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TOTAL SYNTHESIS OF (±)-ALSTOSCHOLARISINES A-E

A Dissertation in

Chemistry

by

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ABSTRACT

Total syntheses of the biologically active monoterpenoid indole alkaloids (±)-alstoscholarisines A-E (**1**-**5**) have been completed in twelve to fourteen steps. The approach commenced with a Michael reaction between the enolate of indole ester **132** and α,β-unsaturated-*N*-sulfonyllactam **130** to form the C15-C16 bond of the alkaloids. A sequence involving chemoselective partial reduction of an *N*-sulfonyllactam and subsequent dehydration to an *N*-sulfonyliminium ion allows for the formation of a bridged aminal **162**, which serves as a common intermediate for the synthesis of the five alkaloids. The degradation of a C20 allyl group to an aldehyde unit by a sequence of olefin transposition and oxidative cleavage allows for the formation of a lactol E ring. The stereochemistry of the α-methyl tetrahydropyran moiety is controlled by stereoselective introduction of axial hydride or methyl nucleophiles to intermediate oxocarbenium ions derived from the lactol. Final functional group manipulations allow for the completion of the syntheses of the alkaloids.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

List of Abbreviations

4 Å M.S.	4 Ångstrom molecular sieves
Ac	Acetyl
amu	Atomic mass unit
aq.	Aqueous solution
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
BOMCl	Benzyl chloromethyl ether
Bu	Butyl
COSY	^{1}H-^{1}H Correlation spectroscopy
Cp	Cyclopentadienyl
Cy	Cyclohexyl
d	Days
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DEAD	Diethyl azodicarboxylate
DIBALH	Diisobutylaluminum hydride
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
dppf	1,1’-Bis(diphenylphosphino)ferrocene
dr	Diastereomeric ratio

ee	Enantiomeric excess
Et	Ethyl
ESI-TOF	Electrospray ionization time-of-flight mass spectrometry
Grubbs II	Grubbs second-generation ruthenium metathesis catalyst
h	Hours
HMBC	Heteronuclear multiple bond correlation spectroscopy
HREIMS	High-resolution electron impact mass spectrometry
HRMS	High-resolution mass spectrometry
IR	Infrared spectroscopy
KHMDS	Potassium hexamethyldisilazide
LDA	Lithium diisopropylamide
LiHMDS	Lithium hexamethyldisilazide
m	Meta
m/z	Mass to charge ratio
m-CBPA	3-Chloroperbenzoic acid
Me	Methyl
min	Minutes
NMO	*N*-Methylmorpholine-*N*-oxide
N.R.	No reaction
NMR	Nuclear magnetic resonance spectroscopy
o	Ortho
OTf	Trifluoromethane sulfonate
p	Para
Ph	Phenyl

PNB	*p*-Nitrobenzoyl
p-TsOH	*p*-Toluenesulfonic acid
ROSEY	Rotating frame nuclear Overhauser effect spectroscopy
rt	Room temperature
satd	Saturated
SMes	1,3-bis(2,4,6-Trimethylphenyl)-2-imidazolidinylidene
TBAF	Tetrabutylammonium fluoride
TBAI	Tetrabutylammonium iodide
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
TEMPO	2,2,6,6-Tetramethylpiperidine-1-oxyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TMDS	Tetramethyldisiloxane
TMS	Trimethylsilyl
Ts	*p*-Toluenesulfonyl
UV-vis	Ultraviolet-visible spectroscopy

ACKNOWLEDGEMENTS

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Lastly, I must thank my friends and family for their support and love. Because of them, I have been able to withstand the challenges and setbacks that come with research and preserve to the end.

Chapter 1. Introduction and Background

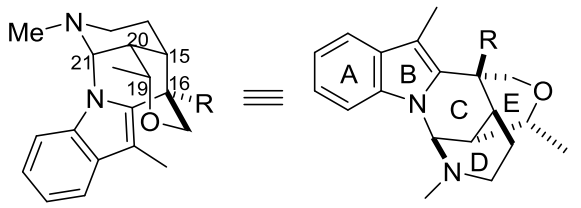
1.1. Isolation, Biological Evaluation, and Structure Determination of the Alstoscholarisines

Central nervous system ailments are a notoriously difficult therapeutic area.[1] However, stem cell-based technologies show promise for the development of new neurological treatments. For example, several Phase I/II clinical trials using stem cell strategies are currently being performed for Alzheimer's disease.[2] Many natural products are known to modulate stem cell fate and population, and may have a key role to play in future treatments for neurogenic disorders.[3]

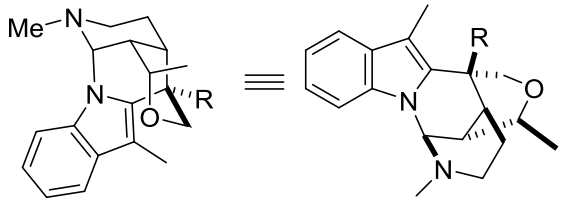
In an ongoing search for biologically active natural products, Luo *et al.* found in 2014 that leaf extracts of the Asian tree *Alstonia scholaris*, an organism with a long history of use in traditional medicines,[4] increased the proliferation of adult mouse hippocampal neural stem cells *in vitro*.[5] Upon purification of the crude total alkaloid mixture by silica gel chromatography, five novel monoterpenoid indole alkaloids, (−)-alstoscholarisines A-E (**1**-**5**) (Figure 1), were isolated and their structures were assigned by extensive NMR studies (*vide infra*), as well as by X-ray crystallographic analysis of **1** and **3**. Furthermore, the absolute configuration of metabolite **1** was assigned by X-ray crystallography, and correlation of the circular dichroism spectra of **1**-**5** allowed for the absolute configurational assignments of alkaloids **2**-**5**. Each pure compound showed greater promotion of stem cell growth than did the crude total alkaloid mixture. (−)-Alstoscholarisine A (**1**) was found to increase the propensity of neural stem cells to transform into neurons.

The structures of compounds **1**-**5** are unusual among monoterpenoid indole alkaloids in that they lack one of the two side-chain carbons originating from a tryptamine unit (*vide infra*).[6] Furthermore, the alkaloids contain a unique pentacyclic 6/5/6/6/6 ring system (rings A-E) that

includes five contiguous stereogenic centers at carbons 15, 16, 19, 20, and 21. Molecules **1** and **2** contain an equatorial methyl group at C19 but differ in the substituent at C16 (H or CO_2Me). Alkaloids **3-5** include an axial methyl group at C19 and again differ at C16 (CO_2Me, CO_2H, or H).



1 (-)-alstoscholarisine A R = H
2 (-)-alstoscholarisine B R = CO_2Me



3 (-)-alstoscholarisine C R = CO_2Me
4 (-)-alstoscholarisine D R = CO_2H
5 (-)-alstoscholarisine E R = H

Figure 1. Structures of (-)-Alstoscholarisines A-E

1.1.1. Structure Determination of Alstoscholarisines A-E

Initial UV-visible analysis of the major component of the total alkaloid mixture, alstoscholarisine A (**1**), indicated the presence of an indole moiety by absorptions at 233 and 287 nm in the spectrum, and HREIMS revealed a molecular formula of $C_{19}H_{24}N_2O$ (*m*/*z* = 296.1890).

The complete structure of (−)-alstoscholarisine A (**1**) was determined by two-dimensional NMR studies and some key interactions are shown in Figure 2. A methyl group directly attached on the indole ring was revealed by ^{1}H-^{13}C HMBC correlations between H6 (CH_3, 2.21) and C2 (136.9), C7 (105.0), and C8 (130.2). The inclusion of an aminal moiety was assigned by ^{1}H-^{13}C

HMBC correlation of a downfield methine (H21, 5.47) with C2 (136.9), C13 (138.5) and N-Me (45.6). An *N*-methylpiperidine ring (D ring) was assigned based on a ^{1}H-^{1}H COSY correlation between H21 (5.47) and H20 (2.12), H20 with H15 (2.18), H15 with H14 (1.74, 2.03), and H14 with H3 (1.84, 2.30), as well as an HMBC cross peak between N-Me (2.24) and C3 (47.3). An HMBC correlation of the H16 methine (3.03) with C2 (136.9) and C7 (105.0) indicated that C16 was attached at C2 of the indole ring. Incorporation of a six-membered ring (C ring) was then elucidated by a COSY relationship between H15 (2.18) and H16 (3.03), as well as the previously discussed correlations between H21, H20, and H15. The presence of a 2-methyltetrahydropyran ring was established by COSY cross peaks between H16 (3.03) and H17 (3.57, 3.60), H20 (2.12) and H19 (3.69), and H19 with the upfield methyl group (H18, 1.22), as well as the downfield chemical shifts of C17 and C19, which indicated the presence of an oxygen in the ring. Furthermore, the H18 methyl group was assigned as being in an equatorial position on the tetrahydropyran ring due to an NOE cross-peak between this signal and H21 in the ROESY spectrum. The proposed structure of (−)-alstoscholarisine A (**1**) was also unambiguously confirmed by single-crystal X-ray analysis.

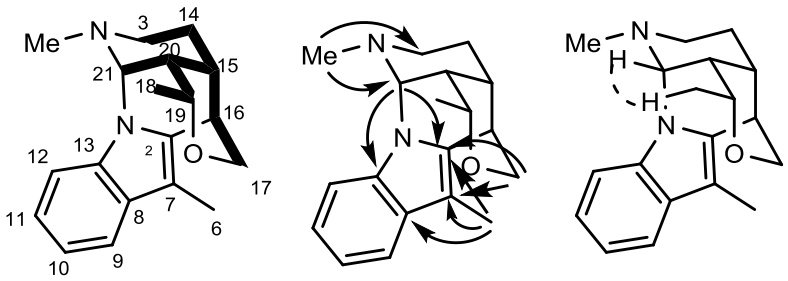


Figure 2. Key Two-Dimensional NMR Correlations for (-)-Alstoscholarisine A (**1**): (left) ^{1}H-^{1}H COSY(▬) (center) ^{1}H-^{13}C HMBC (⌣) (right) ^{1}H-^{1}H ROESY (∿)

(−)-Alstoscholarisine B (**2**) showed a HREIMS peak 68 amu greater (*m*/*z* = 354.1940) than that for alkaloid **1**, which indicated a molecular formula of $C_{21}H_{26}N_2O_3$. The IR spectrum (1730 cm^{-1}) and the ^{13}C NMR spectrum (173.3 ppm) of metabolite **2** indicated the presence of an ester moiety. The COSY and HMBC spectra of **2** showed the same correlations as those discussed above for alkaloid **1**, except for the absence of the C16 methine hydrogen. Furthermore, an NOE correlation between the H18 methyl group and the H21 aminal proton was retained, which indicated an equatorial methyl group, as in compound **1**. It was therefore determined that alkaloid **2** is a structural analogue of (−)-alstoscholarisine A (**1**) containing a methyl ester group at C16.

(−)-Alstoscholarisine C (**3**) had the same HREIMS peak (*m*/*z* = 354.1946) as compound **2**, indicating the possibility that the two alkaloids are stereoisomers. The HMBC and COSY spectra for metabolite **3** were analogous to those for **2**. However, the ROSEY spectrum of (−)-alstoscholarisine C (**3**) revealed an NOE correlation of the H18 methyl group with H15 and H17, indicating an axial methyl group on the tetrahydropyran ring (Figure 3). Furthermore, the H19 methine showed a ROSEY cross peak with the H21 aminal. In addition, the structure of (−)-alstoscholarisine C (**3**) was unambiguously determined by single-crystal X-ray analysis.

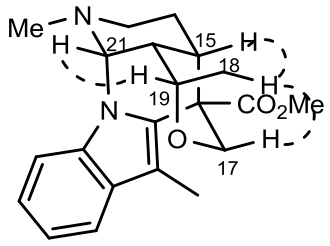


Figure 3. Key ^1H-^1H ROESY (↔) NMR Correlations for (-)-Alstoscholarisine C (**3**)

(−)-Alstoscholarisine D (**4**) showed a HREIMS peak at *m*/*z* = 340.1780, 14 amu less than that for alkaloids **2** and **3**, indicating the possibility that this compound was the ester hydrolysis product of **2** or **3**. Indeed, the IR spectrum of metabolite **4** supported the presence of a carboxylic acid moiety (3418 cm^{-1}). (−)-Alstoscholarisine D (**4**) showed the same HMBC and COSY correlations as seen for alkaloids **2** and **3**. Finally, the methyl group stereochemistry at C19 was determined to be axial due to observed NOE interactions of H18 with H15 and H17, as well as those between H19 and H21.

Alstoscholarisine E (**5**) had the same molecular mass as alkaloid **1** (*m*/*z* = 296.1881), as well as analogous HMBC and COSY spectra. However, compound **5** was assigned to have an axial methyl group at C19, based on the same type of NOE interactions as discussed for metabolites **3** and **4**.

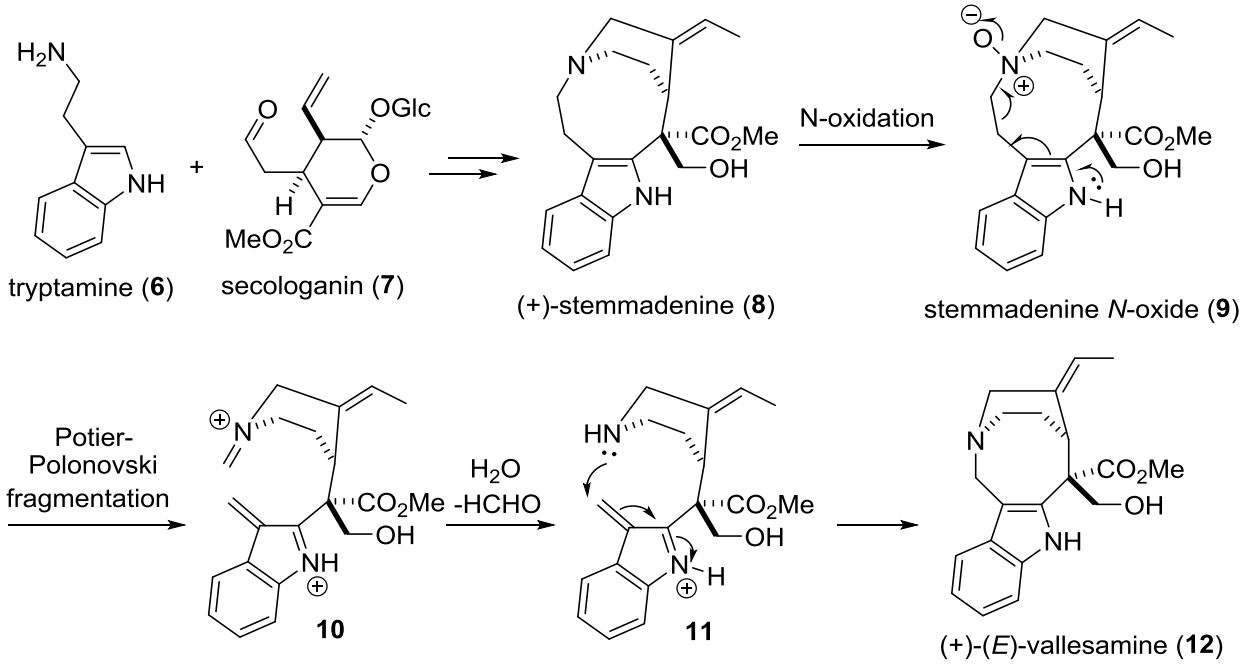
The absolute configuration of (−)-alstoscholarisine A (**1**) was assigned as (15*R*,16*R*,19*R*,20*S*,21*S*) by single-crystal X-ray analysis utilizing the method developed by Hooft and coworkers.[7] The absolute configurations of alkaloids **2-5** were assigned based on the similarity of their UV-circular dichroism spectra with that of (−)-alstoscholarisine A (**1**).

1.2.Proposed Biosynthesis of Alstoscholarisines A-E

The alstoscholarisines likely arise biosynthetically from the known monoterpenoid indole alkaloid (+)-stemmadenine (**8**) as shown in Scheme 1.[8] (+)-Stemmadenine (**8**) arises from two common monoterpenoid indole alkaloid precursors, tryptamine (**6**) and secologanin (**7**). (+)-Stemmadenine (**8**) could be oxidized to stemmadenine *N*-oxide (**9**), which could then undergo a Potier-Polonovski fragmentation to provide azafulvene iminium ion **10**. This intermediate could

be hydrolyzed to the corresponding amine **11**, resulting in the loss of one of the carbons originating from the tryptamine side chain. Amine **11** could then undergo ring-closure to form (+)-(*E*)-vallesamine (**12**), a known alkaloid that has been isolated from *A. scholaris*.[9]

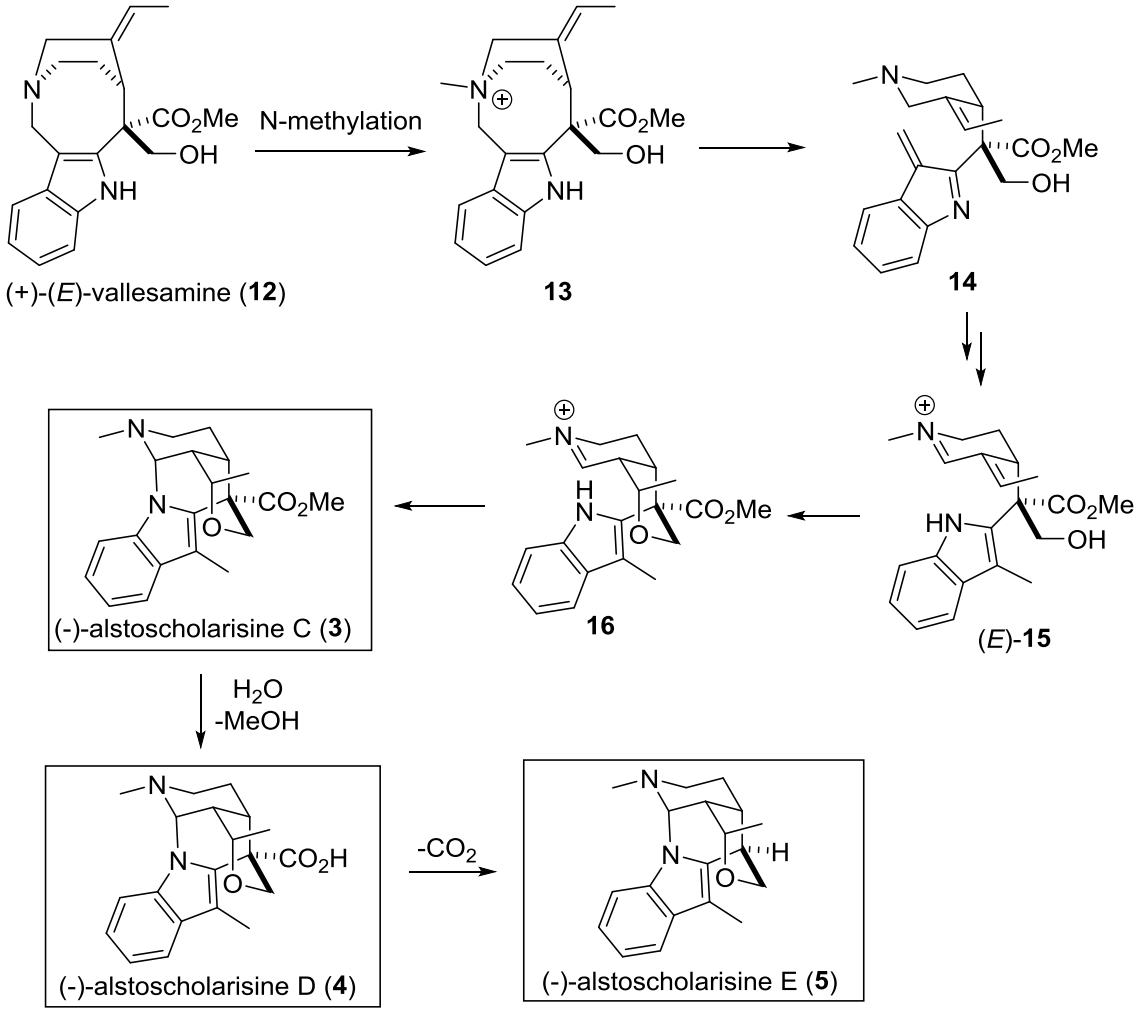
Scheme 1. Biosynthesis of (+)-(*E*)-Vallesamine (**12**)



The biosynthesis of alstoscholarisines C, D, and E (**3**, **4**, and **5**, respectively) could commence from (+)-(*E*)-vallesamine (**12**) as shown in Scheme 2.[5] Thus, (+)-(*E*)-vallesamine (**12**) could be N-methylated to generate quaternary ammonium salt **13**, which could undergo ring-cleavage to form azafulvene **14**. This intermediate could undergo reduction of the azafulvene moiety and oxidation of the piperidine ring to generate (*E*)-α,β-unsaturated iminium ion (*E*)-**15**, which would undergo conjugate addition of the attendant alcohol moiety to form the tetrahydropyran ring in tetracyclic iminium ion **16**. A final nucleophilic addition of the indole

nitrogen onto iminium ion **16** would provide (−)-alstoscholarisine C (**3**). Ester hydrolysis would generate (−)-alstoscholarisine D (**4**), which could undergo decarboxylation to form (−)-alstoscholarisine E (**5**).

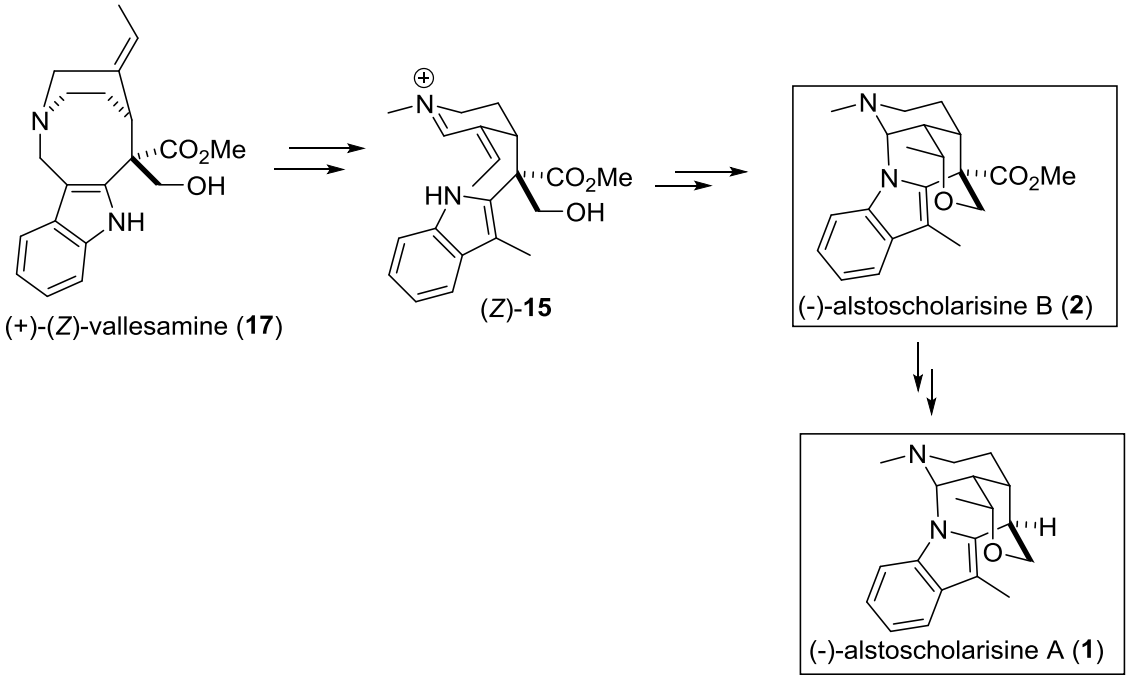
Scheme 2. Proposed Biosynthesis of (-)-Alstoscholarisines C-E (**3-5**) from (+)-(*E*)-Vallesamine (**12**)



The biosynthesis of (−)-alstoscholarisines A (**1**) and B (**2**) was proposed by Luo *et al.*[5] to originate from (+)-(*Z*)-vallesamine (**17**), an alkaloid which is also found in *Alstonia scholaris* (Scheme 3).[9] Thus, by the same pathway described above originating from (+)-(*E*)-vallesamine

(**12**), (+)-(*Z*)-vallesamine (**17**) could be transformed into (*Z*)-α,β-unsaturated iminium ion (*Z*)-**15**. This intermediate could undergo an analogous cyclization sequence as described above for (*E*)-**15** to generate (−)-alstoscholarisine B (**2**). Hydrolysis of the methyl ester and decarboxylation of the intermediate carboxylic acid could produce (−)-alstoscholarisine A (**1**).

Scheme 3. Biosynthesis of (-)-Alstoscholarisines A (**1**) and B (**2**) from (+)-(*Z*)-Vallesamine (**17**)



1.3. Structures and Biosynthesis of Other Alstoscholarisines

A biosynthetically-unrelated alkaloid, named alstoscholarisine F (**18**), was also isolated from *A. scholaris* in 2015 (Figure 4).[10] Additional alstoscholarisines (G-J, **19**-**22**), which are biogenetically related to alstoscholarisines A-E (**1**-**5**), but possess a different skeleton, were isolated in the same year from this organism.[10,11]

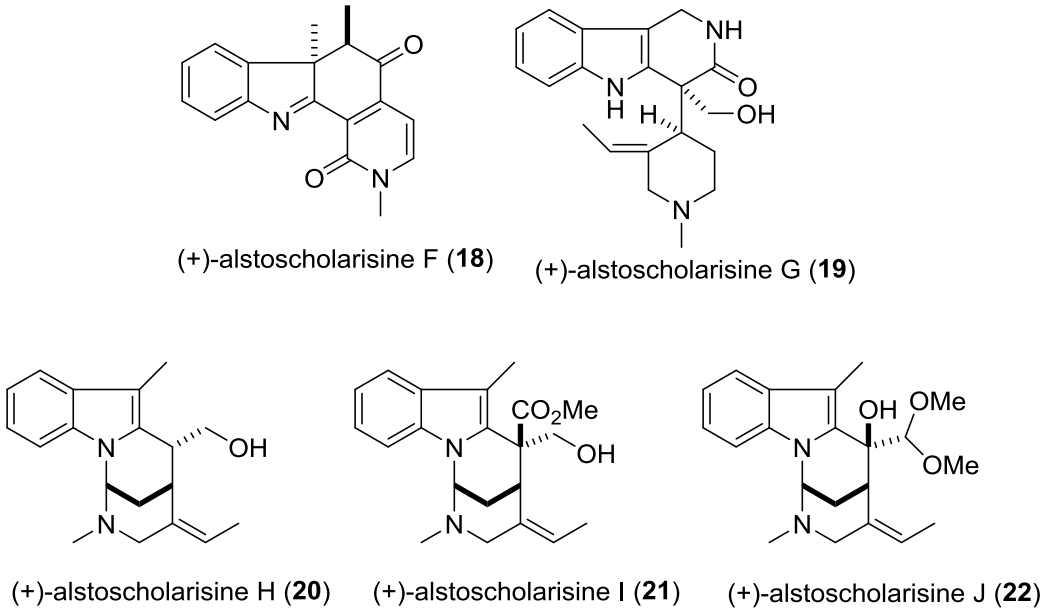
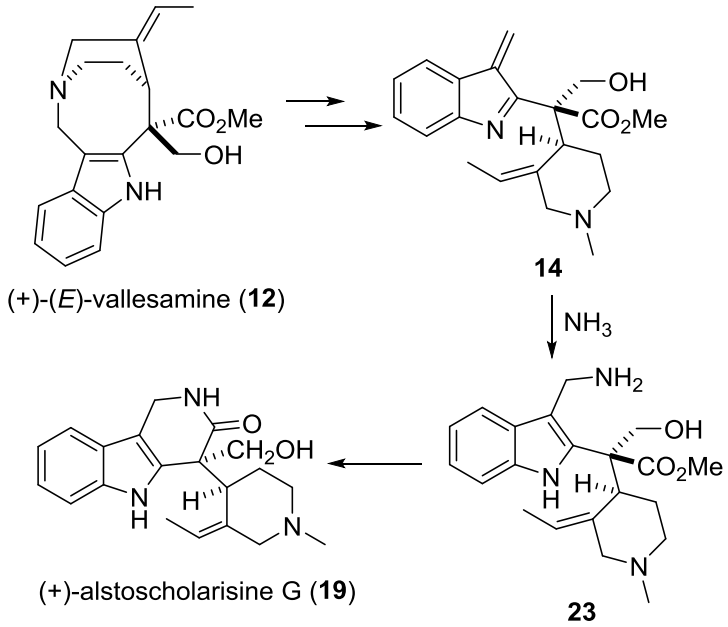


Figure 4. Structures of (+)-Alstoscholarisines F-J (**18-22**)

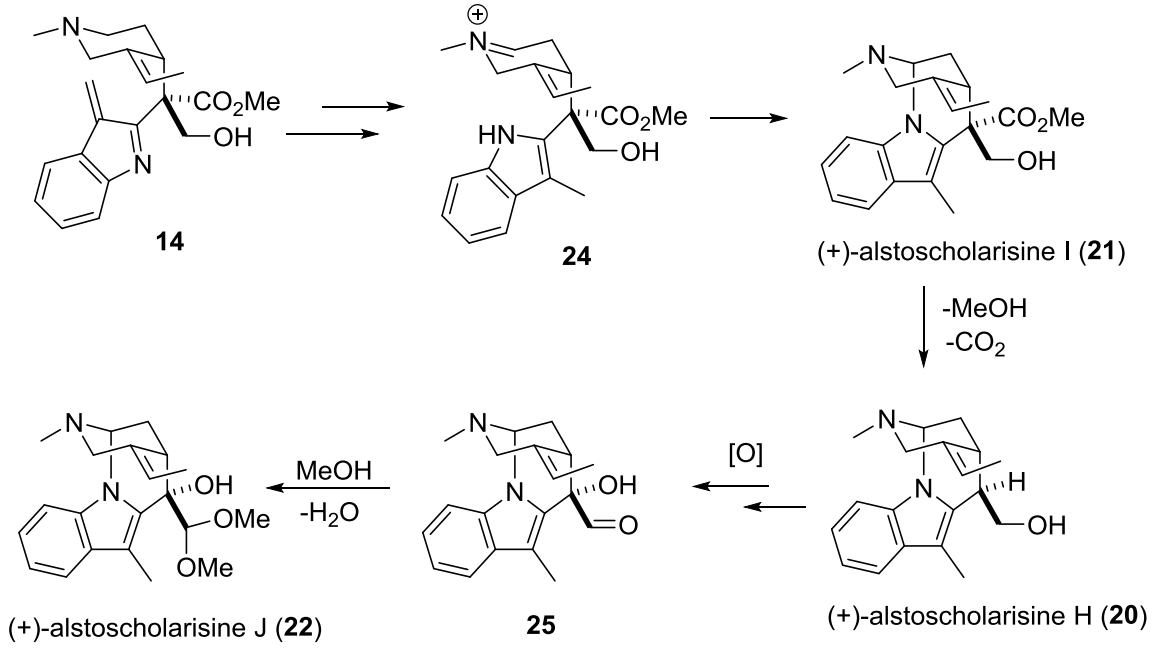
Alstoscholarisines G-J (**19**-**22**) are thought to arise from azafulvene **14**, derived from (+)-(*E*)-vallesamine (**12**, Scheme 4). Alstoscholarisine G (**19**) is proposed to be formed by conjugate addition of ammonia (or an ammonia equivalent) to this intermediate to produce an aminomethyl indole like **23**, which cyclizes onto the attendant methyl ester to form the lactam ring of the alkaloid.

Scheme 4. Biosynthetic Hypothesis for (+)-Alstoscholarisine G (**19**)



Alternatively, the azafulvene moiety of intermediate **14** could be reduced, and the piperidine ring could then be oxidized to form iminium ion **24** (Scheme 5). This intermediate could undergo 1,2-addition of the indole nitrogen onto the iminium ion to generate alstoscholarisine I (**21**). This compound could undergo ester hydrolysis and decarboxylation to form alstoscholarisine H (**20**). Metabolite **20** could be oxidized to form α-hydroxyaldehyde **25**, which would produce alstoscholarisine J (**22**) by formation of the acetal with methanol.

Scheme 5. Proposed Biosynthesis of (+)-Alstoscholarisines H-J (**20-22**)

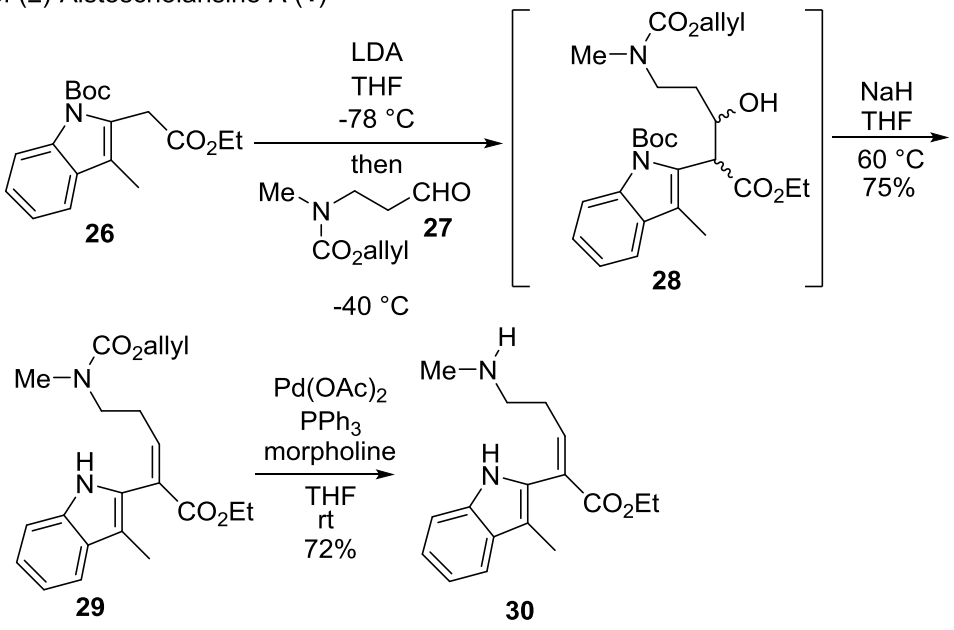


1.4.Previous Syntheses of Alstoscholarisine A

1.4.1. Total Synthesis of (±)-Alstoscholarisine A (1) by Bihelovic and Ferjancic

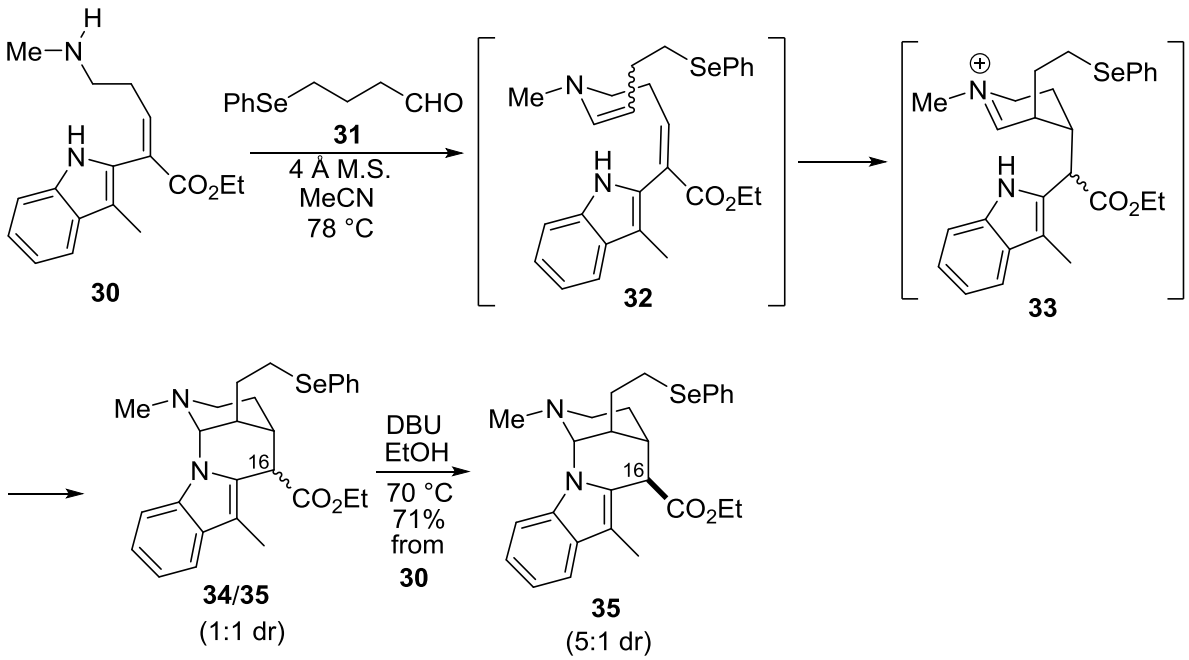
In 2016, Bihelovic and Ferjancic completed a total synthesis of (±)-alstoscholarisine A (**1**) in twelve steps.[12] The synthesis began with an aldol reaction between the enolate of indole ester **26** and protected β-amino aldehyde **27** to provide adduct **28**, which was dehydrated with concomitant Boc removal to form condensation product **29** as a single (*E*)-isomer (Scheme 6). Removal of the allyl carbamate protecting group with $Pd(OAc)_2$/morpholine then gave secondary amine **30**.

Scheme 6. Early-Stages of the Bihelovic/Ferjancic Total Synthesis of (±)-Alstoscholarisine A (**1**)



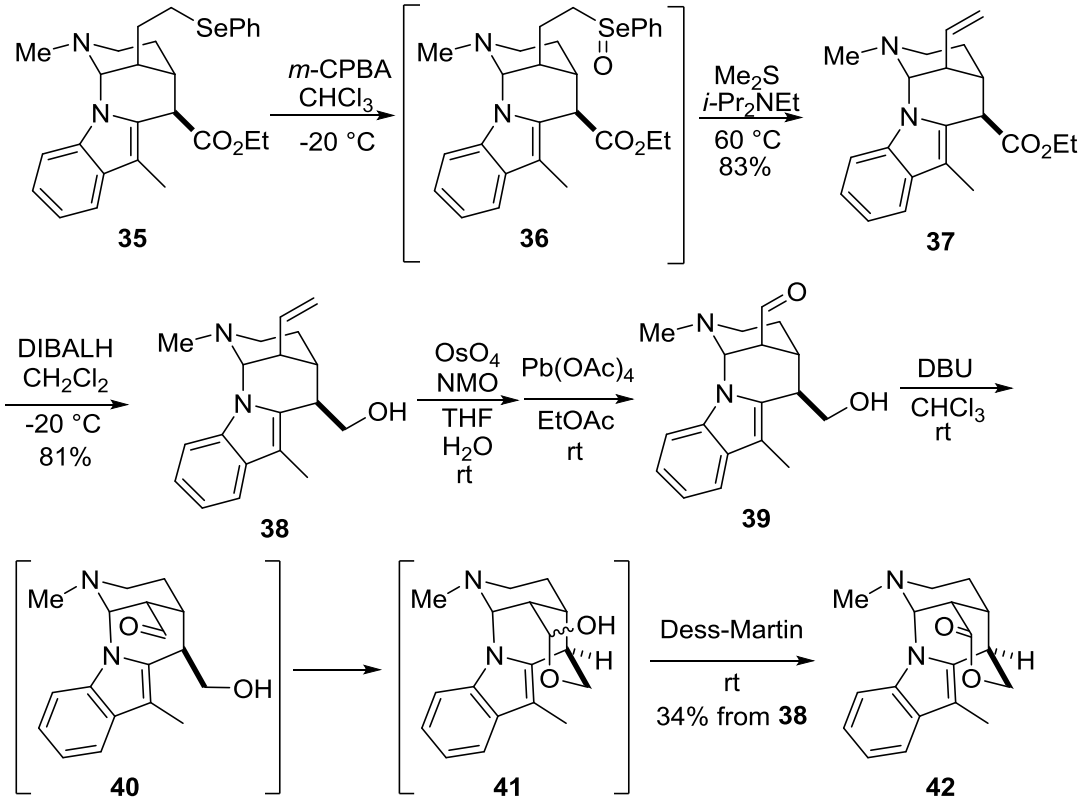
Condensation of amine **30** and γ-phenylselanyl aldehyde **31** then formed enamine **32**, which cyclized via an intramolecular Michael addition with the α,β-unsaturated ester to provide intermediate iminium ion **33** (Scheme 7). This intermediate further cyclized with the indole nitrogen to form bridged aminal **34**/**35** as a separable mixture of C16 epimers (dr ~1:1). Epimerization of the ester moiety with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in ethanol improved the diastereomeric ratio to 5:1, with the major epimer being the desired *exo*-ester **35** needed to continue the synthesis.

Scheme 7. Key Enamine Michael/Aminal Cyclization Sequence and C16 Epimerization



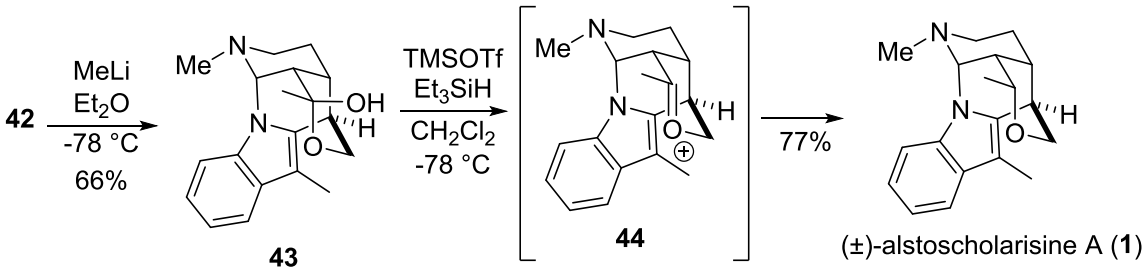
Oxidation of selenide **35** to the corresponding selenoxide **36** with *m*-CPBA, and subsequent elimination provided alkene **37** (Scheme 8). Ester reduction with DIBALH gave alcohol **38**. An Upjohn dihydroxylation[13] of **38**, followed by oxidative diol cleavage with $Pb(OAc)_4$,[14] yielded axial aldehyde **39**, which was epimerized under basic conditions with DBU to equatorial aldehyde **40**. This intermediate spontaneously cyclized to δ-lactol **41**, which was oxidized with Dess-Martin periodinane to produce δ-lactone **42**.

Scheme 8. Formation of the Tetrahydropyran E Ring of (±)-Alstoscholarisine A (**1**)



Chemoselective addition of methyllithium to this lactone **42** provided hemiketal **43** (single diastereomer, configuration not determined), which was further transformed to (±)-alstoscholarisine A (**1**) by conversion to oxocarbenium ion **44** through ionization with trimethylsilyl trifluoromethanesulfonate (TMSOTf), followed by reduction from the least hindered convex face with triethylsilane (Scheme 9). It should be noted that this stereochemical outcome is also consistent with a model predicting axial attack of hydride from triethylsilane based on stereoelectronic stabilization of a chair-like transition state.[15]

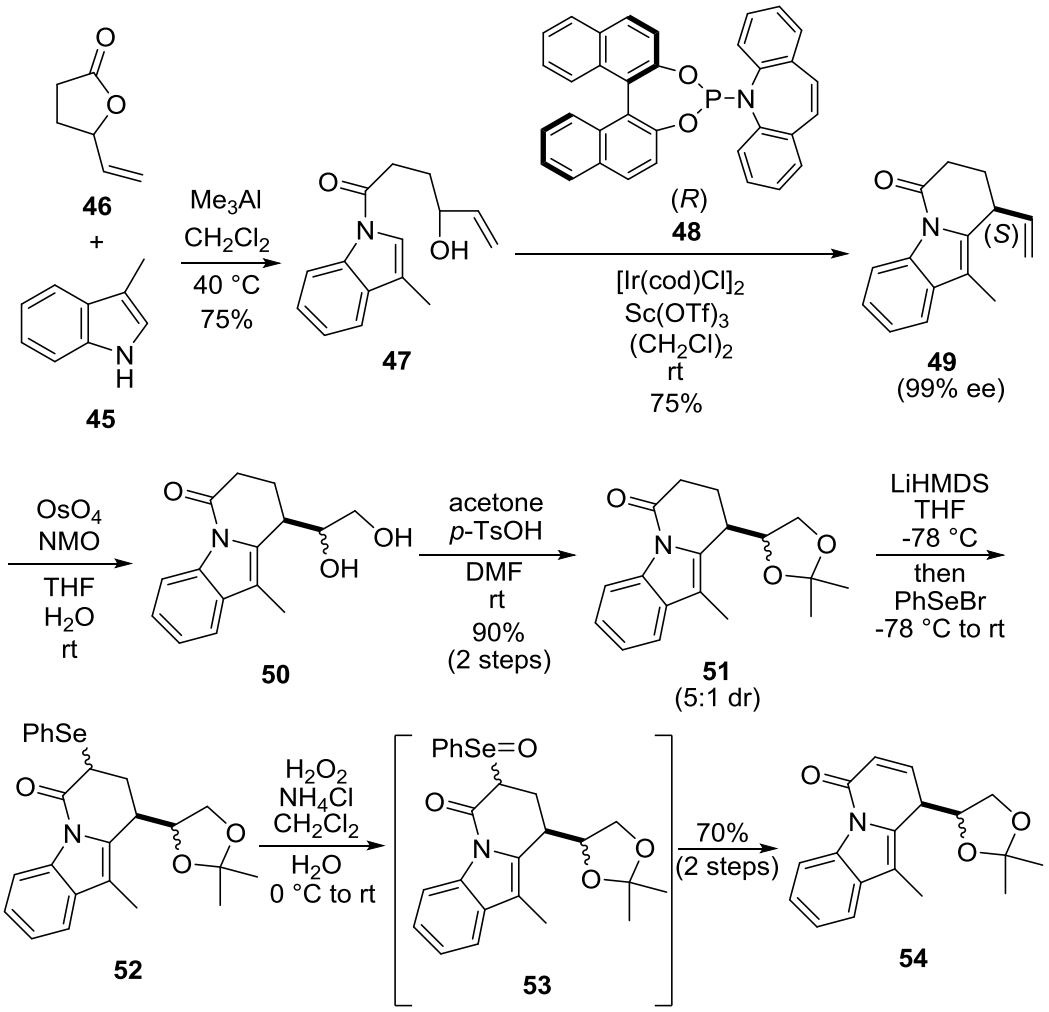
Scheme 9. Completion of the Bihelovic/Ferjancic Total Synthesis of (±)-Alstoscholarisine A (**1**)



1.4.2. Total Synthesis of (−)-Alstoscholarisine A (1) by Yang *et al.*

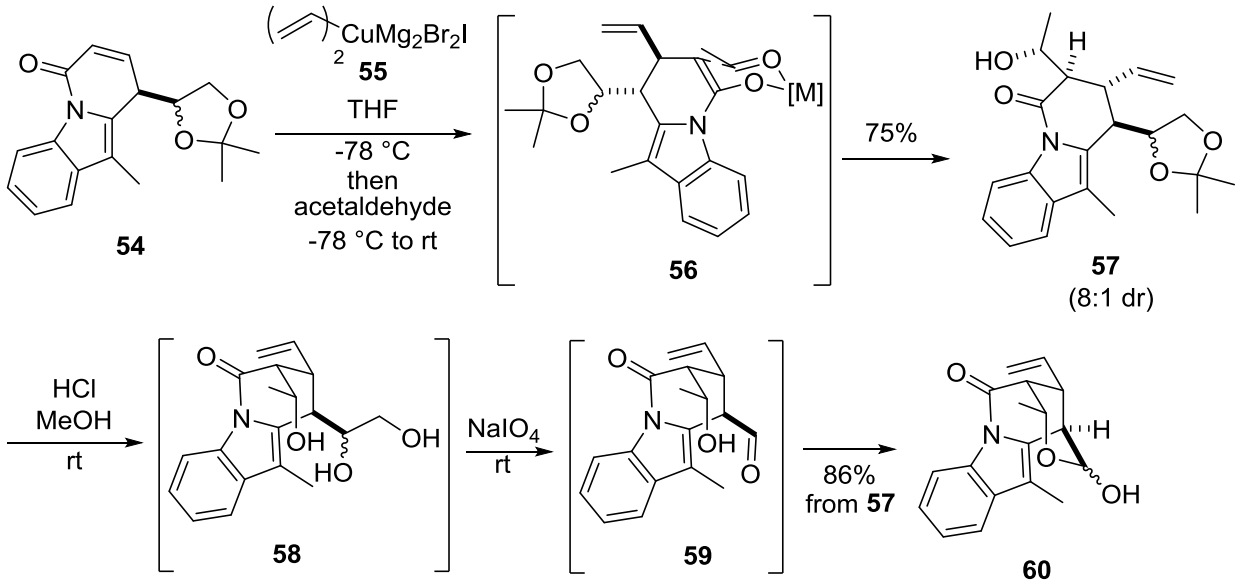
In 2016, Yang and coworkers reported an enantioselective total synthesis of (−)-alstoscholarisine A (**1**) in twelve steps.[16] The synthesis began with an acylation of 3-methylindole (**45**) with vinyl γ-lactone **46** to provide *N*-acyl indole **47** (Scheme 10). This compound underwent a key enantioselective intramolecular Friedel-Crafts alkylation mediated by Carreira's iridium catalyst system using chiral ligand **48** and $Sc(OTf)_3$ to afford tricycle **49** with high enantioselectivity (99% ee) and in good yield.[17] Dihydroxylation of olefin **49** provided diol **50**, which was not isolated but was directly protected as acetonide **51** (5:1 mixture of stereoisomers). The lactam moiety of **51** was deprotonated with lithium hexamethyldisilazide (LiHMDS), and the resulting enolate was trapped with PhSeBr to form selenide **52**. The selenide **52** was then oxidized to the corresponding selenoxide **53**, which underwent elimination to afford α,β-unsaturated lactam **54**.

