Synthesis of Natural and Non-Natural Polycylic Alkaloids

by

Adam Thomas Hoye

B.A., Grinnell College, 2004

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This thesis was presented

by

Adam Thomas Hoye

It was defended on

August 16th, 2010

and approved by

Professor Dennis P. Curran, Department of Chemistry

Professor Paul E. Floreancig, Department of Chemistry

Professor Billy W. Day, Department of Pharmaceutical Sciences

Dissertation Advisor: Professor Peter Wipf, Department of Chemistry

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Adam T. Hoye, PhD

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Part one of this dissertation describes the synthesis of novel polycyclic natural product-like compounds from dicyclopropylmethylamine starting materials. Using methodology previously developed in our group, products from the initial one-pot multicomponent reaction via the rearrangement of a bicyclo[1.1.0]butane intermediate were successfully transformed into polycyclic systems. These small, medium and large heterocycles mimic complex alkaloids found in nature, and were further elaborated to incorporate additional functionalities.

Part two describes our investigation into the parvistemonine class of *Stemona* alkaloids. We developed a unified strategy to target several related *Stemona* natural products. A [3,3]-sigmatropic rearrangement was used to relay key stereochemical information across the characteristic pyrrolo[1,2-*a*]azepine core of these molecules and install contiguous stereocenters in a controlled fashion. This approach produced advanced intermediates towards the syntheses of parvistemonine and sessilifoliamides B and D, and culminated in the first enantioselective total syntheses of sessilifoliamide C and 8-*epi*-stemoamide.

ACKNOWLEDGEMENTS

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I thanks my parents of their priceless guidance and advice, and my brother and sister for their inspiration and encouragement.

Finally, I would like to dedicate this thesis to my wife, Lauren M. Hoye, for without her unwavering support and devotion none of this would have been possible. Thank you.

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LIST OF ABBREVIATIONS

Ac	acetyl
aux	auxiliary
AIBN	2,2’-azo*bis*isobutyronitrile
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Bu	butyl
Cbz	benzyloxycarbonyl
Cp	cyclopentadienyl
CSA	camphorsulfonic acid
Cy	cyclohexyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
o-DCB	*ortho*-dichlorobenzene
DCC	dicyclohexylcarbodiimide
DIAB	(–)-3-exo-(dimethylamino)isoborneol
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminum hydride
DIEA	*N*,*N*-diisopropylethylamine
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide

DMPS	dimethylphenylsilyl
d.r.	diastereomeric ratio
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	enantiomeric excess
eq	equivalent(s)
Et	ethyl
FDPP	pentafluorophenyl diphenylphosphinate
HOBt	1-hydroxybenzotriazole
HMDS	1,1,1,3,3,3-hexamethyldisilazane
HMPA	hexamethylphosphormaide
HRMS	high-resolution mass spectroscopy
IR	infrared spectroscopy
KHMDS	potassium 1,1,1,3,3,3-hexamethyldisilazane
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LiHMDS	lithium 1,1,1,3,3,3-hexamethyldisilazane
*m*CPBA	3-chloroperbenzoic acid
Me	methyl
MOM	methoxymethyl
mp	melting point
MPLC	medium-pressure liquid chromatography
µW	microwave irradiation
NMR	nuclear magnetic resonance

NMO	*N*-methyl morpholine oxide
NOE	Nuclear Overhauser effect
NOESY	Nuclear Overhauser enhancement spectroscopy
NR	no reaction
Nu	nucleophile
Ph	phenyl
PMB	*para*-methoxybenzyl
PPTS	pyridinium *para*-toluenesulfonate
RCM	ring-closing metathesis
SM	starting material
TBAF	tetra-*n*-butylammonium fluoride
TBAI	tetra-*n*-butylammonium iodide
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMS	trimethylsilyl
TPAP	tetra-*n*-propylammonium perruthenate
Ts	*para*-toluenesulfonyl
TS	transition state

1.0 SYNTHESIS OF NON-NATURAL POLYCYCLIC ALKALOIDS

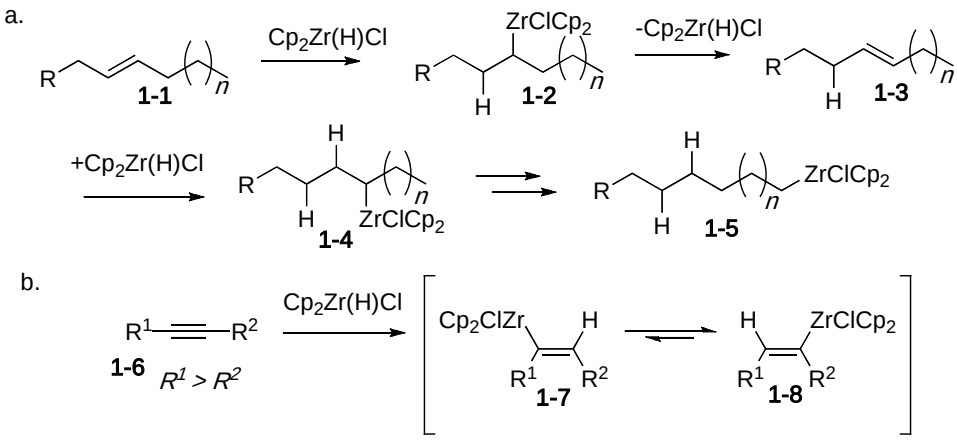
1.1 INTRODUCTION

1.1.1 Preparation and Reactions of Alkenylzirconocenes

Organozirconium compounds are useful reactive intermediates in organic synthesis and have been under significant investigation over the last 20 years following the synthesis of $Cp_2Zr(H)Cl$ by Wailes and Weigold in the 1970's.[1] Previously, the most common zirconium complexes, Cp_2ZrCl_2 and Cp_2ZrBr_2, had been used mainly in Friedel-Crafts and Ziegler-Natta polymerization reactions.[2] The discovery of zirconocene hydrochloride, $Cp_2Zr(H)Cl$, and its reactivity with organic substrates dramatically increased the utility of zirconium in small molecule synthesis. Schwartz and co-workers systematically investigated the reactivity of this complex, now commonly referred to as "Schwartz's reagent," with alkenes[1] and alkynes[3]. Typically, the reagent is formed by addition of a metal-hydride species such as $LiAlH_4$,[4] $LiAlH(O\textit{t}\text{-}Bu)_3$,[3] or $NaAlH_2(OCH_2CH_2OCH_3)_2$) to a zirconocene salt.[5] Although isolable and air-stable, the resulting zirconocenes are often contaminated with metal salts and over-reduced products.[3a] An improved protocol developed by Buchwald and co-workers in 1987 involves a CH_2Cl_2 wash to convert the dihydride species to the desired monochloride, proving a cleaner isolate this versatile reagent.[6] Most recently *in situ* generation of "a convenient and genuine

equivalent to $HZrCp_2Cl$" was reported where the active species is formed by reaction between Cp_2ZrCl_2 and DIBAL-H in THF to circumvent the problem of reagent degradation upon storage, which displays similar activity to the isolated complex in alkyne hydrozirconations.[7]

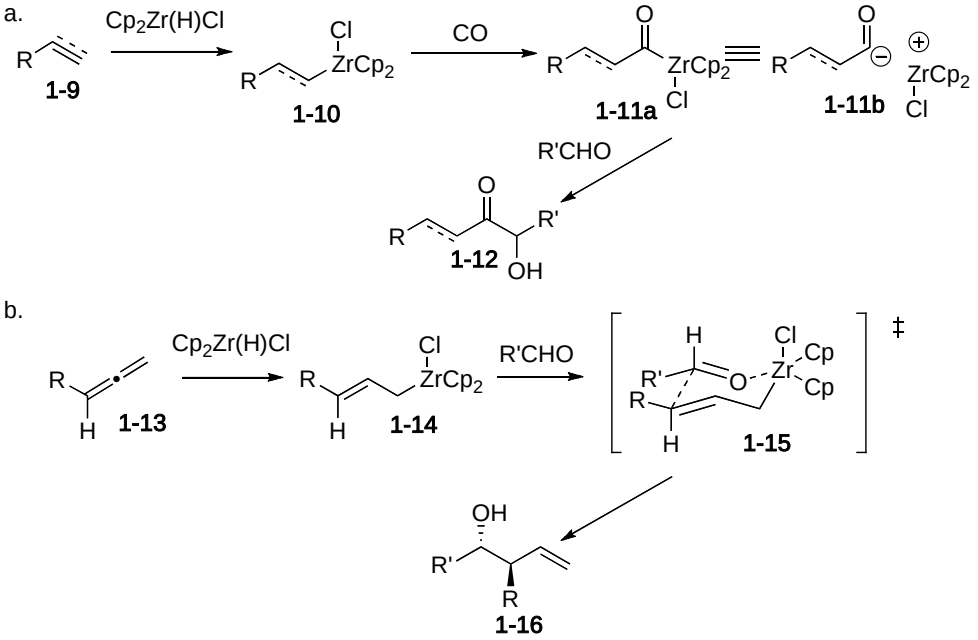
The scope of hydrozirconation reactions using Schwartz's reagent has been investigated extensively.[2] Whereas the formation of many organometallic compounds such as organolithiums and organomagnesiums suffers from poor functional group compatability, the hydrozirconation of alkynes has shown to be tolerant of ethers, bulky esters (e.g., TIPS, *tert*-butyl), acyl silanes, and alkenes (with ≤ 1 equivalent of $Cp_2Zr(H)Cl$),[8] however ketone, aldehyde, amide, and nitrile groups are generally still reactive. In the hydrozirconation of alkenes, zirconium migrates to the least hindered position via a β–hydride elimination/hydrometalation processes (Scheme 1a). Hydrozirconation of internal alkynes under thermodynamic conditions positions the zirconium atom at the less sterically demanding site (Scheme 1-1b).[2]



Scheme 1-1. Hydrozirconation of a. alkenes and b. internal alkynes.

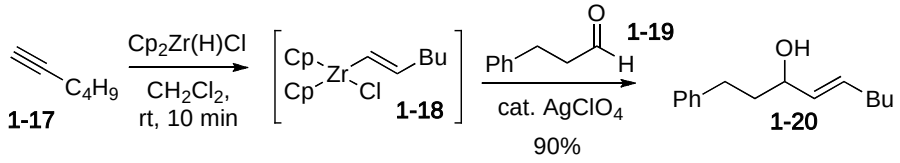
Despite the inherent polarization of the zirconium-carbon bond, organozirconium compounds react selectively and are easily handled due to the steric shielding of the polar

covalent bond by the two bulky cyclopentadienyl ligands. Small electrophiles such as proton, halogens, CO, and dioxygen may be directly inserted into the Zr-C bond. *Z*-Alkenes may be accessed via hydrozirconation of stannylacetylenes and appropriate functionalization thereof (e.g., Stille cross-coupling).[9] Hanzawa and co-workers have showed that acylzirconocenes derived from insertion of CO into the Zr-C bond add directly to aldehydes[10] and imines,[11] and participate in Pd-catalyzed cross-coupling reactions[12] as well as Pd-catalyzed 1,2- or 1,4-additions to α,β–unsaturated ketones (Scheme 1-2a).[13] Along with acylzirconocenes, allylzirconocenes are the only organozirconium reagents that will react directly with organic electrophiles such as aldehydes and imines in the absence of an added catalyst. Suzuki and co-workers showed that these reagents, generated from allene hydrozirconation, react readily with aldehydes to provide allylic alcohols in high diastereoselectivities (Scheme 1-2b).[14]



Scheme 1-2. Formation and aldehyde additions of a. acylzirconocenes and b. allylzirconocenes.

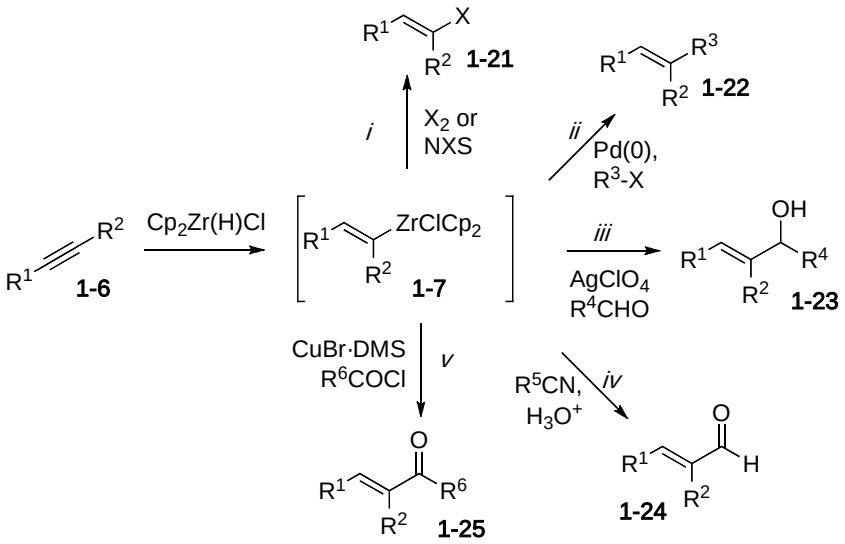
One method that has proven to increase the reactivity of organozirconium compounds has been to relieve the steric shielding around the Zr-C bond, while simultaneously increasing the cationic character of the metal center, via chloride abstraction from the intermediate complex.[15] The resulting cationic zirconium species have been shown by Suzuki and co-workers to generate allylic alcohols from the addition to aldehydes in a direct sequence. For example, treatment of the intermediate alkenylzirconium species (**1-18**) with 5 mol% of $AgClO_4$ in the presence of the aldehyde electrophile yields addition product **1-20** in 90% yield after 10 min (only 17% of the product was isolated after 2 h in the absence of Ag(I) salts) (Scheme 1-3).[15] Wipf and Xu showed that cationic alkenylzirconium intermediates also promote rearrangements of terminal epoxides to the corresponding aldehydes that undergo subsequent vinylation to afford secondary allylic alcohols in moderate yields.[16]



Scheme 1-3. Cationic zirconocene addition to hydrocinnamaldehyde.

The most commonly used method to increase the reactivity of organozirconocenes is transmetallation to another, more highly reactive element. Alkyl- and alkenylzirconocenes can be effectively transmetallated to a multitude of elements including B,[17] Al,[18] Ni,[19] Cu,[20] Pd,[21] Hg,[22] Sn[23] and Zn.[24] Correspondingly, zirconocenes have been used to affect a wide variety of transformations including (*i*) trapping with an electrophilic halogen to afford vinyl halides,[1] (*ii*) cross-coupling reactions to yield trisubstituted olefins,[25] (*iii*) formation of cationic zirconocenes that add to aldehydes to produce allylic alcohols,[26] (*iv*) reaction with isonitriles followed by

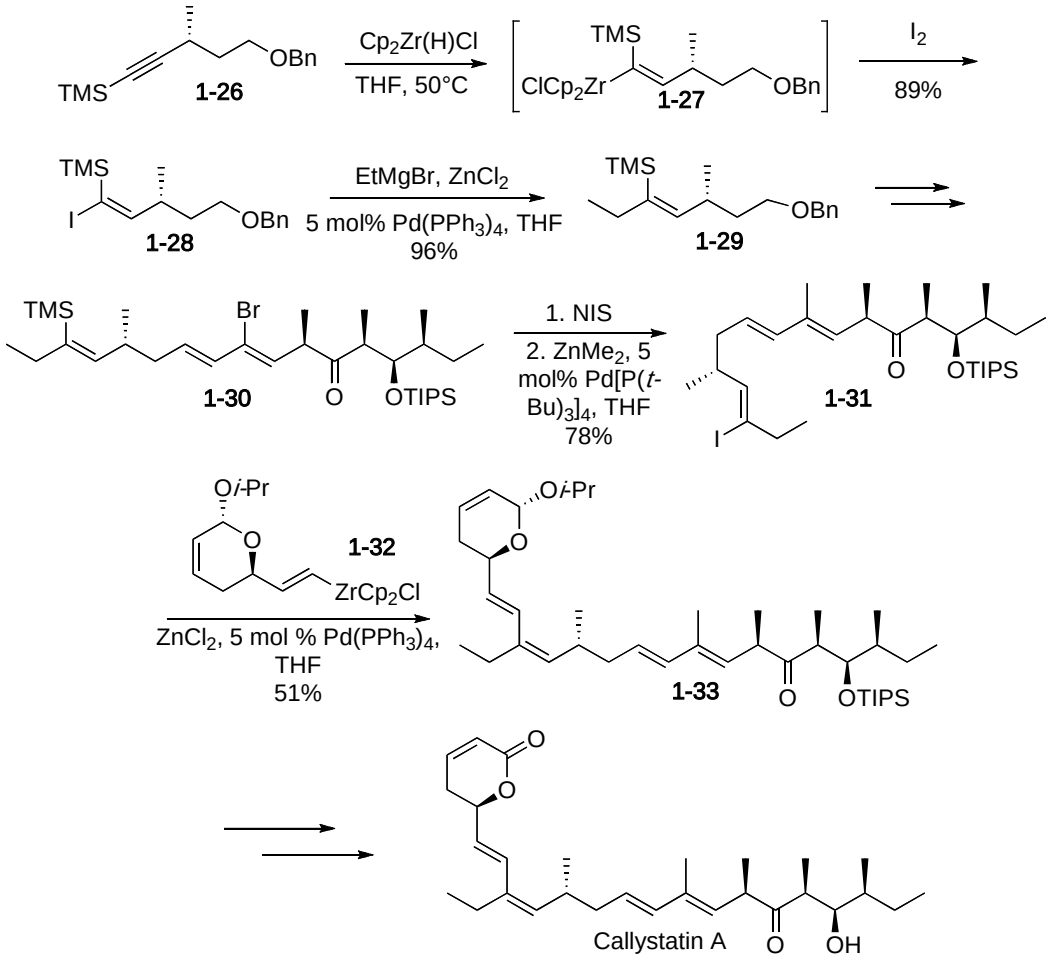
treatment with mild acid to produce enals,[27] and (*v*) additions to acid chlorides resulting in unsaturated enones (Scheme 1-4).[28]



Scheme 1-4. General transformations of alkenylzirconocenes.

While the aforementioned processes have been well established in the literature and remain attractive options for the use of organozirconium compounds in organic synthesis, transmetallation to zinc remains the most studied transformation of organozirconium reagents due to the functional group tolerance and general scope of the resulting reactions.[24] Early uses of zinc halides in organozirconium reactions by Negishi revealed that palladium-mediated cross coupling reactions were greatly accelerated when using $ZnCl_2$ as an additive.[29] The increased reactivity is likely attributed to transmetallation of the vinylzirconocene species to the zinc salt, which facilitates the subsequent transmetallation to palladium and accelerates the palladium cross-coupling catalytic cycle. The Negishi protocol has since held a prominent place in palladium coupling reactions and has been used extensively in natural product synthesis.[30] It is nicely showcased in Panek's total synthesis of callystatin A (Scheme 1.5):[31] a Zn-assisted sp^2-sp^2

coupling between iodide **1-28**, resulting from the hydrozirconation of alkyne **1-26** allows for a bromine-selective Negishi coupling to form the corresponding trisubstituted olefin in intermediate **1-29**. A final coupling reaction between the iodide and organozirconocene **1-32** yields the natural product after deprotection and oxidation steps.



Scheme 1-5. Panek's synthesis of callystatin A.

In 1994, Wipf and Xu reported that vinylzinc reagents prepared from the hydrozirconation of alkynes followed by transmetallation with dimethylzinc add to aldehydes to afford racemic allylic alcohols in good yields.[32] Further investigations found that the reaction

requires only a catalytic amount of $ZnMe_2$, and that zirconium plays a pivotal role in activation of the carbonyl unit, as alkyl- and alkenylzinc reagents do not react in the absence of Lewis acids or bases.[15b] This procedure facilitated access to a critical intermediate in Wipf's synthesis of curacin A,[33] and this approach was also applied to the syntheses of other complex natural products such as asukamycin,[34] nisamycin,[35] ratjadone,[36] laulimalide,[37] sphingosine,[38] and fostriecin,[39] showing good diastereoselectivities in the addition event in some cases (Figure 1.1).

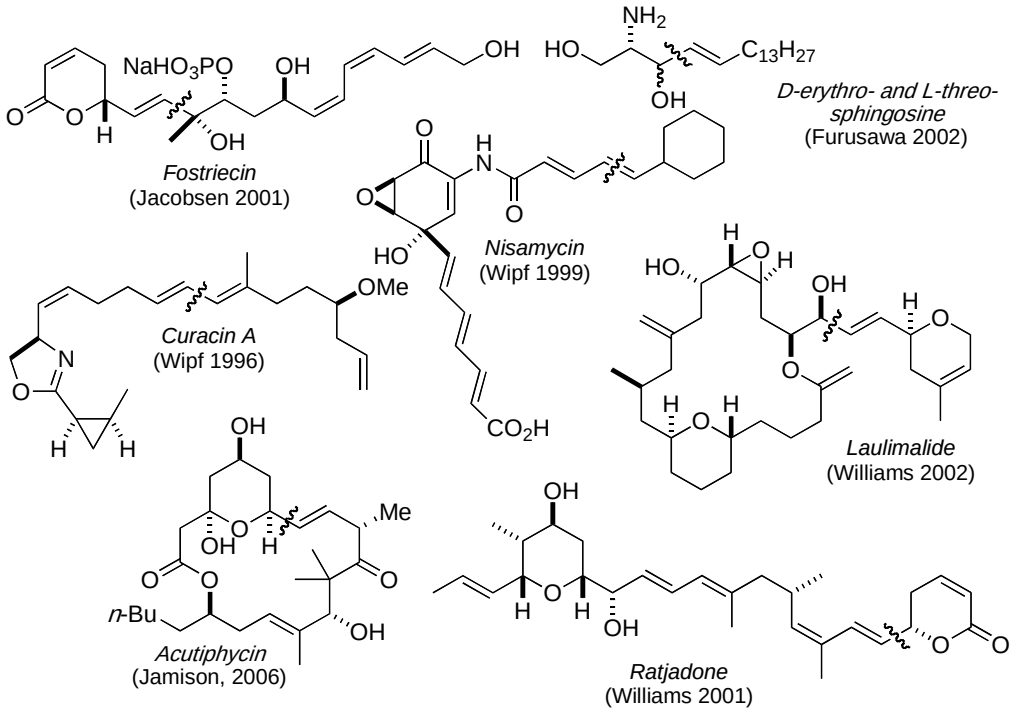
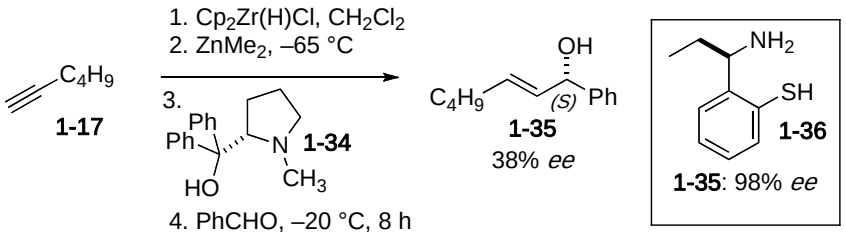


Figure 1-1. Total syntheses using Zr→Zn aldehyde additions to assemble allylic alcohol intermediates.

In their initial Zr∏Zn aldehyde addition report, Wipf and Xu observed that the addition of 8 mol% of proline-based catalyst **1-34** at –20 ^{o}C afforded enantiomerically enriched allylic alcohols in (low) 38% *ee*.[33] Later, Wipf and Ribe showed that novel amino-thiol ligand **1-36** increased the enantioselectivity of the alkenylzinc addition to 95% after a 60 min incubation time

at –30 °C, which was necessary to completely equilibrate the chiral ligand and achieve reproducible selectivities (Scheme 1-6).[40] Catalytic asymmetric ZrΠZn transmetallation/aldehyde additions have since been used to prepare allylic alcohol segments in the syntheses of halichlorine (Danishefsky),[41] leucascandrolide (Wipf, Williams)[42,43] and lobatamine C (Porco)[44] as well as those previously shown in Figure 1-1.[33,35,36,37,39,45]

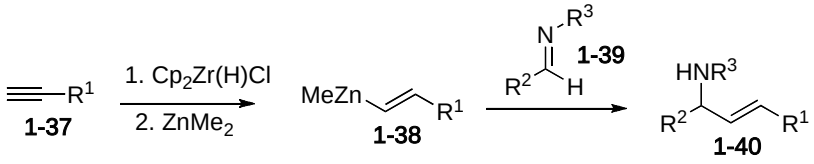


Scheme 1-6. Enantioselective alkenylzinc additions to aldehydes.

While enantioselective additions of organozinc reagents to aldehydes represent a highly utilized method to create synthetically useful intermediates,[46] the aldimine variant of this process remains relatively undeveloped. The reactivity of aldimines suffers due to lower electrophilicity and softer Lewis base character of the C=N double bond as compared to the corresponding carbonyl unit. Successful enantioselective additions to imines include Soai et al.'s use of the diphenylphosphinoyl group to activate aldimines towards the addition of dialkylzinc reagents in the presence of stoichiometric amounts of *N*,*N*-dialkylnorephedrines.[47] Other chiral amino alcohols have been used to afford the same transformation with comparable results.[43] This process is also amenable to other activated imines such as *N*-tosylamines,[48] *N*-arylamines,[49] nitrones,[50] and *N*-(amidobenzyl)benzotriazoles.[51]

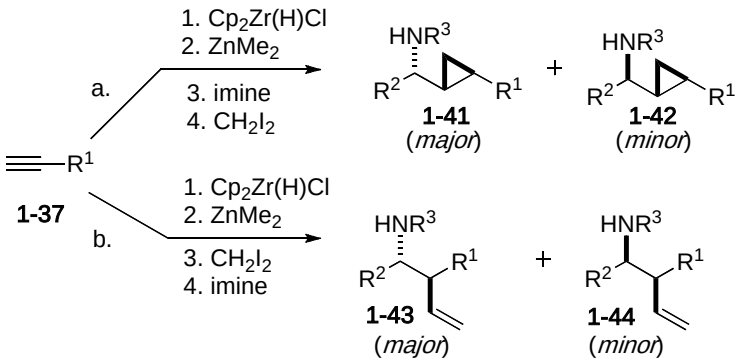
1.1.2 Synthesis of *C*-Cyclopropylalkylamines

Wipf, Kendall and Stephenson applied the Zr∏Zn transmetallation strategy to add alkenylzinc species to *N*-diphenylphosphinoyl and *N*-tosyl aldimines.[8] A variety of alkynes were hydrozirconated using Schwartz's reagent in dichloromethane, then transmetallated with dimethylzinc in toluene and added to aromatic aldimines at room temperature to yield the corresponding allylic amines in modest to good yields in the one-pot procedure (Scheme 1-7). Later, this strategy was successfully applied to the hydrozirconation of allenes and addition of the resulting allyl zirconocenes to imines to generate homoallylic amines.



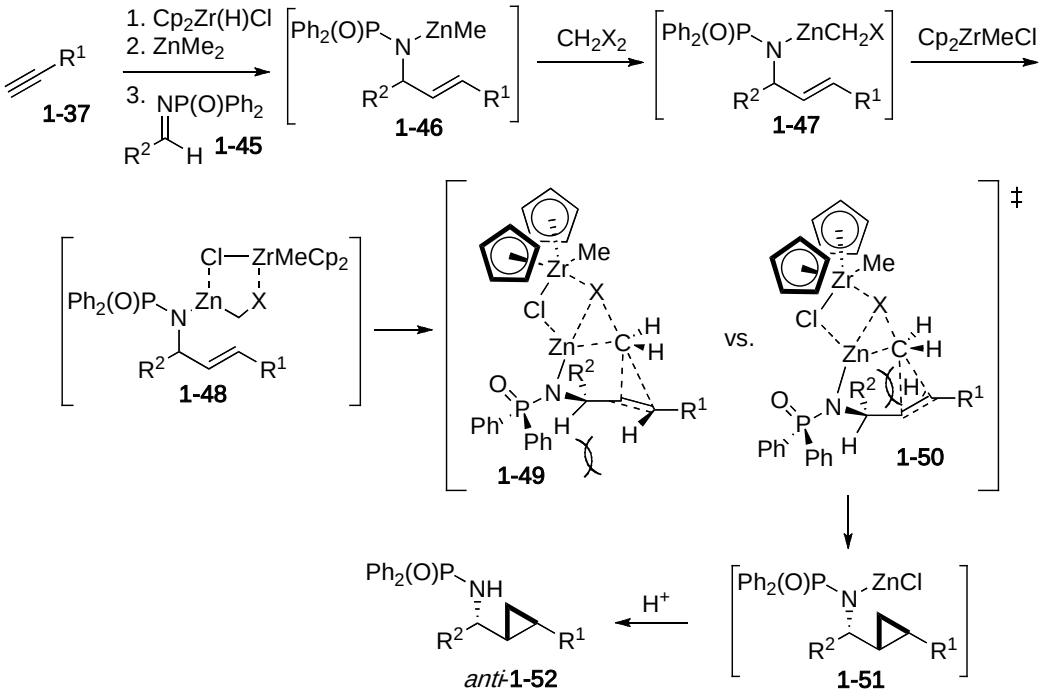
Scheme 1-7. One-pot hydrozironation/transmetallation allylic amine synthesis.

During their studies an unexpected observation was made where a solvent switch from dichloromethane to toluene or THF prior to imine introduction was found to be essential to generate the desired products, and that performing the entire reaction sequence in CH_2Cl_2 led to the formation of cyclopropylalkyl amines (Scheme 1-8). The addition of CH_2I_2 or CH_2Cl_2 to the zinc-amide facilitated the formation of these products (Scheme 1-8, pathway *a*). Furthermore, it was discovered that the order of addition of the reaction components influences the reaction pathway, and addition of the dihalomethane reagent prior to the imine afforded homoallylic amines (Scheme 1-8, pathway *b*).



Scheme 1-8. Product dependence on order of addition.

The one-pot cyclopropylalkyl amine formation was found to be tolerant of silyl ethers, TIPS esters, carbamates, and internal alkynes. The cyclopropanated products were formed in greater than 95:5 diastereoselectivities in most cases. It is proposed that the stereochemical preference is due to a chelated transition state incorporating both zinc and the zirconocene complex (Scheme 1-9). Following hydrozirconation, transmetallation, and imine addition, intermediate **1-46** was treated with dihalomethane (CH_2Cl_2 or CH_2I_2) the halomethylzinc species **1-47** was formed. The zirconocene complex obtained in the transmetallation event then served as a Lewis acid activator for zinc carbeneoid formation by complexation to the halogen atom of the halomethylene intermediate in **1-48**. The carbene was delivered to the proximal olefin by one of the two feasible transition states, **1-49** or **1-50**. Large destabilizing steric interactions between the *N*-diphenylphosphinoyl group and the alkene moiety disfavored conformer **1-49**, whereas transition state **1-50** relieved this steric congestion. However it was itself subjected to a 1,3-allylic strain interaction that usually leads to a preference for *syn* selectivity, but in this case the allylic interaction was less demanding, which explained the diastereomeric ratios of the product cyclopropylalkyl amines.



Scheme 1-9. Proposed mechanism and cyclopropanation transition states.

1.1.3 Simmons-Smith Cyclopropanation and Applications

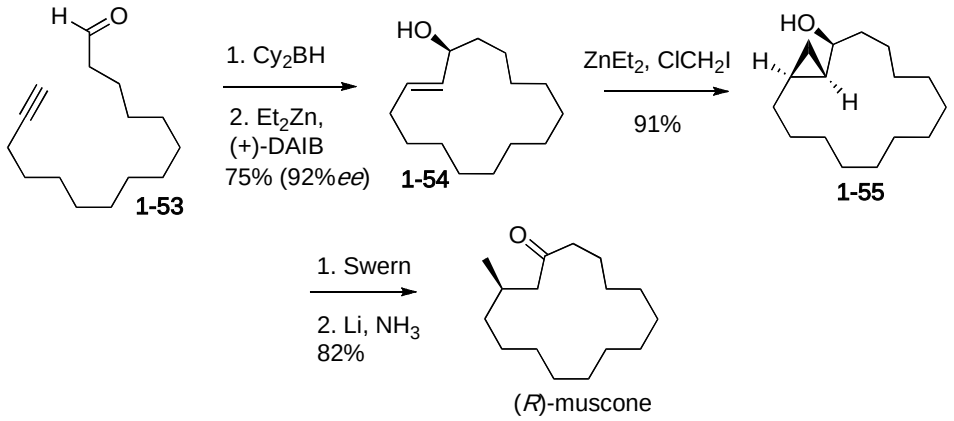
Whereas the Wipf cyclopropylalkyl amine methodology was the first report of a one-pot Zr→Zn transmetallation, imine addition and cyclopropanation sequence, cyclopropanation reactions with zinc carbenoids have been well investigated.[52] This is due in large part to the efforts of Simmons and Smith who, three decades after Emschwiller first reported the preparation of $IZnCH_2I$,[53] reported that the same reagent was effective at achieving stereospecific formations of cyclopropanes from alkenes.[54] The zinc carbenoid, which is now commonly known as the Simmons-Smith reagent, was initially formed via oxidative addition across the X-CH_2X bond using a zinc-copper couple in an ethereal solvent (THF, Et_2O, DME). Due to inconsistent reagent formation in the presence of an excess of metal salts, the reagent has since been prepared in a

number of alternative ways. An early protocol reported by Wittig described treating diazomethane with ZnI_2 to generate $IZnCH_2I$ or $Zn(CH_2I)_2$ via nucleophilic displacement, however nowadays this protocol is rarely used.[55] The most popular method for generating the Simmons-Smith reagent, developed by Furukawa in 1966,[56] is through alkyl exchange between $ZnEt_2$ and CH_2X_2 to give the active species $EtZnCH_2I$ or $Zn(CH_2I)_2$. This process is accelerated by catalytic amounts of oxygen in the solvent, leading to zinc reagents that afford the highest diastereoselectivities in directed Simmons-Smith reactions. The major advantages of the Furukawa method are that coordinating solvents are not required, starting materials are commercially available and can be used without extensive purification, and the reagents are more reactive, although their stabilities are significantly lower. Notably, in a report by Charette, the preparation of Simmons-Smith reagent in CH_2Cl_2 on large scale (8 mmol, ~1 g of $ZnEt_2$) resulted in an explosion.[57] To avoid this dangerous situation, a stoichiometric amount of DME can be added to a solution of diethylzinc prior to CH_2I_2 introduction to sufficiently stabilize the reagent towards exothermic decomposition to allow for safe large-scale usage.

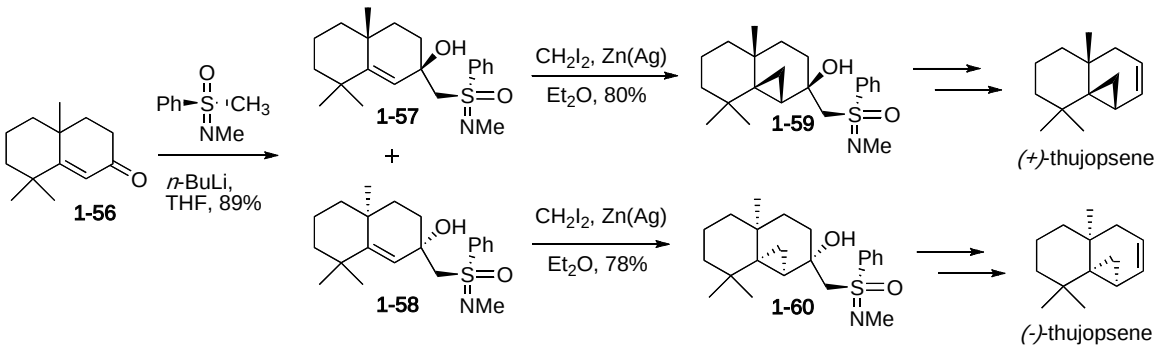
While zinc remains the preferred metal for use in cyclopropanation reactions, a number of other metal reagents have proven effective in promoting the same transformation exhibiting several differences in terms of chemoselectivity.[58] Samarium and zinc are highly selective for reacting with allylic alcohols in the presence of other alkenes whereas aluminum preferentially reacts with isolated olefins in identical systems.[59] The most reactive cyclopropanating reagent, $CF_3CO_2ZnCH_2I$ (Shi reagent), affords a mixture of products when more than one reactive site is present.[53]

Not surprisingly, the Simmons-Smith reaction has been used with neighboring group participation to install allylic cyclopropane moieties in natural product synthesis. Oppolzer nicely

applied this directivity in the synthesis of (*R)*-muscone where the allylic alcohol **1-54** (installed via an intramolecular coupling using Noyori's DIAB ligand) was subjected to Denmark's cyclopropanation conditions[60] to give the *syn*-cylopropylcarbinol as a single diastereomer (Scheme 1-10).[61] Johnson and Barbachyn used a similar approach in their synthesis of both enantiomers of thujopsene where the α– and β–allylic alcohols **1-57** and **1-58** directed a cyclopropanation under the Simmons-Smith protocol (Scheme 1-11).[62]

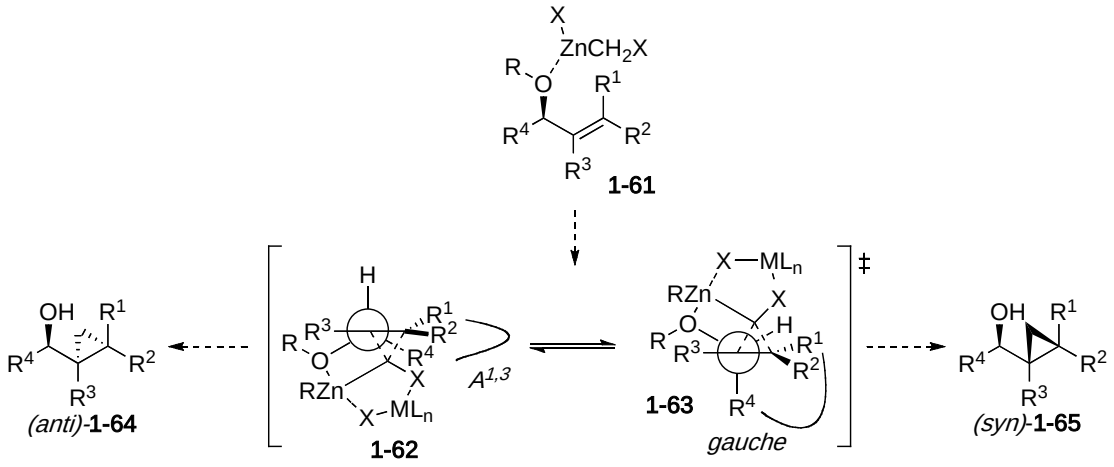


Scheme 1-10. Oppolzer's synthesis of (*R*)-muscone.



Scheme 1-11. Johnson's synthesis of (+)- and (–)-thujopsene.

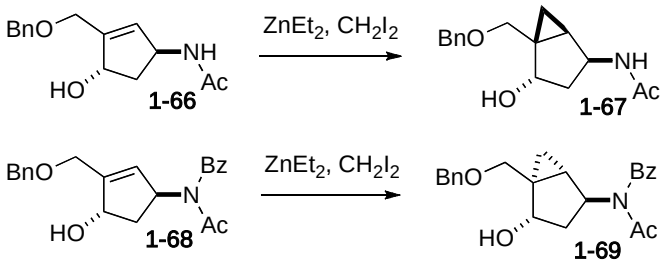
While directed cyclopropanation reactions in cyclic systems are biased by ring conformations and axial vs. equatorial positioning, acyclic systems follow different trends. The cyclopropanation of chiral allylic alcohols tends to favor the *syn*-diastereomer while chiral allylic ethers favor the *anti*-diastereomer.[63] It is not only the substrate that controls stereoselectivity in these reactions, but the choice of the appropriate reagent can have profound effects on the reaction outcome. Whereas the traditional Simmons-Smith reagent provides a roughly 1:1 mixture of *syn*- and *anti*-diastereomers, the Furukawa reagent often affords a much higher selectivity.[63] The substitution pattern around the allylic alcohol or ether changes the observed facial selectvitiy of the reaction as well.[64] As the steric bulk of R^4 increases, the *syn*-diastereomer becomes favored since the minimization of allylic strain dominates the conformational preferences in the transition state (Scheme 1-12).



Scheme 1-12. Diastereoselective transition state models of allylic cyclopropanations.

The directing effect of an amide function in cyclopropanation reactions has not been as widely investigated, although some reports exist in the literature.[65] Marquez et al. performed a study comparing the directing capabilities of an amide versus a hydroxyl group on a

cyclopropene skeleton (Scheme 1-13).[65b] Methylene attack occurs *syn*- to the amide (*anti*- to the hydroxyl function) when an N-H bond is present, and *syn*- to the hydroxyl group when the amide nitrogen is protected as the benzoate. Based on these results, the secondary amide emerges as the stronger directing group; however *N*-substitution appears to significantly suppress the directing capability of this group to the point that the diastereofacial selectivity is reversed. It is important to note that this comparison has not been reproduced on acyclic systems, so any conformational effects of the ring cannot be completely discounted.

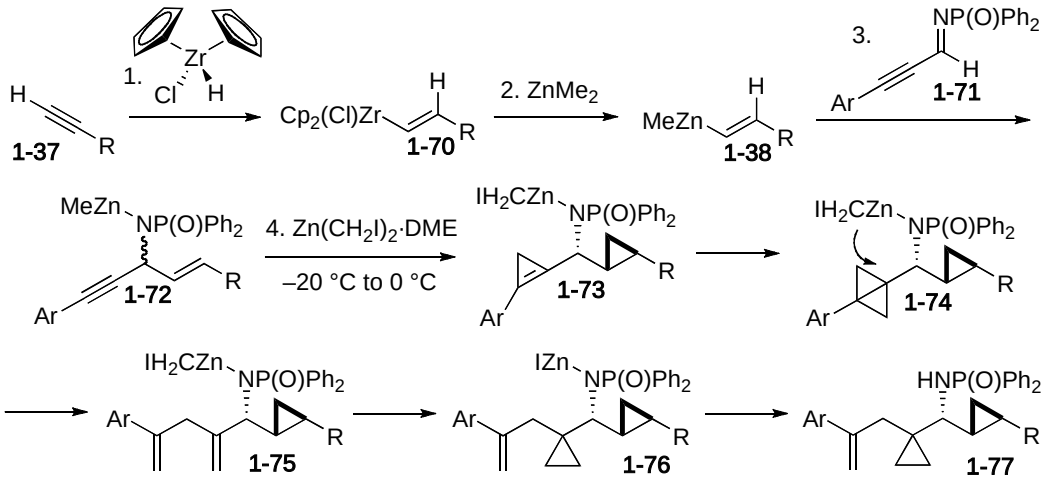


Scheme 1-13. Marquez cyclopropanation study.

1.1.4 Synthesis of *C, C*-Dicyclopropylmethylamines

During the course of our group's study of the one-pot Zr→Zn transmetallation, imine addition and cyclopropanation sequence, another interesting observation was made.[66] Serendipitously, when alkynylimine **1-71** was used in the presence of excess $Zn(CH_2I)_2$, an unexpected polycyclic product, later identified to be dicyclopropylmethylamine **1-77,** was isolated in lieu of the expected cycloproylalkynylamide (**1-72,** Scheme 1-14). Alkynes and alkynylimines with substituents including silyl ethers, carbamates, sulfonamides, silyl esters and orthoesters were tolerated in the multicomponent process. Strikingly, when internal alkynes were used the rare

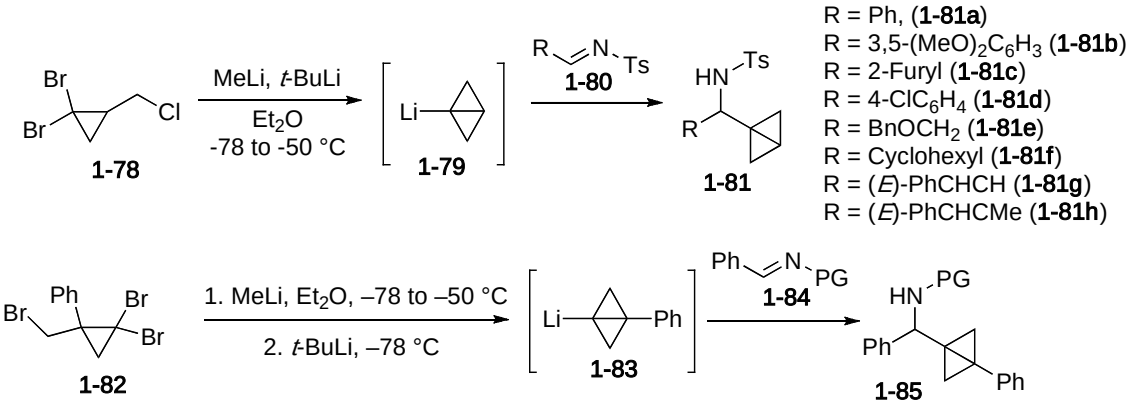
bicyclo[1.1.0]butane scaffold could be successfully isolated, giving a clue into potential reaction intermediates. Mechanistically, a cascade reaction where 10 C-C bonds are formed and 2 C-C bonds are broken was proposed, with a key intermediate in the process being bicyclo[1.1.0]butane **1-74** (Scheme 1-14). In fact, resubjection of isolated **1-72** to the reaction conditions yields the rearranged product and provides support to the hypothesized mechanistic pathway: hydrozirconation, transmetallation and addition to the alkynylimine forms intermediate **1-72**, which undergoes alkyl group exchange and triple cyclopropanation to generate bicyclobutane **1-74**. It has been shown that these intermediates undergo double σ-bond insertions with carbenes[67] to form skipped dienes, and a final cyclopropanation of the allylic π-bond yields the isolated product **1-77** in 43-66% yields (94-96% yield per C-C bond formed). This multicomponent organometallic reaction represents the first synthetically useful example of a double C,C-σ-bond insertion, and can be performed from readily available starting materials.



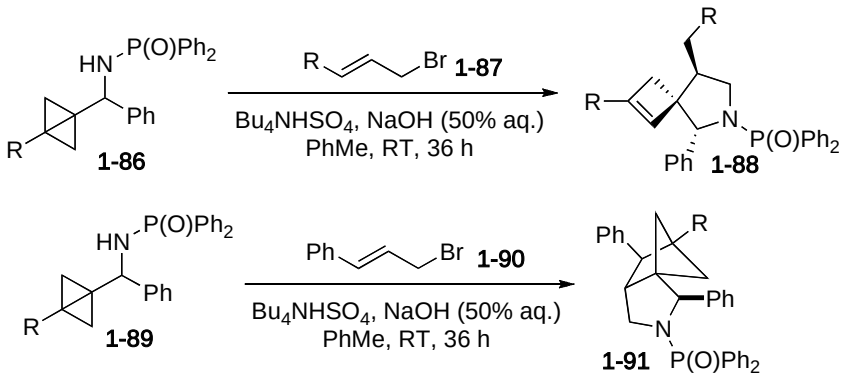
Scheme 1-14. Proposed reaction mechanism for the formation of dicyclopropylmethyl amines.

1.1.5 Synthesis and Applications of Bicyclo[1.1.0]butanes

Historically the bicyclobutane functionality has remained under investigated for its reactive potential. Understandably this is an effect of the technologies known to form the bicycle, which involve lengthy routes and harsh conditions that are incompatible with many common functional groups. Therefore to exploit the intriguing reactivity of the bicyclobutane group an easier method of synthesis needed to be developed. In 2006 Wipf and Walczak discovered a key result towards this goal in that di-lithiation of **1-78** affords, in situ, bicyclo[1.1.0]butyllithium **1-79**, which can be added to aldehydes and imines (Scheme 1-15). The resulting bicyclobutane adducts were allylated and subjected to a formal Alder-ene reaction to produce the novel bicyclic products **1-88** and **1-91** (Scheme 1-16).

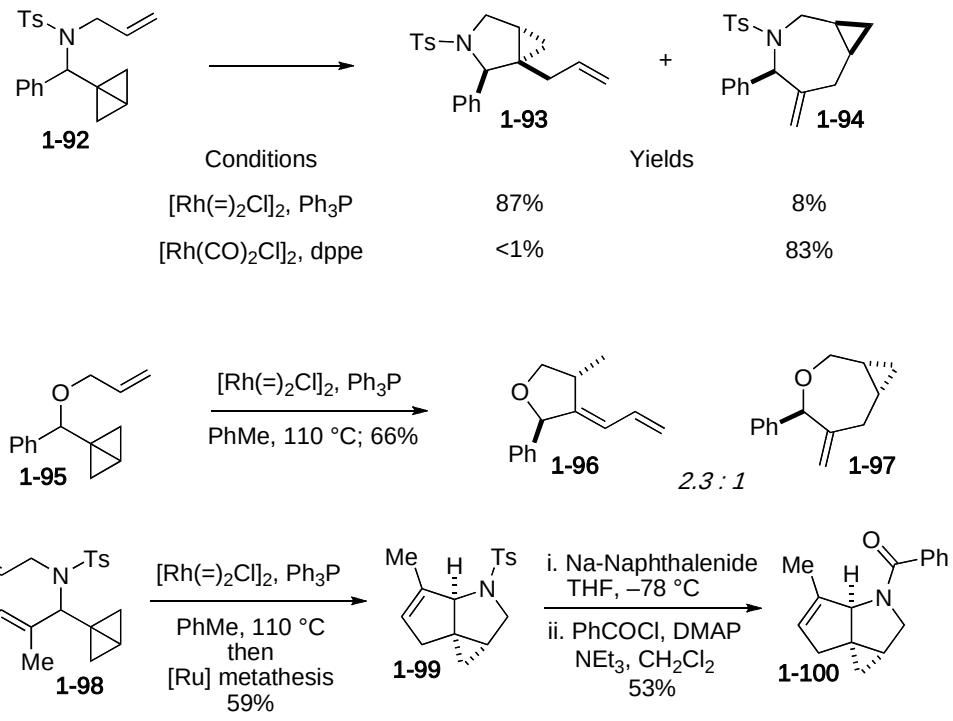


Scheme 1-15. Bicyclo[1.1.0]butyllithium formation and addition to imines.



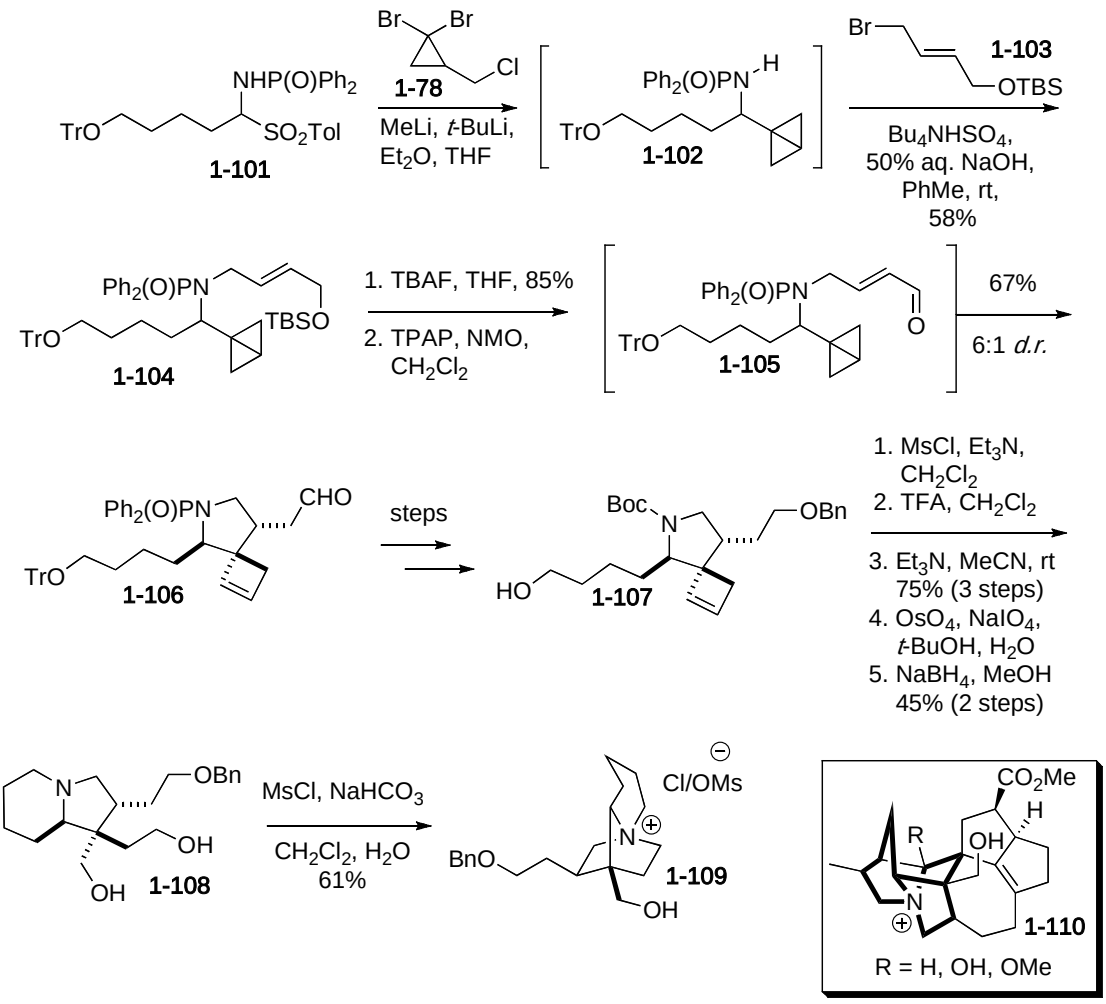
Scheme 1-16. Spontaneous formal Alder-ene rearrangements of *N*-allyl bicyclobutanes.

Transition metal-catalyzed reactions of the bicyclobutylamines were investigated and it was found that rhodium inserts into the central C_{sp3}-C_{sp3} σ-bond of bicyclobutane, which has been likened to a C_{sp2}=C_{sp2} π-bond to explain the reactivity of bicyclobutanes.[68] Rh-insertion is benefited by the release of ~65 kcal/mol in strain energy in forming the rhodium carbene which performs a cyclization/cyclopropanation to form pyrrolidine or azepine products, depending on the phosphine ligand present (Scheme 1-17). Allyl ether **1-95** provides a mixture of 5- and 7-membered heterocycles and sequential isomerization followed by ring-closing metathesis of **1-98** provides the interesting tricyclic scaffold **1-100** in a handsome sequence.



Scheme 1-17. Rh(I)-catalyzed isomerizations of bicyclo[1.1.0]butanes.

More recent uses of bicyclobutanes include the application towards natural product synthesis. Wipf and Ueda have reported the use of the Alder-ene sequence to generate the tricyclic core of the complex daphniglaucin alkaloids (Scheme 1-18).[69] Addition of bicyclo[1.1.0]butan-1-yllithium to imine precursor **1-01** gave the labile adduct **1-02** that was immediately subjected to alkylation with bromide **1-103**. Deprotection and oxidation to the corresponding aldehyde followed by spontaneous rearrangement to afford the formal ene-product in 65% yield as a 6:1 mixture of diastereomers. Elaboration of the scaffold led to **1-107**, which could be deprotected and cyclized, then oxidatively opened to afford diol **1-108**. Mesylation and cyclization to form the ammonium salt completed the tricyclic core. Elaboration of this strategy into the completion of daphniglaucin A and related alkaloids is being pursued.

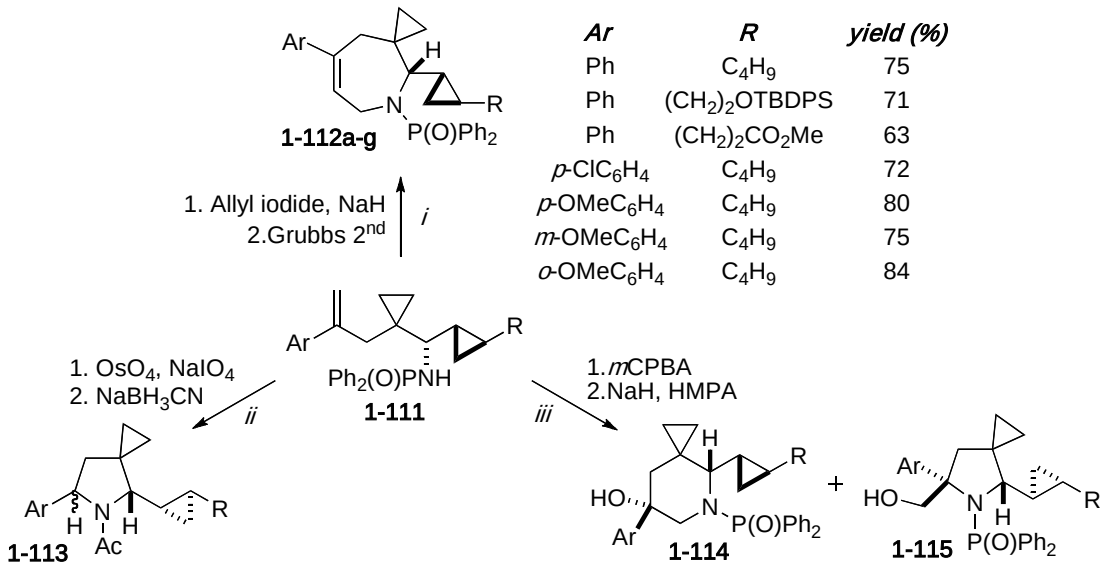


Scheme 1-18. Alder-ene approach to the daphniglaucin core.

1.1.6 Synthesis of Azaspirocycles

In 2004 Wipf, Stephenson and Walczak reported the use of the one-pot dicyclopropylmethylamine cascade reaction to form a libryary of azaspirocyclic compounds.[70] The diversity-oriented approach included metathesis (i), oxidation and reductive amination (ii), and epoxide ring opening (iii) strategies to produce azepine, piperidine and pyrrolidine azaspirocycles (Scheme 14). The novel polycycles allowed for more meaningful biological

analysis of the dicyclopropyl amine functionality since linear chains are generally more rapidly metabolized than heterocyclic rings.



Ar	*R*	*yield (%)*
Ph	C_4H_9	75
Ph	$(CH_2)_2OTBDPS$	71
Ph	$(CH_2)_2CO_2Me$	63
p-ClC_6H_4	C_4H_9	72
p-$OMeC_6H_4$	C_4H_9	80
m-$OMeC_6H_4$	C_4H_9	75
o-$OMeC_6H_4$	C_4H_9	84

Scheme 1-19. Diversity-oriented synthesis of azaspirocycles.

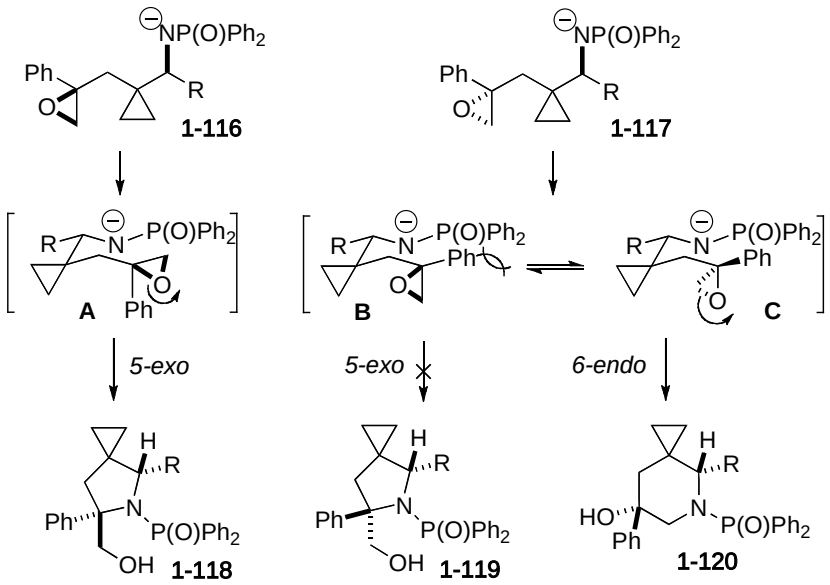
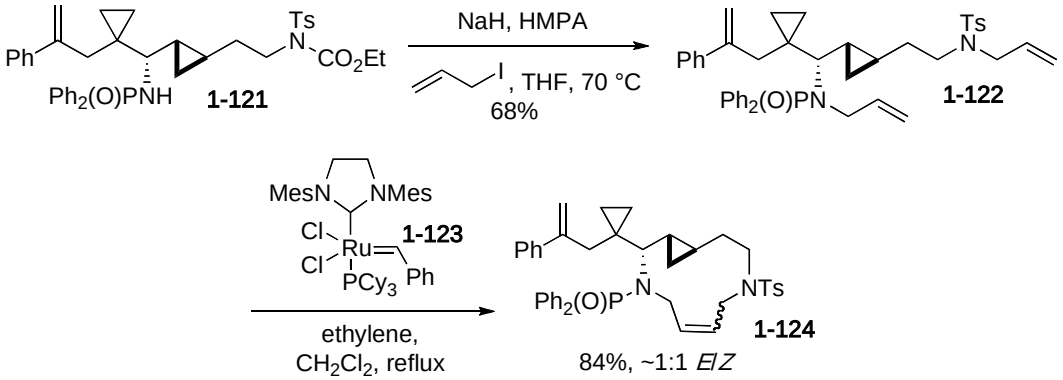


Figure 1-2. Predictive model for the diastereoselective epoxide aminolysis. [71]

As shown in Scheme 1-19, the epoxidation and intramolecular ring-opening sequence (*iii*) afforded two distinctly different products in equal amounts. Mechanistically, this observation was rationalized by the preference of a 5-*exo* vs. 6-*endo* cyclization of the two epoxide diastereomers (Figure 1-2). As anions **1-116** and **1-117** are formed in the reaction the preference for the 5-exo cyclization is demonstrated by the formation of **1-118** from **1-116**. In the case of **1-117**, however, the transition state leading to the 5-*exo* ring closure develops a destabilizing steric interaction between the phenyl and diphenylphosphinoyl groups as shown in **B**. Instead, the epoxide moiety can rotate and present the homo-benzylic carbon for attack in a 6-*endo* manner to produce piperidine **1-120** possessing geminal phenyl and hydroxy substituents.



Scheme 1-20. Unexpected 11-membered ring formation during ring-closing metathesis.

An additional unexpected observation was made in the course of the library synthesis: during the formation of azepines (Scheme 1-19, pathway *i*) under ring-closing metathesis (RCM) conditions, exposure of tosyl-protected carbamate **1-121** to the allylation conditions resulted in carbamate cleavage (presumeably due to sodium hydroxide present in the mixture) and bis-allylation to provide triene **1-122** (Scheme 1-20). Upon treatment with Grubbs 2nd generation metathesis catalyst (**1-123**) in refluxing CH_2Cl_2 under an ethylene atmosphere a chemoselective

cyclization to provide the 11-membered ring, and not the 7-membered azepine, in 84% yield and in a ~1:1 *E*/*Z* ratio. This result is especially intriguing as nitrogen-containing macrocycles are a common structural motif in many biologically active natural products (Figure 1-3).

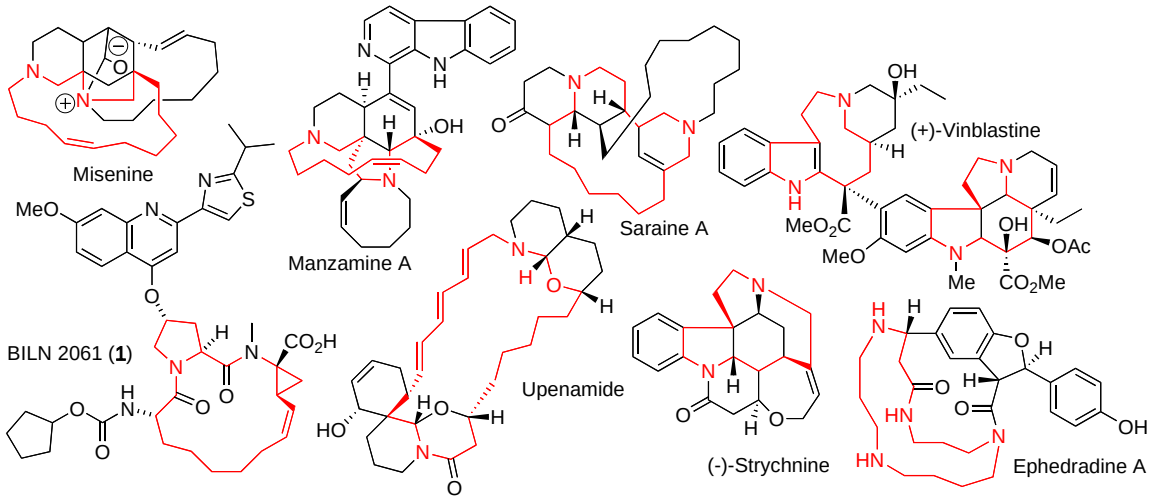


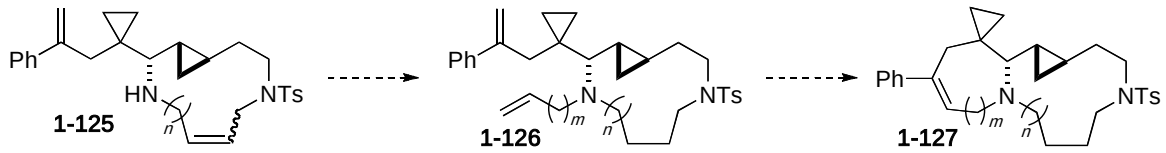
Figure 1-3. Examples of nitrogen-containing macrocycles in natural products.

1.2 RESULTS AND DISCUSSION

1.2.1 Initial Investigations

As part of our continued study of novel polycyclic heterocycles, we wished to expand the unique products derived from our initial one-pot dicyclopropylmethylamine synthesis into polycyclic natural product-like compounds containing a macrocyclic ring system within their polycyclic structures. Natural products containing similar moieties are of considerable relevance both in terms of their molecular complexity and scientific advances made in pursuit of their syntheses as

well as their profound biological activities and modes of action. Our initial goal was to combine the macrocyclic ring system with a smaller ring as shown in Scheme 1-21.

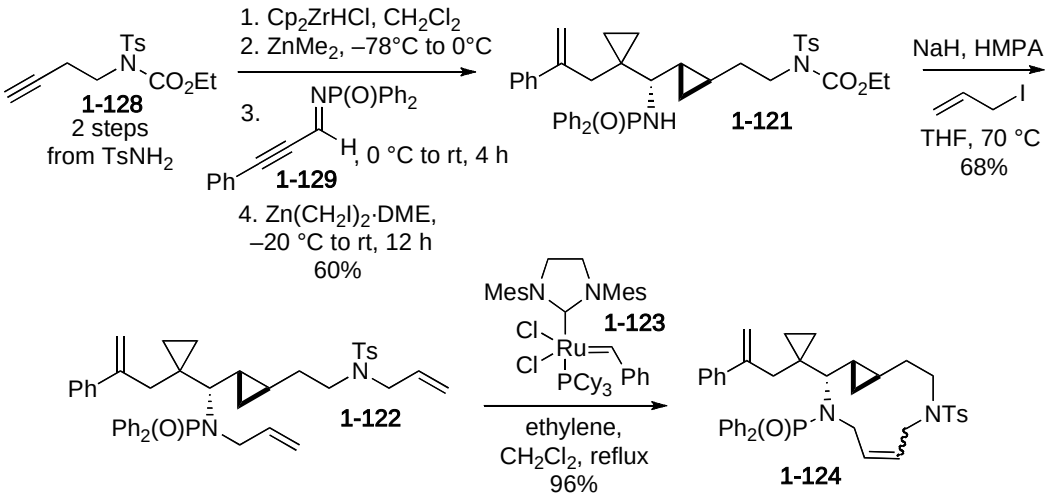


Scheme 1-21. Generic target structures and strategy.

To synthesize the necessary cyclopropyl building blocks, we followed our established procedure for the synthesis of substituted dicyclopropylmethylamines.[66] Alkyne **1-128** was prepared in a straightforward manner in 2 steps from commercially available materials, and the requisite imine (**1-129**) was generated by $TiCl_4$-mediated condensation of diphenylphosphinoylamide and phenylpropargyl aldehyde. Following the general rearrangement protocol, **1-128** was treated successively with $Cp_2Zr(H)Cl$, $ZnMe_2$ and imine **1-129** (Scheme 1). Introduction of 4 equivalents of the Furukawa-modified Simmons-Smith reagent formed the bicyclo[1.1.0]butane intermediate and following insertion, rearrangement to the skipped diene, and final cyclopropanation of the proximal olefin produced dicyclopropylmethylamine **1-121** in 60% yield (95% yield per *C-C* bond formed).

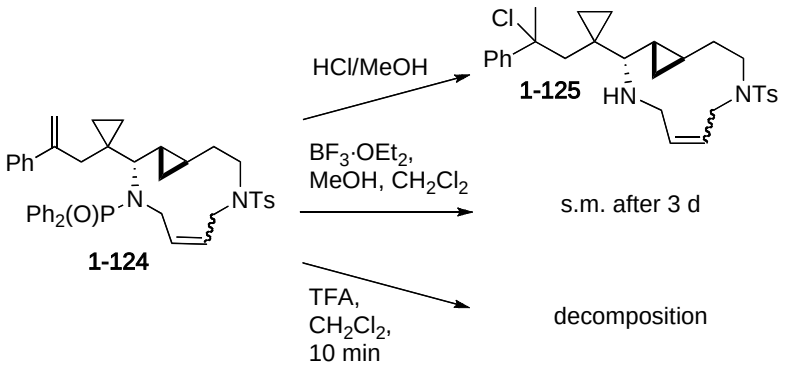
Simultaneous carbamate removal and allylation of the diphenylphosphinoylamide and tosylamide groups occurred in 68% yield using NaH and allyl iodide with HMPA as an additive (to promote nucleophilic substitution and, presumeably, to provide an adventitious amount of water to hydrolyze the carbamate) in THF at reflux to provide **1-122**. This compound, when subjected to the same metathesis conditions as reported in the previous azepine studies (10 mol%

of Grubbs 2nd generation catalyst in CH_2Cl_2 at reflux under ethylene gas), cyclized to afford the macrocyclic product in 96% yield (Scheme 1-22).



