-H56B	108.8
C50-C51-C52	107.5(6)	H56A-C56-H56B	107.6
C56-C52-C51	115.7(6)	C58-C57-C56	111.5(7)
C56-C52-C47	118.1(6)	C56-C57-C12E	112.4(8)
C51-C52-C47	101.3(6)	C58-C57-H57A	109.3
C56-C52-H52	107.0	C56-C57-H57A	109.3
C51-C52-H52	107.0	C58-C57-H57B	109.3
C47-C52-H52	107.0	C56-C57-H57B	109.3
C47-C53-H53A	109.5	H57A-C57-H57B	108.0
C47-C53-H53B	109.5	C71-O7-C74	96.0(5)
H53A-C53-H53B	109.5	C77-O8-H8O	109.5
C47-C53-H53C	109.5	C85-N4-C92	108.5(11)
H53A-C53-H53C	109.5	C85-N4-H4N	125.8
H53B-C53-H53C	109.5	C92-N4-H4N	125.8
O6-C54-C47	111.6(6)	C86-C81-C82	121(2)
O6-C54-H54A	109.3	C86-C81-C80	131.1(17)
C47-C54-H54A	109.3	C82-C81-C80	107(2)
O6-C54-H54B	109.3	C83-C82-C81	122.8(19)
C47-C54-H54B	109.3	C83-C82-H82	118.6
H54A-C54-H54B	108.0	C81-C82-H82	118.6
C51-C55-H55A	109.5	C82-C83-C84	116.9(12)
C51-C55-H55B	109.5	C82-C83-H83	121.6
H55A-C55-H55B	109.5	C84-C83-H83	121.6
C51-C55-H55C	109.5	C87-C84-C85	107.1(12)
H55A-C55-H55C	109.5	C87-C84-C83	135.0(12)
H55B-C55-H55C	109.5	C85-C84-C83	117.8(12)
C52-C56-C57	114.0(6)	N4-C85-C86	127.4(14)
C52-C56-H56A	108.8	N4-C85-C84	108.9(12)

Table 3.8 (Cont'd)

C86-C85-C84	123.7(14)	C12B-C13B-H13B	119.9
C81-C86-C85	117.4(18)	C15B-C14B-C13B	122(2)
C81-C86-H86	121.3	C15B-C14B-H14B	118.9
C85-C86-H86	121.3	C13B-C14B-H14B	118.9
C88-C87-C84	133.9(13)	C14B-C15B-C18B	137(2)
C88-C87-C92	118.4(12)	C14B-C15B-C16B	117.6(19)
C84-C87-C92	107.7(13)	C18B-C15B-C16B	105(2)
C87-C88-C89	120.0(12)	N1B-C16B-C17B	133(2)
C87-C88-H88	120.0	N1B-C16B-C15B	107(2)
C89-C88-H88	120.0	C17B-C16B-C15B	119.7(18)
C88-C89-C90	120.1(12)	C12B-C17B-C16B	121.5(19)
C88-C89-H89	119.9	C12B-C17B-H17B	119.2
C90-C89-H89	119.9	C16B-C17B-H17B	119.2
C91-C90-C89	120.3(13)	C23B-C18B-C15B	111.9(19)
C91-C90-H90	119.9	C23B-C18B-C19B	116(2)
C89-C90-H90	119.9	C15B-C18B-C19B	131.6(18)
C92-C91-C90	119.2(13)	C20B-C19B-C18B	116.4(19)
C92-C91-H91	120.4	C20B-C19B-H19B	121.8
C90-C91-H91	120.4	C18B-C19B-H19B	121.8
C91-C92-N4	130.3(14)	C19B-C20B-C21B	125(3)
C91-C92-C87	122.0(12)	C19B-C20B-H20B	117.6
N4-C92-C87	107.7(13)	C21B-C20B-H20B	117.6
C16B-N1B-C23B	110.0(18)	C22B-C21B-C20B	118(4)
C16B-N1B-H1BN	125.0	C22B-C21B-C80	138(3)
C23B-N1B-H1BN	125.0	C20B-C21B-C80	104(2)
C17B-C12B-C13B	118.7(19)	C23B-C22B-C21B	113(3)
C17B-C12B-H12B	120.6	C23B-C22B-H22B	123.5
C13B-C12B-H12B	120.6	C21B-C22B-H22B	123.5
C14B-C13B-C12B	120(2)	C18B-C23B-C22B	131(2)
C14B-C13B-H13B	119.9	C18B-C23B-N1B	105.5(19)

Table 3.8 (Cont'd)

C22B-C23B-N1B	123(2)	C73-C74-C75	108.5(7)
C77-C70-C76	109.1(7)	C79-C75-C74	117.4(7)
C77-C70-C71	107.9(6)	C79-C75-C70	116.0(7)
C76-C70-C71	115.4(8)	C74-C75-C70	101.0(6)
C77-C70-C75	112.6(7)	C79-C75-H75	107.2
C76-C70-C75	112.3(7)	C74-C75-H75	107.2
C71-C70-C75	99.2(6)	C70-C75-H75	107.2
O7-C71-C72	101.9(6)	C70-C76-H76A	109.5
O7-C71-C70	102.1(6)	C70-C76-H76B	109.5
C72-C71-C70	114.0(7)	H76A-C76-H76B	109.5
O7-C71-H71	112.6	C70-C76-H76C	109.5
C72-C71-H71	112.6	H76A-C76-H76C	109.5
C70-C71-H71	112.6	H76B-C76-H76C	109.5
C71-C72-C73	101.1(6)	O8-C77-C70	111.3(7)
C71-C72-H72A	111.6	O8-C77-H77A	109.4
C73-C72-H72A	111.6	C70-C77-H77A	109.4
C71-C72-H72B	111.6	O8-C77-H77B	109.4
C73-C72-H72B	111.5	C70-C77-H77B	109.4
H72A-C72-H72B	109.4	H77A-C77-H77B	108.0
C74-C73-C72	101.6(6)	C74-C78-H78A	109.5
C74-C73-H73A	111.5	C74-C78-H78B	109.5
C72-C73-H73A	111.5	H78A-C78-H78B	109.5
C74-C73-H73B	111.5	C74-C78-H78C	109.5
C72-C73-H73B	111.5	H78A-C78-H78C	109.5
H73A-C73-H73B	109.3	H78B-C78-H78C	109.5
O7-C74-C78	109.1(7)	C75-C79-C80	113.1(7)
O7-C74-C73	100.9(6)	C75-C79-H79A	109.0
C78-C74-C73	113.2(7)	C80-C79-H79A	109.0
O7-C74-C75	104.5(5)	C75-C79-H79B	109.0
C78-C74-C75	118.8(7)	C80-C79-H79B	109.0

Table 3.8 (Cont'd)

H79A-C79-H79B	107.8	C95-C96-H96A	111.4
C81-C80-C79	116.6(8)	C97-C96-H96B	111.4
C21B-C80-C79	114.9(9)	C95-C96-H96B	111.4
C81-C80-H80A	108.1	H96A-C96-H96B	109.2
C79-C80-H80A	108.1	O9-C97-C101	109.0(6)
C81-C80-H80B	108.2	O9-C97-C96	100.2(6)
C79-C80-H80B	108.2	C101-C97-C96	114.1(7)
H80A-C80-H80B	107.3	O9-C97-C98	102.7(6)
C94-O9-C97	97.5(5)	C101-C97-C98	120.4(7)
C100-O10-H10O	109.5	C96-C97-C98	108.0(6)
C99-C93-C94	115.6(8)	C102-C98-C97	116.5(6)
C99-C93-C100	107.4(7)	C102-C98-C93	116.7(6)
C94-C93-C100	107.1(6)	C97-C98-C93	101.6(6)
C99-C93-C98	113.5(6)	C102-C98-H98	107.1
C94-C93-C98	100.9(6)	C97-C98-H98	107.1
C100-C93-C98	112.2(6)	C93-C98-H98	107.1
O9-C94-C95	102.4(7)	C93-C99-H99A	109.5
O9-C94-C93	100.7(6)	C93-C99-H99B	109.5
C95-C94-C93	112.0(6)	H99A-C99-H99B	109.5
O9-C94-H94	113.5	C93-C99-H99C	109.5
C95-C94-H94	113.5	H99A-C99-H99C	109.5
C93-C94-H94	113.5	H99B-C99-H99C	109.5
C94-C95-C96	101.6(6)	O10-C100-C93	111.8(7)
C94-C95-H95A	111.5	O10-C100-H10A	109.2
C96-C95-H95A	111.5	C93-C100-H10A	109.2
C94-C95-H95B	111.5	O10-C100-H10B	109.2
C96-C95-H95B	111.5	C93-C100-H10B	109.2
H95A-C95-H95B	109.3	H10A-C100-H10B	107.9
C97-C96-C95	102.1(6)	C97-C101-H10C	109.5
C97-C96-H96A	111.4	C97-C101-H10D	109.5

Table 3.8 (Cont'd)

H10C-C101-H10D	109.5	C106-C107-C110	136.4(13)
C97-C101-H10E	109.5	C108-C107-C110	105.0(13)
H10C-C101-H10E	109.5	C109-C108-N5	125.1(14)
H10D-C101-H10E	109.5	C109-C108-C107	125.1(13)
C98-C102-C103	113.3(6)	N5-C108-C107	109.9(14)
C98-C102-H10H	108.9	C108-C109-C104	116.3(15)
C103-C102-H10H	108.9	C108-C109-H109	121.9
C98-C102-H10I	108.9	C104-C109-H109	121.8
C103-C102-H10I	108.9	C111-C110-C115	121.7(13)
H10H-C102-H10I	107.7	C111-C110-C107	130.4(16)
C12A-C103-C102	118.2(8)	C115-C110-C107	107.9(15)
C104-C103-C102	113.0(7)	C110-C111-C112	115.8(15)
C104-C103-H10J	109.0	C110-C111-H111	122.1
C102-C103-H10J	109.0	C112-C111-H111	122.1
C104-C103-H10K	109.0	C113-C112-C111	119.8(16)
C102-C103-H10K	109.0	C113-C112-H112	120.1
H10J-C103-H10K	107.8	C111-C112-H112	120.1
C108-N5-C115	109.3(12)	C114-C113-C112	122.4(15)
C108-N5-H5N	125.3	C114-C113-H113	118.8
C115-N5-H5N	125.3	C112-C113-H113	118.8
C109-C104-C105	120.6(16)	C113-C114-C115	118.2(14)
C109-C104-C103	130.4(15)	C113-C114-H114	120.9
C105-C104-C103	108.9(13)	C115-C114-H114	120.9
C106-C105-C104	120.0(14)	C114-C115-N5	129.9(15)
C106-C105-H105	120.0	C114-C115-C110	122.2(13)
C104-C105-H105	120.0	N5-C115-C110	108.0(14)
C105-C106-C107	119.5(13)	C23A-N1A-C16A	111(2)
C105-C106-H106	120.2	C23A-N1A-H1AN	124.7
C107-C106-H106	120.2	C16A-N1A-H1AN	124.7
C106-C107-C108	118.6(14)	C103-C12A-C17A	139(2)

Table 3.8 (Cont'd)

C103-C12A-C13A	109.7(19)	C23A-C22A-H22A	122.3
C17A-C12A-C13A	112(2)	C21A-C22A-H22A	122.3
C14A-C13A-C12A	129(2)	N1A-C23A-C22A	129(2)
C14A-C13A-H13A	115.7	N1A-C23A-C18A	112(2)
C12A-C13A-H13A	115.7	C22A-C23A-C18A	119(2)
C15A-C14A-C13A	114(2)	C117-O11-C120	96.7(5)
C15A-C14A-H14A	122.8	C123-O12-H12O	109.5
C13A-C14A-H14A	122.8	C131-N6-C138	108.9(8)
C14A-C15A-C18A	131(2)	C131-N6-H6N	125.5
C14A-C15A-C16A	120(2)	C138-N6-H6N	125.5
C18A-C15A-C16A	109(2)	C123-C116-C122	110.0(6)
C17A-C16A-N1A	133(3)	C123-C116-C117	107.1(6)
C17A-C16A-C15A	123(2)	C122-C116-C117	113.6(6)
N1A-C16A-C15A	105(2)	C123-C116-C121	112.5(6)
C16A-C17A-C12A	123(3)	C122-C116-C121	112.4(6)
C16A-C17A-H17A	118.5	C117-C116-C121	100.9(5)
C12A-C17A-H17A	118.5	O11-C117-C118	101.2(5)
C23A-C18A-C15A	104(2)	O11-C117-C116	100.6(5)
C23A-C18A-C19A	122(2)	C118-C117-C116	112.4(6)
C15A-C18A-C19A	134(3)	O11-C117-H117	113.8
C20A-C19A-C18A	117(2)	C118-C117-H117	113.8
C20A-C19A-H19A	121.4	C116-C117-H117	113.8
C18A-C19A-H19A	121.4	C117-C118-C119	102.8(6)
C19A-C20A-C21A	126(3)	C117-C118-H11A	111.2
C19A-C20A-H20A	117.2	C119-C118-H11A	111.2
C21A-C20A-H20A	117.2	C117-C118-H11B	111.2
C20A-C21A-C22A	120(3)	C119-C118-H11B	111.2
C20A-C21A-H21A	119.9	H11A-C118-H11B	109.1
C22A-C21A-H21A	119.9	C120-C119-C118	100.7(6)
C23A-C22A-C21A	115(2)	C120-C119-H11C	111.6

Table 3.8 (Cont'd)

C118-C119-H11C	111.6	H12F-C124-H12G	109.5
C120-C119-H11D	111.6	C120-C124-H12H	109.5
C118-C119-H11D	111.6	H12F-C124-H12H	109.5
H11C-C119-H11D	109.4	H12G-C124-H12H	109.5
O11-C120-C124	106.9(6)	C121-C125-C126	113.1(6)
O11-C120-C121	104.4(5)	C121-C125-H12I	108.9
C124-C120-C121	118.7(6)	C126-C125-H12I	108.9
O11-C120-C119	100.7(6)	C121-C125-H12J	109.0
C124-C120-C119	115.0(6)	C126-C125-H12J	108.9
C121-C120-C119	108.9(6)	H12I-C125-H12J	107.8
C125-C121-C120	116.2(5)	C127-C126-C125	113.5(6)
C125-C121-C116	118.1(6)	C127-C126-H12K	108.9
C120-C121-C116	100.9(5)	C125-C126-H12K	108.9
C125-C121-H121	107.0	C127-C126-H12L	108.9
C120-C121-H121	107.0	C125-C126-H12L	108.9
C116-C121-H121	107.0	H12K-C126-H12L	107.7
C116-C122-H12Q	109.5	C132-C127-C128	118.3(8)
C116-C122-H12R	109.5	C132-C127-C126	122.6(8)
H12Q-C122-H12R	109.5	C128-C127-C126	119.1(8)
C116-C122-H12S	109.5	C129-C128-C127	122.5(9)
H12Q-C122-H12S	109.5	C129-C128-H128	118.8
H12R-C122-H12S	109.5	C127-C128-H128	118.8
O12-C123-C116	111.9(6)	C128-C129-C130	121.9(9)
O12-C123-H12D	109.2	C128-C129-H129	119.1
C116-C123-H12D	109.2	C130-C129-H129	119.1
O12-C123-H12E	109.2	C129-C130-C131	118.5(8)
C116-C123-H12E	109.2	C129-C130-C133	136.5(8)
H12D-C123-H12E	107.9	C131-C130-C133	105.0(8)
C120-C124-H12F	109.5	N6-C131-C132	129.4(9)
C120-C124-H12G	109.5	N6-C131-C130	109.9(8)

Table 3.8 (Cont'd)

C132-C131-C130	120.7(8)	C152-C151-C150	122.5(12)
C127-C132-C131	118.2(8)	C152-C151-H151	118.8
C127-C132-H132	120.9	C150-C151-H151	118.8
C131-C132-H132	120.9	C151-C152-C153	119.5(11)
C138-C133-C134	118.2(9)	C151-C152-H152	120.3
C138-C133-C130	107.2(8)	C153-C152-H152	120.3
C134-C133-C130	134.6(9)	C152-C153-C154	119.4(11)
C135-C134-C133	119.2(10)	C152-C153-C156	135.3(11)
C135-C134-H134	120.4	C154-C153-C156	105.3(10)
C133-C134-H134	120.4	C155-C154-N7	131.0(11)
C134-C135-C136	120.9(10)	C155-C154-C153	120.2(11)
C134-C135-H135	119.5	N7-C154-C153	108.8(11)
C136-C135-H135	119.5	C154-C155-C150	122.2(12)
C137-C136-C135	121.3(10)	C154-C155-H155	118.9
C137-C136-H136	119.4	C150-C155-H155	118.9
C135-C136-H136	119.4	C157-C156-C161	121.8(11)
C138-C137-C136	116.3(10)	C157-C156-C153	133.6(13)
C138-C137-H137	121.8	C161-C156-C153	104.5(12)
C136-C137-H137	121.8	C156-C157-C158	117.4(11)
C137-C138-N6	126.9(10)	C156-C157-H157	121.3
C137-C138-C133	124.1(9)	C158-C157-H157	121.3
N6-C138-C133	109.0(9)	C159-C158-C157	120.3(11)
C140-O13-C143	96.9(5)	C159-C158-H158	119.8
C146-O14-H14O	109.5	C157-C158-H158	119.8
C161-N7-C154	108.6(11)	C160-C159-C158	122.5(12)
C161-N7-H7N	125.7	C160-C159-H159	118.8
C154-N7-H7N	125.7	C158-C159-H159	118.7
C155-C150-C151	116.1(14)	C159-C160-C161	118.5(12)
C155-C150-C149	125.1(10)	C159-C160-H160	120.7
C151-C150-C149	118.0(12)	C161-C160-H160	120.7

Table 3.8 (Cont'd)

N7-C161-C156	112.9(14)	C21F-C20F-C19F	117(4)
N7-C161-C160	127.7(14)	C21F-C20F-H20F	121.3
C156-C161-C160	119.4(10)	C19F-C20F-H20F	121.3
C16F-N1F-C23F	109(3)	C20F-C21F-C22F	125(4)
C16F-N1F-H1FN	125.7	C20F-C21F-H21F	117.7
C23F-N1F-H1FN	125.7	C22F-C21F-H21F	117.7
C13F-C12F-C17F	112(5)	C23F-C22F-C21F	111(3)
C13F-C12F-C149	119(3)	C23F-C22F-H22F	124.7
C17F-C12F-C149	129(3)	C21F-C22F-H22F	124.6
C12F-C13F-C14F	144(3)	C18F-C23F-C22F	122(4)
C12F-C13F-H13F	107.9	C18F-C23F-N1F	109(4)
C14F-C13F-H13F	107.8	C22F-C23F-N1F	129(4)
C13F-C14F-C15F	98(3)	C145-C139-C146	109.6(6)
C13F-C14F-H14F	131.2	C145-C139-C140	113.9(7)
C15F-C14F-H14F	131.2	C146-C139-C140	106.3(6)
C16F-C15F-C18F	104(4)	C145-C139-C144	113.6(6)
C16F-C15F-C14F	127(4)	C146-C139-C144	112.7(6)
C18F-C15F-C14F	129(4)	C140-C139-C144	100.3(5)
C17F-C16F-N1F	133(4)	O13-C140-C141	102.7(6)
C17F-C16F-C15F	120(4)	O13-C140-C139	101.1(6)
N1F-C16F-C15F	107(3)	C141-C140-C139	112.5(6)
C16F-C17F-C12F	119(4)	O13-C140-H140	113.1
C16F-C17F-H17F	120.5	C141-C140-H140	113.1
C12F-C17F-H17F	120.5	C139-C140-H140	113.1
C23F-C18F-C19F	124(4)	C140-C141-C142	101.7(6)
C23F-C18F-C15F	112(4)	C140-C141-H14T	111.4
C19F-C18F-C15F	124(4)	C142-C141-H14T	111.4
C18F-C19F-C20F	122(4)	C140-C141-H14X	111.4
C18F-C19F-H19F	119.1	C142-C141-H14X	111.4
C20F-C19F-H19F	119.1	H14T-C141-H14X	109.3

Table 3.8 (Cont'd)

C141-C142-C143	102.0(6)	C143-C147-H14J	109.5
C141-C142-H14Y	111.4	C143-C147-H14K	109.5
C143-C142-H14Y	111.4	H14J-C147-H14K	109.5
C141-C142-H14Z	111.4	C143-C147-H14L	109.5
C143-C142-H14Z	111.4	H14J-C147-H14L	109.5
H14Y-C142-H14Z	109.2	H14K-C147-H14L	109.5
O13-C143-C147	109.1(6)	C144-C148-C149	113.8(6)
O13-C143-C142	100.4(6)	C144-C148-H14M	108.8
C147-C143-C142	114.9(6)	C149-C148-H14M	108.8
O13-C143-C144	103.7(5)	C144-C148-H14N	108.8
C147-C143-C144	118.4(7)	C149-C148-H14N	108.8
C142-C143-C144	108.1(6)	H14M-C148-H14N	107.7
C148-C144-C143	117.0(6)	C12F-C149-C148	115.4(8)
C148-C144-C139	117.6(6)	C150-C149-C148	111.3(6)
C143-C144-C139	100.8(6)	C150-C149-H201	109.4
C148-C144-H144	106.9	C148-C149-H201	109.4
C143-C144-H144	106.9	C150-C149-H202	109.4
C139-C144-H144	106.9	C148-C149-H202	109.4
C139-C145-H14Q	109.5	H201-C149-H202	108.0
C139-C145-H14R	109.5	C163-O15-C166	95.2(5)
H14Q-C145-H14R	109.5	C169-O16-H16O	109.5
C139-C145-H14S	109.5	C184-N8-C177	110.7(11)
H14Q-C145-H14S	109.5	C184-N8-H8N	124.7
H14R-C145-H14S	109.5	C177-N8-H8N	124.7
O14-C146-C139	112.2(7)	C178-C173-C174	118.1(17)
O14-C146-H14H	109.2	C178-C173-C172	126.4(16)
C139-C146-H14H	109.2	C174-C173-C172	115.4(18)
O14-C146-H14I	109.2	C175-C174-C173	120.6(15)
C139-C146-H14I	109.2	C175-C174-H174	119.7
H14H-C146-H14I	107.9	C173-C174-H174	119.7

Table 3.8 (Cont'd)

C174-C175-C176	123.4(13)	C16C-N1C-C23C	109(3)
C174-C175-H175	118.3	C16C-N1C-H1CN	125.4
C176-C175-H175	118.3	C23C-N1C-H1CN	125.4
C179-C176-C175	138.0(13)	C13C-C12C-C17C	116(4)
C179-C176-C177	107.0(12)	C13C-C12C-C172	98(3)
C175-C176-C177	115.0(12)	C17C-C12C-C172	146(4)
C178-C177-N8	132.0(15)	C14C-C13C-C12C	124(3)
C178-C177-C176	122.6(13)	C14C-C13C-H13C	118.0
N8-C177-C176	105.4(12)	C12C-C13C-H13C	118.0
C177-C178-C173	120.2(16)	C13C-C14C-C15C	118(3)
C177-C178-H178	119.9	C13C-C14C-H203	120.9
C173-C178-H178	119.9	C15C-C14C-H203	120.9
C176-C179-C184	109.3(13)	C14C-C15C-C16C	125(3)
C176-C179-C180	131.8(12)	C14C-C15C-C18C	132(2)
C184-C179-C180	118.9(12)	C16C-C15C-C18C	103(2)
C181-C180-C179	117.0(12)	N1C-C16C-C17C	131(3)
C181-C180-H180	121.5	N1C-C16C-C15C	111(3)
C179-C180-H180	121.5	C17C-C16C-C15C	116(3)
C182-C181-C180	122.4(13)	C16C-C17C-C12C	120(3)
C182-C181-H181	118.8	C16C-C17C-H17C	119.9
C180-C181-H181	118.8	C12C-C17C-H17C	119.9
C181-C182-C183	122.6(12)	C19C-C18C-C23C	121(3)
C181-C182-H182	118.7	C19C-C18C-C15C	135(3)
C183-C182-H182	118.7	C23C-C18C-C15C	104(2)
C184-C183-C182	115.3(13)	C18C-C19C-C20C	120(3)
C184-C183-H183	122.3	C18C-C19C-H19C	119.9
C182-C183-H183	122.3	C20C-C19C-H19C	119.9
N8-C184-C183	128.6(13)	C21C-C20C-C19C	118(3)
N8-C184-C179	107.6(12)	C21C-C20C-H20C	121.0
C183-C184-C179	123.7(14)	C19C-C20C-H20C	121.0

Table 3.8 (Cont'd)

C22C-C21C-C20C	124(3)	C166-C165-H16D	111.5
C22C-C21C-H21C	118.1	C164-C165-H16D	111.5
C20C-C21C-H21C	118.1	H16C-C165-H16D	109.4
C21C-C22C-C23C	119(3)	O15-C166-C165	100.9(6)
C21C-C22C-H22C	120.4	O15-C166-C170	107.7(7)
C23C-C22C-H22C	120.4	C165-C166-C170	113.0(8)
N1C-C23C-C18C	112(3)	O15-C166-C167	103.4(6)
N1C-C23C-C22C	130(3)	C165-C166-C167	109.5(7)
C18C-C23C-C22C	117(2)	C170-C166-C167	120.0(7)
C168-C162-C163	115.8(8)	C171-C167-C166	115.5(7)
C168-C162-C169	107.7(8)	C171-C167-C162	117.5(7)
C163-C162-C169	109.4(6)	C166-C167-C162	101.2(6)
C168-C162-C167	112.6(7)	C171-C167-H167	107.3
C163-C162-C167	99.8(7)	C166-C167-H167	107.3
C169-C162-C167	111.5(7)	C162-C167-H167	107.3
O15-C163-C162	102.4(6)	C162-C168-H16E	109.5
O15-C163-C164	102.2(6)	C162-C168-H16F	109.5
C162-C163-C164	114.1(6)	H16E-C168-H16F	109.5
O15-C163-H163	112.4	C162-C168-H16G	109.5
C162-C163-H163	112.4	H16E-C168-H16G	109.5
C164-C163-H163	112.4	H16F-C168-H16G	109.5
C163-C164-C165	101.3(6)	O16-C169-C162	111.0(8)
C163-C164-H16A	111.5	O16-C169-H16H	109.4
C165-C164-H16A	111.5	C162-C169-H16H	109.4
C163-C164-H16B	111.5	O16-C169-H16I	109.4
C165-C164-H16B	111.5	C162-C169-H16I	109.4
H16A-C164-H16B	109.3	H16H-C169-H16I	108.0
C166-C165-C164	101.1(7)	C166-C170-H17X	109.5
C166-C165-H16C	111.5	C166-C170-H17Y	109.5
C164-C165-H16C	111.5	H17X-C170-H17Y	109.5

Table 3.8 (Cont'd)

C166-C170-H17Z	109.5	H17G-C171-H17H	107.7
H17X-C170-H17Z	109.5	C173-C172-C171	115.7(12)
H17Y-C170-H17Z	109.5	C171-C172-C12C	114.2(19)
C172-C171-C167	113.4(7)	C173-C172-H17I	108.4
C172-C171-H17G	108.9	C171-C172-H17I	108.4
C167-C171-H17G	108.9	C173-C172-H17J	108.4
C172-C171-H17H	108.9	C171-C172-H17J	108.4
C167-C171-H17H	108.9	H17I-C172-H17J	107.4

Table 3.9 Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **3.11**. 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}
O1	33(3)	28(3)	77(4)	-12(2)	-19(2)	-4(2)
O2	28(2)	30(3)	65(4)	-17(2)	-2(2)	-3(2)
N1	23(3)	32(4)	40(4)	-6(3)	-5(3)	-4(3)
C12	36(3)	28(3)	43(3)	-10(3)	-9(2)	2(2)
C13	34(4)	27(4)	43(5)	-11(3)	-3(4)	5(3)
C14	23(4)	24(4)	40(4)	-8(3)	-4(3)	1(3)
C15	19(3)	19(3)	38(3)	-11(3)	-5(3)	1(3)
C16	24(4)	22(4)	37(4)	-11(3)	-6(3)	0(3)
C17	32(4)	24(4)	42(4)	-10(3)	-12(3)	3(3)
C18	22(4)	20(3)	38(4)	-14(3)	-3(3)	1(3)
C19	18(4)	22(4)	35(4)	-13(3)	-4(3)	7(3)
C20	27(4)	21(4)	37(4)	-14(3)	0(4)	-1(4)
C21	31(4)	26(4)	44(4)	-11(3)	0(4)	0(4)
C22	25(4)	26(4)	42(4)	-11(3)	-3(4)	3(3)
C23	26(4)	27(4)	41(4)	-9(3)	-4(3)	1(3)
N1D	24(4)	26(5)	37(4)	-10(4)	0(3)	-9(4)
C12D	36(3)	28(3)	43(3)	-10(3)	-9(2)	2(2)
C13D	37(5)	24(5)	39(5)	-14(4)	-11(4)	7(4)
C14D	28(5)	21(5)	38(5)	-14(4)	-8(4)	1(4)
C15D	25(4)	23(4)	37(4)	-9(3)	-5(3)	-4(4)
C16D	24(4)	21(4)	38(4)	-9(3)	-3(3)	0(4)
C17D	28(5)	24(5)	37(5)	-12(4)	-2(4)	-2(4)
C18D	22(4)	25(4)	37(4)	-10(3)	-1(3)	-1(4)
C19D	22(5)	23(5)	37(5)	-5(4)	-1(4)	2(4)
C20D	24(5)	27(5)	40(5)	-9(4)	-1(4)	6(4)
C21D	24(5)	29(5)	37(5)	-11(4)	-1(4)	5(4)
C22D	24(5)	22(5)	35(5)	-13(4)	0(4)	3(4)
C23D	20(4)	23(4)	36(4)	-11(3)	-2(3)	4(4)

Table 3.9 (Cont'd)

C1	26(3)	32(3)	42(4)	-13(3)	-9(3)	4(2)
C2	31(3)	30(3)	54(4)	-14(3)	-11(3)	1(3)
C3	69(6)	35(4)	52(4)	-14(3)	-23(4)	2(4)
C4	51(4)	32(4)	58(4)	-11(3)	-19(3)	5(3)
C5	48(4)	31(3)	56(4)	-13(3)	-21(3)	1(3)
C6	33(3)	33(3)	55(4)	-17(3)	-20(3)	11(3)
C7	42(4)	65(6)	63(6)	-22(5)	-23(4)	6(4)
C8	35(4)	26(3)	52(4)	-12(3)	-7(3)	3(3)
C9	90(7)	33(4)	83(7)	-10(4)	-48(6)	-12(5)
C10	42(4)	50(4)	53(4)	-21(3)	-17(3)	23(4)
C11	103(7)	70(6)	56(4)	-22(4)	-15(4)	45(5)
O3	24(2)	25(2)	46(3)	-10(2)	-2(2)	-5(2)
O4	21(2)	35(3)	66(4)	-6(2)	-8(2)	-2(2)
N2	29(3)	37(3)	36(3)	-8(2)	-6(2)	-13(3)
C24	24(3)	22(3)	38(3)	-9(2)	-1(2)	-6(2)
C25	22(3)	26(3)	35(3)	-6(2)	-1(2)	-6(2)
C26	38(3)	39(4)	34(3)	-7(3)	-7(3)	-7(3)
C27	30(3)	35(4)	45(4)	-2(3)	-11(3)	-12(3)
C28	18(3)	25(3)	46(3)	-5(2)	-10(2)	0(2)
C29	19(3)	22(3)	36(3)	-9(2)	-2(2)	-7(2)
C30	32(3)	28(3)	52(4)	-14(3)	2(3)	-1(3)
C31	24(3)	32(3)	41(3)	-8(3)	-7(2)	-9(3)
C32	29(3)	28(3)	59(5)	-6(3)	2(3)	-6(3)
C33	26(3)	20(3)	41(3)	-9(2)	-3(2)	1(2)
C34	43(4)	20(3)	38(3)	-7(2)	-3(3)	0(3)
C35	30(3)	20(3)	42(3)	-9(2)	-6(2)	5(2)
C36	29(3)	29(4)	38(3)	-7(3)	-7(2)	3(3)
C37	29(3)	22(3)	38(3)	-7(2)	-11(2)	-7(3)
C38	15(3)	23(3)	47(3)	-9(2)	-8(2)	-9(2)
C39	22(3)	29(3)	42(3)	-9(3)	-9(2)	-8(3)
C40	33(3)	25(3)	41(3)	-12(3)	-8(3)	-4(3)