Scheme 10. Early Stages of the Yang Total Synthesis of (-)-Alstoscholarisine A (**1**)



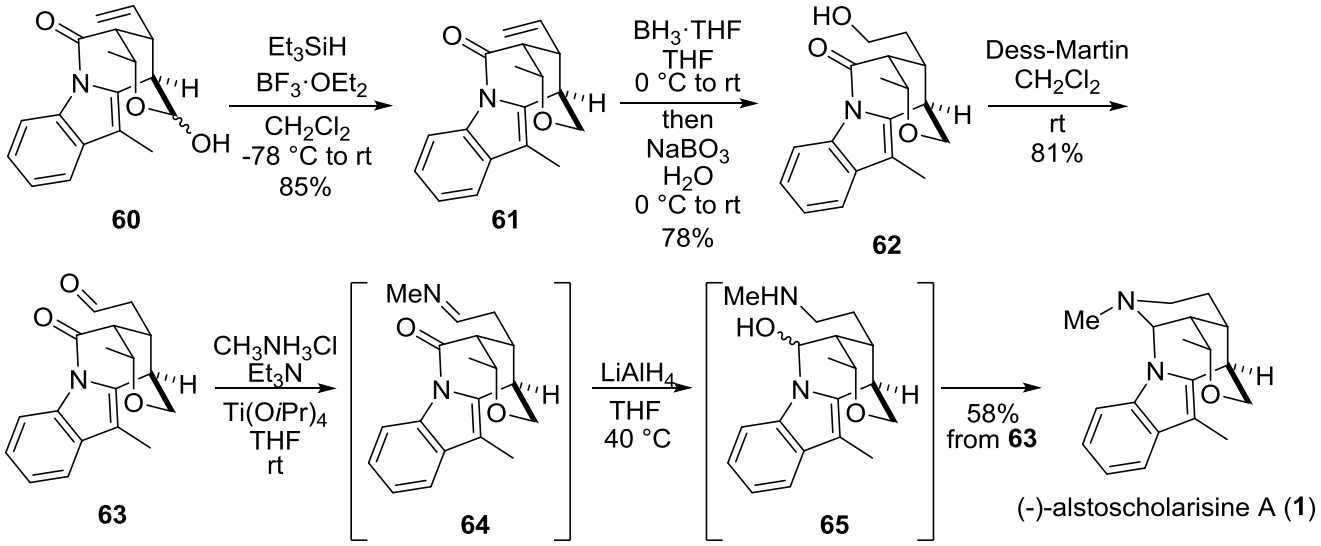
Conjugate addition of vinyl cuprate reagent **55** to α,β-unsaturated lactam **54** from the *re* face, and trapping of the intermediate enolate with acetaldehyde provided alcohol **57** with good (8:1) diastereoselectivity (Scheme 11). The diastereoselectivity of this aldol addition in in line with a Zimmerman-Traxler chair-like transition state **56**, which predicts *anti*-adduct **57** being the major diastereomer.[18] Ketal deprotection with methanolic HCl then resulted in triol **58**. Oxidative cleavage of this intermediate with $NaIO_4$ formed aldehyde **59**, which underwent spontaneous cyclization to lactol **60**.

Scheme 11. Construction of the Tetrahydropyran E Ring of (-)-Alstoscholarisine A (**1**)



Lactol **60** was then reduced to tetrahydropyran **61** with $Et_3SiH/BF_3{\bullet}Et_2O$ (Scheme 12). Hydroboration/oxidation of terminal olefin **61** provided alcohol **62**, which was oxidized with Dess-Martin periodinane to produce aldehyde **63**. The synthesis was completed by condensation of aldehyde **63** with methylamine to form intermediate imine **64**, followed by reduction of both the imine and indole lactam moieties with $LiAlH_4$ to provide hemiaminal **65**, which cyclized directly to form (−)-alstoscholarisine A (**1**).

Scheme 12. Completion of the Total Synthesis of (-)-Alstoscholarisine A (**1**)

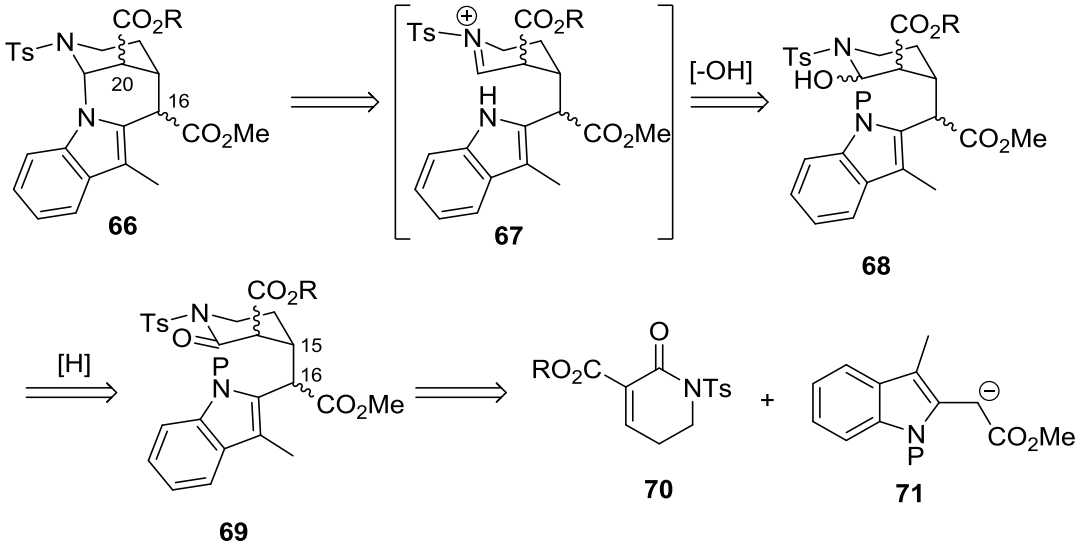


Chapter 2. Results and Discussion

2.1. First-Generation Retrosynthetic Analysis for Alstoscholarisines A-E

Since the only synthetic work that had appeared prior to our undertaking was directed at alstoscholarisine A (**1**), we sought to develop a divergent general strategy[19] that would allow for the total synthesis of alstoscholarisines A-E (**1**-**5**). Thus, it was initially planned to construct the skeleton of the five alkaloids from a bridged aminal intermediate like **66**, possessing functional handles at C16 and C20 that would allow for formation of the tetrahydropyran moiety (E ring) of the alkaloids (Scheme 13). We believed that this system could be constructed from the corresponding lactam **69** via a sequence including partial reduction to *N*,*O*-hemiaminal **68**, and subsequent dehydration to generate the corresponding iminium ion **67**, followed by ring closure onto the indole nitrogen to form the bridged aminal. Tricycle **69** would in turn be prepared by connecting α,β-unsaturated lactam **70** and indole acetic ester enolate **71** via a Michael addition to form the C15, C16 bond of the alkaloids. We chose to utilize an *N*-sulfonyllactam in this approach due to the existence of good methods for the chemoselective partial reduction of such species (i.e. **69** to **68**), as well as the high electrophilicity of the derived *N*-sulfonyliminium ion **67**, which was deemed a promising intermediate for the desired ring closure to form the bridged aminal (*vide infra*).

Scheme 13. First-Generation Retrosynthetic Analysis for (±)-Alstoscholarisines A-E (**1-5**)

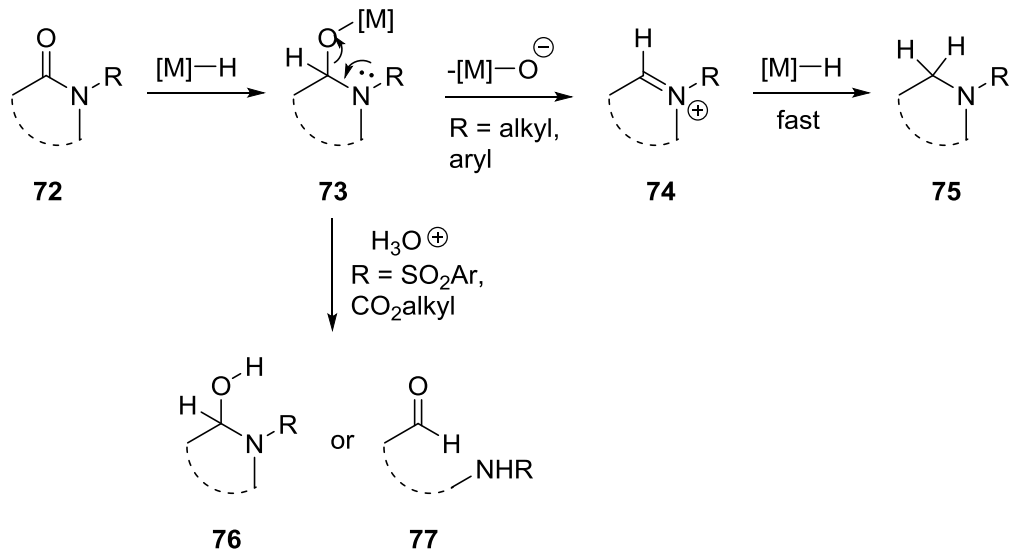


2.2. Background on Key Strategic Steps

2.2.1. Chemoselective Partial Reduction of Lactams to the Aldehyde Oxidation State

In general, the reduction of an *N*-alkyl or *N*-aryl amide/lactam **72** with a metal-hydride reagent ([M]-H) produces the four-electron reduction product, amine **75** (Scheme 14). In this process, the amide/lactam **72** is first reduced to the corresponding metal-bound hemiaminal derivative **73**, which undergoes *in situ* elimination to produce iminium ion **74**. This iminium ion **74** is generally more electrophilic than the starting amide/lactam **72**, and is thus rapidly reduced by the metal-hydride to produce amine **75**. However, if the R group on **72** is an electron-withdrawing group such as a sulfonyl or acyl moiety, the elimination of metal-bound hemiaminal derivitive **73** to iminium ion **74** is relatively slow. Therefore, if this intermediate **73** is quenched with mild aqueous acid at low temperatures, *N*,*O*-hemiaminal **76** can be formed (or the aldehyde and amine derivative **77** in the case of amides).

Scheme 14. General Mechanism for Amide/Lactam Reduction with a Metal-Hydride Reagent



Since the proposed synthesis involves a key chemoselective partial reduction of a lactam in the presence of ester moieties (cf. Scheme 13, **69** to **68**), some discussion of methods for accomplishing this transformation is warranted.[20] Thus, a summary of the known methods is briefly discussed here along with an analysis of the relative rates of amide/lactam/ester reactivity observed in these reactions.

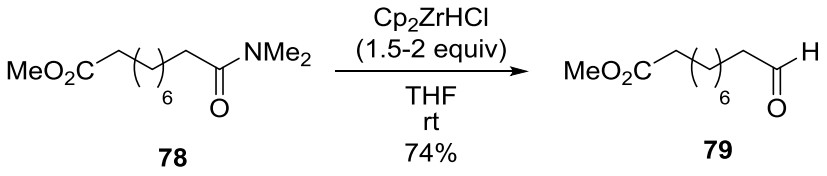
2.2.1.1 Chemoselective Partial Reduction of *N*-Alkyllactams

2.2.1.1.1. Reductions Using Schwartz's Reagent

An effective method for the partial reduction of simple primary, secondary, and tertiary amides to form aldehydes uses Schwartz's reagent (Cp_2ZrHCl) under mild conditions with high selectivity for amide reduction over other functional groups such as esters, nitro groups, and

nitriles.[21] For example, amido ester **78** was reduced to aldehyde **79** in good yield with the ester moiety being unaffected in the reaction (Scheme 15).

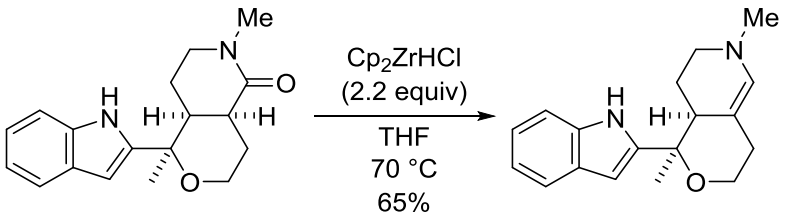
Scheme 15. Schwartz's Reagent for Reduction of Amides to Aldehydes



78 **79**

This method was reported to be ineffective with lactams at room temperature by Georg *et al.*[21a] However, Feldman and Folda reported that *N*-methyl-δ-lactam **80** could be reduced with Schwartz's reagent at elevated temperature to produce enamine **81** in moderate yield (Scheme 16).[22] Due to the high temperature required to complete this transformation and the known ability of Schwartz's reagent to reduce esters and lactones at elevated temperatures,[21b,c] the chemoselectivity between tertiary lactams and esters under these conditions is not known.

Scheme 16. Reduction of an *N*-Methyllactam with Schwartz's Reagent

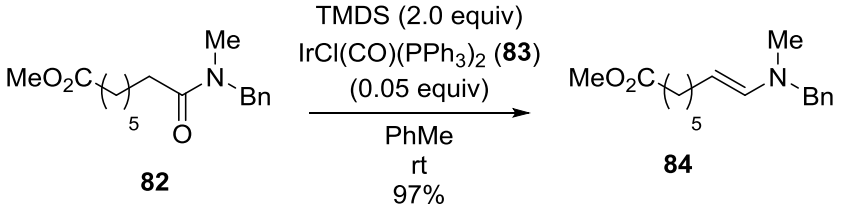


80 **81**

2.2.1.1.2. Reductions Catalyzed by Iridium Complexes

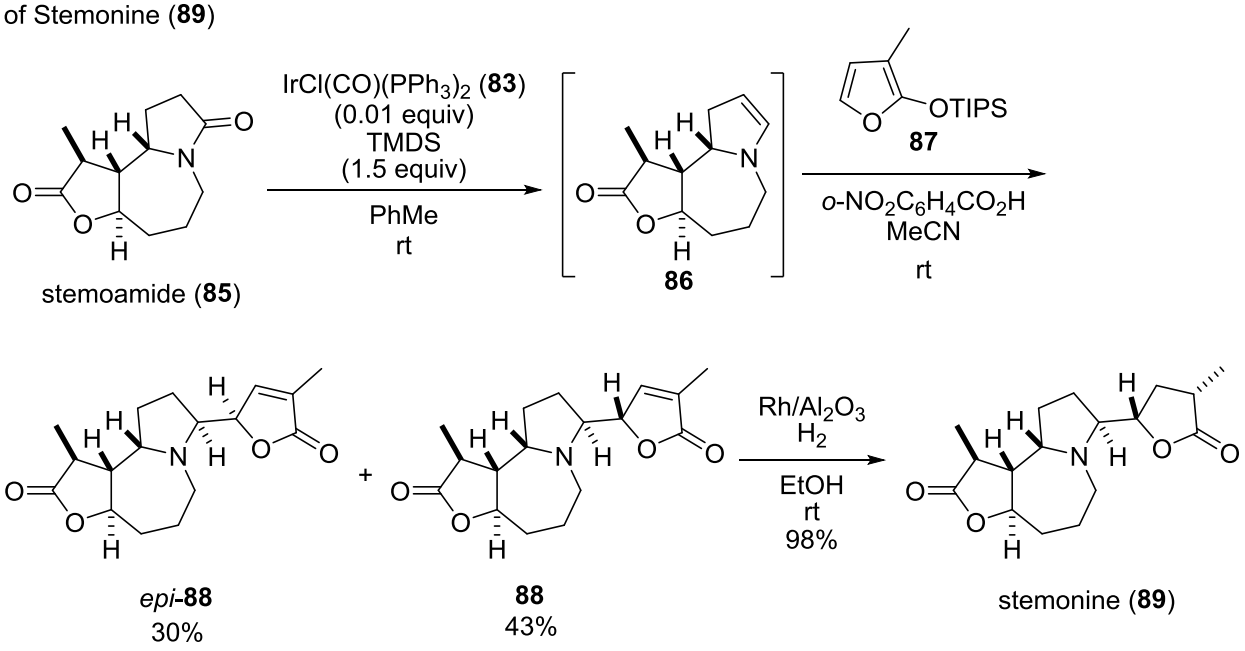
In 2009, Nagashima *et al.* showed that iridium catalysts, along with stoichiometric amounts of silanes, can reduce tertiary amides to enamines with very high chemoselectivity, as esters, ketones, and alkyl bromides are tolerated under the conditions.[23] For instance, amido ester **82** can be reduced to enamine **84** using 1,1,3,3-tetramethyldisiloxane (TMDS) and a catalytic amount of Vaska's complex (**83**) at room temperature without affecting the ester group (Scheme 17).

Scheme 17. Chemoselective Reduction of Tertiary Amide **82** with Vaska's Complex (**83**)



This methodology can effectively reduce lactams to the corresponding cyclic enamines in the presence of other reducible functionalities.[24] For instance, Chida *et al.* showed that the γ-lactam moiety of stemoamide (**85**) can be selectively reduced to enamine **86** under the conditions described above (Scheme 18).[24d] It should be noted that all other reductants examined to effect this transformation (e.g. DIBALH, $Ti(O^iPr)_4/SiH_2Ph_2$,[25] $Mo(CO)_6$/TMDS,[26] Cp_2ZrHCl[21]) were either selective for reduction of the γ-lactone moiety or were nonselective. Without isolation, enamine **86** was treated with siloxyfuran **87** under acidic conditions to provide vinylogous Mannich products **88** and *epi*-**88** in a ratio of 1.2:1. The major product **88** was then converted to stemonine (**89**) by stereoselective hydrogenation of the α,β-unsaturated lactone moiety catalyzed by Rh/Al_2O_3.

Scheme 18. Chemoselctive Reduction of Lactam **85** with Vaska's Complex in a Total Synthesis of Stemonine (**89**)



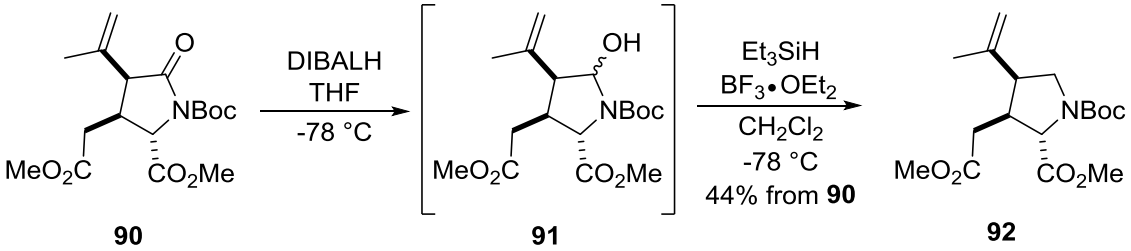
2.2.1.2. Chemoselective Partial Reductions of *N*-Activated Lactams

In light of the difficulties and lack of generality associated with the chemoselective reduction of tertiary lactams to the corresponding hemiaminal or enamine, a common strategy for effecting this transformation involves activation of the lactam as the corresponding *N*-acyllactam or *N*-sulfonyllactam. This manipulation both increases the electrophilicity of the lactam carbonyl group to facilitate the first reduction, and slows the formation of iminium ion **74** by making metal-bound hemiaminal **73** less prone to elimination (cf. Scheme 14).

2.2.1.2.1. Chemoselective Partial Reduction of *N*-Acyllactams in the Presence of Esters

Many examples of chemoselective partial reductions of *N*-acyllactams to *N*,*O*-hemiaminals in the presence of esters can be found in the literature.[27] For example, Clayden *et al.* showed that *N*-Boc-γ-lactam **90** can be chemoselectively reduced with DIBALH at low temperature to the corresponding hemiaminal **91**, which was not isolated (Scheme 19).[27c] The hemiaminal **91** was then further reduced to the corresponding carbamate **92** with $Et_3SiH/BF_3•Et_2O$ in moderate overall yield.

Scheme 19. Chemoselective Reduction of an *N*-Acyllactam

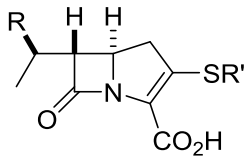


90 **91** **92**

2.2.1.2.2. Chemoselective Partial Reduction of *N*-Sulfonyllactams

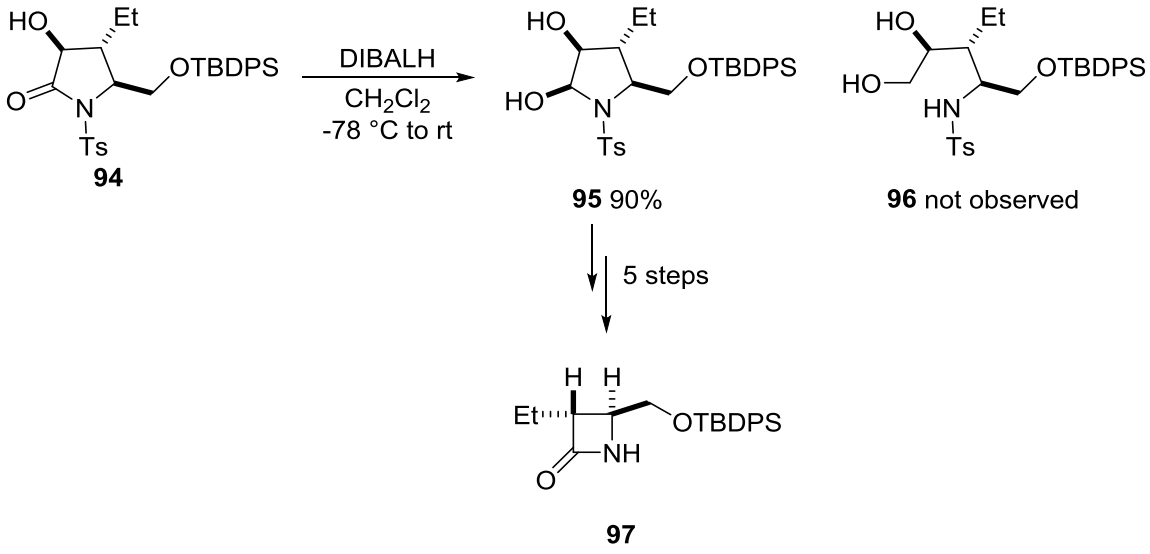
As discussed above, *N*-sulfonyllactams are useful substrates for the preparation of *N*,*O*-hemiaminals due to the electron-withdrawing properties of the sulfonyl group. The first example of a chemoselective partial reduction of an *N*-sulfonyllactam was reported by Somfai, He, and Tanner in 1991.[28] In pursuit of the core of the carbapenem β-lactam antibiotics (e.g. **93**), α-hydroxy-*N*-tosyllactam **94** was partially reduced to the corresponding *N*,*O*-hemiaminal **95** in good yield and as a single stereoisomer (Scheme 20). None of the over-reduced ring-opened diol **96** was observed. This intermediate **95** was then converted to β-lactam **97** in several steps, which contains the core of the carbapenem antibiotics.

Scheme 20. Chemoselective PartialReduction of an *N*-Sulfonyllactam in Preparation of the Carbapenem Core



93 R = OH, H

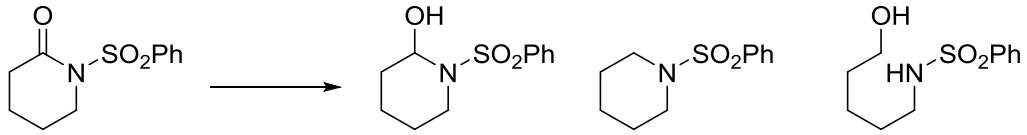
General Structure of the Carbapenems



Nakagawa *et al*. have reported the reactions of a simple *N*-sulfonyllactam **98** with a variety of reducing agents (Table 1).[29] $LiAlH_4$ resulted in a mixture of *N,O*-hemiaminal **99** and ring-opened alcohol **101**, while DIBALH at low temperature provided exclusively hemiaminal **99** in excellent yield. Reduction of **98** with $Zn(BH_4)_2$ resulted in a mixture of hemiaminal **99** (14%) and ring-opened alcohol **101** (49%), as well as over reduction product *N*-benzenesulfonylpiperidine (**100**) (25%). Performing the reduction with *n*-Bu_4NBH_4 provided a mixture of piperidine **100** (62%) and alcohol **101** (34%). $NaBH_4$ reduction of **98** in MeOH resulted exclusively in formation

of the ring-opened alcohol **101** in high yield. These results further cemented DIBALH as the reagent of choice for partial reduction of *N*-sulfonyllactams to *N*,*O*-hemiaminals.

Table 1. Reaction of *N*-Sulfonyllactam **98** with Various Reducing Agents

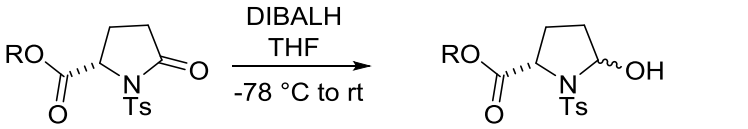


98 **99** **100** **101**

Entry	Reducing Agent (equiv)	Solvent	Temp.	Time	**99**	**100**	**101**
1	$LiAlH_4$ (0.5)	Et_2O	rt	20 min	52%	0%	37%
2	DIBALH (3.0)	PhMe	-78 °C	30 min	97%	0%	0%
3	$Zn(BH_4)_2$ (3.0)	Et_2O	rt	12 h	14%	25%	49%
4	$n Bu_4NBH_4$ (3.0)	$(CH_2Cl)_2$	reflux	30 min	0%	62%	34%
5	$NaBH_4$ (2.0)	MeOH	rt	2 h	0%	0%	96%

Reduction of *N*-sulfonyllactams with DIBALH was also shown to be highly chemoselective, with esters being unaffected in the reaction (Scheme 21). For example, Aggarwal *et al.* found that lactam **102a** could be reduced to the corresponding hemiaminal **103a** in moderate yield without affecting the methyl ester moiety.[30] Although the yield here is only moderate, the authors did not report any other products that were formed in this reaction. Later, Herrera *et al.* showed that the analogous lactam **102b**, which contains a *tert*-butyl ester could be selectively reduced to hemiaminal **103b** in good yield.[31]

Scheme 21. Chemoselective Partial Reductions of *N*-Ts Lactams in the Presence of Esters



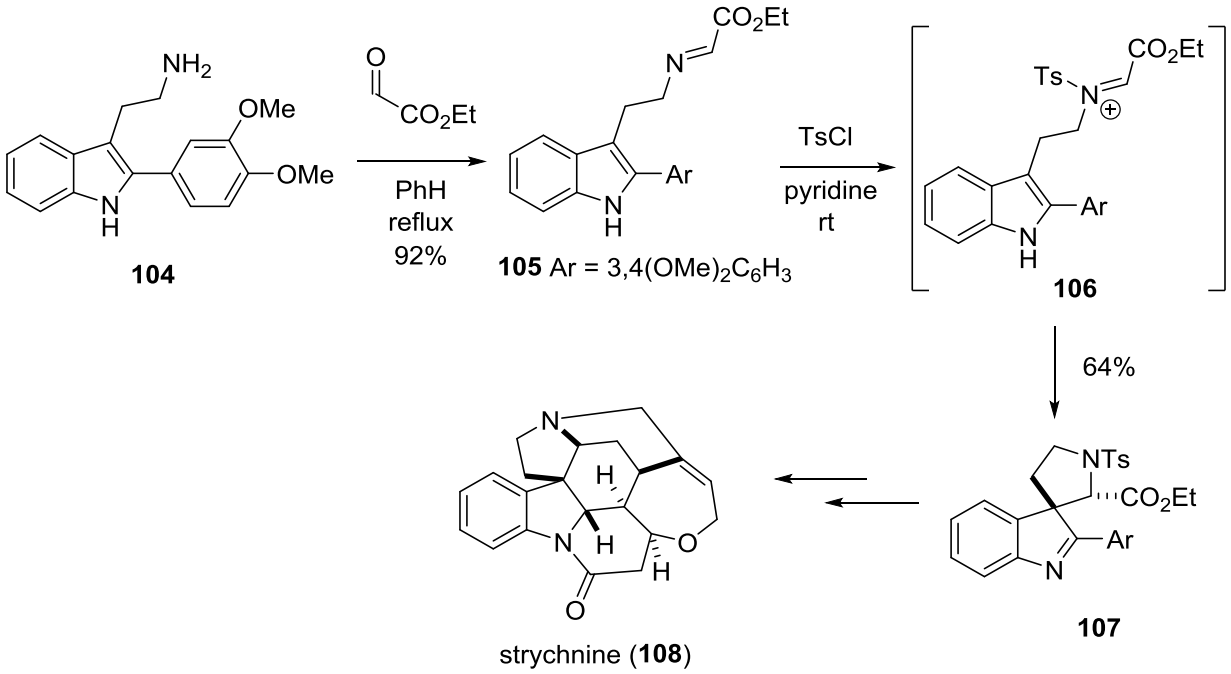
102a R = Me
102b R = ^{t}Bu

103a 48% dr = 8:1 R = Me
103b 74% dr = 1.7:1 R = ^{t}Bu

2.2.2. *N*-Sulfonyliminium Ions as Electrophiles

N-Sulfonyliminium ions are easily prepared and allow otherwise challenging cyclizations to occur due to their high electrophilicity. Such iminium ions have therefore become a useful set of electrophiles for the synthesis of complex molecules. For example, Woodward utilized an *N*-tosyliminium ion **106** as a key intermediate in a landmark total synthesis of strychnine (**108**) (Scheme 22).[32] Thus, condensation of tryptamine derivative **104** with ethyl glyoxalate produced imine **105**, which was N-sulfonylated with TsCl to form *N*-tosyliminium ion **106**. This intermediate then cyclized at C3 of the attendant indole to produce spirocycle **107** as a single stereoisomer. It should be noted that attempts to cyclize imine **105** under Bronsted-acidic conditions did not provide any of the desired spirocycle.

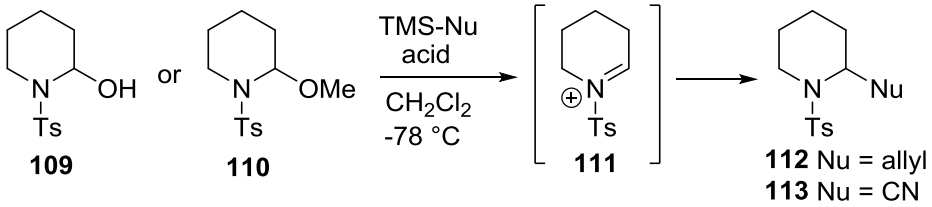
Scheme 22. Cyclization of an *N*-Tosyliminium Ion in Woodward's Total Synthesis of Strychnine



A more common method for the formation of *N*-sulfonyliminium ions involves acid-mediated ionization of *N*,*O*-hemiaminals, hemiaminal ethers, or hemiaminal esters.[33] For example, Ahman and Sonfai showed that *N*,*O*-hemiaminal **109** could be allylated with allyltrimethylsilane under Lewis-acidic (entries 1-2) or Bronsted-acidic (entry 3) conditions at low temperature to provide *N*-tosyl-2-allylpiperidine (**112**) in good yields, via *N*-sulfonyliminium ion **111** (Table 2).[34] Alternatively, using trimethylsilyl cyanide as the nucleophile provided nitrile **113** in good yield using $SnCl_4$ catalysis (entry 4) or in moderate yield using $TiCl_4$ (entry 5).

These reactions also proceeded starting with *N*,*O*-hemiaminal ether **110** using allyltrimethylsilane under Lewis-acidic (entries 6-7) or Bronsted-acidic (entry 8) conditions to provide 2-allylpiperidine **112** in good yields. The reactions also were successful with TMSCN as the nucleophile to give 2-cyanopiperidine **113** in good yield (entries 9-10).

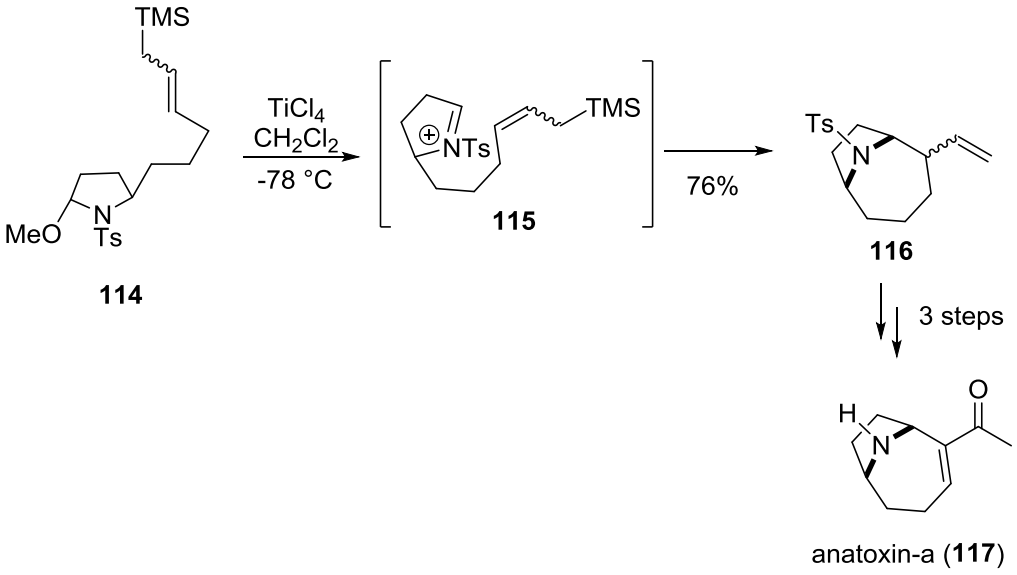
Table 2. Acid-Mediated Addition of Nucleophiles to *N*-Tosyliminium Ion **111** Derived from *N*,*O*-Hemiaminal **109** and *N*,*O*-Hemiaminal Ether **110**



Entry	SM	Nucleophile	Acid (equiv)	Yield (**112**/**113**)
1	**109**	TMS-allyl	$SnCl_4$ (1.0)	100% (**112**)
2	**109**	TMS-allyl	$FeCl_3$ (1.0)	73% (**112**)
3	**109**	TMS-allyl	TFA (4.0)	94% (**112**)
4	**109**	TMSCN	$SnCl_4$ (1.0)	87% (**113**)
5	**109**	TMSCN	$TiCl_4$ (1.0)	61% (**113**)
6	**110**	TMS-allyl	$SnCl_4$ (1.0)	86% (**112**)
7	**110**	TMS-allyl	$FeCl_3$ (1.0)	78% (**112**)
8	**110**	TMS-allyl	TFA (4.0)	100% (**112**)
9	**110**	TMSCN	$SnCl_4$ (1.0)	88% (**113**)
10	**110**	TMSCN	$TiCl_4$ (1.0)	60% (**113**)

The Somfai group has utilized an intramolecular variant of this reaction in a synthesis of (+)-anatoxin-a (**117**) (Scheme 23).[35] Thus, *N*,*O*-hemiaminal ether **114** was treated with $TiCl_4$ at low temperature to induce ionization to *N*-tosyliminium ion **115**, which underwent cyclization with the attendant allylsilane moiety to provide [4.2.1]-bicycle **116** in good yield and as a single stereoisomer (configuration not determined). This intermediate was then transformed into anatoxin-a (**117**) in three steps.

Scheme 23. Total Synthesis of Anatoxin-a (**117**) by Somfai and Ahman

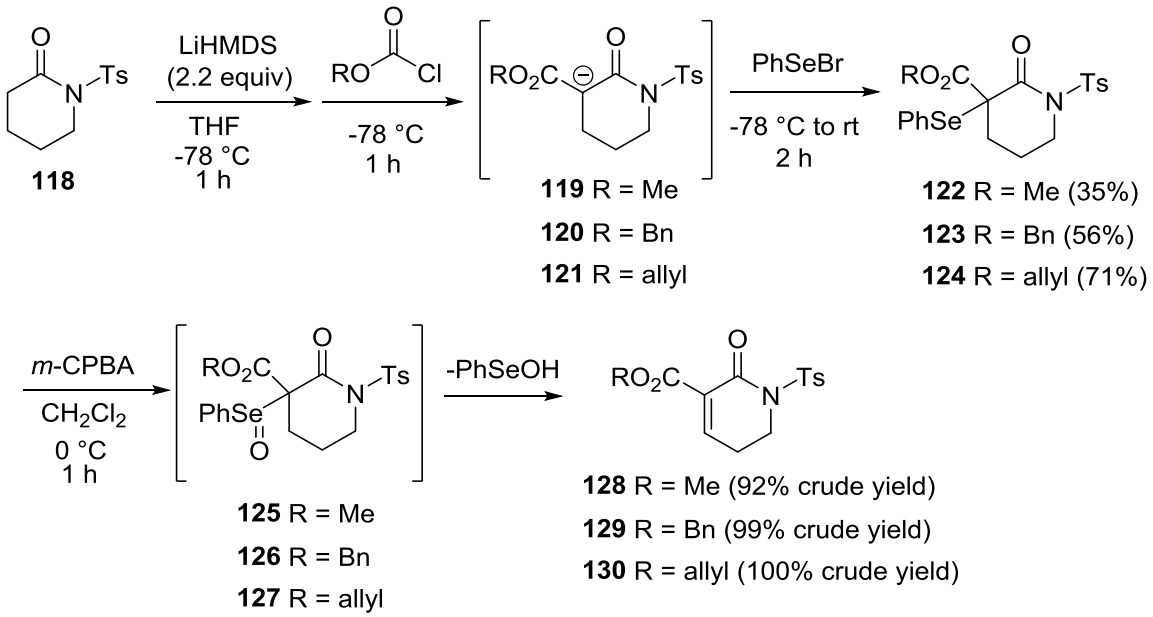


2.3. Exploration of Michael Reactions

Our initial experiments examined the proposed Michael reaction (cf. Scheme 13), and therefore α,β-unsaturated lactam substrates **128**/**129**/**130** were first prepared by a slight modification (*vide infra*) of the known method for the synthesis of benzyl ester **129** (Scheme 24).[36] Thus, known *N*-tosylvalerolactam (**118**)[37] was treated with 2.2 equivalents of lithium hexamethyldisilazide (LiHMDS) and the appropriate chloroformate was added to form intermediate enolates **119**/**120**/**121** *in situ*. After addition of PhSeBr, acylated selenides **122**/**123**/**124** were produced. It was found that the yield of selenides **122**/**123**/**124** could be greatly improved by simply stirring the mixture of the enolate of lactam **118** and the alkyl chloroformate for a longer period of time (1 h) than previously reported in the literature (20 min) prior to the addition of PhSeBr. The isolated selenides **122**/**123**/**124** were treated with *m*-CPBA to form the corresponding selenoxides **125**/**126**/**127**, which underwent spontaneous *in situ* elimination to form

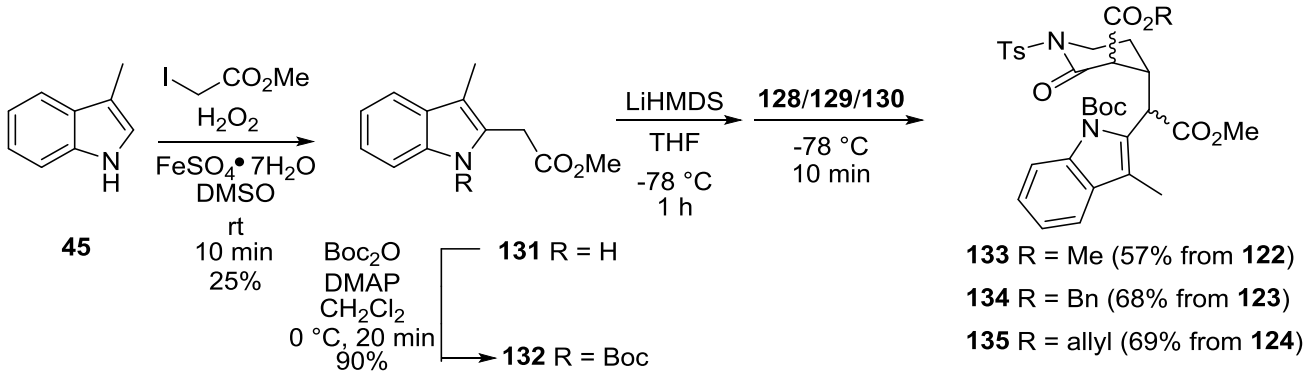
the crude α,β-unsaturated lactams **128**/**129**/**130** in good yields. Since chromatographic purification of these compounds on silica gel resulted in significant decomposition, the unsaturated lactams were used without purification in the ensuing Michael reactions.

Scheme 24. Preparation of Michael Acceptors



Indole ester **131**[38] was prepared by the known radical-mediated addition of methyl iodoacetate to 3-methylindole (**45**) promoted by $H_2O_2/FeSO_4 \cdot 7H_2O$ in DMSO in moderate yield (Scheme 25).[39] In order to prevent the possibility of an undesired conjugate addition of the indole nitrogen in the planned Michael addition, indole **131** was next protected as the Boc carbamate **132** in excellent yield. It was then found that deprotonation of the indole ester with LiHMDS, followed by addition of the Michael acceptors **128**/**129**/**130**, gave the desired Michael adducts **133**/**134**/**135** in acceptable yields as complex mixtures of inseparable diastereomers.

Scheme 25. Michael Reactions

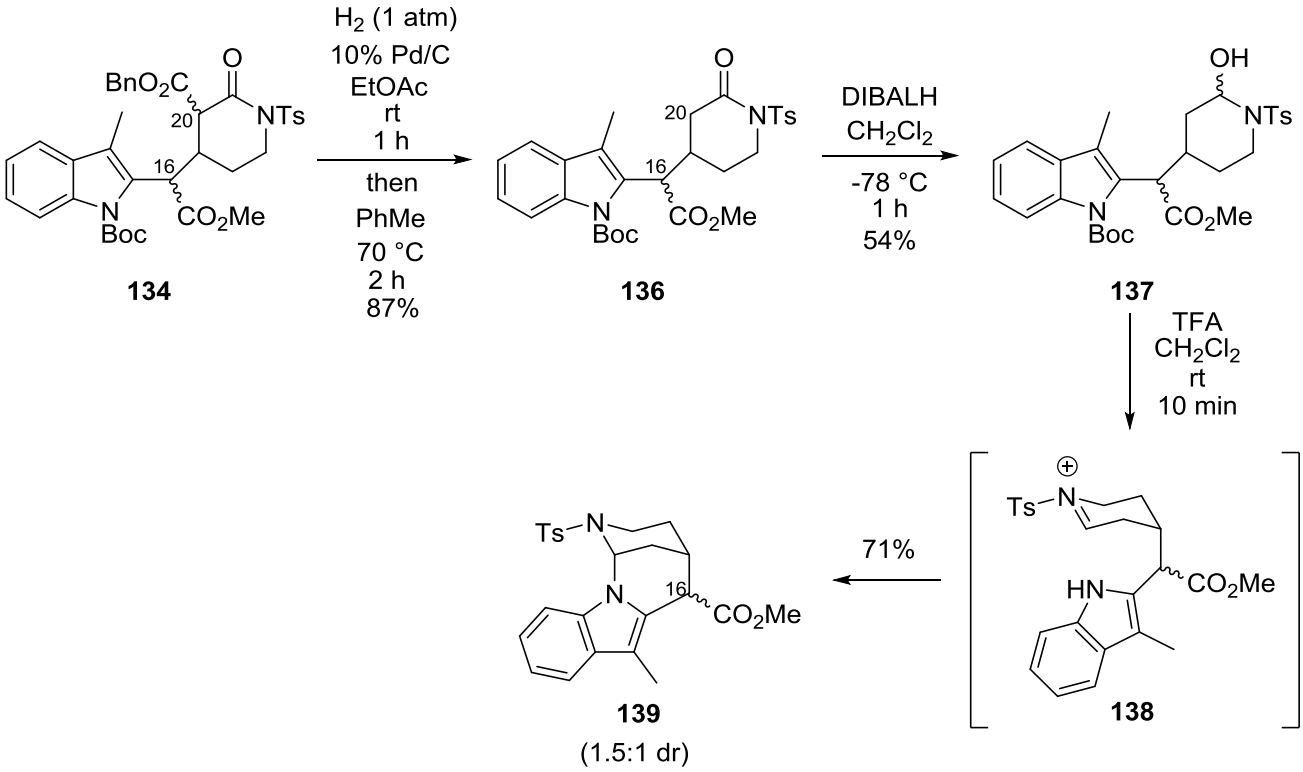


2.4. Construction of a Bridged Aminal C Ring

2.4.1. Model Experiments with a C20-Unsubstituted Lactam

Formation of a bridged aminal like **66** was first explored with a model lactam lacking a substituent at C20. Thus, benzyl ester **134** was hydrogenated and the resulting acid was thermally decarboxylated to produce lactam **136** as a mixture of epimers at C16 (Scheme 26). Selective partial reduction of this lactam with DIBALH at low temperature provided hemiaminal **137** without any observed reduction of the ester group. Treatment of hemiaminal **137** with TFA then induced dehydration of the hemiaminal, as well as removal of the Boc protecting group, providing intermediate *N*-sulfonyliminium ion **138**, which cyclized to form the desired aminal **139** as a 1.5:1 mixture of epimers at C16.

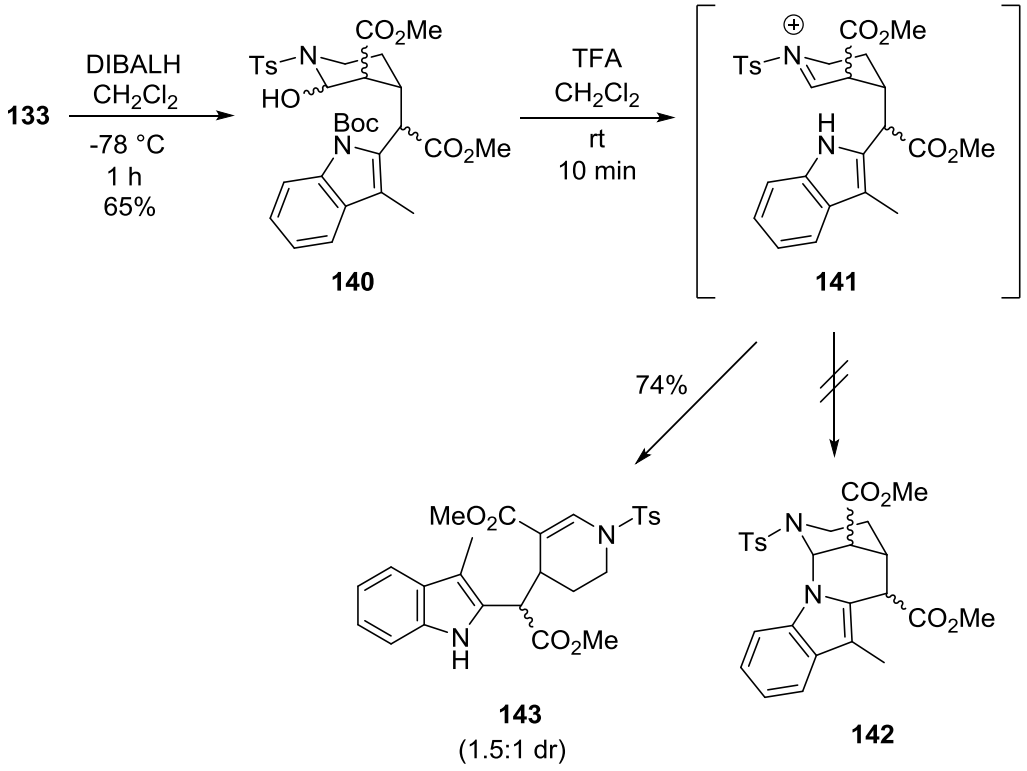
Scheme 26. Model System for Lactam Reduction and Cyclization



2.4.2. Attempted Aminal Formation with a C20-Carbomethoxy-Substituted Lactam

Encouraged by the successful chemoselective reduction and cyclization of C20-unsubstituted lactam **136**, the same partial reduction conditions were then applied to *N*-sulfonyllactam **133**, which contains methyl ester handles at C16 and C20 needed for the synthesis of the alkaloids (Scheme 27). Thus, Michael adduct **133** was successfully reduced selectively with DIBALH to form hemiaminal **140**, which was then treated with TFA to generate *N*-sulfonyliminium ion **141**. However, this intermediate did not cyclize to the desired aminal **142**, but rather vinylogous carbamate **143** was the only product formed (1.5:1 mixture of diastereomers). This compound likely results from tautomerization of α-carbomethoxy-*N*-sulfonyliminium ion **141**.

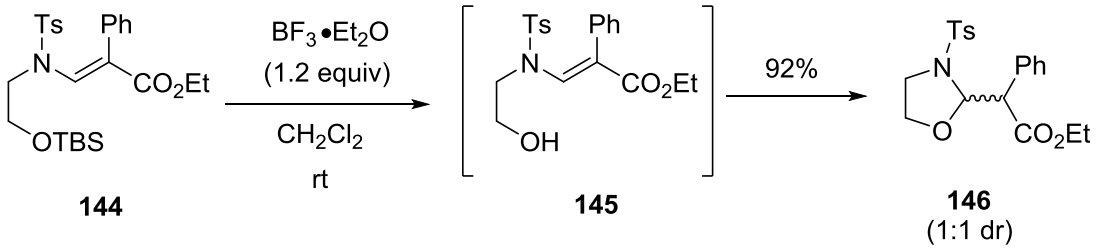
Scheme 27. Attempted Cyclization with Carbomethoxy Lactam **133**



2.4.2.1. Precedent for Lewis Acid-Catalyzed Nucleophilic Conjugate Additions to *N*-Tosyl Vinylogous Carbamates

It has recently been shown that Lewis acids can induce intramolecular conjugate additions of nucleophiles to *N*-tosyl vinylogous carbamates. For example, Khan and Chakraborty showed that oxazolidine **146** can be formed in high yield by treatment of TBS ether **144** with BF_3•Et_2O (Scheme 28).[40] The Lewis acid acts both to deprotect the alcohol and mediate a conjugate addition of the *N*-tosyl vinylogous carbamate **145**.

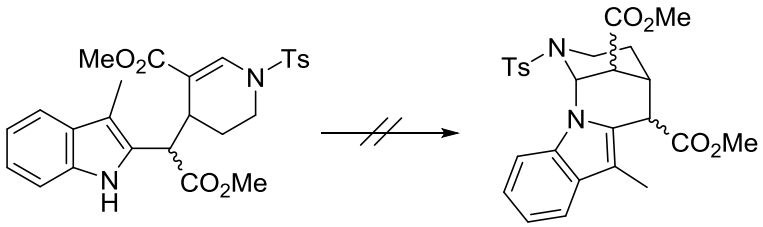
Scheme 28. Lewis Acid-Catalyzed Conjugate Addition to an *N*-Ts Vinylogous Carbamate



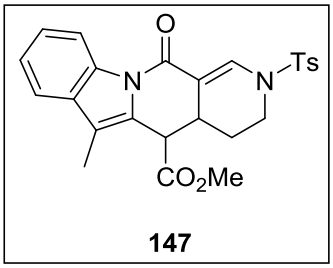
2.4.2.2. Attempts to Cyclize Vinylogous Carbamate 143 to a Bridged Aminal

Based on this precedent, cyclization of vinylogous carbamate **143** to aminal **142** was attempted in the presence of a variety of Lewis and Bronsted acids (Table 3). However in all cases, only unreacted starting material was recovered (entries 1-3) or carboxylic acid by-products were observed (entry 4). Furthermore, attempts to induce a conjugate addition under basic conditions produced only indole lactam **147** (single diastereomer, configuration not determined) (entry 5).