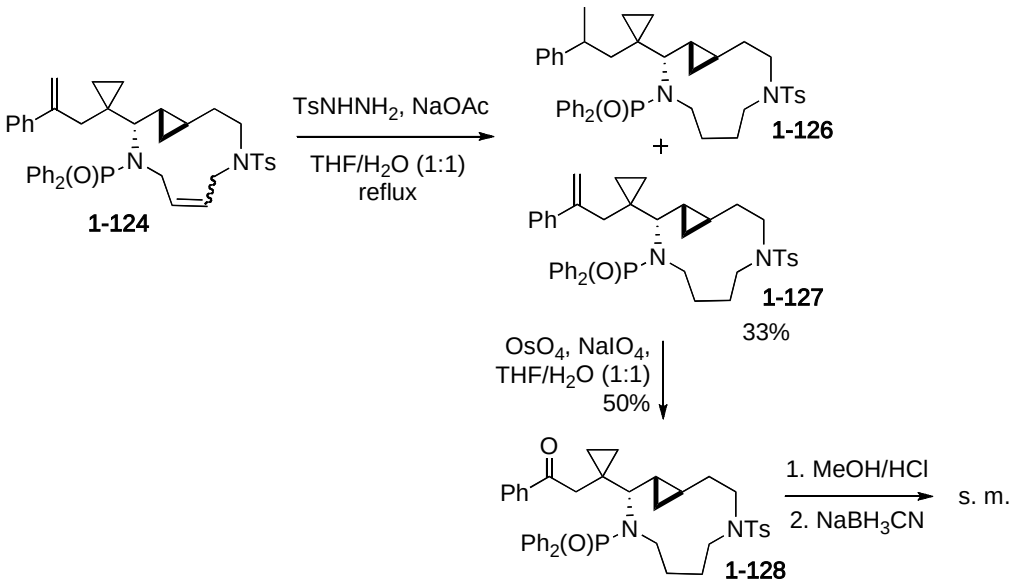
Scheme 1-22. Synthesis of macroyclic compound **1-124**.

After successful formation of the macrocycle, our attention turned towards the annulation of the smaller ring. Removal of the diphenylphosphinoyl group to accommodate further reactions of the free amine proved successful under standard acidic methanol deprotection conditions;[72] however, these conditions also led to the problematic addition of HCl across the styrenyl double bond, thereby destroying one of the olefin moieties we envisioned using in the final ring-closing step. Other methods for removing this protecting group, for example $BF_3{\cdot}OEt_2$ in MeOH, returned starting material or quickly led to complete decomposition (TFA in dichloromethane) (Scheme 1-23).



Scheme 1-23. Attempted removal of the *N*-diphenylphosphinoyl protecting group.

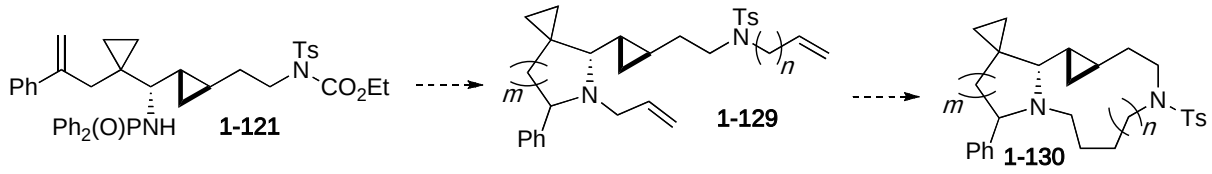
Due to the difficulties associated with removing the diphenylphosphinoyl group from key intermediate **1-124**, we concluded that a second metathesis reaction would not be a feasible approach to generate our desired polycylic core. Instead, we planned to reduce the macrocyclic olefin selectively using diimide conditions to leave the more polarized styrene double bond intact, and form a pyrrolidine ring using a similar oxidation/reductive amination protocol as previously employed in the azaspirocycle studies.[70] Diimide reduction using 1 equivalent of $TsNHNH_2$ led to the formation of the desired product (**1-127**) in only 33% yield accompanied with over-reduced **1-126** and starting material (Scheme 1-24). The osmium-mediated Johnson-Lemieux oxidation of **1-127** led to phenylketone **1-128** in 50% yield, however deprotection did not provide any cyclized product (only starting material was isolated in <5 mg scale reactions).



Scheme 1-24. Reduction and cyclization attempts.

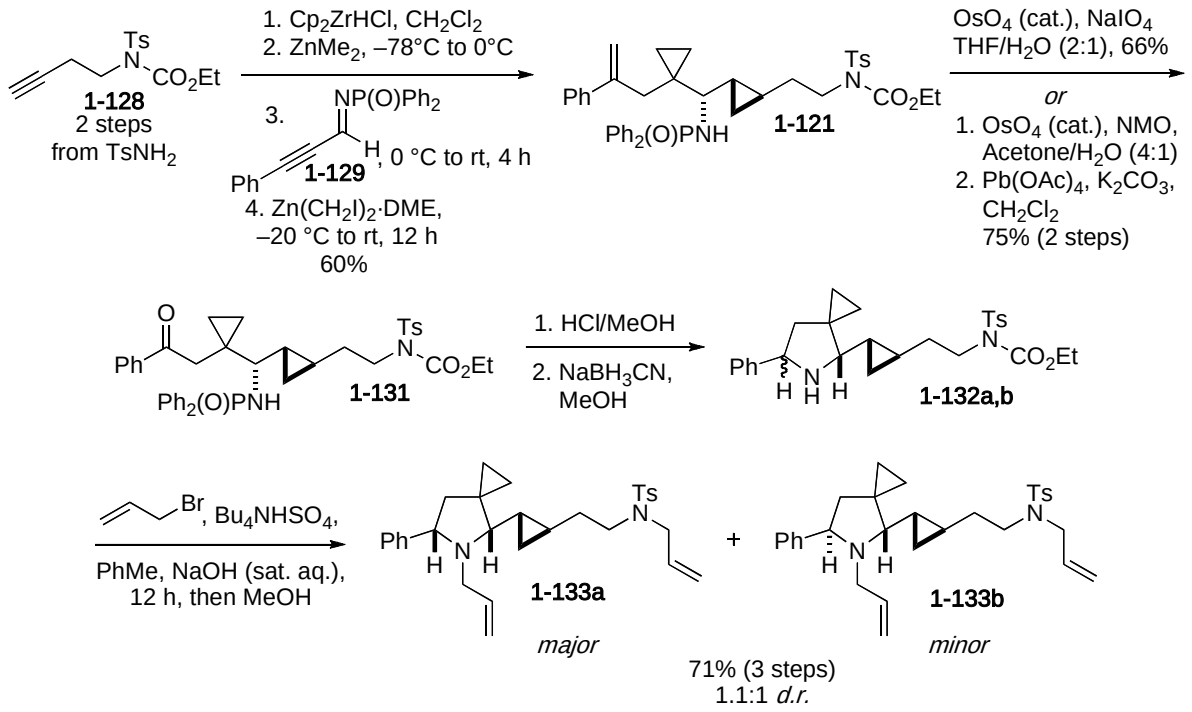
1.2.2 Revised Approach to Polycyclic Structures

From our inability to cyclize the pyrrolidine ring following macrocycle formation we reasoned that the conformational preference of the large ring likely prevented pyrrolidine ring formation. Hence, we once again reevaluated our strategy and surmised that macrocycle formation after cyclization of the smaller ring would be an energetically more favorable process and have a greater chance for success (Scheme 1-25).



Scheme 1-25. Revised cyclization strategy.

In our revised route (Scheme 1-26), Johnson-Lemieux oxidation of rearrangement product **1-121** provided ketone **1-131** in 66% yield, and it was later discovered that the yield could be improved to 75% by performing the two-step Upjohn dihydroxylation followed by Criegee elimination sequence. Deprotection of the diphenylphosphinoyl group with HCl in MeOH and reductive amination of the crude amine using sodium cyanoborohydride afforded pyrrolidines **1-132a** and **1-132b**, which were immediately subjected to allylation conditions without further purification. Simultaneous bis-allylation and carbamate removal using allyl iodide, sodium hydride, and HMPA had proven to be irreproducible and routinely gave mixtures of mono- and bis-allylated products.[73] As an alternative, phase-transfer conditions using tetra-*n*-butylammonium hydrogensulfate and allylbromide partitioned between toluene and saturated aqueous sodium hydroxide (1:1 v/v) were found to be superior in terms of reproducibility and scalability. The addition of ~5% v/v of methanol served to efficiently cleave any remaining carbamate (a byproduct in early attempts), and the desired bis-allylated pyrrolidines **1-133a** and **1-133b** were the only products isolated from the reaction mixture in 71% yield over 3 steps as a 1.1:1 mixture of diastereomers separable by column chromatography.[74] The major and minor diastereomers were tentatively assigned by ^{3}J coupling constant analysis and comparison to analogous pyrrolidine rings formed by reductive aminations during our group's diversity-oriented synthesis of azaspirocycles (Scheme 1-18). Our assignement was confirmed by the X-ray structure of **1-136** a later stage.

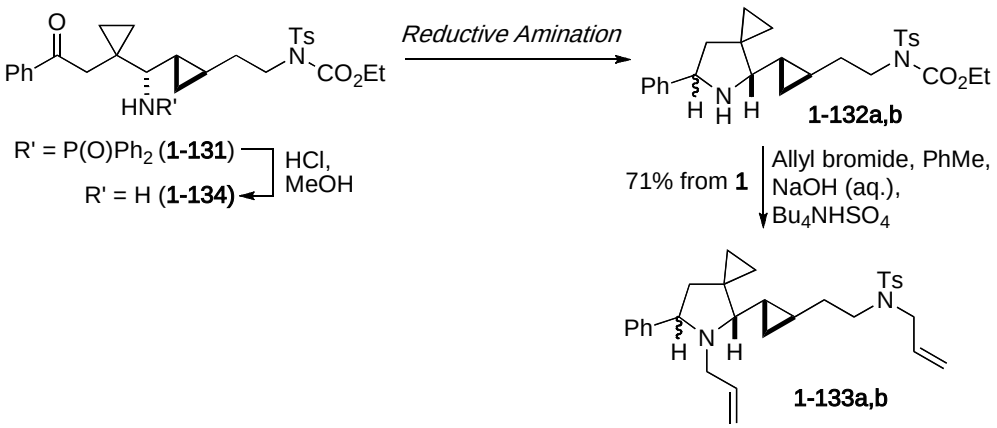


Scheme 1-26. Pyrrolidine formation from **1-121**.

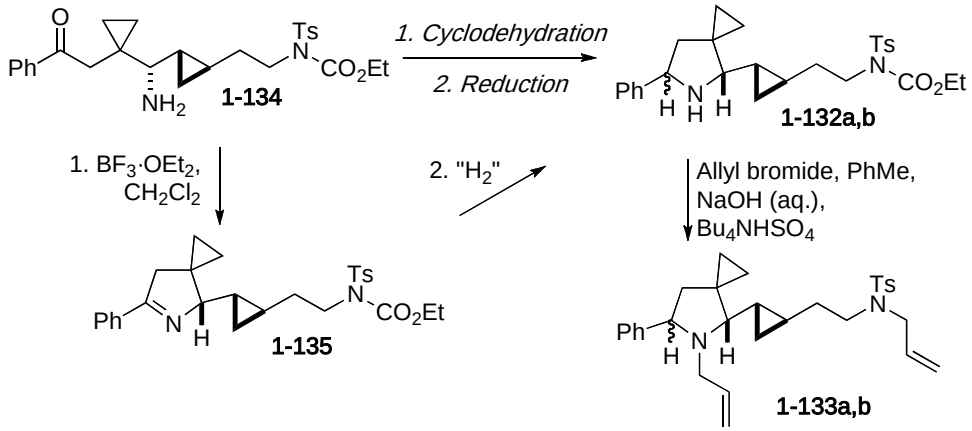
1.2.3 Improvement of Cyclization Diastereoselectivity

Attempts to increase the diastereoselectivity of the reduction event using borohydride reagents of varying steric and electronic properties led to similarly unselective ratios of pyrrolidine products, with the best result occurring when $NaBH(OPiv)_3$ was used (1.6:1 *d.r.*, Table 1-1). As an alternative strategy, we turned to a cyclodehydration/reduction method initiated by $BF_3{\cdot}OEt_2$ and proceeding though cyclic imine **1-135** (Scheme 1-28). Screening various reductants revealed that trichlorosilane possesses the optimal balance between reactivity and steric properties and provided an improved ratio of **1-132a** to **1-132b** (4.6:1). In each case, the crude mixture of *syn*- and *anti*-pyrrolidines was allylated under phase transfer conditions to provide more easily

handled and separable **1-133a** and **1-133b**, which, upon isolation, revealed the selectivity of the reduction step.



Scheme 1-27. Reductive amination approach.



Scheme 1-28. Cyclodehydration/reduction approach.

Table 1-1. Reagent screening for the a. reductive amination and b. cyclodehydration/reduction approaches.

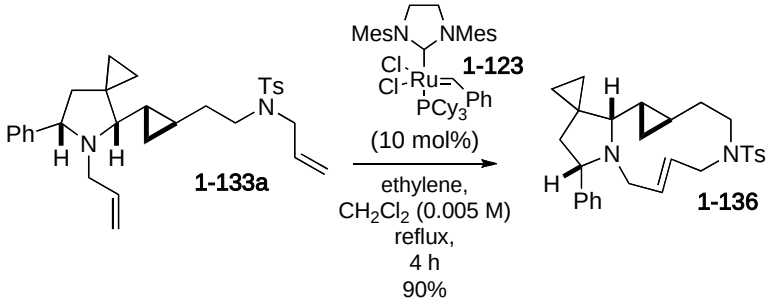
a. Reductive amination of 1-134 in Scheme 1-27	**1-133a : 1-133b**[i]
$NaBH_3CN$, MeOH	1.1 : 1
$NaBH_3CN$, AcOH, MeOH	1.5 : 1
$NaBH(OPiv)_3$	1.6 : 1
$NaBH(OAc)_3$	1.1 : 1
b. Reduction of 1-135 in Scheme 1-28	**1-133a : 1-133b**[i]
Ph_3SiH	SM[ii]
Ph_2SiH_2	SM[ii]
$PhSiH_3$	1.1 : 1
Cl_3SiH	4.6 : 1
$RhCl(PPh_3)_3$, H_2, MeOH	SM[ii]
Raney Ni, H_2, EtOH	2 : 1
DIBAL-H, CH_2Cl_2	1 : 1.3[iii]

[i]ratios of isolated products. [ii]no reduction products observed and **1-135** was recovered from the reaction. [iii]carbamate function was removed during the reaction.

1.2.4 RCM and Completion of the Polycylic Core

Gratifyingly, exposure of the major diastereomer resulting from the cyclization/allylation sequence to the 2nd generation Grubbs metathesis catalyst under ethylene in CH_2Cl_2 at reflux for 4 h led to an efficient formation (90% yield) of our target macrocyclic compound as a single olefin isomer (Scheme 1-29). Unfortunately assignment of the newly formed double-bond was not possible using ^1H NMR coupling constant analysis due to the overlap of the olefin peaks, despite solvent changes and high-field instruments. Fortunately the polycyclic product

crystallized from hexanes/EtOAc and the (*E*)-olefin was unambiguously identified by X-ray crystallography, interestingly as a 3:1 ratio of conformational isomers in the solid state as evidenced by static disorder of the unit crystal in the alkene chain linking the two nitrogen atoms (Figure 1-4).[75,76] Ethylene was essential in this transformation in order to avoid a deleterious polymerization of the starting material that occurred under an N_2 atmosphere. Notably, exposure of *anti*-pyrrolidine **1-133b** to identical RCM conditions led to polymerization of the diene, presumably due to the increased spatial distance of the reacting olefins.



Scheme 1-29. Ring-closing metathesis of **1-133a**.

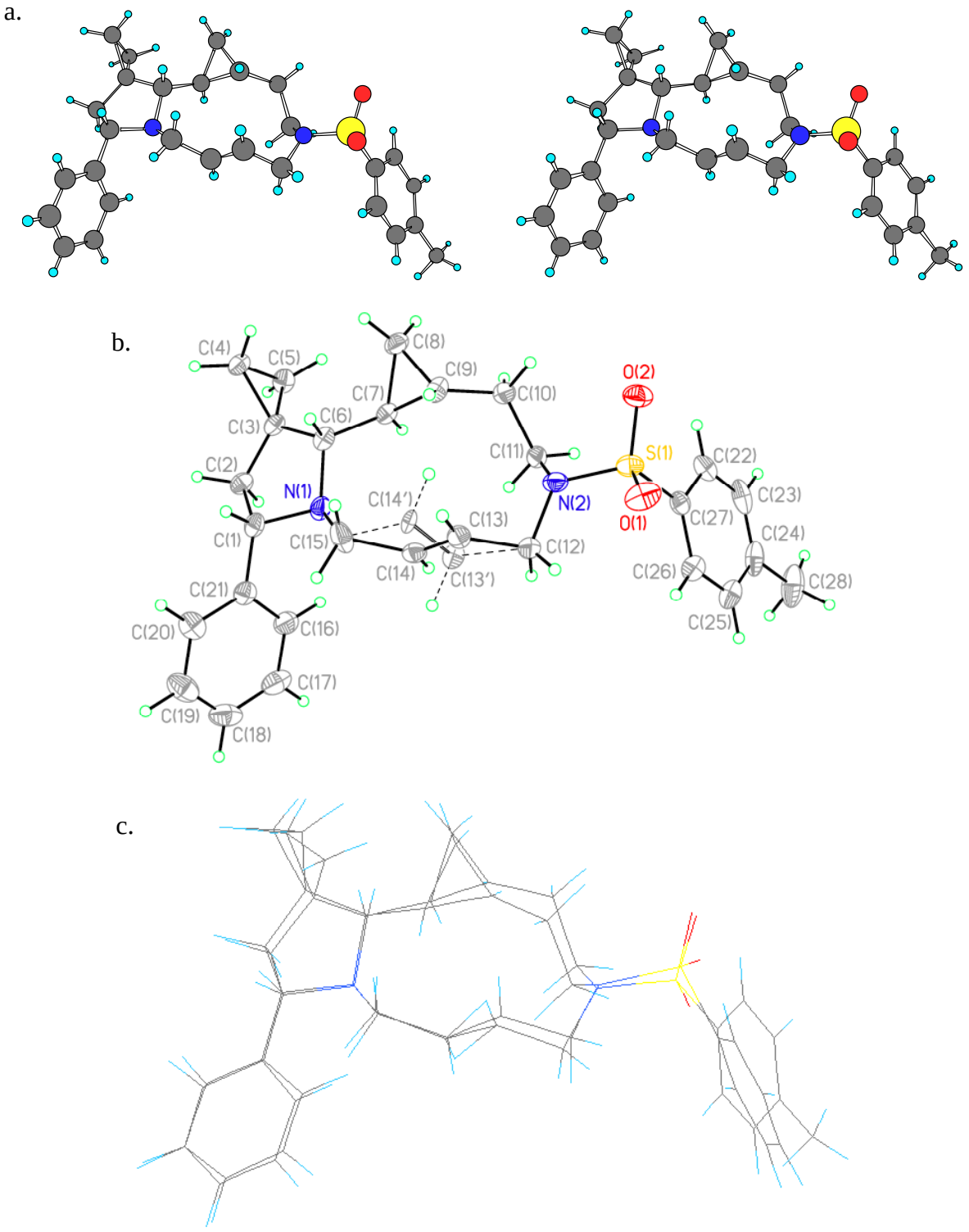
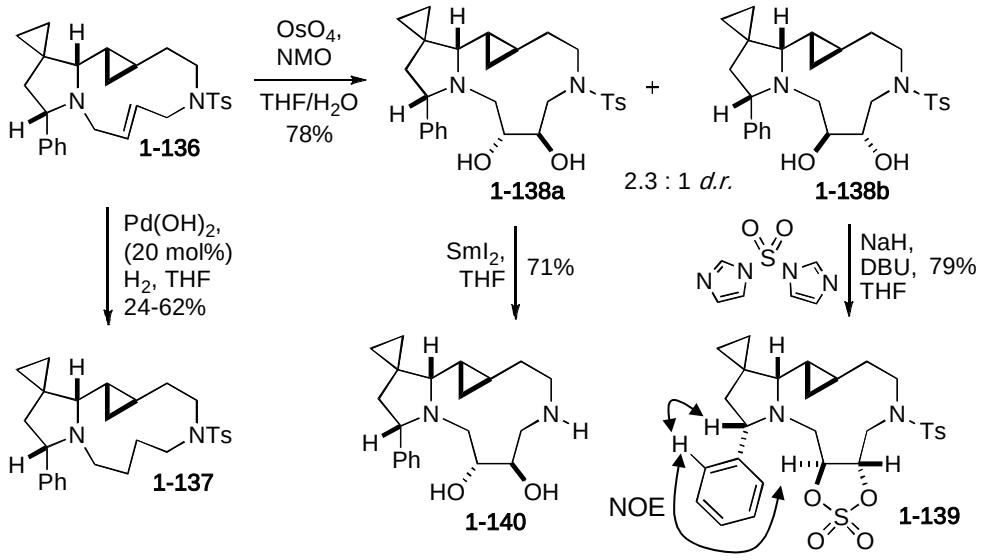


Figure 1-4. a. X-ray crystal structure of **1-136**, b. orientation of butene unit (3:1 solid:dashed ratio), and c. overlaid crystal and calculated lowest energy structures (calculated using MOE; MMFF94x basis set).

Functionalization of the metathesis product proved to be more difficult than originally anticipated. The olefin was resistant towards hydrogenolysis in the presence of a number of catalysts, including Pd-, Ru-, and Pt- complexes, which appeared to open the pyrrolidine ring under hydrogenation conditions due to the benzylic character of the amine. After several trials it was discovered that the use of 20 mol% $Pd(OH)_2$ in THF under 1 atm of H_2 for 10 h saturated the macrocyclic double bond in 24-62% yield (Scheme 1-30). Attempts to epoxidize the olefin under Sharpless and Shi conditions were unsuccessful, and exposure of **1-136** to *m*-CPBA led to formation of the *N*-oxide on the pyrrolidine ring.

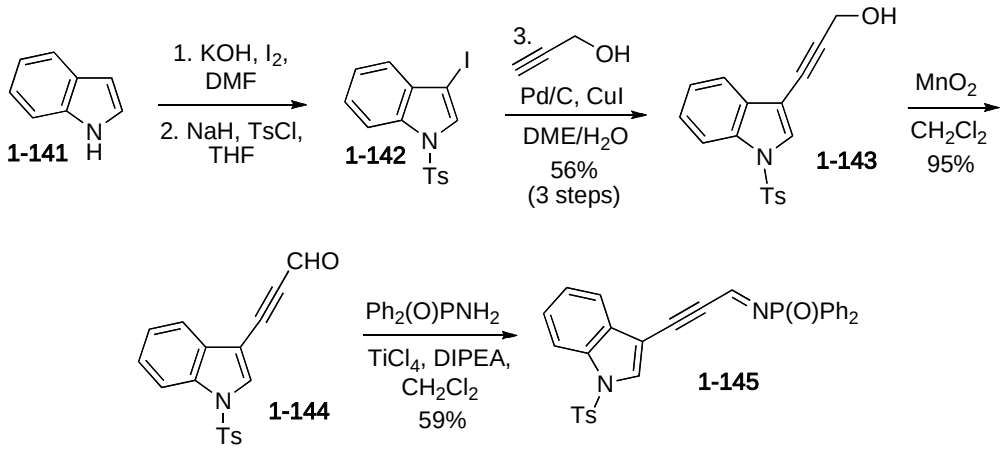
Modification of **1-136** was accomplished by dihydroxylation under Upjohn conditions to produce a 2.3:1 ratio of separable diols (Scheme 1-30). The ratio of diastereomers was found to be related to the catalyst loading: 10 mol% of OsO_4 produced a 1:1 mixture after 12 h (100% conversion by TLC) and 5 mol% of OsO_4 afforded a 2.3:1 ratio after 24 h (100% conversion by TLC). The minor isomer (**1-138b**) was converted into its corresponding cyclic sulfate by treatment with sulfuryl diimidazole. 2D-NOESY spectroscopy of the rigidified heterocycle established the relative stereochemical arrangement of the diol portion of **1-139**, and, by relation, of **1-138a** and **1-138b**. The *N*-tosyl group of **1-138a** was successfully removed using SmI_2 with notable tolerance towards the cyclopropane moieties to reveal the unprotected secondary amine.[77]



Scheme 1-30. Elaboration of metathesis product **1-136**.

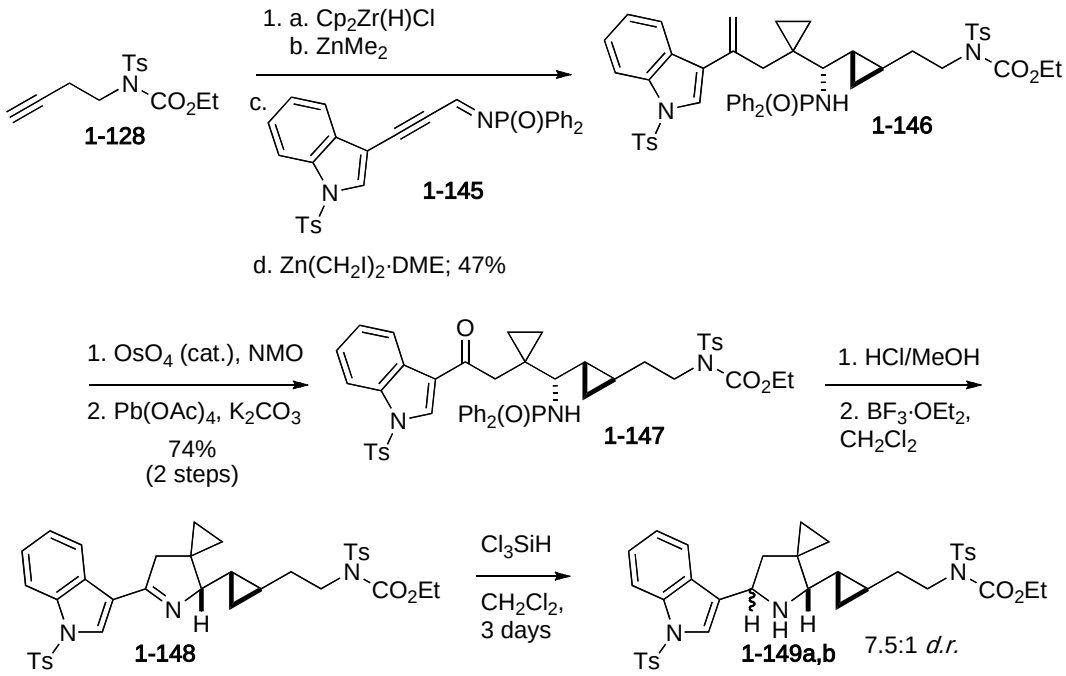
1.2.5 Incorporation of Indole Moiety

Having developed a route to access these polycyclic alkaloid skeletons, we sought to incorporate a heterocyclic unit commonly found in biologically active natural products into the scaffold, and we chose indole as a target structure to accomplish this goal. *N*-Tosylindole imine **1-145** was successfully synthesized through a Sonogashira coupling of propargyl alcohol with readily available iodide **1-142**, followed by MnO_2 oxidation and $TiCl_4$-mediated imine formation (Scheme 1-31). It should be noted that the best results regarding the isolation of **1-145** came when oven-dried, non-deactivated (i.e. no Et_3N in the eluent) silica gel was used in chromatographic purification. Remarkably, the stability of **26** was greatly improved compared to other alkynyl imines, likely owing to the presence of the strongly electron-withdrawing tosyl group. This behavior is consistent with our lab's observations in preparing various electron-rich and electron-deficient aryl substituted alkynyl imines.



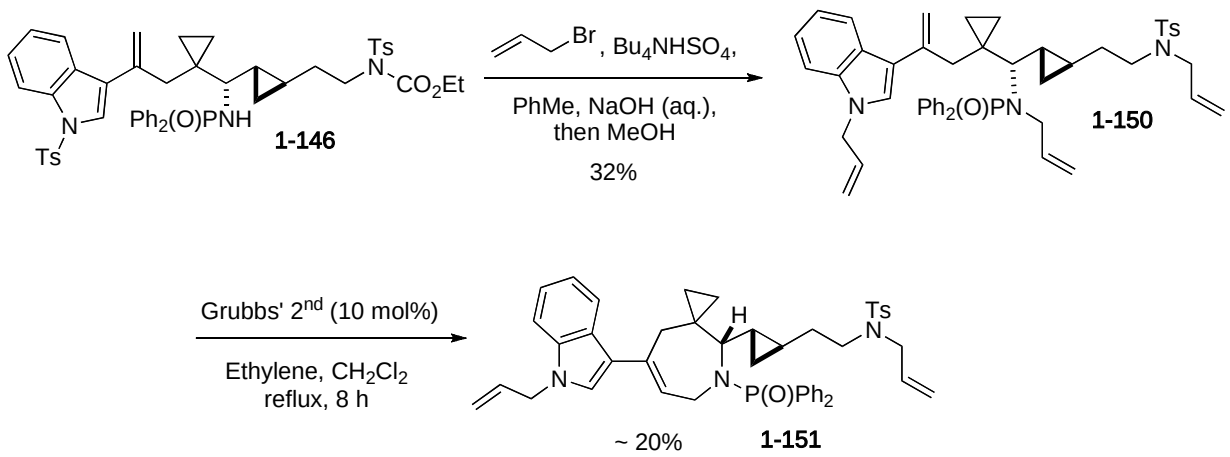
Scheme 1-31. Sonogashira cross-coupling route to **1-145**.

The cascade bicyclobutane insertion/rearrangement sequence using **1-145** proceeded to afford **1-146** in 47% yield (Scheme 5). Similar to what was previously developed for the phenyl-containing substrate, 2-step oxidation, deprotection and cyclodehydration produced isolable cyclic imine **1-148**. Applying our previously identified optimal reduction conditions (excess Cl_3SiH in CH_2Cl_2) yielded an improved 7.5:1 *syn*:*anti* selectivity of pyrrolidines. Molecular modeling of **1-148** (MMFF basis set) suggests that pyramidalization of the sulfur atom of the indole *N*-tosyl group and the resulting facial bias is likely responsible for the increased diastereoselectivity of this reduction compared to phenyl-substituted imine **1-135**.



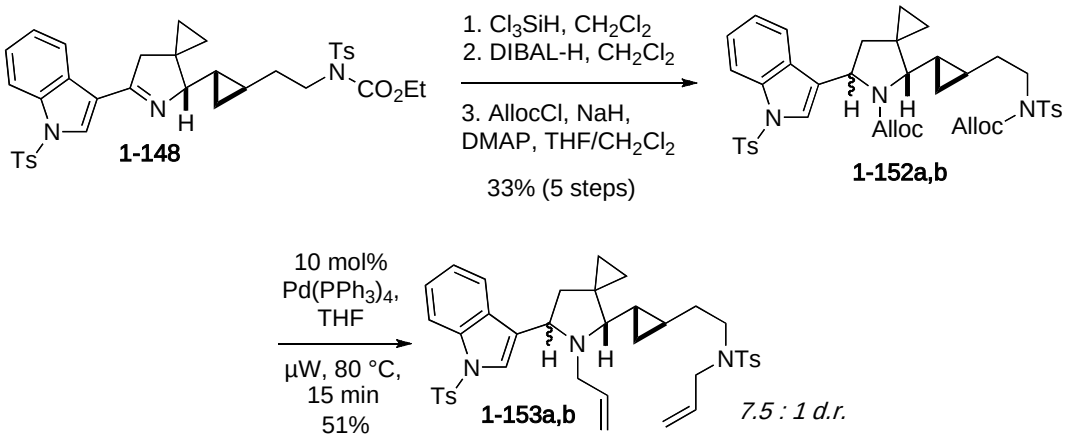
Scheme 1-32. Cascade rearrangment using *N*-tosylindole imine **1-145** and cyclization of **1-147**.

For the allylation of **1-149a**, we foresaw that the phase-transfer allylation conditions that had worked well for our previous system would be incompatible with **1-149** due to the lability of the indole tosyl group towards the basic conditions needed for *in situ* carbamate deprotection. In fact, when uncyclized **1-146** was subjected to the alkylation conditions, the tri-allylated compound **1-150** containing 4 olefins was isolated (Scheme 1-33). Treatment of this material to metathesis conditions produced a number of products, with azepine **1-151** appearing to be the major constituent (smallest ring formation).



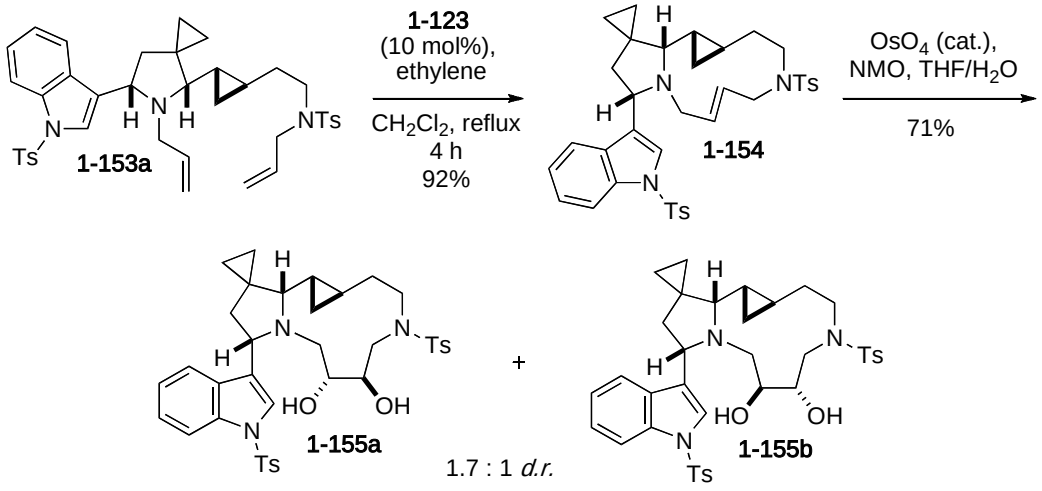
Scheme 1-33. Allylation of **1-146** under phase-transfter conditions and metathesis of **1-150**.

For a solution to the allylation problem we turned to the Pd-catalyzed conversion of allyl carbamates into their *N*-allyl derivatives to prepare our metathesis precursor. The ethyl carbamates of the crude pyrrolidine products from the Cl_3SiH reduction of **1-148** were removed using 3 equivalents of DIBAL-H (which had been observed as a byproduct in the diastereoselective cyclic imine reduction studies, Table 1-1), as opposed to alkoxide conditions. The resulting amines were protected with AllocCl to afford **1-152a** and **1-152b** in 33% isolated yield from **1-148**. The inseparable mixture of bis-Alloc carbamates was exposed to catalytic $Pd(PPh_3)_4$ under microwave heating to provide bis-allylated **1-153a** and **1-153b**, separable by column chromatography, which confirmed the diastereoselectivity of the reduction step.



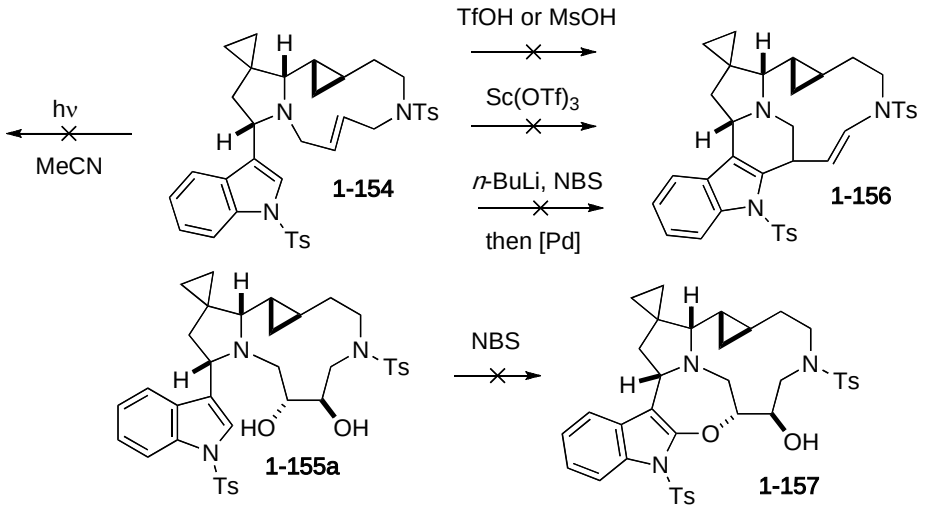
Scheme 1-34. Imine reduction and carbamate cleavage followed by two-step allylation.

In a similar manner as before, RCM of diene **1-153a** under ethylene and 10 mol% of **1-123** provided **1-154** as a single isomer that was dihydroxylated to furnish the polycyclic diols **1-155a** and **1-155b** in a 1.7:1 ratio. Exposure of diol **1-155a** to SmI_2 for bis-tosyl deprotection led to a complex mixture of compounds by ^1H NMR analysis.



Scheme 1-35. RCM to complete **1-154** and subsequent dihydroxylation.

Having successfully constructed the polycyclic indole-containing scaffold, we were intrigued by the possibility of using the indole unit as a handle to perform a final ring closure between the macrocyclic olefin of **1-154** or the diol of **1-155a**. Initially, we attempted to activate the system using Brønsted- (TfOH, MsOH) and Lewis-acid ($Sc(OTf)_3$) catalysis but with no success. Photochemical conditions did not affect any bond formation between indole and the *E*-olefin either. Deprotonation of the indole proton using *n*-BuLi appeared to be promising with **1-154** exhibiting remarkable stability in the presence of the strong base, however trapping of the anion with a halogen source to perform a Heck-coupling was not successful, returning starting material from the reaction mixture. Finally we decided to reverse our approach to use the macrocyclic functionality as the nucleophile. However activation of the indole ring of diol **1-155a** using NBS did not initiate the desired cyclization. Removal of the indole tosyl group would provide the most likely chance of successful cyclization, perhaps by bis-acylation of the diol and indole. However, we found that once the macrocyclic ring had been closed the sulfonamide was surprisingly resistant to conventional deprotection conditions (K_2CO_3, MeOH, heat).



Scheme 1-36. Attempts to connect indole ring and macrocycle.

1.3 CONCLUSION

Organozirconium compounds and their derivatives possess a rich history in organic synthesis due to their versatility, ease of preparation and diversity of transformations. Impressively, the future of these reactive intermediates is not outshined by their past. The ability to access novel functionalities, such as the bicyclo[1.1.0]butane scaffold, and catalyze novel transformations[78] leaves the exciting world of organozirconium chemistry open for deeper exploration.

In our own studies we successfully synthesized natural product-like compounds possessing 3-, 5- and 11-membered rings within their polycyclic frameworks, originating from the carbene insertion/rearrangement of a bicyclo[1.1.0]butane intermediate. We demonstrated that elaboration of these advanced structures is possible under dihydroxylation, reductive desulfonylation and sulfate formation conditions. Additionally we have expanded the scope of our multicomponent one-pot dicyclopropylmethylamine synthesis through the use of indole imine **1-145** in the cascade sequence. Finally, we have contributed to the intrigue of the products derived from this methodology by demonstrating the types of complex molecules that can be accessed.

2.0 STUDIES ON *STEMONA* ALKALOIDS: PARVISTEMOLINE, STEMOAMIDE AND SESSILIFOLIAMIDES

2.1 INTRODUCTION

2.1.1 Introduction to *Stemona* Alkaloids

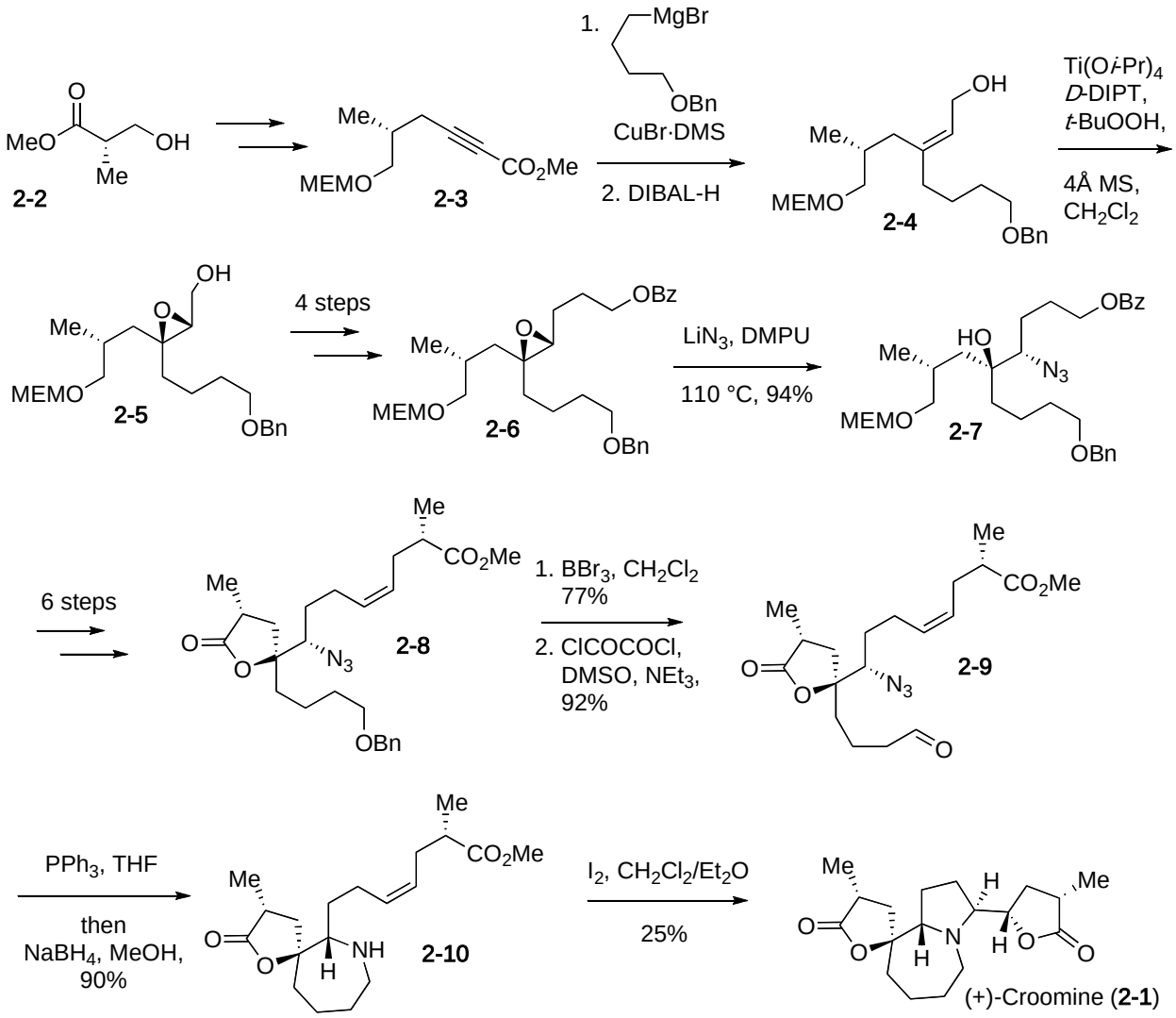
Extracts of the tuberous roots of the *Stemonacae* family of flowering plants have been used for centuries in Asia for their anti-cough and anti-parasitic (anthelmintic) properties.[79] Unbeknownst to the ancient pharmacist was the intense molecular complexity and diversity, yet surprising similarity, of the chemical products these plants produce. Modern methods of extraction, separation and characterization have revealed well over 80 distinct alkaloids from the 3 genera (*Stemona*, *Croomia* and *Stichoneuron)* of *Stemonaceae*. While debate exists over the exact classification of the *Stemona* alkaloids (8 structural classes in 1994[80] vs. 5 in 2000[79a] vs. 3 in 2006[81]), it is safe to say the lines between classification groups are becoming increasingly blurry with the isolation of each new alkaloid and the evidence that they contain hinting at biosynthetic relationships with other *Stemona* members.

In general, the *Stemona* alkaloids are classified by a conserved, pyrrolo[1,2-*a*]azepine core functionalized with carbon chains mostly forming terminal lactone rings.[81] Interestingly, prior to 1980 almost all the structural determined of newly isolated *Stemona* alkaloids could only

be performed by X-ray crystallography due to their structural complexity and general instability. It is this same molecular complexity that has led to a considerable amount of synthetic interest in the scientific community. The pursuit of synthesizing these alkaloids has led to the development of new strategies for the construction of the skeleton along diverse routes including alkylations, acylations, cycloadditions, transition-metal mediated reactions, and radical ring closures.[82] With such a breadth of research existing in the literature regarding the total syntheses of *Stemona* alkaloids only examples and approaches relevant to the material contained in this dissertation will be presented.

2.1.2 Approaches to *Stemona* Alkaloids

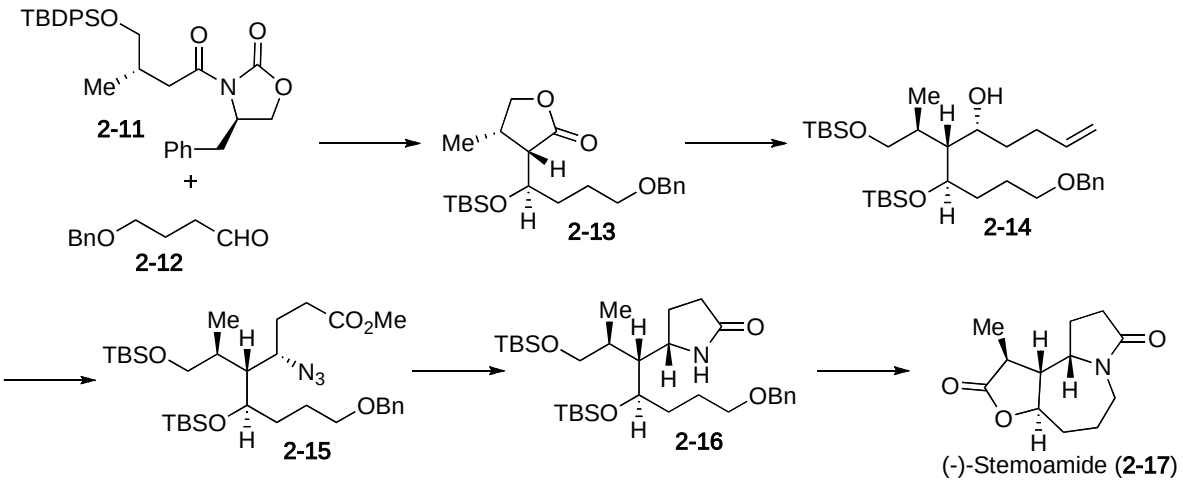
In 1989 Williams and co-workers published the enantioselective total synthesis of (+)-croomine, which was the first reported total synthesis of a *Stemona* alkaloid (Scheme 2-1).[83] In their pioneering work, **2-1** was completed in a 24-step linear route from (*S*)-Roche ester (**2-2**) featuring a Sharpless epoxidation (>80% *de*) on allylic alcohol **2-4** followed by regioselective epoxide opening to form the key vicinal stereocenters in **2-7**. The pyrrolo[1,2-*a*]azepine ring system was completed by performing a Staudinger-aza-Wittig reaction on azido-aldehyde **2-9** followed immediately by an iodo-amination on the proximal *cis*-olefin. Interestingly the final cyclization to form the "eastern" lactone proceeded with retention of configuration, suggesting anchimeric assistance of the pyrrolidine nitrogen and formation of an aziridinium intermediate that was subsequently opened by the methyl ester to afford the observed stereochemical configuration.



Scheme 2-1. Williams' total synthesis of (+)-croomine.

The Staudinger-aza-Wittig/iodoamination sequence became a hallmark of Williams' studies on *Stemona* alkaloids and he also applied this strategy to the syntheses of **(–)**-stemonine[84] and **(–)**-stemospironine.[85] The Staudinger methodology was applied to the total synthesis of the smaller *Stemona* alkaloid, **(–)**-stemoamide as shown in Scheme 2-2.[86] For the synthesis of the pyrrolo[1,2-*a*]azepine core, Williams used established aldol methodology to set the C(8) and C(9) stereocenters of lactone **2-13**. Homoallylation and reduction of the ketone provided alcohol **2-14** that was inverted via the mesylate to afford the key Staudinger substrate (**2-15**). Closure of

the azepine ring under nucleophilic alkylation conditions followed by deprotection and oxidation to the lactone completed the first total synthesis of **(–)**-stemoamide.



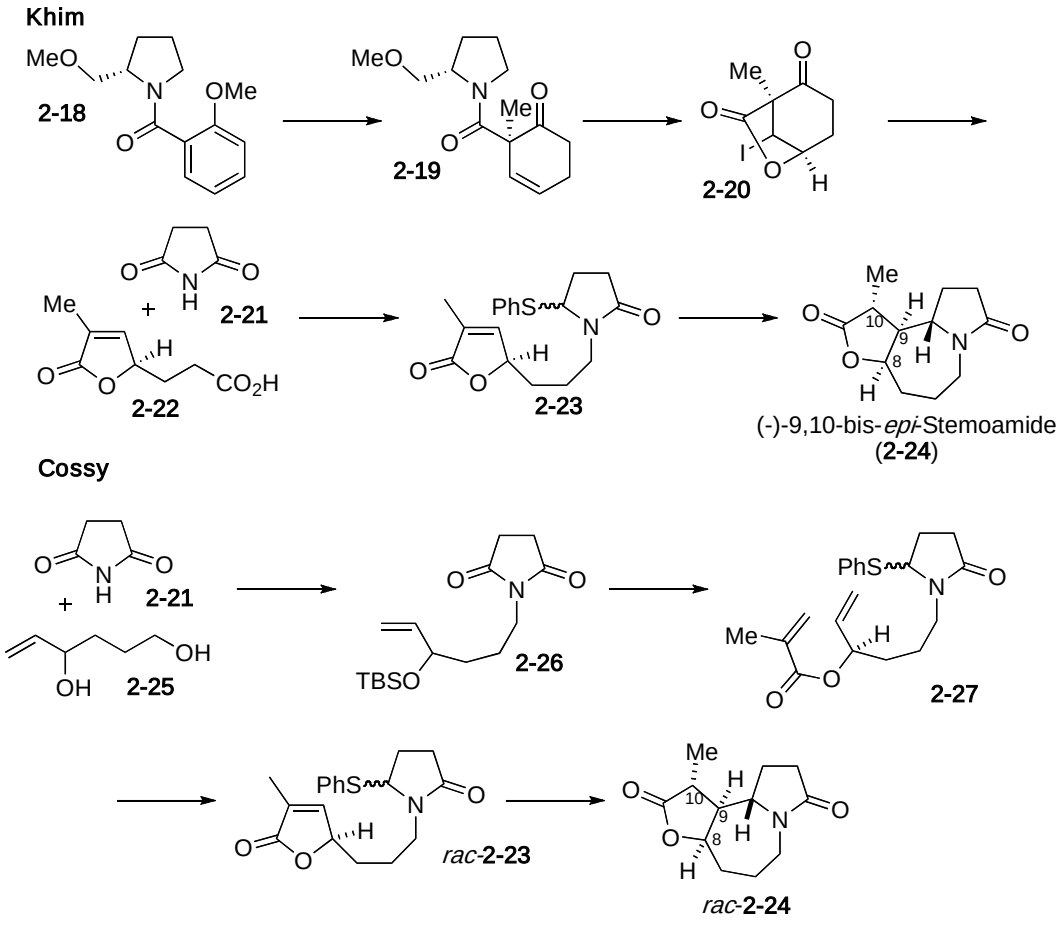
Scheme 2-2. Williams' approach to (–)-stemoamide.

In the years since Williams' publication, stemoamide has become one of the most highly targeted of the *Stemona* alkaloids. Its popularity is likely due to its manageable functionality, intriguing contiguous stereochemical pattern, and amenability of the ring system towards synthetic creativity, as evidenced by the number of diverse approaches towards the alkaloid. Examples of the major strategies- radical cyclizations, cycloadditions, and ring-closing metathesis reactions- are presented below.

Recent syntheses of **(–)**-9,10-bis-*epi*-stemoamide and (+/-)-9,10-bis-*epi*-stemoamide reported by Khim (2004)[87] and by Cossy (2006),[88] respectively, feature a key 7-*exo*-*trig* radical cyclization perfomed in the final steps of each synthesis to complete the azepine ring (Scheme 2-3). In the Khim synthesis, an enantioselective Birch reduction and methylation provides **2-19** possessing a chiral auxiliary, which is removed in the subsequent iodolactonization to afford **2-20**. Lithium hydroxide-mediated fragmentation provides butenolide **2-22**, which after coupling

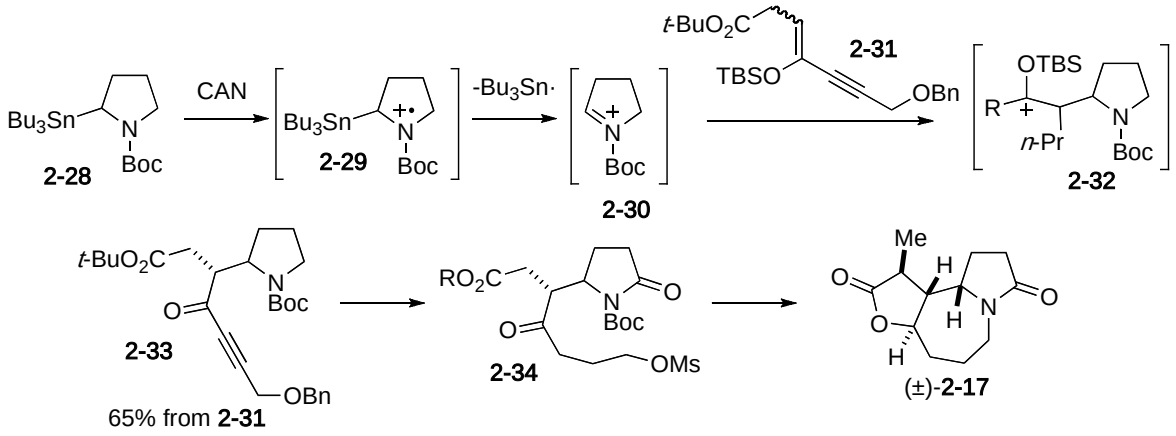
with succinimide is converted into radical precursor **2-23**. Treatment of the sulfide with *n*-Bu_3SnH and AIBN generates the radical species that cyclizes in a 7-*exo*-*trig* fashion to form *syn*-fused **(–)**-9,10-bis-*epi*-stemoamide (**2-24**).

In Cossy's synthesis, a more direct route is taken to the identical sulfide, albeit in racemic fashion. Alkylation of succinimide with diol **2-25** followed by acylation provides **2-26**. Ring-closing metathesis forms butenolide **2-23** which undergoes an identical 7-*exo*-*trig* radical cyclization to furnish the racemic bis-epimer of **2-24**.



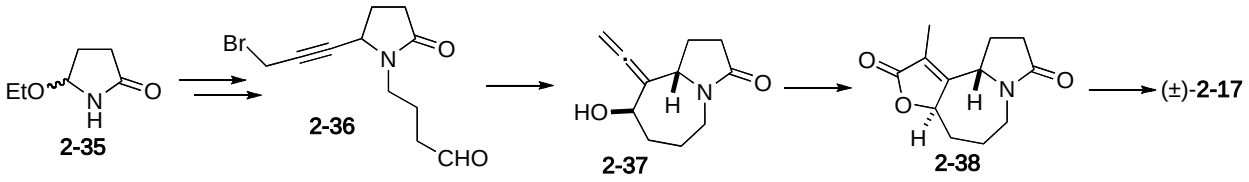
Scheme 2-3. Radical cyclization approaches to stemoamide core.

A unique approach by Narasaka features the single electron transfer reaction of α-stannyl amides to form *N*-acyl imines, which can be subsequently intercepted with various nucleophiles (Scheme 2-4).[89] The oxidation of **2-28** to radical cation **2-29** followed by elimination of tributylstannyl radical generates imine **2-30** that is trapped by silyl enol ether **2-31** to afford ketone **2-33** in 86% yield. Various functional group conversions led to **2-34** and an intramolecular cyclization onto the unprotected pyrrolidone ring furnished the 5,7-core and allowed for the completion of (±)-**2-17**.



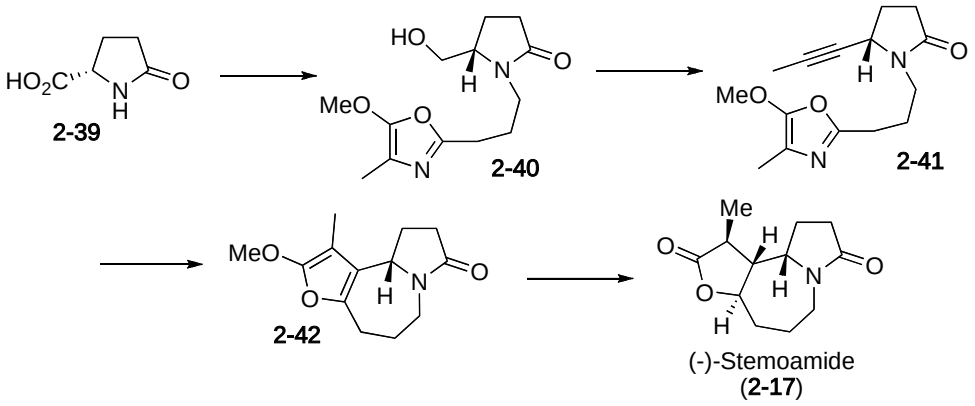
Scheme 2-4. Intermolecular oxidative coupling approach to (±)-stemoamide by Narasaka.

In a recent synthesis reported by Bates and Sridhar,[90] the azepine ring was formed by an inramolecular propargylic Barbier cyclization (Scheme 2-5). Elaboration of succimimide into aminal **2-35** followed by alkylation of the amide, alkynylation, and functional group manipulations provided bromide **2-36** in a 10-step sequence. Screening of various metals to initiate the Barbier cyclization revealed indium to be superior, affording allene **2-37** in 82% yield and a 16:1 ratio of diastereomers. Cyclocarbonylation of the allene formed advanced butenolide **2-38**, which was subsequently reduced to afford the racemate of the target alkaloid.



Scheme 2-5. Intramolecular propargylic Barbier cyclization to synthesize (±)-stemoamide by Bates.

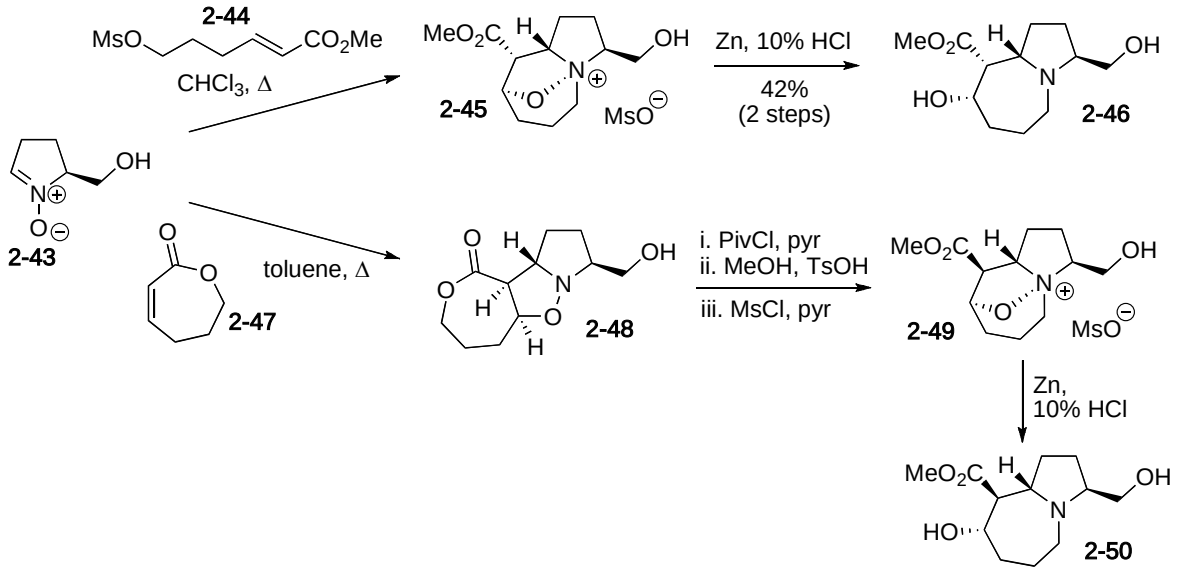
In 1997, Jacobi and co-workers reported a 7-step synthesis of (±)-stemoamide featuring a key Diels-Alder/retro-Diels-Alder process to set the entire skeleton of target molecule.[91] Later introduction of the requisite stereochemical elements in the starting material allowed for the key [4+2] sequence to operate in an enantioselective manner and provide **(–)**-stemoamide in ~20% overall yield for the 9-step enantioselective route.[92]



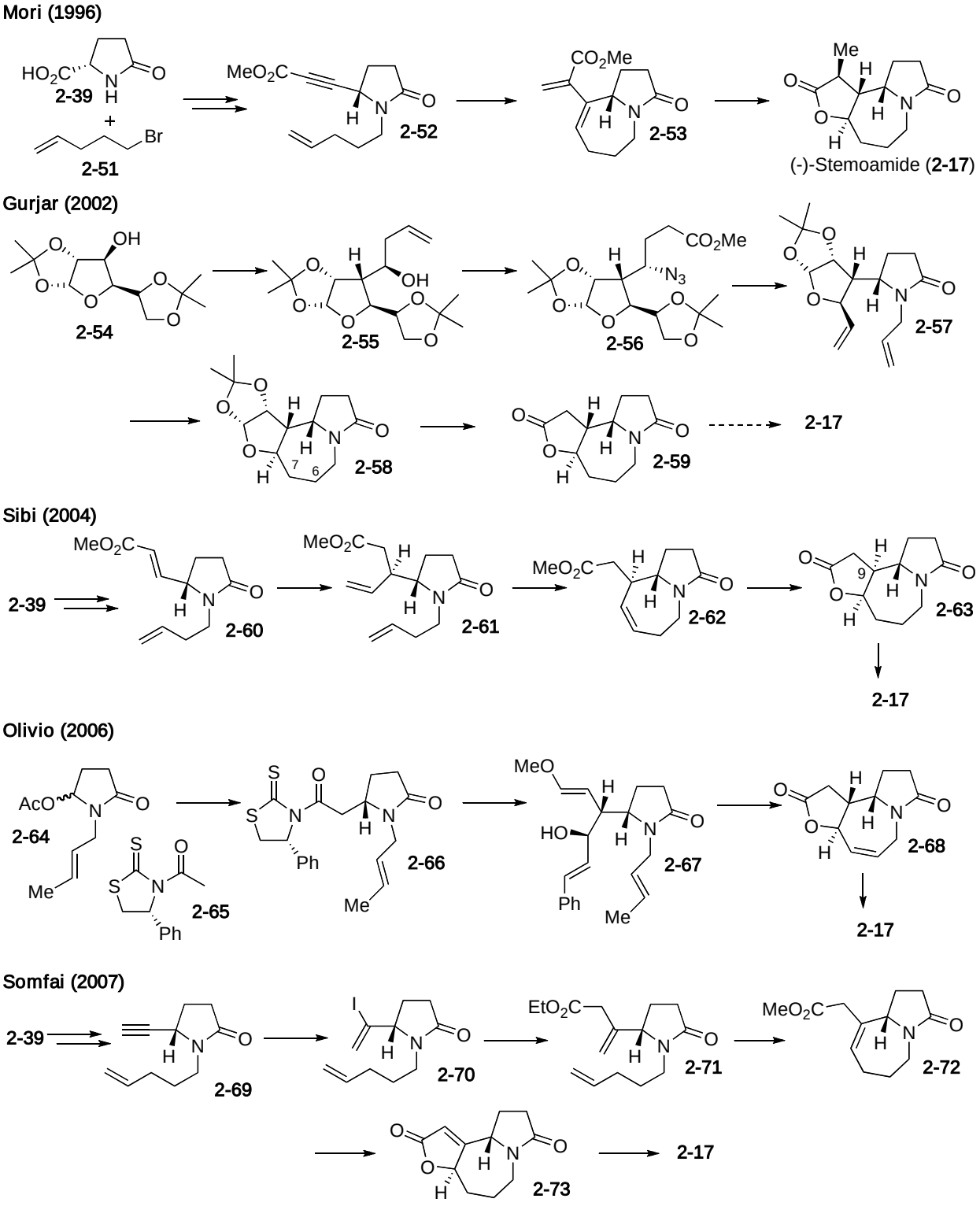
Scheme 2-6. Diels-Alder/retro-Diels-Alder approach used by Jacobi to form the (–)-stemoamide ring system.

In another example for cycloaddition reactions to access the core of *Stemona* alkaloids, Figueredo and co-workers have reported the intermolecular [3+2] cyclization of nitrone **2-43** with α,β-unsaturated esters (**2-44** and **2-47**, Scheme 2-7).[93] Following the initial cyclization, the mesylate in **2-44** was displaced to provide the polycyclic salt, which was successfully opened

using zinc to deliver the *Stemona* pyrrolo[1,2-*a*]azepine core. Alternatively, using α,β-unsaturated lactone **2-47** in the dipolar cycloaddition step provided tricycle **2-48**, which when opened under identical conditions provided **2-50** as the C(9) epimer, which is a useful intermediate for the synthesis of other *Stemona* alkaloids.[82]



Scheme 2-7. Intermolecular nitrone [3+2] cycloadditions by Alibés and Figueredo to access the pyrrolo[1,2-*a*]azepine core of Stemona alkaloids.



Scheme 2-8. Ring-closing metathesis approaches to (–)-stemoamide.

Given the polycyclic nature of the *Stemona* alkaloids, it is not surprising that a large number of groups targeting the stemoamide ring system have used ring-closing metathesis to form the azepine moiety (Scheme 2-8). Mori and Kinoshita are credited with the first application of RCM to the synthesis of **(–)**-stemoamide in their 1996 report.[94] Enyne metathesis of **2-52** (synthesized from (*S*)-pyroglutamic acid and alkyl bromide **2-51**) possessing the conjugated alkyne was successful despite potential complications. Gurjar and Reddy published a formal synthesis of **2-17** using a carbohydrate-based approach. Borrowing from Williams' (and, later, Cossy's)[88] Staudinger approach to form the pyrrolidone ring, Gurjar synthesized diene **2-57**, which was subjected to Grubbs' 1st generation ruthenium metathesis catalyst to close the C(6)-C(7) bond of the azepine ring. Cleavage of the acetonide and deoxygenation provided common intermediate **2-59** to complete the formal synthesis.

In 2004 Sibi and Subramanian used olefin metathesis to close the C(7)-C(8) bond of the azepine from diene **2-61** formed by a substrate-directed conjugate addition.[95] Lactonization, methylation and inversion of the C(9) center completed the synthesis. Olivio and co-workers have used an *anti*-aldol reaction to set the C(9) and C(8) stereocenters prior to azepine and lactone formation.[96] Oxidation of **2-67** to the lactone allowed for metathesis of the two 1,2-disubstituted olefins to complete the pyrroloazepine system. Somfai's group applied RCM in a manner reminiscent of Sibi's cyclization starting from a molecule reminiscent of Mori's approach (**2-52**). In Somfai's synthesis, a 1,1-disubstituted olefin was used as a metathesis partner for the formation of the C(8)-C(9) bond. The C(9) stereocenter was later installed by a nickel hydride reduction of **2-73** prior to α-methylation in a manner similar to Mori and Jacobi.

2.1.3 *Stemona* Alkaloid Synthesis in the Wipf Group

The Wipf group has maintained an active program in the total synthesis of *Stemona* alkaloids since the discovery and development of the oxidative cyclization of tyrosine to hydroindolines.[97] Wipf and co-workers used stenine and tuberostemonine to showcase the versatility of these cyclization products in scaffold-driven total synthesis approaches.

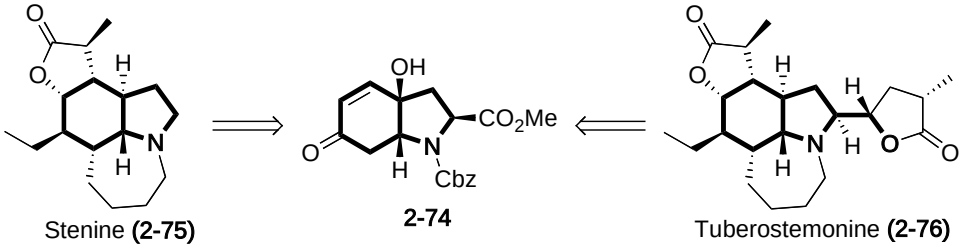
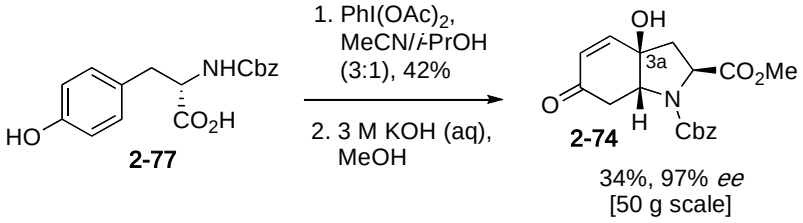


Figure 2-1. Conserved hydroindole core found in stenine and tuberostemonine.

