Synthetic Strategies for the Lepadiformines and Cylindricine C via Tandem Schmidt Reactions

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Abstract

Marine flora and fauna have provided numerous alluring natural products, some of which contribute to treating diseases. The genus *Clavelina* is the source of a variety of tricyclic alkaloids, including the lepadiformine and cylindricine families. Novel approaches to synthesizing these molecules are sought after to increase their accessibility and for analogue development. In this dissertation, reaction sequences involving an intramolecular Schmidt transformation, which can quickly build up the molecular architecture associated with these targets is described. In one approach, the Lewis acid promoted intramolecular Schmidt reaction is combined in series with a Prins reaction to afford an interesting tricyclic lactam. This methodology culminates in a formal synthesis of lepadiformine A and a total synthesis of lepadiformine C. In another project, a tandem Diels–Alder/Schmidt reaction is utilized to prepare a similar tricyclic lactam. This process is applied toward an asymmetric total synthesis of (–)-cylindricine C. The preparation for the optically active starting material for the synthesis of (–)-cylindricine C is also discussed, as it is a prominent figure in the preparation of prostaglandins.

<u>Acknowledgements</u>

Without a shadow of a doubt, my mom has been the most important person in my life. My time in graduate school has been full of challenges and obstacles that I could not have overcome alone. My mom has always been in my corner to support and encourage me in whatever I have chosen to do. But ultimately, she is the reason I am still standing. This dissertation is dedicated to her.

My time in graduate school has been a life-changing experience to say the least. It has been a time of educational growth for sure, but the life experiences I have had are far greater. Many people have influenced my life along the way, and I wouldn't be who I am and where I am without them.

Ultimately, I sincerely thank my advisor, Jeffrey Aubé. His mentorship and incredibly hard work has allowed me to accomplish all of my scientific achievements. I thank him deeply for the kindness and understanding he has shown me throughout my tenure here whether I deserved it or not. I appreciate his always-honest perspective and his acceptance of me in all my forms, even though I'm sure it was difficult at times. Thank you for continuing to believe in me even when I didn't.

I would like to thank all of my committee members, Dr. Thomas E. Prisinzano, Dr. Ryan A. Altman, Dean Kenneth L. Audus, and Dr. Paul R. Hanson for not only taking time to serve on my committee but for their amazing mentorship and support over the years. A special thanks to Paul R. Hanson for allowing me to do an REU in his lab in 2005 and ultimately getting me interested in organic synthesis. A very special thanks to Tom Prisinzano for essentially being responsible for me joining a medicinal chemistry

program and even though I didn't join his lab, he still treated me like part of the family. His unending support and encouragement has gotten me a very long way.

I thank the Medicinal Chemistry Department and the School of Pharmacy at KU for allowing me to come here and the opportunities they have provided over the years.

My great appreciation goes to the Chemical Development Department at Boehringer–Ingelheim, most specifically Steve Han and Chris Senanayake, for providing me with an industrial summer internship in 2009. I learned an extraordinary amount about process chemistry and the pharmaceutical industry in general.

I would like to thank members of the Aubé entourage, past and present, for their scientific discussions, assistance, and mostly for their enjoyable conversation. I wish to especially thank to Dr. Tom Coombs for his invaluable mentorship and his always-willing assistance in science and life. I also wish to sincerely thank Dr. Stephen Slauson for his mentorship and the many highly-intellectual conversations we have had. Charlie Fehl gets my unending gratitude for being so wonderful to work with through the good times and the bad. Also, I extend a heartfelt thank you to Cady Bush and Shelley Sandberg for keeping everything running smoothly and handling everything behind the scenes.

Outside the lab, the most important person to me here at KU was Kimberly Lovell. I wouldn't have made it through the program without her. She is an outstanding scientist and a genuinely beautiful person, inside and out. She helped me through everything along the way, no matter how big or small, especially toward then end when I needed it the most. I appreciate her more than I have the ability to say.

I appreciate my wonderful family for their kind support and understanding while I have been here. I sincerely thank my dad and step-mom for their support in all forms. I deeply appreciate my sister, Marissa, for being so positive all the time and such an inspiration to me in all aspects of my life. And, of course, my mom.

I would like to thank the three wonderful people at Bluejacket Crossing Winery, Kandaya, Vasuki, and Anjali, for adopting me while I've been here. I thank them for always giving me a place to go and feel at home, and for the wine. For without wine, things don't seem to go as well.

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Chapter 1

Introduction to the Lepadiformine and Cylindricine Families of Natural Products

1.1. History for the Lepadiformines and Cylindricines

1.1.1. The Source

The ocean is full of all forms of life, from large, complex animals to microscopic, single-celled bacteria. The copious amounts of biodiversity in the ocean provide novel natural products, many of which are biologically active and some with important therapeutic activities including anti-cancer and anti-microbial effects. Numerous species of marine life have been probed for new molecules with hopes of finding cures for diseases that plague mankind.[1]

Ascidians, also known as sea squirts, are marine organisms and plentiful sources of novel natural products. These filter feeders reside on inanimate oceanic terrain and feed by extracting edible particles from the water flowing through their bodies. The extrusion of water from their siphon was how these fascinating creatures got their name. These marine-dwelling invertebrates are known to be rich sources of natural products.[2] Currently, researchers are investigating the origin of marine natural products and whether or not they result from symbiotic relationships between ascidians and microorganisms or are products of individual species.[1,3,4]

1.1.2. Cylindricine Family

One genus of ascidians known as *Clavelina* is made up of a wide variety of brilliantly colored sea squirts that have contributed a plethora of natural products, including the cylindricine and lepadiformine families. *Clavelina cylindrica* is the source of the cylindricine family of alkaloids, which contains 11 tricyclic alkaloids (Figure 1), isolated off the coast of Tasmania. The natural products were isolated by extraction of freeze-dried *Clavelina cylindrica* and obtained in small yields between 0.0002-0.01%. How these natural products are biosynthesized or their natural functions are currently unknown. The only biological testing done in this family, carried out on the equilibrium mixture of cylindricines A and B only, was a brine shrimp assay (*Artemia salina*), which indicated in modest cytotoxicity (93% mortality after 24 hr at a 3 mM concentration).[5-7] The equilibrium between **1** and **2** was shown when each pure compound in solution converted to a 3:2 mixture after six days at room temperature. Despite the modest biological activity of this family of molecules, the structures pose a synthetic challenge and therefore have made the cylindricines a much sought-after family of molecules for total synthesis.[8]

The common numbering of these molecules is depicted in Figure 1. Atom 1 is the nitrogen and proceeds in a clockwise fashion around the molecule as depicted. The significant structural features include alkyl substitution at C-2, oxidation at C-4, the azadecalin fusion at C-5 and C-10, and a functionalized methylene group at C-13. Also, each ring is associated a specific letter of the tricyclic system such that the A ring is the

cyclohexane ring, the B ring is the piperidine ring, and the C ring represents the pyrrolidine ring. This nomenclature is used throughout this account.

The tricyclic pyrrolidine and tricyclic piperidine scaffolds were the first of their kind to be isolated. Some interesting structural motifs in the cylindricine family include the aza-spirocenter that fuses a *cis*-azadecalin with a pyrrolidine or piperidine ring. This complex center creates an interesting synthetic challenge, as there is no easy, straightforward procedure for preparing it. Features that differ among the cylindricine members include the oxidation state at C-4, either a carbonyl or an acetate, and the substitution at C-2, either a hexyl or butyl group. The major variation in the molecules exists at the C-14 where a multitude of functional groups appear, including a halogen, alcohol, methoxy, acetoxy, or thiocyanate functionality. The absolute configuration of the natural enantiomer remains unknown as no optical rotation was taken after isolation of these molecules, perhaps due to the isolation of an insufficient amount of the compounds.

Cylindricine A: R = Cl (1)
Cylindricine C: R = OH (3)
Cylindricine D: R = OMe (4)
Cylindricine E: R = OAc (5)
Cylindricine F: R = SCN (6)

proposed intermediate

Cylindricine B (2)

Cylindricine G (7)

Cylindricine H: R = SCN (8)
Cylindricine I: R = NCS (9)

Cylindricine J (10)
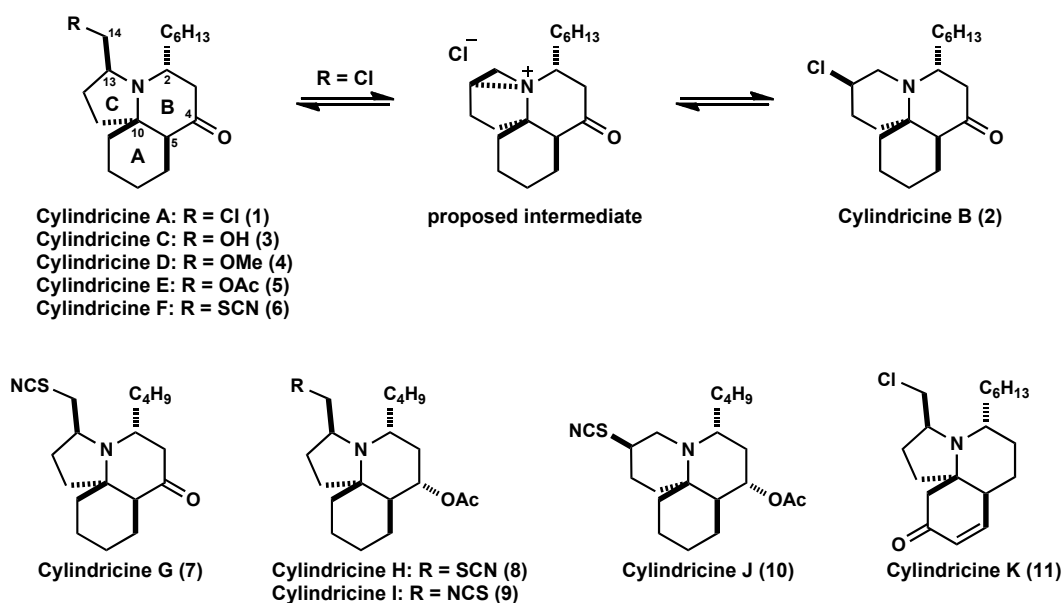
Cylindricine K (11)

Figure 1. The cylindricine family

1.1.3. Lepadiformine Family

Another family of natural products structurally related to the cylindricines is the lepadiformine family, which contains three tricyclic alkaloids (Figure 2). The lepadiformines have been isolated from *Clavelina lepadiformis* off the coast of Tunisia and *Clavelina moluccensis* off the coast of Djibouti.[9,10] Similar to the cylindricines, the biosynthetic details and evolutionary purpose for these molecules remains unknown; however, they demonstrate interesting biological activity. Lepadiformines A and B have inhibitory effects on the inward rectifying potassium current which causes bradycardia, an effect seen in antiarrhythmic agents.[10,11] This activity, along with the interesting synthetic architecture, has made the lepadiformine family a hot target for total synthesis.

Disagreement in the literature about the originally reported structure of lepadiformine A sparked significant synthetic interest. Biard and coworkers originally assigned the structure of lepadiformine A. Weinreb and coworkers prepared the proposed structure, which yielded inequivalent spectral data.[12-14] A short time later, Kibayashi and coworkers prepared the newly proposed version of lepadiformine A (**12**), the spectral data of which coincided with that of the isolated natural product.[15] Weinreb and Kibayashi, separately, also determined the absolute configuration of the natural enantiomer by preparing both enantiomers and comparing the optical rotations.[16,17] The pioneering efforts of both Weinreb and Kibayashi paved the way for an illustrious portfolio of synthetic achievements for these families of molecules.

Although the structures of the lepadiformines are strikingly similar to the cylindricine family, the relative stereochemistry at C-10 represents one major difference.

The inverted stereochemistry at the aza-spirocenter generates a *trans*-azadecalin core in the lepadiformine series in contrast to the *cis*-azadecalin core of the cylindricines. In addition, the lepadiformines lack oxidation at the C-4 position.
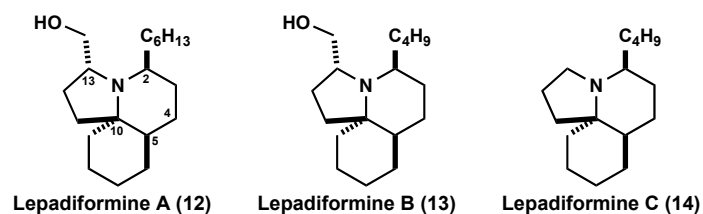
Figure 2. The lepadiformine family

1.1.4. Similar Natural Products

Other molecules with similar architectures to the cylindricines and lepadiformines include fasicularin[18] and polycitorols A and B,[19] all isolated from marine ascidians (Figure 3). Fasicularin was isolated from *Nephteis fasicularin* and has been shown to alkylate DNA through an intermediate similar to the proposed aziridinium intermediate in Figure 1.[20] The polycitorols were isolated from an unknown tunicate species and possess no known biological activity, most likely due to lack of biological testing.

Fasicularin (15)   Polycitorol A (16)   Polycitorol B (17)
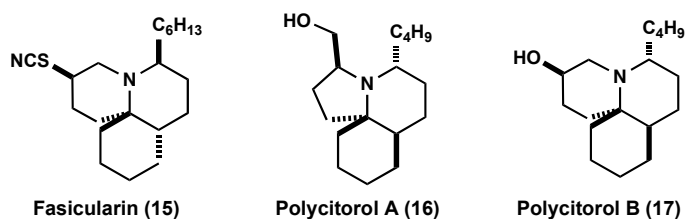
Figure 3. Natural products related to the cylindricines and lepadiformines

1.1.5. Previously Reviewed Syntheses

The lepadiformine and cylindricine families of natural products, as well as fasicularin, have all been the targets of numerous total and formal syntheses, most of which have been reviewed.[8,21-23] Some interesting and innovative methodologies have emerged en route to these classes of molecules. Of the reviews, the one by Weinreb is the most comprehensive and encompasses all of the synthetic achievements pertaining to these families of natural products through 2006. For comparison purposes, Table 1 includes a summary of the syntheses contained in the Weinreb review, which focuses on construction of the aza-spirocenter, other significant ring closure techniques, the source of asymmetry (if applicable), the number of steps, and the overall yield.

The construction of the aza-spirocenter has been carried out in different ways including double conjugate additions, Diels–Alder reactions and other cycloadditions, as well as radical-mediated reaction sequences (Table 1). Also, the chiral pool serves as a major source for chirality. Figure 4 demonstrates several examples to construct the aza-spirocenter.

Table 1. Weinreb review summary[8]

Principle Investigator	Molecule	Construction of the Aza-spirocenter	Significant Cyclizations	Origin of Asymmetry	Steps (Yield)
Snider[24]	(±)-Cylindricine A	Intermolecular double conjugate addition	Radical cyclization	NA	7 (13%)[a]
Heathcock[25]	(±)-Cylindricine A	Intermolecular double conjugate addition	Radical cyclization	NA	11 (19%)[a]
Molander[26]	(−)-Cylindricine C	Intramolecular double conjugate addition	NA	(S)-1,2,4-Butanetriol	11 (12%)[b]
Trost[27]	(+)-Cylindricine C, D, E	Intramolecular conjugate addition	Hydrative diyne cyclization	L-Serine	9 (12%)[b,c]
Kibayashi[28]	(+)-Cylindricine C	Grignard addition to imine	Enamine addition, conjugate addition	(S)-Pyroglutamic acid	14 (9%)[a]

Kibayashi[15]	(±)-Fasicularin	Acylnitroso Diels–Alder reaction	S_N2 Displacement	NA	29 (<1%)[a]
Kibayashi[29]	Putative lepadiformine	Acylnitroso Diels–Alder reaction	Reductive amination	NA	23 (<1%)[a]
Kibayashi[15]	(±)-Lepadiformine A	Acylnitroso Diels–Alder reaction	S_N2 Displacement	NA	21 (5%)[a]
Kibayashi[30]	(−)-Fasicularin	Intramolecular conjugate azaspirocyclization	S_N2 Displacement	(S)-Pyroglutamic acid, (R)-Binal	11 (28%)[a]
Kibayashi[30]	(−)-Lepadiformine A	Intramolecular conjugate azaspirocyclization	S_N2 Displacement	(S)-Pyroglutamic acid, (S)-Binal	9 (31%)[a]
Kibayashi[30]	(+)-Cylindricine C	Intramolecular conjugate azaspirocyclization	S_N2 Displacement	(S)-Pyroglutamic acid, (S)-Binal	12 (12%)[a]
Hsung[31]	(+)-Cylindricine C	Aza-Prins reaction	Aza-conjugate addition	(S)-Pyroglutamic acid	9 (11%)[a]
Hsung[32]	(−)-Lepadiformine A	Aza-Prins reaction	Aza-conjugate addition	(S)-Pyroglutamic acid	12 (7%)[a]
Hsung[33]	(−)-Cylindricine C	Intramolecular aza-[3+3] cycloaddition	NA	L-Serine	22 (5%)[b]
Ciufolini[34]	(−)-Cylindricine C	Oxidative spirocyclization	Reductive amination	D-Homotyrosine	18 (15%)[b]
Ishibashi[35]	Core approach	Radical cascade	NA	NA	NA
Hunter[36]	Core approach	Alkylation of silyloxypyrrole	RCM, S_N2 displacement	NA	NA
Funk[37]	(±)-Fasicularin	2-Amidoacrolein Diels–Alder reaction	Aldol condensation	NA	18 (<1%)[b]
Funk[38]	(±)-Lepadiformine A	2-Amidoacrolein Diels–Alder reaction	S_N2 Displacement, aziridination	NA	16 (13%)[b]
Dake[39]	(+)-Fasicularin (formal)	Silylepoxy semipinacol rearrangement	S_N2 Displacement	L-Glutamic acid	24 (<1%)[b]
Oppolzer[40]	Core approach	Nitroso/olefin dipolar cycloaddition	NA	(2R)-bornane-10,2-sultam	NA
Pearson[41]	Putative lepadiformine	Azaallyl dipolar cycloaddition	Reductive amination	NA	NA
Weinreb[13]	Putative lepadiformine	Nitrone/olefin dipolar cycloaddition	Intramolecular conjugate addition	NA	17 (3%)[a]
Weinreb[42]	(±)-Lepadiformine A	N-Acyliminium spirocyclization	Condensation	NA	15 (11%)[a]
Weinreb[17]	(−)-Lepadiformine A	N-Acyliminium spirocyclization	Condensation	(S)-Pyroglutamic acid	15 (13%)[a]
Kim[43]	(−)-Lepadiformine A (formal)	Amino acid ester-enolate Claisen reaction	RCM, condensation	(S)-Pyroglutamic acid	15[b,d]
Renaud[44]	(±)-Lepadiformine A	Radical carboazidation	Reductive amination, lactonization	NA	10 (15%)[b,c]

[a] Yield from a known intermediate
[b] Yield from commercially-available starting material
[c] Longest linear sequence
[d] No yield to report
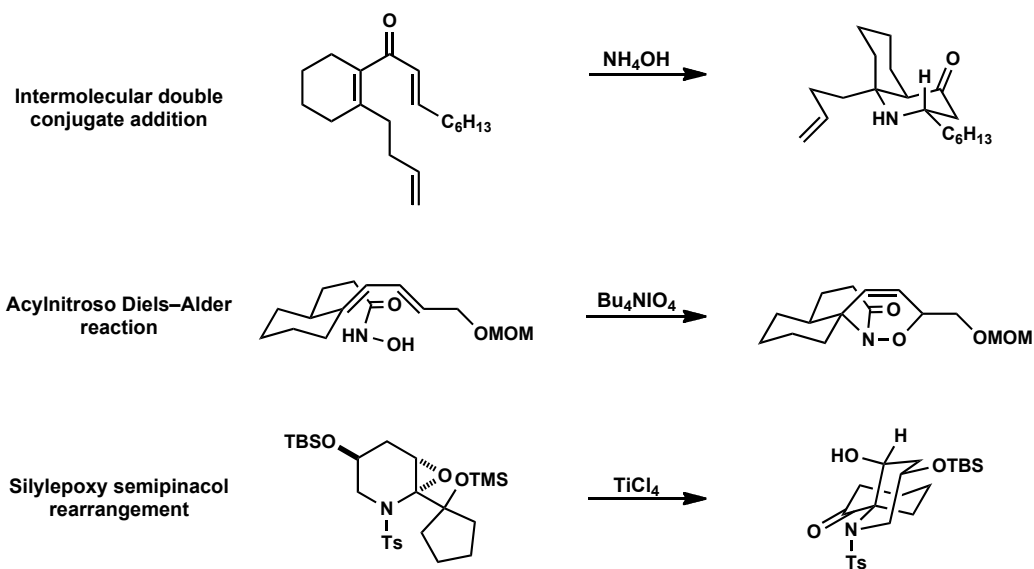
Figure 4. Examples of aza-spirocenter construction from Table 1

Since the Weinreb review, substantial synthetic efforts have been made to synthesize the lepadiformines and cylindricines.[8] The following section will seek to examine the recent synthetic strategies with an emphasis on the construction of the aza-spirocenter.

1.2. Total Syntheses of the Lepadiformines

The following section will discuss the eight syntheses of the lepadiformines that have been published since the release of the 2006 Weinreb review. A variety of transformations were applied to achieve the aza-quaternary center, including radical-mediated transformations and well-known reactions such as the Diels–Alder or Michael reactions.

1.2.1. Radical Reactions

The formation of a fully substituted carbon can require crafty innovation or skilled ingenuity. Radical generation can be manipulated to accomplish this task. However, radical generation at the desired location is not always easy, particularly when sterically crowded. One alternative is to generate the radical at a remote location of the molecule and transfer the radical to the desired location intramolecularly, a task achieved by H. Tokuyama and coworkers in their total synthesis of (±)-lepadiformine A (**12**).[45]

H. Tokuyama and coworkers began with succinimide (**18**) and quickly constructed the key intermediate (**20**) by *N*-alkylation, reduction, and sulfonation to get **19** (Scheme 1). Two more steps afforded **20**, the key step precursor. To initiate the key step, azabisisobutyronitrile (AIBN) and tributyltinhydride (Bu₃SnH) were used to accomplish the deiodination to phenyl radical **21**, which was translocated through a 6-membered transition state to generate a stabilized radical alpha to the amide (**22**). The radical added to the double bond before being terminated by picking up a hydrogen atom to complete the formation of the aza-spirocenter in excellent diastereoselectivity (>95:5 by NMR) due to the preferred pseudo-equatorial conformation of the alkene to avoid a steric interaction between the sulfone and the PMB group, thus forming **23**.

The total synthesis was continued by oxidation with cerium ammonium nitrate (CAN) that removed the PMB protecting group to achieve **24**. The benzyl protected hydroxy methylene was introduced through a series of transformations to yield **25**. Six more steps were required to complete the total synthesis of (±)-lepadiformine A (**12**), including a reductive amination reaction between the deprotected amine and aldehyde

groups in **26** to close the third ring. Although this synthesis was low yielding, 19 steps

and 1% overall yield, the translocation strategy effectively permitted the generation of a

radical at an otherwise difficultly-accessible α-amido carbon. The methodology

presented here was a novel and useful way to stereoselectively set aza-spirocenters from

substituted lactams.
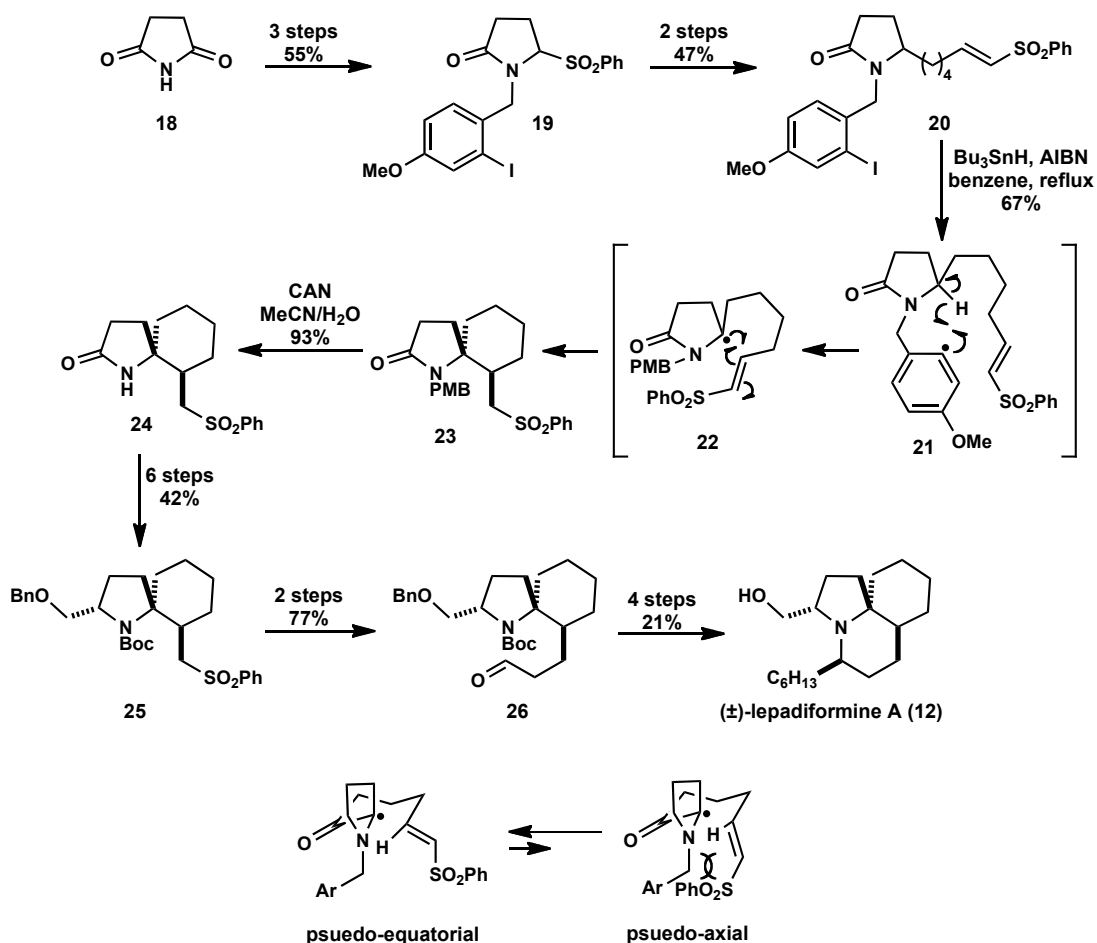
Scheme 1. Tokuyama synthesis of (±)-lepadiformine A (**12**)[45]

In 2010, Rychnovsky and coworkers completed the first asymmetric total

synthesis of (+)-lepadiformine C (**14**) using a nitrile-mediated lithiation methodology

developed in their laboratory.[46] As shown in Scheme 2, the synthesis began with enantiomerically pure propargyl alcohol **27**, which was transformed to **28** in seven steps. With **28** and **29** in hand, the A ring (the cyclohexane ring) was closed by a double displacement reaction initiated by LDA. The first displacement connected the α-cyano carbon of **29** to **28** by an S_N2 reaction on the primary bromide to form intermediate **30**. Subsequent treatment of **30** with more LDA (3.0 equiv total) allowed for the second S_N2 displacement on the secondary bromide to occur to afford **31**. From **31**, the silyl ether was converted to phosphate **32**, the necessary substrate for the key cyclization step to form the pyrrolidine ring. The second cyclization, the aza-spirocenter formation, was initiated by combining lithium di-*tert*-butylbiphenylide (LIDBB) with **32**, which underwent two sequential single-electron transfers. The ring closure occurred through anion **33** to form spirocycle **34**. The total synthesis of (+)-lepadiformine C (**14**) was completed by conversion of **34** to mesylate **35**, followed by S_N2 displacement by the deprotected nitrogen to close the remaining B ring.

This total synthesis of (+)-lepadiformine C (**14**) was completed in 14 linear steps from the known **27** in 7% yield. During the course of this synthesis, all three rings were constructed separately and two of the three stereocenters set via asymmetric reactions, both in **28**. The aza-quaternary center was set using their reductive lithiation methodology in diastereoselective fashion controlled by the cyclohexane ring conformational preference.
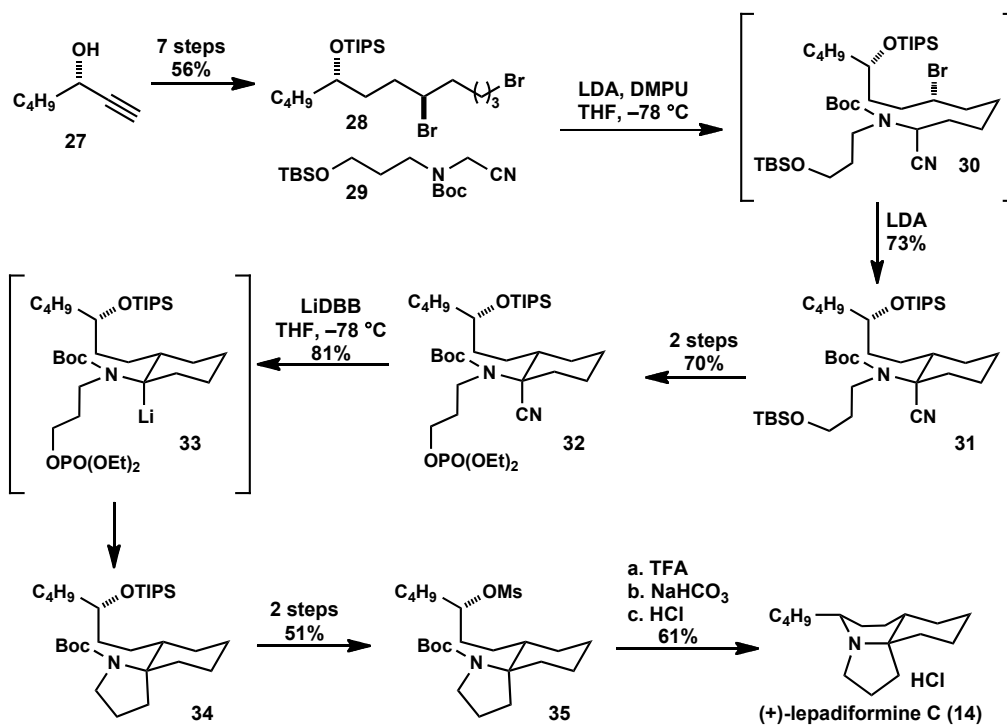
Scheme 2. Rychnovsky synthesis of (+)-lepadiformine C (**14**)[46]

Azides are a useful source of nitrogen in synthesis. As shown in Scheme 3, the Renaud group has devised a way to transfer azide through a radical process to generate an aza-spirocenter en route to a total synthesis of (±)-lepadiformine C (**14**).[47] Enamine **36** was converted in four simple steps to the precursor for the key transformation, **37**. Sulfonylazide **38** was irradiated with di-*tert*-butyldiazene, a radical initiator, to form radical **39** and the azide radical after extruding SO_2. Alkene **37** propagated the sequence by combining with **39** to form radical **40**, which reacted with the azide radical generated from the breakdown of the sulfonylazide, allowing for continuation of the radical cycle by regenerating **39**. The resulting azide **41** (dr = 3:2) was taken on as a mixture of inseparable diastereomers and was reduced to the amine followed by reductive amination to yield decahydroquinoline **42** as the major diastereomer. Treatment of **42** with a strong

Lewis acid, Me$_2$AlCl, closed the lactam and subsequent treatment with lithium aluminum hydride (LAH) reduced the amide to the amine to conclude the total synthesis of (±)-lepadiformine C (**14**).

The carboazidation process developed by Renaud and coworkers was an efficient way to generate sterically-congested amines. This process was especially effective in forming aza-spirocenters because the radical generated from a 1,1-disubstituted double bond favored the tertiary radical formation (Scheme 3). This total synthesis of (±)-lepadiformine C (**14**) was accomplished in seven steps and 23% overall yield from commercially available material.
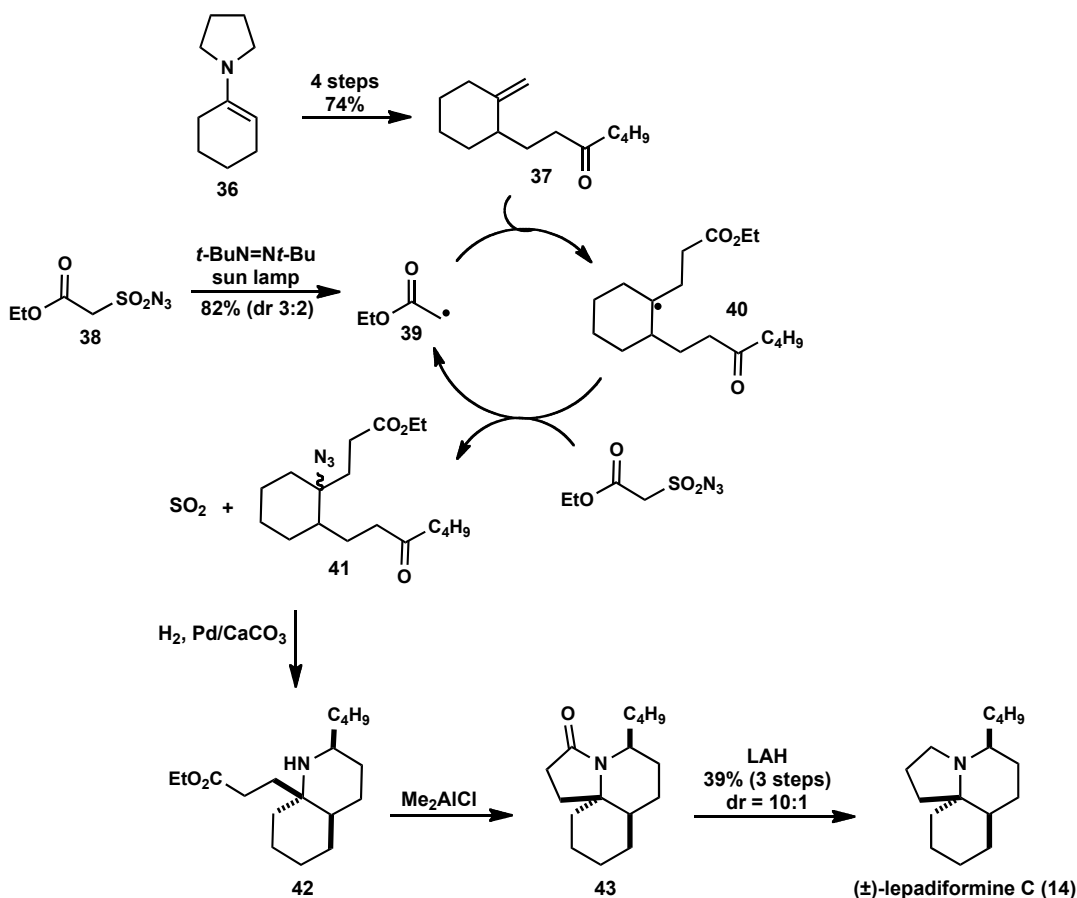
Scheme 3. Renaud synthesis of (±)-lepadiformine C (**14**)[47]

1.2.2. Sulfone-Assisted Transformations

Sulfones are useful functional groups in organic chemistry as they allow for functionalization of carbon atoms without leaving a footprint. The electron-withdrawing nature of the sulfonyl group decreases the pKa of the hydrogens on the adjacent carbon allowing for easy functionalization. The sulfone can then be cleaved by reductive conditions, leaving only the newly functionalized carbon. This process is an excellent way to achieve carbon-carbon bond formation.

In a total synthesis of (±)-lepadiformine A (**12**) by Craig and coworkers, the sulfone group was used in a 5-*endo*-trig cyclization to achieve the pyrrolidine ring formation.[48] As depicted in Scheme 4, Craig's total synthesis of (±)-lepadiformine A (**12**) began with the formation of the aza-spirocenter. Substituted cyclohexanone **44** was converted to epoxide **45** with the desired relative stereochemical configuration using a substrate-controlled epoxidation. In this reaction, the methylene was delivered from the axial face, with the acetal-containing sidechain in the equatorial position, affording excellent diastereoselectivity. Next, the epoxide in **45** was opened with 2-(trimethylsilyl)ethylsulfonamide (SESNH$_2$) to give an *N*-protected amino alcohol, **46**. Using Mitsunobu conditions, the aza-spirocenter configuration was set by displacement of the activated alcohol with complete inversion of configuration. Next, the sulfone was installed to form **48**, the substrate for the key cyclization step.
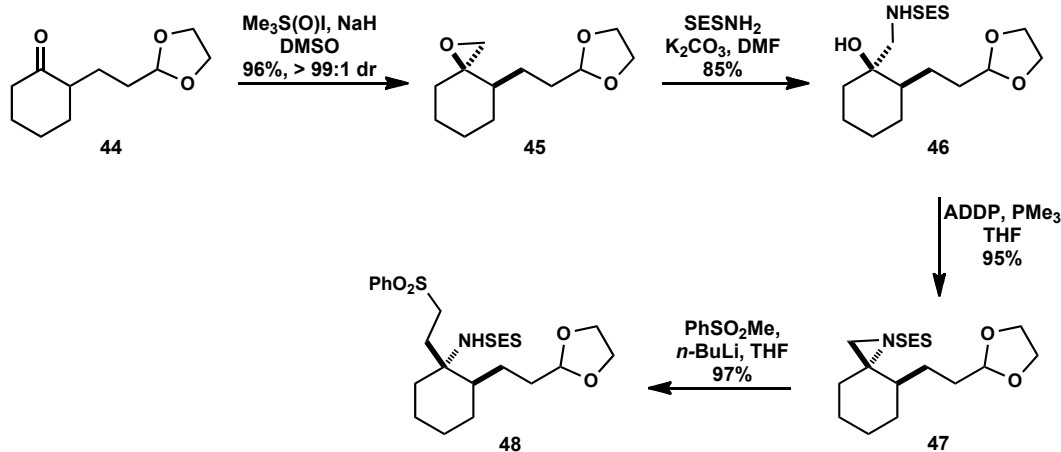
Scheme 4. Craig synthesis of (±)-lepadiformine A (**12**)[48]

With **48** in hand, the sulfone-mediated 5-*endo*-trig cyclization was investigated. The 5-*endo*-trig ring closure is typically disfavored according to Baldwin's rules.[49] As shown in Scheme 5, **48** was treated with *n*-BuLi to form an anion adjacent to the sulfone, which added to the 2-benzyloxyethanal. Activation of the resulting alkoxide with benzoyl chloride and elimination of the resulting ester produced intermediate **49**, which underwent a disfavored 5-*endo*-trig cyclization by the amine to close the C ring, **50**. To continue the total synthesis, **50** was treated first with tetrabutylammonium fluoride (TBAF) to deprotect the amine and secondly with boron tribromide (BBr$_3$), which unveiled the aldehyde as well as debenzylated the alcohol to form intermediate **51**. Subsequent *in situ* condensation of the amine onto the aldehyde and addition of the hydroxymethylene resulted in the desired B ring closure seen in aminal **52**. The aminal was opened with an alkynyl Grignard to provide **53**, which was converted to (±)-lepadiformine A (**12**) in seven more steps.

Although lengthy, the total synthesis of (±)-lepadiformine A (**12**) by Craig and coworkers included a number of interesting and useful chemical transformations. The

epoxidation-aziridination strategy to install the aza-spirocenter was high yielding, effective, and stereoselective. Also, the sulfone strategy to close the pyrrolidine ring was a nice showcase of the disfavored ring-closure. Despite a lengthy end game sequence the total synthesis of (±)-lepadiformine A (**12**) was accomplished in 16 total steps and 19% overall yield.
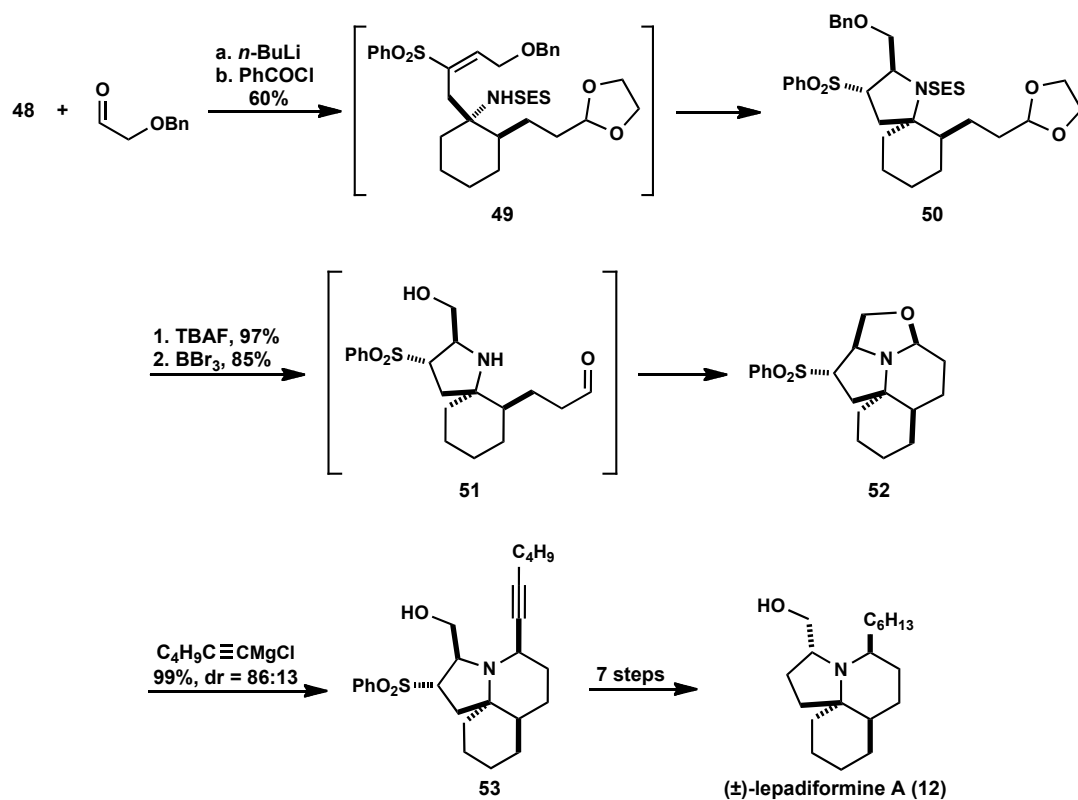
Scheme 5. Craig synthesis of (±)-lepadiformine A (**12**) (continued)[48]

1.2.3. Intramolecular Diels–Alder Approach

The Diels–Alder reaction is a useful and effective way to generate six-membered rings. The intramolecular variation of the Diels–Alder reaction (IMDA) has been used in a plethora of total syntheses and has the potential for quickly generating elevated complexity.[50,51] In an account by Lygo *et. al.*, the power of the aza-IMDA reaction is highlighted in a short, protecting group-free synthesis of (±)-lepadiformine A (**12**).[52]

As shown in Scheme 6, the Lygo synthesis begins with commercially-available *trans*-nonenal (**54**), which was converted to **55** in three steps. Subsequent conjugate addition to **55** by glycine imine **56** followed by acid mediated condensation delivers **57**, the aza-IMDA precursor, in good yield. With **57** in hand, a myriad of standard IMDA conditions were investigated. The aza-IMDA product **58** was ultimately obtained a 5:1 mixture of diastereomers, the major component of which had the relative stereochemistry desired for the synthesis of (±)-lepadiformine A (**12**). During this step, two rings were formed and the aza-spirocenter was set along with two other stereocenters simultaneously. That reaction represents the ability of the IMDA reaction to create high levels of complexity with relative ease in a single step. The total synthesis was completed by olefin hydrogenation and acid reduction.

The Lygo approach to (±)-lepadiformine A (**12**) was achieved in eight linear steps and 14% overall yield. This synthesis was protecting group free and used the powerful IMDA reaction to set the aza-spirocenter and two other stereocenters. The *endo*-adduct, the major Diels–Alder product, set the correct relative stereochemistry of all four

stereocenters in the molecule. This total synthesis represents an excellent example of the

utility of the Diels–Alder reaction in natural product synthesis.
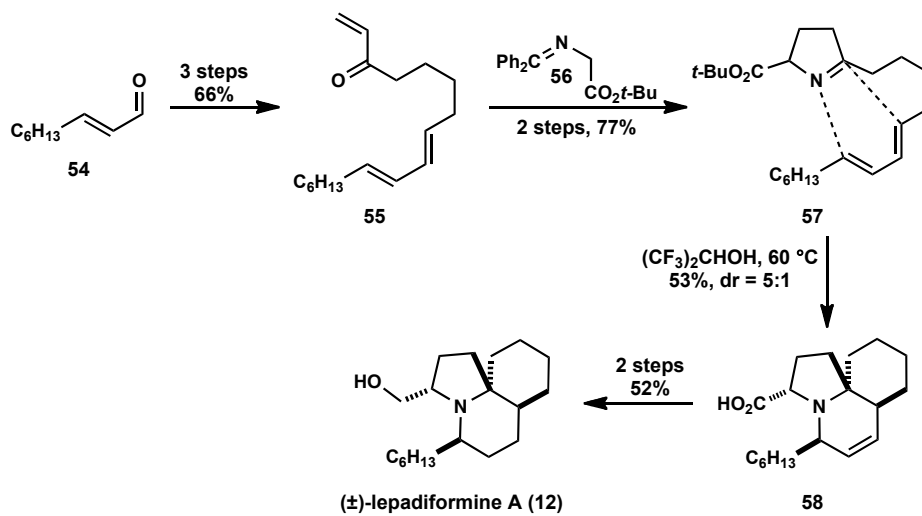
Scheme 6. Lygo synthesis of (±)-lepadiformine A (**12**)[52]

1.2.4. Organocatalyzed Conjugate Addition

Organocatalysis, reactions catalyzed by organic molecules rather than metals, is of increasing interest in the synthetic community due to the lack of often highly toxic metals.[53] In total syntheses of (–)-lepadiformine A (**14**) and (+)-cylindricine C (**3**), an asymmetric conjugate addition was used by the Shibasaki group with an organic catalyst system they developed.[54] The organocatalytic conjugate addition set only one stereocenter but had a dramatic effect over the outcome of the other three stereocenters formed.