Table 3. Attempted Cyclization of Vinylogous Carbamate **143**



143 **142**



147

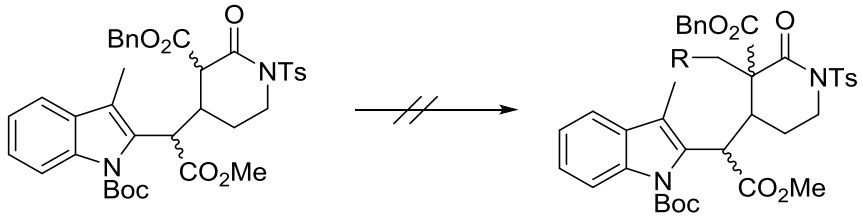
Entry	Conditions	Result
1	TFA, CH_2Cl_2, rt, 2 h	N.R.
2	$MeSO_3H$, PhOMe, rt, 1 h	N.R.
3	$TiCl_4$, CH_2Cl_2, rt, 8 h	N.R.
4	BCl_3, CH_2Cl_2, rt, 2 h	hydrolysis of methyl esters
5	K_2CO_3, MeCN, reflux, 6 h	**147** (68%)

2.4.3. Cyclization of a C20 Alkyl-Substituted Lactam to a Bridged Aminal

2.4.3.1. Attempted Cyclization to a Bridged Aminal Using a C20 Hydroxymethyl Lactam

Since the α-carbomethoxy group at C20 had facilitated tautomerization of the intermediate *N*-sulfonyliminium ion **141** and prevented the desired cyclization to **142** (cf. Scheme 27), an alternative C20 substituent that might allow for aminal cyclization and could later be converted to a carbonyl function was needed to continue the synthesis. However, initial attempts to α-alkylate benzyl ester **134** with functional groups that might serve as a carbonyl equivalent were unsuccessful (Table 4). Retro-Michael reactions (entries 1-3), side products (entry 4), or no reaction (entries 5-6) occurred in these various attempts.

Table 4. Attempted Alkylations of Benzyl Ester **134**

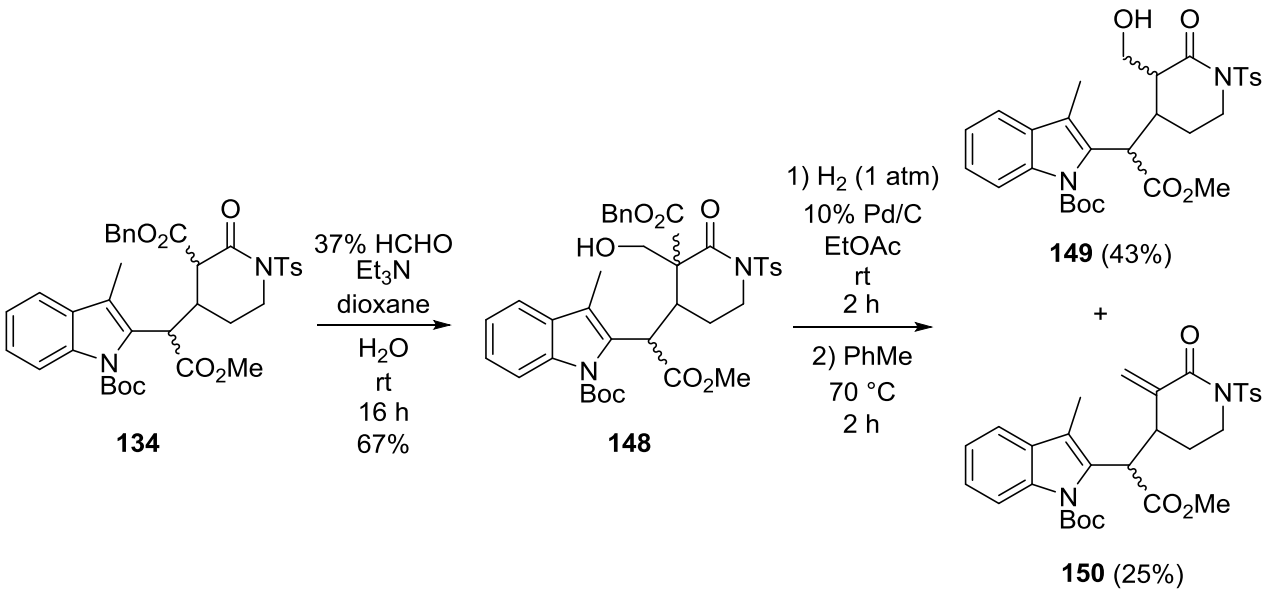


134

Entry	Electrophile	Base	Additive	Conditions	Result
1	PhO_2S I	K_2CO_3	TBAI	MeCN, reflux	Retro-Michael
2	$PhMe_2Si$ I	K_2CO_3	TBAI	MeCN, reflux	Retro-Michael
3	I I	K_2CO_3	AgOTf	MeCN, reflux	Retro-Michael
4	PhSe I	K_2CO_3	TBAI	MeCN, reflux	Addition to indole C3
5	$H_2C{=}NMe_2I$	NaH		THF, rt	N.R.
6	MeO Cl	NaH		THF, rt	N.R.

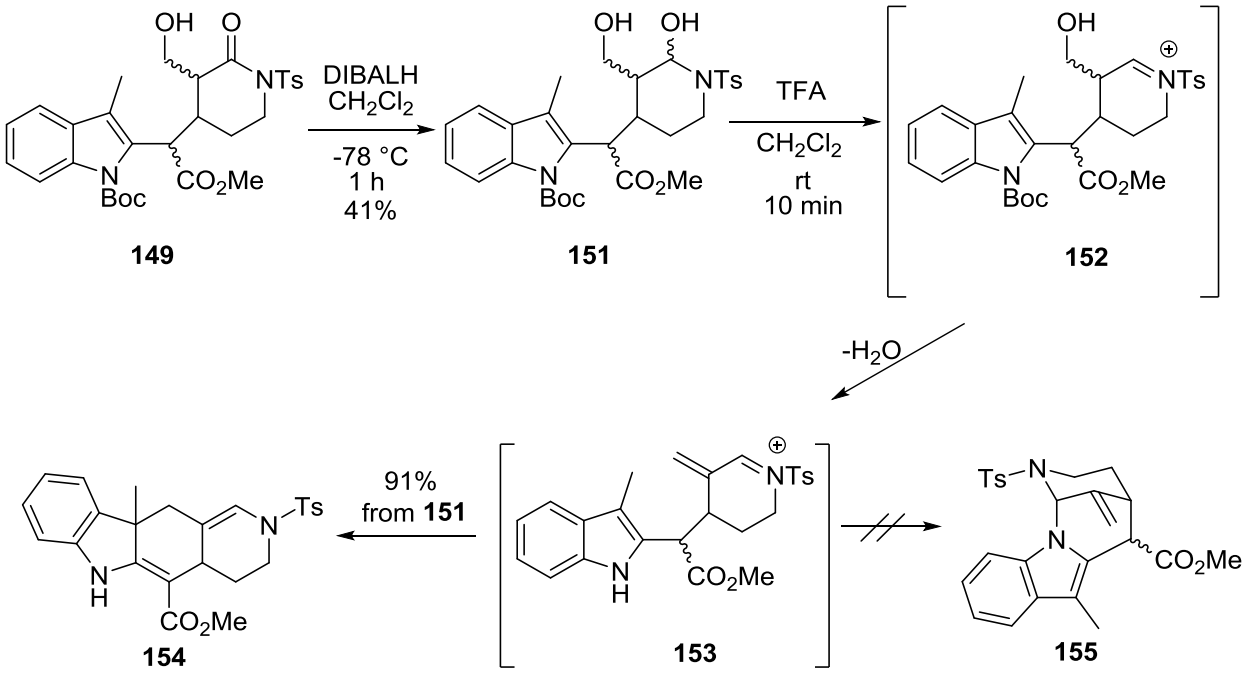
However, it was eventually found that lactam ester **134** could be cleanly alkylated with aqueous formalin to provide aldol adduct **148** (complex mixture of stereoisomers) (Scheme 29). Hydrogenolysis of the benzyl ester and subsequent decarboxylation to the intermediate carboxylic acid provided α-hydroxymethyl lactam **149** (mixture of two stereoisomers) in moderate yield, along with some of the dehydration product **150**.

Scheme 29. Hydroxymethylation and Decarboxylation of Benzyl Ester **134**



α-Hydroxymethyl lactam **149** was then reduced to hemiaminal **151** with DIBALH in moderate yield (41%, unoptimized, Scheme 30). Treatment of intermediate **151** with trifluoroacetic acid induced Boc cleavage and dehydration to the corresponding *N*-sulfonyliminium ion **152**, but further dehydration of the hydroxymethyl group also appears to have occurred under these conditions to provide α,β-unsaturated iminium ion **153**. Unfortunately, this compound cyclized via a conjugate addition at the indole C3 position to provide the undesired fused tetracycle **154** (single stereoisomer, configuration not determined) in excellent yield, rather than form the potentially usable bridged aminal **155**.

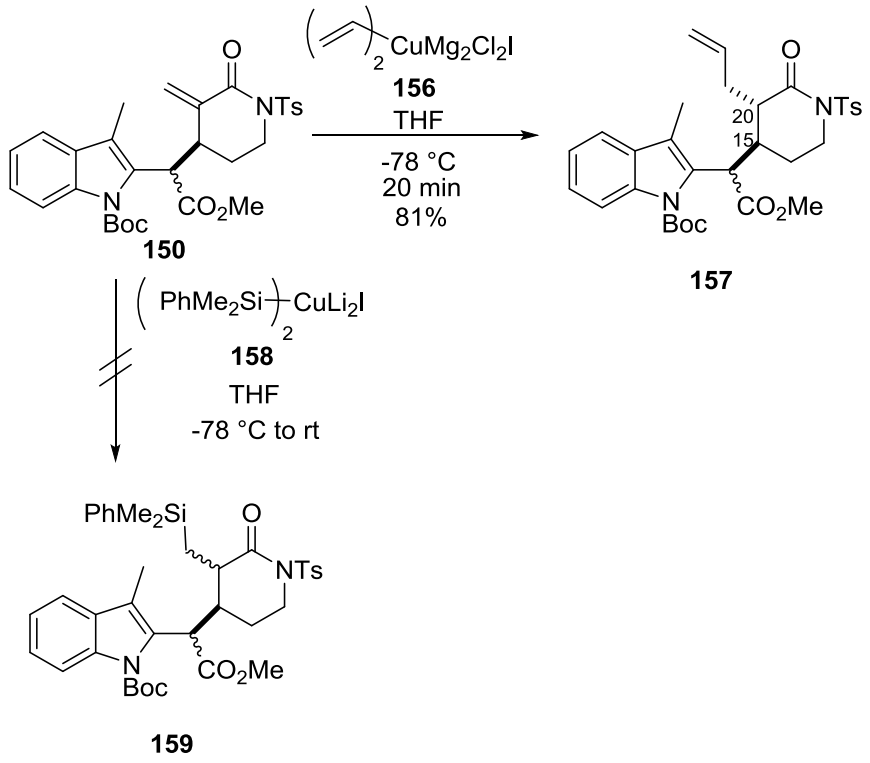
Scheme 30. Reduction and Cyclization of Hydroxymethyl Lactam **149**



2.4.3.2. Formation of a Bridged Aminal Using a C20 Allyl Lactam

Given the problems discussed above, it became clear that we should install a C20 carbonyl equivalent that would not have a propensity to eliminate under acidic conditions. Thus, utilizing α,β-unsaturated lactam **150**, which we had in hand, α-allyl lactam **157** was prepared in good yield by conjugate addition of vinyl cuprate reagent **156** (Scheme 31).[41] This compound proved to have the C20 allyl group *trans* to the indole acetic ester moiety at C15 on the lactam ring (*vide infra*). In addition, all attempts to induce a conjugate addition of silyl cuprate reagent **158** to form **159** under Fleming's conditions were unsuccessful, with only starting material **150** being recovered.[42]

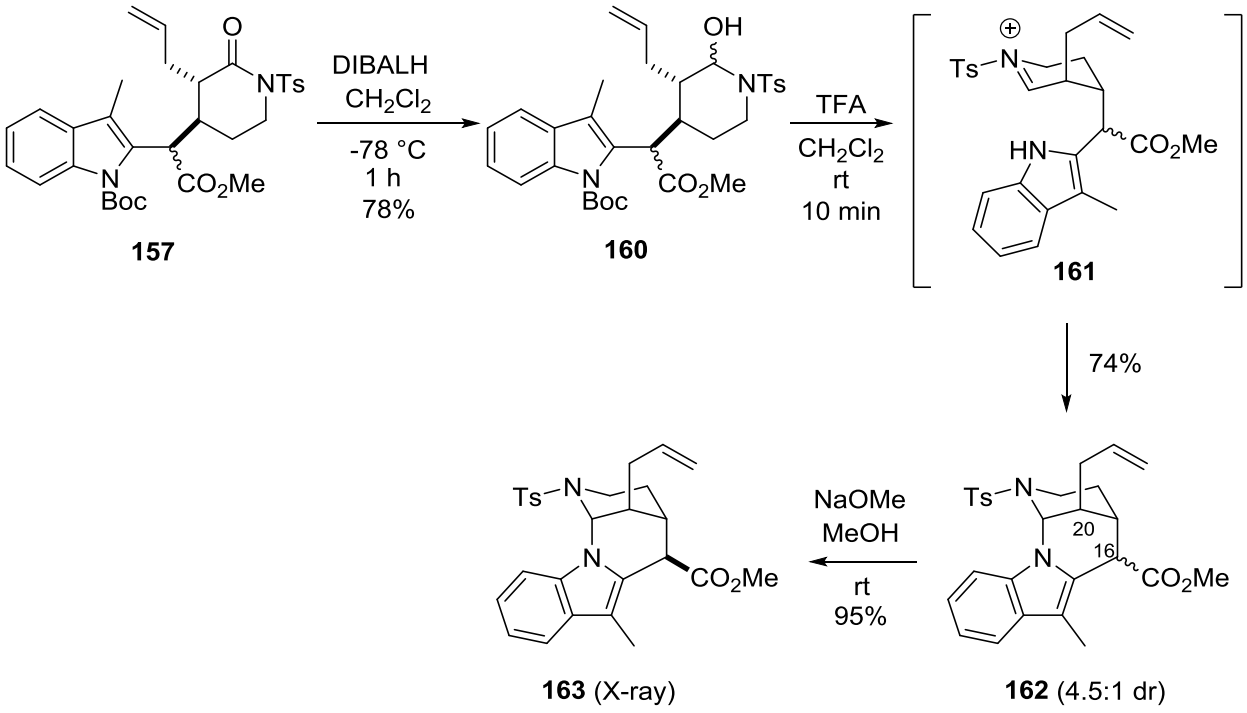
Scheme 31. Conjugate Additions of Cuprates to Methylene Lactam **150**



The α-allyl *N*-sulfonyllactam **157** was then selectively reduced with DIBALH at low temperature to give hemiaminal **160**, which was treated with trifluoroacetic acid to induce Boc cleavage and hemiaminal dehydration to form *N*-sulfonyliminium ion **161** (Scheme 32). This intermediate indeed cyclized to provide the desired bridged aminal **162** as a mixture of C16 ester epimers. It should be noted that the ratio of C16 epimers in the mixture varied a great deal from run to run, probably due to ester epimerization by the TFA and/or during basic aqueous workup. In order to unambiguously assign the stereochemistry of the C20 allyl group, the mixture of epimers was treated with sodium methoxide in methanol at room temperature, which led to complete isomerization to a single diastereomeric ester **163**. Upon recrystallization of this compound from methanol/toluene, clear prisms were obtained which were subjected to X-ray

analysis. The crystal structure showed the presence of an axial allyl group at C20 and that the methyl ester moiety at C16 was on the least congested *exo* face of the bridged bicycle.

Scheme 32. Reduction and Cyclization of Allyl Lactam **157**



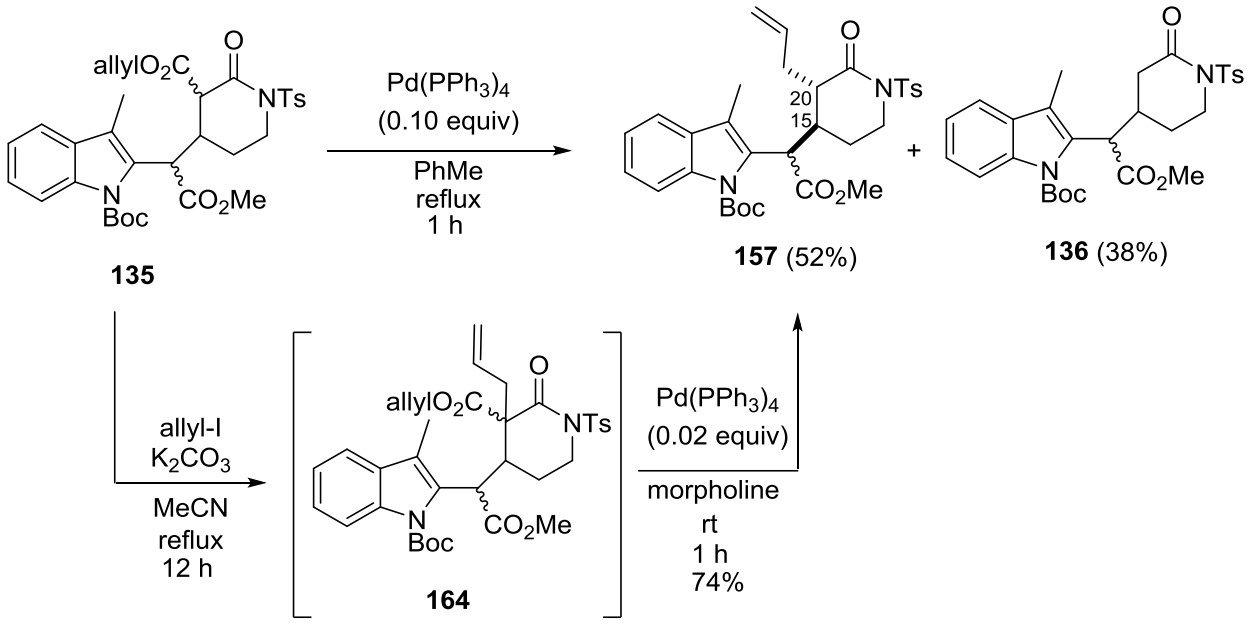
2.4.3.3. Improved Synthesis of Allyl Lactam 157

Since tetracycles **162**/**163** seemed potentially useful for the synthesis of the alstoscholarisines, we decided to explore further transformations of this intermediate. However, it was first necessary to prepare α-allyl lactam **157** in a more efficient manner. A direct decarboxylative allylation[43] of allyl Michael adduct **135** was tried initially, but was only moderately successful (Scheme 33). Thus, treatment of allyl ester **135** with 10 mol% of $Pd(PPh_3)_4$ in refluxing toluene provided the desired α-allyl lactam **157** in moderate (52%) yield, along with

significant amounts of the protodecarboxylation product **136**. Attempts to optimize the allyl transfer by conducting the reaction at lower temperature (60 °C, 45% yield), or utilizing a different catalyst system ($Pd_2(dba)_3$, dppf, 44% yield) were not fruitful.

Alternatively, a higher yield (75% overall) of lactam **157** could be obtained via a two-step, one-pot sequence in which the lactam was first alkylated with allyl iodide at high temperature (82 °C) to form **164**, followed by cooling the reaction mixture to room temperature and adding morpholine and a catalytic amount of $Pd(PPh_3)_4$ to induce decarboxylation.[44] Material prepared by both of these routes had spectra identical to that produced by the previously discussed conjugate addition (cf. Scheme 31), which formed the *trans*-substituted lactam **157**.

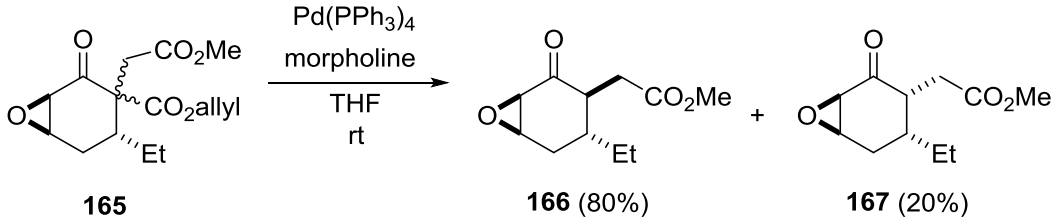
Scheme 33. Preparation of Allyl Lactam **157** from Michael Adduct **135**



The stereochemical outcome of this decarboxylation step has good precedent in the literature. For example, Jorgensen *et al.* showed that allyl β-ketoester **165** underwent

decarboxylation under conditions similar to ours with good diastereoselectivity, favoring the thermodynamically more stable *trans* isomer **166** over the *cis* isomer **167** (Scheme 34).[45]

Scheme 34. Precedent for the Observed Stereoselectivity of Decarboxylation



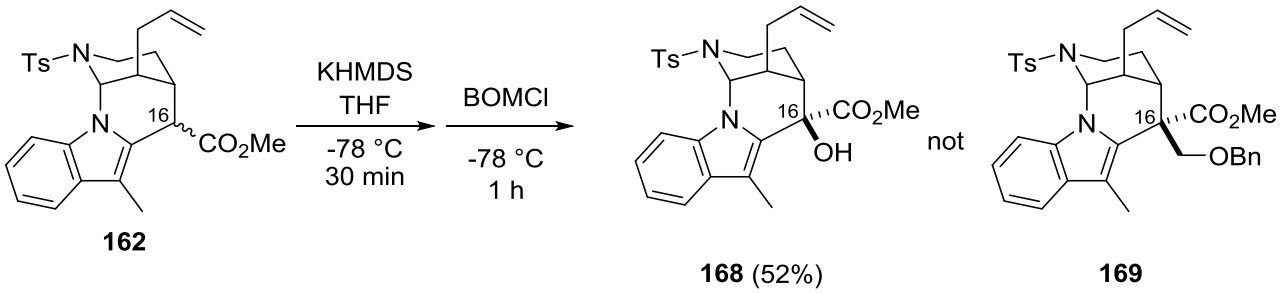
165 **166** (80%) **167** (20%)

2.5. Construction of the Tetrahydropyran E Ring

2.5.1. α-Alkylation of the C16 Ester Moiety

In order to construct the tetrahydropyran ring of alkaloids **2**-**4**, which bear a C16 carboxyl group, the plan was first to alkylate at C16 with either formaldehyde or a formaldehyde equivalent. Thus, ester **162** was treated with potassium hexamethyldisilazide (KHMDS) at low temperature, followed by addition of benzyloxymethyl chloride (BOMCl) (Scheme 35). However, instead of producing the desired benzyl ether **169**, α-hydroxyester **168** was isolated in moderate yield. This product presumably results from oxidation of the enolate of ester **162** by adventitious O_2.

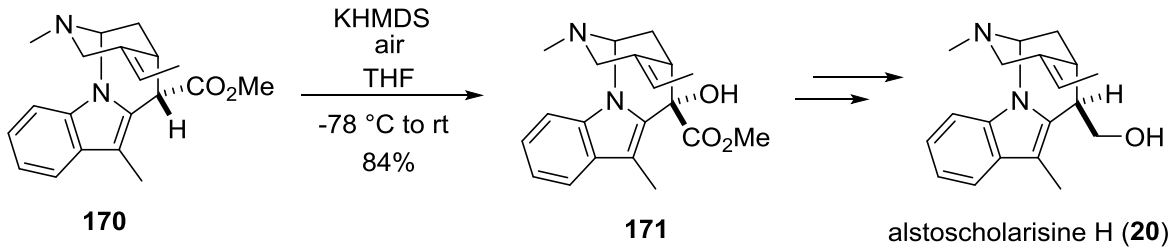
Scheme 35. Attempted α-Alkylation of Ester **162** with BOMCl



162 **168** (52%) **169**

It should be noted that a similar oxidation of an indole ester **170** has been previously utilized in a total synthesis of alstoscholarisine H (**20**) by Xia *et al*., giving α-hydroxyester **171** as a single stereoisomer where oxidation occurred from the least congested face of the bridged bicycle (Scheme 36).[11]

Scheme 36. Aerobic Oxidation of an Bridged Indole Ester



170 **171** alstoscholarisine H (**20**)

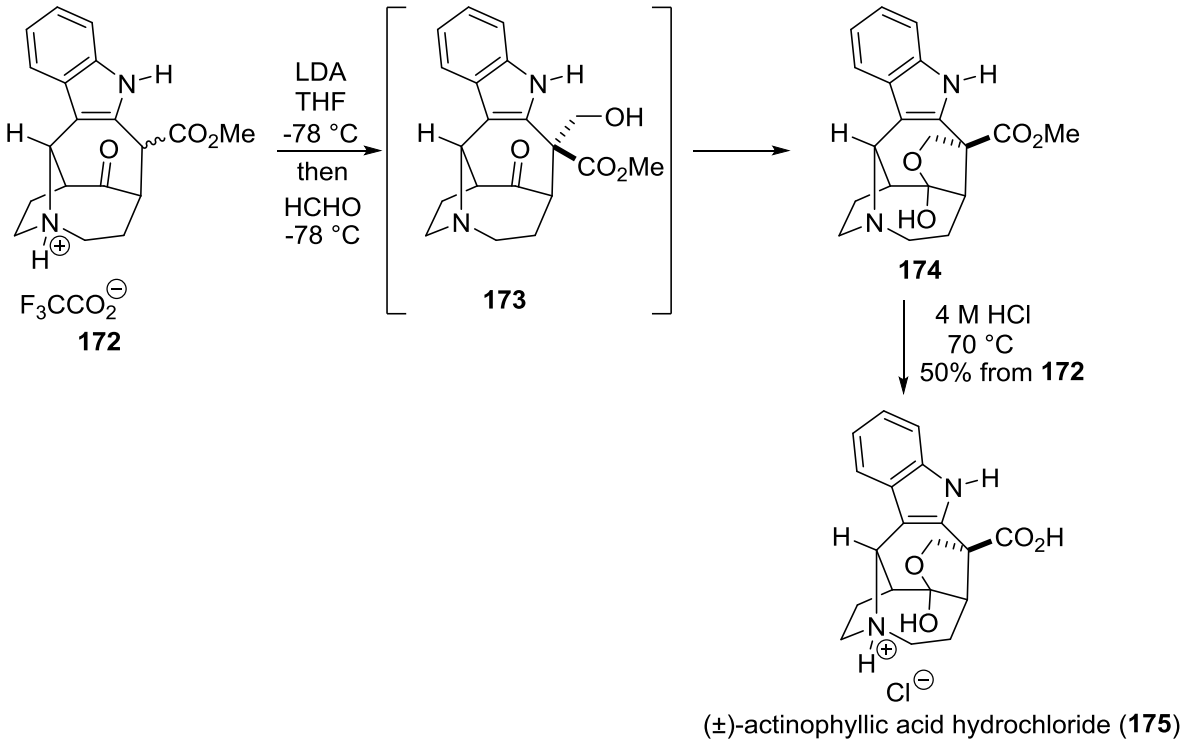
2.5.1.1. Ester α-Alkylation with Monomeric Formaldehyde

Given the propensity of the enolate of ester **162** to undergo autooxidation, more potent electrophiles than BOMCl were explored that might avoid this undesired reaction. Anhydrous monomeric formaldehyde[46] has been found to be a good reagent for the stereoselective introduction of hydroxymethyl groups into indole ester enolates similar to ours. For example,

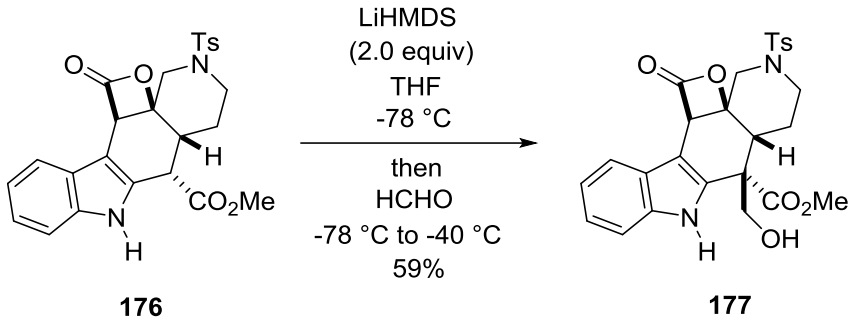
Overman *et al.* used this reagent for a late-stage hydroxymethylation of a bridged indole ester enolate in a total synthesis of the hydrochloride salt of the indole alkaloid (±)-actinophyllic acid (**175**) (Scheme 37).[47] Thus, methyl ester **172** was deprotonated with LDA to form the corresponding enolate, and a solution of monomeric formaldehyde in THF was added to provide hydroxymethyl compound **173**, which cyclized to hemiketal **174**. This methyl ester was immediately hydrolyzed with aqueous HCl to provide the hydrochloride salt of the alkaloid.

Feng *et al.* have also utilized this reagent for the α-alkylation of ester **176** to provide β-hydroxyester **177** as a single stereoisomer in a total synthesis of the alkaloids angustilodine and alstilobanines A and E.[48]

Scheme 37. Aldol Reactions of Indole Ester Enolates with Monomeric Formaldehyde



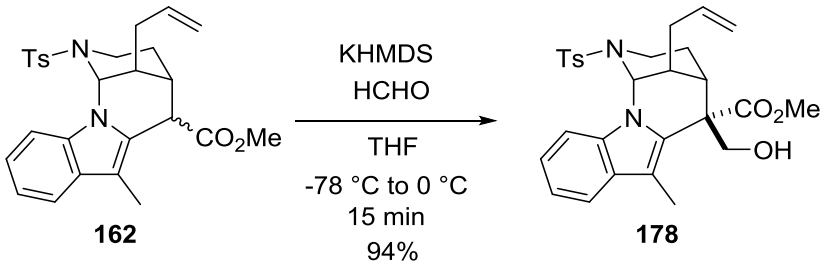
Scheme 37. (continued)



176 **177**

Thus, our ester **162** (mixture of diastereomers) was dissolved in a dilute solution of anhydrous monomeric formaldehyde in THF at -78 °C, then treated with KHDMS, and allowed to warm to 0 °C, providing the desired α-hydroxymethyl ester **178** as a single diastereomer in excellent yield (Scheme 38).

Scheme 38. Alkylation of Ester **162** with Monomeric Formaldehyde



162 **178**

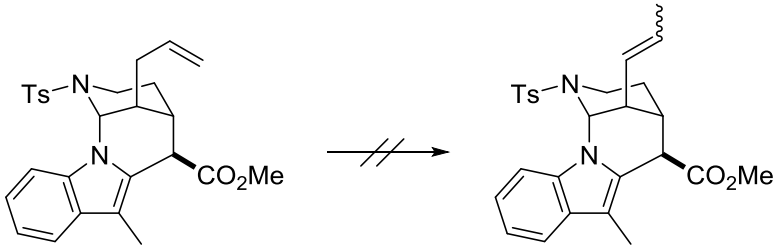
2.5.2. Degradation of the Allyl Group to an Aldehyde

2.5.2.1. Attempted Alkene Isomerizations Using Metal Catalysis

The next stage of the synthesis was to degrade the C20 allyl group into a formyl group in order to construct the tetrahydropyran E ring of the alkaloids. Using ester **163**, several metal

catalysts were screened to induce migration of the terminal alkene to form the corresponding propenyl system **179** (Table 5). Heating alkene **163** with a catalytic amount of $RhCl_3 \bullet H_2O$ in EtOH[49] led only to unidentified products (entry 1), while treatment with $PdCl_2(MeCN)_2$ in toluene[50] resulted in recovery of unreacted starting alkene (entry 2). Using a modification of the method described by Hanessian *et al.*, which involved heating alkene **163** with Grubbs second-generation ruthenium metathesis catalyst (0.40 equiv) in methanol at 60 °C overnight led to a complex mixture of unidentifiable products (entry 3).[51]

Table 5. Initial Experiments Towards Metal-Catalyzed Alkene Isomerization



163 **179**

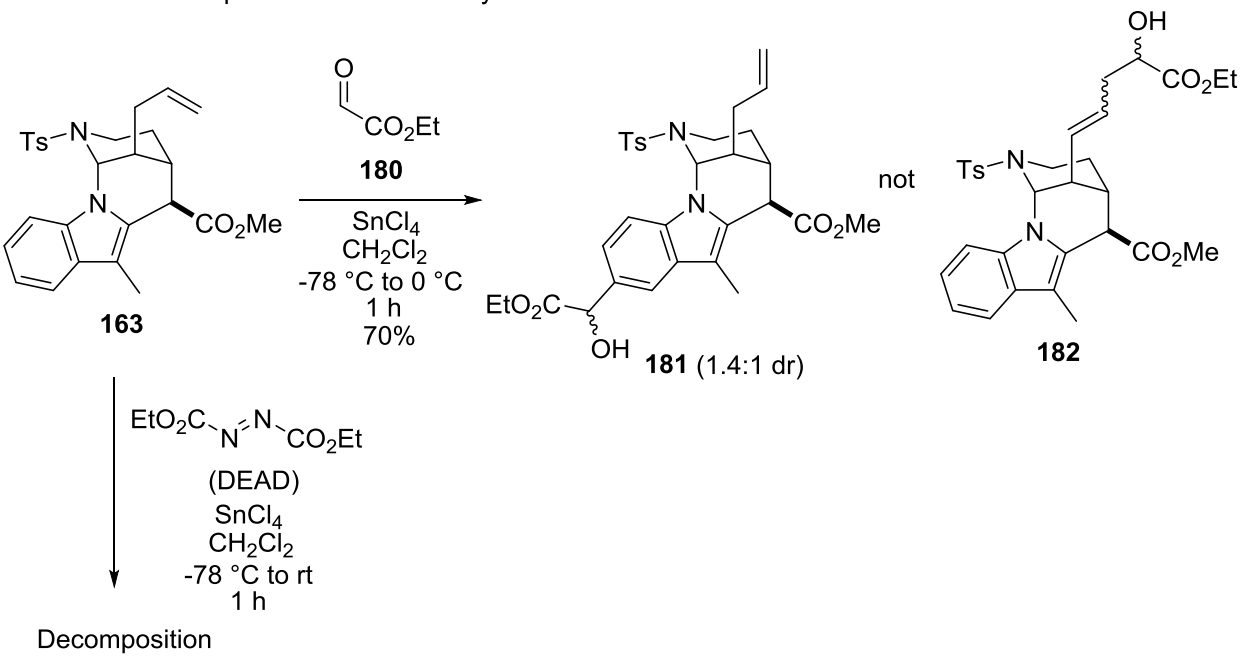
Entry	Conditions	Result
1	$RhCl_3 \bullet H_2O$ (1.0 equiv), EtOH reflux, 3 h	Complex Mixture
2	$PdCl_2(MeCN)_2$ (0.10 equiv), PhMe, 80 °C, 36 h	N.R.
3	Grubbs II (0.40 equiv), MeOH, 60 °C, 24 h	Complex Mixture

2.5.2.2. Attempted Lewis Acid-Catalyzed Ene Reactions

Since the initial results for effecting metal-catalyzed isomerizations were discouraging, an alternative alkene isomerization strategy utilizing an ene reaction was explored. Therefore, terminal alkene **163** was subjected to standard Lewis-acid catalyzed ene reaction conditions with ethyl glyoxalate (**180**) (Scheme 39).[52] However, instead of the desired ene reaction occurring with

the terminal alkene to form **182**, electrophilic addition occurred at the indole C5 position to produce α-hydroxy ester **181** (1.4:1 mixture of inseparable alcohol epimers). Additionally, utilizing diethyl azodicarboxylate (DEAD) as the enophile under similar Lewis acid-catalyzed conditions only led to decomposition of the starting material.[52b]

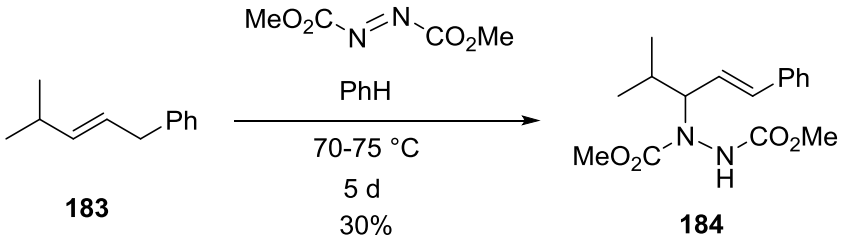
Scheme 39. Attempted Lewis Acid-Catalyzed Ene Reactions of Alkene **163**



2.5.2.3. Thermal Ene Reactions

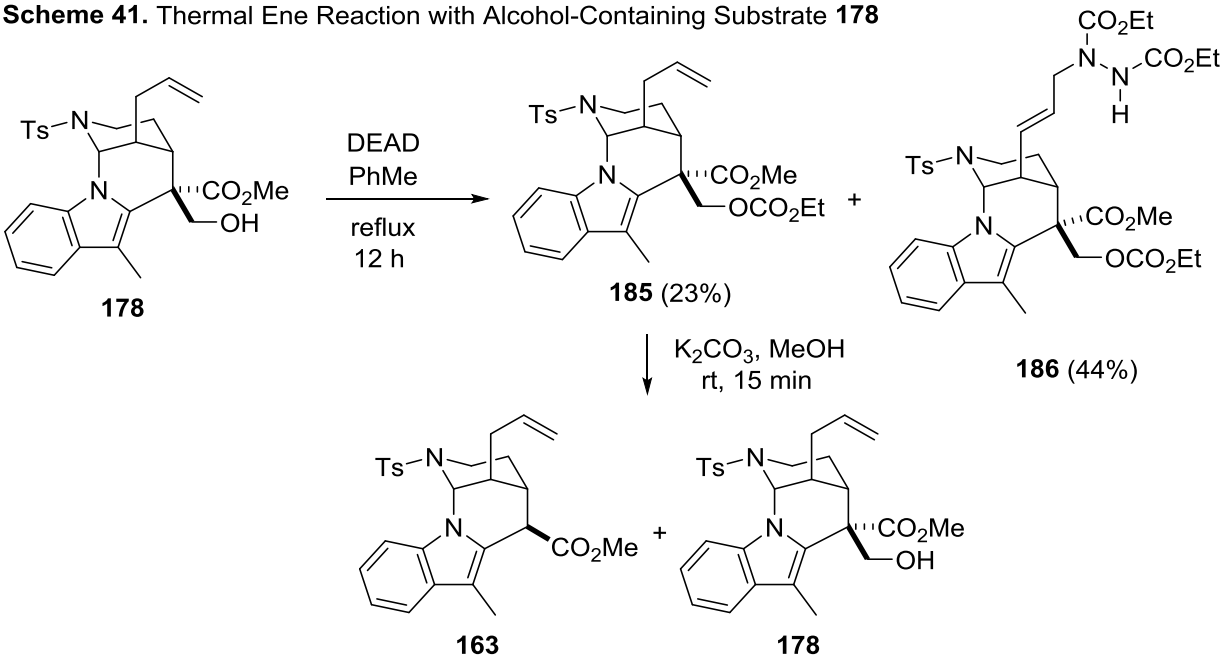
Since the above Lewis acid-mediated reactions were problematic, thermal ene reactions were explored next. Azodicarbonyl compounds are known to undergo ene reactions with alkenes under mild thermal conditions.[53] For example, alkene **183** undergoes an ene reaction with dimethyl azodicarboxylate to provide transposed hydrazine derivative **184** as a single (*E*)-geometric isomer in moderate yield (Scheme 40).[53b]

Scheme 40. Thermal Ene Reaction with Dimethyl Azodicarboxylate



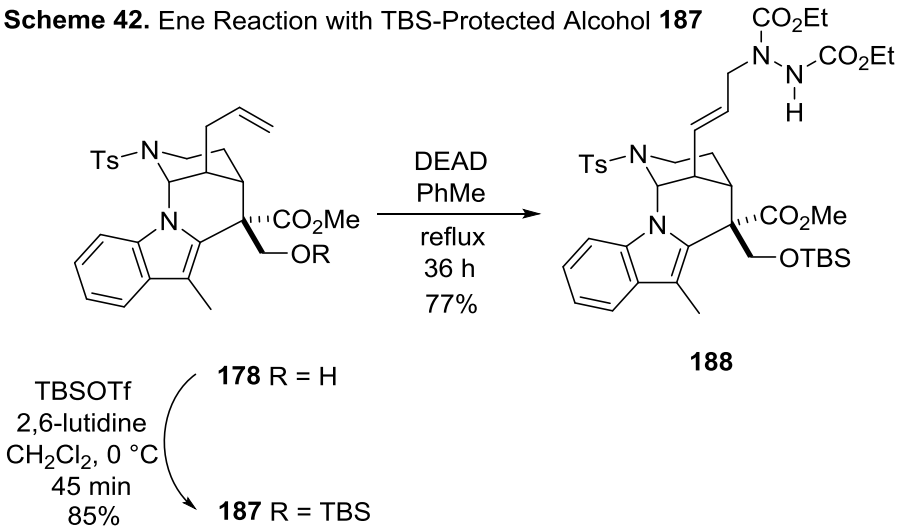
We first explored this method using alkene alcohol substrate **178**. Thus, heating **178** with DEAD provided a mixture of the undesired ethyl carbonate **185** along with ene adduct **186**, which had also undergone transacylation of the alcohol with DEAD, a transformation which has precedent in the literature (Scheme 41).[54] Attempts to cleave the ethyl carbonate moiety of **185** to produce the free alcohol using potassium carbonate in methanol provided the desired alcohol **178** along with a significant amount of the corresponding retro-aldol product **163**. Given the propensity of this system to undergo retro-aldol reactions upon deacylation with base, the ene reaction with the free alcohol **178** was not optimized and a slightly different substrate was examined.

Scheme 41. Thermal Ene Reaction with Alcohol-Containing Substrate **178**



Thus, the hydroxyl group of **178** was first protected as the TBS ether **187** in high yield (Scheme 42). Subsequent subjection of **187** to the thermal ene reaction conditions with DEAD used previously provided the desired hydrazine derivative **188** in good yield, exclusively as the (*E*)-geometric isomer.

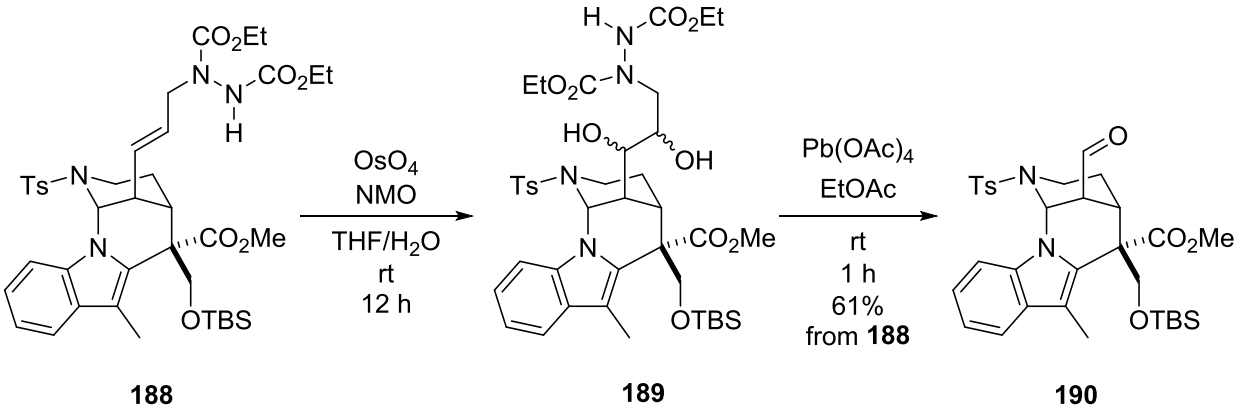
Scheme 42. Ene Reaction with TBS-Protected Alcohol **187**



2.5.3. Formation of a Lactol E Ring

To continue the synthesis, oxidative cleavage of the double bond of the ene product was investigated. Thus, the internal alkene **188** was subjected to dihydroxylation conditions with OsO_4/*N*-methylmorpholine-*N*-oxide (NMO)[13] to provide diol **189**, which without further purification was subjected to a Criegee oxidation with $Pb(OAc)_4$ in EtOAc[14] to afford axial aldehyde **190** (Scheme 43). It should be noted that an attempted Lemieux-Johnson oxidation of ene adduct **188** to form aldehyde **190** directly resulted in a complex product mixture, possibly due to concomitant oxidation of the indole moiety.[55]

Scheme 43. Oxidative Cleavage of Alkene **188**

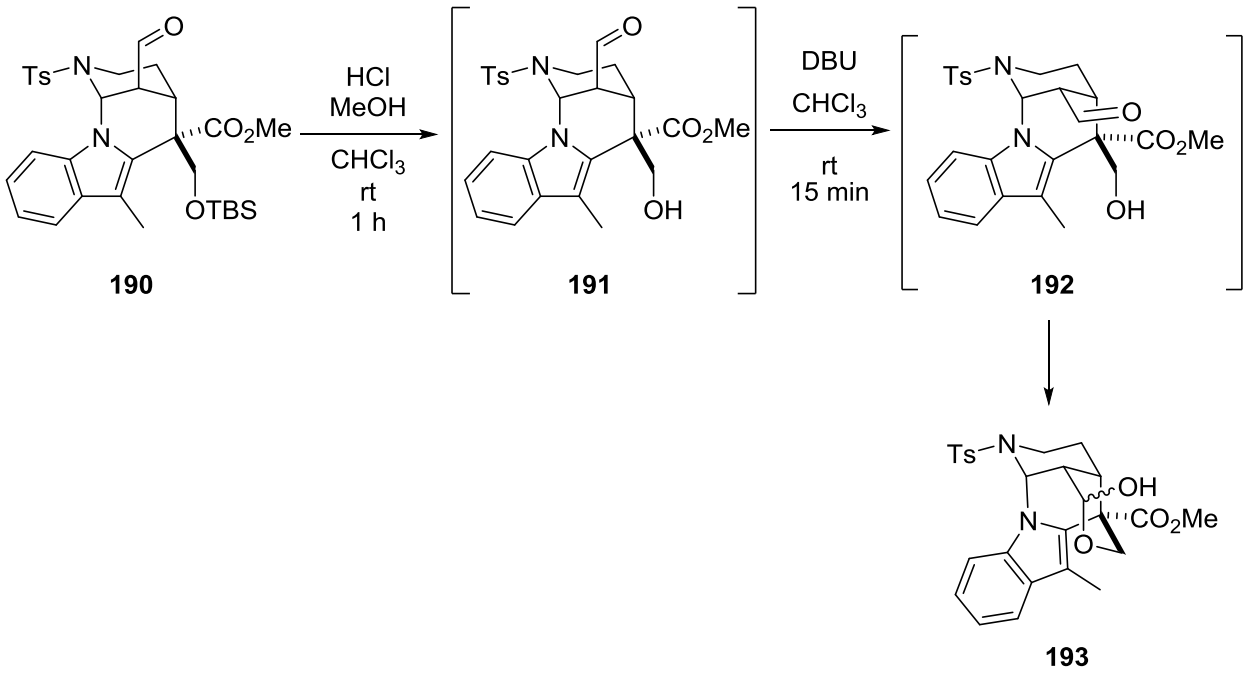


188 **189** **190**

The tetrahydropyran E ring of the alkaloids was then constructed from aldehyde **190** using a strategy which proved successful in the Bihelovic and Ferjancic synthesis of (±)-alstoscholarisine A.[12] Thus, the silyl ether of **190** was cleaved with dry HCl in methanol/chloroform to provide hydroxymethyl aldehyde **191**, which proved to be unstable and was therefore immediately

epimerized with DBU in chloroform to the equatorial aldehyde **192** (Scheme 44). This intermediate then spontaneously cyclized to form isolable lactol **193** (mixture of epimers).