2.1.3.1 Total Synthesis of Stenine

The stenine subfamily of the *Stemona* alkaloids, characterized by the presence of a tetracyclic 5,6,7,5-ring core containing lactone, azepine, and hydroindoline rings, is comprised of seven members, with stenine and tuberostemonine representing the most common derivatives. The absolute configuration of tuberostemonine was unambiguously established by X-ray analysis in 1967 and relayed to other members in this group by simple analogy as well as chemical degradations.[98] Stenine was originally isolated from *Stemona tuberosa* in 1967.[99] This polycyclic alkaloid has attracted a significant amount of synthetic attention, culminating in a number of racemic[100] and enantioselective[101] syntheses starting in 1990 with a pioneering Diels-Alder based synthesis by the Hart group at Ohio State University, and most recently complemented by the

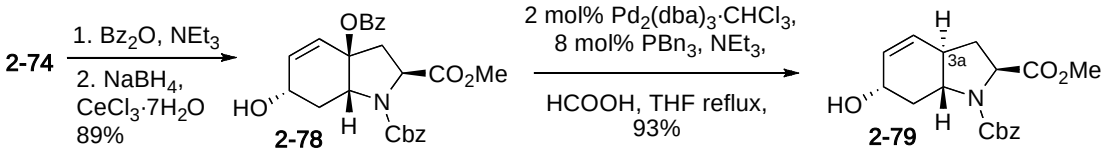
Aubé group at the University of Kansas, who also accomplished the synthesis of neostenine and 13-epineostenine by the aza-Schmidt approach.[79a,82] As stated previously, the Wipf group used stenine and tuberostemonine to showcase the utility of a scaffold-driven total synthesis approach, taking advantage of the versatile oxidative tyrosine cyclization to hydroindolines previously developed by Wipf and co-workers as outlined in Figure 2-1.[97]



Scheme 2-9. Oxidative cyclization of Cbz-L-tyrosine and optimized conditions.

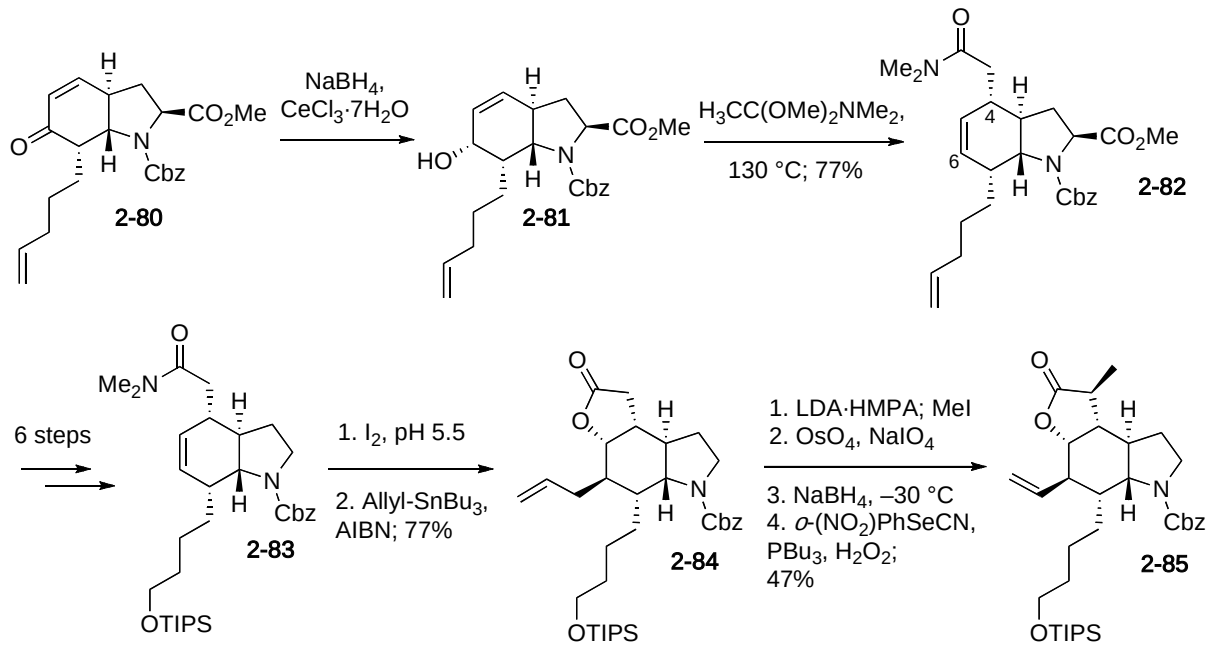
Following their established protocol,[97,102] hydroindoline **2-74** was accessed in one-pot from Cbz-protected *L*-tyrosine (Scheme 2-9). This fragment possesses the 5-6 system conserved in **2-75** and fortuitously offers synthetic handles that would allow for the elaboration of this privileged structure into the *Stemona* target. Unlike the hydroindoline system in the natural product, **2-74** is oxygenated at C(3a) in a *cis*-ring fusion that would need to be inverted for the synthesis of stenine. Fortunately, the convex nature of **2-74** could be exploited, and 1,2-reduction of the benzoyl-protected enone under Luche conditions proceeded by axial attack to provide chemical access to the α-face of the molecule, presumably via oxygen chelation to set the necessary hydrogen-substituted trans-ring fusion at C(3a). It was hypothesized that reduction of the π-allylpalladium complex had the highest chance of success. Not surprisingly, extensive optimization was needed to selectively reduce the palladium intermediate at the more hindered tertiary carbon. Fortunately the use of catalytic tris(benzylideneacetone)dipalladium(0)

chloroform complex (2 mol%), the crystalline and less oxygen-sensitive tribenzylphosphine (8 mol%), with triethylamine and formic acid in THF at reflux proved to maximize the yield of the desired **2-79**.

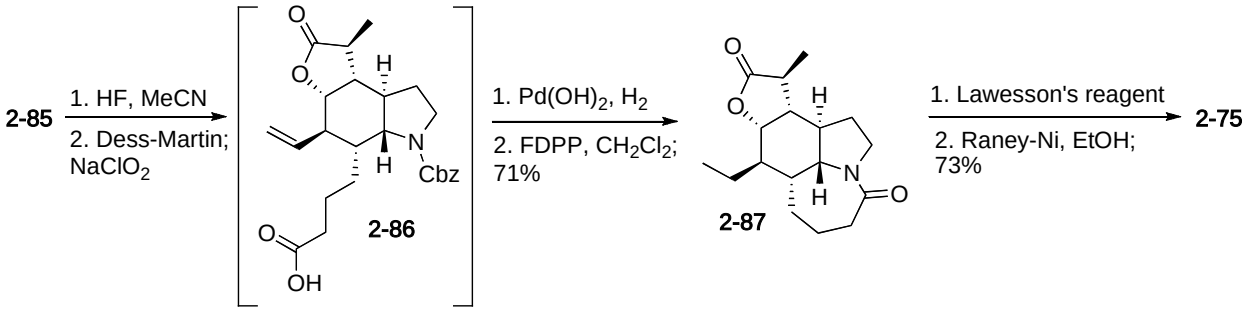


Scheme 2-10. Allylic deoxygenation and C(3a) inversion.

Elaboration of **2-79** through oxidation and alkylation steps provided enone **2-80**. Luche reduction of **2-80** reformed the α-alcohol and allowed for an elegant relay of stereochemistry from C(6) to C(4) via an Eschenmoser-Claisen rearrangement, which had been applied by Hart et al. in their synthesis of (±)-stenine a few years earlier (Scheme 2-11).[100a,100b] Following the radical decarboxylation of the methyl ester and elaboration of the alkyl side chain, iodolactonization of the dimethylamide arising from the Eschenmoser-Claisen rearrangement was successful, with specific care being taken to avoid hydrolysis of the acid-sensitive silyl ether. Keck allylation of the resulting iodide provided the alkyl functionality present in the natural product with retention of stereochemistry, albeit as the propenyl appendage. Following the installation of the methyl group on the γ-lactone that proceeded smoothly using lithium diisopropylamide and methyl iodide in a 23% HMPA/THF mixture to provide a single diastereomer, the carbon-shortened ethenyl moiety (**2-85**) was revealed following oxidation, reduction and Grieco elimination steps.



Scheme 2-11. Eschenmoser-Claisen rearrangment and subsequent iodolactonization and methylation to form the α-methyl-γ-lactone in **2-85**.

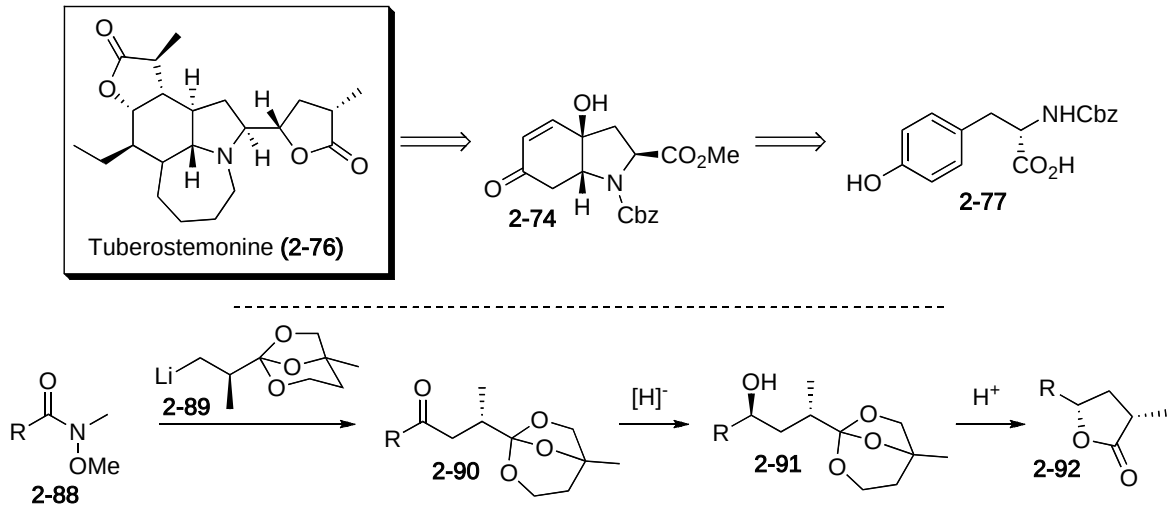


Scheme 2-12. Cyclization and completion of (–)-stenine (**2-75**).

The remaining challenge in the synthesis was the closure of the azepine ring. Initial studies of the endgame strategy where Mitsunobu conditions were used to provide the azepine ring by amine displacement of the activated alcohol were unsuccessful when applied to **2-85**. Thus an amidation approach was used to form the corresponding lactam. Dess-Martin and

sodium chlorite oxidations provided the carboxylic acid that, following tandem Cbz-deprotection and saturation of the ethenyl chain under hydrogenation conditions, was activated with pentafluorophenyl diphenylphosphinate (FDPP)[103] and successfully cyclized to afford lactam **2-87**. Conversion of the amide to the thioamide and desulfurization with Raney nickel provided **2-75** in 73% yield, concluding the first enantioselective synth sesis of (–)-stenine in 25 steps and an overall yield of 2% starting from bicycle **2-74**.

2.1.3.2 Total Synthesis of Tuberostemonine

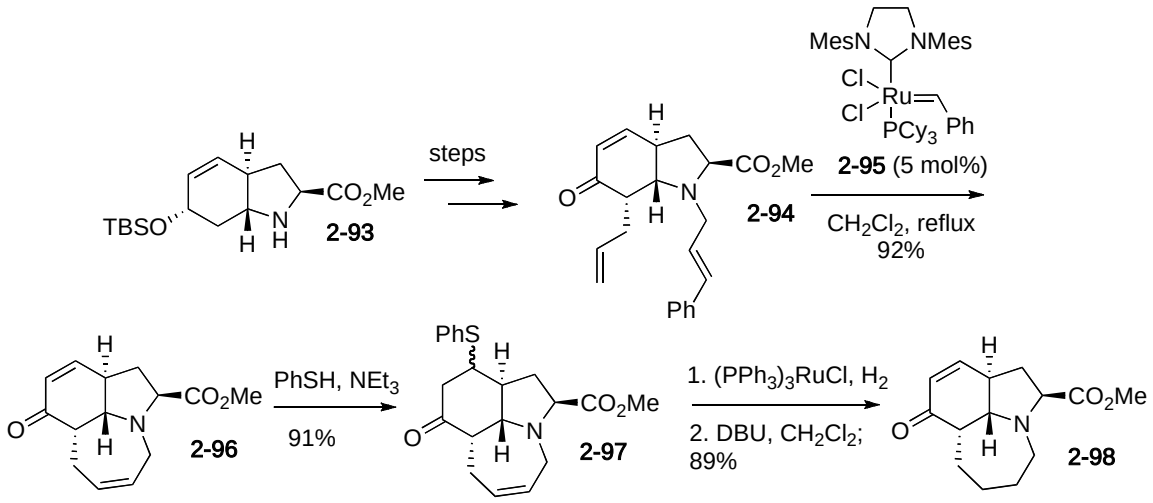


Scheme 2-13. Tuberostemonine retrosynthesis and proposed γ–butyrolactone formation.

Using the stenine synthesis as a template, Wipf and co-workers began the campaign towards tuberostemonine, confident that the chiral ester moiety of bicycle **2-74** would provide a chemical opportunity to elaborate the route. The distinctive γ-butyrolactone moiety in **2-76** remained the key structural feature that was unaddressed in the stenine synthesis, and synthesis of the lactone could be achieved by converting the methyl ester into the Weinreb amide and

performing an addition with lithiated orthoester **2-89**, containing the requisite methyl-bearing stereocenter present in the 5-membered ring. The orthoester could be accessed in a straightforward fashion from the bromide of commercially available methyl-(*S*)-(+)-3-hydroxy-2-methylpropionate (Scheme 2-13). Diastereoselective reduction of the resulting ketone (**2-90**) followed by acid-mediated cyclization between the newly formed alcohol and orthoester would provide the butyrolactone stereospecifically. Several aspects of the stenine synthesis remained laborious and required multiple steps to accomplish "one" chemical transformation; for example the appendage of the ethyl chain and azepine ring formation were targeted for improvement.

In lieu of forming the azepine ring via an amidation-thionation-reduction sequence in the final stages of the synthesis as in the case of stenine, the possibility of using an initial ring-closing metathesis to form the 7-membered ring was pursued (Scheme 2-14). Cyclization of **2-94** was successful, providing **2-96** in 92% yield using Grubbs' 2nd generation metathesis catalyst (**2-95**; however, differentiation of the two resulting olefins in **2-96** using traditionally selective reducing reagents (diimide, borohydride, Wilkinson's catalyst, etc.) was surprisingly unsuccessful. Selective reduction of the azepine ring was finally accomplished by treating the enone with thiophenol to temporarily protect the electrophilic alkene, and reducing the azepine double-bond using Wilkinson's catalyst before treatment with DBU to eliminate thiophenol and reveal the enone.

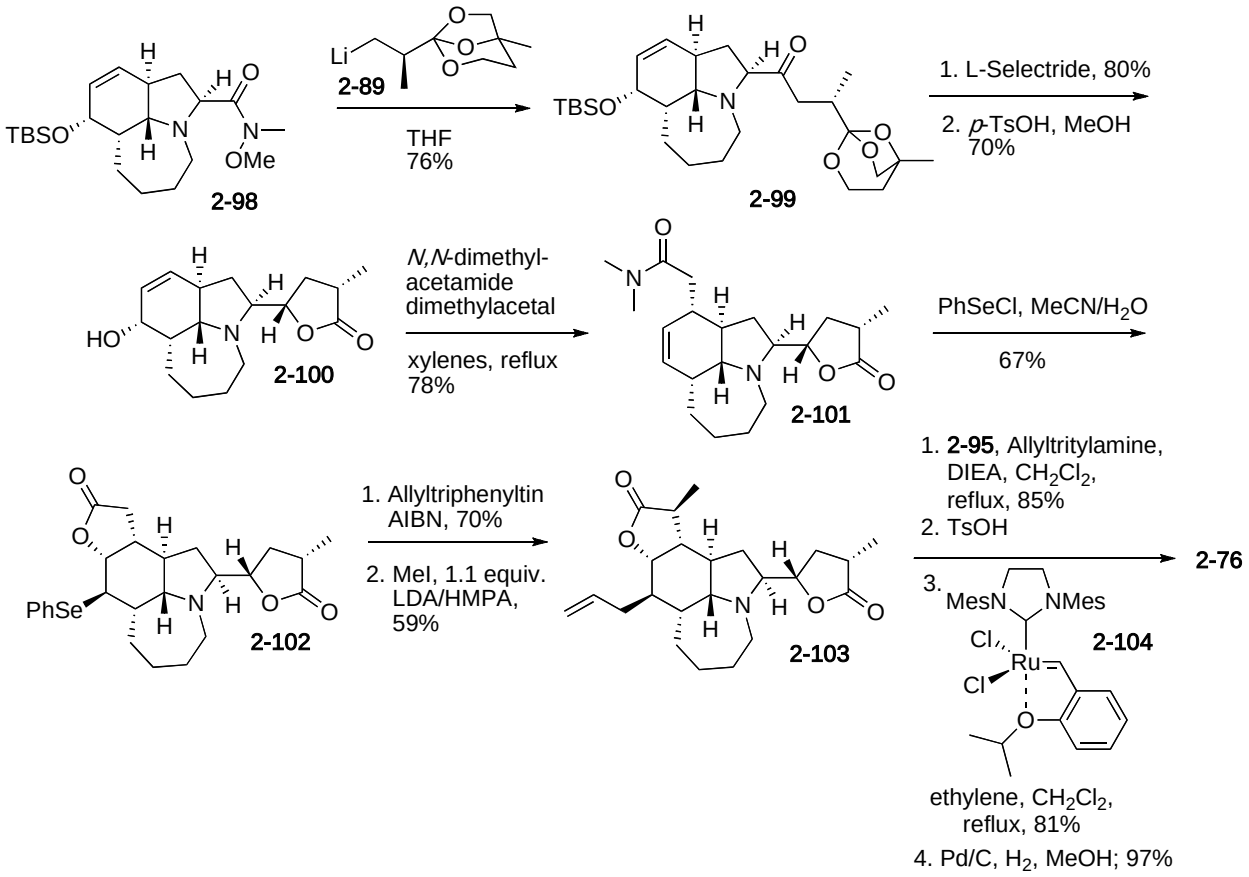


Scheme 2-14. RCM and reduction to form tricycle **2-98**.

Exposure of Weinreb amide **2-99**, accessed from ester **2-98** with *in situ* generated organolithium **2-89**, provided **2-99** in 76% yield. Treatment of the ketone with L-Selectride led to a chelate-controlled reduction to yield a 6-7:1 diastereomeric mixture of alcohols that was subjected to TsOH-mediated orthoester hydrolysis in MeOH to afford the butyrolactone and deprotect the silyl ether in 70%. Gratifyingly, the lactone was tolerant of the elevated temperatures required to initate the [3,3]-rearrangement and **2-101** was isolated, setting the stage for selenolactonization to produce **2-102** in 67% yield.

Following the Keck allylation of selenide **2-102** using AIBN and performing the reaction in neat allyltriphenyltin, it was found that achieving selective alkylation of the core lactone over the eastern γ-butyrolactone was delicate and small changes to the amount of HMPA/LDA complex used in the reaction (i.e. ± 0.1 equivalents) had drastic consequences on the composition of the product mixture. Nonetheless, 59% of the desired material could be isolated using the optimal conditions (1.1 equiv. HMPA/LDA) along with 11% of the dimethylated material and 22% of recovered starting material. Fortunately, *exo*-methyl alkylation resulting in

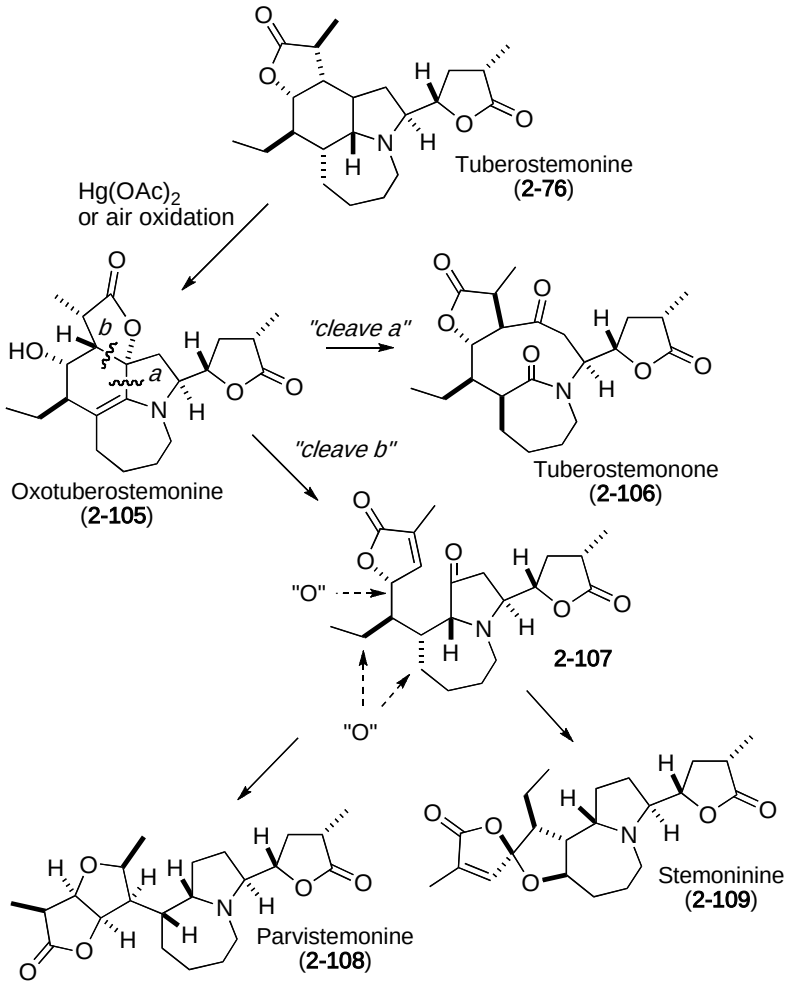
the (*S*)-stereocenter was confirmed by NOESY and ^{1}H coupling constant analysis. Ruthenium-mediated isomerization using Grubbs' 2nd generation catalyst and cross-metathesis using Hoveyda-Grubbs catalyst (**2-104**) proceeded well, and final hydrogenation with catyalytic palladium on carbon afforded **2-76** in 97%, thus concluding the first enantioselective synthesis of tuberostemonine in 27 steps and ca. 1% overall yield from Cbz-L-tyrosine.



Scheme 2-15. Completion of tuberostemonine (**2-76**).

2.1.3.3 Hypothetical Biosynthetic Relationship of the Tuberosteminone Family

Given the structural similarities between many *Stemona* alkaloids, it is not surprising that biosynthetic relationships between the members of several families have been proposed.[104] Wipf and Li hypothesized on the origins of the tuberostemonine family,[105] citing that upon air- or Hg(II)-oxidation of tuberostemonine, oxotuberostemonine (**2-105**) can be isolated (Scheme 2-16).[106] Additional hypothetical but straightforward *C,C*-bond fragmentation reactions provide access to tuberostemonone as well as key intermediate **2-107**. Strategic oxidations of **2-107** followed by intramolecular condensation reactions result in the formation of stemoninine and parvistemonine. In practice, if selective cleavage of the hydroindoline group resulting from the oxidative cyclization of tyrosine could be realized as outlined in Figure 2-2, this concept could prove fruitful for the total syntheses of this family of alkaloids and provide strong support for the existence of common biosynthetic intermediates for many *Stemona* alkaloids.



Scheme 2-16. Proposed biosynthetic origins of *Stemona* alkaloids by Wipf.

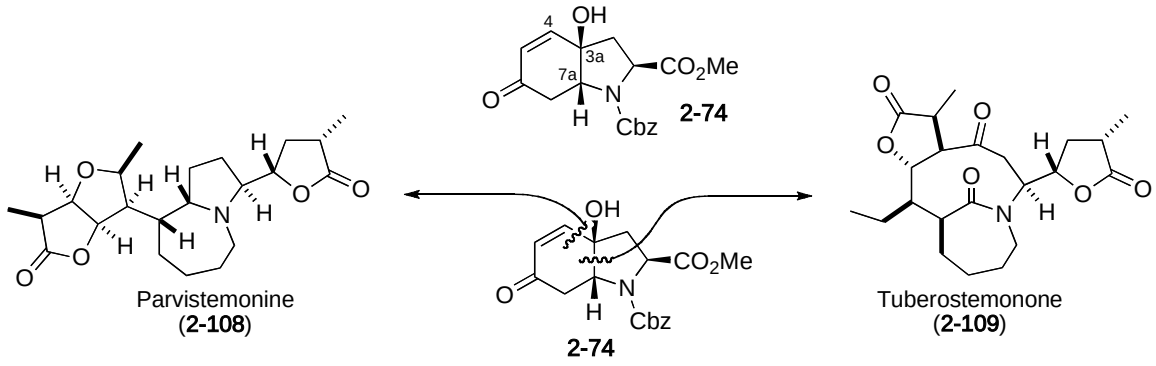
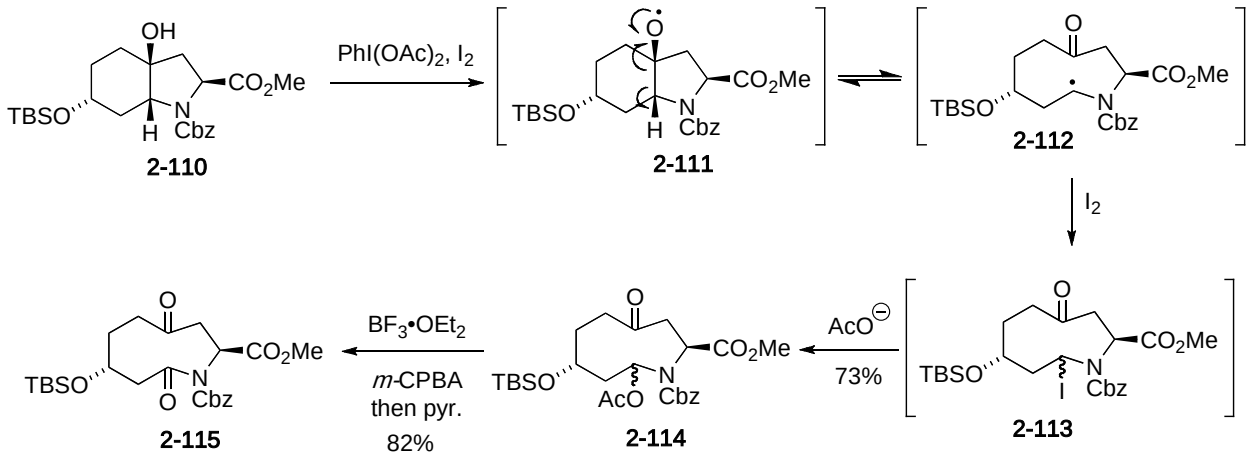


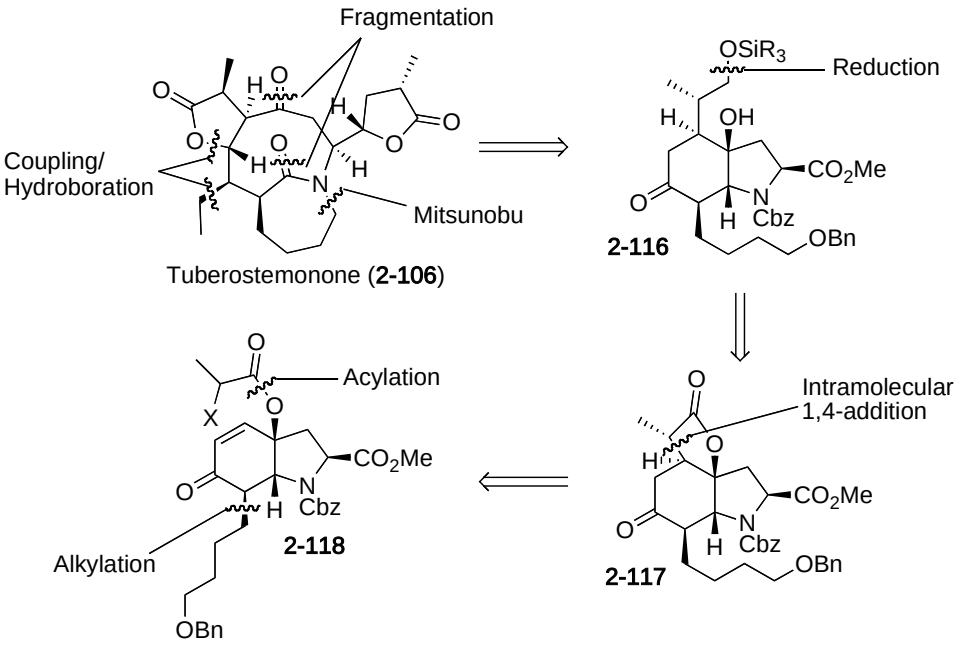
Figure 2-2. Differential fragmentation concept of hydroindoline **2-74** leading to *Stemona* alkaloids.

2.1.3.4 Hydroindoline Fragmentation Approach to Tuberostemonone

To test their hypothesis, Wipf and Li investigated the alkoxy radical fragmentations of hydroindoline model systems targeting the 9-membered lactam ring of tuberostemonone (**2-106**).[105] By using the Suárez reagent ($PhI(OAc)_2$, I_2),[107] hydroindoline **2-110** was converted into aminal **2-114** in 73% yield following trapping of the proposed α-*aza*-radical intermediate (**2-112**) and displacement with acetate (Scheme 2-17). Conversion of the acetate to furnish the requisite keto-lactam in **2-115** was achieved by oxidation of the *in situ*-generated iminium ion by *m*-CPBA and pyridine.[108] The successful and modest-yielding selective hydroindoline fragmentation and subsequent conversion to the 9-membered keto-lactam provided validation for the initial synthetic hypothesis and warranted application towards the total synthesis of tuberostemonone.



Scheme 2-17. Model system for the radical fragmentation of hydroindolines to the 9-membered lactam.

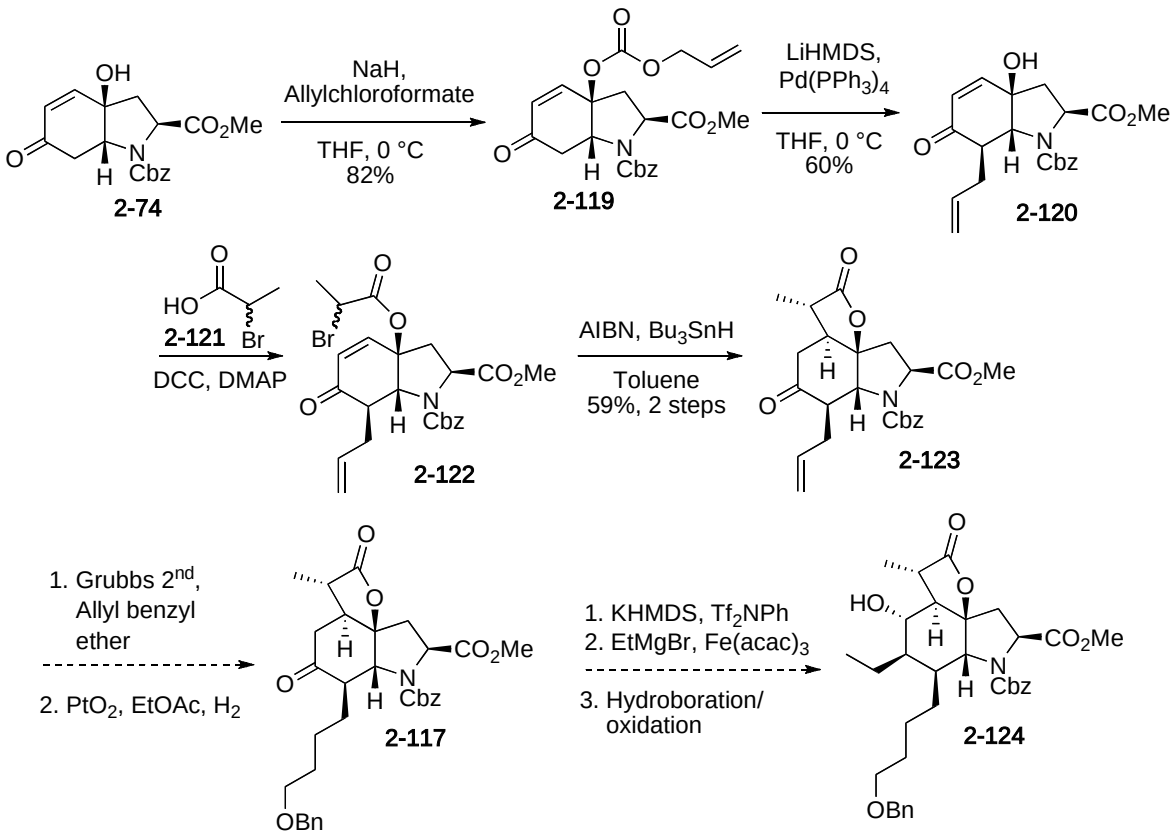


Scheme 2-18. Retrosynthetic analysis of tuberostemonone (**2-106**).

Retrosynthetically, tuberostemonone was simplified to indoline **2-116**, identified to be a key precursor to the featured fragmentation reaction. Using the C(3a)-hydroxyl unit as a key stereochemical directing element, an intramolecular 1,4-conjugate addition was proposed to form lactone **2-117**. This polycycle could be accessed following enolate alkylation and acylation of the hydroindoline arising from the oxidative cyclization of tyrosine.

Wipf and Pierce tested a wide range of substrates for the efficient and selective alkylation of **2-74** and found that the two-step palladium-catalyzed allylic alkylation worked best (Scheme 2-19).[109] Coupling of 2-bromopropionic acid using DCC provided **2-122**, which smoothly participated in a 1,4-addition under radical conditions to afford advanced intermediate **2-123**. To complete the requisite functionalization for the completion of the synthesis, appendage of the side-chain protected as the benzyl ether can be accomplished using cross-metathesis, and enol

triflate formation and coupling will provide the ethyl alkene, on which hydroboration and oxidation can be used to install the final hydroxyl group.

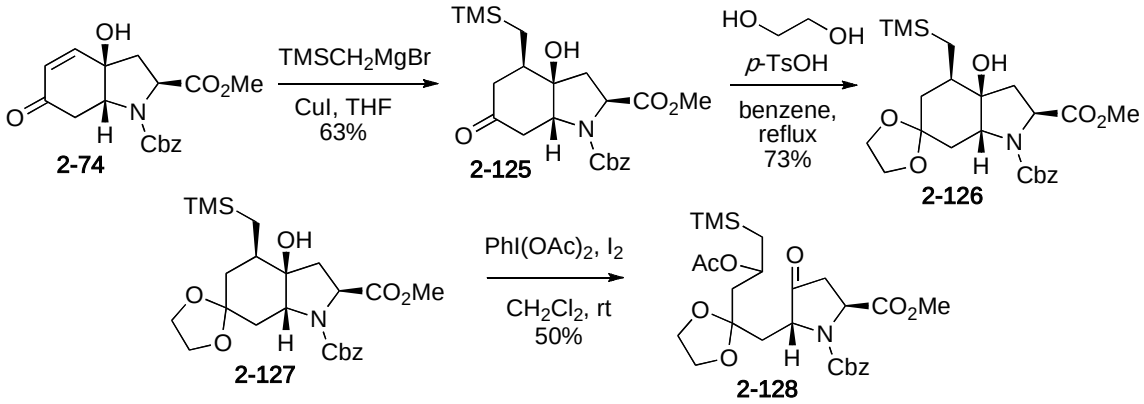


Scheme 2-19. Wipf and Pierce's approach towards tuberostemonone.

2.1.3.5 Hydroindoline Fragmentation Approach to Parvistemonine

Consistent with the hypothesized biosynthetic origins of the *Stemona* alkaloids (Scheme 2-16), the Wipf group investigated the selective fragmentation of the C(3a)-C(4) bond in **2-74** for the synthesis of parvistemonine as outlined in Figure 2-2. After considerable and unfortunately unsuccessful investigation into many model systems for the fragmentation of an azido radical species,[110] Wipf and Joo attempted to exploit the β-stabilizing effect of silicon to promote a more

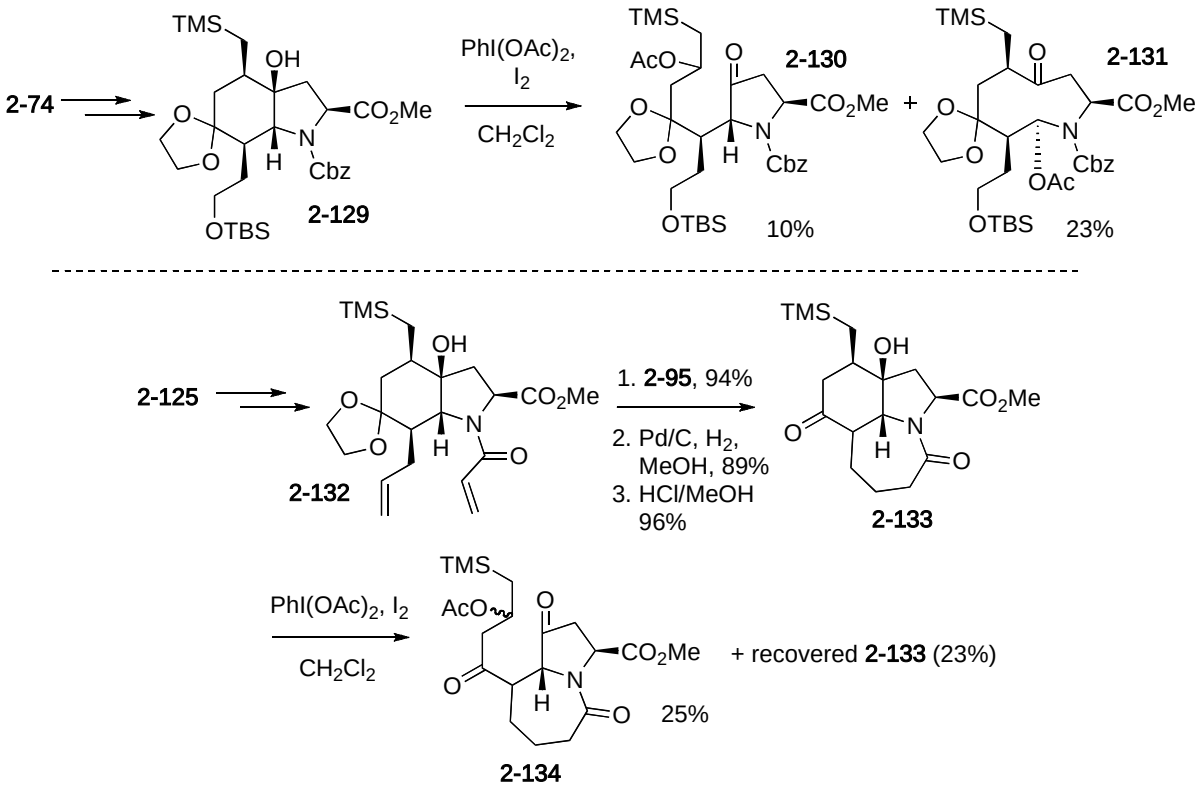
efficient fragmentation process. In fact, the Posner group had earlier reported the successful application of the β-silicon effect in related radical ring expansions of conjugated cycloalkenones into homoallylic lactones.[111] The requisite model system was synthesized starting from indoline **2-74** via a conjugate addition of the TMS-methylene side chain (Scheme 2-20). Protection of the ketone as the acetal and exposure to the Suárez reagent afforded the desired fragmentation product, trapped as the acetate in 50% yield.



Scheme 2-20. Radical fragmentation on unstubstituted model system.

Pleased with the vast improvement in selectivity and efficiency using silicon to stabilize the radical, the requisite side chain for the subsequent azepine formation was appended to the fragmentation precursor via enolate alkylation and functional group manipulations (Scheme 2-21). Quite interestingly, the internally fragmented product (**2-131**) was isolated as the major product in 23% with only 10% of the desired ketone **2-130** produced. Clearly, incorporation of the side-chain had a dramatic effect on the success and selectivity of the fragmentation event, possibly due to conformational effects and differences in orbital overlap of the reacting bonds. As a last resort, the azepine ring was closed by RCM of **2-132** prior to fragmentation. Once again, exposure of **2-132** to the Suárez reagent led to a mixtures of products, with optimized

conditions providing a 25% yield of the desired bicycle along with 23% of unreacted starting material. Likely, the instability of the C(4) ketone of **2-134** plays a major role in the limited success of this process and thus hampers efforts to synthesize parvistemonine via this fragmentation route. However, it should be noted that the fragmentation is possible, and therefore the hypothesized differential fragmentation of oxotuberostemonine (**2-105**) to afford tuberostemonone and parvistemonine in a biosynthetic context cannot be discounted.



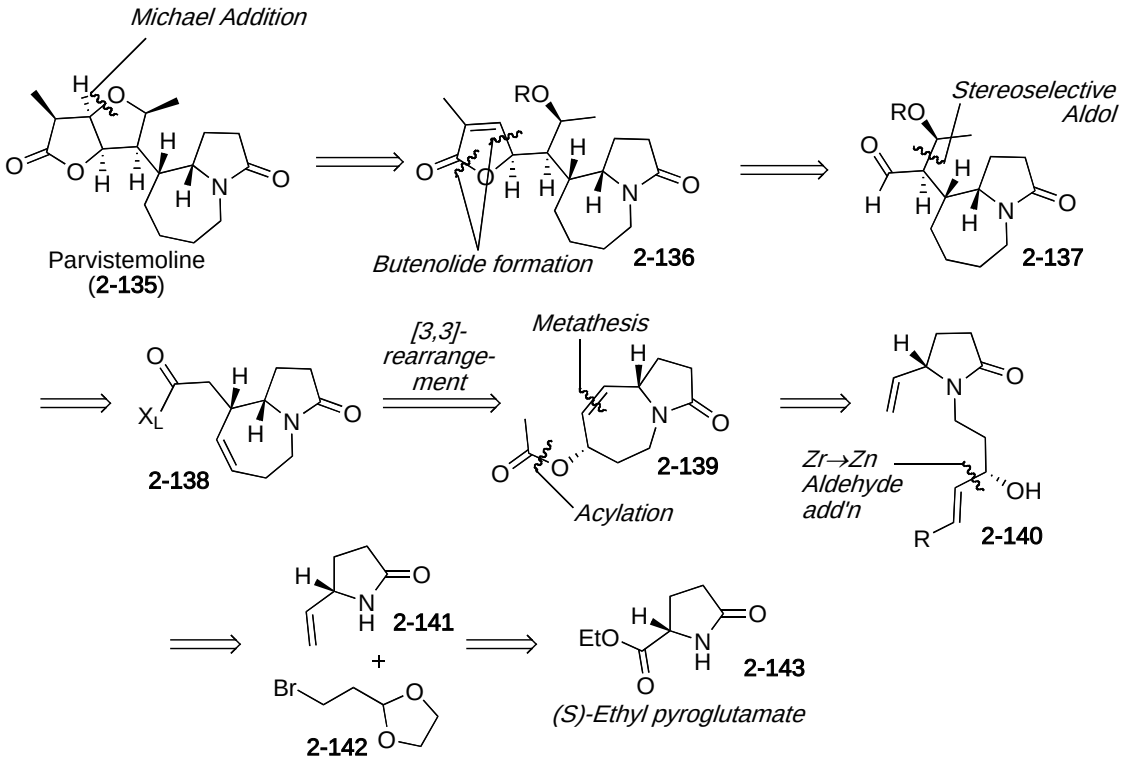
Scheme 2-21. Fragmentation reactions of substituted hydroindolines.

2.2 RESULTS AND DISCUSSION

2.2.1 Retrosynthetic Analysis of Parvistemoline

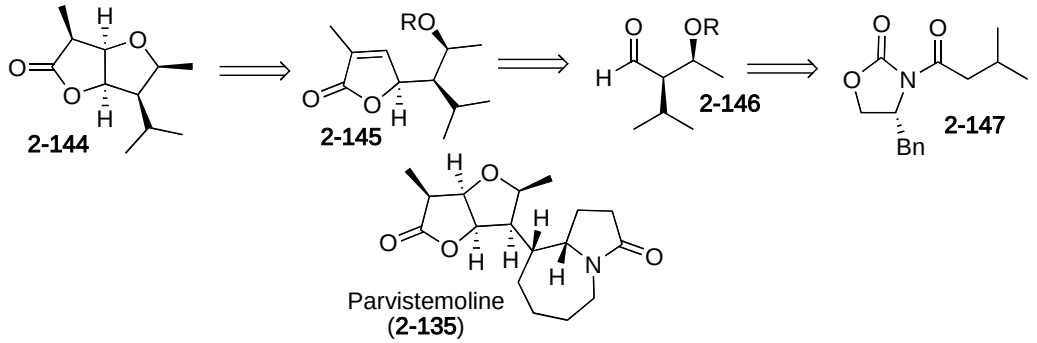
Having experienced mild but ultimately insufficient success in affecting the selective radical fragmentation of indolines for the synthesis of the parvistemonone ring system, our attention turned to the related alkaloid parvistemoline (**2-135**) and the synthesis of the intriguing 5,5-tetrahydrofuranolactone moiety characteristic of this *Stemona* sub-family.

Retrosynthetically, we envisioned forming this unprecedented ring system by performing a Michael addition of the furan oxygen into the corresponding butenolide and protonation to set the requisite stereocenters (Scheme 2-22). The butenolide unit could be accessed via a known method from aldehyde **2-137**,[112] which would be revealed following a stereoselective aldol addition of acetaldehyde to generate the furan precursor fragment in **2-136**. To set the adjacent stereocenters on the azepine ring we imagined using a [3,3]-sigmatropic rearrangement to relay stereochemical information on the α-face of the molecule, in a novel approach to the 5,7-pyrrolo[1,2-*a*]azepine of the *Stemona* alkaloids that is reminiscent of the Eschenmoser-Claisen rearrangement in the stenine and tuberostemonine syntheses from our lab. The [3,3]-rearrangment precursor could be formed by RCM of the azepine ring, and the key stereocenter can be set by application of our group's methodology for the hydrozirconation of alkynes, transmetallation to zinc and chiral ligand-directed addition to aldehydes.[40] The requisite diene could be synthesized in a straightforward fashion from the alkylation of known pyrrolidone **2-141** with commercially available bromoethyl dioxolane (**2-142**), accessible from ethyl pyroglutamate.



Scheme 2-22. Initial retrosynthetic analysis of parvistemoline (**2-135**).

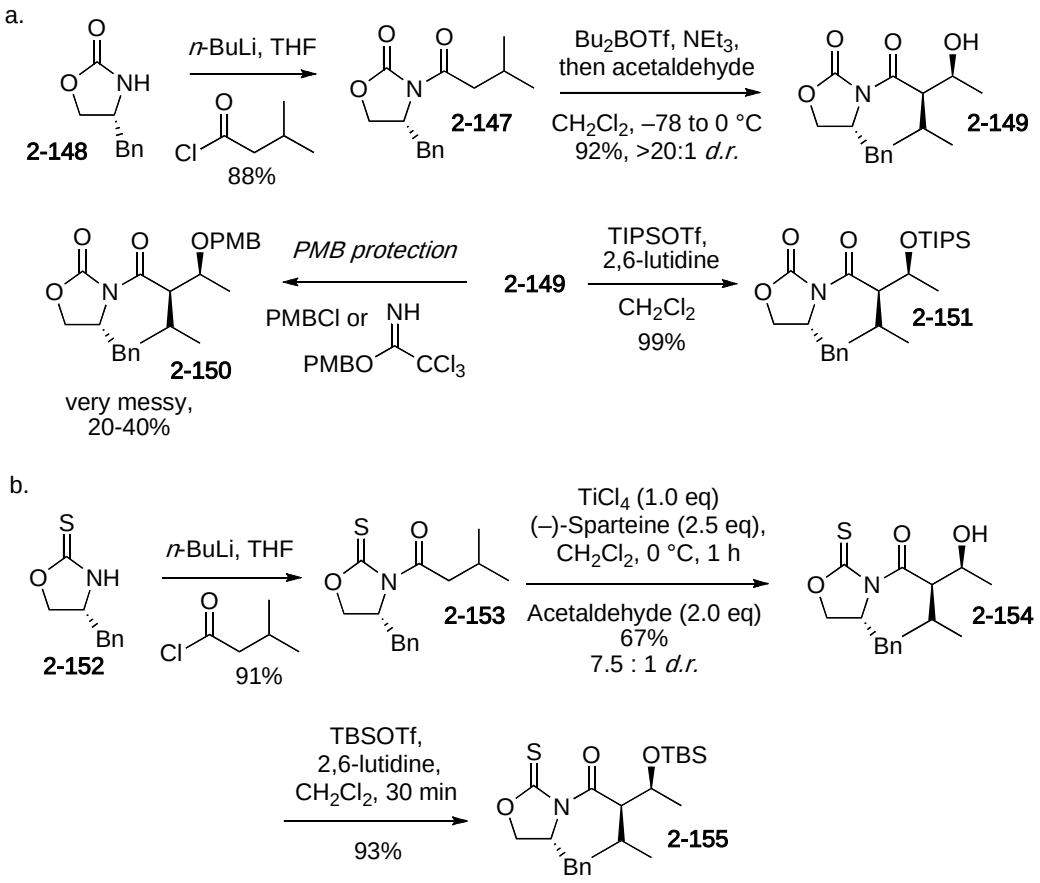
Prior to embarking on the synthesis we decided to study the formation of the furanolactone ring by our proposed endgame Michael addition sequence. Therefore, we first looked to complete the heterocycle on model system **2-144** using an isopropyl group to mimic the azepine ring junction (Scheme 2-23). Butenolide **2-145** could be synthesized from aldehyde **2-146** which we envisioned arising from an auxiliary-controlled *syn*-aldol addition with **2-147**.



Scheme 2-23. Retrosynthesis of model system **2-144**.

2.2.2 Model System Study

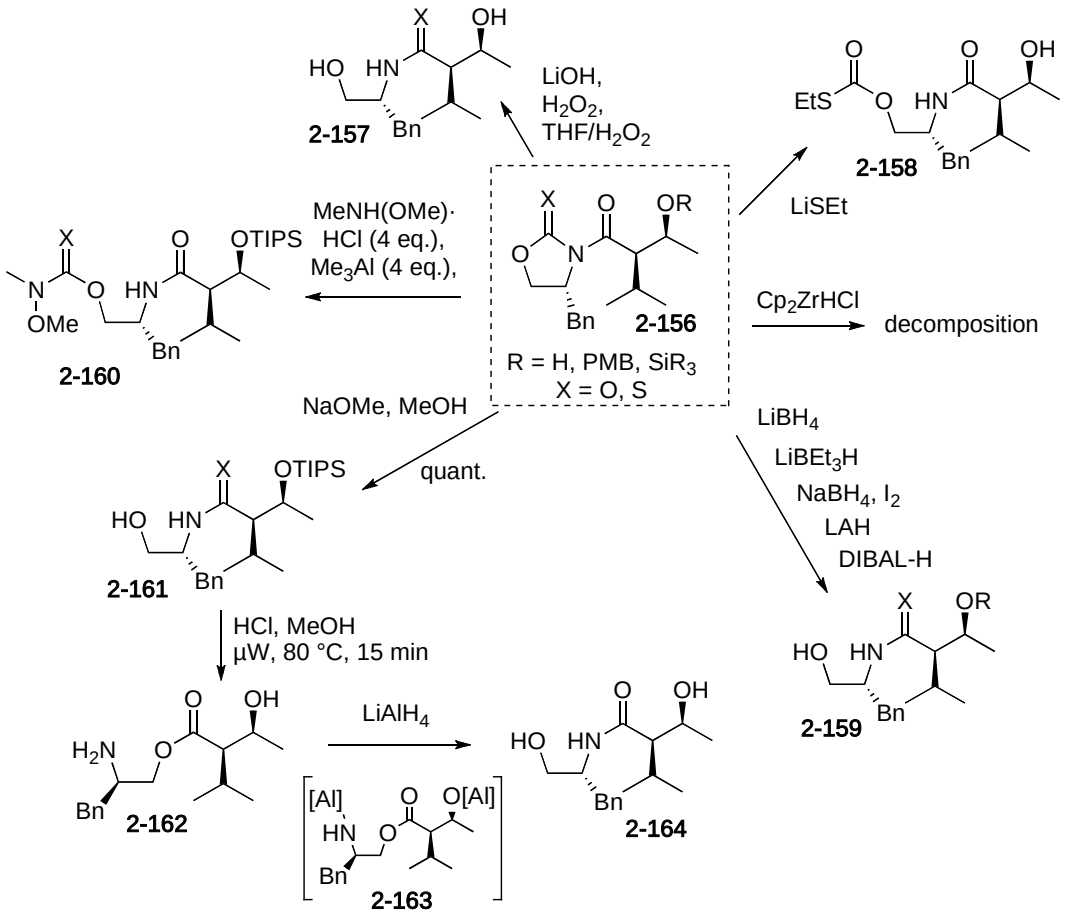
Acylation of Evans' auxiliary with isovaleryl chloride proceeded in good yield and the aldol addition under Bu_2BOTf conditions with freshly distilled acetaldehyde provided **2-147** in high yield and excellent diastereoselectivity (Scheme 2-24). The newly generated hydroxyl group was subsequently protected as the TIPS and PMB ethers. At the same time, the oxazolidinethione, known for its increased chelation and lability during deprotection,[113] was also used in the aldol sequence to afford **2-154**, albeit in lower yield diastereoselectivity under the titanium conditions. TBS protection of the aldol product afforded silyl ether **2-155** in 93% yield.



Scheme 2-24. Diastereoselective aldol additions using a. oxazolidinone and b. oxazolidinethione auxiliaries and protection of the resulting alcohols.

With the variety of aldol adducts in hand we attempted to remove the chiral auxiliary; however, we were not successful despite exploring a wide range of conditions (Scheme 2-25). In practice we found that reagents preferred to react with the carbonyl/thiocarbonyl function of the hererocyclic ring to provide ring-opened products exclusively. Opening of the oxazolidinone ring with sodium methoxide in methanol cleanly provided **2-161**, which we imagined could perform a transesterification under acidic conditions. In fact, heating the primary alcohol in acidic methanol in the microwave initiated the rearrangment (presumably driven by protonation of the more basic nitrogen atom). To our surprise, attempts to reduce ester **2-162** using LAH failed, which we

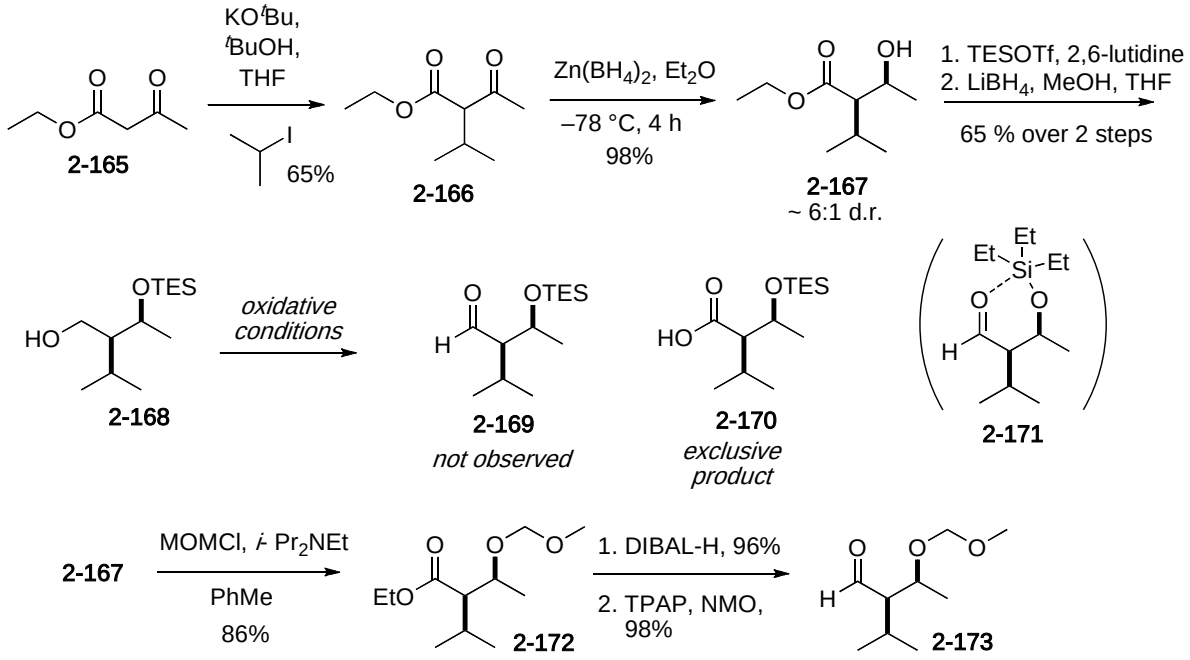
attributed to formation of the aluminum amide and metal-assisted transamidation prior to ester reduction.



Scheme 2-25. Difficulty removing the oxazolidinone/oxazolidinethione auxiliary.

With the removal of the auxiliary proving to be problematic, we abandoned the enantioselective approach to **2-144** and focused on forming the correct bond connectivity in a racemic fashion. In a straightforward manner, ethyl acetoacetate was alkylated with isopropyl iodide in 65% yield to afford **2-166**. Chelated reduction using freshly prepared $Zn(BH_4)_2$ afforded a 6:1 mixture of *syn*:*anti* products. Protection of the newly formed alcohol as the TES ether and reduction gave **2-168**. Surprisingly, when the alcohol was exposed to mild oxidative

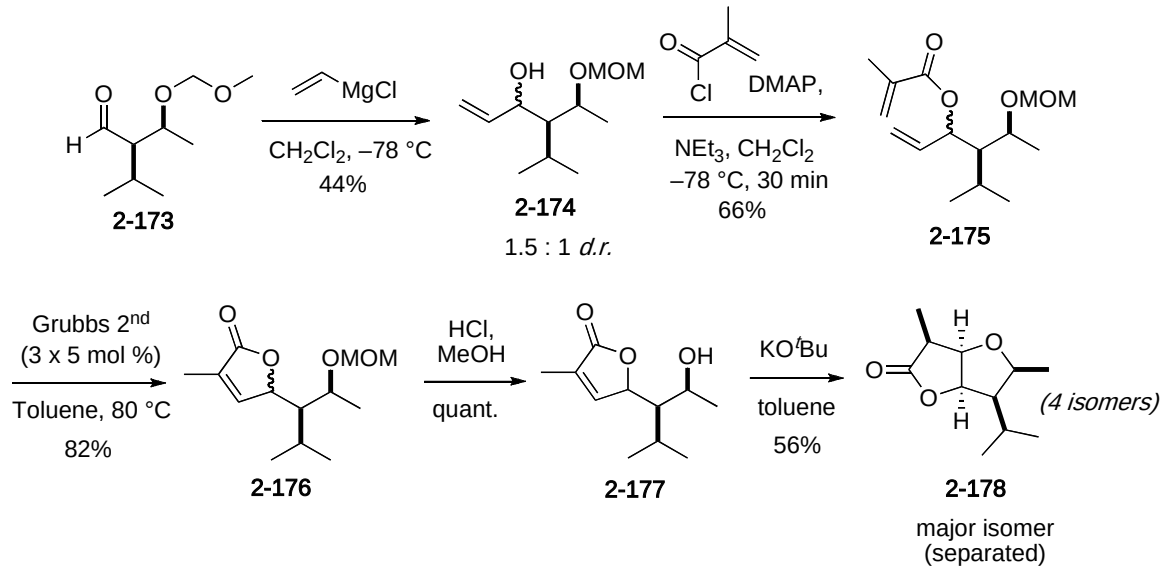
conditions (Swern, TPAP/NMO, Parikh-Doering) the carboxylic acid was the only product observed by ^{1}H NMR and IR spectroscopy. We rationalized this overoxidation by the activation of the generated aldehyde by the neighboring, mildly coordinative TES group (**2-171**) to facilitate further oxidation from the +2 oxidation state to the +3 state of the carboxylate. Revising the protective group strategy to the MOM ether (**2-172**) allowed for the successful formation of aldehyde **2-173** under previously unsuccessful conditions.



Scheme 2-26. Synthesis of aldehyde **2-173** of the racemic model system.

Vinyl Grignard addition to **2-173** proved to be rather unselective, providing a mixture of allylic alcohols that were acylated using methacryloyl chloride to afford **2-175**. RCM by periodic addition of Grubbs 2nd generation catalyst formed the butenolide ring in **2-176** in 82% yield. Smooth MOM deprotection was followed by a base-induced Michael addition of **2-177** to afford

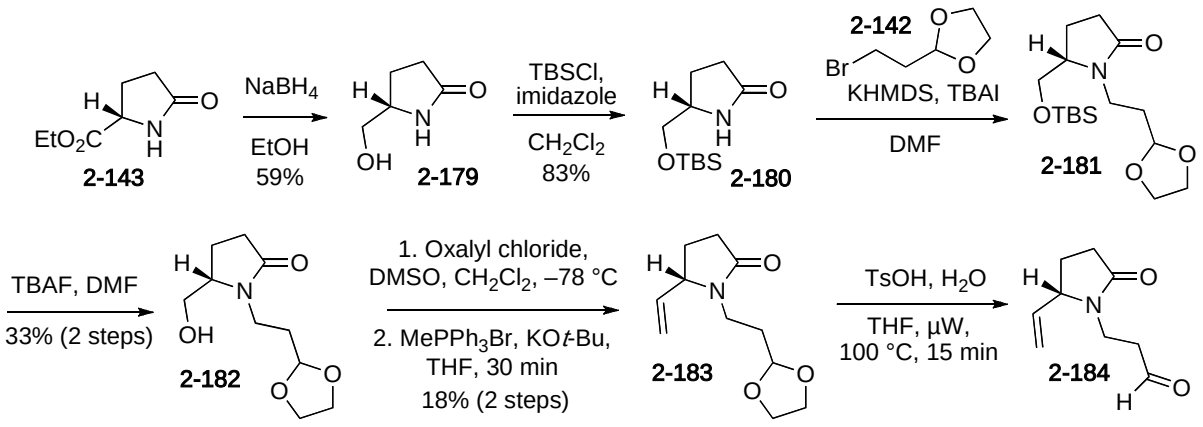
a mixture of cyclized diastereomers. Gratifyingly, the major isomer (**2-178**, assigned by ^{1}H NMR coupling constant analysis) could be separated by MPLC purification.



Scheme 2-27. Completion of the racemic model system by RCM and Michael addition.

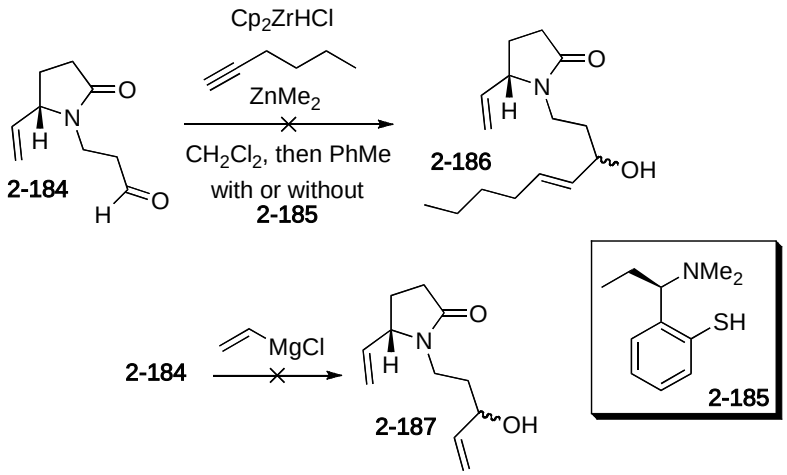
2.2.3 Synthesis of the 5,7-Pyrrolo[1,2-*a*]azepine Core

Confident that our endgame strategy had a reasonable chance of success, we began the synthesis of parvistemoline from (*S*)-ethyl pyroglutamate (**2-143**, Scheme 2-28). Reduction to the alcohol followed by protection as the TBS-ether set the stage for alkylation with **2-142** and deprotection to unmask the primary alcohol in **2-182**. Oxidation to the aldehyde followed by Wittig olefination gave the precursor to the aliphatic aldehyde, which was revealed by *p*-TsOH in THF/H_2O under microwave heating. The low yields in this sequence reflect a surprisingly high water solubility of the intermediates and associated difficulties in purification.



Scheme 2-28. Synthesis of aldehyde **2-184** from ethyl pyroglutamate.

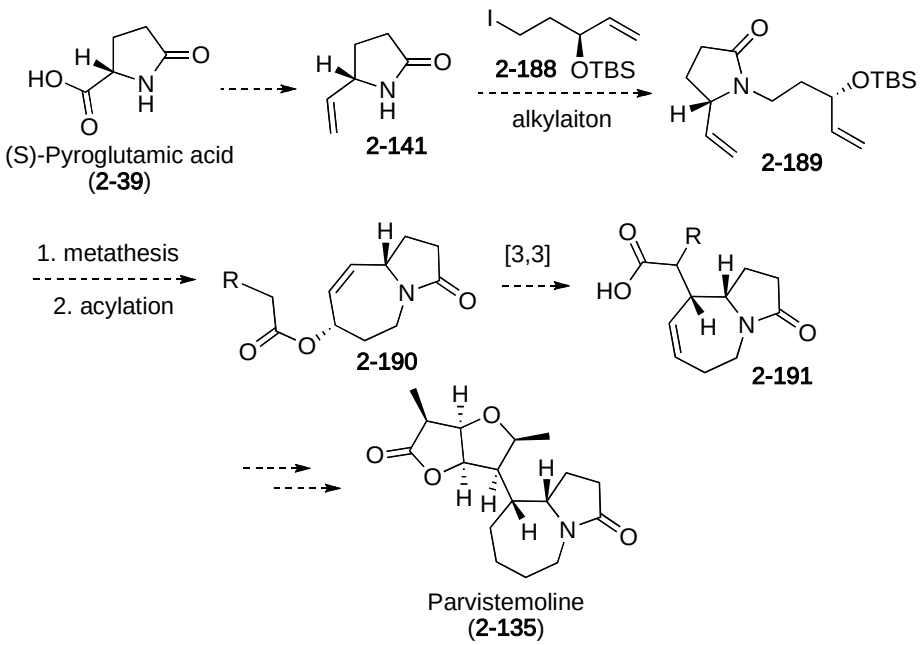
In 1998, Wipf and Ribe reported the successful use of amino-thiol ligand **2-185** in affecting asymmetric additions of vinylzinc reagents, generated from the corresponding vinylzirconocenes via transmetallation, to aliphatic and aromatic aldehydes.[40] Having synthesized aldehyde **2-184** we sought to apply the same conditions to our system; however upon multiple attempts both in the presence and absence of ligand no addition product was observed. It is possible that *in situ* oligomerization of the aldehyde unit or intramolecular cyclization of the amide into the aldehyde could account for the observed behavior. While we have no empirical data to support such a claim, **2-184** was similarly unreactive towards the addition of vinylmagnesium chloride indicating the nucleophile in the former reaction was not solely responsible for the lack of conversion.



Scheme 2-29. Addition attempts to aldehyde **2-184**.

Upon failing to achieve the desired aldehyde addition, we revised our approach in favor of a convergent route that would incorporate the C(7) stereocenter as a pre-set fixture in one of the fragments. As shown in Scheme 2-30, our revised plan involved the alkylation of vinyl pyrrolidone with iodide **2-188** containing the chiral allylic alcohol. RCM and acylation would provide our [3,3]-rearrangment precursor as we had planned before, however, due to the difficulty of affecting a stereoselective aldol addition on our model system, we decided to investigate whether incorporating substitution in the [3,3]-reaction to form **2-191** from **2-190** would be feasible.

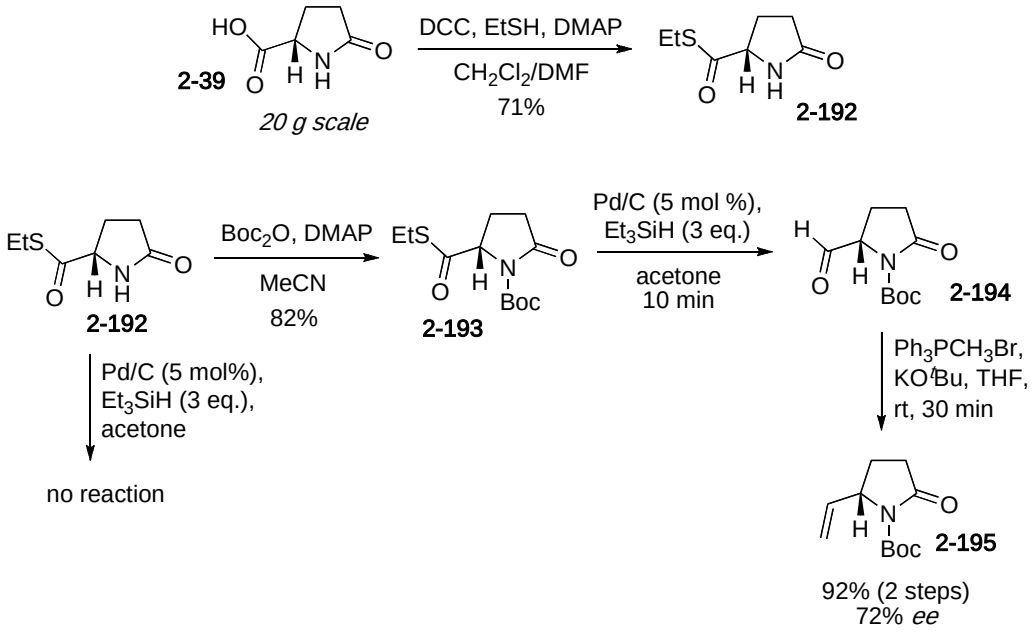
2.2.4 Second-Generation Route to the Pyrroloazepine Core



Scheme 2-30. Revised, convergent approach to parvistemoline.

Discouraged by the inefficiency and low yields of our initial route to pyrrolidone **2-141**, we decided to pursue an alternate strategy. Known methods of constructing **2-141** involve laborious purifications, redox processes, or low-yielding eliminations.[114] We believed we could take advantage of the known reduction of the thioamide group under palladium catalysis to the aldehyde, the Fukuyama reduction,[115] which would allow for a Wittig olefination to install the requisite alkene. Along these lines, the carbodiimide-mediated coupling of (*S*)-pyroglutamic acid and ethanethiol proceeded on large scale to afford the corresponding thioester in 71% yield following purification (Scheme 2-31). Quite surprisingly given the well-documented substrate tolerance of the Fukuyama conditions, thioamide **2-192** did not react in the presence of catalytic palladium and triethylsilane. It was found that protection of the amide was necessary to affect the desired reduction, which, once it did proceed, was complete in under 10 minutes. Isolation of the

crude aldehyde (**2-193**) and immediate exposure to Wittig conditions to minimize racemization of the aminoaldehyde provided the target compound in 91% yield over the two-step sequence. The *N*-Boc group initially installed for the Fukuyama reduction was in fact necessary for the preservation of the vinyl pyrrolidone product which, when unprotected, decomposed in a matter of hours. With the carbamate in place, **2-195** was benchtop stable for months with no noticeable decomposition by ^{1}H NMR analysis. Overall, this sequence provided our desired vinyl pyrrolidone in 4 steps (3 purifications) on multigram (>10 g) scale and was a considerable improvement over known literature methods.