The Shibasaki route to the *Clavelina* natural products began with pimelic acid (**59**), which was converted to dienedione **60** in three steps. The asymmetric conjugate addition mediated by an organocatalyst commenced by combining **60** with **61**. After optimization, the catalyst, (*S,S*)-TaDiAS (TaDiAS; tartrate-derived diammonium salt), was chosen to achieve **62** in 91% es. With **62** in hand, mildly acidic conditions initiated a tandem Mannich/aza-Michael reaction sequence to afford the tricycles **63a**, **63b**, and a third diastereomer. Many conditions and additives were investigated to improve diastereoselectivity. Without the additives, **63a** and **63b** were formed in a 1:2 ratio, with a third diastereomer formed in trace amounts. The addition of additives ($MgCl_2$, LiCl, $AlCl_3$, or $La(OTf)_3$) dramatically increased the amount of **63a** formed over the other two diastereomers; however, in all cases and conditions tried, mixtures of three diastereomers were formed. Interestingly, **63b** was converted to **63a** following subjection to simple basic conditions of K_2CO_3/MeOH or TBAF.
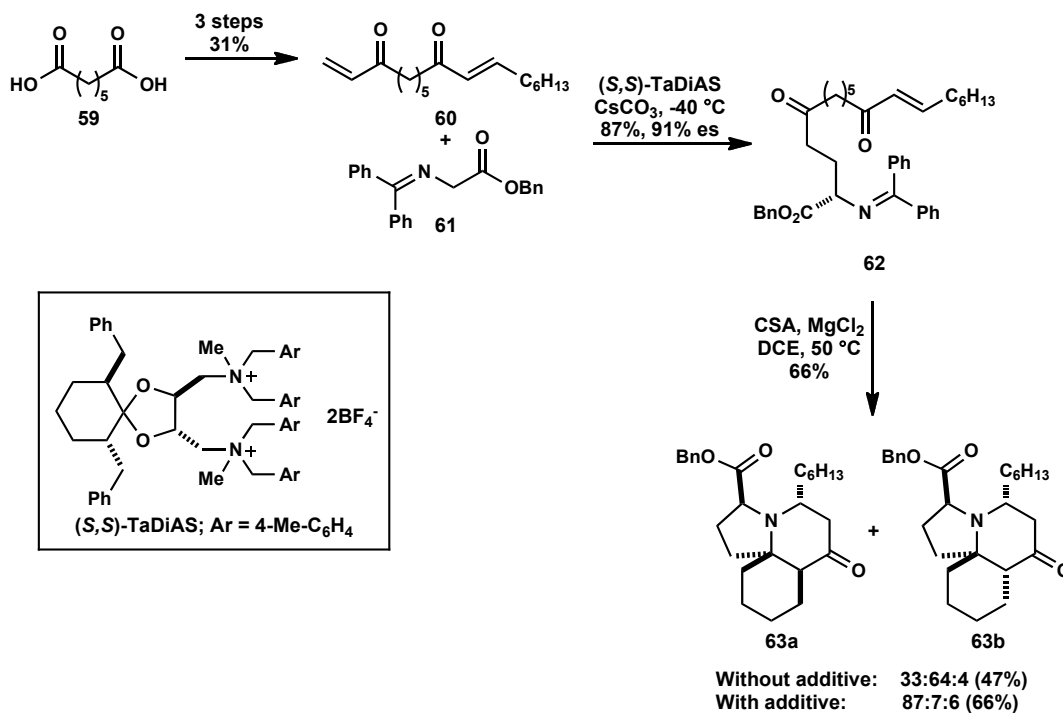
Scheme 7. Shibasaki synthesis of (–)-lepadiformine A (**14**) and (+)-cylindricine C (**3**)[54]

The mechanism for the triple cyclization is shown in Scheme 8. Compound **62** first underwent nitrogen transimination by loss of H_2O and benzophenone onto the nearest carbonyl, forming intermediate **62a**. Next, an intramolecular Mannich reaction to intermediate **62b**, where the second ring was closed to form the aza-spirocenter. From bicycle **62b**, multiple convergent pathways to close the third ring were possible. The first pathway was an aza-Michael addition to afford **63b**, which possessed the *trans*-azadecalin moiety of the lepadiformines. Alternatively, **62b** could undergo enolization through enol **62c**, which can return to the keto form with the adjacent stereocenter inverted, **62d**. From there, an aza-Michael addition formed **63a**, which possessed the *cis*-azadecalin moiety as seen in the cylindricines. As mentioned previously, the additive addition had a dramatic stereochemical outcome. The authors propose that the Lewis

acidity of the additives increase the enol formation and an increased amount of **63a** by

chelating the free hydroxyl and amine groups of **62c**. Without the additive, the

lepadiformine precursor, **63b**, was the major product and taken on to a total synthesis of

(−)-lepadiformine A (**14**). With the additive, the major product formed was **63a**, which

was used in a total synthesis of (+)-cylindricine C (**3**). Although conjugate addition has

been frequently used in other syntheses for these molecules (Table 1),[8] the cascade of

cyclizations shown in Scheme 8 was most impressive as all three rings were formed in a

single step including the formation of three new stereocenters and the challenging aza-

spirocenter.
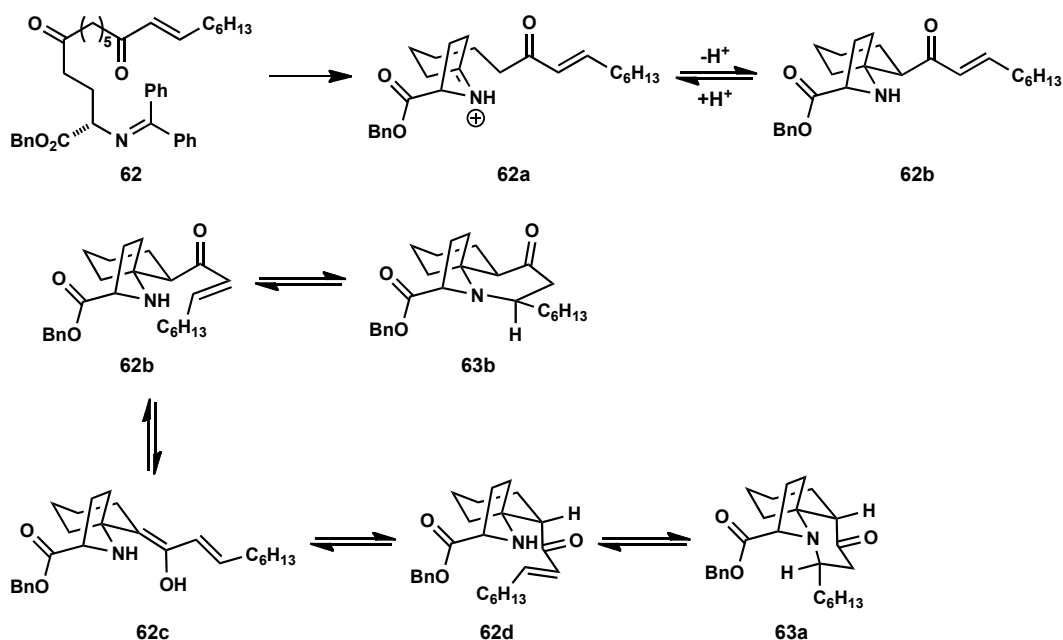
Scheme 8. Shibasaki proposed mechanism[54]

As shown in Scheme 9, a formal synthesis of (−)-lepadiformine A (**12**) was

accomplished by reducing the ester and ketone followed by selective protection of the

primary alcohol to afford **64**, an intermediate in a total synthesis by Hsung and coworkers.[32] (–)-Lepadiformine A (**12**) was completed by dehydroxylation of **64** under Barton–McCombie conditions[55] followed by TBAF to unveil the primary alcohol. With those results, Shibasaki accomplished a formal total synthesis of (–)-lepadiformine A in ten steps and 4% overall yield. Starting from pimelic acid, the total synthesis of (+)-cylindricine C (**3**) was completed in six linear steps and 6% overall yield, the shortest asymmetric synthesis to date.
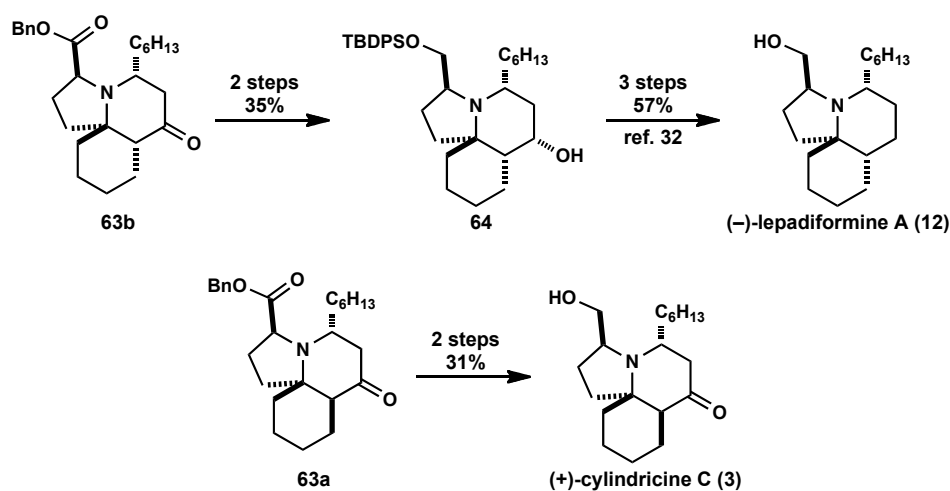
Scheme 9. Shibasaki synthesis of (–)-lepadiformine A (**14**) and (+)-cylindricine C (**3**)

(continued)[54]

1.2.5. Sulfinamide-Mediated Synthesis

Chiral sulfinamides are effective chiral transfer reagents.[56] Following the pioneering work by Davis *et. al.*[57] and Ellman *et. al.*,[58] a myriad of synthetic examples utilizing sulfinamide chemistry surfaced including natural product syntheses and preparations of pharmaceutical agents.[56] Much work has focused on preparation and utilization of sulfinamides in both academia and industry in recent years.[59,60] To add to the list of total syntheses using chiral sulfinamides, a total synthesis of (–)-lepadiformine A (**12**) was accomplished by Mei and Zhao.[61]

Zhao and coworkers established the stereochemistry of the aza-spirocenter using zinc allylation chemistry.[62] The total synthesis began with ethyl 2-(2-oxocyclohexyl)acetate (**65**), which was converted in four steps to **66** in 97% es, where the stereocenter alpha to the imine was set through a Corey-Bakshi-Shibata (CBS) reduction of **65** and separation of the resulting diastereomers (Scheme 10). With **66** in hand, the key step to prepare the aza-spirocenter involving addition of allyl group into the sulfinimide via Zn allylation provided **67** in 89% yield and 12:1 dr. Six steps were needed to deprotect the sulfinamide and homologate the double bond in **68**. Subsequently, the C ring was closed and the third stereocenter set with Sharpless dihydroxylation conditions and displacement of a tosylate over five steps to afford **69**. The acyclic tether was homologated and converted to **70** in three steps.
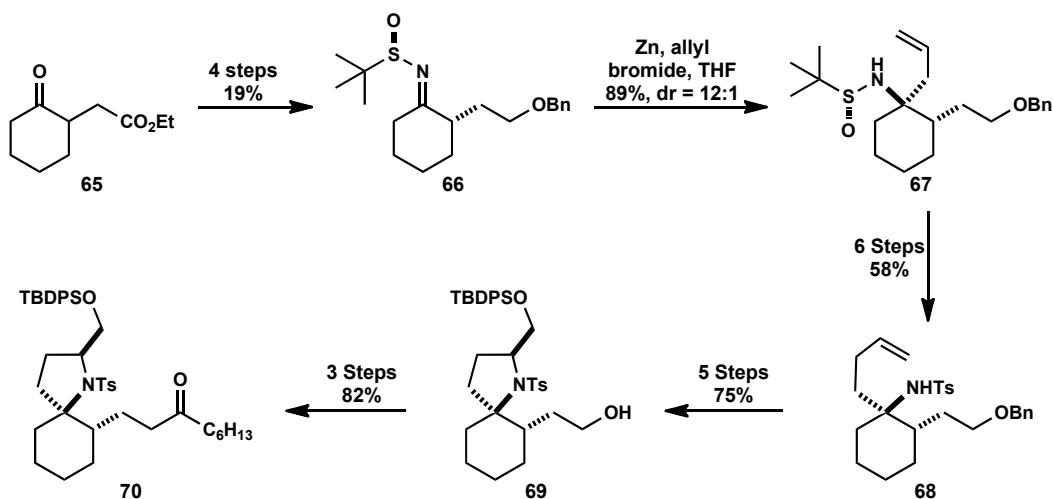
Scheme 10. Zhao syntheses of (–)-lepadiformine A (**12**) and (–)-fasicularin (**15**)[61]

Compound **70** was used to produce (–)-fasicularin (**15**) and (–)-lepadiformine A (**12**) as shown in Scheme 11. First, **70** was converted to **71**, or 2-*epi*-lepadiformine A, by deprotection of the nitrogen atom, which led to cyclization onto the carbonyl to close the third ring, reduction of the enamine intermediate, and deprotection of the TBDPS group. (–)-Fasicularin (**15**) was formed from **71** using Mitsunobu-type conditions to form an aziridinium intermediate (see Figure 1) and was opened with the thiocyanate. The total synthesis of (–)-fasicularin (**15**) was thus completed in 23 steps and 3% overall yield from commercially-available starting material.

In the total synthesis of (–)-lepadiformine A (**12**), **70** was reduced with L-Selectride to alcohol **72** (Scheme 11). The subsequent steps included deprotection of the amine and Mitsunobu-type displacement of the alcohol with the free amine to close the third ring. A TBAF-mediated deprotection of the TBDPS group afforded (–)-lepadiformine A **12**, which completed the total synthesis in 23 steps and 5% overall yield from commercially-available starting material. Both syntheses of (–)-lepadiformine A

(**12**) and (–)-fasicularin (**15**) provided nice examples of the utility of sulfinamides in natural product synthesis as well as effective approaches to generate aza-spirocenters.
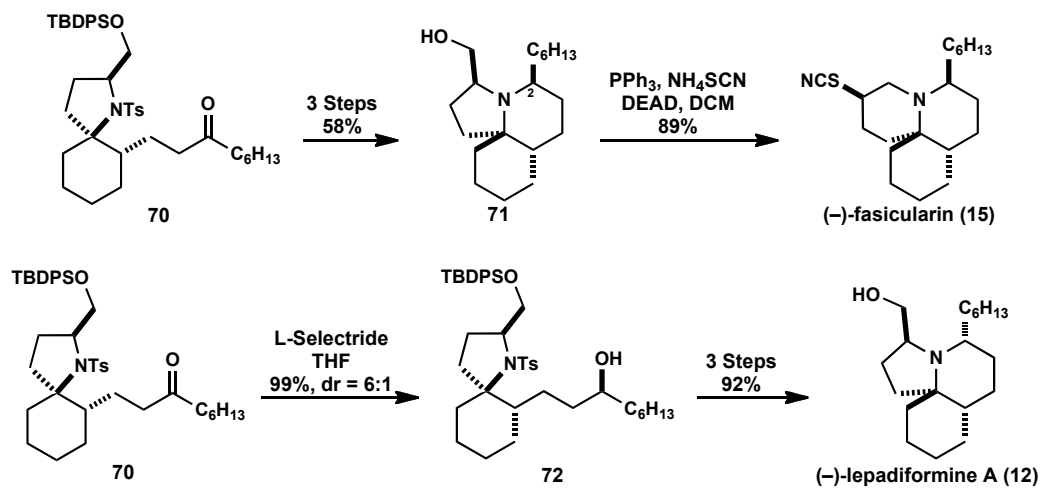
Scheme 11. Zhao syntheses of (–)-lepadiformine A (**12**) and (–)-fasicularin (**15**)

(continued)[61]

1.3. Total Syntheses of Cylindricines

Since the last major review of the cylindricines,[8] a number of additional total syntheses have been published. Three total syntheses of cylindricine C are included here. A fourth total synthesis, the shortest to date and only asymmetric synthesis of cylindricine C covered here was already discussed in Section 1.2.4 as it was accomplished in conjunction with a total synthesis of (–)-lepadiformine A (**12**).[54]

1.3.1. Why Cylindricine C

Cylindricine C is the most commonly synthesized target of all the cylindricines (Table 1). Synthetic chemists often synthesize molecules that display interesting biological activity. Within the cylindricine family, only A and B have been biologically evaluated to date. No biological data has been reported for cylindricine C; therefore, there is no compelling biological reason to synthesize this particular member over the others.

In solution, cylindricine A undergoes interconversion with cylindricine B (in equilibrium as a 3:2 ratio of A:B)[5] through the aziridinium intermediate shown in Figure 1.[24,25] In contrast, the picrates of A and B are stable and do not interconvert. The aziridinium intermediate formation occurs with the cylindricines D and E as it was demonstrated in Blackman's isolation experiments that addition of sodium methoxide or sodium acetate resulted in interconversion between cylindricine A and both D and E.[6] During the isolation, cylindricine C was not interconvertible with cylindricine A.

Cylindricines F-K have not been synthesized to date. The cylindricines G-J contain a butyl sidechain at C-2 rather than the hexyl group, which is a minor difference and could easily be incorporated into many of the known syntheses. In contrast, cylindricines H-J contain an extra stereocenter in the form of an acetoxy group at C-4 rather than a carbonyl, which would pose an additional synthetic challenge. Also noteworthy, cylindricines F-I contain either thiocyanate or isothiocyanate substitutions on methylene C-14, a substitution pattern that has only been prepared synthetically by converting cylindricine A/B to cylindricine F using sodium thiocyanate, as described in

the isolation paper, and by Kibayashi and coworkers in their total synthesis of fasicularin.[30]

The cylindricines are synthetic targets due to their interesting architecture but have little structural diversity within the family. There seems to be no clear reason why there is such a high frequency of cylindricine C syntheses relative to the rest of the cylindricine family. One speculation could be that most other family members could be derived from an accomplished synthesis of cylindricine C and until a biological driving force for their synthesis is discovered, this trend will continue.

1.3.2. Total Syntheses

Using an approach similar to that shown in Scheme 3, Renaud and coworkers synthesized (±)-cylindricine C (**3**) using carboazidation chemistry.[63] As shown in Scheme 12, their synthetic strategy began with 1-octyne. The precursor to the key step, **73**, was prepared in six steps from 1-octyne and used cyclohexanone to incorporate the cyclohexane ring moiety. The carboazidation reaction took place in good yield using similar conditions as shown in Scheme 3, however, the authors also report the reaction occurs in 57% yield under air and triethylborane. Both sets of reaction conditions produced the desired product, **74**, as a mixture of diastereomeric azides, separable by column chromatography, where the major compound **74** was obtained in a 7:3 ratio. The subsequent transformation, reduction of the azide to the amine, was accomplished with $SnCl_2$ and the amine was immediately taken on to the *bis*-reductive amination step without purification. Both pyrrolidine and piperidine rings B and C were formed in a single step under sodium triacetoxyborohydride ($NaBH(OAc)_3$)-mediated conditions as a single diastereomer, **75**. Unfortunately, the stereocenters at C-13 and C-5 where not set correctly and needed to be epimerized. After six steps, **75** was converted to **76**, the epimer at C-13. The final steps involved oxidizing the hydroxymethylene substituent to the carboxylic acid and epimerizing C-13, which completely converted to the desired stereochemistry. From **76**, oxidation of the free hydroxyl group provided an opportunity for the epimerization of C-5. Under TBAF conditions, the C-5 epimerization was precedented,[48] and accomplished in excellent yield to afford (±)-cylindricine C, **3**.

Overall, the total synthesis was completed in 17 steps and 11% overall yield from commercially-available 1-octyne. The key attributes included the effective carboazidation strategy that prepared the aza-spirocenter in good diastereoselectivity and the double reductive amination that closed both of the remaining rings and afforded the product as a single diastereomer. Although it was undesirable to require two epimerization steps, the ability to overcome those issues was another impressive feature of the total synthesis.
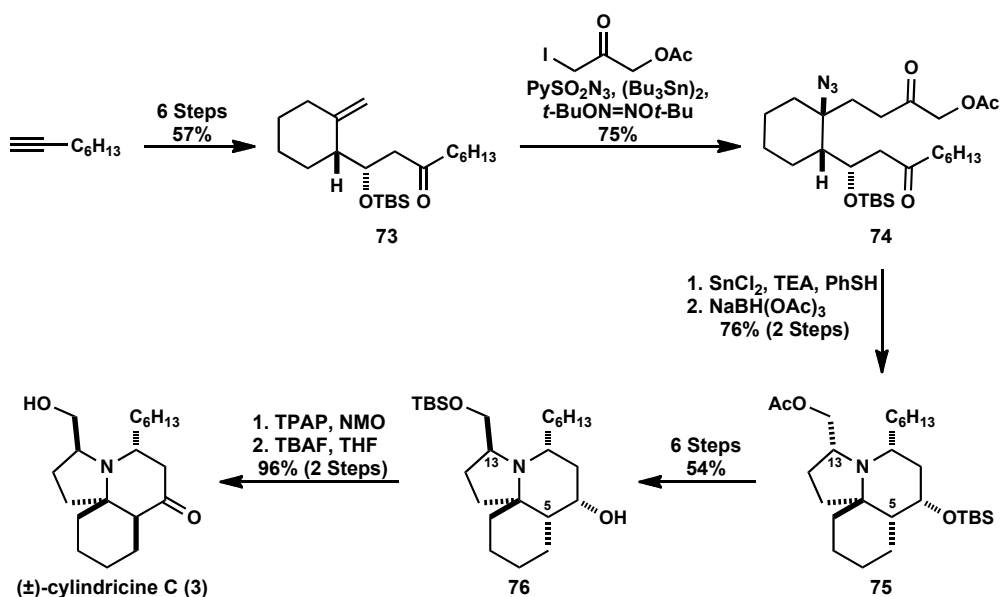
Scheme 12. Renaud synthesis of (±)-cylindricine C (**3**)[63]

In the next synthesis, Donohoe *et. al.* completed a formal and total synthesis of (±)-cylindricine A (**1**) and (±)-cylindricine C (**3**), respectively, to showcase their developed methodology of *ispo*-selective addition of alkyl Grignard reagents to C-2 substituted pyridinium salts.[64] Beginning with picolinic acid, the key pyridinium salt, **77**, was prepared by esterification and *o*-dimethoxybenzyl (DMB) salt formation as shown in Scheme 13. The subsequent key step was a regioselective Grignard addition *ipso* to the

ester to afford **78**, thus establishing the aza-spirocenter. An intriguing aspect of this aza-spirocenter formation was that it occurred via regioselective addition to the most sterically-congested carbon. The authors noted the use of the DMB protecting group was necessary to achieve the desired regioselectivity. The cyclohexane ring was then closed to the exclusively *cis*-fused bicycle, **79**, with sodium amide (NaNH$_2$) and then transformed to **80** in three more steps. Next, the nitrogen was reprotected with a 2-(trimethylsilyl)ethoxycarbonyl (Teoc) group, necessary for the completion of the syntheses. The protection allowed for the homologation of the aldehyde to **81** through olefination, hydrogenation, and reduction to the saturated aldehyde. The construction of **81** provided a divergent intermediate for the syntheses of both cylindricine A and C.
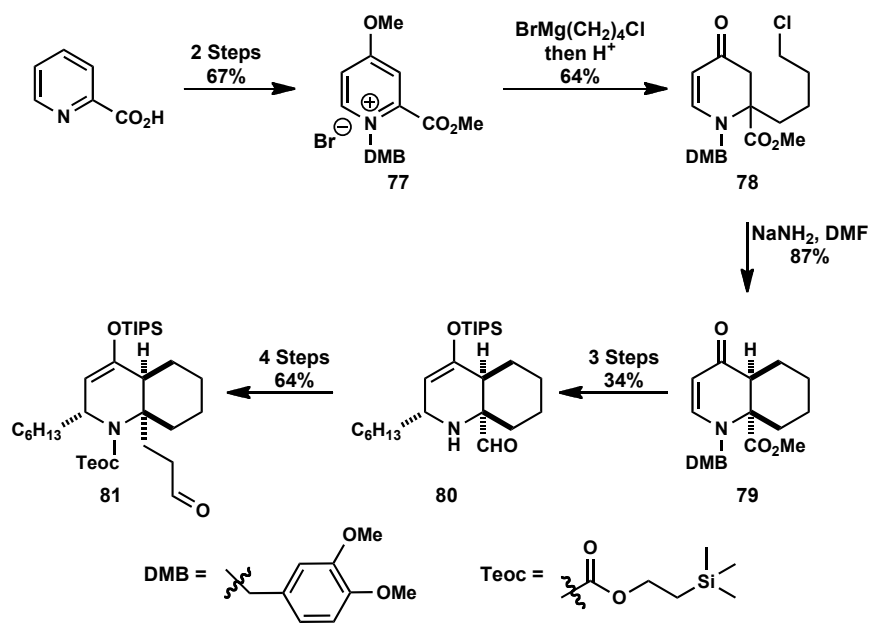
Scheme 13. Donohoe synthesis of (±)-cylindricine A (**1**) and (±)-cylindricine C (**3**)[64]

As shown in Scheme 14, **81** was converted in two steps to **82** by olefination and deprotection, which was the same intermediate used in the total syntheses of (±)-

cylindricine A (**1**) by Snider[24] and Heathcock.[25] Incorporating the two known, final steps, Donohoe and coworkers accomplished the formal total synthesis of (±)-cylindricine A in 15 total steps and 3% overall yield. Separately, **81** was converted to epoxide **83** using the Corey-Chaykovsky ylide,[65] trimethylsulfonium iodide (TMSI), as a 1:1 mixture of diastereomers. Epoxide **83** was converted in a 99% yield to a 1:1 mixture of (±)-cylindricine C (**3**) and 13-*epi*-cylindricine C through a simple deprotecton of the nitrogen, which opened the epoxide to unveil the hydroxymethylene group and complete the total synthesis in 13 total steps and 2% overall yield.
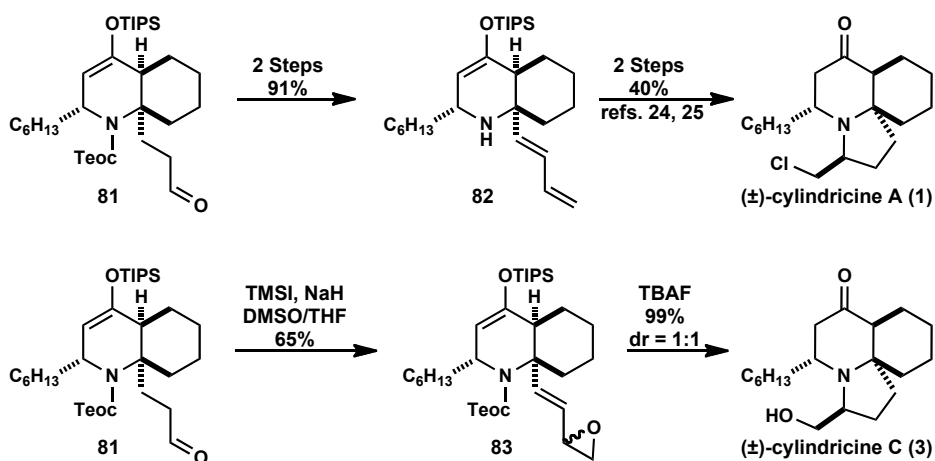
Scheme 14. Donohoe synthesis of (±)-cylindricine A (**1**) and (±)-cylindricine C (**3**)

(continued)[64]

A third total synthesis of (±)-cylindricine C (**3**) by Padwa and coworkers showcases a conjugate addition/dipolar-cycloaddition cascade developed in their laboratory.[66] Their synthesis, shown in Scheme 15, begins with δ-valerolactone, which was converted to hydroxylimine **85** by hydrolysis with methyoxymethylamine to form the Weinreb amide, alcohol protection, Grignard addition to the amide, and condensation

with hydroxylamine. The key transformation was then accomplished between **84,** readily available in two steps from 2-butyne-1,4-diol, and **85**. The formation of **87** commenced with a conjugate addition of nitrogen to afford intermediate **86a**, followed by a [3+2]-dipolar cycloaddition, **86b**, of the activated hydroxylamine and the remaining double bond by heating in a sealed tube. The [2.2.1] bicycle **87** was synthesized in good yield but as a 1:1 mixture of diastereomers. This mixture was submitted to Mn-mediated epoxidation conditions to afford epoxide **88** as a single diastereomer albeit in low yield.

The subsequent transformation was the second of two cascades in this total synthesis. Epoxide **88** was submitted to Zn dust and aqueous ammonium chloride, which began the cascade by cleavage of the N-O bond, followed by extrusion of phenylsulfenic acid to unveiled the carbonyl of the 4-piperidone shown as intermediate **89**. Next, the pyrrolidine ring, ring C, was formed by nitrogen addition to the proximal carbon of the epoxide which gave rise to the necessary hydroxymethylene in compound **90**. The last event that occurred in this sequence was the reductive removal of the second phenylsulfonyl group to afford **90** in 90% yield and high dr of 9:1. The synthesis continued with a benzoyl protection of the hydroxymethylene while the silyl ether was deprotected and tosylated to give **91**. Potassium *tert*-butoxide was used to initiate the enol displacement of the tosyl group to close the A ring of the tricyclic system and mercury acetate was used for the oxidation to enaminone **92**. The total synthesis was completed by a copper-mediated Grignard addition to establish the hexyl group and a basic deprotection of the benzoyl group.

The highlights for this synthesis include two impressive cascades that led to the B ring formation and then the A ring formation. This synthesis further demonstrated

another excellent use of the sulfonyl group and its importance as a synthetic tool in natural product synthesis. The yield for the total synthesis of (±)-cylindricine C (**3**) was 4% over 14 linear steps.
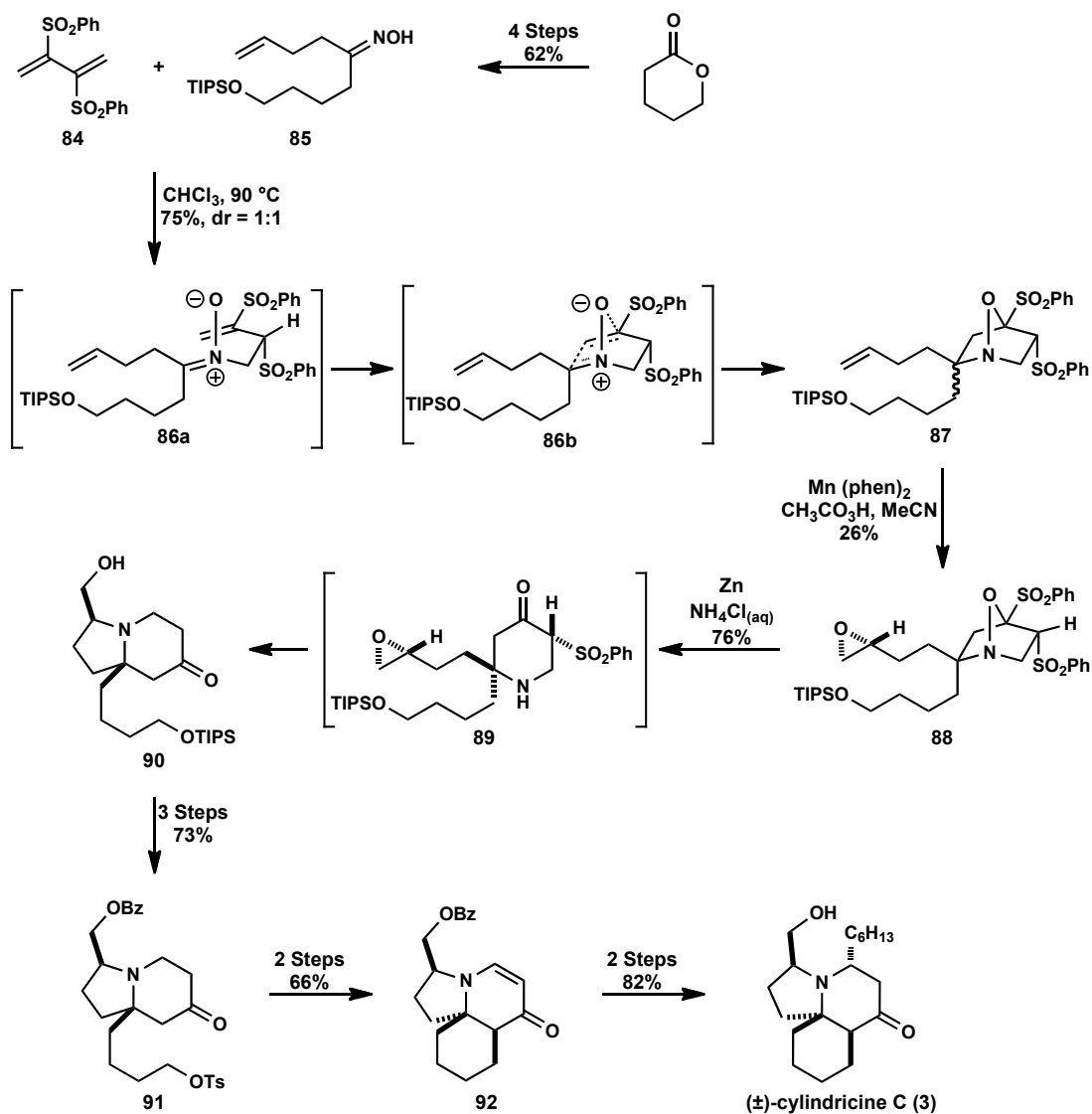
Scheme 15. Padwa synthesis of (±)-cylindricine C (**3**)[66]

1.4. Approaches to the Tricyclic Core

As discussed above, multiple methodologies have been developed for the total syntheses of the lepadiformines and cylindricines. In addition, multiple noteworthy methodologies and strategies have been developed to quickly construct the tricyclic cores of these families of molecules. The core structures that are targeted include the [5.6.6] tricycle containing either the *cis*- or *trans*-azadecalin moieties as in most of the cylindricines and lepadiformines, respectively, as well as the [6.6.6] tricycle found in cylindricine B (**2**) and fasicularin (**15**) containing the *cis*- and *trans*-azadecalin moieties, respectively.

1.4.1. [5.6.6] Tricyclic Core Approaches

Construction of the [5.6.6] tricyclic core quickly and efficiently is an ideal strategy for the synthesis of these families of molecules. Even more ideal is obtaining stereochemical control over the decalin fusion. The following two synthetic approaches to the cylindricine C core, the *cis*-azadecalin containing [5.6.6] tricycle, maintain complete control over the decalin fusion.

The well-known Hajos–Parrish reaction uses L-proline to accomplish a Robinson annulation.[67] Shown in Scheme 16, Tu and coworkers constructed **93** from 1,3-cyclopentadione using adapted Hajos–Parrish conditions en route to the core structure of (±)-cylindricine C (**3**).[68] The catalyst, D-Prolinamide, shown in Scheme 16, was used to prepare **93** in 94% es to begin the asymmetric approach to tricyclic lactam **95**. From **93**, functional group manipulations were done to reduce the enone to the alkene and to convert the mono-substituted alkene to azide **94**. After submission to Lewis acid conditions, in this case boron trifluoride diethyletherate (BF$_3$), azide **94** underwent an intramolecular Schmidt reaction[69,70] to unveil a tricyclic lactam, which was stereoselectively hydrogenated to give **95**. This approach was an effective asymmetric route to the tricyclic ring system of the cylindricines utilizing the power of the Hajos–Parrish cyclization as well as the intramolecular Schmidt reaction.
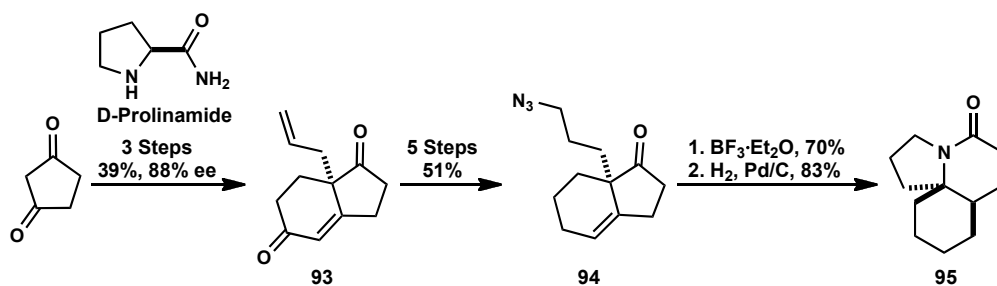
Scheme 16. Tu approach to the core structure of (±)-cylindricine C (**3**)[68]

In Scheme 17, another approach to the *cis*-azadecalin [5.6.6] tricycle was prepared using a novel transannular Mannich reaction, accomplished by Tanner and coworkers.[71] Starting with cycloheptanone, compound **96** was prepared in four steps including an initial homologation, Wittig reaction, hydroboration/oxidation, and Suzuki coupling. The key macrocyclic intermediate, **97**, was prepared in three further steps of tosylation, bicyclic formation, and ozonolysis of the double bond to form the diketone. Trifluoroacetic acid (TFA) was used to initiate the transannular Mannich reaction by first removing the *tert*-butoxycarbonyl (Boc) group, forming an iminium bicycle, and finally, an intramolecular enol addition to quench the iminium ion to achieve tricycle **98**. This method prepared the racemic tricycle **98** as a single diastereomer in few steps and incorporates the C-4 oxidation state.
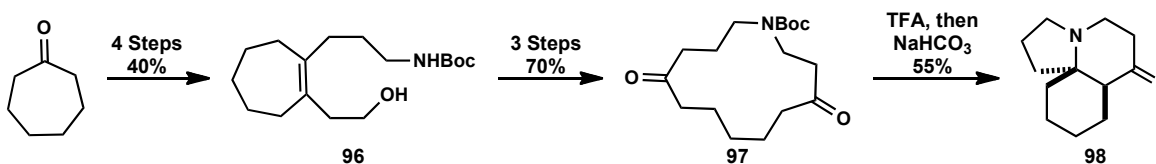
Scheme 17. Tanner approach to the core structure of the cylindricines[71]

1.4.2. [6.6.6] Tricyclic Core Approach.

The [6.6.6] tricycle of (±)-cylindricine B (**2**) and (±)-fasicularin (**15**) was accomplished by Martin and coworkers using a novel iminium cascade reaction.[72] The core construction of the [6.6.6] tricycle began with δ-ketoacetal **99** and aminoallylsilane **100**, shown in Scheme 18. Initiation of the cascade began with condensation of the amine in **100** onto the ketone in **99** in the presence of molecular sieves. TFA was then added to the reaction to convert the acetal to an oxonium ion, to which the imine added to form intermediate **101**. From there, the allyl silane added into the iminium to form the aza-spirocenter as well as set the stereochemistry of the azadecalin moiety. Subsequent submission to sodium cyanide (NaCN) replaced the methoxy ether with a cyano group and ultimately achieve **102** in a 66% overall yield as a mixture of four diastereomers in relatively equal proportions. Although this route did not maintain stereocontrol over construction of the tricycle, the methodology was effective in quickly building a complex structure from simple starting materials through seemingly simple transformations. This methodology was applied to a myriad of natural products and core structures.
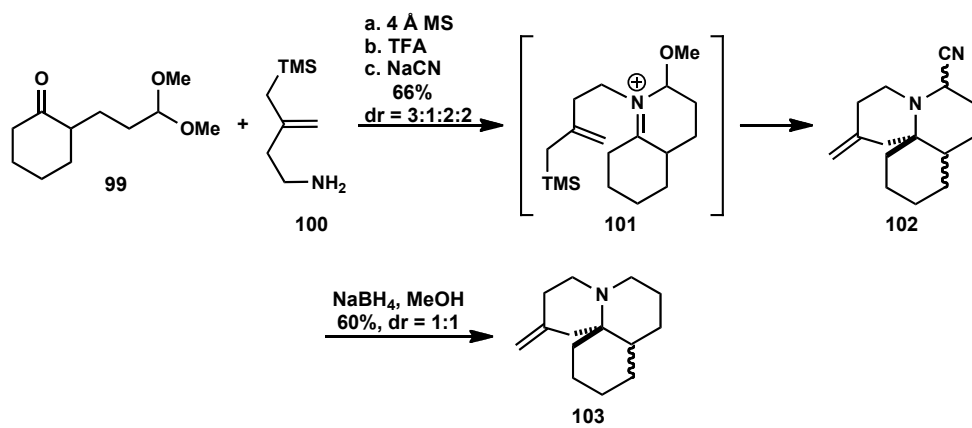
Scheme 18. Martin approach [6.6.6] tricycle[72]

1.5. Conclusion

Although the cylindricine and lepadiformine families currently demonstrate little known biological activity, the congested aza-spirocenter contained within these molecules provides a fascinating challenge for synthetic chemists and has the potential to bring about exquisite methodologies to be used in syntheses of other molecules that present medicinally relevant properties. Many examples for the quick and elegant construction of the congested aza-spirocenter were reviewed. No doubt, these strategies will be utilized in the future for the construction of other medicinally important compounds and natural products. These syntheses have provided useful methodology for organic chemists; however, there is still room for novel approaches to prepare these molecules and their architectures. In the body of this dissertation, our contributions to the methodology development and synthetic approaches to these molecules are reported.

Chapter 2

Tandem Prins/Schmidt Reaction Development: Formal and Total Syntheses of

Lepadiformines A and C

2.1. Introduction to the Schmidt Reaction

In 1991, our laboratory discovered a reaction involving the intramolecular nucleophilic attack of a tethered azide to a cyclic ketone followed by a ring expansion to form a bicyclic lactam.[69] As shown in Scheme 19a, the ketone in **104** underwent an intramolecular addition from the proximal nitrogen of the azide under acidic conditions to form intermediate **105**. Upon collapse of the tetrahedral intermediate, bond migration and extrusion of N_2 afforded bicyclic lactam **106**. That reaction was thoroughly investigated with a variety of tether lengths, ring sizes, and Lewis acids.[70]

Another application of the intramolecular Schmidt reaction is shown in Scheme 19b. Treatment of azidoketone **104** with the cyclopropyldiphenylsulfonium ylide, developed by Trost and coworkers,[73] afforded [5.3]spirocyclic ketone **107**. Exposure of **107** to the strong Lewis acid $TiCl_4$ induced an intramolecular Schmidt reaction to form the [5.6.6] tricycle **108** that contained a *cis*-azadecalin moiety around an aza-spirocenter. As demonstrated by the two examples in Scheme 19, the intramolecular Schmidt reaction provided an effective way to prepare not only tertiary lactams, which could be easily reduced to tertiary amines, but also for synthesizing synthetically challenging aza-spirocenters.

In the decades to follow, the intramolecular Schmidt reaction was utilized in numerous total syntheses and was employed in tandem reaction sequences incorporating other Lewis-acid-mediated reactions.[74] More specifically, the Schmidt reaction has been conducted in tandem with a Diels–Alder reaction[75,76] as well as in domino sequences with aldol and Sakurai reactions.[77] Because of the similarities of the cores of **108** and **3**, we envisaged preparing (±)-cylindricine C (**3**) utilizing a route similar to that in Scheme 19b.
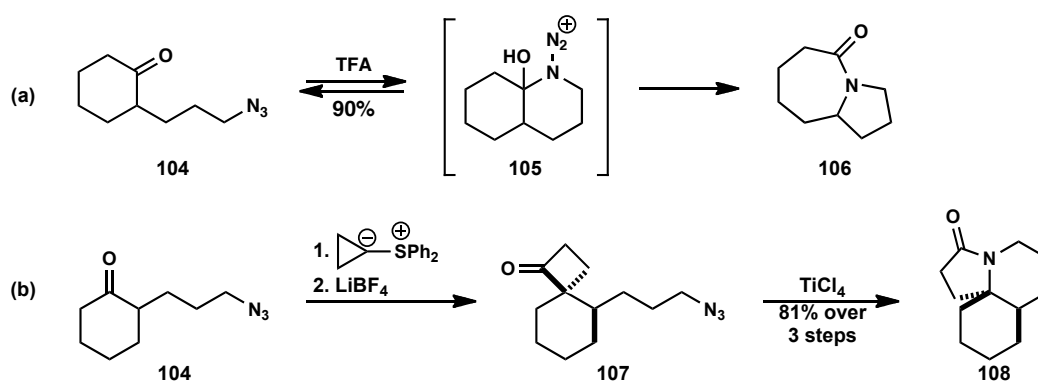
Scheme 19. Intramolecular Schmidt reaction

2.2. Retrosynthetic Analysis

Our retrosynthetic approach, shown in Scheme 20, began with a late-stage functional group conversion of the lactam carbonyl in **109** to the C-13 hydroxy methylene, similar to that reported by Renaud and coworkers in their total synthesis of (±)-lepadiformine A (**12**).[44] Also, a deprotection and oxidation of the C-4 protected alcohol would complete the conversion of **109** to (±)-cylindricine C (**3**). We envisioned **109** coming from an intramolecular Schmidt reaction of **110**. Since the intramolecular Schmidt reaction occurs with retention of configuration,[70] the necessary stereochemistry of the spirocyclobutanone is depicted in **110,** as that would achieve the *cis*-azadecalin ring fusion. The stereochemistry of the protected alcohol would be irrelevant for the completed total synthesis but we needed to control the stereochemistry at the azide so we envisaged a 1,3-*syn*-selective reaction to construct **110**. Investigation into the literature revealed a potential solution to the synthesis of [5.3]spirocyclic ketone **110** by combining vinylcyclopropylsilyl ether **112** with 3-azidoaldehyde **111**, or the acetal equivalent, two relatively simple starting materials.[78,79] This literature example is discussed in detail below. Also, since the Prins reaction was Lewis-acid mediated, we hoped we could achieve a one-pot Prins/Schmidt sequence to achieve **109** directly from **112** and **111**. However, at the time, there was no literature precedent for a 1,3-*syn*-selective addition involving azides.
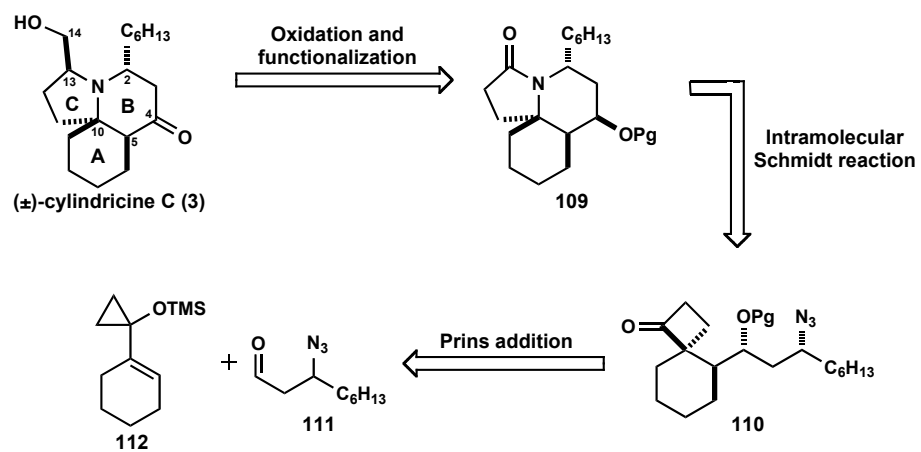
Scheme 20. Retrosynthetic analysis

2.3. Precedent for the Prins Addition Reaction

Trost and coworkers developed an interesting vinylogous cyclopropanol reaction as shown in Scheme 21.[78] The vinylogous cyclopropanol is referred to as a composite functional group because it functions similar to an enol, although the oxygen is not directly attached to the alkene, by transforming through the cyclopropane.[78] The example in Scheme 21 illustrates that, when combined with an acetal under Lewis acid conditions, the alkene of **113** adds into the oxonium species formed by the breakdown of the acetal to form the carbocation in **114**. In this type of Prins reaction, the carbocation is quenched by a ring expansion of the cyclopropane, whereas in a typical Prins reaction, the carbocation is quenched directly by an oxygen; hence the composite functionality of the vinylogous cyclopropanol. The resulting product from the ring expansion is cyclobutanone **115**.
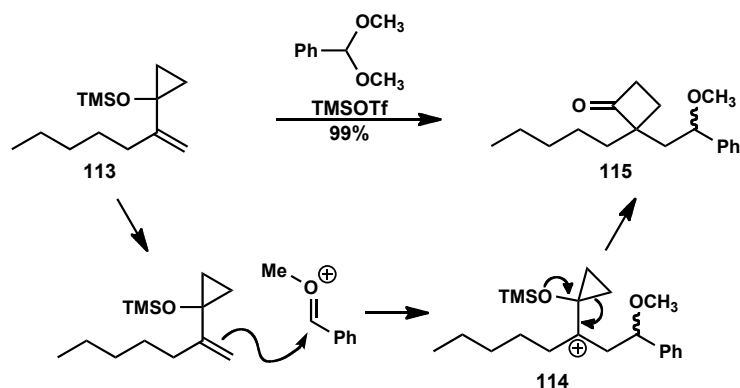
Scheme 21. Trost vinylogous cyclopropanol chemistry

A similar example of vinylogous cyclopropanol addition to acetals was later developed by Cha and coworkers using **112** is shown in Scheme 22.[79,80] The reaction is mechanistically equivalent to the Trost example seen in Scheme 21. Starting with **112**,

the Prins-type reaction generated spirocyclobutanones **117** and **118** and a third

diastereomer with undefined stereochemistry. The diastereochemical difference at the

spirocenter results from the competing ring expansion processes of the two diastereotopic

cyclopropane C-C bonds of intermediate **116**. In this case, the ring expansion was only

slightly selective and gave a diastereomeric mixture. Nonetheless, the reaction produced

spirocyclobutanones with a similar oxygen substitution pattern that we would require for

the synthesis of cylindricine C. Shown later, we completed this reaction where an azide

replaced the bromine and afforded similar results.
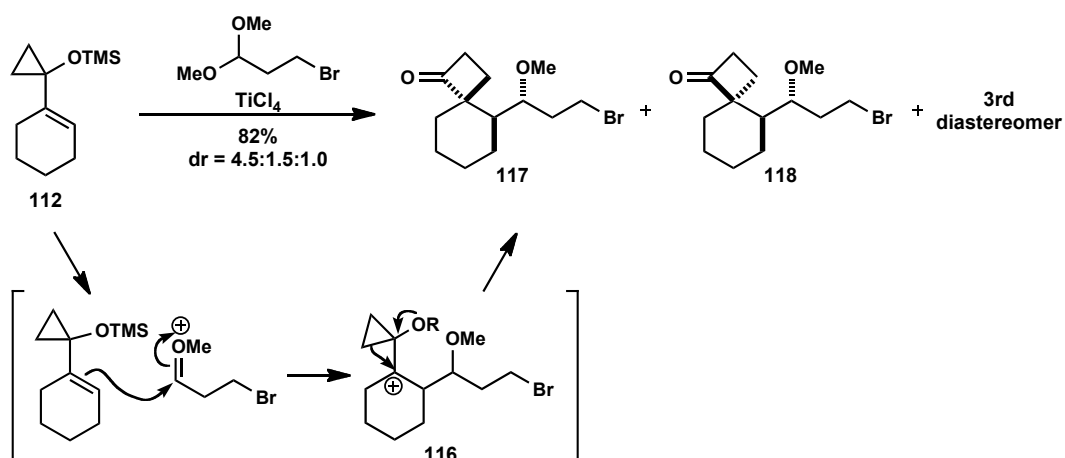
Scheme 22. Cha vinylogous cyclopropanol chemistry

2.4. Starting Materials

Our work began by preparation of compound **112** using the Kulinkovich reaction as shown in Scheme 23, which converts an ester to a cyclopropanol.[79] There is some debate in the literature over the mechanistic details.[81] However, it is proposed that titanium tetraisopropoxide initially combines with ethylmagnesium bromide to generate a diethyl-diisopropoxide titanium species, which undergoes β-hydride elimination to extrude ethane and form a titanocyclopropane. The titanocene can be thought of as an ethyl group that is nucleophilic at both carbons. Upon addition of the ester, the titanocene undergoes a migratory insertion to incorporate the ester. Collapse of the tetrahedral intermediate generates a ketone, which then undergoes an intramolecular migratory insertion to form the cyclopropanol. At that point, the ethylmagnesium bromide displaces the newly formed cyclopropoxide to regenerate the titanium.
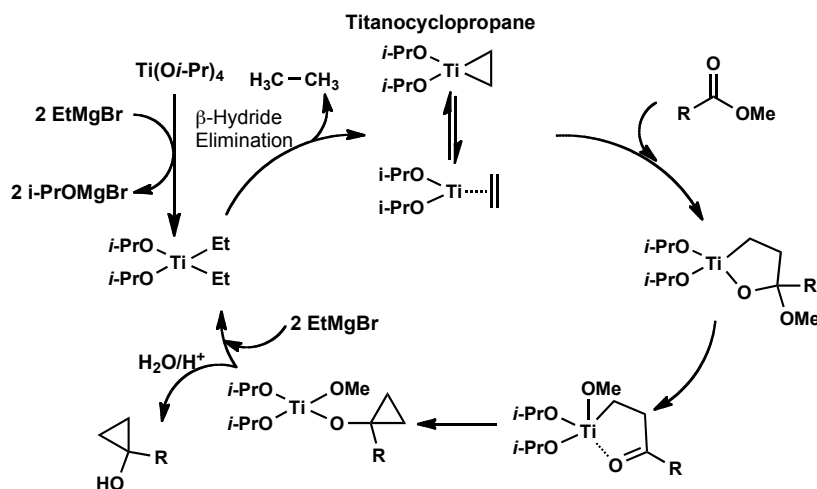
Scheme 23. The mechanism for the Kulinkovich reaction

Thus, the Kulinkovich reaction of commercially-available methyl-1-cyclohexene-1-carboxylate provided cyclopropanol **119**, which was treated with trimethylsilyl triflate (TMSOTf) to afford **112** in quantitative yield (Scheme 24a). With **112** in hand, we required a reaction partner to initiate our investigation of a potential tandem Prins/Schmidt reaction.