Scheme 44. Preparation of Lactol **193**



190 **191** **192** **193**

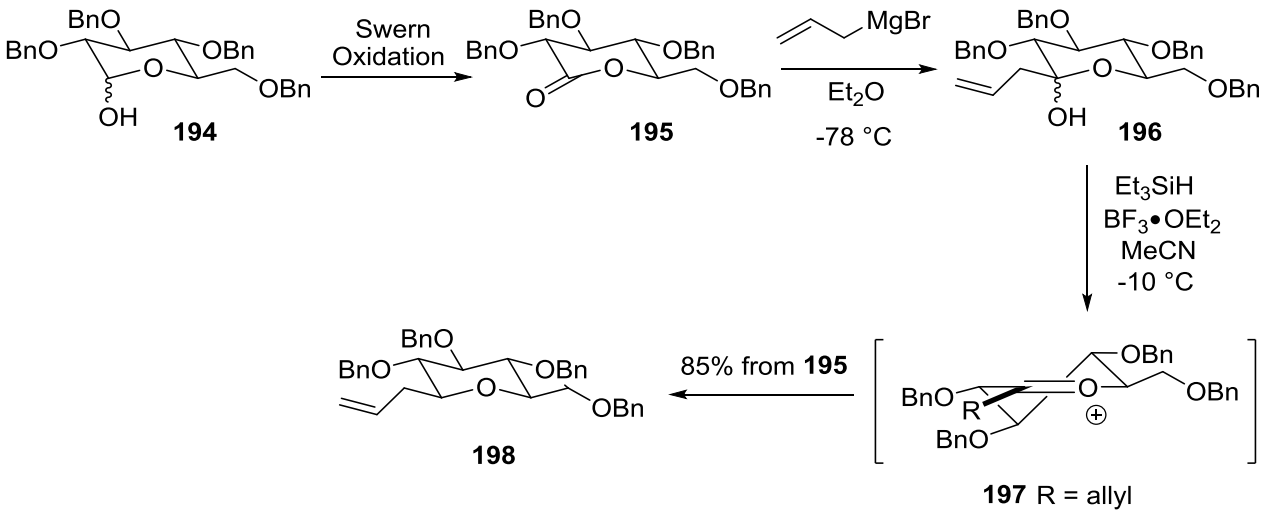
2.6. Introduction of the C18 Methyl Group and Control of the C19 Stereochemistry

2.6.1. Background on Stereoselective α-Alkyl Tetrahydropyran Synthesis from Lactols

Controlling the stereochemistry in construction of ring-substituted tetrahydropyrans has long been an area of interest. For example, Kishi *et al.* showed that both α- and β-allylated gylcopyranosides can be prepared from a common lactol intermediate.[56] Therefore, δ-lactol **194** was oxidized to the corresponding lactone **195**, followed by addition of allyl Grignard reagent to provide the hemiketal **196** (Scheme 45). This intermediate could be ionized with BF_3•Et_2O to

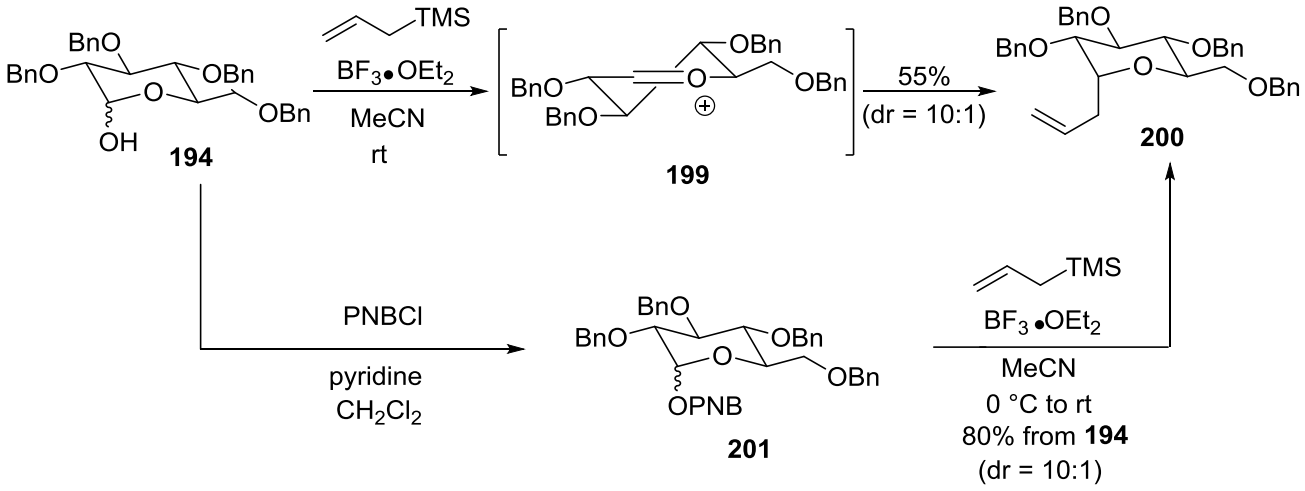
oxocarbenium ion **197** and reduced with Et_3SiH from the axial direction to provide β-allyl tetrahydropyran **198** as a single stereoisomer. It was suggested that the stereochemical result is due to stereoelectronic stabilization of the chair-like transition state in which the nucleophile adds from the axial direction.[15]

Scheme 45. Kishi's Strategy for Installation of an Equatorial Allyl Group on a Tetrahydropyran



Conversely, an axial allyl group could be installed directly from lactol **194** via initial ionization with BF_3•Et_2O to form oxocarbenium ion **199**, followed by addition of allyltrimethylsilane from the axial direction, which provided α-allyl tetrahydropyran **200** with excellent diastereoselectivity and in moderate yield (Scheme 46). Alternatively, the yield of **200** could be improved by first activating the anomeric oxygen as the *p*-nitrobenzoate (PNB) ester **201** and then performing the allylation under similar reaction conditions.

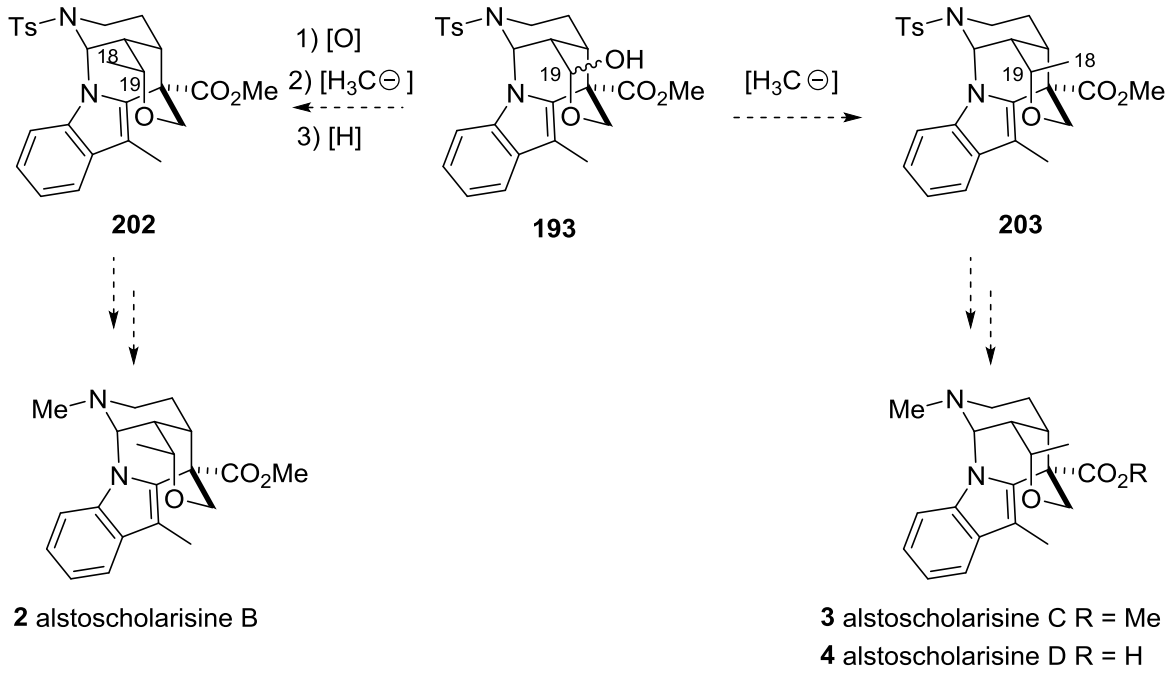
Scheme 46. Kishi's Strategy for Axial Addition of an Allyl Group to a Tetrahydropyran



2.6.2. Planned Application of Kishi's Strategy to the Synthesis of Alstoscholarisines B-D (2-4)

We believed that the Kishi approach to alkylative tetrahydropyran synthesis should allow the preparation of both C19 stereoisomeric sets of the alstoscholarisines starting from lactol **193** (Scheme 47). Thus, oxidation of **193** to an intermediate lactone, followed by chemoselective addition of a methyl nucleophile and stereoselective reduction of a hemiketal intermediate like **196** (cf. Scheme 45) would provide equatorial α-methyl tetrahydropyran **202**, which could then be used to synthesize alstoscholarisine B (**2**). Conversely, direct methylation of lactol **193** (cf. **194** to **200**) could produce axial methyl tetrahydropyran **203**, which would then be converted to alstoscholarisines C (**3**) and D (**4**).

Scheme 47. Planned Syntheses of Alstoscholarisines B, C, and D from Lactol **193**

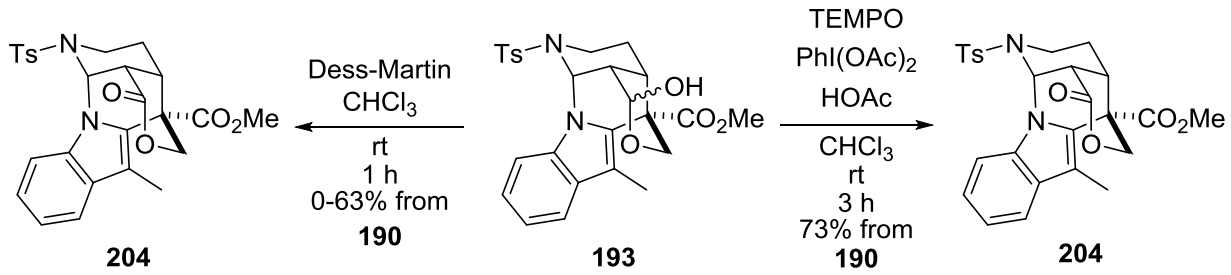


2.7. Synthesis of (±)-Alstoscholarisine B (2)

2.7.1. Installation of a C18 Equatorial Methyl Group

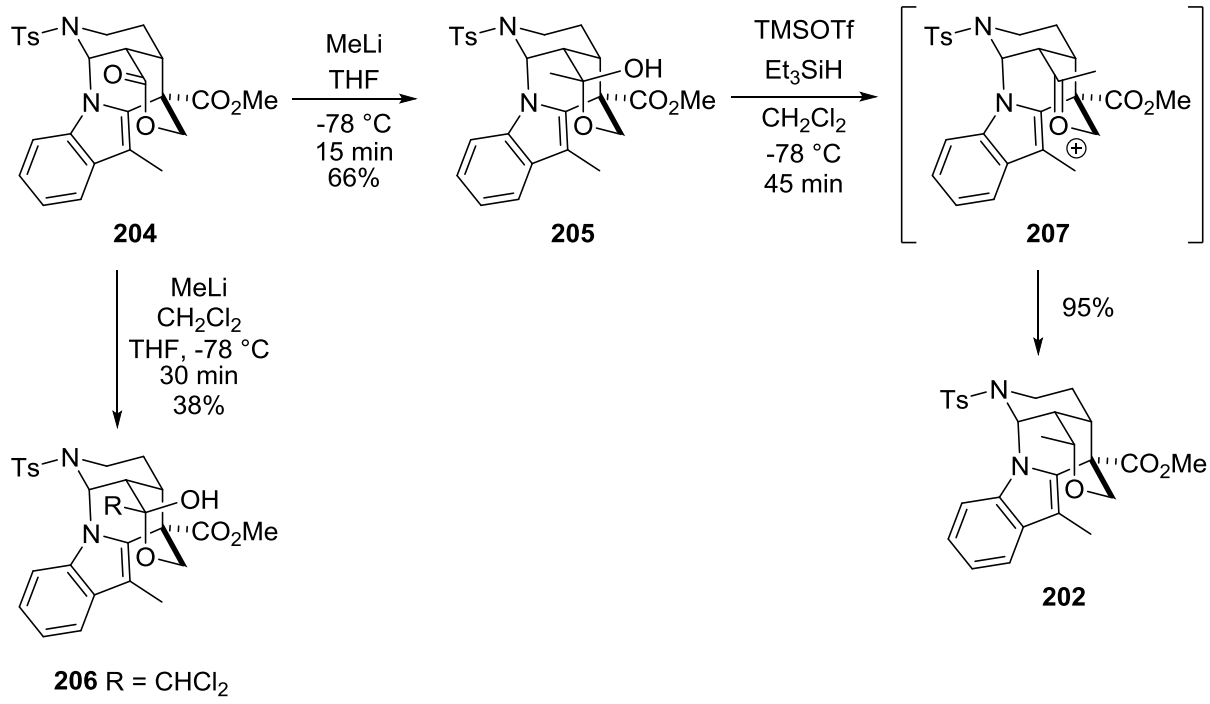
For the synthesis of alstoscholarisine B (**2**), lactol **193** was first oxidized using the Bihelovic/Ferjancic's conditions[12] with Dess-Martin periodinane to provide lactone **204** (Scheme 48). However, this reaction proved to be irreproducible from batch to batch of Dess-Martin reagent, with some runs resulting in complete decomposition of the lactol **193** with none of the desired lactone **204** being formed. Therefore, alternative methods for this oxidation were explored. It was found that the conditions developed by Piancatelli using TEMPO/PhI(OAc)$_2$ were efficient and reproducible for the synthesis of lactone **204** from lactol **193**.[57]

Scheme 48. Oxidation of Lactol **193** to Lactone **204**



Chemoselective addition of methyllithium to this lactone at low temperature provided the corresponding hemiketal **205** in acceptable yield as a single stereoisomer (configuration not determined) (Scheme 49). It should be noted that if any trace of dichloromethane from the workup extraction in the previous step was present in methyllithium reaction, only the undesired dichloromethyl hemiketal **206** was formed in moderate yield. Deoxygenation of hemiketal **205** with triethylsilane and TMSOTf proceeded smoothly and stereoselectivley via reduction of the intermediate oxocarbenium **207** from the least hindered face to form equatorial methyl tetrahydropyran **202** in excellent yield.[58,59] The stereochemical outcome of this reaction is also in line with stereoelectronic stabilization of the transition state for addition of hydride from the axial position.[15]

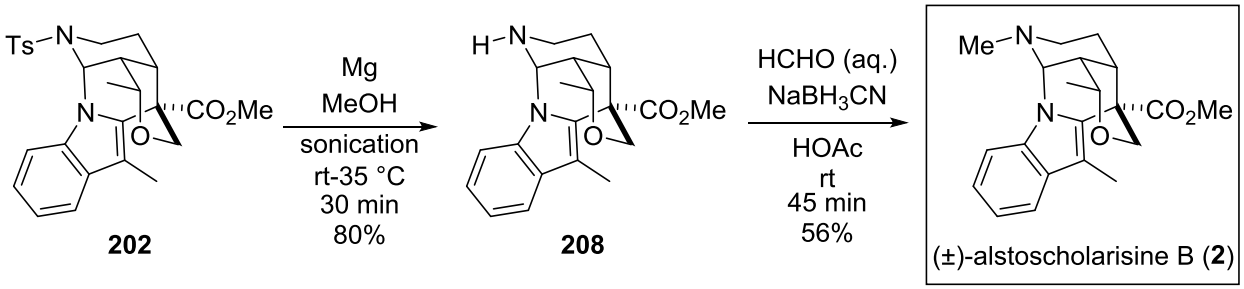
Scheme 49. Installation of an Equatorial Tetrahydropyran Methyl Group



2.7.2. Tosyl Removal and N-Methylation

The synthesis of the alkaloid was completed by first cleaving the tosyl group with magnesium in methanol under sonication in good yield to provide secondary amine **208** in good yield (Scheme 50).[60] Finally, this amine was converted to (±)-alstoscholarisine B (**2**) by a reductive methylation with formalin and $NaBH_3CN$ in glacial acetic acid.[61] The synthetic material had proton and carbon NMR spectra that were identical to those reported by the Luo group.[5]

Scheme 50. Completion of the Synthesis of (±)-Alstoscholarisine B (**2**)

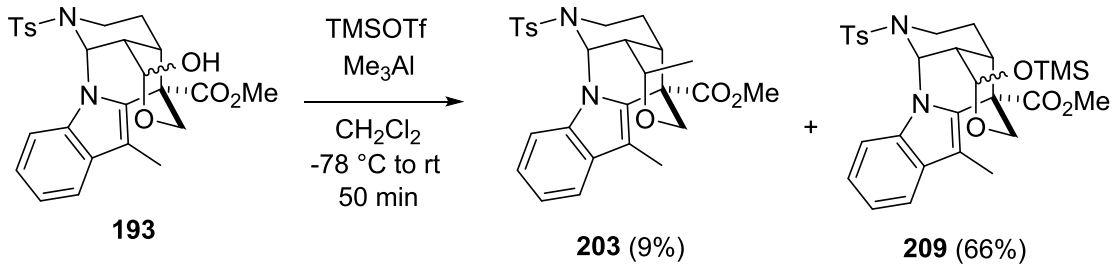


2.8. Syntheses of (±)-Alstoscholarisines C (3) and D (4)

2.8.1. Installation of the C18 Axial Methyl Group

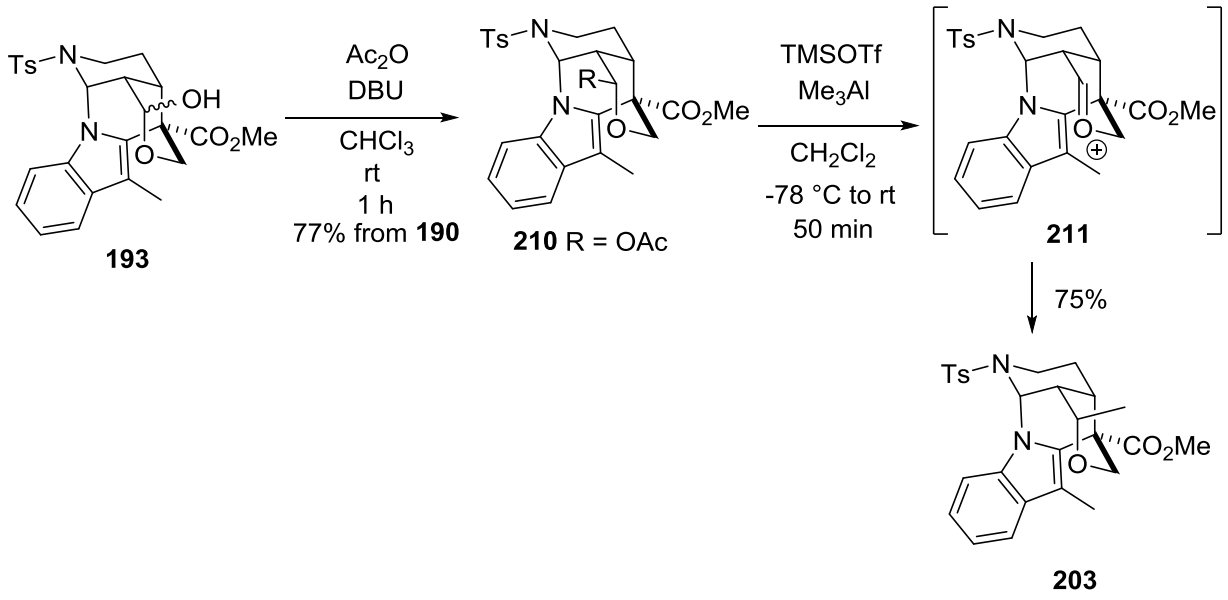
For the synthesis of alstoscholarisine C (**3**) from lactol **193**, it was necessary to install an axial methyl group at C19. Known conditions for the methylation of similar lactols using trimethylsilyl triflate (TMSOTf) and trimethylaluminum were first explored (Scheme 51).[62] However, only a trace amount (9%) of the desired methylated compound **203** was isolated under these conditions, with the major product simply being trimethylsilyl ether **209** (mixture of epimers) (66%).

Scheme 51. Attempted Direct C-Methylation of Lactol **193**



Since lactol acetates can also be utilized for similar Lewis acid-mediated methylations,[63] lactol **193** was treated with acetic anhydride/DBU to provide lactol acetate **210** (single stereoisomer, configuration not determined) in good yield (Scheme 52). Gratifyingly, treatment of the lactol acetate with TMSOTf and trimethylaluminum at -78 °C and subsequent warming to room temperature provided the desired axial α-methyl tetrahydropyran **203** in good yield as a single diastereomer. The reaction likely proceeds via addition of a methyl nucleophile from trimethylaluminum to oxocarbenium ion **211** from the least-encumbered axial direction.

Scheme 52. Methylation via Lactol Acetate **210**

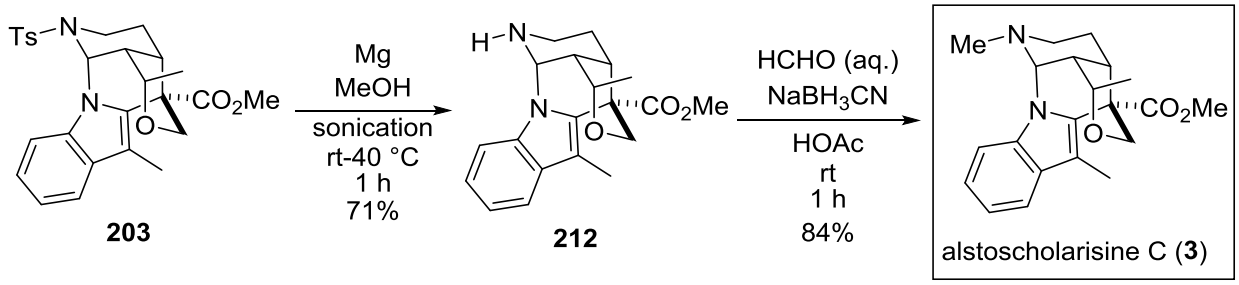


2.8.2. Tosyl Removal and N-Methylation

To complete the synthesis of the alkaloid, the tosyl group was removed with Mg/MeOH under sonication to provide secondary amine **212**,[60] which underwent reductive methylation with

$NaBH_3CN$ and HCHO[61] to provide (±)-alstoscholarisine C (**3**) in good yield (Scheme 53). This material had proton and carbon NMR spectra identical to the naturally occurring material.[5]

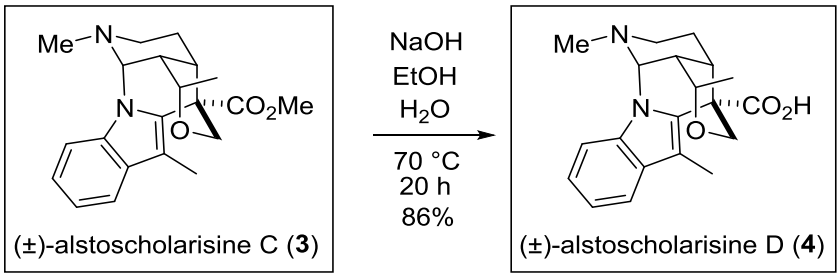
Scheme 53. Synthesis of (±)-Alstoscholarisine C (**3**)



2.8.3. Synthesis of Alstoscholarisine D (4)

(±)-Alstoscholarisine D (**4**) could be prepared by basic hydrolysis of methyl ester **3** in aqueous ethanol at elevated temperature (Scheme 54). Isolation of this amino acid by chromatography on silica gel initially proved to be problematic. However, the alkaloid could be isolated in good yield by first neutralizing the reaction medium with a weakly acidic ion-exchange resin (Amberlite CG-50),[64] and subsequent purification by reverse-phase preparative thin-layer chromatography. The synthetic material proved to have identical proton and carbon NMR spectroscopic data with the material isolated from *Alstonia scholaris*.[5]

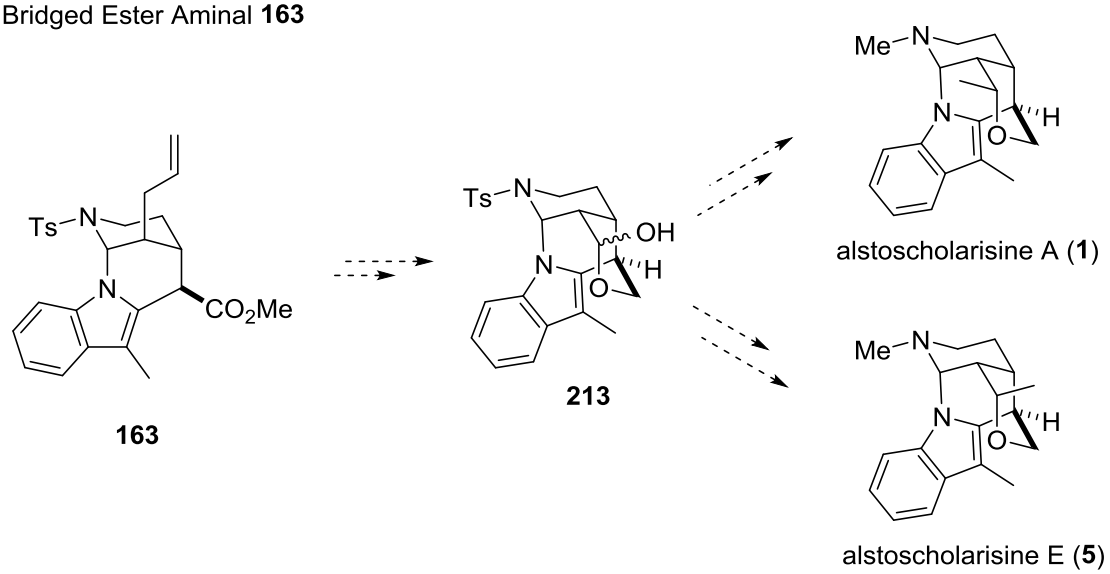
Scheme 54. Synthesis of (±)-Alstoscholarisine D (**4**)



2.9. Syntheses of (±)-Alstoscholarisines A (1) and E (5)

At this point we explored the total syntheses of (±)-alstoscholarisines A (**1**) and E (**5**) from bridged aminal **163**. We believed that the C16 ester handle of bridged system **163** could be utilized to form lactol **213**, which lacks the C16 ester moiety (Scheme 55). Using the strategies outlined above for stereoselective tetrahydropyran synthesis, lactol **213** would be used to access alstoscholarisines A (**1**) and E (**5**) (cf. Schemes 49 and 52).

Scheme 55. Projected Syntheses of (±)-Alstoscholarisines A (**1**) and E (**5**) from Bridged Ester Aminal **163**

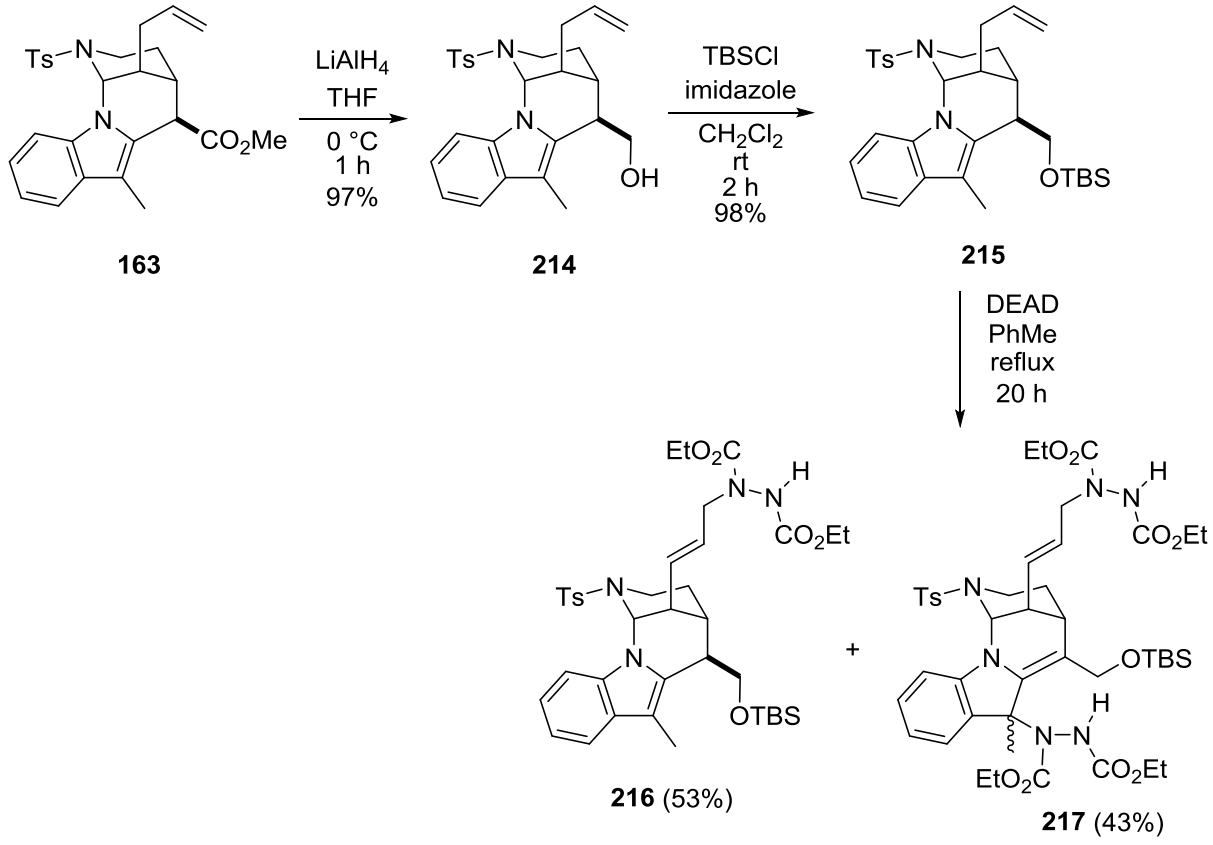


2.9.1. Preparation of Lactol 213

2.9.1.1. Ester Reduction and Ene Reactions

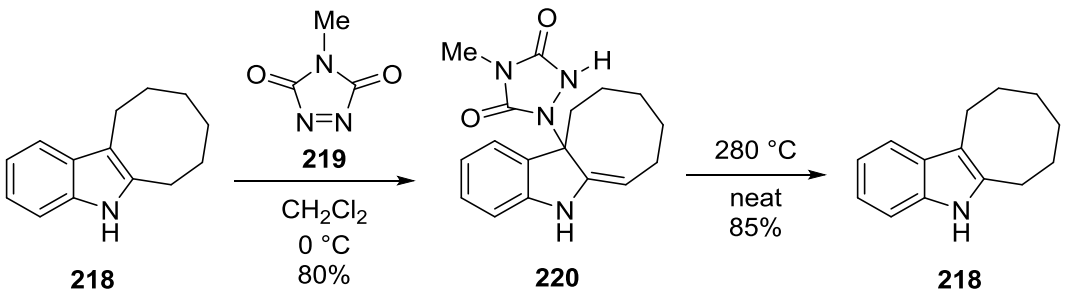
Thus, the ester moiety of bridged aminal **163** was reduced with $LiAlH_4$ in excellent yield to provide hydroxymethyl compound **214** (Scheme 56). The alcohol was then protected as the TBS ether **215** to prevent the type of undesired transacylation previously observed in the ene reaction (cf. Scheme 41). The terminal alkene **215** was then subjected to DEAD in refluxing toluene to provide hydrazine derivative **216** in moderate yield, with a significant amount of the bis-DEAD adduct **217** being formed (3.8:1 mixture of diastereomers).

Scheme 56. Ene Reaction of Silyl Ether **215**



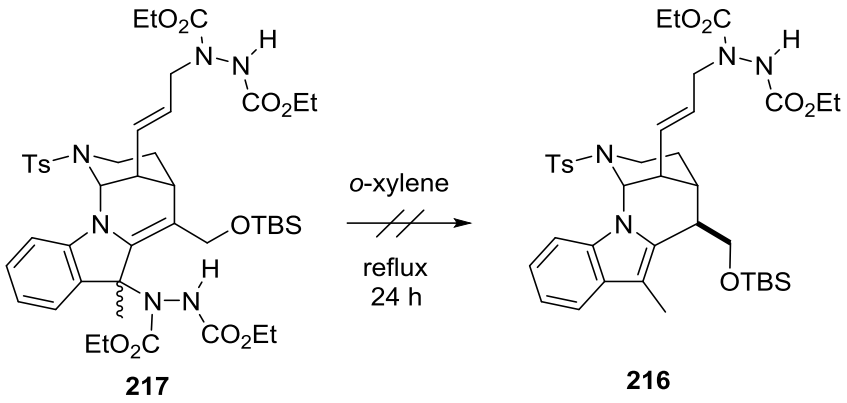
The addition of an azodicarbonyl compound to an indole at the C3 position has literature precedent. For example, Corey and coworkers utilized ene reactions between *N*-methyltriazolidindione **219** and indoles as a way to protect an indole C2,3-π bond (Scheme 57).[65] Thus, indole **218** undergoes an ene reaction with cyclic azo compound **219** at low temperature and in high yield to form urazole **220**. In order to induce a retro-ene reaction and regenerate indole **218**, neat adduct **220** was heated at 280 °C.

Scheme 57. Ene Reaction of Indole **218** and Subsequent Retro-ene Reaction



However, in our system, an attempt to induce a thermal retro-ene reaction on bis-adduct **217** in refluxing *o*-xylene to form the desired mono adduct **216** resulted in complete decomposition of **217** (Scheme 58).

Scheme 58. Attempted Retro-Ene Reaction of **217**



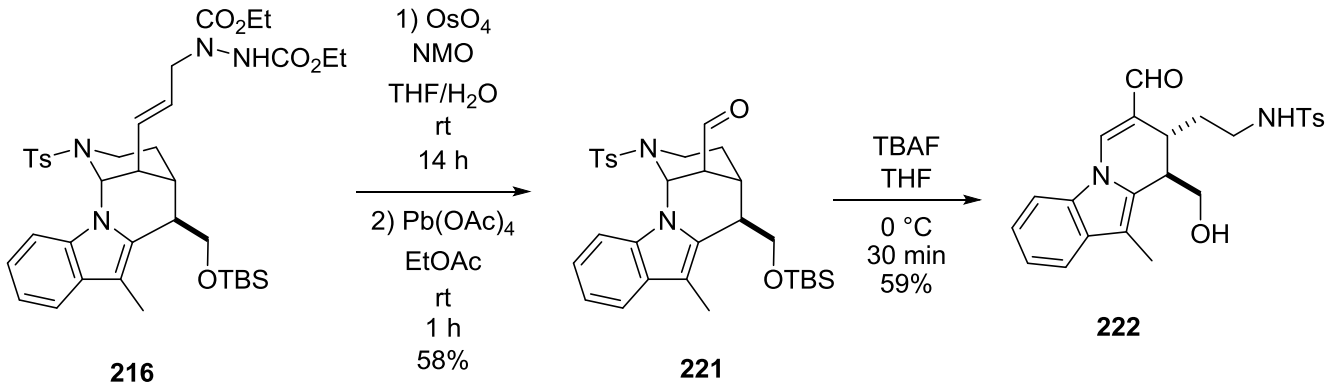
217 **216**

2.9.1.2. Formation of the E Ring from Ene Adduct 216

2.9.1.2.1. Olefin Oxidative Cleavage and Unexpected D Ring Opening

Utilizing the same two-step procedure described above for oxidative olefin cleavage (cf. Scheme 43), allylic hydrazine **216** was converted to axial aldehyde **221** (Scheme 59). However, upon attempted cleavage of the TBS protective group of **221** under either acidic conditions or with a stoichiometric amount of tetrabutylammonium fluoride (TBAF), ring-opened α,β-unsaturated aldehyde **222** was the only product isolated. This compound likely results from acid/base induced β-elimination of the sulfonamide moiety. It should be noted that no ring-opened side products were observed in the series possessing a C16 ester group (i.e. **191** to **193**, Scheme 44).

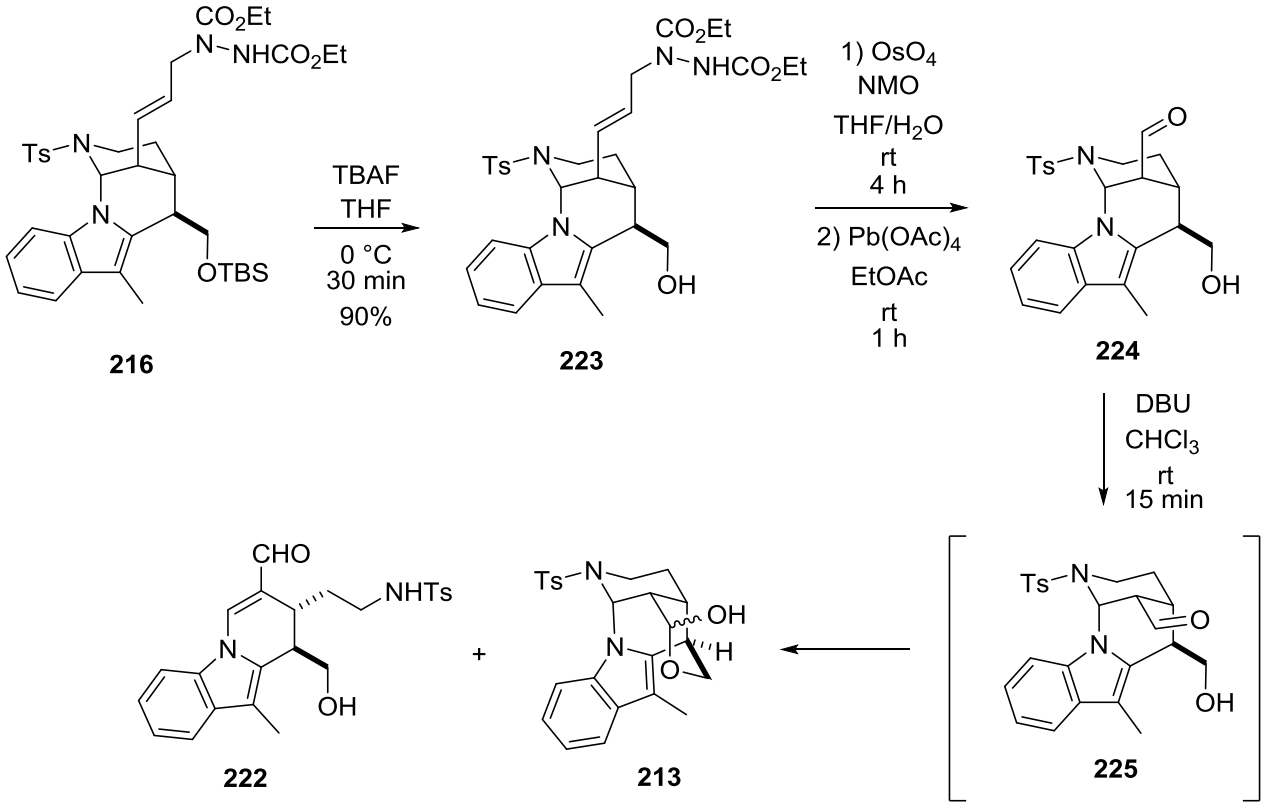
Scheme 59. Oxidative Cleavage of Alkene **216** and Unexpected Ring Opening of Aldehyde **221**



2.9.1.2.2. Formation of a Lactol from Ene Adduct 216

Since it appeared that acidic or basic conditions used remove the TBS group were inducing undesired ring cleavage of aldehyde **221**, it was decided to change the order of steps with the aim of mitigating this problem. Thus, allyl hydrazine **216** was first treated with TBAF to cleanly provide alcohol **223** (Scheme 60). Subsequent two-step oxidative cleavage of the alkene then provided axial aldehyde **224**. This intermediate could be epimerized under basic conditions with DBU to form the equatorial isomer **225**, which cyclized *in situ* to give lactol **213**, along with some of the undesired ring-opened product **222**. The crude mixture was used in subsequent reactions (*vide infra*).

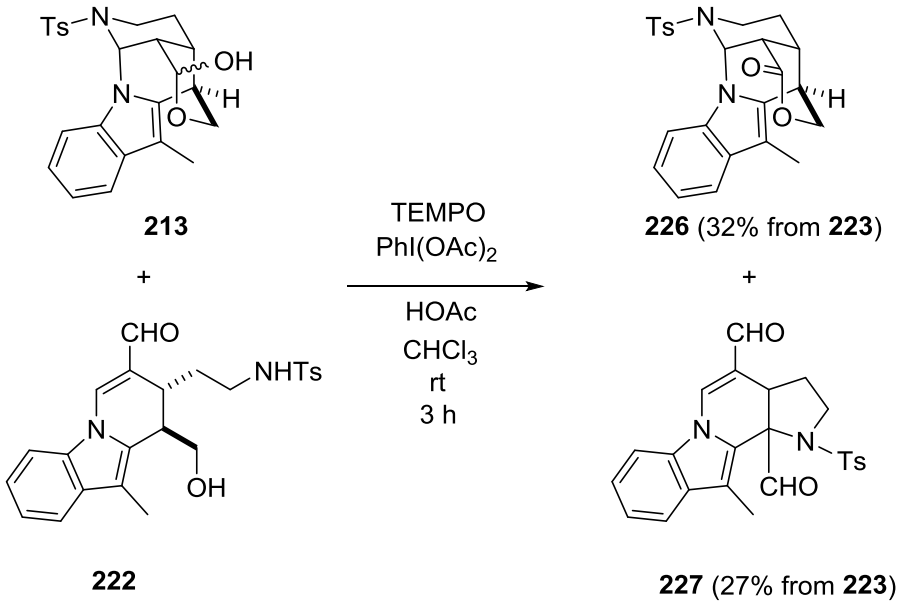
Scheme 60. Preparation of Lactol **213**



2.9.2. Synthesis of (±)-Alstoscholarisine A (1) from Lactol 213

Applying the same strategy utilized for the synthesis of alstoscholarisine B (cf. Scheme 48), the crude mixture of lactol **213** and ring-opened alcohol **222** was immediately oxidized to provide the desired lactone **226** in moderate yield as well as unexpected fused tetracycle **227**, which likely arises via a Hofmann-Loffler-Freytag reaction[66] of alcohol **222**, followed by final alcohol oxidation to provide dialdehyde **227** (*vide infra*) (Scheme 61).

Scheme 61. Oxidation of Lactol **213**



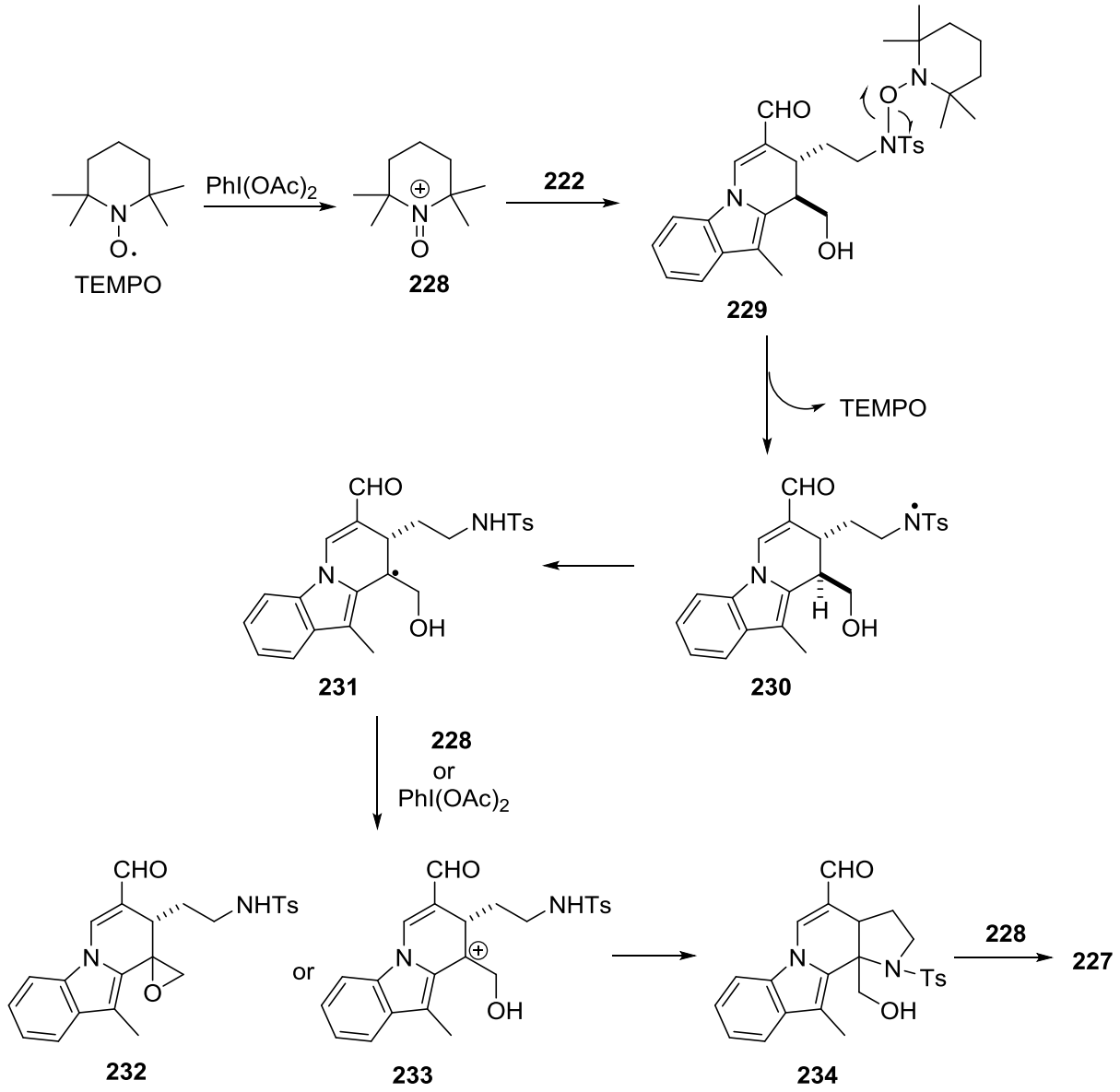
213 + **222** → **226** (32% from **223**) + **227** (27% from **223**)

2.9.2.1. Discussion of the Unexpected Hofmann-Loffler-Freytag Reaction

The formation of fused tetracyclic dialdehyde **227** under the lactol to lactone oxidation conditions was both unexpected and unprecedented. Hofmann-Loffler-Freytag reactions are known to be mediated by hypervalent iodine reagents in combination with I_2[67] or NaI,[68] but no precedent exists for the reaction using a combination of TEMPO and $PhI(OAc)_2$. A plausible mechanism for this transformation involves initial oxidation of TEMPO to oxoammonium species **228** by $PhI(OAc)_2$ (Scheme 62).[69] The sulfonamide moiety of **222** could attack this oxoammonium ion at the electrophilic oxygen to produce adduct **229**, which could undergo N-O bond homolysis to regenerate TEMPO and form sulfonamide radical **230**. This radical would then undergo a 1,5 hydrogen atom abstraction to generate carbon-centered radical **231**, which could undergo further oxidation to form either carbocation **233** or epoxide **232**. Either of these species could undergo a

final intramolecular nucleophilic addition of the sulfonamide nitrogen to generate tetracycle **234**. This alcohol could then be oxidized by oxoammonium species **228** to form dialdehyde **227**.

Scheme 62. Plausible Mechanism for the Generation of Tetracycle **227**

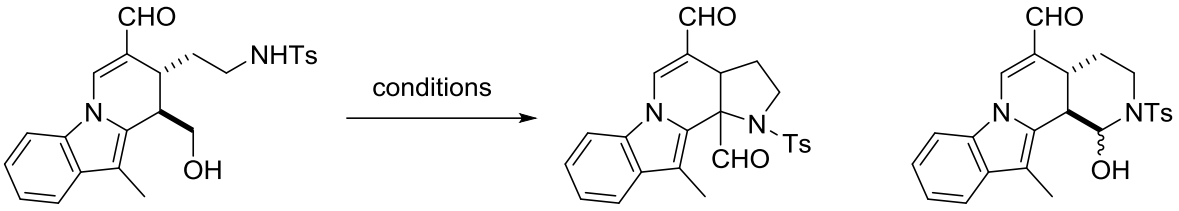


In order to further examine this transformation and the role that each reagent might play, some additional experiments using purified alcohol **222** were performed (Table 6). When alcohol

222 was treated with either TEMPO (entry 1) or $PhI(OAc)_2$ (entry 2) alone, no reaction occurred even after extended reaction times. Interestingly, when the alcohol was subjected to both reagents in a mixture of chloroform and acetic acid (entry 3), none of the Hofmann-Loffler-Freytag product **227** was observed, with the only product formed being hemiaminal **235**. This compound likely results from initial alcohol oxidation and trapping of the intermediate aldehyde by the secondary sulfonamide moiety. It should be noted that this product was never observed when the crude mixture of **213** and **222** were subjected to the lactol oxidation conditions (cf. Scheme 61).

To examine if the presence of DBU in the reaction medium had any effect on the outcome of the oxidation, further experiments were performed in which the alcohol **213** was first stirred with DBU in chloroform prior to addition of glacial acetic acid and the oxidants. Thus, treating alcohol **222** with DBU and then adding acetic acid and TEMPO (entry 4) or $PhI(OAc)_2$ (entry 5) alone resulted in no reaction. However, when the alcohol was first stirred with DBU in chloroform, followed by addition of acetic acid and both oxidants, a mixture of Hofmann-Loffler-Freytag product **227** (18%) and hemiaminal **235** (42%) was obtained. Therefore it can be concluded that the presence of DBU in the reaction medium somehow promotes the Hofmann-Loffler-Freytag reaction. However, these results do not satisfactorily explain why alcohol **222** gives exclusively the Hofmann-Loffler-Freytag product **227** when the crude mixture containing lactol **213** is subjected to the oxidation conditions.

Table 6. Additional Examination of Hofmann-Loffler-Freytag Reaction Conditions

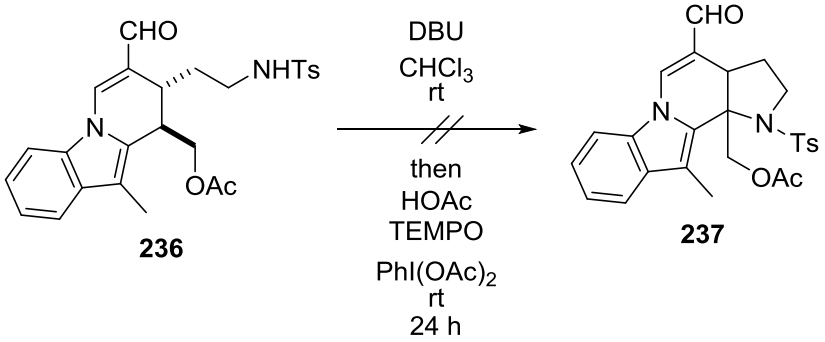


222 **227** **235**

Entry	Conditions	Result
1	$CHCl_3$/HOAc (7:1), TEMPO (2.5 equiv), rt, 12 h	N. R.
2	$CHCl_3$/HOAc (7:1), $PhI(OAc)_2$ (4.0 equiv), rt, 12 h	N. R.
3	$CHCl_3$/HOAc (7:1), TEMPO (0.5 equiv), $PhI(OAc)_2$ (4.0 equiv), rt, 3 h	**235** (62%)
4	DBU (2.0 equiv), $CHCl_3$ then HOAc, TEMPO (2.5 equiv), rt, 12 h	N. R.
5	DBU (2.0 equiv), $CHCl_3$ then HOAc, $PhI(OAc)_2$ (4.0 equiv), rt, 12 h	N. R.
6	DBU (2.0 equiv), $CHCl_3$ then HOAc, TEMPO (0.5 equiv), $PhI(OAc)_2$ (4.0 equiv), rt, 3 h	**227** (18%) + **235** (42%)

To further assess the generality of this transformation, acetate **236** was subjected to the same reaction conditions as used in the lactol oxidation (Scheme 63). However, no reaction occurred under these conditions, as none of Hofmann-Loffler-Freytag product **237** was formed and only starting material **236** was recovered.

