Applications of Allyl and Alkenyl Zirconocenes and Progress Toward the Total Synthesis of Tuberostemonone

by

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Applications of Allyl and Alkenyl Zirconocenes and Progress Toward the Total Synthesis of Tuberostemonone

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This dissertation describes the development of several novel chemical reactions employing allyl and alkenyl zirconocenes. These diverse nucleophiles were employed in the synthesis of a variety of biologically and chemically important molecules. Initially, allyl zirconocenes were employed for the addition to imines, thereby providing rapid access to functionalized homoallylic amines. We were later able to employ alkenyl zirconocenes in both the construction of *C*-glycosidic bonds and the addition to chiral imines. The power of these transformations was realized by a rapid and stereoselective synthesis of an immunostimulant agent and its analogs. Biological evaluation of these compounds showed encouraging activity against malaria. Small molecule radioprotectant agents have also been developed and show promising potential for therapeutic use. Finally, we were able to install key stereocenters of the *Stemona* alkaloid tuberostemonone.

Acknowledgements

The last 5.5 years of my life, with which I have spent pursuing a PhD at the University of Pittsburgh, have been educational, rewarding, and enjoyable. I would like to first thank my advisor, Professor Peter Wipf for being a man of true integrity and a man driven to succeed far beyond anyone I have been around. Through a constant expectation of excellence and a commitment to graduate education, Professor Wipf has provided me with an education second to none. I strive to live up to the high expectations that he has set for me over the years for the rest of my professional career. I would also like to acknowledge Michelle Paul, not only for all her hard work for the group, but also for being a friend and sounding board. Drs. Curran and Nelson have been committee members that have added substantially to my great experience at Pitt.

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her and sharing in all of the experiences and accomplishments we have together. Additionally, I would like to thank my parents for their lifetime of support and love. They have sacrificed to provide me with the opportunities that I have had, and for that I will be forever grateful.

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Ac.....acetyl

Acac…..……acetylacetonyl

AIBN…….2,2'-azo *bis*isobutyronitrile

4-AT……..4-amino tempo

BBN……..9-borabicyclo[3.3.1]nonane

Bn.....benzyl

Boc.....*tert*-butyloxycarbonyl

Bus…….*tert*-butylsulfonyl

cat.....catalytic

Cbz.....benzyloxycarbonyl

CD1d…….....cluster of differentiation 1

COE……cyclooctene

COSY…….correlation spectroscopy

Cp.....cyclopentadienyl

CSA……camphorsulfonic acid

Cy…….. cyclohexyl

DBU.....1,8-diazabicyclo[5.4.0]undec-7-ene

DCC……dicyclohexylcarbodiimide

DIAD……..diisopropyl azodicarboxylate

DMAP.....4-dimethylaminopyridine

DMDO…..…dimethyldioxirane

DMF.....*N*,*N*-dimethylformamide

DMSO.....dimethylsulfoxide

DMPU……1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone

dppbenz.....diphenylphosphinobenzene

dr.....diastereomeric ratio

EDCI……..1-ethyl-3-(3-dimethylaminopropyl)carbodiimide

ESI…….electrospray ionization

ee.....enantiomeric excess

eq……...equivalent(s)

Fmoc……..9-fluorenylmethoxycarbonyl

GC..……..gas chromatography

HOBt……1-hydroxybenzotriazole

HMDS……...1,1,1,3,3,3-hexamethyldisilazane

HPLC.....high performance liquid chromatography

HRMS……high resolution mass spectroscopy

IR……...infrared spectroscopy

LCMS……liquid chromatography mass spectroscopy

LDA…...……lithium diisopropylamide

MAD……..methyl aluminum *bis*(2,6-di-*t*-butyl-4-methylphenoxide)

MCPBA…….3-chloroperbenzoic acid

MOM…….methoxymethyl

MWI……..microwave irradiation

NMR……..nuclear magnetic resonance

NMO……..*N*-methylmorpholine oxide

NOE……...Nuclear Overhauser effect

NOESY……..Nuclear Overhauser enhancement spectroscopy

Nu……..…nucleophile

PPTS……...pyridinium p-toluenesulfonate

p-Tol.....4-tolyl

RCM……..ring closing metathesis

rt.....room temperature

SAE……..…Sharpless asymmetric epoxidation

SM……..…..starting material

TBAF.....tetrabutylammonium fluoride

TBAI……..tetrabutylammonium iodide

TBDPS……...*tert*-butyldiphenylsilyl

TBS.....*tert*-butyldimethylsilyl

TEA……triethyl amine

TFA.....trifluoroacetic acid

TFAA…….trifluoroacetic anhydride

THF.....tetrahydrofuran

TIPS.....triisopropylsilyl

TLC.....thin layer chromatography

TMS.....trimethylsilyl

Ts.....*p*-toluenesulfonyl

TS……transition state

UHP……urea-hydrogen peroxide complex

1. HYDROZIRCONATION-TRANSMETALLATION-IMINE ADDITION OF ALLENES

1.1 INTRODUCTION

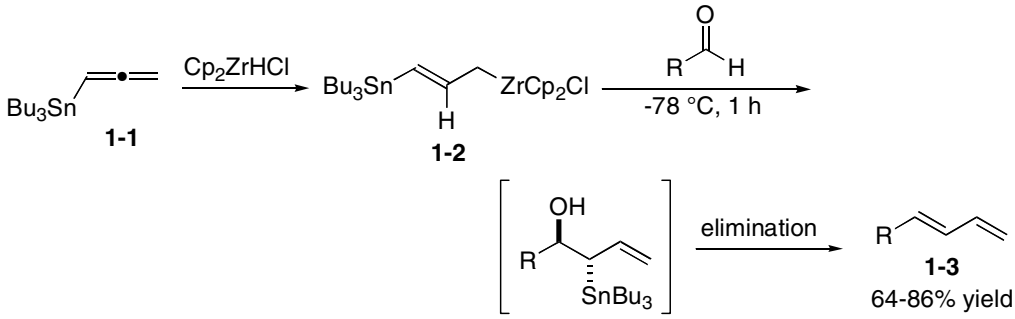
1.1.1 Hydrozirconation of Allenes

Cp_2ZrHCl was first prepared by Wailes and Weigold in 1970[1] and subsequently used to hydrozirconate alkenes[2] and alkynes.[3] The resulting alkyl-[4] and alkenylzirconocenes[5] have been treated with inorganic electrophiles, and transmetallated (from Zr to Al) to increase their reactivity toward organic electrophiles.[6] Zirconocene hydrochloride, also known as Schwartz reagent is a reactive metal hydride reagent that can be handled in air and stored for several weeks in an airtight container.[7]

Reaction of Cp_2ZrHCl with alkynes proceeds within 10 minutes in both CH_2Cl_2 and THF; however, hydrozirconation in toluene proceeds much slower and requires heating to provide reasonable reaction rates. Hydrozirconation of alkenes proceeds slower than alkynes while the hydrozirconation of allenes occurs rapidly at room temperature. Unlike the reaction of Cp_2ZrHCl with alkynes and alkenes, the reagent must be added to a solution of allene at -78 °C, reportedly due to the reaction of Cp_2ZrHCl with CH_2Cl_2 at room temperature.[8] It is unclear where this hypothesis arose since this side reaction is not

problematic in other hydrozirconation reactions. A more reasonable explanation may be that the lower temperature allows for a slower hydrozirconation, thereby providing a more regioselective reaction and fewer side products.

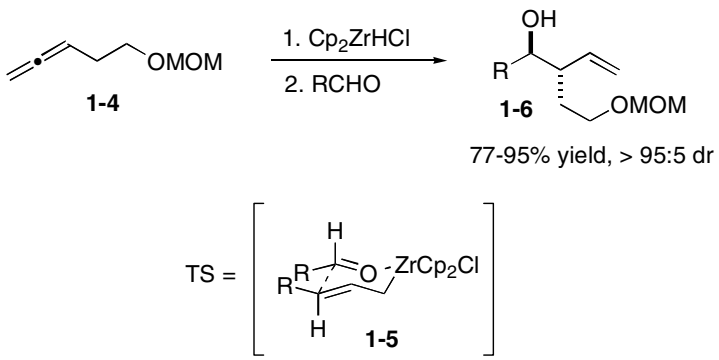
Suzuki and co-workers were first to hydrozirconate allenes to generate allylzirconocenes (Schemes 1-1 and 1-2).[8,9] Targeting the synthesis of three-carbon dianion equivalents such as **1-2**, these authors investigated hydrozirconation of tributylstannyl allene **1-1** as a selective method to generate Sn/Zr-bimetallic species. Upon successful hydrozirconation and subsequent addition to aldehydes or ketones,



Scheme 1-1. One pot diene synthesis via hydrozirconation-aldehyde addition-elimination of stannyl allenes.

spontaneous elimination of the stannyl and oxy functions was observed to afford the 1,3-diene products **1-3** (Scheme 1-1). To further drive elimination to completion, protic or Lewis acids were employed, allowing for a high yielding, one pot synthesis of (*E*)-1,3-dienes.

Furthering the scope of this methodology, Suzuki and co-workers hydrozirconated a variety of mono- and di-substituted allenes to generate allyl zirconocenes that react with aldehydes and ketones in high yield and diastereoselectivity (Scheme 1-2).[8] A chair-like

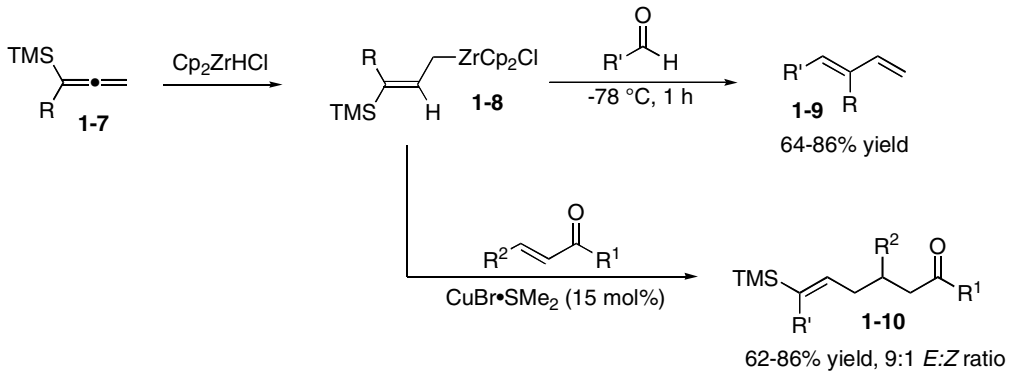


Scheme 1-2. Hydrozirconation of allenes and addition to aldehydes.

transition state **1-5** was proposed by the authors to account for the *anti*-stereoselectivity observed in all known cases. The high reactivity of these allylic zirconocene species should be noted as they, along with acyl zirconocenes, are the only zirconocene species to react with aldehydes or ketones without catalysis.

Since its development in 1993 by Suzuki, allene hydrozirconation saw little attention until the work of Huang and co-workers in 2004.[10a] Revisiting this process, these authors were able to readily hydrozirconate trimethylsilyl-substituted terminal allenes **1-7** and found that the addition of these compounds to aldehydes was analogous to that of the tributyltin-substituted allenes previously reported by Suzuki, yielding 1,3-dienes **1-9** in high yield and selectivity (Scheme 1-3). Interestingly, since the allenes used in this study were 1,1-disubstituted, unsatisfactory results were obtained when the substituent on the allene was bulky, or when ketones were employed as electrophiles. This result is in contrast to the rapid reaction of ketones with mono-substituted allenes previously studied by Suzuki.

In light of this lower reactivity at the γ-position, transmetalation of the allylzirconocene species to copper was envisioned, followed by reaction with enones at

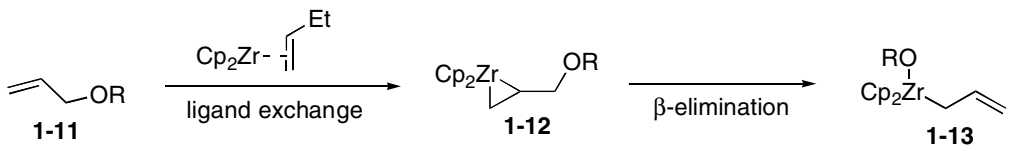


Scheme 1-3. Undesired elimination to yield **1-9** and transmetallation of allylzirconocene **1-8**.

the α-position. Wipf and co-workers reported the first addition of alkylzirconocenes to enones with catalytic CuBr•SMe_2 in 1996.[7c] Applying these conditions to allylzirconocene **1-8** provided a conjugate addition reaction with high regio- and stereoselectivity as long as R^2 was an aromatic group (Scheme 1-3). This served as the first example of transmetalation of an allylzirconocene to generate another allylmetal species.[7c] Subsequently, transmetalation with CuCN has been utilized for the addition of allylzirconocenes to imines.[10b]

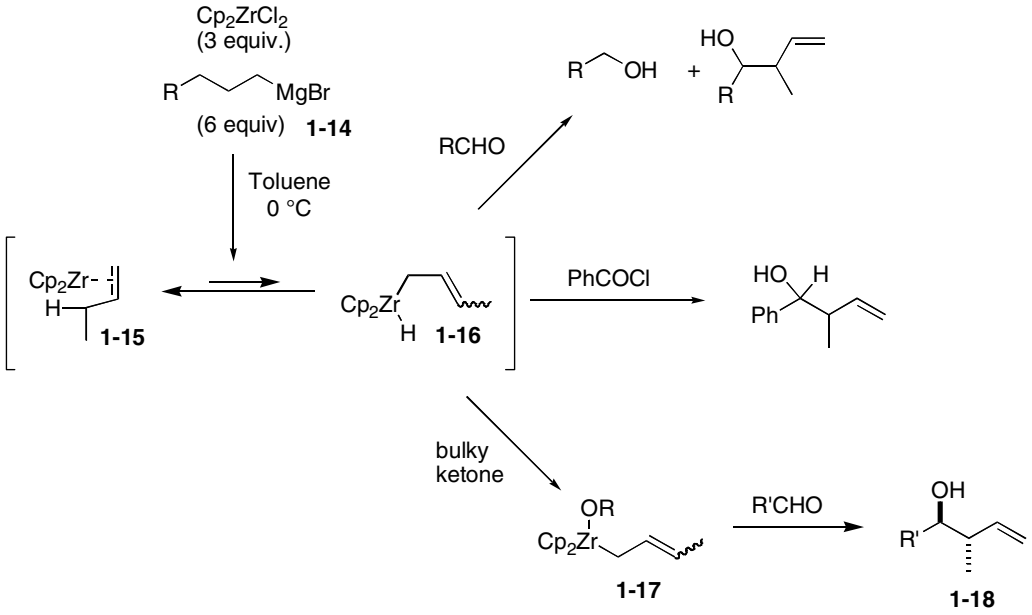
1.1.2 Additional Methods for Generation of Allylzirconocenes

Taguchi and Hanzawa reported that the reaction of zirconocene-olefin complexes with allylic ethers provides allylzirconocene **1-13** after ligand exchange and β-elimination (Scheme 1-4).[11] They were able to react these allylmetals with aldehydes to furnish homoallylic alcohols in high yield and moderate diastereoselectivity. However, preparation of the previously mentioned allenes or zirconocene (II) reagent is, in many



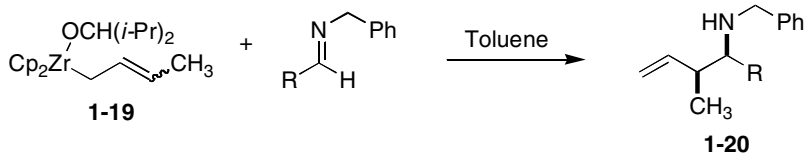
Scheme 1-4. Generation of allylzirconocene via reaction of zirconocene-olefin complexes with allylic ethers.

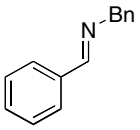
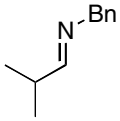
cases not trivial, and the development of a straightforward route to allylzirconocenes would be desirable. Addressing this problem, Oshima and co-workers proposed the synthesis of allylzirconocenes from readily available terminal alkenes (Scheme 1-5).[12] While the zirconocene-olefin complex **1-15** delivers both a hydride and an allyl group to acid chlorides to generate homoallylic alcohols, reactions with aldehydes generate mixtures of reduced and allylated products. To circumvent the hydride reduction



Scheme 1-5. Study of the reactivity of zirconocene-olefin complexes with electrophiles.

Table 1-1. Aldimine addition of allylzirconocenes generated from zirconocene-olefin complexes.

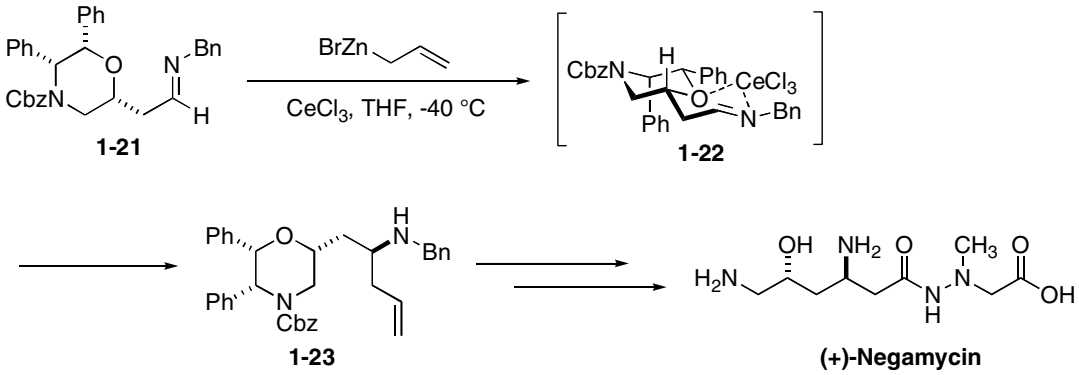


entry	imine	yield (%)	*anti*/*syn*
1		67	11/89
2		73	17/83

pathway, the authors envisioned a reaction of the zirconocene-olefin complex with a bulky ketone to generate an allylzirconocene reagent **1-17** via hydride reduction, followed by addition of this species to aldehydes. Applying this method proved successful, generating *anti*-homoallylic alcohols **1-18** in high yield (Scheme 1-5). Surprisingly, when the reaction mixture was warmed to room temperature before aqueous workup, the reverse selectivity was observed, yielding *syn*-homoallylic alcohols. Extending the addition to aldimines also was efficient; however, these reactions favored the *syn*-addition products in all reported examples (Table 1-1). This report is the first and only example of allylzirconocenes reacting with aldimines without catalysis to furnish homoallylic amines.

1.1.3 Allylzinc Additions to Imines

The addition of organometallics to aldimines has traditionally been limited to strongly basic reagents that do not tolerate sensitive functionality. The much higher reactivity of allyl organometallics reduces this problem and allows for the synthesis of homoallylic amines under mild conditions.[13] Among the many metals employed for this reaction, zinc stands out due to its reactivity, selectivity, and ease of preparation. These points are well demonstrated in Williams' synthesis of (+)-negamycin (Scheme 1-6).[14] Although various allylmetal reagents were screened with a variety of Lewis acids,

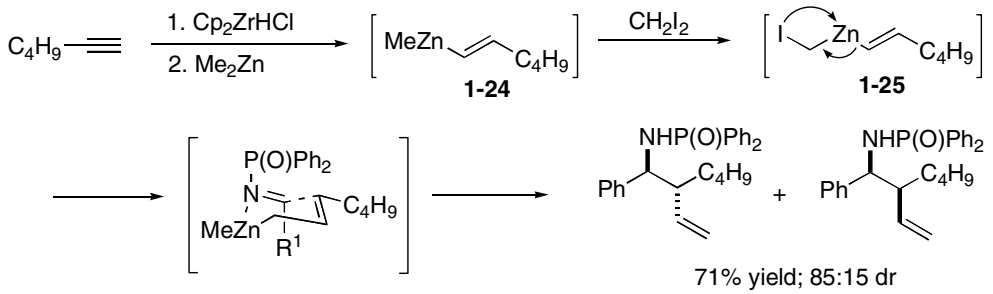


Scheme 1-6. Application of allylzinc-imine addition methodology to natural product total synthesis.

treatment of imine **1-21** with $CeCl_3$ and allylzinc bromide provided essentially quantitative yield and 4.4:1 diastereoselectivity. It is assumed that the *anti*-stereoselectivity in this allylation reaction arises from chelation of $CeCl_3$ with imine **1-21** to generate chair-like transition state **1-22**.

While treatment of an allylic halide with zinc metal has traditionally been the source of allylzinc reagents, there has been significant research on the synthesis of more

complex allylzinc species. Wipf and Kendall have recently shown that hydrozirconation of an alkyne followed by transmetalation with Me_2Zn affords vinylzinc intermediate **1-24** that can react with CH_2I_2 via a [1,2]-shift (**1-25**) to generate an allylic zinc reagent (Scheme 1-7).[15] This functionalized intermediate reacts with aldimines in a diastereoselective fashion to generate homoallylic amides in moderate to high yield. This unique method allows for the preparation of allylic zinc reagents that contain functionality such as esters and ethers that are not readily accessible through traditional allylmetal chemistry.

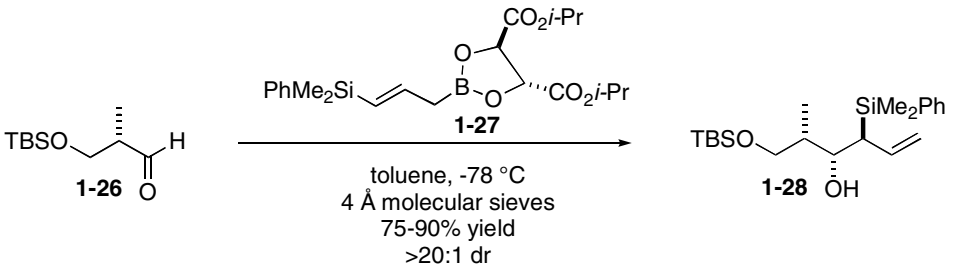


Scheme 1-7. Tandem zirconocene homologation-aldimine allylation.

1.1.4 Synthesis and Reactivity of Vinyl and Allylsilanes

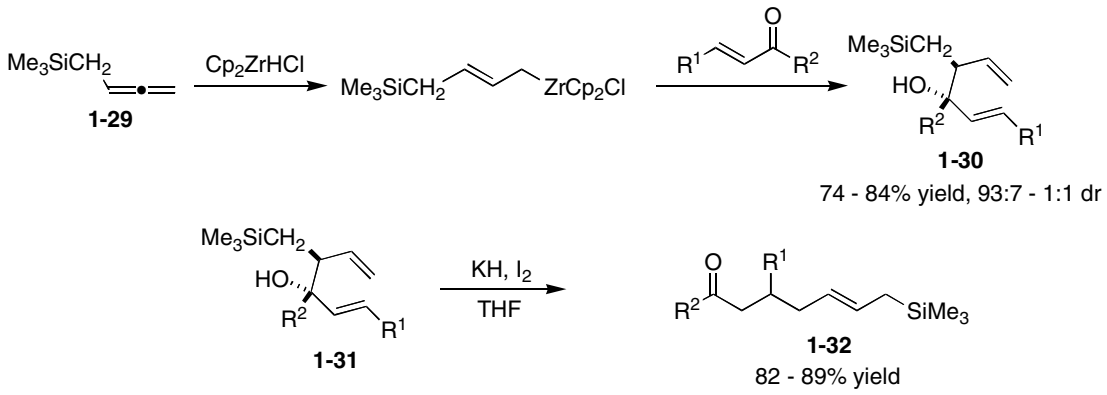
Allylsilanes are versatile intermediates in organic synthesis for a variety of transformations including C-C bond and carbocyclic ring formation.[16] Significant effort has been devoted to the synthesis of these reagents; however, the preparation of allylsilanes containing complex functionality, especially heteroatoms, is an area of limited study.

An attractive synthesis of β-hydroxyallylsilanes was performed by Roush and co-workers who have demonstrated that chiral allylsilanes can be readily synthesized via allylboration reactions as shown in Scheme 1-8.[17] The resulting allylsilanes can be applied to the synthesis of 2,3,5-trisubstituted tetrahydrofurans by [3+2] annulations with aldehydes.[18] Additional work relating to the synthesis of functionalized allylsilanes has been reported by Huang and co- workers (Scheme 1-9).[19] This approach entails the



Scheme 1-8. Synthesis of chiral allylsilanes by a double diastereoselective allylboration reaction.

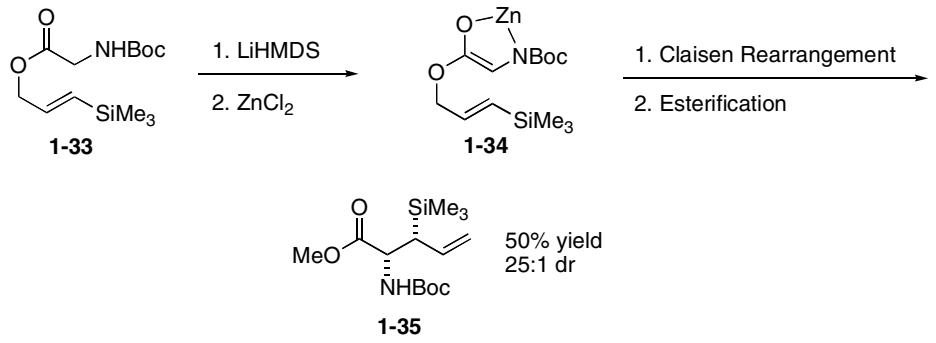
condensation of α,β-unsaturated carbonyl compounds with γ-trimethylsilylmethylallylzirconocene followed by an anionic oxy-Cope rearrangement to



Scheme 1-9. Allylation – anionic oxy-Cope rearrangement yielding functionalized allylsilanes.

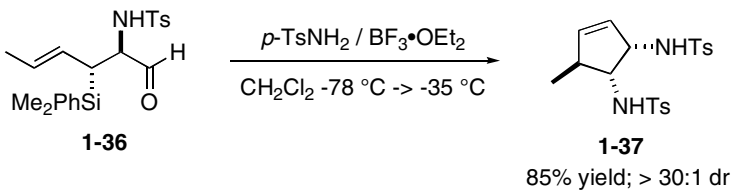
yield the desired allylsilanes **1-32**. Further reactions of these substrates with *n*-Bu_4NF affords cyclopentanols via intramolecular allylsilylation.

β-Amino-substituted allylsilanes are a class of reagents that have seen few applications in the literature, however there are several reports of their synthesis.[20] Brook and co-workers utilized the Claisen rearrangement (Scheme 1-10).[21] While the overall yield of this process is only moderate, good diastereoselectivity was observed and the



Scheme 1-10. Allylsilane-modified amino acids from the Claisen rearrangement.

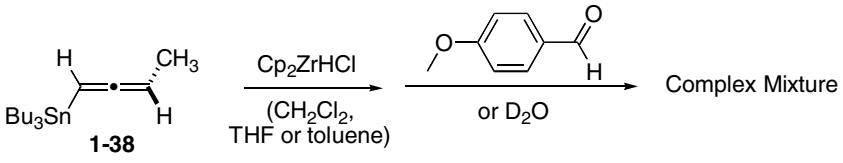
starting materials are readily available. Further applications of these products have not been reported. The sole example of a β-amino-substituted allylsilane undergoing further functionalization is a report by Panek *et al.* (Scheme 1-11).[22] Utilizing BF_3•OEt_2, an intramolecular aminocarbocyclization with silyliminium ions was realized, allowing for the facile synthesis of highly substituted cyclopentenes **1-37**.



Scheme 1-11. Asymmetric aminocarbocyclization of (*E*)-crotylsilanes.

1.2 RESULTS AND DISCUSSION

Previous methodology in the Wipf group focused on the hydrozirconation of alkynes and alkenes and subsequent reactions of these alkenyl or alkyl zirconocenes to produce an array of synthetically useful products. We thought that it would be worthwhile to investigate the hydrozirconation of allenes as an efficient route to complex allylzirconocenes, and were inspired by the work of Suzuki and Huang.[8-10] While previous studies focused on mono-substituted allenes, we initially explored di-substituted allene **1-38** as a test substrate. It was quickly realized that the hydrozirconation of this moiety led to complex mixtures of products under a variety of reaction conditions (Scheme 1-12).

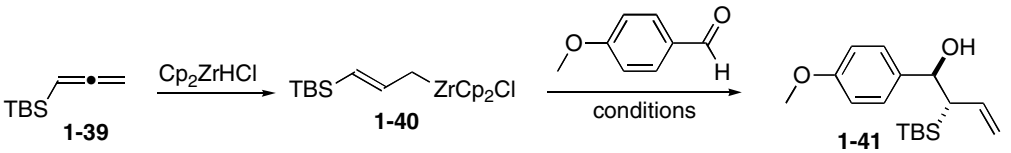


Scheme 1-12. Attempted hydrozirconation followed by aldehyde addition or D_2O quench.

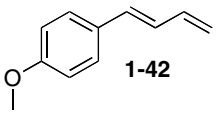
Due to difficulty in the hydrozirconation of **1-38**, mono-substituted allene **1-39** was prepared. It was of interest to see if the increased steric hindrance of the TBS group

prohibited the Peterson-type olefination observed with TMS-allene.[10] Surprisingly, upon hydrozirconation of **1-39** followed by addition of anisaldehyde at -78 ˚C, diene **1-42** was the only observed product. Performing the reaction in the presence of TMSCl did not prevent this elimination process (Table 1-2).

Table 1-2. Hydrozirconation of allene **1-39**, followed by addition to anisaldehyde.

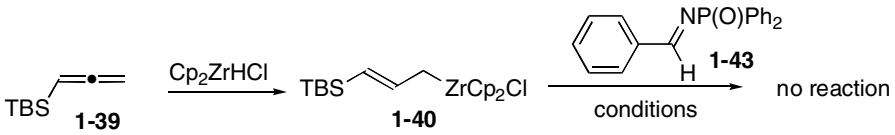


Conditions:	**Results:**
CH_2Cl_2,-78 °C, 1 h	85% yield of **1-42**
CH_2Cl_2, TMSCl, -78 °C -> rt, 1 h	60% yield of **1-42**



While hydroxy groups eliminated under our reaction conditions to form dienes, we felt that aldimines could serve as potential electrophiles and would not be prone to an elimination process. Treatment of aldimine **1-43** with allylzirconocene **1-40** in both dichloromethane and toluene did not produce any addition product even upon heating to 90 ˚C for 8 h (Table 1-3). Although this lack of reactivity was unexpected due to the rapid reaction of allylzirconocene **1-40** with aldehydes at -78 ˚C, we felt that this problem might be solved by utilizing the transmetalation of zirconium to dialkylzinc. This protocol has proven successful for the formation of vinylzinc species via the

Table 1-3. Attempted addition of allylzirconocene **1-40** to aldimine **1-43**.

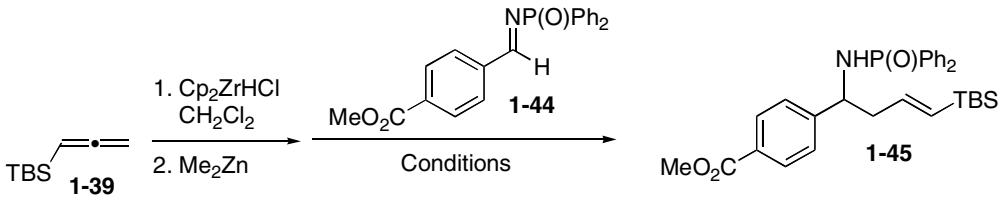


Conditions:	**Results:**
CH_2Cl_2, -78 °C -> rt, 8 h	No reaction
Toluene, 90 °C, 8 h	No reaction

hydrozirconation-transmetalation of alkynes; however, the transmetalation of allylzirconocenes has only been demonstrated with copper (I) salts.[10] Additionally, previous results by Wipf and Kendall have shown that these allylzinc species react with aldimines in a diastereoselective fashion to furnish homoallylic amines in high yield.[15]

Initial reaction conditions involved addition of Cp_2ZrHCl to allene **1-39** in CH_2Cl_2 at -78 ˚C and subsequent warming to room temperature upon which a red solution resulted. This solution was then re-cooled to -78 ˚C and Me_2Zn and aldimine **1-44** were added. To our surprise, these reaction conditions yielded exclusively vinyl silane **1-45**, albeit in a low 18% yield. While intrigued by this regioselectivity, we were interested in improving the reaction yield and first thought to screen solvents, since this has been an effective solution for other hydrozirconation methodology.[23] Although hydrozirconation in THF or toluene produced complex mixtures, it was found that a solvent switch to toluene after hydrozirconation was an effective solution and provided the vinyl silane **1-45** in 80% yield (Table 1-4). A solvent switch to THF after hydrozirconation was complete yielded no desired product and 90% of the starting aldimine was recovered. Additionally,

Table 1-4. Optimization of aldimine allylation reaction.

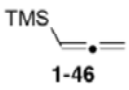
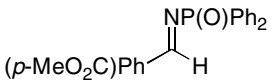
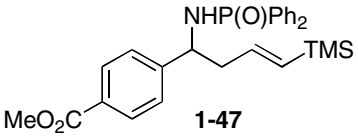
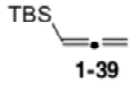
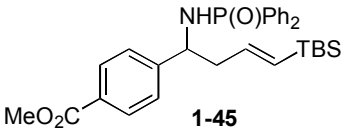
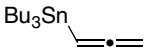
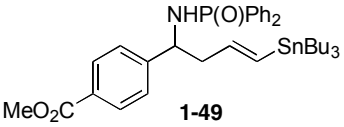
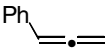
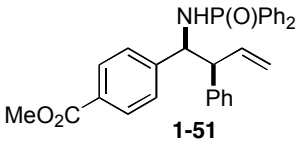
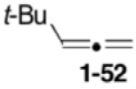
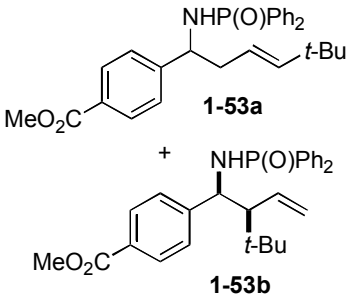


Conditions:	**Results:**
CH_2Cl_2, -78 °C -> rt, 5 h	18% yield
Toluene, -78 °C -> rt, 4 h	80% yield
THF, -78 °C -> rt, 12 h	Recovered Imine (90%)

Et_2Zn provided the homoallylic amines in comparable yields, greatly reducing the cost of this process upon scale-up. Significantly, Et_2Zn was ineffective in previous zirconocene transmetallation methodology.[15]

Encouraged by this result, we sought to investigate the scope of this process and determine if the unexpected regioselectivity was universal or substrate specific. For this purpose, TMS-, TBS-, Bu_3Sn-, and Ph-substituted allenes were synthesized[24] and subjected to the optimized reaction conditions with aldimine **1-44** (Table 1-5). While the silyl- and stannyl- containing allenes **1-39**, **1-46**, and **1-48** produced the expected vinyl-substituted products (entries 1, 2 and 3), the phenyl-substituted allene **1-50** yielded exclusively the terminal alkene product **1-51** typical of allylations of imines or aldehydes (entry 4).[13] This product formation was expected based on our previous results, and the regioselectivity and diastereoselectivity was confirmed though X-ray analysis (Figure 1-1).[15] To further probe the cause of this reversal in selectivity, we synthesized *t*-Bu allene **1-52** and subjected it to the reaction conditions. Although sterically larger than TMS allene **1-46**, this substrate provided a 1.5:1 mixture of vinyl substituted **1-53a** to terminal alkene **1-53b**.

Table 1-5. Hydrozirconation-imine addition of allenes to aromatic aldimine 1-44.[a]

entry	allene	aldimine	homoallylic amide	yield (%)
1	 **1-46**	 **1-44**	 **1-47**	78[b]
2	 **1-39**	**1-44**	 **1-45**	80[b]
3	 **1-48**	**1-44**	 **1-49**	81[b]
4	 **1-50**	**1-44**	 **1-51**	83[c]
5	 **1-52**	**1-44**	 **1-53a** + **1-53b**	64[d]

[a] All reactions were carried out by hydrozirconation of allene (2 eq) with Cp_2ZrHCl (2 eq) in CH_2Cl_2 at -78 °C followed by warming to rt, solvent switch to toluene and addition of Me_2Zn (2 eq) and imine (1 eq). [b] Alkene geometry assigned by coupling constant analysis of the crude reaction products. [c] One diastereomer by ^1H NMR analysis of the crude reaction mixture. Relative configuration confirmed through x-ray analysis. [d] Ratio of products determined to be 1.5:1 (1-53a:1-53b) by ^1H NMR analysis of the crude reaction mixture. Only one alkene isomer and one diastereomer were observed, respectively. The relative configuration of **1-53b** was assigned based on analogy to **1-51**.

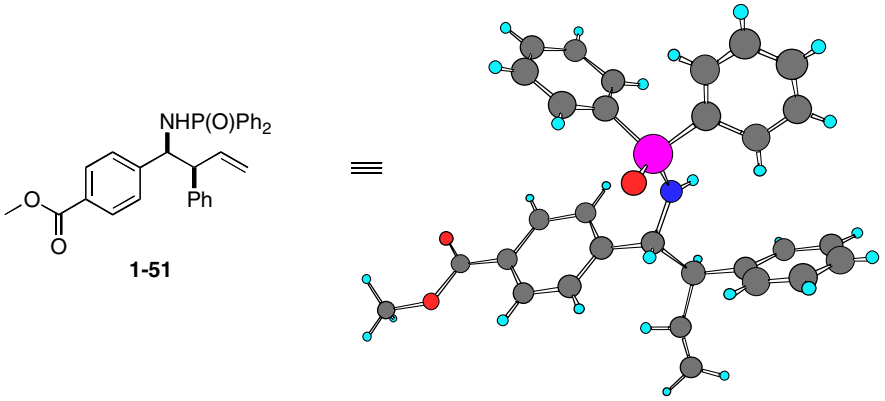


Figure 1-1. X-ray structure of homoallylic amide **1-51**.

Further investigations focused on applying the aforementioned reaction conditions to aliphatic aldimines, as these substrates are generally more demanding,[13] but provide products of higher synthetic value. An initial problem for reactions with aliphatic aldimines is the synthesis of these labile substrates; however, Charette and co-workers recently published a versatile method for the *in situ* generation of *N*-phosphinylalkylimines.[25] Applying this imine preparation to our reaction conditions with allene **1-39** (which simply involved adding an additional equivalent of dialkylzinc) proved efficient, yielding homoallylic amide **1-55** in 79% yield. The regioselectivity of this addition is consistent with the aromatic examples, providing vinylsilane as the only product by ^{1}H NMR analysis of the crude reaction mixture.

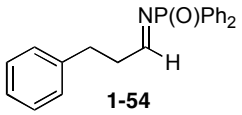
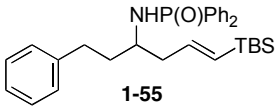
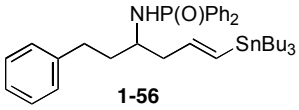
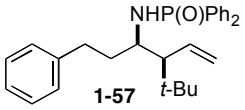
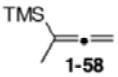
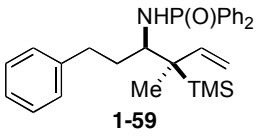
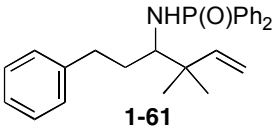
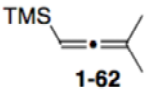
The scope of these additions is illustrated in Table 1-6. Analogous to the addition to aromatic aldimine **1-44**, addition of Bu_3Sn-allene to aldimine **1-54** provided stannyl homoallylic amide as the sole addition product in high yield (entry 2). Interestingly, reaction of *t*-Bu-allene **1-52** under these conditions yielded only the terminal alkene product **1-57**, in contrast to the 1.5:1 ratio in the previously mentioned aromatic case. This result indicates that it is not solely the nature of the allylmetal species that dictates reaction

regioselectivity, but it is also the steric and/or electronic nature of the electrophile. Furthermore, reactions with the aliphatic aldimine **1-54** were noticeably faster, reaching completion in roughly half the time compared to the aromatic aldimine addition reactions.

To explore whether trisubstituted allenes were effective in this reaction, TMS-allene **1-62** was prepared and subjected to the reaction conditions with both aromatic and aliphatic aldimines, but in each case no product was observed. While 1,3-disubstituted and trisubstituted allenes gave rise to complex mixtures during hydrozirconation, we felt that 1,1-disubstituted allenes could serve as useful substrates since they are sterically biased for the approach of the metal complex and have been used successfully in hydroboration reactions.[26] Addition of commercially available 1,1-dimethylallene **1-60** under the optimized reaction conditions to aldimine **1-54** surprisingly yielded only terminal alkene product in high yield (entry 4). Under these reaction conditions, 1-methyl-1-trimethylsilylallene **1-58** yielded 81% of the allylic silane **59** as a single diastereomer (entry 5). The relative configuration of **1-59** was confirmed though X-ray analysis (Figure 1-2). This reaction was of particular interest since we planned to further investigate allylsilanes of type **1-59** (vide infra).

After evaluating the general scope of this process, we desired to explore its extension to tosyl aldimines, or more importantly, *N-tert*-butanesulfinyl imine **1-65**. Addition to *in situ* generated tosyl imine **1-63** proved efficient, yielding allylsilane **1-64** in 85% yield (entry 1, Table 1-7); however, extending our methodology to *N-tert*-butanesulfinyl imines was problematic. A variety of conditions were attempted to

Table 1-6. Hydrozirconation-imine addition of allenes to in situ generated aldimine **1-54**.[a]

entry	allene	aldimine[b]	homoallylic amide	yield (%)
1	**1-39**	 **1-54**	 **1-55**	79[c]
2	**1-48**	**1-54**	 **1-56**	79[c]
3	**1-52**	**1-54**	 **1-57**	80[c,d]
4	 **1-58**	**1-54**	 **1-59**	81[c,e]
6	 **1-60**	**1-54**	 **1-61**	76
7	 **1-62**	**1-44, 1-54**	no reaction	--

[a] All reactions were carried out by hydrozirconation of allene (2 eq) with Cp_2ZrHCl (2 eq) in CH_2Cl_2 at -78 °C, followed by solvent switch to toluene and addition of Me_2Zn (3 eq) and sulfinyl adduct (1 eq). [b] Generated *in situ* from sulfinyl adduct **1-54a**. [c] Only one alkene isomer or diastereomer was observed in each case by ^1H NMR analysis of the crude reaction mixture. [d] Relative configuration based on analogy to **1-51**. [e] Relative configuration based on x-ray analysis.

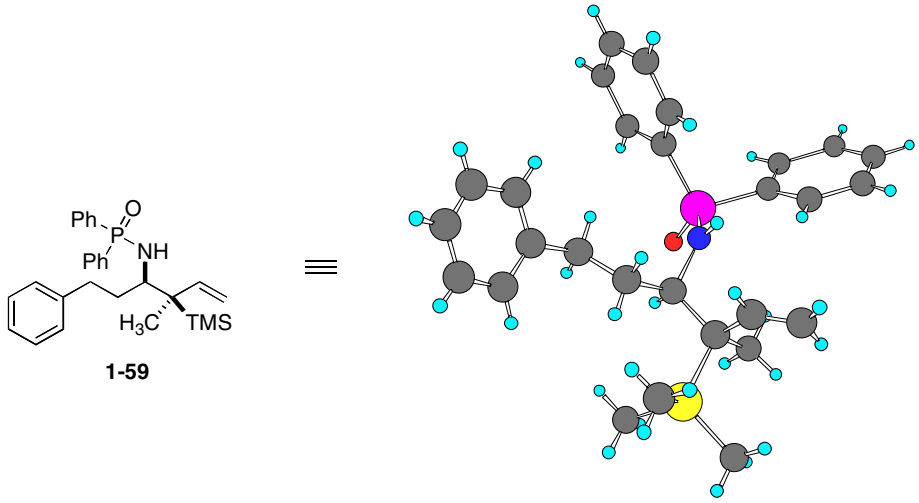
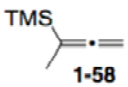
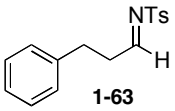
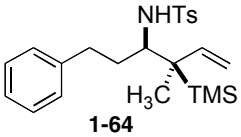
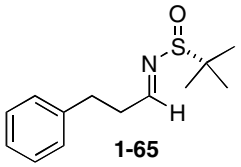
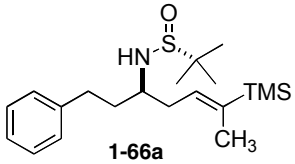
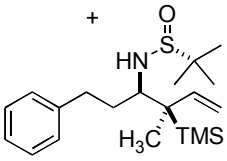


Figure 1-2. X-ray analysis of homoallylic amide **1-59**.

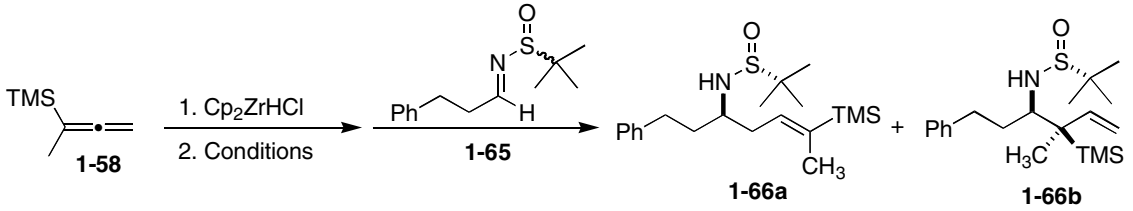
Table 1-7. Extension of allylation reaction to other aldimines.[a]

entry	allene	aldimine[b]	homoallylic amide	yield (%)
1	 **1-58**	 **1-63**	 **1-64**	85[c]
2	**1-58**	 **1-65**	 **1-66a** +  **1-66b**	**1-66a**: 36[d,e] **1-66b**: 45[d,f]

[a] All reactions were carried out by hydrozirconation of allene (2 eq) with Cp_2ZrHCl (2 eq) in CH_2Cl_2 at -78 °C, followed by solvent switch to toluene and addition of Me_2Zn (3 eq) and sulfinyl adduct (1 eq). [b] Generated *in situ* from sulfinyl adduct **1-63a**. [c] Isolated as a single diastereomer. Relative configuration based on analogy to **1-59**. [d] Absolute configuration based on comparison to allylmetal additions in the literature,[18] and relative configuration based on analogy to **1-59**. [e] Assignment of the alkene geometry was based on NOE analysis (see Experimental Part). [f] A single diastereomer was observed by ^1H NMR, and a dr = 96:4 was found by chiral HPLC analysis (Chiralpak AD-H column).

improve the regioselectivity beyond the initial 1.3:1 ratio obtained under the standard dialkylzinc transmetalation conditions (entry 2, Table 1-7). Unfortunately, stronger Lewis acids such as $ZnCl_2$ and BF_3•OEt_2 provided mainly the undesired vinylsilane **1-66a**, while copper salts yielded higher ratios of desired product **1-66b** but at the cost of lower diastereoselectivities (Table 1-8). Rhodium (I) phosphine complexes were also

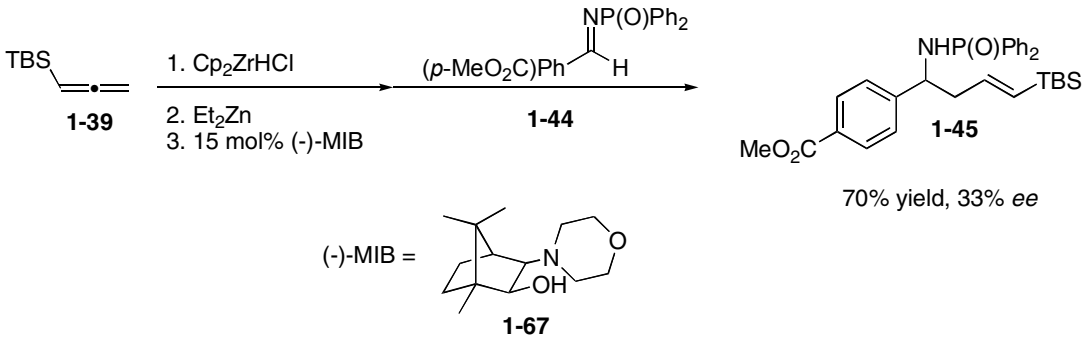
Table 1-8. Application of allylation reaction to *N*-tert-butylsulfinyl imines.[a]



conditions	result (**1-66a:1-66b**)[b]
Me_2Zn, Toluene, -78 °C – rt, 3 h	1:1.3, 94:6 dr; 81% yield
Et_2Zn, CH_2Cl_2, -78 °C – rt, 6 h	1:1, 94:6 dr; 20% yield
10 mol% Et_2Zn, Toluene, -78 °C – rt, 12 h	1:1, 94:6 dr; 70% yield
$ZnCl_2$, Toluene, -78 °C – rt, 4 h	4:1, >95:5 dr; 78% yield
BF_3•OEt_2, Toluene, -78 °C – 0 °C, 6 h	5:1, >95:5 dr; 57% yield
MWI, 150W, 120 °C, 20 min; 180 °C, 20 min	Imine decomposition
1 eq. $AgClO_4$, CH_2Cl_2, -78 °C – rt, 18 h	SM
15 mol% $Yb(OTf)_3$, Toluene, rt – 60 °C, 14 h	SM
10 mol% [$Rh(COE)_2(acac)$], DPPBenz, Toluene, 40 °C, 18 h	SM
10 mol% [$Rh(COE)_2(acac)$], DPPBenz, Dioxane, 40 °C, 18 h	SM
20 mol% CuBr•SMe_2, CH_2Cl_2, 0 °C – rt, 12 h	1:2.3, 2:1 dr; 40% yield
50 mol% CuCl, THF, 0 °C – rt, 12 h	1:2.3, 2:1 dr; 20% yield
10 mol% CuF•3PPh_3•2EtOH, dppf, THF, 40 °C, 18 h	SM

[a] All reactions were carried out by hydrozirconation of allene (2 eq) Cp_2ZrHCl (2 eq) in CH_2Cl_2 at -78 °C, followed by solvent switch to toluene and addition of Me_2Zn (3 eq) and sulfinyl adduct (1 eq). [b] All ratios of **1-66a** to **1-66b** were based on isolated yields. dr determined by ^1H NMR integration of olefin peaks in crude reaction mixture.

explored to facilitate this reaction, but with no success.[27] We finally selected the dialkylzinc transmetalation conditions, due to the high diastereoselectivity and ease of separation by silica gel chromatography even though the regioselectivity was less than ideal. Further unoptimized catalytic asymmetric additions of **1-39** to **1-44** in the presence of 15 mol% of (-) MIB **1-67**[28] as a chiral ligand gave allylic amine **1-45** in a low 33% *ee* (Scheme 1-13). We are continuing our studies to identify a more suitable chiral ligand for this process, mainly encouraged by the enantiomeric enrichment obtained in our first trial.



Scheme 1-13. Catalytic asymmetric addition to aldimine **1-44**.

Mechanistically, we propose a cyclic transition state for vinylsilane formation (Figure 1-3). Hydrozirconation of the allenylsilane **1-46** leads regioselectively to allylzirconocene **1-68**.[8] Upon transmetallation to dimethylzinc, two allylic zinc intermediates are formed. The terminal zinc species **1-69** and the internal zinc **1-70** are in rapid equilibrium,[29] with **1-69** reacting to give the terminal alkene **1-72** (not observed) and **1-70** leading to the vinylsilane **1-47** (observed product). An alternative reaction pathway would involve a direct 1,2-addition of allylzinc reagent **1-69** to the aldimine without allylic inversion to give product **1-47**. However, the exclusive formation of the

vinylsilane with the TMS-substituted zinc species in contrast to the formation of a mixture of both vinylic and allylic products from the *t*-butyl-substituted allene supports the allylic inversion pathway. With 1,1-disubstituted substrates such as **1-58**, the steric strain should position the metal away from the substituents, thereby producing exclusively the terminal vinyl group in the product through allylic inversion.[26]

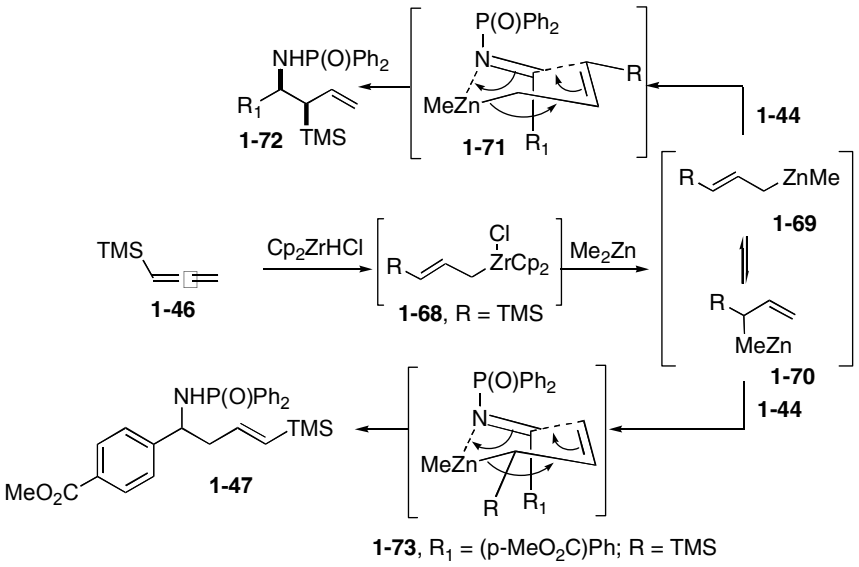
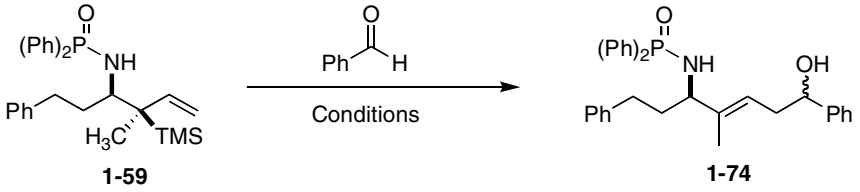


Figure 1-3. Proposed mechanism for homoallylic amine formation.

After developing an efficient methodology for the synthesis of vinylic and allylic silyl homoallylic amines, we were interested in pursuing the further functionalization of several products. Allylsilane **1-59** particularly drew our attention since we felt that its configuration could be transferred though the use of an allylation reaction with an aldehyde or ketone. Attempting this reaction under standard Sakurai conditions (i.e. strong Lewis acids such as $TiCl_4$ or BF_3•OEt_2) proved unsuccessful, yielding only the starting material, or in some cases large amounts of the desilated product **1-75** (Table 1-9).

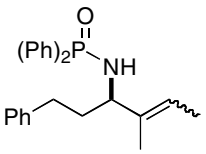
This product arises under acidic conditions, and its formation could be prevented though the use of a hindered base such as 2,6-di-*tert*-butyl-4-methylpyridine (entry 6, Table 1-9). Weaker Lewis acids such as $Yb(OTf)_3$ also provided no conversion in this reaction even

Table 1-9. Attempted allylation of benzaldehyde with allylsilane **1-59**.

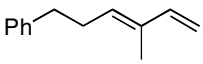


1-59 **1-74**

entry	conditions	results
1	$TiCl_4$, CH_2Cl_2, -78 °C – rt, 18 h	SM
2	$TiCl_4$, THF, rt - 80 °C, 18 h	SM + 50% **1-75**
3	BF_3•OEt_2, CH_2Cl_2, -78 °C – rt, 18 h	SM
4	TiF_4, CH_2Cl_2, -78 °C – rt, 18 h	SM
5	TMSOTf, CH_2Cl_2, -78 °C – rt, 14 h	SM + 65% **1-75**
6	TMSOTf, CH_2Cl_2, -78 °C - rt, 14 h, 1.5 eq 2,6-di-*tert*-butyl-4-methylpyridine	SM
7	$Yb(OTf)_3$, Toluene, MWI 150 °C, 30 min	SM
8	10 mol% TBAF, CH_2Cl_2, -78 °C, 3 h	78% **1-76**
9	NaH, THF then 10 mol% TBAF, CH_2Cl_2 - 78 °C, 60 min	72% **1-76**



1-75



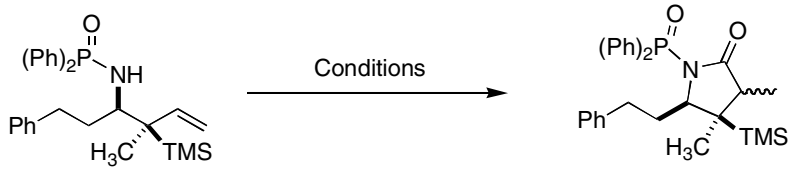
1-76

when the reaction was heated to 150 °C in a microwave. Finally, fluoride ion conditions rapidly eliminated the *N*-diphenylphosphinylamine moiety, generating diene **1-76**. This elimination was facile even after deprotonation of the amide with sodium hydride prior to

the reaction. Although literature precedent for allylsilane chemistry is abundant, there are few examples of successful reactions with a leaving group β to the silicon and/or quaternary silanes undergoing Sakurai reactions. The few existing examples involve intramolecular processes which greatly facilitate the allylation.

Carbonylation reactions of homoallylic amines have proven to be an effective method for the synthesis of lactams. Many of the literature examples for this transformation require harsh conditions (high pressure and temperature); however, mild copper-catalyzed conditions have also been developed.[30] We subjected **1-59** to the latter carbonylation reaction conditions (Table 1-10), but desilylation by the HCl formed after treatment of the amide with $CuCl_2$ was observed.[30] Different conditions including higher temperatures, added base, various metal catalysts, and higher pressures could be explored to further investigate the potential of this transformation.

Table 1-10. Carbonylation reactions of allylsilane **1-59**.



1-59 **1-77**

conditions	results
$PdCl_2(CH_3CN)_2$, $CuCl_2$, PhOH/THF CO/O_2 (1:1, 1 atm)	SM + desilylated material
$PdCl_2(CH_3CN)_2$, $CuCl_2$, *i*-PrOH/THF CO/O_2 (1:1, 1 atm)	SM + desilylated material
$PdCl_2$, CuCl, *i*-PrOH/THF CO/O_2 (1:1, 1 atm)	SM + desilylated material

1.3 CONCLUSION

We have developed a new synthesis of homoallylic amines with vinylic and allylic silane functions, employing both aromatic and aliphatic aldimines. All reaction products were isolated as single diastereomers in high yield. Although further extension of the functionalized products was not accomplished to date, these diverse building blocks hold promide for their application in complex molecule synthesis.

2.0 SILVER (I) - CATALYZED ADDITION OF ZIRCONOCENES TO ACTIVATED EPOXIDES

2.1 INTRODUCTION

2.1.1 Importance of *C*-Glycosides

Oligosaccharides and glycoconjugates are involved in a vast array of biological processes including cell recognition, cell differentiation and cell adhesion. Many glycosides also play key roles in cell signaling.[31] While glycosides often play beneficial roles in the cell, others are thought to be key factors that allow binding between host and cancer cells.[32] A number of carbohydrate based therapeutic agents have been developed to combat various diseases; however, most of these compounds suffer from the susceptibility of the glycosidic linkage to glycosidase enzymes *in vivo*.

The replacement of the anomeric oxygen atom in glycosides with carbon provides carbohydrate mimetics with improved stability toward glycosidases. In principle, the greater chemical and enzymatic stability of these *C*-glycosides bodes well for their application as small molecule inhibitors of cell-surface recognition events and glycoside metabolism, but in practice the mimicry of conformational and electrostatic properties of the parent *O*-glycosides has been challenging to realize. Not surprisingly, biological

activity is often critically dependent on solution conformation.[33] While most synthetic *C*-glycosides show diminished activity versus the corresponding *O*-glycoside lead structures, considerable enhancement of activity has also been observed.[34]

2.1.2 Synthetic Methods for *C*-Glycoside Preparation

Inspired by the desire to develop more potent carbohydrate analogues, the synthetic community has developed new methodologies for *C*-glycoside synthesis for application to important macromolecules such as spongistatin (Figure 2-1).[35] In light of the amount of work in this field, a number of strategies have been developed for *C*-glycoside synthesis for the creation of analogues as well as for complex natural product synthesis.[36] While reductive lithiation to generate α-lithioethers was first demonstrated by Cohen,[37] this methodology was extended to *C*-glycoside synthesis by Sinaÿ and later by

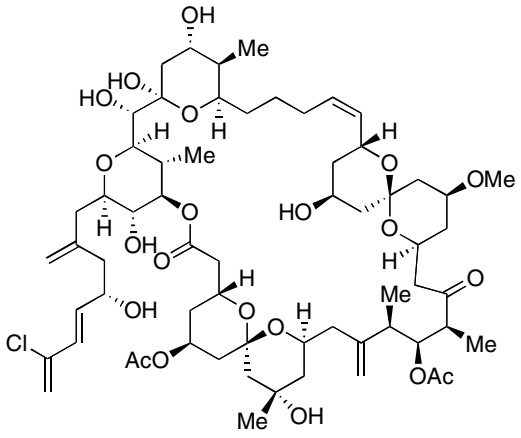
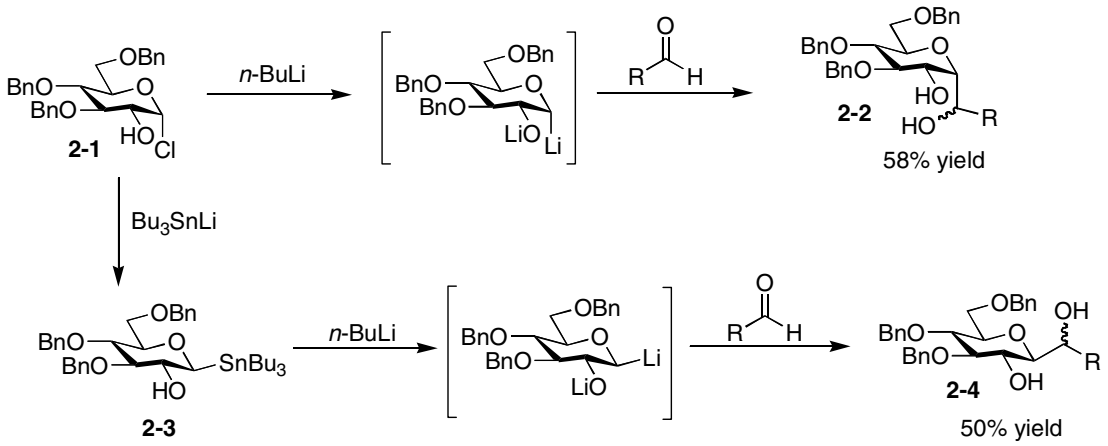


Figure 2-1. Spongistatin.

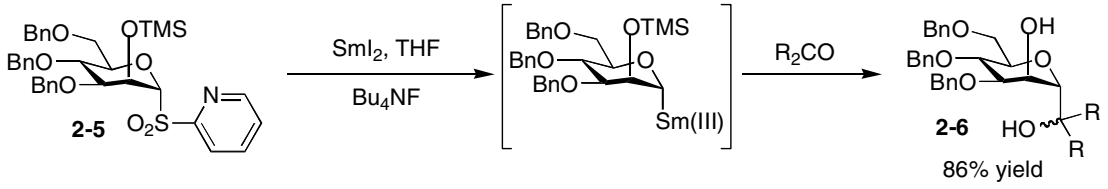
Kessler and co-workers.[38] Kessler showed that the reaction of glycosyl chlorides **2-1** with *n*-BuLi generated a dianion that successfully reacted with various electrophiles with high



Scheme 2-1. Synthesis of *C*-glycosides by reaction of electrophiles with glycosyl dianions.

α-selectivity (Scheme 2-1).[39] β- Glycosides could be generated though the use of an intermediate β-stannane **2-3**, followed by dianion formation and addition of electrophile.

Sinaÿ and Beau introduced the reduction of aryl sulfones with SmI_2 to afford nucleophilic intermediate samarium (III) compounds that stereospecifically react with electrophiles such as aldehydes and ketones (Scheme 2-2).[40] It was later discovered that

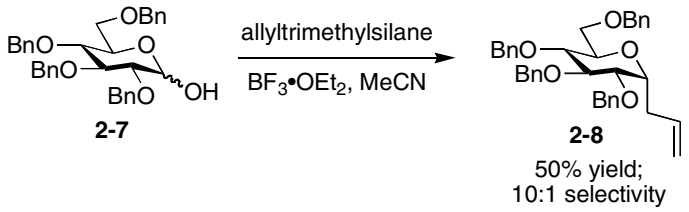


Scheme 2-2. Stereoselective synthesis of α-*C*-glycosides via glycosyl samarium (III) compounds.

treatment of β-aryl sulfones with SmI_2 and NiI_2 as a catalyst allowed for the selective formation of β-*C*-glycosides.[41]

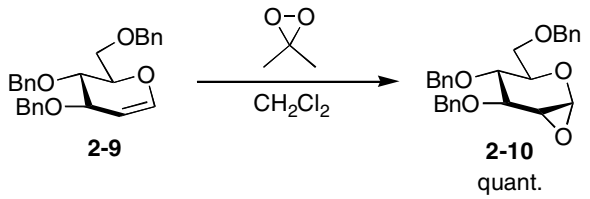
Another approach to *C*-glycosides involves the use of the anomeric carbon as an electrophile. In 1982, Kishi and co-workers showed that treatment of benzylglucose **2-7**

with allyltrimethylsilane and BF_3•OEt_2 yielded *C*-glycoside **2-8** in 50% yield and 10:1 α:β selectivity (Scheme 2-3).[42] This approach was later modified to improve both yield and selectivity.[43]



Scheme 2-3. Allylation of 2,3:4,6-tetra-*O*-benzylglucose with allyltrimethylsilane.

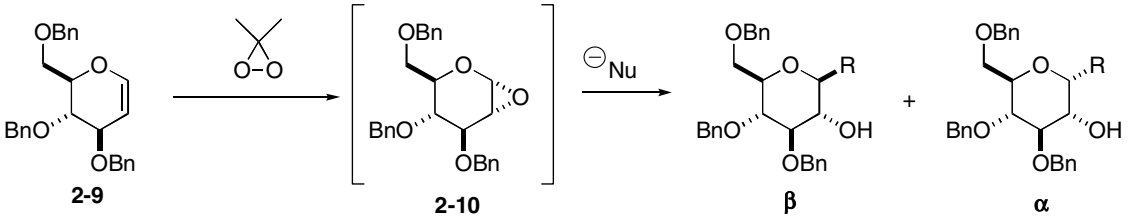
In 1989, Danishefsky and Halcomb demonstrated the use of dimethyldioxirane as an epoxidation reagent for glycals, allowing for the use of 1,2-anhydro sugars as potential glycosyl donors (Scheme 2-4).[44] This development generated considerable research in

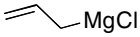
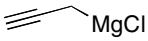
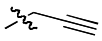
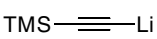
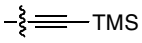
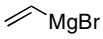
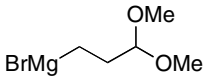
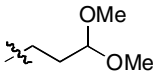
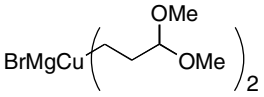
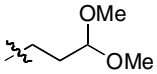
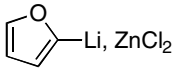
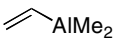


Scheme 2-4. Epoxidation of glycals with dimethyldioxirane.

this field, with a number of groups developing methodology for nucleophilic additions to these activated epoxides.[45] Table 2-1 shows a summary of addition reactions to 1,2-glycal epoxide **2-10** and the selectivity achieved in these additions. Rainier and co-workers demonstrated that depending on the nature of the nucleophile employed in the reaction, exclusive α- and/or β-selectivity could be accomplished (Table 2-1).[45e] While alkylcuprate

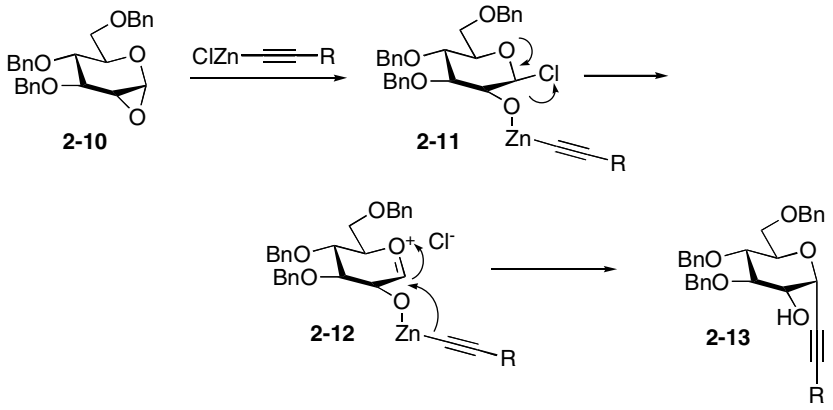
Table 2-1. Addition of nucleophiles to glycal epoxides.



entry	nucleophile	R	temperature	β/α selectivity	yield (%)
1	Me_2CuLi	Me	0 °C	1:0	82
2			0 °C	1:0	82
3			0 °C	1:0	78
4			0 °C	0:1	80
5			0 °C	1:1	n.d.
6			-40 °C	1.7:1	29
7			-30 °C	6:1	74
8			-60 °C – rt	1:0	78
9			-65 °C - rt	0:1	40

reagents, allylmagnesium reagents and propargylmagnesium reagents all provided exclusively β-addition products (entries 1-3, Table 2-1), lithium acetylide and vinylalanes provided the α-anomer as the exclusive product (entries 4,9, Table 2-1). Unfortunately, other magnesium or copper based reagents yielded poorer ratios of products and often much lower yields when heteroatoms were incorporated into the nucleophile. It is interesting to note that the furanyl zinc species (entry 8, Table 2-1) provided exclusively

the β-product even though addition of zinc and titanium reagents is believed to involve an alkoxy carbenium ion as depicted in Scheme 2-5.[45j] Sinaÿ and co-workers proposed that the metallonucleophile, in this case the metalloalkyne, activates the 1,2-anhydrosugar **2-10** by complexation of the Lewis acidic metal atom to the epoxide to generate the alkoxy



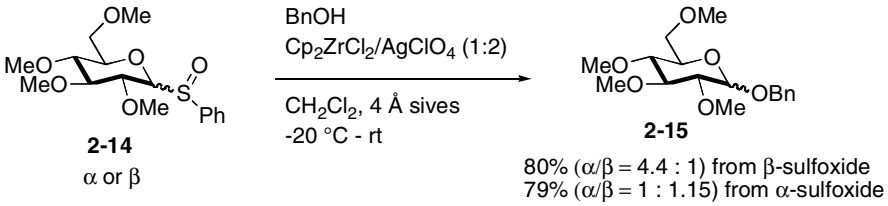
Scheme 2-5. Proposed mechanism for exclusive α-selectivity with zinc nucleophiles.

carbenium ion **2-12**. This process is then followed by intramolecular delivery of the nucleophile from the α-face to yield **2-13**. An analogous mechanism has been proposed to explain α-selectivity in organoaluminium additions to glycal epoxides.[46] While there is evidence to support this mechanism, varying selectivities have been observed by several groups, and an explanation for these discrepancies has yet to be put forth.

2.1.3 Cationic Zirconocenes in Organic Synthesis

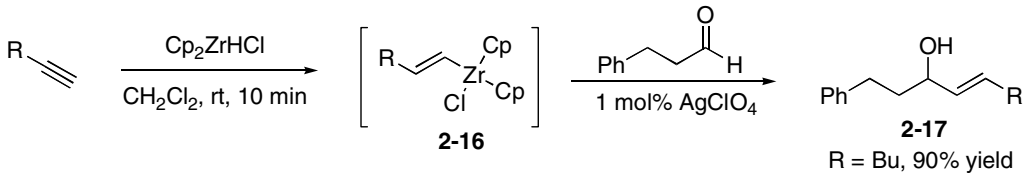
Cationic zirconocenes are reactive species that have seen significant attention from the synthetic community. These reagents are usually formed *in situ* from a neutral complex, often via halide abstraction. The use of $Cp_2ZrCl_2/AgClO_4$ as a cationic

zirconocene system has been extensively investigated as an activator in glycoside synthesis. These reactions have mainly been carried out with glycosyl fluorides,[47] however more recently glycosyl sulfoxides have also proven effective (Scheme 2-6).[48]



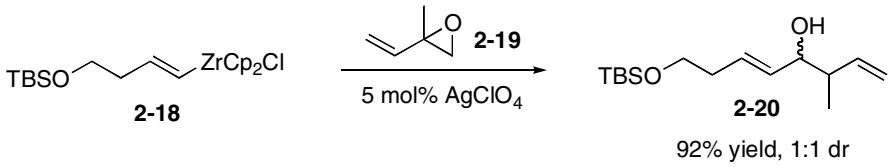
Scheme 2-6. Glycosylation reactions with glycosyl sulfoxides.

While alkyl- and alkenylzirconocene chlorides are readily accessible through hydrozirconation chemistry,[7] they are not sufficiently nucleophilic to add to aldehydes or epoxides. Suzuki and co-workers discovered that a catalytic amount of silver salts strongly accelerated these reactions.[49] $AgClO_4$ was found to be the most effective promoter for the addition of alkenylzirconocenes to aldehydes and ketones, providing allylic alcohols in high yield (Scheme 2-7). Alkylzirconocenes are much less reactive under these conditions and yields are often low in additions of these species to electrophiles. It was later found that $AgAsF_6$ is a similarly effective catalyst for this process and allows for the addition of both alkenyl- and alkylzirconocenes in high yields.[50]



Scheme 2-7. Hydrozirconation followed by cationic zirconocene catalyzed aldehyde addition.

The addition of cationic alkenylzirconocenes to epoxides would be expected to provide homoallylic alcohols; however, research by the Wipf group has shown that allylic alcohols are the observed products from these intermolecular additions to epoxides under $AgClO_4$ catalysis (Scheme 2-8).[51] It was proposed that the strongly Lewis acidic cationic zirconocene caused epoxide opening, followed by a 1,2-hydride shift to generate an aldehyde that can undergo nucleophilic attack to provide allylic alcohols such as **2-20**. Additionally, when an epoxy ester was subjected to the reaction conditions, either acetals or orthoesters were the observed products due to ester-assisted epoxide opening as the initial step.[52]



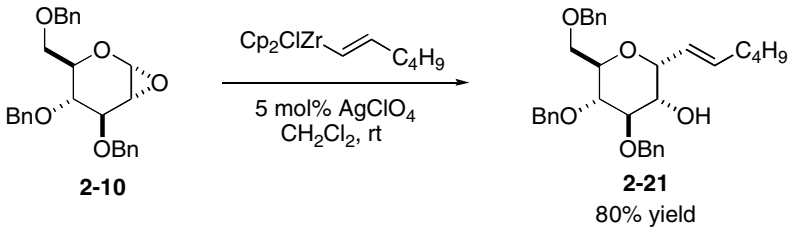
Scheme 2-8. Silver catalyzed reaction of alkenylzirconocenes with epoxides.