Various reports of Prins reactions encouraged us to initially investigate the use of an acetal coupling partner. Further, acetals are more reactive than aldehydes due to the activated oxonium species generated upon submission to acid. Therefore, acetal **121**, lacking an additional complicating stereocenter, was initially evaluated. Acetal **121** was prepared in two steps from acrolein, which was treated with sodium azide and acetic acid in water (Scheme 24b).[82] These conditions generated hydrazoic acid (HN$_3$), which underwent conjugate addition with the acrolein to form 3-azidopropanal, **120**. Treatment of **120** with trimethylorthoformate in methanol with a catalytic amount of *p*-toluenesulfonic acid (TsOH) afforded the dimethoxyacetal **121**. With compounds **112** and **121** in hand, we began our investigation of a Prins/Schmidt methodology toward a total synthesis of (±)-cylindricine C (**3**).
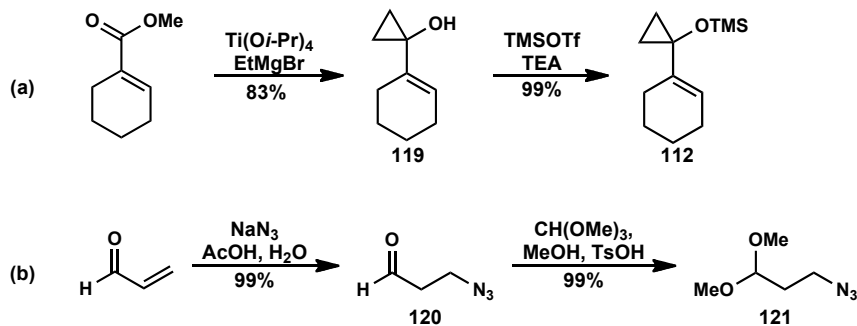
Scheme 24. Initial starting material preparation

2.5. Methodology Overview

The desired tandem transformation is shown in Scheme 25a. For this example we followed the example by Cha and coworkers shown in Scheme 22.[80] Exposure of **112** with **121** to Lewis acidic conditions could afford spirocyclobutanone **124**. The stereochemistry of the methoxy group represents what we expect.[80] The stereochemistry of the spirocyclobutanone **122** represents the desired stereochemistry that would afford the *cis*-decalin configuration of **123**. Since the reaction mixture was already under Lewis acidic conditions, we envisioned that an intramolecular Schmidt reaction could occur *in situ* on **122** similar to Scheme 1b9, resulting in the formation of tricyclic lactam **123**. Alternately, we could form **122** by the same Prins reaction in Scheme 22 followed by azide displacement of the bromide with NaN$_3$ and then attempt the intramolecular Schmidt reaction independently.

Our proposed mechanism for this transformation is shown in Scheme 25b. We envisaged combining **112** with *in situ* generated oxocarbenium ion **124** to form intermediate **125**. Two stereocenters were set during the Prins addition. For the total synthesis, the stereochemistry of the carbon-oxygen bond was irrelevant because it would be stereoablated in the latter stages of the synthesis.

The next stereochemical issue arises from the ring expansion of the cyclopropanol during the conversion of **125** to **122**. We anticipated the ring expansion would occur placing the carbonyl on the same side as the OMe, the opposite of what we wanted.[80] From there, the tethered azide could add to the carbonyl of the cyclobutanone that would be activated by the presence of the Lewis acid, depicted in Scheme 25b as TiCl$_4$. The

intramolecular Schmidt reaction to convert **122** to **123** would proceed through **126**, a seven-membered ring intermediate, with retention of configuration at the spirocenter. Although not an ideal arrangement, similar transformations have been previously observed.[69]
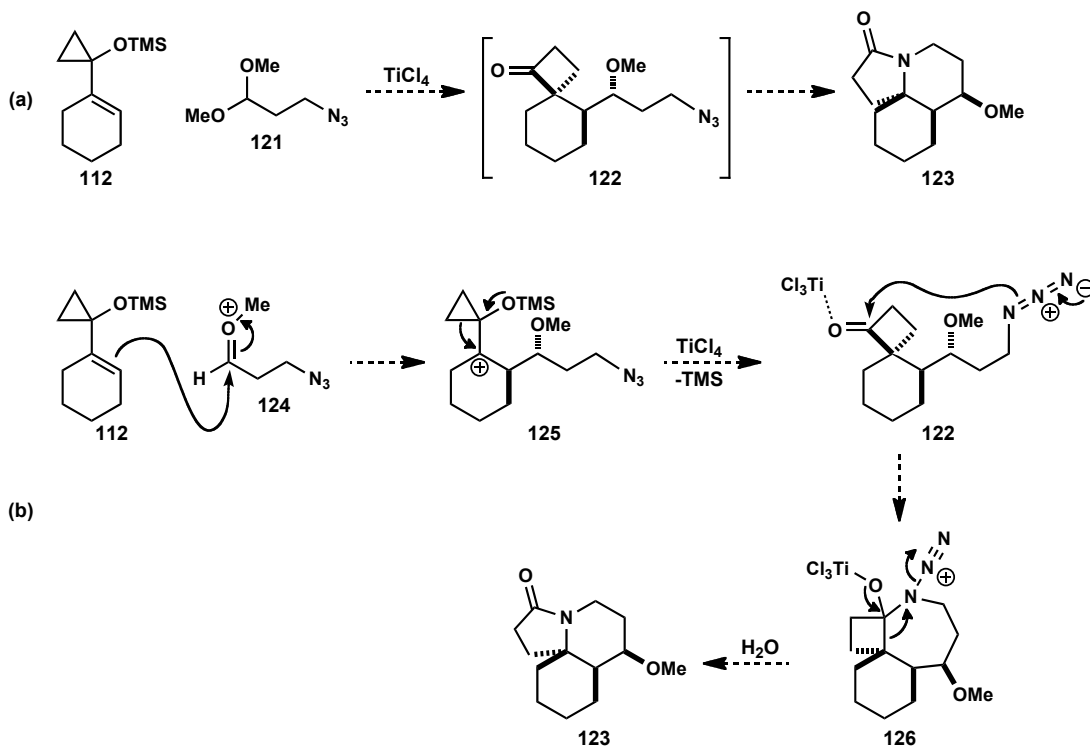
Scheme 25. Desired transformation and proposed mechanism for **112** with **121**

2.6. Acetal Approach

We began our investigation by treating cyclopropane **112** with 3-azidopropanal dimethoxyacetal (**121**) under $TiCl_4$-promoted conditions as shown in Scheme 26.[80] Under these conditions, three diastereomers of the spirocyclobutanones were obtained in a ratio of 10:4:1 (**122a**:**122b**:**122c**) in an 83% yield. The stereochemistry of **122a** was determined by comparison to the product obtained by repeating the Cha reaction and displacing the bromide of **117** with azide using NaN_3. The other two structures, as with most other structures in this chapter, were cyclized to the tricyclic lactam and analyzed by 2-D NMR techniques. The rigid tricyclic structures, like **123b**, provided strong NOE correlations, which facilitated stereochemical elucidation. The structure elucidation information for **123b** is detailed in the experimental section (Chapter 5). The structure of **123c** was determined by comparison of ^1H and ^{13}C NMR to a structure determined by single crystal diffraction, the details of which are in Appendix 1.

Attempted optimizations were unsuccessful. We investigated other Lewis acids under similar conditions: $Sc(OTf)_3$, $Cu(OTf)_2$, $Zn(OTf)_2$, $Yb(OTf)_3$, $ZnCl_2$, TFA, Triflic acid, $SnCl_4$, and $AlCl_3$. Various temperatures were investigated from -78 °C to room temperature (rt), and only $TiCl_4$ gave the Prins adduct in greater than trace amounts. We then moved forward to investigate the intramolecular Schmidt reaction on azides **122a-c**.

As shown in Scheme 26, each of the diastereomers was independently submitted to $TiCl_4$ at rt overnight. Diastereomers **122b** and **122c** were quantitatively converted to the corresponding lactams **123b** and **123c**, respectively. In those two cases, a single diastereomer was used and a single diastereomer was afforded. In contrast, when the

major isomer, **122a**, was submitted to the same conditions, a mixture of lactam diastereomers was observed. The observed complex mixture from **122a** was significant because it indicated that the major product of the Prins reaction did not map to a productive Schmidt pathway.

In an attempt to achieve a one-pot Prins/Schmidt reaction sequence, we treated **112** and **121** with TiCl$_4$ at −78 °C for 2 hr, then treated the reaction with more TiCl$_4$ at 0 °C, and allowed the reaction to warm to rt for 12 hr (Scheme 27). We isolated the tandem Prins/Schmidt product, the lactam, albeit in a significantly diminished yield of 35% as a mixture of three diastereomers. Interestingly, the major diastereomer of the tandem reaction corresponded to the minor diastereomer of the independent Prins addition/Schmidt reaction sequence in Scheme 26.
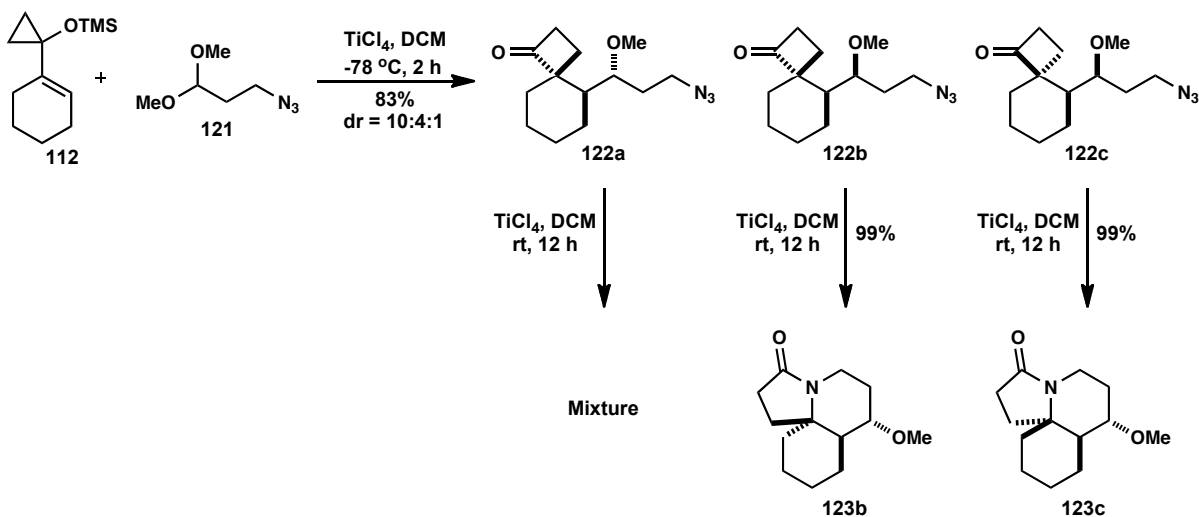
Scheme 26. Independent Prins and Schmidt reactions
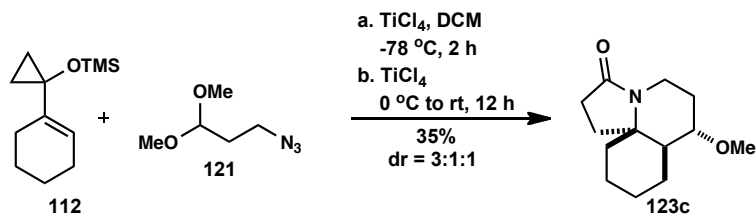
Scheme 27. Tandem Prins/Schmidt reaction

Although the reaction sequence was not fully developed, we explored the use of **123c** in a synthesis of (±)-cylindricine C (**3**). We anticipated that we could achieve a more convergent reaction sequence by incorporating the hexyl side chain at C-2 into the acetal by using 3-azidononenal dimethoxyacetal, **127**. Substrate **127** was prepared the same way as **121** in Scheme 24 starting with *trans*-2-nonenal. Scheme 28 shows the results when we combined **112** with **127** under the previously used conditions. The Prins reaction between **112** and **127** occurred in good yield as a mixture of five inseparable diastereomers of **128**. With hope that perhaps the lactams would be separable, the mixtures of diastereomers of **128** were submitted to the intramolecular Schmidt conditions. This afforded a high yield of lactam (**129**) as a mixture of diastereomers that remained inseparable. The complex diastereomeric mixtures of **128** and **129** made it difficult to determine any stereochemical information from the reaction. Since we were seeking a specific diastereochemical outcome, the mixture was not useful. If the diastereomers were separable or if a major diastereomer existed over the others, this route might have been more useful, but as it stood, we chose not to pursue it.
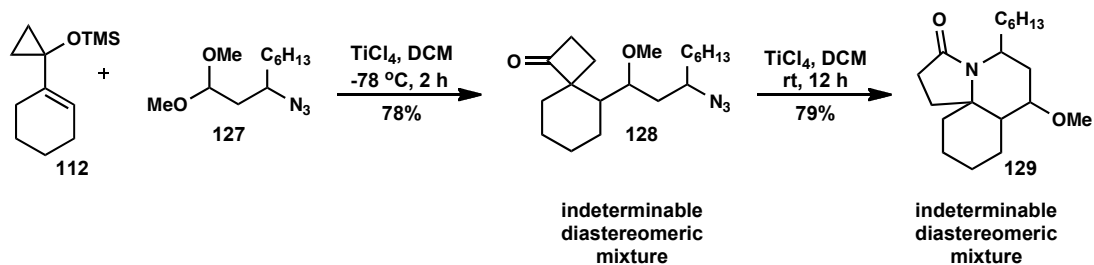
Scheme 28. Prins and Schmidt reactions with 3-azidononenal dimethoxyacetal

Since the direct incorporation of the hexyl group into **128** proved problematic, we briefly explored a way of installation of the hexyl group at a later stage of the synthesis. We considered electrochemical techniques developed in the Moeller lab at Washington University,[83] as shown in Scheme 29a. In that work, lactam **130** was oxidized to **131** using simple conditions of graphite anodes and platinum wire in methanol, the source of the methoxy group. From **131**, allyltrimethyl silane and TiCl$_4$ were used to replace the methoxy group with an allyl group in **133** through the iminium ion **132**. We envisioned being able to apply this chemistry to achieve the correct C-2 substitution in the tricyclic lactam. We attempted to apply that chemistry to our tricyclic lactam **134** in Scheme 29b, to first afford **135**, but the two-step yield of **136** from **134** was low, <16%. We concluded it was unproductive to pursue the electrochemistry route further.
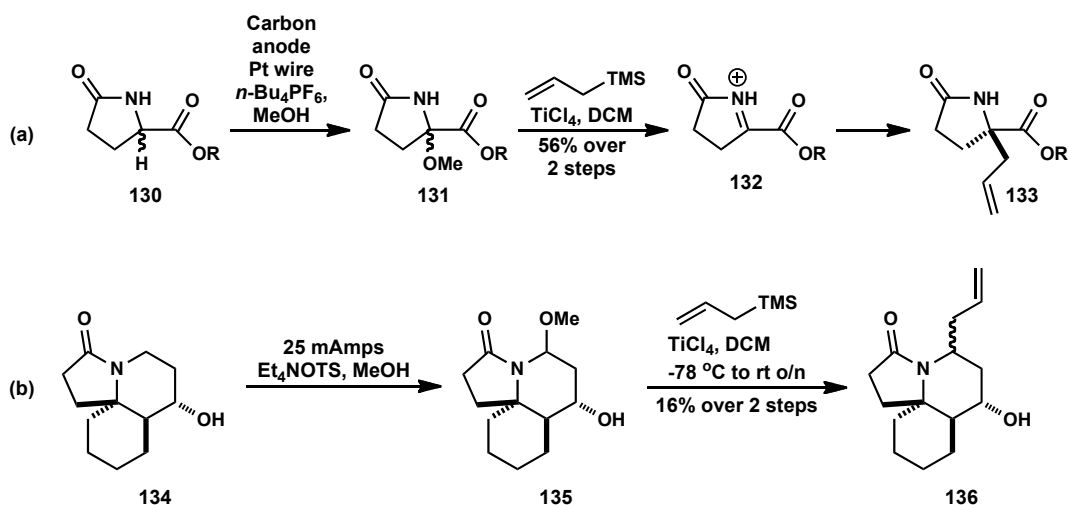
Scheme 29. Electrochemistry of amides

In another effort to assess the acetal version of the Prins/Schmidt approach, we examined deprotecting the methyl ether at C-4 with BBr$_3$ (Scheme 30). Unfortunately, when **123c** was treated with boron tribromide (BBr$_3$) under standard conditions, we did not achieve the desired deprotection but instead isolated a combination of the migrated hydroxy compound **137** and the eliminated product **138** (Scheme 30). The structures of **137** and **138** were determined by ^{13}C DEPT analysis.
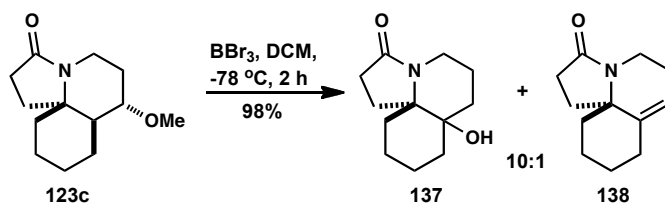
Scheme 30. Deprotection of methyl ether

Our mechanistic hypothesis for this transformation is depicted in Scheme 31. We figured the oxygen displaced a bromine on the boron but instead of the bromine returning

to remove the methyl as expected, a secondary carbocation was formed in place of the oxygen. The cation intermediate could undergo elimination to form **138**, or undergo a 1,2-hydride shift to form the more stable tertiary carbocation. After water adds to the tertiary carbocation, the resulting product is **137**, the major product seen in the reaction. Regardless, at this point, we opted for an alternative pathway.
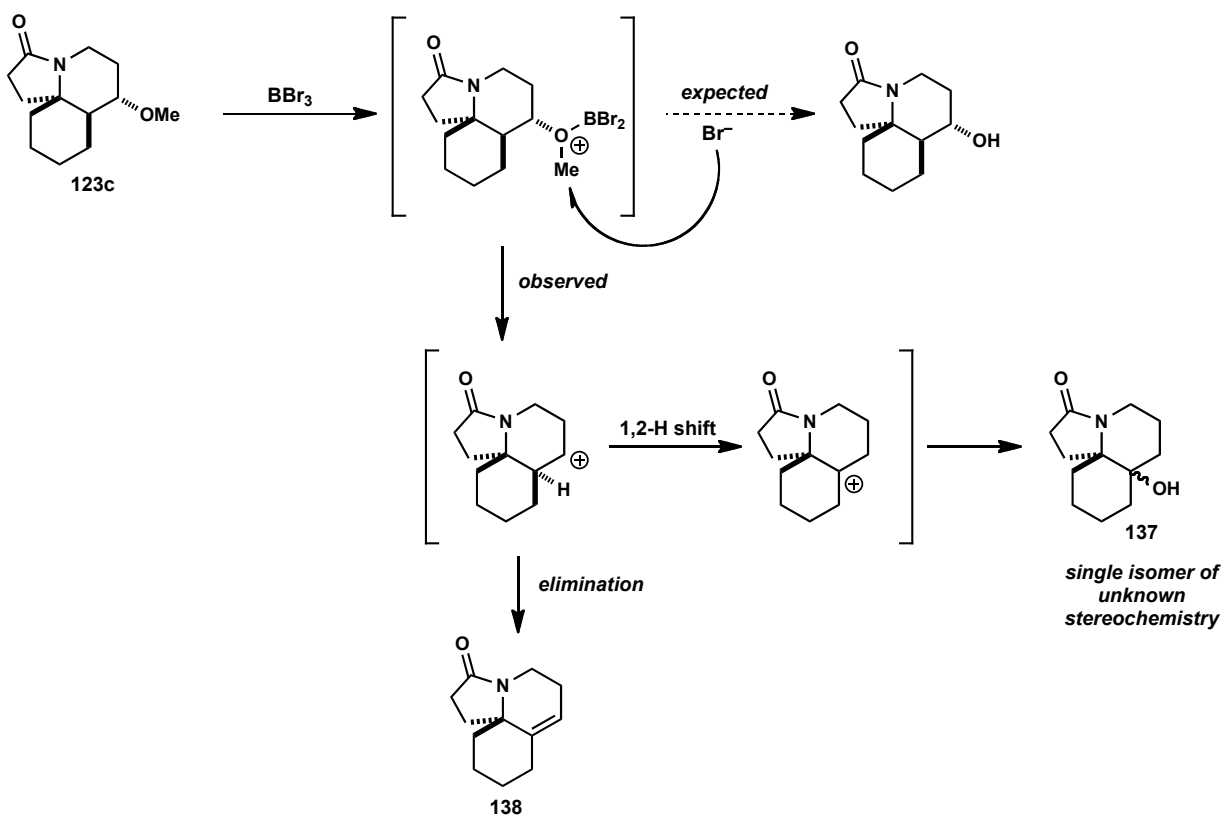
Scheme 31. Mechanistic hypothesis for BBr$_3$ reaction

2.7. Aldehyde Approach

All of the precedent regarding the Prins reaction with the vinylogous cyclopropanols involved an acetal as a coupling partner. Based on the results described above, we decided to embark on an investigation using aldehydes as coupling partners in the same type of reaction. One potential problem for that route included the decreased reactivity of the aldehyde relative to the oxonium species afforded by the acetal.

2.7.1. Non-Substituted 3-Azidoaldehyde

Early efforts toward this project were carried out by Christopher Katz[84] and Sze-Wan Li[85] and I began by reexamining their results as described in this section. To begin, an extensive reaction screen of appropriate conditions for the reaction between **112** and 3-azidopropanal (**120**) was done. Temperatures from −78 °C to 100 °C were examined as well as a variety of Lewis acids (AlCl$_3$, MeAlCl$_2$, BF$_3$•Et$_2$O, TMSOTf, Ti(Oi-Pr)$_4$, Sc(OTf)$_3$, Triflic acid, SnCl$_4$, TiCl$_4$/ Ti(Oi-Pr)$_4$, and TiCl$_4$). Different equivalent ratios of cyclopropanol to aldehyde were examined as well. Most reactions were done in dichloromethane (DCM) as THF is known to polymerize under Lewis acid conditions. Under most conditions, the resulting product was [5.3]spirocyclic ketone **139**, the product of ring expansion and protonation of **112** accomplished by submission to acid (Scheme 32). However, some hope was found using TiCl$_4$ at elevated temperatures.
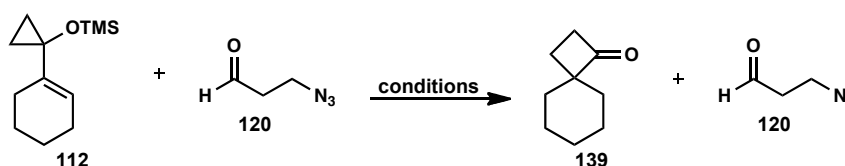
Scheme 32. Unsuccessful attempts at Prins/Schmidt reaction

After an extensive trial of the Prins/Schmidt reaction with TiCl$_4$, we arrived at the optimal conditions. The reaction was initiated by addition of 1.5 equiv of TiCl$_4$ at 0 °C to the mixture of **112** and **120** and then a second addition of TiCl$_4$ two hours later and heating to 40 °C for another two hours (Scheme 33). This led to an interesting result: two different compounds ultimately identified as **140** and **141** were observed as single

diastereomers as shown in Scheme 33, as identified by ^{13}C NMR analysis of the crude reaction mixture.
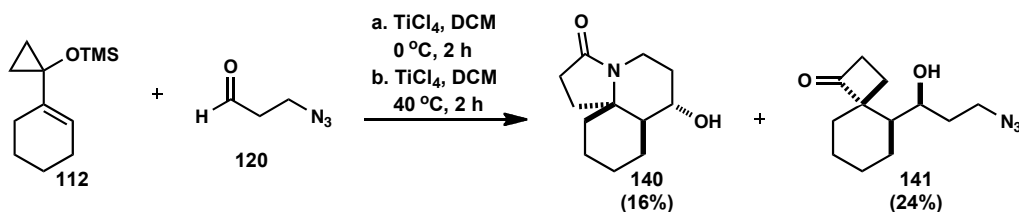
Scheme 33. Prins/Schmidt reaction with 3-azidopropanal

At the time, we were unsure of the stereochemical relationship of **140** and **141**, and so initially concentrated on converting the latter to a lactam. Numerous conditions were attempted, but all failed. Eventually, we decided to protect the hydroxyl group of **141** as an acetate group by treatment with acetic anhydride (Ac$_2$O) to form **142** (Scheme 34). The protection reaction was high yielding for **142** (89%) and was mass balanced by the isolation of byproduct **143** (11%). Azide **142** was submitted to TiCl$_4$ and quickly underwent ring expansion to tricyclic lactam **144** in excellent yield.
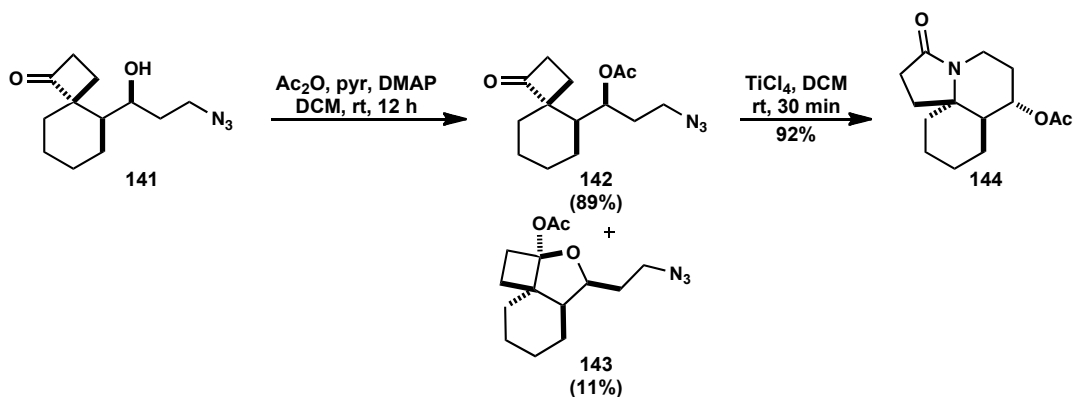
Scheme 34. Tricycle formation from **141**

With tricycles **140** and **144** in hand, we wanted to compare the molecules to see if they were in the same stereochemical series or not. In order to directly compare the two, **140** was converted to the acetate ester **145** (Scheme 35). Comparison of the NMR spectra determined that these compounds were not identical. Eventually we were able to obtain a crystal structure of **140** (See Appendix 1), but we needed to find out the stereochemical differences between **144** and **145**. The details to the structure elucidation are in Chapter 5.
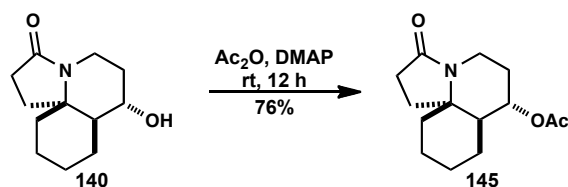
Scheme 35. Conversion of **140** to the acetate

Lactams **144** and **145** were epimeric at the aza-spirocenter. Accordingly, tricycle **145**, modified from **140**, the compound that underwent the tandem Prins/Schmidt reaction shown in Scheme 33, contained a *cis*-azadecalin ring fusion, similar to that seen in the cylindricine family of molecules. In contrast, **144**, derived from the spirocyclobutanone **141** from Scheme 33 and Scheme 34, contained the *trans*-azadecalin ring fusion as present in the lepadiformines. Interestingly, the relative stereochemistry between C-4 and C-5 were the same.

Having determined the structural differences between the two lactams, we were still curious as to why one of the diastereomers of the spirocyclobutanone underwent the intramolecular Schmidt reaction *in situ* while the other diastereomer did not. Scheme 36

shows the divergent pathways of the two spirocyclobutanone diastereomers formed. First, the Prins reaction occurs to form carbocation **146**. From there, the ring expansion can occur two ways, forming **147** and **141**. Diastereomer **141** remained, while the other diastereomer, **147**, was able to undergo azide addition and ring expansion to form **140**. The only difference was the spirocenter stereochemistry.
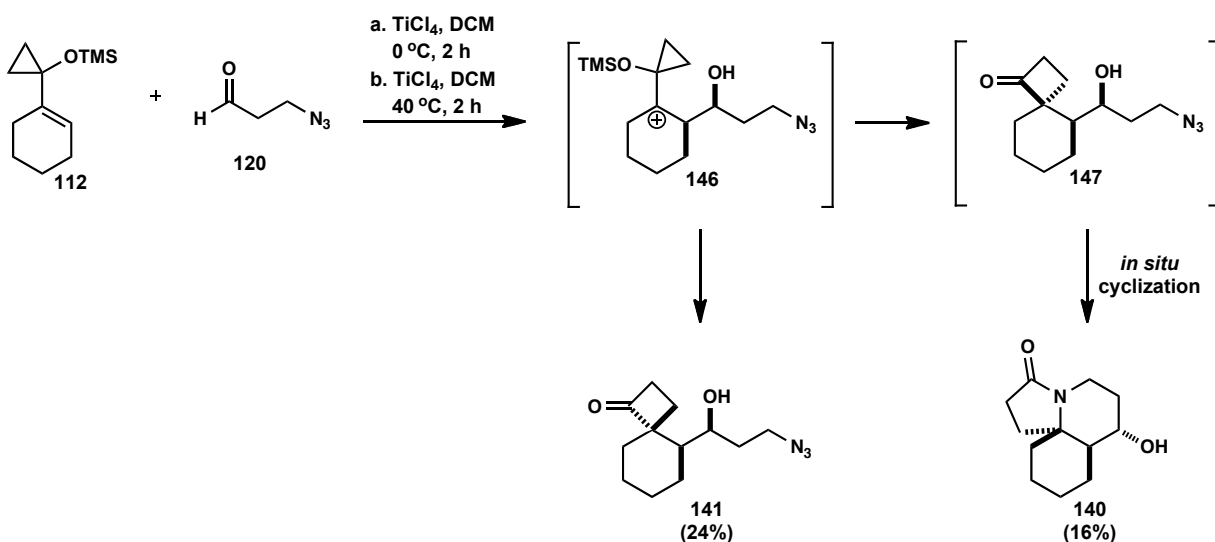
Scheme 36. Divergent pathways

One possible theory to give some insight into the stereochemical divergence was formed after the isolation of ketal **143** shown in Scheme 34. Since the ketal could be protected as the acetate, **141** must be in equilibrium with the corresponding hemiketal. Illustrated in Scheme 37, when **112** was reacted with **120**, two spirocyclobutanones were formed. As also shown in Scheme 36, **147** proceeded to undergo an intramolecular Schmidt reaction to form **140**. However, to the extent that the equilibrium of **141** with **148** favors the hemiketal, it cannot undergo the intramolecular Schmidt reaction.
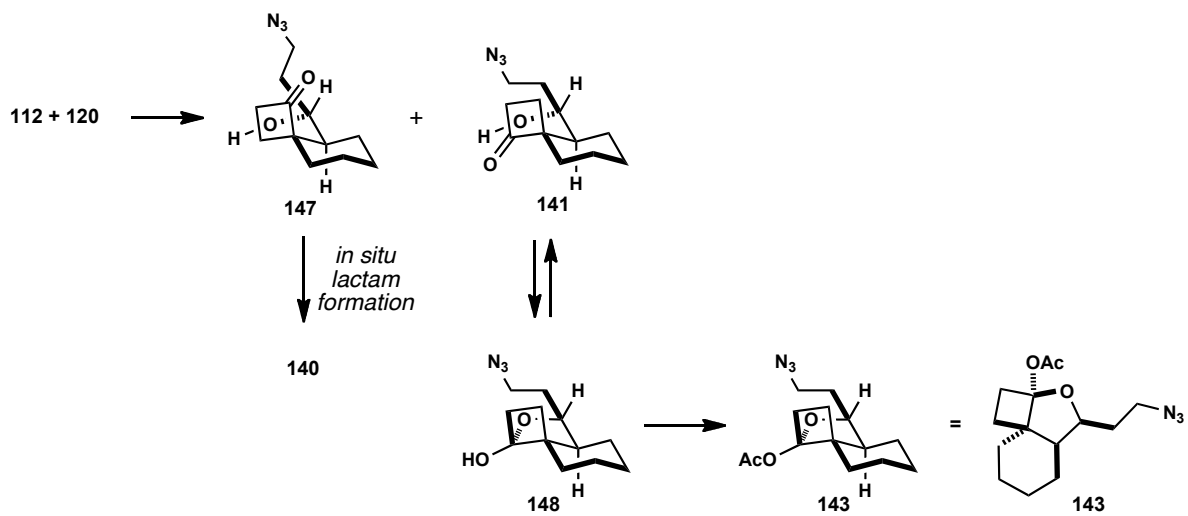
Scheme 37. Hypothesis for stereochemical divergence

2.7.2. Alkyl-Substituted 3-Azidoaldehydes

Since the original idea of the tandem Prins/Schmidt methodology was for the total synthesis of (±)-cylindricine C (**3**), we then investigated the incorporation of an alkyl substitution at the geminal position of the azide in the 3-azidoaldehydes. Using 3-azidononanal, **111**, as the coupling partner, the titanium-promoted reaction with **112** produced four products as shown in Scheme 38. The products isolated from the reaction included a single diastereomer of a spirocyclobutanone **149** in 30% yield, which contained four stereocenters, and three diastereomeric lactams, **150a-c**. The latter each contain four stereocenters and were obtained in 22% yield in a ratio of 3:1:1. The structure of **150a** was determined by first acetylation and then structure elucidation with 2-D NMR techniques. Lactam diastereomer **150b** was assigned based on a crystal structure.[84] The configuration of **150c** was determined by comparison to the equivalent molecule derived from **149**, converted in Scheme 39.

The structures of **150a** and **150b** both contained the *cis*-azadecalin configuration found in the cylindricines; however, only **150b** contained the correct configuration of the hexyl group at C-2. The low yield of **150b** did not bode well for its use in a total synthesis of (±)-cylindricine C (**3**). Interestingly, diastereomer **150c** contained the *trans*-azadecalin moiety and had the configuration for the C-2 hexyl group needed for conversion to (±)-lepadiformine A (**12**).
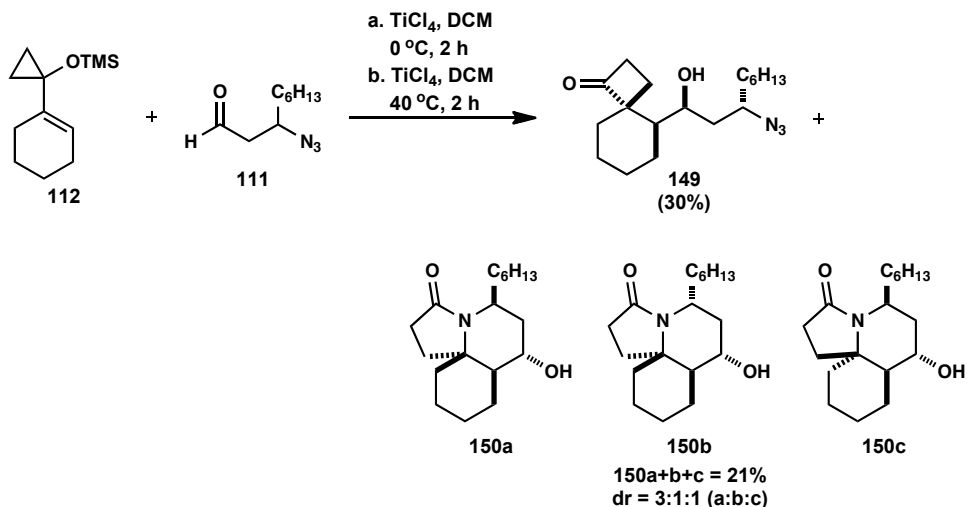
Scheme 38. Prins/Schmidt reaction with 3-azidononanal

In order to determine the stereochemistry of spirocyclobutanone **149**, we converted it to the tricyclic lactam. That was accomplished by protection of the hydroxyl group with an acetate and submission to Lewis acid conditions (Scheme 39). The yield for the conversion of **149** to **151** was slightly diminished (74%) because the corresponding acetoxy ketal **152**, similar to **143**, was also isolated in 19% yield. Submission of **151** to TiCl$_4$ quickly afforded tricyclic lactam **153** in high yield. Structure elucidation of **153** was shown to have the same stereochemistry as **150c** by comparing the 1D NMR spectra, which included the *trans*-azadecalin system and the same hexyl configuration as (±)-lepadiformine A (**12**).
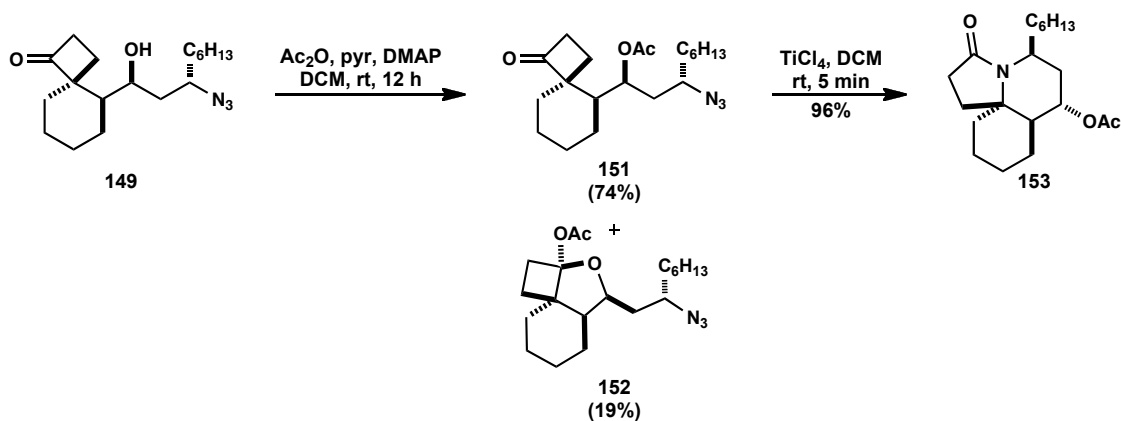
Scheme 39. Cyclization of **149**

We opted to prepare a butyl-substituted analogue as that substitution is found in other cylindricines and lepadiformines. We applied the tandem Prins/Schmidt reaction conditions to **112** and **154**, prepared the same way as other 3-azidoaldehydes except starting with *trans*-2-heptenal, and obtained results similar to those shown in Scheme 38 (Scheme 40). The yield of **155** was decreased to 22% relative to **149** because the corresponding hemiketal was isolated from this reaction mixture. Three diastereomers of the lactam, **156a-c**, were also isolated in 33% yield and dr = 3:1:1, similar to Scheme 38 and also corresponding to the same stereochemistry. The structures of **156a-c** were determined by 2-D NMR structure elucidation (Chapter 5).
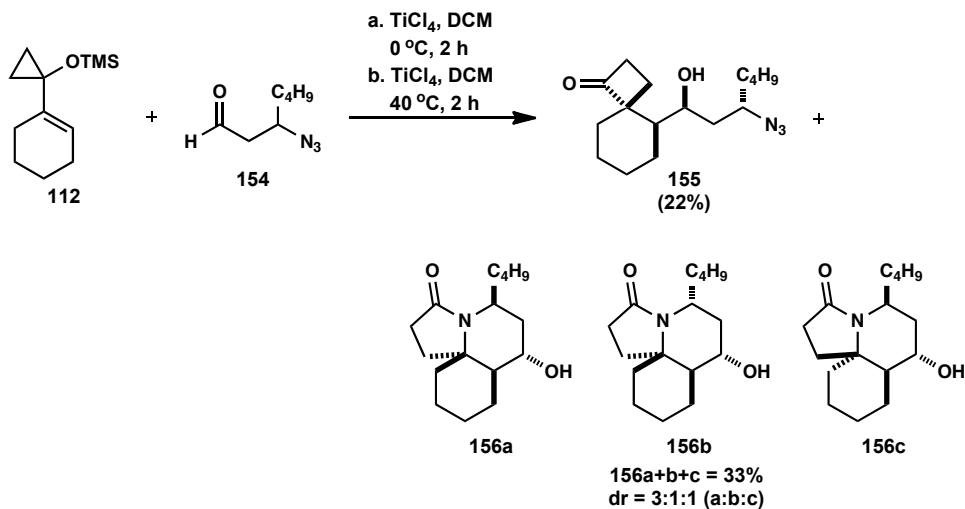
Scheme 40. Prins/Schmidt reaction with 3-azidoheptanal

Spirocyclobutanone **155** was converted to the tricyclic lactam, as was the hexyl-containing **149** (Scheme 41). Thus, the hydroxyl group in **155** was protected as an acetate and the compound was subjected to the intramolecular Schmidt reaction affording tricyclic lactam **158**. The stereochemistry of **158** was deactylated (Scheme 45) and the structure was equivalent to **156c**.
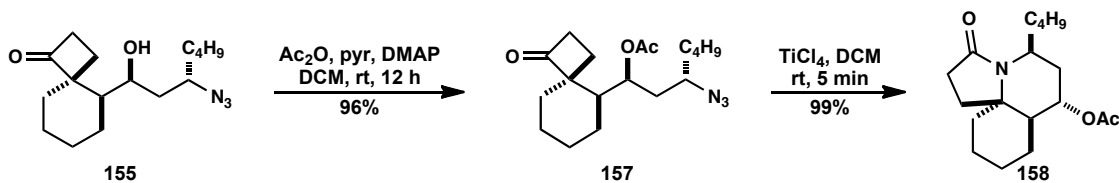
Scheme 41. Cyclization of **155**

In the interest of looking into the stereochemistry a little more, we also chose to examine a 2-alkyl-3-azidoaldehyde. To that end, we began with methacrolein to prepare 3-azido-2-methylpropanal, **159**, in the same way as previous azidoaldehydes, and applied

the tandem Prins/Schmidt conditions (Scheme 42). We expected increased selectivity as a result of the α-substitution but saw not only decreased selectivity, but decreased reactivity as well. Spirocyclobutanone **160** was the major spirocyclobutanone formed, however there was an unknown minor diastereomer of spirocyclobutanone formed also. ^{13}C NMR analysis of the crude reaction mixture indicated the spirocyclobutanones were formed with a dr = 4:1. The minor diastereomer was inseparable and gradually diminished over the course of the next couple reactions before the structure elucidation could occur and we were unable to determine the stereochemistry. Spirocyclobutanone **160** was converted to acetate **162** and then cyclized to **163** in the same way as the previous spirocyclobutanones for structure elucidation. The tricyclic lactams were formed in a slightly different profile than the previous examples. First, four diastereomers of **161** were formed in dr = 4:2:2:1. Second, the lactams were mostly inseparable; a 2:1 mixture of **161a** to **161b** was isolated and their structures were able to be determined. The configurations of the two remaining diastereomers were undetermined.
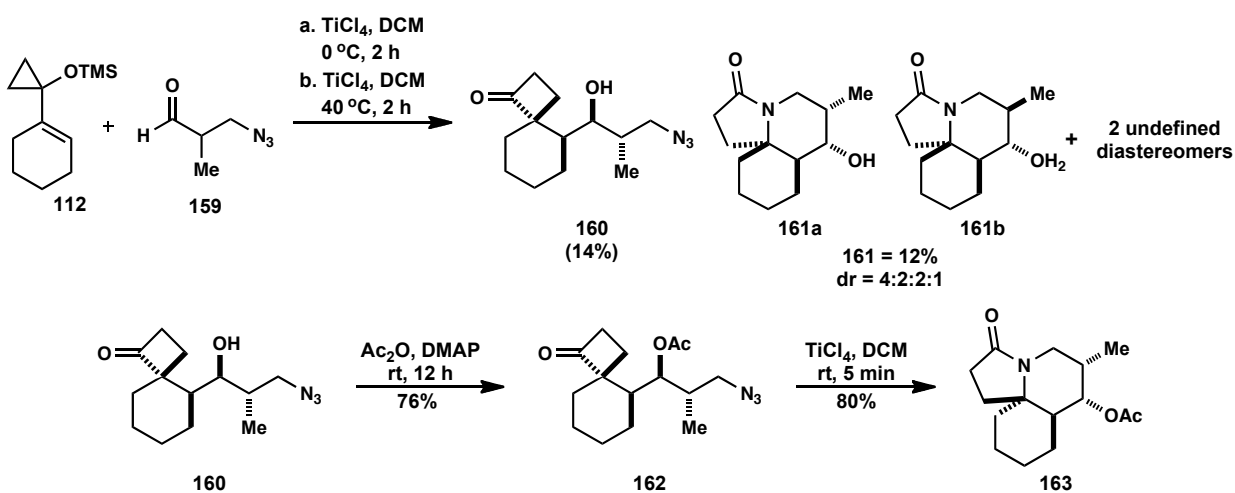
Scheme 42. Prins/Schmidt reaction with 2-methyl-3-azidoaldehyde

2.8. Formal Synthesis of (±)-Lepadiformine A

In the tandem Prins/Schmidt reaction with 3-azidononanal, one of the three diastereomers of the lactams formed, **150b**, contained the required stereochemistry for (±)-cylindricine C (**3**) and was obtained in approximately 4% yield. However, the major product of the reaction mixture, spirocyclobutanone **149**, contained the correct azadecalin configuration and correct relative stereochemistry of the hexyl group as (±)-lepadiformine A (**12**). So instead of continuing to pursue the cylindricine route, we decided to pursue a formal synthesis of (±)-lepadiformine A (**12**) through a common intermediate used by Renaud and coworkers in their total synthesis.[44]

As shown in Scheme 39, **149** was converted in two steps to the tricyclic lactam **153**. Shown in Scheme 43 is the completion of the formal synthesis. Compound **153** was treated with basic conditions to deprotect the alcohol, which afforded **150c**, one of the lactams formed in the tandem Prins/Schmidt reaction shown in Scheme 38. Although **150c** was formed in the tandem reaction, it was produced in such a small amount (*ca.* 4%) making the completion of the synthesis difficult from that stage despite the fact that the sequence would have been three steps shorter. From **150c**, the hydroxyl group was removed using Barton-McCombie conditions: forming xanthate **164** followed by radical C-O bond cleavage to afford **165**.[55]
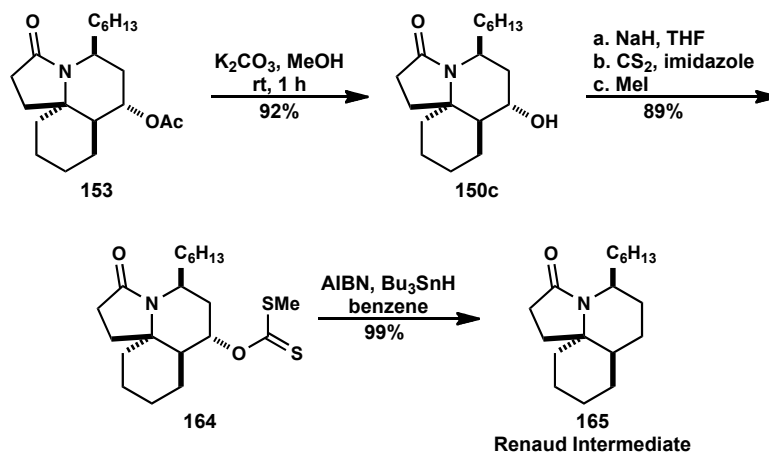
Scheme 43. Formal synthesis of (±)-lepadiformine A (**12**)

From **165**, Renaud and coworkers installed the hydroxymethylene in three steps. First, lactam **165** was converted to the thioamide **166** with Lawesson's reagent (Scheme 44). The thioamide was activated with methyl iodide (MeI) and the alkynyl lithiate was added and then reduced with LAH to afford **167**. The final step for their total synthesis was ozonolysis of **167** with a reductive workup to complete (±)-lepadiformine A (**12**). The Renaud group accomplished the total synthesis in ten linear steps from commercially available starting material in 15% overall yield.