Table 3.9 (Cont'd)

C41	29(3)	21(3)	36(3)	-5(2)	-10(2)	-3(2)
C42	25(3)	23(3)	45(3)	-5(3)	-7(3)	-4(3)
C43	35(3)	26(3)	46(4)	0(3)	2(3)	-7(3)
C44	43(4)	35(4)	41(4)	-7(3)	-12(3)	1(3)
C45	30(3)	26(4)	53(4)	-8(3)	-13(3)	0(3)
C46	18(3)	16(3)	44(3)	-4(2)	-5(2)	0(2)
O5	27(2)	28(3)	42(3)	-10(2)	-8(2)	-4(2)
O6	21(2)	43(3)	61(4)	-22(3)	-10(2)	2(2)
N3	26(3)	30(3)	34(3)	-5(3)	-6(3)	-10(3)
C58	27(3)	32(3)	40(3)	-13(2)	-4(3)	-1(2)
C59	27(4)	31(4)	41(4)	-11(3)	-2(3)	-2(3)
C60	25(4)	28(4)	44(4)	-8(3)	-3(3)	-10(3)
C61	25(3)	21(3)	38(4)	-8(3)	-10(3)	-9(3)
C62	25(3)	25(3)	37(3)	-11(3)	-3(3)	-8(3)
C63	33(4)	28(4)	38(4)	-11(3)	-8(3)	-2(3)
C64	30(3)	26(3)	37(3)	-10(3)	-9(3)	-2(3)
C65	35(4)	24(4)	35(4)	-7(3)	-13(3)	5(3)
C66	37(4)	27(4)	35(4)	-6(3)	-14(3)	7(4)
C67	37(4)	24(4)	34(4)	-11(3)	-12(3)	6(3)
C68	37(4)	22(4)	34(4)	-2(3)	-14(4)	1(3)
C69	37(4)	23(4)	34(3)	-6(3)	-10(3)	-2(3)
N1E	27(4)	29(5)	40(4)	-7(4)	-12(4)	-8(4)
C12E	27(3)	32(3)	40(3)	-13(2)	-4(3)	-1(2)
C13E	23(5)	29(5)	37(5)	-7(4)	-8(4)	4(4)
C14E	28(5)	27(5)	37(4)	-9(4)	-10(4)	0(4)
C15E	27(4)	24(4)	36(4)	-5(4)	-10(3)	-3(4)
C16E	22(4)	29(4)	37(4)	-10(3)	-7(3)	-1(4)
C17E	25(5)	34(5)	39(4)	-10(4)	-3(4)	-2(4)
C18E	30(4)	27(4)	34(4)	-6(3)	-9(3)	-3(4)
C19E	31(5)	18(5)	36(5)	-1(4)	-11(4)	3(4)
C20E	28(5)	23(5)	36(5)	-1(4)	-11(4)	10(5)

Table 3.9 (Cont'd)

C21E	29(5)	25(5)	37(5)	-8(4)	-5(4)	7(5)
C22E	31(5)	23(5)	37(5)	-6(4)	-9(4)	4(4)
C23E	29(4)	25(4)	37(4)	-6(4)	-11(4)	2(4)
C47	27(3)	36(3)	37(3)	-9(3)	-5(2)	-5(2)
C48	20(3)	32(3)	37(3)	-9(2)	-3(2)	-4(2)
C49	25(3)	45(4)	34(3)	-4(3)	1(2)	-8(3)
C50	28(3)	43(4)	40(3)	-13(3)	0(3)	-5(3)
C51	24(3)	33(3)	40(3)	-13(3)	-5(2)	-5(2)
C52	23(3)	27(3)	44(3)	-15(3)	-4(2)	-6(2)
C53	42(4)	34(4)	48(4)	-5(3)	-11(3)	-5(3)
C54	20(3)	38(4)	40(3)	-14(3)	-3(2)	-1(2)
C55	30(3)	37(4)	47(4)	-14(3)	-9(3)	2(3)
C56	21(3)	26(3)	43(3)	-14(3)	-6(2)	5(2)
C57	41(4)	23(3)	42(3)	-14(3)	-2(3)	1(3)
O7	22(2)	31(2)	40(3)	-6(2)	-5(2)	-4(2)
O8	34(3)	32(3)	90(5)	-21(3)	-17(3)	4(2)
N4	20(3)	29(4)	32(3)	-7(3)	-5(3)	-12(3)
C81	34(4)	31(3)	38(3)	-7(2)	-8(3)	5(3)
C82	40(4)	32(4)	36(4)	-6(4)	-10(4)	6(4)
C83	27(4)	25(4)	37(4)	-2(3)	-9(3)	-3(3)
C84	23(3)	19(3)	35(4)	-5(3)	-6(3)	-4(3)
C85	20(4)	20(4)	34(4)	-6(3)	-4(3)	-2(3)
C86	33(4)	27(4)	36(4)	-2(3)	-4(4)	0(4)
C87	24(3)	21(3)	33(3)	-4(3)	-3(3)	-7(3)
C88	25(4)	22(4)	31(4)	-4(3)	-2(3)	-7(3)
C89	32(4)	33(4)	35(4)	-7(4)	-3(4)	-9(4)
C90	33(4)	35(4)	29(4)	-10(3)	0(4)	-7(4)
C91	29(4)	28(4)	33(4)	-10(3)	1(4)	-5(3)
C92	26(4)	21(4)	33(4)	-8(3)	-4(3)	-7(3)
N1B	18(4)	24(4)	36(4)	-4(3)	-6(3)	-5(3)
C12B	32(5)	31(5)	31(5)	-10(4)	-6(4)	-5(4)

Table 3.9 (Cont'd)

C13B	31(5)	35(5)	33(5)	-11(4)	-4(4)	-8(5)
C14B	30(4)	28(5)	32(5)	-11(4)	-5(4)	-6(4)
C15B	23(4)	24(4)	34(4)	-11(3)	-5(3)	-1(4)
C16B	22(4)	24(4)	33(4)	-8(3)	-5(3)	-2(4)
C17B	27(4)	27(5)	32(5)	-8(4)	-6(4)	-6(4)
C18B	20(4)	25(4)	35(4)	-5(3)	-5(3)	-5(3)
C19B	22(4)	26(5)	36(4)	-6(4)	-6(4)	-2(4)
C20B	29(5)	29(5)	36(5)	-4(4)	-4(4)	3(4)
C21B	34(4)	31(3)	38(3)	-7(2)	-8(3)	5(3)
C22B	32(4)	25(5)	34(4)	-9(4)	-6(4)	6(4)
C23B	24(4)	22(4)	33(4)	-5(3)	-7(3)	-3(4)
C70	27(3)	31(3)	49(4)	-11(3)	-12(3)	5(2)
C71	22(3)	35(3)	43(3)	-9(3)	0(2)	-2(2)
C72	45(4)	40(4)	39(4)	-10(3)	-3(3)	4(3)
C73	46(4)	40(4)	38(3)	-18(3)	-4(3)	8(3)
C74	38(3)	25(3)	36(3)	-10(2)	-5(2)	-1(3)
C75	31(3)	36(3)	44(3)	-11(3)	-12(3)	9(3)
C76	28(4)	49(6)	94(7)	-10(5)	-5(4)	4(4)
C77	43(4)	32(3)	61(4)	-22(3)	-22(3)	6(3)
C78	56(5)	34(4)	52(5)	-5(3)	-2(4)	-10(4)
C79	47(4)	42(4)	44(4)	-11(3)	-13(3)	15(3)
C80	97(7)	63(5)	42(4)	-8(3)	-11(4)	43(5)
O9	30(2)	31(2)	45(3)	-10(2)	-10(2)	-9(2)
O10	32(3)	25(2)	70(4)	-13(2)	1(2)	-1(2)
C93	25(3)	25(3)	46(4)	-6(2)	-7(3)	-8(2)
C94	35(3)	34(3)	40(3)	-4(3)	-8(3)	-6(3)
C95	62(5)	40(4)	35(4)	-7(3)	-12(3)	-11(3)
C96	54(4)	39(4)	38(4)	-11(3)	-10(3)	-9(3)
C97	33(3)	26(3)	41(3)	-8(2)	-11(2)	-5(2)
C98	25(3)	27(3)	45(3)	-9(2)	-8(2)	-8(2)
C99	34(4)	38(5)	78(6)	-3(4)	-15(4)	-10(3)

Table 3.9 (Cont'd)

C100	30(3)	26(3)	54(4)	-14(3)	-2(3)	-6(3)
C101	48(4)	32(4)	58(5)	-11(3)	-17(4)	4(3)
C102	27(3)	27(3)	48(4)	-11(3)	-7(3)	-11(3)
C103	69(5)	43(4)	44(4)	-8(3)	-8(3)	-23(4)
N5	20(3)	35(4)	34(3)	-7(3)	-3(3)	6(3)
C104	31(3)	22(3)	38(3)	-11(2)	-6(2)	-10(2)
C105	30(4)	28(4)	40(5)	-6(3)	-4(3)	-8(3)
C106	21(4)	23(4)	37(4)	-10(3)	0(3)	-3(3)
C107	22(3)	23(3)	36(3)	-9(3)	-7(3)	-4(3)
C108	22(3)	28(4)	36(3)	-8(3)	-4(3)	-2(3)
C109	27(4)	23(4)	38(4)	-10(3)	-8(3)	-4(3)
C110	27(4)	24(4)	36(3)	-5(3)	-5(3)	-1(3)
C111	34(4)	28(4)	38(4)	-7(4)	-9(4)	0(3)
C112	38(5)	29(4)	39(4)	-5(4)	-7(4)	1(4)
C113	37(4)	26(4)	31(4)	2(3)	-5(3)	0(4)
C114	36(4)	27(4)	32(4)	-5(3)	-6(4)	4(4)
C115	32(4)	25(4)	32(4)	-6(3)	-4(3)	0(3)
N1A	26(4)	28(4)	37(4)	-6(4)	-8(3)	-1(4)
C12A	31(3)	22(3)	38(3)	-11(2)	-6(2)	-10(2)
C13A	29(5)	23(5)	35(5)	-11(4)	-10(4)	-7(4)
C14A	29(5)	26(5)	37(5)	-7(4)	-10(4)	-1(4)
C15A	25(4)	25(4)	36(4)	-8(3)	-6(3)	0(3)
C16A	22(4)	25(4)	36(4)	-9(3)	-6(3)	-6(4)
C17A	25(5)	25(5)	36(4)	-11(4)	-3(4)	-10(4)
C18A	28(4)	28(4)	37(4)	-6(3)	-7(3)	-2(4)
C19A	32(4)	26(4)	37(4)	-8(4)	-4(4)	-1(4)
C20A	37(5)	31(5)	40(5)	-6(4)	-7(4)	-2(4)
C21A	37(5)	32(5)	38(5)	-7(4)	-3(4)	-1(4)
C22A	34(5)	27(5)	38(5)	-6(4)	-6(4)	-2(4)
C23A	28(4)	25(5)	37(4)	-8(4)	-6(4)	-7(4)
O11	23(2)	27(2)	36(2)	-10(2)	-4(2)	-2(2)

Table 3.9 (Cont'd)

O12	17(2)	38(3)	65(3)	-26(2)	-4(2)	-1(2)
N6	34(3)	42(4)	48(3)	-13(3)	-8(2)	1(3)
C116	25(3)	27(3)	38(3)	-10(2)	-3(2)	-6(2)
C117	26(3)	32(3)	34(3)	-9(2)	-4(2)	-3(2)
C118	33(3)	41(4)	30(3)	-4(3)	-6(2)	4(3)
C119	27(3)	39(4)	36(3)	-14(3)	-9(2)	7(3)
C120	25(3)	28(3)	38(3)	-12(2)	-3(2)	-7(2)
C121	22(3)	20(3)	37(3)	-10(2)	-5(2)	0(2)
C122	32(4)	38(4)	59(5)	-9(3)	2(3)	-13(3)
C123	20(3)	34(3)	40(3)	-16(3)	-5(2)	-4(2)
C124	24(3)	29(3)	49(4)	-16(3)	2(3)	-7(3)
C125	24(3)	23(3)	37(3)	-13(2)	-6(2)	-4(2)
C126	38(4)	30(3)	39(3)	-13(3)	-4(3)	-8(3)
C127	31(3)	21(3)	39(3)	-11(2)	-5(2)	-6(2)
C128	38(3)	30(4)	50(4)	-17(3)	-8(3)	-5(3)
C129	29(3)	36(4)	46(4)	-12(3)	-7(3)	-4(3)
C130	26(3)	25(3)	54(4)	-18(3)	-6(2)	-8(3)
C131	37(3)	22(3)	50(3)	-9(3)	-13(3)	-12(3)
C132	41(4)	20(3)	45(4)	-12(3)	-16(3)	3(3)
C133	43(4)	28(3)	45(3)	-10(3)	-10(3)	-14(3)
C134	45(4)	31(4)	63(4)	-12(3)	-5(3)	-2(3)
C135	55(5)	48(5)	56(4)	-25(4)	8(3)	-2(4)
C136	63(5)	54(5)	43(4)	-13(4)	-7(3)	-2(4)
C137	43(4)	47(5)	53(4)	-14(3)	-16(3)	2(3)
C138	41(4)	35(4)	52(4)	-17(3)	-2(3)	-3(3)
O13	23(2)	19(2)	46(3)	-7(2)	-6(2)	-7(2)
O14	22(2)	35(3)	65(4)	1(3)	-8(2)	-4(2)
N7	26(3)	34(3)	42(3)	-8(3)	-9(3)	8(3)
C150	26(3)	24(3)	43(3)	-8(2)	-8(2)	-9(2)
C151	22(4)	29(4)	46(4)	-4(3)	-5(3)	-7(3)
C152	21(3)	26(4)	47(4)	-8(3)	-7(3)	-2(3)

Table 3.9 (Cont'd)

C153	21(3)	22(3)	45(3)	-7(3)	-9(3)	-1(3)
C154	21(3)	21(3)	45(3)	-5(3)	-6(3)	0(3)
C155	25(3)	22(3)	48(4)	-8(3)	-13(3)	-3(3)
C156	21(3)	22(3)	42(3)	-4(3)	-13(3)	2(3)
C157	27(3)	29(4)	38(4)	-8(3)	-15(3)	1(3)
C158	38(4)	29(4)	38(4)	-5(3)	-16(3)	6(3)
C159	36(4)	30(4)	45(4)	-5(3)	-11(3)	2(3)
C160	29(4)	32(4)	40(4)	-7(3)	-9(3)	4(3)
C161	27(3)	28(3)	40(3)	-6(3)	-9(3)	5(3)
N1F	24(5)	30(5)	42(5)	-7(4)	-9(4)	-2(4)
C12F	26(3)	24(3)	43(3)	-8(2)	-8(2)	-9(2)
C13F	27(5)	20(5)	42(5)	-13(4)	-11(4)	-10(4)
C14F	30(5)	30(5)	43(5)	-9(4)	-10(4)	1(5)
C15F	24(4)	27(4)	41(4)	-7(4)	-9(3)	-1(4)
C16F	23(4)	24(5)	42(4)	-6(4)	-6(4)	-6(4)
C17F	23(5)	29(5)	42(5)	-7(4)	-6(4)	-9(5)
C18F	24(4)	25(4)	40(4)	-6(4)	-8(3)	-1(4)
C19F	27(5)	27(5)	39(5)	-8(4)	-11(4)	1(4)
C20F	29(5)	29(5)	39(5)	-8(4)	-12(4)	0(5)
C21F	29(5)	33(5)	37(5)	-3(4)	-10(4)	3(5)
C22F	29(5)	27(5)	39(5)	-6(5)	-11(4)	3(5)
C23F	25(4)	27(5)	39(4)	-6(4)	-9(4)	-3(4)
C139	21(3)	22(3)	48(4)	-9(2)	-7(2)	-3(2)
C140	31(3)	23(3)	43(3)	-12(2)	-10(2)	-6(2)
C141	34(3)	40(4)	38(3)	-11(3)	-3(3)	-1(3)
C142	27(3)	34(4)	44(4)	-9(3)	-6(3)	-1(3)
C143	26(3)	25(3)	41(3)	-8(2)	-8(2)	-7(2)
C144	19(3)	18(3)	47(3)	-6(2)	-6(2)	-5(2)
C145	33(4)	29(3)	70(5)	-18(3)	-16(3)	-2(3)
C146	24(3)	32(4)	53(4)	-6(3)	-7(3)	-3(3)
C147	30(3)	31(4)	55(4)	-11(3)	-11(3)	-13(3)

Table 3.9 (Cont'd)

C148	19(3)	26(3)	52(4)	-8(3)	-8(3)	-3(2)
C149	43(4)	26(3)	51(4)	-4(3)	-14(3)	-4(3)
O15	29(2)	34(2)	39(3)	-7(2)	-5(2)	-9(2)
O16	28(3)	31(3)	105(5)	-12(3)	-13(3)	-4(2)
N8	25(3)	27(3)	37(3)	-8(3)	-6(3)	-1(3)
C173	30(4)	21(3)	36(3)	-7(2)	-8(3)	-10(3)
C174	34(4)	22(4)	34(4)	-8(3)	-8(3)	-7(3)
C175	29(4)	29(4)	34(4)	-9(3)	-6(3)	-8(3)
C176	26(3)	22(4)	36(3)	-8(3)	-5(3)	-5(3)
C177	27(4)	21(3)	34(3)	-10(3)	-2(3)	-7(3)
C178	30(4)	23(4)	35(4)	-11(3)	-5(3)	-7(4)
C179	22(3)	21(3)	37(3)	-9(3)	-2(3)	-5(3)
C180	31(4)	24(4)	34(4)	-8(3)	-2(3)	-2(3)
C181	32(4)	31(4)	33(4)	-6(4)	-2(4)	-1(3)
C182	34(4)	33(4)	33(4)	-4(3)	-6(4)	2(4)
C183	35(4)	32(4)	35(4)	-3(4)	-4(3)	-1(4)
C184	28(4)	29(4)	37(4)	-5(3)	-4(3)	-6(3)
N1C	28(4)	30(5)	39(4)	-9(4)	-5(3)	-2(4)
C12C	30(4)	21(3)	36(3)	-7(2)	-8(3)	-10(3)
C13C	27(5)	24(5)	35(5)	-6(4)	-4(4)	-9(5)
C14C	25(5)	21(5)	35(5)	-7(4)	-3(4)	-5(4)
C15C	27(4)	25(4)	37(4)	-7(3)	-3(3)	-6(4)
C16C	27(4)	22(4)	35(4)	-7(4)	-5(3)	-6(4)
C17C	30(5)	20(5)	36(5)	-7(4)	-7(4)	-6(4)
C18C	27(4)	24(4)	35(4)	-4(4)	-3(3)	-2(4)
C19C	30(5)	28(5)	36(5)	-6(4)	-3(4)	-2(4)
C20C	36(5)	33(6)	38(5)	-2(5)	0(5)	1(5)
C21C	33(5)	31(6)	34(5)	-1(5)	0(4)	0(5)
C22C	30(5)	26(5)	36(5)	-5(4)	-2(4)	0(4)
C23C	27(4)	23(4)	36(4)	-6(4)	-3(3)	-6(4)
C162	31(3)	32(3)	50(4)	-9(3)	-14(3)	-12(3)

Table 3.9 (Cont'd)

C163	34(3)	34(3)	42(3)	-11(3)	-6(3)	-5(3)
C164	45(4)	42(4)	40(4)	-5(3)	-7(3)	-11(3)
C165	57(4)	41(4)	40(4)	-1(3)	-10(3)	-14(3)
C166	44(4)	31(3)	40(3)	-4(3)	-7(3)	-14(3)
C167	31(3)	32(3)	50(4)	-8(3)	-11(3)	-16(3)
C168	34(4)	66(6)	87(7)	-18(5)	-9(4)	-6(4)
C169	38(4)	35(4)	72(5)	-5(3)	-21(3)	-7(3)
C170	67(5)	38(4)	61(5)	-16(4)	-5(4)	-8(4)
C171	41(4)	39(4)	44(4)	-8(3)	-10(3)	-21(3)
C172	75(5)	51(5)	46(4)	-11(3)	-4(3)	-31(4)

Table 3.10 Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10 ^{3}) for **3.11**.

	x	y	z	U(eq)
H2O	-1086	11457	8633	60
H1	3218	9663	4935	38
H13	-631	7967	6533	41
H14	-739	8021	5439	34
H17	2490	9255	6220	37
H19	-204	8353	4059	29
H20	585	8761	3033	33
H21	2389	9515	2807	40
H22	3351	9826	3654	36
H1D	-609	8072	4933	35
H13D	2314	9054	6711	39
H14D	2946	9450	5608	34
H17D	-606	7921	6186	34
H19D	3293	9762	4220	33
H20D	3075	9802	3141	36
H21D	1443	9173	2845	36
H22D	13	8493	3578	31
H2	-1239	9985	9308	45
H3A	-1291	8534	9949	60
H3B	61	8668	9736	60
H4A	-1352	7401	9380	55
H4B	2	7537	9165	55
H6	782	8533	8378	46
H7A	1155	10463	9048	81
H7B	1808	10022	8487	81
H7C	1377	9388	9151	81
H8A	340	10817	7810	44
H8B	-984	10548	7998	44

Table 3.10 (Cont'd)

H9A	-2372	7626	8415	98
H9B	-1202	7349	8054	98
H9C	-1831	8263	7775	98
H10F	757	9706	7380	55
H10G	-478	9276	7357	55
H11E	1622	8283	7317	89
H11F	398	7796	7359	89
H4O	1451	6285	8669	61
H2N	4273	8065	5107	40
H25	2822	5989	9460	33
H26A	4153	5842	10215	44
H26B	4209	6934	9972	44
H27A	5930	5714	9737	44
H27B	6005	6809	9518	44
H29	5318	7560	8660	30
H30A	3245	8435	8641	56
H30B	3837	8103	9277	56
H30C	2526	7848	9250	56
H31A	2946	7362	7909	38
H31B	3046	6288	8154	38
H32A	6267	5000	8746	59
H32B	6960	5930	8456	59
H32C	5997	5578	8078	59
H33A	4719	6853	7586	34
H33B	6006	7114	7666	34
H34A	4165	8371	7503	40
H34B	5353	8670	7711	40
H36	6963	9050	6945	38
H37	7802	9407	5908	34
H40	4161	7936	6416	38
H42	8269	9616	4531	37

Table 3.10 (Cont'd)

H43	8141	9684	3468	44
H44	6511	9116	3108	47
H45	4994	8468	3843	43
H6O	4043	4445	8677	60
H3N	3161	4622	5134	36
H59	-629	2780	6726	39
H60	-743	2895	5641	39
H63	2468	4140	6410	38
H65	-233	3305	4247	37
H66	521	3771	3225	39
H67	2296	4560	2978	37
H68	3281	4861	3837	37
H1EN	-647	3038	5126	37
H13E	2635	4089	6652	35
H14E	3104	4445	5584	36
H17E	-424	2923	6412	39
H19E	3190	4693	4227	34
H20E	2822	4712	3165	35
H21E	1034	4045	2943	36
H22E	-189	3432	3769	36
H48	2412	4316	9410	35
H49A	774	4041	10154	42
H49B	823	3093	9885	42
H50A	-789	3470	9417	44
H50B	-826	4425	9677	44
H52	227	3216	8554	37
H53A	2766	2560	9170	62
H53B	2300	2329	8542	62
H53C	1443	2313	9172	62
H54A	2931	3787	7855	38
H54B	2712	4731	8107	38

Table 3.10 (Cont'd)

H55A	-852	5664	8735	55
H55B	-1293	4928	8351	55
H55C	-197	5557	8063	55
H56A	1293	4506	7531	35
H56B	-38	4260	7590	35
H57A	1762	2984	7433	42
H57B	438	2693	7538	42
H8O	-3320	9251	8647	75
H4N	-5711	13056	4984	32
H82	-2892	13948	6786	43
H83	-2100	14397	5730	36
H86	-5729	12889	6259	39
H88	-1794	14692	4352	32
H89	-1956	14762	3268	40
H90	-3597	14152	2936	39
H91	-5057	13477	3685	35
H1BN	-1837	14522	5106	31
H12B	-2572	14615	2935	36
H13B	-4424	13908	3122	39
H14B	-5255	13433	4145	35
H17B	-1627	14817	3794	34
H19B	-5835	13003	5474	34
H20B	-5785	12837	6569	38
H22B	-2585	14042	6348	36
H71	-3491	10373	9400	40
H72A	-3715	11470	10067	49
H72B	-4963	11496	9816	49
H73A	-4564	12928	9264	48
H73B	-3299	12886	9494	48
H75	-5061	12342	8465	43
H76A	-5790	10076	9129	86

Table 3.10 (Cont'd)

H76B	-6197	10777	8544	86
H76C	-6053	11111	9200	86
H77A	-4471	10331	7895	51
H77B	-3219	10514	8079	51
H78A	-1932	13178	8539	72
H78B	-2961	13657	8183	72
H78C	-2231	12894	7889	72
H79A	-4706	11730	7462	52
H79B	-3420	12077	7455	52
H80A	-5373	13228	7442	81
H80B	-4116	13590	7488	81
H10O	6027	10747	1365	64
H94	6173	9634	701	44
H95A	6171	8499	58	54
H95B	4835	8477	322	54
H96A	5057	7049	883	51
H96B	6410	7102	659	51
H98	4217	7697	1658	38
H99A	3784	9977	993	75
H99B	3133	9243	1548	75
H99C	3553	8962	877	75
H10A	4616	9715	2209	43
H10B	5939	9541	2020	43
H10C	7415	6875	1640	67
H10D	6257	6360	1969	67
H10E	6795	7142	2279	67
H10H	4148	8332	2645	40
H10I	5439	8007	2669	40
H10J	3540	6788	2671	62
H10K	4832	6462	2695	62
H5N	1824	7170	5015	36

Table 3.10 (Cont'd)

H105	5700	6128	3517	39
H106	5735	5704	4601	32
H109	2571	7319	3805	35
H111	5205	5401	5964	39
H112	4284	5377	7029	42
H113	2492	6069	7173	38
H114	1587	6769	6327	38
H1AN	5734	5574	5109	36
H13A	2610	7297	3475	34
H14A	1995	7193	4553	36
H17A	5593	6035	3823	33
H19A	1815	6840	5892	38
H20A	2132	6404	6875	43
H21A	3765	5676	7188	43
H22A	5266	5347	6397	39
H12O	3472	5545	1437	57
H6N	721	5565	5061	48
H117	2131	5717	657	36
H11A	776	6039	-88	42
H11B	728	6972	198	42
H11C	-1091	6604	633	39
H11D	-1012	5638	386	39
H121	-375	6870	1496	31
H12Q	1728	7712	1534	66
H12R	1093	7745	908	66
H12S	2408	7471	902	66
H12D	2033	6206	2236	36
H12E	1906	5279	1964	36
H12F	-1365	4400	1343	50
H12G	-2012	5159	1684	50
H12H	-1039	4564	2019	50

Table 3.10 (Cont'd)

H12I	201	5561	2547	32
H12J	-1081	5883	2472	32
H12K	774	7018	2654	42
H12L	-422	7435	2468	42
H128	-2028	7382	3231	45
H129	-2774	7245	4256	44
H132	835	6037	3758	41
H134	-3244	6889	5647	55
H135	-3070	6452	6712	63
H136	-1460	5660	7057	63
H137	60	5342	6313	55
H14O	875	3791	1441	63
H7N	1798	2126	5001	40
H151	5600	1095	3415	39
H152	5719	707	4487	37
H155	2499	2245	3751	37
H157	5289	422	5872	36
H158	4438	417	6937	41
H159	2679	1076	7114	44
H160	1692	1750	6292	40
H1FN	5736	611	4963	38
H13F	2464	2189	3455	34
H14F	1712	2178	4514	40
H17F	5394	1086	3642	37
H19F	1912	1785	5717	36
H20F	2091	1433	6788	38
H21F	3671	785	7095	40
H22F	5294	410	6311	38
H140	2540	3981	667	38
H14T	4155	4022	-78	44
H14X	4073	2944	213	44

Table 3.10 (Cont'd)

H14Y	5770	4153	384	42
H14Z	5710	3069	656	42
H144	4718	2421	1544	33
H14Q	2125	2095	965	63
H14R	2673	1548	1567	63
H14S	3455	1862	910	63
H14H	1994	2711	2234	44
H14I	2252	3771	1962	44
H14J	5829	4942	1305	57
H14K	6293	4009	1676	57
H14L	5226	4498	1991	57
H14M	3673	3233	2555	38
H14N	4998	2992	2502	38
H201	3159	1658	2675	48
H202	4474	1393	2567	48
H16O	-1647	-1459	1237	81
H8N	708	597	4964	35
H174	-2118	2262	3094	36
H175	-2790	2253	4118	36
H178	720	903	3666	34
H180	-3293	1891	5476	35
H181	-3106	1514	6568	38
H182	-1539	793	6939	40
H183	36	445	6242	41
H1CN	-3163	2059	4796	38
H13C	867	1144	3357	34
H203	841	751	4398	32
H17C	-2377	2168	3548	34
H19C	369	597	5752	37
H20C	-476	611	6800	44
H21C	-2275	1253	6942	40

Table 3.10 (Cont'd)

H22C	-3292	1790	6121	37
H163	-1610	6	543	43
H16A	-1478	1439	-118	51
H16B	-202	1372	97	51
H16C	-603	2523	651	55
H16D	-1903	2546	473	55
H167	46	1492	1429	45
H16E	951	676	667	92
H16F	684	-391	720	92
H16G	1155	-19	1301	92
H16H	-433	-791	2003	57
H16I	-1725	-555	1874	57
H17X	-3118	2374	1455	82
H17Y	-2087	2606	1833	82
H17Z	-2837	1694	2081	82
H17G	-1532	768	2475	50
H17H	-294	326	2439	50
H17I	584	1658	2515	69
H17J	-521	2243	2358	69

Table 3.11 Torsion angles [°] for **3.11**.