2.2 RESULTS AND DISCUSSION

2.2.1 Additions to Glycal Epoxides

Previous work in our group focused on extending the use of cationic zirconocene species for glycal epoxide opening.[53] In initial reactions performed with alkenylzirconocenes, it was found that 5 mol% $AgClO_4$ promoted the expoxide opening, providing 80% yield of exclusively α-anomer **2-21** (Scheme 2-9). In the course of this

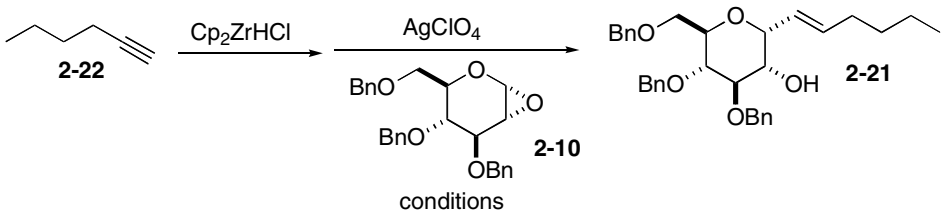
early methodology development it was found that protecting groups on the pyran ring were of considerable importance, with the yield dropping to 54% when acetate protecting groups were employed. The decrease in yield for more deactivating protecting groups such as acetates most likely is due to poor selectivity and low yield in the epoxide formation step.[44]



Scheme 2-9. Initial *C*-glycoside formation developed in the Wipf group.

It was our primary goal to extend this methodology to a variety of alkynes and alkenes to generate alkyl and alkenyl *C*-glycosides with functionality incorporated into the side chain. While hydrozirconation methodology has shown great tolerance to silyl ether, carbamate and bulky ester groups, the addition of organometallic reagents to glycal epoxides has generally been focused on simple, commercially available reagents.[45] Attempts to repeat the reaction shown in Scheme 2-9 provided variable yields ranging from 10 – 70%. Addition of triphenyl phosphite to the reaction mixture did not improve the reproducibility of this process, even though this method has proven useful for other cationic zirconocene methodologies (entry 1, Table 2-2).[52] CH_2Cl_2 has generally proven

Table 2-2. Optimization of cationic zirconocene additions to glucal epoxide **2-10**.

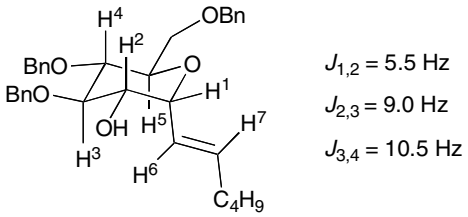


entry	conditions	yield (%)
1	5 mol% $AgClO_4$, CH_2Cl_2, 1 equiv $P(O)Ph_3$, 0 °C – rt, 2 h	58
2	5 mol% $AgClO_4$, THF, 0 °C – rt, 8 h	20
3	5 mol% $AgClO_4$, toluene, 0 °C – rt, 8 h (solvent switch from CH_2Cl_2 after hydrozirconation)	< 10
4	10 mol% $AgClO_4$, CH_2Cl_2, 0 °C – rt, 1.5 h (2x concentration); addition of epoxide to premixed silver/zirconocene	77
5	10 mol% $AgClO_4$ on celite, CH_2Cl_2, 0 °C – rt, 1.5 h (2x concentration); addition of epoxide to premixed silver/zirconocene	78
6	10 mol% $AgClO_4$ on celite, CH_2Cl_2, 0 °C, 3 h (2x concentration); addition of epoxide to premixed silver/zirconocene	76

to be the most effective solvent for both hydrozirconation and cationic zirconocene reactions; however, THF and toluene were also screened to evaluate the solvent effect in this reaction. CH_2Cl_2 proved to be the optimal solvent, with THF and toluene providing very slow conversions (entries 1-3, Table 2-2).

Additional studies focused on the loading of silver perchlorate, the order of addition and the concentration of the reaction (entries 4-6, Table 2-2). These experiments demonstrated that concentration, as well as order of addition were key factors for reaction success, with an increase of silver loading to 10 mol%, doubling of the final concentration and adding a solution of epoxide to the premixed silver/alkenylzirconocene solution yielding 77% of the desired product **2-21**. While silver perchlorate is potentially explosive, silver perchlorate on Celite® is thought to be safer and easier to handle,[54] and proved equally effective in our reactions. Additionally, lowering the reaction temperature to 0 °C was of no obvious advantage.

The scope of this process is summarized in Table 2-3. As it is typical with hydrozirconation methodology, a range of ether, ester, carbamate and sulfonamide functionalities were tolerated (entries 2-4, Table 2-3). All products were obtained in high yield and in all cases only the α-*C*-glycoside was observed. The α-*C*-glycoside configuration was assigned based on the coupling constant $^{3}J_{1,2}$ = 5.5 Hz, which is characteristic for the 1,2-gauche relationship of the neighboring hydrogen atoms and compares well with literature values (Figure 2-2).[55] The stereochemistry of these reactions

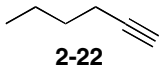
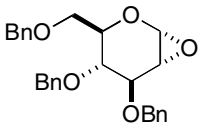
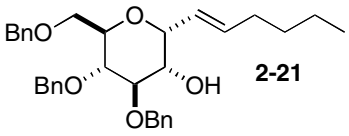
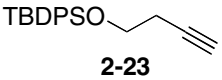
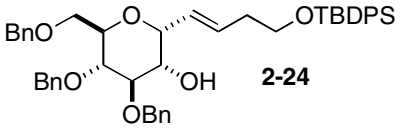
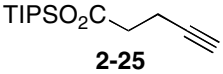
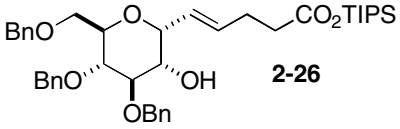
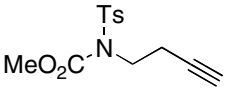
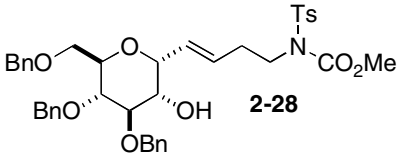


2-21

Figure 2-2. Coupling constant analysis of α-*C*-glycosides.

was also initially confirmed through NOE analysis showing very strong NOEs between hydrogens 2 and 4 and hydrogens 3 and 5, but weak NOEs between hydrogens 1 and 2.[53]

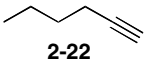
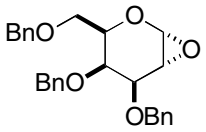
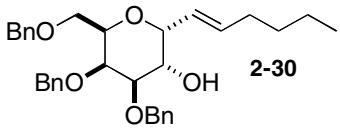
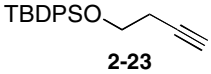
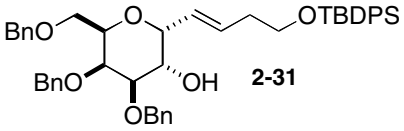
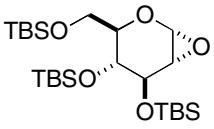
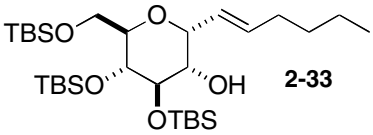
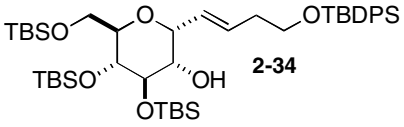
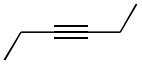
Table 2-3. Addition of a variety of alkenylzirconocenes to benzyl protected glucal epoxide **2-10**.[a]

entry	alkyne	glycal epoxide	product	yield (%)[b]
1	 **2-22**	 **2-10**	 **2-21**	78
2	 **2-23**	**2-10**	 **2-24**	74
3	 **2-25**	**2-10**	 **2-26**	67
4	 **2-27**	**2-10**	 **2-28**	70

[a] All reactions were carried out by hydrozirconation of alkyne (1.5 eq) with Cp_2ZrHCl (2 eq) in CH_2Cl_2 followed by addition of silver perchlorate on Celite® (10 mol%) and glycal epoxide (1 eq). [b] Yields based on glycal epoxides.

In addition to varying the alkyne moiety, both benzyl protected galactose epoxide **2-29** (entries 1 and 2, Table 2-4) and silyl protected glucal epoxide **2-32** (entries 3 and 4, Table 2-4) were used. Both the benzyl ether and silyl ether moieties performed well, and the ability to employ easily removable protecting groups is an advantage. Selective deprotection of the benzyl ethers has not been attempted. Unfortunately, internal alkynes and alkenes did not produce any product under these conditions, most likely due to

Table 2-4. Addition of cationic alkenylzirconocenes to glycal epoxides.[a]

entry	alkyne	glycal epoxide	product	yield (%)[b]
1	 **2-22**	 **2-29**	 **2-30**	73
2	 **2-23**	**2-29**	 **2-31**	72
3	**2-22**	 **2-32**	 **2-33**	74
4	**2-23**	**2-32**	 **2-34**	71
5	 **2-35**	**2-10**	NR	-

[a] All reactions were carried out by hydrozirconation of alkyne (1.5 eq) with Cp_2ZrHCl (2 eq) in CH_2Cl_2 followed by addition of silver perchlorate on Celite® (10 mol%) and glycal epoxide (1 eq). [b]Yields based on glycal epoxides.

increased steric hindrance and decreased reactivity, respectively. The remainder of the material in all reactions appeared to be mainly decomposition products of the glycal epoxides.

Treatment of 1-hexyne with Cp_2ZrHCl provided a stoichiometric alkenyl zirconocene **2-36**,[7] which, upon addition of 10 mol% silver perchlorate on Celite® followed by glucal epoxide **2-10** yielded α-*C*-glycoside **2-21** in 78% yield (Figure 2-2).[56] Due to cationic zirconocene-assisted oxonium ion formation and chelation-directed

delivery of the alkenyl substituent, the reaction proceeded to give exclusively the α-epimer. After initial chloride ligand abstraction and initiation of the catalytic cycle by the silver(I) salt,[49,50] subsequent formation of the cationic zirconium species was a chain transfer process, in which the more Lewis-acidic cationic alkoxy zirconium(IV) species accepted the chloride anion from the alkenyl(chloro)zirconocene **2-36**. A similar

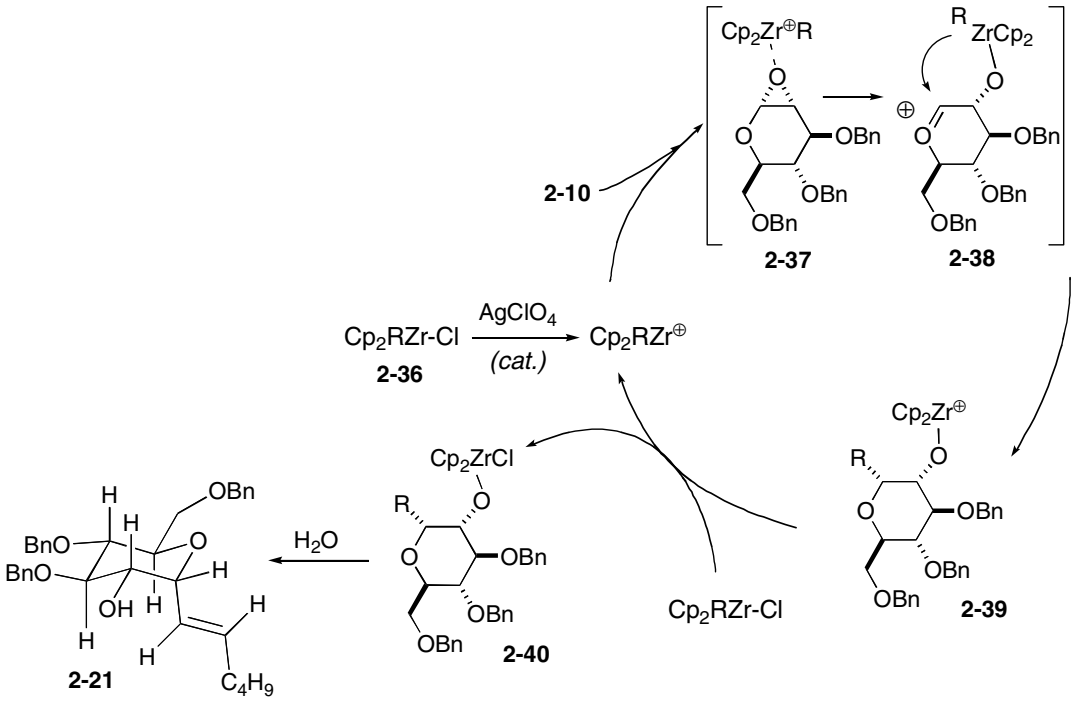
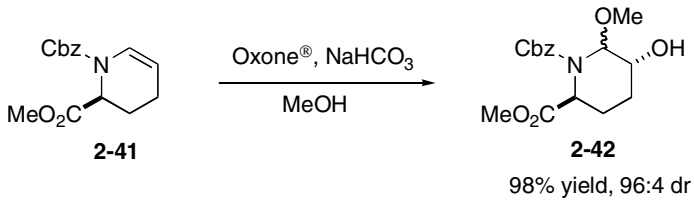


Figure 2-3. Proposed mechanism for cationic alkenylzirconocene addition and exclusive formation of the α-anomer.

mechanism was proposed for the addition of zinc reagents to glycal epoxides, accounting for the high α–selectivity observed in those reactions.[45j]

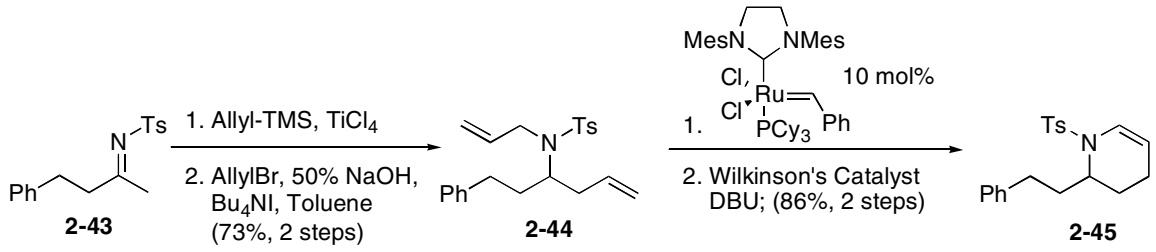
2.1.2 **Application to Tetrahydropyridines**

In the course of Rutjes' synthesis of (2*S*,5*R*)-5-hydroxypipecolic acid, an epoxidation/epoxide opening sequence of enamide **2-41** provided an alcohol intermediate in high yield and selectivity (Scheme 2-10).[57] Inspired by this methodology, we envisioned an epoxidation of cyclic enamines followed by opening with an alkenylzirconocene species as a new method for stereoselective, functionalized piperidine synthesis.



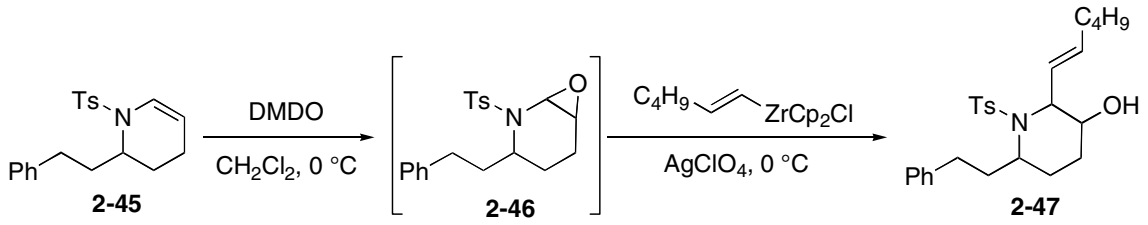
Scheme 2-10. Use of epoxidation/epoxide opening sequence in the synthesis of 5-hydroxypipecolic acid.

Tetrahydropyridine **2-45** was prepared in 4 steps from imine **2-43** as a test substrate for epoxidation (Scheme 2-11). Allylation of imine **2-43**[58] with allyl-TMS and $TiCl_4$ followed by a phase transfer alkylation reaction yielded allylamine **2-44** in 73% yield over 2 steps. Ru-catalyzed ring closing metathesis[59] followed by isomerization of the allylamine to the enamine **2-45**[60] were performed in 94% and 92% yield, respectively.



Scheme 2-11. Synthesis of tetrahydropyridine **2-45**.

With enamine **2-45** in hand, epoxidation of with DMDO, removal of solvent, redissolving the residue in CH_2Cl_2 and addition of the premixed alkenylzirconocene/silver perchlorate mixture provided no addition product by crude NMR and LCMS analysis (Scheme 2-12). Although similar epoxides have been prepared in the literature,[61] the stability of the epoxide to solvent removal seems to be problematic in this sequence.



Scheme 2-12. Attemped opening of epoxide **2-46** with cationic alkenylzirconocene.

2.2 Conclusion

The ability to combine relatively sensitive functional groups with the nucleophilic zirconocene reagent under mild Ag(I)-catalysis allows for rapid conversion of 1,2-anhydrosugars to complex α-*C*-glycosides that have previously not been readily available for synthetic or biological studies. While there are numerous other methods for *C*-glycoside synthesis from glycal epoxides,[45] none of them are as mild and stereoselective as the aforementioned silver-catalyzed alkenylzirconocene addition.

3.0 EXPEDIENT SYNTHESIS OF α-*C*-GLYCOSIDE ANALOGUES OF THE IMMUNOSTIMULANT GALACTOSYLCERAMIDE (KRN7000)

3.1 INTRODUCTION

3.1.1 Biological Significance and Previous Synthetic Approaches

In the mid 1990's, the anticancer drug candidate KRN7000 (α-Gal-Cer, **3-1**) was developed by researchers at Kirin Pharma.[62] Extracts of the Okinawan sponge *Agelas mauritianus* were shown to contain members of the agelasphin family of glycolipids, the lead structures for the chemically simplified KRN7000. **3-1** is a galactose containing glycolipid, bearing a phytosphingosine side chain (Figure 3-1, left). Over a decade of investigation has demonstrated that **3-1** serves as a ligand to CD1d protein with the greasy alkyl chains embedded in deep pockets and the sugar head group exposed for presentation to natural killer T (NKT) cells (Figure 3-1, right).[63] The crystal structure of the bound KRN7000 (triple complex with CD1d and NKT receptor) further demonstrates the importance of the alkyl side chains but also the stereochemistry and presence of the galactose hydroxyl groups.[64] Only the 6-position of galactose has been demonstrated to tolerate substitution to date.[65]

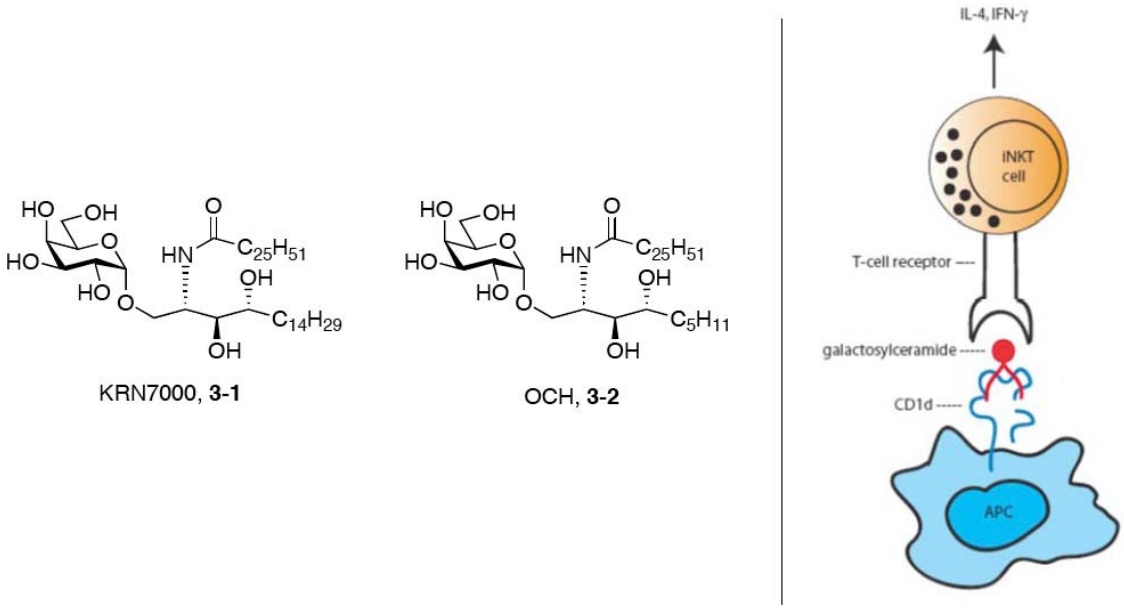


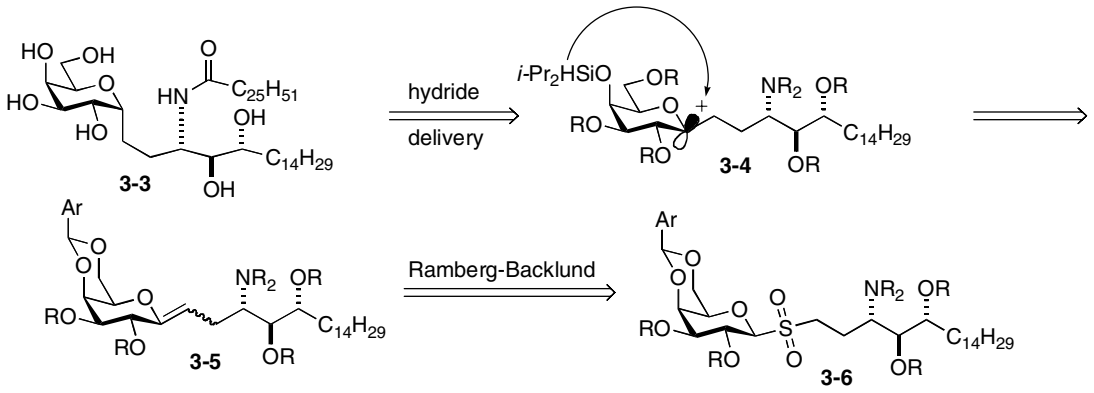
Figure 3-1. Structures of KRN7000 and OCH (left); Mechanism of action for galactosylceramides (right).

Upon formation of the CD1d-(**3-1**) complex, NKT cells are triggered to release both helper Th1 (interferon-γ (IFN-γ)) and Th2 (interleukin-4 (IL-4)) cytokines simultaneously. Th1 and Th2 cytokines play key roles in immunology, with the former participating in protective immune function against external pathogens (ie, cancer) and the later involved in regulatory immune functions (ie, autoimmune disease). KRN7000 promotes significant increases in both types of cytokines, thereby causing adverse effects that have limited its progress as an effective therapy.[66] This lack of success has inspired many research teams to explore the possibility of selectively activating a unique set of cytokines, a strategy that should provide a non-toxic therapy for a wide range of diseases ranging from cancer to malaria.[67] Initial success was described by Miyamoto, who demonstrated that a truncated version of **3-1**, OCH (**3-2**, Figure 3-1), caused selective production of IL-4 providing support for this immunotherapy strategy.[68,69] A chain

shortened analog developed by Wong bearing a terminal phenyl moiety also proved to selectively activate IFN-γ production.[70]

Determined to explore more deep-seated structural modifications, Franck and co-workers proposed exchanging the glycosidic linkage present in **3-1** with an enzymatically stable *C*-glycoside bond (**3-3**, Scheme 3-1).[34] **3-3** not only lacks the additional hydrogen bond acceptor found in the parent molecule, but is also impacted by the loss of the anomeric effect in exchange for an unfavorable axial methylene group in the galactose chair conformation. Additionally, all previous attempts to convert biologically active *O*-glycosides to their *C*-glycoside analogs have been met with dramatically decreased activity. The failure of these *C*-glycoside analogs is most likely due to the conformational change of the compounds that prevents binding in the *O*-glycoside binding site.[33]

From the synthetic standpoint, the initial synthesis of **3-3** involved a late stage intramolecular hydride transfer to a glycosyl cation whose precursor was prepared via Ramberg-Backlund *C*-glycoside methodology (Scheme 3-1).[34] Many difficulties were encountered both with the compatibility of protecting groups and installation of non-glycosidic stereocenters, while the key reactions of the sequence were effective. Although their route to this molecule proceeded in 26 steps and 1.4% overall yield, the Franck group generated enough glycoside to begin preliminary biological testing in collaboration with Tsuji.



Scheme 3-1. Key steps in Franck's first approach to *C*-glycoside **3-3**.

In initial testing, mice were treated with either *O*-glycoside **3-1** or *C*-glycoside **3-3** and then challenged with malaria (Figure 3-2, left).[34] While both compounds were effective at reducing sporozoite levels at dosages of 1 μg, **3-3** was effective even at 1 ng levels proving to be 1000 times more protective than the parent *O*-glycoside. A second assay was carried out with a melanoma challenge in mice, with the *C*-glycoside again proving 100 times more effective than **3-1** (Figure 3-2, right side). The origins of this increased potency were not clear at this stage, as this was the first case of improved activity with *C*-glycoside analogues.

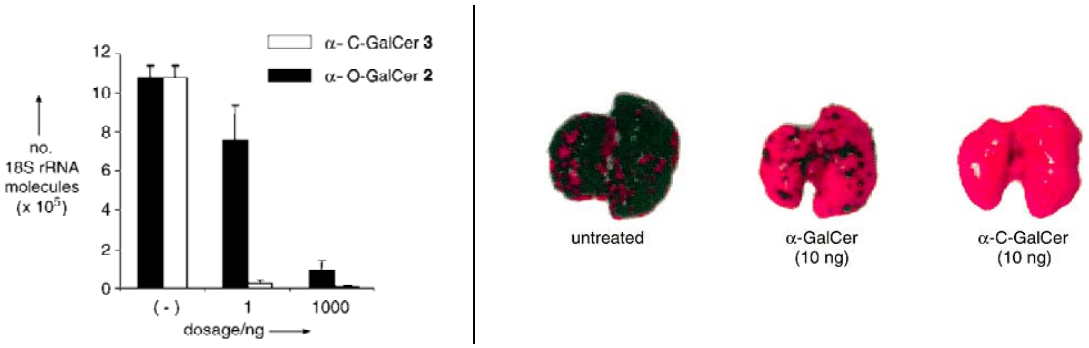
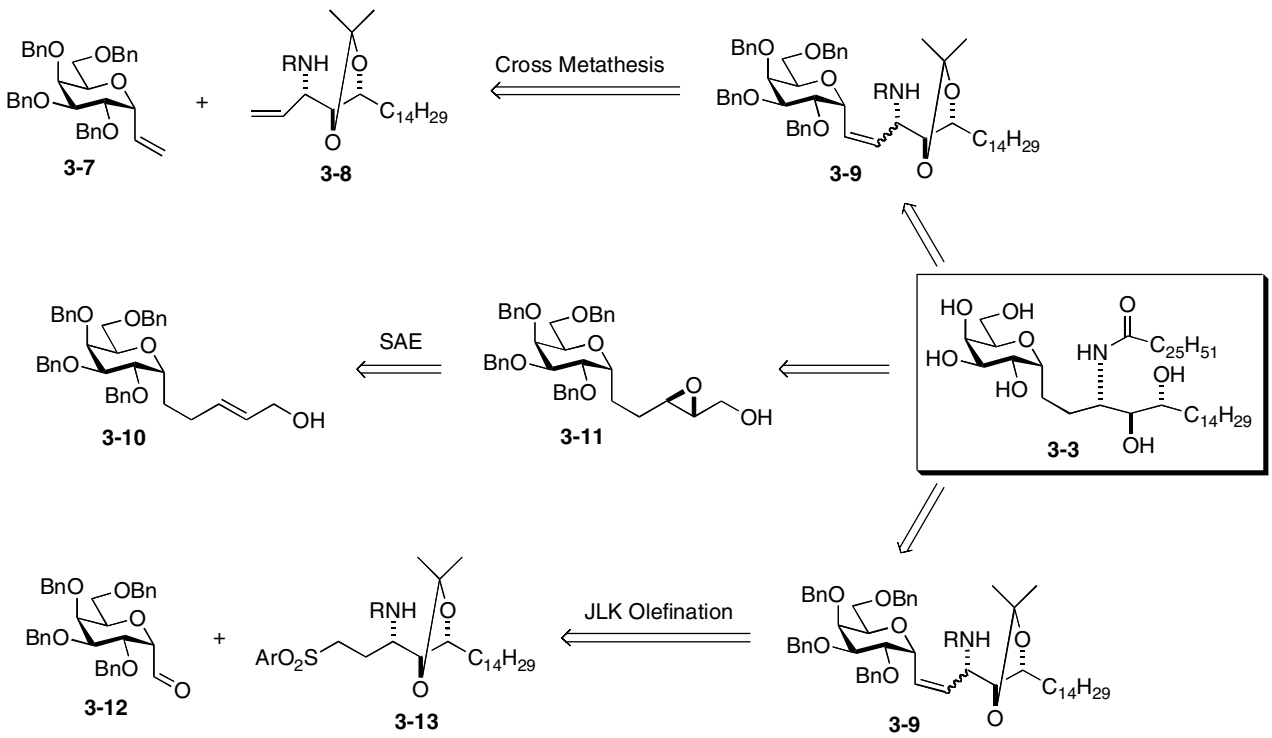


Figure 3-2. Assay for sporozoites in liver (left) and melanoma appearance (black spots) on mouse lung after two weeks (right). *Taken from*: *Angew. Chem. Int. Ed.* **2004**, *43*, 3818.

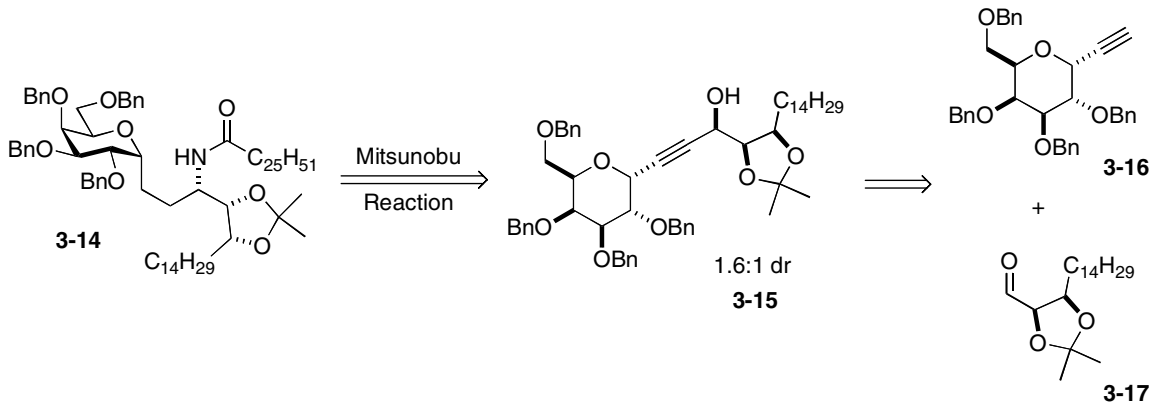
Subsequent to this initial report, Franck developed three additional approaches to **3-3**, consisting of cross-metathesis, Julia olefination and Sharpless asymmetric epoxidation (Scheme 3-2).[71] The cross metathesis approach proved the most efficient and was accomplished in 11 steps while utilizing commercially available phytosphingosine as a coupling partner in the cross-metathesis. Facile scale-up of this route (overall yield of the sequence is 30%) allowed for the synthesis of increased amounts of glycoside for biological testing and analog development. Additionally, the epoxidation/epoxide opening approach provided access to all stereoisomers of **3-3** allowing for their biological evaluation. Interestingly, of the four tested diastereomers, only the natural and unnatural enantiomer of **3-3** showed activity.

Another approach to *C*-glycoside **3-3** was developed that allows for more facile analogue synthesis than either of Franck's routes. The key reaction in this sequence was the alkyne-aldehyde coupling to generate compound **3-15** that was then converted to the desired amide **3-14** through a Mitsunobu inversion (Scheme 3-3).[72] While this route did allow for flexibility in the coupling partners employed, poor selectivity in the alkyne-aldehyde coupling made scale up problematic



Scheme 3-2. Franck's synthetic approaches to **3-3**.

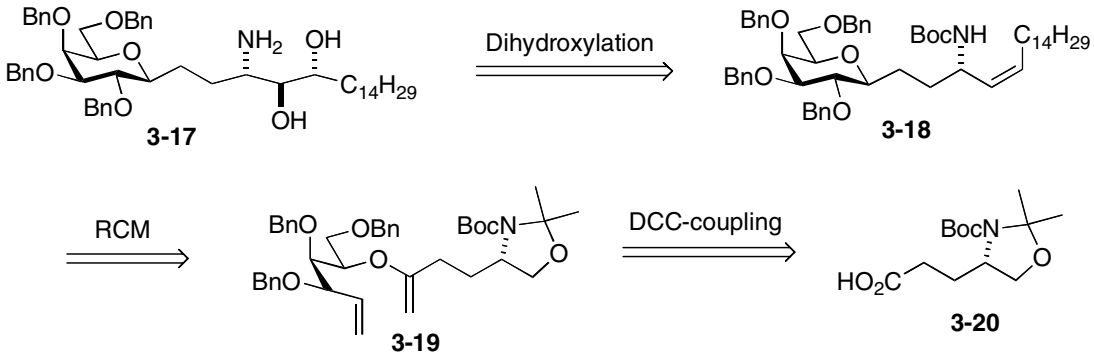
as these diastereomers (1.6:1 ratio) must be separated before being subjected to the Mitsunobu conditions.



Scheme 3-3. Mitsunobu approach to *C*-glycoside **3-14**.

With additional compound in hand, a great deal of effort was put toward evaluating the efficacy of **3-3** *in vivo*, particularly compared to its parent compound **3-1**. Teng *et al.* explored the application of sequential tumor cell apoptosis and amplification of dendridic cell function utilizing either **3-1** or **3-3** provided by Franck.[73] As observed previously, **3-3** provided remarkably increased activity, with complete eradication of established tumors in mice. While the reasons for the greater therapeutic index for **3-3** are still uncertain, it appears that the *C*-glycoside provides a more sustained iNKT cell response than does **3-1**. This response could be due to either tighter binding or a slightly different binding pattern, although the authors have no evidence to support either of these hypotheses.

To further explore the stereochemical properties of **3-3**, Postema and co-workers targeted β-*C*-glycoside derivatives and developed an 18 step synthetic route. Unlike other approaches that introduced the amino-diol stereotriad via a coupling reaction, directed achiral dihydroxylation of allylic amide **3-18** was employed (Scheme 3-4).[74] Disappointingly, this approach only gave a 1:1 mixture of diastereomers, therefore optimization of this step was necessary to improve the efficiency of this synthesis.



Scheme 3-4. Retrosynthesis of a β-*C*-glycoside analogue of KRN7000.

More recently, Mori *et. al.* has synthesized a variety of analogs that include the carbocycle analog **3-21** and conformationally restricted analogs **3-22** and **3-23** (Figure 3-3).[75] The carbocyclic analog showed selective production of Th1 cytokines, very similar to **3-3**; unfortunately, a direct comparison of **3-21** to **3-3** was not performed. The conformationally restricted analogs were more of a disappointment, with only **3-22** showing activity. It could be of interest for future exploration into selective control over cytokine release that this compound appears to promote Th2 cytokine formation.

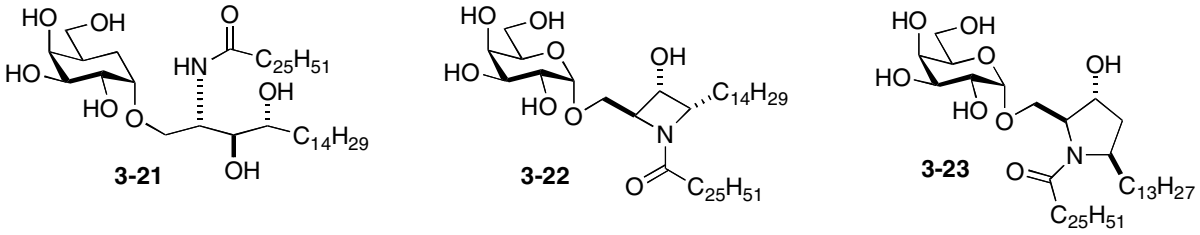


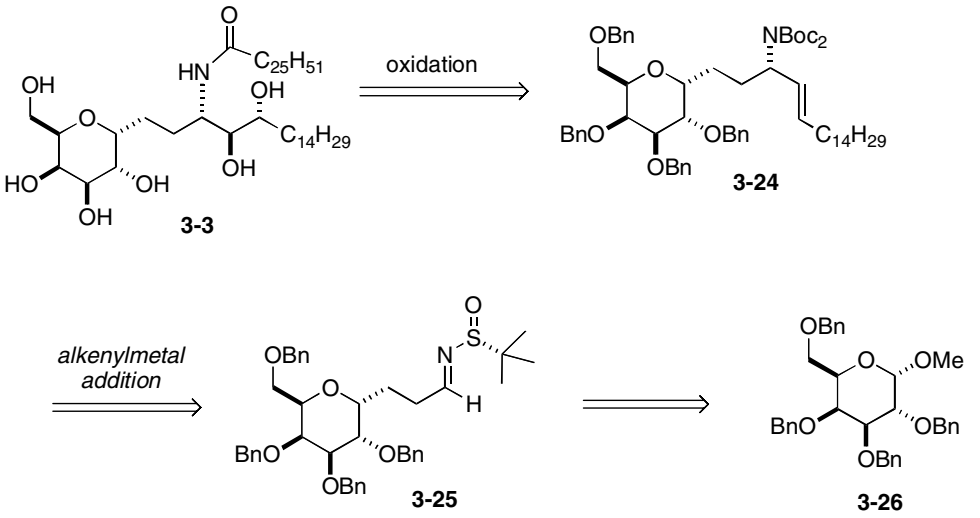
Figure 3-3. Analogs of **3-1** prepared by Mori *et al.*

3.2 RESULTS AND DISCUSSION

3.2.1 Development of an Asymmetric Synthesis of Allylic Amines.

While investigating our cationic zirconocene addition to glycal epoxides, it became clear that the inclusion of nitrogen in the glycoside side chain would provide molecules with interesting biological properties.[76] Accordingly, we envisioned *N-tert*-butanesulfinyl imine **3-25** as a key intermediate that could undergo a diastereoselective alkenylmetal

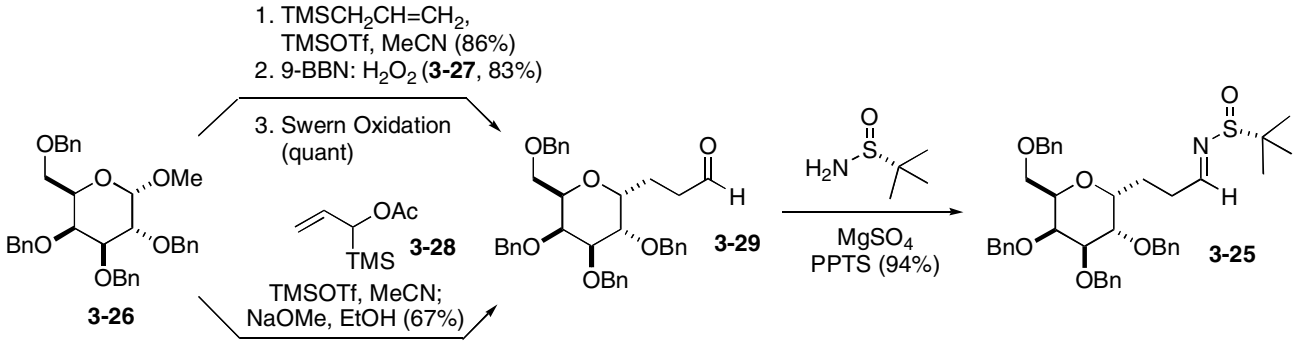
addition followed by epoxidation and carbamate ring opening of **3-24** to generate compounds such as **3-3** in a rapid fashion (Scheme 3-5). From the outset, our requirements for this undertaking were to synthesize **3-3** in the shortest sequence to date while doing so in a modular and stereoselective fashion.



Scheme 3-5. Retrosynthetic analysis of **3-3**.

Although we believed that our glycoside methodology could prove useful for the incorporation of complex functionality into novel glycoside analogs, an existing approach to aldehyde **3-29** was considered to be superior for exploring our planned synthetic strategy.[77] The synthesis of this aldehyde was accomplished in three steps from methoxy galactose **3-26** and could be performed on a multi-gram scale (Scheme 3-6). Later, we found that conditions developed by Panek[78] employing acetyloxy allyl silane as a homoenolate equivalent could be used to convert **3-26** via the resulting enol acetate[79] *in situ* to the desired aldehyde **3-29** in 67% yield (Scheme 3-6). All attempts to employ silyloxy allyl silanes in this transformation failed. With the desired aldehyde in hand, we

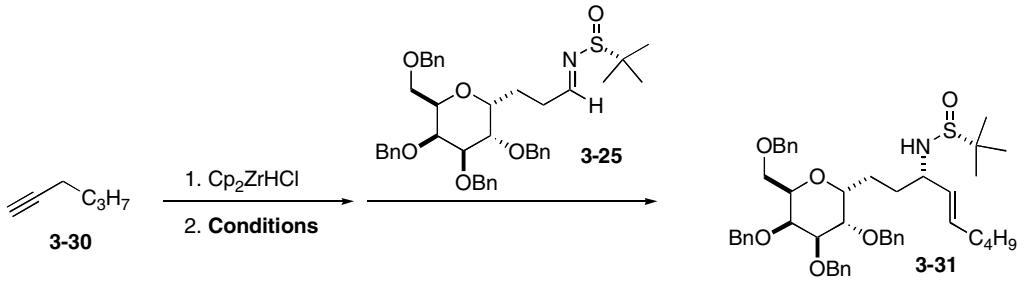
chose to form a sulfinylimine[80] and explore subsequent organometallic additions to this substrate to form the desired stereocenter in our target molecule. Treatment of aldehyde **3-29** with *tert*-butanesulfinamide under dehydrating conditions in the presence of $MgSO_4$ yielded the desired imine **3-25** in 94% yield.



Scheme 3-6. Synthesis of imine **3-25** from glycoside **3-26**.

Previous research in our group has shown that transmetalation of alkenyl-zirconconocenes to dimethylzinc provides organometallic species that react readily with aldehydes and imines.[81] Typically, *N*-diphenylphosphinoyl imines are employed in this methodology; however, to date, no catalytic asymmetric addition to these substrates has been realized.[82] A screen of catalysts to achieve a diastereoselective addition to imine **3-25** was performed (Table 3-1). While dimethylzinc and boron Lewis acids were completely ineffective, either dimethylaluminum chloride or trimethylaluminum proved excellent in this transformation, providing high yield of homoallylic amide **3-31** as a single diastereomer by ^{1}H NMR analysis of the crude reaction mixture.

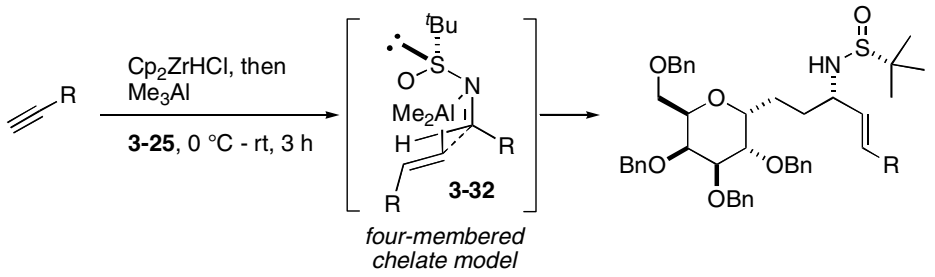
Table 3-1. Optimization of reaction conditions for alkenyl organometallic addition to *N*-tert-butanesulfinyl imine **3-25**.

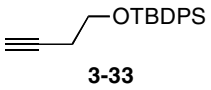
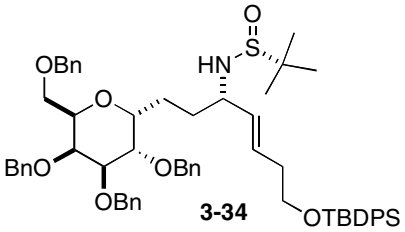
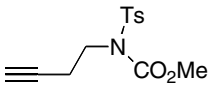
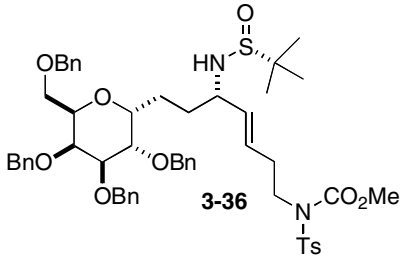
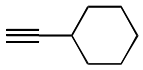
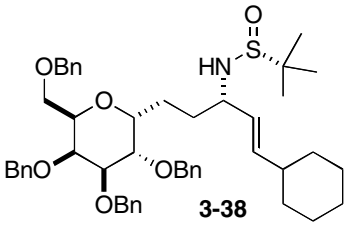


entry	conditions	yield (%)
1	Me_2Zn, toluene, -78 - 100 °C	trace
2	BF_3•OEt_2, CH_2Cl_2, 0 °C - rt	decomposition
3	Me_2AlCl, CH_2Cl_2 0 °C - rt	82
4	Me_3Al, CH_2Cl_2 0 °C - rt	76

Furthermore, we were able to demonstrate that silyl ether, carbamate, and sulfonamide functionalities were well tolerated and provided allylic amides in high yield and excellent diastereoselectivity (entries 1-3, Table 3-2). We propose the 4-membered chelate model **3-32** to account for the observed selectivity, analogous to additions of alkenylalanes derived from alkyne carboalumination.[83] The mild and efficient conditions for generating *N-tert*-butanesulfinyl imines coupled with the rapid, stereoselective and functional group tolerant method of alkenylalane addition described

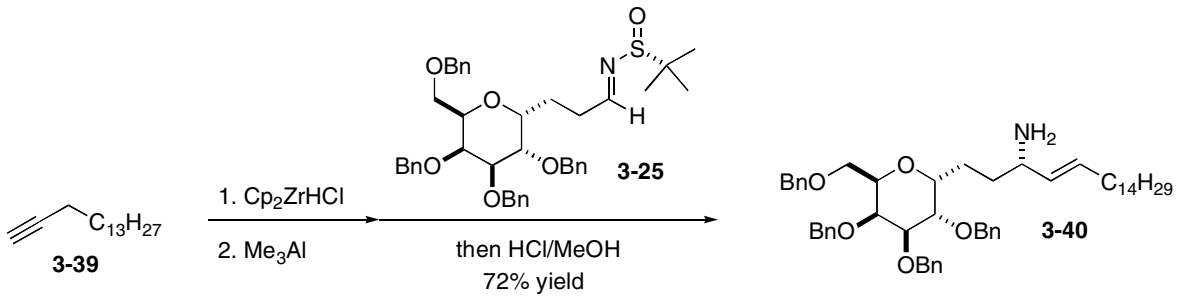
Table 3-2. Exploration of functional group compatibility in organoalane addition to imine **3-25**.



entry	alkyne	product	yield [%]
1	 **3-33**	 **3-34**	81[a]
2	 **3-35**	 **3-36**	65[b]
3	 **3-37**	 **3-38**	85[a]

[a] Products were diastereomerically pure by ^{1}H NMR analysis of the crude reaction mixture. [b]93:7 mixture of diastereomers by HPLC analysis. All yields are based on isolated, pure materials.

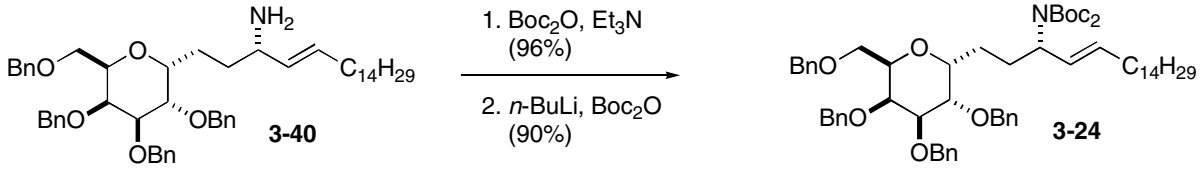
herein provides an attractive method for allylic amine synthesis.[84] After establishing a diastereoselective vinylalane addition to imine **3-25**, we extended this process to the addition of the alkenyl zirconocene derived from **3-39** (Scheme 3-7). Removal of the sulfinyl protecting group upon work-up yielded 72% of the allylic amine **3-40** in a one pot transformation.



Scheme 3-7. Hydrozirconation/transmetalation/imine addition of alkyne **3-39** to imine **3-25** followed by *in situ* deprotection.

3.2.2 Synthesis of the *C*-Glycoside Analog of KRN7000

Our original strategy involved epoxidation of the allylic amide bearing the *tert*-butylsulfinyl protecting group; however, epoxidation of this species also oxidized the sulfur to generate the Bus protecting group[85] that could not be removed even under forcing conditions. To further explore the epoxidation chemistry, bis-Boc protection of **3-40** was accomplished via a 2-step procedure that proved higher yielding upon scale-up (Scheme 3-8).

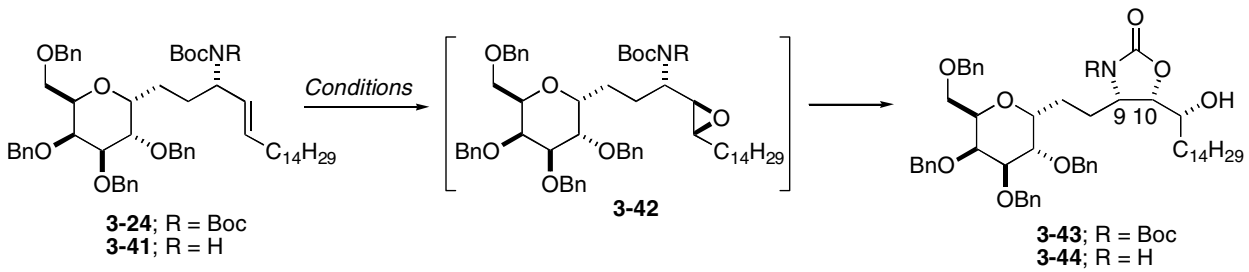


Scheme 3-8. Optimized formation of bis-Boc protected amine **3-24**.

At this stage, conditions had to be indentified to stereoselectively epoxidize the alkene **3-24** and effect the intramolecular addition of the *tert*-butylcarbamate to the epoxide to form oxazolidinone **3-43**.[86] Work by Roush[87a] and O'Brien[86b] has

demonstrated the feasibility of this sequence, although Roush employed trichloroacetamides and O'Brien focused on cyclic allylic amides.[86c] Initial trials focused on MCPBA as the epoxidizing agent, with varying temperatures and solvents. The best result could be obtained at 0 °C in CH_2Cl_2 to yield 85% of **3-43** as a 1.6:1 mixture of diastereomers (entry 1, Table 3-3). *In situ* generated dimethyldioxirane (DMDO) was ineffective, producing no conversion after 20 h at rt. Increasing the electrophilicity of

Table 3-3. Evaluation of oxidation conditions to generate epoxide intermediate **3-42** followed by carbamate opening of the epoxide to form **3-43**.



entry	substrate	conditions	yield [%], dr[a]
1	**3-24**	MCPBA, 0 °C	85, 1.6:1
2	**3-24**	Oxone, $NaHCO_3$, acetone, rt	trace
3	**3-24**	TFAA, UHP, -20 °C, Na_2HPO_4	93, 9:1
4	**3-41**	TFAA, UHP, -20 °C, Na_2HPO_4	50, n.d.

[a] Yields refer to isolated, pure products. Diastereoselectivity was determined by HPLC analysis of the crude reaction mixtures: HPLC separation was preformed using a Chiralcel® AD-H column and elution with 7% *i*-PrOH/Hexanes. Retention times = 12.8 min (major), 19.1 min (minor).

peracids has been shown to increase selectivity in directed epoxidations.[88] Trifluoroperacetic acid (TFAA), generated *in situ* from trifluoroacetic acid and urea-hydrogen peroxide (UHP) inclusion complex,[89] improved the selectivity of the

epoxidation to 9:1 and increased the yield to 93% (entry 3, Table 3-3). Mono-Boc protected amide **3-41** did not perform well in this reaction, seemingly due to increased decomposition pathways. The assignment of the relative configuration in **3-43** was in accordance with previous reports;[86a] moreover, it was confirmed by coupling constant analysis[90] and by converting both diastereomers to the desired *C*-glycosides **3-3** and **3-3'**.[91] The increased selectivity in the TFAA epoxidation was attributed to the increased acidity of the peracid proton, which is essential for the carbamate to direct the approach of the reagent (Figure 3-4).

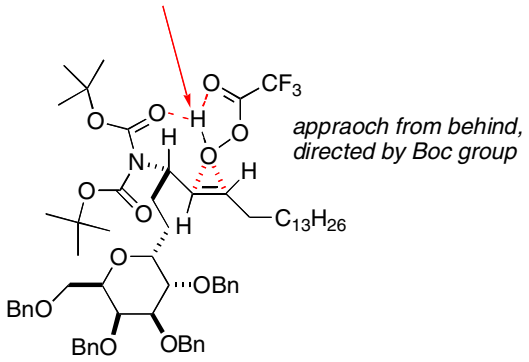
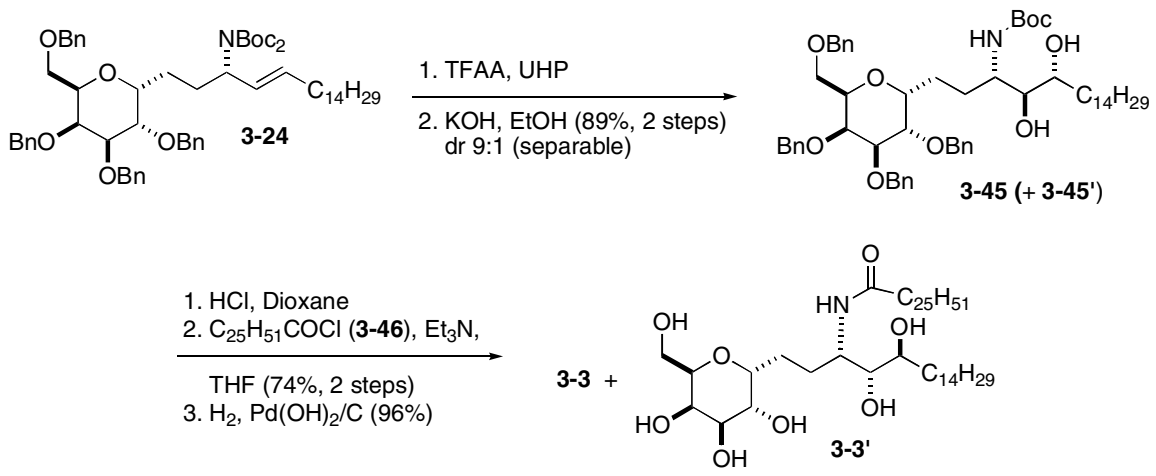


Figure 3-4. Model for stereoselectivity in epoxidation reaction.

Epoxidation of **3-24** under the TFAA conditions from entry 3 in Table 3-3, and subsequent ring opening of the crude material yielded 89% of Boc-amino diol **3-45** as a 9:1 mixture of diastereomers that were separated by column chromatography on SiO_2 (Scheme 3-9).



Scheme 3-9. Completion of the synthesis of **3-3** and **3-3'**.

Removal of the Boc group with HCl, coupling of the amine salt with acid chloride **3-46** and global deprotection of the galactosyl benzyl groups provided **3-3** in 71% yield over 3 steps. This sequence was also carried out on the diastereomer (**3-45**') to provide **3-3**' in comparable yields.

Confirmation of the target structure was obtained by comparison of the $[\alpha]_D$ and ^{13}C NMR data of previously prepared **3-3** with newly synthesized **3-3** and **3-3'**. As shown in Table 3-4, the ^{13}C NMR data for **3-3** and the literature data for this compound compare well, while there are considerable differences between **3-3'** and the previously reported data. Further confirmation was achieved through comparison of $[\alpha]_D$ values which were in agreement.[34]

Table 3-4. Comparison of ^{13}C NMR chemical shift and $[\alpha]_D$ values.[a]

Carbon No.[b]	Difference between literature and experimental shifts	δ **3-3'** (experimental values)	δ **3-3** (from literature)	δ **3-3** (experimental values)	Difference between literature and experimental shifts
12	-2.0	175.9	173.9	173.8	0.1
10	1.2	77.7	78.9	78.8	0.1
1	0.5	76.9	77.4	77.3	0.1
5	0.0	74.1	74.1	74.1	0.0
11	0.6	72.5	73.1	73.0	0.1
4	0.2	72.4	72.6	72.5	0.1
3	0.1	70.7	70.8	70.8	0.0
6	0.4	62.7	63.1	63.1	0.0
9	1.2	51.9	53.1	53.1	0.0
$[\alpha]_D$[c]	31.2	+9.6	+40.8	+38.4	2.4

[a] ^{13}C NMR data for **3** and **3-3'** were obtained in d_5-Pyridine at 126 MHz. [b] Tentative assignments. [c] $[\alpha]_D$ values were obtained in pyridine (c = 0.13) and are reported as average values of 3 measurements.

3.2.3 Biological Evaluation and Analog Synthesis

Malaria is a widespread parasitic disease that is present in tropical regions of the world and results in more than 300 million new infections annually.[92] There are four main plasmodial species known to infect humans, with *Plasmodium falciparum* the most virulent. Multi-drug resistance of the various strains of malaria has only complicated the problem. While there are a number of approved drugs to treat malaria, various problems from toxicity to inefficacy plague many of these treatments (Figure 3-5).[91] Additionally, while vaccine research has provided valuable data, the complex life cycle of malarial parasites has made the effectiveness of such a vaccine very limited. The development of novel drugs for current malarial targets is an important area of current research; however,

the discovery of novel malarial targets and treatment strategies is of pivotal importance in the on-going battle against this widespread disease.

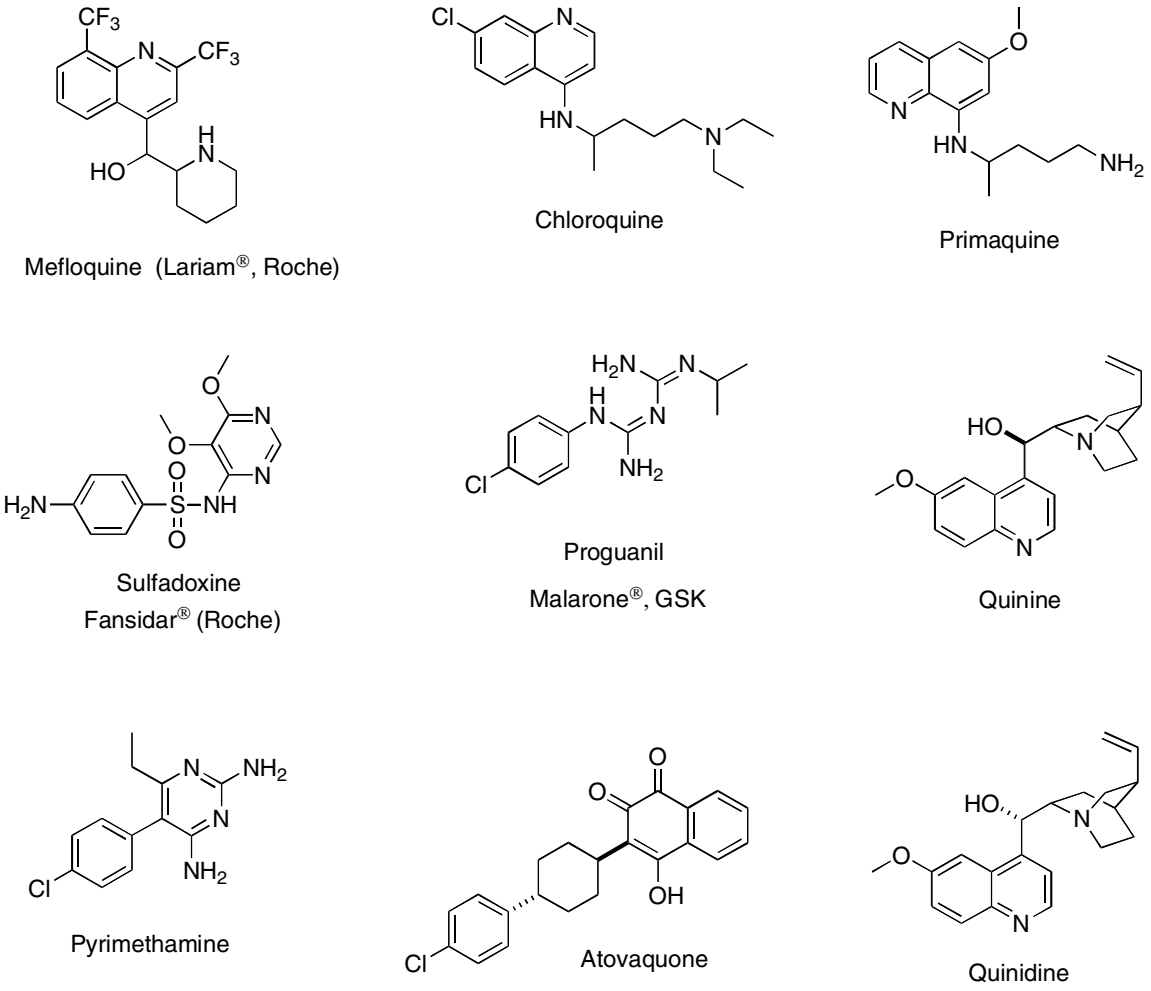


Figure 3-5. Selected examples of currently used drugs for the treatment of malaria.

Our synthesis was able to provide multi-gram quantities of **3-3** and its analogs, and therefore we sought to further explore the biological properties of these immunostimulants. A collaboration with the Walter Reed Army Institute of Research (WRAIR) was established to explore the effects of **3-3** and selected analogs in *in vivo* malaria screens. Initial studies were performed dissolving **3-3** in DMSO and

administering the compound at varying doses, one injection per day for 3 days prior to challenge with the parasite. The sporozoite levels were measured each following day, with the results at day 6 being shown in Figure 3-5 (for daily sporozoite levels and experimental protocols, see Appendix C). To our delight, **3-3** showed substantial activity against the malarial parasite, particularly at the 1 mg/kg/day dosage level and inspired us to begin synthesis of novel analogs for testing.

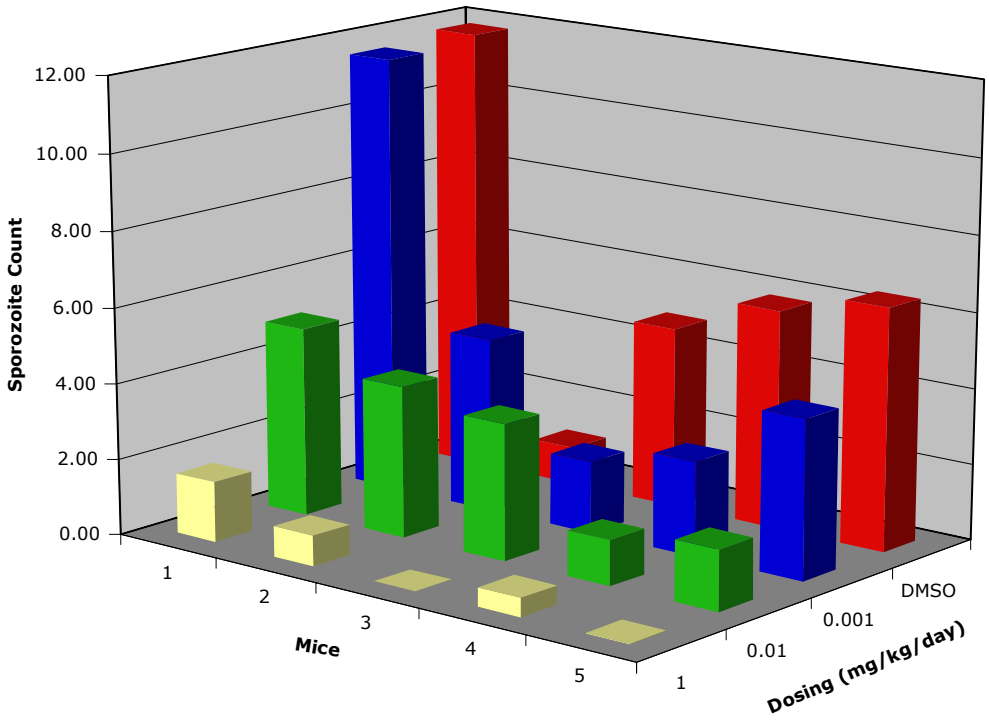


Figure 3-6. Efficacy and dose dependence of **3-3** in mouse model.

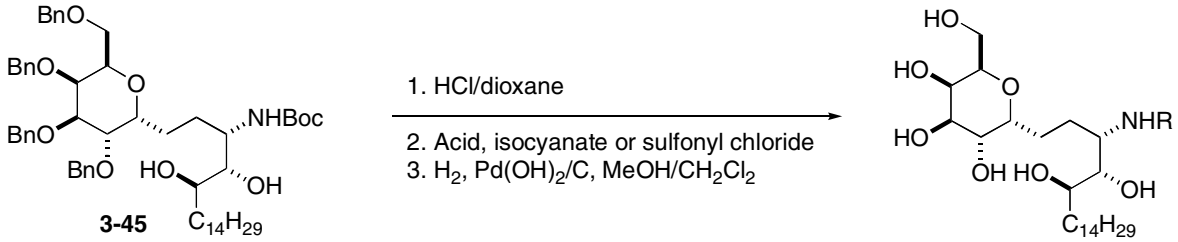
Due to the very limited analog development of the of **3-3**, we sought to first investigate replacement of the fatty acid chain with shortened derivatives bearing aromatic groups, ureas and sulfonamides. Of particular interest to us were the intriguing results by

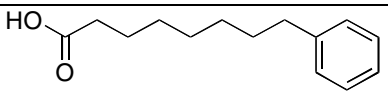
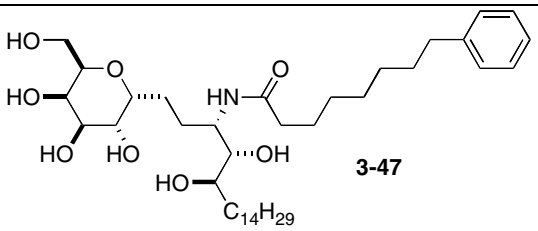
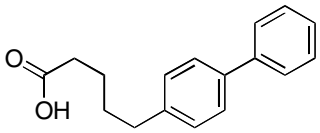
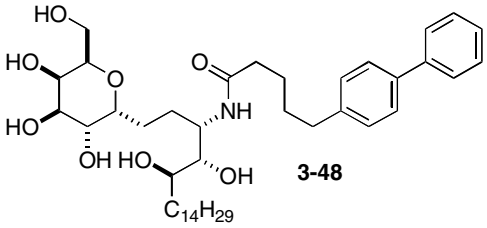
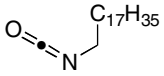
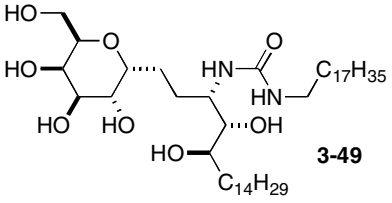
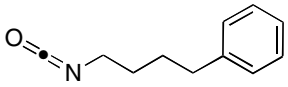
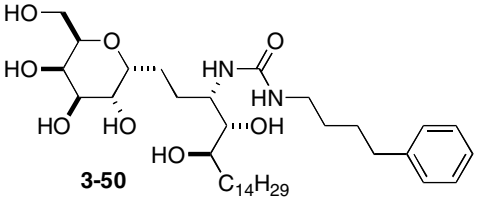
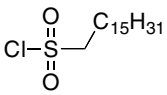
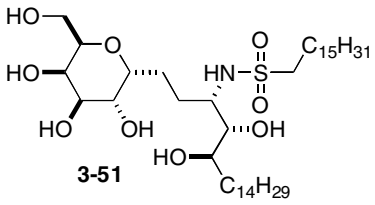
Wong, who demonstrated that shortening the alkyl chain and addition of a suitably positioned aromatic moiety could selectively trigger Th1 vs. Th2 cytokine release.[69] Additionally, we postulated that the urea and sulfonamide groups would retain a Lewis basic moiety shown to be essential for binding to CD1d in X-ray structures, while possibly improving the extremely poor solubility properties of these glycolipids.[93] The solubility of **3-3** in DMSO was below 1-2 mg/mL and non-existent in water.

The synthesis of the first set of analogs began with intermediate **3-45** from the synthesis of **3-3**. Deprotection of the Boc group with HCl followed by coupling to a carboxylic acid (entry 1 and 2, Table 3-5), isocyanate (entry 3 and 4, Table 3-5) or sulfonyl chloride (entry 5, Table 3-5) provided the desired products in high yield with the exception of sulfonamide analog **3-51**. Under a variety of conditions the only products isolated during attempts to synthesize **3-51** appeared to arise from epoxide formation from the diol unit of **3-45**. The solubility properties of these new analogs were greatly improved as compared to the parent compound, and we hoped this would help with various compound administration issues found previously.

With a new set of analogs in hand, additional biological evaluation was conducted at the WRAIR to compare the effectiveness to **3-3**. Administration of 1.85 mg/kg of analogs and **3-3** for three days prior to challenge with sporozoites was performed, followed by monitoring of sporozite levels for 10 days. The reported data are the sporozoite levels at day 6 after sporozoite challenge. While none of the analogs were as active as the parent compound, **3-47** and **3-50** were competent in the study providing encouragement that simple modifications in the molecular structure could be tolerated.

Table 3-5. Synthesis of novel amide and urea analogs of **3-3**.



entry	coupling reagent/ conditions	product	yield [%]
1	 EDCI, DMAP	 **3-47**	65
2	 EDCI, DMAP	 **3-48**	76
3	 Et_3N	 **3-49**	80
4	 Et_3N	 **3-50**	74
5	 Et_3N	 **3-51**	0

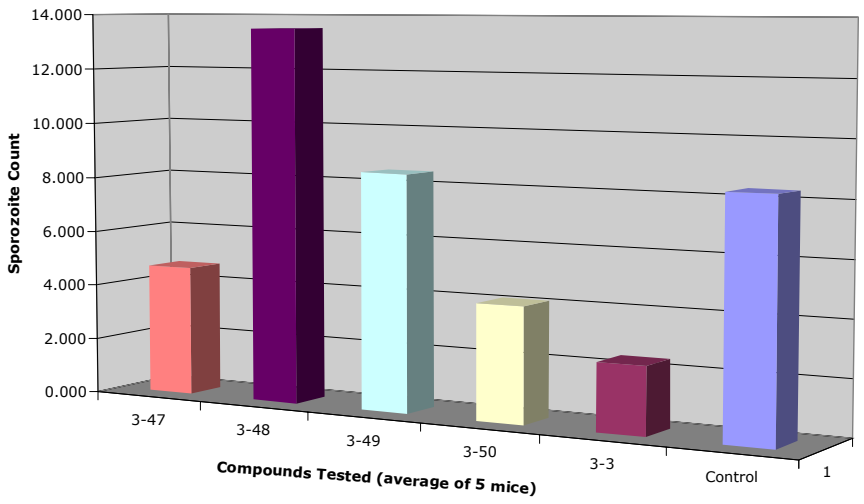
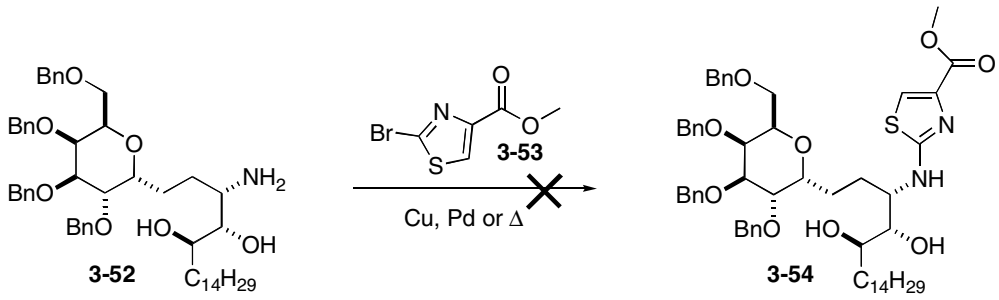


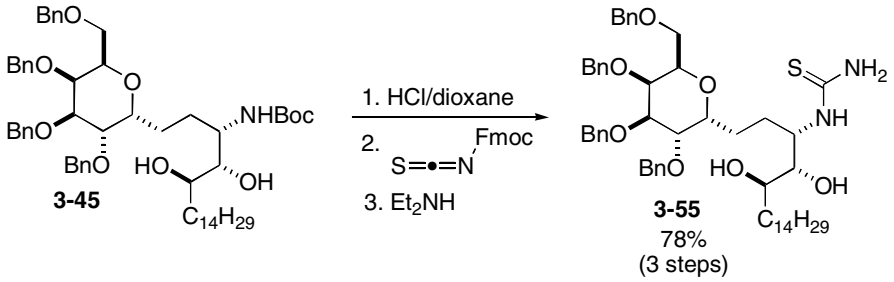
Figure 3-7. Biological evaluation of novel *C*-glycoside analogs.

Seeking to further explore novel analogs of galactoceramide immunostimulants, it was proposed that a thiazole moiety could mimic the Lewis basic amide moiety while providing an analog with improved stability and solubility properties.[94] Initial attempts were focused on the coupling of thiazole bromide **3-53** with amine **3-52** under a variety of transition metal and thermal conditions (Scheme 3-10).[95] Disappointingly, all efforts to achieve this transformation failed.



Scheme 3-10. Attempted synthesis of thiazole containing analog as amide mimic.

An alternative approach that would build the thiazole moiety in a modular fashion was investigated (Scheme 3-11).[96] Treatment of carbamate **3-45** with HCl generated the HCl salt that was subsequently coupled with Fmoc-thioisocyanate followed by Fmoc deprotection to yield thiourea **3-55** in 78% yield over the three steps.



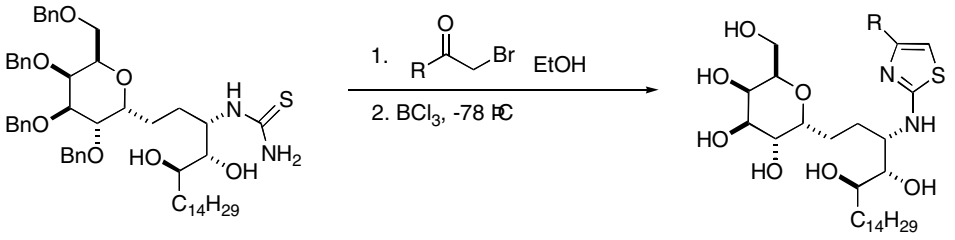
Scheme 3-11. Synthesis of thiourea **3-55**.