Incorporating the Renaud end game, our formal total synthesis of (±)-Lepadiformine A (**12**) corresponds to 12 total steps and 8% overall yield using the spirocyclobutanone **149** as an intermediate. Going through **150c** would shorten the synthesis to nine total steps but would correspond to only 2% overall yield.
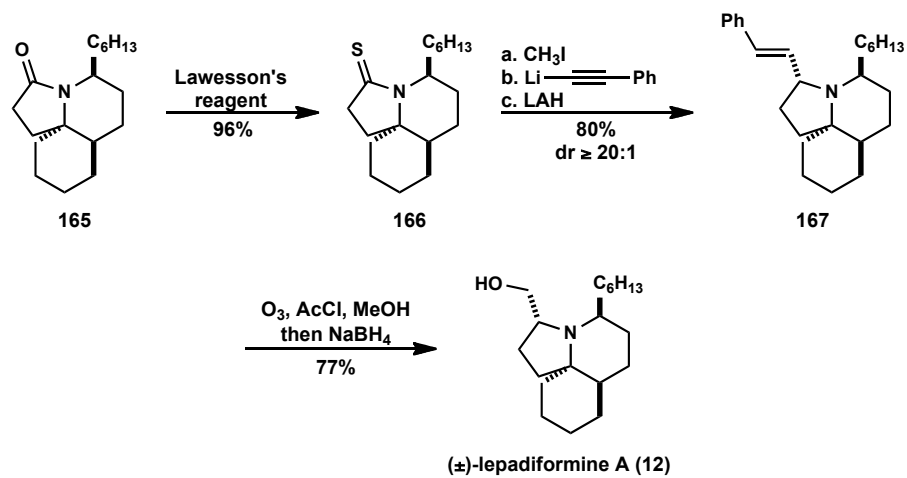
Scheme 44. Renaud end game for their total synthesis of (±)-lepadiformine A (**12**)[44]

2.9. First Total Synthesis of (±)-Lepadiformine C

The tandem Prins/Schmidt reaction with 3-azidoheptanal yielded a slightly higher amount of lactam that corresponded to the cylindricine natural products than did 3-azidononanal; lactam **156b** was formed in a 6% yield, shown in Scheme 40. That lactam could have been used to synthesize any of the cylindricines G-J (7-10). Instead, we chose to pursue a total synthesis of (±)-lepadiformine C (**14**) from spirocyclobutanone **155** in the same way we moved forward with the formal synthesis of (±)-lepadiformine A (**12**) shown in Scheme 43.

For the total synthesis of (±)-lepadiformine C (**14**), we began with lactam **158** as formed from spirocyclobutanone **155** (Scheme 41). As shown in Scheme 45, lactam **158** was treated with base to form **156c**, the same lactam formed in the tandem Prins/Schmidt reaction in Scheme 40. Treating **156c** with Barton-McCombie dehydroxylation conditions, we first formed xanthate **168** and then lactam **169** through a radical transformation. To reduce the amide in **169** to the amine, LAH was used. The resulting amine was protonated with HCl and purified to complete the first total synthesis of (±)-lepadiformine C (**14**).

The total synthesis of (±)-lepadiformine C (**14**) was accomplished in nine total steps and 10% overall yield proceeding through spirocyclobutanone **155**. Using lactam **156c** from the tandem Prins/Schmidt reaction accomplished the total synthesis in seven total steps and an overall yield of 3%.
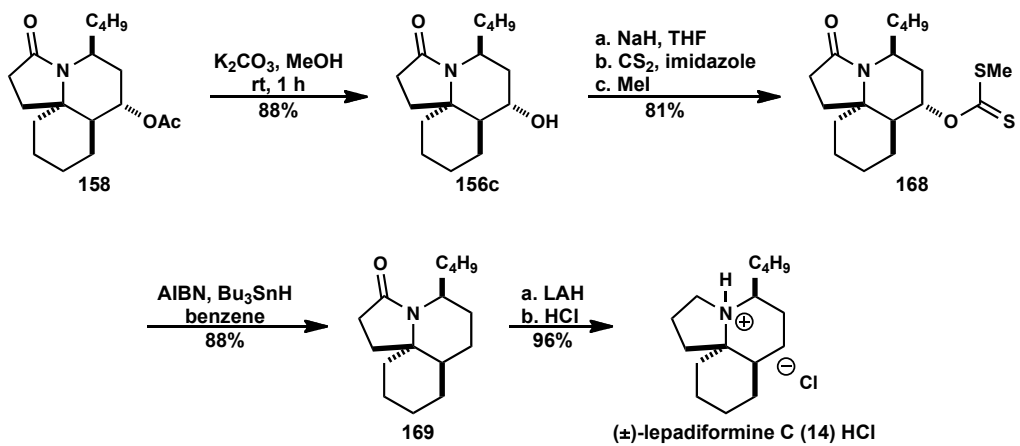
Scheme 45. Total synthesis of (±)-lepadiformine C (**14**)

2.10. Conclusion

The tandem Prins/Schmidt reaction has provided a useful pathway to prepare complex tricyclic lactams from simple starting materials. Although the yields are not outstanding, the complexity and diastereochemical outcome of these sequences remains impressive as, in most cases, four stereocenters were set and two rings were formed in a single-pot reaction. This methodology allowed for the completion of a formal synthesis of (±)-lepadiformine A (**12**) and a total synthesis of (±)-lepadiformine C (**14**). Since this methodology did not furnish the total synthesis of (±)-cylindricine C (**3**), a second-generation approach was needed.

Chapter 3

Efficient Process for the Preparation of Enantiomerically Pure 4-Hydroxy-2-cyclopenten-1-ones

3.1. Importance of 4-Hydroxy-2-cyclopenten-1-ones

4-Hydroxy-2-cyclopenten-1-one (HCP), shown in Figure 5 as a silyl-protected variant, has historically been an important intermediate in prostaglandin synthesis. Many synthetic methods have been developed both to prepare this molecule and to study its reactions.[86-88] A number of naturally-occurring prostaglandin drugs are currently on the US and world pharmaceutical markets, including dinoprostone (PGE_2, used to induce labor), PGE (peptic ulcer treatment), and PGE_1 (treatment of patent ductus arteriosus in newborns). Because HCP is a common intermediate to these important drugs, producing it on large scale is necessary. Efficient processes are required for molecules being made in batch. Although there are many routes to HCP, we developed our own synthesis that was shorter than all previous routes. We have devised a concise, asymmetric approach that is adaptable to large-scale synthesis. Although useful in the area of prostaglandin research and therapeutics, we developed this process for the use of a starting material in a total synthesis approach that will be described in Chapter 4.

4-Hydroxy-2-cyclopenten-1-one
Prostaglandin Intermediate

PGE₂
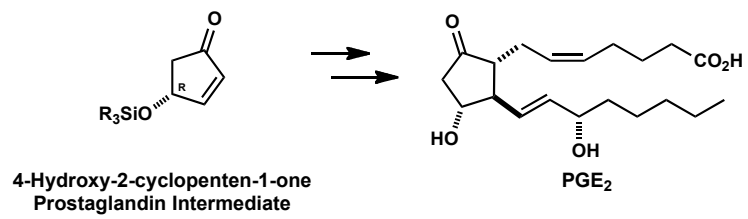
Figure 5. Core of prostaglandins

3.1.1. Prostaglandins

In the 1930's, gynecologists discovered prostaglandins when they observed muscle contraction and relaxation of the uterus when exposed to semen.[89] The active compounds were later named *prostaglandins* because they were identified to exist in the prostate gland. In the 1960's, further investigation led to the discovery of the biosynthesis of some prostaglandins from arachidonic acid (AA) which was followed by reports of biosynthetic inhibition by aspirin and other non-steroidal anti-inflammatory drugs (NSAIDS), culminating in a Nobel prize awarded to Sune Bergström, Bengt Samuelsson, and John Vane in 1982 for their discoveries concerning prostaglandins and related biologically active substances.

Scheme 46 diagrams the biosynthesis of some of the prostaglandins. When a cell detects chemical or physical stress, acyl hydrolases, commonly phospholipase A (PLA_2) are activated. PLA_2 hydrolyses the ester bond of the phospholipids of the cell membrane and releases arachidonic acid (AA). AA is acted on by cyclooxygenase actions of COX-1 or COX-2 to form the cyclic endoperoxide prostaglandin G_2 (PGG_2), which contains an acyclic peroxide in addition to the endoperoxide.[90] PGG_2 is converted to prostaglandin H_2 (PGH_2) by hydroperoxidase action of either COX-1 or COX-2. For clarification, both isoforms of COX enzymes, 1 and 2, perform the cyclooxygenase and hydroperoxidase activities, however, they usually exist in cells such that one isoform is dominant over the other. COX-1 is considered the main source for prostaglandins involved in regulatory functions that occur under conditions of low stress. COX-2 is induced in times of stress and provides prostaglandins for inflammation and cancer.

A variety of synthases convert PGH_2 to different prostaglandins, depending on physiological need. The key structural feature in these prostaglandins that is relevant to the work herein is the cyclopentane rings bearing the stereodefined hydroxyl groups seen in PGE_2, $PGF_{2\alpha}$, PGD_2, and PGI_2.
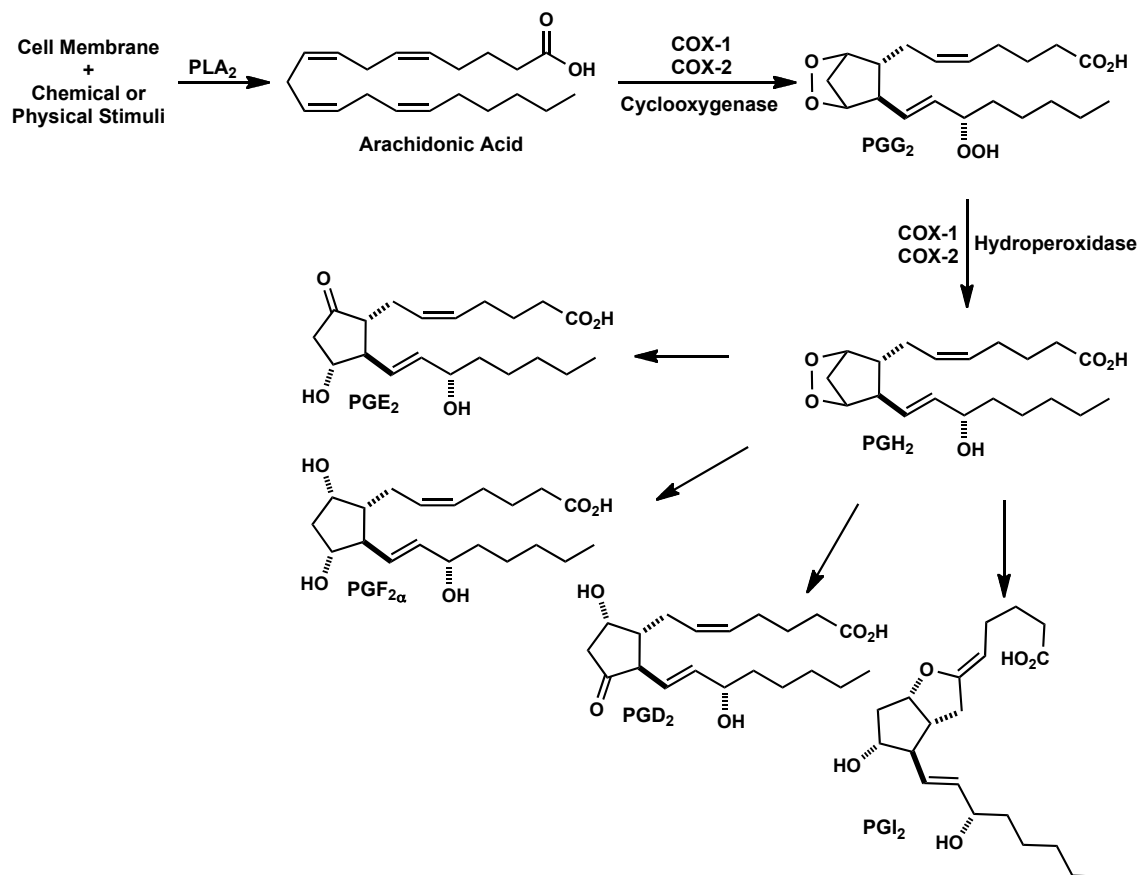
Scheme 46. Prostaglandin biosynthesis

The prostaglandin structures possess vast biological activity profiles. In some cases, it is therapeutically desirable to inhibit prostaglandin actions, such as in the induction of inflammation. For example, COX inhibitors, like aspirin, are widely used anti-inflammatory agents. Obtaining a selectivity profile of COX-2 inhibition over COX-

1 has brought to market some popular drugs for the treatment of rheumatoid arthritis like celecoxib, a current drug on the market developed by Pfizer.

In other cases, the increase of prostaglandin levels is desired. The prostaglandins are agents of autocrine or paracrine signaling, so they are synthesized for use in a specific location. Unfortunately, the half-life of prostaglandins is short, around 30 minutes. Moreover, up-regulation of prostaglandin biosynthetic enzymes might not be advantageous because it would lead to effects in numerous tissues, as this biosynthetic machinery is quite ubiquitous. A solution to this problem involves external synthesis of the prostaglandins and administration as needed in the desired location.

There are many desirable biological effects of the prostaglandins.[91] Some examples of these effects include PGI_2 inhibiting platelet aggregation and breaking up aggregates that have already formed, which has major implications in myocardial infarction and stroke prevention or treatment. PGE_2 maintains the ductus arteriosus, which connects the pulmonary artery to the aortic arch in fetuses to bypass fluid-filled lungs. PGE_2 also has bronchodilating effects, while $PGF_{2\alpha}$ has bronchoconstricting effects. PGE_2 and PGI_2 both play a critical role in maintaining renal blood flow and salt excretion as well as protect cardiac tissue from oxidative injury.

Because of the many biological effects of prostaglandins, they have many therapeutic uses. Because PGEs and PGFs cause uterine contractions, they are used in pregnancy terminations. Dinoprostone, synthetic PGE_2, is approved for inducing labor by ripening the cervix and inducing abortion in the second trimester. PGE_2 in combination with Mifepristone (RU486) is highly effective in terminating early pregnancies. Misoprostol, an analog of PGE_1 (similar to PGE_2 with the *cis*-double bond

hydrogenated), is an approved drug for the treatment of gastric ulcers that were caused by NSAIDS. The effectiveness is similar to that of a proton-pump inhibitor. PGE_1, alprostadil, is used as an injectible therapeutic for the treatment of erectile dysfunction as a result of the vasodilation effects. [89]

Clearly, the vast array of biological targets for the prostaglandins exists. Efficient processes to synthesize enantiomerically pure advanced intermediates to the prostaglandins are desirable to not only recreate the natural prostaglandins, but also to prepare libraries of analogs to further probe their biological portfolio.

3.1.2. Prostaglandin Synthesis from HCP's

Two comprehensive reviews on prostaglandin synthesis have been published, one in 1993 and another in 2007.[87,88] All prostaglandins contain a cyclopentane ring, while only some of them contain a 4-hydroxy-2-cyclopenten-1-one substructure, as in PGE_2 and PGD_2. Two convenient ways to prepare the HCP containing prostaglandins include a two-component coupling and a three-component coupling strategy.

The two-component process has been employed to prepare PGE_1 (Scheme 47).[92] A Suzuki-Miyaura reaction was used to couple iodoenone **170** to an alkylborane to form **171**. The second component involved a cuprate-mediated conjugate addition of vinyl stannane **172** to form the 2,3-substituted cyclopentanone **173**. The stereochemistry of **173** resulted from the conjugate addition adding to the opposite face as the silyl ether. The protonation of the enolate formed after the cuprate addition occurred to orient the alkyl substituents *trans* to each other. Compound **173** was taken on to PGE_1 methyl ester.
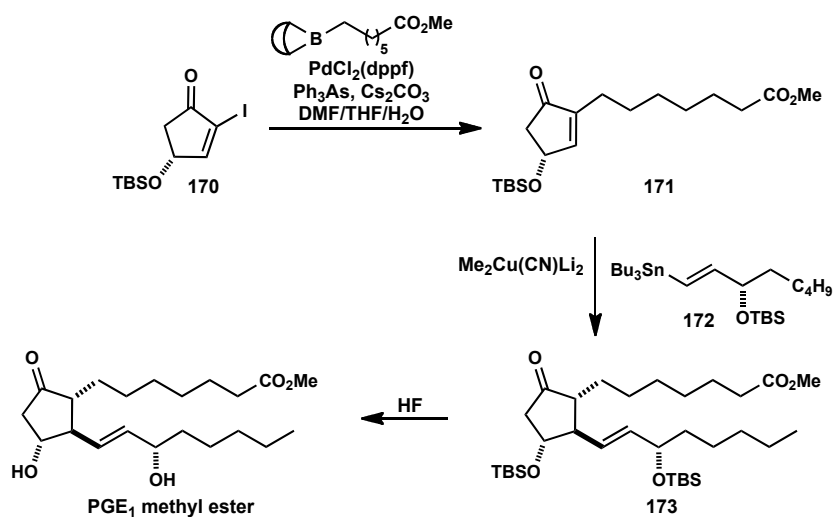
Scheme 47. Two-component coupling process

The other common procedure for the preparation of prostaglandins from HCP's involves a three-component coupling shown in Scheme 48.[93] Starting with **174**, the conjugate addition of **175** to **174** forms enolate **176**. Treatment of enolate **176** with a propargyl iodide, forms **177**. These two steps occur in one-pot.
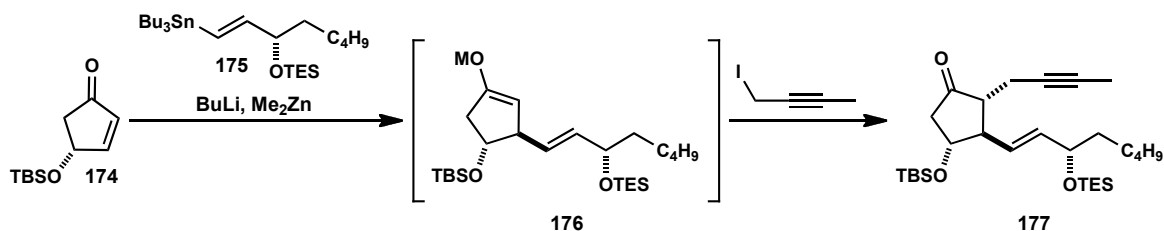
Scheme 48. Three-component coupling process

The two-component and three-component coupling processes are just two simple examples of the utility of the HCP's in the synthesis of prostaglandins. Based on the biological profile of prostaglandins and the facile accessibility from HCP's, a quick and easy approach to prepare HCP's could positively impact this area of therapeutics.

3.2. Previous Synthetic Approaches

We sought to prepare a silyl-protected HCP, a common intermediate for the synthesis of prostaglandins. Current methods for making this intermediate require a multi-step route that entails a number of non-optimal steps, including strong oxidizing conditions for making the initial starting material, the use of an enzymatic reaction to induce stereochemistry, and the possibility that a later key intermediate has the potential for racemization due to a latent plane of symmetry in the molecule. Nonetheless, this route has been used due to the lack of more efficient alternatives.

Scheme 49 outlines the initial steps of the most common approach that has been adapted by many but was originated by Deardorff and coworkers.[94,95] The process began with cyclopentadiene, which was cracked and then treated with peracetic acid in DCM with sodium acetate (NaOAc) and sodium carbonate (NaCO$_3$) to form epoxide **178**. In our hands, this reaction worked well to form a volatile epoxide. The epoxide-opening reaction was less friendly. The reported procedure for the conversion of **178** to ($\pm$)-**179** reported a 72-76% yield, however in our hands, that was never the case. The palladium-mediated S$_N$2' addition of the acetate to **178** was sensitive and not reproducible in our hands. Racemate ($\pm$)-**179** required multiple recrystallizations for sufficient purity as high purity was required for the enzymatic hydrolysis reaction and the diacetate **180** was an oil and accordingly could not be recrystallized. Once in hand, racemic monoacetate ($\pm$)-**179** was converted to diacetate **180** with ease and enantiomerically pure (*1R*,4*S*)-**179**, was prepared via enzymatic hydrolysis with electric eel acetylcholine esterase.
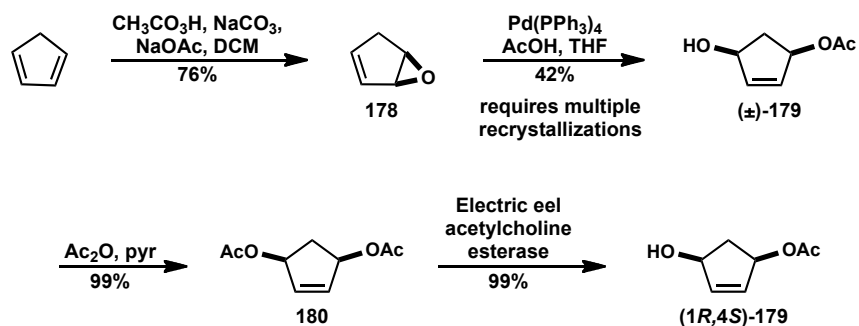
Scheme 49. Initial steps for enantiomerically pure cyclopentene (*1R*,4*S*)-**179**

From (*1R*,4*S*)-**179**, multiple steps were required to obtain the two the silyl-protected HCP enantiomers. As shown in Scheme 50, three more steps were needed to synthesize (*S*)-**181** following a procedure by Danishefsky and coworkers.[96] If the *R* enantiomer was required, one extra protecting group strategy was needed; so five extra steps were required.[97] The extra steps are because the enzyme only hydrolyzed one enantiomer of acetate and that was not interchangeable for the other enantiomer. Therefore, the total steps required to synthesize (*S*)-**181** was seven and nine steps for the (*R*)-**181**.
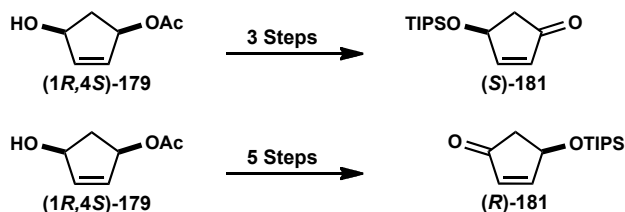
Scheme 50. Literature routes to (*R*)-**181** and (*S*)-**181**

Other routes to HCP included drawing the chirality from the chiral pool, namely sugars. As shown in Scheme 51, (4*S*)-HCP was synthesized from D-arabinose or in two

fewer steps from 2-deoxy-D-ribose.[98] In that approach, the sugars were converted to **182** in eleven or nine steps, respectively. From there, ring-closing metathesis (RCM) formed **183** and subsequent Dess-Martin periodinane (DMP) oxidation afforded (*S*)-**174**. The target was obtained in >98% es with an overall step count of 11 from commercially available 2-deoxy-D-ribose. Also, both enantiomers can be made using this method because L-arabinose is also commercially available.
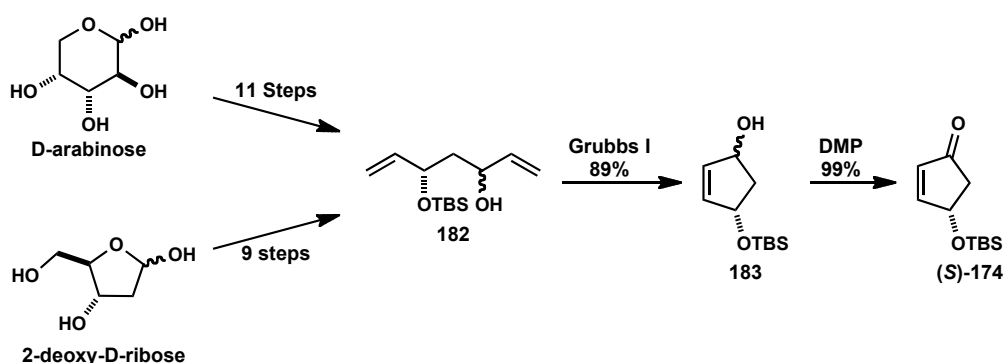
Scheme 51. Sugar approach to HCP

Shown here are just a few of numerous approaches the HCP's. Although there are many other approaches, we sought to develop a route that was short, highly enantiomerically selective, user friendly, and scalable.

3.3. Our Synthetic Strategy

Our initial idea involved a RCM approach similar to that shown in Scheme 51, where the key chiral intermediate could be prepared in enantiomerically pure form from a Noyori reduction (Scheme 52). In an *Organic Syntheses* preparation, **185** was synthesized starting with acetyl acetone, which was converted to **184**. From **184**, a Noyori reduction resulted in **185** in >98% es.[99] From there, a Corey-Chaykovsky reaction converted **185** to **186**, as demonstrated by Hanson and coworkers.[100] The conversion of **186** to **187** would require RCM and a monoprotection step to form **187**, which could be oxidized to **188**, the target molecule. One advantage of this route was that either enantiomer would be accessible by the same route depending on which enantiomer of the chiral catalyst was used. Also, the two alcohols in **186** are equivalent because the molecule is C_2-symmetric.

Our proposed route in Scheme 52 differed from the standard processes in several ways. First, the starting materials are readily available on large scale as was the case with the common route shown in Scheme 49, but that didn't translate well in our lab. Next, the stereochemistry is derived from a non-enzymatic catalyst, which has several advantages over an enzyme; both enantiomers of the target molecule could be made with equal ease using simple reaction conditions. Moreover, the Noyori reduction has considerable precedent on an industrial scale. Third, the key cyclic intermediate en route to the HCP is simply converted to the target HCP molecule in a minimal number of steps.
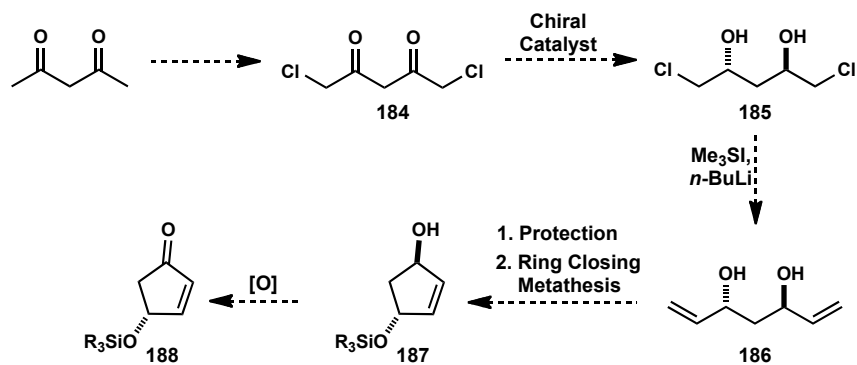
Scheme 52. Proposed route to HCP

We began with acetylacetone and followed the *Organic Synthesis* preparation to synthesize 1,5-dichloro-2,4-pentanedione **184** (Scheme 53).[99] The resulting mixture was purified by distillation. Due to its instability, compound **184** was stored as the copper salt complex, **189**. Complexation was accomplished by stirring with cuprous acetate (Cu(OAc)$_2$), which formed a grey powder that was easy to handle and store. Prior to the subsequent Noyori reduction, **184** was unveiled by stirring the grey powder in a biphasic mixture of sulfuric acid (H$_2$SO$_4$) and ether.

The Noyori reduction was performed in a large Par bomb apparatus under a pressure of 1250 psi of H$_2$ gas. We used the *S*-BINAP version of the ruthenium catalyst because we desired the *R* stereochemistry at the alcohols. The resulting solution of the Noyori reduction was recrystallized from hexanes and DCM and produced **185** as beautiful white needle crystals. The literature value[99] for the enantiomeric purity of **185** is >98% es for this process so we analyzed our solid by melting point and optical rotation to ensure our purity. The reported melting point is 85-86 °C, and we obtained a melting point of 83.6-85.5 °C. The reported optical rotation is [α]$_D$ = +21.1 (*c* 1.125, CHCl$_3$), and we obtained an optical rotation of [α]$_D$ = +20.8 (*c* 1.125, CHCl$_3$). With these data, we felt

confident in a high degree of enantiopurity and moved forward. The white crystals were stable and stored at room temperature until they were needed.
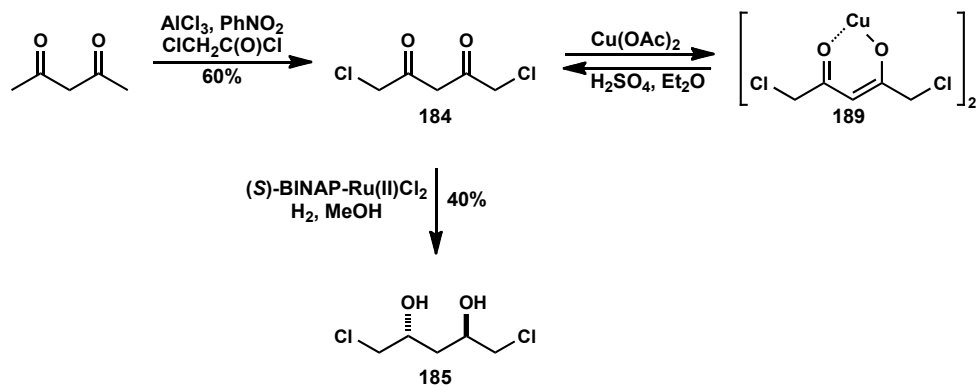
Scheme 53. Preparation of (*2R, 4R*)-*1*,5-dichloro-2,4-pentanediol

The next step of the reaction sequence toward HCP was a Corey-Chaykovsky homologation reaction that converted the terminal chloro- to a terminal alkene (Scheme 54).[65] In that reaction, the trimethylsulfonium iodide (Me$_3$SI) was freshly prepared from dimethylsulfide (DMS) and methyl iodide (MeI) followed by recrystallization from ethanol. The other key to preparing Me$_3$SI was mixing the DMS and MeI in a plastic container because if glassware was used, the product had to be removed by breaking the glass flask and chipping away the glassware from the outside of the hard solid formed on the inside. The plastic container allowed for bending and flexing of the sides to loosen up the hard solid inside.

The freshly prepared Me$_3$SI was deprotonated by *n*-BuLi at –40 °C to prepare the sulfonium ylide. After addition of **185**, presumably an intermediate similar to **190** was formed. Elimination of DMS from each end of **190** formed **186**. Aqueous workup of the reaction removed byproducts and salts. This was followed by the removal of DMS and

solvent by rotary evaporation to afford **186** in 95% yield. This material was usually pure by NMR without further purification but sometimes required column chromatography. The enantiopurity of **186** was analyzed by optical rotation; the literature value is $[\alpha]_D = -29.9$ (*c* 0.33, DCM) and we obtained a value of $[\alpha]_D^{23.6} = -26.4$ (*c* 0.33, DCM).
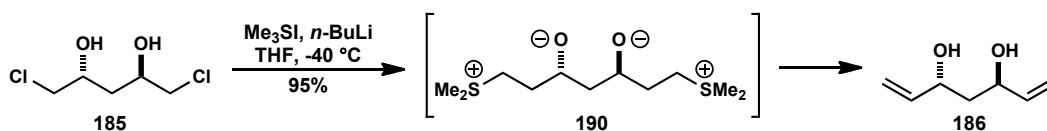
Scheme 54. Corey-Chaykovsky homologation

Initially we envisioned cyclizing **186** and then monoprotecting the resulting diol. Table 2 shows the results of the RCM conversion of **186** to **191**. Three different ruthenium catalysts were tried: Grubbs I,[101] Grubbs II,[102] and Hoveyda–Grubbs II[103] (Figure 6). The reaction concentration for these reactions was 0.0075 M to promote an intramolecular ring closure because higher concentrations resulted in some cross metathesis i.e. polymerization or oligomerization. We achieved a yield of *ca.* 70% using Grubbs II under the conditions shown in entry 7 of Table 2 so we chose to move forward to the protection step.
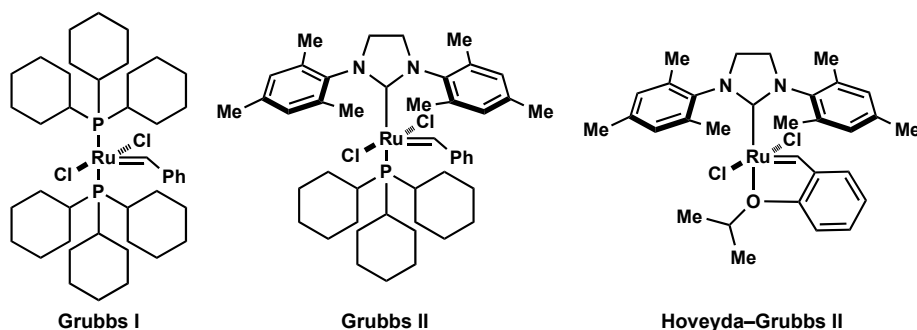
Figure 6. Ring-closing metathesis catalysts

Table 2. RCM of **186**
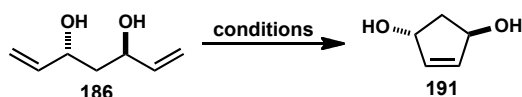
Entry	Catalyst	Solvent	Time/Temp	Yield of 191
1	Grubbs I	DCM	48 h/rt	0%
2	Grubbs II	DCM	24 h/rt	71%
3	Grubbs II	MeOH:H$_2$O (9:1)	24 h/rt	64%
4	Grubbs II	DCE	2 h/ 80 °C	10%
5	Hoveyda-Grubbs II	DCM	12 h/rt	50%
6	Grubbs II	MeOH:DCM (1:1)	12 h/rt	70%

The next step in the sequence involved monoprotection of **191**. At the outset, we expected that with dilute conditions and careful addition of one equivalent of the silylating agent, we could achieve a monoprotected product. However, this step proved more problematic than expected. Table 3 shows the results of the various monoprotection attempts. Initially we targeted a triisopropylsilyl ether as the protecting group, but some other silanes were tried also because all of the results were disappointing.

As evident from Table 3, it became clear that monoprotection of **191** was not a tenable route for the production of cyclopentene **187**. In all cases examined, the

monoprotection of one alcohol seemed to have little if any inhibitory effect on the second

hydroxyl protection and led to the mixture of **187**, **192** and starting material **191**. At that

point we decided to reformulate the protection strategy to increase the amount of

monoprotection over the other two possible products.

Table 3. Monoprotection attempts of **191**
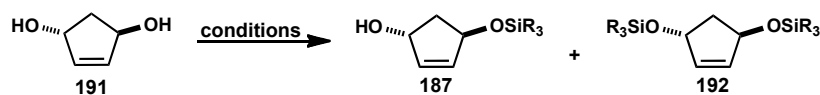
Entry	Silane (equiv)	Base	Solvent (conc)	Temp	Yield of 187	Yield of 191	Yield of 192
1	TIPSCl (1)	Imidazole	DMF (0.5 M)	rt	41%	47%	12%
2	TIPSCl (1)	Imidazole	DCM (0.1 M)	0 °C	23%	NC	16%
3	TIPSCl (1)	Imidazole, DMAP	DMF (0.05 M)	0 °C	39%	NC	NC
4	TIPSCl (1)	Imidazole, DMAP	DMF (1.0 M)	65 °C	44%	NC	10%
5	TIPSCl (2)	Imidazole	DMF (1.0 M)	65 °C	NO	NO	99%*
6	TIPSCl (2)	DMAP	DMF (1.0 M)	rt	NO	NO	99%*
7	TBDPSCl (1.5)	TEA	THF (0.5 M)	60 °C	NO	99%*	NO
8	TBDPSCl (1)	DIPEA	DMF (0.25 M)	rt	NO	99%*	NO
9	TBSCl (2)	Imidazole	DMF (1.0 M)	rt	NO	NO	85%
10	TIPSOTf (1.5)	2,6-Lutidine	THF (0.5 M)	0 °C	21%	NC	10%
11	TIPSCl (1)	*n*-BuLi	THF (0.1 M)	−78 °C	42%	NC	NC

* Conversion by NMR
NC = not calculated
NO = not observed by crude NMR

One observation we noticed was the large difference between **186** and **191** on TLC (ΔR_f *ca.* 0.3), with **191** being more polar. The solubility was also different as **191** was water soluble. That was likely due to the lack of intramolecular hydrogen bonding between the two alcohols in the cyclic diol as opposed to the ready formation of some in **186**. We decided to attempt the protection reaction on **186**.

Table 4 shows the results of the attempts to monoprotect **186**. Thermodynamic conditions with imidazole and DMAP were unproductive but kinetic deprotonation with *n*-BuLi provided a nearly quantitative conversion of **186** to the desired monoprotected product **193**. With the success of monoprotecting diol **186**, we reinvestigated the RCM reaction.

Table 4. Monoprotection of **186**
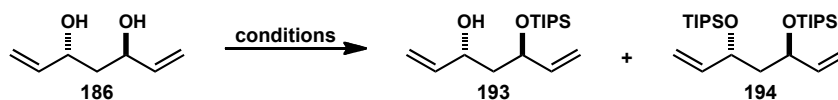
Entry	Silane (equiv)	Base	Solvent	Temp	Yield of 193	Yield of 194
1	TIPSCl (1)	Imidazole	DMF	80 °C	0%	0%
2	TIPSCl (3)	Imidazole, DMAP	DCM	rt	0%	99%*
3	TIPSCl (1.2)	Imidazole, DMAP	DCM	rt	50%*	50%*
4	TIPSOTf	2,6-Lutidine	DCM	0 °C	99%**	-
5	TIPSCl	*n*-BuLi	THF	−78 °C	99%	-

* Conversion by NMR
** Conversion by NMR but not able to be purified

The RCM reaction of **193** to **195** was successful although it occurred in moderate yield. Scheme 55 shows the endgame for the completion of the desired cyclopentenone

(*R*)-**181**. For the RCM, either Grubbs I or Grubbs II worked equally well. An exhaustive

screen of conditions was not conducted. The final step to synthesize the desired

prostaglandin intermediate was an oxidation and we chose pyridinium dichromate (PDC),

which worked well and was simple to run. The workup for the oxidation reaction

required a series of filtrations. Purification by column chromatography was utilized to

remove any residual chromium. MnO_2 has also been shown to achieve this oxidation.[96,104]

The enantiomeric purity was determined to be >98% es by chiral GC analysis. Chiral GC

separation: Astec Chiraldex B-DM fused silica capillary column, 30 m x 0.25 mm x 0.12

µm, temperature gradient from 120 ºC→140 ºC ramping up at 0.25 ºC/min, t_R = 44.13

min, t_S = 45.26 min. Also the optical rotation was measured of (*R*)-**181** to be $[\alpha]_D^{25.2}$ +53.3

(*c* 1.05, MeOH), compared to a literature value of $[\alpha]_D$ −58.8 (*c* 1.05, MeOH) for the

enantiomer.[104]
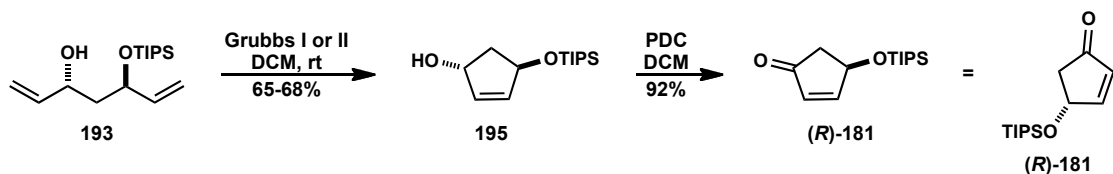
Scheme 55. RCM and oxidation end game

We chose to form the TIPS-protected HCP (*R*)-**181** because we needed the large

steric bulk and stability under Lewis acid conditions for a reaction sequence presented in

Chapter 4. We expect that the sequence could be extended to related protecting groups by

a straight forward modification of the route.

3.4. Conclusion

Herein, we described the novel route to the preparation of (*R*)-**181**. We generated the chirality from a Noyori reduction, which in principle allows synthesis of either the *R* or *S* enantiomer of the product. It was found that first monosilyation and subsequent cyclization gave (*R*)-**181**. The reaction sequence is scalable as most purification can be conducted by distillation or recrystallization. HCP, (*R*)-**181**, could be produced in six steps starting from acetylacetone. This sequence represents the shortest route to the enantiopure material. We utilized this cyclopentenone in an approach toward the total synthesis of (–)-cylindricine C (**3**) as described in Chapter 4.

Chapter 4

Total Synthesis of (–)-Cylindricine C via a Tandem Diels–Alder/Schmidt Reaction

4.1. Diels–Alder/Schmidt Reaction History

As discussed in Chapter 2, the intramolecular Schmidt reaction takes place under Lewis or Brønsted acid conditions. The pairing of the intramolecular Schmidt reaction with other acid-mediated processes, like the Prins reaction was also outlined. In this chapter, the intramolecular Schmidt reaction was performed in tandem with a Diels–Alder reaction to quickly construct a complex tricyclic lactam.

The first example of a tandem Diels–Alder/Schmidt reaction was accomplished in 2002 during a formal synthesis of (±)-stenine (Scheme 56).[76] Scheme 56 outlines the key transformation that converted the triene **196** to the tricyclic lactam **198**. In this sequence, the first step involved a Diels–Alder reaction between the diene and the enone to form bicyclic ketone **197**. The second step involved the intramolecular Schmidt reaction between the ketone and the tethered azide. The order of reactivity was important in these tandem reactions since azides rarely add to the carbonyl of an enone.[105] In this case, the yield represents a single diastereomer; one other diastereomer as well as a regioisomer were also isolated.
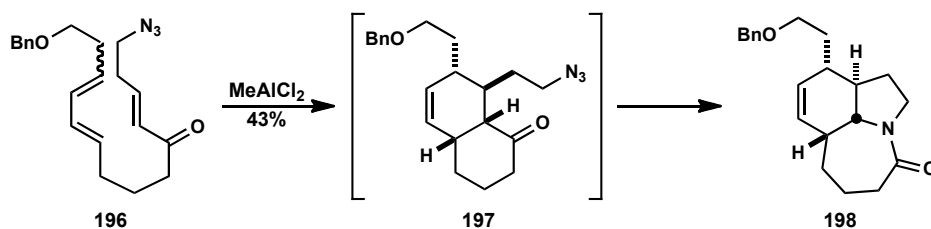
Scheme 56. First tandem Diels–Alder/Schmidt reaction toward the synthesis of stenine

Another variant of this reaction is depicted in Scheme 57. Here, three examples of an intermolecular Diels–Alder reaction in tandem with an intramolecular Schmidt reaction were demonstrated, with variation at the location of the azide tether.[75] In Scheme 57a, the azide was tethered to the β-position of enone **199**. When **199** was combined with 1,3-butadiene under Lewis acid conditions, Diels–Alder adduct **200** was formed, which then underwent an intramolecular Schmidt reaction to form bicycle **201**. In Scheme 57b, where the azide was tethered to the α-position of enone **202**, the Diels–Alder reaction formed intermediate **203**, which underwent the intramolecular Schmidt reaction to form tricycle **204** in 85% yield. This example shows that simple starting materials like **202** and substituted butadienes can quickly form complex structures, like the aza-spirocenter in **204**.