Scheme 2-31. Improved route to pyrrolidone **2-195** featuring a Fukuyama reduction/Wittig olefination sequence.

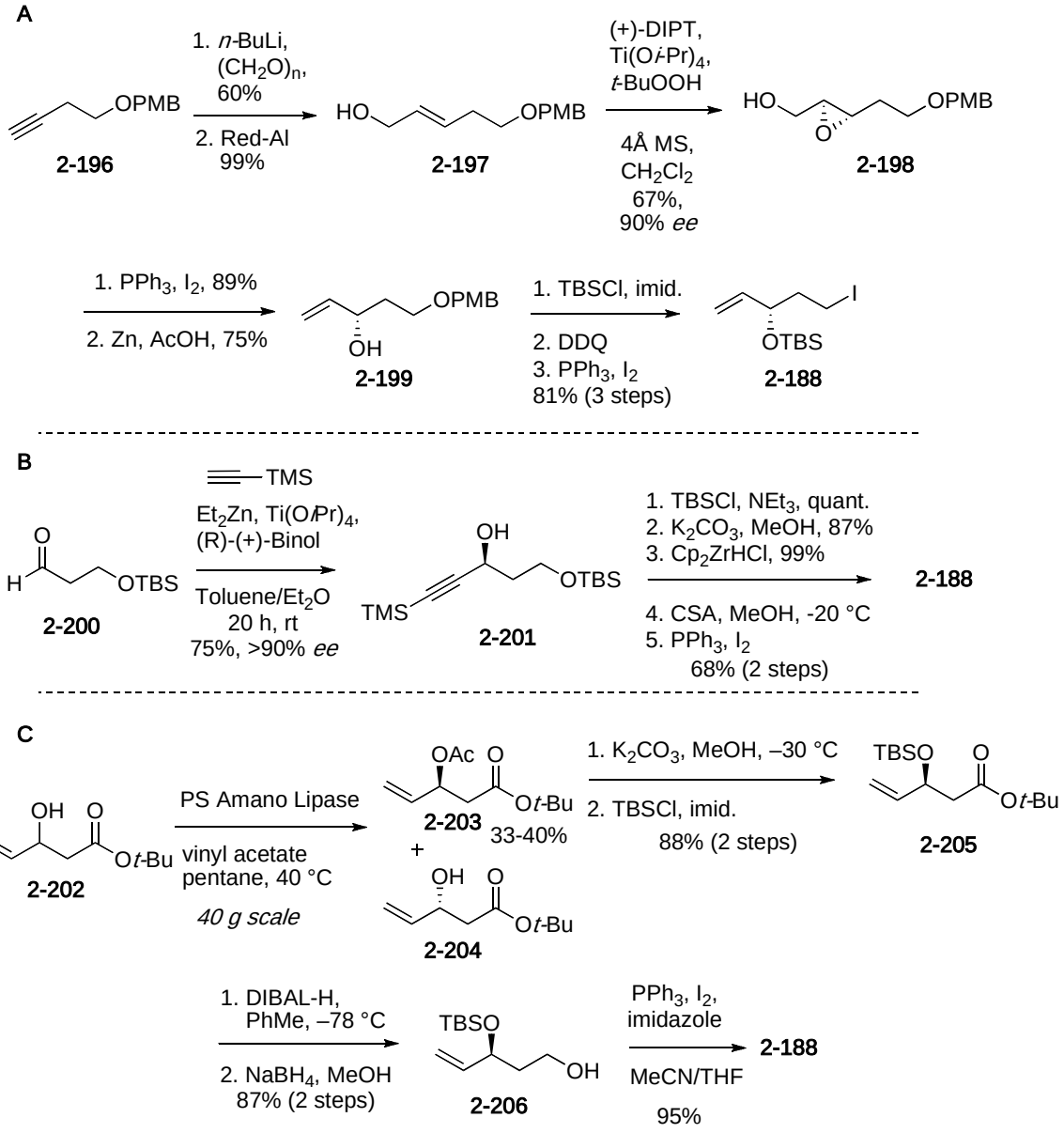
Next, we had the task of preparing the known iodide **2-188**. Following a literature protocol, PMB-protected 3-butyn-1-ol was homologated using paraformaldehyde, followed by conversion to the *trans*-olefin using Red-Al (Scheme 2-32, route A). Sharpless asymmetric epoxidation of **2-197** provided the allylic epoxide that was converted to the primary iodide for

epoxide opening and formation of chiral allylic alcohol **2-199** under zinc conditions. Protection of the newly formed alcohol as the TBS-ether and removal of the PMB group allowed for primary iodide formation to complete **2-188**. While the desired material was accessible, the route was step intensive (8 steps from commercial materials) which hindered material throughput. Unfortunately the asymmetric epoxidation step proved to be particularly sensitive to reaction conditions, reagent quality and scale, making it a poor choice for introducing the chiral element into our substrate. Ultimately, we opted for a shorter route that would provide optically pure material in a more direct sequence.

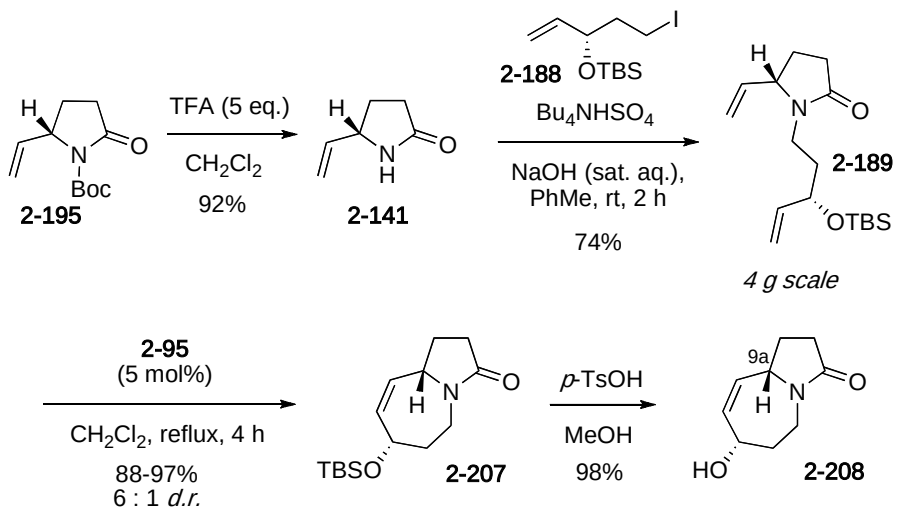
In 2002, Pu and co-workers reported the Ti-BINOL-mediated addition of alkynylzinc reagents to aldehydes.[116] The Wipf group applied these addition conditions to the synthesis of disorazole C1 using TMS-acetylene and aldehyde **2-200** in 2004.[117] Following the 2004 protocol, aldehyde **2-200**, obtained on large scale in 2 steps from commercial materials, was subjected to the addition conditions to afford propargyl alcohol **2-201** in 75% yield and good enantioselectivity by comparison of optical rotation data (Scheme 2-32, route B). Removal of the TMS group and reduction to the alkene using Schwartz reagent furnished the allylic alcohol moiety. TBS protection and selective cleavage of the primary silyl ether using acidic methanol at low temperature followed by iodination successfully provided **2-188**. While route B proved to be shorter than the epoxidation route, it suffered from the need to use neat diethylzinc in the enantioselectivity-defining step, which limited the scalability for obvious safety concerns.

Finally, we decided to pursue a chiral resolution route to access the allylic alcohol following a route developed by De Risi, Polliini and co-workers in for their studies on the Geissman-Waiss lactone[118] and later applied by Ghosh and co-workers in their synthesis of largazole.[119] Alcohol **2-202**, prepared in one-step from *tert*-butyl acetate,[120] could be selectively

acylated by PS Amano lipase in the presence of vinyl acetate in refluxing pentane. The resulting products could be separated and the desired enantiomer (**2-203**) was hydrolyzed and re-protected as the TBS-ether (**2-205**). Direct reduction of the *tert*-butyl ester to the alcohol using 3 equivalents of DIBAL-H or other metal hydride reagents led to the formation of unidentifiable side products and a decreased yield of the isolated product. We found the best strategy was to reduce **2-205** to the aldehyde using DIBAL-H (no side products detected) and treat the crude aldehyde with sodium borohydride in methanol. In a similar manner to the previous two routes, iodination of the alcohol provided our desired material on multigram scale. The chiral resolution route proved to be superior for our purposes given the scalability of the enzymatic resolution (perfomed on ~40g scale without complication) and the ability to recycle batches of enzyme in successive reactions. A large amount of chiral material could be produced in a facile process at the beginning of the synthetic sequence, thus minimizing resources bringing racemic material forward to the resolution step.



Scheme 2-32. Routes used to synthesize iodide **2-188**.

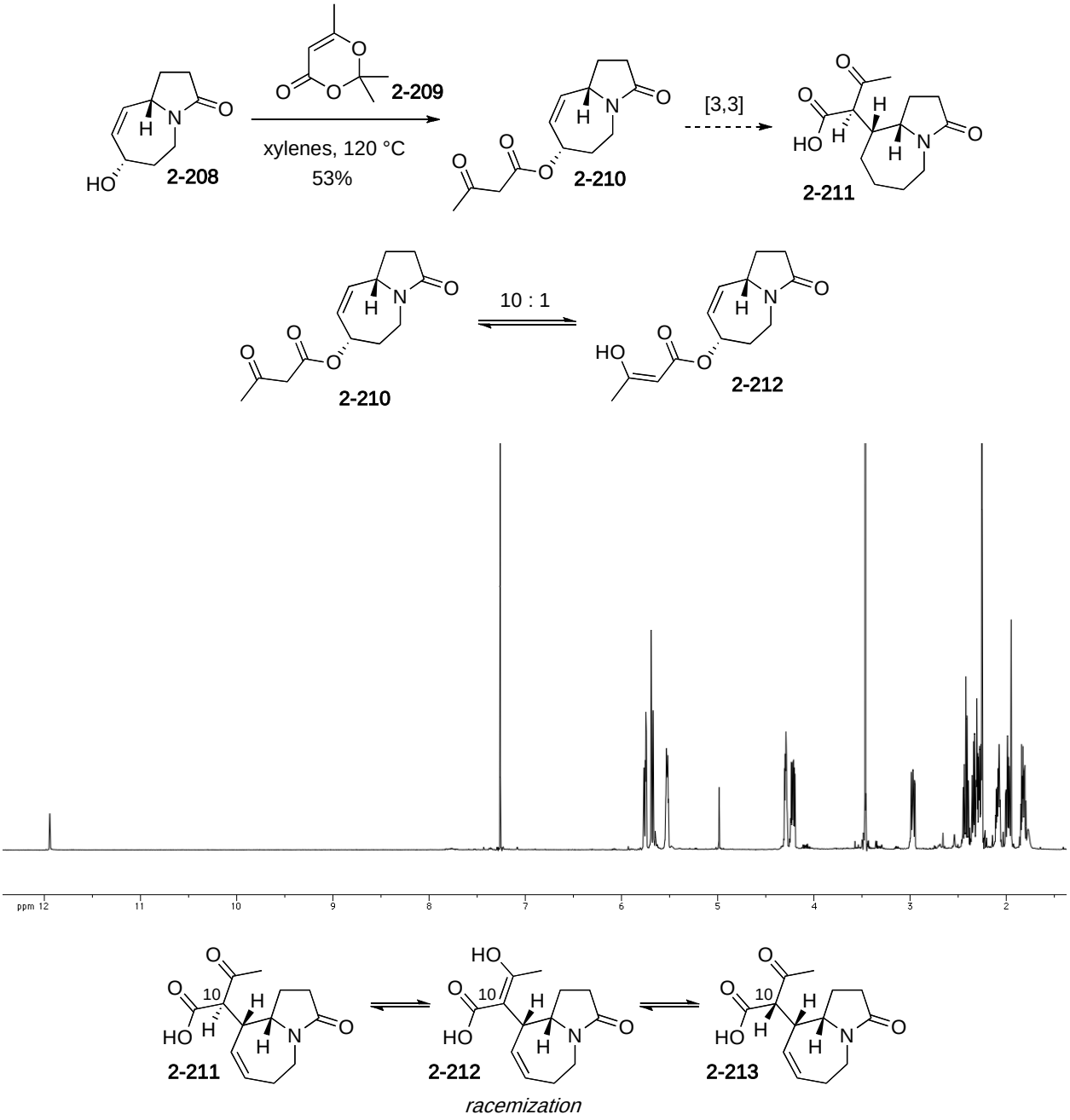


Scheme 2-33. Pyrrolo[1,2-*a*]azepine core completed by alkylation and RCM.

With our alkylation components in hand, we were ready for segment condensation following the deprotection of the *N*-Boc group of **2-195**, taking care to avoid loss of the volatile material upon workup. Initially, the alkylation was performed with sodium hydride and TBAI in DMF; however, the yields were irreproducible (40-76%) and extended reaction times were required. Fortunately, phase-transfer conditions proved to be superior in terms of reproducibility and rate as well as scalability to allow for the production of **2-189** on multigram scale. RCM of the diene using Grubbs 2nd generation catalyst (**2-95**) and completion of the pyrrolo[1,2-*a*]azepine core proceeded in 98% yield. Deprotection of the unstable TBS-ether under acidic conditions afforded our key allylic alcohol (**2-208**), which was found to be sensitive to oxygen (oxidation at C(9a) of the homoallylic amide), water soluble, and quite hygroscopic.

2.2.5 [3,3]-Sigmatropic Rearrangement Strategy

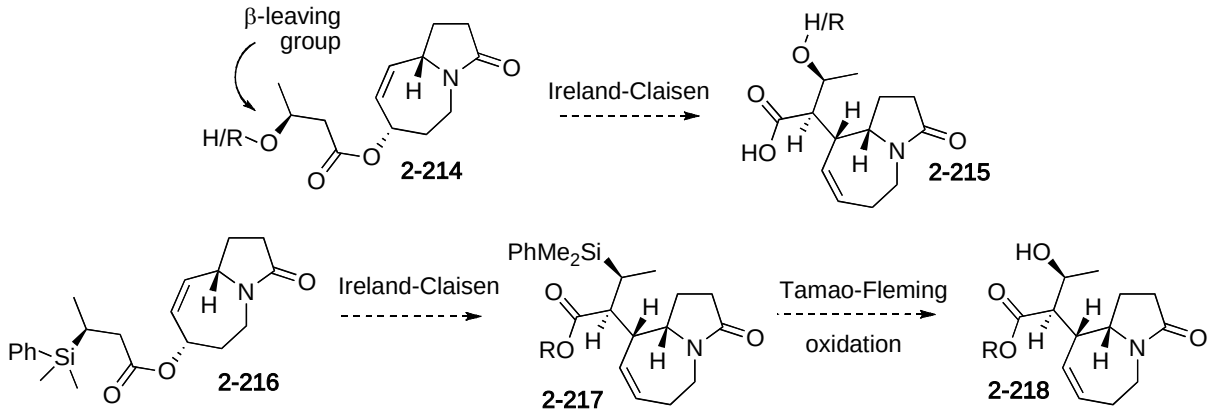
At this point, we transformed **2-208** into the β-keto ester in anticipation of performing a Carroll rearrangement that would furnish the desired oxidation state at C(16) needed to form the furanolactone ring system as demonstrated in our model system. Acylation of **2-208** using the acetone adduct of diketene (**2-209)** proceeded in 53% yield (Scheme 2-34). However, prior to performing the [3,3]-rearrangement, we observed a dynamic keto-enol tautomerism, evident in the ^{1}H NMR spectrum of **2-210** (δ 11.9 ppm, Scheme 2-34), and we foresaw certain epimerization of the product β-keto acid **2-211**, thereby sabotaging our efforts to install the correct configuration at C(10).



Scheme 2-34. Synthesis and ^{1}H NMR spectrum of β-keto ester **2-210**.

Rethinking our rearrangement strategy, we believed the most convergent pathway to our desired product would be to use ester **2-214** containing the requisite chiral secondary alcohol pre-installed, which would not participate in tautomerizaiton to racemize the α-stereocenter (Scheme

2-35). However, under the strongly basic conditions required to form the silyl ketene acetal intermediate of the Ireland-Claisen reaction the β-oxygenation would certainly lead to elimination. Our solution was to make the substrate containing a dimethylphenylsilyl group (**2-216**) that would act as a non-eliminating placeholder for later introduction of the required oxygenation through a late-stage Tamao-Fleming oxidation. These reactions occur with retention of configuration so no additional redox steps would be needed, and the remaining functionality should be tolerant of the selective transformation of the silane.



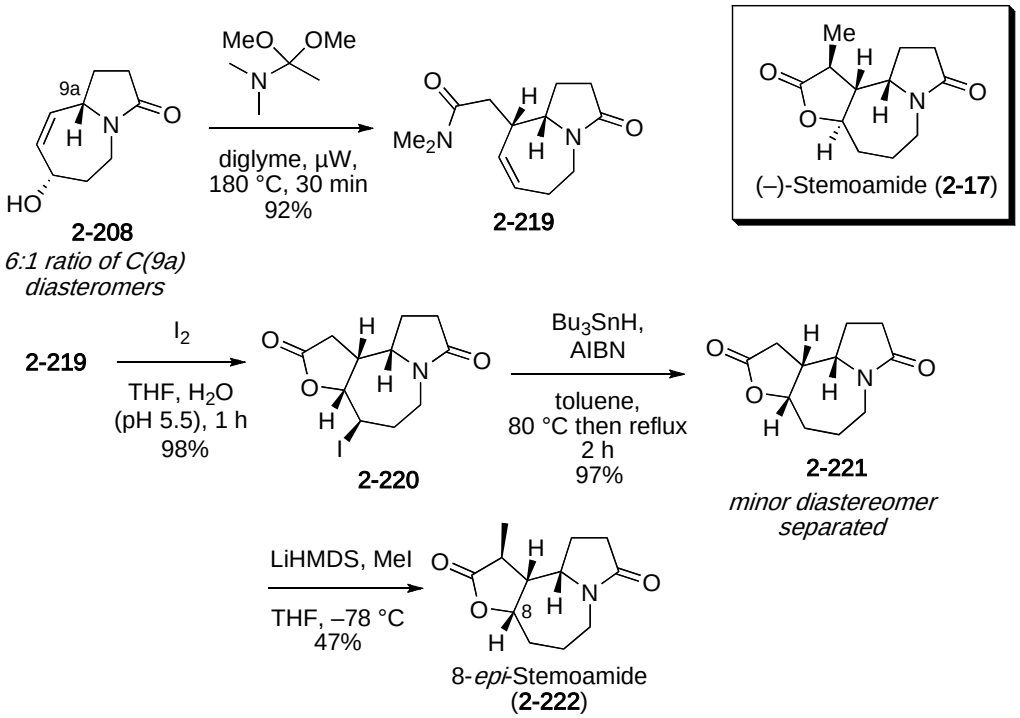
Scheme 2-35. [3,3]-Sigmatropic rearrangment strategy revisited.

2.2.6 Eschenmoser-Claisen Rearrangement and Synthesis of *epi*-Stemoamide

What still remained unknown to us was whether any [3,3]-sigmatropic reaction could take place on the concave face of the pyrroloazepine core at the sp2-hybridized C(8)-carbon adjacent to the C(9)-stereocenter responsible for the concavity of the bicyclic system. We decided to attempt the Eschenmoser-Claisen rearrangement to probe the reactivity, both due to its prior successful use in our stenine and tuberostemonine syntheses as well as the increased

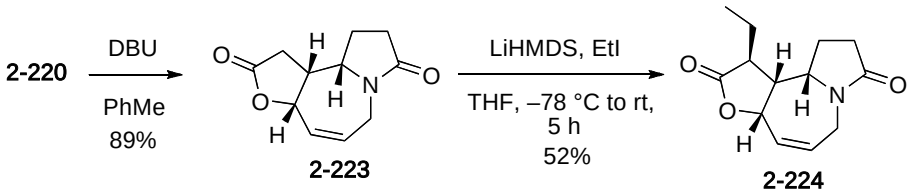
nucleophilicity of the enamine intermediate to facilitate the rearrangement. Gratifyingly, treatment of **2-208** to the rearrangement conditions (excess dimethylacetamide dimethylacetal in diglyme at 180 °C under microwave heating for 15 min) afforded dimethylamide **2-219** (Scheme 2-36).

While analyzing the structure of **2-219**, we were struck by the relation of the product to the stemoamide core and the resemblance of this intermediate to those found in prior syntheses of the tricyclic alkaloid (Section 2.1.2, Scheme 2-8). Once again using conditions from our stenine and tuberostemonine work, dimethylamide **2-219** was subjected to iodolactonization using a buffered solvent system to provide the corresponding lactone in excellent yield. Radical de-iodination of **2-220** proceeded smoothly to afford the unsubstituted ring system of stemoamide, and we were able to install the methyl group using conditions reported by Sibi to complete the first total synthesis of (–)-8-*epi*-stemoamide in a total of 12 steps and 14.3% overall yield from pyroglutamic acid. It is worth noting the originality of our approach to the stemoamide core compared to those outlined in section 2.1.2. While we employ an RCM strategy for the construction of the pyrroloazepine core as other groups have previously done, we successfully relay the stereochemical information from C(7) to C(9) in what is a novel transformation for this class of *Stemona* alkaloids.



Scheme 2-36. Successful Eschenmoser-Claisen rearrangement and synthesis of 8-*epi*-stemoamide.

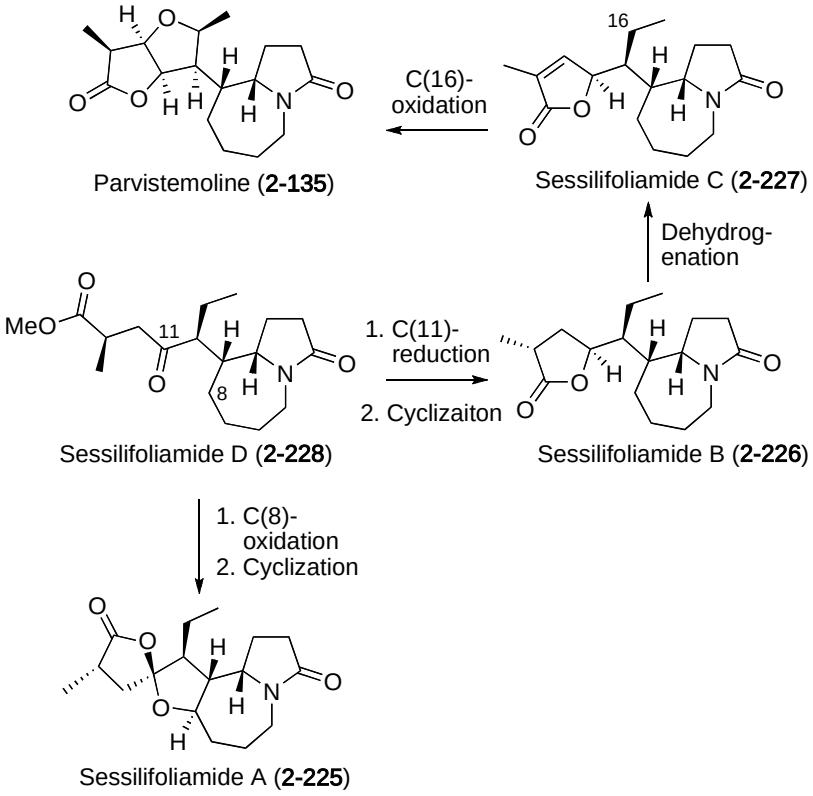
Interestingly, iodide **2-220** was labile towards basic conditions and the elimination product (**2-223**) could be formed upon treatment with DBU. Enolate alkylation of this intermediate provided **2-224**, possessing the vinyl lactone handle which could be of potential use in future studies of related alkaloids.



Scheme 2-37. Iodide elimination and alkylation of lactone **2-223**.

2.2.7 Sessilifoliamides and Hypothetical Biosynthetic Relationship to Parvistemoline

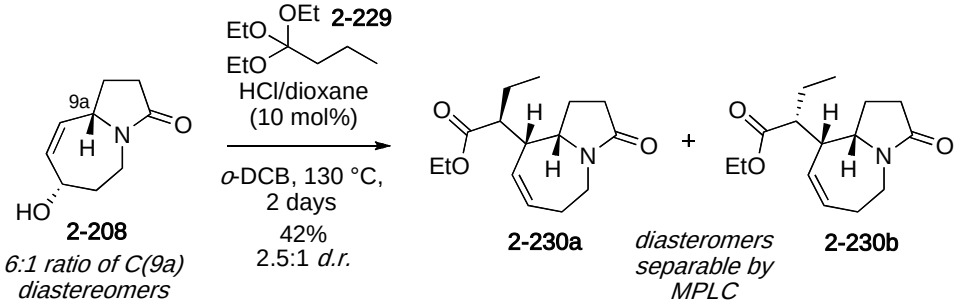
Having demonstrated the success of the [3,3]-rearrangement and the opportunistic use of the product for the synthesis of the stemoamide epimer, we now investigated whether alkyl substitution on the rearranging fragment would be tolerated and what the stereochemical consequences would be. Initially, we were hesitant to investigate the substitution pattern containing the proposed bulky silane moiety (**2-216**, Scheme 2-35) for fear of hindering reactivity, and a more gradual investigation (i.e. saturated alkyl chain) into tolerated substitution was encouraged by the 2003 isolation of the sessilifoliamde family of *Stemona* alkaloids and their striking similarities to parvistemoline (Scheme 2-38).[121] Sessilifoliamides A-D were isolated from the roots of *Stemona sessilifolia* along with five known alkaloids including stenine (**2-75**), 2-oxostenine and tuberostemonone (**2-106**). The structures of **2-225**-**2-228** were unambiguously determined by X-ray crystallography and chemical derivatization. In a similar manner to our proposed biosynthetic relationship between tuberostemonine, tuberostemonone and parvistemonone (Scheme 2-16), parvistemoline and the individual sessilifoliamides can be related through oxidation and cyclization events as shown in Scheme 2-38. Developing a strategy to take advantage of these structural similarities for a total synthesis would be highly desirable and would lend support to the idea of common biosynthetic precursors. In our case, the common strategy would begin with the successful [3,3]-rearrangement and the ethyl substitution pattern conserved throughout the sessilifoliamides.



Scheme 2-38. Hypothesized biosynthetic relationship between the sessilifoliamides and parvistemoline.

We initially opted to attempt the Johnson orthoester Claisen conditions for the alkyl-substituted [3,3]-sigmatropic rearrangement in lieu of the Eschenmoser-Claisen protocol due to the commercial availability of a variety of orthoesters and the ease of functionalizing the resulting compounds (i.e. methyl/ethyl ester vs. dimethylamide/morpholine amide). Alcohol **2-208** was treated with excess triethylorthobutyrate (**2-229**) and catalytic acid in *o*-dichlorobenzene for 2 days at 130 °C to provide a 42% yield of ethyl esters **2-230a** and **2-230b** in a 2.5:1 mixture of diastereomers, which could be successfully separated by MPLC purification. Varying the acid source, reaction temperature, solvent, heating method and the time of the reaction did not appear to have dramatic effects on the outcome of the reaction (Table 3-1). Interestingly, entries 5 and 6 indicate that acid is not necessary for the rearrangement to occur, however the overall yield

suffers. In regards to stereoselectivity, there was a mild increase in the *d.r.* of the reaction products when *o*-DCB was used as a solvent instead of xylenes. In many reactions at elevated temperatures the remaining mass balance was the corresponding ketone of the starting material, indicating an acid-mediated oxidation of the allylic alcohol was operative under the reaction conditions.

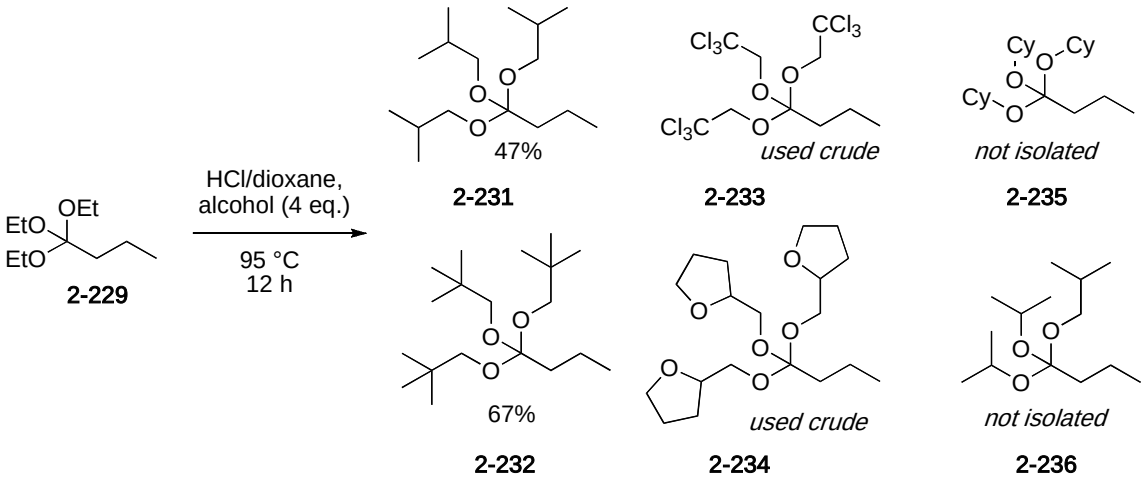


Scheme 2-39. Orthoester Johnson-Claisen rearrangement to produce **2-230a** and **2-230b**.

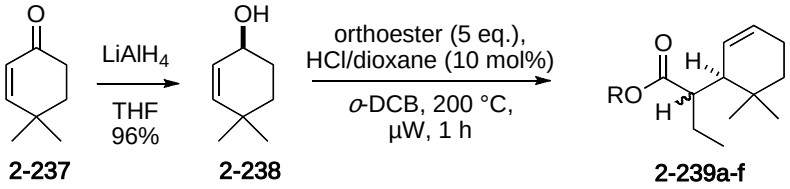
Table 2-1. Conditions screened for the Johnson-Claisen rearrangement in Scheme 3-39.

Reaction	Solvent	Acid (10 mol%)	Temperature	Time	Yield	*d.r.*
1	Xylenes	Propionic acid	130 °C	2 h	n/a	-
2	Xylenes	CSA	130 °C	2 h	n/a	-
3	Xylenes	2,4,6-trichlorophenol	130 °C	2 h	37%	1.3:1
4	Xylenes	HCl/dioxane	130 °C	2 h	52%	1.6:1
5	Xylenes	-	130 °C	4 h	39%	1.6:1
6	*o*-DCB	-	200 °C (μW)	40 min	30%	2:1
7	*o*-DCB	HCl/dioxane	240 °C (μW)	40 min	36%	2.1:1
8	THF	HCl/dioxane	rt	4 days	n/a	-
9	*o*-DCB	HCl/dioxane	130 °C	2 days	42%	2.5:1

We concluded that increasing the diastereoselectivity of the orthoester Claisen rearrangement by varying the reaction conditions was not likely to be successful. Therefore, we wanted to assess the feasibility of using steric effects to accomplish our goal, and we proposed that increasing the bulk of the alkyl groups on the orthoester carbon would affect the transition state of the reacting ketene acetal. There are few literature reports of acyclic, bulky orthoesters, and certainly none have been used in a [3,3]-rearrangement. Reported methods of forming acyclic orthoesters are extremely few, essentially falling into two categories: 1) Pinner reaction of nitriles to amidates and alcoholysis to the corresponding orthoester and 2) Brønsted acid-mediated thermal displacement using LeChatelier's principle.[122] The Pinner method for orthoester formation requires lengthy reaction times to fully convert the amidate intermediate into the orthoester, and was shown to be extremely sensitive to steric factors.[123] The displacement method proved to be optimal for the formation of β-branched orthoesters with the sole condition being a significant boiling point difference between the alcohol to be incorporated and that which is departing form the orthoester- in our case, ethanol. Attempting to incorporate α-branching into the orthoester was unsuccessful, providing incomplete conversion and several side products (hydrolysis of the orthoester to the ethyl ester being the major constituent) by ^{13}C NMR spectroscopy of the crude reaction mixture.



Scheme 2-40. Branched orthoesters produced by trans-orthoesterification.



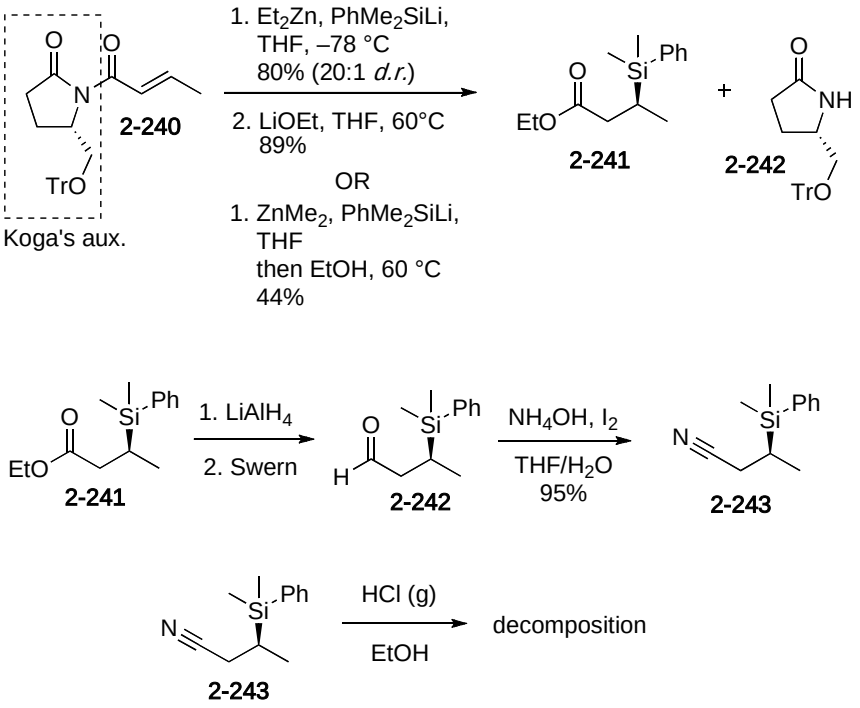
Scheme 2-41. Johnson-Claisen rearrangement on a model system using substituted orthoesters.

Table 2-2. Screening various orthoesters in the Johnson-Claisen rearrangement of **2-238** shown in Scheme 2-41.

orthoester	d.r.
2-229	1.5-2 : 1
2-231	2 : 1
2-232	2 : 1
2-233	2 : 1
2-234	NR

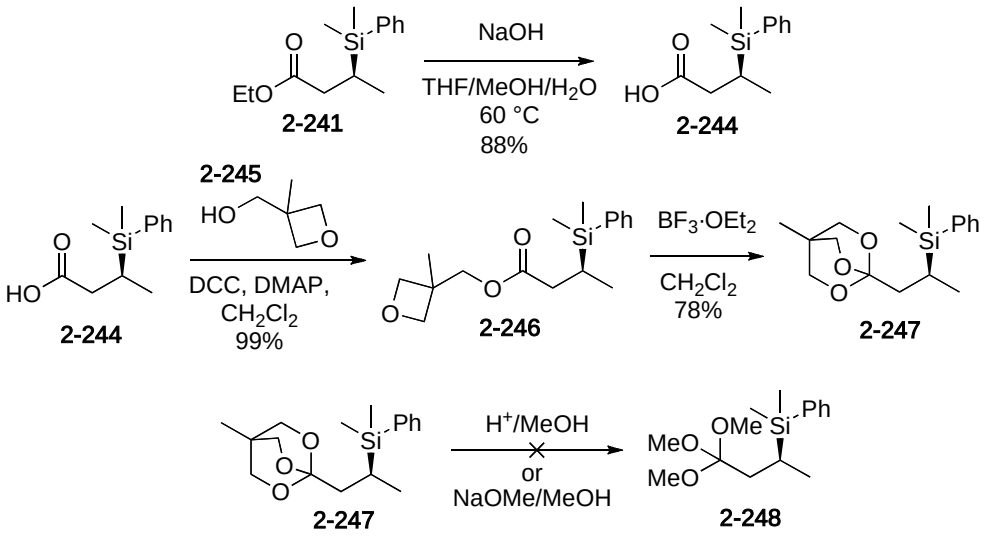
To assess the capacity of the substituted orthoesters to increase the diastereoselectivity of the [3,3]-rearrangement, we used allylic alcohol **2-238** as a model system possessing the geminal dimethyl substitution pattern to mimic the ring junction of the *Stemona* molecules and thus sufficiently increase the steric environment at the reacting sp^2-hybridized carbon. Exposure of **2-238** to the thermal reaction conditions using **2-229**-**2-234** proved to us that β-branched orthoesters did not sufficiently increase the diastereoselectivity of the rearrangement. Since we were unsuccessful in forming any α-branched orthoesters that would increase the steric environment closer to the reacting atoms we turned our attention elsewhere.

Concurrent to the orthoester study, we were investigating the feasibility of performing the [3,3]-sigmatropic rearrangement possessing the β-silane moiety in a one-pot, Eschenmoser-Claisen-like process. To set the silicon-bearing stereocenter, we followed methodology reported by Fleming and co-workers describing the conjugate addition of dimethylphenylsilyllithium to enones directed by Koga's lactam auxiliary (Scheme 2-42).[124] The auxiliary was smoothly removed using lithium methoxide to provide ethyl ester **2-241**, and the lactam would be easily recovered following chromatography of the reaction mixture on SiO_2 to isolate **2-242** by flushing the column with dichloromethane. Reduction of the ester to the alcohol using LAH followed by Swern oxidation afforded aldehyde **2-242**. Conversion of the aldehyde into the nitrile using NH_4OH and I_2[125] provided the precursor for orthoester formation. Unfortunately, the silane proved too labile for the harsh conditions required for the Pinner reaction and decomposition of the nitrile occurred rapidly.



Scheme 2-42. Diastereoselective silane addition and attempt to form orthoester via the Pinner route.

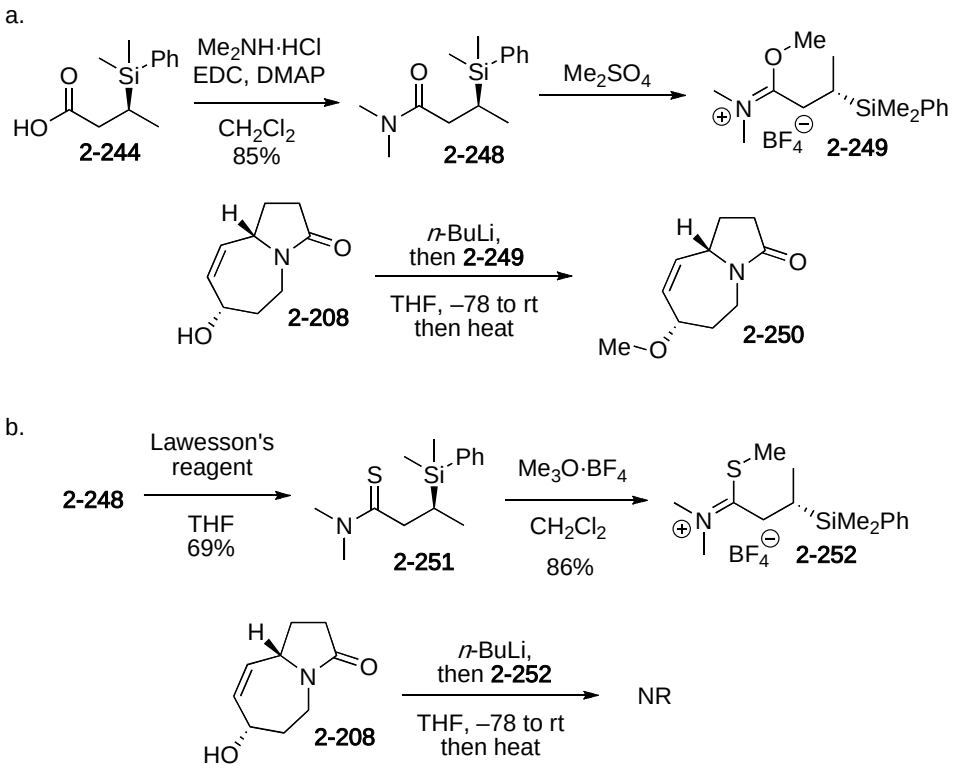
Alternatively, we succeeded in synthesizing the cyclic OBO-orthoester derivative (**2-247**) through saponification of ester **2-241** and carbodiimide coupling of oxetane **2-245** to provide **2-246**, which upon treatment with $BF_3{\cdot}OEt_2$ cyclized to form the orthoester in 78% yield. However, attempts to perform an intermolecular trans-orthoesterification were unsuccessful, as was performing a Johnson-Claisen rearrangement with **2-247** in the presence of methanol, hoping to intercept the intermediate oxocarbenium ion and affect irreversible C-C bond formation.



Scheme 2-43. Synthesis of OBO orthoester **2-247**.

As a final effort, we imagined a way to access the adduct of alcohol **2-208** with the β-silane fragment and we hypothesized that an activated amide (or imidate) similar to that which is generated under the Eschenmoser-Claisen conditions could have a chance at success. Towards this goal, EDC-coupling of acid **2-244** and dimethylamine provided the corresponding dimethyl amide (**2-248**, Scheme 2-44). Activation of the amide with dimethylsulfate provided our target compound, imidate **2-249**. Once again, the desired transformation remained elusive with reaction between the lithium alkoxide of **2-208** and **2-249** only supplying methylated material, indicating a polarized O-Me bond and consequent facile methyl transfer compared to addition to the C-N π-bond. Attempts to convert **2-249** into the corresponding dimethylacetal under basic and acidic conditions were not fruitful. To combat the methyl transfer problem, we synthesized the corresponding thio-analog (**2-252**); presumably a less polarized S-Me bond could suppress methyl transfer to the alkoxide in the rearrangement step. Thioamide **2-251**, formed using Lawesson's reagent from **2-248**, was alkylated using Meerwein's salt to provide **2-252**. Using this reagent in the alkoxide addition pathway did not produce any detectable methylated product

2-250, however no rearrangement product could be observed either. ^{1}H NMR monitoring of the reaction in C_6D_6 did not reveal any conversion between the thioimidate and the lithium salt of **2-208**.

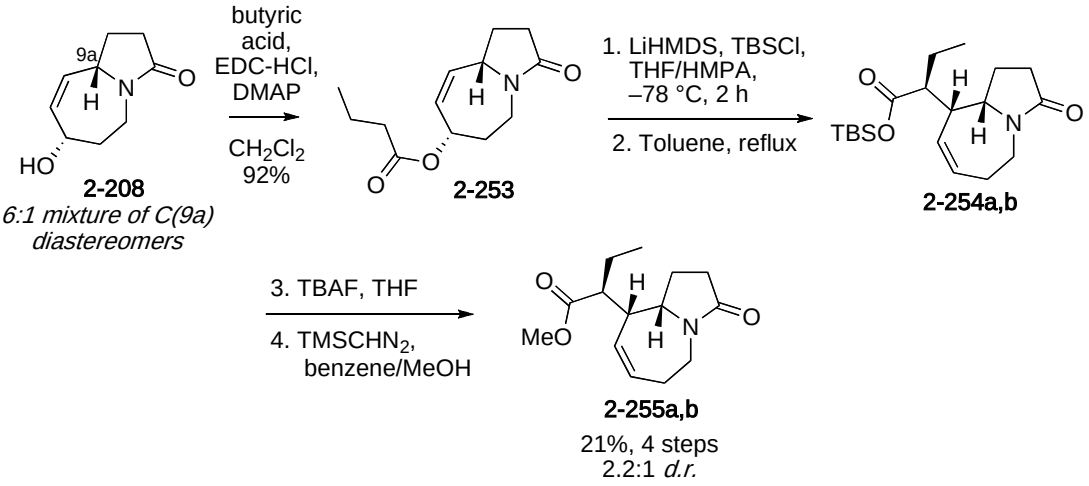


Scheme 2-44. Formation of a. imidate **2-249** and b. thioimidate **2-252** and attempted [3,3]-rearrangements.

2.2.8 Ireland-Claisen Rearrangement and Application to Sessilifoliamides and Parvistemoline

With our hopes of a facile one-pot [3,3]-rearrangement dwindling, we returned to our initial strategy of using an Ireland-Claisen reaction (Scheme 2-45), and we initially chose the ethyl substitution pattern of the sessilifoliamides to test our route. Esterification of **2-208** using butyric

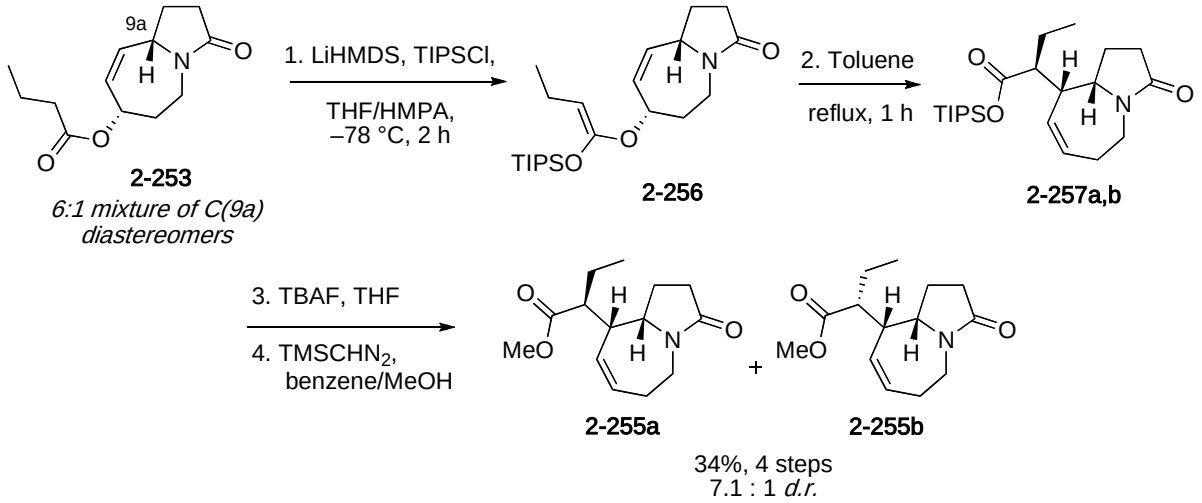
acid and DCC afforded **2-253** in high yield. Using conditions reported by Kishi for silyl ketene acetal formation and rearrangement of glycal esters,[126] the TBS-ketene acetal was isolated and subjected to heating in toluene to affect the rearrangement. To our pleasure the silyl ester was formed in the reaction and it was immediately subjected to deprotection with TBAF.[127] Methylation of the crude acid allowed for straightforward isolation of **2-255a** and **2-255b** in 21% yield over the 4-step sequence. Unlike ethyl esters **2-230a** and **2-230b**, the methyl esters could not be separated by MPLC, although isolation of the mixture did confirm the diastereoselectivity of the rearrangement to be an unremarkable 2.2:1 ratio.



Scheme 2-45. Ireland-Claisen rearrangement of **2-253** and conversion to the corresponding methyl ester.

Once again we were met with a less than desirable selectivity in the rearrangement event. From our initial studies on the Johnson-Claisen rearrangement we hypothesized modified steric parameters would have the greatest chance for increasing the diastereoselectivity in the rearrangement. Therefore, we attempted the Ireland-Claisen sequence using triisopropylsilyl chloride in place of TBSCl to bias the steric environment of the transition state further (Scheme 2-46). As for the TBS-ketene acetal, heating the TIPS-ketene acetal in toluene for 2 hours

initiated the [3,3]-rearrangement to produce what appeared to be an increased ratio of silyl esters **2-257a** and **2-257b**. Desilylation followed by methylation and purification by MPLC confirmed the increase in diastereoselectivity, and much to our delight **2-255a** and **2-255b** were obtained in 34% yield as a 7.1:1 ratio of methyl esters.



Scheme 2-46. Effect of using the TIPS-ketene acetal (**2-256**) in the Ireland-Claisen rearrangement.

We propose the nearly four-fold increase in diastereoselectivity to be a result of a significant destabilization of one of the two possible transition states for the rearrangement (Figure 2-3). As suggested by Ireland[128] and more recently by Kishi,[126] Ireland-Claisen rearrangements on cyclic substrates proceed via chair-like or boat-like orientations of the reacting atoms. We hypothesize that by increasing the steric environment around silicon by going from TBS to TIPS, we are significantly destabilizing the chair transition state (TS) orienting the silicon atom underneath the 5,7-ring system, which favors the boat TS holding the silane away from any steric interaction with the azepine ring. It is worthwhile to note that although the TBS-ketene acetal does possess a *tert*-butyl group we imagine it would likely be

held in an axial orientation away from the ring system to minimize sterics, thereby orienting the two methyl groups on silicon towards the ring. Therefore, perhaps a more accurate comparison of the steric environments around silicon in the TS of the rearrangement would be TMS vs. TIPS. Although we have not performed this reaction we would expect the TMS ketene acetal to give similar diastereoselection as observed with TBS. Additionally, this TS analysis could explain the similar selectivity in the Johnson-Claisen and Ireland-Claisen reactions (ethyl ketene acetal vs. methyl silyl ketene acetal).

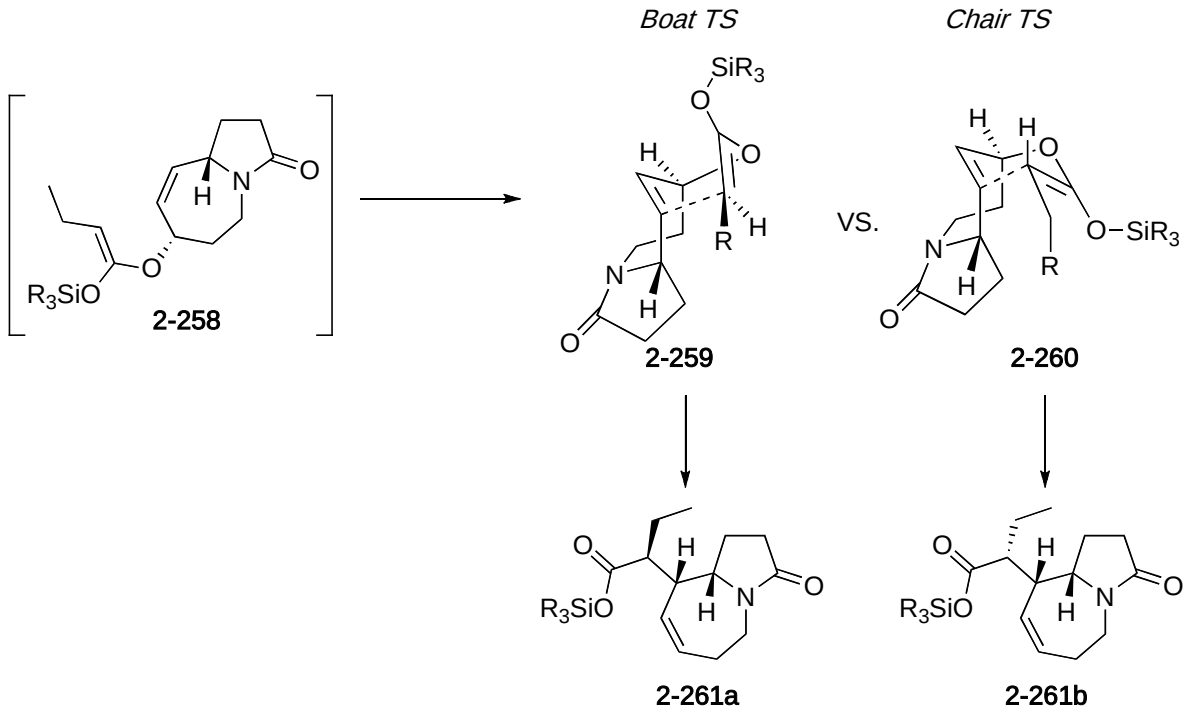
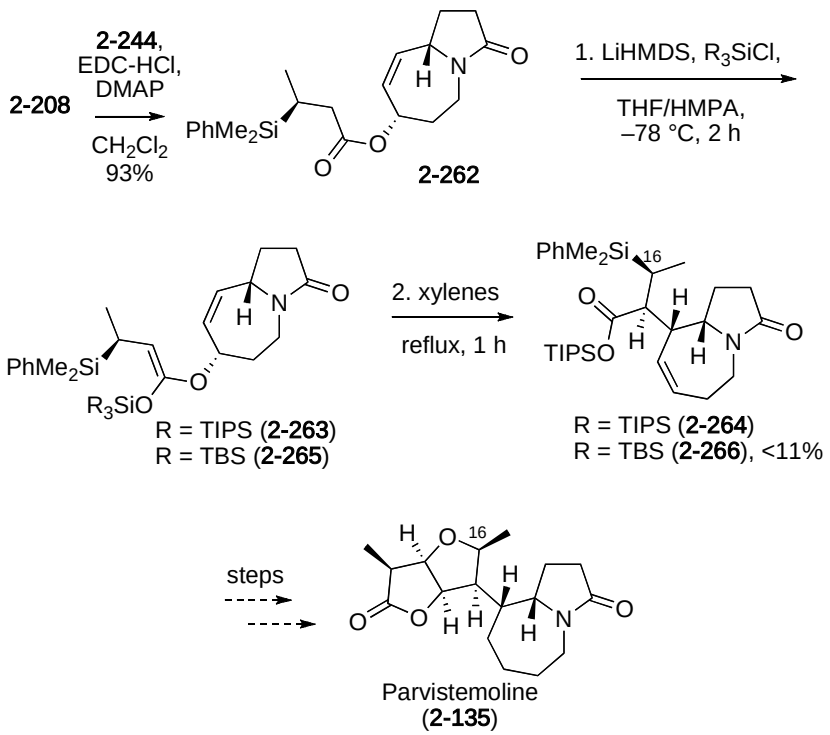


Figure 2-3. Proposed transition states for the Ireland-Claisen rearrangement.

Having enjoyed success with the ethyl substitution pattern in the Ireland-Claisen rearrangement, we synthesized β-silyl ester **2-262** from **2-208** and **2-244** to determine whether our optimized [3,3]-rearrangement conditions could be successfully applied to the silyl-bearing

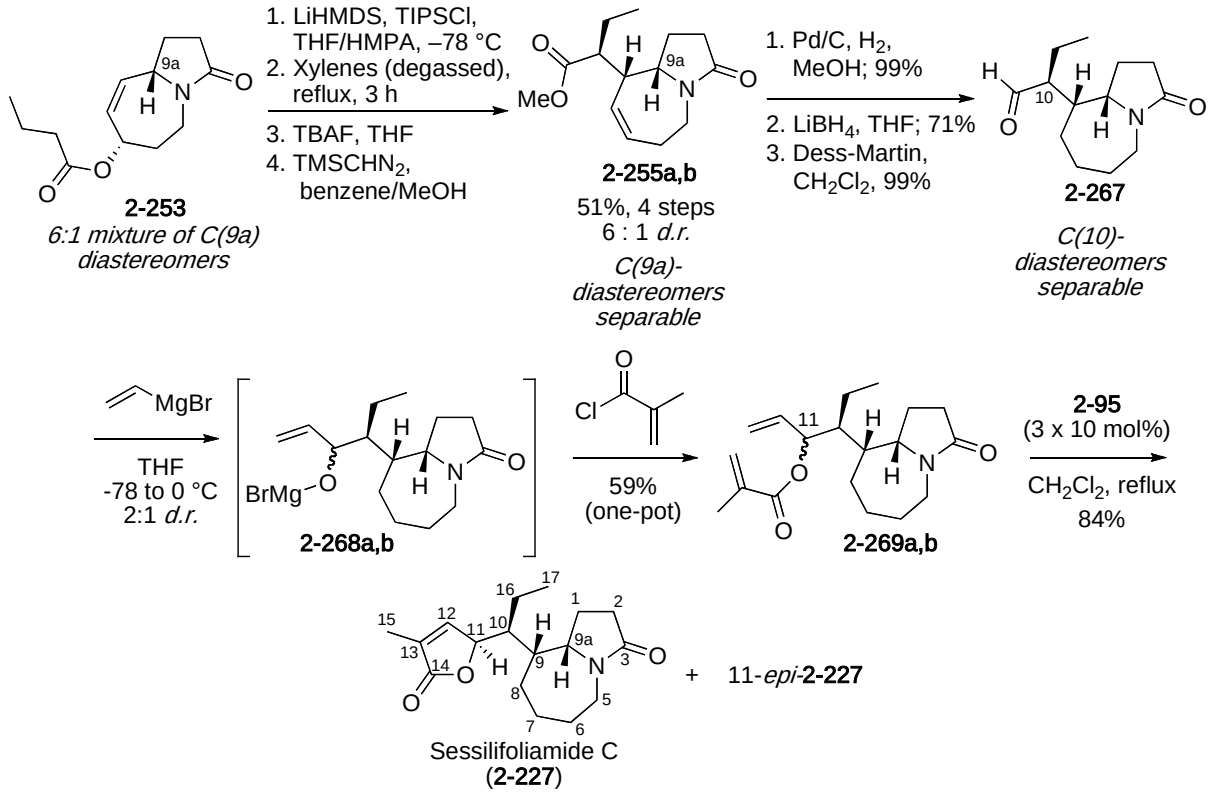
derivative. Treatment of **2-262** with TIPSCl and LiHMDS in a 23% THF/HMPA mixture at –78 °C generated **2-263** and heating this material in distilled, degassed xylenes at reflux provided a mixture of products by ^{1}H NMR, with a very small amount of the desired [3,3]-product **2-264** present. We re-attempted the Ireland-Claisen protocol using TBSCl to determine if a less sterically demanding silyl ketene acetal was required for the [3,3]-rearrangement to occur in the presence of the bulky silane moiety in **2-262**. While **2-265** formed without issue, the rearrangement conditions once again provided a mixture of compounds, although it did provide a better ratio of **2-266** to various side products than when **2-265** was used. From the crude reaction mixture silyl ester **2-266** could be isolated in 11% yield after chromatography on deactivated SiO_2, although it remained contaminated with several unidentifiable compounds by ^{1}H NMR analysis. After attempting several different rearrangement conditions (*o*-DCB, 240°C, μW, 30 min; toluene, reflux, 2 h) and seeing no change in the ratio of products, we concluded that using the silane substitution as a placeholder for the necessary oxygenation at C(16) for the completion of parvistemoline would not be compatible with the Ireland-Claisen strategy due to steric effects.



Scheme 2-47. Ireland-Claisen rearrangement attempts using **2-262**.

Despite failing to achieve the Ireland-Claisen reaction possessing the requisite silane substitution for the synthesis of parvistemoline, we had managed to increase the diastereoselectivity of the ethyl-substituted rearrangement products to a respectable level. Therefore, we forged onwards towards the sessilifoliamides. While methyl esters **2-255a** and **2-255b** could not be separated by MPLC, the minor diastereomer arising from the C(9a) stereocenter of the pyrrolidone **2-195** as well as side products from the [3,3]-rearrangement could be removed at this stage (Scheme 2-47). Additionally, we discovered that the use of distilled, degassed xylenes to suppress oxidative decomposition of the silyl ketene acetal during heating provided the desired [3,3]-products in a much improved 51% yield over the sequence. Nucleophilic addition to the ester in **2-255a** proved to be challenging as attempts to add Grignard and organolithium reagents were unsuccessful, returning unaltered starting material.

Additionally, attempts to convert the methyl ester to the corresponding Weinreb amide, even in refluxing toluene, were similarly unsuccessful in affecting any reaction with the ester. Therefore, we decided to generate a more flexible skeleton and lower the oxidation state to the aldehyde to affect reactivity. Hydrogenation of the endocyclic double-bond and conversion of the methyl ester to the aldehyde provided **2-267**, which could be separated from its diastereomer at this stage. Gratifyingly, addition to the aldehyde using vinylmagnesium bromide provided a 2:1 mixture of allylic alcohols that were acylated using methacryloyl chloride, as per our initial model studies on the furanolactone moiety, in a one-pot sequence. Direct subjection of unstable allylic esters **2-269a** and **2-269b** to RCM conditions closed the butenolide ring in 84% yield, and separation of the diastereomers by MPLC revealed the major isomer to be sessilifoliamide C by comparison of the natural and synthetic ^{1}H and ^{13}C NMR data (Tables 2-2, 2-3). Notably, there exists a discrepancy between the mangnitudes of our measured specific rotation ($[a]_D^{23}$ –84.6 (*c* 0.25, $CHCl_3$); –43.4 (*c* 5.0, EtOH) of **2-227** and that which has been reported for sessilifoliamide C ($[a]_D^{26}$ –140° (*c* 0.17, $CHCl_3$).[121] In summary, **2-227** was synthesized in 18 steps from (*S*)-pyroglutamic acid and in 5.6% overall yield.



Scheme 2-48. Completion of sessilifoliamide C.

Table 2-3. ^{1}H NMR comparison of synthetic and natural **2-227.**

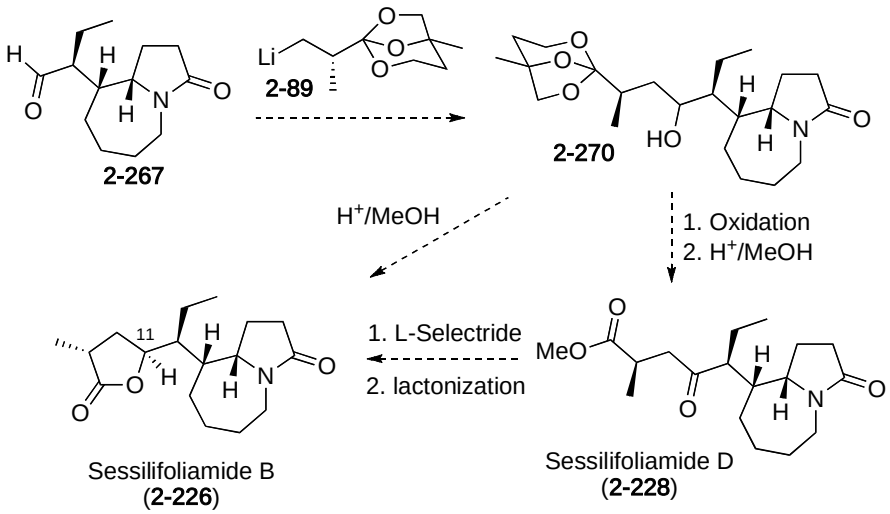
C#	Natural[121] – ^{1}H δ[ppm], mult (J) $CDCl_3$, (500 MHz)	Synthetic – ^{1}H δ[ppm], mult (J) (600 MHz)
1	1.67, m	1.70-1.66, m
	1.95, m	1.98-1.92, m
2	2.38, m	2.43-2.33, m
	2.38, m	2.43-2.33, m
5	2.66 brt (12.3 Hz)	2.66, dt (1.3, 13.6 Hz)
	4.04, brd (12.9 Hz)	4.03, dt (3.2, 13.6 Hz)
6	1.45, m	1.49-1.41, m
	1.72, m	1.74-1.72, bm
7	1.34, m	1.40-1.30, m
	1.88, m	1.90-1.86, bm
8	1.35, m	1.40-1.30, m
	1.68, m	1.70-1.66, m
9	2.20, m	2.20, ddd (5.8, 8.3, 8.3 Hz)
9a	3.93, m	3.93, ddd (5.9, 5.9, 10.7 Hz)
10	1.67, m	1.70-1.66, m
11	5.16, brd (1.9 Hz)	5.17, bm (2.1 Hz)
12	7.02, d (1.4 Hz)	7.03, bm (1.6 Hz)
15	1.94, d (1.5 Hz)	1.95, t (1.6 Hz)
16	1.20, m	1.19, sept (7.3 Hz)
	1.36, m	1.40-1.30, m
17	0.85, t (7.4 Hz)	0.84, t (7.6 Hz)

Table 2-4. ^{13}C NMR comparison of synthetic and natural **2-227.**

C#	Natural[121] – ^{13}C δ[ppm], $CDCl_3$, (125 MHz)	Synthetic – ^{13}C δ[ppm], (150 MHz)
1	22.0	22.1
2	30.8	31.0
3	174.4	174.6
5	40.6	40.7
6	28.8	29.0
7	29.4	29.5
8	24.5	24.6
9	43.3	43.3
9a	60.8	60.9
10	44.2	44.2
11	82.1	82.3
12	148.3	148.2
13	130.4	130.5
14	174.3	174.5
15	10.7	10.9
16	19.1	19.1
17	13.3	13.5

2.2.9 Future Directions

To complete the syntheses of sessilifoliamides B and D, we propose using aldehyde **2-262** as a key advanced intermediate (Scheme 2-48). Addition of the lithiated orthoester **2-89** used in our previous tuberostemonine work would provide **2-265**, which following oxidation and orthoester cleavage in acidic methanol will complete sessilifoliamide D. Sessilifoliamide B can be accessed from sessilifoliamide D by reduction and cyclization steps or in a more direct fashion from **2-270** using acidic methanol and separating the C(11) diastereomers.

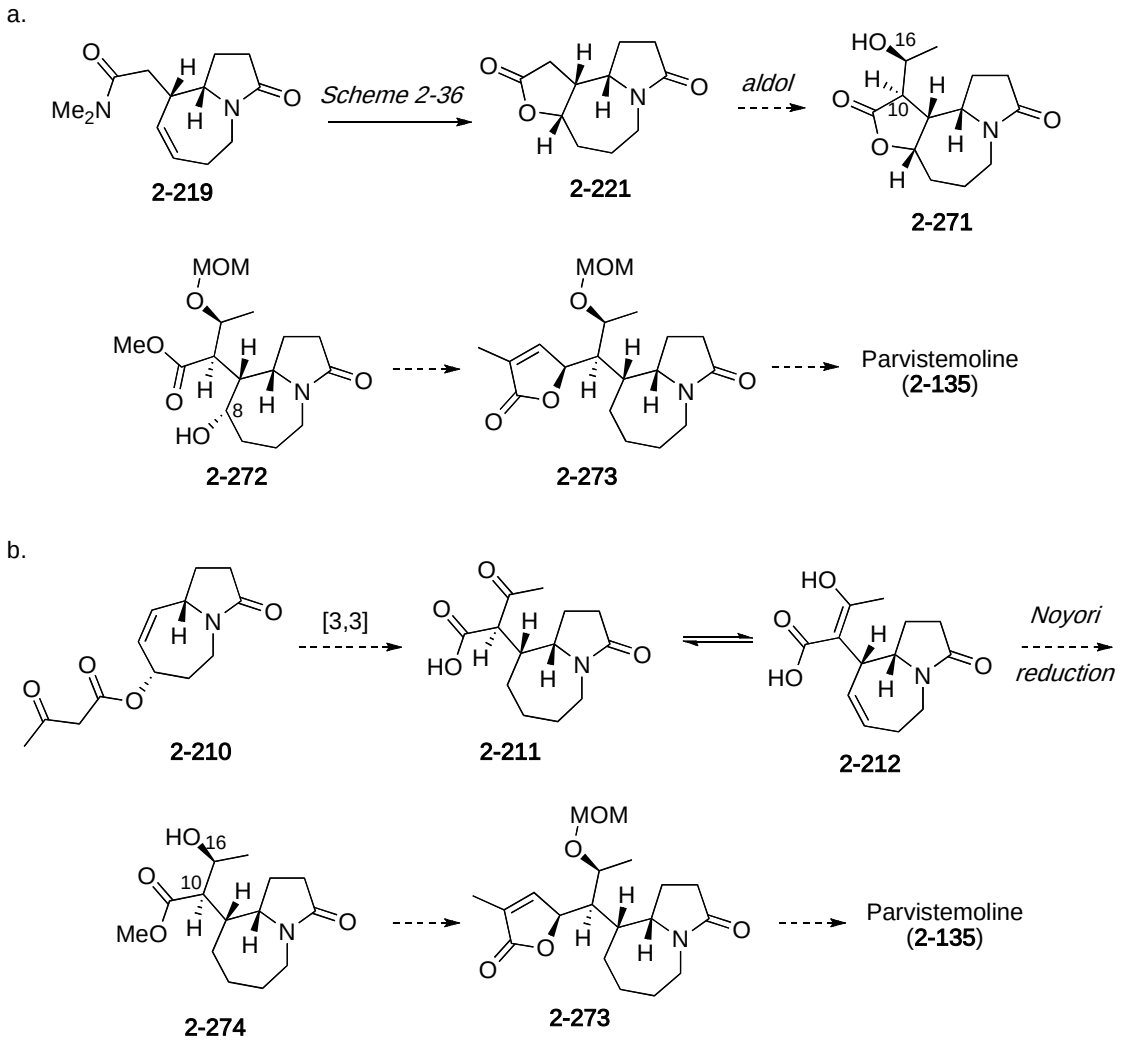


Scheme 2-49. Proposed route for the completion of sessilifoliamides B and D.

Future directions towards the completion of parvistemoline are summarized in Scheme 2-50. Possible approaches include an aldol reaction between acetaldehyde and tricyclic intermediate **2-221**, which we accessed from alcohol **2-208** via the Eschenmoser-Claisen rearrangement as shown in Scheme 2-36. We have demonstrated that stereospecific alkylation of the enolate of the lactone ring is possible, and the approach of the incoming electrophile would

be substrate directed to install the C(10) and C(16) stereocenters of aldol product **2-271**. Protection of the alcohol and opening of the lactone in **2-271** will allow for deoxygenation at C(8), followed by formation of butenolide in **2-273** according to our sessilifoliamide C synthesis (Scheme 2-48). MOM-ether deprotection and Michael addition steps should furnish parvistemoline, similar to our initial model system.

Alternatively, we propose re-visiting our Carroll rearrangement strategy (Scheme 2-34) to assess the viability of performing a Noyori reduction on rearrangement product **2-211**. The keto-enol tautomerization should not effect the facial selectivity in the hydrogenation event, and the C(10) and C(16) stereocenters should be set in a catalyst-controlled manner. Elaboration of **2-274** into **2-273** would mirror our sessilifoliamide C sequence, and completion of the target alkaloid could be achieved from this common intermediate as described for approach a.



