The Dissertation Committee for Amy C. Bonaparte certifies that this is the approved version of the following dissertation:

Synthesis of β-Heteroaryl Propionates via Trapping of Carbocations with π-Nucleophiles, Efforts towards the Total Synthesis of Acutumine, and the Design, Synthesis, and Thermodynamics of Protein-Ligand Interactions at the Src SH2 Domain

Committee:

Stephen F. Martin, Supervisor

Jonathan L. Sessler

Katherine Willets

Sean Kerwin

Hung-Wen (Ben) Liu

Guangbin Dong

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by

Amy C. Bonaparte, B.S.

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Dedication

To my parents, Heather, and Branden. I couldn't have made it through this process without you.

Acknowledgements

I'd like to acknowledge Stephen F. Martin for all his guidance, wisdom, and most importantly, patience throughout the years. I'd also like to thank all of the past and current members of the Martin group for all your help and support. I would also like to acknowledge the "Dallas Bonaparte's" for giving me a little piece of home on Thanksgiving and Easter. Finally, I'd like to acknowledge and thank my Austin family: Katie Cl., Craig, Courtney, Ryan, Ting, Lauren, Zach, Micah, Katie Cr., Mary, Anna, and Rachel. I couldn't have done it without you.

Synthesis of β-Heteroaryl Propionates via Trapping of Carbocations with π-Nucleophiles, Efforts towards the Total Synthesis of Acutumine, and the Design, Synthesis, and Thermodynamics of Protein-Ligand Interactions at the Src SH2 Domain

Amy C. Bonaparte, Ph.D.

The University of Texas at Austin, 2013

Supervisor: Stephen F. Martin

Heterocyclic alcohols were coupled with π-nucleophiles in the presence of trimethylsilyl trifluoromethanesulfonate to provide a variety of substituted β-heteroaryl propionates, including those with contiguous quaternary centers. This reaction also provided β-heteroaryl propionates which were previously inaccessible by known methods by exploiting non-traditional Friedel Crafts reactivity. Good diastereoselectivity was also achieved when a chiral auxiliary was incorporated into the π-nucleophile.

Progress towards the synthesis of acutumine, an alkaloid possessing a densely functionalized aza-propellane core, two quaternary centers, and a neopentylic chlorine atom, was pursued. A variety of routes were employed, with some of the key steps explored including a Moore cyclization between dimethyl squarate and protected butyn-3-ols, a SmI_2 mediated ring opening of a densely functionalized dihydroisoquinoline ring, and a Stille reaction to install an key allyl functional handle.

The thermodynamics behind the binding affinity of various ligands to the Src SH2 domain was also investigated. A series of four ligands were designed and

enantioselectively synthesized in order to compare how differences in the conformations of the ligands affect the thermodynamics of binding. Namely, cyclopropanes were introduced into tetrapeptides to restrict the ligands to their binding conformations. The constricted ligands will then be compared to their appropriate flexible controls *via* the use of isothermal titration calorimetry (ITC) to determine the thermodynamics differences of binding between the two.

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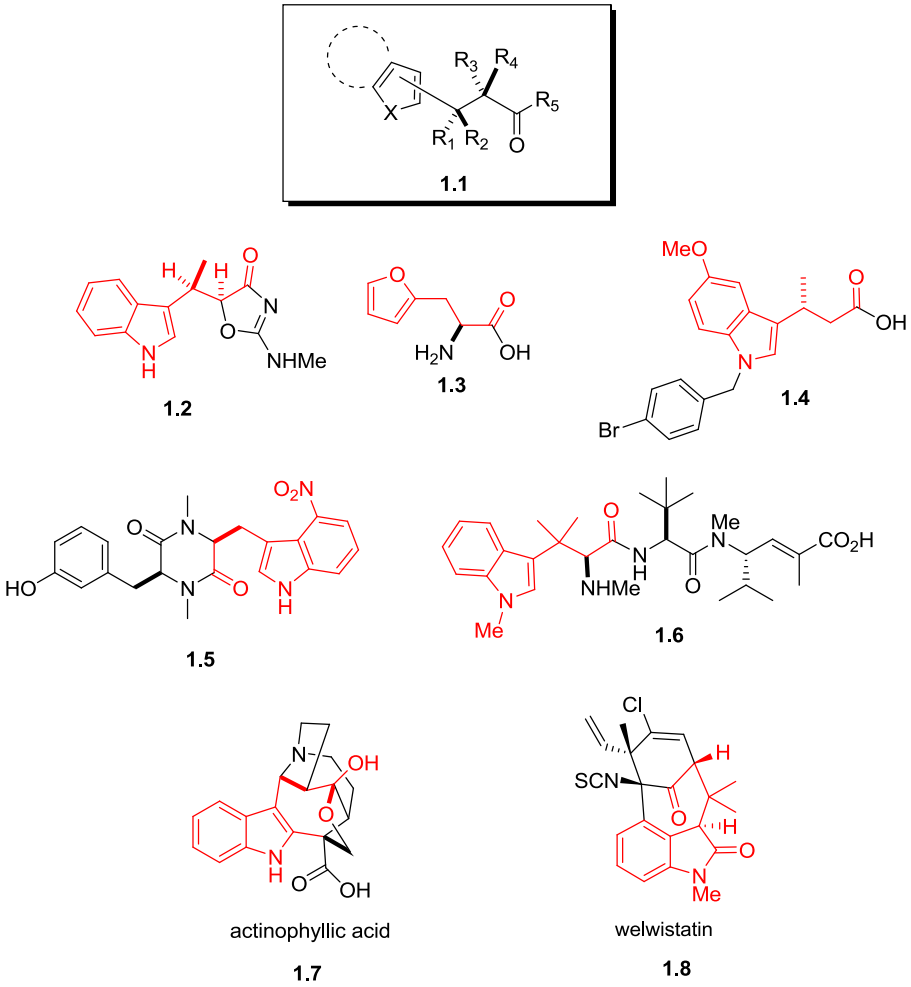
CHAPTER 1: FORMATION OF β-HETEROARYL PROPIONATES *VIA* LEWIS ACID MEDIATED TRAPPING OF BENZYLIC CARBOCATIONS WITH π-NUCLEOPHILES

1.1 INTRODUCTION

β-Heteroaryl propionates **1.1**, are important synthetic targets because they are found in a variety of biologically active compounds. Some examples of such compounds are depicted in Figure 1.1, and in each case the β-heteroaryl propionate moiety is highlighted. The propionates include a large range of α- and/or β-substituents, and while only indole and furan are shown below, many other electron-rich heterocyclic propionates can be found in the literature. β-Heteroaryl propionates also exhibit a wide range of biological activities. Indolmycin (**1.2**) is an antibiotic that exhibits significant activity against bacterial *Staphylococci aureus*.[1] Furylalanine (**1.3**) is a common fungicide, whereas thaxtomine A (**1.5**) acts as a phytotoxin to induce necrotic lesions on potato minitubers .[2,3] Indolobutyric acid (**1.4**) is an anti-inflammatory agent that specifically targets the COX-2 enzyme and hemiasterlin (**1.6**) can disrupt the mitosis of cancer cells.[4,5] Two other natural products that also contain β-heteroaryl scaffold include welwistatin (**1.8**) and actinophyllic acid (**1.7**), which have both been recently synthesized by the Martin group using methodology that will be described later.[6] Welwistatin (**1.8**) has been shown to reverse multiple drug resistance of human cancer cells in combination with several anticancer drugs, while actinophyllic acid (**1.7**) can inhibit fibrinolysis.[7,8]

Figure 1.1

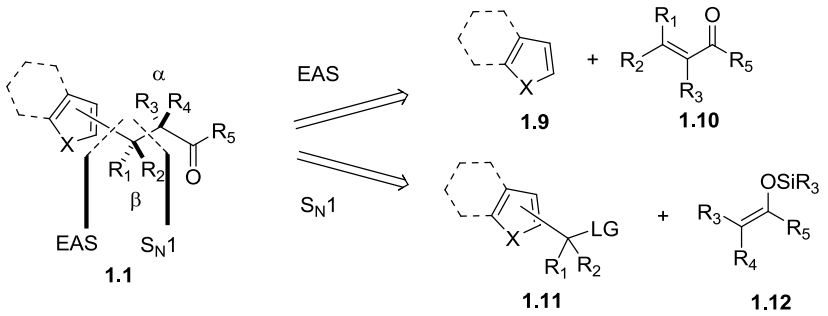


1.2 Main Methods to Synthesize β-Heteroaryl Propionates

There exist two main paths to access β-heteroaryl propionates. The first, (EAS), involves the conjugate addition of heteroaromatic nucleophiles to α-β-unsaturated carbonyl derivatives (Scheme 1.1). The second route to β-heteroaryl propionates, (S_N1), involves an S_N1-type reaction in which the heteroaryl ring bears a benzylic-like leaving group, which ionizes in the presence of a suitable Lewis acid (Scheme 1.1). The nascent

carbocation can then be captured by a suitable π-nucleophile to produce the desired propionate.

Scheme 1.1



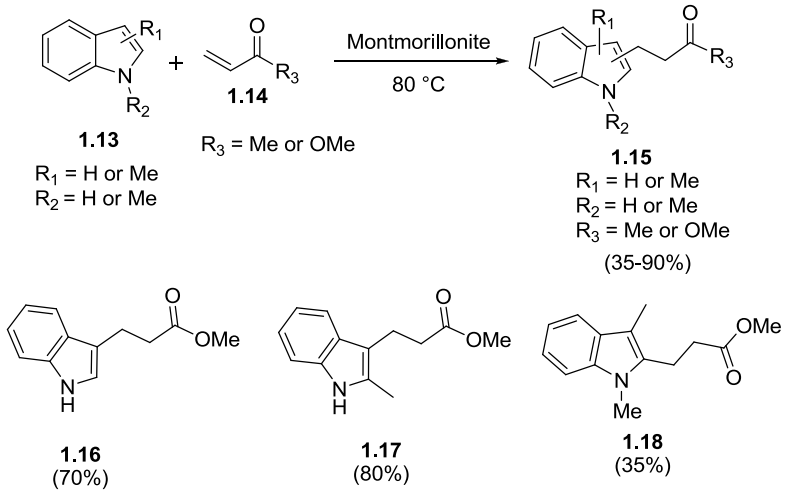
1.3 SYNTHESIS OF β-HETEROARYL PROPIONATES BY EAS

One of the most direct and widely utilized methods to prepare β-heteroaryl propionates is the Michael addition of electron rich heterocycles to π-acceptors. These conjugate additions are usually catalyzed by either Lewis or Bronsted acids. High yielding examples of both achiral and chiral reactions of this type are well precedented in the literature, with high stereoselectivity present in many chiral cases.[9-28] However, this type of reaction is limited to the site of the heteroaromatic ring favored by classical electrophilic aromatic substitution reactions, and polyalkylation can be a significant problem for heterocycles that bear more than one active nucleophilic site. Moreover, substitution on the unsaturated moiety (Scheme 1.1, R_1, R_2 = alkyl) is limited,[10,29,30] with α,α-disubstitution products (Scheme 1.1, R_3, R_4 = alkyl) seemingly completely inaccessible through this route. Specific examples from this route will be found in the succeeding paragraphs.

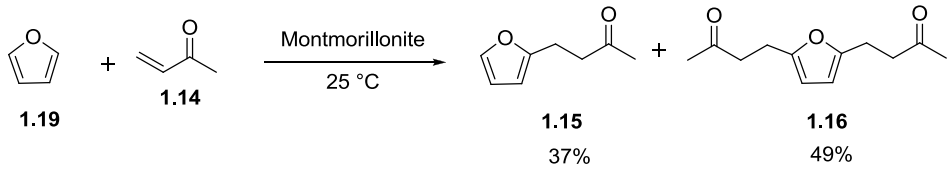
1.3.1 Conjugate Additions of Electron Rich Heteroaromatic Rings with π-acceptors Catalyzed by Bronsted Acids

Acidic clays are efficient promoters of the conjugate additions of various indole derivatives to α,β-unsaturated ketones and esters (Schemes 1.2 and 1.3).[9] The reactions are moderate to high yielding (70-90%) for 3-unsubstituted indoles using both types of electrophiles, with α,β-unsaturated ketones providing the best results. The yields of α,β-unsaturated esters can be improved with higher reaction temperatures and longer reaction times, but polyalkylation may then become problematic. It is interesting to note that Jackson and coworkers were able to effect the Michael reaction between a 3-substituted indole and methyl acrylate to provide **1.18**, albeit in low (35%) yield (Scheme 1.2).[9] Cintas *et al.* showed that addition of furan to methyl vinyl ketone (**1.14**) could also be catalyzed by Montmorillonite clay, though in this case the major product was dialkylation **1.16** (Scheme 1.3).[31] While this method boasts fairly straightforward reaction conditions and an easy workup (filtration of the catalyst from the reaction mixture), the use of unsaturated esters as electrophiles requires harsher reaction conditions that may not be amenable to acid sensitive substrates. Moreover, α,β-substitution on the Michael acceptor has not been shown, which would make this route a poor method to access α,β-substituted heteroaryl propionates.

Scheme 1.2

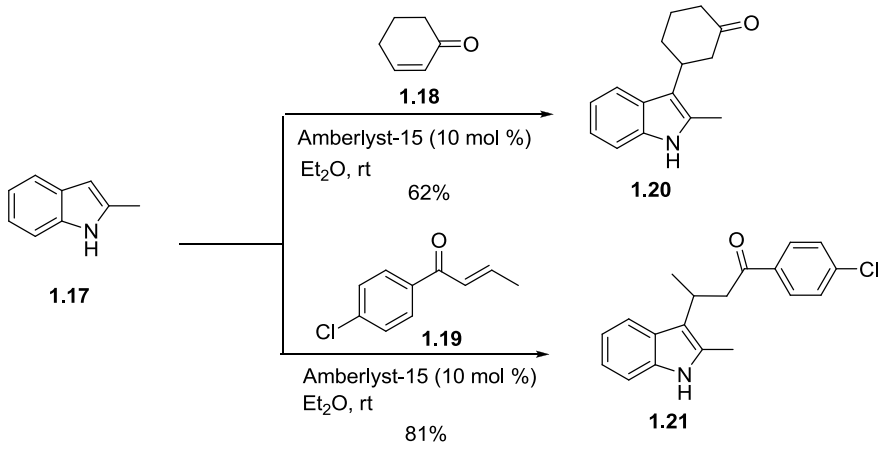


Scheme 1.3



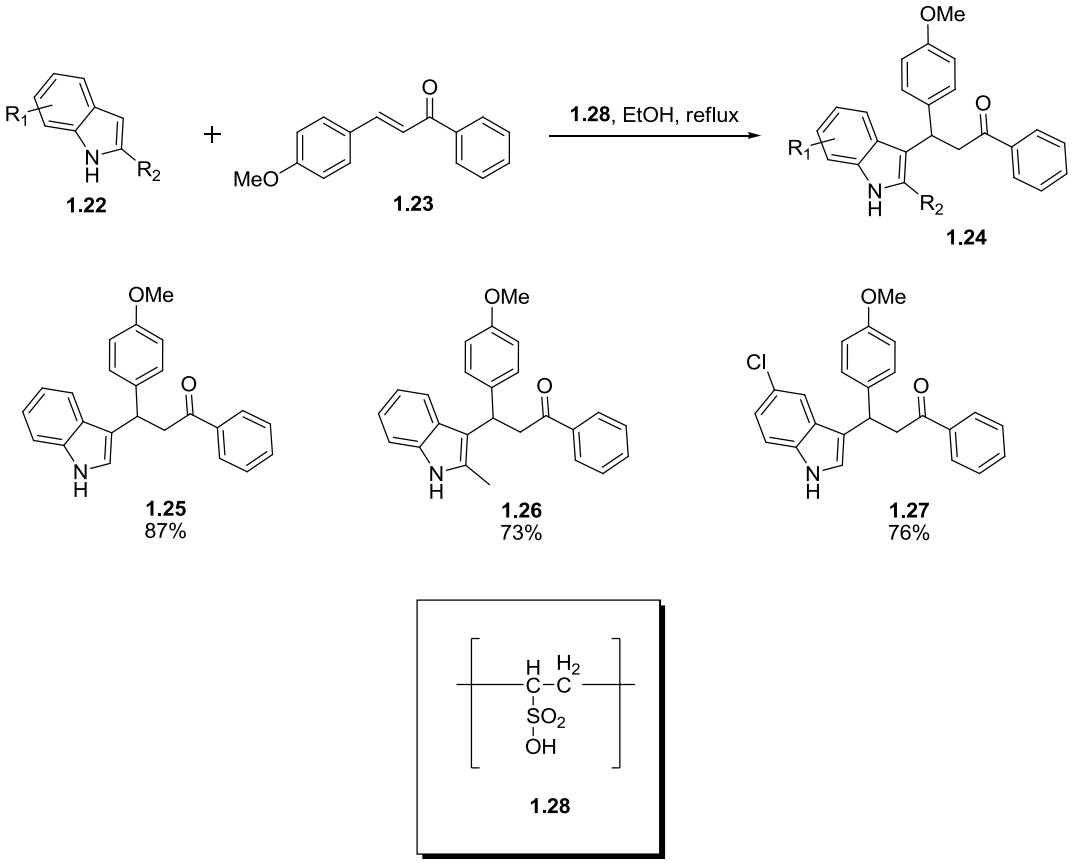
Amberlyst-15 has also been used as an efficient Bronsted acid-promoter of Michael additions of indoles to α,β-unsaturated ketones (Scheme 1.4).[32] The reaction conditions were less harsh than using Montmorillonite clay, and the catalyst loadings were also lower (10 mol % vs. 20 mol %). The conjugate additions took place in moderate to excellent yields (60-95%), and a limited number of α-substituents were tolerated on the Michael acceptor. However, the substrate scope was limited to 2-methylindole and a few different unsaturated ketones. No examples of additions to unsaturated esters, which would provide the most direct access to α,β-heteroaryl propionates, were reported.

Scheme 1.4



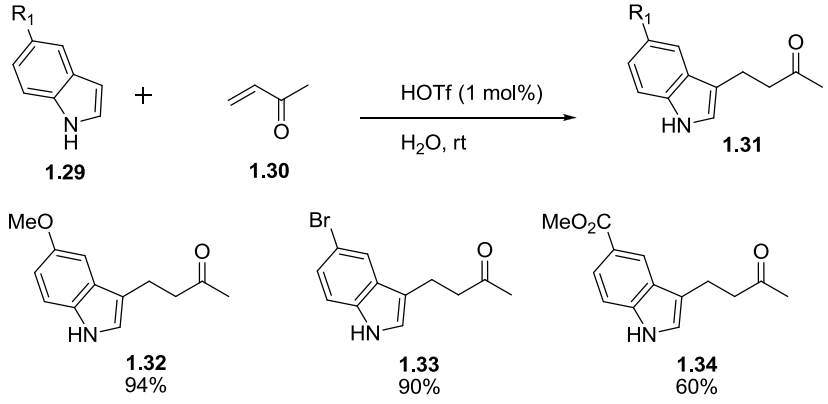
Bhanage and coworkers successfully catalyzed heterocyclic conjugate additions using polyvinylsulfonic acid (PVSA), a Bronsted acidic polymer **1.28** (Scheme 1.5).[33] A variety of indoles were allowed to react with chalcones to provide the desired α-substituted adducts in moderate to good yields (46-92%). Electron-rich indoles paired with electron-poor chalcones gave the best results, but like previous examples, the scope of the reaction was limited to a single heterocycle and a select few unsaturated ketones. The reaction conditions were also somewhat harsh as they required heating at elevated temperatures for long periods of time.

Scheme 1.5

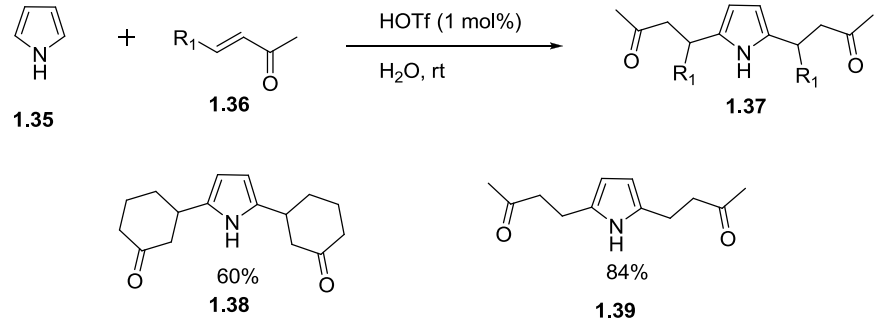


Triflic acid (TfOH) has been shown to catalyze Michael additions of indoles and pyrroles to α,β-unsaturated ketones in moderate to excellent yields (60-94%) (Schemes 1.6 and 1.7).[16] The reaction conditions are very mild and environmentally friendly as the solvent was water. However, the scope of this reaction is also limited to unsaturated ketones, and dialkylated propionates were the major products of the reaction when the acid sensitive pyrrole was employed as the nucleophilic partner.

Scheme 1.6



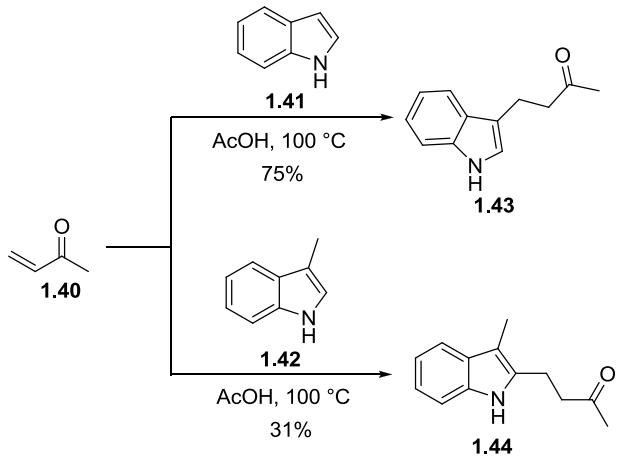
Scheme 1.7



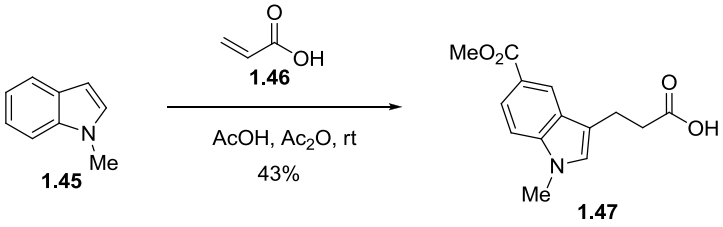
Acetic acid (AcOH) has also been used to catalyze Michael reactions with indoles and unsaturated ketones (Schemes 1.8 and 1.9). In 1957, Szmuszkovicz and coworkers reacted indole with methyl vinyl ketone in acetic acid at elevated temperatures.[34] The conditions were rather harsh, and the yields of the resulting adducts were poor to moderate at best (31-75%). However, Szmuszkovicz was able to effect addition at the 2-position of the indole when the 3-position was substituted, albeit in only 31% yield. Dinnell and co-workers expanded upon the methodology to catalyze the conjugate addition of indole **1.45** with acrylic acid (**1.46**) using acetic anhydride as an additive to provide the β-heteroaryl propionic acid **1.44** in a single step in 46% yield.[35] This method

still suffers from a narrow substrate scope that does not encompass α,β-substitution on the electrophile.

Scheme 1.8

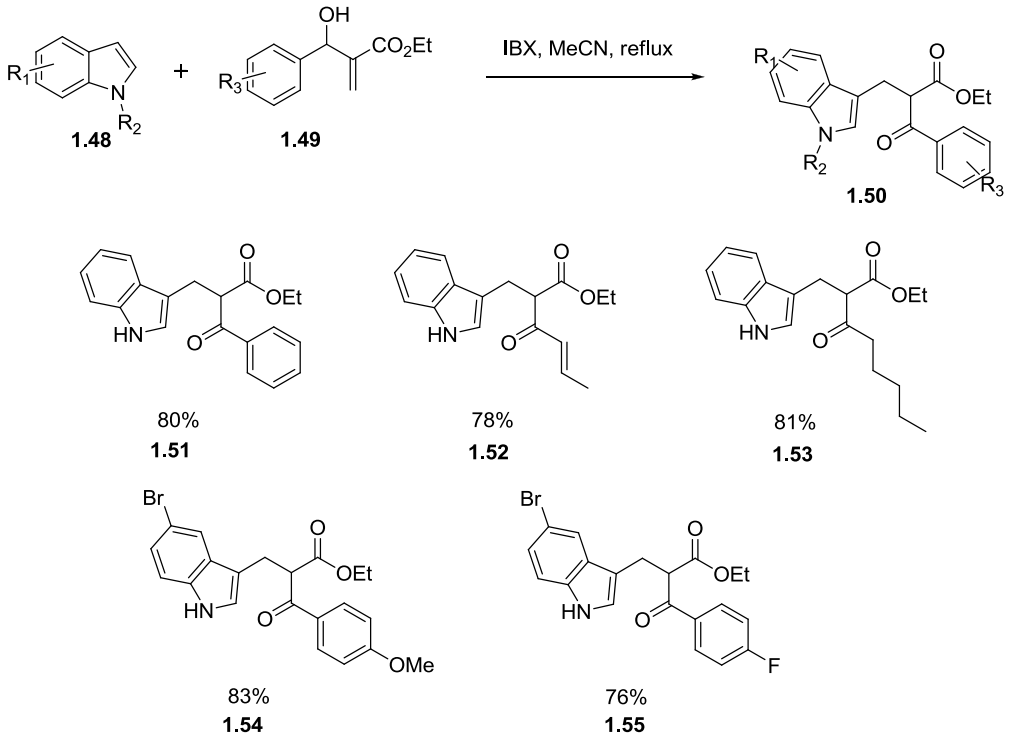


Scheme 1.9



In 2007, 2-iodoxybenzoic acid (IBX) was used to catalyze a one-pot oxidative Michael reaction of Baylis-Hillman adducts with indoles to provide α-keto propionates in good yields (70-80%) (Scheme 1.10).[36] The reaction was applied to a variety of Baylis-Hilman adducts with both electron rich and electron poor indoles, but the scope seems rather limited to forming α-keto, β-unsubstituted indole propionates.

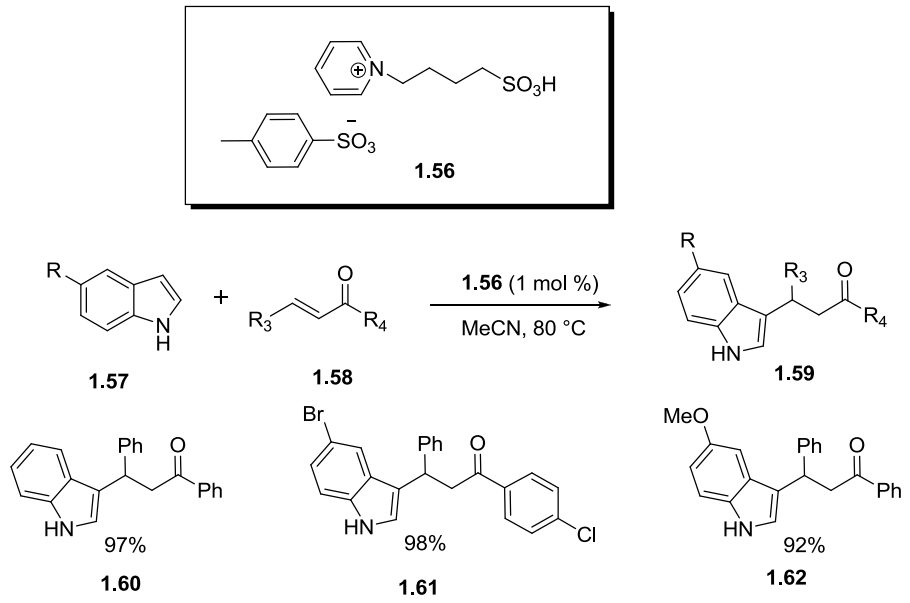
Scheme 1.10



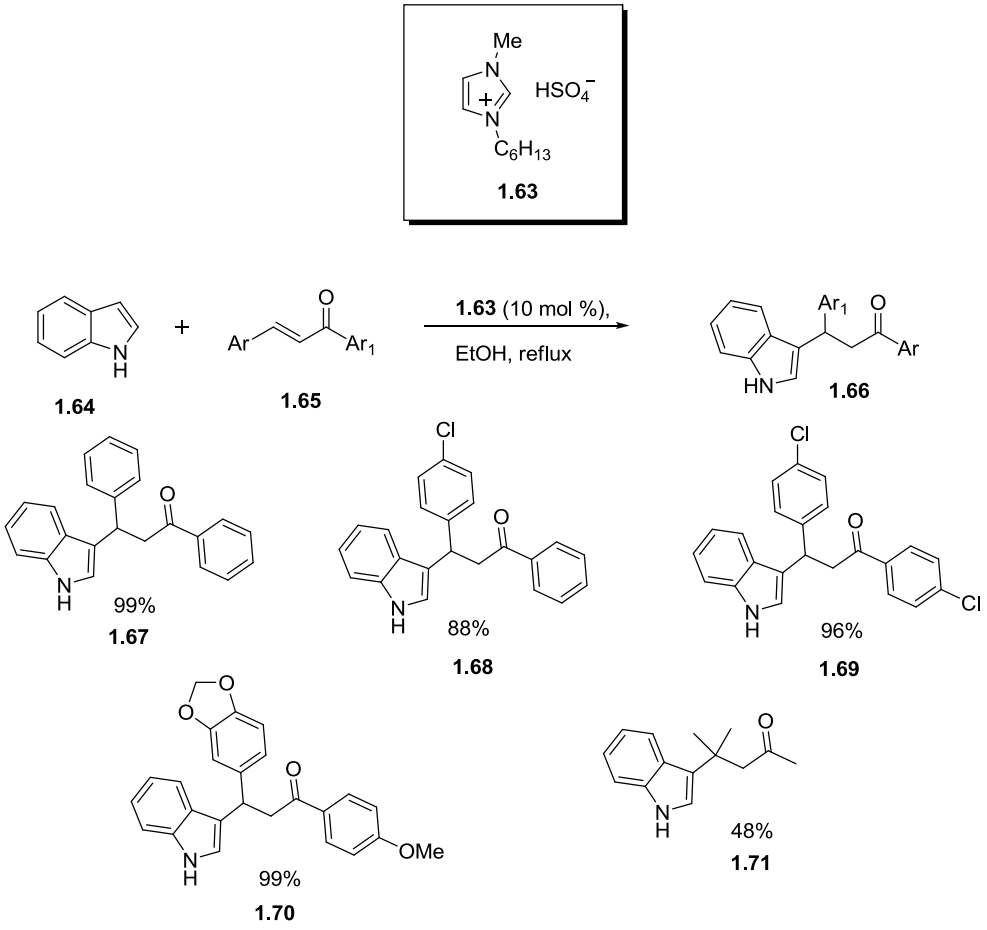
A variety of acidic ionic liquids have also been shown to promote heterocyclic conjugate additions (Schemes 1.11 and 1.12). For example, the pyridyl ionic liquid **1.56** can be used in a very low catalyst loading (1 mol %) to promote the addition of electron-rich and electron-poor indoles to chalcones in very high yields (> 90%), though the scope of the electrophile was limited to chalcones.[37] Imidazolium salt **1.63** also promotes conjugate additions of indoles to chalcones in excellent yields (>88%).[38] However, the most interesting example using catalyst **1.63** involved the addition of indole to a β,β-disubstituted unsaturated ketone to provide the β,β-disubstituted propionate **1.71** in 48%

yield. While both of these catalysts show promise, their efficacy in Michael additions with indole seem limited to chalcones as the acceptor.

Scheme 1.11



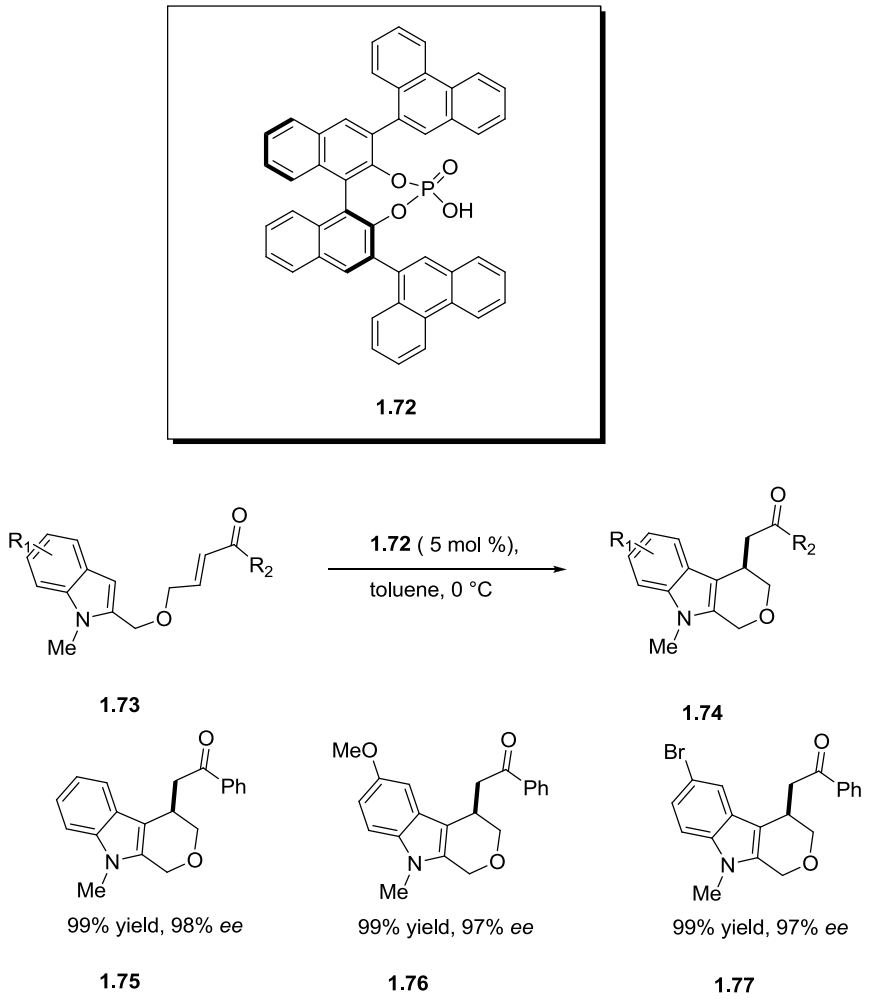
Scheme 1.12



A few examples of chiral Bronsted catalysis of heterocyclic conjugate additions to α,β-unsaturated ketones are also known (Schemes 1.13 and 1.14).[28,39] Two examples shown below both utilize a chiral phosphoric acid scaffold to enable the Michael reactions. In the first example, catalyst **1.72** (5 mol %) was used to promote the intramolecular Michael addition of indoles to α,β-unsaturated ketones attached at the 2-position of the indole (Scheme 1.13).[39] The reaction produced the bicyclic adducts in

excellent yield and enantioselectivity regardless of the electronic nature of any other substituents present on the indole. However, the reactions were very narrow in scope, and it is unclear whether or not this enantiocontrol can be expanded to intermolecular reactions.

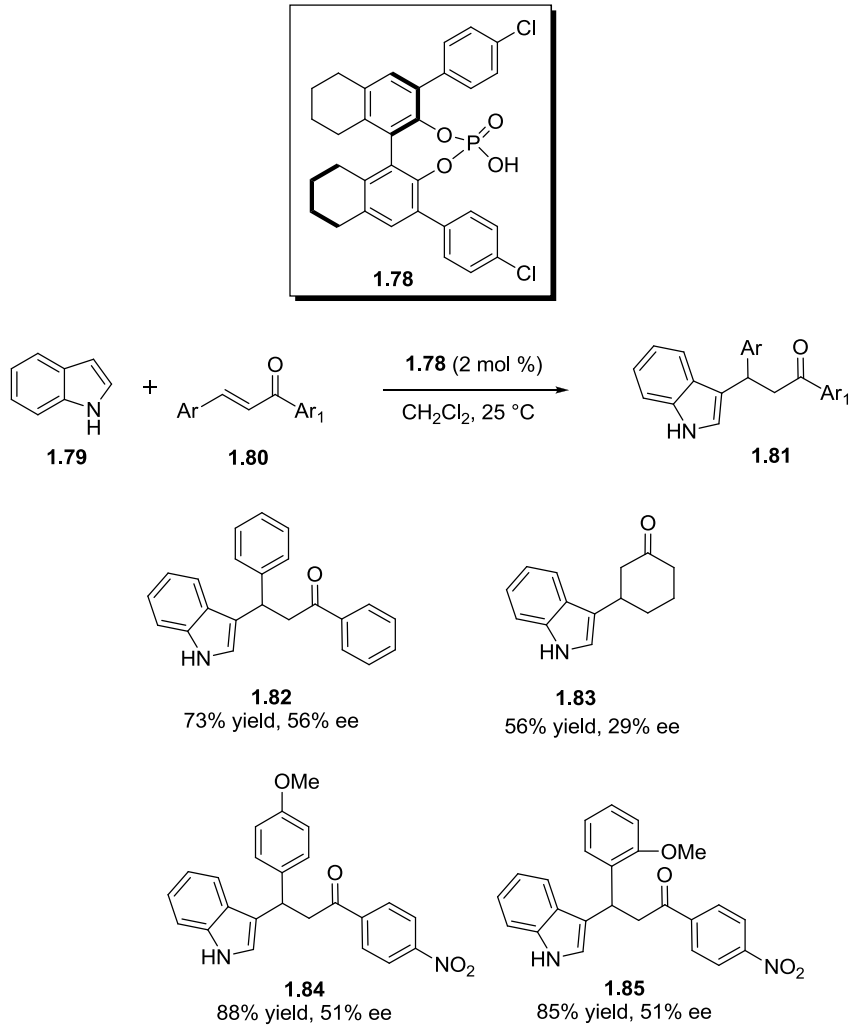
Scheme 1.13



The second example of using a chiral phosphoric acid catalyst **1.78** to promote the addition of indole to α,β-unsaturated ketones is shown in Scheme 1.14.[28] While the

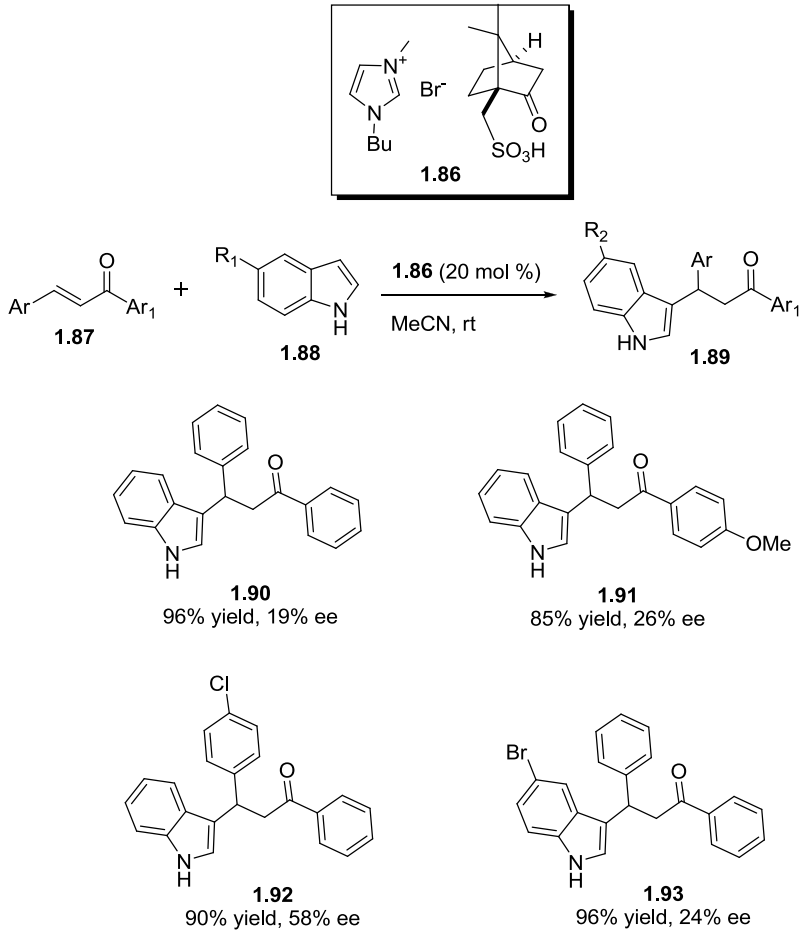
catalyst loading was low (2 mol %) and the conditions were mild, the reactions between indole and the electrophiles were moderate yielding with poor enantioselectivity. Chalcone electrophiles gave the best results with *ee*'s of 50%, while cyclic ketones gave the worst results (29% *ee*). As poor as these results are, they established important proof of principle that intermolecular Michael additions of indoles to α,β-unsaturated electrophiles can be facilitated by chiral phosphoric acid catalysts.

Scheme 1.14



Another example of a chiral Bronsted catalyst is shown in Scheme 1.15. The imidazolium camphorsulfonic acid complex **1.86** was used to promote the addition of various indoles to chalcones in high yield (>85%), but very poor enantioselectivity (19-58%).[18] Although the enantioselectivies were poor and the substrate scope was narrow, this catalyst provided another example of the possibility of achieving α,β-heterocyclic propionates *via* Bronsted acid catalysis.

Scheme 1.15

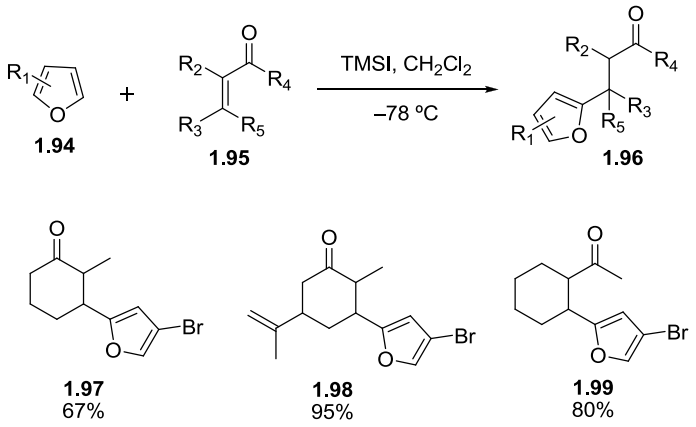


1.3.2 Conjugate Additions of Electron Rich Heteroaromatic Rings with π-Acceptors Catalyzed by Lewis Acids

Like the Bronsted acid-catalyzed conjugate additions, there are many examples of Lewis acid-catalyzed Michael reactions between heterocycles and π-acceptors. Highlights of some of the more useful and versatile processes will be discussed.

Some of the earliest examples of Lewis acid-catalyzed heterocyclic, Michael reactions include the use of iodotrimethylsilane (TMSI) and boron trifluoride etherate ($BF_3 \cdot OEt_2$). In 1983, Kraus and coworkers showed that a variety of furans add to hindered cyclic enones in moderate to good yields (67-95%) in the presence of stoichiometric amounts of TMSI (Scheme 1.16).[40] The scope of the reaction is fairly limited, both with regard to nucleophile and electrophile, but it is important to note that significant amounts of mono-alkylated product were produced as the major product of the reactions. In many of the previous examples, polyalkylation plagued the use of furans in acid catalyzed conjugate additions.

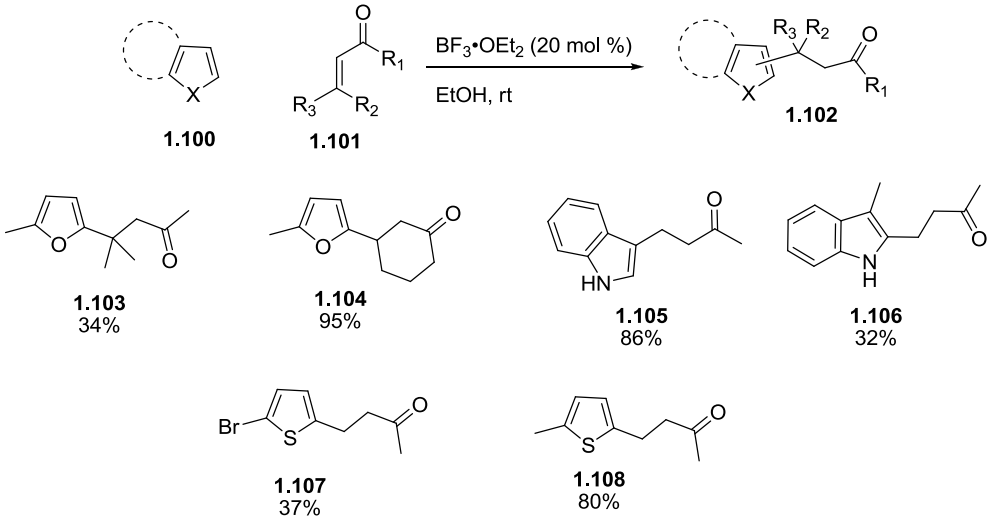
Scheme 1.16



Another early example utilized catalytic amounts of boron trifluoride etherate ($BF_3 \cdot OEt_2$) to promote the reaction between indoles, furans, and thiophenes with enones

(Scheme 1.17).[41] The reaction yields varied wildly (32-95%) with heterocycles containing electron donating groups and electrophiles possessing minimal, if any, substitution providing the highest yields. Some of the most interesting products include furan **1.103**, which bears β,β-disubstitution, and indole **1.106**, which reacted at the 2-position of the indole, albeit in low yield. α,β-Unsaturated esters were not examined in the reactions, and the low yields indicated a lot of room for improvement.

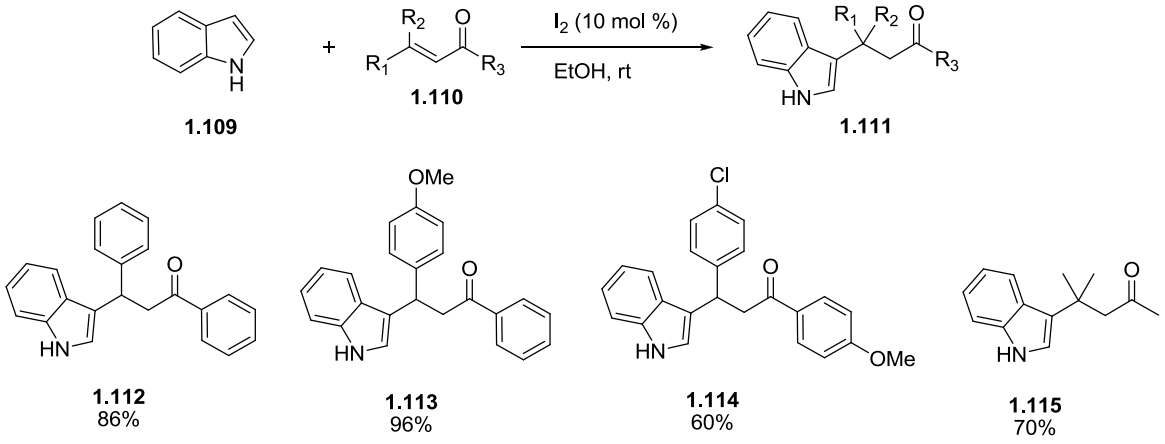
Scheme 1.17



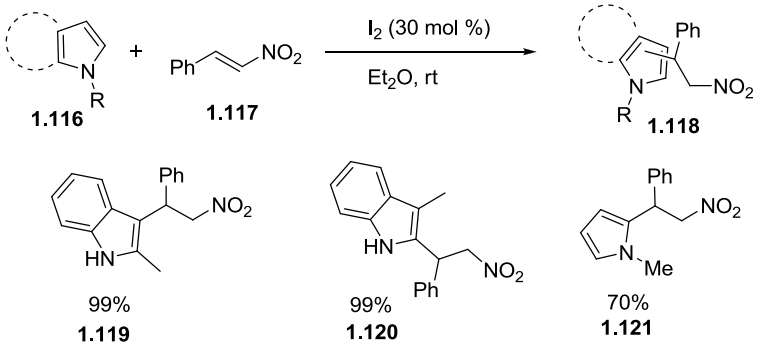
One of the cheapest and easiest Lewis catalysts employed in heterocyclic Michael reactions is elemental iodine (I_2). Bench stable, cheap, and easy to handle, iodine is an attractive option for catalysis. Iodine promotes the reactions between indoles and chalcones (Scheme 1.18),[42] α,β-unsaturated ketones (Scheme 1.18),[42] nitroolefins (Scheme 1.19),[15] and Baylis-Hilman products (Scheme 1.20).[43] In all instances, the reactions proceeded under mild conditions to produce the addition products in moderate to high yield (60-90%). Some of the best examples include adduct **1.115**, which contains

β,β-disubstitution and was obtained in relatively good yield (70%), and 3-substituted indole **1.120**, which was obtained in excellent yield (99%) when reacted with nitroalkene **1.117** at the 2-position. Pyrrole was also effectively used as a nucleophile with β-nitrostyrene (**1.117**), producing **1.121** in 70% yield. While the results of these studies are are impressive, the scope of the electrophile remain narrow. None of these reactions produced α,β-heteroaryl propionates in a single step, nor do they include α-substitution on the propionate.

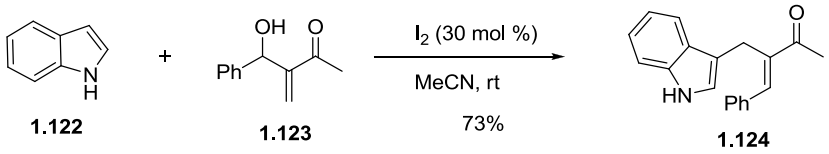
Scheme 1.18



Scheme 1.19



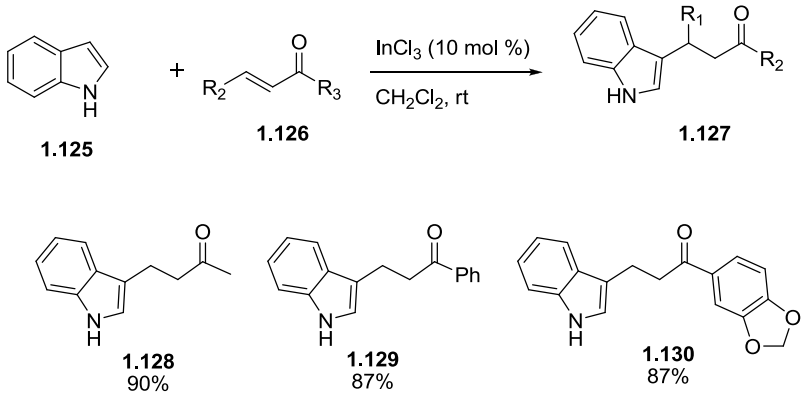
Scheme 1.20



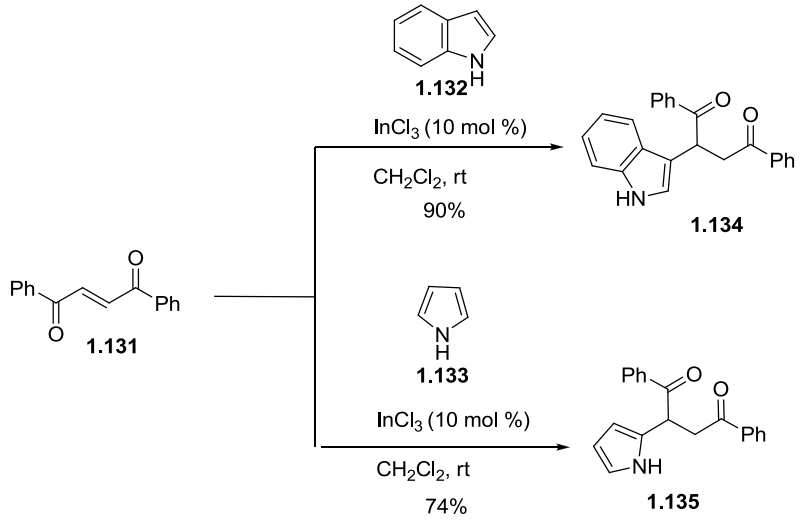
1.3.2.1 METAL HALIDES

Metal halides are another class of Lewis acidic catalysts that are frequently used in Michael reactions between heterocycles and π-acceptors. In 2001, Yadav and coworkers found that $InCl_3$ efficiently promoted the reaction between indoles and a variety of α,β-unsaturated ketones in good yield (>85%) (Scheme 1.21).[11] The conditions were mild and featured short reaction times as well as low catalyst loading (10 mol %). However, no α,β-unsaturated esters were examined, nor were any α- and/or β-substituents present on the ketones. In 2009, Blay *et al.* expanded the scope of the nucleophile to include pyrrole, and he expanded the scope of the electrophile to include (E)-1,4-diaryl-2-buten-1,4-diones **1.131** (Scheme 1.22).[44]

Scheme 1.21

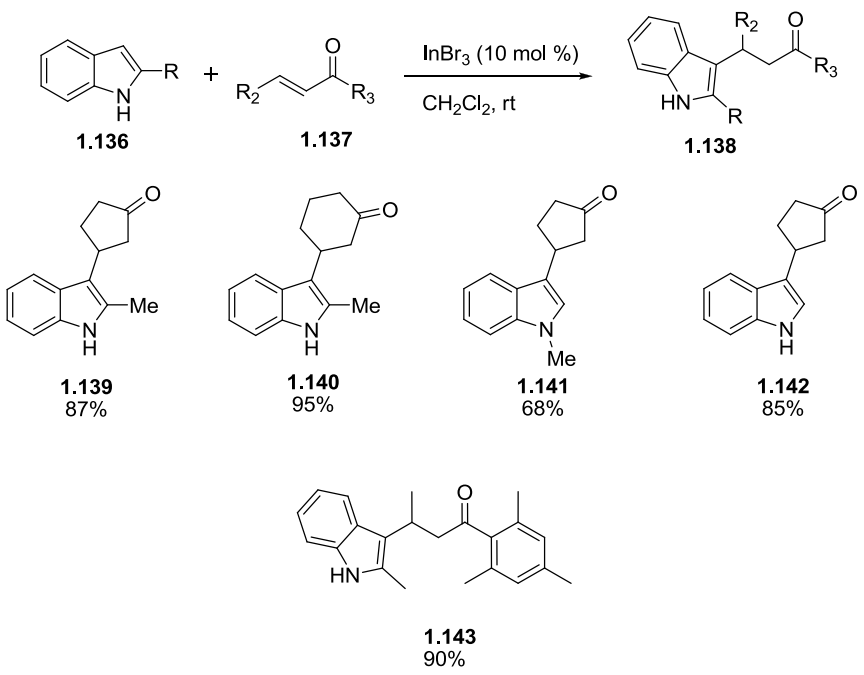


Scheme 1.22



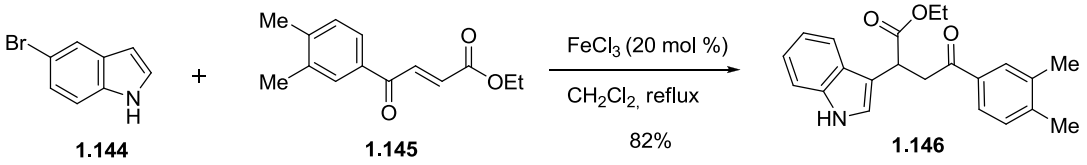
Bandini and coworkers showed that $InBr_3$ exhibited similar reactivity towards promoting heterocyclic Michael additions as did $InCl_3$ (Scheme 1.23). A variety of indoles were allowed to react with cyclic α,β-unsaturated ketones in good yields (68-95%), with N-H and N-Me indoles exhibiting similar results.[12] Bandini reported an example of a hindered 2-substituted indole reacting with a hindered α-substituted enone to provide indole **1.143** in an impressive 90% yield. However, no examples with unsaturated esters were presented, so extra steps must be implemented to reach α,β-heterocyclic propionates.

Scheme 1.23

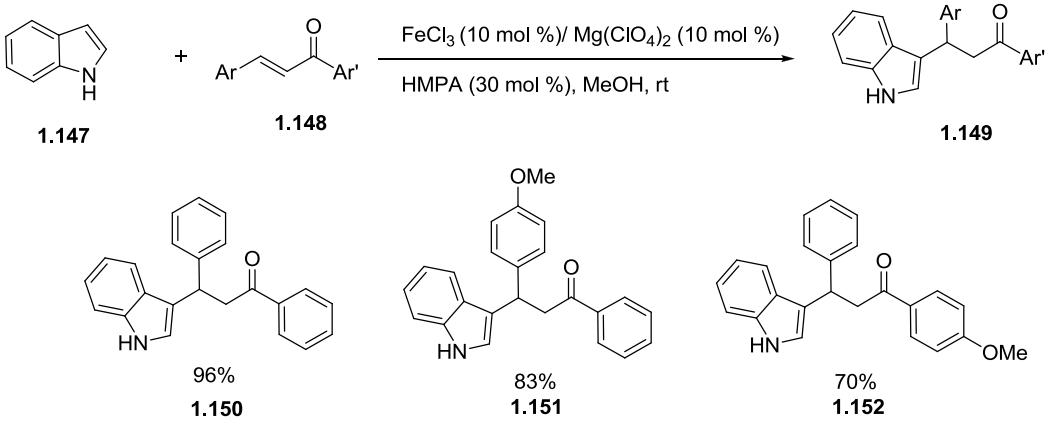


Some other common halide salts that have been successfully employed in heterocyclic conjugate additions include $FeCl_3$, $ZnCl_2$, $ZrCl_4$ and $TiCl_4$. In 2008, Wang and coworkers used $FeCl_3$ (20 mol %) to promote the addition of various indoles to 4-aryl-4-oxobut-2-enoates (**1.145**) in good yields (73-92%) (Scheme 1.24).[45] Both electron rich and electron poor groups were tolerated on the nucleophile and electrophile to give the corresponding α-substituted indoles. Zhou and coworkers also used $FeCl_3$ in conjunction with $Mg(ClO_4)_2$ and HMPA to induce the reaction of indoles with chalcones in modest yields (Scheme 1.25).[46]

Scheme 1.24

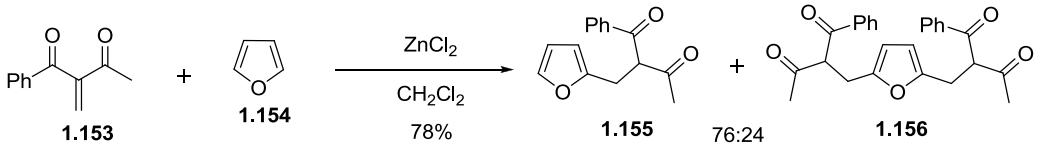


Scheme 1.25



Yamauchi showed that when furan (**1.154**) was treated with 1-acetyl-1-benzoylethylene (**1.153**) in the presence of stoichiometric $ZnCl_2$, Michael adducts were formed in good yield (Scheme 1.18).[47] Unfortunately, polyalkylation was a major side product of the reaction, thereby limiting its utility. In fact, when the reaction time was increased the dialkylated adduct **1.156** became the sole product.

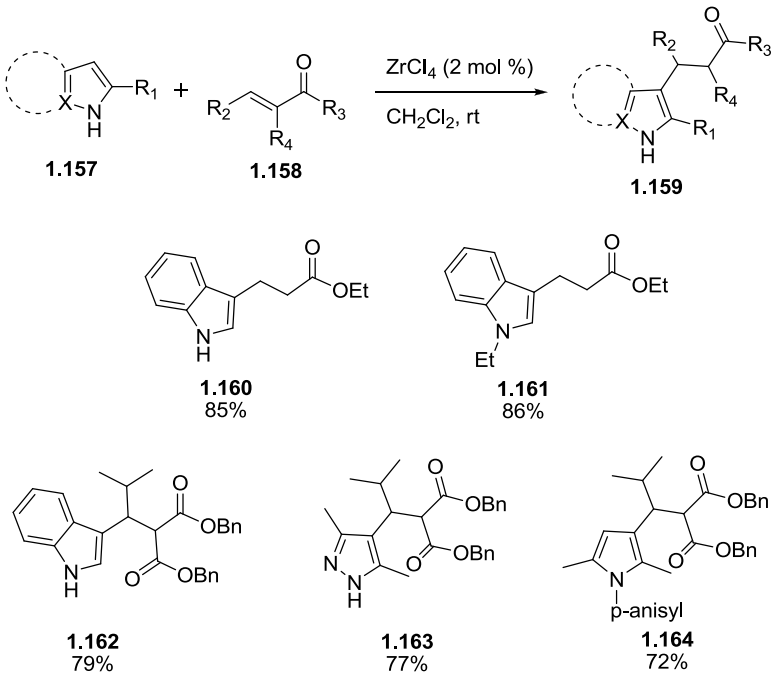
Scheme 1.26



Zirconium (IV) chloride ($ZrCl_4$) was also used as a catalyst for heterocyclic conjugate additions. In 2006, Kumar and coworkers accessed a variety of β-heteroaryl

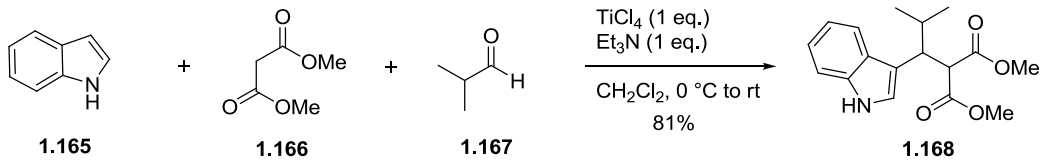
propionates by using α,β-unsaturated esters and α,β-unsaturated malonates in Michael additions with indole, pyrrole, and pyrazole. Some of their best results are shown in Scheme 1.27. All heterocycles produced β-heteroaryl propionates in good yields (72-86% yield), under mild conditions and low catalyst loading (2 mol %).[30] The method also worked well with various cyclic and acyclic α,β-unsaturated ketones as the electrophiles, often with better yields than the aforementioned esters and malonates, but those adducts did not provide direct access to β-heteroaryl propionates. The only ester examined was ethyl acrylate, which provided the desired propionates in moderate yields (85-86%). The malonate alkylidene **1.158** (where R_3 = OBn and R_4 = CO_2Bn) reacted with the heterocycles in good yield, even tolerating the bulky isopropyl group at the β-position of the propionate, as illustrated by formation of **1.162-1.164**. However, unless an ester was desired at the α-position, saponification and decarboxylation would be required to obtain a β-substituted heteroaryl propionate. The only major drawback to this method is the lack of scope of α,β-substituted esters.

Scheme 1.27



The alkylidene malonate electrophile **1.158** (where R_3 = OBn and R_4 = CO_2Bn) (Scheme 1.27) can also be generated in the presence of a heterocyclic nucleophile, such as indole (**1.165**) to provide the same α,β-substituted heteroaryl propionates (Scheme 1.28). This one pot procedure may save a step by *in situ* generation of the electrophile, but it requires the use of stoichiometric $TiCl_4$ as opposed to 2 mol of $ZrCl_4$.[48]

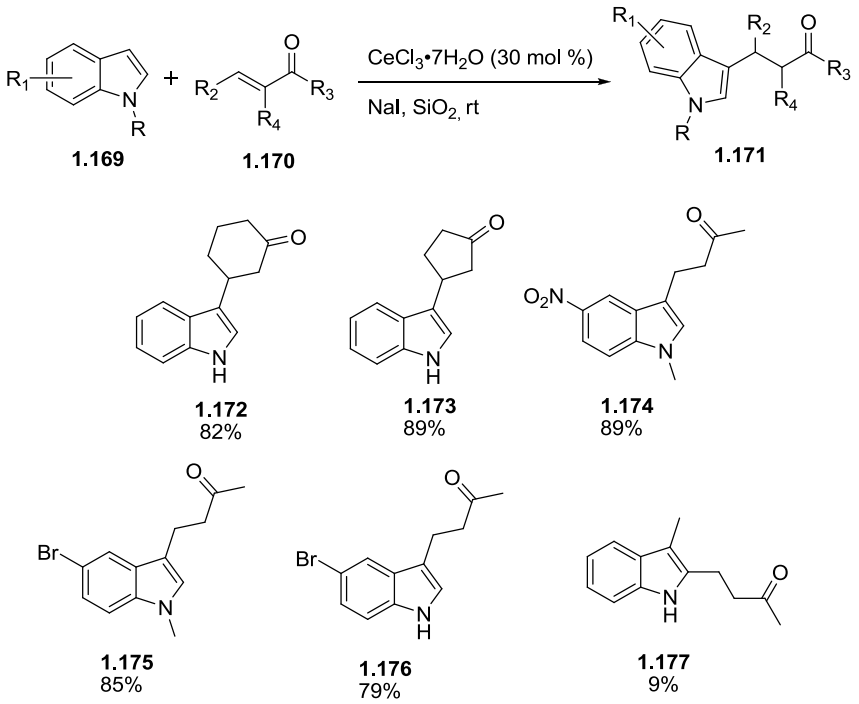
Scheme 1.28



In addition to the more common metal halides discussed previously, more exotic and expensive metal halides have been investigated in the context of heterocyclic

conjugate additions. For example, in 2003 Bartoli used a solid supported cerium (III) chloride hydrate in conjunction with NaI to promote the reaction of various indoles to cyclic and acyclic enones in good yields (79-89%) (Scheme 1.29).[13] Electron rich and electron poor indoles were equally effective in the reaction, but when a 3-substituted indole was subjected to the reaction conditions, the desired adduct was formed in only 9% yield. No α,β-unsaturated esters were investigated.

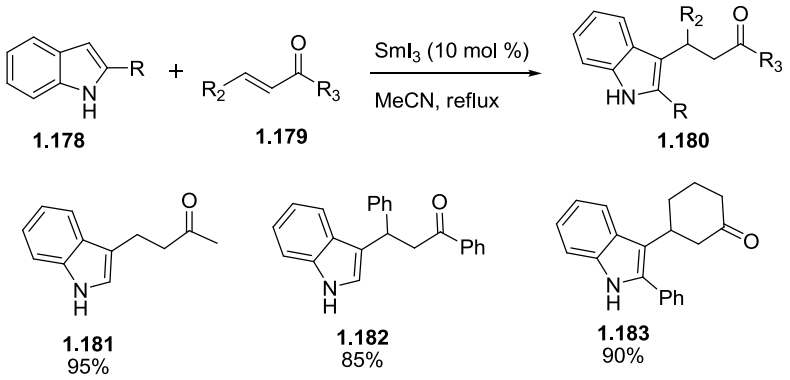
Scheme 1.29



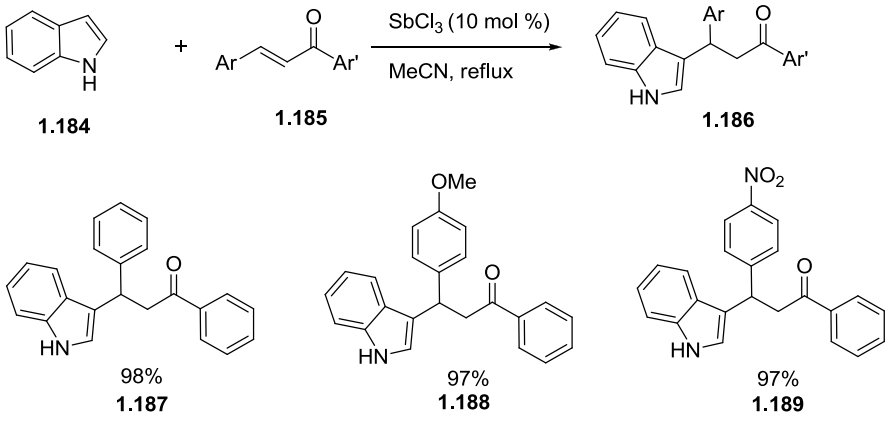
In 2005, Zhan and coworkers showed that SmI_3 (20 mol %) promoted Michael additions of indoles to various cyclic and acyclic enones, as well as nitroolefins in good yields (>85%) (Scheme 1.30).[49] While the reactions proceeded in high yields (85-95%), no α,β-esters were examined, and SmI_3 is an expensive choice for a Lewis acid, especially when the reaction conditions require a somewhat high catalyst loading of 20

mol %. A couple of years later Kundu *et al.* used antimony (III) chloride to affect the reaction between indoles and chalcones in excellent yields (Scheme 1.31).[50] The reaction worked equally as well on electron-rich and electron-poor electrophiles, but again, the scope of the reaction was limited to chalcones, and the cost of $SbCl_3$ makes it an unattractive choice for a catalyst.

Scheme 1.30



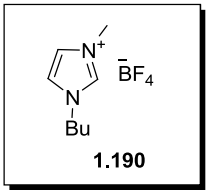
Scheme 1.31



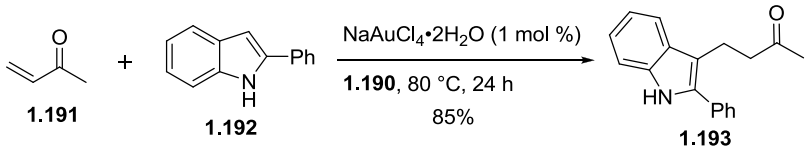
Gold (III) catalysts have also been widely explored in the context of promoting Michael reactions of heterocyclic nucleophiles. In 2007, Ambrogio and coworkers

reported the use of tetrachloroaurate (III) dehydrate ($NaAuCl_4 \cdot 2H_2O$) to promote conjugate additions between indoles and methyl vinyl ketone (Scheme 1.32).[51] Although the catalyst loading was low (1 mol %) and the use of ionic salt **1.190** as a solvent rendered the reaction environmentally friendly, the reaction conditions called for prolonged stirring at elevated temperatures. The scope of the electrophile was also limited to methyl vinyl ketone. Arcadi and coworkers expanded the scope of the reaction to include conjugate additions between indoles and a variety α,β-enones (Scheme 1.33).[52] Though the catalyst loading was slightly higher (5 mol %) than used by Ambrogio, the reactions could be run at ambient temperatures for shorter periods of time. The Michael additions worked well with both cyclic and acyclic enones (83-92%), and many had β-substituents present on the enone. Even 3-substituted indoles worked surprisingly well in the reaction, but the larger the substituent on the 3-position the lower the yield of the conjugate addition. Arcadi also successfully employed nitroolefins as the electrophiles in the Michael reactions of heterocycles, expanding the scope of the catalyst even further. The scope of the reaction was further extended to include pyrroles as nucleophiles (Scheme 1.34).[53] Various pyrroles were reacted with methyl vinyl ketone to provide mainly dialkylated product, unless there was already a substituent present at the 2-position of the pyrrole. The yields were also considerably lower than those of the indole examples. While $NaAuCl_4 \cdot 2H_2O$ shows promise as a catalyst for these Michael reactions, the scope of the reactions are not sufficient to overcome the cost of the catalyst, especially when it has been shown that other, less expensive catalysts produce similar or even better results.

Scheme 1.32

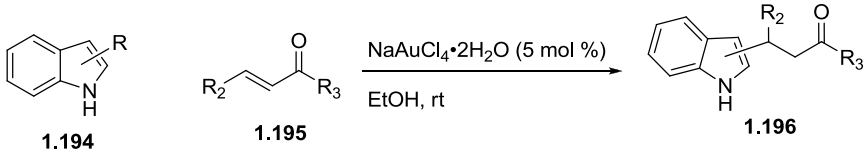


1.190

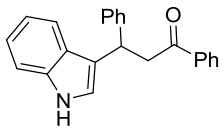


1.191 **1.192** **1.193**

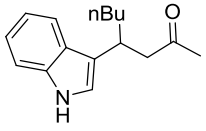
Scheme 1.33



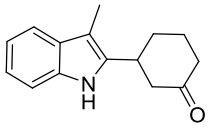
1.194 **1.195** **1.196**



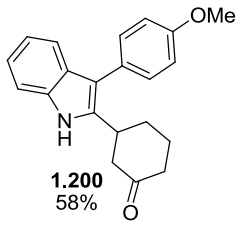
1.197
88%



1.198
83%

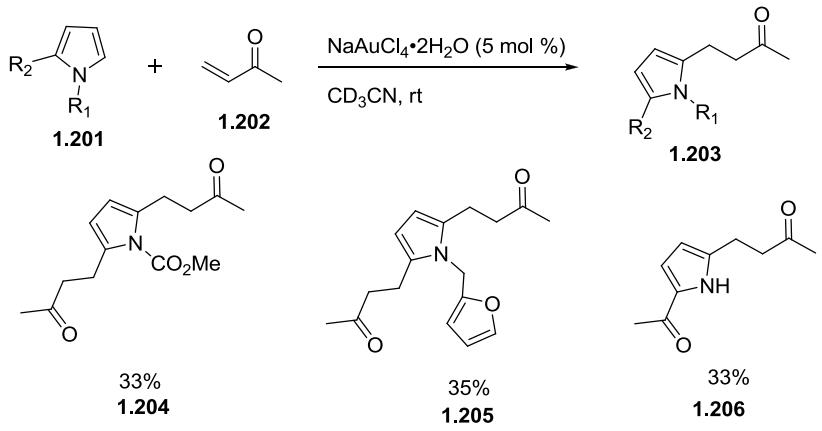


1.199
75%



1.200
58%

Scheme 1.34



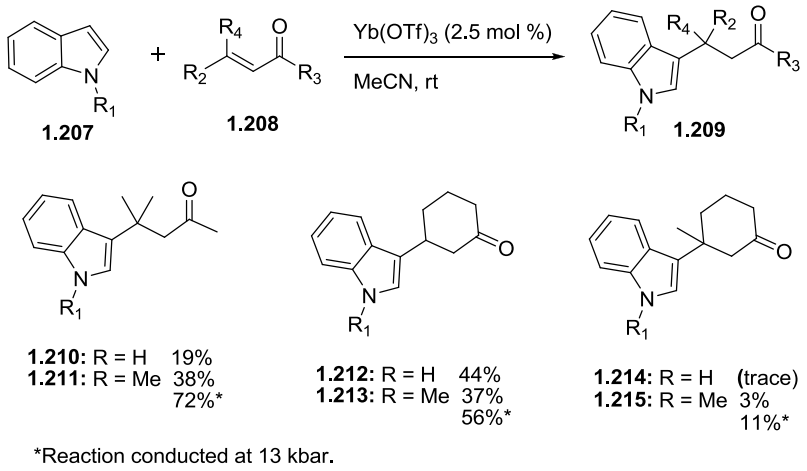
1.3.2.2 METAL TRIFLATES

In addition to metal halides, metal triflates also promote the conjugate additions between heterocycles and various π-acceptors. First the achiral catalysts will be presented, followed by examples of enantioselective heterocyclic Michael additions.

In 1996, Harrington and Kerr demonstrated the use of ytterbium (III) triflate in conjugate reactions between indole and α,β-unsaturated enones (Scheme 1.35).[54] In general, the reactions involving unsubstituted or mono-substituted enones proceeded in moderate to excellent yields (73-95%), whereas the reactions involving bulky or di-substituted electrophiles proceeded in poor to modest yields (3-44%). *N*-Methyl indole appeared to work better than indole itself as a nucleophile. In 1998, Harrington and Kerr improved their method by subjecting the reactions involving the bulkiest enones to increased pressure to facilitate addition (Scheme 1.35).[10] While the increased pressure did improve yields (11-72%), the yields of β- or β,β- substituted indoles were still relatively low. Examples involving a nitroolefin and a malonate were also shown to be compatible with the catalyst, although no reactions involving α,β-unsaturated esters were performed. The

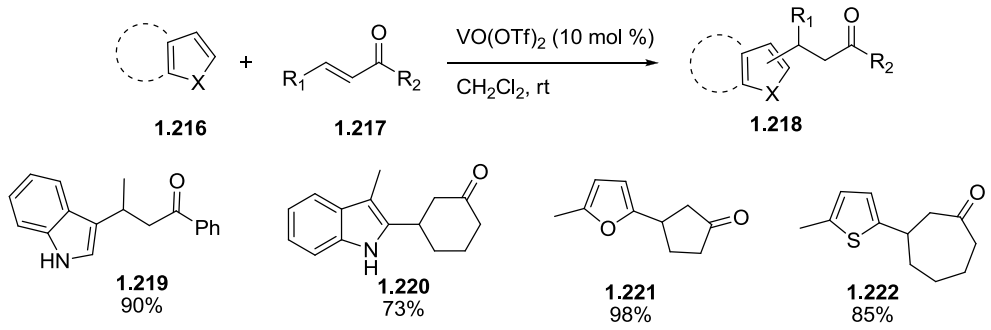
scope of this reaction seems limited to fairly unsubstituted ketones, which will not provide a satisfactory general method to access α,β-heteroaryl propionates.

Scheme 1.35



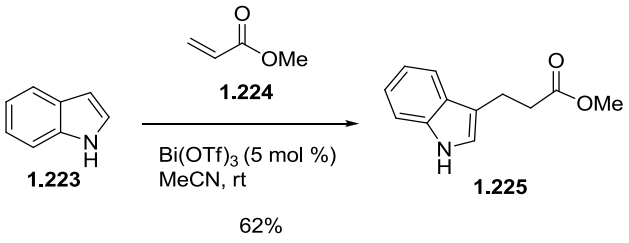
Vanadyl triflate ($VO(OTf)_2$) has also been shown to catalyze the conjugate addition between indoles and α,β-unsaturated ketones in comparable (or better) yields to those obtained using $Yb(OTf)_3$ (Scheme 1.36).[55] In addition, the scope of the heterocyclic nucleophile was expanded to encompass furan and thiophene, which both reacted with cyclic enones in good to excellent yields (85-98%). The vanadyl triflate conditions also tolerated β-substituents on the electrophiles to provide the corresponding adducts **1.218** in good yields (ca. 90%). However, no α,β-unsaturated esters were examined, so the scope of this promising reaction may also be limited.

Scheme 1.36



In 2003, Alam reported that bismuth (III) triflate was an efficient catalyst to promote the addition of indole (**1.223**) to methyl acrylate (**1.224**) (Scheme 1.37).[56] While the yield was modest (62%) and there was no substitution present on the electrophile, this example is one of the only ones to show that α,β-unsaturated esters can be used in Lewis acid-catalyzed Michael reactions with heterocycles.

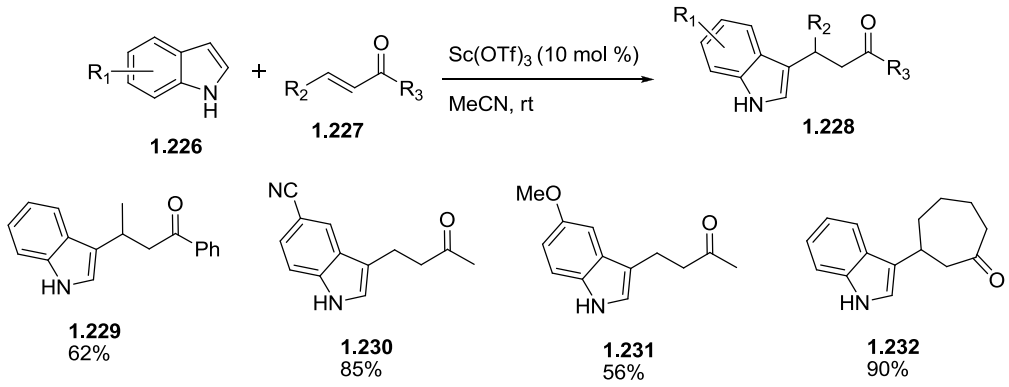
Scheme 1.37



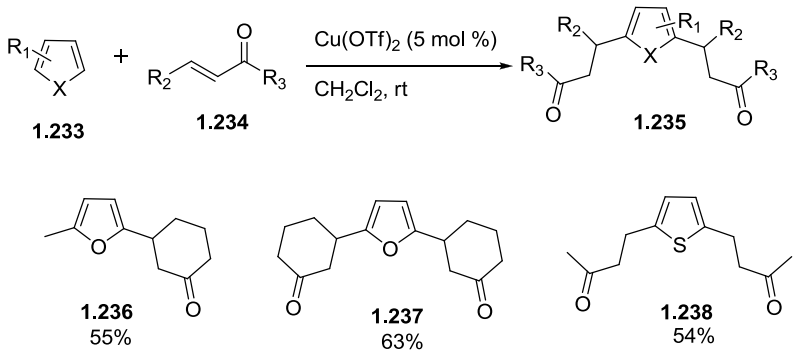
Scandium (III) triflate ($Sc(OTf)_3$) and copper (II) triflate ($Cu(OTf)_2$) are two more triflates that effectively catalyze the addition of heterocycles to α,β-unsaturated ketones (Schemes 1.38 and 1.39). $Sc(OTf)_3$ was used by Kawatsura to induce the reaction of electron rich and electron poor indoles to cyclic and acyclic enones (Scheme 1.38).[57] The reactions proceed in moderate to good yields (62-90%) and tolerated β-methyl substituents on the electrophile, but no α,β-esters were examined. Bulbule showed that

$Cu(OTf)_2$ promotes the reaction of furan and thiophene derivatives to cyclic and acyclic α,β-unsaturated ketones in moderate yields (55-63%) (Scheme 1.39).[58] However, dialkylation was a major problem unless the 2-position of furan or thiophene was already substituted. While the scope of the $Sc(OTf)_3$ -$Cu(OTf)_2$ promoted reactions are limited, they are particularly important Lewis acids to consider because they were eventually developed into chiral catalysts for the enablement of heterocyclic Michael additions.

Scheme 1.38



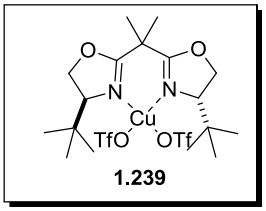
Scheme 1.39



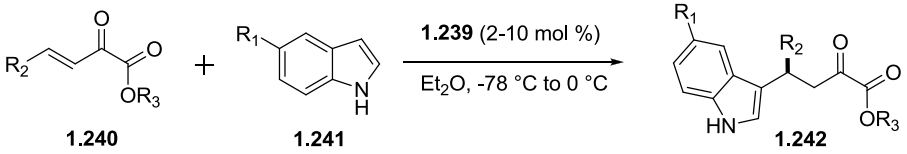
1.3.2.3 CHIRAL LEWIS ACIDS

Jørgensen and coworkers were the first to develop an enantioselective Lewis acid-catalyzed heterocyclic Michael reaction in 2001 (Schemes 1.40 and 1.41).[59] Using the copper bisoxazoline catalyst **1.239**, they showed that indoles and 2-substituted furans reacted with β,γ-unsaturated α-ketoesters **1.240** in good yields (69-99%) and good to excellent enantioselectivities (79-99.5%). Electron rich indoles generally performed better then electron poor indoles and the enantioselectivities of reactions involving indole were significantly higher than those of furan, though both the reactions were high yielding. While this work is impressive, it is unclear how the products might be elavorated to α,β-heterocyclic propionates. Due to the bidentate nature of the catalyst, the electrophilic partner of the conjugate addition must have at least two Lewis basic sites, so α,β-unsaturated esters would be unsuitable partners in the reaction. Another potential pitfall associated with this method is that dialkylation of heterocycles other than indole may be a problem that would substantially limit the scope of the method. All examples involving furans were performed with 2-substituted furans, thereby obviating the possibility of dialkylation.

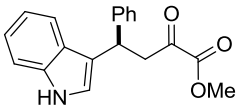
Scheme 1.40



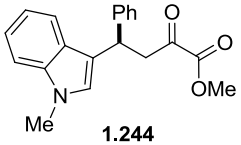
1.239



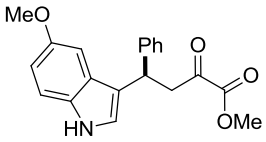
1.240 **1.241** **1.242**



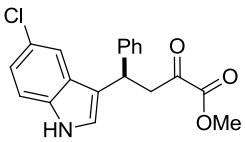
1.243
77%, 99.5% ee



1.244
98%, 96% ee

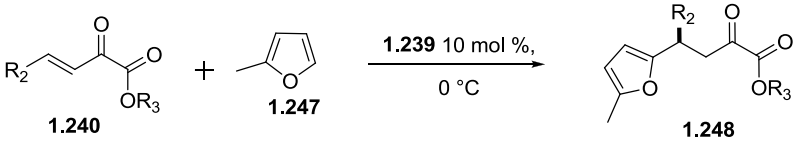


1.245
95%, > 99.5% ee

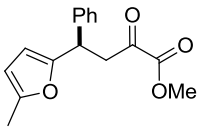


1.246
69%, 97% ee

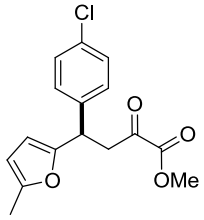
Scheme 1.41



1.240 **1.247** **1.248**



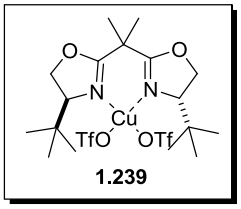
1.249
99%, 88% ee



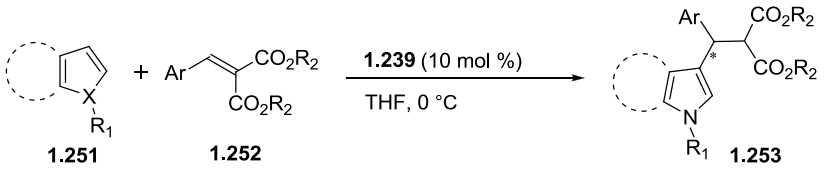
1.250
90%, 79% ee

A few months after their seminal publication, Jørgensen and coworkers published a second paper in which they utilized the same copper catalyst **1.239** in conjugate additions between indole, pyrrole, or furan and aryl substituted alkylidene malonates **1.253** (Scheme 1.42).[60] The yields of the reactions were comparable to those observed previously, but the enantionselectivities from the reactions involving alkylidene malonate as electrophiles were significantly lower. Many of the same limitations from the previous examples apply to the malonate reactions, although the products of these reactions are α,β-substituted heteroaryl propionates, albeit very specific ones. A few years later, Reiser *et al.* used the aza(bisoxazoline) copper catalyst **1.260** at only 5 mol% to promote the reaction between indole and phenyl alkylidene malonate **1.262** in 97% yield and 99% ee; this represents a significant improvement over the initial work of Jørgensen (Scheme 1.43).[61]

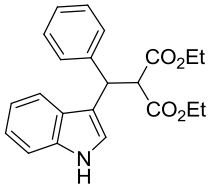
Scheme 1.42



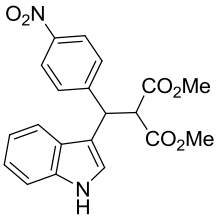
1.239



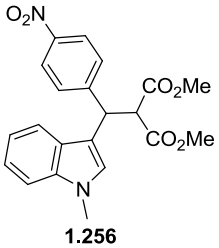
1.251 **1.252** **1.253**



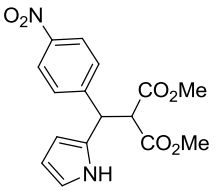
1.254
73% yield, 60% ee



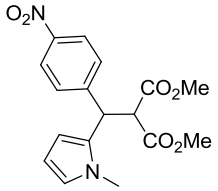
1.255
92% yield, 56% ee



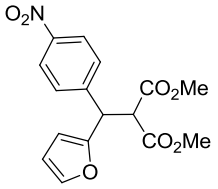
1.256
99% yield, 48% ee



1.257
99% yield, 28% ee

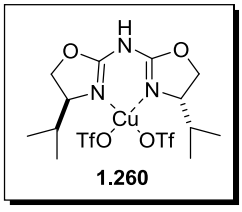


1.258
99% yield, 36% ee

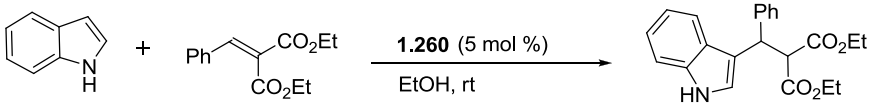


1.259
99% yield, 12% ee

Scheme 1.43



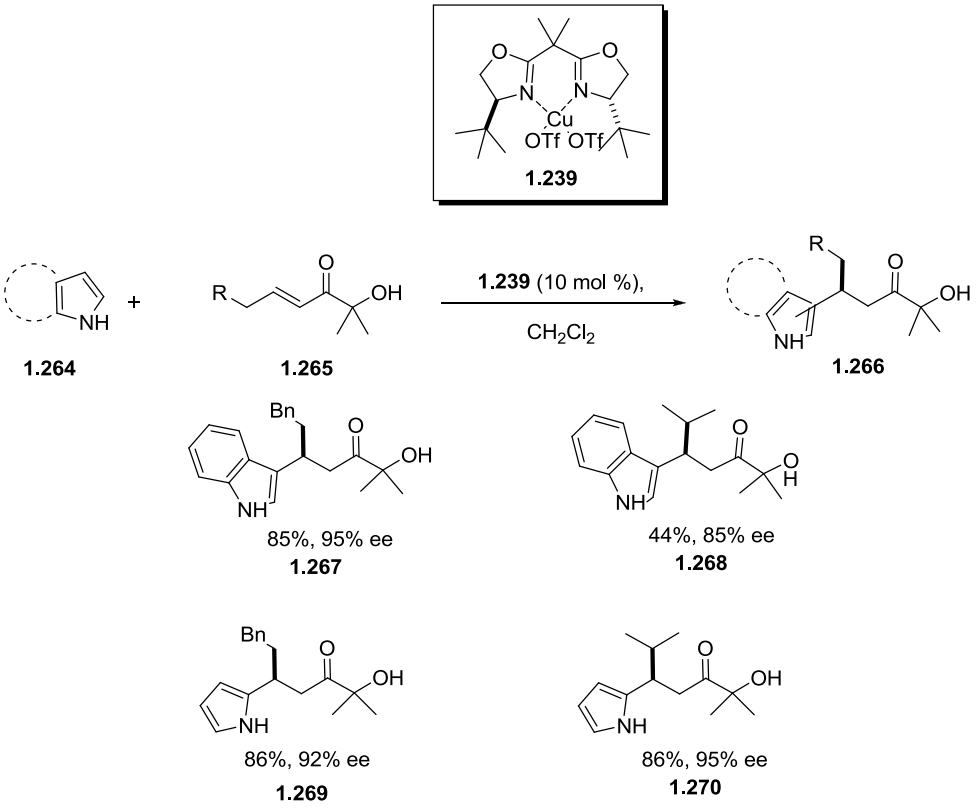
1.260



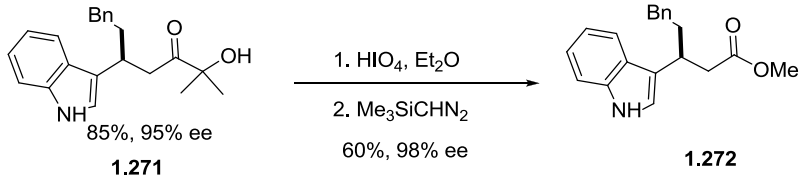
1.261 **1.262** 97%, 99% *ee* **1.263**

In 2005, Linden and coworkers further expanded on the scope of catalyst **1.239** by incorporating α'-hydroxy enones as electrophiles into Michael reactions with indole and pyrrole nucleophiles (Scheme 1.44).[62] The yields of the reactions were moderate to good (44-86%), but the enantioselectivities were high (85-95%). The reaction also tolerated bulky groups, such as isopropyl. Owing, however, to the bidentate nature of the copper catalyst, α,β-heteroaryl propionates cannot be directly accessed using this catalyst. The authors did show that their α'-hydroxy products **1.266** could be transformed into the heteroaryl propionates by oxidative cleavage with periodic acid (HIO_4) and subsequent esterification (Scheme 1.45).

Scheme 1.44

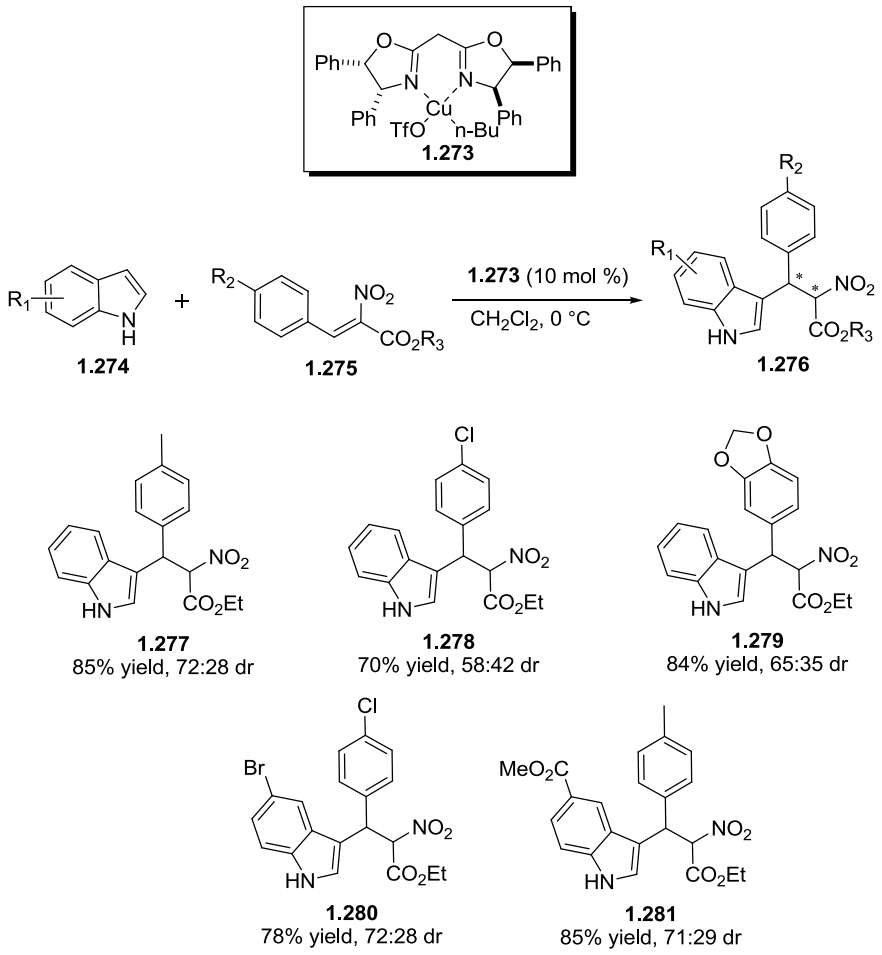


Scheme 1.45

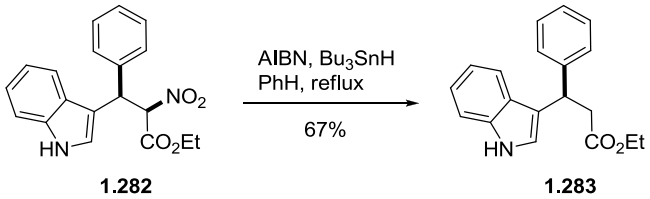


In 2007, a slightly different copper bisoxazolone catalyst **1.273** was developed by Chen and coworkers to synthesize chiral tryptophan derivatives.[20] β-Aryl substituted nitroacrylates were allowed to react with various indoles in the presence of **1.273** (10 mol %) to yield α-nitro, β-aryl substituted β-heteroaryl propionates in good yields (70-85%) and modest diastereoselectivities (Scheme 1.46). They then reduced the nitro group using zinc and acetic acid to provide the desired tryptophan analogues. The nitro group could also be reduced to provide β-aryl, β-heteroaryl propionates in moderate yield, but this method would be incompatible with halogenated heterocycles (Scheme 1.47).

Scheme 1.46



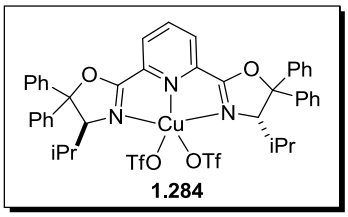
Scheme 1.47



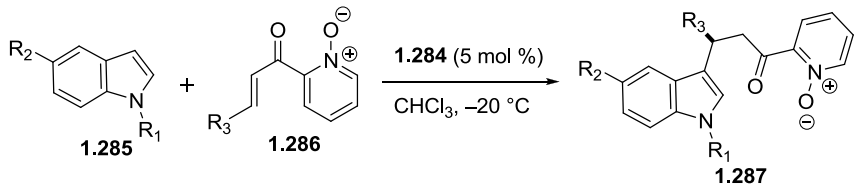
Singh and coworkers found that copper pyridyl bisoxazoline catalyst **1.284** promoted the Friedel-Crafts reaction between indoles and 2-enoylpyridine 1-oxides **1.286**

in good to excellent yields (75-97%) (Scheme 1.48).[27] When the β-substituent on the electrophile was an aryl group, the enantioselectivities of the reactions were high (83-99%), but if the aryl substituent was replaced with any other group, the enantioselectivities of the corresponding reactions plummeted **1.291** (5%). In addition to the narrow scope of the electrophile for the reactions, the further elaboration of the pyridine oxides to the desired β-aryl, β-heteroaryl propionates required rather harsh and forcing conditions (Scheme 1.49).

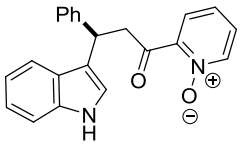
Scheme 1.48



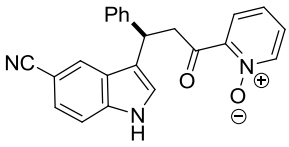
1.284



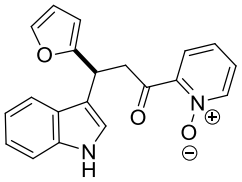
1.285 **1.286** **1.287**



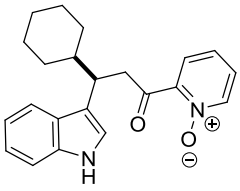
1.288
97%, 99% ee



1.289
86%, 83% ee

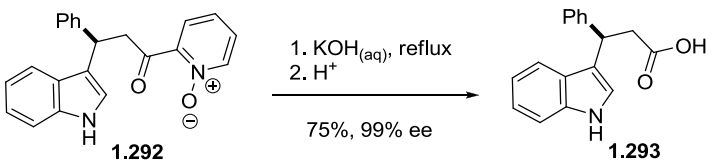


1.290
97%, 87% ee



1.291
75%, 5% ee

Scheme 1.49



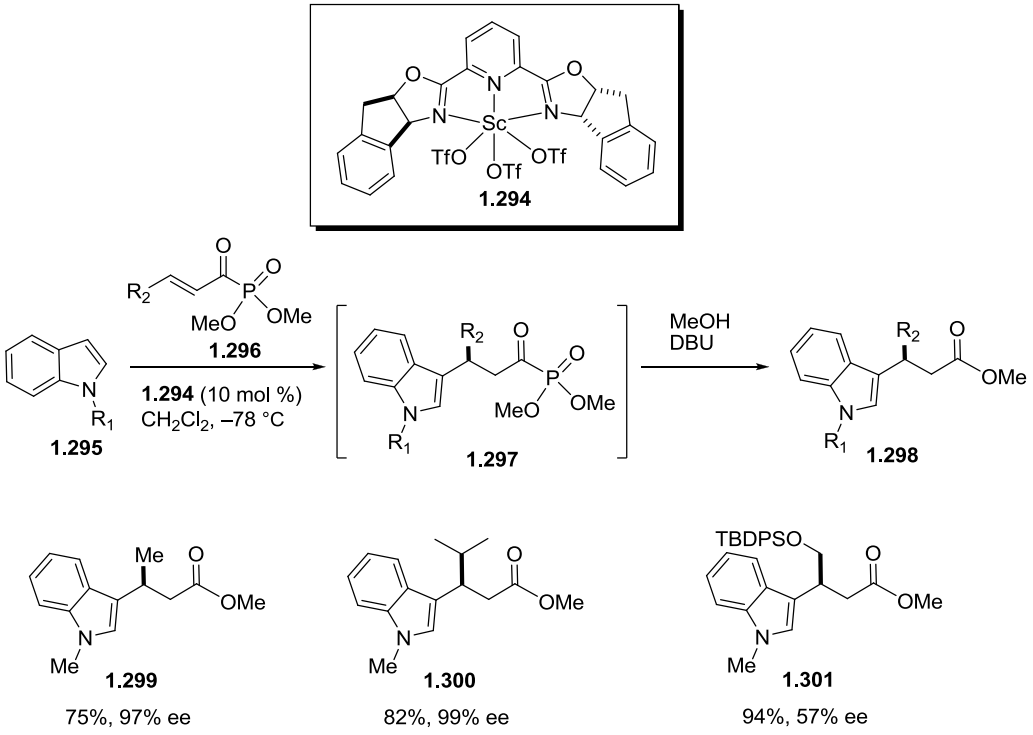
Copper bisoxazolone catalysts and their related derivatives have been a widely explored area of Michael reactions involving heterocyclic nucleophiles and the examples shown above are just some of the many methods available in the literature. However, useful work in the field has also been accomplished with other metals, including scandium, aluminum, zirconium, and hafnium; all of which will be discussed below.

In 2003, Evans and coworkers developed the bis(oxazolinyl)pyridine scandium (III) triflate catalyst **1.294** to effect the reaction between indoles **1.295** and crotonyl acyl phosphonates **1.296** to provide β-substituted, β-heteroaryl propionates in a single step in the presence of DBU and MeOH (Scheme 1.50).[63] The method provides a convenient and clever solution to accessing β-heteroaryl propionates directly from Friedel-Crafts reactions using bidentate catalysts. Recall that in the previous copper catalyzed reactions, all of the products obtained from the Michael reactions between the heterocycles and their corresponding electrophiles required at least one further elaboration to obtain the desired β-heteroaryl propionates (*cf.* Schemes 1.45, 1.47, and 1.49). This is because the electrophiles that were used, such as α'-hydroxy enones (**1.265**), β-aryl substituted nitroacrylates (**1.275**), and 2-enoylpyridine 1-oxides (**1.286**), needed to possess at least two Lewis basic sites in order to accommodate the bidentate ligands to achieve some measure of enantiocontrol. Evans avoided this problem because he hydrolyzed the intermediate β-indolyl acyl phosphonates **1.297** *in situ* with a suitable base and alcohol as

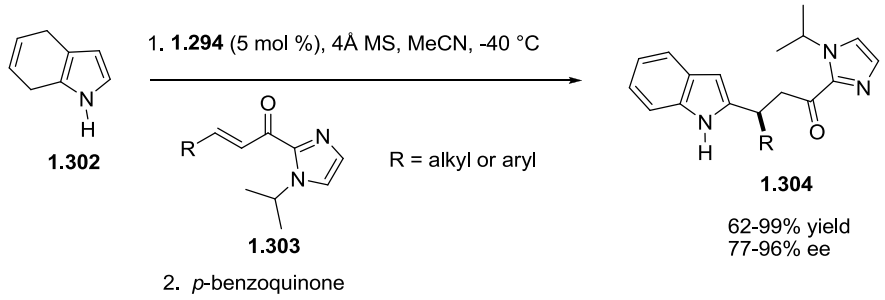
part of a one pot procedure. As shown in Scheme 1.50, the reaction produced the β-substituted, β-heteroaryl propionates in good yields (75-94%) and high enantioselectivities (97-99%), with the exception of when the β-substituent was the highly hindered TBDPS-protected alcohol **1.301**. Limitations to this method include the preparation of and lack of α-substituents on the electrophile (Scheme 1.50).

A few years later in 2007, Evans further developed his method by using catalyst **1.294** in reactions with dihydroindoles **1.302** to provide exclusively 2-substituted indole adducts after oxidation with *p*-benzoquinone (Scheme 1.51).[64] When **1.302** was catalyzed with **1.294** in the presence of electrophiles of the type **1.303**, dihydroindole behaved as a pyrrole, and underwent electrophilic aromatic reactions at the 2-position of the dihydroindole ring. Oxidation of the addition product then provided the 2-substituted indolyl propionates in 75-94% yield and 57-99% enantioselectivities.[64] Evans and coworkers developed a very clever method towards chiral 2-substituted indolyl propionates **1.304**, but the use of the dihydroindole is more of a work around than a true solution towards obtaining 2-substituted indolyl propionates in a general and direct fashion.

Scheme 1.50



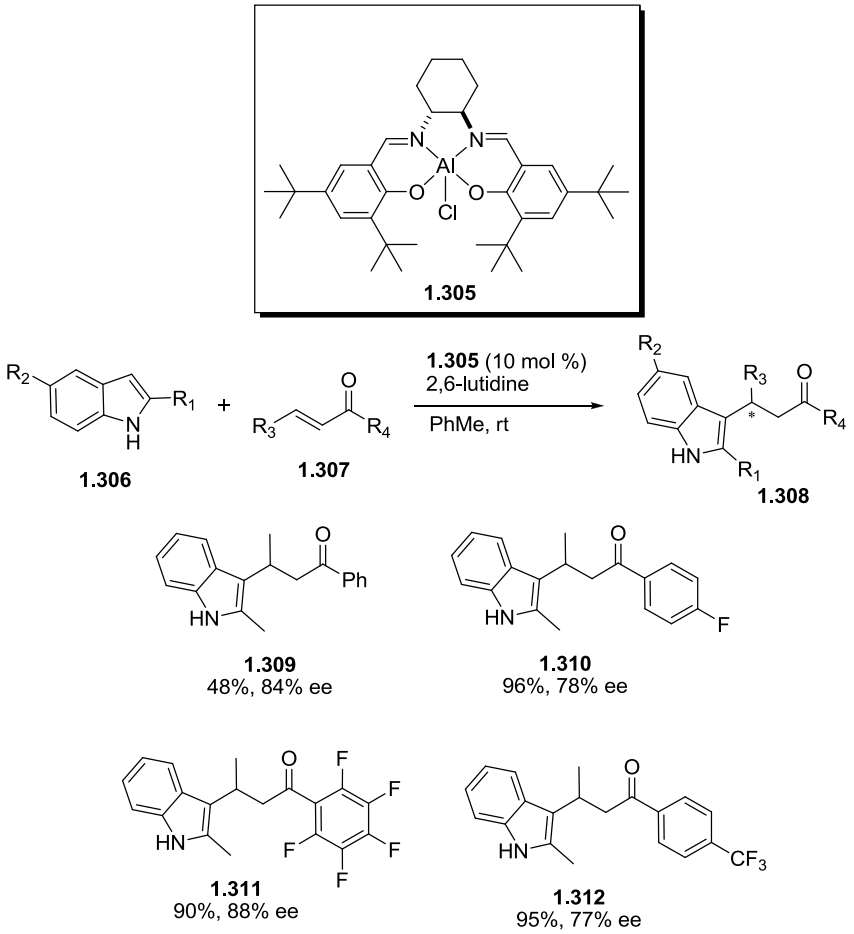
Scheme 1.51



Another catalyst successfully employed in Michael reactions of heterocyclic nucleophiles include the aluminum (III) salen complex **1.305** developed by Bandini and coworkers (Scheme 1.52).[65] α,β-Unsaturated ketones underwent addition with 2-substituted indoles in the presence of catalyst **1.305** to provide β-methyl, β-heteroaryl

ketones **1.308** in moderate to good yields (48-96%) and modest enantioselectivities (77-88%). The more electron-withdrawing the aryl group attached to the ketone electrophile, the better the reaction appeared to work. Although the enantioselectivies of these reactions are not as good as some previous work, this salen catalyst was an important contribution to the field because it was the first example of a catalyst requiring only a monodentate chelating Lewis basic site on the electrophile. This suggests that β-heteroaryl propionates could be accessed in a single step if α,β-unsaturated esters were capable of being employed as electrophiles.

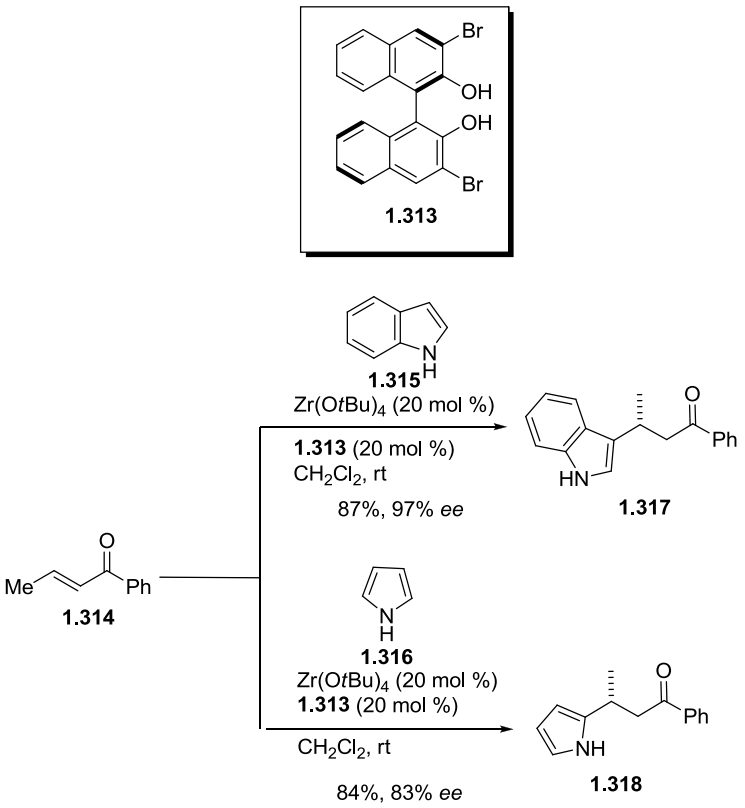
Scheme 1.52



The last example of a chiral catalyst used in heteroaryl conjugate additions was developed by Blay and coworkers and employs a BINOL-derived scaffold (Scheme 1.53). In 2007, the authors treated indole (**1.315**) and pyrrole (**1.316**) with enone **1.314** in the presence of catalyst **1.313** and $Zr(OtBu)_4$ to yield the corresponding β-methyl, β-heteroaryl ketones in good yields and enantioselectivities; with indole providing slightly better results than pyrrole.[66] If the scope of the electrophile were expanded to α,β-

unsaturated esters, then this method would provide direct access to β-substituted, β-heteroaryl propionates.

Scheme 1.53

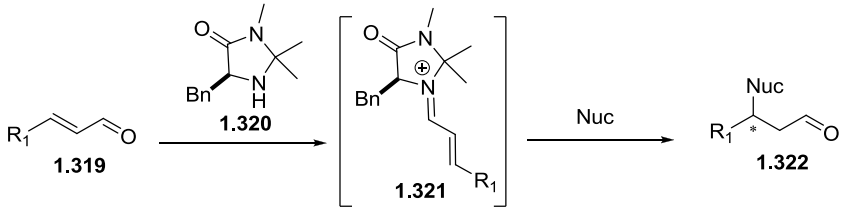


1.3.3 ORGANOCATALYSTS

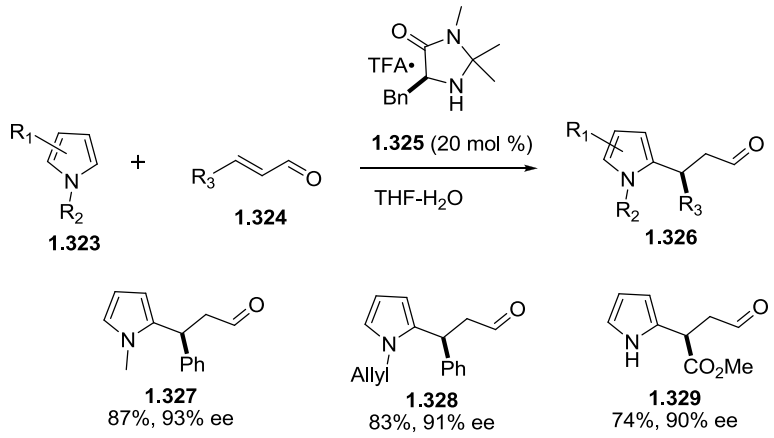
The early work done on organocatalytic Micheal reactions of heterocycles to α,β-unsaturated aldehydes was published by MacMillan *et al.* in 2001 (Schemes 1.54 and 1.55).[67] The authors developed the imidazolidinone catalyst **1.320** to lower the LUMO of various enal electrophiles *via* reversible formation of intermediate chiral iminium ions such as **1.321**. In the presence of suitable nucleophiles, such as heterocycles, attack of the extended iminium ion would occur in a 1,4- vs. 1,2-fashion due to the steric hindrance

about the iminium ion, thus producing β-substituted, β-heteroaryl aldehydes **1.322** in good yield and excellent enantioselectivity. One of the most impressive features about this method was that no polyalkylation was observed with respect to pyrroles, probably due to the steric nature of the active electrophile. Recall that both for furan and pyrrole, dialkylation was a major problem with respect to Michael additions of heterocyclic nucleophiles catalyzed by both Bronsted and Lewis acids. Another nice feature of the method is that catalyst **1.325** can be recovered and reused. One of the limitations in scope, however, is that α-substitution on the β-heteroaryl aldehydes appears inaccessible due to the steric hindrance of the catalyst used to impart the desired enantioselectivity over the reaction.