Scheme 63. Attempted Hofmann-Loffler-Freytag Reaction Using Acetate **236**

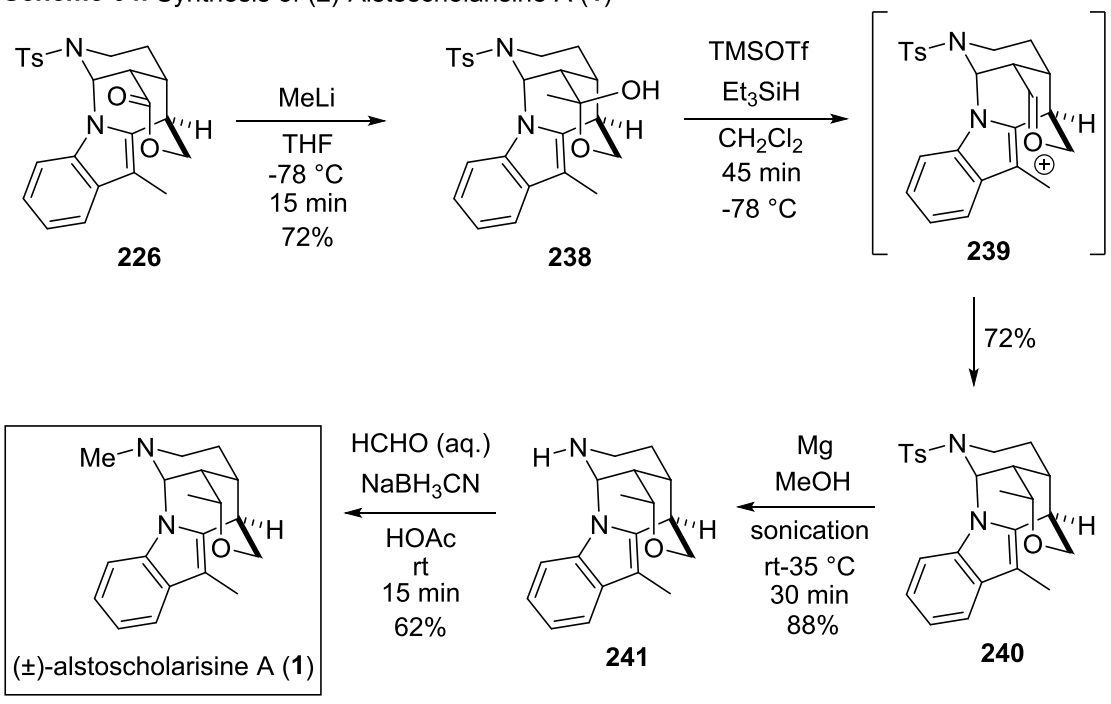


236 **237**

2.9.2.2. Completion of the Synthesis of (±)-Alstoscholarisine A (1)

The total synthesis of alstoscholarisine A was completed by initial addition of methyllithium to lactone **226** to provide hemiketal **238** (single diastereomer, configuration not determined) (Scheme 64). Ionization of hemiketal **238** to oxocarbenium ion **239** with TMSOTf and reduction from the less hindered face with triethylsilane afforded equatorial methyl tetrahydropyran **240**.[58,59] Removal of the tosyl group of **240** with magnesium in methanol under sonication[60] provided secondary amine **241**, which underwent reductive methylation with aqueous formalin/$NaBH_3CN$[61] to yield (±)-alstoscholarisine A (**1**). Our synthetic material had NMR spectra identical to those reported in the literature for the natural alkaloid.[5]

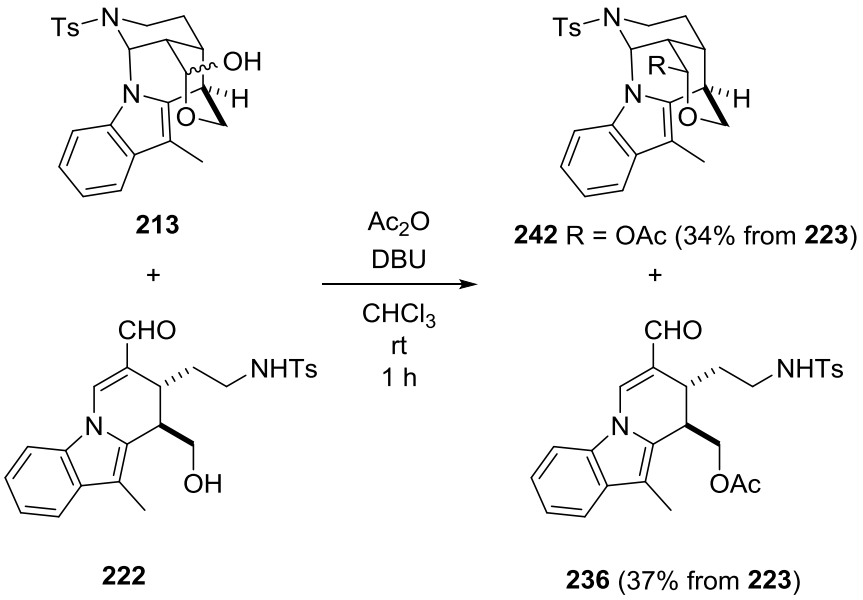
Scheme 64. Synthesis of (±)-Alstoscholarisine A (**1**)



2.9.3. Synthesis of (±)-Alstoscholarisine E (5)

Given the low yield observed previously upon attempted direct methylation of the C16 ester-bearing lactol **193** (cf. Scheme 51), such a transformation was not attempted in this series. Thus, the crude mixture of lactol **213** and ring-opened alcohol **222** was acetylated with acetic anhydride/DBU to provide a chromatographically separable mixture of lactol acetate **242** (single stereoisomer, configuration not determined) and ring-opened acetate **236**, both in moderate yield (Scheme 65).

Scheme 65. Acetylation of Lactol **213**

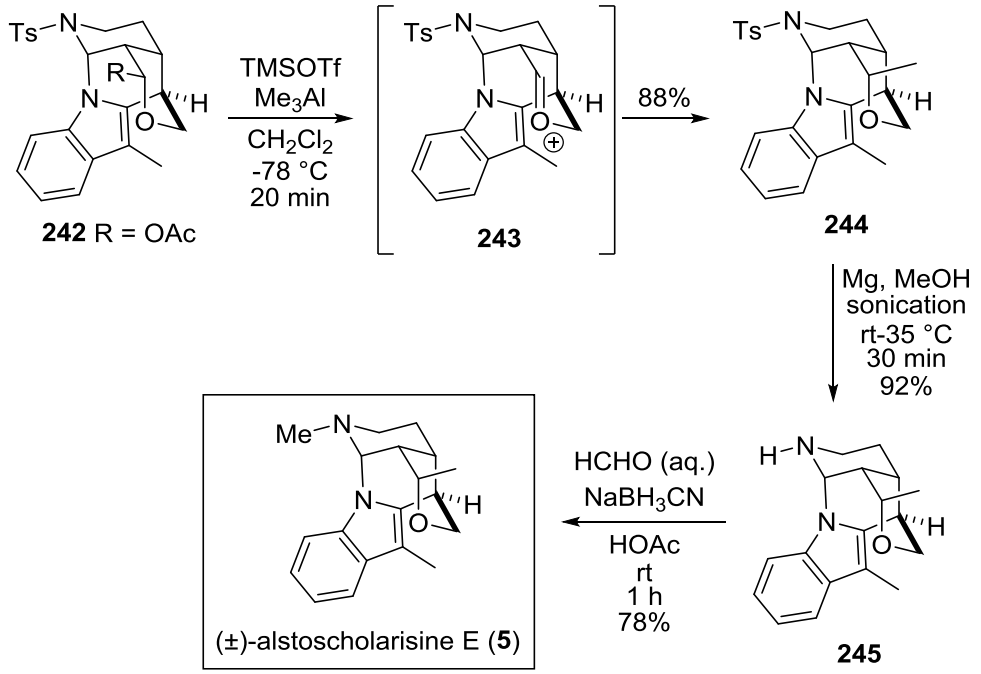


To effect the desired axial methylation, lactol acetate **242** was subjected to the same conditions as used for the synthesis of alstoscholarisine C (cf. Scheme 52, TMSOTf, Me_3Al, -78 °C to rt). Unexpectedly in this case, only a mixture of unidentifiable products could be isolated (Scheme 66). However, it was found that the reaction proceeded smoothly if the reaction mixture

was maintained and quenched at -78 °C, providing the requisite axial methyl tetrahydropyran **244** in excellent yield. The difference in the temperature required for generation of oxocarbenium **243** compared to **211** could be due to the electron-withdrawing properties of the C16 ester moiety, which destabilizes the intermediate oxocarbenium ion and thus requires higher temperatures for its formation (cf. Scheme 52).

The tosyl group of **244** was then removed with Mg/MeOH under sonication[60] to provide secondary amine **245**, which was N-methylated with formalin/$NaBH_3CN$ in glacial acetic acid[61] to yield (±)-alstoscholarisine E (**5**). The synthetic material had spectra identical to those reported for the natural material.[5]

Scheme 66. Synthesis of (±)-Alstoscholarisine E (**5**)



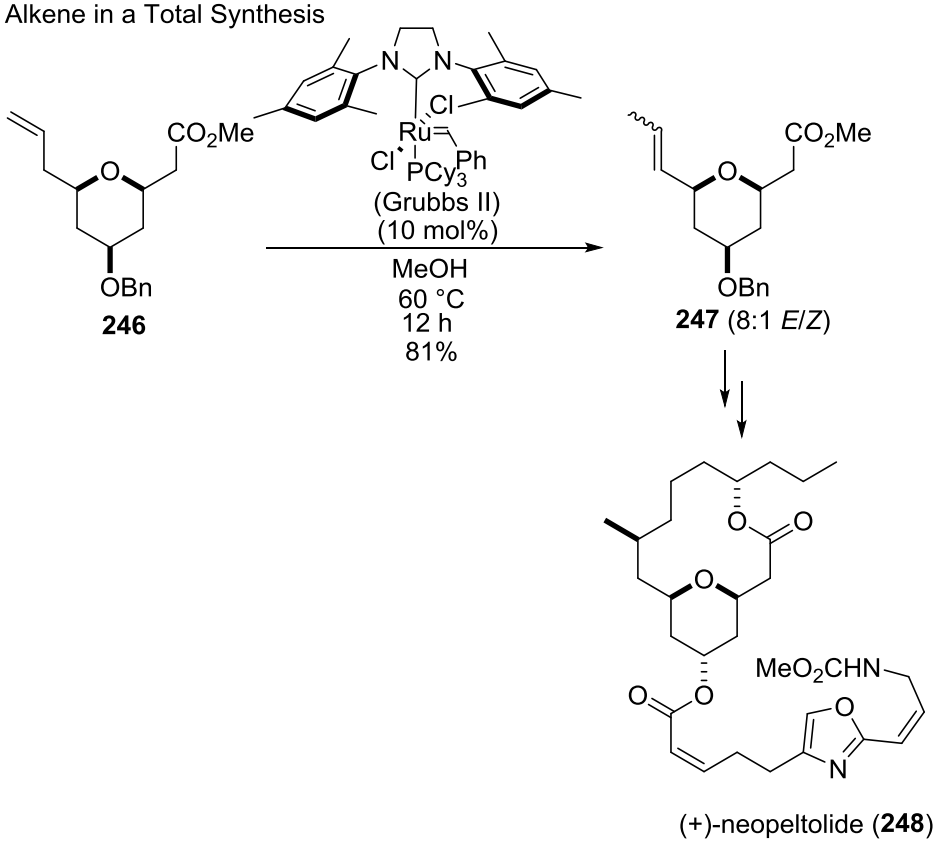
2.10. Plan for Improved Syntheses of (±)-Alstoscholarisines A-E (1-5)

The syntheses of alkaloids **1**-**5** described above include an undesirable and inefficient alcohol protection/deprotection sequence necessitated by undesired transacylation with DEAD in the thermal ene reactions of terminal alkenes **178** and **214**. Furthermore, the yield in the transformation of silyl ether-containing alkene **215** to ene adduct **216** was only moderate due to competing formation of the unexpected bis-ene adduct **217** by reaction of DEAD with the indole moiety at C3 (cf. Scheme 56). We therefore sought to effect a direct transformation of terminal alkenes **163** and **178** to the corresponding propenyl compounds, thereby avoiding an ene reaction. Although the aforementioned results of metal-catalyzed alkene isomerization reactions in this system were initially discouraging (cf. Table 5), at this point we decided to reexamine such a strategy.

2.10.1. Grubbs II-Mediated Alkene Isomerizations

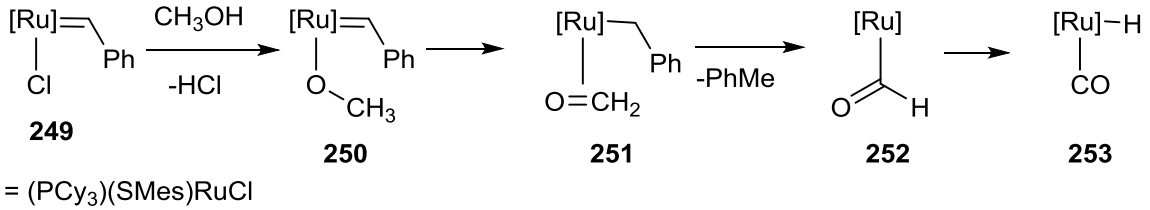
The method developed by Hanessian *et al.* utilizing Grubbs second-generation ruthenium metathesis catalyst in methanol at elevated temperature has emerged as an effective method for the selective isomerization of terminal alkenes to internal alkenes, with the (*E*)-geometric isomer generally being favored.[51] For example, She *et al.* utilized this method for the isomerization of terminal alkene **246** to internal olefin **247** in a synthesis of (+)-neopeltolide (**248**) (Scheme 67).[70]

Scheme 67. Isomerization of a Terminal Alkene to an Internal Alkene in a Total Synthesis



The isomerization reaction is believed to proceed through the *in situ*-generation of a ruthenium hydride complex.[71] Thus, association of methanol to Grubbs second-generation catalyst (**249**) and loss of HCl generates methoxycarbene complex **250** (Scheme 68). Hydride transfers generate formyl complex **252** (via formaldehyde adduct **251**), which can undergo α-hydride elimination to generate ruthenium hydride complex **253**.

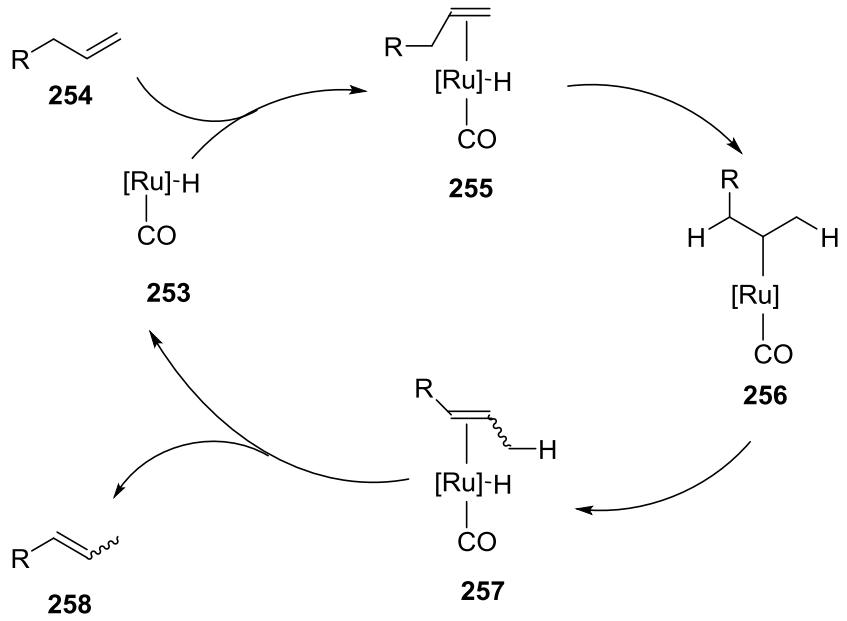
Scheme 68. Generation of Ruthenium Hydride **253** from Grubbs Catalyst (**249**)



[Ru] = $(PCy_3)(SMes)RuCl$

This hydride complex could associate with the terminal alkene **254** to form olefin complex **255**, which would undergo hydride migratory insertion to generate alkylruthenium complex **256** (Scheme 69). β-Hydride elimination of an internal hydrogen would then form internal alkene complex **257**. Internal alkene **258** could then dissociate from this complex and regenerate ruthenium hydride **253**.

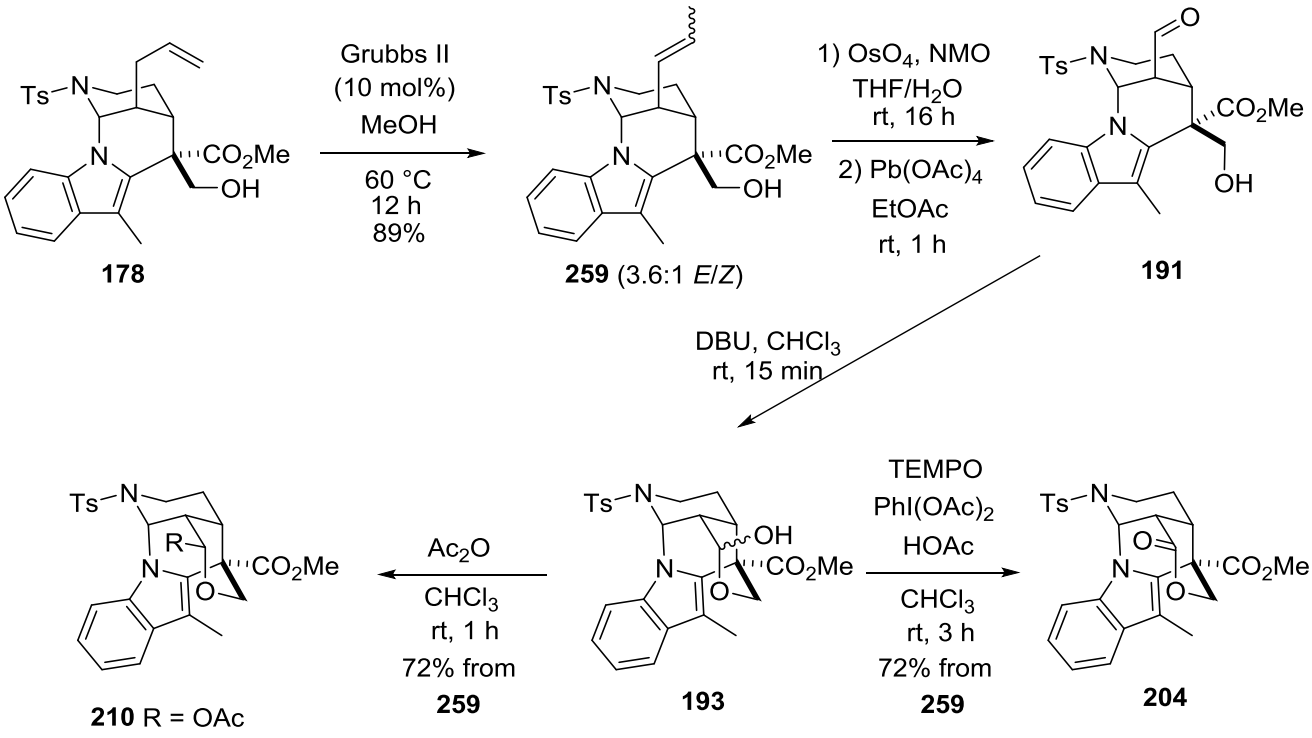
Scheme 69. Catalytic Cycle for Ruthenium Hydride-Mediated Olefin Isomerization



2.11. More Efficient Syntheses of (±)-Alstoscholarisines B-D (2-4)

In our initial experiment applying this method for the isomerization of terminal alkene **163** (cf. Table 5, entry 3), we had used a high catalyst loading (40 mol%) and extended reaction time (24 h) that led to a complex mixture of products. Gratifyingly, reexamining the reaction using the standard conditions reported by Hanessian, treatment of hydroxymethyl ester **178** with Grubbs second-generation catalyst (10 mole %) in methanol at 60 °C for 12 h provided the desired internal alkene **259** in excellent yield as a 3.6:1 mixture of (*E*/*Z*) isomers (Scheme 70). Subjection of this alkene to the two-step dihydroxylation/oxidative cleavage sequence provided axial aldehyde **191**. Epimerization of aldehyde **191** with DBU resulted in lactol **193** which could be oxidized to lactone **204** in 72% yield, or alternatively acetylated to form lactol acetate **210** in identical yield. These intermediates were then carried through the routes described above in order to prepare the natural products.

Scheme 70. Grubbs II-Mediated Isomerization and Transformation to **204** and **210**



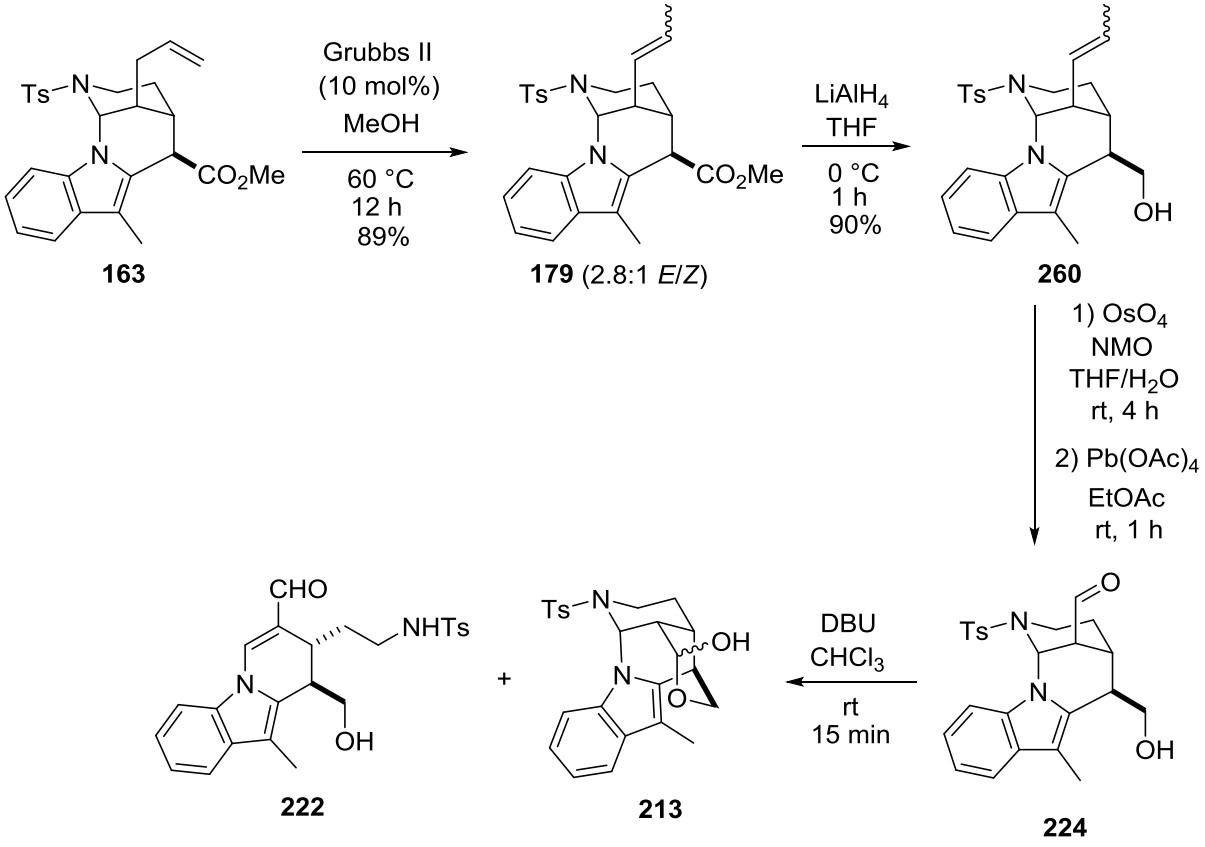
Inclusion of this simplified sequence improved the routes from Michael acceptor **130** for (±)-alstoscholarisine B (**2**) from fifteen steps (2.3% overall yield) to thirteen steps (5.0% overall yield), (±)-alstoscholarisine C (**3**) from fourteen steps (3.8% overall yield) to twelve steps (8.0% overall yield), and (±)-alstoscholarisine D (**4**) from fifteen steps (3.3% overall yield) to thirteen steps (6.9% overall yield).

2.12. More Efficient Syntheses of (±)-Alstoscholarisines A (1) and E (5)

The alkene isomerization methodology was also applied to ester **163** in order to streamline the syntheses of the two alkaloids lacking the C16 carboxy group. Thus, treatment of terminal alkene **163** with Grubbs second-generation catalyst (10 mol%) in MeOH at 60 °C provided internal

alkene **179** as a 2.8:1 mixture of (*E*/*Z*) isomers in excellent yield (Scheme 71). The ester moiety was then reduced with $LiAlH_4$ to provide alcohol **260**. The alkene was dihydroxylated and the resulting triol was cleaved to unstable axial aldehyde **224**. This aldehyde was epimerized with DBU to form lactol **213**, as well as some of the ring-opened alcohol **222**.

Scheme 71. Alkene Isomerization and Transformation to Lactol **213**

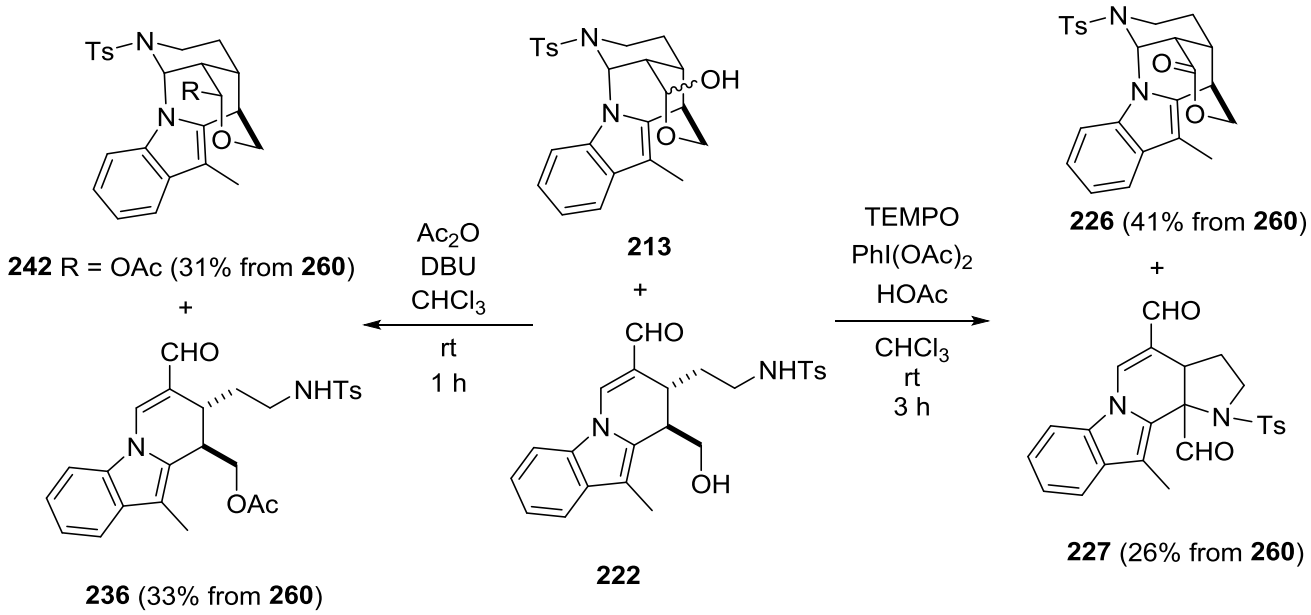


163 **179** (2.8:1 *E*/*Z*) **260** **222** **213** **224**

The crude mixture of lactol **213** and ring-opened alcohol **222** could then be oxidized or acetylated to give lactone **226** (41% from **260**, with 26% of **227**) or lactol acetate **241** (31% from **260**, with 33% of **236**) (Scheme 72). These intermediates were carried through to the natural products as described above, improving the routes from Michael acceptor **130** from sixteen steps

(1.1% overall yield) to fourteen steps (2.6% overall yield) and fifteen steps (2.7% overall yield) to thirteen steps (4.4% overall yield) for (±)-alstoscholarisine A and E, respectively.

Scheme 72. Oxidation/Acetylation of Lactol **213**



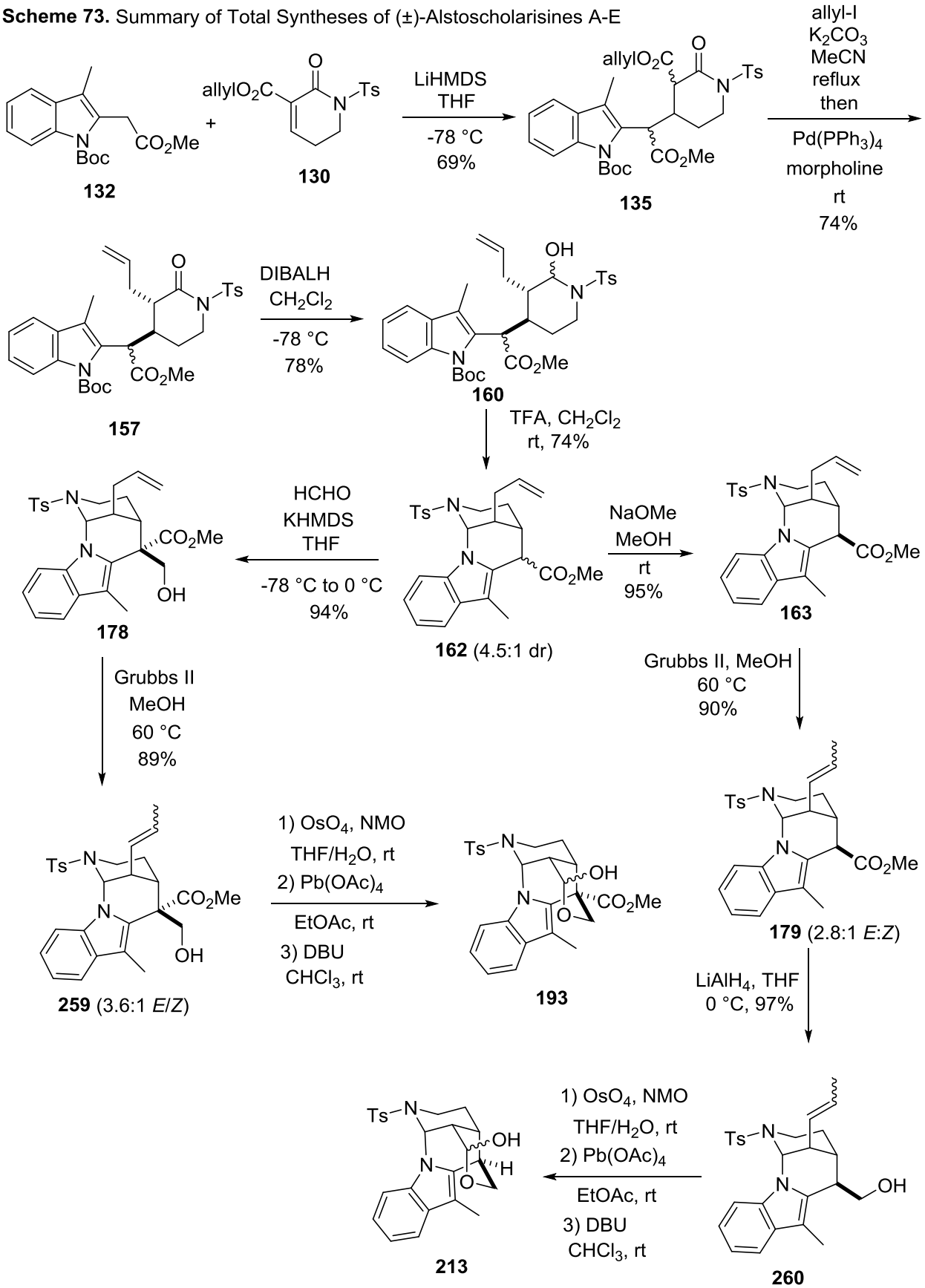
2.13. Concluding Remarks

In conclusion, the first total syntheses of (±)-alstoscholarisines B-E (**2**-**5**) have been completed, along with a new synthesis of (±)-alstoscholarisine A (**1**).[72] The syntheses commenced with a convergent Michael reaction between an indole ester enolate and an α,β-unsaturated *N*-sulfonyllactam to form the C15-C16 bond of the alkaloids. Elaboration of this Michael adduct via installation of an allyl group at C20 and subsequent lactam reduction and dehydration/indole deprotection/cyclization provides a bridged aminal **162** which serves as a common intermediate for syntheses of all five of the alkaloids. Installation of a hydroxymethyl group at C16 via ester enolate aldol chemistry or methyl ester reduction, followed by degradation of the C20 allyl group

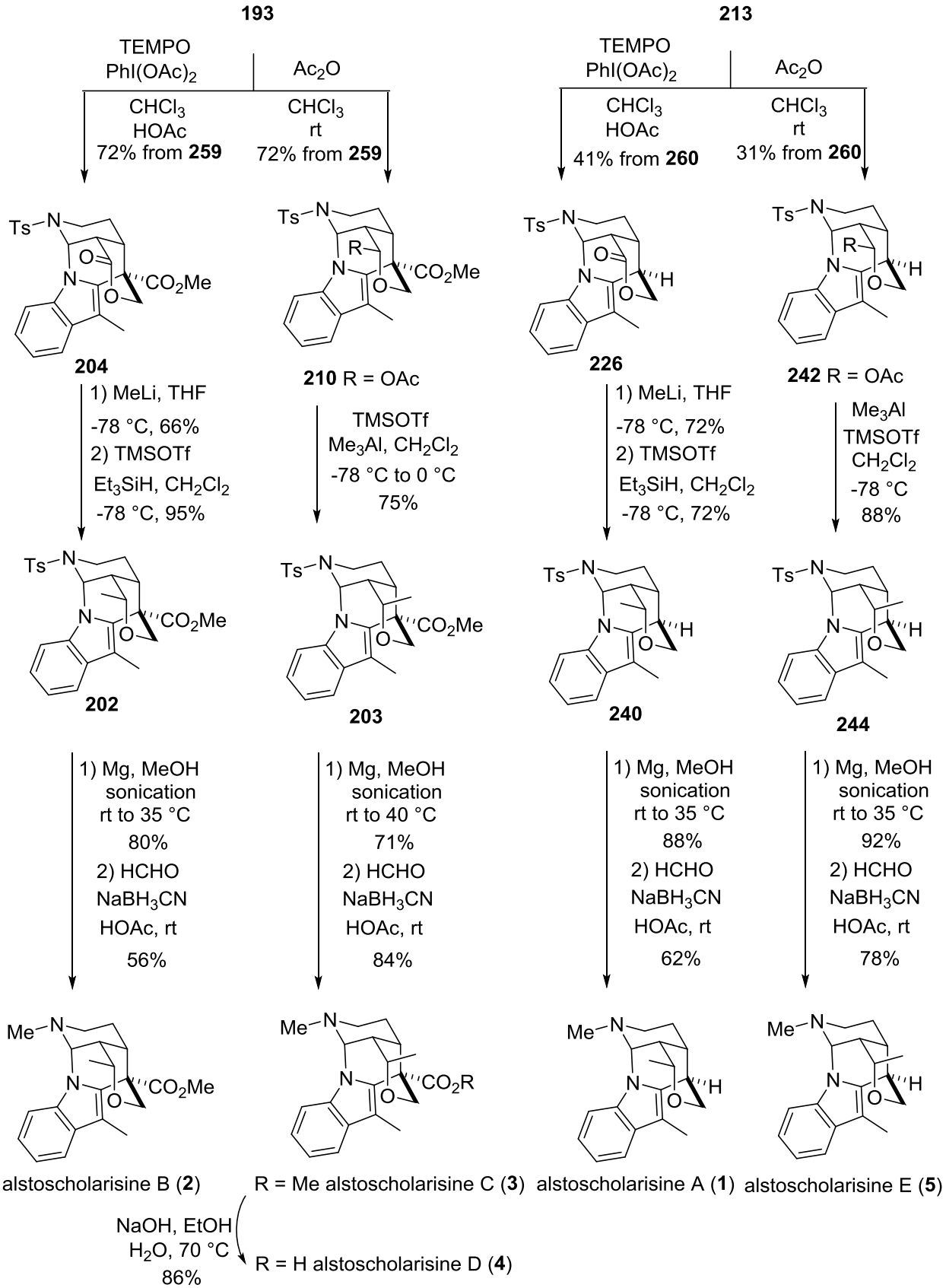
to a formyl group allows for the formation of the tetrahydropyran E-ring of the target molecules. Lactol oxidation followed by methylation and stereoselective reduction leads to the formation of the equatorial methyl-containing alkaloids (i.e. **1** and **2**), while acetylation and stereoselective methylation gives the axial methyl-containing compounds (i.e. **3**,**4**, and **5**). A detailed summary of the routes is shown in Scheme 73.

The total syntheses of these natural products could allow further biological studies to be performed without the need to obtain the necessary quantities from *A. scholaris*, as the alkaloids occur in very low levels (0.000044-0.00057%) in the leaves of the organism.[5] Furthermore, the synthetic strategy allows for the creation of unnatural analogues that would allow structure-activity relationships to be developed on the natural product class to better understand their mechanism of action. These studies could have implications for the creation of new strategies for the development of treatments for human neurological disorders.

Scheme 73. Summary of Total Syntheses of (±)-Alstoscholarisines A-E



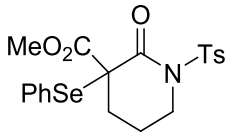
Scheme 73. (continued)



Chapter 3. Experimental Procedures

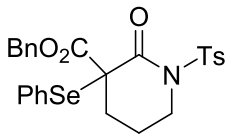
General Methods. All non-aqueous reactions were carried out in oven- or flame-dried glassware under an atmosphere of argon. All reagents were purchased from commercial vendors and used as received, unless otherwise specified. Anhydrous tetrahydrofuran (THF), dichloromethane (CH_2Cl_2), toluene (PhMe), and acetonitrile (MeCN) were obtained from a solvent purification system (Glass Contour). Reactions were stirred magnetically and monitored by thin layer chromatography (TLC) with 250 μm EMD 60 F254 precoated silica gel plates. Flash chromatographic separations were performed using silica gel (240-400 mesh). FT-IR spectra were recorded on a Thermo-Nicolet FT-IR spectrometer equipped with a diamond ATR accessory. NMR spectral data were recorded on Bruker DPX-300 or AVANCE III HD 500 (Prodigy BBO cryoprobe) spectrometers. Proton and carbon-13 NMR chemical shifts are reported relative to chloroform for ^{1}H and ^{13}C NMR (δ 7.26 and 77.16, respectively), acetone (δ 2.05 and 20.94, respectively), or methanol (δ 3.31 and 49.00, respectively). High resolution mass spectra were recorded on a time-of-flight (TOF) mass spectrometer.

General Procedure for Selenide Synthesis. A 1.0 M solution of LiHMDS in THF (2.2 equiv) was added dropwise to a -78 °C solution of lactam **118** in THF (0.072 M) and the solution was stirred at -78 °C for 1 h. The appropriate alkyl chloroformate (1.2 equiv) was added and the mixture was stirred at -78 °C for 1 h, after which a solution of PhSeBr (1.1 equiv) in THF (1.75 M) was added dropwise. The reaction mixture was stirred at -78 °C for 30 min and at rt for 1.5 h, diluted with satd NH_4Cl and extracted twice with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel to provide the selenide.



122

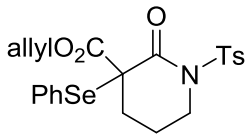
*Methyl 2-Oxo-3-(phenylselanyl)-1-tosylpiperidine-3-carboxylate (**122**).* Prepared by the general procedure using the following quantities: lactam **118** (1.816 g, 7.17 mmol), 1.0 M LiHMDS in THF (15.8 mL, 15.8 mmol), methyl chloroformate (0.66 mL, 812 mg, 8.60 mmol), and PhSeBr (1.861 g, 7.89 mmol). The product was purified by flash chromatography on silica gel (gradient 15% to 25% EtOAc in hexanes) to provide selenide **122** (1.378 g, 35%) as a pale yellow solid. IR (neat) 2952, 1729, 1688, 1351, 1167 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.3 Hz, 2H), 7.55 (d, *J* = 7.0 Hz, 2H), 7.46-7.25 (m, 5H), 3.96-3.75 (m, 2H), 3.65 (s, 3H), 2.48 (s, 3H), 2.31-2.20 (m, 1H), 2.03-1.89 (m, 2H), 1.86-1.71 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2, 167.3, 145.4, 138.8, 135.8, 130.4, 129.8, 129.4, 126.5, 55.9, 53.9, 46.5, 32.0, 22.2, 21.8; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{20}H_{22}NO_5SSe$ 468.0384; found 468.0360.



123

*Benzyl 2-Oxo-3-(phenylselanyl)-1-tosylpiperidine-3-carboxylate (**123**).* Prepared by the general procedure using the following quantities: lactam **118** (1.505 g, 5.94 mmol), 1.0 M LiHMDS in THF (13.0 mL, 13.0 mmol), benzyl chloroformate (1.02 mL, 1.220 g, 7.13 mmol), and PhSeBr (1.541 g, 6.53 mmol). The product was purified by flash chromatography on silica gel (20% EtOAc in hexanes) to provide selenide **123** (1.810 g, 56%) as white needles. IR (neat) 2980, 1727, 1692, 1352, 1168 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.2 Hz, 2H), 7.45 (d, *J* = 8.0 Hz, 2H), 7.41-7.17 (m, 10H), 5.10 (s, 2H), 3.85-3.70 (m, 2H), 2.40 (s, 3H), 2.28-2.15 (m, 1H),

2.02-1.83 (m, 2H), 1.77-1.61 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 166.6, 144.7, 138.2, 135.2, 134.8, 129.7, 129.2, 128.9, 128.7, 128.5, 128.4, 128.3, 128.1, 127.8, 125.7, 67.6, 55.5, 45.7, 31.2, 21.5, 21.0; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{26}H_{26}NO_5SSe$ 544.0697; found 544.0687.

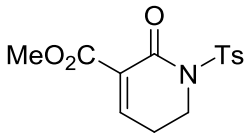


124

*Allyl 2-Oxo-3-(phenylselanyl)-1-tosylpiperidine-3-carboxylate (**124**).* Prepared by the general procedure using the following quantities: lactam **118** (16.08 g, 63.4 mmol), 1.0 M LiHMDS in THF (140 mL, 140 mmol), allyl chloroformate (8.0 mL, 9.072 g, 75.2 mmol), and PhSeBr (16.47 g, 69.8 mmol). The product was purified by flash chromatography on silica gel (gradient 20% to 25% EtOAc in hexanes) to provide selenide **124** (22.10 g, 71%) as pale yellow needles. IR (neat) 2956, 1728, 1699, 1353, 1170 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.2 Hz, 2H), 7.55 (d, *J* = 7.1 Hz, 2H), 7.44-7.23 (m, 5H), 5.71 (ddt, *J* = 5.5, 9.5, 15.2 Hz, 1H), 5.27 (d, *J* = 15.2 Hz, 1H), 5.16 (d, *J* = 9.5 Hz, 1H), 4.52 (d, *J* = 5.5 Hz, 2H), 3.92-3.79 (m, 2H), 2.45 (s, 3H), 2.22 (dt, *J* = 4.9, 13.4 Hz, 1H), 2.02-1.89 (m, 2H), 1.82-1.69 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 166.7, 144.9, 138.3, 135.3, 130.8, 129.8, 129.3, 128.8, 128.8, 125.9, 118.7, 66.6, 55.6, 46.0, 31.4, 21.6, 21.3; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{22}H_{24}NO_5SSe$ 494.0540; found 494.0535.

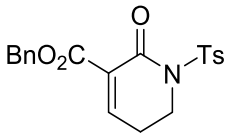
General Procedure for Formation of α,β-Unsaturated Lactams. The selenide was dissolved in CH_2Cl_2 (0.05 M) and the solution was cooled to 0 °C. Solid *m*-CPBA (73% purity, 2.0 equiv) was added and the reaction mixture was stirred at 0 °C for 1 h, and was diluted with satd $Na_2S_2O_3$. The organic layer was washed sequentially with satd $NaHCO_3$ and water, and dried

over Na_2SO_4. The solution was concentrated *in vacuo* to provide the crude Michael acceptor, which was used directly in the next step. For characterization purposes, a sample of the crude product was purified by flash chromatography on silica gel.



128

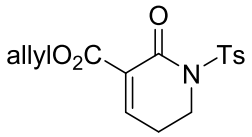
Methyl 2-Oxo-1-tosyl-1,2,5,6-tetrahydropyridine-3-carboxylate ***(128).*** Prepared by the general procedure using the following quantities: selenide **122** (981 mg, 2.10 mmol) and *m*-CPBA (73% purity, 1.04 g, 725 mg of *m*-CPBA, 4.20 mmol) provided crude Michael acceptor **128** (601 mg, 92%) as a yellow oil. A sample was purified by flash chromatography on silica gel (45% EtOAc in hexanes) to provide unsaturated lactam **128** as a colorless oil. IR (neat) 2952, 1740, 1687, 1346, 1164 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.2 Hz, 2H), 7.58 (t, *J* = 4.3 Hz, 1H), 7.30 (d, *J* = 8.2 Hz, 2H), 4.10 (t, *J* = 6.4 Hz, 2H), 3.76 (s, 3H), 2.65 (td, *J* = 4.4, 6.4 Hz, 2H), 2.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.8, 159.6, 151.1, 145.0, 135.8, 129.6, 129.2, 128.8, 52.7, 43.5, 25.6, 21.8; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{14}H_{16}NO_5S$ 310.0749; found 310.0742.



129

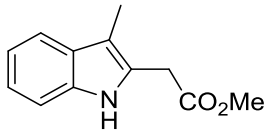
Benzyl 2-Oxo-1-tosyl-1,2,5,6-tetrahydropyridine-3-carboxylate ***(129).*** Prepared by the general procedure using the following quantities: selenide **123** (2.54 g, 4.68 mmol) and *m*-CPBA (73% purity, 2.21 g, 1.62 g of *m*-CPBA, 9.36 mmol) provided crude Michael acceptor **129** (1.78 g, 99%) as a yellow oil. A sample was purified by flash chromatography on silica gel (35% EtOAc

in hexanes) to provide unsaturated lactam **129** as a colorless oil. IR (neat) 2952, 1739, 1690, 1360, 1167 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.4 Hz, 2H), 7.56 (t, *J* = 4.4 Hz, 1H), 7.37-7.28 (m, 7H), 5.20 (s, 2H), 4.09 (t, *J* = 6.4 Hz, 2H), 2.64 (td, *J* = 4.4 Hz, 6.4 Hz, 2H), 2.42 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.7, 159.4, 150.8, 145.1, 135.8, 135.4, 129.6, 129.2, 128.8, 128.7, 128.5, 128.4, 67.3, 43.5, 25.6, 21.8; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{20}H_{20}NO_5S$ 386.1062; found 386.1048.



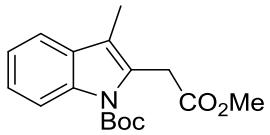
130

*Allyl 2-Oxo-1-tosyl-1,2,5,6-tetrahydropyridine-3-carboxylate (**130**).* Prepared by the general procedure using the following quantities: selenide **124** (13.17 g, 26.74 mmol) and *m*-CPBA (73% purity, 12.00 g, 9.23 g of *m*-CPBA, 53.5 mmol) provided crude Michael acceptor **130** (8.96 g, 100%) as a yellow oil. A sample was purified by flash chromatography on silica gel (30% EtOAc in hexanes) to provide unsaturated lactam **130** as a colorless oil. IR (neat) 2952, 1732, 1692, 1356, 1165 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.2 Hz, 2H), 7.60 (t, *J* = 4.3 Hz, 1H), 7.33 (d, *J* = 8.2 Hz, 2H), 5.92 (ddt, *J* = 5.7, 10.9, 17.4 Hz, 1H), 5.34 (d, *J* = 17.4 Hz, 1H), 5.25 (d, *J* = 10.9 Hz, 1H), 4.68 (d, *J* = 5.7 Hz, 2H), 4.12 (t, *J* = 6.4 Hz, 2H), 2.68 (td, *J* = 6.4, 4.3 Hz, 2H), 2.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.6, 159.4, 150.9, 145.1, 135.7, 131.5, 129.6, 129.2, 128.8, 119.0, 66.1, 43.4, 25.6, 21.7; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{18}NO_5S$ 336.0906; found 336.0893.



131

*Methyl 2-(3-Methyl-1H-indol-2-yl)acetate (**131**).*[38] Iron (II) sulfate heptahydrate (25.55 g, 91.9 mmol) was added to a solution of 3-methylindole (**45**, 24.11 g, 184 mmol) in DMSO (235 mL) and the suspension was submerged in a rt water bath. Solutions of methyl iodoacetate (36.76 g, 184 mmol) in DMSO (16 mL) and 30% H_2O_2 (22.5 mL, 7.50 g of H_2O_2, 221 mmol) were concurrently added dropwise via syringe pumps over 10 min. The mixture was stirred for 5 min at rt and was quenched by addition of 30% H_2O_2 (4.0 mL). Brine (400 mL) was added and the mixture was extracted with Et_2O (4 × 500 mL). The combined organic layers were washed with H_2O (3 × 500 mL) and brine (2 × 500 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (gradient 15% to 20% EtOAc in hexanes) to provide indole acetic ester **131** (9.41 g, 25%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 (br s, 1H), 7.61 (d, *J* = 7.8 Hz, 1H), 7.37 (d, *J* = 7.5 Hz, 1H), 7.29-7.16 (m, 2H), 3.85 (s, 2H), 3.82 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7, 136.1, 129.2, 126.7, 122.3, 119.7, 118.9, 111.1, 109.5, 52.8, 32.1, 8.9.

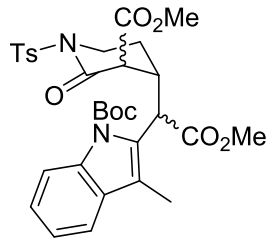


132

*tert-Butyl 2-(2-Methoxy-2-oxoethyl)-3-methyl-1H-indole-1-carboxylate (**132**).* Indole ester **131** (9.41 g, 46.3 mmol) was dissolved in CH_2Cl_2 (200 mL) and the solution was cooled to 0 °C. A solution of Boc_2O (10.61 g, 48.6 mmol) in CH_2Cl_2 (20 mL) was added, followed by DMAP (5.94 g, 48.6 mmol). The reaction mixture was stirred at 0 °C for 20 min and concentrated *in vacuo*.