Conversion of thiourea **3-55** to the desired thiazole scaffold was accomplished via treatment with α-bromo ketones and triethylamine followed by global deprotection of the benzyl ethers (Table 3-6). In this way, aryl ether analog **3-57** and aliphatic analog **3-59** were prepared in high yield. Initial attempts to perform the benzyl ether deprotection under palladium hydrogenation conditions failed under a variety of conditions, most likely due to catalyst poisoning by the thiazole moiety.[97]

Biological evaluation of these novel thiazole glycolipids was performed; unfortunately, the assay suffered from irreproducibility. Poor solubility of the parent compound and most analogs was the proposed cause for these assay complications. To address these solubility issues a study to determine a more suitable delivery method was performed (Table 3-7). While **3-3** was not soluble in a variety of aqueous solutions, it was discovered that cremophore EL® allows dissolving of **3-3** in aqueous media. With the

optimized conditions (10% cremophore EL®, 10% DMSO, 80% water) employed, >10 mg/mL of **3-3** could be dissolved in 1 mL of delivery media. Although this new delivery cocktail allowed for higher dosing of **3-3**, complete cures of treated mice were not obtained in mice studies. Greatly reduced sporozoite counts were achieved showing the utility of this class of galactoceramides as immunostimulants; however, the lack of complete eradication of the malarial sporozoites may demonstrate the inability of such a therapeutic strategy from being employed as a stand alone malarial treatment.[65-68]

Table 3-6. Conversion of thiourea to thiazole analogs of **3-3**.



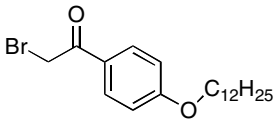
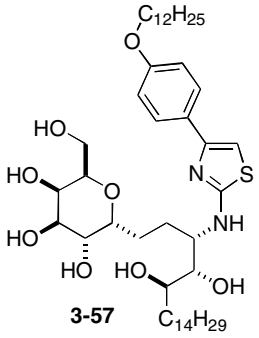
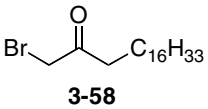
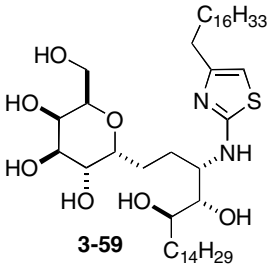
entry	ketone	product	yield [%]
1	 **3-56**	 **3-57**	83
2	 **3-58**	 **3-59**	88

Table 3-7. Solubility studies of **3-3**.

entry	conditions	solubility
1	DMSO	< 2 mg/mL
2	50% EtOH, 50% DMSO	< 1 mg/mL
3	20% cremophore EL®, 80% water	< 5 mg/mL
4	10% cremophore EL®, 10% DMSO, 80% water	> 10 mg/mL

3.3 CONCLUSION

We have demonstrated that an organometallic addition to *N-tert*-butyl sulfinyl imines followed by an epoxidation-epoxide opening sequence can be used to construct the necessary stereocenters for target molecules such as **3-3**. Unlike other approaches, our current route is short and stereoselective while allowing for facile analogue synthesis. To this end we have synthesized a series of analogs that allowed for the biological evaluation of this class of immunostimulants. Although complete cures of malaria were not obtained in mice studies, a greatly reduced sporozoite count was achieved. These results provide proof of principle for the use of galactoceramides as immunostimulants, but also highlight the inability of these agents to act as stand alone therapies.

4.0 ADDITION OF IN-SITU GENERATED ORGANOALANES TO ACYLIMINIUM IONS AND IMINES: FROM ISOINDOLINONES TO RADIOPROTECTANTS

4.1 ISOINDOLINONES

4.1.1 Introduction

Isoindolinones constitute the core structures of numerous naturally occurring biologically active compounds such as magallanesine **4-1**[98] and lennoxamine **4-2**[99] as well as many drug candidates such as pagoclone **4-3**[100] (Figure 4-1). Isoindolinones

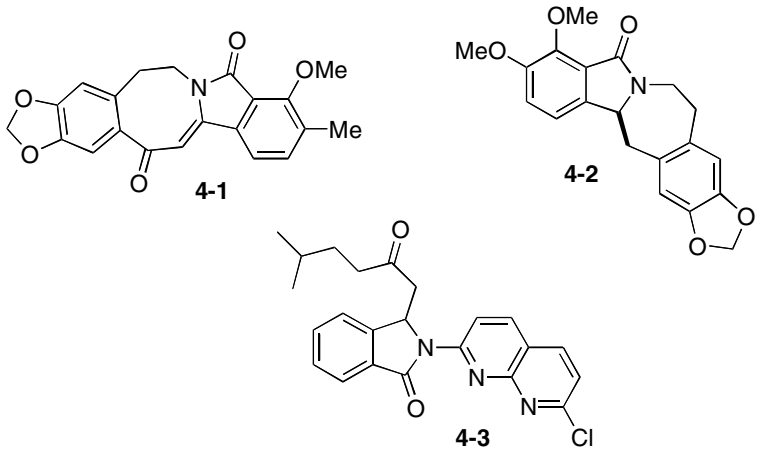
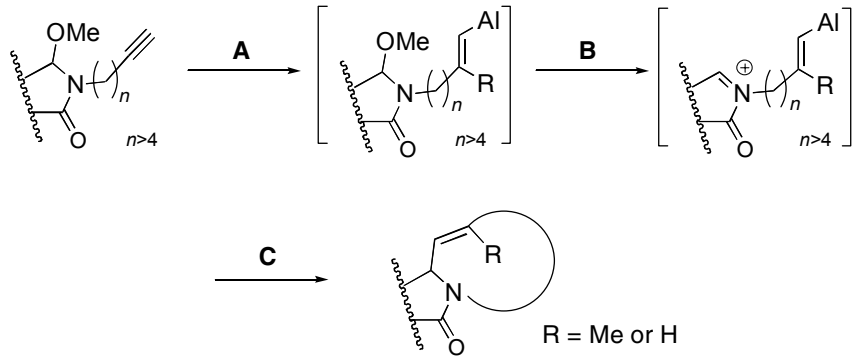


Figure 4-1. Biologically active isoindolinones.

demonstrate a remarkably wide array of biological activity, including anti-inflammatory,[101] antihypertensive,[102] antipsychotic,[103] vasodilatory[104] and antileukemic[105] effects, which makes the development of new synthetic routes to these heterocycles particularly attractive. While multiple methods have been reported for the preparation of isoindolinones,[106] some leading to the synthesis of natural products[107] and libraries,[108] many suffer from a lack of generality or functional group compatibility.

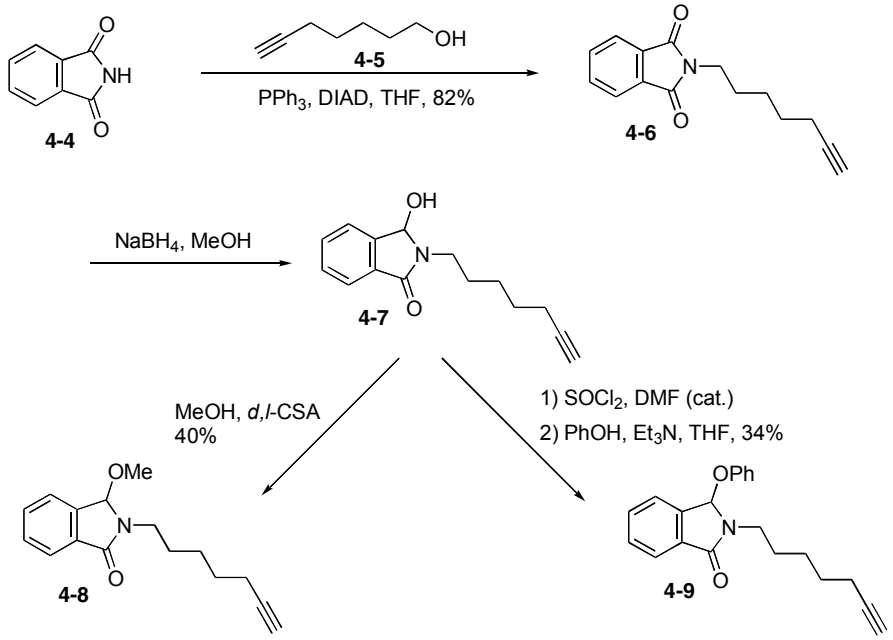
In view of the potent and diverse biological activity of isoindolinones, previous studies by Waller and Wipf were directed at their preparation as part of a program for the synthesis of nitrogen containing heterocycles.[109] The combination of water-accelerated carboalumination[110] with an intramolecular *N*-acyliminium ion addition in a cascade process that would generate medium-ring containing isoindolinones was envisioned (Scheme 4-1). *N*-Acyliminium ions are versatile synthetic intermediates[111] and have previously been employed in the formation of simple isoindolinones;[112] however, with the exception of allylsilanes, the addition of functionalized organometallic reagents to



Scheme 4-1. Proposed intramolecular addition of alkenylalanes to *N*-acyliminium ions. **A**: Zirconium-Catalyzed, Water-Accelerated Carboalumination or Hydrozirconation/Transmetallation; **B**: Elimination; **C**: Addition/Ring Closure.

these systems has not yet been exploited. Moreover, the intramolecular addition would potentially provide an entry toward strained medium rings containing (*E*)-alkenes.

Investigations began with the synthesis of methoxy-**4-8** and phenoxy lactam **4-9** (Scheme 4-2). Alcohol **4-5** was obtained in 85% yield by the isomerization of the commercially available hept-3-yne-1-ol with the KAPA reagent in 85% yield.[113] Imide **4-6** could then be constructed by a Mitsunobu alkylation with alkynol **4-5**, which proceeded in 82% yield. Reduction with sodium borohydride was followed by a methanol exchange to give methoxylactam **4-8** in 40% overall yield (Scheme 4-2). With the key substrate in hand, submission of **4-8** to Wipf's water accelerated carboalumination conditions ($AlMe_3$ (3 eq), H_2O (1 eq), zirconocene dichloride (10 mol%)) only returned starting material with no evidence for elimination or carboalumination (Scheme 4-3).



Scheme 4-2. Synthesis of lactam precursors.

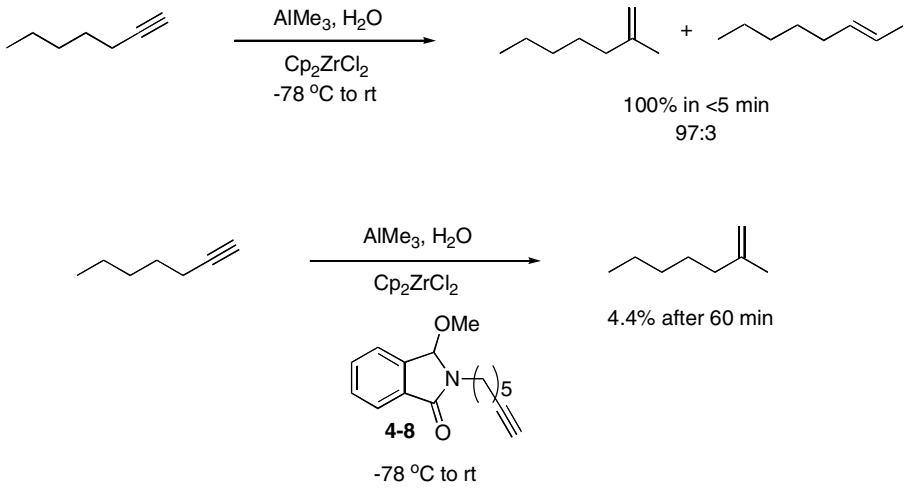
To explore the effect of the leaving group on the aminal, phenoxy lactam **4-9** was generated by treatment of **4-7** with $SOCl_2$ and catalytic DMF. The resulting unstable chloride intermediate was immediately treated with phenol in the presence of triethylamine to yield **4-9** in 34% yield.[114]

Scheme 4-3. Attempted cascade cyclization of **4-8** and **4-9**.

When **4-9** was subjected to the carboalumination conditions, only alkylated lactam **4-10** (10%), starting material (52%), and decomposition products were observed by NMR analysis (Scheme 4-3).

These experiments demonstrated that the functionality present in these lactam acetals was inhibiting the carboalumination step. It was postulated that the lactam group was responsible for the observed inhibition, as highly Lewis basic functionality has been noted to decrease the reactivity of aluminoxanes.[115] Therefore, a series of GC experiments to test this hypothesis with 1-heptyne, which is known to undergo rapid water-accelerated carboalumination, were performed. A control experiment demonstrated that the carboalumination of heptyne with $AlMe_3$ (3 eq), H_2O (1 eq), and Cp_2ZrCl_2 (10 mol%) proceeded to completion in under 5 min at low temperatures (-78 °C to -25 °C) to furnish a 97:3 mixture of regioisomers by GC (Scheme 4-4). Conducting the identical experiment

in the presence of 1 equivalent of methoxylactam **4-8** dramatically inhibited carboalumination, with only 4.4% of heptyne undergoing conversion after 1 h at ambient temperature. Most likely, this inhibition is due to the coordination of Lewis basic functional groups to $AlMe_3$ oligomers, thus preventing alkyne carboalumination.

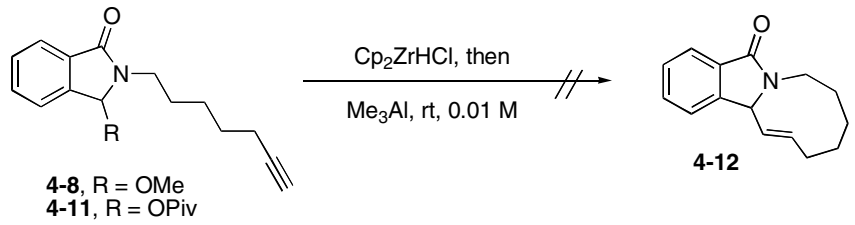


Scheme 4-4. GC analysis of the water-accelerated carboalumination of heptyne in the presence of **4-8**.

4.1.2 Results and Discussion

Due to the lack of reactivity in the previously investigated carboalumination approach, we turned to hydrozirconation, known to be quite tolerant of diverse functionality.[14] When lactam **4-8** was treated with Cp_2ZrHCl, only the corresponding alkene was recovered (Scheme 4-5). Treatment of the intermediate alkenylzirconocene with $AgClO_4$ or trimethylaluminum also provided no desired cyclization products. Enhancing the leaving group ability by using the pivaloate **4-11** also failed to promote cyclization under any of the above conditions. Highly concentrated reaction mixtures or

prolonged heating resulted only in slow methyl group addition. Possibly, the ring strain incorporated in these systems is too high to allow the reaction to proceed under the current conditions.

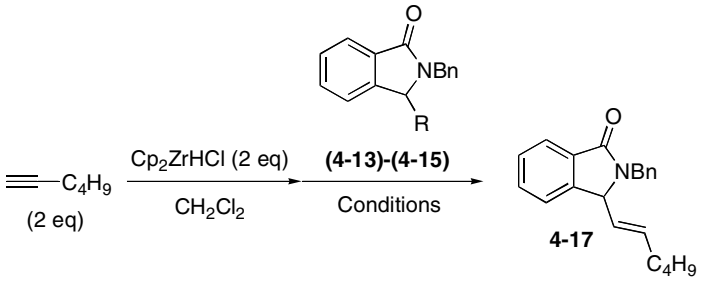


Scheme 4-5. Attempted hydrozirconation and medium ring formation.

Because the cyclizations proved elusive, we turned our attention toward an alternative construction of these systems starting with an intermolecular addition process. Alkenylation of *N*-acyliminium ions can often require harsh reaction conditions[116] or unusual anomeric leaving groups[117] with the exception of the intermolecular addition of alkenyl boronates used by Batey et al.[118] Accordingly, we first explored the hydrozirconation of terminal alkynes as a method to generate alkenyl nucleophiles (Table 4-1). Hydrozirconation of 1-hexyne, followed by treatment with silver perchlorate[119] and lactam **4-13** yielded only a trace of addition product after 24 h at rt (entry 1, Table 4-1). Transmetallation to dimethylzinc also proved unsuccessful (entry 2, Table 4-1). Gratifyingly, hydrozirconation-transmetallation to trimethylaluminum[120] generated an alkenylalane that reacted with lactam **4-13** in a moderate 43% yield (entry 3, Table 4-1). Again, we increased the leaving group ability by using acetate **4-14**; however, product **4-17** was only formed in 30% yield while the remaining starting material was consumed (entry 4, Table 4-1). Attempts to perform this reaction in THF or toluene led to recovered starting material. In an effort to prevent decomposition pathways while retaining leaving

group ability, pivaloate **4-15** was synthesized and treated with the *in situ* generated alane to provide hexenyl isoindolinone **4-17** in 81% yield without any observed isomerization of the alkene moiety (entry 5, Table 4-1). Attempts to achieve this transformation under cationic conditions with silver perchlorate[20] led to complex

Table 4-1. Reaction optimization for the addition of hexenylzirconocene to lactams (**4-13**)-(**4-15**).



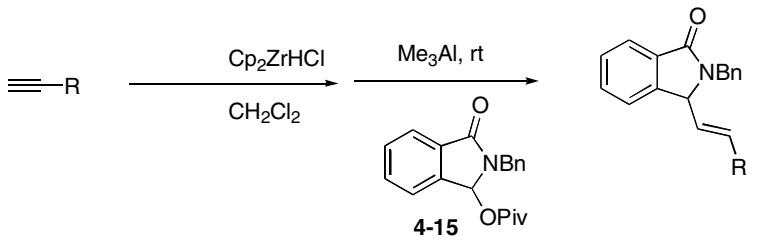
entry	conditions	R(lactam acetal)	**4-17** [%]
1	$AgClO_4$ (10 mol%), 24 h, rt	OMe (**4-13**)	Trace[a]
2	Me_2Zn (2 eq), 12 h, rt	OMe (**4-13**)	-
3	Me_3Al (2 eq), 12 h, rt	OMe (**4-13**)	43[b]
4	Me_3Al (2 eq), 4 h, rt	OAc (**4-14**)	30
5	Me_3Al (2 eq), 4 h, rt	OPiv (**4-15**)	81
6	$AgClO_4$ (10 mol%), 12 h, rt	OPiv (**4-15**)	Complex mixture

[a] Product was formed as a mixture of alkene isomers. [b] Starting material observed after 12 h.

mixtures, seemingly arising from alkene isomerization. The mild conditions under which the reaction proceeded and the ability to utilize readily available alkynes and pivaloate iminium ion precursors encouraged us to explore this addition further.

Among the numerous methods known for the synthesis of substituted isoindolinones, only a few examples of Heck-type cyclizations install an alkenyl moiety at the 3-position.[121] The modularity of our approach warranted further investigation, and therefore we evaluated the substrate scope of this process. As shown in Table 4-2, silyl ether, carbamate, and sulfonamide functionalities are well tolerated, generating functionalized isoindolinones in a high yielding, one-pot procedure. To further extend the scope of this addition we synthesized succinimide derived pivaloate **4-25** and subjected it

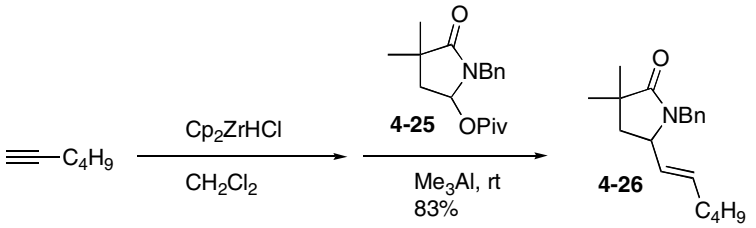
Table 4-2. Examination of substrate scope.



entry	R (alkyne)	product [%][a]
1	C_4H_9 (**4-16**)	**4-17** [81]
2	*c*-C_6H_{11} (**4-18**)	**4-19** [79]
3	$CH_2CH_2OTBDPS$ (**4-20**)	**4-21** [71]
4	$CH_2CH_2N(CO_2Me)Ts$ (**4-22**)	**4-23** [62]

[a] All reactions were carried out by hydrozirconation of alkyne (2 eq) in CH_2Cl_2 with Cp_2ZrHCl (2.2 eq), followed by cooling to 0 °C and addtion of Me_3Al (2.2 eq) and **4-15**.

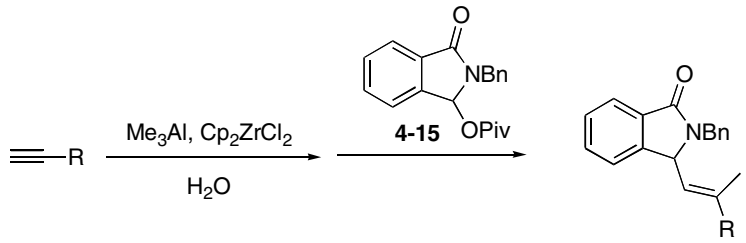
to our optimized conditions to provide **4-26** in 83% yield (Scheme 4-6). The success of this reaction bodes well for the extension of this alkenylation methodology to a broad class of heterocyclic electrophiles.



Scheme 4-6. Addition to succinimide derived iminium ion precursor.

Additionally, we explored the formation of trisubstituted alkenes in this transformation. Although the lactam functionality had prevented the intramolecular addition, preforming the alkenylalane under our water-accelerated conditions followed by addition of **4-15** provided isoindolinones **4-27** and **4-29** in 77% yield after only 15 minutes (Table 4-3). The flexibility and mild nature of these transformations are well

Table 4-3. Water-accelerated carboalumination – addition to lactam 4-15.



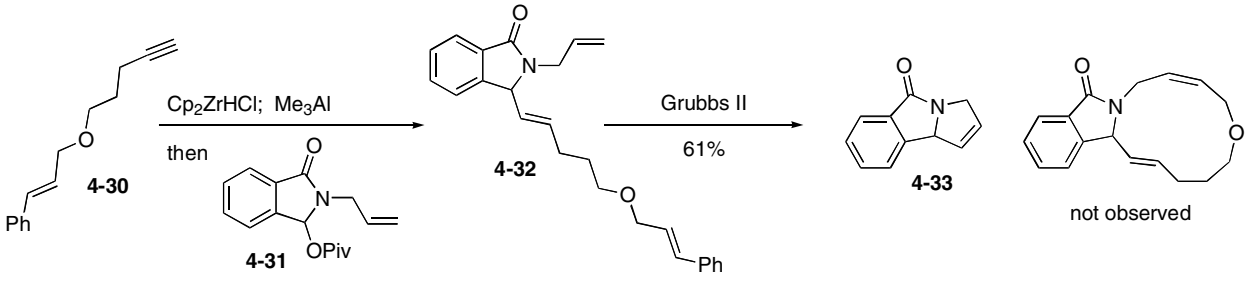
entry	R	product [%]
1	C_4H_9 (**4-16**)	**4-27** [77]
2	Ph (**4-28**)	**4-29** [77][a]

[a] Product contains ~5% of a carbometallation regioisomer.

suited for their application in the synthesis of biologically interesting targets and libraries.

With a methodology in hand to generate alkenyl-functionalized phthalimides, we sought to revisit our initial goal of generating medium rings, this time employing ring

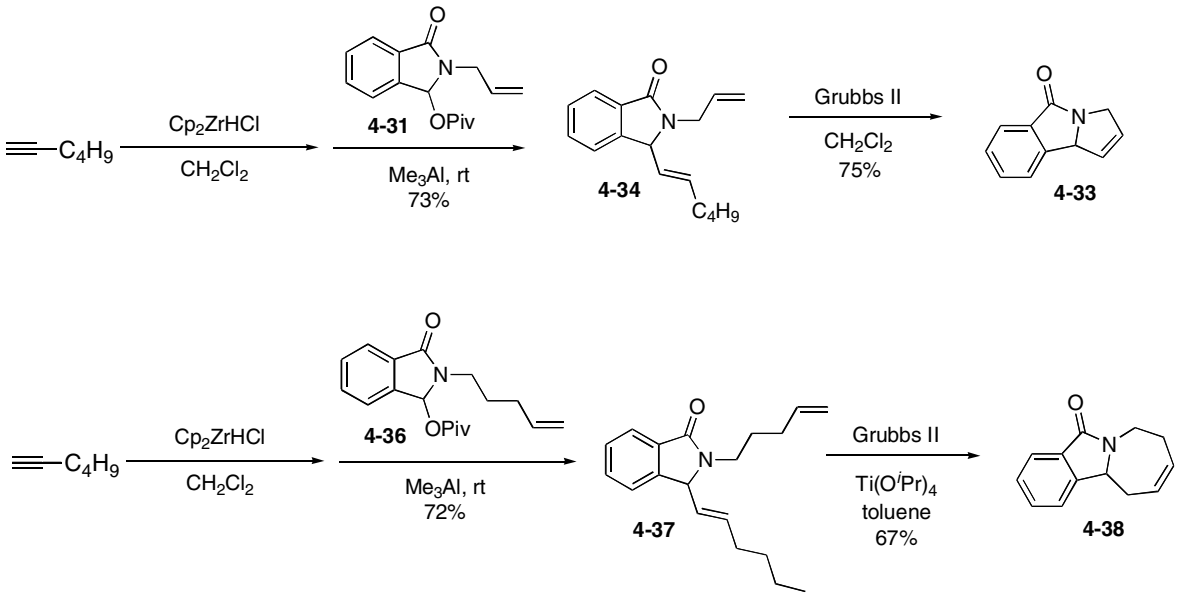
closing metathesis.[23] To begin exploring this approach, we synthesized alkyne **4-30** and allyl-pivaloate **4-31** and subjected them to our hydrozirconation-transmetallation conditions to generate **4-32** in 55% yield accompanied by considerable methyl addition side product (Scheme 4-7). It should be noted that carbometallation of **4-30** failed and the rate of addition for the alkenyl alane generated via the transmetallation was retarded due to the presence of the ether functionality. With **4-32** in hand we screened conditions to form the desired 12-membered macrocycle. Although ring closing metathesis methodology has been demonstrated to perform well for the synthesis of a variety of macrocycles,[122] rapid formation of the undesired 5-membered ring **4-33** was observed (Scheme 4-7).[123] Increased dilution, change of metathesis catalyst, addition of $Ti(O^iPr)_4$,[124] or varying solvents did not influence the reaction pathway.



Scheme 4-7. Attempted medium ring formation via ring closing metathesis.

Due to the ease of formation of **4-33**, we explored the synthesis of this compound via addition of hexyne to **4-31** and subsequent ring closing metathesis to provide the tricycle **4-33** in 75% yield (Scheme 4-8). Extension of this approach to the synthesis of 7-membered rings was achieved though the synthesis of pivaloate **4-36** and subsequent

addition of hexyne in 72% yield. Ring closing metathesis of **4-37** proved to be problematic in CH_2Cl_2 with either Grubbs 1st or 2nd generation catalyst yielding only starting material or decomposition products. Addition of $Ti(O^iPr)_4$ in toluene at rt proved to be the most successful conditions yielding **4-38** in 67% yield. Surprisingly, the alkene of the product azepene had isomerized, most likely due to a ruthenium hydride species generated during the extended reaction times.[125] Possible deactivation of the metathesis intermediate by the neighboring amide carbonyl could explain the difficulty of this transformation.[126] While not fully optimized, these reactions provide proof of concept for the extension of our phthalimide substrates to yield structurally diverse tricyclic products.



Scheme 4-8. Application of ring closing metathesis to generate 5- and 7-membered rings.

Further derivatization of these scaffolds has been accomplished in the University of Pittsburgh Center for Chemical Methodology and Library Development (UPCMLD). To this end, **4-38** has been selectively epoxidized with MCPBA and subsequently opened via treatment with amines or anilines to provide a small library of isoindolinones that will be screened for biological activity (Figure 4-2).

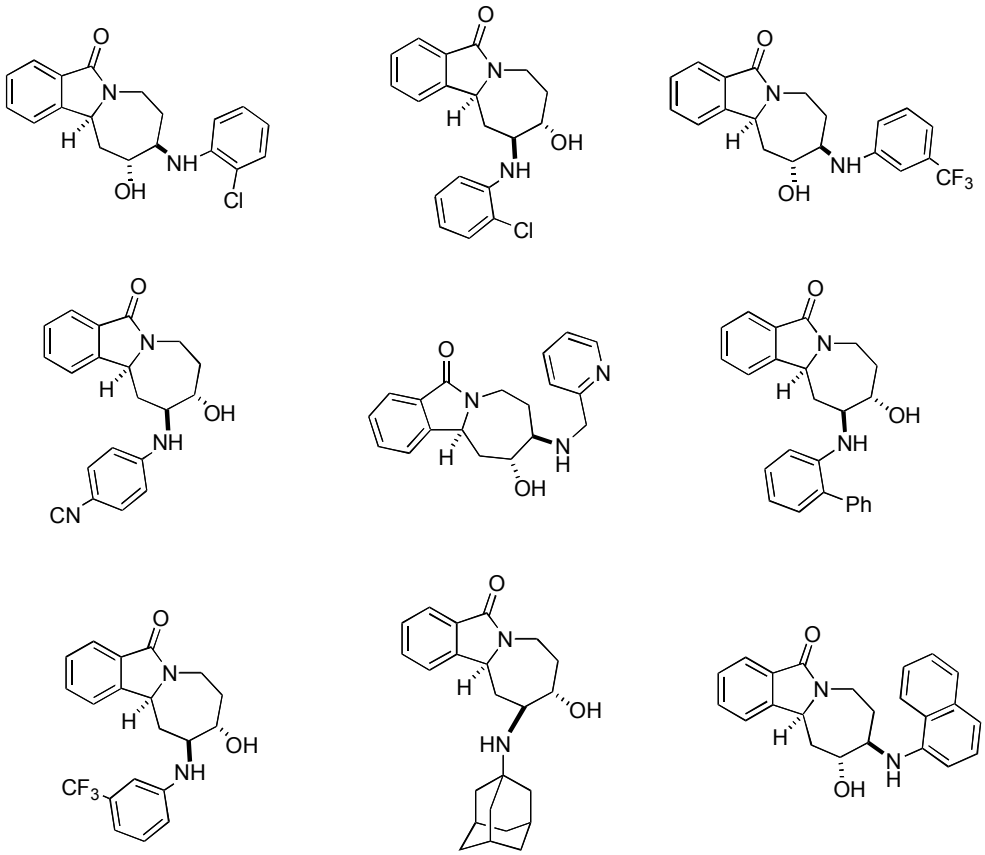


Figure 4-2. Selected examples of a library of isoindolinones.

4.1.3 Conclusions

We have demonstrated that *in situ* generated alkenylalanes represent versatile nucleophiles for additions to *N*-acyliminium ions. While carboalumination is inhibited by the phthalamide functionality, preforming alkenylalanes via hydrozirconation-transmetalation or carboalumination and subsequent addition to the lactam acetal substrates yields functionalized isoindolinones. This method uses easily prepared or commercially available starting materials that provide opportunities for diversification at numerous points and yields synthetically useful heterocyclic products in a one-pot

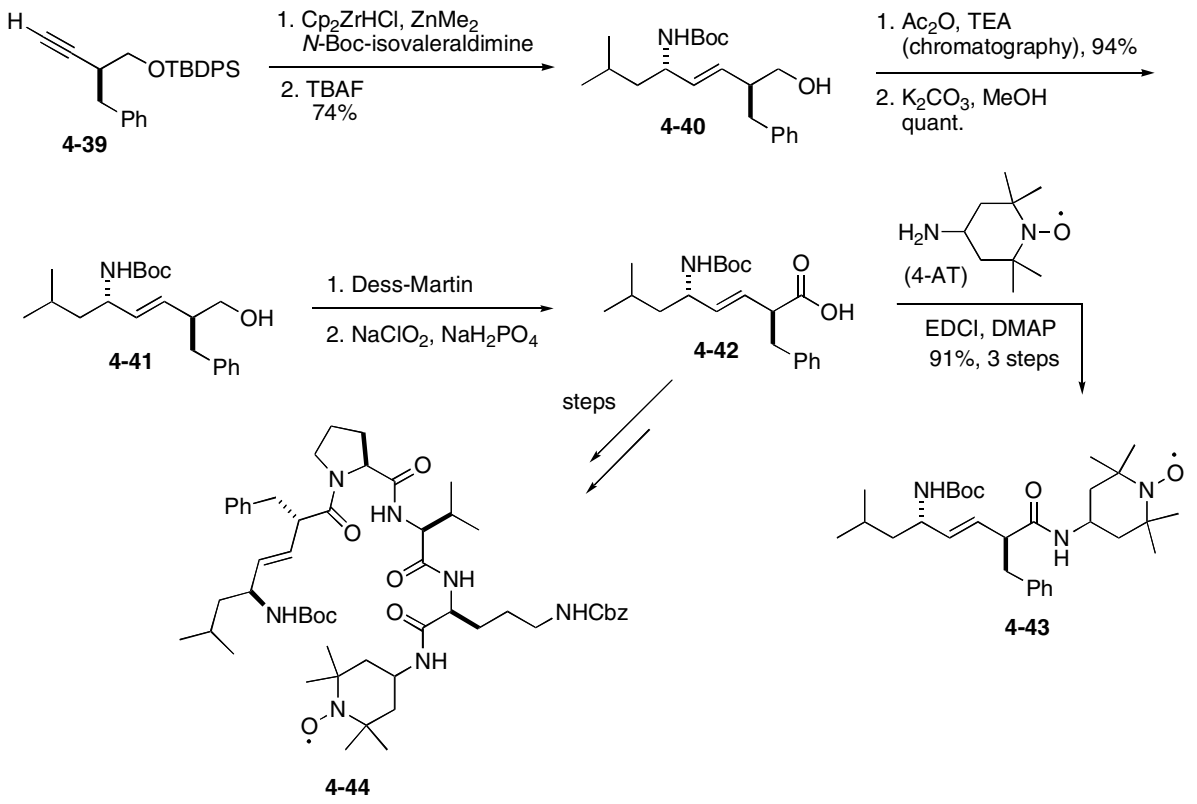
transformation. Further elaboration of the alkenyl heterocycles through the use of ring closing metathesis provides tri-cyclic products that are common motifs in natural products and drug-like molecules. An initial demonstration of the utility of these products was accomplished by a library synthesis in the UPCMLD.

4.2 SYNTHESIS OF NOVEL RADIOPROTECTANTS

4.2.1 Introduction

The role of intracellular reactive oxygen species in mitochondria has been an area of increasing study.[127] Cellular damage, including aging, and cardiovascular damage are two examples of areas that are thought to be directly affected by the build-up of reactive oxygen species (ROS) in the mitochondrial membrane.[128] Nitroxide radicals have been shown to prevent the formation of ROS upon their reduction to hydroxylamine radical scavengers via the mitochondrial electron transport chain.[129] Traditionally, the delivery of therapeutically useful amounts of nitroxides to the mitochondria has proven difficult, thereby limiting the application of this strategy.[130]

To circumvent these delivery issues, Wipf *et al.* has developed hemigramicidin-TEMPO conjugates (**4-44**, Scheme 4-9) that rely on the similarity of mitochondrial membranes to bacterial cell walls that gramicidin natively targets.[131] The key intermediate in the synthesis of these peptide conjugates is acid **4-42**. The synthesis of this compound begins with alkyne **4-39**, which is synthesized via a known route.[132] Hydrozirconation of **4-39**, subsequent transmetalation to dimethylzinc and addition to *N*-

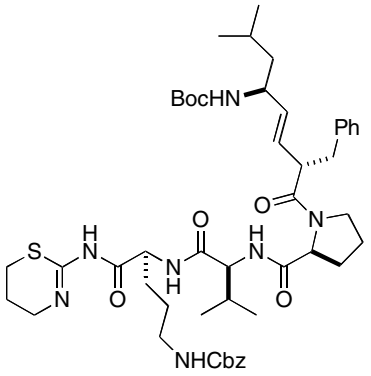


Scheme 4-9. Synthesis of novel hemigramicidin conjugates by Xiao and Wipf.

Boc-isovaleraldimine provided **4-40** as a mixture of diastereomers. Acylation, separation of the diastereomers and deprotection provided the necessary alcohol to undergo a 2-step oxidation that yielded **4-42** in good overall yield. **4-42** was subsequently coupled with 4-amino tempo (4-AT) to provide truncated analog **4-43** and with the tri-peptide H-Pro-Val-Orn(Cbz)-OMe followed by 4-AT to provide hemigramicidin conjugate **4-44**. This compound proved to be an effective conjugate for the delivery of nitroxides into mitochondria where they accumulate, are reduced, and provide impressive protection against apoptosis.

Further exploration into the utility of these conjugates revealed their efficacy as radioprotectants.[133] Ionizing radiation activates a variety of cytoplasmic transduction

pathways, some of which are likely mediated by ROS.[134] It has been demonstrated that exposure to radiation activates nitric oxide synthase in the uroepithelial cells that line the bladder, causing increased nitric oxide production and decreased respiration resulting in superoxide production.[135] Utilizing a potent NOS inhibitor, 2-amino-6-methylthiazine (AMT), conjugated to a hemigramicidin targeting sequence (**4-45**, Figure 4-3), Wipf and Kanai were able to demonstrate the localization of the inhibitor in the mitochondria and its ability to perform its protective duties.[131]



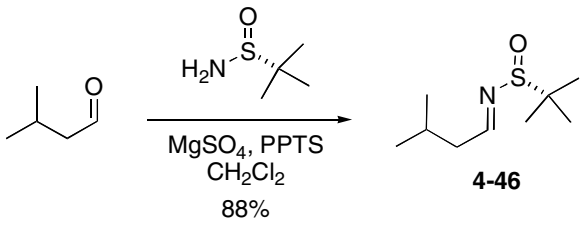
4-45

Figure 4-3. AMT conjugated to hemigramicidin prepared for radiation protection studies.

4.2.2 Results and Discussion

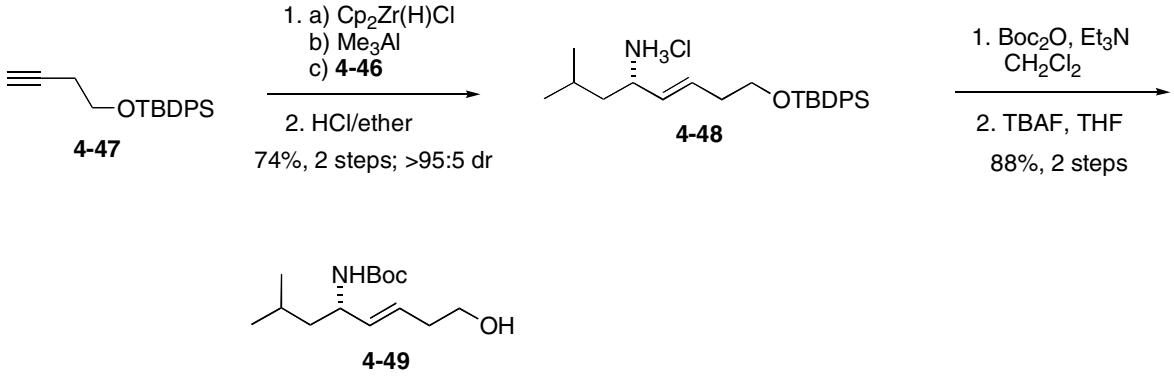
Having previously developed an efficient method for the asymmetric synthesis of allylic amines,[119] we envisioned employing this method for the preparation of peptide conjugates such as **4-44**. Approaches to this class of compounds were effective at providing small amounts of material for biological testing, but the 20-step routes proved daunting upon scale up. Additionally, analog development was hindered by the synthetic effort involved. To explore the *N*-*tert*-butyl sulfinyl imine chemistry, imine **4-46** was

prepared from isovaleraldehyde in 88% yield. Simple filtration through a plug of silica gel provided imine of high purity, and the imine proved stable on the order of months on the bench top – in stark contrast to the Boc-imine previously employed.



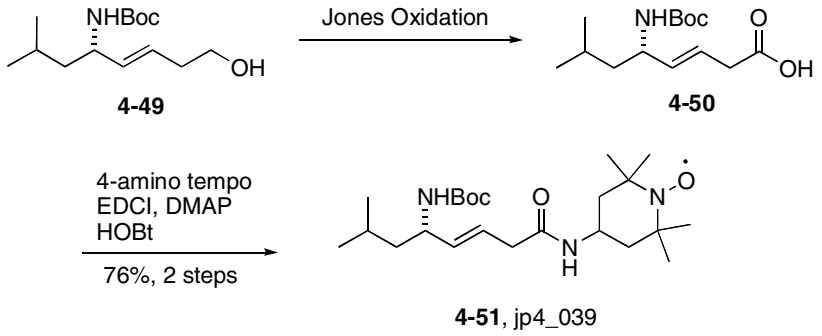
Scheme 4-10. Synthesis of imine **4-46**.

As a common intermediate for a number of our proposed endeavors, alcohol **4-49** served as our initial target for synthetic studies (Scheme 4-11). Hydrozirconation of alkyne **4-47**, transmetalation to trimethylaluminum, and addition to **4-46** provided an allylic amine that was >95:5 dr by ^{1}H NMR analysis of the crude reaction mixture. Treatment of this crude reaction mixture with HCl in diethyl ether yielded the amine hydrochloride **4-48** as a colorless solid in 74% yield over the 2 steps. Boc-protection and TBAF mediated deprotection of the silyl ether provided the desired alcohol **4-49**.



Scheme 4-11. Application of alkenyl alane methodology to the synthesis of 4-49.

With alcohol **4-49** in hand, our focus turned to the synthesis of a number of novel tempo-peptide conjugates as well as the development of an improved approach to acid **4-42**. Oxidation of alcohol **4-49** to the desired carboxylic acid was achieved by treatment with Jones' reagent in acetone (Scheme 4-12). This method proved quite tolerant of the Boc-protecting group and was significantly simplified from the previous 2-step oxidation procedures. Subsequent coupling of the acid with 4-AT provided the desired amide **4-51** (jp4_039) in 76% yield. The purity of this compound was initially determined to be 85-90% by LCMS analysis, and has subsequently been improved by SFC purification to >98%.[136]

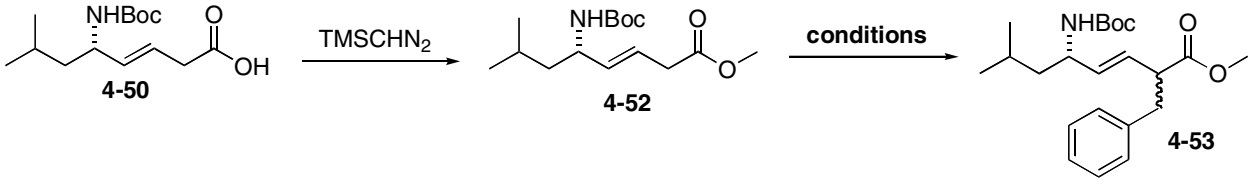


Scheme 4-12. Oxidation and coupling of **4-49** to yield **4-51** (jp4_039).

With acid **4-50** readily available, attention was turned to a stereoselective alkylation to install the benzyl side chain of **4-43**. Conversion of acid **4-50** to methyl ester **4-52** was accomplished in 84% yield via the action of $TMSCHN_2$. Alkylation of this ester proved challenging, usually providing mixtures of mono- and bis-alkylated products upon treatment of the enolates with benzyl bromide. The potassium enolate exclusively provided the bis-alkylated product **4-54** (entry 1, Table 4-4). Gratifyingly, after variation of solvent, additives, bases and temperatures, formation of the lithium enolate in THF

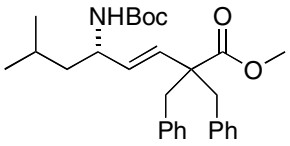
employing DMPU as an additive and treatment with benzyl bromide at -30 ˚C yielded 78% of alkylated product as a 1.5:1 mixture of diastereomers that have not been assigned (entry 4, Table 4-4). Interestingly, no δ-alkylation or *N*-alkylation was observed in any of the studied cases.

Table 4-4. Development of alkylation conditions for the preparation of **4-53**.



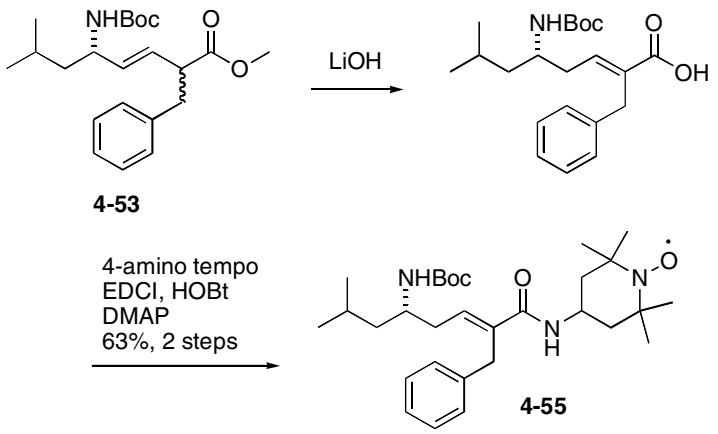
entry	conditions	alkylating agent (eq)	yield [%] (product)
1	KHMDS, -78 ˚C - -20 ˚C, 4 h	BnBr (1.2 eq)	45 (**4-54**)
2	NaHMDS, -78 ˚C - -20 ˚C, 6 h	BnBr (1.2 eq)	**4-53** + **4-54**[a]
3	LDA, THF, -78 ˚C - -30 ˚C, 14 h	BnBr (5 eq)	23 (**4-53**)
4	LiHMDS, DMPU, -78 ˚C - -30 ˚C, 14 h	BnBr (5 eq)	78 (**4-53**, 1.5:1 dr)[b]

[a] Yield not determined. [b] Yield of isolated and purified product. dr determined by HPLC analysis: Chiracel® AD-H column and elution with 3% *i*-PrOH/hexanes. Major diastereomer not assigned.



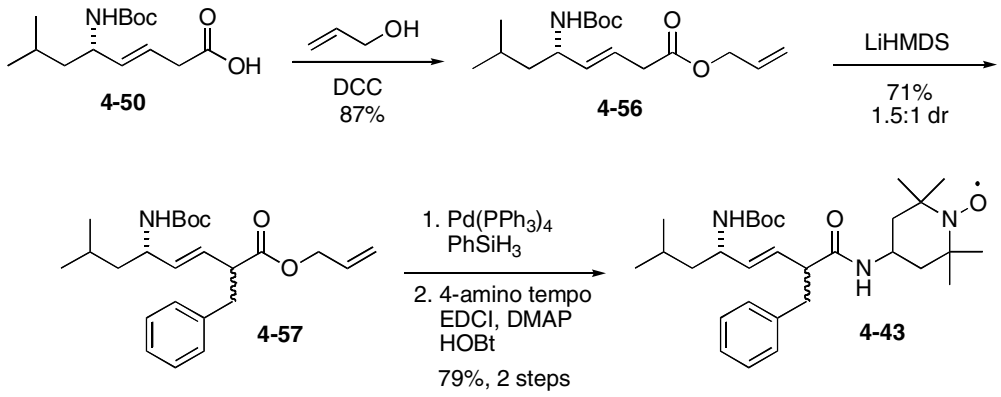
4-54

Unfortunately, attempts to hydrolize the methyl ester to generate the requisite acid for coupling to 4-amino tempo failed, yielding only conjugated alkene product (Scheme 4-13). This product was converted to the corresponding 4-AT adduct **4-55** for biological testing.



Scheme 4-13. Hydrolysis and coupling of methyl ester **4-53**.

To circumvent the problems associated with ester hydrolysis, acid **4-50** was converted to allyl ester **4-56** by treatment with allyl alcohol and DCC. Alkylation of this ester went smoothly under the previously optimized conditions, providing an inseparable 1.5:1 mixture of diastereomers of **4-57** that has not been assigned. Allyl ester **4-56** was smoothly deprotected under palladium catalysis conditions and the acid subsequently converted to an inseparable mixture of **4-43** by coupling with 4-AT.



Scheme 4-14. Synthesis of allyl ester alkylaton substrate and synthesis of **4-43**.

With this streamlined approach to novel nitroxide compounds, a collaboration with the newly formed University of Pittsburgh Center for Medical Countermeasures Against Radiation was established. Upon screening of a variety of nitroxide containing conjugates it was discovered that **4-51** (jp4_039) was the most effective radioprotectant screened *in-vitro*.[137] To our delight, positive results also extended to *in-vivo* studies. C57BL/6NHsd female mice injected with 1 mg/kg jp4-039 before irradiation had a significant increase in survival of 80% compared to 20% for control irradiated mice ($p = 0.0005$) (Figure 4-4).[137] These impressive results are under further examination; additionally, jp4-039 will be produced on a 200 gram scale to begin primate studies in the near future.

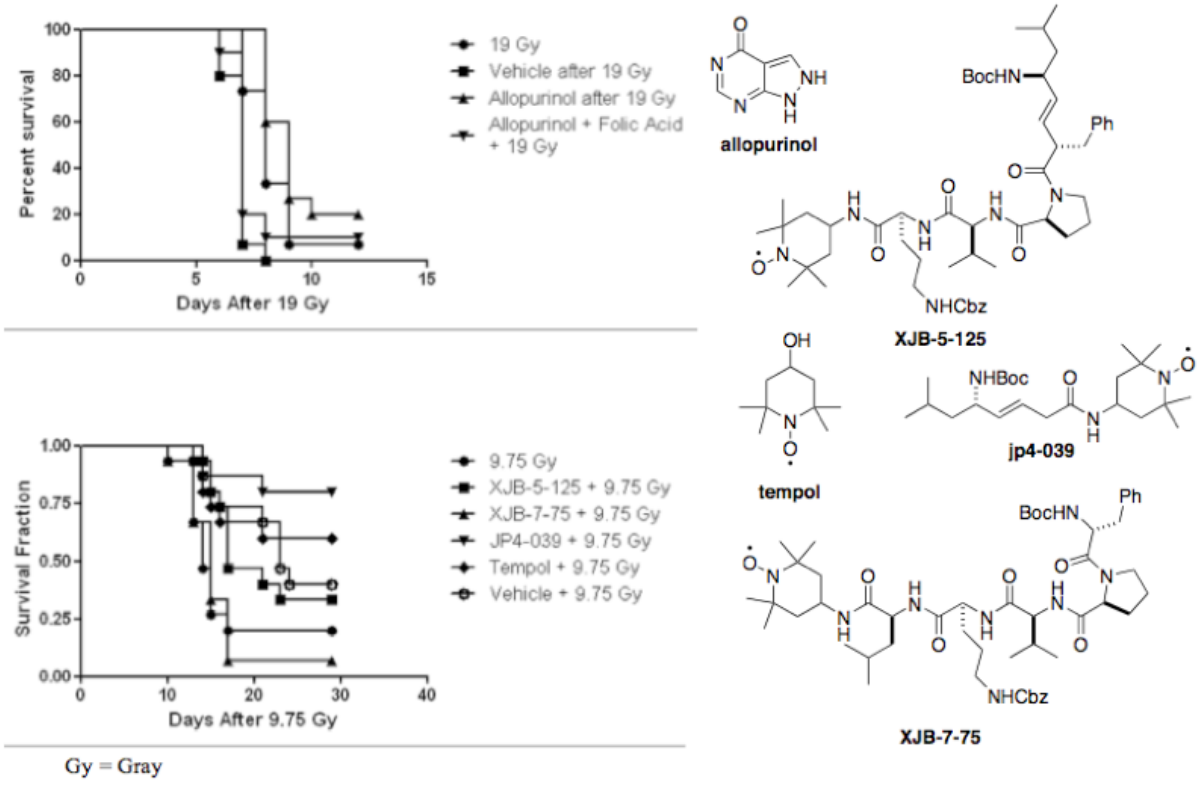


Figure 4-4. *In-vivo* studies of various nitroxide containing conjugates for radiation protection.[138]

Although detailed experiments to determine the mechanism of action of jp4_039 are only beginning, the current hypothesis is that through targeting of jp4_039 to the mitochondria, reduction of damaging superoxide radical anion is achieved. While jp4_039 is smaller than XJB-5-125, early experiments have demonstrated that the current compound is also preferentially located in the mitochondria.[139] Further studies to determine the mechanism of action of jp4_039 are currently underway.

4.2.3 Conclusion

We have extended our alkenyl alane addition to imines to the synthesis of biologically relevant peptide mimetics. These studies have led to an improved route to a key fragment of hemigramicidin tempo hybrid molecules as well as to a novel radiation protection agent. Biological evaluation has shown the *in-vivo* ability of **4-51** (jp4_039) to prevent death from intense radiation exposure. Future studies aim at the large scale synthesis and primate studies of this readily accessible compound.

5.0 L-TYROSINE AS A SYNTHETIC BUILDING BLOCK: THE SYNTHESIS OF OCTAHYDROINDOLES AND PROGRESS TOWARD THE TOTAL SYNTHESIS OF TUBEROSTEMONONE

5.1 INTRODUCTION

5.1.1 *Stemona* Alkaloids: Tuberostemonone

The *Stemonaceae* plant family, which comprises over 30 species, produces a large class of structurally diverse alkaloids featuring a conserved pyrrolo[1,2-a]azepine nucleus (Figure 5-1).[140] The natural products isolated from these plants are classified into 6

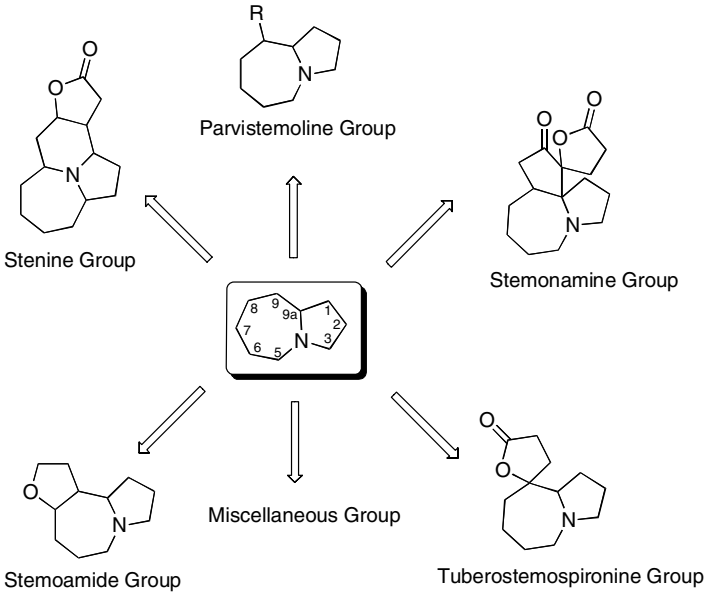


Figure 5-1. Classification of the *Stemona* alkaloids.

groups, each bearing a unique molecular architecture around the azepine core. Natural products from *Stemona* and *Croomia* plants have been isolated since before the 1930's in the western literature and possess a broad array of complex functionality (Figure 5-2).[141] The plant extracts have been used for centuries in eastern cultures as remedies for respiratory conditions, such as bronchitis and tuberculosis. To date, with the exception of insecticide activity, few human health benefits have been observed from the purified compounds of the *Stemona* family.[142]

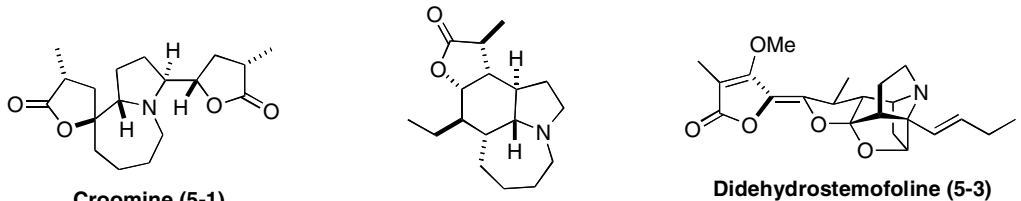
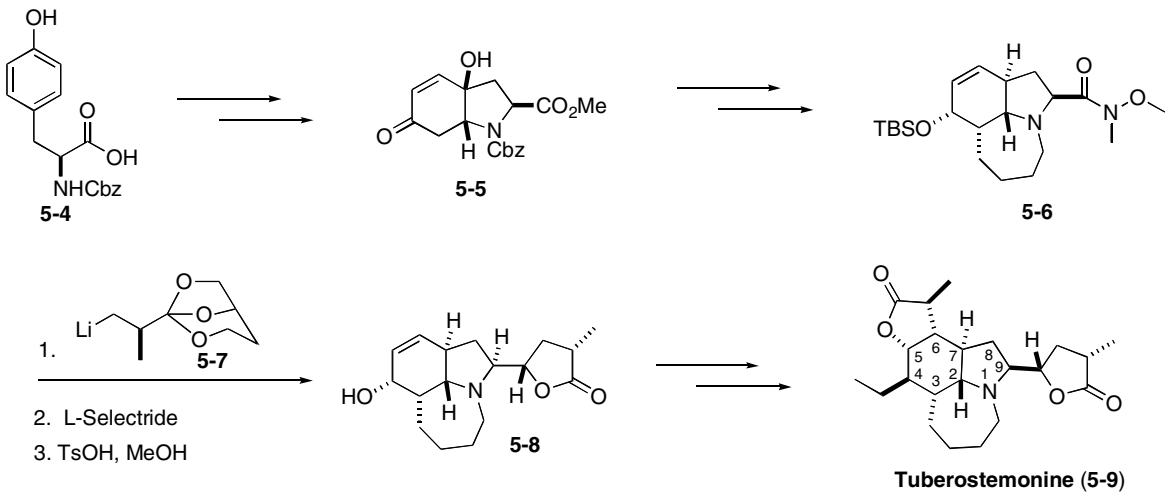


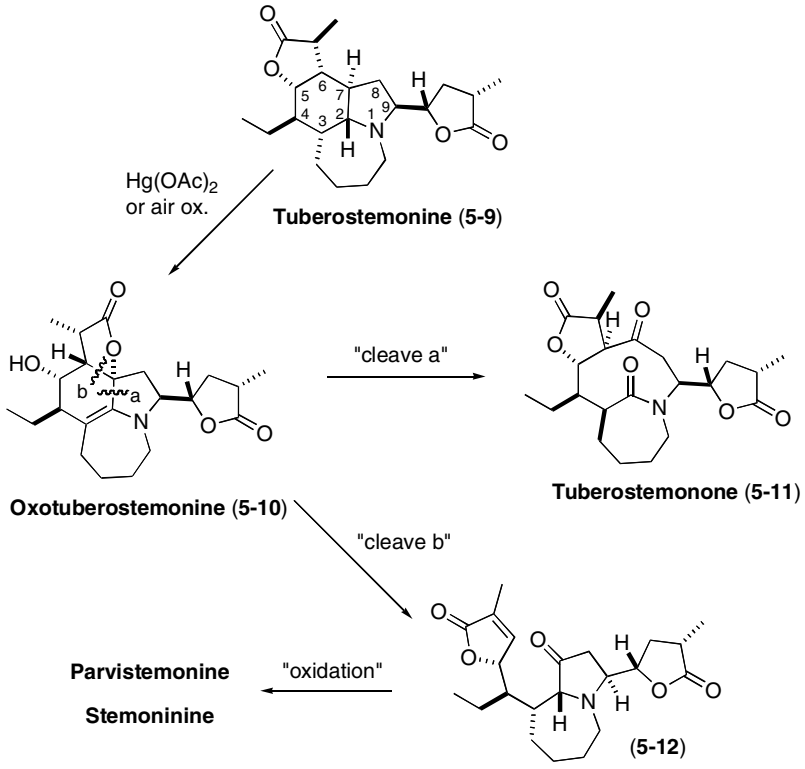
Figure 5-2. Representative structural diversity in the *Stemona* alkaloid family.

Synthetic efforts to this family of natural products has spanned two decades, beginning with the first total synthesis of croomine in 1989 by Williams et al.[143a] Since this time, a number of novel synthetic strategies have been developed to synthesize *Stemona* alkaloids.[143,138] Of particular interest are the elegant syntheses of stenine and tuberostemonine by Wipf et al. who rapidly construct the core of these natural products via functionalization of a hydroxyhydroindole derived from *L*-tyrosine (Scheme 5-1).[144] The synthesis of tuberostemonine was particularly interesting due to the development of a novel synthesis of the appended lactone by the addition of an anionic ortho ester to a Weinreb amide (**5-6** – **5-8**, Scheme 5-1).



Scheme 5-1. Overview of Wipf's total synthesis of tuberostemonine.

Tuberostemonone (**5-11**, Scheme 5-2), a *Stemona* alkaloid isolated in 1991 and structurally assigned by X-ray and spectroscopic means, bears a unique 9-membered lactam core.[145] The origin of this unusual structure sparked the interest of Wipf et al. and

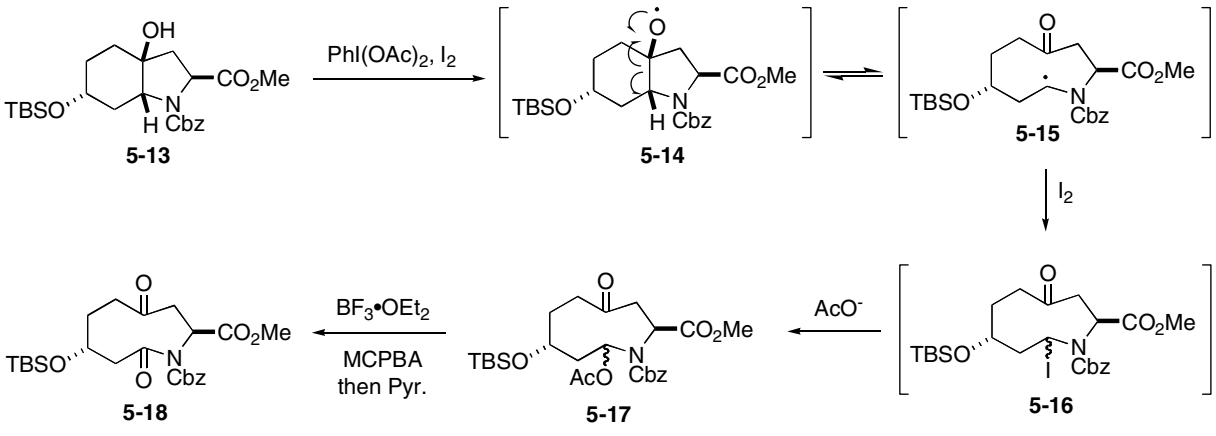


Scheme 5-2. Proposed biosynthetic origins of several *Stemona* alkaloids by Wipf.

studies toward the synthesis of this natural compound began. A key element to the initial approach was the concept that **5-11** could arise via an oxidative cleavage of tuberostemonine.[146] In this way, it was envisioned that a number of the members of the *Stemona* family had a common biological precursor and were linked through a series of oxidations and fragmentations (Scheme 5-2).

5.1.2 Alkoxy Radical Fragmentations

To transform the biosynthetic concept to a synthetic reality, Wipf and Li explored the alkoxy radical fragmentations of hydroxyhydroindole model systems.[140] Utilizing the Suarez reagent[147] ($PhI(OAc)_2$, I_2), hydroxyhydroindole **5-13** was readily converted to aminal **5-17** in 80% yield. The reaction proceeded via an intermediate unstable iodine trapping product which was displaced by acetate under the reaction conditions. Further conversion of the acetal to the required 9-membered keto-lactam **5-18** was achieved by treatment with MCPBA and pyridine.[148]



Scheme 5-3. Radical fragmentation of hydroxyhydroindoles developed by Wipf and Li.

Although only demonstrated on a model substrate, this chemistry provided support for the hypothesis that tuberostemonone arises via oxidative fragmentation of tuberostemonine or a related alkaloid.

5.1.3 Hydroindoles

Aeruginosin 298-A **(5-19**, Figure 5-3**)** is a serine protease inhibitor that was isolated from a fresh water blue green algae in 1994.[149] Approximately sixteen members of the aeruginosin family have been identified, and fourteen share the unusual bicyclic amino acid L-Choi [(2*S*,3a*S*,6*R*,7a*S*)-2-carboxy-6-hydroxyoctahydroindole] or a close derivative as a common motif.[150] L-Choi is an example of the growing class of sterically encumbered proline analogues that exert a profound influence on the secondary structure when embedded in oligopeptide sequences. Several synthetic approaches to Choi and aeruginosin natural products have been reported.[151] Many other natural and synthetic compounds contain fused bicyclic scaffolds that closely resemble Choi.[152] The naturally occurring di-, tri- and tetrahydroxylated indolizidine alkaloids, lentiginosine (an amyloglucosidase inhibitor), swainsonine (an α-mannosidase inhibitor), and castanospermine (**5-20**, an α-glucosidase inhibitor; analog **5-21**[145f]) are particularly noteworthy (Figure 1). Parkacine (**5-22**) is an alkaloid from *Amaryllis belladonna var blanda Brunsvigia josephinae.* The significance of these fused bicyclic scaffolds for biologically active natural products has inspired the development of novel chemical libraries.[153]

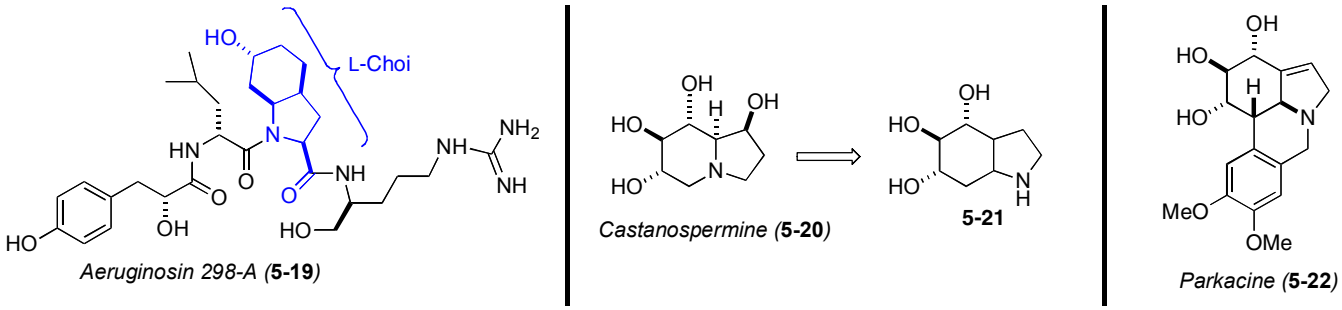
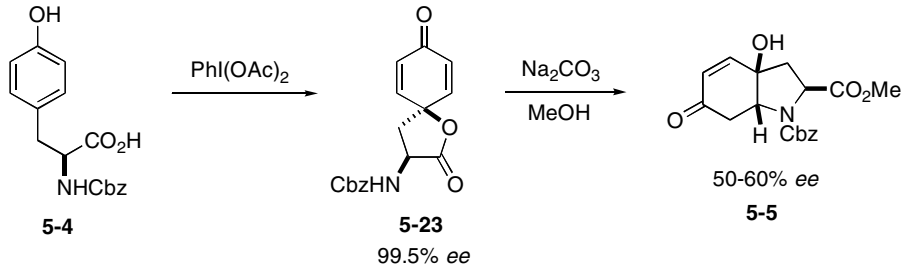


Figure 5-3. Representative biologically active hydroxyhydroindoles.

5.2 RESULTS AND DISCUSSION

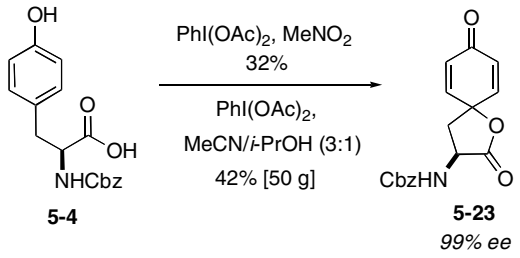
5.2.1 Hydroxyhydroindole Synthesis

At the outset of this project it was envisioned that the previously developed oxidative cyclization/methanolysis methodology would provide ample access to our requisite hydroxyhydroindole. Unfortunately, at this time it was discovered that significant racemization of the hydroindole product was occurring during the basic methanolysis protocol.[138,154] Since this was the starting material for our proposed synthesis, as well as for other current and previous natural product targets, a thorough



Scheme 5-4. Previously developed oxidative spiro-cyclization / methanolysis.

evaluation and optimization of this reaction sequence needed to be performed. Initial efforts were focused on the large scale synthesis of spirocycle **5-23** via a protocol previously developed by Wipf.[147] Although this oxidation was originally performed in methanol and subsequently nitromethane, a 3:1 mixture of acetonitrile:isopropanol has proven more successful upon scale-up (Scheme 5-6). This optimized procedure led to spirocycle **5-23** in 42% yield and >99% *ee* as determined by chiral HPLC analysis.

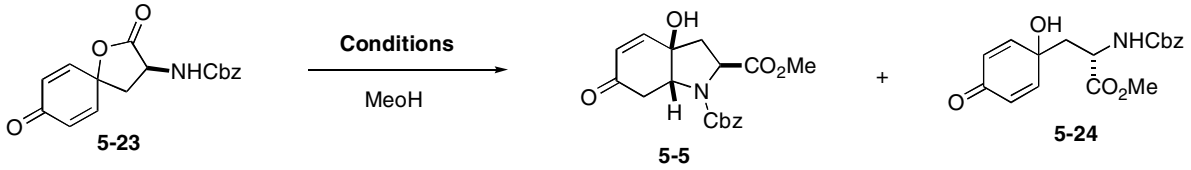


Scheme 5-5. Improved protocol for oxidative cyclization.

With spirocycle **5-23** in hand, methanolysis conditions were screened to explore the effects of bases, solvents, temperatures and additives on the desired transformation (Table 5-1). We measured product ratios and enantiomeric excess by chiral HPLC analysis. Stronger bases and/or extended reaction times gave products with further deteriorated enantiomeric purity, while weak bases (NaOAc, entry 5) or nucleophilic bases (DMAP, entry 9) promoted only spirocycle opening to generate hydroxydienone **5-24**. Lowering the reaction temperature and using NaOMe had a beneficial effect, providing **5-5** in 87% *ee* (Table 5-1, entry 11). Addition of water and switching the base to KOH not only improved the *ee* further to 97%, but also decreased the reaction time to 10 min and

increased the yield to 80%. Utilizing this optimized protocol, **5-5** could be prepared in overall 34% yield and 97% *ee* from *L*-tyrosine on a 50 gram scale.

Table 5-1. Optimization of methanolysis to avoid racemization.

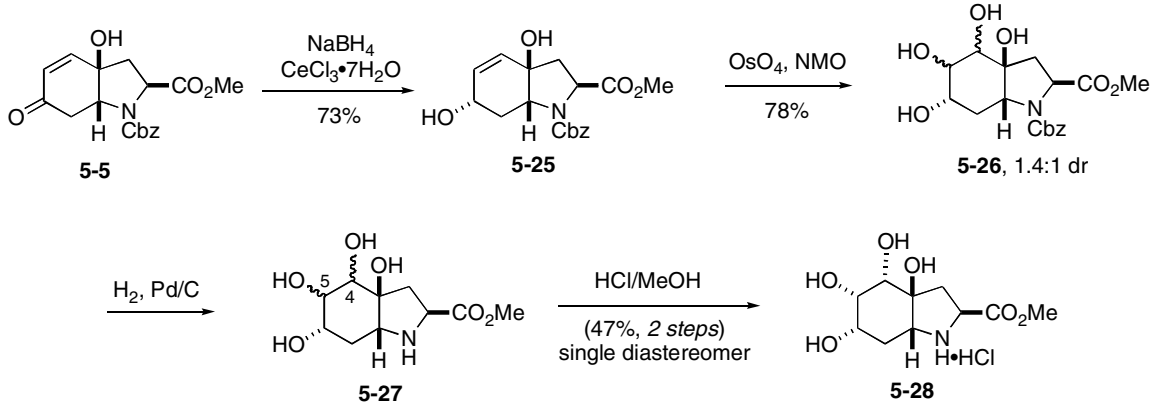


entry	conditions	ratio[a]	*ee* (%)[a]
1	Na_2CO_3 (1 eq), rt, 3 h	**5-5** only	53
2	$NaHCO_3$ (2 eq), rt, 14 h	**5-5** only	67
3	$NaHCO_3$ (2 eq), MWI, 80 °C, 20 min	**5-5**:**5-23**, 6:1	12, 2
4	Na_2HPO_4 (1 eq), rt, 27 h	**5-24**:**5-23**, 3.6:1	93, 86
5	NaOAc (1 eq), rt, 12 h	**5-24**:**5-23**, 4.6:1	92, 89
6	Li_2CO_3 (1 eq), rt, 16 h	**5-5** only	50
7	Cs_2CO_3 (1 eq), rt, 5 min	**5-5** only	51
8	*i*-Pr_2NEt (1 eq), rt, 19 h	**5-5** only	58
9	DMAP (1 eq), rt, 20 min	**5-24**:**5-23**, 2.3:1	97, 93
10	NaOMe (1 eq), -78 °C, 80 min	**5-24**:**5-23**, 9:1	99, 99
11	NaOMe (1 eq), - 25 °C, 14 h	**5-5** only	87
12	3 M KOH/H_2O, -20 °C, 10 min	**5-5** only	97

[a] Determined by HPLC analysis of crude reaction mixtures using a Chiracel AD-H column; individual yields were not determined.

After identifying a stereoselective protocol to desired hydroindole **5-5**, our focus turned toward the synthesis of hydroxylated L-Choi derivatives. Realizing the potential to generate a number of stereoisomers from the common intermediate **5-5**, we first subjected the enone to $NaBH_4$ at 0 °C to provide in 73% yield the axial alcohol **5-25**, which upon dihydroxylation led to tetrol **5-26** in 1.4:1 facial selectivity and 78% yield (Scheme 5-7). The Cbz group was removed by hydrogenolysis to yield a mixture of amines (**5-27**), and separation of diastereomers was achieved by formation of their hydrochloride salts in

methanol, followed by selective precipitation to generate **5-28** as a single diastereomer in 47% yield based on **5-26**.



Scheme 5-6. Synthesis of tetrahydroxy hydroindole **5-28**.

The configuration at the C_4 and C_5 positions of **5-28** was initially assigned based on ^{1}H NMR analysis; specifically, the hydrogen atoms were assigned by COSY and HMQC and the relative configuration was determined in ^{1}H NMR double resonance experiments from the coupling constants $J_{4,5}$ = 3.5 Hz and $J_{5,6}$ = 2.4 Hz for **5-28** (Figure 5-4). Among the C_6-α-hydroxy isomers **5-28** and **5-29**, only **5-28** provided a good agreement between the dihedral angles of the minimized structure and these coupling constants.[155] This assignment was further confirmed by an X-ray analysis of the *N*-alkylated derivative **5-30**. In the solid state, this compound adopted a conformation closely analogous to the calculated structure of **5-28** shown in Figure 5-4, with dihedral angles τ HC_6-C_5H = -63.3° and τ HC_5-C_4H = 53.7°. It is interesting to note that the osmate in the dihydroxylation step favors an approach from the concave α–face which is sterically only slightly shielded by the equatorial secondary alcohol.[156] This result demonstrates the role of the tertiary

alcohol at the bridgehead position in controling the *anti*-approach of osmium tetraoxide to the allylic double bond.