C17-C12-C13-C14	-0.15(18)	C15-C18-C23-N1	0.1(3)
C11-C12-C13-C14	-172.5(7)	C17D-C12D-C13D-C14D	0.02(19)
C12-C13-C14-C15	0.1(3)	C11-C12D-C13D-C14D	179.2(7)
C13-C14-C15-C16	-0.1(4)	C12D-C13D-C14D-C15D	0.0(3)
C13-C14-C15-C18	179.8(2)	C13D-C14D-C15D-C16D	0.0(4)
C23-N1-C16-C15	0.0(3)	C13D-C14D-C15D-C18D	-179.9(3)
C23-N1-C16-C17	179.9(2)	C23D-N1D-C16D-C17D	-180.0(3)
C18-C15-C16-N1	0.0(3)	C23D-N1D-C16D-C15D	0.0(3)
C14-C15-C16-N1	179.9(2)	C14D-C15D-C16D-C17D	0.0(4)
C18-C15-C16-C17	-179.8(2)	C18D-C15D-C16D-C17D	179.9(3)
C14-C15-C16-C17	0.1(4)	C14D-C15D-C16D-N1D	-180.0(2)
N1-C16-C17-C12	-179.95(19)	C18D-C15D-C16D-N1D	0.0(3)
C15-C16-C17-C12	-0.2(4)	N1D-C16D-C17D-C12D	179.9(2)
C13-C12-C17-C16	0.2(2)	C15D-C16D-C17D-C12D	0.0(4)
C11-C12-C17-C16	171.9(8)	C13D-C12D-C17D-C16D	0.0(3)
C16-C15-C18-C19	179.9(3)	C11-C12D-C17D-C16D	-178.9(10)
C14-C15-C18-C19	0.0(6)	C14D-C15D-C18D-C19D	-0.2(6)
C16-C15-C18-C23	-0.1(3)	C16D-C15D-C18D-C19D	179.9(3)
C14-C15-C18-C23	-180.0(3)	C14D-C15D-C18D-C23D	180.0(3)
C15-C18-C19-C20	180.0(3)	C16D-C15D-C18D-C23D	0.1(3)
C23-C18-C19-C20	-0.1(4)	C15D-C18D-C19D-C20D	-179.9(3)
C18-C19-C20-C21	0.0(4)	C23D-C18D-C19D-C20D	-0.1(4)
C19-C20-C21-C22	0.2(4)	C18D-C19D-C20D-C21D	0.2(4)
C20-C21-C22-C23	-0.2(4)	C19D-C20D-C21D-C22D	-0.2(4)
C21-C22-C23-N1	-180.0(2)	C20D-C21D-C22D-C23D	0.2(4)
C21-C22-C23-C18	0.1(4)	C21D-C22D-C23D-N1D	180.0(3)
C16-N1-C23-C22	-180.0(3)	C21D-C22D-C23D-C18D	-0.1(4)
C16-N1-C23-C18	-0.1(2)	C16D-N1D-C23D-C22D	-180.0(3)
C19-C18-C23-C22	0.0(4)	C16D-N1D-C23D-C18D	0.1(3)
C15-C18-C23-C22	180.0(3)	C19D-C18D-C23D-C22D	0.1(4)
C19-C18-C23-N1	-179.9(2)	C15D-C18D-C23D-C22D	180.0(3)

Table 3.11 (Cont'd)

C19D-C18D-C23D-N1D	-180.0(2)	C7-C1-C8-O2	-61.0(9)
C15D-C18D-C23D-N1D	-0.1(3)	C2-C1-C8-O2	65.9(8)
C5-O1-C2-C3	-57.4(8)	C6-C1-C8-O2	175.1(6)
C5-O1-C2-C1	60.5(7)	C5-C6-C10-C11	-87.1(11)
C7-C1-C2-O1	-162.9(7)	C1-C6-C10-C11	154.7(10)
C8-C1-C2-O1	74.3(7)	C13-C12-C11-C12D	50(12)
C6-C1-C2-O1	-43.4(7)	C17-C12-C11-C12D	-122(12)
C7-C1-C2-C3	-54.3(10)	C13-C12-C11-C10	-94.0(12)
C8-C1-C2-C3	-177.1(6)	C17-C12-C11-C10	94.2(12)
C6-C1-C2-C3	65.2(8)	C13D-C12D-C11-C12	53(12)
O1-C2-C3-C4	36.0(9)	C17D-C12D-C11-C12	-128(12)
C1-C2-C3-C4	-73.2(9)	C13D-C12D-C11-C10	90.8(13)
C2-C3-C4-C5	-0.1(9)	C17D-C12D-C11-C10	-90.0(15)
C2-O1-C5-C9	178.4(8)	C6-C10-C11-C12	174.6(11)
C2-O1-C5-C4	57.7(7)	C6-C10-C11-C12D	170.7(14)
C2-O1-C5-C6	-53.6(7)	C28-O3-C25-C26	-57.3(6)
C3-C4-C5-O1	-34.7(8)	C28-O3-C25-C24	60.8(6)
C3-C4-C5-C9	-150.6(10)	C30-C24-C25-O3	-164.9(6)
C3-C4-C5-C6	73.9(9)	C31-C24-C25-O3	73.5(6)
O1-C5-C6-C10	-99.4(8)	C29-C24-C25-O3	-43.3(6)
C9-C5-C6-C10	20.9(12)	C30-C24-C25-C26	-55.2(8)
C4-C5-C6-C10	153.6(7)	C31-C24-C25-C26	-176.8(6)
O1-C5-C6-C1	26.5(7)	C29-C24-C25-C26	66.4(7)
C9-C5-C6-C1	146.8(8)	O3-C25-C26-C27	33.9(7)
C4-C5-C6-C1	-80.6(8)	C24-C25-C26-C27	-74.6(7)
C7-C1-C6-C10	-101.3(9)	C25-C26-C27-C28	2.1(7)
C2-C1-C6-C10	135.9(7)	C25-O3-C28-C32	178.7(6)
C8-C1-C6-C10	21.5(10)	C25-O3-C28-C27	57.1(6)
C7-C1-C6-C5	131.9(8)	C25-O3-C28-C29	-54.1(6)
C2-C1-C6-C5	9.1(7)	C26-C27-C28-O3	-36.1(7)
C8-C1-C6-C5	-105.3(7)	C26-C27-C28-C32	-151.6(6)

Table 3.11 (Cont'd)

C26-C27-C28-C29	70.6(7)	C41-C38-C39-C40	-178.6(7)
O3-C28-C29-C33	-102.8(6)	C36-C35-C40-C39	-2.7(11)
C32-C28-C29-C33	16.4(9)	C34-C35-C40-C39	-178.8(7)
C27-C28-C29-C33	152.3(6)	N2-C39-C40-C35	-177.1(8)
O3-C28-C29-C24	26.6(7)	C38-C39-C40-C35	3.1(12)
C32-C28-C29-C24	145.8(6)	C39-C38-C41-C42	179.8(9)
C27-C28-C29-C24	-78.3(6)	C37-C38-C41-C42	4.5(16)
C30-C24-C29-C33	-101.0(7)	C39-C38-C41-C46	-1.8(8)
C31-C24-C29-C33	22.9(8)	C37-C38-C41-C46	-177.1(8)
C25-C24-C29-C33	137.1(6)	C46-C41-C42-C43	2.3(11)
C30-C24-C29-C28	131.0(7)	C38-C41-C42-C43	-179.4(9)
C31-C24-C29-C28	-105.1(6)	C41-C42-C43-C44	-0.7(13)
C25-C24-C29-C28	9.1(6)	C42-C43-C44-C45	-0.4(13)
C30-C24-C31-O4	-55.8(7)	C43-C44-C45-C46	-0.4(13)
C25-C24-C31-O4	68.7(7)	C44-C45-C46-N2	178.1(8)
C29-C24-C31-O4	177.8(5)	C44-C45-C46-C41	2.2(12)
C28-C29-C33-C34	-168.1(6)	C39-N2-C46-C45	-176.9(8)
C24-C29-C33-C34	70.7(8)	C39-N2-C46-C41	-0.5(9)
C29-C33-C34-C35	169.1(6)	C42-C41-C46-C45	-3.2(11)
C33-C34-C35-C40	80.0(9)	C38-C41-C46-C45	178.1(7)
C33-C34-C35-C36	-96.2(8)	C42-C41-C46-N2	-179.8(7)
C40-C35-C36-C37	2.0(12)	C38-C41-C46-N2	1.4(8)
C34-C35-C36-C37	178.2(7)	C63-C58-C59-C60	-0.33(18)
C35-C36-C37-C38	-1.4(12)	C57-C58-C59-C60	-170.1(6)
C36-C37-C38-C39	1.7(11)	C58-C59-C60-C61	0.2(3)
C36-C37-C38-C41	176.5(8)	C59-C60-C61-C62	-0.1(4)
C46-N2-C39-C38	-0.7(9)	C59-C60-C61-C64	179.7(2)
C46-N2-C39-C40	179.5(8)	C64-C61-C62-N3	0.0(3)
C37-C38-C39-N2	177.5(7)	C60-C61-C62-N3	179.9(2)
C41-C38-C39-N2	1.6(9)	C64-C61-C62-C63	-179.7(2)
C37-C38-C39-C40	-2.6(12)	C60-C61-C62-C63	0.1(4)

Table 3.11 (Cont'd)

C69-N3-C62-C61	0.0(2)	C14E-C15E-C16E-N1E	-179.9(2)
C69-N3-C62-C63	179.8(2)	C18E-C15E-C16E-C17E	179.9(2)
C59-C58-C63-C62	0.3(3)	C14E-C15E-C16E-C17E	-0.1(4)
C57-C58-C63-C62	169.6(6)	C13E-C12E-C17E-C16E	-0.1(3)
C61-C62-C63-C58	-0.2(4)	C57-C12E-C17E-C16E	-172.5(9)
N3-C62-C63-C58	-179.92(18)	N1E-C16E-C17E-C12E	179.9(2)
C62-C61-C64-C65	179.8(3)	C15E-C16E-C17E-C12E	0.1(4)
C60-C61-C64-C65	0.0(6)	C14E-C15E-C18E-C19E	-0.1(6)
C62-C61-C64-C69	-0.1(3)	C16E-C15E-C18E-C19E	180.0(3)
C60-C61-C64-C69	-179.9(3)	C14E-C15E-C18E-C23E	180.0(3)
C61-C64-C65-C66	-180.0(3)	C16E-C15E-C18E-C23E	0.0(3)
C69-C64-C65-C66	-0.1(4)	C23E-C18E-C19E-C20E	-0.1(4)
C64-C65-C66-C67	0.1(4)	C15E-C18E-C19E-C20E	180.0(3)
C65-C66-C67-C68	-0.1(4)	C18E-C19E-C20E-C21E	0.1(4)
C66-C67-C68-C69	0.1(4)	C19E-C20E-C21E-C22E	-0.1(4)
C62-N3-C69-C68	-180.0(3)	C20E-C21E-C22E-C23E	0.1(4)
C62-N3-C69-C64	-0.1(2)	C19E-C18E-C23E-C22E	0.1(4)
C67-C68-C69-N3	179.8(2)	C15E-C18E-C23E-C22E	-179.9(2)
C67-C68-C69-C64	-0.1(4)	C19E-C18E-C23E-N1E	180.0(2)
C65-C64-C69-N3	-179.8(2)	C15E-C18E-C23E-N1E	-0.1(3)
C61-C64-C69-N3	0.1(3)	C21E-C22E-C23E-C18E	-0.1(4)
C65-C64-C69-C68	0.1(4)	C21E-C22E-C23E-N1E	-179.9(2)
C61-C64-C69-C68	-180.0(2)	C16E-N1E-C23E-C18E	0.1(2)
C17E-C12E-C13E-C14E	0.06(18)	C16E-N1E-C23E-C22E	179.9(3)
C57-C12E-C13E-C14E	173.4(8)	C51-O5-C48-C47	60.4(6)
C12E-C13E-C14E-C15E	-0.1(3)	C51-O5-C48-C49	-57.1(6)
C13E-C14E-C15E-C18E	-179.9(3)	C54-C47-C48-O5	75.2(7)
C13E-C14E-C15E-C16E	0.1(4)	C53-C47-C48-O5	-162.9(6)
C23E-N1E-C16E-C15E	-0.1(2)	C52-C47-C48-O5	-41.8(6)
C23E-N1E-C16E-C17E	-179.9(2)	C54-C47-C48-C49	-176.2(6)
C18E-C15E-C16E-N1E	0.0(3)	C53-C47-C48-C49	-54.3(8)

Table 3.11 (Cont'd)

C52-C47-C48-C49	66.8(7)	C52-C56-C57-C58	176.0(8)
O5-C48-C49-C50	34.0(7)	C52-C56-C57-C12E	-176.9(12)
C47-C48-C49-C50	-74.4(8)	C17E-C12E-C57-C58	-26(7)
C48-C49-C50-C51	0.8(8)	C13E-C12E-C57-C58	161(8)
C48-O5-C51-C55	179.6(6)	C17E-C12E-C57-C56	-109.7(9)
C48-O5-C51-C50	57.3(7)	C13E-C12E-C57-C56	76.9(9)
C48-O5-C51-C52	-53.9(6)	C86-C81-C82-C83	0.02(19)
C49-C50-C51-O5	-35.6(7)	C80-C81-C82-C83	176.0(6)
C49-C50-C51-C55	-152.5(7)	C81-C82-C83-C84	-0.1(3)
C49-C50-C51-C52	72.0(7)	C82-C83-C84-C87	180.0(3)
O5-C51-C52-C56	-101.4(7)	C82-C83-C84-C85	0.1(3)
C55-C51-C52-C56	18.2(9)	C92-N4-C85-C86	180.0(3)
C50-C51-C52-C56	152.3(6)	C92-N4-C85-C84	0.0(2)
O5-C51-C52-C47	27.6(7)	C87-C84-C85-N4	0.0(3)
C55-C51-C52-C47	147.2(6)	C83-C84-C85-N4	179.9(2)
C50-C51-C52-C47	-78.7(7)	C87-C84-C85-C86	-179.9(3)
C54-C47-C52-C56	21.7(9)	C83-C84-C85-C86	0.0(4)
C48-C47-C52-C56	135.8(6)	C82-C81-C86-C85	0.1(3)
C53-C47-C52-C56	-102.1(8)	C80-C81-C86-C85	-174.8(8)
C54-C47-C52-C51	-105.8(7)	N4-C85-C86-C81	-179.99(19)
C48-C47-C52-C51	8.3(7)	C84-C85-C86-C81	-0.1(4)
C53-C47-C52-C51	130.4(7)	C85-C84-C87-C88	-180.0(3)
C48-C47-C54-O6	66.9(8)	C83-C84-C87-C88	0.1(6)
C53-C47-C54-O6	-58.0(8)	C85-C84-C87-C92	0.0(3)
C52-C47-C54-O6	176.1(6)	C83-C84-C87-C92	-180.0(3)
C51-C52-C56-C57	-166.1(6)	C84-C87-C88-C89	179.9(3)
C47-C52-C56-C57	73.6(8)	C92-C87-C88-C89	0.0(4)
C63-C58-C57-C56	81.8(7)	C87-C88-C89-C90	0.0(4)
C59-C58-C57-C56	-108.3(6)	C88-C89-C90-C91	-0.1(4)
C63-C58-C57-C12E	-17(7)	C89-C90-C91-C92	0.1(4)
C59-C58-C57-C12E	153(8)	C90-C91-C92-N4	180.0(2)

Table 3.11 (Cont'd)

C90-C91-C92-C87	0.0(4)	C15B-C18B-C23B-C22B	-180.0(3)
C85-N4-C92-C91	180.0(3)	C19B-C18B-C23B-C22B	0.1(4)
C85-N4-C92-C87	-0.1(2)	C15B-C18B-C23B-N1B	0.0(3)
C88-C87-C92-C91	0.0(4)	C19B-C18B-C23B-N1B	-179.9(2)
C84-C87-C92-C91	-179.9(3)	C21B-C22B-C23B-C18B	0.0(4)
C88-C87-C92-N4	-180.0(2)	C21B-C22B-C23B-N1B	-180.0(2)
C84-C87-C92-N4	0.1(3)	C16B-N1B-C23B-C18B	0.0(2)
C17B-C12B-C13B-C14B	-0.05(18)	C16B-N1B-C23B-C22B	180.0(2)
C12B-C13B-C14B-C15B	0.1(3)	C74-O7-C71-C72	-57.9(6)
C13B-C14B-C15B-C18B	180.0(3)	C74-O7-C71-C70	60.1(6)
C13B-C14B-C15B-C16B	-0.1(4)	C77-C70-C71-O7	74.8(7)
C23B-N1B-C16B-C17B	180.0(3)	C76-C70-C71-O7	-162.9(7)
C23B-N1B-C16B-C15B	0.0(2)	C75-C70-C71-O7	-42.7(7)
C14B-C15B-C16B-N1B	-180.0(2)	C77-C70-C71-C72	-176.2(7)
C18B-C15B-C16B-N1B	0.0(3)	C76-C70-C71-C72	-53.9(10)
C14B-C15B-C16B-C17B	0.0(4)	C75-C70-C71-C72	66.4(8)
C18B-C15B-C16B-C17B	-180.0(2)	O7-C71-C72-C73	34.0(8)
C13B-C12B-C17B-C16B	0.0(3)	C70-C71-C72-C73	-75.2(8)
N1B-C16B-C17B-C12B	-180.0(2)	C71-C72-C73-C74	2.0(8)
C15B-C16B-C17B-C12B	0.0(4)	C71-O7-C74-C78	178.4(6)
C14B-C15B-C18B-C23B	180.0(3)	C71-O7-C74-C73	58.9(6)
C16B-C15B-C18B-C23B	0.0(3)	C71-O7-C74-C75	-53.6(6)
C14B-C15B-C18B-C19B	-0.1(6)	C72-C73-C74-O7	-37.1(7)
C16B-C15B-C18B-C19B	179.9(3)	C72-C73-C74-C78	-153.5(7)
C23B-C18B-C19B-C20B	-0.1(4)	C72-C73-C74-C75	72.4(8)
C15B-C18B-C19B-C20B	180.0(3)	O7-C74-C75-C79	-100.5(7)
C18B-C19B-C20B-C21B	0.1(4)	C78-C74-C75-C79	21.4(11)
C19B-C20B-C21B-C22B	0.0(4)	C73-C74-C75-C79	152.5(7)
C19B-C20B-C21B-C80	-179.2(7)	O7-C74-C75-C70	26.7(7)
C20B-C21B-C22B-C23B	0.0(4)	C78-C74-C75-C70	148.5(7)
C80-C21B-C22B-C23B	178.9(10)	C73-C74-C75-C70	-80.3(7)

Table 3.11 (Cont'd)

C77-C70-C75-C79	23.3(9)	C94-C95-C96-C97	3.9(8)
C76-C70-C75-C79	-100.3(9)	C94-O9-C97-C101	178.0(6)
C71-C70-C75-C79	137.2(7)	C94-O9-C97-C96	57.9(7)
C77-C70-C75-C74	-104.8(7)	C94-O9-C97-C98	-53.3(7)
C76-C70-C75-C74	131.6(8)	C95-C96-C97-O9	-37.2(8)
C71-C70-C75-C74	9.1(7)	C95-C96-C97-C101	-153.5(7)
C76-C70-C77-O8	-62.9(9)	C95-C96-C97-C98	69.8(8)
C71-C70-C77-O8	63.2(8)	O9-C97-C98-C102	-102.0(6)
C75-C70-C77-O8	171.7(6)	C101-C97-C98-C102	19.2(9)
C74-C75-C79-C80	-82.8(10)	C96-C97-C98-C102	152.7(6)
C70-C75-C79-C80	157.6(9)	O9-C97-C98-C93	26.0(7)
C86-C81-C80-C21B	160(6)	C101-C97-C98-C93	147.2(7)
C82-C81-C80-C21B	-16(6)	C96-C97-C98-C93	-79.3(7)
C86-C81-C80-C79	80.4(13)	C99-C93-C98-C102	-98.7(9)
C82-C81-C80-C79	-95.1(12)	C94-C93-C98-C102	137.0(6)
C22B-C21B-C80-C81	166(7)	C100-C93-C98-C102	23.4(9)
C20B-C21B-C80-C81	-15(6)	C99-C93-C98-C97	133.5(8)
C22B-C21B-C80-C79	-90.1(15)	C94-C93-C98-C97	9.2(7)
C20B-C21B-C80-C79	88.9(12)	C100-C93-C98-C97	-104.5(7)
C75-C79-C80-C81	175.7(12)	C99-C93-C100-O10	-60.6(8)
C75-C79-C80-C21B	167.4(17)	C94-C93-C100-O10	64.2(8)
C97-O9-C94-C95	-55.9(7)	C98-C93-C100-O10	174.0(6)
C97-O9-C94-C93	59.7(6)	C97-C98-C102-C103	-80.4(9)
C99-C93-C94-O9	-165.1(6)	C93-C98-C102-C103	159.4(7)
C100-C93-C94-O9	75.2(7)	C98-C102-C103-C12A	173.9(13)
C98-C93-C94-O9	-42.3(6)	C98-C102-C103-C104	180.0(9)
C99-C93-C94-C95	-56.9(9)	C12A-C103-C104-C109	-143(8)
C100-C93-C94-C95	-176.6(7)	C102-C103-C104-C109	82.7(9)
C98-C93-C94-C95	65.9(8)	C12A-C103-C104-C105	33(8)
O9-C94-C95-C96	31.4(8)	C102-C103-C104-C105	-101.8(8)
C93-C94-C95-C96	-75.7(9)	C109-C104-C105-C106	-0.16(18)

Table 3.11 (Cont'd)

C103-C104-C105-C106	-176.3(5)	C104-C103-C12A-C17A	-141(8)
C104-C105-C106-C107	0.1(3)	C102-C103-C12A-C17A	-92.9(13)
C105-C106-C107-C108	-0.1(4)	C104-C103-C12A-C13A	35(8)
C105-C106-C107-C110	179.8(3)	C102-C103-C12A-C13A	82.9(11)
C115-N5-C108-C109	179.9(2)	C103-C12A-C13A-C14A	-177.0(7)
C115-N5-C108-C107	0.0(2)	C17A-C12A-C13A-C14A	0.00(17)
C106-C107-C108-C109	0.1(4)	C12A-C13A-C14A-C15A	0.0(3)
C110-C107-C108-C109	-179.8(3)	C13A-C14A-C15A-C18A	-180.0(2)
C106-C107-C108-N5	180.0(2)	C13A-C14A-C15A-C16A	0.0(3)
C110-C107-C108-N5	0.0(3)	C23A-N1A-C16A-C17A	-179.9(3)
N5-C108-C109-C104	-179.97(18)	C23A-N1A-C16A-C15A	-0.1(2)
C107-C108-C109-C104	-0.1(4)	C14A-C15A-C16A-C17A	0.0(4)
C105-C104-C109-C108	0.2(3)	C18A-C15A-C16A-C17A	179.9(2)
C103-C104-C109-C108	175.3(6)	C14A-C15A-C16A-N1A	-179.9(2)
C106-C107-C110-C111	0.1(5)	C18A-C15A-C16A-N1A	0.0(3)
C108-C107-C110-C111	180.0(3)	N1A-C16A-C17A-C12A	179.92(19)
C106-C107-C110-C115	180.0(3)	C15A-C16A-C17A-C12A	0.1(4)
C108-C107-C110-C115	-0.1(3)	C103-C12A-C17A-C16A	175.7(10)
C115-C110-C111-C112	0.0(4)	C13A-C12A-C17A-C16A	0.0(3)
C107-C110-C111-C112	180.0(3)	C14A-C15A-C18A-C23A	180.0(3)
C110-C111-C112-C113	0.0(4)	C16A-C15A-C18A-C23A	0.0(3)
C111-C112-C113-C114	0.0(4)	C14A-C15A-C18A-C19A	-0.1(5)
C112-C113-C114-C115	-0.1(4)	C16A-C15A-C18A-C19A	180.0(3)
C113-C114-C115-N5	179.9(2)	C23A-C18A-C19A-C20A	-0.1(4)
C113-C114-C115-C110	0.1(4)	C15A-C18A-C19A-C20A	179.9(3)
C108-N5-C115-C114	-179.9(3)	C18A-C19A-C20A-C21A	0.1(4)
C108-N5-C115-C110	-0.1(2)	C19A-C20A-C21A-C22A	-0.1(4)
C111-C110-C115-C114	-0.1(4)	C20A-C21A-C22A-C23A	0.0(3)
C107-C110-C115-C114	180.0(2)	C16A-N1A-C23A-C22A	180.0(2)
C111-C110-C115-N5	-179.9(2)	C16A-N1A-C23A-C18A	0.1(2)
C107-C110-C115-N5	0.1(3)	C21A-C22A-C23A-N1A	-179.9(2)

Table 3.11 (Cont'd)

C21A-C22A-C23A-C18A	0.0(3)	C123-C116-C121-C120	-104.5(6)
C15A-C18A-C23A-N1A	0.0(3)	C122-C116-C121-C120	130.6(7)
C19A-C18A-C23A-N1A	180.0(2)	C117-C116-C121-C120	9.3(7)
C15A-C18A-C23A-C22A	-180.0(2)	C122-C116-C123-O12	-56.4(8)
C19A-C18A-C23A-C22A	0.0(4)	C117-C116-C123-O12	67.6(7)
C120-O11-C117-C118	-56.5(6)	C121-C116-C123-O12	177.5(5)
C120-O11-C117-C116	59.1(6)	C120-C121-C125-C126	-168.9(6)
C123-C116-C117-O11	75.6(6)	C116-C121-C125-C126	71.1(8)
C122-C116-C117-O11	-162.7(6)	C121-C125-C126-C127	170.5(6)
C121-C116-C117-O11	-42.2(6)	C125-C126-C127-C132	84.3(9)
C123-C116-C117-C118	-177.5(6)	C125-C126-C127-C128	-96.5(8)
C122-C116-C117-C118	-55.8(8)	C132-C127-C128-C129	1.3(11)
C121-C116-C117-C118	64.7(7)	C126-C127-C128-C129	-177.9(7)
O11-C117-C118-C119	32.1(7)	C127-C128-C129-C130	-0.3(12)
C116-C117-C118-C119	-74.4(7)	C128-C129-C130-C131	-0.4(11)
C117-C118-C119-C120	3.5(7)	C128-C129-C130-C133	178.3(8)
C117-O11-C120-C124	179.7(6)	C138-N6-C131-C132	177.7(7)
C117-O11-C120-C121	-53.6(6)	C138-N6-C131-C130	-0.9(9)
C117-O11-C120-C119	59.3(6)	C129-C130-C131-N6	178.9(7)
C118-C119-C120-O11	-38.0(6)	C133-C130-C131-N6	-0.2(8)
C118-C119-C120-C124	-152.6(6)	C129-C130-C131-C132	0.2(10)
C118-C119-C120-C121	71.4(7)	C133-C130-C131-C132	-178.9(6)
O11-C120-C121-C125	-102.5(7)	C128-C127-C132-C131	-1.5(10)
C124-C120-C121-C125	16.4(10)	C126-C127-C132-C131	177.7(6)
C119-C120-C121-C125	150.5(6)	N6-C131-C132-C127	-177.6(7)
O11-C120-C121-C116	26.4(7)	C130-C131-C132-C127	0.8(10)
C124-C120-C121-C116	145.4(7)	C129-C130-C133-C138	-177.7(9)
C119-C120-C121-C116	-80.5(7)	C131-C130-C133-C138	1.2(8)
C123-C116-C121-C125	23.2(8)	C129-C130-C133-C134	0.1(15)
C122-C116-C121-C125	-101.7(7)	C131-C130-C133-C134	179.0(8)
C117-C116-C121-C125	137.0(6)	C138-C133-C134-C135	-0.9(12)

Table 3.11 (Cont'd)

C130-C133-C134-C135	-178.5(8)	C161-C156-C157-C158	-0.1(4)
C133-C134-C135-C136	-1.1(14)	C153-C156-C157-C158	-179.9(3)
C134-C135-C136-C137	1.4(16)	C156-C157-C158-C159	0.0(4)
C135-C136-C137-C138	0.3(15)	C157-C158-C159-C160	0.0(4)
C136-C137-C138-N6	-179.2(9)	C158-C159-C160-C161	0.0(4)
C136-C137-C138-C133	-2.4(14)	C154-N7-C161-C156	-0.1(2)
C131-N6-C138-C137	178.8(8)	C154-N7-C161-C160	180.0(2)
C131-N6-C138-C133	1.7(9)	C157-C156-C161-N7	-179.8(2)
C134-C133-C138-C137	2.8(13)	C153-C156-C161-N7	0.1(3)
C130-C133-C138-C137	-179.0(8)	C157-C156-C161-C160	0.2(4)
C134-C133-C138-N6	-180.0(7)	C153-C156-C161-C160	-180.0(2)
C130-C133-C138-N6	-1.8(9)	C159-C160-C161-N7	179.8(2)
C155-C150-C151-C152	-0.36(17)	C159-C160-C161-C156	-0.1(4)
C149-C150-C151-C152	-170.6(5)	C17F-C12F-C13F-C14F	0.1(2)
C150-C151-C152-C153	0.3(3)	C149-C12F-C13F-C14F	178.5(9)
C151-C152-C153-C154	-0.2(3)	C12F-C13F-C14F-C15F	0.0(3)
C151-C152-C153-C156	179.6(2)	C13F-C14F-C15F-C16F	0.0(3)
C161-N7-C154-C155	179.7(3)	C13F-C14F-C15F-C18F	-179.9(3)
C161-N7-C154-C153	0.1(2)	C23F-N1F-C16F-C17F	-179.9(3)
C152-C153-C154-C155	0.2(4)	C23F-N1F-C16F-C15F	-0.1(3)
C156-C153-C154-C155	-179.7(2)	C18F-C15F-C16F-C17F	179.9(3)
C152-C153-C154-N7	179.9(2)	C14F-C15F-C16F-C17F	0.0(4)
C156-C153-C154-N7	0.0(3)	C18F-C15F-C16F-N1F	0.0(3)
N7-C154-C155-C150	-179.85(19)	C14F-C15F-C16F-N1F	-179.9(2)
C153-C154-C155-C150	-0.3(4)	N1F-C16F-C17F-C12F	179.9(2)
C151-C150-C155-C154	0.4(3)	C15F-C16F-C17F-C12F	0.1(4)
C149-C150-C155-C154	169.9(5)	C13F-C12F-C17F-C16F	-0.1(3)
C152-C153-C156-C157	-0.1(5)	C149-C12F-C17F-C16F	-178.3(10)
C154-C153-C156-C157	179.8(3)	C16F-C15F-C18F-C23F	0.0(3)
C152-C153-C156-C161	-179.9(3)	C14F-C15F-C18F-C23F	179.9(3)
C154-C153-C156-C161	0.0(3)	C16F-C15F-C18F-C19F	180.0(3)

Table 3.11 (Cont'd)

C14F-C15F-C18F-C19F	-0.1(5)	O13-C143-C144-C148	-101.0(7)
C23F-C18F-C19F-C20F	0.0(5)	C147-C143-C144-C148	20.0(10)
C15F-C18F-C19F-C20F	-180.0(3)	C142-C143-C144-C148	153.0(6)
C18F-C19F-C20F-C21F	0.0(4)	O13-C143-C144-C139	27.8(7)
C19F-C20F-C21F-C22F	-0.1(4)	C147-C143-C144-C139	148.8(7)
C20F-C21F-C22F-C23F	0.1(4)	C142-C143-C144-C139	-78.2(7)
C19F-C18F-C23F-C22F	0.0(5)	C145-C139-C144-C148	-102.2(8)
C15F-C18F-C23F-C22F	180.0(3)	C146-C139-C144-C148	23.2(8)
C19F-C18F-C23F-N1F	180.0(2)	C140-C139-C144-C148	135.9(6)
C15F-C18F-C23F-N1F	-0.1(3)	C145-C139-C144-C143	129.4(7)
C21F-C22F-C23F-C18F	0.0(4)	C146-C139-C144-C143	-105.2(7)
C21F-C22F-C23F-N1F	-180.0(2)	C140-C139-C144-C143	7.5(7)
C16F-N1F-C23F-C18F	0.1(3)	C145-C139-C146-O14	-57.2(8)
C16F-N1F-C23F-C22F	-180.0(3)	C140-C139-C146-O14	66.3(7)
C143-O13-C140-C141	-56.8(7)	C144-C139-C146-O14	175.2(5)
C143-O13-C140-C139	59.6(6)	C143-C144-C148-C149	-166.7(6)
C145-C139-C140-O13	-163.1(6)	C139-C144-C148-C149	73.0(8)
C146-C139-C140-O13	76.2(7)	C13F-C12F-C149-C150	133(10)
C144-C139-C140-O13	-41.3(7)	C17F-C12F-C149-C150	-49(10)
C145-C139-C140-C141	-54.1(8)	C13F-C12F-C149-C148	79.5(11)
C146-C139-C140-C141	-174.9(6)	C17F-C12F-C149-C148	-102.4(10)
C144-C139-C140-C141	67.6(7)	C155-C150-C149-C12F	-44(10)
O13-C140-C141-C142	33.5(7)	C151-C150-C149-C12F	125(10)
C139-C140-C141-C142	-74.4(7)	C155-C150-C149-C148	84.8(7)
C140-C141-C142-C143	1.7(8)	C151-C150-C149-C148	-105.8(6)
C140-O13-C143-C147	178.0(6)	C144-C148-C149-C12F	-178.8(15)
C140-O13-C143-C142	56.9(6)	C144-C148-C149-C150	175.4(8)
C140-O13-C143-C144	-54.9(6)	C178-C173-C174-C175	3(3)
C141-C142-C143-O13	-35.6(7)	C172-C173-C174-C175	178.3(13)
C141-C142-C143-C147	-152.5(7)	C173-C174-C175-C176	-2.2(19)
C141-C142-C143-C144	72.7(7)	C174-C175-C176-C179	-178.3(13)

Table 3.11 (Cont'd)