Scheme 2-50. Proposed routes to parvistemoline involving a. aldol addition and b. Noyori reduction steps.

2.3 CONCLUSION

The *Stemona* alkaloids possess a rich history in organic synthesis and the number of creative approaches that have been reported for the total syntheses of these molecules is a testament to their complexity and intrigue. Our group has maintained a fascination with these

molecules, resulting in the syntheses of stenine and tuberostemonine as well as the development of key hydroindoline fragmentation methodology as outlined in section 2.1.3.

In our current investigation, we successfully developed a novel, convergent route to the characteristic pyrrolo[1,2-*a*]azepine core of the *Stemona* alkaloids, featuring a Fukuyama reduction, intermolecular alkylation of two chiral fragments and ring-closing metathesis to complete the azepine ring. Careful design of our synthetic strategy allowed for the relay of stereochemical information across the 7-membered ring in a [3,3]-sigmatropic rearrangement. Performing an Eschenmoser-Claisen rearrangement allowed for the straightforward completion of 8-*epi*-stemoamide.

We also developed an Ireland-Claisen approach for the relay of stereochemical information, which we discovered had the advantage of tolerating substitution on the intermediate silyl ketene acetal to install 3 contiguous stereocenters in a controlled fashion. Optimization of the reaction conditions to bias the transition state on steric grounds provided good levels of diastereoselection and we were successful in using the rearrangement products to complete the first total synthesis of sessilifoliamide C, as well as synthesize key intermediates for the completion of related sessilifoliamides.

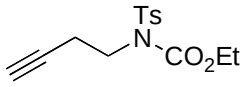
3.0 EXPERIMENTAL

3.1 GENERAL

All moisture-sensitive reactions were performed using syringe-septum cap techniques under an inert atmosphere of N_2. All glassware was flame dried or dried in an oven (140 °C) for at least 2 h prior to use. THF and Et_2O were dried by distillation over Na/benzophenone ketyl or $LiAlH_4$. CH_2Cl_2 and toluene were dried by passage through alumina columns in a solvent purification system. NEt_3 and DME were distilled from CaH_2. Me_2Zn and Et_2Zn were purchased from the Aldrich Chemical Company and $Cp_2Zr(H)Cl$ was prepared according to a literature protocol.[129] Unless otherwise stated, solvents and reagents were used as received. Analytical thin layer chromatography was performed on pre-coated silica gel 60 F-254 plates (particle size 0.040-0.055 mm, 230-400 mesh) and visualized with a 254 nm UV light or by staining with a solution of *p*-anisaldehyde (7.5 mL *p*-anisaldehyde, 25 mL concentrated H_2SO_4 and 7.5 mL glacial acetic acid in 675 mL of 95% ethanol), $KMnO_4$ (1.5 g of $KMnO_4$, 10 g of potassium carbonate and 2.5 mL of 5 % aqueous NaOH in 150 mL H_2O), or Vaughn's reagent (4.8 g of $(NH_4)_6Mo_7O_{24}{\cdot}4\ H_2O$ and 0.2 g of $Ce(SO_4)_2$ in 100 mL of a 3.5 N H_2SO_4 solution). NMR spectra were recorded at 300 MHz/75 MHz (^{1}H NMR/^{13}C NMR) on a Bruker Avance instrument or 600 MHz/150 MHz (^{1}H NMR/^{13}C NMR) on a cryoprobe-equipped Bruker Avance instrument at 21 °C unless otherwise noted. $CDCl_3$ was filtered through dried basic alumina prior to sample preparation. Chemical

shifts are reported in parts per million with the residual solvent peak as an internal standard. ^{1}H NMR spectra are tabulated as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, dd=doublet of doublets, ddd= doublet of doublet of doublets, dddd= doublet of doublet of doublet of doublets, dt= doublet of triplets, m=multiplet, b=broad) coupling constant and integration. ^{13}C spectra are tabulated by observed peak. Melting points were determined using a Laboratory Devices Mel-Temp II. Infrared spectra were measured on a Nicolet AVATAR 160 FT-IR E.S.P. spectrometer or a Perkin-Elmer Spectrum 100 FT-IR/ATR spectrometer. Mass spectra were obtained on a Micromass Autospec double focusing instrument. Optical rotations were recorded on a Perkin-Elmer 242 polarimeter at 23 °C; $CHCl_3$ was filtered through dried basic alumina prior to sample preparation.

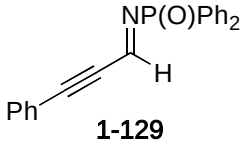
3.2 EXPERIMENTAL PROCEDURES



1-128

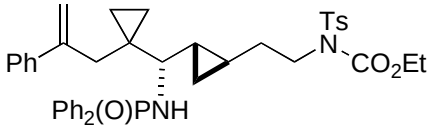
***O*-Ethyl-*N*-but-3-ynyl-*N*-[(4-methylphenyl)sulfonyl]carbamate** (**1-128**)**.** According to a literature procedure, [130] 3-butyn-1-ol (1.78 mL, 23.5 mmol) was added to a cooled (0 °C) solution of $TsNHCO_2Et$ (8.56 g, 35.2 mmol) and PPh_3 (18.5 g, 70.4 mmol) in THF (300 mL). The solution became cloudy after 10 min and the suspension was stirred for 18 h, and concentrated in vacuo. The residue was purified by chromatography on SiO_2 (20% EtOAc/Hex) to yield **1-128** (6.19 g, 60%) as a colorless oil that solidified upon standing. Analytical data matched previously reported data for **1-128**:[130] mp 60.2 - 61.7 °C; ^{1}H NMR δ ($CDCl_3$) 7.83 (d, *J*

= 8.4 Hz, 2 H), 7.30 (d, *J* = 8.1 Hz, 2 H), 4.13 (q, *J* = 6.9 Hz, 2 H), 4.01 (t, *J* = 7.2 Hz, 2 H), 2.64 (dt, *J* = 7.5, 2.7 Hz, 2 H), 2.43 (s, 3 H), 2.02 (t, *J* = 2.7 Hz, 1 H), 1.19 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR δ ($CDCl_3$) 152.0, 144.6, 136.4, 129.3, 128.3, 80.1, 70.5, 63.5, 45.2, 21.9, 21.6, 19.9, 13.9.



1-129

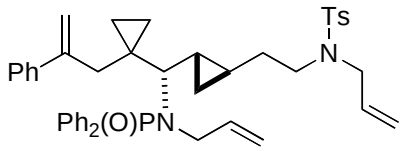
***N*-(3-Phenylprop-2-ynylidene)-*P,P*-diphenylphosphinamide (1-129).** According to a known procedure,[131,132,66,70,8] to a mixture of $Ph_2(O)PNH_2$ (7.25g, 33.4 mmol), NEt_3 (13.3 mL, 100 mmol), and phenylpropargyl aldehyde (4.35 g, 33.4 mmol) in CH_2Cl_2 (260 mL) at 0 °C was added with a solution of $TiCl_4$ (2.58 mL, 23.4 mmol) in CH_2Cl_2 (45.0 mL) using a syringe pump over 1 h. The reaction was stirred for 2 h and diluted with dry Et_2O (500 mL). The slurry was filtered through a 1:1 Celite/florisil mixture and concentrated in vacuo. The residue was purified through a pad of dry, deactivated SiO_2 (80% EtOAc/Hex with 1% NEt_3 v/v) to yield **1-129** (3.80 g, 35%) as a 10:1 mixture of imine and aldehyde. Analytical data matched previously reported datat for **1-129**:[131] ^{1}H NMR ($CDCl_3$) δ (characteristic signals) 9.38 (s, 1 H), 8.71 (d, *J* = 31.2 Hz, 1 H), 7.92 (dd, *J* = 7.8, 1.5 Hz, 2 H), 7.88 (dd *J* = 8.1, 1.5 Hz, 2 H), 7.58 (dd, *J* = 7.8, 1.2 Hz, 2 H), 7.46-7.33 (m, 9 H).



1-121

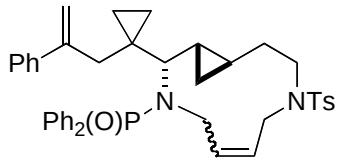
(*S)-[(1*R**,2*S**)-2-(2-{*P,P*-Diphenylphosphinoylamino-[1-(2-phenylallyl) cyclopropyl]methyl}cyclopropyl)ethyl]-(4-methylphenylsulfonyl)carbamic acid ethyl ester**

(**1-121**). According to a literature procedure,[66] a suspension of $Cp_2Zr(H)Cl$ (3.77 g, 14.6 mmol) in CH_2Cl_2 (65.0 mL) at 0 °C was treated with **1-128** (3.74 g, 12.7 mmol) in CH_2Cl_2 (10.0 mL). The slurry was stirred for 15 min during which time the reaction became a pale yellow solution. The reaction mixture was then cooled to –78 °C and $ZnMe_2$ (6.35 mL of a 2.0 M solution in toluene) was added. The resulting solution was warmed to 0 °C over 15 min. A solution of **1-129** (2.09 g, 6.35 mmol) in CH_2Cl_2 (20.0 mL) was added and the reaction mixture was allowed to warm to room temperature and stirred for 4 h. In a separate flask, diethylzinc (3.13 g, 25.4 mmol) was diluted in CH_2Cl_2 (22.0 mL) and treated with freshly distilled DME (2.64 mL, 25.4 mmol) followed by dropwise introduction of CH_2I_2 (4.09 mL, 50.8 mmol) at –20 °C. The mixture was stirred for 15 min and cannulated into the reaction flask at –20 °C. The solution was allowed to warm to room temperature while stirring overnight. The reaction mixture was quenched with sat. NH_4Cl (aq.), filtered through a 1:1 mixture of Celite/Florisil, extracted with EtOAc (3 x 20 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The crude product was purified by chromatography on deactivated SiO_2 (20% EtOAc/Hex, then 50% EtOAc/Hex then 80% EtOAc/Hex containing 1% v/v NEt_3) to yield **1-121** (2.64 g, 60%) as a colorless foam: ^{1}H NMR δ ($CDCl_3$) 7.93-7.75 (m, 8 H), 7.53-7.44 (m, 4 H), 7.40-7.24 (m, 7 H), 5.28 (d, *J* = 1.2 Hz, 1 H), 5.13 (s, 1 H), 4.09 (q, *J* = 6.9 Hz, 2 H), 3.83 (t, *J* = 7.8 Hz, 2 H), 3.13 (app t, *J* = 6.6 Hz, 2 H), 2.54 (d, *J* = 14.7 Hz, 1 H), 2.43 (s, 3 H), 2.25 (q, *J* = 9 Hz, 1 H), 1.85 (m, 1 H), 1.34-1.24 (m, 2 H), 1.15 (t, *J* = 7.2 Hz, 3 H), 0.80-0.70 (m, 1 H), 0.49-0.33 (m, 8 H); ^{13}C NMR δ ($CDCl_3$) 152.04, 145.70, 145.11, 144.15, 141.63, 136.64, 134.33, 133.56, 132.62, 132.12, 131.99, 131.83, 131.71, 131.49, 129.05, 128.31, 128.24, 128.14, 128.08, 128.03, 127.22, 126.02, 115.06, 62.94, 61.03, 46.85, 37.79, 33.96, 24.19, 24.11, 22.69, 22.64, 21.40, 15.10, 13.81, 10.93, 10.50, 10.03.



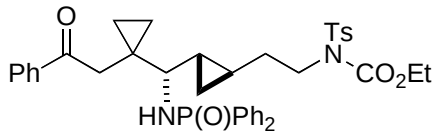
1-122

***N*-Allyl-[2-((1*R**,2*S**)-2-{((*S**)-*N*-allyl-*N*-diphenylphosphinoylamino)-[1-(2-phenylallyl)cyclopropyl]methyl}cyclopropyl)ethyl]-4-methylphenylsulfonamide (1-122)**. Following a literature procedure,[70] a solution of **1-121** (43.0 mg, 0.062 mmol) in THF (800□L) was treated with NaH (10.0 mg, 0.42 mmol) followed by HMPA (53.0□L, 0.304 mmol) and allyl iodide (60.0□L, 0.657 mmol). The reaction mixture was heated to 70 °C for 2 h, then cooled to room temperature and quenched with sat. aq. $NaHCO_3$. The aqueous phase was extracted with EtOAc (3 x 5 mL), dried ($MgSO_4$), filtered, and concentrated. The resulting residue was purified by chromatography on deactivated SiO_2 (50% EtOAc/Hex with 1% v/v NEt_3) to yield **1-122** (28.7 mg, 68%) as a pale yellow foam: IR (neat) 3058, 2990, 2921, 2359, 2342, 2219, 1438, 1341, 1198, 1156, 1108, 1046, 912, 724 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.85-7.78 (m, 4 H), 7.70 (d, *J* = 8.1 Hz, 2 H), 7.48-7.37 (m, 7 H), 7.32-7.2 (m, 6 H), 5.95-5.82 (m, 1 H), 5.63 (dddd, *J* = 16.5, 10.2, 6.3, 6.3 Hz, 1 H), 5.33-5.12 (m, 3 H), 4.99-4.82 (m, 3 H), 3.99-3.71 (m, 4 H), 3.19-3.02 (m, 3 H), 2.46 (d, *J* = 12.6 Hz, 1 H), 2.42 (s, 3 H), 2.08-2.04 (m, 1 H), 1.64 (s, 2 H), 0.97-0.59 (m, 5 H), 0.39-0.17 (m, 4 H); ^{13}C NMR δ 144.91, 143.08, 142.04, 138.83, 138.68, 137.11, 133.34, 132.73, 132.61, 132.49, 131.57, 129.63, 128.39, 128.27, 128.22, 127.29, 127.21, 125.97, 118.71, 115.59, 114.48, 63.14, 51.01, 47.13, 46.97, 39.03, 33.14, 21.49, 19.75, 19.48, 14.73, 9.45, 6.97; MS (ESI) *m*/*z* (rel. intensity) 727 $[M+Na]^+$ (100), 705 $[M+H]^+$ (55), 413 (23), 212 (14).



1-124

(2*S,11*S**,12*R**)-3-(*N*-Diphenylphosphinoyl)-2-[1-(2-phenylallyl)cyclopropyl]-8-(4-methylphenylsulfonyl)-3,8-diazabicyclo[9.1.0]dodec-5-ene (1-124)**. A flask containing **1-122** (185 mg, 0.263 mmol) and **1-123** (22.3 mg, 0.0263 mmol) in dry CH_2Cl_2 (50.0 mL) was purged under aspirator vacuum and filled with ethylene gas (5 times), then heated to reflux under a balloon of ethylene for 4 h. The reaction mixture was cooled to room temperature, filtered through Celite, concentrated, and purified by chromatography on deactivated SiO_2 (50% EtOAc/Hex containing 1% v/v NEt_3) to yield **1-124** (172 mg, 96%) as a colorless foam: IR (neat) 3055, 2925, 2855, 1732, 1438, 1335, 1265, 1184, 1104, 738 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.08 (t, *J* = 8.1 Hz, 2 H), 7.89 (t, *J* = 7.8 Hz, 2 H), 7.77 (d, *J* = 7.8 Hz, 2 H), 7.59-7.40 (m, 13 H) 5.99 (bm, 1 H), 5.69 (bm, 1 H), 5.45 (bs, 1 H), 5.02 (bs, 1 H), 4.20 (bm, 1 H), 3.85 (bm, 1 H), 3.43 (bm, 1 H), 3.26 (bd, *J* = 14.7 Hz, 1 H), 3.03 (bd, *J* = 14.4 Hz, 1 H), 2.86 (bd, *J* = 14.4 Hz, 1 H), 2.62 (bt, *J* = 12 Hz, 1 H), 2.54 (s, 3 H), 1.38 (bs, 1 H), 1.09 (bt, *J* = 11.4 Hz, 1 H), 0.93 (bs, 2 H), 0.73 (bm, 1 H), 0.56 (bm, 1 H), 0.43 (bs, 1 H), 0.30-0.23 (bm, 2 H); ^{13}C NMR ($CDCl_3$) δ 143.75, 143.08, 141.25, 136.51, 134.92, 133.03, 132.92, 132.67, 132.55, 131.68, 131.29, 129.52, 128.63, 128.47, 128.25, 128.08, 127.35, 127.27, 126.89, 125.54, 114.61, 65.25, 52.00, 45.96, 44.75, 38.48, 36.60, 21.68, 21.38, 20.94, 16.35, 15.78, 9.63, 6.62; MS (ESI) *m*/*z* (rel. intensity) 699 ($[M+Na]^+$, 100) 677 ($[M+H]^+$, 37); HRMS (ESI) *m*/*z* calculated for $C_{41}H_{45}N_2O_3SPNa$ $[M+Na]^+$ 699.2786, found 699.2798.

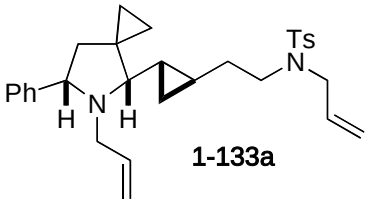


1-131

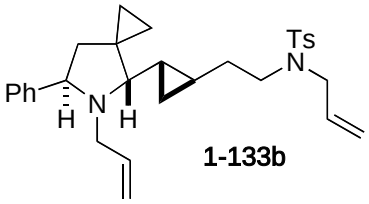
Ethyl [2-(2-(1*R, 2*S**)-{(*S**)-(*N*-dipenylphosphinoylamino)-[1-(2-oxo-2-phenylethyl)-cyclopropyl]methyl}cyclopropyl)ethyl]-*N*-(4-methylphenylsulfonyl)carbamate (1-131).** To a stirred solution of **1-121** (2.71 g, 3.90 mmol) in acetone (36 mL) and H_2O (9 mL) was added *N*-methylmorpholine *N*-oxide (564 mg, 4.66 mmol) followed by OsO_4 (590 µL, 0.194 mmol, 0.33 M solution in toluene). After 4 h additional OsO_4 was added (260 µL, 0.095 mmol) and the reaction mixture was allowed to stir overnight at room temperature. The black slurry was quenched by addition of H_2O (20 mL) and sat. aq. $Na_2S_2O_3$ solution (20 mL). The aqueous phase was extracted with EtOAc (3 x 20 mL), and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated to provide a brown foam.

The mixture of diastereomeric diols was taken up in CH_2Cl_2 (75 mL) and treated with K_2CO_3 (1.07 g, 7.78 mmol) followed by $Pb(OAc)_4$ (2.15 g, 4.67 mmol) at room temperature. After 30 min the reaction volume was reduced to one-third under reduced pressure and the resulting slurry was diluted with sat. aq. NH_4Cl, brine, and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered, concentrated, and purified by chromatography on SiO_2 (50% EtOAc/Hex, then 60% EtOAc/Hex) to afford **1-131** (2.05 g, 2.93 mmol, 75%) as a colorless, lustrous foam: IR (neat) 3296, 3058, 2993, 2928, 2359, 2340, 1729, 1675, 1652, 1596, 1448, 1370, 1266, 1171, 1088, 1019, 977, 813 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.19 (d, *J* = 7.2 Hz, 2 H), 7.89-7.84 (m, 4 H), 7.77 (d, *J* = 8.3 Hz, 2 H), 7.57 (t, *J* = 7.4 Hz, 1 H), 7.48-7.39 (m, 8 H), 7.28 (d, *J* = 8.3 Hz, 2 H), 4.65 (t, *J* = 8.8 Hz, 1 H), 4.10-4.05 (m, 2 H), 3.95 (d, *J* = 17.7 Hz, 1 H), 3.76 (t, *J* = 7.9 Hz, 2 H), 2.69 (d, *J* = 17.8 Hz,

1 H), 2.42 (s, 3 H), 2.22 (q, *J* = 9.0 Hz, 1 H), 1.86-1.81 (m, 1 H), 1.19-1.14 (m, 1 H), 1.14 (t, *J* = 7.2 Hz, 3 H), 0.94-0.91 (m, 1 H), 0.66 (dddd, *J* = 5.1, 5.1, 8.8, 8.8, 1 H), 0.57-0.43 (m, 4 H) 0.38-0.33 (m, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 201.1, 152.4, 144.5, 137.3, 137.0, 134.4, 134.2, 133.6, 133.41, 133.37, 132.35, 132.28, 132.1, 132.0, 131.7, 129.4, 128.8, 128.6, 128.5, 128.41, 128.40, 128.3, 63.3, 61.3, 47.1, 44.5, 34.2, 23.30, 23.27, 22.42, 22.38, 21.8, 15.7, 14.1, 13.8, 11.2, 10.4; HRMS (ESI) *m/z* calculated for $C_{39}H_{43}N_2O_6PSNa$ $[M+Na]^+$ 721.2477, found 721.2473.



1-133a



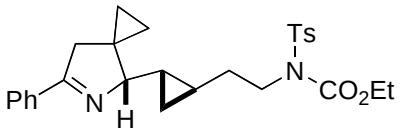
1-133b

***N*-Allyl-*N*-{2-[2-(1*R**,2*S**)-((6*S**,4*S**)-5-allyl-6-phenyl-5-azaspiro[2.4]hept-4-yl)cyclopropyl]ethyl}-4-methylbenzenesulfonamide (1-133a) and *N*-Allyl-*N*-{2-[2-(1*R**,2*S**)-((6*R**,4*S**)-5-allyl-6-phenyl-5-azaspiro[2.4]hept-4-yl)cyclopropyl]ethyl}-4-methylbenzenesulfonamide (1-133b)**. To a solution of **1-131** (2.05 g, 2.93 mmol) in MeOH (5 mL) was added a solution of HCl in MeOH (acetyl chloride (1.34 mL, 18.5 mmol) added dropwise to MeOH (5 mL) at 0 ºC, stirred for 30 min) and this mixture was allowed to stir overnight at room temperature. The volatiles were removed under reduced pressure to afford the deprotected primary amine as a brown foam.

The crude amine was taken up in MeOH (17 mL) and treated with $NaBH_3CN$ (970 mg, 14.7 mmol), and the orange slurry was stirred for 5 h at room temperature. The volatiles were removed under reduced pressure and the orange residue was partitioned between toluene (57 mL) and sat. aq. NaOH (57 mL), and Bu_4NHSO_4 (862 mg, 3.52 mmol) was added followed by

allyl bromide (2.57 mL, 29.3 mmol). This biphasic mixture was stirred vigorously for 12 h at which point additional PhMe (25 mL), sat. aq. NaOH (25 mL), and allyl bromide (2.57 mL, 29.3 mmol) were added. The emulsion was stirred for another 24 h and the mixture was diluted with EtOAc (50 mL) and H_2O (50 mL), and the aqueous phase was extracted with EtOAc (3 x 30 mL). The combine organic layers were dried ($MgSO_4$), filtered, concentrated, and purified by chromatography on SiO_2 (10% EtOAc/Hex) to afford **1-133a** (537 mg, 1.09 mmol, 37%) and **1-133b** (496 mg, 1.01 mmol, 34%) as yellow syrups, (1.1:1 ratio of diastereomers): **1-133a**: IR (neat) 3068, 2994, 2924, 2858, 1726, 1599, 1454, 1344, 1160, 1091, 923, 815 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.2 Hz, 2 H), 7.38 (d, *J* = 7.9 Hz, 2 H), 7.30 (t, *J* = 7.4 Hz, 2 H), 7.27 (d, *J* = 7.9 Hz, 2 H), 7.23 (dt, *J* = 1.3, 7.3 Hz, 1 H), 5.80 (dddd, *J* = 6.6, 6.6, 10.2, 16.9 Hz, 1 H), 5.65 (dddd, *J* = 6.4, 6.4, 10.1, 16.6 Hz, 1 H), 5.17 (dd, *J* = 1.4, 17.1 Hz, 1 H), 5.13 (dd, *J* = 1.2, 10.1 Hz, 1 H), 5.03 (dd, *J* = 1.9, 10.2 Hz, 1 H), 4.96 (dd, *J* = 1.7, 17.1 Hz, 1 H), 3.88 (dd, *J* = 6.8, 9.3 Hz, 1 H), 3.80, 3.77 (dd_{AB}, *J* = 6.4, 15.4 Hz, 2H), 3.33 (dd, *J* = 6.5, 15.1 Hz, 1 H), 3.26 (ddd, *J* = 5.7, 10.5, 13.9 Hz, 1 H), 3.18-3.13 (m, 2 H), 2.40 (s, 3 H), 2.06 (d, *J* = 8.2 Hz, 1 H), 1.89 (dd, *J* = 9.4, 12.2 Hz, 1 H), 1.79 (dd, *J* = 6.8, 12.2 Hz, 1 H), 1.71 (dddd, J = 5.7, 5.7, 10.9, 13.5 Hz, 1 H), 1.29-1.22 (m, 1 H), 0.97 (ddd, *J* = 4.3, 5.5, 9.6 Hz, 1 H), 0.51-0.46 (m, 3 H), 0.41 (ddd, *J* = 4.0, 6.1, 9.9 Hz, 1 H), 0.36 (ddd, *J* = 4.2, 6.1, 9.6 Hz, 1 H), 0.15 (ddddd, *J* = 4.8, 4.8, 7.9, 10.4 14.2 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.2, 143.2, 137.2, 134.3, 133.5, 129.8, 128.3, 127.7, 127.2, 126.9, 118.8, 117.2, 69.7, 65.7, 53.1, 50.9, 47.4, 45.7, 32.9, 25.2, 21.6, 21.5, 13.4, 12.9, 8.9, 7.0; HRMS (ESI) *m/z* calculated for $C_{30}H_{39}N_2O_2S$ $[M+H]^+$ 491.2732, found 491.2725. **1-133b**: IR (neat) 2065, 2992, 2923, 2866, 1641, 1598, 1493, 1455, 1343, 1159, 1091, 921, 814, 741 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.3 Hz, 2 H), 7.37 (d, *J* = 7.2 Hz, 2 H), 7.31-7.26 (m, 4 H), 7.22 (t, *J* = 7.2 Hz, 1 H), 5.76 (dddd, *J* = 4.3, 7.3, 10.4, 11.5

Hz, 1 H), 5.63 (dddd, *J* = 6.4, 6.4, 10.1, 16.6 Hz, 1 H), 5.15 (dd, *J* = 1.3, 17.1 Hz, 1 H), 5.12 (dd, *J* = 1.3, 10.1 Hz, 1 H), 5.07 (dd, *J* = 1.1, 17.3 Hz, 1 H), 5.00 (dd, *J* = 1.0, 10.3 Hz, 1 H), 4.12 (dd, *J* = 4.4, 8.2 Hz, 1 H), 3.80, 3.77 (dd_{AB}, *J* = 6.4, 15.4 Hz, 2 H), 3.25 (dddd, *J* = 2.1, 2.1, 4.2, 14.9 Hz, 1 H), 3.22-3.12 (m, 2 H), 3.03 (dd, *J* = 7.3, 14.9 Hz, 1 H), 2.45 (dd, *J* = 8.3, 12.7 Hz, 1 H), 2.41 (s, 3 H), 2.09 (d, *J* = 9.8 Hz, 1 H), 1.84-1.89 (m, 1 H), 1.61 (dd, *J* = 4.4, 12.7 Hz, 1 H), 1.11-1.02 (m, 2 H), 0.60-0.56 (m, 2 H), 0.52-0.47 (m, 1 H), 0.45-0.38 (m, 2 H), 0.20 (ddd, *J* = 4.9, 4.9, 8.4 Hz, 1 H), 0.07 (ddd, *J* = 4.9, 4.9, 8.9 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 143.9, 143.2, 137.3, 137.1, 133.4, 129.7, 128.2, 128.1, 127.2, 126.9, 118.8, 115.5, 70.3, 65.5, 50.9, 50.8, 47.2, 43.6, 32.6, 25.6, 21.6, 18.7, 14.7, 14.2, 9.4, 7.4; HRMS (ESI) *m/z* calculated for $C_{30}H_{39}N_2O_2S$ $[M+H]^+$ 491.2732, found 491.2722.

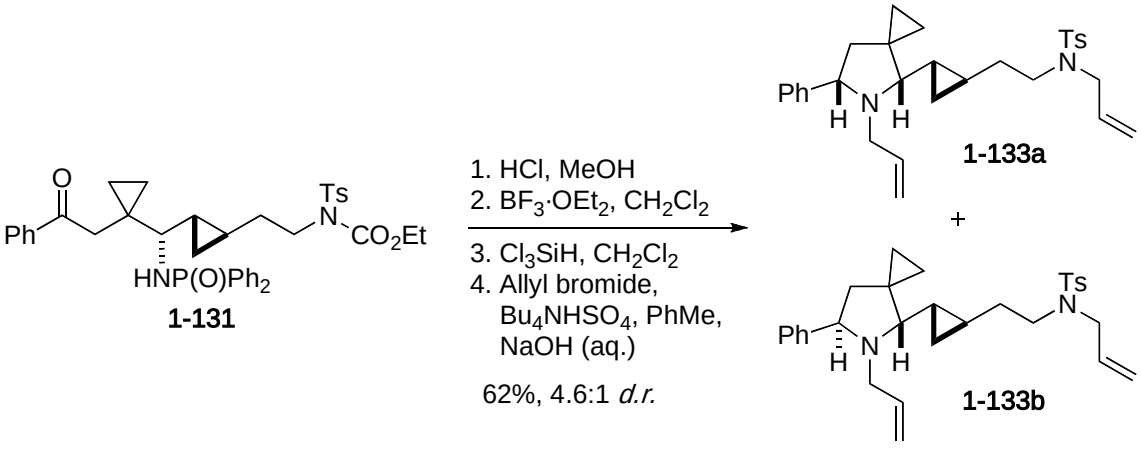


1-135

Ethyl {2-[(1*R,2*S**)-2-((1*S**)-6-phenyl-5-azaspiro[2.4]hept-5-en-4-yl)cyclopropyl]-ethyl}-(*N*-4-methylphenylsulfonyl)carbamate (1-135)**. To a stirred solution of **1-131** (724 mg, 1.04 mmol) in MeOH (1 mL) was added HCl in MeOH (acetyl chloride (800 µL, 11.3 mmol) added dropwise to MeOH (5 mL) at 0 ºC, stirred for 30 min) and the reaction mixture was stirred overnight at room temperature and the volatiles were removed under reduced pressure to give **1-134** as a brown foam.

The crude amine was taken up in CH_2Cl_2 (12 mL), cooled to –78 ºC and treated with $BF_3{\cdot}OEt_2$ (156 µL, 1.24 mmol). The reaction mixture was allowed to warm to room temperature and was stirred for 3 h. The volatiles were removed under reduced pressure and the resulting residue was purified by chromatography on SiO_2 (20% EtOAc/Hex containing 1% v/v NEt_3) to

afford **1-135** (417 mg, 0.869 mmol, 84%) as a colorless foam: IR (neat) 3067, 2992, 2925, 1732, 1448, 1370, 1266, 1169, 1089, 761, 739, 674 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.82-7.78 (m, 4 H), 7.39-7.37 (m, 3 H), 7.25 (d, *J* = 8.5 Hz, 2 H), 4.08 (q, *J* = 7.1 Hz, 2 H), 3.94 (app t, *J* = 7.5 Hz, 2 H), 3.40 (d, *J* = 8.2 Hz, 1 H), 3.05, 2.98 (d_{AB}, *J* = 18.9 Hz, 2 H), 2.38 (s, 3 H), 1.86-1.74 (m, 1 H), 1.68-1.55 (m, 1 H), 1.13 (t, *J* = 7.1 Hz, 3 H), 1.08-1.02 (m, 1 H), 0.82-0.66 (m, 2 H), 0.61-0.46 (m, 4 H), 0.38 (ddd, *J* = 4.7, 4.7, 9.2 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 152.3, 144.3, 136.8, 134.8, 130.3, 129.2, 128.3, 128.2, 127.5, 79.9, 63.0, 47.1, 45.5, 34.3, 24.0, 21.5, 21.1, 14.0, 12.7, 12.7, 9.8, 9.5; HRMS (EI+) *m/z* calculated for $C_{27}H_{32}N_2O_4S$ ($M^{\bullet+}$) 480.2082, found 480.2079.



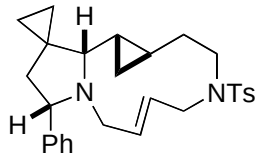
Cyclodehydration/Reduction procedure: To a stirred solution of **1-131** (3.1 g, 4.41 mmol) in MeOH (20 mL) was added a solution of HCl in MeOH (acetyl chloride (4.25 mL, 59.8 mmol) added to MeOH (25 mL) at 0 °C, stirred for 30 min). The reaction mixture was allowed to stir overnight at which point the volatiles were removed under reduced pressure.

The crude amine **1-134** was taken up in dry CH_2Cl_2 (55 mL), cooled to –78 °C, and treated with $BF_3{\cdot}OEt_2$ (669 µL, 5.33 mmol). The reaction mixture was allowed to warm to room

temperature and was stirred for 3 h at which point the volatiles were removed under reduced pressure.

To a solution of crude **1-135** in CH_2Cl_2 (25 mL) was added Cl_3SiH (25 mL) and the reaction was allowed to stir at room temperature for 72 h. Upon consumption of the starting material by MS analysis, the reaction was carefully quenched at 0 °C by dropwise addition of sat. aq. $NaHCO_3$ (100 mL). The slurry was extracted with EtOAc (3 x 50 mL) and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduce pressure.

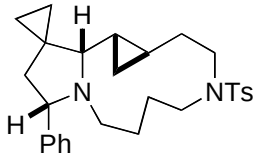
The crude residue of **1-132a** and **1-132b** was partitioned between PhMe (88 mL) and sat. aq. NaOH (88 mL) and treated with Bu_4NHSO_4 (1.50 g, 4.43 mmol) and allyl bromide (3.80 mL, 44.3 mmol), and the resulting gemulsion was stirred vigorously for 24 h. The aqueous phase was extracted with EtOAc (3 x 100 mL) and the combined organic layers were dried ($MgSO_4$), filtered, concentrated, and the crude residue was purified by chromatography on SiO_2 (10% EtOAc/Hex) to afford **1-133a** (1.10 g, 2.24 mmol, 51%) followed by **1-133b** (225 mg, 0.459 mmol, 11%). Analytical data of material obtained by this method was identical to the aforementioned procedure.



1-136

{1-[(13*S)-13-Phenyl-7-(4-methylphenylsulfonyl)-(1*S**,2*S**,4*R**)-7,12-diazatetracyclo [$10^{9.1}.5^{4.2}$](15-spiro[2.4]heptane)]cyclopropyl}hept-9-ene (1-136)**. To a solution of **1-133a** (380 mg, 0.775 mmol) in dry CH_2Cl_2 (165 mL) was added **1-123** (69.2 mg, 0.078 mmol). The reaction vessel was purged under aspirator vacuum and refilled with ethylene gas (5 times) and

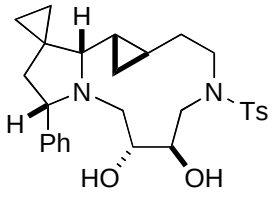
kept under a balloon of ethylene while the reaction was heated to reflux for 4 h. The brown solution was cooled to room temperature and filtered through a pad of Celite/florisil (1:1 v/v) and concentrated. The crude material was purified by chromatography on SiO_2 (10% EtOAc/Hex) to afford **1-136** (320 mg, 0.492 mmol, 90%) as a colorless solid: m.p. 155.5-160.3 (decomp.); IR (neat) 3060, 2991, 2919, 2855, 2359, 1599, 1492, 1453, 1341, 1161, 1091, 1006, 968, 903, 731 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.1 Hz, 2 H), 7.41 (d, *J* = 7.2 Hz, 2 H), 7.32-7.26 (m, 4 H), 7.21 (t, *J* = 7.2 Hz, 1 H), 5.61-5.53 (m, 2 H), 4.09 (d, *J* = 11.0 Hz, 1 H), 3.73 (dd, *J* = 5.7, 10.7 Hz, 1 H), 3.36 (d, *J* = 13.7 Hz, 1 H), 3.25 (d, *J* = 14.6 Hz, 1 H), 2.84-2.79 (m, 2 H), 2.72-2.68 (m, 1 H), 2.43 (s, 3 H), 2.45-2.40 (m, 1 H), 2.00 (app t, *J* = 11.4 Hz, 1 H), 1.74 (d, *J* = 9.5 Hz, 1 H), 1.57 (dd, *J* = 5.7, 12.0 Hz, 1 H), 1.11 (ddd, *J* = 5.0, 5.0, 9.7 Hz, 1 H), 0.75-0.67 (m, 2 H), 0.56-0.53 (m, 2 H), 0.42-0.38 (m, 1 H), 0.34-0.30 (m, 1 H), 0.20 (ddd, *J* = 4.3, 4.3, 8.6 H, 1 H), 0.14 (ddd, *J* = 4.7, 4.7, 8.3 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.2, 143.3, 138.7, 135.1, 129.7, 128.4, 127.5, 127.1, 124.7, 77.9, 70.0, 57.6, 52.3, 47.6, 46.5, 36.9, 26.3, 23.8, 21.6, 16.6, 15.2, 10.6, 8.8; HRMS (EI+) *m/z* calculated for $C_{28}H_{34}N_2O_2S$ ($M^{\bullet+}$) 462.2341, found 462.2344.



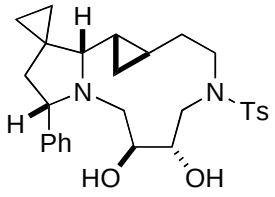
1-137

(13*S)-13-Phenyl-7-(4-methylphenylsulfonyl)-(1*R**,2*S**,4*R**)-7,12-diazatetracyclo [10.5$^{4.2}$.0.0$^{0.0}$](2-spiro[2.4]heptane)decane (1-137)**. To a vigorously stirred solution of **1-136** (40.0 mg, 0.087 mmol) in THF (2 mL) was added $Pd(OH)_2$ (12.2 mg, 0.017 mmol). The system was evacuated and filled with H_2 (3 times) and stirred under a balloon atmosphere for 10 h. The

reaction mixture was filtered through Celite, concentrated under reduced pressure, and the residue was purified by chromatography on deactivated SiO_2 (15% EtOAc/Hex with 1% v/v NEt_3) to yield **1-137** (24.8 mg, 62%) contaminated with an unidentifiable byproduct as an impure colorless oil that solidified upon standing: IR (neat) 2922, 2854, 2359, 2342, 1733, 1456, 1342, 1162, 1111, 711 cm^{-1}; ^1H NMR (C_6D_6) δ (characteristic signals) 7.65 (d, *J* = 8.1 Hz, 2 H), 7.46, (d, *J* = 8.4 Hz, 2 H), 7.26 (t, *J* = 7.5 Hz, 3 H), 6.81 (d, *J* = 8.1 Hz, 2 H), 3.71 (dd, *J* = 11.7, 7.2 Hz, 1 H), 3.50 (dt, *J* = 15.3, 2.7 Hz, 1 H), 3.04 (tt, *J* = 12.9, 4.5 Hz, 1 H), 2.80-2.57 (m, 3 H), 2.45 (dt, *J* = 11.7, 3.6 Hz, 1 H), 2.29-2.15 (m, 1 H), 2.12-2.05 (m, 2 H), 1.92 (s, 3 H), 1.86-1.81 (m, 1 H), 1.38-1.30 (m, 1 H), 1.21-1.10 (m, 2 H), 0.94-0.82 (m, 2 H), 0.80-0.72 (m, 2 H), 0.67-0.58 (m, 1 H), 0.45 (t, *J* = 10.8 Hz, 1 H), 0.33-0.28 (m, 2 H), 0.19-0.08 (m, 2 H); ^{13}C NMR (C_6D_6) (characteristic signals) δ 145.8, 142.5, 134.9, 129.4, 128.1, 127.8, 127.1, 75.1, 71.1, 54.9, 50.9, 46.8, 46.0, 34.8, 27.4, 26.8, 25.0, 22.9, 21.0, 14.7, 14.5, 10.2, 6.4; MS (ESI) *m*/*z* (rel. inensity) 465 $[M+H]^+$.



1-138a

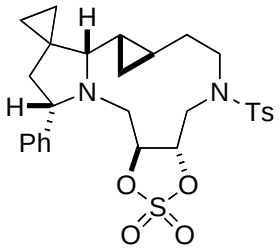


1-138b

(9*R, 10*R**)-{1-[(13*S**)-13-Phenyl-7-(4-methylphenylsulfonyl)-(1*S**,2*S**,4*R**)-7,12-diazatetracyclo[$10^{9.1}.5^{4.2}$](15-spiro[2.4]heptane)]cyclopropyl}heptane-9,10-diol (1-138a) and (9*S**, 10*S**)-{1-[(13*S**)-13-Phenyl-7-(4-methylphenylsulfonyl)-(1*S**,2*S**,4*R**)-7,12-diazatetracyclo[$10^{9.1}.5^{4.2}$](15-spiro[2.4]heptane)]cyclopropyl}heptane-9,10-diol (1-138b).** To a solution of **1-136** (36 mg, 0.077mmol) in THF (1.6 mL) and H_2O (0.4 mL) at room temperature was added NMO (12.6 mg, 0.093 mmol) followed by a solution of OsO_4 in toluene (23.6 µL of

0.33 M, 0.008 mmol). The pale yellow reaction mixture was stirred at room temperature for 16 h, and the reaction mixture was quenched by addition of sat. aq. NH_4Cl (2 mL), and sat. aq. $Na_2S_2O_3$ (2 mL). The mixture was stirred for 30 min, and the aqueous phase was extracted with EtOAc (3 x 10mL) and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. MPLC purification of the residue yielded **1-138b** (9.2 mg, 0.019 mmol, 24%) followed by **1-138a** (20.9 mg, 0.042 mmol, 54%) as beige powders: **1-138a**: IR (neat) 3486, 3026, 2924, 2854, 1727, 1598, 1493, 1354, 1336, 1160, 1118, 1021, 730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.3 Hz, 2 H), 7.42 (d, *J* = 8.4 Hz, 2 H), 7.35-7.30 (m, 4 H), 7.27-7.22 (m, 1 H), 4.18 (bs, 1 H), 3.75-3.67 (m, 2 H), 3.59 (d, *J* = 13.0 Hz, 1 H) 3.38 (bs, 1 H), 3.10 (bd, *J* = 8.2 Hz, 1 H), 2.93 (dd, *J* = 3.2, 13.9 Hz, 1 H), 2.81 (dd, *J* = 4.0, 12.7 Hz, 1 H), 2.80-2.67 (m, 2 H), 2.44 (s, 3 H), 2.16 (dd, *J* = 7.7, 12.7 Hz, 1 H), 2.02 (d, *J* = 9.6 Hz, 1 H), 1.89 (dd, *J* = 8.0, 12.6 Hz, 1 H), 1.30-1.22(m, 2 H), 1.15 (ddd, *J* = 5.0, 5.0, 9.6 Hz, 1 H), 0.77-0.68 (m, 1 H), 0.62-0.46 (m, 3 H), 0.42-0.36 (m, 1 H), 0.28-0.23 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.1, 144.0, 132.5, 130.0, 128.8, 128.0, 127.9, 127.8, 77.4, 74.9, 74.4, 72.4, 66.9, 60.9, 53.1, 52.0, 45.2, 33.6, 24.5, 21.7, 13.8, 11.0, 10.5, 9.0; HRMS (ESI) *m/z* calculated for $C_{28}H_{37}N_2O_4S$ $[M+H]^+$ 497.2474, found 497.2447. **1-138b**: IR (neat) 3436, 3307, 3057, 2953, 2924, 2852, 1729, 1439, 1344, 1162, 1114, 1089, 728 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.2 Hz, 2 H), 7.43 (d, *J* = 8.2 Hz, 2 H), 7.34-7.29 (m, 4 H), 7.25-7.20 (m, 1 H), 4.45-4.37 (bm, 1 H), 4.16 (dd, *J* = 5.9, 10.9 Hz, 1 H), 3.90 (dd, *J* = 5.4, 10.7 Hz, 1 H), 3.55 (dd, *J* = 11.2, 12.9 Hz, 1 H), 3.27 (ddd, *J* = 4.3, 14 Hz, 1 H), 2.89-2.75 (m, 2 H), 2.70-2.59 (m, 2 H), 2.50 (dd, *J* = 4.3, 13.0 Hz, 1 H), 2.43 (s, 3 H), 2.21 (t, *J* = 11.6 Hz, 1 H), 1.69 (d, *J*= 9.6 Hz, 1 H), 1.48-1.39 (m, 2 H), 0.97-0.90 (m, 3 H), 0.85-0.78 (m, 2 H), 0.54-0.44 (m, 3 H), 0.41-0.32 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.4, 143.7, 134.1, 129.9, 128.6, 127.7, 127.6, 127.5, 76.3, 70.7, 67.5, 66.0,

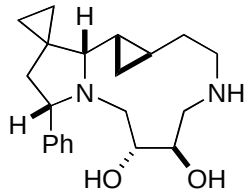
56.0, 51.5, 49.3, 44.9, 34.1, 27.8, 25.6, 21.6, 15.3, 14.5, 11.0, 6.0; HRMS (ESI) *m/z* calculated for $C_{28}H_{37}N_2O_4S$ $[M+H]^+$ 497.2427, found 497.2439.



1-139

{14-[(18*S)-18-Phenyl-7-(4-methylphenylsulfonyl)-(11*R**,13*S**,14*S**)-4,6-dioxa-5-thia-1,9-diazapentacyclo[$10^{9.1,9.3}$.$5^{4.2}$](15-spiro[2.4]heptane)]cyclopropyl}dodecane-5,5-dioxide (1-139)**. To a stirred solution of **1-138b** (9.00 mg, 0.017 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (5.41 uL, 0.036 mmol) in dry THF (1 mL) at room temperature was added sulfuryl diimidazole (3.95 mg, 0.020 mmol) followed by NaH (1.81 mg, 0.045 mmol, 60% disp. in oil). The colorless slurry quickly became pale yellow and the reaction mixture was stirred for 30 min at room temperature. The volatiles were removed under reduced pressure and the reaction mixture was filtered through a plug of SiO_2 followed by chromatography on oven-dried SiO_2 (10% EtOAc/Hex) to afford **1-139** (8.0 mg, 0.014 mmol, 79%) as a colorless film contaminated with grease by NMR spectroscopy: IR (neat) 2953, 2922, 2853, 1734, 1597, 1458, 1378, 1334, 1266, 1209, 1160, 1015, 815, 732, 700 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.3 Hz, 2 H), 7.42 (d, *J* = 7.5 Hz, 2 H), 7.36 (d, *J* = 8.5 Hz, 2 H), 7.33 (t, *J* = 7.5 Hz, 2 H), 7.23 (t, *J* = 7.4 Hz, 1 H), 5.19 (ddd, *J* = 4.6, 4.6, 11.3 Hz, 1 H), 5.11 (ddd, *J* = 3.3, 5.0, 6.4 Hz, 1 H), 3.90 (app t, *J* = 3.9 Hz, 1 H), 3.53 (app t, *J* = 13.1 Hz, 1 H), 3.38 (dd, *J* = 6.4, 14.7 Hz, 1 H), 3.31 (dd, *J* = 3.1, 14.7 Hz, 1 H), 3.12 (dd, *J* = 3.1, 16.9 Hz, 1 H), 3.03-2.95 (m, 2 H), 2.49-2.46 (m, 1 H), 2.45 (s, 3 H), 2.10 (dd, *J* = 7.2, 12.1 Hz, 1 H), 2.06 (d, *J* = 9.7 Hz, 1 H), 1.82 (dd, *J* =

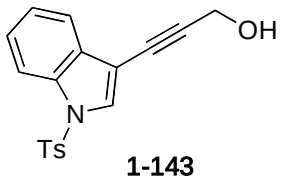
6.1, 12.2 Hz), 1.03-0.99 (m, 1 H), 0.85-0.83 (m, 2 H), 0.81-0.78 (m, 1 H), 0.48 (ddd, *J* = 4.3, 4.3, 6.6, 7.9, 7.9 Hz, 2 H), 0.37-0.30 (m, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.7, 144.6, 132.5, 130.2, 128.5, 128.0, 127.5, 127.0, 84.3, 78.9, 75.8, 71.1, 56.1, 53.1, 53.0, 44.5, 33.5, 32.1, 29.9, 29.8, 29.5, 25.7, 22.9, 21.8, 14.3, 13.9, 9.0, 8.7. HRMS (ESI) *m/z* calculated for $C_{28}H_{35}N_2O_6S_2$ $[M+H]^+$ 559.1937, found 559.1966.



1-140

(9*R, 10*R**)-{1-[(13*S**)-13-Phenyl-(1*S**,2*S**,4*R**)-7,12-diazatetracyclo[$10^{9.1}$.$5^{4.2}$](15-spiro[2.4]heptane)]cyclopropyl}heptane-9,10-diol (1-140).** A solution of **1-138a** (10.0 mg, 0.020 mmol, 1.0 equiv) in dry THF (1 mL) was added to a solution of freshly prepared SmI_2 in THF (1.55 mL, 0.13 M, 0.20 mmol). The reaction mixture was allowed to stir for 15 min and was quenched with H_2O (10 uL, 0.600 mmol) and pyrrolidine (34 uL, 0.402 mmol). The resulting white slurry was diluted with sat. aq. $NaHCO_3$ (1 mL) and extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. The crude mixture was purified by chromatography on SiO_2 (30% acetone/CH_2Cl_2) to afford **1-140** (4.9 mg, 0.014 mmol, 71%) containing an inseparable, unidentifiable impurity, as an orange film: IR (neat) 3345, 2924, 2853, 2453, 1726, 1601, 1454, 1260, 1079, 1038, 1014, 911, 729, 707 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.56 (t, *J* = 7.7 Hz, 2 H), 7.51 (d, *J* = 7.2 Hz, 2 H), 7.34 (t, *J* = 7.4 Hz, 1 H), 4.09 (dd, *J* = 6.3, 10.5 Hz, 1 H), 3.84 (t, *J* = 8.6 Hz, 1 H), 3.55 (t, *J* = 8.8 Hz, 1 H), 3.43 (dd, *J* = 1.6, 13.2 Hz, 1 H), 3.33 (bd, *J* = 10.6 Hz, 1 H), 3.17 (s, 1 H), 3.11-3.06 (bm, 1 H), 3.06 (dd, *J* = 10.1, 13.1 Hz, 1 H), 2.94 (d, *J* = 13.0 Hz, 1 H), 2.59 (dd, *J* = 10.7, 13.1 Hz, 1 H), 2.30-

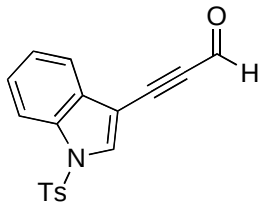
2.27 (m, 1 H), 2.03 (t, *J* = 11.0 Hz, 1 H), 1.97 (d, *J* = 10.7 Hz, 1 H), 1.81 (dd, *J* = 6.2, 13.2 Hz, 1 H), 1.60 (bs, 1 H), 1.49-1.42 (m, 1 H), 1.03-0.98 (m, 1 H), 0.81 (d, *J* = 9.5 Hz, 1 H), 0.70 (ddd, *J* = 5.1, 5.1, 8.8 Hz, 1 H), 0.64-0.54 (m, 5 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 130.2, 128.7, 127.9, 80.3, 73.6, 70.7, 69.5, 53.8, 48.6, 46.8, 44.1, 29.7, 29.3, 28.3, 25.1, 24.7, 14.8, 12.9, 9.2, 5.1; HRMS (EI+) *m/z* calculated for $C_{21}H_{30}N_2O_2$ ($M^{\bullet+}$) 342.2307, found 342.2308.



1-143

3-[1-(4-Methylbenzenesulfonyl)-1*H*-indol-3-yl]prop-2-yn-1-ol (1-143). According to a literature procedure,[133] indole (2.00 g, 17.1 mmol) was dissolved in dry DMF (30 mL) and treated with KOH (2.39 g, 42.7 mmol). After 10 min, I_2 (4.38 g, 17.2 mmol) in dry DMF (30 mL) was introduced gradually. The solution was stirred for 1 h and poured into H_2O (400 mL) containing solid $Na_2S_2O_5$ (800 mg) and aq. NH_4OH (2 mL). The resulting slurry was filtered and the colorless filtrate was dissolved in Et_2O (50 mL), dried ($MgSO_4$), filtered, and concentrated to afford 3-iodoindole. The crude product was immediately dissolved in dry DMF (100 mL), cooled to 0 °C, and NaH (615 mg, 25.6 mmol) was introduced portionwise. After 30 min, *p*-toluenesulfonyl chloride (4.89 g, 25.7 mmol) was added slowly and the reaction was stirred for 2 h and quenched with sat. aq. $NaHCO_3$ (100 mL). The aqueous phase was extracted with Et_2O (3 x 50 mL) and the combined organic layers were washed with H_2O (50 mL), brine (100 mL), dried ($MgSO_4$), filtered, and concentrated to afford **1-142** as a cream-colored solid that was used without further purification.

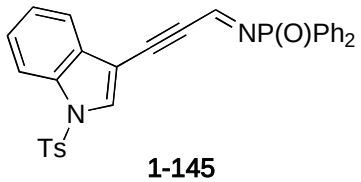
To a stirred solution of **1-142** (6.76 g, 17.1) in DME (50 mL) and H_2O (25 mL) was added K_2CO_3 (5.89 g, 42.7 mmol), CuI (293 mg, 1.54 mmol), PPh_3 (537 mg, 2.05 mmol), and 10% Pd/C (544 mg, 0.512 mmol). The slurry was stirred for 15 min and propargyl alcohol (2.50 mL, 42.9 mmol) was introduced. The reaction mixture was stirred at room temperature for 48 h and was filtered through a pad of Celite, diluted with H_2O (25 mL) and the aqueous phase was extracted with EtOAc (3 x 10 mL). The comnbined organic layers were dried ($MgSO_4$), filtered, concentrated, and the crude product was purified by chromatography on SiO_2 (20% EtOAc/Hex, then 50% EtOAc/Hex) to afford **1-143** (3.08 g, 9.47 mmol, 56% over 3 steps) as an orange crystalline solid: mp 163.2 - 165.1 °C; IR (neat) 3540, 3130, 2915, 2225, 1739, 1593, 1447, 1378, 1362, 1280, 1228, 1174, 1163, 1132, 1102, 1031, 988, 965, 812, 748, 717, 661 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.3 Hz, 1 H), 7.76 (d, *J*= 8.3 Hz, 2 H), 7.74 (s, 1 H), 7.62 (d, *J* = 7.8 Hz, 1 H), 7.35 (t, *J* = 7.8 Hz, 1 H), 7.29 (t, *J* = 7.8 Hz, 1 H), 7.22 (d, *J* = 8.5 Hz, 2 H), 4.55 (s, 2 H), 2.34 (s, 3 H), 1.74 (bs, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.5, 134.9, 134.2, 130.8, 130.2, 129.4, 127.1, 125.6, 123.9, 120.6, 113.7, 104.6, 91.6, 77.0, 51.9, 21.7; HRMS (ESI) *m/z* calculated for $C_{18}H_{15}NO_3SNa$ [M+Na]+ 348.0670, found 348.0684.



1-144

[1-(4-Methylbenzenesulfonyl)-1*H*-indol-3-yl]propynal (1-144). To a vigorously stirred solution of **1-143** (20.0 g, 61.5 mmol) in CH_2Cl_2 (1 L) was added MnO_2 (60.0 g, 586 mmol) in a single portion. The black slurry was stirred overnight and an additional portion of MnO_2 (20.0 g, 195 mmol) was added, and the reaction was complete after 6 h. The slurry was filtered through a

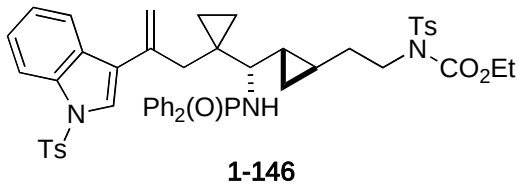
pad of Celite and concentrated to an orange sticky mass. Purification of the crude product by chromatography on SiO_2 (25% EtOAc/Hex) afforded **1-144** (18.8 g, 58.1 mmol, 95%) as an orange-red oil: IR (neat) 2980, 2924, 2193, 1734, 1597, 1447, 1372, 1341, 1240, 1174, 1160, 1089, 1044, 951, 814, 720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.45 (s, 1 H), 8.03 (s, 1 H), 7.98 (d, *J* = 8.1 Hz, 1 H), 7.82 (d, *J* = 8.5 Hz, 2 H), 7.69 (d, *J* = 7.8 Hz, 1 H), 7.41 (dt, *J* = 1.4, 7.3 Hz, 1 H), 7.35 (dt, *J* = 1.2, 7.7 Hz, 1 H), 7.28 (d, *J* = 8.6 Hz, 2 H), 2.37 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.3, 146.2, 134.6, 134.2, 133.6, 130.4, 130.0, 127.3, 126.3, 124.6, 120.7, 113.8, 101.5, 93.5, 87.9, 21.8; HRMS (EI+) *m/z* calculated for $C_{18}H_{13}NO_3S$ ($M^{\bullet+}$) 323.0616, found 323.0604.



1-145

3-[1-(Methylphenylsulfonyl)indol-3-yl]-prop-2-ynyl-*N*-(*P*,*P*-diphenylphosphinoyl) imine (1-145). To a stirred solution of **1-144** (8.00 g, 24.7 mmol) and $Ph_2P(O)NH_2$ (6.66 g, 32.2 mmol) in dry CH_2Cl_2 (450 mL) was added *i*-Pr_2NEt (13.8 mL, 79.1 mmol). The yellow solution was cooled to –78 °C and a solution of $TiCl_4$ (2.73 mL, 24.7 mmol) in dry CH_2Cl_2 (16 mL) was added dropwise over 5 minutes. The stirred reaction mixture was slowly allowed to warm to room temperature over 2 h. The solvent volume of the reaction was reduced to one-quarter volume under reduced pressure, and the resulting brown syrup was passed through a short column (~6") of oven-dried SiO_2 using 70% EtOAc/Hex as the eluent to yield **1-145** (7.68 g, 14.7 mmol, 59%) as an orange foam: IR (neat) 3057, 2188, 1739, 1649, 1591, 1530, 1437, 1374, 1284, 1232, 1173, 1125, 1101, 934, 826, 746, 725, 694, 664 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ

8.76 (d, *J* = 31.5 Hz, 1 H), 8.00 (s, 1 H), 7.97-7.88 (m, 5 H), 7.80 (d, *J* = 8.4 Hz, 2 H), 7.70 (d, *J* = 7.8 Hz, 1 H), 7.54-7.43 (m, 6 H), 7.39-7.30 (m, 2 H), 7.23 (d, *J* = 9.9 Hz, 2 H), 2.33 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.73, 157.66, 145.0, 134.5, 134.4, 132.8, 132.7, 132.19, 132.15, 131.8, 131.7, 131.1, 130.3, 130.0, 128.7, 128.6, 127.1, 126.1, 124.4, 120.7, 113.7, 102.6, 93.3, 93.1, 93.0, 92.8, 21.7; HRMS (ESI) *m/z* calculated for $C_{30}H_{23}N_2O_3SPNa$ [M+Na]+ 545.1065, found 545.1088.



1-146

(*S)-[(1*R**,2*S**)-2-(2-{*P*,*P*-Diphenylphosphinoylamino-[1-(2-{1-(Methylphenyl-sulfonyl)indol-3-yl}allyl)cyclopropyl]methyl}cyclopropyl)ethyl]-(4-methylphenyl-sulfonyl)carbamic acid ethyl ester (1-146)**. To a stirred solution of **1-128** (6.75 g, 22.9 mmol) in dry CH_2Cl_2 (125 mL) was added $Cp_2Zr(H)Cl$ (4.81 g, 23.9 mmol). The resulting slurry cleared after 5 min and the reaction mixture was cooled to –78 °C after 30 min. To the yellow solution was added $ZnMe_2$ (11.4 mL, 22.9 mmol, 2 M solution in toluene) and the reaction mixture was stirred at –78 °C for 30 min, allowed to warm to 0 °C over 10 minutes, and a solution of **1-145** (5.43 g, 10.4 mmol) in dry CH_2Cl_2 (90 mL) was added via cannula. The orange solution was warmed to room temperature and stirred for 3 h before being cooled to –30 °C.

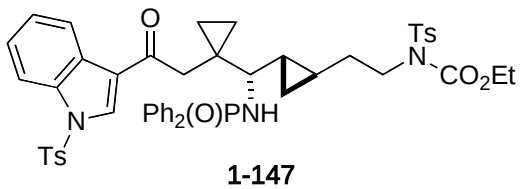
In a separate flask under an inert atmosphere, neat $ZnEt_2$ (5.13 g, 41.6 mmol) was carefully diluted with dry CH_2Cl_2 (30 mL), cooled to –30 °C and treated with freshly distilled DME (4.40 mL, 41.6 mmol). The colorless solution was stirred for 10 min at –30 °C and CH_2I_2

(6.70 mL, 83.13 mmol) was introduced dropwise (CAUTION: EXPLOSION HAZARD).[1] The resulting solution was stirred at –30 °C for 30 min and cannulated into the imine addition pot at –30 °C.

The reaction mixture was allowed to warm to room temperature and was stirred for 16 h, at which point the reaction was carefully quenched with the dropwise addition of sat. aq. NH_4Cl (75 ml), and the mixture was diluted with EtOAc (100 mL). The resulting biphasic slurry was filtered through Celite, and the aqueous phase was extracted with EtOAc (3 x 150 mL). The combined organic layers were dried ($MgSO_4$), filtered through Celite, and concentrated in vacuo. The crude reside was purified by chromatography on SiO_2 (60% followed by 80% EtOAc/Hex) to afford **1-146** (4.30 g, 4.83 mmol, 47%) as a brown foam: IR (neat) 3352, 3206, 3060, 2992, 2926, 1727, 1596, 1438, 1369, 1353, 1265, 1169, 1122, 1089, 735, 699, 670 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.3 Hz, 1 H), 7.86 (d, *J* = 11.8 Hz, 1 H), 7.85 (dd, *J* = 1.4, 11.9 Hz, 1 H), 7.79 (d, *J* = 8.4 Hz, 2 H), 7.77 (m, 1 H), 7.76 (d, *J* = 8.4 Hz, 2 H), 7.63 (d, *J* = 8.0 Hz, 1 H), 7.61 (s, 1 H), 7.50 (t, *J* = 7.6 Hz, 1 H), 7.46-7.43 (m, 2 H), 7.40 (t, *J* = 7.6 Hz, 1 H), 7.32-7.28 (m, 5 H), 7.24-7.16 (m, 4 H), 5.47 (s, 1 H), 5.30 (s, 1 H), 4.13-4.07 (m, 2 H), 3.85 (t, *J* = 7.5 Hz, 2 H), 3.19 (dd, *J* = 7.2, 8.9 Hz, 1 H), 3.07 (d, *J* = 14.9 Hz, 1 H), 2.55 (d, *J* = 14.8 Hz, 1 H), 2.43 (m, 1 H), 2.41 (s, 3 H), 2.30 (s, 3 H), 1.85 (ddd, *J* = 7.1, 7.1, 13.5 Hz, 1 H), 1.34 (dddd, *J* = 8.1, 8.1, 13.2, 16.4 Hz, 1 H), 1.15 (t, *J* = 7.1 Hz, 3 H), 0.76-0.71 (m, 1 H), 0.58-0.53 (m, 1 H), 0.48-0.38 (m, 4 H), 0.35-0.30 (m, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 152.4, 145.2, 144.5, 137.8, 137.0, 135.6, 135.2, 132.5, 132.35, 132.28, 132.14, 132.08, 131.90, 131.88, 131.80, 130.1, 129.4, 129.1, 128.7, 128.62, 128.55, 128.46, 128.42, 127.0, 125.0, 124.3, 123.70, 123.67, 121.1, 116.3,

[1] The preparation of the unstabilized zinc carbenoid reagent has been reported to be explosive on large scale. See Ref 57.

113.9, 63.3, 61.1, 47.2, 39.4, 34.3, 24.28, 24.24, 23.16, 23.1, 21.8, 21.7, 15.5, 14.2, 11.5, 10.9, 10.0. HRMS (ESI) *m/z* calculated for $C_{49}H_{53}N_3O_7PS_2$ $[M+H]^+$ 890.3063, found 890.3073.

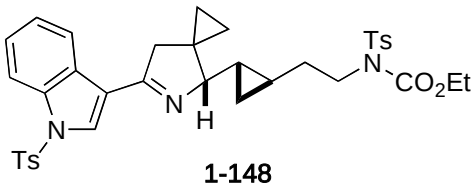


1-147

(*S)-[(1*R**,2*S**)-2-(2-{*P*,*P*-Diphenylphosphinoylamino-[1-(2-{1-(Methylphenyl-sulfonyl)indol-3-yl}-2-oxoethyl)cyclopropyl]methyl}cyclopropyl)ethyl]-(4-methylphenyl-sulfonyl)carbamic acid ethyl ester (1-147).** A solution of **1-146** (2.45 g, 2.75 mmol) and NMO (399 mg, 3.30 mmol) in acetone (27 mL) and H_2O (6.75 mL) was treated with OsO_4 (834 uL, 0.275 mmol, 0.33 M solution in toluene). After 10 h the black slurry was quenched by the addition of H_2O (10 mL) and sat. aq. Na_2SO_3 (10 mL), and diluted with EtOAc (50 mL). The aqueous phase was extracted with EtOAc (3 x 20 mL), and the combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to afford the diastereomeric diols that were used without further purification.

The crude brown foam was taken up in dry CH_2Cl_2 (39 mL) and to this solution was added K_2CO_3 (763 mg, 5.51 mmol) followed by $Pb(OAc)_4$ (1.53 g, 3.30 mmol). After 2 h at room temperature the reaction was concentrated to one-third volume under reduced pressure and the mixture was purified by chromatography on SiO_2 (50% EtOAc/Hex followed by 60% EtOAc/Hex) to afford **2-147** (1.81 g, 2.03 mmol, 74%) as a yellow foam: IR (neat) 3305, 3058, 2993, 2360, 2218, 1730, 1659, 1596, 1596, 1440, 1378, 1286, 1172, 1138, 1019, 980, 910, 813, 729 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.30 (s, 1 H), 8.26 (dd, *J* = 1.2, 7.5 Hz, 1 H), 7.95 (dd, *J* = 1.2, 7.5 Hz, 1 H), 7.89-7.72 (m, 8 H), 7.48-7.29 (m, 11 H), 4.63 (app t, *J* = 8.7 Hz, 1 H), 4.09

(dq, *J* = 1.2, 7.2 Hz, 2 H), 4.07 (1, *J* = 6.9 Hz, 1 H), 3.81-3.75 (m, 3 H), 2.64 (d, *J* = 16.8 Hz, 1 H), 2.42 (s, 3 H), 2.34 (s, 3 H), 2.21 (dd, *J* = 9, 17.7 Hz, 1 H), 1.89-1.78 (m, 1 H), 1.23-1.14 (m, 1 H), 1.13 (t, *J* = 6.9 Hz, 3 H), 0.81 (bd, *J* = 16.2, 1H), 0.81-0.78 (m, 1H), 0.58-0.49 (m, 4 H), 0.47-0.35 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.9, 152.4, 146.1, 144.4, 137.0, 135.04, 134.99, 134.8, 134.6, 133.3, 133.1, 132.5, 132.4, 132.2, 132.1, 131.9, 131.64, 131.61, 131.59, 131.55, 130.4, 129.4, 128.5, 128.41, 128.37, 113.3, 63.3, 61.6, 47.1, 45.4, 34.3, 23.4, 23.3, 22.9, 22.8, 21.76, 21.75, 15.7, 14.2, 13.8, 11.3, 10.5; HRMS (ESI) *m/z* calculated for $C_{48}H_{50}N_3O_8NaPS_2$ [M+Na]+ 914.2675, found 914.2702.

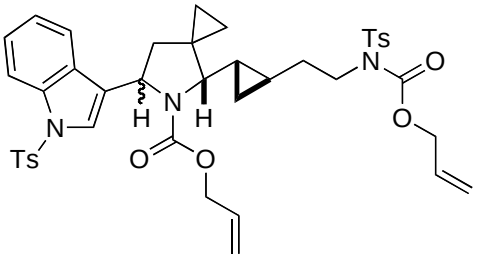


1-148

Ethyl {2-[(1*R,2*S**)-2-((1*S**)-6-[1-(methylphenylsulfonyl)indol-3-yl]-5-azaspiro[2.4] hept-5-en-4-yl)cyclopropyl]ethyl}-(*N*-4-methylphenylsulfonyl)carbamate (1-148)**. To a stirred solution of **1-147** (1.68 g, 1.88 mmol) in MeOH (15 mL) was added a preformed solution of HCl in MeOH (acetyl chloride (3.45 mL) added to MeOH (13 mL) at 0 °C, stirred for 30 min) and the reaction mixture was stirred overnight at room temperature. The volatiles were removed under reduced pressure to afford the crude primary amine.

The dark residue was taken up in dry CH_2Cl_2 (25 mL), cooled to –78 °C, and $BF_3{\cdot}OEt_2$ (286 µL, 2.26 mmol) was added. The reaction mixture was allowed to warm to room temperature and after 2 h the solution was concentrated under reduced pressure to afford **1-148** that was used without further purification. An analytical sample was purified by MPLC (20% EtOAc/Hex) to afford a beige foam: IR (neat) 3127, 3070, 2993, 2926, 2258, 1730, 1615, 1598, 1545, 1446,

1370, 1266, 1221, 1134, 1105, 1089, 1019, 911, 812, 734 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.45 (d, *J* = 7.2 Hz, 1 H), 7.97 (d, *J* = 8.1 Hz, 1 H), 7.78 (d, *J* = 8.4 Hz, 2 H), 7.77 (s, 1 H), 7.73 (d, *J* = 8.4 Hz, 2 H), 7.36 (dt, *J* = 1.2, 7.5 Hz, 1 H), 7.30 (dt, *J* = 1.2, 7.8 Hz, 1 H), 7.22 (d, *J* = 8.7 Hz, 2 H), 7.19 (d, *J* = 8.4 Hz, 2 H), 4.08 (q, *J* = 6.9 Hz, 2 H), 3.95 (t, *J* = 7.8 Hz, 2 H), 3.49 (d, *J* = 7.5 Hz, 1 H), 3.05 (s, 2 H), 2.39 (s, 3 H), 2.32 (s, 3 H), 1.81-1.62 (m, 2 H), 1.13 (t, *J* = 7.2 Hz, 3 H), 1.11-1.03 (m, 1 H), 0.79-0.73 (m, 2 H), 0.65-0.53 (m, 4 H), 0.45-0.38 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 152.4, 145.5, 144.4, 136.9, 135.4, 135.0, 129.3, 128.6, 128.36, 128.30, 127.0, 125.4, 124.4, 123.7, 118.8, 113.3, 80.0, 63.3, 47.4, 46.6, 34.5, 23.5, 21.7, 21.2, 14.1, 12.8, 12.5, 10.0, 9.7; HRMS (ESI) *m/z* calculated for $C_{36}H_{40}N_3O_6S_2$ $[M+H]^+$ 674.2359, found 674.2346.