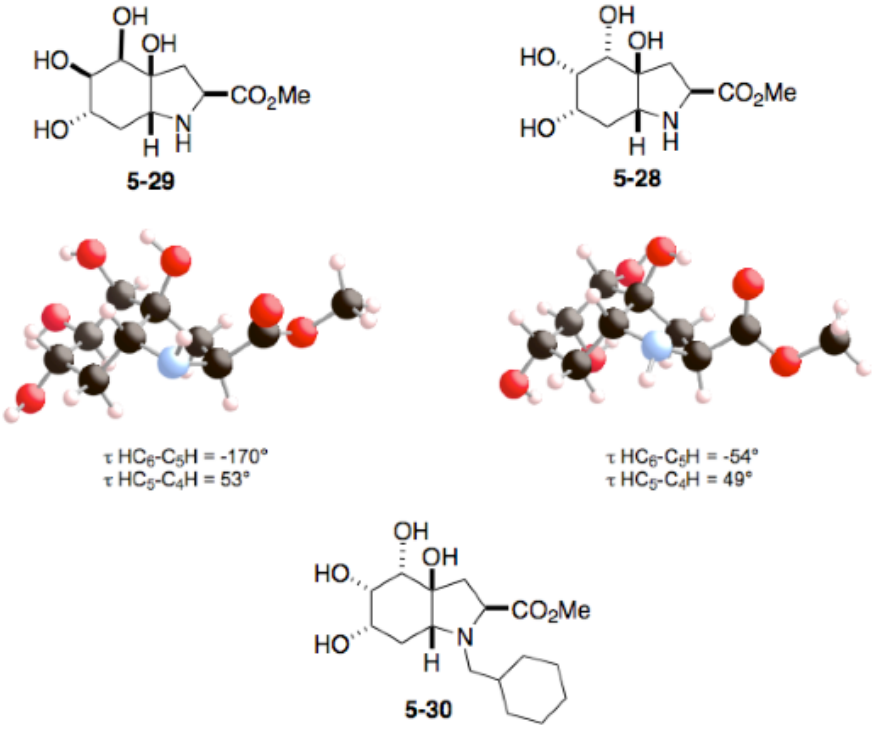
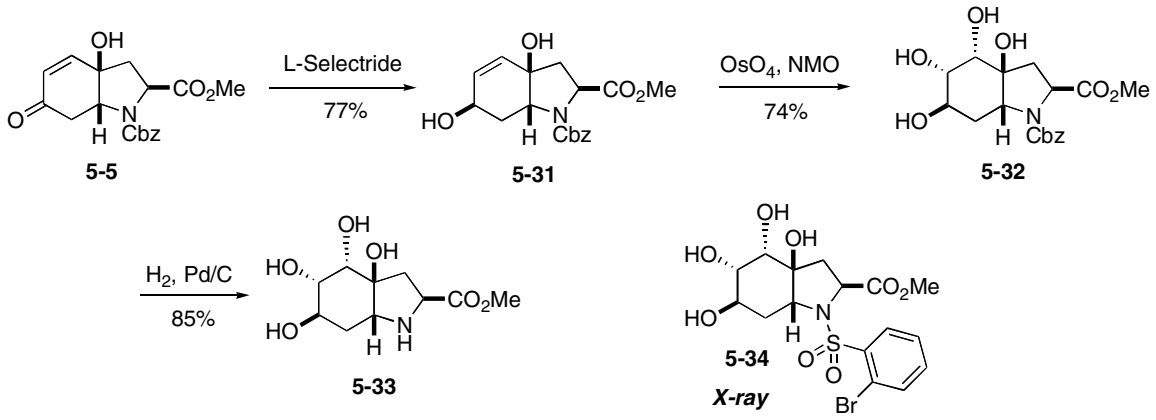


Figure 5-4. Conformational analysis of **5-28** and **5-29**.

The synthesis of the C_6-epimer **5-33** began with a reduction of enone **5-5** with L-Selectride at -78 °C to give the axial alcohol in 77% yield and in >95:5 selectivity when the reagent was added by syringe pump (Scheme 5-7). Subsequent dihydroxylation of the diol gave **5-32** as a single diastereomer by ^{1}H NMR analysis. Tetrol **5-32** was subsequently deprotected to provide hydroindole **5-33**.

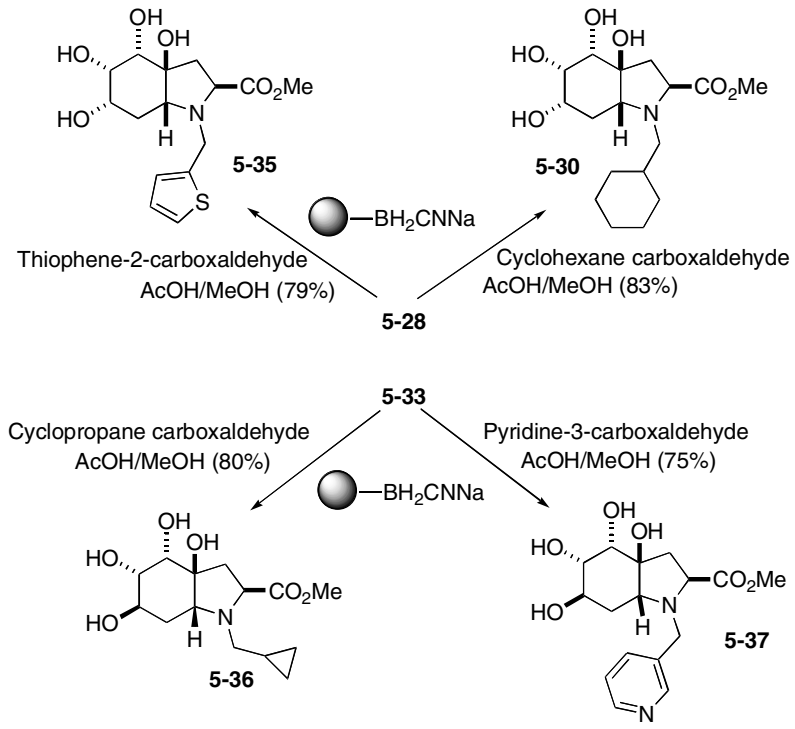


Scheme 5-7. Synthesis of hydroxyhydroindole **5-33**.

In contrast to **5-28**, the differentiation of the two possible diastereomers of **5-33** by coupling constant analysis was not possible, since the two energy minimized structures had very similar dihedral angles. Fortunately, sulfonylation of **5-33** provided the crystalline material **5-34** which enabled the unambiguous assignment of the relative configuration through X-ray analysis. Based on our previous result, it was not surprising that the approach of the osmium reagent occurred opposite to the *cis*-1,4-diol functionality, exclusively from the α-face of alkene **5-31**.

After establishing a facile approach to hydroxylated L-Choi derivatives, we pursued a reductive amination as a way to install diverse functionality onto the secondary amine. To this end, a number of conditions were screened to achieve high yields in the amination. MP-cyanoborohydride resin[157] was found to be the most effective reducing agent, which we attributed to its greater stability in methanol. Applying these optimized conditions to both intermediates **5-28** and **5-33**, we produced tertiary amines bearing thiophene (**5-35**), cyclohexyl (**5-30**), cyclopropyl (**5-36**) and pyridine (**5-37**) hetero- and

carbocyclic ring functionality (Scheme 5-8). These conversions illustrate the broad substituent diversity that can be introduced with this transformation.

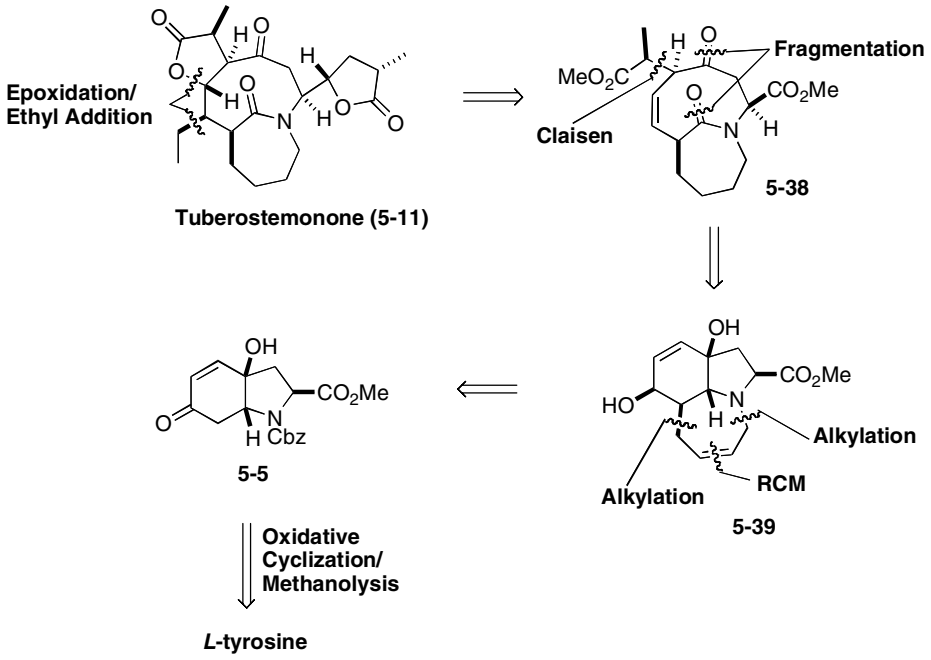


Scheme 5-8. Functionalization of hydroindoles through reductive amination.

5.2.2 Tuberostemonone

The stereochemical difference between **5-11** and tuberostemonine (**5-9**) or stenine (**5-2**) provided substantially different chemical problems and therefore required a novel approach for its synthesis. Retrosynthetically, it was envisioned that tuberostemonone would arise from late-stage epoxidation/epoxide opening of alkene **5-38**, readily available from a Claisen rearrangement of allylic alcohol **5-39** (Scheme 5-9). The 9-membered lactam would arise via fragmentation of an appropriately functionalized

hydroxyhydroindole, utilizing the Suarez reagent as previously investigated by Wipf and Li.[140] Synthesis of alcohol **5-39** from hydroxyhydroindole **5-5** could be envisioned by a sequential bis-alkylation, ring-closing metathesis and reduction protocol. Hydroxyhydroindole **5-5** is a known compound[158] that would arise from the oxidative cyclization and subsequent methanolysis of *L*-tyrosine.

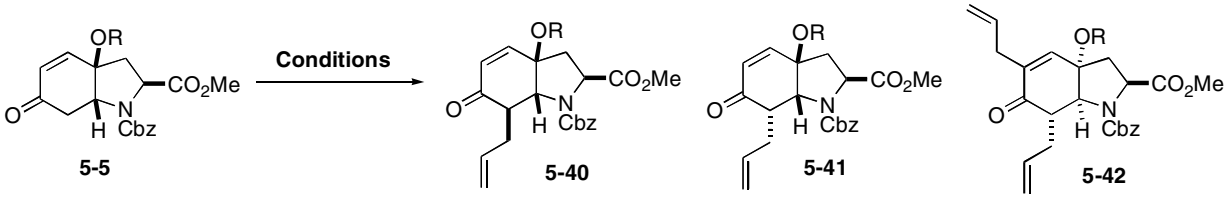


Scheme 5-9. Initial retrosynthetic analysis of tuberostemonone.

Key to a successful synthesis of tuberostemonone is the ability to install the requisite stereocenters of the natural product from the functionalized hydroindole **5-5**. While this scaffold has been transformed to stenine and tuberostemonine, early removal of the tertiary alcohol and opposite stereochemistry at several centers facilitated these efforts.[138] Previous work by Wipf and Li focused on the alkylation of enone **5-5**, and this work demonstrated the difficulties in this reaction.[159] Although troublesome, this

transformation provided the most rapid access to the core of tuberostemonone and therefore warranted further investigation. To this end, a variety of bases and protecting groups were screened to explore the alkylation of hydroindole **5-5** with a simple allyl electrophile (Table 5-2). Treatment of **5-5** with lithium, sodium or potassium

Table 5-2. Attempted alkylation of hydroindole **5-5**.



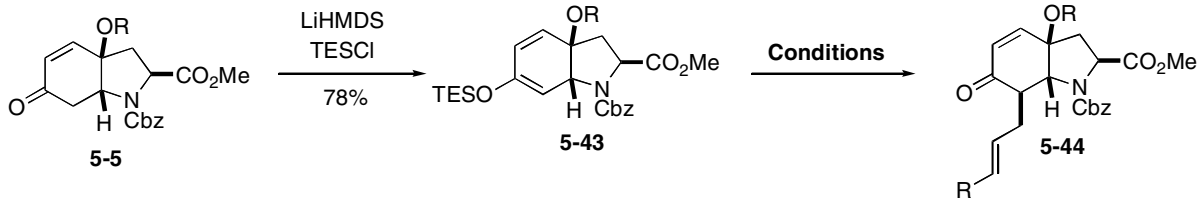
entry	R	conditions	result
1	TMS	LiHMDS, allyl iodide, THF, - 40 ˚C, 12 h	25% (**5-40** + **5-41**, 3:1) + **5-42**
2	TMS	NaHMDS, allyl iodide, THF, - 40 ˚C, 12 h	10% **5-40** + 50% **5-42**
3	TMS	KHMDS, allyl iodide, THF, - 40 ˚C, 6 h	65% **5-42**
4	MOM	LiHMDS, allyl iodide, THF, - 40 ˚C, 12 h	40% (**5-40** + **5-41**, 1.1:1) + **5-42**
5	THP	LiHMDS, allyl iodide, THF, - 40 ˚C, 12 h	35% (**5-40** + **5-41**, 1.2:1) + **5-42**
6	H	LiHMDS, allyl iodide, THF, -40 ˚C, 4 h	33% **5-40**, 100 mg scale
			22% **5-40**, 2 g scale
7	H	LiHMDS, allyl chloride, THF, -30 ˚C, 8 h	12% **5-40**, 2 g scale

bistrimethylsilyl amide followed by reaction with allyl iodide, led to low yields of the desired product **5-40** and often mixtures of diastereomers. Rapid elimination of the carbamate moiety upon enolate formation can be blamed for the observed difficulties. To further complicate matters, further deprotonation-elimination-alkylation of the desired product **5-40** to provide **5-42** is a rapid process, particularity when employing potassium

bases. Difficulty in the alkylation of dieneolates has been well documented, and solutions have been developed (such as hydrazone formation).[160] Unfortunately, none of these approaches were successful in our system.

To further probe the reactivity of these systems, the alkylation of silyl enol ethers was explored (Table 5-3). Formation of the required silyl enol ether was straightforward as this reaction could be performed at -78 ˚C and thereby avoid carbamate elimination. With **5-43** in hand, it quickly became apparent that this substrate did not perform well in typical reactions of silyl enol ethers, with low yields or no conversion observed in all explored cases.[161]

Table 5-3. Formation of silyl enol ether and attempted alkylation.

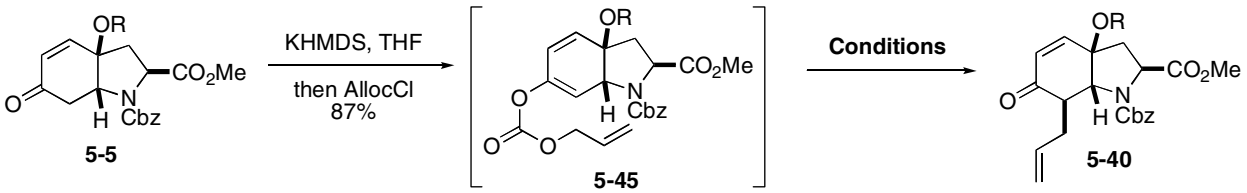


entry	R	conditions	result
1	TMS	$AgBF_4$ or $AgOC(O)CF_3$, allyl iodide, CH_2Cl_2, -20 ˚C, 4 h	12% **5-44** + **5-5**
2	TMS	Pd $(PPh_3)_4$, butadiene monoxide, THF, rt, 10 h	complex
3	TMS	MeLi, allyl iodide, THF, -78 ˚C - rt	**5-5** + dec
4	MOM	MAD, CH_2Cl_2, MeOTf, rt, 24 h	**5-43**

Previous work in the area of ketone allylation has shown the power of palladium catalyzed intramolecular allylations in both a diastereoselective and enantioselective sense.[162,163] We envisioned that formation of the requisite enol carbonate **5-45** would be straightforward as in the case of the silyl enol ether **5-43** and proposed that the subsequent

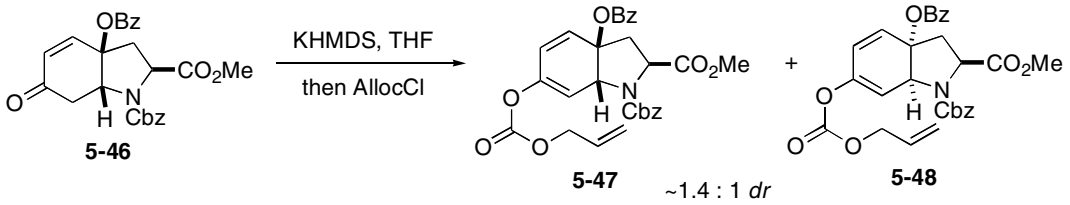
allylation reaction would proceed rapidly, thereby circumventing many of the previously observed difficulties (Table 5-4). Subjecting of **5-5** to KHMDS and allyl chloroformate provided enol carbonate **5-45**; unfortunately, treatment of **5-45** under a variety of palladium catalysis conditions led to poor diastereoselectivities in the allylation reaction. Variation of the protecting group on the tertiary alcohol also did not improve the reaction selectivity.

Table 5-4. Palladium catalyzed intramolecular allylation of **5-45**.



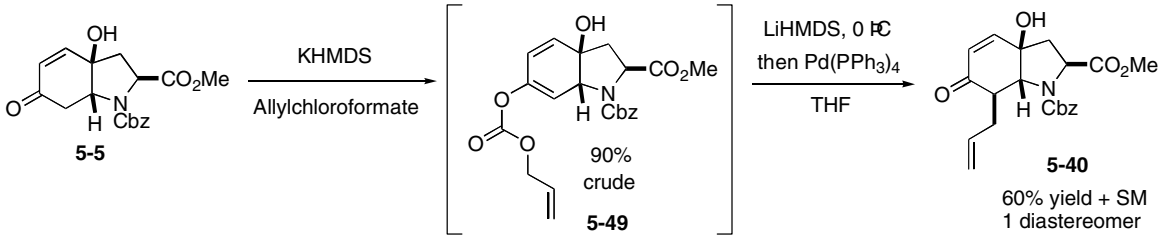
entry	R	conditions	result
1	TMS	$Pd(PPh_3)_4$, THF, -50 ˚C, 14 h	90%, 1.5:1 dr
2	TMS	$Pd_2(dba)_3$, DPPE, THF, -40 ˚C, 12 h	complex
3	Bz	$Pd(PPh_3)_4$, THF, -50 ˚C, 14 h	70%, 1.2:1 dr
4	MOM	$Pd(PPh_3)_4$, THF, -50 ˚C, 14 h	81%, 1.1:1 dr

After obtaining these disappointing results, we sought to determine if the problematic step in the reaction was the palladium catalyzed allylation or the formation of the enol carbonate (Scheme 5-10). Treatment of **5-46** with KHMDS at -78 ˚C followed by addition of allyl chloroformate and warming to -40 ˚C provided a 1.4:1 mixture of diastereomers (**5-47** and **5-48**) thereby demonstrating the troublesome step was the enol carbonate formation. All attempts at improving this transformation were not successful.



Scheme 5-10. Observed deterioration of diastereoselectivity in enol carbonate formation.

The limited success that was previously obtained in the allylation of **5-5** occurred when no protecting group was employed on the tertiary alcohol. This observation inspired us to explore the effect of an alkoxide ion at this position on the palladium allylation chemistry. With this goal in mind, **5-5** was treated with KHMDS and allyl chloroformate to provide a compound that was assumed to be enol carbonate **5-49** (Scheme 5-11). To our delight, subjecting this compound to LiHMDS and $Pd(PPh_3)_4$ provided the desired allyated product **5-40** in 60% yield as a single diastereomer. While this result was encouraging, the reasons for the success were unclear and prompted a closer inspection of the reaction intermediates.

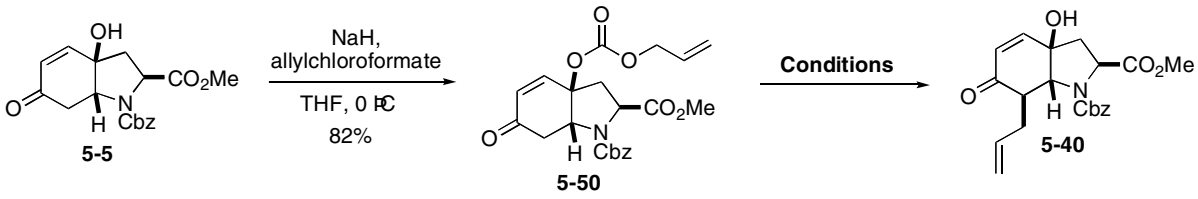


Scheme 5-11. Successful intramolecular allylation of proposed enol carbonate **5-49**.

Purification and characterization of intermediate **5-49** quickly revealed that the product of the previous enol carbamate forming reaction was the tertiary carbonate and not the enol carbonate. Accordingly, tertiary carbonate **5-50** was synthesized by treatment

with NaH and allyl chloroformate to provide the desired product in 82% yield (Table 5-5). This compound was identical to the intermediate in the previous reaction sequence. A variety of conditions were screened to explore this intriguing reaction. Interestingly, of all the bases and palladium sources explored, the lithium enolate and $Pd(PPh_3)_4$ were the only effective combination to promote this allylation reaction. Although no mechanistic details have been explored to date, these observations could be rationalized by a soft-soft interaction between the π-allyl palladium complex and the lithium enolate. The instability of the allylic carbonate upon prolonged exposure to palladium could also play a role in the observed limitations.

Table 5-5. Optimization of palladium catalyzed intramolecular allylation reaction.

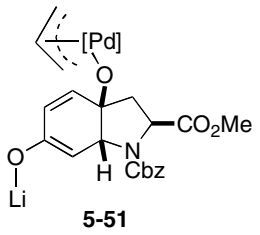


entry	conditions[a]	result
1	LiHMDS, $Pd(PPh_3)_4$, THF, 0 ˚C, 15 min	60%
2	NaHMDS, $Pd(PPh_3)_4$, THF, 0 ˚C, 30 min	trace
3	KHMDS, $Pd(PPh_3)_4$, THF, 0 ˚C, 30 min	NR
4	DBU, $Pd(PPh_3)_4$, -20 ˚C – rt, 6 h	**5-5**
5	Cs_2CO_3, $Pd(PPh_3)_4$, -20 ˚C – rt, 6 h	**5-5**
6	LiHMDS, $ZnCl_2$, THF, 0 ˚C, 30 min	trace
7	LiHMDS, $Pd(OAc)_2$, DPPE, THF, 0 ˚C, 2 h	complex

[a] All reactions were performed on a 100 mg scale.

The extremely rapid nature of the allylation reaction (10 min at 0 ˚C) when compared to other palladium catalyzed reactions of allyl carbonates raises interesting

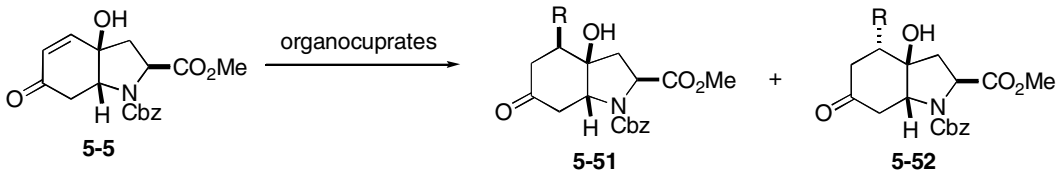
mechanistic questions. We propose, upon lithium enolate formation and addition of Pd^0, an intramolecular transfer of the π-allyl palladium intermediate to the enolate and regeneration of Pd^0 (Scheme 5-12). Experiments to further probe the mechanistic details of this transformation have not been performed, but we observed that the reaction was not affected by 5x dilution.



5-51

Scheme 5-12. Proposed intermediate for allylation.

While investigating the use of the allylation as the first step in the construction of **5-11**, we also became interested in investigating the conjugate addition of organometallic reagents to enone **5-5** (Scheme 5-13). Disappointingly, a number of nucleophiles, including organocuprates and allyl silanes, provided poor diastereoselectivity.[164] This is most likely due to the electronic repulsion by the hydroxy group, as this was also a problem in the previously discussed dihydroxylation chemistry.

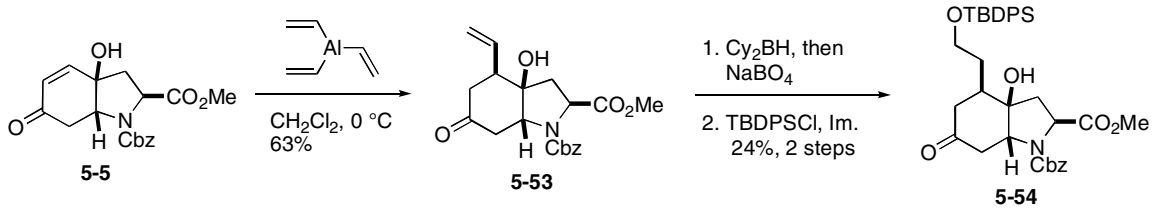


5-5 **5-51** **5-52**

1.5:1 - 1:1 mixtures

Scheme 5-13. Addition of organocuprates provided poor diastereoselection.

To circumvent these selectivity issues, we chose to investigate organometallic agents that would be directed by, as opposed to repelled by, the tertiary hydroxyl group. Gratifyingly, the use of triorganoaluminum reagents, prepared *in-situ* from the corresponding Grignard reagents and aluminum trichloride, proved effective for the desired conjugate addition (Scheme 5-14).[165] In this manner, vinylated product **5-53** was obtained in 63% yield as a single diastereomer.

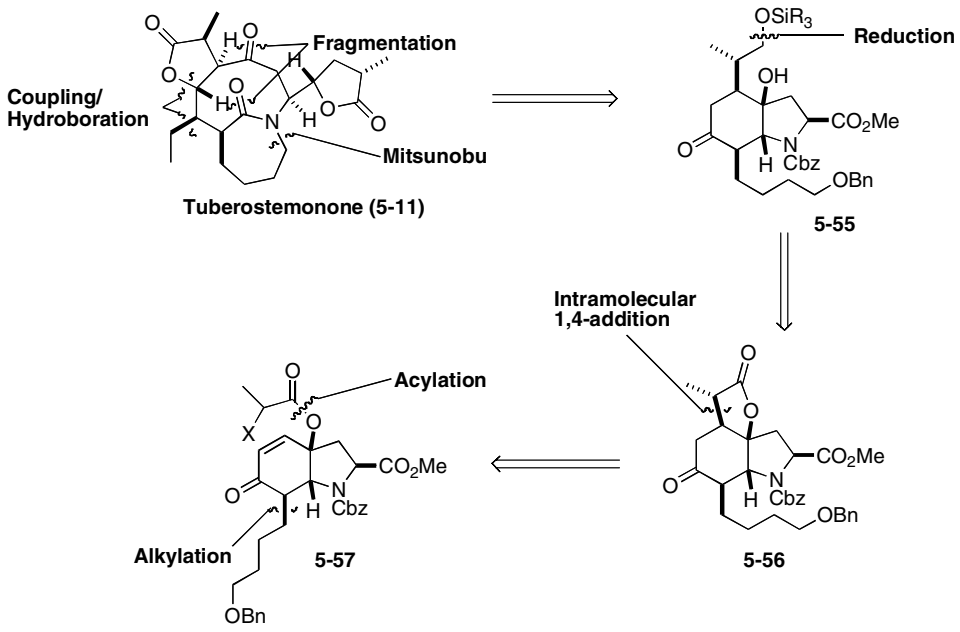


Scheme 5-14. Application of organoalane addition reaction to provide vinylated product.

Conversion of the alkene to the terminal primary alcohol was explored via hydroboration chemistry. Upon screening of a variety of hydroboration conditions, dicyclohexylborane was chosen as the most effective reagent in terms of both yield and chemoselectivity. Although promising, the low 24% yield over the hydroboration-oxidaton-silyl protection sequence and the inability to install the needed methyl group on this side chain in a selective manner led us to reconsider our overall synthetic strategy.

Having spent considerable effort exploring alkylation and conjugate addition, we became convinced that the tertiary alcohol moiety of the hydroindole was an essential directing element to install key stereocenters of tuberostemonone. Although previous attempts at functionalization of hydroindole **5-5** had been hindered by this tertiary alcohol,

we envisioned employing it not only to direct the palladium allylation previously discussed, but to also utilize it to direct an intramolecular 1,4-addition (Scheme 5-15). In

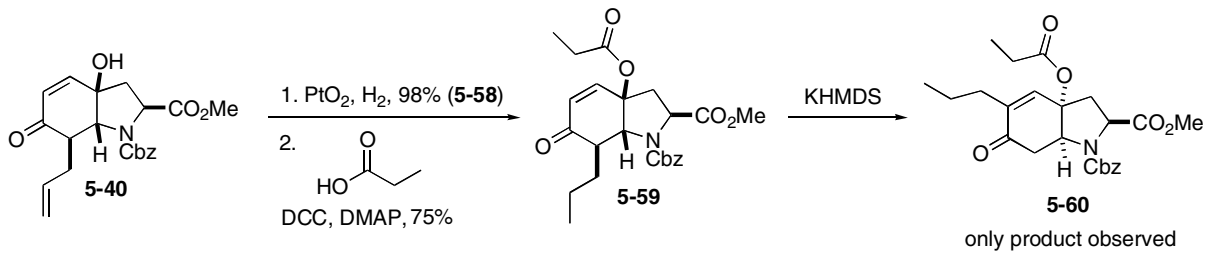


Scheme 5-15. Revised retrosynthesis: Tertiary alcohol as pivotal directing group.

this fashion we would target the installation of the newly formed carbon-carbon bond while hopefully also achieving the introduction of the neighboring methyl group early in the synthesis. This new retrosynthetic analysis provides, upon allylation and 1,4-addition, ketone **5-55** that serves as a versatile intermediate for addition of the remaining two stereocenters of the natural product's core.

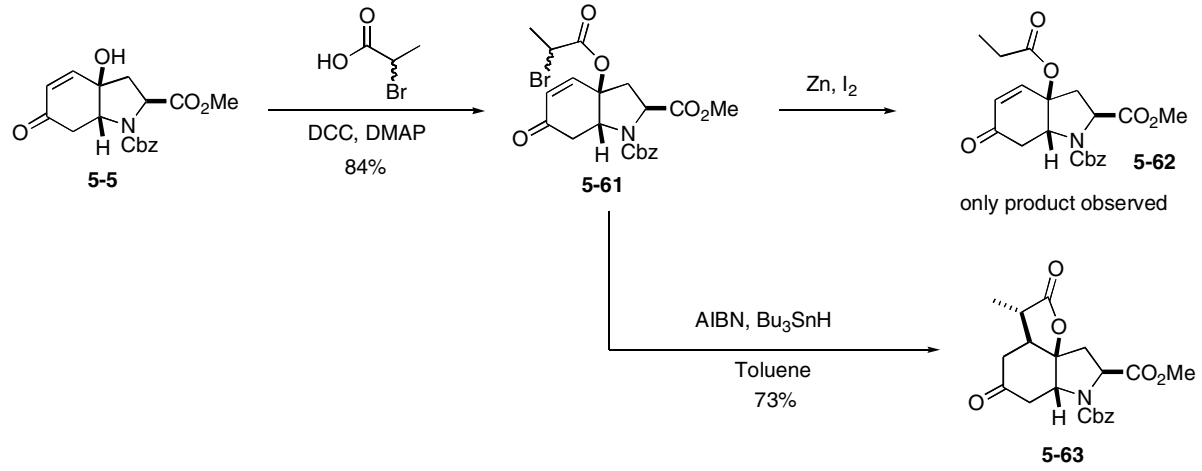
Initial attempts to explore the nature of intramolecular 1,4-additions of ester enolates focused on ester **5-59**, readily available by coupling alcohol **5-58** with propionic acid (Scheme 5-16). Upon treatment with KHMDS, **5-59** was converted to a new compound which unfortunately was found to be the elimination/carbamate addition

product **5-60**. This result is not surprising given the readiness of the potassium enolate to eliminate the carbamate moiety as was previously seen in the enolate alkylation studies.



Scheme 5-16. Initial attempts at an intramolecular Michael addition of **5-59**.

Requiring chemoselective deprotonation of the ester moiety, we turned our attention to the Reformatsky reaction.[166] The synthesis of α-bromo ester **5-61** was readily accomplished by coupling with 2-bromopropionic acid. Disappointingly, treatment of this ester with activated zinc only led to de-bromination products and none



Scheme 5-17. Utilization of α-bromo esters to install two stereocenters of tuberostemonone.

of the desired 1,4-addition. Already having access to **5-61**, attempts at employing an intramolecular radical addition into the enone were also explored. While radical additions of organohalide derived radicals to alkenes have a long history, the intramolecular addition of α-halo esters to enones by radical means has seen less study.[167] To our delight, treatment of **5-61** with tributyltin hydride and AIBN in toluene at 100 ˚C provided lactone **5-63** in 73% yield and as a single diastereomer. It is not clear at this time whether this exclusive product formation is due to selective decomposition of the undesired diastereomer or exclusive diastereoselectivity in the radical addition.

The stereochemical outcome of this transformation was confirmed through 2D NMR analysis (ROESY, Figure 5-5). Key correlations are between the α-methyl group, hydroindole methylene and α-methyl ester proton.

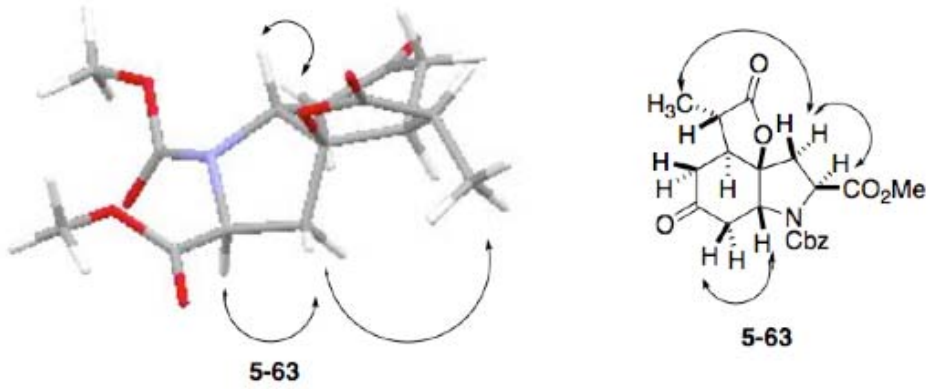
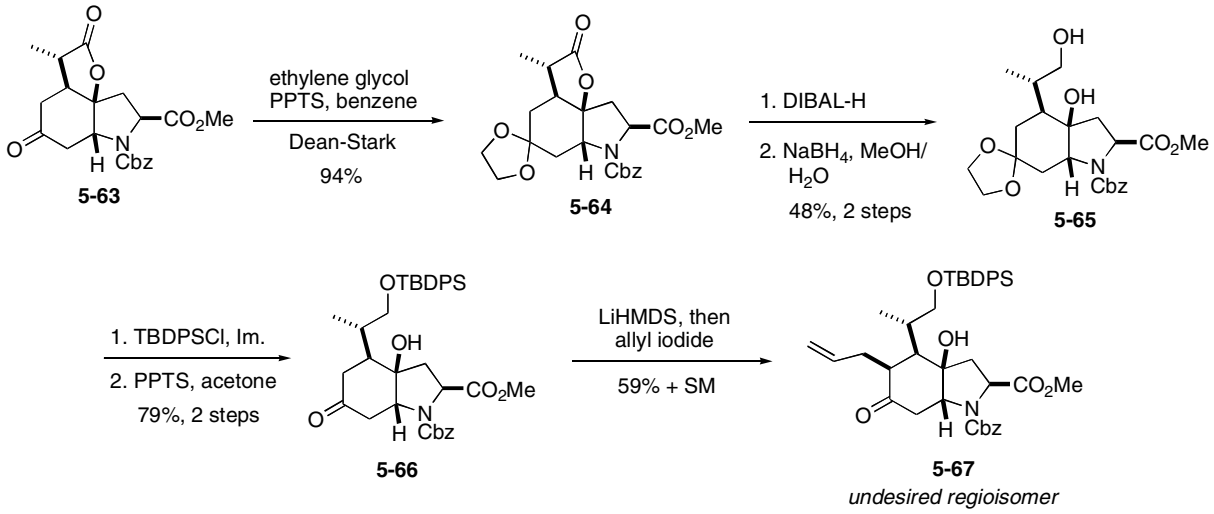


Figure 5-5. Key ROESY interactions to confirm stereochemical assignment of **5-63**. Methyl carbamate used on 3-D structure (left) for clarity.

With **5-63** in hand, we investigated the conversion of this compound to ketone **5-66**, which could serve as a useful intermediate in our synthesis after selective alkylation (Scheme 5-18). Protection of ketone **5-63** as its ketal with ethylene glycol, reduction of

the lactone to the primary alcohol, protection of the newly formed alcohol as a silyl ether and deprotection of the ketal provided ketone **5-66**. Previously studied alkylations of unsymmetrical ketones of this type by Wipf and Joo allowed us to postulate that the desired alkylation would occur.[168] Surprisingly, subjecting **5-66** to LiHMDS followed by allyl iodide led to exclusive formation of the undesired regioisomer **5-67** in 59% yield.



Scheme 5-18. Synthesis of ketone **5-66** and subsequent alkylation.

Confirmation of this selectivity was achieved by inspection of the ^{1}H NMR, which clearly showed a doublet of doublet for the proton next to the carbamate (Figure 5-6). Additionally, initial 2-D NMR studies (NOESY) showed a correlation between the allylic methylene and the β-proton next to the carbonyl. While the regioselectivity assignment is concrete, additional experiments are necessary to confidently assign the stereochemical outcome of this alkylation reaction.

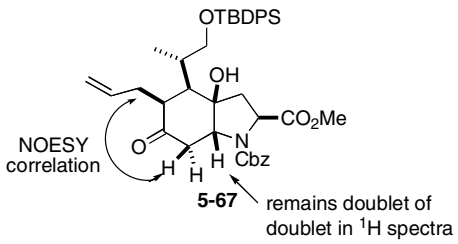
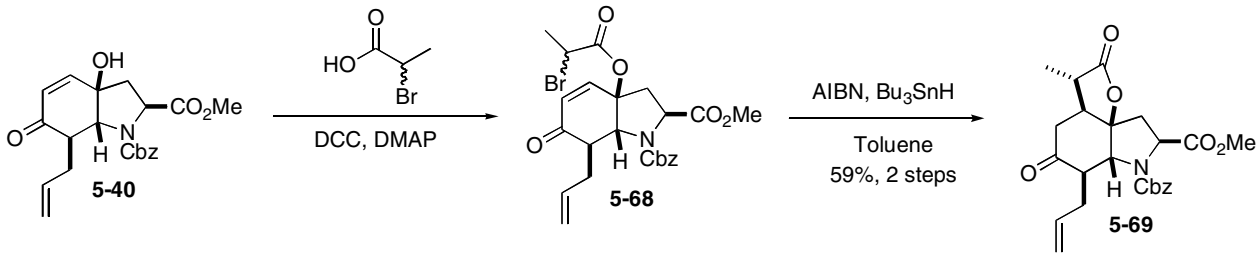


Figure 5-6. Tentative assignment of regio- and stereoselectivity in the alkylation reaction of **5-66**.

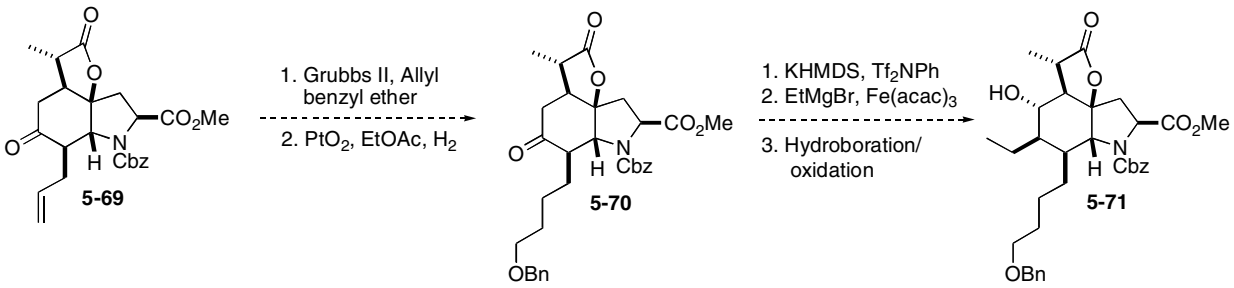
Having demonstrated the success of the radical chemistry on unsubstituted hydroindole **5-5**, we sought to apply this reaction to the allylated substrate **5-40** (Scheme 5-19). Acylation of the tertiary alcohol was efficient as before, providing α-bromo ester **5-68**. Subjection of **5-68** to the tributyltin / AIBN conditions led to formation of the desired lactone **5-69**, albeit in a lower 59% yield. This reaction provides, for the first time, access to the correct stereochemistry of several core stereocenters in tuberostemonone for application to the natural product.



Scheme 5-19. Successful installation of 4 of the 6 stereocenters in the core of tuberostemonone.

Upon further optimization of the radical reaction to produce **5-69**, extension of this ketone to tuberostemonone should be straightforward. Regioselective enol triflate formation, coupling and hydroboration[169] will install all of the stereocenters in the core of

5-11, while cross metathesis and reduction elaborates the allyl side chain for subsequent azapane formation (Scheme 5-20).



Scheme 5-20. Proposed installation of the remaining stereocenters of **5-11**.

5.3 CONCLUSION

Initial exploration in the synthesis of the hydroindoles for the synthesis of the *Stemona* alkaloids provided an unforeseen obstacle: deterioration of the enantiomeric excess of these compounds. During the optimization of this reaction we were able to not only achieve high enantiomeric excess for the desired products, but also improve the overall yield and technical ease of this reaction. Subsequently, we explored the synthesis of *L*-Choi derivatives and produced a small set of functionalized analogs.

The hydroindole intermediate also served as a key starting material for our approach toward tuberostemonone. Through the use of an intramolecular palladium allylation and stereoselective radical additions to enones we were able to construct the core of tuberostemonone that for the first time bears the correct stereochemistry of the natural product. Key to this success was the realization that the tertiary alcohol moiety could serve as a handle to install the stereocenters around the core of tuberostemonone,

including serving as the radical fragmentation origin for late-stage formation of the 9-membered lactam.

6.0 EXPERIMENTAL

6.1 GENERAL

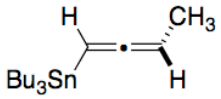
All reactions were performed under an N_2 atmosphere and all glassware was dried in an oven at 140 °C for 2 h prior to use. Reactions carried out at –78 °C employed a CO_2 / acetone bath. THF was distilled over sodium / benzophenone ketyl, Et_3N was distilled from CaH_2, and CH_2Cl_2 and toluene were purified using an alumina filtration system.

Reactions were monitored by TLC analysis (EM Science pre-coated silica gel 60 F_{254} plates, 250 μm layer thickness) and visualization was accomplished with a 254 nm UV light and by staining with a PMA solution (5 g of phosphomolybdic acid in 100 mL of 95% EtOH), *p*-anisaldehyde solution (2.5 mL of *p*-anisaldehyde, 2 mL of AcOH, and 3.5 mL of conc. H_2SO_4 in 100 mL of 95% EtOH), Vaughn's reagent (4.8 g of $(NH_4)_6Mo_7O_{24}\bullet 4\ H_2O$ and 0.2 g of $Ce(SO_4)_2$ in 100 mL of a 3.5 N H_2SO_4 solution) or a $KMnO_4$ solution (1.5 g of $KMnO_4$ and 1.5 g of K_2CO_3 in 100 mL of a 0.1% NaOH solution). Flash chromatography on SiO_2 was used to purify the crude reaction mixtures.

Melting points were determined using a Laboratory Devices Mel-Temp II. Infrared spectra were determined on a Nicolet Avatar 360 FT-IR spectrometer. ^1H and ^{13}C NMR spectra were obtained on a Bruker Avance 300 instrument in $CDCl_3$ unless otherwise noted. Chemical shifts were reported in parts per million with the residual

solvent peak used as an internal standard. ^{1}H NMR spectra were run at 300 MHz (unless otherwise noted) and are tabulated as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sept = septet, m = multiplet), number of protons, and coupling constant(s). ^{13}C NMR spectra were obtained at 76 MHz using a proton-decoupled pulse sequence with a d_1 of 3 sec, and are tabulated by observed peak. Mass spectra were obtained on a Micromass Autospec double focusing instrument.

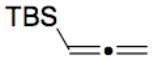
6.2 EXPERIMENTAL PROCEDURES



1-38

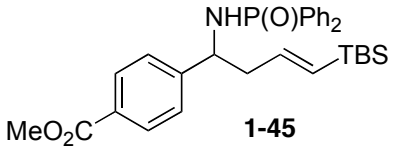
(*S*)-Buta-1,2-dienyltributylstannane (1-38).[170] To a solution of diisopropylamine (4.0 mL, 28.0 mmol) in THF (100 mL) was added 11.2 mL (28.0 mmol) of *n*-BuLi (2.5 M in hexanes) at 0 °C. After 30 min, tributyltin hydride (8.15 g, 28.0 mmol) was added dropwise and the mixture was stirred for an additional 30 min. The yellow solution was cooled to –78 °C and $CuBr{\cdot}SMe_2$ (5.76 g, 28.0 mmol) was added over 10 min. The dark solution was stirred for an additional 30 min and (*R*)-3-butyn-2-yl mesylate (4.47 g, 27.6 mmol) was added. The mixture was stirred for 15 min, and poured into a rapidly stirred solution of 9:1 sat. aq. NH_4Cl/NH_4OH (400 mL) solution and Et_2O (300 mL). Once the Et_2O layer clarified, it was separated, dried ($MgSO_4$), filtered, and concentrated under

reduced pressure. The crude oil was purified by bulb-to-bulb distillation (120 °C/ 0.5 mmHg) to yield 5.77 g (88%) of **1-38** as a yellow oil: ^{1}H NMR δ 5.12-4.87 (m, 1 H), 4.71–4.45 (m, 1 H), 1.70-0.80 (m, 30 H); ^{13}C NMR δ 209.0, 75.2, 74.3, 28.9, 27.2, 13.7, 10.3.



1-39

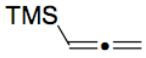
***Tert*-butyldimethyl(propa-1,2-dienyl)silane (1-39)**.[24a] A solution of triphenylphosphine (15.7 g, 60.0 mmol) in THF (120 mL) was treated at –15 °C with DIAD (11.3 mL, 57.5 mmol) over 2 min, followed by addition of 3-(*tert*-butyldimethylsilyl)-2-propyn-1-ol (8.52 g, 50.0 mmol) in THF (18 mL). After 2 min, a solution of *o*-nitrobenzenesulfonyl hydrazide (13.0 g, 60.0 mmol) in THF (65 mL) was added over 5 min via cannula. The resulting orange-red solution was stirred at –15 °C for 45 min and allowed to warm to rt for 5 h. The reaction mixture was diluted with of pentane (400 mL) and washed with ice-cold water (4 x 500 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* at 0 °C to avoid loss of product. The residue was purified by chromatography on SiO_2 (pentane) and the fractions containing the product were concentrated *in vacuo* at 0 °C to yield 5.39 g (70%) of **1-39** as a colorless oil: ^{1}H NMR δ 4.87 (app t, 1 H, J = 7.2 Hz), 4.32 (app d, 2 H, J = 7.2 Hz), 0.91 (s, 9 H), 0.07 (s, 6 H).



1-45

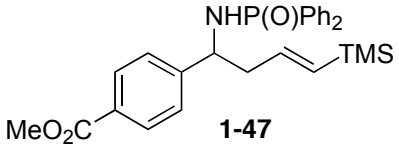
(*E*) - Methyl 4-[4-(*tert*-butyldimethylsilyl) – 1 - (diphenylphosphinamido) - but-3-enyl]benzoate (1-45). General Protocol A. A solution of allene **1-39 (**31.9 mg, 0.207 mmol) in CH_2Cl_2 (1 mL) was treated at –78 °C with Cp_2ZrHCl (53.4 mg, 0.207 mmol) and allowed to warm to room temperature over 20 min. After approximately 90% of the CH_2Cl_2 was removed under reduced pressure, toluene (1 mL) was added. The resulting red solution was cooled to –78 °C, and treated with Me_2Zn (104 μL, 0.207 mmol, 2.0 M in toluene) and imine **1-44 (**50.0 mg, 0.138 mmol). The reaction mixture was warmed to room temperature and stirred for 3 h, quenched with saturated aqueous $NaHCO_3$, extracted with EtOAc (3x), dried ($MgSO_4$), and concentrated *in vacuo*. Analysis of the crude reaction mixture by ^1H NMR showed one geometric isomer of the alkene. The residue was purified by chromatography on SiO_2 (7:3, EtOAc:hexanes) to yield 57.2 mg (80%) of **1-45** as a colorless solid: mp 114-115 °C (CH_2Cl_2); IR (KBr) 3167, 2951, 2854, 1723, 1611, 1437, 1279, 1187, 1110, 828, 725, 698 cm^{-1}; ^1H NMR (CD_2Cl_2) δ 7.93 (d, 2 H, *J* = 8.3 Hz), 7.89-7.70 (m, 4 H), 7.58-7.40 (m, 4 H), 7.40-7.30 (m, 2 H), 7.28 (d, 2 H, *J* = 8.3 Hz), 5.83 (dt, 1 H, *J* = 18.6, 6.4 Hz), 5.73 (d, 1 H, *J* = 18.6 Hz), 4.38 (tt, 1 H, *J* = 9.8, 6.5 Hz), 3.88 (s, 3 H), 3.50 (dd, 1 H, *J* = 9.4, 6.3 Hz), 2.81-2.95 (m, 2 H), 0.753 (s, 9 H), -0.046 (s, 3 H), -0.072 (s, 3 H); ^{13}C NMR (CD_2Cl_2) δ 167.13, 149.08, 143.02, 134.49, 134.18, 132.67, 132.55, 132.35, 129.95, 129.60, 129.08, 128.91, 128.71, 127.14, 54.79, 52.28, 47.16, 47.11, 26.55, 16.60, -5.91, -6.08; ESIMS *m/z* 542

([M+Na]$^+$, 100), 520 ([M+H]$^+$, 45); HRMS (ESI) *m/z* calcd for $C_{30}H_{38}NO_3PSiNa$ 542.2256 (M+Na), found 542.2283.



1-46

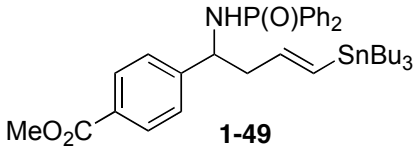
Trimethyl(propa-1,2-dienyl)silane (1-46).[24a] A solution of triphenylphosphine (15.7 g, 60.0 mmol) in THF (120 mL) was treated at –15 °C with DIAD (11.3 mL, 57.5 mmol) over 2 min followed by addition of 3-(trimethylsilyl)-2-propyn-1-ol (6.41 g, 50.0 mmol) in THF 18 mL. After 2 min, a solution of o-nitrobenzenesulfonyl hydrazide (13.0 g, 60.0 mmol) in THF 65 mL was added over 5 min via cannula. The resulting orange-red solution was stirred at –15 °C for 45 min and allowed to warm to rt for 5 h. The reaction mixture was diluted with pentane 400 mL and washed with ice-cold water (4 x 500 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* at 0 °C to avoid loss of product. The residue was purified by chromatography on SiO_2 (pentane) and the fractions containing the product were concentrated *in vacuo* at 0 °C to yield 2.97 g (53%) of **1-46** as a colorless oil: ^{1}H NMR δ 4.87 (app t, 1 H, J = 7.1 Hz), 4.32 (app d, 2 H, J = 7.1 Hz), 0.07 (s, 9 H).



1-47

(*E*) - Methyl 4 - [1 - (diphenylphosphinamido) – 4 - (trimethylsilyl) but – 3 - enyl] benzoate (1-47). According to the General Protocol A, allene **1-46 (**23.2 mg, 0.207 mmol), Cp_2ZrHCl (53.4 mg, 0.207 mmol), Me_2Zn (104 μL, 0.207 mmol, 2.0 M in

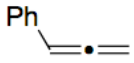
toluene), and imine **1-44** (50.0 mg, 0.138 mmol) afforded 51.6 mg (78%) of **1-47** as a colorless solid: mp 147-148 °C (CH_2Cl_2); IR (KBr) 3169, 2952, 1721, 1611, 1437, 1280, 1186, 1110, 838, 697 cm^{-1}; ^1H NMR (CD_2Cl_2) δ 7.93 (d, 2 H, J = 8.3 Hz), 7.88-7.70 (m, 4 H), 7.58-7.41 (m, 4 H), 7.40-7.30 (m, 2 H), 7.28 (d, 2 H, J = 8.3 Hz), 5.87 (dt, 1 H, J = 18.5, 6.3 Hz), 5.75 (d, 1 H, J = 18.6 Hz), 4.34 (tt, 1 H, J = 9.4, 6.5 Hz), 3.88 (s, 3 H), 4.46 (dd, 1 H, J = 9.4, 6.8 Hz), 2.73-2.56 (m, 2 H), 0.00 (s, 9 H); ^{13}C NMR (CD_2Cl_2) δ 166.59, 148.70, 141.35, 135.66, 133.97, 133.67, 132.11, 131.99, 131.84, 131.72, 129.38, 129.02, 128.52, 128.35, 128.18, 126.54, 54.34, 51.76, 46.55, 46.48, -1.80; ESIMS *m/z* 500 ($[M+Na]^+$, 100), 478 ($[M+H]^+$, 33); HRMS (ESI) *m/z* calcd for $C_{27}H_{32}NO_3PSiNa$ 500.1787 (M+Na), found 500.1778.



1-49

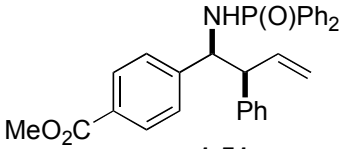
(*E*)-Methyl 4 - [1 - (diphenylphosphinamido) – 4 - (tributylstannyl) but – 3 - enyl] benzoate (1-49). According to the General Protocol A, allene **1-48 (**68.1 mg, 0.207 mmol), Cp_2ZrHCl (53.4 mg, 0.207 mmol), Me_2Zn (104 μL, 0.207 mmol, 2.0 M in toluene), and imine **1-44** (50.0 mg, 0.138 mmol) afforded 77.6 mg (81%) of **1-49** as a colorless solid: mp 63-64 °C (CH_2Cl_2); IR (KBr) 3168, 2955, 2925, 2871, 2852, 1723, 1437, 1278, 1186, 1109, 696 cm^{-1}; ^1H NMR δ 7.98 (d, 2 H, J = 8.3 Hz), 7.95-7.73 (m, 4 H), 7.58-7.41 (m, 4 H), 7.38-7.26 (m, 2 H), 7.28 (d, 2 H, J = 7.3 Hz), 6.04 (d, 1 H, $^2J_{H\text{-}Sn}$ = 74.0, $J_{H\text{-}H}$ = 16.5 Hz), 5.64 (dt, 1 H, J = 18.8, 7.4 Hz), 4.53-4.41 (m, 1 H), 3.92 (s, 3 H), 3.49 (dd, 1 H, J = 9.6, 5.8 Hz), 2.90-2.65 (m, 2 H), 1.56-1.17 (m, 12 H), 0.97-0.70 (m, 15 H); ^{13}C NMR δ 166.87, 148.46, 142.92, 134.80, 133.12, 132.42, 132.29, 131.83, 131.39,

129.64, 128.98, 128.62, 128.45, 128.24, 126.65, 54.13, 51.95, 47.55, 47.50, 29.03, 27.16, 13.56, 9.49; ESIMS *m/z* 718 ([M+Na]$^+$, 85), 696 ([M+H]$^+$, 100); HRMS (ESI) *m/z* calcd for $C_{36}H_{50}NO_3PSnNa$ 718.2448 (M+Na), found 718.2469.



1-50

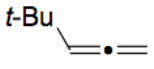
Propa-1,2-dienylbenzene (1-50).[24b] To a solution of propargyl bromide (5.02 g, 42.1 mmol) and copper(I) bromide (7.20 g, 50.0 mmol) in THF 100 mL at –40 °C was added phenylmagnesium bromide (16.7 mL, 50.0 mmol, 3.0 M in Et_2O) over 15 min. The reaction mixture was stirred at 0 °C for 1 h, and poured into an separatory funnel containing ice-cold 3 N HCl (1 L) and xylenes (250 mL). The organic layer was washed with 3 N HCl (5 x 50 mL) and dried ($MgSO_4$). The volatile product was isolated by distillation (distillation at 80 °C, 30 mmHg; receiving flask at –78 °C) to yield 3.42 g (70%) of **1-50** as a colorless oil: ^{1}H NMR δ 7.46 – 7.18 (m, 5 H), 6.18 (app t, 1 H, J = 6.8 Hz), 5.16 (app d, 2 H, J = 6.8 Hz).



1-51

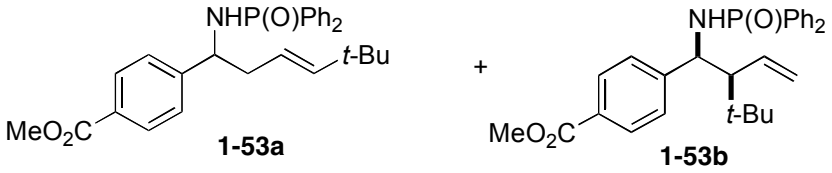
Methyl 4-[(1*S,2*S**)-1-(diphenylphosphinamido)-2-phenylbut-3-enyl]benzoate (1-51).** According to the General Protocol A, allene **1-50** (24.0 mg, 0.207 mmol), Cp_2ZrHCl (53.4 mg, 0.207 mmol), Me_2Zn (104 μL, 0.207 mmol, 2.0 M in toluene), and imine **1-44** (50.0 mg, 0.138 mmol) (1.5 h reaction time) afforded 55.1 mg (83%) of **1-51**

as a colorless solid: mp 192-193 °C (CH_2Cl_2); IR (KBr) 3176, 3059, 2924, 2854, 1721, 1437, 1281, 1184, 1109, 698 cm^{-1}; ^1H NMR δ 7.88 (d, 2 H, *J* = 8.3 Hz), 7.70-7.56 (m, 4 H), 7.55-7.47 (m, 1 H), 7.46-7.37 (m, 3 H), 7.34-7.23 (m, 5 H), 7.08-7.02 (m, 2 H), 6.98 (d, 2 H, *J* = 8.4 Hz), 6.01 (dt, 1 H, *J* = 19.6, 10.2 Hz), 5.18 (d, 1 H, *J* = 10.2 Hz), 5.15 (d, 1 H, *J* = 17.4 Hz), 4.56 (ddd, 1 H, *J* = 9.8, 6.3 Hz), 3.94 (s, 3 H), 3.85 (dd, 1 H, *J* = 9.1, 6.3 Hz), 3.54 (dd, 1 H, *J* = 9.7, 6.2 Hz); ^{13}C NMR δ 166.90, 146.23, 139.91, 136.15, 133.70, 132.97, 132.39, 132.26, 131.73, 131.60, 129.11, 128.60, 128.37, 128.28, 128.11, 127.72, 127.12, 118.83, 59.36, 57.95, 57.89, 51.95; ESIMS *m/z* 504 ($[M+Na]^+$, 100), 482 ($[M+H]^+$, 98); HRMS (ESI) *m/z* calcd for $C_{30}H_{28}NO_3PNa$ 504.1705 (M+Na), found 504.1703.



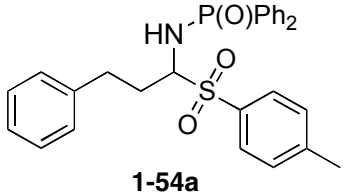
1-52

4,4-Dimethylpenta-1,2-diene (1-52).[24b] To a solution of propargyl bromide (5.00 g, 42.0 mmol) and copper(I) bromide (7.20 g, 50.0 mmol) in THF (100 mL) at –40 °C was added *tert*-butylmagnesium chloride (25.0 mL, 50.0 mmol, 2.0 M in Et_2O) over 15 minutes. The reaction mixture was stirred at 0 °C for 1 h, and poured into a separatory funnel containing ice-cold 3 N HCl (1 L) and xylenes (250 mL). The organic layer was washed with 3 N HCl (5 x 50 mL) and dried ($MgSO_4$). The volatile product was isolated by distillation (20 – 30 mmHg, receiving flask at –78 °C) to yield 2.62 g (65%) of **1-52** as a colorless oil: bp 79 °C (30 mmHg); ^1H NMR δ 5.12 (app t, 1 H, *J* = 6.7 Hz), 4.72 (app d, 2 H, *J* = 6.6 Hz), 1.06 (s, 9 H).



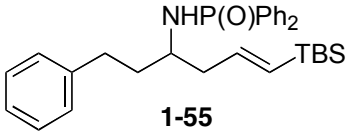
(*E*)-Methyl 4 - [1-(diphenylphosphinamido) - 5,5-dimethylhex-3-enyl]benzoate (1-53a) and methyl 4-[(1*S,2*S**)-2-*tert*-butyl-1-(diphenylphosphinamido)but-3-enyl]benzoate (1-53b).** According to the General Protocol A, allene **1-52 (**19.9 mg, 0.207 mmol), Cp_2ZrHCl (53.4 mg, 0.207 mmol), Me_2Zn (104 μL, 0.207 mmol, 2.0 M in toluene), and imine **1-44** (50.0 mg, 0.138 mmol) (12 h reaction time) afforded 40.6 mg (64%) of a 1.5:1 mixture of **1-53a**:**1-53b** (determined by analysis of the crude reaction mixture): IR (KBr) 3183, 3058, 2954, 1721, 1611, 1437, 1280, 1190, 1109, 1019, 972, 914, 725, 698 cm^{-1}; ^1H NMR δ 7.96-7.71 (m, 6 H), 7.55-7.37 (m, 4 H), 7.34-7.25 (m, 3.2 H), 7.12 (d, 0.8 H, *J* = 8.3 Hz), 5.87 (dt, 0.4 H, *J* = 16.9, 10.5 Hz), 5.53 (d, 0.6 H, *J* = 15.6 Hz), 5.39 (dd, 0.4 H, *J* = 10.4, 2.2 Hz), 5.36 (dd, 0.4 H, *J* = 16.6, 2.2 Hz), 5.09 (dt, 0.6 H, *J* = 15.7, 7.0 Hz), 4.54 (dt, 0.4 H, *J* = 10.8, 3.6 Hz), 4.38 (tt, 0.6 H, *J* = 10.0, 6.4 Hz), 3.93 (s, 1.2 H), 3.92 (s, 1.8 H), 3.75 (dd, 0.4 H, *J* = 10.4, 7.1 Hz), 3.47-3.37 (m, 0.6 H), 2.65-2.53 (m, 1.2 H), 2.47 (dd, 0.4 H, *J* = 11.2, 4.0 Hz), 0.91 (s, 5.6 H), 0.70 (s, 3.4 H); ^{13}C NMR δ 166.91, 166.84, 148.62, 148.55, 147.86, 147.74, 146.99, 134.85, 133.85, 133.58, 132.80, 132.64, 132.55, 132.42, 132.37, 132.24, 132.16, 131.90, 131.86, 131.80, 131.74, 131.62, 131.51, 131.07, 130.91, 130.15, 130.02, 129.54, 129.25, 128.78, 128.72, 128.57, 128.40, 128.36, 128.22, 128.19, 128.06, 126.53, 120.96, 118.76, 62.85, 62.81, 54.41, 53.93, 52.06, 52.03, 42.46, 42.39, 33.10, 32.65, 31.54, 30.89, 29.47, 29.25, 28.19, 25.22,

22.65, 22.61, 14.09; EIMS *m/z* 430 ([M-OCH_3]$^+$, 20), 364 (95), 201 (100); HRMS (EI) *m/z* calcd for $C_{27}H_{29}NO_2P$ 430.1936 (M-OCH_3), found 430.1920.



1-54a

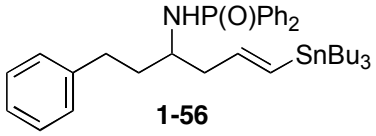
***P*,*P*-Diphenyl-*N*-(3-phenyl-1-tosylpropyl)phosphinic amide (1-54a).**[25] To a solution of *P*,*P*-diphenylphosphinic amide (1.00 g, 4.60 mmol) and sulfinic acid (1.08 g, 6.90 mmol) in Et_2O was added hydrocinnamaldehyde (926 mg, 0.910 mmol) and the resulting suspension was stirred for 15 h at rt. The white precipitate was filtered, washed with anhydrous Et_2O, and dried under reduced pressure to yield 1.40 g (91%) of **1-54a** as a colorless solid. ^{1}H NMR δ 7.92–7.80 (m, 2 H), 7.74–7.62 (m, 2 H), 7.60–7.41 (m, 6 H), 7.37–7.10 (m, 9 H), 4.51–4.20 (m, 1 H), 3.62–3.40 (m, 1 H), 3.12–2.97 (m, 1 H), 2.97–2.80 (m, 1 H), 2.68 (s, 3 H), 2.21 – 2.08 (m, 1 H), 1.62–1.50 (m, 1 H); HRMS (ESI) *m/z* calcd for $C_{28}H_{28}NO_3PSNa$ 512.1425 (M+Na), found 512.1434.



1-55

(*E*) - *N*- [6-(*tert*-Butyldimethylsilyl)-1-phenylhex-5-en-3-yl]-*P*,*P*-diphenyl phosphinamide (1-55). General Protocol B. A solution of allene **1-39** (23.2 mg, 0.207 mmol) in CH_2Cl_2 (1 mL) was treated at –78 °C with Cp_2ZrHCl (53.4 mg, 0.207 mmol) and allowed to warm to room temperature over 20 min. After approximately 90% of the CH_2Cl_2 was removed under reduced pressure, toluene (1 mL) was added. The resulting

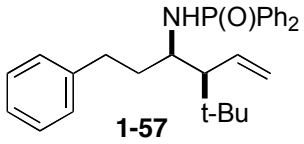
red solution was cooled to –78 °C, treated with Me_2Zn (173 μL, 0.345 mmol, 2.0 M in toluene) and sulfinyl adduct **1-54a (**67.6 mg, 0.138 mmol), and allowed to stir at –78 °C for 15 min. The reaction mixture was then warmed to room temperature and stirred for an additional 3 h, quenched with saturated aqueous $NaHCO_3$, extracted with EtOAc (3x), dried ($MgSO_4$), and concentrated *in vacuo*. Analysis of the crude reaction mixture by ^1H NMR showed one geometric isomer of the alkene. The residue was purified by chromatography on SiO_2 (6:4, EtOAc:hexanes) to yield 53.3 mg (79%) of **1-55** as a colorless solid: mp 109-110 °C (CH_2Cl_2); IR (KBr) 3180, 2926, 2854, 1438, 1186, 1122, 828, 697 cm^{-1}; ^1H NMR δ 8.02-7.85 (m, 4 H), 7.60-7.41 (m, 6 H), 7.32-7.21 (m, 2 H), 7.21-7.11 (m, 3 H), 6.05 (dt, 1 H, *J* = 18.5, 7.1 Hz), 5.83 (d, 1 H, *J* = 18.5 Hz), 3.38-3.20 (m, 1 H), 2.87 (dd, 1 H, *J* = 10.3, 6.3 Hz), 2.81-2.61 (m, 2 H), 2.61-2.41 (m, 2 H), 1.96-1.84 (m, 2 H), 0.81 (s, 9 H), 0.46 (s, 6 H); ^{13}C NMR δ 143.46, 141.82, 134.32, 134.10, 132.40, 132.26, 132.21, 132.17, 132.12, 132.04, 131.67, 131.64, 128.53, 128.36, 125.79, 50.83, 44.27, 44.21, 38.23, 38.17, 32.03, 26.44, 16.37, -5.98, -6.08; EIMS *m/z* 490 ($[M+H]^+$, 3), 432 (100), 335 (75), 201 (52); HRMS (EI) *m/z* calcd for $C_{30}H_{40}NOPSi$ 489.2617, found 489.2626.



1-56

(*E*) - *P*,*P* – Diphenyl – *N* - [1 – phenyl – 6 - (tributylstannyl) hex – 5 – en – 3 - yl]phosphinamide (1-56). According to the General Protocol B, allene **1-48** (68.1 mg, 0.207 mmol), Cp_2ZrHCl (53.4 mg, 0.207 mmol), Me_2Zn (173 μL, 0.345 mmol, 2.0 M in toluene), and sulfinyl adduct **1-54a** (67.6 mg, 0.138 mmol) afforded 72.1 mg (79%) of **1-**

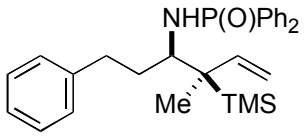
56 as a colorless solid: mp 57.9-58.4 °C (CH_2Cl_2); IR (KBr) 3183, 3059, 2925, 1438, 1376, 1190, 1122, 991, 723, 698 cm^{-1}; ^1H NMR δ 8.00-7.82 (m, 4 H), 7.58-7.40 (m, 6 H), 7.29-7.20 (m, 2 H), 7.20-7.09 (m, 3 H), 6.09 (d, 1 H, J_{H-H} = 18.8, $^2J_{H-Sn}$ = 75.0 Hz), 5.92 (dt, 1 H, *J* = 18.6, 6.6 Hz), 3.35-3.19 (m, 1 H), 2.88 (dd, 1 H, *J* = 10.6, 6.3 Hz), 2.82-2.61 (m, 2 H), 2.60-2.39 (m, 2 H), 1.95-1.82 (m, 2 H), 1.71-1.22 (m, 12 H), 1.10-0.75 (m, 15 H); ^{13}C NMR δ 144.15, 141.85, 134.11, 133.94, 133.24, 132.20, 132.12, 132.00, 131.67, 128.49, 128.32, 125.73, 50.65, 45.02, 44.97, 38.05, 37.99, 32.04, 29.10, 27.20, 13.61, 9.46; ESI *m/z* 672 ($[M+Li]^+$, 45), 666 ($[M+H]^+$, 100); HRMS (ESI) *m/z* calcd for $C_{36}H_{52}NOPSnLi$ 672.2969 (M+Li), found 672.2968.



1-57

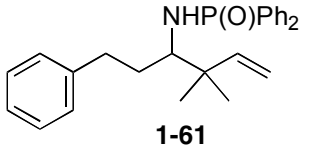
***N* - [(3*R**,4*S**) - 4-*tert* – Butyl – 1 – phenylhex – 5 – en – 3 - yl] - *P*,*P* - diphenyl phosphinamide (1-57).** According to the General Protocol B, allene **1-52 (**19.1 mg, 0.207 mmol), Cp_2ZrHCl (53.4 mg, 0.207 mmol), Me_2Zn (173 µL, 0.345 mmol, 2.0 M in toluene), and sulfinyl adduct **1-54a** (67.6 mg, 0.138 mmol) afforded 47.5 mg (80%) of **1-57** as a colorless solid: mp 109-110 °C (CH_2Cl_2); IR (KBr) 3216, 3060, 2960, 1438, 1365, 1198, 1122, 1057, 918, 725, 699 cm^{-1}; ^1H NMR δ 8.04-7.92 (m, 4 H), 7.55-7.41 (m, 6 H), 7.30-7.21 (m, 2 H), 7.21-7.13 (m, 3 H), 5.74 (dt, 1 H, *J* = 16.9, 10.4 Hz), 5.23 (dd, 1 H, *J* = 16.9, 2.5 Hz), 5.21 (dd, 1 H, 10.1, 2.5 Hz), 3.32 (q, 1 H, *J* = 10.8 Hz), 3.10-2.95 (m, 2 H), 2.63-2.51 (m, 1 H), 2.23 (dd, 1 H, *J* = 10.7, 1.7 Hz), 2.0-1.8 (m, 1 H), 1.56-1.40 (m, 1 H), 0.70 (s, 9 H); ^{13}C NMR δ 142.51, 135.48, 132.47, 132.36, 131.85, 128.74, 128.60, 128.41, 125.84, 119.48, 62.15, 51.62, 36.83, 36.62, 33.29, 32.49, 28.73; EIMS *m/z* 374

([M-C_3H_9]$^+$, 4), 335 (80), 201 (65); HRMS (EI) *m/z* calcd for $C_{24}H_{25}NOP$ 374.1674 (M-C_3H_9), found 374.1665.



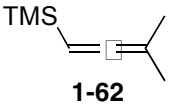
1-59

***N* - [(3*R**,4*S**) – 4 – Methyl – 1 – phenyl – 4 - (trimethylsilyl) hex – 5 – en – 3 - yl] - *P*,*P*-diphenylphosphinamide (1-59).** According to the General Protocol B, allene **1-58 (**26.1 mg, 0.207 mmol), Cp_2ZrHCl (53.4 mg, 0.207 mmol), Me_2Zn (173 μL, 0.345 mmol, 2.0 M in toluene), and of sulfinyl adduct **1-54a** (67.6 mg, 0.138 mmol) afforded 51.8 mg (81%) of **1-59** as a colorless solid: mp 155-156 °C (CH_2Cl_2); IR (KBr) 3230, 3058, 2954, 1619, 1437, 1248, 1190, 1122, 1108, 838, 697 cm^{-1}; ^1H NMR δ 8.10-7.82 (m, 4 H), 7.60-7.42 (m, 6 H), 7.31-7.22 (m, 2 H), 7.21-7.10 (m, 3 H), 6.04 (dd, 1 H, *J* = 17.2, 10.7 Hz), 5.19 (dd, 1 H, *J* = 10.7, 1.2 Hz), 4.99 (dd, 1 H, *J* = 17.2, 1.4 Hz), 3.24 (q, 1 H, *J* = 8.6 Hz), 2.99 (ddd, 1 H, *J* = 11.8, 4.8, 1.8 Hz), 2.80 (t, 1 H, *J* = 9.5 Hz), 2.50 (ddd, 1 H, *J* = 11.4, 5.8, 2.1 Hz), 2.15-1.98 (m, 1 H), 1.9-1.7 (m, 1 H), 1.10 (s, 3 H), -0.02 (s, 9 H); ^{13}C NMR δ 142.33, 139.38, 131.94, 131.49, 128.30, 128.13, 125.50, 114.58, 57.64, 38.72, 38.10, 33.67, 17.57, -2.50; EIMS *m/z* 461 ([M]$^+$, 10), 356 (75), 201 (95); HRMS (EI) *m/z* calcd for $C_{28}H_{36}NOPSi$ 461.2304, found 461.2284.