C174-C175-C176-C177 2.4(16)	C13C-C14C-C15C-C16C 1(4)
C184-N8-C177-C178 -178.0(14)	C13C-C14C-C15C-C18C 180(3)
C184-N8-C177-C176 -0.1(12)	C23C-N1C-C16C-C17C 174(3)
C179-C176-C177-C178 176.8(11)	C23C-N1C-C16C-C15C 4(3)
C175-C176-C177-C178 -3.7(17)	C14C-C15C-C16C-N1C 175(2)
C179-C176-C177-N8 -1.3(12)	C18C-C15C-C16C-N1C -4(3)
C175-C176-C177-N8 178.2(9)	C14C-C15C-C16C-C17C 3(4)
N8-C177-C178-C173 -177.8(15)	C18C-C15C-C16C-C17C -176(2)
C176-C177-C178-C173 5(2)	N1C-C16C-C17C-C12C -174(3)
C174-C173-C178-C177 -4(3)	C15C-C16C-C17C-C12C -4(4)
C172-C173-C178-C177 -179.0(16)	C13C-C12C-C17C-C16C 0(5)
C175-C176-C179-C184 -177.1(14)	C172-C12C-C17C-C16C -180(5)
C177-C176-C179-C184 2.2(13)	C14C-C15C-C18C-C19C 6(5)
C175-C176-C179-C180 3(2)	C16C-C15C-C18C-C19C -175(3)
C177-C176-C179-C180 -177.5(11)	C14C-C15C-C18C-C23C -177(2)
C176-C179-C180-C181 -179.4(12)	C16C-C15C-C18C-C23C 2(3)
C184-C179-C180-C181 1.0(16)	C23C-C18C-C19C-C20C 0(4)
C179-C180-C181-C182 -2.2(18)	C15C-C18C-C19C-C20C 176(3)
C180-C181-C182-C183 2(2)	C18C-C19C-C20C-C21C -2(4)
C181-C182-C183-C184 0.4(19)	C19C-C20C-C21C-C22C 2(4)
C177-N8-C184-C183 177.7(12)	C20C-C21C-C22C-C23C 0(4)
C177-N8-C184-C179 1.4(13)	C16C-N1C-C23C-C18C -2(3)
C182-C183-C184-N8 -177.4(12)	C16C-N1C-C23C-C22C 173(2)
C182-C183-C184-C179 -1.6(19)	C19C-C18C-C23C-N1C 177(2)
C176-C179-C184-N8 -2.2(14)	C15C-C18C-C23C-N1C 0(3)
C180-C179-C184-N8 177.5(9)	C19C-C18C-C23C-C22C 2(4)
C176-C179-C184-C183 -178.8(12)	C15C-C18C-C23C-C22C -176(2)
C180-C179-C184-C183 1.0(18)	C21C-C22C-C23C-N1C -176(2)
C17C-C12C-C13C-C14C 5(6)	C21C-C22C-C23C-C18C -1(4)
C172-C12C-C13C-C14C -175(3)	C166-O15-C163-C162 60.8(6)
C12C-C13C-C14C-C15C -5(5)	C166-O15-C163-C164 -57.6(6)

Table 3.11 (Cont'd)

C168-C162-C163-O15	-164.1(7)	C168-C162-C167-C171	-101.1(9)
C169-C162-C163-O15	74.0(8)	C163-C162-C167-C171	135.6(7)
C167-C162-C163-O15	-43.1(6)	C169-C162-C167-C171	20.1(9)
C168-C162-C163-C164	-54.5(10)	C168-C162-C167-C166	132.2(8)
C169-C162-C163-C164	-176.4(7)	C163-C162-C167-C166	8.8(7)
C167-C162-C163-C164	66.6(8)	C169-C162-C167-C166	-106.7(7)
O15-C163-C164-C165	33.1(7)	C168-C162-C169-O16	-62.8(9)
C162-C163-C164-C165	-76.6(9)	C163-C162-C169-O16	63.8(9)
C163-C164-C165-C166	3.4(8)	C167-C162-C169-O16	173.2(6)
C163-O15-C166-C165	59.7(7)	C166-C167-C171-C172	-88.5(9)
C163-O15-C166-C170	178.3(7)	C162-C167-C171-C172	152.1(8)
C163-O15-C166-C167	-53.6(7)	C178-C173-C172-C171	91(2)
C164-C165-C166-O15	-38.7(8)	C174-C173-C172-C171	-84(2)
C164-C165-C166-C170	-153.5(7)	C178-C173-C172-C12C	170(25)
C164-C165-C166-C167	69.9(8)	C174-C173-C172-C12C	-5(22)
O15-C166-C167-C171	-100.6(7)	C167-C171-C172-C173	164.0(12)
C165-C166-C167-C171	152.5(6)	C167-C171-C172-C12C	157(2)
C170-C166-C167-C171	19.4(9)	C13C-C12C-C172-C173	-2(21)
O15-C166-C167-C162	27.4(7)	C17C-C12C-C172-C173	177(29)
C165-C166-C167-C162	-79.5(7)	C13C-C12C-C172-C171	102(3)
C170-C166-C167-C162	147.4(7)	C17C-C12C-C172-C171	-79(7)

Table 3.12 Hydrogen bonds for **3.11** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O2-H2O...O7	0.84	1.97	2.805(7)	175.3
O4-H4O...O5	0.84	1.94	2.776(8)	174.3
O6-H6O...O3	0.84	1.95	2.789(8)	175.0
O8-H8O...O1	0.84	1.91	2.740(9)	170.0
O10-H10O...O15#1	0.84	1.95	2.784(7)	173.1
O12-H12O...O13	0.84	1.98	2.814(8)	176.5
O14-H14O...O11	0.84	1.94	2.776(8)	175.1
O16-H16O...O9#2	0.84	1.95	2.765(8)	163.2

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

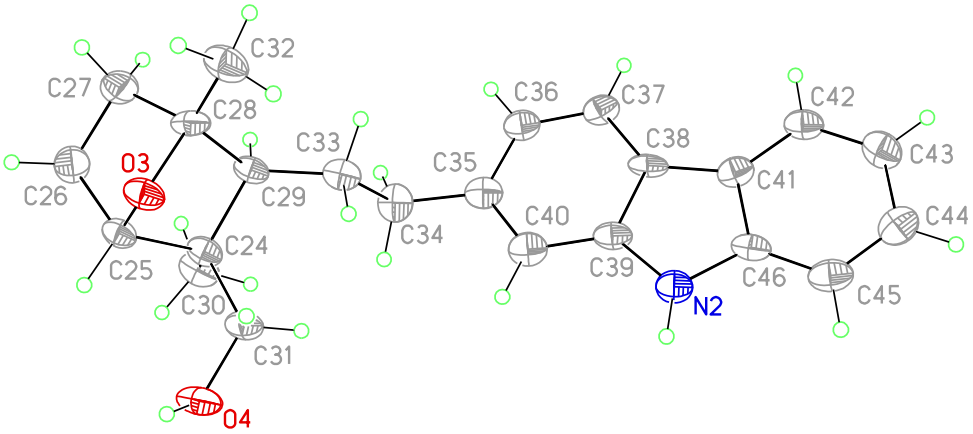


Figure 3.3 View of molecule 2 of **3.11** showing the atom labeling scheme. Displacement ellipsoids are scaled to the 50% probability level.

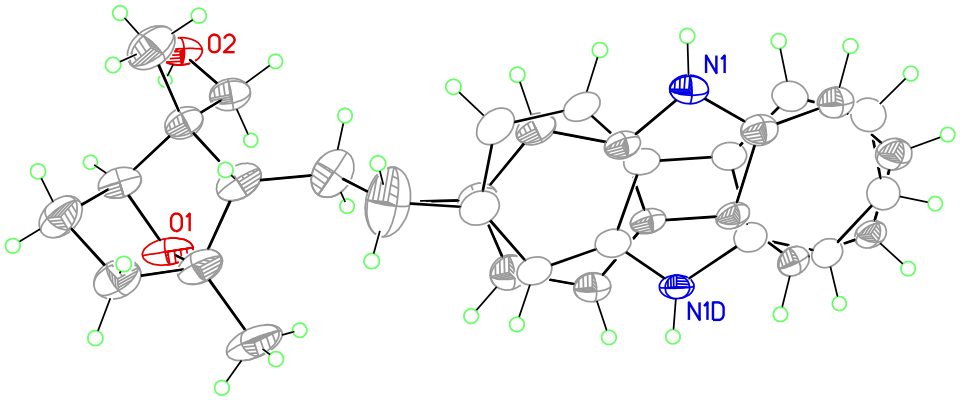


Figure 3.4 View of molecule 1 of **3.11** showing the partial atom labeling scheme. Displacement ellipsoids are scaled to the 50% probability level. The disorder of the carbazole group can be seen in the figure.

X-ray Experimental for $C_{23}H_{27}NO_2$ (3.12)

Crystals grew as clusters of colorless prisms by slow evaporation from benzene and ether. The data crystal was cut from a large cluster of crystals and had approximate dimensions; 0.20 x 0.10 x 0.06 mm. The data were collected on a Rigaku AFC12 diffractometer with a Saturn 724+ CCD using a graphite monochromator with MoKα radiation (λ = 0.71073Å). A total of 1288 frames of data were collected using ω-scans with a scan range of 0.5° and a counting time of 45 seconds per frame. The data were collected at 100 K using a Rigaku XStream low temperature device. Details of crystal data, data collection and structure refinement are listed in Table 3.13. Data reduction were performed using the Rigaku Americas Corporation's Crystal Clear version 1.40.[75] The structure was solved by direct methods using SIR2004[76] and refined by full-matrix least-squares on F^2 with anisotropic displacement parameters for the non-H atoms using SHELXL-2014/7.[77] Structure analysis was aided by use of the programs PLATON98[70] and WinGX.[71] The hydrogen atoms on carbon 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 nitrogen and the hydroxyl oxygen atoms were located in a ΔF map and refined with isotropic displacement parameters. The absolute configuration was assigned by internal comparison to the known configuration of the molecule.

The function, $\Sigma w(|F_O|^2 - |F_C|^2)^2$, was minimized, where $w = 1/[(\sigma(F_O))^2 + (0.0562*P)^2 + (0.1009*P)]$ and $P = (|F_O|^2 + 2|F_C|^2)/3$. $R_W(F^2)$ refined to 0.109, with R(F) equal to 0.0440 and a goodness of fit, S, = 1.09. Definitions used for calculating R(F), $R_W(F^2)$ and the goodness of fit, S, are given below.[72] 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).[73] All figures were generated using SHELXTL/PC.[74] Tables of positional and thermal parameters, bond lengths and angles, torsion angles and figures are found elsewhere.

Table 3.13 Crystal data and structure refinement for **3.12**.

Empirical formula	C23 H27 N O2	
Formula weight	349.45	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 7.590(2) Å	□= 90°.
	b = 10.101(3) Å	□= 90°.
	c = 24.188(7) Å	□ = 90°.
Volume	1854.4(10) $Å^3$	
Z	4	
Density (calculated)	1.252 Mg/m^3	
Absorption coefficient	0.079 mm^{-1}	
F(000)	752	
Crystal size	0.200 x 0.100 x 0.060 mm^3	
Theta range for data collection	1.684 to 27.493°.	
Index ranges	-9<=h<=9, -13<=k<=13, -30<=l<=31	
Reflections collected	26641	
Independent reflections	4237 [R(int) = 0.0497]	
Completeness to theta = 25.242°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00 and 0.726	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4237 / 0 / 249	
Goodness-of-fit on F^2	1.090	
Final R indices [I>2sigma(I)]	R1 = 0.0440, wR2 = 0.1071	
R indices (all data)	R1 = 0.0465, wR2 = 0.1088	
Absolute structure parameter	-0.3(5)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.189 and -0.157 $e.Å^{-3}$	

Table 3.14 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **3.12**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C1	3421(3)	6050(2)	4269(1)	24(1)
C2	2512(3)	6198(2)	4770(1)	29(1)
C3	773(3)	6603(2)	4744(1)	32(1)
C4	-58(3)	6848(2)	4240(1)	30(1)
C5	834(3)	6686(2)	3743(1)	27(1)
C6	2589(3)	6273(2)	3756(1)	23(1)
C7	3896(3)	5987(2)	3334(1)	22(1)
C8	3897(3)	6018(2)	2757(1)	24(1)
C9	5409(3)	5702(2)	2459(1)	21(1)
C10	5393(3)	5753(2)	1821(1)	22(1)
C11	4159(3)	6860(3)	1623(1)	28(1)
C12	4339(3)	7127(3)	1001(1)	27(1)
C13	6197(3)	7566(2)	867(1)	24(1)
C14	7619(3)	6537(2)	1023(1)	24(1)
C15	7306(3)	6106(2)	1636(1)	23(1)
C16	8575(3)	5023(3)	1829(1)	32(1)
C17	8631(3)	4939(3)	2454(1)	36(1)
C18	6941(3)	5303(2)	2748(1)	24(1)
C19	6957(3)	5261(2)	3326(1)	24(1)
C20	5450(3)	5624(2)	3614(1)	23(1)
C21	4678(4)	4412(3)	1615(1)	34(1)
C22	7619(3)	5364(2)	619(1)	29(1)
C23	9429(3)	7235(3)	985(1)	33(1)
N1	5155(3)	5688(2)	4181(1)	26(1)
O1	6380(2)	7858(2)	285(1)	29(1)
O2	8187(2)	5733(2)	71(1)	32(1)

Table 3.15 Bond lengths [Å] and angles [°] for **3.12**.

C1-N1	1.383(3)	C13-H13	1.00
C1-C2	1.401(3)	C14-C22	1.535(3)
C1-C6	1.411(3)	C14-C23	1.547(3)
C2-C3	1.384(3)	C14-C15	1.563(3)
C2-H2	0.95	C15-C16	1.531(3)
C3-C4	1.395(3)	C15-H15	1.00
C3-H3	0.95	C16-C17	1.514(3)
C4-C5	1.389(3)	C16-H16A	0.99
C4-H4	0.95	C16-H16B	0.99
C5-C6	1.396(3)	C17-C18	1.512(3)
C5-H5	0.95	C17-H17A	0.99
C6-C7	1.453(3)	C17-H17B	0.99
C7-C8	1.396(3)	C18-C19	1.398(3)
C7-C20	1.409(3)	C19-C20	1.388(3)
C8-C9	1.392(3)	C19-H19	0.95
C8-H8	0.95	C20-N1	1.390(3)
C9-C18	1.416(3)	C21-H21A	0.98
C9-C10	1.543(3)	C21-H21B	0.98
C10-C11	1.536(3)	C21-H21C	0.98
C10-C21	1.543(3)	C22-O2	1.442(3)
C10-C15	1.561(3)	C22-H22A	0.99
C11-C12	1.533(3)	C22-H22B	0.99
C11-H11A	0.99	C23-H23A	0.98
C11-H11B	0.99	C23-H23B	0.98
C12-C13	1.514(3)	C23-H23C	0.98
C12-H12A	0.99	N1-H1N	0.92(3)
C12-H12B	0.99	O1-H1O	0.87(4)
C13-O1	1.445(3)	O2-H2O	0.96(4)
C13-C14	1.545(3)		

Table 3.15 (Cont'd)

N1-C1-C2	129.1(2)	C21-C10-C15	115.74(19)
N1-C1-C6	109.39(19)	C9-C10-C15	106.74(16)
C2-C1-C6	121.5(2)	C12-C11-C10	112.36(18)
C3-C2-C1	117.6(2)	C12-C11-H11A	109.1
C3-C2-H2	121.2	C10-C11-H11A	109.1
C1-C2-H2	121.2	C12-C11-H11B	109.1
C2-C3-C4	121.5(2)	C10-C11-H11B	109.1
C2-C3-H3	119.3	H11A-C11-H11B	107.9
C4-C3-H3	119.3	C13-C12-C11	110.19(18)
C5-C4-C3	121.0(2)	C13-C12-H12A	109.6
C5-C4-H4	119.5	C11-C12-H12A	109.6
C3-C4-H4	119.5	C13-C12-H12B	109.6
C4-C5-C6	118.7(2)	C11-C12-H12B	109.6
C4-C5-H5	120.6	H12A-C12-H12B	108.1
C6-C5-H5	120.6	O1-C13-C12	111.01(18)
C5-C6-C1	119.6(2)	O1-C13-C14	107.92(17)
C5-C6-C7	134.1(2)	C12-C13-C14	113.66(19)
C1-C6-C7	106.3(2)	O1-C13-H13	108.0
C8-C7-C20	119.11(19)	C12-C13-H13	108.0
C8-C7-C6	134.3(2)	C14-C13-H13	108.0
C20-C7-C6	106.59(19)	C22-C14-C13	111.35(18)
C9-C8-C7	120.88(19)	C22-C14-C23	108.35(19)
C9-C8-H8	119.6	C13-C14-C23	107.42(19)
C7-C8-H8	119.6	C22-C14-C15	112.87(19)
C8-C9-C18	119.07(19)	C13-C14-C15	108.18(17)
C8-C9-C10	120.24(18)	C23-C14-C15	108.49(18)
C18-C9-C10	120.68(18)	C16-C15-C10	109.51(19)
C11-C10-C21	108.89(19)	C16-C15-C14	113.14(18)
C11-C10-C9	110.00(18)	C10-C15-C14	118.56(17)
C21-C10-C9	107.28(18)	C16-C15-H15	104.7
C11-C10-C15	108.11(18)	C10-C15-H15	104.7

Table 3.15 (Cont'd)

C14-C15-H15	104.7	C10-C21-H21B	109.5
C17-C16-C15	111.3(2)	H21A-C21-H21B	109.5
C17-C16-H16A	109.4	C10-C21-H21C	109.5
C15-C16-H16A	109.4	H21A-C21-H21C	109.5
C17-C16-H16B	109.4	H21B-C21-H21C	109.5
C15-C16-H16B	109.4	O2-C22-C14	112.65(19)
H16A-C16-H16B	108.0	O2-C22-H22A	109.1
C18-C17-C16	115.6(2)	C14-C22-H22A	109.1
C18-C17-H17A	108.4	O2-C22-H22B	109.1
C16-C17-H17A	108.4	C14-C22-H22B	109.1
C18-C17-H17B	108.4	H22A-C22-H22B	107.8
C16-C17-H17B	108.4	C14-C23-H23A	109.5
H17A-C17-H17B	107.4	C14-C23-H23B	109.5
C19-C18-C9	120.7(2)	H23A-C23-H23B	109.5
C19-C18-C17	117.13(19)	C14-C23-H23C	109.5
C9-C18-C17	122.20(19)	H23A-C23-H23C	109.5
C20-C19-C18	119.1(2)	H23B-C23-H23C	109.5
C20-C19-H19	120.4	C1-N1-C20	108.56(19)
C18-C19-H19	120.4	C1-N1-H1N	122(2)
C19-C20-N1	129.8(2)	C20-N1-H1N	129(2)
C19-C20-C7	121.11(19)	C13-O1-H1O	112(2)
N1-C20-C7	109.10(19)	C22-O2-H2O	99(2)
C10-C21-H21A	109.5		

Table 3.16 Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **3.12**. 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	28(1)	23(1)	21(1)	0(1)	2(1)	-5(1)
C2	39(1)	30(1)	19(1)	-1(1)	3(1)	-7(1)
C3	38(1)	31(1)	27(1)	-4(1)	10(1)	-5(1)
C4	29(1)	33(1)	29(1)	-4(1)	6(1)	-2(1)
C5	27(1)	29(1)	24(1)	-2(1)	1(1)	-2(1)
C6	27(1)	22(1)	21(1)	-1(1)	2(1)	-5(1)
C7	22(1)	24(1)	21(1)	1(1)	0(1)	-2(1)
C8	21(1)	28(1)	22(1)	2(1)	0(1)	0(1)
C9	22(1)	25(1)	17(1)	2(1)	0(1)	-1(1)
C10	23(1)	28(1)	16(1)	1(1)	0(1)	0(1)
C11	22(1)	39(1)	22(1)	4(1)	1(1)	6(1)
C12	24(1)	36(1)	22(1)	6(1)	-1(1)	4(1)
C13	29(1)	28(1)	16(1)	1(1)	0(1)	0(1)
C14	23(1)	31(1)	19(1)	1(1)	2(1)	1(1)
C15	20(1)	30(1)	20(1)	0(1)	-1(1)	2(1)
C16	29(1)	45(1)	23(1)	4(1)	2(1)	11(1)
C17	28(1)	58(2)	23(1)	5(1)	1(1)	13(1)
C18	21(1)	28(1)	23(1)	2(1)	1(1)	0(1)
C19	22(1)	28(1)	20(1)	3(1)	-3(1)	-1(1)
C20	26(1)	24(1)	19(1)	2(1)	-1(1)	-3(1)
C21	43(1)	35(1)	24(1)	1(1)	-1(1)	-10(1)
C22	36(1)	34(1)	18(1)	0(1)	5(1)	5(1)
C23	25(1)	53(2)	22(1)	5(1)	1(1)	-5(1)
N1	28(1)	32(1)	17(1)	0(1)	0(1)	-3(1)
O1	32(1)	38(1)	18(1)	5(1)	2(1)	4(1)
O2	33(1)	44(1)	18(1)	0(1)	6(1)	5(1)

Table 3.17 Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for **3.12**.

	x	y	z	U(eq)
H2	3070	6026	5114	35
H3	129	6717	5078	38
H4	-1252	7129	4236	36
H5	262	6855	3401	32
H8	2853	6258	2565	29
H11A	2926	6611	1706	33
H11B	4428	7683	1829	33
H12A	4056	6312	792	33
H12B	3495	7825	889	33
H13	6443	8396	1079	29
H15	7627	6901	1860	28
H16A	8195	4160	1676	39
H16B	9771	5213	1687	39
H17A	8953	4024	2559	43
H17B	9579	5530	2589	43
H19	7985	4989	3519	28
H21A	5488	3703	1724	51
H21B	4578	4431	1211	51
H21C	3516	4250	1777	51
H22A	8409	4665	763	35
H22B	6414	4991	597	35
H23A	10370	6571	994	50
H23B	9566	7840	1299	50
H23C	9499	7737	639	50
H1O	5470(50)	8280(40)	157(14)	69(11)
H2O	7420(50)	6480(40)	12(15)	78(12)
H1N	5900(50)	5460(30)	4466(13)	60(10)

Table 3.18 Torsion angles [°] for **3.12**.

N1-C1-C2-C3	178.6(2)	O1-C13-C14-C22	-49.6(2)
C6-C1-C2-C3	-1.6(3)	C12-C13-C14-C22	74.0(2)
C1-C2-C3-C4	0.5(4)	O1-C13-C14-C23	68.9(2)
C2-C3-C4-C5	0.3(4)	C12-C13-C14-C23	-167.54(18)
C3-C4-C5-C6	0.0(3)	O1-C13-C14-C15	-174.20(17)
C4-C5-C6-C1	-1.1(3)	C12-C13-C14-C15	-50.6(2)
C4-C5-C6-C7	179.0(2)	C11-C10-C15-C16	179.80(18)
N1-C1-C6-C5	-178.2(2)	C21-C10-C15-C16	-57.8(2)
C2-C1-C6-C5	1.9(3)	C9-C10-C15-C16	61.5(2)
N1-C1-C6-C7	1.7(2)	C11-C10-C15-C14	-48.3(3)
C2-C1-C6-C7	-178.1(2)	C21-C10-C15-C14	74.1(3)
C5-C6-C7-C8	0.0(4)	C9-C10-C15-C14	-166.63(19)
C1-C6-C7-C8	-179.9(3)	C22-C14-C15-C16	53.0(3)
C5-C6-C7-C20	179.3(2)	C13-C14-C15-C16	176.70(19)
C1-C6-C7-C20	-0.7(2)	C23-C14-C15-C16	-67.1(3)
C20-C7-C8-C9	-0.3(3)	C22-C14-C15-C10	-77.2(2)
C6-C7-C8-C9	178.9(2)	C13-C14-C15-C10	46.4(3)
C7-C8-C9-C18	2.1(3)	C23-C14-C15-C10	162.7(2)
C7-C8-C9-C10	-179.4(2)	C10-C15-C16-C17	-63.3(3)
C8-C9-C10-C11	33.1(3)	C14-C15-C16-C17	162.0(2)
C18-C9-C10-C11	-148.4(2)	C15-C16-C17-C18	31.0(3)
C8-C9-C10-C21	-85.1(3)	C8-C9-C18-C19	-1.7(3)
C18-C9-C10-C21	93.3(2)	C10-C9-C18-C19	179.8(2)
C8-C9-C10-C15	150.2(2)	C8-C9-C18-C17	179.8(2)
C18-C9-C10-C15	-31.3(3)	C10-C9-C18-C17	1.3(3)
C21-C10-C11-C12	-73.1(2)	C16-C17-C18-C19	-178.8(2)
C9-C10-C11-C12	169.65(18)	C16-C17-C18-C9	-0.3(4)
C15-C10-C11-C12	53.4(2)	C9-C18-C19-C20	-0.4(3)
C10-C11-C12-C13	-61.1(3)	C17-C18-C19-C20	178.2(2)
C11-C12-C13-O1	-178.40(18)	C18-C19-C20-N1	-178.6(2)
C11-C12-C13-C14	59.7(3)	C18-C19-C20-C7	2.2(3)

Table 3.18 (Cont'd)

C8-C7-C20-C19	-1.9(3)	C15-C14-C22-O2	-170.60(18)
C6-C7-C20-C19	178.7(2)	C2-C1-N1-C20	177.7(2)
C8-C7-C20-N1	178.8(2)	C6-C1-N1-C20	-2.2(2)
C6-C7-C20-N1	-0.6(3)	C19-C20-N1-C1	-177.5(2)
C13-C14-C22-O2	67.5(2)	C7-C20-N1-C1	1.7(3)
C23-C14-C22-O2	-50.4(3)		

Table 3.19 Hydrogen bonds for **3.12** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C13-H13...N1#1	1.00	2.69	3.319(3)	121.2
O1-H1O...O2#2	0.87(4)	2.07(4)	2.940(3)	174(3)
O2-H2O...O1	0.96(4)	1.73(4)	2.599(3)	148(3)
N1-H1N...O2#3	0.92(3)	2.02(3)	2.878(3)	154(3)

Symmetry transformations used to generate equivalent atoms:
#1 -x+1,y+1/2,-z+1/2 #2 x-1/2,-y+3/2,-z #3 -x+3/2,-y+1,z+1/2

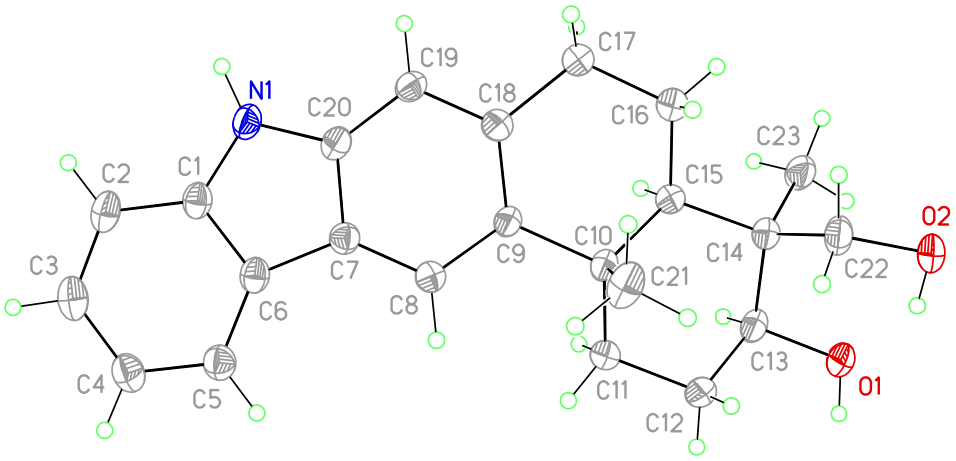


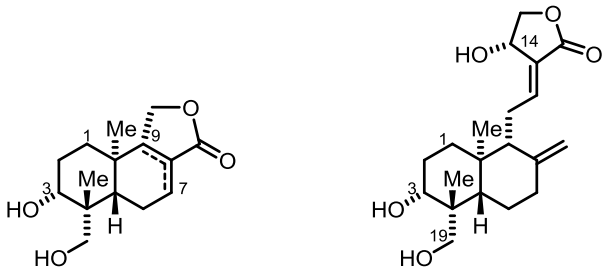
Figure 3.5 View of **3.12** showing the atom labeling scheme. Displacement ellipsoids are scaled to the 50% probability level.

Chapter 4: Total Synthesis of Isoiresin and Ongoing Effort toward Synthesis of Andrographolide: Modular Terpenoid Construction via Ir-Catalyzed *tert*-(Hydroxy)prenylation and Diels-Alder Cycloaddition*

4.1 INTRODUCTION

As introduced in the previous chapter, terpenoids are a very important family of natural products on earth. A concise asymmetric synthesis of terpenoid natural products oridamycin A, triptoquinones B and C, which is enabled via diastereo- and enantioselective *tert*-(hydroxy)prenylation, has been described in the former chapter. It still makes one wonder, however, whether this methodology can be combined with other strategy to access structurally different molecules.

Isoiresin,[1,2] the C8-C9 double bond isomer of iresin,[1–11] is a sesquiterpenoid[12] from drimane (iresane) family[13] in which members contain a bicyclofarnesol skeleton (Figure 4.1, left). This skeleton more often presents in heavier di- and triterpenoids, and therefore it was regarded as the link between lower and higher terpenoids. There are two known synthetic reports (one is asymmetric) with step-count ranging from 24 to 27.[14,15]



Isoiresin 8,9-didehydro (**4.1**)
Iresin 7,8-didehydro

Andrographolide (4.2)

Figure 4.1 Structures of isoiresin and andrographolide.

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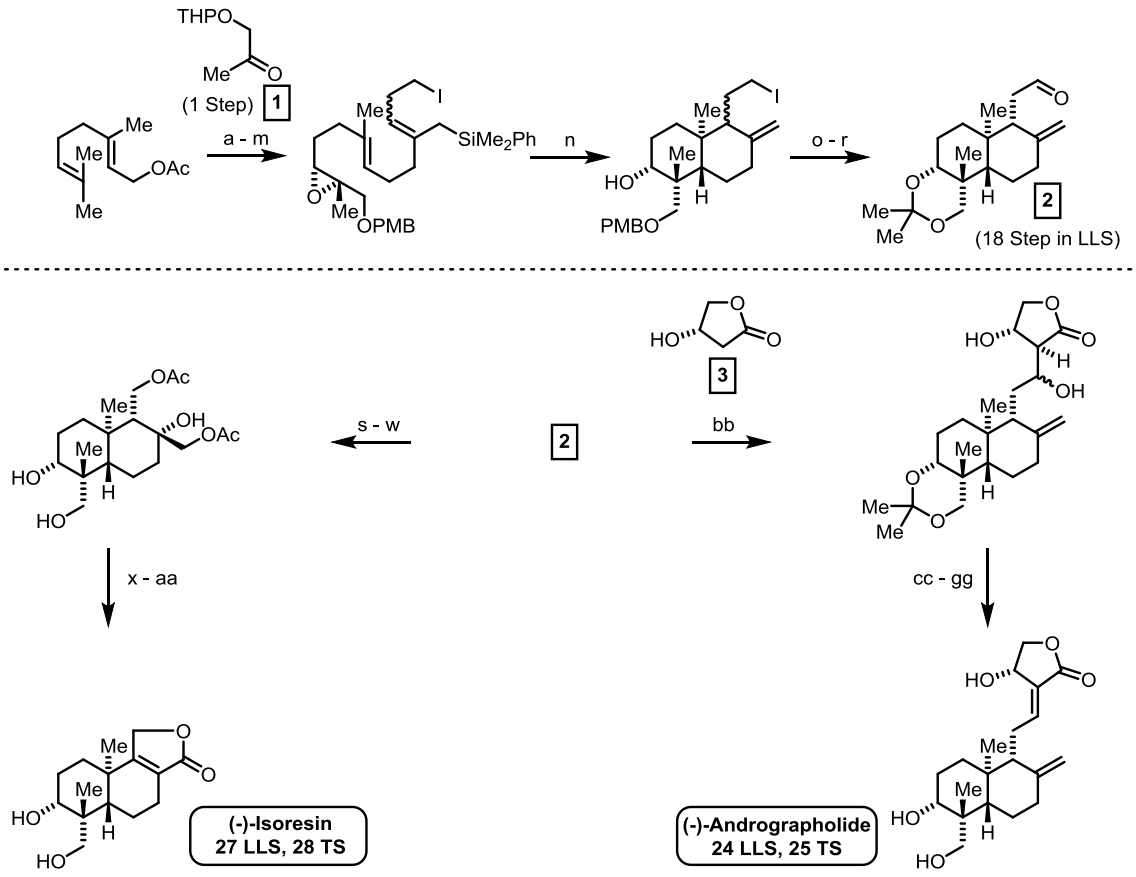
* This chapter is partially based on the previously published work:
Feng, J.; Noack, F.; Krische, M. J. *J. Am. Chem. Soc.* **2016**, *138*, 12364–12367.
J. F. contributed to route designs (Scheme 4.2), synthesis of isoiresin (Table 4.1, Table 4.2, Scheme 4.3, and Scheme 4.4), synthesis of andrographolide (Table 4.3, Table 4.4, Scheme 4.7, and Scheme 4.8), and preparation of manuscript and supporting information.