In a third example, the azide tether resides on the diene rather than the enone (Scheme 57c). Diene **205** was combined with 2-cyclopenten-1-one under Lewis acidic conditions to form the Diels–Alder adduct **206**, which underwent an intramolecular Schmidt reaction exclusively on the cyclopentane carbonyl to afford complex tricycle **207**. This type of Diels–Alder/Schmidt reaction was applied to another total synthesis of (±)-stenine[106] and other *Stemona* alkaloids.[107] The Diels–Alder/Schmidt chemistry was further utilized in the synthesis of chemical libraries based on the *Stemona* alkaloids.[108]
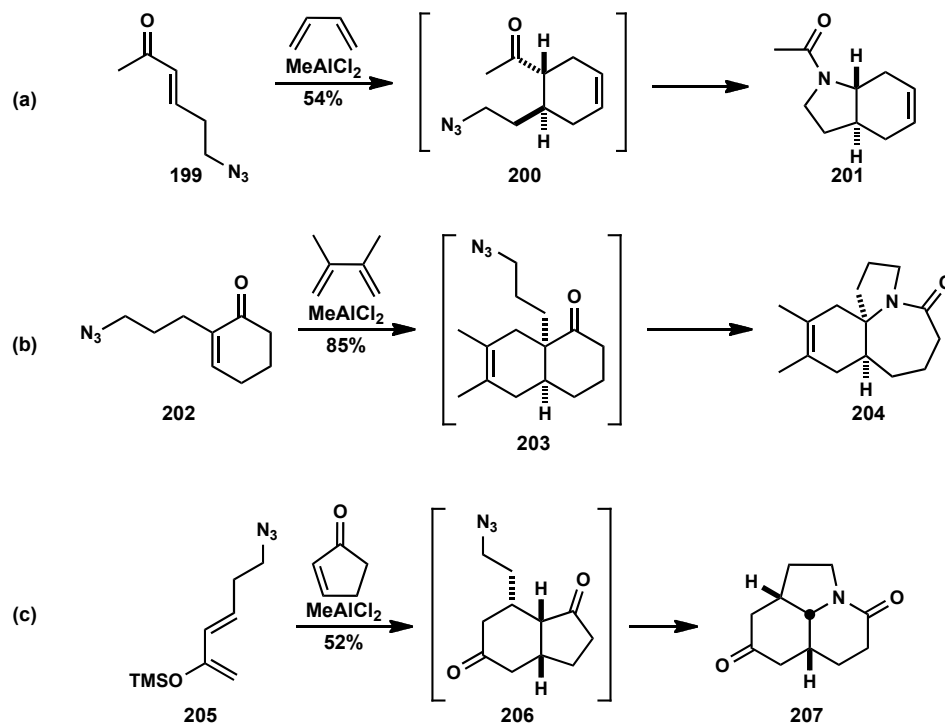
Scheme 57. Examples of intermolecular Diels–Alder/Schmidt reactions

The tandem Diels–Alder/Schmidt reaction has the ability to expeditiously construct a variety of complex bi- and tricyclic lactams. We chose to pursue a total synthesis of (–)-cylindricine C (**3**) using this methodology.

4.2. Retrosynthetic Analysis

Our retrosynthetic analysis is depicted in Scheme 58. We envisioned the final steps of the total synthesis to involve functional group manipulations of **208** that would include reduction and alkylation of the lactam, conversion of the OTIPS group to a ketone, and a hydrogenation to accomplish both reduction of the cyclohexene and hydrogenolysis of the benzyl group. We anticipated **208** to arise from our key reaction, a tandem Diels–Alder/Schmidt reaction, between **210** and 1,3-butadiene that reacts through **209**. Since we planned to conduct an asymmetric synthesis, we intended to construct **210** in enantiomerically pure form.

When considering the construction of **210**, we sought to unite (*R*)-**181** with either (*S*)-**211** or (*R*)-**212**. We knew (*R*)-**181** could be prepared in enantiomerically pure form from the methodology discussed in Chapter 3 and we chose the TIPS-protected variant to provide the maximum steric effect during the Diels–Alder reaction. In addition, we thought that a robust, bulky protecting group would have the best chance of surviving treatment with strong Lewis acid treatment. We wanted a convergent route to append the alkyl portion to the silyl-protected 4-hydroxy-2-cyclopenten-1-one (HCP). This would involve uniting an azide coupling partner (*R*)-**181** with (*R*)-**212** using either a Mukaiyama aldol or a Baylis–Hillman reaction. Alternatively, we could combine (*R*)-**181** with (*S*)-**211** through a Suzuki-Miyaura coupling. The azide could not be used in the Suzuki-Miyaura coupling because an allylic azide continuously undergoes a [3,3]-sigmatropic rearrangement at room temperature and therefore the preinstalled stereochemistry at that center would be stereoablated. The most convergent route would involve adding in a

synthon with the azide installed. Therefore, we began our investigation by attempting to combine (R)-**181** with (R)-**212**.
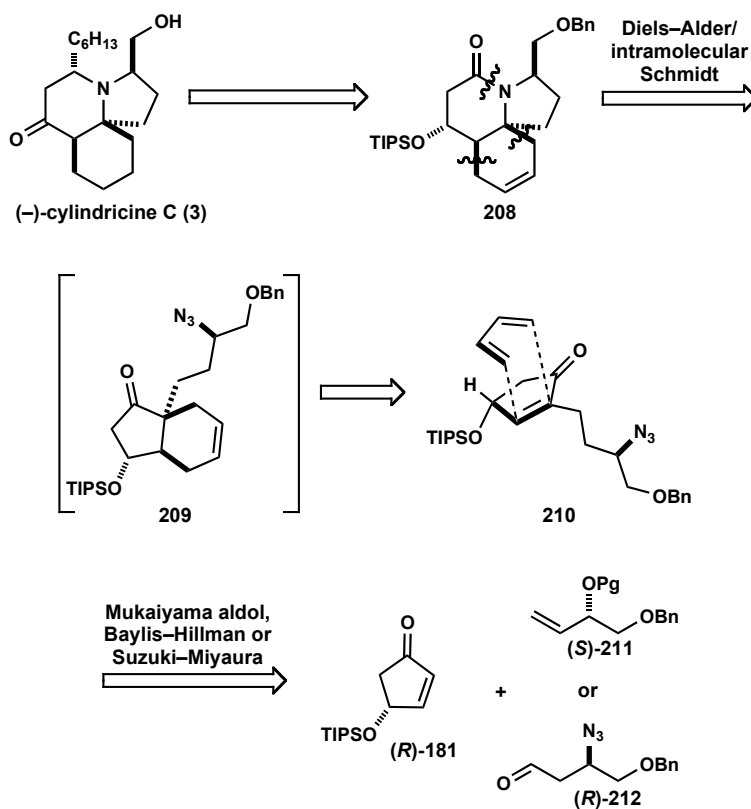
Scheme 58. Retrosynthesis of (–)-cylindricine C (**3**)

4.3. Preparing the Azide for the Key Reaction

4.3.1. Racemic Starting Materials

Our initial methodology development was conducted on racemic compounds, as they were easier and cheaper to make. We prepared racemic **181** from furfuryl alcohol following a procedure by Curran and coworkers as shown in Scheme 59.[109] Furfuryl alcohol was treated with aqueous potassium dihydrogen phophate (KH_2PO_4) in a buffered solution with a pH of 4.1, which isomerized the furfuryl alcohol to **213** after heating. Also included in the Curran paper were results on the hydroxyl protection by a variety of protecting groups; TIPS was not one of the protecting groups discussed. Since we desired the TIPS-protected HCP, we tried multiple conditions using either TIPSCl or TIPSOTf and in both cases, the yields were between 0-20%. Although **213** could be made in 10 g batches, the disappointing yield of the TIPS protection led us to look elsewhere for a preparation of racemic **181**.
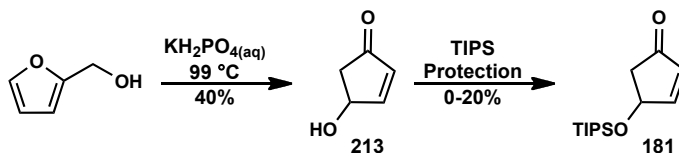
Scheme 59. Furfuryl alcohol approach to racemic HCP

Since we wanted to prepare **181** in large quantities, we opted for the well-known procedure of Deardorff *et. al.* to prepare **179** (Scheme 60).[94] From there, using procedures from Gracias and coworkers developed in our lab, we formed racemic **180**.[104]

Treatment of **180** with K_2CO_3 and methanol formed **214**. Subsequent oxidation with PDC, as done in Chapter 3, provided **181** in good overall yield and sufficient quantities.
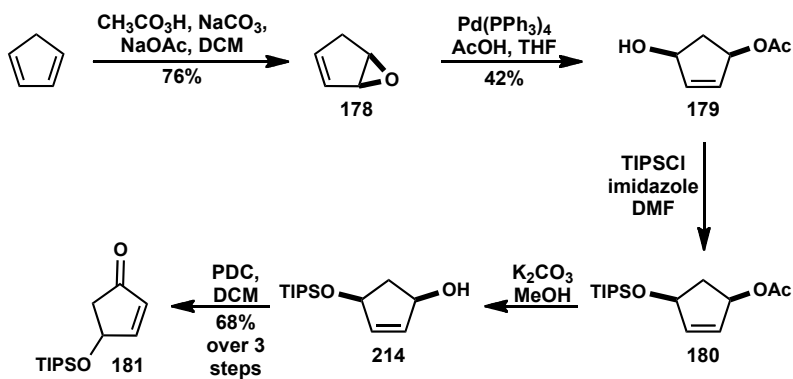
Scheme 60. Preparation of (±)-**181**

4.3.2. Mukaiyama Aldol Approach

With **181** in hand, we set out to investigate a Mukaiyama aldol approach to prepare **210**. We intended to follow a similar procedure to that used in a formal synthesis of (–)-lasubine accomplished in our lab.[104] We sought to convert **215** to **218** according to the reaction sequence shown in Scheme 61. Mukaiyama aldol addition to **212** should afford **216** and subsequent dehydration would result in **217**. We strongly desired the aldol addition and dehydration to occur in one pot for step economy, but we planned on investigating both one- and two-step processes. Finally, we anticipated isomerizing the double bond in **217** inside the cyclopentane ring to ultimately generate **218**, our targeted intermediate for our key reaction.
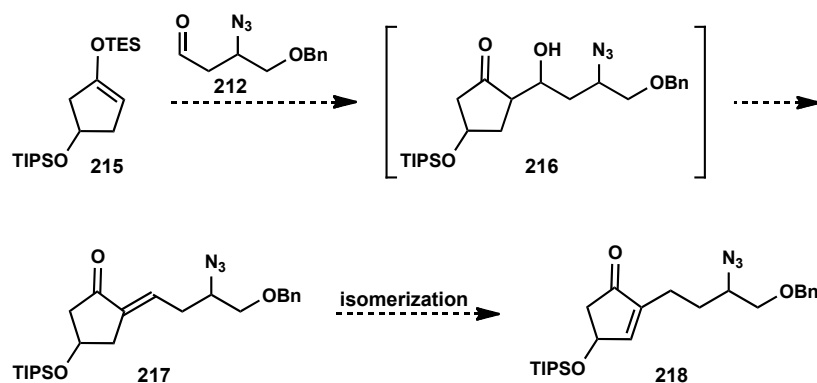
Scheme 61. Desired Mukaiyama aldol approach

Before we could begin our investigation, we needed to regioselectively prepare the silyl enol ether. As depicted in Scheme 62, we used Karstedt's catalyst to achieve the silyl enol ether formation to make **215**.[104] Karstedt's catalyst is a divinyltetramethyl-disiloxane complex that, in the presence of triethylsilane (TES), converts an enone to a

silyl enol ether by delivering a hydride to the β-carbon of the enone and trapping the resulting enolate in a regioselective manner.

We then attempted to adjoin **215** to 3-azidopropanal. To our disappointment, the best result obtained was 28% (Scheme 62). We tried a one-pot aldol addition/dehydration reaction, but under all conditions tried, including TiCl₄, TMSOTf, and TsOH, we never observed any trace of the desired product. One potential problem could have been the instability of azides to high temperature required for dehydration reactions. Without any promising results, we opted to change our strategy.
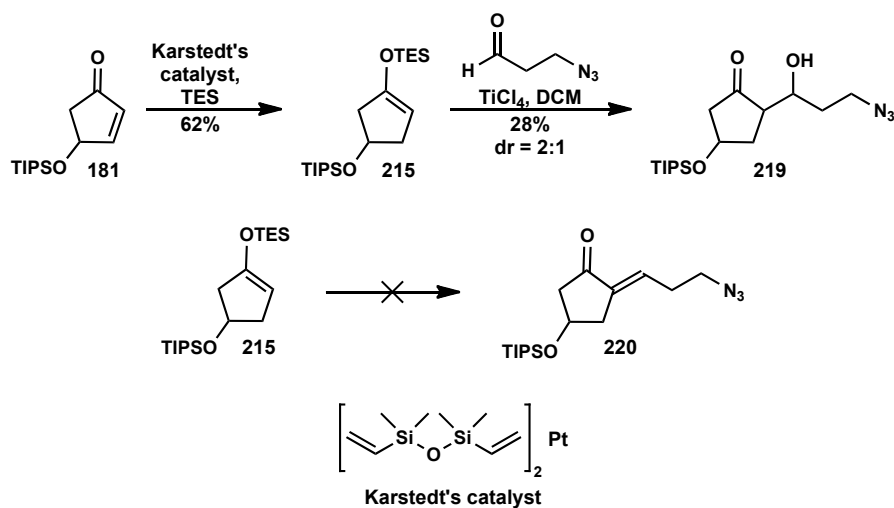
Scheme 62. Mukaiyama aldol attempts

4.3.3. Baylis–Hillman Approach

The next reaction type we investigated involved the Baylis–Hillman reaction approach (Scheme 63). We envisioned **181** adding into aldehyde **212** to form **221**. Two benefits of this process over the Mukaiyama aldol approach included (1) directly using **181** instead of requiring an oxidation state adjustment like **215**, and (2) forming the double bond in the desired location directly without requiring isomerization. However, the hydroxyl group formed in **221** would need to be removed in order to form **218**. Since the azide could be installed prior to the Baylis–Hillman reaction, this route was still convergent and could theoretically afford the desired intermediate **218** quickly.
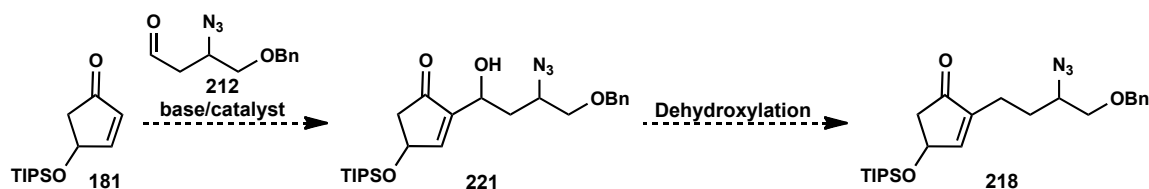
Scheme 63. Baylis–Hillman approach

We began our investigation of the Baylis–Hillman with a simple model study involving the reaction of 2-cyclopenten-1-one with 3-azidopropanal. Table 5 lists the results of the model study. Initially, we attempted the reaction only on 2-cyclopenten-1-one and 3-azidopropanal and obtained no positive results. As a control, we repeated the results on benzaldehyde, a non-enolizable aldehyde known to undergo Baylis–Hillman reactions. Under some of the conditions investigated, the benzaldehyde reaction partner produced positive results, but we did not observe formation of an adduct between 2-

cyclopenten-1-one and 3-azidopropanal under any conditions investigated. A variety of

bases and solvent systems were investigated, but nothing worked as desired. At that

point, we opted to change strategies again.

Table 5. Baylis–Hillman reaction results
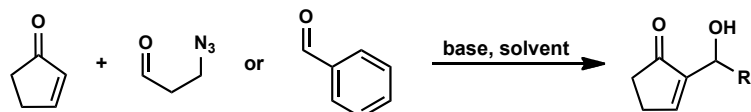
Aldehyde	Base	Solvent	Desired product
azide	**PBu$_3$**	3:1 CHCl$_3$/MeOH	No
azide	**PBu$_3$**	7:3 THF/H$_2$O	No
benzaldehyde	**PBu$_3$**	3:1 CHCl$_3$/MeOH	No
benzaldehyde	**PBu$_3$**	7:3 THF/H$_2$O	Yes
azide	**DBU**	7:3 THF/H$_2$O	No
benzaldehyde	**DBU**	7:3 THF/H$_2$O	Yes
azide	TMEDA	7:3 THF/H$_2$O	No
benzaldehyde	TMEDA	7:3 THF/H$_2$O	No
azide	DABCO	3:1 CHCl$_3$/MeOH	No
benzaldehyde	DABCO	3:1 CHCl$_3$/MeOH	No
azide	imidazole	7:3 THF/H$_2$O	No
benzaldehyde	imidazole	7:3 THF/H$_2$O	Yes
azide	DMAP	3:1 CHCl$_3$/MeOH	No
benzaldehyde	DMAP	3:1 CHCl$_3$/MeOH	No

4.3.4. Suzuki–Miyaura Approach

We next investigated an approach based on the Suzuki–Miyaura reaction. Similar reactions have been published by Johnson and coworkers in syntheses of prostaglandins that involved 2-iodo-2-cyclopenten-1-ones (Scheme 64).[92,110] In one example, 4-benzyloxy-1-butene (**223**) was treated with 9-borabicyclo(3.3.1)nonane (9-BBN) to hydroborate the alkene and form the borane needed for the coupling reaction. Separately, **222** was combined with the palladium catalyst followed by the borane solution and then an aqueous base solution of potassium phosphate. The Suzuki–Miyaura reaction produced **224**, resulting from an sp^2-sp^3 coupling that was similar to our desired transformation.
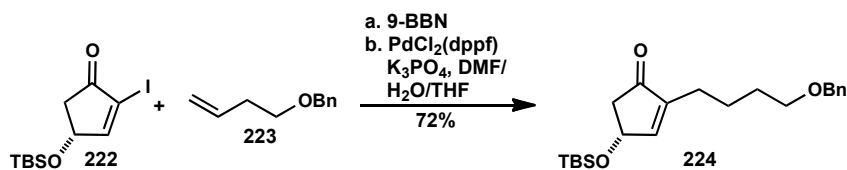
Scheme 64. Johnson precedent[92]

The coupling reaction we hoped to achieve is outlined in Scheme 65. Beginning with (*S*)-**211**, hydroboration with 9-BBN would form borane **227**. In parallel, the palladium(II) catalyst would be reduced to Pd(0) *in situ*, and would then undergo oxidative addition into the carbon-iodide bond of (*R*)-**225** to form intermediate **226**. Then, the borane would react with water to form the borate **227**, which would undergo transmetallation with the palladium species **226** to form **228**. Reductive elimination of the palladium should regenerate the Pd(0) catalyst and form the desired product, **229**. From

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229, we figured a simple deprotection of the hydroxyl group and conversion to the azide would form **210**, given an appropriate protecting group for the alcohol. Before we began work on the completely functionalized system, we investigated a model system.
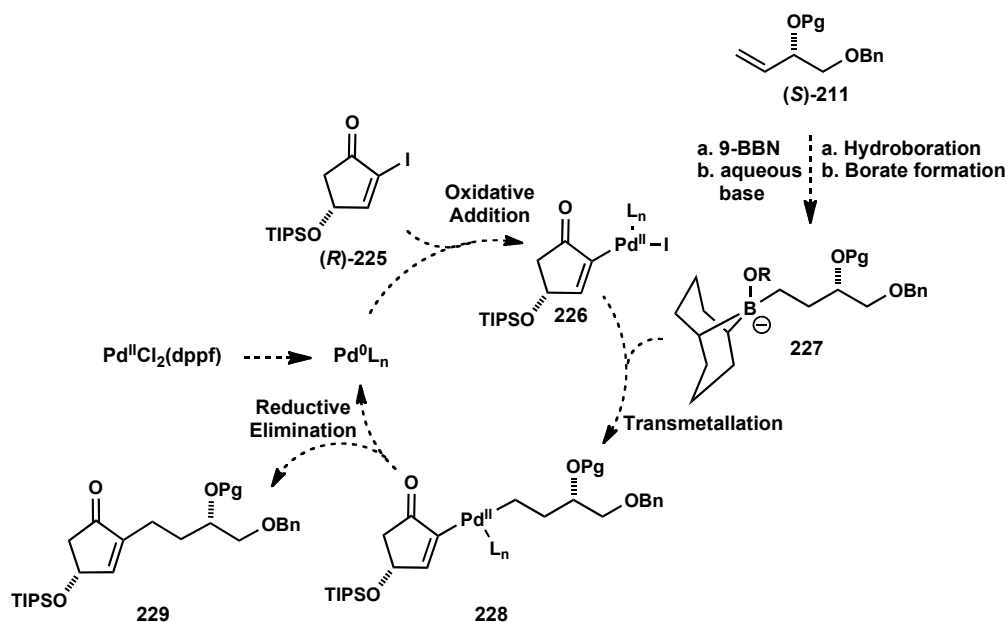
Scheme 65. Catalytic cycle for desired Suzuki-Miyaura coupling

The initial step was investigated as shown in Scheme 66. We first wanted to develop conditions for the hydroboration reaction because the borane would be prepared *in situ* for the coupling reaction. We first treated allyl alcohol with 1.2 equiv of 9-BBN in a 0.5 M solution of THF, Scheme 66a. The reaction was stirred at room temperature for 12 h and then heated to 60 °C for three hours, but only starting material was recovered. We then attempted the reaction on commercially available allyl *tert*-butyldimethylsilyl ether under the same conditions, Scheme 66b, and again, no hydroboration was observed. The reaction concentration was increased, Scheme 66c, and still no reaction was observed. Finally, the 9-BBN solution was added to the neat alkene, Scheme 66d, and

after 12 h at rt all of the alkene was consumed as determined by NMR analysis of the crude reaction mixture. The neat conditions were also tried on commercially available allyl acetate with successful hydroboration reactivity. From this set of experiments, we determined it was necessary to carry out the hydroboration without adding solvent beyond that already present in the 9-BBN reagent.
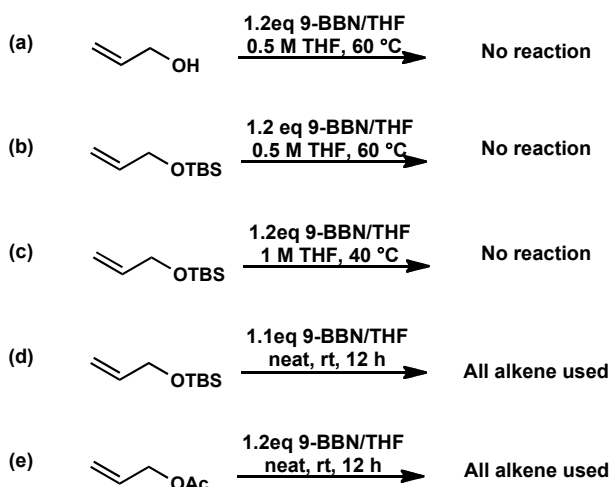
Scheme 66. Hydroboration investigation

Next, we attempted incorporating the hydroboration step using 2-iodo-2-cyclopenten-1-one, **230**, prepared from iodination of 2-cyclopenten-1-one following a procedure from Krafft and coworkers.[111] Scheme 67 depicts the initial attempts at the Suzuki–Miyaura reaction using allyl *tert*-butyldimethylsilyl ether and **230**. Having figured out the hydroboration step, we could do a controlled study of the actual coupling conditions. We chose [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (PdCl$_2$(dppf)) as the catalyst as this is the catalyst used by Johnson and coworkers for a similar type of sp^2-sp^3 coupling.[92] Different bases were tried, including NaOH, Cs$_2$CO$_3$,

and K_3PO_4. A variety of different solvents and solvent mixtures of water, DCM, DMF, and THF were investigated. A range of temperatures was tried, including rt, 40 °C, 60 °C and 75 °C. The reaction was ran with and without triphenylarsine as an additive. All of these reactions were attempted with **230** as the limiting reagent with the alkene equivalents ranging from 1.1 to 5. For all the reactions tried, no more than a trace amount of the coupled product was observed.
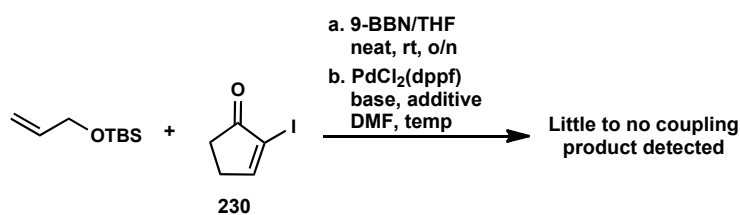
Scheme 67. Unsatisfactory coupling results

Next tried was to switch the limiting reagent to the alkene in the presence of 1.5 equiv of **230** (Scheme 68). This was not a desirable change because in the functionalized system the cyclopentenone component was the most difficult to make. However, we obtained the desired product **231** in 60% yield using 3 M K_3PO_4 as the base and with no additive. We also attempted the reaction on allyl acetate for comparison of the protecting groups and formed **232**, albeit at a lesser yield of 33%.
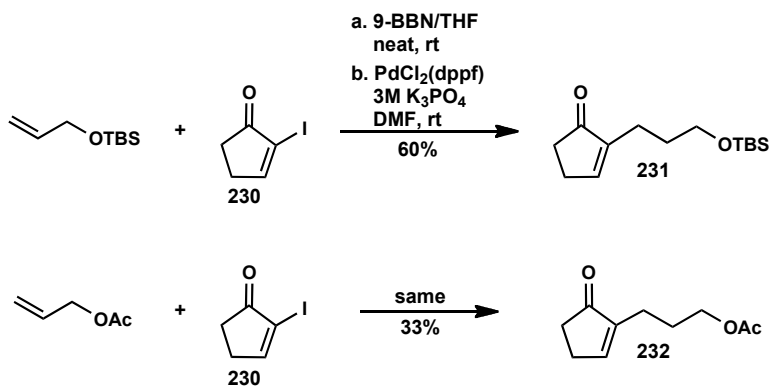
Scheme 68. Successful coupling results

With the success of the Suzuki–Miyaura reaction on a model system, we sought to incorporate more functionalization and work up to the fully-functionalized reaction in a systematic manner. Shown in Scheme 69 is the coupling reaction with the functionalized cyclopentenone, **225**, which was prepared from **181** with iodine and pyridine (pyr) in ether. The coupling of **225** with allyl *tert*-butyldimethylsilyl ether achieved the desired product **233** in 55% yield. This was significant because the TIPS group is large and it was reassuring to know that steric hindrance did not decrease the reactivity.
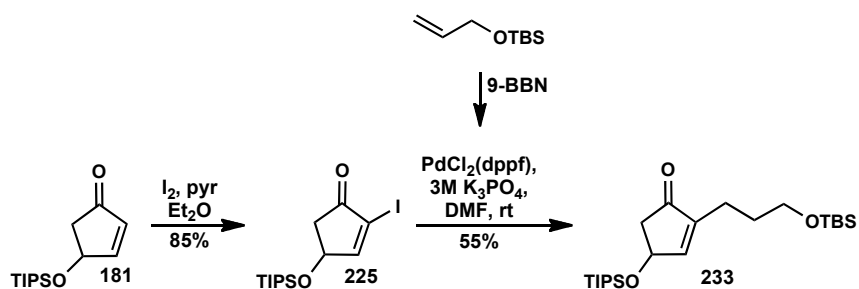
Scheme 69. Suzuki–Miyaura reaction with **225**

Before attempting to prepare the completely functionalized system, we did one more model study, in which 2-cyclopenten-1-one was treated with the 3,4-dihydroxy-1-butene synthon. Scheme 70 shows the preparation of racemic 4-benzyloxy-3-hydroxy-1-butene, **234**, from benzyloxyacetaldehyde using vinylmagnesium bromide, a reaction developed by Ghosh and coworkers.[112] With **234** in hand, we began to investigate the Suzuki–Miyaura coupling reaction with 2-cyclopenten-1-one.
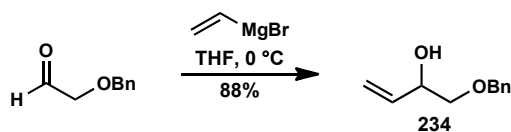
Scheme 70. Formation of 4-benzyloxy-3-hydroxy-1-butene

As depicted in Scheme 71, we used a variety of different protecting groups on the secondary hydroxyl group on **234**. We initially attempted to couple **234** with **230**, but no coupling product was detected using 1.2 equiv of 9-BBN. This was a slight obstacle because in order to accomplish the coupling, a third protecting group (TIPS and Bn being the other two) was going to be needed. Ideally we wanted an easily removed protecting group to ensure that the TIPS group remained in place. The first group we tried was a TMS protecting group, shown in Scheme 71, because it is labile and could be easily removed in a workup step and would not add steps to the linear sequence. We converted **234** to **235** by treatment with TMSCl and TEA in THF. We submitted the TMS-protected allylic alcohol with 2-cyclopenten-1-one to Suzuki–Miyaura conditions to determine if coupling could be achieved. NMR analysis of the crude reaction mixture indicated no

coupling had occurred and the TMS group was removed. Obviously, this was not going to be a productive pathway, so we moved on to a different protecting group.

The next protecting group we tried was a triethylsilane (TES) group (Scheme 71). The TES group is slightly more stable than the TMS group but can still be easily removed under mild acidic conditions. The conversion of **234** to **236** was performed using TESCl and pyridine in DCM. Silyl alcohol **236** was treated with the same coupling conditions as described in schemes 68, 69 and 71. Crude reaction analysis by NMR also indicated no coupling product and the TES group was again removed.

Continuing on, we moved away from a silyl protecting group and tried an acetate. Scheme 71c shows the protection of **234** under standard conditions of Ac$_2$O, pyridine and catalytic dimethylaminopyridine (DMAP) in DCM to form **237**. Under the same reaction conditions, we combined **237** with **230** and unfortunately the same results as in (a) and (b) were observed: no coupling product was observed and the acetate group was removed. Clearly, the basic conditions required for the Suzuki–Miyaura reaction were removing the protecting groups tried. Our strategy needed to be modified to use a much more robust protecting group that could survive the basic conditions.

Shown in Scheme 71, we opted for a TBS group because we knew it worked in the previous examples done on simpler systems (Schemes 68 and 69), despite the likelihood that removing it would a step instead of just using a workup. Also, we were not confident about the selective deprotection of the secondary acyclic OTBS in the presence of the secondary cyclic OTIPS group. Nonetheless, we moved forward anyway because we were most concerned with accomplishing the coupling reaction. We prepared **238** from **234** using TBSCl and imidazole in DMF following a procedure from Yadav

and coworkers.[113] With **238** in hand, we proceeded with the Suzuki–Miyaura reaction using the conditions developed and isolated the coupled product **239**. With this coupling result accomplished, the next step was to attempt the coupling on the fully-functionalized system. However, before we committed to the idea of needing the third protecting group, we tried one more option.
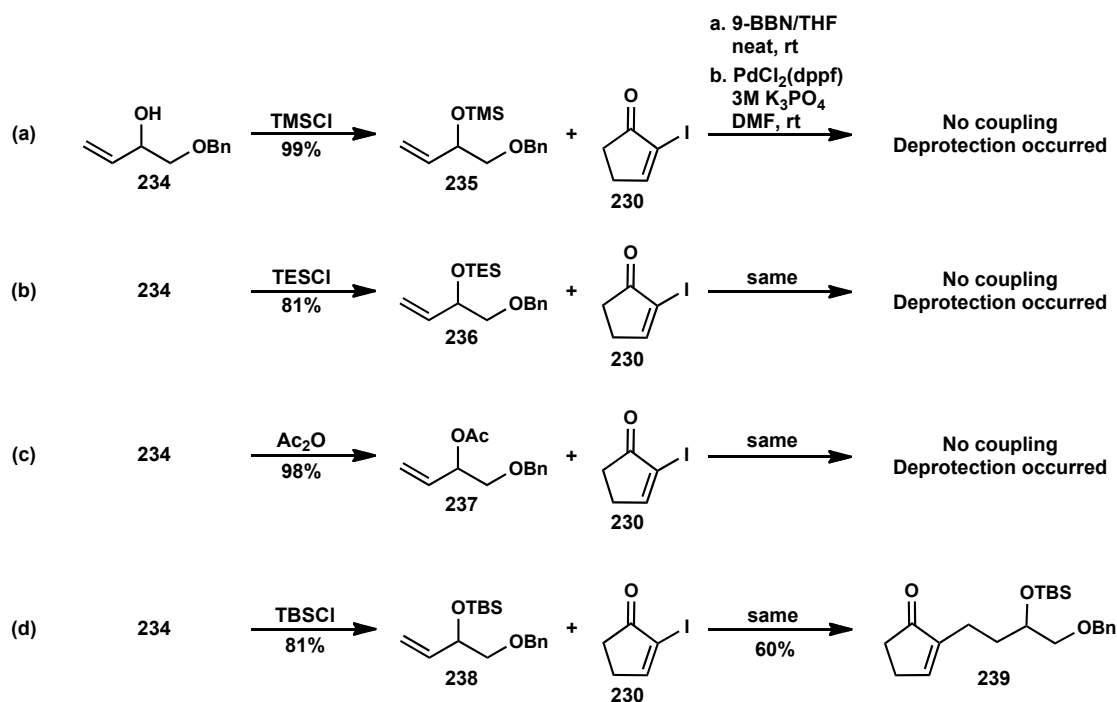
Scheme 71. Suzuki–Miyaura reaction with functionalized alkene

Perhaps instead of protecting the two alcohols of the alkene synthon separately, we could protect them as one. We looked into the possibility of using a benzylidene protecting group on the 3,4-dihydroxybutene (Scheme 72). 3,4-Dihydroxybutene could be protected with benzaldehyde to form **240** following a procedure by Buono and coworkers.[114] Suzuki–Miyaura coupling with **225** would afford **241** and a single hydride-

mediated reduction would unveil **242**. The alcohol in **242** could then be converted to the desired azide **218** in one or two steps. Another attribute of **242** is the terminal benzyloxy group, which we desired because it could be removed in the last step along with the hydrogenation of an alkene and would not require a separate step to be removed (Section 4.2).
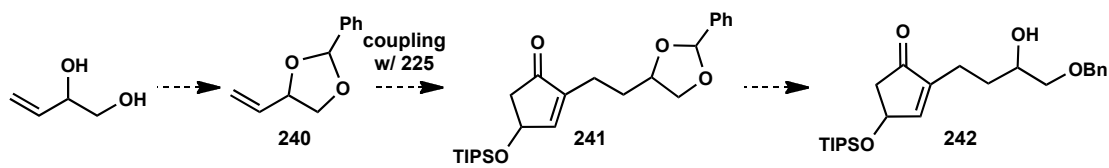
Scheme 72. Benzylidene protecting group idea

Accordingly, we prepared **240** following literature precedent, albeit at a dismal yield that moreover seemed to be irreproducible (Scheme 73).[114] However, with some **240** to work with, we attempted the coupling reaction under the standard conditions with **230**, which afforded **243** in good yield. However, when we took this reaction one step further to attempt the monodeprotection with diisobutylaluminum hydride (DIBAL),[114] the carbonyl was reduced rather than the benzylidene to form **244**. With the disappointing reduction result and the difficulty to reproduce **240**, we abandoned this approach and returned to the TBS protection strategy.
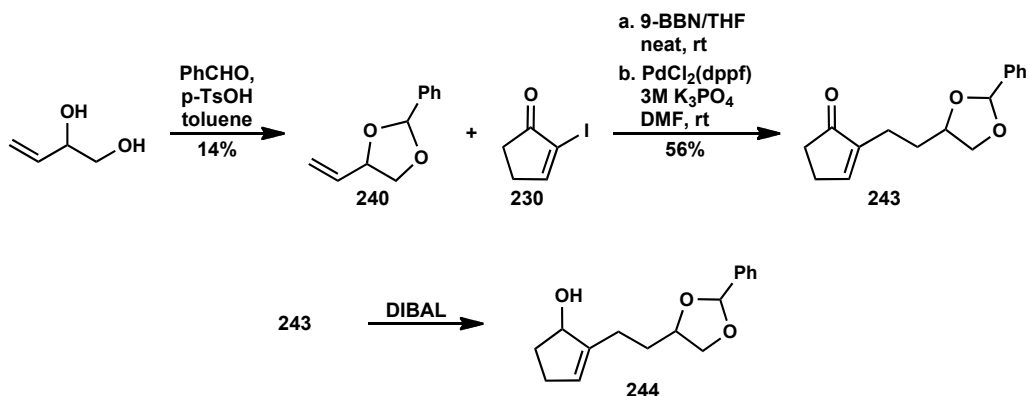
Scheme 73. Benzylidene protecting group attempt

Since other protecting groups were unpromising, a TBS protecting group was examined. Pleasingly, when we combined **238** and **225**, we not only achieved the desired coupling product **245**, but also in a high yield of 70%, in a 1:1 a mixture of diastereomers (Scheme 74). We were not concerned with the diastereomeric mixture at this point because for the total synthesis, we would be coupling together enantiomerically pure materials. With the coupling step worked out, we could move forward with the total synthesis.
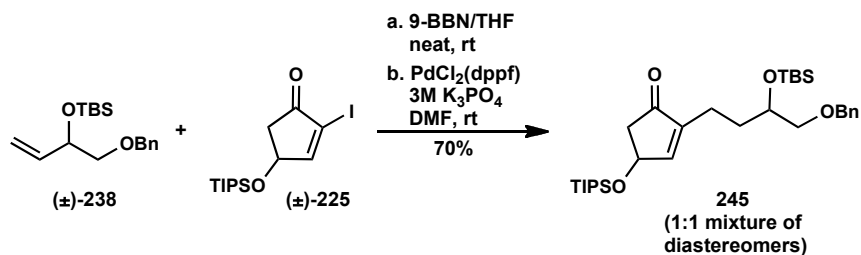
Scheme 74. Suzuki–Miyaura reaction for functionalized system

4.3.5. Conversion to Desired Azide

In order to begin investigation on the tandem Diels–Alder/Schmidt reaction, we first needed to deprotect the silyl ether of **245** to afford alcohol **242**. We felt this should be a straightforward deprotection as a TBS is known to be deprotected faster than a TIPS group under acidic, basic and fluoride conditions.[115] As depicted in Scheme 75, we first tried deprotection using 1% HCl in ethanol. We achieved the selective deprotection in a 70% yield to afford **242** as a 1:1 mixture of diastereomers but we were hoping for a better result. When we tried the deprotection under basic conditions of 5% NaOH in EtOH (Scheme 75), the result was a messy mixture of products. We finally tried deprotection with TBAF (Scheme 75) and observed solely the selective deprotection of the TIPS group, **246**. Therefore we returned to acidic conditions; when pyridinium *p*-toluenesulfonate (PPTS) was used, we received similar yields to the HCl conditions, however, they were much more reproducible. A byproduct we noticed from these reactions resulted from conjugate addition of the alcohol onto the cyclopentenone. Accepting these conditions and yields as sufficient, we moved on to conversion of the alcohol to the azide.

Scheme 75. Removal of TBS protecting group

With **242** in hand, we next sought to convert the free hydroxyl group to the azide functionality. Initially we wanted to achieve this transformation in a one-step procedure for step economy, which can be accomplished with diphenylphosphoryl azide (DPPA). However, under a variety of conditions, using DPPA, a 44% yield was the maximum achieved. Although one step is good for step economy, a 44% yield would be a large material depletion at this stage in the synthesis.

To improve the yield, we tried a two-step sequence to convert the alcohol to the azide (Scheme 76). First, **242** was treated with methanesulfonyl chloride (MsCl) and TEA to mesylate the hydroxyl group, **247**. In the second step, we treated the mesylate with sodium azide (NaN$_3$) and DMSO. Both steps in Scheme 76 followed a procedure from Molander and coworkers.[26] Mesylate **247** was converted with ease to **218** in a two-step yield of 98%. Therefore, although there are two steps to convert the alcohol to the azide, the yield is almost quantitative. Also, no purification was needed between the two steps as both of the reactions were clean.

Scheme 76. Conversion to the desired azide

4.4. Diels–Alder/Schmidt Reaction

Prior to accessing **218**, we were able to synthesize tethered azides on the model systems. Shown in Scheme 77, compound **231** was deprotected to alcohol **248** with TBAF although the yield was poor. The spectral data for **248** matched that in the literature.[116] We subsequently converted the alcohol **248** to azide **249** using DPPA; the spectral data matched the literature values.[77] With **249** in hand, we were able to attempt the Diels–Alder/Schmidt reaction. Using a procedure previously published by this group, this involved bubbling gaseous 1,3-butadiene through a solution of the azide in 0.1 M DCM at 0 °C.[75] The solution was then treated with methylaluminum dichloride. After the reaction was stirred at 0 °C and allowed to warm up to room temperature, most of the solution became a solid mass as the butadiene polymerized. In order to attempt extracting the reaction, the solid gelatinous mass was ground up in a mortar and pestle with sand. This allowed for some release of any non-polymeric molecules from the solid matrix. The ground up solid was extracted with DCM and filtered. We tried the reaction again using a much more dilute concentration of 0.025 M and we were able to avoid the gelatinous mass and isolate the desired product, **250**, in 63% yield.
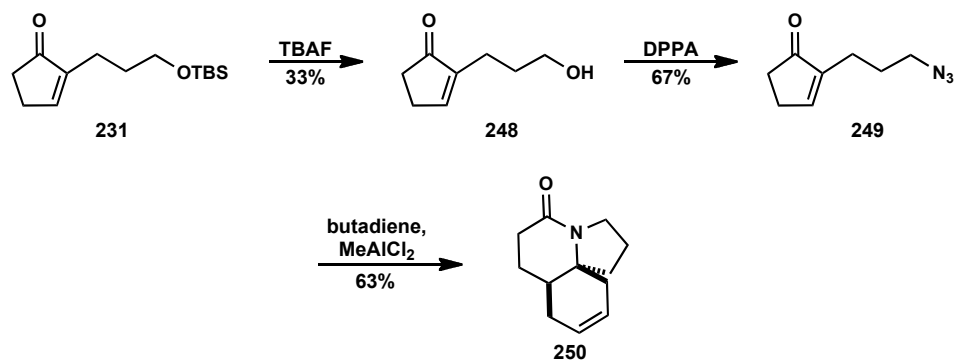
Scheme 77. Diels–Alder/Schmidt reaction on basic model system

With the result shown in Scheme 77, we were confident about the tandem Diels–Alder/Schmidt reaction on the fully functionalized system (Scheme 78). We used the same conditions as for the unfunctionalized system except we used a solution of 1,3-butadiene instead of bubbling gaseous butadiene, which allowed for more control over the number of equivalents used in order to avoid any gelatin formation. From **218**, we achieved the formation of **251** in 71% yield. An interesting outcome of the reaction was that two diastereomers of **218** went into the reaction and two diastereomers came out in a near 1:1 ratio. This confirms that the Diels–Alder reaction is facially selective, with addition to one side of the cyclopentenone as the other face is blocked by the allylic silyl ether.
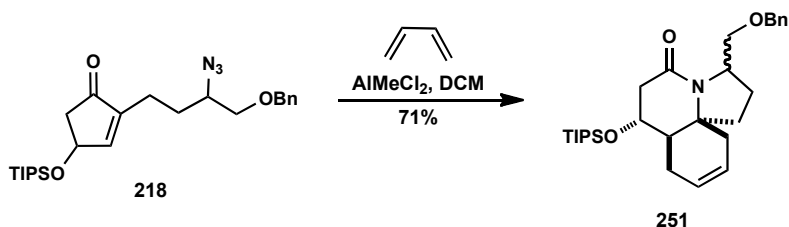
Scheme 78. Diels–Alder/Schmidt reaction on functionalized system

4.5. Enantiomerically Pure Synthesis Toward (–)-Cylindricine C

Our asymmetric synthesis begins with the starting material described in Chapter 3, (*R*)-**181**, which was converted to iodide (*R*)-**225** as shown in Scheme 69. The asymmetric alkene used in the Suzuki–Miyaura reaction was prepared from (*R*)-(+)-glycidol (Scheme 79), which was treated with sodium hydride (NaH) and benzyl bromide (BnBr) to form (*R*)-**252**. Homologation of (*R*)-**252** using a Corey-Chaykovsky reaction with trimethylsulfonium iodide and *n*-BuLi afforded (*S*)-**234** in excellent yield.[117] At this stage, analysis of the enantiopurity was >98% es determined by chiral GC analysis. Chiral GC separation: Astec Chiraldex B-DM fused silica capillary column, 30 m x 0.25 mm x 0.12 μm, isothermal temperature of 115 °C, t_S = 42.39 min, t_R = 43.60 min. Also, an optical rotation was determined of $[\alpha]_D^{24.7}$ −3.3 (*c* 1.6, CHCl$_3$), compared to the literature value of $[\alpha]_D$ +6.2 (*c* 1.6, CHCl$_3$) of the enantiomer.[113] From (*S*)-**234**, protection with a TBS group formed (*S*)-**238**, the alkene synthon in the Suzuki–Miyaura coupling reaction. Although (*R*)-**238** is a known compound in the literature, the optical rotation was not reported. We determined the optical rotation for (*S*)-**238** to be $[\alpha]_D^{24.4}$ −17.0 (*c* 1.17, CHCl$_3$).
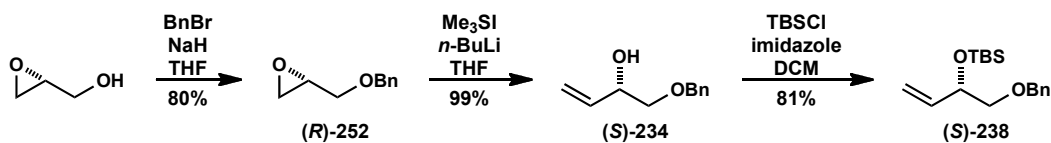
Scheme 79. Preparation of (*S*)-**238**

With the two synthons for the coupling reaction in hand and in enantiomerically-pure form, we progressed with the coupling. Scheme 80 shows the results of the coupling reaction between (*S*)-**238** and *(R)*-**225** to afford *(R,S)*-**245** in 88% yield. PPTS was used to remove the TBS group to form *(R,S)*-**242**. The hydroxyl group was quantitatively converted to the azide with inversion of configuration, *(R,R)*-**218**. The tandem Diels–Alder/Schmidt reaction occurred in good yield to ultimately form a single diastereomer of **251**. From here, we envisioned only a couple more steps to complete the total synthesis.
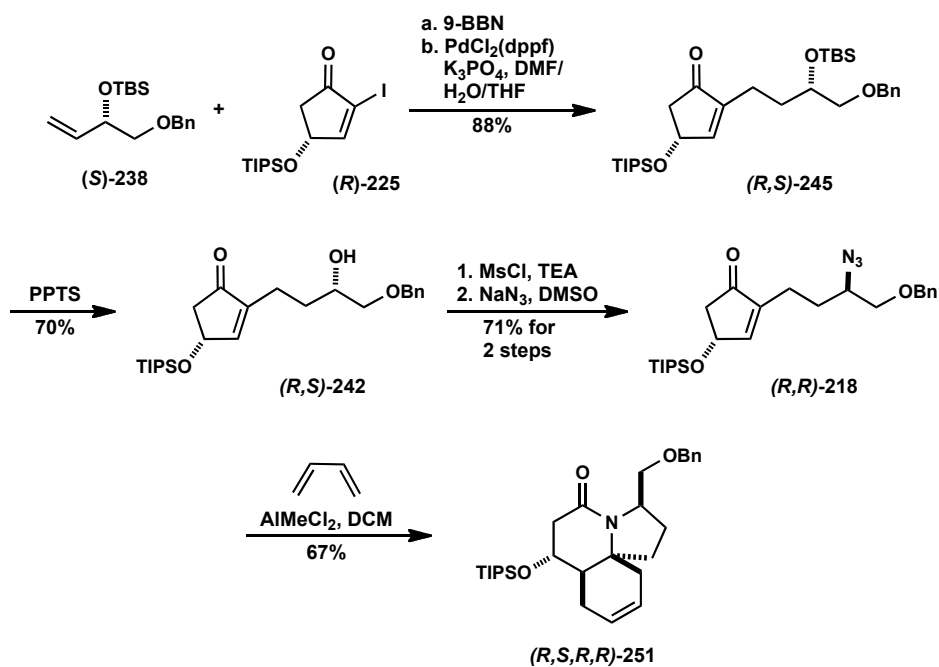
Scheme 80. Asymmetric tricyclic lactam construction

4.6. Final Approach

Our initial attempts to complete the synthesis of (–)-cylindricine C (**3**) are depicted in Scheme 81. From (*4R,5R,10S,13R*)-**251**, we intended to functionalize the lactam by hexylmagnesium bromide addition followed by a hydride to form tertiary amine (*2S,4R,5R,10S,13R*)-**254**. We envisioned the desired stereochemical outcome to result from a hydride delivery to the iminium **253** as shown because there seem to be less diaxial interactions from the face of the cyclohexene. From **254**, removal of the TIPS group and oxidation of the unveiled hydroxyl group would complete the installation of the distal carbonyl, **255**. The last step would be a global hydrogenation to saturate the alkene and hydrogenolysis to complete the total synthesis.
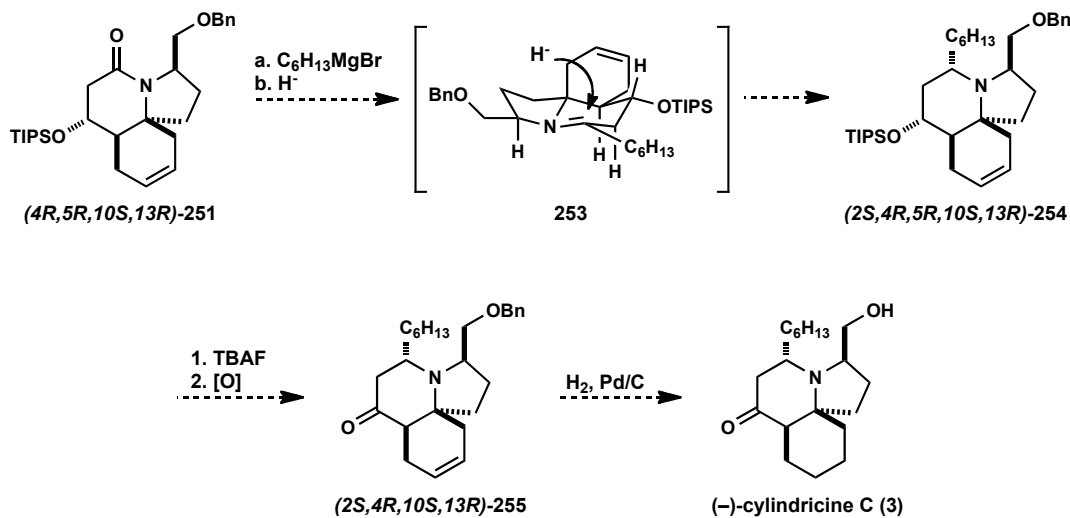
Scheme 81. Proposed end game

Scheme 82 shows the attempts at functionalizing the lactam. Scheme 82a represents the results of multiple reactions where hexylmagnesium bromide was added to

251 along with a hydride source. Although the order of addition was tried both ways between the Grignard and the hydride source, the results were either **256** or **257**. These results are unsatisfactory because the hydroxyl was necessary for the installation of the carbonyl.