1-61

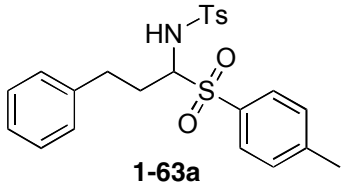
***N* - (4,4-Dimethyl-1-phenylhex-5-en-3-yl) - *P,P* - diphenylphosphinamide (1-61).** According to the General Protocol B, allene **1-60 (**14.1 mg, 0.207 mmol), Cp_2ZrHCl (53.4 mg, 0.207 mmol), Me_2Zn (173 μL, 0.345 mmol, 2.0 M in toluene), and sulfinyl adduct **1-54a** (67.6 mg, 0.138 mmol) afforded 42.0 mg (76%) of **1-61** as a colorless solid: mp 173-174 °C (CH_2Cl_2); IR (KBr) 3207, 3058, 2962, 1437, 1185, 1122, 985, 910, 721, 697 cm^{-1}; ^1H NMR δ 8.00-7.82 (m, 4 H), 7.58-7.40 (m, 6 H), 7.29-7.21 (m, 2 H), 7.20-7.07 (m, 3 H), 5.77 (dd, 1 H, *J* = 17.3, 10.9 Hz), 5.05 (d, 1 H, 10.8 Hz), 5.02 (d, 1 H, *J* = 17.7 Hz), 3.00-2.82 (m, 2 H), 2.79-2.68 (m, 1 H), 2.55-2.42 (m, 1 H), 2.10-1.92 (m, 1 H), 1.65-1.42 (m, 1 H), 1.04 (s, 3 H), 1.01 (s, 3 H); ^{13}C NMR δ 145.00, 142.37, 132.31, 132.26, 132.18, 132.14, 131.78, 131.74, 131.66, 131.62, 130.85, 128.53, 128.44, 128.38, 128.21, 125.63, 113.38, 59.73, 41.98, 41.91, 36.09, 33.64, 25.44, 23.27; EIMS *m/z* 403 (M^+, 20), 334 (100), 201 (100); HRMS (EI) *m/z* calcd for $C_{26}H_{30}NOP$ 403.2065, found 403.2050.



1-62

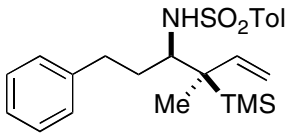
Trimethyl (3-methylbuta - 1,2-dienyl) silane (1-62).[171] A solution of methyllithium (4.00 mL, 1.84 M), 1,1-dimethylallene (1.00 g, 14.7 mmol), and diisopropylamine (20.0 μL, 0.143 μmol) in Et_2O (10 mL) was cooled to -78 °C and trimethylchlorosilane (0.88 g, 8.10 mmol) in 1 mL of ether was added dropwise. The mixture was warmed to rt and stirred for 30 min, and quenched with H_2O. The organic

layer was separated and solvents were removed by distillation using a Vigreux column. The residue was purified by distillation (bp 63-65 °C, 82 mmHg) to yield 0.86 g (66%) of **1-62** as a yellow oil: ^{1}H NMR δ 4.77 (sept, 1 H, *J* = 3.7 Hz), 1.66 (d, 6 H, *J* = 3.7 Hz), 0.07 (s, 9 H).



1-63a

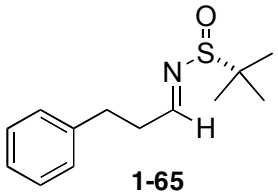
4-methyl-*N*-(3-phenyl-1-tosylpropyl)benzenesulfonamide (1-63a).[57] A solution of hydrocinnamaldehyde (2.68 g, 2.63 mmol), *p*-tolunesulfonamide (3.42 g, 20.0 mmol), *p*-toluenesulfinate (3.57 g, 20.0 mmol) and formic acid (30 mL) in water (30 mL) was stirred at rt for 24 h, filtered, washed with water (30 mL) and pentane (10 mL) and dried under reduced pressure to yield 7.36 g (83%) of **1-63a** as a colorless solid. ^{1}H NMR δ 7.70 (d, 2 H, *J* = 8.2 Hz), 7.55 (d, 2 H, *J* = 8.3 Hz), 7.35–7.15 (m, 7 H), 7.06–7.00 (m, 2 H), 5.74 (d, 1 H, *J* = 10.3 Hz), 4.60 (dt, 1 H, *J* = 9.4, 4.2 Hz), 2.69–2.47 (m, 3 H), 2.44 (s, 3 H), 2.41 (s, 3 H), 2.04–1.89 (m, 1 H).



1-64

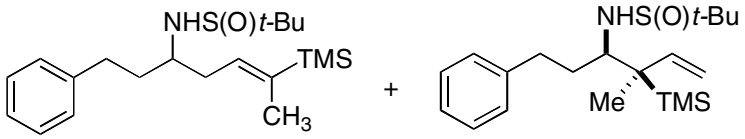
4 - Methyl – *N* - [(3*R,4*R**) – 4 – methyl – 1 – phenyl – 4 - (trimethylsilyl) hex-5-en-3-yl] benzenesulfonamide (1-64).** A solution of allene **1-58** (210 mg, 1.65 mmol) in CH_2Cl_2 (5 mL) was treated at –78 °C with Cp_2ZrHCl (425 mg, 1.65 mmol) and allowed to warm to room temperature over 20 min. After approximately 90% of the CH_2Cl_2 was

removed under reduced pressure, toluene (5 mL) was added. The resulting red solution was cooled to –78 °C, treated with Et_2Zn (2.47 mL, 2.47 mmol, 1.0 M in hexane) and sulfinyl adduct **1-63a (**500 mg, 1.10 mmol), and allowed to stir at –78 °C for 15 min. The reaction mixture was then warmed to room temperature and stirred for an additional 3 h, quenched with saturated aqueous $NaHCO_3$, extracted with EtOAc (3x), dried ($MgSO_4$), and concentrated *in vacuo*. Analysis of the crude reaction mixture by ^{1}H NMR showed one diastereomer. The residue was purified by chromatography on SiO_2 (6:4, EtOAc:hexanes) to yield 401 mg (85%) of **1-64** as a colorless solid: mp 131.2-132.4 °C (CH_2Cl_2); IR (KBr) 3286, 3027, 2953, 1496, 1323, 1157, 840 cm^{-1}; ^{1}H NMR δ 7.84-7.75 (m, 2 H), 7.35-7.21 (m, 4 H), 7.21-7.13 (m, 1 H), 7.03-6.96 (m, 2 H), 5.89 (dd, 1 H, *J* = 17.2, 10.7 Hz), 5.14 (dd, 1 H, *J* = 10.7, 1.3 Hz), 4.89 (dd, 1 H, *J* = 17.2, 1.4 Hz), 4.31 (d, 1 H, *J* = 9.3 Hz), 3.56 (dt, 1 H, *J* = 9.5, 2.7 Hz), 2.58-2.43 (m, 2 H), 2.43 (s, 3 H), 1.95-1.84 (m, 1 H), 1.73-1.58 (m, 1 H), 0.88 (s, 3 H), 0.01 (s, 9 H); ^{13}C NMR δ 142.83, 141.78, 139.44, 138.81, 129.40, 128.20, 128.16, 128.12, 126.74, 125.68, 114.76, 60.51, 37.28, 36.65, 33.57, 21.36, 16.56, -2.67; ESIMS *m/z* 438 ([M+Na]$^+$, 100); HRMS (ESI) *m/z* calcd for $C_{23}H_{33}NO_2SSiNa$ (M+Na) 438.1899, found 438.1891.



1-65

(*R*,*E*)-2-Methyl-*N*-(3-phenylpropylidene)propane-2-sulfinamide (1-65).[172] To a solution of hydrocinnamaldehyde (255 mg, 1.90 mmol) in CH_2Cl_2 (10 mL) was added *tert*-butanesulfinamide (200 mg, 1.65 mmol), $MgSO_4$ (993 mg, 8.25 mmol) and PPTS (41.5 mg, 0.165 mmol). The suspension was stirred at rt for 12 h, filtered through a pad of Celite®, concentrated and purified by chromatography on SiO_2 (7:3, EtOAc:hexanes) to yield 3.13 g (80%) of **1-65** as a yellow oil. ^{1}H NMR δ 8.12 (t, 1 H, J = 4.3 Hz), 7.38–7.10 (m, 5 H), 3.03–2.94 (m, 2 H), 2.92–2.83 (m, 2 H), 1.39 (s, 9 H).



1-66a **1-66b**

(*E*) – 2 – Methyl – *N* - (1-phenyl – 6 - (trimethylsilyl) hept – 5 – en – 3 - yl) propane – 2 - sulfinamide (1-66a) and 2-methyl-*N*-((3*R,4*R**)-4-methyl-1-phenyl-4-(trimethylsilyl)-hex-5-en-3-yl)propane-2-sulfinamide (1-66b).** A solution of allene **1-58** (222 mg, 1.75 mmol) in CH_2Cl_2 (6 mL) was treated at –78 °C with Cp_2ZrHCl (450 mg, 1.75 mmol) and allowed to warm to room temperature over 20 min. After approximately 90% of the CH_2Cl_2 was removed under reduced pressure, toluene (6 mL) was added. The resulting red solution was cooled to –78 °C, treated with Et_2Zn (1.75 mL, 1.75 mmol, 1.0 M in hexane) and imine **1-65** (312 mg, 1.31 mmol) in toluene (6 mL), and allowed to stir at –78 °C for 15 min. The reaction mixture was then warmed to room temperature and

stirred for an additional 3 h, quenched with saturated aqueous $NaHCO_3$, extracted with EtOAc (3x), dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (1:4, EtOAc:hexanes to 1:2 EtOAc:hexanes) to yield 167 mg (36%) of **1-66a** and 221 mg (45%) of **1-66b** as colorless oils. **1-66a**: IR (neat) 3213, 3026, 2953, 1618, 1496, 1247, 1055, 836 cm^{-1}; ^1H NMR δ 7.35-7.25 (m, 2 H), 7.24-7.15 (m, 3 H), 5.72 (dt, 1 H, *J* = 7.0, 1.6 Hz), 3.45-3.31 (m, 1 H), 3.24 (d, 1 H, *J* = 5.85 Hz), 2.82-2.60 (m, 2 H), 2.54-2.41 (m, 2 H), 1.92-1.81 (m, 2 H), 1.73 (d, 3 H, *J* = 1.0 Hz), 1.23 (s, 9 H), 0.06 (s, 9 H); ^{13}C NMR δ 141.73, 140.57, 133.68, 128.34, 128.24, 125.80, 55.56, 54.75, 36.86, 34.73, 31.70, 22.56, 14.73, -2.23; ESIMS *m/z* 388 ($[M+Na]^+$, 100), 332 (10), 260 (30); HRMS (ESI) *m/z* calcd for $C_{20}H_{35}NOSSiNa$ (M+Na) 388.2106, found 388.2087. **1-66b**: IR (neat) 3312, 3084, 3026, 2955, 1618, 1454, 1250, 1077, 889 cm^{-1}; ^1H NMR δ 7.31-7.22 (m, 2 H), 7.20-7.13 (m, 3 H), 5.96 (dd, 1 H, *J* = 17.2, 10.7 Hz), 5.15 (dd, 1 H, *J* = 10.7, 1.4), 4.94 (dd, 1 H, *J* = 17.2, 1.5 Hz), 3.48 (d, 1 H, *J* = 6.3 Hz), 3.18 (ddd, 1 H, *J* = 10.4, 6.3, 1.6 Hz), 2.86 (ddd, 1 H, *J* = 14.2, 10.0, 4.8 Hz), 2.54 (ddd, 1 H, *J* = 16.5, 9.8, 6.8 Hz), 2.05-1.92 (m, 1 H), 1.86-1.71 (m, 1 H), 1.27 (s, 9 H), 1.12 (s, 3 H), -0.02 (s, 9 H); ^{13}C NMR δ 141.79, 139.37, 128.32, 125.78, 114.59, 61.13, 56.64, 37.69, 37.07, 33.44, 23.09, 17.15, -2.59; ESIMS *m/z* 388 ($[M+Na]^+$, 100), 366 (20), 332 (25); HRMS (ESI) *m/z* calcd for $C_{20}H_{35}NOSSiNa$ (M+Na) 388.2106, found 388.2090.

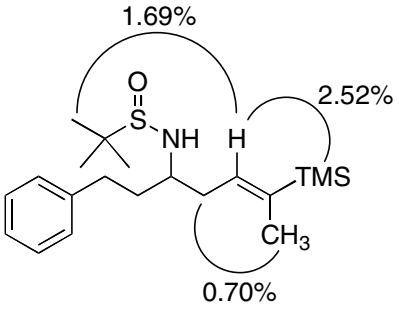
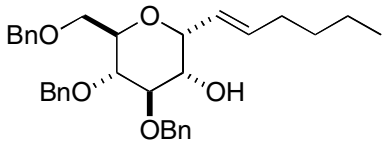


Figure 6-1. NOE Data for **1-66a.**

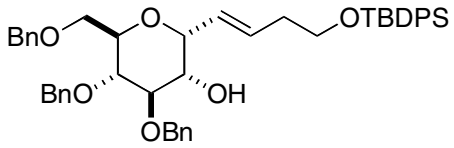
Silver perchlorate on Celite®. To a 100 mL round bottom flask charged with silver perchlorate (1.00 g, 4.80 mmol) in H_2O (30 mL) was added Celite® (5.02 g). The resulting suspension was stirred for 30 min, filtered though a Buchner funnel, and dried in a vacuum oven (60 °C, 24 h) to yield 6.01 g of silver perchlorate on Celite® (20 wt %) as an off-white powder.



2-21

(2*R*,3*S*,4*R*,5*R*,6*R*,*E*) - 4,5 - Bis(benzyloxy) – 6 - (benzyloxymethyl) – 2 - (hex – 1 - enyl) – tetrahydro - 2H – pyran – 3 - ol (2-21). General Protocol C. To a suspension of zirconocene hydrochloride (38 mg, 0.15 mmol) in CH_2Cl_2 (1 mL) was added alkyne **2-22** (17 μL, 0.15 mmol). The yellow reaction mixture was stirred at room temperature for 10 min, treated with $AgClO_4$ on Celite® (15.5 mg, 15.0 μmol), stirred for 5 min, and treated dropwise with a solution of glycal epoxide **2-10** (44 mg, 0.10 mmol) in CH_2Cl_2 (1 mL). The reaction mixture was stirred for 1 h, quenched with saturated aqueous $NaHCO_3$, extracted with EtOAc, dried ($MgSO_4$), and concentrated *in vacuo*.

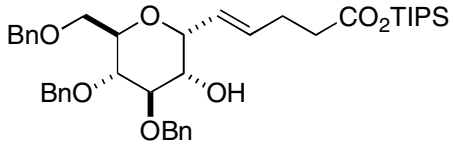
Analysis of the crude reaction mixture by ^{1}H NMR showed one diastereomer. The residue was purified by chromatography on SiO_2 (3:7, EtOAc:hexanes) to yield 39 mg (76%) of **2-21** as a colorless oil: $[\alpha]_D$ + 49.2 (*c* 1.7, $CHCl_3$); IR (neat) 3455, 3030, 2924, 2870, 1496, 1454, 1361, 1208, 1084, 1028, 734, 697 cm^{-1}; ^{1}H NMR (600 MHz) δ 7.40-7.25 (m, 12 H), 7.25-7.15 (m, 3 H), 5.87 (dt, 3 H, *J* = 15.5, 6.7 Hz), 5.70 (dd, 1 H, *J* = 15.6, 6.7 Hz), 4.79 (d, 1 H, *J* = 11.5 Hz), 4.70 (t, 2 H, *J* = 10.9 Hz), 4.62 (d, 1 H, *J* = 12.1 Hz), 4.56 (d, 1 H, *J* = 11.1 Hz), 4.53 (d, 1 H, *J* = 12.1 Hz), 4.43 (t, 1H, *J* = 5.5 Hz), 4.00-3.94 (m, 1 H), 3.78 (dd, 1 H, *J* = 10.5, 10.4 Hz), 3.77 (dd, 1 H, *J* = 9.0, 8.5 Hz), 3.70 (dd, 1 H, *J* = 10.5, 10.2 Hz), 3.70 (t, 1 H, *J* = 7.1 Hz), 3.66 (t, 1 H, *J* = 6.7 Hz), 2.50 (bs, 1 H), 2.10 (q, 2 H, *J* = 6.9 Hz), 1.42-1.37 (m, 2 H), 1.37-1.27 (m, 2 H), 0.90 (t, 3 H, *J* = 7.2 Hz); ^{13}C NMR (126 MHz) δ 138.3, 138.2, 137.8, 137.2, 128.6, 128.6, 128.5, 128.1, 128.0, 127.8, 124.0, 80.5, 76.6, 74.3, 74.1, 73.9, 73.5, 73.1, 71.0, 68.6, 32.5, 31.2, 22.4, 14.0; ESIMS *m/z* 539 ([M+Na]$^+$, 100); HRMS (ESI) *m/z* calcd for $C_{33}H_{40}O_5Na$ (M+Na) 539.2773, found 539.2762.



2-24

(2*R*,3*S*,4*R*,5*R*,6*R*,*E*) - 4,5 - Bis(benzyloxy) - 6 - (benzyloxymethyl) - 2 - (4-(tert - butyl diphenylsilyloxy)but-1-enyl)-tetrahydro-2H-pyran-3-ol (2-24). According to the General Protocol C, zirconocene hydrochloride (38 mg, 0.15 mmol), alkyne **2-23** (93 mg, 0.30 mmol), $AgClO_4$ on Celite® (15.5 mg, 15.0 μmol) and glycal epoxide **2-10** (44 mg, 0.10 mmol) afforded 55 mg (74%) of **2-24** as a colorless oil after purification on SiO_2

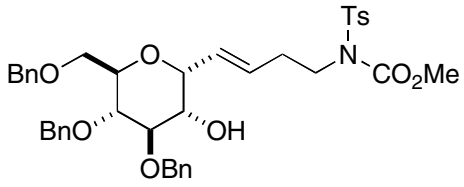
(1:9, EtOAc:hexanes): $[\alpha]_D$ + 34.2 (*c* 1.2, $CHCl_3$); IR (neat) 3454, 3067, 3030, 2930, 2858, 1454, 1428, 1110, 736, 700 cm^{-1}; ^1H NMR δ 7.67 (d, 4 H, *J* = 6.6 Hz), 7.44-7.35 (m, 6 H), 7.35-7.28 (m, 13 H), 7.20 (d, 2 H, *J* = 7.0 Hz), 5.87 (dt, 1 H, *J* = 15.6, 6.5 Hz), 5.76 (dd, 1 H, *J* = 15.7, 6.2 Hz), 4.77 (d, 1 H, *J* = 11.5 Hz), 4.71 (d, 1 H, *J* = 11.1 Hz), 4.67 (d, 1 H, *J* = 11.5 Hz), 4.60 (d, 1 H, *J* = 12.1 Hz), 4.55 (d, 1 H, *J* = 11.1 Hz), 4.51 (d, 1 H, *J* = 12.2 Hz), 4.43 (t, 1 H, *J* = 4.8 Hz), 3.98-3.93 (m, 1 H), 3.80-3.70 (m, 4 H), 3.70-3.64 (m, 3 H), 2.50 (d, 1 H, 6.4 Hz), 2.36 (q, 2 H, *J* = 6.5 Hz), 1.05 (s, 9 H); ^{13}C NMR δ 138.2, 138.0, 137.7, 135.5, 133.8, 133.0, 129.5, 128.5, 128.4, 128.3, 127.9, 127.8, 127.6, 127.6, 126.1, 80.4, 76.4, 74.7, 73.9, 73.7, 73.4, 73.0, 70.9, 68.4, 63.3, 36.1, 26.8, 19.2; ESIMS *m/z* 565 ($[M+Na]^+$, 100); HRMS (ESI) *m/z* calcd for $C_{47}H_{54}O_6SiNa$ (M+Na) 765.3587, found 765.3550.



2-26

(*E*) - Triisopropylsilyl 5 - ((2*R*,3*S*,4*R*,5*R*,6*R*) - 4,5 - bis(benzyloxy) – 6 - (benzyloxymethyl) – 3 – hydroxy – tetrahydro - 2H – pyran – 2 - yl)pent – 4 - enoate (2-26). According to the General Protocol C, zirconocene hydrochloride (38 mg, 0.15 mmol), alkyne **2-25** (76 mg, 0.30 mmol), $AgClO_4$ on Celite® (15.5 mg, 15.0 μmol) and glycal epoxide **2-10** (44 mg, 0.10 mmol) afforded 46 mg (67%) of **2-26** as a colorless oil after purification on SiO_2 (6:4, CH_2Cl_2:hexanes): IR (neat) 3479, 3030, 2944, 2867, 1716, 1454, 1365, 1073, 884, 735, 697 cm^{-1}; ^1H NMR δ 7.38-7.28 (m, 13 H), 7.21 (d, 2 H, *J* = 6.1 Hz), 5.88 (dt, 1 H, *J* = 15.6, 6.0 Hz), 5.76 (dd, 1 H, *J* = 15.6, 6.1 Hz), 4.77 (d, 1 H, *J* =

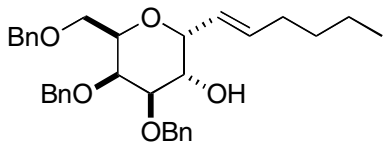
11.5 Hz), 4.70 (t, 2 H, *J* = 10.9 Hz), 4.61 (d, 1 H, *J* = 12.1 Hz), 4.56 (d, 1 H, *J* = 11.2 Hz), 4.52 (d, 1 H, *J* = 12.2 Hz), 4.43 (t, 1 H, *J* = 4.5 Hz), 4.00-3.93 (m, 1 H), 3.80-3.73 (m, 2 H), 3.73-3.64 (m, 3 H), 2.62 (d, 1 H, *J* = 6.7 Hz), 2.51-2.45 (m, 2 H), 2.45-2.38 (m, 2 H), 1.34-1.25 (m, 3 H), 1.08 (d, 18 H, *J* = 7.4 Hz); ^{13}C NMR δ 173.0, 138.2, 138.0, 137.7, 134.3, 128.5, 128.4, 128.4, 127.9, 127.8, 127.7, 125.3, 80.1, 77.2, 76.2, 74.1, 73.6, 73.4, 73.2, 70.8, 68.4, 35.1, 28.2, 17.8, 11.9; ESIMS *m/z* 711 ([M+Na]$^+$, 100), 515 (57); HRMS (ESI) *m/z* calcd for $C_{41}H_{56}O_7SiNa$ (M+Na) 711.3693, found 711.3687.



2-28

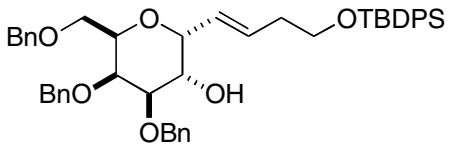
Methyl (*E*) – 4 - ((2*R*,3*S*,4*R*,5*R*,6*R*)-4,5-bis(benzyloxy)-6-(benzyloxymethyl)-3-hydroxy-tetrahydro-2H-pyran-2-yl)but-3-enyl(tosyl)carbamate (2-28). According to the General Protocol C, zirconocene hydrochloride (38 mg, 0.15 mmol), alkyne **2-27** (84 mg, 0.30 mmol), $AgClO_4$ on Celite® (15.5 mg, 15.0 μmol) and glycal epoxide **2-10** (44 mg, 0.10 mmol) afforded 50 mg (70%) of **2-28** as a colorless oil after purification on SiO_2 (4:6, EtOAc:hexanes): IR (neat) 3521, 3030, 2921, 1736, 1453, 1359, 1168, 910, 734, 699 cm^{-1}; ^{1}H NMR δ 7.84 (d, 2 H, *J* = 8.1 Hz), 7.39-7.23 (m, 15 H), 7.21 (d, 2 H, *J* = 6.0 Hz), 5.89-5.77 (m, 2 H), 4.79 (d, 1 H, *J* = 11.5 Hz), 4.72 (d, 1 H, *J* = 11.3 Hz), 4.62 (d, 1 H, *J* = 12.1 Hz), 4.54 (t, 2 H, 11.4 Hz), 4.45 (t, 1 H, *J* = 4.4 Hz), 3.97-3.88 (m, 3 H), 3.82-3.74 (m, 2 H), 3.73-3.64 (m, 6 H), 2.63 (d, 1 H, *J* = 6.7 Hz), 2.58-2.51 (m, 2 H), 2.42 (s, 3 H); ^{13}C NMR δ 152.8, 144.5, 138.3, 138.2, 137.9, 136.8, 131.3, 129.3, 128.5, 128.4, 127.9, 127.8, 127.7, 127.6, 80.4, 74.1, 73.7, 73.4, 73.3, 71.0, 68.6, 53.7, 46.6, 33.4, 21.6; ESIMS

m/z 738 ([M+Na]$^+$, 100); HRMS (ESI) *m/z* calcd for $C_{40}H_{45}O_9SNa$ (M+Na) 738.2713, found 738.2692.



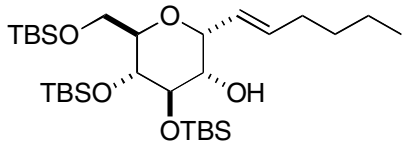
2-30

(2*R*,3*S*,4*R*,5*S*,6*R*,*E*)-4,5-Bis(benzyloxy)-6-(benzyloxymethyl)-2-(hex-1-enyl)-tetrahydro-2H-pyran-3-ol (2-30). According to the General Protocol C, zirconocene hydrochloride (38 mg, 0.15 mmol), alkyne **2-22** (17 μL, 0.30 mmol), $AgClO_4$ on Celite® (15.5 mg, 15.0 μmol) and glycal epoxide **2-29** (44 mg, 0.10 mmol) afforded 38 mg (73%) of **2-30** as a colorless oil after purification on SiO_2 (1:9, EtOAc:hexanes): IR (neat) 3453, 3030, 2925, 2871, 1454, 1094, 735, 698 cm^{-1}; ^{1}H NMR δ 7.33-7.23 (m, 15 H), 5.84 (dt, 1 H, *J* = 15.6, 6.7 Hz), 5.56 (dd, 1 H, *J* = 15.9, 5.5 Hz), 4.74 (d, 1 H, *J* = 11.6 Hz), 4.71 (d, 1 H, *J* = 11.6 Hz), 4.55 (d, 1 H, *J* = 11.7 Hz), 4.52 (d, 1 H, *J* = 5.7 Hz), 4.50 (d, 1 H, *J* = 6.1 Hz), 4.45 (d, 1 H, *J* = 11.9 Hz), 4.16-4.09 (m, 1 H), 4.04-3.97 (m, 2 H), 3.75-3.68 (m, 1 H), 3.65-3.57 (m, 2 H), 2.10-2.02 (m, 3 H), 1.38-1.22 (m, 4 H), 0.86 (t, 3 H, *J* = 7.3 Hz); ^{13}C NMR δ 138.5, 138.3, 138.1, 136.4, 128.6, 128.5, 128.4, 128.0, 130.0, 127.8, 123.1, 79.3, 73.8, 73.6, 73.5, 72.4, 68.8, 68.1, 32.5, 31.3, 22.4, 14.1; ESIMS *m/z* 539 ([M+Na]$^+$, 100), 536 (20); HRMS (ESI) *m/z* calcd for $C_{33}H_{40}O_5Na$ (M+Na) 539.2773, found 539.2800.



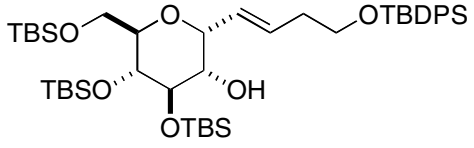
2-31

(2*R*,3*S*,4*R*,5*S*,6*R*,*E*)-4,5-Bis(benzyloxy)-6-(benzyloxymethyl)-2-(4-(tert-butyl diphenylsilyloxy)but-1-enyl)-tetrahydro-2H-pyran-3-ol (2-31). According to the General Protocol C, zirconocene hydrochloride (38 mg, 0.15 mmol), alkyne **2-23** (93 mg, 0.30 mmol), $AgClO_4$ on Celite® (15.5 mg, 15.0 μmol) and glycal epoxide **2-29** (44 mg, 0.10 mmol) afforded 53 mg (72%) of **2-31** as a colorless oil after purification on SiO_2 (hexanes to EtOAc:hexanes, 0.5:9.5): IR (neat) 3459, 3066, 3030, 2929, 2857, 1454, 1428, 1110, 736, 700 cm^{-1}; ^1H NMR δ 7.69 (d, 4 H, *J* = 6.8 Hz), 7.45-7.35 (m, 6 H), 7.35-7.28 (m, 15 H), 5.89 (dt, 1 H, *J* = 15.6, 6.6 Hz), 5.68 (dd, 1 H, *J* = 15.7, 4.5 Hz), 4.78 (d, 1 H, *J* = 11.5 Hz), 4.72 (d, 1 H, *J* = 11.6 Hz), 4.62-4.55 (m, 2 H), 4.53 (d, 1 H, *J* = 6.7 Hz), 4.51 (d, 1 H, *J* = 6.3 Hz), 4.49-4.45 (m, 1 H), 4.19-4.13 (m, 1 H), 4.09-4.04 (m, 1 H), 4.04-4.01 (m, 1 H), 3.73 (t, 3 H, *J* = 6.4 Hz), 3.69-3.63 (m, 1 H), 3.61 (d, 1 H, *J* = 6.9 Hz), 2.37 (q, 2 H, *J* = 6.5 Hz), 2.11 (d, 1 H, *J* = 2.5 Hz), 1.06 (s, 9 H); ^{13}C NMR δ 138.4, 138.1, 138.0, 135.6, 133.8, 132.1, 129.6, 128.5, 128.3, 128.3, 128.1, 127.9, 127.8, 127.6, 127.6, 125.3, 79.2, 77.2, 73.7, 73.5, 73.3, 72.5, 72.2, 68.6, 67.8, 63.3, 36.1, 26.8, 19.2; ESIMS *m/z* 765 ($[M+Na]^+$, 100), 391 (10); HRMS (ESI) *m/z* calcd for $C_{47}H_{54}O_6SiNa$ (M+Na) 765.3587, found 765.3582.



2-33

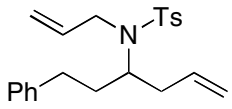
(2*R*,3*S*,4*R*,5*R*,6*R*,*E*)- 4,5 – Bis (tert - butyldimethylsilyloxy) - 6 - ((tert-butyl dimethylsilyloxy) methyl) – 2 - (hex – 1 - enyl) – tetrahydro - 2H – pyran - 3- ol (2 - 33). According to the General Protocol C, zirconocene hydrochloride (38 mg, 0.15 mmol), alkyne **2-22** (17 μL, 0.30 mmol), $AgClO_4$ on Celite® (15.5 mg, 15.0 μmol) and glycal epoxide **2-32** (50 mg, 0.10 mmol) afforded 44 mg (74%) of **2-33** as a colorless oil after purification on SiO_2 (1:9, EtOAc:hexanes): IR (neat) 3532, 2930, 2858, 1472, 1254, 1093, 836, 778 cm^{-1}; ^1H NMR (300 MHz) δ 5.81-5.66 (m, 2 H), 4.25-4.17 (m, 1 H), 4.10-3.93 (m, 2 H), 3.92-3.81 (m, 3 H), 3.82-3.78 (m, 1 H), 3.71 (d, 1 H, *J* = 11.5 Hz), 3.34-3.26 (m, 1 H), 2.15-2.00 (m, 2 H), 1.43-1.30 (m, 4 H), 0.96-0.84 (m, 30 H), 0.17-0.02 (m, 18 H); ^{13}C NMR δ 134.1, 127.9, 80.3, 72.3, 70.6, 69.8, 68.9, 61.3, 32.1, 31.2, 25.9, 25.8, 22.3, 17.9, 13.9, -4.9, -5.0, -5.1, -5.3; ESIMS *m/z* 611 ($[M+Na]^+$, 100), 439 (20); HRMS (ESI) *m/z* calcd for $C_{30}H_{64}O_5Si_3Na$ (M+Na) 611.3959, found 611.3936.



2-34

(2*R*,3*S*,4*R*,5*R*,6*R*,*E*) - 4,5 – Bis (tert - butyldimethylsilyloxy) – 6 - ((tert – butyl dimethylsilyloxy) methyl) – 2 - (4 - (tert - butyldiphenylsilyloxy) but – 1 - enyl) – tetra hydro - 2H – pyran – 3 - ol (2-34). According to the General Protocol C, zirconocene hydrochloride (38 mg, 0.15 mmol), alkyne **2-23** (93 mg, 0.30 mmol), $AgClO_4$ on Celite®

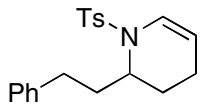
(15.5 mg, 15.0 μmol) and glycal epoxide **2-32** (50 mg, 0.10 mmol) afforded 58 mg (71%) of **2-34** as a colorless oil after purification on SiO_2 (hexanes to EtOAc:hexanes, 0.5:9.5): IR (neat) 3528, 2930, 2858, 1472, 1255, 1095, 836, 778, 702 cm^{-1}; ^1H NMR (300 MHz) δ 7.70-7.64 (m, 4 H), 7.45-7.33 (m, 6 H), 5.84-5.70 (m, 2 H), 4.25-4.18 (m, 1 H), 3.91 (t, 1 H, *J* = 2.5 Hz), 3.89-3.79 (m, 3 H), 3.76-3.73 (m, 1 H), 3.71 (d, 2 H, *J* = 6.7 Hz), 3.35-3.27 (m, 1 H), 2.43-2.33 (m, 2 H), 1.04 (s, 9 H), 1.00-0.86 (m, 27 H), 0.13-0.05 (m, 18 H); ^{13}C NMR δ 135.7, 134.1, 130.5, 129.9, 129.6, 127.7, 80.3, 72.2, 70.4, 69.9, 68.8, 63.7, 61.3, 35.9, 31.7, 26.9, 26.0, 25.9, 22.8, 19.3, 18.3, 18.0, 14.2, -4.5, -4.9, -5.1, -5.2; ESIMS *m/z* 765 ($[M+Na]^+$, 100), 391 (10); HRMS (ESI) *m/z* calcd for $C_{47}H_{54}O_6SiNa$ (M+Na) 765.3587, found 765.3582.



2-44

***N*-Allyl-4-methyl-*N*-(1-phenylhex-5-en-3-yl)benzenesulfonamide (2-44).** To a solution of (*E*)-4-methyl-*N*-(4-phenylbutan-2-ylidene)benzenesulfonamide (4.30 g, 15.0 mmol) and allyl-TMS (7.15 mL, 45.0 mmol) in CH_2Cl_2 (150 mL) was added at -78 °C $TiCl_4$ (1.75 mL, 16.0 mmol). The resulting solution was allowed to warm to rt and stirred at this temperature for 1 h, quenched with sat. aq. NH_4Cl, extracted with EtOAc, dried ($MgSO_4$) and concentrated *in vacuo*. The crude allyl amine was carried on without further purification. To a solution of allyl amine in toluene (150 mL) was added allyl bromide (6.50 mL, 75.0 mmol), 50% NaOH in H_2O (150 mL) and Bu_4NI (5.50 g, 15.0 mmol) and the biphasic reaction mixture was rapidly stirred at rt for 6 h. After dilution with H_2O, the solution was extracted with EtOAc, and the organic layer was separated, dried ($MgSO_4$)

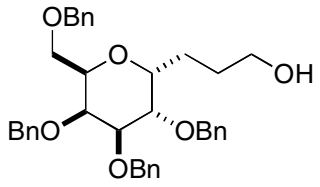
and concentrated *in vacuo*. The crude residue was purified by chromatography on SiO_2 (3:7, EtOAc:hexanes) to yield 4.04 g (73%) of **2-44** as a yellow oil: IR (neat) 3063, 3023, 2926, 1641, 1599, 1339, 1159, 1091 cm^{-1}; ^1H NMR δ 7.74 (d, 2 H, J = 8.1 Hz), 7.36-7.25 (m, 4 H), 7.25-7.18 (m, 1 H), 7.13 (d, 2 H, J = 7.2 Hz), 6.05-5.88 (m, 1 H), 5.70-5.53 (m, 1 H), 5.24 (dd, 1 H, J = 17.2, 0.9 Hz), 5.15 (dd, 1 H, J = 10.1, 0.8 Hz), 5.05-4.94 (m, 2 H), 4.00-3.85 (m, 2 H), 3.85-3.68 (m, 1 H), 2.75-2.60 (m, 1 H), 2.60-2.49 (m, 1 H), 2.45 (s, 3 H), 2.27-2.10 (m, 2 H), 1.88-1.57 (m, 2 H); ^{13}C NMR δ 143.2, 141.8, 138.4, 136.4, 135.0, 129.6, 128.5, 128.4, 127.4, 126.0, 117.5, 117.4, 58.6, 46.6, 38.3, 34.9, 33.1, 21.6; ESIMS *m/z* 392 ($[M+Na]^+$, 100); HRMS (ESI) *m/z* calcd for $C_{22}H_{27}O_2SNa$ (M+Na) 392.1660, found 392.1667.



2-45

2-Phenethyl-1-tosyl-1,2,3,4-tetrahydropyridine (2-45). To a solution of amine **2-44** (890 mg, 2.4 mmol) in CH_2Cl_2 (32 mL) was added 1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro-(phenylmethylene)tricyclohexylphosphine)ruthenium (200 mg, 0.236 mmol). The resulting solution was stirred at rt for 2 h, filtered through a pad of SiO_2 and concentrated in vacuo. To a solution of cyclic amine in EtOH (16 mL) was added tris(triphenylphosphine)rhodium(I) chloride (333 mg, 0.360 mmol) and DBU (183 mg, 1.20 mmol). The reaction mixture was heated at 60 °C for 2 h, concentrated in vacuo and the crude residue was purified by chromatography on SiO_2 (1.5:8.5, EtOAc:hexanes) to yield 705 mg (86%) of **2-45** as a colorless solid: mp 105.1-107.3 °C (CH_2Cl_2); IR (KBr) 3026, 2925, 2848, 1644, 1340, 1168, 1098 cm^{-1}; ^1H NMR δ 7.68 (d, 2 H, J = 8.0 Hz),

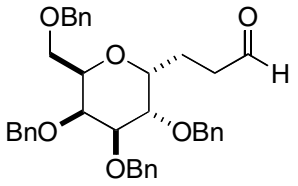
7.38-7.15 (m, 7 H), 6.65 (d, 1 H, J = 8.1 Hz), 5.10-5.00 (m, 1 H), 4.07-3.97 (m, 1 H), 2.91-2.68 (m, 2 H), 2.40 (s, 3 H), 2.05-1.85 (m, 2 H), 1.85-1.72 (m, 1 H), 1.72-1.57 (m, 1 H), 1.51 (dd, 1 H, J = 13.5, 5.2 Hz), 0.98-0.82 (m, 1 H); ^{13}C NMR δ 143.1, 141.7, 129.4, 128.2, 128.1, 126.8, 125.6, 123.4, 109.2, 52.6, 33.2, 32.1, 23.0, 21.2, 17.1; ESIMS *m/z* 364 ([M+Na]$^+$, 100); HRMS (ESI) *m/z* calcd for $C_{20}H_{23}NO_2SNa$ (M+Na) 364.1347, found 364.1360.



3-27

3 - ((2*R*,3*S*,4*R*,5*S*,6*R*) - 3,4,5 - Tris(benzyloxy)-6-(benzyloxymethyl)tetrahydro-2*H*-pyran-2-yl)propan-1-ol (3-27).[112] To a solution of 2,3,4,6-tetra-*O*-benzyl methyl-α-D-glucopyranoside (**3-26**) (6.54 g, 11.8 mmol) and allylsilane (5.8 mL, 36.0 mmol) in acetonitrile (60 mL) at - 50 °C was added dropwise trimethylsilyl trifluoromethanesulfonate (2.49 mL, 12.8 mmol). The reaction mixture was stirred at rt for 16 h, quenched with sat. aq. $NaHCO_3$, extracted with EtOAc, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (2:8, EtOAc:hexanes) to yield 5.72 g (86%) of allylgalactose as a colorless oil with traces of β-*C*-glycoside present: ^{1}H NMR δ 7.52-6.80 (m, 20 H), 5.90-5.73 (m, 1 H), 5.14 (d, 1 H, J = 18.2 Hz), 5.09 (d, 1 H, J = 10.2 Hz), 4.80-4.35 (m, 3 H), 4.18-3.98 (m, 3 H), 3.92 (dd, 1 H, J = 10.3, 7.2 Hz), 3.85-3.60 (m, 3 H), 2.55-2.30 (m, 2 H); ESIMS *m/z* 587 ([M+Na]$^+$, 100); HRMS (ESI) *m/z* calcd for $C_{37}H_{40}O_5Na$ (M+Na) 587.2773, found 587.2725.

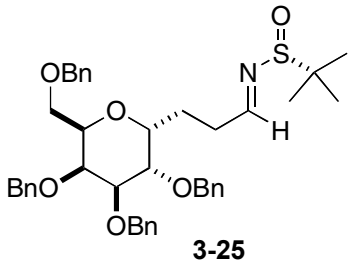
A 0.5 M solution of 9-BBN in THF (11.4 mL, 5.70 mmol) was added dropwise to a solution of allylgalactose (2.91 g, 5.20 mmol) in THF (12 mL) at 0 °C. The resulting solution was stirred at 65 °C for 16 h, then cooled to 0 °C. To this solution was successively added EtOH (1.75 mL, 55.0 mmol), 3 N NaOH (1.75 mL, 0.33 eq,), and 30% H_2O_2 solution in water (1.3 eq, 1.75 mmol) and the resulting cloudy solution was heated at 55 °C for 2 h. The reaction mixture was allowed to cool to rt and poured into a mixture of Et_2O (120 mL) and H_2O (60 mL). The aqueous layer was saturated with K_2CO_3, and the organic phase was separated, dried ($MgSO_4$), and and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (1:1, EtOAc:hexanes) to yield 2.52 g (83%) of **3-27** as a colorless oil: ^{1}H NMR δ 7.45 – 7.05 (m, 20 H), 4.80-4.41 (m, 8 H), 4.08-3.93 (m, 3 H), 3.87-3.77 (m, 2 H), 3.72 (dd, 1 H, *J* = 7.3, 2.7 Hz), 3.69-3.61 (m, 2 H), 3.58 (dd, 1 H, *J* = 10.3, 4.2 Hz), 2.11 (bs, 1 H), 1.82-1.53 (m, 4 H); ESIMS *m/z* 605 ([M+Na]$^+$, 100); HRMS (ESI) *m/z* calcd for $C_{37}H_{42}O_6Na$ 605.2879 (M+Na), found 605.2848.



3-29

3-((2*R*,3*S*,4*R*,5*S*,6*R*)-3,4,5-Tris(benzyloxy)-6-(benzyloxymethyl)tetrahydro-2*H*-pyran-2-yl)propanal (3-29). Prepared according to literature procedure (on a 5+ gram scale),[173] or by the following procedure: To a solution of **3-26** (1.00 g, 1.80 mmol) and **3-28** (930 mg, 5.40 mmol) in MeCN (5 mL) was added TMSOTf[174] (489 μL, 2.70 mmol) at 0 °C. The resulting solution was stirred at this temp for 18 h, allowed to warm to rt and stirred an additional 5 h followed by addition of EtOH (10 mL) and NaOMe

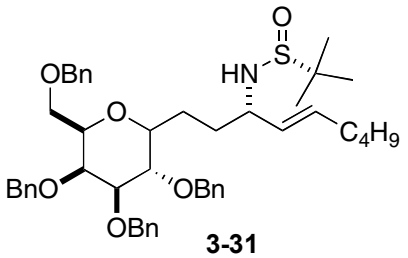
(1.00 g, 18.5 mmol). The reaction was allowed to stir until the enol acetate was consumed by TLC analysis (3:7, EtOAc:hexanes). After completion, the reaction was diluted with H_2O (10 mL), extracted with Et_2O (3 x 25 mL), the organic layer was separated, dried ($MgSO_4$), concentrated[175] and purified by chromatography on SiO_2 (3:7, EtOAc:hexanes) to yield 700 mg (67%) of **3-29** as a light yellow syrup which slowly decomposed upon storage: ^{1}H NMR δ 9.76 (s, 1 H), 7.45-7.15 (m, 20 H), 4.81-4.41 (m, 8 H), 4.02-3.86 (m, 3 H), 3.85-3.78 (m, 2 H), 3.75 (dd, 1 H, *J* = 7.1, 2.0 Hz), 3.63 (dd, 1 H, *J* = 10.5, 4.6 Hz), 2.55-2.40 (m, 2 H), 2.10-1.85 (m, 2 H); ESIMS *m/z* 603 ([M+Na]$^+$, 100); HRMS (ESI) *m/z* calcd for $C_{37}H_{40}O_6Na$ (M+Na) 603.2723, found 603.2664.



3-25

(*R*,*E*) – 2 – Methyl – *N* - (3 - ((2*R*,3*S*,4*R*,5*S*,6*R*) - 3,4,5 – tris (benzyloxy) – 6 - (benzyloxymethyl)tetrahydro- 2*H*-pyran-2-yl)propylidene)propane-2-sulfinamide (3-25). To a solution of **3-29** (2.18 g, 3.75 mmol) in CH_2Cl_2 (30 mL) was added $MgSO_4$ (2.53 g, 21.0 mmol), (*R*)-2-methylpropane-2-sulfinamide (500 mg, 4.13 mmol), and PPTS (104 mg, 0.410 mmol). The resulting suspension was stirred at rt for 24 h, filtered through Celite®, and concentrated in vacuo. The residue was purified by chromatography on SiO_2 (4:6, EtOAc:hexanes) to yield 2.40 g (94%) of **3-25** as a colorless oil: $[\alpha]_D$ -32.3 (*c* 1.1, CH_2Cl_2); IR (neat) 3063, 3030, 2921, 1622, 1454, 1185 cm^{-1}; ^{1}H NMR δ 8.08 (t, 1 H, *J* = 4.1 Hz), 7.40-7.15 (m, 20 H), 4.79-4.41 (m, 8 H), 4.05-3.95 (m, 3 H), 3.89-3.79 (m, 1 H),

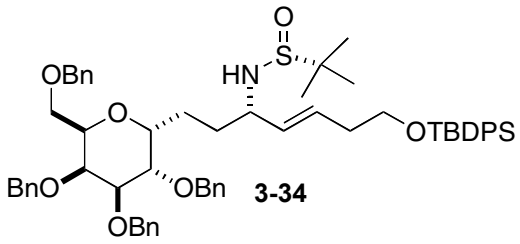
3.79-3.70 (m, 2 H), 3.70-3.61 (m, 1 H), 2.70-2.52 (m, 1 H), 2.50-2.36 (m, 1 H), 2.04-1.80 (m, 2 H); ^{13}C NMR δ 168.7, 138.1, 138.0, 137.9, 137.8, 128.0, 128.0, 127.9, 127.6, 127.5, 127.4, 127.2, 127.2, 127.1, 76.2, 73.8, 72.8, 72.8, 72.6, 72.1, 69.9, 67.1, 56.0, 32.1, 22.9, 21.9; ESIMS *m/z* 706 ([M+Na]$^+$, 100), 684 ([M+H]$^+$, 20); HRMS (ESI) *m/z* calcd for $C_{41}H_{49}NO_6SNa$ (M+Na) 706.3178, found 706.3201.



3-31

(*R*) – 2 – Methyl – *N* - ((*E*) – 1 - ((3*S*,4*R*,5*S*,6*R*) - 3,4,5 - tris(benzyloxy) – 6 - (benzyloxymethyl)tetrahydro - 2*H* - pyran-2 - yl) non – 4 – en – 3 - yl) propane – 2 - sulfinamide (3-31). General Protocol D. To a solution of 1-hexyne (**3-30**) (18.9 mg, 0.230 mmol) in CH_2Cl_2 (1 mL) was added zirconocene hydrochloride (72.2 mg, 0.280 mmol) and the resulting suspension was stirred for 5 min. The yellow solution was cooled to 0 °C and Me_3Al (115 μL, 0.230 mmol, 2.0 M in CH_2Cl_2)[176] and imine **3-25** (100 mg, 0.150 mmol) in CH_2Cl_2 (1 mL) were added. The mixture was stirred at rt for 3 h, quenched with sat. aq. NH_4Cl, extracted with CH_2Cl_2, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (1:1, EtOAc:hexanes) to yield 94.4 mg (82%) of **3-31** as a colorless oil: $[\alpha]_D$ +5.1 (*c* 0.8, CH_2Cl_2); ^{1}H NMR δ 7.50-7.15 (m, 20 H), 5.70 (dt, 1 H, *J* = 15.3, 6.7 Hz), 5.19 (dd, 1 H, *J* = 15.3, 8.3 Hz), 4.82-4.43 (m, 8 H), 4.05-3.90 (m, 3 H), 3.90-3.69 (m, 4 H), 3.64 (dd, 1 H, *J* = 10.5, 4.5 Hz), 3.13 (d, 1 H, *J* = 2.4 Hz), 2.15-1.92 (m, 2 H), 1.80-1.25 (m, 8 H), 1.20 (s, 9 H), 0.91 (t, 3 H, *J* = 7.1

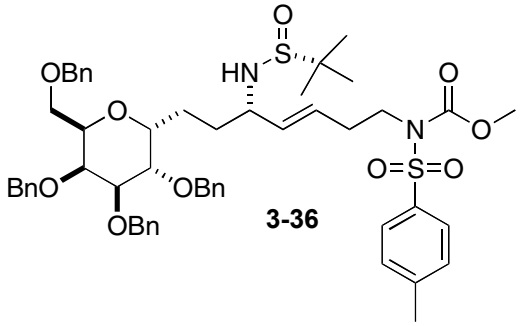
Hz); ^{13}C NMR δ 138.3, 138.2, 138.1, 137.9, 134.1, 130.1, 128.1, 127.7, 127.6, 127.4, 127.3, 127.2, 76.3, 74.1, 73.0, 72.9, 72.8, 71.8, 70.9, 67.5, 57.2, 54.8, 32.7, 31.6, 30.9, 23.1, 22.3, 21.9, 13.6; ESIMS *m/z* 790 ([M+Na]$^+$, 100), 768 ([M+H]$^+$, 80); HRMS (ESI) *m/z* calcd for $C_{47}H_{61}NO_6SNa$ (M+Na) 790.4117, found 790.4153.



3-34

(*R*) – *N* - ((*S*,*E*) – 7 - (*tert*-Butyldiphenylsilyloxy) – 1 - ((2*R*,3*S*,4*R*,5*S*,6*R*) - 3,4,5 – tris (benzyloxy) – 6 - (benzyloxymethyl)tetrahydro-2*H*-pyran-2-yl)hept-4-en-3-yl) - 2-methylpropane-2-sulfinamide (3-34). According to General Protocol D, alkyne **3-33** (51.5 mg, 0.167 mmol), zirconocene hydrochloride (43.1 mg, 0.167 mmol), Me_3Al (167 μL, 0.167 mmol, 1.0 M in CH_2Cl_2) and imine **3-25** (57.0 mg, 0.0833 mmol) in CH_2Cl_2 (1 mL) afforded 67.1 mg (81%) of **3-34** as a colorless oil after purification on SiO_2 (1:1, EtOAc:hexanes): $[\alpha]_D$ + 3.6 (*c* 0.4, CH_2Cl_2); IR (neat) 3030, 2929, 2859, 1496, 1454, 1428, 1110, 736, 700 cm^{-1}; ^{1}H NMR δ 7.71-7.65 (m, 4 H), 7.46-7.21 (m, 26 H), 5.64 (dt, 1 H, *J* = 15.1, 6.9 Hz), 5.25 (dd, 1 H, *J* = 15.5, 8.0 Hz), 4.80-4.41 (m, 8 H), 4.00-3.88 (m, 3 H), 3.87-3.68 (m, 6 H), 3.63 (dd, 1 H, *J* = 10.5, 4.5 Hz), 3.10 (d, 1 H, *J* = 2.9 Hz), 2.31 (app q, 2 H, *J* = 6.6 Hz), 1.78-1.35 (m, 4 H), 1.16 (s, 9 H), 1.05 (s, 9 H); ^{13}C NMR δ 138.6, 138.5, 138.4, 138.3, 135.5, 133.9, 132.6, 130.1, 129.6, 128.3, 128.0, 127.9, 127.7, 127.6, 127.5, 127.4, 74.5, 73.3, 73.2, 73.1, 73.0, 72.1, 71.4, 67.8, 57.4, 55.2, 35.8, 33.1,

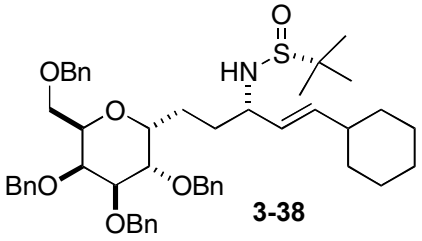
26.9, 23.4, 22.6, 19.2; ESIMS *m/z* 1016 ([M+Na]$^+$, 100), 995 (20); HRMS (ESI) *m/z* calcd for $C_{61}H_{75}NO_7SiSNa$ (M+Na) 1016.4931, found 1016.4927.



3-36

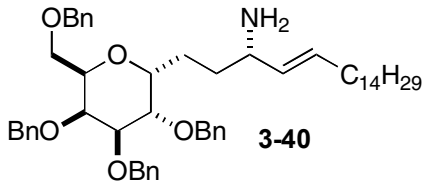
Methyl (*S*,*E*)-5-((*R*)-1,1-dimethylethylsulfinamido)-7-((2*R*,3*S*,4*R*,5*S*,6*R*)-3,4,5-tris (benzyloxy) - 6 - (benzyloxymethyl)tetrahydro-2*H*-pyran-2-yl) hept - 3 - enyl (tosyl) carbamate (3-36). According to General Protocol D, alkyne **3-35** (90.6 mg, 0.322 mmol), zirconocene hydrochloride (91.3 mg, 0.354 mmol), Me_3Al (322 μL, 0.322 mmol, 1.0 M in CH_2Cl_2) and imine **3-25** (110 mg, 0.161 mmol) in CH_2Cl_2 (2 mL) afforded 101 mg (65%) of **3-36** (93:7 mixture of diastereomers by chiral HPLC analysis)[177] as a colorless oil after purification on SiO_2 (7:3, EtOAc:hexanes) (data for major diastereomer reported): $[\alpha]_D$ + 13.7 (*c* 1.0, CH_2Cl_2); IR (neat) 3436, 3030, 2922, 2243, 1735, 1495, 1453, 1360, 1168, 1090, 910, 734, 698 cm^{-1}; ^{1}H NMR δ 7.86-7.78 (m, 2 H), 7.39-7.20 (m, 22 H), 5.62 (dt, 1 H, *J* = 15.4, 6.9 Hz), 5.35 (dd, 1 H, *J* = 15.4, 7.9 Hz), 4.80-4.40 (m, 8 H), 4.03-3.90 (m, 3 H), 3.90-3.70 (m, 6 H), 3.67 (s, 3 H), 3.70-3.56 (m, 1 H), 3.18 (d, 1 H, *J* = 2.6 Hz), 2.58-2.45 (m, 2 H), 2.43 (s, 3 H), 1.78-1.60 (m, 2 H), 1.60-1.33 (m, 2 H), 1.19 (s, 9 H); ^{13}C NMR δ 152.7, 144.4, 138.7, 138.6, 138.5, 138.4, 136.8, 134.0, 129.3, 128.9, 128.3, 128.3, 128.2, 128.0, 127.9, 127.8, 127.7, 127.4, 76.8, 74.6, 73.4, 73.2, 73.0, 72.1, 71.5, 68.0, 57.4, 55.3, 46.8, 33.1, 33.0, 23.4, 22.6, 21.5; ESIMS *m/z* 990 ([M+Na]$^+$, 100),

968 ([M]$^+$, 8); HRMS (ESI) *m/z* calcd for $C_{54}H_{66}N_2O_{10}S_2Na$ (M+Na) 989.4057, found 989.4066.



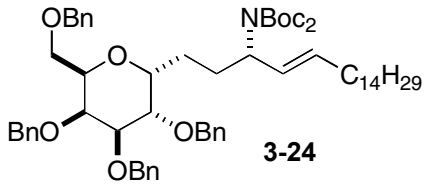
3-38

(*R*) – *N* - ((*S*,*E*) – 1 – Cyclohexyl – 5 - ((2*R*,3*S*,4*R*,5*S*,6*R*) -3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)tetrahydro-2*H*-pyran-2-yl) pent-1-en-3-yl)-2- methylpropane - 2-sulfinamide (3-38). According to General Protocol D, alkyne **3-37** (18.1 mg, 0.167 mmol), zirconocene hydrochloride (43.1 mg, 0.167 mmol), Me_3Al (167 μL, 0.167 mmol, 1.0 M in CH_2Cl_2) and imine **3-25** (57.0 mg, 0.0833 mmol) in CH_2Cl_2 (1 mL) afforded 56.2 mg (85%) of **3-38** as a colorless oil after purification on SiO_2 (1:1, EtOAc:hexanes): $[\alpha]_D$ + 13.7 (*c* 0.7, CH_2Cl_2); IR (neat) 3434, 3063, 3030, 2922, 2852, 1665, 1496, 1453, 971, 1363, 1207, 734, 697 cm^{-1}; ^{1}H NMR δ 7.45-7.20 (m, 20 H), 5.59 (dd, 1 H, *J* = 15.5, 6.7 Hz), 5.12 (dd, 1 H, *J* = 15.5, 8.2 Hz), 4.79-4.40 (m, 8 H), 4.00-3.87 (m, 3 H), 3.86-3.67 (m, 4 H), 3.62 (dd, 1 H, *J* = 10.8, 4.5 Hz), 3.09 (d, 1 H, *J* = 2.2 Hz), 2.20-1.85 (m, 1 H), 1.78-1.57 (m, 7 H), 1.57-1.33 (m, 2 H), 1.33-0.95 (m, 5 H), 1.18 (s, 9 H); ^{13}C NMR δ 140.2, 138.6, 138.5, 138.3, 138.2, 128.3, 128.3, 128.3, 128.0, 127.9, 127.9, 127.8, 127.7, 127.6, 127.5, 127.5, 74.3, 73.3, 73.2, 73.0, 73.0, 72.1, 67.7, 57.5, 55.1, 40.3, 33.1, 32.8, 32.8, 26.1, 25.9, 23.4, 22.6; ESIMS *m/z* 816 ([M+Na]$^+$, 100), 794 ([M]$^+$, 40); HRMS (ESI) *m/z* calcd for $C_{49}H_{63}NO_6SNa$ (M+Na) 816.4274, found 816.4245.



3-40

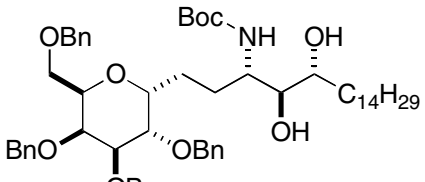
(*S*,*E*)-1-((2*R*,3*S*,4*R*,5*S*,6*R*)-3,4,5- Tris (benzyloxy) - 6 - (benzyloxymethyl) tetra hydro-2*H*-pyran-2-yl)nonadec-4-en-3-amine (3-40). To a solution of 1-hexadecyne (**3-39**) (979 mg, 4.40 mmol) in CH_2Cl_2 (20 mL) was added zirconocene hydrochloride (1.13 g, 4.40 mmol) and the resulting suspension was stirred at rt for 5 min. The yellow solution was cooled to 0 °C and treated with $AlMe_3$ (2.20 mL, 4.40 mmol, 2.0 M in CH_2Cl_2) and a solution of imine **3-25** (2.01 g, 2.92 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred at rt for 5 h, quenched with 25 mL of MeOH and 10 mL of 3 M HCl were added and stirred at rt for 1 h. The solution was diluted with EtOAc, washed with $NaHCO_3$, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (3:7, MeOH:CH_2Cl_2) to yield 1.69 g (72%) of **3-40** as a colorless oil: $[\alpha]_D$ +28.5 (*c* 0.9, CH_2Cl_2); IR (neat) 3063, 3030, 2927, 2853, 1454, 1097 cm^{-1}; ^1H NMR δ 7.50-7.10 (m, 20 H), 5.51 (dt, 1 H, *J* = 15.1, 6.5 Hz), 5.32 (dd, 1 H, *J* = 15.3, 7.2 Hz), 4.80-4.41 (m, 8 H), 4.02-3.90 (m, 3 H), 3.85-3.75 (m, 2 H), 3.75-3.70 (m, 1 H), 3.64 (dd, 1 H, *J* = 10.2, 4.5 Hz), 3.24 (app q, 1 H, *J* = 6.6 Hz), 2.05-1.90 (m, 2 H), 1.75-1.42 (m, 6 H), 1.42-1.10 (m, 24 H), 0.89 (t, 3 H, *J* = 6.3 Hz); ^{13}C NMR δ 138.6, 138.4, 138.2, 134.2, 130.7, 128.3, 128.2, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 127.4, 76.7, 74.3, 73.2, 73.2, 73.0, 72.9, 71.9, 67.6, 53.6, 33.9, 32.3, 31.9, 29.6, 29.6, 29.5, 29.3, 29.3, 29.2, 22.6, 14.1; ESIMS *m/z* 805 ($[M+H]^+$, 100); HRMS (ESI) *m/z* calcd for $C_{53}H_{74}NO_5$ (M+H) 804.5567, found 804.5587.



3-24

[(*S*,*E*)-1-((2*R*,3*S*,4*R*,5*S*,6*R*)-3,4,5-Tris (benzyloxy) - 6 - (benzyloxymethyl) tetra hydro-2*H*-pyran-2-yl)nonadec-4-en-3-yl]-bis carbamic acid *tert*-butyl ester (3-24). To a solution of allylic amine **3-40** (1.50 g, 2.25 mmol) and Et_3N (627 μL, 4.50 mmol) in CH_2Cl_2 (25 mL) was added a solution of Boc_2O (515 mg, 2.36 mmol) and DMAP (27.5 mg, 0.225 mmol) and the mixture was stirred at rt for 1 h. The reaction was filtered through a pad of SiO_2 and concentrated to yield 1.95 g (96%) of mono-boc amide **3-41** as a colorless solid which was carried on without further purification. To a solution of **3-41** (1.95 g, 2.16 mmol) in THF (25 mL) at -78 °C was added *n*-BuLi (1.66 mL, 2.16 mmol, 1.3M in hexanes) and the yellow solution was stirred at -78 °C for 30 min. To this solution was then added Boc_2O (565 mg, 2.59 mmol) and the resulting solution was warmed to rt and stirred for 1 h. The reaction was quenched with sat. aq. NH_4Cl, extracted with EtOAc, organic layer separated, dried ($MgSO_4$), concentrated and purified by chromatography on SiO_2 (1.5:8.5, EtOAc:hexanes) to yield 1.95 g (90%, 86% over 2 steps) of **3-24** as a yellow oil: $[\alpha]_D$ +24.7 (*c* 1.1, $CHCl_3$); IR (neat) 3063, 3030, 2924, 2854, 1740, 1701, 1454, 1343, 1112 cm^{-1}; ^1H NMR δ 7.45-7.10 (m, 20 H), 5.80-5.65 (m, 2 H), 4.90-4.40 (m, 9 H), 4.10-3.95 (m, 3 H), 3.90-3.80 (m, 2 H), 3.80-3.65 (m, 2 H), 2.10-2.05 (m, 2 H), 2.00-1.63 (m, 4 H), 1.60-1.45 (m, 18 H), 1.40-1.25 (m, 24 H), 0.94 (t, 3 H, *J* = 6.4 Hz); ^{13}C NMR δ 153.0, 138.6, 138.3, 133.6, 129.0, 128.2, 127.7, 127.6, 127.5, 127.3, 81.6, 74.5, 73.2, 73.0, 72.9, 71.9, 71.7, 67.7, 59.0, 32.2, 31.8, 29.6, 29.2, 29.1, 27.9,

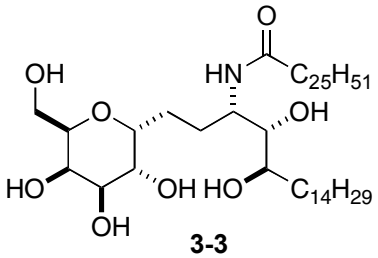
27.7, 24.0, 22.6, 14.0; ESIMS *m/z* 1026 ($[M+Na]^+$, 100), 905 ($[M-Boc]^+$, 30), 805 ($[M-2Boc]^+$, 100); HRMS (ESI) *m/z* calcd for $C_{63}H_{89}NO_9Na$ (M+Na) 1026.6435, found 1026.6396.



3-45

***tert* - Butyl (3*S*,4*S*,5*R*) - 4,5 – dihydroxy – 1 - ((2*R*,3*S*,4*R*,5*S*,6*R*) - 3,4,5 - tris (benzyloxy) – 6 - (benzyloxymethyl) tetrahydro - 2*H* – pyran – 2 - yl) nonadecan - 3-ylcarbamate (3-45).** To a solution of carbamate **3-24** (400 mg, 0.398 mmol) in CH_2Cl_2 (25 mL) at -40 °C was added urea hydrogen peroxide (169 mg, 1.79 mmol), dibasic sodium phosphate (283 mg, 1.99 mmol) and trifluoroacetic anhydride (167 mg, 0.796 mmol). The mixture was stirred at -40 °C for 8 h and at rt for 4 h, quenched with sat. aq. $NaHCO_3$, extracted with CH_2Cl_2, dried ($MgSO_4$) and concentrated *in vacuo*. HPLC analysis of the crude mixture showed a 9:1 mixture of diastereomers).[178] To the crude residue was added EtOH (10 mL) and KOH (100 mg, 1.78 mmol) and the reaction mixture was heated at 40 °C for 2 h,[179] extracted with EtOAc, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (1:1, EtOAc:hexanes) to yield 298 mg (80%) of **3-45** and 33.7 mg (9%) of **3-45**' as greasy colorless waxes: **3-45**: $[\alpha]_D$ +27.1 (*c* 1.0, CH_2Cl_2); IR (neat) 3436, 3357, 2921, 2852, 1682, 1526, 1108 cm^{-1}; ^1H NMR (500 MHz) δ 7.40-7.25 (m, 20 H), 5.12 (d, 1 H, *J* = 8.3 Hz), 4.78-4.71 (m, 1 H), 4.71-4.61 (m, 3 H), 4.60-4.45 (m, 4 H), 4.08-3.97 (m, 2 H), 3.96-3.92 (m, 1 H), 3.92-3.79 (m, 2 H), 3.78-3.68 (m, 2 H), 3.52 (app d, 2 H, *J* = 7.1 Hz), 3.43 (app t, 1 H, *J* = 4.5 Hz),

2.80-2.30 (bs, 2 H), 1.95-1.63 (m, 4 H), 1.61-1.47 (m, 2 H), 1.45 (s, 9 H), 1.39-1.22 (m, 24 H), 0.92 (t, 3 H, J = 6.7 Hz); ^{13}C NMR δ 156.6, 138.6, 138.4, 138.2, 128.3, 128.2, 127.9, 127.8, 127.6, 127.6, 127.5, 79.4, 74.7, 73.2, 73.1, 72.9, 72.0, 68.2, 53.3, 33.2, 31.8, 29.6, 29.3, 28.4, 26.3, 25.9, 23.6, 22.6, 14.0; ESIMS *m/z* 960 ([M+Na]$^+$, 50), 839 ([M-Boc]$^+$, 100); HRMS (ESI) *m/z* calcd for $C_{58}H_{84}NO_9$ 938.6146, found 938.6176.



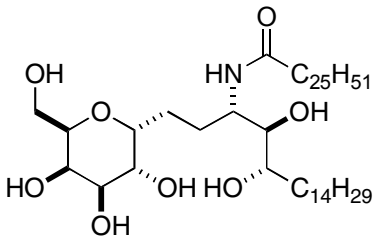
3-3

***N* - ((3*S*,4*S*,5*R*) - 4,5 – Dihydroxy – 1 - ((2*R*,3*R*,4*R*,5*R*,6*R*) - 3,4,5 -trihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl)nonadecan-3-yl)hexacosanamide (3-3)**. To a solution of **3-45** (89.5 mg, 0.0954 mmol) in Et_2O (5 mL) at rt was added HCl (0.25 mL, 1.00 mmol, 4.0 M in dioxane) and the reaction was stirred at rt for 30 min, concentrated, and the crude amine salt carried on without further purification.

To a solution of the crude amine salt in THF (2 mL) was added Et_3N (22.6 μL, 0.191 mmol) and **3-46** (39.6 mg, 0.0954 mmol, in 1 mL THF).[180] The reaction was stirred at rt for 20 min, quenched with sat. aq. NH_4Cl, extracted with CH_2Cl_2 (3x), organic layer separated, dried ($MgSO_4$), concentrated and purified by chromatography on SiO_2 (3:7, EtOAc:hexanes) to yield 86.0 mg (74%, 2 steps) as a colorless wax.

To a solution the amide (41.0 mg, 0.0337 mmol) in CH_2Cl_2 (2 mL) and MeOH (2 mL) was added $Pd(OH)_2/C$ (~ 20 mol% Pd, 10 mg) and the atmosphere was exchanged with hydrogen gas (3x). The reaction was allowed to stir under an atmosphere of

hydrogen at rt for 12 h and the reaction was filtered though a pad of Celite® and concentrated. The crude reside was purified by chromatography on SiO_2 (2.5:7.5, MeOH:$CHCl_3$) to yield 27.7 mg (96%) of **3-3** as a colorless waxy solid: $[\alpha]_D$ +38.4 (*c* 0.13, pyridine); IR (neat) 3583, 3350, 2916, 2848, 1729, 1681, 1613, 1529, 1453, 1063 cm^{-1}; ^1H NMR (500 MHz, d_5-Pyridine) δ 8.37 (d, 1 H, *J* = 8.9 Hz), 5.59 (bs, 4 H), 5.09 (dd, 1 H, *J* = 9.4, 9.4 Hz), 4.70 (dd, 1 H, *J* = 8.7, 5.5 Hz), 4.55-4.43 (m, 3 H), 4.35 (dd, 1 H, *J* = 11.2, 4.5 Hz), 4.26-4.15 (m, 4 H), 2.75-2.62 (m, 1 H), 2.61-2.51 (m, 1 H), 2.51-2.37 (m, 2 H), 2.37-2.25 (m, 2 H), 2.25-2.13 (m, 1 H), 2.00-1.78 (m, 4 H), 1.78-1.61 (m, 1 H), 1.50-1.21 (m, 68 H), 0.89 (t, 6 H, *J* = 6.4 Hz); ^{13}C NMR (126 MHz, d_5-Pyridine) δ 173.8, 78.8, 77.3, 74.1, 73.0, 72.5, 70.9, 70.8, 63.1, 53.1, 37.3, 34.8, 32.4, 30.7, 30.5, 30.3, 30.1, 29.9, 26.9, 23.0, 14.6; ESIMS *m/z* 857 ($[M]^+$, 15), 839 ($[M-H_2O]^+$, 100); HRMS (ESI) *m/z* calcd for $C_{51}H_{102}NO_8$ 856.7605, found 856.7690.

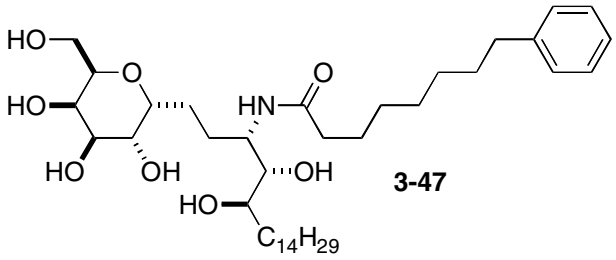


3-3'

***N*-((2*R*,3*S*)-2-Hydroxy-1-(tridecyloxy)-5-((2*R*,3*R*,4*R*,5*R*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl)pentan-3-yl)hexacosanamide (3-3')**. To a solution of **3-45'** (26.9 mg, 0.0287 mmol) in Et_2O (2 mL) at rt was added HCl (0.10 mL, 0.400 mmol, 4.0 M in dioxane) and the reaction was stirred at rt for 30 min, concentrated, and the crude amine salt carried on without further purification.

To a solution of the crude amine salt in THF (0.5 mL) was added Et_3N (6.78 μL, 0.0486 mmol) and **3-46** (11.9 mg, 0.0287 mmol, in 0.1 mL THF).[119] The reaction was stirred at rt for 20 min, quenched with sat. aq. NH_4Cl, extracted with CH_2Cl_2 (3x), organic layer separated, dried ($MgSO_4$), concentrated and purified by chromatography on SiO_2 (3:7, EtOAc:hexanes) to yield 25.3 mg (73%, 2 steps) as a colorless wax.

To a solution the amide (25.3 mg, 0.0208 mmol) in CH_2Cl_2 (1 mL) and MeOH (1 mL) was added $Pd(OH)_2/C$ (~ 20 mol% Pd, 5 mg) and the atmosphere was exchanged with hydrogen gas (3x). The reaction was allowed to stir under an atmosphere of hydrogen at rt for 12 h and the reaction was filtered though a pad of Celite® and concentrated. The crude residue was purified by chromatography on SiO_2 (2.5:7.5, MeOH:$CHCl_3$) to yield 17.3 mg (97%) of **3-3'** as a colorless waxy solid: $[\alpha]_D$ +9.6 (*c* 0.13, pyridine); ^{1}H NMR (d_5-Pyridine) δ 8.88 (d, 1 H, *J* = 8.8 Hz), 5.50-5.00 (bs, 4 H + H_2O), 5.00-4.88 (m, 1 H), 4.72 (dd, 1 H, *J* = 9.0, 5.5 Hz), 4.65-4.58 (m, 1 H), 4.47-4.36 (m, 3 H), 4.28 (dd, 1 H, *J* = 9.2, 3.3 Hz), 4.19 (app t, 1 H, *J* = 4.7 Hz), 3.98-3.81 (m, 2 H), 2.60-2.41 (m, 3 H), 2.41-2.20 (m, 4 H), 2.00-1.61 (m, 5 H), 1.60-1.20 (m, 68 H), 0.97-0.77 (m, 6 H); ^{13}C NMR (126 MHz, d_5-Pyridine) δ 175.9, 77.7, 76.9, 74.1, 72.5, 72.4, 70.7, 62.7, 51.9, 36.9, 34.6, 32.4, 30.7, 30.5, 30.3, 30.1, 30.1, 29.9, 27.1, 26.9, 23.4, 23.3, 14.6; ESIMS *m/z* 878 ($[M+Na]^+$, 100); HRMS (ESI) *m/z* calcd for $C_{51}H_{101}NO_8Na$ (M+Na) 878.7425, found 878.7659.



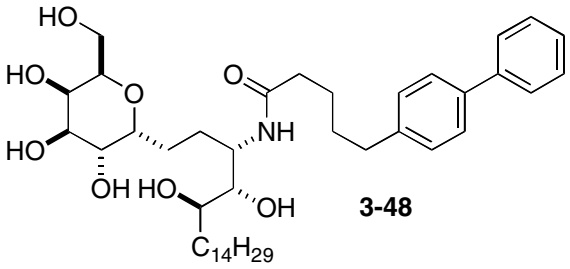
3-47

***N* - ((3*S*,4*S*,5*R*) - 4,5 - Dihydroxy – 1 - ((2*R*,3*R*,4*R*,5*R*,6*R*) - 3,4,5 - trihydroxy – 6 - (hydroxymethyl)tetrahydro-2*H*-pyran-2-yl) nonadecan-3-yl)-8-phenyloctanamide (3-47).** To a solution of **3-45** (150 mg, 0.160 mmol) in CH_2Cl_2 (2 mL) at rt was added HCl (1.00 mL, 4.00 mmol, 4.0 M in dioxane) and the reaction mixture was stirred at rt for 2 h, concentrated, and the crude amine salt carried on without further purification.