Andrographolide, a diterpenoid with *ent*-labdane backbone (Figure 4.1, right), was first isolated from *Andrographis paniculata* Nees.[16–19] As the main bitter component in this Chinese traditional medicinal herb, andrographolide and its congeners exhibit various attractive bioactivities[20–23] such as anti-inflammatory, antivirus,[21] anticancer,[22] etc. Beside obtained from natural source, there is one asymmetric total synthesis of andrographolide known in literature.[24]

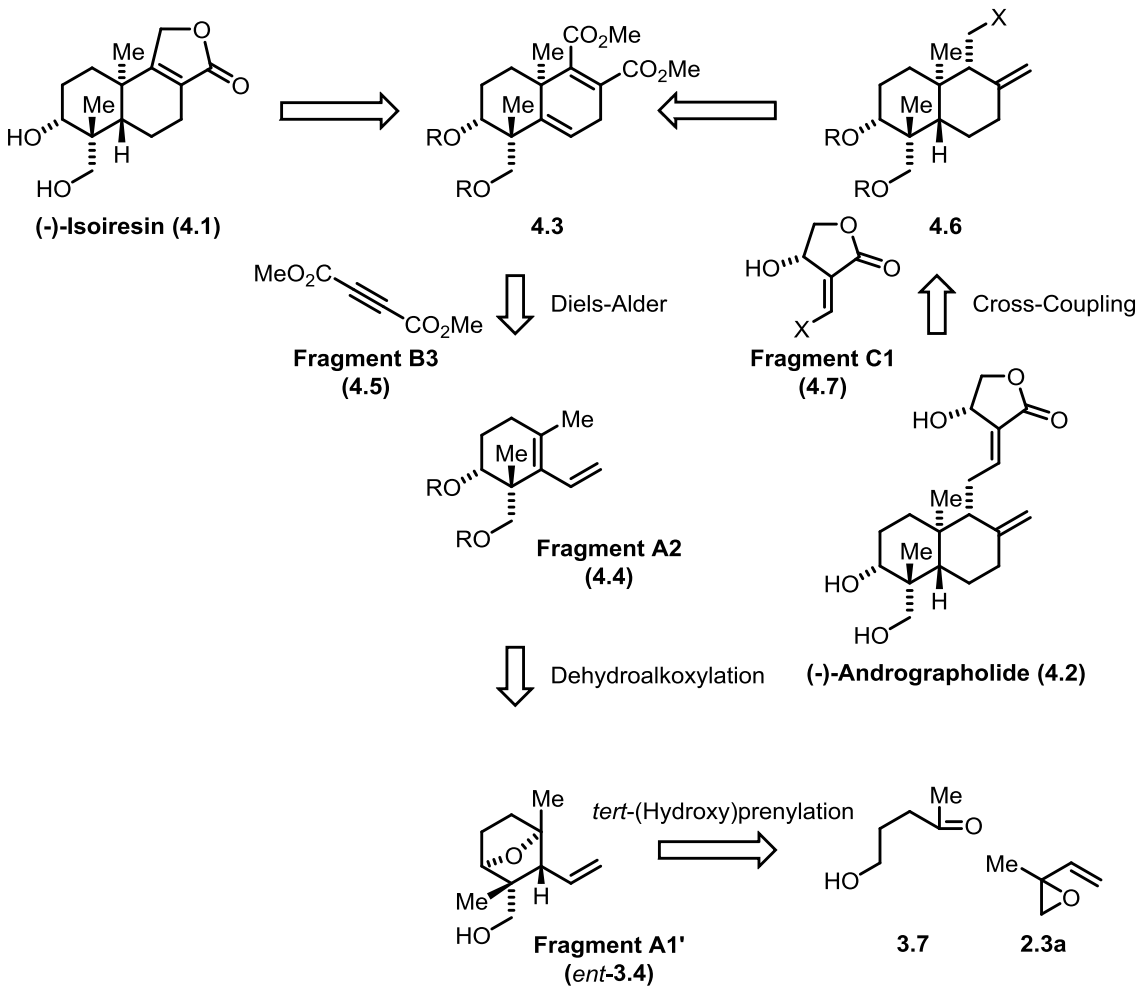


Key: (a) O_3, pyridine, then $NaBH_4$, MeOH; (b) I_2, Ph_3P, imid; (c) K_2CO_3, MeOH; (d) PPh_3; (e) *n*-BuLi, then **A**; (f) I_2, Ph_3P, imid; (g) cyclopropyl methyl ketone, LDA; (h) PTSA; (i) $Ti(Oi\text{-}Pr)_4$, L-(+)-DIPT, *t*-BuOOH, CaH_2, silica gel, 4A MS; (j) PMBBr, NaH, TBAI; (k) $PhMe_2SiCH_2MgCl$, $CeCl_3$; (l) $MgI_2{\bullet}(OEt_2)_n$; (m) K_2CO_3; (n) $SnCl_4$; (o) DDQ; (p) K_2CO_3; (q) $Me_2C(OMe)_2$, PPTS; (r) DMSO, $NaHCO_3$; (s) CH_3Li; (t) $(COCl)_2$, DMSO, Et_3N; (u) TFAA, H_2O_2 (50% aq.), NaH_2PO_4; (v) 6N HCl; (w) Ac_2O, DMAP, pyridine; (x) MsCl, Et_3N; (y) NaOMe, MeOH; (z) Ag_2CO_3/Celite; (aa) $NaBH_4$; (bb) **3**, LDA; (cc) TBSCl, imid; (dd) MsCl, Et_3N; (ee) DIPEA; (ff) TBAF; (gg) $HOAc/H_2O$.

Scheme 4.1 Prior asymmetric syntheses of isoiresin and andrographolide.

Polyene-cyclization strategy was used in both prior asymmetric syntheses of isoiresin and andrographolide to set the contiguous stereocenters in correct manner, but it took too many steps to prepare the cyclizing precursor which made the whole route impractical (Scheme 4.1).

4.2 RETROSYNTHETIC ANALYSIS



Scheme 4.2 Retrosynthetic analysis of isoiresin and andrographolide.

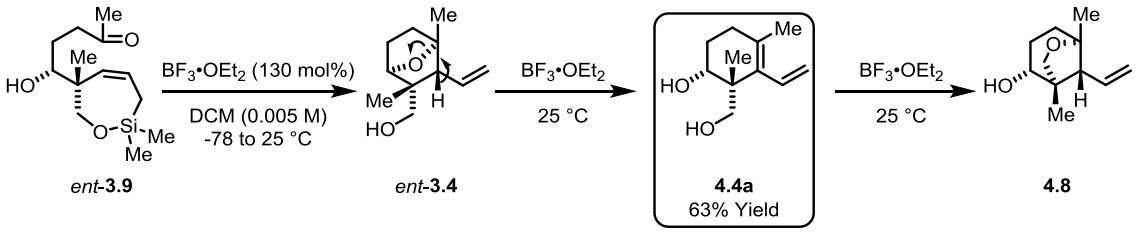
Success of constructing the *trans*-decalin moiety in oridamycin A, triptoquinones B and C via Ir-catalyzed stereoselective *tert*-(hydroxy)prenylation and intramolecular

Friedel-Crafts cyclization encouraged us to explore similar modular synthetic strategy in total synthesis of isoiresin and andrographolide. We envisioned that isoiresin could be synthesized from **4.3**, which is the product of Diels-Alder cycloaddition between diene **4.4** (Fragment **A2**) and acetylenedicarboxylate **4.5** (Fragment **B3**). Fragment **A2** is the dehydroalkoxylation product from known compound *ent*-**3.4** (enantiomer of Fragment **A1** in synthesis of oridamycin and triptoquinones). Therefore, the previously developed route to the oxabicycle **3.4** was modified and used in this synthesis to quickly access material for the above-mentioned fragment union (Scheme 4.2, left).

Andrographolide retrosynthetically is constructed from *trans*-decalin and lactone fragment (**4.6** and **4.7**) via cross-coupling. **4.6** is expected to be prepared from **4.3**, the same intermediate in synthetic plan of isoiresin (Scheme 4.2, right). Therefore, the two natural products could be synthesized via a uniformed strategy including *tert*-(hydroxy)prenylation and intermolecular Diels-Alder reaction as key steps.

4.3 Completion of Synthesis of Isoiresin

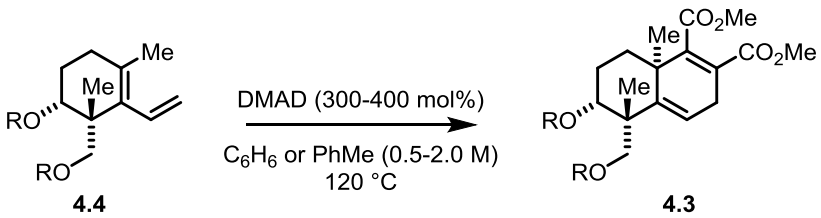
During the process of exploring optimal condition for formation of Fragment **A1** via Sakurai annulation from cyclic siloxane **3.9** in the synthesis of oridamycin A, triptoquinones B and C, diene *ent*-**4.4a** was once isolated as side product in the reaction. This observation suggested that it was possible to obtain **4.4a** directly from allylic silane *ent*-**3.9** upon modification of the developed condition. Indeed, when *ent*-**3.9** (prepared from the exact route in Scheme 3.7 but using (*S*)-**2.5h** instead in the first step) was exposed to BF_3•OEt_2 at ambient temperature, *ent*-**3.4** was formed at the beginning but slowly transformed to the desired diene **4.4a** as reaction proceeded. Yield of **4.4a** was quite sensitive to reaction time, as the diene continued to react under Lewis acidic condition to form another more stable oxabyclic byproduct **4.8** (Scheme 4.3).



Scheme 4.3 Synthesis of diene **4.4a** from cyclic siloxane *ent*-**3.9**.

Attempt to use **4.4a** directly in the following Diels-Alder reaction[25] was not successful because of the instability of unprotected dienol at high temperature. Carboxylates **4.4b-d** were therefore prepared and reacted with dimethyl acetylenedicarboxylate (DMAD, **4.5**). Gratifyingly, cycloadducts were obtained, and an apparent trend which correlated the size of carboxylates and the diastereoselectivity of angular methyl group in products was observed (Table 4.1). A larger protecting group led to a much higher facial selectivity, and a 10:1 diastereomeric ratio in favor of the desired stereoisomer was achieved when pivalate was used.

Table 4.1 Diels-Alder reaction between diene **4.4** and DMAD.

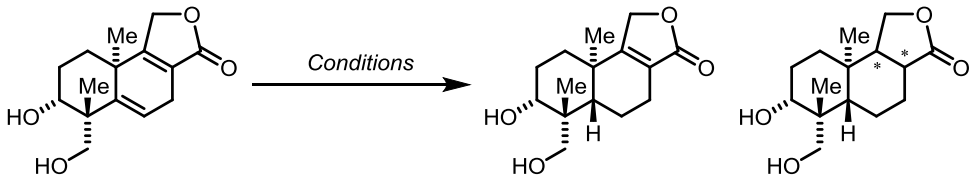


Entry	R	Product	**4.3** Yield (*dr*)
1	Ac (**4.4b**)	**4.3b**	61% (2.5:1)
2	*i*BuCO (**4.4c**)	**4.3c**	59% (4.5:1)
3	Piv (**4.4d**)	**4.3d**	74% (10:1)

With the [4+2] adduct in hand, a global reduction by lithium aluminum hydride was performed to obtain tetraol **4.9** in 78% yield. A chemoselective oxidation of the less

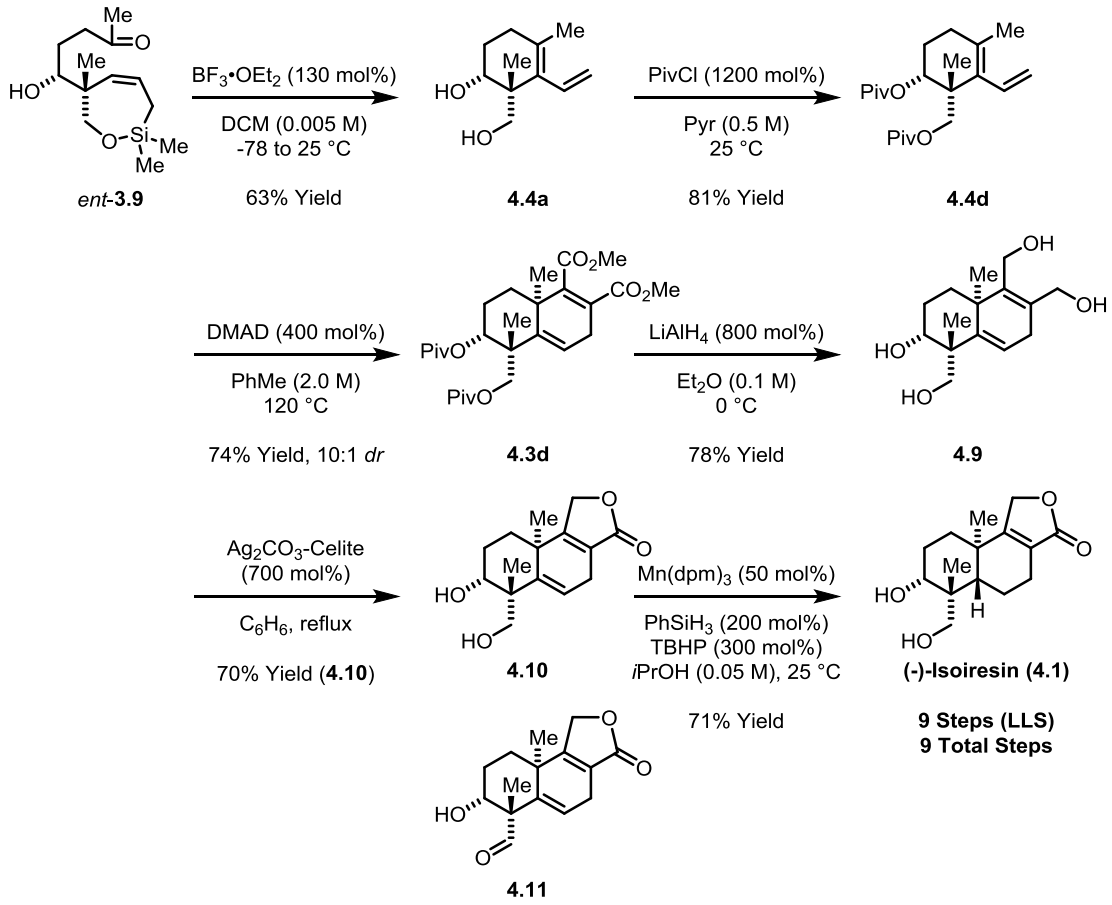
steric hindered allylic primary alcohol with Fétizon's reagent[26–29] gave the desired lactonized product **4.10** in good yield with a small amount of over-oxidized side product **4.11**. The last step was regio- and stereoselective reduction of the trisubstituted olefin in **4.10**, and transformation in similar systems have been reported by using Pd/C catalyzed hydrogenation.[30,31] However, when **4.10** was exposed to the hydrogenative condition, instead of isoiresin, over-reduction product **4.12** was obtained (Table 4.2). Switching solvents or using other metal catalysts did alternate the outcome of reactions, but we could only obtain a mixture of isoiresin and **4.12** at best. The unsatisfactory results with heterogeneous catalysts led us to explore chemical reduction methods. Fortunately, the Mn-catalyzed silane reduction reported by Shenvi and coworkers[32] managed to give the desired mono-reduction product isoiresin chemoselectively. Therefore, asymmetric total synthesis of terpenoid isoiresin (**4.1**) was completed in 9 steps (Scheme 4.4), which is significantly shorter than prior reports.

Table 4.2 Selected reaction conditions for olefin reduction to isoiresin **4.1**.



4.10 **(-)-Isoiresin (4.1)** **4.12**

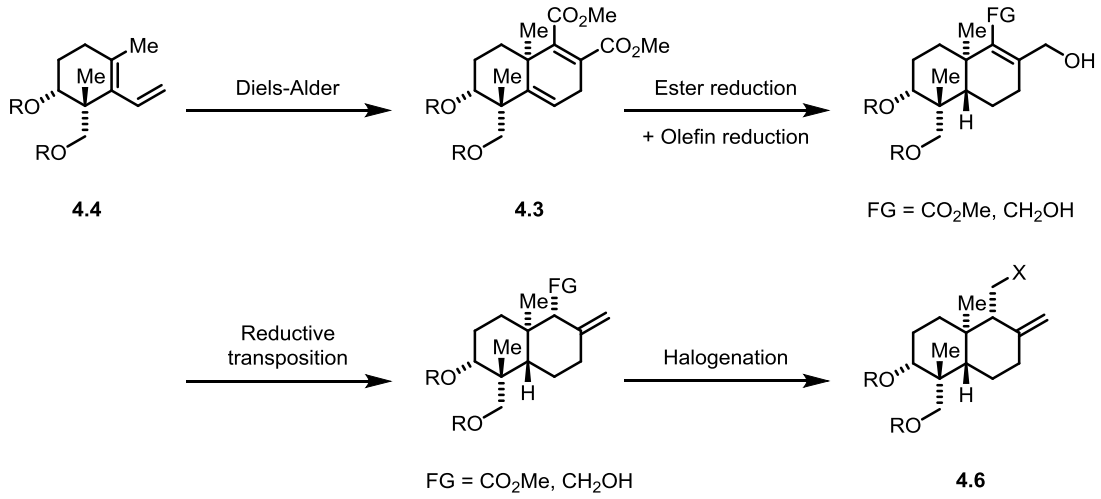
Entry	Condition	**4.1** Yield	**4.12** Yield	Chemoselectivity (**4.1**/**4.12**)
1	H_2, Pd/C MeOH, 25 °C	--	40%	--
2	H_2, Pd/C EtOH, 25 °C	21%	18%	1.2
3	H_2, Pd/C EtOAc, 25 °C	--	--	n.d.
4	H_2, Rh/C EtOH, 25 °C	n.d.	n.d.	1.2
5	H_2, PtO_2 EtOH, 25 °C	--	--	n.d.
6	**$PhSiH_3$, $Mn(dpm)_3$ TBHP, *i*PrOH, 25 °C**	**71%**	**--**	**n.d.**



Scheme 4.4 Asymmetric synthesis of isoiresin via diastereoselective Diels-Alder addition.

4.4 PROGRESS TOWARDS SYNTHESIS OF ANDROGRAPHOLIDE

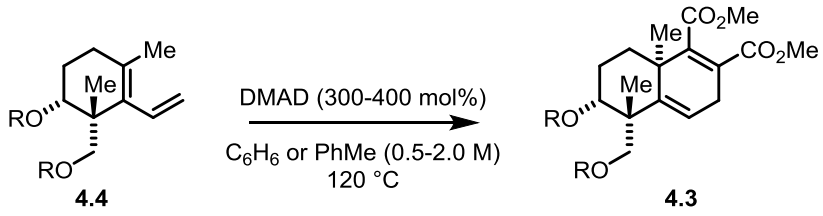
The successful application of Diels-Alder reaction in synthesis of isoiresin encouraged us to commence total synthesis of andrographolide. The synthetic plan of *trans*-decalin fragment **4.6** is shown in Scheme 4.5: after obtaining the cycloadduct, chemoselective reduction of alkene and methyl ester would be performed. A reductive transposition would be applied to form the exocyclic double bond, and halogenation of this compound would lead to target fragment **4.6**.



Scheme 4.5 Synthetic plan of *trans*-decalin fragment **4.6**.

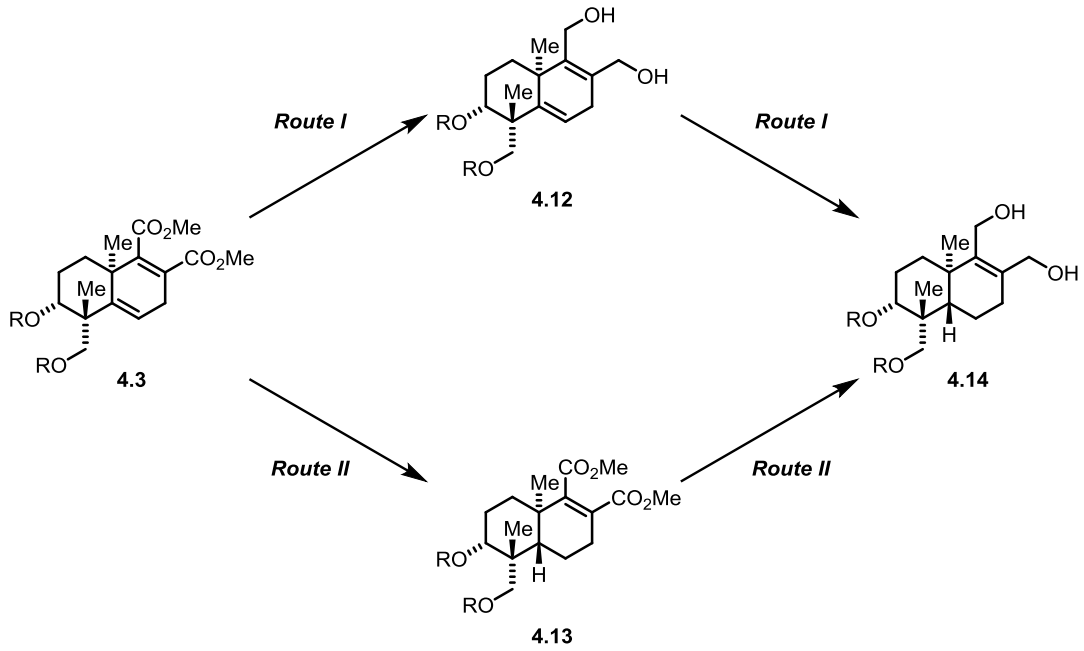
In order to perform transformations at the northeastern part of molecule but keep the dihydroxy motif intact, dienes with different protecting groups (**4.4e-g**) were prepared in moderate to good yield. [4+2]-Cycloaddition of these dienes with DMAD went smoothly, and it was found that substrates with cyclic protecting groups gave much better diastereoselectivity (Table 4.3).

Table 4.3 Diels-Alder reaction of **4.4e-g** with DMAD.

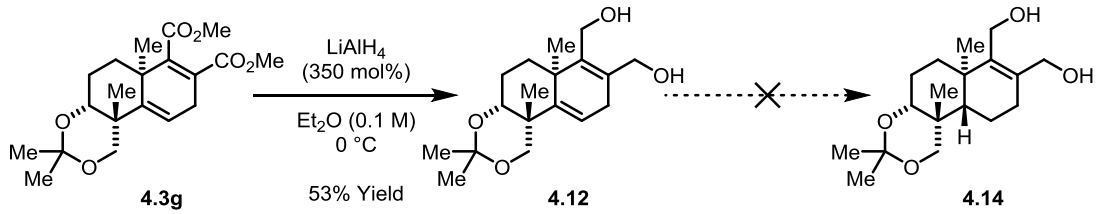


Entry	R	Product	**4.3** Yield (*dr*)
1	TES (**4.4e**)	**4.3e**	48% (6:1)
2	$[(t\text{Bu})_2\text{Si}]_{0.5}$ (**4.4f**)	**4.3f**	67% (>20:1)
3	$(\text{Me}_2\text{C})_{0.5}$ (**4.4g**)	**4.3g**	71% (>20:1)

Attempt to reduce only one methyl carboxylate in Diels-Alder adducts **4.3** was not successful due to a strong tendency to form an *α,β*-unsaturated *γ*-lactone. Nevertheless, there were still two strategies to continue the synthesis: reduce both methyl esters first to form **4.12**, and hydrogenate the trisubstituted olefin to access **4.14** (Scheme 4.6, Route **I**); or perform hydrogenation on alkene to generate **4.13**, and then reduce the carboxylates to primary alcohols to form the same **4.14** (Scheme 4.6, Route **II**).



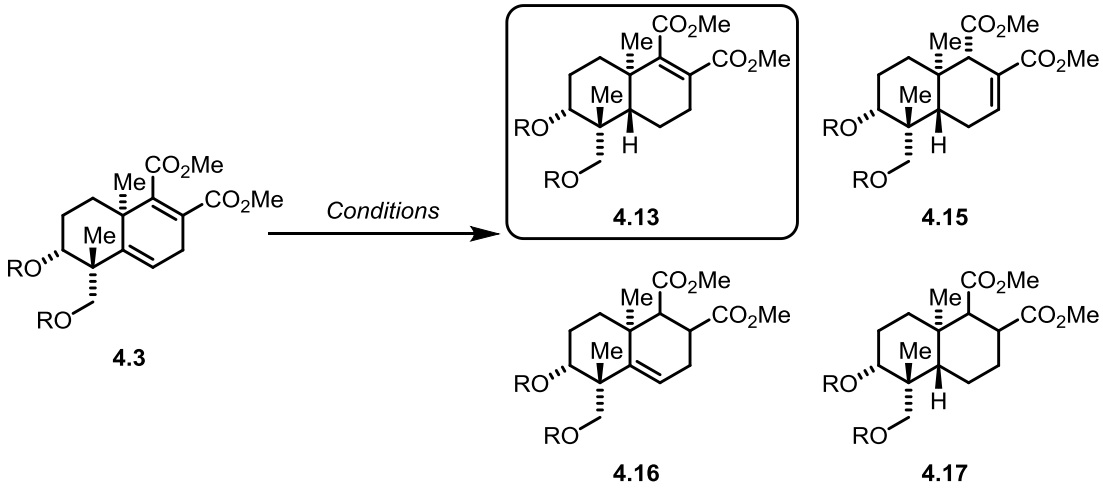
Scheme 4.6 Strategies to perform sequential reductions on cycloaddition adduct **4.3**.



Scheme 4.7 Attempt to access **4.14** through intermediate **4.12**.

LAH reduction of **4.3g** led to the formation of diol **4.12**, while reducing **4.3f** resulted in decomposition of substrate. However, olefin reduction on **4.12** did not deliver the desired product under any condition that was tried, and the compounds seemed quite unstable probably due to conformational strain (Scheme 4.7).

Table 4.4 Selected reaction conditions for reducing **4.3** to **4.13**.

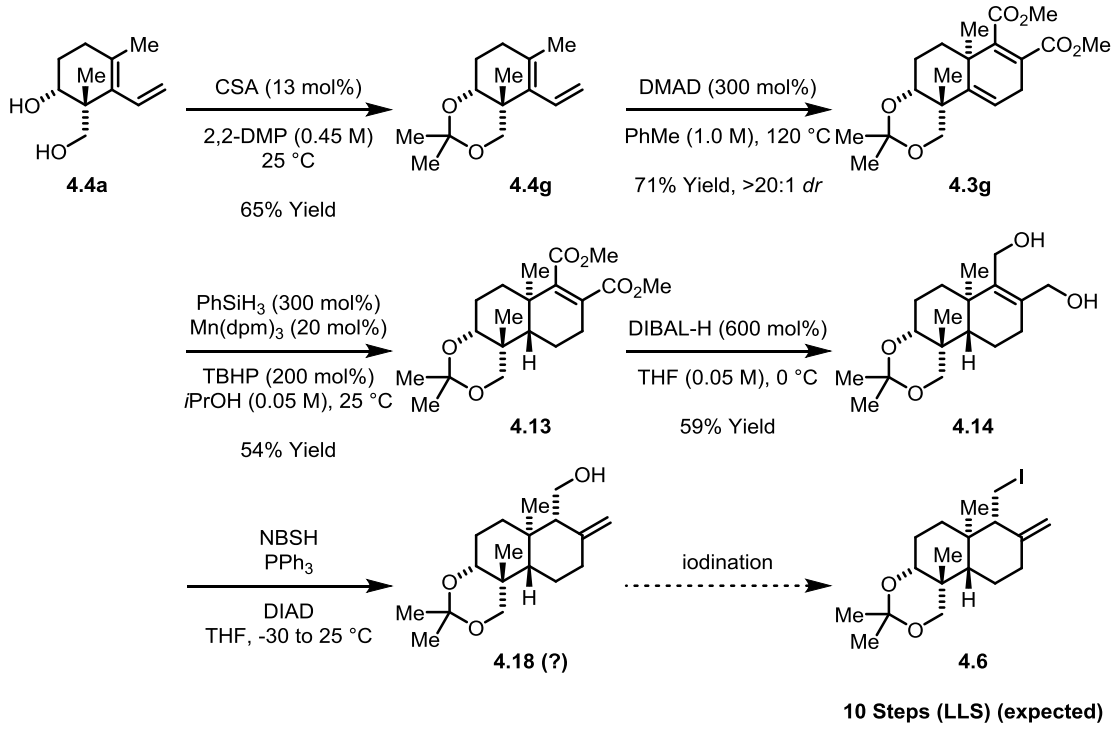


Entry	Substrate	Condition	Product (Yield)
1	**4.3f**	H_2, Pd/C MeOH, 25 °C	**4.15** (32%), **4.16**+**4.17** (64%)
2	**4.3f**	$TsNHNH_2$, NaOAc diglyme, 95 °C	**4.16** (56%)
3	**4.3g**	H_2, $[Rh(nbd)_2]BF_4$ DCE, 25 °C	--
4	**4.3g**	**$PhSiH_3$, $Mn(dpm)_3$ TBHP, *i*PrOH, 25 °C**	**4.13 (54%)**

Therefore, we turned to focus on Route **II**. Chemoselective reduction of the trisubstituted alkene was tested under various conditions (Table 4.4). Hydrogenation promoted by heterogeneous catalysts usually resulted in double bond isomerization and non-selective reduction, and homogeneous catalysis exhibited lower reactivity and returned starting material most of the time. Chemical reduction by *in situ* generation of

diimide species[33,34] surprisingly delivered a side product with tetrasubstituted alkene reduced (**4.16**), probably due to the directing effect of carboxylate groups. Finally, Shenvi reduction gave the desired **4.13** as mere product in the reaction, again proving the generality of this novel methodology.

With the hydrogenated product in hand, DIBAL-H reduction provided diol **4.14** in reasonable yield. Regioselective reductive transposition of the allylic alcohol with *o*-nitrobenzenesulfonylhydrazine (NBSH)[35] was then performed, and a product was isolated which was tentatively assigned as the desired exocyclic olefinic compound. Full characterization will be required to confirm the structure and stereochemistry of this unknown molecule. If this is the correct product, iodination of the remaining hydroxy group will give the target compound **4.6** *en route* to andrographolide (Scheme 4.8).

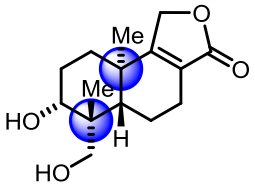


Scheme 4.8 Current progress on synthesis of **4.6**.

4.5 CONCLUSION

Isoiresin
Pelletier 1968, 24 Steps (LLS), 24 Total Steps (rac)
Li 2015, 27 Steps (LLS), 28 Total Steps

Now 9 Steps (LLS), 9 Total Steps



Andrographolide
Li 2014, 24 Steps (LLS), 25 Total Steps

Expected 12 Steps (LLS), 18 Total Steps

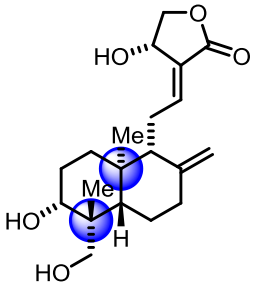


Figure 4.2 Summary of total synthesis of isoiresin and andrographolide.

A short asymmetric synthesis of isoiresin was achieved in 9 steps (LLS) via enantioselective Ir-catalyzed *tert*-(hydroxy)prenylation and diastereoselective Diels-Alder cycloaddition. The same modular strategy was also applied to the synthesis of andrographolide, which is in progress currently. It has demonstrated that the highly stereoselective *tert*-(hydroxy)prenylation methodology developed in our lab can couple with different synthetic methods to construct complex natural products with various scaffolds and contiguous stereocenters including all-carbon quaternary centers.