Scheme 1.54

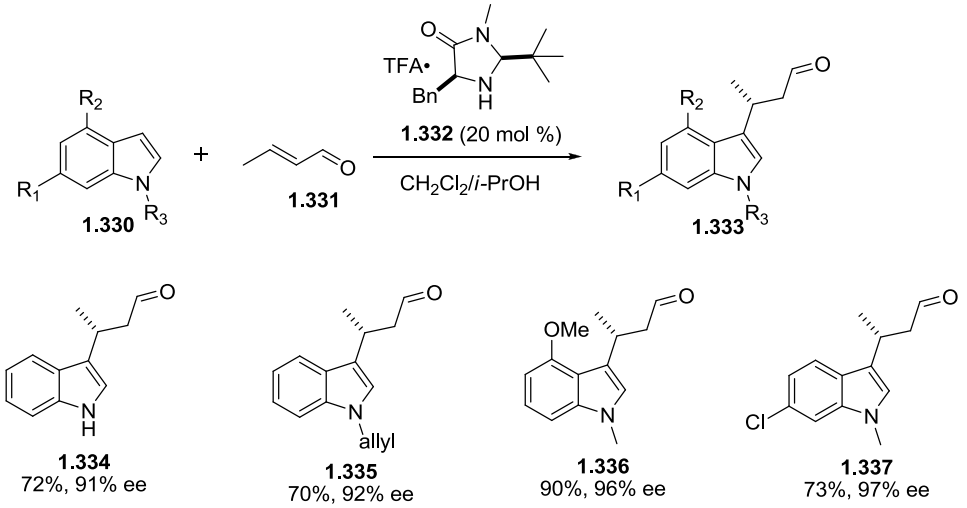


Scheme 1.55

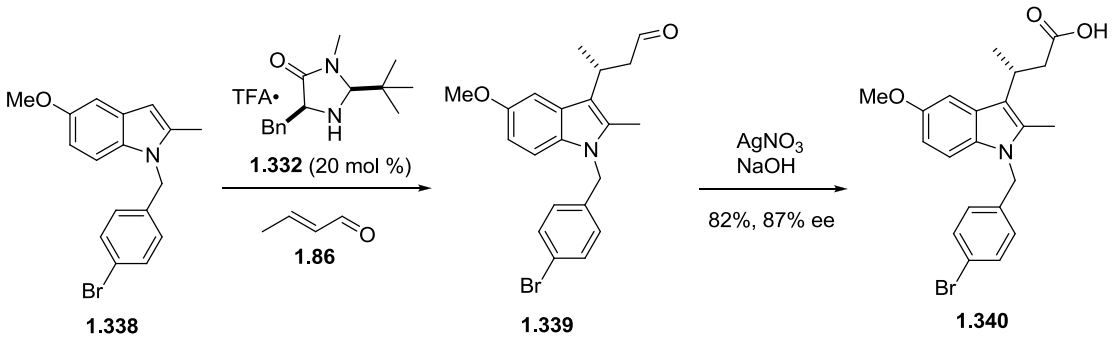


A year later, MacMillan and coworkers expanded the scope of their reaction to encompass indoles (Scheme 1.56).[4] Imidazolidinone catalyst **1.332**, which featured a slight structural deviation from **1.325**, promoted the reaction between a variety of electron rich and electron poor indoles with α,β-unsaturated enals. Like the pyrrole examples, the β-substituted, β-indolyl aldehydes were obtained in good yields and excellent enantioselectivities, though no examples bore an α-substituent. The authors further showed that the β-substituted, β-heteroaryl aldehydes could be converted to the corresponding propionic acids *via* oxidation with silver (I) nitrate in the presence of sodium hydroxide in good yield and enantioselectivity. In fact, indole **1.340** is a known COX-2 inhibitor developed by Merck (Scheme 1.57).[4]

Scheme 1.56

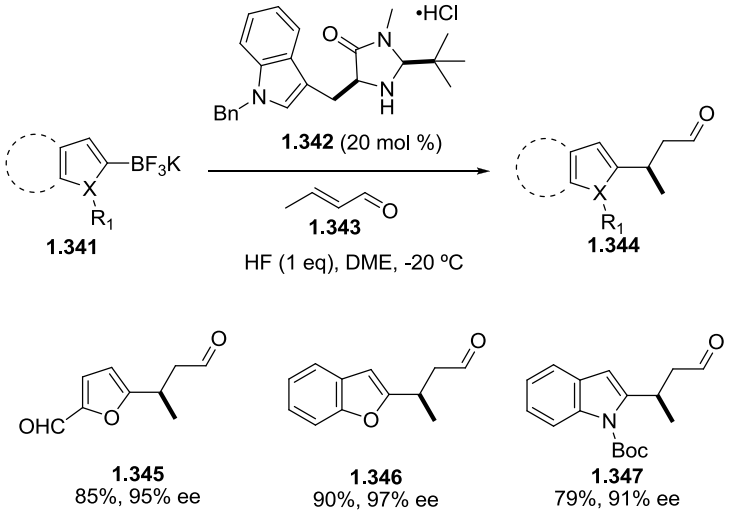


Scheme 1.57



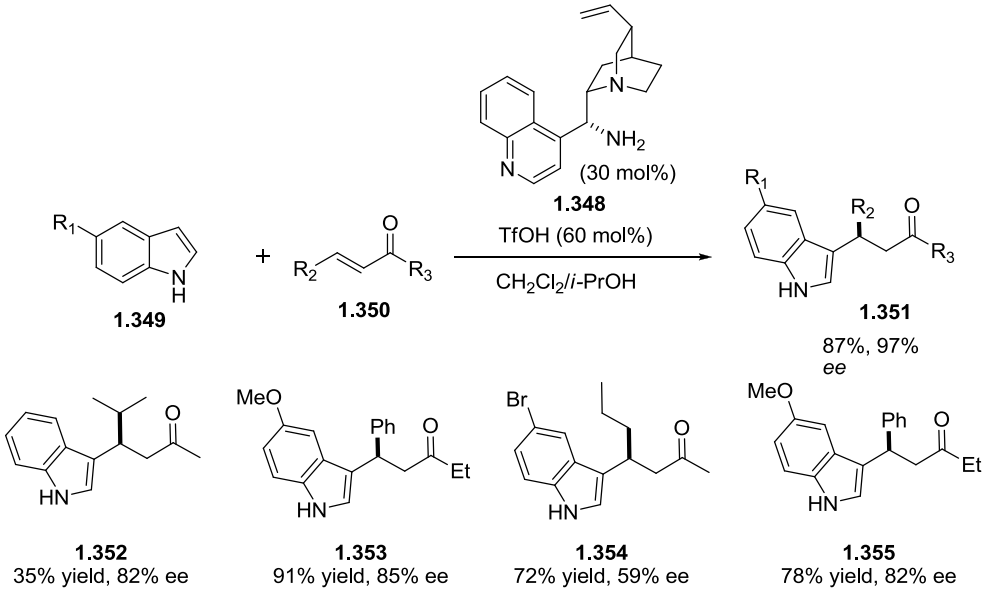
The scope of the reaction was further expanded in 2007. MacMillan and coworkers found that heterocyclic tetrafluoroborate salts **1.341** underwent reaction with β-substituted, α,β-unsaturated enals **1.343** in good yields and excellent enantioselectivities in the presence of **1.342** (Scheme 1.58).[68] At first glance this method may seem more cumbersome due to the additional step of creating tetrafluoroborate salts, but the addition of the salts to the nucleophiles enabled less reactive heterocycles to participate in the reaction. For example, benzofuran, which has poor π-nucleophilicity, and furfuryl aldehyde, which is electron deficient both produced the desired β-substituted, β-heteroaryl propionaldehydes in excellent yields and enantioselectivities **1.345-1.346**. The addition of the tetrafluoroborate salt to the nucleophile also allowed for more reactive heterocycles (ie indoles) to react at non-classical electrophilic aromatic substitution positions (the 2 vs 3-position of indole) as shown with indole **1.347**. While this is certainly a useful method, a route that would not require the special preparation of a borate salt would be preferable, as would a route that could prepare α-substituted, β-heteroaryl propionaldehydes.

Scheme 1.58



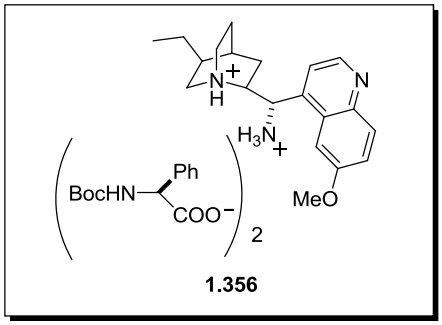
The cinchinone catalyst **1.348** was developed by Chen *et. al.* in 2007 and was found to successfully catalyze the Friedel-Crafts reaction between indoles and α,β-unsaturated ketones (Scheme 1.59).[69] The yields varied depending on the size of the β-substituent of the ketone, but they were generally good for most ketones examined (72-90%). The enantioselectivities also varied, with electron rich indoles generally performing better than electron poor indoles. While there is room for improvement, the method was impressive because it was the first example of an enantioselective organocatalyzed Michael addition between a heterocycle and an α,β-enone.

Scheme 1.59

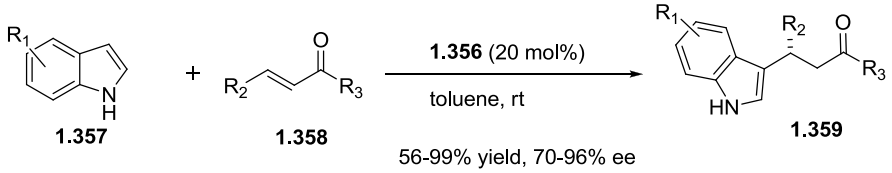


Just a few months after Chen's work was published, Bartoli and coworkers published a second report of enantioselective organocatalytic heterocyclic reactions using a quinine-like catalyst (Scheme 1.60).[70] In the method of Bartoli, a chiral cinchona amine was coupled with two equivalents of D-*N*-Boc phenylglycine to provide the bifunctional catalyst **1.356**. Bartoli's catalyst performed better than Chen's catalyst, providing β-substituted, β-heteroaryl ketones **1.359** in high yields (56-99%) and high enantioselectivities (70-96%). Unfortunately the scope of the nucleophile was limited to indoles, and α-substituted enones were still out of reach as electrophiles.

Scheme 1.60



1.356



1.357 1.358 1.359

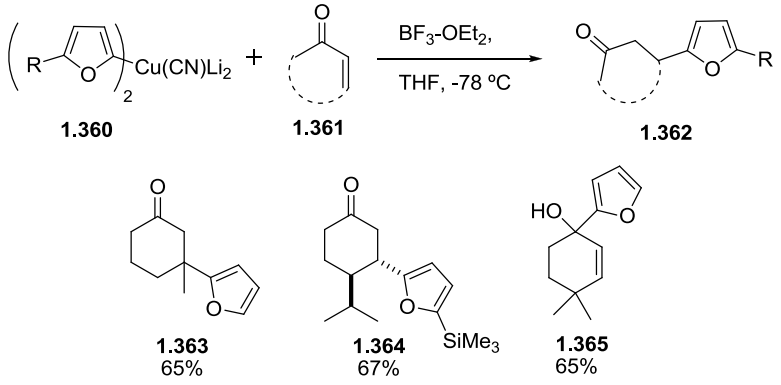
56-99% yield, 70-96% ee

1.3.4 HETEROCYCLIC ORGANOMETALLICS

Another common way to obtain β-heteroaryl propionates *via* the conjugate addition pathway is to utilize heterocyclic organometallics as nucleophiles in Michael reactions. In general, these reactions tend to have a broader nucleophile scope as the inherent π-nucleophilicity of the heterocycles can be overcome. However, these reactions also tend to require more steps and to utilize more expensive metallic reagents. A brief survey of both chiral and achiral examples will be presented.

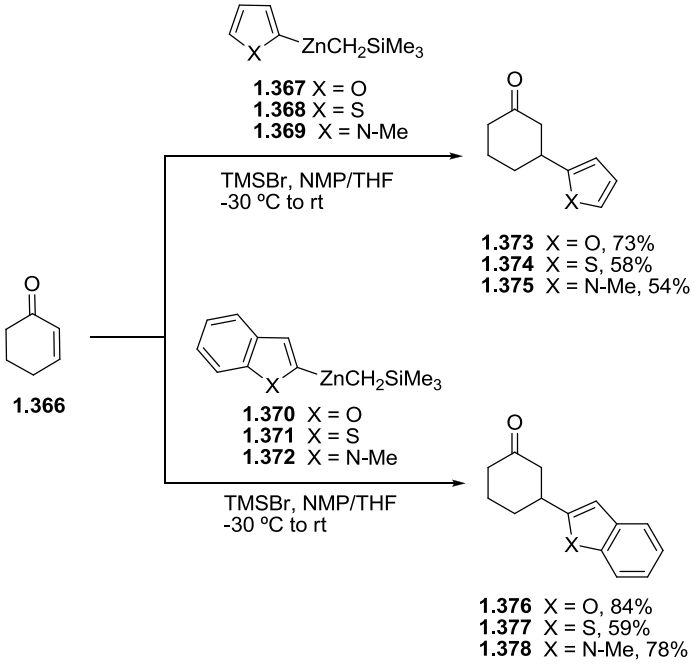
In 1988 Lipshutz and coworkers showed that lithiated higher order cuprates derived from furans could react with cyclic α,β-unsaturated ketones in the presence of boron trifluoroetherate to produce the desired Michael adducts in moderate yields (ca. 65%) (Scheme 1.61).[71] The conjugate additions proceeded with considerably hindered enones, but when the steric bulk became too large to overcome 1,2-addition of the furan to the carbonyl would become the predominant product **1.365**.

Scheme 1.61

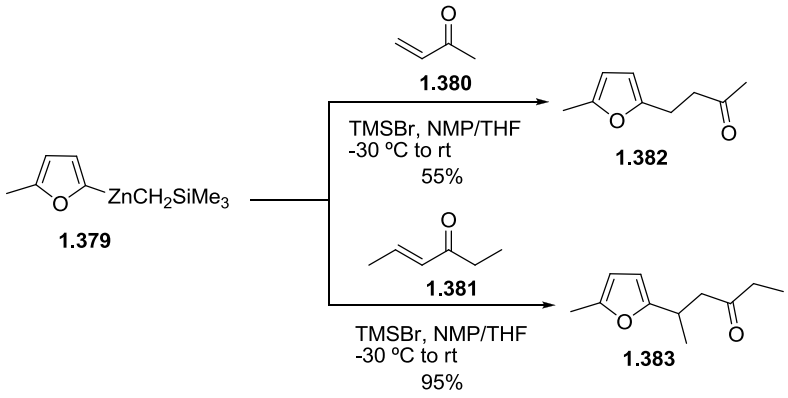


Organozinc heterocycles were also developed for use in Michael reactions. Knochel *et al.* examined the use of (trimethylsilyl)-heteroarylzincs **1.367**-**1.372** in reactions with cyclic and acyclic α,β-unsaturated enones (Schemes 1.62 and 1.63).[72] Furan, thiophene, pyrrole, benzofuran, benzothiophene, and indole were all lithiated and transformed to their corresponding trimethylsilyl zinc methyl derivatives **1.367**-**1.372** that were then treated with cyclic and acyclic enones to provide the corresponding adducts in moderate to good yield (Scheme 1.62). Knoechel's work provides some of the only examples of conjugate additions wherein the less reactive benzofuran and benzothiophene were utilized as nucleophiles.

Scheme 1.62



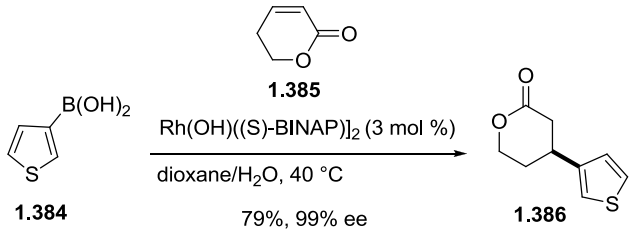
Scheme 1.63



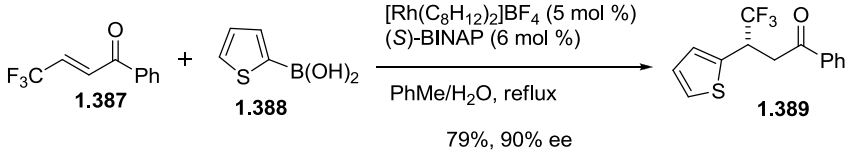
Since 2003, a number of research groups had begun to investigate the use of rhodium catalysis in Michael additions of heterocyclic organometallic reagents. Hayashi first reported the enantioselective conjugate addition of 3-thiophene boronic acid (**1.384**) to α,β-unsaturated lactone **1.385** in good yield (79%) and excellent enantioselectivity

(99%) using 3 mol % of a rhodium BINAP catalyst (Scheme 1.64).[73] Interestingly, the conjugate addition took place at the 3-position of thiophene as opposed to the EAS preferred 2-position. While this was an impressive example of an enantioselective heterocyclic Michael addition, this was the only example presented in the paper. It is unclear whether the scope of both the nucleophile and electrophile can be expanded. A similar thiophene boronic acid **1.388** was shown by Konno in 2008 (Scheme 1.65).[74]

Scheme 1.64



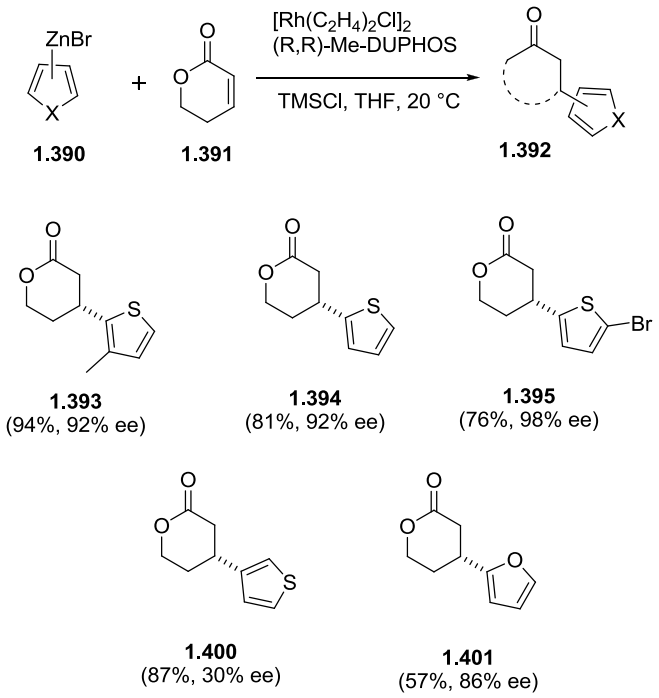
Scheme 1.65



In 2008, Frost and coworkers reported the enantioselective conjugate addition of furyl and thiophenyl zincs to the α,β-unsaturated lactone **1.391** in good yields (57-94%) and excellent enantioselectivities (86-98%) using a rhodium DUPHOS catalyst (Scheme 1.66).[75] The use of heteroaryl zinc reagents was generally favorable as compared to the use of their corresponding heteroaryl boronic acids due to the propensity of the heteroaryl boronic acids to undergo protodeboronation side reactions. Interestingly, most of the reactions involving thiophenyl zincs worked very well with the exception of the 3-

thiophene zinc reagent **1.400**, which underwent reaction with Hayashi's catalyst providing **1.386** in 99% enantioselectivity.

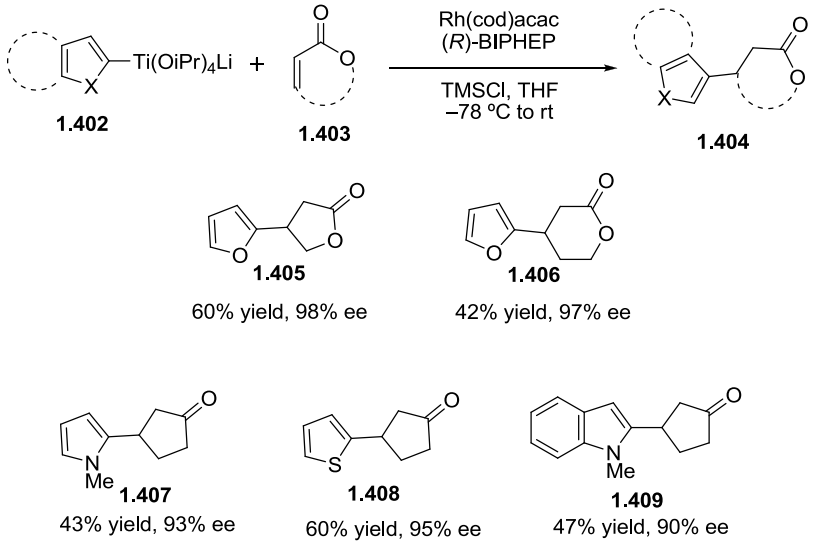
Scheme 1.66



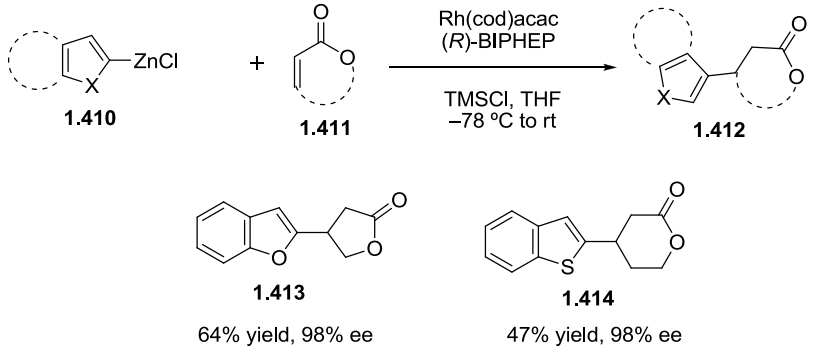
As previously mentioned, the use of heteroaryl boronic acids in conjugate addition reactions suffered from the major problem of protodeboronation. The Martin group developed chemistry in order to avoid this problem when the Michael adduct **1.405** was needed as an intermediate in an ongoing natural product synthesis. We discovered that 2-furyl titanium tetraisopropoxide underwent reaction with furan-2(5H)-one using a rhodium BIPHEP catalyst to provide **1.405** in 60% yield and 98% *ee* (Scheme 1.67).[76] The scope of the nucleophile was expanded when cyclopentenone underwent reactions with pyrrole, thiophene, and indole in moderate to good yields (43-60%) and excellent enantioselectivities (90-95%). Benzothiophene and benzofuran were also examined, but

due to their low π-nucleophilicity, it was necessary to use the more reactive 2-substituted zinc reagents to achieve satisfactory yields (47-64%) and excellent enantioselectivities (98%) (Scheme 1.68).

Scheme 1.67



Scheme 1.68

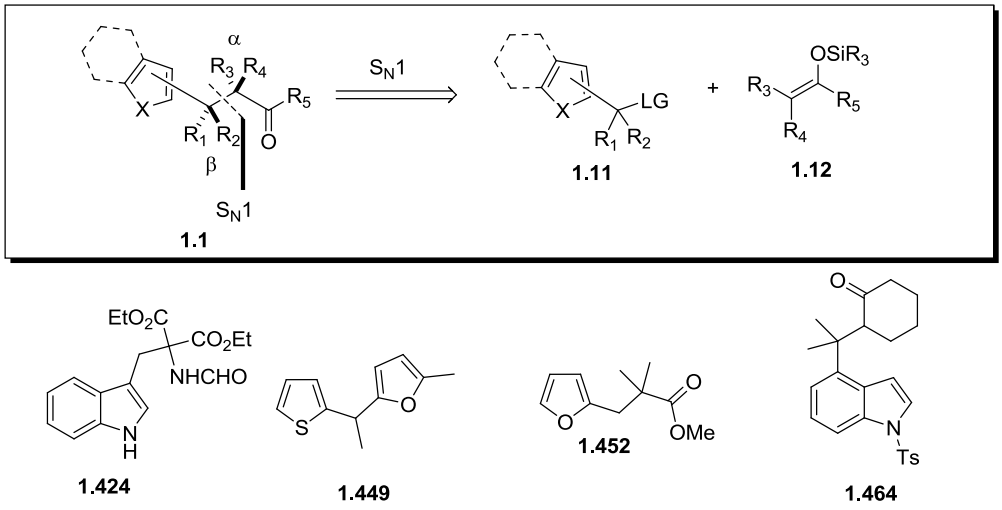


1.4 Synthesis of β-Heteroaryl Propionates by S_N1 Type Reactions

The second major route to β-heteroaryl propionates, (S_N1), involves an S_N1-type reaction in which the heteroaryl ring bears a benzylic-like leaving group that ionizes in

the presence of a suitable Lewis acid (Scheme 1.69). The nascent carbocation can then be captured by a suitable π-nucleophile to produce the desired propionate. Precedent exists for reactions involving cations derived from various heterocyclic carbinols, as well as thiophen-2-yl chloride,[77] and furan-2-yl acetate,[78] but the scope of this process appears to be limited to a few combinations of heteroaryls and π-nucleophiles (Scheme 1.69).[18,79-88]

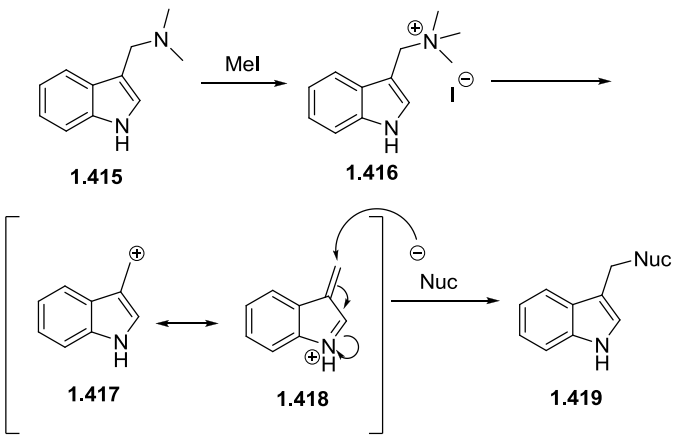
Scheme 1.69



1.4.1 GRAMINE

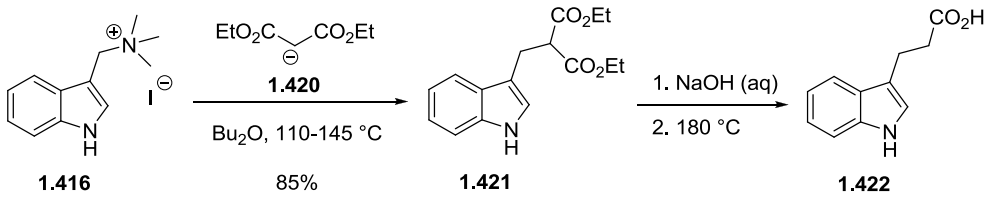
The first, and the most classic, example of generating heteroaromatic benzylic cations was developed with gramine (**1.415**). Gramine is an indole bearing a dimethylamino methyl group at the 3-position. While stable in its neutral form, when gramine is quaternized **1.416**, usually with MeI, the dimethylamino group is transformed into a good leaving group. When the amino group leaves, a stabilized carbocation is formed that can be represented by the two contributing resonance structures **1.417** and **1.418**. The carbocation can then be captured by a number of nucleophiles.

Scheme 1.70



Snyder was one of the early pioneers of gramine chemistry in the 1940's. In 1944, Snyder and coworkers showed that gramine could be alkylated by diethyl malonate to provide diester **1.421** in 85% yield, though the conditions were extremely harsh (Scheme 1.71).[89] Diester **1.421** could further be elaborated to 3-indole propionic acid (**1.422**), which has been used as a plant growth regulator and also as a key starting material for the synthesis of lysergic acid.[90,91]

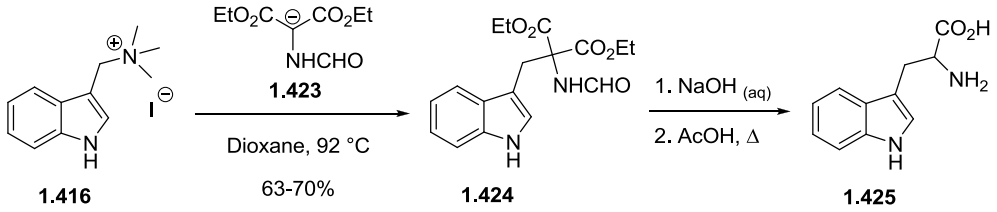
Scheme 1.71



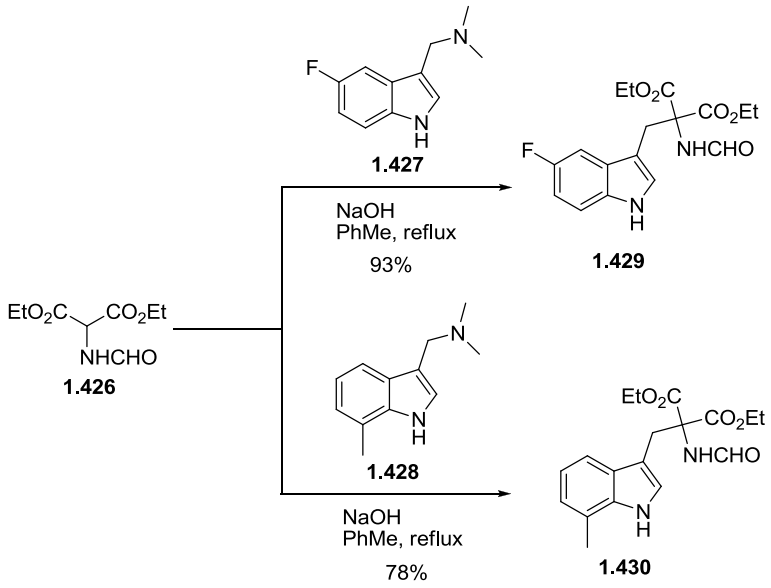
Snyder also showed that α-amido malonate **1.423** could undergo addition with gramine in modest yield to provide tryptophan (**1.425**) after subsequent saponification and decarboxylation (Scheme 1.72).[92] A few decades later Hoffmann and coworkers expanded the scope of the reaction to include a variety of different indoles (Scheme

1.73).[93] The reaction worked well for both electron-poor and hindered indoles, though the conditions were still rather harsh.

Scheme 1.72

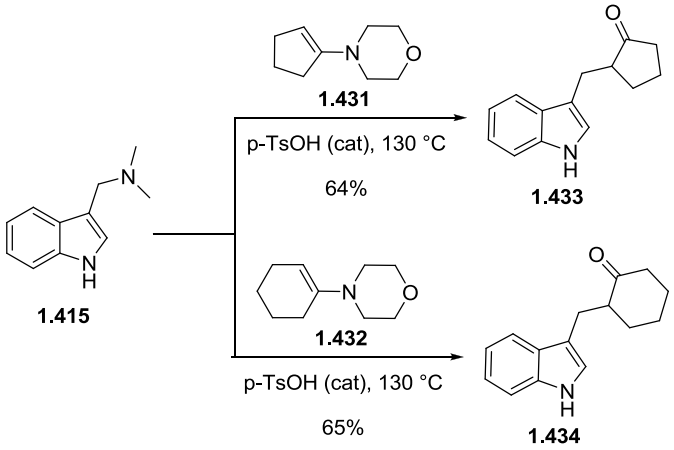


Scheme 1.73

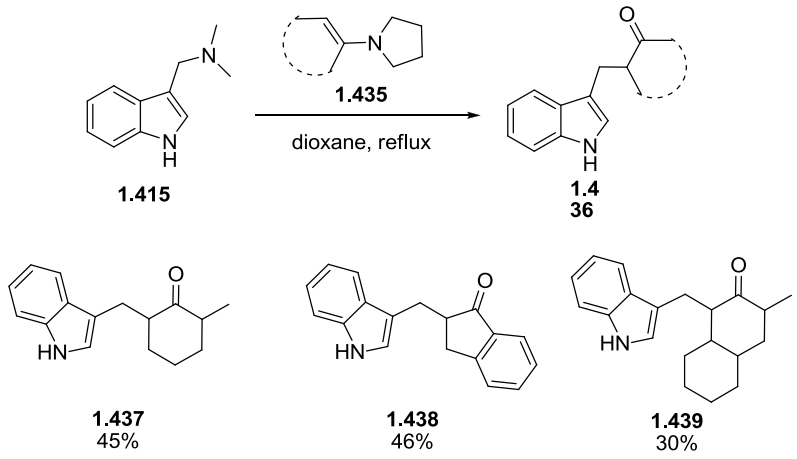


Enamines have also been shown to be effective nucleophilic partners in reactions with gramine (Schemes 1.74 and 1.75). In 1965, two papers were published which featured the reactions of cyclic enamines with gramine.[94,95] In both cases, harsh reaction conditions were used, and the resulting adducts were formed in poor to moderate yields.

Scheme 1.74



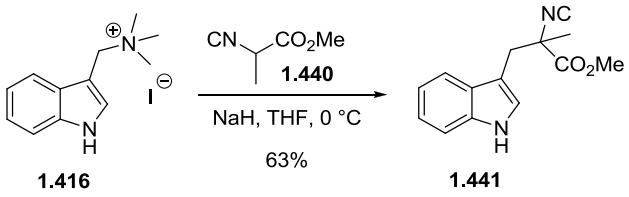
Scheme 1.75



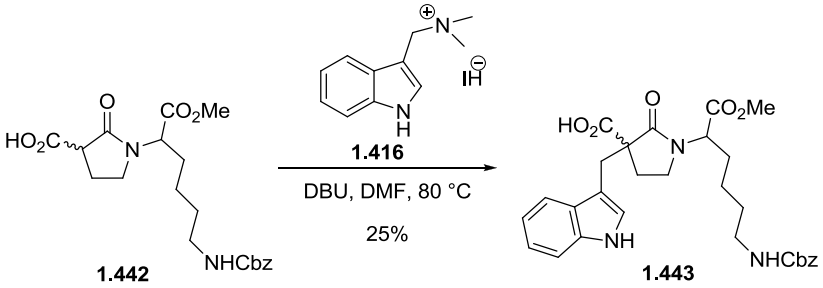
Other examples of nucleophiles used with gramine are shown in Schemes 1.76-1.78. In 1974, Matsumoto found that gramine methiodide (**1.416**) underwent reaction with α-isocyanopropionate (**1.440**) to provide β-heteroaryl propionate **1.441** in 63% yield (Scheme 1.76).[96] Propionate **1.441** was further elaborated to substituted tryptophan derivatives. While the yields were moderate, the conditions were considerably less harsh than in earlier examples. In 1985, Freidinger alkylated gramine methiodide (**1.416**) with

α-carboxylactam **1.442** to give the complex α,α-disubstituted β-indolyl propionate **1.443**, albeit in low yield (25%) (Scheme 1.77).[97] Propionate **1.443** was used to investigate biologically active peptides. In 1996, Mortier and coworkers alkylated gramine methosulfate (**1.445**) with the enolate of diketopiperazine to provide the corresponding product in 57% yield (Scheme 1.78).[98]

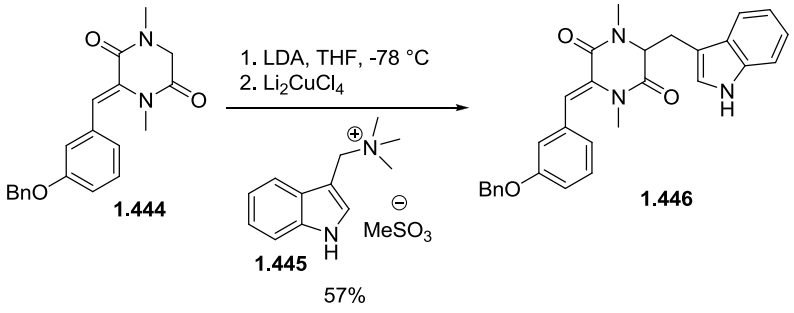
Scheme 1.76



Scheme 1.77



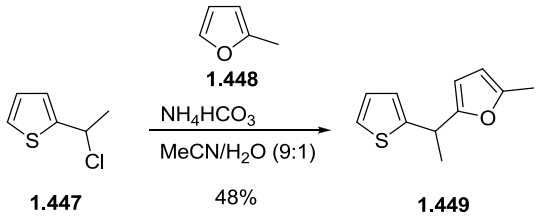
Scheme 1.78



1.4.2 IONIZATION OF BENZYLIC HETEROAROMATIC HALIDES

While the ionization of benzylic halides and their subsequent capture with appropriate nucleophiles is well known, only a few examples are known in which heteroaromatic benzylic halides are employed as the electrophilic partners. In 2004, Mayr and coworkers showed that the ionization of thiophene benzyl chloride **1.447** proceeded in the presence of a stoichiometric amount of ammonium bicarbonate (NH_4HCO_3) to generate a heteroaromatic cation that was subsequent captured by 2-methyl furan (**1.448**) in 48% yield (Scheme 1.79).[77] The scope of the ionization of heterocyclic benzyl halides is extremely narrow, and there are no examples using nucleophiles such as silyl ketene acetals, which would provide β-heteroaryl propionates directly. Benzylic heteroaromatic halides are also known to be unstable and are prone to polymerizations that further limit their utility.

Scheme 1.79

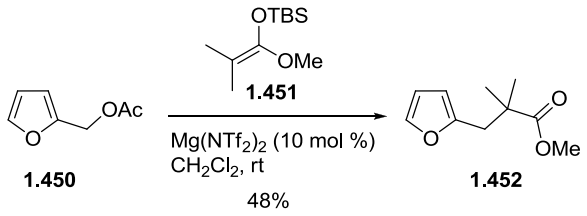


1.4.3 IONIZATION OF BENZYLIC HETEROAROMATIC ACETATES

Prior to our work in the area, there was only one known example of a π-nucleophile alkylating a benzylic cation derived from a heterocyclic benzylic acetate. In 1997, Grieco and coworkers showed that the α,α-disubstituted silyl ketene acetal **1.451** reacted with furan-2-ylmethyl acetate (**1.450**) in the presence of catalytic magnesium triflimide ($Mg(NTf_2)_2$) in 48% yield (Scheme 1.80).[78] While the yield of the addition was

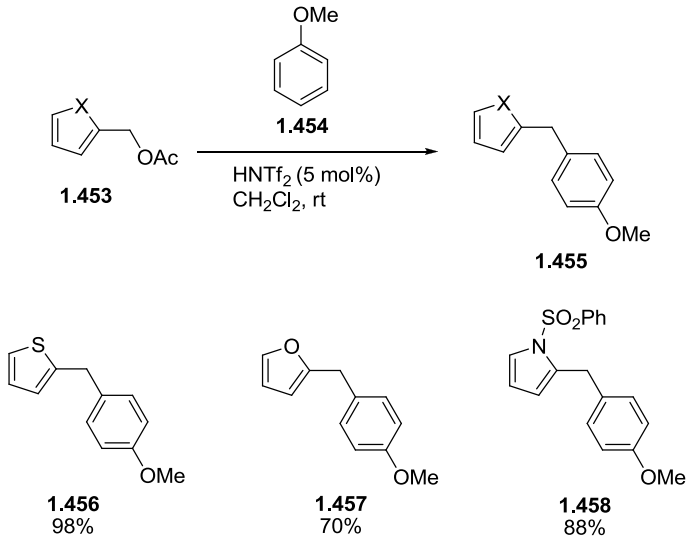
low, the reaction was one of the first to show that α,α-disubstituted, β-heteroaryl propionates could be accessed relatively easily. This result was particularly important because α,α-disubstituted β-heteroaryl propionate scaffolds had been completely inaccessible *via* any of the EAS methods described earlier.

Scheme 1.80



After our work was completed, Ghosez reported the ionization of primary heteroaromatic acetates with triflimide to produce electron-rich biaryls (Scheme 1.81).[99] Primary 2-thiophenyl, 2-furanyl, and 2-pyrrolyl acetates reacted with anisole (**1.454**) to produce the corresponding biaryls (**1.456-1.458**) in 70-98% yield. 2-Thiophenyl acetate (**1.453**, X = S) was the best electrophile in the triflimide promoted coupling, while 2-furanyl acetate (**1.453**, X = O) was the worst. The reaction of the 2-pyrrolyl acetate (**1.453**, X = NSO_2Ph) with anisole (**1.454**) was particularly interesting because it showed that electron-withdrawing groups may be tolerated on heterocyclic electrophiles in S_N1 type reactions.

Scheme 1.81

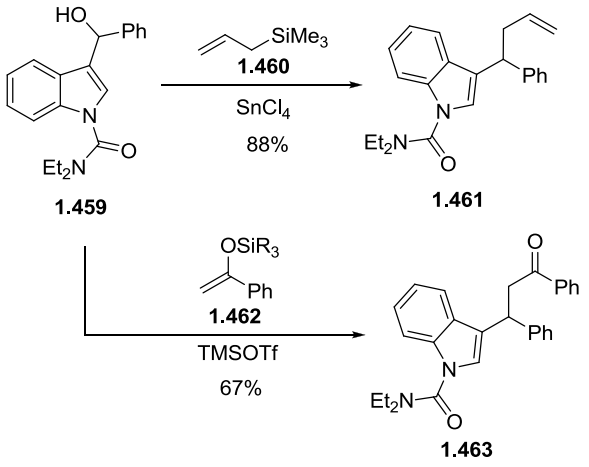


1.4.4 IONIZATION OF BENZYLIC HETEROAROMATIC ALCOHOLS

Although heteroaromatic benzylic halides and acetates have been shown to be successful electrophiles in the S_N1 type pathway towards β-heteroaryl propionate scaffolds, the use of heteroaromatic benzylic alcohols as electrophiles would be preferable, because they are typically intermediates en route to heteroaromatic halides and acetates.

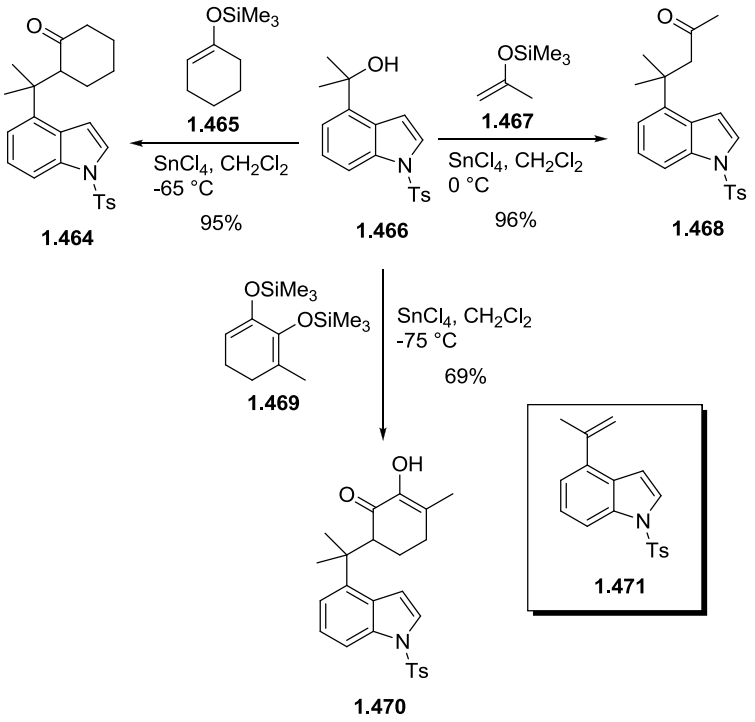
Comins and coworkers were the first to incorporate 3-indolyl carbinols into ionization reactions with π-nucleophiles (Scheme 1.82). Alcohol **1.459** was ionized in the presence of either $SnCl_4$ or TMSOTf to produce a stabilized carbocation that was then captured by allyl trimethyl silane (**1.460**) or silyl enol ether **1.462** to provide the corresponding adducts in good yields (67-88%). Both **1.461** and **1.463** could be further elaborated to the desired β-substituted, β-heteroaryl propionates when subjected to suitable oxidation conditions.

Scheme 1.82



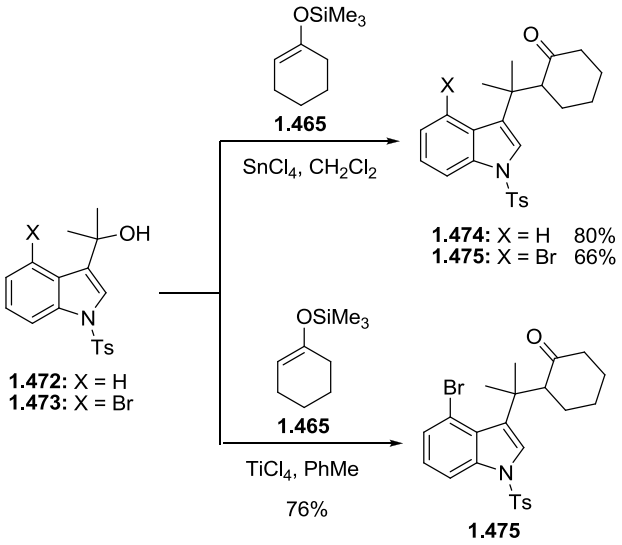
Natsume *et al.* expanded the scope of Comin's work by ionizing 4-indolyl carbinols with $SnCl_4$ in the presence of silyl enol ethers in their synthetic work directed toward the hapalindole alkaloids (Scheme 1.83).[83] The reaction of indole **1.466** with both cyclic **1.465** and acyclic **1.467** enol ethers provided excellent yields of the corresponding β,β-disubstituted, β-heteroaryl ketones **1.464**, **1.468**, and **1.470**, though when the nucleophile became too hindered, elimination of the alcohol to an alkene **1.471** became a significant side reaction. These reactions are important because the site of ionization can take place at a variety of places on the heterocycle, depending on the site of the reacting benzylic alcohol. In addition to providing hindered β-heteroaryl ketones in a single step, these reactions also demonstrated that high yields could be achieved with electron withdrawing groups present on the indole. The only downsides to this reaction are that the scope of the reaction appears to be limited to 4-indolyl tertiary carbinols and silyl enol ethers, which would require additional steps to elaborate to the desired β-heteroaryl propionates.

Scheme 1.83



Shortly after we began our studies, Rawal and coworkers reported a similar process in their work toward the welwitindolinone alkaloids (Scheme 1.84).[82,100,101] Tosyl protected 3-indolyl carbinols **1.472** and **1.473** were allowed to react with cyclohexyl silyl enol ether **1.465** in the presence of both $SnCl_4$ and $TiCl_4$ to provide β-heteroaryl ketones **1.474** and **1.475** in good yields. Although Rawal did not extensively expand the scope of the reaction, he did show that halogenated indoles may participate in the coupling reaction. This is important as aromatic halogens can serve as important functional handles in natural product synthesis.

Scheme 1.84

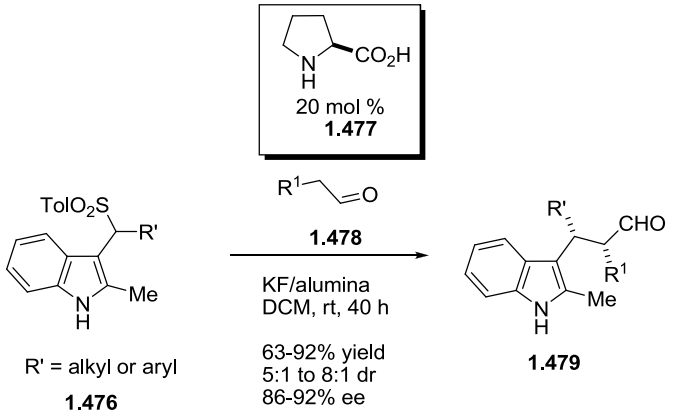


1.4.5 CHIRAL IONIZATIONS

There were two examples of chiral S_N1 type reactions to provide β-heteroaryl carbonyl compounds contemporaneous with our investigations. The first is from Melchiorre and coworkers (Scheme 1.85).[102] Using proline **1.477** as an organocatalyst, Melchiorre ionized aryl sulfonyl indoles with KF and alumina in the presence of a variety of propionaldehydes **1.478** to yield α,β-substituted β-heteroaryl aldehydes **1.479**. The products were obtained in good to excellent yields (63-92%), good diastereoselectivities (5:1 to 8:1 in favor of the syn-adducts), and good enantioselectivity (86-92%). If the 2-position of the indole is not substituted with a methyl group then the enantioselectivity and diastereoselectivity suffer. The authors speculate the methyl group provides the necessary steric bulk with which to interact with the proline catalyst to induce diastereoselectivity during the addition.[102] Also, the scope of both reactions is currently limited to aldehydes, the catalyst loading is high, and reaction times are long. While the

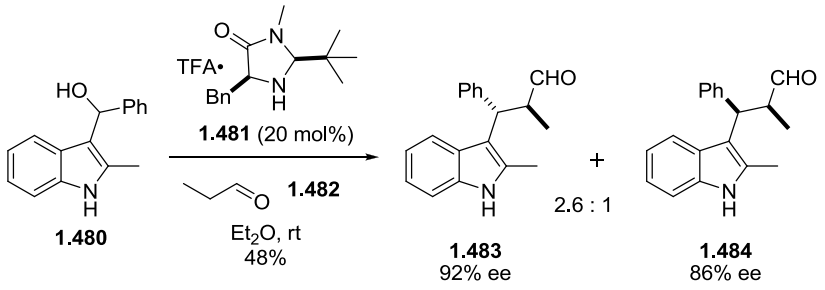
results of both Cozzi and Melchiorre's work were impressive, there remained room for improvement.

Scheme 1.85



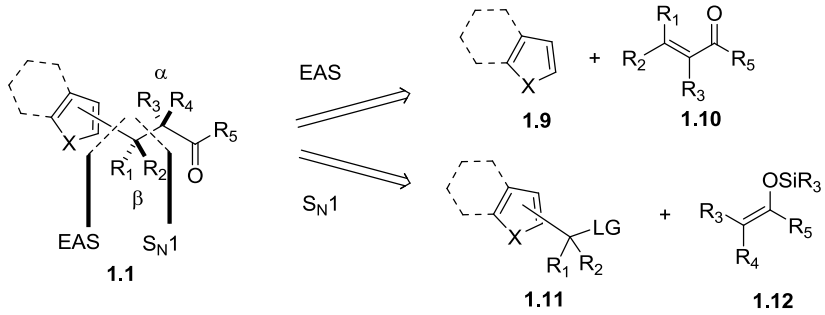
The second chiral example of the S_N1 type nucleophilic capture of a heterocyclic benzylic cation came from Cozzi and coworkers who utilized MacMillan imidazolinone catalyst **1.481** to promote ionizations of indoles of the type **1.480** in the presence of propionaldehyde (**1.482**) and other aldehydes (Scheme 1.86).[103] The resulting β-substituted, β-heteroaryl ketones were produced in moderate yield (48%) and diastereoselectivity (2.6:1) in favor of the anti-adduct **1.483**, while both syn- and anti-adducts, **1.484** and **1.483** respectfully, were formed in good enantioselectivities (86-92%). Cozzi's work was impressive as proof of principle, but the scope of the reaction is extremely limited. If the indole is not-substituted at the 2-position the enantioselectivities of the products plummet.

Scheme 1.86



1.5 SUMMARY OF PRIOR ART

Scheme 1.87



It is evident from the preceeding survey that there are two main paths to access β-heteroaryl propionates. The first, which was designated as EAS, involves the conjugate addition of heteroaromatic nucleophiles to α-β-unsaturated carbonyl derivatives according to classic Friedel-Crafts reactivity pathways (Scheme 1.87). Both achiral and chiral examples of this process are well precedented, and yields and stereoselectivities can be high employing both Lewis and Bronsted acids[9-28]. However, this type of reaction is limited because new bond construction on the heterocycle only occurs at the site of the heteroaromatic ring that is favored in classical electrophilic aromatic substitution reactions, and indoles and pyrroles comprise the bulk of the examples. Another

limitation is that substitution on the unsaturated reaction partner **1.10** (Scheme 1.87, R_1, R_2 = alkyl) is limited,[10,29,30] with α,α-disubstitution products **1.1** (Scheme 1.87, R_3, R_4 = alkyl) seemingly inaccessible through this route. Moreover, most successful examples of enantioselective processes of this type require either an electrophilic partner with two Lewis basic sites to accommodate the bidentate metallic catalysts or an aldehyde on the unsaturated reaction partner that can form chiral iminium ions.

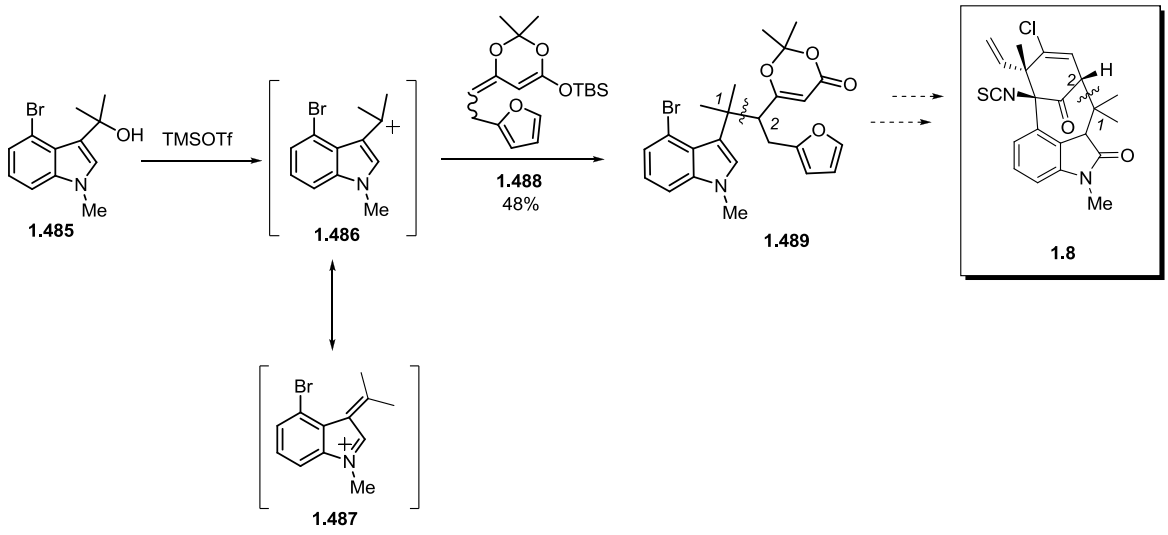
The second route to β-heteroaryl propionates, which was designated as S_N1, involves an S_N1-type reaction in which the heteroaryl aromatic ring bears a benzylic-like leaving group that ionizes in the presence of a suitable Lewis acid (Scheme 1.87). The incipient carbocation is then captured by a π-nucleophile to produce the propionate **1.1**. Precedent exists for reactions involving cations derived from various heterocyclic carbinols, as well as thiophen-2-yl chloride,[77] and furan-2-yl acetate,[78] but the scope of this process is limited to a few combinations of heteroaryls and π-nucleophiles. Moreover, the two enantioselective examples in the literature demonstrate proof of principle more than synthetic utility.

While there are methods for preparing compounds such as **1.1**, it is evident that limitations persist, and there is no direct precedent for a number of possible bond forming processes. After considering the available options, we determined that the greatest opportunity for development resided with the S_N1 pathway. Our first goal was to develop a concise and facile method to access a variety of β-heteroaryl propionates, with varying degrees of α- and β- substitution.

1.6 MARTIN GROUP APPROACH

In the Martin group's total synthesis of welwistatin[6] (**1.8**) a potentially useful methodology arose from a key carbon-carbon (C1 and C2 of **1.489**) bond formation between the tertiary hydroxy indole **1.485** and the π-nucleophile **1.488** (Scheme 1.88).[104] After considering the available options towards accessing compounds of the type **1.489**, we determined that the greatest opportunity for development lied with the S_N1-type pathway (*cf*. Scheme 1.87) and we decided to investigate the reaction further in order to develop a concise and facile method to access a variety of β-heteroaryl propionates with varying degrees of α- and β- substitution.

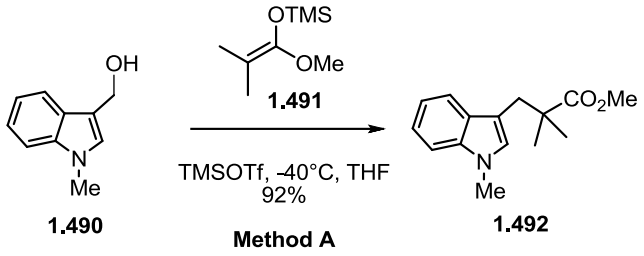
Scheme 1.88



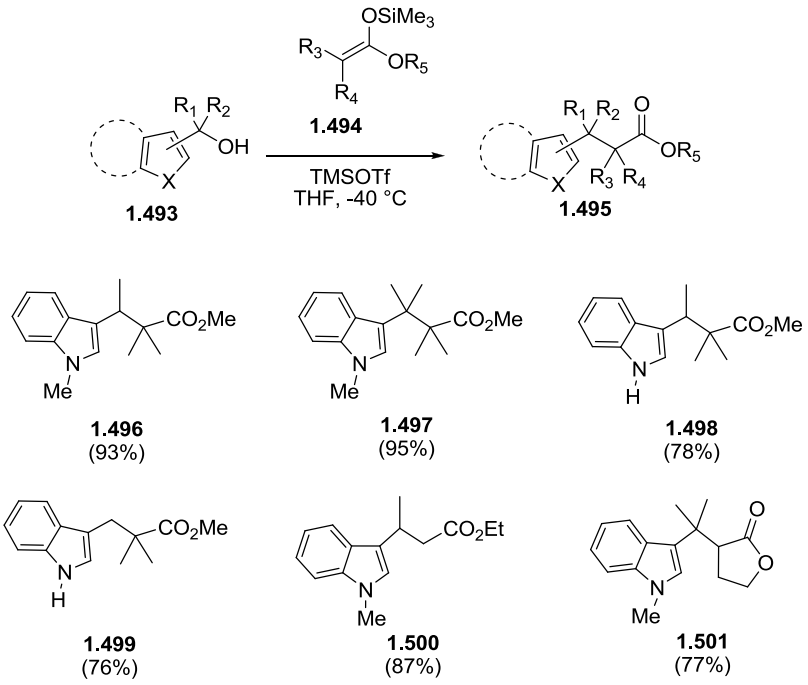
Toward that end, Dr. Tsung-Hao (Bob) Fu, a former Martin group member, expanded the scope of the coupling between **1.490** and **1.491** by examining the reactivity of other 3-indolyl carbinols with various silyl ketene acetals in the Lewis acid-catalyzed reaction. Tsung-Hao first examined the reaction of the alcohol **1.490** with the silyl ketene

acetal **1.491** under a variety of conditions to furnish ester **1.492**, eventually finding that the reaction proceeded in an optimized yield of 92% using THF as the solvent, 0.9 equivalents of trimethylsilyl trifluoromethanesulfonate (TMSOTf) as the Lewis acid, and a reaction temperature of -40 °C (Scheme 1.89, Method A). Encouraged by this result, the same conditions were applied to reactions of other 3-indolyl carbinols and π-nucleophiles to explore the scope of the reaction (Scheme 1.90). In general, the yields for primary, secondary, and tertiary hydroxy indoles were comparable, and the reactions involving *N*-methyl indoles were higher yielding than were their *N*-H analogues. It is also important to note that Tsung-Hao was able to achieve the formation of two contiguous quaternary centers in one transformation **1.497**, which was one of the major limitations of the EAS pathway in Scheme 1.[105]

Scheme 1.89

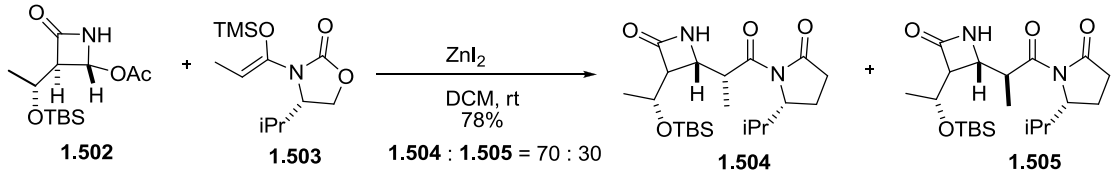


Scheme 1.90

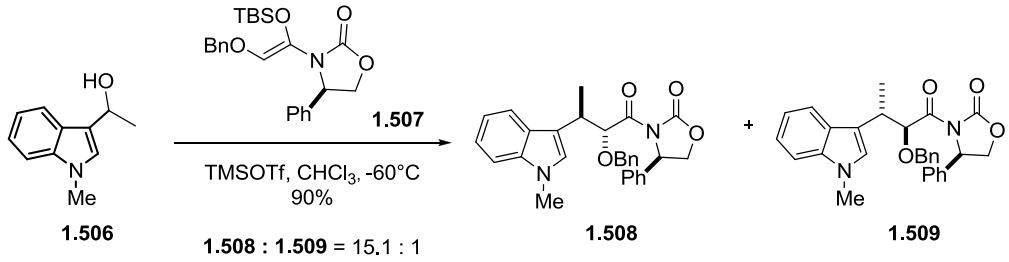


Having established that the reaction worked well with various combinations of indol-3-yl carbinols and achiral nucleophiles, it was a natural extension of the methodology to see if a diastereoselective version of the reaction was feasible. In order to achieve this goal, Tsung-Hao explored the use of a chiral oxazolidinone on a π-nucleophile. This type of reaction had been precedented by Fuentes and co-workers, who reacted the chiral silyl ketene N,O-acetal **1.503** with the *N*-acyl iminium ion generated from β-lactam **1.502,** to provide **1.504** and **1.505** in moderate diastereoselectivity (Scheme 1.91).[106] Tsung-Hao reacted alcohol **1.506** with chiral π-nucleophile **1.507** to give a mixture of **1.508** and **1.509** (15.1:1) in 90% yield, of which **1.502** was isolated as the major product (Scheme 1.92).[105,107]

Scheme 1.91



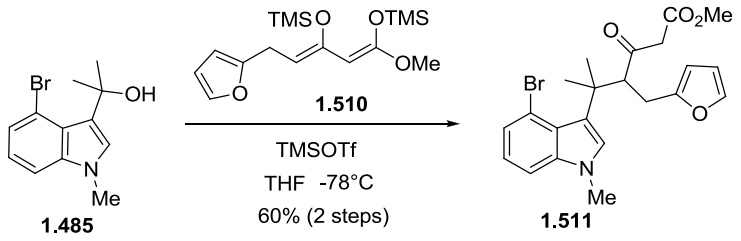
Scheme 1.92



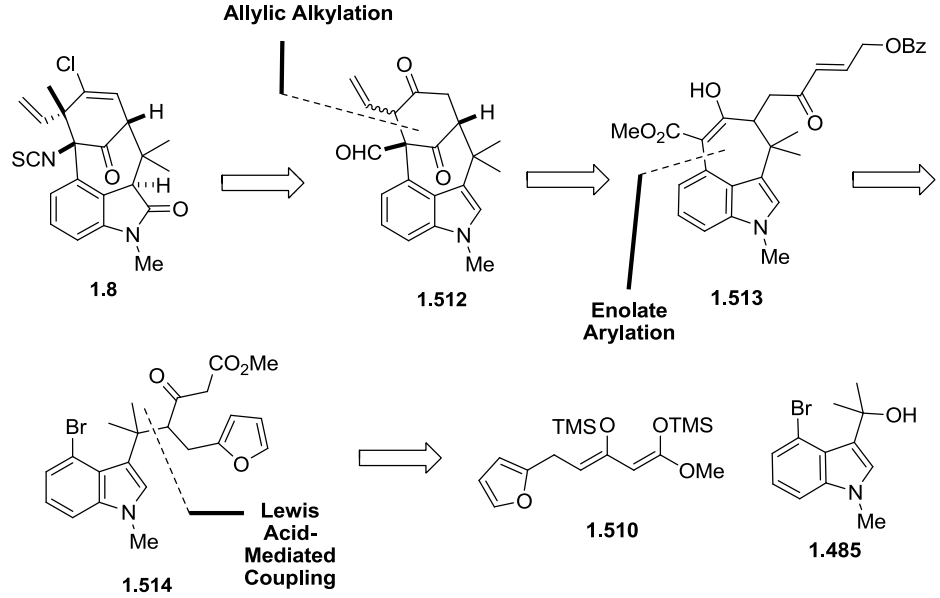
The efficient synthesis of **1.508** is noteworthy because it illustrates the versatility of the S_N1 pathway (*cf.* Scheme 1.87) and its potential for the enantioselective preparation of β-heteroaryl-α-hydroxy propionates, which like β-heteroaryl propionates, are important structural subunits of many natural products and their precursors.[108,109]

The utility of this method was further reinforced by the completion of a formal synthesis of *N*-methylwelwitindolinone C isothiocyanate (**1.8**) by Tsung Hao (Scheme 1.93).[6] One of the key features of the synthesis was the TMSOTf mediated reaction between vinylogous silyl ketene acetal **1.510** and 3-indolyl carbinol **1.485** to provide the highly functionalized β,β-disubstituted, β-heteroaryl ketone **1.511** in 60% yield. Ketone **1.511** was further elaborated to welwistatin (**1.8**) through a series of steps including an enolate arylation, and allylic alkylation (Scheme 1.94).

Scheme 1.93



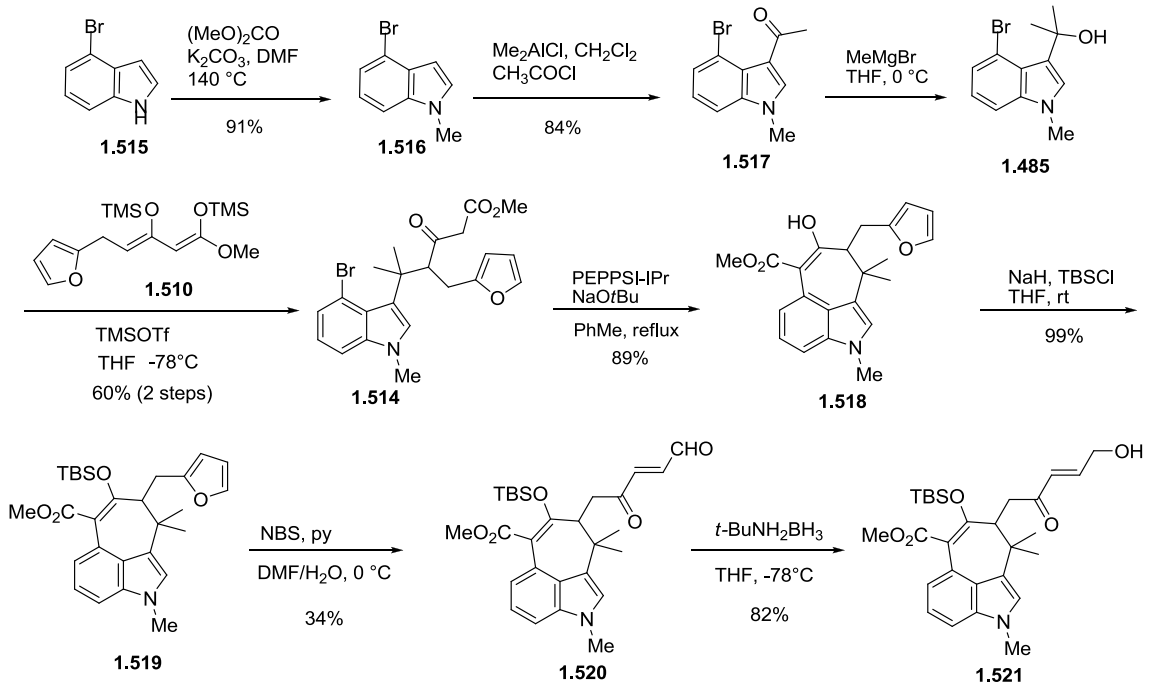
Scheme 1.94



Commercially available 4-bromoindole (**1.515**) was first *N*-methylated and then acylated to provide **1.516** (Scheme 1.95).[6] Ketone **1.517** was alkylated using methyl magnesium bromide (MeMgBr) to furnish tertiary alcohol **1.485**, which was immediately subjected to a Lewis acid-mediated coupling reaction with **1.510** to furnish **1.514** in 60% yield over two steps. A Pd (0) catalyzed intramolecular enolate arylation of aryl bromide **1.514** was promoted by the PEPPSI-IPr catalyst in the presence of sodium *tert*-butoxide (NaO*t*-Bu) to provide tricycle **1.518**. Silyl protection of the enol, followed by oxidative

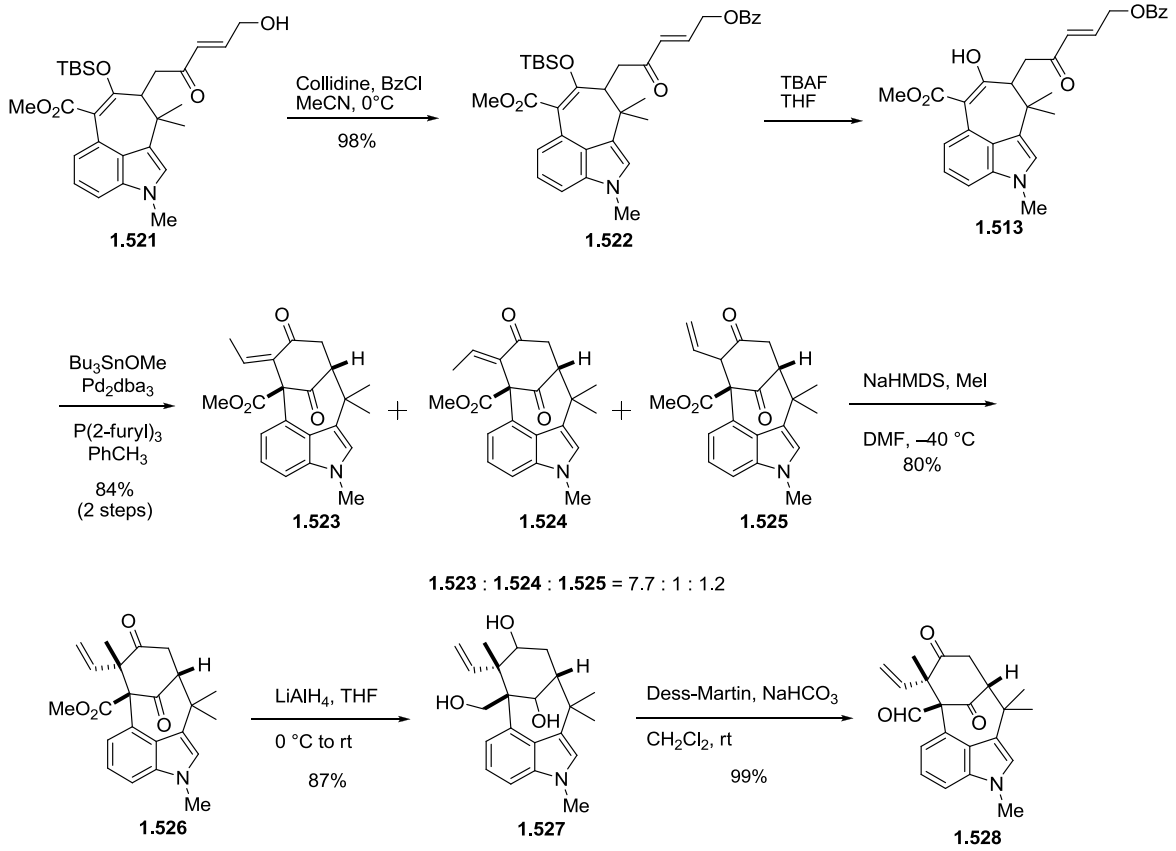
rearrangement of the furan ring with *N*-bromosuccinimide (NBS), and selective reduction of the resulting ketone with borane provided allyl alcohol **1.521**.

Scheme 1.95



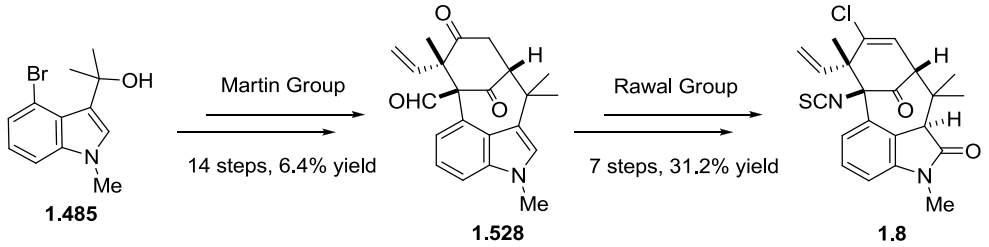
After protection of allyl alcohol **1.521**, enol **1.513** was unmasked, and treated directly with Bu_3SnOMe, Pd_2dba_3, and trifurylphosphine [P(2-furyl)$_3$] to deliver a mixture (7.7:1:1.2) of enones **1.523** and **1.524** and vinyl ketone **1.525** (Scheme 1.96).[6] When the mixture of **1.523**-**1.525** was deprotonated with NaHMDS, the thus dienolate generated was captured with MeI to provide tetracycle **1.526** as a single diastereomer. A two step sequence involving the global reduction and oxidation of the carbonyl moieties of **1.526** then provided the intermediate aldehyde **1.528** over 14 steps from bromoindole **1.515** in 6.4% yield.

Scheme 1.96



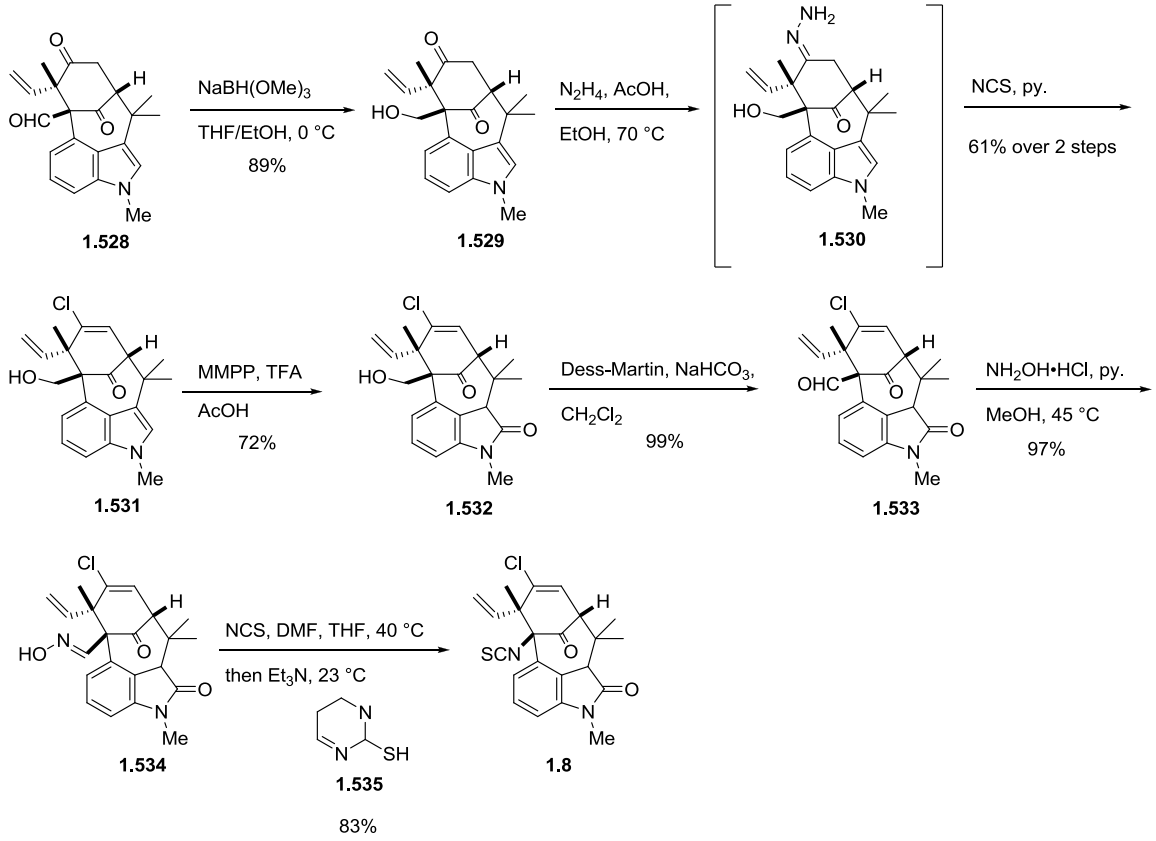
Contemporaneous to the efforts of the Martin group, Rawal and coworkers published a total synthesis of *N*-methylwelwitindolinone C isothiocyanate (**1.8**) featuring common intermediate **1.528** (Scheme 1.96).[101] While our synthesis towards **1.528** was three steps shorter than Rawal's, his route toward **1.528** was slightly higher yielding (7.2%).[100] We independently tried to synthesize **1.8** from **1.526** and **1.528**, but we were unsuccessful in our attempts to install the vinyl chloride moiety. We then decided to exploit an opportunity to complete a formal synthesis of *N*-methylwelwitindolinone C isothiocyanate (**1.8**), using Rawal's endgame strategy.

Scheme 1.97



Rawal first reduced aldehyde **1.528** to alcohol **1.529**, and then hydrazone formation followed by chlorination using *N*-chlorosuccinimide provided vinyl chloride **1.531** in 60% yield over two steps (Scheme 1.98).[101] Oxidation of indole **1.531** with magnesium monoperoxyphthalate (MMPP) followed by treatment with Dess-Martin periodinane then furnished oxindole **1.532**. Condensation of **1.533** with hydroxylamine produced oxime **1.534** which then underwent a modified Kim oxime rearrangement[101,110,111] to provide *N*-methylwelwitindolinone C isothiocyanate (**1.8**) in seven steps and 31.2% yield from **1.528**.

Scheme 1.98



1.7 SUMMARY OF PREVIOUS MARTIN GROUP WORK

Tsung-Hao had developed a good route toward β-indol-3-yl propionates, but we desired a more general method to obtain all types of α,α,β,β-substituted heteroaryl propionates. In order to expand this methodology beyond the use of indol-3-yl carbinols, a broader array of heterocycles, including indol-2-yl carbinols, were envisioned as potential substrates. If successful, the reactions of these carbinols would further illustrate the versatility of the S_N1 pathway in Scheme 1.1, because it would enable C-C bond formation at site not accessible through the use of Friedel-Crafts chemistry. Recall that there were no known examples of indol-2-yl propionates being prepared through S_N1-

type reactions (*cf.* Section 1.4), though Natsume did report some examples in which a indol-4-yl carbinols underwent reactions with silyl enol ethers to produce substituted indol-4-yl ketones (*cf.* Scheme 1.82).[83] Examples of indol-2-yl propionates prepared using EAS-type reactions were special cases that required the use of 3-substituted indoles, heterocyclic organometallics, or in the case of Evans,[64] dihydroindoles (*cf.* Scheme 1.51), as nucleophilic partners (Section 1.3). Furthermore, the indol-2-yl propionates and ketones products obtained from the EAS pathway were limited in two major ways. The first was that the the indol-2-yl adducts were more likely to be ketones, as opposed to esters, because ketones are more electrophilic, and hence, more reactive partners in Michael additions. Thus, extra steps would be required if we wanted to obtain indol-2-yl propionates. The second limitation was that α-substitution on the electrophilic enones or acrylates was not well tolerated in the conjugate additions, with α,α-disubstituted indol-2-yl propionates seemingly inaccessible through this route. We believed that our approach would be able to overcome many of these problems to provide highly substituted α,α,β,β-substituted indol-2-yl propionates in a single transformation if Tsung-Hao's originally reactions could be generalized. Ideally, the conditions would also be used in S_N1-type reactions with other heterocycles, such as furan, pyrrole, and thiophene.

We also sought to elucidate the scope and limitations of the π-nucleophile in our ionization reactions. As already discussed, most of the EAS examples required the use of α,β-unsaturated enones or enals as electrophilic coupling partners, which would provide β-heteroaryl ketones and aldehydes as opposed to β-heteroaryl propionates (*cf.* Section 1.3). Moreover, if an enantioselective reaction were desired, then the electrophilic

coupling partner is further limited to include either two Lewis basic sites to accommodate bidentate metallic catalysts or an enal that can form chiral iminium ions (*cf.* Sections 1.3.2.3 and 1.3.3). The S_N1 pathway is more amenable to the direct production of β-heteroaryl propionates; however, far less work has been done in the area, and the scope of this process appears to be limited to a few combinations of heteroaryls and π-nucleophiles (*cf.* Section 1.4). The π-nucleophiles also tended to be heterocycles themselves, rather than more versatile silyl enol ethers or silyl ketene acetals that could be used to provide access to a larger array of β-heterocyclic scaffolds. Tsung-Hao had undertaken an initial survey of π-nucleophiles, including those with α-substituents and those that were cyclic, acyclic, and vinylogous, but most of the nucleophiles were silyl ketene acetals, and he had only examined them on one indol-3-yl system (*cf.* Section 1.6). We desired to test Tsung-Hao's original π-nucleophiles, among others, with a variety of heterocyclic carbinols in the ionization reaction to see how the results compared to the indol-3-yl system.

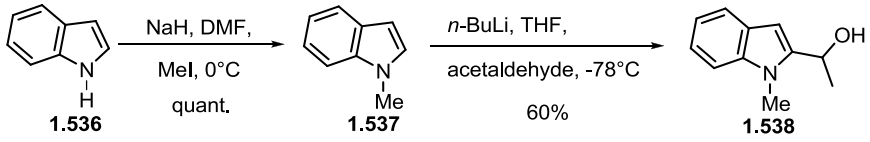
There were only two enantioselective examples of S_N1-type ionizations in the literature and that they demonstrated proof of principle more than synthetic utility (*cf.* Section 1.4.5). Both examples were undertaken with 2-methylindol-3-yl systems and the methyl substituent at the 2-position of the indoles was necessary for interaction with the catalyst to induce enantioselectivity during the reactions.[102,103] Tsung-Hao was able to affect a diastereoselective coupling with his indol-3-yl system when a chiral oxazoldinone was appended to the attacking π-nucleophile, but he had only examined a single example (*cf.* Scheme 1.92). We sought to expand upon Tsung-Hao's initial

diastereoselective work, and ideally, develop our own enantioselective catalyst for the ionization as it was evident that there was room for improvement within the field.

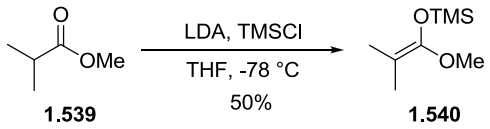
1.8 Expanding the Martin Group Methodology to Include Indol-2-yl Carbinols

The first systems we examined in our S_N1-type ionization reactions were 2-substituted indole carbinols (*cf.* Section 1.7). Very little work had been done on the indol-2-yl systems, and if successful, the reactions of these carbinols would further illustrate the versatility of the S_N1 pathway outlined in Scheme 1.1, because it would enable C-C bond formation at site not accessible through the use of Friedel-Crafts chemistry. Toward that end, we synthesized carbinol **1.538** (Scheme 1.99) and silyl ketene acetal **1.540** (Scheme 1.100) according to known literature procedures.[112-114] Indole (**1.536**) was *N*-methylated using NaH and MeI in DMF to give **1.537**. Deprotonation of **1.537** at the 2-position by *n*-BuLi followed by subsequent addition of acetaldehyde, produced carbinol **1.538** in 60% yield. Enolization of methyl isobutyrate (**1.539**) in the presence of TMSCl provided silyl ketene acetal **1.540**.

Scheme 1.99

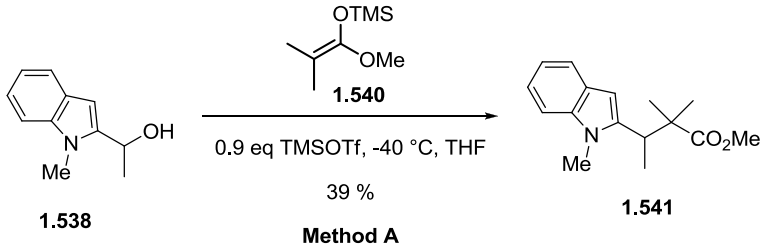


Scheme 1.100



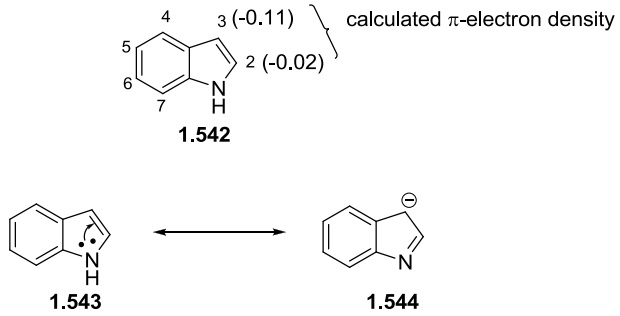
We began our investigations by applying Tsung-Hao's optimized conditions (Scheme 1.100, Method A) to alcohol **1.533**, resulting in a 39% yield of propionate **1.535**. While the result of the reaction was disappointing, it was not entirely unexpected. Alcohol **1.533** is in a more difficult position on the indole to ionize compared to the indol-3-yl carbinol (Scheme 1.101).[115]

Scheme 1.101



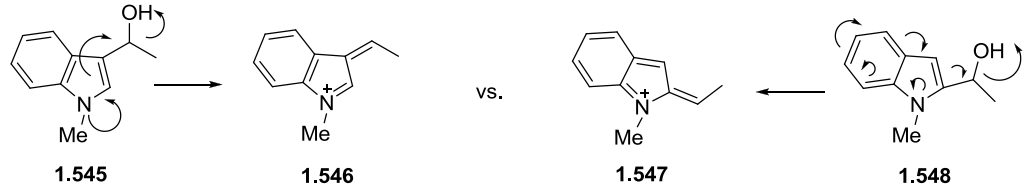
It is a long standing and well established fact that the 3-position of indole (**1.542**) is more reactive towards electrophilic aromatic substitution than the 2-position (Scheme 1.102).[115] This increased reactivity can be explained by the larger amount of π-electron density that is present on the C3 vs. C2 of indole, which has been proven from both empirical experimentation and molecular orbital calculations.[115,116] The electrons of the weakly basic nitrogen atoms readily delocalize into the pi system to adopt resonance structure **1.544** that can readily react with electrophiles to promote alkylation at the C3 position.[115]

Scheme 1.102



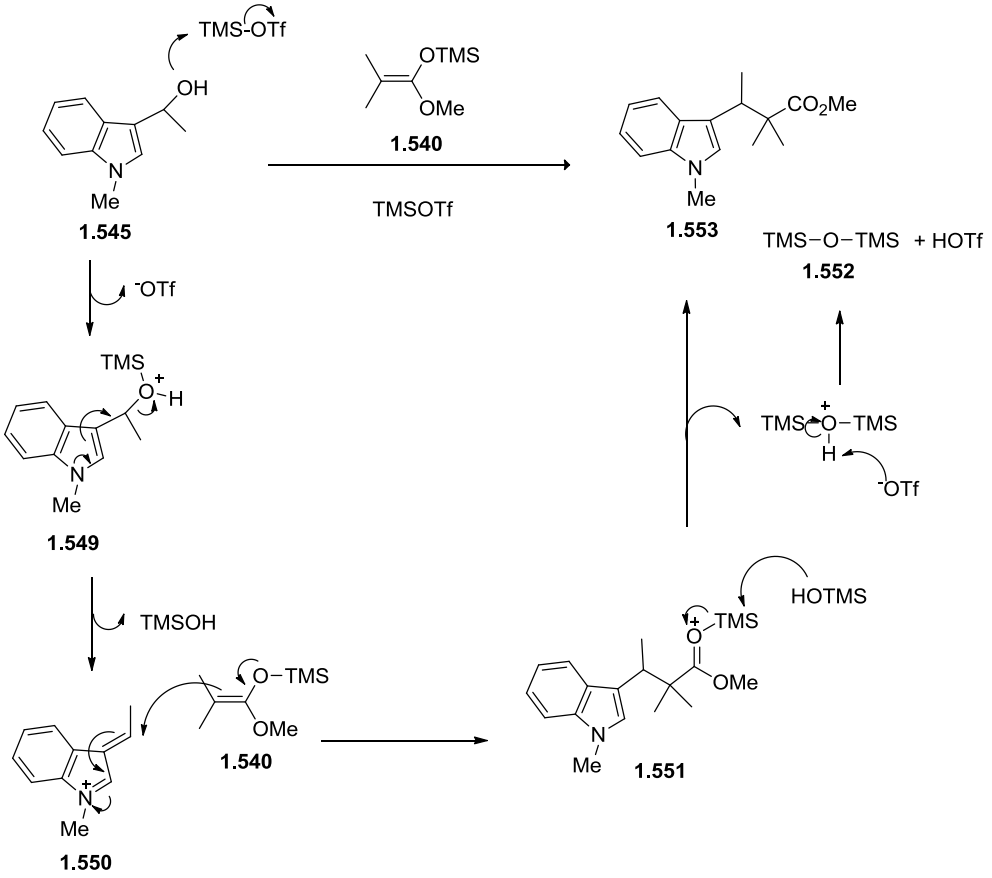
Though our method uses heterocyclic carbinols as electrophiles, the extra density at the C3 carbon of indole helps to stabilize the cation formed upon ionization of the indol-3-yl carbinol **1.545** with TMSOTf (Scheme 1.103). We can show this extra stabilization by depicting the heterobenzylic cation of **1.545** as the extended iminium ion **1.546**.[115] However, an extended resonance form can also be drawn from the cation formed upon ionization of 2-indolyl carbinol **1.548**, namely the extended iminium ion **1.547**. When the structures of both extended iminium ions are compared, we can see why indol-3-yl carbinols are more easily ionized than indol-2-yl carbinols. To achieve the cation stabilization of **1.546**, the aromaticity of the benzene moiety of indole is left wholly intact, whereas to achieve the cation stabilization of **1.548** the aromaticity of the entire indole ring must be disrupted.[115] Though both **1.546** and **1.548** can be stabilized through π-interactions, formation of **1.546** is both thermodynamically and kinetically more favorable. Its formation causes less of an energetic penalty and which results in faster and more facile ionization of indol-3-yl carbinols vs. indol-2-yl carbinols.[115]

Scheme 1.103



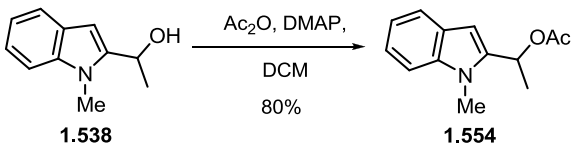
Once ionization of **1.545** had occurred, we speculated that a suitable π-nucleophile, in this case silyl ketene acetal **1.540**, underwent reaction in the presence of TMSOTF to provide adduct **1.550** and silanol (Scheme 1.104). Upon loss of the TMS group, the desired β-heteroaryl propionate **1.553** can be formed along with by-products TMS ether **1.552** and triflic acid (TfOH).

Scheme 1.104



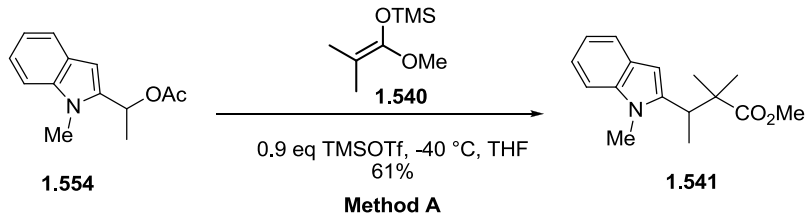
Realizing the problematic step in the reaction of silyl ketene acetal **1.540** with 2-indolyl carbinol **1.538** was most likely the ionization event, we sought to increase the reactivity of the alcohol by increasing its leaving group ability. Thus, acetate **1.554** was prepared according to a known literature procedure from carbinol **1.538** (Scheme 1.105).[113]

Scheme 1.105



When acetate **1.554** underwent reaction with **1.540** using Tsung-Hao's reaction conditions, we were gratified to find that propionate **1.541** was formed in 61% yield (Scheme 1.106). The addition of the acetyl group seemingly facilitated the ionization reaction; however, we still thought that there was room for improvement.

Scheme 1.106

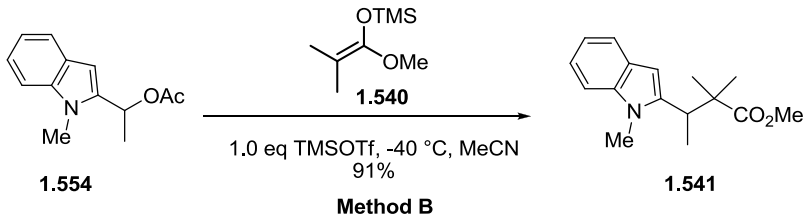


We conducted the reaction between acetate **1.554** and/or alcohol **1.538** and silyl ketene acetal **1.540** using a series of different temperatures, solvents, stoichiometries, and Lewis acids (Scheme 1.107). Of the five Lewis acids screened, TMSOTf and $Yb(OTf)_3$ were the only two that produced the desired propionates, though $Yb(OTf)_3$ provided lower yields of **1.541** than TMSOTf, presumably due to its insolubility in many of the solvents screened. The rest of the Lewis acids provided either returned starting material or decomposition product, so we decided to continue using TMSOTf as our ionization promoter.

After extensive optimization of the reaction temperature, stoichiometry, and solvent we found that the reaction generally gave the best results at lower temperatures and in polar solvents when TMSOTf was used as a Lewis acid promoter (Scheme 1.107). Presumably the polar solvents facilitated formation of the intermediate cation, and TMSOTf was more stable when kept at lower temperatures. When acetate **1.554** was treated with stoichiometric TMSOTf in acetonitrile at -40 °C in the presence of a slight

excess of silyl ketene acetal **1.540** (1.5 eq) (Method B), we were extremely gratified to find that propionate **1.541** was formed in 91% yield. These optimized conditions were later applied to alcohol **1.538**, resulting in 69% yield of **1.541**, thereby underscoring the superiority of the acetate **1.554** as a substrate (Scheme 1.108).

Scheme 1.107

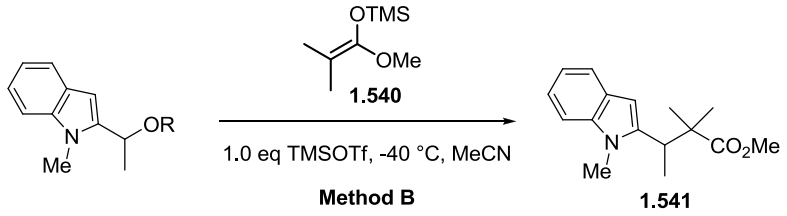


Solvents: MeCN, DCM, THF, Et_2O, DMF, PhMe

Temperatures: -78 °C, -40 °C, 0 °C, rt

Lewis Acids: TMSOTf, $AlMe_3$, $Mg(ClO_4)_2$, $SnCl_4$, $Yb(OTf)_3$

Scheme 1.108



1.538: R = H — 69%

1.554: R = Ac — 91%

Secondary acetate **1.554** also underwent reactions with π-nucleophiles **1.555** and **1.556** when treated with stoichiometric TMSOTf (Scheme 1.109). Reaction of acetate **1.554** with α-unsubstituted TBS protected silyl ketene acetal **1.555**[117] provided the β-substituted propionate **1.558** in 68% yield, whereas the reaction of **1.554** with vinylogous

α,β,γ,δ-unsaturated silyl ketene acetal **1.556**[118,119] provided enoate **1.559** in 47% yield as a single regioisomer. *O*-Silylated dienolates are known to undergo γ–regioselective addition to carbonyl compounds, presumably due to steric bulk of the *O*-silyl group which creates significant hindrance near the α-carbon of the nucleophile.[120,121] The relative stereochemistry of the double bond of enoate **1.559** was not established unequivocally, but NOE studies supported structure **1.559** (as opposed to **1.560**) (Figure 1.2). Namely, we observed an NOE interaction between the vinylic proton H_a and protons H_b of structure **1.559** but not between the vinylic proton H_a and the protons of the vinyl methyl group of **1.560**.

Scheme 1.109

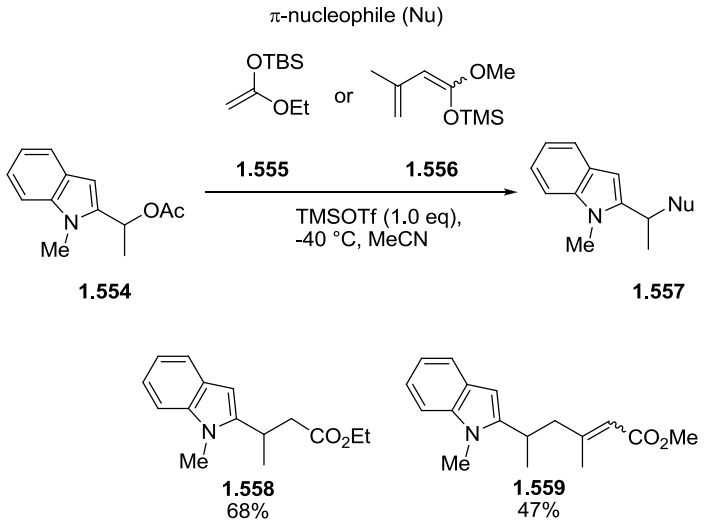
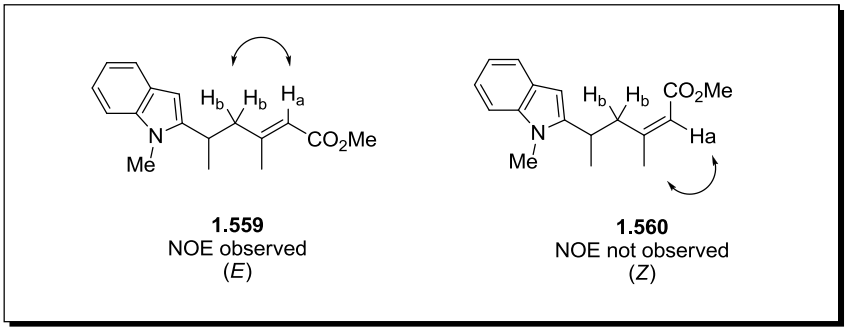
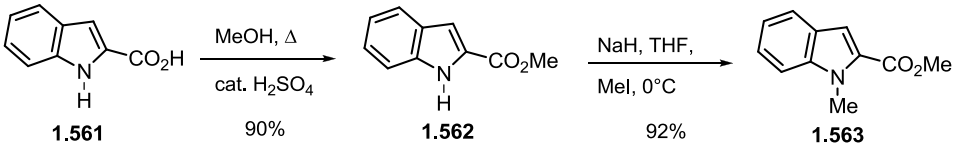


Figure 1.2

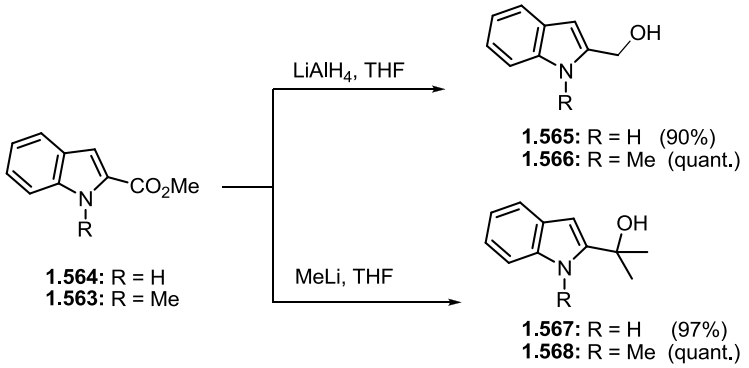


Pleased with the results of our TMSOTf mediated ionizations of secondary indol-2-yl acetate **5.554** in the presence of a variety of silyl ketene acetals, we sought to use primary and tertiary indol-2-yl carbinols and/or acetates as electrophilic partners in the ionization reactions. Toward that end, primary and tertiary indol-2-yl carbinols **1.565-1.568** were synthesized from commercially available 1H-indole-2-carboxylic acid (**1.561**) according to known literature procedures (Schemes 1.110 and 1.111).[122-126] Depending on whether *N*-H or *N*-Me indoles were desired, *N*-H compound **1.562** could be methylated using NaH and MeI to provide **1.563** in 92% yield (Scheme 1.110). Primary indol-2-yl carbinols **1.565** and **1.566** were prepared from treatment of indol-2-yl esters **1.564** and **1.563** with lithium aluminum hydride ($LiAlH_4$), while tertiary indol-2-yl carbinols **1.567** and **1.568** were prepared from indol-2-yl esters **1.564** and **1.563** through reaction with excess methyllithium (MeLi) (Scheme 1.111).

Scheme 1.110

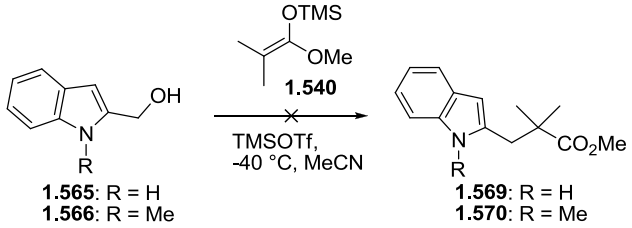


Scheme 1.111

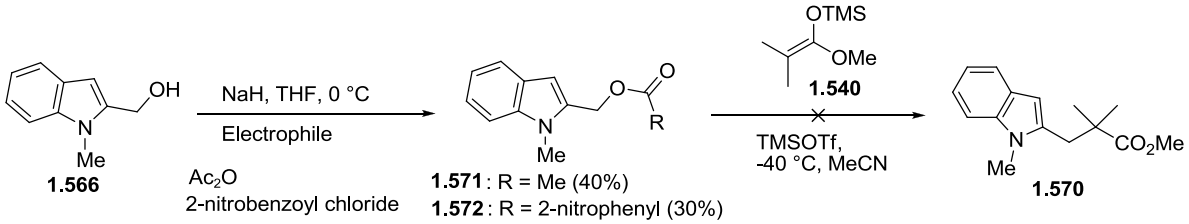


Unfortunately, the reactions of the primary alcohols **1.565** and **1.566** with silyl ketene acetal **1.540** produced no isolable quantities of desired propionates **1.569** or **1.570** (Scheme 1.112). Realizing that primary indol-2-yl systems were less capable of stabilizing a carbocation than secondary indol-2-yl systems, we sought to increase the leaving group ability of the primary carbinols as we had done previously with secondary indol-2-yl carbinol **1.538** (*cf.* Scheme 1.105). Towards that end esters **1.571** and **1.572** were synthesized.[127] However, we were disappointed to find that neither **1.571** nor **1.572** reacted with TMSOTf in the presence of π-nucleophile **1.540** to produce propionate **1.570** (Scheme 1.113). While we were saddened at the failure of our reactions, we decided that our time was better spent investigating propionates that were seemingly inaccessible through the EAS pathway, namely α,α,β,β-substituted heteroaryl propionates, than trying to optimize the reaction between primary indol-2-yl carbinols and π-nucleophiles. Thus, we turned our attention towards tertiary indol-2-yl carbinols.

Scheme 1.112

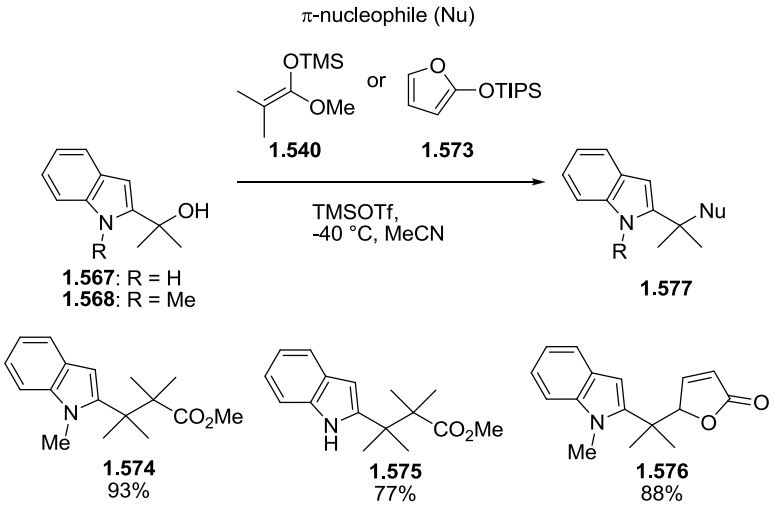


Scheme 1.113



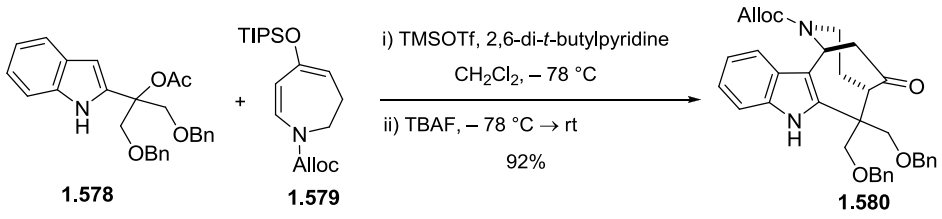
When treated with stoichiometric amounts of TMSOTf in the presence of silyl ketene acetal **1.540**, tertiary indol-2-yl carbinols provided α,α,β,β-tetrasubstituted propionates **1.575** and **1.574** in 77% and 93% yield, respectively (Scheme 1.114). *N*-Methyl Carbinol **1.568** was a superior electrophile in the reaction as compared to **1.557**, presumably due to the extra electron density that the methyl group provided to stabilize the intermediate benzylic cation (*cf*. Schemes 1.102 and 1.103). Indole **1.568** was also shown to couple successfully with cyclic TIPS furan acetal **1.573**[128] to provide butanoate **1.576** in 88% yield, further underscoring the utility of our method.

Scheme 1.114



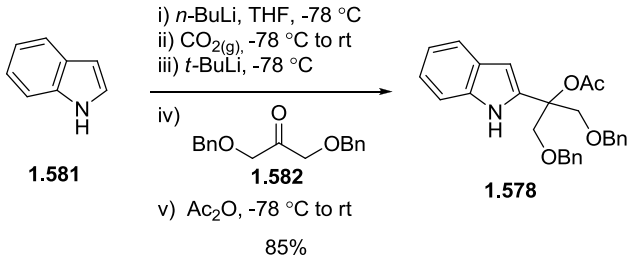
Our work on indol-2-yl propionates enabled the Martin group to complete a novel total synthesis of actinophyllic acid (**1.587**) (Schemes 1.115 - 1.117).[129] The synthesis featured a key TMSOTf mediated coupling between tertiary indol-2-yl acetate **1.578** and silyl enol ether **1.579**, followed by an intramolecular addition to provide the complex tricyclic intermediate **1.580** in 92% yield in a single step (Scheme 1.115).

Scheme 1.115

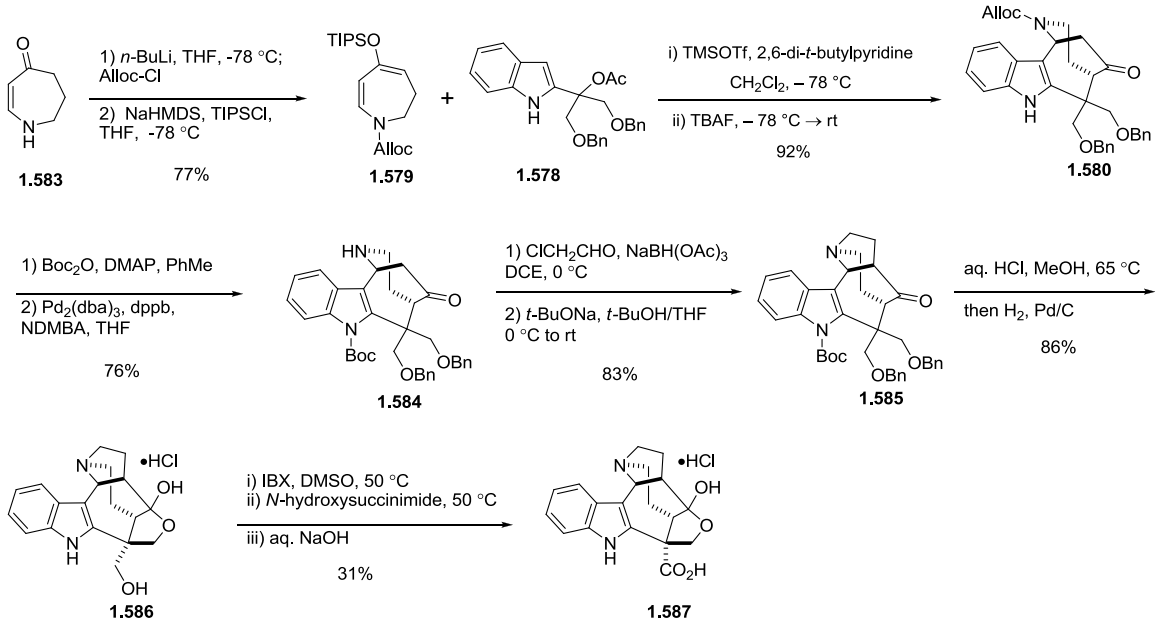


Tertiary indol-2-yl acetate **1.578** was obtained in 85% yield from indole (**1.581**) through a carboxylate directed lithiation/acylation sequence (Scheme 1.116) and dihydroazepinone **1.579** was accessed from known hydroazepinone **1.583** in 77% yield over two steps (Scheme 1.117).[129]

Scheme 1.116



Scheme 1.117



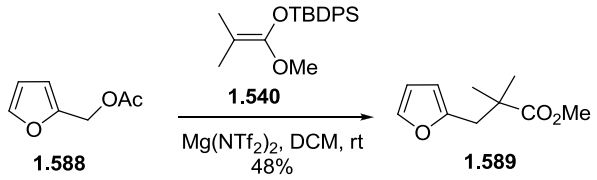
After the key S_N1-type ionization reaction between carbinol **1.578** and π-nucleophile **1.579**, protection of the indole nitrogen and Pd (0) catalyzed removal of the Alloc group in the presence of *N,N*-dimethylbarbituric acid (NDMBA) provided tetracycle **1.584** (Scheme 1.117).[129] The secondary amine of **1.584** was reductively alkylated with 2-chloroacetaldehyde ($ClCH_2CHO$) and then enolate formation using *t*-BuONa induced an intramolecular ring closing reaction to provide pyrrolidine **1.585**.

The Boc and benzyl ether protecting groups of pentacycle **1.585** were removed, and the resulting diol spontaneously cyclized to provide lactol **1.586**, the structure of which was confirmed by single crystal X-ray analysis. Oxidation of lactol **1.586** provided the hydrochloride salt of actinophyllic acid (**1.587**) in 10.1% yield only ten steps.

1.9 S_N1-TYPE IONIZATION REACTIONS INVOLVING FURANYL CARBINOLS

The reaction between primary furanyl acetate **1.588** and silyl ketene acetal **1.540** had been reported by Grieco prior to our investigations, but the yield of ester **1.589** was only 48% (Scheme 1.118).[78] Obviously there was room for improvement, and we believed that our method might be able to improve upon his results.

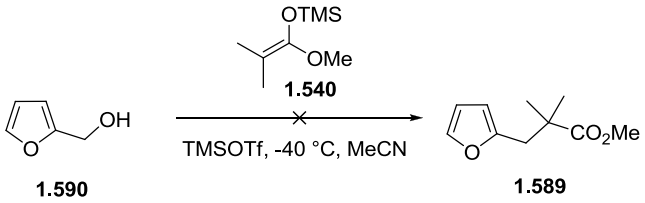
Scheme 1.118



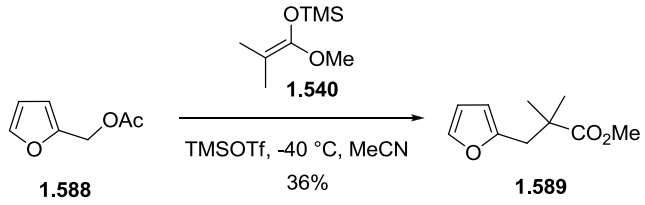
We explored the TMSOTf mediated ionization reaction between primary furan-2-yl carbinol **1.590** and π-nucleophile **1.540**, but we did not see formation of the desired propionate **1.589** (Scheme 1.119). Indeed, the reaction appeared to provide only decomposition products. We then treated acetate **1.588**, the same electrophile that Grieco used, with stoichiometric TMSOTf in the presence of silyl ketene acetal **1.540**, and we found that propionate **1.589** was produced in 36% yield (Scheme 1.120). After numerous attempts to optimize the reaction by changing the solvent, temperature, rate of addition, length, and stoichiometry of the reagents of the reaction, we were unable to improve the yield of propionate **1.589**. We suspected that either acetate **1.588** and/or propionate

1.589 were unstable to the reaction conditions. Furans are known to be unstable in strongly acidic conditions, and if any adventitious water were present in the reaction then triflic acid was likely being generated as a byproduct. Our hypothesis was seemingly confirmed when we independently subjected carbinol **1.588** and propionate **1.589** to the reaction conditions in the absence of a π-nucleophile and found that in both cases significant decomposition had occurred. Adding a proton sponge, such as 2,6-di-*tert*-butylpyridine, to the reaction did not improve the yield. We also tried the addition of 4 Å molecular sieves to remove any adventitious water that might be present, but they also failed to improve the yields of **1.589**.

Scheme 1.119



Scheme 1.120

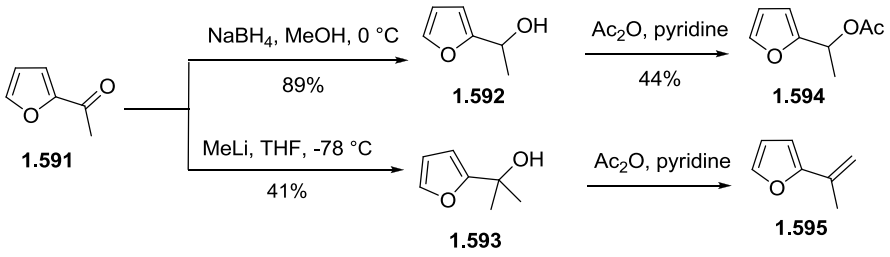


Grieco utilized magnesium triflimide $Mg(NTf_2)_2$ as the Lewis acid for his coupling reaction, touting it as a safe alternative to magnesium perchlorate.[78] However, $Mg(NTf_2)_2$ is not commercially available, so we prepared it[130] and investigated its use a possible replacement for TMSOTf in the acid sensitive furanyl S_N1-type ionization reactions. While we were able to replicate Grieco's original results, namely the reaction

between acetate **1.588** and π-nucleophile **1.540**, we could not improve upon his yield. We even investigated the use of hexafluoroisopropanol (HFIP) as both solvent and Lewis acid for the coupling, but π-nucleophile **1.540** had only a half-life of minutes in HFIP so that approach was quickly abandoned.[131] When we tried to promote indol-2-yl carbinols ionizations with $Mg(NTf_2)_2$, we did not observe any of our desired propionates (*cf.* Section 1.8). Although the $Mg(NTf_2)_2$ mediated reaction between **1.588** and **1.540** provided furan-2-yl propionate **1.589** in a 10% higher yield than did the reaction mediated by TMSOTf, it appeared that TMSOTf would be the more suitable Lewis acid for the development of a general method towards β-heteroaryl propionates.