To the crude amine salt in $CHCl_3$ (1.5 mL) was added Et_3N (5.0 eq, 116 μL, 0.800 mmol), 8-phenyloxtanoic acid (1.1 eq, 38.8 mg, 0.176 mmol), DMAP (1.1 eq, 21.5 mg, 0.176 mmol) and EDCI (1.1 eq, 33.7 mg, 0.176 mmol) and the reaction mixture was stirred at rt for 5 h. The reaction was quenched with sat. aq. NH_4Cl, extracted with CH_2Cl_2 (2x), washed with brine, dried ($MgSO_4$), filtered and concentrated. The crude residue was purified by chromatography on SiO_2 (40% EtOAc/hexanes) to yield 142 mg (85% over 2 steps) as a colorless waxy solid.

To a solution of coupled product (142 mg, 0.136 mmol) in $CHCl_3$/MeOH (3:1, 5 mL) was added $Pd(OH)_2/C$ (10 mg) and the reaction mixture was stirred under and atmosphere of H_2 for 2 h. The reaction mixture was filtered though a pad of Celite, concentrated and the crude residue purified by chromatography on SiO_2 (20% MeOH/$CHCl_3$) to yield 70.3 mg, (76%) of **3-47** as a colorless waxy solid: $[\alpha]_D$ +13.2 (*c* 0.11, pyridine); IR (neat) 3446, 3398, 2922, 2852, 2256, 1636, 1586, 1549, 1372, 1144, 1075 cm^{-1};^{1}H NMR (600 MHz, d_5-Pyridine) δ 8.39 (d, 1 H, *J* = 9.0 Hz), 7.61-7.56 (m, 2

H), 7.54-7.49 (m, 2 H), 7.36-7.31 (m, 2 H), 7.26-7.21 (m, 1 H), 7.20-7.15 (m, 2 H), 5.25 (bs, 6 H), 5.09-5.02 (m, 1 H), 4.64 (dd, 1 H, J = 9.0, 6.0 Hz), 4.46-4.36 (m, 3 H), 4.26 (dd, 1 H, J = 11.4, 4.8 Hz), 4.17-4.06 (m, 4 H), 2.67-2.57 (m, 1 H), 2.54-2.43 (m, 3 H), 2.43-2.29 (m, 2 H), 2.27-2.16 (m, 2 H), 2.16-2.05 (m, 1 H), 1.88-1.73 (m, 4 H), 1.67-1.53 (m, 3 H), 1.37-1.22 (m, 2 H), 1.22-1.03 (m, 20 H), 0.75 (t, 3 H, J = 6.6 Hz); ^{13}C NMR (150 MHz, d_5-Pyridine) δ 173.1, 142.2, 141.4, 138.7, 129.4, 129.3, 127.5, 127.3, 127.3, 78.5, 77.1, 73.8, 72.6, 72.2, 70.6, 70.4, 62.8, 52.7, 36.7, 35.6, 34.6, 32.1, 31.5, 30.4, 30.2, 30.0, 30.0, 30.0, 29.9, 29.6, 26.6, 26.3, 23.0, 22.7, 14.3; ESIMS *m/z* 738 (5), 737 (10), 736 ([M+Na]$^+$, 100); HRMS (ESI) *m/z* calcd for $C_{42}H_{67}NO_8Na$ (M+Na) 736.4764, found 736.4821.



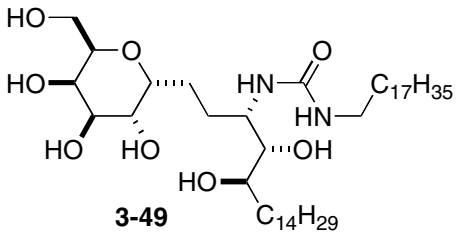
3-48

5 - (Biphenyl - 4 - yl) – *N* - ((3*S*,4*S*,5*S*) - 4,5 – dihydroxy - 1-((2*R*,3*R*,4*R*,5*R*,6*R*)-3,4,5- trihydroxy - 6 - (hydroxymethyl) tetrahydro-2*H*-pyran-2-yl) nonadecan - 3 - yl) pentanamide (3-48). To a solution of **3-45** (114 mg, 0.122 mmol) in CH_2Cl_2 (2 mL) at rt was added HCl (1.00 mL, 4.00 mmol, 4.0 M in dioxane) and the reaction mixture was stirred at rt for 2 h, concentrated, and the crude amine salt carried on without further purification.

To the crude amine salt in $CHCl_3$ (2 mL) was added Et_3N (3.0 eq, 51.0 μL, 0.366 mmol), biphenyl propionic acid (1.2 eq, 37.1 mg, 0.146 mmol), DMAP (.05 eq, 0.745 mg,

0.00610 mmol) and EDCI (1.1 eq, 25.7 mg, 0.134 mmol) and the reaction mixture was stirred at rt for 5 h. The reaction was quenched with sat. aq. NH_4Cl, extracted with CH_2Cl_2 (2x), washed with brine, dried ($MgSO_4$), filtered and concentrated. The crude residue was purified by chromatography on SiO_2 (40% EtOAc/hexanes) to yield 97.4 mg (79% over 2 steps) as a colorless waxy solid.

To a solution of coupled product (97.4 mg, 0.0906 mmol) in $CHCl_3$/MeOH (3:1, 4 mL) was added $Pd(OH)_2/C$ (10 mg) and the reaction mixture was stirred under and atmosphere of H_2 for 2 h. The reaction mixture was filtered though a pad of Celite, concentrated and the crude residue purified by chromatography on SiO_2 (20% MeOH/$CHCl_3$) to yield 62.1 mg, (96%) of **3-48** as a colorless waxy solid: $[\alpha]_D$ +18.2 (*c* 0.10, pyridine); IR (neat) 3444, 3397, 2921, 2852, 2256, 1739, 1624, 1587, 1548, 1455, 1372, 1143, 1079 cm^{-1};^{1}H NMR (300 MHz, d_5-Pyridine) δ 8.47 (d, 1 H, *J* = 9.0 Hz), 7.36-7.27 (m, 2 H), 7.25-7.17 (m, 3 H), 6.80-5.80 (m, 6 H), 5.13 (dd, 1 H, *J* = 9.6, 9.6 Hz), 4.72 (dd, 1 H, *J* = 8.7, 5.4 Hz), 4.56-4.43 (m, 3 H), 4.34 (dd, 1 H, *J* = 11.1, 4.2 Hz), 4.27-4.09 (m, 4 H), 2.80-2.63 (m, 1 H), 2.63-2.54 (m, 1 H), 2.54-2.45 (m, 2 H), 2.45-2.36 (m, 2 H), 2.36-2.08 (m, 3 H), 2.01-1.83 (m, 2 H), 1.83-1.72 (m, 2 H), 1.72-1.59 (m, 1 H), 1.54-1.11 (m, 30 H), 0.85 (t, 3 H, *J* = 5.4 Hz); ^{13}C NMR (150 MHz, d_5 pyridine) δ 173.4, 143.3, 128.9, 128.7, 126.1, 78.5, 77.1, 73.8, 72.6, 72.2, 70.6, 70.4, 62.8, 52.7, 37.0, 36.1, 34.5, 32.2, 31.9, 30.4, 30.2, 30.1, 30.0, 30.0, 29.7, 29.7, 29.6, 29.5, 26.6, 26.5, 26.4, 23.0, 22.6, 14.3; ESIMS *m/z* 675 (5), 702 ($[M+Na]^+$, 100), 707 (10), 708 (3); HRMS (ESI) *m/z* calcd for $C_{39}H_{69}NO_8Na$ (M+Na) 702.4921, found 702.4881.



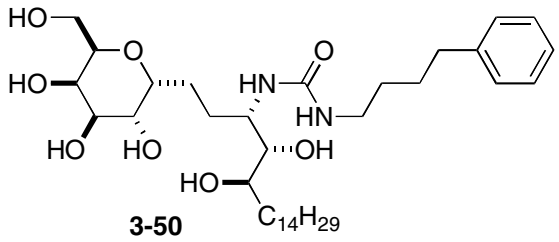
3-49

1 - ((3*S*,4*S*,5*R*) - 4,5 – Dihydroxy – 1 - ((2*R*,3*R*,4*R*,5*R*,6*R*) - 3,4,5 – trihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl)nonadecan-3-yl) - 3 - octadecylurea (3-49). To a solution of **3-45** (150 mg, 0.160 mmol) in CH_2Cl_2 (2 mL) at rt was added HCl (1.00 mL, 4.00 mmol, 4.0 M in dioxane) and the reaction mixture was stirred at rt for 2 h, concentrated, and the crude amine salt carried on without further purification.

To the crude amine salt in acetonitrile (3 mL) and diethyl ether (2 mL) was added Et_3N (3.0 eq, 67.0 μL, 0.480 mmol) and octadecyl isocyanate (1.0 eq, 55.8 μL, 0.160 mmol), and the reaction mixture was stirred at rt for 6 h. The reaction was quenched with H_2O, extracted with CH_2Cl_2 (2x), washed with brine, dried ($MgSO_4$), filtered and concentrated. The crude residue was carried on without further purification.

To a solution of crude urea in $CHCl_3$/MeOH (3:1, 6 mL) was added $Pd(OH)_2$/C (10 mg) and the reaction mixture was stirred under and atmosphere of H_2 for 2 h. The reaction mixture was filtered though a pad of Celite, concentrated and the crude residue purified by chromatography on SiO_2 (20% MeOH/$CHCl_3$) to yield 99.0 mg, (80%, 3 steps) of **3-49** as a colorless waxy solid: $[\alpha]_D$ +9.4 (*c* 0.09, pyridine); IR (neat) 3327, 2918, 2850, 1630, 1561, 1467, 1305, 1068 cm^{-1};^{1}H NMR (300 MHz, d_5-Pyridine) δ 6.81-6.57 (m, 5 H), 6.47 (bs, 1 H), 6.24 (bs, 1 H), 6.00 (bd, 1 H, *J* = 4.8 Hz), 4.99-4.83 (m, 1 H), 4.74-4.63 (m, 1 H), 4.63-4.46 (m, 3 H), 4.41-4.29 (m, 1 H), 4.29-4.10 (m, 4 H), 3.59-3.33 (m, 2 H), 2.58 (bd, 2 H, *J* = 8.4 Hz), 2.44-2.18 (m, 3 H), 2.00-1.77 (m, 2 H), 1.77-1.48 (m, 3 H), 1.45-1.12 (m, 52 H), 0.85 (t, 3 H, *J* = 6.9 Hz), 0.85 (t, 3 H, *J* = 6.9 Hz); ^{13}C

NMR (150 MHz, d_5-Pyridine) δ 160.3, 79.0, 76.9, 74.0, 73.0, 72.2, 70.6, 70.5, 64.9, 62.7, 57.4, 53.5, 49.7, 40.8, 35.0, 32.2, 31.1, 30.5, 30.3, 30.1, 30.0, 29.8, 29.7, 27.5, 26.8, 26.6, 23.0, 22.6, 19.3, 14.4.



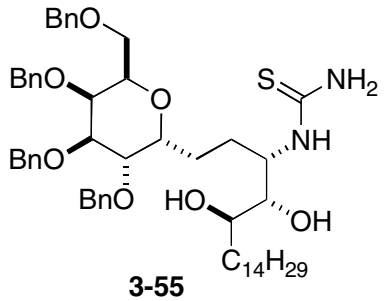
3-50

1 - ((3*S*,4*S*,5*R*) - 4,5 – Dihydroxy – 1 - ((2*R*,3*R*,4*R*,5*R*,6*R*) - 3,4,5 – trihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl)nonadecan-3-yl)-3-(4-phenylbutyl) urea (3-50). To a solution of **3-45** (100 mg, 0.107 mmol) in CH_2Cl_2 (1.5 mL) at rt was added HCl (0.75 mL, 3.00 mmol, 4.0 M in dioxane) and the reaction mixture was stirred at rt for 2 h, concentrated, and the crude amine salt carried on without further purification.

To the crude amine salt in acetonitrile (2.5 mL) and diethyl ether (1.5 mL) was added Et_3N (3.0 eq, 44.7 μL, 0.321 mmol) and 4-phenylbutyl isocyanate (1.0 eq, 18.3 μL, 0.109 mmol), and the reaction mixture was stirred at rt for 6 h. The reaction was quenched with H_2O, extracted with CH_2Cl_2 (2x), washed with brine, dried ($MgSO_4$), filtered and concentrated. The crude residue was carried on without further purification.

To a solution of crude urea in $CHCl_3$/MeOH (3:1, 4 mL) was added $Pd(OH)_2$/C (10 mg) and the reaction mixture was stirred under and atmosphere of H_2 for 2 h. The reaction mixture was filtered though a pad of Celite, concentrated and the crude residue purified by chromatography on SiO_2 (20% MeOH/$CHCl_3$) to yield 51.7 mg, (74%) of **3-50** as a colorless waxy solid: $[\alpha]_D$ +15.2 (*c* 0.17, pyridine); IR (neat) 3329, 2922, 2853, 1627, 1561, 1454, 1248, 1071 cm^{-1};^{1}H NMR (300 MHz, d_5-Pyridine) δ 7.33-7.23 (m, 2 H), 7.22-

7.11 (m, 3 H), 6.74 (d, 1 H, J = 8.7 Hz), 6.65 (dd, 1 H, J = 5.4, 5.4 Hz), 6.50-5.10 (bs, 6 H), 4.92 (dd, 1 H, J = 7.5, 7.5 Hz), 4.70 (dd, 1 H, 8.7, 5.4 Hz), 4.62-4.51 (m, 2 H), 4.51-4.45 (m, 1 H), 4.33 (dd, 1 H, J = 11.4, 4.2 Hz), 4.28-4.09 (m, 4 H), 3.53-3.22 (m, 2 H), 2.65-2.54 (m, 2 H), 2.54-2.45 (m, 2 H), 2.41-2.20 (m, 3 H), 1.98-1.77 (m, 2 H), 1.72-1.48 (m, 3 H), 1.45-1.09 (m, 24 H), 0.85 (t, 3 H, J = 6.9 Hz); ^{13}C NMR (76 MHz, d_5-Pyridine) δ 160.2, 142.9, 128.9, 128.7, 126.1, 79.0, 76.9, 74.1, 72.8, 72.2, 70.6, 70.5, 62.7, 53.5, 40.4, 35.8, 35.1, 32.2, 30.7, 30.4, 30.2, 30.1, 30.0, 30.0, 29.6, 29.2, 26.7, 26.6, 23.0, 22.6, 14.3; ESIMS *m/z* 675 ([M+Na]$^+$, 100), 676 (8); HRMS (ESI) *m/z* calcd for $C_{36}H_{64}N_2O_8Na$ (M+Na) 675.4560, found 675.4512.

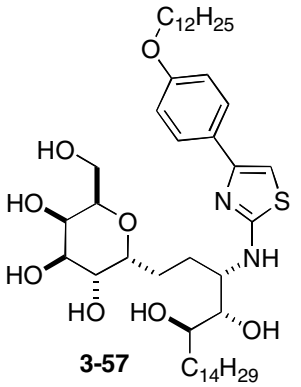


3-55

1 - ((3*S*,4*S*,5*S*) - 4,5 – Dihydroxy – 1 - ((2*R*,3*S*,4*R*,5*S*,6*R*) -3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)tetrahydro-2*H*-pyran-2-yl)nonadecan-3-yl)thiourea (3-55). To a solution of **3-45** (100 mg, 0.107 mmol) in CH_2Cl_2 (1.5 mL) at rt was added HCl (0.75 mL, 3.00 mmol, 4.0 M in dioxane) and the reaction mixture was stirred at rt for 2 h, concentrated, and the crude amine salt carried on without further purification.

To the crude amine salt in THF (4 mL) was added Et_3N (3.0 eq, 44.7 μL, 0.321 mmol) and Fmoc isothiocyanate (1.0 eq, 30.1 mg, 0.107 mmol), and the reaction mixture was stirred at rt for 6 h. The reaction mixture was treated with Et_2NH (10 eq, 111 μL, 1.07 mmol) and stirred at rt for 2 h. The reaction was quenched with sat. aq. NH_4Cl,

extracted with CH_2Cl_2 (2x), washed with brine, dried ($MgSO_4$), filtered and concentrated. The crude residue was purified by chromatography on SiO_2 (40% EtOAc/hexanes) to yield 74.9 mg (78%) of thiourea **3-55** as a yellow solid.

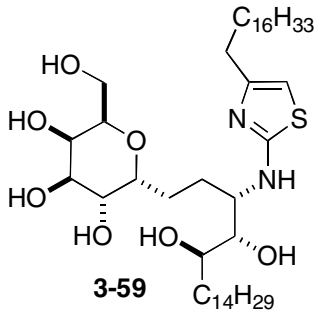


3-57

(2*R*,3*R*,4*R*,5*R*,6*R*) – 2 - ((3*S*,4*S*,5*S*) – 3 - (4 - (4 - (Dodecyloxy) phenyl) thiazol-2-ylamino) -4,5-dihydroxynonadecyl)-6-(hydroxymethyl) tetrahydro-2*H*-pyran-3,4,5-triol (3-57). To a solution of crude thiourea (75.7 mg, 0.0844 mmol) in EtOH (1 mL) was added bromo ketone **3-56** (32.4 mg, 0.0844 mmol) and the reaction mixture was heated at 60 ˚C for 4 h. The reaction mixture was concentrated and the crude solid carried on without further purification.

To a solution of crude thiazole in CH_2Cl_2 (2 mL) at -78 ˚C was added BCl_3 (1.0 M in hexanes, 10 eq, 0.844 mmol, 0.844 mL) and the reaction mixture stirred at -78 ˚C for 30 min. The reaction mixture was quenched at this temperature with sat. aq. NH_4Cl, extracted with $CHCl_3$ (2x), washed with brine, dried ($MgSO_4$), filtered and concentrated. The crude residue was purified by chromatography on SiO_2 (20% MeOH/$CHCl_3$) to provide 57.5 mg (83%, 2 steps) of aryl thiazole **3-57** as a light yellow waxy solid: $[\alpha]_D$ +20.2 (*c* 0.10, pyridine); IR (neat) 3348, 2922, 2853, 1688, 1606, 1467, 1251, 1076 cm^{-}

[1];[1]H NMR (600 MHz, $CDCl_3$/MeOD) δ 7.61-7.57 (m, 2 H), 6.89-6.84 (m, 2 H), 6.48 (s, 1 H), 3.98-3.92 (m, 3 H), 3.91-3.82 (m, 3 H), 3.79 (dd, 1 H, *J* = 12.6, 8.4 Hz), 3.70-3.65 (m, 2 H), 3.61 (dd, 1 H, *J* = 9.6, 3.6 Hz), 3.57 (dd, 1 H, *J* = 7.8, 3.6 Hz), 3.50 (ddd, 1 H, *J* = 9.0, 2.4, 2.4 Hz), 1.93-1.86 (m, 1 H), 1.86-1.72 (m, 4 H), 1.71-1.62 (m, 2 H), 1.56-1.47 (m, 1 H), 1.47-1.41 (m, 2 H), 1.40-1.17 (m, 40 H), 0.85 (t, 3 H, *J* = 7.2 Hz), 0.85 (t, 3 H, *J* = 7.2 Hz); [13]C NMR (150 MHz, $CDCl_3$/MeOD) δ 169.1, 158.1, 149.6, 127.0, 126.3, 113.6, 97.7, 77.4, 77.0, 76.6, 76.5, 74.8, 71.7, 71.4, 69.9, 68.5, 67.2, 60.8, 57.3, 28.9, 28.9, 28.8, 28.8, 28.8, 28.6, 28.5, 28.5, 28.5, 25.2, 25.0, 24.6, 21.8, 21.0, 12.8.

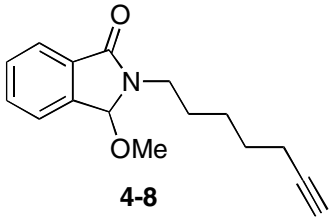


3-59

(2*R*,3*R*,4*R*,5*R*,6*R*) – 2 - ((3*S*,4*S*,5*S*) – 3 - (4 - Heptadecylthiazol-2-ylamino) -4,5-dihydroxynonadecyl)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol (3-59). To a solution of crude thiourea (75.7 mg, 0.0844 mmol) in EtOH (1 mL) was added bromo ketone **3-58** (30.5 mg, 0.0844 mmol) and the reaction mixture was heated at 60 ˚C for 4 h. The reaction mixture was concentrated and the crude solid carried on without further purification.

To a solution of crude thiazole in CH_2Cl_2 (2 mL) at -78 ˚C was added BCl_3 (1.0 M in hexanes, 10 eq, 0.844 mmol, 0.844 mL) and the reaction mixture stirred at -78 ˚C for 30 min. The reaction mixture was quenched at this temperature with sat. aq. NH_4Cl, extracted with $CHCl_3$ (2x), washed with brine, dried ($MgSO_4$), filtered and concentrated.

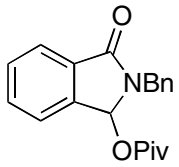
The crude residue was purified by chromatography on SiO_2 (20% MeOH/$CHCl_3$) to provide 59.4 mg (88%) of aryl thiazole **3-59** as a light yellow waxy solid: $[\alpha]_D$ +17.7 (*c* 0.12, pyridine); IR (neat) 3330, 2918, 2850, 1557, 1519, 1467, 1075 cm^{-1};^{1}H NMR (600 MHz, d_5-Pyridine) δ 8.59 (dd, 1 H, *J* = 8.4, 3.0 Hz), 6.23 (s, 1 H), 6.20-5.60 (bs, 6 H), 4.95-4.86 (m, 1 H), 4.74-4.68 (m, 1 H), 4.57-4.47 (m, 3 H), 4.42-4.32 (m, 2 H), 4.29-4.18 (m, 3 H), 2.79-2.71 (m, 1 H), 2.71-2.62 (m, 3 H), 2.50-2.40 (m, 1 H), 2.40-2.30 (m, 2 H), 1.98-1.86 (m, 2 H), 1.85-1.76 (m, 2 H), 1.73-1.61 (m, 1 H), 1.52-1.17 (m, 50 H), 0.89 (t, 3 H, *J* = 7.2 Hz), 0.88 (t, 3 H, *J* = 7.2 Hz); ^{13}C NMR (150 MHz, d_5-Pyridine) δ 170.5, 154.2, 99.8, 78.2, 77.7, 74.3, 73.2, 72.7, 71.2, 70.9, 63.3, 59.5, 35.6, 32.9, 32.7, 30.9, 30.7, 30.6, 30.5, 30.4, 30.3, 30.2, 29.8, 27.0, 26.6, 23.5, 23.3, 14.8; EIMS *m/z* 781 (30), 782 (30), 800 ($[M+H]^+$, 100); HRMS (EI) *m/z* calcd for $C_{45}H_{86}N_2O_7S$ 799.6234, found 799.6198.



4-8

2-(Hept-6-ynyl)-3-methoxyisoindolin-1-one (4-8). To a 0 °C solution of imide **4-6** (40.0 mg, 0.166 mmol) in MeOH (4 mL) was added $NaBH_4$ (5.00 mg, 0.125 mmol). The reaction mixture was stirred at rt for 2.5 h, quenched with H_2O (1 mL) and the MeOH was removed *in vacuo*. The residue was extracted with CH_2Cl_2 (5 x 3 mL) and the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to provide crude hydroxylactam which was immediately dissolved in MeOH (4 mL), treated with *d,l*-camphorsulfonic acid (3.85 mg, 0.0166 mmol) and stirred for 16 h. The solvent was removed *in vacuo* and the residue was partitioned between H_2O (5 mL) and CH_2Cl_2 (5

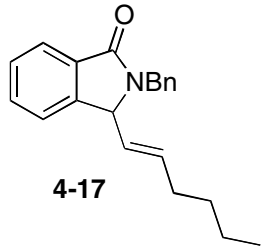
mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), concentrated and chromatographed on SiO_2 (EtOAc:hex, 1:4) to yield methoxy lactam **4-8** (17.0 mg, 0.0661 mmol, 40% over two steps) as a colorless oil: IR (neat) 3298, 2925, 2854, 2115, 1702, 1466, 1412, 1059, 746 cm^{-1}; ^1H NMR δ 7.84-7.80 (m, 1 H), 7.61-7.49 (m, 3 H), 5.88 (s, 1 H), 3.79 (ddd, 1 H, *J* = 13.7, 8.1, 7.3 Hz), 3.24 (ddd, 1 H, *J* = 14.0, 8.0, 6.3 Hz), 2.87 (s, 3 H), 2.19 (td, 2 H, *J* = 6.7, 2.6 Hz), 1.92 (t, 1 H, *J* = 2.6 Hz), 1.75-1.63 (m, 2 H), 1.62-1.43 (m, 4 H); ^{13}C NMR δ 167.6, 140.3, 133.2, 131.9, 129.9, 123.4, 86.2, 84.3, 68.4, 49.1, 39.3, 28.0, 27.6, 26.0, 18.3; MS (EI) *m/z* (rel intensity) 257 ($[M]^+$, 18), 242 (17), 226 (20), 176 (66), 146 (100), 132 (39), 117 (21); HRMS (EI) *m/z* calcd for $C_{16}H_{19}NO_2$ 257.1416, found 257.1419.



4-15

2-Benzyl-3-oxoisoindolin-1-yl pivaloate (4-15). To a solution of benzyl phtalimide (8.89 g, 37.5 mmol) in MeOH (130 mL) was added sodium borohydride (1.42 g, 37.5 mmol) at 0 °C. The resulting reaction mixture was stirred at 0 °C for 2 h and carefully quenched with H_2O. The aqueous layer was extracted with EtOAc (2x) and the organic layer was separated, dried ($MgSO_4$) and concentrated. The residue was dried to yield a white solid which was carried on to the next step without further purification. To a solution of the crude reduced phthalamide (1.00 g, 4.20 mmol) in THF (30 mL) was added Et_3N (1.17 mL, 8.40 mmol) and pivaloyl chloride (621 μL, 5.04 mmol) at 0 °C and the reaction mixture was allowed to warm to rt and stirred at this temperature for 4 h. The

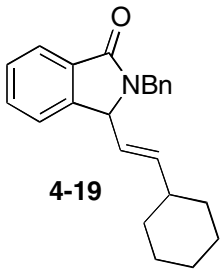
mixture was quenched with sat. aq. $NaHCO_3$, extracted with EtOAc (2x), dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 (EtOAc:Hex, 3:7) to yield 1.09 g (80% over 2 steps) of **4-15** as a colorless solid: mp 88.1 - 89.0 °C (CH_2Cl_2); IR (neat) 3419, 3062, 3031, 2973, 2934, 2872, 1717, 1408, 1276, 1122, 959, 751 cm^{-1}; ^1H NMR δ 7.92-7.84 (m, 1 H), 7.61-7.53 (m, 2 H), 7.50-7.43 (m, 1 H), 7.38-7.22 (m, 5 H), 6.89 (s, 1 H), 5.01 (d, 1 H, *J* = 15 Hz), 4.44 (d, 1 H, *J* = 15 Hz), 1.13 (s, 9 H); ^{13}C NMR δ 178.4, 167.9, 141.3, 136.8, 132.5, 131.9, 130.2, 128.7, 128.1, 127.7, 123.7, 123.7, 81.0, 44.2, 39.0, 26.8; MS (EI) *m/z* (rel intensity) 323 ($[M]^+$, 35), 221 (100), 133 (65), 91 (100); HRMS (EI) *m/z* calcd for $C_{21}H_{23}NO$ 323.1521, found 323.1515.



4-17

(*E*)-2-Benzyl-3-(hex-1-enyl)isoindolin-1-one (4-17). General Protocol E. To a solution of 1-hexyne (**4-16**) (60.5 µL, 0.526 mmol) in CH_2Cl_2 (1.5 mL) was added zirconocene hydrochloride (156 mg, 0.605 mmol) and the resulting suspension was stirred at rt for 10 min. The resulting yellow solution was cooled to 0 °C and Me_3Al (1.0 M in CH_2Cl_2, 0.605 mL, 0.605 mmol) and **4-15** (85.0 mg, 0.263 mmol) were added. The mixture was warmed to rt and stirred at this temperature for 1 h, quenched with sat. aq. NH_4Cl, and extracted with CH_2Cl_2. The organic layers were separated, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 (EtOAc:Hex, 3:7) to yield 65.1 mg (81%) of **4-17** as a colorless oil: IR (neat) 3479, 3031, 2927, 2857, 1694,

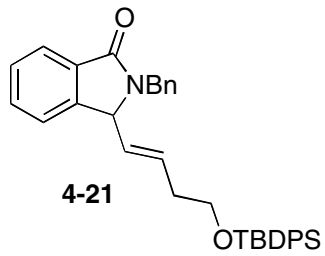
1615, 1400, 972 cm^{-1}; ^1H NMR δ 7.91-7.86 (m, 1 H), 7.56-7.42 (m, 2 H), 7.36-7.21 (m, 6 H), 5.90 (dt, 1 H, *J* = 15.0, 6.8 Hz), 5.30 (d, 1 H, *J* = 14.8 Hz), 5.09 (dd, 1 H, *J* = 15.2, 9.2 Hz), 4.70 (d, 1 H, *J* = 9.2 Hz), 4.17 (d, 1 H, *J* = 14.9 Hz), 2.13 (app q, 2 H, *J* = 6.7 Hz), 1.50-1.30 (m, 4 H), 0.94 (t, 3 H, *J* = 7.2 Hz); ^{13}C NMR δ 167.9, 145.1, 138.3, 137.5, 131.8, 131.5, 128.6, 128.3, 127.3, 126.1, 123.6, 123.0, 62.7, 43.8, 31.8, 31.1, 22.1, 13.8; MS (EI) *m/z* (rel intensity) 305 ($[M]^+$, 100), 248 (40), 237 (70), 214 (40); HRMS (EI) *m/z* calcd for $C_{21}H_{23}NO$ 305.1780, found 305.1785.



4-19

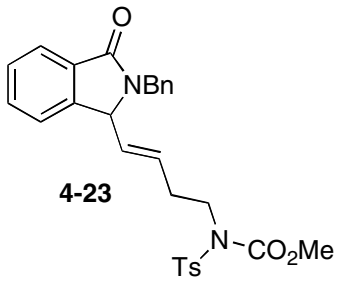
(*E*)-2-Benzyl-3-(2-cyclohexylvinyl)isoindolin-1-one (4-19). According to general protocol E, alkyne **4-18** (66.9 mg, 0.618 mmol), CH_2Cl_2 (1.5 mL), zirconocene hydrochloride (183 mg, 0.711 mmol), Me_3Al (1.0 M in CH_2Cl_2, 0.711 mL, 0.711 mmol) and **4-15** (100 mg, 0.309 mmol) afforded 80.8 mg (79%) of **4-19** as a colorless oil after purification on SiO_2 (EtOAc:Hex, 3:7): IR (neat) 3375, 3030, 2921, 2851, 2243, 1220, 1200, 1097, 844 cm^{-1}; ^1H NMR δ 7.92-7.86 (m, 1 H), 7.54-7.41 (m, 2 H), 7.35-7.20 (m, 6 H), 5.85 (dd, 1 H, *J* = 15.3, 6.6 Hz), 5.28 (d, 1 H, *J* = 14.8 Hz), 5.02 (ddd, 1 H, *J* = 15.3, 9.2, 1.2 Hz), 4.67 (d, 1 H, *J* = 9.2 Hz), 4.18 (d, 1H, *J* = 14.8 Hz), 2.14-1.96 (m, 1 H), 1.85-1.60 (m, 4 H), 1.42-1.00 (m, 6 H); ^{13}C NMR δ 167.9, 145.1, 144.1, 137.4, 131.8, 131.4, 128.5, 128.3, 128.2, 127.3, 123.6, 122.9, 62.8, 43.8, 40.3, 32.6, 26.0, 25.8; MS (EI) *m/z*

(rel intensity) 331 ([M]$^+$, 86), 248 (40), 237 (100); HRMS (EI) *m/z* calcd for $C_{23}H_{25}NO$ 331.1936, found 331.1951.



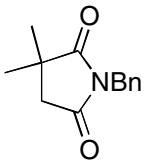
4-21

(*E*)-2-Benzyl-3-(4-(*tert*-butyldiphenylsilyloxy)but-1-enyl)isoindolin-1-one (4-21). According to general protocol E, alkyne **4-20** (94.4 mg, 0.306 mmol), CH_2Cl_2 (1 mL), zirconocene hydrochloride (78.9 mg, 0.306 mmol), Me_3Al (1.0 M in CH_2Cl_2, 0.306 mL, 0.306 mmol) and **4-15** (50.0 mg, 0.153) afforded 57.6 mg (71%) of **4-21** as a colorless oil after purification on SiO_2 (EtOAc:Hex, 2:8): IR (neat) 3450, 2930, 2857, 1692, 1428, 1111, 735, 701 cm^{-1}; ^{1}H NMR δ 7.92-7.86 (m, 1 H), 7.72-7.65 (m, 4 H), 7.53-7.35 (m, 9 H), 7.32-7.21 (m, 5 H), 5.96 (dt, 1 H, *J* = 15.3, 6.8 Hz), 5.27 (d, 1 H, *J* = 14.9 Hz), 5.16 (dddd, 1 H, *J* = 15.3, 9.1, 1.2, 1.2 Hz), 4.71 (d, 1 H, *J* = 9.1 Hz), 4.16 (d, 1 H, *J* = 14.9 Hz), 3.77 (dt, 2 H, *J* = 6.3, 1.2 Hz), 2.37 (app q, 2 H, *J* = 6.6 Hz), 1.08 (s, 9 H); ^{13}C NMR δ 168.0, 144.9, 137.5, 135.6, 134.8, 133.8, 131.9, 131.5, 129.7, 128.6, 128.4, 128.2, 127.7, 127.4, 123.6, 123.1, 63.2, 62.6, 43.9, 35.6, 26.9, 19.2; MS (EI) *m/z* (rel intensity) 532 ([M]$^+$, 35), 488 (100), 474 (45), 306 (65), 252 (75); HRMS (EI) *m/z* calcd for $C_{35}H_{37}NO_2Si$ 532.2664, found 532.2664.



4-23

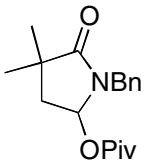
(*E*)-Methyl 4-(2-benzyl-3-oxoisoindolin-1-yl)but-3-enyl(tosyl)carbamate (4-23). According to general protocol E, alkyne **4-22** (174 mg, 0.618 mmol), CH_2Cl_2 (1.5 mL), zirconocene hydrochloride (183 mg, 0.711 mmol), Me_3Al (1.0 M in CH_2Cl_2, 0.711 mL, 0.711 mmol) and **15** (100 mg, 0.309) afforded 95.1 mg (62%) of **4-23** as a colorless oil after purification on SiO_2 (acetone:CH_2Cl_2, 0.3:9.7): IR (neat) 3467, 3032, 2957, 2245, 1735, 1686, 1359, 1168, 733 cm^{-1}; ^1H NMR δ 7.92-7.78 (m, 3 H), 7.56-7.41 (m, 2 H), 7.39-7.18 (m, 9 H), 5.93 (dt, 1 H, *J* = 15.2, 7.0 Hz), 5.26 (d, 1 H, *J* = 14.9 Hz), 5.21 (dd, 1 H, *J* = 15.1, 9.1 Hz), 4.73 (d, 1 H, *J* = 9.0), 4.18 (d, 1 H, *J* = 14.9 Hz), 3.95 (t, 2 H, *J* = 7.0 Hz), 3.69 (s, 3 H), 2.58 (app q, 2 H, *J* = 7.0 Hz), 2.43 (s, 3 H); ^{13}C NMR δ 168.0, 152.8, 144.8, 144.6, 137.4, 136.5, 133.0, 131.7, 131.6, 129.7, 129.4, 128.6, 128.3, 128.3, 127.4, 123.6, 123.2, 62.3, 53.8, 46.5, 43.8, 32.9, 21.6; MS (EI) *m/z* (rel intensity) 504 ($[M]^+$, 50), 262 (40), 155 (100); HRMS (EI) *m/z* calcd for $C_{28}H_{28}N_2O_5S$ 504.1719, found 504.1724.



4-24

1-Benzyl-3,3-dimethylpyrrolidine-2,5-dione (4-24). A mixture of 2,2-dimethylsuccinic anhydride (710 mg, 5.55 mmol) and benzyl amine (712 mg, 6.66 mmol, 1.2 eq) was heated over a bunsen burner for ~ 1 min. The cooled mixture was purified by

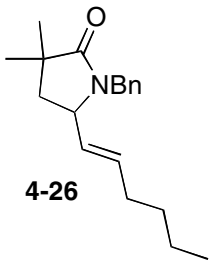
chromatography on SiO_2 (EtOAc:hex, 1:1) to furnish 1.14 g (95%) of **4-24** as a colorless oil: IR (neat) 2969, 2933, 1777, 1702, 1344, 1142, 709 cm^{-1}; ^1H NMR δ 7.29-7.21 (m, 5 H), 4.57 (s, 2 H), 2.47 (s, 2 H), 1.22 (s, 6 H); ^{13}C NMR δ 182.5, 175.1, 135.8, 128.3, 128.1, 127.5, 43.2, 42.0, 39.7, 25.1; MS (EI) *m/z* (rel intensity) 217 ($[M]^+$, 100), 174 (33), 133 (22); HRMS (EI) *m/z* calcd for $C_{13}H_{15}NO_2$ 217.1103, found 217.1104.



4-25

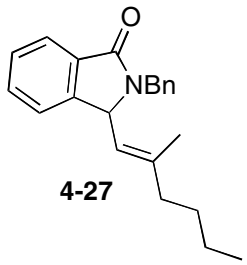
1-Benzyl-4,4-dimethyl-5-oxopyrrolidin-2-yl pivalate (4-25). A solution of imide **4-24** (1.14 g, 5.25 mmol) in MeOH (53 mL) was treated with $NaBH_4$ (200 mg, 2.62 mmol) at ambient temperature. After 6 h, the reaction mixture was concentrated, the residue dissolved in CH_2Cl_2 (50 mL) and treated with sat. aq. NH_4Cl. The aqueous layer was separated and washed with CH_2Cl_2 (2x) and the combined organic layers were dried ($MgSO_4$), filtered, concentrated and the resulting oil used without further purification. The crude oil was dissolved in CH_2Cl_2 (50 mL) and treated sequentially with Et_3N (2.19 mL, 15.7 mmol, 3 eq), DMAP (128 mg, 1.05 mmol, 20 mol %) and pivaloyl chloride (1.29 mL, 10.5 mmol, 2 eq) at ambient temperature. After 6 h, the reaction mixture was quenched with 3 M HCl and the aqueous layer washed with CH_2Cl_2 (3x). The combined organic layers were washed with H_2O, dried ($MgSO_4$), filtered, concentrated and the residue purified by chromatography on SiO_2 (EtOAc:hex, 1:2) to yield 398 mg (25%) of **4-25** as a colorless oil: IR (neat) 2971, 1710, 1419, 1125, 707 cm^{-1}; ^1H NMR δ 7.33-7.21(m, 5 H), 5.99 (d, 1 H, J = 6.3 Hz), 4.74 (d, 1 H, J = 14.7 Hz), 4.15 (d, 1 H, J = 14.7

Hz), 2.14 (dd, 1 H, J = 14.1, 6.3 Hz), 1.87 (d, 1 H, J = 14.4 Hz), 1.32 (s, 3 H), 1.22 (s, 3 H), 1.10 (s, 9 H); ^{13}C NMR δ 180.6, 177.9, 136.6, 128.7, 128.2, 127.6, 82.1, 44.8, 41.5, 39.3, 38.7, 26.8, 26.5, 25.6; MS (EI) *m/z* (rel intensity) 303 ([M]$^+$, 36), 275 (15), 202 (85), 158 (46); HRMS (EI) *m/z* calcd for $C_{18}H_{25}NO_3$ 303.1834, found 303.1827.



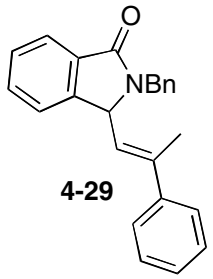
4-26

(*E*)-1-Benzyl-5-(hex-1-enyl)-3,3-dimethylpyrrolidin-2-one (4-26). According to general protocol E, hexyne (**4-16**) (9.77 mg, 0.119 mmol), CH_2Cl_2 (1 mL), zirconocene hydrochloride (30.7 mg, 0.119 mmol), Me_3Al (1.0 M in CH_2Cl_2, 0.119 mL, 0.119 mmol) and **4-25** (18.0 mg, 0.0593 mmol) afforded 14.0 mg (83%) of **4-26** as a colorless oil after purification on SiO_2 (EtOAc:hex, 2.5:7.5): IR (neat) 2958, 2928, 2868, 1692, 1411, 1262, 972, 752 cm^{-1}; ^{1}H NMR δ 7.35-7.23 (m, 3 H), 7.21-7.13 (m, 2 H), 5.53 (dt, 1 H, J = 15.0, 6.6 Hz), 5.16 (dd, 1 H, J = 15.3, 9.0 Hz), 4.94 (d, 1 H, J = 14.4 Hz), 3.88 (d, 1 H, J = 14.4 Hz), 3.73 (app q, 1 H, J = 7.8 Hz), 2.10-1.98 (m, 2 H), 1.99 (dd, 1 H, J = 12.9, 7.2 Hz), 1.58 (dd, 1 H, J = 12.9, 8.1 Hz), 1.42-1.28 (m, 4 H), 1.24 (s, 3 H), 1.11 (s, 3 H), 0.92 (t, 3 H, J = 6.9 Hz); ^{13}C NMR δ 179.6, 137.2, 135.8, 129.8, 128.4, 128.3, 127.2, 56.9, 44.2, 42.0, 40.3, 31.8, 31.2, 25.5, 24.7, 22.2, 13.9; MS (EI) *m/z* (rel intensity) 285 ([M]$^+$, 20), 228 (20), 175 (30), 91 (100); HRMS (EI) *m/z* calcd for $C_{19}H_{27}NO$ 285.2093, found 285.2090.



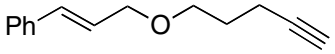
4-27

(*E*)-2-Benzyl-3-(2-methylhex-1-enyl)isoindolin-1-one (4-27). General Protocol F. To a -30 °C solution of $AlMe_3$ (89.0 mg, 1.24 mmol) and Cp_2ZrCl_2 (9.00 mg, 0.0309 mmol) in CH_2Cl_2 (1.5 mL) was added H_2O (11.1 mg, 0.619 mmol) dropwise. The reaction mixture was warmed to ambient temperature, cooled to 0 °C, treated with 1-hexyne (**4-16**) (71.0 μL, 0.619 mmol), stirred for 30 min and treated with **4-15** (100 mg, 0.309 mmol). The reaction mixture was warmed to rt and stirred at this temperature for 1 h, quenched with sat. aq. NH_4Cl, and extracted with CH_2Cl_2. The organic layers were separated, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 (EtOAc:Hex, 3:7) to yield 76.0 mg (77%) of **4-27** as a colorless oil: IR (neat) 2956, 2929, 2858, 1694, 1468, 1401, 749, 703 cm^{-1}; ^1H NMR δ 7.89-7.50 (m, 1 H), 7.53-7.40 (m, 2 H), 7.35-7.20 (m, 6 H), 5.31 (d, 1 H, J = 14.9 Hz), 5.06 (d, 1 H, J = 9.8), 4.81 (dq, 1 H, J = 9.8, 1.2 Hz), 4.09 (d, 1 H, J = 14.9 Hz), 2.07 (t, 2 H, J = 7.1 Hz), 1.67 (d, 3 H, J = 1.3 Hz), 1.50-1.22 (m, 4 H), 0.91 (t, 3 H, J = 7.2 Hz); ^{13}C NMR δ 168.1, 145.7, 143.4, 137.5, 132.0, 131.4, 128.5, 128.2, 128.0, 127.3, 123.6, 122.8, 120.6, 57.9, 43.9, 39.3, 29.8, 22.2, 16.5, 13.8; MS (EI) *m/z* (rel intensity) 319 ($[M]^+$, 100), 221 (40); HRMS (EI) *m/z* calcd for $C_{22}H_{25}NO$ 319.1936, found 319.1921.



4-29

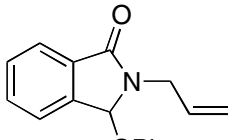
(*E*)-2-Benzyl-3-(2-phenylprop-1-enyl)isoindolin-1-one (4-29). According to general protocol F, alkyne **4-28** (68.0 μL, 0.619 mmol), $AlMe_3$ (89.0 mg, 1.24 mmol), Cp_2ZrCl_2 (9.00 mg, 0.0309 mmol), CH_2Cl_2 (1.5 mL), H_2O (11.1 mg, 0.619 mmol) and **4-15** (100 mg, 0.309 mmol) afforded 81.0 mg (77%) of **4-29** as a colorless oil and a 95:5 mixture of regioisomers after purification on SiO_2 (EtOAc:Hex, 1:3): Major isomer: IR (neat) 3030, 2918, 1693, 1602, 1432, 1400, 1250, 749 cm^{-1}; ^1H NMR δ 7.93 (dd, 1 H, *J* = 6.3, 2.1 Hz), 7.54-7.46 (m, 2 H), 7.35-7.26 (m, 11 H), 5.41 (dd, 1 H, *J* = 9.6, 0.9 Hz), 5.35 (d, 1 H, *J* = 15.0 Hz), 5.27 (d, 1 H, *J* = 9.9 Hz), 4.21 (d, 1 H, *J* = 15.0 Hz), 2.12 (d, 3 H, *J* = 0.9 Hz); ^{13}C NMR δ 168.1, 145.0, 142.0, 141.3, 137.4, 132.0, 131.6, 128.6, 128.3, 127.8, 127.5, 125.8, 123.8, 123.7, 122.9, 58.2, 44.3, 16.3; MS (EI) *m/z* (rel intensity) 339 ($[M]^+$, 41), 248 (47), 234 (77), 91 (100); HRMS (EI) *m/z* calcd for $C_{24}H_{21}NO$ 339.1623, found 339.1631. Minor isomer (characteristic peaks): ^1H NMR δ 1.44 (d, 3 H, *J* = 6.9 Hz); ^{13}C NMR δ 128.0, 121.9, 18.0.



4-30

(*E*)-(3-(Pent-4-ynyloxy)prop-1-enyl)benzene (4-30). To a solution of 4-pentyn-1-ol (4.03 mL, 43.3 mmol) in hexanes (75 mL) was added 50% NaOH (75 mL), TBAI (801 mg, 2.17 mmol) and cinnamyl bromide (8.97 g, 45.5 mmol). The reaction mixture

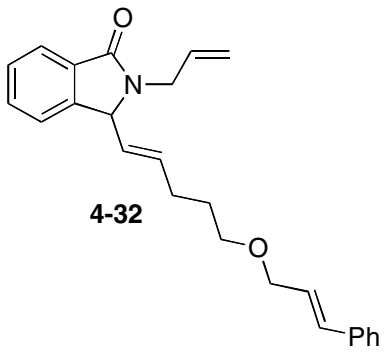
was rapidly stirred for 10 h, the organic layer was separated, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 (EtOAc:Hex, 1:9) to yield 9.00 g (69%) of **4-30** as a colorless oil: IR (neat) 3298, 3027, 2951, 2854, 2117, 1478, 1365, 1111, 967 cm^{-1}; ^1H NMR δ 7.44-7.37 (m, 2 H), 7.37-7.27 (m, 2 H), 7.27-7.21 (m, 1 H), 6.62 (d, 1 H, *J* = 15.9 Hz), 6.30 (dt, 1 H, *J* = 15.9, 6.0), 4.15 (dd, 2 H, *J* = 6.0, 0.9 Hz), 3.60 (t, 2 H, *J* = 6.3 Hz), 2.34 (dt, 2 H, *J* = 7.2, 2.7 Hz), 1.96 (t, 1 H, *J* = 2.7 Hz), 1.85 (app p, 2 H, *J* = 6.6 Hz); ^{13}C NMR δ 136.5, 131.8, 128.3, 127.4, 126.2, 126.0, 83.7, 71.2, 68.5, 68.3, 28.5, 15.1; MS (EI) *m/z* (rel intensity) 199 ($[M]^+$, 100), 186 (35), 173 (35), 131 (100); HRMS (EI) *m/z* calcd for $C_{14}H_{16}O$ 199.1123, found 199.1126.



4-31

2-Allyl-3-oxoisoindolin-1-yl pivalate (4-31). To a solution of 2-allylisoindoline-1,3-dione (3.64 g, 19.4 mmol) in MeOH (100 mL) was added sodium borohydride (734 mg, 19.4 mmol) at 0 °C. The resulting reaction mixture was stirred at 0 °C for 2 h and carefully quenched with H_2O. The aqueous layer was extracted with EtOAc (2x) and the organic layer was separated, dried ($MgSO_4$) and concentrated. The residue was dried to yield a white solid which was carried on to the next step without further purification. To a solution of the crude reduced phthalamide (3.60 g, 19.0 mmol) in THF (100 mL) was added Et_3N (7.90 mL, 57.0 mmol) and pivaloyl chloride (2.81 mL, 22.8 mmol) at 0 °C and the reaction mixture was allowed to warm to rt and stirred at this temperature for 4 h. The mixture was quenched with sat. aq. $NaHCO_3$, extracted with EtOAc (2x), dried ($MgSO_4$)

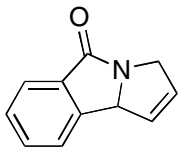
and concentrated. The residue was purified by chromatography on SiO_2 (EtOAc:Hex, 2.5:7.5) to yield 4.40 g (83% over 2 steps) of **4-31** as a colorless oil: IR (neat) 2976, 1716, 1405, 1135, 753; ^{1}H NMR δ 7.88-7.80 (m, 1 H), 7.62-7.46 (m, 3 H), 6.99 (s, 1 H), 5.94-5.77 (m, 1 H), 5.29-5.15 (m, 2 H), 4.44 (dd, 1 H, *J* = 15.9, 5.1 Hz), 3.88 (dd, 1 H, *J* = 15.3, 6.6 Hz), 1.23 (s, 9 H) cm^{-1}; ^{13}C NMR δ 178.3, 167.5, 141.2, 132.4, 132.4, 131.8, 130.0, 123.6, 123.5, 118.0, 80.9, 42.8, 39.0, 26.9; MS (EI) *m/z* (rel intensity) 273 ([M]$^+$, 60), 172 (100; HRMS (EI) *m/z* calcd for $C_{16}H_{19}NO_3$ 273.1365, found 273.1358.



4-32

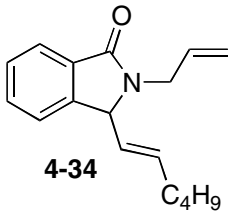
2-Allyl-3-((*E*)-5-(cinnamyloxy)pent-1-enyl)isoindolin-1-one (4-32). According to general protocol E, alkyne **4-30** (733 mg, 3.66 mmol), CH_2Cl_2 (10 mL), zirconocene hydrochloride (944 mg, 3.66 mmol), Me_3Al (1.0 M in CH_2Cl_2, 3.66 mL, 3.66 mmol) and **4-31** (500 mg, 1.83 mmol) (reaction time increased to 12 h) afforded 376 mg (55%) of **4-32** as a colorless oil after purification on SiO_2 (Acetone:CH_2Cl_2, 0.7:9.3): IR (neat) 2924, 2853, 1694, 1468, 1289, 1098, 968, 746 cm^{-1}; ^{1}H NMR δ 7.85 (d, 1 H, *J* = 6.6 Hz), 7.57-7.20 (m, 8 H), 6.61 (d, 1 H, *J* = 15.9 Hz), 6.29 (dt, 1 H, *J* = 15.9, 6.0 Hz), 6.02 (dt, 1 H, *J* = 13.8, 6.9 Hz), 5.90-5.73 (m, 1 H), 5.25-5.07 (m, 3 H), 4.87 (d, 1 H, *J* = 9.0 Hz), 4.60 (ddd, 1 H, *J* = 15.6, 4.5, 2.7 Hz), 4.15 (dd, 2 H, *J* = 6.0, 1.2 Hz), 3.70 (dd, 1 H, *J* = 15.3, 7.2 Hz), 3.53 (t, 2 H, *J* = 6.3 Hz), 2.25 (app q, 2 H, *J* = 6.9 Hz), 1.77 (app p, 2 H, *J* = 7.8

Hz); ^{13}C NMR δ 167.7, 144.9, 137.2, 136.6, 133.2, 132.3, 131.8, 131.4, 128.5, 128.3, 127.6, 126.7, 126.4, 126.1, 123.5, 122.9, 117.5, 71.5, 69.4, 62.9, 42.5, 29.2, 28.9; MS (ESI) *m/z* (rel intensity) 396 ([M+Na]$^+$, 100), 307 (20), 297 (20); HRMS (ESI) *m/z* calcd for $C_{25}H_{27}NO_2Na$ 396.1939, found 396.1928.



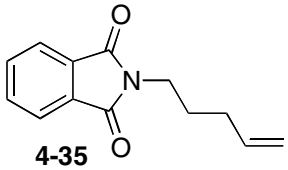
4-33

3*H*-Pyrrolo[2,1-*a*]isoindol-5(9b*H*)-one (4-33). To a solution of **4-32** (41.7 mg, 0.112 mmol) in CH_2Cl_2 (6 mL) was added Grubbs 2nd generation catalyst (4.75 mg, 5.60 μmol) and the red solution was heated at 50 °C for 1 h, cooled to rt and concentrated. The residue was purified by chromatography on SiO_2 (Acetone:CH_2Cl_2, 0.4:9.6) to yield 11.7 mg (61%) of **4-33** as a colorless oil: IR (neat) 2872, 1614, 1468, 1395, 1366, 1080, 746 cm^{-1}; ^{1}H NMR δ 7.74-7.66 (m, 2 H), 7.66-7.58 (m, 1 H), 7.54-7.45 (m, 1 H), 6.28-6.20 (m, 1 H), 6.08-5.99 (m, 1 H), 5.53 (app d, 1 H, *J* = 1.8 Hz), 4.57-4.43 (m, 1 H), 3.98-3.83 (m, 1 H); ^{13}C NMR δ 175.4, 148.4, 133.6, 133.1, 131.9, 129.4, 129.2, 124.6, 124.0, 71.1, 52.0; MS (EI) *m/z* (rel intensity) 171 ([M]$^+$, 60), 160 (70), 130 (55), 105 (60), 83 (100); HRMS (EI) *m/z* calcd for C11H9NO 171.0684, found 171.0676.



4-34

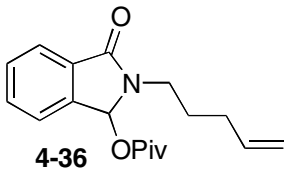
(*E*)-2-Allyl-3-(hex-1-enyl)isoindolin-1-one (4-34). According to general protocol E, hexyne (**4-16**) (420 μL, 3.66 mmol), CH_2Cl_2 (10 mL), zirconocene hydrochloride (944 mg, 3.66 mmol), Me_3Al (1.0 M in CH_2Cl_2, 3.66 mL, 3.66 mmol) and **4-31** (500 mg, 1.83 mmol) afforded 341 mg (73%) of **4-34** as a colorless oil after purification on SiO_2 (EtOAc:Hex, 3:7): IR (neat) 2957, 2926, 1697, 1468, 1396, 971, 748 cm^{-1}; ^1H NMR δ 7.83 (d, 1 H, *J* = 7.2 Hz), 7.57-7.38 (m, 2 H), 7.33 (d, 1 H, *J* = 7.5 Hz), 5.97 (dt, 1 H, *J* = 15.0, 6.9 Hz), 5.88-5.71 (m, 1 H), 5.22-4.97 (m, 3 H), 4.85 (d, 1 H, *J* = 9.3 Hz), 4.59 (dd, 1 H, *J* = 15.6, 4.5 Hz), 3.69 (dd, 1 H, *J* = 15.3, 7.2 Hz), 2.12 (app q, 2 H, *J* = 6.6 Hz), 1.48-1.28 (m, 4 H), 0.91 (t, 3 H, *J* = 6.9 Hz); ^{13}C NMR δ 167.7, 145.0, 138.2, 133.1, 131.7, 131.4, 128.2, 126.0, 123.4, 122.9, 117.4, 62.9, 42.5, 31.8, 31.1, 27.0, 22.0, 13.8; MS (EI) *m/z* (rel intensity) 255 ($[M]^+$, 30), 198 (100), 172 (55); HRMS (EI) *m/z* calcd for $C_{17}H_{21}NO$ 255.1623, found 255.1627.



4-35

2-(Pent-4-enyl)isoindoline-1,3-dione (4-35). A solution of 4-penten-1-ol (3.51 mL, 34.0 mmol), phthalimide **4-4** (5.00 g, 34.0 mmol), and PPh_3 (8.92 g, 34.0 mmol) in THF (220 mL) was cooled to 0 °C and treated with DIAD (6.69 mL, 34.0 mmol) over 5 min. The reaction mixture was warmed to rt and stirred for 6 h. The solvent was

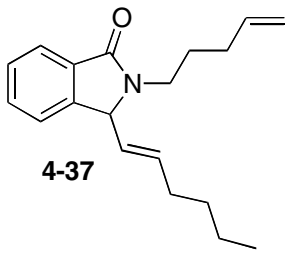
evaporated, the residue was dissolved in EtOAc/hex (1:1, 100 mL) and the solids were filtered off. The filtrate was concentrated and chromatographed on SiO_2 (EtOAc:hex, 1:5) to yield 6.44 g (88%) of imide **4-35** as a colorless oil: IR (neat) 3466, 3077, 2939, 1773, 1641, 1397, 995, 720 cm^{-1}; ^1H NMR δ 7.88-7.81 (m, 2 H), 7.76-7.67 (m, 2 H), 5.90-5.73 (m, 1 H), 5.12-4.94 (m, 2 H), 3.70 (dt, 2 H, J = 7.5, 4.5 Hz), 2.20-2.07 (m, 2 H), 1.87-1.73 (m, 2 H); ^{13}C NMR δ 168.1, 137.1, 133.7, 131.9, 122.9, 115.1, 37.3, 30.8, 27.4; MS (EI) *m/z* (rel intensity) 215 ($[M]^+$, 45), 173 (70), 160 (100), 148 (80), 130 (80), 104 (90); HRMS (EI) *m/z* calcd for $C_{13}H_{13}NO_2$ 215.0946, found 215.0946.



4-36

3-Oxo-2-(pent-4-enyl)isoindolin-1-yl pivalate (4-36). To a solution of imide **4-35** (4.42 g, 20.5 mmol) in MeOH (100 mL) was added sodium borohydride (776 mg, 20.5 mmol) at 0 °C. The resulting reaction mixture was stirred at 0 °C for 2 h and carefully quenched with H_2O. The aqueous layer was extracted with EtOAc (2x) and the organic layer was separated, dried ($MgSO_4$) and concentrated. The residue was dried to yield a white solid which was carried on to the next step without further purification. To a solution of the crude reduced phthalamide (4.23 g, 19.5 mmol) in THF (100 mL) was added Et_3N (8.15 mL, 58.5 mmol), pivaloyl chloride (3.61 mL, 29.3 mmol) and DMAP (119 mg, 0.975 mmol) at 0 °C and the reaction mixture was allowed to warm to rt and stirred at this temperature for 8 h. The mixture was quenched with sat. aq. $NaHCO_3$, extracted with EtOAc (2x), dried ($MgSO_4$) and concentrated. The residue was purified by

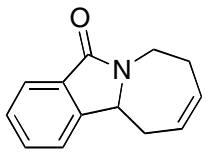
chromatography on SiO_2 (EtOAc:Hex, 1:5) to yield 4.70 g (76% over 2 steps) of **4-36** as a colorless oil: IR (neat) 3077, 2974, 2873, 1739, 1641, 1618, 1369, 1208, 1141, 959, 751 cm^{-1}; ^1H NMR δ 7.67 (d, 1 H, *J* = 6.0 Hz), 7.49-7.32 (m, 3 H), 6.89 (s, 1 H), 5.79-5.58 (m, 1 H), 4.91 (d, 1 H, *J* = 17.1 Hz), 4.84 (d, 1 H, *J* = 10.5 Hz), 3.73-3.55 (m, 1 H), 3.27-3.09 (m, 1 H), 2.07-1.93 (m, 2 H), 1.77-1.50 (m, 2 H), 1.11 (s, 9 H); ^{13}C NMR δ 178.2, 167.4, 140.9, 137.1, 132.0, 131.8, 129.8, 123.2, 123.1, 114.9, 80.8, 39.5, 38.7, 30.7, 27.1, 26.6; MS (EI) *m/z* (rel intensity) 301 ($[M]^+$, 15), 246 (45), 216 (65), 200 (85), 146 (85), 133 (65); HRMS (EI) *m/z* calcd for $C_{18}H_{23}NO_3$ 301.1678, found 301.1681.



4-37

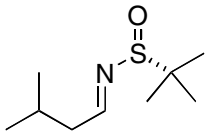
(*E*)-3-(Hex-1-enyl)-2-(pent-4-enyl)isoindolin-1-one (4-37). According to general protocol E, hexyne (**4-16**) (420 μL, 3.66 mmol), CH_2Cl_2 (10 mL), zirconocene hydrochloride (944 mg, 3.66 mmol), Me_3Al (1.0 M in CH_2Cl_2, 3.66 mL, 3.66 mmol) and **4-36** (552 mg, 1.83 mmol) afforded 368 mg (72%) of **4-37** as a colorless oil after purification on SiO_2 (EtOAc:Hex, 3:7): IR (neat) 3076, 2967, 2928, 2860, 1693, 1468, 1404, 972, 749 cm^{-1}; ^1H NMR δ 7.72 (d, 1 H, *J* = 7.5 Hz), 7.44-7.28 (m, 2 H), 7.23 (d, 1 H, *J* = 7.2 Hz), 5.94 (dt, 1 H, *J* = 14.4, 6.6 Hz), 5.80-5.63 (m, 1 H), 5.03-4.82 (m, 3 H), 4.75 (d, 1 H, *J* = 9.0 Hz), 3.83-3.65 (m, 1 H), 3.23-3.07 (m, 1 H), 2.13-1.93 (m, 4 H), 1.75-1.51 (m, 2 H), 1.42-1.19 (m, 4 H), 0.83 (t, 3 H, *J* = 6.9 Hz); ^{13}C NMR δ 167.6, 144.6, 137.5, 137.3, 131.7, 131.0, 127.9, 126.2, 122.9, 122.6, 114.7, 39.4, 31.5, 30.8, 30.7, 27.3,

26.9, 21.8, 13.5; MS (EI) *m/z* (rel intensity) 283 ($[M]^+$, 20), 228 (70), 160 (100), 146 (50), 76 (50); HRMS (EI) *m/z* calcd for $C_{19}H_{25}NO$ 283.1936, found 283.1934.



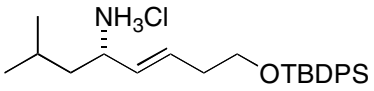
4-38

(*Z*)-7,8,9,11a-Tetrahydro-5*H*-azepino[2,1-*a*]isoindol-5-one (4-38). To a solution of **4-37** (150 mg, 0.529 mmol) in toluene (100 mL) was added $Ti(O^iPr)_4$ (157 μL, 0.529 mmol) and Grubbs 2nd generation catalyst (22.5 mg, 0.0265 mmol) and the red solution was stirred at rt for 12 h and concentrated. The residue was purified by chromatography on SiO_2 (acetone:CH_2Cl_2, 0.4:9.6) to yield 70.7 mg (67%) of **4-38** as a colorless oil: IR (neat) 3024, 2926, 1680, 1469, 1419, 1298, 938, 709 cm^{-1}; ^1H NMR δ 7.76 (dd, 1 H, *J* = 6.9, 1.2 Hz), 7.58-7.51 (m, 1 H), 7.46 (app t, 2 H, 7.2 Hz), 6.13-6.02 (m, 1 H), 6.02-5.91 (m, 1 H), 4.49 (dd, 1 H, *J* = 11.4, 2.1 Hz), 4.26 (ddd, 1 H, *J* = 13.5, 6.6, 3.0 Hz), 3.22 (ddd, 1 H, *J* = 12.6, 9.6, 2.7 Hz), 2.81 (app ddd, 1 H, *J* = 15.9, 7.8, 2.4 Hz), 2.53-2.26 (m, 2 H), 2.25-2.09 (m, 1 H); ^{13}C NMR δ 167.5, 145.9, 133.0, 132.7, 131.6, 128.8, 128.5, 123.5, 122.4, 60.6, 41.6, 35.2, 28.2; MS (EI) *m/z* (rel intensity) 199 ($[M]^+$, 45), 145 (100), 117 (40), 90 (35); HRMS (EI) *m/z* calcd for $C_{13}H_{13}NO$ 199.0997, found 199.0991.



4-46

(*R*,*E*)-2-Methyl-*N*-(3-methylbutylidene)propane-2-sulfinamide (4-46).[181] To a solution of isovaleraldehyde (5.41 mL, 48.5 mmol) in CH_2Cl_2 (250 mL) was added (*R*)-2-methylpropane-2-sulfinamide (5.00 g, 40.4 mmol), $MgSO_4$ (5.0 eq, 24.3 g, 202 mmol) and PPTS (10 mol%, 1.05 g, 4.04 mmol) and the resulting suspension was stirred at rt for 24 h. The reaction was filtered through a pad of Celite® and the crude residue was purified by chromatography on SiO_2 (3:7, EtOAc:hexanes) to yield 6.75 g (88%) of **4-46** as a colorless oil: ^{1}H NMR δ 8.07 (t, 1 H, *J* = 5.2 Hz), 2.47-2.38 (m, 2 H), 2.18-1.90 (m, 1 H), 1.21 (s, 9 H), 1.00 (d, 6 H, *J* = 6.7 Hz). As an alternative, filtration through a pad of SiO_2 provides crude imine that functions equally well in subsequent reactions.

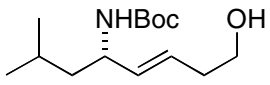


4-48

(*S*,*E*)-8-(*tert*-Butyldiphenylsilyloxy)-2-methyloct-5-en-4-amine hydrochloride (4-48). To a solution of **4-47** (15.9 g, 51.5 mmol) in CH_2Cl_2 (300 mL) was added zirconocene hydrochloride (15.1 g, 58.4 mmol) in 3 portions and the resulting suspension was stirred at rt for 10 min. The resulting yellow solution was cooled to 0 °C and Me_3Al (2.0 M in hexanes, 27.5 mL, 54.9 mmol) was added and stirred for 5 minutes followed by addition of a solution of imine **4-46** (6.50 g, 34.3 mmol) in CH_2Cl_2 (50 mL). The orange solution was stirred for an additional 4 h while being allowed to warm to rt. The reaction was quenched with MeOH, diluted with H_2O and CH_2Cl_2 and HCl (1 M) was added to

break up the emulsion (prolonged stirring with Rochelle's salt can also be utilized). The organic layer was separated and the aqueous layer was washed with CH_2Cl_2 (2x). The organic layers were combined, washed with brine, dried ($MgSO_4$), filtered though a pad of Celite® and concentrated. Since the crude oil was contaminated with metal salts, the oil was dissolved in Et_2O, allowed to sit for 2 h, and then filtered though a pad of Celite® and concentrated. Analysis of the crude residue by ^1H NMR showed only 1 diastereomer (> 95:5 dr).

To the crude residue in Et_2O (800 mL) was added HCl (4.0 M in dioxane, 17.2 mL, 68.7 mmol) and the reaction mixture was stirred for 30 minutes, during which time a white precipitate formed. The precipitate was filtered, washed with dry Et_2O, and dried to afford 11.0 g (74% over 2 steps) of **4-48** as a colorless solid: $[\alpha]_D$ -2.9 (*c* 1.0, CH_2Cl_2); ^1H NMR δ 8.42 (bs, 3 H), 7.70-7.55 (m, 4 H), 7.48-7.30 (m, 6 H), 5.90 (dt, 1 H, *J* = 14.9, 7.5 Hz), 5.52 (dd, 1 H, *J* = 15.4, 8.4 Hz), 3.69 (app t, 3 H, *J* = 6.5 Hz), 2.45-2.20 (m, 2 H), 1.80-1.50 (m, 3 H), 1.03 (s, 9 H), 0.95-0.84 (m, 6 H); ^{13}C NMR δ 135.5, 134.5, 133.7, 129.5, 127.6, 127.3, 63.0, 52.9, 42.1, 35.6, 26.7, 24.4, 22.9, 21.5, 19.1; EIMS *m/z* 395 ($[M-HCl]^+$, 40), 338 (86), 198 (100); HRMS (EI) *m/z* calcd for $C_{25}H_{37}NOSi$ (M-HCl) 395.2644, found 395.2640.

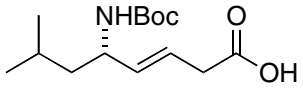


4-49

(*S*,*E*)-*tert*-Butyl 8-hydroxy-2-methyloct-5-en-4-ylcarbamate (4-49). To a solution of **4-48** (10.5 g, 24.3 mmol) in CH_2Cl_2 (400 mL) was added Et_3N (3.0 eq, 10.3 mL, 72.9 mmol) and Boc_2O (1.05 eq, 5.74 g, 25.5 mmol) and the resulting suspension was

stirred at rt for 14 h. The reaction was quenched with sat. aq. NH_4Cl. The organic layers were separated, dried ($MgSO_4$), filtered and concentrated. The crude residue was carried onto the next step without further purification.

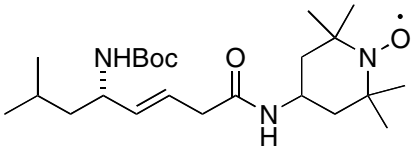
To a solution of crude TBDPS ether (12.0 g, 24.3 mmol) in THF (200 mL) at 0 °C was added TBAF (1.0 M in THF, 1.25 eq, 30.4 mL, 30.4 mmol) and the reaction mixture was warmed to rt, stirred for 2 h, and quenched with sat. aq. NH_4Cl. The organic layer was washed with brine, dried ($MgSO_4$), filtered and concentrated. The crude residue was purified by chromatography on SiO_2 (3:7, EtOAc:hexanes) to yield 5.51 g (88%, 2 steps) of **4-49** as a colorless oil: $[\alpha]_D$ -12.7 (*c* 1.0, CH_2Cl_2); IR 3335, 2956, 2870, 1689, 1525, 1366, 1173, 1046, 1022 cm^{-1}; ^1H NMR δ 5.53 (dt, 1 H, *J* = 15.4, 6.9 Hz), 5.37 (dd, 1 H, *J* = 15.4, 6.5 Hz), 4.50 (bs, 1 H), 4.11-3.95 (m, 1 H), 3.60 (t, 2 H, *J* = 6.2 Hz), 2.42 (bs, 1 H), 2.25 (app q, 2 H, *J* = 6.4 Hz), 1.70-1.51 (m, 1 H), 1.41 (s, 9 H), 1.37-1.20 (m, 2 H), 0.89 (d, 3 H, *J* = 6.6 Hz), 0.88 (d, 3 H, *J* = 6.6 Hz); ^{13}C NMR δ 155.4, 134.3, 126.9, 79.2, 61.5, 50.9, 44.5, 35.6, 28.3, 24.6, 22.5; EIMS *m/z* 257 ($[M]^+$, 10), 227 (55), 171 (65); HRMS (EI) *m/z* calcd for $C_{14}H_{27}NO_3$ 257.1991, found 257.1994.



4-50

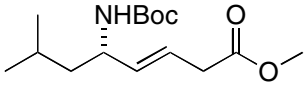
(*S*,*E*)-5-(*tert*-Butoxycarbonylamino)-7-methyloct-3-enoic acid (4-50). To a solution of **4-49** (1.00 g, 3.89 mmol) in acetone (40 mL) at 0 °C was added a freshly prepared solution of Jones Reagent (2.5 M, 3.89 mL, 9.71 mmol) and the reaction mixture was stirred at 0 °C for 1 h. The dark solution was extracted with Et_2O (3 x 50 mL). The organic layers were washed with water (2 x 75 mL), brine (1 x 50 mL), dried (Na_2SO_4),

filtered and concentrated to yield 990 mg (94% crude) of acid **4-50** as a yellow oil that was used without further purification.



4-51 (jp4_039)

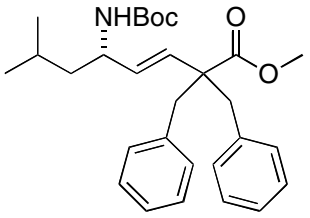
(*S*,*E*)-5-(*tert*-Butoxycarbonylamino)-7-methyloct-3-enoic acid-TEMPO (4-51). To a solution of **4-50** (678 mg, 2.50 mmol, crude) in CH_2Cl_2 (35 mL) at 0 °C was added 4-amino tempo (1.5 eq, 662 mg, 3.75 mmol), EDCI (1.2 eq, 575 mg, 3.00 mmol), DMAP (1.1 eq, 339 mg, 2.75 mmol) and HOBt-hydrate (1.1 eq, 377 mg, 2.75 mmol) and the resulting orange solution was stirred at rt for 14 h. The reaction mixture was diluted with CH_2Cl_2 and washed with sat. aq. NH_4Cl. The organic layer was dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by chromatography on SiO_2 (1:1 to 2:1, EtOAc/hexanes) to yield 857 mg (76%, 2 steps) of **4-51** as a peach colored solid: ESIMS *m/z* 365 (40), 391 (50), 447 ($[M+Na]^+$, 100), 527 (20); HRMS (ESI) *m/z* calcd for $C_{23}H_{42}N_3O_4Na$ (M + Na) 447.3073, found 447.3109.



4-52

(*S*,*E*)-Methyl 5-(*tert*-butoxycarbonylamino)-7-methyloct-3-enoate (4-52). To a solution of **4-50** (116 mg, 0.427 mmol) in benzene/MeOH (4:1, 2.5 mL) was added $TMSCHN_2$ (2.0 M in Et_2O, 5 eq., 1.07 mL, 2.13 mmol) and the reaction was stirred at rt for 20 min. The yellow solution was concentrated and the crude residue purified by chromatography on SiO_2 (30% EtOAc/hexanes) to yield 103 mg (84%) of **4-52** as a

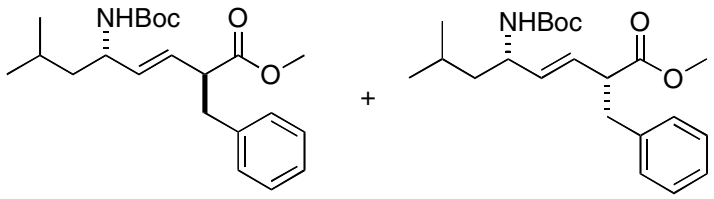
colorless oil: $[\alpha]_D$ -11.3 (*c* 1.0, CH_2Cl_2); IR 3374, 2957, 2927, 2855, 1697, 1515, 1366, 1253, 1170 cm^{-1}; ^1H NMR δ 5.70 (ddt, 1 H, *J* = 15.4, 6.9, 1.0 Hz), 5.49 (dd, 1 H, 15.5, 5.0 Hz), 4.39 (bs, 1 H), 4.24-4.02 (m, 1 H), 3.69 (s, 3 H), 3.07 (d, 2 H, *J* = 6.9 Hz), 1.74-1.56 (m, 1 H), 1.45 (s, 9 H), 1.40-1.20 (m, 2 H), 0.93 (d, 3 H, *J* = 6.5 Hz), 0.92 (d, 3 H, *J* = 6.6 Hz); ^{13}C NMR δ 172.0, 155.2, 135.4, 121.8, 79.2, 51.7, 50.2, 44.6, 37.5, 28.4, 24.7, 22.5, 22.4; EIMS *m/z* 228 ([M-*t*Bu]$^+$, 60), 172 (85), 128 (85), 117 (65), 96 (70); HRMS (EI) *m/z* calcd for $C_{11}H_{18}NO_4$ (M-*t*Bu) 228.1236, found 228.1239.