4.6 EXPERIMENTAL DETAILS

General Information

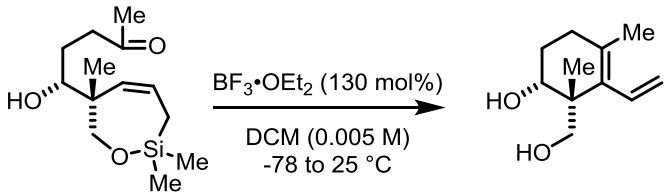
All reactions were performed under an atmosphere of argon, unless specifically noted in detailed procedures. Tetrahydrofuran, diethyl ether and toluene were distilled from sodium-benzophenone immediately prior to use. Dichloromethane, 1,2-dichloroethane were distilled from calcium hydride prior to use. Anhydrous solvents were transferred by oven-dried syringes and needles. Reagents purchased from commercial sources were used as received, or purified via Hickman distillation over appropriate drying agent. Analytical thin-layer chromatography (TLC) was carried out using 0.25 mm commercial silica gel plates (Dynanmic Absorbents F_{254}). Visualization was accomplished with UV light followed by dipping in appropriate stain solution then heating. Flash column chromatography was performed on Sorbent silica gel (40-63 μm, unless indicated specifically) or Sigma-Aldrich aluminum oxide (activated, neutral, Brockmann I, ~150 mesh, 58 Å pore size).

Spectroscopy, Spectrometry, and Data Collection

Infrared spectra were recorded on a Perkin-Elmer 1600 spectrometer. High-resolution mass spectra (HRMS) were obtained on an Agilent Technologies 6530 Accurate Mass Q-Tof LC/MS instrument for electrospray ionisation (ESI) or a Micromass Autospec Ultima instrument for chemical ionization (CI), and are reported as m/z (relative intensity). Accurate masses are reported for the molecular ion (M, M+H, M-H or M+Na), or a suitable fragment ion. ^{1}H Nuclear magnetic resonance spectra were recorded using an Agilent MR (400 MHz), Varian DirectDrive (400, 600 MHz), or Varian INOVA (500 MHz) spectrometer in $CDCl_3$ or CD_3OD solution. Coupling constants are reported in Hertz (Hz) with one decimal place, and chemical shifts are reported as parts per million (ppm) relative to residual solvent peaks ($CDCl_3$ δ_H 7.26 ppm; CD_3OD δ_H 3.31 ppm). ^{13}C Nuclear magnetic resonance spectra were recorded using an Agilent MR (400 MHz), Varian DirectDrive (400, 600 MHz), or Varian INOVA (500 MHz) spectrometer in $CDCl_3$ or CD_3OD solution, and chemical shifts are reported as parts per million (ppm) relative to solvent peaks ($CDCl_3$ δ_C 77.2 ppm; CD_3OD δ_C 49.0 ppm). Specific optical rotations ($[\alpha]_D$) were obtained on an Atago AP-300 automatic polarimeter at the sodium line (589.3 nm) in $CHCl_3$ or CH_3OH solution. Melting points were taken on a Stuart SMP3 melting point apparatus or SRS OptiMelt automated melting point system.

Detailed Procedures and Spectral Data for Asymmetric Synthesis of Isoiresin

(1*R*,2*R*)-2-(Hydroxymethyl)-2,4-dimethyl-3-vinylcyclohex-3-en-1-ol (Fragment A2, 4.4a)



ent-**3.9** 63% Yield **4.4a**

Detailed Procedures

To a solution of *ent*-**3.9**[36] (0.320 g, 1.25 mmol, 100 mol%) in DCM (250 mL) at -78 ˚C, $BF_3 \cdot OEt_2$ (0.46 mL, 3.74 mmol, 130 mol%) was added dropwise. The resulted solution was allowed to warm to ambient temperature in an hour, and stirred for 22 hours. The reaction was quenched by addition of saturated $NaHCO_3$ (aq., 250 mL) and vigorously stirred for overnight. The mixture was separated, and the aqueous layer was extracted with DCM (50 mL × 2). The combined organic layer was washed with brine (100 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure (<30 ˚C), and the residue was submitted to flash column chromatography on a short plug of neutral alumina (Et_2O/MeOH = 30:1 to 5:1). The title compound was obtained as a light brown oil (0.143 g, 0.79 mmol) in 63% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.22 (ddtd, *J* = 15.3, 11.2, 2.0, 1.0 Hz, 1H), 5.32 (dd, *J* = 11.2, 2.5 Hz, 1H), 5.05 (dd, *J* = 17.7, 2.5 Hz, 1H), 3.81 (t, *J* = 4.9 Hz, 1H), 3.79 (d, *J* = 9.8 Hz, 1H), 3.59 (d, *J* = 11.5 Hz, 1H), 3.14 (br, 1H), 3.01 (br, 1H), 2.27 (dt, *J* = 16.2, 7.0 Hz, 2H), 2.02 (dt, *J* = 17.4, 5.5 Hz, 1H), 1.87-1.80 (m, 2H), 1.74 (d, *J* = 1.0 Hz, 3H), 1.02 (s, 3H).

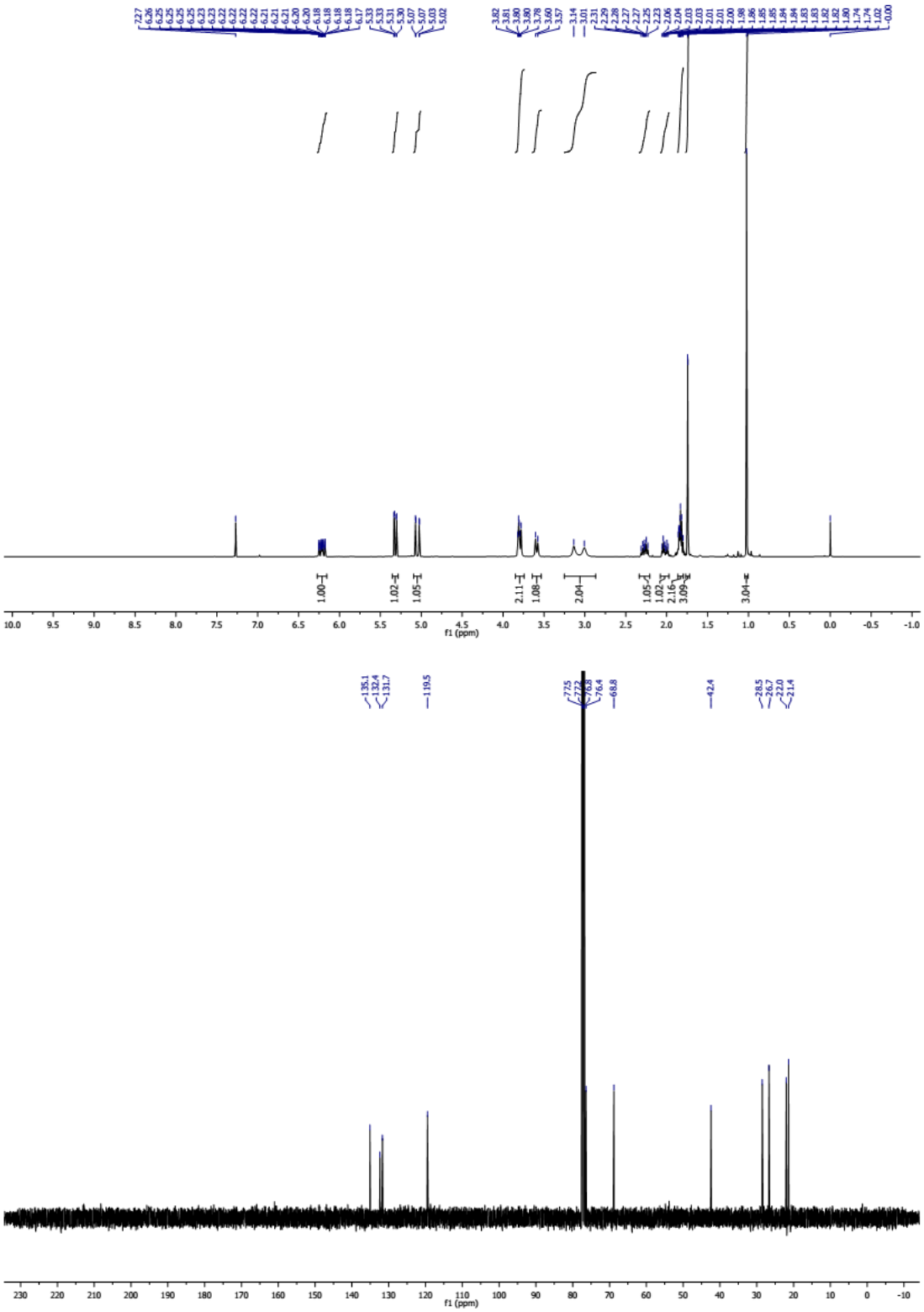
^{13}C NMR (100 MHz, $CDCl_3$) δ 135.1, 132.4, 131.7, 119.5, 76.4, 68.8, 42.4, 28.5, 26.7, 22.0, 21.4.

R_f 0.35 (hexanes/EA = 2:1 (twice), UV/*p*-anisaldehyde)

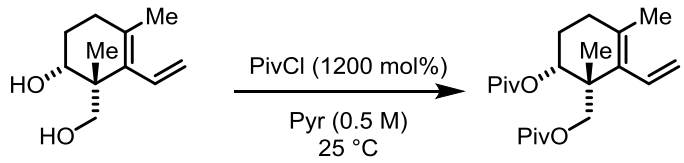
HRMS (ESI) Calcd. for $C_{11}H_{18}O_2$ $[M+Na]^+$: 205.1199, Found: 205.1204.

FTIR (neat): 3348, 2969, 2931, 2875, 1431, 1375, 1250, 1231, 1217, 1200, 1093, 1044, 1019, 1003, 918, 836, 809 cm^{-1}.

Optical Rotation $[\alpha]_D^{30}$ = -8.0° (*c* = 1.0, $CHCl_3$)



(1*R*,2*R*)-2,4-Dimethyl-2-((pivaloyloxy)methyl)-3-vinylcyclohex-3-en-1-yl pivalate (4.4d)



4.4a 81% Yield **4.4d**

Detailed Procedures

To a pyridine (0.8 mL) solution of diol (0.0712 g, 0.39 mmol, 100 mol%) in ice-cooled bath, freshly distilled pivaloyl chloride (0.58 mL, 4.7 mmol, 1200 mol%) was added slowly. White precipitate was formed immediately. The reaction mixture was allowed to warm to ambient temperature, and stirred for 18 hours. Water (1.0 mL) and DCM (1.0 mL) was added to quench the reaction. The resulted two layers were separated, and the aqueous layer was extracted with DCM (5 mL). The combined organic layers were added MeOH (3.2 mL), Et_3N (0.60 mL) and DMAP (0.020 g), and stirred overnight to decompose the excess PivCl. The DCM solution was washed with 0.5 M H_3PO_4 (5 mL) and saturated $NaHCO_3$ (aq., 5 mL × 2), and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was submitted to flash column chromatography on silica gel (Hexanes/EA = 100:1). The title compound was obtained as a colorless oil (0.116 g, 0.33 mmol) in 81% yield, which solidified upon standing in -20 ˚C freezer.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.11 (dd, *J* = 17.5, 11.2 Hz, 1H), 5.31 (dd, *J* = 11.2, 2.4 Hz, 1H), 5.01 (dd, *J* = 17.6, 2.4 Hz, 1H), 4.93 (dd, *J* = 7.1, 2.7 Hz, 1H), 4.09 (d, *J* = 10.8 Hz, 1H), 4.00 (d, *J* = 10.8 Hz, 1H), 2.20-1.90 (m, 3H), 1.81 (dddd, *J* = 13.7, 8.9, 6.7, 2.7 Hz, 1H), 1.73 (s, 3H), 1.18 (s, 9H), 1.17 (s, 9H), 1.10 (s, 3H).

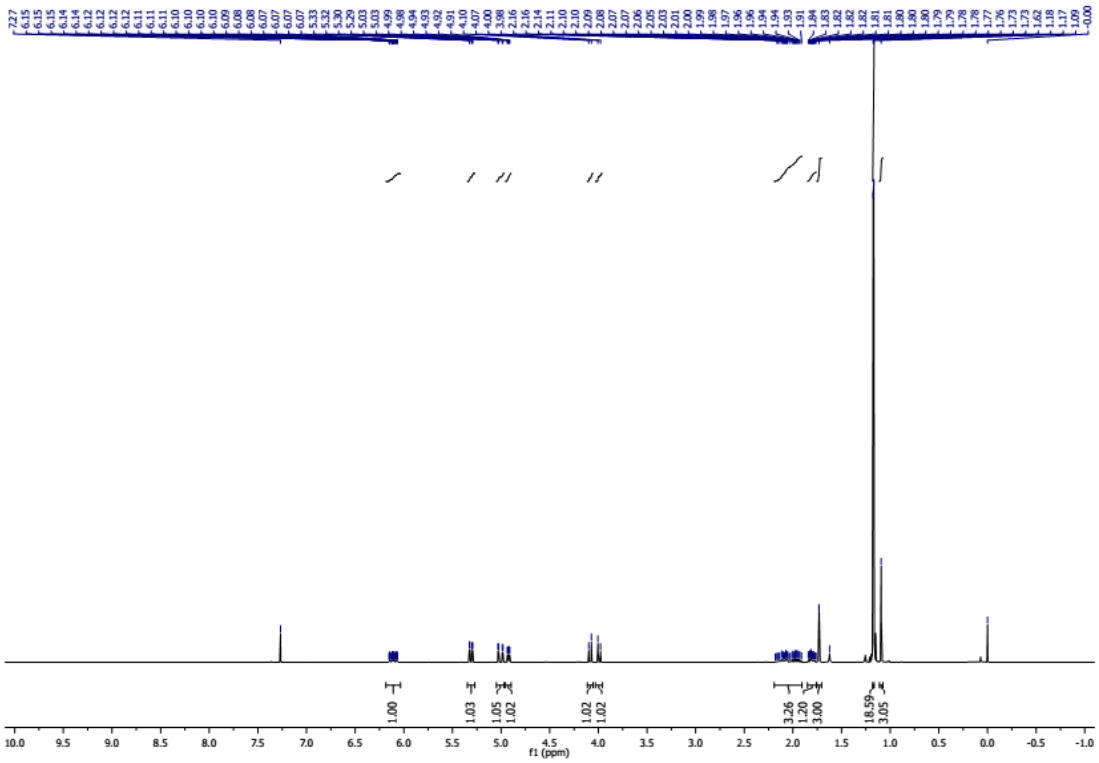
^{13}C NMR (100 MHz, $CDCl_3$) δ 178.4, 177.7, 134.0, 132.2, 130.7, 120.0, 73.8, 67.4, 41.0, 39.2, 39.0, 28.5, 27.3, 27.3, 22.8, 22.3, 21.3.

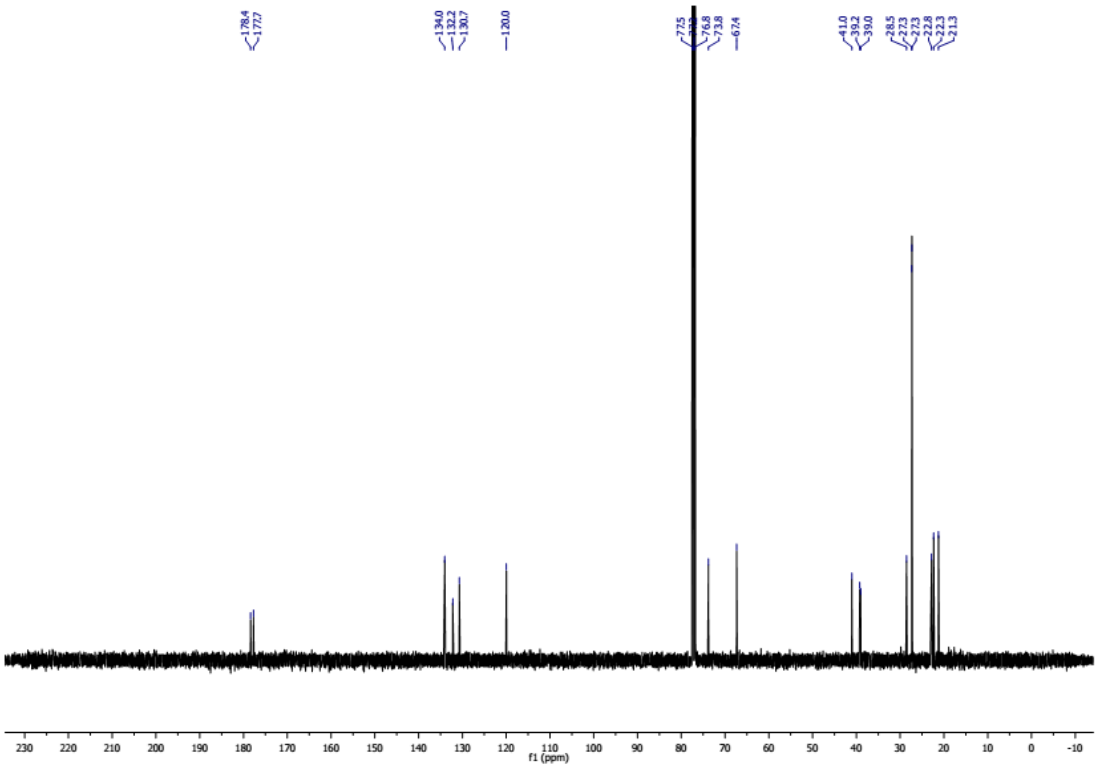
HRMS (ESI) Calcd. for $C_{21}H_{34}O_4$ $[M+Na]^+$: 373.2349, Found: 373.2350.

FTIR (neat): 2970, 2931, 2872, 1727, 1480, 1460, 1397, 1364, 1282, 1164, 1143, 1033, 989, 921 cm^{-1}.

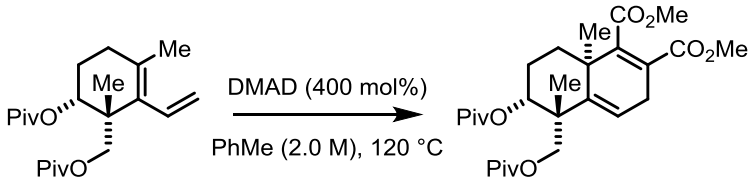
MP 44.4-45.3 ˚C (Et_2O)

Optical Rotation $[\alpha]_D^{30}$ = -2.2˚ (c = 0.5, $CHCl_3$)





Dimethyl (5*R*,6*R*,8a*R*)-5,8a-dimethyl-6-(pivaloyloxy)-5-((pivaloyloxy)methyl)-3,5,6,7,8,8a-hexahydronaphthalene-1,2-dicarboxylate (4.3d)



4.4d 74% Yield, 10:1 *dr* **4.3d**

Detailed Procedures

To a solution of **4.4d** (0.0905 g, 0.26 mmol, 100 mol%) in toluene (0.13 mL) was added dimethyl acetylenedicarboxylate (DMAD, 0.13 mL, 1.03 mmol, 400 mol%). The mixture was heated to 120 ˚C in seal tube for 24 hours. After cooled to ambient temperature, the solvent was removed under reduced pressure and the residue was submitted to flash column chromatography on silica gel (hexanes/EA = 15:1). The title compound was obtained with its inseparable diastereomer in 10:1 ratio as a white solid (0.0941 g, 0.19 mmol) in 74% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83 (dd, *J* = 5.6, 2.3 Hz, 1H (major)), 5.61* (dd, *J* = 5.7, 2.2 Hz, 1H (minor)), 4.94-4.90* (m, 1H (minor)), 4.63 (dd, *J* = 9.7, 5.9 Hz, 1H (major)), 4.46 (d, *J* = 11.3 Hz, 1H (major)), 4.25* (d, *J* = 10.2 Hz, 1H (minor)), 4.05* (d, *J* = 10.3 Hz, 1H (minor)), 4.01 (d, *J* = 11.3 Hz, 1H (major)), 3.85* (s, 3H (minor)), 3.80 (s, 3H (major)), 3.75* (s, 3H (minor)), 3.75 (s, 3H (major)), 3.24 (dd, *J* = 22.8, 5.5 Hz, 1H (major)), 3.21* (dd, *J* = 22.7, 5.7 Hz, 1H (minor)), 2.86 (dd, *J* = 22.8, 2.3 Hz, 1H (major)), 2.83* (dd, *J* = 22.6, 2.2 Hz, 1H (minor)), 2.08-1.71* (m, 4H (minor)), 1.88-1.75 (m, 3H (major)), 1.62 (dd, *J* = 9.6, 3.4 Hz, 1H (major)), 1.47* (s, 3H (minor)), 1.37 (s, 3H (major)), 1.32* (s, 3H (minor)), 1.22 (s, 9H (major)), 1.20 (s, 3H (major)), 1.19* (s, 9H (minor)), 1.17 (s, 9H (major)), 1.13* (s, 9H (minor)).

^{13}C NMR (100 MHz, $CDCl_3$) δ 178.4, 177.7, 169.3, 166.2, 149.3, 139.3, 125.3, 123.6, 77.3, 66.6, 52.4, 52.3, 44.3, 39.2, 39.1, 38.2, 32.8, 27.4, 27.3, 27.1, 25.1, 23.3, 23.1.

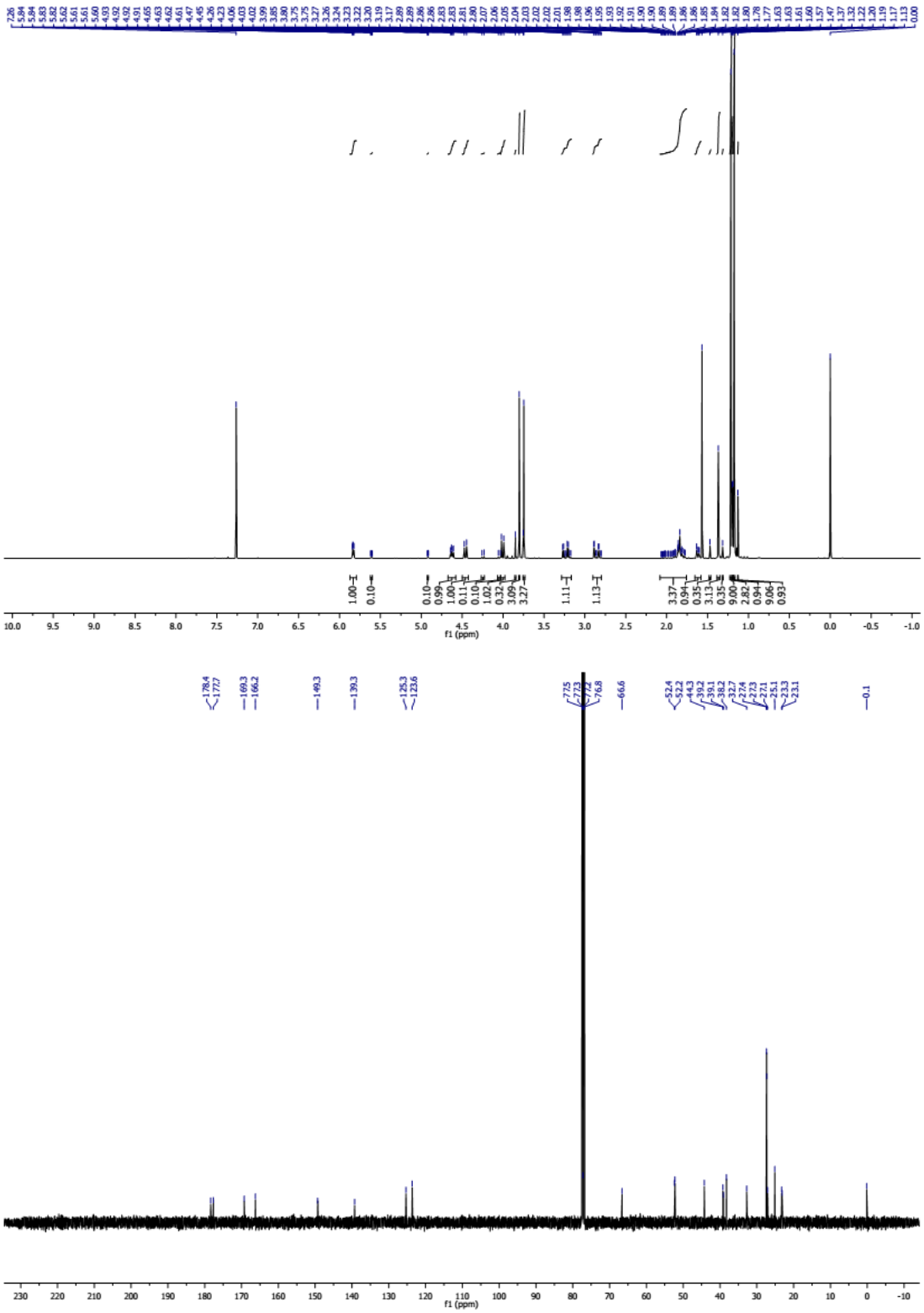
R_f 0.15 (hexanes/EA = 10:1, UV/*p*-anisaldehyde)

HRMS (ESI) Calcd. for $C_{27}H_{40}O_8$ $[M+Na]^+$: 515.2615, Found: 515.2628.

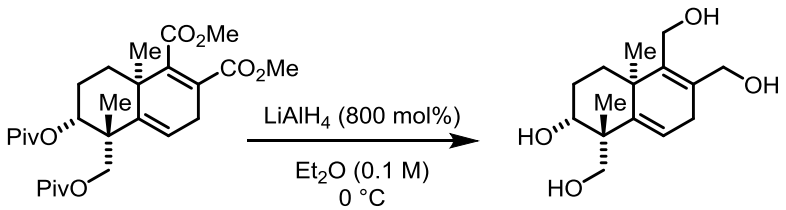
FTIR (neat): 2975, 2873, 1725, 1639, 1480, 1459, 1434, 1397, 1367, 1281, 1252, 1144, 1023, 993, 768, 743 cm^{-1}.

MP 63.6-65.6 ˚C (Et_2O)

Optical Rotation $[\alpha]_D^{30}$ = -18.3˚ (*c* = 0.4, $CHCl_3$)



((5*R*,6*R*,8a*R*)-6-Hydroxy-5,8a-dimethyl-3,5,6,7,8,8a-hexahydronaphthalene-1,2,5-triyl)trimethanol (4.9)



4.3d 78% Yield **4.9**

Detailed Procedures

To a solution of **4.3d** (0.0507 g, 0.103 mmol, 100 mol%) in diethyl ether (1.0 mL) at 0 ˚C was added $LiAlH_4$ (0.0312 g, 0.823 mmol, 800 mol%). The resulted mixture was stirred vigorously at the same temperature for 2 hours. Water (0.031 mL) was slowly added to quench the reaction, followed by addition of 15% NaOH (aq., 0.031 mL) and water (0.093 mL). The mixture was allowed to stir for 10 min, and was dried over $MgSO_4$. Silica gel was added and solvent was removed under reduced pressure. The resulted residue was directly loaded onto column and submitted to flash chromatography on silica gel (DCM/MeOH = 10:1). The title compound was obtained as a white solid (0.0216 g, 0.0805 mmol) in 78% yield.

^{1}H NMR (400 MHz, CD_3OD) δ 5.83 (dd, *J* = 4.9, 3.0 Hz, 1H), 4.30 (d, *J* = 12.0 Hz, 1H), 4.25 (d, *J* = 12.3 Hz, 1H), 4.14 (d, *J* = 12.0 Hz, 1H), 4.14 (d, *J* = 12.2 Hz, 1H), 3.92 (d, *J* = 11.0 Hz, 1H), 3.59 (d, *J* = 11.1 Hz, 1H), 3.37 (dd, *J* = 11.8, 4.4 Hz, 1H), 2.85 (d, *J* = 3.5 Hz, 1H), 2.84 (d, *J* = 5.3 Hz, 1H), 2.05-1.92 (m, 2H), 1.83-1.76 (m, 1H), 1.64 (td, *J* = 13.9, 3.9 Hz, 1H), 1.31 (s, 3H), 1.18 (s, 3H).

^{13}C NMR (100 MHz, CD_3OD) δ 144.4, 141.8, 134.6, 124.3, 78.6, 67.7, 62.8, 57.5, 47.7, 39.6, 34.8, 30.8, 28.2, 26.4, 23.2.

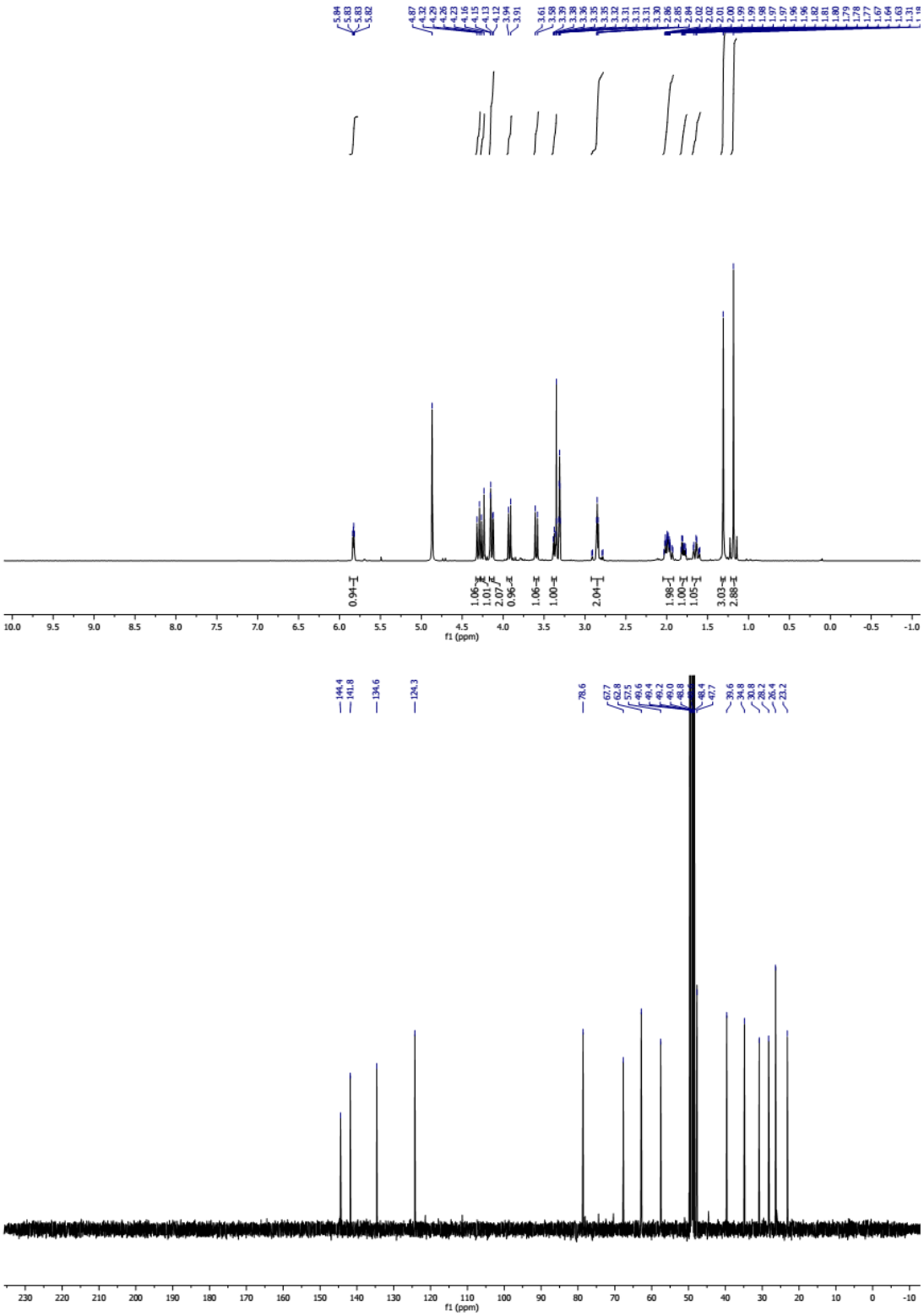
R_f 0.15 (DCM/MeOH = 12.5:1, *p*-anisaldehyde)

HRMS (ESI) Calcd. for $C_{15}H_{24}O_4$ $[M+Na]^+$: 291.1567, Found: 291.1575.