1-152a, 1-152b

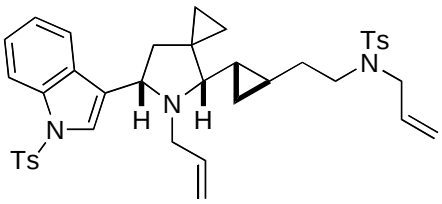
***N*-Allyloxycarbonyl-*N*-{2-[2-(1*R**,2*S**)-((6*S**,4*S**)-5-allyloxycarbonyl-6-[1-(methylphenylsulfonyl)indol-3-yl]-5-azaspiro[2.4]hept-4-yl)cyclopropyl]ethyl}-4-methylbenzenesulfonamide (1-152a) and *N*-Allyloxycarbonyl-*N*-{2-[2-(1*R**,2*S**)-((6*R**,4*S**)-5-allyloxycarbonyl-6-[1-(methylphenylsulfonyl)indol-3-yl]-5-azaspiro[2.4]hept-4-yl)cyclopropyl]ethyl}-4-methylbenzenesulfonamide (1-152b).** To crude **1-148** (1.81 g, 2.67 mmol) dissolved in dry CH_2Cl_2 (15 mL) was added Cl_3SiH (12.0 mL, 119 mmol) and the mixture was stirred at room temperature for 72 h until progress had stalled by MS analysis of quenched, filtered reaction aliquots (ca. 25 μL). The reaction mixture was cooled to 0 °C and

was carefully quenched by the dropwise addition of sat. aq. $NaHCO_3$ (20 mL), and the resulting slurry was extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered, concentrated, and the brown foamy reside was taken up in dry CH_2Cl_2 (15 mL) and treated with Cl_3SiH (12.0 mL, 119 mmol). The reaction mixture was stirred for 24 h and was cooled to 0 °C and was carefully quenched by the dropwise addition of sat. aq. $NaHCO_3$ (20 mL). The resulting slurry was extracted with EtOAc (3 x 20 mL) and the combined organics were dried ($MgSO_4$), filtered, and concentrated to a brown foam that was used without further purification.

The crude pyrrolidines were separated into 4 batches[134] (100, 200, 250 and 278 mg) with the following procedure being representative for each: a solution of crude pyrrolidine (200 mg, 0.37 mmol) in dry CH_2Cl_2 (5 mL) at room temperature was treated with DIBAL-H (813 µL, 0.814 mmol), dropwise. The reaction mixture was stirred for 1 h and an additional amount of DIBAL-H (406 µL, 0.406 mmol) was added. After 30 min the reaction mixture was quenched with H_2O (5 mL) and stirred for 30 min. The aqueous phase was extracted with EtOAc (3 x 5 mL) and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated to a pale yellow foam (164 mg, 0.272 mmol, 92% theoretical) that was used without further purification.

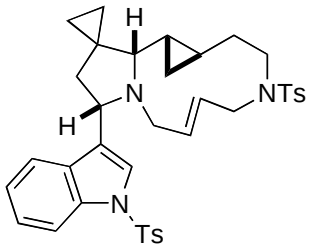
The combined batches of deprotected material (659 mg, 1.09 mmol) were dissolved in a mixture of dry THF (10 mL) and CH_2Cl_2 (1 mL) and to this mixture was added DMAP (13.3 mg, 0.109 mmol) and AllocCl (478 µL, 4.37 mmol) followed by NaH (131 mg, 5.46 mmol). The reaction mixture was stirred at room temperature for 14 h and was quenched with sat. aq. $NaHCO_3$ (10 mL) and the aqueous phase was extracted with EtOAc (3 x 5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to provide a mixture of starting material, mono- and bis-Alloc protected products. This complex mixture was resubjected to the

initial reaction conditions [dissolved in dry THF (10 mL) and CH_2Cl_2 (1 mL) and to this mixture was added DMAP (13.3 mg, 0.109 mmol) and AllocCl (478 µL, 4.37 mmol) followed by NaH (131 mg, 5.46 mmol)] and was stirred for 18 h before being quenched with sat. aq. $NaHCO_3$ (10 mL) and extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated to give a brown foam that was purified by chromatography on SiO_2 (30% EtOAc/Hex) to afford **1-152a, 1-152b** (480 mg, 0.622 mmol, 57% theoretical, 33% from **1-147**) as a yellow sticky foam and an inseparable mixture of diastereomers and rotamers by NMR spectroscopy: ^{1}H NMR (300 MHz, $CDCl_3$) *major peaks* δ 7.98 (d, *J* = 8.6 Hz), 7.82 (t, *J* = 8.2 Hz), 7.73 (d, *J* = 8.3 Hz), 7.54 (d, *J*= 7.9 Hz), 7.45 (s), 7.28 (d, *J* 8.3 Hz), 7.23-7.17 (m), 5.84-5.69 (m), 5.30-5.14 (m), 4.56-4.52 (m), 3.96-3.87 (m), 3.1 (d, *J* = 9.3 Hz), 3.04 (d, *J* = 90.4 Hz), 2.42 (s), 2.40 (s), 2.32 (s), 2.24 (dd, *J* = 7.4, 12.8 Hz), 2.10 (dd, *J* = 8.0, 12.8 Hz), 0.92-0.72 (m), 0.60-0.35 (m), 0.11-0.04 (m); ^{13}C NMR (75 MHz, $CDCl_3$) *major peaks* δ 155.8, 152.1, 144.8, 144.4, 136.8, 135.7, 135.4, 123.0, 131.2, 129.9, 129.8, 129.4, 128.44, 128.38, 126.8, 126.7, 124.7, 123.2, 123.1, 122.5, 122.2, 119.8, 119.0, 114.0, 113.9, 77.4, 68.5, 67.6, 65.9, 65.4, 54.8, 54.1, 47.2, 47.1, 41.6, 34.7, 34.4, 29.8, 26.0, 25.2, 23.1, 22.7, 21.7, 21.6, 15.8, 15.8, 13.6, 12.9, 10.2, 9.2, 7.0, 3.2; HRMS (ESI) *m/z* calculated for $C_{41}H_{45}N_3O_8S_2Na$ [M+Na]+ 794.2546, found 794.2594.



1-153

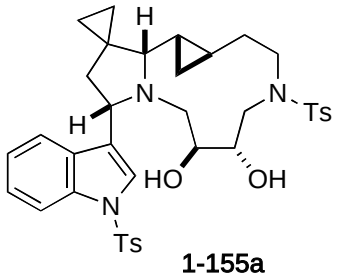
***N*-Allyl-*N*-{2-[2-(1*R**,2*S**)-((6*S**,4*S**)-5-allyl-6-[1-(methylphenylsulfonyl)indol-3-yl]-5-aza-spiro[2.4]hept-4-yl)-cyclopropyl]ethyl}-4-methylbenzenesulfonamide (1-153)**. A solution of **1-152a** and **1-152b** (480 mg, 0.622 mmol) was taken up in dry CH_2Cl_2 (6.5 mL) and partitioned between two microwave vials. To each vial was added $Pd(PPh_3)_4$ (35.6 mg, 0.031 mmol), and each vial was heated in the microwave to 80 °C for 15 min. The reaction mixtures were combined and concentrated under reduced pressure and the residue was purified by MPLC (10% EtOAc/Hex) to afford **1-153a** (190 mg, 0.28 mmol, 45%) and **1-153b** (25.0 mg, 0.037 mmol, 6%) as brown foams (7.5 : 1 *d.r.*, 51% overall): **1-153a**: IR (neat) 3068, 2924, 2856, 1597, 1446, 1368, 1342, 1172, 1119, 1093, 992, 912, 813, 746 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.3 Hz, 1 H), 7.73 (d, *J* = 8.4 Hz, 3 H), 7.67 (d, *J* = 8.2 Hz, 2 H), 7.48 (s, 1 H), 7.28 (t, *J* = 8.3 Hz, 1 H), 7.24 (d, *J* = 8.4 Hz, 2 H), 7.21-7.18 (m, 3 H), 5.75 (dddd, *J* = 6.6, 6.6, 10.3, 16.9 Hz, 1 H), 5.64 (dddd, *J* = 6.4, 6.4, 10.1, 16.7 Hz, 1 H), 5.17 (dd, *J* = 1.3, 17.1 Hz, 1 H), 5.13 (dd, *J* = 1.0, 10.1 Hz, 1 H), 4.92-4.88 (m, 2 H), 4.07 (t, *J* = 7.9 Hz, 1 H), 3.81, 3.77 (dd_{AB}, *J* = 6.3, 15.7 Hz, 2 H), 3.31 (dd, *J* = 6.5, 15.1 Hz, 1 H), 3.26-3.13 (m, 3 H), 2.39 (s, 3 H), 2.33 (s, 3 H), 2.05 (d, *J* = 9.2 Hz, 1 H), 1.97 (dd, *J* = 8.7, 12.2 Hz, 1 H), 1.88 (dd, *J* = 7.4, 12.2 Hz, 1 H), 1.78 (dddd, *J* = 5.7, 10.4, 13.5, 15.7 Hz, 1 H), 1.24-1.19 (m, 1 H), 1.01 (ddd, *J* = 5.2, 5.2, 9.9 Hz, 1 H), 0.49-0.40 (m, 4 H), 0.29 (ddd, *J* = 4.9, 5.7, 10.1 Hz, 1 H), 0.18-0.13 (m, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.8, 143.2, 137.2, 136.0, 135.4, 134.3, 133.5, 130.0, 129.9, 129.8, 127.2, 126.9, 125.7, 124.6, 123.9, 123.0, 120.9, 118.8, 117.1, 113.9, 69.7, 58.1, 53.6, 50.9, 47.4, 42.8, 32.9, 24.9, 21.7, 21.6, 21.0, 13.7, 11.8, 9.4, 6.7; HRMS (EI+) *m/z* calculated for $C_{39}H_{46}N_3O_4S_2$ ($M^{\bullet+}$) 684.2930, found 684.2919.



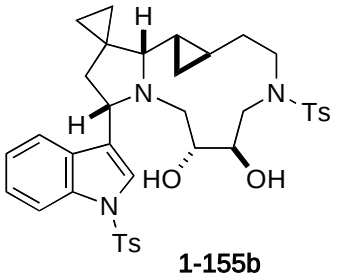
1-154

{1-[(13*S)-13-[1-(Methylphenylsulfonyl)indol-3-yl]-7-(4-methylphenylsulfonyl)-(1*S**,2*S**,4*R**)-7,12-diazatetracyclo[$10^{9.1}.5^{4.2}$](15-spiro[2.4]heptane)]cyclopropyl}hept-9-ene (1-154)**. To a solution of **1-153a** (87.0 mg, 0.127 mmol) in dry CH_2Cl_2 (25 mL) was added **1-123** (10.8 mg, 0.013 mmol, 10 mol%). The reaction vessel was purged under aspirator vacuum and refilled with ethylene gas (5 times) and kept under a balloon of ethylene while the reaction was heated to reflux for 4 h. The brown solution was cooled to room temperature and filtered through a pad of Celite/florisil (1:1 v/v) and concentrated. The crude product was purified by MPLC (20% EtOAc/Hex) to afford **1-154** (77.0 mg, 0.117 mmol, 92%) as a yellow foam: IR (neat) 3056, 2924, 2859, 1597, 1446, 1639, 1341, 1212, 1160, 1120, 1093, 996, 813, 748 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.2 Hz, 1 H), 7.77 (d, *J* = 7.8 Hz, 1 H), 7.71 (d, *J* = 8.7 Hz, 2 H), 7.68 (d, *J* = 9.3 Hz, 2 H), 7.52 (s, 1 H), 7.31 (d, *J* = 8.2 Hz, 2 H), 7.27-7.24 (m, 1 H), 7.19-7.14 (m, 3 H), 5.63-5.44 (m, 2 H), 4.11 (dd, *J* = 4.2, 11.7 Hz, 1 H), 3.95 (dd, *J* = 6.0, 10.4 Hz, 1 H), 3.43 (d, *J* = 14.5 Hz, 1 H), 3.26 (d, *J* = 14.5 Hz, 1 H), 2.82-2.68 (m, 2 H), 2.46-2.40 (m, 1 H), 2.42 (s, 3 H), 2.32 (s, 3 H), 2.15 (t, *J* = 11.5 Hz, 1 H), 1.76 (d, *J* = 9.5 Hz, 1 H), 1.63 (dd, *J* = 6.0, 12.0 Hz, 1 H), 1.13 (ddd, *J* = 5.1, 5.1, 9.7 Hz, 1 H), 0.79-0.66 (m, 2 H), 0.58-0.50 (m, 2 H), 0.43 (ddd, *J* = 6.2, 6.2, 10.0 Hz, 1 H), 0.30 (ddd, *J* = 4.9, 4.9, 10.2 Hz, 1 H), 0.24-0.13 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.9, 143.4, 138.3, 136.0, 135.4, 135.2, 129.96, 129.89, 129.81, 127.5, 126.9, 125.5, 125.0, 124.7, 123.8, 122.9, 120.9, 113.9, 77.7, 62.4, 57.8, 52.3, 47.6,

43.7, 36.9, 26.1, 23.6, 21.64, 21.61, 16.6, 14.9, 10.8, 9.1; HRMS (ESI) *m/z* calculated for $C_{37}H_{42}N_3O_4S_2$ $[M+H]^+$ 656.2617, found 656.2609.



1-155a

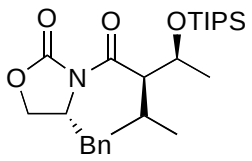


1-155b

(9*R*, 10*R***)-{1-[(13*S***)-13-[1-(Methylphenylsulfonyl)indol-3-yl]-7-(4-methylphenyl sulfonyl)-(1*S***,2*S***,4*R***)-7,12-diazatetracyclo[$10^{9.1}.5^{4.2}$](15-spiro[2.4]heptane)]cyclopropyl} heptane-9,10-diol (1-155a) and (9*S***, 10*S***)-{1-[(13*S***)-13-[1-(Methylphenylsulfonyl)indol-3-yl]-7-(4-methylphenylsulfonyl)-(1*S***,2*S***,4*R***)-7,12-diazatetracyclo[$10^{9.1}.5^{4.2}$](15-spiro[2.4] heptane)]cyclopropyl}heptane-9,10-diol (1-155b).** To a stirred solution of **1-154** (120 mg, 0.183 mmol) in THF (3.6 mL) and H_2O (0.9 mL) was added *N*-methylmorpholine *N*-oxide (29.7 mg, 0.220 mmol) at room temperature and the reaction was treated with a solution of OsO_4 in toluene (55.4 µL of 0.33 M solution, 0.018 mmol). The pale yellow slurry was stirred for 36 h at which point the reaction mixture was quenched with sat. aq. $Na_2S_2O_3$ (5 mL) and stirred for 30 min. The biphasic mixture was diluted with EtOAc (5 mL) and the aqueous phase was extracted with EtOAc (3 x 5 mL). The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and the crude diols were subjected to MPLC purification (40% EtOAc/Hex) to afford **1-155b** (33.0 mg, 0.048 mmol, 26%) and **1-155a** (57.0 mg, 0.082 mmol, 45%) as yellow foams: **1-155a**: IR (neat) 3492, 3060, 2993, 2924, 2862, 1591, 1446, 1365, 1328, 1265, 1155, 1171, 1119, 1090, 1018, 989, 812, 733 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.3 Hz), 7.76 (d, *J* = 8.3 Hz, 2 H), 7.68 (d, *J* = 6.6 Hz, 1 H), 7.65 (d, *J* = 8.2 Hz, 2 H), 7.61 (s, 1 H), 7.34

(d, *J* = 8.2 Hz, 2 H), 7.28 (t, *J* = 7.9 Hz, 1 H), 7.20 (d, *J* = 8.3 Hz, 2 H), 7.18 (t, *J* = 7.9 Hz, 1 H), 3.98 (t, *J* = 7.4 Hz, 1 H), 3.57 (bs, 1 H), 3.53 (bs, 1 H), 3.49-3.35 (bm, 2 H), 3.06 (bs, 1 H), 2.85 (bs, 1 H), 2.82 (dd, *J* = 4.4, 13.1 Hz, 1 H), 2.65 (bs, 1 H), 2.45 (s, 3 H), 2.32 (s, 3 H), 2.19 (bs, 1 H), 2.05 (d, *J* = 9.3 Hz), 1.97 (bs, 1 H), 1.27-1.10 (m, 1 H), 1.17-1.11 (m, 2 H), 0.82-0.80 (m, 1 H), 0.59 (dddd, *J* = 4.8, 4.8, 9.4, 13.5 Hz, 1 H), 0.56-0.50 (m, 2 H), 0.35-0.27 (m, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.9, 144.1, 135.9, 135.3, 132.9, 129.98, 129.96, 129.1, 127.8, 126.9, 125.3, 125.0, 124.6, 123.2, 120.4, 114.1, 74.9, 73.8, 67.9, 63.5, 61.2, 53.1, 51.7, 42.3, 33.6, 29.8, 24.5, 21.7, 13.8, 10.4, 9.3; HRMS (EI+) *m/z* calculated for $C_{37}H_{43}N_3O_6S_2$ ($M^{\bullet+}$) 689.2593, found 689.2577. **1-155b**: IR (neat) 3524, 3063, 2991, 2954, 2919, 1917, 1597, 1447, 1366, 1338, 1160, 1119, 1091, 990, 909, 814, 726 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) *mix of conformational isomers* δ 7.95 (d, *J* = 8.4 Hz), 7.93 (d, *J* = 8.3 Hz), 7.78 (d, *J* = 8.3 Hz), 7.77 (d,*J* = 8.3 Hz), 7.69 (s), 7.68 (d, *J* = 8.2 Hz), 7.66 (d, *J* = 8.0 Hz), 7.64 (s), 7.3 (d, *J* = 8.0 Hz), 7.29 (t, *J* = 7.3 Hz), 7.25 (t, *J* = 7.4 Hz), 7.22 (t, *J* = 7.3 Hz), 7.18 (d, *J* = 8.3 Hz), 7.16 (t, *J* = 7.7 Hz), 4.36 (bs), 4.21 (bs), 4.14 (dd, *J* = 5.6, 10.5 Hz), 4.05 (dd, *J* = 6.5, 9.8 Hz), 3.69-3.61 (m), 3.56 (ddd, *J* = 3.4, 3.4, 6.4 Hz), 3.50 (dd, *J* = 10.9, 13.1 Hz), 3.27 (bdd, *J* = 4.2, 14.3 Hz), 3.09 (dd, *J* = 4.9, 13.6 Hz), 2.94 (bt, *J* = 10.1 Hz), 2.86-2.77 (m), 2.67 (dd, *J* = 3.9, 14.2 Hz), 5.60 (ddd, *J* = 5.2, 11.0, 11.0 Hz), 2.50 (dd, *J* = 4.2, 13.0 Hz), 2.43 (s), 2.31 (s), 2.27 (t, *J* = 11.3 Hz), 2.22 (t, *J* = 11.6 Hz), 2.05 (d, *J* = 9.8 Hz), 1.73 (d, *J* = 9.7 Hz), 1.57-1.54 (m), 1.17 (ddd, *J* = 5.3, 10.1 Hz), 0.99 (ddd, *J* = 4.8, 4.8, 9.5 Hz), 0.97-0.75 (m), 0.57 (ddd, *J* = 4.4, 5.5, 9.8 Hz), 0.55-0.43 (m), 0.40 (ddd, *J* = 4.6, 4.6, 8.9 Hz), 0.36 (dddd, *J* = 3.9, 3.9, 8.8, 8.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) *mix of conformational isomers* δ 145.0. 144.8, 143.9, 143.8, 135.8, 135.5, 135.3, 135.2, 133.8, 129.97, 129.93, 129.90, 129.87, 127.6, 127.5, 127.1, 127.0, 125.0, 124.8, 124.7, 124.1, 123.3, 122.8, 119.9, 119.7, 114.1, 114.0, 75.9, 67.6, 66.0, 63.0, 62.4, 56.3, 52.8, 51.9,

49.2, 34.2, 33.8, 29.8, 27.4, 25.5, 21.71, 21.68, 16.1, 15.2, 14.6, 14.34, 14.27, 11.0; HRMS (ESI) *m/z* calculated for $C_{37}H_{44}N_3O_6S_2$ $[M+H]^+$ 690.2672, found 690.2681.

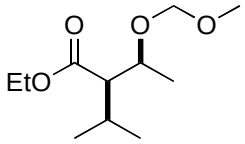


2-151

(*R*)-4-Benzyl-3-((2*R*,3*S*)-2-isopropyl-3-(triisopropylsilyloxy)butanoyl)oxazolidin-2-one (2-151). To a solution of **2-147** (2.29 g, 8.76 mmol) in dry CH_2Cl_2 (23 mL) at 0 °C was added Bu_2BOTf (2.42 mL, 9.63 mmol) followed by NEt_3 (1.49 mL, 10.5 mmol). The reaction mixture was stirred for 15 min and was cooled to –78 °C, and freshly distilled acetaldehyde (1.10 mL, 19.3 mmol) was added dropwise. The reaction mixture was stirred at –78 °C for 20 min and allowed to warm to 0 °C over 1 h at which point pH 7 phosphate buffer (5 mL) and MeOH (5 mL) was added. A solution of H_2O_2 (15 mL, 2:1 v/v H_2O_2/MeOH) was introduced and the biphasic mixture was stirred for 45 min. The volatiles were removed under reduced pressure and the resulting aqueous phase was extracted with EtOAc (3 x 15 mL). The combined organic layers were dried ($MgSO_4$), filtered and concetreated. The crude material was purified by chromatography on SiO_2 (4:1 Hex/EtOAc) to afford **2-149** as a pale yellow oil.

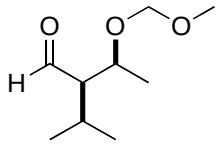
To a solution of **2-149** (200 mg, 0.65 mmol) in dry CH_2Cl_2 (2 mL) was added 2,6-lutidine (154 µL, 1.31 mmol) followed by TIPSOTf (272 µL, 0.982 mmol) and the solution was allowed to stir for 1 h. The reaction mixture was quenched upon the addition of sat. aq. NH_4Cl (5 mL) and the aqueous phase was extracted with EtOAc (3 x 5 mL). The combined organic layers were dried ($MgSO_4$), filtered, concentrated and the crude product was purified by MPLC (95:5 Hex/Et_2O) to afford **2-151** (298 mg, 0.645 mmol, 99%) as a yellow oil: ^{1}H NMR (300 MHz,

$CDCl_3$) δ 7.34-7.21 (m, 5 H), 4.69-4.62 (m, 1 H), 4.35-4.23 (m, 2 H), 4.07 (dd, *J* = 2.2, 9.1 Hz, 1 H), 4.02 (app q, *J* = 8.6 Hz, 1 H), 3.42 (dd, *J* = 3.1, 13.1 Hz, 1 H), 2.62 (dd, *J* = 10.6, 13.1 Hz, 1 H), 2.11-1.99 (m, 1 H), 1.31 (d, *J* = 6.0 Hz, 3 H), 1.03 (s, 6 H), 1.02 (s, 18 H), 0.99 (d, *J* = 2.6 Hz, 3 H), 0.96 (d, *J* = 2.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.0, 153.4, 136.0, 129.6, 129.1, 127.3, 69.4, 65.5, 56.2, 54.5, 38.1, 29.2, 21.1, 20.4, 18.9, 18.3, 18.2, 12.8.



2-172

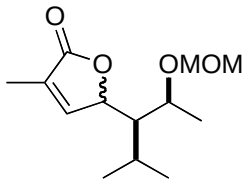
(2*R*,3*S*)-Ethyl 2-isopropyl-3-(methoxymethoxy)butanoate (2-172). To a solution of MOMCl, prepared according to a literature procedure,[135] was added a solution of **2-167** (5.00 g, 28.7 mmol) in toluene (20 mL) followed by *i*-Pr_2NEt (38.1 mL, 230 mmol) dropwise via an addition funnel. The cloudy reaction mixture was stirred overnight and became a yellow slurry. After 48 h the reaction mixture was cooled to 0 °C and was carefully quenched with sat. aq. $NaHCO_3$, diluted with H_2O, and the aqueous phase was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), concentrated and the crude product was purified by chromatography on SiO_2 (4:1 Hex:EtOAc) to afford **2-172** (5.38 g, 24.6 mmol, 86%) as a yellow oil and a 6:1 ratio of diastereomers by ^{1}H NMR spectroscopy: ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.67 (q, *J* = 6.9 Hz, 2 H), 4.18-4.12 (m, 2 H), 3.96 (dd, *J* = 6.4, 7.5 Hz, 1 H), 3.38 (s, 2 H), 2.42 (t, *J* = 7.6 Hz, 1 H), 2.09 (sextet, *J* = 6.9 Hz, 1 H), 1.28-1.26 (m, 1 H), 1.26 (t, *J* = 7.1 Hz, 3 H), 1.23 (d, *J* = 6.3 Hz, 3 H), 0.95 (d, *J* = 6.9 Hz, 3 H), 0.93 (d, *J* = 6.7 Hz, 3 H).



2-173

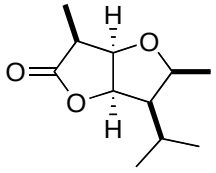
(2*R*,3*S*)-2-Isopropyl-3-(methoxymethoxy)butanal (2-173). A solution of **2-172** (250 mg, 1.14 mmol) in dry CH_2Cl_2 (10 mL) was cooled to –78 °C and DIBAL-H (1.14 mL, 1.14 mmol, 1 M in hexane) was introduced dropwise and the colorless solution was stirred for 1 h and additional DIBAL-H (2.2 mL, 2.28 mmol, 1 M in hexane) was introduced. The reaction mixture was allowed to warm to room temperature and was stirred for 30 min, and carefully quenched with sat. aq. Rochelle's salt solution (10 mL). The colorless slurry was stirred for 30 min until it cleared, and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried ($MgSO_4$), concentrated under reduced pressure, and purified by MPLC (4:1 Hex/EtOAc) to afford the alcohol (195 mg, 1.11 mmol, 96%) as a thin pale yellow oil.

To a solution of the alcohol (155 mg, 0.88 mmol) in CH_2Cl_2 (8 mL) was added 4A powdered molecular seives (155 mg) followed by NMO (212 mg, 1.76 mmol). The colorless slurry was cooled to 0 °C and TPAP (16 mg, 0.09 mmol) was added. The black slurry was stirred for 2 h at room temperature and the reaction mixture was filtered thorugh SiO_2 washed with 4:1 Hex/EtOAc and concentrated. The resulting yellow oil, **2-173** (148 mg, 0.849 mmol, 97%), was used without purification as a 6:1 mixture of diastereomers by ^{1}H NMR spectroscopy: ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.80 (d, *J* = 3.7, 1 H), 4.70 (d, *J* = 7.0 Hz, 1 H), 4.65 (d, *J* = 7.0 Hz, 1 H), 4.09 (t, *J* = 6.4 Hz, 1 H), 3.38 (s, 3 H), 2.37 (ddd, *J* = 3.7, 6.5, 7.7 Hz, 1 H), 2.16 (sextet, *J* = 6.8 Hz, 1 H), 1.24 (d, *J* = 6.5, 3 H), 1.02 (d, *J* = 6.9 Hz, 3 H), 0.96 (d, *J* = 6.8 Hz, 3 H).



2-176

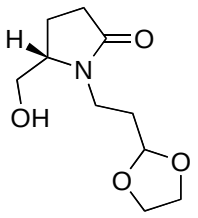
5-((2*S*,3*R*)-2-(Methoxymethoxy)-4-methylpentan-3-yl)-3-methylfuran-2(5*H*)-one (2-176). A solution of **2-175** (30 mg, 0.111 mmol) in toluene (10 mL), and treated with Grubbs 2nd generation metathesis catalyst (4.70 mg, 0.006 mmol), and the pink solution was heated to 80 °C. for 2 h, and more Grubbs 2nd (4.70 mg, 0.006 mmol) was added. After heating the reaction mixture for another 1 h at 80 °C, more catalyst (4.70 mg, 0.006 mmol) was added. After 1 h the reaction mixture was filtered through Celite and the product was purified by MPLC (4:1 Hex:EtOAc) to afford **2-175** (22.0 mg, 0.091 mmol, 82%) as a dark oil and a 1.4:1 mixture of inseparable diastereomers by ^{1}H NMR spectroscopy: ^{1}H NMR (600 MHz, $CDCl_3$) δ (major peaks) 7.23 (t, *J* = 1.5 Hz) 7.18 (t, *J* = 1.5 Hz), 5.18-5.17 (m), 5.15-5.13 (m), 4.64 (t, *J* = 6.8 Hz), 4.61 (t, *J* = 6.6 Hz), 4.54 (d, *J* = 6.9 Hz), 4.01-3.97 (m), 3.87-3.82 (m), 3.35 (s), 3.33 (s), 2.08-2.01 (m), 1.98-1.92 (m), 1.91 (ddd, *J* = 1.8, 1.8, 4.3 Hz), 1.71-1.68 (m), 1.68-1.65 (m), 1.25 (d, *J* = 6.5 Hz), 1.13 (d, *J* = 6.6 Hz), 1.02 (d, *J* = 6.8 Hz), 0.99 (d, *J* = 7.1 Hz), 0.98 (d, *J* = 7.0 Hz), 0.96 (d, *J* = 6.9 Hz).



2-178

(3*S*,3a*R*,5*S*,6*R*,6a*R*)-6-Isopropyl-3,5-dimethyltetrahydrofuro[3,2-*b*]furan-2(5*H*)-one (2-178). To a solution of **2-177** (18.0 mg, 0.091 mmol) in toluene (1 mL) at room temperature

was added KO*t*-Bu (3 mg, 0.027 mmol). A brown precipitate developed, and the reaction mixture was stirred for 5 h at which point additional KO*t*-Bu (10 mg, 0.089 mmol) was added. The reaction became orange and was allowed to stir for 4 h before being quenched with sat. aq. $NaHCO_3$, diluted with H_2O (1 mL) and Et_2O (1 mL), and the aqueous phase was extracted with Et_2O (3 x 5 mL). The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and MPLC purification (9:1 Hex:EtOAc) of the crude material yielded 4 peaks (10 mg, 0.050 mmol, 56%). The major peak was isolated and ^{1}H NMR spectroscopy confirms **2-178**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.88 (t, *J* = 4.0 Hz, 1 H), 4.63 (dd, *J* = 4.0, 5.6 Hz, 1 H), 4.42 (p, *J* = 6.9 Hz, 1 H), 2.69 (ddd, *J* = 5.8, 7.3, 13.1 Hz, 1 H), 2.03-1.94 (m, 2 H), 1.30 (d, *J* = 7.3 Hz, 3 H), 1.13 (d, *J* = 6.7 Hz, 3 H), 1.11 (t, *J* = 6.1 Hz, 3 H), 0.96 (d, *J* = 6.2 Hz, 3 H).

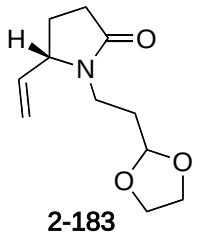


2-182

(*S*)-1-(2-(1,3-Dioxolan-2-yl)ethyl)-5-(hydroxymethyl)pyrrolidin-2-one (2-182). A solution of **2-180** (300 mg, 1.31 mmol), TBAI (48 mg, 0.13 mmol) and dioxolane **2-142** (313 µL, 2.62 mmol) in dry DMF (20 mL) was cooled to –15 °C, and treated with KHMDS (1.6 mL, 1.57 mmol, 1.0 M in THF) dropwise. The solution turned orange during course of addition and the reaction mixture was allowed to warm to room temperature after 30 min and was stirred overnight. The reaction mixture was quenched with sat. aq. NH_4Cl (10 mL) and diluted with H_2O (50 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with H_2O (2 x 10 mL) and brine (2 x 10 mL), dried ($MgSO_4$), filtered and

concentrated to an orange oil (**2-181** and DMF). The crude material was used without further purification.

To a solution of crude **2-181** in THF (10 mL) was added TBAF (1.44 mL, 1.44 mmol, 1 M in THF) and the resulting solution was stirred for 45 min at room temperature. The reaction mixture was quenched with H_2O (10 mL) and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. The crude product was purified by chromatography on SiO_2 (7:3 EtOAc/MeOH followed by 1:1 EtOAc/MeOH). The rich fractions were concentrated and the residue was dissolved in a minimal amount of CH_2Cl_2 and filtered through a cotton plug to provide **2-182** (94 mg, 0.436 mmol, 33% over 2 steps) as a colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.96 (dd, *J* = 3.6, 5.5 Hz, 1 H), 3.99-3.94 (m, 2 H), 3.89-3.81 (m, 3 H), 3.67 (dddd, *J* = 3.1, 3.1, 4.6, 7.7 Hz 1 H), 3.58 (bd, *J* = 12.0 Hz, 1 H), 3.53-3.43 (m, 2 H), 2.82 (bs, 1 H), 2.49 (ddd, *J* = 7.1, 10.1, 17.1 Hz, 1 H), 2.30 (ddd, *J* = 5.6, 10.3, 15.9 Hz, 1 H), 2.13-2.08 (m, 1 H), 2.06-2.01 (m, 1 H), 2.01-1.97 (m, 1 H), 1.96-1.89 (m, 1 H),

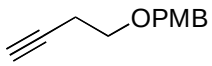


2-183

(*S*)-1-(2-(1,3-Dioxolan-2-yl)ethyl)-5-vinylpyrrolidin-2-one (2-183). To a solution of DMSO (90.0 µL, 1.25 mmol) in dry CH_2Cl_2 (5 mL) at –78 °C was added oxalyl chloride (54.9 µL, 0.627 mmol) and the colorless solution was stirred for 40 min. To this mixture was added **2-182** (90.0 mg, 0.418 mmol) in dry CH_2Cl_2 (2 mL) dropwise. The reaction mixture was stirred for 2 h at –78 °C and the pale yellow slurry was treated with NEt_3 (308 µL, 2.17 mmol) and the

slurry cleared to a pale yellow solution that was allowed to stir for 1 h at –78 °C before warming to room temperature. The reaction mixture was quenched with H_2O (5 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL), dried ($MgSO_4$), and concentrated to afford the crude aldehyde, which was taken on to the next step without purification.

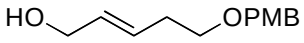
To a slurry of KOtBu (147 mg, 1.31 mmol) in dry THF (1 mL) was added $MePPh_3Br$ (202 mg, 1.27 mmol) and a canary-yellow slurry developed immediately. To the reaction mixture was added a solution of crude aldehyde (90.0 mg, 0.422 mmol). The slurry became brown immediately and was stirred at room temperature for 30 min. The reaction mixture was quenched with sat. aq. NH_4Cl (3 mL), and the aqueous phase was extracted with EtOAc (3 x 5 mL), dried ($MgSO_4$), concentrated, and purified by MPLC (100% EtOAc) to yield **2-183** (16 mg, 0.076 mmol, 18%) as an orange oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.65 (ddd, *J* = 8.5, 10.0, 17.0 Hz, 1 H), 5.24 (d, *J* = 17.0 Hz, 1 H), 5.20 (ddd, *J* = 0.7, 0.7, 10.0 Hz, 1 H), 4.86 (t, *J* = 4.6 Hz, 1 H), 4.07 (ddd, *J* = 5.8, 8.1, 8.1 Hz, 1 H), 3.96-3.91 (m, 2 H), 3.84-3.80 (m, 2 H), 3.72 (ddd, *J* = 7.4, 7.4, 14.1 Hz, 1 H), 3.01 (ddd, *J* = 5.7, 8.3, 13.8 Hz, 1 H), 2.40 (ddd, *J* = 5.9, 9.5, 16.4 Hz, 1 H), 2.32 (ddd, *J* = 7.2, 9.5, 16.7 Hz, 1 H), 2.24-2.18 (m, 1 H), 1.90-1.80 (m, 2 H), 1.73 (dddd, *J* = 5.7, 7.0, 9.5, 12.8 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.2, 137.9, 118.2, 102.9, 65.0, 64.9, 61.5, 36.1, 31.6, 30.2, 25.7; HRMS (EI) *m/z* calculated for $C_{11}H_{17}NO_3$ ($M^{\cdot+}$) 211.1208, found 211.1207.



2-196

1-(4-Methoxyphenyl)methoxy-3-butyne (2-196). To a cooled solution of 3-butynol (4.86 mL, 64.2 mmol) in dry THF (110 ml) and dry DMF (20 mL) at 0 °C was added NaH (3.08

g, 77.04 mmol, 60% disp. in mineral oil) in a single portion. After bubbling had ceased, freshly prepared PMBI[136] (19.11 g, 77.04 mmol) was introduced via an addition funnel and the reaction mixture was allowed to warm to room temperature. After 16 h sat. aq. NH_4Cl (20 mL) was added and the biphasic mixture was diluted with H_2O (50 mL) and extracted with Et_2O (3 x 30 mL), The combined organic layers were washed with brine (3 x 25 mL), dried ($MgSO_4$), filtered, concentrated in vacuo, and the product was purified by chromatography on SiO_2 (10% EtOAc/Hex) to yield **2-196** (11.0 g, 57.8 mmol, 90%) as a yellow oil. Analytical data matched previously reported data for **2-196**:[137] ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.6 Hz, 2 H), 6.88 (d, *J* = 8.6 Hz, 2 H), 4.49 (s, 2 H), 3.81 (s, 3 H), 3.57 (t, *J* = 7.0 Hz, 2 H), 2.48 (dt, *J* = 2.6, 7.0 Hz, 2 H), 1.99 (t, *J* = 2.6 H, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.4, 130.2, 129.5, 113.9, 81.5, 72.8, 69.4, 67.9, 55.4, 20.0.

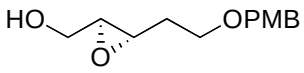


2-197

5-(4-Methoxy-benzyloxy)-2*E*-penten-1-ol (2-197). To a solution of **2-196** (10 g, 52.6 mmol) in THF (140 mL) cooled to 0 °C was added *n*-BuLi (53.0 mL, 57.8 mmol, 1.09 M solution in hexanes). The reaction mixture was stirred for 15 min at 0 °C and paraformaldehyde (3.02 mL, 84.1 mmol) was added in a single porotion. The reaction mixture was stirred for 1 h and quenched with H_2O (50 mL) and the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried ($MgSO_4$), concentrated in vacuo, and the crude propargyl alcohol (6.98 g, 31.7 mmol, 60%) was carried on without further purification.

To a stirred solution of the alcohol (6.72 g, 30.5 mmol) in dry THF (175 mL) cooled to 0 °C was added Red-Al (32.2 mL, 107 mmol), dropwise. The reaction mixture was allowed to warm to room temperature, stirred for 4 h and carefully quenched with H_2O (200 mL). The

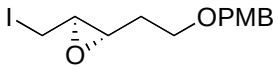
aqueous phase was extracted with EtOAc (3 x 100 mL) and the combined organic layers were dried ($MgSO_4$), filtered through Celite, and concentrated in vacuo. The crude yellow oil (3.78 g, 99%, 10:1 pdt:sm by ^1H NMR) was used without further purification, and analytical data matched the previously reported data for **2-197**:[2] ^1H NMR (600 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.6 Hz, 2 H), 6.88 (d, *J* = 8.6 Hz, 2 H), 5.72-5.70 (m, 2 H), 4.44, (s, 2 H), 4.09 (bm, 2 H), 3.81 (s, 3 H), 3.49 (t, *J* = 6.7 Hz, 2 H), 2.36 (m, 2 H), 1.33 (bs, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.3, 131.0, 130.5, 129.5, 128.8, 113.9, 72.7, 69.4, 63.8, 55.4, 32.8.



2-198

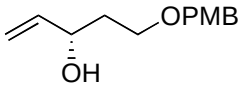
(2*S*, 3*S*)-5-(4-Methoxyphenyl)methoxy-2,3-epoxy-1-pentanol (2-198). (+)-Diisopropyl-L-tartrate (5.18 mL, 24.4 mmol) was added to a solution of freshly distilled Ti(O*i*-Pr)$_4$ (6.79 mL, 22.1 mmol) in dry CH_2Cl_2 (20 mL) at room temperature. The colorless solution was stirred for 30 min and the volatiles were removed in vacuo. The residue was placed under reduced pressure (~1 torr) for 1 h. The resulting pale yellow foam was redissolved in dry CH_2Cl_2 (250 mL) and the resulting solution was cooled to –20 °C. To this mixture was added 4 Å molecular sieves (4 g) and **2-197** (4.30 g, 18.8 mmol). After 30 min a solution of *t*-BuOOH in toluene[138] (14.4 mL, 56.3 mmol, 3.9 M) was added and the reaction was allowed to stir at –20 °C for 16 h. The reaction was quenched with sat. aq. $Na_2S_2O_3$ (100 mL) and diluted with sat. aq. Rochelle's salt (100 mL) and EtOAc (100 mL). The aqueous slurry was extracted with EtOAc (3 x 50 mL), and the combined organic extracts were washed with brine (30 mL) and dried ($MgSO_4$), filtered through a pad of Celite, and concentrated. The crude residue was purified by chromatography on SiO_2 (50% EtOAc/Hex) to provide **2-198** (2.95 g, 12.4 mmol, 66%, 94% *ee*)

as colorless oil. Analytical data matches previously reported data for **2-198**:[139] $[\alpha]_D$ -26.0 (*c* 1.0, $CHCl_3$) (lit. $[\alpha]_D^{21}$ = -27.7 (*c* 0.9, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.25 (d, *J* = 7.9 Hz, 2 H), 6.79 (d, *J* = 8.7 Hz, 2 H), 4.46 (d, *J* = 11.5 Hz, 1 H), 4.44 (d, *J* = 11.5 Hz, 1 H), 3.89 (ddd, *J* = 2.7, 5.5, 12.6 Hz, 1 H), 3.80 (s, 3 H), 3.61 (ddd, *J* = 4.4, 7.3, 11.8 Hz, 1 H), 3.59-3.56 (m, 2 H), 3.09 (ddd, *J* = 2.3, 4.8, 6.8 Hz, 1 H), 2.97 (ddd, *J* = 2.5, 2.5, 4.7 Hz, 1 H), 1.92 (dddd, *J* = 4.8, 6.1, 7.3, 12.1 Hz, 1 H), 1.85-1.78 (m, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.3, 130.4, 129.4, 113.9, 72.9, 66.6, 61.8, 58.5, 55.4, 53.8, 32.2.



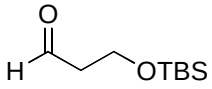
3-1

(1*S*, 2*R*)-2-Iodomethyl-3-[2-(4-methoxy-benzyloxy)-ethyl]-oxirane (3-1). A well-stirred solution of **4** (2.00 g, 8.39 mmol) in a mixture of THF/MeCN (120 mL, 30 mL) at room temperature was treated with imidazole (4.33 g, 63.0 mmol), PPh_3 (6.60 g, 25.2 mmol) and I_2 (6.39 g, 25.2 mmol). After 5 min the reaction mixture was diluted with Et_2O (200 mL) and washed with sat. aq. $NaHCO_3$ (100 mL), sat. aq. $NaHSO_3$ (25 mL, to remove remaining iodine), and brine (100 mL). The combined organic extracts were dried ($MgSO_4$), concentrated in vacuo, and passed through a pad of SiO_2 (10% EtOAc/Hex) to provide of **3-1** (2.61 g, 7.49 mmol, 89%) as a colorless oil. Analytical data matched previously reported data for **3-1**:[139] ^{1}H NMR (600 MHz, C_6D_6) δ 7.19 (d, *J* = 8.6 Hz, 2 H), 6.81 (d, *J* = 8.6 Hz, 2 H), 4.25 (d, *J* =16.1 Hz, 1 H), 4.23 (d, *J* = 16.1 Hz, 1 H), 3.29 (s, 3 H), 3.31-3.23 (m, 1 H), 2.63-2.58 (m, 2 H), 2.50-2.47 (m, 1 H), 1.56 (dddd, *J* = 5.3, 5.3, 7.6, 10.4 Hz, 1 H), 1.47 (dddd, *J* = 6.0, 6.0, 11.5, 11.5 Hz, 1 H); ^{13}C NMR (150 MHz, C_6D_6) δ 160.4, 131.5, 130.0, 128.9, 128.7, 128.5, 114.7, 73.5, 73.5, 67.1, 64.5, 60.5, 58.7, 55.4, 33.2, 14.0, 6.0.



2-199

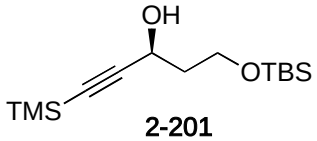
(3*S*)-5-(4-Methoxy-benzyloxy)-pent-1-en-3-ol (2-199). According to a literature procedure,[3] a slurry of **3-1** (2.55 g, 7.32 mmol) and zinc dust (1.43 g, 22.0 mmol) in MeOH (95 mL) was sonicated at room temperature for 90 min. The grey slurry was diluted with Et_2O (100 mL), filtered through Celite, and washed with 5% aq. HCl (25 mL), sat. aq. $NaHCO_3$ (25 mL), and brine (25 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo to afford **2-199** (1.22 g, 5.49 mmol, 75%) as a yellow oil that was used without further purification: ^{1}H NMR δ 7.13 (d, *J* = 8.8 Hz, 2 H), 6.76 (d, *J* = 8.6 Hz, 2 H), 5.78 (ddd, *J* = 5.2, 10.4, 15.7 Hz, 1 H), 5.31 (ddd, *J* = 1.7, 1.7, 17.1 Hz, 1 H), 5.00 (ddd, *J* = 1.7, 1.7, 10.5 Hz, 1 H), 4.25 (bm, 1 H), 4.20 (d, *J* = 11.6 Hz, 1 H), 4.17 (d, *J* = 11.6 Hz, 1 H), 3.43 (ddd, *J* = 5.1, 6.1, 9.2 Hz, 1 H), 3.32 (ddd, *J* = 5.0, 6.8, 9.2 Hz, 1 H), 3.28 (s, 3 H), 1.69-1.61 (m, 2 H); ^{13}C NMR (150 MHz, C_6D_6) δ 159.8, 141.7, 130.7, 129.5, 128.4, 128.1, 128.0, 114.1, 113.7, 73.0, 71.7, 68.1, 54.8.



2-200

3-(*tert*-Butyldimethylsilyloxy)propionaldehyde (**2-200).** To a stirred solution of DMSO (8.39 mL, 118 mmol) in dry CH_2Cl_2 (450 mL) at –78 °C was added oxalyl chloride (5.17 mL, 59.1 mmol) at a dropwise rate and the colorless solution was stirred for 1 h until gas evolution subsided. 3-(*tert*-Butyldimethylsilyloxy)-propan-1-ol (8.25 mL, 7.50 g, 39.4 mmol) was added dropwise and the resulting colorless slurry was stirred at –78 °C for 30 min. Triethylamine (29.1

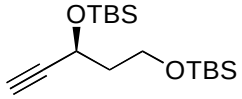
mL, 205 mmol) was introduced slowly and the reaction mixture was stirred at –78 °C for an additional 30 min before being allowed to warm to 0 °C over 30 min. H_2O (200 mL) was added and the biphasic mixture was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to afford a cloudy yellow oil that was taken up in a minimal amount of CH_2Cl_2 and passed through a pad of silica gel (1:1 EtOAc/Hex) and concentrated to yield **2-200** (7.41 g, 7.42 mmol, 99% yield) as a pungent yellow oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.80 (t, *J* = 2.1 Hz, 1 H), 3.99 (t, *J* = 6.1 Hz, 2 H), 2.60 (dt, *J* = 2.1, 6.1 , 2 H), 0.88 (s, 9 H), 0.06 (s, 6 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 202.1, 57.4, 46.6, 41.0, 25.8, 18.2, –5.4.



2-201

(3*S*)-5-(*tert*-Butyldimethylsilyloxy)-1-(trimethylsilyl)pent-1-yn-3-ol (2-201). To an oven-dried 1 L RBF charged with TMS-acetylene (18.5 mL, 127 mmol) in dry toluene (147 mL) under an atmosphere of N_2 at room temperature was added dropwise with EXTREME CAUTION (PYROPHORIC) neat $ZnEt_2$ (13.7 mL, 10.4 mmol). The brown turbid solution was heated to reflux for 1 h under N_2 during which time a grey precipitate formed. The reaction was allowed to cool to room temperature and (*R*)-binol (4.60 g, 15.9 mmol) was added in one portion followed by the slow addition of dry Et_2O (620 mL). To the well-stirred slurry was added Ti(O*i*-Pr)$_4$ (9.77 mL, 31.86 mmol) and the resulting orange slurry was stirred at room temperature for 1 h before **2-200** (6.00 g, 31.9 mmol) was added in dry Et_2O (20 mL). The reaction mixture was stirred vigorously for 20 h and was carefully quenched with brine (20 mL) and poured into a 2 L erlynmeyer flask containing brine (180 mL) and Rochelle's salt solution (200 mL, 1.0 M aq.),

and the biphasic mixture was stirred vigorously for 1 h. The aqueous phase was extracted with Et_2O (4 x 100 mL) and the combined organic layers were dried ($MgSO_4$), filtered, concentrated in vacuo, and the residue was purified by chromatography on SiO_2 (10 % Et_2O/Hex) to yield **2-201 (**7.01 g, 24.2 mmol, 76%) as a pale yellow oil: $[\alpha]_D$ -16.4 (*c* 1.07, $CHCl_3$); IR (neat) 3375, 2952, 2925, 2855, 2171, 1470, 1248, 1088, 831, 773 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 4.60 (dd, *J* = 4.3, 6.4 Hz, 1 H), 4.05 (ddd, *J* = 3.8, 8.2, 10.2 Hz, 1 H), 3.83 (ddd, *J* = 4.3, 5.9, 10.2 Hz, 1 H), 3.44 (bs, 1 H), 2.00 (dddd, *J* = 4.3, 4.3, 8.3, 14.2 Hz, 1 H), 1.85 (dddd, *J* = 3.8, 6.1, 6.1, 14.2 Hz, 1 H), 0.90 (s, 9 H), 0.17 (s, 9 H), 0.09 (s, 3 H), 0.08 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 106.3, 89.4, 62.6, 61.3, 38.5, 26.0, 18.3, 0.06, –5.4, –5.4.

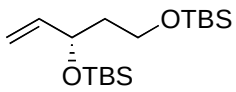


3-2

(3*S*)-3,5-Bis-(*tert*-butyldimethylsilyloxy)-pent-1-yne (3-2). A solution of **2-201** (6.9 g, 24.1 mmol) in dry DMF (60 mL) and treated with imidazole (3.31 g, 48.16 mmol) and a solution of TBSCl (5.50 g, 36.12 mmol) in DMF (10 mL). The reaction mixture was stirred for 4 h and was quenched with H_2O (50 mL) and diluted with Et_2O (50 mL). The biphasic mixture was separated and the aqueous phase was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with H_2O (50 mL) and brine (3 x 100 mL). The organic layer was dried ($MgSO_4$), filtered, concentrated, and the crude oil was used without further purification (9.80 g, 24.5 mmol, 101%).

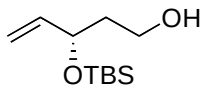
To a stirred solution of **2-201** (1.00 g, 2.49 mmol) in MeOH (25 mL) was added K_2CO_3 (1.13 g, 8.23 mmol) and the reaction mixture became cloudy within 15 min. After stirring for 1 h the reaction mixture was diluted with H_2O (30 mL) and Et_2O (30 mL). The aqueous phase was

extracted with Et_2O (3 x 30 mL) and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo to afford **3-2** as a yellow oil (716 mg, 2.17 mmol, 87%) with a small amount of silane byproducts by ^1H NMR analysis: IR (neat) 2952, 2925, 2883, 1470, 1360, 1250, 1090, 831, 773 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 4.56 (ddd, *J* = 2.1, 5.9, 7.7 Hz, 1 H), 3.76-3.69 (m, 1 H), 2.38 (d, *J* = 2.2 Hz, 1 H), 1.93-1.82 (m, 2 H), 0.90 (s, 9 H), 0.89 (s, 9 H), 0.14 (s, 3 H), 0.11 (s, 3 H), 0.04 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 85.7, 72.2, 59.7, 59.0, 41.8, 26.1, 25.9, 25.8, 18.4, –2.8, –4.5, –5.0, –5.2.



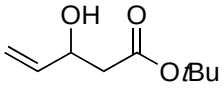
3-3

(3*S*)-3,5-(bis-*tert*-Butyldimethysiloxy)-pent-1-ene (3-3). A solution of **3-2** (674 mg, 2.16 mmol) in dry CH_2Cl_2 (7 mL) was treated with $Cp_2Zr(H)Cl$ (537 mg, 2.67 mmol). The yellow reaction mixture cleared after 15 min and TLC showed the starting material had been consumed (R_f = 0.1, 100% Hex, yellow stain in *p*-anisaldehyde stain; product stains blue). The reaction mixture was quenched with H_2O (5 mL), and the aqueous phase was extracted with Et_2O (3 x 20 mL), and the combined organic extracts were dried ($MgSO_4$), filtered through Celite, and concentrated in vacuo to afford a yellow solid. The residue was suspended in Et_2O (10 mL) and filtered through a pad of Celite and concentrated to afford pure **3-3** (678 mg, 2.05 mmol, 99%) as a yellow oil: ^1H NMR (600 MHz, $CDCl_3$) δ 5.81 (ddd, *J* = 6.1, 10.4, 17.1 Hz, 1 H), 5.15 (ddd, *J* = 1.4, 1.4, 17.1 Hz, 1 H), 5.02 (ddd, *J* = 1.3, 1.8, 10.4 Hz, 1 H), 4.27 (app qt, *J* = 1.2, 6.0 Hz, 1 H), 3.70-3.61 (m, 2 H), 1.75-1.62 (m, 2 H), 0.89 (s, 9 H), 0.89 (s, 9 H), 0.06 (s, 3 H), 0.04 (s, 3 H), 0.04 (s, 3 H), 0.03 (s, 3 H).



2-206

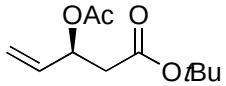
(3*S*)-3-(*tert*-Butyldimethysiloxy)-pent-1-en-5-ol (2-206). Method A from 3-3: A cooled (–30 °C) solution of **13** (100 mg, 0.302 mmol) in CH_2Cl_2 (5 mL) and MeOH (5mL) was cooled to –30 °C in a CO_2/acetone bath and was treated with CSA (7.00 mg, 0.0302 mmol). The colorless solution was stirred at –30 °C for 5 h until the starting material was consumed by TLC analysis (R_f sm = 0.9, 30% Et_2O/Hex). The reaction mixture was quenched with sat. aq. $NaHCO_3$ (10 mL), washed with EtOAc (3 x 10 mL), dried (MgSO4), concentrated and purified by chromatography on SiO_2 (20% Et_2O/Hex) to afford **3-4** (44.7 mg, 0.206 mmol, 68%) as a pale yellow oil. Analytical data matched previously reported data for **3-3**:[139] ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.85 (ddd, *J* = 5.8, 10.4, 17.2 Hz, 1 H), 5.23 (ddd, *J* = 1.5, 1.5, 17.2 Hz), 5.11 (ddd, *J* = 1.5, 1.5, 10.4 Hz, 1 H), 4.42 (ddddd, *J* = 1.4, 1.4, 4.5, 6.0, 6.0 Hz, 1 H), 3.82 (ddd *J* = 3.8, 8.3, 11.2 Hz, 1 H), 3.72 (app q, *J* = 5.0, 1 H), 2.42 (bs, 1 H), 1.86 (dddd, *J* = 4.4, 4.4, 8.3, 14.3 Hz, 1 H), 1.72 (dddd, *J* = 3.8, 6.2, 6.2, 14.3 Hz, 1 H), 0.91 (s, 9 H), 0.09 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 140.7, 114.6, 73.4, 60.3, 39.2, 26.0, 18.3, –4.3, –4.9.



2-202

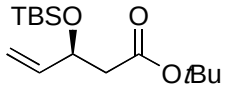
***tert*-Butyl 3-hydroxypent-4-enoate (2-202).** Following a literature procedure,[140] a cooled solution of *i*-Pr_2NH (47.1 mL, 0.330 mol) at –78 °C in dry THF (600 mL) was treated with *n*-BuLi (244 mL, 0.330 mol, 1.3 M in hexanes) over 20 min. The yellow solution was stirred at –78 °C for 20 min, before *t*-BuOAc (40.9 mL, 0.300 mol) was added. The mixture was stirred for 1 h at –78 °C before freshly distilled acrolein (22.5 mL, 0.300 mol) in dry THF (150 mL) was

introduced to the reaction mixture by cannula. The reaction was stirred for 1 h and was quenched with sat. aq. NH_4Cl (200 mL), extracted with Et_2O (3 x 100 mL), dried ($MgSO_4$) and concentrated to afford **2-202** (47.0 g, 91%) as an orange oil that was used without further purification. Analytical data matched previously reported data for **12**:[140] ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.87 (ddd, *J* = 5.5, 10.5, 17.2 Hz, 1 H), 5.30 (dm, *J* = 17.2 Hz, 1 H), 5.14 (dm, *J* = 10.5 Hz, 1 H), 4.49 (bm, 1 H), 3.13 (bs, 1 H), 2.51 (dd *J* = 3.8, 16.2 Hz, 1 H), 2.43 (dd, *J* = 8.2, 16.5 Hz, 1 H), 1.46 (s, 9 H).



2-203

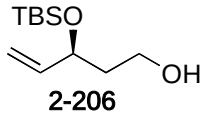
(*S*)-*tert*-Butyl 3-(acetoxy)pent-4-enoate (2-203). Following a literature procedure,[119,141] a solution of **2-202** (7.3 g, 42.4 mmol) and vinyl acetate (7.89 mL, 84.8 mmol) in pentane (260 mL) was added PS Amano lipase (3.3 g) and the slurry was heated to reflux for 45 h. The reaction slurry was filtered and concentrated in vacuo to afford a yellow oil that was purified by chromatography on SiO_2 (10% Et_2O/Hex) to provide **13** (4.00 g, 18.7 mmol, 44%) as a colorless oil followed by enantioenriched **2-204** (3.2 g, 18.6 mmol, 44%). Analytical data matched previously reported data for **2-203**:[119,141] ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.82 (ddd, *J* = 6.2, 10.5, 17.1 Hz, 1 H), 5.60 (app q, *J* = 6.8 Hz, 1 H), 5.30 (dt, *J* = 1.1, 17.2 Hz, 1 H), 5.20 (dt, *J* = 1.3, 10.5 Hz, 1 H), 2.60, (dd, *J* = 8.2, 15.3 Hz, 1 H), 2.52 (dd, *J* = 5.7, 15.3 Hz, 1 H), 2.06 (s, 3 H), 1.44 (s, 9 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.8, 169.0, 135.1, 117.4, 81.1, 71.1, 40.7, 28.0, 21.1.



2-205

(*S*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)pent-4-enoate (2-205). Following a literature procedure,[119] **2-203** (14.0 g, 65.2 mmol) in MeOH (300 mL) was cooled to –30 °C and treated with K_2CO_3 (13.5 g, 98.0 mmol) and the slurry was stirred for 16 h at –30 °C. The mixture was quenched with sat. aq. NH_4Cl (300 mL) and the aqueous phase was extracted with Et_2O (3 x 50 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated to afford the free alcohol (10.9 g, 63.3 mmol, 97%) as a yellow oil that was used in the next reaction without further purification.

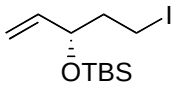
The crude oil (10.9 g, 63.3 mmol) was taken up in dry CH_2Cl_2 (290 mL) and to this solution was added imidazole (6.52 g, 94.9 mmol) and TBSCl (11.7 g, 75.9 mmol). The reaction mixture was stirred for 48 h, and additional portions of imidazole (6.52 g, 94.9 mmol) and TBSCl (11.7 g, 75.9 mmol) were added. After 24 h the reaction was quenched with sat. aq. NH_4Cl (300 mL) and the aqueous phase was extracted with Et_2O (3 x 100 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. The crude material was purified by chromatography on SiO_2 (100% Hex, followed by 5% Et_2O/Hex) to afford **2-205** (15.93 g, 55.6 mmol, 88%) as a pale yellow oil. Analytical data matched previously reported data for **14**:[119] ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.83 (ddd, *J* = 6.2, 10.3, 16.9 Hz, 1 H), 5.2 (dt, *J* = 1.2, 17.2 Hz, 1 H), 5.05 (dt, *J* = 1.0, 10.4 Hz, 1 H), 4.53 (dddd *J* = 1.2, 1.2, 6.1, 7.4, 10.3 Hz, 1 H), 2.45 (dd, *J* = 7.4, 14.7 Hz, 1 H), 2.34 (dd, *J* = 5.7, 14.7 Hz, 1 H), 1.44 (s, 9 H), 0.88 (s, 9 H), 0.07 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.5, 140.6, 114.6, 80.6, 71.0, 44.9, 28.3, 26.0, 18.3, -4.2, -4.8.



2-206

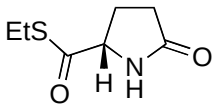
(*S*)-3-(*tert*-Butyldimethylsilyloxy)pent-4-en-1-ol (2-206). **Method B from 2-205**: To a solution of **2-206** (8.70 g, 30.4 mmol) in dry toluene (175 mL) was cooled to –78 °C and treated with DIBAL-H (36.4 mL, 36.4 mmol, 1 M solution in hexanes). The mixture was stirred for 30 min and was quenched at –78 °C with NH_4Cl (20 mL, sat. aq.) dropwise. The reaction mixture was allowed to warm to room temperature and was treated with sat. aq. Rochelle's salt solution (100 mL) and was stirred until the slurry cleared. The biphasic mixture was diluted with brine (100 mL) and more sat. aq. Rochelle's salt solution (100 mL), and the aqueous phase was extracted with EtOAc (3 x 100 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated to afford a colorless oil.

The crude oil was taken up in MeOH (100 mL), cooled to 0 °C, and treated with $NaBH_4$ (1.26 g, 33.4 mmol). The reaction was stirred for 30 min and sat. aq. NH_4Cl (150 mL) was added. The biphasic mixture was extracted with Et_2O (3 x 50 mL), dried ($MgSO_4$), filtered and concentrated. The crude material was purified by chromatography on SiO_2 (20% Et_2O/Hex) to afford **1** (5.7 g, 26.4 mmol, 87%) as a colorless oil. Analytical data matched previously reported data for **1**:[139] ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.85 (ddd, *J* = 5.8, 10.4, 17.1 Hz, 1 H), 5.21 (dt, *J* = 1.6, 17.2 Hz, 1 H), 5.10 (dt, *J* = 1.2, 10.4 Hz, 1 H), 4.41 (dddd, *J* = 1.4, 1.4, 4.5, 5.9 Hz, 1 H), 3.84-3.79 (m, 1 H), 3.73-3.69 (m, 1 H), 2.46 (t, *J* = 5.4 Hz, 1 H), 1.85 (dddd, *J* = 4.4, 4.4, 12.6, 14.3 Hz, 1 H), 1.71 (dddd, *J* = 3.9, 6.2, 6.2, 14.3 Hz, 1 H), 0.90 (s, 9 H), 0.09 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 140.8, 114.6, 73.4, 60.3, 39.2, 26.0, 18.3, -4.3, -4.9.



2-188

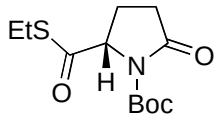
(3*S*)-3-(*tert*-Butyldimethysiloxy)-5-iodopent-1-ene (2-188). Following a literature procedure,[118] to a stirred solution of PPh_3 (16.4 g, 62.4 mmol), imidazole (10.7 g, 156 mmol) and I_2 (15.8 g, 62.4 mmol) in dry THF (400 mL) and dry MeCN (100 mL) was added **2-206** (4.5 g, 20.8 mmol) in dry THF (40 mL). After 15 min the reaction was quenched with $NaHCO_3$ (200 mL), and the organic phase was washed with sat. aq. $NaHSO_3$ (100 mL), dried ($MgSO_4$), filtered, concentrated in vacuo, and purified by chromatography on SiO_2 (5% Et_2O/Hex) to afford **2-188** as a yellow oil (6.39 g, 19.6 mmol, 95% yield). Analytical data matched previously reported data for **2-188**:[118] ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.78 (ddd, *J* = 6.4, 10.4, 17.2 Hz, 1 H), 5.21 (ddd, *J* = 1.3, 1.6, 17.2 Hz, 1 H), 5.09 (ddd *J* = 1.2, 1.6, 10.4 Hz, 1 H), 4.19 (ddddd, *J* = 1.2, 1.2, 4.8, 6.0, 7.3 Hz, 1 H), 3.24-3.17 (m, 2 H), 2.05-1.94 (m, 2 H), 0.90 (s, 9 H), 0.10 (s, 3 H), 0.05 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 140.5, 115.0, 73.8, 41.8, 26.0, 2.8, -4.1, -4.6.



2-192

(5*S*)-Pyrrolidin-2-one-5-carbothioic acid ethyl ester (2-192). A solution of (*S*)-pyroglutamic acid (**2-39**) (20.0 g, 150 mmol) in a mixture of dry CH_2Cl_2 (300 mL) and dry DMF (160 mL) was cooled to 0 °C and treated with DMAP (1.85 g, 15.0 mmol) and EtSH (13.8 mL, 180 mmol). To this colorless solution was added DCC (40.5 g, 180 mmol) in one batch and a colorless suspension developed quickly. The reaction was allowed to warm to room temperature over 16 h and a thick slurry developed, which was filtered through Celite washed with CH_2Cl_2 (200 mL) and concentrated in vacuo. The crude material was taken up in EtOAc (200 mL) and

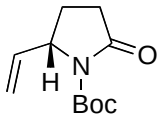
washed with brine (3 x 100 mL), dried ($MgSO_4$), filtered, concentrated in vacuo, and the mixture was purified by chromatography on SiO_2 (90% EtOAc/Hex followed by 100% EtOAc) to afford the rich fractions of **2-192** as a slurry (urea byproduct) that were suspended in a minimal amount of EtOAc and filtered through Celite to yield pure **2-192** (18.6 g, 107 mmol, 71%) as a yellow oil (stench): $[\alpha]_D$ = -83.0 (*c* 1.0, $CHCl_3$); IR (neat) 3227, 2933, 1679, 1417, 1265, 1231, 1084, 730, 700 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.78 (bs, 1 H), 4.28 (dd, *J* = 3.3, 8.3 Hz, 1 H), 2.90 (dq, *J* = 7.4, 12.6 Hz, 2 H), 2.53-2.41 (m, 2 H), 2.31 (ddd, *J* = 4.4, 9.4, 14.2 Hz, 1 H), 2.19 (ddd, *J* = 4.4, 9.8, 13.4 Hz, 1 H), 1.26 (t, *J* = 7.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 201.2, 178.7, 62.6, 28.9, 26.1, 23.4, 14.6; HRMS (EI) *m/z* calculated for $C_7H_{12}NOS$ $[M+H]^+$ 174.0589 found 174.0589.



2-193

(5*S*)-*N*-(*tert*-Butyloxycarbonyl)pyrrolidin-2-one-5-carbothioic acid ethyl ester (2-193). To a stirred solution of **2-192** (6.00 g, 34.6 mmol) in MeCN (34 mL) cooled to 0 °C was added Boc_2O (8.28 mL, 35.0 mmol) followed by DMAP (470 mg, 3.46 mmol), and the reaction mixture developed a dark red color accompanied by gas evolution that ceased after 20 min. After stirring for 1 h at room temperature, the reaction mixture was quenched with sat. aq. NH_4Cl (50 mL), diluted with H_2O (50 mL) and EtOAc (100 mL). The organic layer was separated and washed with H_2O (25 mL), brine (25 mL), dried ($MgSO_4$), filtered, concentrated in vacuo, and the residue was purified by chromatography on SiO_2 (30% EtOAc/Hex) to afford **2-193** (7.9 g, 28.7

mmol, 83% yield) as a colorless oil that solidified upon standing: mp 58.7 - 60.9 °C; $[\alpha]_D$ -47.4 (*c* 1.02, $CHCl_3$); IR (neat) 2969, 2929, 1791, 1704, 1675, 1456, 1366, 1331, 1302, 1251, 1152, 1022, 988, 837, 716 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 4.71 (dd, *J* = 2.4, 9.7 Hz, 1 H), 2.95 (m, 2 H), 2.66 (ddd, *J* = 10.3, 10.3, 17.7 Hz, 1 H), 2.48 (ddd *J* = 2.9, 9.5, 17.6 Hz, 1 H), 2.32 (dddd, *J* = 10.1, 10.1, 13.4, 20.0 Hz, 1 H), 2.03 (dddd, *J* = 2.6, 2.6, 9.72, 12.5 Hz, 1 H), 1.49 (s, 9 H), 1.28 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 199.4, 173.6, 149.1, 84.0, 65.5, 31.0, 28.0, 23.4, 22.5, 14.8; HRMS (ESI) *m/z* calculated for $C_{12}H_{19}NO_4Na$ $[M+Na]^+$ 296.0932 found 296.0928.