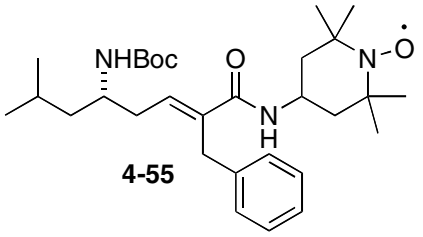
4-54

(*S*,*E*)-Methyl 2,2-dibenzyl-5-(*tert*-butoxycarbonylamino)-7-methyloct-3-enoate (4-54). To a solution of **4-52** (47.8 mg, 0.167 mmol) in THF (2.5 mL) at -78 ˚C was added DMPU (0.5 mL) and KHMDS (2.1 eq, 73.7 mg, 0.351 mmol) and the reaction was stirred at this temperature for 45 min. To the resulting yellow solution at -78 ˚C was added BnCl (1.1 eq, 21.2 μL, 0.184 mmol) in one portion and the reaction warmed to -40 ˚C and stirred at this temperature for 2 h. The reaction was quenched with sat. aq. NH_4Cl, extracted with EtOAc, washed with brine, dried ($MgSO_4$), filtered and concentrated. The crude residue was purified by chromatography on SiO_2 (20% EtOAc/hexanes) to yield 35.0 mg (45%) of **4-54** as a light yellow oil: ^1H NMR δ 7.50-7.05 (m, 10 H), 5.80 (d, 1 H, *J* = 16.1 Hz), 5.39 (dd, 1 H, *J* = 16.2, 6.4 Hz), 4.42-4.23 (m, 1 H), 4.23-4.05 (m, 1 H), 3.63 (s, 3 H), 3.23 (d, 1 H, *J* = 13.8 Hz), 3.22 (d, 1 H, *J* = 13.7 Hz), 3.03 (d, 1 H, *J* = 13.7 Hz),

3.00 (d, 1 H, J = 13.8 Hz), 1.75-1.60 (m, 1 H), 1.47 (s, 9 H), 1.35-1.15 (m, 2 H), 0.87 (d, 6 H, J = 6.6 Hz).



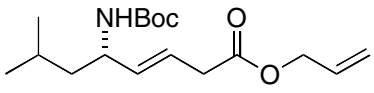
(2*S*,5*S*,*E*)-Methyl 2 – benzyl – 5 - (*tert* - butoxycarbonylamino) - 7-methyloct-3-enoate (4-53). To a solution of **4-52** (549 mg, 1.92 mmol) in THF (30 mL) and DMPU (2.0 mL) at -78 ˚C was added LiHMDS (1.0 eq, 321 mg, 1.92 mmol) in one portion. The reaction was stirred at this temperature for 1 h, followed by addition of BnBr (5 eq, 1.14 mL, 9.60 mmol) and the resulting yellow solution allowed to warm to -40 ˚C and stirred at this temperature for 5 h. The reaction was quenched with sat. aq. NH_4Cl, extracted with EtOAc, washed with brine, dried (MgSO4), filtered and concentrated. The crude residue was purified by chromatography on SiO_2 (20% EtOAc/hexanes) to yield 561 mg (78%) of **4-53** as an inseperable 1.5:1 mixture of diastereomers: ^{1}H NMR δ 7.35-7.08 (m, 5 H), 5.62 (dt, 1 H, J = 15.3, 7.8 Hz), 5.32 (dd, 1 H, J = 15.5, 6.1 Hz), 4.28 (bs, 1 H), 4.10 (bs, 1 H), 3.63 (s, 1.2 H), 3.63 (s, 1.8 H), 3.38-3.22 (m, 1 H), 3.08 (dd, 1 H, J = 13.4, 7.4 Hz), 2.80 (ddd, 1 H, J = 11.5, 7.5, 2.0 Hz), 1.60-1.48 (m, 1 H), 1.45 (s, 5.4 H), 1.44 (s, 3.6 H), 1.35-1.13 (m, 2 H), 0.92-0.83 (m, 6 H); ESIMS *m/z* 423 (10), 398 ([M+Na]$^+$, 60), 362 (40), 342 (100); HRMS (ESI) *m/z* calcd for $C_{22}H_{33}NO_4Na$ (M+Na) 398.2307, found 398.2313.



4-55

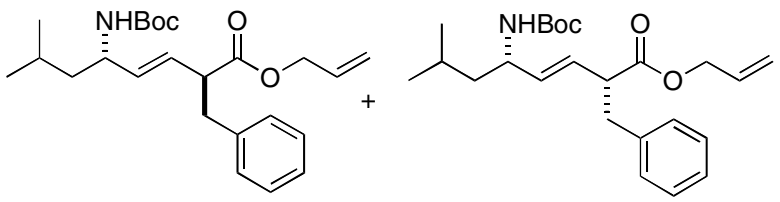
(*S*,*E*) – 2 – Benzyl – 5 - (*tert*-butoxycarbonylamino) - 7-methyloct -2-enoic acid - TEMPO (4-55). To a soluton of **4-53** (250 mg, 0.666 mmol) in THF (10 mL) at 0 ˚C was added LiOH (2.0 M in H_2O, 5.0 eq, 1.67 mL, 3.33 mmol) and the reaction was allowed to stir for 2 h. The reaction mixture was acidified with 1 N HCl, extracted with EtOAc, washed with brine, dried ($MgSO_4$), filtered and concentrated. The crude acid was carried on without further purification. Key ^{1}H NMR data: 7.09 (dd, 1 H, J = 7.3, 7.3 Hz).

To a solution of crude acid (242 mg, 0.669 mmol, crude) in CH_2Cl_2 (14 mL) at 0 °C was added 4-amino tempo (1.5 eq, 171 mg, 1.00 mmol), EDCI (1.2 eq, 154 mg, 0.803 mmol), DMAP (1.1 eq, 89.9 mg, 0.736 mmol) and HOBt-hydrate (1.1 eq, 99.4 mg, 0.736 mmol) and the resulting orange solution was stirred at rt for 14 h. The reaction was diluted with CH_2Cl_2, washed with sat. aq. NH_4Cl and the organic layer dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by chromatography on SiO_2 (1:1 to 2:1, EtOAc/hexanes) to yield 215 mg (63%, 2 steps) of **4-55** as a peach colored solid: ESIMS *m/z* 537 ([M+Na]$^+$, 100), 481 (95), 415 (60); HRMS (ESI) *m/z* calcd for $C_{30}H_{48}N_3O_4Na$ (M + Na) 537.3543, found 537.3580.

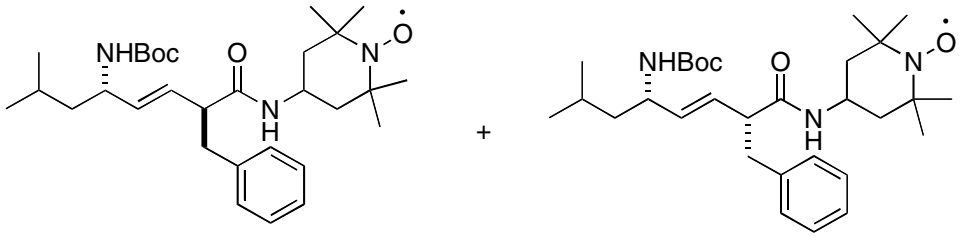


4-56

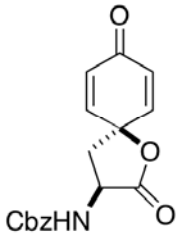
(*S*,*E*)-Allyl 5-(*tert*-butoxycarbonylamino)-7-methyloct-3-enoate (4-56). To a solution of **4-52** (250 mg, 0.921 mmol, crude) in CH_2Cl_2 (10 mL) at rt was added allyl alcohol (2.0 eq, 125 μL, 1.84 mmol), EDCI (1.1 eq, 157 mg, 1.01 mmol) and DMAP (0.1 eq, 11.3 mg, 0.0921 mmol) and the reaction was stirred at rt for 12 h. The reaction was diluted with CH_2Cl_2, washed with 10% HCl, washed with brine, dried ($MgSO_4$), filtered and concentrated. The crude residue was purified by chromatography on SiO_2 (15% EtOAc/hexanes) to yield 249 mg (87%) of **4-56** as a colorless oil: $[\alpha]_D$ -8.6 (*c* 1.1, CH_2Cl_2); IR 3361, 2757, 2930, 2871, 1737, 1696, 1513, 1366, 1246, 1161 cm^{-1}; ^1H NMR δ 6.01-5.83 (m, 1 H), 5.71 (ddt, 1 H, *J* = 15.4, 8.3, 1.0 Hz), 5.50 (dd, 1 H, *J* = 14.6, 5.2 Hz), 5.32 (app ddd, 1 H, *J* = 17.1, 1.5, 1.5 Hz), 5.24 (app ddd, 1 H, *J* = 10.4, 1.3, 1.2 Hz), 4.60 (dd, 1 H, *J* = 1.3, 1.3 Hz), 4.58 (dd, 1 H, *J* = 1.3, 1.3 Hz), 4.39 (bs, 1 H), 4.16 (bs, 1 H), 3.10 (d, 2 H, *J* = 6.9 Hz), 1.76-1.50 (m, 1 H), 1.45 (s, 9 H), 1.40-1.25 (m, 2 H), 0.92 (d, 3 H, *J* = 6.5 Hz), 0.92 (d, 3 H, *J* = 6.6 Hz); ^{13}C NMR δ 171.2, 155.3, 135.5, 132.1, 121.9, 118.3, 79.3, 65.3, 44.7, 37.7, 28.4, 24.7, 22.7, 22.5; ESIMS *m/z* 536 (10), 334 ($[M+Na]^+$, 70), 278 (100), 219 (60); HRMS (ESI) *m/z* calcd for $C_{17}H_{29}NO_4Na$(M+Na) 334.1994, found 334.1983.



(2*S*,5*S*,*E*) - Allyl 2 -benzyl-5-(*tert*-butoxycarbonylamino)-7-methyloct-3-enoate (4-57). To a solution of **4-56** (196 mg, 0.629 mmol) in THF (8 mL) and DMPU (0.5 mL) at -78 ˚C was added LiHMDS (1.05 eq, 114 mg, 0.660 mmol) and resulting solution was stirred at this temperature for 1 h. To the yellow solution was added BnBr (1.05 eq, 78.9 μL, 0.660 mmol) and the reaction was warmed to -40 ˚C and stirred at this temperature for 6 h. The reaction was quenched with sat. aq. NH_4Cl, extracted with EtOAc, washed with brine, dried (MgSO4), filtered and concentrated. The crude residue was purified by chromatography on SiO_2 (15% EtOAc/hexanes) to yield 179 mg (71%) of **4-57** as an inseperable 1.5:1 mixture of diastereomers: $[\alpha]_D$ -4.5 (*c* 1.0, CH_2Cl_2); IR 3375, 2956, 2932, 1734, 1701, 1497, 1365, 1247, 1160 cm^{-1}; ^1H NMR δ 7.44-7.18 (m, 5 H), 6.20-5.87 (m, 1 H), 5.83-5.68 (m, 1 H), 5.46 (dd, 1 H, *J* = 15.4, 6.2 Hz), 5.40-5.25 (m, 2 H), 4.65 (d, 2 H, *J* = 5.6 Hz), 4.42 (bs, 1 H), 4.22 (bs, 1 H), 3.49-3.34 (m, 1 H), 3.21 (dd, 1 H, *J* = 13.5, 7.6 Hz), 2.97-2.75 (m, 1 H), 1.75-1.60 (m, 1 H), 1.57 (s, 5.4 H), 1.56 (s, 3.4 H), 1.45-1.25 (m, 2 H), 1.08-0.91 (m, 6 H); ^{13}C NMR δ 173.0, 173.0, 155.1, 138.6, 138.5, 134.7, 132.0, 129.1, 129.1, 128.3, 127.2, 126.4, 118.1, 79.2, 65.2, 50.8, 44.6, 44.5, 38.7, 28.4, 24.6, 24.6, 22.5; ESIMS *m/z* 424 ($[M+Na]^+$, 100), 368 (20); HRMS (ESI) *m/z* calcd for $C_{24}H_{35}NO_4Na$ (M+Na) 424.2464, found 424.2464.

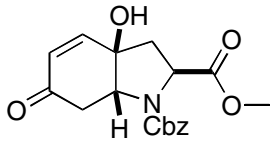


(2*S*,5*S*,*E*) -2-Benzyl-5-(*tert*-butoxycarbonylamino)-7-methyloct - 3 - enoic acid-TEMPO (4-43). To a solution of **4-57** (67.0 mg, 0.167 mmol) in CH_2Cl_2 (1 mL) was added phenyl silane (2.0 eq, 41.2 μL, 0.334 mmol) and $Pd(PPh_3)_4$ (0.02 eq, 3.86 mg, 3.34 μmol) and the reaction was stirred at rt for 8 h. The reaction was filtered through a pad of Celite and concentrated. To a solution of crude acid (60.4 mg, 0.167 mmol, crude) in CH_2Cl_2 (5 mL) at 0 °C was added 4-amino tempo (1.5 eq, 42.9 mg, 0.251 mmol), EDCI (1.0 eq, 25.9 mg, 0.167 mmol) and DMAP (1.0 eq, 20.4 mg, 0.167 mmol) and the resulting orange solution was stirred at rt for 13 h. The reaction was diluted with CH_2Cl_2, washed with sat. aq. NH_4Cl and the organic layer dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by chromatography on SiO_2 (1:1 to 2:1, EtOAc/hexanes) to yield 67.7 mg (79%, 2 steps) of **4-43** as a peach colored solid: ESIMS *m/z* 537 ($[M+Na]^+$, 100), 481 (60); HRMS (ESI) *m/z* calcd for $C_{30}H_{48}N_3O_4Na$ (M + Na) 537.3543, found 537.3528.



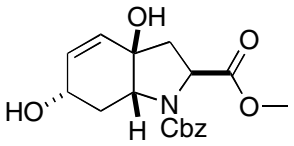
5-23

(*S*)-Benzyl 2,8-dioxo-1-oxaspiro[4.5]deca-6,9-dien-3-ylcarbamate (5-23). To a solution of iodobenzene diacetate (39.1 g, 119 mmol) in MeCN/*i*-PrOH (4:1, 130 mL) was added a solution of Cbz-tyrosine (25.0 g, 79.3 mmol) in MeCN/*i*-PrOH (4:1, 150 mL) dropwise over 1 h. The reaction mixture was stirred for an additional 2 h, quenched with sat. aq. $NaHCO_3$ (500 mL), and extracted with EtOAc (2x). The combined organic layers were washed with $NaHCO_3$ (3 x 500 mL) and brine, dried ($MgSO_4$) and concentrated. The crude residue was dissolved in 80% EtOAc/hexanes (400 mL) and the heterogeneous mixture was filtered though a pad of SiO_2. The resulting solution was concentrated and purified by chromatography on SiO_2 (45% EtOAc/hexanes to 60% EtOAc/hexanes). The orange solid was recrystallized from hot EtOAc/hexanes (placed in -20 °C freezer overnight after being dissolved in boiling solvent) to yield 9.57 g (39%) of spirocycle **5-23** as a colorless solid (white fuzzy needles): $[\alpha]_D$ -26.0 (*c* 1.08, CH_2Cl_2); IR (CH_2Cl_2) 3060, 2956, 1789, 1710, 1674, 1635, 1523, 1198 cm^{-1}; ^1H NMR δ 7.53-7.20 (m, 5 H), 6.86 (bd, 2 H, *J* = 7.5 Hz), 6.43-6.20 (m, 2 H), 5.59 (bs, 1 H), 5.14 (bs, 2 H), 4.70-4.54 (m, 1 H), 2.74 (dd, 1 H, *J* = 11.1, 10.2 Hz), 2.49 (app t, 1 H, *J* = 12.3 Hz); ^{13}C NMR δ 184.2, 173.8, 156.1, 146.3, 144.4, 135.8, 129.8, 129.2, 128.8, 128.6, 128.3, 67.7, 50.5, 38.0; EIMS *m/z* 313 (M^+, 15), 269 (15), 226 (15), 107 (95), 91 (100); HRMS (EI) *m/z* calcd for $C_{17}H_{15}NO_5$ 313.0950, found 313.0940.



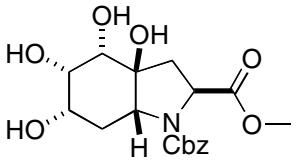
5-5

(2*S*,3a*R*,7a*R*) - 1-Benzyl 2-methyl 3a-hydroxy-6-oxo-3,3a,7,7a-tetrahydro-1*H*-indole-1,2(2*H*,6*H*)-dicarboxylate (5-5). To a solution of KOH (3.0 M in H_2O, 200 mL) and MeOH (200 mL) at -20 °C was added a solution of **5-23** (6.48 g, 20.7 mmol) in 150 mL of MeOH in one portion. The reaction mixture was allowed to stir at -20 °C for 20 min during which time the solution became brown in color. The mixture was quenched by addition of 10% HCl (100 mL), extracted with EtOAc (3 x 150 mL), washed with brine, dried ($MgSO_4$), filtered and concentrated. The crude residue was purified by chromatography on SiO_2 (60% EtOAc/hexames to 80% EtOAc/hexanes) to yield 5.68 g (80%) of methyl ester **5-5** as a colorless waxy solid: $[\alpha]_D$ -130 (*c* 1.0, CH_2Cl_2); IR (CH_2Cl_2) 3034, 2953, 1756, 1686, 1415, 1351, 1124 cm^{-1}; ^1H NMR (DMSO, 380 K) δ 7.43-7.26 (m, 5 H), 6.76 (d, 1 H, *J* = 10.2 Hz), 5.90 (d, 1 H, *J* = 10.5 Hz), 5.40 (bs, 1 H), 5.18-5.03 (m, 2 H), 4.50 (dd, 1 H, *J* = 9.3, 3.0 Hz), 4.24 (dd, 1 H, *J* = 9.3, 5.7 Hz), 3.61 (s, 3 H), 2.93 (dd, 1 H, *J* = 15.9, 5.4 Hz), 2.62 (dd, 1 H, *J* = 16.2, 9.6 Hz), 2.58 (dd, 1 H, *J* = 13.2, 9.3 Hz), 2.29 (ddd, 1 H, *J* = 13.2, 3.0, 0.6 Hz); ^{13}C NMR (DMSO, 380 K) δ 195.4, 170.9, 153.0, 148.8, 136.1, 127.7, 127.6, 127.2, 126.9, 126.9, 73.9, 65.8, 63.7, 58.0, 51.0; ESI-MS *m/z* 368 ($[M+Na]^+$, 50), 302 (10); HRMS (ESI) *m/z* calcd for $C_{18}H_{19}NO_6Na$ (M+Na) 368.1110, found 368.1121.



5-25

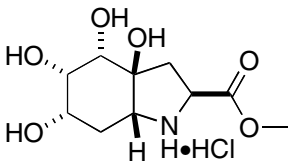
(2*S*,3a*R*,6*S*,7a*R*)-1-Benzyl 2-methyl 3a,6-dihydroxy-3,3a,7,7a-tetrahydro-1*H*-indole-1,2(2*H*,6*H*)-dicarboxylate (5-25). To a solution of **5-5** (1.80 g, 5.21 mmol) in MeOH (35 mL) and THF (35 mL) was added cerium (III) chloride heptahydrate (1.94 g, 5.16 mmol) followed by cooling to 0 °C and addition of sodium borohydride (217 mg, 5.73 mmol) in one portion. The reaction mixture was stirred at 0 °C for 2 h, diluted with EtOAc (200 mL), quenched with water (100 mL) and the layers were separated. The organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated. The crude residue was purified by chromatography on SiO_2 (EtOAc) to yield 1.32 g (73%) of **5-25** as a colorless waxy solid: $[\alpha]_D$ -12.4 (*c* 1.16, CH_2Cl_2); IR (CH_2Cl_2) 3417, 3031, 2953, 1754, 1687, 1417, 1355, 1122 cm^{-1}; ^1H NMR (DMSO, 380 K) δ 7.55-7.20 (m, 5 H), 5.67 (d, 1 H, *J* = 9.9 Hz), 5.53 (dd, 1 H, *J* = 10.2, 2.4 Hz), 5.10 (bs, 2 H), 4.61-4.43 (m, 3 H), 4.16 (bd, 1 H, *J* = 6.0 Hz), 3.90 (dd, 1 H, *J* = 12.3, 4.8 Hz), 3.58 (s, 3 H), 2.60-2.40 (m, 1 H), 2.32 (dd, 1 H, *J* = 13.2, 9.6 Hz), 2.14 (app d, 1 H, *J* = 13.5 Hz), 1.37-1.17 (m, 1 H); ^{13}C NMR (DMSO, 380 K) δ 171.2, 153.2, 136.4, 133.1, 128.7, 127.6, 127.0, 126.8, 74.7, 65.6, 64.0, 63.6, 58.1, 50.8, 40.4, 37.1; EIMS *m/z* 347 (M^+, 10), 329 (40), 244 (100); HRMS (EI) *m/z* calcd for $C_{18}H_{21}NO_6$ 347.1369, found 347.1368.



5-26

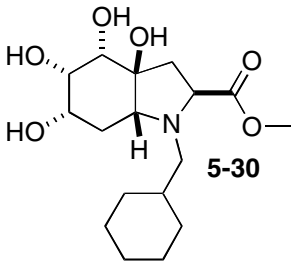
(2*S*,3a*S*,4*S*,5*S*,6*S*,7a*R*) - 1 - Benzyl 2-methyl 3a,4,5,6 – tetrahydroxyhexahydro -1*H*-indole-1,2(2*H*,3*H*)-dicarboxylate (5-26). To a solution of **5-25** (500 mg, 1.44 mmol) in H_2O/THF (1:10, 15 mL) was added OsO_4 (480 μL, 0.144 mmol), NMO (596 mg, 4.32 mmol) and methanesulfonamide (154 mg, 1.58 mmol). The reaction mixture was stirred at rt for 72 h, quenched with $NaSO_3$, diluted with H_2O and EtOAc, extracted with EtOAc (4x), washed with brine, dried ($MgSO_4$) and concentrated. The crude residue was purified by chromatography on SiO_2 (EtOAc to 5% MeOH/EtOAc) to yield 426 mg (78%) of **5-26** as a colorless waxy solid and a 1.4:1 mixture of diastereomers: $[\alpha]_D$ -45.8 (*c* 0.67, MeOH); IR (CH_2Cl_2) 3419, 3033, 2952, 1700, 1417, 1353, 1213, 1069 cm^{-1}; ^1H NMR (MeOD, 600 MHz, rotamers) δ 7.41-7.26 (m, 5 H), 5.20-5.10 (m, 1.60 H), 5.02 (app dd, 0.40 H, *J* = 12.6, 2.4 Hz), 4.48 (app dd, 0.40 H, *J* = 15.0, 9.6 Hz), 4.40 (app dd, 0.60 H, *J* = 15.0, 9.6 Hz), 4.15-3.94 (m, 0.40 H), 3.94-3.89 (m, 0.60 H), 3.85-3.73 (m, 1.60 H), 3.72 (app d, 1.70 H, *J* = 7.2 Hz), 3.67-3.61 (m, 0.60 H), 3.61-3.58 (m, 0.40 H), 3.58-3.54 (m, 1.70 H), 3.46-3.39 (m, 0.40 H), 3.03-2.93 (m, 0.60 H), 2.60-2.50 (m, 0.60 H), 2.45-2.37 (m, 0.14 H), 2.34-2.27 (m, 0.36 H), 2.17 (app dd, 1 H, *J* = 14.4, 7.8 Hz), 2.05 (app dd, 0.40 H, *J* = 13.2, 7.8 Hz); ^{13}C NMR (MeOD, 600 MHz, rotamers) δ 175.1, 174.4, 174.3, 173.9, 156.6, 156.5, 156.2, 156.1, 137.8, 137.8, 129.6, 129.4, 129.2, 129.1, 128.9, 82.2, 81.3, 80.9, 80.1, 75.3, 75.2, 75.1, 75.1, 74.4, 74.3, 73.8, 73.7, 68.4, 68.3, 68.2, 68.1, 68.0, 67.7, 67.6, 64.4, 64.1, 63.4, 63.1, 58.6, 58.5, 52.8, 52.8, 52.7, 38.7, 38.5, 37.7, 37.5, 36.8,

35.9, 33.1, 32.1; ESI-MS *m/z* 404 ([M+Na]$^+$, 100), 365 (25); HRMS (ESI) *m/z* calcd for $C_{18}H_{23}NO_8Na$ (M+Na) 404.1321, found 404.1338.



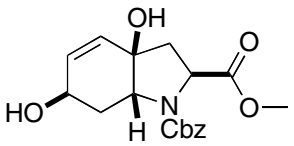
5-28

(2*S*,3a*S*,4*S*,5*S*,6*S*,7a*R*) - Methyl 3a,4,5,6-tetrahydroxyoctahydro - 1*H*-indole-2-carboxylate hydrochloride salt (5-28). To a solution of **5-26** (264 mg, 0.692 mmol) in MeOH (10 mL) was added 10% Pd/C (50 mg). The reaction mixture was stirred under an atmosphere of H_2 for 6 h, filtered though a pad of Celite®, concentrated, and redissolved in MeOH (10 mL). After addition of HCl (5.0 mL, 4.0 M in dioxane), the solution was heated at reflux for 30 min, allowed to cool to rt, and filtered. The solid was dried in vacuo to yield 93 mg (47%) of amine hydrochloride **5-28** as a colorless powder with a dr of >95:5 as determined by ^{1}H NMR analysis of the crude reaction mixture: ^{1}H NMR (MeOD, 600 MHz, crude) δ 4.61 (dd, 1 H, *J* = 11.4, 3.6 Hz), 3.96-3.89 (m, 1 H), 3.85 (s, 3 H), 3.79-3.71 (m, 1 H), 3.71-3.65 (m, 1 H), 3.63-3.53 (m, 1 H), 3.18 (dd, 1 H, *J* = 14.4, 11.4 Hz), 2.34 (dd, 1 H, *J* = 13.8, 2.4 Hz), 1.99-1.89 (m, 2 H).



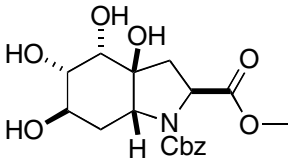
5-30

(2*S*,3a*S*,4*S*,5*S*,6*S*,7a*R*) - Methyl 1 - (cyclohexylmethyl) - 3a,4,5,6-tetrahydroxy - octahydro-1*H*-indole-2-carboxylate (5-30). To a suspension of amine hydrochloride **5-28** (40.0 mg, 0.141 mmol) in MeOH (2 mL) was added acetic acid (40.7 μL, 0.705 mmol, 5 eq), cyclopropanecarboxaldehyde (26.1 μL, 0.211 mmol, 1.5 eq) and MP-cyanoborohydride resin (2.34 mmol/g, 2.5 eq, 151 mg, 0.352 mmol). The reaction mixture was stirred at rt for 48 h and filtered. The filtrate was neutralized with 2 M NH_3 in MeOH, concentrated and purified by chromatography on SiO_2 (5% MeOH/EtOAc) to provide 40.0 mg (83%) of **5-30** as a colorless oil that solidified upon standing: $[\alpha]_D$ -53.1 (*c* 0.91, CH_2Cl_2); IR (CH_2Cl_2) 3334, 2919, 2847, 1732, 1196, 1176, 1134, 1114, 1063 cm^{-1}; ^1H NMR (MeOD) δ 3.85 (app t, 1 H, *J* = 2.7 Hz), 3.63 (s, 3 H), 3.58 (app d, 1 H, *J* = 3.9 Hz), 3.52 (dt, 1 H, *J* = 11.4, 3.9 Hz), 3.31 (dd, 1 H, *J* = 11.1, 3.3 Hz), 2.98 (dd, 1 H, *J* = 14.1, 10.8 Hz), 2.92 (dd, 1 H, *J* = 11.1, 5.1 Hz), 2.47 (dd, 1 H, *J* = 12.3, 6.0 Hz), 2.25 (dd, 1 H, *J* = 12.3, 8.7 Hz), 1.86-1.74 (m, 1 H), 1.74-1.53 (m, 6 H), 1.53-1.36 (m, 1 H), 1.35-1.18 (m, 1 H), 1.18-1.00 (m, 3 H), 0.86-0.65 (m, 2 H); ^{13}C NMR (MeOD) δ 178.7, 82.9, 74.4, 73.8, 69.5, 66.9, 63.6, 57.1, 52.9, 38.7, 37.6, 32.9, 32.8, 28.1, 27.4, 27.2, 26.8; ESIMS *m/z* 344 ($[M+H]^+$, 50), 326 (100), 308 (30); HRMS (ESI) *m/z* calcd for $C_{17}H_{30}NO_6$ (M+H) 344.2073, found 344.2090.



5-31

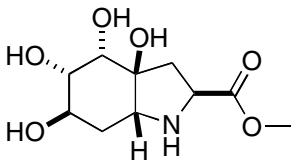
(2*S*,3a*R*,6*R*,7a*R*)-1-Benzyl 2-methyl 3a,6-dihydroxy-3,3a,7,7a-tetrahydro-1*H*-indole-1,2(2*H*,6*H*)-dicarboxylate (5-31). To a solution of **5-5** (4.42 g, 12.8 mmol) in freshly distilled THF (100 mL) at -78 °C was added L-selectride (19.2 mL, 19.2 mmol, 1.5 eq) dropwise (syringe pump) over 1.5 h. The reaction mixture was stirred for an additional hour at -78 °C, quenched with 10% HCl (10 mL) and warmed to rt. The solution was extracted with EtOAc (2x), washed with brine, dried ($MgSO_4$), filtered and concentrated to provide 3.41 g (77%) of **5-31** that was carried on without further purification: $[\alpha]_D$ -15.7 (*c* 1.09, CH_2Cl_2); IR (CH_2Cl_2) 3422, 3031, 2952, 1701, 1416, 1353, 1210 cm^{-1}; ^1H NMR (DMSO, 380 K) δ 7.45-7.25 (m, 5 H), 5.79 (dd, 1 H, *J* = 9.9, 3.9 Hz), 5.60 (d, 1 H, *J* = 10.2 Hz), 4.38 (bs, 2 H), 4.24 (dd, 1 H, *J* = 8.7, 4.5 Hz), 4.05-3.93 (m, 2 H), 3.58 (s, 3 H), 2.22 (dd, 1 H, *J* = 12.9, 8.7 Hz), 2.17-2.04 (m, 2 H), 2.01-1.83 (m, 1 H); ^{13}C NMR (DMSO, 380 K) δ 171.5, 153.2, 136.3, 130.5, 130.3, 127.6, 127.0, 126.8, 73.9, 65.5, 61.1, 60.6, 57.6, 50.8, 40.4, 32.9; ESI-MS *m/z* 370 ($[M+Na]^+$, 25), 286 (10); HRMS (ESI) *m/z* calcd for $C_{18}H_{21}NO_6Na$ (M+Na) 370.1267, found 370.1287.



5-32

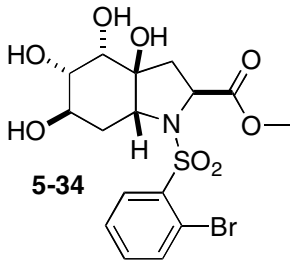
(2*S*,3a*S*,4*S*,5*S*,6*R*,7a*R*) - 1 - Benzyl 2 -methyl 3a,4,5,6-tetrahydroxyhexahydro -1*H*-indole-1,2(2*H*,3*H*)-dicarboxylate (5-32). To a solution of **5-31** (1.00 g, 2.88 mmol in THF (25 mL) and water (2.5 mL) was added methanesulfonamide (307 mg, 3.17 mmol, 1.1 eq), NMO-H_2O (1.19 g, 8.64 mmol, 3.0 eq) and osmium tetroxide (0.3 M in toluene, 747 mg, 0.288 mmol, 0.960 mL) and the reaction mixture was stirred at rt for 48 h. After this time additional osmium tetroxide (0.3 M in toluene, 747 mg, 0.288 mmol, 0.960 mL) was added and the mixture was stirred for an additional 72 h. The solution was quenched with $NaSO_3$, diluted with H_2O and EtOAc, extracted with EtOAc (4x), washed with brine, dried ($MgSO_4$) and concentrated. The crude residue was purified by chromatography on SiO_2 (EtOAc to 5% MeOH/EtOAc) to yield 810 mg (74%) of tetraol **5-32** as a colorless waxy solid: $[\alpha]_D$ -33.4 (*c* 0.44, MeOH); IR (CH_2Cl_2) 3410, 3063, 2952, 2901, 1686, 1419, 1216, 1056 cm^{-1}; ^1H NMR (MeOD, 600 MHz, rotamers) δ 7.42-7.26 (m, 5 H), 5.18 (d, 0.5 H, *J* = 12.6 Hz), 5.15 (d, 0.5 H, *J* = 12.6 Hz), 5.14 (d, 0.5 H, *J* = 12.6 Hz), 4.99 (d, 0.5 H, *J* = 12.6 Hz), 4.41 (app ddd, 1 H, *J* = 19.8, 10.2, 1.2 Hz), 4.12-4.04 (m, 1 H), 3.96 (app dd, 1 H, *J* = 16.8, 3.6 Hz), 3.92-3.87 (m, 0.5 H), 3.87-3.82 (m, 1.5 H), 3.71 (s, 1.5 H), 3.56 (s, 1.5 H), 2.92 (app ddd, 1 H, *J* = 13.8, 10.8, 1.2 Hz), 2.37-2.29 (m, 0.5 H), 2.25-2.18 (m, 0.5 H), 2.15 (app dd, 1 H, *J* = 14.4, 0.6 Hz), 1.63 (ddd, 0.5 H, *J* = 13.8, 10.8, 2.4 Hz), 1.59 (ddd, 0.5 H, *J* = 13.8, 10.8, 2.4 Hz); ^{13}C NMR (MeOD, 150 MHz, rotamers) δ 175.3, 174.9, 156.6, 156.0, 138.0, 137.8, 129.5, 129.4, 129.1, 129.0, 129.0, 128.9, 82.3, 81.3, 73.6, 706., 70.5, 68.2, 68.1, 63.6, 63.4, 58.8, 58.7, 52.8, 52.7, 38.5, 37.4, 32.1, 31.3;

ESIMS *m/z* 404 ([M+Na]$^+$, 100), 365 (15); HRMS (ESI) *m/z* calcd for $C_{18}H_{23}NO_8Na$ (M+Na) 404.1321, found 404.1305.



5-33

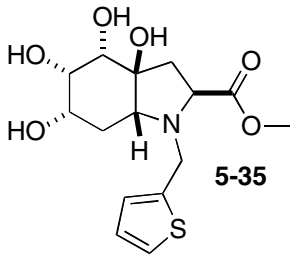
(2*S*,3a*S*,4*S*,5*S*,6*R*,7a*R*) - Methyl 3a,4,5,6 -tetrahydroxyoctahydro-1*H*-indole-2-carboxylate (5-33). To a solution of **5-32** (456 mg, 1.20 mmol) in MeOH (10 mL) was added 10% Pd/C (63.4 mg). The reaction mixture was stirred under an atmosphere of H_2 for 10 h, filtered through a pad of Celite and concentrated to provide 251 mg (85%) of amine **5-33** as an off-white solid that was carried on without further purification: ^{1}H NMR (MeOD, 600 MHz, crude) δ 3.95-3.87 (m, 1 H), 3.87 (app d, 1 H, *J* = 3.6 Hz), 3.81 (dd, 1 H, *J* = 10.2, 4.2 Hz), 3.77 (dd, 1 H, *J* = 5.4, 3.6 Hz), 3.73 (s, 3 H), 3.37-3.27 (m, 1 H), 2.83 (dd, 1 H, *J* = 13.8, 10.2 Hz), 1.99 (dd, 1 H, *J* = 13.8, 4.2 Hz), 1.86-1.76 (m, 1 H), 1.76-1.67 (m, 1 H).



5-34

(2*S*,3a*S*,4*S*,5*S*,6*R*,7a*R*) - Methyl 1 - (2 - bromophenylsulfonyl) - 3a,4,5,6 – tetra hydroxy-octahydro-1*H*-indole-2-carboxylate (5-34). To a solution of **5-33** (24.7 mg, 0.100 mmol) in THF (2 mL) at rt was added Et_3N (15.3 μL, 0.110 mmol), 2-

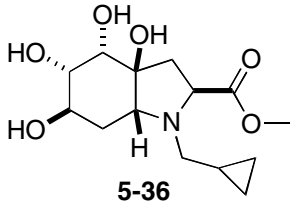
bromobenzenesulfonylchloride (25.6 mg, 0.100 mmol) and DMAP (2.44 mg, 0.0200 mmol). The reaction mixture was stirred at this temperature for 17 h, quenched with 1 M HCl, extracted with EtOAc (4x), washed with brine, dried ($MgSO_4$) and concentrated. The crude residue was purified by chromatography on SiO_2 (EtOAc to 5% MeOH/EtOAc) to yield 26.3 mg (56%) of **5-34** as a colorless solid: Mp 182 ˚C (MeOH); $[\alpha]_D$ +7.6 (*c* 1.8, MeOH; obtained for an 58% *ee* sample); IR (CH_2Cl_2) 3650-2800 (br), 1725, 1434, 1323, 1158, 1102, 1054 cm^{-1}; ^1H NMR (MeOD) δ 8.24 (dd, 1 H, *J* = 7.5, 1.8 Hz), 7.81 (dd, 1 H, *J* = 7.5, 1.8 Hz), 7.57-7.43 (m, 2 H), 4.74 (dd, 1 H, *J* = 10.2, 1.5 Hz), 4.22 (dd, 1 H, *J* = 10.8, 5.7 Hz), 3.96 (d, 1 H, *J* = 3.9 Hz), 3.82 (appt, 1 H, *J* = 3.9 Hz), 3.75-3.67 (m, 1 H), 3.54 (s, 3 H), 3.09 (dd, 1 H, *J* = 14.1, 10.2 Hz), 2.15 (d, 1 H, *J* = 13.8 Hz), 1.90-1.63 (m, 2 H); ^{13}C NMR (MeOD) δ 175.6, 142.4, 136.8, 135.2, 133.3, 129.0, 122.1, 82.9, 73.4, 73.3, 70.7, 67.0, 61.6, 53.1, 38.9, 32.4; HRMS (ESI) *m/z* calcd for $C_{16}H_{20}NO_8NaSBr$ (M+Na) 487.9991, found 487.9994.



5-35

(2*S*,3a*S*,4*S*,5*S*,6*S*,7a*R*) - Methyl 3a,4,5,6-tetrahydroxy-1-(thiophen-2-ylmethyl) octahydro-1*H*-indole-2-carboxylate (5-35). A suspension of amine hydrochloride **5-28** (40.0 mg, 0.141 mmol) in MeOH (2 mL), acetic acid (40.7 μL, 0.705 mmol, 5 eq), thiophene-2-carboxaldehyde (20.0 μL, 0.211 mmol, 1.5 eq) and MP-cyanoborohydride resin (2.34 mmol/g, 2.5 eq, 151 mg, 0.211 mmol) was stirred at rt for 48 h. The reaction

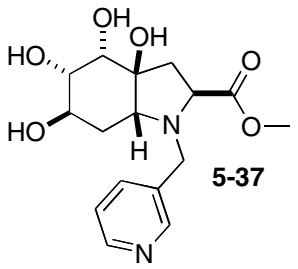
mixture was filtered, neutralized with 2 M NH_3 in MeOH, concentrated and purified by chromatography on SiO_2 (5% MeOH/EtOAc) to provide 38.2 mg (79%) of **5-35** as a colorless oil: $[\alpha]_D$ -64.8 (*c* 1.06, CH_2Cl_2); IR (CH_2Cl_2) 3357, 2949, 1731, 1438, 1213, 1068 cm^{-1}; ^1H NMR (MeOD) δ 7.34 (dd, 1 H, *J* = 5.1, 1.2 Hz), 7.06-6.99 (m, 1 H), 6.96 (dd, 1 H, *J* = 5.1, 3.6 Hz), 4.13, 4.07 (AB, 2 H, *J* = 13.8 Hz), 3.98 (app t, 1 H, *J* = 2.7 Hz), 3.73-3.57 (m, 3 H), 3.66 (s, 3 H), 3.24-3.07 (m, 2 H), 1.95-1.67 (m, 3 H); ^{13}C NMR (MeOD) δ 177.9, 143.3, 127.3, 127.3, 126.4, 82.4, 74.8, 73.6, 69.4, 66.5, 62.4, 52.7, 39.1, 27.2; ESI-MS *m/z* 366 ($[M+Na]^+$, 30), 344 ($[M+H]^+$, 10); HRMS (ESI) *m/z* calcd for $C_{15}H_{22}NO_6S$ (M+H) 344.1168, found 344.1184.



5-36

(2*S*,3a*S*,4*S*,5*S*,6*R*,7a*R*) - Methyl 1 - (cyclopropylmethyl) -3a,4,5,6-tetrahydroxy octahydro-1*H*-indole-2-carboxylate (5-36). To a solution of **5-33** (50.0 mg, 0.202 mmol) in MeOH (2 mL) was added acetic acid (57.9 μL, 1.01 mmol, 5 eq), cyclopropanecarboxaldehyde (23.1 μL, 0.303 mmol, 1.5 eq) and MP-cyanoborohydride resin (2.34 mmol/g, 2.5 eq, 216 mg, 0.506 mmol). The reaction mixture was stirred at rt for 48 h, filtered, neutralized with 2 M NH_3 in MeOH, concentrated and purified by chromatography on SiO_2 (5% MeOH/EtOAc) to provide 49.0 mg (80%) of **5-36** as a colorless oil: $[\alpha]_D$ -69.1 (*c* 1.05, CH_2Cl_2); IR (CH_2Cl_2) 3334, 3001, 2950, 1733, 1438, 1213, 1062 cm^{-1}; ^1H NMR (MeOD) δ 3.97-3.75 (m, 4 H), 3.77 (s, 3 H), 3.51 (app t, 1 H, *J* = 6.0 Hz), 2.99 (dd, 1 H, *J* = 13.8, 10.5 Hz), 2.80 (dd, 1 H, *J* = 12.6, 5.7 Hz), 2.35 (dd, 1

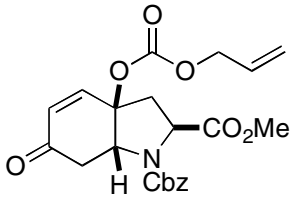
H, *J* = 12.6, 7.8 Hz), 1.99-1.71 (m, 3 H), 1.00-0.81 (m, 1 H), 0.63-0.40 (m, 2 H), 0.24-0.06 (m, 2 H); ^{13}C NMR (MeOD) δ 177.1, 80.9, 75.8, 74.4, 69.1, 66.6, 62.2, 54.6, 52.8, 39.9, 27.8, 10.7, 4.6; EIMS *m/z* 302 ([M+H]$^+$, 5), 284 (100), 230 (50), 224 (70); HRMS (EI) *m/z* calcd for $C_{14}H_{23}NO_6$ 302.1604, found 302.1615.



5-37

(2*S*,3a*S*,4*S*,5*S*,6*R*,7a*R*) - Methyl 3a,4,5,6 - tetrahydroxy-1-(pyridin-3-ylmethyl) octahydro-1*H*-indole-2-carboxylate (5-37). To a solution of **5-33** (50.0 mg, 0.202 mmol) in MeOH (2 mL) was added acetic acid (57.9 µL, 1.01 mmol, 5 eq), pyridine-3-carboxaldehyde (29.1 µL, 0.303 mmol, 1.5 eq) and MP-cyanoborohydride resin (2.34 mmol/g, 2.5 eq, 216 mg, 0.506 mmol). The reaction mixture was stirred at rt for 48 h, filtered, neutralized with 2 M NH_3 in MeOH, concentrated in vacuo and purified by chromatography on SiO_2 (short plug, 5% MeOH/EtOAc to 10% MeOH/EtOAc) to yield 51.0 mg (75%) of **5-37** as a colorless oil: $[\alpha]_D$ -32.6 (*c* 0.95, CH_2Cl_2); IR (CH_2Cl_2) 3319, 2949, 1730, 1432, 1365, 1211, 1063 cm^{-1}; ^{1}H NMR (MeOD) δ 8.40 (bs, 1 H), 8.30 (d, 1 H, *J* = 3.9 Hz), 7.78 (d, 1 H, *J* = 7.5 Hz), 7.27 (dd, 1 H, *J* = 7.5, 4.8 Hz), 3.92-3.64 (m, 5 H), 3.52-3.40 (m, 1 H), 3.44 (s, 3 H), 3.30-3.21 (m, 1 H), 2.87 (dd, 1 H, *J* = 13.8, 10.5 Hz), 1.80-1.61 (m, 3 H); ^{13}C NMR (MeOD) δ 177.4, 150.5, 149.0, 139.1, 136.7, 125.3, 81.8, 74.6, 74.2, 69.7, 66.0, 62.6, 52.5, 51.1, 39.6, 27.5; ESI-MS *m/z* 339 ([M+H]$^+$, 10),

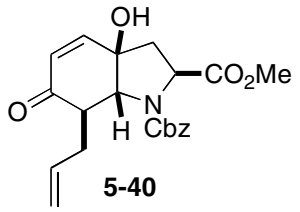
321 (100), 261 (30), 246 (40); HRMS (ESI) *m/z* calcd for $C_{16}H_{22}N_2O_6$ (M+H) 339.1556, found 339.1544.



5-50

(2*S*,3a*R*,7a*R*) - 1 - Benzyl 2 - methyl 3a -(allyloxycarbonyloxy)-6-oxo-3,3a,7,7a - tetrahydro-1*H*-indole-1,2(2*H*,6*H*)-dicarboxylate (5-50). To a solution of **5-5** (7.00 g, 20.3 mmol) in THF (190 mL) was added NaH (60% in mineral oil, 1.2 eq, 973 mg, 24.3 mmol) and the reaction mixture stirred at rt for 30 min followed by addition of allylchloroformate (2.0 eq, 4.44 mL, 40.5 mmol). The reaction mixture was stirred at rt for 4.5 h, quenched with sat. aq. NH_4Cl, extracted with EtOAc (2x), washed with brine, dried ($MgSO_4$), filtered and concentrated. The crude residue was purified by chromatography on SiO_2 (40% EtOAc/hexanes) to yield 7.11 g (82%) of **5-50** as a colorless oil: $[\alpha]_D$ -30.7 (*c* 0.9, $CHCl_3$); IR (CH_2Cl_2) 2953, 2919, 2851, 1743, 1705, 1680, 1410, 1244, 1229, 1034 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz, rotamers) δ 7.39-7.26 (m, 5 H), 6.93 (d, 0.5 H, *J* = 8.4 Hz), 6.91 (d, 0.5 H, *J* = 8.4 Hz), 6.11 (d, 0.5 H, *J* = 10.2 Hz), 6.10 (d, 0.5 H, *J* = 10.8 Hz), 5.93-5.84 (m, 1 H), 5.36 (dd, 0.5 H, *J* = 2.4, 1.2 Hz), 5.33 (dd, 0.5 H, *J* = 3.0, 0.6 Hz), 5.28 (d, 0.5 H, *J* = 1.8 Hz), 5.26 (d, 0.5 H, *J* = 1.8 Hz), 5.22 (d, 0.5 H, *J* = 12.0 Hz), 5.20 (d, 0.5 H, *J* = 12.0 Hz), 5.12 (d, 0.5 H, *J* = 12.0 Hz), 5.03 (d, 0.5 H, *J* = 12.0 Hz), 4.89 (dd, 0.5 H, *J* = 9.6, 6.6 Hz), 4.84 (dd, 0.5 H, *J* = 10.2, 6.6 Hz), 4.67 (d, 0.5 H, *J* = 9.0 Hz), 4.61-4.55 (m, 2.5 H), 3.74 (s, 1.5 H), 3.56 (s, 1.5 H), 3.37 (dd, 0.5 H, *J* = 16.8, 6.6 Hz), 3.20 (dd, 0.5 H, *J* = 16.8, 6.6 Hz), 2.93 (d, 0.5 H, *J* = 14.4 Hz), 2.88 (d, 0.5

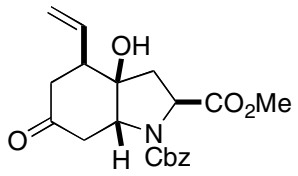
H, J = 14.4 Hz), 2.61 (dd, 0.5 H, J = 13.8, 9.0 Hz), 2.56 (dd, 0.5 H, J = 14.4, 9.6 Hz), 2.43 (dd. 0.5 H, J = 16.8, 10.2 Hz), 2.33 (dd, 0.5 H, J = 16.8, 10.8 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz, rotamers) δ 194.6, 194.5, 171.1, 170.5, 153.9, 153.6, 152.6, 152.5, 143.6, 143.2, 135.9, 135.7, 130.9, 130.6, 130.3, 128.5, 128.4, 128.3, 128.2, 128.1, 128.1, 119.3, 119.2, 84.8, 83.5, 68.6, 67.7, 67.3, 61.3, 60.8, 58.3, 58.1, 52.5, 52.3, 42.6, 41.4, 39.5, 38.3.



5-40

(2*S*,3a*R*,7*R*,7a*R*) - 1 - Benzyl 2 - methyl 7 – allyl - 3a -hydroxy-6-oxo-3,3a,7,7a-tetrahydro-1*H*-indole-1,2(2*H*,6*H*)-dicarboxylate (5-40). To a solution of **5-50** (99.1 mg, 0.231 mmol) in THF (5 mL) at 0 °C was added LiHMDS (41.8 mg, 0.243 mmol) and the resulting yellow solution stirred for 20 min. To this reaction mixture was added $Pd(PPh_3)_4$ (20 mol %, 53.3 mg, 0.0462 mmol) and the reaction stirred at 0 °C for an additional 30 min. The reaction mixture was quenched with sat. aq. NH_4Cl, washed with brine, dried ($MgSO_4$), filtered and concentrated. The crude residue was purified by chromatography on SiO_2 (50% EtOAc/hexanes) to yield 59.0 mg (66%) of **5-40** as a light yellow oil: $[\alpha]_D$ -21.2 (*c* 1.2, $CHCl_3$); IR (CH_2Cl_2) 3419, 2955, 1682, 1408, 1341, 1213, 1121, 916 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz, rotamers) δ 7.41-7.29 (m, 5 H), 6.81 (d, 0.5 H, J = 10.2 Hz), 6.80 (d, 0.5 H, J = 10.2 Hz), 6.03 (d, 0.5 H, J = 12.0 Hz), 6.01 (d, 0.5 H, J = 12.0 Hz), 5.93-5.83 (m, 0.5 H), 5.72-5.60 (m, 0.5 H), 5.23-5.16 (m, 2 H), 5.12 (d, 0.5 H, J = 12.0 Hz), 5.05 (d, 0.5 H, J = 10.8 Hz), 5.01 (d, 0.5 H, J = 12.0 Hz), 4.94-4.85 (m, 1 H), 4.79 (s, 0.5 H), 4.57 (d, 0.5 H, J = 10.8 Hz), 4.51 (d, 0.5 H, J = 10.2 Hz), 4.47 (d, 0.5

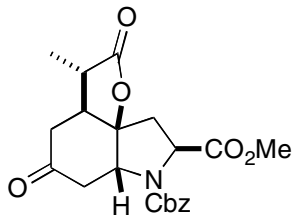
H, J = 9.6 Hz), 4.41 (d, 0.5 H, J = 10.8 Hz), 3.88 (s, 1.5 H), 3.44 (s, 1.5 H), 2.70-2.61 (m, 1 H), 2.59 (d, 0.5 H, J = 10.2 Hz), 2.57 (d, 0.5 H, J = 10.2 Hz), 2.50-2.43 (m, 0.5 H), 2.43-2.35 (m, 1 H), 2.33-2.23 (m, 1.5 H); ^{13}C NMR ($CDCl_3$, 150 MHz, rotamers) δ 197.1, 197.0, 175.5, 175.2, 154.9, 154.3, 147.2, 147.2, 135.4, 135.2, 135.1, 129.1, 129.0, 128.6, 128.5, 128.4, 117.4, 117.0, 77.1, 76.1, 69.9, 69.5, 68.2, 67.9, 59.0, 58.6, 53.4, 52.9, 52.7, 52.6, 41.3, 40.1, 30.5, 30.0; EIMS m/z 385 ($[M]^+$, 65), 344 (45), 282 (100), 250 (45); HRMS (EI) m/z calcd for $C_{21}H_{23}NO_6$ 385.1525, found 385.1533.



5-53

(2*S*,3a*R*,4*S*,7a*R*) - 1-Benzyl 2-methyl 3a-hydroxy-6-oxo-4-vinylhexahydro-1*H*-indole-1,2(2*H*,3*H*)-dicarboxylate (5-53). To a suspension of $AlCl_3$ (11.7 g, 86.9 mmol) in CH_2Cl_2 (50 mL) at 0 °C was added vinylmagnesium chloride (1.6 M in THF, 163 mL, 261 mmol) dropwise. The reaction mixture was stirred at 0 ˚C for 4 h followed by addition of **5-5** (10.0 g, 29.0 mmol) in CH_2Cl_2 (25 mL) in one portion and the mixture was allowed to stir for an additional 4 h at this temperature. The reaction mixture was carefully quenched with 10% aq. HCl, extracted with EtOAc (3x), washed with brine, dried ($MgSO_4$) and concentrated. The crude residue was purified by chromatography on SiO_2 (40% EtOAc/hexanes to 50% EtOAc/hexanes) to yield 6.79 g (63%) of **5-53** as a light yellow oil that was > 95:5 dr by ^{1}H NMR analysis of the crude reaction mixture: $[\alpha]_D$ -25.9 (*c* 1.1, $CHCl_3$); IR (CH_2Cl_2) 3452, 2953, 1749, 1702, 1406, 1349, 1206, 1115 cm^{-1}; ^{1}H NMR (CD_2Cl_2, 600 MHz, rotamers) δ 7.41-7.27 (m, 5 H), 5.98-5.90 (m, 1 H), 5.25-

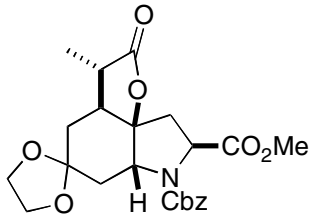
5.11 (m, 3.4 H), 5.01 (d, 0.6 H, J = 12 Hz), 4.54 (s, 0.4 H), 4.53 (s, 0.6 H), 4.13-4.03 (m, 1 H), 3.76 (s, 1.4 H), 3.59 (s, 1.6 H), 3.37 (bs, 0.4 H), 3.12 (dd, 0.6 H, J = 16.2, 5.4 Hz), 3.07 (bs, 0.6 H), 2.95 (dd, 0.4 H, J = 16.2, 4.8 H), 2.67-2.59 (m, 1 H), 2.57-2.45 (m, 1 H), 2.40 (d, 0.4 H, J = 9.0 Hz), 2.38 (d, 0.6 H, J = 9.0 Hz), 2.32-2.18 (m, 3 H); ^{13}C NMR (CD_2Cl_2, 150 MHz, rotamers) δ 208.2, 208.1, 174.8, 174.5, 154.9, 154.3, 136.4, 135.3, 135.2, 128.6, 128.5, 128.2, 128.2, 128.0, 128.0, 117.7, 117.5, 80.6, 79.4, 67.5, 67.2, 65.3, 64.7, 59.4, 59.2, 52.8, 52.6, 46.0, 43.4, 42.3, 41.7, 40.6, 40.6, 40.5; EIMS m/z 373 ($[M]^+$, 20), 355 (40), 314 (60), 270 (100), 92 (90); HRMS (EI) m/z calcd for $C_{20}H_{23}NO_6$ 373.1525, found 373.1522.



5-63

(3a*S*,6a*R*,8*S*,9^1*R*) - 7 - Benzyl 8 - methyl 3-methyl-2,5-dioxooctahydrofuro[2,3-*d*]indole-7,8(2*H*)-dicarboxylate (5-63). To a solution of **5-5** (1.00 g, 2.90 mmol) in toluene (30 mL) at 0 °C was added 2-bromopropionic acid (1.05 eq, 275 μL, 3.04 mmol) and DMAP (10 mol%, 35.4 mg, 0.290 mmol). To this reaction mixture was added a solution of DCC (1.05 eq, 683 mg, 304 mmol) in toluene (10 mL) over the course of 1 h. After addition was complete the reaction mixture was stirred for an additional 3 h, quenched with sat. aq. NH_4Cl, washed with $NaHCO_3$, washed with brine, dried ($MgSO_4$), filtered and concentrated. The crude residue was purified by chromatography on SiO_2 (40% EtOAc/hexanes) to yield 1.17 g (84%) of α-bromo ester **5-61** as a colorless oil.

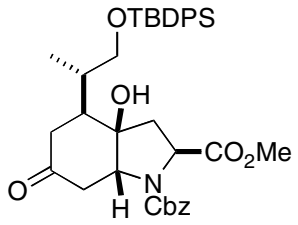
To a solution of **5-61** (1.05 g, 2.19 mmol) in toluene (300 mL) at 100 °C was added Bu_3SnH (1.03 mL, 3.72 mmol, 1.7 eq.) and AIBN (10 mol%, 35.9 mg, 0.219 mmol) in toluene (20 mL) via syringe pump over 15 h. The reaction mixture was cooled to rt, concentrated *in vacuo* and the crude residue purified by chromatography on SiO_2 (70% EtOAc/hexanes) to yield 640 mg (73%) of **5-63** as a colorless solid: $[\alpha]_D$ -42.4 (*c* 1.0, $CHCl_3$); IR (CH_2Cl_2) 2953, 1775, 1699, 1408, 1346, 1202, 1166, 1113, 1035 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz, rotamers) δ 7.32-7.21 (m, 5 H), 5.16-5.08 (m, 1.45 H), 4.96 (d, 0.55 H, *J* = 12.0 Hz), 4.59 (d, 0.45 H, *J* = 9.0 Hz), 4.54 (d, 0.55 H, *J* = 9.0 Hz), 4.31 (dd, 0.55 H, *J* = 11.4, 6.0 Hz), 4.24 (dd, 0.45 H, *J* = 12.0, 6.0 Hz), 3.69 (s, 1.35 H), 3.54 (s, 1.65 H), 3.18 (dd, 0.55 H, *J* = 16.2, 5.4 Hz), 2.96 (dd, 0.45 H, *J* = 15.6, 5.4 Hz), 2.65 (d, 0.45 H, *J* = 9.6 Hz), 2.62 (d, 0.55 H, *J* = 9.6 Hz), 2.56-2.46 (m, 2 H), 2.43-2.36 (m, 1 H), 2.36-2.25 (m, 2 H), 2.17-2.09 (m, 1 H), 1.25 (d, 1.65 H, *J* = 7.2 Hz), 1.24 (d, 1.35 H, 6.6 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz, rotamers) δ 205.1, 205.1, 175.8, 175.6, 170.9, 170.3, 153.8, 153.7, 135.8, 135.7, 128.6, 128.4, 128.3, 128.2, 128.2, 128.1, 88.4, 87.5, 67.7, 67.4, 61.7, 61.3, 58.2, 58.2, 52.7, 52.6, 44.4, 44.3, 43.6, 42.4, 40.9, 40.8, 40.5, 40.2, 40.1, 38.7, 15.2, 15.0; EIMS *m/z* 401 ($[M]^+$, 25), 342 (50), 298 (90), 266 (35), 208 (25); HRMS (EI) *m/z* calcd for $C_{21}H_{23}NO_7$ 401.1475, found 401.1461.



5-64

(3a'*S*,6a'*R*,8'*S*,9^{1}'*R*) - 7' - Benzyl 8' - methyl 3' – methyl - 2' – oxohexahydro - 2'*H*-spiro [[1,3] dioxolane-2,5'-furo[2,3-*d*]indole]-7',8'(3'*H*)-dicarboxylate (5-64). To a solution of **5-63** (4.65 g. 11.6 mmol) in benzene (150 mL) was added ethylene glycol (5 eq, 3.23 mL, 57.9 mmol) and PPTS (728 mg, 2.90 mmol) and the resulting solution was heated at reflux for 2 h (azeotropically removing water via a Dean-Stark apparatus). The reaction mixture was cooled to rt and the benzene removed *in vacuo* to provide a colorless solid. The solid was dissolved in EtOAc (required heating), washed with $NaHCO_3$, washed with brine, dried ($MgSO_4$), filtered and concentrated to yield 4.89 g (94%) of **5-64** as a colorless solid: $[\alpha]_D$ -31.2 (*c* 1.1, $CHCl_3$); IR (CH_2Cl_2) 2976, 2934, 2883, 1761, 1713, 1411, 1342, 1196, 1130, 1047, 990 cm^{-1}; ^{1}H NMR (d_6-DMSO, 600 MHz, 1:1 ratio of rotamers) δ 7.46-7.31 (m, 5 H), 5.22 (d, 0.5 H, *J* = 12.6 Hz), 5.13 (d, 0.5 H, *J* = 12.6 Hz), 5.09 (d, 0.5 H, *J* = 12.6 Hz), 5.03 (d, 0.5 H, *J* = 12.6 Hz), 4.56 (d, 0.5 H, *J* = 10.2 Hz), 4.49 (d, 0.5 H, *J* = 10.2 Hz), 4.03-3.74 (m, 5 H), 3.68 (s, 1.5 H), 3.60 (s, 1.5 H), 3.08-2.95 (m, 2 H), 2.52-2.44 (m, 1 H), 2.34 (ddd, 0.5 H, *J* = 13.2, 6.0, 2.4 Hz), 2.25 (d, 0.5 H, *J* = 14.4 Hz), 2.21 (d, 0.5 H, *J* = 15.0 Hz), 2.19 (ddd, 0.5 H, 13.2, 5.4, 2.4 Hz), 1.94-1.78 (m, 2 H), 1.56 (d, 0.5 H, *J* = 12.6 Hz), 1.54 (d, 0.5 H, *J* = 12.6 Hz), 1.13 (d, 1.5 H, *J* = 6.6 Hz), 1.11 (d, 1.5 H, *J* = 7.2 Hz); ^{13}C NMR (d_6-DMSO, 150 MHz, rotamers) δ 177.8, 177.8, 172.1, 171.5, 154.2, 154.1, 137.5, 129.4, 129.3, 129.0, 128.8, 128.7, 128.3, 107.8, 107.7,

88.8, 87.7, 67.3, 67.2, 65.3, 65.2, 64.2, 64.0, 62.4, 62.0, 57.7, 57.6, 52.9, 52.9, 43.8, 43.8, 39.2, 39.2, 38.3, 37.8, 37.2, 37.1, 30.8, 30.8, 13.8, 13.8.

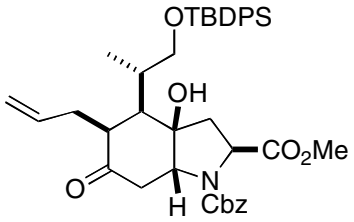


5-66

(2*S*,3a*R*,4*S*,7a*R*)-1-Benzyl 2-methyl 4-(1-(*tert*-butyldiphenylsilyloxy) propan-2-yl)-3a-hydroxy-6-oxohexahydro-1*H*-indole-1,2(2*H*,3*H*)-dicarboxylate (5-66). To a solution of **5-64** (4.89 g, 10.9 mmol) in THF (120 mL) at -78 ˚C was added DIBAL-H (1.0 M in hexanes, 12.0 mL, 12.0 mmol) in one portion. The reaction mixture was allowed to warm to rt and stirred at this temp for 18 h. The reaction mixture was carefully quenched with 10% aq. HCl, extracted with EtOAc (3x), washed with brine, dried ($MgSO_4$), filtered and concentrated. The crude residue was dissolved in MeOH/H_20 (80 mL, 10:1) and $NaBH_4$ (4.0 eq, 1.65 g, 43.7 mmol) was added in 4 portions. The reaction mixture was heated to 70 ˚C and stirred at this temperature for 8 h, diluted with EtOAc (200 mL), washed with sat. aq. $NaHCO_3$, washed with brine, dried ($MgSO_4$), filtered and concentrated to provide 2.37 g (48%) of crude **5-65** as an off-white solid.

To a solution of **5-65** (1.75 g, 3.88 mmol) in dichloromethane/DMF (5:1, 30 mL) was added imidazole (267 mg, 3.88 mmol) and TBDPSCl (1.03 mL, 3.88 mL) and the resulting reaction mixture was stirred at rt for 6 h. The reaction mixture was filtered through a pad of silica gel (washed with EtOAc) and concentrated to provide 2.25 g (84%) of crude ketal as a light yellow oil.

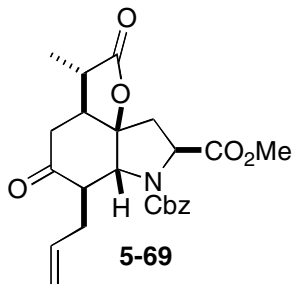
To a solution of crude ketal (2.12 g, 3.07 mmol) in acetone (40 mL) was added PPTS (77.0 mg, 0.306 mmol) and water (0.1 mL) and the reaction mixture was heated to reflux and stirred at this temperature for 14 h. The reaction mixture was concentrated, dissolved in EtOAc, washed with sat. aq. $NaHCO_3$, washed with brine, dried ($MgSO_4$), filtered and concentrated. The crude residue was purified by chromatography on SiO_2 (30% EtOAc/hexanes) to provide 1.87 g (94%) of **5-66** as a colorless oil: ^{1}H NMR ($CDCl_3$, 600 MHz, 1:1 ratio of rotamers) δ 7.65-7.58 (m, 4 H), 7.47-7.28 (m, 11 H), 5.22 (d, 0.5 H, *J* = 12.6 Hz), 5.21 (d, 0.5 H, *J* = 12.0 Hz), 5.13 (d, 0.5 H, *J* = 12.6 Hz), 5.02 (d, 0.5 H, 12.0 Hz), 4.54 (d, 0.5 H, *J* = 9.6 Hz), 4.51 (d, 0.5 H, *J* = 9.0 Hz), 4.16 (dd, 0.5 H, *J* = 13.2, 4.8 Hz), 4.09 (dd, 0.5 H, *J* = 13.2, 4.8 Hz), 4.01 (s, 0.5 H), 3.82 (s, 1.5 H), 3.76 (s, 0.5 H), 3.58 (s, 1.5 H), 3.55 (app dd, 1 H, *J* = 10.8, 4.2 Hz), 3.39 (app dd, 1 H, *J* = 9.6, 9.6 Hz), 3.18 (dd, 0.5 H, *J* = 16.8, 5.4 Hz), 2.93 (dd, 0.5 H, *J* = 16.8, 4.2 Hz), 2.43-2.19 (m, 3 H), 2.18-2.03 (m, 4 H), 1.05 (s, 4.5 H), 1.05 (s, 4.5 H), 0.90 (d, 1.5 H, *J* = 7.2 Hz), 0.89 (d, 1.5 H, *J* = 6.6 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz, rotamers) δ 210.0, 209.7, 175.4, 175.1, 154.9, 154.1, 135.9, 135.9, 135.5, 133.2, 133.1, 133.1, 133.0, 129.9, 129.8, 128.6, 128.5, 128.3, 128.2, 128.1, 128.1, 127.8, 127.8, 82.4, 81.3, 67.7, 67.4, 67.1, 67.0, 66.1, 65.4, 59.5, 59.2, 53.0, 52.7, 43.1, 42.1, 42.1, 41.3, 41.1, 41.0, 37.5, 37.3, 35.4, 35.3, 26.9, 19.1, 13.9, 13.8.



5-67

(2*S*,3a*R*,4*R*,5*S*,7a*R*)-1-Benzyl 2-methyl 5-allyl-4-(1-(*tert*-butyldiphenylsilyloxy) propan-2-yl)-3a-hydroxy-6-oxohexahydro-1*H*- indole - 1,2(2*H*,3*H*) - dicarboxylate (5-67). To a solution of **5-66** (725 mg, 1.12 mmol) in THF (15 mL) at -78 ˚C was added LiHMDS (2.5 eq, 474 mg, 2.81 mmol) and the resulting yellow solution stirred at this temperature for 1 h. Allyl iodide (5.0 eq, 531 μL, 5.61 mmol) was then added in one portion and the reaction mixture allowed to warm to -40 ˚C and stirred at this temperature for 5 h. The reaction mixture was quenched at this temperature with sat. aq. NH_4Cl, extracted with EtOAc (3x), washed with brine, dried ($MgSO_4$), filtered and concentrated. The crude residue was purified by chromatography on SiO_2 (15% EtOAc/hexanes) to yield 457 mg (59%) of **5-67** as a light yellow oil: ^{1}H NMR ($CDCl_3$, 600 MHz, 1:1 ratio of rotamers) δ 7.70-7.61 (m, 4 H), 7.49-7.28 (m, 11 H), 5.69-5.57 (m, 1 H), 5.22 (d, 0.5 H, *J* = 12.0 Hz), 5.21 (d, 0.5 H, *J* = 12.6 Hz), 5.13 (d, 0.5 H, *J* = 12.6 Hz), 5.01 (d, 0.5 H, *J* = 12.6 Hz), 4.99-4.92 (m, 2 H), 4.56 (s, 0.5 H), 4.49 (d, 0.5 H, *J* = 9.0 Hz), 4.46 (s, 0.5 H), 4.45 (d, 0.5 H, *J* = 8.4 Hz), 4.22 (dd, 0.5 H, *J* = 9.6, 6.6 Hz), 4.16-4.09 (m, 0.5 H), 3.79 (s, 1.5 H), 3.75-3.69 (m, 1 H), 3.60-3.54 (m, 1 H), 3.56 (s, 1.5 H), 3.15 (dd, 0.5 H, *J* = 15.6, 6.6 Hz), 2.95 (dd, 0.5 H, *J* = 15.6, 6.0 Hz), 2.54-2.41 (m, 2 H), 2.40-2.26 (m, 3 H), 2.26-2.11 (m, 3 H), 1.11-1.03 (m, 3 H), 1.07 (s, 9 H); ^{13}C NMR ($CDCl_3$, 150 MHz, rotamers) δ 211.1, 174.5, 174.3, 154.8, 154.1, 136.1, 136.0, 135.8, 135.6, 134.9, 134.7, 132.9, 132.8, 132.8, 130.0, 129.9, 129.9, 128.6, 128.5, 128.3, 128.2, 128.1, 127.8, 127.8, 117.7, 117.6,

81.2, 79.8, 67.6, 67.3, 66.0, 65.9, 65.4, 64.7, 52.9, 52.5, 46.8, 46.7, 46.2, 45.9, 43.6, 42.8, 42.4, 35.2, 35.0, 33.0, 32.8, 26.9, 19.2, 15.7, 15.6, 14.2.



5-69

(3a*S*,6*R*,6a*R*,8*S*,9[1]*R*) – 7 - Benzyl 8 - methyl 6 – allyl – 3 – methyl - 2,5 – dioxo octahydrofuro [2,3-*d*]indole-7,8(2*H*)-dicarboxylate (5-69). To a solution of **5-40** (127 mg, 0.330 mmol) in toluene (12 mL) at 0 °C was added 2-bromopropionic acid (1.05 eq, 32.4 μL, 0.346 mmol) and DMAP (10 mol%, 4.03 mg, 0.0330 mmol). To the resulting reaction mixture was added a solution of DCC (1.0 eq, 68.0 mg, 0.330 mmol) in toluene (3 mL) over the course of 1 h and the reaction mixture was stirred for an additional 2 h. The reaction mixture was washed with sat. aq. NH_4Cl, washed with $NaHCO_3$, washed with brine, dried ($MgSO_4$), filtered and the toluene solution was carried on to the next step without concentration or further purification.

To a solution of **5-68** (171 mg, 0.329 mmol) in toluene (20 mL) at 90 °C was added a solution of Bu_3SnH (2.0 eq, 182 μL, 0.657 mmol) and AIBN (10 mol%, 5.4 mg, 0.0329 mmol) in toluene (1 mL) via syringe pump over 5 h. The reaction mixture was cooled to rt, concentrated *in vacuo* and the crude residue purified by chromatography on SiO_2 (60% EtOAc/hexanes) to yield 85.0 mg (59%, 2 steps) of **5-69** as a colorless solid: IR (CH_2Cl_2) 2951, 1760, 1708, 1406, 1340, 1216, 1166, 1121, 1010 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz, 6:4 mixture of rotamers – contains EtOAc and tin by-product) δ 7.40-

7.28 (m, 5 H), 5.84-5.74 (m, 0.6 H), 5.64-5.56 (m, 0.4 H), 5.25-4.82 (m, 4 H), 4.63-4.57 (m, 1 H), 4.35 (d, 0.6 H, J = 10.8 Hz), 4.15 (d, 0.4 H, J = 10.8 Hz), 3.79 (s, 1.2 H), 3.54 (s, 1.8 H), 2.95-2.86 (m, 1 H), 2.75-2.58 (m, 2 H), 2.58-2.25 (m, 7 H), 1.33-1.24 (m, 3 H).