We then synthesized the secondary and tertiary furan-2-yl carbinols **1.592**[84] and **1.593** respectively, from commercially available 2-acetyl furan **1.591**, via the addition of either $NaBH_4$ or MeLi (Scheme 1.121). Acetylation of **1.592** with acetic anhydride in the presence of pyridine then provided acetal **1.594**.[132] Attempted acetylation of the tertiary alcohol **1.593** under the same conditions resulted in sole formation of the elimination product **1.595**.

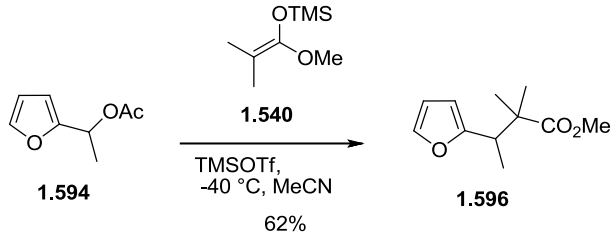
Scheme 1.121



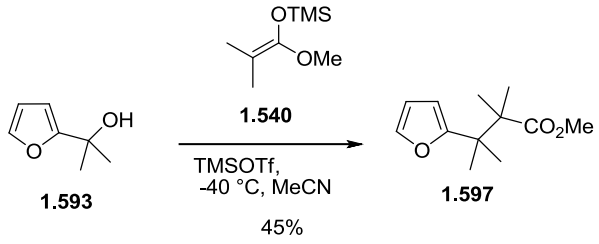
The reaction of secondary acetate **1.592** and silyl ketene acetal **1.540** worked the best of the furan series to give propionate **1.596** in 62% yield, while the reaction of secondary carbinol **1.592** and **1.540** resulted in decomposition (Scheme 1.122).

Treatment of tertiary furan-2-yl carbinol **1.593** with TMSOTf in the presence silyl ketene acetal **1.540** provided propionate **1.597** in 45% yield (Scheme 1.123). In general, tertiary alcohols worked the best in the reaction of π-nucleophiles with heterocyclic alcohols, but in this case the increased acid sensitivity of the furan may have led to the decreased yield. Carbinols would produce stoichiometric triflic acid in the reaction as compared to acetates, where triflic acid formation would be dependent on the presence of adventitious water (*cf.* Scheme 1.104). With the more robust indole series, this was not a problem, but with the furans and pyrroles acid sensitivity became an issue. Ionizations reactions using secondary acetate **1.594** and tertiary carbinol **1.593** in the presence of 2,6-di-*tert*-butylpyridine, 4 Å molecular sieves, and $Mg(NTf_2)_2$ were also examined, but the yields of propionates **1.596** and **1.597** remained unchanged.

Scheme 1.122



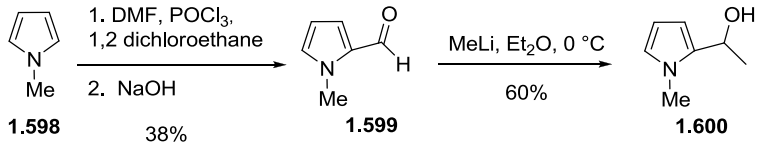
Scheme 1.123



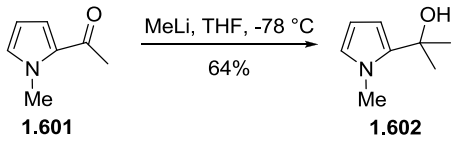
1.10 S_N1-TYPE IONIZATION REACTIONS INVOLVING PYRROLE CARBINOLS

We prepared tertiary pyrrole carbinol **1.602** and secondary pyrrole carbinols **1.600** and **1.605** according to known literature procedures for use as substrates in our TMSOTf mediated coupling reactions (Schemes 1.124 – 1.126).[133-136] Secondary carbinol **1.600** was obtained from *N*-methyl pyrrole (**1.598**) via a Vilsmeier –Haack formylation followed by reaction with methyllithium (Scheme 1.124), while tertiary carbinol **1.602** was obtained from the addition of methyllithium to 2-acetyl pyrrole **1.601** (Scheme 1.125). There were few examples of S_N1-type reactions using heterocycles containing withdrawing groups, so we synthesized **1.605** in order to investigate whether the ionization would proceed (Scheme 1.126).[82,83,137] *N*-Protection of **1.604** with phenylsulfonyl chloride ($PhSO_2Cl$) followed by sodium borohydride ($NaBH_4$) reduction provided secondary carbinol **1.605** (Scheme 1.126).

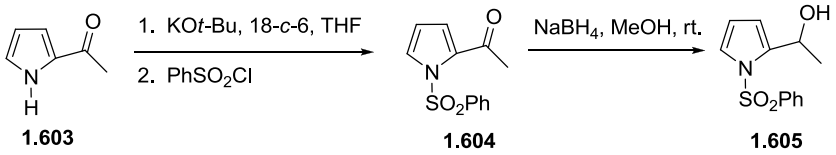
Scheme 1.124



Scheme 1.125

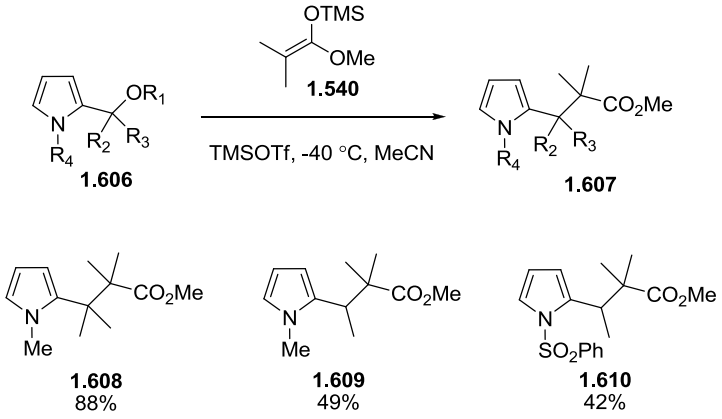


Scheme 1.126



When stoichiometric TMSOTf was used to promote the reaction between secondary carbinol **1.600** and silyl ketene acetal **1.540**, propionate **1.609** was formed in 49% yield (Scheme 1.127). We surmised that the instability of the starting alcohol, which is known to oligomerize at room temperature in as little as one hour, as well as the underlying acid sensitivity of primary and secondary pyrrole carbinols and acetals, most likely contributed to the mediocre results.[133] We varied many of the same reaction variables as we had in the furan series of experiments, but we were unable to increase the yield of **1.609**. The corresponding *N*-methyl secondary acetate was not examined in the reaction because of its known instability.[133]

Scheme 1.127



We also examined the reaction of secondary carbinol **1.605** with TMSOTf in the presence of silyl ketene acetal **1.540** to provide propionate **1.610** in 42% yield (Scheme 1.127). This result showed that the coupling reaction can proceed in reasonable yield with an electron withdrawing group present on the pyrrole nitrogen atom. Although this type of reaction has been precedented to work with electron withdrawing groups on the

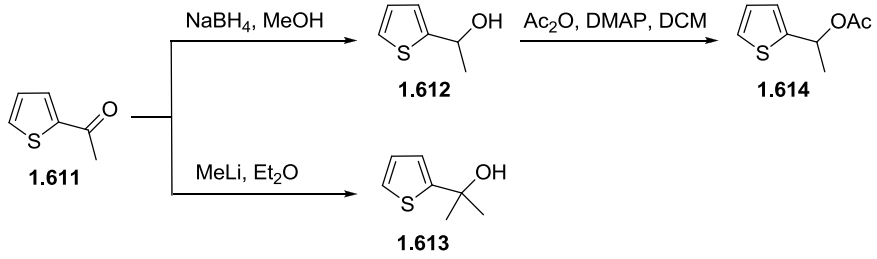
indole nitrogen atom,[82,83,137] this is the first example of using an electron withdrawing group on a pyrrole nitrogen atom.

Tertiary alcohol **1.602** underwent reaction with π-nucleophile **1.540** in the presence of TMSOTf to provide **1.608** in 88% yield (Scheme 1.127). This result underscores the general superiority of tertiary heteroaromatic benzylic carbinols as electrophiles in S_N1-type ionization reactions.

1.11 S_N1-TYPE IONIZATION REACTIONS INVOLVING THIOPHEN-2-YL CARBINOLS

Thiophene derived carbinols **1.612** and **1.613** were synthesized for use as substrates in our TMSOTf mediated ionization reaction (Scheme 1.128). Secondary and tertiary alcohols, **1.612**[84] and **1.613**, respectively, were synthesized in much the same manner as previous heterocyclic alcohols. Namely, $NaBH_4$ or MeLi was added to 2-acetylthiophene (**1.611**) to produce the corresponding secondary **1.612** and tertiary **1.613** alcohols. Secondary alcohol **1.612** was then reacted with acetic anhydride in the presence of DMAP according to standard literature procedure to give acetate **1.614**.[138]

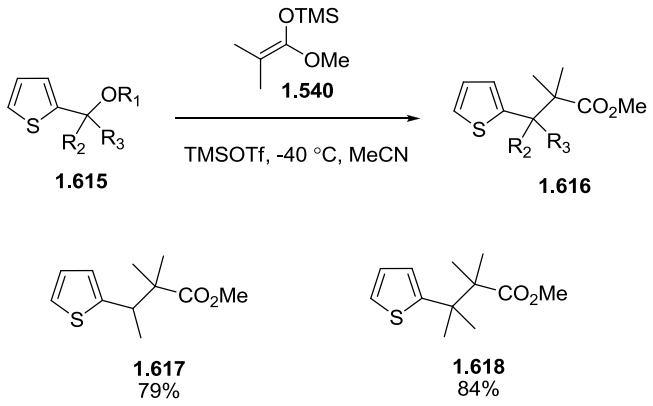
Scheme 1.128



Secondary thiophen-2-yl acetate **1.614** was ionized with a stoichiometric amount of TMSOTf in the presence of silyl ketene acetal **1.540** to provide ester **1.617** in 79%

yield (Scheme 1.129), whereas the same ionization reaction using tertiary thiophen-2-yl carbinol **1.613** provided propionate **1.618** in 84% yield. Secondary thiophen-2-yl carbinol **1.612** was also investigated as an electrophile, but its reaction with **1.540** provided propionate **1.617** in only 50% yield.

Scheme 1.129



1.12 CONCLUSION

In conclusion, we developed and expanded upon Tsung-Hao's original S_N1-type reaction between indol-3-yl carbinols and silyl ketene acetals to create a general method for forming α,α,β,β-tetrasubstituted β-heteroaryl propionates using a variety of different heterocycles. Ten heterocycles, including indol-2-yl, furan-2-yl, pyrrol-2-yl, and thiophen-2-yl carbinols and/or acetates, were found to couple with four different achiral π-nucleophiles, **1.540**, **1.573**, **1.556**, and **1.555**, to provide highly substituted β-heteroaryl propionates in a single step in moderate to excellent yields (42-93%) (Scheme 1.130 and Figures 1.3-1.6). In general, secondary acetates and tertiary alcohols were better substrates than primary carbinols, which either did not work at all or provided poor yields of the desired propionates. The more acid sensitive members of the furan and pyrrole

series (Figures 1.4 and 1.5) also provided lower yields of β-heteroaryl propionates than the indole and thiophene series (Figures 1.3 and 1.6).

Scheme 1.130

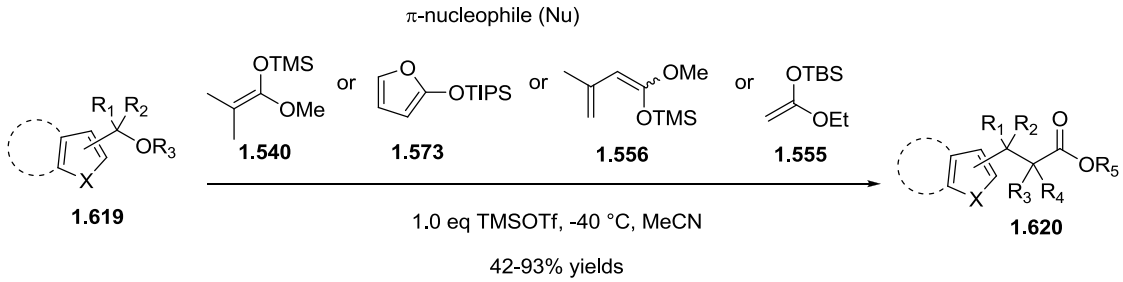


Figure 1.3

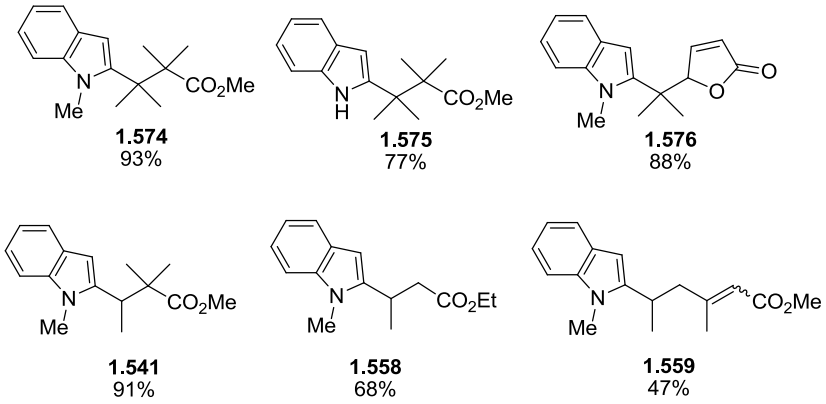


Figure 1.4

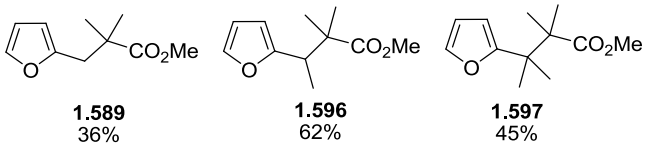


Figure 1.5

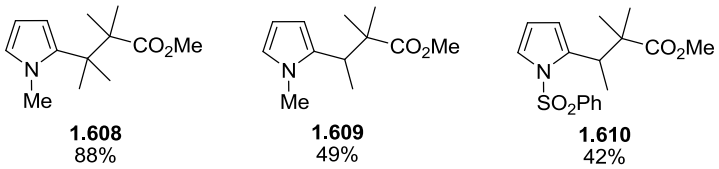
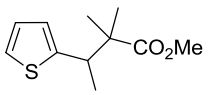
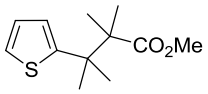


Figure 1.6



1.617
79%



1.618
84%

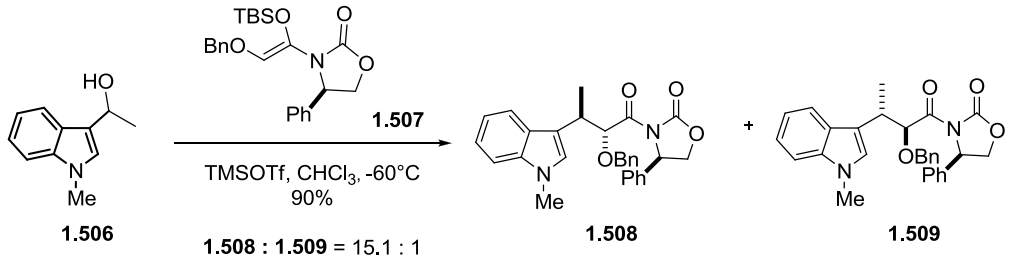
We were very pleased to find that the TMSOTf mediated reaction between tertiary heterocyclic carbinols and α,α-disbstituted silyl ketene acetal **1.540** produced α,α,β,β-tetramethyl β-heteroaryl propionates in high yield, which was a major limitation of earlier EAS and S_N1-type routes. The ability to form contiguous quaternary centers in a single step is a powerful, and often difficult, synthetic transformation,[139] and we were gratified that our method could provide those products with such ease. In fact, the preparation of **1.574** was the first example of an extremely hindered α,α,β,β-tetrasubstituted, β-heteroaryl propionate being formed in a single step (Figure 1.3).

We were also able to achieve high yields of β-heteroaryl propionates from reactions using heterocyclic carbinols that did not follow classical Friedel-Crafts reactivity pathways, such as indoly-2-yl carbinols and acetates (Figure 1.3). Prior to our work, there were very few examples of indol-2-yl propionates in the literature, and of those special cases there were no known examples of indol-2-yl propionates being prepared through S_N1-type reactions (*cf.* Section 1.4). Propionate **1.574** really highlights the best parts of the method, namely, the ability to form contiguous quaternary centers, as well as the ability to overcome traditional Friedel-Crafts reactivity pathways.

While our work has made a valuable contribution to the field, there is still room for improvement. [140,141] We reported the formation of a single diastereoselective propionate from the reaction of indol-3-yl carbinol **1.506** and *N,O*-acetal **1.507** (Scheme

1.131), but extensions of this work would provide a wide variety of diastereoselective α,β-substituted β-heteroaryl propionates. Future work would be focused toward the development of an asymmetric catalyst which we could use to obtain enantioselective β-heteroaryl propionates in a single step. Also, while we showed that vinylogous, α-substituted and unsubstituted, cyclic and acyclic silyl ketene acetals were tolerated in the reaction, future work on the π-nucleophile would be directed toward nucleophiles with α-substituents other than carbon to provide α-hydroxy or α-amino β-heteroaryl propionates.

Scheme 1.131

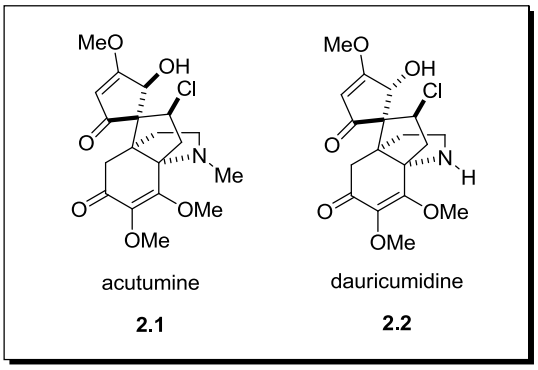


Chapter 2: Acutumine

2.1 INTRODUCTION

The alkaloid acutumine (**2.1**), first isolated from the rhizome of the Asian vine *Menispermum dauricum* in 1929,[142] has long been used in traditional Chinese medicine as an analgesic and antipyretic (Figure 2.1).[143] However, its unique tetracyclic, chlorine-containing structure was not fully elucidated by X-ray crystallography until the late sixties.[144-147] Since that time, acutumine has garnered much interest in the synthetic community because of its moderate, selective inhibition of human T-cell growth (IC_{50} = 13.2 mM).[143] This cytotoxicity could potentially be used as a therapy for T-cell related leukemia and lymphoma.[143] Acutumine and its closely related analogue dauricumidine (**2.2**) have recently been shown to exhibit activity against the hepatitis B virus surface antigen secretion of the Hep G2.2.15 cell line, with IC_{50}'s of 1.415 mM and 0.450 mM, respectively. [148] Acutumine has also been suggested to have anti-amnesiac properties in animal experimental models.[149]

Figure 2.1

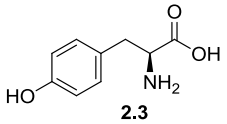


acutumine **2.1** dauricumidine **2.2**

2.2 PROPOSED BIOSYNTHESES

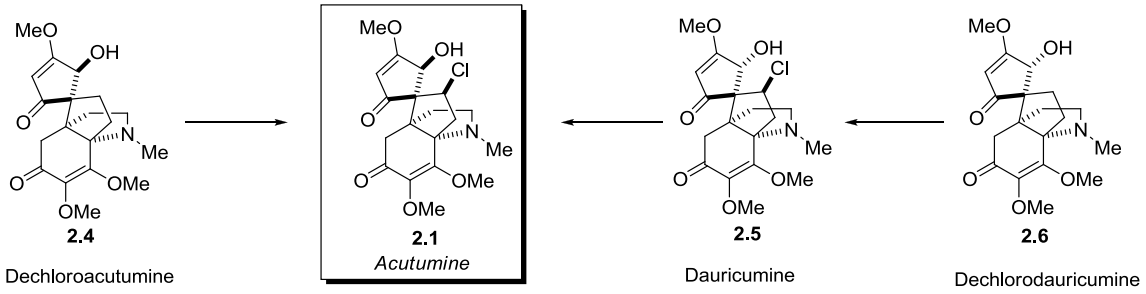
Sugimoto and coworkers (Scheme 2.1) have discovered, through carbon labeling experiments, that acutumine (**2.1**) is derived from two molecules of tyrosine (**2.3**).[150] Sugimoto *et al.* have also shown that the immediate biosynthetic precursors to acutumine (**2.1**) are dechloroacutumine (**2.4**) and its hydroxyl epimer dauricumine (**2.5**), which once chlorinated can epimerize to provide acutumine (**2.1**).[151-153] Also of note, the pathway proceeding from dechlorodauricumine (**2.6**) to actumine (**2.1**) was also found to proceed more successfully as compared to the seemingly more efficient route from dechloroacutumine (**2.4**) to acutumine (**2.1**). While the beginning and end stages of the biosynthesis of acutumine have been elucidated, only hypotheses exist as to the remaining intermediary steps of the process.

Scheme 2.1



2.3

L- [3-^{13}C] tyrosine and *L*-[U-^{14}C] tyrosine incorporated into acutumine



2.4 Dechloroacutumine

2.1 *Acutumine*

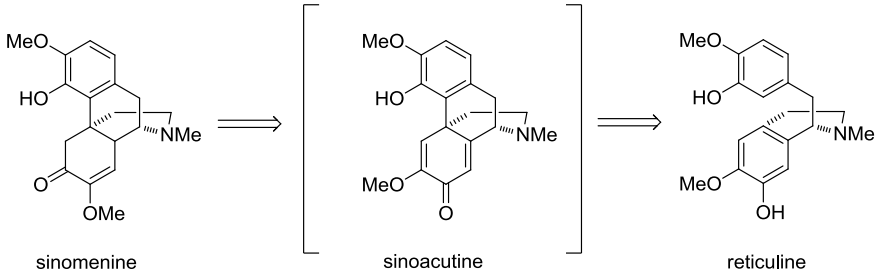
2.5 Dauricumine

2.6 Dechlorodauricumine

Barton proposed a biosynthesis of acutumine (**2.1**) based upon the biosynthesis of the related alkaloid sinomenine (**2.7**) in 1968 (Scheme 2.2). He and his co-workers

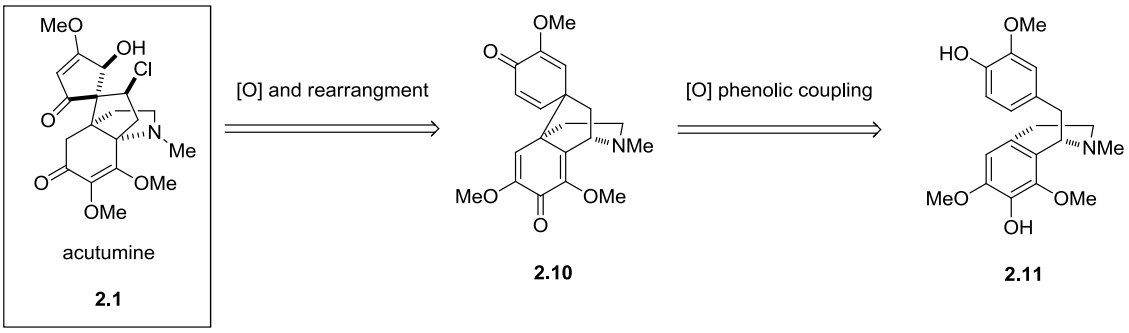
showed that sinomenine is derived from reticuline (**2.8**) through an oxidative aromatic coupling via sinoacutine (**2.9**).[154]

Scheme 2.2



Based on his observations of reticuline, Barton proposed a similar biosynthesis of acutumine (**2.1**). An oxidative phenolic coupling of starting biaryl **2.10a** would provide intermediate **2.10**, which could then be further elaborated to acutumine by ring contraction and isomerization (Scheme 2.3).[155] Barton also provided a possible mechanism for the ring contraction (Scheme 2.4), but this process was later cast into doubt by two independent studies (Schemes 2.5 and 2.6).[155-157]

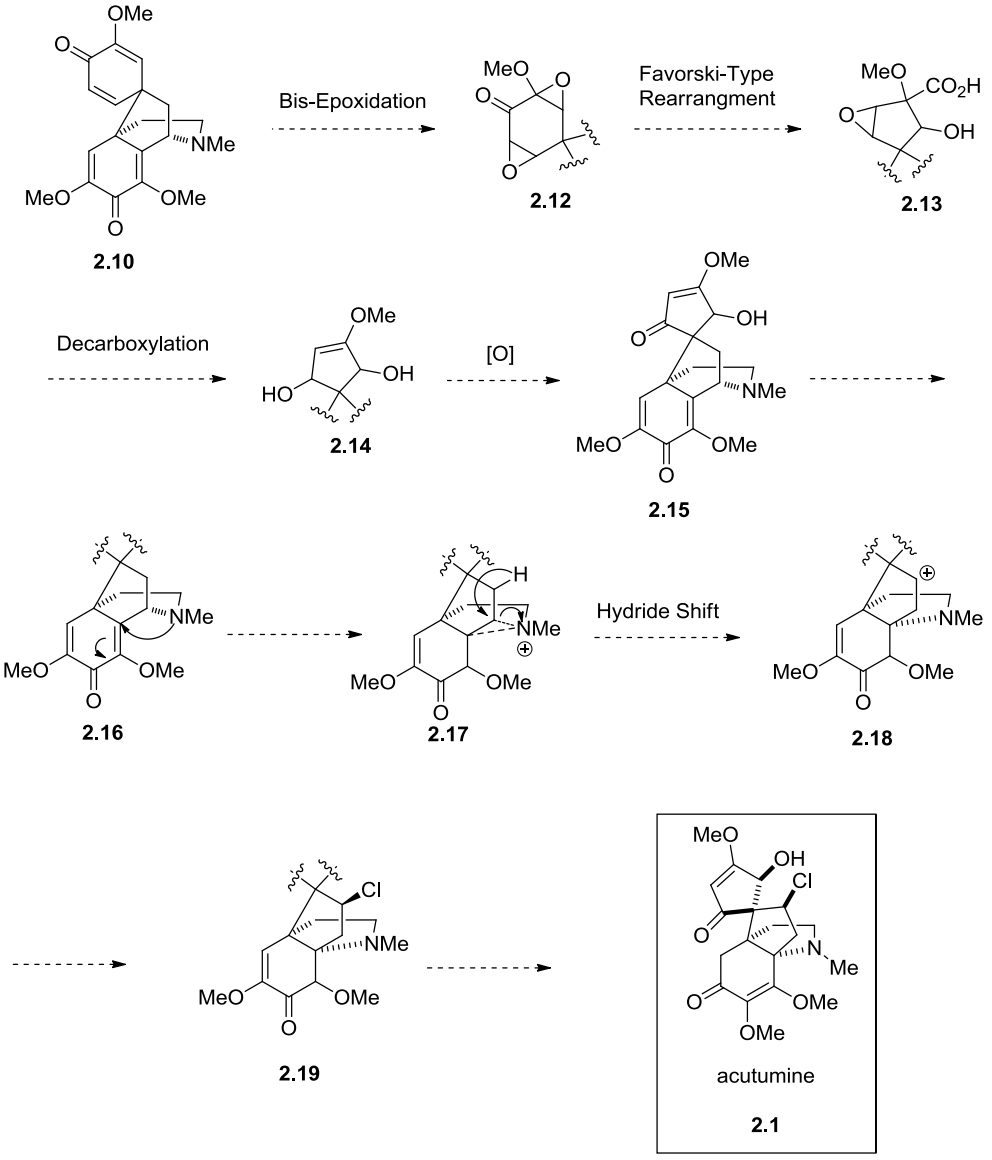
Scheme 2.3



Barton had originally proposed that dienone **2.10** would undergo bis-epoxidation to provide ring **2.12**.[155] He then envisioned that bis-epoxide **2.12** could undergo a Favorski-type rearrangement to provide **2.13**, whereupon decarboxylation and oxidation

would provide cyclopentene ring **2.15**. Rearrangement of **2.16** followed by a hydride shift would then provide the secondary cation **2.18**, which could be stereoselectively captured by a chloride ion to produce acutumine (**2.1**). However, this proposal was highly speculative, and attempts to justify the route experimentally did not provide support for the overall transformation (Schemes 2.5 and 2.6).[155-157]

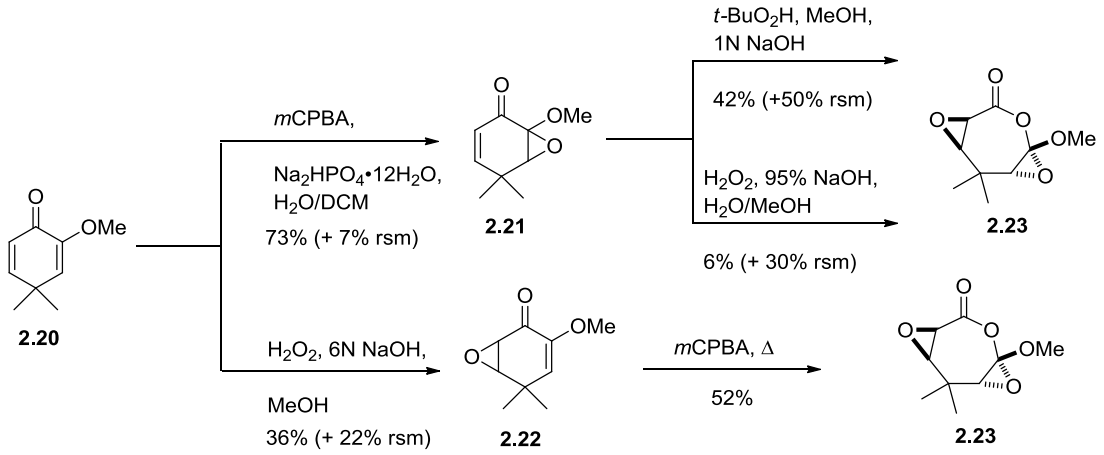
Scheme 2.4



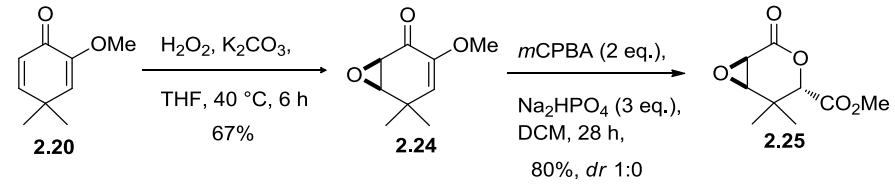
In two independent investigations, a bis-epoxidation of the cyclohexenone moiety of intermediate **2.10**, namely compound **2.20**, was carried out in an attempt to produce a bis-epoxide (Schemes 2.5 and 2.6).[155-157] However, neither study obtained a bis-epoxide product, which was a key intermediate in Barton's proposed acutumine biosynthesis. In

the first study by Matoba *et. al.*, it was proposed that lactone **2.23** was the product of two subsequent oxidations of compound **2.20** with epoxidizing agents (Scheme 2.5).[156] However, Wipf suggested that Bayer-Villiger products **2.25**, rather than bis-epoxides, were obtained as products (Scheme 2.6).[157]

Scheme 2.5

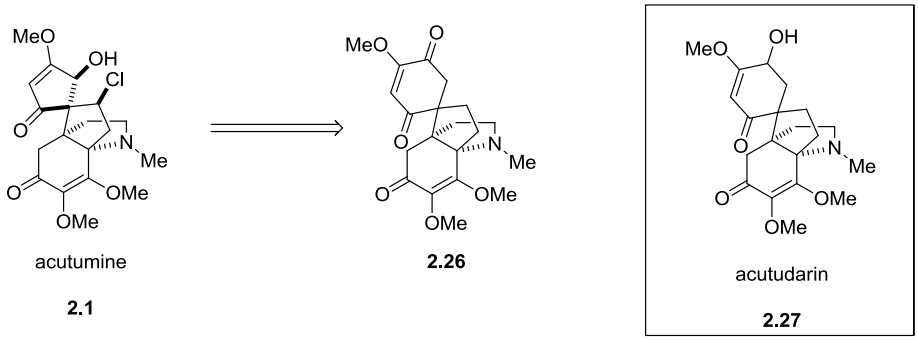


Scheme 2.6

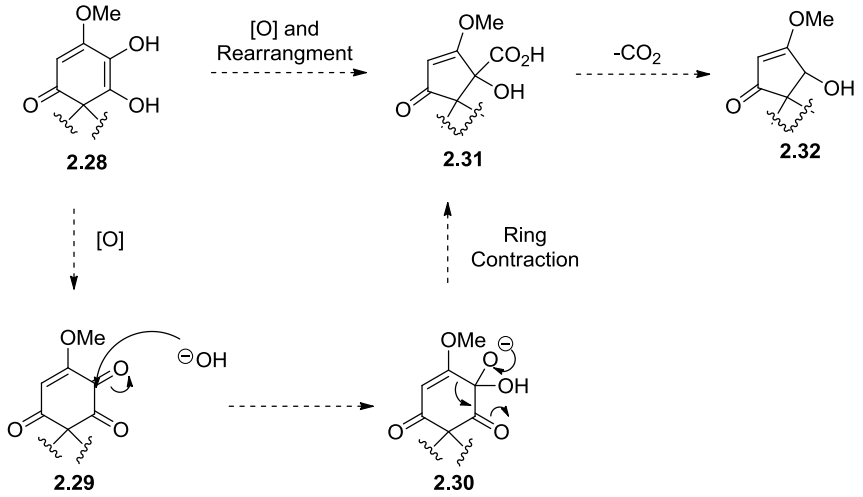


Wipf *et. al.* also proposed an alternative biosynthetic pathway of acutumine (Scheme 2.7). Acutumine could come from compound **2.26**, which is very similar to the natural product acutudarin (**2.27**). The mechanism by which this ring contraction may take place is shown in Scheme 2.8. Oxidation of cyclohexenone **2.28** to the *o*-quinone like structure **2.29**, followed by a rearrangement and decarboxylation could provide the cyclopentenone ring of acutumine **2.32**.[157-161]

Scheme 2.7



Scheme 2.8



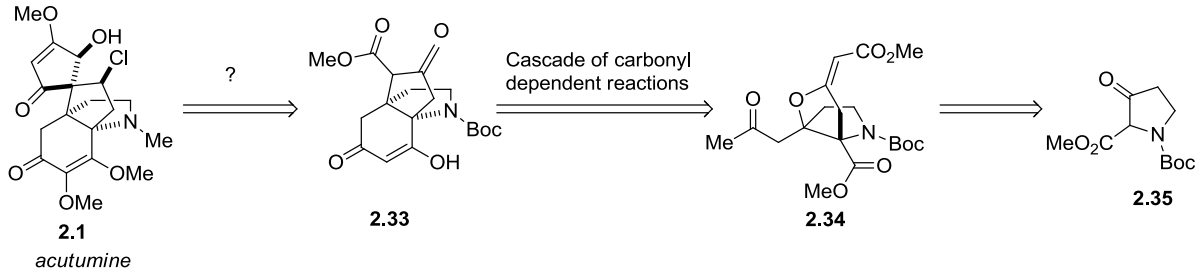
2.3 PREVIOUS SYNTHESES

While acutumine poses a great deal of interest within the synthetic community, thus far only four synthetic studies have been reported.[162-165] Of those four, two are approaches to the propellane core of acutumine (**2.1**), while the other two are enantioselective routes to the desired compound. All four will be discussed in detail in the forthcoming sections.

2.3.1 PARTIAL APPROACHES TOWARD THE SYNTHESIS OF ACUTUMINE

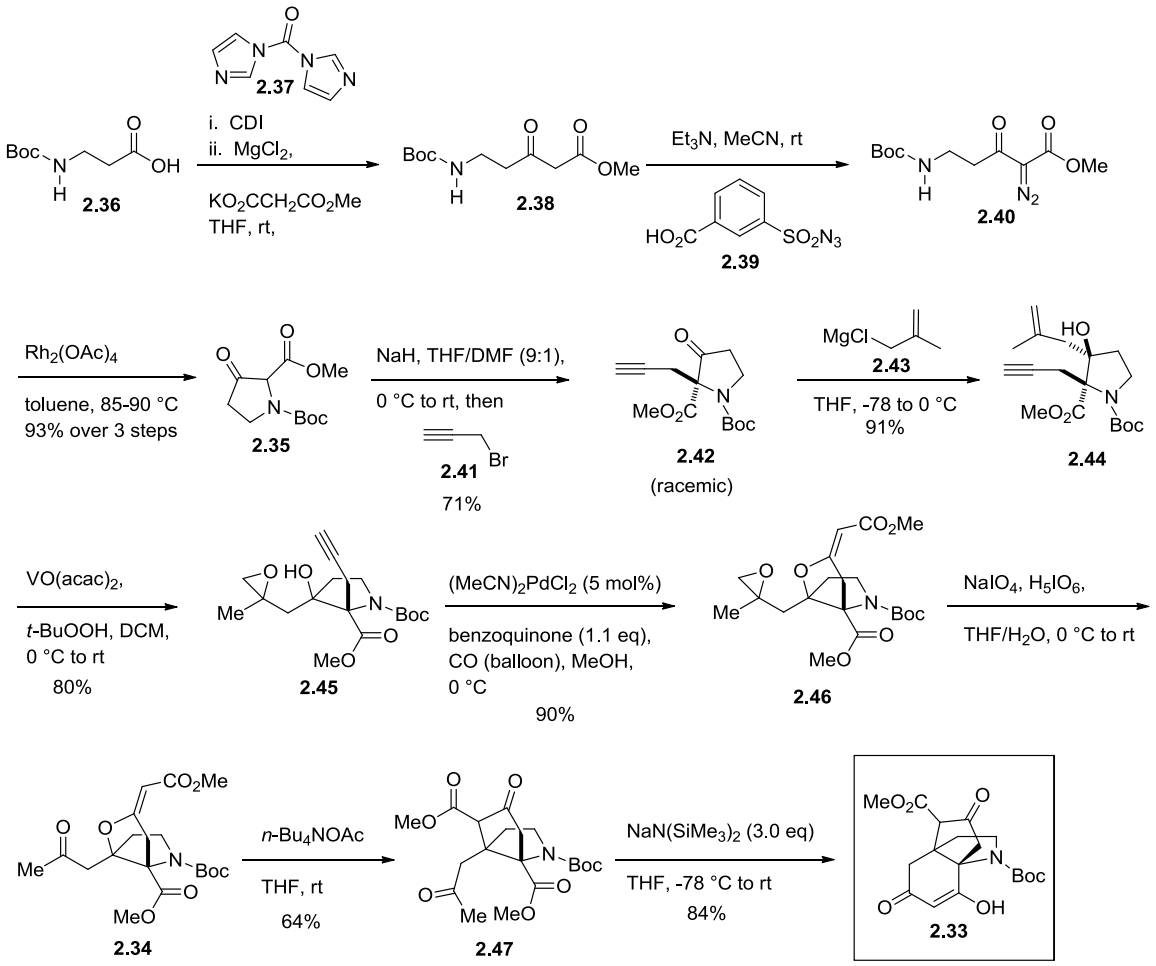
The first published synthesis of the tricylic core of acutumine **2.33** was developed by Sorensen in 2007.[162] The key step in the synthesis of **2.33** involved a cascade of carbonyl dependent reactions starting from pyrrolidine **2.34**, which was synthesized from known pyrrolidinone **2.35** (Scheme 2.9).

Scheme 2.9



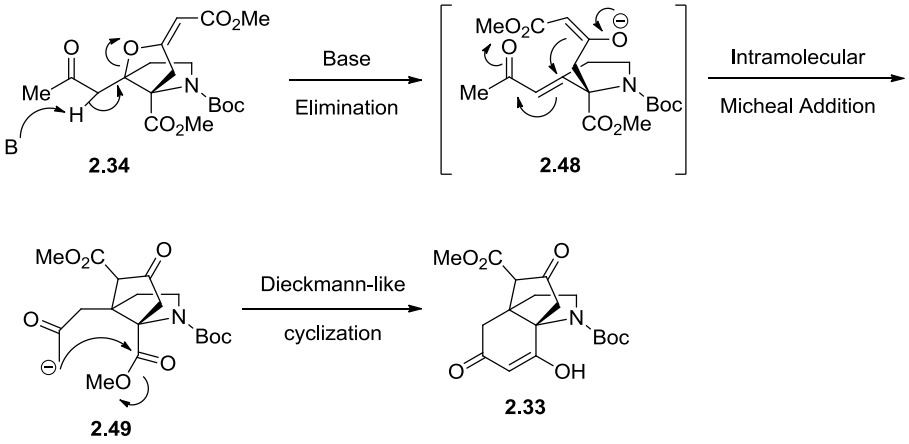
Pyrrolidinone **2.35** was available in three steps from *N*-Boc protected 3-aminopropanoic acid (**2.36**) in 93% yield (Scheme 2.10).[162,166] Pyrrolidinone **2.35** was alkylated with propargyl bromide (**2.41**) to provide racemic **2.42**, which was then subjected to a Grignard reaction with **2.43** to provide tertiary alcohol **2.44** in 91% yield. The terminal alkene of **2.44** was then epoxidized using standard conditions to provide **2.45**, which was a good substrate for the palladium (II)-catalyzed carbonylative cyclization reaction between the alcohol and alkyne moieties to provide vinylogous carbonate **2.46**. The epoxide was then transformed to ketone **2.34**, the key intermediate of the synthesis, thereby setting the stage for the carbonyl cascade that would lead to the tricyclic core **2.33**.[162]

Scheme 2.10



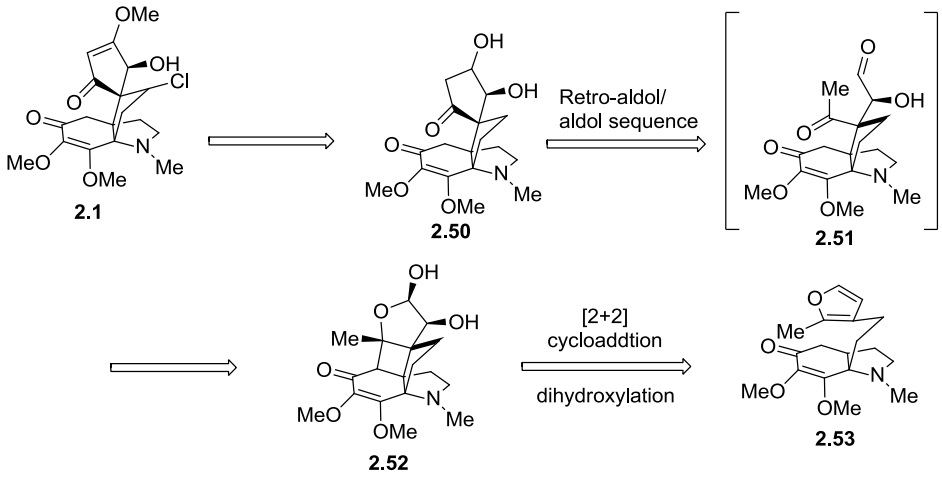
The first step of the cascade sequence involved the base catalyzed β-elimination reaction of **2.34** to generate the intermediate enolate **2.48** that then underwent an intramolecular Michael addition to provide diester **2.49** (Scheme 2.11). Upon enolate formation, **2.49** engaged in a Dieckmann-like condensation to provide **2.33**.[162] Despite this concise approach to the tricyclic core, Sorensen has yet to report a total synthesis of acutumine, and it is unclear whether his route will be amenable to an enantioselective synthesis of the molecule.

Scheme 2.11



A second approach towards the acutumine propellane core was reported by Reisman *et al.* in 2012 (Scheme 2.12). The main features of the approach include a site selective [2+2] cycloaddition followed by a retro-aldol/aldol sequence to provide the tetracyclic core **2.50**.[164]

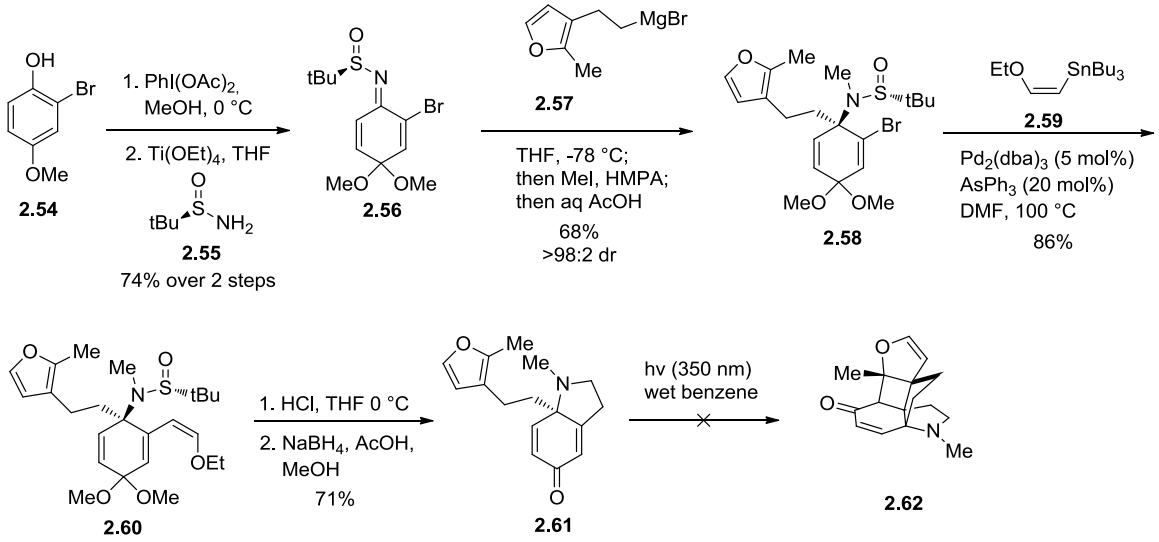
Scheme 2.12



Reisman and coworkers used commercially available bromo-phenol **2.54** as their starting material and followed their previous route to convert it to dihydroindolone **2.61** (Scheme 2.13).[167] Phenol **2.54** was first converted to sulfinimine **2.56** over two steps in

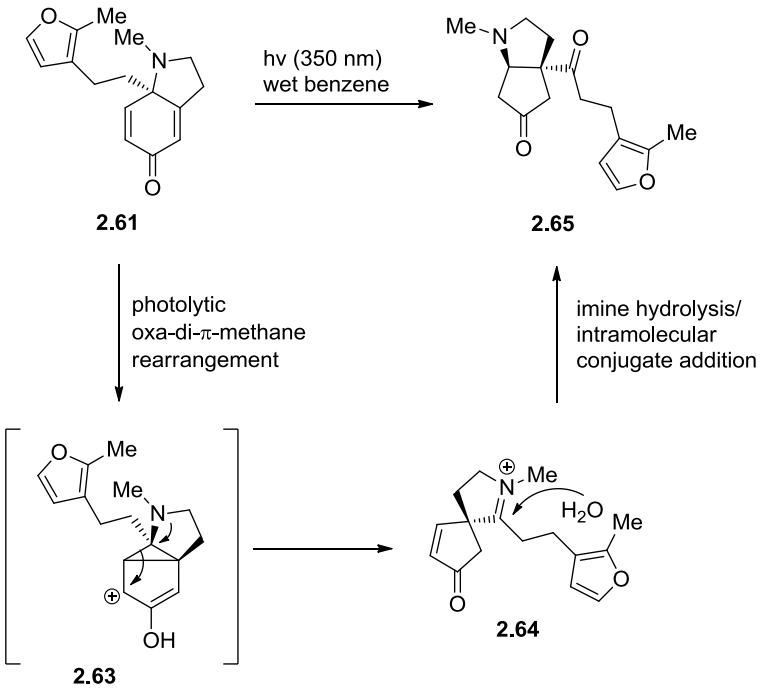
74% yield, which then underwent Grignard addition with furanyl nucleophile **2.57** to provide the corresponding adduct **2.58** in 68% yield and >98:2 diastereoselectivity. Vinyl bromide **2.58** was subjected to a Stille reaction with vinyl stannane **2.59** to furnish enol ether **2.60** in 86% yield. The sulfonyl group of **2.60** was cleaved by acid to provide an intermediary indolone that was immediately reduced to the dihydroindolone **2.61** by $NaBH_4$. However, further elaboration to the desired pentacyclic [2+2] product **2.62** was unsuccessful.

Scheme 2.13



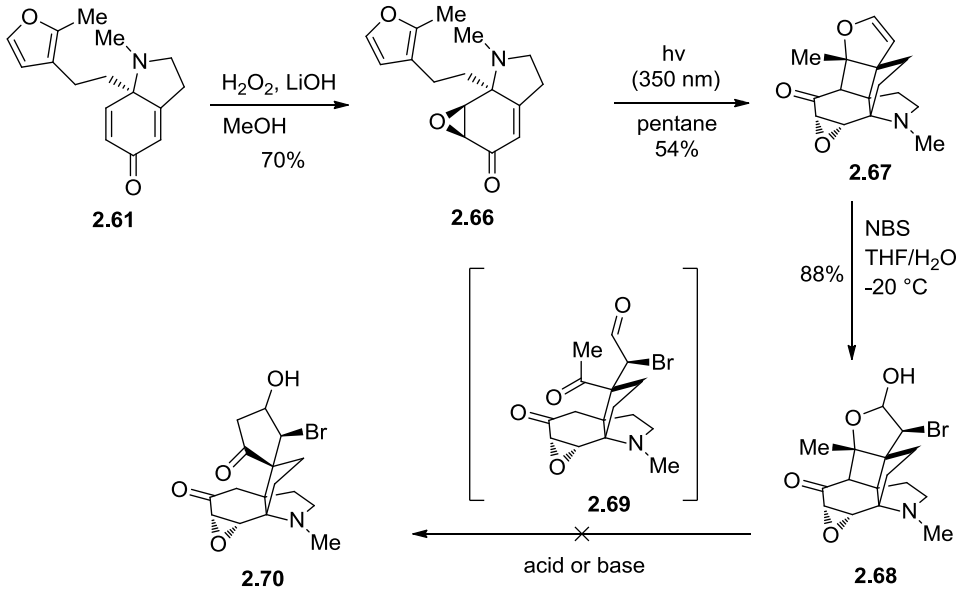
It was later found that the reason for the unsuccessful [2+2] reaction was due to a photolytic oxa-di-π-methane rearrangement (Scheme 2.14).[168] The rearrangement product **2.63** was hypothesized to fragment to the unstable spirocyclic iminium ion **2.64**, which was captured by adventitious water from the reaction to provide pyrrolidine **2.65**. The structure of pyrrolidine **2.65** was assigned based upon ^{1}H NMR, ^{13}C NMR, IR and HRMS analysis.

Scheme 2.14



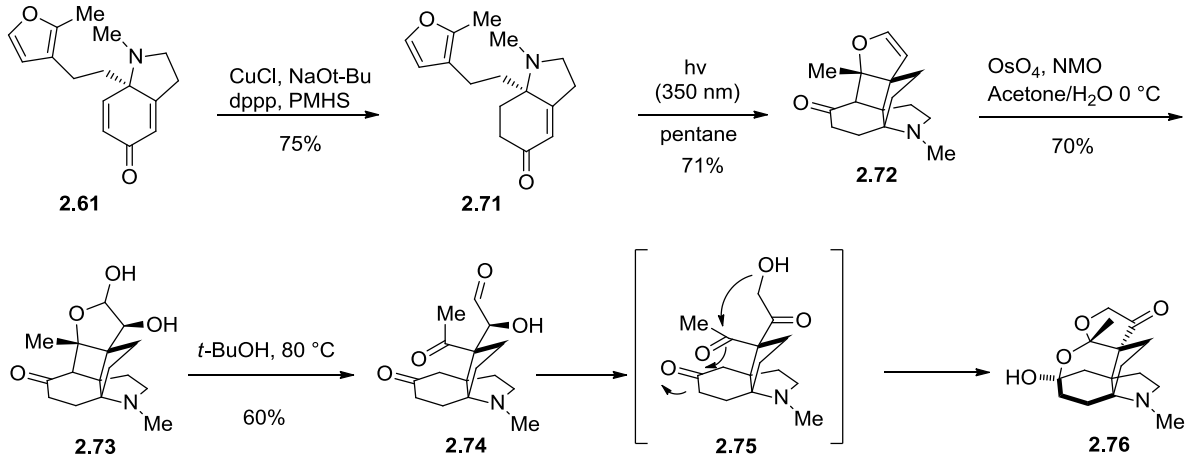
In order to circumvent the undesired rearrangement, Reisman and coworkers amended the route by masking one of the alkenes of the dienone **2.61** as an epoxide (Scheme 2.15). Dienone **2.61** was epoxidized exclusively at the least hindered olefin to provide **2.66** in 70% yield. When enone **2.66** was subjected to the photolytic [2+2] conditions, the desired adduct **2.67** was obtained in 54% yield, thereby providing the quaternary centers of acutumine in a single step. Dihydrofuran **2.67** was then elaborated to the corresponding bromohydrin **2.68** in 88% yield. However, when **2.68** was subjected to either mildly acidic or basic conditions, decomposition predominated, and none of the desired tetracyclic **2.70** was detected. Reisman and coworkers hypothesized that the reason for this was the undesired reactivity of the epoxide in **2.68**.

Scheme 2.15



As the epoxide had proven an ineffective protecting group for dienone **2.61**, they removed the troublesome alkene *via* reduction (Scheme 2.16). Dienone **2.61** underwent a site-selective copper-mediated conjugate reduction with polymethylhydrosiloxane (PMHS) to provide tetrahydroindolone **2.71** in 75% yield. When **2.71** was irradiated, the desired pentacyclic product **2.72** was produced in 71% yield. Dihydroxylation of **2.72** with OsO_4 and NMO provided lactol **2.73**, which was further elaborated to hemiketal **2.76** *via* the desired retro-aldol/aldol sequence in 60% yield. Unfortunately, hemiketal **2.76** was resistant to all additional efforts to elaborate it to acutumine (**2.1**).

Scheme 2.16



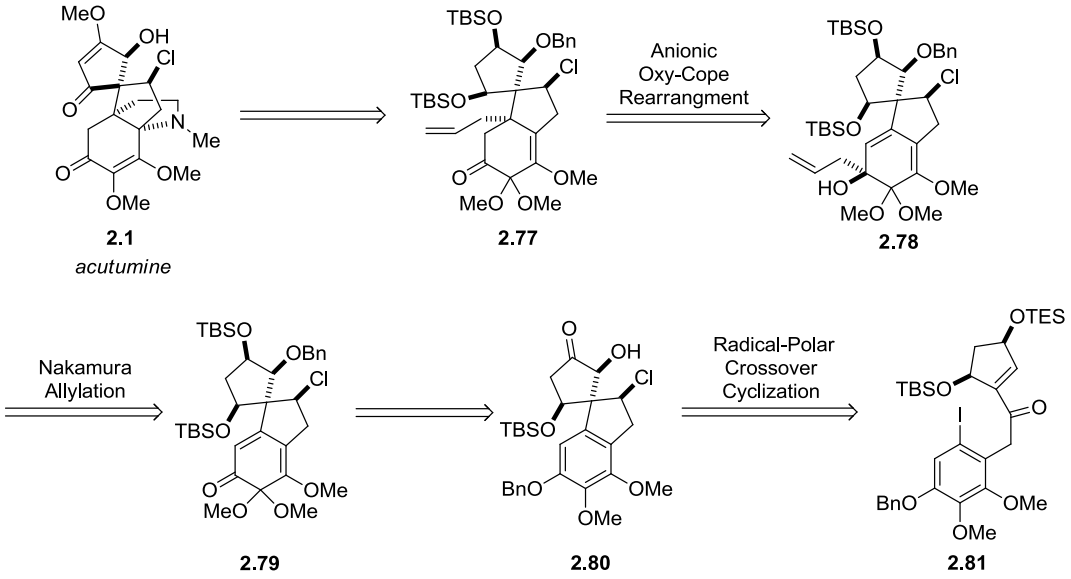
In conclusion, Reisman and coworkers have enantioselectively prepared hemiketal **2.76** in 10 steps and 6.9% overall yield effectively using a [2+2] cycloaddition retro-aldol/adol sequence. While Reisman was able to obtain the propellane core in a short sequence of steps and high yield, she admitted that hemiketal **2.76** was most likely not a viable precursor to acutumine. The route also features a key Stille reaction, which is not desirable to perform on a large scale due to all the tin and triphenyl arsine byproducts produced.

2.3.2 Enantioselective Total Syntheses of Acutumine

There have been two total syntheses of acutumine to date.[163,165] After publishing two different studies towards the core of acutumine,[169,170] Castle *et. al* reported the first total synthesis of (-)-acutumine in 2009.[163] Some key features of the synthesis include a regio- and stereo-selective, oxidative radical-polar crossover reaction to establish the spirocyclic acutumine core **2.80**[169] and an asymmetric Nakamura allylation[171] followed

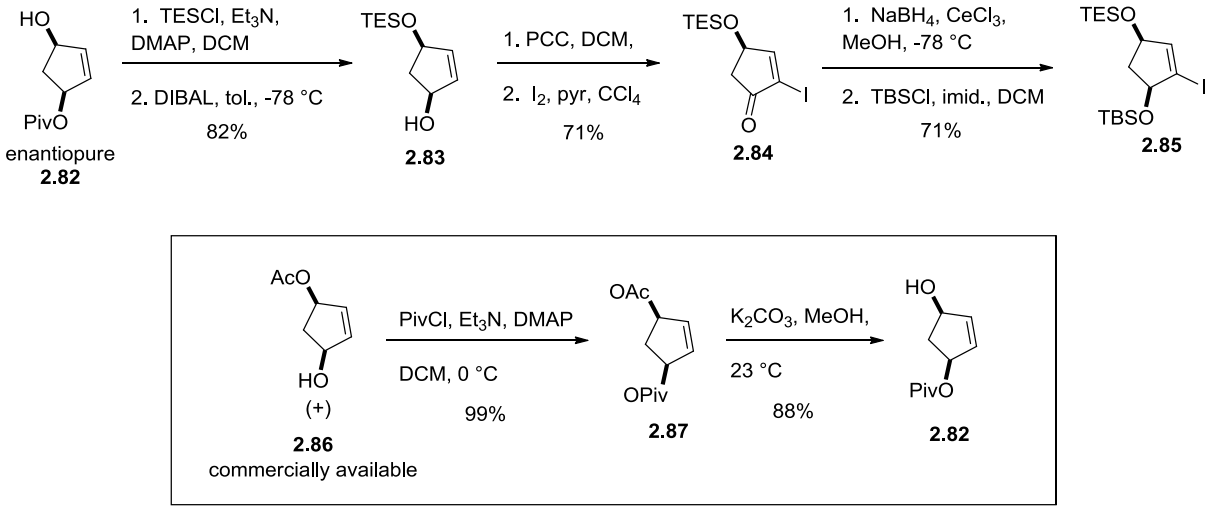
by an anionic oxy-Cope rearrangement to set up the formation of the final pyrrolidine ring **2.1** (Scheme 2.17).[163]

Scheme 2.17



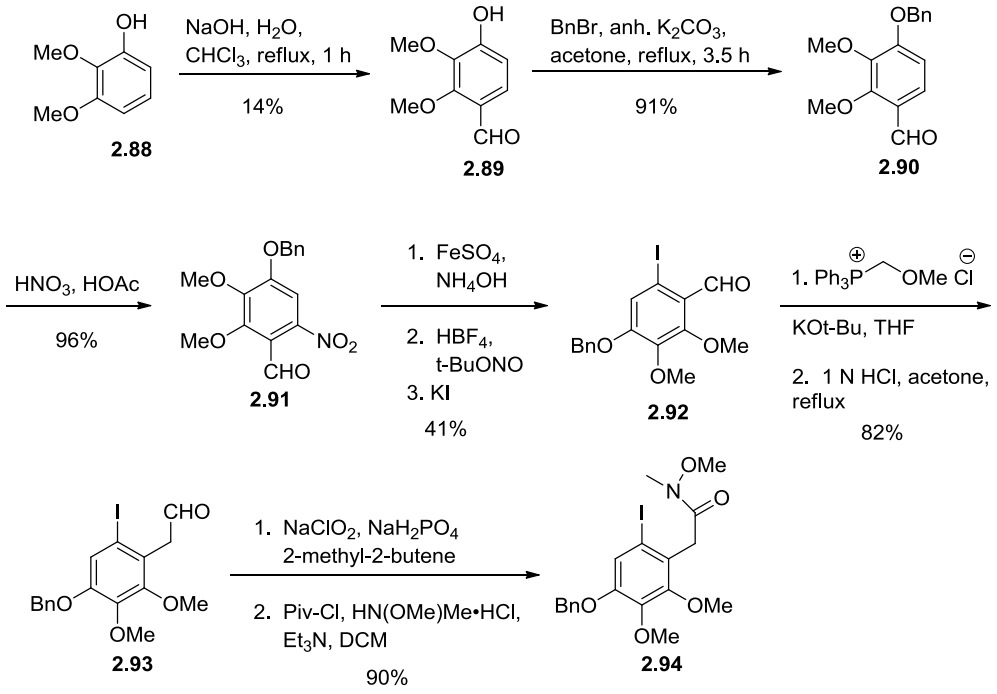
Castle first prepared cyclopentene **2.85**, which was obtained from the enantiopure mono-protected diol **2.82** (Scheme 2.18). Compound **2.82** is not commercially available, but may be readily accessed from the commercially available, albeit expensive (approximately $138/g), enantiopure acetate **2.86** via a pivalate protection/acetate deprotection sequence.[172] With **2.82** in hand, Castle protected the free alcohol as its triethylsilyl (TES) ether and then removed the pivalate group to reveal alcohol **2.83**. This alcohol was then oxidized to the corresponding enone, which was iodinated to provide **2.84**. The ketone was next reduced via the Luche procedure to provide the free alcohol that was subsequently protected as the *tert*-butyldimethylsilyl (TBS) ether to give cyclopentene ring **2.85**.

Scheme 2.18



Castle's key radical-polar crossover reaction required **2.94**, which was prepared in six steps from 2,3-dimethoxyphenol (**2.88**) (Scheme 2.19). Compound **2.88** was first subjected to a Reimer-Tiemann reaction to provide aldehyde **2.89**, although in only 14% yield. The phenol was next protected, and the ring was regioselectively nitrated to provide compound **2.91**. The nitro group was then transformed to aryl iodide **2.92** in 41% yield under standard reaction conditions. The aldehyde was subjected to a Wittig homologation to provide the new aldehyde **2.93**, which was oxidized to a carboxylic acid that was converted into the Weinreb amide **2.94**.[169]

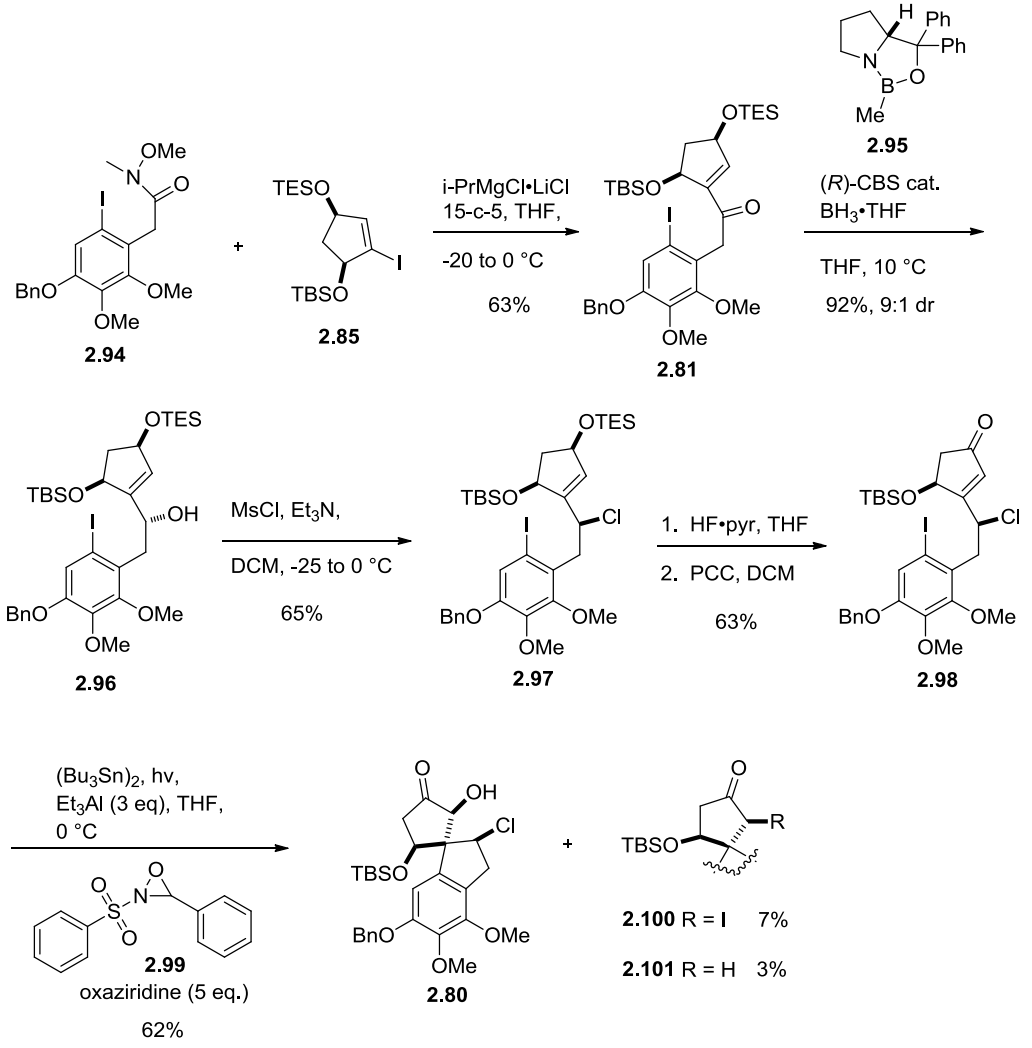
Scheme 2.19



Fragments **2.85** and **2.94** were coupled *via* a Grignard reaction to provide intermediate **2.81** in 63% yield (Scheme 2.20). Ketone **2.81** was stereoselectively reduced using the Corey-Bakshi-Shibata (CBS) catalyst (**2.95**) to provide alcohol **2.96**, which was subsequently mesylated and displaced with chloride to provide **2.97**. The TES ether was cleaved using hydrofluoric acid and pyridine (HF·pyr), and the resulting alcohol was oxidized to the enone in the presence of pyridinium chlorochromate (PCC) to provide **2.98**, thus setting the stage for the radical-polar crossover reaction. When irradiated in the presence of hexabutylditin ($(Bu_3Sn)_2$), iodide **2.98** presumably generated an aryl radical that combined with the double bond of the enone to form a spirocycle, repositioning the radical α- to the ketone. Triethylaluminum is then believed to have acted as a one-electron donor in order to generate an enolate that then trapped the oxaziridine **2.99** to provide α-hydroxy ketone **2.80** in 62% overall yield. This elegant

transformation proceeded with complete stereoselectivity to give the enantiomerically pure hydroxy-ketone **2.80** with small amounts of side products **2.100** and **2.101**.[169]

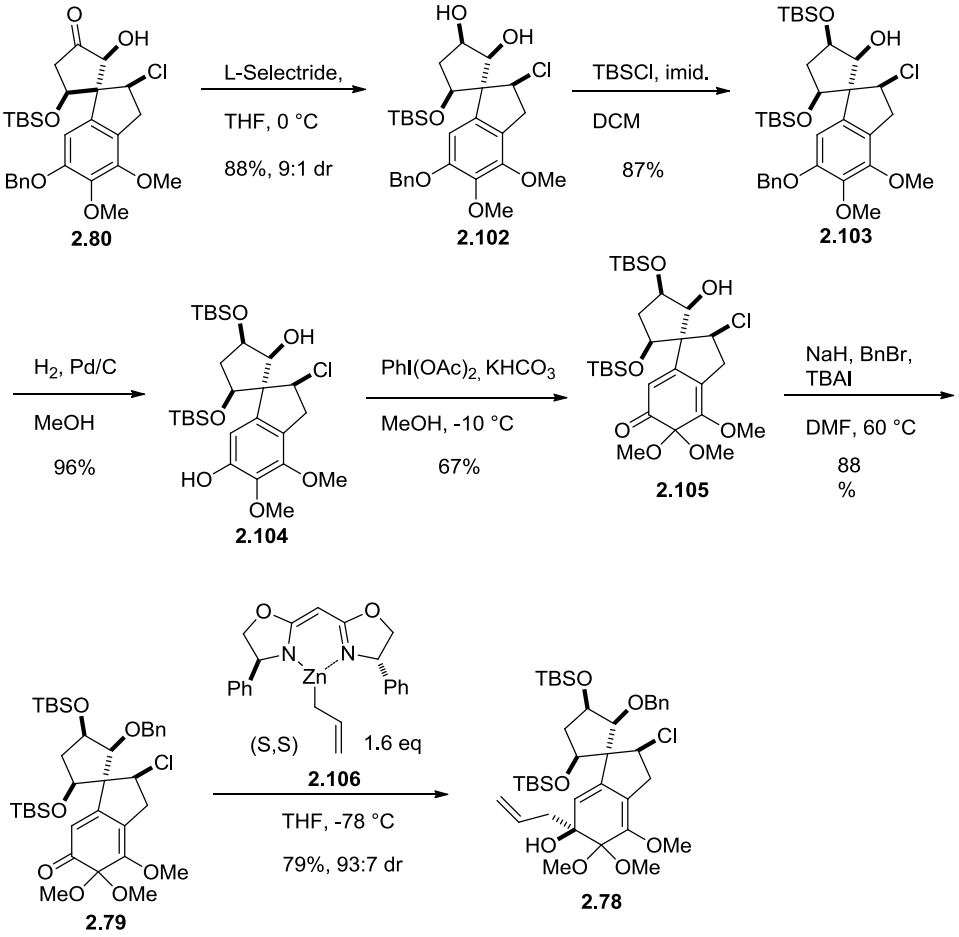
Scheme 2.20



The hydroxy-ketone **2.80** was then stereoselectively reduced to diol **2.102**, the more sterically accessible alcohol of which was silylated to provide **2.103** (Scheme 2.21). The benzyl ether was removed by hydrogenation to selectively reveal phenol **2.104**, and oxidation with phenyliodonium diacetate (PIDA) provided the masked ortho-

benzoquinone **2.105**. After protection of the secondary alcohol of **2.105** with benzyl bromide (BnBr), a Nakamura asymmetric allylation[171] was performed to provide homoallylic alcohol **2.78** in 79% yield and 93:7 diastereoselectivity.[163]

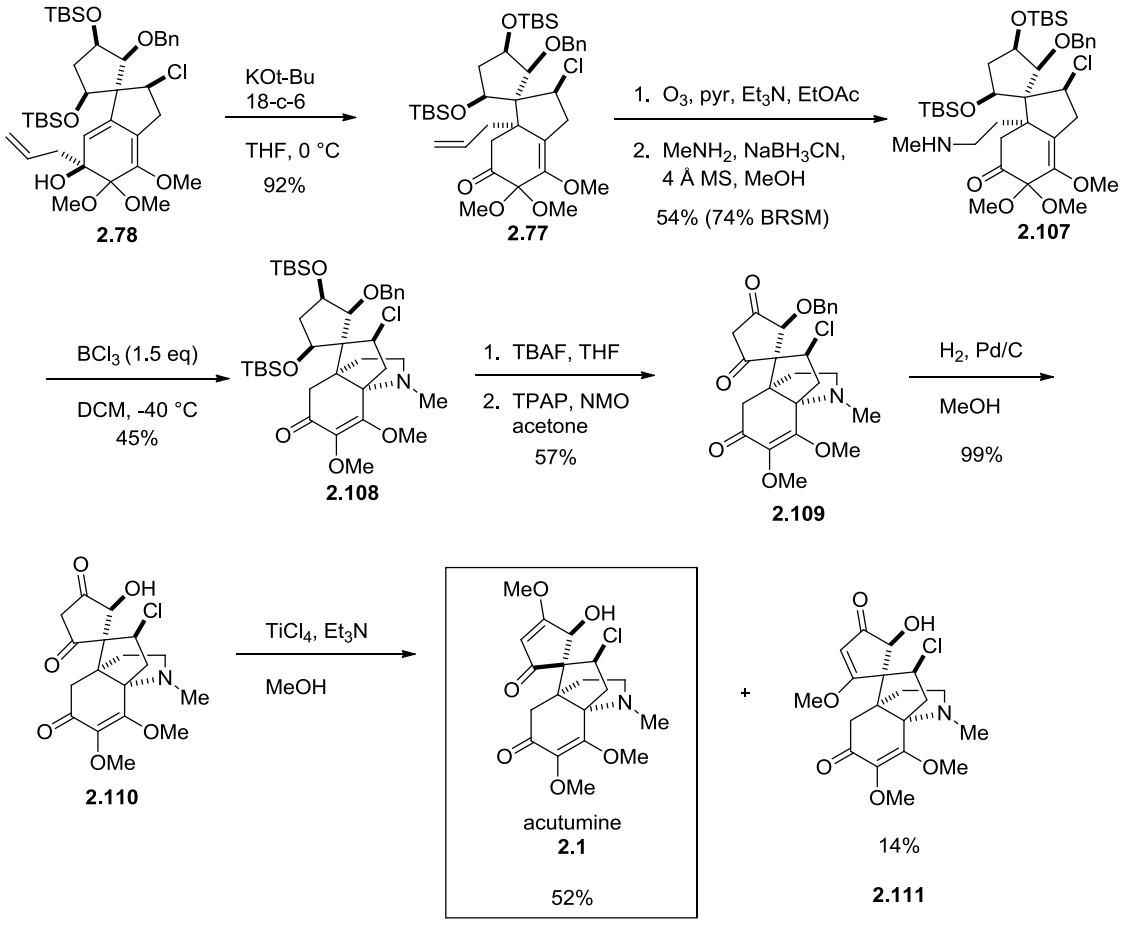
Scheme 2.21



An anionic oxy-Cope rearrangement of homoallylic alcohol **2.78** provided **2.77** in 92% yield with retention of stereochemistry (Scheme 2.22). Next, the alkene moiety of **2.77** was oxidatively cleaved to an aldehyde which underwent a reductive amination to provide secondary amine **2.107**. In the presence of boron trichloride (BCl_3), the amine engaged in a Lewis-acid catalyzed cyclization to provide tetracyclic **2.108** in moderate

yield. Following cleavage of the TBS ethers, the resultant alcohols were oxidized to their respective ketones **2.109**, and removal of the benzyl groups furnished secondary alcohol **2.110**. Treatment of **2.110** with titanium tetrachloride ($TiCl_4$) and base in methanol (MeOH) provided acutumine (**2.1**) as a 3.7:1 separable mixture of acutumine (**2.1**) and its regioisomer **2.111**.[163]

Scheme 2.22

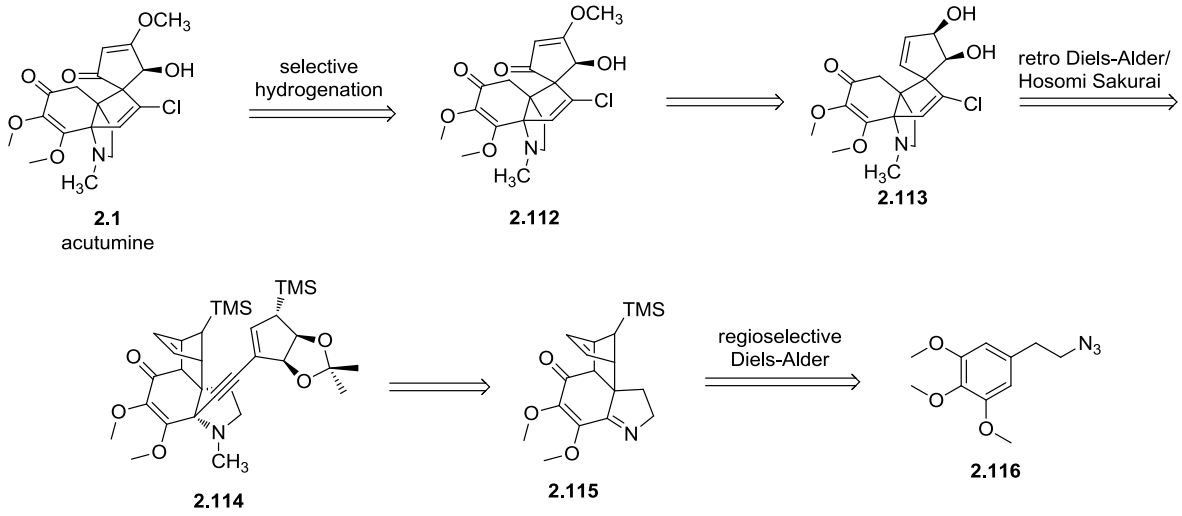


While Castle's work is the first successful synthesis of acutumine, there is still ample room for improvement. The total number of steps is not reported, but is most

likely to be in low thirties. It is unclear how many steps it took the authors to prepare the two main starting materials **2.85** and **2.94**. Starting from 2,3-dimethoxyphenol, it is six steps to Weinreb amide **2.94**,[169,173,174] and from the expensive and not widely available (1*R*,4*S*)-4-hydroxycyclopent-2-enyl acetate (**2.86**), and five steps are required to prepare **2.85**.[169,172]

The most recent synthesis of acutumine was reported by Herzon and coworkers in 2013.[165] Some key features of their route include an early stage regioselective Diels-Alder reaction that set the stereochemistry for all subsequent reactions as well as a retro Diels-Alder/Hosomi-Sakurai sequence to provide the tetracyclic core **2.113**, and a late stage selective hydrogenation to furnish acutumine (**2.1**) (Scheme 2.23).

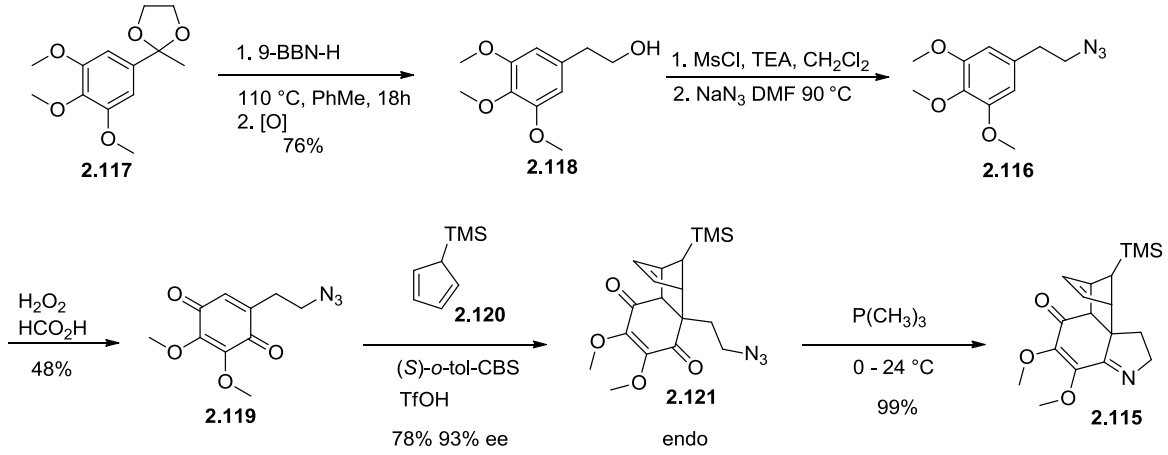
Scheme 2.23



Herzon used mescaline derivative **2.116**, which can be obtained from the commercially available acetal **2.117** in four steps, as his starting material (Scheme 2.24).[175] In the event, acetal **2.117** was reductively cleaved with 9-BBN, and then oxidized to provide alcohol **2.118** in 76% yield.[175] Alcohol **2.118** was then converted to

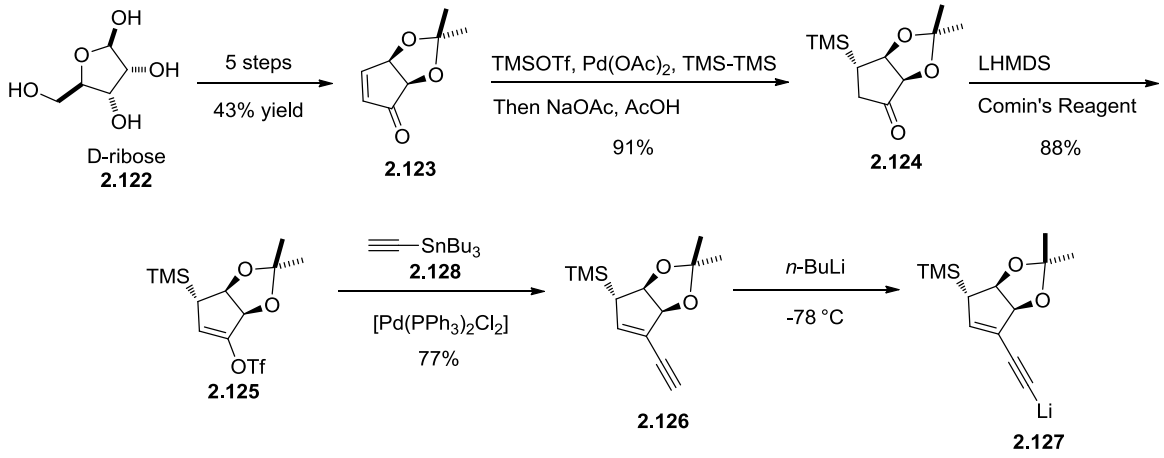
azide **2.116** according to standard protocols, though the yield was not given.[175] Azide **2.116** was oxidized to *p*-quinone **2.119** in 48% yield. Quinone **2.119** then underwent a regioselective Diels-Alder reaction with cyclopentadiene **2.120** in good yield and enantioselectivity to provide **2.121** exclusively as the endo adduct.[176] Quinone **2.121** was then subjected to Staudinger reaction conditions to provide iminoquinone **2.115** in excellent yield.

Scheme 2.24



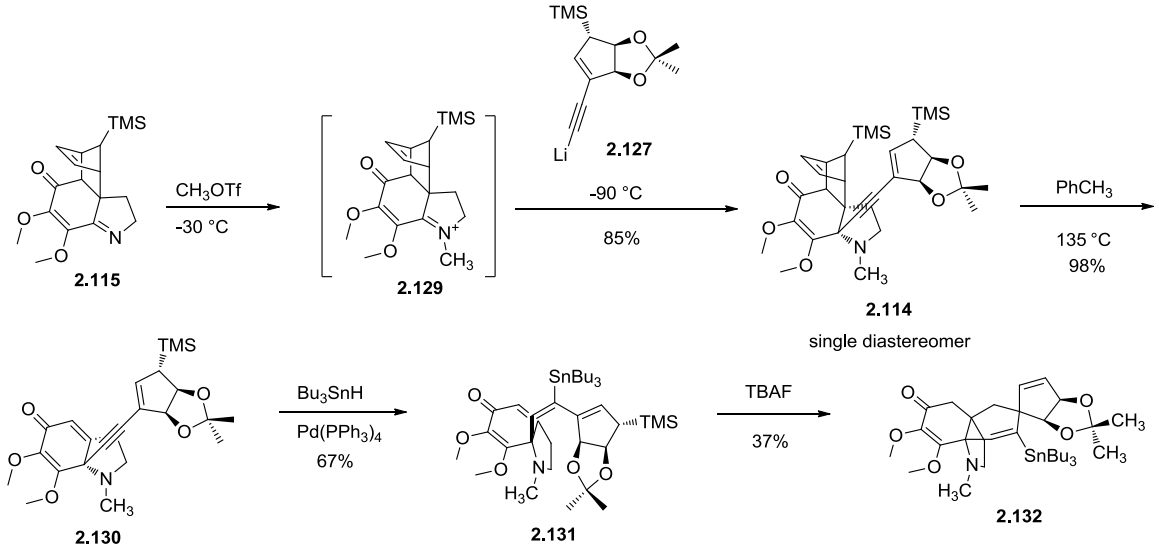
The coupling partner for the iminoquinone **2.115** was synthesized from readily available D-ribose (**2.122**) (Scheme 2.25). Ribose **2.122** was converted into acetal **2.123** in five steps *via* known procedures.[177] Palladium catalyzed disilylation followed by hydrolysis of the trimethylsilyl enol ether thus provided acetal **2.124** in 91% yield.[178] Acetal **2.124** was next transformed into enol triflate **2.125** using Comin's reagent in 88% yield. Vinyl triflate **2.125** underwent a Stille coupling with the propargyl tin reagent **2.128** to provide alkyne **2.126** in 77% yield, which was then deprotonated with *n*-Buli to provide the lithiated anion **2.127**.

Scheme 2.25



Iminoquinone **2.115** was methylated under standard conditions to produce the iminium ion **2.129**, which was captured by the alkynyl anion **2.127** to provide the addition product **2.116** as a single diastereomer (Scheme 2.26). The somewhat counterintuitive stereoselectivity from the addition was attributed to the orientation of pyrrolidine ring in the iminium ion. Adduct **2.114** was next heated to effect a retro Diels-Alder reaction to provide the dienone **2.130** in 98% yield. Alkyne **2.130** was reduced by hydrostannylation [179] to provide vinyl stannane **2.131**, which in the presence of TBAF underwent a Hosomi-Sakurai reaction to provide the complete tetracyclic core **2.132**, albeit in only 37% yield. The regioselectivity of the hydrostannylation was believed to be due to the propensity of alkyne **2.130** to insert into a palladium hydride to form an intermediate with π-allyl character, as well as the steric hindrance present at the carbon α- to the cyclopentene ring.

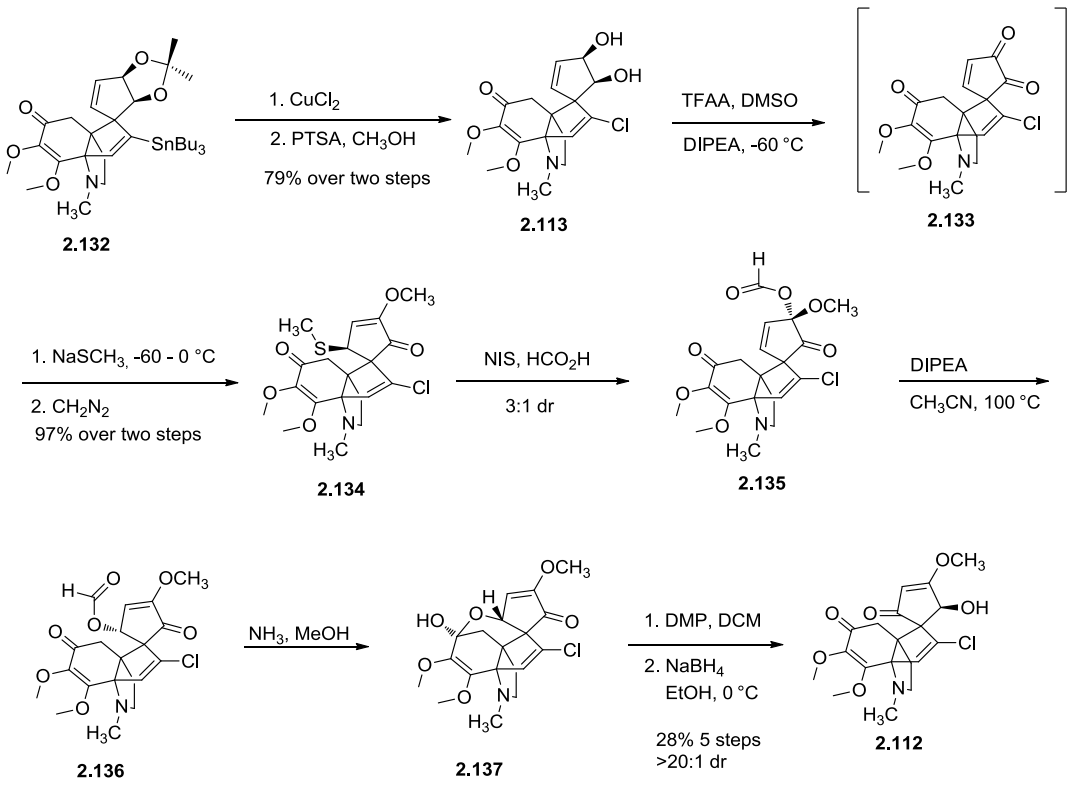
Scheme 2.26



Once **2.132** was obtained, two main challenges remained. These were the introduction of the chlorine atom and the oxidation of the spirocyclic cyclopentene ring to the desired vinylogous ester of the natural product. Towards this end, vinyl stannane **2.132** was transformed into the corresponding vinyl chloride in the presence of copper (II) chloride ($CuCl_2$),[180]with subsequent acid catalyzed cleavage of the acetal to provide diol **2.113** in 79% yield over two steps (Scheme 2.27). Diol **2.113** was then oxidized under Swern conditions to provide the intermediary dione **2.133**, which was not isolated, but was instead immediately subjected to sequential reaction with sodium thiomethoxide and diazomethane to yield tetracycle **2.134** in 97% yield over two steps. Treatment of **2.134** with *N*-iodosuccimide (NIS) and formic acid (HCO_2H), resulted in the elimination of the thioxide group to provide mixed ketal **2.135** as a mixture (3:1) of diastereomers). Mixed ketal **2.135** then underwent a rearrangenent in the presence of Hunig's base (DIPEA) to provide enone **2.136**. Enone **2.136** was treated with ammonia in methanol to

cleave the formyl group, and the resulting lactol **2.137** was oxidized with Dess-Martin periodinane (DMP) and then reduced with sodium tetraborohydride ($NaBH_4$) to provide **2.112** in 28% yield over five steps.

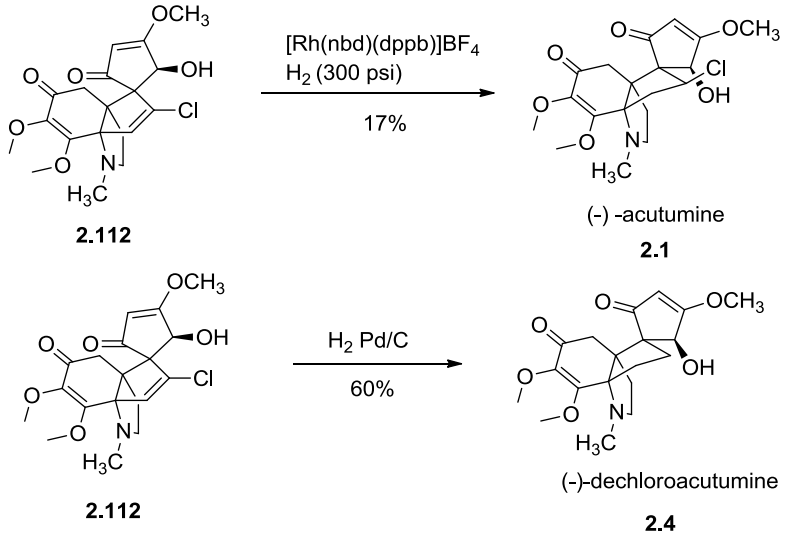
Scheme 2.27



All that remained in Herzon's synthesis was the stereoselective reduction of vinyl chloride **2.112** to the correct diastereomeric alkyl chloride to provide acutumine (**2.1**). This was accomplished using homogeneous hydrogenation conditions[181-184] to obtain acutumine (**2.1**), albeit in only 17% yield (Scheme 2.28). Presumably the stereoselectivity of the reduction was directed by the hydroxyl group and tertiary amine of vinyl chloride **2.112**.[181-184] The majority of the material recovered was the

dechlorinated product dechloroacutumine (**2.4**), which was the exclusive product obtained using more standard catalytic hydrogenation conditions (H_2, Pd/C).

Scheme 2.28



In conclusion, Herzon *et al.* have developed an enantioselective synthesis of acutumine comprising 31 steps with an overall yield of 0.06%. Some of the key features included an early stage regioselective Diels-Alder reaction which enabled substrate control of all subsequent reactions as well as a hydrostannylation/Hosomi-Sakurai sequence which provided expedient access to the tetracyclic core. However, some challenges remained. For example, the synthesis would have been more impressive had a cyclopentenone of the desired oxidation state could have participated in the Hosomi-Sakurai reaction, eliminating the need for all the additional oxidative manipulations. The authors did examine a variety of other conditions for closing the tetracycle with a variety of different cyclopentenones in the presence of Lewis acids and heat, yet none of the desired tetracyclic core was obtained. Thus, the Hosomi-Sakurai reaction with the TMS group present on the cyclopentenone was the only option available to them. Another

major drawback of the synthesis is the low yield of the final hydrogenation step. While they can easily access the dechlorinated acutumine precursor **2.4**, the authors did not disclose how they would elaborate that intermediate to the acutumine.

While the work of Sorensen, Reisman, Castle, and Herzon highlighted some interesting chemistry towards the formation of acutumine, there is still room for improvement. Sorensen was able to furnish the propellane core of acutumine **2.33** in 23% yield over 10 steps using elegant enolate chemistry, and Reisman was able to synthesize the complex pentacyclic core **2.76** in 6.8% yield over 10 steps using a clever regioselective [2+2] cycloaddition. Yet as efficient and high yielding as these syntheses were, it was unclear whether **2.33** or **2.76** could be further elaborated to acutumine. Reisman even admitted that **2.76** was most likely not a viable precursor to acutumine while Sorensen's work was completed over 10 years ago with no subsequent work having been published since that time.

Castle completed an enantioselective total synthesis of acutumine in 2007, furnishing the molecule in 0.004% yield over at least 30 steps. Pioneering a novel radical-polar crossover reaction, he was able to stereoselectively furnish the spirocycle of acutumine in a single step. However, the synthesis was lengthy, and with the exception of the radical polar crossover reaction, lacked efficiency and to a certain degree, creativity. The synthesis disclosed a number of protecting group manipulations and most of the reactions in the sequence could be considered routine. It seemed to us that a more streamlined approach to acutumine might be possible. However, Castle's efforts are not to be belittled as he was the first to accomplish the total synthesis of this incredibly complex molecule.

Herzon also completed an enantioselective total synthesis of acutumine fairly recently. The molecule was obtained in 0.06% yield over 31 steps. His route featured a regioselective Diels-Alder reaction between an iminoquinone and a silyl cyclopentadiene, wherein the cyclopentadiene was cleverly used as a chiral auxiliary to guide a key acetylide addition. The route also featured Hosomi-Sakurai reaction to close the spirocyclic ring of the acutumine core. However, the route was not without its faults. The route was lengthy and though Herzon was able to furnish the tetracyclic core of acutumine quickly and uniquely, a large amount of his synthesis was spent functionalizing the γ-hydroxy vinylogous ester cyclopentene ring of the spirocycle. The repeated functional group and oxidation manipulations of that particular moeity of acutumine were largely responsible for the high step count of the total synthesis. Also, the last step of the synthesis, a selective hydrogenation of a vinyl chloride group, proceeded in only 14% yield. Clearly there was still room for improvement within the field.

It is also important to note that we were pursuing our studies concurrent to those of Herzon and Reisman. As will be shown in subsequent sections, we also favored a strategy in which an iminoquinone played an important role. When we started our investigations, only the work of Sorensen and Castle had been known. While their work was commendable, as discussed above, we believed that we could come up with a more streamlined and elegant approach to the acutumine. We were interested in the biosynthesis of acutumine and wanted to develop a strategy towards that end.

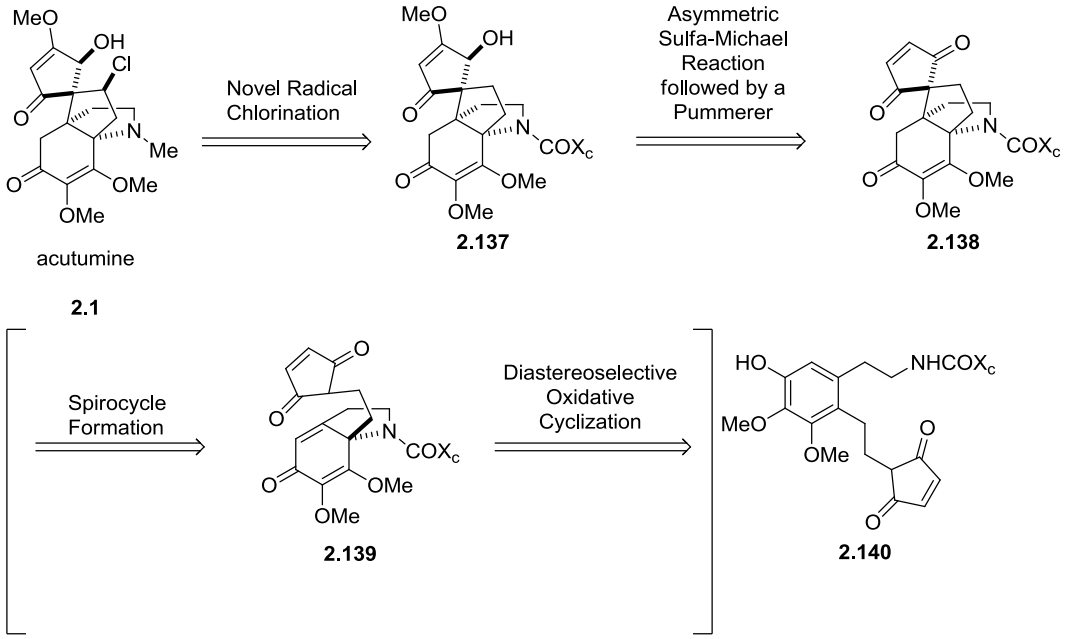
To quickly summarize section **2.2**, what was known for sure about the biosynthesis of acutumine was that it was derived from two molecules of tyrosine and

that the last step of the biosynthesis involved the installation of a neopentylic chlorine atom.[150,152,153] The route from tyrosine to dechloroacutumine was believed to consist of an oxidative coupling followed by benzylic acid type rearrangement, yet nothing has been proven.[154-157] Neither Sorensen nor Castle pursued a strategy similar to the proposed biosynthesis, and we saw an opportunity to both explore new and interesting chemistry as well as test some of the hypotheses with regards to the biosynthesis of acutumine.[154-157] Herzon and Reisman also appear to have found inspiration in the biosynthesis of acutumine, as our strategies show some similarities, though we did not, and could not, have known this at the start of our investigations.

2.4 MARTIN GROUP BIOMIMETIC APPROACH

In our proposed synthesis towards acutumine, we envisioned the incorporation of two key biomimetic steps. The first, was a novel latestage stereoselective radical chlorination that would exploit the existing stereochemistry of the spirocyclic hydroxyl group to direct the addition of the chlorine radical to the correct face of the molecule (Scheme 2.29). The second key step we had envisioned was a diastereoselective oxidation cyclization/Micheal addition sequence that would set up the tetracyclic core of acutumine **2.138**, preferably in a single one-pot reaction. Both will be discussed in detail below.

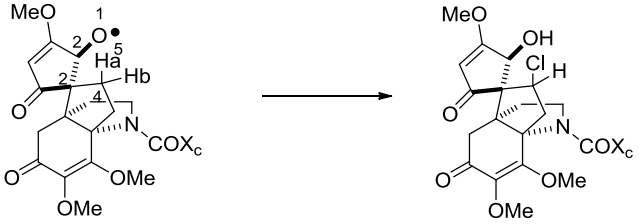
Scheme 2.29



As Sugimoto and coworkers had discovered, the chlorine atom of acutumine was incorporated in the last stages of the biosynthesis.[152,153] We were intrigued by this concept and believed that we could access acutumine (**2.1**) from tetracycle **2.137** via a novel radical chlorination in which an oxygen-centered radical at the secondary alcohol **2.141** would generate a carbon centered radical that will regio- and stereoselectively deliver the chlorine atom to the propellane core (Scheme 2.30). The oxygen radical could be generated by any number of standard techniques, including a possible Hofmann-Loffler-Freytag radical initiation.[185-187] Though directed radical functionalizations are known to proceed better in rigid substrates, which would certainly describe the tetracycle of **2.141**, almost all of precedented directed radical functionalizations occur through 1,5-hydrogen abstraction; our substrate would require a 1,4-hydrogen abstraction.[185-187] However, **2.141** has no accessible protons available for a 1,5-hydrogen abstraction, so the

directed functionalization may still occur as desired. When a three-dimensional model was built, it looked as if the desired diastereotopic proton, Ha, would have been more accessible to the oxygen atom of the hydroxyl group than Hb, futher encouraging our pursuit of a late stage radical chlorination. It was a scientific question that we were very interested in answering. However, if our original plan proved to be too bold then we could also elaborate our free hydroxyl to a carbamate group, such as the trifluoroethyl carbamates of Baran,[188] which can proceed through oxygen or nitrogen centered radicals to provide more favorable 1,5 and 1,6-hydrogen abstractions while still providing our desired "1,4-hydrogen abstraction" product, **2.142**.

Scheme 2.30

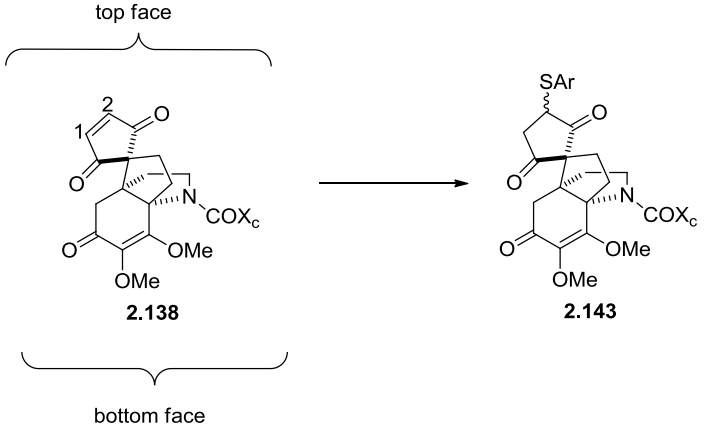


2.141 **2.142**

We envisioned accessing **2.143** from cyclopentenedione **2.138** via an asymmetric sulfa-Michael addition /Pummerer sequence. In order for this sequence to be successful, we required a way to desymmetrize the cyclopentenedione ring so that we would be able to selectively oxidize the C2 position as opposed to the C1 position (Scheme 2.31). Thiols have been shown add to 1,2-maleic acid esters and cyclic enones in the presence of chiral catalysts, both organocatalytic and transition metal based, to provide regioselective and/or diastereoselective Michael addition products.[189-191] A thiol moiety at the C2 position of the cyclopentenedione ring would provide an excellent functional handle with which to elaborate **2.143** to acutumine. Fortunately the complexity of

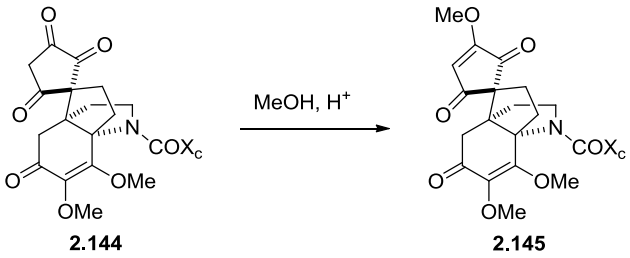
tetracycle **2.138** should help to reinforce a spatial bias between C1 and C2 to facilitate differentiation between the two. Also, we will not need to worry about whether thiol addition occurs from the top or bottom face of the molecule, as the chiral center at will be destroyed to provide the vinylogous ester of **2.137**.

Scheme 2.31



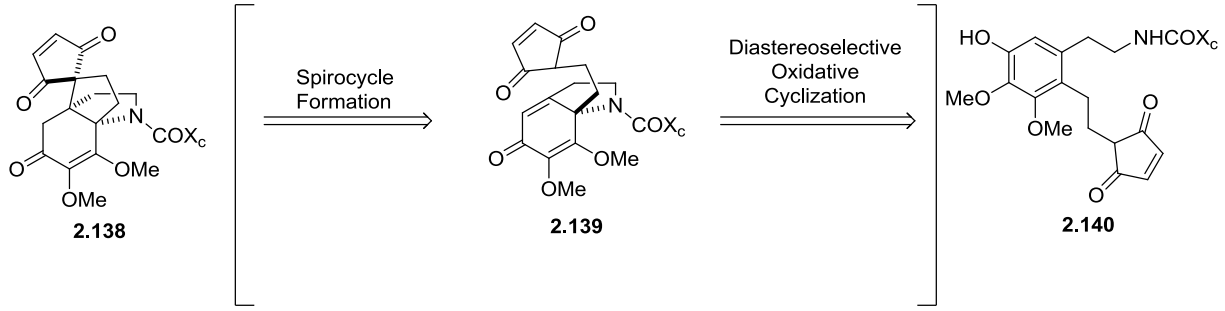
Once the two carbonyl groups are differentiated, subsequent oxidation of the thiol of **2.143** to its corresponding sulfoxide will enable the Pummerer rearrangement to take place. Elimination of the thiol group would provide the trione **2.144**, which should selectively enolize to **2.145** in the presence of acid and methanol.[192] Stereoselective reduction of the ketone would then provide tetracycle **2.137** (*cf.* Scheme 2.29).

Scheme 2.32



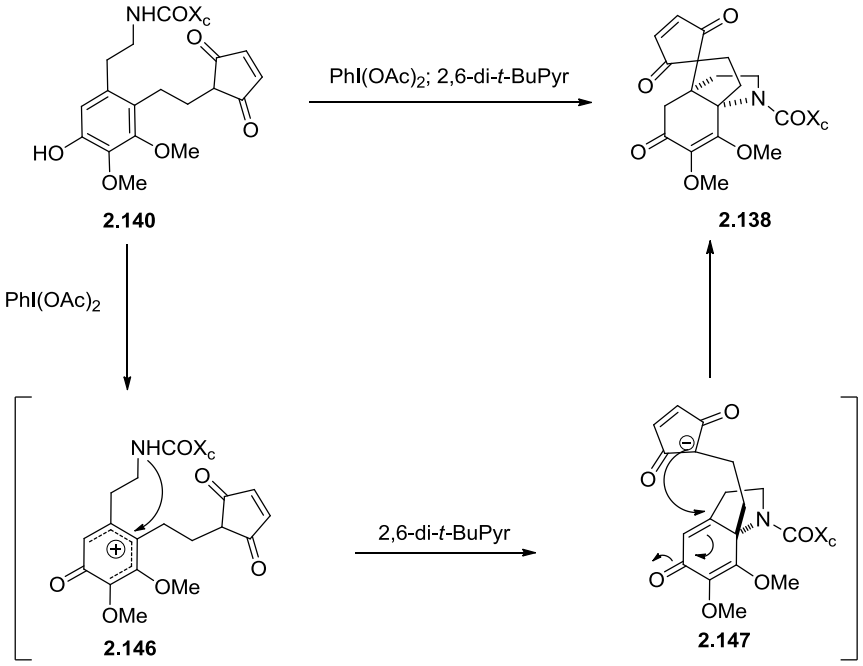
Our second biomimetic key step involves a diastereoselective oxidative cyclization/Michael addition sequence to provide tetracycle **2.138**. The sequence could be envisioned as a discrete two step process, or ideally, as a "one pot" reaction (Scheme 2.33). A proposed mechanism for the sequence is described below (Scheme 2.34).

Scheme 2.33



We proposed that phenethyl amine **2.140** could be oxidized in the presence of a hypervalent iodine reagent, such as phenyliodonium diacetate (PIDA), to furnish the aromatic cation **2.146** (Scheme 2.34).[193-196] Intramolecular capture of said cation with the appended chiral carbamate of **2.147** would provide the tetracycle **2.138**. We had hoped to control the stereoselectivity of the reaction with the chiral auxiliary appended to the attacking nitrogen atom.[197-199] Though hypervalent iodine mediated intramolecular cyclizations are well-precedented for electron rich aromatic phenethyl amines and alcohols,[193-196] we were curious to see if we could effect the cyclization at an extremely hindered site and in a stereoselective manner. Oxidative cyclizations to create masked *p,p*-disubstituted quinones was known, but one or both of the *p*-substituents are usually a low molecular weight alcohol (*ie* methanol or ethanol) which carries considerably less steric bulk as compared to our system **2.140**.[193-196]

Scheme 2.34



Another interesting scientific question we sought to answer with our oxidative cyclization was whether we could also effect an intramolecular Michael addition between the cyclopentenedione ring and newly formed quinone of **2.147**. The cyclopentenedione anion formed upon the addition of an appropriate non-nucleophilic base to the oxidative cyclization mixture should add regioselectively to the enone of **2.147** as opposed to the vinylogous ester, thus providing the tetracyclic core of acutumine, in most preferably, a single step. The diastereoselectivity of the Michael addition should not be of concern because the anion should add to the same face of the quinone as the ethyl substituent to which it is attached.

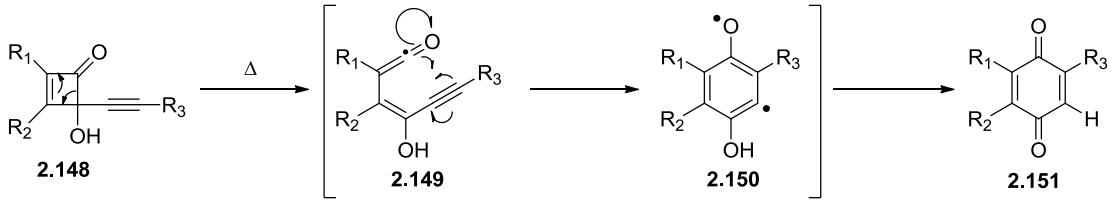
If both the oxidative cyclization and Michael addition were found to be successful, then we would have been the first to create an efficient and elegant biomimetic synthesis of acutumine's core. It is also important to point out that the

cyclopentene ring of the tetracyclic core we hoped to achieve, namely **2.138**, would require minimal oxidation and protecting group manipulations to achieve the hydroxyl cyclopentenone found in the final product. Recall that the synthesis of the said hydroxyl cyclopentenone had been a significant problem for both Castle and Herzon's syntheses, requiring numerous steps.

2.5 First Generation Martin Group Approach

Though we were excited to test the viability of our biomimetic key steps, we had to devise a way to quickly and efficiently obtain intermediate **2.140**. Towards that end, we pursued a number of different strategies simultaneously, the first of which features a reaction called the Moore cyclization (Scheme 2.35).[200-203]

Scheme 2.35

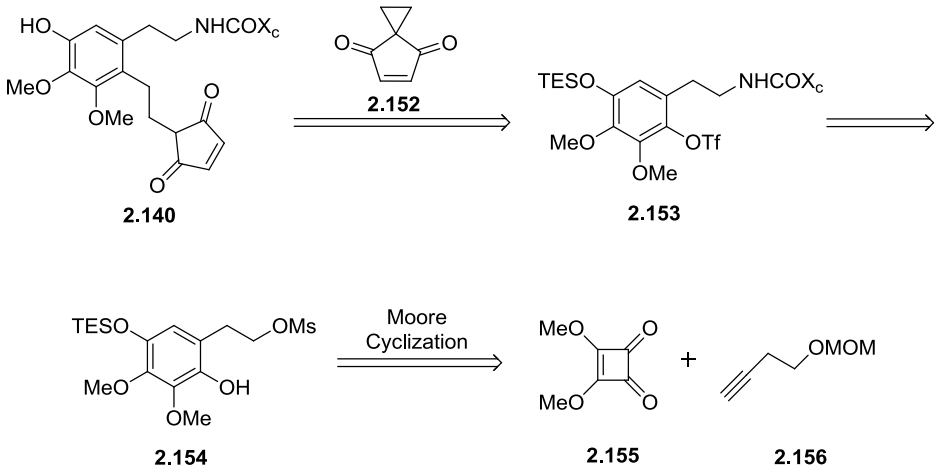


The Moore cyclization is a well-known process for making highly substituted quinones. The cyclization features a 4π-electrocyclic opening of a cyclobutene ring **2.148** to deliver a reactive ketene intermediate **2.149** that cyclizes in a 6-*exo*-dig fashion to provide a diradical intermediate **2.150**. Intermediate **2.150** then abstracts a hydrogen atom to provide quinones of the type **2.151**.[200-203] The Moore cyclization was appealing to us because it could provide highly substituted quinones in a minimal amount of steps. We envisioned using this strategy to access our key intermediate **2.140** (Scheme 2.36).

Working backwards, we believed that phenethyl amine **2.140** could be obtained through a transition metal mediated coupling between aryl triflate **2.153**[204] and the known

cyclopropyl cyclopentenedione **2.152** (Scheme 2.36).[205] Though we had seen precedent for the opening of a similar cyclopropyl ring with an aryl cuprate, we anticipated that the reaction might be difficult given that the aryl triflate was *o,o*-disubstituted.[204] Triflate **2.153** could be furnished from phenethyl mesylate **2.154** through a series of fairly routine functionalizations, including a selective mono triethylsilyl (TES) phenolic protection. We would obtain mesylate **2.154** from the lithium acetylide addition of **2.156** with dimethoxysquarate (**2.155**)[206] to produce the requisite cyclobutene ring with which to carry out the Moore cyclization[207] described above.