The residue was purified by flash chromatography on silica gel (7.5% EtOAc in hexanes) to provide Boc-protected indole **132** (12.63 g, 90%) as a white solid. IR (neat) 2983, 2939, 1741, 1713, 1460, 1355, 1333, 1165 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.0 Hz, 1H), 7.53 (d, *J* = 7.6 Hz, 1H), 7.41-7.27 (m, 2H), 4.11 (s, 2H), 3.77 (s, 3H), 2.28 (s, 3H), 1.73 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 150.6, 135.7, 130.2, 128.6, 124.1, 122.4, 118.4, 116.4, 115.5, 83.8, 51.9, 32.9, 28.1, 8.6; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{17}H_{21}NO_4Na$ 326.1368; found 326.1335.

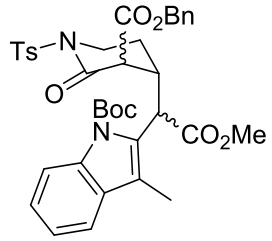
General Procedure for Michael Reactions. A solution of LiHMDS (1.0 M in THF, 1.32 equiv) was added dropwise to a -78 °C solution of indole ester **132** (1.2 equiv) in THF (0.08 M) and the reaction mixture was stirred at -78 °C for 1 h. A solution of the crude Michael acceptor (1.0 equiv) in THF (0.31 M) was added and the reaction mixture was stirred at -78 °C for 10 min. The reaction mixture was diluted with satd NH_4Cl and extracted twice with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel to provide the Michael adduct.



133

*tert-Butyl 2-(1-(3-((Methyloxy)carbonyl)-2-oxo-1-tosylpiperidin-4-yl)-2-methoxy-2-oxoethyl)-3-methyl-1H-indole-1-carboxylate (**133**).* Prepared by the general procedure using the following quantities: LiHMDS (1.0 M in THF, 0.46 mL, 0.46 mmol), indole ester **132** (127 mg, 0.418 mmol), and crude Michael acceptor **128** (107.7 mg, 0.348 mmol). The product was purified by flash chromatography on silica gel (gradient 20% to 25% EtOAc in hexanes) to provide Michael

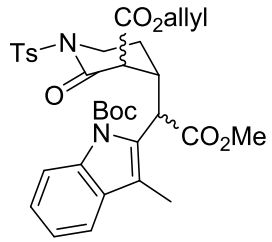
adduct **133** (121 mg, 57%) as a colorless oil (complex mixture of inseparable stereoisomers). IR (neat) 2951, 1724, 1455, 1356, 1168, 1134 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.05-7.80 (m, 3H), 7.57-7.18 (m, 5H), 4.71-3.83 (m, 2H), 3.80-3.35 (m, 7.3 H), 3.21-3.07 (m, 0.7H), 2.90 (s, 0.7H), 2.70-2.58 (m, 0.3H), 2.45 (s, 1.5H), 2.43 (s, 1.5H), 2.22 (s, 1.5H), 2.19 (s, 0.5H), 2.13 (s, 1H), 2.02-1.90 (m, 1H), 1.76-1.60 (m, 1H), 1.71 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 171.5, 171.3, 171.2, 169.2, 168.6, 167.6, 166.5, 166.1, 165.7, 165.4, 150.9, 150.7, 144.9, 144.9, 135.5, 135.4, 135.2, 135.1, 130.5, 130.1, 130.0, 129.9, 129.9, 129.4, 129.3, 129.3, 128.7, 128.6, 128.6, 124.8, 124.8, 124.7, 122.8, 122.8, 122.7, 119.1, 118.8, 188.6, 118.5, 118.4, 115.8, 84.7, 84.6, 84.6, 56.8, 54.3, 52.9, 52.7, 52.2, 52.1, 52.0, 46.4, 46.0, 45.5, 44.8, 44.6, 43.5, 37.0, 36.5, 36.4, 28.2, 28.1, 28.0, 25.8, 25.4, 23.2, 21.6, 21.6, 9.3, 9.2, 9.0; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{31}H_{37}N_2O_9S$ 613.2220; found 612.2227.



134

*tert-Butyl 2-(1-(3-((Benzyloxy)carbonyl)-2-oxo-1-tosylpiperidin-4-yl)-2-methoxy-2-oxoethyl)-3-methyl-1H-indole-1-carboxylate (**134**).* Prepared by the general procedure using the following quantities: LiHMDS (1.0 M in THF, 0.81 mL, 0.81 mmol), indole ester **132** (244 mg, 0.805 mmol), and crude Michael acceptor **129** (259 mg, 0.671 mmol). The product was purified by flash chromatography on silica gel (gradient 20% to 25% EtOAc in hexanes) to provide Michael adduct **134** (316 mg, 68%) as a colorless oil (complex mixture of inseparable stereoisomers). IR (neat) 2975, 1725, 1358, 1327, 1162 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.08-7.71 (m, 3H), 7.59-6.80 (m, 10H), 5.32-5.06 (m, 1H), 4.98-4.50 (m, 1H), 4.30-3.72 (m, 3H), 3.69-3.52 (m, 3H), 3.51-

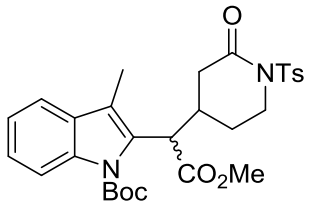
3.37 (m, 0.5 H), 3.15-2.88 (m, 0.5 H), 2.68-2.33 (m, 4H), 2.25-2.06 (m, 3H), 2.01-1.86 (m, 1H), 1.76-1.45 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 171.3, 168.6, 168.3, 166.4, 166.0, 165.8, 151.0, 150.8, 144.9, 135.6, 135.4, 135.3, 134.9, 131.0, 130.2, 130.0, 129.9, 129.7, 129.4, 129.4, 128.7, 128.6, 128.5, 128.1, 127.9, 127.8, 127.7, 127.1, 124.9, 124.8, 124.7, 122.9, 119.4, 118.8, 118.7, 118.5, 118.3, 116.1, 115.8, 84.8, 84.7, 68.0, 67.4, 67.1, 66.3, 66.0, 60.4, 57.1, 54.4, 52.2, 52.2, 46.1, 45.5, 44.7, 44.5, 42.7, 36.9, 36.6, 33.5, 29.0, 28.2, 25.9, 22.0, 21.7, 21.5, 10.4, 9.3, 9.0, 8.8; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{37}H_{41}N_2O_9S$ 689.2533; found 689.2509.



135

*tert-Butyl 2-(1-(3-((Allyloxy)carbonyl)-2-oxo-1-tosylpiperidin-4-yl)-2-methoxy-2-oxoethyl)-3-methyl-1H-indole-1-carboxylate (**135**).* Prepared by the general procedure using the following quantities: LiHMDS (1.0 M in THF, 35.5 mL, 35.5 mmol), indole ester **132** (9.73 g, 32.1 mmol), and crude Michael acceptor **130** (8.96 g, 26.74 mmol). The product was purified by flash chromatography on silica gel (gradient 20% to 30% EtOAc in hexanes) to provide Michael adduct **135** (11.80 g, 69%) as a white foam (complex mixture of inseparable stereoisomers). IR (neat) 2976, 2939, 1725, 1452, 1357, 1162, 1131 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02-7.80 (m, 3H), 7.52 (d, *J* = 7.4 Hz, 0.5H), 7.45 (d, *J* = 7.5 Hz, 0.5H), 7.41-7.18 (m, 4H), 5.90-5.67 (m, 0.4H), 5.34-5.10 (m, 1H), 4.95-4.81 (m, 0.6H), 4.75-4.35 (m, 2H), 4.33-3.10 (m, 8H), 2.50-2.40 (m, 3H), 2.32-1.90 (m, 4H), 1.75-1.58 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4, 168.5, 168.1, 166.5, 166.0, 165.7, 151.0, 150.8, 145.0, 135.6, 135.3, 131.4, 131.1, 130.2, 130.1, 129.9, 129.5, 129.4, 129.4, 128.8, 128.7, 124.9, 124.9, 124.8, 122.8, 119.3, 118.9, 118.8, 118.4, 118.3, 116.0,

115.9, 84.8, 84.7, 66.3, 66.1, 54.4, 52.3, 52.2, 46.1, 45.6, 44.8, 44.6, 36.9, 36.6, 36.5, 28.3, 28.2, 25.9, 21.8, 9.4, 9.1; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{33}H_{39}N_2O_9S$ 639.2376; found 639.2366.

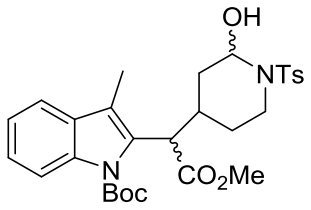


136

*tert-Butyl 2-(2-Methoxy-2-oxo-1-(2-oxo-1-tosylpiperidin-4-yl)ethyl)-3-methyl-1H-indole-1-carboxylate (**136**).* Benzyl ester **134** (225.8 mg, 0.328 mmol) was dissolved in EtOAc (7.3 mL) and 10% Pd/C (44 mg) was added. The atmosphere was evacuated and backfilled with H_2 and the mixture was stirred under H_2 (1 atm) for 1 h. The mixture was diluted with EtOAc (20 mL) and filtered through a pad of Celite. The filtrate was concentrated *in vacuo* and the residue was dissolved in toluene (10 mL) and heated at 70 °C for 2 h. The solution was concentrated *in vacuo* and the residue was purified by flash chromatography on silica gel (gradient 20% to 25% EtOAc in hexanes) to provide lactam **136** (1.4:1 mixture of inseparable stereoisomers, 158.8 mg, 87%) as a white foam. For characterization purposes, the two isomers were separated by flash chromatography on silica gel (20% EtOAc in hexanes).

Less polar isomer (minor): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97-7.89 (m, 3H), 7.46 (d, *J* = 6.3 Hz, 1H), 7.36-7.22 (m, 4H), 4.39-4.22 (m, 2H), 3.77 (td, *J* = 3.8, 11.9 Hz, 1H), 3.63 (s, 3H), 3.00-2.78 (m, 2H), 2.49-2.40 (m, 4H), 2.19 (s, 3H), 2.03 (d, *J* = 5.9 Hz, 1H), 1.68 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 169.8, 151.0, 144.9, 135.9, 135.2, 130.6, 130.1, 129.4, 128.9, 128.9, 124.8, 122.9, 118.8, 117.9, 115.9, 84.7, 52.1, 46.6, 46.3, 38.3, 33.6, 30.2, 28.3, 21.8, 9.3; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{29}H_{35}N_2O_7S$ 555.2165; found 555.2147.

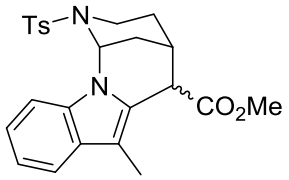
More polar isomer (major): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, *J* = 7.8 Hz, 2H), 7.93 (d, *J* = 8.2 Hz, 1H), 7.53 (d, *J* = 7.0 Hz, 1H), 7.40-7.25 (m, 4H), 4.29 (br s, 1H), 4.20-4.08 (m, 1H), 3.63 (s, 3H), 3.49 (td, *J* = 3.8, 12.1 Hz, 1H), 3.25 (dd, *J* = 3.5, 17.6 Hz, 1H), 3.00-2.85 (m, 1H), 2.47 (s, 3H), 2.42-2.29 (m, 2H), 2.23 (s, 3H), 1.71 (s, 9H), 1.53-1.40 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 169.5, 150.9, 144.9, 135.9, 135.2, 130.9, 130.2, 129.4, 128.8, 124.7, 122.9, 118.8, 117.9, 115.9, 84.7, 52.2, 47.5, 46.0, 41.0, 34.0, 28.3, 27.3, 21.8, 9.4; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{29}H_{35}N_2O_7S$ 555.2165; found 555.2153.



137

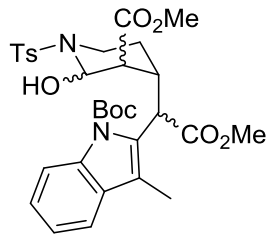
*tert-Butyl 2-(1-(2-Hydroxy-1-tosylpiperidin-4-yl)-2-methoxy-3-oxoethyl)-3-methyl-1H-indole-1-carboxylate (**137**).* Lactam **136** (98.0 mg, 0.177 mmol) was dissolved in CH_2Cl_2 (9.0 mL) and the solution was cooled to -78 °C. A solution of DIBALH in PhMe (1.0 M, 0.35 mL, 0.35 mmol) was added dropwise and the mixture was stirred at -78 °C for 1 h. The reaction mixture was quenched by sequential addition of H_2O (0.02 mL), 15% NaOH (0.02 mL) and H_2O (0.04 mL). The mixture was warmed to rt and stirred for 30 min, after which $MgSO_4$ was added and the suspension was filtered through a Celite pad. The filtrate was washed with a saturated aqueous solution of Rochelle's salt (20 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (25% EtOAc in hexanes) to provide hemiaminal **137** (53.4 mg, 54%) as a colorless oil (complex mixture of inseparable diastereomers). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99-7.91 (m, 1H), 7.71 (d, *J* = 8.2 Hz, 1H), 7.63 (d, *J* = 8.2 Hz, 1H), 7.46 (t, *J* = 6.1 Hz, 1H), 7.33-7.20 (m, 3H), 6.67 (d, *J* = 8.4 Hz, 1H), 5.68 (br s, 0.4H), 5.49

(br d, *J* = 6.8 Hz, 0.6H), 4.33-4.06 (m, 1.4H), 3.59 (s, 3H), 3.52-3.35 (m, 1.6H), 3.22-2.82 (m, 2.4H), 2.57 (br d, *J* = 12.5 Hz, 0.6H), 2.46-2.37 (m, 3H), 2.18 (s, 1.5H), 2.10-2.02 (m, 2.5H), 1.70-1.57 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1, 150.7, 143.7, 135.3, 134.8, 131.4, 130.3, 129.8, 127.5, 127.2, 124.7, 124.5, 122.7, 118.7, 117.5, 115.8, 84.4, 77.4, 52.0, 47.3, 42.7, 32.5, 28.3, 28.2, 25.1, 21.7, 9.3.



139
(1.5:1 dr)

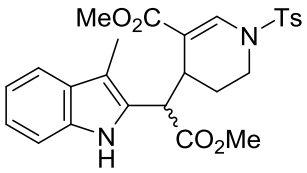
*Methyl 7-Methyl-2-tosyl-1,2,3,4,5,6-hexahydro-1,5-methano[1,3]diazocino[1,8-a]indole-6-carboxylate (**139**).* Hemiaminal **137** (39.6 mg, 0.0711 mmol) was dissolved in CH_2Cl_2 (0.36 mL) and TFA (0.36 mL) was added. The reaction mixture was stirred at rt for 10 min and carefully diluted with satd $NaHCO_3$ (20 mL). The mixture was extracted with CH_2Cl_2 (2 × 20 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (20% EtOAc in hexanes) to provide bridged aminal **139** (22.1 mg, 71%) as a white foam (1.5:1 mixture of inseparable C16 epimers). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69-7.62 (m, 2H), 7.53-7.46 (m, 2H), 7.25-7.12 (m, 4H), 6.51 (s, 0.4H), 6.48 (s, 0.6H), 4.27 (d, *J* = 6.7 Hz, 0.4H), 3.98 (s, 0.6H), 3.78 (s, 1H), 3.68 (s, 2H), 3.42-3.33 (m, 1H), 3.01 (td, *J* = 3.0, 14.0 Hz, 0.4H), 2.78-2.74 (m, 0.4H), 2.67-2.64 (m, 0.6H), 2.58-2.46 (m, 1.4H), 2.40-2.36 (m, 3H), 2.29 (dt, *J* = 3.3, 13.1 Hz, 0.6H), 2.19 (s, 1.8H), 2.12-2.06 (m, 2.2H), 1.96-1.77 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.6, 172.1, 143.6, 137.7, 135.1, 134.5, 129.9, 129.3, 128.9, 127.9, 127.3, 127.3, 122.2, 122.0, 120.2, 118.3, 118.3, 110.7, 110.0, 109.2, 108.6, 59.8, 59.2, 52.5, 52.4, 44.1, 43.8, 38.5, 38.4, 32.8, 30.5, 29.8, 29.2, 28.2, 27.6, 27.5, 21.6, 9.1, 8.6.



140

*tert-Butyl 2-(1-(2-Hydroxy-3-(methoxycarbonyl)-tosylpiperidin-4-yl)-2-methoxy-2-oxoethyl)-3-methyl-1H-indole-1-carboxylate (**140**).* A 1.0 M solution of DIBALH in PhMe (0.40 mL, 0.40 mmol) was added dropwise to a -78 °C solution of *N*-sulfonyllactam **133** (81.9 mg, 0.134 mmol) in CH_2Cl_2 (13 mL). The reaction mixture was stirred at -78 °C for 1 h, and was quenched by sequential addition of H_2O (0.02 mL), 15% NaOH (0.02 mL), and H_2O (0.04 mL). The mixture was warmed to rt and stirred for 30 min, after which $MgSO_4$ was added and the suspension was filtered through a Celite pad. The filtrate was washed with a saturated aqueous solution of Rochelle's salt (20 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (25% EtOAc in hexanes) to provide hemiaminal **140** (53.8 mg, 65%) as a colorless oil (complex mixture of inseparable stereoisomers). IR (neat) 3485, 2950, 1724, 1454, 1325, 1227, 1158, 1133 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.07-7.90 (m, 1H), 7.78 (d, *J* = 7.9 Hz, 1H), 7.72 (d, *J* = 7.3 Hz, 1H), 7.57-7.47 (m, 1H), 7.38-7.23 (m, 4H), 5.97 (s, 0.6H), 5.85 (s, 0.4H), 4.80 (d, *J* = 8.5 Hz, 0.5H), 4.20-4.08 (m, 0.5H), 3.75 (s, 1H), 3.64-3.38 (m, 7H), 3.27-2.92 (m, 2H), 2.84 (s, 0.5H), 2.62 (d, *J* = 11.4 Hz, 0.5H), 2.43 (s, 3H), 2.37-2.20 (m, 3H), 1.98-1.83 (m, 1H), 1.68 (s, 9H), 1.51-1.42 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4, 172.6, 172.2, 171.1, 150.7, 143.7, 143.6, 136.5, 136.1, 135.5, 131.8, 131.0, 130.3, 130.1, 129.7, 129.5, 128.1, 127.6, 127.5, 124.6, 124.3, 122.8, 122.6, 118.7, 115.9, 84.5, 84.4, 78.1, 77.4, 52.7, 52.5,

52.1, 51.8, 51.7, 47.8, 44.9, 43.5, 39.8, 32.7, 32.2, 28.7, 28.3, 28.2, 25.1, 21.6, 9.3; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{31}H_{38}N_2O_9SNa$ 637.2196; found 637.2174.



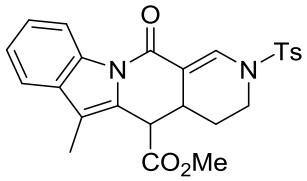
143
(1.5:1 dr)

*Methyl 4-(2-Methoxy-1-(3-methyl-1H-indol-2-yl)-2-oxoethyl)-1-tosyl-1,4,5,6-tetrahydropyridine-3-carboxylate (**143**).* Hemiaminal **140** (202 mg, 0.329 mmol) was dissolved in CH_2Cl_2 (3.0 mL) and TFA (3.0 mL) was added. The solution was stirred at rt for 10 min and carefully diluted with satd $NaHCO_3$ (100 mL). The mixture was extracted with CH_2Cl_2 (2 × 50 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (30 % EtOAc in hexanes) to provide vinylogous carbamate **143** (120.4 mg, 74%) as a white foam (1.5:1 mixture of diastereomers). For characterization purposes, the two isomers were separated by flash chromatography on silica gel (50% Et_2O in hexanes).

Less polar isomer (major): white powder, IR (neat) 3404, 2951, 1728, 1712, 1622, 1459, 1356, 1269, 1166, 1107 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.66 (s, 1H), 7.88 (s, 1H), 7.71 (d, *J* = 8.2 Hz, 2H), 7.41 (d, *J* = 7.9 Hz, 1H), 7.35 (d, *J* = 8.1 Hz, 2H), 7.27 (d, *J* = 8.1 Hz, 1H), 7.12 (t, *J* = 8.0 Hz, 1H), 7.04 (t, *J* = 7.1 Hz, 1H), 3.92-3.88 (m, 1H), 3.80-3.77 (m, 1H), 3.63 (s, 3H), 3.40-3.35 (m, 1H), 3.18 (td, *J* = 3.4, 12.9 Hz, 1H), 3.11 (s, 3H), 2.46 (s, 3H), 1.96 (s, 3H), 1.88-1.82 (m, 1H), 1.71-1.63 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.0, 166.6, 145.0, 135.8, 135.3, 134.4, 130.3, 129.6, 128.4, 127.8, 127.3, 122.1, 119.2, 118.6, 110.8, 109.3, 52.4, 51.5, 46.6, 39.3, 33.8,

23.9, 21.8, 8.5; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{26}H_{29}N_2O_6S$ 497.1746; found 497.1734.

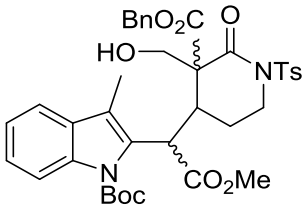
More polar isomer (minor): white powder, IR (neat) 3391, 2950, 1730, 1704, 1622, 1439, 1352, 1273, 1165, 1097 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.80 (s, 1H), 8.06 (s, 1H), 5.49 (d, *J* = 8.1 Hz, 2H), 7.35-7.29 (m, 2H), 7.18 (d, *J* = 8.1 Hz, 2H), 7.14 (t, *J* = 7.4 Hz, 1H), 7.06 (t, *J* = 7.5 Hz, 1H), 3.90 (d, *J* = 6.7 Hz, 1H), 3.81 (s, 3H), 3.67 (s, 3H), 3.56 (br d, *J* = 11.6 Hz, 1H), 3.30 (t, *J* = 5.8 Hz, 1H), 2.43 (s, 3H), 1.91 (s, 3H), 1.85 (d, *J* = 14.2 Hz, 1H), 1.54-1.46 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.2, 167.4, 144.8, 136.7, 136.0, 134.1, 130.2 128.5, 128.0, 127.0, 122.3, 119.2, 118.7, 111.0, 110.4, 108.8, 52.5, 51.8, 46.0, 39.3, 33.6, 23.2, 21.8, 8.8; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{26}H_{29}N_2O_6S$ 497.1746; found 497.1763.



147

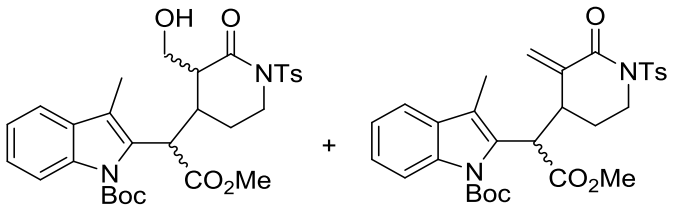
*Methyl 6-Methyl-12-oxo-2-tosyl-2,3,4,4a,5,12-hexahydroindolo[1,2-b][2,7]naphthyridine-5-carboxylate (**147**).* Vinylogous carbamate **143** (34.9 mg, 0.0751 mmol) was dissolved in MeCN (7.5 mL) and K_2CO_3 (260 mg, 1.88 mmol) was added. The suspension was refluxed for 6 h, cooled to rt and filtered through a Celite pad. The filtrate was concentrated *in vacuo* and the residue was purified by flash chromatography on silica gel (25% EtOAc in hexanes) to provide indole lactam **147** (22.1 mg, 68%) as a white solid. IR (neat) 2951, 1735, 1683, 1610, 1455, 1367, 1348, 1166 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.51 (d, *J* = 8.1 Hz, 1H), 8.29 (s, 1H), 7.74 (d, *J* = 8.1 Hz, 2H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.39-7.32 (m, 3H), 7.30-7.26 (m, 1H), 4.18 (d, *J* = 5.8 Hz, 1H), 4.02 (dt, *J* = 3.3, 12.3 Hz, 1H), 3.53 (s, 3H), 3.07 (td, *J* = 2.5, 12.3 Hz, 1H), 2.95 (dtd, *J* = 1.9, 5.4, 11.5 Hz, 1H), 2.43 (s, 3H), 2.22 (s, 3H), 2.20-2.13 (m, 1H), 1.65-1.59

(m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.5, 161.6, 144.9, 136.0, 135.3, 134.6, 130.5, 130.3, 128.1, 127.4, 125.2, 123.7, 118.6, 116.5, 114.6, 108.9, 52.4, 43.2, 42.0, 32.4, 25.2, 21.8, 8.5; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{25}H_{25}N_2O_5S$ 465.1484; found 465.1481.



148

*tert-Butyl 2-(1-(3-((Benzyloxy)carbonyl)-3-(hydroxymethyl)-2-oxo-1-tosylpiperidin-4-yl)-2-methoxy-2-oxoethyl)-3-methyl-1H-indole-1-carboxylate (**148**).* Michael adduct **134** (606 mg, 0.88 mmol) was dissolved in a mixture of dioxane (8.8 mL) and 37% aqueous formaldehyde (5.6 mL, 2.26 g of HCHO, 75 mmol), and Et_3N (0.74 mL, 534 mg, 5.28 mmol) was added. The solution was stirred at rt for 16 h, and was diluted with satd NH_4Cl (50 mL). The mixture was extracted with EtOAc (2 × 50 mL) and the combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (gradient 30% to 35% EtOAc in hexanes) to provide aldol adduct **148** (423 mg, 67%) as a white foam (complex mixture of inseparable stereoisomers). IR (neat) 3514, 2977, 1723, 1455, 1357, 1328, 1164 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15-7.73 (m, 4H), 7.59-7.08 (m, 9H), 5.26-4.97 (m, 2H), 4.60-4.51 (m, 1H), 4.39-4.30 (m, 1H), 4.15-3.98 (m, 2H), 3.70-3.53 (m, 4H), 2.47-2.32 (m, 4H), 2.25-2.06 (m, 3H), 1.76-1.48 (m, 11H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 169.8, 168.5, 151.0, 144.6, 135.8, 134.7, 134.6, 130.4, 130.1, 129.8, 129.2, 128.6, 128.5, 128.4, 127.4, 127.1, 124.9, 122.9, 119.0, 118.7, 115.7, 84.8, 67.6, 66.2, 66.0, 63.7, 62.9, 52.8, 45.8, 42.7, 37.0, 28.3, 28.1, 23.8, 22.0, 21.7, 21.5, 8.9; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{38}H_{43}N_2O_{10}S$ 719.2638; found 719.2627.



149 **150**

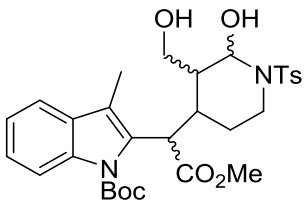
*tert-Butyl 2-(1-(3-(Hydroxymethyl)-2-oxo-1-tosylpiperidin-4-yl)-2-methoxy-2-oxoethyl)-3-methyl-1H-indole-1-carboxylate (**149**) and tert-Butyl 2-(2-Methoxy-1-(3-methylene-2-oxo-1-tosylpiperidin-4-yl)-2-oxoethyl)-3-methyl-1H-indole-1-carboxylate (**150**).* Benzyl ester **148** (335.6 mg, 0.467 mmol) was dissolved in EtOAc (9.5 mL) and 10% Pd/C (56 mg) was added. The atmosphere was evacuated and backfilled with H_2 from a balloon and the reaction mixture was vigorously stirred under H_2 (1 atm) for 2 h. The mixture was diluted with EtOAc (30 mL), filtered through a Celite pad, and the filtrate was concentrated *in vacuo*. The residue was dissolved in toluene (10 mL) and heated at 70 °C for 2 h. The solution was concentrated *in vacuo* and the residue was purified by flash chromatography on silica gel (gradient 20% to 35% EtOAc in hexanes) to provide a mixture of two alcohols **149** (118.2 mg, 43%) and α-methylene lactam **159** (67.1 mg, 25%, inseparable mixture of stereoisomers) as white foams. For characterization purposes, a sample of the two isomers of alcohol **149** was separated by flash chromatography on silica gel (30% EtOAc in hexanes).

Less polar isomer **149**: IR (neat) 3523, 2933, 1723, 1454, 1355, 1327, 1163, 1132 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.2 Hz, 1H), 7.86 (d, *J* = 7.5 Hz, 2H), 7.49 (d, *J* = 7.4 Hz, 1H), 7.35-7.27 (m, 4H), 4.20-3.94 (m, 3H), 3.57 (s, 3H), 3.49-3.15 (m, 3H), 2.52 (t, *J* = 5.6 Hz, 1H), 2.45 (s, 3H), 2.16 (s, 3H), 1.73-1.62 (m, 1H), 1.68 (s, 9H), 1.48 (br d, *J* = 12.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.8, 172.3, 151.0, 144.9, 136.0, 135.2, 131.3, 130.3, 129.5, 128.8,

124.8, 122.9, 119.0, 115.9, 84.7, 61.6, 52.4, 49.4, 45.9, 43.6, 35.6, 28.3, 25.8, 25.8, 21.8, 9.0; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{30}H_{37}N_2O_8S$ 585.2271; found 585.2245.

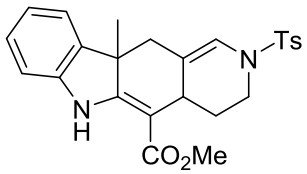
More polar isomer **149**: IR (neat) 3519, 2975, 1722, 1455, 1355, 1328, 1165, 1134 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.3 Hz, 1H), 7.88 (d, *J* = 8.3 Hz, 2H), 7.50 (d, *J* = 7.2 Hz, 1H), 7.36-7.27 (m, 4H), 4.06 (ddd, *J* = 3.5, 9.0, 11.6 Hz, 1H), 3.98 (dt, *J* = 4.8, 12.3 Hz, 1H), 3.82 (dt, *J* = 4.4, 11.4 Hz, 1H), 3.66-3.59 (m, 1H), 3.60 (s, 3H), 3.19-3.01 (m, 2H), 2.51 (ddd, *J* = 4.0, 5.0, 8.3 Hz, 1H), 2.43 (s, 3H), 2.20 (s, 3H), 1.86-1.78 (m, 1H), 1.72-1.64 (m, 1H), 1.68 (s, 9H), 1.36 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.0, 171.9, 151.1, 145.0, 136.0, 135.2, 130.7, 130.1, 129.5, 128.7, 124.9, 123.0, 119.0, 118.2, 115.9, 84.9, 62.2, 53.4, 52.6, 46.5, 45.2, 34.7, 28.3, 26.6, 21.8, 9.5; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{30}H_{37}N_2O_8S$ 585.2271; found 585.2281.

Methylene lactam **150:** IR (neat) 2929, 1723, 1689, 1453, 1354, 1165, 1134 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.00-7.92 (m, 3H), 7.50 (d, *J* = 7.5 Hz, 1H), 7.36-7.27 (m, 4H), 6.43 (s, 1H), 5.71 (s, 1H), 3.96 (ddd, *J* = 4.3, 8.4, 12.4 Hz, 1H), 3.83-3.71 (m, 2H), 3.56 (s, 3H), 2.47-2.42 (m, 1H), 2.44 (s, 3H), 2.25 (s, 3H), 1.96-1.90 (m, 1H), 1.74-1.68 (m, 1H), 1.71 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4, 163.8, 150.9, 144.8, 136.3, 135.4, 130.4, 130.2, 129.4, 128.9, 127.9, 124.9, 122.9, 118.8, 118.4, 115.9, 84.9, 52.3, 49.3, 44.5, 38.2, 34.1, 29.8, 28.3, 26.1, 25.7, 25.1, 21.8, 9.4; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{30}H_{35}N_2O_7S$ 567.2151; found 567.2165.



151

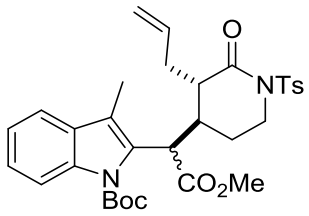
*tert-Butyl 2-(1-(2-Hydroxy-3-(hydroxymethyl)-1-tosylpiperidin-4-yl)-2-methoxy-2-oxoethyl)-3-methyl-1H-indole-1-carboxylate (**151**).* A 1.0 M solution of DIBALH in PhMe (1.05 mL, 1.05 mmol) was added dropwise to a -78 °C solution of lactams **149** (77.4 mg, 0.132 mmol) in CH_2Cl_2 (6.5 mL). The reaction mixture was stirred at -78 °C for 1 h, and was quenched by dropwise addition of a saturated aqueous solution of Rochelle's salt (50 mL). The organic layer was dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (gradient 40% to 50% EtOAc in hexanes) to provide hemiaminal **151** (31.7 mg, 41%) as a colorless oil (complex mixture of inseparable stereoisomers). IR (neat) 3509, 2931, 1725, 1456, 1328, 1161 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.2 Hz, 1H), 7.76-7.69 (m, 2.4H), 7.60 (d, *J* = 8.2 Hz, 0.6H), 7.46 (d, *J* = 7.7 Hz, 1H), 7.32-7.22 (m, 3H), 5.67 (s, 1H), 3.94 (dd, *J* = 5.5, 11.3 Hz, 1H), 3.77 (dd, *J* = 7.1, 11.1 Hz, 1H), 3.61-3.54 (m, 4H), 3.51-3.44 (m, 2H), 3.00 (td, *J* = 3.1, 12.6 Hz, 1H), 2.47-2.35 (m, 6H), 2.21 (s, 3H), 1.89 (br s, 1H), 1.68-1.62 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4, 150.8, 143.8, 136.7, 135.4, 131.9, 130.3, 129.9, 127.4, 127.2, 124.7, 124.4, 122.9, 122.7, 118.8, 118.6, 115.9, 84.7, 84.5, 78.7, 64.4, 60.3, 52.7, 52.0, 44.2, 43.1, 40.9, 40.0, 32.5, 30.7, 29.8, 28.3, 28.2, 24.8, 21.7, 9.2, 8.9; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{30}H_{38}N_2O_8SNa$ 609.2247; found 609.2254.



154

*Methyl 10b-Methyl-2-tosyl-3,4,4a,6,10b,11-hexahydro-2H-pyrido[4,3-b]carbazole-5-carboxylate (**154**).* Trifluoroacetic acid (0.32 mL) was added to a solution of hemiaminal **151** (19.0 mg, 32.4 μmol) in CH_2Cl_2 (0.32 mL) and the mixture was stirred at rt for 10 min. The reaction

mixture was diluted with CH_2Cl_2 (40 mL) and washed with satd $NaHCO_3$ (40 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by preparative thin-layer chromatography on silica gel (20% EtOAc in hexanes) to provide fused tetracycle **154** (13.3 mg, 91%) as a white powder. IR (neat) 3357, 2924, 1674, 1604, 1466, 1356, 1165 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.28 (br s, 1H), 7.73 (d, *J* = 8.1 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 7.20-7.13 (m, 2H), 6.93 (t, *J* = 7.5 Hz, 1H), 6.83 (d, *J* = 7.7 Hz, 1H), 6.70 (s, 1H), 4.01 (dt, *J* = 2.8, 12.1 Hz, 1H), 3.74 (s, 3H), 3.20-3.09 (m, 2H), 2.50 (d, *J* = 12.6 Hz, 1H), 2.49-2.45 (m, 1H), 2.44 (s, 3H), 2.36 (d, *J* = 12.6 Hz, 1H), 1.24-1.17 (m, 1H), 1.17 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.3, 167.0, 143.8, 143.5, 136.5, 134.9, 130.1, 129.9, 128.2, 127.2, 122.1, 121.1, 116.4, 109.5, 93.1, 51.1, 47.6, 45.0, 38.1, 33.1, 28.8, 28.7, 21.7; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{25}H_{27}N_2O_4S$ 451.1692; found 451.1676.



157

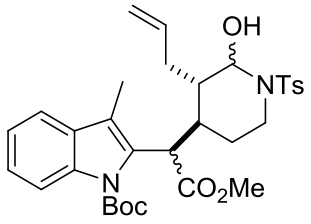
tert-Butyl 2-((R/S*)-1-((3R*,4S*)-3-Allyl-2-oxo-1-tosylpiperidin-4-yl)-2-methoxy-2-oxoethyl)-3-methyl-1H-indole-1-carboxylate* ***(157).*** Method A: A solution of vinylmagnesium bromide (1.0 M in THF, 0.74 mL, 0.74 mmol) was added dropwise to a suspension of CuI (70.0 mg, 0.368 mmol) in THF (2.3 mL) at -78 °C. The mixture was stirred at -78 °C for 10 min and warmed to -15 °C for 5 min, after which it was cooled back to -78 °C and a solution of methylene lactam **150** (40.6 mg, 0.074 mmol) in THF (3.2 mL) was added. The reaction mixture was stirred at -78 °C for 20 min and diluted with satd NH_4Cl (20 mL). The mixture was extracted with EtOAc (2 × 30 mL) and the combined organic layers were washed with brine (30 mL) and dried over

Na_2SO_4. The solution was concentrated *in vacuo* and the residue was purified by flash chromatography on silica gel (20% EtOAc in hexanes) to provide *N*-sulfonyllactam **157** (35.6 mg, 81%) as a white solid. IR (neat) 2976, 2947, 1723, 1452, 1354, 1326, 1163 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.02-7.89 (m, 3H), 7.51 (d, *J* = 6.7 Hz, 1H), 7.39-7.25 (m, 4H), 5.83-5.63 (m, 1H), 5.03 (d, *J* = 10.7 Hz, 1H), 5.02 (d, *J* = 16.3 Hz, 1H), 3.92-3.67 (m, 2H), 3.65-3.52 (m, 4H), 3.10-2.97 (m, 1H), 2.82-2.70 (m, 1H), 2.68-2.49 (m, 2H), 2.46 (s, 3H), 2.21 (s, 3H), 1.75-1.59 (m, 11H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5, 171.7, 150.9, 144.8, 136.2, 135.4, 134.5, 130.7, 130.2, 129.3, 128.8, 124.8, 122.9, 118.8, 118.1, 115.8, 84.7, 52.2, 48.8, 45.7, 44.2, 37.4, 36.0, 28.3, 24.3, 21.8, 9.5; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{32}H_{39}N_2O_7S$ 595.2478; found 595.2456.

Method B: K_2CO_3 (8.97 g, 64.8 mmol) and allyl iodide (3.0 mL, 5.44 g, 32.4 mmol) were added to a solution of Michael adduct **135** (10.35 g, 16.2 mmol) in MeCN (162 mL) and the mixture was heated at reflux for 8 h. Additional allyl iodide (1.5 mL, 2.72 g, 16.2 mmol) was added and the mixture was refluxed for an additional 4 h. The reaction mixture was cooled to rt and morpholine (5.6 mL, 5.65 g, 48.6 mmol) was added, followed by $Pd(PPh_3)_4$ (374 mg, 0.32 mmol) and the mixture was stirred at rt for 30 min. The suspension was filtered through a coarse frit and the filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (20% EtOAc in hexanes) to provide *N*-sulfonyllactam **157** (7.09 g, 74%) as an off-white solid (inseparable mixture of stereoisomers). Material prepared by this procedure had spectroscopic data identical to that prepared by Method A.

Method C: Allyl ester **135** (200.0 mg, 0.313 mmol) was dissolved in PhMe (10.5 mL) and $Pd(PPh_3)_4$ (36.0 mg, 0.031 mmol) was added. The mixture was refluxed for 1 h and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (gradient 15% to 20%

EtOAc in hexanes) to provide allyl lactam **157** (96.7 mg, 52%). Material prepared by this procedure had spectroscopic data identical to that prepared by Method A.



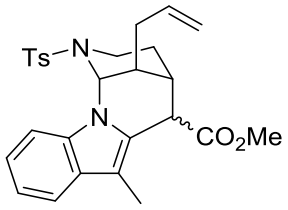
160

tert-Butyl 2-((R/S*)-1-((2R*/S*,3R*,4S*)-3-Allyl-2-hydroxy-1-tosylpiperidin-4-yl)-2-methoxy-2-oxoethyl)-3-methyl-1H-indole-1-carboxylate (**160**).* A 1.0 M solution of DIBALH in PhMe (13.0 mL, 13.0 mmol) was added dropwise to a -78 °C solution of *N*-sulfonyllactam **157** (3.88 g, 6.52 mmol) in CH_2Cl_2 (325 mL). The reaction mixture was stirred at -78 °C for 1 h, and was quenched by sequential dropwise addition of H_2O (0.52 mL), 15% NaOH (0.52 mL), and H_2O (1.3 mL). The mixture was warmed to rt and stirred for 30 min, after which $MgSO_4$ was added and the suspension was filtered through a Celite pad. The filtrate was washed with a saturated aqueous solution of Rochelle's salt (100 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (gradient 20% to 25% EtOAc in hexanes) to provide hemiaminal **160** (3.05 g, 78%) as a colorless oil (1:1.1 mixture of stereoisomers). For characterization purposes, the two isomers were separated by flash chromatography on silica gel (35% Et_2O in hexanes).

Less polar isomer (major): IR (neat) 3507, 2976, 2946, 1723, 1453, 1327, 1156 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, *J* = 7.6 Hz, 1H), 7.71 (d, *J* = 8.1 Hz, 2H), 7.50 (d, *J* = 7.6 Hz, 1H), 7.39-7.18 (m, 4H), 5.88 (ddt, *J* = 6.9, 9.0, 15.6 Hz, 1H), 5.58-5.52 (m, 1H), 5.22 (d, *J* = 15.6 Hz, 1H), 5.17 (d, *J* = 9.0 Hz, 1H), 4.50 (br s, 1H), 3.62 (s, 3H), 3.43 (d, *J* = 11.8 Hz, 1H), 3.15-2.88 (m, 2H), 2.43 (s, 3H), 2.39-2.30 (m, 3H), 2.21 (s, 3H), 1.82-1.56 (m, 10H), 1.46 (d, *J* = 13.7

Hz, 1H), 1.17-0.99 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 150.8, 143.5, 136.8, 136.3, 135.2, 131.8, 130.2, 129.8, 127.4, 124.4, 122.7, 118.6, 117.6, 117.5, 115.7, 84.4, 77.9, 52.2, 48.0, 45.2, 40.1, 33.9, 33.6, 29.0, 28.3, 21.6, 9.3; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{32}H_{40}N_2O_7SNa$ 619.2454; found 619.2431.

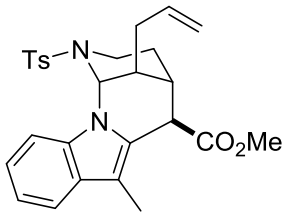
More polar isomer (minor): IR (neat) 3497, 2980, 2936, 1724, 1453, 1326, 1156 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.8 Hz, 1H), 7.72 (d, *J* = 8.1 Hz, 2H), 7.46 (d, *J* = 7.5 Hz, 1H), 7.32-7.21 (m, 4H), 5.90-5.66 (m, 1H), 5.47 (s, 1H), 5.03 (d, *J* = 10.4 Hz, 1H), 4.99 (d, *J* = 17.6 Hz, 1H), 3.59 (s, 3H), 3.48 (d, *J* = 9.4 Hz, 1H), 3.20-2.86 (m, 2H), 2.41 (s, 3H), 2.36-2.24 (m, 2H), 2.22 (s, 3H), 2.15-2.08 (m, 1H), 1.71-1.60 (m, 10H), 1.42 (d, *J* = 15.4 Hz, 1H), 1.00-0.86 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 150.9, 143.7, 136.9, 136.6, 136.3, 135.4, 131.9, 129.8, 127.6, 127.4, 124.4, 122.7, 118.6, 117.3, 115.8, 84.5, 79.1, 52.3, 52.0, 48.0, 45.3, 41.6, 40.3, 33.5, 28.3, 21.6, 9.4; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{32}H_{40}N_2O_7SNa$ 619.2454; found 619.2426.



162 (4.5:1 dr)

Methyl (1R,5S*,6R*/S*,13R*)-13-Allyl-7-methyl-2-tosyl-1,2,3,4,5,6-hexahydro-1,5-methano[1,3]diazocino[1,8-a]indole-6-carboxylate (**162**).* TFA (25 mL) was added to a solution of hemiaminal **160** (3.054 g, 5.12 mmol) in CH_2Cl_2 (25 mL) and the reaction mixture was stirred at rt for 10 min. The mixture was diluted with PhMe (50 mL) and concentrated *in vacuo*. The

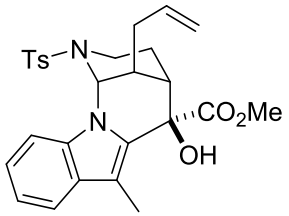
residue was purified by flash chromatography on silica gel (15% EtOAc in hexanes) to provide aminal **162** (1.808 g, 74%) as a white solid (4.5:1 mixture of inseparable C16 epimers). IR (neat) 2944, 1731, 1457, 1322, 1154 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.72-7.64 (m, 0.9H), 7.60 (d, *J* = 8.2 Hz, 0.5H), 7.53 (d, *J* = 8.0 Hz, 2H), 7.39 (d, *J* = 4.2 Hz, 0.5H), 7.25-7.05 (m, 4H), 6.48 (s, 1H), 5.95 (ddt, *J* = 7.4, 10.4, 17.8 Hz, 1H), 5.30 (d, *J* = 17.8 Hz, 1H), 5.24 (d, *J* = 10.4 Hz, 1H), 4.33 (d, *J* = 6.7 Hz, 0.2H), 4.06 (s, 0.8 H), 3.83 (s, 0.5H), 3.74 (s, 2.2H), 3.22 (dd, *J* = 6.1, 13.8 Hz, 1H), 3.02-2.89 (m, 0.2H), 2.85-2.65 (m, 2H), 2.63-2.40 (m, 3H), 2.34 (s, 3H), 2.29-2.14 (m, 4H), 1.54 (d, *J* = 13.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5, 171.8, 143.5, 143.4, 136.7, 136.6, 134.8, 134.6, 134.3, 129.8, 129.6, 129.4, 129.2, 128.8, 128.5, 128.3, 128.1, 127.4, 127.0, 121.8, 121.7, 120.2, 120.0, 118.3, 118.2, 118.0, 110.9, 108.8, 108.4, 62.2, 61.8, 52.4, 52.3, 45.3, 45.0, 40.5, 38.1, 36.9, 34.0, 33.8, 31.6, 30.9, 25.6, 22.1, 21.4, 9.0, 8.6.



163

Methyl (1R,5S*,6R*,13R*)-13-Allyl-7-methyl-2-tosyl-1,2,3,4,5,6-hexahydro-1,5-methano[1,3]diazocino[1,8-a]indole-6-carboxylate (**163**).* The mixture of ester epimers **162** was isomerized by suspending a sample (1.210 g, 2.53 mmol) in MeOH (50.0 mL) and 0.5 M NaOMe in MeOH (50.0 mL, 25.0 mmol) was added. The mixture was stirred at rt for 3 h and was diluted with satd NH_4Cl (100 mL) and extracted with EtOAc (2 × 150 mL). The combined organic layers were washed with brine (150 mL), dried over Na_2SO_4, and concentrated *in vacuo* to provide aminal **163** (1.154 g, 95% recovery) as a single diastereomer. This material was recrystallized from

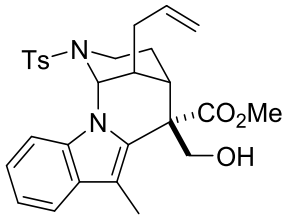
MeOH/PhMe to provide colorless prisms which were subjected to X-ray analysis.[73] Mp 136-138 °C; IR (neat) 2946, 1728, 1457, 1310, 1153 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.62 (d, *J* = 7.5 Hz, 1H), 7.50-7.44 (m, 3H), 7.16-7.09 (m, 2H), 7.05 (d, *J* = 8.0 Hz, 2H), 6.43 (s, 1H), 5.91 (ddt, *J* = 7.0, 10.0, 17.0 Hz, 1H), 5.25 (d, *J* = 17.0 Hz, 1H), 5.20 (d, *J* = 10.0 Hz, 1H), 4.04 (s, 1H), 3.73 (s, 3H), 3.18 (dd, *J* = 6.0, 13.5 Hz, 1H), 2.74 (t, *J* = 7.0 Hz, 1H), 2.67 (dd, *J* = 6.5, 14.1 Hz, 1H), 2.56 (br s, 1H), 2.40-2.51 (m, 2H), 2.31 (s, 3H), 2.23-2.15 (m, 1H), 2.18 (s, 3H), 1.51 (d, *J* = 14.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 143.8, 137.1, 135.3, 135.2, 129.8, 129.6, 128.6, 127.8, 122.2, 120.6, 118.6, 118.4, 111.3, 109.2, 62.6, 52.8, 45.4, 38.5, 37.3, 34.2, 32.0, 26.0, 21.8, 9.0; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{27}H_{31}N_2O_4S$ 479.2005; found 479.1993.