The addition of an alkynyl lithiate was then attempted (Scheme 82b), used because it is small and linear.[23] However, only **256** was observed as before. Scheme 82c utilizes triflic anhydride (Tf$_2$O) to first activate the amide for hydride addition followed by Grignard addition but again, only **256** was observed from the crude reaction mixture.[118] In Scheme 82d we tried using Schwartz's reagent following a precedent by Spletstoser *et. al.*,[119] however, no reaction occurred. Scheme 82e represents what happened when LAH was added: complete reduction of the lactam and hydroxy group occurred to form **258**.

Unfortunately, nothing we tried produced the outcome we were looking for. In order to complete this total synthesis, further investigation into the lactam functionalization will be necessary.

(a) **(4R,5R,10S,13R)-251** → a. C₆H₁₃MgBr / b. DIBAL → **256** or **257**

(b) **(4R,5R,10S,13R)-251** → Li—≡—C₄H₉ → **256**

(c) **(4R,5R,10S,13R)-251** → a. Tf₂O, DTBMP / b. DIBAL / c. HexylMgBr → **256**

(d) **(4R,5R,10S,13R)-251** → a. Cp₂ZrCl(H) / b. HexylMgBr → No Reaction

(e) **(4R,5R,10S,13R)-251** → LAH → **258**
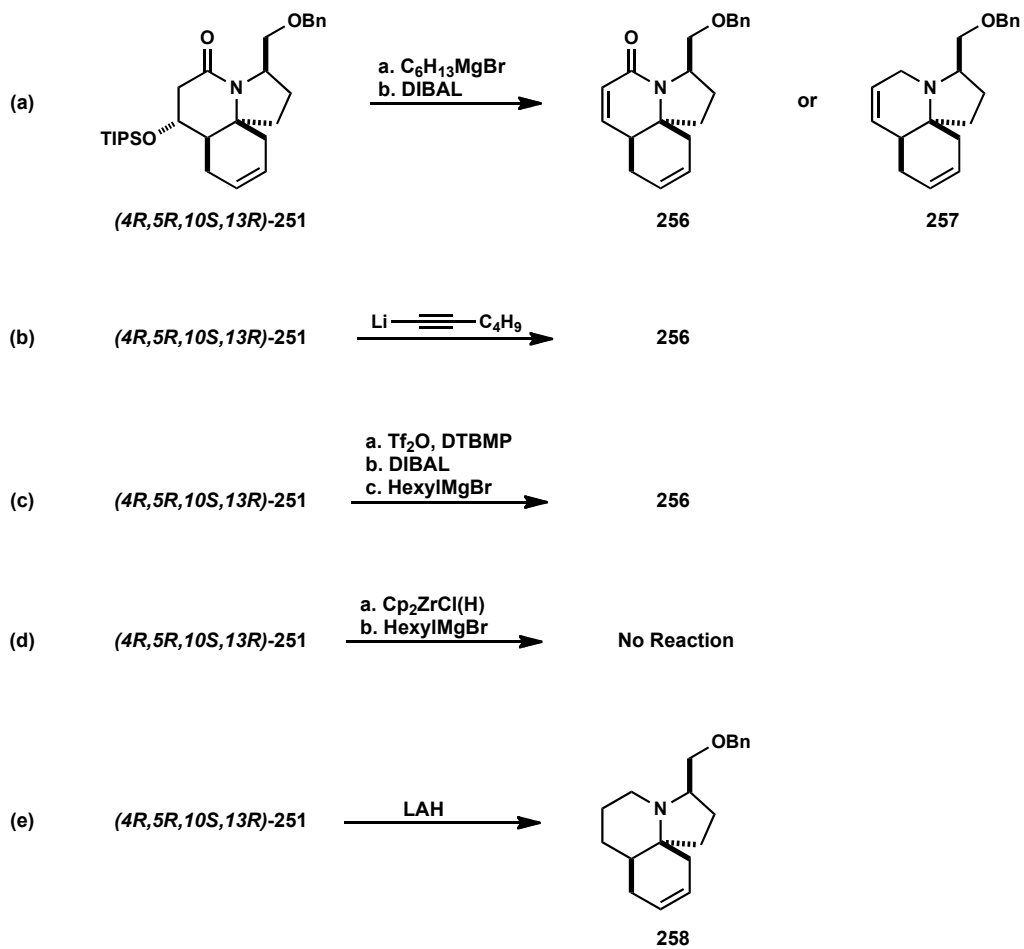
Scheme 82. Unsatisfactory attempts to functionalize the lactam

4.7. Conclusion

We have developed a novel asymmetric route toward the ring system of (–)-cylindricine C (**3**). Key steps were a Suzuki–Miyaura cross coupling and a key diastereoselective tandem Diels–Alder/Schmidt reaction, which quickly assembled the functionalized tricyclic core. Further investigation will be necessary to complete the total synthesis of (–)-cylindricine C (**3**).

Chapter 5

Conclusions

In this dissertation, the development of a tandem Prins/Schmidt reaction for the rapid construction of [5.6.6] tricyclic lactams containing four stereocenters has been described. Using this chemistry, we observed the formation of only three of eight possible diastereomers. The major diastereomer was purified and subsequently used in a formal synthesis of lepadiformine A and additionally completed the first total synthesis of lepadiformine C in ten total steps and 10% overall yield. Although the yields of the developed methodology were low, the high molecular complexity achieved was noteworthy and the stereochemical diversity was interesting and unexpected. The tandem Prins/Schmidt methodology is currently being used for library development.

We also developed an approach to the versatile prostaglandin precursor, 4-hydroxy-2-cyclopenten-1-one, which has been used in multiple prostaglandin syntheses. This concise route can afford either enantiomer in high enantiopurity (>98% es) in six steps instead of the standard seven or nine steps reported for the *S*- and *R*- enantiomers, respectively. The stereocenters were set with a Noyori reduction and the ring formed by ring closing metathesis. This short process involves inexpensive, readily available materials with the potential of being used in a process setting for large-scale production of prostaglandin therapeutics.

Finally, we explored the use of a tandem Diels–Alder/Schmidt reaction toward the synthesis of (–)-cylindricine C. The enantiopure *R*-4-hydroxy-2-cyclopenten-1-one was

subjected to a Suzuki-Miyaura coupling reaction for the construction of the key precursor. The Diels–Alder reaction was highly diastereoselective. The lactam functionalization finishing strategy has not been successful. Efforts are currently underway to conclude the total synthesis of (–)-cylindricine C.

Chapter 6

Experimental Procedures

General Information: All reactions were performed under an argon atmosphere in flame-dried glassware. The stainless steel needles used for handling anhydrous solvents and reagents were oven dried and flushed with dry argon prior to use. Plastic syringes were flushed with dry argon before use. Methylene chloride and tetrahydrofuran were purified using a solvent purification system.[120] Materials that were purchased from commercial sources were used without further purification. All nuclear magnetic resonance spectra were recorded on Bruker spectrometers. These spectrometers include Bruker AV 400, Bruker AV-III 500, Bruker DRX 400, and Bruker Avance 800. All NMR samples were recorded in deuterochloroform. Chemical shifts are reported in parts per million (ppm) and are referenced to the deuterosolvent centerline of deuterochloroform (δ 7.26 ppm ^{1}H NMR, 77.0 ppm ^{13}C NMR). Structure elucidations were assigned based on DEPT, COSY, HSQC, HMQC, and NOESY spectra. Coupling constants are given in Hertz (Hz). IR was taken with a Shimadzu FTIR-8400S. Melting points were determined using a Staford Research Systems Optimelt Automated melting point system. Low-resolution mass spectra (ESI) and high resolution mass spectra (HRMS) were taken using a Waters LCT Premier Micromass from MS Technologies. GC was performed on an Agilent Technologies 6850 Network GC System with a 5975C VL MSD triple-axis detector.
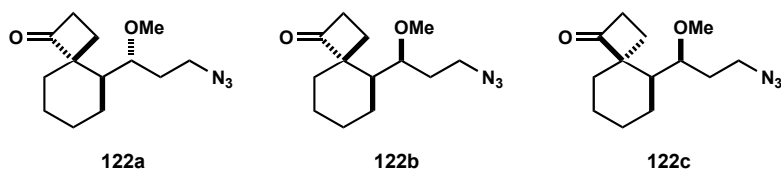
**(3R*,4R*,5S*)-5-(3´-Azido-1´-methoxypropyl)spiro[3.5]nonan-1-one (122a),
(3S* , 4R*,5S*)-5-(3´-azido-1´-methoxypropyl)spiro[3.5]nonan-1-one (122b), and
(3S*,4S*,5S*)-5-(3´-azido-1´-methoxypropyl)spiro[3.5]nonan-1-one (122c)**. To a
stirred solution of 3-azido-1,1-dimethoxypropane (220 mg, 1.5 mmol) and (1-
cyclohexenylcyclopropoxy)trimethylsilane[79] (210 mg, 1.0 mmol) in DCM (10 mL) at −78
°C was added 1.0 M $TiCl_4$ in DCM (1.5 mL). Ether (10 mL) and brine (10 mL) were
added to the reaction after 2 h, which was then allowed to warm to rt. The aqueous layer
was extracted 3× with ether, dried with Na_2SO_4, filtered, and concentrated. The resulting
yellow oil was purified by silica gel chromatography (10% EtOAc/hexanes), to afford a
yellow oil (82%) that contained three diastereomers in a ca. 10:4:1 ratio (estimated by ^{13}C
NMR of the crude reaction mixture). For mixture: IR (neat) 2092, 1768 cm^{-1}; MS (ES+)
m/z 274 (M$^+$+H); HRMS calculated for $C_{13}H_{22}N_3O_2$ (M$^+$+H): 274.1531, found 274.1428.
122a: R_f = 0.28 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.90 (distorted qd,
J = 12.4, 3.2 Hz, 1H), 1.19 (m, 2H), 1.39 (distorted t, J = 12.8 Hz, 1H), 1.51-1.74 (m,
6H), 1.80 (ddd, J = 12.8, 10.0, 3.6 Hz, 1H), 1.87-1.98 (m, 2H), 2.86 (m, 2H), 3.12 (m,
1H), 3.20 (s, 3H), 3.31 (t, J = 7.2 Hz, 2H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 18.2, 21.8,
25.1, 26.1, 28.7, 33.8, 41.2, 44.2, 46.8, 55.9, 66.8, 80.0, 214.6. **122b** (containing ca. 12%
of **122c**): R_f = 0.40 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.15-1.40 (m,
3H), 1.46 (m, 1H), 1.60-1.80 (m, 9H), 2.34 (m, 1H), 2.87 (ddd, J = 16.0, 12.0, 4.0 Hz,

1H), 3.00 (ddd, J = 20.0, 12.0, 8.0 Hz, 1H), 3.16 (m, 2H), 3.28 (s, 3H), 3.31 (t, J = 6.8 Hz, 2H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 19.8, 22.0, 22.8, 25.7, 31.1, 34.6, 42.2, 43.2, 48.3, 57.5, 69.2, 80.0, 216.6. **7c**: R_f = 0.44 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.47–1.77 (m, 11H), 1.95 (m, 1H), 2.23 (ddd, J = 10.8, 9.2, 7.2 Hz, 1H), 2.89 (ddd, J = 8.8, 7.2, 1.2 Hz, 2H), 3.29 (s, 3H), 3.37-3.42 (m, 3H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 22.9, 23.3, 25.3, 25.8, 31.4, 35.5, 41.3, 46.2, 48.0, 57.7, 66.9, 79.4, 214.7. The stereochemical determination of compound **122a** was determined via an S$_N$2 displacement reaction of the corresponding bromide (compound **117** reported by Cha and coworkers[80]) using NaN$_3$ (structure of **117** proven by X-ray crystallography).
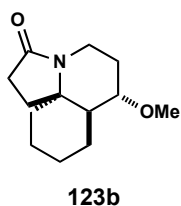
123b

(7S*,7aS*,11^1R*)-7-Methoxyoctahydro-1H-pyrrolo[1,2-j]quinolin-3(2H)-one (123b). To a stirred solution of cyclobutanone **122b** (39 mg, 0.16 mmol) in DCM (1 mL) at 0 °C was added 1.0 M TiCl$_4$ in DCM (0.8 mL). The reaction was stirred overnight at rt. The reaction was partitioned between ether (5 mL) and aqueous NH$_4$Cl (5 mL). The aqueous layer was extracted with DCM (3×), washed with brine, dried with MgSO$_4$, filtered, and concentrated. Purification by silica gel chromatography with 100% EtOAc afforded 36 mg (99%) of **123b** (containing ca. 12% minor diastereomer **123c**). R_f = 0.13 (20% EtOAc/hexanes); IR (neat) 1687 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 1.09 (qd, J = 12.5, 3.5 Hz, 1H), 1.30 (m, 1H), 1.41 (m, 1H), 1.47 (m, 1H), 1.54 (m, 1H), 1.66 (m, 1H), 1.71-1.80 (m, 4H), 1.95 (m, 1H), 2.04 (dd, J = 12.5, 7.5 Hz, 1H), 2.19 (dd, J = 16.5, 9.0

Hz, 1H), 2.32 (m, 1H), 2.49 (ddd, J = 16.5, 12.5, 8.0 Hz, 1H), 2.94 (ddd, J = 13.5, 11.0, 6.5 Hz, 1H), 3.11 (ddd, J = 11.5, 8.0, 6.0 Hz, 1H), 3.27 (s, 3H), 3.95 (dd, J = 13.5, 8.0 Hz, 1H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 22.5, 23.6, 25.6, 26.2, 30.5, 31.0, 33.2, 34.2, 47.4, 56.5, 63.3, 74.2, 175.6. MS (ES+) m/z 224 (M$^+$+H); HRMS calculated for C$_{13}$H$_{22}$NO$_2$ (M$^+$+H): 224.1651, found 224.1468.
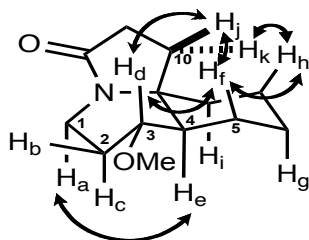
Structure determination of 123b. The structure for compound **123b** was determined beginning with the NOE between H$_d$ and H$_j$. As the J values for H$_d$ (11.5, 8.0, 6.0 Hz) indicate an axial orientation, this NOE supports the trans-fused aza-decalin system. Further support includes NOEs observed between H$_j$ with H$_f$ and H$_h$, as well as H$_d$ with H$_f$. The boat-like shape of the piperidine ring is supported by an NOE between H$_a$ and H$_e$.
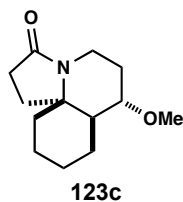
123c

(7S*,7aS*,11^1S*)-7-Methoxyoctahydro-1H-pyrrolo[1,2-j]quinolin-3(2H)-one (123c). To a stirred solution of **140** (33 mg, 0.16 mmol) in THF (3 mL) was added 60%

NaH in mineral oil (8.5 mg, 1.2 mmol). After 10 min, MeI (0.02 mL, 2.0 mmol) was added and the reaction was allowed to stir over night at ambient temperature. The reaction was quenched with water (3 mL) and the phases separated. The organic phase was washed with EtOAc (3×), dried with Na_2SO_4, filtered, and concentrated to afford a yellow oil (35 mg, 99%). $R_f = 0.10$ (25% EtOAc/hexanes); IR (neat) 1660 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.88 (m, 1H), 1.17-1.53 (m, 8H), 1.75 (m, 2H), 2.18 (m, 2H), 2.38 (m, 2H), 2.75 (distorted t, $J = 13.6$ Hz, 1H), 3.39 (s, 3H), 3.54 (td, $J = 10.8$, 4.0 Hz, 1H), 4.14 (ddd, $J = 13.6$, 5.2, 2.0 Hz, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 19.6, 22.2, 23.1, 29.1, 29.5, 29.6, 30.4, 34.7, 48.6, 56.7, 62.7, 74.9, 172.6; MS (ES+) *m/z* 224 (M$^+$+H); HRMS calculated for $C_{13}H_{22}NO_2$ (M$^+$+H): 224.1610, found 224.1644.

127
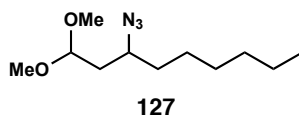
3-Azido-1,1-dimethoxynonane (127). To a stirred solution of 3-azidononanal (975 mg, 5.33 mmol) and MeOH (6 mL) at 0 °C was added a spatula tip of *p*-toluenesulfonic acid and trimethylorthoformate (1.27 mL, 11.6 mmol). The reaction was allowed to warm to rt overnight. MeOH was removed under rotary evaporation and the remaining residue was diluted in ether and NaHCO$_3$. The aqueous layer was extracted with ether (3×), washed with brine, dried with Na_2SO_4, filtered and concentrated. A clear oil was obtained (94%). $R_f = 0.80$ (25% EtOAc/hex); IR (neat) 2104 cm^{-1}; ^{1}H NMR (400 M Hz, CDCl$_3$) δ 0.88 (distorted t, $J = 7.2$ Hz, 3H), 1.21-1.45 (m, 7H), 1.49-1.58 (m, 3H), 1.75 (m, $J = 14.4$, 7.6, 4.0 Hz, 2H), 3.35 (s, 3H), 3.37 (s, 3H), 3.38 (m, 1H), 4.54 (dd, $J = 4.0$, 7.6 Hz, 1H); ^{13}C NMR (100.6 M Hz, CDCl$_3$) δ 13.9, 22.5, 25.8, 28.9, 31.6, 34.7,

37.6, 53.0, 53.4, 59.4, 102.2; MS (FAB+) m/z 230 (M$^+$+H); HRMS calculated for $C_{11}H_{24}N_3O_2$ (M$^+$+H) 230.1869, found 230.1858.

128
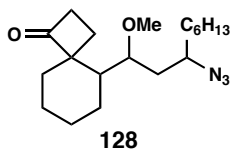
5-(3′-Azido-1′-methoxynonyl)spiro[3.5]nonan-1-one (128; complex isomeric mixture). To a stirred solution of 3-azido-1,1-dimethoxynonane (244 mg, 1.5 mmol) and (1-cyclohexenylcyclopropoxy)trimethylsilane (210 mg, 1.0 mmol) in DCM (10 mL) at − 78 °C was added 1.0 M TiCl$_4$ in DCM (1.5 mL). The reaction was allowed to stir for 2 h, at which time ether and brine were added and the solution was allowed to warm to rt. The aqueous layer was extracted 3× with DCM, dried with Na$_2$SO$_4$, filtered and concentrated. The resulting yellow oil was purified by silica gel chromatography (10% EtOAc/hexanes). After chromatography, two mixtures of otherwise inseparable diastereomers were isolated, comprising five diastereomers in total, and totaling 260 mg (78%). Mixture of 3 diastereomers: 96 mg (4:3:2.5 by ^{13}C NMR); R_f = 0.42 (10% EtOAc/hexanes); IR (neat) 2098, 1770 cm^{-1}. Major diastereomer (unambiguous peaks only): (400 MHz, CDCl$_3$) δ 0.87 (distorted t, J = 6.0, 3H), 3.26 (s, 3H); ^{13}C NMR (100.6 M Hz, CDCl$_3$) δ 14.0, 56.6, 60.0, 79.6, 216.7. Minor diastereomer (diagnostic peaks only): (400 MHz, CDCl$_3$) δ 0.87 (distorted t, J = 6.0, 3H), 3.23 (s, 3H); ^{13}C NMR (100.6 M Hz, CDCl$_3$) δ 14.0, 80.2, 216.2. Minor diastereomer (diagnostic peaks only): (400 MHz, CDCl$_3$) δ 0.87 (distorted t, J = 6.0, 3H), 3.29 (s, 3H); ^{13}C NMR (100.6 M Hz, CDCl$_3$) δ 14.0, 80.7, 214.3; MS (ES+) m/z 308 (M$^+$+H − N$_2$); HRMS calculated for $C_{19}H_{34}NO_2$ (M$^+$+H − N$_2$): 308.2590, found 308.2718. Mixture of 2 diastereomers: 164

mg (1.1:1 mixture estimated by ^{13}C NMR); R_f = 0.28 (10% EtOAc/hexanes); IR (neat) 2098, 1770 cm^{-1}. Major diastereomer (unambiguous peaks only): (400 MHz, CDCl$_3$) δ 0.84 (distorted t, J = 6.4 Hz, 3H), 3.24 (s, 3H), 3.43 (m, 1H); ^{13}C NMR (100.6 M Hz, CDCl$_3$) δ 14.0, 18.3, 45.2, 55.6, 59.3, 67.0, 80.4, 214.7. Minor diastereomer (diagnostic peaks only): (400 MHz, CDCl$_3$) δ 0.84 (distorted t, J = 6.4 Hz, 3H), 3.26 (s, 3H), 3.35 (m, 1H); ^{13}C NMR (100.6 M Hz, CDCl$_3$) δ 14.0, 18.7, 45.4, 56.5, 59.8, 67.2, 79.5, 215.0. MS (ES+) m/z 308 (M$^+$+H − N$_2$); HRMS calculated for C$_{19}$H$_{34}$NO$_2$ (M$^+$+H − N$_2$): 308.2590, found 308.2474.

129
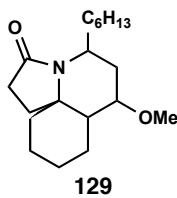
5-Hexyl-7-methoxyoctahydro-1H-pyrrolo[1,2-j]quinolin-3(2H)-one (129). To a stirred solution of cyclobutanone **128** (mixture of 3 diastereomers as obtained above) (367 mg, 1.10 mmol) in DCM (1 mL) at 0 °C was added 1.0 M TiCl$_4$ in DCM (5.5 mL). The reaction was allowed to stir overnight at rt, at which time it was partitioned between ether (10 mL) and aqueous NH$_4$Cl (10 mL). The aqueous layer was extracted with DCM (3×), washed with brine, dried with MgSO$_4$, filtered, and concentrated. Purification by silica gel chromatography with 20% EtOAc yielded 266 mg of **129** as a mixture of inseparable diastereomers in a ca. 4:3:2.9 mixture estimated by ^{13}C NMR (79%). Mixture of diastereomers: R_f = 0.30 (20% EtOAc/hexanes); IR (neat) 1690 cm^{-1}; MS (ES+) m/z 308 (M$^+$+H − N$_2$); HRMS calculated for C$_{19}$H$_{34}$NO$_2$ (M$^+$+H − N$_2$): 308.2590, found 308.2579. Major diastereomer (unambiguous peaks only): ^{1}H NMR (400 M Hz, CDCl$_3$) δ

0.85 (distorted t, J = 6 Hz, 3H), 3.26 (s, 3H); ^{13}C NMR (100.6 M Hz, CDCl₃) δ 14.0, 47.7, 51.1, 56.4, 64.8, 74.6, 175.8. Minor diastereomer (diagnostic peaks only): ^{1}H NMR (400 M Hz, CDCl₃) δ 0.85 (distorted t, J = 6 Hz, 3H), 3.28 (s, 3H); ^{13}C NMR (100.6 M Hz, CDCl₃) δ 14.0, 57.1, 65.3, 82.0, 174.8. Minor diastereomer (diagnostic peaks only): ^{1}H NMR (400 M Hz, CDCl₃) δ 0.85 (distorted t, J = 6 Hz, 3H), 3.34 (s, 3H); ^{13}C NMR (100.6 M Hz, CDCl₃) δ 14.0, 56.5, 64.7, 75.4, 175.3.

141   **140**
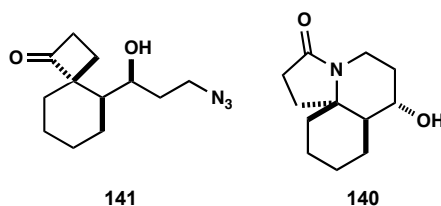
(4S*,5R*)-5-(3′-Azido-1′-hydroxypropyl)spiro[3.5]nonan-1-one **(141)** and **(7R*,7aR*,11^1R*)-7-hydroxyoctahydro-1H-pyrrolo[1,2-j]quinolin-3(2H)-one** **(140)**. To a stirred solution of 3-azido-1-propanal (**120**)(470 mg, 4.8 mmol) and (1-cyclohexenylcyclopropoxy)trimethylsilane (**112**)(880 mg, 4.0 mmol) in DCM (20 mL) at 0 °C was added 1.0 M TiCl₄ in DCM (4.8 mL). After 2 h, a second amount of 1.0 M TiCl₄ in DCM (4.8 mL) was added and the reaction was heated to reflux. After 2 h, the reaction was cooled to rt and partitioned between ether (20 mL) and water (20 mL). The aqueous layer was extracted with DCM (3×). The combined organic extracts were dried with MgSO₄, filtered, and concentrated. The yellow oil was first purified by silica gel chromatography (0→10% MeOH/EtOAc) followed by subsequent chromatography of the fractions containing the cyclobutanone products using 10% EtOAc/hexanes. Cyclobutanone **141** (24%) was isolated as a yellow oil and lactam **140** (16%) as a white powder. Cyclobutanone **141**: R_f = 0.19 (20% EtOAc/hexanes); IR (neat) 3468, 2097,

1761 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.21-1.47 (m, 3H), 1.52 (m, 1H), 1.59-1.84 (m, 9H), 2.60 (m, 1H), 2.87-3.12 (m, 2H), 3.42-3.55 (m, 2H), 3.79 (br d, J = 8.4 Hz); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 19.8, 21.8, 21.9, 25.5, 34.6, 35.5, 42.4, 45.3, 49.0, 69.6, 70.5, 217.8; MS (ES+) m/z 260 (M$^+$+Na); HRMS calculated for C$_{12}$H$_{19}$N$_3$O$_2$Na (M$^+$+Na): 260.1375, found 260.1390. Lactam **140**: R_f = 0.11 (10% MeOH/EtOAc); mp = 210 °C (dec); IR (CH$_2$Cl$_2$) 1649 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.24-1.54 (m, 7H), 1.69-1.83 (m, 3H), 2.02 (m, 1H), 2.13-2.22 (m, 2H), 2.24 (br s, 1H), 2.31-2.49 (m, 2H), 2.79 (m, 1H), 4.02 (dt, J =10.8, 4.4 Hz, 1H), 4.09 (ddd, J = 13.6, 5.2, 1.6 Hz, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) d 19.3, 22.3, 23.0, 29.1, 29.6, 30.3, 34.3, 34.8, 50.3, 62.9, 65.9, 172.7; MS (ES+) m/z 210 (M$^+$+H); HRMS calculated for C$_{12}$H$_{20}$NO$_2$ (M$^+$+H): 210.1494, found 210.1315. Stereochemistry was confirmed by X-ray crystallography.

142   143
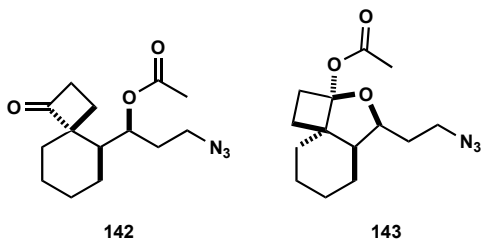
(1S*,4S*,5R*)-3-Azido-1-(1´-oxospiro[3.5]nonan-5´-yl)propyl acetate (142) and (2aS,4S,4aS,8^1R)-4-(2-azidoethyl)octahydro-1H-benzo[c]cyclobuta[b]furan-2a-yl acetate (143). A solution of alcohol **141** (285 mg, 1.2 mmol) dissolved in DCM (12 mL) was cooled to 0 °C and pyridine (1 mL, 10 mmol), glacial acetic acid (1.13 mL, 10 mmol), and a single crystal of DMAP were added. The reaction was slowly warmed to rt and stirred overnight. The reaction was partitioned between DCM (20 mL) and water (20 mL) and the aqueous layer was extracted with DCM (3×). The combined organic extracts

were washed with aqueous $NaHCO_3$, 1M HCl, and then brine. The organic layer was dried with Na_2SO_4, filtered, and concentrated. The resulting yellow oil was further purified by silica gel chromatography (10% EtOAc/hexanes). Acetates **142** and **143** were separated by silica gel chromatography and obtained as yellow oils. Acetate **142** (89%): R_f = 0.20 (20% EtOAc/hexanes); IR (neat) 2098, 1770, 1735 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (m, 2H), 1.33 (m, 1H), 1.46 (br t, J = 12.8 Hz, 1H), 1.59-1.84 (m, 8H), 2.05 (s, 3H), 2.05-2.13 (m, 1H), 2.80-3.06 (m, 2H), 3.16-3.30 (m, 2H), 4.99 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 19.6, 21.0, 21.8, 23.0, 25.3, 33.1, 34.3, 42.3, 43.3, 47.9, 68.9, 71.6, 170.5, 215.8; MS (ES+) m/z 297 (M$^+$+NH$_4$); HRMS calculated for $C_{14}H_{22}N_3O_3$ (M$^+$+NH$_4$): 297.1927, found 297.1790. Acetate **143** was isolated as a yellow oil (11%) and was accompanied by ca. 20% of an unidentified impurity. **143**: R_f = 0.70 (20% EtOAc/hexanes); IR (neat) 2096, 1747 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05-1.36 (m, 4H), 1.43-1.57 (m, 2H), 1.60-1.81 (m, 7H), 1.81-1.98 (m, 2H), 2.04 (s, 3H), 2.26-2.46 (m, 2H), 3.47 (ddd, J = 7.6, 6.0, 4.0 Hz, 2H), 3.96 (ddd, J = 10.0, 8.0, 3.6 Hz, 1H); ^{13}C NMR (101 MHz, CDCl3) δ 20.5, 21.4, 21.6, 23.0, 25.2, 30.7, 21.9, 33.1, 48.4, 49.2, 56.6, 81.5, 106.6, 169.2; MS (ES+) m/z 302 (M$^+$+Na); HRMS calculated for $C_{14}H_{21}N_3O_3$ (M$^+$+Na): 302.1481, found 302.1382. Impurity (diagnostic peaks only): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.52 (ddd, J = 11.6, 9.2, 2.8 Hz, 1H); ^{13}C NMR (101 MHz, CDCl3) δ 47.8, 49.2, 57.3, 82.2, 107.6.
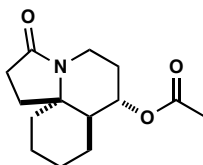
144

(7*R**,7a*S**,11[1]*R**)-3-Oxodecahydro-1*H*-pyrrolo[1,2-j]quinolin-7-yl   acetate

(144). To a neat sample of acetate **142** (161 mg, 0.58 mmol) was added 1.0 M TiCl$_4$ in

DCM (2.9 mL). Gas evolution was immediately observed. The reaction was stirred at rt

for 30 min and then partitioned between equivalent amounts of ether and water. The

aqueous layer was extracted twice with ether and once with EtOAc. The combined

organic layers were washed thrice with NaHCO$_3$ and then with brine, then dried with

MgSO$_4$, filtered, and concentrated. Purification by silica gel chromatography (EtOAc)

afforded **144** as a yellow oil (92%). R_f = 0.4 (EtOAc); IR (neat) 1735, 1693 cm^{-1}; ^{1}H

NMR (400 MHz, CDCl$_3$) δ 1.14 (qd, *J* = 12.4, 3.2, 1H), 1.32 (m, 1H), 1.43-1.65 (m, 3H),

1.67-1.73 (m, 2H), 1.76-1.83 (m, 2H), 1.89 (br t, *J* = 12 Hz, 2H), 2.05 (s, 3H), 2.08 (m,

1H), 2.25 (dd, *J* = 16.8, 8.8 Hz, 1H), 2.38-2.57 (m, 2H), 2.99 (ddd, *J* = 18.4, 11.6, 6.8 Hz,

1H), 3.99 (dd, *J* = 10.8, 8.0 Hz, 1H), 4.75 (ddd, *J* = 12.4, 8.8, 6.0 Hz, 1H); ^{13}C NMR

(100.6 MHz, CDCl$_3$) δ 20.9, 22.7, 23.5, 25.4, 26.1, 30.3, 31.3, 33.1, 34.2, 46.0, 63.3,

68.4, 170.4, 175.5; MS (ES+) *m/z* 252 (M$^+$+H); HRMS calculated for C$_{14}$H$_{22}$NO$_3$

(M$^+$+H): 252.1600, found 252.1570.
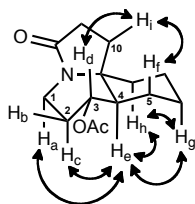
Structure determination of 144. The structure of compound **144** is proposed

beginning with the NOE observed between H$_a$ and H$_e$. This NOE supports a boat

conformation of the piperidine ring. This conformation is substantiated by H$_e$ also

exhibiting NOEs with H$_c$, H$_g$, and H$_h$. Since H$_i$ has an observed NOE with H$_f$ as well as

H_d, this supports a trans-azadecalin ring structure. The axial orientation of H_d is supported by the J value of 12.4 Hz, indicating a trans-axial interaction.

145
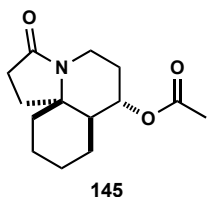
(7S*,7aS*,11^{1}S*)-3-Oxodecahydro-1H-pyrrolo[1,2-j]quinolin-7-yl   acetate (145). Lactam **140** was acetylated as described in the procedure for compound **142**. Acetylated lactam **145** was isolated as a yellow oil (76%). R_f = 0.37 (EtOAc); IR (neat) 1731, 1687 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.25-1.52 (m, 6H), 1.59 (m, 1H), 1.72-1.89 (m, 4H), 2.05 (m, 1H), 2.07 (s, 3H), 2.20 (m, 1H), 2.34-2.52 (m, 2H), 2.84 (br t, J = 13.6 Hz, 1H), 4.12 (m, 1H), 5.27 (tdd, J = 11.2, 4.4, 1.2 Hz, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 19.3, 21.1, 22.6, 22.8, 29.0, 29.4, 30.3, 30.7, 34.4, 47.2, 62.8, 68.5, 170.6, 172.6; MS (ES+) m/z 252 (M$^+$+H); HRMS calculated for C$_{14}$H$_{22}$NO$_3$ (M$^+$+H): 252.1600, found 252.1521.
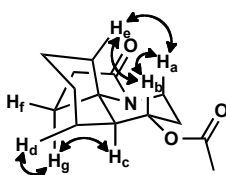
Structure determination of 145. This structure is proposed beginning with the J values of H_b, 11.2(t) and 4.4(d) Hz. The triplet J value indicates the presence of two trans relationships; hence, H_b must be axial. The observed NOE of H_b with H_a gave further support for the axial orientation of H_b. An observed NOE between H_e with H_a and H_b was

supportive of the cis ring fusion of the aza-decalin. This was further supported by the NOE present between H_g with H_c and H_d.
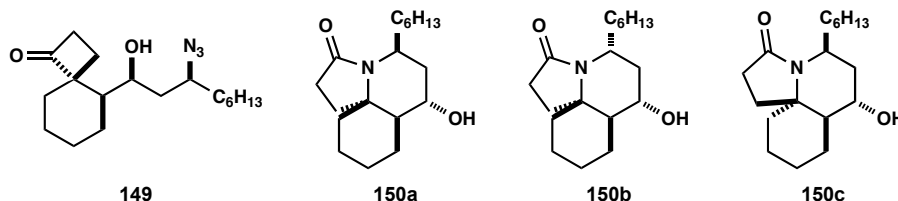
(1R*,3R*,4S*,5R*)-5′-(3′-Azido-1′-hydroxynonyl)spiro[3.5]nonan-1-one (149), **(5R*,7R*,7aR*,11^1R*)-5-hexyl-7-hydroxyoctahydro-1H-pyrrolo[1,2-j] quinolin-3(2H)-one (150a), (5S*,7R*,7aR*,11^1R*)-5-hexyl-7-hydroxyoctahydro-1H-pyrrolo[1,2-j]quinolin-3(2H)-one (150b) and (5S*,7S*,7aS*,11^1R*)-5-hexyl-7-hydroxyoctahydro-1H-pyrrolo[1,2-j]quinolin-3(2H)-one (150c)**. Obtained as described in procedure for compounds **140** and **141**. Examination of carbonyl region in the crude ^{13}C NMR spectrum indicated the formation of one diastereomeric cyclobutanone and three diastereomeric lactams in a ca. 3:1:1 ratio of **a**:**b**:**c**. Silica gel chromatography (50% EtOAc/hexanes→10% MeOH/EtOAc) afforded cyclobutanone **149** (30%) containing ≤5% of a minor diastereomer (estimated by ^{1}H NMR), plus three diastereomers of lactams (21%); all samples were obtained as yellow oils. Analytical samples of lactams **150a–c** were obtained by careful chromatography of the latter mixture. Cyclobutanone **149**: R_f = 0.20 (20% EtOAc/hexanes); IR (neat) 3456, 2100, 1766 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.90 (t, J = 6.4 Hz, 3H), 1.23-1.85 (complex, 21H), 2.40 (br s, 1H), 2.73 (m, 1H), 2.85-3.07 (m, 3H), 3.46 (m, 1H), 3.80 (d, J = 8.8 Hz, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 14.2, 20.2, 21.5, 22.1, 22.6, 25.8, 25.9, 29.3, 31.8, 34.8, 34.9, 41.0, 42.6, 46.0, 62.1, 70.0, 71.9, 218.2; MS (ES+) m/z 344 (M$^+$+Na); HRMS calculated for

$C_{18}H_{31}N_3O_2Na$ (M$^+$+Na): 344.2314, found 344.2287. Lactam **150a**: R_f = 0.27 (EtOAc); IR (CH$_2$Cl$_2$) 3350, 1645 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.87 (distorted t, J = 5.6 Hz, 3H), 1.20-1.76 (complex, 21H), 2.02 (dd, J = 12.4, 3.2 Hz, 1H), 2.17 (m, 1H), 2.22-2.34 (m, 2H), 2.45 (m, 1H), 4.16 (td, J = 11.2, 4.0 Hz, 1H), 4.28 (q, J = 7.2 Hz, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 14.1, 19.6, 22.3, 22.6, 23.8, 27.2, 29.3, 29.5, 31.4, 31.8, 32.0, 36.0, 37.3, 48.5, 51.7, 62.8, 64.1, 173.6; MS (ES+) m/z 294 (M$^+$+H); HRMS calculated for $C_{18}H_{32}NO_2$ (M$^+$+H): 294.2433, found 294.2417. Lactam **150b**: R_f = 0.49 (EtOAc); IR (CH$_2$Cl$_2$) 3361, 1666 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.89 (t, J = 5.4 Hz, 3H), 1.28-1.52 (complex, 18H), 1.65-2.15 (complex, 6H), 2.32 (m, 1H), 2.54 (m, 1H), 3.24 (m, 1H), 3.98 (td, J = 10.7, 4.8 Hz, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 14.0 (2C), 19.5, 22.6, 22.9, 27.1, 29.2, 29.6, 30.6, 31.0, 31.8, 31.9, 40.8, 48.1, 52.0, 65.0, 66.5, 174.9; MS (ES+) m/z 294 (M$^+$+1); HRMS calculated for $C_{18}H_{32}NO_2$ (M$^+$+H): 294.2433, found 294.2299. The stereochemistry of **150b** was confirmed by X-ray crystallography. Lactam **150c**: R_f = 0.43 (EtOAc); IR (neat) 3402, 1662 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.89 (distorted t, J = 6.8 Hz, 3H), 1.15 (qd, J = 12.4, 2.8 Hz, 1H), 1.24-1.37 (m, 8H), 1.42 (m, 1H), 1.48-1.63 (m, 3H), 1.64-1.77 (m, 4H), 1.82 (m, 2H), 1.90-2.03 (m, 3H), 2.10 (dd, J = 16.4, 9.2 Hz, 1H), 2.29 (ddd, J = 13.6, 11.6, 8.8 Hz, 1H), 2.40-2.53 (m, 2H), 3.35 (m, 1H), 3.69 (ddd, J = 12.0, 8.8, 6.0 Hz, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 14.1, 22.3, 22.7, 23.7, 25.6, 25.7, 27.6, 29.1, 31.5, 31.7, 31.8, 33.5, 42.3, 48.9, 51.4, 65.1, 66.0, 175; MS (ES+) m/z 294 (M$^+$+H); HRMS calculated for $C_{18}H_{32}NO_2$ (M$^+$+H): 294.2433, found 294.2371.

151   152
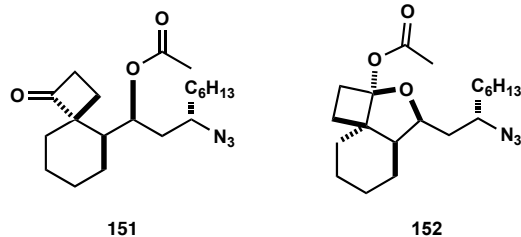
(1S*,3S*,4R*,5S*)-3-Azido-1-(1′-oxospiro[3.5]nonan-5′-yl)nonyl acetate (151)

and (2aS*,2′S*,4S*,4aS*,8^{1}R*)-4-(2′-azidooctyl)octahydro-1H-benzo[c]cyclobuta[b]

furan-2a-yl acetate (152). The reaction was carried out as described in the procedure for

compound **142**. Starting with compound **149**, acetate **151** was isolated as a yellow oil

(74%). R_f = 0.41 (20% EtOAc/hexanes); IR (neat) 2100, 1770, 1737 cm^{-1}; ^{1}H NMR (400

MHz, CDCl$_3$) δ 0.88 (t, J = 6.8 Hz, 3H), 1.18-1.88 (m, 22H), 2.08 (s, 3H), 2.08 (m, 1H),

2.83-3.06 (m, 2H), 3.19 (m, 1H), 5.07 (m, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 14.0,

19.8, 21.2, 21.8, 22.5, 22.8, 25.4, 25.8, 29.0, 31.6, 34.2, 34.4, 38.3, 42.4, 43.5, 59.9, 69.2,

71.7, 170.6, 215.9; MS (ES+) m/z 386 (M$^+$+Na); HRMS calculated for C$_{20}$H$_{33}$N$_3$O$_3$Na

(M$^+$+Na): 386.2420, found 386.2391. Acetate **152** was isolated as a yellow oil (19%)

containing ca. 10% of an unidentified impurity. R_f = 0.77 (20% EtOAc/hexanes); IR

(neat) 2098, 1749 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.91 (distorted t, J = 6.4 Hz, 3H),

1.08-1.25 (m, 2H), 1.26-1.37 (m, 7H), 1.42-1.58 (m, 4H), 1.58-1.85 (m, 9H), 1.94 (m,

1H), 2.04 (s, 3H), 2.29-2.44 (m, 2H), 3.49 (m, 1H), 3.99 (ddd, J = 11.6, 6.8, 4.4 Hz, 1H);

^{13}C NMR (101 MHz, CDCl3) δ 14.0, 20.6, 21.4, 21.5, 22.6, 23.4, 25.9, 29.1, 30.8, 31.7,

31.9, 34.5, 38.4, 49.4, 56.7, 59.7, 81.6, 106.6, 169.2; MS (ES+) m/z 386 (M$^+$+Na);

HRMS calculated for C$_{20}$H$_{33}$N$_3$O$_3$Na (M$^+$+Na): 386.2420, found 386.2279. Impurity

(diagnostic peaks only): ^{1}H NMR (400 MHz, CDCl$_3$) δ 3.64 (m, 1H), 4.04 (m, 1H); ^{13}C

NMR (101 MHz, CDCl3) δ 14.0, 49.5, 60.2, 81.2.