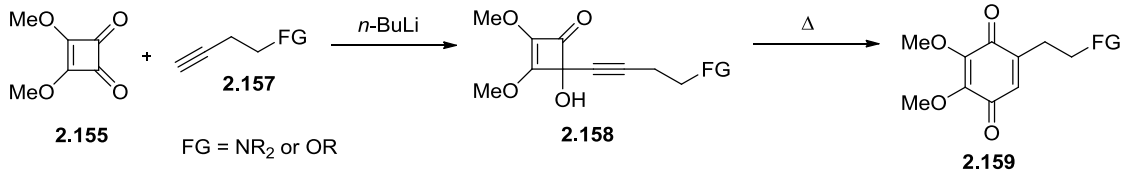
Scheme 2.36



The first challenge that we encountered in the forward synthesis was the preparation of a suitable alkyne with which to add to dimethoxysquarate **2.155** (Scheme 2.37). We were considering both but-3-yn-1-amines and but-3-yn-1-ols but ideally we wanted to introduce a nitrogen atom as early as possible in the synthesis to increase to minimize the step count. Protected alkynols were known to be well tolerated in Moore

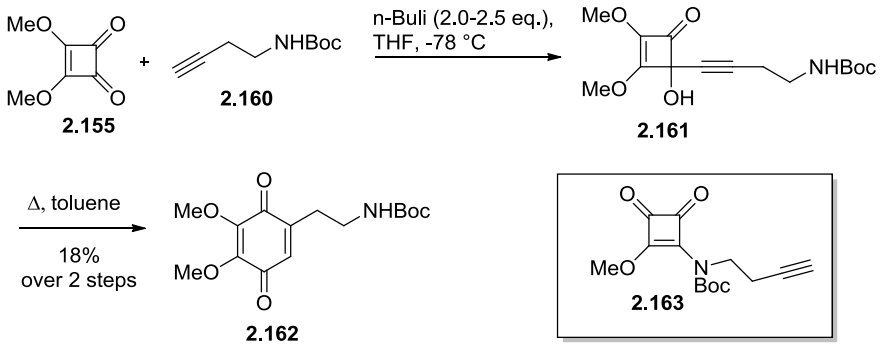
cyclizations, as were tertiary amines, though we did not know what to expect from primary or secondary amines as they were not mentioned in the literature.[208-210]

Scheme 2.37



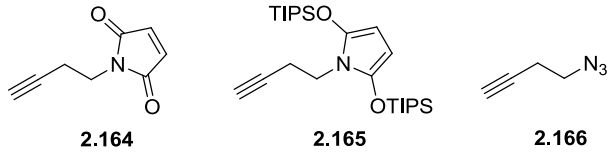
Towards that end, the reaction between dimethoxysquarate (**2.155**) and Boc-protected homopropargyl amine **2.160**[211] was investigated (Scheme 2.38). The dianion of **2.160** was prepared[212] with *n*-BuLi and added to a solution of dimethoxysquarate (**2.155**) at -78 °C. The cyclobutene ring **2.161** was heated under reflux in toluene to provide quinone **2.162** in 18% yield over two steps. Unfortunately, a major side product was formed upon the addition to squarate **2.155**, and that that side product was carried through the following Moore cyclization. The side product was isolated through column chromatography and was identified by ^{1}H NMR and LRMS data to be squarate **2.163** (Scheme 2.38). While the acidic carbamate hydrogen was found to survive the Moore cyclization, the initial addition of the dianion of **2.160** to dimethoxysquarate (**2.155**) was unfortunately not selective under the aforementioned conditions.

Scheme 2.38



The reaction was carried out in the presence of a couple other common bases (*ie* CaH_2 and LDA), both alone and in combination with one another, but side product formation continued to predominate. Attempts were made to access other nitrogen acetylides, namely **2.164-2.166**, however phthalimide **2.164** did not add to dimethoxysquarate (**1.155**), and the bis-siloxypyrrole **2.165** and azide **2.166** could not be obtained through known procedures (Figure 2.2).[213-215]

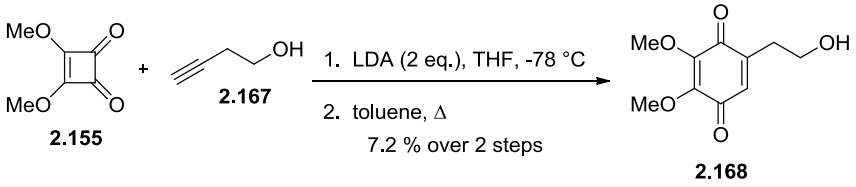
Figure 2.2



In light of our unsuccessful attempts to incorporate a nitrogen atom into the acetylide addition, we decided that the next most desirable alkyne for the synthesis would be but-3-yn-1-ol (**2.167**). Its use would preclude the need for a protection/deprotection sequence, leaving our total step count unaffected. In order for the reaction to proceed, it was necessary to use the dianion of alcohol **2.167** (Scheme 2.39). After initial deprotonation experiments, it was found that two equivalents of lithium diisopropylamide (LDA) provided the best results, but the yield of quinone **2.168** never exceeded 10% and,

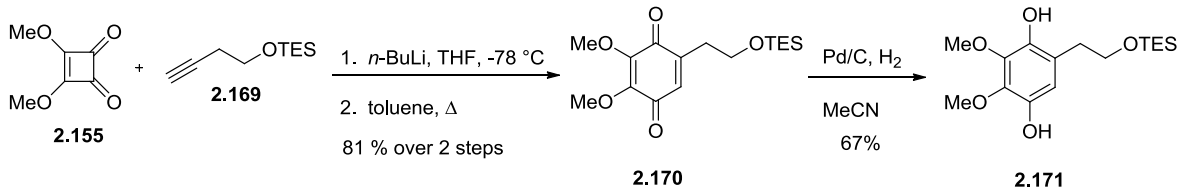
like carbamate **2.160**, but-3-yn-1-ol (**2.167**) was abandoned in favor of an alkyne that would provide the desired quinone **2.159** in higher yield (*cf.* Scheme 2.37).

Scheme 2.39



Thinking that a silyl group would impart the desired stability for the alkyne partner while still retaining the ability to be chemoselectively cleaved, **2.169** was synthesized in a single step from but-3-yn-ol (**2.167**) according to established literature procedures.[216] Alkyne **2.169** was lithiated and added to dimethoxysquarate (**2.155**). The subsequent cyclobutene ring underwent a Moore cyclization to provide quinone **2.170** in 81% yield over two steps (Scheme 2.40). We also briefly examined the *tert*-butyldimethylsilyl (TBS) protected alkyne in the sequence, but found that it performed worse than the TES variant.

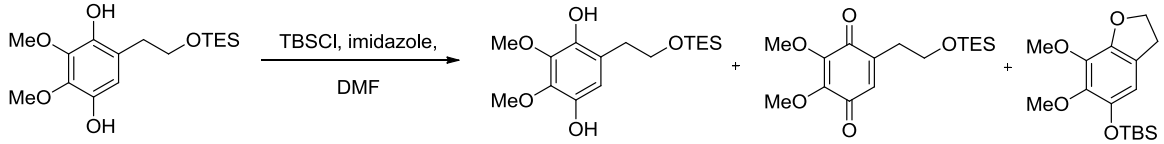
Scheme 2.40



Reduction of quinone **2.170** to its corresponding hydroquinone **2.171** was accomplished in 67% yield via a catalytic hydrogenation in acetonitrile (MeCN) (Scheme 2.40). Ethyl acetate (EtOAc) and methanol (MeOH) were also screened as solvents, but use of ethyl acetate provided the hydroquinone **2.171** in lower yields, whereas use of methanol led to silyl group cleavage.

The next step in the synthesis was to differentiate between the two phenol functionalities in hydroquinone **2.171** by selectively protecting the less hindered of the two with a bulky protecting group. The *tert*-butyldimethylsilyl (TBS) group was chosen due to its large size and ease of removal; however, all attempts to isolate the TBS-protected hydroquinone were fruitless (Scheme 2.41). The only products isolated from the reaction were starting material **2.171**, quinone **2.170**, and what was believed to be bicycle **2.172** based on ^{1}H NMR and mass spectrometry evidence. Namely we saw loss of the –TBS group and phenolic hydrogen in the ^{1}H NMR spectrum. We also saw the loss of the –TBS group in the mass spectrograph. Since it appeared that the TES group was not surviving the reaction conditions and that there might be selectivity issues with cleaving a TES vs. TBS group, we decided to pursue another starting alkyne partner for use in a Moore cyclization.

Scheme 2.41

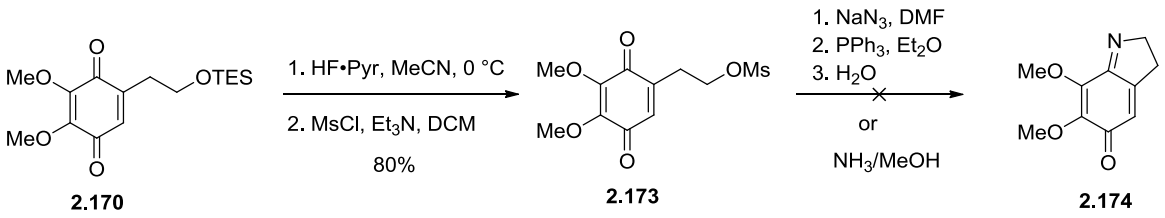


2.171 **2.171** **2.170** **2.172**

The TES-protected quinone **2.170** was used to test the feasibility of introducing a nitrogen functionality into the system immediately after the Moore cyclization (Scheme 2.42). First, the silyl group of **2.170** was cleaved with a solution of hydrofluoric acid (HF) and pyridine (Pyr) in MeCN to provide the free hydroxyl group, which was next mesylated to provide **2.173** in 80% yield (Scheme 2.42). Neither the reaction of the mesylate **2.173** with sodium azide (NaN_3) followed by Staudinger reduction nor the reaction of **2.1173** with ammonia in methanol appeared to produce any of the desired

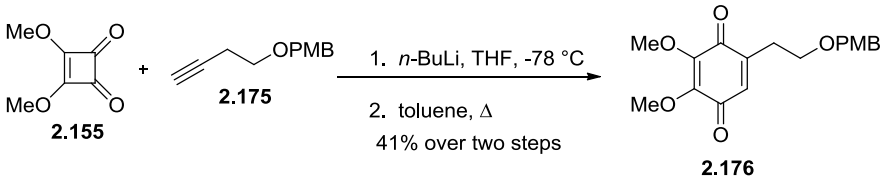
iminoquinone **2.174**.[217,218] Both reactions produced complex reaction mixtures, and no identifiable compounds were able to be separated and characterized from the mixtures.

Scheme 2.42



We then focused upon finding alternative alkynes of type **2.157** (*cf* Scheme 2.37, FG = OR) for which to try in the acetylide additions/Moore cyclization sequence. We decided upon a *p*-methoxybenzyl (PMB) protected but-3-yn-1-ol **2.175**, (Scheme 2.43) as the PMB group would be easily removed by mild oxidants and was robust enough to survive the quinone reduction. Synthesized from but-3-yn-1-ol (**2.167**) by an established literature procedure,[219] PMB-protected alkyne **2.175** was subjected to the acetylide addition/Moore cyclization sequence to provide quinone **2.176** in 41% yield.[208,209,220]

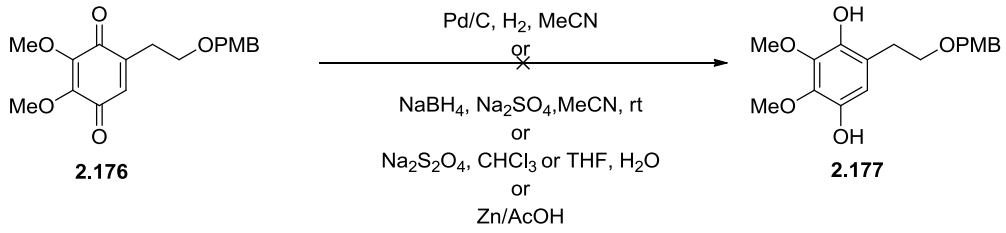
Scheme 2.43



Reduction of **2.176** to hydroquinone **2.177** was problematic (Scheme 2.44).[221] While the TES-protected quinone **2.170** (*cf.* Scheme 2.40) underwent reduction to its corresponding hydroquinone **2.171** in the presence of Pd/C and hydrogen gas (H_2), this method was not successful for the reduction of **2.176**. The product of the reaction was a complex mixture, from which no compound could be cleanly isolated. Based on the ^1H

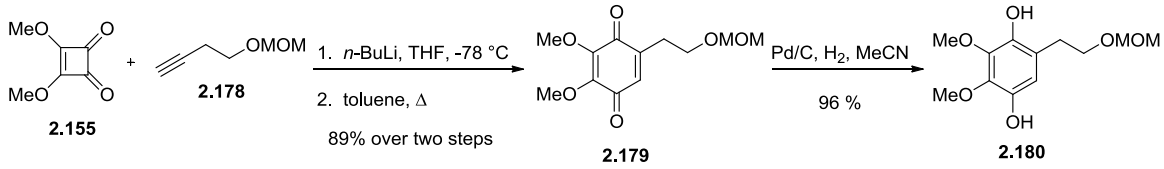
NMR spectrum of the crude reaction mixture, we hypothesized that PMB cleavage was most likely a competing reaction. A variety of other standard reduction conditions were examined, but all reactions provided either a complex mixture of productions or no reaction at all.

Scheme 2.44



The next butynol protecting group selected for examination was methoxymethyl (MOM). Alkyne **2.178**, which was prepared in one step from the commercially available but-3-yn-1-ol (**2.167**) by an established literature procedure,[222] was subjected to an acetylide addition/Moore cyclization sequence to provide quinone **2.179** in 89% yield (Scheme 2.45). Reduction of quinone **2.179** by hydrogenation provided the desired hydroquinone **2.180** in 96% yield.

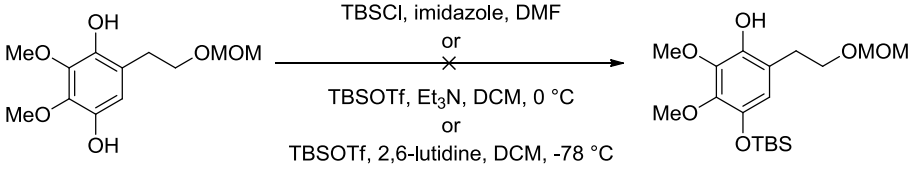
Scheme 2.45



It was again time to focus on selective silyl protection of the least hindered phenol in order to advance hydroquinone **2.180**. There was no literature precedent available for the selective protection of a less hindered phenol in the presence of a more hindered one but we again reasoned that a bulky silyl group such as TBS might preferentially silylate

the least hindered phenol (Scheme 2.46). However, attempts to incorporate TBS into hydroquinone **2.180** resulted solely in returned starting material. Accordingly, we examined the less hindered TES protecting group. After a brief survey of conditions, we found that the reaction of **2.180** with triethylsilyltriflate (TESOTf) in the presence of 2,6-lutidine provided quinone **2.182** in 25% yield (Scheme 2.47).[223] Two-dimensional ^{1}H NMR and ^{13}C NMR experiments were carried out on compound **2.182** to support its identity (Figure 2.3). NOESY correlations were used to identify the orientation of the TES-group. There were two main NOESY correlations that led to the assignment of compound **2.182** as the desired regioisomer (Figure 2.3). There was a correlation between the phenolic OH peak and the two benzylic hydrogens atoms (Hb) of the MOM side chain and also a correlation between the hydrogen atoms of the TES-protecting group and the aryl hydrogen atom (Ha).

Scheme 2.46



Scheme 2.47

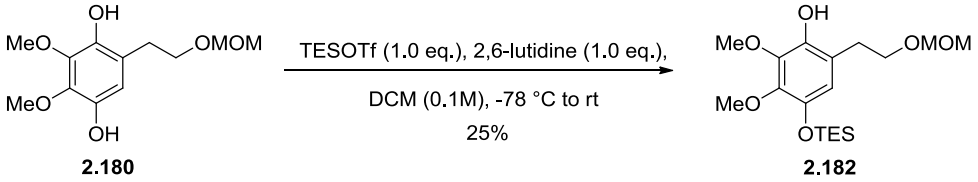
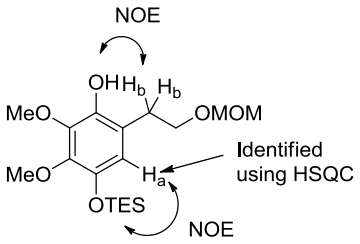


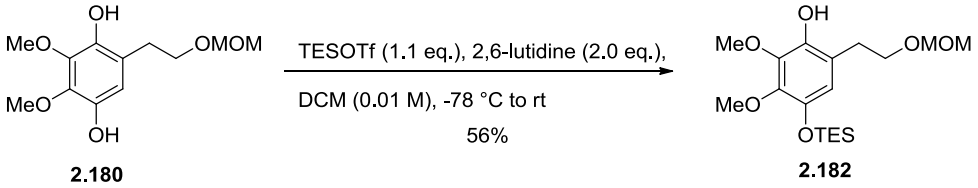
Figure 2.3:



2.182

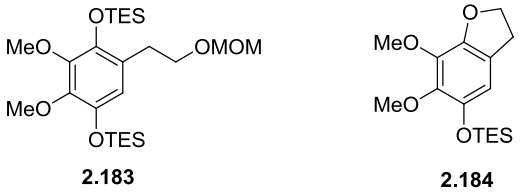
After a survey of different reaction conditions, we found that the optimal conditions involved a slow (syringe pump) addition of a solution of TESOTf in DCM (1.1 eq., 0.7 M) to a solution of hydroquinone **2.180** and 2,6-lutidine (2.0 eq.) in DCM (0.014 M) at -78 °C to provide the desired mono-protected compound **2.182** in 56% yield (Scheme 2.48). Two main problems had to be overcome. The first was the formation of the bis-silylated side product **2.183** (Figure 2.4). Adding the TESOTf in a solution of DCM over time and decreasing the overall concentration of the reaction mixture eliminated the bis-silylation problem. However, the reaction still did not proceed to completion, so further optimization was required. In some reactions, the bicycle **2.184** appeared as a major side product (Figure 2.4). The structure of **2.184** was supported by LCMS and ^{1}H NMR experiments, which showed the loss of both the phenol proton and the -OMOM moiety. Operationally, the TESOTf solution had always been added to the hydroquinone solution before the 2,6-lutidine. We reasoned that if the order of addition were reversed then the side product formation would be suppressed as the Lewis mediated cyclization could not take place in a sufficiently basic environment. This was indeed the case and the formation of bis-silylated **2.183** and bicycle **2.184** were suppressed.

Scheme 2.48



2.180 **2.182**

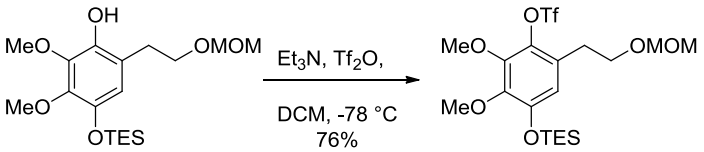
Figure 2.4



2.183 **2.184**

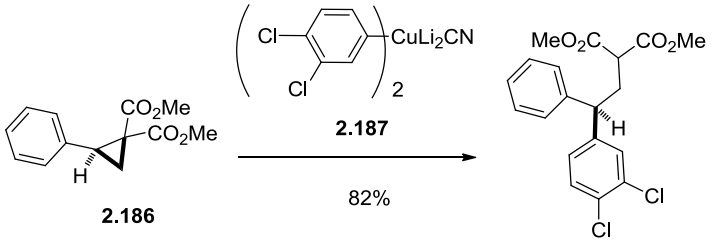
Phenol **2.182** was reacted with triflic anhydride (Tf_2O) and triethylamine (Et_3N) to provide aryl triflate **2.185** in 76% yield (Scheme 2.49).[224] Recall that we desired to effect a metal mediated coupling between **2.185** and the known cyclopropylpentenedione **2.152**[225] in order to obtain our key oxidative cyclization precursor **2.140** (*cf.* Scheme 2.36). However, after a thorough search of the literature, we found that there was no precedent for a metal mediated reaction between an *o,o*-disubstituted aryl triflate and a cyclopropane containing multiple electron withdrawing groups. The most relevant prior art was a reaction between aryl cuprate **2.187** and cyclopropyl dicarboxylate **2.186** to produce **2.188** in 82% yield (Scheme 2.50).[204] However, the precedent was far from ideal. Our reaction would require an electron rich aryl *o,o*-disubstituted cuprate be made from triflate **2.185** (Scheme 2.51), which is not at all similar to the precedented dichloro aryl cuprate **2.187**. Nonetheless, we set out to try the precedented conditions on our system.

Scheme 2.49



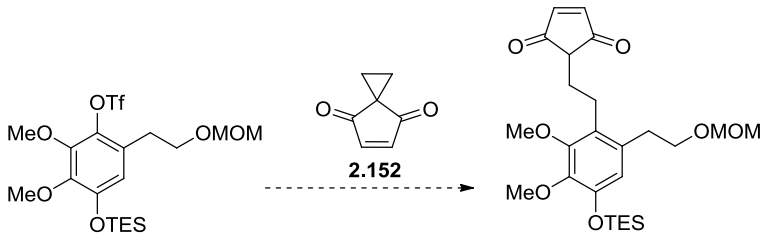
2.182 **2.185**

Scheme 2.50



2.187 **2.186** **2.188**

Scheme 2.51



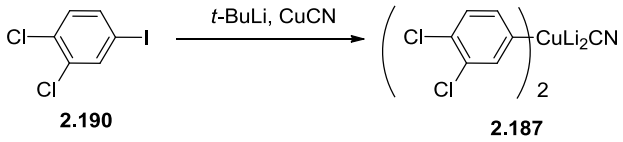
2.152

2.185 **2.189**

In order to effect the desired copper mediated cyclopropane coupling, it was first necessary to convert aryl triflate **2.185** to an organocuprate. Our precedent had shown that cuprate **2.187** was obtained from reaction between 1,2-dichloro-4-iodobenzene (**2.190**), *t*-BuLi, and copper (I) cyanide (Scheme 2.52),[204] so we set out to obtain aryl iodide **2.191** (Scheme 2.53). Replacement of the triflate with iodide was attempted with sodium iodide,[226] but our efforts failed to produce anything other than returned starting material (Scheme 2.53). A likely hypothesis for the failure of this reaction is that our aryl ring was too electron rich for the triflate to be reactive towards nucleophilic aromatic

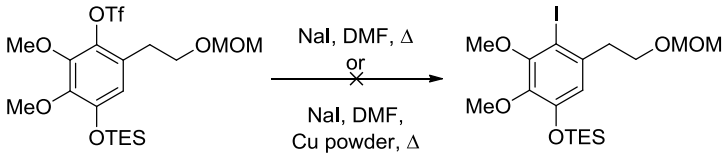
substitution.[227] We desired to form an organocuprate directly from triflate **2.185**,[228,229] but we needed to bring through more material.

Scheme 2.52



2.190 **2.187**

Scheme 2.53

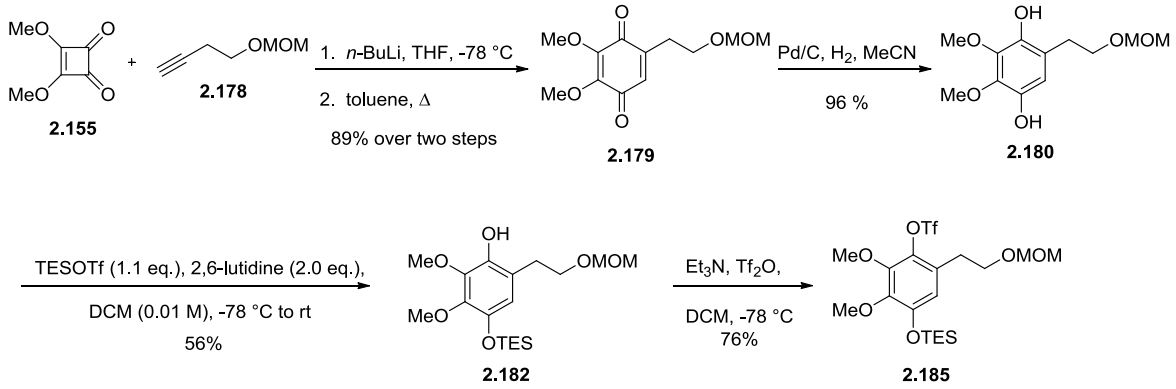


2.185 **2.191**

Unfortunately, upon attempted scale up of the synthetic sequence, we were faced with three major problems. The first was that we could not scale up the selective mono TES protection without a considerable loss in yield (Scheme 2.54). When run on a scale of approximately 100 mg or smaller, the reactions proceeded reliably in about 56% yield, but when the silylation was attempted on a larger scale, the yields decreased to less than 20%. While this was a solvable problem, we did not want to expend considerable effort to solve it until we were sure that triflate **2.185** was a viable precursor to our desired intermediate **2.189** (*cf.* Scheme 2.51). Towards that end, a series of smaller (ca. 100 mg or smaller) silylation reactions were run, and all of the phenol **2.182** obtained was combined and stored in a freezer under nitrogen. Our second major problem was that phenol **2.182** was not amenable to being stored, even for short periods (three to five days) under nitrogen in a freezer. The material was found to decompose rapidly into a complex mixture, from which none of **2.182** was recovered. While this could be solved by quickly

transforming phenol **2.182** to triflate **2.185**, we again, needed to bring through more material from the beginning of the synthesis.

Scheme 2.54



The third major problem with the route was our starting material. Dimethoxysquarate (**2.155**) is a known irritant,[206] and the slightest exposure caused an allergic-like reaction that would present itself in the form of hives and last from three to four weeks (Scheme 2.54). While the risks associated with **2.155** did not automatically preclude its use as a starting material in our synthesis, this problem, in addition to the other two previously mentioned gave us pause to reconsider the route. During this time, it is important to know that we were also pursuing a parallel route towards key intermediate **2.140**, and that the route appeared to be the more promising of the two (*cf.* Scheme 2.36). With three considerable problems occurring within the first five steps of this route, and the viability of the use of *o,o*-disubstituted triflate **2.185** in a metal mediated coupling in question, we decided to abandon this route and devote our full resources to what we felt was the better synthesis.

2.6 SECOND GENERATION MARTIN GROUP APPROACH

At the time the synthesis featuring the Moore cyclization was being investigated, another route towards intermediate **2.140** was also being developed (Scheme 2.55). We envisioned that phenol **2.140** would come from aryl bromide **2.192** through a sequence including aryl bromide and enone olefin reductions, preferably undertaken in a single step, and an alkylation/elimination sequence at either of the α-carbonyl carbons in cyclopentadione **2.192** to provide cyclopentenedione **2.140**. Aryl bromide **2.192** would be obtained from the alkylation of ethyl ester **2.193** with 1,3-cyclopentadione and subsequent elimination of the resulting tertiary alcohol. Ester **2.193** would come from a SmI_2 mediated cleavage[230] of tetrahydroisoquinoline **2.194**, which would be obtained from a regioselective Pictet-Spengler reaction between amine **2.195** and ethyl glyoxylate. The bromine atom of **2.195** serves the very important purpose of directing the Pictet-Spengler reaction. When we developed this route, we found no precedent for controlling the regioselectivity of a Pictet-Spengler reaction with a phenethylamine of type **2.197** (Figure 2.5).[231] Though the ether groups adjacent to Ha and Hb were different, Battersby had suggested that a benzyl ether would not serve a bulky enough group with which to significantly affect the regiochemistry of the Pictet-Spengler reaction. Therefore, we came up with the unconventional solution to use a bromine atom as a blocking group, with which to direct the reaction. We envisioned that the desired phenethylamine **2.195** could be obtained from the readily available phenol **2.196**.

Scheme 2.55

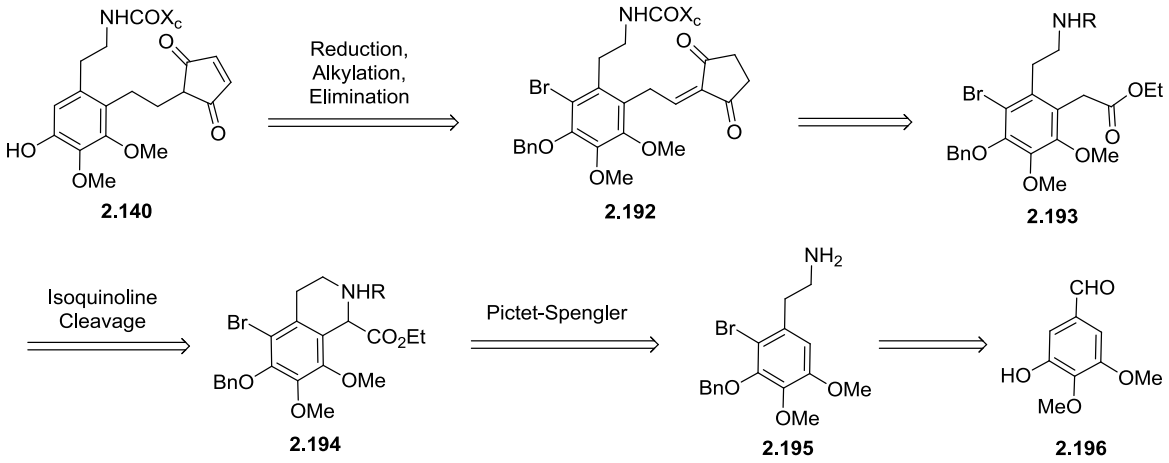
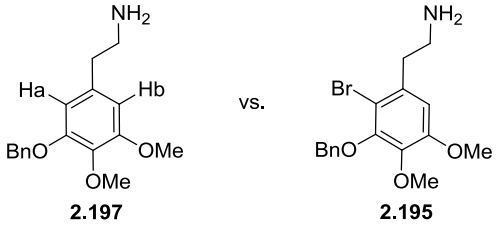
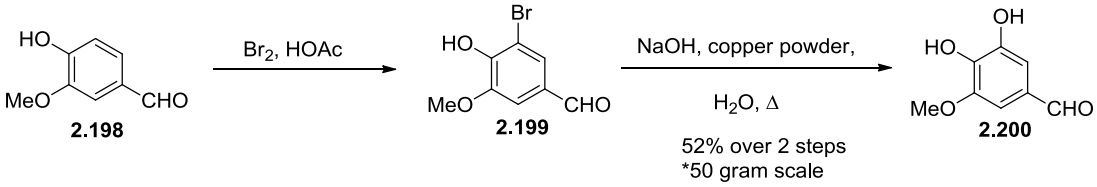


Figure 2.5



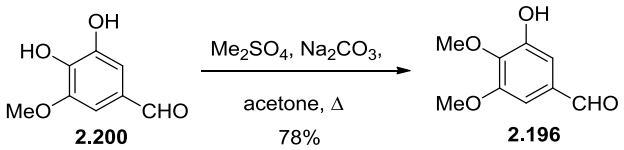
The route started with the bromination of commercially available vanillin (**2.198**) to provide 5-bromovanillin (**2.199**) according to a well-established procedure (Scheme 2.56).[232] Crude aryl bromide **2.199** was then subjected to a copper-catalyzed nucleophilic aromatic substitution reaction to provide diol **2.200**, which is also commercially available, but much more expensive than vanillin (**2.198**), in 52% yield over two steps.[233] It is notable that this route was already an improvement over the Moore cyclization route as it worked well on multigram scales (ca. 50 g).

Scheme 2.56



The next step in the sequence was the known regioselective methylation[233] of **2.200** (Scheme 2.57) which proceeded in 78% yield. As electron-rich phenolic anions are known to be easily oxidized in the presence of oxygen,[234] an attempt was made to improve the yield of phenol **2.196** by removing oxygen from the solvent via the freeze/pump/thaw method; however, there was no improvement.

Scheme 2.57



The regioselectivity of the methylation can be explained by the enhanced acidity of the phenol *para*- to the electron-withdrawing aldehyde moiety. The structure of **2.196** was also supported by the lack of symmetry present in the ^{1}H NMR spectrum. Phenol **2.196** was then selectively brominated *ortho*- to the phenolic hydroxyl group using bromine (Br_2) and acetic acid (HOAc) to provide aryl bromide **2.201** in 79% yield (Scheme 2.58). The regioselectivity of the reaction was again supported by NOE data (Figure 2.6). The bromine would serve as a blocking group to ensure the correct regioselectivity of the upcoming Pictet-Spengler reaction. Phenol **2.201** was protected as its benzyl ether **2.202** in 91% yield. It is important to note that as in the above methylation reaction (*cf.* Scheme 2.57), the electron rich phenolic anion of **2.201** appeared to be susceptible to oxidation in the presence of oxygen. When the reaction was

performed in DMF, the yield of **2.202** was 61%; however, when the reaction was performed in freeze/pump/thaw deoxygenated DMF the yield of **2.202** increased to a reproducible 91% yield (Scheme 2.58).

Scheme 2.58

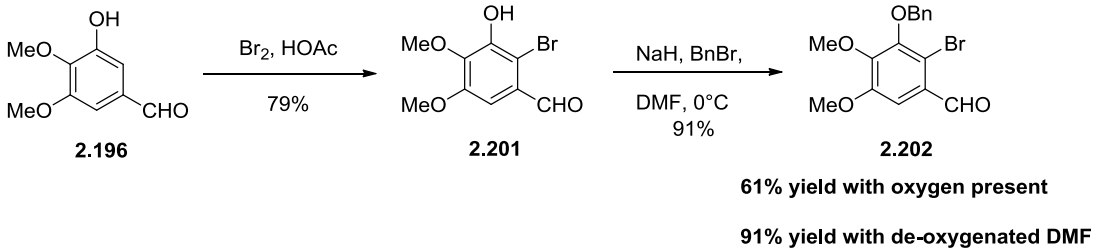
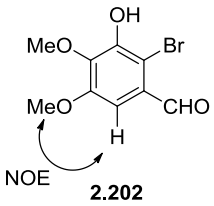
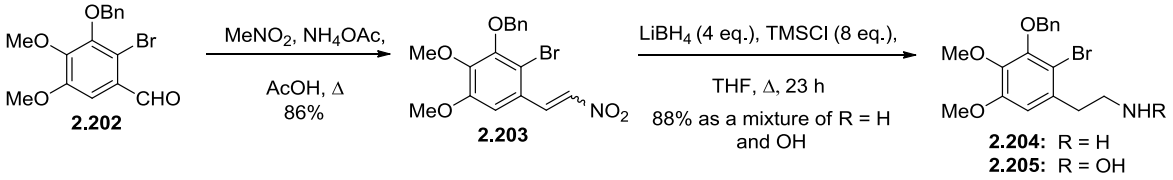


Figure 2.6

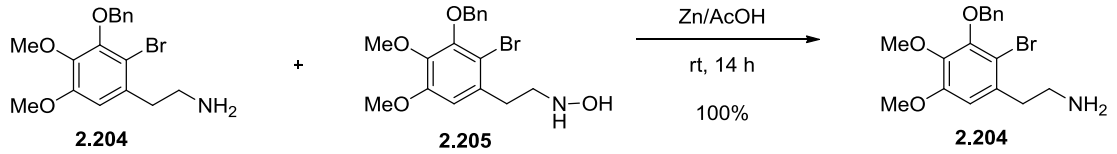


Aldehyde **2.202** was then subjected to standard Henry reaction conditions with nitromethane to give nitroalkene **2.203** in 86% yield. Nitroalkene **2.203** was reduced using lithium borohydride ($LiBH_4$), chlorotrimethylsilane (TMSCl) and THF (forming $BH_3 \cdot THF$ *in situ*) to provide a mixture of amine and N-OH compounds **2.204** and **2.205** according to LCMS and ^1H NMR data (Scheme 2.59).[235] Sodium borohydride ($NaBH_4$) and lithium aluminum hydride (LAH) were also examined as reducing agents, but all resulted in debromination. While the mixtures of amine and hydroxyl amine **2.204** and **2.205** were inseparable by acid/base extraction and column chromatography, **2.205** was quantitatively converted to amine **2.204** upon further reduction by stirring with zinc (Zn) in acetic acid (AcOH) at room temperature for 14 h (Scheme 2.60).[236,237]

Scheme 2.59

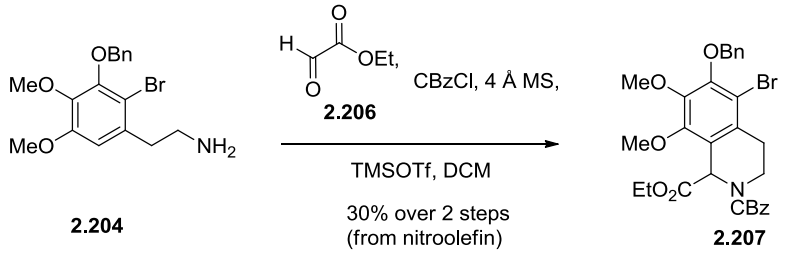


Scheme 2.60



The crude amine **2.204** was next mixed with ethyl glyoxylate (**2.206**) in the presence of molecular sieves to generate an imine, and benzyl chloroformate (CbzCl) and trimethylsilyl trifluromethansulfonate (TMSOTf) were added to effect the Pictet-Spengler reaction (Scheme 2.61).[238] Tetrahydroisoquinoline **2.207** was thus obtained in 30% yield (unoptimized) over two steps from nitroalkene **2.203** (*cf.* Scheme 2.59).

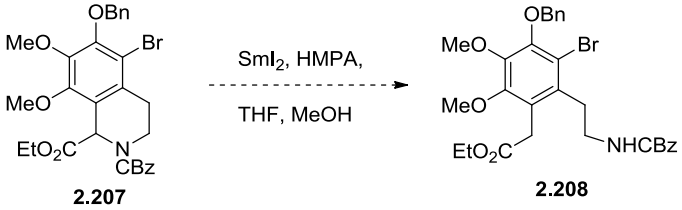
Scheme 2.61



The next step in the synthesis was to subject tetrahydroisoquinoline **2.207** to a reductive ring opening reaction (Scheme 2.62). Although known for being a difficult reagent to work with,[239,240] samarium diiodide (SmI_2) had been shown to be an effective promoter of reductive ring opening reactions in systems similar to **2.207**.[241,242] Samarium diiodide is a powerful reductant, and in the presence of oxygen will readily, and for all

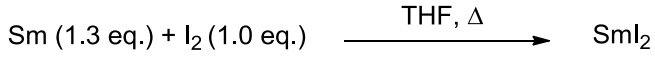
intent and purposes irreversibly, oxidize to SmI_3 which would not promote the reductive ring opening reaction.[239] There are a variety of ways to prepare SmI_2,[239] but the most simple and atom-economical method is to add iodine to a solution of samarium powder in deoxygenated THF (Equation 2.1).[243]

Scheme 2.62



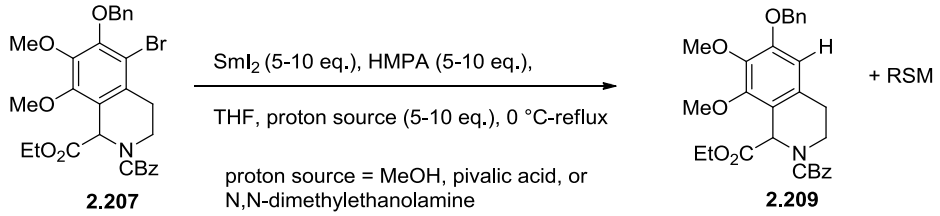
2.207 **2.208**

Equation 2.1

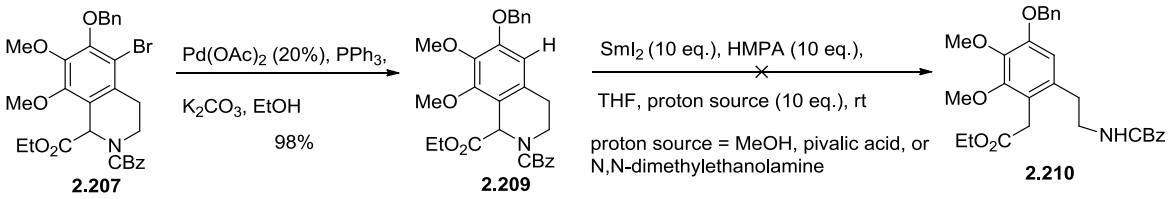


When **2.207** was subjected to SmI_2 in the presence of HMPA and a proton source, none of the desired ring opened product **2.209** was observed (Scheme 2.63). After extensive optimization of such factors as stoichiometries, proton sources, and temperature, the only product observed other than returned starting material was debrominated tetrahydroisoquinoline **2.209**. The bromine, having served its purpose in the previous Pictet-Spengler reaction, was no longer needed, and its loss was of no great concern. However, the possibility that the aryl anion generated by the loss of the bromine from **2.207** in the SmI_2 reaction was interfering with the ring opening reaction did pose a concern. Toward that end, the aryl bromide was removed from **2.207** prior to the ring opening reaction (Scheme 2.64).[244] However, the SmI_2 reaction with **2.209** provided only returned starting material.

Scheme 2.63



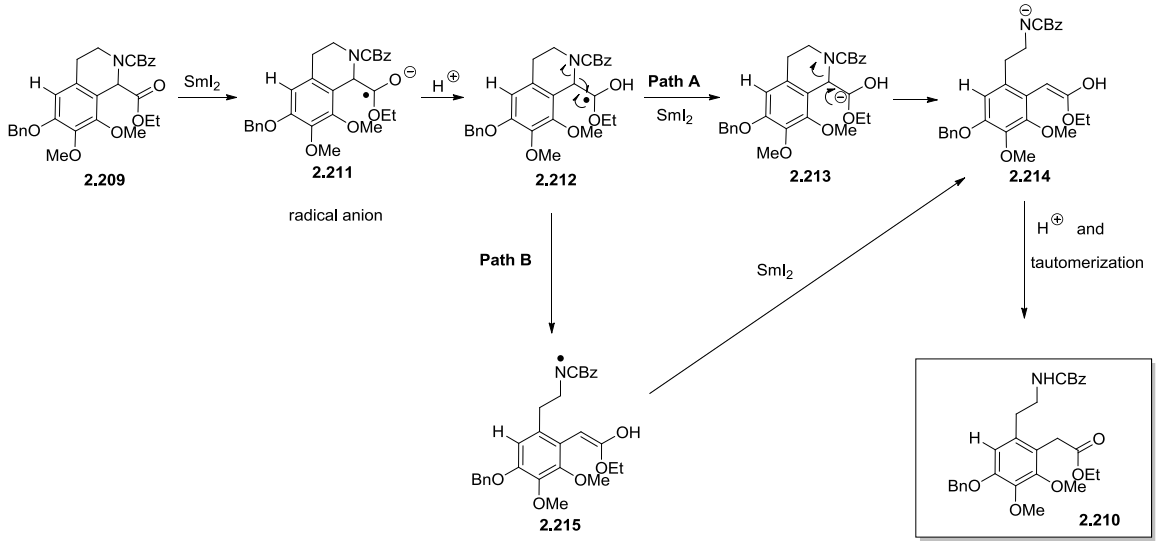
Scheme 2.64



We looked to the proposed mechanism of the SmI_2 mediated ring-opening and a model of tetrahydroisoquinoline **2.209** for answers. The mechanism for the ring opening reaction, as hypothesized by Honda,[230] would begin with the addition of an electron to the carbonyl group of the ester moiety of **2.209** to create the radical anion **2.211** (Scheme 2.65). The hydroxyl anion could then be quenched *in situ* with an appropriate proton source to provide the radical **2.212**. At this point, Honda presumed that the mechanism may diverge into one of two distinct pathways (Path A and Path B), though he has shown no support for one over the other. In Path A, a second molecule of SmI_2 could donate a single electron to the radical species **2.212** to create anion **2.213**, the carbon-nitrogen bond of which could ionically fragment to form the enol **2.214**. In path B, the radical species **2.212** could first undergo homolytic carbon-nitrogen bond cleavage to provide **2.215**, which upon contact with a single electron from a second molecule of SmI_2, could form the enol **2.214**. Acidification and tautomerization of **2.214** would provide the desired phenethyl carbamate **2.210**. In either case, Path A or Path B, carbon-nitrogen

bond cleavage would preferred if there were an anti-periplanar orbital alignment between the ester *p*-orbital containing the radical or anion and the σ* orbital of the carbon-nitrogen bond.

Scheme 2.65



We next looked for any structural features within dihydroquinoline **2.209** that might disrupt the orbital alignment necessary for carbon-nitrogen bond cleavage to occur. After building a model of **2.209**, it was thought that the Cbz group on nitrogen might be forcing the ethyl ester to adopt an axial conformation on the cyclohexane ring (Scheme 2.66 and Figure 2.7).[245,246] We usually depict carbamates as drawn in compound **2.209**; however, it is well- established that the nitrogen-carbon bond of a carbamate contains significant sp^2 character, because of contributions from the resonance form **2.216** (Scheme 2.66). Such resonance contributions can have a significant effect the preferred conformation of a carbamate, especially for to 2- and/or 6-substituted N-carbamoyl piperidines, and heterocycles that include these rings, including tetrahydroisoquinolines

(Scheme 2.66). The sp^2 character of the nitrogen-carbon carbamoyl bond can create significant $A_{1,3}$ strain between the carbamate and any 2- and/or 6-substituents on the ring (Scheme 2.66 **2.218** and Figure 2.7 **2.220**). In order to mitigate the unfavorable steric interaction, the 2- and/or 6-substituents will preferentially adopt an axial, spatial orientation on the piperidine ring if possible (Scheme 2.66, chair **2.219** as opposed to chair **2.217**).[245] We believed that as a result of the ester adopting an axial conformation, as shown in **2.219**, the σ* orbital of the carbon-nitrogen bond would be aligned orthogonally to the *p*-orbitals of the carbonyl π-system, thereby preventing the orbital alignment necessary for the ring opening to occur according to the proposed radical mechanism (*cf.* Scheme 2.65 and Figure 2.7). However, we can see from the simplified 2-ester substituted piperidine structures **2.220** and **2.221**, where the ester is shown adopting a position under the ring, that the *p*-orbitals of the axially 2-substituted ester moiety of **2.221** can align anti-periplanar to the σ*-antibonding orbital of the C-N bond. It appears that the axial conformation of the ester should not prevent the SmI_2 mediated ring opening from occurring.

Scheme 2.66

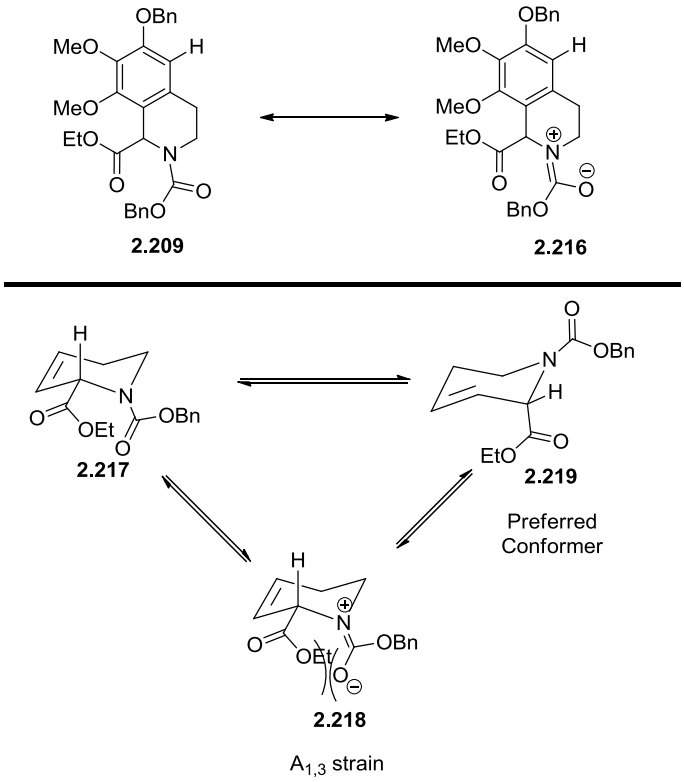
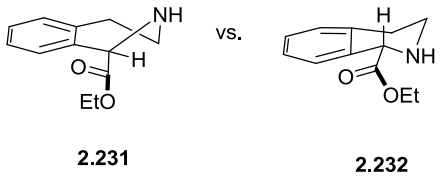
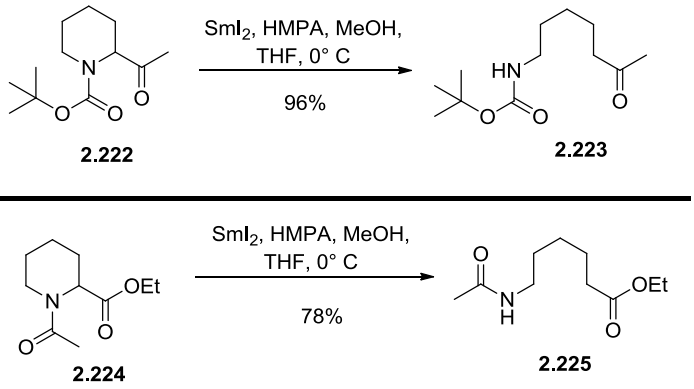


Figure 2.7



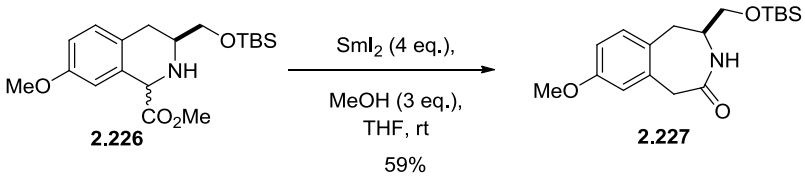
Our assumption was supported by Honda and coworkers, who successfully induced the SmI_2 promoted ring openings of acyl protected piperidines with ester or ketone substituents at the 2-position of the ring, which presumably adopted the orientation of conformer **2.221** during reaction (Scheme 2.67).[242]

Scheme 2.67

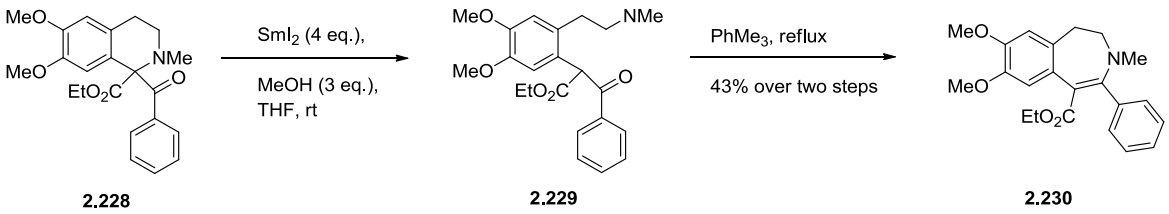


Honda has also promoted the ring opening of isoquinoline derivatives, such as **2.226** and **2.228**, with SmI_2 (Scheme 2.68 and Scheme 2.69).[230] The SmI_2 ring opening reactions tended to be more successful when the 2-substituent of the piperidine ring was a ketone, as opposed to an ester, and also when tetrahydroisoquinolines were used as substrates. In general, the more electron withdrawing the heterocyclic substrate, the better the ring opening reaction proceeded. Though the piperidine ring of tetrahydroisoquinolines cannot adopt a true chair conformation, a conformational analysis of a physical model of *N*-H tetrahydroisoquinoline shows that whether the ester moiety of the ring is in a pseudoaxial (**2.231**) or pseudoequatorial (**2.232**) position, orbital alignment appears favorable for SmI_2 mediated C-N bond cleavage (Figure 2.7).

Scheme 2.68



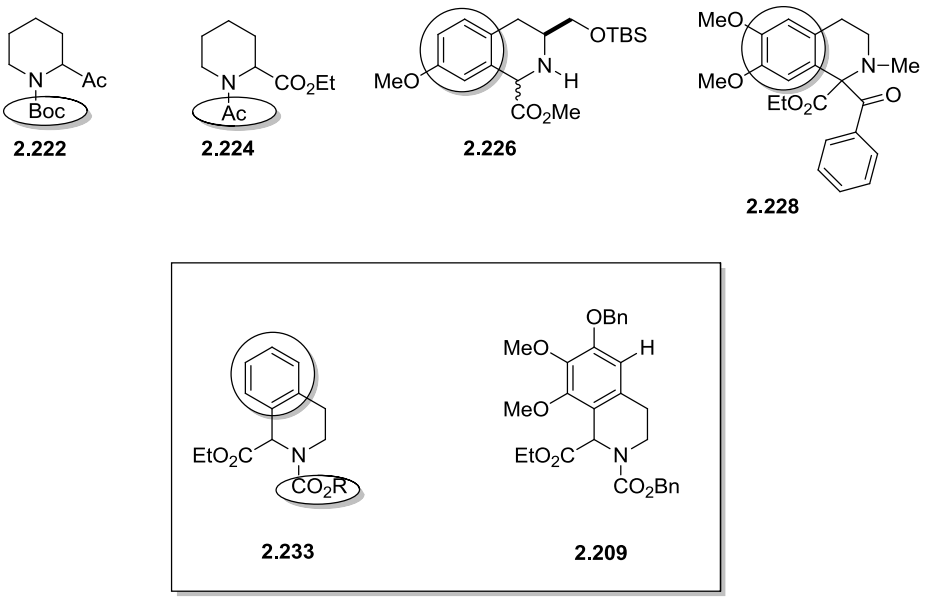
Scheme 2.69



2.228 **2.229** **2.230**

Based on Honda's precedent, we were optimistic that the SmI_2 ring opening of **2.209** would proceed without incident (Figure 2.9). Our substrate contained an isoquinoline ring, an ester at the 2-position of the piperidine ring, and a carbamate on the isoquinoline nitrogen. All three features had been shown to be tolerated using Honda's conditions, yet tetrahydroisoquinoline **2.209** remained resistant to the ring opening. However, while Honda had disclosed that the ring opening reaction worked separately with *N*-acylated/carbamoylated piperidines (**2.222** and **2.224**) and 2-ester/acetyl substituted tetrahydroisoquinolines (**2.226** and **2.228**), he had not shown an example where both were combined, namely a compound of the type **2.233**. Our key intermediate **2.209** was a 2-ester substituted *N*-carbamoylated tetrahydroisoquinoline that remained resistant toward all attempts to cleave the C-N bond using SmI_2 (Figure 2.9). We concluded, based on our empirical experimental evidence, that Cbz-protected isoquinoline **2.209** was in some way forcing an unfavorable conformation of the ester to the carbamate, thereby preventing SmI_2 promoted ring opening.

Figure 2.9



Recall that the mechanism of the ring opening required alignment of an ester *p*-orbital containing the radical or anion and the σ* orbital of the carbon-nitrogen bond in order to be successful (*cf.* Scheme 2.65). At first we believed that the ester moiety of **2.209** adopted an axial orientation in order to avoid $A_{1,3}$ strain with the Cbz moiety. With the success of *N*-acylated/carbamoylated, 2-acetyl/ester substituted piperidines **2.222** and **2.224**, we made two assumptions that made us rethink our original hypothesis. The first was that the ester or ketone substituents of **2.222** and **2.224** were in an axial position, and the second was that the axial orientation of the acyl group appeared to facilitate the reaction rather than prevent it. Honda had also shown the ring opening to be successful when tetrahydroisoquinolines were employed as substrates; therefore we concluded that the failure of **2.209** to undergo reaction with SmI_2 was most likely due to the combination of the two features. While we can only speculate as to the true cause, we hypothesized

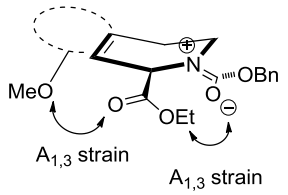
that the rigidity imposed upon the piperidine moiety of **2.209** by the phenyl ring of the isoquinoline system in conjunction with the *N*-carbamate caused the piperidine ring to adopt a twisted chair conformation in which the ester ended up in neither an axial nor equatorial, yet wholly unproductive, position (Figure 2.10).

When a physical model of a simplified *N*-carbamoylated, 2-ester substituted tetrahydroisoquinoline was built and studied three configurations of the molecule seemed possible (Figure 2.10). Tetrahydroquinoline systems, similar to those of **2.209**, have been shown to adopt boat conformations (**2.234**).[245-248] While this analysis is highly speculative and no computational studies have been done, we surmised that the most favorable conformation for our desired intermediate **2.209** (*cf.* Figure 2.9) would not be **2.234**, though it did seem to have the orbital alignment required for SmI_2 mediated C-N cleavage to occur. In **2.234**, it appears that the ester can adopt an axial orientation, which we had already surmised was favorable toward the SmI_2 ring opening conditions. However, the boat structure would also be associated with unfavorable gauche and $A_{1,3}$ interactions that would decrease the likelihood of **2.209** adopting the conformation depicted in **2.234**.[247,248]

While we are unsure of the exact cause, it seems clear that the ester at the 2-position of the tetrahydroisoquinoline ring will not be able to adapt either a pseudo axial nor pseudo equatorial conformation, resulting in poor orbital alignment between the π-orbital of the ester and the σ^* orbital of the C-N bond. The orbital alignment appears favorable in the boat conformer **2.234**, but our empirical experimental results imply that is not the conformation that our intermediate **2.209** has adopted as all out attempts toward SmI_2 mediated cleavage of the C-N bond have failed. Admittedly this is a rather

simplistic way to look at the system, and computational and two-dimensional NMR studies would be needed to provide a more comprehensive picture of the system.

Figure 2.10



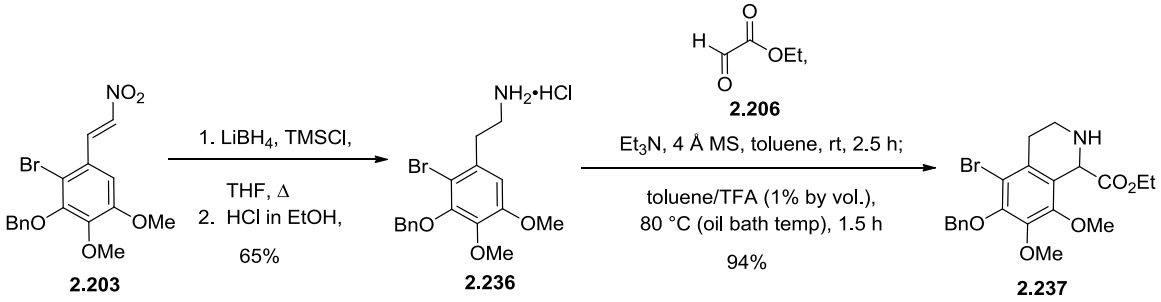
2.234

While we can only speculate as to the true cause of the failure of **2.209** to react with SmI_2 ring opening conditions, we hypothesized that the rigidity imposed upon the piperidine moiety of **2.209** by the phenyl ring of the isoquinoline system in conjunction with the *N*-carbamate caused the piperidine ring to adopt a twisted chair conformation in which the ester ended up in neither an axial nor equatorial, yet wholly unproductive, position (Figure 2.10). We decided to remove the carbamoyl group of **2.209** in the hope of alleviating whatever unfavorable strain was causing our desired ring opening to fail. Also, *N*-H and *N*-Me, 2-ester substituted tetrahydroisoquinolines had already been precedented to work well using Honda's conditions.[230]

Eager to test our hypothesis, we synthesized tetrahydroisoquinoline **2.237** using a Pictet-Spengler reaction (Scheme 2.70). Hydrochloride salt **2.236** was mixed with ethyl glyoxylate (**2.206**) and triethylamine (Et_3N) in the presence of molecular sieves to produce the corresponding imine, which could be isolated and characterized. The crude imine was then dissolved in a solution of toluene/TFA (1% by volume) and heated for 1.5 h to provide the desired tetrahydroisoquinoline **2.237** in 94% yield.[249] A lot of time was spent optimizing this reaction, and some key points to its eventual success include using

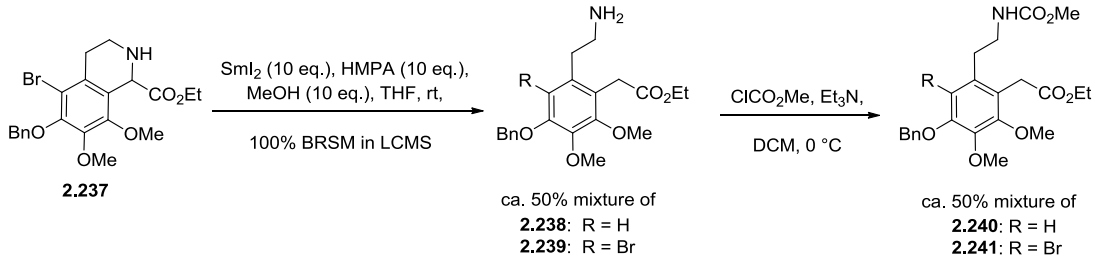
precisely one equivalent of ethyl glyoxylate, as well as running the imine formation reaction at room temperature in the presence of base as opposed to solely heating the salt. Without both of the aforementioned conditions in place, side products related to multiple incorporations of ethyl glyoxylate (**2.206**) appear in significant quantities as shown by ^{1}H NMR and LCMS evidence.

Scheme 2.70



Tetrahydroisoquinoline **2.237** (Scheme 2.71) was then treated with SmI_2 in the presence of HMPA and a proton source to provide a mixture (50:50) of compounds **2.238** and **2.239** according to LCMS results. Attempts to separate the mixture by chromatography or making amine salts failed to provide clean material for characterization, so the mixture was used directly in the next step. Methylchloroformate was added to the mixture of **2.238** and **2.239** in the presence of triethylamine to provide a mixture of carbamates **2.240** and **2.241**. Carbamate **2.241** (R=Br), could be cleanly separated by chromatography and was used in subsequent steps.

Scheme 2.71



Carbamate **2.241** was reduced by hydrogen gas in the presence of a palladium catalyst to provide phenol **2.242** in 64% yield, removing the benzyl group and aryl bromide in a single step (Scheme 2.72). Phenol **2.242** was next subjected to hypervalent iodine mediated oxidative cyclization conditions to provide either of dienones **2.243** or **2.244** or a mixture of both in 41% yield.[250] Hexafluoroisopropanol (HFIP) is commonly used as a solvent in oxidative cyclizations due to its high dielectric constant and low nucleophilicity. [195,251] Based on ^{1}H NMR and ^{13}C NMR spectral evidence, the product of the oxidative reaction was tentatively assigned as compound **2.244** (Figure 2.11).

Scheme 2.72

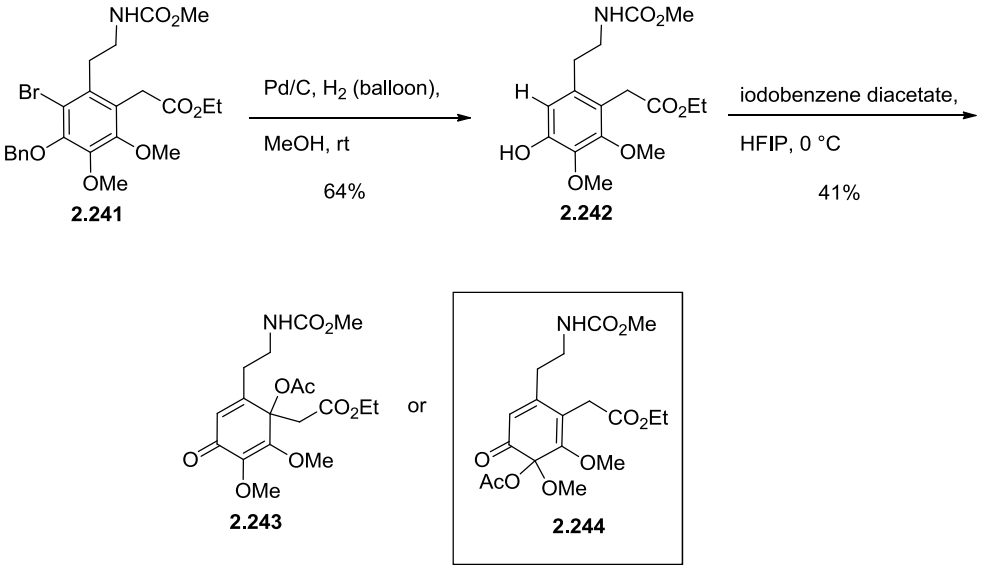
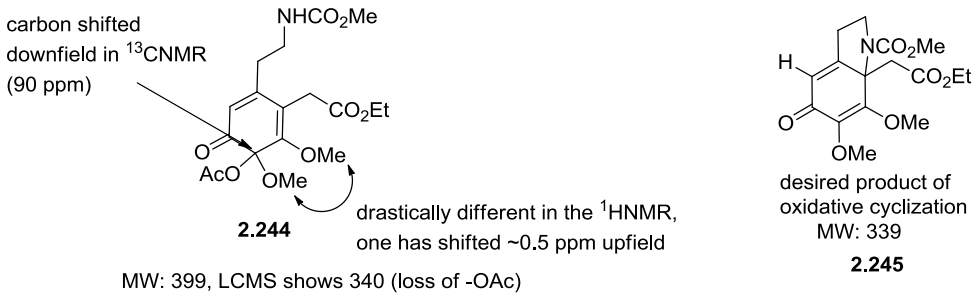


Figure 2.11

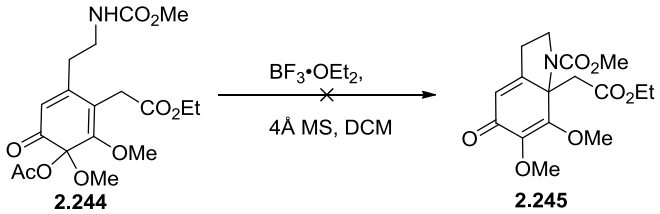


Identification of the product from the oxidative cyclization was initially misleading due to its LCMS. The desired product of the reaction, bicycle **2.245** (*cf.* Figure 2.11), has a molecular weight of 339 g/mol, corresponding to an LCMS mass of 340 (M+1), which was the observed mass from the reaction mixture. However, when the reaction was repeated on a larger scale, enough of the product was isolated so that reliable ^{1}H NMR and ^{13}C NMR spectra could be acquired and analyzed. The presence of an acetate peak in the ^{1}H NMR suggested that the product was likely **2.243** or **2.244** (*cf.* Scheme 2.72), which are known to be possible products in these oxidative conditions, especially in more nucleophilic solvents.[195,196] Uncyclized products **2.243** and **2.244** could also exhibit a mass of 340 in the LCMS, provided the –OAc group was easily ionized either by the mass spectrophotometer or the TFA present in the LCMS solvent. The ^{1}H NMR and ^{13}C NMR data of the product were more consistent with the *ortho*-acetoxy substituted dienone **2.244** than the *para*-acetoxy substituted dienone **2.243**. For example, the ^{1}H NMR spectrum showed two drastically different methoxy groups, with one group shifted approximately 0.5 ppm upfield, whereas the ^{13}C NMR spectrum showed a carbon atom shifted to approximately 90 ppm. While the desired product was not obtained from the oxidative cyclization reaction, there was cause for optimism

because there is precedent for obtaining ring closed products like **2.245** by treating ring-opened products like **2.243** and **2.244** with acid.[195,196]

Following the closest precedent available,[252] *ortho*-substituted dienone **2.244** was treated with boron trifluoride diethyerate ($BF_3 \cdot OEt_2$) in the presence of 4 Å molecular sieves at 0 °C for 45 min, resulting in complete consumption of starting material (Scheme 2.73). Unfortunately, either the starting material or product appears to have decomposed under the reaction conditions, as the product LCMS trace showed at least five peaks, none of them matching the mass of the desired product **2.245**. The reaction was repeated at -78 ºC with the same results. More experiments were planned to attain the desired bicycle **2.245**, but as will be discussed below, the SmI_2 ring opening reaction could not be repeated, resulting in the ultimate abandonment of this route, much to our chagrin.

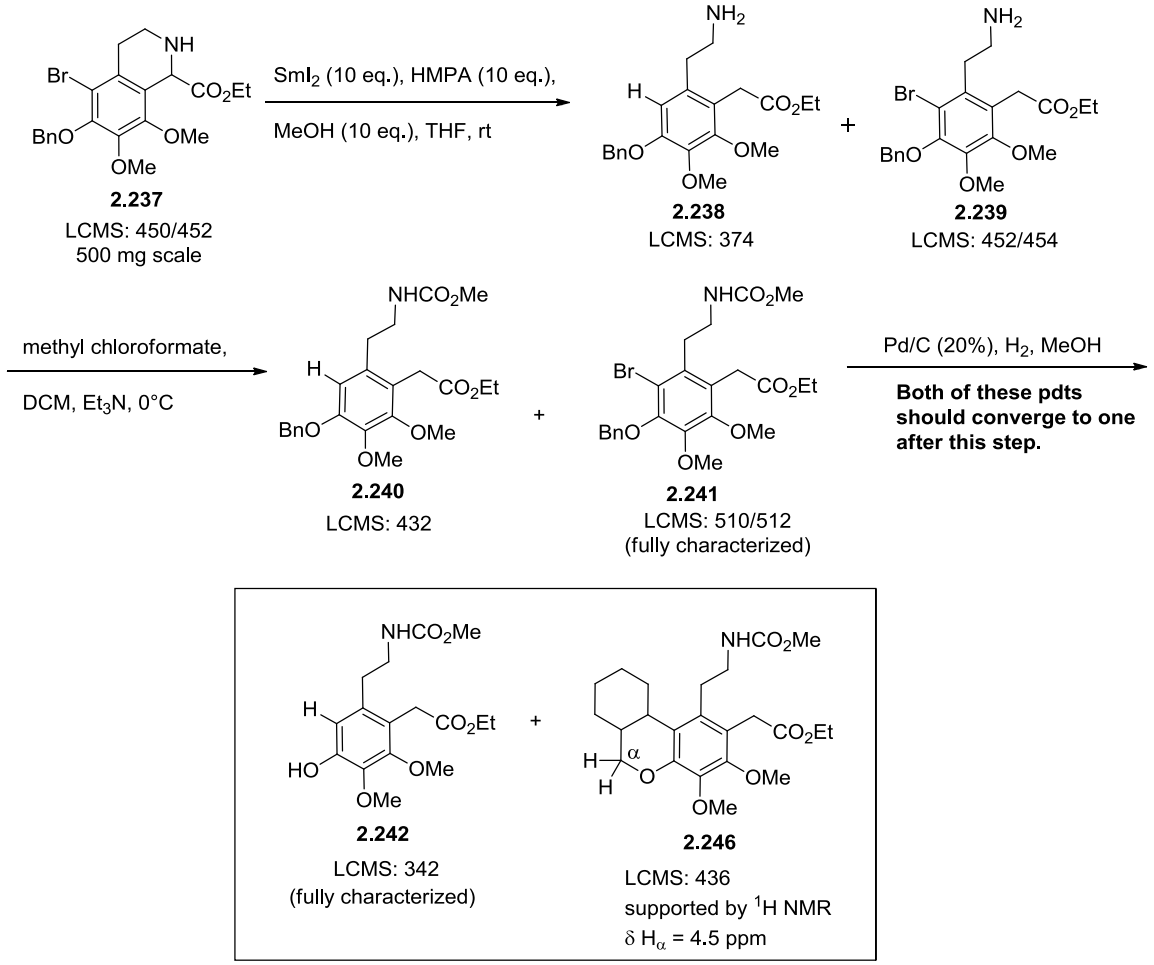
Scheme 2.73



We were excited and optimistic about our initial oxidative cyclization results and eager to continue our investigation, but we had run out of phenol **2.242** and needed to obtain more in order to proceed (*cf.* Schemes 2.71 and 2.72). Towards that end, a large scale SmI_2 ring opening reaction was carried out on 500 mg of tetrahydroisoquinoline **2.237** to provide what was thought to be a mixture of products **2.238** and **2.239** by LCMS (Scheme 2.74 and *cf.* Scheme 2.71). We could not purify the crude product mixture to verify the structures, but we felt our assumption was justified as we had experienced

debromination of the Cbz protected isoquinoline **2.209** with SmI_2 (*cf*. Scheme 2.63). The crude mixture was treated with methylchloroformate, and the resulting mixture was then partially separable by flash chromatography. Brominated product **2.241** was the first product eluted from the column, but all other products eluted from the column as mixtures. Therefore, the ^{1}H NMR spectrum of the other major product was not definitive. Hence, the best way to identify this product was from the LCMS, which suggested a mass of 432, corresponding to the same mass as **2.240**. A mixture of the fully characterized **2.241** and what was believed to be major side product **2.240** was then subjected to the hydrogenolysis reaction to give two products corresponding to LCMS masses of 342, the mass of the desired product **2.242**, and 436. This result was unexpected as it was believed that **2.240** and **2.241** should have converged to the same product **2.242**. Upon purification by chromatography, the desired product **2.242** was fully characterized. The other product having a mass of 436, appeared to be tricycle **2.246**. The ^{1}H NMR spectrum of **2.246** showed a doublet representing the protons alpha to the cyclic ether at approximately 4.5 ppm, broadened proton signals in the 1-2 ppm range corresponding to a cyclohexane ring, and the lack of a phenol or aromatic proton, all in support of structure **2.246**.

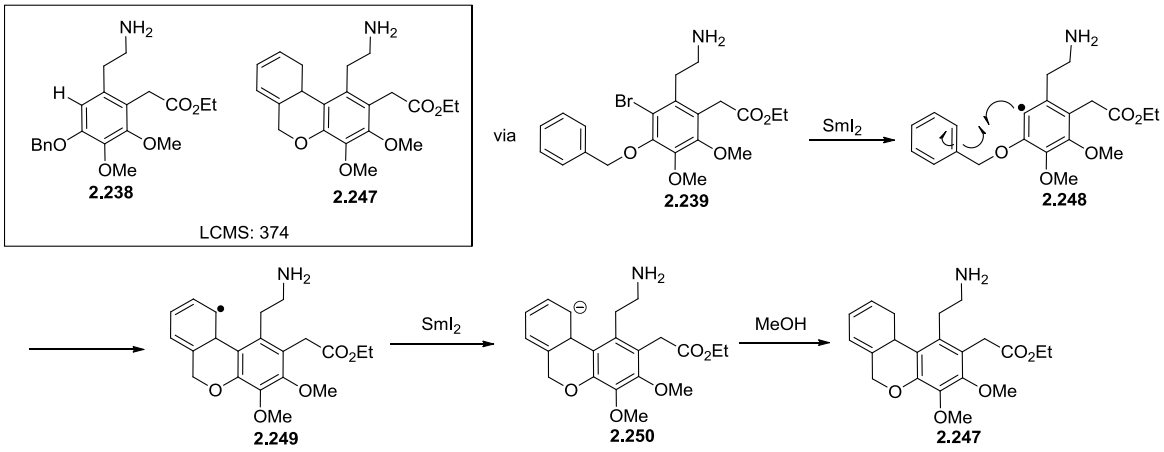
Scheme 2.74



Though unprecedented, we speculate that tricycle **2.246** most likely arose from the unsaturated tricycle **2.247**, which could be formed under the SmI_2 reaction conditions according to the proposed mechanism shown in Scheme 2.75. SmI_2 could react with the aryl bromide of **2.239** to form a radical, which could then react with the benzyl ether **2.248** to produce a different aryl radical **2.249**. A second SmI_2 molecule could then donate a second electron to the aryl radical, generating an intermediate carbanion **2.250**,

which upon protonation with methanol would produce tricycle **2.247**. It is important to note that tricycle **2.247** has not been fully characterized and could be any number of double bond regioisomers; only one possibility is shown for the sake of simplicity. There is no precedent for this type of reaction with samarium diiodide. However, the LCMS and ^{1}H NMR evidence shows that the product of the reaction does not have two fully aromatic benzene rings. Namely, the LCMS mass of 436 that led us to believe the benzene ring had not been cleanly removed and the ^{1}H NMR spectrum had shown a series of complex broadened peaks between 1-2 ppm, characteristic of cyclohexane rings that integrated to 15 protons (including the ethyl group of the ester moiety) and a doublet representing the protons alpha to the cyclic ether at approximately 4.5 ppm. Another convincing piece of evidence was the lack of aromatic protons in the ^{1}H NMR spectrum.

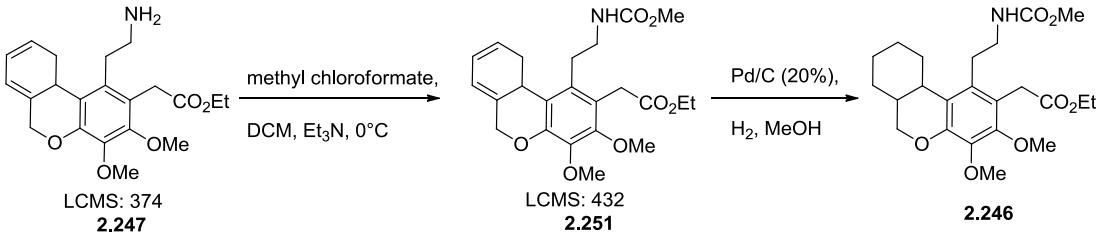
Scheme 2.75



With the new tricycle **2.247** proposed as the other major product of the SmI_2 ring opening reaction (*cf.* Scheme 2.74), a pathway for the production of **2.246** is shown below (Scheme 2.76). Carbamate formation to give tricycle **2.251** would provide a

product with the same mass as observed by LCMS (432). Diene **2.251** would then be reduced in the hydrogenation reaction to provide tricycle **2.246**.

Scheme 2.76



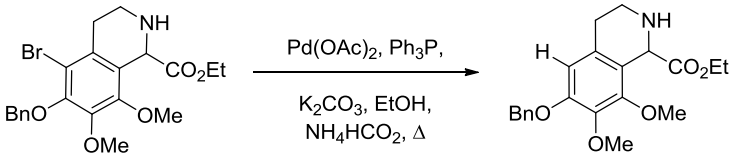
LCMS: 374
2.247

LCMS: 432
2.251

2.246

In order to combat the undesired side product formation, the next modification in the synthesis was to remove the aryl bromide prior to running the SmI_2 mediated cleavage. Using transfer hydrogenation conditions,[244] we were able to reduce the aryl bromide in the presence of the benzyl ether to provide the desired **2.252** in 51% yield (Scheme 2.77). With amine **2.252** in hand, the ring-opening reaction was once again investigated (Scheme 2.78). Somewhat disappointingly, after 30 reactions the success rate of the reaction was approximately 50%, with the highest isolated yield of any reaction being 25%. The yield, however, was promising in the fact that LCMS analysis of crude reaction mixtures showed that the only peaks present at the end of reaction were those that corresponded to HMPA and the desired product **2.238**.

Scheme 2.77

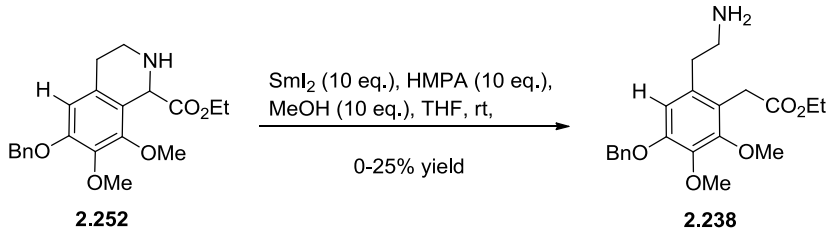


2.237

51% on 600 mg scale

2.252

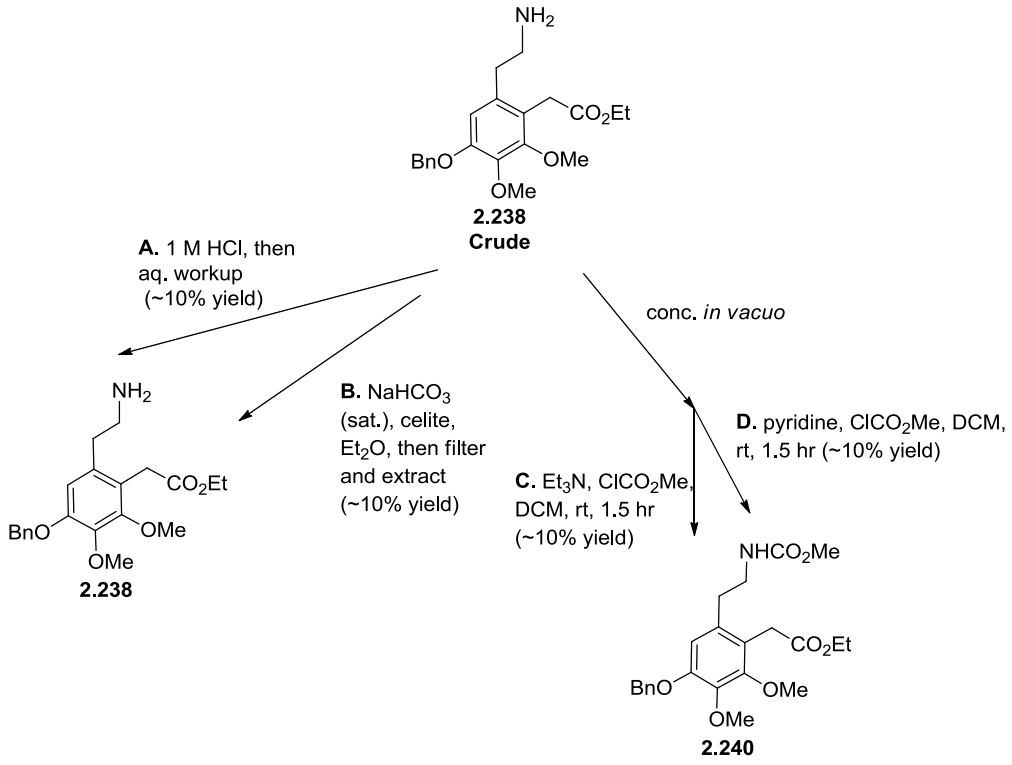
Scheme 2.78



2.252 **2.238**

As nitrogen atoms were known to be a good ligands for Sm (III),[253,254] it was suspected that the low yielding cleavage reactions might be attributed to the complexation of product **2.238** to the Sm (III) salts generated from the reaction. A variety of work-up procedures were investigated in order to separate **2.238** from the Sm (III) salts (Scheme 2.79). Samarium (III) salts can be solubilized in aqueous acidic solutions (Path **A**) or removed via filtration (Path **B**). Both pathways produced approximately the same low yield (~10%) of amine **2.238.** In Path **A**, this may have be attributed to the water solubility of the primary amine product under acidic conditions, and in Path **B**, the amine may have formed an insoluble complex with the filtered samarium (III) salt. A third option for work-up then, was to concentrate the crude reaction mixture and attempt to break the Sm (III) – amine chelate by functionalizing the amine in the presence of the Sm (III) salts (Paths **C** and **D**). However, these routes also produced comparably low yields (~10%) of the carbomethoxy carbamate **2.240**. This was particularly disheartening as we were unable to advance the synthesis because we could not bring up more of the desired intermediate **2.242** (*cf.* Scheme 2.72).

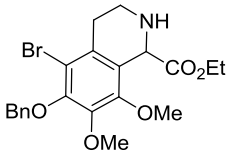
Scheme 2.79



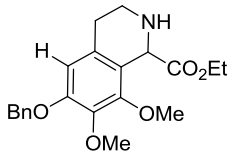
Recall that we had started subjecting tetrahydroisoquinoline **2.252** to the SmI_2 reaction because of the problems we had previously encountered with the use of tetrahydroisoquinoline **2.237**, namely significant side product formation (Figure 2.12 and *cf*. Scheme 2.74). Also recall, that the purpose of the SmI_2 mediated ring opening reaction with **2.237** and **2.252** was to provide more material with which to investigate a key oxidative coupling step within our synthesis (*cf*. Scheme 2.72). By the time we were working with tetrahydroisoquinoline **2.252**, we had already invested a significant amount of time and effort into improving the SmI_2 ring opening reaction, though we had yet to figure out if our key oxidative cyclization reaction was viable. In the interest of time, we decided to momentarily forego additional optimization of the SmI_2 reaction in favor of

advancing material through the reaction between **2.237** and SmI_2 in order to investigate our biomimetic key reaction.

Figure 2.12



2.237



2.252

Unfortunately, we were never able to further investigate our key oxidative cyclization. Much to our surprise, we were unable to reproduce any of our previous success in reacting **2.237** with SmI_2. The trouble started when we had to switch our source of samarium metal for the preparation of SmI_2. While for a time we were able to reliably produce 0.1 M solutions of SmI_2 in THF, when we ran out of the particular bottle of samarium that we had been using, we were unable to replicate any of our previous results. We had been using a bottle of 40 mesh samarium powder obtained from Acros, and when that was consumed, we ordered more from the same vendor. The new bottle we received had the same lot number as the previous bottle, yet the results were irreproducible. The preparation of SmI_2, and the many problems that plague it, will be discussed in detail below.

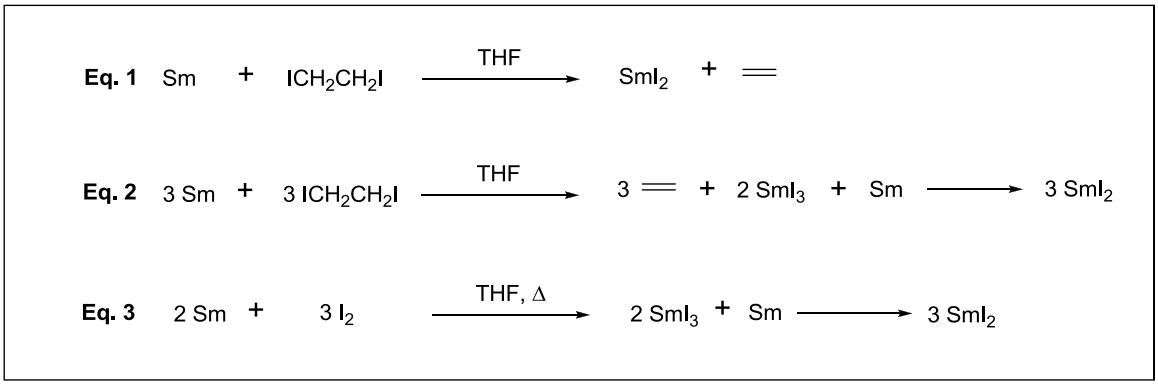
2.6.1 SmI_2

While a variety of methods to prepare SmI_2 have been published, there are two main preparations that are the most frequently used (Figure 2.13).[239] The first, which is based upon the original Kagan paper from 1980,[255] generates SmI_2 from samarium 40 mesh powder and 1,2-diiodoethane in THF distilled from sodium benzophenone ketyl

under nitrogen at room temperature. Kagan reported that if the solvent was very pure, then the induction period was instantaneous. The presence of excess samarium in the mixture was observed to increase its stability. The reaction is believed to proceed either directly to SmI_2 via an oxidative insertion and β-elimination pathway (Eq. 1) or through formation of a Sm (III) iodide, which then further disproportionates to SmI_2 and ethylene in the presence of excess samarium metal (Eq. 2).[243,255]

The second way to prepare SmI_2 involves the use of samarium 40 mesh powder and iodine, first reported by Imamoto in 1987.[243] Imamoto was the first to propose that the formation of Sm (III) iodide and subsequent disproportionation into SmI_2 and ethylene was a valid pathway for SmI_2 formation (Eq. 2). His hypothesis proved accurate, as he was able to use iodine, which is a less expensive and easier to handle than 1,2-diiodoethane, as the iodide source for the reaction (Eq. 3). The reaction requires heating under reflux and a longer reaction time (ca. 12 h) than Kagan's method.

Figure 2.13

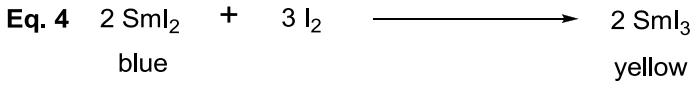


In the course of this project, there have been 84 attempts to generate SmI_2. Iodine and 1,2-diiodoethane have been used as iodide sources; THF was used from a solvent

system, in which it was passed through two columns of activated neutral alumina prior to use and toluene was passed through a column of activated neutral alumina as well as further deoxygenated by being passed through a column of activated Q5, as was THF freshly distilled over potassium benzophenone ketyl, either sparging or freeze/pump/thawing the former in order to deoxygenate it; and the reactions have been run at room temperature, under reflux, in the sonicator, and/or numerous combinations of each. Samarium has always been used in excess (ranging from 1.2 to 2.0 eq.) and the reactions have even monitored the reactions under nitrogen vs. argon gas.

In general, Imamoto's procedure has been the most reliable.[243] Iodine and samarium (40 mesh powder or chips both work, although the chips take longer due to their lower surface area) were mixed together in deoxygenated THF (via freeze/pump/thaw) under either nitrogen or argon at room temperature, and the mixture was then heated under reflux. In most instances, the characteristic "Prussian blue" color would appear after 20 min., and on smaller scales the reaction was complete within an hour. However, the reaction was sensitive to scale, and larger batches of SmI_2 often required more time to come to completion. In Imamoto's orginal paper, he prepared a solution of SmI_2 from 3 g of samarium metal via heating under reflux overnight; this is a good rule of thumb for SmI_2 preparation on larger scales. One can check the final concentration of SmI_2 in THF by iodometric titration (Figure 2.14).[253] Samarium diiodide reacts with iodine to provide samarium (III) iodide with a visible color change from blue to yellow. It is important to note that the maximum concentration of SmI_2 in THF is 0.13 M,[256] even though references in the literature may claim to prepare and use 0.2 M solutions; solid SmI_2 is extremely susceptible to oxidation.[253]

Figure 2.14

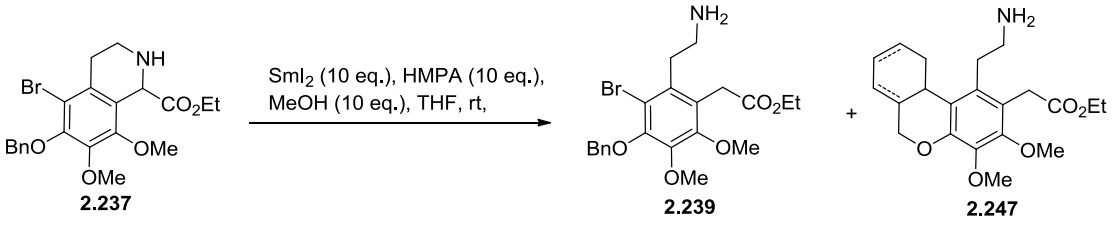


After trying numerous different methods and ideas based upon the literature, we were at a standstill. The project could not move forward with our present route unless we could reliably produce SmI_2 (*cf.* Scheme 2.71-2.72), so we decided to reach out to an author of a recent SmI_2 book, Dr. Robert A. Flowers, II.[239,253] Among the various suggestions that he and his graduate student shared with us, many of them echoing what we had stated in preceding paragraphs, he mentioned that samarium metal can form oxides when left to sit for long periods of time. Apparently the only way to remove the samarium oxides was to crush the powder with a mortar and pestle in a glove box, thereby releasing more "fresh" surface area. When we tested this theory on our "new" Acros bottle, the SmI_2 reaction instantly starting working as it had before; we were able to reliably produce 0.1 M solutions of SmI_2 in THF on a weekly basis. The SmI_2 solutions can be stored for up to a week under argon and at room temperature as long as excess samarium metal is present in the solution. Soon after finding the source of the problem, and excellent article was published by Procter *et al.* which investigated many factors in relation to the production of SmI_2 and came to the same conclusion that we did.[240] Namely, that the quality of the metal is the main factor in preparation and as long as it is activated either by crushing or stirring under an Argon atmosphere overnight, will produce SmI_2 by any of the methods described above.

2.6.2 SUMMARY OF PICTET SPENGLER ROUTE

Having solved the problem of generating solutions of SmI_2, efforts to reproduce earlier successes were initiated (Scheme 2.80). Much to our chagrin, we were still unable to repeat our previous work. At this point in the project, work had been focused on the SmI_2 mediated isoquinoline ring opening for over a year, and we needed to make a difficult decision. The overall goal of the project was to synthesize acutumine and not to optimize reactions between SmI_2 and tetrahydroisoquinolines so we decided to abandon our current route. It was clear that we needed another strategy to reach our desired oxidative cyclization precursor.

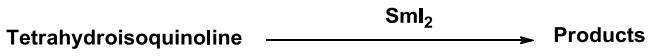
Scheme 2.80

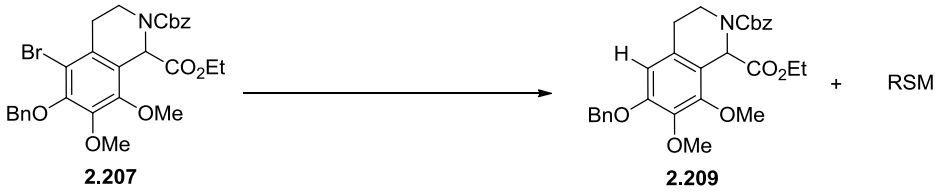


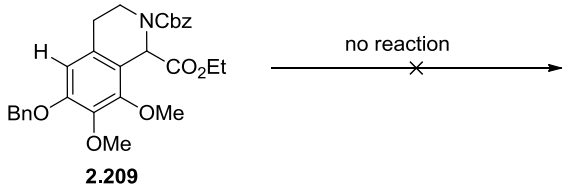
A summary of all the work that had been done with SmI_2 and isoquinolines over the course of the project can be seen in Scheme 2.81. Recall that we began our investigations with Cbz-protected tetrahydroisoquinoline **2.207**. We found that when SmI_2 and **2.207** were allowed to react, the only products obtained were debrominated **2.209** and returned **2.207**. Hypothesizing that the reduction of the bromine atom interrupted the radical process necessary for carbon-nitrogen bond cleavage to occur, we subjected **2.209** to the reaction conditions; however, the tetrahydroisoquinoline did not react. After a mechanistic and structural analysis, we then came to the conclusion that the Cbz carbamate group might be forcing the piperidine ring into a twisted chair conformation, resulting in the misalignment of the *p* orbital of the ester group and the σ*

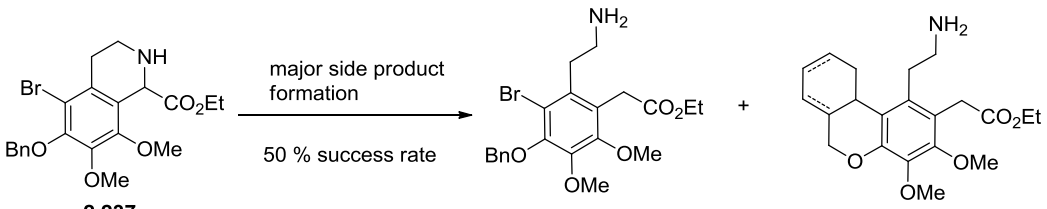
orbital of the breaking carbon-nitrogen bond. We then synthesized the free amine **2.237** and were gratified to find that it reacted with SmI_2 to produce the desired ring opened product **2.239**. However, the reaction also produced significant quantities of the tricycle **2.247**. In an effort to rid ourselves of the unproductive **2.247**, we synthesized **2.252**. Tetrahydroquinoline **2.252** was also found to produce the desired ring opened product **2.238**, however, we had difficulties isolating the free amine.

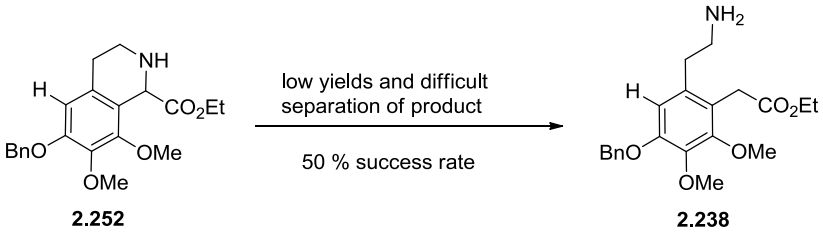
Scheme 2.81











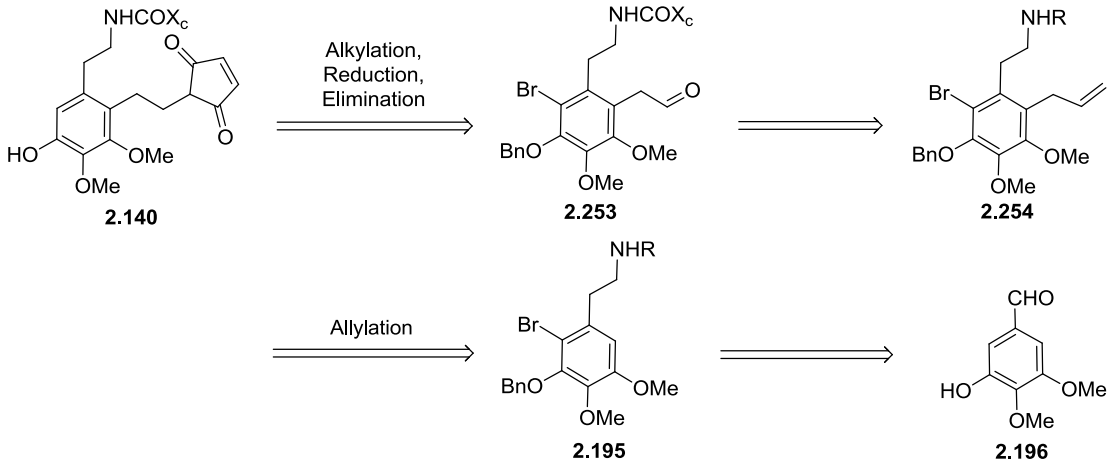
In general, the SmI_2 mediated ring opening reaction worked best with the free amines **2.237** and **2.252**, though both reactions resulted in poor yields and of the desired

products. The reactions also proved to be notoriously unreliable, and in the end we decided that our efforts would be better spent on a different route than trying to optimize either reaction.

2.7 THIRD GENERATION MARTIN GROUP APPROACH

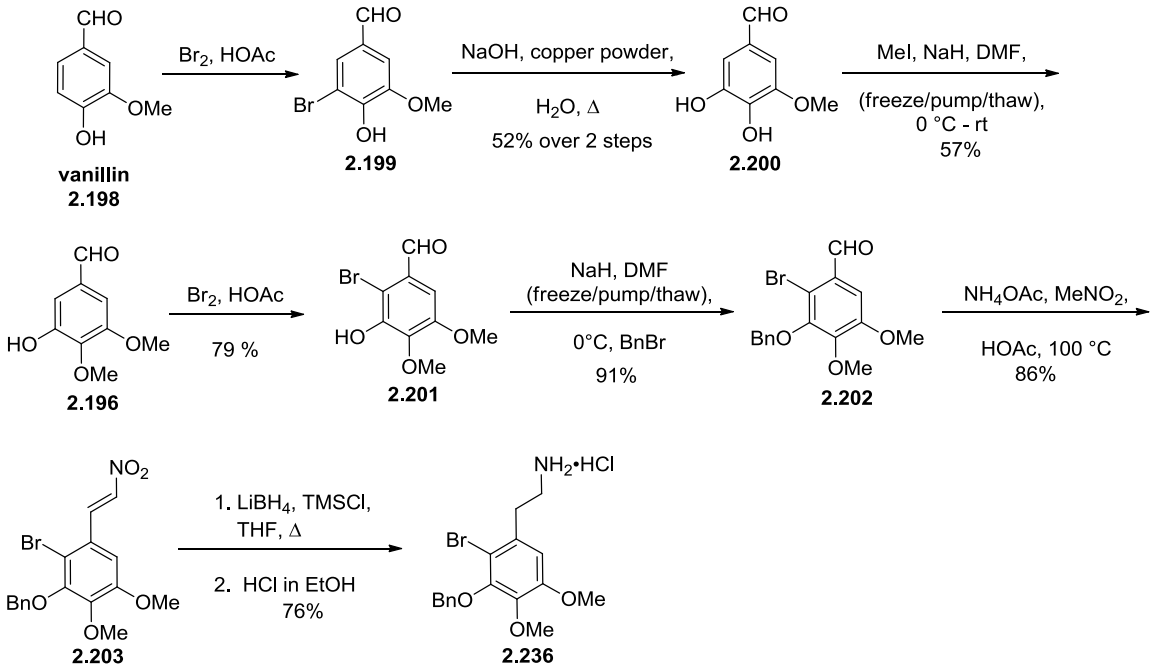
The most recent incarnation of the Martin group approach to acutumine is shown in Scheme 2.82. The approach features much of the same chemistry that we had used in our second generation approach (*cf*. Scheme 2.55), though a key difference was the use of a chemoselective allylation/oxidation sequence (**2.225** to **2.253**) to install our cyclopentenedione precursor as opposed to the troublesome Pictet-Spengler/SmI_2 sequence. We envisioned that phenol **2.140** would come from aldehyde **2.253** through a fairly standard alkylation/elimination/reduction sequence. Aldehyde **2.253** would be furnished from oxidation cleavage of the allyl group in **2.254**, and **2.254** could be obtained from aryl bromide **2.195**, a well-established intermediate from our second generation synthesis.

Scheme 2.82



We had already developed a reliable and scalable route from phenol **2.196** to aryl bromide **2.195**, so we used that to our advantage (*cf*. Section 6 and Scheme 2.83). As a brief summary, commercially available aldehyde **2.196**, which is also readily available from vanillin (**2.198**) in three steps,[257] was first brominated ortho- to the phenol, and the resultant phenol **2.201** was immediately protected as its benzyl ether **2.202** in 91% yield (Scheme 2.83). Aldehyde **2.202** was then subjected to standard Henry reaction conditions with nitromethane to give nitroalkene **2.203** in 86% yield and **2.203** was reduced and acidified to provide the amine salt **2.236** in 76% yield.[235]

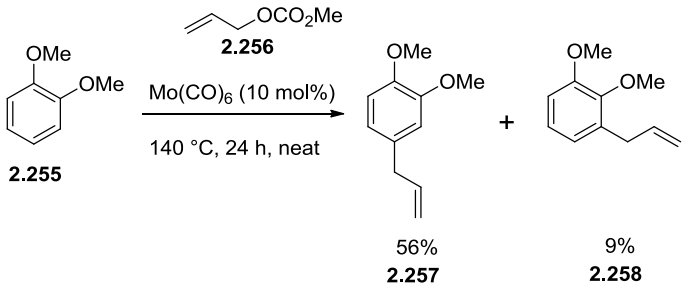
Scheme 2.83



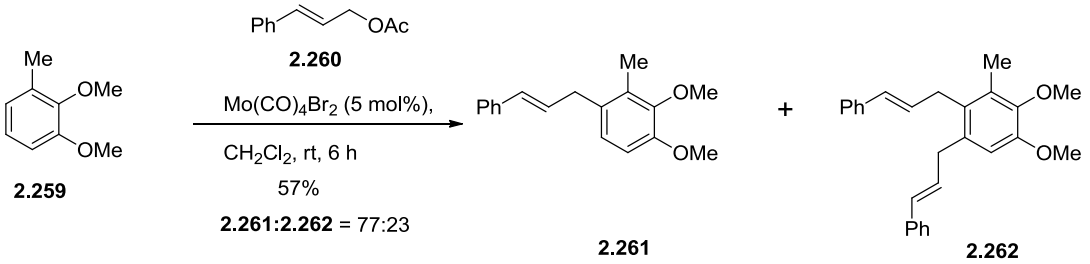
We then sought to allylate compound **2.236**; and similar to what we had done in our second generation sequence (*cf.* Scheme 2.61), we planned to use the bromine atom of **2.236** as a blocking group to direct the regioselectivity of the reaction. A search of the literature presented us with an attractive molybdenum mediated allylation, wherein electron-rich aromatics were allylated with allyl acetates and esters under relatively mild conditions, which we were eager to try (Scheme 2.84 and 2.85).[258,259] Molybdenum hexacarbonyl ($Mo(CO)_6$), or Mo (0), was known to promote the reaction between veratrol (**2.255**) and allyl methyl carbonate (**2.256**) to provide a mixture of mono-allylated regioisomers (**2.257** and **2.258**) in 67% yield (Scheme 2.84).[104] Some disadvantages to the procedure included a high reaction temperature, a 24 h reaction time, and the requirement for a large excess of veratrol (**2.255**); however, as Malkov and coworkers have shown, a Mo (II) catalyst can also promote similar reactions under much milder

conditions (Scheme 2.85).[258,259] They showed that the allylation reaction between 1,2-dimethoxy-3-methylbenzene (**2.259**) and cinnamyl acetate (**2.260**) could be catalyzed by $Mo(CO)_4Br_2$[105], a Mo (II) catalyst, to produce a mixture (77:23) of **2.261** and **2.262** in 57% yield at rt over 6 h. The more Lewis acidic Mo (II) catalysts presumably facilitate coordination of the catalyst to a Lewis basic site on the leaving group of the allyl group, thus promoting Mo π-allyl formation. The electron-rich aromatic nucleophile can then attack the Mo π-allyl, thus completing the allylation. The reaction works best between electron-rich aromatics (**2.225** and **2.259**) and allyl groups that can stabilize the positive charge created upon π-allyl formation (**2.260**).[258,259]

Scheme 2.84



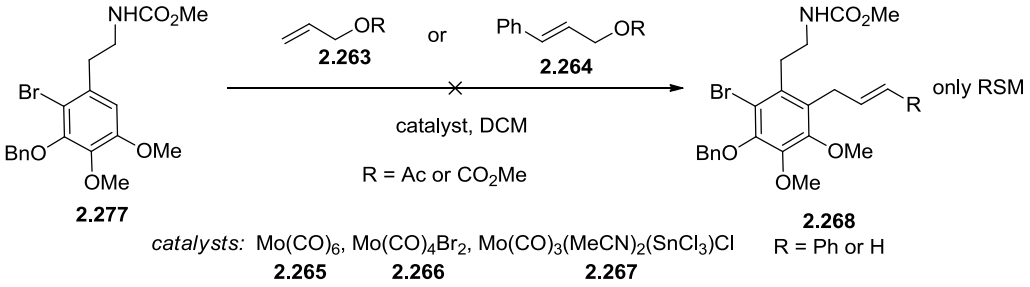
Scheme 2.85



Carbamate **2.277**, which was synthesized in 57% yield from amine hydrochloride salt **2.236** (*cf.* Scheme 2.83), was subjected to molybdenum catalyzed allylation reactions under the conditions precented above (*cf.* Schemes 2.84 and 2.85), but no reaction was ever observed (Scheme 2.86). These failures likely result from complexation of anilines

and amides derived from anilines with Lewis acidic, molybdenum catalysts, effectively shutting down the reaction. Accordingly, we surmised that the carbamate **2.277** may have been too Lewis basic.[259] The nitro-olefin **2.203** and aldehyde **2.202** were thus screened using a variety of molybdenum catalyzed allylation conditions, but to no avail (Scheme 2.81).

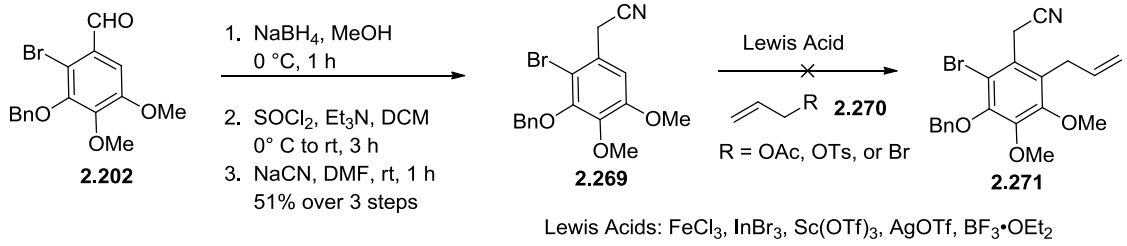
Scheme 2.86



Because many of our synthetic intermediates were electron-rich aromatic rings (*cf.* Scheme 2.83, **2.202** and **2.236**), we queried whether they might be good substrates in Friedel-Crafts allylations.[260-264] Previously we had speculated that carbamate **2.277** was too Lewis basic for use with the Lewis acid molybdenum catalyst, (*cf.* Scheme 2.86) and as a nitrogen atom was ultimately needed at that position, nitrile **2.269** was prepared according to standard procedures (Scheme 2.87). Aldehyde **2.202** was reduced, and the resulting primary alcohol was activated by thionyl chloride ($SOCl_2$) and replaced with a chlorine atom. The chloride was then treated with sodium cyanide (NaCN) to furnish **2.269**. Nitrile **2.269** was screened in a variety of Lewis acid-mediated, Friedel-Crafts reactions, varying the electrophile, **2.270**, time, temperature, solvent, and Lewis acid,[262] but none of the desired product **2.271** was ever observed. Aldehyde **2.202** and nitro-

olefin **2.203** (*cf.* Scheme 2.83) were also investigated as substrates in Friedel-Crafts reactions, yet none of the desired product was ever observed.

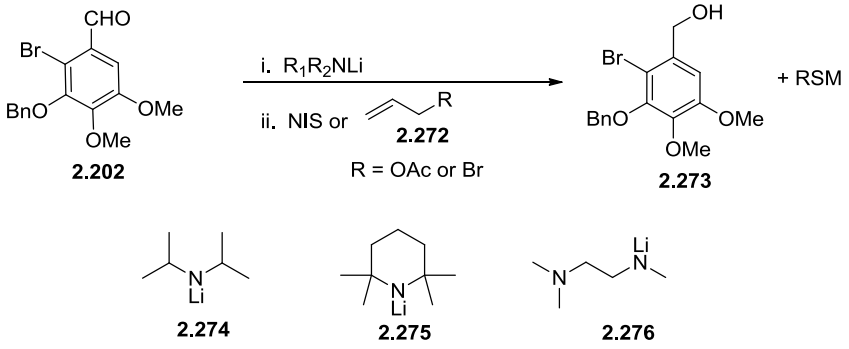
Scheme 2.87



We then investigated whether the allyl group could be introduced into an aromatic compound using anionic chemistry. There was only one aryl proton on aldehyde **2.202**, so we envisioned that it might be possible to deprotonate this proton with a strong enough base to generate an anion that could be alkylated with a suitable electrophile (Scheme 2.88). We examined the deprotonation of **2.202** with three different amide bases, LDA (**2.274**), lithium 2,2,6,6-tetramethylpiperidine (**2.275**), and a combination of lithiated N,N,N'-trimethylenediamine (**2.276**) and LDA (**2.274**).[265-267] The reaction between **2.202** and LDA (**2.274**) produced alcohol 2.273, while reaction between **2.202** and lithium 2,2,6,6-tetramethylpiperidine (**2.275**) produced returned starting material. We then sought to try the combination of lithiated N,N,N'-trimethylenediamine (**2.276**) and LDA (**2.274**). Aldehyde **2.202** was reacted with lithiated N,N,N'-trimethylenediamine (**2.276**) *in situ* to protect the aldehyde against reduction as a hemiaminal, which then when LDA (**2.274**) was added, would direct the base to the proton *ortho* to the aldehyde.[266,267] Although there was only one aryl proton in system **2.202** and regioselectivity was not an issue, it was believed that the coordination between the

methylenediamine and LDA would facililtate deprotonation; however, the only product obtained was alcohol **2.273**.

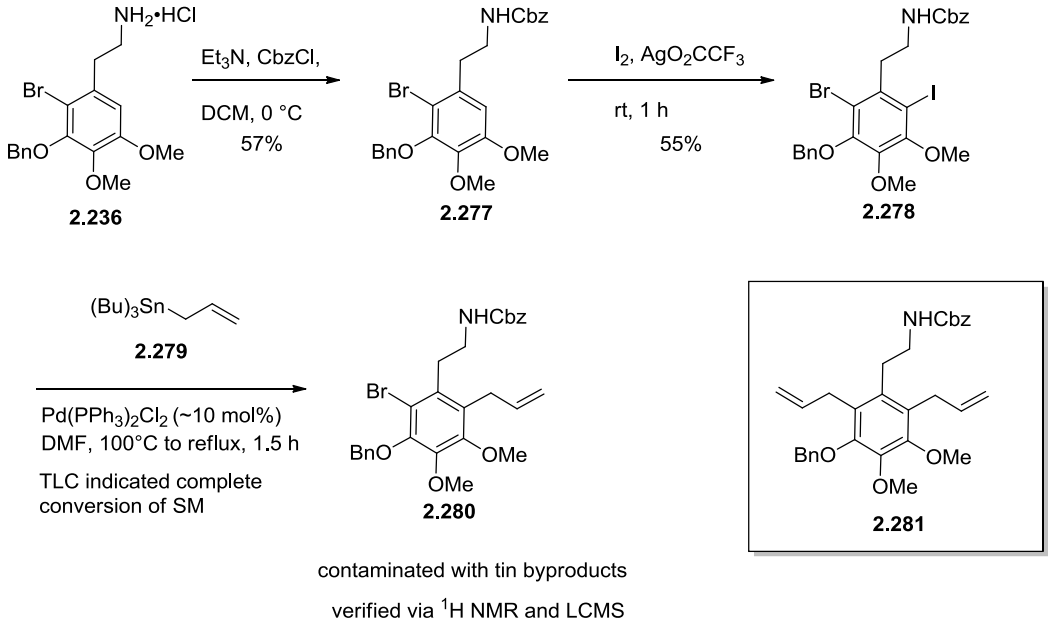
Scheme 2.88



The possibility of transition metal cross coupling reactions was then examined. We had a large stockpile of amine hydrochloride salt **2.236** which we thought we could elaborate to an acceptable cross-coupling precursor (Scheme 2.89). The aryl bromide of **2.277** would have served as a good functional handle for oxidative addition of a transition metal catalyst; however, the bromine atom was not at the site of the ring that we needed to allylate. We needed to introduce a moiety at the desired allylation site which would preferentially undergo oxidative addition with a transition metal catalyst in the presence of the aryl bromide of **2.277**. Towards that end, we found a useful, albeit expensive, procedure to introduce iodine atoms into electron-rich aromatic groups involving the use of iodine and silver (I) trifluoroacetate. [268,269] The iodination proceeded in modest yield (55%) to provide aryl iodide **2.278** (Scheme 2.89). The aryl iodide was then subjected to Stille conditions[270] to provide the desired compound **2.280**. The first time the reaction was run, bis-allylation product **2.281** was also obtained, but when the reaction was run with a substoichiometric amount of allyl stannane, all bis-allylation was eliminated. Unfortunately, we could never obtain a good yield for the reaction as the product

remained contaminated with tin by-products, despite multiple column chromatography purifications.