168

Methyl (1R,5S*,6R*,13R*)-13-Allyl-6-hydroxy-7-methyl-2-tosyl-1,2,3,4,5,6-hexahydro-1,5-methano[1,3]diazocino[1,8-a]indole-6-carboxylate (**168**).* Ester **162** (38.2 mg, 0.080 mmol) was dissolved in THF (0.80 mL) and the solution was cooled to -78 °C. A solution of potassium hexamethyldisilazide (0.5 M in PhMe, 0.24 mL, 0.12 mmol) was added dropwise and the mixture was stirred at -78 °C for 30 min, after which benzyloxymethyl chloride (0.03 mL, 25 mg, 0.16 mmol) was added and the solution was stirred at -78 °C for 1 h. The reaction mixture was diluted with satd NH_4Cl (20 mL), extracted with EtOAc (2 × 30 mL), and the combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (30% EtOAc in hexanes) to provide α-hydroxy ester **168** (20.4 mg, 52%) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.0 Hz, 1H), 7.63

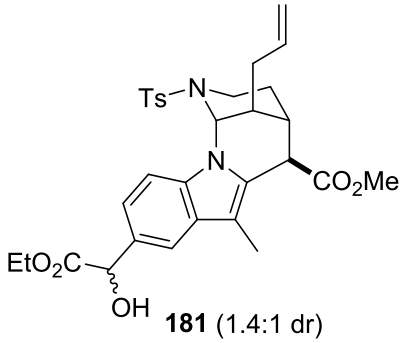
(d, *J* = 8.2 Hz, 2H), 7.57 (d, *J* = 7.9 Hz, 1H), 7.32-7.11 (m, 4H), 6.46 (s, 1H), 5.93 (ddt, *J* = 7.6, 10.2, 17.2 Hz, 1H), 5.29 (d, *J* = 17.2 Hz, 1H), 5.23 (d, *J* = 10.2 Hz, 1H), 3.87 (s, 3H), 3.56 (s, 1H), 3.19 (dd, *J* = 5.6, 13.3 Hz, 1H), 2.92-2.64 (m, 3H), 2.52-2.45 (m, 1H), 2.36 (s, 3H), 2.25-2.16 (m, 1H), 2.18 (s, 3H), 2.05-1.96 (m, 1H), 1.37 (br d, *J* = 14.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.0, 143.6, 136.7, 134.6, 134.2, 130.4, 129.6, 128.7, 127.6, 122.8, 120.3, 118.9, 118.2, 110.8, 109.8, 74.8, 62.2, 53.3, 41.8, 37.8, 36.4, 33.7, 21.5, 21.4, 8.7; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{27}H_{31}N_2O_5S$ 495.1954; found 495.1947.



178

Methyl (1R,5S*,6S*,13R*)-13-Allyl-6-(hydroxymethyl)-7-methyl-2-tosyl-1,2,3,4,5,6-hexahydro-1,5-methano[1,3]diazocino[1,8-a]indole-6-carboxylate (**178**).* Ester **162** (2.486 g, 5.194 mmol, 1:4.5 mixture of epimers) was dissolved in a solution of monomeric formaldehyde in THF[46] (0.19 M, 135 mL, 26 mmol) and the solution was cooled to -78 °C. A solution of KHMDS (0.5 M in toluene, 15.5 mL, 7.8 mmol) was added dropwise and the mixture was stirred at -78 °C for 5 min and at 0 °C for 15 min. The reaction mixture was diluted with satd NH_4Cl (100 mL) and extracted with EtOAc (200 mL). The organic layer was washed with brine (100 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (30% EtOAc in hexanes) to provide alcohol **178** (2.483 g, 94%) as a white powder. IR (neat) 3525, 2925, 1709, 1459, 1319, 1154 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.0 Hz, 1H),

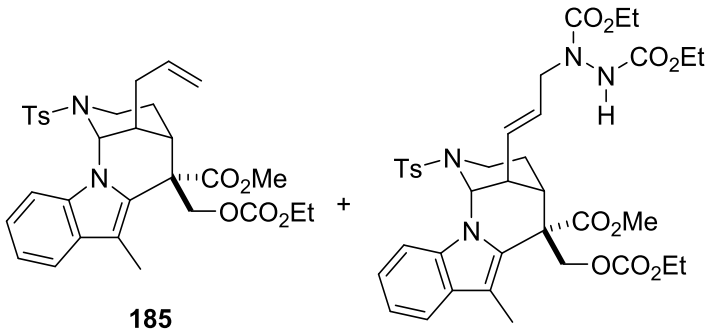
7.61 (d, *J* = 8.2 Hz, 2H), 7.53 (d, *J* = 7.6 Hz, 1H), 7.28-7.02 (m, 4H), 6.48 (s, 1H), 5.98 (ddt, *J* = 6.8, 10.2, 17.1 Hz, 1H), 5.34 (d, *J* = 17.1 Hz, 1H), 5.26 (d, *J* = 10.2 Hz, 1H), 4.16 (d, *J* = 11.5 Hz, 1H), 3.81 (s, 3H), 3.62 (t, *J* = 11.7 Hz, 1H), 3.51 (d, *J* = 11.7 Hz, 1H), 3.23 (dd, *J* = 5.1, 13.3 Hz, 1H), 2.98-2.86 (m, 2H), 2.81-2.69 (m, 1H), 2.56-2.43 (m, 2H), 2.36 (s, 3H), 2.25-2.11 (m, 4H), 1.25 (d, *J* = 14.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.1, 143.5, 136.6, 134.6, 134.2, 129.5, 129.4, 128.9, 127.4, 122.2, 120.2, 118.2, 118.2, 110.5, 108.6, 64.8, 61.5, 52.7, 52.3, 38.0, 36.3, 33.9, 31.2, 22.5, 21.4, 9.7; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{28}H_{33}N_2O_5S$ 509.2110; found 509.2109.



181 (1.4:1 dr)

Methyl (1R,5S*,6R*,13R*)-13-Allyl-9-((R*/S*)-2-ethoxy-1-hydroxy-2-oxoethyl)-7-methyl-2-tosyl-1,2,3,4,5,6-hexahydro-1,5-methano[1,3]diazocino[1,8-a]indole-6-carboxylate (**181**).* Terminal alkene **163** (44.5 mg, 0.093 mmol) was dissolved in CH_2Cl_2 (0.53 mL) and the solution was cooled to -78 °C. A solution of ethyl glyoxalate (50% in PhMe, 0.02 mL, 10.2 mg of ethyl glyoxalate, 0.10 mmol) was added, followed by a solution of stannic chloride (1.0 M in CH_2Cl_2, 0.10 mL, 0.10 mmol). The reaction mixture was stirred at -78 °C for 15 min, warmed to 0 °C for 45 min, and diluted with satd $NaHCO_3$ (20 mL). The mixture was extracted with CH_2Cl_2 (2 × 20 mL), and the combined organic layers were washed with a saturated solution of Rochelle's salt (30 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash

chromatography on silica gel (30% EtOAc in hexanes) to provide α-hydroxy ester **181** (38.2 mg, 70%) as a colorless oil (1.4:1 mixture of inseparable diastereomers). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (s, 0.6H), 7.67 (s, 0.4H), 7.57-7.53 (m, 1.5H), 7.50-7.44 (m, 1.5H), 7.22-7.15 (m, 1H), 7.12-7.04 (m, 2H), 6.45 (d, *J* = 1.8 Hz, 0.6H), 6.43 (d, *J* = 1.9 Hz, 0.4H), 5.89 (ddt, *J* = 6.2, 10.1, 17.1 Hz, 1H), 5.30 (s, 0.6H), 5.25 (d, *J* = 17.1 Hz, 1H), 5.20 (d, *J* = 10.1 Hz, 1H), 5.20 (s, 0.4H), 4.33-4.25 (m, 1.2H), 4.14-4.05 (m, 0.8H), 4.00-3.97 (m, 1H), 3.70 (s, 3H), 3.15 (dd, *J* = 6.0, 13.7 Hz, 1H), 2.75-2.63 (m, 2H), 2.54 (s, 1H), 2.47-2.36 (m, 2.6H), 2.30 (s, 3H), 2.24-2.16 (m, 0.4H), 2.15 (s, 3H), 1.50 (br d, *J* = 13.9 Hz, 1H), 1.24-1.19 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.2, 172.5, 143.5, 136.6, 134.8, 132.5, 129.6, 129.6, 129.3, 127.8, 127.5, 119.2, 118.9, 118.8, 118.5, 118.2, 109.2, 108.9, 73.8, 73.6, 62.2, 52.6, 45.1, 38.2, 37.9, 37.0, 33.9, 31.7, 29.8, 25.7, 21.5, 14.2, 8.7.



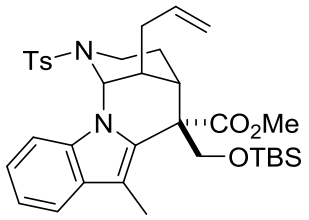
185 **186**

Methyl (1R,5S*,6S*,13R*)-13-Allyl-6-(((ethoxycarbonyl)oxy)methyl)-7-methyl-2-tosyl-1,2,3,4,5,6-hexahydro-1,5-methano[1,3]diazocino[1,8-a]indole-6-carboxylate (**185**) and Diethyl 1-((E)-3-((1R*,5S*,6S*,13R*)-6-(((Ethoxycarbonyl)oxy)methyl)-6-(methoxycarbonyl)-7-methyl-2-tosyl-1,2,3,4,5,6-hexahydro-1,5-methano[1,3]diazocino[1,8-a]indol-13-yl)allyl)hydrazine-1,2-dicarboxylate (**186**).* Terminal alkene alcohol **178** (133 mg, 0.261 mmol) was dissolved in PhMe (4.6 mL) and DEAD (40% in PhMe, 0.60 mL, 228 mg DEAD, 1.31 mmol) was added. The solution

was heated at reflux for 12 h, cooled to rt and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (gradient 20% to 40% EtOAc in hexanes) to provide carbonate **185** (35.0 mg, 23%) as a colorless oil and hydrazine **186** (86.8 mg, 44%) as a white powder.

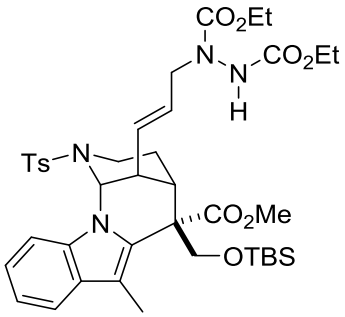
Carbonate **185**: Colorless oil IR (neat) 2954, 1742, 1460, 1319, 1156 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.2 Hz, 1H), 7.52-7.47 (m, 3H), 7.18 (ddd, *J* = 1.1, 7.1, 8.0 Hz, 1H), 7.12 (ddd, *J* = 1.0, 7.1, 7.8 Hz, 1H), 7.06 (d, *J* = 8.1 Hz, 2H), 6.45 (d, *J* = 2.0 Hz, 1H), 5.89 (ddt, *J* = 6.5, 10.1, 17.0 Hz, 1H), 5.28 (dd, *J* = 1.4, 17.0 Hz, 1H), 5.21 (d, *J* = 10.1 Hz, 1H), 4.63 (d, *J* = 11.2 Hz, 1H), 4.48 (d, *J* = 11.2 Hz, 1H), 4.09 (q, *J* = 7.1 Hz, 2H), 3.77 (s, 3H), 3.16 (dd, *J* = 5.4, 13.6 Hz, 1H), 2.80 (td, *J* = 3.1, 13.5 Hz, 1H), 2.77-2.69 (m, 1H), 2.58-2.43 (m, 3H), 2.30 (s, 3H), 2.18 (s, 3H), 2.15-2.06 (m, 1H), 1.29-1.23 (m, 1H), 1.22 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.3, 154.9, 143.5, 136.7, 134.4, 129.6, 129.3, 128.3, 127.5, 122.4, 120.3, 118.6, 110.6, 69.7, 64.4, 61.9, 52.6, 52.1, 38.0, 37.0, 34.3, 34.0, 22.5, 21.5, 14.3, 10.3; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{31}H_{37}N_2O_7S$ 581.2321; found 581.2298.

Hydrazine **186**: IR (neat) 3334, 2981, 1744, 1461, 1258 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.1 Hz, 1H), 7.52 (d, *J* = 7.6 Hz, 1H), 7.47 (d, *J* = 8.1 Hz, 2H), 7.20 (ddd, *J* = 1.1, 7.2, 8.1 Hz, 1H), 7.14 (ddd, *J* = 0.9, 7.0, 7.8 Hz, 1H), 7.05 (d, *J* = 7.9 Hz, 2H), 6.53 (s, 1H), 6.02 (dd, *J* = 5.2, 15.7 Hz, 1H), 5.95 (dt, *J* = 5.5, 15.7 Hz, 1H), 4.67 (d, *J* = 11.2 Hz, 1H), 4.53 (d, *J* = 11.2 Hz, 1H), 4.31-4.15 (m, 6H), 4.09 (q, *J* = 7.1 Hz, 2H), 3.77 (s, 3H), 3.28 (br s, 1H), 3.13 (dd, *J* = 5.2, 13.7 Hz, 1H), 2.78 (t, *J* = 13.1 Hz, 1H), 2.30 (s, 3H), 2.24-2.16 (m, 1H), 2.18 (s, 3H), 1.32-1.25 (m, 7H), 1.20 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.0, 156.4, 154.8, 143.8, 136.4, 134.4, 130.5, 129.6, 129.4, 129.2, 127.9, 127.6, 122.6, 120.5, 118.8, 110.9, 110.5, 69.8, 64.4, 62.7, 62.0, 52.7, 51.9, 39.3, 38.0, 36.2, 30.5, 29.8, 23.2, 21.5, 14.7, 14.3, 10.3; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{37}H_{46}N_4O_{11}S$ 755.2962; found 755.2950.



187

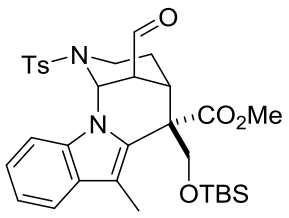
Methyl (1R,5S*,6S*,13R*)-13-Allyl-6-(((tert-butyldimethylsilyl)oxy)methyl)-7-methyl-2-tosyl-1,2,3,4,5,6-hexahydro-1,5-methano[1,3]diazocino[1,8-a]indole-6-carboxylate* ***(187).*** A solution of alcohol **178** (273 mg, 0.537 mmol) in CH_2Cl_2 (10.5 mL) was cooled to 0 °C and 2,6-lutidine (0.63 mL, 575 mg, 5.4 mmol) was added followed by TBSOTf (0.62 mL, 710 mg, 2.69 mmol). The mixture was stirred at 0 °C for 45 min. The solution was diluted with CH_2Cl_2 (100 mL) and washed with 1 M HCl (50 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (gradient 8% to 12% EtOAc in hexanes) to yield silyl ether **187** (282 mg, 85%) as a clear oil. IR (neat) 2927, 1731, 1461, 1319, 1154 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, *J* = 7.4 Hz, 1H), 7.52-7.46 (m, 3H), 7.18-7.08 (m, 2H), 7.04 (d, *J* = 8.1 Hz, 2H), 6.43 (s, 1H), 5.91 (ddt, *J* = 5.6, 10.1, 17.1 Hz, 1H), 5.27 (d, *J* = 17.1 Hz, 1H), 5.19 (d, *J* = 10.1 Hz, 1H), 4.13 (d, *J* = 10.1 Hz, 1H), 3.97 (d, *J* = 10.1 Hz, 1H), 3.74 (s, 3H), 3.16 (dd, *J* = 5.5, 13.6 Hz, 1H), 2.90-2.65 (m, 3H), 2.64-2.56 (m, 1H), 2.54-2.42 (m, 1H), 2.29 (s, 3H), 2.16 (s, 3H), 2.14-2.05 (m, 1H), 1.23 (d, *J* = 16.0 Hz, 1H), 0.77 (s, 9H), 0.00 (s, 3H), -0.12 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 143.4, 136.8, 134.9, 134.3, 130.7, 129.5, 129.4, 127.5, 121.8, 120.0, 118.3, 118.1, 110.4, 108.9, 68.4, 62.0, 53.8, 52.1, 38.2, 36.8, 35.2, 34.2, 25.7, 22.8, 21.5, 18.2, 10.5, -5.5, -5.8; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{34}H_{47}N_2O_5SSi$ 623.2975; found 623.2951.



188

Diethyl 1-((E)-3-((1R,5S*,6S*,13R*)-6-(((tert-Butyldimethylsilyl)oxy)methyl)-6-(methoxycarbonyl)-7-methyl-2-tosyl-1,2,3,4,5,6-hexahydro-1,5-methano[1,3]diazocino[1,8-a]indol-13-yl)allyl)hydrazine-1,2-dicarboxylate (**188**).* DEAD (40% in PhMe, 5.2 mL, 1.97 g of DEAD, 11.3 mmol) was added to a solution of terminal olefin **187** (1.409 g, 2.26 mmol) in PhMe (40 mL) and the mixture was heated at reflux for 12 h, after which additional DEAD (40% in PhMe, 2.6 mL, 0.98 g of DEAD, 5.7 mmol) was added. The solution was refluxed for 12 h, and additional DEAD (40% in PhMe, 2.6 mL, 0.98 g of DEAD, 5.7 mmol) was again added, followed by an additional 12 h at reflux. The mixture was concentrated *in vacuo* and the residue was purified by flash chromatography on silica gel (gradient 20% to 30% EtOAc in hexanes) to provide ene adduct **188** (1.400 g, 77%) as a pale yellow foam. IR (neat) 3323, 2931, 1723, 1462, 1318, 1249, 1203, 1097 cm^{-1} ; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.8 Hz, 1H), 7.50 (d, *J* = 7.9 Hz, 1H), 7.47 (d, *J* = 8.2 Hz, 2H), 7.19-7.10 (m, 2H), 7.03 (d, *J* = 7.9 Hz, 2H), 6.50 (s, 1H), 6.04 (dd, *J* = 6.1, 15.4 Hz, 1H), 5.89 (dt, *J* = 5.6, 15.4 Hz, 1H), 4.27-4.13 (m, 7H), 4.03 (d, *J* = 10.0 Hz, 1H), 3.74 (s, 3H), 3.52-3.48 (m, 1H), 3.11 (dd, *J* = 5.1, 13.7 Hz, 1H), 2.78 (t, *J* = 13.0 Hz, 1H), 2.64-2.59 (m, 1H), 2.29 (s, 3H), 2.23-2.17 (m, 1H) 2.16 (s, 3H), 1.32-1.21 (m, 7H), 0.74 (s, 9H), -0.01 (s, 3H), -0.14 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.8, 156.4, 143.6, 136.6, 134.3, 131.3, 130.3, 129.6, 128.4, 127.5, 122.0, 120.2, 118.5, 110.2, 109.3, 68.9, 62.7, 62.1, 61.9, 53.7, 52.2,

39.1, 38.1, 37.4, 25.7, 23.5, 21.5, 18.2, 14.7, 10.5, -5.5, -5.7; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{40}H_{57}N_4O_9SSi$ 797.3616; found 797.3625.

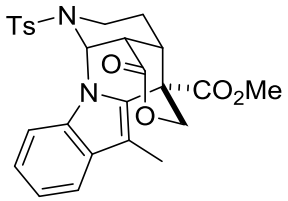


190

Methyl (1R,5S*,6S*,13R*)-6-(((tert-Butyldimethylsilyl)oxy)methyl)-13-formyl-7-methyl-2-tosyl-1,2,3,4,5,6-hexahydro-1,5-methano[1,3]diazocino[1,8-a]indole-6-carboxylate (**190**).* Ene adduct **188** (116.2 mg, 0.146 mmol) was dissolved in a mixture of THF (2.1 mL) and H_2O (1.0 mL), and NMO (86 mg, 0.73 mmol) was added followed by a solution of OsO_4 (2.5% in *tert*-butanol, 0.03 mL, 0.7 mg of OsO_4, 0.003 mmol). The reaction mixture was stirred at rt for 12 h and diluted with satd Na_2SO_3 (10 mL). The mixture was stirred for 10 min and extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to yield the crude diol as a colorless oil.

The diol was dissolved in EtOAc (42 mL) and $Pb(OAc)_4$ (99 mg, 0.223 mmol) was added. The reaction mixture was stirred at rt for 1 h. The orange solution was filtered through a silica gel pad and the filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (25% EtOAc in hexanes) to provide axial aldehyde **190** (54.5 mg, 61%) as white needles. IR (neat) 2931, 1727, 1460, 1320, 1143 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.03 (s, 1H), 7.73 (d, *J* = 7.9 Hz, 1H), 7.55 (d, *J* = 8.2 Hz, 2H), 7.50 (d, *J* = 7.7 Hz, 2H), 7.21-7.09 (m, 4H), 4.23 (d, *J* = 10.0 Hz, 1H), 4.06 (d, *J* = 10.0 Hz, 1H), 3.84 (s, 1H), 3.76 (s, 3H), 3.19-3.12 (m, 1H), 3.05 (dd, *J* = 5.0, 13.1 Hz, 1H), 2.91 (td, *J* = 2.7, 13.4 Hz, 1H), 2.33 (s, 3H), 2.15 (s, 3H), 1.96-1.79 (m, 1H), 1.34 (d, *J* = 14.9 Hz, 1H), 0.65 (s, 9H), -0.06 (s, 3H), -0.25 (s, 3H); ^{13}C NMR

(75 MHz, $CDCl_3$) δ 199.0, 172.5, 143.9, 136.1, 134.3, 130.2, 129.7, 129.6, 127.7, 122.2, 120.4, 118.3, 110.5, 109.4, 69.4, 58.9, 53.0, 52.3, 50.3, 38.1, 33.8, 25.6, 25.1, 21.6, 18.0, 10.4, -5.6, -5.9; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{32}H_{43}N_2O_6SSi$ 611.2611; found 611.2617.



204

Methyl (1R,5S*,6S*,16S*)-7-Methyl-15-oxo-2-tosyl-2,3,4,5-tetrahydro-1,5,6-(epiethane[1.1.2]triyloxymethano)[1,3]diazocino[1,8-a]indole-6(1H)-carboxylate (**204**).* Method A: Silyl ether **190** (286.6 mg, 0.469 mmol) was dissolved in $CHCl_3$ (5.1 mL) and a solution of HCl in MeOH (1.0 M, 5.1 mL, 5.1 mmol) was added. The mixture was stirred at rt for 1 h, was poured into satd $NaHCO_3$ (50 mL) and the resulting mixture was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to yield the crude alcohol, which was used directly in the next step.

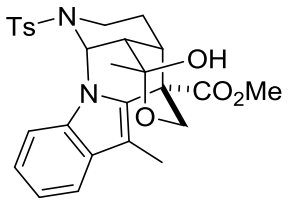
The crude alcohol was dissolved in $CHCl_3$ (7.8 mL) and DBU (0.14 mL, 143 mg, 0.938 mmol) was added. The mixture was stirred at rt for 1 h, after which acetic acid (1.2 mL) was added, followed by TEMPO (37.5 mg, 0.235 mmol) and $PhI(OAc)_2$ (604 mg, 1.88 mmol). The mixture was stirred at rt for 3 h, and was diluted with satd $Na_2S_2O_3$ (20 mL) and satd $NaHCO_3$ (20 mL). The mixture was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (35% EtOAc in hexanes) to provide lactone **204** (169.6 mg, 73% from **190**) as a pale yellow foam. IR (neat) 2920, 1728, 1458, 1259, 1159 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.1 Hz, 2H), 7.53 (d, *J* = 7.7 Hz, 1H), 7.41 (d, *J* = 7.5 Hz, 1H), 7.33 (d, *J* = 7.9 Hz, 2H), 7.25-7.17 (m, 2H), 6.58 (d, *J* = 2.8 Hz, 1H), 4.86 (d, *J* = 10.7 Hz, 1H), 4.44 (d, *J* = 10.7 Hz, 1H), 3.86 (s, 3H),

3.50 (dd, *J* = 4.9, 14.6 Hz, 1H), 3.26-3.19 (m, 1H), 2.89 (td, *J* = 3.4, 14.0 Hz, 1H), 2.79-2.72 (m, 1H), 2.44 (s, 3H), 2.12 (s, 3H), 1.76 (d, *J* = 13.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 167.2, 144.3, 137.2, 134.3, 130.2, 129.2, 127.8, 127.3, 123.2, 121.0, 118.6, 110.5, 109.1, 76.7, 61.8, 53.0, 45.9, 43.4, 37.2, 34.4, 25.4, 21.7, 9.0; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{26}H_{27}N_2O_6S$ 495.1590; found 495.1573.

Method B: Internal alkene **259** (53.1 mg, 0.104 mmol) was dissolved in a mixture of THF (1.6 mL) and H_2O (0.8 mL), and NMO (61 mg, 0.52 mmol) was added followed by a solution of OsO_4 (4% in H_2O, 0.01 mL, 0.5 mg of OsO_4, 0.002 mmol). The reaction mixture was stirred at rt for 16 h and quenched by addition of satd Na_2SO_3 (5 mL). The resulting mixture was stirred for 10 min and extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, and concentrated *in vacuo* to yield the crude triol as a colorless oil.

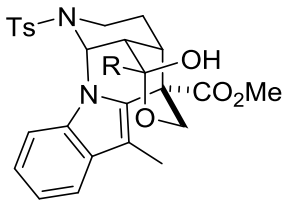
The triol was dissolved in EtOAc (30 mL) and $Pb(OAc)_4$ (70 mg, 0.16 mmol) was added. The reaction mixture was stirred at rt for 1 h. The orange solution was filtered through a silica gel pad and the filtrate was concentrated *in vacuo* to provide the crude aldehyde as a colorless oil.

The aldehyde was dissolved in $CHCl_3$ (1.8 mL) and DBU (0.03 mL, 31 mg, 0.20 mmol) was added. The mixture was stirred at rt for 15 min, after which glacial acetic acid (0.27 mL) was added, followed by TEMPO (8.2 mg, 0.05 mmol) and $PhI(OAc)_2$ (134 mg, 0.42 mmol). The mixture was stirred at rt for 3 h and was diluted with satd $Na_2S_2O_3$ (10 mL) and satd $NaHCO_3$ (10 mL). The mixture was extracted with CH_2Cl_2 (2 × 20 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (35% EtOAc in hexanes) to provide lactone **204** (36.9 mg, 72% from **259**) as a pale yellow foam. This material had spectroscopic data identical to that prepared using Method A.



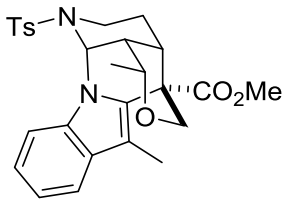
205

Methyl (1R,5S*,6S*,15R*/S*,16S*)-15-Hydroxy-7,15-dimethyl-2-tosyl-2,3,4,5-tetrahydro-1,5,6-(epiethane[1.1.2]triyloxymethano)[1,3]diazocino[1,8-a]indole-6(1H)-carboxylate (**205**).* Lactone **204** (137.8 mg, 0.279 mmol) was dissolved in THF (11.0 mL) and the solution was cooled to -78 °C. A solution of methyllithium in Et_2O (1.6 M, 0.35 mL, 0.56 mmol) was added dropwise and the mixture was stirred at -78 °C for 15 min. The reaction mixture was diluted with satd NH_4Cl (20 mL) and extracted with EtOAc (2 × 30 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (35% EtOAc in hexanes) to provide hemiketal **205** (94.5 mg, 66%) as an off-white solid. IR (neat) 3312, 2926, 1719, 1458, 1325, 1261 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.1 Hz, 2H), 7.51 (d, *J* = 6.2 Hz, 1H), 7.43 (d, *J* = 6.9 Hz, 1H), 7.23 (d, *J* = 8.1 Hz, 2H), 7.18-7.10 (m, 2H), 6.50 (s, 1H), 4.40 (d, *J* = 10.5 Hz, 1H), 3.81 (s, 3H), 3.65 (d, *J* = 10.5 Hz, 1H), 3.29 (dd, *J* = 4.9, 14.5 Hz, 1H), 2.96-3.89 (m, 1H), 2.72 (td, *J* = 3.5, 13.9 Hz, 1H), 2.40 (s, 3H), 2.37-2.33 (m, 1H), 2.17-2.12 (br s, 1H), 2.08 (s, 3H), 1.83 (d, *J* = 14.4 Hz, 1H), 1.78-1.71 (m, 1H), 1.48 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1, 143.8, 137.6, 134.3, 130.8, 129.9, 129.5, 127.2, 122.2, 120.4, 118.6, 109.7, 106.9, 95.5, 68.2, 60.7, 52.3, 47.0, 43.7, 37.9, 33.5, 27.3, 27.0, 21.6, 9.0; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{27}H_{31}N_2O_6S$ 511.1903; found 511.1880.



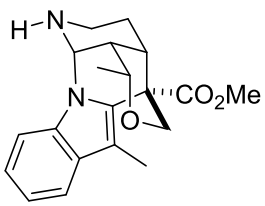
206 R = $CHCl_2$

Methyl (1R,5S*,6S*,15R*/S*,16S*)-15-(Dichloromethyl)-15-hydroxy-7-methyl-2-tosyl-2,3,4,5-tetrahydro-1,5,6-(epiethane[1.1.2]triyloxymethano)[1,3]diazocino[1,8-a]indole-6(1H)-carboxylate (**206**).* Lactone **204** (inadequately dried, 84.0 mg, 0.170 mmol) was dissolved in THF (6.5 mL) and the solution was cooled to -78 °C. A solution of methyllithium in Et_2O (1.6 M, 0.32 mL, 0.51 mmol) was added dropwise and the mixture was stirred at -78 °C for 15 min, after which additional methyllithium solution (1.6 M in Et_2O, 0.32 mL, 0.51 mmol) was added and the solution was stirred for a further 15 min. The reaction mixture was diluted with satd NH_4Cl (20 mL) and extracted with EtOAc (2 × 30 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (30% EtOAc in hexanes) to provide dichloromethyl hemiketal **206** (37.7 mg, 38%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.2 Hz, 2H), 7.53 (d, *J* = 8.0 Hz, 2H), 7.25-7.15 (m, 4H), 6.58 (s, 1H), 5.58 (s, 1H), 4.41 (d, *J* = 10.7 Hz, 1H), 3.82 (s, 3H), 3.77 (d, *J* = 10.6 Hz, 1H), 3.33 (dd, *J* = 5.5, 14.6 Hz, 1H), 3.17 (s, 1H), 2.93-2.89 (m, 1H), 2.82-2.73 (m, 2H), 2.41 (s, 3H), 2.08 (s, 3H), 1.84 (br d, *J* = 14.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 143.9, 137.5, 134.2, 130.2, 130.0, 129.6, 127.3, 122.7, 120.8, 118.7, 109.8, 107.5, 96.2, 75.3, 69.3, 59.6, 52.5, 46.7, 41.4, 37.6, 34.0, 27.3, 21.6, 9.0; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{27}H_{28}Cl_2N_2O_6S$ 579.1123; found 579.1118.



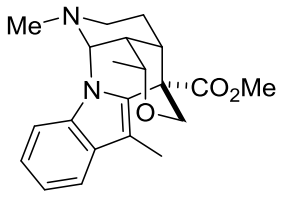
202

Methyl (1R,5S*,6S*,15R*,16S*)-7,15-Dimethyl-2-tosyl-2,3,4,5-tetrahydro-1,5,6-(epiethane[1.1.2]triyloxymethano)[1,3]diazocino[1,8-a]indole-6(1H)-carboxylate (**202**).* Et_3SiH (0.08 mL, 54 mg, 0.51 mmol) and TMSOTf (0.07 mL, 81 mg, 0.37 mmol) were added to a -78 °C solution of hemiketal **205** (74.7 mg, 0.146 mmol) in CH_2Cl_2 (4.4 mL). The solution was stirred at -78 °C for 45 min, was quenched with Et_3N (0.10 mL) and warmed to rt. Saturated $NaHCO_3$ (20 mL) was added and the mixture was extracted with CH_2Cl_2 (2 × 30 mL). The organic phase was dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (30% EtOAc in hexanes) to provide tetrahydropyran **202** (68.6 mg, 95%) as a white solid. IR (neat) 2923, 1727, 1459, 1260, 1157 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.0 Hz, 2H), 7.55-7.48 (m, 1H), 7.45-7.38 (m, 1H), 7.24 (d, *J* = 8.9 Hz, 2H), 7.18-7.12 (m, 2H), 6.54 (s, 1H), 3.95 (d, *J* = 10.6 Hz, 1H), 3.90 (d, *J* = 10.6 Hz, 1H), 3.82 (s, 3H), 3.75 (qd, *J* = 2.6, 6.3 Hz, 1H), 3.35 (dd, *J* = 4.5, 15.0 Hz, 1H), 2.72 (td, *J* = 4.2, 13.0 Hz, 1H), 2.45-2.40 (m, 1H), 2.40 (s, 3H), 2.15-2.10 (m, 1H), 2.09 (s, 3H), 1.88-1.77 (m, 2H), 1.32 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 143.8, 137.6, 134.3, 131.0, 129.9, 129.5, 127.2, 122.0, 120.3, 118.6, 109.6, 106.7, 74.1, 74.0, 59.7, 52.2, 47.2, 40.9, 38.9, 38.2, 27.8, 21.6, 18.0, 9.0; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{27}H_{31}N_2O_5S$ 495.1954; found 495.1967.



208

Methyl (1S,5S*,6S*,15R*,16S*)-7,15-Dimethyl-2,3,4,5-tetrahydro-1,5,6-(epiethane[1.1.2]triyloxymethano)[1,3]diazocino[1,8-a]indole-6(1H)-carboxylate* ***(208).*** Sulfonamide **202** (68.6 mg, 0.139 mmol) was dissolved in MeOH (14 mL) and Mg ribbon (1.69 g, 69.5 mmol) was added. The mixture was sonicated for 30 min, as the bath temperature was increased from rt to 35 °C. The mixture was poured into satd NH_4Cl (100 mL) and extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (gradient 90% to 95% EtOAc in hexanes) to provide secondary amine **208** (37.6 mg, 80%) as a white solid. IR (neat) 3331, 2923, 2853, 1729, 1456, 1257, 1095 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.6 Hz, 1H), 7.27-7.03 (m, 3H), 5.59 (s, 1H), 3.99-3.90 (m, 2H), 3.84 (s, 3H), 3.82-3.76 (m, 1H), 2.63-2.51 (m, 2H), 2.45-2.38 (m, 1H), 2.34 (dd, *J* = 4.5, 11.5 Hz, 1H), 2.29-2.21 (m, 1H), 2.11 (s, 3H), 1.95-1.88 (m, 1H), 1.26 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 133.7, 132.5, 129.7, 121.3, 119.5, 119.1, 107.9, 104.6, 74.4, 74.1, 60.6, 52.1, 47.7, 41.2, 39.7, 37.3, 28.6, 18.1, 9.1; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{20}H_{24}N_2O_3$ 341.1865; found 341.1858.



(±)-alstoscholarisine B (**2**)

(±)-Alstoscholarisine B (2). Secondary amine **208** (37.6 mg, 0.110 mmol) was dissolved in a mixture of glacial acetic acid (2.4 mL) and 37% aqueous formaldehyde (0.40 mL, 161 mg of formaldehyde, 5.37 mmol), and $NaBH_3CN$ (41.5 mg, 0.66 mmol) was added. The mixture was stirred at rt for 45 min, diluted with CH_2Cl_2 (50 mL), and poured into satd Na_2CO_3 (50 mL). The layers were separated and the aqueous layer was further extracted with CH_2Cl_2 (30 mL). The

combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (gradient 80% to 90% EtOAc in hexanes) to provide (±)-alstoscholarisine B (**2**) (21.9 mg, 56%) as a white solid. IR (neat) 2919, 2855, 1723, 1456, 1319, 1198, 1039, 737 cm^{-1}; ^1H NMR (500 MHz, $(CD_3)_2CO$) δ 7.60 (d, *J* = 8.2 Hz, 1H), 7.45 (d, *J* = 7.9 Hz, 1H), 7.07 (t, *J* = 7.8 Hz, 1H), 6.99 (t, *J* = 7.7 Hz, 1H), 5.52 (d, *J* = 1.8 Hz, 1H), 3.90 (s, 3H), 3.82 (d, *J* = 10.4 Hz, 1H), 3.75 (qd, *J* = 3.3, 6.5 Hz, 1H), 3.73 (d, *J* = 10.4 Hz, 1H), 2.40-2.34 (m, 2H), 2.33 (s, 3H), 2.32-2.28 (m, 1H), 2.20 (td, *J* = 5.2, 11.6 Hz, 1H), 2.08 (s, 3H), 1.97-1.86 (m, 2H), 1.14 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ 173.4, 137.4, 133.9, 129.7, 121.3, 119.4, 118.5, 110.8, 105.4, 75.0, 74.7, 67.0, 52.2, 49.0, 46.4, 45.2, 42.7, 39.4, 29.1, 18.3, 9.2; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{21}H_{27}N_2O_3$ 355.2022; found 355.2026.

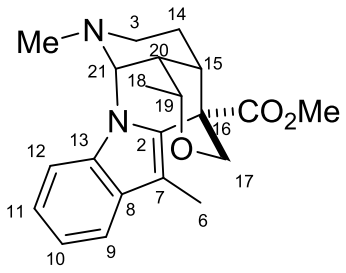
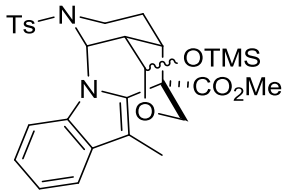


Table 7. Comparison of ^{1}H NMR Spectra of Natural and Synthetic Alstoscholarisine B (**2**) in $(CD_3)_2CO$

	natural (600 MHz)[5]	synthetic (500 MHz)
H-3	2.22 (td, *J* = 4.5, 12.0 Hz)	2.20 (td, *J* = 5.2, 11.6 Hz)
	2.38 (m)	2.40-2.34 (m)
H-6	2.10 (s)	2.08 (s)
H-9	7.48 (d, *J* = 7.9 Hz)	7.45 (d, *J* = 7.9 Hz)
H-10	7.02 (t, *J* = 7.9 Hz)	6.99 (t, *J* = 7.7 Hz)
H-11	7.10 (t, *J* = 7.9 Hz)	7.07 (t, *J* = 7.8 Hz)
H-12	7.66 (d, *J* = 7.9 Hz)	7.60 (d, *J* = 8.2 Hz)
H-14	1.96 (m)	1.97-1.86 (m)
	1.93 (m)	1.97-1.86 (m)
H-15	2.41 (m)	2.40-2.34 (m)
H-17	3.75 (d, *J* = 10.5 Hz)	3.73 (d, *J* = 10.4 Hz)
	3.85 (d, *J* = 10.5 Hz)	3.82 (d, *J* = 10.4 Hz)
H-18	1.16 (d, *J* = 6.4 Hz)	1.14 (d, *J* = 6.5 Hz)
H-19	3.80 (qd, *J* = 3.4, 6.4 Hz)	3.75 (qd, *J* = 3.3, 6.5 Hz)
H-20	2.33 (m)	2.32-2.28 (m)
H-21	5.57 (d, *J* = 2.3 Hz)	5.52 (d, *J* = 1.8 Hz)
NCH_3	2.35 (s)	2.33 (s)
OCH_3	3.87 (s)	3.90 (s)

Table 8. Comparison of ^{13}C NMR Spectra of Natural and Synthetic Alstoscholarisine B (**2**) in $(CD_3)_2CO$

	natural (150 MHz)[5]	synthetic (125 MHz)
C-2	133.8	133.9
C-3	46.3	46.4
C-6	9.1	9.2
C-7	105.3	105.4
C-8	129.6	129.7
C-9	118.4	118.5
C-10	119.4	119.4
C-11	121.2	121.3
C-12	110.8	110.8
C-13	137.3	137.4
C-14	29.0	29.1
C-15	39.2	39.4
C-16	48.8	49.0
C-17	74.8	75.0
C-18	18.2	18.3
C-19	74.5	74.7
C-20	42.5	42.7
C-21	66.9	67.0
NCH_3	45.1	45.2
-CO-	173.3	173.4
OCH_3	52.1	52.2



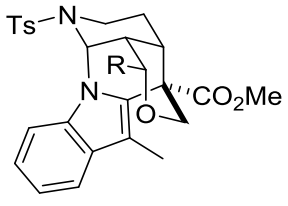
209

Methyl (1R,5S*,6S*,15R*/S*,16S*)-7-Methyl-2-tosyl-15-((trimethylsilyl)oxy)-2,3,4,5-tetrahydro-1,5,6-(epiethane[1.1.2]triyloxymethano)[1,3]diazocino[1,8-a]indole-6(1H)-carboxylate (**209**).* Lactol **193** (26.4 mg, 0.053 mmol) was dissolved in CH_2Cl_2 (1.1 mL) and the solution was cooled to -78 °C. TMSOTf (0.05 mL, 59 mg, 0.27 mmol) was added followed by a solution of trimethylaluminum in hexanes (2.0 M, 0.27 mL, 0.54 mmol). The reaction mixture was

stirred at -78 °C for 30 min and allowed to warm to rt over 10 min. The solution was stirred for an additional 10 min at rt and poured into a saturated aqueous solution of Rochelle's salt (30 mL). The mixture was extracted with CH_2Cl_2 (2 × 30 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (gradient 20 to 30% EtOAc in hexanes) to provide tetrahydropyran **203** (2.3 mg, 9%) as a white powder and *O*-silylated lactol **209** (20.0 mg, 66%) as a colorless oil. For characterization purposes, the two silyl lactam isomers were separated by preparative thin-layer chromatography on silica gel (20% EtOAc in hexanes).

Less polar isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.2 Hz, 2H), 7.49 (d, *J* = 7.2 Hz, 1H), 7.41 (d, *J* = 7.6 Hz, 1H), 7.21 (d, *J* = 8.1 Hz, 2H), 7.17-7.09 (m, 2H), 6.46 (d, *J* = 2.2 Hz, 1H), 5.21 (s, 1H), 4.28 (d, *J* = 10.5 Hz, 1H), 3.81 (s, 3H), 3.60 (d, *J* = 10.5 Hz, 1H), 3.22 (dd, *J* = 5.1, 14.7 Hz, 1H), 2.87-2.83 (m, 1H), 2.67 (td, *J* = 3.8, 13.2 Hz, 1H), 2.41 (s, 1H), 2.38 (s, 3H), 2.07 (s, 3H), 1.88-1.76 (m, 2H), 0.16 (s, 9H).

More polar isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.2 Hz, 2H), 7.48 (d, *J* = 7.3 Hz, 1H), 7.40 (d, *J* = 7.9 Hz, 1H), 7.24 (d, *J* = 8.1 Hz, 2H), 7.16-7.08 (m, 2H), 6.63 (s, 1H), 4.88 (d, *J* = 3.0 Hz, 1H), 3.94-3.87 (m, 2H), 3.81 (s, 3H), 3.39 (dd, *J* = 5.8, 14.8 Hz, 1H), 2.68 (td, *J* = 3.2, 13.8 Hz, 1H), 2.41 (s, 3H), 2.41-2.35 (m, 1H), 2.22-2.18 (m, 1H), 2.06 (s, 3H), 1.85 (br d, *J* = 14.5 Hz, 1H), 1.73-1.65 (m, 1H), 0.10 (s, 9H).



210 R = OAc

Methyl (1R,5S*,6S*,15R*,16S*)-15-Acetoxy-7-methyl-2-tosyl-2,3,4,5-tetrahydro-1,5,6-(epiethane[1.1.2]triyloxymethano)[1,3]diazocino[1,8-a]indole-6(1H)-carboxylate (**210**).* Method

A: Silyl ether **190** (146.6 mg, 0.240 mmol) was dissolved in $CHCl_3$ (2.8 mL) and a solution of HCl in MeOH (1.0 M, 2.8 mL, 2.8 mmol) was added. The solution was stirred at rt for 1 h and was poured into satd $NaHCO_3$ (50 mL). The mixture was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to yield the crude alcohol, which was used directly in the next step.

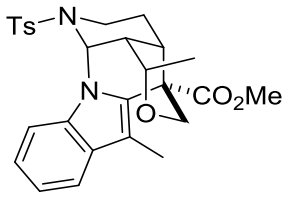
The crude alcohol was dissolved in $CHCl_3$ (4.2 mL). DBU (0.08 mL, 80 mg, 0.53 mmol) was added and the resulting mixture was stirred at rt for 1 h. Ac_2O (0.23 mL, 245 mg, 2.4 mmol) was added and the solution was stirred for a further 1 h. The reaction mixture was diluted with satd NH_4Cl (50 mL) and extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were dried over Na_2SO_4, concentrated *in vacuo*, and the residue was purified by flash chromatography on silica gel (35% EtOAc in hexanes) to provide lactol acetate **210** (99.6 mg, 77% from **190**) as a white solid. IR (neat) 2925, 1758, 1728, 1461, 1325, 1157 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, J = 8.1 Hz, 2H), 7.55-7.45 (m, 3H), 7.24-7.12 (m, 3H), 6.66 (s, 1H), 5.82 (d, *J* = 2.9 Hz, 1H), 4.04 (d, *J* = 11.2 Hz, 1H), 3.96 (d, *J* = 11.2 Hz, 1H), 3.82 (s, 3H), 3.33 (dd, *J* = 5.3, 14.7 Hz, 1H), 2.69 (td, *J* = 3.1, 14.5 Hz, 1H), 2.52-2.42 (m, 2H), 2.40 (s, 3H), 2.16 (s, 3H), 2.08 (s, 3H), 1.89 (d, *J* = 14.4 Hz, 1H), 1.82-1.71 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 169.0, 143.9, 137.4, 134.4, 130.2, 129.9, 129.4, 127.2, 122.3, 120.5, 118.7, 110.1, 107.1, 92.6, 72.5, 59.4, 52.5, 46.6, 39.4, 38.1, 37.1, 27.0, 21.6, 21.1, 9.0; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{28}H_{31}N_2O_7S$ 539.1852; found 539.1852.

Method B: Internal alkene **259** (246.2 mg, 0.484 mmol) was dissolved in a mixture of THF (6.9 mL) and H_2O (3.4 mL), and NMO (284 mg, 2.42 mmol) was added, followed by a solution of OsO_4 (4% in H_2O, 0.06 mL, 2.5 mg of OsO_4, 0.010 mmol). The reaction mixture was stirred at rt for 10 h and quenched by addition of satd Na_2SO_3 (10 mL). The resulting mixture was stirred

for 10 min and extracted with EtOAc (2 × 30 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, and concentrated *in vacuo* to yield the crude triol as a colorless oil.

The crude triol was dissolved in EtOAc (138 mL) and $Pb(OAc)_4$ (322 mg, 0.73 mmol) was added. The reaction mixture was stirred at rt for 1 h. The orange solution was filtered through a silica gel pad and the filtrate was concentrated *in vacuo* to provide the crude aldehyde as a colorless oil.

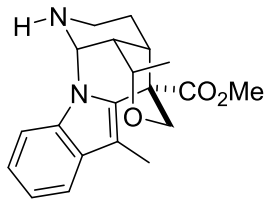
The crude aldehyde was dissolved in $CHCl_3$ (8.5 mL) and DBU (0.14 mL, 147 mg, 0.97 mmol) was added. The resulting mixture was stirred at rt for 15 min, after which Ac_2O (0.46 mL, 494 mg, 4.8 mmol) was added. The reaction mixture was stirred at rt for 1 h, and was diluted with satd NH_4Cl (30 mL). The mixture was extracted with CH_2Cl_2 (2 × 30 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (35% EtOAc in hexanes) to provide lactol acetate **210** (187.7 mg, 72% from **259**) as a white solid. This material had spectral data identical to that prepared by Method A.



203

Methyl (1R,5S*,6S*,15S*,16S*)-7,15-Dimethyl-2-tosyl-2,3,4,5-tetrahydro-1,5,6-(epiethane[1.1.2]triyloxymethano)[1,3]diazocino[1,8-a]indole-6(1H)-carboxylate (**203**).* Lactol acetate **210** (58.2 mg, 0.108 mmol) was dissolved in CH_2Cl_2 (2.2 mL) and the solution was cooled to -78 °C. TMSOTf (0.10 mL, 120 mg, 0.54 mmol) was added followed by a solution of trimethylaluminum in hexanes (2.0 M, 0.54 mL, 1.08 mmol). The reaction mixture was stirred at

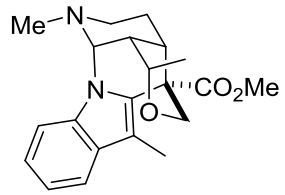
-78 °C for 30 min and allowed to warm to rt over 10 min. The solution was stirred for an additional 10 min at rt and poured into a saturated aqueous solution of Rochelle's salt (30 mL). The mixture was extracted with CH_2Cl_2 (2 × 30 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (30% EtOAc in hexanes) to provide tetrahydropyran **203** (40.0 mg, 75%) as a white powder. IR (neat) 2923, 1726, 1459, 1349, 1259, 1156 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.2 Hz, 2H), 7.52-7.49 (m, 1H), 7.37-7.34 (m, 1H), 7.21 (d, *J* = 8.2 Hz, 2H), 7.14-7.11 (m, 2H), 6.39 (d, *J* = 2.3 Hz, 1H), 4.16-4.11 (m, 2H), 3.80 (s, 3H), 3.66 (d, *J* = 10.9 Hz, 1H), 2.72-2.63 (m, 2H), 2.38 (s, 3H), 2.20-2.17 (m, 1H), 2.07 (s, 3H), 1.86-1.80 (m, 2H), 1.34 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4, 143.8, 137.4, 134.5, 131.3, 129.8, 129.6, 127.4, 122.0, 120.3, 118.6, 109.8, 106.7, 71.0, 68.0, 63.9, 52.3, 47.7, 41.6, 38.1, 33.3, 27.7, 21.6, 17.4, 9.0; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{27}H_{31}N_2O_5S$ 495.1954; found 495.1956.