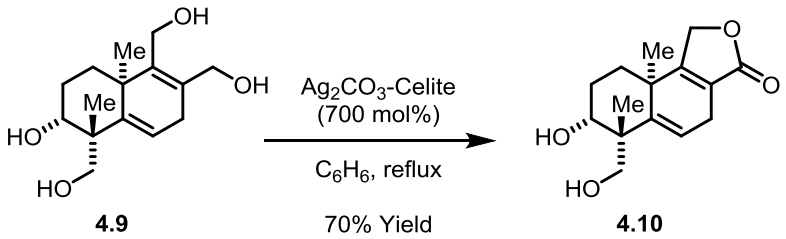
FTIR (neat): 3356, 2930, 2874, 1562, 1408, 1060, 1030, 1001 cm^{-1}.

MP 128.0-129.0 ˚C (MeOH)

Optical Rotation $[\alpha]_D^{30}$ = +12.2˚ (c = 0.15, CH_3OH)



(6*R*,7*R*,9a*R*)-7-Hydroxy-6-(hydroxymethyl)-6,9a-dimethyl-4,6,7,8,9,9a-hexahydronaphtho[1,2-c]furan-3(1H)-one (4.10)



4.9 **4.10**

Detailed Procedures

A suspension of tetraol **4.9** (0.0300 g, 0.11 mmol, 100 mol%, dried by azeotropic distillation with benzene) and freshly made Ag_2CO_3-Celite[37] (Fétizon's reagent, 0.4461g, 0.78 mmol, 700 mol%) in anhydrous benzene (5.5 mL) was heated to reflux (a portion of benzene could be removed by distillation to eliminate water in the system). The mixture was vigorously stirred until all the starting material was consumed (about 3.5 hours). The reaction was allowed to cool to ambient temperature and filter through filter paper. The precipitate was washed with MeOH (10 mL × 3), and the combined filtrate was concentrated under reduced pressure. The residue was submitted to flash column chromatography on silica gel (DCM/EA = 15:1 to DCM/MeOH = 25:1). The title compound was obtained as a colorless gel (0.0208 g, 0.079 mmol) in 70% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.97 (dd, *J* = 5.1, 2.5 Hz, 1H), 4.87 (ddd, *J* = 16.8, 3.4, 1.4 Hz, 1H), 4.73 (dt, *J* = 16.9, 2.6 Hz, 1H), 4.20 (d, *J* = 11.1 Hz, 1H), 3.54 (dd, *J* = 11.8, 3.9 Hz, 1H), 3.51 (d, *J* = 11.9 Hz, 1H), 3.00 (dddd, *J* = 22.4, 4.8, 2.6, 1.4 Hz, 2H), 2.88 (dq, *J* = 22.4, 2.6 Hz, 1H), 2.42 (br, 1H), 2.24 (br, 1H), 2.10 (tdd, *J* = 13.6, 11.8, 3.9 Hz, 1H), 1.92 (dq, *J* = 13.5, 3.9 Hz, 1H), 1.74 (dt, *J* = 13.1, 3.6 Hz, 1H), 1.65 (dd, *J* = 13.4, 4.0 Hz, 1H), 1.44 (s, 3H), 1.34 (s, 3H).

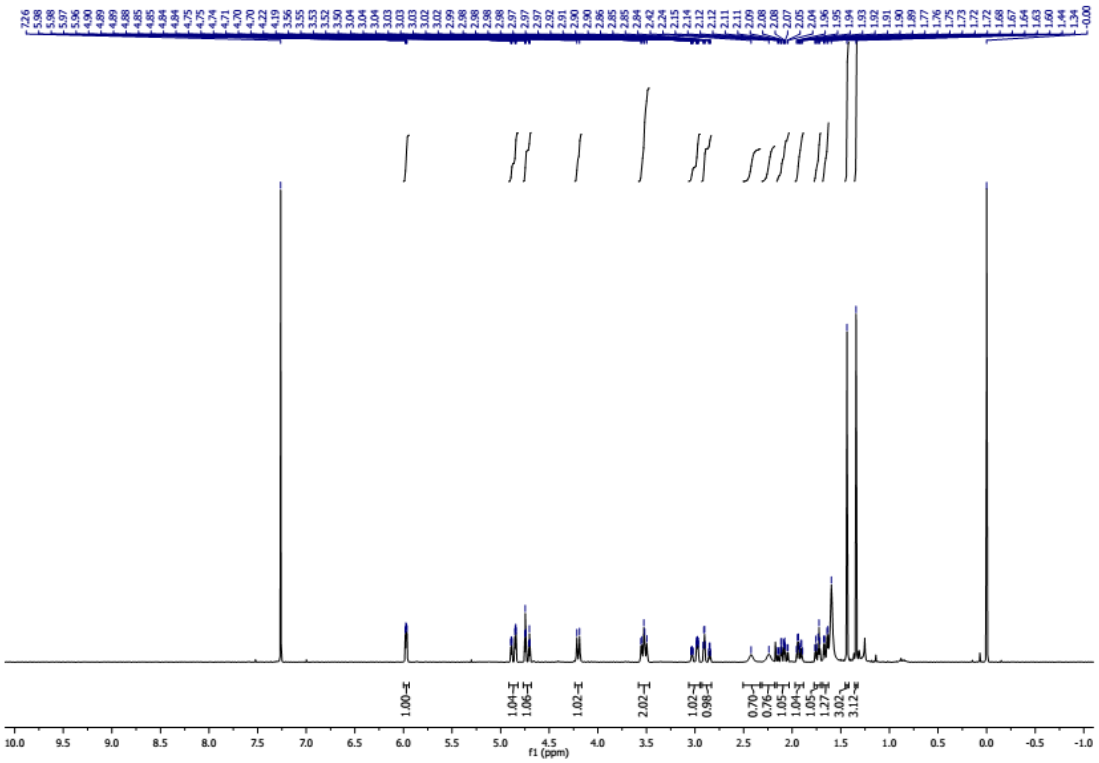
^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 167.4, 142.9, 123.3, 122.2, 77.9, 68.7, 67.9, 47.3, 37.2, 33.7, 27.2, 27.2, 22.9, 22.6.

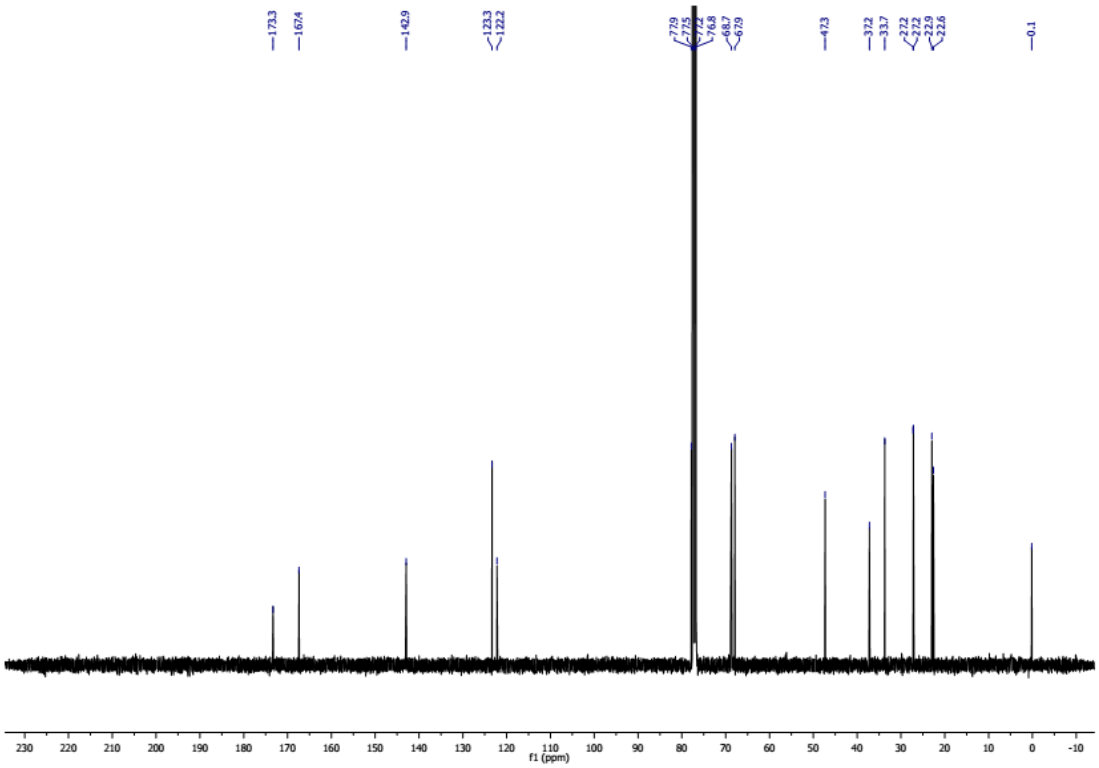
R_f 0.20 (DCM/EA = 1:1, *p*-anisaldehyde)

HRMS (ESI) Calcd. for $C_{15}H_{20}O_4$ $[M+Na]^+$: 287.1254, Found: 287.1262.

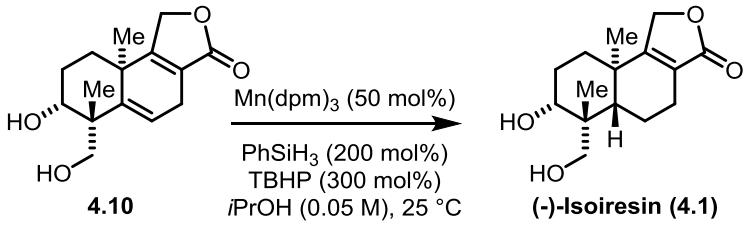
FTIR (neat): 3400, 2927, 2858, 1743, 1696, 1555, 1456, 1260, 1031, 992, 799, 750, 667 cm^{-1}.

Optical Rotation $[\alpha]_D^{30} = +2.0^\circ$ (c = 0.18, $CHCl_3$)





(5a*S*,6*R*,7*R*,9a*R*)-7-Hydroxy-6-(hydroxymethyl)-6,9a-dimethyl-4,5,5a,6,7,8,9,9a-octahydronaphtho[1,2-c]furan-3(1H)-one ((-)-Isoiresin, 4.1)



Detailed Procedures

To a reaction vessel containing **4.10** (0.0078g, 0.030 mmol, 100 mol%) was added a degassed solution of $PhSiH_3$ (0.011 mL, 0.089 mmol, 300 mol%) in anhydrous 2-propanol (0.18 mL), *tert*-butyl hydroperoxide (5.5 M in decane, 0.011 mL, 0.060 mmol, 200 mol%) and a degassed solution of $Mn(dpm)_3$[32] (0.0089 g, 0.015 mmol, 50 mol%) in 2-propanol (0.59 mL). The resulted mixture was degassed by bubbling with argon for 10 seconds, and was allowed to stir at ambient temperature for 5 hours. The solvent was removed under reduced pressure and the residue was submitted to flash column chromatography on silica gel (DCM/MeOH = 50:1). The title compound was obtained as a white solid (0.0055 g, 0.021 mmol) in 71% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.73 (dt, *J* = 16.9, 2.8 Hz, 1H), 4.64 (ddd, *J* = 16.9, 3.7, 1.6 Hz, 1H), 4.23 (d, *J* = 11.2 Hz, 1H), 3.52 (dd, *J* = 11.3, 4.8 Hz, 1H), 3.41 (d, *J* = 11.2 Hz, 1H), 2.49-2.36 (m, 1H), 2.15 (ddddd, *J* = 17.8, 11.0, 6.7, 3.7, 2.8 Hz, 1H), 2.06-1.85 (m, 3H), 1.72 (dt, *J* = 13.0, 3.5 Hz, 1H), 1.58-1.43 (m, 2H), 1.34-1.31 (m, 1H), 1.31 (s, 3H), 1.14 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 169.1, 123.8, 80.1, 68.1, 63.8, 51.0, 42.9, 36.0, 33.8, 27.5, 22.5, 21.7, 21.5, 18.1.

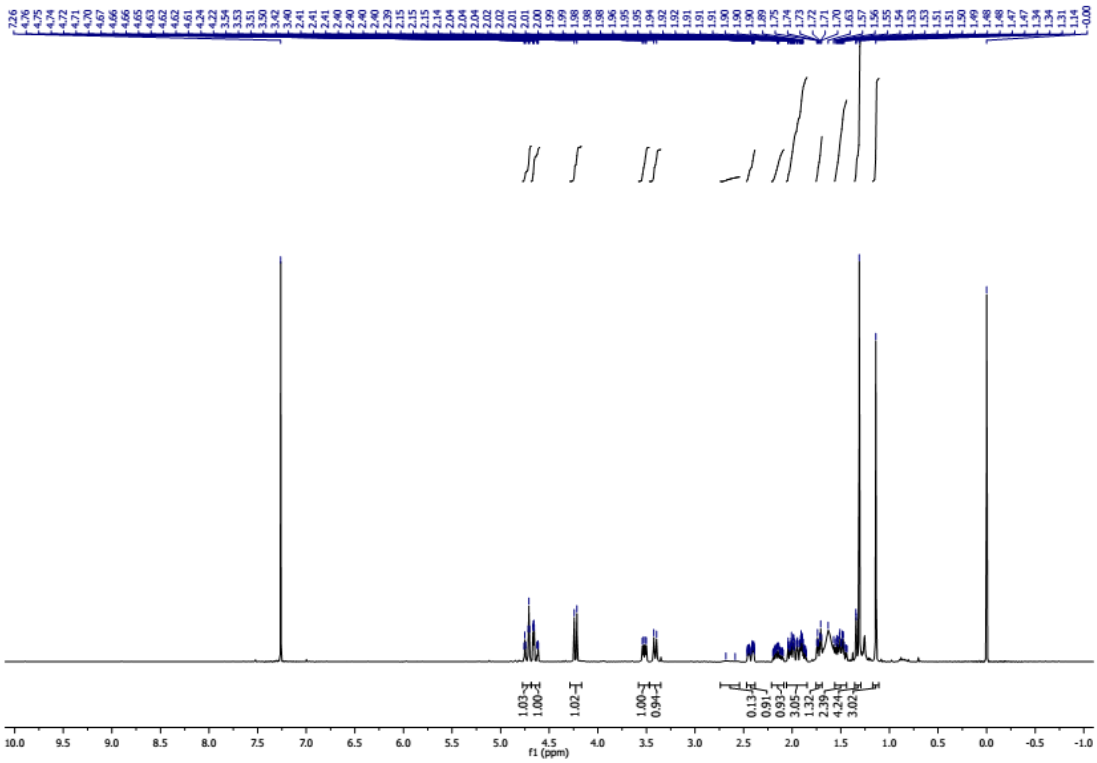
R_f 0.23 (DCM/EA = 1:1, *p*-anisaldehyde)

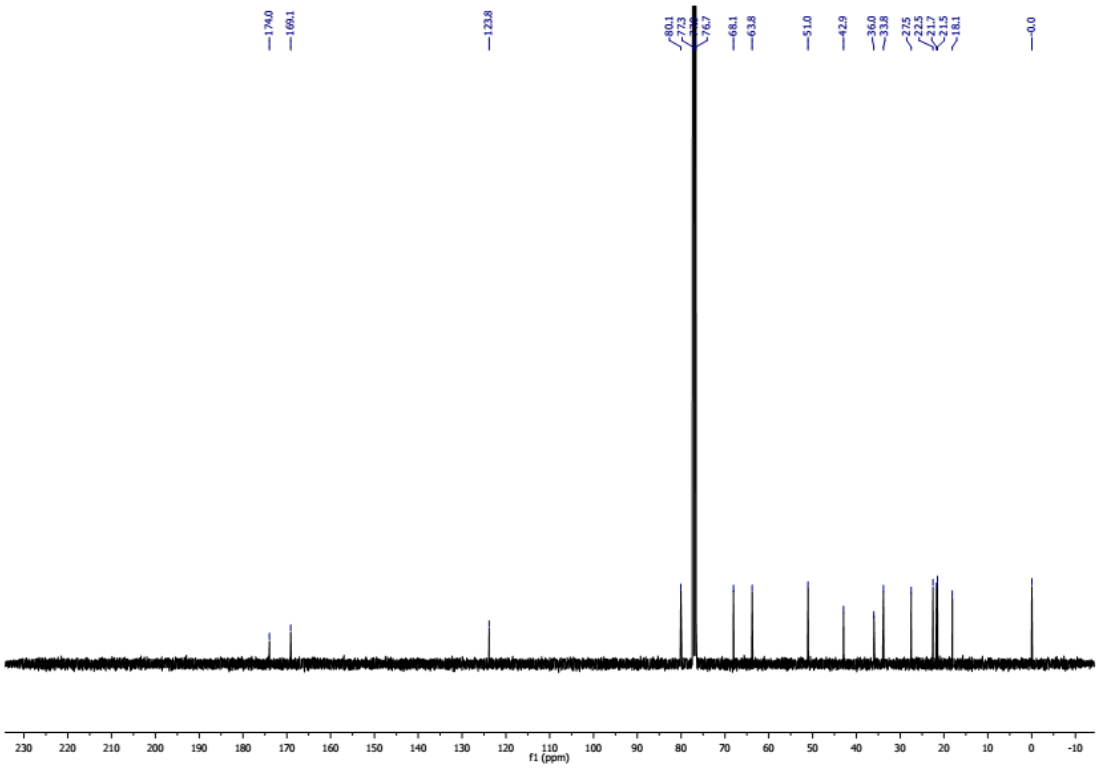
HRMS (ESI) Calcd. for $C_{15}H_{22}O_4$ $[M+Na]^+$: 289.1410, Found: 289.1413.

FTIR (neat): 3331, 2925, 2853, 1739, 1558, 1456, 1436, 1404, 1386, 1289, 1258, 1202, 1193, 1083, 1039, 1012, 991, 799, 731 cm^{-1}.

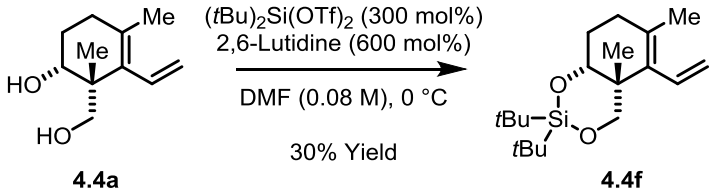
MP 190.4-194.3 ˚C ($CHCl_3$)

Optical Rotation $[\alpha]_D^{30}$ = -37.0˚ (*c* = 0.18, $CHCl_3$)





(4a*R*,8a*R*)-2,2-Di-*tert*-butyl-4a,6-dimethyl-5-vinyl-4a,7,8,8a-tetrahydro-4H-benzo[d][1,3,2]dioxasiline (4.4f)



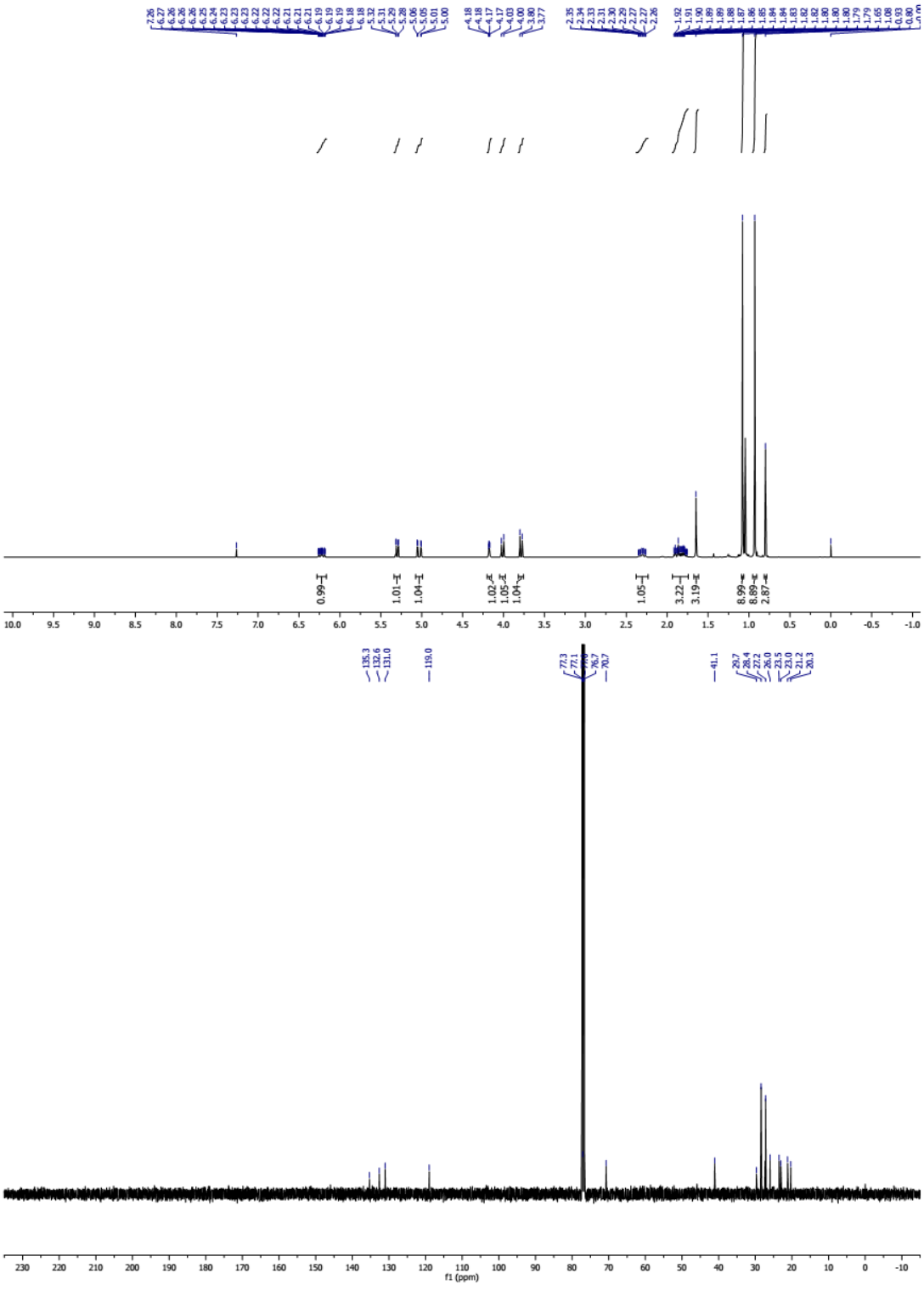
Detailed Procedures

To a solution of diol (0.164 g, 0.9 mmol, 100 mol%) and 2,6-lutidine (0.88 mL, 2.7 mmol, 300 mol%) in DMF (10.8 mL) at 0 ˚C was added di-*tert*-butylsilyl ditriflate (0.63 mL, 5.4 mmol, 600 mol%) dropwise. The reaction mixture was stirred at the same temperature for 1.5 hours and quenched by addition of saturated $NaHCO_3$ (aq., 10 mL). The organic layer was separated, and washed with water (10 mL × 3). After dried over anhydrous Na_2SO_4, the solvent was removed under reduced pressure, and the residue was submitted to flash column chromatography on silica gel (hexanes/acetone/Et_3N = 200:0:1 to 200:1:1). The title compound was obtained as a colorless oil (0.0886 g, 0.27 mmol) in 30% yield.

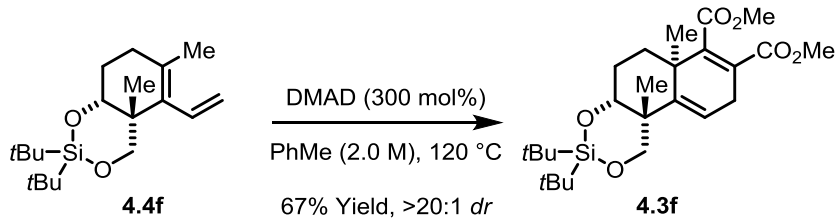
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.22 (dddt, *J* = 17.7, 11.2, 2.6, 1.3 Hz, 1H), 5.30 (dd, *J* = 11.2, 2.6 Hz, 1H), 5.03 (dd, *J* = 17.8, 2.6 Hz, 1H), 4.18 (dd, *J* = 4.3, 1.7 Hz, 1H), 4.01 (d, *J* = 11.8 Hz, 1H), 3.79 (d, *J* = 11.8 Hz, 1H), 2.38-2.23 (m, 1H), 1.94-1.75 (m, 3H), 1.65 (s, 3H), 1.08 (s, 9H), 0.93 (s, 9H), 0.80 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 135.3, 132.6, 131.0, 119.0, 77.1, 70.7, 41.1, 29.7, 28.4, 27.2, 26.0, 23.5, 23.0, 21.2, 20.3.

R_f 0.70 (hexanes/EA = 20:1, UV/*p*-anisaldehyde)



Dimethyl (4a*R*,6a*R*,10b*R*)-3,3-di-*tert*-butyl-6a,10b-dimethyl-4a,5,6,6a,9,10b-hexahydro-1H-naphtho[2,1-d][1,3,2]dioxasiline-7,8-dicarboxylate (4.3f)



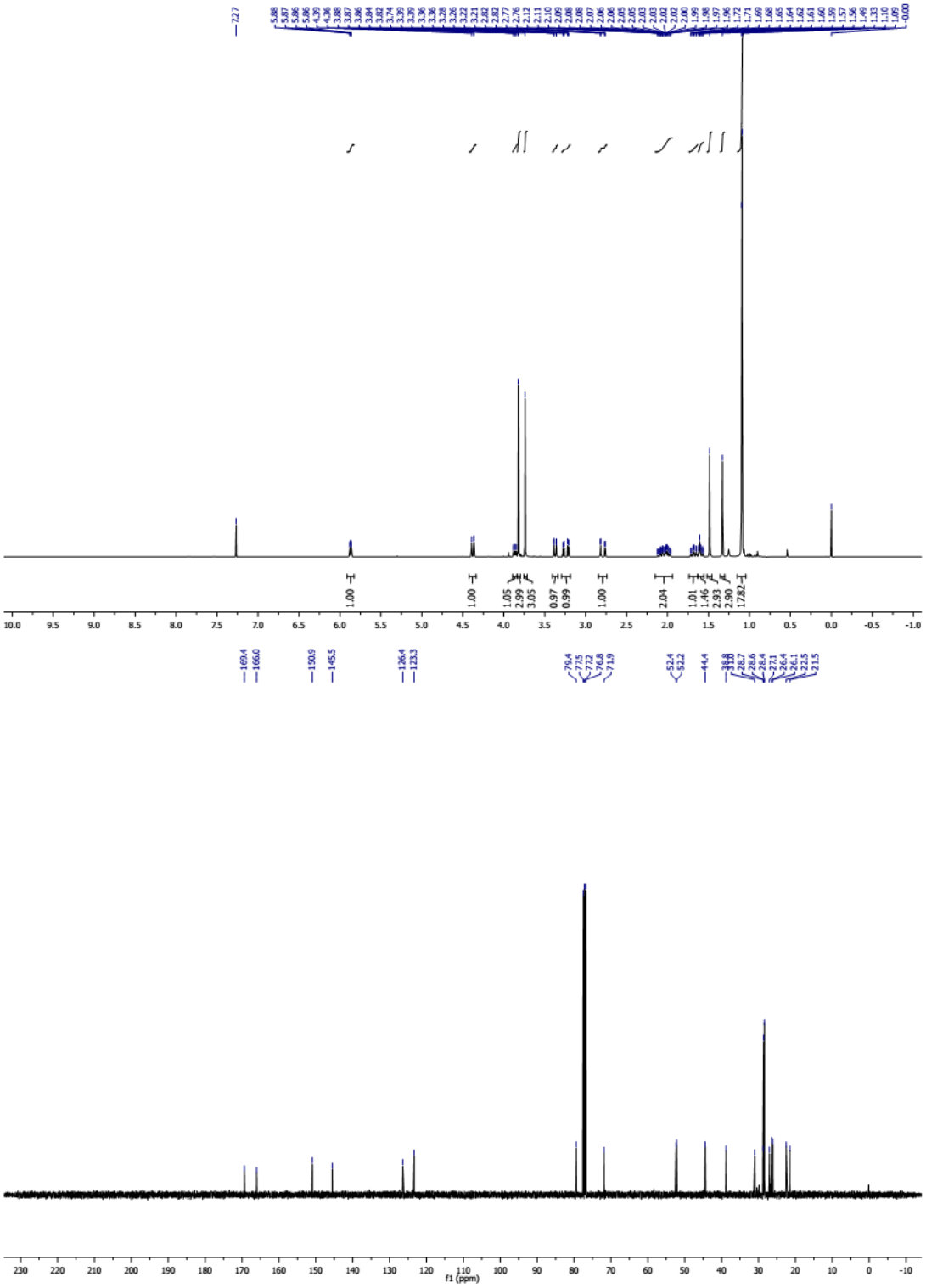
Detailed Procedures

To a solution of diene **4.4f** (0.0430 g, 0.13 mmol, 100 mol%) in toluene (0.070 mL) was added dimethyl acetylenedicarboxylate (DMAD, 0.049 mL, 0.40 mmol, 300 mol%). The mixture was heated to 120 ˚C in seal tube for 24 hours. After cooled to ambient temperature, the solvent was removed under reduced pressure and the residue was submitted to flash column chromatography on silica gel (hexanes/acetone = 100:1 to 50:1). The title compound was obtained as a white solid (0.0418 g, 0.090 mmol) in 67% yield.

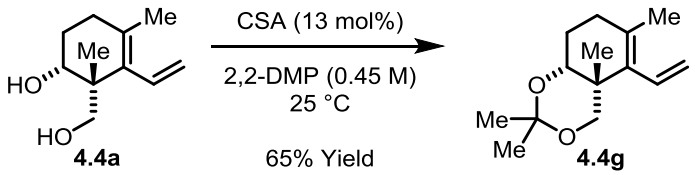
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87 (dd, *J* = 6.2, 2.0 Hz, 1H), 4.38 (d, *J* = 11.6 Hz, 1H), 3.86 (dd, *J* = 10.1, 5.5 Hz, 1H), 3.82 (s, 3H), 3.74 (s, 3H), 3.37 (dd, *J* = 11.6, 1.0 Hz, 1H), 3.24 (dd, *J* = 22.4, 6.2 Hz, 1H), 2.79 (dd, *J* = 22.4, 2.0 Hz, 1H), 2.13-1.95 (m, 2H), 1.68 (td, *J* = 13.0, 3.9 Hz, 1H), 1.59 (dt, *J* = 13.4, 4.2 Hz, 1H), 1.49 (s, 3H), 1.33 (s, 3H), 1.10 (s, 9H), 1.09 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 166.0, 150.9, 145.5, 126.4, 123.3, 79.4, 71.9, 52.4, 52.2, 44.4, 38.8, 31.0, 28.7, 28.6, 28.4, 27.1, 26.4, 26.1, 22.5, 21.5.

R_f 0.30 (hexanes/acetone = 10:1, UV/*p*-anisaldehyde)



(4a*R*,8a*R*)-2,2,4a,6-Tetramethyl-5-vinyl-4a,7,8,8a-tetrahydro-4H-benzo[*d*][1,3]dioxine (4.4g)



Detailed Procedures

To a solution of diol (0.0821 g, 0.45 mmol, 100 mol%) in 2,2-dimethoxypropane (2,2-DMP, 1.0 mL) was added camphorsulfonic acid (CSA, 0.0139g, 0.06 mmol, 13 mol%) at ambient temperature. The resulted mixture was allowed to stir at the same temperature overnight. The reaction was diluted with Et_2O (1.0 mL) and quenched by addition of saturated $NaHCO_3$ (aq., 1.0 mL). The organic layer was separated, and washed with water (1.0 mL × 2). After dried over anhydrous Na_2SO_4, the solvent was removed under reduced pressure, and the residue was submitted to flash column chromatography on silica gel (hexanes/acetone = 100:1). The title compound was obtained as a colorless oil (0.0644 g, 0.29 mmol) in 65% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.20 (dddt, *J* = 17.7, 11.3, 2.4, 1.2 Hz, 1H), 5.27 (dd, *J* = 11.3, 2.5 Hz, 1H), 5.03 (dd, *J* = 17.7, 2.5 Hz, 1H), 3.84-3.81 (m, 1H), 3.81 (d, *J* = 11.9 Hz, 1H), 3.48 (d, *J* = 11.8 Hz, 1H), 2.39-2.25 (m, 1H), 1.89-1.76 (m, 2H), 1.74 (s, 3H), 1.73-1.66 (m, 1H), 1.44 (s, 3H), 1.32 (s, 3H), 0.92 (s, 3H).