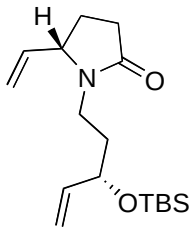


2-195

(5*S*)-*N*-(*tert*-Butyloxylcarbonyl)-5-vinylpyrrolidin-2-one (2-195). To a solution of **2-193** (3.90 g, 14.3 mmol) in acetone (30 mL) cooled to 0 °C was added Pd/C (0.64 g, 0.60 mmol), and Et_3SiH (6.83 mL, 42.80 mmol) was added to the black slurry dropwise over 15 minutes. The reaction mixture was allowed to warm to room temperature, and vigorous gas evolution was observed. After 20 min the reaction mixture was filtered through Celite washed with 1:1 EtOAc/Hex and the volatiles were removed in vacuo at 30 °C. The resulting pale yellow oil, **2-194**, was immediately used in the next step without further purification.

In a separate flask, a colorless slurry of $MePPh_3Br$ (17.2 g, 47.1 mmol) in dry THF (70 mL) was treated with KO*t*-Bu (4.80 g, 42.77 mmol) cooled with a water bath at room temperature. The resulting yellow slurry was stirred for 30 min and crude **2-194** in dry THF (35 mL) was added dropwise via an addition funnel. After 30 min the reaction mixture was quenched

with sat. aq. NH_4Cl (50 mL) and extracted with EtOAc (3 x 25mL). The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and the residue was purified by chromatography on SiO_2 (70% EtOAc/Hex) to afford **2-194** (2.90 g, 13.7 mmol, 96% yield over 2 steps) as a light yellow oil: $[\alpha]_D$ -24.3 (*c* 1.07, $CHCl_3$); IR (neat) 2980, 2934, 1780, 1749, 1715, 1367, 1302, 1285, 1254, 1148, 1019, 849 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 5.84 (ddd, *J* = 6.1, 10.2, 16.6 Hz, 1 H), 5.18 (dd, *J* = 1.3, 1.7 Hz), 5.16 (dd, *J* = 1.0, 4.2 Hz, 1 H), 4.63, 2.56 (ddd, *J* = 9.0, 10.9, 17.5 Hz, 1 H), 2.42 (ddd, *J* = 2.9, 9.0, 17.5 Hz, 1 H), 2.21 (dddd, *J* = 8.8, 8.8, 11.0, 12.8 Hz, 1 H), 1.80 (dddd, *J* = 2.6, 2.6, 8.9, 12.6 Hz, 1 H), 1.49 (s, 9 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.5, 149.9, 136.8, 115.5, 83.0, 59.8, 31.2, 28.1, 24.4; HRMS (EI) *m/z* calculated for $C_{11}H_{17}NO$ ($M^{\cdot+}$) 211.1208 found 211.1205.

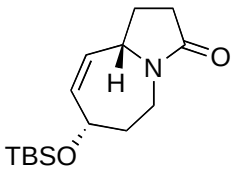


2-189

(5*S*)-*N*-[(3*S*)-3-(*tert*-Butyldimethylsilyloxy)pent-4-enyl]-5-vinylpyrrolidin-2-one (189). To a stirred solution of **2-195** (7.0 g, 33.1 mmol) in dry CH_2Cl_2 (480 mL) was added TFA (12.4 mL, 166 mmol). The reaction mixture was stirred at room temperature for 1 h and sat. aq. $NaHCO_3$ (400 mL) was added. The biphasic mixture was diluted with H_2O (100 mL), and the aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to afford **2-141** (3.51 g, 31.6 mmol, 95%) as a yellow oil: ^1H NMR (600 MHz, $CDCl_3$) δ 7.01 (bs, 1 H), 5.77 (ddd, *J* = 6.6, 10.2, 17.0 Hz, 1 H), 5.19 (ddd, *J* =

0.9, 0.9, 17.1 Hz, 1 H), 5.08 (ddd, *J* = 1.0, 1.0, 10.2 Hz, 1 H), 4.13 (m, 1 H), 2.35-2.23 (m, 3 H), 1.82-1.75 (m, 1 H).

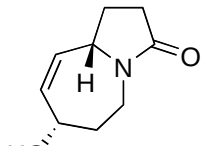
To a mixture of **2-141** (2.00 g, 18.0 mmol) and **2-188** (6.46 g, 19.8 mmol) in toluene (300 ml) and NaOH (sat. aq, 300 mL) in a 2 L RBF was added Bu_4NHSO_4 (5.29 g, 21.6 mmol) and the biphasic mixture was vigorously stirred with an overhead stirrer into an emulsion for 1 h. The biphasic mixture was diluted with H_2O (300 mL) and extracted with EtOAc (3 x 200 mL), dried, filtered, concentrated, and the crude orange oil was purified by chromatography on SiO2 (50% EtOAc/Hex) to afford **2-189** (4.20 g, 13.6 mmol, 75%) as a light yellow oil and a : $[\alpha]_D$ +40.3 (*c* 0.63, $CHCl_3$); IR (neat) 2954, 2929, 2856, 1689, 1413, 1249, 1085, 923, 833, 774 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 5.78 (ddd, *J* = 5.9, 10.3, 17.0 Hz, 1 H), 5.64 (ddd, *J* = 8.5, 9.9, 17.0 Hz, 1 H), 5.23 (d, *J* = 17.0, 1 H), 5.20 (d, *J* = 10.1, 1 H), 5.16 (ddd, *J* = 1.5, 1.5 17.1 Hz, 1 H), 5.02 (ddd, *J* = 1.4, 1.4, 10.4 Hz, 1 H), 4.13 (dddd, *J* = 1.3, 1.3, 4.7, 11.9 Hz, 1 H), 4.02 (ddd, *J* = 5.6, 8.2, 8.2 Hz, 1 H), 3.54 (ddd, *J* = 5.5, 11.0, 13.6 Hz, 1 H), 3.00 (ddd, *J* = 5.1, 10.7, 13.7 Hz, 1 H), 2.40 (ddd, *J* = 6.1, 9.7, 16.6 Hz, 1 H), 2.31 (ddd, *J* = 6.8, 9.6, 13.2 Hz, 1 H), 2.20 (dddd, *J* = 6.0, 7.7, 9.5, 13.0 Hz, 1 H), 1.76-1.60 (m, 3 H), 0.88 (s, 9 H), 0.04 (s, 3 H), 0.01 (s, 3 H)); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.9, 141.2, 137.9, 118.1, 114.2, 72.1, 61.5, 37.8, 35.3, 30.3, 26.0, 18.3, -4.2, -4.8. HRMS (EI) *m/z* calculated for $C_{17}H_{31}NO_2Si$ ($M^{\cdot+}$) 309.2124 found 309.2119.



2-207

(7*S*,9a*S*)-7-(*tert*-Butyldimethylsilyloxy)-1,2,5,6,7,9a-hexahydropyrrolo[1,2-*a*]azepin-3-one (2-207). To a solution of **2-189** (2.85 g, 9.21 mmol) in dry CH_2Cl_2 (460 mL) was added

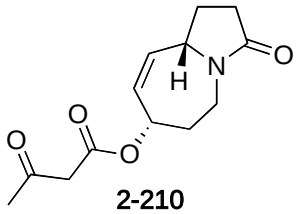
Grubbs 2nd generation catalyst (390 mg, 0.460 mmol, 5 mol %) and the resulting pink solution was heated to reflux for 5 h. The reaction was cooled to room temperature and the entire reaction volume was directly applied to a column of SiO_2 (14" length, 3" diameter) and the system was eluted with 50% EtOAc/Hex then 100% EtOAc to afford **2-207** (2.37 g, 8.42 mmol, 91%) as an off-white solid and a 6:1 ratio of diastereomers. An analytical sample was purified by chromatography on SiO_2 (50% EtOAc/Hex followed by 100% EtOAc) to afford **2-207** as a single diastereomer: mp 90.9 - 92.9 °C; $[\alpha]_D$ –28.1 (*c* 0.27, $CHCl_3$); IR (neat) 2954, 2928, 2885, 2857, 1664, 1470, 1455, 1432, 1418, 1360, 1277, 1252, 1073, 1050, 861, 835, 774 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 5.74 (dddd, *J* = 1.0, 3.4, 3.4, 12.1 Hz, 1 H), 5.47 (ddd, *J* = 2.4, 2.4, 12.1 Hz, 1 H), 4.44 (dddd, *J* = 2.0, 3.6, 5.5, 8.9 Hz, 1 H), 4.26-4.19 (m, 2 H), 2.91 (ddd, *J* = 2.5, 10.0, 10.0 Hz, 1 H), 2.34 (ddd, *J* = 6.6, 9.7, 16.4 Hz, 1 H), 2.34-2.21 (m, 2 H), 1.97-1.92 (m, 1 H), 1.83-1.77 (m, 2 H), 0.89 (s, 9 H), 0.07 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.9, 138.1, 129.8, 71.3, 58.0, 38.9, 36.0, 30.2, 26.5, 25.9, 18.3, -4.5, -4.6. HRMS (ESI) *m/z* calculated for $C_{15}H_{27}NO_2SiNa$ $[M+Na]^+$ 304.1709 found 304.1736.



2-208

(7*S*,9a*S*)-7-Hydroxy-1,2,5,6,7,9a-hexahydropyrrolo[1,2-*a*]azepin-3-one (**2-208**). To a solution of **2-207** (480 mg, 1.70 mmol) in MeOH (8 mL) was added *p*-TsOH (32.4 mg, 0.170 mmol) and the pale yellow solution was stirred at rt for 4. The reaction mixture was treated with pyridine (0.2 mL) and the volatiles were removed in vacuo. The brown residue was purified by chromatography on SiO_2 (100% EtOAc, then 10% MeOH in EtOAc) to afford **2-208** (279 mg,

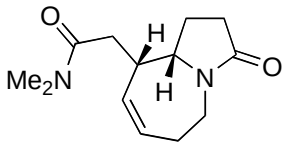
1.67 mmol, 98%) as a green-brown hygroscopic solid and an inseparable mixture of diastereomers: IR (neat) 3296, 2949, 2925, 2853, 1643, 1421, 1317, 1261, 1052, 910 cm^{-1}; Major diastereomer: ^1H NMR (600 MHz, $CDCl_3$) δ 5.82 (ddddd, *J* = 1.2, 2.7, 3.6, 6.0, 12.1 Hz, 1 H), 5.55 (ddd, *J* = 2.3, 2.3, 12.1 Hz, 1 H), 4.47-4.45 (m, 1 H), 4.28-4.22 (m, 2 H), 2.93 (dddd, *J* = 3.2, 9.6, 12.3, 13.6 Hz, 1 H), 2.44 (ddd, *J* = 6.9, 9.7, 16.5 Hz, 1 H), 2.35-2.23 (m, 2 H), 2.08 (dddd, *J* = 1.2, 2.5, 3.7, 7.3 Hz, 1 H), 2.02 (d, *J* = 6.1 Hz, 1 H), 1.87-1.78 (m, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.1, 136.4, 131.1, 70.5, 58.2, 38.6, 35.7, 30.1, 26.5; Minor diastereomer: ^1H NMR (600 MHz, $CDCl_3$) δ (distinctive peaks) 5.73 (dm, *J* = 11.7 Hz, 1 H), 4.32 (dddd, *J* = 2.4, 2.4, 2.4, 4.7, 1 H), 4.00 (ddd, *J* = 5.7, 9.9, 13.9 Hz, 1 H), 3.14 (dd, *J* = 5.3, 5.3, 13.9 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.7, 135.6, 131.7, 68.7, 58.0, 37.9, 35.1, 29.9, 26.8; HRMS (ESI) *m/z* calculated for $C_9H_{13}NO_2Na$ $[M+Na]^+$ 190.0844, found 190.0829.



2-210

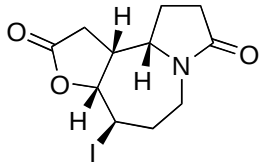
(7*S*, 9a*S*)-7-[3-Oxobutyryloxy]-1,2,5,6,7,9a-hexahydropyrrolo[1,2-*a*]azepin-3-one (2-210). A solution of **2-208** (30.0 mg, 0.179 mmol) and **2-209** (27.6 µL, 0.197 mmol) in xylenes (1 mL) was heated to 130 °C for 10 min. The dark reaction mixture was allowed to cool to room temperature and was directly subjected to purification by chromatography on SiO_2 (100% EtOAc followed by 10% MeOH/EtOAc) to afford **2-210** (24.0 mg, 0.096 mmol, 53%) as a bright yellow oil and a mixture of keto and enol tautomers (~10:1 by ^1H NMR analysis): IR (neat) 3369, 2929, 1740, 1699, 1607, 1408, 1362, 1302, 1253, 1170, 1151, 1046 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 5.76 (ddd, *J* = 3.5, 3.5, 12.1 Hz, 1 H), 5.68 (ddd, *J* = 1.9, 1.9, 12.1 Hz, 1 H), 5.54-5.51 (m, 1

H), 4.31-4.27 (m, 1 H), 4.22 (ddd, *J* = 3.7, 7.4, 11.0, 1 H), 3.47 (s, 2 H), 2.97 (ddd, *J* = 3.1, 8.9, 12.4 Hz, 1 H), 2.44-2.39 (m, 1 H), 2.34 (dd, *J* = 5.6, 9.3 Hz, 1 H), 2.31-2.27 (m, 1 H), 2.61 (s, 3 H), 2.11-2.06 (m, 1 H), 2.01-1.96 (m, 1 H), 1.85-1.79 (m, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 200.4, 174.1, 166.5, 133.9, 131.2, 72.5, 58.2, 50.1, 38.2, 31.9, 30.4, 30.0, 26.4, enol: 176.3, 171.8, 133.2, 132.0, 89.8, 71.2, 58.1, 38.5, 32.1, 31.8, 30.1, 26.4, 21.4.



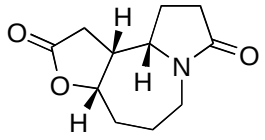
2-219

(9*R*, 9a*S*)-*N*,*N*-Dimethyl-2-(2,3,5,6,9,9a-hexahydro-1*H*-pyrrolo[1,2-*a*]azepin-3-on-9-yl)acetamide (**2-219**)**.** A microwave vial charged with **19** (106 mg, 0.634 mmol) and *N*,*N*-dimethylacetamide dimethyl acetal (823 µL, 5.07 mmol) in diglyme (4 mL) was capped and heated in the microwave reactor to 180 °C for 15 min. The brown solution was directly applied to a column of SiO_2 and chromatography (100 % CH_2Cl_2 then 5% MeOH/CH_2Cl_2) afforded **22** (138 mg, 0.584 mmol, 92%) as a brown syrup and a mixture of inseparable diastereomers: Major diastereomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.71-5.66 (m, 2 H), 4.10 (ddd, *J* = 2.9, 7.0, 7.0 Hz, 1 H), 3.64 (ddd, *J* = 5.2, 5.2, 11.6 Hz, 1 H), 3.45 (ddd, *J* = 5.9, 5.9, 12.3 Hz, 1 H), 3.17-3.13 (m, 1 H), 2.99 (s, 3 H), 2.95 (s, 3 H), 2.42-2.33 (m, 6 H), 2.13-2.07 (m, 1 H), 1.71-1.65 (m, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.9, 171.1, 132.3, 129.6, 61.2, 41.0, 39.1, 37.5, 35.8, 33.1, 31.0, 27.6, 22.6. Minor diastereomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ (distinctive peaks) 5.84 (dddd, *J* = 2.5, 6.0, 6.0, 11.4 Hz, 1 H), 5.48-5.46 (m, 1 H), 3.91 (ddd, *J* = 3.2, 7.5, 10.6 Hz, 1 H), 3.72 (ddd, *J* = 6.7, 6.7, 9.9 Hz, 1 H), 3.13-3.09 (m, 1 H), 2.48-2.42 (m, 1 H); HRMS (ESI) *m/z* calculated for $C_{13}H_{20}N_2O_2Na$ $[M+Na]^+$ 259.1422, found 259.1421.



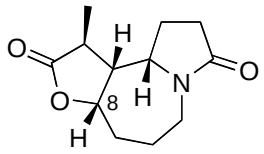
2-220

(2*R*,3*R*,4*R*,6a*S*)-4-Iodooctahydro-3-oxa-6a-azacyclopenta[*e*]azulene-2,7-dione (2-220). A stirred solution of **2-219** (273 mg, 1.16 mmol) in THF (3 mL) and pH 5.5 phosphate buffer (3 mL) was treated with I_2 (880 mg, 3.47 mmol). The flask was wrapped with with aluminum foil and stirred for 1 h at room temperature. The reaction mixture was quenched with sat. aq. $Na_2S_2O_3$ (3 mL) and stirred for 5 min. The mixture was partitioned between EtOAc (15 mL) and H_2O (15 mL), and the aqueous phase was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried ($MgSO_4$), filtered, concentrated and the crude reside was purified by chromatography on SiO_2 (100% CH_2Cl_2 followed by 10% MeOH/CH_2Cl_2) to afford **2-220** (383 mg, 1.14 mmol, 98%) as a light yellow solid as a 6:1 inseparable mixture of diastereomers by ^{1}H NMR spectroscopy: mp 183.7 - 184.7 °C (decomp.); $[\alpha]_D$ –11.7 (*c* 1.5, CH_2Cl_2); Major diastereomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.14 (dd, *J* = 4.2, 9.0 Hz, 1 H), 4.61-4.59 (m, 2 H), 4.26 (ddd, *J* = 3.8, 5.7, 14.4 Hz, 1 H), 3.16-3.08 (m, 2 H), 2.56 (dd, *J* = 9.8, 17.8 Hz, 1 H), 2.52 (dd, *J* = 10.8, 17.6 Hz, 1 H), 2.41-2.29 (m, 3 H), 2.03 (dddd, *J* = 2.8, 5.8, 8.0, 10.0 Hz, 1 H), 1,82 (dddd, *J* = 1.7, 3.8, 9.9, 15.6 Hz, 1 H), 1.65-1.61 (m, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.7, 173.7, 85.4, 55.5, 44.6, 42.2, 30.7, 29.7, 29.4, 27.8, 24.5. Minor diastereomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ (distinctive peaks) 4.80 (app t, *J* = 6.1 Hz, 1 H), 4.07 (ddd, *J* = 4.8, 9.5, 14.3 Hz, 1 H), 3.02-2.97 (m, 1 H), 2,84-2.79 (m, 1 H), 2.11-2.07 (m, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.7, 173.9, 85.9, 56.4, 43.8, 43.6, 34.9, 30.2, 28.7, 24.8, 24.6. HRMS (EI) *m/z* calculated for $C_{11}H_{14}NO_3I$ ($M^{\cdot+}$) 335.0018, found 335.0011.



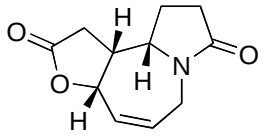
2-221

(8*S*, 9*R*, 9a*S*)-1,2,5,6,7,8,9,9a-octahydrodihydrofuro[3,2-*c*]pyrrolo[1,2-*a*]azepine-3,11-dione (2-221). To **2-220** (180 mg, 0.254 mmol) suspended in dry toluene (4 mL) was added with *n*-Bu_3SnH (180 uL, 0.645 mmol) and the system was degassed (freeze, pump, thaw x 3) and heated to 80 °C using an oil bath. Through the reflux condensor was added 1 mL of a stock solution of AIBN (57.3 mg, 0.349 mmol) in dry toluene (2 mL) and the system was heated to reflux for 1 h, cooled to 80 °C and the remainder of the AIBN solution was added over 1 h. The reaction mixture was heated to reflux for another 1 h allowed to cool to room temperature, and directly applied to a column of SiO_2 impregnated with 10% w/w KF (s) and eluted with 5% MeOH/DCM to afford a yellow syrup (109 mg, 0.521 mmol, 97%). MPLC purification (5% MeOH/EA) provided **2-221** as a light yellow solid and a single diastereomer: $[\alpha]_D$ –21.0 (c = 0.3, $CHCl_3$); IR (neat) 3470, 2929, 2858, 1761, 1670, 1427, 1372, 1280, 1185, 1078, 992 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 4.86 (ddd, *J* = 4.4, 4.4, 8.9 Hz, 1 H), 4.28 (ddd, *J* = 3.9, 5.7, 13.8 Hz, 1 H), 3.95-3.93 (m, 1 H), 3.03 (dddd, *J* = 1.9, 9.2, 10.8, 10.8 Hz, 1 H), 2.72 (ddd, *J* = 3.2, 10.2, 13.4 Hz, 1 H), 2.50 (d, *J* = 10.7 Hz, 1 H), 2.42-2.32 (m, 3 H), 2.17 (ddd, *J* = 4.9, 8.4, 14.5 Hz, 1 H), 1.91 (dddd, *J* = 1.0, 3.8, 10.4, 15.4 Hz, 1 H), 1.73-1.68 (m, 2 H), 1.57 (dddd, *J* = 3.7, 10.7, 10.7, 19.3 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.7, 175.3, 81.0, 56.6, 44.8, 43.9, 31.9, 29.5, 27.8, 24.8, 21.3; HRMS (ESI) *m/z* calculated for $C_{11}H_{15}NO_3Na$ $[M+Na]^+$ 232.0950, found 232.0936.



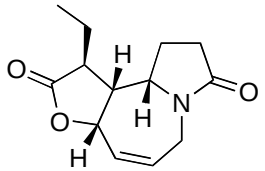
8-*epi*-stemoamide
(**2-222**)

(8*S*, 9*R*, 9a*S*, 10*S*)-10-Methyl-1,2,5,6,7,8,9,9a-octahydrodihydrofuro[3,2-*c*]pyrrolo [1,2-*a*]azepine-3,11-dione (2-222). To a cooled solution of **2-221** (40.0 mg, 0.191 mmol) in dry THF (2 mL) at –78 °C was added a feshly prepared solution of LiHMDS in THF (0.286 µL, 0.286 mmol, 1.0 M) and the colorless solution was kept at –78 °C for 2 h. MeI (54.0 µL, 0.860 mmol) was added and the solution was stirred for 4 h and the reaction mixture was quenched with sat. aq. NH_4Cl (2 mL). The biphasic system was allowed to warm to room temperature and the aqueous phase was extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried ($MgSO_4$), filtered, concentrated, and MPLC purification (5% MeOH/EtOAc) provided **2-222** (20.0 mg, 0.090 mmol, 47%) as a colorless solid: $[\alpha]_D$ –60.0 (c = 0.10, $CHCl_3$); IR (neat) 2958, 2929, 2858, 1740, 1687, 1448, 1422, 1330, 1278, 1188, 1074, 991 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 4.81 (ddd, *J* = 3.7, 3.7, 9.5 Hz, 1 H), 4.31 (dddd, *J* = 0.9, 4.5, 4.5, 13.9 Hz, 1 H), 3.96 (dm, 9.3 Hz, 1 H), 2.64 (ddd, *J* = 1.6, 10.4, 10.4 Hz, 1 H), 2.64-2.61 (m, 1 H), 2.56 (ddddd, *J* = 7.0, 7.0, 10.3, 14.1, 14.1 Hz, 1 H), 2.49-2.43 (m, 1 H), 2.40-2.34 (m, 2 H), 2.24 (ddddd *J* = 1.0, 1.0, 4.0, 8.0, 14.3 Hz, 1 H), 1.88-1.82 (m, 2 H), 1.72-1.67 (dddd, *J* = 3.7, 7.7, 7.7, 11.9 Hz, 1 H), 1.45 (dddd, *J* = 3.6, 11.6, 11.6, 15.0, 1 H), 1.40 (d, *J* = 7.0 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 178.6, 175.6, 79.2, 57.3, 52.1, 43.8, 34.3, 32.2, 29.3, 24.0, 21.6, 18.2; HRMS (EI) *m/z* calculated for $C_{12}H_{17}NO_3$ ($M^{\cdot+}$) 223.1208, found 223.1201.



2-223

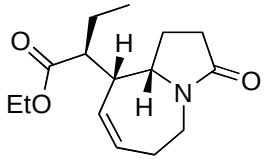
(2*R*,3*S*,6a*S*)-3a,6,8,9,9a,9b-Hexahydro-1*H*-3-oxa-6a-azacyclopenta[*e*]azulene-2,7-dione (**2-223**)**.** A stirred solution of **2-220** (40.0 mg, 0.119 mmol) in toluene (1 mL) was treated with DBU (44.6 µL, 0.298 mmol) and the reaction mixture was heated to 80 °C for 4 h. The volatiles were removed in vacuo and the reside was purified by chromatography on SiO_2 (5% MeOH/CH_2Cl_2) to provide **2-223** (22.0 mg, 0.106 mmol, 89%) contaminated with grease as a colorless crystalline solid and a mixture of diastereomers: $[\alpha]_D$ +95.5 (c = 0.31, $CHCl_3$); IR (neat) 2917, 2850, 1770, 1684, 1661, 1448, 1428, 1377, 1319, 1271, 1234, 1167, 979, 916, 740 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 5.75 (dddd, *J* = 1.7, 3.3, 5.1, 12.8 Hz, 1 H), 5.65 (bdd, *J* = 1.2, 12.7 Hz, 1 H), 5.17 (ddd, *J* = 1.6, 3.7, 7.5 Hz, 1 H), 4.62 (dddd, *J* = 1.5, 1.5, 5.5, 18.7 Hz, 1 H), 4.05-4.01 (m, 1 H), 3.62 (bdd, *J* = 1.4, 18.7 Hz, 1 H), 3.04-2.99 (m, 1 H), 2.54 (dd, *J* = 12.1, 16.8 Hz, 1 H), 2.44, (dd, *J* = 7.9, 16.7 Hz, 1 H), 2.42-2.33 (m, 4 H), 1.78-1.75 (m, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.0, 174.9, 126.8, 126.3, 79.2, 55.6, 45.7, 42.2, 29.4, 27.5, 24.5; HRMS (ESI) *m/z* calculated for $C_{11}H_{13}NO_3Na$ $[M+Na]^+$ 230.0793, found 230.0782.



2-224

(1*S*, 8*S*, 9*R*, 9a*S*)-1-Ethyl-1,2,5,8,9,9a-hexahydrodihydrofuro[3,2-*c*]pyrrolo[1,2*a*]azepine-3,11-dione (2-224). To a stirred suspension of **2-223** (41.0 mg, 0.199 mmol) in dry THF (2 mL) cooled to –78 °C was added freshly prepared LiHMDS (515 µL, 0.258 mmol, 0.5 M in

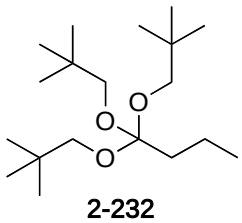
THF/Hex) and the brown solution that developed was allowed to warm to 0 °C after 15 min, then cooled to –78 °C after 5 min. The solution was treated with EtI (158 µL, 1.98 mmol) and the mixture was allowed to passively warm to room temperature over 5 h. To the brown reaction mixture was added SiO_2 (~0.5 g) and the slurry was directly applied to a column of SiO_2 and was eluted with 5% MeOH/CH_2Cl_2 followed by 10% MeOH/EA to afford **2-224** (24.0 mg, 0.102 mmol, 52%) as a brown gum: IR (neat) 3262, 2954, 2929, 2856, 1697, 1404, 1250, 1169, 1084, 926, 834, 775cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.87-5.86 (m, 2 H), 5.07 (ddd, *J* = 1.4, 2.9, 8.2 Hz, 1 H), 4.24 (d, *J* = 16.2 Hz, 1 H), 4.07 (ddd, *J* = 2.1, 4.6, 9.1 Hz, 1 H), 3.95-3.92 (dm, 1 H), 2.73 (ddd, *J* = 2.1, 8.2, 8.2, 1 H), 2.62 (ddd, *J* = 5.4, 5.4, 8.1 Hz, 1 H), 2.52 (ddd, *J* = 7.4, 10.3, 17.2 Hz, 1 H), 2.43-2.38 (m, 1 H), 2.32 (dddd, *J* = 7.3, 9.0, 10.6, 13.2 Hz, 1 H), 1.95 (ddd, *J* = 2.4, 7.4, 14.9 Hz, 1 H), 1.78 (dddd, *J* = 5.6, 5.6, 13.4, 15.2 Hz, 1 H), 1.72 (dddd, *J* = 5.9, 7.4, 7.4, 13.2 Hz, 1 H), 1.05 (t, *J* = 7.4 Hz, 3 H).



2-230a

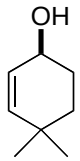
Ethyl (*S*)-2-((9*R*,9a*S*,*Z*)-3-oxo-2,3,5,6,9,9a-hexahydro-1*H*-pyrrolo[1,2-*a*]azepin-9-yl) butanoate (2-230a). To a flask charged with **2-208** (73.0 mg, 0.437 mmol) was added degassed *o*-DCB (3.6 mL), triethyl orthobutyrate (524 µL, 2.19 mmol) and HCl in dioxane (11.0 µL, 0.437 mmol, 0.1 equiv). The reaction mixture was heated in oil bath to 130 °C for 36 h at which point the reaction mixture was transferred to a microwave vial and was twice heated to 200 °C for 1 h in the microwave reactor. The reaction mixture was directly applied to a column of SiO_2 and purified (5% MeOH/CH_2Cl_2) to afford **2-230a** and **2-230b** (49.0 mg, 0.184 mmol, 42%), which

existed as a 2.5:1 mixture by ^{1}H NMR spectroscopy that were separated by MPLC (100% EtOAc): $[\alpha]_D$ –27.2 (*c* 0.33, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.53 (dddd, *J* = 2.6, 5.6, 8.6, 11.2 Hz, 1 H), 5.25 (ddd, *J* = 2.5, 5.4, 11.4, 1 H), 4.21-4.11 (m, 2 H), 4.01 (ddd, *J* = 5.8, 5.8, 8.9 Hz, 1 H) 3.86 (ddd, *J* = 2.6, 7.4, 14.0 Hz, 1 H), 3.18 (ddd, *J* = 5.7, 10.6, 14.2 Hz, 1 H), 3.14-3.11 (m, 1 H), 2.56-2.49 (m, 1 H), 2.41-2.29 (m, 4 H), 1.94 (dddd, *J* = 2.3, 6.5, 8.7, 12.3 Hz, 1 H), 1.70-1.62 (m, 3 H), 1.27 (t, *J* = 7.1 Hz, 3 H), 0.92 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.9, 174.8, 130.4, 126.3, 60.8, 60.7, 48.5, 41.5, 37.6, 31.0, 28.9, 23.7, 21.9, 14.4, 11.8; HRMS (ESI) *m/z* calculated for $C_{15}N_{23}N_2O_3Na$ $[M+Na]^+$ 288.1576, found 288.1565.



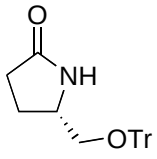
2-232

Trineopentyl orthobutyrate (2-232). A solution of triethyl orthobutyrate (2.38 mL, 9.93 mmol) and neopentyl alcohol (3.54 g, 39.7 mmol) was treated with HCl/dioxane (124 µL, 0.500 mmol) and heated to 95 °C in an uncapped flask in an oil bath overnight. Orthoester **2-232** was isolated by distillation under reduced pressure (105 °C at 2 Torr) as a colorless oil (2.11 g, 6.67 mmol, 67%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.14 (s, 6 H), 1.68-1.66 (m, 2 H), 1.45-1.39 (m, 2 H), 0.91 (s, 27 H), 0.90 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 114.0, 71.5, 32.5, 31.9, 27.1, 16.9, 14.5.



2-238

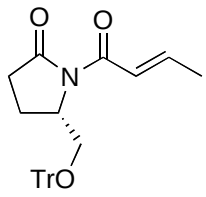
4,4-Dimethylcyclohex-2-enol (2-238). To a flask containing $LiAlH_4$ (20.3 mL, 20.3 mmol, 1 M in Et_2O) in dry THF (200 mL) cooled to 0 °C was added 4,4-dimethyl-2-cyclohexen-1-one (10.6 mL, 78.1 mmol) in dry THF (700 mL) by addition funnel. The reaction was allowed to warm to room temperature and was stirred for 2 h. The reaction mixture was carefully poured into a separatory funnel containing Et_2O (200 mL) and brine (200 mL). The aqueous phase was extracted with Et_2O (3 x 100 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated to afford **2-238** (9.42 g, 74.6 mmol, 96%) as a yellow oil. Analytical data matched previously reported data for **2-238**:[142] ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.59 (dd, *J* = 3.0, 10.0 Hz, 1 H), 5.52 (d, *J* = 10.0 Hz, 1 H), 4.14 (bm, 1 H), 1.94-1.89 (m, 1 H), 1.65-1.55 (m, 2 H), 1.44-1.40 (m, 1 H), 1.37 (d, *J* = 6.4 Hz, 1 H), 1.01 (s, 3 H), 0.97 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 140.7, 127.5, 66.0, 33.7, 32.0, 30.4, 29.2, 29.2.



3-4

(5*S*)-5-(Trityloxymethyl)-2-pyrrolidinone (**3-4**). Following a literature procedure,[143] to a solution of (*S*)-(+)-5-(hydroxymethyl)-2-pyrrolidinone (2.30 g, 19.4 mmol) in dry CH_2Cl_2 (200 mL) was added DMAP (355 mg, 2.91 mmol) and NEt_3 (4.12 mL, 29.1 mmol), and the solution

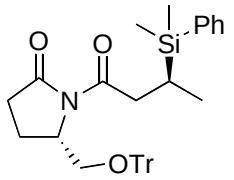
was cooled to 0 °C. Trityl chloride (8.10 g, 29.1 mmol) was added in a single portion and the reaction mixture was allowed to warm to room temperature overnight. The reaction mixture was poured into sat. aq. $NaHCO_3$ (200 mL) and the biphasic system was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and the yellow syrup was purified by chromatography on SiO_2 (100% CH_2Cl_2 then 5% MeOH/CH_2Cl_2) to afford **3-4** (6.58 g, 18.4 mmol, 95% yield) as a colorless foamy solid. Analytical data matched previously reported data for **3-4**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40-7.39 (m, 6 H), 7.32-7.29 (m, 6 H), 7.27-7.24 (m, 3 H), 5.85 (bs, 1 H), 3.86 (dddd, *J* = 3.9, 5.8, 8.1, 8.1 Hz, 1 H), 3.21 (dd, *J* = 3.9, 9.3 Hz, 1 H), 2.99 (dd, *J* = 8.1, 9.3 Hz, 1 H), 2.32 (app t, *J* = 8.0 Hz, 2 H), 2.14 (dddd, *J* = 7.8, 7.8, 13.0, 15.4 Hz, 1 H), 1.66 (dddd, *J* = 5.8, 8.3, 8.3, 13.0 Hz, 1 H).



2-240

(5*S*)-1-Crotonoyl-5-(trityloxymethyl)-2-pyrrolidinone (**2-240**)**.** According to a literature procedure,[143] to a stirred solution of **3-4** (2.00 g, 5.59 mmol) in dry THF (50 mL) at –78 °C was added *n*-BuLi (5.59 mL, 6.71 mmol, l.2 M in hexanes) and the mixture was stirred for 30 minutes at –78 °C and *trans*-crotonoyl chloride (774 µL, 7.27 mmol) was added dropwise. After 40 min, the reaction was warmed to 0 °C and quenched with sat. aq. NH_4Cl (50 mL), diluted with H_2O (20 mL), and extracted with EtOAc (3 x 25 mL). The combined organic extracts were dried ($MgSO_4$), filtered, concentrated and purified by chromatography on SiO_2 (20% EtOAc/Hex) to afford **2-240** (4.47 g, 10.5 mmol, 85% yield) as a colorless foam. Analytical data matched previously reported data for **2-240**:[143] ^{1}H NMR (600 MHz, $CDCl_3$) δ

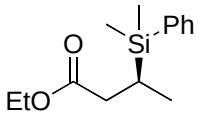
7.36-7.26 (m, 13 H), 7.22 (app tt, *J* = 1.2, 7.1 Hz, 3 H), 7.10 (dq, *J* = 7.0, 15.3 Hz, 1 H), 4.55-4.52 (m, 1 H), 5.82 (dd, *J* = 3.9, 9.8 Hz, 1 H), 3.13 (dd, *J* = 2.7, 9.8 Hz, 1 H), 2.97 (ddd, *J* = 10.0, 11.0, 17.9 Hz, 1 H), 2.50 (ddd, *J* = 1.8, 10.0, 11.8 Hz, 1 H), 2.12-2.05 (m, 1 H), 1.98 (dd, *J* = 1.7, 6.9 Hz, 3 H); ^{13}C NMR (150 MHz, CDCl3) δ 176.6, 165.9, 145.8, 143.8, 128.6, 128.1, 127.2, 124.1, 87.1, 64.3, 56.9, 33.6, 21.3, 18.7.



3-5

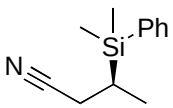
(5*S*)-1-{(3*S*)-3-[Dimethyl(phenyl)silyl]butanoyl}-5-(triphenylmethoxymethyl) pyrrolidin-2-one (**3-5**)**.** According to a literature procedure,[124] a solution of neat $ZnEt_2$ (180 µL, 1.76 mmol) in dry THF (5 mL) cooled to –78 °C was added a feshly prepared solution of $PhMe_2SiLi$ (1.60 mL, 1.88 mmol, 1.17 M in THF). The cooled reaction mixture was stirred for 30 min and **2-240** (500 mg, 1.175 mmol) was added in a single portion. The reaction was stirred for 1 h at –78 °C and was allowed to warm to 0 °C. The reaction mixture was carefully quenched with H_2O (10 mL) and diluted with sat. aq. Rochelle's salt solution (5 mL). The biphasic system was stirred 30 min and the aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and purified by chromatography on SiO_2 (10% EtOAc/Hex) to afford **3-5** (531 mg, 0.945 mmol, 80%, >20:1 *d.r.*) as a colorless foam. Analytical data matches previously reported data for **3-5**:[4] ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.58-7.56 (m, 2 H), 7.39-7.34 (m, 9 H), 7.27-7.20 (m, 9 H), 4.48-4.45 (m, 1 H), 3.51 (dd, *J* = 4.0, 9.8), 3.19 (dd, *J* = 2.7, 9.8 Hz, 1 H), 2,98 (dd, *J* = 3.2, 16.2 Hz, 1 H), 2.94 (dd, *J* = 9.8, 11.3 Hz, 1 H), 2.78 (dd, *J* = 11.4, 16.2 Hz, 1 H), 2.45 (ddd, *J* = 1.7, 9.9, 17.8 Hz, 1 H), 2.06 (dddd, *J* = 9.7, 11.2, 12.9,

19.1 Hz, 1 H), 1.96 (dddd, *J* = 1.4, 1.4, 9.7, 12.7 Hz, 1 H), 1.58 (ddddd, *J* = 3.3, 7.3, 7.3, 7.3, 18.6 Hz, 1 H), 0.94 (d, *J* = 7.3 Hz, 3 H), 0.38 (s, 3 H), 0.36 (s, 3 H).



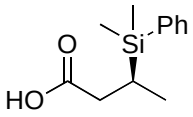
2-241

(3*S*)-3-Dimethyl(phenyl)silyl butyric acid ethyl ester (**2-241**). To a cooled solution of EtOH (1.08 mL, 16.4 mmoll) in THF (25 mL) at 0 °C was added *n*-BuLi (10.7 mL, 11.7 mmol, 1.1 M in hexanes). After 30 min the solution was warmed to room temperature for 30 min, then cooled to 0 °C for 15 min. A solution of **3-5** (1.32 g, 2.34 mmol) in THF (10 mL) was added and the reaction mixture was allowed to warm to room temperature over 1 h and was quenched with sat. aq. NH_4Cl (10 mL). The biphasic mixture was diluted with H_2O (10 mL) and Et_2O (10 mL) and the aqueous phase was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and purification of the crude residue by chromatography on SiO_2 (10% Et_2O/Hex) gave **2-241** (525 mg, 2.10 mmol, 89%) as a yellow, sweet-smelling oil. Analytical data matches previously reported data for **17**:[124] ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.5-7.48 (m, 2 H), 7.37-7.34 (m, 3 H), 4.08 (q, *J* = 7.1 Hz, 2 H), 2.37 (dd, *J* = 4.0, 15.2 Hz, 1 H), 2.04 (dd, *J* = 11.3, 15.2 Hz, 1 H), 1.44 (ddddd, *J* = 4.0, 7.4, 7.4, 7.4, 14.9 Hz, 1 H), 1.23 (t, *J* = 7.1 Hz, 3 H), 0.97 (d, *J* = 7.4 Hz, 3 H), 0.28 (s, 3 H), 0.28 (s, 3 H); ^{13}C NMR (150 MHz, CDCl3) δ 174.1, 137.4, 134.0, 129.2, 127.9, 60.3, 37.0, 16.6, 14.6, 14.4, –4.9, –5.2.



2-243

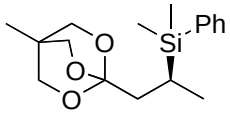
(*S*)-3-(Dimethyl(phenyl)silyl)butanenitrile (2-243). To a solution of **2-242** (158 mg, 0.765 mmol) in THF (2.4 mL) was added 28% NH_4OH in H_2O (2.39 mL, 19.1 mmol) followed by I_2 (213 mg, 0.842 mmol). The flask was wrapped in foil and the solution was stirred for 2 h. The reaction mixture was quenched by addition of sat. aq. $Na_2S_2O_3$ (2 mL), and the aqueous phase was extracted with Et_2O (3 x 5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to afford crude oil that was purified by chromatography on SiO_2 (10% Et_2O/Hex) to afford **2-243** (148 mg, 0.728 mmol, 95%) as a colorless oil: IR (neat) 3070, 2955, 2870, 2240, 1746, 1632, 1456, 1427, 1251, 1110, 832, 812, 773, 734, 699 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.48-7.47 (m, 2 H), 7.41-7.35 (m, 3 H), 2.39 (dd, *J* = 4.3, 16.9 Hz, 1 H), 2.08 (dd, *J* = 10.4, 16.9 Hz, 1 H), 1.27-1.22 (m, 1 H), 1.16 (d, *J* = 7.2 Hz, 3 H), 0.34 (s, 6 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 136.0, 133.9, 129.8, 128.2, 120.0, 2.06, 17.4, 14.6, –4.8, –5.5.



2-244

(3*S*)-3-Dimethyl(phenyl)silyl butyric acid (**2-244**)**.** A solution of **2-241** (936 mg, 3.73 mmol) in THF (10.5 mL) and MeOH (10.5 mL) at room temperature treated with 2M NaOH (3.73 mL, 7.47 mmol) and the reaction mixture was heated to 60 °C for 3 h. The solution was allowed to cool to room temperature and was diluted with sat. aq. NH_4Cl (10 mL) and acidified with 1N HCl to pH 2. The hazy solution was extracted with EtOAc (3 x 25 mL), and the combined organic layers were dried ($MgSO_4$), filtered, concentrated and purified by chromatography on SiO_2 (100% Hex followed by 20% EtOAc/Hex then 50% EtOAc/Hex) to afford **2-244** (831 mg, 3.73 mmol. 99%) as a yellow oil. Analytical data matches previously reported data for **18**:[144] ^1H NMR (600 MHz, $CDCl_3$) δ 11.1 (bs, 1 H), 7.50-7.49 (m, 2 H), 7.37-

7.35 (m, 3 H), 2.43 (dd, *J* = 3.8, 15.5 Hz, 1 H), 2.07 (dd, *J* = 11.4, 15.5 Hz, 1 H), 1.45-1.39 (ddddd, *J* = 3.8, 7.4, 7.4, 7.4, 14.7 Hz, 1 H), 1.01 (d, *J* = 7.3 Hz, 3 H), 0.30 (s, 3 H), 0.29 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 180.3, 137.1, 134.0, 129.3, 127.9, 36.7, 16.4, 14.5, –4.9, –5.3.

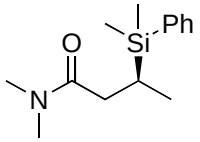


2-247

(*S*)-3-(Dimethyl(phenyl)silyl)-(1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl) propane (40). To a stirred solution of **2-244** (130 mg, 0.585 mmol) in dry CH_2Cl_2 (2 mL) was added DMAP (21.4 mg, 0.175 mmol) followed by DCC (132 mg, 0.643 mmol) and 3-methyl-3-oxetanemethanol (**2-245**) (65.0 µL, 0.643 mmol). The resulting slurry was stirred at room temperature for 3 h, and filtered through a plug of Celite and diluted with H_2O (2 mL). The aqueous phase was extracted with EtOAc (3 x 1 mL) and the combined organic extracts were dried ($MgSO_4$), filtered, concentrated, and the residue was purified by chromatography on SiO_2 (10% EtOAc/Hex) to afford **2-246** (179 mg, 0.584 mmol, 99%) as a colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.50-7.49 (m, 2 H), 7.37-7.36 (m, 3 H), 5.50 (d, *J* = 6.0 Hz, 2 H), 4.37 (d, *J* = 6.0 Hz, 2 H), 4.12 (d, *J* = 11.1 Hz, 1 H), 4.09 (d, *J* = 11.1 Hz, 1 H), 2.43 (dd, *J* = 3.9, 15.3 Hz, 1 H), 2.09 (dd, *J* = 11.4, 15.3 Hz, 1 H), 1.48-1.42 (m, 1 H), 1.32 (s, 3 H), 0.98 (d, *J* = 7.3 Hz, 3 H), 0.29 (s, 6 H).

A solution of **2-246** (170 mg, 0.557 mmol) in dry CH_2Cl_2 (550 µL) was cooled to 0 °C and treated with $BF_3{\cdot}OEt_2$ (17.5 µL, 0.14 mmol). The reaction mixture was allowed to warm to room temperature and was stirred overnight. The reaction mixture was quenched with NEt_3 (79.0 µL, 0.555 mmol) and diluted with Et_2O (1 mL). The cloudy mixture was filtered through a plug of SiO_2 and was concentrated. The resulting residue was purified by chromatography on SiO_2 (20%

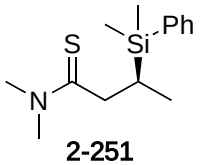
EtOAc/Hex) to afford **2-247** (132 mg, 0.431 mmol, 78%) as a colorless oil that solidified upon standing: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.50-7.48 (m, 2 H), 7.33-7.31 (m, 3 H), 3.86-3.82 (m, 6 H), 1.84 (dd, *J* = 3.2, 14.5 Hz, 1 H), 1.51 (dd, *J* = 11.0, 14.5 Hz, 1 H), 1.30-1.24 (m, 1 H), 1.01 (d, *J* = 7.3 Hz, 3 H), 0.77 (s, 3 H), 0.25 (s, 3 H), 0.24 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.4, 124.1, 128.8, 1277, 109.9, 72.6, 38.3, 30.4, 14.9, 14.7, 14.2, 4.7, 4.9; HRMS (EI) *m/z* calculated for $C_{17}H_{26}O_3Si$ ($M^{\cdot+}$) 306.1651, found 306.1642.



2-248

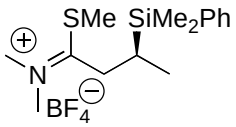
(3*S*)-3-Dimethylphenylsilanyl-*N*,*N*-dimethyl butyramide (**2-248**)**.** To a stirred solution of **2-244** (231 mg, 1.04 mmol) in dry CH_2Cl_2 (10 mL) was added *i*-Pr_2NEt (381 uL, 2.29 mmol), EDC·HCl (177 mg, 1.14 mmol), HOBt (154 mg, 1.14 mmol), and Me_2NH·HCl (94.0 mg, 1.14 mmol). The clear solution became cloudy after 15 min and the slurry was stirred overnight at room temperature. The slurry was filtered through a plug of cotton and diluted with H_2O (10 mL) and EtOAc (10 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL), and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated. The crude oil was purified by chromatography on SiO_2 (50% EtOAc/Hex) to provide **2-248** (220 mg, 0.882 mmol, 85%) as a colorless oil: $[\alpha]_D$ –8.5 (*c* 1.0, $CHCl_3$); IR (neat) 3068, 2952, 2866, 1641, 1393, 1248, 1111, 982, 814, 767, 734, 700 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.51-7.49 (m, 2 H), 7.36-7.33 (m, 3 H), 2.90 (s, 3 H), 2.88 (s, 3 H), 2.32 (dd, *J* = 3.6, 15.1 Hz, 1 H), 2.08 (dd, *J* = 11.1, 15.1 Hz, 1 H), 1.54-1.47 (m, 1 H), 0.98 (d, *J* = 7.3 Hz, 3 H), 0.29 (s, 3 H), 0.29 (s, 3 H). ^{13}C (150

MHz, $CDCl_3$) δ 173.1, 137.9, 134.1, 129.1, 127.9, 37.4, 35.6, 35.3, 16.3, 14.8, –4.6, –5.2; HRMS (EI) *m/z* calculated for $C_{14}H_{23}NOSi$ ($M^{\cdot+}$) 249.1549, found 249.1538.



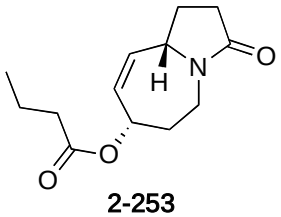
2-251

(*S*)-3-(Dimethyl(phenyl)silyl)-*N*,*N*-dimethylbutanethioamide (2-251). To a stirred solution of **2-248** (96.0 mg, 0.385 mmol) in dry THF (1 mL) was added Lawesson's reagent (110 mg, 0.270 mmol) and the slurry was stirred at room temperature for 24 h. An additional portion of Lawesson's reagent (110 mg, 0.270 mmol) was added and afer 48 h the reaction mixture was quenched with sat. aq. NH_4Cl (1 mL) and diluted with H_2O (5 mL). The aqueous phase was extracted with EtOAc (3 x 5 mL) and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. The resulting residue was purified by chromatography on SiO_2 (20% EtOAc/hex) to afford **2-251** (70 mg, 0.26 mmol, 69%) as a pale yellow oil: IR (neat) 3067, 2952, 2866, 1512, 1389, 1276, 1260, 1111, 1046, 980, 812, 765, 700 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.52-7.50 (m, 2 H), 7.37-7.34 (m, 3 H), 3,43 (s, 3 H), 3.09 (s, 3 H), 2.78 (dd, *J* = 3,3, 13.9 Hz, 1 H), 2.67 (dd, *J* = 11.7, 13.9 Hz, 1 H), 1.63-1.57 (m, 1 H), 1.04 (d, *J* = 7.3 Hz, 3 H), 0.32 (s, 3 H), 0.32 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 204.7, 137.6, 134.1, 129.3, 128.0, 44.9, 44.8, 41.7, 20.3, 13.8, 4.6, 5.4; HRMS (EI) *m/z* calculated for $C_{14}H_{23}NSiS$ ($M^{\cdot+}$) 265.1321, found 265.1317.



2-252

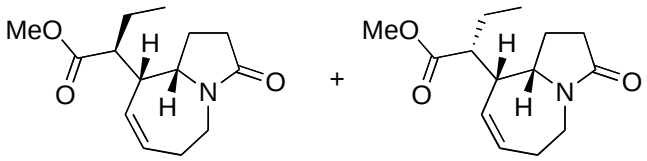
(*S*)-3-(Dimethyl(phenyl)silyl)-*N*,*N*-dimethylbutanethiomethylimidolium tetrafluoroborate (2-252). To a solution of **2-252** (64.0 mg, 0.241 mmol) in dry CH_2Cl_2 (1 mL) at room temperature was added $Me_3O{\cdot}BF_4$ (37.1 mg, 0.241 mmol). The slurry was stirred overnight and cleared to a pale orange solution. The volatiles were removed in vacuo to provide **2-252** (76.0 mg, 0.207 mmol, 86%) as an orange oil: $[\alpha]_D$ +105.5 (*c* 0.83, $CHCl_3$); IR (neat) 2965, 2873, 1596, 1427, 1261, 1048, 1034, 834, 812, 779, 738, 702 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.54-7.53 (m, 2 H), 7.41-7.40 (m, 3 H), 3.51 (s, 3 H), 3.47 (s, 3 H), 2.99 (dd, *J* = 2.8, 15.2 Hz, 1 H), 2.85 (dd, *J* = 12.6, 15.0 Hz, 1 H), 2.43 (s, 3 H), 1.22-1.56 (m, 1 H), 1.05 (d, *J* = 7.3 Hz, 3 H), 0.41 (s, 6 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.2, 135.3, 134.1, 130.2, 128.5, 46.2, 45.6, 34.9, 21.2, 17.0, 13.4, 5.0, 6.3; HRMS (EI) *m/z* calculated for $C_{15}H_{26}NSiS$ ($M\text{-}BF_4^-$) 280.1555, found 280.1555.



2-253

(7*S*,9a*S*)-7-Butyryloxy-1,2,5,6,7,9a-hexahydropyrrolo[1,2-*a*]azepin-3-one (2-253). To a solution of **2-208** (1.23 g, 7.37 mmol) in dry CH_2Cl_2 (25 mL) was added DMAP (90 mg, 0.74 mmol), butyric acid (744 µL, 8.11 mmol) and EDC·HCl (1.55 g, 8.11 mmol). The reaction mixture was stirred overnight at room temperature and was filtered through a plug of Celite. The volatiles were removed under reduced pressure and the residue was purified by chromatography on SiO_2 (100% EtOAc) to afford **2-253** (1.61 g, 6.8 mmol, 92%) as a pale yellow oil and a 6:1 inseparable mixture of diastereomers by ^1H NMR spectroscopy: $[\alpha]_D$ –48.0 (*c* 0.55, $CHCl_3$); IR (neat) 2964, 2935, 2876, 1727, 1681, 1419, 1252, 1173, 1085, 1001, 971 cm^{-1}; ^1H NMR (600

MHz, $CDCl_3$) δ 5.72 (dt, *J* = 2.9, 12.0 Hz, 1 H), 5.64 (dt, *J* = 2.1, 12.1 Hz, 1 H), 5.50-5.48 (m, 1 H), 4.30 (ddddd, *J* = 2.3, 2.3, 4.6, 7.8, 7.8), 4.21 (ddd, *J* = 3.4, 7.2, 14.2 Hz, 1 H), 2.98 (ddd, *J* = 2.8, 9.3, 13.2 Hz, 1 H), 2.43 (ddd, *J* = 6.9, 10.0, 16.5 Hz, 1 H), 2.36-2.26 (m, 4 H), 2.09-2.04 (m, 1 H), 1.92 (dddd, *J* = 3.4, 9.1, 9.1 14.1 Hz, 1 H), 1.84-1.79 (m, 1 H), 1.64 (sextet, *J* = 7.4 Hz, 2 H), 0.93 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.0, 173.0, 133.1, 132.2, 71.5, 58.1, 38.5, 36.4, 32.1, 30.1, 26.5, 18.6, 13.8; HRMS (EI) *m/z* calculated for $C_{13}H_{19}NO_3Na$ $[M+Na]^+$ 260.1263, found 260.1269.



2-255a **2-255b**

Methyl (*S*)-2-((9*R*,9a*S*,*Z*)-3-oxo-2,3,5,6,9,9a-hexahydro-1*H*-pyrrolo[1,2-*a*]azepin-9-yl) butanoate (2-255a) and Methyl (*R*)-2-((9*R*,9a*S*,*Z*)-3-oxo-2,3,5,6,9,9a-hexahydro-1*H*-pyrrolo[1,2-*a*]azepin-9-yl)butanoate (2-255b). To a cooled solution of TIPSCl (1.38 mL, 6.32 mmol) in dry HMPA (6.0 mL) and dry THF (16.2 mL) was added a freshly prepared solution of LiHMDS (5.47 mL, 5.47 mmol, 1.0 M in THF) and the solution was stirred at –78 °C for 15 min. To this mixture was added **2-253** (500 mg, 2.11 mmol) in dry THF (4.2 mL). The homogeneous reaction mixture turned a dark color and became a deep brown over 2 h at –78 °C. The reaction mixture was allowed to warm to 0 °C and was quenched upon addition of cold (~–30 °C) Et_2O (20 mL). The solution was allowed to warm to room temperature and the organic solution was washed with H_2O (5 x 20 mL), brine (20 mL) and dried ($MgSO_4$. The volatiles were removed

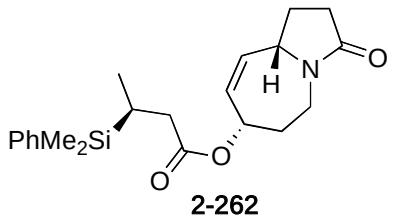
under reduced pressure to afford a brown oil that was used without further purification. ^{1}H NMR analysis confirmed complete conversion to a single silyl ketene acetal isomer.

The brown oil was taken up in dry, degassed xylenes (16 mL) and the solution was heated to reflux for 3 h. The resulting yellow solution was allowed to warm to room temperature and the volatiles were removed under reduced pressure to afford a brown oil that was used without further purification.

A solution of the brown oil (829 mg, 2.11 mmol, theoretical) in THF (15.2 mL) was treated with a solution of TBAF (2.52 mL, 2.53 mmol, 1 M in THF). The brown solution became dark brown immediately upon addition and the reaction mixture was stirred for 2 h at room temperature. The solution was diluted with EtOAc (40 mL) and H_2O (25 mL) followed by 1N HCl (25 mL). The organic layer was extracted 3 x 20 mL H_2O, and the aqueous layers were back-extracted with EtOAc (3 x 20 mL) and the combined organic layers were washed with brine (30 mL), filtered, dried ($MgSO_4$) and concentrated to a brown oil that solidified in vacuo.

This residue was taken up in benzene (30 mL) and MeOH (7 mL) and the solution was treated with TMSdiazomethane (1.26 mL, 2.53 mmol, 2 M in hexanes) and gas evolution was observed immediately. After 20 min the reaction mixture was concentrated under reduced pressure and the residue was purified by MPLC (90% EtOAc/Hex) to provide **2-255a** and **2-255b** (269 mg, 1.07 mmol, 51%) as an amber oil and a 6:1 ratio of diastereomers by ^{1}H NMR spectroscopy: $[\alpha]_D$ –28.8 (*c* 0.54, CH_2Cl_2); IR (neat) 2964, 2878, 1732, 1683, 1457, 1422, 1274, 1166, 1077, 987 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.54 (dddd, *J* = 2.3, 2.3, 5.3, 8.6 Hz, 1 H), 5.24 (ddd, *J* = 2.3, 5.0, 11.2 Hz, 1 H), 4.02 (ddd, *J* = 6.0, 6.0, 9.1 Hz, 1 H), 3.84 (ddd, *J* = 3.0, 7.4, 14.1 Hz, 1 H), 3.70 (s, 3 H), 3.18 (ddd, *J* = 5.7, 10.6, 14.2 Hz, 1 H), 3.14-3.10 (m, 1 H), 2.56-2.49 (m, 1 H), 2.42 (ddd, *J* = 5.0, 9.7, 9.7 Hz, 1 H), 2.39-2.30 (m, 3 H), 1.95 (ddddd, *J* =

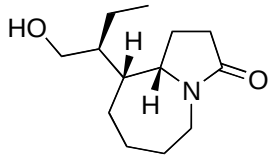
2.4, 6.7, 8.7, 8.7, 12.0 Hz, 1 H), 1.71-1.63 (m, 3 H), 0.91 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.3, 174.8, 130.5, 126.3, 60.7, 51.8, 18.5, 41.6, 37.7, 31.0, 28.8, 23.8, 21.9, 11.8; HRMS (ESI) *m/z* calculated for $C_{14}H_{21}NO_3Na$ $[M+Na]^+$ 274.1419, found 274.1409.



2-262

(7*S*,9a*S*)-7-([*3S*]-*3*-Dimethyl(phenyl)silylbutyryloxy-1,2,5,6,7,9a-hexahydropyrrolo[1,2-*a*]azepin-3-one (2-262). A solution of **2-208** (520 mg, 3.11 mmol) in dry CH_2Cl_2 (7.5 mL) was treated with DMAP (38.0 mg, 0.311 mmol) and EDC-HCl (715 mg, 3.73 mmol). To this solution was added **2-244** (705 mg, 3.17 mmol) in dry CH_2Cl_2 (2 x 1 mL) and the yellow reaction mixture was stirred overnight at room temperature. The reaction mixture was diluted with sat. aq. NH_4Cl (10 mL) and H_2O (10 mL) and CH_2Cl_2 (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL), and the combined organic layers were dried ($MgSO_4$), filtered, concentrated and the crude residue was purified by chromatography on SiO_2 (80% EtOAc/Hex) to afford **2-262** (1.08 g, 2.90 mmol, 93% yield) as a colorless oil and a 6:1 ratio of inseparable diastereomers by ^{1}H NMR spectroscopy that becomes orange upon storage: $[\alpha]_D$ –41.9 (*c* 0.21, $CHCl_3$); IR (neat) 2954, 2870, 1726, 1686, 1426, 1250, 1205, 1111, 999, 813, 732, 700 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.49-7.48 (m, 2 H), 7.37-7.35 (m, 3 H), 5.65 (ddd, *J* = 2.4, 2.4,12.2 Hz, 1 H), 5.61 (ddd, *J* = 1.8, 1.8 Hz, 12.2 Hz, 1 H), 5.47-5.45 (m, 1 H), 4.8 (dddd, *J* = 2.3, 4.4, 7.9, 10.3 Hz, 1 H), 4.21 (ddd, *J* = 3.1, 7.1, 10.3 Hz, 1 H), 2.97 (ddd, *J* = 2.3, 9.7, 13.1 Hz, 1 H), 2.45-2.40 (m, 1 H), 2.39 (dd, *J* = 3.9, 15.3 Hz, 1 H), 2.35-2.31 (m, 1 H), 2.30-2.24 (m, 1 H), 2.05 (dd, *J* = 11.5, 15.3 Hz, 1 H), 2.06-2.01 (m, 1 H), 1.90-1.84 (m, 1 H), 1.84-1.78 (m, 1 H), 1.43 (ddddd, *J* = 4.0,

7.4, 7.4, 7.4, 14.8 Hz, 1 H), 0.96 (d, *J* = 7.3 Hz, 3 H), 0.28 (s, 3 H), 0.27 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.0, 173.3, 137.3, 134.1, 132.7, 132.3, 129.3, 127.9, 71.9, 58.1, 38.6, 37.0, 32.3, 30.1, 26.4, 16.7, 14.6, -4.8, -5.2.

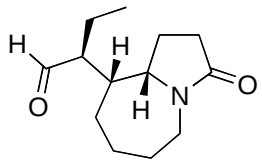


3-6

(9*R*,9a*S*)-9-((*S*)-1-Hydroxybutan-2-yl)hexahydro-1*H*-pyrrolo[1,2-*a*]azepin-3(2*H*)-one (3-6). A solution of **2-255a,b** (125 mg, 0.497 mmol) in MeOH (5.0 mL) was treated with Pd/C (52.9 mg, 0.050 mmol) and the system was purged with H_2 and stirred under balloon pressure for 2 h. The black slurry was filtered through Celite, washed with CH_2Cl_2 and concentrated to afford the crude product as a yellow film (126 mg, 0.497 mmol, 99%).

To a solution of the crude hydrogenation product (126 mg, 0.497 mmol) in dry THF (3 mL) at 0 °C was added a solution of $LiBH_4$ (1.24 mL, 2.49 mmol, 2.0 M in THF) and the colorless reaction mixture was allowed to warm to room temperature overnight. An additional amount of $LiBH_4$ (1.24 mL, 2.49 mmol, 2 M in THF) was added and the reaction mixture was stirred for a total of 48 h. The turbid mixture was carefully quenched with sat. aq. NH_4Cl (3 mL) and diluted with H_2O (3 mL) and EtOAc (5 mL). The aqueous phase was extracted with EtOAc (3 x 5 mL), and the combined organic layers were dried ($MgSO_4$), filtered, concentrated, and purified by MPLC (5 % MeOH/EtOAc) to afford **3-6** (65.0 mg, 0.288 mmol, 58%) as a yellow oil and a single diastereomer along with mixed fractions (15.0 mg, 0.067 mmol, 13%): $[\alpha]_D$ –195 (*c* 0.22, $CHCl_3$); IR (neat) 3379, 2927, 2876, 1655, 1458, 1434, 1422, 1320, 1281, 1159, 1033 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.99 (ddd, *J* = 3.0, 3.0, 13.7 Hz, 1 H), 3.91 (ddd, *J* = 6.0,

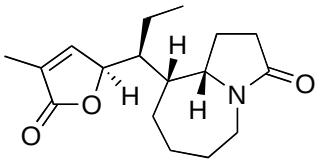
6.0, 10.2 Hz, 1 H), 3.73 (dd, *J* = 3.9, 11.1 Hz, 1 H), 3.70 (dd, *J* = 4.7, 11.0 Hz, 1 H), 2.65 (ddd, *J* = 1.8, 12.5, 14.1 Hz, 1 H), 2.38-2.29 (m, 2 H), 2.00 (ddd, *J* = 6.0, 8.2, 8.2 Hz, 1 H), 1.94 (dddd, *J* = 2.2, 6.1, 8.1, 12.6, 1 H), 1.87-1.83 (bm, 1 H), 1.70-1.61 (m, 2 H), 1.58-1.50 (m, 2 H), 1.46-1.34 (m, 3 H), 1.27-1.24 (m, 2 H), 0.93 (t, *J* = 7.3 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.7, 62.1, 60.7, 43.6, 42.2, 40.7, 31.0, 29.9, 29.1, 24.4, 22.0, 21.5, 11.7; HRMS (EI) *m/z* calculated for $C_{13}H_{23}NO_2$ ($M^{\cdot+}$) 225.1729, found 225.1724.



2-267

(*S*)-2-(9*R*, 9a*S*)-oxooctahydro-1*H*-pyrrolo[1,2-*a*]azepin-9-yl)butanal (2-267). To a stirred solution of crude **3-6** (77 mg, 0.34 mmol, theoretical) in dry CH_2Cl_2 (3.5 mL) at room temperature was added Dess-Martin reagent (147 mg, 0.343 mmol). The slurry was stirred for 3 h and sat. aq. $NaHCO_3$ (1 mL) was added followed by sat. aq. $Na_2S_2O_3$ (1 mL) and diluted with EtOAc (3 mL). The aqueous layer was extracted with EtOAc (3 x 1 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated. MPLC purification (100% EtOAc) of the residue provided **2-262** (27.0 mg, 0.121 mmol, 35% from **2-255a,b**) as an orange oil and a single diastereomer by ^{1}H NMR spectroscopy that is unstable upon storage overnight: $[\alpha]_D$ – 100.4 (*c* 0.27, $CHCl_3$); IR (neat) 3018, 2963, 2929, 2877, 1717, 1681, 1458, 1423, 1278 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.56 (d, *J* = 3.5 Hz, 1 H), 4.03 (ddd, *J* = 3.9, 3.9, 13.9, 1 H), 3.89 (ddd, *J* = 5.8, 5.8, 10.1, 1 H), 2.64 (ddd, *J* = 1.7, 12.4, 14.1 Hz, 1 H), 2.38-2.39 (m, 2 H), 2.25-2.21 (m, 2 H), 1.91 (dddd, *J* = 3.3, 6.4, 6.4, 12.6 Hz, 1 H), 1.87-1.82 (m, 1 H), 1.73-1.69 (m, 2 H), 1.66-1.56 (m, 2 H), 1.46-1.38 (m, 1 H), 1.37-1.34 (m, 2 H), 1.34-1.28 (m, 1 H), 0.89 (t, *J* =

7.5 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 204.1, 174.5, 59.9, 55.4, 41.7, 40.8, 30.8, 29.6, 29.1, 25.6, 21.9, 20.8, 11.3.



Sessilifoliamide C
(**2-227**)

(9*R*,9a*S*)-9-((*S*)-1-((*R*)-4-methyl-5-oxo-2,5-dihydrofuran-2-yl)propyl)hexahydro-1*H*-pyrrolo[1,2-*a*]azepin-3(2*H*)-one; Sessilifoliamide C (2-227).

To a solution of **2-262** (57 mg, 0.255 mmol) in dry THF (3.7 mL) at –78 °C was added vinylMgBr (1.02 mL, 1.02 mmol, 1 M in THF). The resulting yellow solution was stirred at –78 °C overnight. To the pale yellow slurry was added acryloyl chloride (165 µL, 1.53 mmol) and NEt_3 (362 µL, 2.55 mmol) and the reaction mixture was allowed to warm to room temperature and homogeneity was achieved. The reaction mixture was stirred for 2 h and was quenched by the addition of sat. aq. NaHCO3 (10 mL) and the biphasic mixture was diluted with EtOAc (5 mL). The aqueous phase was extracted with EtOAc (3 x 10 mL) and the combined organic layers were washed with brine (20 mL), dried (MgSO4), filtered, and concentrated to afford a yellow oil that was purified by MPLC (4:1 EtOAc/Hex) to provide **2-269a** and **2-269b** (48.0 mg, 0.150 mmol, 59%) as an orange film and a 2:1 mixture of diastereomers by 1H NMR spectroscopy: ^{1}H NMR (600 MHz, $CDCl_3$) δ (distinctive peaks) 6.14 (t, *J* = 1.0 Hz), 6.11 (t, *J* = 3.4 Hz), 5.89 (ddd, *J* = 5.8, 10.3, 16.9 Hz), 5.84 (ddd, *J* = 5.8, 10.9, 16.5 Hz), 5.66-5.64 (m), 5.64-5.63 (m), 5.61 (t, *J* = 1.5 Hz), 5.27 (t, *J* = 1.4 Hz), 5.25 (ddd, *J* = 1.2, 1.2, 4.4 Hz), 5.23 (bs), 5.21 (ddd, *J* = 1.3, 1.3, 8.1 Hz), 4.01 (bd, *J* = 13.7 Hz), 3.91-3.86 (m), 2.67-2.56 (m), 2.37-2.31 (m), 1.97 (s), 1.97 (s), 2.04-1.91 (m), 1.97 (s), 1.97 (s), 1.87-1.81 (m), 1.71-1.66 (m), 1.64-1.58 (m), 1.52-1.31

(m), 1.26-1.20 (m), 1.15-1.07 (m), 1.01 (t, *J* = 7.4 Hz), 0.98 (t, *J* = 7.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ *(major diastereomer)* 174.5, 166.4, 136.4, 135.2, 125.9, 116.5, 75.6, 60.6, 44.5, 42.1, 40.8, 30.9, 29.7, 29.0, 23.6, 21.9, 21.0, 18.5, 12.2, *(minor diastereomer)* 174.5, 166.6, 136.5, 134.7, 125.8, 117.4, 75.5, 60.4, 47.3, 42.7, 40.6, 31.1, 29.1, 26.1, 22.8, 20.8, 13.7.