Scheme 2.89



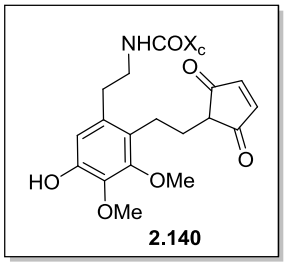
Though efforts will be ongoing to optimize the promising the promising Stille reaction between **2.278** and **2.279**, allyl compound **2.280** was the furthest we were able to advance our total synthesis of acutumine in the time given (Scheme 2.89).

2.8 SUMMARY

Though we faced a number of difficulties throughout our efforts towards the total synthesis of acutumine, we were able to overcome many of the problems encountered and achieve some notable successes. First we investigated a route toward key intermediate **2.140** (Figure 2.15) which featured an acetylide addition/Moore cyclization sequence (Scheme 2.90 and *cf.* Section **2.5**). We developed conditions for the previously

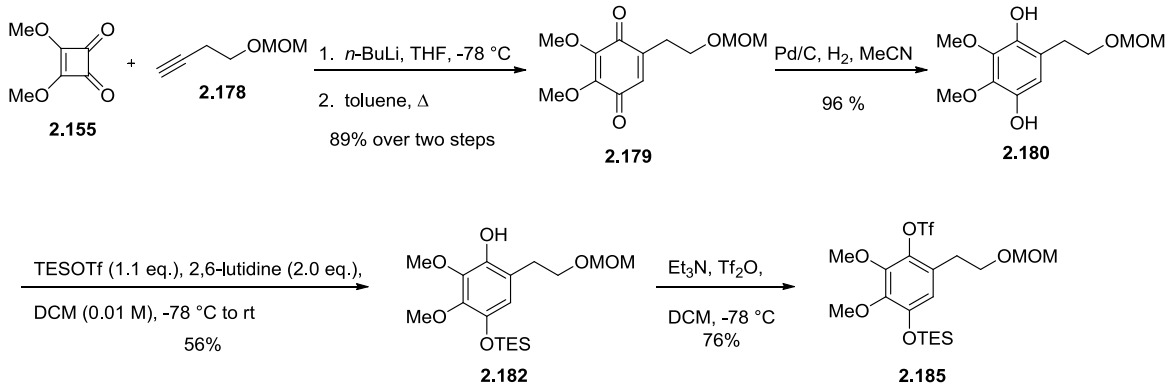
unprecedented mono-TES silylation of the least hindered phenol of diphenol **2.180** and were able to expand upon the scope and limitations of but-3-ynol derivatives, for example **2.178**, in acetylide addition/Moore cyclization sequences.

Figure 2.15



2.140

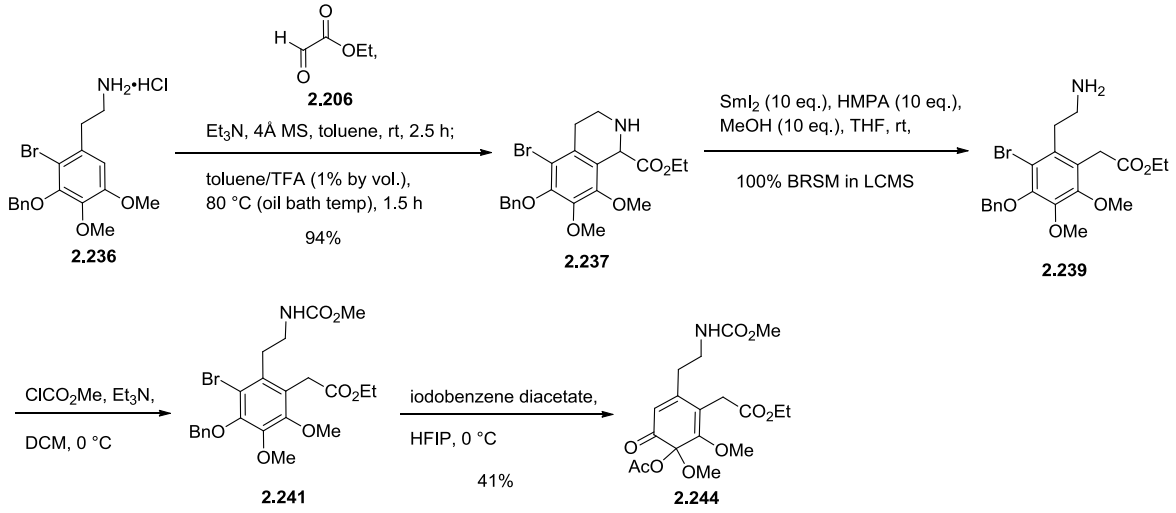
Scheme 2.90



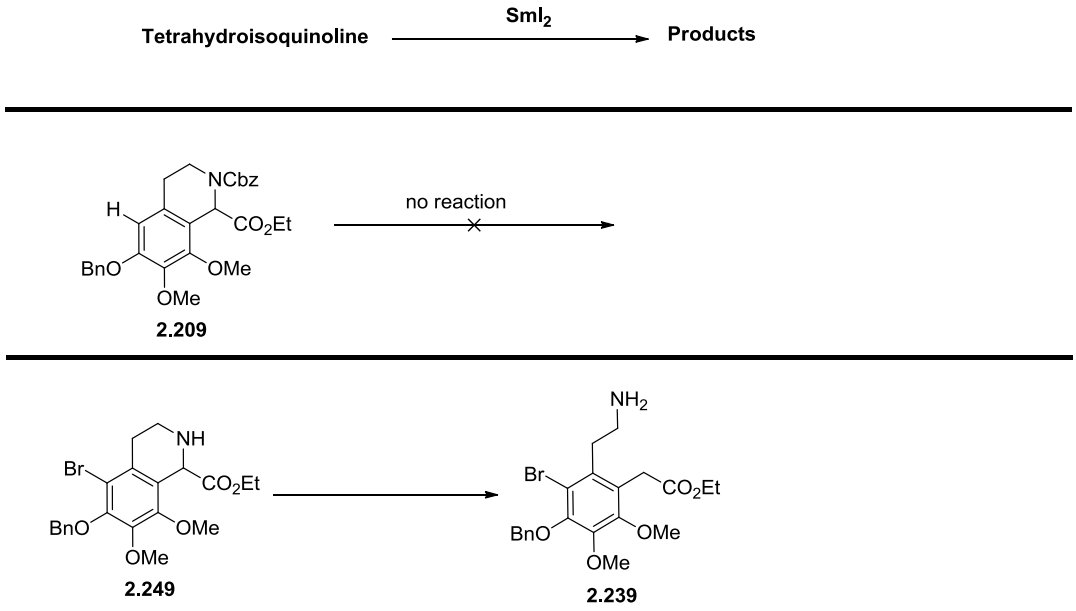
We then explored a route which featured a Pictet-Spengler/SmI_2 mediated ring opening sequence to provide **2.146** (Scheme 2.90 and *cf.* Sections **2.6** and **2.7**). We developed a regioselective Pictet-Spengler, in which we used the bromine atom of **2.236** as a blocking group in a reaction with ethyl glyoxylate (**2.206**) to provide tetrahydroisoquinoline **2.237** in 94% yield. We also discovered an important limitation of SmI_2 mediated ring opening reactions (Schemes 2.91 and 2.92). Honda had shown that SmI_2 had been previously shown to be an effective promoter carbon-nitrogen bond cleavage of both piperidine and isoquinoline systems,[230] but we found that the reaction

did not work when a carbamoylated isoquinoline system, namely **2.227**, was employed as a substrate. Proposing that the presence of a carbamate on the piperidine ring of a tetrahydroisoquinoline system disrupted the orbital alignment necessary for carbon-nitrogen bond cleavage to occur, we were gratified to find that when the carbamoyl group was removed from **2.227** to provide tetrahydroisoquinoline **2.249,** the reaction proceeded to provide phenethyl amine **2.251**. We were also able to conduct preliminary oxidative cyclization studies towards our key intermediate **2.146**. We were pleased to see that carbamate **2.253** was oxidized to mixed *o*-ketal **2.225** when treated with a hypervalent iodine reagent, thus providing support towards the viability of our key step (Scheme 2.86).

Scheme 2.91



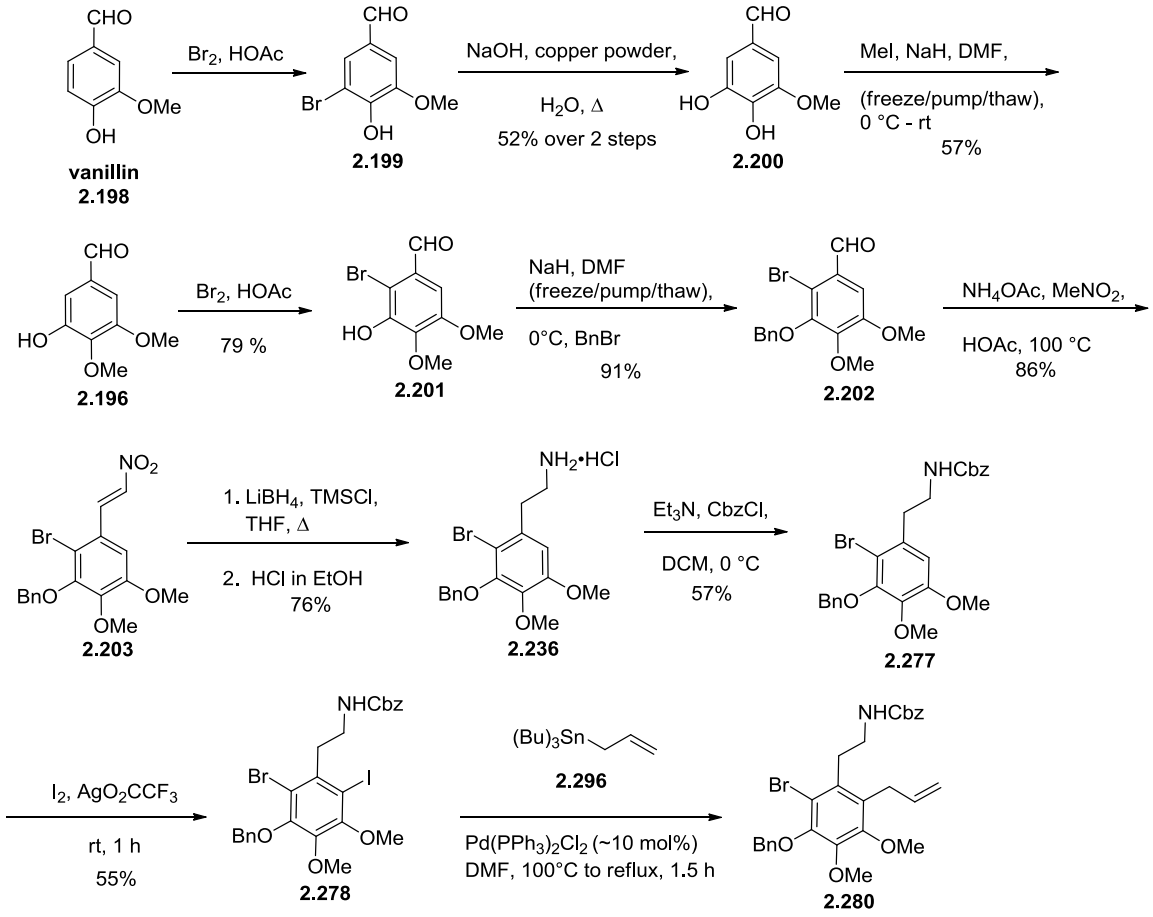
Scheme 2.92



2.9 FUTURE DIRECTIONS

The most recent route towards acutumine featured an allylation reaction in order to access key intermediate **2.140**. Towards the end of my time on the project we found some promise using a Stille reaction to install an allyl group on aryl bromide **2.278** that we believed we could potentially functionalize to key intermediate **2.140** (Scheme 2.93). While the results are preliminary, we are optimistic that our efforts will provide us with a viable intermediate to reach acutumine.

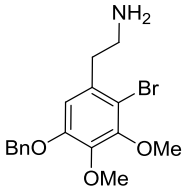
Scheme 2.93



Upon accessing aryl bromide **2.278**, we realized that the synthesis could be shortened if **2.282** could be used as a starting material (Figure 2.16). Fortunately, we were able to find precedent for preparing aryl bromide **2.289** (Scheme 2.94),[271] which we envisioned we could then elaborate to the desired amine **2.282** using procedures we had successfully developed in our second generation approach (*cf.* Scheme 2.83). Radix and co-workers were able to obtain aryl bromide **2.289** from the commercially available ester

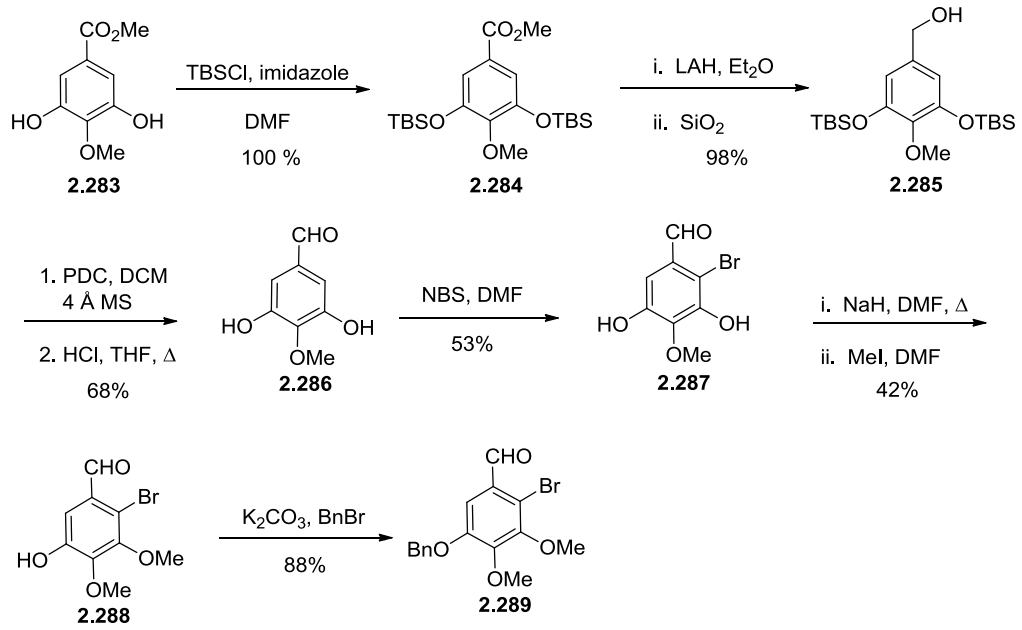
2.283 (Scheme 2.94).[271] The phenol groups of **2.283** were protected as their TBS ethers, and then the ester group of **2.284** was reduced to alcohol **2.285**. The alcohol was oxidized to an aldehyde and the TBS groups were cleaved in HCl/THF to provide the diphenol **2.286** in 67% yield over four steps.[271,272] A mono-bromination of aldehyde **2.286** with NBS provided aryl bromide **2.287**, which was then selectively methylated to provide phenol **2.288**. The main product of the reaction was RSM, with a little over-methylated material.[271] Phenol **2.288** was then protected as its benzyl ether to provide **2.289** in 88% yield. We envisioned that aldehyde **2.289** could undergo a Henry reaction to provide nitro-alkene **2.290**, and that reduction with diborane could provide the desired amine **2.282** (Scheme 2.95).

Figure 2.16

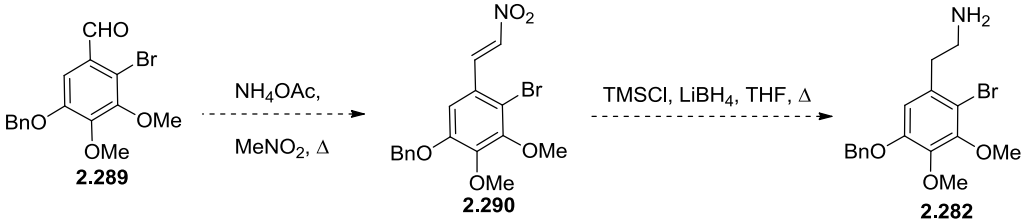


2.282

Scheme 2.94

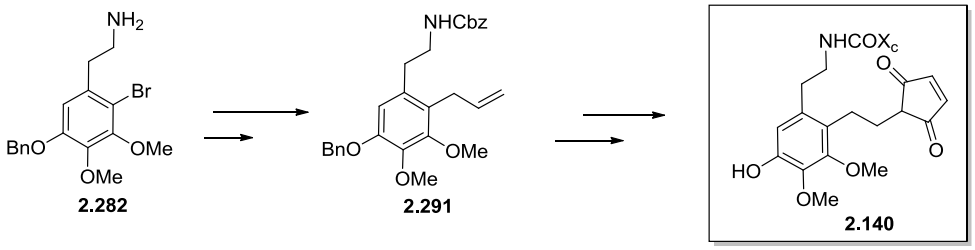


Scheme 2.95



We could then explore a Stille allylation reaction with aryl bromide **2.282** (Scheme 2.96 and *cf.* Scheme 2.89) to provide **2.291**, which upon further oxidation, alkylation, and reduction could provide our key intermediate **2.140**.

Scheme 2.96



Chapter 3: Design and Synthesis of Ligands for the Thermodynamic Evaluation of Protein Ligand Interactions

3.1 The Role of Protein–Ligand Interactions in Drug Design

Small peptides have been shown to bind to a variety of therapeutically important receptors, so optimizing the protein binding affinity (K_a or IC_{50}) of small peptide ligands is critical to the development of new drug candidates.[273-275] Unfortunately, the complexities involved in molecular recognition phenomena in biological systems are not well understood, and it is often difficult to predict how ligands will bind to biological targets.[274-282] When a ligand binds to a receptor, specifically a protein in the context of this discussion, in an aqueous media, a number of noncovalent interactions are initiated that can effect conformational changes to the entire macromolecule.[273-275] These processes are complex and often comprise a number of competing associations, such as solvent reorganization.[274-282] As a result of this complexity, it has been historically difficult to separate the processes into discreet components that can be quantified.[274,275,278] Thus, a method to systematically examine the factors that influence protein-ligand interactions would enhance our ability to understand how modification of a ligand will correlate to changes in binding affinity. This method would be a particularly powerful tool for scientists working in the field of drug design.[273]

The rational design of small molecule and peptide drug leads usually begins with the modification of a compound that is known to bind to a receptor with a favorable affinity, meaning the compound is associated with either a high K_a or low IC_{50} value.[273-276] Ideally, structural data of the ligand in its biologically active conformation within the binding pocket of the protein would also be known. Examples of structural data may include information regarding van der Waals (vdW) interactions, polar contacts, such as

hydrogen bonds and ionic interactions, or the orientation of water molecules at the protein-ligand interface.[274,275] An analysis of these data can provide a good starting place with which to modify ligands in order to enhance binding affinity. However, while structurally modifying a ligand may result in a change in binding affinity, the numerical K_a or IC_{50} value does not explain the *cause* of the change. Knowing this information is equally as valuable as knowing the binding affinity as it would provide the first steps toward truly *de novo* ligand design in order to study molecular recognition phenomena in biological systems. Currently there is no definitive method that can be used to predict ligand design, though some general guidelines do exist.[273-282]

As previously mentioned when protein-ligand binding events are investigated, usually only the binding affinities as measured by either a K_a or an IC_{50} value are reported.[273-275] A deeper understanding of protein-ligand binding might be achieved if more information were available. It is our belief that knowing how the thermodynamics for protein-ligand associations differ among various protein-ligand systems will provide valuable information about binding events. Specifically, information relating to the changes in binding enthalpy (ΔH^o) and binding entropy (ΔS^o) are critical. However, information relating to both ΔH^o and ΔS^o is not readily available from routine studies of binding events without the use of either a van't Hoff analysis or isothermal titration calorimetry (ITC).[273-282] A comprehensive investigation of both the structure and energetics of protein-ligand interactions would provide a much more detailed picture of molecular recognition phenomena in biological systems.

While many principles are often invoked to explain differences in the activity resulting from molecular recognition phenomena, we will focus specifically on the effects

of conformational constraints. Making predictions about how these complex biological systems will behave is formidable because of their dependence on solvent reorganization and protein dynamics, among others. A "ligand-centric" approach, namely the analyzing the effects of conformational constraints onto the ligands, is an attractive option for study of molecular recognition phenomena.[274] While the effects of other factors involved in the association processes are difficult to approximate, a ligand constraint provides something tangible that can be measured and analyzed, hence our interest. In order to obtain meaningful thermodynamic data of protein-ligand interactions a systematic experimental approach should be followed.[274,275] Ideally, the structure of a known small molecule should be incrementally changed, and the effects should be measured by a suitable analytical method to provide comparative thermodynamic data. If the native peptide cannot be easily modified to incorporate a conformational constraint, then a suitable flexible peptide mimic should be synthesized for use as a control molecule. The constrained peptide mimics should be as close in structure as possible to the native and/or control compound. For example, control molecules should have the same number of heavy atoms, the same functional groups, and the same number of hydrogen bond donors and acceptors. Most importantly, both flexible and constrained ligands, must bind in the same or similar matter to the target protein.[274,275] In the context of conformational constraints, we will examine flexible vs. constrained ligands that follow these guidelines in order to elucidate the enthalpy (ΔH^{o}), entropy (ΔS^{o}), and free energy (ΔG^{o}) of binding.

3.1.1 BINDING THERMODYNAMICS

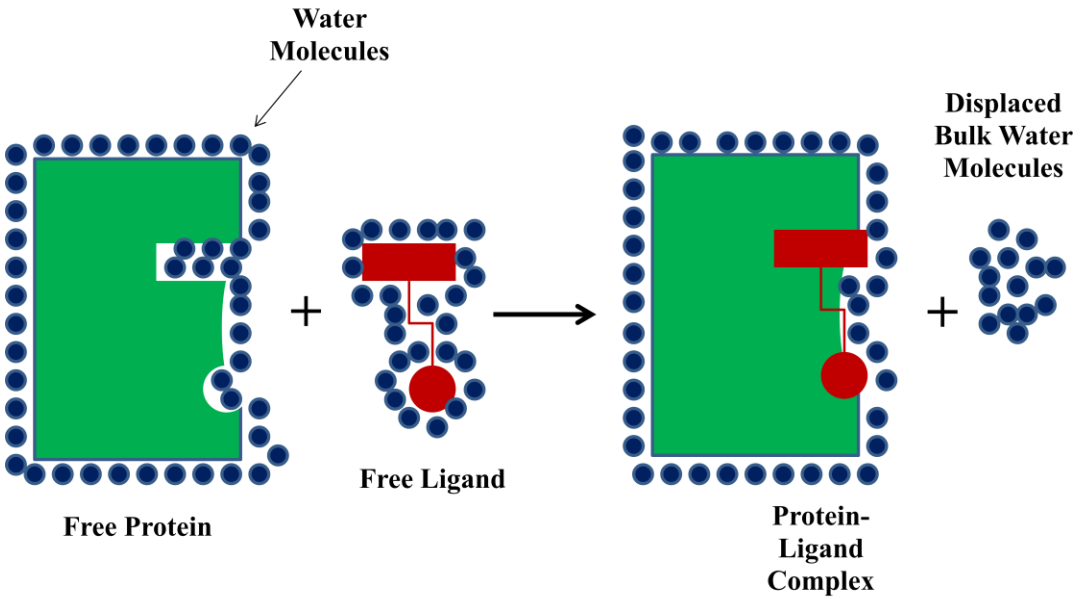
Protein-ligand interactions may be most simply explained as an equilibrium between the free protein (*P*) and ligand (*L*) and the protein-ligand complex (*PL*) in water (eq. 3.1). The subscripts *n*, *m,* represent the number of water surrounding the native protein and free ligand, while the subscript *x* represents the number of water molecules surrounding the protein-ligand complex. The other water molecules represent the bulk aqueous solution.

Equation 3.1

$$(P)_nH_2O + (L)_mH_2O + H_2O \rightleftharpoons (P{\bullet}L) + {}_{(m+n-x)}H_2O$$

A simple representation of the complexation event in water is shown in Figure 3.1. Water molecules surround the *apo* protein and free ligand, but upon association, some water molecules must be displaced into the bulk solution as interactions between the protein and ligand replace the interactions from the water molecules. Then the remaining water molecules reorganize themselves around the new complex, creating a new system of hydrogen bonds.

Figure 3.1 The reorganization of water molecules upon protein-ligand binding



The association constant (K_a), and dissociation constant (K_d), for the forward and reverse interactions in eq. 3.1 can be expressed by eq. 3.2,

Equation 3.2

$$K_a = K_d^{-1} = \frac{[PL]}{[P][L]}$$

which is a rearrangement of the Arrhenius equation. K_a is related to the free energy (ΔG^o), enthalpy (ΔH^o), and entropy (ΔS^o) of the protein-ligand interaction through the Gibbs' free energy equation (eq. 3.3),

Equation 3.3

$$\Delta G^\circ = -RT\ln(K_a)$$

where R is the universal gas constant (1.985 cal $K^{-1}mol^{-1}$), and T is the temperature in Kelvin. Equation 3.3 can also be rewritten as eq. 3.4,

Equation 3.4

$$\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ$$

which relates ΔG^o directly to ΔH^o and ΔS^o.

The enthalpy of binding represents the heats of formation and/or breaking of all possible non-bonded interactions (*ie* dispersive van der Waals (vdW) and polar contacts) while the entropy of binding represents changes in the order of the system.[273] As can be seen by equations 3.3 and 3.4, ΔG^o, and subsequently K_a, is dependent upon the interplay between the enthalpy and entropy terms. If one could optimize either ΔH^o and ΔS^o, or ideally both terms, then the binding K_a of the protein-ligand complex could be greatly enhanced.

The enthalpy of binding is often considered more difficult to optimize than the entropy of binding because the enthalpic term is reliant upon distance and angle dependent polar interactions, as well as non-dispersive vdW interactions, but some guidelines exist for how to carry out such investigations.[274,275,283-285] Two common strategies toward optimizing the binding enthalpies of protein-ligand interactions include maximizing existing favorable interactions between protein and ligand and/or creating *de novo* favorable non-bonded contacts.[274,275] These optimization studies are largely guided by structural information obtained from the bound native ligand/protein complex through x-ray crystallography. However, some major disadvantages of this method include the static nature of crystallography, and the fact that bulk water molecules, or those that are displaced from the protein and ligand upon formation of the protein-ligand complex, are invisible using crystallography (*cf*. Figure 3.1).[274,275] Crystallography can only capture a single snapshot in a dynamic complexation process, and while some hydrogen bond

interactions between water and the complex can be seen in the crystal structure, the interactions amongst the water molecules themselves are large contributors to the overall thermodynamics of molecular recognition phenomena in biological systems (*ie* solvation/desolvation processes). Nondirectional vdW forces may also be optimized, but they are much weaker than the more specific polar contacts.[286]

The entropy of binding is often considered the more desirable thermodynamic term to optimize because it is generally easier to restrict rotors of a ligand through conformational constraints than it is to induce precise orientation and angle dependent polar interactions between a ligand and protein.[274,275,287] Introducing conformational constraints, usually rings, onto ligands restricts their flexibility, and their inclusion has been shown to increase the binding affinity of the association process.[274,275,287] The increase in affinity is usually attributed to the entropy, rather than the enthalpy of binding. The general belief is that the restriction of independent rotors in a ligand ideally preorganizes the ligand into its biologically active binding conformation, therefore lessening the entropic penalty paid upon binding.[274,275,287] However, this is a hypothesis and little hard data exists to prove that the increase in affinity is due to entropic, and not enthalpic effects.[274,275]

Another common strategy that is used to increase binding affinity is to add nonpolar surface area to the ligand.[274,275] There exists a phenomenon in molecular recognition of biological systems called the "hydrophobic effect", and it is directly related to solvent reorganization upon binding.[288-292] It is generally believed that the desolvation of non-polar surface area leads to favorable changes in entropy, but we have found that that is not always the case a little later.[274,275,280,293]

3.1.2 ISOTHERMAL TITRATION CALORIMETRY

As mentioned previously, when work is done in the field of protein-ligand interactions, the binding affinity is usually expressed as a K_a, an IC_{50}, or a K_i (inhibition constant) value, though these are not direct measures of affinity. While K_a is a direct measure of the binding energy (*cf.* eq. 3.3-3.4); K_i's and IC_{50}'s are calculated quantities that measure a biological effect and not an actual thermodynamic parameter. However, they are still frequently reported as measures of ligand potency in the literature. The Cheng-Prusoff equation[294] (eq. 3.5) relates K_i to IC_{50},

Equation 3.5

$$K_i = \frac{I_{50}}{(1 + S/K_m)}$$

where I_{50} represents the free concentration of inhibitor at 50% maximal activity, S is the free concentration of the substrate being measured at 50% maximal activity, and K_m is the concentration of the substrate at 50% maximal activity.

When thermodynamic parameters such as ΔH° and ΔS° are desired, there are only a few methods available with which to determine them.[284,285,295,296] One way is to conduct a van't Hoff analysis (equation 3.6),

Equation 3.6

$$\ln K_a = -\frac{\Delta H^\circ}{RT} + \frac{\Delta S^\circ}{R}$$

where R is the universal gas constant, and T is the temperature in Kelvin. However, one of the largest problems with the van't Hoff analysis is that K_a is not truly independent of temperature; moreover, if slope of the resulting graph is off by even a small amount then

ΔH^o and ΔS^o will yield inaccurate values. Another major problem with van't Hoff analyses is that the method requires a large number of experiments to be performed at different temperatures to generate a plot, which consequently requires large amounts of valuable protein and ligand that may not be readily available. However, most of these problems can be avoided through the use of isothermal titration calorimetry (ITC).[296,297] ITC measures ΔH^o and K_a directly with one experiment, and only ΔS^o need be calculated. This method is generally easier and more accurate than the van't Hoff analysis.

An experiment involving ITC is performed by incrementally adding small amounts of a solution of a ligand to a calorimeter held at a constant temperature, and filled with a solution of protein. The energy required to hold the calorimeter at the constant temperature gives ΔH^o, while the K_a for the interaction can be determined by integrating ΔH^o against stoichiometry.[296,297] Though ITC is a powerful tool, many researchers choose not to report values for ΔH^o and ΔS^o, choosing only to focus on K_a. While we know that K_a can provide a measure for how well a ligand binds, it does not explain the how or why of the protein-ligand interaction; for that we need to know more details about the reactions, namely ΔH^o and ΔS^o. The Martin group has already made significant contributions to this area and those results will be discussed below.

3.1.3 Solvent Reorganization and the Hydrophobic Effect

Protein-ligand interactions involve reorganization of solvent water molecules about both the protein and ligand. Bulk water molecules are generally disordered, but when a solute is introduced, a cavity forms. The solute occupies the cavity, and then the water molecules re-arrange themselves around the solute molecule in order to maximize the available hydrogen bonds.[298] This same principle applies to the introduction of

proteins and ligands into an aqueous solution. The tendency of nonpolar molecules to aggregate with one another in an aqueous solution is called the "hydrophobic effect".[288-292] When nonpolar surface area is added to a ligand, its binding affinity usually increases, and the increase can be either entropically or enthalpically driven.[274,275] When the hydrophobic effect is entropically driven, it is believed that the displacement of an ordered water molecule from the cage surrounding the cavity of the non-polar protein and/or native ligand into the bulk solution is favorable, as the newly freed water molecule gains more degrees of freedom (*cf.* Figure 3.1).[288,290,292] However, other studies have shown that the displacement of a water molecule from an unbound protein or ligand is enthalpically driven, as sub-optimal hydrogen bonds are replaced with more favorable distance and orientation dependent contacts within the bulk solvent.[291]

Desolvation effects on binding are generally determined by measuring changes in the heat capacity (ΔC_p) of complex formation.[273,278,295] Complexation heat capacity is dependent upon temperature and can be represented by Equation 3.7,

Equation 3.7

$$\Delta \mathbf{C_p} = \left(\frac{\delta(\Delta \mathbf{H°})}{\delta \mathbf{T}} \right)_p$$

where T represents temperature in Kelvin and p represents that the change in enthalpy over time occurs under constant pressure. The ΔC_p for a given protein-ligand association may be determined from ITC experiments by performing the association at a variety of different temperatures and then plotting ΔH^o against temperature. If the hydrophobic effect is present in the protein-ligand system, then ΔC_p will be negative, regardless of whether the effect is enthalpically or entropically driven.[273,278,295]

3.1.4 ENTHALPY-ENTROPY COMPENSATION

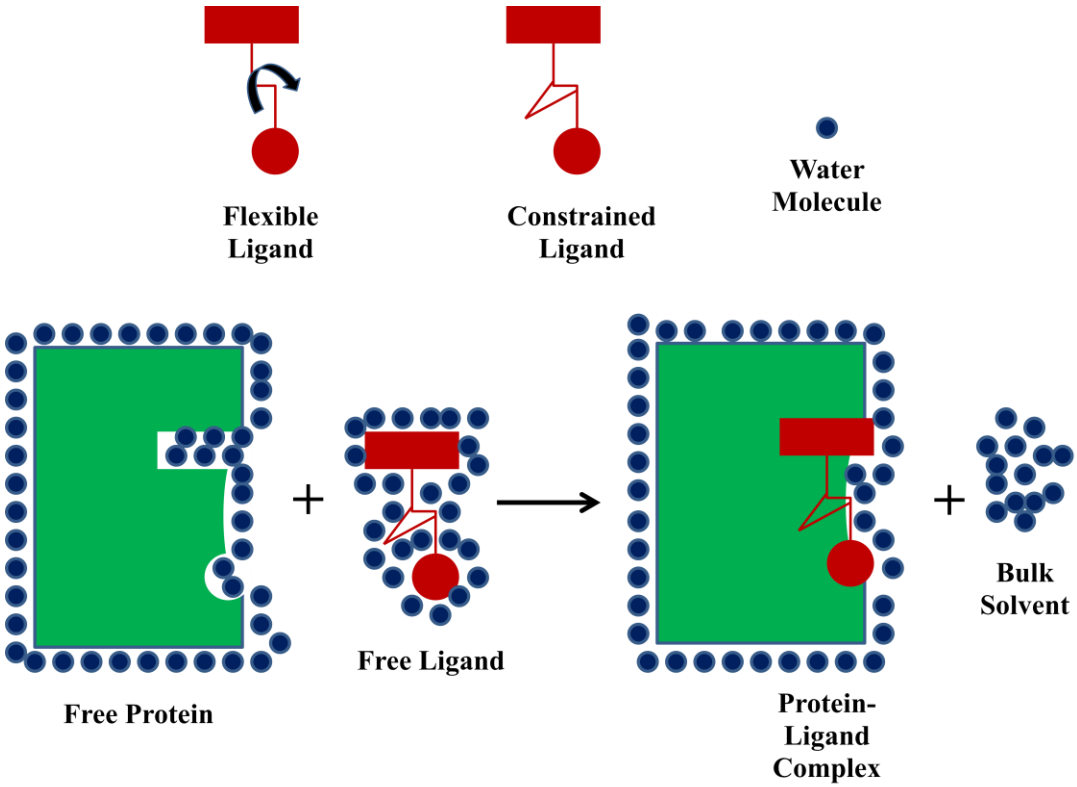
It can be difficult to design experiments that would only affect either the enthalpy or entropy of a protein-ligand association. For example, if the enthalpic term is enhanced to cause the protein and ligand to bind tighter, then the entropic term may become unfavorable due to the increased order in the system and offset some of the enthalpic gain. Conversely, if the order of the system were to become more disordered then favorable non-covalent interactions may be broken which may adversely affect the enthalpic term this phenomenon is referred to as "enthalpy-entropy compensation".[273,299-304]. Although it is not well understood, it appears that solvent reorganization and protein dynamics upon binding play important roles. Our group was most focused on using ligand-preorganization as a means to enhance binding affinity by lessening the entropic penalty paid upon the association event, and a more detailed discussion follows.

3.1.5 LIGAND PREORGANIZATION

Binding affinity may be improved by constraining a peptide, traditionally in its biologically active or bound, conformation.[274,275,287] This is also commonly called ligand preorganization. When ligand preorganization is utilized and an increase in binding affinity is observed, the enhancement is usually attributed to a smaller entropic penalty upon binding because the ligand is already preorganized into the desired binding conformation.[284,285,295] Figure 3.2 represents a simple illustration of the ligand preorganization concept. The "constrained" ligand possesses fewer degrees of freedom (translational, rotational, and conformational, though conformational is the most predominant) than its "free" counterpart, which theoretically leads to an increase in binding affinity due to the lessening of the entropic penalty paid upon complexation of

the protein and ligand. Preorganization also includes the benefit of a possible increase in selectivity of the ligand for the protein receptor.[305]

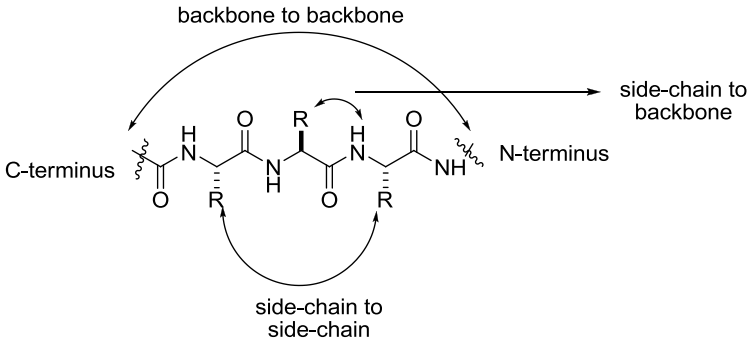
Figure 3.2: The entropic benefits of ligand preorganization.



A number of options are available to introduce a constraint into a peptide ligand, and they fall into two main classes: non-covalent and covalent.[306] Non-covalent constraints are also referred to as "local constraints" and comprise α- and *N*-methyl amino acids and D-amino acids. A local constraint is generally defined as a constraint that affects a single residue of a peptide. Non-covalent constraints typically constrain the ligand through intramolecular H-bonds, which induce a secondary structure in the peptide (*ie* α-helices, β-turns, etc.).[306] Covalent constraints are generally comprised of cyclic

modifications to known peptide binders. These cyclic modifications can either be incorporated into the side-chain or backbone of the peptide, or they can be a combination of both (Figure 3.2). Examples of cyclic covalent constraints range from cyclopropane rings to large macrocycles. The work of the Martin group with cyclopropanes will be discussed in depth in succeeding sections.

Figure 3.3: Types of ligand preorganization.

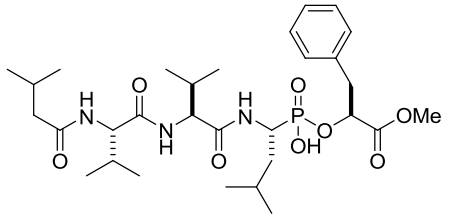


3.2 Early Work in Ligand Preorganization

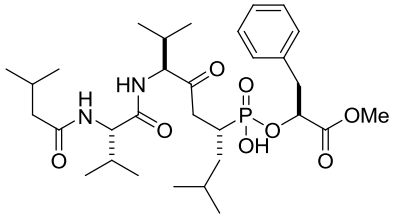
One of the seminal examples of associating ligand preorganization with enhanced binding affinities was accomplished by Bartlett and coworkers.[307-310] Bartlett was interested in inhibitors of aspartic protease penicillopepsin, namely phosphorylated pseudopeptide **3.1** (Table 3.1). Believing that native ligand bound with penicillopepsin in a bent (**3.1b**), as opposed to linear (**3.1a**) conformation, Bartlett first designed the macrocyclic peptide mimic **3.2**, as well as the acyclic mimics **3.3** and **3.4**, in order to investigate whether ligand preorganization would result in an enhanced binding affinity. They found that the most constrained mimic, macrocycle **3.2**, was found to bind to the protease with the best affinity, as measured by K_i's. Though **3.2** did not bind nearly as

well as native ligand **3.1**, this was still one of the first successful applications of a conformational constraint used to enhance binding affinity.[309]

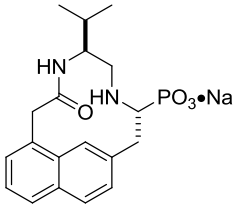
Table 3.1



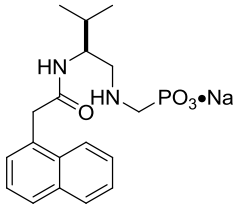
3.1a



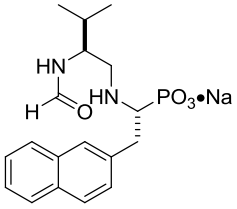
3.1b



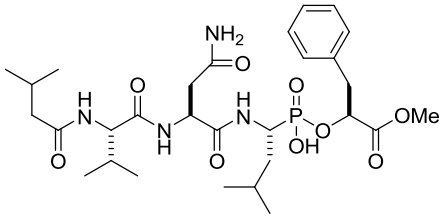
3.2



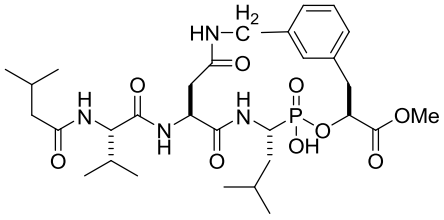
3.3



3.4



3.5



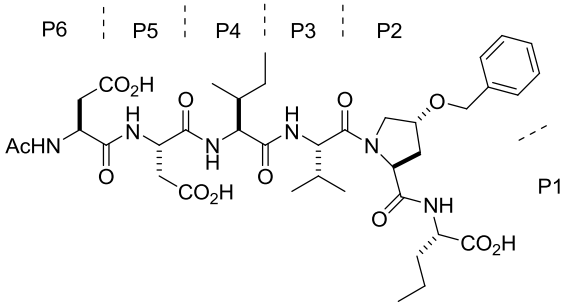
3.6

Ligand	K_i (nM) penicillopepsin
3.1	2.8
3.2	800
3.3	7600
3.4	1 x 10^5
3.5	42
3.6	0.10

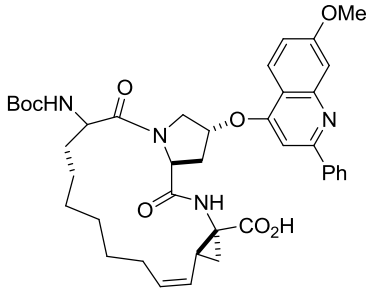
Bartlett then synthesized acyclic mimic **3.5** and macrocycle **3.6**, which were more accurate structural comparisons to the original pseudopeptide **3.1** (Table 3.1).[307,310] Both **3.5** and **3.6** were found to bind to aspartic protease penicillopepsin more favorably than mimics **3.2**-**3.4**, with macrocycle **3.6** being a 420-fold more potent binder over that of flexible control **3.5**. [307-310] When x-ray structures of **3.5** and **3.6** bound with the protein were obtained, both ligands were found to bind to the protein in the same manner, indicating that Barlett had successfully designed a flexible/constrained peptide mimic pair. Though he did not collect thermodynamic data, Barlett speculated that the increased affinity was due to an entropic and not enthalpic benefit.

Another early success exhibiting enhanced binding affinity through ligand preorganization was accomplished by Tsantrizos and coworkers in their investigation of inhibitors of hepatitis C viral NS3 protease (Table 3.2).[311] Based on known hexamer **3.7**, macrocyclic mimic **3.8** and its flexible control **3.9** were synthesized and constrained **3.8** was found to be a 36-fold more potent binder than flexible **3.9**. Again, no thermodynamic data were collected so the authors could not elucidate whether the enhanced affinity was due to a more favorable entropy or enthalpy of binding.

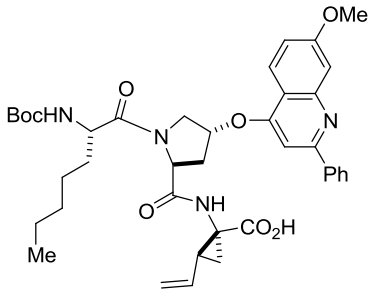
Table 3.2



3.7



3.8



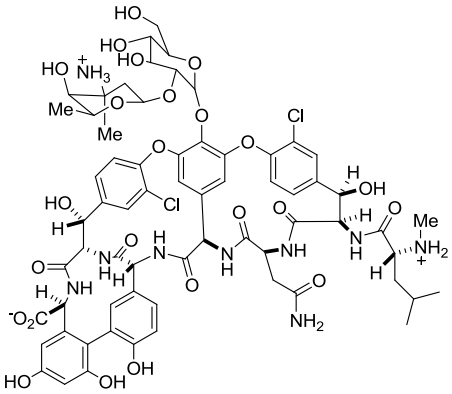
3.9

Ligand	**IC_{50} (μM) NS3-NS4A**
3.8	0.011
3.9	0.400

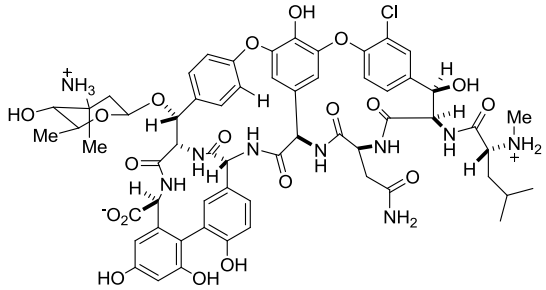
One of the first ligand preorganization studies that collected thermodynamic data, in addition to binding affinity values, was done by Williams. He investigated the thermodynamics of a series of glycopeptidic mimics of the antibiotic vancomycin (**3.10**) and found that glycopeptide **3.11** dimerized with itself with 21-fold more potency than did vancomycin (**3.10**) (Table 3.3).[279,292,312,313] The increase affinity was attributed to both a more favorable enthalpy and entropy of dimerization. Williams further went on to

do extensive work towards understanding entropy-enthalpy compensation and non-covalent interactions in aqueous biomolecular systems. [21,39,40]

Table 3.3



3.10



3.11

Ligand	K_{dim}	$\Delta H°_{obs}$ (kJ mol^{-1})	$T\Delta S°_{obs}$ (kJ mol^{-1})
3.10	700	-36 ± 2	-20 ± 5
3.11	1.5 x 10^4	-51 ± 3	-27 ± 3

3.3 Previous Work in the Martin Group

Recall that our major goal was to examine flexible vs. constrained ligands in order to elucidate the enthalpy (ΔH^o), entropy (ΔS^o), and free energy (ΔG^o) of binding of molecular recognition phenomena in biological systems. Our strategy was to change the structure of a known small molecule incrementally and then measure the thermodynamics effects by ITC to provide comparative thermodynamic data. Structural data of the ligand in the binding pocket was crucial, as that allows for interpretation of the thermodynamic results. If the native peptide was not easily modified then a suitable flexible peptide mimic was synthesized as a control molecule to compare against constrained peptide

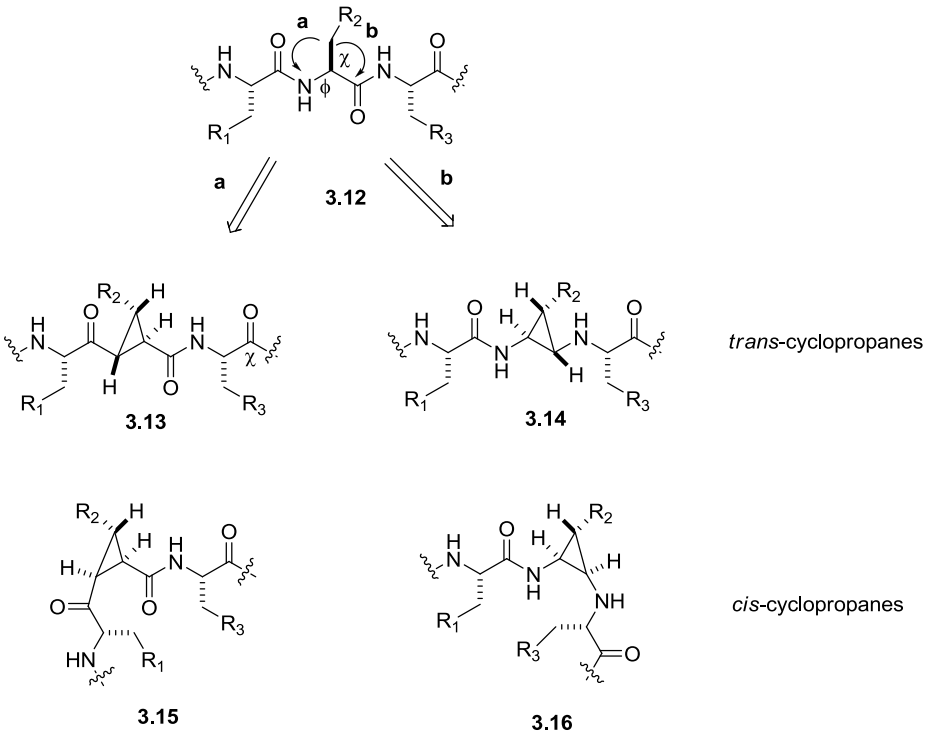
mimics. The constrained peptides were as close in structure as possible to their flexible control compounds, meaning that control molecules had the same number of heavy atoms, the same functional groups, similar numbers of hydrogen atoms, and the same number of hydrogen bond donors and acceptors. Most importantly, the flexible and constrained peptide mimics had to bind to the target protein in the same or similar manner.

Four types of cyclopropane pseudopeptides were developed by our group in the nineties. [274,275,314-323] As shown in Figure 3.4, we were interested in side-chain to backbone constraints (*cf.* Figure 3.3) in order to simultaneously restrict the backbone and rigidify the side-chain to a single orientation. Side chains are known to make important contributions to the binding affinity of certain molecules, but their spatial orientation is often overlooked in the field of ligand design and we had hoped to rectify this.[306]

A side chain may be constrained to the backbone of the peptide *via* the N- or C-linkage (Figure 3.4, path a and b, respectively).[274,275] If we followed path a, then the amide nitrogen was replaced with a carbon atom in order to form the desired cyclopropane, while if we followed path b, we excised the carbonyl group to provide the desired cyclopropane. By controlling the stereochemistry of the cyclopropane ring, we reinforced the backbone structure to either provide an extended (**3.13** and **3.14**) or turn inducing (**3.15** and **3.16**) local structure to the peptide, represented by the backbone angle ϕ. The side chain orientation was also controlled to mimic either a *gauche (-)* (-60º), *gauche* (+60º), or *anti* conformation with respect to the peptide backbone, as represented by angle χ.[274,275,306] The *gauche (-)* conformation is illustrated by the position of R_2 in peptide **3.13**, whereas the *anti* conformation is illustrated by the position of substituent R_2

in peptide **3.14**. The use of specific examples of pseudopeptides **3.13-3.16** will be discussed in detail in the following examples.

Figure 3.4: Types of ligand constraints.

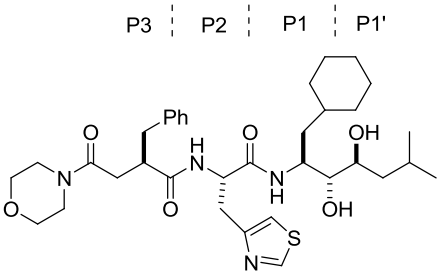


3.3.1 RENIN PROTEASE INHIBITORS

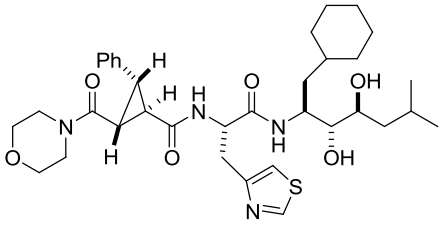
The Martin group first investigated the use of trisubstituted cyclopropane constraints in binding studies with renin protease inhibitors.[274,275,316] Renin protease inhibitor **3.17** (Table 3.4) was chosen because of its potency, as well as because it was thought to bind to the enzyme in an extended, β-strand conformation. As such, constrained peptides **3.18** and **3.19** were designed and synthesized by methods developed within our group to constrain both the side-chain and backbone of **3.17** at the P3 position. In both peptides **3.18** and **3.19**, the *trans* stereochemistry of the cyclopropane constraint

had locked the backbones of the peptides into extended conformations, while the phenyl group orientations differed to represent both the *gauche (-)* and *gauche (+)* orientations, **3.18** and **3.19**, respectively, of linear peptide **3.17**. Peptide **3.17** was an appropriate control for compounds **3.18** and **3.19** because all three contained the same number of heavy atoms and hydrogen bond donors/acceptors, as well as the same functional groups.

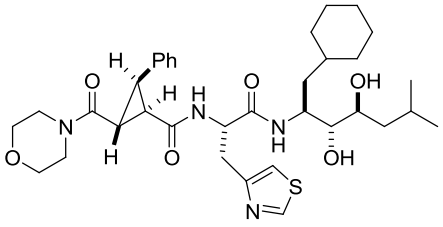
Table 3.4



3.17



3.18



3.19

Ligand	**IC_{50}, nM at pH 6.0**
3.17	0.36
3.18	0.7
3.19	200

When the activities of the ligands were tested under standard assay conditions, it was found that flexible **3.17** bound with approximately the same affinity as the

constrained **3.18**, while its cyclopropyl diastereomer **3.19**, was found to be 300-fold less potent as an inhibitor.[274,275,316] The data thus support the conclusion that the phenyl group side chain of **3.17** bound to aspartate protease renin preferentially in a *gauche (-)* conformation, though we did not observe any noticeable increase in binding affinity due to the preorganization of the ligand. However, this study did prove that cyclopropane backbone/side-chain restraints were valid peptidomimics for ligand-receptor binding studies setting the stage for future experiments.

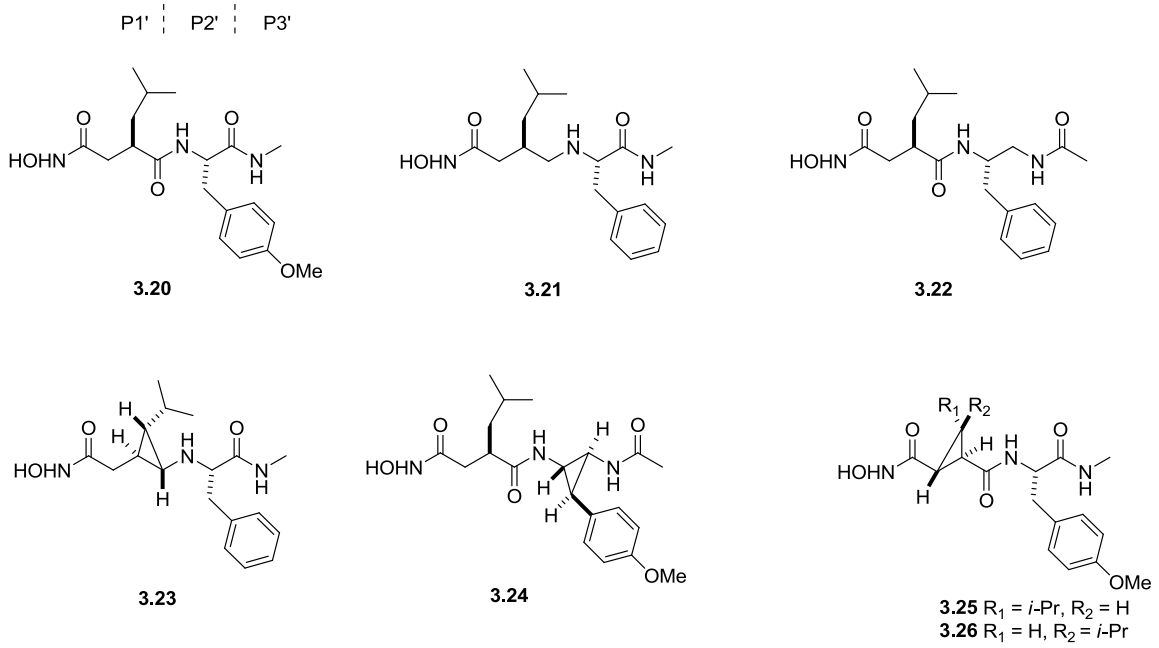
3.3.2 MATRIX METALLOPROTEASE INHIBITORS

We next turned our attention toward introducing cyclopropyl restraints into the known matrix metalloprotease (MMP) inhibitor **3.20** (Table 3.5).[274,275,324] Peptides **3.25** and **3.26** were synthesized to orient the backbone of the peptides in an extended orientation, due to the *trans* stereochemistry of the cyclopropanes, while also orienting the isopropyl group of P1' in both the *gauche (-)* **3.25** and *gauche (+)* **3.26** conformations. When biological assays of **3.25** and **3.26** were run against four different varieties of MMP's, the binding affinities of **3.25** and **3.26** were found to be significantly lower than that of the parent compound **3.20**, suggesting that neither **3.25** nor **3.26** bound in a similar manner to MMP as **3.20**.

Crystallographic data were available for the bound complex MMP-1 and **3.20** and it indicated that the isopropyl group of P1' and the phenyl group of P2' were oriented *anti* to one another in the bound structure.[274,275,324] As we had already shown the design and synthesis of cyclopropanes of the type **3.14** (*cf.* Figure 3.4), which are formed *via* the excision of a carbonyl group in the parent compound **3.12**, we decided to incorporate cyclopropanes of type **3.3** into peptide **3.20**. Thus, compounds **3.23** and **3.24** were

synthesized, with the cyclopropyl group constraining the isopropyl group of P1' in **3.23** and the cyclopropyl group constraining the phenyl group of P2' in **3.24**. Also notice that the amide functionality of **3.24** was transposed as opposed to **3.20**. However, now that we had excised a carbonyl group from **3.20**, the peptide was no longer a suitable flexible control. Peptides **3.21** and **3.22** were synthesized to act as flexible controls for **3.23** and **3.24**, respectively. Both **3.21** and **3.22** contain the same number of heavy atoms and hydrogen bond donors/acceptors as the restricted peptides **3.23** and **3.24**. When the efficacies of peptides **3.21-3.24** were tested towards various MMP enzymes, it was found that they were two to four orders of magnitude less effective than the original inhibitor **3.20**. Clearly the P2' carbonyl group, which was excised in peptides **3.21** and **3.23,** and the P3' amide, which was transposed in peptides **3.22** and **3.24**, were important to the bioactivity of inhibitor **3.20**. While the overall efficacy of peptides **3.21-3.24** went down, we did notice significant differences in bioactivity between the flexible (**3.21** and **3.23**) and constrained (**3.23** and **3.24**) peptides. Constrained peptides **3.23** and **3.24** were found to be more potent than their flexible controls (**3.21** and **3.22**), indicating that ligand preorganization did provide a thermodynamic benefit to the complexation event, though we did not know if the increase in affinity was due to ΔH^{o}, ΔS^{o} or a combination thereof. We did not measure the discreet thermodynamic parameters because it was not available at the time.[274,275,324]

Table 3.5



IC_{50} Values (μM) for MMP inhibitors				
Ligand	**MMP-1 HFC**	**MMP-2 gelatinase A**	**MMP-3 stromelysin-1**	**MMP-7 matrilysin**
3.20	0.0025	0.0007	0.016	0.0065
3.21	26% @ 100 μM	6.0	124	2.5% @ 100 μM
3.22	36% @10 μM	6.15	Inactive @ 10 μM	40% @ 10 μM
3.23	0.054	0.064	1.0	0.78
3.24	1.9	0.26	6.9	6.7

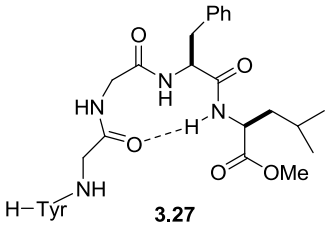
3.3.3 ENKEPHALINS

Enkephalins, a class peptides that bind to opioid receptors (μ- and δ-), were believed to bind to the receptors in a conformation that incorporated a β-turn according to structural and computational studies. The intramolecular hydrogen bond between the carbonyl group of Gly^2 and the amide nitrogen atom of Leu^5 in potent opioid binder Leu-enkephalin methyl ester **3.27** (Table 3.6) was believed to reinforce the observed β-turn in

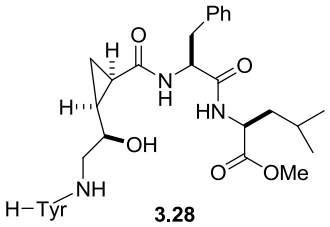
the binding conformation.[274,275,325] We had already developed a method with which to access constrained peptides that we believed would reinforce β-turns through the use of *cis* oriented cyclopropanes (*cf* Figure 3.4, peptides **3.15** and **3.16**), so we designed and synthesized ligands **3.28-3.30**. Extended peptide **3.31**, which incorporated the use of a *trans*-cyclopropane as a constraint, was also synthesized in order to act as an extended control for peptide **3.28**; if **3.27** actually did bind to the opioid receptors in a "turned" orientation (as opposed to an extended conformation), then we would expect **3.31** to perform worse than **3.28**. As a number of carbonyl group and amine nitrogens were excised from the original binder **3.27**, we also synthesized flexible control ligand **3.32**, which had the requisite number of heavy atoms and hydrogen bond donors/acceptors.

Ligands **3.28-3.32** were tested against μ- and δ- opioid receptors to provide mixed results. Compounds **3.29** and **3.30**, which both incorporated *cis* cyclopropanes into the Phe^4 residue, did not exhibit any activity towards either the μ- or δ- opioid receptor. It appears that the introduction of a β-turn reinforcing constraint could not overcome the loss of the hydrogen bond between Gly^2 and Leu^5 in **3.27**. Peptide **3.28**, however, did show some affinity for the μ-receptor, as did its extended conformer **3.31** and flexible control **3.32**. Unfortunately, **3.28**, **3.31**, and **3.32** all bound with approximately the same affinity, which was overall approximately 100-500 fold less than the original ligand **3.27**; and we were unable to make any significant contributions to the hypothesis that *cis* cyclopropanes can stabilize β-turns in binding conformations.[274,275,325]

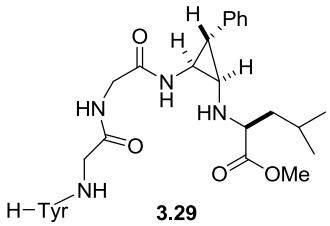
Table 3.6



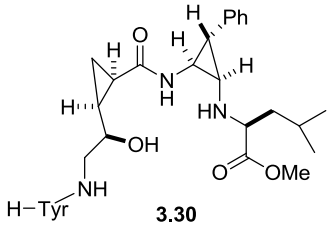
3.27



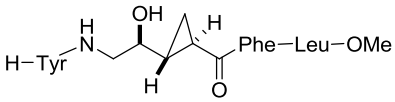
3.28



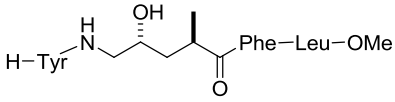
3.29



3.30



3.31



3.32

	K_i (nM)		IC_{50} (nM)	
Ligand	**[^{3}H]DAMGO (μ)**	**[^{3}H]Cl-DPDPE (δ)**	**GPI(μ)**	**MVD (δ)**
3.27	3.9 ± 1.1	10.6 ±3.0	167 ± 14	87 ± 15
3.28	1355 ± 263	>10000	640 ± 241	4261 ± 921
3.29	>10000	>10000	NA	NA
3.30	>10000	>10000	NA	NA
3.31	2159 ± 95	>10000	NA	NA
3.32	438 ± 230	>10000	NA	NA

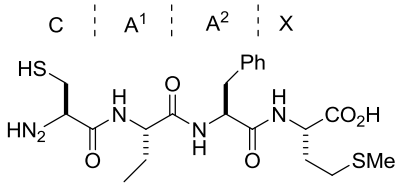
3.3.4 RAS FARNESYLTRANSFERASE INHIBITORS

Ras farnesyltransferase inhibitors of the type **3.33** were first presumed to adopt a β-turn conformation upon binding in early literature studies, but then later studies supported an extended binding conformation, though neither was definitively confirmed

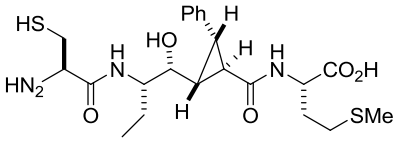
(Table 3.7).[274,275,326] We decided to synthesize both *cis* and *trans* cyclopropyl constrained peptides **3.34**, **3.36**, and **3.37** as replacements for **3.33** to determine whether they could provide evidence for either a β-turn or extended binding conformation between the ligands ras farnesyltransferase receptors. As significant structural changes between compounds **3.34**, **3.36**, and **3.37** and original inhibitor **3.33** were present, the flexible peptide **3.35** was synthesized as a suitable control molecule.

Ligands **3.34-3.37** were all found to be less potent that the original inhibitor **3.33** when subjected to standard biological assays with ras farnesyltransferase, with flexible control **3.35** exhibiting the best bioactivity.[275,326] Constrained *cis* cyclopropyl ligand **3.36** and its corresponding *trans* cyclopropyl extended conformer **3.34** bound with similar activity, though **3.36** was slightly more favored. Peptide **3.37** was found to exhibit the worst activity, indicating that the phenyl group of residue A^2, depicted in structure **3.33**, most likely prefers the *gauche (-)* orientation exhibited in **3.36**. Additional crystallographic studies were performed on compound **3.36** itself, but no compelling evidence was found to indicate that **3.36** actually did induce a locally turned structure. In fact, further modeling studies showed that both **3.36** and **3.37** were capable of adopting extended conformations in the binding pocket of ras farnesyltransferase.[275,326]

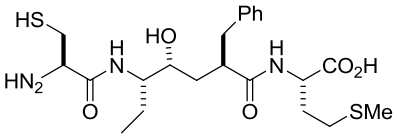
Table 3.7



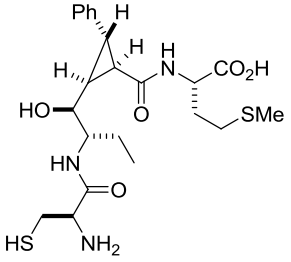
3.33



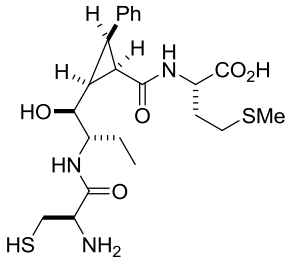
3.34



3.35



3.36



3.37

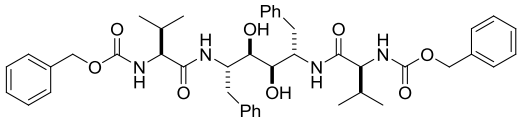
Inhibitor	IC_{50} (nM)
3.33	38
3.34	1055
3.35	320
3.36	760
3.37	7200

3.3.5 HIV-1 PROTEASE INHIBITORS

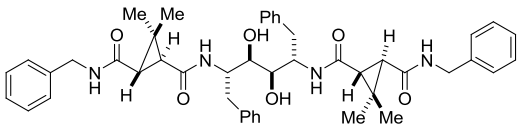
HIV-1 protease inhibitors, **3.38**, are known to bind in extended conformations to the corresponding receptor, specifically as β-strands.[274,275,320] Having previously had

luck with reinforcing extended structures with *trans*-cyclopropyl constraints (*cf.* Table 3.6), we hypothesized that the introduction of *trans*-cyclopropyl constraints at the P2 and P2' residues of **3.38** would further reinforce the β-strand conformation which, in turn, would increase binding affinity. Toward this end we designed and synthesized compounds **3.39-3.42**. When tested as inhibitors of HIV-1 protease, it was found that all the peptides **3.39-3.42** bound with comparable affinity to the original peptide **3.38**, with compounds **3.40** and **3.42** providing a slightly more favorable binding affinity.[274,275,320]

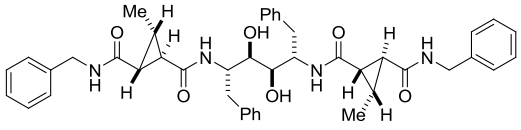
Table 3.8



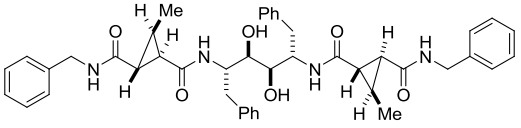
3.38



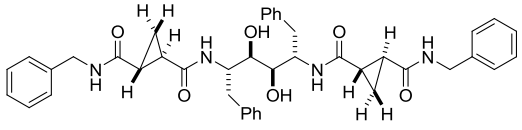
3.39



3.40



3.41

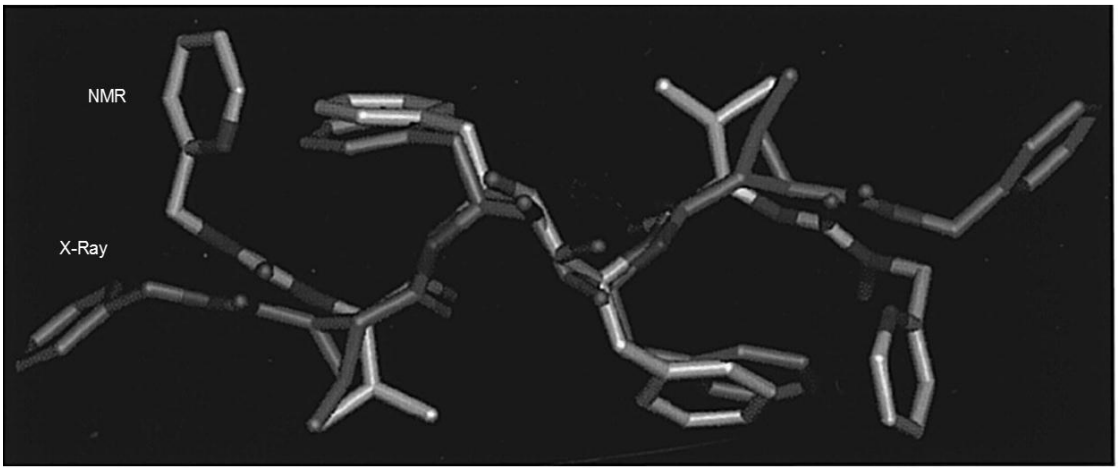


3.42

Inhibitor	IC_{50} (nM)
3.38	0.22
3.39	0.31-0.35
3.40	0.16-0.21
3.41	0.47
3.42	0.17

After several investigations into cyclopropanes as constrained peptide mimics, it was becoming clear that we were not seeing any significant increase in binding affinity due to preorganization of the ligands (*cf* Tables 3.3-3.7).[274,275] In most of the previous examples, with the exception of Table 3.8, the constrained ligands were compared to appropriate control ligands with the same number and type of heavy atoms as well as the same number of hydrogen bond donors and acceptors, so we should have been able to observe any discrete differences in binding affinity that arose from preorganization of the ligands. We needed more information in order to determine if our cyclopropyl constraints were actually restricting the ligands in the favorable binding conformation. Towards that end, an X-ray crystallographic study was conducted on the complex of HIV-1 protease and ligand **3.40**. The bound structure of compound **3.40** was found to resemble that of other known inhibitors. The data from this study were then compared to a separate NMR study, which determined the preferred structure of ligand **3.38** in solution (Figure 3.5).[274,275,320] This result was particularly exciting because for the first time we were able to compare the structure of a stabilized flexible bound protein-ligand conformation in solution to an X-ray crystal structure of the constrained complex.

Figure 3.5: A crystal structure of bound **3.40** overlaid with the NMR structure of unbound **3.38**.[a]



[a] Adapted with permission from Martin, S. F.; Dorsey, G. O.; Gane, T.; Hillier, M. C.; Kessler, H.; Baur, M.; Mathae, B.; Erickson, J. W.; Bhat, T. N.; Munshi, S.; Gulnik, S. V.; Topol, I. A. "Cyclopropane-Derived Peptidomimetics. Design, Synthesis, Evaluation, and Structure of Novel HIV-1 Protease Inhibitors" *J. Med. Chem.* **1998**, *41*, 1581-1597. Copyright (1998) American Chemical Society.

When the crystal structure of bound **3.40** was overlaid with the NMR structure of unbound **3.38** there was generally good agreement between the two.[274,275,320] The most noticeable difference between the two structures was that the orientation of the benzyl groups at the P3 and P3' residues were mismatched. However, it must be noted that the benzyl groups are freely rotating and that only one conformation was shown [274,275,320] This study answered two main questions for our research project. One, we knew that cyclopropyl constrained peptides bound to receptors in approximately the same conformation as known inhibitors; and two, we knew that the bound conformation of the ligand was similar to the conformation of the unbound ligand in solution. Our hypothesis that cyclopropyl constraints could act as viable peptide replacements was validated, but the question remained. Why did we not see any change in binding affinity

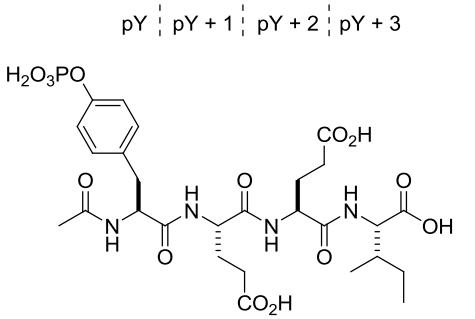
due to ligand preorganization? We needed more data to better interpret our results, thus the time had come to investigate the discrete components of the binding free energy: the enthalpy and the entropy of binding.

3.3.6 THE THERMODYNAMICS OF PSEUDOPEPTIDES BINDING TO THE SRC SH2 DOMAIN

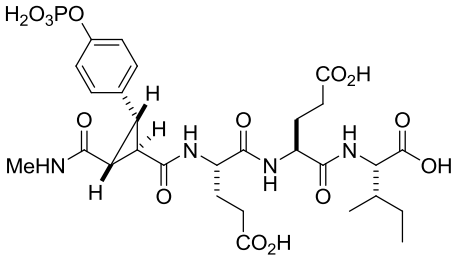
The Src SH2 domain, a small protein domain which is involved in the regulation of signal transduction pathways, like the Grb2 SH2 domain, is known to bind to phosphotyrosine peptides.[327,328] After our success obtaining crystal structure data for the HIV-protease bound complexes, we desired to study another system that was structurally well-defined, as was the case for the Src SH2 domain.[327-330] Specifically, peptide **3.43**, which is a tetrapeptide fragment, has been shown to bind to the Src SH2 domain in an extended conformation with high affinity (Table 3.9).[274,275,331,332] Knowing that the phosphotyrosine residue was a key component to the bioactivity of **3.43**, as it is for all SH2 domains, we designed and synthesized the cyclopropyl constrained ligand **3.44** in which the backbone of the peptide was locked in an extended conformation and the phosphotyrosine residue was restricted to its predicted *gauche (-)* binding orientation.[274,275,333] While we excised an amide nitrogen atom from molecule **3.43** in order to make compound **3.44**, the nitrogen atom was not predicted to participate in any key hydrogen bonding interactions in the binding pocket so we had hoped to avoid any significant enthalpic penalties. The terminal amide group of **3.43** was also replaced by the transposed *N*-methyl amide of **3.44** in order to accommodate the cyclopropyl restraint, while retaining the vital C=O bond. The structural changes resulting in the creation of **3.44** from **3.43**, namely the addition of an extra carbon atom to introduce the cyclopropane ring and the transposed amide, were significant enough so as to require a

more appropriate control molecule, namely flexible ligand **3.45**, which contains the same number of hydrogen bond donors and heavy atoms as **3.44**.

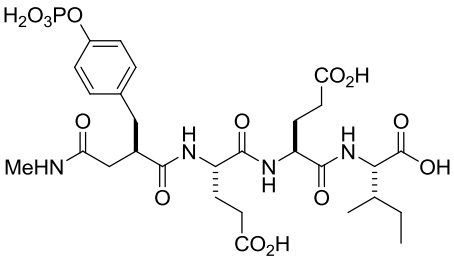
Table 3.9



3.43



3.44



3.45

Ligand	**K_a**	**$\Delta G°_{obs}$ (kcal mol^{-1})**	**$\Delta H°_{obs}$ (kcal mol^{-1})**	**$\Delta S°_{obs}$ (cal mol^{-1} K^{-1})**	**$\Delta C_{p,obs}$ (cal mol^{-1} K^{-1})**
3.43	4.1 (± 0.1) x 10^6	-9.01 ± 0.01	-6.06 ± 0.05	9.9 ± 0.2	-
3.44	1.0 (± 0.1) x 10^7	-9.55 ± 0.07	-5.91 ± 0.04	17 ± 1.0	-225 (± 9)
3.45	1.7 (± 0.6) x 10^7	-9.80 ± 0.20	-7.33 ± 0.03	8.3 ± 0.5	-213 (± 17)

When ITC experiments were carried out for complexes of **3.44** and **3.45** with the Src SH2 domain, it was found that **3.44** and **3.45** were approximately equipotent binders,

showing slightly better affinity than native ligand **3.43**.[274,275,333] Whereas in our previous ligand-protein binding endeavors we had not found a definitive correlation between ligand constraints leading to greater entropic benefits, we were gratified to see that the ITC data from this set of experiments showed that the constrained peptide **3.44** had a considerably more favorable entropy of binding than its flexible control **3.45** (by a margin of approximately 9 eu/mol).[274,275,333] We were finally able to obtain data which lent support towards the general hypothesis that constraining ligands in their bioactive conformations would lead to a lesser entropic penalty on binding; however, we had also hypothesized that the lessening of the entropic penalty should have also lead to an increase in binding affinity, yet it did not. Still, we were extremely gratified to find that our group had provided the first evidence that ligand preorganization can result in entropic benefits during binding.

Recall that the constrained and flexible ligands, **3.44** and **3.45** respectively, were found to bind to the Src SH2 domain with comparable affinities even though **3.44** bound with a more favorable entropy.[274,275,333] As discussed previously, the phenomenon of enthalpy-entropy compensation is notoriously hard to predict and complicates our understanding of molecular recognition in biological systems.[274,275] Changing either the enthalpy or entropy of the association does not guarantee a favorable increase in binding affinity because it is difficult to predict how a change in one thermodynamic parameter will affect the other, nor is the compensation effect required to balance out. What is known is that solvent reorganization and protein dynamics play an important role in the process.[274,275] As the entropy of binding became more favorable for ligand **3.44**, the added advantage was most likely offset by unfavorable enthalpic interactions throughout

the bound complex, resulting in equipotent binding affinity of the constrained and flexible ligands of constrained **3.44** and flexible **3.45**.

In an effort to determine the specific causes of the enthalpic penalty, a series of ITC, X-ray crystallography, and computational studies were undertaken in order to elucidate the structure of the bound ligand-protein complex. We utilized ITC in order to obtain the observed changes in heat capacity ($\Delta C_{p,obs}$) of the complexes by graphing the enthalpy of binding of the complexes at different temperatures (*cf*. Equation 3.7).[274,275,333] Our experiments showed that no such significant interactions seemed to account for the enthalpic differences between **3.44** and **3.45** as the heat capacity values were found to be identical within experimental error.[274,275,333]

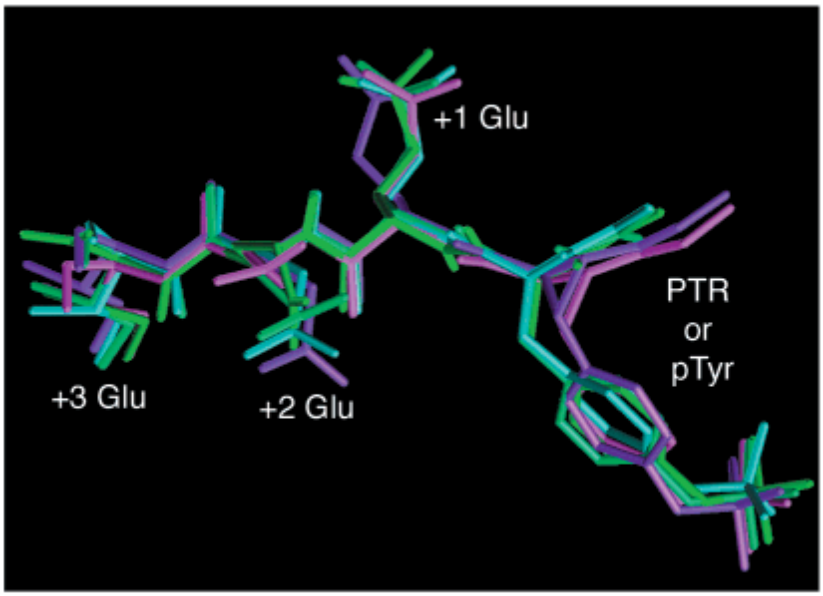
Next a crystal structure of the bound complex of **3.44** with Src was investigated by X-ray crystallography.[274,275,333] Unfortunately, a crystal of the flexible ligand-protein complex (**3.45**) was not available for comparison at the time of the original investigation, so the original crystal data from Waksman, using native peptide **3.43**, was used instead. While not an ideal structural comparison, the binding affinities of **3.43**-**3.45** were all within experimental error of one another so the comparison should still have been able to yield some useful insights.

In Figure 3.6, three bound structures of the native peptide **3.43** were overlaid with two bound conformations of **3.44**.[274,275,333] As predicted from our experimental binding affinities, the bound conformations of **3.43** and **3.44** were very similar to one another. The only significant structural differences appeared to arise in the orientations of the +1 and +2 Glu side chains (pY+1 and pY+2 residues as defined in Table 3.9). However, these variations were not viewed as significant as the differences were found to be

qualitatively no greater than the differences observed between similar complex structures in the asymmetric units of the crystals. Also, the side chains were exposed to solvent, which may have made a contribution to the slight differences in orientation. Again, no compelling evidence was found to account for the differences in enthalpy between **3.44** and **3.45**.

A computational study was undertaken with collaborators in order to investigate the effects of surface contact areas on the enthalpic binding terms of **3.44** and **3.45**; however, this study also revealed no significant qualitative differences between the two complexes.[274,275,333] To summarize, while we were gratified to discover that introducing conformation constraints into a ligand lessened the entropic penalties on binding, we were not able to significantly improve the binding affinity of our constrained ligand due to enthalpy-entropy compensation. Nor were we able to find any physical evidence to explain the differences in the binding enthalpies between **3.44** and **3.45**. It seemed likely that the enthalpic penalty of **3.44** arose from the combination of differences in H-bonding interactions that were not detectable by x-ray crystallography.

Figure 3.6: Three bound structures of native peptide **3.43** were overlaid with two bound conformations of **3.44**.



[a] Reprinted with permission from Davidson, J. P.; Lubman, O.; Rose, T.; Waksman, G.; Martin, S. F. "Calorimetric and Structural Studies of 1,2,3-Trisubstituted Cyclopropanes as Conformationally Constrained Peptide Inhibitors of Src SH2 Domain Binding" *J. Am. Chem. Soc.* **2002**, *124*, 205-215. Copyright (2002) American Chemical Society.

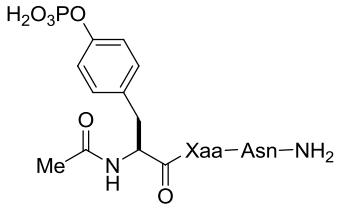
3.3.7 Growth Receptor Binding Protein 2 (Grb2) SH2 Domain

The growth receptor binding protein 2 (Grb2) SH2 domain is known to recognize and selectively bind to phosphotyrosine (pY) peptides of the general structure **3.46** (Table 3.10).[332] We wanted to investigate the effects of a cyclopropyl restraint on known inhibitor **3.46**, where X = valine so we first synthesized the flexible control molecule **3.47** and the restrained peptide **3.53**. When **3.47** and **3.53** were titrated against Grb2 SH2, we were gratified to find that that we observed an increase in binding affinity associated with constrained mimic **3.53**, but we were very surprised to find that the enhanced affinity

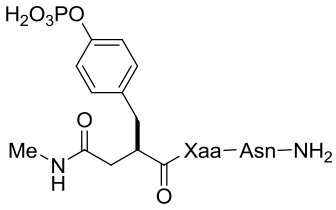
appeared to be *enthalpically*, not *entropically*, driven.[274,332] The entropy of binding was actually found to be unfavorable, which went against existing paradigms regarding ligand preorganization being linked to entropic benefits. Naturally we were intrigued to learn more.

A number of different residues are tolerated at the pY + 1 (illustrated as Xaa in Table 3.10) position of **3.46** in potent binders of the Grb2 SH2 domain.[275,331,332] We designed and synthesized the constricted cyclopropyl peptides **3.54**-**3.58**, displaying both hydrophobic and hydrophilic character at the Xaa residue, in order to further evaluate their thermodynamics of binding with the Grb2 SH2 domain. We were particularly interested to see if ligand preorganization was always accompanied by unfavorable entropies of binding. Peptides **3.54**-**3.58** were synthesized *via* the addition of a methylene group and transposition of the amide functionality of the pY residue of **3.46**, compounds **3.48**-**3.52** were also synthesized to act as suitable flexible controls (fpYXN) for the constrained compounds **3.54**-**3.58** (cpYXN).

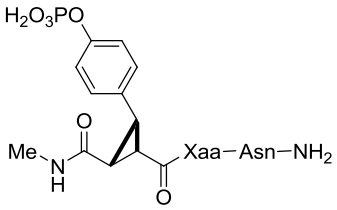
Table 3.10



3.46: Ac-pYXN



3.47: Xaa = Val (fpYVN)
3.48: Xaa = Ile (fpYIN)
3.49: Xaa = Leu (fpYLN)
3.50: Xaa = Gln (fpYQN)
3.51: Xaa = Glu (fpYEN)
3.52: Xaa = Lys (fpYKN)



3.53: Xaa = Val (cpYVN)
3.54: Xaa = Ile (cpYIN)
3.55: Xaa = Leu (cpYLN)
3.56: Xaa = Gln (cpYQN)
3.57: Xaa = Glu (cpYEN)
3.58: Xaa = Lys (cpYKN)

Ligand	K_a (M^{-1})	ΔG° (kcal mol^{-1})	ΔH° (kcal mol^{-1})	ΔS° (cal mol^{-1} K^{-1})	- TΔS° (kcal mol^{-1})
3.47 (fYVN)	$(4.5 \pm 0.12) \times 10^5$	-7.7 ± 0.02	-5.4 ± 0.14	7.9 ± 0.22	-2.4 ± 0.07
3.53 (cYVN)	$(2.8 \pm 0.10) \times 10^6$	-8.8 ± 0.02	-7.9 ± 0.29	3.0 ± 0.30	-0.9 ± 0.09
3.48 (fYIN)	$(4.0 \pm 0.15) \times 10^5$	-7.7 ± 0.02	-5.5 ± 0.20	7.4 ± 0.30	-2.2 ± 0.09
3.54 (cYIN)	$(2.1 \pm 0.08) \times 10^6$	-8.6 ± 0.02	-8.3 ± 0.30	1.3 ± 0.30	-0.4 ± 0.09
3.49 (fYLN)	$(1.7 \pm 0.06) \times 10^5$	-7.1 ± 0.02	-4.6 ± 0.17	8.6 ± 0.30	-2.6 ± 0.09
3.55 (cYLN)	$(7.1 \pm 0.27) \times 10^5$	-8.0 ± 0.02	-6.0 ± 0.22	6.6 ± 0.30	-2.0 ± 0.09
3.50 (fYQN)	$(5.6 \pm 0.15) \times 10^5$	-7.8 ± 0.02	-8.7 ± 0.23	-2.8 ± 0.22	0.8 ± 0.07
3.56 (cYQN)	$(1.2 \pm 0.06) \times 10^6$	-8.3 ± 0.01	-9.8 ± 0.20	-5.2 ± 0.18	1.5 ± 0.05
3.51 (fYEN)	$(3.0 \pm 0.08) \times 10^5$	-7.5 ± 0.02	-8.8 ± 0.23	-4.3 ± 0.22	1.3 ± 0.07
3.57 (cYEN)	$(3.6 \pm 0.10) \times 10^5$	-7.6 ± 0.02	-10.3 ± 0.27	-9.0 ± 0.22	2.7 ± 0.07
3.52 (fYKN)	$(9.8 \pm 0.23) \times 10^4$	-6.8 ± 0.02	-7.7 ± 0.20	-3.0 ± 0.21	0.9 ± 0.07
3.58 (cYKN)	$(5.5 \pm 0.15) \times 10^5$	-7.8 ± 0.02	-9.2 ± 0.24	-4.6 ± 0.22	1.4 ± 0.07

Binding thermodynamics of peptides **3.47**-**3.58** for Grb2 SH2 were determined by ITC, and it was found that the constrained ligands **3.53-3.58** typically bound to the domain with higher affinities than their flexible controls **3.47-3.52**, regardless of the

amino acid present at the pY + 1 position (Table 3.10, column 2 and 3, K_a and $\Delta G°$).[275,331,332] The respective $\Delta\Delta G°$'s between the constrained and flexible controls ranged from 0.1 to 1.1 kcal mol^{-1}, the latter which represented a significant increase in affinity . We were gratified to see that the first part of our original hypothesis, namely that ligand preorganization would increase binding affinity between ligands and protein receptors, was validated; however, we also wanted to know if the said increase in binding affinity was entropically driven.

When we calculated $\Delta S°$ from $\Delta G°$ (which was itself calculated from K_a *via* equation 3.3) and $\Delta H°$ (which was obtained directly from the ITC experiments along with K_a) using the Gibb's free energy equation (eq. 3.4), we made a surprising discovery. Without exception, the binding entropies for the constrained (*ie* preorganized) ligands **3.53-3.58** were found to be more unfavorable than their flexible controls **3.47-3.52** (Table 3.10, column 4), while the binding enthalpies of the constrained ligands **3.53-3.58** were more favorable than their flexible controls **3.47-3.52** (column 4). Also, the contributions of the binding enthalpies dominated the contributions of the binding entropies (columns 4 vs. 6).[274,331,332]

After observing that ligand preorganization was enthalpically, not entropically driven, we sought more information in order to understand this surprising result. We measured the heat capacity changes between the sets of flexible and constrained ligands, but we found no significant differences in the values. Thus, desolvation effects did not appear to be the driving force behind the favorable enthalpies that had dominated binding with the Grb2 SH2 system[274,332].

We then studied X-ray crystal structures of the complexes of ligands **3.34** (fpYVN), **3.35** (fpYIN)**, 3.37** (fpYQN)**, 3.40** (cpYVN)**, 3.41** (cpYIN)**,** and **3.43** (cpYQN) with the Grb2 SH2 domain. Through a detailed a systematic investigation of the X-ray crystallographic data of the three sets of flexible and constrained protein-ligand complexes it was found that there were few structural differences between the two types of complexes. While both the flexible and constrained ligands were found to bind to Grb2 in similar orientations, there were a few significant differences. Namely, the constrained ligands were shown to make more direct contacts (*ie* non-polar interactions that do not involve water molecules) with the Grb2 domain than their flexible counterparts. From these observations and those of our ITC studies, it appears that there is a positive correlation between the number of direct contacts that a ligand makes with the Grb2 SH2 domain and the enthalpy of binding. The more direct contacts a ligand was found to make Grb2, the more favorable the enthalpy, and therefore the Gibb's free energy of binding. This effect may help to explain why the preorganization of ligands was observed to be enthalpically driven.

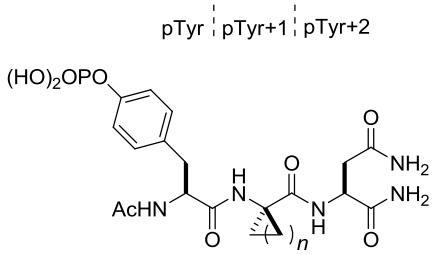
We found no compelling evidence that any of the above processes was solely responsible for the enthalpic compensation that we observed during binding. In conclusion, what we learned from this investigation was that protein-ligand interactions are highly complex processes that can still defy understanding in the face of a wealth of thermodynamic and structural data; however this only further underscored the need for more information with which to characterize and interpret these systems. Toward that end, we collaborated with Dr. Pengyu Ren to carry out computational studies of our Grb2 SH2 protein-ligand complexes.[334] The complexes of flexible/constrained ligand pairs

3.34 (fpYVN)/**3.40** (cpYVN) and **3.35** (fpYIN)/**3.41** (cpYIN) and the Grb2 SH2 domain were examined using molecular dynamics simulations with a polarizable force field.[334] We were pleased to find that our calculated values for the binding free energies, enthalpies, and entropies of the complexes matched those that we obtained experimentally from ITC. Additionally, the computational studies indicated the introduction of the cyclopropyl conformational constraint onto ligands **3.40** and **3.41** prevented them from adopting a stabilized macrocyclic structure in solution that entropically benefitted ligands **3.34** and **3.35** upon binding with the domain. Analysis of these conformational ensembles suggested that the differences in the unbound structures of the flexible and constrained ligands did account for the unfavorable binding entropies of the constrained ligands. The most significant finding from our computational studies was that the introduction of a conformational constraint into a ligand does not automatically correlate with a lower entropy in solution. Though flexible ligands **3.34** and **3.35** existed as stabilized macrocycles in solution, which does not correlate with their bound structures with the Grb2 SH2 domain, they exhibited a lower entropy in solution because of a series of subtle and complex inter- and intramolecular interactions. Our results highlight the need for detailed structural information on the unbound ligands in solution in addition to structural information about the bound ligand-protein complex.[334]

We also investigated another series of ligands of type **3.46** in which the Xaa residue was comprised of α,α-cycloaliphatic amino acids, containing three to seven-membered rings (Table 3.11).[335] In addition to furthering our studies on the effects of ligand preorganization on the thermodynamics of binding, the study of ligands **3.59-3.63** also enabled us to investigate the effects of non-polar surface area on binding

thermodynamics. When the ring size of the ligand constraint was increased, so was the non-polar surface on the ligand. When ligands **3.59**-**3.63** were titrated against Grb2 SH2 using ITC, we saw binding affinities increase with ring size from three to six-membered rings, with six and seven-membered rings being equipotent. Amazingly, we also saw that the increased binding affinity was accompanied by favorable binding enthalpies, which dominated less favorable binding entropies. Thus, we had obtained evidence of an enthalpically driven hydrophobic effect. When the x-ray crystal structures of ligands **3.59**-**3.63** in the domain were examined, the only significant differences to account for the favorable enthalpy appeared to be in the number of vdW contacts between the domain and the Xaa residues. Once again the results of our studies have continued to question the validity of long existing ligand design paradigms.

Table 3.11



3.59: n = 1
3.60: n = 2
3.61: n = 3
3.62: n = 4
3.63: n = 5

Ligand	K_a (x 10^5 M^{-1})	$\Delta G°_{obs}$ (kcal mol^{-1})	$\Delta H°_{obs}$ (kcal mol^{-1})	$-T\Delta S°_{obs}$ (cal mol^{-1})
3.59	1.6 ± 0.1	-7.1 ± 0.1	-3.3 ± 0.3	-3.8 ± 0.1
3.60	4.3 ± 0.4	-7.7 ± 0.1	-5.4 ± 0.3	-2.3 ± 0.2
3.61	16.1 ± 0.6	-8.5 ± 0.1	-6.3 ± 0.4	-2.2 ± 0.2
3.62	69.6 ± 12	-9.3 ± 0.1	-8.5 ± 0.4	-0.8 ± 0.4
3.63	37.0 ± 3.3	8.9 ± 0.1	-6.8 ± 0.3	-2.1 ± 0.2

3.3.8 SRC SH2 DOMAIN REVISITED

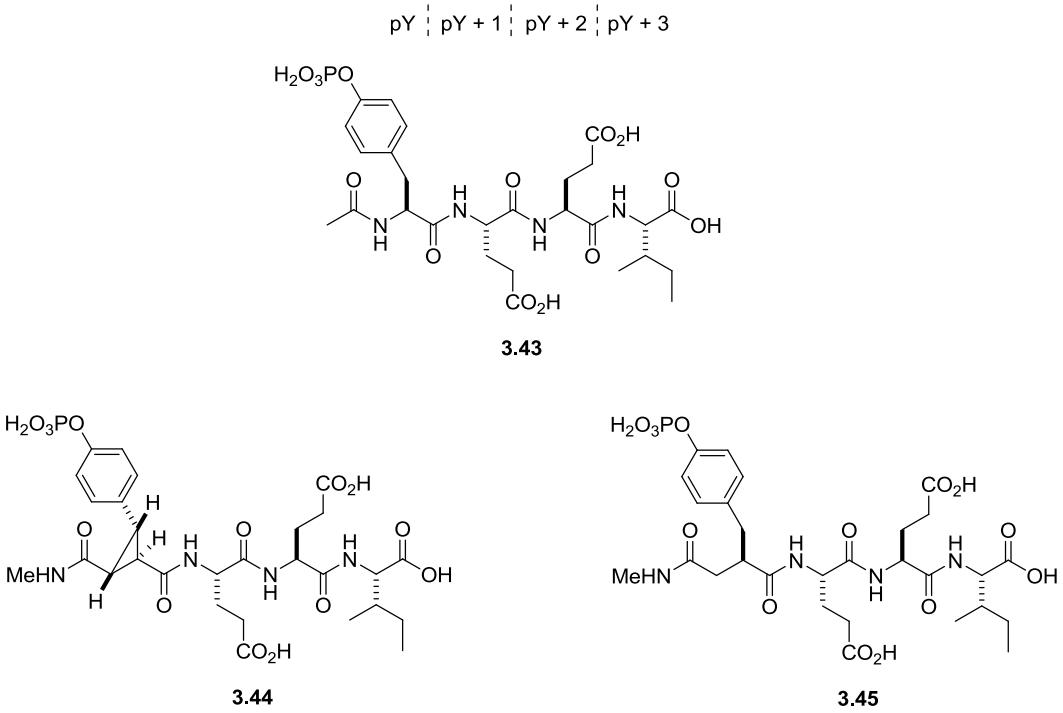
Contemporaneous to our work on the Grb SH2 system, we were also undertaking collaborative NMR and molecular dynamics (MD) experiments on the Src SH2 system.[336] Recall that while the Grb SH2 system showed enthalpically driven binding affinity increases due to ligand preorganization,[332,335] the Src SH2 system had showed entropically driven binding affinity increases due to ligand preorganization.[333] Also recall that enthalpy-entropy compensation caused the entropic benefit gained through

ligand preorganization in the Src system to be offset by competing unfavorable enthalpic interactions, though we could not find a definitive reason as to why this enthalpic compensation was occurring.[333] We were also perplexed by the fact that this trend was not observed in the Grb2 SH2 system (*cf*. Section 3.3.7).[332,335] All our studies with Grb2 found that enthalpy was the driving factor in enhanced binding affinities accompanied by ligand preorganization and that enthalpy-entropy compensation was not a complicating factor during binding. It appeared as though molecular recognition phenomena in aqueous systems was even more complex than we had first thought and that making generalized predictions will require comprehensive studies over a series of different protein-ligand systems. Through additional NMR and MD experiments, we had hoped to better explain the enthalpy-entropy compensation phenomenon within our Src system and perhaps gain insight into why it had not affected our Grb2 system.[336]

It is well known that the thermal motions of proteins, and thus their corresponding conformational fluctuations, play an important role in protein-ligand interactions.[273,275,336] Quantifying these motions however, proves a more difficult task. While X-ray crystallography can provide accurate three dimensional representations of bound protein-ligand complexes, it is a static technique and therefore cannot measure dynamic differences within the complexes. In the past, NMR relaxation and molecular dynamics simulations have been used as valuable tools with which to investigate the internal dynamics of protein-ligand interactions.[273,275,336] When the dynamic results are combined with the structural data obtained from X-ray crystallographic studies, an even more complete and useful picture of protein-ligand interactions emerges.

In a joint collaboration with Dr. Carol Post, we further expanded our investigations of protein-ligand interactions between ligands **3.43-3.45** (*cf*. Table 3.9 and Figure 3.7) and Src using both NMR relaxation studies and molecular dynamics simulations.[336] We found that relative chemical shift differences (CSD's) within ^{1}H-^{15}N HSQC spectra of the *apo*-protein and protein-ligand complexes correlated with small differences in the bound state geometries of **3.43-3.45** which were previously invisible to us from X-ray crystallography.[336] The CSD's reflected differences in proton shielding and deshielding within the system, and these appear to correlate linearly with the enthalpies of binding Namely, the ligand that was shifted the most upfield in the spectrum corresponded to the flexible mimic **3.44**, which possessed the most favorable enthalpy of binding of the series **3.43-3.45**.[274,336]

Figure 3.7: Previous ligands for the Src SH2 protein domain.



The stronger hydrogen-bonding interactions suggested by CSD's were found to be consistent with the observed enthalpic penalty that we observed in our previous Src binding studies regarding ligand **3.45**. These results suggest that introducing a conformational constraint at the pY site of the native peptide can lead to unfavorable enthalpic interactions due to a disturbance of the distance and orientation dependent hydrogen bonds. The pY site is known as a binding "hot spot" because the residue contains interactions that contribute to the majority of the free energy of binding.[336] Furthermore, MD simulations and ^{15}N NMR relaxation measurements suggested that the dynamic motion of the protein was not significantly different between **3.44** and **3.45**, and thus do not significantly contribute to differences in binding entropy or enthalpy.

However, such computational studies are not necessarily sensitive enough to detect subtle differences, and it will be essential to probe variations in protein dynamics in the complexes by NMR experiments.

3.4 Summary of Previous Martin Group Work

In summary, we investigated a variety of protein-ligand interactions and have found that the binding process is incredibly complex and difficult to predict. Our early studies on renin protease inhibitors, matrix metalloprotease inhibitors, enkephalins, ras farnesyltransferase inhibitors, and HIV-1 protease inhibitors (*cf.* sections 3.3.1-3.3.5)[275] showed that the binding affinities of constrained ligands were equipotent or only slightly more favorable than those of their flexible counterparts. However, we had not carried out ITC experiments, so we could not correlate any of our results with the enthalpies or entropies of binding, though we did obtain the first X-ray crystal structure of an HIV-1 protease-ligand bound complex.[320]

Through our work with the Src SH2 domain (*cf.* Section 3.3.6), we provided the first evidence that ligand preorganization was accompanied by a more favorable binding entropy. We also found that the binding affinity of the Src SH2-ligand complexes was not enhanced to the degree that we had expected as the entropic benefits were accompanied by significant enthalpic penalties.[333] Restricting independent rotors, *ie* bonds, in flexible ligands should be accompanied by an entropic advantage ranging from 0.7-1.6 kcal mol^{-1},[308,337-339] and while we did find that the constrained ligands showed a 1.5-2.7 kcal mol^{-1} entropic advantage over the flexible ligands, the entropic advantage was offset by an enthalpic penalty of 1.4-1.9 kcal mol^{-1}.[333] Thus, the overall binding affinity of the constrained vs. flexible ligands remained unchanged. However, this result

was by no means universal across all protein-ligand systems. When we examined the Grb2 SH2 domain (*cf.* Section 3.3.7), we found that ligand preorganization *did* lead to an *increase* in binding affinity, though much to our surprise we also found that increased binding affinity was attributed to an *enthalpic,* not an entropic benefit.[332] Additionally, unlike the Src SH2 system the enthalpic benefit was not offset by an accompanying entropic penalty. We were incredibly intrigued by how complex bimolecular associations in aqueous media really are.

Though we had made some significant contributions toward understanding molecular recognition phenomena in biological systems, we seemed to create more questions than we had answered. While enthalpy-entropy compensation played an important role in our Src SH2 binding studies, it did not affect our Grb SH2 system to nearly as large an extent, which further underscored the need for continued investigations into this complex and interesting phenomenon. While we had succeeded in providing evidence that ligand preorganization lead to increased binding affinity due to enthalpic benefits in our Grb SH2 work, we had also found that ligand preorganization produced favorable binding entropies without a resulting increase in binding affinity. These results were completely unexpected and challenged a long-standing paradigm of protein-ligand thermodynamics. Further study is required.

In his original Src SH2 publications, Waksman had reported that the crystal structure of pYEEI and Src showed two well-defined binding pockets that "resemble a two-pronged plug engaging a two-holed socket".[327,328] The first pocket contained the phosphotyrosine residue, which is known to be a key residue in all SH2 domains, while the second pocket, also called the hydrophobic pocket, showed that the isoleucine residue

of the ligand was also responsible for key binding interactions within the domain. Waksman surmised that the hydrophobic pocket was critical to determining peptide specificity, meaning the isoleucine residue served to orient and anchor the peptide to the Src SH2 domain.[327,328] During our collaboration with Dr. Post, our CSD data also indicated to us that the the pY + 3 sidechain (Ile) of the native peptide **3.43** played an important role in binding between the Src SH2 protein pocket pYEEI.[336] Based on this information, we formulated a hypothesis that we may be able to introduce a cyclopropyl conformation constraint in the pY + 3 residue, which resided outside of the hot spot region. Hopefully, we will be able to gain the same entropic benefit from ligand preorganization that we saw before without incurring an offsetting enthalpic penalty. We had already found that even the smallest, almost invisible, of changes in orientation between the hot spot of the peptide and the binding pocket can cause drastic changes in the binding enthalpy, but we didn't know anything about how a conformational constraint would behave in a non hotspot region. Perhaps this technology would emerge as a useful tool towards rational ligand design. Our current work towards designing, synthesizing, and analyzing the thermodynamics of constrained and flexible pY + 3 mimics for pYEEI will be discussed in detail.

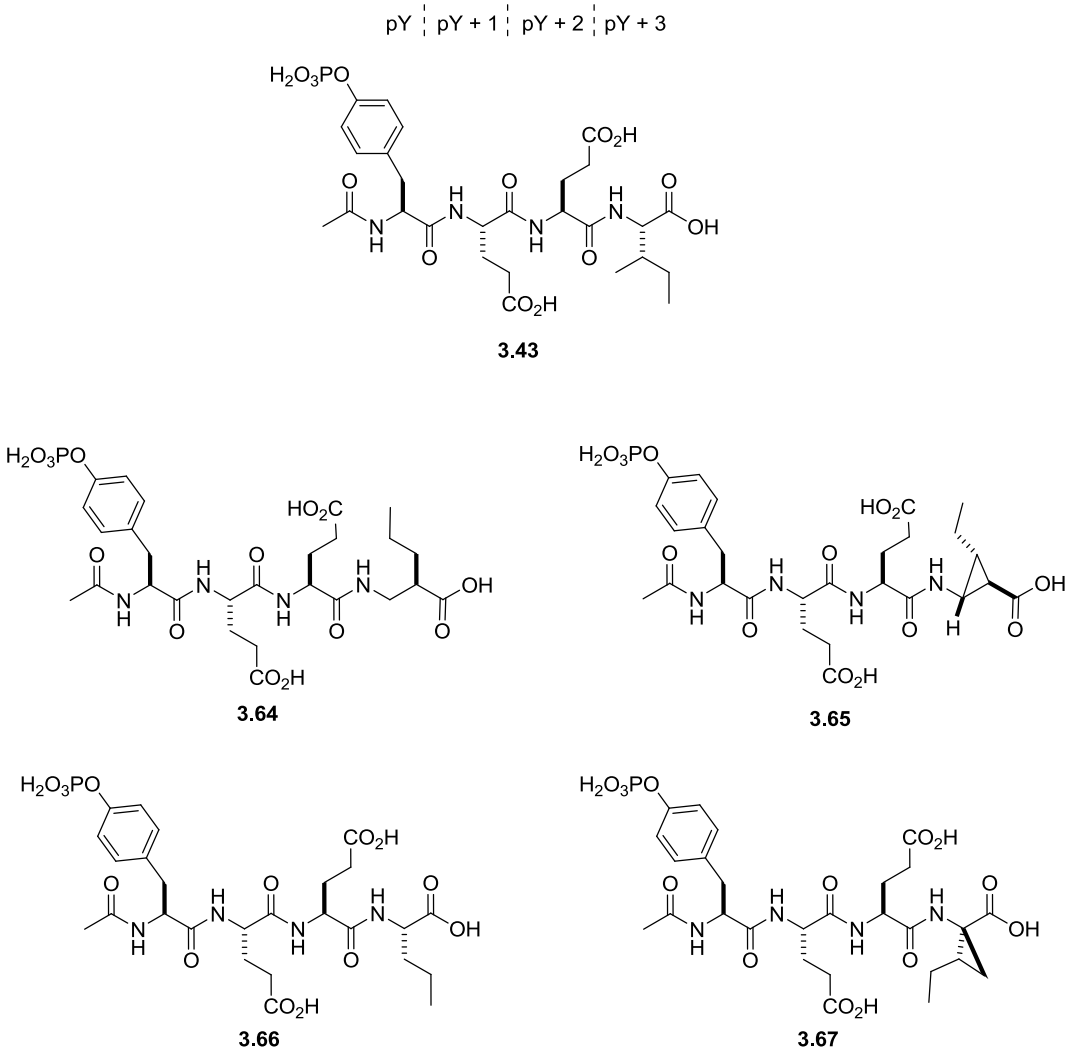
3.5 Design and Synthesis of Src-SH2 pY +3 Constrained and Flexible Ligands

Based on Waksman's original crystal data and the CSD data obtained through collaboration with Dr. Post, we formulated a hypothesis that we may be able to introduce a cyclopropyl conformation constraint in the pY + 3 residue, which resided outside of the hot spot region.[327,328,336] Hopefully we will be able to gain the same entropic benefit from ligand preorganization that we saw before without incurring an offsetting enthalpic

penalty. We had already found that even the smallest, almost invisible, of changes in orientation between the hot spot of the peptide and the binding pocket can cause favorable and unfavorable binding enthalpies, but we didn't know anything about how a conformational constraint would behave in a non hotspot region. Presumably any weak vdW forces that we might disrupt at the pY+3 ligand would prove less crucial to the overall binding affinity than the disruption of the distance and orientation dependent hydrogen bonds created between the pY residue and the binding pocket.

Toward that end, two sets of ligands **3.64** and **3.65**, as well as **3.66** and **3.67** were designed to investigate the effects of adding a conformational constraint at a non hot-spot residue (Figure 3.8). Molecular modeling experiments between constrained mimic **3.44** and the Src binding pocket (*cf*. Figure 3.6)[333,336] suggested that the trans-cyclopropane ring of **3.65** would position the ethyl group in the orientation required to make optimal vdW contacts within the Src SH2 domain (Figure 3.8). We also designed cyclopropane ring **3.67** in order to assess the thermodynamic effects associated with restricting the side chain of a ligand as compared to restricting the backbone and sidechain as we were planning to do with ligand **3.65**. We designed ligands **3.64** and **3.66** to act as flexible controls for the constrained **3.65** and **3.67**, respectively. Preparation of **3.64** and **3.65** would require the addition of an extra carbon atom into the pY+3 residue, as well as replacement of the isoleucine sidechain with a propyl chain. Ligands **3.66** and **3.67** would also require replacement of the isoleucine sidechain with a propyl group, and ethyl cyclopropane, respectively. Their synthesis will be described shortly.

Figure 3.8: pY+3 Peptide mimics for Src SH2.

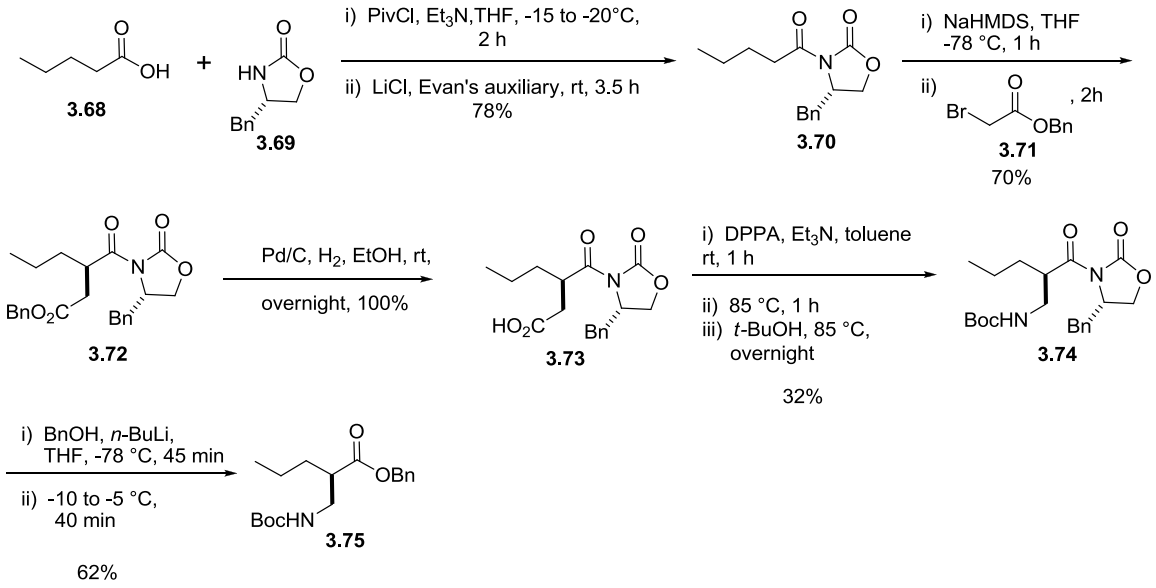


3.5.1 SYNTHESIS OF FLEXIBLE CONTROL LIGAND 3.64

The forward synthesis of **3.64** had been partially accomplished previously by Dr. Jianhua Tian, a former post doc within the Martin lab (Scheme 3.1).[340] Valeric acid (**3.68**) was coupled to Evan's auxiliary **3.69** in 78% yield, followed by the alkylation of chiral imide **3.70** with benzyl-2-bromoacetate (**3.71**) in 70% yield. The benzyl ester of

3.72 was then reductively cleaved in quantitative yield, and the resulting acid **3.73** was subjected to one-pot Curtius rearrangement conditions[341,342] to provide a modest 32% yield of the desired carbamate **3.74**, which was contaminated with a significant amount of urea.[340] The chiral auxiliary was then cleaved with lithium benzyloxide to provide β-amino ester **3.75** in 62% yield, which was ready for use in standard peptide coupling conditions.