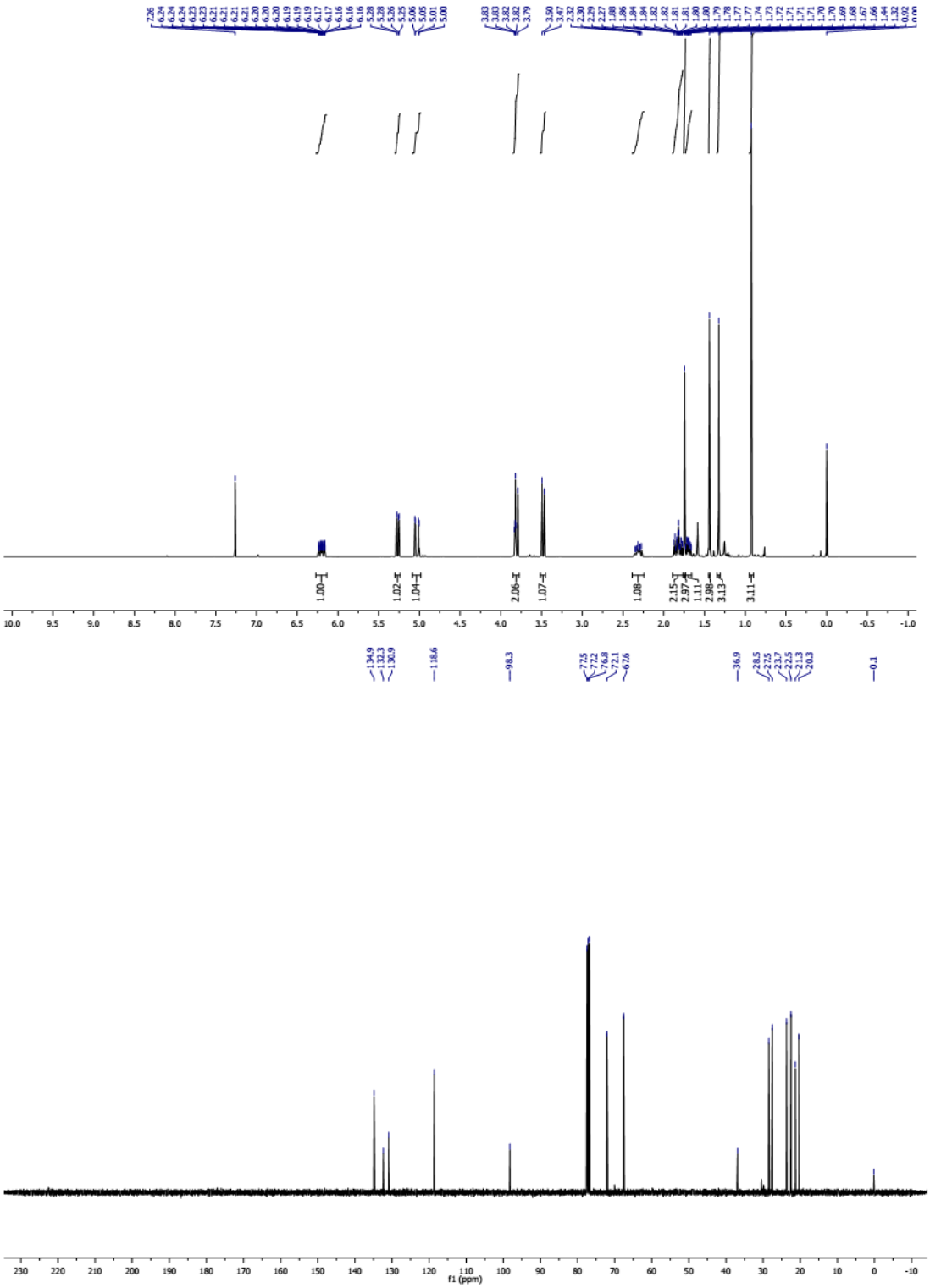
^{13}C NMR (100 MHz, $CDCl_3$) δ 134.9, 132.3, 130.9, 118.6, 98.3, 72.1, 67.6, 36.9, 28.5, 27.5, 23.7, 22.5, 21.3, 20.3.

R_f 0.85 (hexanes/acetone = 15:1, UV/*p*-anisaldehyde)

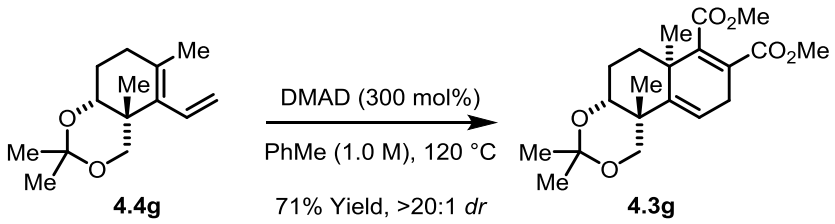
HRMS (CI) Calcd. for $C_{14}H_{22}O_2$ $[M+H]^+$: 223.1696, Found: 223.1698.

FTIR (neat): 2989, 2930, 2864, 1622, 1449, 1375, 1240, 1227, 1198, 1159, 1122, 1078, 1049, 1022, 1000, 917, 857, 768 cm^{-1}.

Optical Rotation $[\alpha]_D^{25}$ = -275° (*c* = 0.5, $CHCl_3$)



Dimethyl (4a*R*,6a*R*,10b*R*)-3,3,6a,10b-tetramethyl-4a,5,6,6a,9,10b-hexahydro-1H-naphtho[2,1-d][1,3]dioxine-7,8-dicarboxylate (4.3g)



Detailed Procedures

To a solution of diene **4.4g** (0.0222 g, 0.1 mmol, 100 mol%) in toluene (0.10 mL) was added dimethyl acetylenedicarboxylate (DMAD, 0.037 mL, 0.3 mmol, 300 mol%). The mixture was heated to 120 ˚C in seal tube for 18 hours. After cooled to ambient temperature, the solvent was removed under reduced pressure and the residue was submitted to flash column chromatography on silica gel (hexanes/acetone = 50:1 to 25:1). The title compound was obtained as a colorless oil (0.0260 g, 0.071 mmol) in 71% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85 (dd, *J* = 6.3, 1.8 Hz, 1H), 3.98 (d, *J* = 12.1 Hz, 1H), 3.82 (s, 3H), 3.83-3.79 (m, 1H), 3.74 (s, 3H), 3.51 (d, *J* = 12.1 Hz, 1H), 3.21 (dd, *J* = 22.0, 6.3 Hz, 1H), 2.89 (dd, *J* = 22.0, 1.9 Hz, 1H), 2.20-2.07 (m, 1H), 1.91-1.75 (m, 3H), 1.63-1.56 (m, 1H), 1.52 (s, 3H), 1.42 (d, *J* = 0.7 Hz, 3H), 1.37 (d, *J* = 0.7 Hz, 3H), 1.01 (s, 3H).

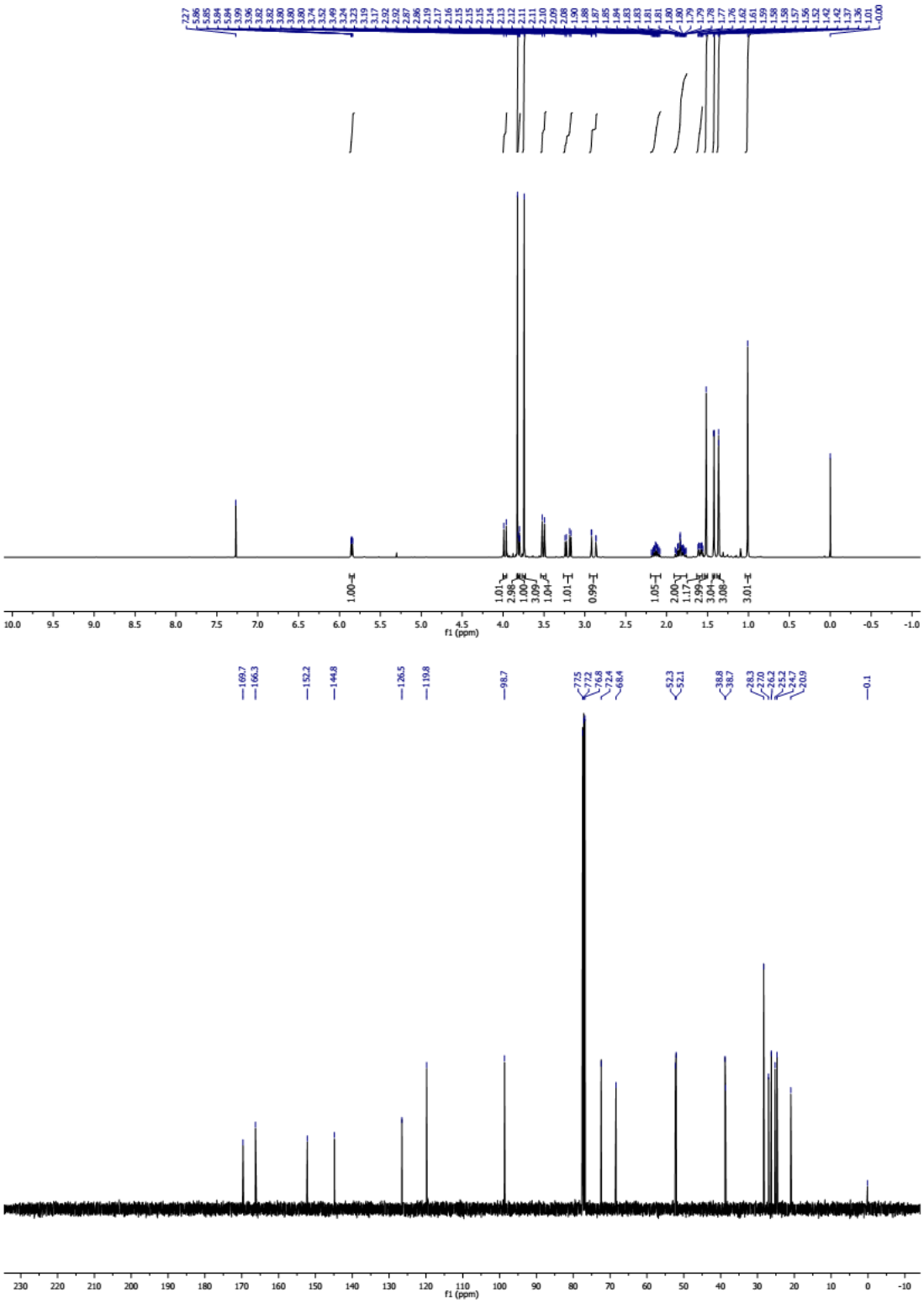
^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 166.3, 152.2, 144.8, 126.5, 119.8, 98.7, 72.4, 68.4, 52.3, 52.1, 38.8, 38.7, 28.3, 27.0, 26.2, 25.2, 24.7, 20.9.

R_f 0.20 (hexanes/acetone = 10:1, UV/*p*-anisaldehyde)

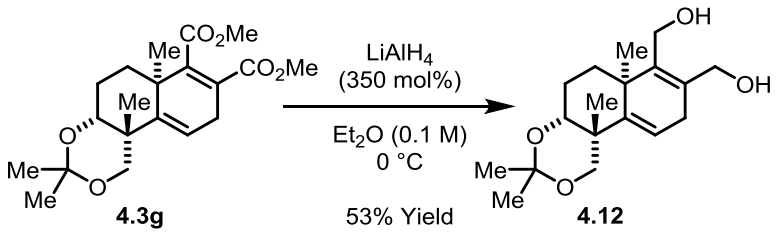
HRMS (ESI) Calcd. for $C_{20}H_{28}O_6$ $[M+Na]^+$: 387.1778, Found: 387.1789.

FTIR (neat): 2988, 2953, 1725, 1437, 1378, 1258, 1198, 1100, 1071, 1021, 1000, 860, 733 cm^{-1}.

Optical Rotation $[\alpha]_D^{25}$ = -31˚ (*c* = 0.8, $CHCl_3$)



((4a*R*,6a*R*,10b*R*)-3,3,6a,10b-Tetramethyl-4a,5,6,6a,9,10b-hexahydro-1H-naphtho[2,1-*d*][1,3]dioxine-7,8-diyl)dimethanol (4.12)



Detailed Procedures

To an ice-cooled solution of dicarboxylate **4.3g** (0.0563 g, 0.15 mmol, 100 mol%) in Et_2O (1.5 mL) was added $LiAlH_4$ (0.0205 g, 0.54 mmol, 350 mol%). The resulted mixture was stirred vigorously at the same temperature for 1.5 hours. Water (0.020 mL) was slowly added to quench the reaction, followed by addition of 15% NaOH (aq., 0.020 mL) and water (0.060 mL). The mixture was allowed to stir for 10 min before it was filtered through Celite. The filtrate was washed with brine (1.0 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was submitted to flash chromatography on silica gel (hexanes/acetone = 3:1). The title compound was obtained as a colorless oil (0.0255 g, 0.083 mmol) in 53% yield.

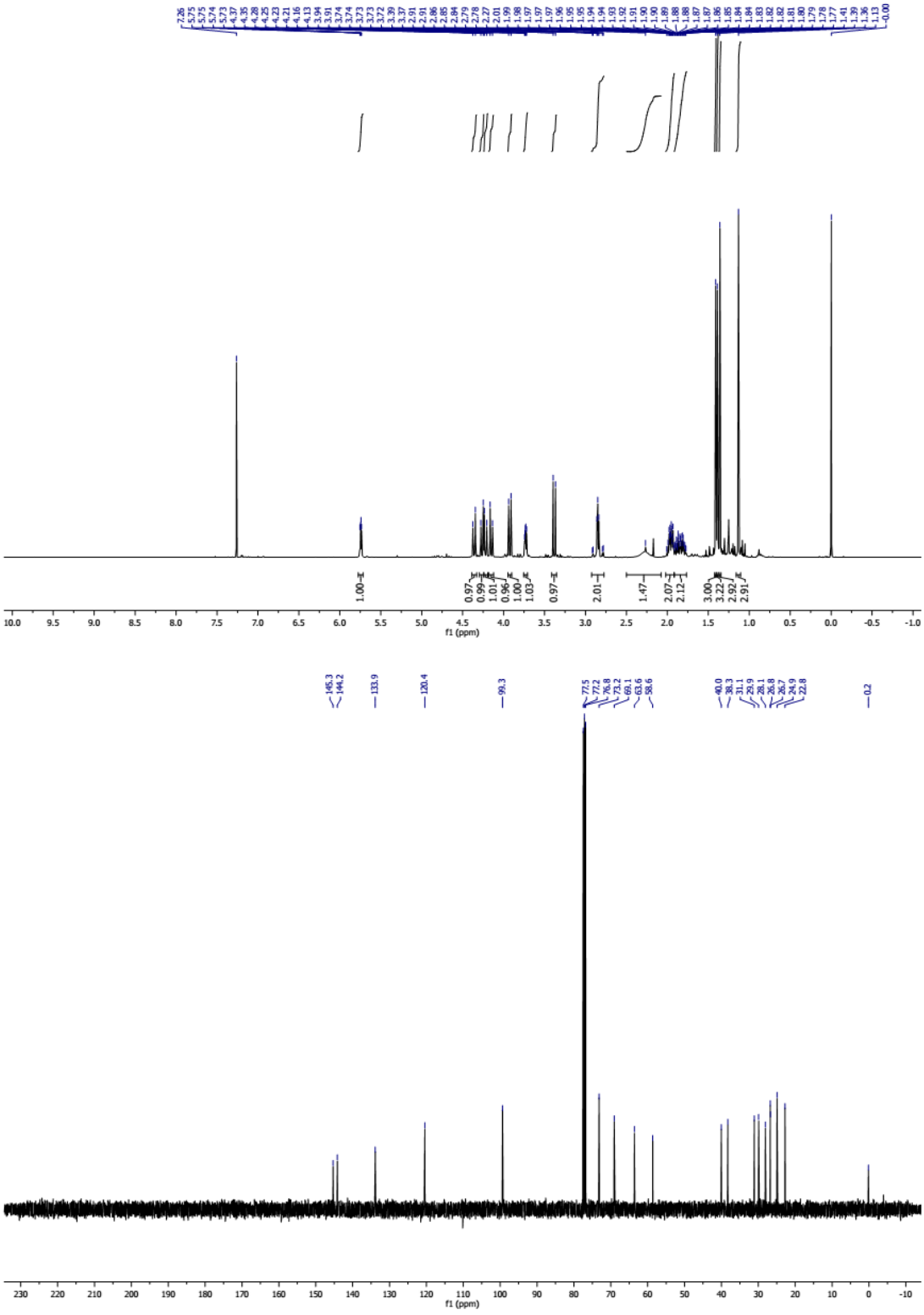
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.74 (dd, *J* = 4.9, 2.9 Hz, 1H), 4.36 (d, *J* = 11.8 Hz, 1H), 4.26 (d, *J* = 11.6 Hz, 1H), 4.22 (d, *J* = 11.8 Hz, 1H), 4.15 (d, *J* = 11.6 Hz, 1H), 3.92 (d, *J* = 11.8 Hz, 1H), 3.76-3.71 (m, 1H), 3.38 (d, *J* = 11.7 Hz, 1H), 2.92-2.77 (m, 2H), 2.27 (br, 2H), 2.02-1.92 (m, 2H), 1.92-1.77 (m, 2H), 1.41 (s, 3H), 1.39 (s, 3H), 1.36 (s, 3H), 1.13 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 145.3, 144.2, 133.9, 120.4, 99.3, 73.2, 69.1, 63.6, 58.6, 40.0, 38.3, 31.1, 29.9, 28.1, 26.8, 26.7, 24.9, 22.8.

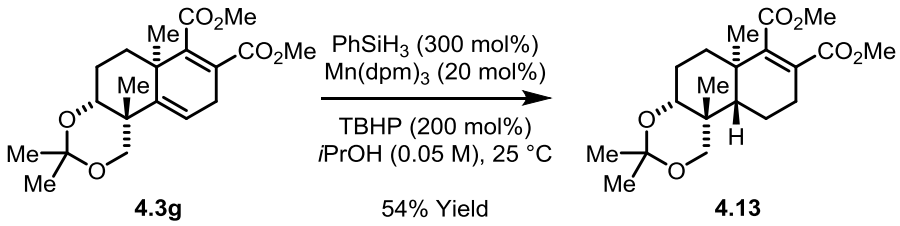
R_f 0.10 (hexanes/acetone = 4:1, *p*-anisaldehyde)

FTIR (neat): 3425, 2985, 2933, 1686, 1456, 1377, 1225, 1199, 1065, 998, 861, 824 cm^{-1}.

Optical Rotation $[\alpha]_D^{30}$ = -144° (*c* = 0.7, $CHCl_3$)



Dimethyl (4a*R*,6a*R*,10a*S*,10b*R*)-3,3,6a,10b-tetramethyl-4a,5,6,6a,9,10,10a,10b-octahydro-1H-naphtho[2,1-d][1,3]dioxine-7,8-dicarboxylate (4.13)



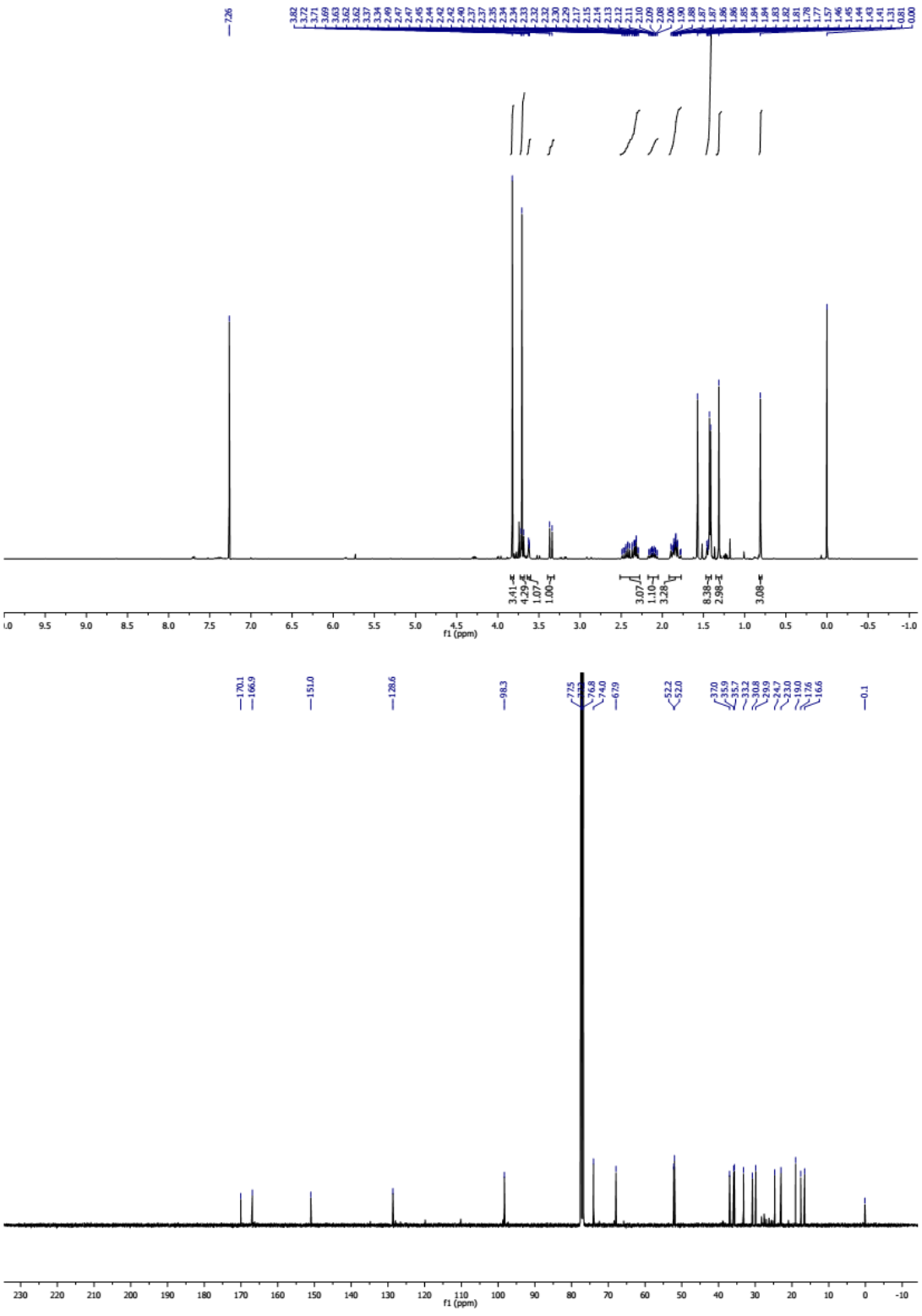
Detailed Procedures

To a degassed solution of **4.3g** (0.0036g, 0.01 mmol, 100 mol%) in anhydrous 2-propanol (0.060 mL) was added a degassed solution of $PhSiH_3$ (0.0037 mL, 0.03 mmol, 300 mol%) in 2-propanol (0.060 mL), *tert*-butyl hydroperoxide (5.5 M in decane, 0.0036 mL, 0.04 mmol, 200 mol%) and a degassed solution of $Mn(dpm)_3$ (0.0012 g, 0.002 mmol, 20 mol%) in 2-propanol (0.080 mL). The resulted mixture was degassed by bubbling with argon for 5 seconds, and was allowed to stir at ambient temperature for 4 hours. The reaction was diluted with DCM (0.2 mL) and quenched by addition of saturated $NaHCO_3$ (aq., 0.2 mL). The organic layer was separated and washed with water (0.2 mL × 2). After dried over anhydrous Na_2SO_4, the solvent was removed under reduced pressure and the residue was submitted to flash column chromatography on silica gel (hexanes/acetone = 25:1 to 10:1). The title compound was obtained as a white solid (0.0020 g, 0.0054 mmol) in 54% yield.

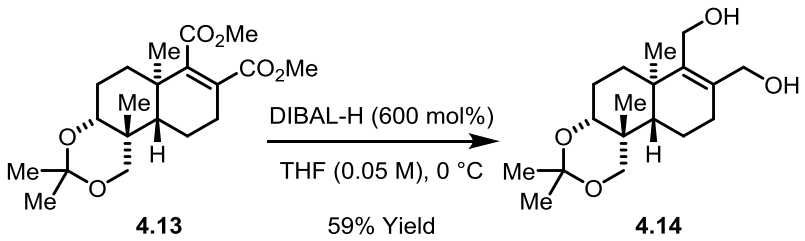
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.82 (s, 3H), 3.71 (s, 3H), 3.70 (d, *J* = 12.1 Hz, 1H), 3.64-3.60 (m, 1H), 3.35 (d, *J* = 12.2 Hz, 1H), 2.51-2.28 (m, 3H), 2.11 (dtd, *J* = 16.4, 9.7, 6.8 Hz, 1H), 1.92-1.76 (m, 3H), 1.47-1.44 (m, 2H), 1.43 (s, 3H), 1.41 (s, 3H), 1.31 (s, 3H), 0.81 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 166.9, 151.0, 128.6, 98.3, 74.0, 67.9, 52.2, 52.0, 37.0, 35.9, 35.7, 33.2, 30.8, 29.9, 24.7, 23.0, 19.0, 17.6, 16.6.

R_f 0.40 (hexanes/acetone = 10:1 (twice), UV/*p*-anisaldehyde)



((4a*R*,6a*R*,10a*S*,10b*R*)-3,3,6a,10b-Tetramethyl-4a,5,6,6a,9,10,10a,10b-octahydro-1H-naphtho[2,1-d][1,3]dioxine-7,8-diyl)dimethanol (4.14)



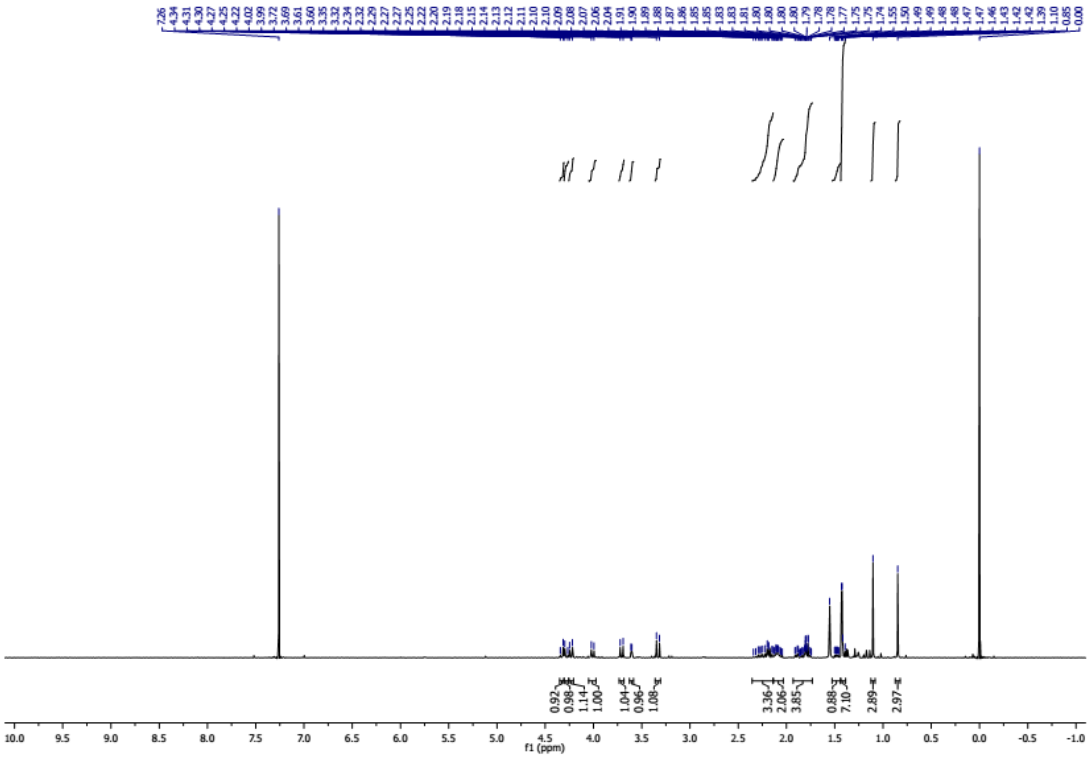
4.13 59% Yield **4.14**

Detailed Procedures

To an ice-cooled solution of dicarboxylate **4.13** (0.0020 g, 0.0054 mmol, 100 mol%) in THF (0.10 mL) was added diisobutylaluminum hydride (DIBAL-H, 1.0 M solution in hexane, 0.033 mL, 600 mol%) slowly. The resulted mixture was allowed to stir at 0 ˚C for 1 hour. The reaction was diluted with DCM (0.5 mL) and quenched by addition of Rochelle salt solution (1.0 M aqueous solution, 0.4 mL). The two layers were separated, and the aqueous phase was extracted with DCM (0.5 mL). The combined organic phases were washed with water (0.5 mL × 2), and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was submitted to flash column chromatography on silica gel (hexanes/acetone = 10:1 to 3:1). The title compound was obtained as a colorless oil (0.0010 g, 0.0032 mmol) in 59% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.33 (d, *J* = 11.7 Hz, 1H), 4.28 (d, *J* = 11.8 Hz, 1H), 4.23 (d, *J* = 11.6 Hz, 1H), 4.01 (d, *J* = 11.5 Hz, 1H), 3.71 (d, *J* = 12.1 Hz, 1H), 3.61 (d, *J* = 4.2 Hz, 1H), 3.33 (d, *J* = 12.1 Hz, 1H), 2.36-2.14 (m, 3H), 2.14-2.04 (m, 2H), 1.92-1.74 (m, 4H), 1.48 (ddd, *J* = 7.8, 5.3, 3.8 Hz, 1H), 1.43 (s, 3H), 1.42 (s, 3H), 1.40 (d, *J* = 9.5 Hz, 1H), 1.10 (s, 3H), 0.85 (s, 3H).

R_f 0.15 (hexanes/acetone = 3:1, *p*-anisaldehyde)


f1 (ppm)

Comparison of NMR Data between Synthetic Isoiresin

Table 4.5 ^{13}C NMR data of synthetic isoiresin (**4.1**).

Synthetic 1[15]	**Synthetic 2 (This Work)**
δ_C (ppm)	δ_C (ppm)
174.0	174.0
169.2	169.1
123.8	123.8
80.1	80.1
68.1	68.1
63.8	63.8
51.0	51.0
42.9	42.9
36.0	36.0
33.8	33.8
27.5	27.5
22.6	22.5
21.7	21.7
21.5	21.5
18.1	18.1

Appendix

List of Abbreviations and Acronyms

FLAP	5-lipoxygenase-activating protein
NHC	*N*-heterocyclic carbene
9-BBN	9-borabicyclo[3.3.1]nonane
ee	enantiomeric excess
dr	diastereomeric ratio
rr	regiomeric ratio
B(pin)	(pinacolato)boronate
OA	oxidative addition
TM	transmetallation
RE	reductive elimination
Py	2-pyridyl
acac	acetylacetonate
DME	dimethoxyethane
BINAP	2,2′-Bis(diphenylphosphino)-1,1′-binaphthalene
Cp	cyclopentadienyl
LA	Lewis acid
HMDS	bis(trimethylsilyl)amide
MS	molecular sieves
cod	1,4-cyclooctadiene
MTBE	methyl *tert*-butyl ether
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
CFL	compact fluorescent light

bpy	2,2'-bipyridine
TBAI	tetrabutylammonium iodide
BARF	tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
BQ	1,4-benzoquinone
HMPA	hexamethylphosphoramide
LLS	longest linear steps
TASF	tris(dimethylamino)sulfonium difluorotrimethylsilicate
TMSE	2-(trimethylsilyl)ethyl
EVK	ethyl vinyl ketone
PPA	polyphosphoric acid
AIBN	azobisisobutyronitrile
TFE	2,2,2-trifluoroethanol
THP	tetrahydropyranyl
LDA	lithium diisopropylamide
PTSA	*p*-toluenesulfonic acid
DIPT	diisopropyl tartrate
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
PPTS	pyridinium *p*-toluenesulfonate
DMSO	dimethyl sulfoxide
TFAA	trifluoroacetic anhydride
DMAP	4-dimethylaminopyridine
DIPEA	diisopropylethylamine
TBAF	tetrabutylammonium fluoride
dpm	dipivaloylmethanate

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Chapter 1

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