APPENDIX A

X-ray Structrure and Data for **1-51**

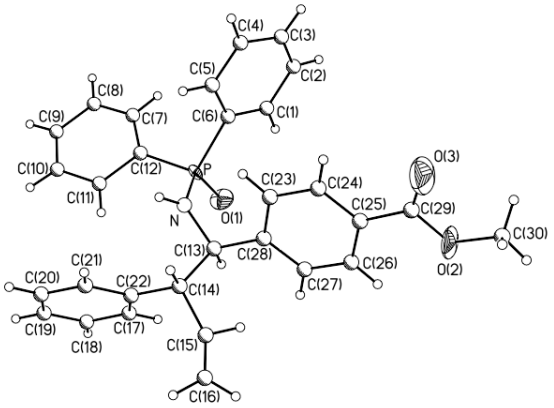


Table 6-1. Crystal data and structure refinement for **1-51.**

Identification code	1-51
Empirical formula	C30 H28 N O3 P
Formula weight	481.50
Temperature	295(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)/c
Unit cell dimensions	a = 10.4622(16) Å α= 90°.
	b = 24.020(4) Å β= 99.629(4)°.
	c = 10.5456(17) Å γ = 90°.
Volume	2612.8(7) $Å^3$
Z	4
Density (calculated)	1.224 Mg/m^3
Absorption coefficient	0.136 mm^{-1}
F(000)	1016
Crystal size	0.37 x 0.03 x 0.03 mm^3
Theta range for data collection	1.70 to 22.50°.
Index ranges	-11<=h<=11, -25<=k<=25, -11<=l<=11
Reflections collected	16213

Independent reflections	3414 [R(int) = 0.3255]
Completeness to theta = 22.50°	100.0 %
Absorption correction	sadabs
Max. and min. transmission	0.9959 and 0.9513
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3414 / 0 / 161
Goodness-of-fit on F^2	1.156
Final R indices [I>2sigma(I)]	R1 = 0.2114, wR2 = 0.3576
R indices (all data)	R1 = 0.2941, wR2 = 0.3990
Largest diff. peak and hole	0.537 and -0.545 e.$Å^{-3}$

Table 6-2. Atomic coordinates and equivalent isotropic displacement parameters for **1-51.**

Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **1-51**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
P	4252(4)	2444(2)	2(3)	15(1)
N	5334(10)	2294(4)	1261(10)	13(3)
O(1)	4832(10)	2431(5)	-1173(9)	41(3)
C(1)	3486(16)	3496(7)	-765(16)	37(5)
O(2)	9718(13)	4709(5)	1589(15)	67(5)
C(2)	2950(20)	4030(10)	-650(20)	79(7)
C(3)	2560(20)	4154(11)	430(20)	76(7)
O(3)	8385(17)	4885(6)	2962(19)	103(7)
C(4)	2550(20)	3789(9)	1430(20)	65(6)
C(5)	3044(19)	3260(9)	1320(20)	58(6)
C(6)	3510(14)	3133(6)	211(14)	23(4)
C(7)	1726(16)	2035(8)	-513(16)	40(5)
C(8)	804(19)	1660(8)	-586(17)	46(5)
C(9)	1110(20)	1136(9)	-120(18)	57(6)
C(10)	2290(20)	1008(9)	432(19)	60(6)
C(11)	3290(18)	1400(7)	480(16)	41(5)
C(12)	2977(16)	1961(7)	-6(15)	30(4)
C(13)	6738(16)	2363(7)	1314(16)	38(5)
C(14)	7427(15)	1935(6)	2284(15)	26(4)
C(15)	8860(30)	1946(14)	2370(30)	122(11)
C(16)	9840(20)	1751(10)	2650(20)	72(7)
C(17)	6930(20)	1060(9)	1000(20)	61(6)
C(18)	6480(20)	516(10)	830(20)	73(7)
C(19)	6010(20)	270(10)	1780(20)	75(7)
C(20)	5970(20)	558(9)	2920(20)	64(6)
C(21)	6434(18)	1097(8)	3080(19)	52(6)
C(22)	6912(17)	1351(7)	2060(16)	37(5)
C(23)	6667(17)	3306(7)	2227(16)	36(4)
C(24)	7190(17)	3835(8)	2462(17)	42(5)
C(25)	8235(16)	4009(7)	1896(15)	29(4)
C(26)	8793(17)	3640(7)	1148(16)	37(5)
C(27)	8287(14)	3121(6)	936(14)	25(4)
C(28)	7241(14)	2943(6)	1494(14)	22(4)
C(29)	8750(19)	4569(9)	2263(19)	47(5)
C(30)	10300(20)	5233(10)	1940(20)	78(7)

Table 6-3. Bond lengths [Å] and angles [°] for **1-51.**

P-O(1)	1.468(10)	C(3)-C(2)-C(1)	118(2)
P-N	1.635(11)	C(2)-C(3)-C(4)	124(3)
P-C(12)	1.767(16)	C(3)-C(4)-C(5)	118(2)
P-C(6)	1.858(15)	C(6)-C(5)-C(4)	118(2)
N-C(13)	1.470(19)	C(1)-C(6)-C(5)	123.0(17)
C(1)-C(6)	1.35(2)	C(1)-C(6)-P	116.2(12)
C(1)-C(2)	1.41(3)	C(5)-C(6)-P	120.8(14)
O(2)-C(29)	1.37(2)	C(8)-C(7)-C(12)	126.2(19)
O(2)-C(30)	1.42(2)	C(7)-C(8)-C(9)	119(2)
C(2)-C(3)	1.30(3)	C(10)-C(9)-C(8)	121(2)
C(3)-C(4)	1.37(3)	C(9)-C(10)-C(11)	120(2)
O(3)-C(29)	1.16(2)	C(10)-C(11)-C(12)	119.1(17)
C(4)-C(5)	1.38(3)	C(7)-C(12)-C(11)	114.2(16)
C(5)-C(6)	1.37(2)	C(7)-C(12)-P	126.9(14)
C(7)-C(8)	1.31(2)	C(11)-C(12)-P	118.7(13)
C(7)-C(12)	1.34(2)	N-C(13)-C(28)	116.1(13)
C(8)-C(9)	1.37(2)	N-C(13)-C(14)	107.7(13)
C(9)-C(10)	1.32(3)	C(28)-C(13)-C(14)	115.0(13)
C(10)-C(11)	1.40(2)	C(15)-C(14)-C(22)	110.8(18)
C(11)-C(12)	1.46(2)	C(15)-C(14)-C(13)	112.6(18)
C(13)-C(28)	1.49(2)	C(22)-C(14)-C(13)	113.7(13)
C(13)-C(14)	1.54(2)	C(16)-C(15)-C(14)	151(3)
C(14)-C(15)	1.48(3)	C(22)-C(17)-C(18)	123(2)
C(14)-C(22)	1.51(2)	C(19)-C(18)-C(17)	119(2)
C(15)-C(16)	1.12(3)	C(18)-C(19)-C(20)	120(2)
C(17)-C(22)	1.32(2)	C(21)-C(20)-C(19)	121(2)
C(17)-C(18)	1.39(3)	C(20)-C(21)-C(22)	118.4(19)
C(18)-C(19)	1.32(3)	C(17)-C(22)-C(21)	118.6(18)
C(19)-C(20)	1.40(3)	C(17)-C(22)-C(14)	124.7(17)
C(20)-C(21)	1.38(3)	C(21)-C(22)-C(14)	116.7(16)
C(21)-C(22)	1.40(2)	C(28)-C(23)-C(24)	119.1(17)
C(23)-C(28)	1.37(2)	C(23)-C(24)-C(25)	120.7(17)
C(23)-C(24)	1.39(2)	C(26)-C(25)-C(24)	119.4(16)
C(24)-C(25)	1.39(2)	C(26)-C(25)-C(29)	124.4(16)
C(25)-C(26)	1.38(2)	C(24)-C(25)-C(29)	115.9(16)
C(25)-C(29)	1.48(2)	C(27)-C(26)-C(25)	119.5(16)
C(26)-C(27)	1.36(2)	C(26)-C(27)-C(28)	121.7(15)
C(27)-C(28)	1.39(2)	C(23)-C(28)-C(27)	119.4(15)
O(1)-P-N	110.7(6)	C(23)-C(28)-C(13)	119.3(14)
O(1)-P-C(12)	113.6(7)	C(27)-C(28)-C(13)	121.3(14)
N-P-C(12)	106.2(7)	O(3)-C(29)-O(2)	121.2(19)
O(1)-P-C(6)	111.0(7)	O(3)-C(29)-C(25)	128.0(19)
N-P-C(6)	110.3(6)	O(2)-C(29)-C(25)	110.8(16)
C(12)-P-C(6)	104.8(7)		
C(13)-N-P	123.9(10)		
C(6)-C(1)-C(2)	118.5(18)		
C(29)-O(2)-C(30)	113.8(16)		

Symmetry transformations used to generate equivalent atoms:

Table 6-4. Anisotropic displacement parameters for **1-51.**

Units: ($Å^2 x\ 10^3$). The anisotropic displacement factor exponent takes the form:
$-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
P	26(2)	11(2)	7(2)	2(2)	3(1)	5(2)
O(1)	44(7)	57(8)	25(6)	9(6)	19(5)	9(7)
O(2)	65(10)	30(8)	115(13)	-29(8)	42(9)	-32(7)
O(3)	110(15)	42(10)	175(19)	-32(12)	78(14)	-27(10)

Table 5. Hydrogen coordinates ($x\ 10^4$) and isotropic displacement parameters ($Å^2 x\ 10^3$) for **1-51**.

	x	y	z	U(eq)
H(0A)	5066	2167	1933	16
H(1B)	3813	3397	-1501	44
H(2A)	2884	4286	-1315	95
H(3A)	2259	4514	525	92
H(4A)	2230	3895	2162	78
H(5A)	3058	2999	1975	70
H(7A)	1488	2386	-844	48
H(8A)	-44	1749	-949	55
H(9A)	463	866	-195	68
H(10A)	2469	657	790	72
H(11A)	4140	1304	818	50
H(13A)	6914	2244	471	45
H(14A)	7249	2048	3130	31
H(15)	9024	2285	2006	146
H(16A)	9912	1402	3046	87
H(16B)	10573	1937	2498	87
H(17A)	7255	1229	325	73
H(18A)	6515	328	68	88
H(19A)	5708	-94	1681	90
H(20A)	5628	386	3577	76
H(21A)	6427	1287	3848	63
H(23A)	5937	3200	2563	43
H(24A)	6839	4076	3002	50
H(26A)	9510	3747	791	45
H(27A)	8647	2879	405	29
H(30A)	10965	5304	1434	117
H(30B)	10675	5228	2835	117
H(30C)	9654	5520	1787	117

APPENDIX B

X-ray Structrure and Data for **1-59**

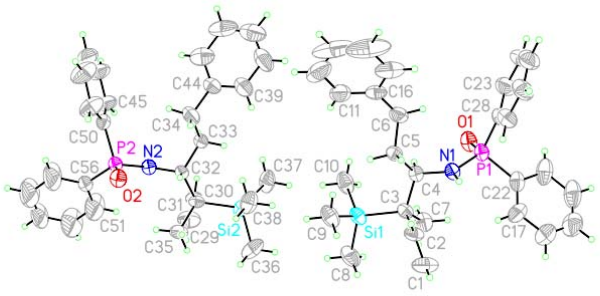


Table 6-5. Crystal data and structure refinement for unit cell of **1-59**.

Identification code	1-59 (unit cell)	
Empirical formula	C28 H36 N O P Si (for single component of unit cell)	
Formula weight	461.64	
Temperature	295(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 10.9313(5) Å	α= 90.8080(10)°.
	b = 13.4272(7) Å	β= 90.8930(10)°.
	c = 19.5603(10) Å	γ = 105.9390(10)°.
Volume	2759.8(2) $Å^3$	
Z	4	
Density (calculated)	1.111 Mg/m^3	
Absorption coefficient	0.162 mm^{-1}	
F(000)	992	
Crystal size	0.35 x 0.04 x 0.04 mm^3	
Theta range for data collection	1.58 to 25.00°.	
Index ranges	-12<=h<=12, -15<=k<=15, -23<=l<=23	
Reflections collected	22360	

Independent reflections	9704 [R(int) = 0.0408]
Completeness to theta = 25.00°	100.0 %
Absorption correction	Sadabs
Max. and min. transmission	0.9936 and 0.9455
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	9704 / 0 / 565
Goodness-of-fit on F^2	1.275
Final R indices [I>2sigma(I)]	R1 = 0.0813, wR2 = 0.1862
R indices (all data)	R1 = 0.1219, wR2 = 0.1998
Largest diff. peak and hole	0.521 and -0.405 e.Å^{-3}

Table 6-6. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for **1-59**.

U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Si(1)	9192(1)	7401(1)	5595(1)	62(1)
Si(2)	6738(1)	5634(1)	3248(1)	66(1)
P(1)	8485(1)	7854(1)	8352(1)	54(1)
P(2)	6458(1)	2094(1)	1686(1)	48(1)
O(1)	7149(2)	7654(2)	8117(1)	71(1)
O(2)	7823(2)	2347(2)	1865(1)	64(1)
N(1)	9427(3)	7660(2)	7755(1)	53(1)
N(2)	5751(2)	2890(2)	2042(1)	49(1)
C(1)	11643(5)	9329(4)	6467(3)	108(2)
C(2)	10950(4)	8416(3)	6574(2)	67(1)
C(3)	9530(3)	7992(3)	6499(2)	52(1)
C(4)	9011(3)	7204(3)	7075(2)	48(1)
C(5)	9315(3)	6158(3)	7017(2)	53(1)
C(6)	8432(4)	5334(3)	7439(2)	76(1)
C(7)	8855(4)	8854(3)	6557(2)	76(1)
C(8)	9401(5)	8439(4)	4956(2)	99(2)
C(9)	10305(4)	6630(4)	5337(2)	85(1)
C(10)	7515(4)	6597(4)	5542(2)	95(2)
C(11)	8381(5)	3741(4)	6755(3)	100(2)
C(12)	8612(8)	2757(6)	6716(5)	160(4)
C(13)	9034(11)	2354(9)	7283(8)	205(9)
C(14)	9235(10)	2855(8)	7851(8)	195(7)
C(15)	9042(5)	3821(5)	7911(3)	115(2)
C(16)	8634(4)	4276(3)	7374(3)	69(1)
C(17)	10276(6)	9786(4)	8418(3)	106(2)
C(18)	10793(8)	10777(5)	8681(4)	137(2)
C(19)	10234(9)	11137(5)	9179(4)	126(2)
C(20)	9131(8)	10564(6)	9435(3)	123(2)
C(21)	8575(5)	9538(5)	9177(3)	108(2)
C(22)	9181(4)	9167(3)	8666(2)	66(1)
C(23)	7557(5)	6564(4)	9431(3)	96(2)
C(24)	7683(6)	5995(5)	10009(3)	113(2)
C(25)	8837(7)	5901(4)	10203(3)	105(2)
C(26)	9876(6)	6383(4)	9862(2)	94(2)
C(27)	9786(5)	6955(3)	9296(2)	76(1)
C(28)	8628(4)	7062(3)	9071(2)	60(1)
C(29)	4839(5)	5399(4)	1707(3)	101(2)
C(30)	5065(4)	4795(3)	2188(2)	63(1)

C(31)	6307(3)	4703(3)	2469(2)	50(1)
C(32)	6217(3)	3573(3)	2637(2)	44(1)
C(33)	5445(3)	3131(3)	3265(2)	50(1)
C(34)	5748(5)	2173(4)	3528(2)	85(1)
C(35)	7390(4)	5067(3)	1956(2)	77(1)
C(36)	7284(5)	6982(3)	2946(3)	113(2)
C(37)	5351(4)	5589(4)	3806(3)	100(2)
C(38)	8055(4)	5322(4)	3742(3)	89(2)
C(39)	5674(5)	2325(4)	4799(3)	90(2)
C(40)	5218(8)	1985(6)	5431(3)	122(2)
C(41)	4253(8)	1146(7)	5450(5)	132(3)
C(42)	3699(6)	556(6)	4913(5)	126(3)
C(43)	4204(5)	908(4)	4250(3)	100(2)
C(44)	5187(4)	1789(4)	4200(2)	67(1)
C(45)	4333(4)	464(4)	1951(3)	88(1)
C(46)	3707(6)	-499(4)	2146(3)	116(2)
C(47)	4341(7)	-1156(4)	2331(3)	109(2)
C(48)	5615(8)	-887(5)	2316(3)	126(2)
C(49)	6277(5)	102(4)	2101(3)	103(2)
C(50)	5631(4)	791(3)	1922(2)	54(1)
C(51)	5919(5)	3035(3)	515(2)	179(4)
C(52)	5761(6)	3101(4)	-188(2)	215(5)
C(53)	5831(6)	2285(5)	-616(1)	157(3)
C(54)	6060(6)	1402(4)	-342(2)	216(5)
C(55)	6218(5)	1335(3)	361(2)	189(4)
C(56)	6147(3)	2152(3)	789(1)	62(1)

Table 6-7. Bond lengths [Å] and angles [°] for **1-59**.

Si(1)-C(10)	1.854(4)	C(3)-C(7)	1.539(5)
Si(1)-C(8)	1.855(5)	C(3)-C(4)	1.560(5)
Si(1)-C(9)	1.871(4)	C(4)-C(5)	1.532(5)
Si(1)-C(3)	1.917(4)	C(4)-H(4A)	0.9800
Si(2)-C(36)	1.852(5)	C(5)-C(6)	1.516(5)
Si(2)-C(38)	1.866(4)	C(5)-H(5A)	0.9700
Si(2)-C(37)	1.870(5)	C(5)-H(5B)	0.9700
Si(2)-C(31)	1.925(4)	C(6)-C(16)	1.500(6)
P(1)-O(1)	1.475(2)	C(6)-H(6A)	0.9700
P(1)-N(1)	1.633(3)	C(6)-H(6B)	0.9700
P(1)-C(28)	1.805(4)	C(7)-H(7A)	0.9600
P(1)-C(22)	1.813(4)	C(7)-H(7B)	0.9600
P(2)-O(2)	1.473(2)	C(7)-H(7C)	0.9600
P(2)-N(2)	1.635(3)	C(8)-H(8A)	0.9600
P(2)-C(56)	1.788(3)	C(8)-H(8B)	0.9600
P(2)-C(50)	1.805(4)	C(8)-H(8C)	0.9600
N(1)-C(4)	1.468(4)	C(9)-H(9A)	0.9600
N(1)-H(1B)	0.8600	C(9)-H(9B)	0.9600
N(2)-C(32)	1.467(4)	C(9)-H(9C)	0.9600
N(2)-H(2B)	0.8600	C(10)-H(10A)	0.9600
C(1)-C(2)	1.274(5)	C(10)-H(10B)	0.9600
C(1)-H(1C)	0.9300	C(10)-H(10C)	0.9600
C(1)-H(1D)	0.9300	C(11)-C(16)	1.384(7)
C(2)-C(3)	1.503(5)	C(11)-C(12)	1.414(8)
C(2)-H(2C)	0.9300	C(11)-H(11A)	0.9300

C(12)-C(13)	1.368(15)	C(38)-H(38C)	0.9600
C(12)-H(12A)	0.9300	C(39)-C(40)	1.375(7)
C(13)-C(14)	1.275(18)	C(39)-C(44)	1.386(6)
C(13)-H(13A)	0.9300	C(39)-H(39A)	0.9300
C(14)-C(15)	1.374(11)	C(40)-C(41)	1.316(9)
C(14)-H(14A)	0.9300	C(40)-H(40A)	0.9300
C(15)-C(16)	1.353(7)	C(41)-C(42)	1.339(9)
C(15)-H(15A)	0.9300	C(41)-H(41A)	0.9300
C(17)-C(22)	1.357(6)	C(42)-C(43)	1.453(9)
C(17)-C(18)	1.383(7)	C(42)-H(42A)	0.9300
C(17)-H(17A)	0.9300	C(43)-C(44)	1.369(6)
C(18)-C(19)	1.312(9)	C(43)-H(43A)	0.9300
C(18)-H(18A)	0.9300	C(45)-C(46)	1.350(6)
C(19)-C(20)	1.348(9)	C(45)-C(50)	1.367(5)
C(19)-H(19A)	0.9300	C(45)-H(45A)	0.9300
C(20)-C(21)	1.425(8)	C(46)-C(47)	1.314(7)
C(20)-H(20A)	0.9300	C(46)-H(46A)	0.9300
C(21)-C(22)	1.368(6)	C(47)-C(48)	1.341(8)
C(21)-H(21A)	0.9300	C(47)-H(47A)	0.9300
C(23)-C(24)	1.399(7)	C(48)-C(49)	1.400(7)
C(23)-C(28)	1.387(6)	C(48)-H(48A)	0.9300
C(23)-H(23A)	0.9300	C(49)-C(50)	1.355(5)
C(24)-C(25)	1.351(7)	C(49)-H(49A)	0.9300
C(24)-H(24A)	0.9300	C(51)-C(52)	1.3900
C(25)-C(26)	1.335(7)	C(51)-C(56)	1.3900
C(25)-H(25A)	0.9300	C(51)-H(51A)	0.9300
C(26)-C(27)	1.374(6)	C(52)-C(53)	1.3900
C(26)-H(26A)	0.9300	C(52)-H(52A)	0.9300
C(27)-C(28)	1.379(5)	C(53)-C(54)	1.3900
C(27)-H(27A)	0.9300	C(53)-H(53A)	0.9300
C(29)-C(30)	1.315(5)	C(54)-C(55)	1.3900
C(29)-H(29A)	0.9300	C(54)-H(54A)	0.9300
C(29)-H(29B)	0.9300	C(55)-C(56)	1.3900
C(30)-C(31)	1.494(5)	C(55)-H(55A)	0.9300
C(30)-H(30A)	0.9300	C(10)-Si(1)-C(8)	108.3(2)
C(31)-C(32)	1.533(5)	C(10)-Si(1)-C(9)	111.0(2)
C(31)-C(35)	1.544(5)	C(8)-Si(1)-C(9)	105.3(2)
C(32)-C(33)	1.533(5)	C(10)-Si(1)-C(3)	108.50(18)
C(32)-H(32A)	0.9800	C(8)-Si(1)-C(3)	110.3(2)
C(33)-C(34)	1.508(5)	C(9)-Si(1)-C(3)	113.34(17)
C(33)-H(33A)	0.9700	C(36)-Si(2)-C(38)	109.3(2)
C(33)-H(33B)	0.9700	C(36)-Si(2)-C(37)	105.9(3)
C(34)-C(44)	1.496(6)	C(38)-Si(2)-C(37)	111.0(2)
C(34)-H(34A)	0.9700	C(36)-Si(2)-C(31)	109.1(2)
C(34)-H(34B)	0.9700	C(38)-Si(2)-C(31)	108.41(18)
C(35)-H(35A)	0.9600	C(37)-Si(2)-C(31)	113.07(19)
C(35)-H(35B)	0.9600	O(1)-P(1)-N(1)	113.32(15)
C(35)-H(35C)	0.9600	O(1)-P(1)-C(28)	111.43(18)
C(36)-H(36A)	0.9600	N(1)-P(1)-C(28)	108.24(16)
C(36)-H(36B)	0.9600	O(1)-P(1)-C(22)	113.57(17)
C(36)-H(36C)	0.9600	N(1)-P(1)-C(22)	105.71(19)
C(37)-H(37A)	0.9600	C(28)-P(1)-C(22)	103.94(18)
C(37)-H(37B)	0.9600	O(2)-P(2)-N(2)	112.78(14)
C(37)-H(37C)	0.9600	O(2)-P(2)-C(56)	113.35(16)
C(38)-H(38A)	0.9600	N(2)-P(2)-C(56)	104.89(15)
C(38)-H(38B)	0.9600	O(2)-P(2)-C(50)	111.65(16)

N(2)-P(2)-C(50)	108.39(16)	Si(1)-C(10)-H(10A)	109.5
C(56)-P(2)-C(50)	105.26(17)	Si(1)-C(10)-H(10B)	109.5
C(4)-N(1)-P(1)	125.2(2)	H(10A)-C(10)-H(10B)	109.5
C(4)-N(1)-H(1B)	117.4	Si(1)-C(10)-H(10C)	109.5
P(1)-N(1)-H(1B)	117.4	H(10A)-C(10)-H(10C)	109.5
C(32)-N(2)-P(2)	126.4(2)	H(10B)-C(10)-H(10C)	109.5
C(32)-N(2)-H(2B)	116.8	C(16)-C(11)-C(12)	117.5(7)
P(2)-N(2)-H(2B)	116.8	C(16)-C(11)-H(11A)	121.3
C(2)-C(1)-H(1C)	120.0	C(12)-C(11)-H(11A)	121.3
C(2)-C(1)-H(1D)	120.0	C(13)-C(12)-C(11)	120.0(9)
H(1C)-C(1)-H(1D)	120.0	C(13)-C(12)-H(12A)	120.0
C(1)-C(2)-C(3)	129.0(4)	C(11)-C(12)-H(12A)	120.0
C(1)-C(2)-H(2C)	115.5	C(14)-C(13)-C(12)	121.2(14)
C(3)-C(2)-H(2C)	115.5	C(14)-C(13)-H(13A)	119.4
C(2)-C(3)-C(7)	111.6(3)	C(12)-C(13)-H(13A)	119.4
C(2)-C(3)-C(4)	110.2(3)	C(13)-C(14)-C(15)	120.9(14)
C(7)-C(3)-C(4)	107.3(3)	C(13)-C(14)-H(14A)	119.5
C(2)-C(3)-Si(1)	106.7(2)	C(15)-C(14)-H(14A)	119.5
C(7)-C(3)-Si(1)	107.4(2)	C(16)-C(15)-C(14)	121.5(8)
C(4)-C(3)-Si(1)	113.6(2)	C(16)-C(15)-H(15A)	119.2
N(1)-C(4)-C(5)	108.7(3)	C(14)-C(15)-H(15A)	119.2
N(1)-C(4)-C(3)	111.4(3)	C(15)-C(16)-C(11)	118.8(5)
C(5)-C(4)-C(3)	116.3(3)	C(15)-C(16)-C(6)	121.5(5)
N(1)-C(4)-H(4A)	106.6	C(11)-C(16)-C(6)	119.7(4)
C(5)-C(4)-H(4A)	106.6	C(22)-C(17)-C(18)	120.9(6)
C(3)-C(4)-H(4A)	106.6	C(22)-C(17)-H(17A)	119.5
C(6)-C(5)-C(4)	112.2(3)	C(18)-C(17)-H(17A)	119.5
C(6)-C(5)-H(5A)	109.2	C(19)-C(18)-C(17)	120.5(7)
C(4)-C(5)-H(5A)	109.2	C(19)-C(18)-H(18A)	119.8
C(6)-C(5)-H(5B)	109.2	C(17)-C(18)-H(18A)	119.8
C(4)-C(5)-H(5B)	109.2	C(18)-C(19)-C(20)	121.1(7)
H(5A)-C(5)-H(5B)	107.9	C(18)-C(19)-H(19A)	119.4
C(16)-C(6)-C(5)	114.8(3)	C(20)-C(19)-H(19A)	119.4
C(16)-C(6)-H(6A)	108.6	C(19)-C(20)-C(21)	119.8(6)
C(5)-C(6)-H(6A)	108.6	C(19)-C(20)-H(20A)	120.1
C(16)-C(6)-H(6B)	108.6	C(21)-C(20)-H(20A)	120.1
C(5)-C(6)-H(6B)	108.6	C(22)-C(21)-C(20)	118.4(6)
H(6A)-C(6)-H(6B)	107.5	C(22)-C(21)-H(21A)	120.8
C(3)-C(7)-H(7A)	109.5	C(20)-C(21)-H(21A)	120.8
C(3)-C(7)-H(7B)	109.5	C(17)-C(22)-C(21)	119.3(5)
H(7A)-C(7)-H(7B)	109.5	C(17)-C(22)-P(1)	122.5(4)
C(3)-C(7)-H(7C)	109.5	C(21)-C(22)-P(1)	118.2(4)
H(7A)-C(7)-H(7C)	109.5	C(24)-C(23)-C(28)	119.8(5)
H(7B)-C(7)-H(7C)	109.5	C(24)-C(23)-H(23A)	120.1
Si(1)-C(8)-H(8A)	109.5	C(28)-C(23)-H(23A)	120.1
Si(1)-C(8)-H(8B)	109.5	C(25)-C(24)-C(23)	120.2(5)
H(8A)-C(8)-H(8B)	109.5	C(25)-C(24)-H(24A)	119.9
Si(1)-C(8)-H(8C)	109.5	C(23)-C(24)-H(24A)	119.9
H(8A)-C(8)-H(8C)	109.5	C(26)-C(25)-C(24)	120.4(5)
H(8B)-C(8)-H(8C)	109.5	C(26)-C(25)-H(25A)	119.8
Si(1)-C(9)-H(9A)	109.5	C(24)-C(25)-H(25A)	119.8
Si(1)-C(9)-H(9B)	109.5	C(25)-C(26)-C(27)	120.8(5)
H(9A)-C(9)-H(9B)	109.5	C(25)-C(26)-H(26A)	119.6
Si(1)-C(9)-H(9C)	109.5	C(27)-C(26)-H(26A)	119.6
H(9A)-C(9)-H(9C)	109.5	C(26)-C(27)-C(28)	121.1(5)
H(9B)-C(9)-H(9C)	109.5	C(26)-C(27)-H(27A)	119.5

C(28)-C(27)-H(27A)	119.5	H(38A)-C(38)-H(38C)	109.5
C(27)-C(28)-C(23)	117.7(4)	H(38B)-C(38)-H(38C)	109.5
C(27)-C(28)-P(1)	122.3(3)	C(40)-C(39)-C(44)	122.1(6)
C(23)-C(28)-P(1)	120.0(4)	C(40)-C(39)-H(39A)	118.9
C(30)-C(29)-H(29A)	120.0	C(44)-C(39)-H(39A)	118.9
C(30)-C(29)-H(29B)	120.0	C(41)-C(40)-C(39)	117.7(7)
H(29A)-C(29)-H(29B)	120.0	C(41)-C(40)-H(40A)	121.1
C(29)-C(30)-C(31)	129.6(4)	C(39)-C(40)-H(40A)	121.1
C(29)-C(30)-H(30A)	115.2	C(40)-C(41)-C(42)	126.2(8)
C(31)-C(30)-H(30A)	115.2	C(40)-C(41)-H(41A)	116.9
C(30)-C(31)-C(32)	110.5(3)	C(42)-C(41)-H(41A)	116.9
C(30)-C(31)-C(35)	111.8(3)	C(41)-C(42)-C(43)	115.7(7)
C(32)-C(31)-C(35)	107.6(3)	C(41)-C(42)-H(42A)	122.2
C(30)-C(31)-Si(2)	106.7(2)	C(43)-C(42)-H(42A)	122.2
C(32)-C(31)-Si(2)	113.7(2)	C(44)-C(43)-C(42)	120.4(6)
C(35)-C(31)-Si(2)	106.5(3)	C(44)-C(43)-H(43A)	119.8
N(2)-C(32)-C(33)	109.5(3)	C(42)-C(43)-H(43A)	119.8
N(2)-C(32)-C(31)	110.9(3)	C(43)-C(44)-C(39)	117.8(5)
C(33)-C(32)-C(31)	116.7(3)	C(43)-C(44)-C(34)	122.2(5)
N(2)-C(32)-H(32A)	106.4	C(39)-C(44)-C(34)	120.0(5)
C(33)-C(32)-H(32A)	106.4	C(46)-C(45)-C(50)	122.3(5)
C(31)-C(32)-H(32A)	106.4	C(46)-C(45)-H(45A)	118.8
C(34)-C(33)-C(32)	112.9(3)	C(50)-C(45)-H(45A)	118.8
C(34)-C(33)-H(33A)	109.0	C(47)-C(46)-C(45)	120.3(6)
C(32)-C(33)-H(33A)	109.0	C(47)-C(46)-H(46A)	119.8
C(34)-C(33)-H(33B)	109.0	C(45)-C(46)-H(46A)	119.8
C(32)-C(33)-H(33B)	109.0	C(46)-C(47)-C(48)	120.5(6)
H(33A)-C(33)-H(33B)	107.8	C(46)-C(47)-H(47A)	119.7
C(44)-C(34)-C(33)	116.1(3)	C(48)-C(47)-H(47A)	119.7
C(44)-C(34)-H(34A)	108.3	C(47)-C(48)-C(49)	119.8(5)
C(33)-C(34)-H(34A)	108.3	C(47)-C(48)-H(48A)	120.1
C(44)-C(34)-H(34B)	108.3	C(49)-C(48)-H(48A)	120.1
C(33)-C(34)-H(34B)	108.3	C(50)-C(49)-C(48)	120.0(5)
H(34A)-C(34)-H(34B)	107.4	C(50)-C(49)-H(49A)	120.0
C(31)-C(35)-H(35A)	109.5	C(48)-C(49)-H(49A)	120.0
C(31)-C(35)-H(35B)	109.5	C(49)-C(50)-C(45)	117.0(4)
H(35A)-C(35)-H(35B)	109.5	C(49)-C(50)-P(2)	121.2(4)
C(31)-C(35)-H(35C)	109.5	C(45)-C(50)-P(2)	121.8(3)
H(35A)-C(35)-H(35C)	109.5	C(52)-C(51)-C(56)	120.0
H(35B)-C(35)-H(35C)	109.5	C(52)-C(51)-H(51A)	120.0
Si(2)-C(36)-H(36A)	109.5	C(56)-C(51)-H(51A)	120.0
Si(2)-C(36)-H(36B)	109.5	C(53)-C(52)-C(51)	120.0
H(36A)-C(36)-H(36B)	109.5	C(53)-C(52)-H(52A)	120.0
Si(2)-C(36)-H(36C)	109.5	C(51)-C(52)-H(52A)	120.0
H(36A)-C(36)-H(36C)	109.5	C(54)-C(53)-C(52)	120.0
H(36B)-C(36)-H(36C)	109.5	C(54)-C(53)-H(53A)	120.0
Si(2)-C(37)-H(37A)	109.5	C(52)-C(53)-H(53A)	120.0
Si(2)-C(37)-H(37B)	109.5	C(53)-C(54)-C(55)	120.0
H(37A)-C(37)-H(37B)	109.5	C(53)-C(54)-H(54A)	120.0
Si(2)-C(37)-H(37C)	109.5	C(55)-C(54)-H(54A)	120.0
H(37A)-C(37)-H(37C)	109.5	C(56)-C(55)-C(54)	120.0
H(37B)-C(37)-H(37C)	109.5	C(56)-C(55)-H(55A)	120.0
Si(2)-C(38)-H(38A)	109.5	C(54)-C(55)-H(55A)	120.0
Si(2)-C(38)-H(38B)	109.5	C(55)-C(56)-C(51)	120.0
H(38A)-C(38)-H(38B)	109.5	C(55)-C(56)-P(2)	119.6(2)
Si(2)-C(38)-H(38C)	109.5	C(51)-C(56)-P(2)	120.3(2

Table 6-8. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **1-59**.

The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Si(1)	57(1)	89(1)	47(1)	7(1)	2(1)	29(1)
Si(2)	53(1)	58(1)	87(1)	-11(1)	-6(1)	19(1)
P(1)	47(1)	68(1)	50(1)	-7(1)	-1(1)	22(1)
P(2)	41(1)	55(1)	50(1)	0(1)	2(1)	16(1)
O(1)	47(2)	103(2)	66(2)	-14(2)	-1(1)	29(2)
O(2)	44(1)	77(2)	75(2)	-7(1)	0(1)	23(1)
N(1)	38(2)	73(2)	48(2)	-4(2)	-2(1)	15(2)
N(2)	39(2)	58(2)	53(2)	0(1)	-5(1)	18(1)
C(1)	82(3)	106(4)	118(4)	52(3)	-7(3)	-8(3)
C(2)	62(3)	72(3)	62(3)	27(2)	-1(2)	9(2)
C(3)	52(2)	62(2)	48(2)	11(2)	2(2)	25(2)
C(4)	36(2)	61(2)	50(2)	-2(2)	-1(2)	20(2)
C(5)	48(2)	61(2)	53(2)	7(2)	9(2)	18(2)
C(6)	78(3)	73(3)	75(3)	11(2)	29(2)	15(2)
C(7)	89(3)	80(3)	72(3)	7(2)	-7(2)	44(3)
C(8)	126(4)	124(4)	60(3)	21(3)	4(3)	55(4)
C(9)	77(3)	127(4)	65(3)	3(3)	10(2)	52(3)
C(10)	69(3)	149(5)	64(3)	-18(3)	-8(2)	25(3)
C(11)	113(4)	72(4)	113(5)	9(3)	43(3)	17(3)
C(12)	153(7)	75(5)	231(10)	-30(5)	115(7)	-12(4)
C(13)	111(8)	101(8)	410(30)	116(11)	109(12)	32(6)
C(14)	93(5)	141(11)	350(20)	146(10)	-6(9)	24(7)
C(15)	83(4)	96(4)	153(6)	60(4)	-13(3)	0(3)
C(16)	50(2)	64(3)	91(3)	23(3)	19(2)	9(2)
C(17)	126(5)	63(3)	114(4)	-17(3)	14(4)	-1(3)
C(18)	188(7)	77(4)	125(6)	-11(4)	5(5)	4(4)
C(19)	195(8)	75(4)	116(6)	-6(4)	-22(5)	55(5)
C(20)	169(7)	126(6)	99(5)	-41(4)	-21(5)	89(5)
C(21)	114(4)	119(5)	106(4)	-47(4)	-21(3)	63(4)
C(22)	83(3)	73(3)	55(3)	-7(2)	-20(2)	45(3)
C(23)	84(3)	114(4)	76(3)	15(3)	9(3)	4(3)
C(24)	125(5)	120(5)	76(4)	28(3)	27(4)	-2(4)
C(25)	157(6)	91(4)	75(4)	21(3)	14(4)	48(4)
C(26)	135(5)	98(4)	70(3)	20(3)	14(3)	65(4)
C(27)	90(3)	84(3)	67(3)	13(2)	16(2)	47(3)
C(28)	70(3)	63(3)	44(2)	-7(2)	13(2)	17(2)
C(29)	89(4)	105(4)	112(4)	42(3)	-9(3)	30(3)
C(30)	55(2)	59(3)	73(3)	15(2)	1(2)	15(2)
C(31)	41(2)	49(2)	59(2)	13(2)	8(2)	10(2)
C(32)	33(2)	55(2)	45(2)	0(2)	1(2)	13(2)
C(33)	49(2)	53(2)	52(2)	4(2)	5(2)	20(2)
C(34)	121(4)	90(3)	65(3)	21(2)	33(3)	60(3)
C(35)	74(3)	68(3)	82(3)	17(2)	21(2)	7(2)
C(36)	108(4)	56(3)	173(6)	-10(3)	-14(4)	19(3)
C(37)	83(3)	110(4)	117(4)	-42(3)	6(3)	47(3)
C(38)	71(3)	96(4)	104(4)	-31(3)	-25(3)	30(3)
C(39)	116(4)	102(4)	69(3)	16(3)	20(3)	55(3)
C(40)	186(7)	149(6)	62(4)	19(4)	18(4)	97(6)
C(41)	134(7)	121(7)	159(8)	59(5)	69(6)	60(5)

C(42)	88(4)	89(5)	210(9)	65(5)	35(5)	33(4)
C(43)	84(4)	92(4)	135(5)	38(4)	-6(3)	41(3)
C(44)	77(3)	73(3)	66(3)	21(2)	17(2)	47(3)
C(45)	75(3)	60(3)	124(4)	14(3)	19(3)	8(2)
C(46)	103(4)	64(4)	168(6)	12(4)	38(4)	-2(3)
C(47)	155(6)	66(4)	90(4)	9(3)	-6(4)	6(4)
C(48)	157(6)	79(4)	148(6)	19(4)	-58(5)	45(4)
C(49)	87(3)	71(3)	155(5)	8(3)	-31(3)	30(3)
C(50)	60(2)	55(2)	51(2)	-3(2)	-6(2)	21(2)
C(51)	346(12)	137(6)	67(4)	-3(4)	-49(5)	94(7)
C(52)	428(15)	175(8)	62(4)	11(5)	-42(6)	121(9)
C(53)	285(9)	152(7)	45(3)	-4(4)	1(4)	79(6)
C(54)	403(15)	183(9)	65(5)	-20(5)	-11(6)	89(9)
C(55)	361(12)	160(7)	63(4)	-15(4)	-10(5)	101(7)
C(56)	69(3)	66(3)	52(2)	-1(2)	4(2)	19(2)

Table 6-9. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for **1-59**.

	x	y	z	U(eq)
H(1B)	10231	7840	7847	64
H(2B)	5036	2911	1862	59
H(1C)	11272	9838	6322	129
H(1D)	12520	9487	6534	129
H(2C)	11382	7946	6718	80
H(4A)	8082	7056	7056	57
H(5A)	9241	5932	6542	64
H(5B)	10186	6242	7169	64
H(6A)	8542	5553	7916	91
H(6B)	7561	5289	7304	91
H(7A)	9006	9167	7006	114
H(7B)	7957	8564	6481	114
H(7C)	9180	9370	6222	114
H(8A)	9229	8133	4505	148
H(8B)	10260	8874	4983	148
H(8C)	8824	8847	5048	148
H(9A)	10090	6356	4882	128
H(9B)	10235	6070	5647	128
H(9C)	11163	7069	5350	128
H(10A)	7331	6295	5092	143
H(10B)	6959	7022	5637	143
H(10C)	7388	6056	5872	143
H(11A)	8071	4019	6379	120
H(12A)	8477	2382	6305	193
H(13A)	9178	1704	7253	245
H(14A)	9515	2562	8230	234
H(15A)	9197	4171	8331	138
H(17A)	10684	9540	8067	128
H(18A)	11543	11191	8504	164
H(19A)	10606	11798	9358	151
H(20A)	8733	10837	9778	147
H(21A)	7819	9131	9352	129
H(23A)	6758	6607	9289	115

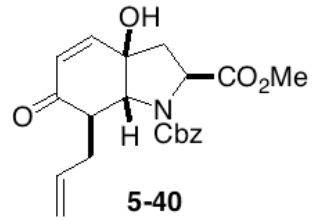
H(24A)	6970	5680	10260	136
H(25A)	8909	5498	10576	126
H(26A)	10668	6331	10010	113
H(27A)	10519	7276	9062	91
H(29A)	5512	5854	1490	121
H(29B)	4005	5372	1584	121
H(30A)	4346	4361	2382	75
H(32A)	7090	3543	2731	53
H(33A)	5616	3656	3626	60
H(33B)	4546	2964	3146	60
H(34A)	5455	1622	3189	102
H(34B)	6665	2315	3570	102
H(35A)	7216	4622	1557	115
H(35B)	8181	5042	2164	115
H(35C)	7446	5765	1826	115
H(36A)	7497	7450	3333	170
H(36B)	6617	7138	2680	170
H(36C)	8020	7057	2669	170
H(37A)	5619	6067	4184	150
H(37B)	5023	4901	3975	150
H(37C)	4698	5775	3545	150
H(38A)	8281	5779	4133	134
H(38B)	8782	5407	3456	134
H(38C)	7781	4618	3890	134
H(39A)	6329	2934	4774	108
H(40A)	5580	2335	5830	146
H(41A)	3926	945	5878	158
H(42A)	3032	-41	4962	151
H(43A)	3859	532	3856	120
H(45A)	3866	920	1831	106
H(46A)	2823	-698	2149	140
H(47A)	3902	-1813	2474	130
H(48A)	6059	-1356	2447	151
H(49A)	7160	287	2082	123
H(51A)	5872	3581	802	214
H(52A)	5608	3692	-371	258
H(53A)	5726	2330	-1086	189
H(54A)	6107	856	-629	259
H(55A)	6370	745	544	227

APPENDIX C

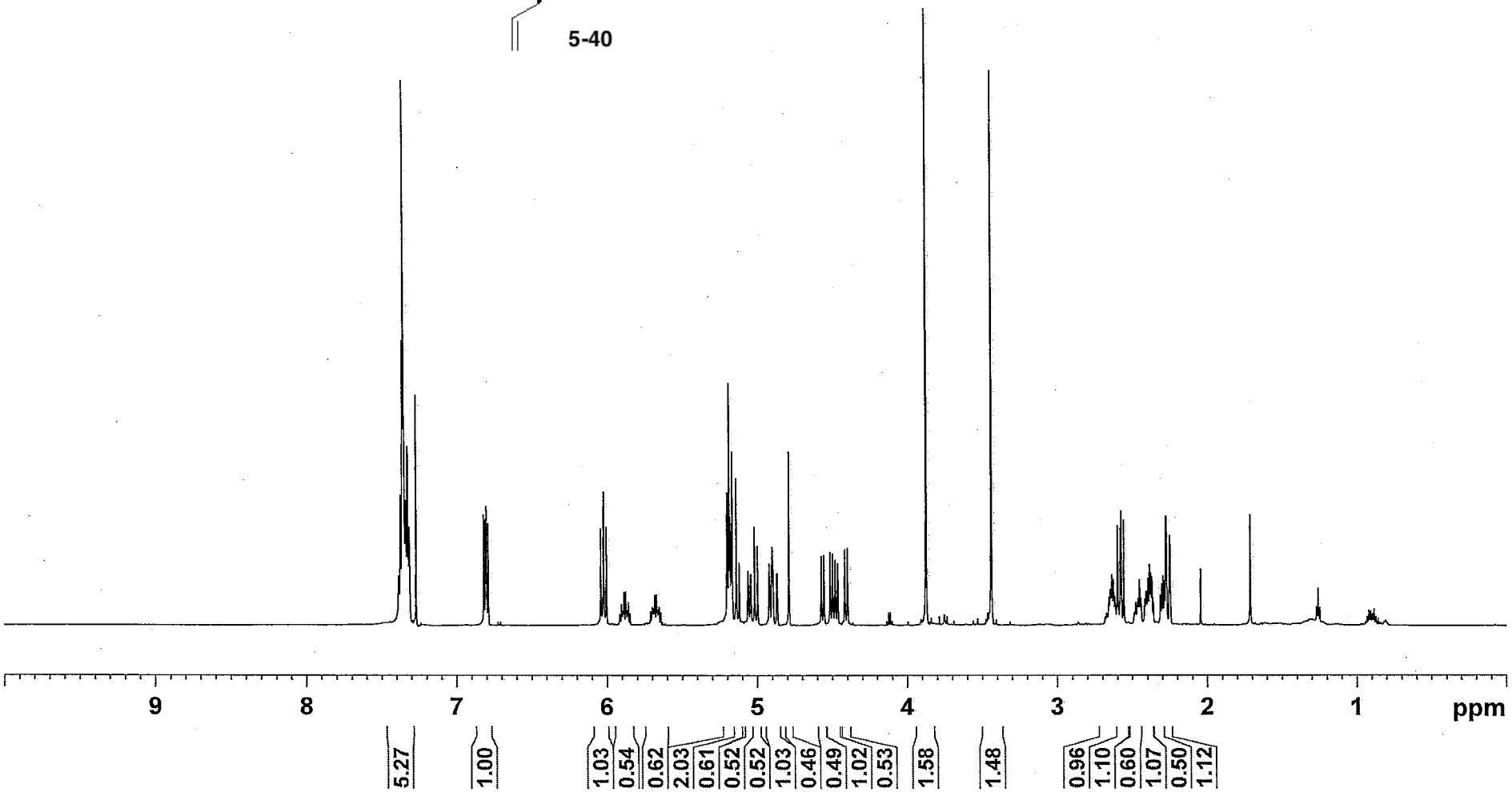
SELECTED ^{1}H AND ^{13}C NMR DATA FOR COMPOUNDS **5-40, 5-53, 5-63, 5-64, 5-66,** AND **5-69.**

jp7_021 1H NMR 600 MHz CDCl3 rt 9-16-08

7.385 7.374 7.361 7.353 7.342 7.338 7.327 7.326 7.314 7.270 6.819 6.807 6.802 6.790 5.202 5.189 5.182 5.168 5.141 5.121 5.062 5.044 5.019 4.999 4.920 4.902 4.900 4.870 4.869 4.790 4.574 4.556 4.515 4.498 4.481 4.465 4.418 4.400 3.875 3.441 2.638 2.628 2.600 2.583 2.576 2.559 2.454 2.396 2.387 2.379 2.370 2.297 2.287 2.277 2.252

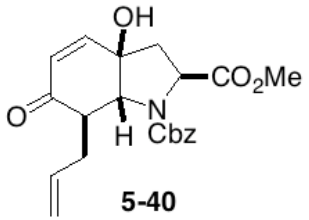


5-40



jp7_021 13C NMR 150 MHz CDCl3 rt 9-16-08

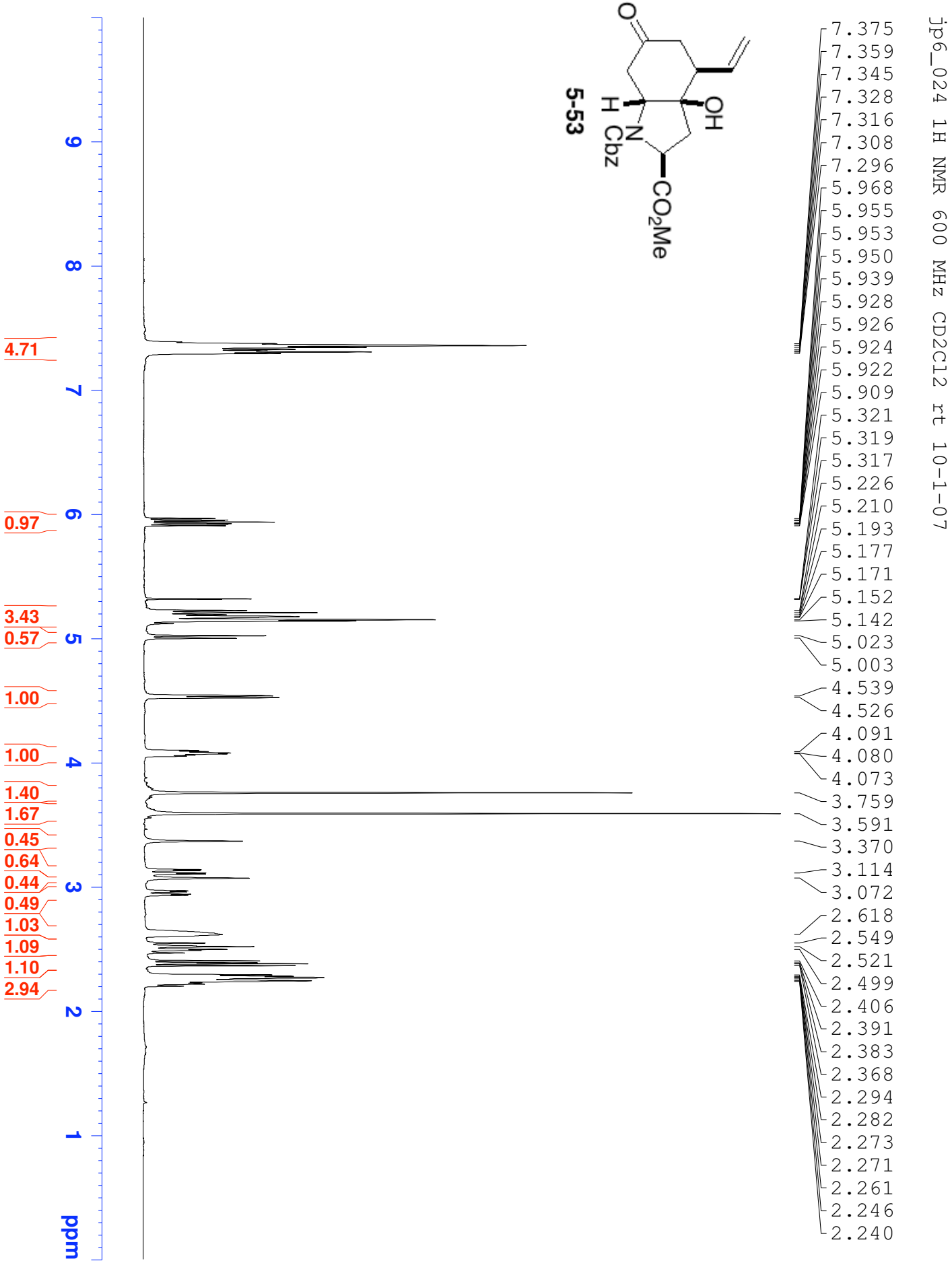
197.10
197.03
175.46
175.18
154.94
154.34
147.24
147.22
135.42
135.21
135.10
129.10
129.03
128.58
128.56
128.49
128.41
117.43
116.95
77.21
77.07
77.00
76.79
76.13
69.86
69.49
68.21
67.93
59.00
58.60
53.42
52.87
52.72
52.57
41.32
40.14
30.46
30.02



5-40

228

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm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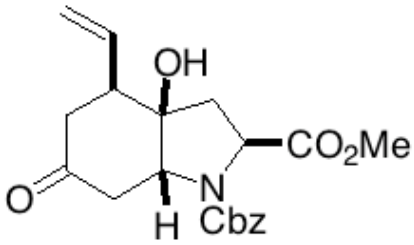
7.375
7.359
7.345
7.328
7.316
7.308
7.296
5.968
5.955
5.953
5.950
5.939
5.928
5.926
5.924
5.922
5.909
5.321
5.319
5.317
5.226
5.210
5.193
5.177
5.171
5.152
5.142
5.023
5.003
4.539
4.526
4.091
4.080
4.073
3.759
3.591
3.370
3.114
3.072
2.618
2.549
2.521
2.499
2.406
2.391
2.383
2.368
2.294
2.282
2.273
2.271
2.261
2.246
2.240
5-53
OH
N
H Cbz
CO2Me
O
4.71
0.97
3.43
0.57
1.00
1.00
1.40
1.67
0.45
0.64
0.44
0.49
1.03
1.09
1.10
2.94
9
8
7
6
5
4
3
2
1
ppm

jp6_024 13C NMR 150 MHz CD2Cl2 rt 10-1-07

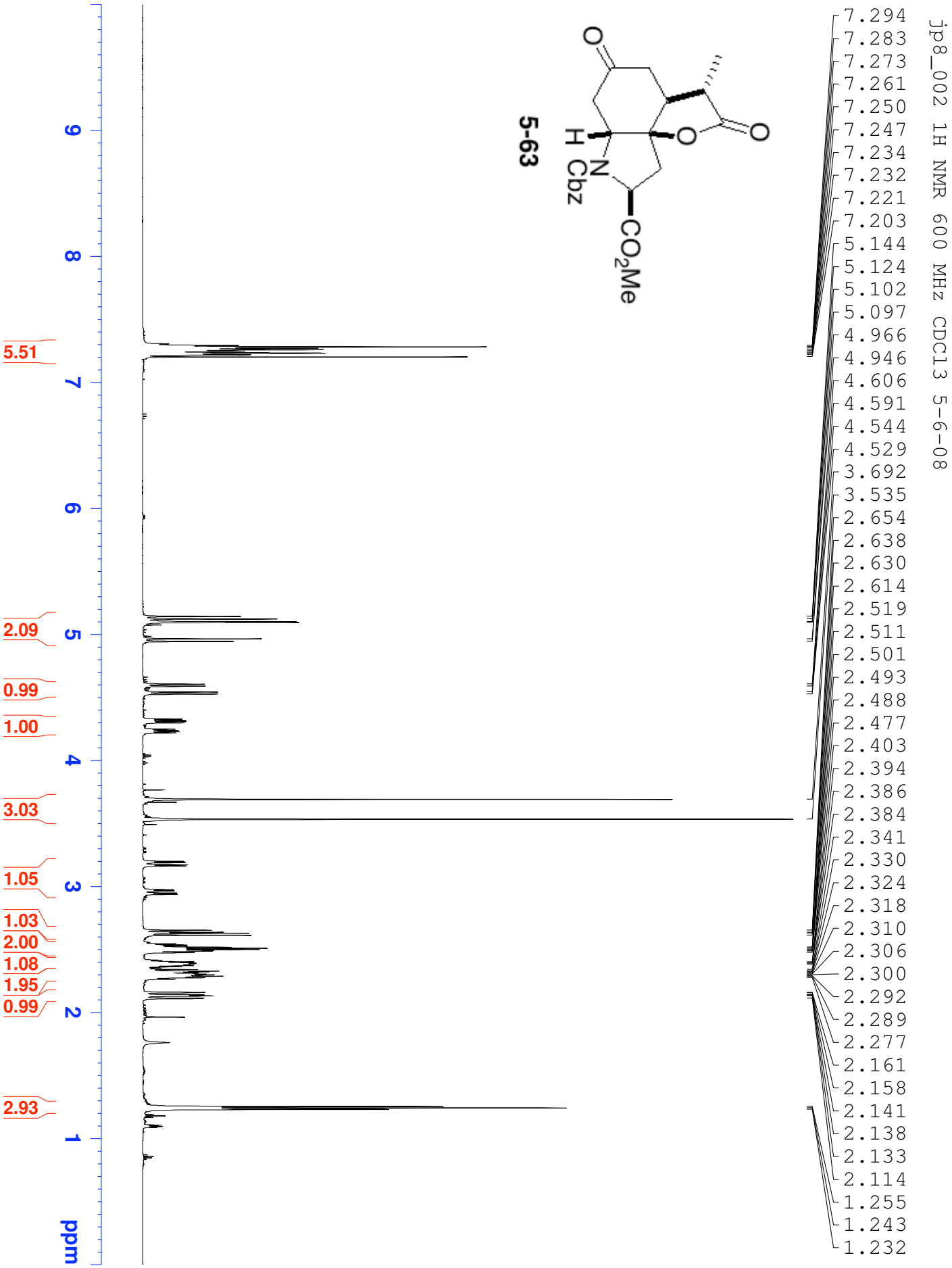
208.23
208.14
174.79
174.50
154.85
154.27
136.36
135.27
135.17
128.55
128.45
128.19
128.15
128.01
127.97
117.72
117.51
80.55
79.42
67.50
67.24
65.27
64.67
59.39
59.18
53.86
53.68
53.50
53.32
53.14
52.82
52.61
45.97
43.36
42.26
41.72
40.64
40.55
40.47



5-53

230

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm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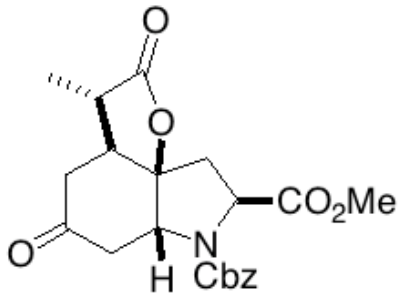
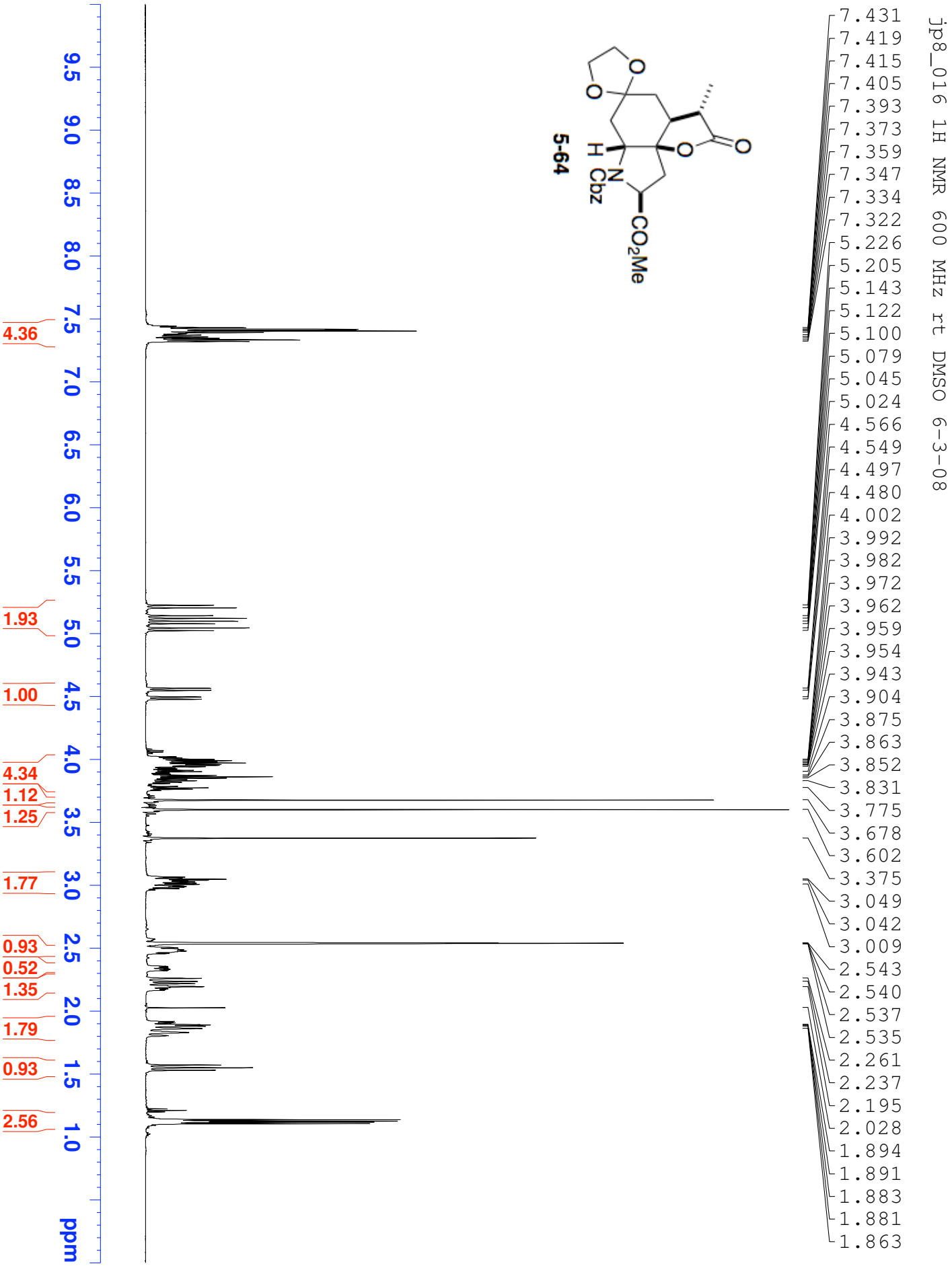
7.283
7.273
7.261
7.250
7.247
7.234
7.232
7.221
7.203
5.144
5.124
5.102
5.097
4.966
4.946
4.606
4.591
4.544
4.529
3.692
3.535
2.654
2.638
2.630
2.614
2.519
2.511
2.501
2.493
2.488
2.477
2.403
2.394
2.386
2.384
2.341
2.330
2.324
2.318
2.310
2.306
2.300
2.292
2.289
2.277
2.161
2.158
2.141
2.138
2.133
2.114
1.255
1.243
1.232
5-63
H
N
Cbz
O
O
O
O
CO2Me
5.51
2.09
0.99
1.00
3.03
1.05
1.03
2.00
1.08
1.95
0.99
2.93
9
8
7
6
5
4
3
2
1
ppm

jp8_002 13C NMR 150 MHz CDCl3 5-6-08

205.08
205.05
175.76
175.61
170.92
170.32
153.80
153.67
135.81
135.68
128.56
128.40
128.31
128.17
128.15
128.09
88.38
87.51
77.21
77.00
76.79
67.72
67.37
61.71
61.30
58.24
58.22
52.69
52.55
44.36
44.26
43.60
42.43
40.92
40.77
40.46
40.20
40.12
38.69
15.23
14.96



5-63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7.431
7.419
7.415
7.405
7.393
7.373
7.359
7.347
7.334
7.322
5.226
5.205
5.143
5.122
5.100
5.079
5.045
5.024
4.566
4.549
4.497
4.480
4.002
3.992
3.982
3.972
3.962
3.959
3.954
3.943
3.904
3.875
3.863
3.852
3.831
3.775
3.678
3.602
3.375
3.049
3.042
3.009
2.543
2.540
2.537
2.535
2.261
2.237
2.195
2.028
1.894
1.891
1.883
1.881
1.863
5-64
Cbz
CO2Me
4.36
1.93
1.00
4.34
1.12
1.25
1.77
0.93
0.52
1.35
1.79
0.93
2.56
ppm

jp8_016 13C NMR 150 MHz rt DMSO 6-4-08

177.82
177.79
172.06
171.48
154.24
154.05
137.47
129.42
129.28
128.98
128.76
128.71
128.33
107.76
107.74
88.77
87.72
67.29
67.23
65.33
65.16
64.20
64.03
62.36
62.04
57.72
57.61
52.90
52.88
43.77
43.75
40.99
40.87
40.73
40.59
40.45
40.31
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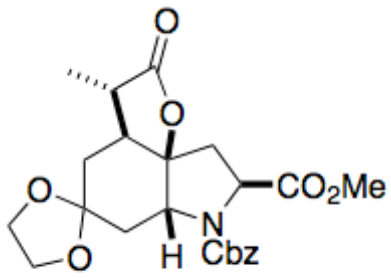
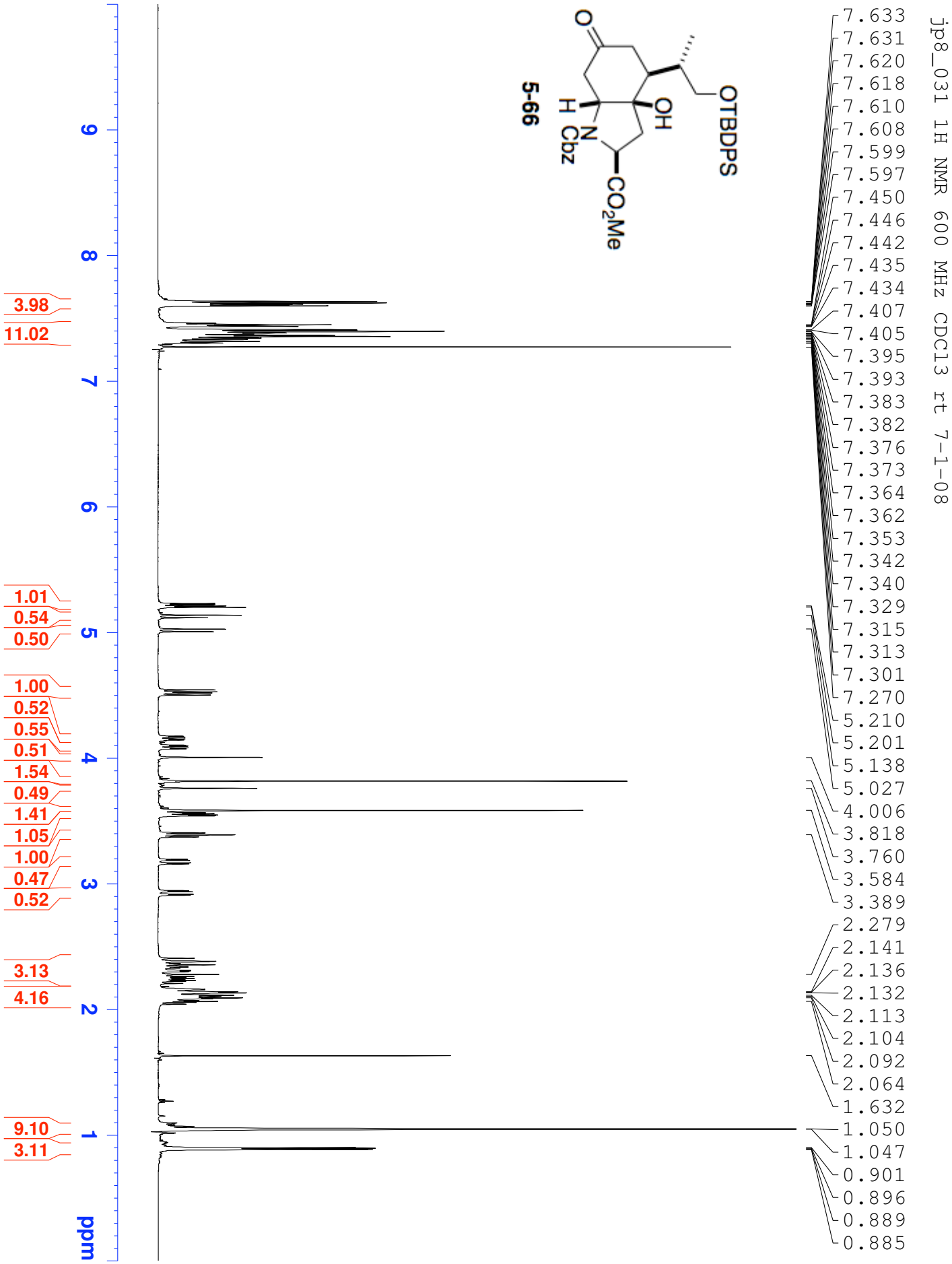
37.20
37.09
30.81
30.80
13.83
13.81



5-64

234

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm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5-66
OTBDPS
OH
N
H
Cbz
CO2Me
O
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7.631
7.620
7.618
7.610
7.608
7.599
7.597
7.450
7.446
7.442
7.435
7.434
7.407
7.405
7.395
7.393
7.383
7.382
7.376
7.373
7.364
7.362
7.353
7.342
7.340
7.329
7.315
7.313
7.301
7.270
5.210
5.201
5.138
5.027
4.006
3.818
3.760
3.584
3.389
2.279
2.141
2.136
2.132
2.113
2.104
2.092
2.064
1.632
1.050
1.047
0.901
0.896
0.889
0.885
3.98
11.02
1.01
0.54
0.50
1.00
0.52
0.55
0.51
1.54
0.49
1.41
1.05
1.00
0.47
0.52
3.13
4.16
9.10
3.11
9
8
7
6
5
4
3
2
1
ppm

jp8_031 13C NMR 150 MHz CDCl3 rt 7-1-08

209.97
209.73
175.44
175.10
154.93
154.05
135.94
135.86
135.48
133.17
133.14
133.08
133.03
129.88
129.82
128.61
128.45
128.30
128.20
128.11
128.08
127.79
127.77
82.42
81.30
77.21
77.00
76.79
67.73
67.40
67.06
67.04
66.07
65.41
59.49
59.18
53.00
52.65
43.08
42.10
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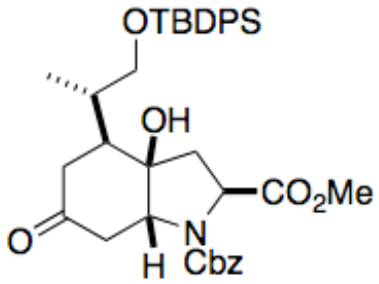
13.75



5-66

236

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

jp8_060 1H NMR 600 MHz CDCl3 rt 9-17-08
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7.365
7.354
7.345
7.336
7.330
7.324
7.270
5.209
5.166
5.146
5.117
5.088
5.069
5.007
4.599
4.585
4.363
4.345
4.135
4.123
3.792
3.536
2.704
2.509
2.493
2.485
2.462
2.442
2.438
2.430
2.412
2.371
2.368
2.365
2.356
1.373
1.361
1.296
1.285
1.280
1.273
1.268
1.261
1.256
0.943
0.931
0.919
0.902
0.891
0.879
0.876
0.864
5-69
Cbz
CO2Me
5.48
0.56
0.34
3.57
0.38
0.32
0.97
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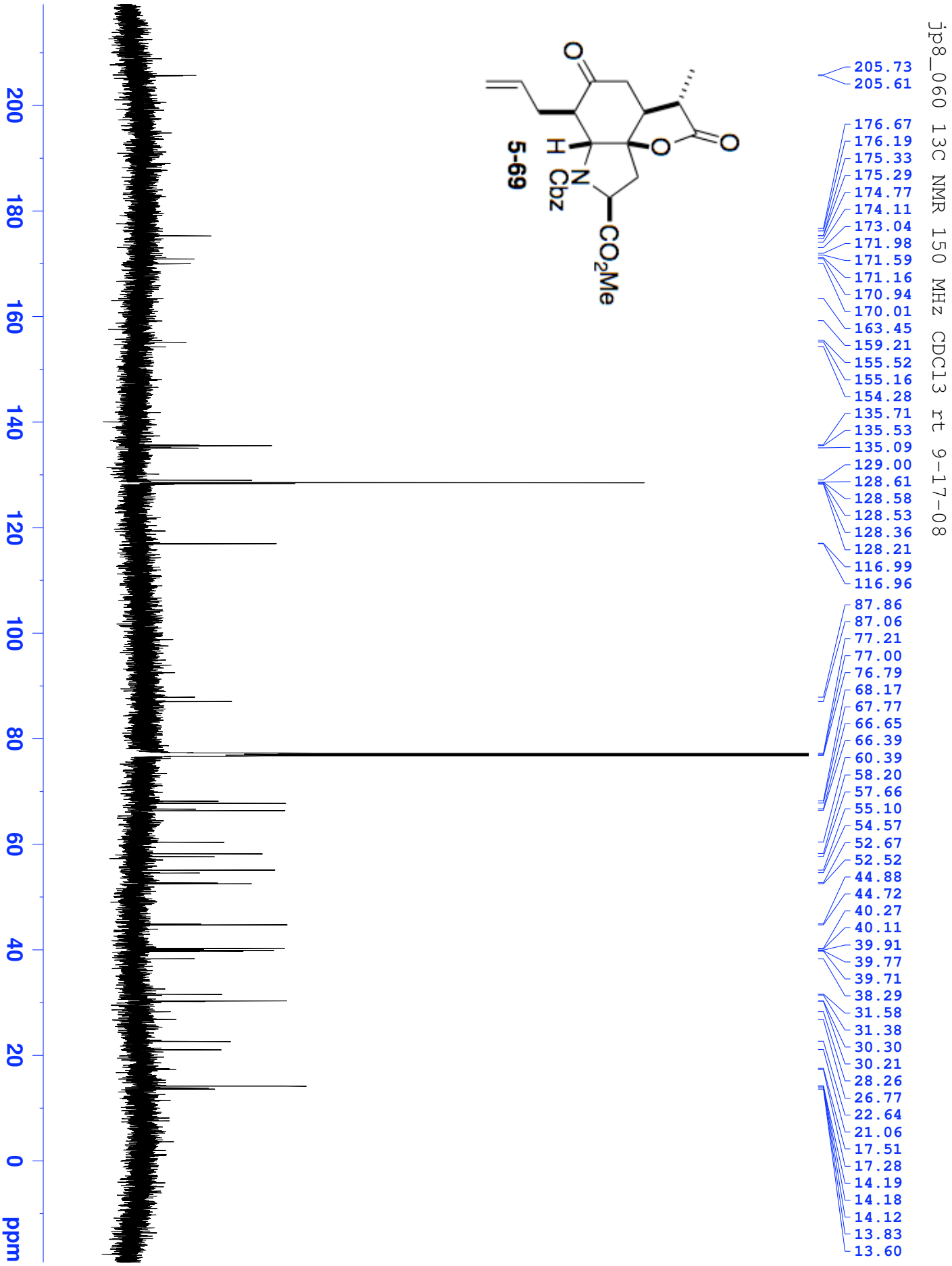
6.43
0.74
1.33
6.49
ppm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205.73
205.61
176.67
176.19
175.33
175.29
174.77
174.11
173.04
171.98
171.59
171.16
170.94
170.01
163.45
159.21
155.52
155.16
154.28
135.71
135.53
135.09
129.00
128.61
128.58
128.53
128.36
128.21
116.99
116.96
87.86
87.06
77.21
77.00
76.79
68.17
67.77
66.65
66.39
60.39
58.20
57.66
55.10
54.57
52.67
52.52
44.88
44.72
40.27
40.11
39.91
39.77
39.71
38.29
31.58
31.38
30.30
30.21
28.26
26.77
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21.06
17.51
17.28
14.19
14.18
14.12
13.83
13.60
200
180
160
140
120
100
80
60
40
20
0
ppm
5-69
H
N
Cbz
O
O
O
O
CO2Me

7.0 REFERENCES

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174. BF_3OEt_2 can also be used in this reaction, however with substrates such as **3-28**, the reaction is sluggish.

175. Analysis of the crude reaction mixture by ^1H NMR showed an α/β selectivity of 10:1 based on integration of the 2 aldehyde peaks.

176. The quality of Me_3Al is of critical importance in this reaction. Commercial solutions of Me_3Al were ineffective, possibly due to aggregate formation or traces of metal oxides; neat Me_3Al that was freshly diluted with CH_2Cl_2 was used in all cases.

177. HPLC separation was preformed using a Chiralcel® OD column and elution with 5% *i*-PrOH/Hexanes. Retention times = 16.5 min (major diastereomer), 20.8 min (minor diastereomer).

178. HPLC separation was preformed using a Chiralcel® AD-H column and elution with 7% *i*-PrOH/Hexanes. Retention times = 12.8 min (major diastereomer), 19.1 min (minor diastereomer).

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