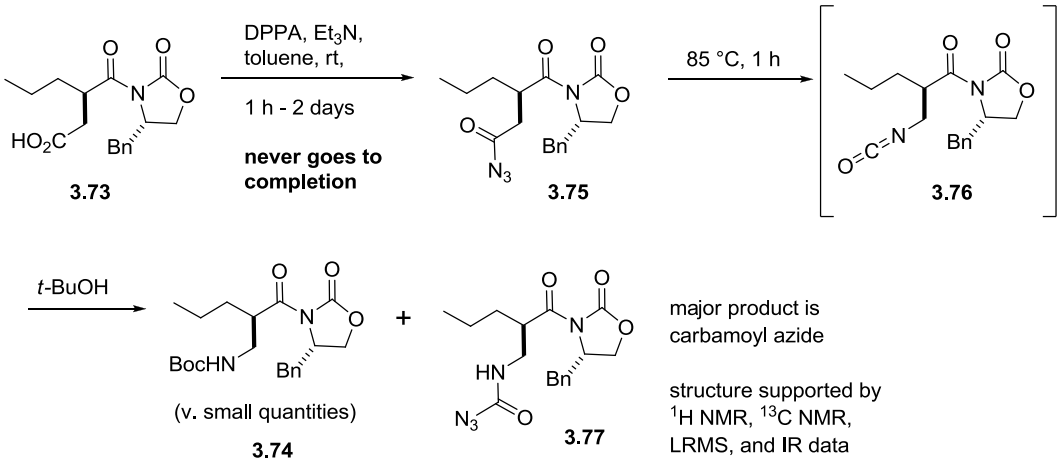
Scheme 3.1



When Jianhua's results were reproduced, we found an opportunity to improve the Curtius rearrangement of acid **3.73** to amide **3.74**, which had proceeded in only 32% yield. While trying to optimize this key reaction, we noticed that the reaction between DPPA and acid **3.73** would not proceed to completion, even after stirring at room temperature for two days. Nevertheless, we carried out the heating required for

rearrangement of acyl azide **3.75** to isocyanate **3.76**, in the presence of the leftover (diphenylphosphoryl azide) DPPA. DPPA has been touted as a useful reagent to transform carboxylic acids to acyl azides because it serves to activate the acid as well as supplies the requisite azide functionality under mild conditions.[343] When acid **3.73** was subjected to the rearrangement conditions, two products were isolated from the reaction mixture. The desired carbamate **3.74** was the minor product, and the major product was a compound that we could not identify via ^{1}H NMR analysis. When an IR of the unknown compound was obtained, a distinctive stretch appeared in the 2100 cm^{-1} region, which is indicative of acyl azide compounds. Acyl azides are expected intermediates in Curtius rearrangements (**3.75**, Scheme 3.2), so the unknown product was re-subjected to re-arrangement conditions (heating under reflux in the presence of *t*-BuOH). However, no carbamate **3.74** was ever obtained. The only compound recovered from the reaction mixture was starting material, which we had originally presumed to be acyl azide **3.75**, but now appeared to be something else.

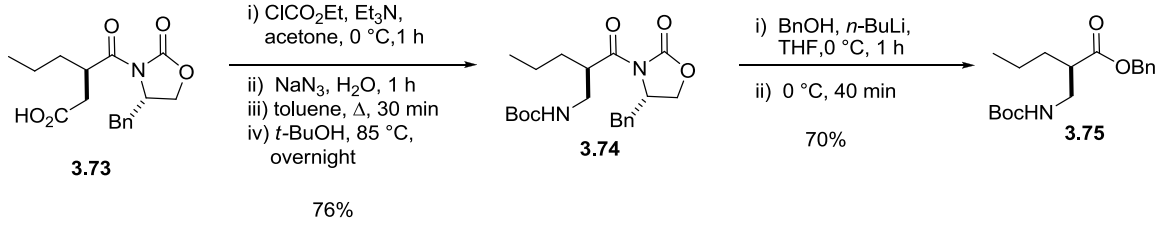
Scheme 3.2



A literature search then showed us that carbamoyl azides, such as **3.77,** could be formed in Curtius rearrangements when DPPA was present in the reaction mixture (Scheme 3.2).[344] After re-examining the ^{1}H NMR and IR data of our unknown compound and comparing these with those of similar known compounds, we surmised that our unknown compound, was in fact, carbamoyl azide **3.77** (Scheme 3.2). This was soon supported with LRMS and ^{13}C NMR data that helped us to explain the resistance of the unknown compound to convert to the desired carbamate **3.74** when re-subjected to re-arrangement conditions. We surmised that when DPPA was heated under rearrangement conditions it could undergo dissociation into hydrazoic acid, which could then compete with *t*-BuOH as nucleophile in the addition to isocyanate **3.76**.

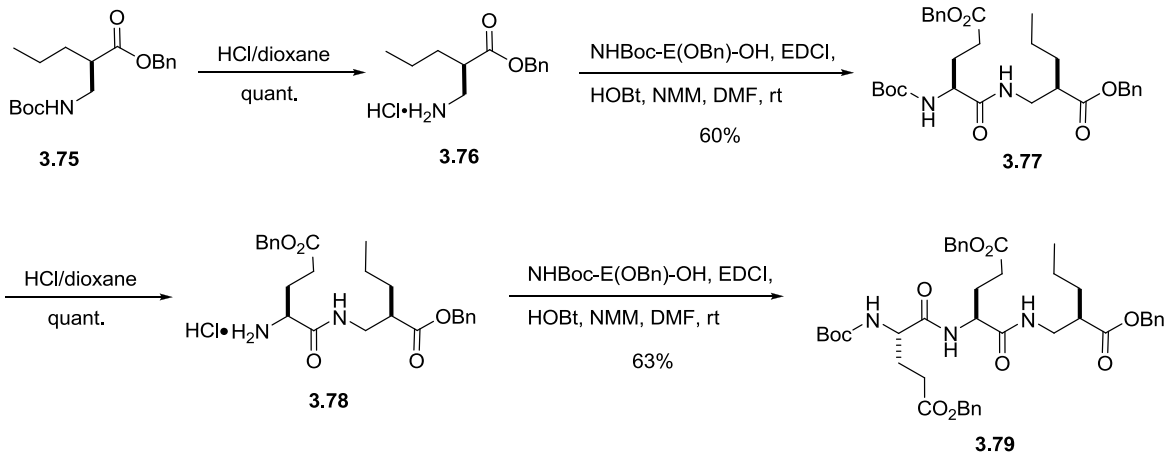
Since DPPA did not seem to convert acid **3.73** to acyl azide **3.75** in good yields without heat, the decision was made to switch to a two-step procedure in which a mixed anhydride was made, and then subsequently displaced with sodium azide (Scheme 3.3).[333] When followed by a mild aqueous work-up, this would ensure that all of the azide would be removed from the mixture prior to the start of the isocyanate formation. After some optimization, the two-step route provided the desired carbamate **3.74** in 76% yield, which was a large improvement over the previous yield of 32% (Scheme 3.3).[345] The chiral auxiliary was then cleaved to provide the β-amino ester **3.75** in 70% yield.

Scheme 3.3



Carbamate **3.75** was treated with HCl in dioxanes to provide HCl salt **3.76** in quantitative yield, and then **3.76** underwent a peptide coupling with protected glutamic acid NHBoc-E(OBn)-OH using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI), hydroxybenzotriazole (HOBt), and 4-methylmorpholine (NMM) to provide the pseudopeptide **3.77** in 60% yield (Scheme 3.4). After another deprotection/peptide coupling sequence, tripeptide **3.79** was obtained in 63% yield over two steps.

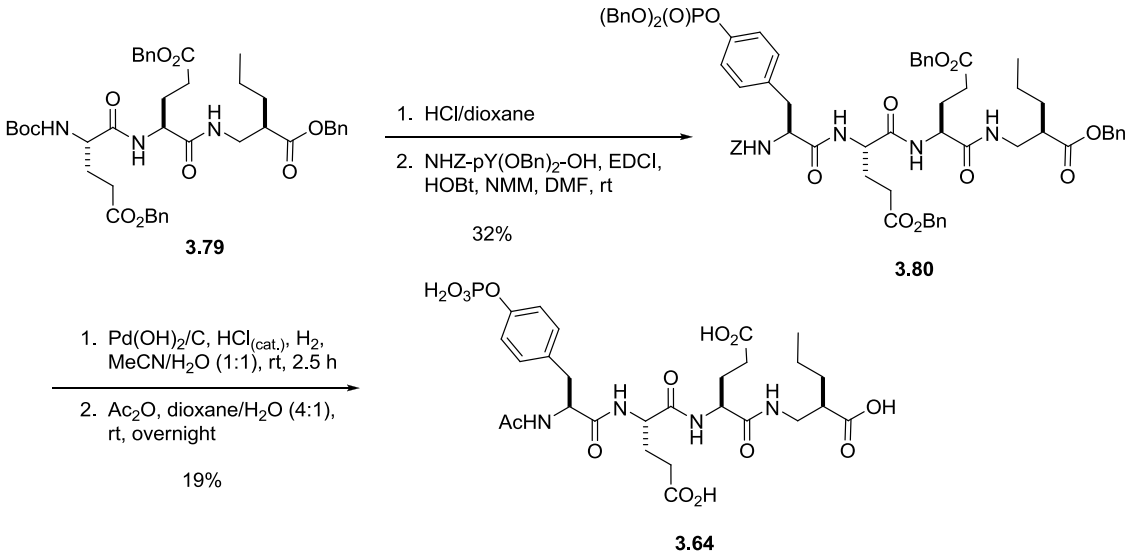
Scheme 3.4



3.75 **3.76** **3.77** **3.78** **3.79**

The amine of tripeptide **3.79** was unmasked and immediately subjected to reaction with protected phosphotyrosine NHZ-pY(OBn)$_2$-OH to provide tetrapeptide **3.80** in 32% yield over two steps (Scheme 3.5). Acid-catalyzed hydrogenation of **3.80** with Pearlman's catalyst (Pd(OH)$_2$/C) and hydrogen gas followed by treatment with acetic anhydride (Ac$_2$O) provided our desired flexible peptide mimic **3.64** in 19% yield over the final two steps.

Scheme 3.5

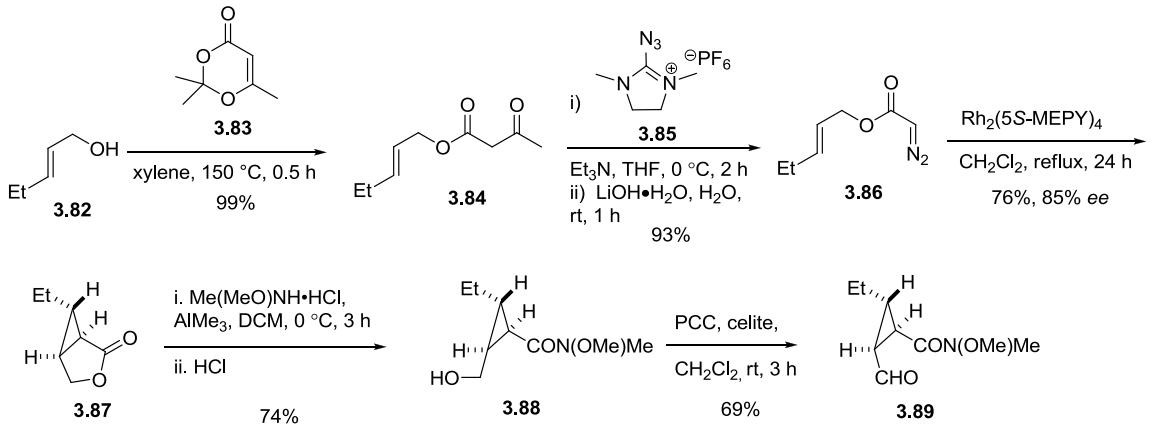


3.5.2 SYNTHESIS OF CONSTRAINED LIGAND 3.65

The flexible peptide mimic **3.64** was synthesized in order to act as a control molecule for ITC studies involving the constrained ligand **3.65** (*cf.* Figure 3.8). In order to obtain the *trans*- cyclopropyl peptide mimic **3.65**, we planned to follow a synthetic strategy similar to a route we used to obtain our matrix metalloprotease inhibitors (*cf.* compounds **3.23-3.26**, Section 3.3.2).[324] The route began with the formation of β-keto ester **3.84** from the reaction of alcohol **3.82** with dioxinone **3.83** in 99% yield (Scheme 3.6).[346,347] β-Keto ester **3.84** was then subjected to diazo transfer conditions using 2-azido-1,3-dimethylimidazolinium hexafluorophosphate (ADMP) (**3.85**),[348] followed by a lithium hydroxide-mediated hydrolysis to provide the diazo compound **3.86** in 93% yield over two steps.[319,349] An asymmetric rhodium catalyzed cyclopropanation was next carried out on **3.86** to provide cyclopropane **3.87** in modest yield (76%) and e.r. (85:15).[314,315,317-319,323,349,350] An undergraduate student in our lab, Joseph Lee, carried out

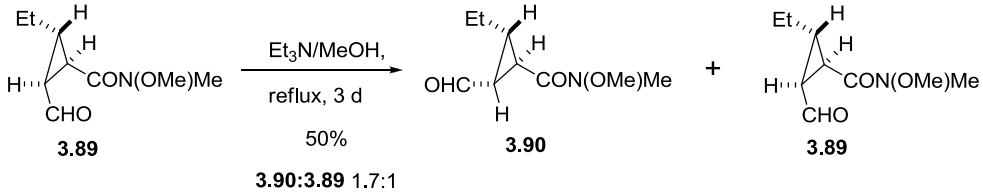
the racemic cyclopropanation of **3.86** with $Cu(TBS)_2$ in 6% overall yield, which enabled the determination of the enantiomeric ratio by HPLC.[319,349,351] Lactone **3.87** was opened with an aluminum-amine salt[322] to provide the Weinreb amide **3.88** in 74% yield, and the alcohol was oxidized to aldehyde **3.89** with PCC in 69% yield.

Scheme 3.6



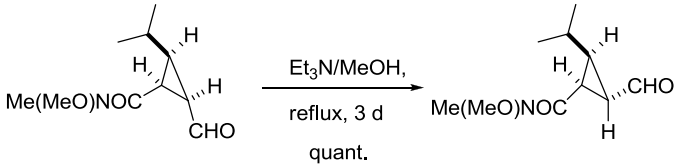
We then attempted to epimerize *cis*-aldehyde **3.89** to *trans*-aldehyde **3.90** by heating a solution of **3.89** in MeOH with triethylamine over reflux for three days, following previous precedent from our work with MMP inhibitors (Schemes 3.7 and 3.8).[324] However, we were disappointed to find that we could not achieve favorable conversion of **3.89** to **3.90**. The reaction proceeded in 50% yield and only slightly favored the desired *trans*-cyclopropane epimer.

Scheme 3.7



When we compared our system to those of our MMP inhibitors, we noticed a significant difference in the orientation of the cyclopropyl substituents.[324] In the MMP system, isopropyl substituent of **3.91** was positioned on the same face of the cyclopropane ring as the Weinreb amide and aldehyde functionalities (Scheme 3.8). Upon exposure to epimerization conditions, the aldehyde moiety of **3.91** adopted an orientation on the opposite side of the isopropyl substituent. Presumably alleviation of the steric congestion of **3.91** provided the driving force for the quantitative conversion of **3.91** to *trans*-cyclopropane **3.92**. This driving force was not present in our Src SH2 system as the ethyl cyclopropane substituent of **3.89** was already on the opposite side of both the Weinreb amide and aldehyde moieties (*cf.* Scheme 3.7). Epimerization of the ethyl substituent of **3.89** would provide steric hindrance as opposed to alleviating it and we speculated that the poor epimerization results of **3.89** to **3.90** were due to this phenomenon.

Scheme 3.8

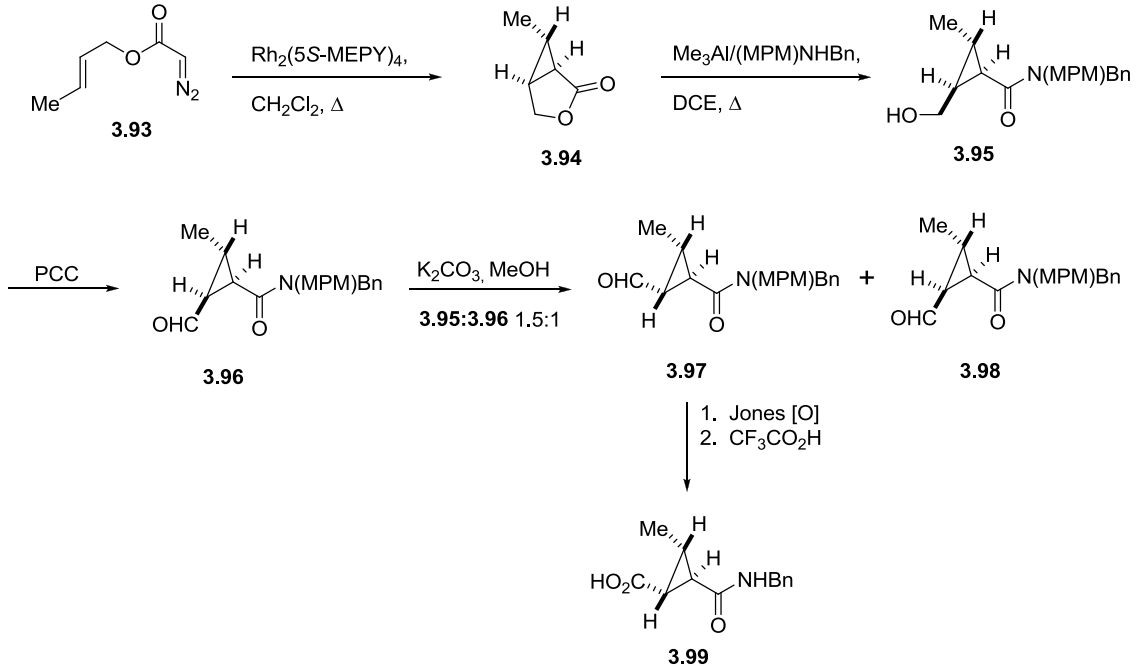


3.91 **3.92**

We had run into a similar aldehyde epimerization problem before while working with our HIV-1 protease system (*cf.* Section 3.3.5).[320] Using the same method as we used to synthesize **3.89**, we had obtained the very similar *cis*-cyclopropane **3.97** from diazoester **3.93** (Scheme 3.9). Cyclopropane **3.97** differed from **3.89** through a different amide protecting group and a methyl, as opposed to ethyl, substituent on the cyclopropane ring. When we attempted to epimerize the aldehyde functionality of **3.97**

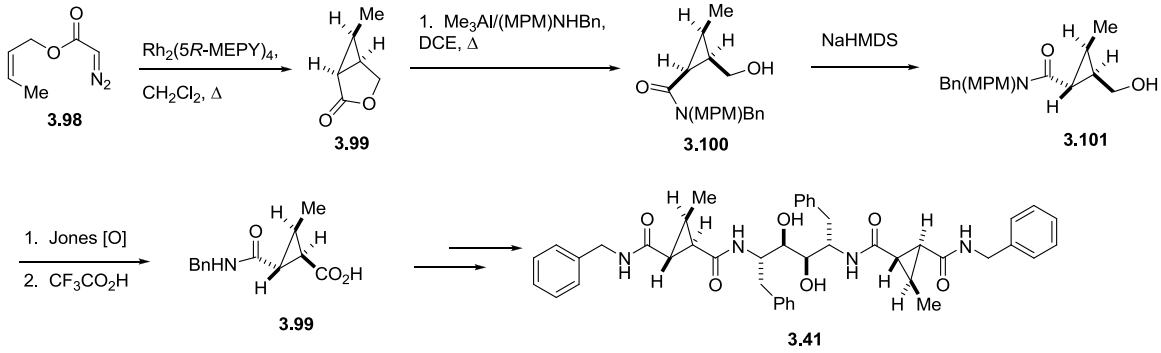
we had observed the poor conversion **3.98**, presumably due to the same steric issues as our Src SH2 system.

Scheme 3.9



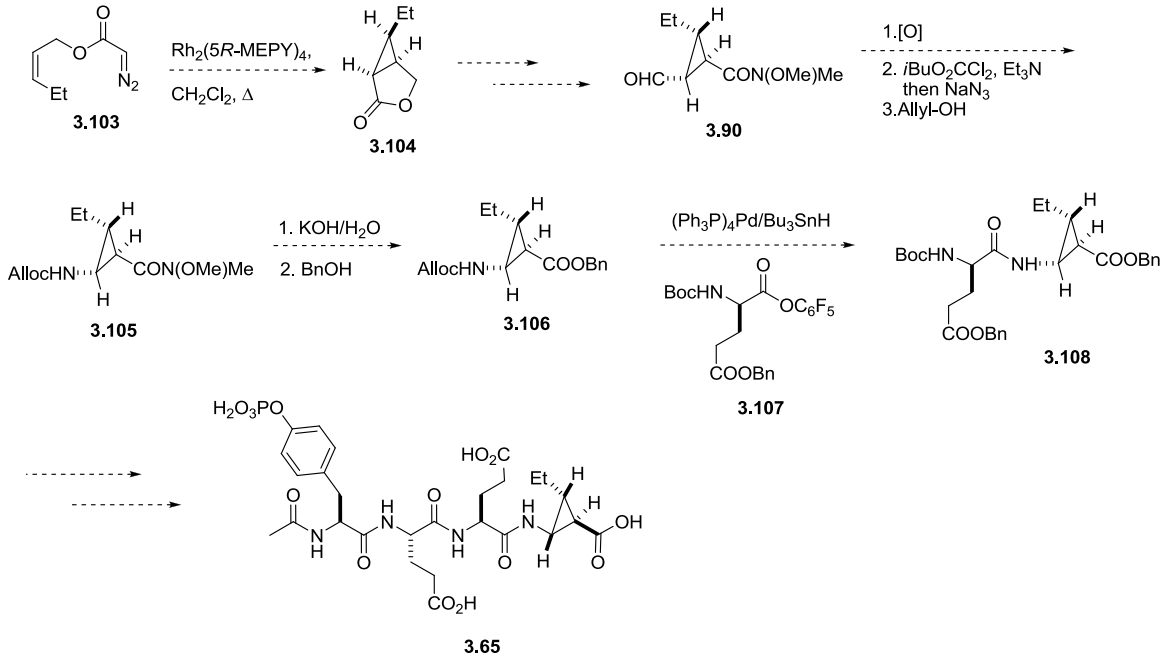
We were eventually able to overcome the problem by redesigning the route in order to avoid the troublesome aldehyde epimerization step. Starting from the opposite diastereomer of **3.93**, diazoester **3.98** underwent rhodium catalyzed cyclopropanation to provide lactone **3.99** (Scheme 3.10). The lactone was opened using the same aluminum-amine complex to provide the alcohol **3.100**. However, instead of oxidation of the alcohol and epimerization of the resulting aldehyde, the amide of **3.100** was epimerized using sodium hexamethyldisilazane (NaHMDS) to provide *trans*-cyclopropane **3.101**. Oxidation of **3.101** followed by treatment with acid provided cyclopropane **3.99**, which contained the requisite stereochemistry and functionality for the successful elaboration to the final ligand **3.41**.

Scheme 3.10



Future work towards the constrained peptide mimic **3.65** will focus on utilizing the method from our work with HIV-1 protease inhibitors (Scheme 3.11). Starting from diazoester **3.103**, we will follow the route described in Scheme 3.9 to obtain the desired *trans*-cyclopropane ring **3.90**. Once we are able to obtain cyclopropane **3.90**, we envision exposing it to the same Curtius rearrangement conditions we developed from the synthesis of flexible control **3.64** (*cf.* Scheme 3.3) to provide the alloc-protected **3.105**. Hydrolysis of the Weinreb amide and protection of the resulting ester with benzyl alcohol would provide amide **3.106**. A mild palladium (0) catalyzed coupling between alloc-amide **3.106** and pentafluorophenyl ester **3.107** would provide the pseudo di-peptide **3.108**, which could be further elaborated to the desired constrained ligand **3.65** using the same standard peptide coupling conditions we had used to obtain **3.65**

Scheme 3.11

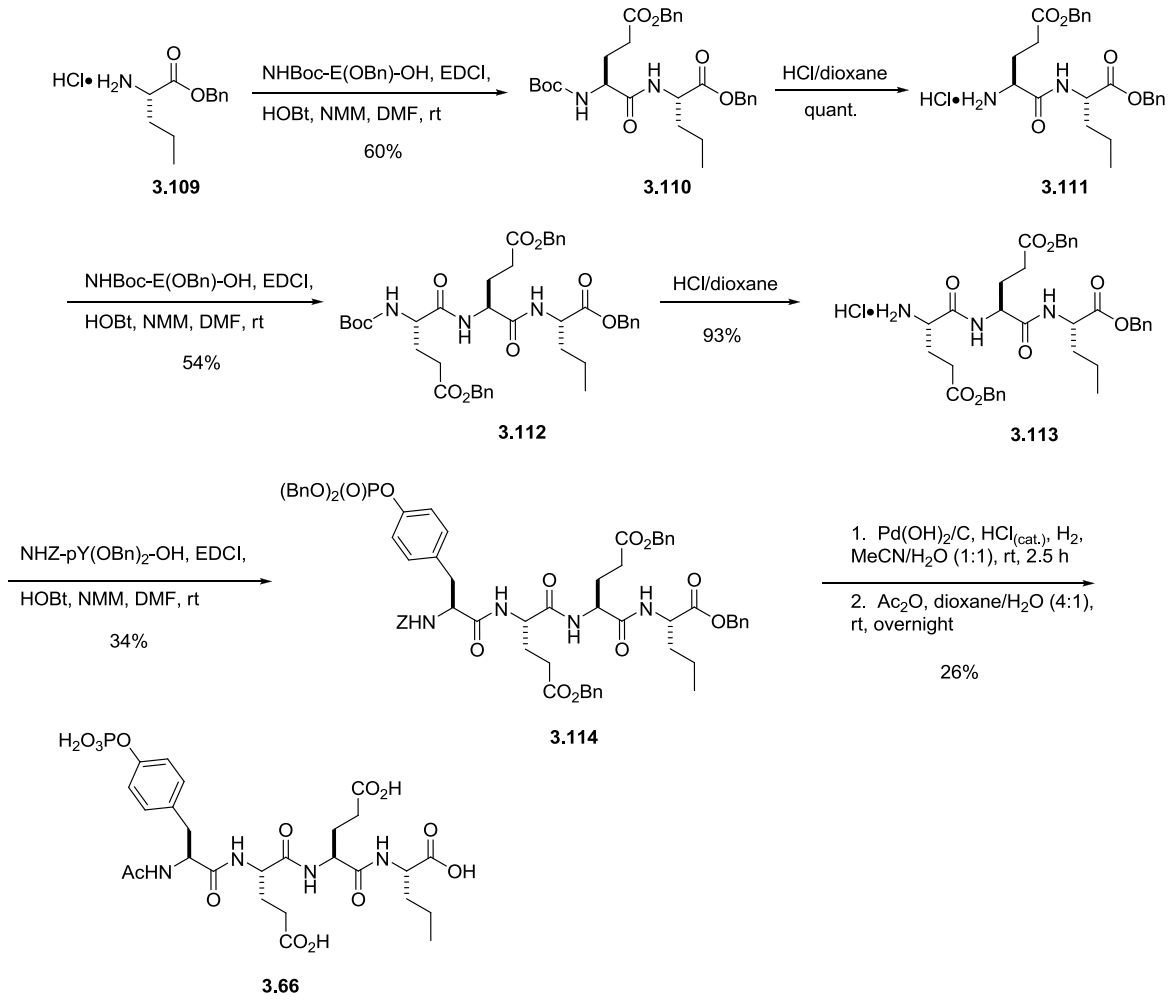


3.5.3 SYNTHESIS OF FLEXIBLE CONTROL LIGAND 3.66

Synthesis of the flexible ligand **3.66** was fairly straightforward and was comprised of a series of standard peptide coupling steps (Scheme 3.12). The commercially available HCl salt of norvaline was coupled with protected glutamic acid NHBoc-E(OBn)-OH using EDCI, HOBt, and NMM to provide the pseudopeptide **3.77** in 60% yield (Scheme 3.12). A standard deprotection/peptide coupling/deprotection sequence then provided **3.113** in 50% yield over three steps. The amine salt of tripeptide **3.113** was unmasked and immediately subjected to reaction with protected phosphotyrosine NHZ-pY$(OBn)_2$-OH to provide tetrapeptide **3.114** in 34% yield over two steps. Acid catalyzed hydrogenation with Pearlman's catalyst ($Pd(OH)_2/C$) and hydrogen gas followed by

treatment with acetic anhydride (Ac_2O) provided our desired flexible peptide mimic **3.66** in 26% yield over the final two steps.

Scheme 3.12

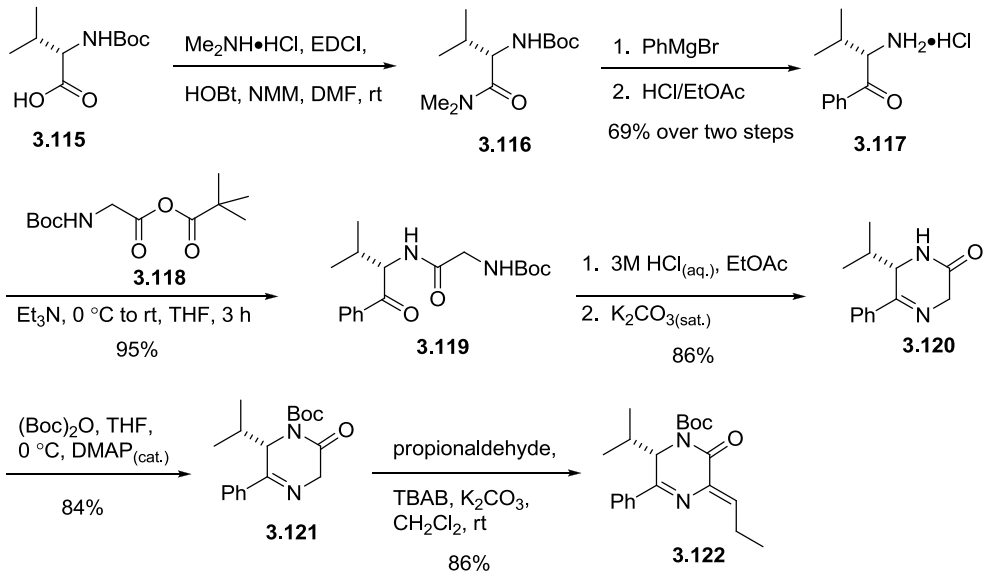


3.5.4 SYNTHESIS OF CONSTRAINED LIGAND 3.67

The flexible peptide mimic **3.66** was synthesized in order to act as a control molecule for ITC studies involving the constrained ligand **3.67** (*cf.* Figure 3.8).

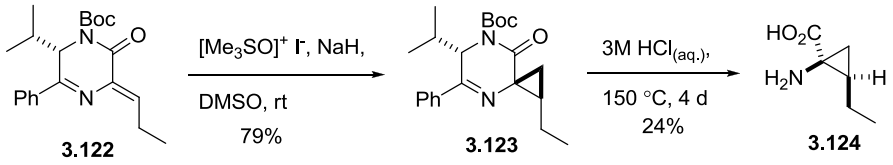
Fortunately a route was reported by Najera and coworkers towards our desired cyclopropyl restraint **3.124** (Schemes 3.13 and 3.14).[352,353] Boc-valine **3.115** was coupled with the hydrochloride salt of dimethylamine to provide amide **3.116**, which was immediately treated with phenyl magnesium bromide (PhMgBr) and acid to provide phenyl ketone **3.117** in 69% yield over two steps. Hydrochloride salt **3.117** was coupled with mixed anhydride **3.118** in the presence of triethylamine to provide **3.119** in 95% yield. Upon treatment with aqueous HCl in EtOAc and saturated potassium carbonate, pyrazinone **3.120** was formed in 86% yield. Protection of the amide, followed by Knoevenagel condensation with propionaldehyde provided unsaturated pyrazinone **3.122** in 72% yield over two steps.

Scheme 3.13



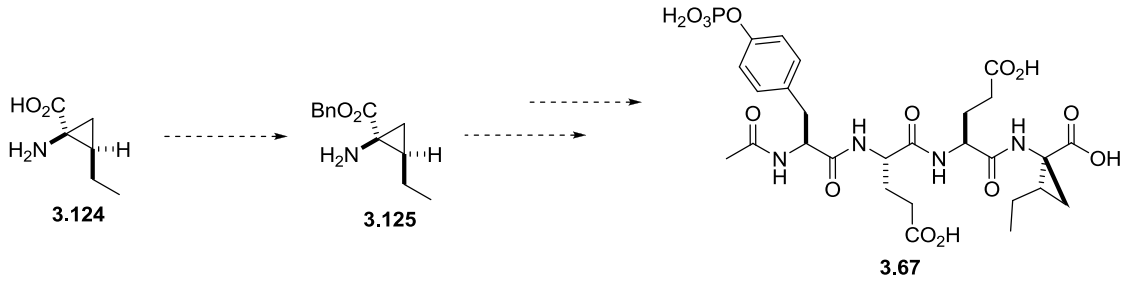
Pyrazinone **3.122** then underwent a diastereoselective Corey-Chaykovsky cyclopropanation to provide **3.123** in 79% yield, which was then heated under reflux in the presence of 3 M aqueous hydrochloric acid to provide cyclopropane **3.124** in 24% yield (Scheme 3.14).

Scheme 3.14



We have successfully reproduced Najera's procedure to obtain cyclopropane **3.124**, and attempts are ongoing to elaborate **3.124** to the desired constrained mimic **3.67.** We envisioned benzyl protection of **3.124** using Dean-Stark conditions would provide **3.125**, which could then be elaborated to **3.67** using the standard peptide coupling conditions used to synthesize **3.64** and **3.66**.

Scheme 3.15

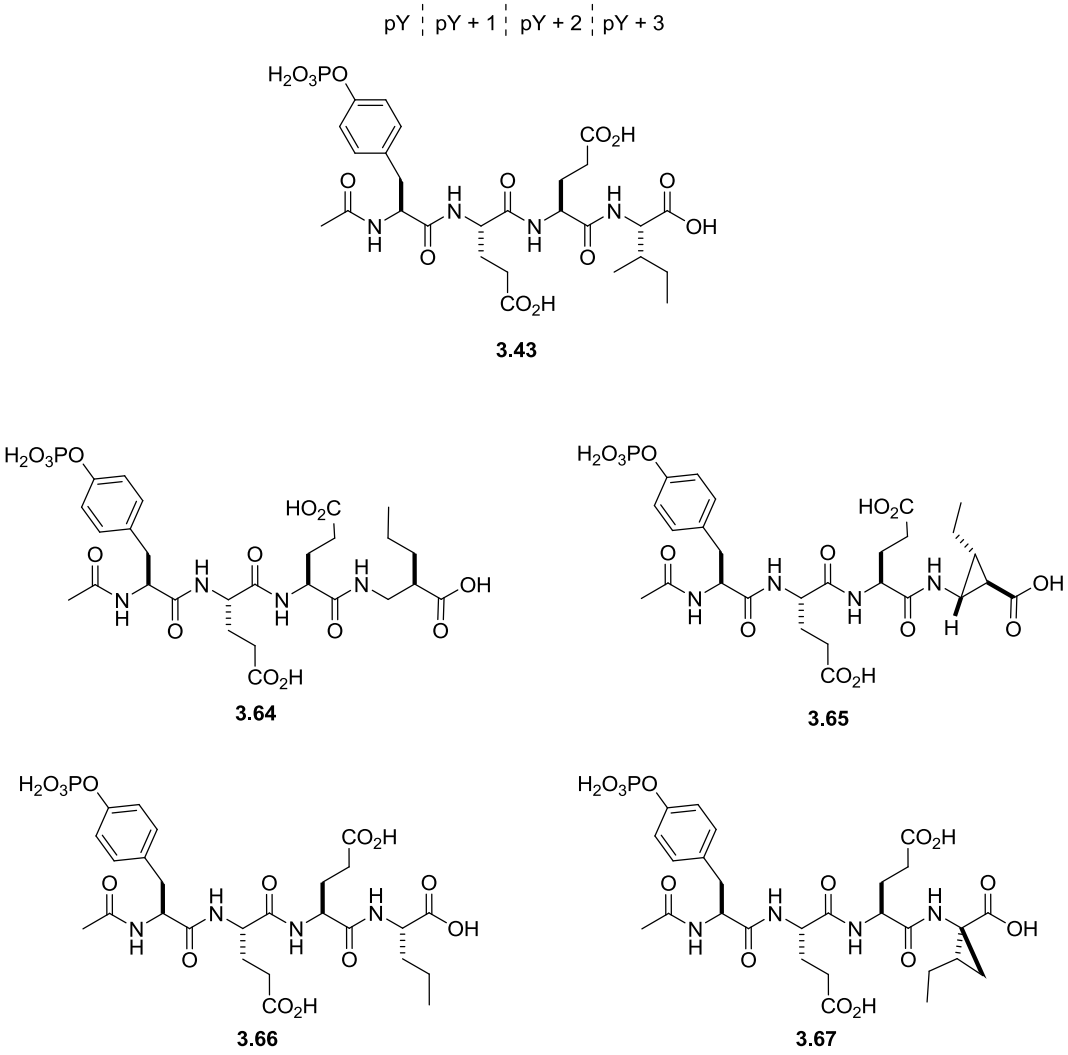


3.6 Summary and Future Directions

In conclusion, we designed routes toward four pY+3 peptide mimics for the Src SH2 domain (Figure 3.8). We successfully synthesized both flexible mimics **3.64** and

3.66, which included the optimization of a troublesome Curtius rearrangement. We also made significant progress towards the constrained mimics **3.65** and **3.67**. Approximately halfway through the synthesis of **3.65**, we discovered a troubling epimerization reaction. However, we believe that redesigning our route using other existing Martin group methodology will enable us to overcome the problem and complete the synthesis of **3.65**. We also obtained a significant quantity (ca. 200 mg) of cyclopropane **3.124**, that when subjected to a Dean-Stark benzyl ester protection, will be a short sequence of peptide couplings away from the desired ligand **3.67**.

Figure 3.8: pY+3 Peptide mimics for Src SH2.



Once we have obtained all of our desired ligands, namely **3.64-3.67**, we can test the hypothesis we developed based on our collaboration with Dr. Carol Post. CSD data showed us a potentially important interaction between the Src SH2 protein pocket and the pY + 3 sidechain (Ile) of the native peptide **3.43**,[336] and based on this information, we

formulated a hypothesis that we may be able to introduce a cyclopropyl conformation constraint in the pY + 3 residue, which resided outside of the hot spot region. Hopefully we will be able to gain the same entropic benefit from ligand preorganization that we saw before without incurring an offsetting enthalpic penalty. We had already found that even the smallest, almost invisible, of changes in orientation between the hot spot of the peptide and the binding pocket can cause drastic changes in the enthalpy of the binding event, but we didn't know anything about how a conformational constraint would behave in a non hotspot region. Perhaps this technology would emerge as a useful tool towards rational ligand design. We look forward to obtaining preliminary ITC thermodynamic data.

Chapter 4: Experimental Procedures

4.1 General methods

Methanol (MeOH), acetonitrile (CH_3CN), and *N*,*N*-dimethylformamide (DMF) were dried by filtration through two columns of activated molecular sieves. Tetrahydrofuran (THF) was passed through two columns of activated neutral alumina prior to use and toluene was passed through a column of activated neutral alumina as well as further deoxygenated by being passed through a column of activated Q5. Diisopropylamine, triethylamine (Et_3N), ethanol (EtOH), pyridine (Pyr), dichloromethane (DCM), chlorotrimethylsilane (TMSCl), methylchloroformate, and hexamethylphosphoramide (HMPA) were distilled from CaH_2 prior to use. TMSOTf was distilled over CaH_2 and phenyl isocyanate was distilled over P_2O_5 before use. Samarium powder (40 mesh, 99% trace metals basis) was purchased from Acros and crushed with a mortar and pestle under nitrogen prior to use. All hydrogenations were performed as follows: the round-bottom flask containing the reaction mixture was evacuated under high vacuum and backfilled with N_2 (x 3) to remove any oxygen present. The round-bottom flask was evacuated under high vacuum a fourth time, and then placed under 1 atm of H_2 (2 "double bagged" 9 inch latex helium grade balloons) at room temperature. All other reagents were purchased and used as received. Glassware used in the reactions was dried overnight in an oven at 120 °C or flame-dried under a high pressure vacuum. All reactions were performed under an atmosphere of argon or nitrogen. All reaction temperatures reported are those of the oil bath surrounding the reaction vessel. Reverse phase HPLC was conducted using a binary solvent system, where solvent system A was 0.1% aqueous TFA and solvent system B was 0.1% TFA in acetonitrile, with a C18

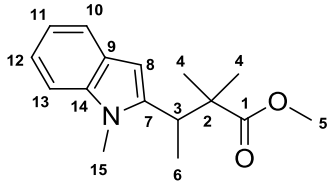
column (10 mm particle size, 300 Å pore size), 22 mm diameter x 250 mm (flow rate of 5 mL/min). Concentration *in vacuo* or concentration under reduced pressure was performed using a rotary evaporator with a bath temperature at 25-30 ºC. Lyophilization to provide the final ligands was performed using a three phase procedure: first the HPLC mixture was lyophilized, then the ligand was dissolved in H_2O and lyophilized, and finally the ligand was dissolved in a mixture of MeCN/H_2O (2:1) and lyophilized to provide the final product.

Melting points were determined using a Thomas-Hoover Uni-melt capillary melting point apparatus and are uncorrected. Infrared (IR) spectra were obtained with a Perkin-Elmer FTIR 1600 series spectrometer, on sodium chloride plates as solutions in the solvent indicated. Band positions are given in reciprocal centimeters (cm^{-1}). Proton nuclear magnetic resonance (^{1}H NMR) spectra were obtained on a 400 MHz spectrometer as solution in $CDCl_3$. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) and for $CDCl_3$ are referenced to an internal TMS standard (δ 0.00). Coupling constants (*J*) are reported in Hz and the splitting abbreviations used are: s, singlet; d, doublet; t, triplet; q, quartet; dt, doublet of triplets; ddd, doublet of doublets of doublets; dtd, doublet of triplets of doublets; dq, doublet of quartets; m, multiplet; comp, overlapping multiplets of magnetically non-equivalent protons; br, broad. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were obtained using the above-mentioned instrument operating at 100 MHz and chemical shifts are reported in ppm relative to the center line of the multiplet for deuterium solvent peaks (δ 77.0 for $CDCl_3$). Thin layer chromatography (TLC) was performed on glass-backed pre-coated silica gel plates (0.25 mm thick with 60 F_{254}) and were visualized using one or both of the

following manners: UV light (254 nm) and staining with either p-anisaldehyde (PAA), phosphomolybdic acid (PMA) or potassium permanganate ($KMnO_4$). Flash chromatography was performed using glass columns and "medium pressure" silica gel (Sorbent Technologies, 45-70 μ). Some of the previous work and characterization was first done by Dr. Jianhua Tian, and subsequently repeated by the author. This is indicated by compound names starting with JT.

4.2 EXPERIMENTALS

Representative procedure for the reaction of heterocyclic carbinols/acetates with π-nucleophiles

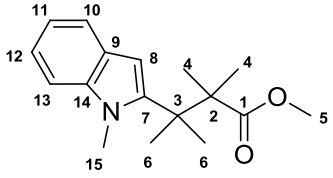


1.541

Methyl 2,2-dimethyl-3-(1-methyl-1H-indol-2-yl) butanoate (1.541). (ab02094). Freshly distilled TMSOTf (516 mg, 0.42 mL, 2.30 mmol) was added dropwise to a solution of (1-methoxy-2-methylprop-1-enyloxy)trimethylsilane (**1.540**)[114] (601 mg, 0.70 mL, 3.45 mmol) and 1-(1-methyl-1H-indol-2-yl)ethyl acetate (**1.538**) (500 mg, 2.30 mmol) in MeCN (3 mL) at -40 °C under argon. The solution was stirred at -40 °C for 1 h, whereupon saturated $NaHCO_3$ (20 mL) was added. The layers were separated, and the aqueous layer was extracted with Et_2O (2 x 15 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with Et_2O/pentane (1:4) to give 525 mg (88 %) of ester **1.541** as a white solid (mp = 95 - 97 °C). ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.2 Hz, 1 H), 7.29 (d, *J* = 7.2 Hz, 1 H), 7.17 (t, *J* = 7.2 Hz, 1 H),

7.08 (t, *J* = 7.2 Hz, 1 H), 6.34 (s, 1 H), 3.75 (s, 3 H), 3.68 (s, 3 H), 3.52 (q, *J* = 7.2 Hz, 1 H), 1.28 (d, *J* = 7.2 Hz, 3 H), 1.25 (s, 3 H), 1.1 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.4, 142.5, 137.1, 127.9, 121.1, 120.2, 119.7, 109.4, 100.3, 52.2, 47.2, 37.3, 30.3, 24.6, 20.2, 18.0; IR (DCM) 1730, 1466, 1300, 1250, 1231, 1188, 1136, 776, 734 cm^{-1}; mass spectrum (CI) *m/z* 260.1653 [$C_{16}H_{22}NO_2$ (M+1) requires 260.1651], 260 (base), 158.

NMR Assignments: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.2 Hz, 1 H, C10-H), 7.29 (d, *J* = 7.2 Hz, 1 H, C13-H), 7.17 (t, *J* = 7.2 Hz, 1 H, C12-H), 7.08 (t, *J* = 7.2 Hz, 1 H, C11-H), 6.34 (s, 1 H, C8-H), 3.75 (s, 3 H, C15-H), 3.68 (s, 3 H, C5-H), 3.52 (q, *J* = 7.2 Hz, 1 H, C3-H), 1.28 (d, J = 7.2 Hz, 3 H, C6-H), 1.25 (s, 3 H, C4-H), 1.1 (s, 3 H, C4-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.4 (C 1), 142.5 (C 7), 137.1 (C 14), 127.9 (C 9), 121.1 (C 10 or C 12), 120.2 (C 10 or C 12), 119.7 (C 11), 109.4 (C 13), 100.3 (C 8), 52.2 (C 5), 47.2 (C 15), 37.3 (C 2), 30.3 (C 3), 24.6 (C 4 or C 6), 20.2 (C 4 or C 6), 18.0 (C 4 or C 6).

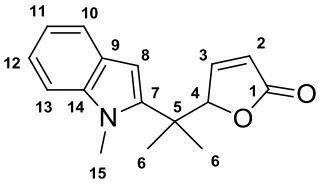


1.574

Methyl 2,2,3-trimethyl-3-(1-methyl-1H-indol-2-yl)butanoate (1.574). (ab02055). The residue was purified by flash chromatography eluting with Et_2O: pentane (1:4) to give 93% of ester **1.574** as a white solid (mp = 79 - 81 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.8 Hz, 1 H), 7.25 (d, *J* = 7.8 Hz, 1 H), 7.18 (t, *J* = 7.8 Hz, 1 H), 7.08 (t, *J* = 7.8 Hz, 1 H), 6.43 (s, 1 H), 3.84 (s, 3 H) 3.59 (s, 3 H), 1.58 (s, 6 H), 1.21 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2, 144.6, 138.2, 126.8, 121.1, 119.9,

119.4, 109.1, 103.6, 51.6, 49.7, 42.3, 33.5, 26.7, 22.5; IR (DCM) 1720, 1468, 1270, 1130 cm^{-1}; mass spectrum (CI) *m/z* 274.1807 [$C_{17}H_{24}NO_2$ (M+1) requires 274.1807], 274 (base), 172.

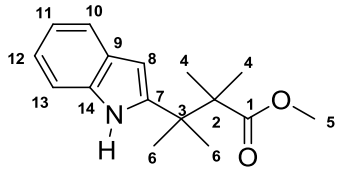
NMR Assignments: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.8 Hz, 1 H, C10-H), 7.25 (d, *J* = 7.8 Hz, 1 H, C13-H), 7.18 (t, *J* = 7.8 Hz, 1 H, C12-H), 7.08 (t, *J* = 7.8 Hz, 1 H, C11-H), 6.43 (s, 1 H, C8-H), 3.84 (s, 3 H, C15-H) 3.59 (s, 3 H C5-H), 1.58 (s, 6 H, C6-H), 1.21 (s, 6 H, C4-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2 (C 1), 144.6 (C 7), 138.2 (C 14), 126.8 (C 9), 121.1 (C 12), 119.9 (C 10), 119.4 (C 11), 109.1 (C 13), 103.6 (C 8), 51.6 (C 2), 49.7 (C 5), 42.3 (C 15), 33.5 (C 3), 26.7 (C 6), 22.5 (C 4).



1.576

5-(2-(1-Methyl-1H-indol-2-yl)propan-2-yl)furan-2(5H)-one (1.576). (ab02086). The residue was purified by flash chromatography eluting with Et_2O to give 88% of ester **1.576** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.6 Hz, 1 H), 7.31 (d, *J* = 7.6 Hz, 1 H), 7.25-7.21 (comp, 2 H), 7.11 (t, *J* = 7.6 Hz, 1 H), 6.38 (s, 1 H), 6.10 (dd, *J* = 5.8, 2.2Hz, 1 H), 5.40 (t, *J* = 1.8 Hz, 1H), 3.94 (s, 3 H), 1.66 (s, 3 H), 1.43 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 154.5, 142.8, 138.9, 126.9, 122.7, 121.9, 120.4, 119.9, 109.1, 101.0, 87.9, 39.7, 33.0, 25.6, 22.5; IR (DCM) 1755, 1469, 1316, 1162, 1094, 735 cm^{-1}; mass spectrum (ESI) *m/z* 256.13321 [$C_{16}H_{18}NO_2$ (M+1) requires 256.1332], 256 (base), 173, 172, 158.

NMR Assignments: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.6 Hz, 1 H, C10-H), 7.31 (d, *J* = 7.6 Hz, 1 H, C13-H), 7.25-7.21 (comp, 2 H, C12-H and C 3-H), 7.11 (t, *J* = 7.6 Hz, 1 H, C11-H), 6.38 (s, 1 H, C8-H), 6.10 (dd, *J* = 5.8, 2.2 Hz, 1 H, C2-H), 5.40 (t, *J* = 1.8 Hz, 1H, C4-H), 3.94 (s, 3 H, C15-H), 1.66 (s, 3 H, C6-H), 1.43 (s, 3 H, C6-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9 (C 1), 154.5 (C 3), 142.8 (C 7), 138.9 (C 14), 126.9 (C 9), 122.7 (C 2), 121.9 (C 12), 120.4 (C 10), 119.9 (C 11), 109.1 (C 13), 101.0 (C 8), 87.9 (C 4), 39.7 (C 15), 33.0 (C 5), 25.6 (C 6), 22.5 (C 6).

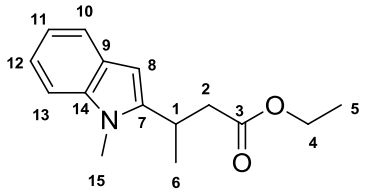


1.575

Methyl 3-(1H-indol-2-yl)-2,2,3-trimethylbutanoate (1.575). (ab02090). The residue was purified by flash chromatography eluting with Et_2O: pentane (1:2) to give 77% of ester **1.575** as a brown solid (mp = 99 - 102 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (br, 1 H), 7.55 (d, *J* = 8.0 Hz, 1 H), 7.33 (d, *J* = 8.0 Hz, 1 H), 7.13 (t, *J* = 8.0 Hz, 1 H), 7.06 (t, *J* = 8.0 Hz, 1 H), 6.33 (s, 1 H), 3.61 (s, 3 H), 1.46 (s, 6 H), 1.18 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ178.6, 144.7, 135.9, 128.1, 121.5, 120.2, 119.7, 110.8, 101.0, 52.0, 49.1, 40.6, 24.7, 22.5; IR (DCM) 1707, 1459, 1275, 1132 cm^{-1}; mass spectrum (CI) *m/z* 260.1654 [$C_{16}H_{22}NO_2$ (M+1) requires 260.1651], 260 (base), 158.

NMR Assignments: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (br, 1 H, N-H), 7.55 (d, *J* = 8.0 Hz, 1 H, C10-H), 7.33 (d, *J* = 8.0 Hz, 1 H, C13-H), 7.13 (t, *J* = 8.0 Hz, 1 H, C12-H), 7.06 (t, *J* = 8.0 Hz, 1 H, C11-H), 6.33 (s, 1 H, C8-H), 3.61 (s, 3 H, C5-H), 1.46 (s, 6

H, C6-H), 1.18 (s, 6 H, C4-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ178.6 (C 1), 144.7 (C 7), 135.9 (C 14), 128.1 (C 9), 121.5 (C 12), 120.2 (C 10), 119.7 (C 11), 110.8 (C 13), 101.0 (C 8), 52.0 (C 2), 49.1 (C 5), 40.6 (C 3), 24.7 (C 6), 22.5 (C 4).

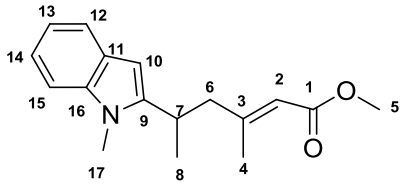


1.558

Ethyl 3-(1-methyl-1H-indol-2-yl)butanoate (1.558). (ab02073). The residue was purified by flash chromatography eluting with Et_2O: pentane (1:4) to give 68% of ester **1.558** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.6 Hz, 1 H), 7.28 (d, *J* = 7.6 Hz, 1 H), 7.17 (t, *J* = 7.6 Hz, 1 H), 7.07 (t, *J* = 7.6 Hz, 1 H), 6.27 (s, 1 H), 4.13 (q, *J* = 7.2 Hz, 2 H), 3.73 (s, 3 H), 3.51 (sextet, *J* = 6.7 Hz, 1 H), 2.79 (dd, *J* = 16.0, 6.7 Hz, 1 H), 2.58 (dd, *J* = 16.0, 6.7 Hz, 1 H), 1.36 (d, *J* = 6.7 Hz, 3 H), 1.23 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 144.8, 137.3, 127.7, 120.9, 120.0, 119.4, 108.9, 97.0, 60.5, 41.5, 29.5, 28.0, 20.9, 14.2; IR (DCM) 1733, 1468, 1184, 1036, 749 cm^{-1}; mass spectrum (ESI) *m/z* 246.14886 [$C_{15}H_{20}NO_2$ (M+1) requires 246.1487], 246, 158 (base), 143.

NMR Assignments: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.6 Hz, 1 H, C10-H), 7.28 (d, *J* = 7.6 Hz, 1 H, C13-H), 7.17 (t, *J* = 7.6 Hz, 1 H, C12-H), 7.07 (t, *J* = 7.6 Hz, 1 H, C11-H), 6.27 (s, 1 H, C8-H), 4.13 (q, *J* = 7.2 Hz, 2 H, C4-H), 3.73 (s, 3 H, C15-H), 3.51 (sextet, *J* = 6.7 Hz, 1 H, C1-H), 2.79 (dd, *J* = 16.0, 6.7 Hz, 1 H, C2-H), 2.58 (dd, *J* = 16.0, 6.7 Hz, 1 H, C2-H), 1.36 (d, *J* = 6.7 Hz, 3 H, C6-H), 1.23 (t, *J* = 7.2

Hz, 3 H, C5-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1 (C 3), 144.8 (C 7), 137.3 (C 14), 127.7 (C 9), 120.9 (C 12), 120.0 (C 10), 119.4 (C 11), 108.9 (C 13), 97.0 (C 8), 60.5 (C 4), 41.5 (C 2), 29.5 (C 15), 28.0 (C 1), 20.9 (C 6), 14.2 (C-5).

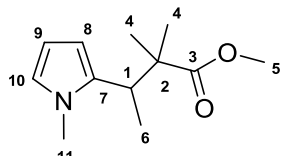


1.559

(*E*)-Methyl 3-methyl-5-(1-methyl-1H-indol-2-yl)hex-2-enoate (1.559). (ab02067). The residue was purified by flash chromatography eluting with Et_2O: pentane (1:4) to give 47% of ester **1.559** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.8 Hz, 1 H), 7.28 (d, *J* = 7.8 Hz, 1 H), 7.17 (t, *J* = 7.8 Hz, 1 H), 7.07 (t, *J* = 7.8 Hz, 1 H), 6.29 (s, 1 H), 5.75 (s, 1 H), 3.72 (s, 3 H), 3.69 (s, 3 H), 3.21 (sextet, *J* = 6.6 Hz, 1 H), 2.65 (dd, *J* = 13.5, 6.6 Hz, 1 H), 2.35 (dd, *J* = 13.5, 6.6 Hz), 2.20 (s, 3 H), 1.30 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ166.9, 157.3, 145.2, 137.3, 127.8, 120.9, 120.0, 119.4, 117.4, 108.9, 97.3, 50.9, 48.2, 29.5, 29.1, 20.2, 18.8; IR (DCM) 1717, 1647, 1467, 1227, 1152, 748 cm^{-1}; mass spectrum (ESI) *m/z* 272.16451 [$C_{17}H_{22}NO_2$ (M+1) requires 272.1650], 272 (base).

NMR Assignments: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.8 Hz, 1 H, C12-H), 7.28 (d, *J* = 7.8 Hz, 1 H, C15-H), 7.17 (t, *J* = 7.8 Hz, 1 H, C14-H), 7.07 (t, *J* = 7.8 Hz, 1 H, C13-H), 6.29 (s, 1 H, C10-H), 5.75 (s, 1 H, C2-H), 3.72 (s, 3 H, C17-H), 3.69 (s, 3 H, C5-H), 3.21 (sextet, *J* = 6.6 Hz, 1 H, C7-H), 2.65 (dd, *J* = 13.5, 6.6 Hz, 1 H, C6-H), 2.35 (dd, *J* = 13.5, 6.6 Hz, C6-H), 2.20 (s, 3 H, C4-H), 1.30 (d, *J* = 6.6 Hz, 3 H,

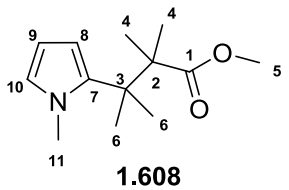
C8-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ166.9 (C 1), 157.3 (C 3), 145.2 (C 9), 137.3 (C 16), 127.8 (C 11), 120.9 (C 14), 120.0 (C 12), 119.4 (C 13), 117.4 (C 2), 108.9 (C 15), 97.3 (C 10), 50.9 (C 5), 48.2 (C 6), 29.5 (C 17), 29.1 (C 7), 20.2 (C 8), 18.8 (C 4).



1.609

Methyl 2,2-dimethyl-3-(1-methyl-1H-pyrrol-2-yl)butanoate (1.609). (ab02058). The residue was purified by flash chromatography eluting with Et_2O: pentane (1:9) to give 49% of ester **1.609** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.51 (t, *J* = 3.2 Hz, 1 H), 6.08 (t, *J* = 3.2 Hz, 1 H), 5.95 (d, *J* = 3.2 Hz, 1 H), 3.67 (s, 3 H), 3.60 (s, 3 H), 3.30 (q, *J* = 7.2 Hz, 1 H), 1.18 (s, 3 H), 1.16 (d, *J* = 7.2 Hz, 3 H), 1.04 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.4, 134.3, 121.1, 106.6, 51.8, 47.2, 37.0, 34.2, 24.4, 19.8, 17.8; IR (DCM) 1729, 1259, 1145, 1123, 706 cm^{-1}; mass spectrum (CI) *m/z* 210.1496 [$C_{12}H_{20}NO_2$ (M+1) requires 210.1494], 210 (base), 108.

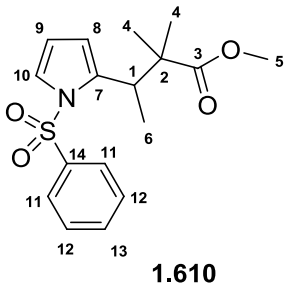
NMR Assignments: ^{1}H NMR (400 MHz, $CDCl_3$) δ6.51 (t, *J* = 3.2 Hz, 1 H, C10-H), 6.08 (t, *J* = 3.2 Hz, 1 H, C9-H), 5.95 (d, *J* = 3.2 Hz, 1 H, C8-H), 3.67 (s, 3 H, C11-H), 3.60 (s, 3 H, C5-H), 3.30 (q, *J* = 7.2 Hz, 1 H, C1-H), 1.18 (s, 3 H, C4-H), 1.16 (d, *J* = 7.2 Hz, 3 H, C6-H), 1.04 (s, 3 H, C4-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.4 (C 3), 134.3 (C 7), 121.1 (C 10), 106.6 (C 8 and C 9), 51.8 (C 5), 47.2 (C 2), 37.0 (C 1), 34.2 (C 11), 24.4 (C 4), 19.8 (C 4), 17.8 (C 6).



1.608

Methyl 2,2,3-trimethyl-3-(1-methyl-1H-pyrrol-2-yl)butanoate (1.608). (ab02065). The residue was purified by flash chromatography eluting with Et_2O: pentane (1:4) to give 88% of ester **1.608** as a white solid (mp = 52 - 55 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.43-6.42 (comp, 1 H), 6.04-6.01 (comp, 2 H), 3.71 (s, 3 H), 3.61 (s, 3 H), 1.46 (s, 6 H), 1.15 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.5, 136.4, 124.3, 110.4, 105.6, 51.5, 50.1, 41.7, 38.4, 26.3, 22.4; IR (DCM) 1719, 1298, 1268, 1134, 1093 cm^{-1}; mass spectrum (CI) *m/z* 224.16451 [$C_{13}H_{22}NO_2$ (M+1) requires 224.1649], 224 (base).

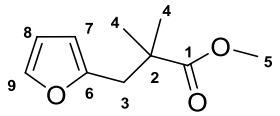
NMR Assignments: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.43 (comp, 1 H, C10-H), 6.03 (comp, 2 H, C8-H and C9-H), 3.71 (s, 3 H, C11-H), 3.61 (s, 3 H, C5-H), 1.46 (s, 6 H, C6-H), 1.15 (s, 6 H, C4-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.5 (C 1), 136.4 (C 7), 124.3 (C 10), 110.4 (C 9), 105.6 (C 8), 51.5 (C 2), 50.1 (C 5), 41.7 (C 11), 38.4 (C 3), 26.3 (C 6), 22.4 (C 4).



1.610

Methyl 2,2-dimethyl-3-(1-(phenylsulfonyl)-1H-pyrrol-2-yl)butanoate (1.610). (ab02075). The residue was purified by flash chromatography eluting with Et_2O: pentane (1:2) to give 42% of ester **1.610** as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.6 Hz, 2 H), 7.59 (t, *J* = 7.6 Hz, 1 H), 7.50 (t, *J* = 7.6 Hz, 2 H), 7.33 (dd, *J* = 3.6, 1.6 Hz, 1 H), 6.25 (t, *J* = 3.6 Hz, 1 H), 6.08 (dd, *J* = 3.6, 1.6 Hz, 1 H), 3.86 (q, 7.0 Hz, 1 H), 3.66 (s, 3 H), 1.11 (s, 3 H), 1.05 (s, 3 H), 0.83 (d, *J* = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 134.3, 132.2, 128.4, 124.0, 121.3, 117.4, 107.9, 106.5, 46.5, 41.5, 31.6, 19.8, 14.8, 12.6; IR (DCM) 1727, 1365, 1267, 1177, 1151, 729 cm^{-1}; mass spectrum (CI) *m/z* 336.1270 [$C_{17}H_{22}NO_4S$ (M+1) requires 336.1270], 336, 304, 234, 173 (base), 157, 113.

NMR Assignments: ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.6 Hz, 2 H, C11-H), 7.59 (t, *J* = 7.6 Hz, 1 H, C13-H), 7.50 (t, *J* = 7.6 Hz, 2 H, C12-H), 7.33 (dd, *J* = 3.6, 1.6 Hz, 1 H, C10-H), 6.25 (t, *J* = 3.6 Hz, 1 H, C9-H), 6.08 (dd, *J* = 3.6, 1.6 Hz, 1 H, C8-H), 3.86 (q, 7.0 Hz, 1 H, C1-H), 3.66 (s, 3 H, C5-H), 1.11 (s, 3 H, C4-H), 1.05 (s, 3 H, C4-H), 0.83 (d, *J* = 7.0 Hz, 3 H, C6-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5 (C 3), 134.3 (C 14), 132.2 (C 13), 128.4 (C 7), 124.0 (C 11), 121.3 (C 12), 117.4 (C 10), 107.9 (C 9), 106.5 (C 8), 46.5 (C 5), 41.5 (C 2), 31.6 (C 1), 19.8 (C 4), 14.8 (C 4), 12.6 (C 6).

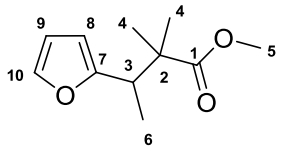


1.589

Methyl 3-(furan-2-yl)-2,2-dimethylpropanoate (1.589). (ab02068). The residue was purified by flash chromatography eluting with Et_2O: pentane (1:9) to give

36% of ester **1.589** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, *J* = 3.2 Hz, 1 H), 6.27 (d, *J* = 3.2 Hz, 1 H), 6.01 (d, *J* = 3.2 Hz, 1 H), 3.68 (s, 3 H), 2.88 (s, 2 H), 1.20 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.7, 152.7, 141.3, 110.1, 107.4, 51.9, 43.0, 38.4, 24.9; IR (DCM) 1735, 1259, 1193, 1147 cm^{-1}; mass spectrum (CI) *m/z* 183.1016 [$C_{10}H_{15}O_3$ (M+1) requires 183.1021], 183 (base), 149, 123, 113.

NMR Assignments: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, *J* = 3.2 Hz, 1 H, C9-H), 6.27 (d, *J* = 3.2 Hz, 1 H, C8-H), 6.01 (d, *J* = 3.2 Hz, 1 H, C7-H), 3.68 (s, 3 H, C5-H), 2.88 (s, 2 H, C3-H), 1.20 (s, 6 H, C4-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.7 (C 1), 152.7 (C 6), 141.3 (C 9), 110.1 (C 8), 107.4 (C 7), 51.9 (C 5), 43.0 (C 2), 38.4 (C 3), 24.9 (C 4).

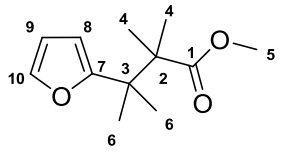


1.596

Methyl 3-(furan-2-yl)-2,2-dimethylbutanoate (1.596). (ab02056). The residue was purified by flash chromatography eluting with Et_2O: pentane (1:9) to give 62% of ester **1.596** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 1.8 Hz, 1 H), 6.28 (d, *J* = 1.8 Hz, 1 H), 6.03 (d, *J* = 1.8 Hz, 1 H), 3.68 (s, 3 H), 3.30 (q, *J* = 7.4 Hz, 1 H), 1.20 (d, *J* = 7.4 Hz, 3 H), 1.14 (s, 3 H), 1.09 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 152.1, 136.2, 105.1, 101.6, 47.0, 41.4, 35.5, 18.6, 16.3, 9.4; IR (DCM) 1731, 1263, 1133, 736 cm^{-1}; mass spectrum (ESI) *m/z* 197.11722 [$C_{11}H_{17}O_3$ (M+1) requires 197.1173], 197, 165, 137 (base).

NMR Assignments: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 1.8 Hz, 1 H, C10-H), 6.28 (d, *J* = 1.8 Hz, 1 H, C9-H), 6.03 (d, *J* = 1.8 Hz, 1 H, C8-H), 3.68 (s, 3 H,

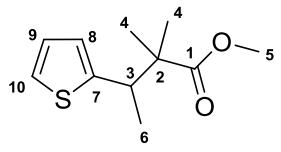
C5-H), 3.30 (q, *J* = 7.4 Hz, 1 H, C3-H), 1.20 (d, *J* = 7.4 Hz, 3 H, C6-H), 1.14 (s, 3 H, C4-H), 1.09 (s, 3 H, C4-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2 (C 1), 152.1 (C 7), 136.2 (C 10), 105.1 (C 9), 101.6 (C 8), 47.0 (C 5), 41.4 (C 2), 35.5 (C 3), 18.6 (C 6), 16.3 (C 4), 9.4 (C 4).



1.597

Methyl 3-(furan-2-yl)-2,2,3-trimethylbutanoate (1.597). (ab02076). The residue was purified by flash chromatography eluting with Et_2O: pentane (1:9) to give 45% of ester **1.597** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 1.8 Hz, 1 H), 6.28 (d, *J* = 1.8 Hz, 1 H), 6.03 (d, *J* = 1.8 Hz, 1 H), 3.58 (s, 3 H), 1.34 (s, 6 H), 1.14 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0, 160.5, 140.7, 109.7, 105.5, 51.4, 48.8, 40.9, 23.2, 22.0; IR (DCM) 1727, 1280, 1135, 733 cm^{-1}; mass spectrum (ESI) *m/z* 211.13287 [$C_{12}H_{19}O_3$ (M+1) requires 211.1330], 211 base).

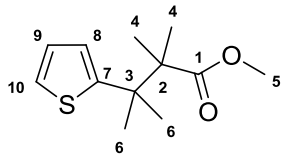
NMR Assignments: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 1.8 Hz, 1 H, C10-H), 6.28 (d, *J* = 1.8 Hz, 1 H, C9-H), 6.03 (d, *J* = 1.8 Hz, 1 H, C8-H), 3.58 (s, 3 H, C5-H), 1.34 (s, 6 H, C6-H), 1.14 (s, 6 H, C4-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0 (C 1), 160.5 (C 7), 140.7 (C 10), 109.7 (C 9), 105.5 (C 8), 51.4 (C 5), 48.8 (C 2), 40.9 (C 3), 23.2 (C 6), 22.0 (C 4).



1.617

Methyl 2,2-dimethyl-3-(thiophen-2-yl)butanoate (1.617). (ab02062). The residue was purified by flash chromatography eluting with Et_2O: pentane (1:9) to give 79% of ester **1.617** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (d, *J* = 4.2 Hz, 1 H), 6.93 (d, *J* = 4.2 Hz, 1 H), 6.82 (d, *J* = 4.2 Hz, 1 H), 3.67 (s, 3 H), 3.52 (q, *J* = 7.0 Hz, 1 H), 1.29 (d, *J* = 7.0 Hz, 3 H), 1.19 (s, 3 H), 1.11 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.9, 145.9, 126.2, 125.4, 123.3, 51.8, 46.7, 42.1, 23.3, 21.2, 17.7; IR (DCM) 1732, 1260, 1133, 696 cm^{-1}; mass spectrum (ESI) *m/z* 213.09438 [$C_{11}H_{17}O_2S$ (M+1) requires 213.0942], 213 (base).

NMR Assignments: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (d, *J* = 4.2 Hz, 1 H, C10-H), 6.93 (d, *J* = 4.2 Hz, 1 H, C9-H), 6.82 (d, *J* = 4.2 Hz, 1 H, C8-H), 3.67 (s, 3 H, C5-H), 3.52 (q, *J* = 7.0 Hz, 1 H, C3-H), 1.29 (d, *J* = 7.0 Hz, 3 H, C6-H), 1.19 (s, 3 H, C4-H), 1.11 (s, 3 H, C4-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.9 (C 1), 145.9 (C 7), 126.2 (C 8), 125.4 (C 9), 123.3 (C 10), 51.8 (C 5), 46.7 (C 2), 42.1 (C 3), 23.3 (C 6), 21.2 (C 4), 17.7 (C 4).

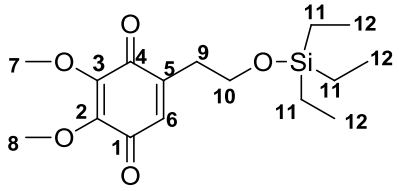


1.618

Methyl 2,2,3-trimethyl-3-(thiophen-2-yl)butanoate (1.618). (ab02050). The residue was purified by flash chromatography eluting with Et_2O: pentane (1:9) to give 84% of ester **1.618** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (d, *J* = 4.2 Hz, 1 H), 6.93 (d, *J* = 4.2 Hz, 1 H), 6.84 (d, *J* = 4.2 Hz, 1 H), 3.57 (s, 3 H), 1.46 (s, 6 H), 1.71 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0, 151.5, 126.0, 124.7, 123.1, 51.4, 49.2,

42.2, 26.6, 22.2; IR (DCM) 2977, 1726, 1466, 1270, 1129, 696 cm^{-1}; mass spectrum (ESI) *m/z* 227.11003 [$C_{12}H_{19}O_2S$ (M+1) requires 227.1104], 227 (base), 125.

NMR Assignments: ^1H NMR (400 MHz, $CDCl_3$) δ 7.14 (d, *J* = 4.2 Hz, 1 H, C10-H), 6.93 (d, *J* = 4.2 Hz, 1 H, C9-H), 6.84 (d, *J* = 4.2 Hz, 1 H, C8-H), 3.57 (s, 3 H, C5-H), 1.46 (s, 6 H, C6-H), 1.71 (s, 6 H, C4-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0 (C 1), 151.5 (C 7), 126.0 (C 8), 124.7 (C 9), 123.1 (C 10), 51.4 (C 2), 49.2 (C 5), 42.2 (C 3), 26.6 (C 6), 22.2 (C 4).

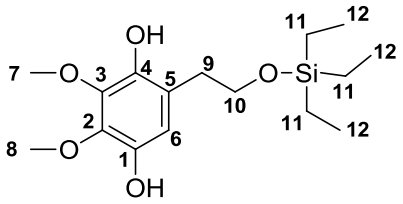


2.170

2,3-Dimethoxy-5-(2-(triethylsilyloxy)ethyl)cyclohexa-2,5-diene-1,4-dione (2.170). (ab02250). *n*-BuLi (1.20 mL, 2.70 mmol, 2.30 M in hexanes) was added to a solution of **2.169**[216] (500 mg, 2.70 mmol) in anhydrous THF (20 mL) at -78 °C. The reaction was stirred for 30 min, and a solution of dimethoxysquarate[241] (**2.155**) (384 mg, 2.70 mmol) in THF (8 mL) was then added. The mixture was stirred for 1 h, and the cold bath was replaced with a 0 °C bath. The reaction was stirred for an additional 30 min, whereupon aqueous saturated NH_4Cl (ca 30 mL) was added. The layers were separated, and the aqueous layer was extracted with Et_2O (2 x 10 mL). The organic layers were combined, washed with brine (ca. 50 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude squarate thus obtained was dissolved in anhydrous toluene (28 mL), and the solution was sparged with argon for 30 min. The solution was then

heated under reflux for 2 h. The solution was cooled to room temperature and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with hexanes/EtOAc (4:1) to yield quinone **2.170** in 690 mg (78% over 2 steps) as a brown oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.43 (t, *J* = 1.3 Hz, 1 H), 3.94 (s, 3 H), 3.92 (s, 3 H), 3.69 (t, *J* = 6.1 Hz, 2 H), 2.56 (td, *J* = 6.1, 1.3 Hz, 2 H), 0.85 (t, *J* = 8.0 Hz, 9 H), 0.50 (q, *J* = 8.0 Hz, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.1, 184.0, 144.9, 144.6, 144.4, 132.2, 61.1, 61.0, 60.5, 32.2, 6.6, 4.3; IR (DCM) 2954, 2877, 1779, 1657, 1603, 1458, 1280, 1100, 745 cm^{-1} LRMS (CI), *m/z* calculated for $C_{16}H_{26}O_5\ Si^{+}$ (M+1), 327; found, 327; mass spectrum, 195, 197, 297, 327 (base).

NMR Assignments: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.43 (t, *J* = 1.3 Hz, 1 H, C6-H), 3.94 (s, 3 H, C7 or C8-H), 3.92 (s, 3 H, C7 or C8-H), 3.69 (t, *J* = 6.1 Hz, 2 H, C10-H), 2.56 (td, *J* = 6.1, 1.3 Hz, 2 H, C9-H), 0.85 (t, *J* = 8.0 Hz, 9 H, C12-H), 0.50 (q, *J* = 8.0 Hz, 6 H, C11-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.1 (C1 or C4), 184.0 (C1 or C4), 144.9 (C2 or C3), 144.6 (C2 or C3), 144.4 (C5), 132.2 (C6), 61.1 (C7 or C8), 61.0 (C7 or C8), 60.5 (C10), 32.2 (C9), 6.6 (C12), 4.3 (C11).

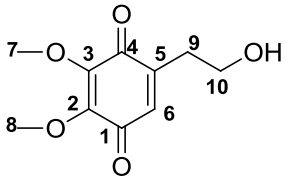


2.171

2,3-Dimethoxy-5-(2-(triethylsilyloxy)ethyl)benzene-1,4-diol (2.171). (ab02269). To a solution of **2.170** (50 mg, 0.15 mmol) in anhydrous MeCN (3 mL) was

added Pd/C (5 mg, 10% by wt). The flask was evacuated with a high vacuum pump (< 1 torr) through a N_2 line until bubbles appeared in the solution, at which point the flask was backfilled with N_2. This was repeated once and then the flask was evacuated for a third time and placed under H_2 (9" helium grade latex balloon). The reaction was stirred at room temperature for 1 h, whereupon the solids were removed by vacuum filtration through a fritted funnel containing a thin layer of Celite. The filter pad was washed with Et_2O (4 x 5 mL), and the combined washings were concentrated under reduced pressure. The residue was purified by flash chromatography eluting with hexanes/EtOAc (1:2) to yield 33 mg (67%) of hydroquinone **2.171** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (s, 1 H), 6.42 (s, 1 H), 5.30 (s, 1 H), 3.92 (s, 3 H), 3.91 (s, 3 H), 3.83 (t, 2 H), 2.80 (t, 2 H), 0.90 (t, 9 H), 0.60 (q, 6 H); LRMS (CI), *m/z* calculated for $C_{16}H_{28}O_5Si^+$ (M+1), 329; found, 329; mass spectrum, 183, 197 (base), 215, 227, 299, 327, 329.

NMR Assignments: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (s, 1 H, C1-OH, C4-OH, or C6-H), 6.42 (s, 1 H, C1-OH, C4-OH, or C6-H), 5.30 (s, 1 H, C1-OH, C4-OH, or C6-H), 3.92 (s, 3 H, C7 or C8-H), 3.91 (s, 3 H, C7 or C8-H), 3.83 (t, 2 H, C10-H), 2.80 (t, 2 H, C9-H), 0.90 (t, 9 H, C12-H), 0.60 (q, 6 H, C11-H).

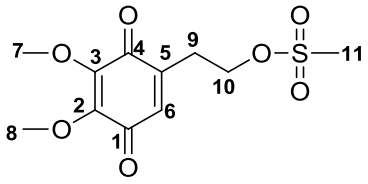


2.168

5-(2-Hydroxyethyl)-2,3-dimethoxycyclohexa-2,5-diene-1,4-dione (2.168). (ab02239): Pyridine (10 mg, 0.01 mL, 0.15 mmol) and HF·Pyridine (44 mg, 0.04 mL, 0.33 mmol, 70% HF in 30% pyridine) were added sequentially to a solution of TES-

protected quinone **2.171** (100 mg, 0.30 mmol) in anhydrous MeCN (3 mL) at 0 °C. The reaction was stirred for 5 min, and H_2O (ca 1 mL) and Et_2O (ca 1 mL) were added. The layers were separated, and the aqueous layer was extracted with Et_2O (2 x 5 mL). The organic layers were combined, washed with 1 M HCl (ca 10 mL), H_2O (ca 10 mL), and brine (ca 10 mL), dried (Na_2SO_4), and concentrated under reduced pressure to yield 62 mg (97%) of quinone **2.168** as an orange oil which was not purified further. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.51 (s, 1 H), 4.01 (s, 3 H), 3.99 (s, 3 H), 3.81 (t, *J* = 6.0 Hz, 2 H), 2.67 (td, *J* = 6.0, 0.80 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.4, 184.1, 145.0, 144.8, 144.4, 132.2, 61.3, 61.2, 60.8, 32.3; IR (DCM) 3404, 1631, 1467, 1368, 1198, 1113, 1073; LRMS (CI), *m/z* calculated for $C_{10}H_{12}O_5^+$ (M+1), 213; found, 214; mass spectrum, 183, 196, 197, 213, 214 (base), 215.

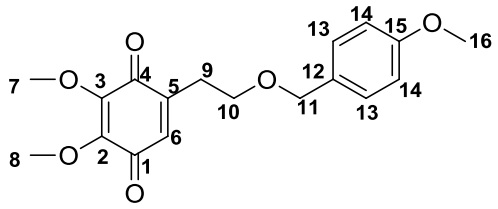
NMR Assignments: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.51 (s, 1 H, C6-H), 4.01 (s, 3 H, C7 or C8-H), 3.99 (s, 3 H, C7 or C8-H), 3.81 (t, *J* = 6.0 Hz, 2 H, C10-H), 2.67 (td, *J* = 6.0, 0.80 Hz, C9-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.4 (C1 or C4), 184.1 (C1 or C4), 145.0 (C3 or C2), 144.8 (C3 or C2), 144.4 (C5), 132.2 (C6), 61.3 (C7 or C8), 61.2 (C7 or C8), 60.8 (C10), 32.3 (C9).



2.173

2-(4,5-Dimethoxy-3,6-dioxocyclohexa-1,4-dienyl)ethyl methanesulfonate (2.173). (ab02256). Mesyl chloride (74 mg, 0.05 mL, 0.71 mmol) was added to a solution of **2.168** (100 mg, 0.47 mmol) and Et_3N (73 mg, 0.10 mL, 0.71 mmol) in anhydrous DCM (5 mL). The reaction was stirred for 14.5 h, whereupon aqueous saturated NH_4Cl (ca 5 mL) was added. The layers were separated, and the aqueous layer was extracted with DCM (2 x 3 mL). The organic layers were combined, washed with 1 M HCl (2 x 10 mL), H_2O (ca 10 mL), and brine (ca 10 mL), dried (Na_2SO_4), and concentrated under reduced pressure to yield 112 mg (82%) of **2.173** as a red oil which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.50 (s, 1 H), 4.40 (t, 2 H), 4.05 (s, 3 H), 4.00 (s, 3 H), 3.00 (s, 3 H), 2.85 (t, 2 H); IR (DCM) 2851, 2256, 1659, 1604, 913, 744; HRMS (CI), *m/z* calculated for $C_{11}H_{15}O_7S^+$ (M+1), 291.0583; found, 291.0538; mass spectrum, 290, 291 (base), 292.

NMR Assignments: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.50 (s, 1 H, C6-H), 4.40 (t, 2 H, C10-H), 4.05 (s, 3 H, C7 or C8-H), 4.00 (s, 3 H, C7 or C8-H), 3.00 (s, 3 H, C11-H), 2.85 (t, 2 H, C9-H).

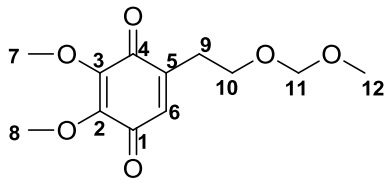


2.176

2,3-Dimethoxy-5-(2-(4-methoxybenzyloxy)ethyl)cyclohexa-2,5-diene-1,4-dione (2.176). (ab02291). *n*-BuLi (0.16 mL, 0.39 mmol, 2.20 M in hexanes) was added

to a solution of **2.175**[219] (75 mg, 0.39 mmol) in anhydrous THF (2 mL) at -78 °C. The reaction was stirred for 1 h, and a solution of dimethoxysquarate[241] (**2.155**) (50 mg, 0.39 mmol) in THF (1.5 mL) was then added. The mixture was stirred for 1 h, whereupon aqueous saturated NH_4Cl (ca 5 mL) was added. The layers were separated, and the aqueous layer was extracted with Et_2O (2 x 5 mL). The organic layers were combined, washed with brine (ca 10 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude squarate thus obtained was dissolved in anhydrous toluene (3.5 mL), and the solution was sparged with argon for 10 min. The solution was then heated under reflux for 50 min. The solution was cooled to room temperature and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with pentanes/EtOAc (4:1) to yield quinone **2.176** in 48 mg (41% over 2 steps) as an orange oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.8 Hz, 2 H), 6.86 (d, *J* = 8.8 Hz, 2 H), 6.48 (t, *J* = 1.2 Hz), 4.42 (s, 2 H), 4.01 (s, 3 H), 3.97 (s, 3 H), 3.80 (s, 3 H), 3.61 (t, *J* = 8.0 Hz, 2 H), 2.69 (td, *J* = 8.0, 1.2 Hz, 2 H); IR (DCM) 1652, 1603, 1513, 1455, 1247, 1092; HRMS (CI), *m/z* calculated for $C_{18}H_{20}O_6^+$ (M+1), 332.1260; found, 332.1258; mass spectrum, 332 (base), 334.

NMR Assignments: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.8 Hz, 2 H, C13 or C14-H), 6.86 (d, *J* = 8.8 Hz, 2 H, C13 or C14-H), 6.48 (t, *J* = 1.2 Hz, C6-H), 4.42 (s, 2 H, C11-H), 4.01 (s, 3 H, C7 or C8-H), 3.97 (s, 3 H, C7 or C8-H), 3.80 (s, 3 H, C16-H), 3.61 (t, *J* = 8.0 Hz, 2 H, C10-H), 2.69 (td, *J* = 8.0, 1.2 Hz, 2 H, C9-H).



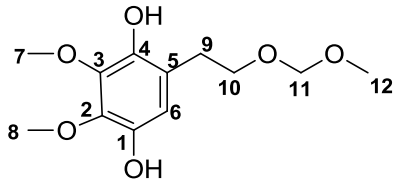
287

2.179

2,3-Dimethoxy-5-(2-(methoxymethoxy)ethyl)cyclohexa-2,5-diene-1,4-dione (2.179). (ab03034). *n*-BuLi (0.30 mL, 0.70 mmol, 2.10 M in hexanes) was added to a solution of **2.178**[222] (80 mg, 0.70 mmol) in anhydrous THF (4 mL) at -78 °C. The reaction was stirred for 2 h, and a solution of dimethoxysquarate[241] (**2.155**) (100 mg, 0.70 mmol) in THF (3 mL) was added. The mixture was stirred for 3 h, whereupon aqueous saturated NH_4Cl (ca. 10 mL) was added. The layers were separated, and the aqueous layer was extracted with Et_2O (2 x 5 mL). The organic layers were combined, washed with brine (ca. 20 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude squarate thus obtained was dissolved in anhydrous toluene (7 mL), and the solution was sparged with Argon for 10 min. The solution was then heated under reflux for 1.5 h. The solution was cooled to room temperature and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with hexanes/EtOAc (1:1) to yield quinone **2.179** in 160 mg (89% over 2 steps) as a red oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.45 (t, *J* = 1.5 Hz, 1 H), 4.53 (s, 2 H), 3.95 (s, 3 H), 3.93 (s, 3 H), 3.65 (t, *J* = 6.1 Hz, 2 H), 3.27 (s, 3 H), 2.64 (td, *J* = 6.1, 1.5 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.2, 184.0, 145.0, 144.7, 144.4, 131.9, 96.4, 64.9, 61.3, 61.2, 55.4, 29.2; IR (DCM) 1656, 1604, 1456, 1280, 1217, 1149, 1109, 1031; HRMS (CI), *m/z* calculated for $C_{12}H_{16}O_6^+$ (M+1), 257.1025; found, 257.1026; mass spectrum, 239 (base), 257, 258.

NMR Assignments: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.45 (t, *J* = 1.5 Hz, 1 H, C6-H), 4.53 (s, 2 H, C11-H), 3.95 (s, 3 H, C7 or C8-H), 3.93 (s, 3 H, C7 or C8-H), 3.65 (t, *J* = 6.1 Hz, 2 H, C10-H), 3.27 (s, 3 H, C12-H), 2.64 (td, *J* = 6.1, 1.5 Hz, 2 H, C9-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.2 (C1 or C4), 184.0 (C1 or C4), 145.0 (C2 or C3), 144.7

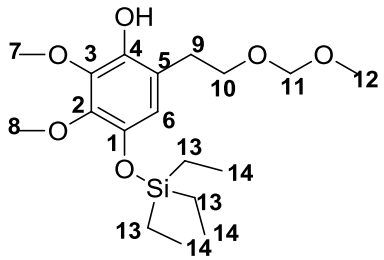
(C2 or C3), 144.4 (C5), 131.9 (C6), 96.4 (C11), 64.9 (C10), 61.3 (C7 or C8), 61.2 (C7 or C8), 55.4 (C12), 29.2 (C9).



2.180

2,3-Dimethoxy-5-(2-(methoxymethoxy)ethyl)benzene-1,4-diol (2.180). (ab03042). To a solution of **2.179** (377 mg, 1.50 mmol) in anhydrous MeCN (15 mL) was added Pd/C (38 mg, 10% by wt). The flask was evacuated with a high vacuum pump (< 1 torr) through a N_2 line until bubbles appeared in the solution, at which point the flask was backfilled with N_2. This was repeated once and then the flask was evacuated for a third time and placed under H_2 (9" helium grade latex balloon). The reaction was stirred at room temperature for 1 h, whereupon the solids were removed by vacuum filtration through a fritted funnel containing a thin layer of Celite. The filterpad was washed with Et_2O (4 x 10 mL), and the combined washings were concentrated under reduced pressure to yield 372 mg (96%) of hydroquinone **2.180** as a yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.49 (s, 1 H), 6.11 (s, 1 H), 5.18 (s, 1 H), 4.62 (s, 2 H), 3.89 (s, 3 H), 3.89 (s, 3 H), 3.75 (t, *J* = 6.4 Hz, 2 H), 3.30 (s, 3 H), 2.83 (t, *J* = 6.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 141.9, 141.2, 140.2, 138.2, 121.1, 110.8, 96.3, 68.0, 60.9, 60.7, 55.3, 31.0; IR (DCM) 3396, 1468, 1112, 1077, 1029; HRMS (CI), *m/z* calculated for $C_{12}H_{18}O_6^+$ (M+1), 258.1103; found, 258.1098; mass spectrum, 227 (base), 258.

NMR Assignments: ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.49 (s, 1 H, C6-H), 6.11 (s, 1 H, C4-OH), 5.18 (s, 1 H, C1-OH), 4.62 (s, 2 H, C11-H), 3.89 (s, 3 H, C7 or C8-H), 3.89 (s, 3 H, C7 or C8-H), 3.75 (t, *J* = 6.4 Hz, 2 H, C10-H), 3.30 (s, 3 H, C12-H), 2.83 (t, *J* = 6.4 Hz, 2 H, C9-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 141.9 (C1 or C4), 141.2 (C1 or C4), 140.2 (C2 or C3), 138.2 (C2 or C3), 121.1 (C5), 110.8 (C6), 96.3 (C11), 68.0 (C10), 60.9 (C7 or C8), 60.7 (C7 or C8), 55.3 (C12), 31.0 (C9).

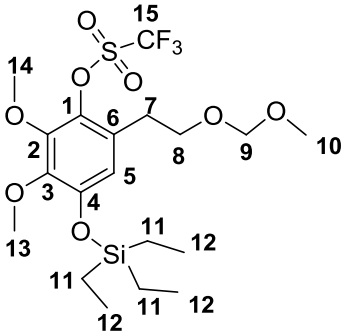


2.182

2,3-Dimethoxy-6-(2-(methoxymethoxy)ethyl)-4-(triethylsilyloxy)phenol (2.182). (ab03060). A solution of TESOTf (105 mg, 0.090 mL, 0.73 mmol) in DCM (0.07M) was added to a solution of **2.180** (94 mg, 0.36 mmol) and 2,6-lutidine (0.090 mL, 0.73 mmol) in anhydrous DCM (26 mL, 0.014M) at -78 °C via syringe pump (10 mL syringe, 15 mm diameter, 10 mL/h) over 1 h. The reaction was stirred for 30 min, and then the -78 °C cold bath was replaced with a 0 °C cold bath. The reaction was stirred for 1 h, the cold bath was removed, and the reaction was warmed to room temperature and stirred for 22 h, whereupon aqueous saturated NH_4Cl (ca 50 mL) was added. The layers were separated, and the aqueous layer was extracted with DCM (2 x 20 mL). The organic layers were combined, washed with brine (ca 50 mL), dried

($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with hexanes/EtOAc (4:1) to provide 75 mg (56%) of TES-protected hydroquinone **2.182** as a yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.39 (s, 1 H), 5.90 (s, 1 H), 4.60 (s, 2 H), 3.89 (s, 3 H), 3.81 (s, 3 H), 3.72 (t, *J* = 6.7 Hz, 2 H), 3.29 (s, 3 H), 2.81 (t, *J* = 6.7 Hz, 2 H), 0.97 (t, *J* = 8.0 Hz, 9 H), 0.71 (q, *J* = 8.0 Hz, 6 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 142.6, 141.9, 141.7, 140.7, 119.7, 116.7, 96.3, 67.8, 61.1, 60.5, 55.2, 30.7, 6.6, 5.0; IR (DCM) 3402, 1495, 1463, 1366, 1111, 1081, 1020, 959; HRMS (CI), *m/z* calculated for $C_{18}H_{32}O_6Si^+$ (M+1), 372.1968; found, 372.1968; mass spectrum, 372 (base), 373, 374.

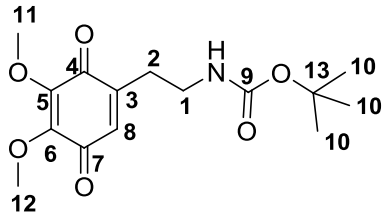
NMR Assignments: ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.39 (s, 1 H, C6-H), 5.90 (s, 1 H, C4-OH), 4.60 (s, 2 H, C11-H), 3.89 (s, 3 H, C7-H), 3.81 (s, 3 H, C8-H), 3.72 (t, *J* = 6.7 Hz, 2 H, C10-H), 3.29 (s, 3 H, C12-H), 2.81 (t, *J* = 6.7 Hz, 2 H, C9-H), 0.97 (t, *J* = 8.0 Hz, 9 H, C14-H), 0.71 (q, *J* = 8.0 Hz, 6 H, C13-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 142.6 (C4), 141.9 (C3), 141.7 (C2), 140.7 (C1), 119.7 (C5), 116.7 (C6), 96.3 (C11), 67.8 (C10), 61.1 (C7), 60.5 (C8), 55.2 (C12), 30.7 (C9), 6.6 (C14), 5.0 (C13).



2.185

2,3-Dimethoxy-6-(2-(methoxymethoxy)ethyl)-4-(triethylsilyloxy)phenyl trifluoromethanesulfonate (2.185). (ab03063). Triethylamine (0.04 mL, 29.0 mg, 0.28 mmol) was added to a solution of 2,3-dimethoxy-6-(2-(methoxymethoxy)ethyl)-4-(triethylsilyloxy)phenol (**2.182**) (52.0 mg, 0.14 mmol) in DCM (2.0 mL) at -78 °C. The reaction was stirred for 10 min, whereupon Tf_2O (0.03 mL, 50.3 mg, 0.17 mmol) was added. After 30 min $NH_4Cl_{(sat)}$ (ca 2 mL) was added, and the mixture was allowed to warm to room temperature. The layers were separated, and the aqueous layer was extracted with DCM (1 x 3 mL). The organic layers were combined, washed with 1 M HCl (ca 5 mL) and brine (ca 5 mL), dried ($MgSO_4$), and concentrated to yield 54 mg (76%) of triflate **2.185** as a colorless oil that was used in further reactions without purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.57 (s, 1 H), 4.60 (s, 2 H), 3.95 (s, 3 H), 3.83 (s, 3 H), 3.70 (t, *J* = 6.8 Hz, 2 H), 3.30 (s, 3 H), 2.87 (t, *J* = 6.8 Hz, 2 H), 0.10 (t, *J* = 7.8 Hz, 9 H), 0.77 (q, *J* = 7.8 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.0, 146.0, 143.3, 135.2, 126.8, 118.7 (q, *J* = 320.1 Hz), 116.2, 96.4, 66.7, 61.3, 60.7, 55.2, 30.0, 6.6, 5.0; IR (DCM) 1576, 1416, 1210, 1141, 1111, 1020, 951; HRMS (CI), *m/z* calculated for $C_{19}H_{31}O_8SSiF_3^+$ (M+1), 504.1461; found, 504.1458; mass spectrum 504 (base), 505, 506.

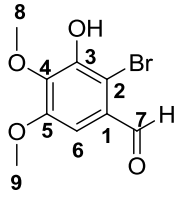
NMR Assignments: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.57 (s, 1 H, C5-H), 4.60 (s, 2 H, C9-H), 3.95 (s, 3 H, C13 or C14-H), 3.83 (s, 3 H, C13 or C14-H), 3.70 (t, *J* = 6.8 Hz, 2 H, C7-H), 3.30 (s, 3 H, C10-H), 2.87 (t, *J* = 6.8 Hz, 2 H, C8-H), 0.10 (t, *J* = 7.8 Hz, 9 H, C12-H), 0.77 (q, *J* = 7.8 Hz, 6 H, C11-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.0 (C1), 146.0 (C2 or C3), 143.3 (C2 or C3), 135.2 (C4), 126.8 (C6), 118.7 (q, *J* = 320.1 Hz, C15), 116.2 (C5), 96.4 (C9), 66.7 (C8), 61.3 (C13 or C14), 60.7 (C13 or C14), 55.2 (C10), 30.0 (C7), 6.6 (C11), 5.0 (C12).



2.162

***tert*-Butyl 2-(4,5-dimethoxy-3,6-dioxocyclohexa-1,4-dienyl)ethylcarbamate (2.162). (ab03154).** *n*-BuLi (5.0 mL, 1.05 mmol, 2.10 M) was added to a solution of *tert*-butylbut-3-ynylcarbamate (**2.160**) (90 mg, 0.53 mmol) in THF (1 mL) at 0 °C, and the pale yellow solution darkened to a bright yellow. The reaction was stirred for 1.5 h before the temperature was cooled to -78 °C, and a solution of dimethoxysquarate (**2.155**) (50.0 mg, 0.35 mmol) in THF (3 mL) was added dropwise. After 1 h, $NH_4Cl_{(sat)}$ (ca. 5 mL) was added, and the mixture was allowed to warm to room temperature. The layers were separated, and the aqueous layer was extracted with Et_2O (2 x5 mL). The organic layers were combined, dried ($MgSO_4$), and concentrated to yield a yellow oil. This oil was immediately dissolved in toluene (4 mL), and the resulting solution was sparged with argon for 5 min. The solution was then heated under reflux for 2 h, cooled to room temperature and concentrated. The residue was purified by flash chromatography eluting with EtOAc/hexanes (1:2) to yield 20 mg (18% over 2 steps) of quinone **2.162** as a red oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.48 (s, 1 H), 5.92 (br, 1 H), 4.19 (t, 2 H), 4.05 (s, 3 H), 4.01 (s, 3H), 3.79 (t, 2 H), 1.55 (s, 9 H); LRMS (CI), *m/z* calculated for $C_{15}H_{21}NO_6^-$ (M), 311.14; found, 311; mass spectrum, 310, 311 (base), 312.

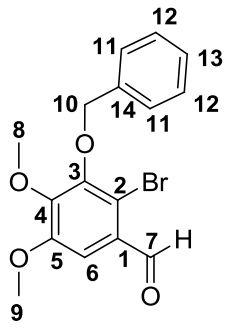
NMR Assignments: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.48 (s, 1 H, C8-H), 5.92 (br, 1 H, NH), 4.19 (t, 2 H, C1-H), 4.05 (s, 3 H, C11 or C12-H), 4.01 (s, 3H, C11 or C12-H), 3.79 (t, 2 H, C2-H), 1.55 (s, 9 H, C10-H).



2.201

2-Bromo-3-hydroxy-4,5-dimethoxybenzaldehyde (2.201). (ab03257). Bromine (0.65 mL, 2.03 g, 12.60 mmol) was added to a solution of **2.196** (2.29 g, 12.60 mmol) in HOAc (14 mL). The reaction was stirred for 17 h, whereupon it was added to a mixture of H_2O and ice. The brown precipitate was collected via vacuum filtration and washed with H_2O, to yield 2.59 g (79%) of crude **2.201** as a brown solid. An analytical sample was prepared by recrystallization from hexanes to give **2.201** as a tan solid; mp = 144-145 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.29 (s, 1 H), 7.17 (s, 1 H), 6.27 (br, 1 H), 4.03 (s, 3 H), 3.92 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.1, 151.5, 146.9, 140.9, 128.5, 106.7, 104.5, 61.3, 56.2; IR (DCM) 3375, 1680, 1588, 1575, 1427, 1344, 1331, 1147; HRMS (ESI), *m/z* calculated for $C_9H_9BrO_4Na^+$ (M+1), 282.95764; found 282.9575; mass spectrum, 282 (base), 284.

NMR Assignments: ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.29 (s, 1 H, C7-H), 7.17 (s, 1 H, C6-H), 6.27 (br, 1 H, OH), 4.03 (s, 3 H, C8 or C9-H), 3.92 (s, 3 H, C8 or C9-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.1 (C7), 151.5 (C4 or C5), 146.9 (C4 or C5), 140.9 (C3), 128.5 (C1), 106.7 (C2), 104.5 (C6), 61.3 (C8 or C9), 56.2 (C8 or C9).

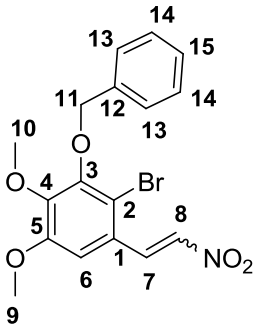


2.202

3-(Benzyloxy)-2-bromo-4,5-dimethoxybenzaldehyde (2.202). (ab03215). A mixture of NaH (1.32 g, 33.0 mmol, 60%) and crude phenol **2.201** (7.82 g, 30.0 mmol) in deoxygenated (freeze/pump/thaw x 3) DMF (60 mL) was stirred for 1.5 h at 0 °C, and then BnBr (3.60 mL, 5.18 g, 30.0 mmol) was added. The reaction was allowed to warm to room temperature and stirred for 4 h, whereupon the solution was added to a mixture of H_2O and ice. The pale yellow precipitate was collected via vacuum filtration and washed with H_2O, to yield 9.58 g (91%) of crude **2.202** as a pale yellow solid. An analytical sample was prepared by recrystallization from petroleum ether to give **2.202** as a pale yellow solid; mp = 108-109 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.31 (s, 1 H), 7.57 (d, *J* = 7.6 Hz, 2 H), 7.41-7.33 (comp, 4 H), 5.07 (s, 2 H), 3.97 (s, 3 H), 3.93 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 191.2, 153.1, 149.7, 149.0, 136.4, 128.6, 128.5, 128.4, 116.0, 107.6, 75.6, 61.4, 56.3; IR (DCM) 1688, 1372, 1329, 1110; HRMS (CI) *m/z* calculated for $C_{16}H_{16}O_4Br^+$ (M+1), 351.0232; found, 351.0234; mass spectrum, 351 (base), 353, 354.

NMR Assignments: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.31 (s, 1 H, C7-H), 7.57 (d, *J* = 7.6 Hz, 2 H, C11-H), 7.41-7.33 (comp, 4 H, C6, C12, and C13-H), 5.07 (s, 2 H, C10-

H), 3.97 (s, 3 H, C8 or C9-H), 3.93 (s, 3 H, C8 or C9-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.2 (C7), 153.1 (C3), 149.7 (C4 or C5), 149.0 (C4 or C5), 136.4 (Ar), 128.6 (C11 or C12), 128.5 (C11 or C12), 128.4 (Ar), 116.0 (Ar), 107.6 (Ar), 75.6 (C10), 61.4 (C8 or C9), 56.3 (C8 or C9).

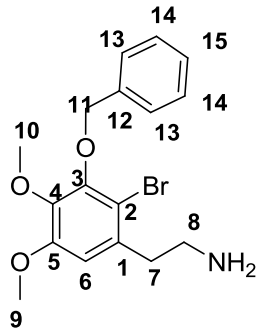


2.203

3-(Benzyloxy)-2-bromo-4,5-dimethoxy-1-(2-nitrovinyl)benzene (2.203). (ab03287). A solution of aldehyde **2.202** (1.46 g, 4.20 mmol), NH_4OAc (1.90 g, 25.20 mmol), and $MeNO_2$ (1.36 mL, 1.53 g) in HOAc (20 mL) was heated in an oil bath at 100 °C. The reaction was stirred for 3.5 h, and the solution was cooled to room temperature and added to a mixture of H_2O and ice. The bright yellow precipitate was collected via vacuum filtration and washed with H_2O, to yield 1.43 g (86%) of **2.203** as a bright yellow oily solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, J = 13.6, 1 H), 7.55-7.36 (comp, 6 H), 6.90 (s, 1 H), 5.06 (s, 2 H), 3.95 (s, 3 H), 3.92 (s, 3 H); ^{13}CNMR (150 MHz, $CDCl_3$) δ 153.1, 150.6, 146.7, 138.2, 138.0, 136.4, 128.6, 128.6, 128.5, 128.5, 128.5, 125.5, 115.0, 106.8, 75.5, 61.4, 56.4; IR (DCM) 3103, 1625, 1508, 1483, 1328, 1110; HRMS (CI) *m/z*

calculated for $C_{17}H_{16}BrNO_5^+$ (M+1), 393.0212; found, 393.0209; mass spectrum, 392, 393 (base), 394, 395 (base) 396.

NMR Assignments: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, *J* = 13.6, 1 H, C8), 7.55-7.36 (comp, 6 H, C7, C13, C14, C15-H), 6.90 (s, 1 H, C6-H), 5.06 (s, 2 H, C11-H), 3.95 (s, 3 H, C9 or C10-H), 3.92 (s, 3 H, C9 or C10-H). ^{13}CNMR (150 MHz, $CDCl_3$) δ 153.1 (C3), 150.6 (C5), 146.7 (C4), 138.2 (C7, C8, or C12), 138.0 (C7, C8, or C12), 136.4 (C7, C8, or C12), 128.6 (CAr), 128.6 (CAr), 128.5 (CAr), 128.5 (CAr), 128.5 (CAr), 125.5 (CAr), 115.0 (CAr), 106.8 (CAr), 75.5 (C11), 61.4 (C9 or C10), 56.4 (C9 or C10).

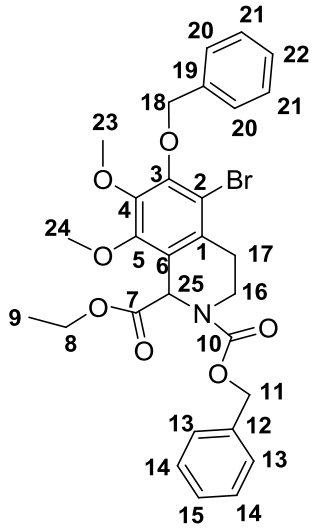


2.204

2-(3-(Benzyloxy)-2-bromo-4,5-dimethoxyphenyl)ethanamine (2.204). (ab03261). TMSCl (3.20 mL, 2.74 g, 25.60 mmol) was added to a solution of $LiBH_4$ (280.0 mg, 12.80 mmol) in THF (10 mL). The solution was purged with N_2 for 10 min, whereupon a solution of **2.203** (1.28 g, 3.20 mmol) in THF (10 mL) was added dropwise. The mixture was heated under under reflux for 23 h and then cooled room temperature. MeOH (ca 5 mL) was added slowly dropwise, and the mixture was concentrated under

reduced pressure. Et_2O (ca 5 mL) and 6 M NaOH (ca 5 mL) were added to the residue, and the layers were separated. The aqueous layer was extracted with Et_2O (2 x 5 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated to yield 1.03 g (100% conversion, 88% mass balance) of amine **2.204** as a brown oil. *NMR data shown is for a mixture of amine and what is presumed to be the N-OH compound **2.205**. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.8 Hz, 2 H), 7.39 (t, *J* = 7.2 Hz, 2 H), 7.34, (t, *J* = 6.6 Hz, 1 H), 6.68 (s, 1 H), 5.05 (s, 2 H), 3.87 (s, 6 H), 3.20 (t, *J* = 7.2 Hz, 1 H), 3.01 (t, *J* = 7.2 Hz, 1 H), 2.98 (br, 1 H), 2.90 (br, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 152.6, 150.0, 142.0, 137.1, 134.8, 134.5, 128.5, 128.42, 128.40, 128.2, 111.3, 109.8, 75.3, 61.2, 56.2, 53.4, 34.2; IR (DCM) 3436, 3198, 2385, 1556, 1483, 1110; HRMS (ESI) *m/z* calculated for $C_{17}H_{21}NO_3Br^+$ (M+1), 366.05; found, 366.0694; mass spectrum, 366 (base), 367, 368, 369.

NMR Assignments: *NMR data shown is for a mixture of amine and what is presumed to be the N-OH compound. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.8 Hz, 2 H, C13-H), 7.39 (t, *J* = 7.2 Hz, 2 H, C14-H), 7.34, (t, *J* = 6.6 Hz, 1 H, C15-H), 6.68 (s, 1 H, C6-H), 5.05 (s, 2 H, C11-H), 3.87 (s, 6 H, C9 and C10-H), 3.20 (t, *J* = 7.2 Hz, 1 H, C8-H), 3.01 (t, *J* = 7.2 Hz, 1 H, C8-H), 2.98 (br, 1 H, C7-H), 2.90 (br, 1 H, C7-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 152.6 (CAr), 150.0 (CAr), 142.0 (CAr), 137.1 (CAr), 134.8 (CAr), 134.5 (CAr), 128.5 (CAr), 128.42 (CAr), 128.40 (CAr), 128.2 (CAr), 111.3 (CAr), 109.8 (CAr), 75.3 (C11), 61.2 (C9 or C10), 56.2 (C9 or C10), 53.4 (C7 or C8), 34.2 (C7 or C8).

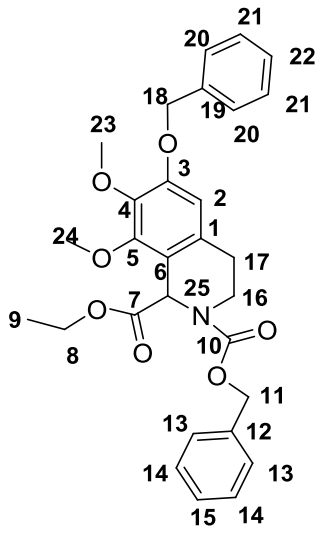


2.207

2-Benzyl 1-ethyl 6-(benzyloxy)-5-bromo-7,8-dimethoxy-3,4-tetrahydroisoquinoline-1,2(1H)-dicarboxylate (2.207). (ab03267). Ethyl glyoxylate (0.67 mL, 0.345 g, 3.4 mmol, 50%) was added to a solution of crude amine **2.204** (1.24 g, 3.40 mmol) and 4 Å molecular sieves in DCM (10 mL). The reaction was stirred for 1 h and then cooled to 0 °C. CbzCl (0.49 mL, 0.600 g, 3.40 mmol) and TMSOTf (0.12 mL, 0.147 g, 0.68 mmol) were added, and the reaction was stirred for 2 h at room temperature. $NaHCO_{3(sat)}$ (ca. 10 mL) was added, and the layers were separated. The aqueous layer was extracted with DCM (3 x 5 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated to yield a yellow oil. The residue was purified by flash chromatography eluting with EtOAc/hexanes (1:4) to yield 0.570 g (30% over 2 steps from the amine) of **2.207** as a colorless oil. ^{1}H NMR (500 MHz, DMSO-d_6, 130°C) δ 7.53 (d, *J* =7.0 Hz, 2 H), 7.40-7.29 (comp, 8 H), 5.94 (s, 1 H), 5.18 (dd, *J* = 12.5, 15.0 Hz, 2 H), 5.08 (dd, *J* = 12.0, 14.0 Hz, 2 H), 4.13 (m, 2 H), 3.90 (s, 3 H), 3.85 (comp, 4

H), 3.51 (dtd, *J* = 5.5, 6.5, 8.0 Hz, 1 H), 2.84 (comp, 2 H), 1.16 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6, 130°C) δ 168.8, 154.0, 149.4, 148.9, 144.3, 136.2, 136.1, 129.8, 127.6, 127.5, 127.4, 127.3, 127.2, 127.1, 126.7, 125.8, 121.9, 112.2, 74.2, 66.3, 60.5, 60.1, 59.8, 52.5, 40.0-39.0, 27.4, 13.0; LCMS (ESI) *m/z* calculated for $C_{29}H_{30}BrNO_7^+$ (M+1), 584; found, 584; mass spectrum, 584 (base), 586.