153
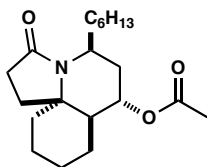
(5R*,7R*,7aR*,11^1S*)-5-Hexyl-3-oxodecahydro-1H-pyrrolo[1,2-j]quinolin-7-yl acetate (153). The reaction was carried out as described in the procedure for compound **144**. Acetate **151** produced lactam **153** as a yellow oil (96%) containing a minor diastereomer in a ca. 12:1 ratio (^{1}H NMR). R_f = 0.48 (EtOAc); IR (neat) 1735, 1693 cm^{-1}; MS (ES+) m/z 336 (M$^+$+H); HRMS calculated for C$_{20}$H$_{34}$NO$_3$ (M$^+$+H): 336.2539, found 336.2419. Major diastereomer: ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.87 (distorted t, J = 6.8 Hz, 3H), 1.21-1.38 (m, 8H), 1.45-1.62 (m, 4H), 1.63-1.72 (m, 4H), 1.75-1.89 (m, 4H), 2.0 (m, 1H), 2.04 (s, 3H), 2.12 (dd, J = 16.4, 8.8 Hz, 1H), 2.34 (m, 1H), 2.41-2.53 (m, 2H), 3.34 (m, 1H), 4.77 (ddd, J = 14.8, 9.2, 6.0 Hz, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 14.1, 21.1, 22.6, 22.7, 23.5, 25.5, 25.6, 27.6, 29.1, 31.4, 31.5, 31.8, 33.6, 39.3, 46.4, 51.2, 64.8, 68.9, 170.5, 175.8. Minor diastereomer (diagnostic peaks only): ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.87 (distorted t, J = 6.8 Hz, 3H), 2.90-3.11 (m, 2H), 3.16 (m, 1H), 5.10 (m, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 14.1, 38.7, 42.3, 47.3, 59.7, 71.5.
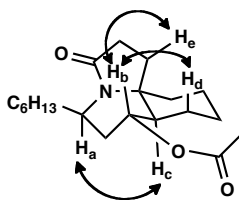
Structure determination of 153. The proposed structure of **153** is supported beginning with the NOE between H$_a$ and H$_c$. This correlation supports a boat-like

conformation of the piperidine ring as well as well as suggesting that the hexyl side chain is equatorial. Unfortunately, the complex proton signal of H_a does not allow for proper J value calculations in order to further confirm it as being axial. The trans-azadecalin system was supported by the NOE between H_b and both H_d and H_e. The axial orientation of H_b is further substantiated by the J value of 14.8 Hz, indicating a diaxial relationship.
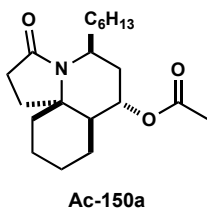
Ac-150a

(5R*,7R*,7aR*,11^1R*)-5-Hexyl-3-oxodecahydro-1H-pyrrolo[1,2-j]quinolin-7-yl acetate (Ac-150a). The reaction was carried out as described in the procedure for compound **142**. Acetate **Ac-150a** was isolated as a yellow oil (84%). R_f = 0.53 (EtOAc); IR (neat) 1737, 1681 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.87 (distorted t, J = 6.4 Hz, 3H), 1.26 (m, 8H), 1.42 (m, 5H), 1.52-1.68 (m, 5H), 1.71-1.82 (m, 3H), 2.01 (m, 1H), 2.07 (s, 3H), 2.23-2.36 (m, 2H), 2.47 (m, 1H), 4.32 (q, J = 7.6 Hz, 1H), 5.42 (td, J = 11.2, 4.0 Hz, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 14.1, 19.6, 21.2, 22.5, 22.6, 23.6, 27.1, 29.2, 29.4, 31.4, 31.7, 31.9, 33.9, 35.8, 48.0, 48.8, 63.8, 66.2, 170.6, 173.4; MS (ES+) m/z 336 (M$^+$+H); HRMS calculated for C$_{20}$H$_{34}$NO$_3$ (M$^+$+H): 336.2539, found 336.2498.
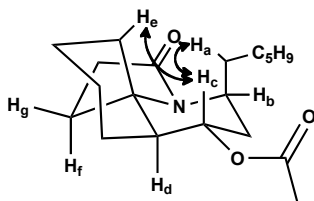
Structure determination of Ac-150a. The structure was proposed based on NOEs between H_c and H_a as well as between H_c and H_e. These NOEs support the axial position of the hexyl sidechain as H_c is axial by the calculated J value of 11.2 Hz for the triplet, indicative of two diaxial couplings. The two trans-trans couplings also support an axial orientation of H_d as there must be an axial proton on each side of H_c. The NOE between H_c and H_e along with the axial position of H_d leads to the assignment of the *cis*-fused azadecalin ring system.

154
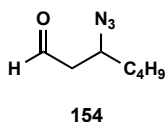
3-Azidoheptanal (154). To a stirred solution of sodium azide (2.92 g, 45 mmol) in water (8 mL) at 0 °C was added glacial AcOH (3.45 mL, 60 mmol). After 1 h, 2-heptenal (2.0 mL, 15 mmol) was added and the reaction mixture allowed to slowly warm to rt overnight. The reaction was cooled to 0 °C and DCM (10 mL) and aqueous $NaHCO_3$ (10 mL) were added. Upon warming to rt, the aqueous layer was extracted with DCM (3×), washed with $NaHCO_3$ (3×) then brine, dried with Na_2SO_4, filtered and concentrated. The resulting yellow oil was purified by silica gel chromatography (10% EtOAc/hexanes) to yield 2.27 g (99%) of **154** as a yellow oil. $R_f = 0.54$ (20% EtOAc/hexanes); IR (neat) 2100, 1726 cm^{-1}; ^{1}H NMR (400 M Hz, CDCl$_3$) δ 0.91 (distorted t, $J = 6.8$ Hz, 3H), 1.28-1.47 (m, 4H), 1.50-1.63 (m, 2H), 2.62 (m, 2H), 3.87 (ddd, $J = 13.2, 7.6, 5.2$ Hz, 1H), 9.78 (br t, $J = 1.6$ Hz, 1H); ^{13}C NMR (100.6 M Hz, CDCl$_3$) δ 13.8, 22.3, 27.9, 34.1, 48.1, 57.0, 199.4; MS (ES$^-$) m/z 127 (M$^+$ – N$_2$); HRMS calculated for C$_7$H$_{13}$NO (M$^+$ – N$_2$): 127.0997, found 127.0777.

155   156a   156b   156c
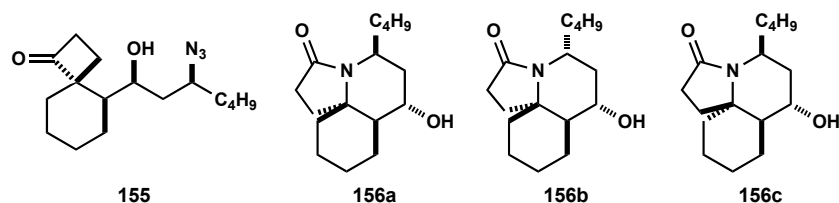
(1S*,3S*,4R*,5S*)-5-(3-Azido-1-hydroxyheptyl)spiro[3.5]nonan-1-one (155),

(5S*,7S*,7aS*,11¹S*)-5-butyl-7-hydroxyoctahydro-1H-pyrrolo[1,2-j]quinolin-3(2H)-

one (156a), (5R*,7S*,7aS*,11¹S*)-5-butyl-7-hydroxyoctahydro-1H-pyrrolo[1,2-

j]quinolin-3(2H)-one (156b), (5S*,7S*,7aS*,11¹R*)-5-butyl-7-hydroxyoctahydro-1H-

pyrrolo[1,2-j]quinolin-3(2H)-one (156c). Obtained as described in procedure for

compounds **140** and **141**. Examination of carbonyl region in the crude ^{13}C NMR

spectrum indicated the formation of one diastereomeric cyclobutanone and three

diastereomeric lactams in ca. 3:1:1 ratio of **a**:**b**:**c**. Chromatography (5% EtOAc/hexanes

→10% MeOH/EtOAc) afforded cyclobutanone **155** (22%) plus a mixture containing

three diastereomers of lactams (30%) as yellow oils. Analytical samples of lactams **156a–**

c were obtained by careful chromatography of the latter mixture. Cyclobutanone **155**: R_f

= 0.51 (20% EtOAc/hexanes); IR (neat) 3498, 2100, 1759 cm^{-1}; ^{1}H NMR (400 MHz,

CDCl$_3$) δ 0.90 (distorted t, J = 6.8 Hz, 3H), 1.22 (dd, J = 10.7, 14.2 Hz, 1H), 1.27-1.43

(m, 7H), 1.45-1.53 (m, 3H), 1.54-1.66 (m, 5H), 1.67-1.88 (m, 4H), 2.39 (d, J = 3.6 Hz,

1H), 2.69 (dd, J = 10.4, 17.4 Hz, 1H), 2.79-3.07 (m, 2H), 3.43 (dd, J = 4.0, 9.7 Hz, 1H),

3.77 (d, J = 9.0 Hz, 1H); ^{13}C NMR (101 MHz, CDCl$_3$) δ 13.9, 19.9, 21.3, 21.9, 22.5,

25.7, 27.8, 34.3, 34.7, 40.9, 42.5, 45.8, 61.9, 69.9, 71.6, 217.9; MS (ES+) *m/z* 316

(M$^+$+Na); HRMS calculated for C$_{16}$H$_{27}$N$_3$O$_2$Na (M$^+$+Na): 316.2001, found 316.1916.

Lactam **156a**: R_f = 0.43 (10%MeOH/EtOAc); IR (neat) 3380, 1654 cm^{-1}; ^{1}H NMR (500

MHz, CDCl$_3$) δ 0.84 (distorted t, J = 7.1 Hz, 3H), 1.14-1.32 (m, 6H), 1.33-1.39 (m, 3H), 1.42-1.53 (m, 5H), 1.57 (dd, J = 9.9, 20.0 Hz, 1H), 1.63-1.71 (m, 2H), 1.99 (dd, J = 3.0, 12.7 Hz, 1H), 2.09-2.16 (m, 1H), 2.17-2.30 (m, 2H), 2.42 (ddd, J = 9.3, 11.1, 17.0 Hz, 1H), 4.12 (td, J = 4.0, 11.1 Hz, 1H), 4.25 (q, J = 7.3 Hz, 1H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 14.0, 19.5, 22.2, 22.6, 23.7, 29.3, 29.4, 31.3, 32.0, 35.6, 37.3, 48.3, 51.7, 62.8, 63.9, 173.4; MS (ES+) *m/z* 266 (M$^+$+H); HRMS calculated for C$_{16}$H$_{28}$NO$_2$ (M$^+$+H): 266.2120, found 266.2087. Lactam **156b**: R_f = 0.45 (EtOAc); IR (neat) 3367, 1666 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 0.87 (distorted t, J = 6.9, 3H), 1.19-1.39 (m, 9H), 1.45-1.55 (m, 3H), 1.72 (d, J = 13.4 Hz, 1H), 1.76-1.88 (m, 3H), 1.91 (m, 1H), 1.96-2.03 (m, 1H), 2.08 (d, J = 14.8 Hz, 1H), 2.22-2.36 (m, 2H), 2.50 (m, 1H), 3.20 (d, J = 9.9 Hz, 1H), 3.94 (td, J = 4.7, 10.8 Hz, 1H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 14.1, 19.5, 22.6 (2), 22.9, 29.4, 29.6, 30.6, 31.0, 31.7, 40.8, 48.0, 52.0, 65.1, 66.5, 175.1; MS (ES+) *m/z* 266 (M$^+$+H); HRMS calculated for C$_{16}$H$_{28}$NO$_2$ (M$^+$+H): 266.2120, found 266.1846. Lactam **156c**: R_f = 0.24 (60% EtOAc/hexanes); IR (neat) 3384, 1654 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 0.88 (distorted t, J = 7.1 Hz, 3H), 1.11 (ddd, J = 3.3, 12.6, 25.2 Hz, 1H), 1.21-1.40 (m, 6H), 1.42-1.58 (m, 3H), 1.61-1.73 (m, 5H), 1.79 (d, J = 11.9 Hz, 2H), 1.89 (d, J = 10.5 Hz, 1H), 1.96 (dd, J = 8.1, 12.6 Hz, 1H), 2.07 (m, 1H), 2.27 (ddd, J = 8.8, 11.8, 13.6 Hz, 1H), 2.35-2.55 (m, 2H), 3.31 (dt, J = 6.1, 11.9 Hz, 1H), 3.66 (ddd, J = 5.8, 8.7, 11.8 Hz, 1H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 14.1, 22.3, 22.5, 23.7, 25.6, 25.7, 29.8, 31.33, 31.5, 33.5, 42.3, 48.9, 51.3, 65.0, 66.0, 175.79; MS (ES+) *m/z* 266 (M$^+$+H); HRMS calculated for C$_{16}$H$_{28}$NO$_2$ (M$^+$+H): 266.2120, found 266.1917.

Structure determination of 156a. The structure of **156a** is proposed based on the observed NOE between H_a and H_d. This NOE suggests an axial orientation of the butyl side chain. An axial orientation of the butyl chain is also supported by the coupling constant of H_b, J = 7.3 Hz, which suggests no possible trans-axial couplings. The coupling constants of H_d, however, are indicative of trans-axial coupling with a triplet J value of 11.1 Hz, thus supporting the diaxial interaction with the butyl sidechain. Next, the observed NOE between H_e and H_f supports the cis-azadecalin geometry. Also, the NOE between H_g and H_d supports the facial orientation of the cyclohexane ring being on the same face as the butyl group.
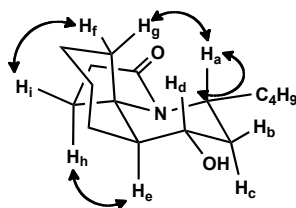
Structure determination of 156b. The proposed structure for **156b** is supported by observation of an NOE between H_a and H_d. This NOE supports a chair conformation of the piperidine ring as well as the orientation of the butyl side chain and hydroxy side chain. The chair conformation is also upheld by the splitting pattern of a triplet of doublets and coupling constants, 11.0 and 5.0 Hz, of H_d. The cis-azadecalin moiety is backed by the NOEs between H_f and H_i as well as H_e and H_h. The orientation of the cis-azadecalin ring is supported by the NOE between H_a and H_g.
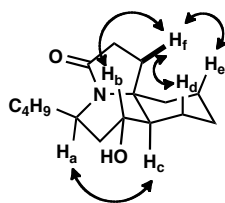
Structure determination of 156c. The proposed structure of compound **156c** was assigned by beginning with the NOE between H_a and H_c. This correlation supports a boat-like conformation of the piperidine ring as well as well as suggesting that the butyl side chain is equatorial. Unfortunately, the complex proton signal of H_a does not allow for proper J value calculations in order to further confirm it as being axial. The trans-azadecalin system was supported by the observed NOEs between H_b with H_f, H_d with H_f as well as H_e with H_f. The axial orientation of H_b is further substantiated by an observed J value of 12.0 Hz, indicating a diaxial relationship.

157
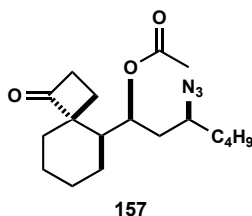
(1S*,3S*,4R*,5S*)-3-Azido-1-(-1-oxospiro[3.5]nonan-5-yl)heptyl acetate (157). The reaction was carried out as described in the procedure for compound **142**. Starting with cyclobutanone **155**, Acetate **157** was isolated as a yellow oil (88%). $R_f =$ 0.60 (20% EtOAc/hexanes); IR (neat) 2098, 1770, 1735 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.88 (distorted t, $J = 6.8$ Hz), 1.19-1.39 (m, 7H), 1.48-1.56 (m, 3H), 1.58-1.86 (m, 8H), 2.05 (s, 3H), 2.08 (m, 1H), 2.86 (ddd, $J = 16.4, 10.4, 6.4$ Hz, 1H), 2.99 (ddd, $J = 17.2, 10.0, 6.8$ Hz, 1H), 3.17 (ddd, $J = 13.2, 8.0, 5.6$ Hz, 1H), 5.05 (ddd, $J = 7.6, 4.4, 2.8$

Hz, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 13.8, 19.7, 21.1, 21.8, 22.3, 22.7, 25.3, 27.9, 33.8, 34.3, 38.3, 42.3, 43.5, 59.8, 69.1, 71.6, 170.5, 215.7; MS (ES+) *m/z* 358 (M$^+$+Na); HRMS calculated for C$_{18}$H$_{29}$N$_3$O$_3$Na (M$^+$+Na): 358.2107, found 358.1805.

158
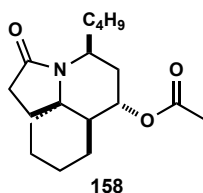
5-Butyl-3-oxodecahydro-1*H*-pyrrolo[1,2-*j*]quinolin-7-yl acetate (158). The reaction was carried out as described in the procedure for compound **144**. Acetate **157** afforded lactam **158** as a yellow oil (99%). R_f = 0.50 (60% EtOAc/hexanes); IR (neat) 1737, 1693 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 0.87 (distorted t, *J* = 8.5 Hz, 3H), 1.10 (qd, *J* = 15.5, 4.0 Hz, 1H), 1.20-1.42 (m, 6H), 1.45-1.59 (m, 3H), 1.60-1.69 (m, 3H), 1.72-1.87 (m, 3H), 1.97 (dd, *J* = 15.5, 9.5 Hz, 1H), 2.02 (s, 3H), 2.10 (dd, *J* = 20.5, 11.5 Hz, 1H), 2.32 (ddd, *J* = 17.0, 14.5, 11.0 Hz, 1H), 2.38-2.51 (m, 2H), 3.32 (m, 1H), 4.74 (ddd, *J* = 15.5, 11.0, 7.0 Hz, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 14.0, 20.9, 22.4, 22.6, 23.4, 25.4, 25.5, 29.7, 31.1, 31.2, 33.5, 39.2, 46.3, 51.1, 64.7, 68.8, 170.4, 175.7; MS (ES+) *m/z* 308 (M$^+$+H); HRMS calculated for C$_{18}$H$_{30}$NO$_3$ (M$^+$+H): 308.2226, found 308.2031.
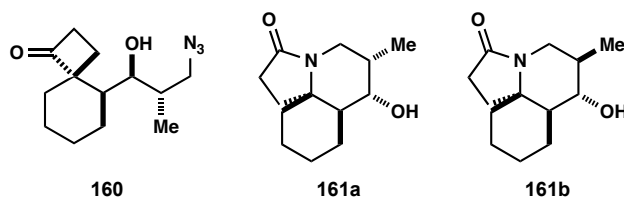
(1S*,2R*,4S*,5R*)-3-Azido-1-(1´-hydroxy-2-methylpropyl)spiro[3.5]nonan-1-one (160), **(6R*,7R*,7aR*,11^{1}R*)-7-hydroxy-6-methyloctahydro-1H-pyrrolo[1,2-j]quinolin-3(2H)-one (161a)** and **(6S*,7R*,7aR*,11^{1}R*)-7-hydroxy-6-methyloctahydro-1H-pyrrolo[1,2-j]quinolin-3(2H)-one (161b)**. The reaction was carried out as described for compounds **140** and **141**. Examination of the carbonyl region in the crude ^{13}C NMR indicated the formation of two diastereomeric cyclobutanones in ca. 4:1 ratio and four diastereomeric amide peaks in ca. 4:2:2:1 ratio. An inseparable mixture of four diastereomers along with a mixture of two diastereomers in ca. 2:1 ratio was afforded from column chromatography. This resulted in a yield of 12% of a mixture of all four diastereomers. Both mixtures were isolated as yellow oils. Lactam **161a** (major): R_f = 0.28 (10% MeOH/EtOAc); IR (CH$_2$Cl$_2$) 3336, 1666 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.92 (d, J = 6.8 Hz, 3H), 1.25 (m, 1H), 1.36-1.50 (m, 3H), 1.62 (d, J = 12.0 Hz, 1H), 1.71-1.83 (m, 3H), 2.06 (m, 1H), 2.12-2.25 (m, 2H), 2.40-2.51 (m, 3H), 2.59 (br s, 1H), 2.96 (d, J = 13.6 Hz, 1H), 3.88 (dd, J = 13.6, 1.6 Hz, 1H), 4.12 (dd, J = 11.2, 4.4 Hz, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 9.9, 19.2, 22.2, 23.1, 28.6, 29.6, 30.6, 34.5, 40.7, 43.1, 63.1, 67.6, 173.6. Minor diastereomer **161b** (diagnostic peaks only): ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.04 (d, J = 6.8 Hz, 3H), 3.98 (dd, J = 13.6, 5.2 Hz, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 49.8, 51.6, 71.5, 172.6. MS (ES+) m/z 224 (M$^+$+1); HRMS calculated for C$_{13}$H$_{22}$NO$_2$ (M$^+$+H): 224.1650, found 224.1557. Cyclobutanone **160** was isolated as a yellow oil

(NMR showed the presence of an unknown diastereomer, ca. 10:1) (14%). R_f = 0.20

(20% EtOAc/hexanes); IR (neat) 3492, 2096, 1759 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$)

δ 0.94 (d, J = 5.2 Hz, 3H), 1.22-1.44 (m, 3H), 1.51 (m, 1H), 1.57 (m, 1H), 1.65-1.83 (m,

7H), 1.97 (d, J = 5.6 Hz, 1H), 2.65 (ddd, J = 14.8, 5.6, 1.2 Hz, 1H), 2.86 (ddd, J = 14.8,

8.4, 4.8 Hz, 1H), 3.05 (m, 1H), 3.42 (m, 2H); ^{13}C NMR (100.6 MHz, CDCl$_3$)

δ 15.2, 19.8, 21.3, 22.0, 25.6, 34.6, 37.7, 41.7, 42.5, 55.4, 69.9, 75.4, 217.6;   MS   (ES+)

m/z 274 (M + Na); HRMS calculated for C$_{13}$H$_{21}$N$_3$O$_2$Na (M + Na): 274.1531, found

274.1511.
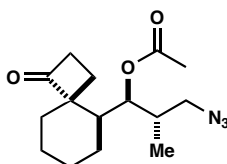
162

(1S*,2R*,4S*,5R*)-3-Azido-2-methyl-1-(1′-oxospiro[3.5]nonan-5′-yl)propyl

acetate (162). The reaction was carried out as described in the general procedure. The

diastereomeric mixture of alcohol **160** produced acetate **162** as a mixture with an

unknown diastereomer in ca. 10:1 ratio as a yellow oil (76%). Major: R_f = 0.70 (20%

EtOAc/hexanes); IR (neat) 2100, 1770, 1731 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.92

(d, J = 6.8 Hz, 3H), 1.15-1.38 (m, 3H), 1.46 (br t, J = 12.8 Hz, 1H), 1.58-1.76 (m, 5H),

1.81-1.88 (m, 2H), 1.95 (m, 1H), 2.06 (s, 3H), 2.83 (m, 1H), 2.98 (m, 2H), 3.30 (dd, J =

12.0, 4.4 Hz, 1H), 4.79 (dd, J = 6.8, 3.2 Hz, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 15.1,

19.3, 21.0, 21.8, 23.1, 25.4, 34.3, 36.8, 41.0, 42.3, 53.5, 69.2, 75.4, 170.6, 215.9. Minor

diastereomer (diagnostic peaks only): ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.87 (d, J = 6.8 Hz,

3H), 2.05 (s, 3H), 3.11 (t, J = 7.2 Hz, 2H), 4.95 (dd, J = 5.2, 4.0 Hz, 1H); MS (ES+) m/z 316 (M + Na); HRMS calculated for $C_{15}H_{23}N_3O_3$ (M + Na): 316.1637, found 316.2632.
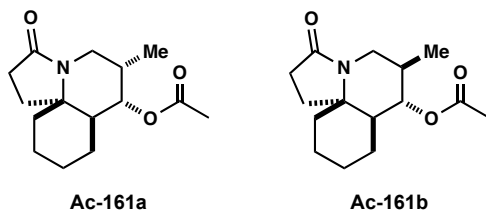
Ac-161a   **Ac-161b**

(6R*,7R*,7aR*,11^1R*)-6-Methyl-3-oxodecahydro-1H-pyrrolo[1,2-j]quinolin-7-yl acetate (Ac-161a) and **(6S*,7R*,7aR*,11^1R*)-6-methyl-3-oxodecahydro-1H-pyrrolo[1,2-j]quinolin-7-yl acetate (Ac-161b)**. The reaction was carried out as described for compound**142**. Lactams **Ac-161a** and **Ac-161b** were isolated as an inseparable mixture of diastereomers in ca. 3:1 ratio estimated by ^{1}H NMR as a yellow oil (83%). Acetate-**161a**: R_f = 0.22 (EtOAc); IR (neat) 1735, 1689 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.92 (distorted d, J = 6.8 Hz, 3H), 1.22-1.51 (m, 5H), 1.53-1.96 (m, 5H), 2.08 (s, 3H), 2.16-2.33 (m, 2H), 2.34-2.55 (m, 2H), 3.01 (m, 1H), 3.88 (d, J = 14.0 Hz, 1H), 5.33 (dd, J = 12.0, 4.8 Hz, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 10.8, 19.2, 21.0, 22.4, 22.9, 28.5, 29.4, 30.5, 31.6, 40.3, 40.6, 62.8, 70.4, 170.4, 173.3. Acetate-**161b** (diagnostic peaks only): ^{1}H NMR (400 MHz, CDCl$_3$) δ 2.10 (s, 3H), 4.10 (m, 1H), 5.10 (distorted t, J = 10.8 Hz, 1H); ^{13}C NMR (400 MHz, CDCl$_3$) δ 15.1, 36.6, 47.4, 73.5, 172.4. For mixture: MS (ES+) m/z 266 (M + 1); HRMS calculated for $C_{15}H_{23}NO_3$ (M + H): 266.1756, found 266.1682.
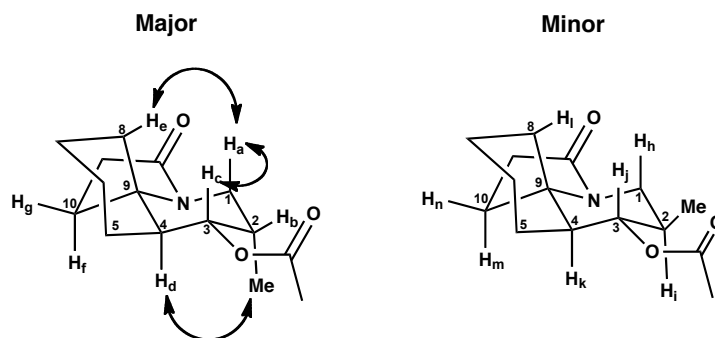
Structure determination for Ac-161a and Ac-161b. The structure of the major diastereomer of compound **Ac-161a** was proposed starting with H_a being in the axial position based on chemical shift compared to the other C-**1** proton (3.01 ppm vs. 3.89 ppm). The existing NOE between H_a and H_c gave evidence for the chair-like conformation of the piperidine ring. The J coupling values for H_c of 12.0 and 4.8 Hz indicate one axial and one equatorial proton on adjacent carbons. Since an NOE was observed between the methyl group and H_d indicating a 1,3-diaxial orientation, then H_b must be equatorial to leave the methyl axial and therefore H_d is axial. These proposed orientations are supported by the observed J values for H_c. The *cis* ring fusion was supported by the observed NOEs between both H_a and H_c with H_e, the axial proton on C-8.

The minor diastereomer **Ac-161b** was inseparable from the major diastereomer but the structure shown could be proposed due to differences in prominent protons. It was determined that the minor diastereomer was epimeric at C-2 due to the difference J values of H_j relative to H_c. H_j has two equivalent J values of 10.8 Hz, which it having relations with both H_i and H_k. Although NOE's were not clearly observed due to

diminished signals, the shift of H$_i$ is significantly lower than H$_b$, which also supports the proposed epimer.

163
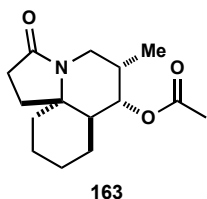
(6R*,7R*,7aR*,11^{1}S*)-6-Methyl-3-oxodecahydro-1H-pyrrolo[1,2-j]quinolin-7-yl acetate (163). The reaction was carried out as described for compound **144**. Acetate **162** produced lactam **163** as a 10:1 diastereomeric mixture with an unknown diastereomer isolated as a yellow oil and characterized without further purification (80%). R_f = 0.47 (EtOAc); IR (neat) 1737, 1693 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.79 (d, J = 6.8 Hz, 3H), 1.11 (m, 1H), 1.32 (m, 1H), 1.45-1.61 (m, 2H), 1.62-1.73 (m, 2H), 1.76-1.85 (m, 3H), 1.93 (m, 1H), 2.04 (m, 1H), 2.08 (s, 3H), 2.25 (dd, J = 16.4, 8.8 Hz, 1H), 2.44-2.63 (m, 3H), 4.05 (dd, J = 12.8, 6.8 Hz, 1H), 4.77 (dd, J = 12.4, 8.0 Hz, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 12.2, 20.6, 22.4, 23.3, 25.4, 25.9, 30.2, 32.6, 33.9, 41.1, 43.0, 63.9, 70.0, 170.5, 175.0; MS (ES+) m/z 266 (M$^+$+1); HRMS calculated for C$_{15}$H$_{24}$NO$_3$ (M$^+$+H): 266.1756, found 266.1620.
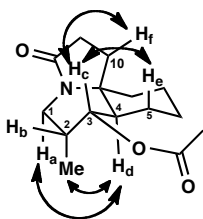
Structure determination for 163. The structure of compound **163** was proposed starting with H$_a$ that was assigned the axial proton of C-**1** based on the more upfield shift

(2.54 ppm vs. 4.04 ppm). H_e was assigned as axial due to the more upfield shift relative to the juxtapositional proton on C-**5**. Based on a present NOE between H_c and H_e, H_c must be axial, placing the acetoxy group equatorial. The J values for H_c of 12.4 and 8.0 Hz indicate one trans-diaxial and one axial-equatorial coupling. This suggests that H_b is equatorial since H_d must be axial based on the ring orientation. Thus, the methyl group is assigned axial. An NOE present between H_a and H_d supports the boat conformation of the piperidine ring, which is further supported by an NOE between the methyl group and H_d. The trans-fused ring system was supported by the NOE between H_c and H_e as well as the NOE between H_c and H_f.
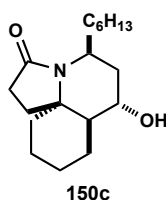
150c

(5S*,7S*,7aS*,11^1R*)-5-Hexyl-7-hydroxyoctahydro-1H-pyrrolo[1,2-

j]quinolin-3(2H)-one (150c). To a stirred solution of acetate **153** (135 mg, 0.40 mmol) in 5 mL of a 1:1 MeOH/H$_2$O mixture was added K$_2$CO$_3$ (165 mg, 1.2 mmol) at rt. After 1 h, TLC analysis indicated no remaining starting material, at which point the reaction was filtered and concentrated by rotary evaporation. The residue was redissolved in EtOAc and filtered to remove the remaining salts. The resulting yellow oil was purified by silica gel chromatography (EtOAc) to afford 107 mg (91%) of **150c** as a yellow oil. R_f = 0.43 (EtOAc); IR (neat) 3402, 1662 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.89 (distorted t, J = 6.8 Hz, 3H), 1.15 (qd, J = 12.4, 2.8 Hz, 1H), 1.24-1.37 (m, 8H), 1.42 (m, 1H), 1.48-1.63 (m, 3H), 1.64-1.77 (m, 4H), 1.82 (m, 2H), 1.90-2.03 (m, 3H), 2.10 (dd, J = 16.4, 9.2 Hz,

1H), 2.29 (ddd, J = 13.6, 11.6, 8.8 Hz, 1H), 2.40-2.53 (m, 2H), 3.35 (m, 1H), 3.69 (ddd, J = 12.0, 8.8, 6.0 Hz, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) d 144.1, 22.3, 22.7, 23.7, 25.6, 25.7, 27.6, 29.1, 31.5, 31.7, 31.8, 33.5, 42.3, 48.9, 51.4, 65.1, 66.0, 175.8; MS (ES+) m/z 294 (M$^+$+H); HRMS calculated for C$_{18}$H$_{32}$NO$_2$ (M$^+$+H): 294.2433, found 294.2371.

164
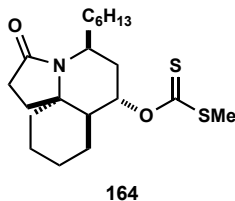
O-(5*S**,7*S**,7a*S**,11^1*R**)-5-Hexyl-3-oxodecahydro-1*H*-pyrrolo[1,2-*j*]quinolin-7-yl *S*-methyl carbonodithioate (164). The alcohol **150c** (16 mg, 0.05 mmol) in THF (1 mL) was added to a suspension of NaH (95% NaH, 12 mg, 0.5 mmol) in THF (1 mL) at – 78 °C. The solution was slowly warmed to 0 °C over 30 min when CS$_2$ (0.1 mL, 1 mmol) was added along with a few flakes of imidazole. The reaction was warmed to rt for 15 min and heated to reflux for 45 min. MeI (0.06 mL, 1 mmol) was added and refluxing was allowed to continue for 30 min. The reaction was cooled to rt and poured into a separatory funnel containing DCM and water (10 mL each). The aqueous layer was extracted twice with DCM (10 mL). The combined organic layers were dried over MgSO$_4$, filtered, and concentrated. The residual oil was purified by preparative thin layer chromatography (10% EtOAc/hexanes), which afforded **164** as a yellow oil (89%). R_f = 0.22 (20% EtOAc/hexanes); IR (neat) 1692, 1341, 1230, 1057 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.89 (distorted t, J = 6.4 Hz, 3H), 1.17-1.38 (m, 10H), 1.48-1.63 (m, 2H), 1.64-1.76 (m, 4H), 1.77-1.92 (m, 3H), 2.07 (m, 2H), 2.18 (dd, J = 16.4, 8.8 Hz, 1H), 2.43-2.55 (m, 3H), 2.58 (s, 3H), 3.42 (m, 1H), 5.62 (ddd, J = 12.4, 8.8, 5.2 Hz, 1H); ^{13}C NMR

(100.6 MHz, CDCl$_3$) δ 14.1, 19.2, 22.6, 22.9, 23.5, 25.5, 25.8, 27.6, 29.1, 31.4, 31.5, 31.8, 33.6, 38.7, 46.9, 51.4, 64.9, 78.7, 175.9, 215.6; MS (ES+) *m/z* 384 (M$^+$+H); HRMS calculated for C$_{20}$H$_{34}$NO$_2$S$_2$ (M$^+$+H): 384.2031, found 384.2023.

165
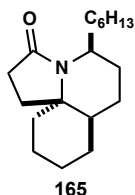
(5*S**,7a*R**,11^1*R**)-5-Hexyloctahydro-1*H*-pyrrolo[1,2-*j*]quinolin-3(2*H*)-one

(165). To a stirred solution of **164** (13 mg, 0.03 mmol) in benzene (1 mL) was added a spatula tip of 2,2′-azobis(2-methylpropionitrile) followed by tributyltin hydride (0.03 mL, 0.09 mmol) at rt. The reaction was allowed to reflux for 6 h before being cooled to rt and concentrated by rotary evaporation. The resulting yellow oil was purified by silica gel chromatography (20% → 40% EtOAc/hexanes). The fractions containing the lactam were passed through a short pad of silica impregnated with 10% KF using EtOAc. Lactam **165** was isolated as a yellow oil (99%). R_f = 0.10 (20% EtOAc/hexanes); IR (neat) 1689 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.87 (distorted t, *J* = 6.4 Hz, 3H), 1.16 (qd, *J* = 12.4, 3.2 Hz, 1H), 1.23-1.39 (m, 10H), 1.40-1.48 (m, 2H), 1.48-1.58 (m, 2H), 1.59-1.81 (m, 8H), 1.88 (dd, *J* = 12.4, 8.0 Hz, 1H), 2.11 (dd, *J* = 16.0, 8.8 Hz, 1H), 2.40-2.54 (m, 2H), 3.17 (m, 1H); ^{13}C NMR (101 MHz, CDCl$_3$) δ 14.1, 22.2, 22.7, 23.6, 24.5, 26.2, 27.3, 27.8, 29.2, 30.5, 31.7, 31.9, 31.9, 33.3, 42.5, 51.7, 66.2, 176.3; MS (ES+) *m/z* 278 (M$^+$+H); HRMS calculated for C$_{18}$H$_{32}$NO (M$^+$+H): 278.2484, found 278.2267.

Lactam **165** is equivalent to the a late-stage intermediate reported in Renaud's total synthesis of lepadiformine A.[44]

Renaud's Intermediate	Observed shifts	Difference
14.3	14.1	0.2
22.3	22.2	0.1
22.8	22.7	0.1
23.7	23.6	0.1
24.6	24.5	0.1
26.3	26.2	0.1
27.4	27.2	0.2
28	27.8	0.2
29.3	29.2	0.1
30.6	30.5	0.1
31.8	31.7	0.1
32	31.9	0.1
32	31.9	0.1
33.4	33.3	0.1
42.7	42.5	0.2
51.8	51.7	0.1
66.3	66.2	0.1
176.5	176.3	0.2
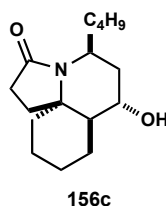
156c

(5S*,7S*,7aS*,11¹R*)-5-Butyl-7-hydroxyoctahydro-1H-pyrrolo[1,2-j]

quinolin-3(2H)-one (156c). The reaction was carried out as described in the procedure

for compound **150c**. Acetate **158** afforded lactam **156c** as a yellow oil (75%). R_f = 0.24

(60% EtOAc/hexanes); IR (neat) 3384, 1654 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 0.88

(distorted t, J = 7.1 Hz, 3H), 1.11 (ddd, J = 3.3, 12.6, 25.2 Hz, 1H), 1.21-1.40 (m, 6H),

1.42-1.58 (m, 3H), 1.61-1.73 (m, 5H), 1.79 (d, J = 11.9 Hz, 2H), 1.89 (d, J = 10.5 Hz,

1H), 1.96 (dd, J = 8.1, 12.6 Hz, 1H), 2.07 (m, 1H), 2.27 (ddd, J = 8.8, 11.8, 13.6 Hz, 1H),

2.35-2.55 (m, 2H), 3.31 (dt, J = 6.1, 11.9 Hz, 1H), 3.66 (ddd, J = 5.8, 8.7, 11.8 Hz, 1H);

^{13}C NMR (126 MHz, CDCl$_3$) δ 14.1, 22.3, 22.5, 23.7, 25.6, 25.7, 29.8, 31.33, 31.5, 33.5, 42.3, 48.9, 51.3, 65.0, 66.0, 175.79; MS (ES+) *m/z* 266 (M$^+$+H); HRMS calculated for C$_{16}$H$_{28}$NO$_2$ (M$^+$+H): 266.2120, found 266.1917.

168

O-(5S*,7S*,7aS*,11^{1}R*)-5-Butyl-3-oxodecahydro-1H-pyrrolo[1,2-j]quinolin-7-yl S-methyl carbonodithioate (168). The reaction was carried out as described in the procedure for **164**. Lactam **156c** was used to afford xanthate **168** (81%) as a yellow oil after purification by preparative TLC (15% EtOAc/hexanes). R_f = 0.28 (20% EtOAc/hexanes); IR (neat) 1695, 1228, 1209, 1056 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.90 (distorted t, *J* = 7.0 Hz, 3H), 1.14-1.45 (m, 6H), 1.46-1.91 (m, 9H), 1.98-2.10 (m, 2H), 2.15 (ddd, *J* = 8.9, 16.3 Hz, 1H), 2.56 (s, 3H), 2.53 – 2.40 (m, 3H), 3.37 (m, 1H), 5.61 (ddd, *J* = 14.4, 8.8, 5.6 Hz, 1H); ^{13}C NMR (101 MHz, CDCl$_3$) δ 14.1, 19.2, 22.5, 22.9, 23.5, 25.5, 25.8, 29.8, 31.2, 31.4, 33.6, 38.7, 46.9, 51.4, 64.9, 78.7, 175.8, 215.6; MS (ES+) *m/z* 356 (M$^+$+H); HRMS calculated for C$_{18}$H$_{30}$NO$_2$S$_2$ (M$^+$+H): 356.1718, found 356.1369.

169
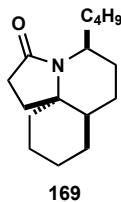
(5*S**,7a*R**,11^1*R**)-5-Butyloctahydro-1*H*-pyrrolo[1,2-*j*]quinolin-3(2*H*)-one

(169). Lactam **169** was prepared following the procedure of compound **165** starting from

168. Purification provided **169** as a yellow oil (88%). R_f = 0.27 (20% EtOAc/hexanes); IR

(neat) 1689 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.89 (distorted t, *J* = 7.1 Hz, 3H), 1.15

(ddd, *J* = 3.4, 12.4, 24.8 Hz, 1H), 1.39 – 1.23 (m, 7H), 1.40 – 1.55 (m, 4H), 1.80 – 1.58

(m, 9H), 1.86 (m, 1H), 2.10 (dd, *J* = 8.9, 16.1 Hz, 1H), 2.58 – 2.35 (m, 2H), 3.20 (m,

1H); ^{13}C NMR (101 MHz, CDCl$_3$) δ 14.1, 22.1, 22.5, 23.5, 24.4, 26.1, 27.2, 30.0, 30.4,

31.6 (2), 33.2, 42.5, 51.6, 66.1, 176.3; MS (ES+) *m/z* 250 (M$^+$+1); HRMS calculated for

C$_{16}$H$_{28}$NO (M$^+$+H): 250.2171, found 250.2036.

14-HCl
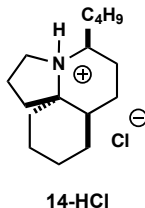
(5*S**,7a*R**,11^1*R**)-5-butyldodecahydropyrrolo[1,2-*j*]quinolinium   chloride

(Lepadiformine C hydrochloride, 14). To a stirred solution of **169** (20 mg, 0.08 mmol)

in THF (2 mL) at 0 °C was added 1M lithium aluminum hydride in ether (0.4 mL, 0.4

mmol). The solution was heated to 60 °C for 5 h and then cooled to 0 °C. The reaction

was diluted with ether followed by the addition of ca. 1 mL of H$_2$O, then 1 mL of 10%

NaOH/H$_2$O, and subsequently Na$_2$SO$_4$. The reaction was stirred and warmed to rt. The

phases were separated and the aqueous phase was extracted twice with DCM (10 mL),

washed with brine (10 mL), dried with MgSO$_4$, filtered and concentrated. Compound **14**

was dissolved in a minimum amount of DCM and about 1 mL of HCl/dioxane (4.0 M)

was added dropwise. The solution was allowed to stir at rt for 30 min followed by

concentration. Purification with silica gel chromatography (5% MeOH/DCM) yielded **14-HCl** as a yellow oil (20 mg, 95%). IR (neat) 3392, 2927, 1645, 1464 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.89 (distorted t, J = 5.6 Hz, 3H), 1.06 (dq, J = 10.0, 2.8 Hz, 1H), 1.18-1.42 (m, 7H), 1.46-1.55 (m, 2H), 1.60 (m, 1H), 1.68-1.75 (m, 3H), 1.83-1.87 (m, 2H), 1.90-2.15 (m, 6H), 2.18 (m, 1H), 2.35 (m, 1H), 2.86 (m, 1H), 3.53 (m, 1H), 3.67 (dd, J = 7.6, 4.8 Hz, 1H); ^{13}C NMR (101 MHz, CDCl$_3$) δ 13.9, 19.8, 20.8, 22.3, 22.4, 23.7, 25.1, 27.6, 28.2, 29.8, 30.8, 35.3, 37.7, 46.9, 55.3, 74.8; MS (ES+) m/z 236 (M$^+$+H); HRMS calculated for C$_{16}$H$_{30}$N (M$^+$+H): 236.2378, found 236.2303.

The data for amine **14-HCl** are equivalent to those reported for the isolated natural product.[10]

Reported	Observed	Difference
13.9	13.9	0
20	19.8	0.2
21	20.8	0.2
22.4	22.3	0.1
22.4	22.4	0
23.7	23.7	0
25.1	25.1	0
27.6	27.6	0
28.3	28.2	0.1
29.9	29.8	0.1
30.8	30.8	0
35.5	35.3	0.2
37.8	37.7	0.1
46.9	46.9	0
55.3	55.3	0
74.6	74.8	-0.2
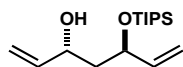
193

(3*R*,5*R*)-5-((Triisopropylsilyl)oxy)hepta-1,6-dien-3-ol (193). To a stirred solution of (3*R*,5*R*)-hepta-1,6-diene-3,5-diol (2.7 g, 21.1 mmol) in THF (200 mL) at −78 °C, was added *n*-BuLi (9.3 mL, 2.5 M in hexanes, 23.2 mmol) dropwise. The solution was allowed to stir for 20 min at −78 °C followed by the slow addition of TIPSCl (4.9 mL, 23.2 mmol). After 2 hrs, the reaction was allowed to slowly warm to rt over night and was quenched with $NH_4Cl_{(aq)}$ (100 mL) and the phases separated. The organic phase was washed with $NH_4Cl_{(aq)}$ (3×), brine, dried with $MgSO_4$, filtered, and concentrated. The crude extract was purified by silica gel chromatography (0→10% EtOAc/hexanes) to afford a yellow oil (6 g, 99%). R_f = 0.73 (20% EtOAc/hexanes); IR (neat) 3423, 1645, 1463, 1064 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.03-1.10 (m, 21H), 1.68 (ddd, *J* = 14.4, 4.4, 2.8 Hz,1H), 1.87 (ddd, *J* = 14.0, 9.6, 4.4 Hz, 1H), 3.59 (s, 1H), 4.43 (m, 1H), 4.62 (m, 1H), 5.06 (dt, *J* = 10.8, 1.2 Hz, 1H), 5.17 (dt, *J* = 10.4, 1.2 Hz, 1H), 5.26 (ddt, *J* = 17.2, 12.0, 1.6 Hz, 2H), 5.83 (ddd, *J* = 16.0, 10.4, 5.6 Hz, 1H), 5.94 (ddd, *J* = 6.0, 10.4, 16.4 Hz, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 12.2, 18.0 (2), 43.2, 69.6, 73.2, 114.0, 114.9, 140.0, 140.9; MS (ES+) *m/z* 285 (M$^+$+H); HRMS calculated for C$_{16}$H$_{32}$O$_2$Si (M$^+$+H): 285.2272, found 285.2255; [α]$_D^{23.6}$ −5.4 (*c* 1.02, DCM).