A solution of **2-264a** and **2-264b** (17 mg, 0.053 mmol) and **2-95** (5.3 mg, 0.005 mmol) in dry CH_2Cl_2 (10 mL) was heated to reflux overnight. An additional batch of **2-95** was added (5.3 mg, 0.005 mmol) and the reaction mixture was heated for 4 h. A third batch of **2-95** was added (5.3 mg, 0.005 mmol) and the reaction mixture was heated to reflux for an additional 3 h. The brown solution was allowed to cool to room temperature and was directly subjected to MPLC purification (100% EtOAc) to afford **2-227** and ***epi*-2-227** (13 mg, 0.045 mmol, 84%), which could be separated by MPLC (100% EtOAc). Analytical data for the slower-eluting major diastereomer matches the reported isolation data for sessilifoliamide C:[121] **2-227:** $[\alpha]_D$ –84.6 (*c* 0.25, $CHCl_3$), –43.4 (*c* 0.5, EtOH); IR (neat) 2928, 2877, 1749, 1676, 1449, 1422, 1323, 1282, 1091, 923, 729 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.03 (t, *J* = 1.5 Hz, 1 H), 5.17 (bq, *J* = 2.0 Hz, 1 H), 4.03 (ddd, *J* = 3.3, 3.3, 13.8 Hz, 1 H), 3.92 (ddd, *J* = 5.9, 5.9, 10.1 Hz, 1 H), 2.66 (ddd, *J* = 1.7, 12.4, 12.4 Hz, 1 H), 2.43-2.33 (m, 2 H), 2.20 (ddd, *J* = 5.8, 8.3, 8.3 Hz, 1 H), 1.98-1.92 (m, 1 H), 1.95 (t, *J* = 1.7 Hz, 3 H), 1.90-1.86 (bm, 1 H), 1.75-1.65 (m, 4 H), 1.49-1.41 (m, 1 H), 1.40-1.31 (m, 3 H), 1.19 (sept, *J* = 7.3 Hz, 1 H), 0.84 (t, *J* = 7.5 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.6, 174.5, 148.2, 130.5, 82.3, 60.9, 44.2, 43.3, 40.7, 31.0, 29.5, 29.0, 24.6, 22.1, 19.1, 13.5, 10.9; HRMS (EI) *m/z* calculated for $C_{17}H_{25}NO_3$ ($M^{\cdot+}$) 291.1834, found 291.1836.

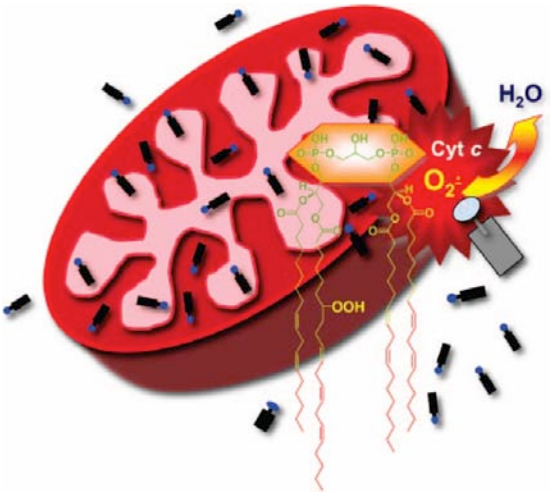
APPENDIX A

TARGETING MITOCHONDRIA

The following review article co-authored by A. T. Hoye is reproduced without alteration.[145] Primary authorship is indicated for each section.

A.1 INTRODUCTION

(P. Wipf, V. Kagan and M. Fink, authors)



Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are closely linked to degenerative diseases such as Alzheimer's disease, Parkinson's, neuronal death including ischemic and hemorrhagic stroke, acute and chronic degenerative cardiac myocyte death, and cancer. As a byproduct of oxidative phosphorylation, a steady stream of reactive species emerge from our cellular energy plants, the mitochondria. ROS and RNS potentially cause damage to all

cellular components. Structure alteration, biomolecule fragmentation, and oxidation of side chains are trade-offs of cellular energy production. ROS and RNS escape results in the activation of cytosolic stress pathways, DNA damage, and the upregulation of JNK, p38, and p53. Incomplete scavenging of ROS and RNS particularly affects the mitochondrial lipid cardiolipin (CL), triggers the release of mitochondrial cytochrome c, and activates the intrinsic death pathway.

Due to the active redox environment and the excess of NADH and ATP at the inner mitochondrial membrane, a broad range of agents including electron acceptors, electron donors, and hydride acceptors can be used to influence the biochemical pathways. The key to therapeutic value is to enrich selective redox modulators at the target sites.

Our approach is based on conjugating nitroxides to segments of natural products with relatively high affinity for mitochondrial membranes. For example, a modified gramicidin S segment was successfully used for this purpose and proven to be effective in preventing superoxide production in cells and CL oxidation in mitochondria and in protecting cells against a range of pro-apoptotic triggers such as actinomycin D, radiation, and staurosporine. More importantly, these mitochondriatargeted nitroxide/gramicidin conjugates were able to protect against apoptosis in vivo by preventing CL oxidation induced by intestinal hemorrhagic shock. Optimization of nitroxide carriers could lead to a new generation of effective antiapoptotic agents acting at an early mitochondrial stage.

Alternative chemistry-based approaches to targeting mitochondria include the use of proteins and peptides, as well as the attachment of payloads to lipophilic cationic compounds, sulfonylureas, anthracyclines, and other agents with proven or hypothetical affinities for mitochondria. Manganese superoxide dismutase (MnSOD), SS tetrapeptides with 2’,6’-

dimethyltyrosine (Dmt) residues, rhodamine, triphenylphosphonium salts, nonopioid analgesics, adriamycin, and diverse electron-rich aromatics and stilbenes were used to influence mitochondrial biochemistry and the biology of aging.

Some general structural principles for effective therapeutic agents are now emerging. Among these are the presence of basic or positively charged functional groups, hydrophobic substructures, and, most promising for future selective strategies, classes of compounds that are actively shuttled into mitochondria, bind to mitochondria-specific proteins, or show preferential affinity to mitochondria-specific lipids.

In 1956, Harman proposed the "free radical theory" of aging and associated degenerative diseases.[146] According to this hypothesis, "...the reaction of active free radicals, normally produced in the organisms, with cellular constituents initiates the changes associated with aging." Consequences of these biochemical alterations are an up-regulation of p53 and the activation of cytosolic stress signaling pathways. Ultimately, both life span and life quality are severely negatively affected. While some controversy regarding the generality of the Harman theory continues, experimental evidence for the link between reactive oxygen species (ROS) and the biology of aging is steadily solidifying.[147] In particular, mitochondrial metabolism and the oxidative phosphorylation cascade are emerging as key factors in the generation of ROS associated with a large number of disease states, including atherosclerosis, Alzheimer's disease, Parkinson's, neuronal death including ischemic and hemorrhagic stroke, acute and chronic degenerative cardiac myocyte death, and cancer.[148,149]

With a notable exception of NADPH oxidase in activated inflammatory cells, the lion's share, possibly up to 90%[147] of intracellular ROS are generated in mitochondria during the controlled oxidation of NADH and FADH with molecular oxygen coupled with the

phosphorylation of ADP to give ATP in a multienzyme complex embedded in the mitochondrial membrane (Figure 1). In addition to superoxide radical anion ($O_2^{-\bullet}$), major reactive species generated in this process include H2O2 and HO$^{\bullet}$. Furthermore, ROS collectively include both oxygen radicals and nonradical oxidizing species such as 1O2, O3, and ROOR; a large variety of these reactive molecules are produced *in vivo*, even though the specific reaction mechanisms involved in their generation remain still unclear.[150,151] Upon reaction with nitric oxide (NO·), $O2^{-\bullet}$ also participate in the formation of reactive nitrogen species (RNS), such as ONOO-. Several efficient enzymatic processes are continuously operational to quench ROS and RNS, including superoxide dismutase (SOD) and superoxide reductase (SOR),[152] catalase,[153] peroxiredoxin (Prx),[154] glutathione peroxidase (GP), and thioredoxin/thioredoxin reductase (Trx/TrxR) (Figure 2).[155] However, if, as a result of aging or pathological processes, the production of ROS and RNS exceeds the scavenging capacity of endogenous systems, then both mitochondrial and extramitochondrial cellular components, including proteins, nucleic acids, and lipids, can be damaged. Under these circumstances, an external chemical intervention might be beneficial. Pharmaceuticals that provide ROS and RNS scavenging systems are most effective if they address the problem at its source, in the inner mitochondrial membrane.[156] This Account summarizes some of the current strategies used to target antioxidants to mitochondria, including peptide and nonpeptide delivery systems.

In the past ten years, the search for new protective remedies against damage caused by excessive free radical formation in mitochondria has accelerated. Similar to our body's own natural defenses against ROS, research has been primarily focused on molecules combining antioxidant utilities with recycling capacities.[157] Large doses of antioxidants proved ineffective at preventing oxidative damage in animal disease models, presumably because the antioxidants and proteins

such as manganese superoxide dismutase (MnSOD) cannot penetrate cell membranes effectively and therefore do not reach the relevant sites of ROS and RNS generation. One solution to this general problem is to attach a molecule with antioxidant properties onto a vehicle that can penetrate both the cellular and outer mitochondrial membranes and thereby deliver the "payload" to a site where it can scavenge ROS and ameliorate oxidative damage (Figure 3). Since the mitochondrial membrane spans across a negative potential, most agents have a positively charged moiety that takes advantage of electrostatic forces in locating its target.

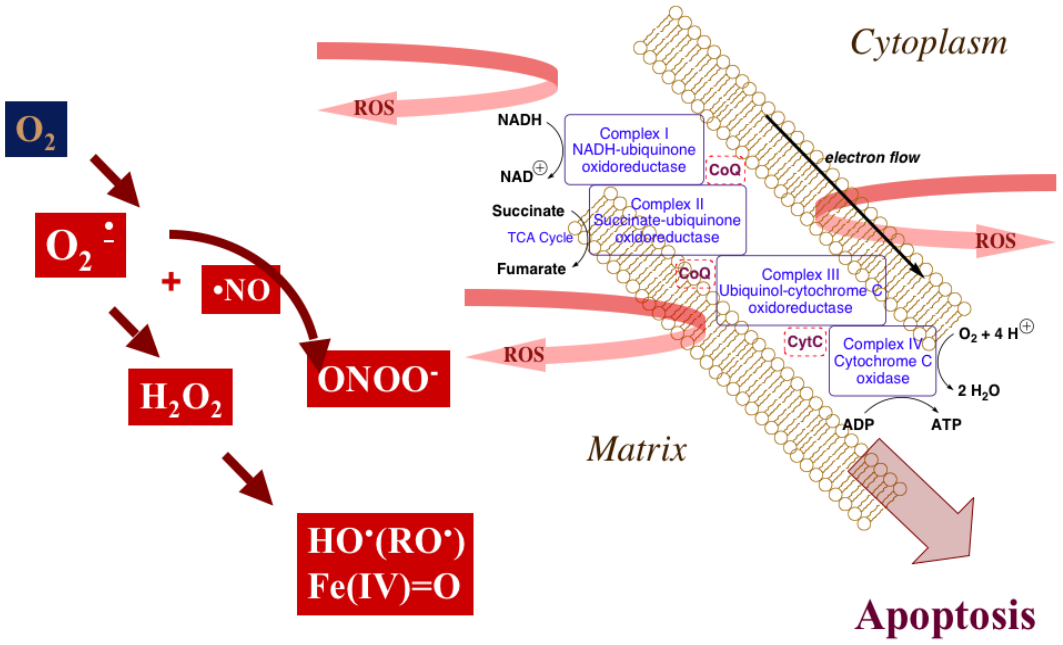


FIGURE 1. Schematic model for generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) during the oxidative phosphorylation in the mitochondrial

membrane. The formation of superoxide radical anion initiates a cascade process that can induce programmed cell death (apoptosis).

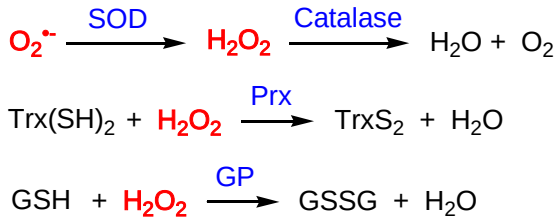


FIGURE 2. Antioxidant scavenging reactions that eliminate ROS. SOD = superoxide dismutase, Prx = peroxiredoxin, GP = glutathione peroxidase, Trx = thioredoxin, GSH = glutathione.

A.2 PROTEINS, PEPTIDES, AND PEPTIDE MIMETICS AS MITOCHONDRIAL TARGETING SYSTEMS

(J. Davoren, A. Hoye and P. Wipf, authors)

A.2.1 Proteins

For polypeptide strands to be properly recognized and imported into mitochondria, precursor proteins that are synthesized in the cytosol require specific sequence information that is recognized by an import pathway.[158] While precursor proteins are prone to misfolding and aggregation, cytosolic chaperone proteins maintain them in an import-competent form.[159] The processed protein is then bound by translocases of the outer and inner membranes (TOM and TIM), which transport the target across the lipid bilayers.[160]

Protein import and recognition is generally directed by an N-terminal or, less frequently, a C-terminal signal sequence consisting of about 20–30 amino acid residues, which are cleaved by mitochondrial processing peptidase (MPP) either during import or once inside the mitochondrial matrix. Comparison of known presequences reveals that they do not share a common primary structure. In these cases, however, a common secondary structure as well as certain basic (arginine), hydrophobic (alanine, leucine), and polar residues (serine) might be present. Alternatively, proteins such as cytochrome *c* and superoxide dismutases are imported with minimal processing since they contain the necessary recognition elements as part of their primary sequence.[161,162] The N-terminal regions are postulated to fold into amphiphilic helices.[163] It is proposed that this amphiphilicity in combination with localized positive charges emanating from basic residues are the two main features required for successful protein import. Electrostatic interactions are thought to occur between the positive charges found on the helix and the negative charges of the TOM receptors.[164] then, in an electrophoretic event, the presequence follows the very large membrane potential (typically 150-180 mV) and is pulled across the inner membrane.[165]

A.2.2 Manganese superoxide dismutase (MnSOD).

Superoxide dismutases (SOD) are responsible for catalyzing the dismutation of superoxide into oxygen and hydrogen peroxide and are therefore an important part of the antioxidant defense in most cells exposed to oxygen.[166] Several families of SOD are known, and the activities of each family depend on a redox-active metal cofactor such as manganese, iron, copper, or nickel. A single metal cofactor will catalyze a single electron oxidation and reduction

of two separate superoxide anions to give oxygen and hydrogen peroxide, respectively. These reactions are self-contained and do not require an external source of redox equivalents.

A generic mechanism for the catalytic breakdown of superoxide anion is:

$$M^{(n+1)+}\text{-SOD} + O_2^{\bullet -} \rightleftharpoons M^{n+}\text{-SOD} + O_2$$
$$M^{n+}\text{-SOD} + O_2^{\bullet -} + 2H^+ \rightleftharpoons M^{(n+1)+}\text{-SOD} + H_2O_2$$

where M = Cu (n=1) ; Mn (n=2) ; Fe (n=2) ; Ni (n=2).

The family of manganese superoxide dismutases (MnSOD)[167] consists of dimers or tetramers of approximately 21 kDa subunits and contains considerable sequence homology and well conserved protein folds across various phyla.[168] Dimeric forms of MnSOD are typical of bacteria, while in eukaryotes the tetramer is most commonly observed. At the active site of the enzyme, a single manganese atom catalyzes the disproportionation of superoxide and is coordinated in a trigonal bipyramidal geometry to three histidine residues, one aspartate, and a solvent water molecule (Figure 4).[169]

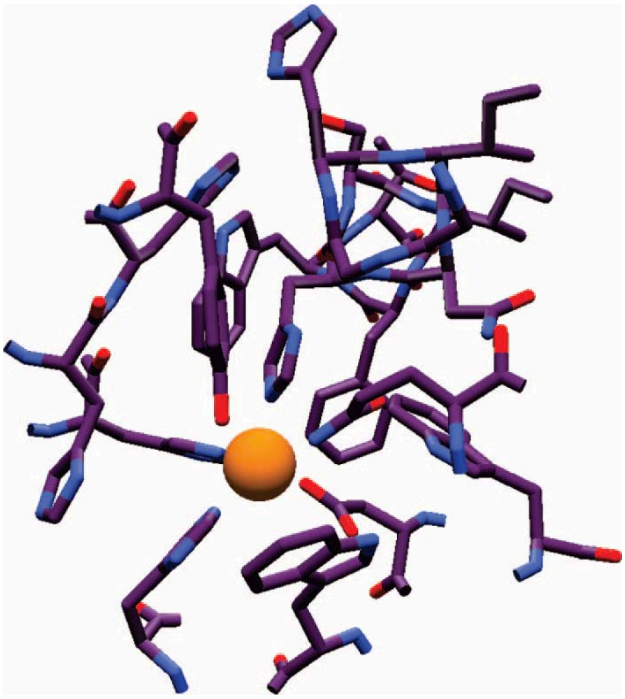


FIGURE 4. Structure of the active site of human superoxide dismutase 2. His74, His26, His163, and Asp159 provide a tight complex for manganese(III).

In the case of eukaryotic MnSOD (SOD2), the polypeptide is initially encoded by a nuclear gene as a precursor polypeptide containing the requisite mitochondrial targeting sequence at its N-terminus. The mechanism by which SOD obtain their manganese cofactors is still unknown; however, the manganese- containing form of SOD typically resides in the matrix of the mitochondrion. Enzymatically inactive mutant forms of *Saccharomyces cerevisiae* SOD2 lacking the mitochondrial targeting sequence [denoted as SOD2P] were found to accumulate in the cytosol rather than the mitochondria.[170] Their inactivity was attributed to a manganese deficiency, and further investigations suggested that SOD2P required mitochondrial localization in order to efficiently acquire manganese. Therefore it is proposed that as the SOD2 polypeptide precursor enters mitochondria, manganese is inserted into the polypeptide, and the complex then assembles into the quaternary enzyme structure.[166]

MnSOD plays an essential role in oxidative stress protection, and the assembly of this tetrameric peptide into the active manganese-containing enzyme is critical for survival. For example, in neonatal mice, the loss of MnSOD is lethal,[171] while its modification in fruit flies leads to a severely reduced adult life span.[172] In contrast, due to its role as a negative modulator of apoptosis, inhibition of MnSOD in cancer cells is considered to be a promising target for anticancer therapies.[173] The MnSOD gene is known to be induced by tumor necrosis factor alpha (TNFR) and provides protection against TNF-induce apoptosis.[174] As such, even small amounts of this enzyme are considered crucial for tumor cell resistance to inflammatory stimuli, ionizing radiations, and commonly employed anticancer drugs.[173]

A.2.3 Peptides and Peptide Mimetics.

Several cell-permeable mitochondrial targeting peptides with attached antioxidants have been conceived and tested, including SS peptides,[175] which feature a 2,6-dimethyltyrosine (Dmt) payload, as wellas the XJB peptide mimetics,[176] which deliver a 4-amino-TEMPO (4-AT), a stable nitroxide radical.

A.2.3.1 SS tetrapeptides.

The SS tetrapeptides represent a series of mitochondria-targeting antioxidant peptides that feature a common structural motif of alternating aromatic and basic residues (Figure 5).[175]

Prior to the discovery of their antioxidant properties, these tetrapeptides were already extensively studied due to their high affinity and selectivity to the μ-opioid receptor, and they were found to be surprisingly potent andlong-acting analgesics.[177]

The antioxidant properties of **SS-02** and **SS-31** are likely to originate from their dimethyltyrosine (Dmt) residues.[178] More specifically, tetrapeptides **SS-31** and **SS-02** were found to be equally effective in scavenging H_2O_2 and inhibiting linoleic acid oxidation *in vitro*. This result indicates that the specific location of the Dmt residue in the sequence of the antioxidant peptide is inconsequential. The basic residues provide for localization in the inner mitochondrial membrane, and the Dmt phenol moieties of **SS-02** and **SS-31** are likely responsible for chemically reducing reactive oxygen species and peroxide bonds. Tetrapeptide **SS-20**, where Dmt is substituted with a phenylalanine residue, was devised as a control and, in agreement with the hypothesis, demonstrated no ROS scavenging ability.

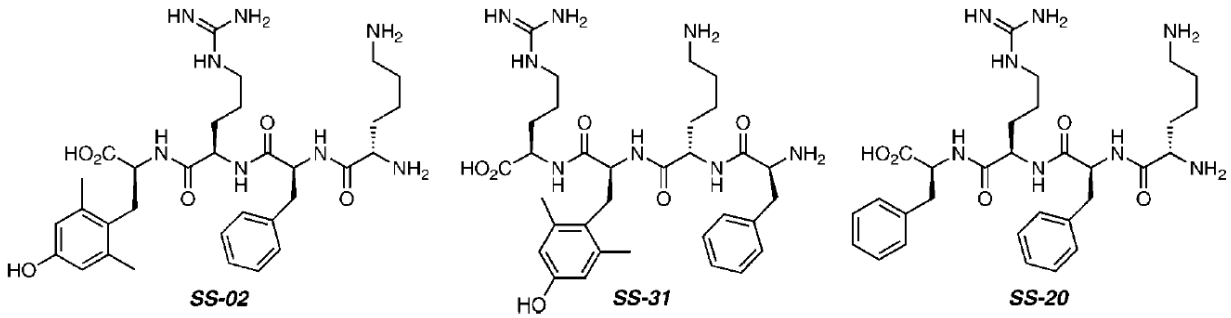


FIGURE 5. Structures of active and control SS peptides.

Despite the net positive charge of these small peptides at physiological pH values, their amino acid sequence allows them to freely penetrate cells in an energy-independent nonsaturable passive manner.[179] A fluorescent SS-peptide analogue (Dmt-DArg-PheantDap-NH2; ant = β-anthraniloyl-L-α,β-diaminopropionic acid), **SS-19**, was prepared to study mitochondrial and cellular uptake in living cells. Confocal images showed that the pattern of localization of the fluorescent analogue was similar to that of Mitotracker TMRM, a fluorescent dye that is readily taken up by mitochondria. To ensure that uptake was not an artifact caused by

the presence of the fluorophore, these aromatic cationic peptides were further studied by incubating [3H]**SS-03** with mouse liver mitochondria. The uptake of [3H]**SS-03** reached maximal levels within 2 min and reflected a 100-fold concentration in mitochondria.

In consideration of their positive net charge, these peptides were expected to pass through the inner membrane of the mitochondria (IMM) into the matrix; however, pretreatment with the mitochondrial uncoupler carbonylcyanide-*p*-trifluoromethoxyphenylhydrazone (FCCP) only decreased **SS-19** or [3H]**SS-03** uptake by about 20%. This finding suggests that the bulk of the peptide was localized in the IMM, while only 20% was delivered to the matrix in a potential-driven manner.

tert-Butyl hydroperoxide (*t*BHP) is a membrane permeable oxidant known to induce apoptosis in treated cells.[180] Apoptosis induced by *t*-BHP is triggered by a phenomenon called the mitochondrial permeability transition (MPT),[181] which delivers an increase in the permeability of the mitochondrial membranes to small molecules of less than 1500 Da molecular weight. In a series of *in vitro* studies, the peptides **SS-02** and **SS-31** were demonstrated to be effective antioxidants, which inhibited triggering of the MTP and partially ameliorated apoptosis of *t*-BHP-treated cells.[182]

Reperfusion injury following ischemia or hemorrhagic shock is thought to include ROS production and mitochondrial permeability transition.[183] Once blood loss occurs, if intravascular volume expansion successfully restores arterial blood pressure before hemostasis has been achieved, then paradoxically, resuscitation can actually promote bleeding and reduce the chances of survival.[184] In animal models, the overexpression of SOD was associated with protection against reperfusion injury, while SOD knockout animals were more susceptible.

In an *ex vivo* reperfusion study on guinea pig heart, both **SS-02** and **SS-31** were able to

prevent myocardial stunning and significantly improve contractile force, albeit at drastically different doses (100 μM and 1 nM, respectively).[175,185] The discrepancy in activity must be attributed to the amino acid sequence alone, since both **SS-02** and **SS-31** were of similar efficiency as antioxidants in the nonenzymatic *in vitro* assay. **SS-20**, which lacks the scavenging Dmt moiety, was unable to prevent myocardial stunning when administered upon reperfusion. Furthermore *in vivo* testing of **SS-02** was found to protect against myocardial stunning in rats,[185] thus supporting the theory that ROS play a major role in reperfusion-induced myocardial stunning Since mitochondria contain μ-type opiod receptors, further study on these SS tetrapeptides is required to determine whether it is the opiod receptor association of these peptides that mediates mitochondrial targeting and whether this event is the cause of cardiac protection at reperfusion.[186]

A.2.3.2 XJB Gramicidin S Analogs.

XJB peptides and peptide mimetics are based on the sequence of the membrane-active gramicidin S (GS) antibiotics (Figure 6); their antioxidant properties stem from the attachment to the stable free radical, 4-amino-TEMPO (4-AT).[187] Among the advantages of TEMPO is the ability to use electron spin resonance (ESR) to measure distribution of the spin label and detect oxidative stress in the local cellular environment.[188]

In addition to **XJB-5-131**, initial proof-of-principle experiments also used two different hemi-GS segments (Leu-D-Phe-Pro-Val-Orn and D-Phe-Pro-Val-Orn-Leu) in conjugation with 4-AT (**XJB-5-125** and **XJB-7-75**, respectively, Figure 7). Incubation of mouse embryonic cells with either **XJB-5-125** or **XJB-7-75** attenuated ActD-induced phosphatidylserine (PS) externalization in a dose-dependent manner at a concentration nearly 1000 times lower than

untargeted 4-AT. Hemi-GS-TEMPO derivatives almost completely inhibited superoxide production in ActDtreated mouse embryonic cells. The shortened peptide isostere sequence **XJB-5-208** showed no antiapoptotic effects, and, in accordance with the functional hypothesis, control fragments with slightly altered sequences such as **XJB-5-197** and **XJB-5-194** also provided no protection.[189] Most subsequent follow up studies used the peptide isostere **XJB-5-131**,[187] since the replacement of an amide bond with an alkene group often leads to an extended bioavailability, possibly due to increased resistance against protease action.[190]

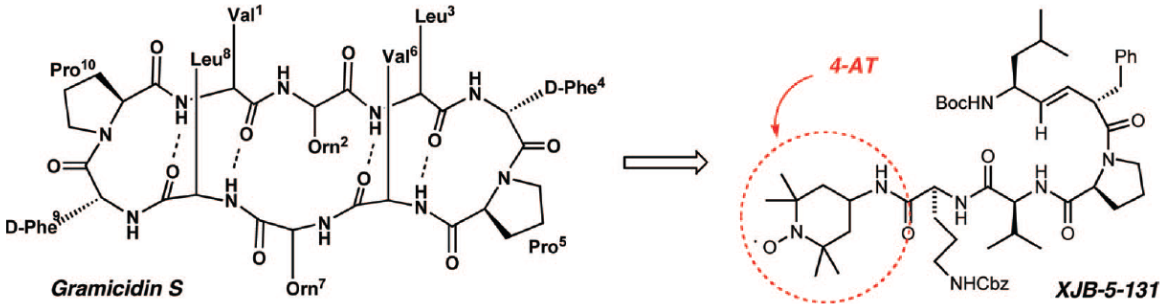


FIGURE 6. Structures of the cyclodecapeptide antibiotic, microbial lipid targeting gramicidin S, and the designed **XJB-5-131**, which delivers the ROS scavenging unit 4-AT to mitochondrial membranes.

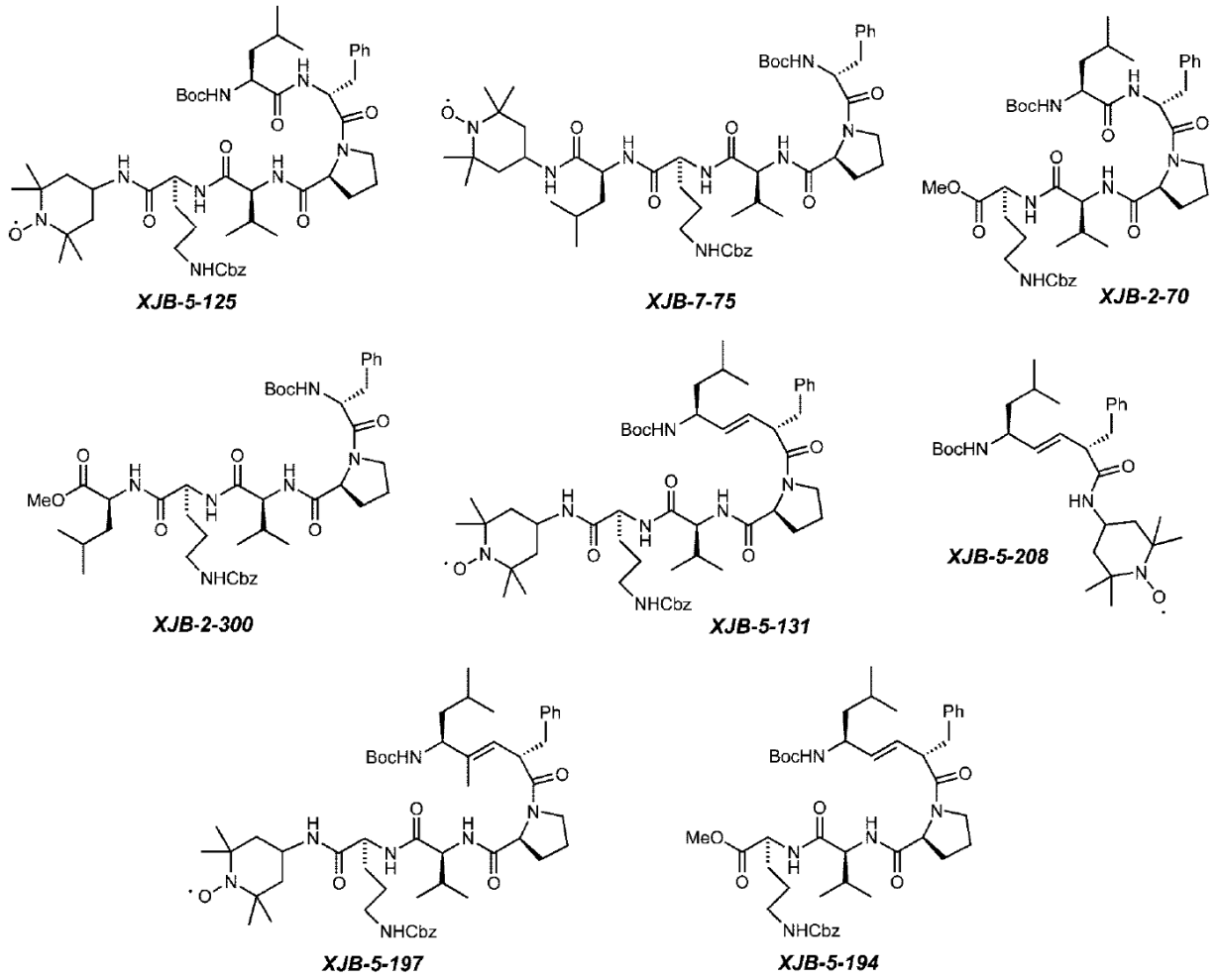


FIGURE 7. Structures of **XJB-5-131** analogs.

The levels of internalization of **XJB-5-125**, **XJB-5-131**, and **XJB-5-208**, as well as untethered 4-AT, after their incubation with mouse embryonic cells were tested using ESR spectroscopy and ESI-MS. **XJB-5-125**, **XJB-5-131**, and **XJB-5-208** were readily detected in mitochondria, whereas the presence of free 4-AT was not observed. The biodistribution profile of non-antiapoptotic **XJB-5-208** indicates that the simple accumulation of nitroxides in the mitochondria is not sufficient for preventing ActD-induced apoptosis. It was speculated that both the nitroxide functionality and the reverse turn (β-turn) of the targeting sequence are essential for the antiapoptotic properties of the hemi-GS-TEMPO derivatives.[189]

Since **XJB-5-131** proved to be a novel and effective mitochondrial ROS and electron scavenger,[191] a follow up study was performed to assess its ability to prolong the survival of rats with lethal hemorrhagic shock.[184] Thirteen rats were bled over 60 min with a total blood loss of 33.5 mL/kg or approximately 55% of total blood volume. Six were randomly assigned to receive **XJB-5-131**, and seven received only its vehicle, a 1:2 (vol/vol) mixture of DMSO and normal saline. All seven of the vehicle-treated (control) group died within 125 min, whereas animals treated with **XJB-5-131** survived significantly longer. Three survived longer than 3 h and one survived for the whole postbleeding observation period. This study showed for the first time that acute administration of a single dose of a mitochondria-targeting ROS scavenger, **XJB-5-131**, can have a dramatic physiological effect in a whole animal model of critical illness. Furthermore, these studies suggest that treatment with **XJB-5-131** might prolong the period of time that patients can survive after losing large quantities of blood, thereby allowing transport of otherwise mortally wounded individuals to locations where additional care can be provided. Further assays of these compounds to determine toxicity, half-life, distribution, metabolism, and physiological elimination are currently being pursued.

A.3 NON-PEPTIDIC MITOCHONDRIAL TARGETING SPECIES

(A. Hoye, author)

A.3.1 Lipophilic cationic compounds

Mitochondria use ion channel pumps and oxidation pathways to maintain a constant

membrane potential of ca. -180 mV across their lipid bilayer. The magnitude of this potental is unprecedented in any other organelle; it is twice that of the plasma membrane of excitable cells and roughly six times higher than the plasma membrane of nonexcitable cells.[192] The unique nature of the mitochondrial membrane distinguishes it from its intracellular counterparts and offers a unique chemical opportunity for selectively targeting the mitochondrion.

The use of lipophilic cations as selective targeting agents has been explored to capitalize on this physiological phenomenon. Rhodamine 123 (**1**) and similar compounds containing cationic functionality in an otherwise nonpolar framework have the ability to traverse the mitochondrial lipid membrane by using the negative potential gradient of the organelle as an electrostatic driving force. According to the Nernst equation, this can result in a 100-500-fold increase in accumulation. Rhodamine 123 and related analogs have been used to assess the accumulation of this class of fluorescent dyes in mitochondria, and as a result of the success and reproducibility of their selective incorporation into mitochondria, practical rhodamine-based stains for mitochondrial assays have been developed and are routinely employed.

Rhodamine 123 has also been successfully used as a chaperone to direct tethered compounds into mitochondria. The anticancer drug cisplatin was selectively incorporated into the mitochondria of cancer cells using this method,[193] and similar approaches have been demonstrated with other small molecules. Arguably the most beneficial outcome of the rhodamine trials has been the discovery of the utility of the chaperone effect, which was further extended toward the development of lipophilic triphenylphosphonium (TPP) salts. The latter compound class includes the majority of the nonpeptidic mitochondrial targeting agents synthesized to date (Figure 8).[192,193,194,195]

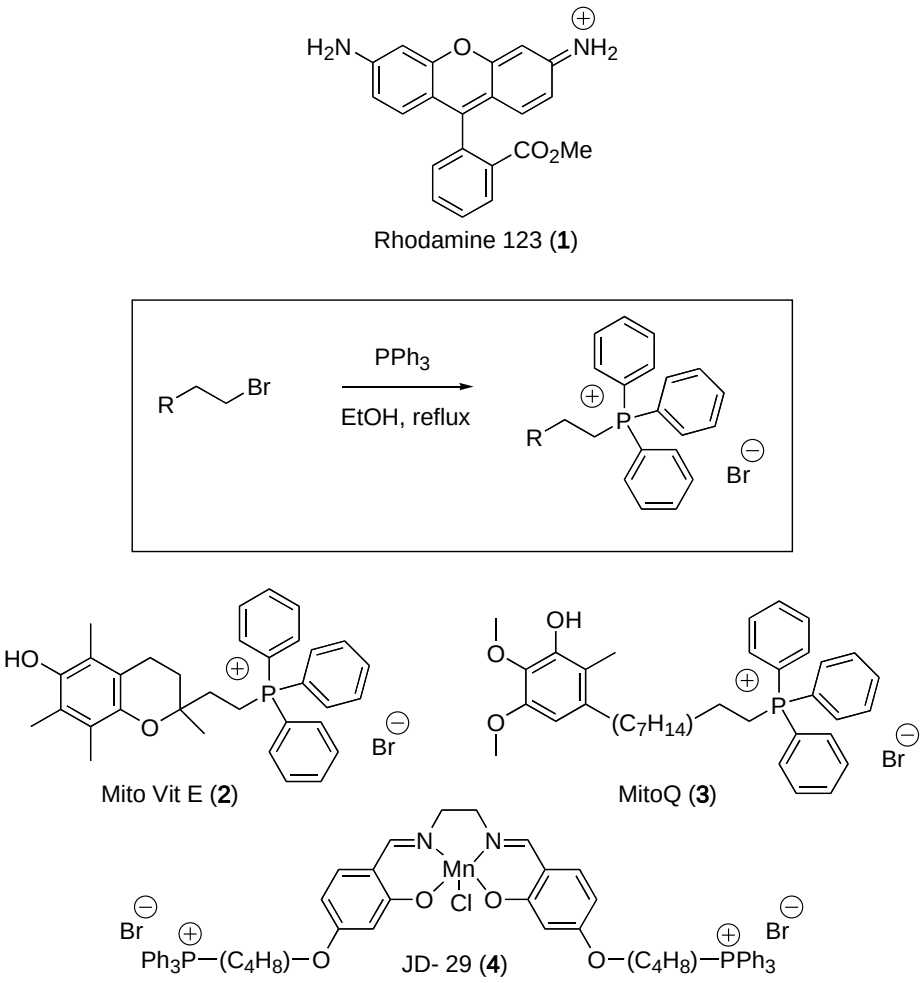


FIGURE 8. Lipophilic cationic targeting agents.

Given the similar uptake and selectivity profile of alkyl TPP compounds to that of the more structurally complex rhodamine analogues, a number of antioxidant-tethered lipophilic TPP cations have been synthesized.[195,196] The common synthetic strategy for constructing this class of compounds proceeds via the displacement of the corresponding primary bromide using triphenylphosphine as outlined in Figure 8. Vitamin E has been shown to diminish the amount of ROS-associated mitochondrial damage by itself, but because the compound cannot effectively accumulate within mitochondria and due to health concerns related to higher dosages, only a limited effectiveness was observed without the use of the lipophilic cation transport tether. In

contrast, MitoVit E (**2**), named in reference to the tethered benzopyran moiety of vitamin E, is localized in energized mitochondria and protects isolated rat liver mitochondria from iron/ ascorbate- and *tert*-butylhydroperoxide-induced oxidative damage.[197] MitoQ (**3**) is a related redox-active compound using ubiquinol as the active moiety, which selectively protects mitochondria against cardiac ischemia-reperfusion oxidative injury.[198] Both **3** and the salen-bound manganese compound JD-29 (**4**) were shown to exhibit MnSOD-like behavior and prevent mitochondrial oxidative damage.[199] MitoPBN, MitoCP, and Tempol-TPP (**5**-**7**) contain N-oxide moieties that scavenge ROS by mimicking SOD (Figure 9).[192,195,200,] MitoPeroxidase (**8**) contains the glutathione peroxidase mimic ebselen to achieve its protective effects against Fe2+/H2O2-induced lipid peroxidation; it is part of a larger class of biologically significant organoselenium antioxidants.[195,201]

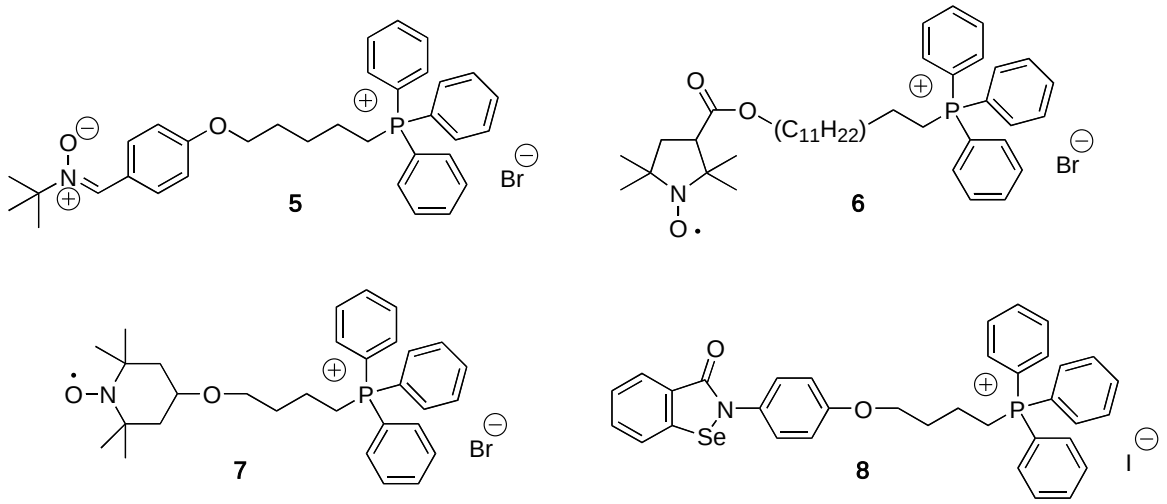
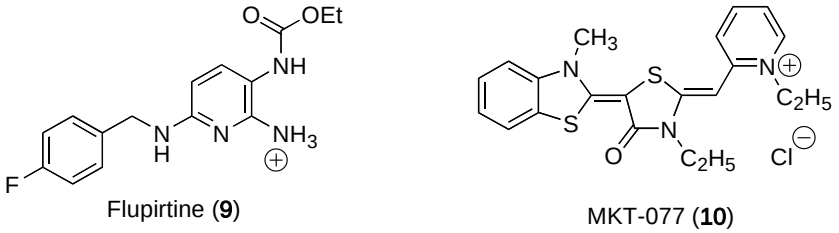


FIGURE 9. Natural ROS scavenger mimic TPP lipophilic cations.

Other lipophilic cations also show selectivity for mitochondria and are attractive candidates for potential therapeutic development. Flupirtine (**9**) is a nonopioid analgesic localized within mitochondria and protects against cell injury induced by *N*-methyl-D-aspartate

and against ischemic injury and prevents glutamate-induced increase of intracellular Ca2+ levels leading to apoptosis (Figure 10).[202,203] MKT-077 (**10**) accumulates in mitochondria due to its cationic amino function and relatively nonpolar scaffold. However, instead of acting in a protective fashion, **10** displays selective toxicity to carcinoma mitochondria due to the increased mitochondrial membrane potential in cancer cells compared to normal cells.[204,205]



Flupirtine (**9**) MKT-077 (**10**)

FIGURE 10. Other lipophilic cation targeting agents.

While lipophilic cations elicit protective effects toward mitochondrial injury, their dependence on the membrane potential in mitochondria also constitutes a major drawback. As increasing numbers of lipophilic cations enter the organelle, the potential gradient diminishes to the point where a rapid efflux of the inhibitor from the mitochondrion results in loss of activity until entry is regained. Therefore, unless inhibition is irreversible, uninterrupted activity of the lipophilic cation cannot occur. This deficiency poses a potential problem depending on the rates of influx and efflux of cationic species.[193]

A.3.2 Sulfonylurea and related compounds

Compounds **11–15** were observed to both activate and inhibit mitochondrial potassium ATP-regulated ion channels (mitoKATP) (Figure 11). They bind with high affinity to sulfonylurea

receptors (SURs) in the plasma membrane across a number of cell types. A potassium channel structurally related to the SUR was detected in the inner membrane of mitochondria and identified as the target of these compounds, although the exact mechanism of action and specificity have not been elucidated.[203,206] Potassium channel openers and inhibitors exhibit diverse activity ranging from vasodilation to hair growth, and recent evidence indicates that KATP channel openers could prove to be effective as pharmacological lead structures for the cardioprotection of tissues against ischemic necrosis and ultimately coronary artery disease, the main cause for fatalities in the industrialized world. [207]

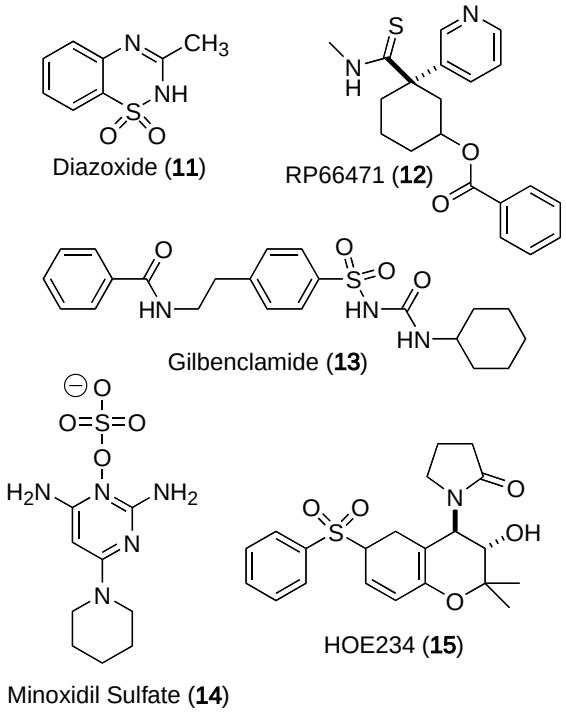
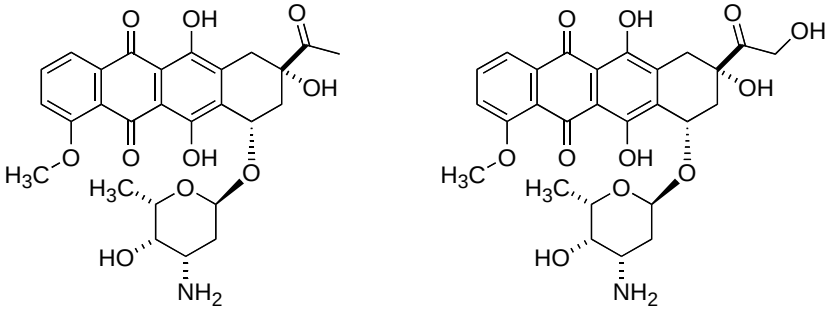


FIGURE 11. Sulfonyl-urea and related mitochondrial targeting agents.

A.3.3 Anthracyclines

Adriamycin (**16**) and daunomycin (**17**) belong to a class of anthracyclines that exhibit potent antitumor activity, presumably through direct binding to DNA in an intercalative fashion, that is, through insertion between stacked bases and charge interaction on the outer regions of the DNA helix (Figure 12). However, data has emerged that suggests these compounds interact, perhaps exclusively, with mitochondria by the disruption of major mitochondrial functions.[208] The cytotoxic side effects of anthracyclines have been attributed to the accumulation of these compounds in the mitochondrial lipid membrane and subsequent redox activity of the quinone moiety, resulting in damage of membranebound proteins and enzymes. The mitochondrial specificity of these compounds is noteworthy and has been correlated to their high affinity toward binding an inner mitochondrial membrane-specific phospholipid, cardiolipin. The glycosidic amino function in **16** and **17** was critical for the observed activity and differentiates them from related anthracycline analogues.[208]



Adriamycin (**16**) Daunomycin (**17**)

FIGURE 12. Mitochondrial-targeting anthracyclines Adriamycin and Daunomycin.

A.3.4 Other structural classes

Several other structural classes have been shown to target mitochondria selectively, but more detailed investigations are required before their utility can be established. For example, resveratrol (**18**) and its analogues **19** and **20** selectively initiate the apoptotic mitochondrial pathway in cancer cell lines while leaving normal cells untouched; however, their precise mechanism of action is not fully understood (Figure 13).[209]

The mitochondrial targeting ability of porphyrin-based antitumor compounds such as verteporfin (**21**, Visudyne, Novartis AG) was postulated to derive from the enrichment of these compounds within mitochondria. Apparently, this accumulation is due to an interaction with mitochondrial-specific benzodiazepine receptors. The porphyrin moiety serves as a photosensitizer and induces the apoptotic pathways in tumor cell lines.[210] BMD188 (**22**) is a cyclic hydroxamic acid derivative that has shown potent activity against prostate cancer, an effect that is hypothesized to be the result of an interaction with mitochondria. A number of other structurally diverse compounds, including curcumin (**23**), the steroid betulinic acid (**24**), and the retinoid CD437 (**25**) have also been shown to induce mitochondrial apoptosis through an opening of the mitochondrial transition permeability pore.[210]

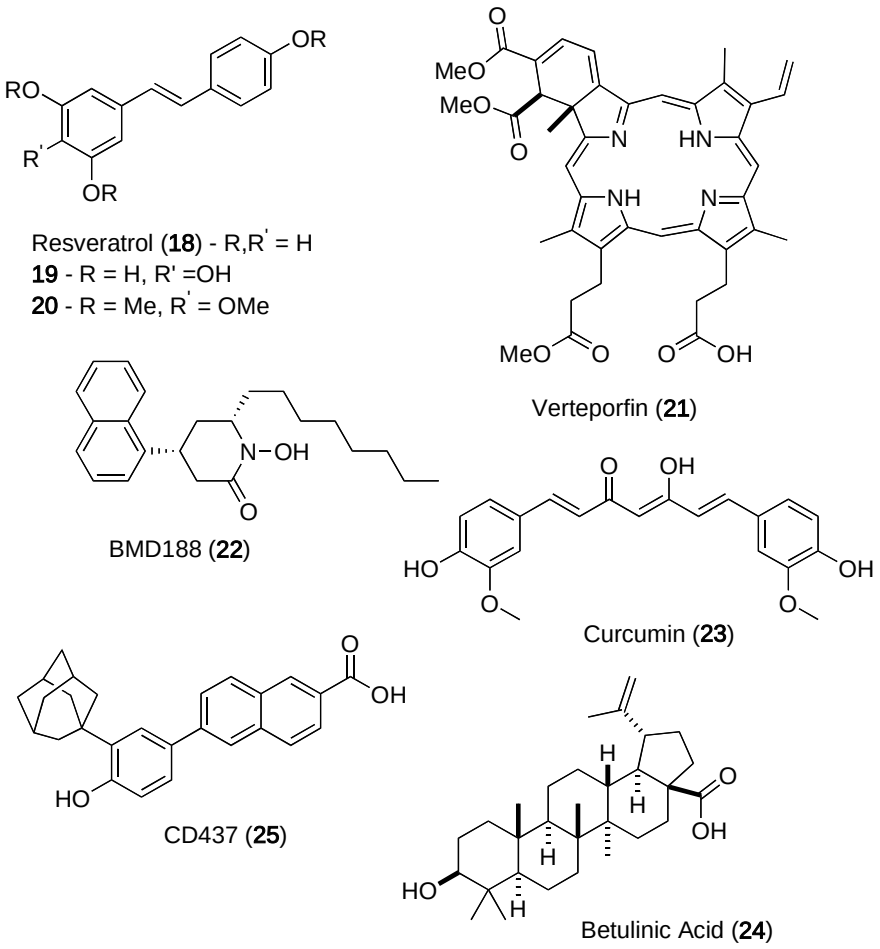


FIGURE 12. Other structural mitochondria targeting small molecules.

A.4 CONCLUSIONS

(P. Wipf, V. Kagan and M. Fink, authors)

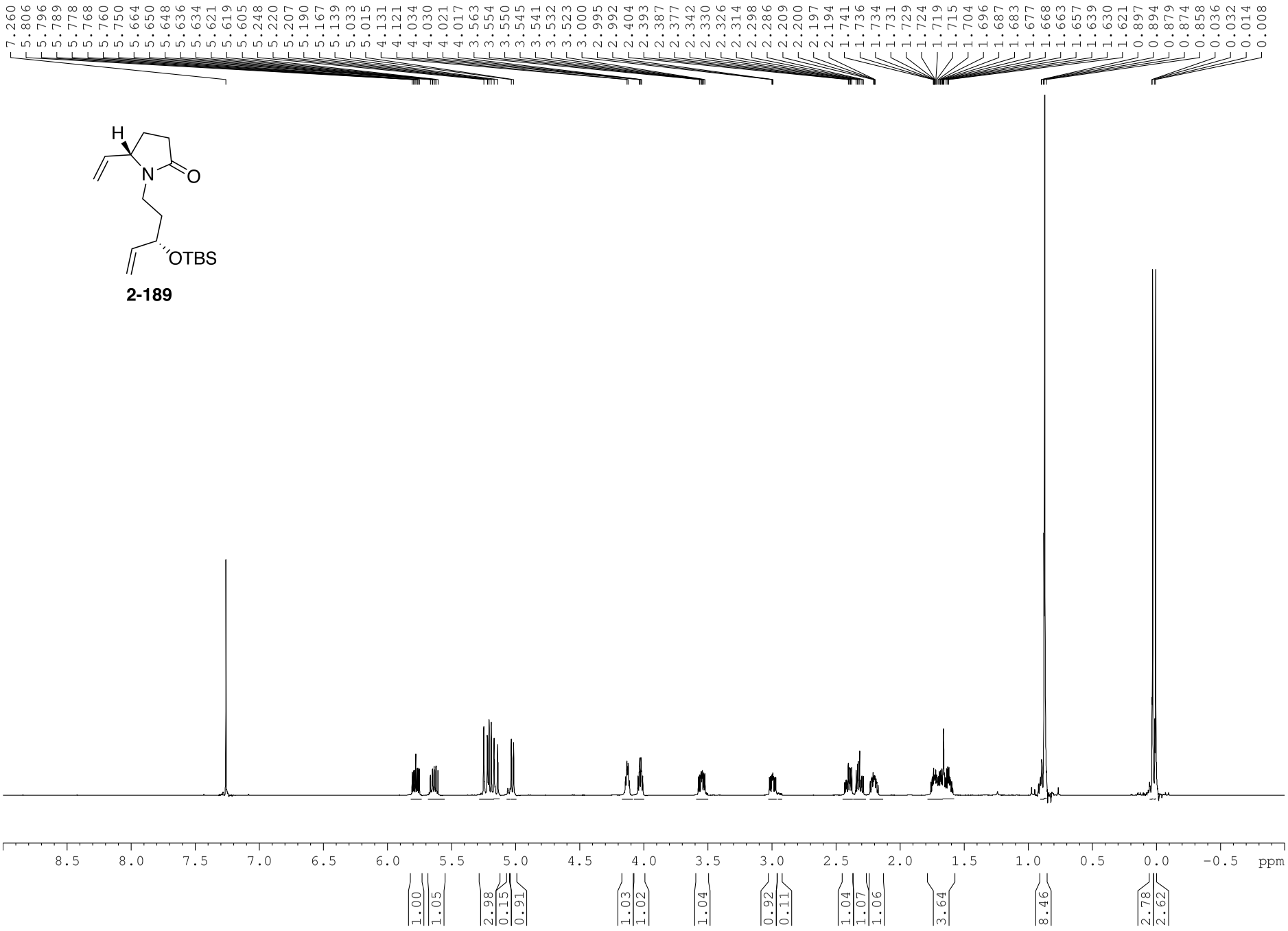
Due to the high concentration of mitochondria in heart tissue, it is not surprising that a major goal in cardioprotection is a decrease in the burst of mitochondrial ROS formation that characterizes postischemic reperfusion. Other important areas for therapeutic intervention based on controlling the mitochondrial pathway for apoptosis include neurodegeneration, diabetes, cancer, and antiviral diseases.[211]

Accordingly, mitochondrial targeting of ROS scavengers or compounds that interfere with the unique biochemistry in mitochondria is emerging as a novel and highly relevant approach in drug discovery for the treatment of degenerative diseases and acute conditions derived from surging ROS and RNS. No pharmaceutical agents specifically designed to deliver a therapeutic compound to mitochondria have yet reached the market, but it is likely that a significant number of essential nutrients, including ascorbic acid, selenium, vitamins E and Q10, carotenoids, etc., fulfill at least part of their function by controlling the surge of reactive byproducts of the oxidative phosphorylation process and ATP generation in mitochondria. Since age-related conditions are rapidly becoming a major source of a declining quality of life in a graying population, we can only hope that the near future will show the emergence of a new class of effective therapies that involve mitochondrial survival strategies. This is an exciting development for synthetic chemists who are being challenged with the discovery of innovative approaches to deliver functional small organic compounds as well as larger biomolecules across cell membranes to specific intracellular targets.[212]

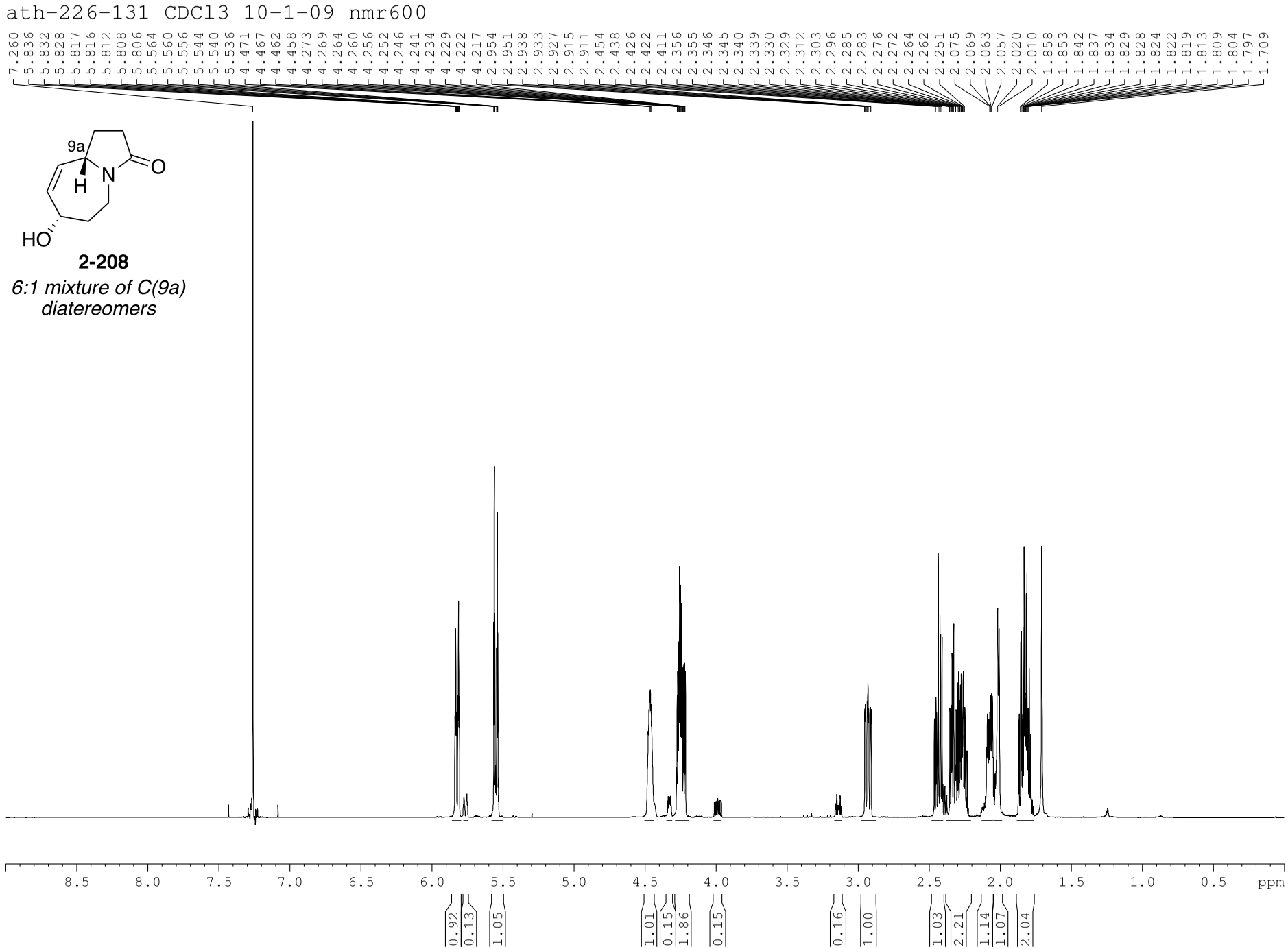
APPENDIX B

SELECTED ^{1}H AND ^{13}C NMR SPECTRA FOR COMPOUNDS **2-189**, **2-208**, **2-221**, **2-222**, **2-255a,b**, **3-6**, **2-267**, and **2-227**

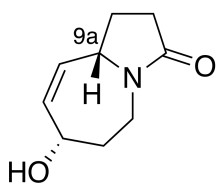
ath-285-391-2 CDCl3 7-14-10 nmr600



ath-285-391-3 CDC13 7-14-10 nmr600
2-189
OTBS
N
O
H
174.94
141.11
140.64
137.99
137.85
118.18
118.11
114.57
114.15
77.36
77.15
76.94
72.03
71.92
61.46
37.71
37.37
35.33
35.18
30.25
25.95
25.67
25.54
18.28
-4.21
-4.27
-4.85
ppm


ath-226-131 CDCl3 10-1-09 nmr600
7.260
5.836
5.832
5.828
5.817
5.816
5.812
5.808
5.806
5.564
5.560
5.556
5.544
5.540
5.536
4.471
4.467
4.462
4.458
4.273
4.269
4.264
4.260
4.256
4.252
4.246
4.241
4.234
4.229
4.222
4.217
2.954
2.951
2.938
2.933
2.927
2.915
2.911
2.454
2.438
2.426
2.422
2.411
2.356
2.355
2.346
2.345
2.340
2.339
2.330
2.329
2.312
2.303
2.296
2.285
2.283
2.276
2.272
2.264
2.262
2.251
2.075
2.069
2.063
2.057
2.020
2.010
1.858
1.853
1.842
1.837
1.834
1.829
1.828
1.824
1.822
1.819
1.813
1.809
1.804
1.797
1.709
9a
N
H
O
HO
2-208
6:1 mixture of C(9a) diatereomers
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
0.92
0.13
1.05
1.01
0.15
1.86
0.15
0.16
1.00
1.03
2.21
1.14
1.07
2.04

ath-226-131 CDCl3 10-1-09 nmr600



2-208

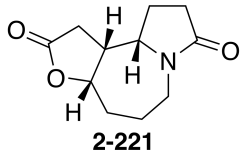
6:1 mixture of C(9a) diatereomers

174.11
136.40
135.56
131.64
131.04
115.84
115.36
111.49
111.12
105.39
103.79
97.31
77.36
77.15
76.94
70.45
68.73
58.16
57.97
38.58
37.87
35.63
35.05
30.11
29.92
26.75
26.45

217

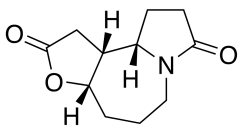
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

ath-266-331 CDCl3 4-20-10 nmr600



2-221

ath-266-331 CDCl3 4-20-10 nmr60



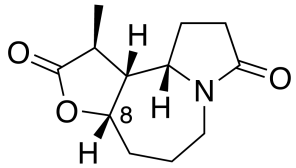
2-221

175.79
175.32
80.97
77.36
77.15
76.94
56.59
44.82
43.92
31.93
29.46
27.80
24.77
21.31

219

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 ppm

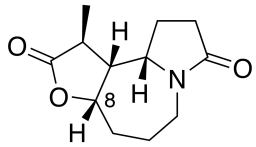
ath-285-781-11 CDCl3 8-6-10 nmr600



8-*epi*-stemoamide
(**2-222**)

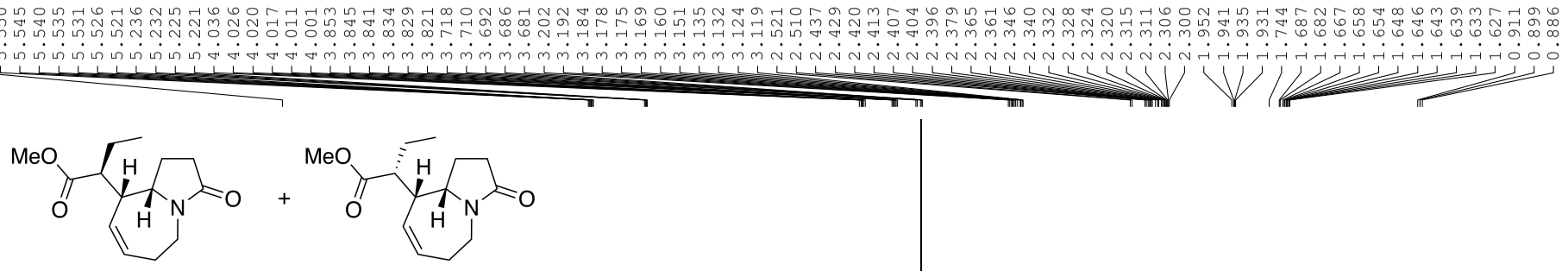
220

ath-285-781-9 CDCl3 8-6-10 nmr600



8-*epi*-stemoamide
(**2-222**)

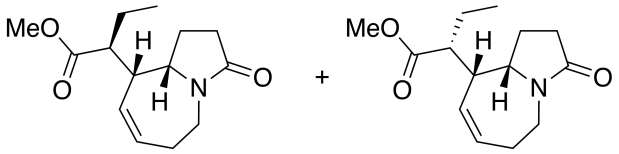
ath-285-721-3 CDCl3 7-27-10 nmr600



2-255a + **2-255b**

222

ath-285-721-4 CDCl3 7-27-10 nmr600



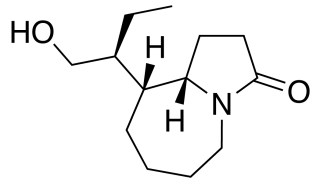
2-255a

+

2-255b

ath-252-391 CDCl3 1-28-10 nmr600

7.260 4.002 3.979 3.927 3.918 3.910 3.901 3.891 3.749 3.742 3.730 3.724 3.710 3.703 3.692 3.684 2.676 2.674 2.653 2.632 2.630 2.357 2.343 2.337 2.333 2.324 2.320 2.317 2.309 2.022 2.009 1.998 1.985 1.962 1.959 1.949 1.938 1.928 1.918 1.915 1.847 1.830 1.705 1.684 1.667 1.664 1.647 1.631 1.627 1.611 1.581 1.572 1.561 1.552 1.543 1.539 1.530 1.526 1.521 1.513 1.501 1.439 1.431 1.426 1.415 1.401 1.389 1.378 1.372 1.369 1.364 1.357 1.350 1.274 1.263 1.254 1.250 1.240 1.235 0.942 0.930 0.918



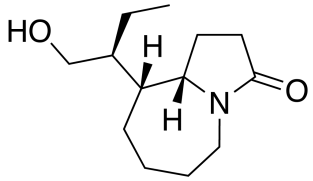
3-6

224

8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

0.99 1.00 1.99 1.00 2.03 1.04 1.11 1.81 2.14 2.03 3.06 2.33 2.94

ath-252-391 CDCl3 1-28-10 nmr600



3-6

174.67

77.36
77.15
76.94

62.09
60.65

43.58
42.18
40.69

31.02
29.87
29.12
24.40
21.97
21.51

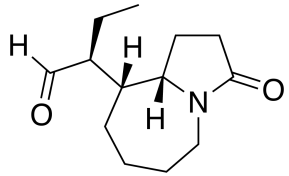
11.67

225

200 180 160 140 120 100 80 60 40 20 0 ppm

ath-285-541 CDCl3 7-16-10 nmr600

9.558 9.553 7.260 4.046 4.023 3.912 3.902 3.894 3.885 3.876 2.667 2.665 2.644 2.623 2.621 2.375 2.362 2.356 2.349 2.344 2.339 2.247 2.237 2.229 2.223 1.937 1.932 1.927 1.921 1.916 1.911 1.906 1.901 1.895 1.890 1.857 1.854 1.851 1.847 1.833 1.732 1.728 1.721 1.716 1.709 1.704 1.697 1.692 1.684 1.680 1.672 1.667 1.661 1.649 1.635 1.623 1.615 1.596 1.579 1.576 1.559 1.441 1.433 1.428 1.417 1.412 1.391 1.374 1.361 1.356 1.348 1.345 1.325 1.321 1.308 1.300 1.292 1.286 1.278 1.233 0.902 0.889 0.877



2-267

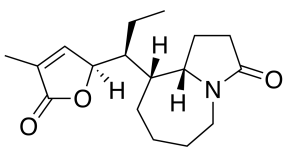
226

10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

0.87 1.01 1.00 1.07 2.06 1.97 1.06 1.06 4.31 4.33 2.90

ath-285-541-2 CDCl3 7-16-10 nmr600
2-267
204.08
174.49
77.36
77.15
76.94
59.90
55.44
41.66
40.84
30.79
29.63
29.06
25.59
21.86
20.75
11.32
200
180
160
140
120
100
80
60
40
20
0
ppm

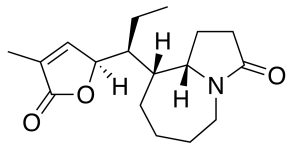
ath-285-592-3 CDCl3 7-28-10 nmr600



Sessilifoliamide C
(**2-227**)

ath-285-592-3 CDCl3 7-28-10 nmr600

174.55
174.50
148.52
130.48
82.27
77.36
77.15
76.94
60.87
44.20
43.26
40.74
31.06
30.96
29.61
29.51
28.97
24.55
22.11
19.11
13.63
13.45
10.87



Sessilifoliamide C
(**2-227**)

229

190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

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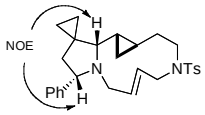
73. These allylation conditions would give, to varying degrees, mono-allylated species with and without the carbamate function still intact along with the desired bis-allylated compound. The ratios of isolated compounds did not appear to correlate with the purity of reagents, reaction time, or concentration.

74. The relative configuration was assigned on the basis of previous reductive amination studies on related cyclopropyl pyrrolidines performed by Wipf, Stephenson, and Walczak (ref. 63), and later confirmed by X-ray and NMR analysis.

75. Molecular modeling experiments (performed using MOE modeling program applying a MMFF94x basis set) of both (*E*)- and (*Z*)-olefins reveal a 0.68 kcal difference between the lowest energy conformations of the two isomers, favoring the (*E*)-alkene. Performing the reaction under an ethylene atmosphere theoretically allows the interconversion of both compounds to the thermodynamic product.

76. The relative configuration was also confirmed by nOe correlations observed between pyrrolidine ring protons: 

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