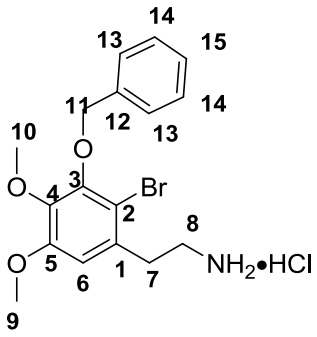
NMR Assignments: ^{1}H NMR (500 MHz, DMSO-d_6, 130°C) δ 7.53 (d, *J* =7.0 Hz, 2 H, CAr-H), 7.40-7.29 (comp, 8 H, CAr-H), 5.94 (s, 1 H, C25-H), 5.18 (dd, *J* = 12.5, 15.0 Hz, 2 H, C11 or C18-H), 5.08 (dd, *J* = 11.0, 14.0 Hz, 2 H, C11 or C18-H), 4.13 (m, 2 H, C8-H), 3.90 (s, 3 H, C24 or C24-H), 3.85 (comp, 4 H, C23 or C24-H and C16 or C17-H), 3.51 (dtd, *J* = 5.5, 6.5, 8.0 Hz, 1 H, C16 or C17-H), 2.84 (comp, 2 H, C16 or C17-H), 1.16 (t, *J* = 7.0 Hz, 3 H, C9-H); ^{13}C NMR (125 MHz, DMSO-d_6, 130°C) δ 168.8 (C7), 154.0 (C10), 149.4 (CAr), 148.9 (CAr), 144.3 (CAr), 136.2 (CAr), 136.1 (CAr), 129.8, (CAr), 127.6 (2 CAr), 127.5 (CAr), 127.4 (CAr), 127.3 (CAr), 127.2 (CAr), 127.1 (CAr), 126.7 (2 CAr), 125.8 (CAr), 121.9 (CAr), 112.2 (CAr), 74.2 (C11 or C18), 66.3 (C11 or C18), 60.5 (C8), 60.1 (C23 or C24), 59.8 (C23 or C24), 52.5 (C25), 40.0-39.0 (C16 or C17), 27.4 (C16 or C17), 13.0 (C9).



2.209

2-Benzyl 1-ethyl 6-(benzyloxy)-7,8-dimethoxy-3,4-tetrahydroisoquinoline-1,2(1H)-dicarboxylate (2.209). (ab03302). A solution of **2.207** (60.0 mg, 0.10 mmol), $Pd(OAc)_2$ (5.0 mg, 0.020 mmol), PPh_3 (5.0 mg, 0.020 mmol), and K_2CO_3 (28.0 mg, 0.20 mmol) in EtOH (5 mL) was sparged with N_2 for 10 min. The reaction was heated under reflux for 1 h, cooled to room temperature and then concentrated under reduced pressure. Et_2O (ca 5 mL) and $NaHCO_{3(sat)}$ (ca 5 mL) were added to the residue, and the layers were separated. The aqueous layer was extracted with Et_2O (3 x 2 mL), and the combined organic layers dried ($MgSO_4$) and concentrated to yield a yellow oil. The residue was purified by flash chromatography eluting with EtOAc/hexanes (1:4) to yield 50.0 mg (98%) of **2.209** as a pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.5-7.2 (comp, 10 H), 6.5 (d, 1 H), 6.0 (d, 1 H), 5.3-5.1 (comp, 4 H), 4.3-4.1 (comp, 2 H), 4.0 (d, 3 H), 3.8 (s, 3 H), 3.8-3.4 (comp, 2 H), 3.0-2.6 (comp, 2 H), 1.2 (dt, 3 H); LCMS (APCI) *m/z* calculated for $C_{29}H_{31}NO_7^+$ (M+1), 506; found, 506; mass spectrum, 506 (base), 507.

NMR Assignments: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.5-7.2 (comp, 10 H, CAr-H), 6.5 (d, 1 H, C2-H), 6.0 (d, 1 H, C25-H --rotamers), 5.3-5.1 (comp, 4 H, C18 and C11-H), 4.3-4.1 (comp, 2 H, C8), 4.0 (d, 3 H, C23 or C24-H), 3.8 (s, 3 H, C23 or C24-H), 3.8-3.4 (comp, 2 H, C16-H), 3.0-2.6 (comp, 2 H, C17-H), 1.2 (dt, 3 H, C10-H).

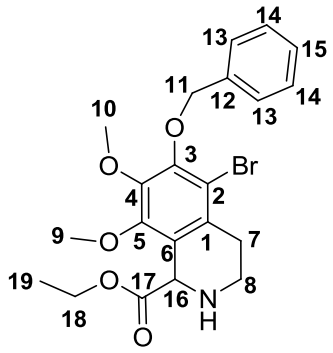


2.236

2-(3-(Benzyloxy)-2-bromo-4,5-dimethoxyphenyl)ethanamine hydrochloride salt (2.236). (ab04067). Chlorotrimethylsilane (29.0 mL, 24.8 g, 228.9 mmol) was added to a solution of lithium borohydride (2.5 g, 114.0 mmol) in THF (100 mL) at room temperature. The reaction was purged with N_2 for 10 min to remove silane, whereupon 3-(benzyloxy)-2-bromo-4,5-dimethoxy-1-(2-nitrovinyl)benzene (**2.203**) (11.25 g, 28.5 mmol) was added to the mixture. The reaction was heated under reflux for 14 h before being cooled to room temperature. MeOH (ca. 100 mL) was added, and the mixture was concentrated under reduced pressure. NaOH (6 M, ca. 100 mL) and Et_2O (ca. 100 mL) were added to the residue, and the layers were separated. The aqueous layer was extracted with Et_2O (2 x 100 mL), and the organic layers were combined, dried ($MgSO_4$), and concentrated to yield a brown oil. Anhydrous HCl (6 M in EtOH, ca. 100 mL) was

added and after 2 h, the mixture was concentrated. The crude salt was recrystallized from Et_2O/isopropanol (95:5) to yield 7.5 g (65%) of **2.236** as a brown solid; mp 140-142 °C. ^{1}H NMR (600 MHz, CD_3OD) δ 7.52 (d, *J* = 7.3 Hz, 2 H), 7.36 (t, *J* = 7.3 Hz, 2 H), 7.32 (t, *J* = 7.3 Hz, 1 H), 6.88 (s, 1 H), 5.03 (s, 2 H), 3.88 (s, 3 H), 3.83 (s, 3 H), 3.16-3.15 (m, 2 H), 3.11-3.09 (m, 2 H); ^{13}C NMR (150 MHz, CD_3OD) δ 154.7, 151.3, 144.1, 138.4, 132.9, 129.5 (2C), 129.4 (2C), 129.2, 111.8, 111.5, 76.4, 61.5, 56.8, 40.4, 35.2; IR (DCM) 3398, 2939, 1568, 1485, 1370, 1116; HRMS (CI) *m/z* calculated for $C_{17}H_{21}NO_3Br^{79+}$ (M+1), 366.07; found, 366.0708; mass spectrum, 366 (base).

NMR Assignments: ^{1}H NMR (600 MHz, CD_3OD) δ 7.52 (d, *J* = 7.3 Hz, 2 H, C13-H), 7.36 (t, *J* = 7.3 Hz, 2 H, C14-H), 7.32 (t, *J* = 7.3 Hz, 1 H, C15-H), 6.88 (s, 1 H, C6-H), 5.03 (s, 2 H, C11-H), 3.88 (s, 3 H, C9 or C10-H), 3.83 (s, 3 H, C9 or C10-H), 3.16-3.15 (m, 2 H, C8-H), 3.11-3.09 (m, 2 H, C7-H); ^{13}C NMR (150 MHz, CD_3OD) δ 154.7 (C3), 151.3 (C5), 144.1 (C4), 138.4 (C-Ar), 132.9 (C-Ar), 129.5 (2C, C-Ar), 129.4 (2C, C-Ar), 129.2 (C-Ar), 111.8 (C-Ar), 111.5 (C-Ar), 76.4 (C11), 61.5 (C9 or C10), 56.8 (C9 or C10), 40.4 (C8), 35.2 (C7).

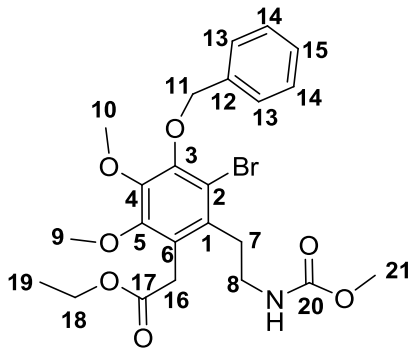


2.237

Ethyl 6-(benzyloxy)-5-bromo-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carboxylate (2.237). (ab04083). A solution of amine hydrochloride salt **2.236** (1.42 g, 3.5 mmol), triethylamine (0.98 mL, 0.71 g, 7.00 mmol), ethyl glyoxylate (0.69 mL, 50% toluene solution, 0.071 g, 3.5 mmol) and 4 Å molecular sieves (ca. 20) in toluene (50 mL) was stirred at room temperature for 3 h. The mixture was then vacuum filtered through a fritted funnel containing a layer of celite, washing with toluene. The combined filtrate and washings were concentrated to provide 1.65 g of the intermediate imine. A solution of toluene/TFA (1% by volume) (60 mL) was added to the imine, and the reaction was heated at 80 °C (oil bath temperature). The reaction was stirred for 1.5 h and then cooled to room temperature. The mixture was concentrated, and 1 M NaOH (ca. 50 mL) and Et_2O (ca. 50 mL) were added. The layers were separated, and the aqueous layer was extracted with Et_2O (4 x 20 mL). The organic layers were combined, dried ($MgSO_4$), and concentrated to provide 1.48 g (94%) of **2.237** as a yellow oil. The product was carried on without further purification. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.4 Hz, 2 H), 7.40 (t, *J* = 7.4 Hz, 2 H), 7.34 (t, *J* = 7.4 Hz, 1 H), 7.26 (s, 1 H), 5.05 (d, *J* = 15.6 Hz, 1 H), 5.03 (d, *J* = 15.6 Hz, 1 H), 4.23 (qd, *J* = 2.1, 7.2 Hz, 2 H), 3.88 (s, 3 H), 3.87 (s, 3 H), 3.15-3.11 (m, 1 H), 3.04-2.99 (m, 1 H), 2.78-2.73 (m, 1 H), 2.71-2.65 (m, 1 H), 1.30 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.8, 150.2, 149.5, 144.7, 137.1, 131.0, 128.5 (2C), 128.4 (2C), 128.2, 124.1, 114.6, 75.2, 61.2, 61.0, 60.4, 55.7, 40.5, 30.0, 14.3; IR (DCM) 1733, 1463, 1410, 1342, 1184, 1092, 1020; HRMS (CI) *m/z* calculated for $C_{21}H_{25}NO_5Br^{79+}$ (M+1), 450.0916; found, 450.0916; mass spectrum, 450 (base).

NMR Assignments: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.4 Hz, 2 H, C13-H), 7.40 (t, *J* = 7.4 Hz, 2 H, C14-H), 7.34 (t, *J* = 7.4 Hz, 1 H, C15-H), 7.26 (s, 1 H, C16-H), 5.05 (d, *J* = 15.6 Hz, 1 H, C11-H), 5.03 (d, *J* = 15.6 Hz, 1 H, C11-H), 4.23 (qd, *J* = 2.1, 7.2 Hz, 2 H, C18-H), 3.88 (s, 3 H, C9 or C10-H), 3.87 (s, 3 H, C9 or C10-H), 3.15-3.11 (m, 1 H, C8-H), 3.04-2.99 (m, 1 H, C8-H), 2.78-2.73 (m, 1 H, C7-H), 2.71-2.65 (m, 1 H, C7-H), 1.30 (t, *J* = 7.2 Hz, 3 H, C19-H); ^{13}C NMR (150 MHz, $CDCl_3$) 172.8 (C17), 150.2 (C3), 149.5 (C5), 144.7 (C4), 137.1 (C-Ar), 131.0 (C-Ar), 128.5 (2C, C13), 128.4 (2C, C14), 128.2 (C-Ar), 124.1 (C-Ar), 114.6 (C-Ar), 75.2 (C11), 61.2 (C9 or C10), 61.0 (C9 or C10), 60.4 (C16 or C18), 55.7 (C16 or C18), 40.5 (C8), 30.0 (C7), 14.3 (C19).

Preparation of Samarium Diiodide (SmI_2, 0.1 M solution in THF) (ab04270). Samarium powder (2.0 g, 13.3 mmol, Acros), which had been crushed with a mortar and pestle under nitrogen prior to use, was added to a 250 mL flame-dried RB flask outfitted with a stir bar, followed by 100 mL of THF. The slurry was deoxygenated via freeze/pump/thaw (x 3), and iodine (2.54 g, 10.0 mmol) was added. The mixture was purged with argon, and the flask was outfitted with a reflux condenser. The reaction was heated under reflux for 20 h and then cooled to room temperature. The 0.1 M solution can be stored under argon and at room temperature for approximately one week.

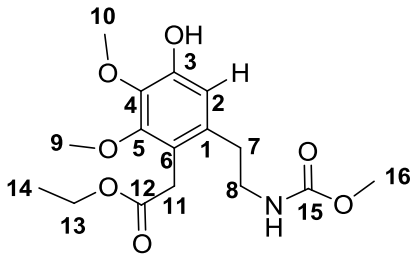


2.241

Ethyl 2-(4-(benzyloxy)-3-bromo-5,6-dimethoxy-2-(2-(methoxycarbonylamino)ethyl)phe-nyl)acetate. (2.241). (ab04110). SmI_2 (24.0 mL, 0.2 M in THF, 4.80 mmol) was added to a deoxygenated (f/p/t x 3) solution of **2.237** (216 mg, 0.48 mmol), HMPA (0.84 mL, 0.87 g, 4.80 mmol), and MeOH (0.19 mL, 0.15 g, 4.80 mmol) in THF (3 mL) at room temperature. The reaction was stirred for 18 h, whereupon $NaHCO_{3(sat)}$ (ca. 5 mL) was added. The solids were removed by vacuum filtration through a fritted funnel containing a layer of celite, washing with H_2O and Et_2O. The layers of the filtrate were separated, and the aqueous layer was extracted with Et_2O (3 x 10 mL). The organic layers were combined and concentrated. The residue was then washed with H_2O (3 x 20 mL) to remove excess HMPA. Et_2O (ca. 10 mL) was added to the residue, and the solution was washed with brine (1 x 10 mL), dried ($MgSO_4$) and concentrated to yield 165 mg of a brown oil. DCM (3 mL) and triethylamine (0.18 mL, 0.14 g, 1.3 mmol) were added to the oil, and the mixture was cooled to 0 °C. Methylchloroformate (0.04 mL, 0.05 g, 0.48 mmol) was added dropwise, and the reaction was stirred for 2 h. $NaHCO_3$(sat) (ca. 5 mL) was added, and the mixture was warmed to room temperature. The layers were separated, and the aqueous layer was extracted with

DCM (3 x 5 mL). The organic layers were combined, dried ($MgSO_4$), and concentrated to yield a yellow oil. The crude mixture was purified by flash chromatography eluting with EtOAc/hexanes (1:1) to provide 66 mg (27% over 2 steps) of **2.241** as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.1 Hz, 2 H), 7.40 (t, *J* = 7.1 Hz, 2 H), 7.34 (t, *J* = 7.1 Hz, 1 H), 5.04 (s, 2 H), 4.95 (br, 1 H), 4.19 (q, *J* = 7.1 Hz, 2 H), 3.89 (s, 3 H), 3.88 (s, 3 H), 3.78, (s, 2 H), 3.67 (s, 3 H), 3.32 (q, *J* = 7.0 Hz, 2 H), 3.03 (t, *J* = 7.0 Hz, 2 H), 1.29 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1, 157.3, 152.2, 149.6, 145.9, 137.2, 133.2, 128.7 (2C), 128.6 (3C), 128.4, 115.9, 75.4, 61.2 (2C), 61.0, 52.3, 40.4, 33.9, 33.4, 14.4; IR (DCM) 3367, 1731, 1526, 1463, 1407, 1327, 1242, 1189, 1107, 1025; HRMS (ESI) *m/z* calculated for $C_{23}H_{29}NO_7Br^{79+}$ (M+1), 510.11219; found, 510.1125; mass spectrum, 510, 532 (M +1+Na) (base).

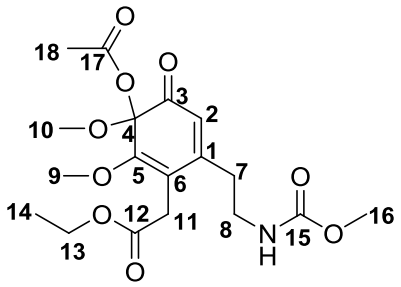
NMR Assignments: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.1 Hz, 2 H, C13-H), 7.40 (t, *J* = 7.1 Hz, 2 H, C14-H), 7.34 (t, *J* = 7.1 Hz, 1 H, C15-H), 5.04 (s, 2 H, C11-H), 4.95 (br, 1 H, NH), 4.19 (q, *J* = 7.1 Hz, 2 H, C18-H), 3.89 (s, 3 H, C9 or C10-H), 3.88 (s, 3 H, C9 or C10-H), 3.78, (s, 2 H, C16-H), 3.67 (s, 3 H, C21-H), 3.32 (q, *J* = 7.0 Hz, 2 H, C8-H), 3.03 (t, *J* = 7.0 Hz, 2 H, C7-H), 1.29 (t, *J* = 7.1 Hz, 3 H, C19-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1 (C17), 157.3 (C20), 152.2 (C3), 149.6 (C5), 145.9 (C4), 137.2 (CAr), 133.2 (CAr), 128.7 (2C, CAr), 128.6 (3C, CAr), 128.4 (CAr), 115.9 (CAr), 75.4 (C11), 61.2 (2C, C9, C10, or C18), 61.0 (C9, C10, or C18), 52.3 (C21), 40.4 (C8 or C16), 33.9 (C8 or C16), 33.4 (C7), 14.4 (C19).



2.242

Ethyl 2-(4-hydroxy-2,3-dimethoxy-6-(2-(methoxycarbonylamino)ethyl)phenyl)acetate (2.242). (ab04113). A solution of benzyl ether **2.241** (67 mg, 0.13 mmol) and Pd/C (10 % by wt, 14 mg) in MeOH (5 mL) was evacuated with a vacuum pump and backfilled with H_2 (balloon) (3x). The reaction was stirred at room temperature for 24 h. The solids were removed by vacuum filtration through a fritted funnel containing a layer of celite, washing with MeOH. The filtrate was concentrated, and H_2O (ca. 10 mL) and DCM (ca. 10 mL) were added. The layers were separated, and the aqueous layer was extracted with DCM (2 x 5 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography eluting with EtOAc/hexanes (1:1) to provide 28 mg (64%) of **2.242** as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.57 (s, 1 H), 5.79 (s, 1 H), 4.93 (br, 1 H), 4.17 (q, J = 7.1 Hz, 2 H), 3.88 (s, 3 H), 3.83 (s, 3 H), 3.66 (br, 3 H), 3.63 (s, 2 H), 3.36 (q, J = 6.6 Hz, 2 H), 2.72 (t, J = 6.6 Hz, 2H), 1.26 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.6, 157.3, 151.6, 148.8, 138.5, 134.1, 119.2, 111.6, 61.1, 60.7, 60.4, 52.3, 41.8, 33.3, 32.0, 14.4; IR (DCM) 3366, 2849, 2362, 1706, 1493, 1461, 1261, 1194, 1025; HRMS (CI) *m/z* calculated for $C_{16}H_{24}NO_7^+$ (M+1), 342.1553; found, 342.1550; mass spectrum, 342 (base).

NMR Assignments: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.57 (s, 1 H, C2-H), 5.79 (s, 1 H, OH), 4.93 (br, 1 H, NH), 4.17 (q, *J* = 7.1 Hz, 2 H, C13-H), 3.88 (s, 3 H, C9 or C10-H), 3.83 (s, 3 H, C9 or C10-H), 3.66 (br, 3 H, C16-H), 3.63 (s, 2 H, C11-H), 3.36 (q, *J* = 6.6 Hz, 2 H, C8-H), 2.72 (t, *J* = 6.6 Hz, C7-H), 1.26 (t, *J* = 7.1 Hz, 3 H, C14-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.6 (C12), 157.3 (C15), 151.6 (C5), 148.8 (CAr), 138.5 (CAr), 134.1 (CAr), 119.2 (CAr), 111.6 (CAr), 61.1 (C9, C10 or C13), 60.7 (C9, C10, or C13), 60.4 (C9, C10, or C13), 52.3 (C16), 41.8 (C8), 33.3 (C7 or C11), 32.0 (C7 or C11), 14.4 (C14).

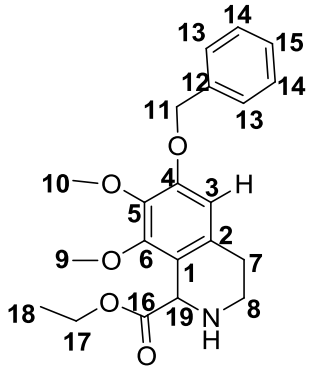


2.244

Ethyl 2-(3-acetoxy-2,3-dimethoxy-6-(2-(methoxycarbonylamino)ethyl)-4-oxocyclohexa-1,5-dienyl)acetate (2.244). (ab04101). Iodobenzene diacetate (39 mg, 0.12 mmol) was added to a solution of phenol **2.242** (40 mg, 0.12 mmol) in hexafluoroisopropanol (5 mL) at 0 °C. The reaction was stirred for 1.5 h, and the solvent was evaporated under reduced pressure. $NaHCO_3$(sat) (ca. 5 mL) and DCM (ca. 5 mL) were added to the residue, and the layers were separated. The aqueous layer was extracted with DCM (3 x 5 mL), and the organic layers were combined, dried ($MgSO_4$), and concentrated to give 17 mg (35%) of **2.244** as a yellow oil. ^{1}H NMR (600 MHz,

$CDCl_3$) δ 5.81 (s, 1 H), 4.94 (br, 1 H), 4.16 (q, *J* = 7.1 Hz, 2 H), 3.89 (s, 3 H), 3.67 (br, 3 H), 3.47 (d, *J* = 16.8 Hz, 1 H), 3.42 (s, 3 H), 3.36 (m, 2 H), 3.26 (d, *J* = 16.8 Hz, 1 H), 2.56 (t, *J* = 6.8 Hz, 2 H), 2.14 (s, 3 H), 1.26 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 189.7, 171.0, 168.8, 156.9, 156.0, 155.7, 119.4, 114.8, 93.7, 61.1, 59.6, 52.2, 50.9, 39.2, 34.4, 31.1, 20.4, 14.2; IR (DCM) 3382, 1730, 1527, 1463, 1275, 1260, 1084, 1026; LRMS (APCI/ESI) *m/z* calculated for $C_{18}H_{25}NO_9^+$ (M+1), 400.39; found, 340.2 (M+1-OAc); mass spectrum, 340 (base).

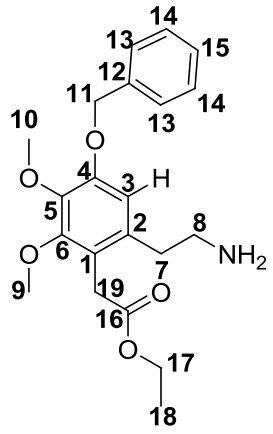
NMR Assignments: ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.81 (s, 1 H, C2-H), 4.94 (br, 1 H, NH), 4.16 (q, *J* = 7.1 Hz, 2 H, C13-H), 3.89 (s, 3 H, C9-H), 3.67 (br, 3 H, C16-H), 3.47 (d, *J* = 16.8 Hz, 1 H, C11-H), 3.42 (s, 3 H, C10-H), 3.36 (m, 2 H, C8-H), 3.26 (d, *J* = 16.8 Hz, 1 H, C11-H), 2.56 (t, *J* = 6.8 Hz, 2 H, C7-H), 2.14 (s, 3 H, C18-H), 1.26 (t, *J* = 7.1 Hz, 3 H, C14-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 189.7 (C3), 171.0 (C12 or C17), 168.8 (C12 or C17), 156.9 (C15), 156.0 (C5 or C7), 155.7 (C5 or C7), 119.4 (C4, C6, or C2), 114.8 (C4, C5, or C2), 93.7 (C4, C5, or C2), 61.1 (C13), 59.6 (C9), 52.2 (C10 or C16), 50.9 (C10 or C16), 39.2 (C7, C8, or C11), 34.4 (C7, C8, or C11), 31.1 (C7, C8, or C11), 20.4 (C18), 14.2 (C14).



2.252

Ethyl 6-(benzyloxy)-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carboxylate (2.252). (ab04257). A deoxygenated (freeze/pump/thaw x 3) mixture of **2.237** (627 mg, 1.32 mmol), $Pd(OAc)_2$ (58 mg, 0.260 mmol), PPh_3 (68 mg, 0.260 mmol), K_2CO_3 (365 mg, 2.64 mmol), and NH_4HCO_2 (416 mg, 6.60 mmol) in EtOH (7 mL) was heated under reflux for 2.5 h, whereupon it as allowed to cool to room temperature. The mixture was then vacuum filtered through a fritted funnel containing a layer of Celite, washing with EtOH (ca. 10 mL). The combined filtrate and washings were collected and concentrated under reduced pressure. Et_2O (ca. 20 mL) and H_2O (ca. 20 mL) were added to the residue, and the layers were separated. The aqueous layer was extracted with Et_2O (2 x 30 mL), and the organic layers were combined, washed (ca. 100 mL brine), dried ($MgSO_4$), and concentrated under reduced pressure. The crude mixture was purified by flash chromatography eluting with MeOH/CH_2Cl_2 (5:95) to provide 250 mg (51%) of **2.252** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-7.30 (comp, 5 H), 6.48 (s, 1 H), 5.09 (s, 2 H), 4.68 (s, 1 H), 4.23 (q, *J* = 6.8 Hz, 2 H), 3.87 (s, 3 H), 3.85 (s, 3 H), 3.06-3.04 (comp, 2 H), 2.78-2.63 (comp, 2 H), 2.07 (br, 1 H), 1.30 (t, *J* = 6.8 Hz, 3 H). LCMS (ESI/APCI) *m/z* calculated for $C_{21}H_{25}NO_5^+$ (M+1), 372; found, 372.

NMR Assignments: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-7.30 (comp, 5 H, H-Ar), 6.48 (s, 1 H, C3-H), 5.09 (s, 2 H, C11-H), 4.68 (s, 1 H, C19-H), 4.23 (q, *J* = 6.8 Hz, 2 H, C17-H), 3.87 (s, 3 H, C9 or C10-H), 3.85 (s, 3 H, C9 or C10-H), 3.06-3.04 (comp, 2 H, C8-H), 2.78-2.63 (comp, 2 H, C7-H), 2.07 (br, 1 H, N-H) 1.30 (t, *J* = 6.8 Hz, 3 H, C18-H).

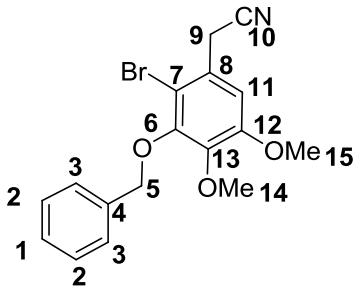


2.238

Ethyl 2-(6-(2-aminoethyl)-4-(benzyloxy)-2,3-dimethoxyphenyl)acetate (2.238). (ab04158). SmI_2 (0.2 M in THF, 13.5 mL, 2.7 mmol) was added to a deoxygenated (freeze/pump/thaw x 3) solution of **2.252** (147 mg, 0.4 mmol), HMPA (0.47 mL, 484 mg, 2.7 mmol), and MeOH (0.10 mL, 79 mg, 2.7 mmol) in THF (1 mL) at room temperature. The reaction was then stirred for 16 h, whereupon Celite, $NaHCO_3$ (sat.) (ca. 2 mL), and Et_2O (ca. 2 mL) were added. The mixture was vacuum filtered through a fritted funnel containing a layer of Celite, washing with H_2O (ca. 5 mL) and Et_2O (ca. 5 mL). The combined filtrate and washings were collected and the layers were separated. The aqueous layer was extracted with Et_2O (3 x 20 mL), and the organic layers were combined, dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was washed with H_2O (in order to remove any remaining HMPA), diluted with Et_2O (ca. 5 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude mixture was purified by flash chromatography eluting with MeOH/CH_2Cl_2 (1:10) to provide 37 mg (25%) of **2.238** as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.5 (d, 2 H), 7.4 (t, 3 H), 6.7 (s, 1 H), 5.2 (s, 2 H), 4.2 (q, 2 H), 3.8 (s, 3 H), 3.8 (s, 3 H), 3.7 (s, 2

H), 3.3 (t, 2 H), 3.1 (t, 2 H), 1.3 (t, 3 H). LCMS (ESI/APCI) *m/z* calculated for $C_{21}H_{27}NO_5^+$ (M+1), 374; found, 374.

NMR Assignments: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.5 (d, 2 H, C13-H), 7.4 (t, 3 H, C14 and C15-H), 6.7 (s, 1 H, C3-H), 5.2 (s, 2 H, C11-H), 4.2 (q, 2 H, C17-H), 3.8 (s, 3 H, C9 or C10-H), 3.8 (s, 3 H, C9 or C10-H), 3.7 (s, 2 H, C19-H), 3.3 (t, 2 H, C8-H), 3.1 (t, 2 H, C7-H), 1.3 (t, 3 H, C18-H).

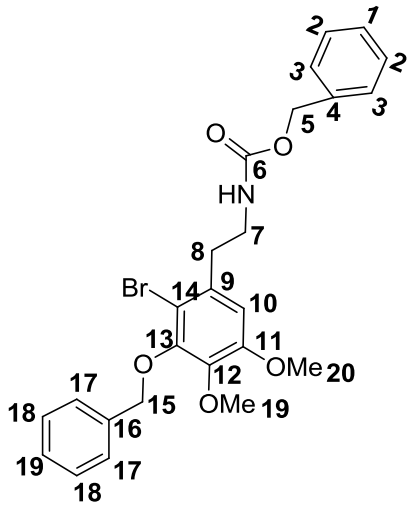


2.269

2-(3-(Benzyloxy)-2-bromo-4,5-dimethoxyphenyl)acetonitrile (2.269). (ab05059). $NaBH_4$ (117.0 mg, 3.1 mmol) was added portionwise to a solution of aldehyde **2.202** (1.0 g, 2.8 mmol) in MeOH (50 mL) at 0 ºC. The reaction was stirred for 1 h, warmed to room temperature, and concentrated under reduced pressure. H_2O (ca. 20 mL) and Et_2O (ca. 20 mL) were added to the residue, and the layers were separated. The aqueous layer was extracted with Et_2O (2 x 20 mL), and then the organic layers were combined, washed (1 x brine), dried ($MgSO_4$), and concentrated under reduced pressure to yield 989 mg of the intermediate alcohol as a white solid. The crude alcohol was dissolved in DCM (30 mL) and the solution was cooled to 0 ºC. Et_3N (0.04 mL, 0.28 mmol) was added, followed by $SOCl_2$ (0.3 mL, 4.2 mmol). The ice bath was removed and the reaction was stirred at room temperature for 3 h. $NaHCO_{3\ (sat.)}$ (ca. 30 mL) was

added and the layers were separated. The aqueous layer was extracted with DCM (2 x 30 mL) and the organic layers were combined, dried ($MgSO_4$) and concentrated under reduced pressure. DMF (30 mL) was added to the residue, followed by NaCN (686 mg, 14.0 mmol). The reaction was stirred at room temperature for 1 h before $NaHCO_{3\ (sat.)}$ (ca. 30 mL) and Et_2O (ca. 30 mL) were added. The layers were separated and the aqueous layer was extracted with Et_2O (2 x 30 mL). The organic layers were combined, washed (3 x H_2O then 1 x brine), dried ($MgSO_4$), and concentrated under reduced pressure to yield a tan oily solid. The crude mixture was purified by flash chromatography eluting with EtOAc/hexanes (1:4) to provide 520 mg (51%) of nitrile **2.269** over 3 steps. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.6 (d, 2 H), 7.5-7.3 (m, 3 H), 6.9 (s, 1 H), 5.1 (s, 2 H), 3.95 (s, 3 H), 3.90 (s, 3 H).

NMR Assignments: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.6 (d, 2 H, Ar-H), 7.5-7.3 (m, 3 H, Ar-H), 6.9 (s, 1 H, C11-H), 5.1 (s, 2 H, C9-H), 3.95 (s, 3 H, C14 or C15-H), 3.90 (s, 3 H, C14 or C15-H).

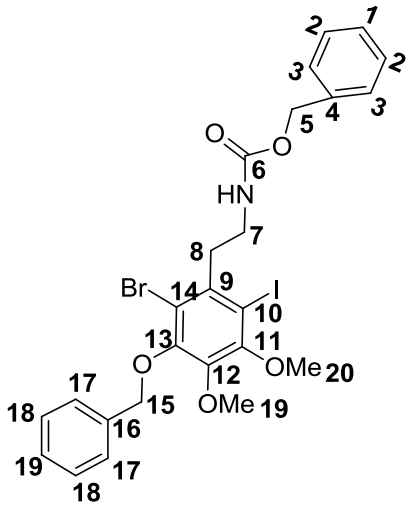


2.277

Benzyl 3-(benzyloxy)-2-bromo-4,5-dimethoxyphenethylcarbamate (2.277). (ab05109). CbzCl (0.12 mL, 0.87 mmol), was added to a solution of amine salt **2.236** (233 mg, 0.58 mmol) and Et_3N (0.16 mL, 1.16 mmol) in DCM (20 mL) at 0 ºC. The reaction was stirred for 2.75 h, whereupon $NaHCO_{3\ (sat.)}$ (ca. 30 mL) was added. The layers were separated, and the aqueous layer was extracted with DCM (2 x 20 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated under reduced pressure to yield a light yellow oil. The crude mixture was purified by column chromatography eluting with EtOAc/hexanes (1:4) to provide 166 mg (57%) of carbamate **2.277** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.6 (d, 2 H), 7.4-7.2 (comp, 8 H), 6.6 (s, 1 H), 5.2 (s, 2 H), 5.0 (s, 2 H), 4.8 (br, 1 H), 3.9 (s, 3 H), 3.8 (s, 3 H), 3.4-3.5 (m, 2 H), 3.0-2.9 (m, 2 H); LCMS (ESI/APCI) *m/z* calculated for $C_{25}H_{26}BrNO_5^{+79}$ (M+1), 500; found, 500; mass spectrum, 502 (M^{+81}+1).

NMR Assignments: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.6 (d, 2 H), 7.4-7.2 (comp, 8 H, Ar-H), 6.6 (s, 1 H, C10-H), 5.2 (s, 2 H, C5 or C15-H), 5.0 (s, 2 H, C5 or C15-H), 4.8

(br, 1 H, N-H), 3.9 (s, 3 H, C19 or C20-H), 3.8 (s, 3 H, C19 or C20-H), 3.4-3.5 (m, 2 H, C8-H), 3.0-2.9 (m, 2 H, C7-H).

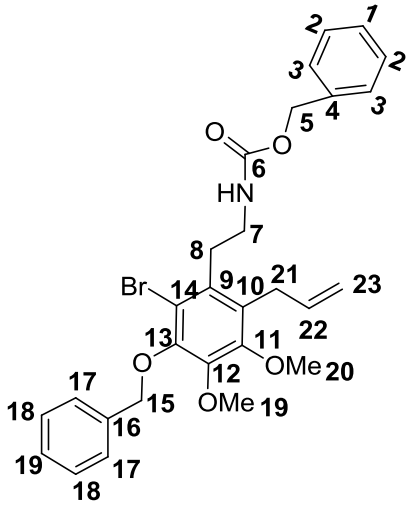


2.278

Benzyl 3-(benzyloxy)-2-bromo-6-iodo-4,5-dimethoxyphenethylcarbamate (2.278). (ab05118). A round bottom flask containing a stirbar and AgOTf (33 mg, 0.15 mmol) was flame dried under vacuum. The flask was then cooled to 0 ºC and a solution of carbamate **2.277** (73 mg, 0.15 mmol, azeotroped 3x with benzene) in DCM (4 mL), and neat iodine (38 mg, 0.15 mmol) were added. The reaction was stirred for 1 h before being warmed to room temperature and vacuum filtered through a coarse fritted funnel containing a layer of celite. The residue and celite were washed with DCM (ca. 10 mL) and then the filtrate and washings were collected and concentrated under reduced pressure to yield a white solid. The crude mixture was purified by column chromatography eluting with EtOAc/hexanes (1:4) to provide 52 mg (55%) of aryl iodide **2.278** as well as 10 mg (14%) of RSM **2.277**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, 2

H), 7.41-7.33 (m, 8 H), 5.11 (s, 2 H), 5.04 (2, 2 H), 4.90 (br, 1 H), 3.89 (s, 3 H), 3.88 (s, 3 H), 3.48-3.40 (m, 2 H), 3.37-3.33 (m, 2 H); LCMS (ESI/APCI) *m/z* calculated for $C_{25}H_{25}BrINO_5{}^{+79}$(M+1), 626; found, 636.

NMR Assignments: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, 2 H, Ar-H 7.41-7.33 (m, 8 H, Ar-H), 5.11 (s, 2 H, C7 or C15-H), 5.04 (2, 2 H, C7 or C15-H), 4.90 (br, 1 H, N-H), 3.89 (s, 3 H, C19 or C20-H), 3.88 (s, 3 H, C19 or C20-H), 3.48-3.40 (m, 2 H, C8-H), 3.37-3.33 (m, 2 H, C7-H).

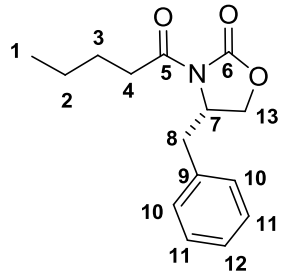


2.280

Benzyl 2-allyl-5-(benzyloxy)-6-bromo-3,4-dimethoxyphenethylcarbamate (2.280). (ab05125). A slurry of aryl iodide **2.278** (29 mg, 0.046 mmol), allyltributylstannane (13 uL, 0.041 mmol), and $Pd(PPh_3)Cl_2$ (6.0 mg) in DMF (0.5 mL) was deoxygenated *via* freeze/pump/thaw 3x. The reaction was then stirred under reflux for 1.5 h. The mixture was cooled to room temperature and vacuum filtered through a

fritted funnel containing a layer of celite. The residue and celite were washed with Et_2O (ca. 10 mL), and the filtrate and washings were transferred to a separatory funnel where they were washed with (3 x ca. 10 mL H_2O). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude mixture was purified by column chromatography eluting with EtOAc/hexanes (1:9) to yield the desired product **2.280** contaminated with a tin byproduct. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.6 (d, 2 H), 7.5-7.3 (comp, 8 H), 6.0-5.9 (m, 1 H), 5.2-4.8 (comp, 6 H), 3.9 (s, 3 H), 3.8 (s, 3 H), 3.5-3.4 (m, 2 H), 3.4-3.3 (m, 2 H), 3.0 (t, 2 H); LRMS (ESI/APCI) *m/z* calculated for $C_{28}H_{30}BrNO_5^{+79}$ (M+1), 540; found, 540; mass spectrum, 542 (M^{+81}+1).

NMR Assignments: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.6 (d, 2 H, Ar-H), 7.5-7.3 (comp, 8 H, Ar-H), 6.0-5.9 (m, 1 H, C22-H), 5.2-4.8 (comp, 6 H, C7, C15, C23-H), 3.9 (s, 3 H, C19-H), 3.8 (s, 3 H, C20-H), 3.5-3.4 (m, 2 H, 21-H), 3.4-3.3 (m, 2 H, C7 or C8-H), 3.0 (t, 2 H, C7 or C8-H).

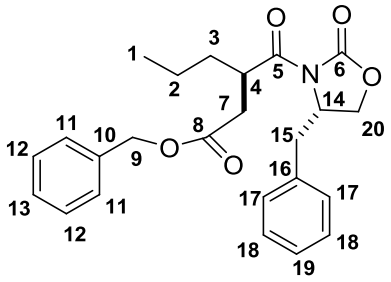


3.70

(*S*)-4-Benzyl-3-pentanoyloxazolidin-2-one (3.70). (JT-03-180). Pivaloyl chloride (816 mg, 834 μL, 6.77 mmol) was added to a solution of valeric acid (576 mg, 903 μL, 5.64 mmol) and Et_3N (1.14 g, 1.57 mL, 11.3 mmol) in THF (10 mL) at -15 ºC. After stirring at this temperature for 2 h, LiCl (287 mg, 6.77 mmol) was added. A

solution of auxiliary **3.69** (1.29 g, 6.77 mmol) in THF (15 mL) was then added dropwise, the cooling bath was removed, and the reaction mixture was stirred at room temperature for 3.5 h. EtOAc (50 mL) was added to the reaction mixture, and the mixture was washed with saturated $NaHCO_3$ (3 x 15 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (15 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with hexane/EtOAc (5/1) to give 1.15 g (78%) of **3.70** as colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.32 (comp, 2 H), 7.30-7.27 (m, 1 H), 7.23-7.21 (comp, 2 H), 4.71-4.65 (m, 1 H), 4.23-4.15 (comp, 2 H), 3.30 (dd, *J* = 3.2, 13.6 Hz, 1 H), 3.03-2.89 (comp, 2 H), 2.77 (dd, *J* = 9.6, 13.6 Hz, 1 H), 1.73-1.63 (comp, 2 H), 1.42 (hex, *J* = 7.2 Hz, 2 H), 0.96 (t, *J* = 7.2, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 173.7, 153.7, 135.6, 129.7, 129.2, 127.6, 66.4, 55.4, 38.1, 35.5, 26.6, 22.5, 14.1; IR (DCM) 3385, 1778, 1697, 1385, 1352, 1197; HRMS (CI) *m/z* calcd for $C_{15}H_{20}NO_3^+$ (M + 1), 262.1443; found, 262.1438.

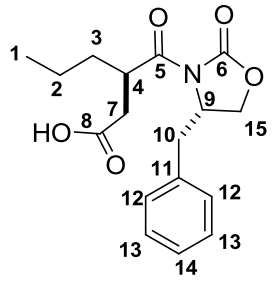
NMR Assignment. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.32 (comp, 2 H, C11-H), 7.30-7.27 (m, 1 H, C12-H), 7.23-7.21 (comp, 2 H, C10-H), 4.71-4.65 (m, 1 H, C7-H), 4.23-4.15 (comp, 2 H, C13-H), 3.30 (dd, *J* = 3.2, 13.6 Hz, 1 H, C8-H), 3.03-2.89 (comp, 2 H, C4-H), 2.77 (dd, *J* = 9.6, 13.6 Hz, 1 H, C8-H), 1.73-1.63 (comp, 2 H, C3-H), 1.42 (hex, *J* = 7.2 Hz, 2 H, C2-H), 0.96 (t, *J* = 7.2, 3 H, C1-H); ^{13}C NMR (100 MHz, $CDCl_3$) 173.7 (C5), 153.7 (C6), 135.6 (C9), 129.7 (C11), 129.2 (C10), 127.6 (C12), 66.4 (C13), 55.4 (C7), 38.1 (C8), 35.5 (C4), 26.6 (C3), 22.5 (C2), 14.1 (C1).



3.72

Benzyl 3-((*S*)-4-benzyl-2-oxooxazolidine-3-carbonyl)hexanoate (3.72). (JT-03-192). NaHMDS (1.78 M, 191 μL, 0.34 mmol) was added to a solution of **3.70** (68.3 mg, 0.26 mmol) in THF (3 mL) at -78 °C. The solution was stirred for 1 h, and a solution of benzyl 2-bromoacetate (**3.71**) (83 mg, 0.36 mmol) in THF (1.5 mL) was added. The resulting solution was stirred at -78 °C for 2 h and quenched with saturated NH_4Cl (2 mL). The mixture was extracted with EtOAc (3 X 10 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by flash chromatography, eluting with hexane/EtOAc (9/1 to 7/1) to give 523 mg (70%) of **3.72** as colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.21 (comp, 10 H), 5.11 (s, 2 H), 4.65-4.61 (m, 1 H), 4.30-4.26 (m, 1 H), 4.18-4.09 (m, 2 H), 3.24 (dd, *J* = 2.8, 13.6 Hz, 1 H), 2.98 (dd, *J* = 11.2, 17.2 Hz, 1 H), 2.62 (dd, *J* = 4.4, 17.2 Hz, 1 H), 2.48 (dd, *J* = 10.4, 13.6 Hz, 1 H), 1.71-1.62 (m, 1 H), 1.52-1.32 (comp, 3 H), 0.92 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 172.2, 153.3, 136.0, 136.0, 129.7, 129.1, 128.8, 128.6, 128.5, 127.4, 66.8, 66.1, 55.8, 39.2, 37.5, 36.1, 34.5, 20.3, 14.2; IR (DCM) 3450, 1781, 1734, 1697, 1387, 1350, 1174; HRMS (CI) *m/z* calcd for $C_{24}H_{28}NO_5^+$ (M + 1), 410.1967; found, 410.1942.

NMR Assignment. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.21 (comp, 10 H, C11-H & C12-H & C13-H & C17-H & C18-H & C19-H), 5.11 (s, 2 H, C9-H), 4.65-4.61 (m, 1 H, C14-H), 4.30-4.26 (m, 1 H, C4-H), 4.18-4.09 (m, 2 H, C20-H), 3.24 (dd, *J* = 2.8, 13.6 Hz, 1 H, C15-H), 2.98 (dd, *J* = 11.2, 17.2 Hz, 1 H, C7-H), 2.62 (dd, *J* = 4.4, 17.2 Hz, 1 H, C7-H), 2.48 (dd, *J* = 10.4, 13.6 Hz, 1 H, C15-H), 1.71-1.62 (m, 1 H, C3-H), 1.52-1.32 (comp, 3 H, C3-H & C2-H), 0.92 (t, *J* = 7.2 Hz, 3 H, C1-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0 (C8), 172.2 (C5), 153.3 (C6), 136.0 (C10 & C16), 129.7 (C18), 129.1 (C17), 128.8 (C12), 128.6 (C11), 128.5 (C13), 127.4 (C19), 66.8 (C9), 66.1 (C20), 55.8 (C14), 39.2 (C4), 37.5 (C15), 36.1 (C7), 34.5 (C3), 20.3 (C2), 14.2 (C1).

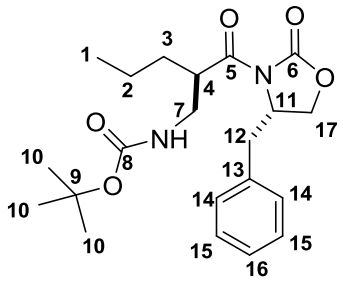


3.73

(*R*)-3-((*S*)-4-Benzyl-2-oxooxazolidine-3-carbonyl)hexanoic acid (3.73). (JT-03-194). A mixture of **3.72** (523 mg, 1.28 mmol) and Pd/C (109 mg, 0.102 mmol) in EtOH (10 mL) was stirred under 1 atm of H_2 at room temperature for 2 h. The mixture was filtered through a celite plug, which was washed with EtOH (8 mL). The combined filtrate and washings were concentrated under reduced pressure to give 406 mg (99%) of **3.73** as colorless oil. The product was sufficiently pure by ^{1}H NMR to carry on without further purification; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.24 (comp, 5 H), 4.69-4.65 (m,

1 H), 4.23-4.16 (comp, 3 H), 3.28 (dd, *J* = 3.2, 13.6 Hz, 1 H), 2.95 (dd, *J* = 10.8, 17.6 Hz, 1 H), 2.75 (dd, *J* = 10.0, 13.6 Hz, 1 H), 2.59 (dd, *J* = 4.0, 17.6 Hz, 1 H), 1.68-1.61 (m, 1 H), 1.51-1.32 (comp, 3 H), 0.92 (t, *J* = 7.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0, 175.9, 153.3, 135.7, 129.8, 129.2, 127.5, 66.2, 55.8, 39.1, 37.6, 35.4, 34.3, 20.3, 14.2; IR (DCM) 3422, 2361, 1780, 1699, 1390, 1213, 1195; HRMS (CI) *m/z* calcd for $C_{17}H_{22}NO_5^+$ (M + 1), 320.1498; found, 320.1496.

NMR Assignment. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.24 (comp, 5 H, C12-H & C13-H & C14-H), 4.69-4.65 (m, 1 H, C9-H), 4.23-4.16 (comp, 3 H, C4-H & C15-H), 3.28 (dd, *J* = 3.2, 13.6 Hz, 1 H, C10-H), 2.95 (dd, *J* = 10.8, 17.6 Hz, 1 H, C7-H), 2.75 (dd, *J* = 10.0, 13.6 Hz, 1 H, C10-H), 2.59 (dd, *J* = 4.0, 17.6 Hz, 1 H, C7-H), 1.68-1.61 (m, 1 H, C3-H), 1.51-1.32 (comp, 3 H, C2-H & C3-H), 0.92 (t, *J* = 7.6 Hz, 3 H, C1-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0 (C8), 175.9 (C5), 153.3 (C6), 135.7 (C11), 129.8 (C13), 129.2 (C12), 127.5 (C14), 66.2 (C15), 55.8 (C9), 39.1 (C10), 37.6 (C4), 35.4 (C7), 34.3 (C3), 20.3 (C2), 14.2 (C1).



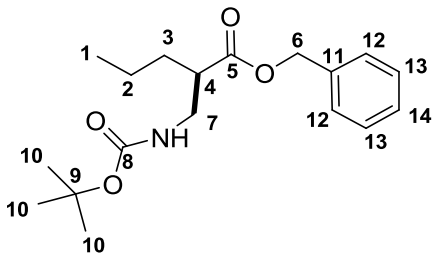
3.74

***tert*-Butyl (*R*)-2-((*S*)-4-benzyl-2-oxooxazolidine-3-carbonyl)pentylcarbamate 3.74. (ab05249).** Ethyl chloroformate (250 mg, 0.22 mL, 2.3 mmol) was added to a

solution of acid **3.73** (670 mg, 2.1 mmol) and Et_3N (254 mg, 0.35 mL, 2.5 mmol) in acetone (15 mL) at 0 ºC. The reaction was stirred for 2 h, and a solution of NaN_3 (345 mg, 5.3 mmol) in H_2O (15 mL) was added. The reaction was stirred for 2 h and then concentrated in a cold rotovap (0 ºC) bath to remove the acetone. Benzene (ca. 15 mL) was added to the mixture, and the layers were separated. The aqueous layer was extracted with benzene (2 x 10 mL), and the organic layers were combined, dried ($MgSO_4$), and concentrated *in vacuo*. Toluene (ca. 80 mL) was added to the residue, and the solution was stored in the freezer overnight. The solution was then heated under reflux, and the toluene was removed by distillation until only about 5 mL remained. *t*-BuOH (5 mL) was added to the solution, and the mixture was heated at 80 ºC for 17 h before being cooled to room temperature and concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with hexane/EtOAc (4/1) to give 471 mg (57%) of **3.74** as colorless oil; ^{1}H NMR (500 MHz, DMSO, 130 °C) δ 7.31 (t, *J* = 7.6 Hz, 2 H), 7.24 (t, *J* = 6.9 Hz, 3 H), 6.08 (br, 1 H), 4.70 (hep, *J* = 3.4 Hz, 1 H), 4.33 (t, *J* = 8.5 Hz, 1 H), 4.14 (dd, *J* = 3.4, 8.5 Hz, 1 H), 3.90 (q, *J* = 6.4 Hz, 1 H), 3.32-3.23 (comp, 2 H), 3.17 (dd, *J* = 3.4, 13.9 Hz, 1 H), 2.89 (dd, *J* = 8.5, 13.9 Hz, 1 H), 1.62 (hex, *J* = 7.3 Hz, 1 H), 1.50-1.40 (comp, 10 H), 1.37-1.28 (comp, 2 H), 0.88 (t, *J* = 7.3 Hz, 3 H); ^{13}C NMR (125 MHz, DMSO, 130 °C) δ 173.9, 154.8, 152.3, 135.4, 128.6, 128.6, 127.7, 127.7, 126.0, 77.2, 65.5, 54.1, 42.4, 41.4, 36.7, 31.0, 27.6, 27.6, 27.6, 18.7, 12.9; IR (DCM) 3405, 2264, 1779, 1697, 1505, 1390, 1259, 1211, 1171; HRMS (CI) *m/z* calcd for $C_{21}H_{31}N_2O_5^+$ (M + 1), 391.2233; found, 391.2237.

NMR Assignment. ^{1}H NMR (500 MHz, DMSO, 130 °C) δ 7.31 (t, *J* = 7.6 Hz, 2 H, C14-H), 7.24 (t, *J* = 6.9 Hz, 3 H, C15 and C16-H), 6.08 (br, 1 H, N-H), 4.70 (hep, *J* =

3.4 Hz, 1 H, C11-H), 4.33 (t, *J* = 8.5 Hz, 1 H, C17-H), 4.14 (dd, *J* = 3.4, 8.5 Hz, 1 H, C17-H), 3.90 (q, *J* = 6.4 Hz, 1 H, C4-H), 3.32-3.23 (comp, 2 H, C7-H), 3.17 (dd, *J* = 3.4, 13.9 Hz, 1 H, C12-H), 2.89 (dd, *J* = 8.5, 13.9 Hz, 1 H, C12-H), 1.62 (hex, *J* = 7.3 Hz, 1H, C3-H), 1.50-1.40 (comp, 10 H, C3-H and C10-H), 1.37-1.28 (comp, 2 H, C2-H), 0.88 (t, *J* = 7.3 Hz, 3 H, C1-H); ^{13}C NMR (125 MHz, DMSO, 130 °C) δ 173.9 (C5), 154.8 (C6 or C8), 152.3 (C6 or C8), 135.4 (C13), 128.6 (C14), 128.6 (C14), 127.7 (C15), 127.7 (C15), 126.0 (C16), 77.2 (C9), 65.5 (C17), 54.1 (C11), 42.4 (C7, C4 or C12), 41.4 (C7, C4 or C12), 36.7 (C7, C4, or C12), 31.0 (C3), 27.6 (C10), 27.6 (C10), 27.6 (C10), 18.7 (C2), 12.9 (C1).

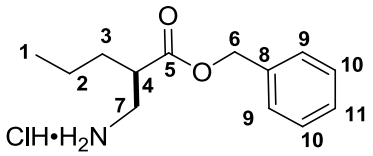


3.75

(*R*)-Benzyl 2-((tert-butoxycarbonylamino)methyl)pentanoate 3.75. (ab05207). *n*-BuLi (0.51 mL, 2.1 M in hexanes, 1.08 mmol) was added to solution of BnOH (157 mg, 0.15 mL, 1.44 mmol) in THF (5 mL) at -15 to -20 ºC. The reaction was stirred for 2 h, whereupon a solution of amide **3.74** (280 mg, 0.72 mmol) in THF (14 mL) was added dropwise. After stirring the mixture for 4 h, H_2O (5 mL) was added, and the reaction was warmed to room temperature. The layers were separated, and the aqueous layer was extracted with Et_2O (2 x 10 mL). The organic layers were combined, dried ($MgSO_4$), and concentrated *in vacuo*. The crude product was purified by flash

chromatography eluting with hexane/EtOAc (4/1) to give 161 mg (70%) of **3.75** as colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.27 (comp, 5 H), 5.14 (s, 2 H), 4.88 (br, 1 H), 3.39-3.21 (comp, 2 H), 2.68-2.61 (m, 1 H), 1.66-1.19 (comp, 13 H), 0.89 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 155.8, 135.9, 128.6, 128.6, 128.2, 128.2, 128.1, 79.3, 66.3, 45.5, 41.6, 31.9, 28.3, 28.3, 28.3, 20.3, 13.9; IR (DCM) 3383, 2506, 1715, 1504, 1455, 1366, 1252, 1170; HRMS (CI) *m/z* calcd for $C_{18}H_{28}NO_4^+$ (M + 1), 322.2018; found, 322.2010.

NMR Assignments: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.27 (comp, 5 H, C12, C13, and C14-H), 5.14 (s, 2 H, C6-H), 4.88 (br, 1 H, N-H), 3.39-3.21 (comp, 2 H, C7-H), 2.68-2.61 (m, 1 H, C4-H), 1.66-1.19 (comp, 13 H, C3, C2, C10-H), 0.89 (t, *J* = 7.2 Hz, 3 H, C1-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3 (C5), 155.8 (C8), 135.9 (C11), 128.6 (C12), 128.6 (C12), 128.2 (C13), 128.2 (C13), 128.1 (C14), 79.3 (C9), 66.3 (C6), 45.5 (C7 or C4), 41.6 (C7 or C4), 31.9 (C3), 28.3 (C10), 28.3 (C10), 28.3 (C10), 20.3 (C2), 13.9 (C1).

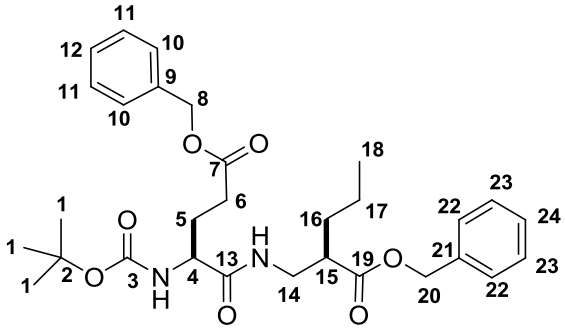


3.76

(*R*)-Benzyl 2-(aminomethyl)pentanoate hydrochloride salt 3.76. (ab05208). A solution of HCl in dioxane (5 mL, ca. 4 M) was added to a round-bottom flask containing amide **3.75** (161 mg. 0.50 mmol) at room temperature. The reaction was stirred for 21 h, and the solvents were removed *in vacuo*. The crude product was washed

with cold hexanes to yield 128 mg (quant.) of **3.76** as a viscous oil; ^{1}H NMR (400 MHz, CD_3OD) δ 7.40-7.32 (comp, 5 H), 5.20 (dd, *J* = 12.0, 35.6 Hz, 2 H), 3.22 (dd, *J* = 9.0, 13.0 Hz, 1 H), 3.06 (dd, *J* = 4.4, 13.0 Hz, 1 H), 2.86-2.79 (m, 1 H), 1.70-1.54 (comp, 2 H), 1.37-1.25 (comp, 2 H), 0.90 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR (100 MHz, CD_3OD) δ 173.0, 135.7, 128.2, 128.2, 128.2, 128.2, 128.1, 66.7, 42.6, 39.9, 31.7, 19.4, 12.7; IR (DCM) 3435, 2528, 2079, 1642, 1455; HRMS (ESI) *m/z* calcd for $C_{13}H_{20}NO_2^+$ (M+1), 222.14886; found, 222.14862.

NMR Assignments: ^{1}H NMR (400 MHz, CD_3OD) δ 7.40-7.32 (comp, 5 H, C9, C10, and C11 H)), 5.20 (dd, *J* = 12.0, 35.6 Hz, 2 H, C6-H), 3.22 (dd, *J* = 9.0, 13.0 Hz, 1 H, C7-H), 3.06 (dd, *J* = 4.4, 13.0 Hz, 1 H, C7-H), 2.86-2.79 (m, 1 H, C4-H), 1.70-1.54 (comp, 2 H, C3-H), 1.37-1.25 (comp, 2 H, C2-H), 0.90 (t, *J* = 7.4 Hz, 3 H, C1-H); ^{13}C NMR (100 MHz, CD_3OD) δ 173.0 (C5), 135.7 (C8), 128.2 (C9), 128.2 (C9), 128.2 (C10), 128.2 (C10), 128.1 (C11), 66.7 (C6), 42.6 (C7), 39.9 (C4), 31.7 (C3), 19.4 (C2), 12.7 (C1).



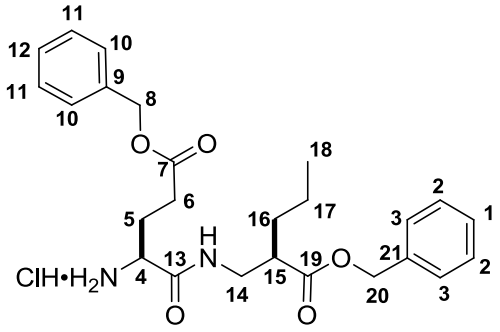
3.77

(*S*)-Benzyl 5-((*R*)-2-(benzyloxycarbonyl)pentylamino)-4-(*tert*-butoxycarbonylamino)-5-oxopentanoate 3.77. (ab05211). NMM (166 mg, 0.18 mL, 1.62 mmol) was added to a solution of the HCl salt **3.76** (140 mg, 0.54 mmol), protected

glutamic acid NHBoc-E(OBn)-OH (183 mg, 0.54 mmol), EDCI·HCl (114 mg, 0.59 mmol), and HOBt (146 mg, 1.08 mmol) in DMF (10 mL) at room temperature, and the reaction was stirred for 16 h. $NaHCO_{3(sat.)}$ (40 mL) and Et_2O (20 mL) were then added. The layers were separated, and the aqueous layer was extracted with Et_2O (2 x 20 mL). The organic layers were combined, washed with H_2O (4 x 80 mL) and $NaCl_{(sat)}$ (1 x 100 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The crude product was purified by flash chromatography eluting with hexane/EtOAc (1/2) to give 175 mg (60%) of **3.77** as colorless oil; ^{1}H NMR (400 MHz, CD_3OD) δ 7.35-7.28 (comp, 10 H), 5.15-5.03 (comp, 4 H), 4.02 (dd, *J* = 5.6, 8.8 Hz, 1 H), 3.41 (dd, *J* = 5.8, 13.4 Hz, 1 H), 3.33-3.27 (comp, 1 H), 2.73-2.66 (m, 1 H), 2.41 (t, *J* = 7.6 Hz, 2 H), 2.04-1.96 (m, 1 H), 1.87-1.77 (m, 1 H), 1.60-1.42 (comp, 11 H), 1.32-1.23 (m, 2 H), 0.86 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, CD_3OD) δ 174.5, 173.2, 172.8, 156.3, 136.1, 136.1, 128.1, 128.1, 128.1, 128.1, 128.1, 128.1, 128.1, 128.1, 128.0, 127.8, 79.3, 66.0, 66.0, 53.8, 44.9, 40.6, 31.65, 29.9, 27.3, 27.3, 27.3, 27.2, 19.8, 12.8; IR (DCM) 3435, 2090, 1646, 1168; HRMS (ESI) *m/z* calcd for $C_{30}H_{40}N_2NaO_7^+$ (M+22), 563.27277; found, 563.27328.

NMR Assignments: ^{1}H NMR (400 MHz, CD_3OD) δ 7.35-7.28 (comp, 10 H, CAr-H), 5.15-5.03 (comp, 4 H, C8 and C20-H), 4.02 (dd, *J* = 5.6, 8.8 Hz, 1 H, C4-H), 3.41 (dd, *J* = 5.8, 13.4 Hz, 1 H, C14-H), 3.33-3.27 (comp, 1 H, C14-H), 2.73-2.66 (m, 1 H, C15-H), 2.41 (t, *J* = 7.6 Hz, 2 H, C6-H), 2.04-1.96 (m, 1 H, C5-H), 1.87-1.77 (m, 1 H, C5-H), 1.60-1.42 (comp, 11 H, C1 and C16), 1.32-1.23 (m, 2 H, C17-H), 0.86 (t, *J* = 7.2 Hz, 3H, C18-H); ^{13}C NMR (100 MHz, CD_3OD) δ 174.5 (C7 or C19), 173.2 (C7 or C19), 172.8 (C13), 156.3 (C3), 136.1 (C9), 136.1 (C21), 128.1 (CAr), 128.1 (CAr), 128.1 (CAr), 128.1 (CAr), 128.1 (CAr), 128.1 (CAr), 128.1 (CAr), 128.0 (C24 or

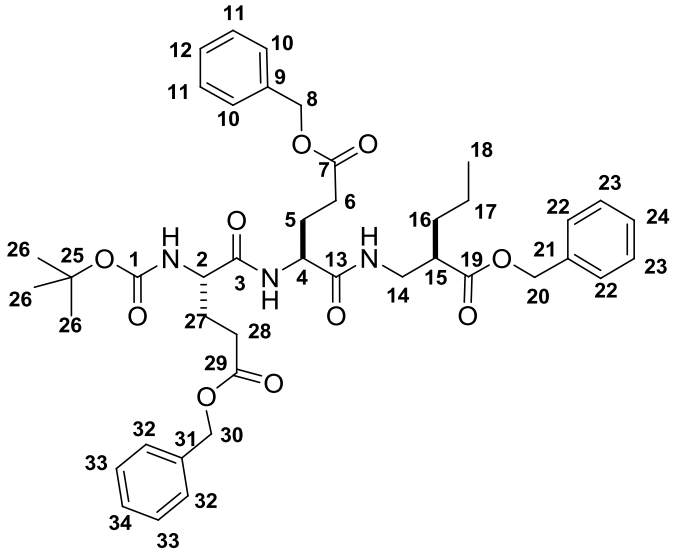
C12), 127.8 (C24 or C12), 79.3 (C2), 66.0 (C20 or C8), 66.0 (C20 or C8), 53.8 (C4), 44.9 (C15), 40.6 (C14), 31.7 (C6), 29.9 (C5), 27.3 (C1), 27.3 (C1), 27.3 (C1), 27.2 (C16), 19.8 (C17), 12.8 (C18).



3.78

(*S*)-Benzyl 4-amino-5-((*R*)-2-(benzyloxycarbonyl)pentylamino)-5-oxopentanoate hydrochloride salt 3.78. (ab05213). A solution of HCl in dioxane (5 mL, ca. 4 M) was added to a round-bottom flask containing amide **3.77** (175 mg. 0.32 mmol) at room temperature. The reaction was stirred for 16 h, and the solvents were then removed *in vacuo*. The crude product was washed with cold hexanes to yield 151 mg (100%) of **3.78** as a viscous oil; ^{1}H NMR (400 MHz, CD_3OD) δ 7.36-7.26 (comp, 10 H), 5.14-5.02 (comp, 4 H), 3.92 (t, *J* = 6.4 Hz, 1 H), 3.54 (dd, *J* = 5.2, 13.6 Hz, 1 H), 3.31-3.24 (m, 1 H), 2.76-2.69 (m, 1 H), 2.56-2.46 (m, 2 H), 2.14-2.08 (m, 2 H), 1.63-1.59 (m, 1 H), 1.51-1.42 (m, 1 H), 1.31-1.21 (m, 2 H), 0.86 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, CD_3OD) δ 174.3, 172.0, 168.4, 136.0, 135.9, 128.2, 128.2, 128.2, 128.2, 128.2, 128.2, 128.2, 128.2, 128.0, 128.0, 66.3, 66.1, 52.1, 44.8, 40.9, 31.7, 28.8, 26.2, 19.8, 12.8; IR (DCM) 3415, 2360, 2341, 1732, 1683, 1276, 1261; HRMS (ESI) *m/z* calcd for $C_{25}H_{32}N_2NaO_5^+$ (M+22), 463.22034; found, 463.22062.

NMR Assignments: ^{1}H NMR (400 MHz, CD_3OD) δ 7.36-7.26 (comp, 10 H, CAr-H), 5.14-5.02 (comp, 4 H, C8 and C20-H), 3.92 (t, *J* = 6.4 Hz, 1 H, C4-H), 3.54 (dd, *J* = 5.2, 13.6 Hz, 1 H, C14-H), 3.31-3.24 (m, 1 H, C14-H), 2.76-2.69 (m, 1 H, C15-H), 2.56-2.46 (m, 2 H, C6-H), 2.14-2.08 (m, 2 H, C5-H), 1.63-1.59 (m, 1 H, C16-H), 1.51-1.42 (m, 1 H, C16-H), 1.31-1.21 (m, 2 H, C17-H), 0.86 (t, *J* = 7.2 Hz, 3 H, C18-H); ^{13}C NMR (100 MHz, CD_3OD) δ 174.3 (C7 or C19), 172.0 (C7 or C19), 168.4 (C13), 136.0 (C21 or C9), 135.9 (C21 or C9), 128.2 (CAr), 128.2 (CAr), 128.2 (CAr), 128.2 (CAr), 128.2 (CAr), 128.2 (CAr), 128.2 (CAr), 128.2 (CAr), 128.0 (C1 or C12), 128.0 (C1 or C12), 66.3 (C8 or C20), 66.1 (C8 or C20), 52.1 (C4), 44.8 (C15), 40.9 (C14), 31.7 (C6), 28.8 (C5), 26.2 (C16), 19.8 (C17), 12.8 (C18).



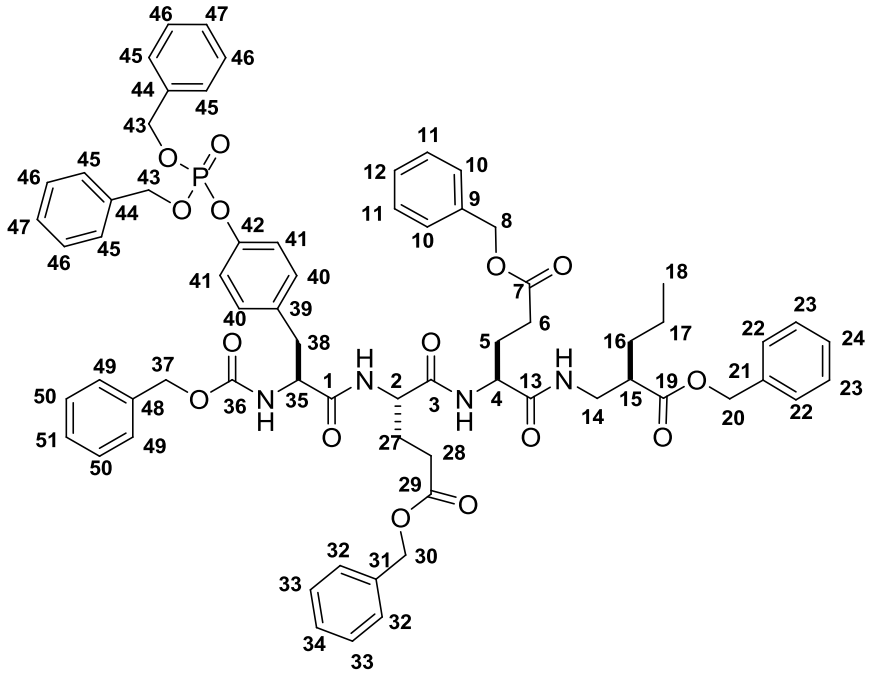
3.79

(6*S*, 9*S*, 13*R*)-Benzyl 6,9-bis(3-(benzyloxy)-3-oxopropyl)-2,2-dimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazahexadecane-13-carboxylate 3.79. (ab05215). NMM (55

mg, 0.06 mL, 0.50 mmol) was added to a solution of the HCl salt **3.78** (80 mg, 0.17 mmol), protected glutamic acid NHBoc-E(OBn)-OH (57 mg, 0.17 mmol), EDCI·HCl (35 mg, 0.19 mmol), and HOBt (45 mg, 0.34 mmol) in DMF (5 mL) at room temperature, and the reaction was stirred for 16 h. $NaHCO_{3(sat.)}$ (20 mL) and Et_2O (10 mL) were then added. The layers were separated, and the aqueous layer was extracted with Et_2O (2 x 20 mL). The organic layers were combined, washed with H_2O (4 x 40 mL) and $NaCl_{(sat.)}$ (1 x 50 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The crude product was purified by flash chromatography eluting with hexane/EtOAc (1/2) to give 81 mg (63%) of **3.79** as colorless oil; ^{1}H NMR (400 MHz, CD_3OD) δ 7.35-7.27 (comp, 15 H), 5.13-5.05 (comp, 6 H), 4.32 (dd, *J* = 5.1, 8.9 Hz, 1 H), 4.04 (dd, *J* = 5.9, 8.3 Hz, 1 H), 3.40 (dd, *J* = 5.5, 13.5 Hz, 1 H), 3.31-3.26 (m, 1 H), 2.72-2.67 (m, 1 H), 2.47-2.41 (comp, 4 H), 2.08-2.04 (m, 1 H), 1.92-1.85 (m, 1 H), 1.59-1.53 (m, 1 H), 1.48-1.40 (comp, 11 H), 1.31-1.22 (comp, 3 H), 0.86 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR (100 MHz, CD_3OD) δ 175.9, 174.5, 174.5, 174.3, 173.5, 158.0, 137.60, 137.50, 137.59, 129.6, 129.6, 129.6, 129.6, 129.6, 129.6, 129.6, 129.6, 129.6, 129.4, 129.4, 129.3, 129.3, 129.2, 129.2, 80.9, 67.5, 67.5, 55.5, 53.8, 46.4, 42.2, 33.1, 31.4, 31.2, 28.8, 28.8, 28.8, 28.4, 28.1, 21.3, 14.2; IR (DCM) 3630, 3319, 3282, 1734, 1645, 1521, 1456, 1391, 1366, 1251, 1168; HRMS (ESI) *m/z* calcd for $C_{42}H_{53}N_3NaO_{10}^+$ (M+22), 783.36557; found, 783.36556.

NMR Assignments: ^{1}H NMR (400 MHz, CD_3OD) δ 7.35-7.27 (comp, 15 H, CAr-H), 5.13-5.05 (comp, 6 H, C8, C20, C30-H), 4.32 (dd, *J* = 5.1, 8.9 Hz, 1 H, C2 or C4-H), 4.04 (dd, *J* = 5.9, 8.3 Hz, 1 H, C2 or C4-H), 3.40 (dd, *J* = 5.5, 13.5 Hz, 1 H, C14-H), 3.31-3.26 (m, 1 H, C14-H), 2.72-2.67 (m, 1 H, C15-H), 2.47-2.41 (comp, 4 H, C28 and C6-H), 2.08-2.04 (m, 1 H, C5 or C27-H), 1.92-1.85 (m, 1 H, C5 or C27-H), 1.59-

1.53 (m, 1 H, C5 or C27-H), 1.48-1.40 (comp, 11 H, C5 or C27-H, C26-H, C16-H), 1.31-1.22 (comp, 3 H, C16, C17-H), 0.86 (t, J = 7.4 Hz, 3 H, C18-H); ^{13}C NMR (100 MHz, CD_3OD) δ 175.9 (C7, C19, or C29), 174.5 (C7, C19, or C29), 174.5 (C7, C19 or C29), 174.3 (C13 or C3), 173.5 (C13 or C3), 158.0 (C1), 137.60 (C9, C21, or C31), 137.50 (C9, C21, or C31), 137.59 (C9, C21, or C31), 129.6 (CAr), 129.6 (CAr), 129.6 (CAr), 129.6 (CAr), 129.6 (CAr), 129.6 (CAr), 129.6 (CAr), 129.6 (CAr), 129.6 (CAr), 129.4 (CAr), 129.4 (CAr), 129.3 (CAr), 129.3 (C12, C24, or C34), 129.2 (C12, C24, or C34), 129.2 (C12, C24, or C34), 80.9 (C25), 67.5 (C8, C20 or C30), 67.5 (C8, C20, or C30), 67.5 (C3, C20, or C30), 55.5 (C2), 53.8 (C4), 46.4 (C15), 42.2 (C14), 33.1 (C6 or C28), 31.4 (C6 or C28), 31.2 (C16), 28.8 (C26), 28.8 (C26), 28.8 (C26), 28.4 (C27 or C5), 28.1 (C27 or C5), 21.3 (C17), 14.2 (C18).



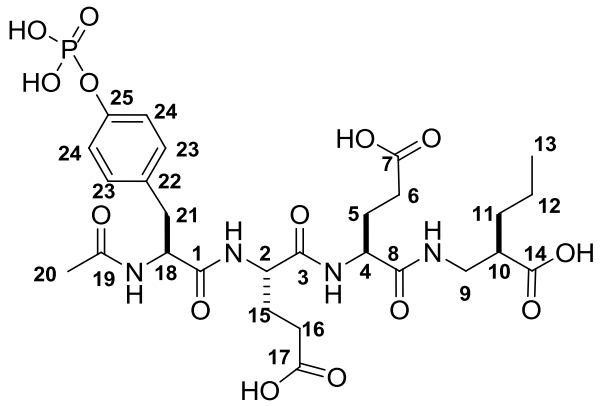
3.80

(5*S*, 8*S*, 11*S*, 15*R*)-Benzyl 8,11-bis(3-(benzyloxy)-3-oxopropyl)-5-(4-(bis(benzyloxy)phosphoryloxy)benzyl)-3,6,9,12-tetraoxo-1-phenyl-15-propyl-2-oxa-4,7,10,13-tetraazahexadecan-16-oate 3.80. (ab06111). A solution of HCl in dioxanes (4 mL, 4 M) was added to a round-bottom flask containing amide **3.79** (110 mg, 0.14 mmol). The reaction was stirred for 20 h, and the solvents were removed *in vacuo*. The residue was washed with cold Et_2O to yield 100 mg of its HCl salt as a clear oil. The crude salt was dissolved in DMF (2 mL), and protected phosphotyrosine NHZ-pY$(OBn)_2$-OH (81 mg, 0.14 mmol), EDCI·HCl (29 mg, 0.15 mmol), HOBt (38 mg, 0.28 mmol), and NMM (46 mg, 0.05 mL, 0.42 mmol) were added. The reaction was stirred at room temperature for 18 h, whereupon $NaHCO_{3(sat.)}$ (10 mL) and Et_2O (5 mL) were added. The layers were separated, and the aqueous layer was extracted with Et_2O (2 x 10 mL). The organic layers were combined, washed with H_2O (4 x 20 mL) and NaCl (1 x 20 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The crude product was purified by a flash chromatography eluting with EtOAc to give 54 mg (32%) of **3.80** as colorless oil; ^{1}H NMR (500 MHz, CD_3OD) δ 7.32-7.21 (comp, 30 H), 7.15 (d, *J* = 8.5 Hz, 2 H), 7.00 (d, *J* = 8.5 Hz, 2 H), 5.11-4.95 (comp, 12 H), 4.35-4.29 (comp, 3 H), 3.34-3.33 (m, 1 H), 3.06 (dd, *J* = 14.1, 5.2 Hz, 1 H), 2.84 (dd, *J* = 14.1, 9.1 Hz, 1 H), 2.71-2.67 (m, 1 H), 2.40 (t, *J* = 7.6 Hz, 4 H), 2.13-2.05 (comp, 2 H), 1.96-1.88 (comp, 2 H), 1.57-1.50 (m, 1 H), 1.47-1.40 (m, 1 H), 1.31-1.20 (comp, 2 H), 0.83 (t, *J* = 7.3 Hz, 3 H); ^{13}C NMR (125 MHz, CD_3OD) δ 175.8, 174.4, 174.3 174.2, 174.1, 173.4, 173.3, 158.5, 150.6, 150.6, 138.0, 137.5, 137.5, 137.5, 136.8, 136.8, 135.8, 131.8, 131.8, 129.8, 129.8, 129.7, 129.7, 129.7, 129.7, 129.5, 129.5, 129.5, 129.5, 129.5, 129.5, 129.5, 129.4, 129.4, 129.3, 129.3, 129.3, 129.3, 129.2, 129.2, 129.2, 129.2, 129.2, 129.2, 129.2, 129.0, 128.8, 121.1,

121.0, 71.5, 71.5, 67.8, 67.5, 67.4, 67.4, 57.8, 54.4, 54.0, 46.3, 42.1, 37.9, 33.1, 31.3, 31.3, 28.2, 27.7, 21.2, 14.2; IR (DCM) 3422, 2359, 2342, 1685, 1652, 1636; HRMS (ESI) *m/z* calcd for $C_{68}H_{74}N_4NaO_{15}P^+$ (M+22), 1239.47023; found, 1239.46894.

NMR Assignments: ^{1}H NMR (500 MHz, CD_3OD) δ 7.32-7.21 (comp, 30 H, CAr-H), 7.15 (d, *J* = 8.5 Hz, 2 H, C40 or C41-H), 7.00 (d, *J* = 8.5 Hz, 2 H, C40 or C41-H), 5.11-4.95 (comp, 12 H, C43, C37, C30, C8, and C20), 4.35-4.29 (comp, 3 H, C35, C2, and C4-H), 3.34-3.33 (m, 2 H, C14-H), 3.06 (dd, *J* = 14.1, 5.2 Hz, 1 H, C38-H), 2.84 (dd, *J* = 14.1, 9.1 Hz, 1 H, C38-H), 2.71-2.67 (m, 1 H, C15-H), 2.40 (t, *J* = 7.6 Hz, 4 H, C6 and C28-H), 2.13-2.05 (comp, 2 H, C5 or C27-H), 1.96-1.88 (comp, 2 H, C5 or C27-H), 1.57-1.50 (m, 1 H, C16-H), 1.47-1.40 (m, 1 H, C16-H), 1.31-1.20 (comp, 2 H, C17-H), 0.83 (t, *J* = 7.3 Hz, 3 H, C18-H); ^{13}C NMR (125 MHz, CD_3OD) δ 175.8 (C36, C1, C29, C3, C7, C13, or C19), 174.4 8 (C36, C1, C29, C3, C7, C13, or C19), 174.3 8 (C36, C1, C29, C3, C7, C13, or C19), 174.2 8 (C36, C1, C29, C3, C7, C13, or C19), 174.1 8 (C36, C1, C29, C3, C7, C13, or C19), 173.4 8 (C36, C1, C29, C3, C7, C13, or C19), 173.3 8 (C36, C1, C29, C3, C7, C13, or C19), 158.5 (C48, C44, C42, C39, C31, C9, or C21), 150.6 (C48, C44, C42, C39, C31, C9, or C21), 150.6 (C48, C44, C42, C39, C31, C9, or C21), 138.0 (C48, C44, C42, C39, C31, C9, or C21), 137.5(C48, C44, C42, C39, C31, C9, or C21), 137.5 (C48, C44, C42, C39, C31, C9, or C21), 137.5 (C48, C44, C42, C39, C31, C9, or C21), 136.8 (C48, C44, C42, C39, C31, C9, or C21), 136.8 (C48, C44, C42, C39, C31, C9, or C21), 135.8 (CAr), 131.8 (C40 or C41), 131.8 (C40 or C41), 129.8 (CAr), 129.8 (CAr), 129.7 (CAr), 129.7 (CAr), 129.7 (CAr), 129.7 (CAr), 129.5 (CAr), 129.5 (CAr), 129.5 (CAr), 129.5 (CAr), 129.5 (CAr), 129.5 (CAr), 129.5 (CAr), 129.5 (CAr), 129.4 (CAr), 129.4 (CAr), 129.3 (CAr), 129.3 (CAr), 129.3 (CAr), 129.3

(CAr), 129.2 (CAr), 129.2 (CAr), 129.2 (CAr), 129.2 (CAr), 129.2 (CAr), 129.2 (CAr), 129.2 (CAr), 129.0 (CAr), 128.8 (CAr), 121.1 (C40 or C 41), 121.0 (C40 or C41), 71.5 (C37, C30, C43, C8, or C20), 71.5 (C37, C30, C43, C8, or C20), 67.8 (C37, C30, C43, C8, or C20), 67.5 (C37, C30, C43, C8, or C20), 67.4 (C37, C30, C43, C8, or C20), 67.4 (C37, C30, C43, C8, or C20), 57.8 (C35, C2, or C4), 54.4 (C35, C2, or C4), 54.0 (C35, C2, or C4), 46.3(C15), 42.1 (C14), 37.9 (C38), 33.1 (C16), 31.3 (C6 or C28), 31.3 (C6 or C28), 28.2 (C5 or C27-H), 27.7 (C5 or C27-H), 21.2 (C17), 14.2 (C18).



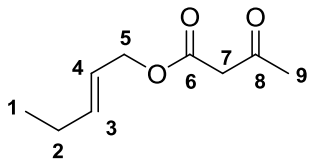
3.64

(4*S*, 7*S*, 10*S*, 14*R*)-7,10-Bis(2-carboxyethyl)-2,5,8,11-tetraoxo-4-(4-(phosphonooxy)benzyl)-14-propyl-3,6,9,12-tetraazapentadecan-15-oic acid 3.64. (ab06121). A slurry of tetrapeptide **3.80** (42 mg, 0.04 mmol), Pearlman's catalyst (5 mg), and HCl (6 drops, 6 M) in MeCN (5 mL) and H_2O (5 mL) was stirred under 1 atm of H_2 at room temperature for 2.5 h. The mixture was heated and vacuum filtered hot through a fritted funnel containing a layer of celite, washing with MeCN/H_2O. The combined filtrate and washings were concentrated under reduced pressure. The residue

was dissolved in dioxane/H_2O (4/1, 1 mL) and Ac_2O (184 mg, 0.17 mL, 1.75 mmol) was added. The reaction was stirred for 19 h at room temperature and then concentrated *in vacuo*. The residue was purified *via* reverse phase HPLC (11.6 min) and lyophilized to yield 5 mg (19%) of ligand **3.64** as a white solid; ^{1}H NMR (500 MHz, D_2O) δ 7.13 (d, J = 8.5 Hz, 2 H), 7.04 (d, J = 7.8 Hz, 2 H), 4.45 (t, J = 7.4 Hz, 1 H), 4.24-4.15 (comp, 2 H), 3.36-3.32 (m, 1 H), 3.29-3.25 (m, 1 H), 2.99-2.90 (comp, 2 H), 2.63-2.58 (m, 1 H), 2.40-2.28 (comp, 4 H), 2.02-1.79 (comp, 7 H), 1.49-1.39 (comp, 2 H), 1.27-1.22 (comp, 2 H), 0.81 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (125 MHz, D_2O) δ 179.4, 177.5, 177.3, 174.6, 173.7, 173.5, 172.9, 151.4, 132.2, 130.7, 120.9, 55.7, 53.8, 53.1, 45.2, 41.1, 36.6, 31.7, 30.3, 30.1, 26.5, 26.3, 22.0, 20.0, 13.5; HRMS (ESI) *m/z* calcd for $C_{27}H_{38}N_4O_{14}P^-$ (M-1), 673.21276; found, 673.21413.

NMR Assignments: ^{1}H NMR (500 MHz, D_2O) δ 7.13 (d, J = 8.5 Hz, 2 H, C23 or C24-H), 7.04 (d, J = 7.8 Hz, 2 H, C23 or C24-H), 4.45 (t, J = 7.4 Hz, 1 H, C18-H), 4.24-4.15 (comp, 2 H, C2 and C4-H), 3.36-3.32 (m, 1 H, C9-H), 3.29-3.25 (m, 1 H, C9-H), 2.99-2.90 (comp, 2 H, C21-H), 2.63-2.58 (m, 1 H, C10-H), 2.40-2.28 (comp, 4 H, C6 and C16-H), 2.02-1.79 (comp, 7 H, C5, C15, and C20-H), 1.49-1.39 (comp, 2 H, C11-H), 1.27-1.22 (comp, 2 H, C12-H), 0.81 (t, J = 7.3 Hz, 3 H, C13-H). ^{13}C NMR (125 MHz, D_2O) δ 179.4 (C1, C19, C17, C3, C7, C8, or C14), 177.5 (C1, C19, C17, C3, C7, C8, or C14), 177.3 (C1, C19, C17, C3, C7, C8, or C14), 174.6 (C1, C19, C17, C3, C7, C8, or C14), 173.7 (C1, C19, C17, C3, C7, C8, or C14), 173.5 (C1, C19, C17, C3, C7, C8, or C14), 172.9 (C1, C19, C17, C3, C7, C8, or C14), 151.4 (C25), 132.2 (C22), 130.7 (C23 or C24), 120.9 (C23 or C24), 55.7 (C18), 53.8 (C2 or C4), 53.1 (C2 or C4), 45.2 (C10),

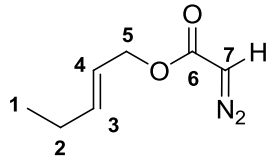
41.1 (C9), 36.6 (C21), 31.7 (C11), 30.3 (C6 or C16), 30.1 (C6 or C16), 26.5 (C5, C15, or C20), 26.3 (C5, C15 or C20), 22.0 (C5, C15 or C20), 20.0 (C12), 13.5 (C13).



3.84

(*E*)-Pent-2-enyl 3-oxobutanoate 3.84. (ab05168). A solution of (*E*)-pent-2-en-1-ol (**3.82**) (1.2 mL, 1.0 g, 11.6 mmol) and 2,2,6-trimethyl-4H-l,3-dioxin-4-one (**3.83**)[346,347] (2.0 mL, 2.14 g, 12.8 mmol) in 6 mL of xylene was immersed in a pre-heated oil bath (150 °C). The evolution of acetone became apparent within several minutes. Heating was continued for a total of 1 h. The reaction was cooled to room temperature, and the reaction was concentrated *in vacuo*. The product was purified via column chromatography (EtOAc/ hexane 1:4) to yield 1.95 g (99%) of β-ketoester **3.84** as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ β-ketoester (> 90%) 5.89-5.81 (m, 1 H), 5.61-5.52 (m, 1 H), 4.59 (d, *J* = 5.6 Hz, 2 H), 3.47 (s, 2 H), 2.28 (s, 3 H), 2.08 (p, *J* = 7.6 Hz, 2 H), 1.01 (t, *J* = 7.6 Hz, 3 H); enol tautomer (<10%) 5.89-5.81 (m, 1 H), 5.61-5.52 (m, 1 H), 5.00 (s, 1 H), 4.14 (t, *J* = 6.8 Hz, 2 H), 1.96 (s, 3 H), 1.67-1.63 (m, 2 H), 0.91 (t, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.6, 166.9, 138.8, 122.1, 66.2, 50.1, 30.1, 25.2, 13.0; IR (DCM) 3447, 2361, 2339, 1734, 1717, 1699, 1684, 1671, 1652, 1636, 1559, 1541, 1457; HRMS (CI) *m/z* calcd for $C_9H_{15}O_3^+$ (M + 1), 171.1021; found, 171.1020.

NMR Assignments: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89-5.81 (m, 1 H, C3 or C4-H), 5.61-5.52 (m, 1 H, C3 or C4-H), 4.59 (d, *J* = 5.6 Hz, 2 H, C5-H), 3.47 (s, 2 H, C7-H), 2.28 (s, 3 H, C9-H), 2.08 (p, *J* = 7.6 Hz, 2 H, C2-H), 1.01 (t, *J* = 7.6 Hz, 3 H, C1-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.6 (C8), 166.9 (C6), 138.8 (C3 or C4), 122.1 (C3 or C4), 66.2 (C5), 50.1 (C7), 30.1 (C9), 25.2 (C2), 13.0 (C1).

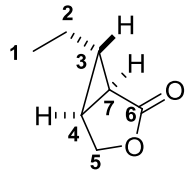


3.86

(*E*)-Pent-2-enyl 2-diazoacetate 3.86. (ab05204). A solution of **3.84** (100 mg, 0.59 mmol) and Et_3N (0.16 mL, 116 mg, 1.18 mmol) in THF (5 mL) was added to a solution of 2-azido-1,3-dimethylimidazolinium hexafluorophosphate (ADMP)[348] **3.85** (200 mg, 0.71 mmol) in MeCN (1 mL) at 0 °C. Stirring was continued for 2 h, whereupon a solution of $LiOH{\cdot}H_2O$ (82 mg, 1.95 mmol) in H_2O (5 mL) was added in one portion. The reaction was warmed to room temperature and stirred for 1 h. Et_2O/EtOAc (2/1) was added (ca. 10 mL), and the layers were separated. The aqueous layer was extracted with Et_2O/EtOAc (2/1) (2 x 10 mL), and then the organic layers were combined, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified via column chromatography (EtOAc/hexanes 1/9) to yield 84 mg (93%) of diazoester **XX** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85-5.79 (m, 1 H), 5.59-5.52 (m, 1 H), 4.75 (br, 1 H), 4.60 (d, *J* = 6.8 Hz, 2 H), 2.08 (p, *J* = 7.6 Hz, 2 H), 1.00 (t, *J* = 7.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.2, 122.7, 122.7, 65.6, 46.2, 25.2, 13.1; IR (DCM)

3430, 2111, 1682, 1392, 1355, 1240, 1181, 969; HRMS (CI) *m/z* calcd for $C_7H_{11}N_2O_2^+$ (M + 1), 155.0821; found, 155.0822.

NMR Assignments: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85-5.79 (m, 1 H, C3 or C4-H), 5.59-5.52 (m, 1 H, C3 or C4-H), 4.75 (br, 1 H, C7-H), 4.60 (d, *J* = 6.8 Hz, 2 H, C5-H), 2.08 (p, *J* = 7.6 Hz, 2 H, C2-H), 1.00 (t, *J* = 7.6 Hz, 3 H, C1-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.2 (C6), 122.7 (C3 or C4), 122.7 (C3 or C4), 65.6 (C5), 46.2 (C7), 25.2 (C2), 13.1 (C1).

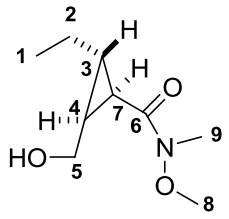


3.87

(1*R*, 5*S*, 6*S*)-6-Ethyl-3-oxabicyclo[3.1.0]hexan-2-one 3.87. (ab06039). A solution of diazoester **3.86** (500 mg, 3.24 mmol) in CH_2Cl_2 (35 mL) was added to a solution of Rh_2(*5S*-MEPY)$_4$(MeCN)$_2$(*i*-PrOH)[314-318,323] (29 mg, 0.032 mmol) in CH_2Cl_2 (10 mL) via a syringe pump (syringe diameter: 30 mm (60 mL)) over 24 h (1.5 mL/h) at 50 °C (oil bath). The reaction was cooled to room temperature and concentrated *in vacuo*. The residue was purified *via* column chromatography (EtOAc/hexanes 1/4) to yield 310 mg (76%) of cyclopropane **3.87** as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.31 (dd, *J* = 5.0, 9.0 Hz, 1 H), 4.22 (d, *J* = 9.0 Hz, 1 H), 2.03 (q, *J* = 5.0 Hz, 1 H), 1.86 (dd, *J* = 2.5, 5.0 Hz, 1 H), 1.43-1.37 (comp, 2 H), 1.21-1.17 (m, 1 H), 1.03 (t, *J* = 7.5 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1, 69.5, 28.0, 24.4, 23.8, 23.7, 12.9; IR (DCM) 3500, 2361, 1767, 1644, 1460, 1372, 1276, 1172; HRMS (CI) *m/z* calcd for

$C_7H_{11}O_2^+$ (M + 1), 127.0759; found, 127.0760; HPLC (210 nm): Whelk-O1 (6% CH_3CN / 20% *i*-PrOH / hexanes, 1.2 mL/min) 16.5 min (minor), 17.6 min (major); 93:7 er.

NMR Assignments: ^1H NMR (400 MHz, $CDCl_3$) δ 4.31 (dd, *J* = 5.0, 9.0 Hz, 1 H, C5-H), 4.22 (d, *J* = 9.0 Hz, 1 H, C5-H), 2.03 (q, *J* = 5.0 Hz, 1 H, C4), 1.86 (dd, *J* = 2.5, 5.0 Hz, 1 H, C7-H), 1.43-1.37 (comp, 2 H, C2-H), 1.21-1.17 (m, 1 H, C3-H), 1.03 (t, *J* = 7.5 Hz, 3 H, C1-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1 (C6), 69.5 (C5), 28.0 (C7), 24.4 (C2) , 23.8 (C3 or C4), 23.7 (C3 or C4), 12.9 (C1).

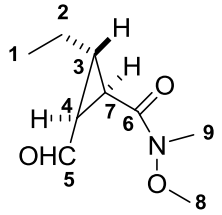


3.88

(1*R*, 2*S*, 3*S*)-2-Ethyl-3-(hydroxymethyl)-*N*-methoxy-*N*-methylcyclopropanecarboxamide 3.88. (ab06051). $AlMe_3$ (9.0 mL, 2.0 M in toluene, 18 mmol) was added dropwise to a slurry of N,O-dimethylhydroxylamine (1.46 g, 15 mmol) in DCM (5 mL) at 0 ºC. The reaction was stirred for 1.5 h, and then a solution of lactone **3.87** (310 mg, 2.5 mmol) in DCM (10 mL) was added. The reaction was warmed to room temperature and stirred for 3 h before being re-cooled to 0 ºC. 1 M HCl was added slowly until the evolution of bubbles had ceased and the reaction warmed to room temperature, and the layers were then separated. The aqueous layer was extracted with DCM (2 x 10 mL), and the organic layers were combined, washed (1 x brine), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash

chromatography eluting with hexane/EtOAc (1/1) to give 344 mg (74%) of **3.88** as a pale yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.95 (dd, *J* = 12.0, 4.2 Hz, 1 H), 3.78-3.73 (comp, 4 H), 3.22 (s, 3 H), 2.93 (br, 1 H), 2.02-1.99 (m, 1 H), 1.58 (p, *J* = 6.6 Hz, 1 H), 1.45-1.38 (comp, 3 H), 0.99 (t, *J* = 7.5 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.8, 61.6, 60.2, 32.6, 30.8, 26.7, 26.2, 22.5, 13.1; IR (DCM) 3430, 2361, 2341, 1635, 1458; HRMS (ESI) *m/z* calcd for $C_9H_{17}NNaO_3^+$ (M + 22), 210.11006; found, 210.10998.

NMR Assignments: ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.95 (dd, *J* = 12.0, 4.2 Hz, 1 H, C5-H), 3.78-3.73 (comp, 4 H, C8-H and C5-H), 3.22 (s, 3 H, C9-H), 2.93 (br, 1 H, OH), 2.02-1.99 (m, 1 H, C3 or C4-H), 1.58 (p, *J* = 6.6 Hz, 1 H, C3 or C4-H), 1.45-1.38 (comp, 3 H, C2 and C7-H), 0.99 (t, *J* = 7.5 Hz, 3 H, C1-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.8 (C6), 61.6 (C8), 60.2 (C5), 32.6 (C9), 30.8 (C3, C4, or C2), 26.7 (C3 or C4), 26.2 (C3, C4 or C2), 22.5 (C7), 13.1 (C1).

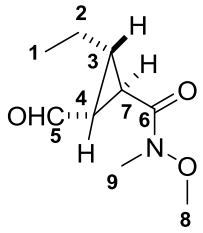


3.89

(1*R*, 2*S*, 3*S*)-2-Ethyl-3-formyl-N-methoxy-N-methylcyclopropanecarboxamide 3.89. (ab06140). A slurry of alcohol **3.88** (137 mg, 1.3 mmol), PCC (560 mg, 2.6 mmol) and celite in DCM (20 mL) was stirred at room temperature for 3 h. The reaction was concentrated under reduced pressure, and Et_2O (ca. 20 mL) was added to the residue. The residue was vacuum filtered through a fritted

funnel containing a layer of celite, followed by washing with Et_2O (ca. 20 mL). The combined filtrate and washings were collected and concentrated. The residue was purified by flash chromatography eluting with hexane/EtOAc (1/1) to give 165 mg (69%) of **3.89** as a pale yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.32 (d, *J* = 6.7 Hz, 1 H), 3.74 (s, 3 H), 3.22 (s, 3 H), 2.60-2.57 (m, 1 H), 2.34 (p, *J* = 6.5 Hz, 1 H), 1.92-1.88 (m, 1 H), 1.59-1.45 (comp, 2 H), 1.03 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.3, 169.9, 61.8, 37.7, 32.5, 28.6, 27.6, 25.0, 12.9; IR (DCM) 3446, 2360, 1699, 1648; HRMS (ESI) *m/z* calcd for $C_9H_{15}NNaO_3^+$ (M + 22), 208.09441; found, 208.09436.

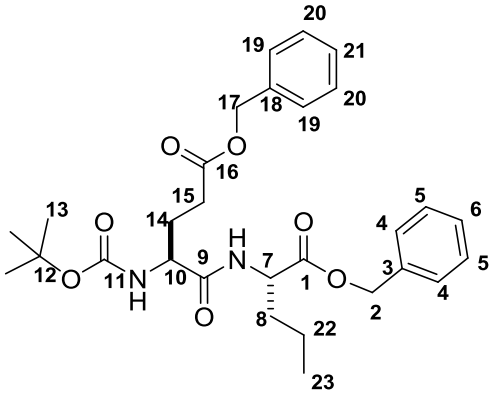
NMR Assignments: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.32 (d, *J* = 6.7 Hz, 1 H, C5-H), 3.74 (s, 3 H, C8-H), 3.22 (s, 3 H, C9-H), 2.60-2.57 (m, 1 H, C7-H), 2.34 (p, *J* = 6.5 Hz, 1 H, C3-H), 1.92-1.88 (m, 1 H, C4-H), 1.59-1.45 (comp, 2 H, C2-H), 1.03 (t, *J* = 7.4 Hz, 3 H, C1-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.3 (C5), 169.9 (C6), 61.8 (C8), 37.7 (C9), 32.5 (C7), 28.6 (C3 or C4), 27.6 (C3 or C4), 25.0 (C2), 12.9 (C1).



3.90

(1*R*, 2*S*, 3*R*)-2-Ethyl-3-formyl-N-methoxy-N-methylcyclopropanecarboxamide 3.90. (ab06108). A solution of aldehyde **3.90** (34 mg, 0.18 mmol) and Et_3N (276 mg, 0.38 mL, 2.7 mmol) in MeOH (1 mL) was heated under reflux for 3 d, whereupon it was cooled to room temperature and concentrated *in*

vacuo. The residue was purified by flash chromatography eluting with hexane/EtOAc (1/1) to give 16 mg (50%) of a 63:37 inseparable mixture of product **3.90** to RSM **3.89**. Indicative aldehyde peaks: ^{1}H NMR (400 MHz, $CDCl_3$) δ product **3.90** 9.70 (d, J < 6.7 Hz, 0.63 H) : RSM **3.89** 9.32 (d, J = 6.7 Hz, 0.37 H).

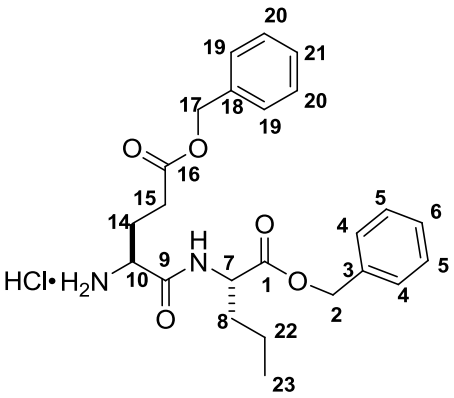


3.110

(*S*)-Benzyl 5-((*S*)-1-(benzyloxy)-1-oxopentan-2-ylamino)-4-(tert-butoxycarbonylamino)-5-oxopentanoate 3.110. (ab05199). NMM (368 mg, 0.4 mL, 3.6 mmol) was added to a solution of the HCl salt **3.109** (247 mg, 1.2 mmol), protected glutamic acid NHBoc-E(OBn)-OH (405 mg, 1.2 mmol), EDCI·HCl (249 mg, 1.3 mmol), and HOBt (324 mg, 2.4 mmol) in DMF (30 mL) at room temperature, and the reaction was stirred for 16 h. $NaHCO_{3(sat.)}$ (120 mL) and Et_2O (60 mL) were added. The layers were separated, and the aqueous layer was extracted with Et_2O (2 x 60 mL). The organic layers were combined, washed with H_2O (4 x 240 mL) and $NaCl_{(sat)}$ (1 x 300 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The crude product was purified by flash chromatography eluting with hexane/EtOAc (1/2) to give 380 mg (60%) of **3.110** as a

colorless oil; ^{1}H NMR (400 MHz, CD_3OD) δ 7.33-7.27 (comp, 10 H), 5.15-5.07 (comp, 4 H), 4.43 (dd, *J* = 9.0, 5.0 Hz, 1 H), 4.14 (dd, *J* = 8.0, 6.0 Hz, 1 H), 2.44 (t, *J* = 7.6 Hz, 2 H), 2.09-2.00 (m, 1 H), 1.92-1.74 (comp, 2 H), 1.71-1.62 (m, 1 H), 1.41-1.25 (m, 11 H), 0.88 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR (100 MHz, CD_3OD) δ 173.1, 172.9, 171.9, 156.3, 136.2, 135.8, 128.2, 128.2, 128.2, 128.2, 128.0, 128.0, 128.0, 127.8, 127.8, 127.8, 79.3, 66.5, 66.0, 53.5, 52.3, 33.0, 29.9, 27.4, 27.4, 27.4, 27.2, 18.5, 12.6; IR (DCM) 3442, 2486, 1739, 1660, 1456, 1415, 1171; HRMS (ESI) *m/z* calcd for $C_{29}H_{38}N_2NaO_7^+$ (M + 22), 549.25712; found, 549.25764.

NMR Assignments: ^{1}H NMR (400 MHz, CD_3OD) δ 7.33-7.27 (comp, 10 H, CAr-H), 5.15-5.07 (comp, 4 H, C2 and C17-H), 4.43 (dd, *J* = 9.0, 5.0 Hz, 1 H, C7 or C10-H), 4.14 (dd, *J* = 8.0, 6.0 Hz, 1 H, C7 or C10-H), 2.44 (t, *J* = 7.6 Hz, 2 H, C15-H), 2.09-2.00 (m, 1 H, C8 or C14-H), 1.92-1.74 (comp, 2 H, C8 or C14-H), 1.71-1.62 (m, 1 H, C8 or C14-H), 1.41-1.25 (m, 11 H, C22 and C13-H), 0.88 (t, *J* = 7.4 Hz, 3 H, C23-H); ^{13}C NMR (100 MHz, CD_3OD) δ 173.1 (C1, C9, or C16), 172.9 (C1, C9, or C16), 171.9 (C1, C9, or C16), 156.3 (C11), 136.2 (C3 or C18), 135.8 (C3 or C18), 128.2 (CAr), 128.2 (CAr), 128.2 (CAr), 128.2 (CAr), 128.0 (CAr), 128.0 (CAr), 128.0 (CAr), 127.8 (CAr), 127.8 (CAr), 127.8 (CAr), 79.3 (C12), 66.5 (C2 or C17), 66.0 (C2 or C17), 53.5 (C7 or C10), 52.3 (C7 or C10), 33.0 (C15), 29.9 (C8), 27.4 (C13), 27.4 (C13), 27.4 (C13), 27.2 (C14), 18.5 (C22), 12.6 (C23).

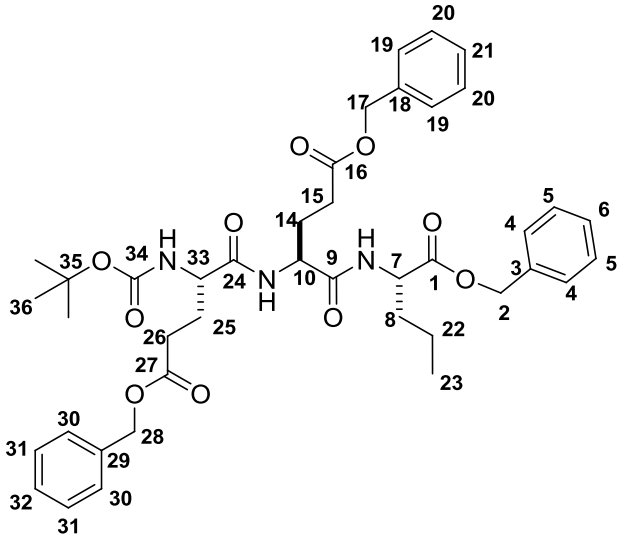


3.111

(*S*)-Benzyl 4-amino-5-((*S*)-1-(benzyloxy)-1-oxopentan-2-ylamino)-5-oxopentanoate hydrochloride salt 3.111. (ab05205). A solution of HCl in dioxane (10 mL, ca. 4 M) was added to a round-bottom flask containing amide **3.110** (342 mg. 0.65 mmol) at room temperature. The reaction was stirred for 16 h, and the solvents were then removed *in vacuo*. The crude product was washed with cold hexanes to give 300 mg of **3.111** (100%) as a viscous colorless oil; ^{1}H NMR (400 MHz, CD_3OD) δ 7.34-7.28 (comp, 10 H), 5.16-5.07 (comp, 4 H), 4.47 (dd, *J* = 9.2, 5.2 Hz, 1 H), 4.06 (t, *J* = 6.2 Hz, 1 H), 2.63-2.58 (comp, 2 H), 2.22-2.14 (comp, 2 H), 1.83-1.69 (comp, 2 H), 1.43-1.36 (comp, 2 H), 0.90 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR (100 MHz, CD_3OD) δ 172.3, 171.6, 168.5, 136.0, 135.7, 128.3, 128.3, 128.3, 128.3, 128.1, 128.1, 128.1, 127.9, 127.9, 127.9, 66.7, 66.3, 52.6, 52.0, 32.8, 28.8, 26.3, 18.6, 12.5; IR (DCM) 1739, 1680, 1498, 1456, 1190, 1003; HRMS (ESI) *m/z* calcd for $C_{24}H_{30}N_2NaO_5^+$ (M + 22), 449.20469; found, 449.20469.

NMR Assignments: ^{1}H NMR (400 MHz, CD_3OD) δ 7.34-7.28 (comp, 10 H, CAr-H), 5.16-5.07 (comp, 4 H, C2 and C17-H), 4.47 (dd, *J* = 9.2, 5.2 Hz, 1 H, C7-H), 4.06 (t, *J* = 6.2 Hz, 1 H, C10-H), 2.63-2.58 (comp, 2 H, C15-H), 2.22-2.14 (comp, 2 H,

C14 or C8-H), 1.83-1.69 (comp, 2 H, C14 or C8-H), 1.43-1.36 (comp, 2 H, C22-H), 0.90 (t, J = 7.4 Hz, 3 H, C23-H); ^{13}C NMR (100 MHz, CD_3OD) δ 172.3 (C1, C9, or C16), 171.6 (C1, C9, or C16), 168.5 (C1, C9, or C16), 136.0 (C3 or C18), 135.7 (C3 or C18), 128.3 (CAr), 128.3 (CAr), 128.3 (CAr), 128.3 (CAr), 128.1 (CAr), 128.1 (CAr), 128.1 (CAr), 127.9 (CAr), 127.9 (CAr), 127.9 (CAr), 66.7 (C2 or C17), 66.3 (C2 or C17), 52.6 (C7 or C10), 52.0 (C7 or C10), 32.8 (C15), 28.8 (C8 or C14), 26.3 (C8 or C14), 18.6 (C22), 12.5 (C23).



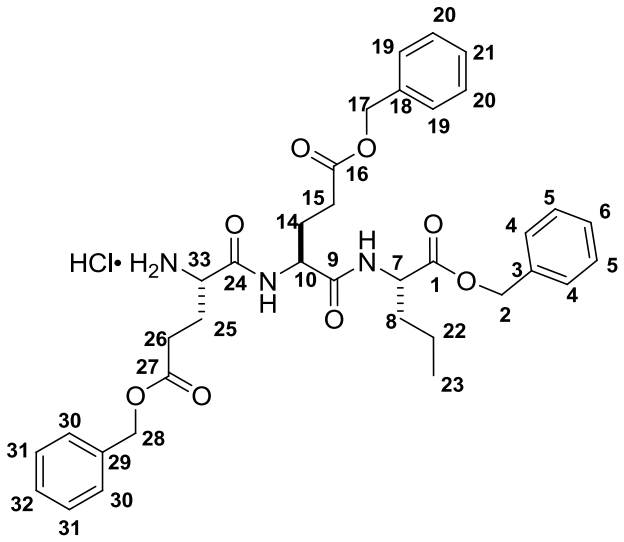
3.112

(6*S*, 9*S*, 12*S*)-Benzyl 6,9-bis(3-(benzyloxy)-3-oxopropyl)-2,2-dimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazapentadecane-12-carboxylate 3.112. (ab05206). NMM (221 mg, 0.24 mL, 2.2 mmol) was added to a solution of the HCl salt **3.111** (300 mg, 0.73 mmol), protected glutamic acid NHBoc-E(OBn)-OH (246 mg, 0.73 mmol), EDCI·HCl (153 mg, 0.8 mmol), and HOBt (197 mg, 1.5 mmol) in DMF (8 mL) at room temperature, and the

reaction was stirred for 16 h. $NaHCO_{3(sat.)}$ (40 mL) and Et_2O (20 mL) were then added. The layers were separated, and the aqueous layer was extracted with Et_2O (2 x 20 mL). The organic layers were combined, washed with H_2O (4 x 80 mL) and $NaCl_{(sat)}$ (1 x 100 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The crude product was purified by flash chromatography eluting with hexane/EtOAc (1/2) to give 259 mg (54%) of **3.112** as a viscous colorless oil; ^{1}H NMR (400 MHz, CD_3OD) δ 7.33-7.28 (comp, 15 H), 5.15-5.07 (comp, 6 H), 4.46-4.38 (comp, 2 H), 4.09-4.06 (m, 1 H), 2.45 (q, *J*= 7.6 Hz, 4 H), 2.15-2.01 (comp, 2 H), 1.97-1.83 (comp, 2 H), 1.81-1.72 (m, 1 H), 1.70-1.60 (m, 1 H), 1.39-1.28 (comp, 11 H), 0.86 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR (100 MHz, CD_3OD) δ 172.9, 172.9, 172.0, 171.9, 171.9, 156.4, 136.1, 136.1, 135.8, 128.2, 128.2, 128.2, 128.2, 128.0, 128.0, 128.0, 127.9, 127.9, 127.9, 127.8, 127.8, 127.8, 127.8, 127.8, 79.3, 66.5, 66.0, 66.0, 53.8, 52.3, 52.1, 32.9, 30.0, 29.7, 27.3, 27.3, 27.3, 27.1, 26.8, 18.6, 12.1; IR (DCM) 2358, 2343, 1737, 1639, 1458, 1390, 1167; HRMS (ESI) *m/z* calcd for $C_{41}H_{51}N_3NaO_{10}^+$ (M + 22), 768.34667; found, 768.34612.