OH

TIPSO
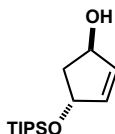
195

(1*R*,4*R*)-4-((Triisopropylsilyl)oxy)cyclopent-2-enol (195). To a stirred solution

of Grubbs I catalyst (362 mg, 0.44 mmol) in DCM (1200 mL) was added **193** (2.5 g, 8.8

mmol) at rt. The reaction was allowed to stir over night followed by concentration under

rotary evaporation. The crude material was purified by column chromatography (0→20%

EtOAc/hexanes) to yield a yellow oil (1.5 g, 68%). R_f = 0.41 (20% EtOAc/hexanes); IR

(neat) 3322, 1463, 1062 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.03-1.07 (m, 21H), 2.03-

2.08 (m, 2H), 2.10 (s, 1H), 4.98 (m, 1H), 5.15 (m, 1H), 5.91-5.98 (m, 2H); ^{13}C NMR

(100.6 MHz, CDCl$_3$) δ 12.0, 17.9 (2), 44.7, 76.0, 76.5, 135.4, 138.4; MS (ES+) *m/z* 239

(M$^+$-H$_2$O); HRMS calculated for C$_{14}$H$_{27}$OSi (M$^+$-H$_2$O): 239.1826, found 239.1834;

$[\alpha]_D^{23.7}$ +107.9 (*c* 2.15, DCM)

O

TIPSO
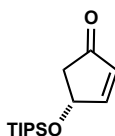
(*R*)-181

(*R*)-4-((Triisopropylsilyl)oxy)cyclopent-2-enone (181). To a stirred solution of

195 (2.0 g, 7.8 mmol) in DCM (40 mL) was added pyridinium dichlorochromate (4.4 g,

11.7 mmol). The reaction stirred at rt for 24 hr followed by filtration through filter paper

with Et$_2$O two sequential times. The solution was concentrated under rotary evaporation

and the concentrate was purified by silica gel column chromatography (0→10%

EtOAc/hexanes) to afford a yellow oil (1.8 g, 92%). R_f = 0.30 (10% EtOAc/hexanes); IR

(neat) 1725, 1463, 1111 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.02-1.12 (m, 21H), 2.28

(dd, J = 18.0, 2.0 Hz,1H), 2.73 (dd, J = 18.0, 6.0 Hz, 1H), 5.06 (m, 1H), 6.16 (d, J = 5.6

Hz, 1H), 7.48 (dd, J = 5.2, 2.0 Hz, 1H), ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 12.0, 17.8 (2),

45.3, 70.9, 134.3, 163.8, 206.4; MS (ES+) m/z 255 (M$^+$+H); HRMS calculated for

C$_{14}$H$_{27}$O$_2$Si (M$^+$+H): 255.1780, found 255.1735; $[\alpha]_D^{25.2}$ +53.3 (c 1.05, MeOH). Lit. value

for enantiomer is $[\alpha]_D$ −58.8 (c 1.05, MeOH).[121] Chiral GC separation: Astec Chiraldex

B-DM fused silica capillary column, 30 m x 0.25 mm x 0.12 μm, temperature gradient

from 120 ºC–140 ºC ramping up at 0.25 ºC/min, t_R = 44.13 min, t_S = 45.26 min.
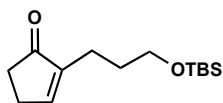
231

2-(3-((*tert*-Butyldimethylsilyl)oxy)propyl)cyclopent-2-enone (231). Following a procedure by Johnson and coworkers,[110] to neat allyl *tert*-butyldimethylsilyl ether (340 mg, 2.0 mmol) was added 4.8 mL of 9-BBN (0.5 M, 2.4 mmol) and stirred at 40 ºC for two hours and cooled to rt. In a separate flask, $PdCl_2$(dppf) (82 mg, 0.1 mmol) was added to a solution of **230** (620 mg, 1.5 mmol) in 4 mL of DMF (0.5 M based on allyl ether). Immediately following the catalyst addition, the solution of allyl ether and 9-BBN was added followed by 3 M K_3PO_4 (2.0 mL, 6.0 mmol). The combined solution was stirred at 60 ºC for four hours. Equal parts of DCM (20 mL) and $NH_4Cl_{(aq)}$ (20 mL) were added to the reaction and the layers were separated. The aqueous phase was extracted with DCM (3×), brine, dried with Na_2SO_4 and celite, filtered and concentrated. The resulting oil was purified by silica gel column chromatography (0→10% EtOAc/hexanes) to afford a yellow oil (295 mg, 58%). R_f = 0.40 (10% EtOAc/hexanes); IR (neat) 1705, 1252, 1104 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.01 (s, 6H), 0.85 (s, 9H), 1.67 (p, J = 8.0 Hz, 2H), 2.19 (t, J = 7.2 Hz, 2H), 2.32-2.39 (m, 2H), 2.49-2.56 (m, 2H), 3.58 (t, J = 6.4 Hz, 2H), 7.29 (s, 1H), ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 5.4, 18.2, 21.2, 25.9, 26.3, 30.7, 34.5, 62.5, 145.9, 157.4, 209.8; MS (ES+) *m/z* 255 (M$^+$+H); HRMS calculated for $C_{14}H_{27}O_2Si$ (M$^+$+H): 255.1780, found 255.1776.
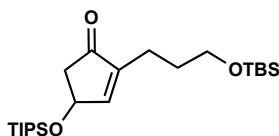
233

2-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-4-((triisopropylsilyl)oxy)cyclopent-2-enone (233). Obtained according to the procedure for the formation of **231** starting with allyl *tert*-butyldimethylsilylether and **225**. The crude mixture was purified by silica gel column chromatography (5% EtOAc/hexanes) to afford a yellow oil (470 mg, 55%). R_f = 0.63 (10% EtOAc/hexanes); IR (neat) 1706, 1463, 1100 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.04 (s, 6H), 0.89 (s, 9H), 1.04-1.10 (m, 21H), 1.71 (p, J = 6.4 Hz, 2H), 2.24 (t, J = 7.6 Hz, 2H), 2.32 (dd, J = 18.4, 2.0 Hz, 1H), 2.77 (dd, J = 18.0, 5.6 Hz, 1H), 3.62 (t, J = 6.4 Hz, 2H), 7.10 (s, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 5.3, 12.0, 17.9, 17.7, 20.9, 25.9, 30.3, 45.9, 62.4, 69.0, 146.7, 156.9, 206.2; MS (ES+) *m/z* 427 (M$^+$+H); HRMS calculated for C$_{23}$H$_{47}$O$_3$Si$_2$ (M$^+$+H): 427.3064, found 427.3047.
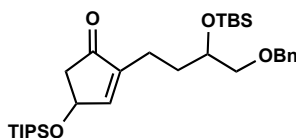
245

2-(4-(Benzyloxy)-3-((*tert*-butyldimethylsilyl)oxy)butyl)-4-((triisopropylsilyl)-oxy)cyclopent-2-enone (245). Obtained according to the procedure for the formation of **231** starting from **238** and **225**. The crude mixture was purified by silica gel column chromatography (0→10% EtOAc/hexanes) to afford a yellow oil (190 mg, 70%) as an inseparable mixture of two diastereomers. R_f = 0.77 (20% EtOAc/hexanes); IR (neat) 1716, 1462, 1251, 1088 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.07 (s, 6H), 0.08 (s, 6H),

0.91 (s, 18H), 1.06-1.12 (m, 42H), 1.61-1.74 (m, 2H), 1.74-1.87 (m, 4H), 2.16-2.39 (m, 6H), 2.79 (dd, J = 18.4, 6.0 Hz, 2H), 3.42 (ddd, J = 19.2, 9.6, 5.6 Hz, 4H), 3.88 (p, J = 5.2 Hz, 2H), 4.54 (s, 4H),4.96-5.00 (m, 2H), 7.11 (s, 2H), 7.25-7.38 (m, 10H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ -4.9, -4.5, 12.0, 12.2, 17.6, 17.8, 17.9, 18.1, 20.2, 25.8, 32.1, 32.2, 45.9, 69.0, 70.8, 70.9, 73.2, 74.2, 74.3, 127.4, 127.5, 128.0, 128.2, 138.2, 146.9, 147.0, 156.5, 156.6, 206.0, 206.1; MS (ES+) m/z 564 (M$^+$+NH$_4$); HRMS calculated for C$_{31}$H$_{55}$O$_4$Si$_2$ (M$^+$+H): 547.3639, found 547.3725.
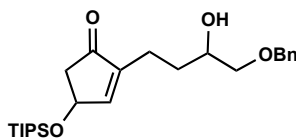
242

2-(4-(Benzyloxy)-3-hydroxybutyl)-4-((triisopropylsilyl)oxy)cyclopent-2-enone (242). To a stirred solution of 1% HCl in EtOH (140 mL) was added **245** (750 mg, 1.4 mmol) at rt. After 2 hr, NaHCO$_3$ (100 mL) and DCM (100 mL) were added and the layers separated. The aqueous layer was extracted 3× with DCM and the combined organic layers were washed with brine, dried with Na$_2$SO$_4$, filtered and concentrated. The crude oil was purified by silica gel column chromatography (20% EtOAc/hexanes) to afford **242** as a yellow oil (415 mg, 70%) as an inseparable mixture of two diastereomers. R_f = 0.25 (20% EtOAc/hexanes); IR (neat) 3432, 1710, 1463, 1088 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.04-1.13 (m, 42H), 1.60-1.69 (m, 4H), 1.74-1.87 (m, 4H), 2.16-2.39 (m, 6H), 2.50 (dd, J = 24.8, 4.0 Hz, 2H), 2.78 (ddd, J = 18.0, 6.0, 1.2 Hz, 4H), 3.36 (ddd, J = 10.0, 7.6, 2.8 Hz, 2H), 3.50 (dt, J = 9.2, 2.4 Hz, 2H), 3.74-3.82 (m, 2H), 4.55 (s, 4H), 4.95-4.99 (m, 2H), 7.11-7.15 (m, 2H), 7.27-7.38 (m, 10H); ^{13}C NMR (100.6 MHz,

CDCl$_3$) δ 12.0, 17.8, 17.8, 20.5, 20. 6, 30.9, 31.2, 45.8, 68.9, 68.9, 69.5, 69.6, 73.2, 73.3, 74.2, 74.2, 127.6, 127.6, 127.7, 127.7, 128.3, 137.8, 137.9, 146.3, 146.4, 157.3, 157.4, 206.3, 206.4; MS (ES+) m/z 450 (M$^+$+NH$_4$); HRMS calculated for C$_{25}$H$_{41}$O$_4$Si (M$^+$+H): 433.2774, found 433.2790.
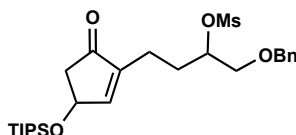
247

1-(Benzyloxy)-4-(5-oxo-3-((triisopropylsilyl)oxy)cyclopent-1-en-1-yl)butan-2-yl methanesulfonate (247). Following a procedure by Molander and coworkers,[26] to a stirred solution of **242** (100 mg, 0.23 mmol) in DCM (2 mL) was sequentially added TEA (0.06 mL, 0.46 mmol), a spatula tip of DMAP, and MsCl (0.02 mL, 0.28 mmol) at rt. After no more than 20 min, the reaction was concentrated under rotary evaporation and passed through a plug of silica with 30% EtOAc/hexanes to afford **247** as a yellow oil (117 mg, 99%) as an inseparable mixture of two diastereomers. R_f = 0.21 (20% EtOAc/hexanes); IR (neat) 1713, 1463, 1350, 1173, 1095 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.04-1.14 (m, 42H), 1.85-1.94 (m, 4H), 2.26-2.39 (m, 6H), 2.77 (dd, J = 18.4, 6.0 Hz, 2H), 3.02 (s, 6H), 3.56-3.67 (m, 4H), 4.54 (dd, J = 18.0, 12.0 Hz, 4H), 4.75-4.86 (m, 2H), 4.94-4.99 (m, 2H), 7.17-7.21 (m, 2H), 7.27-7.38 (m, 10H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 12.0, 17.8, 17.9, 20.3, 20. 4, 29.2, 29.4, 38.6, 38.6, 45.8, 45.9, 68.9, 68.9, 71.3, 71.4, 73.4, 73.4, 81.4, 127.7, 127.8, 127.9, 128.5, 137.2, 137.2, 144.9, 145.1, 157.9, 158.3, 205.9, 206.0; MS (ES+) m/z 528 (M$^+$+NH$_4$); HRMS calculated for C$_{26}$H$_{46}$O$_6$SNSi (M$^+$+NH)$_4$: 528.2816, found 528.2781.
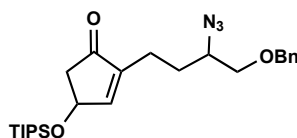
218

2-(3-Azido-4-(benzyloxy)butyl)-4-((triisopropylsilyl)oxy)cyclopent-2-enone

(218). Following a procedure from Molander and coworkers,[26] to a stirred solution of **247** (780 mg, 1.5 mmol) in DMSO (6 mL) was added NaN$_3$ (487 mg, 7.5 mmol) at rt. The reaction was heated to 60 ºC for 2 hr. At rt, DCM (20 mL) and H$_2$O (20 mL) were added and the layers were separated. The aqueous layer was extracted 3× with DCM and the combined organic layers were washed with brine, dried with Na$_2$SO$_4$, filtered and concentrated. The crude oil was purified by silica gel column chromatography (10% EtOAc/hexanes) to afford **218** as a yellow oil (640 mg, 94%) as an inseparable mixture of two diastereomers. R_f = 0.36 (20% EtOAc/hexanes); IR (neat) 2095, 1713, 1091 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.97-1.09 (m, 42H), 1.48-1.59 (m, 2H), 1.60-1.72 (m, 2H), 2.11-2.33 (m, 6H), 2.70 (dd, J = 18.0, 6.0 Hz, 2H), 3.36-3.55 (m, 6H), 4.49 (s, 4H), 4.87-4.91 (m, 2H), 7.03-7.05 (m, 2H), 7.18-7.30 (m, 10H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 12.0, 17.9, 17.9, 21.3, 21.3, 28.6, 28.7, 45.9, 61.3, 61.3, 68.9, 72.6, 73.3, 73.4,127.6, 127.8, 128.4, 137.7, 145.6, 157.5, 206.0; MS (ES+) m/z 430 (M$^+$-N$_2$+H); HRMS calculated for C$_{25}$H$_{40}$NO$_3$Si (M$^+$-N$_2$+H): 430.2783, found 430.2766
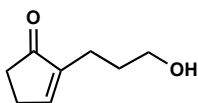
248

2-(3-Hydroxypropyl)cyclopent-2-enone (248). To a stirred solution of **231** (1.3 g, 5.1 mmol) in THF (3 mL) was slowly added a 1M solution of TBAF (10.2 mL, 10.2 mmol) in THF at 0 ℃. The reaction was allowed to slowly warm to rt. After 12 h the reaction was concentrated and purified by silica gel column chromatography (50→100% EtOAc/hexanes) to afford **248** as a yellow oil (230 mg, 33%). Spectral data matched the literature values.[116]
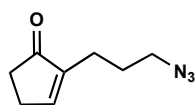
249

2-(3-Azidopropyl)cyclopent-2-enone (249). To a stirred solution of **248** (90 mg, 0.64 mmol) in THF (1.5 mL) was added PPh₃ (340 mg, 1.3 mmol) at 0 ℃. DIAD (0.25 mL, 1.3 mmol) was added after 5 minutes and DPPA (0.31 mL, 1.4 mmol) was added 10 minutes later. The reaction was allowed to slowly warm up to room temperature over 1 hr and DCM (5 mL) and NaHCO₃ (5 mL) were added. The layers were separated and the aqueous layer was extracted 3× with DCM. The combined organic extracts were washed with brine, dried with Na₂SO₄, filtered, and concentrated. The resulting yellow oil was further purified by silica gel chromatography (10% EtOAc/hexanes) to afford a yellow oil (70 mg, 67%). The spectral data matched that in the literature.[122]
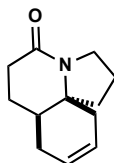
250

(7a*R**,11a*S**)-2,3,6,7,7a,8-Hexahydro-1*H*-pyrrolo[2,1-*j*]quinolin-5(11*H*)-one

(250). To a stirred solution of **249** (16 mg, 0.10 mmol) in DCM (4 mL) was bubbled 1,3-butadiene gas for 5 min at 0 ℃. A 1M solution of MeAlCl$_2$ in hexanes (0.3 mL, 0.3 mmol) was added after 5 min and a temperature of 0 ℃ was maintained for 1 hr and then allowed to warm to rt. The reaction media was gelatin so DCM (10 mL) was added to loosen up the mixture. NaHCO$_3$ (10 mL) was subsequently added and the layers were separated. The aqueous layer was extracted with DCM (2×). The combined organic layers were washed with NaHCO$_3$ followed by brine, dried with MgSO$_4$, filtered and concentrated. The resulting oil was purified by silica gel column chromatography (EtOAc) to afford a yellow oil (12 mg, 63%). R_f = 0.33 (EtOAc); IR (neat) 1638, 1439 cm^{-1}; MS (ES+) *m/z* 192 (M$^+$+H); HRMS calculated for C$_{12}$H$_{18}$NO (M$^+$+H): 192.1390, found 192.1371.
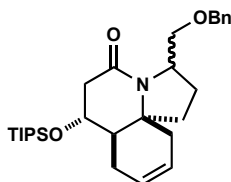
251

(7*R**,7a*R**,11a*S**)-3-((Benzyloxy)methyl)-7-((triisopropylsilyl)oxy)-

2,3,6,7,7a,8-hexahydro-1*H*-pyrrolo[2,1-*j*]quinolin-5(11*H*)-one (251). To a stirred solution of the diastereomeric mixture of **218** (40 mg, 0.08 mmol) in DCM (1 mL) was added 20% wt 1,3-butadiene in toluene (0.94 mL, 2.8 mmol) at 0 ℃. After 5 min, 1M MeAlCl$_2$ in hexanes (0.16 mL, 0.16 mmol) was added and the temperature of 0 ℃ was maintained for 2 hr and allowed to warm to rt. After 2 hr, NaHCO$_3$ (5 mL) and EtOAc (5

mL) were added and the layers were separated and the aqueous layer was extracted with EtOAc (2×). The combined organic layers were washed with brine, dried with $MgSO_4$, filtered and concentrated. Analysis of the crude NMR mixture indicated *ca.* 1:1 mixture of two diastereomers. The resulting oil was purified by silica gel preparative TLC (30% EtOAc/hexanes) to afford a yellow oil (30 mg, 71%) as a 5:1 mixture of diastereomers. R_f = 0.41 (30% EtOAc/hexanes); IR (neat) 1645, 1429, 1100 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (s, 21H), 1.64-1.85 (m, 3H), 1.88-1.97 (m, 2H), 1.99-2.15 (m, 2H), 2.29-2.42 (m, 2H), 2.55(dd, *J* = 18.0, 3.2, 1H), 2.81 (dd, *J* = 18.0, 7.6 Hz, 1H), 3.60-3.76 (m, 2H), 4.28 (m, 1H), 4.38 (m, 1H), 4.43-4.55 (m, 2H), 5.53 (m, 1H), 5.61 (m, 1H), 7.23-7.36 (m, 5H); Major diastereomer: ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 12.7, 18.2, 25.0, 26.9, 33.9, 36.7, 41.8, 43.7, 57.3, 63.3, 69.2, 69.8, 73.1, 124.9, 126.3, 127.4, 127.5, 128.3, 138.6, 168.0;); Minor diastereomer (diagnostic peaks only): ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 42.4, 46.1, 56.8, 62.4, 66.6, 69.0, 124.0, 125.4, 138.5, 168.1; MS (ES+) *m/z* 484 (M^++H); HRMS calculated for $C_{29}H_{46}NO_3Si$ (M^++H): 484.3247, found 484.3238.
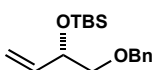
(*S*)-238

(*S*)-((1-(Benzyloxy)but-3-en-2-yl)oxy)(*tert*-butyl)dimethylsilane (238). To a stirred solution of (*S*)-1-(benzyloxy)but-3-en-2-ol[117] (1.0 g, 5.6 mmol) in DMF (6 mL) was added TBSCl (2.5 g, 17 mmol) and imidazole (1.5 g, 23 mmol) at rt. Ether (10 mL) and water (10 mL) were added to the reaction after 24 h, which was then allowed to warm to rt. The aqueous layer was extracted 3× with ether. The combined organic extracts were washed with aqueous 1M HCl, $NaHCO_3$, and then brine. The organic layer

was dried with Na$_2$SO$_4$, filtered, and concentrated. The resulting yellow oil was further purified by silica gel chromatography (0 → 5% EtOAc/hexanes) to afford a yellow oil (1.3 g, 81%), %). R_f = 0.81 (10% EtOAc/hexanes); Spectral data matched literature;[113] $[\alpha]_D^{23.7}$ −17.0 (c 1.17, CHCl$_3$).
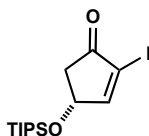
(R)-225

(R)-2-Iodo-4-((triisopropylsilyl)oxy)cyclopent-2-enone (225). To a stirred solution of I$_2$ (10.7 g, 42 mmol) in Et$_2$O (70 mL) was added pyridine (2.0 mL, 25 mmol) followed by dropwise addition of (R)-**181** (8.9 g, 35 mmol) at rt. The reaction flask was covered completely with aluminum foil. After 24 hr, the reaction was quenched with Na$_2$S$_2$O$_{3(aq)}$ (50 mL) and allowed to stir until the solution changed from dark in color to clear and light yellow. Subsequently, the layers were partitioned and the organic layer was washed with Na$_2$S$_2$O$_{3(aq)}$ (3×), 1 M HCl (3×), again with Na$_2$S$_2$O$_{3(aq)}$ (3×), and brine. The organic layer was then dried with MgSO$_4$, filtered and concentrated under rotary evaporation and the resulting oil was purified using silica gel column chromatography (0→10% Et$_2$O/hexanes) to afford a yellow oil (11 g, 85%). R_f = 0.45 (10% EtOAc/hexanes); IR (neat) 1726, 1463, 1093 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.03-1.10 (m, 21H), 2.38 (dd, J = 18.0, 2.0 Hz,1H), 2.89 (dd, J = 18.0, 5.6 Hz, 1H), 5.03 (dt, J = 6.0, 2.0 Hz, 1H), 7.82 (d, J = 2.8 Hz, 1H), ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 11.9, 17.8 (2), 42.8, 72.2, 104.8, 169.2, 200.1; MS (ES+) m/z 398 (M$^+$+NH$_4$); HRMS calculated for C$_{14}$H$_{26}$O$_2$Si (M$^+$+NH$_4$): 398.1012, found 398.0972; $[\alpha]_D^{23.7}$ +25.5 (c 4.3, DCM).
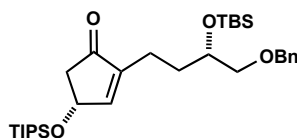
(*R*,*S*)-**245**

(*R*)-2-((*S*)-4-(Benzyloxy)-3-((*tert*-butyldimethylsilyl)oxy)butyl)-4-

((triisopropylsilyl) oxy)cyclopent-2-enone (245). Obtained according to the procedure

for the formation of **231** starting from (*S*)-**238** and (*R*)-**225**. The crude mixture was

purified by silica gel column chromatography (0→10% EtOAc/hexanes) to afford a

yellow oil (3.6 g, 88%). R_f = 0.77 (20% EtOAc/hexanes); IR (neat) 1716, 1462, 1251,

1088 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.05 (s, 3H), 0.06 (s, 3H), 0.89 (s, 9H), 1.06-

1.12 (m, 21H), 1.65 (m, 1H), 1.78 (m, 1H), 2.14-2.39 (m, 3H), 2.77 (dd, J = 18.4, 6.0 Hz,

2H), 3.41 (ddd, J = 19.2, 9.6, 5.6 Hz, 4H), 3.86 (m, 1H), 4.52 (s, 2H),4.96 (m, 1H), 7.09

(m, 1H), 7.25-7.38 (m, 5H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ -4.8, -4.4, 12.0, 17.7, 17.8,

17.9, 20.2, 25.8, 32.2, 45.9, 69.0, 70.8, 73.2, 74.3, 127.4, 127.5, 128.2, 138.3, 147.0,

156.5, 205.9; MS (ES+) m/z 564 (M$^+$+NH$_4$); HRMS calculated for C$_{31}$H$_{55}$O$_4$Si$_2$ (M$^+$+H):

547.3639, found 547.3725; ; [α]$_D^{23.7}$ +4.91 (*c* 3.8, DCM).
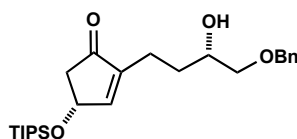
(*R*,*S*)-**242**

(*R*)-2-((*S*)-4-(Benzyloxy)-3-hydroxybutyl)-4-((triisopropylsilyl)oxy)cyclopent-

2-enone (242). To a stirred solution of (*R*,*S*)-**245** (1.0 g, 1.8 mmol) in MeOH (4 mL) was

added PPTS (900 mg, 3.6 mmol) at rt. After 12 hr, DCM (20 mL) and H$_2$O (20 mL) were

added and the layers were partitioned and the aqueous layer was extracted with DCM (3×). The combined organic layers were washed with 1 M HCl (3×) followed by brine. The organic layer was then dried with MgSO$_4$, filtered and concentrated under rotary evaporation and the resulting oil was purified using silica gel column chromatography (0→10% Et$_2$O/hexanes) to afford a yellow oil (540 mg, 70%). R_f = 0.25 (20% EtOAc/hexanes); IR (neat) 3432, 1710, 1463, 1088 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.98-1.18 (m, 21H), 1.63 (q, J = 6.8 Hz, 2H), 2.22-2.42 (m, 3H), 2.64 (br s,1H), 2.78 (dd, J = 18.0, 6.0 Hz, 1H), 3.36 (t, J = 8.0 Hz, 1H), 3.49 (dd, J = 9.6, 3.2 Hz, 1H), 3.78 (m, 1H), 4.54 (s, 2H), 4.95 (m, 1H), 7.13 (s, 1H), 7.25-7.37 (m, 5H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 12.0, 17.8, 17.9, 20.5, 31.2, 45.9, 69.0, 69.6, 73.3, 74.2, 127.7, 127.7, 128.4, 137.9, 146.4, 157.5, 206.4; MS (ES+) m/z 450 (M$^+$+NH$_4$); HRMS calculated for C$_{25}$H$_{41}$O$_4$Si (M$^+$+H): 433.2774, found 433.2790; [α]$_D^{23.7}$ +8.1 (c 1.0, DCM).
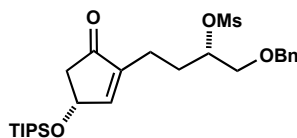
(R,S)-247

(S)-1-(Benzyloxy)-4-((R)-5-oxo-3-((triisopropylsilyl)oxy)cyclopent-1-en-1-yl)butan-2-yl methanesulfonate (247). Obtained according to the procedure for the formation of **247** starting from (R,S)-**242** to afford (R,S)-**247** (340 mg, 99%) as a yellow oil. R_f = 0.21 (20% EtOAc/hexanes); IR (neat) 1713, 1463, 1350, 1173, 1095 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.03-1.12 (m, 21H), 1.89 (q, J = 7.6 Hz, 2H), 2.27-2.35 (m, 3H), 2.77 (dd, J = 18.4, 6.0 Hz, 1H), 3.01 (s, 3H), 3.61 (ddd, J = 22.8, 10.8, 7.2 Hz, 2H), 4.54 (dd, J = 17.6, 12.0 Hz, 2H), 4.81 (ddd, J = 10.0, 6.4, 3.6 Hz, 1H), 4.96 (m, 1H), 7.18

(s, 1H), 7.25-7.37 (m, 5H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 12.0, 17.8, 17.8, 20.2, 29.3, 38.6, 45.8, 68.9, 71.2, 73.3, 81.3, 127.7, 127.9, 128.4, 137.2, 145.1, 157.9, 205.9; MS (ES+) *m/z* 528 (M$^+$+NH$_4$); HRMS calculated for C$_{26}$H$_{46}$O$_6$NSSi (M$^+$+NH)$_4$: 528.2816, found 528.2781; ; $[\alpha]_D^{23.7}$ +17.2 (*c* 4.3, DCM).
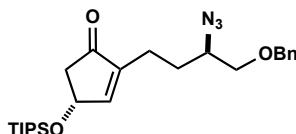
(*R,R*)-**218**

(*R*)-2-((*R*)-3-Azido-4-(benzyloxy)butyl)-4-((triisopropylsilyl)oxy)cyclopent-2-enone (218). Obtained according to the procedure for the formation of **218** starting from (*R,S*)-**247** to afford (*R,S*)-**218** (160 mg, 72%) as a yellow oil. R_f = 0.36 (20% EtOAc/hexanes); IR (neat) 2095, 1713, 1091 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.03-1.16 (m, 21H), 1.62 (m, 1H), 1.74 (m, 1H), 2.19-2.40 (m, 3H), 2.78 (dd, *J* = 18.4, 6.0 Hz, 1H), 3.47-3.55 (m, 2H), 3.59 (m, 1H), 4.56 (s, 2H), 4.97 (m, 1H), 7.12 (m, 1H), 7.25-7.38 (m, 5H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 12.0, 17.8, 17.9, 21.3, 28.5, 45.8, 61.3, 68.9, 72.6, 73.3, 127.5, 127.7, 128.4, 137.6, 145.6, 157.4, 205.9; MS (ES+) *m/z* 430 (M$^+$-N$_2$+H); HRMS calculated for C$_{25}$H$_{40}$NO$_3$Si (M$^+$-N$_2$+H): 430.2783, found 430.2766; ; $[\alpha]_D^{23.7}$ +31.5 (*c* 1.00, DCM).
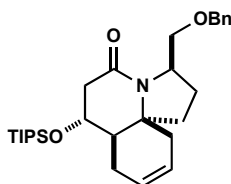
(*R,S,R,R*)-**251**

(3*R*,7*R*,7a*R*,11a*S*)-3-((Benzyloxy)methyl)-7-((triisopropylsilyl)oxy)-

2,3,6,7,7a,8-hexahydro-1*H*-pyrrolo[2,1-*j*]quinolin-5(11*H*)-one **(251).** Obtained

according to the procedure for the formation of **251** starting from (*R,S*)-**218** to afford

(*R,S,R,R*)-**251** (32 mg, 67%) as a yellow oil. NMR analysis of the crude reaction mixture

indicated a single diastereomer. R_f = 0.41 (30% EtOAc/hexanes); IR (neat) 1645, 1429,

1100 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.06 (s, 21H), 1.70-1.85 (m, 3H), 1.92-1.99 (m,

2H), 2.00-2.15 (m, 2H), 2.29-2.42 (m, 2H), 2.57 (dd, *J* = 18.0, 3.2, 1H), 2.83 (dd, *J* =

18.0, 7.6 Hz, 1H), 3.62-3.78 (m, 2H), 4.30 (m, 1H), 4.40 (ddd, *J* = 7.6, 5.6, 3.6 Hz, 1H),

4.51 (dd, *J* = 21.6, 11.6 Hz, 2H), 5.55 (m, 1H), 5.64 (m, 1H), 7.26-7.38 (m, 5H); ^{13}C

NMR (100.6 MHz, CDCl$_3$) δ 12.7, 18.2, 25.0, 26.9, 33.9, 36.7, 41.8, 43.7, 57.3, 63.3,

69.2, 69.8, 73.1, 124.9, 126.3, 127.4, 127.5, 128.3, 138.6, 168.0; MS (ES+) *m/z* 484

(M$^+$+H); HRMS calculated for C$_{29}$H$_{46}$NO$_3$Si (M$^+$+H): 484.3247, found 484.3238; ; $[\alpha]_D^{23.7}$

−16.5 (*c* 2.2, DCM).

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General Methods. X-ray crystal structure determination was performed by Victor Day, Ph.D. at the University of Kansas. Intensity data were collected using a Bruker APEX CCD area detector mounded on a Bruker D8 geniometer with graphite-monochromated MoK radiation.

140
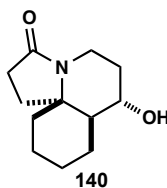
Specific methods for structure determination and refinement of compound 140. The compound was recrystallized from DCM. Colorless plate-shaped crystals of $C_{12}H_{19}NO_2$ are, at 100(2) K, monoclinic, space group Cc – C_s^4 (No. 9) [1] with **a** = 15.052(2) Å, **b** = 7.812(1) Å, **c** = 10.978(1) Å, = 127.009(2), V = 1030.8(2) Å^3 and Z = 4 molecules {d_{calcd} = 1.348 g/cm^3; $_a$(MoK) = 0.091 mm^{-1}}. A full hemisphere of diffracted intensities (1850 20-second frames with a scan width of 0.30) was measured for a single-domain specimen using graphite-monochromated MoK radiation (= 0.71073 Å) on a Bruker SMART APEX CCD Single Crystal Diffraction System [2]. X-rays were provided by a fine-focus sealed x-ray tube operated at 50kV and 30mA. Lattice constants were determined with the Bruker SAINT software package using peak centers for 1580 reflections. A total of 5843 integrated reflection intensities having 2((MoK)< 61.00 were produced using the Bruker program SAINT[3]; 2882 of these were unique and gave R_{int} = 0.042 with a coverage which was

98.0% complete. The data were corrected empirically for variable absorption effects using equivalent reflections; the relative transmission factors ranged from 0.906 to 1.000. The Bruker software package SHELXTL was used to solve the structure using "direct methods" techniques. All stages of weighted full-matrix least-squares refinement were conducted using F_o^2 data with the SHELXTL Version 6.10 software package[4].

The final structural model incorporated anisotropic thermal parameters for all nonhydrogen atoms and isotropic thermal parameters for all hydrogen atoms. All hydrogen atoms were located in a difference Fourier and included in the structural model as independent isotropic atoms whose parameters were allowed to vary in least-squares refinement cycles. When a couple isotropic thermal parameters for these hydrogen atoms refined to non-positive-definite values, the isotropic thermal parameters for all hydrogen atoms except the hydroxyl hydrogen were fixed at values 1.2 times the equivalent isotropic thermal parameter of the carbon atom to which they were covalently bonded. A total of 194 parameters were refined using 2 restraints, 2882 data and weights of w = 1/ $[^2(F^2) + (0.0932\ P)^2]$, where P = $[F_O^2 + 2F_C^2]$ / 3. Final agreement factors at convergence are: R_1(unweighted, based on F) = 0.069 for 2542 independent absorption-corrected "observed" reflections having 2(MoK)< 61.00 and I>2(I); R_1(unweighted, based on F) = 0.078 and wR_2(weighted, based on F^2) = 0.162 for all 2882 independent absorption-corrected reflections having 2(MoK)< 61.00. The largest shift/s.u. was 0.000 in the final refinement cycle. The final difference map had maxima and minima of 0.40 and -0.25 e$^-$/Å^3, respectively.
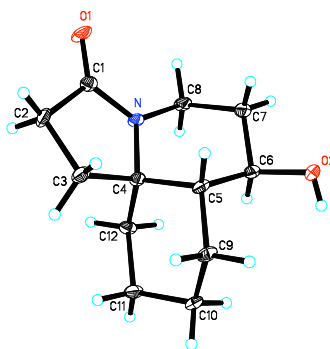
Figure 7. Ellipsoid drawing of **140**

Table 6. Crystal data and structure refinement for $C_{12}H_{19}NO_2$.

Empirical formula	$C_{12}H_{19}NO_2$
Formula weight	209.28
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$Cc - C_s^4$ (No. 9)
Unit cell dimensions	**a** = 15.052(2) Å $\quad$ = 90.000°
	b = 7.812(1) Å $\quad$ = 127.009(2)°.
	c = 10.978(1) Å $\quad$ = 90.000°
Volume	1030.8(2) Å^3
Z	4
Density (calculated)	1.348 Mg/m^3
Absorption coefficient	0.091 mm^{-1}
F(000)	456
Crystal size	0.20 x 0.16 x 0.05 mm^3
Theta range for data collection	3.11° to 30.50°
Index ranges	-21 h 20, -10 k 10, -15 l 15
Reflections collected	5843
Independent reflections	2882 [R_{int} = 0.042]
Completeness to theta = 30.50°	98.0 %
Absorption correction	Multi-scans
Max. and min. transmission	1.000 and 0.906

Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2882 / 2 / 194
Goodness-of-fit on F^2	1.054
Final R indices [I>2sigma(I)]	$R_1 = 0.069$, $wR_2 = 0.156$
R indices (all data)	$R_1 = 0.078$, $wR_2 = 0.162$
Absolute structure parameter	0.0(18)
Largest diff. peak and hole	0.40 and -0.25 $e^-/\text{Å}^3$

$R_1 = ||F_o| - |F_c|| / |F_o|$

$wR_2 = \{ [w(F_o^2 - F_c^2)^2] / [w(F_o^2)^2] \}^{1/2}$

Table 7. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3) for $C_{12}H_{19}NO_2$. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
O(1)	6219(2)	3137(3)	4625(2)	19(1)
O(2)	2827(2)	7766(3)	4174(3)	24(1)
N	4922(2)	3762(3)	5020(2)	11(1)
C(1)	5346(2)	2834(4)	4441(3)	13(1)
C(2)	4569(2)	1338(4)	3568(3)	16(1)
C(3)	3507(2)	1773(4)	3393(3)	17(1)
C(4)	3834(2)	3194(3)	4581(3)	11(1)
C(5)	3037(2)	4725(3)	3887(3)	12(1)
C(6)	3528(2)	6324(4)	4905(3)	15(1)
C(7)	4634(2)	6781(4)	5237(3)	18(1)
C(8)	5453(2)	5290(4)	5947(3)	14(1)
C(9)	1897(2)	4196(4)	3465(3)	13(1)
C(10)	1984(2)	3484(4)	4824(3)	13(1)
C(11)	2813(2)	2015(4)	5584(3)	15(1)
C(12)	3951(2)	2488(4)	5977(3)	14(1)

Table 8. Bond lengths [Å] and angles [°] for $C_{12}H_{19}NO_2$.

O(1)-C(1)	1.227(3)	C(3)-H(3B)	0.99(4)
O(2)-C(6)	1.417(4)	C(3)-H(3A)	0.95(4)
O(2)-H(2O)	0.73(6)	C(4)-C(5)	1.533(3)
N-C(1)	1.350(3)	C(4)-C(12)	1.535(4)
N-C(8)	1.456(3)	C(5)-C(6)	1.536(4)
N-C(4)	1.471(3)	C(5)-C(9)	1.540(3)
C(1)-C(2)	1.518(4)	C(5)-H(5)	1.01(3)
C(2)-C(3)	1.528(4)	C(6)-C(7)	1.517(4)
C(2)-H(2A)	0.96(4)	C(6)-H(6)	0.89(4)
C(2)-H(2B)	0.91(4)	C(7)-C(8)	1.526(4)
C(3)-C(4)	1.550(4)	C(7)-H(7A)	0.96(4)

C(7)-H(7B)	0.95(4)	C(10)-H(10A)	0.90(4)
C(8)-H(8A)	0.98(4)	C(10)-H(10B)	0.92(4)
C(8)-H(8B)	0.98(3)	C(11)-C(12)	1.538(4)
C(9)-C(10)	1.522(4)	C(11)-H(11A)	0.92(4)
C(9)-H(9A)	0.98(4)	C(11)-H(11B)	0.98(4)
C(9)-H(9B)	1.00(3)	C(12)-H(12A)	0.98(4)
C(10)-C(11)	1.522(4)	C(12)-H(12B)	0.96(4)

Table 9. Bond angles [°] for C$_{12}$H$_{19}$NO$_2$.

C(6)-O(2)-H(2O)	105(5)	C(4)-C(5)-C(6)	112.5(2)
C(1)-N-C(8)	123.6(2)	C(4)-C(5)-C(9)	109.7(2)
C(1)-N-C(4)	115.6(2)	C(6)-C(5)-C(9)	113.5(2)
C(8)-N-C(4)	120.7(2)	C(4)-C(5)-H(5)	107(2)
O(1)-C(1)-N	125.6(3)	C(6)-C(5)-H(5)	106(2)
O(1)-C(1)-C(2)	126.4(2)	C(9)-C(5)-H(5)	108(2)
N-C(1)-C(2)	107.9(2)	O(2)-C(6)-C(7)	106.5(2)
C(1)-C(2)-C(3)	104.9(2)	O(2)-C(6)-C(5)	111.5(2)
C(1)-C(2)-H(2A)	102(2)	C(7)-C(6)-C(5)	110.1(2)
C(3)-C(2)-H(2A)	114(2)	O(2)-C(6)-H(6)	114(2)
C(1)-C(2)-H(2B)	115(2)	C(7)-C(6)-H(6)	110(2)
C(3)-C(2)-H(2B)	114(2)	C(5)-C(6)-H(6)	105(2)
H(2A)-C(2)-H(2B)	107(3)	C(6)-C(7)-C(8)	112.1(2)
C(2)-C(3)-C(4)	106.0(2)	C(6)-C(7)-H(7A)	104(2)
C(2)-C(3)-H(3B)	111(2)	C(8)-C(7)-H(7A)	113(2)
C(4)-C(3)-H(3B)	112(2)	C(6)-C(7)-H(7B)	114(2)
C(2)-C(3)-H(3A)	105(2)	C(8)-C(7)-H(7B)	109(2)
C(4)-C(3)-H(3A)	109(2)	H(7A)-C(7)-H(7B)	105(3)
H(3B)-C(3)-H(3A)	113(3)	N-C(8)-C(7)	109.5(2)
N-C(4)-C(5)	108.2(2)	N-C(8)-H(8A)	105(2)
N-C(4)-C(12)	110.20(2)	C(7)-C(8)-H(8A)	110(2)
C(5)-C(4)-C(12)	111.2(2)	N-C(8)-H(8B)	108(2)
N-C(4)-C(3)	102.6(2)	C(7)-C(8)-H(8B)	109(2)
C(5)-C(4)-C(3)	112.6(2)	H(8A)-C(8)-H(8B)	116(3)
C(12)-C(4)-C(3)	111.7(2)	C(10)-C(9)-C(5)	112.3(2)

C(10)-C(9)-H(9A)	113(2)	
C(5)-C(9)-H(9A)	113(2)	
C(10)-C(9)-H(9B)	110(2)	
C(5)-C(9)-H(9B)	109(2)	
H(9A)-C(9)-H(9B)	100(3)	
C(11)-C(10)-C(9)	111.8(2)	
C(11)-C(10)-H(10A)	116(2)	
C(9)-C(10)-H(10A)	108(2)	
C(11)-C(10)-H(10B)	104(2)	
C(9)-C(10)-H(10B)	113(2)	
H(10A)-C(10)-H(10B)	105(3)	
C(10)-C(11)-C(12)	112.3(2)	

C(10)-C(11)-H(11A)	111(2)
C(12)-C(11)-H(11A)	109(2)
C(10)-C(11)-H(11B)	112(2)
C(12)-C(11)-H(11B)	106(2)
H(11A)-C(11)-H(11B)	105(3)
C(4)-C(12)-C(11)	111.5(2)
C(4)-C(12)-H(12A)	109(2)
C(11)-C(12)-H(12A)	105(2)
C(4)-C(12)-H(12B)	110(2)
C(11)-C(12)-H(12B)	111(2)
H(12A)-C(12)-H(12B)	111(3)

Table 10. Anisotropic displacement parameters $(\text{Å}^2 \times 10^3)$ for $C_{12}H_{19}NO_2$. 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}
O(1)	13(1)	26(1)	25(1)	-2(1)	15(1)	1(1)
O(2)	25(1)	15(1)	45(1)	9(1)	29(1)	8(1)
N	6(1)	14(1)	14(1)	-1(1)	6(1)	-1(1)
C(1)	9(1)	15(1)	14(1)	2(1)	6(1)	1(1)
C(2)	15(1)	15(1)	21(1)	-5(1)	12(1)	2(1)
C(3)	14(1)	19(1)	23(1)	-6(1)	14(1)	-2(1)
C(4)	7(1)	13(1)	14(1)	-3(1)	6(1)	-2(1)
C(5)	10(1)	17(1)	13(1)	1(1)	9(1)	2(1)
C(6)	20(1)	14(1)	23(1)	-2(1)	19(1)	-1(1)
C(7)	20(1)	14(1)	27(2)	-3(1)	19(1)	-3(1)
C(8)	8(1)	18(1)	18(1)	-4(1)	8(1)	-4(1)
C(9)	7(1)	21(1)	11(1)	2(1)	5(1)	2(1)
C(10)	11(1)	18(1)	15(1)	-1(1)	10(1)	1(1)
C(11)	11(1)	18(1)	19(1)	7(1)	10(1)	3(1)
C(12)	6(1)	15(1)	17(1)	7(1)	5(1)	2(1)

Table 11. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for $C_{12}H_{19}NO_2$.

	x	y	z	U(eq)
H(2O)	2400(50)	7680(80)	4300(60)	68(19)
H(2A)	4980(30)	400(50)	4240(40)	19
H(2B)	4450(30)	1100(50)	2670(40)	19
H(3B)	3200(30)	750(50)	3550(40)	20
H(3A)	3020(30)	2250(50)	2400(40)	20
H(5)	2930(30)	5030(50)	2910(40)	15
H(6)	3630(30)	6030(50)	5770(40)	19
H(7A)	4450(30)	7110(50)	4270(40)	21
H(7B)	4980(30)	7760(50)	5860(40)	21
H(8A)	5630(30)	5000(50)	6940(40)	17
H(8B)	6090(30)	5560(50)	5960(40)	17
H(9A)	1340(30)	5110(50)	2940(40)	16
H(9B)	1550(30)	3330(40)	2630(40)	16
H(10A)	2110(30)	4370(50)	5430(40)	16
H(10B)	1330(30)	3010(40)	4560(40)	16
H(11A)	2910(30)	1650(50)	6450(40)	18
H(11B)	2550(30)	1000(50)	4920(40)	18
H(12A)	4240(30)	3400(50)	6740(40)	16
H(12B)	4440(30)	1510(50)	6380(40)	16

Table 12. Torsion angles [°] for $C_{12}H_{19}NO_2$.

C(8)-N-C(1)-O(1)	0.7(4)	C(8)-N-C(4)-C(5)	50.9(3)
C(4)-N-C(1)-O(1)	177.2(2)	C(1)-N-C(4)-C(12)	112.5(2)
C(8)-N-C(1)-C(2)	179.2(2)	C(8)-N-C(4)-C(12)	-70.9(3)
C(4)-N-C(1)-C(2)	-4.4(3)	C(1)-N-C(4)-C(3)	-6.6(3)
O(1)-C(1)-C(2)-C(3)	-168.0(3)	C(8)-N-C(4)-C(3)	170.0(2)
N-C(1)-C(2)-C(3)	13.5(3)	C(2)-C(3)-C(4)-N	14.5(3)
C(1)-C(2)-C(3)-C(4)	-17.2(3)	C(2)-C(3)-C(4)-C(5)	130.5(2)
C(1)-N-C(4)-C(5)	-125.7(2)	C(2)-C(3)-C(4)-C(12)	-103.5(2)

N-C(4)-C(5)-C(6)	-50.7(3)		C(1)-N-C(8)-C(7)	124.9(3)
C(12)-C(4)-C(5)-C(6)	70.4(3)		C(4)-N-C(8)-C(7)	-51.3(3)
C(3)-C(4)-C(5)-C(6)	-163.3(2)		C(6)-C(7)-C(8)-N	51.2(3)
N-C(4)-C(5)-C(9)	-178.0(2)		C(4)-C(5)-C(9)-C(10)	56.6(3)
C(12)-C(4)-C(5)-C(9)	-56.9(3)		C(6)-C(5)-C(9)-C(10)	-70.2(3)
C(3)-C(4)-C(5)-C(9)	69.4(3)		C(5)-C(9)-C(10)-C(11)	-54.3(3)
C(4)-C(5)-C(6)-O(2)	174.0(2)		C(9)-C(10)-C(11)-C(12)	52.0(3)
C(9)-C(5)-C(6)-O(2)	-60.7(3)		N-C(4)-C(12)-C(11)	175.5(2)
C(4)-C(5)-C(6)-C(7)	56.0(3)		C(5)-C(4)-C(12)-C(11)	55.6(3)
C(9)-C(5)-C(6)-C(7)	-178.7(2)		C(3)-C(4)-C(12)-C(11)	-71.2(3)
O(2)-C(6)-C(7)-C(8)	-176.6(2)		C(10)-C(11)-C(12)-C(4)	-52.8(3)
C(5)-C(6)-C(7)-C(8)	-55.6(3)			

Table 13. Hydrogen bonds for $C_{12}H_{19}NO_2$ [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(2)-H(2O)...O(1)#1	0.73(6)	2.05(6)	2.762(3)	165(7)

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

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