NMR Assignments: ^{1}H NMR (400 MHz, CD_3OD) δ 7.33-7.28 (comp, 15 H, CAr-H), 5.15-5.07 (comp, 6 H, C2, C17, and C28-H), 4.46-4.38 (comp, 2 H, C10 and C33-H), 4.09-4.06 (m, 1 H, C7-H), 2.45 (q, *J*= 7.6 Hz, 4 H, C15 and C26-H), 2.15-2.01 (comp, 2 H, C14 or C25-H), 1.97-1.83 (comp, 2 H, C14 or C25-H), 1.81-1.72 (m, 1 H, C8-H), 1.70-1.60 (m, 1 H, C8-H), 1.39-1.28 (comp, 11 H, C36 and C22-H), 0.86 (t, *J* = 7.4 Hz, 3 H, C23-H); ^{13}C NMR (100 MHz, CD_3OD) δ 172.9 (C16), 172.9 (C27), 172.0 (C1), 171.9 (C9), 171.9 (C24), 156.4 (C34), 136.1 (C29), 136.1 (C18), 135.8 (C3), 128.2 (CAr), 128.2 (CAr), 128.2 (CAr), 128.2 (CAr), 128.0 (CAr), 128.0 (CAr), 128.0 (CAr), 127.9 (CAr), 127.9 (CAr), 127.9 (CAr), 127.8 (CAr), 127.8 (CAr), 127.8 (CAr), 127.8

(CAr), 127.8 (CAr), 79.3 (C35), 66.5 (C2), 66.0 (C17), 66.0 (C28), 53.8 (C7), 52.3 (C10 or C33), 52.1 (C10 or C33), 32.9 (C8), 30.0 (C15 or C26), 29.7 (C15 or C26), 27.3 (C36), 27.3 (C36), 27.3 (C36), 27.1 (C14), 26.8 (C25), 18.6 (C22), 12.1 (C23).

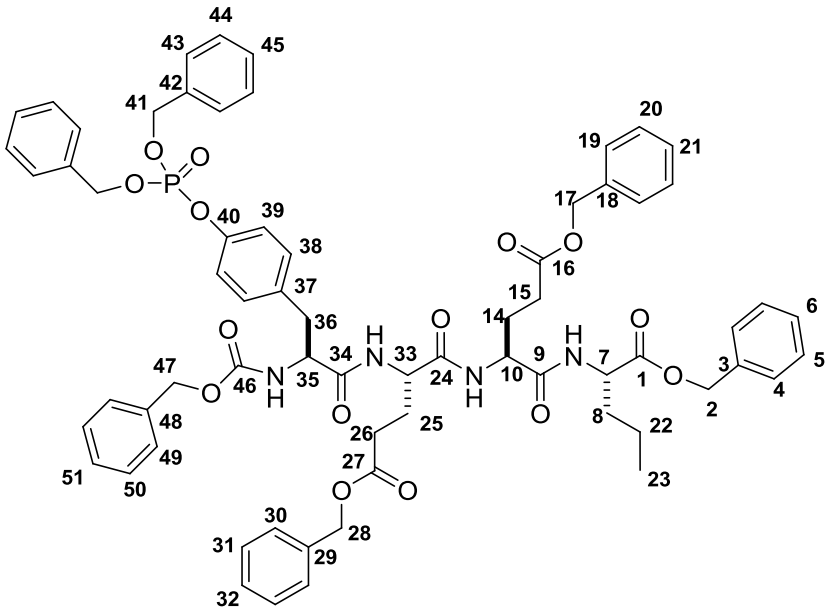


3.113

(*S*)-Benzyl 4-amino-5-((*S*)-5-(benzyloxy)-1-((*S*)-1-(benzyloxy)-1-oxopentan-2-ylamino)-1,5-dioxopentan-2-ylamino)-5-oxopentanoate hydrochloride salt 3.113. (ab05210). A solution of HCl in dioxane (5 mL, ca. 4 M) was added to a round-bottom flask containing amide **3.112** (259 mg. 0.35 mmol) at room temperature. The reaction was stirred for 16 h, and the solvents were removed *in vacuo*. The crude product was washed with cold hexanes to give to give 223 (93%) mg of **3.113** as a viscous colorless oil; ^{1}H NMR (400 MHz, CD_3OD) δ 7.35-7.27 (comp, 15 H), 5.15-5.07 (comp, 6 H), 4.46 (dd, *J* = 7.8, 6.4 Hz, 1 H), 4.39 (dd, *J* = 11, 5.2 Hz, 1 H), 3.99 (t, *J* = 6.4 Hz, 1 H), 2.57 (t, *J* = 7.6 Hz, 2 H), 2.49 (t, *J* = 7.6 Hz, 2 H), 2.19-2.06 (comp, 3 H), 2.02-1.92 (m, 1 H),

1.81-1.73 (m, 1 H), 1.72-1.60 (m, 1 H), 1.41-1.24 (comp, 2 H), 0.85 (t, J = 7.6 Hz, 3 H); ^{13}C NMR (100 MHz, CD_3OD) δ 172.7, 172.2, 171.7, 171.8, 168.1, 136.1, 135.9, 135.7, 128.2, 128.2, 128.2, 128.2, 128.2, 128.0, 128.0, 128.0, 128.0, 128.0, 127.9, 127.9, 127.9, 127.9, 127.9, 66.5, 66.3, 66.1, 52.5, 52.4, 52.0, 32.9, 29.7, 28.7, 26.9, 26.2, 18.6, 12.5; IR (DCM) 3401, 1648, 1559, 1542, 1508, 1458; HRMS (ESI) *m/z* calcd for $C_{36}H_{43}N_3NaO_8^+$ (M + 22), 668.29424; found, 668.29448.

NMR Assignments: ^{1}H NMR (400 MHz, CD_3OD) δ 7.35-7.27 (comp, 15 H, CAr-H), 5.15-5.07 (comp, 6 H, C2, C17, and C28-H), 4.46 (dd, J = 7.8, 6.4 Hz, 1 H, C10 or C33-H), 4.39 (dd, J = 11, 5.2 Hz, 1 H, C10 or C33-H), 3.99 (t, J = 6.4 Hz, 1 H, C7-H), 2.57 (t, J = 7.6 Hz, 2 H, C15 or C26-H), 2.49 (t, J = 7.6 Hz, 2 H, C15 or C26-H), 2.19-2.06 (comp, 3 H, C8 and C14 or C25-H), 2.02-1.92 (m, 1 H, C14 or C25-H), 1.81-1.73 (m, 1 H, C14 or C25-H), 1.72-1.60 (m, 1 H, C14 or C25-H), 1.41-1.24 (comp, 2 H, C22-H), 0.85 (t, J = 7.6 Hz, 3 H, C23-H); ^{13}C NMR (100 MHz, CD_3OD) δ 172.7 (C1, C9, C16, C24, or C27), 172.2 (C1, C9, C16, C24, or C27), 171.7 (C1, C9, C16, C24, or C27), 171.8 (C1, C9, C16, C24, or C27), 168.1 (C1, C9, C16, C24, or C27), 136.1 (C3, C18, or C29), 135.9 (C3, C18, or C29), 135.7 (C3, C18, or C29), 128.2 (CAr), 128.2 (CAr), 128.2 (CAr), 128.2 (CAr), 128.2 (CAr), 128.0 (CAr), 128.0 (CAr), 128.0 (CAr), 128.0 (CAr), 128.0 (CAr), 127.9 (CAr), 127.9 (CAr), 127.9 (CAr), 127.9 (CAr), 127.9 (CAr), 66.5 (C2, C17, or C28), 66.3 (C2, C17, or C28), 66.1 (C2, C17, or C28), 52.5 (C7, C10, or C33), 52.4 (C7, C10, or C33), 52.0 (C7, C10, or C33), 32.9 (C8), 29.7 (C15 or C26), 28.7 (C15 or C26), 26.9 (C14 or C25), 26.2 (C14 or C25), 18.6 (C22), 12.5 (C23).



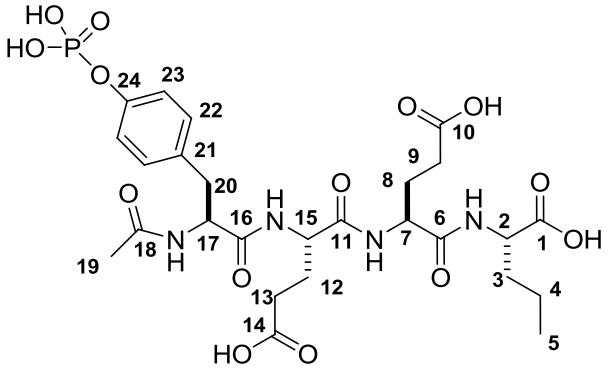
3.114

(5*S*, 8*S*, 11*S*, 14*S*)-Benzyl 8,11-bis(3-(benzyloxy)-3-oxopropyl)-5-(4-(bis(benzyloxy)phosphoryloxy)benzyl)-3,6,9,12-tetraoxo-1-phenyl-2-oxa-4,7,10,13-tetraazaheptadecane-14-carboxylate 3.114. (ab05287). Amine salt **3.113** (227 mg, 0.33 mmol) was dissolved in DMF (12 mL), and protected phosphotyrosine NHZ-pY(OBn)$_2$-OH (190 mg, 0.33 mmol), EDCI·HCl (69 mg, 0.36 mmol), HOBt (90 mg, 0.66 mmol), and NMM (101 mg, 0.11 mL, 0.99 mmol) were added. The reaction was stirred at room temperature for 18 h, whereupon $NaHCO_{3(sat.)}$ (20 mL) and Et_2O (10 mL) were added. The layers were separated, and the aqueous layer was extracted with Et_2O (2 x 20 mL). The organic layers were combined, washed with H_2O (4 x 40 mL) and NaCl (1 x 40 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The crude product was purified by a flash chromatography eluting with EtOAc to give 136 mg (34%) of **3.114** as a viscous colorless oil; ^{1}H NMR (500 MHz, CD_3OD) δ 7.33-7.22 (comp, 30 H), 7.16 (d, *J*

= 8.5 Hz, 2 H), 7.00 (d, *J* = 8.5 Hz, 2 H), 5.15-4.96 (comp, 12 H), 4.41-4.38 (m, 2 H), 4.36-4.32 (m, 2 H), 3.07 (dd, *J* = 14.0, 5.0 Hz, 1 H), 2.83 (dd, *J* = 14.0, 9.2 Hz, 1 H), 2.46-2.39 (comp, 4 H), 2.12-2.08 (m, 1 H), 1.98-1.93 (m, 1 H), 1.78-1.72 (m, 1 H), 1.69-1.63 (m, 1 H), 1.38-1.28 (m, 4 H), 0.85 (t, *J* = 5.5 Hz, 3 H); ^{13}C NMR (125 MHz, CD_3OD) δ 174.2, 174.2, 174.0, 173.5, 173.4, 173.3, 173.2, 138.1, 137.5, 137.5, 137.2, 137.2, 136.9, 131.8, 131.8, 129.9, 129.9, 129.9, 129.7, 129.7, 129.7, 129.7, 129.7, 129.7, 129.5, 129.5, 129.5, 129.5, 129.5, 129.5, 129.5, 129.5, 129.5, 129.5, 129.5, 129.4, 129.4, 129.4, 129.4, 129.3, 129.3, 129.3, 129.2, 129.2, 129.2, 128.8, 128.8, 121.1, 121.1, 71.5, 71.5, 67.9, 67.9, 67.4, 67.4, 57.7, 53.8, 53.8, 53.8, 37.9, 34.4, 31.3, 31.3, 28.2, 20.0, 20.0, 13.9; IR (DCM) 3437, 2088, 1735, 1636, 1539, 1507, 1455, 1386, 1215, 1168, 1016; HRMS (ESI) *m/z* calcd for $C_{67}H_{71}N_4NaO_{15}P^+$ (M + 22), 1225.45458; found, 1225.45406.

NMR Assignments: ^{1}H NMR (500 MHz, CD_3OD) δ 7.33-7.22 (comp, 30 H, CAr-H), 7.16 (d, *J* = 8.5 Hz, 2 H, C38 or C39-H), 7.00 (d, *J* = 8.5 Hz, 2 H, C38 or C39-H), 5.15-4.96 (comp, 12 H, C2, C17, C28, C41, and C47-H), 4.41-4.38 (m, 2 H, C7, C10, C33 or C35-H), 4.36-4.32 (m, 2 H, C7, C10, C33 or C35-H), 3.07 (dd, *J* = 14.0, 5.0 Hz, 1 H, C36-H), 2.83 (dd, *J* = 14.0, 9.2 Hz, 1 H, C36-H), 2.46-2.39 (comp, 4 H, C15 and C26-H), 2.12-2.08 (m, 1 H, C14 or C25-H), 1.98-1.93 (m, 1 H, C14 or C25-H), 1.78-1.72 (m, 1 H, C14 or C25-H), 1.69-1.63 (m, 1 H, C14 or C25-H), 1.38-1.28 (m, 4 H, C8 and C22-H), 0.85 (t, *J* = 5.5 Hz, 3 H, C23-H); ^{13}C NMR (125 MHz, CD_3OD) δ 174.2 (C1, C9, C16, C24, C27, C34, or C46), 174.2 (C1, C9, C16, C24, C27, C34, or C46), 174.0 (C1, C9, C16, C24, C27, C34, or C46), 173.5 (C1, C9, C16, C24, C27, C34, or C46), 173.4 (C1, C9, C16, C24, C27, C34, or C46), 173.3 (C1, C9, C16, C24, C27, C34, or C46), 173.2 (C1, C9, C16, C24, C27, C34, or C46), 138.1 (C3, C18, C29, C42, or C48), 137.5

(C3, C18, C29, C42, or C48), 137.5 (C3, C18, C29, C42, or C48), 137.2 (C3, C18, C29, C42, or C48), 137.2 (C3, C18, C29, C42, or C48), 136.9 (C3, C18, C29, C42, or C48), 131.8 (C37), 131.8 (C37), 129.9 (CAr), 129.9 (CAr), 129.9 (CAr), 129.7 (CAr), 129.7 (CAr), 129.7 (CAr), 129.7 (CAr), 129.7 (CAr), 129.7 (CAr), 129.5 (CAr), 129.5 (CAr), 129.5 (CAr), 129.5 (CAr), 129.5 (CAr), 129.5 (CAr), 129.5 (CAr), 129.5 (CAr), 129.5 (CAr), 129.5 (CAr), 129.4 (CAr), 129.4 (CAr), 129.4 (CAr), 129.4 (CAr), 129.3 (CAr), 129.3 (CAr), 129.3 (CAr), 129.2 (CAr), 129.2 (CAr), 129.2 (CAr), 128.8 (CAr), 128.8 (CAr), 121.1 (C40), 121.1 (C40), 71.5 (C2, C17, C28, C41, or C47), 71.5 (C2, C17, C28, C41, or C47), 67.9 (C2, C17, C28, C41, or C47), 67.9 (C2, C17, C28, C41, or C47), 67.4 (C2, C17, C28, C41, or C47), 67.4 (C2, C17, C28, C41, or C47), 57.7 (C7, C10, C33 or C35), 53.8 (C7, C10, C33 or C35), 53.8 (C7, C10, C33 or C35), 53.8 (C7, C10, C33 or C35), 37.9 (C36), 34.4 (C14 or C25), 31.3 (C15 or C26), 31.3 (C15 or C26), 28.2 (C14 or C25), 20.0 (C8 or C22), 20.0 (C8 or C22), 13.9 (C23).



3.66

(4*S*, 7*S*, 10*S*, 13*S*)-7,10-Bis(2-carboxyethyl)-2,5,8,11-tetraoxo-4-(4-(phosphonooxy)benzyl)-3,6,9,12-tetraazahexadecane-13-carboxylic acid 3.66.

(ab06100). A slurry of tetrapeptide **3.114** (45 mg, 0.04 mmol), Pearlman's catalyst (5 mg), and HCl (6 drops, 6 M) in MeCN (0.5 mL) and H_2O (0.5 mL) was stirred under 1 atm of H_2 at room temperature for 3.75 h. The mixture was heated, and filtered through a fritted funnel containing a layer of celite, which was then washed with MeCN/H_2O (ca. 5 mL). The combined filtrate and washings were concentrated under reduced pressure. The residue was dissolved in dioxane/H_2O (4/1, 1 mL) and Ac_2O (130 mg, 0.12 mL, 1.32 mmol) was added. The reaction was stirred for 19 h at room temperature before being concentrated *in vacuo*. The residue was purified *via* reverse phase HPLC (11.28 min) and lyophilized to yield 7 mg (26%) of ligand **3.66** as a white solid; ^{1}H NMR (600 MHz, D_2O) δ 7.10 (d, *J* = 8.5 Hz, 2 H), 7.01 (d, *J* = 7.6 Hz, 2 H), 4.42 (t, *J* = 7.5 Hz, 1 H), 4.25-4.22 (comp, 2 H), 4.19 (dd, *J* = 9.0, 5.6 Hz, 1 H), 2.96-2.87 (comp, 2 H), 2.41 (t, *J* = 7.6 Hz, 2 H), 2.26 (t, *J* = 7.4 Hz, 2 H), 2.04-1.86 (comp, 7 H), 1.81-1.69 (m, 1 H), 1.66-1.60 (m, 1 H), 1.32-1.21 (comp, 2 H), 0.79 (t, *J* = 7.3 Hz, 3 H); ^{13}C NMR (125 MHz, D_2O) δ 177.0, 176.9, 175.8, 174.2, 173.2, 173.0, 172.4, 150.5 131.8, 130.2, 130.2, 120.5, 120.5, 55.2, 52.8, 52.6, 52.6, 36.2, 32.4, 29.8, 29.7, 26.0, 26.0, 21.6, 18.4, 12.7; HRMS (ESI) *m/z* calcd for $C_{26}H_{36}N_4O_{14}P^-$ (M - 1), 659.19711; found, 659.19717.

NMR Assignments: ^{1}H NMR (600 MHz, D_2O) δ 7.10 (d, *J* = 8.5 Hz, 2 H, C23 or C24-H), 7.01 (d, *J* = 7.6 Hz, 2 H, C23 or C24-H), 4.42 (t, *J* = 7.5 Hz, 1 H, C17-H), 4.25-4.22 (comp, 2 H, C7 and C15-H), 4.19 (dd, *J* = 9.0, 5.6 Hz, 1 H, C2-H), 2.96-2.87 (comp, 2 H, C20-H), 2.41 (t, *J* = 7.6 Hz, 2 H, C9 or C13-H), 2.26 (t, *J* = 7.4 Hz, 2 H, C9 or C13-H), 2.04-1.86 (comp, 7 H, C8, C12, and C19-H), 1.81-1.69 (m, 1 H, C3-H), 1.66-1.60 (m, 1 H, C3-H), 1.32-1.21 (comp, 2 H, C4-H), 0.79 (t, *J* = 7.3 Hz, 3 H, C5-H); ^{13}C NMR (125 MHz, D_2O) δ 177.0 (C1, C6, C10, C11, C14, C16, or C18), 176.9 (C1, C6,

C10, C11, C14, C16, or C18), 175.8 (C1, C6, C10, C11, C14, C16, or C18), 174.2 (C1, C6, C10, C11, C14, C16, or C18), 173.2 (C1, C6, C10, C11, C14, C16, or C18), 173.0 (C1, C6, C10, C11, C14, C16, or C18), 172.4 (C1, C6, C10, C11, C14, C16, or C18), 150.5 (C24), 131.8 (C21, C22, or C23), 130.2 (C21, C22, or C23), 130.2 (C21, C22, or C23), 120.5 (C21, C22, or C23), 120.5 (C21, C22, or C23), 55.2 (C2, C7, C15, or C17), 52.8 (C2, C7, C15, or C17), 52.6 (C2, C7, C15, or C17), 52.6 (C2, C7, C15, or C17), 36.2 (C20), 32.4 (C3), 29.8 (C9 or C13), 29.7 (C9 or C13), 26.0 (C8 or C12), 26.0 (C8 or C12), 21.6 (C19), 18.4 (C4), 12.7 (C5).

Bibliography

(1) Hurdle, J. G.; O'Neill, A. J.; Chopra, I. "Anti-staphylococcal activity of indolmycin, a potential topical agent for control of staphylococcal infections" *J. Antimicrob. Chemother.* **2004**, *54*, 549-552.

(2) Lawrence, C. H.; Clark, M. C.; King, R. R. "Induction of common scab symptoms in aseptically cultured potato tubers by the vivotoxin, thaxtomin" *Phytopathology* **1990**, *80*, 606-608.

(3) Kitagawa, T.; Akiyama, N. "An improved method for the synthesis of DL-3-(2-furyl)alanine" *Chem. Pharm. Bull.* **1997**, *45*, 1865-1866.

(4) Austin, J. F.; MacMillan, D. W. C. "Enantioselective Organocatalytic Indole Alkylations. Design of a New and Highly Effective Chiral Amine for Iminium Catalysis" *J. Am. Chem. Soc.* **2002**, *124*, 1172-1173.

(5) Nieman, J. A.; Coleman, J. E.; Wallace, D. J.; Piers, E.; Lim, L. Y.; Roberge, M.; Andersen, R. J. "Synthesis and Antimitotic/Cytotoxic Activity of Hemiasterlin Analogues" *J. Nat. Prod.* **2003**, *66*, 183-199.

(6) Fu, T.-h.; McElroy, W. T.; Shamszad, M.; Martin, S. F. "Formal Syntheses of Naturally Occurring Welwitindolinones" *Org. Lett.*, *14*, 3834-3837.

(7) Zhang, X.; Smith, C. D. "Microtubule effects of welwistatin, a cyanobacterial indolinone that circumvents multiple drug resistance" *Mol. Pharmacol.* **1996**, *49*, 288-294.

(8) Carroll, A. R.; Hyde, E.; Smith, J.; Quinn, R. J.; Guymer, G.; Forster, P. I. "Actinophyllic Acid, a Potent Indole Alkaloid Inhibitor of the Coupled Enzyme Assay Carboxypeptidase U/Hippuricase from the Leaves of Alstonia actinophylla (Apocynaceae)" *Journal of Organic Chemistry* **2005**, *70*, 1096-1099.

(9) Iqbal, Z.; Jackson, A. H.; Rao, K. R. N. "Reactions on solid supports. Part IV: reactions of alpha ,beta -unsaturated carbonyl compounds with indoles using clay as a catalyst" *Tetrahedron Lett.* **1988**, *29*, 2577-2580.

(10) Harrington, P.; Kerr, M. A. "The ultra high pressure conjugate addition of indoles to electron-deficient olefins" *Can. J. Chem.* **1998**, *76*, 1256-1265.

(11) Yadav, J. S.; Abraham, S.; Reddy, B. V. S.; Sabitha, G. "InCl3-catalyzed conjugate addition of indoles with electron-deficient olefins" *Synthesis* **2001**, 2165-2169.

(12) Bandini, M.; Cozzi, P. G.; Giacomini, M.; Melchiorre, P.; Selva, S.; Umani-Ronchi, A. "Sequential One-Pot InBr3-Catalyzed 1,4- then 1,2-Nucleophilic Addition to Enones" *J. Org. Chem.* **2002**, *67*, 3700-3704.

(13) Bartoli, G.; Bartolacci, M.; Bosco, M.; Foglia, G.; Giuliani, A.; Marcantoni, E.; Sambri, L.; Torregiani, E. "The Michael Addition of Indoles to alpha ,beta -Unsaturated Ketones Catalyzed by CeCl3.7H2O-NaI Combination Supported on Silica Gel" *J. Org. Chem.* **2003**, *68*, 4594-4597.

(14) Shi, M.; Cui, S.-C.; Li, Q.-J. "Zirconium triflate-catalyzed reactions of indole, 1-methylindole, and pyrrole with alpha ,beta -unsaturated ketone" *Tetrahedron* **2004**, *60*, 6679-6684.

(15) Lin, C.; Hsu, J.; Sastry, M. N. V.; Fang, H.; Tu, Z.; Liu, J.-T.; Ching-Fa, Y. "I2-catalyzed Michael addition of indole and pyrrole to nitroolefins" *Tetrahedron* **2005**, *61*, 11751-11757.

(16) Zhang, H.-B.; Liu, L.; Liu, Y.-L.; Chen, Y.-J.; Wang, J.; Wang, D. "Triflic acid-catalyzed Michael reactions of indole and pyrrole compounds with alpha ,beta -unsaturated ketones in water" *Synth. Commun.* **2007**, *37*, 173-181.

(17) Poulsen, T. B.; Jorgensen, K. A. "Catalytic Asymmetric Friedel-Crafts Alkylation Reactions-Copper Showed the Way" *Chem. Rev. (Washington, DC, U. S.)* **2008**, *108*, 2903-2915.

(18) Zhou, W.; Xu, L.-W.; Lyi, L.; Yang, L.; Xia, C.-G. "Enantioselective Michael-type Friedel-Crafts reactions of indoles to enones catalyzed by a chiral camphor-based Broensted acid" *Eur. J. Org. Chem.* **2006**, 5225-5227.

(19) Chen, W.; Du, W.; Yue, L.; Li, R.; Wu, Y.; Ding, L.-S.; Chen, Y.-C. "Organocatalytic enantioselective indole alkylations of alpha ,beta -unsaturated ketones" *Org. Biomol. Chem.* **2007**, *5*, 816-821.

(20) Sui, Y.; Liu, L.; Zhao, J. L.; Wang, D.; Chen, Y. J. "Catalytic and asymmetric Friedel-Crafts alkylation of indoles with nitroacrylates. Application to the synthesis of tryptophan analogues" *Tetrahedron* **2007**, *63*, 5173-5183.

(21) Singh, P. K.; Bisai, A.; Singh, V. K. "Enantioselective Friedel-Crafts alkylation of indoles with nitroalkenes catalyzed by a bis(oxazoline)-Cu(II) complex" *Tetrahedron Lett.* **2007**, *48*, 1127-1129.

(22) Itoh, J.; Fuchibe, K.; Akiyama, T. "Chiral phosphoric acid catalyzed enantioselective Friedel-Crafts alkylation of indoles with nitroalkenes: cooperative effect of 3.ANG. molecular sieves" *Angew. Chem., Int. Ed.* **2008**, *47*, 4016-4018.

(23) Cozzi Pier, G.; Benfatti, F.; Zoli, L. "Organocatalytic asymmetric alkylation of aldehydes by S(N)1-type reaction of alcohols" *Angew Chem Int Ed Engl* **2009**, *48*, 1313-1316.

(24) Desimoni, G.; Faita, G.; Toscanini, M.; Boiocchi, M. "Asymmetric Friedel-Crafts alkylation of indoles with methyl (E)-2-oxo-4- aryl-3-butenoates catalyzed by Sc(OTf)3/pybox" *Chem.--Eur. J.* **2008**, *14*, 3630-3636.

(25) Schatz, A.; Grass Robert, N.; Stark Wendelin, J.; Reiser, O. "TEMPO supported on magnetic C/Co-nanoparticles: a highly active and recyclable organocatalyst" *Chemistry* **2008**, *14*, 8262-8266.

(26) Silvanus, A. C.; Heffernan, S. J.; Liptrot, D. J.; Kociok-KoÌˆhn, G.; Andrews, B. I.; Carbery, D. R. "Stereoselective Double Friedel-Crafts Alkylation of Indoles with Divinyl Ketones" *Org. Lett.* **2009**, *In Press, Accepted Manuscript*.

(27) Singh, P. K.; Singh, V. K. "Highly Enantioselective Friedel-Crafts Reaction of Indoles with 2-EnoylPyridine 1-Oxides Catalyzed by Chiral Pyridine 2,6-Bis(5',5'-diphenyloxazoline)-Cu(II) Complexes" *Org. Lett.* **2008**, *10*, 4121-4124.

(28) Tang, H.-Y.; Lu, A.-D.; Zhou, Z.-H.; Zhao, G.-F.; He, L.-N.; Tang, C.-C. "Chiral phosphoric acid catalyzed asymmetric Friedel-Crafts alkylation of indoles with simple alpha ,beta -unsaturated aromatic ketones" *Eur. J. Org. Chem.* **2008**, 1406-1410.

(29) Banik, B. K.; Fernandez, M.; Alvarez, C. "Iodine-catalyzed highly efficient Michael reaction of indoles under solvent-free condition" *Tetrahedron Lett.* **2005**, *46*, 2479-2482.

(30) Kumar, V.; Kaur, S.; Kumar, S. "Zirconium chloride-catalyzed highly selective and efficient Michael addition of heterocyclic enamines with alpha ,beta - unsaturated carbonyl compounds" *Tetrahedron Lett.* **2006**, *47*, 7001-7005.

(31) Avalos, M.; Babiano, R.; Bravo, J. L.; Cintas, P.; Jiminez, J. L.; Palacios, J. C. "Clay-catalyzed solventless addition reactions of furan with Î±,Î²-unsaturated carbonyl compounds" *Tetrahedron Lett.* **1998**, *39*, 9301-9304.

(32) Bandini, M.; Fagioli, M.; Umani-Ronchi, A. "Solid acid-catalysed Michael-type conjugate addition of indoles to electron-poor C=C bonds: Towards high atom economical semicontinuous processes" *Adv. Synth. Catal.* **2004**, *346*, 545-548.

(33) Ekbote, S. S.; Panda, A. G.; Bhor, M. D.; Bhanage, B. M. "Polyvinylsulfonic acid as a novel Bronsted acid catalyst for Michael addition of indoles to Î±,Î²-unsaturated ketones" *Catal. Commun.* **2009**, *10*, 1569-1573.

(34) Szmuszkovicz, J. "Reaction of substituted indoles with methyl vinyl ketone. New synthesis of 2-methylcarbazole" *J. Am. Chem. Soc.* **1957**, *79*, 2819-2821.

(35) Dinnell, K.; Chicchi, G. G.; Dhar, M. J.; Elliott, J. M.; Hollingworth, G. J.; Kurtz, M. M.; Ridgill, M. P.; Rycroft, W.; Tsao, K. L.; Williams, A. R.; Swain, C. J. "2-Aryl indole NK1 receptor antagonists: optimization of the 2-Aryl ring and the indole nitrogen substituent" *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1237-1240.

(36) Yadav, J. S.; Reddy, B. V. S.; Singh, A. P.; Basak, A. K. "The first one-pot oxidative Michael reaction of Baylis-Hillman adducts with indoles promoted by iodoxybenzoic acid" *Tetrahedron Lett.* **2007**, *48*, 4169-4172.

(37) Yu, C.-J.; Liu, C.-J. "Conjugate addition of indoles to Î±,Î²-unsaturated ketones using a Bronsted acid ionic liquid as an efficient catalyst" *Molecules* **2009**, *14*, 3222-3228.

(38) Gu, D.-g.; Ji, S.-j.; Wang, H.-x.; Xu, Q.-y. "Acidic ionic liquid-catalyzed highly efficient reaction of indoles to Î±,Î²-unsaturated ketones" *Synth. Commun.* **2008**, *38*, 1212-1223.

(39) Cai, Q.; Zhao, Z.-A.; You, S.-L. "Asymmetric construction of polycyclic indoles through olefin cross-metathesis/intramolecular Friedel-Crafts alkylation under sequential catalysis" *Angew. Chem., Int. Ed.* **2009**, *48*, 7428-7431, S7428/7421-S7428/7102.

(40) Kraus, G. A.; Gottschalk, P. "Conjugate additions of furans to enones mediated by iodotrimethylsilane" *Tetrahedron Lett.* **1983**, *24*, 2727-2730.

(41) Dujardin, G.; Poirier, J.-M. "Michael addition of aromatic heterocyclic compounds to Î±,Î²-unsaturated ketones. 3-Oxoalkylation of furans, indoles, and thiophenes" *Bull. Soc. Chim. Fr.* **1994**, *131*, 900-909.

(42) Wang, S.-y.; Ji, S.-j.; Loh, T.-p. "The Michael addition of indole to Î±,Î²-unsaturated ketones catalyzed by iodine at room temperature" *Synlett* **2003**, 2377-2379.

(43) Ramesh, C.; Kavala, V.; Raju, B. R.; Kuo, C.-W.; Yao, C.-F. "Novel synthesis of indolylquinoline derivatives via the C-alkylation of Baylis-Hillman adducts" *Tetrahedron Lett.* **2009**, *50*, 4037-4041.

(44) Blay, G.; Fernandez, I.; Monleon, A.; Pedro, J. R.; Vila, C. "Indirect regioselective heteroarylation of indoles through a Friedel-Crafts reaction with (E)-1,4-diaryl-2-butene-1,4-diones" *Tetrahedron* **2009**, *65*, 9264-9270.

(45) Wang, X.; Zhang, Y.; Xiao, X.; Li, X. "Catalytic conjugate addition of indoles to 4-aryl-4-oxobut-2-enoates by FeCl3" *Chem. Lett.* **2008**, *37*, 1284-1285.

(46) Zhou, W.; Li, L.; Xu, L.-W.; Qiu, H.-Y.; Lai, G.-Q.; Xia, C.-G.; Castanet, A.-S. "Highly efficient heterobimetallic iron-magnesium-HMPA-catalyzed Michael-type Friedel-Crafts reactions of indoles and chalcones" *Synth. Commun.* **2008**, *38*, 1638-1645.

(47) Yamauchi, M.; Shirota, M.; Watanabe, T. "Reactions of 2-methylene-1,3-dicarbonyl compounds with furan" *Heterocycles* **1990**, *31*, 1699-1704.

(48) Marrone, A.; Renzetti, A.; De, M. P.; Gerard, S.; Sapi, J.; Fontana, A.; Re, N. "Condensation of Î²-Diester Titanium Enolates with Carbonyl Substrates: A Combined DFT and Experimental Investigation" *Chem. - Eur. J.* **2009**, *15*, 11537-11550, S11537/11531-S11537/11523.

(49) Zhan, Z.-P.; Yang, R.-F.; Lang, K. "Samarium triiodide-catalyzed conjugate addition of indoles with electron-deficient olefins" *Tetrahedron Lett.* **2005**, *46*, 3859-3862.

(50) Maiti, G.; Kundu, P. "Antimony trichloride-catalyzed Michael addition of indoles to the Î±,Î²-unsaturated ketones" *Synth. Commun.* **2007**, *37*, 2309-2316.

(51) Ambrogio, I.; Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F. "Gold-catalyzed synthesis of 2-substituted, 2,3-disubstituted and 1,2,3-trisubstituted indoles in [bmim]BF4" *Synlett* **2007**, 1775-1779.

(52) Arcadi, A.; Bianchi, G.; Chiarini, M.; D'Anniballe, G.; Marinelli, F. "Gold-catalyzed conjugate addition type reaction of indoles with Î±,Î²-enones" *Synlett* **2004**, 944-950.

(53) Hashmi, A. S. K.; Salathe, R.; Frey, W. "Gold catalysis: selectivity problems in hydroarylations with pyrroles" *Eur. J. Org. Chem.* **2007**, 1648-1652.

(54) Harrington, P. E.; Kerr, M. A. "Reaction of indoles with electron deficient olefins catalyzed by Yb(OTf)3.3H2O" *Synlett* **1996**, 1047-1048.

(55) Lin, Y.-D.; Kao, J.-Q.; Chen, C.-T. "Catalytic conjugate additions of nitrogen-, phosphorus-, and carbon-containing nucleophiles by amphoteric vanadyl triflate" *Org. Lett.* **2007**, *9*, 5195-5198.

(56) Alam, M. M.; Varala, R.; Adapa, S. R. "Conjugate addition of indoles and thiols with electron-deficient olefins catalyzed by Bi(OTf)3" *Tetrahedron Lett.* **2003**, *44*, 5115-5119.

(57) Kawatsura, M.; Aburatani, S.; Uenishi, J. "Hafnium trifluoromethanesulfonate [Hf(OTf)4]-catalyzed conjugate addition of indoles to Î±,Î²-enones" *Synlett* **2005**, 2492-2494.

(58) Bulbule, V. J.; Deshpande, V. H.; Bedekar, A. V. "Cu(OTf)2 catalysed reactions of furan and thiophene with Î±,Î²-unsaturated ketones" *J. Chem. Res., Synop.* **2000**, 220-221.

(59) Jensen, K. B.; Thorbauge, J.; Hazell, R. G.; Joergensen, K. A. "Catalytic asymmetric Friedel-Crafts alkylation of Î²,Î³-unsaturated Î±-keto esters: enantioselective addition of aromatic C-H bonds to alkenes" *Angew. Chem., Int. Ed.* **2001**, *40*, 160-163.

(60) Zhuang, W.; Hazell, R. G.; Jorgensen, K. A. "Catalytic enantioselective addition of aromatic amines to enones: synthesis of optically active Î²-amino acid derivatives" *Chem. Commun. (Cambridge, U. K.)* **2001**, 1240-1241.

(61) Rasappan, R.; Hager, M.; Gissibl, A.; Reiser, O. "Highly Enantioselective Michael Additions of Indole to Benzylidene Malonate Using Simple Bis(oxazoline) Ligands: Importance of Metal/Ligand Ratio" *Org. Lett.* **2006**, *8*, 6099-6102.

(62) Palomo, C.; Oiarbide, M.; Kardak, B. G.; Garcia, J. M.; Linden, A. "Highly Enantioselective Friedel-Crafts Alkylations of Pyrroles and Indoles with Î±'-Hydroxy Enones under Cu(II)-Simple Bis(oxazoline) Catalysis" *J. Am. Chem. Soc.* **2005**, *127*, 4154-4155.

(63) Evans, D. A.; Scheidt, K. A.; Fandrick, K. R.; Lam, H. W.; Wu, J. "Enantioselective Indole Friedel-Crafts Alkylations Catalyzed by Bis(oxazolinyl)pyridine-Scandium(III) Triflate Complexes" *J. Am. Chem. Soc.* **2003**, *125*, 10780-10781.

(64) Evans, D. A.; Fandrick, K. R.; Song, H.-J.; Scheidt, K. A.; Xu, R. "Enantioselective Friedel-Crafts Alkylations Catalyzed by Bis(oxazolinyl)pyridine-Scandium(III) Triflate Complexes" *J. Am. Chem. Soc.* **2007**, *129*, 10029-10041.

(65) Bandini, M.; Fagioli, M.; Melchiorre, P.; Melloni, A.; Umani-Ronchi, A. "Catalytic enantioselective conjugate addition of indoles to simple Î±,Î²-unsaturated ketones" *Tetrahedron Lett.* **2003**, *44*, 5843-5846.

(66) Blay, G.; Fernandez, I.; Pedro, J. R.; Vila, C. "Highly Enantioselective Friedel-Crafts Alkylations of Indoles with Simple Enones Catalyzed by Zirconium(IV)-BINOL Complexes" *Org. Lett.* **2007**, *9*, 2601-2604.

(67) Paras, N. A.; MacMillan, D. W. C. "New Strategies in Organic Catalysis: The First Enantioselective Organocatalytic Friedel-Crafts Alkylation" *J. Am. Chem. Soc.* **2001**, *123*, 4370-4371.

(68) Lee, S.; MacMillan, D. W. C. "Organocatalytic Vinyl and Friedel-Crafts Alkylations with Trifluoroborate Salts" *J. Am. Chem. Soc.* **2007**, *129*, 15438-15439.

(69) Chen, W.; Du, W.; Yue, L.; Li, R.; Wu, Y.; Ding, L.-S.; Chen, Y.-C. "Organocatalytic enantioselective indole alkylations of Î±,Î²-unsaturated ketones" *Org. Biomol. Chem.* **2007**, *5*, 816-821.

(70) Bartoli, G.; Bosco, M.; Carlone, A.; Pesciaioli, F.; Sambri, L.; Melchiorre, P. "Organocatalytic Asymmetric Friedel-Crafts Alkylation of Indoles with Simple Î±,Î²-Unsaturated Ketones" *Org. Lett.* **2007**, *9*, 1403-1405.

(71) Ng, J. S.; Behling, J. R.; Campbell, A. L.; Duy, N.; Lipshutz, B. "Reactions of higher order cyanocuprates derived from 2-lithiated furans: scope, limitations, and synthetic utility" *Tetrahedron Lett.* **1988**, *29*, 3045-3048.

(72) Jones, P.; Reddy, C. K.; Knochel, P. "Conjugate Michael additions with mixed diorganozincs" *Tetrahedron* **1998**, *54*, 1471-1490.

(73) Yoshida, K.; Hayashi, T. "Rhodium-catalyzed asymmetric 1,4-addition of 3-thiopheneboronic acid to Î±,Î²-unsaturated carbonyl compounds" *Heterocycles* **2003**, *59*, 605-611.

(74) Konno, T.; Tanaka, T.; Miyabe, T.; Morigaki, A.; Ishihara, T. "A first high enantiocontrol of an asymmetric tertiary carbon center attached with a fluoroalkyl group via Rh(I)-catalyzed conjugate addition reaction" *Tetrahedron Lett.* **2008**, *49*, 2106-2110.

(75) Le, N. J.; Allen, J. C.; Frost, C. G. "Enantioselective rhodium-catalyzed 1,4-additions of 2-heteroarylzinc donors using Me-DUPHOS" *Chem. Commun. (Cambridge, U. K.)* **2008**, 3795-3797.

(76) Smith, A. J.; Abbott, L. K.; Martin, S. F. "Enantioselective Conjugate Addition Employing 2-Heteroaryl Titanates and Zinc Reagents" *Org. Lett.* **2009**, *11*, 4200-4203.

(77) Hofmann, M.; Hampel, N.; Kanzian, T.; Mayr, H. "Electrophilic alkylations in neutral aqueous or alcoholic solutions" *Angew. Chem., Int. Ed.* **2004**, *43*, 5402-5405.

(78) Grieco, P. A.; Handy, S. T. "Magnesium trifluoromethanesulfonimide(triflimide) promoted substitution reactions of allylic and benzylic acetates. Magnesium triflimide as a substitute for magnesium perchlorate." *Tetrahedron Lett.* **1997**, *38*, 2645-2648.

(79) Balaban, A. T.; Bota, A.; Zlota, A. "1,1-Bis[2-furyl]ethanes from 1-(2-furyl)ethanols" *Synthesis* **1980**, 136-138.

(80) Caron, S.; Vazquez, E. "The Synthesis of a Selective PDE4/TNFalpha Inhibitor" *Org. Process Res. Dev.* **2001**, *5*, 587-592.

(81) Comins, D. L.; Stroud, E. D. "Synthesis of 3-substituted indoles via N-acylindolium ions" *Tetrahedron Lett.* **1986**, *27*, 1869-1872.

(82) MacKay, J. A.; Bishop, R. L.; Rawal, V. H. "Rapid Synthesis of the N-Methylwelwitindolinone Skeleton" *Org. Lett.* **2005**, *7*, 3421-3424.

(83) Muratake, H.; Natsume, M. "Synthetic Studies of Marine Alkaloids Hapalindoles .1. Total Synthesis of (+/-)-Hapalindole-J and (+/-)-Hapalindole-M" *Tetrahedron* **1990**, *46*, 6331-6342.

(84) Noji, M.; Ohno, T.; Fuji, K.; Futaba, N.; Tajima, H.; Ishii, K. "Secondary Benzylation Using Benzyl Alcohols Catalyzed by Lanthanoid, Scandium, and Hafnium Triflate" *J. Org. Chem.* **2003**, *68*, 9340-9347.

(85) Oh, K.-T.; Ka, J.-W.; Park, J.-Y.; Lee, C.-H. "Convenient synthesis of dipyrromethanes containing heteroatoms other than nitrogen" *Bull. Korean Chem. Soc.* **1997**, *18*, 222-224.

(86) Rueping, M.; Nachtsheim, B. J.; Moreth, S. A.; Bolte, M. "Asymmetric Broensted acid catalysis: enantioselective nucleophilic substitutions and 1,4-additions" *Angew. Chem., Int. Ed.* **2008**, *47*, 593-596.

(87) Schwenter, M.-E.; Vogel, P. "A new, non-iterative asymmetric synthesis of long-chain 1,3-polyols" *Chem.--Eur. J.* **2000**, *6*, 4091-4103.

(88) Sessler, J. L.; An, D.; Cho, W.-S.; Lynch, V. "Calix[2]bipyrrole[2]furan and Calix[2]bipyrrole[2]thiophene: New Pyrrolic Receptors Exhibiting a Preference for Carboxylate Anions" *J. Am. Chem. Soc.* **2003**, *125*, 13646-13647.

(89) Snyder, H. R.; Smith, C. W.; Stewart, J. M. "C-Alkylation with quaternary ammonium salts. A new approach to the synthesis of compounds containing the Î²-indolemethylene group" *J. Am. Chem. Soc.* **1944**, *66*, 200-204.

(90) Kornfeld, E. C.; Fornefeld, E. J.; Kline, G. B.; Mann, M. J.; Morrison, D. E.; Jones, R. G.; Woodward, R. B. "Total synthesis of lysergic acid" *J. Am. Chem. Soc.* **1956**, *78*, 3087-3114.

(91) Johnson, H. E.; Crosby, D. G. "3-Indolepropionic acid" *J. Org. Chem.* **1960**, *25*, 569-571.

(92) Snyder, H. R.; Smith, C. W. "Convenient synthesis of dl-tryptophan" *J. Am. Chem. Soc.* **1944**, *66*, 350-351.

(93) Hoffmann, E.; Ikan, R.; Galun, A. B. "The synthesis of 5-fluoro- and 7-menthylindole and -tryptophan" *J. Heterocycl. Chem.* **1965**, *2*, 298-299.

(94) Semenov, A. A.; Terent'eva, I. V. "Indole derivatives. I. Î²-(3-Indolyl) ketones" *Khim. Geterotsikl. Soedin.* **1965**, 235-239.

(95) Von, S. M.; Cohen, M. P.; Shavel, J., Jr. "Carbon-carbon alkylations of enamines with Mannich bases" *J. Org. Chem.* **1965**, *30*, 3240-3242.

(96) Suzuki, M.; Miyahara, T.; Yoshioka, R.; Miyoshi, M.; Matsumoto, K. "Synthesis of amino acids and related compounds. Synthesis of Î±-methylamino acids" *Agric. Biol. Chem.* **1974**, *38*, 1709-1715.

(97) Freidinger, R. M. "Synthesis of Î³-lactam-constrained tryptophyl-lysine derivatives" *J. Org. Chem.* **1985**, *50*, 3631-3633.

(98) Moyroud, J.; Gelin, J.; Chene, A.; Mortier, J. "Synthesis of structural analogs of thaxtomins, phytotoxins responsible for potato scab" *Tetrahedron* **1996**, *52*, 8525-8534.

(99) Mendoza, O.; Rossey, G.; Ghosez, L. "Broensted acid-catalyzed synthesis of diarylmethanes under non-genotoxic conditions" *Tetrahedron Lett.*, *52*, 2235-2239.

(100) Bhat, V.; Allan, K. M.; Rawal, V. H. "Total Synthesis of N-Methylwelwitindolinone D Isonitrile" *J. Am. Chem. Soc.* **2011**, *133*, 5798-5801.

(101) Allan, K. M.; Kobayashi, K.; Rawal, V. H. "A Unified Route to the Welwitindolinone Alkaloids: Total Syntheses of (-)-N-Methylwelwitindolinone C Isothiocyanate, (-)-N-Methylwelwitindolinone C Isonitrile, and (-)-3-Hydroxy-N-methylwelwitindolinone C Isothiocyanate" *J. Am. Chem. Soc.* **2012**, *134*, 1392-1395.

(102) Shaikh, R. R.; Mazzanti, A.; Petrini, M.; Bartoli, G.; Melchiorre, P. "Proline-catalyzed asymmetric formal Î±-alkylation of aldehydes via vinylogous iminium

ion intermediates generated from arylsulfonyl indoles" *Angew. Chem., Int. Ed.* **2008**, *47*, 8707-8710.

(103) Cozzi, P. G.; Benfatti, F.; Zoli, L. "Organocatalytic asymmetric alkylation of aldehydes by SN-1-type reaction of alcohols" *Angew. Chem., Int. Ed.* **2009**, *48*, 1313-1316.

(104) Gulledge, D. B. Thesis, 2005.

(105) Fu, T.-h.; Bonaparte, A.; Martin, S. F. "Synthesis of β-Heteroaryl Propionates via Trapping of Carbocations with π-Nucleophiles" *Tetrahedron Lett.* **2009**, *In Press, Accepted Manuscript*.

(106) Fuentes, L. M.; Shinkai, I.; Salzmann, T. N. "Lewis Acid Mediated Condensation of Chiral Imide Enolates - a General-Approach to the Synthesis of Chiral Carbapenem Precursors" *J. Am. Chem. Soc.* **1986**, *108*, 4675-4676.

(107) Fu, T.-h.; Bonaparte, A.; Martin, S. F. "Synthesis of β-heteroaryl propionates via trapping of carbocations with π-nucleophiles [Erratum to document cited in CA151:148032]" *Tetrahedron Lett.* **2011**, *53*, 3530.

(108) Rao, K. V. "PA 155 A: A new antibiotic" *Antibiot. Chemother. (Washington, D. C.)* **1960**, *10*, 312-315.

(109) Marsh, W. S.; Garretson, A. L.; Wesel, E. M. "PA 155 A, B, and X. Antibiotics produced by a strain of Streptomyces albus" *Antibiot. Chemother. (Washington, D. C.)* **1960**, *10*, 316-320.

(110) Kim, J. N.; Jung, K. S.; Lee, H. J.; Son, J. S. "A facile one-pot preparation of isothiocyanates from aldoximes" *Tetrahedron Lett.* **1997**, *38*, 1597-1598.

(111) Kim, J. N.; Ryu, E. K. "A convenient synthesis of isothiocyanates from nitrile oxides" *Tetrahedron Lett.* **1993**, *34*, 8283-8284.

(112) Kitano, M.; Kojima, A.; Nakano, K.; Miyagishi, A.; Noguchi, T.; Ohashi, N. "Synthesis and biological activity of N-(aminoiminomethyl)-1H-indole carboxamide derivatives as Na+/H+ exchanger inhibitors" *Chem. Pharm. Bull.* **1999**, *47*, 1538-1548.

(113) Lin, S. C.; Yang, F. D.; Shiue, J. S.; Yang, S. M.; Fang, J. M. "Indolecarbonyl coupling reactions promoted by samarium diiodide. Application to the synthesis of indole-fused compounds" *J. Org. Chem.* **1998**, *63*, 2909-2917.

(114) Mikami, K.; Matsumoto, S. "Light-Catalyzed Carbon-Carbon Bond Formation of C-60 with Ketene Silyl Acetals - Fullerene Functionalization Chemistry" *Synlett* **1995**, 229-230.

(115) Sundberg, R. J. *The Chemistry of Indoles (Organic Chemistry; a Series of Monographs, Vol. 18)*; Academic, 1970.

(116) Bloor, J. E.; Breen, D. L. "Valence-shell calculations on polyatomic molecules. I. Complete neglect of differential overlap self consistent field calculations on nitrogen and oxygen heterocyclics" *J. Amer. Chem. Soc.* **1967**, *89*, 6835-6841.

(117) Kita, Y.; Segawa, J.; Haruta, J.; Yasuda, H.; Tamura, Y. "Ketene silyl acetal chemistry; simple synthesis of methyl jasmonate and related compounds by utilising ketene methyl dimethyl-tert-butylsilyl acetal" *J. Chem. Soc., Perkin Trans. 1* **1982**, 1099-1104.

(118) Camiletti, C.; Dhavale, D. D.; Donati, F.; Trombini, C. "Regioselective addition of 1-trimethylsilyloxy-1-methoxy-1,3-dienes to aldonitrones catalyzed by trimethylsilyl triflate" *Tetrahedron Lett.* **1995**, *36*, 7293-7296.

(119) Savard, J.; Brassard, P. "Reactions of ketene acetals - 14. The use of simple mixed vinylketene acetals in the annulation of quinones" *Tetrahedron* **1984**, *40*, 3455-3464.

(120) Damiletti, C.; Dhavale, D. D.; Donati, F.; Trombini, C. "Regioselective addition of 1-trimethylsilyloxy-1-methoxy-1,3-dienes to aldonitrones catalyzed by trimethylsilyl triflate" *Tetrahedron Lett.* **1995**, *36*, 7293-7296.

(121) Paterson, I.; Price, L. G. "O-silylated dienolates in organic synthesis: Î³-selective alkylation of unsaturated carbonyl compounds by 1,3-dithienium fluoroborate" *Tetrahedron Lett.* **1981**, *22*, 2833-2836.

(122) Agnusdei, M.; Bandini, M.; Melloni, A.; Umani-Ronchi, A. "New versatile route to the synthesis of tetrahydro-beta-carbolines and tetrahydro-pyrano[3,4-b]indoles via an intramolecular Michael addition catalyzed by $InBr_3$" *J. Org. Chem.* **2003**, *68*, 7126-7129.

(123) Meyer, M. D.; Kruse, L. I. "Ergoline synthons: Synthesis of 3,4-dihydro-6-methoxybenz[cd]indol-5(1H)-one (6-methoxy-Uhle's ketone) and 3,4-dihydrobenz[cd]indol-5(1H)-one (Uhle's ketone) via a novel decarboxylation of indole-2-carboxylates" *J. Org. Chem.* **1984**, *49*, 3195-3199.

(124) Sechi, M.; Derudas, M.; Dallocchio, R.; Dessi, A.; Bacchi, A.; Sannia, L.; Carta, F.; Palomba, M.; Ragab, O.; Chan, C.; Shoemaker, R.; Sei, S.; Dayam, R.; Neamati, N. "Design and synthesis of novel indole beta-diketo acid derivatives as HIV-1 integrase inhibitors" *J. Med. Chem.* **2004**, *47*, 5298-5310.

(125) Bergman, J.; Norrby, P. O.; Tilstam, U.; Venemalm, L. "Structure elucidation of some products obtained by acid-catalyzed condensation of indole with acetone" *Tetrahedron* **1989**, *45*, 5549-5564.

(126) Ganton, M. D.; Kerr, M. A. "A domino amidation route to indolines and indoles: Rapid syntheses of anhydrolycorinone, hippadine, oxoassoanine, and pratosine" *Org. Lett.* **2005**, *7*, 4777-4779.

(127) Gajewski, J. J.; Gee, K. R.; Jurayj, J. "Energetic and Rate Effects of the Trifluoromethyl Group at C-2 and C-4 on the Aliphatic Claisen Rearrangement" *J. Org. Chem.* **1990**, *55*, 1813-1822.

(128) Pelter, A.; Ward, R. S.; Sirit, A. "Asymmetric synthesis of butenolide and butyrolactone derivatives" *Tetrahedron: Asymm.* **1994**, *5*, 1745-1762.

(129) Granger, B. A.; Jewett, I. T.; Butler, J. D.; Hua, B.; Knezevic, C. E.; Parkinson, E. I.; Hergenrother, P. J.; Martin, S. F. "Synthesis of (Â±)-Actinophyllic Acid and Analogs: Applications of Cascade Reactions and Diverted Total Synthesis" *J. Am. Chem. Soc.*, *135*, 12984-12986.

(130) Earle, M. J.; McAuley, B. J.; Ramani, A.; Sedden, K. R.; Thomson, J. M.; (The Queen's University of Belfast, UK). Application: WO, 2002, p 85 pp.

(131) Ratnikov, M. O.; Tumanov, V. V.; Smit, W. A. "Lewis acid catalyst free electrophilic alkylation of silicon-capped pi donors in 1,1,1,3,3,3-hexafluoro-2-propanol" *Angew. Chem., Int. Ed.* **2008**, *47*, 9739-9742.

(132) Drueckhammer, D. G.; Barbas, C. F., III; Nozaki, K.; Wong, C. H.; Wood, C. Y.; Ciufolini, M. A. "Chemoenzymic synthesis of chiral furan derivatives: useful building blocks for optically active structures" *J. Org. Chem.* **1988**, *53*, 1607-1611.

(133) Noland, W. E.; Lee, C. K.; Bae, S. K.; Chung, B. Y.; Hahn, C. S.; Kim, K. J. "Diels-Alder Reactions of Vinyl Derivatives of 5-Membered Monoheterocyclic Compounds" *J. Org. Chem.* **1983**, *48*, 2488-2491.

(134) Wallace, D. M.; Leung, S. H.; Senge, M. O.; Smith, K. M. "Rational Tetraarylporphyrin Syntheses - Tetraarylporphyrins from the Macdonald Route" *J. Org. Chem.* **1993**, *58*, 7245-7257.

(135) Artico, M.; Silvestri, R.; Massa, S.; Loi, A. G.; Corrias, S.; Piras, G.; La Colla, P. "2-Sulfonyl-4-chloroanilino moiety: A potent pharmacophore for the anti-human immunodeficiency virus Type 1 activity of pyrrolyl aryl sulfones" *J. Med. Chem.* **1996**, *39*, 522-530.

(136) Xiao, D.; Ketcha, D. M. "Diels-Alder reactions of 2- and 3-vinyl-1-(phenylsulfonyl)pyrroles" *J. Heterocycl. Chem.* **1995**, *32*, 499-503.

(137) Xiong, C. Y.; Wang, W.; Cai, C. Z.; Hruby, V. J. "Regioselective and stereoselective nucleophilic ring opening reactions of a phenyl-substituted aziridine: Enantioselective synthesis of beta-substituted tryptophan, cysteine, and serine derivatives" *J. Org. Chem.* **2002**, *67*, 1399-1402.

(138) Martin-Matute, B.; Edin, M.; Bogar, K.; Kaynak, F. B.; Baeckvall, J.-E. "Combined Ruthenium(II) and Lipase Catalysis for Efficient Dynamic Kinetic Resolution of Secondary Alcohols. Insight into the Racemization Mechanism" *J. Am. Chem. Soc.* **2005**, *127*, 8817-8825.

(139) Martin, S. F. "Methodology for the construction of quaternary carbon centers" *Tetrahedron* **1980**, *36*, 419-460.

(140) Naredla, R. R.; Klumpp, D. A. "Contemporary Carbocation Chemistry: Applications in Organic Synthesis" *Chem. Rev. (Washington, DC, U. S.)*, Ahead of Print.

(141) Saulnier, M. G.; Dodier, M.; Frennesson, D. B.; Langley, D. R.; Vyas, D. M. "Nucleophilic Capture of the Imino-Quinone Methide Type Intermediates Generated from 2-Aminothiazol-5-yl Carbinols" *Org. Lett.* **2009**, *11*, 5154-5157.

(142) Goto, K.; Sudzuki, H. "Sinomenine and disinomenine. IX. Acutumine and sinactine" *Bull. Chem. Soc. Jpn.* **1929**, *4*, 220-224.

(143) Yu, B.-W.; Chen, J.-Y.; Wang, Y.-P.; Cheng, K.-F.; Li, X.-Y.; Qin, G.-W. "Alkaloids from Menispermum dauricum" *Phytochemistry* **2002**, *61*, 439-442.

(144) Goto, K.; Tomita, M.; Okamoto, Y.; Kikuchi, T.; Osaki, K.; Nishikawa, M.; Kamiya, K.; Sasaki, Y.; Matoba, K. "Structures of acutumine and acutumidine" *Proc. Jap. Acad.* **1967**, *43*, 499-504.

(145) Goto, K.; Tomita, M.; Okamoto, Y.; Sasaki, Y.; Matoba, K. "Characterization of acutumine" *Proc. Jpn. Acad.* **1966**, *42*, 1181-1184.

(146) Tomita, M.; Okamoto, Y.; Kikuchi, T.; Osaki, K.; Nishikawa, M.; Kamiya, K.; Sasaki, Y.; Matoba, K.; Goto, K. "Acutumine and acutumidine, chlorine-containing alkaloids with a novel skeleton. I. X-ray analysis of acutumine" *Tetrahedron Lett.* **1967**, 2421-2424.

(147) Tomita, M.; Okamoto, Y.; Kikuchi, T.; Osaki, K.; Nishikawa, M.; Kamiya, K.; Sasaki, Y.; Matoba, K.; Goto, K. "Acutumine and acutumidine, chlorine-containing alkaloids with a novel skeleton. II. Chemical proof" *Tetrahedron Lett.* **1967**, 2425-2430.

(148) Cheng, P.; Ma, Y.-b.; Yao, S.-y.; Zhang, Q.; Wang, E.-j.; Yan, M.-h.; Zhang, X.-m.; Zhang, F.-x.; Chen, J.-j. "Two new alkaloids and active anti-hepatitis B virus constituents from Hypserpa nitida" *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5316-5320.

(149) Qin, G.-W.; Tang, X.-C.; Lestage, P.; Caignard, D.-H.; Renard, P.; (Shanghai Institute of Materia Medica, Peop. Rep. China; Les Laboratoires Servier). Application: WO, 2003, p 37 pp.

(150) Sugimoto, Y.; Uchida, S.; Inanaga, S.; Kimura, Y.; Hashimoto, M.; Isogai, A. "Early steps of dauricine biosynthesis in cultured roots of Menispermum dauricum" *Biosci., Biotechnol., Biochem.* **1996**, *60*, 503-505.

(151) Babiker, H. A. A.; Sugimoto, Y.; Saisho, T.; Inanaga, S.; Hashimoto, M.; Isogai, A. "Biosynthetic relationship between acutumine and dechloroacutumine in Menispermum dauricum root cultures" *Biosci., Biotechnol., Biochem.* **1999**, *63*, 515-518.

(152) Sugimoto, Y.; Babiker, H. A. A.; Saisho, T.; Furumoto, T.; Inanaga, S.; Kato, M. "Chlorinated alkaloids in Menispermum dauricum DC. root culture" *J. Org. Chem.* **2001**, *66*, 3299-3302.

(153) Sugimoto, Y.; Matsui, M.; Babiker, H. A. A. "Conversion of dechlorodauricumine into chlorinated alkaloids in Menispermum dauricum root culture" *Phytochemistry (Elsevier)* **2007**, *68*, 493-498.

(154) Barton, D. H. R.; Kirby, A. J.; Kirby, G. W. "Biosynthesis of sinomenine" *Chem. Commun. (London)* **1965**, 52.

(155) Barton, D. H. R.; Kirby, A. J.; Kirby, G. W. "Phenol oxidation and biosynthesis. XVII. Biosynthesis of sinomenine" *J. Chem. Soc.* **1968**, 929-936.

(156) Matoba, K.; Karibe, N.; Yamazaki, T. "Chemistry of 2-methoxy-2,5-cyclohexadienones. II. Oxidation of 2-methoxy-4,4-dimethyl-2,5-cyclohexadienone" *Chem. Pharm. Bull.* **1984**, *32*, 2639-2645.

(157) Waller David, L.; Stephenson Corey, R. J.; Wipf, P. "Spiroketals via oxidative rearrangement of enol ethers" *Org Biomol Chem* **2007**, *5*, 58-60.

(158) Georgian, V.; Kundu, N. "Transformation of D-homosteroids to steroids. Stereospecific benzilic acid rearrangement" *Tetrahedron* **1963**, *19*, 1037-1049.

(159) Greenhalgh, N. "Preparation of 1,4- and 2,4-dichloro-9-hydroxyfluorene-9-carboxylic acids" *J. Chem. Soc.* **1954**, 4699-4700.

(160) Holzel, R.; Leftwick, A. P.; Weedon, B. C. L. "Synthesis of violerythrin and actinioerythrol" *Chem. Commun.* **1969**, 128-129.

(161) Liu, H.; Siegel, D. R.; Danishefsky, S. J. "Studies Directed toward the Synthesis of Terreulactone A: Rapid Construction of the A, B, C Rings" *Org. Lett.* **2006**, *8*, 423-425.

(162) Moreau, R. J.; Sorensen, E. J. "Classical carbonyl reactivity enables a short synthesis of the core structure of acutumine" *Tetrahedron* **2007**, *63*, 6446-6453.

(163) Li, F.; Tartakoff, S. S.; Castle, S. L. "Total Synthesis of (-)-Acutumine" *J. Am. Chem. Soc.* **2009**, *131*, 6674-6675.

(164) Navarro, R.; Reisman, S. E. "Rapid Construction of the Aza-Propellane Core of Acutumine via a Photochemical [2 + 2] Cycloaddition Reaction" *Org. Lett.*, *14*, 4354-4357.

(165) King, S. M.; Calandra, N. A.; Herzon, S. B. "Total Syntheses of (-)-Acutumine and (-)-Dechloroacutumine" *Angew. Chem., Int. Ed.* **2013**, *52*, 3642-3645.

(166) Moyer, M. P.; Feldman, P. L.; Rapoport, H. "Intramolecular nitrogen-hydrogen, oxygen-hydrogen and sulfur-hydrogen insertion reactions. Synthesis of heterocycles from alpha -diazo beta -keto esters" *J. Org. Chem.* **1985**, *50*, 5223-5230.

(167) Chuang, K. V.; Navarro, R.; Reisman, S. E. "Short, Enantioselective Total Syntheses of (-)-8-Demethoxyrunanine and (-)-Cepharatines A, C, and D" *Angew. Chem., Int. Ed.*, *50*, 9447-9451, S9447/9441-S9447/9483.

(168) Barton, D. H. R.; De, M. P.; Shafiq, M. "Photochemical transformations. V. Constitutions of photosantonic acid and derivatives" *J. Chem. Soc.* **1958**, 3314-3319.

(169) Li, F.; Castle, S. L. "Synthesis of the Acutumine Spirocycle via a Radical-Polar Crossover Reaction" *Org. Lett.* **2007**, *9*, 4033-4036.

(170) Reeder, M. D.; Srikanth, G. S. C.; Jones, S. B.; Castle, S. L. "Synthesis of the Core Structure of Acutumine" *Org. Lett.* **2005**, *7*, 1089-1092.

(171) Nakamura, M.; Hirai, A.; Sogi, M.; Nakamura, E. "Enantioselective Addition of Allylzinc Reagent to Alkynyl Ketones" *J. Am. Chem. Soc.* **1998**, *120*, 5846-5847.

(172) Myers, A. G.; Hammond, M.; Wu, Y. "An improved preparation of highly enantiomerically enriched (R)-(+)-4-tert-butyldimethylsiloxy-2-cyclopenten-1-one" *Tetrahedron Lett.* **1996**, *37*, 3083-3086.

(173) Jones, S. B.; He, L.; Castle, S. L. "Total Synthesis of (+-)-Hasubanonine" *Org. Lett.* **2006**, *8*, 3757-3760.

(174) Kurosawa, K.; Ollis, W. D.; Sutherland, I. O.; Gottlieb, O. R.; De Oliveira, A. B. "Neoflavonoid group of natural products. Part 7. Mucronustyrene, mucronulastyrene and villostyrene, cinnamylphenols from Machaerium mucronulatum and M. villosum" *Phytochemistry* **1978**, *17*, 1389-1394.

(175) Soderquist, J. A.; Kock, I.; Estrella, M. E. "Reductive Cleavage of Acetals and Ketals with 9-Borabicyclo[3.3.1]nonane" *Org. Process Res. Dev.* **2006**, *10*, 1076-1079.

(176) Ryu, D. H.; Zhou, G.; Corey, E. J. "Enantioselective and Structure-Selective Diels-Alder Reactions of Unsymmetrical Quinones Catalyzed by a Chiral Oxazaborolidinium Cation. Predictive Selection Rules" *J. Am. Chem. Soc.* **2004**, *126*, 4800-4802.

(177) Smith, A. B., III; Han, Q.; Breslin, P. A. S.; Beauchamp, G. K. "Synthesis and Assignment of Absolute Configuration of (-)-Oleocanthal: A Potent, Naturally Occurring Non-steroidal Anti-inflammatory and Anti-oxidant Agent Derived from Extra Virgin Olive Oils" *Org. Lett.* **2005**, *7*, 5075-5078.

(178) Ogoshi, S.; Tomiyasu, S.; Morita, M.; Kurosawa, H. "Palladium/Me3SiOTf-Catalyzed Bis-silylation of Î±,Î²-Unsaturated Carbonyl Compounds without Involving Oxidative Addition of Disilane" *J. Am. Chem. Soc.* **2002**, *124*, 11598-11599.

(179) Alami, M.; Ferri, F. "Regio- and stereocontrolled hydrostannation of (E)- and (Z)-chloro enynes. An efficient preparation of chloro dienyl tributyltin reagents" *Synlett* **1996**, 755-756.

(180) Takeda, T.; Kanamori, F.; Matsusita, H.; Fujiwara, T. "The Friedel-Crafts reaction of 1-(phenylthio)vinyl chlorides" *Tetrahedron Lett.* **1991**, *32*, 6563-6566.

(181) Brown, J. M.; Naik, R. G. "Chelate control in the rhodium-catalyzed homogeneous hydrogenation of chiral allylic and homoallylic alcohols" *J. Chem. Soc., Chem. Commun.* **1982**, 348-350.

(182) Crabtree, R. H.; Davis, M. W. "Occurrence and origin of a pronounced directing effect of a hydroxyl group in hydrogenation with [Ir(cod)P(C6H11)3(py)]PF6" *Organometallics* **1983**, *2*, 681-682.

(183) Stork, G.; Kahne, D. E. "Stereocontrol in homogeneous catalytic hydrogenation via hydroxyl group coordination" *J. Am. Chem. Soc.* **1983**, *105*, 1072-1073.

(184) Evans, D. A.; Morrissey, M. M. "Rhodium(I)-catalyzed hydrogenation of olefins. The documentation of hydroxyl-directed stereochemical control in cyclic and acyclic systems" *J. Am. Chem. Soc.* **1984**, *106*, 3866-3868.

(185) Majetich, G.; Wheless, K. "Remote intramolecular free radical functionalizations: an update" *Tetrahedron* **1995**, *51*, 7095-7129.

(186) Togo, H.; Katohgi, M. "Synthetic uses of organohypervalent iodine compounds through radical pathways" *Synlett* **2001**, 565-581.

(187) Hawari, J. A.; Davis, S.; Engel, P. S.; Gilbert, B. C.; Griller, D. "The free radical reaction between alkanes and carbon tetrachloride" *J. Am. Chem. Soc.* **1985**, *107*, 4721-4724.

(188) Chen, K.; Richter, J. M.; Baran, P. S. "1,3-Diol Synthesis via Controlled, Radical-Mediated C-H Functionalization" *J. Am. Chem. Soc.* **2008**, *130*, 7247-7249.

(189) Yamashita, H.; Mukaiyama, T. "Asymmetric Michael addition of thiophenol to maleic acid esters" *Chem. Lett.* **1985**, 363-366.

(190) McDaid, P.; Chen, Y.; Deng, L. "A highly enantioselective and general conjugate addition of thiols to cyclic enones with an organic catalyst" *Angew. Chem., Int. Ed.* **2002**, *41*, 338-340.

(191) Enders, D.; Luettgen, K.; Narine, A. A. "Asymmetric sulfa-Michael additions" *Synthesis* **2007**, 959-980.

(192) Strunz, G. M.; Ren, W.-Y.; Stillwell, M. A.; Valenta, Z. "Structure and synthesis of a new cyclopentenone derivative from Trichoderma album" *Can. J. Chem.* **1977**, *55*, 2610-2612.

(193) Wipf, P.; Spencer, S. R. "Asymmetric Total Syntheses of Tuberostemonine, Didehydrotuberostemonine, and 13-Epituberostemonine" *J. Am. Chem. Soc.* **2005**, *127*, 225-235.

(194) Onoda, T.; Takikawa, Y.; Fujimoto, T.; Yasui, Y.; Suzuki, K.; Matsumoto, T. "First total synthesis of (+)-11-hydroxyerythratidine" *Synlett* **2009**, 1041-1046.

(195) Ciufolini, M. A.; Braun, N. A.; Canesi, S.; Ousmer, M.; Chang, J.; Chai, D. "Oxidative amidation of phenols through the use of hypervalent iodine reagents. Development and applications" *Synthesis* **2007**, 3759-3772.

(196) Pouysegu, L.; Deffieux, D.; Quideau, S. "Hypervalent iodine-mediated phenol dearomatization in natural product synthesis" *Tetrahedron*, *66*, 2235-2261.

(197) Comins, D. L.; Thakker, P. M.; Baevsky, M. F.; Badawi, M. M. "Chiral auxiliary mediated Pictet-Spengler reactions: asymmetric syntheses of (-)-laudanosine, (+)-glaucine and (-)-xylopinine" *Tetrahedron* **1997**, *53*, 16327-16340.

(198) Tsuji, R.; Nakagawa, M.; Nishida, A. "An efficient synthetic approach to optically active Î²-carboline derivatives via Pictet-Spengler reaction promoted by trimethylchlorosilane" *Tetrahedron: Asymmetry* **2003**, *14*, 177-180.

(199) Banwell, M.; Edwards, A.; Harvey, J.; Hockless, D.; Willis, A. "Ï€-Allyl cation cyclisations initiated by silver(I)-promoted electrocyclic ring opening of ring-fused gem-dibromocyclopropanes possessing tethered nucleophiles: the influence of chiral auxiliaries on the diastereoselectivity of cyclisations involving meso-substrates" *Perkin 1* **2000**, 2175-2178.

(200) Knueppel, D.; Martin, S. F. "Tandem electrocyclic ring opening/radical cyclization: application to the total synthesis of cribrostatin 6" *Tetrahedron*, *67*, 9765-9770.

(201) Knueppel, D.; Martin, S. F. "Total synthesis of cribrostatin 6" *Angew. Chem., Int. Ed.* **2009**, *48*, 2569-2571.

(202) Nichols, A. L.; Zhang, P.; Martin, S. F. "Concise approach to 1,4-dioxygenated xanthones via novel application of the Moore rearrangement" *Tetrahedron*, *68*, 7591-7597.

(203) Nichols, A. L.; Zhang, P.; Martin, S. F. "General and Expedient Synthesis of 1,4-Dioxygenated Xanthones" *Org. Lett.*, *13*, 4696-4699.

(204) Corey, E. J.; Gant, T. G. "A catalytic enantioselective synthetic route to the important antidepressant sertraline" *Tetrahedron Lett.* **1994**, *35*, 5373-5376.

(205) Bestmann, H. J.; Dostalek, R.; Bauroth, B. "A simple method of substituting a phosphonium ylide group for the hydroxyl group in free carboxylic acids" *Angew. Chem.* **1992**, *104*, 1062-1064 (See also Angew. Chem., Int. Ed. Engl., 1992, 1031(1068), 1064-1066).

(206) Liu, H.; Tomooka, C. S.; Xu, S. L.; Yerxa, B. R.; Sullivan, R. W.; Xiong, Y.; Moore, H. W. "Dimethyl squarate and its conversion to 3-ethenyl-4-methoxycyclobutene-1,2-dione and 2-butyl-6-ethenyl-5-methoxy-1,4-benzoquinone (3-cyclobutene-1,2-dione, 3-ethenyl-4-methoxy- and 2,5-

cyclohexadiene-1,4-dione, 5-butyl-3-ethenyl-2-methoxy- from 3-cyclobutene-1,2-dione, 3,4-dimethoxy-)" *Org. Synth.* **1999**, *76*, 189-198.

(207) Foland, L. D.; Karlsson, J. O.; Perri, S. T.; Schwabe, R.; Xu, S. L.; Patil, S.; Moore, H. W. "Rearrangement of 4-alkynylcyclobutenones. A new synthesis of 1,4-benzoquinones" *J. Am. Chem. Soc.* **1989**, *111*, 975-989.

(208) Xiong, Y.; Moore, H. W. "Ring Expansion of 4-Alkynylcyclobutenones. Synthesis of Piperidinoquinones, Highly Substituted Dihydrophenanthridines, Benzophenanthridines, and the Naturally Occurring Pyrrolophenanthridine, Assoanine" *J. Org. Chem.* **1996**, *61*, 9168-9177.

(209) Hergueta, A. R.; Moore, H. W. "Rearrangements of Cyclobutenones. Synthesis of N-Methyl-7,8-dihydrobenzophenanthridine-9,12-diols and Related Compounds" *J. Org. Chem.* **1999**, *64*, 5979-5983.

(210) Zehr, P. S.; Kayali, R.; Pena-Cabrera, E.; Robles-Resendiz, O.; Villanueva-Rendon, A. D.; Soederberg, B. C. G. "A novel entry to cyclopenta[b]quinolines via thermal ring-expansion of (2-aminophenyl)-ethynyl-substituted squaric acid derivatives" *Tetrahedron* **2008**, *64*, 5336-5344.

(211) Dieltiens, N.; Stevens, C. V.; Masschelein, K.; Hennebel, G.; Van, d. J. S. "Ring-closing metathesis and ring-closing metathesis-isomerisation approach to 1-phosphonylated 2-benzazocines" *Tetrahedron* **2008**, *64*, 4295-4303.

(212) Ishizaki, M.; Niimi, Y.; Hoshino, O.; Hara, H.; Takahashi, T. "A formal total synthesis of lycopodium alkaloid, (Â±)-magellanine, by using the intramolecular Pauson-Khand reaction" *Tetrahedron* **2005**, *61*, 4053-4065.

(213) Cava, M. P.; Deana, A. A.; Muth, K.; Mitchell, M. j. "N-Phenylmaleimide" *Org. Synth.* **1961**, *41*, 93-95.

(214) Martin, S. F.; Limberakis, C. "Diprotection of primary amines as N-substituted-2,5-bis[(triisopropylsilyl)oxy]pyrroles (BIPSOP)" *Tetrahedron Lett.* **1997**, *38*, 2617-2620.

(215) Sarkis, M.; Tran, D. N.; Kolb, S.; Miteva, M. A.; Villoutreix, B. O.; Garbay, C.; Braud, E. "Design and synthesis of novel bis-thiazolone derivatives as micromolar CDC25 phosphatase inhibitors: Effect of dimerisation on phosphatase inhibition" *Bioorg. Med. Chem. Lett.*, *22*, 7345-7350.

(216) VanNieuwenhze, M. S.; Sharpless, K. B. "The asymmetric dihydroxylation cis-allylic and homoallylic alcohols" *Tetrahedron Lett.* **1994**, *35*, 843-846.

(217) Roychowdhury, A.; Illangkoon, H.; Hendrickson, C. L.; Benner, S. A. "2'-Deoxycytidines Carrying Amino and Thiol Functionality: Synthesis and Incorporation by Vent (Exo-) Polymerase" *Org. Lett.* **2004**, *6*, 489-492.

(218) Kita, Y.; Tohma, H.; Inagaki, M.; Hatanaka, K. "A general formation of quinone imines and quinone imine acetals: an efficient synthesis of 5-oxygenated indoles" *Heterocycles* **1992**, *33*, 503-506.

(219) Banfi, L.; Basso, A.; Guanti, G.; Riva, R. "A new convergent and stereoselective synthesis of 2,5-disubstituted N-acylpyrrolidines" *Tetrahedron* **2006**, *62*, 4331-4341.

(220) Wipf, P.; Hopkins, C. R. "Efficient Synthesis of 1,4-Dihydro-2H-isoquinoline-3,5,8-triones via Cyclobutene Ring Expansion" *J. Org. Chem.* **1999**, *64*, 6881-6887.

(221) Chan, C.; Zheng, S.; Zhou, B.; Guo, J.; Heid, R. M.; Wright, B. J. D.; Danishefsky, S. J. "The solution to a deep stereochemical conundrum: studies toward the tetrahydroisoquinoline alkaloids" *Angew. Chem., Int. Ed.* **2006**, *45*, 1749-1754.

(222) Overman, L. E.; Lesuisse, D.; Hashimoto, M. "Synthetic applications of N-acylamino-1,3-dienes. 10. Importance of allylic interactions and stereoelectronic effects in dictating the steric course of the reaction of iminium ions with nucleophiles. An efficient total synthesis of (Â±)-gephyrotoxin" *J. Am. Chem. Soc.* **1983**, *105*, 5373-5379.

(223) Myers, A. G.; Glatthar, R.; Hammond, M.; Harrington, P. M.; Kuo, E. Y.; Liang, J.; Schaus, S. E.; Wu, Y.; Xiang, J.-N. "Development of an Enantioselective Synthetic Route to Neocarzinostatin Chromophore and Its Use for Multiple Radio-Isotopic Incorporation" *J. Am. Chem. Soc.* **2002**, *124*, 5380-5401.

(224) Ooi, T.; Kameda, M.; Maruoka, K. "Design of N-Spiro C2-Symmetric Chiral Quaternary Ammonium Bromides as Novel Chiral Phase-Transfer Catalysts: Synthesis and Application to Practical Asymmetric Synthesis of Î±-Amino Acids" *J. Am. Chem. Soc.* **2003**, *125*, 5139-5151.

(225) Donde, Y.; Nguyen, J. H.; Kedzie, K. M.; Gil, D. W.; Donello, J. E.; Im, W.-B. 2005, p 27 pp., Cont.-in-part of U.S. Ser. No. 772,720.

(226) Trost, B. M.; O'Boyle, B. M. "Synthesis of 7-Epi (+)-FR900482: An Epimer of Comparable Anti-Cancer Activity" *Org. Lett.* **2008**, *10*, 1369-1372.

(227) Terrier, F.; Wiley.

(228) McMurry, J. E.; Mohanraj, S. "Synthesis of arenes from phenols by coupling of aryl triflates with organocopper reagents" *Tetrahedron Lett.* **1983**, *24*, 2723-2726.

(229) Gilbertson, S. R.; Challener, C. A.; Bos, M. E.; Wulff, W. D. "An examination of the coupling of vinyl and aryl triflates with stannyl cuprates for the purpose of providing regioselective access to vinyllithiums" *Tetrahedron Lett.* **1988**, *29*, 4795-4798.

(230) Honda, T. "Development of samarium diiodide-promoted reductive carbon-nitrogen bond cleavage reaction of Î±-amino carbonyl compounds. Application to the synthesis of biologically active alkaloids" *Heterocycles* **2011**, *83*, 1-46.

(231) Battersby, A. R.; Jones, R. C. F.; Kazlauskas, R.; Thornber, C. W.; Ruchirawat, S.; Staunton, J. "Biosynthesis. Part 24. Speculative incorporation experiments with 1-benzylisoquinolines and a logical approach via C6-C2 and C6-C3 precursors to the biosynthesis of hasubanonine and protostephanine" *J. Chem. Soc., Perkin Trans. 1* **1981**, 2016-2029.

(232) Tadross, P. M.; Gilmore, C. D.; Bugga, P.; Virgil, S. C.; Stoltz, B. M. "Regioselective reactions of highly substituted arynes" *Org. Lett.*, *12*, 1224-1227.

(233) Ellis, J. E.; Lenger, S. R. "A convenient synthesis of 3,4-dimethoxy-5-hydroxybenzaldehyde" *Synth. Commun.* **1998**, *28*, 1517-1524.

(234) Stoddart, J. F.; Editor *Comprehensive Organic Chemistry: The Synthesis and Reactions of Organic Compounds, Vol. 1: Stereochemistry, Hydrocarbons, Halo Compounds, Oxygen Compounds*; Pergamon, 1979.

(235) Peschko, C.; Winklhofer, C.; Terpin, A.; Steglich, W. "Biomimetic syntheses of lamellarin and lukianol-type alkaloids" *Synthesis* **2006**, 3048-3057.

(236) Cooper, T. S.; Larigo, A. S.; Laurent, P.; Moody, C. J.; Takle, A. K. "Chiral oxime ethers in asymmetric synthesis. Part 7. O-(1-

Phenylbutyl)benzyloxyacetaldoxime, a versatile reagent for the asymmetric synthesis of protected 1,2-amino alcohols, Î±-amino acid derivatives, and 2-hydroxymethyl nitrogen heterocycles including imino sugars" *Org. Biomol. Chem.* **2005**, *3*, 1252-1262.

(237) Dochnahl, M.; Fu, G. C. "Catalytic asymmetric cycloaddition of ketenes and nitroso compounds: Enantioselective synthesis of Î±-hydroxy carboxylic acid derivatives" *Angew. Chem., Int. Ed.* **2009**, *48*, 2391-2393.

(238) Yamanaka, E.; Shibata, N.; Sakai, S. "A development of Pictet-Spengler reaction in aprotic media using chloroformates; a short synthesis of borrerine" *Heterocycles* **1984**, *22*, 371-374.

(239) David J. Procter, R. A. F. I., and Troels Skrydstrup *Organic Synthesis using Samarium Diiodide: A Practical Guide*; The Royal Society of Chemistry: Cambridge, 2010.

(240) Szostak, M.; Spain, M.; Procter, D. J. "Preparation of Samarium(II) Iodide: Quantitative Evaluation of the Effect of Water, Oxygen, and Peroxide Content, Preparative Methods, and the Activation of Samarium Metal" *J. Org. Chem.*, *77*, 3049-3059.

(241) Honda, T.; Aranishi, E.; Kaneda, K. "Facile Synthesis of a Benzindenoazepine Alkaloid, Bulgaramine, via Samarium Diiodide Promoted Ring Expansion of an Î±-Aminocarbonyl Compound" *Org. Lett.* **2009**, *11*, 1857-1859.

(242) Honda, T.; Ishikawa, F. "Reductive deamination of Î±-amino carbonyl compounds by means of samarium iodide" *Chem. Commun. (Cambridge)* **1999**, 1065-1066.

(243) Imamoto, T.; Ono, M. "The reaction of samarium(III) iodide with samarium metal in tetrahydrofuran. A new method for the preparation of samarium(II) iodide" *Chem. Lett.* **1987**, 501-502.

(244) Chen, J.; Zhang, Y.; Yang, L.; Zhang, X.; Liu, J.; Li, L.; Zhang, H. "A practical palladium catalyzed dehalogenation of aryl halides and Î±-haloketones" *Tetrahedron* **2007**, *63*, 4266-4270.

(245) Johnson, F. "Allylic strain in six-membered rings" *Chem. Rev.* **1968**, *68*, 375-413.

(246) Johnson, R. A. "Conformations of alkylpiperidine amides" *J. Org. Chem.* **1968**, *33*, 3627-3632.

(247) de Koning, C. B.; van Otterlo, W. A. L.; Michael, J. P. "Amide rotamers of N-acetyl-1,3-dimethyltetrahydroisoquinolines: synthesis, variable temperature NMR spectroscopy and molecular modelling" *Tetrahedron* **2003**, *59*, 8337-8345.

(248) Eustache, J.; Van, d. W. P.; Le, N. D.; Uyehara, H.; Kabuto, C.; Yamamoto, Y. "Controlled Synthesis of Cis or Trans Isomers of 1,3-Disubstituted Tetrahydroisoquinolines and 2,5-Disubstituted Pyrrolidines" *J. Org. Chem.* **2005**, *70*, 4043-4053.

(249) Bois-Choussy, M.; Cadet, S.; De, P. M.; Zhu, J. "Diethyl oxomalonate as a three carbon synthon for synthesis of functionalized 1,1'-disubstituted tetrahydroisoquinoline" *Tetrahedron Lett.* **2001**, *42*, 4503-4506.

(250) Yasui, Y.; Suzuki, K.; Matsumoto, T. "Transmission of axial chirality to spiro center chirality, enabling enantiospecific access to erythrinan alkaloids" *Synlett* **2004**, 619-622.

(251) Canesi, S.; Belmont, P.; Bouchu, D.; Rousset, L.; Ciufolini, M. A. "Efficient oxidative spirocyclization of phenolic sulfonamides" *Tetrahedron Lett.* **2002**, *43*, 5193-5195.

(252) Yasui, Y.; Koga, Y.; Suzuki, K.; Matsumoto, T. "A novel approach to erythrinan alkaloids by utilizing substituted biphenyl as building block" *Synlett* **2004**, 615-618.

(253) Dr. Robert A. Flowers, I., Skype Conversation.

(254) Fratiello, A.; Kubo-Anderson, V.; Bolanos, E.; Chavez, O.; Laghaei, F.; Ortega, J. V.; Perrigan, R. D.; Reyes, F. "A direct carbon-13 and nitrogen-15 NMR study of samarium(III) complexation with nitrate and isothiocyanate in aqueous solvent mixtures" *J. Solution Chem.* **1994**, *23*, 1019-1047.

(255) Girard, P.; Namy, J. L.; Kagan, H. B. "Divalent lanthanide derivatives in organic synthesis. 1. Mild preparation of samarium iodide and ytterbium iodide and their use as reducing or coupling agents" *J. Am. Chem. Soc.* **1980**, *102*, 2693-2698.

(256) Teprovich, J. A., Jr.; Antharjanam, P. K. S.; Prasad, E.; Pesciotta, E. N.; Flowers, R. A., II "Generation of SmII reductants using high intensity ultrasound" *Eur. J. Inorg. Chem.* **2008**, 5015-5019.

(257) Rao, D. V.; Stuber, F. A. "An efficient synthesis of 3,4,5-trimethoxybenzaldehyde from vanillin" *Synthesis* **1983**, 308.

(258) Shimizu, I.; Sakamoto, T.; Kawaragi, S.; Maruyama, Y.; Yamamoto, A. "Molybdenum- and tungsten-catalyzed allylation of aromatic compounds with allylic esters and alcohols" *Chem. Lett.* **1997**, 137-138.

(259) Malkov, A. V.; Davis, S. L.; Baxendale, I. R.; Mitchell, W. L.; Kocovsky, P. "Molybdenum(II)-Catalyzed Allylation of Electron-Rich Aromatics and Heteroaromatics" *J. Org. Chem.* **1999**, *64*, 2751-2764.

(260) Bandini, M.; Tragni, M. "Ї€-Activated alcohols: an emerging class of alkylating agents for catalytic Friedel-Crafts reactions" *Org. Biomol. Chem.* **2009**, *7*, 1501-1507.

(261) Jana, U.; Maiti, S.; Biswas, S. "An FeCl3-catalyzed highly C3-selective Friedel-Crafts alkylation of indoles with alcohols" *Tetrahedron Lett.* **2007**, *48*, 7160-7163.

(262) Rueping, M.; Nachtsheim, B. J. "A review of new developments in the Friedel-Crafts alkylation. From green chemistry to asymmetric catalysis" *Beilstein J. Org. Chem.* **2010**, *6*, No. 6, No pp. given, No. 6.

(263) Tsuchimoto, T.; Tobaita, K.; Hiyama, T.; Fukuzawa, S.-i. "Scandium(III) triflate catalyzed Friedel-Crafts alkylation with benzyl and allyl alcohols" *Synlett* **1996**, 557-559.

(264) Yadav, J. S.; Reddy, B. V. S.; Aravind, S.; Kumar, G. G. K. S. N.; Reddy, A. S. "InBr3 as a versatile and highly efficient catalyst for the synthesis of 3-allyl- and 3-benzylindoles" *Tetrahedron Lett.* **2007**, *48*, 6117-6120.

(265) Majewski, M. "Lithium diisopropylamide as a hydride donor. Reduction of aldehydes" *Tetrahedron Lett.* **1988**, *29*, 4057-4060.

(266) Su, J. *Unpublished Results.*

(267) Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. "Beyond thermodynamic acidity: A perspective on the complex-induced proximity effect (CIPE) in deprotonation reactions" *Angew. Chem., Int. Ed.* **2004**, *43*, 2206-2225.

(268) Brown, M. A.; Kerr, M. A. "A convenient preparation of 4-iodoindoles from indoles: application to the chemical synthesis of hapalindole alkaloids" *Tetrahedron Lett.* **2001**, *42*, 983-985.

(269) Tietze, L. F.; Schirok, H. "Enantioselective Highly Efficient Synthesis of (-)-Cephalotaxine Using Two Palladium-Catalyzed Transformations" *J. Am. Chem. Soc.* **1999**, *121*, 10264-10269.

(270) ten, B. H. T.; Rijkers, D. T. S.; Kemmink, J.; Hilbers, H. W.; Liskamp, R. M. J. "Ring-closing metathesis for the synthesis of side chain knotted pentapeptides inspired by vancomycin" *Org. Biomol. Chem.* **2004**, *2*, 2658-2663.

(271) Radix, S.; Barret, R. "Total synthesis of two natural phenanthrenes: Confusarin and a regioisomer" *Tetrahedron* **2007**, *63*, 12379-12387.

(272) Node, M.; Kodama, S.; Hamashima, Y.; Katoh, T.; Nishide, K.; Kajimoto, T. "Biomimetic synthesis of (Â±)-galanthamine and asymmetric synthesis of (-)-galanthamine using remote asymmetric induction" *Chem. Pharm. Bull.* **2006**, *54*, 1662-1679.

(273) Babine, R. E.; Bender, S. L. "Molecular Recognition of Protein-Ligand Complexes: Applications to Drug Design" *Chem. Rev. (Washington, D. C.)* **1997**, *97*, 1359-1472.

(274) Martin, S. F.; Clements, J. H. "Correlating structure and energetics in protein-ligand interactions: paradigms and paradoxes" *Annu. Rev. Biochem.* **2013**, *82*, 267-293.

(275) Reichelt, A.; Martin, S. F. "Synthesis and Properties of Cyclopropane-Derived Peptidomimetics" *Acc. Chem. Res.* **2006**, *39*, 433-442.

(276) Gohlke, H.; Klebe, G. "Approaches to the description and prediction of the binding affinity of small-molecule ligands to macromolecular receptors" *Angew. Chem., Int. Ed.* **2002**, *41*, 2644-2676.

(277) Teague, S. J. "Implications of protein flexibility for drug discovery" *Nat. Rev. Drug Discovery* **2003**, *2*, 527-541.

(278) Hunter, C. A. "Quantifying intermolecular interactions: Guidelines for the molecular recognition toolbox" *Angew. Chem., Int. Ed.* **2004**, *43*, 5310-5324.

(279) Williams, D. H.; Stephens, E.; O'Brien, D. P.; Zhou, M. "Understanding noncovalent interactions: Ligand binding energy and catalytic efficiency from ligand-induced reductions in motion within receptors and enzymes" *Angew. Chem., Int. Ed.* **2004**, *43*, 6596-6616.

(280) Homans, S. W. "Dynamics and thermodynamics of ligand-protein interactions" *Top. Curr. Chem.* **2007**, *272*, 51-82.

(281) Mobley, D. L.; Dill, K. A. "Binding of Small-Molecule Ligands to Proteins: "What You See" Is Not Always "What You Get"" *Structure (Cambridge, MA, U. S.)* **2009**, *17*, 489-498.

(282) Bissantz, C.; Kuhn, B.; Stahl, M. "A Medicinal Chemist's Guide to Molecular Interactions" *J. Med. Chem.* **2010**, *53*, 5061-5084.

(283) Velazquez-Campoy, A.; Todd, M. J.; Freire, E. "HIV-1 Protease Inhibitors: Enthalpic versus Entropic Optimization of the Binding Affinity" *Biochemistry* **2000**, *39*, 2201-2207.

(284) Mann, A.; Le, C. H.-L.; Elsevier: 2003, p 233-250.

(285) Nakanishi, H.; Kahn, M.; Ibsen, H.; Elsevier: 2003, p 477-500.

(286) Wear, M. A.; Kan, D.; Rabu, A.; Walkinshaw, M. D. "Experimental determination of van der Waals energies in a biological system" *Angew. Chem., Int. Ed.* **2007**, *46*, 6453-6456.

(287) Chang, C.-e. A.; Chen, W.; Gilson, M. K. "Ligand configurational entropy and protein binding" *Proc. Natl. Acad. Sci. U. S. A.* **2007**, *104*, 1534-1539.

(288) Chandler, D. "Interfaces and the driving force of hydrophobic assembly" *Nature (London, U. K.)* **2005**, *437*, 640-647.

(289) Dill, K. A.; Truskett, T. M.; Vlachy, V.; Hribar-Lee, B. "Modeling water, the hydrophobic effect, and ion solvation" *Annu. Rev. Biophys. Biomol. Struct.* **2005**, *34*, 173-199, 174 plates.

(290) Kyte, J. "The basis of the hydrophobic effect" *Biophys. Chem.* **2003**, *100*, 193-203.

(291) Meyer, E. A.; Castellano, R. K.; Diederich, F. "Interactions with aromatic rings in chemical and biological recognition" *Angew. Chem., Int. Ed.* **2003**, *42*, 1210-1250.

(292) Olsson, T. S. G.; Williams, M. A.; Pitt, W. R.; Ladbury, J. E. "The Thermodynamics of Protein-Ligand Interaction and Solvation: Insights for Ligand Design" *J. Mol. Biol.* **2008**, *384*, 1002-1017.

(293) Barratt, E.; Bronowska, A.; Vondrasek, J.; Cerny, J.; Bingham, R.; Phillips, S.; Homans, S. W. "Thermodynamic Penalty Arising from Burial of a Ligand Polar Group Within a Hydrophobic Pocket of a Protein Receptor" *J. Mol. Biol.* **2006**, *362*, 994-1003.

(294) Munson, P. J.; Rodbard, D. "An exact correction to the "Cheng-Prusoff" correction" *J. Recept. Res.* **1988**, *8*, 533-546.

(295) Boehm, H.-J.; Klebe, G. "What can we learn from molecular recognition in protein-ligand complexes for the design of new drugs?" *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2588-2614.

(296) Wiseman, T.; Williston, S.; Brandts, J. F.; Lin, L. N. "Rapid measurement of binding constants and heats of binding using a new titration calorimeter" *Anal. Biochem.* **1989**, *179*, 131-137.

(297) Ladbury, J. E.; Klebe, G.; Freire, E. "Adding calorimetric data to decision making in lead discovery: A hot tip" *Nat. Rev. Drug Discovery*, *9*, 23-27.

(298) Snyder, P. W.; Mecinoviv, J.; Moustakas, D. T.; Thomas, S. W., III; Harder, M.; Mack, E. T.; Lockett, M. R.; Heroux, A.; Sherman, W.; Whitesides, G. M. "Mechanism of the hydrophobic effect in the biomolecular recognition of arylsulfonamides by carbonic anhydrase" *Proc. Natl. Acad. Sci. U. S. A.*, *108*, 17889-17894, S17889/17881-S17889/17810.

(299) Gilli, P.; Ferretti, V.; Gilli, G.; Borea, P. A. "Enthalpy-entropy compensation in drug-receptor binding" *J. Phys. Chem.* **1994**, *98*, 1515-1518.

(300) Dunitz, J. D. "Win some, lose some: enthalpy-entropy compensation in weak intermolecular interactions" *Chem. Biol.* **1995**, *2*, 709-712.

(301) Liu, L.; Guo, Q.-X. "Isokinetic Relationship, Isoequilibrium Relationship, and Enthalpy-Entropy Compensation" *Chem. Rev. (Washington, D. C.)* **2001**, *101*, 673-695.

(302) Sharp, K. "Entropy-enthalpy compensation: fact or artifact?" *Protein Sci.* **2001**, *10*, 661-667.

(303) Krishnamurthy, V. M.; Bohall, B. R.; Semetey, V.; Whitesides, G. M. "The Paradoxical Thermodynamic Basis for the Interaction of Ethylene Glycol, Glycine, and Sarcosine Chains with Bovine Carbonic Anhydrase II: An Unexpected Manifestation of Enthalpy/Entropy Compensation" *J. Am. Chem. Soc.* **2006**, *128*, 5802-5812.

(304) Lafont, V.; Armstrong, A. A.; Ohtaka, H.; Kiso, Y.; Amzel, L. M.; Freire, E. "Compensating enthalpic and entropic changes hinder binding affinity optimization" *Chem. Biol. Drug Des.* **2007**, *69*, 413-422.

(305) Veber, D. F.; Johnson, S. R.; Cheng, H.-Y.; Smith, B. R.; Ward, K. W.; Kopple, K. D. "Molecular Properties That Influence the Oral Bioavailability of Drug Candidates" *J. Med. Chem.* **2002**, *45*, 2615-2623.

(306) Hruby, V. J.; Li, G.; Haskell-Luevano, C.; Shenderovich, M. "Design of peptides, proteins, and peptidomimetics in chi space" *Biopolymers* **1997**, *43*, 219-266.

(307) Ding, J.; Fraser, M. E.; Meyer, J. H.; Bartlett, P. A.; James, M. N. G. "Macrocyclic Inhibitors of Penicillopepsin. 2. X-ray Crystallographic Analyses of Penicillopepsin Complexed with a P3-P1 Macrocyclic Peptidyl Inhibitor and with Its Two Acyclic Analogs" *J. Am. Chem. Soc.* **1998**, *120*, 4610-4621.

(308) Khan, A. R.; Parrish, J. C.; Fraser, M. E.; Smith, W. W.; Bartlett, P. A.; James, M. N. G. "Lowering the Entropic Barrier for Binding Conformationally Flexible Inhibitors to Enzymes" *Biochemistry* **1998**, *37*, 16839-16845.

(309) Meyer, J. H.; Bartlett, P. A. "Macrocyclic Inhibitors of Penicillopepsin. 1. Design, Synthesis, and Evaluation of an Inhibitor Bridged between P1 and P3" *J. Am. Chem. Soc.* **1998**, *120*, 4600-4609.

(310) Smith, W. W.; Bartlett, P. A. "Macrocyclic Inhibitors of Penicillopepsin. 3. Design, Synthesis, and Evaluation of an Inhibitor Bridged between P2 and P1'" *J. Am. Chem. Soc.* **1998**, *120*, 4622-4628.

(311) Tsantrizos, Y. S.; Bolger, G.; Bonneau, P.; Cameron, D. R.; Goudreau, N.; Kukolj, G.; LaPlante, S. R.; Llinas-Brunet, M.; Nar, H.; Lamarre, D. "Macrocyclic inhibitors of the NS3 protease as potential therapeutic agents of hepatitis C virus infection" *Angew. Chem., Int. Ed.* **2003**, *42*, 1356-1360.

(312) Williams, D. H.; Searle, M. S.; Mackay, J. P.; Gerhard, U.; Maplestone, R. A. "Toward an estimation of binding constants in aqueous solution: Studies of associations of vancomycin group antibiotics" *Proc. Natl. Acad. Sci. U. S. A.* **1993**, *90*, 1172-1178.

(313) Calderone, C. T.; Williams, D. H. "An Enthalpic Component in Cooperativity: The Relationship between Enthalpy, Entropy, and Noncovalent Structure in Weak Associations" *J. Am. Chem. Soc.* **2001**, *123*, 6262-6267.

(314) Martin, S. F.; Austin, R. E.; Oalmann, C. J. "Stereoselective synthesis of 1,2,3-trisubstituted cyclopropanes as novel dipeptide isosteres" *Tetrahedron Lett.* **1990**, *31*, 4731-4734.

(315) Doyle, M. P.; Pieters, R. J.; Martin, S. F.; Austin, R. E.; Oalmann, C. J.; Mueller, P. "High enantioselectivity in the intramolecular cyclopropanation of allyl diazoacetates using a novel rhodium(II) catalyst" *J. Am. Chem. Soc.* **1991**, *113*, 1423-1424.

(316) Martin, S. F.; Austin, R. E.; Oalmann, C. J.; Baker, W. R.; Condon, S. L.; DeLara, E.; Rosenberg, S. H.; Spina, K. P.; Stein, H. H.; et, a. "1,2,3-Trisubstituted cyclopropanes as conformationally restricted peptide isosteres: application to the design and synthesis of novel renin inhibitors" *J. Med. Chem.* **1992**, *35*, 1710-1721.

(317) Martin, S. F.; Oalmann, C. J.; Liras, S. "Cyclopropanes as conformationally restricted peptide isosteres. Design and synthesis of novel collagenase inhibitors" *Tetrahedron* **1993**, *49*, 3521-3532.

(318) Martin, S. F.; Spaller, M. R.; Liras, S.; Hartmann, B. "Enantio- and Diastereoselectivity in the Intramolecular Cyclopropanation of Secondary Allylic Diazoacetates" *J. Am. Chem. Soc.* **1994**, *116*, 4493-4494.

(319) Doyle, M. P.; Austin, R. E.; Bailey, A. S.; Dwyer, M. P.; Dyatkin, A. B.; Kalinin, A. V.; Kwan, M. M. Y.; Liras, S.; Oalmann, C. J.; et, a. "Enantioselective Intramolecular Cyclopropanations of Allylic and Homoallylic Diazoacetates and

Diazoacetamides Using Chiral Dirhodium(II) Carboxamide Catalysts" *J. Am. Chem. Soc.* **1995**, *117*, 5763-5775.

(320) Martin, S. F.; Dorsey, G. O.; Gane, T.; Hillier, M. C.; Kessler, H.; Baur, M.; Mathae, B.; Erickson, J. W.; Bhat, T. N.; Munshi, S.; Gulnik, S. V.; Topol, I. A. "Cyclopropane-Derived Peptidomimetics. Design, Synthesis, Evaluation, and Structure of Novel HIV-1 Protease Inhibitors" *J. Med. Chem.* **1998**, *41*, 1581-1597.

(321) Martin, S. F.; Dwyer, M. P. "Iodocyclopropanes as versatile intermediates for the synthesis of substituted cyclopropanes" *Tetrahedron Lett.* **1998**, *39*, 1521-1524.

(322) Martin, S. F.; Dwyer, M. P.; Lynch, C. L. "Application of AlMe3-mediated amidation reactions to solution phase peptide synthesis" *Tetrahedron Lett.* **1998**, *39*, 1517-1520.

(323) Martin, S. F.; Hillier, M. "Diastereo-differentiation in intramolecular cyclopropanations of chiral secondary allylic diazoacetates" *Tetrahedron Lett.* **1998**, *39*, 2929-2932.

(324) Reichelt, A.; Gaul, C.; Frey, R. R.; Kennedy, A.; Martin, S. F. "Design, Synthesis, and Evaluation of Matrix Metalloprotease Inhibitors Bearing Cyclopropane-Derived Peptidomimetics as P1' and P2' Replacements" *J. Org. Chem.* **2002**, *67*, 4062-4075.

(325) Martin, S. F.; Dwyer, M. P.; Hartmann, B.; Knight, K. S. "Cyclopropane-Derived Peptidomimetics. Design, Synthesis, and Evaluation of Novel Enkephalin Analogues" *J. Org. Chem.* **2000**, *65*, 1305-1318.

(326) Hillier, M. C.; Davidson, J. P.; Martin, S. F. "Cyclopropane-Derived Peptidomimetics. Design, Synthesis, and Evaluation of Novel Ras Farnesyltransferase Inhibitors" *J. Org. Chem.* **2001**, *66*, 1657-1671.

(327) Waksman, G.; Kominos, D.; Robertson, S. C.; Pant, N.; Baltimore, D.; Birge, R. B.; Cowburn, D.; Hanafusa, H.; Mayer, B. J.; et, a. "Crystal structure of the phosphotyrosine recognition domain SH2 of v-src complexed with tyrosine-phosphorylated peptides" *Nature (London)* **1992**, *358*, 646-653.

(328) Waksman, G.; Shoelson, S. E.; Pant, N.; Cowburn, D.; Kuriyan, J. "Binding of a high affinity phosphotyrosyl peptide the the Src SH2 domain: Crystal structures

of the complexed and peptide-free forms" *Cell (Cambridge, Mass.)* **1993**, *72*, 779-790.

(329) Bradshaw, J. M.; Grucza, R. A.; Ladbury, J. E.; Waksman, G. "Probing the "Two-Pronged Plug Two-Holed Socket" Model for the Mechanism of Binding of the Src SH2 Domain to Phosphotyrosyl Peptides: A Thermodynamic Study" *Biochemistry* **1998**, *37*, 9083-9090.

(330) Bradshaw, J. M.; Waksman, G. "Calorimetric Examination of High-Affinity Src SH2 Domain-Tyrosyl Phosphopeptide Binding: Dissection of the Phosphopeptide Sequence Specificity and Coupling Energetics" *Biochemistry* **1999**, *38*, 5147-5154.

(331) Plake, H. R.; Sundberg, T. B.; Woodward, A. R.; Martin, S. F. "Design and synthesis of conformationally constrained, extended and reverse turn pseudopeptides as Grb2-SH2 domain antagonists" *Tetrahedron Lett.* **2003**, *44*, 1571-1574.

(332) DeLorbe, J. E.; Clements, J. H.; Teresk, M. G.; Benfield, A. P.; Plake, H. R.; Millspaugh, L. E.; Martin, S. F. "Thermodynamic and Structural Effects of Conformational Constraints in Protein-Ligand Interactions: Entropic Paradoxy Associated with Ligand Preorganization" *J. Am. Chem. Soc.* **2009**, *131*, 16758-16770.

(333) Davidson, J. P.; Lubman, O.; Rose, T.; Waksman, G.; Martin, S. F. "Calorimetric and Structural Studies of 1,2,3-Trisubstituted Cyclopropanes as Conformationally Constrained Peptide Inhibitors of Src SH2 Domain Binding" *J. Am. Chem. Soc.* **2002**, *124*, 205-215.

(334) Shi, Y.; Zhu, C. Z.; Martin, S. F.; Ren, P. "Probing the Effect of Conformational Constraint on Phosphorylated Ligand Binding to an SH2 Domain Using Polarizable Force Field Simulations" *The Journal of Physical Chemistry B* **2012**, *116*, 1716-1727.

(335) Myslinski, J. M.; DeLorbe, J. E.; Clements, J. H.; Martin, S. F. "Protein-Ligand Interactions: Thermodynamic Effects Associated with Increasing Nonpolar Surface Area" *J. Am. Chem. Soc.* **2011**, *133*, 18518-18521.

(336) Ward, J. M.; Gorenstein, N. M.; Tian, J.; Martin, S. F.; Post, C. B. "Constraining Binding Hot Spots: NMR and Molecular Dynamics Simulations Provide a

Structural Explanation for Enthalpy-Entropy Compensation in SH2-Ligand Binding" *J. Am. Chem. Soc.* **2010**, *132*, 11058-11070.

(337) Gerhard, u.; Searle, M. S.; Williams, D. H. "The free energy change of restricting a bond rotation in the binding of peptide analogs to vancomycin group antibiotics" *Bioorg. Med. Chem. Lett.* **1993**, *3*, 803-808.

(338) Searle, M. S.; Williams, D. H. "The cost of conformational order: entropy changes in molecular associations" *J. Am. Chem. Soc.* **1992**, *114*, 10690-10697.

(339) Page, M. I.; Jencks, W. P. "Entropic contributions to rate accelerations in enzymic and intramolecular reactions and the chelate effect" *Proc. Nat. Acad. Sci. U. S.* **1971**, *68*, 1678-1683.

(340) Tian, J. "Martin Group Final Report" **2011**.

(341) Lelais, G.; Campo, M. A.; Kopp, S.; Seebach, D. "Enantioselective preparation of Î²2-amino acids with aspartate, glutamate, asparagine, and glutamine side chains" *Helv. Chim. Acta* **2004**, *87*, 1545-1560.

(342) Micuch, P.; Seebach, D. "Preparation of Î²2-homotryptophan derivatives for Î²-peptide synthesis" *Helv. Chim. Acta* **2002**, *85*, 1567-1577.

(343) Shioiri, T.; Ninomiya, K.; Yamada, S. "Diphenylphosphoryl azide. New convenient reagent for a modified Curtius reaction and for peptide synthesis" *J. Amer. Chem. Soc.* **1972**, *94*, 6203-6205.

(344) Ninomiya, K.; Shioiri, T.; Yamada, S. "Phosphorus in organic synthesis. VII. Diphenyl phosphorazidate (DPPA). A new convenient reagent for a modified Curtius reaction" *Tetrahedron* **1974**, *30*, 2151-2157.

(345) Sibi, M. P.; Deshpande, P. K. "A new methodology for the synthesis of b-amino acids" *J. Chem. Soc., Perkin Trans. 1* **2000**, 1461-1466.

(346) Sato, M.; Ogasawara, H.; Komatsu, S.; Kato, T. "Synthesis of Î²-ketocarboxamide derivatives using 2,2-dimethyl-2H,4H-1,3-dioxin-4-ones" *Chem. Pharm. Bull.* **1984**, *32*, 3848-3856.

(347) Clemens, R. J.; Hyatt, J. A. "Acetoacetylation with 2,2,6-trimethyl-4H-1,3-dioxin-4-one: a convenient alternative to diketene" *J. Org. Chem.* **1985**, *50*, 2431-2435.

(348) Kitamura, M.; Tashiro, N.; Miyagawa, S.; Okauchi, T. "2-Azido-1,3-dimethylimidazolinium salts: efficient diazo-transfer reagents for 1,3-dicarbonyl compounds" *Synthesis*, 1037-1044.

(349) Doyle, M. P.; Winchester, W. R.; Protopopova, M. N.; Kazala, A. P.; Westrum, L. J. "(1R,5S)-(-)-6,6-dimethyl-3-oxabicyclo[3.1.0]hexan-2-one. Highly enantioselective intramolecular cyclopropanation catalyzed by dirhodium(II) tetrakis[methyl 2-pyrrolidone-5(R)-carboxylate] ((3-oxabicyclo[3.1.0]hexan-2-one, 6,6-dimethyl-, (1R-cis)-)" *Org. Synth.* **1996**, *73*, 13-24.

(350) Martin, S. F.; Hom, R. K. "Stereoselective elaboration of side chain residues in cyclopropane-containing dipeptide isosteres" *Tetrahedron Lett.* **1999**, *40*, 2887-2890.

(351) Lee, J. *Unpublished Results.* **2012**.

(352) Abellan, T.; Chinchilla, R.; Galindo, N.; Guillena, G.; Najera, C.; Sansano, J. M. "Glycine and alanine imines as templates for asymmetric synthesis of Î±-amino acids" *Eur. J. Org. Chem.* **2000**, 2689-2697.

(353) Abellan, T.; Mancheno, B.; Najera, C.; Sansano, J. M. "Asymmetric synthesis of Î±-amino acids from Î±,Î²-(Z)-didehydroamino acid derivatives with 1,2,3,6-tetrahydropyrazin-2-one structure" *Tetrahedron* **2001**, *57*, 6627-6640.