212

Methyl (1S,5S*,6S*15S*,16S*)-7,15-Dimethyl-2,3,4,5-tetrahydro-1,5,6-(epiethane[1.1.2]triyloxymethano)[1,3]diazocino[1,8-a]indole-6(1H)-carboxylate* ***(212).*** Sulfonamide **203** (40.0 mg, 80.9 μmol) was dissolved in MeOH (8.5 mL) and Mg ribbon (983 mg, 40.5 mmol) was added. The suspension was sonicated for 1 h, as the bath temperature was increased from rt to 40 °C. The mixture was poured into satd NH_4Cl (50 mL) and the resulting mixture was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (2% MeOH/1% Et_3N in CH_2Cl_2) to provide amine **212** (19.5 mg, 71%) as a white powder. IR

(neat) 3393, 2923, 1726, 1458, 1254 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.8 Hz, 1H), 7.26 (d, *J* = 8.1 Hz, 1H), 7.18 (t, *J* = 7.2 Hz, 1H), 7.11 (t, *J* = 7.7 Hz, 1H), 5.42 (s, 1H), 4.15 (d, *J* = 10.8 Hz, 1H), 4.05 (q, *J* = 6.7 Hz, 1H), 3.83 (s, 3H), 3.68 (d, *J* = 10.8 Hz, 1H), 2.63-2.59 (m, 1H), 2.55 (dd, *J* = 4.9, 12.0 Hz, 1H), 2.35 (td, *J* = 2.6, 12.2 Hz, 1H), 2.26-2.23 (m, 1H), 2.10 (s, 3H), 1.92 (d, *J* = 13.7 Hz, 1H), 1.86-1.82 (m, 1H), 1.36 (d, *J* = 6.7 Hz, 3H), 1.71-1.61 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 133.8, 132.7, 129.7, 121.4, 119.6, 119.0, 108.2, 104.6, 71.9, 68.1, 65.7, 52.1, 48.0, 41.6, 37.2, 33.9, 28.3, 17.7, 9.0; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{20}H_{25}N_2O_3$ 341.1865; found 341.1861.



alstoscholarisine C (**3**)

*(±)-Alstoscholarisine C (**3**).* Secondary amine **212** (9.1 mg, 26.7 μmol) was dissolved in a mixture of glacial acetic acid (0.60 mL) and 37% aqueous formaldehyde (0.10 mL, 40 mg of formaldehyde, 1.34 mmol), and $NaBH_3CN$ (10.0 mg, 0.159 mmol) was added. The mixture was stirred at rt for 1 h, poured into satd Na_2CO_3 (20 mL) and the resulting mixture was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were dried over Na_2SO_4, concentrated *in vacuo*, and the residue was purified by preparative thin-layer chromatography (75% EtOAc in hexanes) to provide (±)-alstoscholarisine C (**3**) (8.0 mg, 84%) as a white solid. IR (neat) 2941, 1724, 1457, 1257, 1199, 1121, 1081, 743 cm^{-1}; ^1H NMR (500 MHz, $(CD_3)_2CO$) δ 7.53 (d, *J* = 8.2 Hz, 1H), 7.44 (d, *J* = 7.8 Hz, 1H), 7.05 (t, *J* = 7.3 Hz, 1H), 6.98 (t, *J* = 7.6 Hz, 1H), 5.39 (d, *J* = 2.1 Hz, 1H), 4.05 (d, *J* = 10.5 Hz, 1H), 3.95 (q, *J* = 6.8 Hz, 1H), 3.84 (s, 3H), 3.48 (d, *J* = 10.5 Hz, 1H), 2.58 (dd, *J* = 3.4, 6.8 Hz, 1H), 2.35 (dd, *J* = 2.7, 4.9 Hz, 1H), 2.33 (s, 3H), 2.29 (t, *J* = 2.5 Hz, 1H), 2.22-2.17 (m, 1H), 2.14 (s, 3H), 1.92-1.87 (m, 2H), 1.30 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz,

$(CD_3)_2CO$) δ 173.5, 137.6, 134.0, 129.7, 121.2, 119.4, 118.4, 111.2, 105.3, 72.2, 71.9, 69.1, 52.2, 49.2, 46.1, 45.1, 43.1, 33.7, 28.8, 18.0, 9.1; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{21}H_{27}N_2O_3$ 355.2022; found 355.2008.

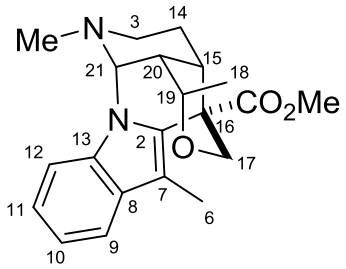
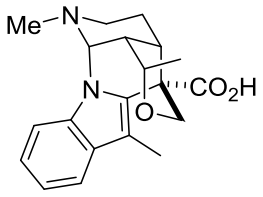


Table 9. Comparison of ^1H NMR Spectra of Natural and Synthetic Alstoscholarisine C (**3**) in $(CD_3)_2CO$

	natural (600 MHz)[5]	synthetic (500 MHz)
H-3	2.18 (m)	2.22-2.17 (m)
	2.34 (m)	2.37-2.34 (m)
H-6	2.06 (s)	2.14 (s)
H-9	7.44 (d, *J* = 7.9 Hz)	7.44 (d, *J* = 7.8 Hz)
H-10	6.98 (t, *J* = 7.9 Hz)	6.98 (t, *J* = 7.6 Hz)
H-11	7.05 (t, *J* = 7.9 Hz)	7.05 (t, *J* = 7.3 Hz)
H-12	7.52 (d, *J* = 7.9 Hz)	7.53 (d, *J* = 8.2 Hz)
H-14	1.88 (m)	1.92-1.87 (m)
	1.88 (m)	1.92-1.87 (m)
H-15	2.57 (m)	2.61-2.56 (m)
H-17	3.48 (d, *J* = 10.5 Hz)	3.48 (d, *J* = 10.5 Hz)
	4.04 (d, *J* = 10.5 Hz)	4.05 (d, *J* = 10.4 Hz)
H-18	1.28 (d, *J* = 6.8 Hz)	1.30 (d, *J* = 6.8 Hz)
H-19	3.94 (q, *J* = 6.8 Hz)	3.95 (q, *J* = 6.8 Hz)
H-20	2.28 (t, *J* = 3.0 Hz)	2.29 (t, *J* = 2.5 Hz)
H-21	5.38 (d, *J* = 3.0 Hz)	5.39 (d, *J* = 2.1 Hz)
NCH_3	2.31 (s)	2.33 (s)
OCH_3	3.82 (s)	3.84 (s)

Table 10. Comparison of ^{13}C NMR Spectra of Natural and Synthetic Alstoscholarisine C (**3**) in $(CD_3)_2CO$

	natural (150 MHz)[5]	synthetic (125 MHz)
C-2	133.9	134.0
C-3	46.0	46.1
C-6	9.0	9.1
C-7	105.1	105.3
C-8	129.5	129.7
C-9	118.3	118.4
C-10	119.3	119.4
C-11	121.1	121.2
C-12	111.1	111.2
C-13	137.5	137.6
C-14	28.7	28.8
C-15	33.5	33.7
C-16	49.1	49.2
C-17	68.9	69.1
C-18	17.9	18.0
C-19	72.1	72.2
C-20	42.9	43.1
C-21	71.8	71.9
NCH_3	45.0	45.1
-CO-	173.4	173.5
OCH_3	52.2	52.2



(±)-alstoscholarisine D (**4**)

(±)-Alstoscholarisine D (4). (±)-Alstoscholarisine C (**3**) (15.3 mg, 0.0432 mmol) was dissolved in a mixture of absolute ethanol (2.7 mL) and 1 M NaOH (4.4 mL) and the solution was stirred at 70 °C for 20 h. The mixture was cooled to rt and Amberlite CG-50 (600 mg) was added. The suspension was filtered through a pad of Celite and the filtrate was concentrated *in vacuo*. The residue was purified by preparative thin-layer chromatography on RP-8 modified silica gel (50%

MeOH in H_2O) to provide (±)-alstoscholarisine D (**4**) (12.6 mg, 86%) as an off white solid. IR (neat) 3358, 2925, 1589, 1459, 1379, 1202, 1033, 739 cm^{-1}; ^1H NMR (500 MHz, D_3COD) δ 7.46 (d, *J* = 8.2 Hz, 1H), 7.42 (d, *J* = 7.8 Hz, 1H), 7.03 (t, *J* = 7.8 Hz, 1H), 6.96 (t, *J* = 7.5 Hz, 1H), 5.34 (d, *J* = 1.6 Hz, 1H), 4.08 (d, *J* = 10.6 Hz, 1H), 3.93 (q, *J* = 6.7 Hz, 1H), 3.49 (d, *J* = 10.6 Hz, 1H), 2.55 (br s, 1H), 2.45 (td, *J* = 3.4, 12.7 Hz, 1H), 2.40-2.35 (m, 1H), 2.34 (s, 3H), 2.29-2.20 (m, 2H), 2.23 (s, 3H), 1.87-1.78 (m, 1H), 1.34 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, D_3COD) δ 178.3, 138.2, 137.6, 130.8, 121.1, 119.6, 118.5, 110.9, 106.5, 73.2, 72.0, 71.0, 51.5, 47.1, 45.0, 43.5, 33.4, 29.0, 18.3, 9.8; HRMS (ESI-TOF) *m/z*: $[M - H]^-$ calcd for $C_{20}H_{23}N_2O_3$ 339.1709; found 339.1728.

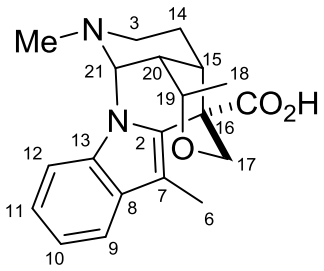
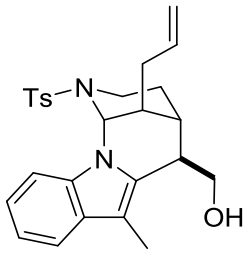


Table 11. Comparison of ^{1}H NMR Spectra of Natural and Synthetic Alstoscholarisine D (**4**) in CD_3OD

	natural (600 MHz)[5]	synthetic (500 MHz)
H-3	2.46 (br d, *J* = 10.5 Hz)	2.40-2.35 (m)
	2.46 (br d, *J* = 10.5 Hz)	2.45 (td, *J* = 3.4, 12.7 Hz)
H-6	2.21 (s)	2.23 (s)
H-9	7.44 (d, *J* = 7.9 Hz)	7.42 (d, *J* = 7.8 Hz)
H-10	7.00 (t, *J* = 7.9 Hz)	6.96 (t, *J* = 7.5 Hz)
H-11	7.07 (t, *J* = 7.9 Hz)	7.03 (t, *J* = 7.8 Hz)
H-12	7.48 (d, *J* = 7.9 Hz)	7.46 (d, *J* = 8.2 Hz)
H-14	1.85 (m)	1.87-1.78 (m)
	2.24 (m)	2.29-2.20 (m)
H-15	2.57 (br s)	2.55 (br s)
H-17	3.50 (d, *J* = 10.5 Hz)	3.49 (d, *J* = 10.6 Hz)
	4.10 (d, *J* = 10.5 Hz)	4.08 (d, *J* = 10.6 Hz)
H-18	1.33 (d, *J* = 6.8 Hz)	1.34 (d, *J* = 6.7 Hz)
H-19	3.94 (q, *J* = 6.8 Hz)	3.93 (q, *J* = 6.7 Hz)
H-20	2.27 (br s)	2.29-2.20 (m)
H-21	5.49 (d, *J* = 2.3 Hz)	5.34 (d, *J* = 1.6 Hz)
NCH_3	2.38 (s)	2.34 (s)

Table 12. Comparison of ^{13}C NMR Spectra of Natural and Synthetic Alstoscholarisine D (**4**) in CD_3OD

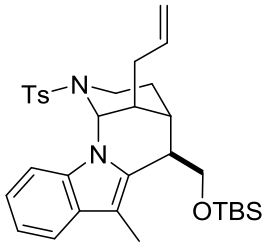
	natural (150 MHz)[5]	synthetic (125 MHz)
C-2	136.7	137.6
C-3	47.1	47.1
C-6	9.8	9.8
C-7	107.1	106.5
C-8	130.8	130.8
C-9	118.7	118.5
C-10	120.1	119.6
C-11	121.7	121.1
C-12	110.9	110.9
C-13	138.1	138.2
C-14	28.5	29.0
C-15	33.1	33.4
C-16	50.8	51.5
C-17	70.6	71.0
C-18	18.2	18.3
C-19	72.9	73.2
C-20	42.9	43.5
C-21	71.9	72.0
NCH_3	44.5	45.0
-CO-	179.3	178.3



214

((1R,5S*,6R*,13R*)-13-Allyl-7-methyl-2-tosyl-1,2,3,4,5,6-hexahydro-1,5-methano[1,3]diazocino[1,8-a]indol-6-yl)methanol (**214**).* Powdered $LiAlH_4$ (125 mg, 3.30 mmol) was added to a 0 °C solution of ester **163** (1.055 g, 2.20 mmol) in THF (8.8 mL) and the mixture was stirred at 0 °C for 1 h. The reaction mixture was quenched by sequential dropwise addition of

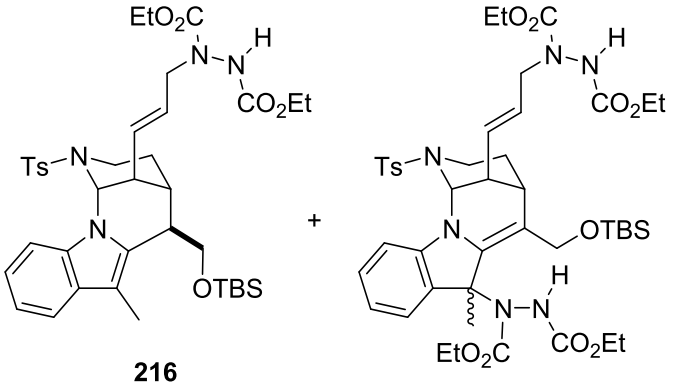
H_2O (0.13 mL), 15% NaOH (0.13 mL), and H_2O (0.39 mL) and was warmed to rt. $MgSO_4$ was added and the suspension was filtered through a Celite pad. The filtrate was concentrated *in vacuo* and the residue was purified by flash chromatography on silica gel (35% EtOAc in hexanes) to provide alcohol **214** (0.967 g, 97%) as a white powder. IR (neat) 3539, 2934, 1460, 1321, 1154 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.65-7.57 (m, 1H), 7.49-7.41 (m, 3H), 7.16-7.08 (m, 2H), 7.04 (d, *J* = 8.0 Hz, 2H), 6.39 (s, 1H), 5.95 (ddt, *J* = 7.4, 10.2, 17.2 Hz, 1H), 5.28 (d, *J* = 17.2 Hz, 1H), 5.20 (d, *J* = 10.2 Hz, 1H), 3.86 (dd, *J* = 4.3, 10.8 Hz, 1H), 3.65 (t, *J* = 10.3 Hz, 1H), 3.25 (dd, *J* = 4.3, 9.2 Hz, 1H), 3.15 (dd, *J* = 5.8, 13.4 Hz, 1H), 2.78-2.61 (m, 1H), 2.55-2.37 (m, 4H), 2.30 (s, 3H), 2.26 (s, 3H), 2.23-2.15 (m, 1H), 1.76 (br s, 1H), 1.42 (d, *J* = 13.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.4, 136.8, 135.3, 134.9, 132.0, 129.6, 129.5, 127.5, 121.5, 120.2, 117.9, 110.9, 107.2, 64.0, 62.3, 41.9, 38.7, 36.4, 34.1, 29.5, 26.1, 21.5, 9.0; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{26}H_{31}N_2O_3S$ 451.2055; found 451.2049.



215

(1R,5S*,6R*,13R*)-13-Allyl-6-(((tert-butyldimethylsilyl)oxy)methyl)-7-methyl-2-tosyl-1,2,3,4,5,6-hexahydro-1,5-methano[1,3]diazocino[1,8-a]indole (**215**).* Alcohol **214** (278.1 mg, 0.617 mmol) was dissolved in CH_2Cl_2 (6.2 mL) and imidazole (126 mg, 1.85 mmol) was added followed by TBSCl (140 mg, 0.93 mmol). The solution was stirred at rt for 2 h and was diluted with satd NH_4Cl (20 mL). The mixture was extracted with CH_2Cl_2 (2 × 25 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (5% to 7.5% EtOAc in hexanes) to provide silyl ether **215**

(340.9 mg, 98%) as a white foam. IR (neat) 2929, 1460, 1322, 1155, 1088 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.62-7.56 (m, 1H), 7.49-7.40 (m, 3H), 7.15-7.07 (m, 2H), 7.03 (d, *J* = 8.0 Hz, 2H), 6.39 (s, 1H), 5.98 (ddt, *J* = 7.0, 10.3, 17.1 Hz, 1H), 5.28 (d, *J* = 17.1 Hz, 1H), 5.19 (d, *J* = 10.3 Hz, 1H), 3.82 (dd, *J* = 4.5, 10.3 Hz, 1H), 3.53 (t, *J* = 10.4 Hz, 1H), 3.22 (dd, *J* = 4.5, 10. 4 Hz, 1H), 3.17 (dd, *J* = 5.7, 13.3 Hz, 1H), 2.77-2.64 (m, 1H), 2.62-2.56 (m, 1H), 2.52-2.37 (m, 3H), 2.30 (s, 3H), 2.25 (s, 3H), 2.23-2.16 (m, 1H), 1.41 (d, *J* = 13.2 Hz, 1H), 0.91 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.2, 136.9, 135.4, 134.8, 132.5, 129.5, 129.4, 127.5, 121.4, 120.1, 117.8, 117.8, 110.9, 106.9, 63.3, 62.3, 41.9, 38.8, 36.0, 34.1, 28.2, 26.1, 26.0, 21.5, 18.3, 8.9, -5.2, -5.3; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{32}H_{45}N_2O_3SSi$ 565.2920; found 565.2941.



216 **217**

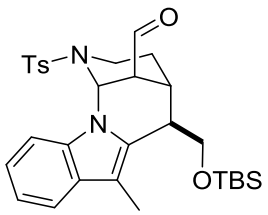
Diethyl 1-((E)-3-((1R,5S*,6R*,13R*)-6-(((tert-Butyldimethylsilyl)oxy)methyl)-7-methyl-2-tosyl-1,2,3,4,5,6-hexahydro-1,5-methano[1,3]diazocino[1,8-a]indol-13-yl)allyl)hydrazine-1,2-dicarboxylate (**216**) and Diethyl 1-((E)-3-((1R*,5S*,7R*/S*,13R*)-7-(1,2-Bis(ethoxycarbonyl)hydrazinyl)-6-(((tert-butyldimethylsilyl)oxy)methyl)-7-methyl-2-tosyl-1,2,3,4,5,7-hexahydro-1,5-methano[1,3]diazocino[1,8-a]indol-13-yl)allyl)hydrazine-1,2-dicarboxylate (**217**).* DEAD (40% in PhMe, 1.1 mL, 431 mg of DEAD, 2.48 mmol) was added to a solution of terminal olefin **215** (279.7 mg, 0.495 mmol) in PhMe (8.8 mL) and the mixture was

heated at reflux for 12 h. Additional DEAD (40% in PhMe, 0.55 mL, 215 mg of DEAD, 1.24 mmol) was added and the solution was refluxed for a further 8 h. The mixture was concentrated *in vacuo* and the residue was purified by flash chromatography on silica gel (gradient 15% to 25% acetone in hexanes) to provide ene adduct **216** (193.8 g, 53%) as a white foam and bis-hydrazine **217** (192.8 mg, 43%, 3.8:1 mixture of inseparable stereoisomers) as a pale yellow solid.

Ene adduct **216**: IR (neat) 3309, 2930, 1709, 1460, 1319, 1207, 1154, 1087 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58-7.53 (m, 1H), 7.49-7.44 (m, 1H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.16-7.09 (m, 2H), 7.01 (d, *J* = 7.9 Hz, 2H), 6.45 (s, 1H), 6.01 (dd, *J* = 6.0, 15.8 Hz, 1H), 5.92 (dt, *J* = 5.7, 15.7 Hz, 1H), 4.27-4.16 (m, 6H), 3.84 (dd, *J* = 4.5, 10.5 Hz, 1H), 3.57 (t, *J* = 10.4 Hz, 1H), 3.24 (dd, *J* = 4.4, 10.1 Hz, 1H), 3.17-3.09 (m, 2H), 2.67-2.62 (m, 1H), 2.47-2.38 (m, 1H), 2.34-2.28 (m, 1H), 2.29 (s, 3H), 2.25 (s, 3H), 1.41 (d, *J* = 13.6 Hz, 1H), 1.33-1.20 (m, 6H), 0.89 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.5, 143.5, 136.7, 134.8, 132.2, 129.7, 129.5, 128.0, 127.5, 121.6, 120.4, 118.0, 110.7, 107.3, 63.6, 62.6, 61.9, 41.7, 38.7, 38.3, 29.9, 29.4, 26.5, 26.0, 21.5, 18.4, 14.7, 9.0, -5.1, -5.2; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{38}H_{55}N_4O_7SSi$ 739.3561; found 739.3574.

Bis-hydrazine **217**: IR (neat) 3297, 2933, 1708, 1463, 1324, 1256, 1090 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, *J* = 7.0 Hz, 1H), 7.53-7.37 (m, 3H), 7.22-7.02 (m, 4H), 6.44 (s, 0.8H), 6.33 (s, 0.2H), 6.19 (s, 1H), 6.07-5.75 (m, 2H), 4.98 (d, *J* = 13.0 Hz, 1H), 4.79 (d, *J* = 13.0 Hz, 1H), 4.35-3.96 (m, 10H), 3.81-3.69 (m, 1H), 3.60 (t, *J* = 9.8 Hz, 1H), 3.48-3.05 (m, 3H), 2.62 (s, 1H), 2.31 (s, 3H), 1.48-1.04 (m, 15H), 0.86 (s, 9H), 0.04 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.4, 143.7, 136.6, 136.2, 135.2, 131.6, 129.5, 128.6, 128.3, 127.5, 122.2, 121.2, 118.5, 111.2, 106.5, 65.0, 63.0, 62.7, 62.0, 54.0, 41.1, 38.6, 38.1, 31.9, 30.1, 29.4, 26.2, 25.9, 21.5, 18.4,

14.7, -5.2, -5.4; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{44}H_{64}N_6O_{11}SiSNa$ 935.4021; found 935.4035.

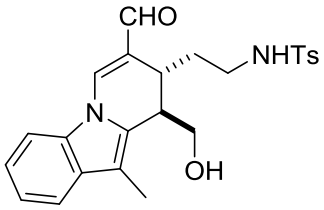


221

(1R,5R*,6R*,13R*)-6-(((tert-Butyldimethylsilyl)oxy)methyl)-7-methyl-2-tosyl-1,2,3,4,5,6-hexahydro-1,5-methano[1,3]diazocino[1,8-a]indole-13-carbaldehyde* ***(221).*** Ene adduct **216** (184.1 mg, 0.249 mmol) was dissolved in a mixture of THF (3.6 mL) and H_2O (1.8 mL), and NMO (146 mg, 1.25 mmol) was added followed by a solution of OsO_4 (2.5% in *tert*-butanol, 0.06 mL, 1.3 mg of OsO_4, 0.005 mmol). The reaction mixture was stirred at rt for 14 h and quenched by addition of satd Na_2SO_3 (10 mL). The mixture was stirred for 10 min and extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to yield the crude diol as a colorless oil.

The diol was dissolved in EtOAc (71 mL) and $Pb(OAc)_4$ (166 mg, 0.37 mmol) was added. The reaction mixture was stirred at rt for 1 h. The orange solution was filtered through a silica gel pad and the filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (gradient 15% to 20% EtOAc in hexanes) to provide aldehyde **221** (80.4 mg, 58%) as white needles. IR (neat) 2927, 1727, 1460, 1321, 1155, 1087 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.06 (s, 1H), 7.71 (d, *J* = 7.6 Hz, 1H), 7.52 (d, *J* = 8.2 Hz, 2H), 7.47 (d, *J* = 7.1 Hz, 1H), 7.20-7.09 (m, 4H), 7.06 (s, 1H), 3.85 (dd, *J* = 4.1, 10.4 Hz, 1H), 3.51 (t, *J* = 10.0 Hz, 1H), 3.27 (dd, *J* = 3.5, 8.9 Hz, 1H), 3.24-3.14 (m, 2H), 3.02 (dd, *J* = 5.9, 13.6 Hz, 1H), 2.54 (td, *J* = 3.0, 13.2, Hz, 1H), 2.34 (s, 3H), 2.26 (s, 3H), 2.06-1.90 (m, 1H), 1.52 (d, *J* = 15.3 Hz, 1H), 0.87 (s, 9H), 0.05 (s,

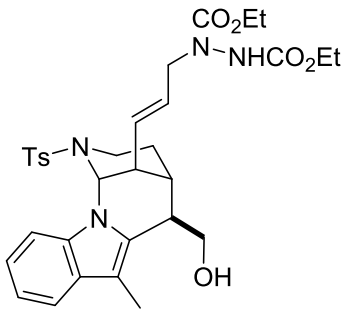
3H), 0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.9, 143.9, 136.2, 134.8, 132.0, 129.8, 129.6, 127.8, 122.0, 120.6, 118.0, 111.2, 107.9, 63.9, 59.2, 49.0, 41.3, 38.7, 27.7, 26.2, 26.0, 21.6, 18.4, 9.0, -5.2, -5.3; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{30}H_{41}N_2O_4SSi$ 553.2556; found 553.2538.



222

N-(2-((8R,9R*)-7-Formyl-9-(hydroxymethyl)-10-methyl-8,9-dihydropyrido[1,2-a]indol-8-yl)ethyl)-4-methylbenzenesulfonamide (**222**).* Silyl ether **221** (18.5 mg, 33.5 μmol) was dissolved in THF (0.34 mL) and the solution was cooled to 0 °C. A solution of TBAF in THF (1.0 M, 0.05 mL, 0.05 mmol) was added and the mixture was stirred at 0 °C for 30 min. The reaction mixture was diluted with satd NH_4Cl (20 mL) and extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (gradient 55% to 65% EtOAc in hexanes) to provide α,β-unsaturated aldehyde **222** (8.7 mg, 59%) as a pale yellow solid. IR (neat) 3463, 3272, 2923, 1657, 1606, 1464, 1318, 1154 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.45 (s, 1H), 7.83 (s, 1H), 7.72 (d, *J* = 8.1 Hz, 2H), 7.51 (d, *J* = 7.3 Hz, 1H), 7.42 (d, *J* = 7.8 Hz, 1H), 7.31-7.24 (m, 4H), 5.79 (dd, *J* = 4.2, 8.8 Hz, 1H), 3.53-3.44 (m, 2H), 3.26-3.19 (m, 2H), 3.04 (ddd, *J* = 4.9, 9.2, 17.9 Hz, 1H), 2.55 (ddd, *J* = 4.3, 9.4, 17.9 Hz, 1H), 2.40 (s, 3H), 2.29 (s, 3H), 1.90 (br s, 1H), 1.75-1.67 (m, 1H), 1.38-1.30 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.7, 143.2, 139.6, 137.5, 134.5, 131.5, 129.9, 129.7, 127.2, 124.1, 123.4, 122.0, 119.5, 117.3, 108.9, 64.0, 40.4, 40.0, 34.9,

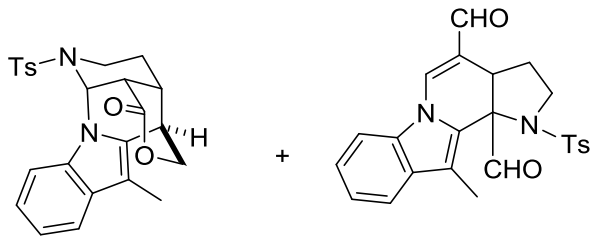
27.5, 21.6, 8.7; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{24}H_{27}N_2O_4S$ 439.1692; found 439.1675.



223

Diethyl 1-((E)-3-((1R,5S*,6R*,13R*)-6-(Hydroxymethyl)-7-methyl-2-tosyl-1,2,3,4,5,6-hexahydro-1,5-methano[1,3]diazocino[1,8-a]indol-13-yl)allyl)hydrazine-1,2-dicarboxylate* ***(223).*** A solution of silyl ether **216** (681 mg, 0.922 mmol) in THF (9.2 mL) was cooled to 0 °C and a solution of TBAF in THF (1.0 M, 1.4 mL, 1.4 mmol) was added dropwise. The mixture was stirred at 0 °C for 30 min, diluted with satd NH_4Cl (30 mL), and extracted with EtOAc (2 × 30 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (gradient 60% to 70% EtOAc in hexanes) to provide alcohol **223** (519 mg, 90%) as a white foam. IR (neat) 3477, 3330, 2929, 1710, 1461, 1348, 1155 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.5 Hz, 1H), 7.49-7.45 (m, 1H), 7.42 (d, *J* = 8.1 Hz, 2H), 7.16-7.10 (m, 2H), 7.02 (d, *J* = 7.8 Hz, 2H), 6.45 (s, 1H), 6.02 (dd, *J* = 6.0, 15.7 Hz, 1H), 5.92 (dt, *J* = 5.8, 15.7 Hz, 1H), 4.26-4.17 (m, 6H), 3.89 (dd, *J* = 4.0, 10.8 Hz, 1H), 3.71 (t, *J* = 10.0 Hz, 1H), 3.28 (dd, *J* = 4.4, 9.3 Hz, 1H), 3.21-3.16 (m, 1H), 3.13 (dd, *J* = 5.7, 13.5 Hz, 1H), 2.60-2.56 (m, 1H), 2.44 (t, *J* = 13.3 Hz, 1H), 2.29 (s, 3H), 2.26 (s, 3H), 1.93 (br s, 1H), 1.44 (d, *J* = 13.8 Hz, 1H), 1.34-1.23 (m, 7H); ^{13}C NMR (125 MHz,

$CDCl_3$) δ 156.4, 143.5, 136.7, 134.9, 131.9, 131.7, 129.7, 129.5, 128.2, 127.5, 121.8, 120.4, 118.1, 110.8, 107.5, 64.1, 62.7, 62.6, 62.0, 41.6, 38.7, 38.6, 31.1, 29.8, 21.5, 14.7, 14.7, 9.0; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{32}H_{41}N_4O_7S$ 625.2696; found 625.2679.



226 **227**

(1R,5R*,6R*,16S*)-7-Methyl-2-tosyl-1,2,3,4,5,6-hexahydro-1,5,6-(epiethane[1,1,2]triyloxymethano)[1,3]diazocino[1,8-a]indol-15-one* ***(226)*** *and 11-Methyl-1-tosyl-1,2,3,3a-tetrahydro-11bH-pyrrolo[2',3',3,4]pyrido[1,2-a]indole-4-11b-dicarbaldehyde* ***(227).*** Method A: Ene adduct **223** (128.5 mg, 0.206 mmol) was dissolved in a mixture of THF (2.9 mL) and H_2O (1.4 mL), and NMO (121 mg, 1.03 mmol) was added followed by a solution of OsO_4 (4% in H_2O, 0.05 mL, 2.0 mg of OsO_4, 0.008 mmol). The reaction mixture was stirred at rt for 4 h and diluted with satd Na_2SO_3 (10 mL). The resulting mixture was stirred for 10 min and extracted with EtOAc (2 × 30 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, and concentrated *in vacuo* to yield the crude triol as a colorless oil.

The triol was dissolved in EtOAc (59 mL) and $Pb(OAc)_4$ (137 mg, 0.31 mmol) was added. The reaction mixture was stirred at rt for 1 h. The orange solution was filtered through a silica gel pad and the filtrate was concentrated *in vacuo* to provide the crude aldehyde as a colorless oil.

The aldehyde was dissolved in $CHCl_3$ (3.4 mL) and DBU (0.06 mL, 63 mg, 0.41 mmol) was added. The mixture was stirred at rt for 15 min, after which glacial acetic acid (0.53 mL) was added, followed by TEMPO (16.1 mg, 0.103 mmol) and $PhI(OAc)_2$ (265 mg, 0.82 mmol). The mixture was stirred at rt for 3 h and was diluted with satd $Na_2S_2O_3$ (10 mL) and satd $NaHCO_3$ (10

mL). The mixture was extracted with CH_2Cl_2 (2 × 30 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (35% EtOAc in hexanes) to provide lactone **226** (28.5 mg, 32%) as a pale yellow foam and bis-aldehyde **227** (24.3 mg, 27%) as a pale yellow powder.

Lactone **226**: IR (neat) 2916, 1732, 1460, 1350, 1326, 1158 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.2 Hz, 2H), 7.52-7.49 (m, 1H), 7.38-7.35 (m, 1H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.19-7.15 (m, 2H), 6.51 (d, *J* = 3.3 Hz, 1H), 4.57 (dd, *J* = 2.4, 10.3 Hz, 1H), 4.31 (dd, *J* = 1.4, 10.4 Hz, 1H), 3.44 (br s, 1H), 3.40 (dd, *J* = 5.7, 14.9 Hz, 1H), 3.17-3.12 (m, 1H), 2.67-2.63 (m, 1H), 2.43 (s, 3H), 2.39-2.33 (m, 1H), 2.24 (s, 3H), 1.83-1.66 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3, 144.1, 137.5, 135.2, 131.1, 130.2, 129.8, 127.2, 122.8, 121.1, 118.5, 111.0, 108.0, 75.8, 62.7, 43.4, 37.5, 32.3, 29.9, 26.8, 21.7, 8.3; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{24}H_{25}N_2O_4S$ 437.1535; found 437.1529.

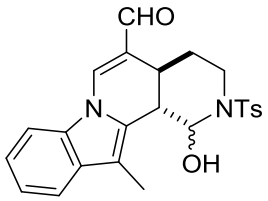
Bis-aldehyde **227**: IR (neat) 2923, 1740, 1668, 1629, 1466, 1157 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 10.23 (s, 1H), 9.38 (s, 1H), 7.58-7.55 (m, 1H), 7.48 (d, *J* = 1.4 Hz, 1H), 7.34-7.28 (m, 2H), 7.13-7.10 (m, 1H), 7.06 (d, *J* = 8.2 Hz, 2H), 6.69 (d, *J* = 8.0 Hz, 2H), 4.09 (td, *J* = 1.9, 9.7 Hz, 1H), 3.61-3.52 (m, 2H), 2.74-2.68 (m, 1H), 2.40 (s, 3H), 2.16 (s, 3H), 2.12-2.04 (m, 1H), 1.43 (s, 1H), 1.25 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.4, 188.6, 143.0, 139.6, 137.1, 134.7, 130.8, 128.7, 126.1, 125.4, 123.6, 122.5, 122.1, 120.3, 118.2, 108.9, 72.5, 49.4, 41.5, 26.0, 21.5, 11.0; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{24}H_{23}N_2O_4S$ 435.1379; found 435.1350.

Method B: Internal alkene **260** (150.8 mg, 0.335 mmol) was dissolved in a mixture of THF (4.8 mL) and H_2O (2.4 mL), and NMO (196 mg, 1.68 mmol) was added followed by a solution of OsO_4 (4% in H_2O, 0.04 mL, 1.7 mg of OsO_4, 0.007 mmol). The reaction mixture was stirred at rt for 4 h and quenched by addition of satd Na_2SO_3 (10 mL). The mixture was stirred for 10 min and

extracted with EtOAc (2 × 30 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, and concentrated *in vacuo* to yield the crude triol as a colorless oil.

The triol was dissolved in EtOAc (96 mL) and $Pb(OAc)_4$ (223 mg, 0.503 mmol) was added. The reaction mixture was stirred at rt for 1 h. The orange solution was filtered through a silica gel pad and the filtrate was concentrated *in vacuo* to provide the crude aldehyde as a colorless oil.

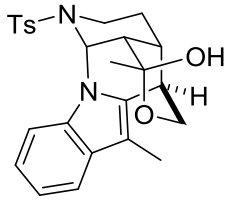
The aldehyde was dissolved in $CHCl_3$ (5.9 mL) and DBU (0.10 mL, 102 mg, 0.67 mmol) was added. The mixture was stirred at rt for 15 min, after which glacial acetic acid (0.86 mL) was added, followed by TEMPO (26.2 mg, 0.17 mmol) and $PhI(OAc)_2$ (432 mg, 1.34 mmol). The mixture was stirred at rt for 3 h and was diluted with satd $Na_2S_2O_3$ (10 mL) and satd $NaHCO_3$ (10 mL). The mixture was extracted with CH_2Cl_2 (2 × 30 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (35% EtOAc in hexanes) to provide lactone **226** (59.8 mg, 41%) as a pale yellow foam and bis-aldehyde **227** (37.5 mg, 26%) as a pale yellow powder. Both compounds had spectroscopic data identical to material prepared by Method A.



235

(1R/S*,4aR*,12bR*)-1-Hydroxy-12-methyl-2-tosyl-1,2,3,4,4a,12b-hexahydroindolo[2,1-a][2,7]naphthyridine-5-carbaldehyde (**235**).* Ring-opened alcohol **222** (3.9 mg, 8.9 μmol) was dissolved in a mixture of $CHCl_3$ (0.16 mL) and glacial acetic acid (0.02 mL), and TEMPO (3.5 mg, 0.022 mmol) was added, followed by $PhI(OAc)_2$ (11.5 mg, 0.036 mmol). The reaction mixture was stirred at rt for 3 h and was diluted with satd $Na_2S_2O_3$ (10 mL) and satd $NaHCO_3$ (10 mL). The mixture was extracted with CH_2Cl_2 (2 × 20 mL), dried over Na_2SO_4 and concentrated *in vacuo*.

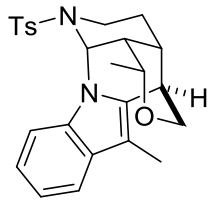
The residue was purified by preparative thin-layer chromatography on silica gel (35% EtOAc in hexanes) to provide hemiaminal **235** (2.4 mg, 62%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.42 (s, 1H), 7.72 (s, 1H), 7.61 (d, *J* = 8.2 Hz, 2H), 7.55 (d, *J* = 7.3 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 1H), 7.33-7.27 (m, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 5.31 (d, *J* = 6.9 Hz, 1H), 3.60-3.52 (m, 1H), 3.49-3.43 (m, 1H), 2.85 (q, *J* = 7.1 Hz, 1H), 2.60 (s, 3H), 2.38 (s, 3H), 2.19-2.12 (m, 1H), 1.86-1.79 (m, 1H), 1.45-1.41 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 188.8, 144.0, 138.6, 135.4, 134.7, 131.8, 129.9, 127.3, 126.4, 124.6, 123.2, 120.3, 119.9, 119.8, 108.9, 77.3, 56.9, 47.4, 35.4, 30.4, 21.7, 9.3.



238

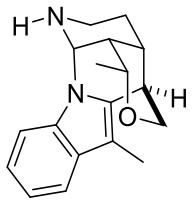
(1R,5R*,6R*,15R*/S*,16S*)-7,15-Dimethyl-2-tosyl-1,2,3,4,5,6-hexahydro-1,5,6-(epiethane[1,1,2]triyloxymethano)[1,3]diazocino[1,8-a]indol-15-ol (**238**).* Lactone **226** (14.5 mg, 33.2 μmol) was dissolved in THF (1.3 mL) and the solution was cooled to -78 °C. A solution of methyllithium in Et_2O (1.6 M, 0.04 mL, 0.064 mmol) was added dropwise and the mixture was stirred at -78 °C for 15 min. The reaction was diluted with satd NH_4Cl (20 mL) and extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by preparative thin-layer chromatography on silica gel (50% EtOAc in hexanes) to provide hemiketal **238** (10.8 mg, 72%) as a colorless oil. IR (neat) 3472, 2927, 1461, 1327, 1157, 1092 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.1 Hz, 2H), 7.51-7.47 (m, 1H), 7.43-7.40 (m, 1H), 7.24 (d, *J* = 8.1 Hz, 2H), 7.15-7.11 (m, 2H), 6.44 (d, *J* = 2.0 Hz, 1H), 4.18 (d, *J* = 10.2 Hz, 1H), 3.54 (dd, *J* = 2.1, 10.2 Hz, 1H), 3.21 (dd, *J* = 6.5, 14.6 Hz, 1H), 3.08 (s, 1H), 2.86-2.82 (m, 1H), 2.40 (s, 3H), 2.30-2.26 (m, 1H),

2.25-17 (m, 1H), 2.21 (s, 3H), 2.02 (s, 1H), 1.93-1.84 (m, 1H), 1.63 (d, *J* = 14.0 Hz, 1H), 1.56 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.7, 137.9, 135.2, 134.2, 130.1, 129.9, 127.2, 121.7, 120.4, 118.4, 110.2, 105.8, 95.9, 67.4, 61.8, 43.6, 38.2, 33.7, 29.1, 28.8, 27.6, 21.6, 8.1; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{25}H_{29}N_2O_4S$ 453.1848; found 453.1853.



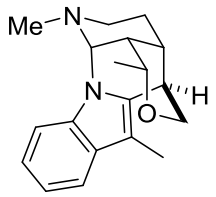
240

(1R,5R*,6R*,15R*,16S*)-7,15-Dimethyl-2-tosyl-1,2,3,4,5,6-hexahydro-1,5,6-(epiethane[1,1,2]triyloxymethano)[1,3]diazocino[1,8-a]indole (**240**).* Et_3SiH (0.04 mL, 29 mg, 0.25 mmol) and TMSOTf (0.03 mL, 40 mg, 0.18 mmol) were added to a -78 °C solution of hemiketal **238** (32.3 mg, 0.071 mmol) in CH_2Cl_2 (3.0 mL). The solution was stirred at -78 °C for 45 min and Et_3N (0.05 mL) was added and the mixture was warmed to rt. Satd $NaHCO_3$ (20 mL) was added and the mixture was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (30% EtOAc in hexanes) to provide tetrahydropyran **240** (22.3 mg, 72%) as a colorless film. IR (neat) 2916, 1462, 1348, 1326, 1139, 1095 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.2 Hz, 2H), 7.52-7.45 (m, 1H), 7.39-7.33 (m, 1H), 7.23 (d, *J* = 9.0 Hz, 2H), 7.15-7.07 (m, 2H), 6.47 (s, 1H), 3.81 (dd, *J* = 1.8, 10.2 Hz, 1H), 3.76-3.67 (m, 2H), 3.25 (dd, *J* = 6.2, 14.2 Hz, 1H), 3.11 (s, 1H), 2.40 (s, 3H), 2.38-2.32 (m, 1H), 2.24-2.15 (m, 1H), 2.20 (s, 3H), 2.07-1.88 (m, 2H), 1.63 (d, *J* = 13.5 Hz, 1H), 1.37 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.6, 138.0, 135.3, 134.5, 130.0, 129.9, 127.2, 121.5, 120.3, 118.4, 110.2, 105.7, 74.3, 72.9, 60.9, 41.2, 38.5, 34.5, 34.2, 29.6, 21.6, 18.5, 8.1; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{25}H_{29}N_2O_3S$ 437.1899; found 437.1904.



241

(1S,5R*,6R*,15R*,16S*)-7,15-Dimethyl-1,2,3,4,5,6-hexahydro-1,5,6-(epiethane[1,1,2]triyloxymethano)[1,3]diazocino[1,8-a]indole (**241**).* Sulfonamide **240** (18.3 mg, 0.042 mmol) was dissolved in MeOH (2.8 mL) and Mg ribbon (509 mg, 21.0 mmol) was added. The mixture was sonicated for 30 min, as the bath temperature was increased from rt to 35 °C. The reaction was poured into satd NH_4Cl (30 mL) and extracted with EtOAc (2 × 30 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by preparative thin-layer chromatography on silica gel (EtOAc) to provide secondary amine **241** (10.4 mg, 88%) as a colorless film. IR (neat) 3308, 2918, 2851, 1460, 1337, 1091 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.5 Hz, 1H), 7.34 (d, *J* = 7.8 Hz, 1H), 7.18-7.09 (m, 2H), 5.65 (s, 1H), 3.83 (dd, *J* = 2.3, 10.3 Hz, 1H), 3.79 (qd, *J* = 2.6, 6.5 Hz, 1H), 3.74 (d, *J* = 10.3 Hz, 1H), 3.11 (s, 1H), 2.55 (dd, *J* = 6.0, 12.0 Hz, 1H), 2.36 (br s, 1H), 2.29 (s, 1H), 2.23 (s, 3H), 2.16-2.07 (m, 1H), 1.85 (td, *J* = 3.4, 12.7 Hz, 1H), 1.74 (br d, *J* = 13.9 Hz, 1H), 1.32 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.0, 134.7, 130.2, 121.0, 119.8, 118.8, 108.6, 104.1, 74.5, 72.9, 61.3, 40.9, 37.5, 34.7, 34.5, 29.8, 18.5, 8.1; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{23}N_2O$ 283.1810; found 283.1802.



(±)-alstoscholarisine A (**1**)

(±)-Alstoscholarisine A (1). Secondary amine **241** (9.5 mg, 33.6 μmol) was dissolved in a mixture of glacial acetic acid (0.75 mL) and 37% aqueous formaldehyde (0.13 mL, 52 mg of formaldehyde, 1.75 mmol), and $NaBH_3CN$ (12.7 mg, 0.20 mmol) was added. The mixture was stirred at rt for 15 min and was poured into satd Na_2CO_3 (25 mL). The resulting mixture was extracted with CH_2Cl_2 (2 × 25 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by preparative thin-layer chromatography on silica gel (90% EtOAc in hexanes) to provide (±)-alstoscholarisine A (**1**) (6.2 mg, 62%) as a colorless film. IR (neat) 2861, 1640, 1458, 1327, 1126, 1092, 736 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 7.53 (d, *J* = 8.2 Hz, 1H), 7.43 (d, *J* = 7.8 Hz, 1H), 7.06 (t, *J* = 7.5 Hz, 1H), 7.00 (t, *J* = 7.5 Hz, 1H), 5.56 (d, *J* = 1.9 Hz, 1H), 3.81 (qd, *J* = 3.0, 6.5 Hz, 1H), 3.72 (d, *J* = 10.1 Hz, 1H), 3.64 (dd, *J* = 2.5, 10.1 Hz, 1H), 3.16 (br s, 1H), 2.41 (dd, *J* = 6.1, 12.0 Hz, 1H), 2.36-2.32 (m, 1H), 2.32 (s, 3H), 2.24 (s, 3H), 2.23-2.19 (m, 1H), 2.15-2.08 (m, 1H), 1.94 (td, *J* = 4.0, 12.6 Hz, 1H), 1.86 (br d, 15.3 Hz, 1H), 1.26 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 138.5, 136.8, 130.3, 121.4, 120.0, 118.8, 111.3, 105.4, 75.5, 74.4, 67.9, 47.4, 45.4, 43.0, 36.0, 34.6, 31.1, 18.6, 8.0; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{25}N_2O$ 297.1967; found 297.1960.

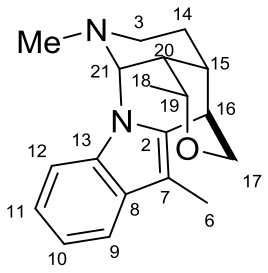
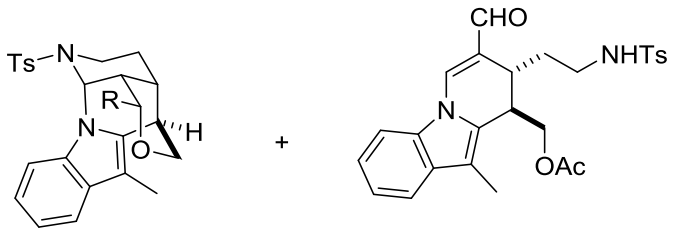


Table 13. Comparison of ^{1}H NMR Spectra of Natural and Synthetic Alstoscholarisine A (**1**) in CD_3OD

	natural (600 MHz)[5]	synthetic (500 MHz)
H-3	1.84 (td, *J* = 4.0, 12.0 Hz)	1.94 (td, *J* = 4.0, 12.6 Hz)
	2.30 (dd, *J* = 6.4, 12.0 Hz)	2.30 (dd, *J* = 6.1, 12.0 Hz)
H-6	2.21 (s)	2.24 (s)
H-9	7.42 (d, *J* = 7.9 Hz)	7.43 (d, *J* = 7.8 Hz)
H-10	6.98 (t, *J* = 7.9 Hz)	7.00 (t, *J* = 7.5 Hz)
H-11	7.04 (t, *J* = 7.9 Hz)	7.06 (t, *J* = 7.5 Hz)
H-12	7.50 (d, *J* = 7.9 Hz)	7.53 (d, *J* = 7.5 Hz)
H-14	1.74 (br d, *J* = 13.6 Hz)	1.86 (br d, *J* = 15.3 Hz)
	2.03 (m)	2.15-2.08 (m)
H-15	2.18 (m)	2.36-2.32 (m)
H-16	3.03 (br s)	3.16 (br s)
H-17	3.57 (dd, *J* = 2.6, 10.2 Hz)	3.64 (dd, *J* = 2.5, 10.1 Hz)
	3.60 (br d, *J* = 10.2 Hz)	3.72 (br d, *J* = 10.1 Hz)
H-18	1.22 (d, *J* = 6.8 Hz)	1.26 (d, *J* = 6.5 Hz)
H-19	3.69 (qd, *J* = 3.0, 6.8 Hz)	3.81 (qd, *J* = 3.0, 6.5 Hz)
H-20	2.12 (br s)	2.23-2.19 (m)
H-21	5.47 (d, *J* = 2.6 Hz)	5.56 (d, *J* = 1.9 Hz)
NCH_3	2.24 (s)	2.32 (s)

Table 14. Comparison of ^{13}C NMR Spectra of Natural and Synthetic Alstoscholarisine A (**1**) in CD_3OD

	natural (150 MHz)[5]	synthetic (125 MHz)
C-2	136.9	136.8
C-3	47.3	47.4
C-6	8.1	8.0
C-7	105.0	105.4
C-8	130.2	130.3
C-9	118.7	118.8
C-10	119.8	120.0
C-11	121.3	121,4
C-12	111.3	111.3
C-13	138.5	138.5
C-14	31.1	31.1
C-15	34.5	34.6
C-16	35.8	36.0
C-17	74.3	74.4
C-18	18.7	18.6
C-19	75.3	75.5
C-20	43.0	43.0
C-21	67.7	67.9
NCH_3	45.6	45.4



242 R = OAc **236**

(1R,5R*,6R*,15R*,16S*)-7-Methyl-2-tosyl-1,2,3,4,5,6-hexahydro-1,5,6-(epiethane[1,1,2]triyloxymethano)[1,3]diazocino[1,8-a]indol-15-yl Acetate* (***242***) *and ((8R*,9R*)-7-Formyl-10-methyl-8-(2-((4-methylphenyl)sulfonamide)ethyl)-8,9-dihydropyridol[1,2-a]indol-9-yl)methyl Acetate* (***236***)**.** Method A: OsO_4 (4% in H_2O, 0.02 mL, 0.8

mg OsO_4, 3.0 μmol) was added to a solution of ene adduct **223** (68.2 mg, 0.110 mmol) and NMO (65 mg, 0.55 mmol) in a mixture of THF (1.6 mL) and H_2O (0.8 mL). The reaction mixture was stirred at rt for 3 h and diluted with satd Na_2SO_3. The resulting mixture was extracted with EtOAc (2 × 30 mL) and the combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, and concentrated *in vacuo* to provide the crude triol as a colorless oil.

The residue was dissolved in EtOAc (36 mL) and $Pb(OAc)_4$ (73 mg, 0.164 mmol) was added. The reaction mixture was stirred at rt for 30 min. The orange solution was filtered through a silica gel pad, and the filtrate was concentrated *in vacuo* to provide an unstable aldehyde, which was used without further purification.

The aldehyde was dissolved in $CHCl_3$ (1.9 mL) and DBU (0.04 mL, 41 mg, 0.26 mmol) was added. The solution was stirred at rt for 15 min and Ac_2O (0.10 mL, 110 mg, 1.08 mmol) was added. The reaction mixture was stirred at rt for 1 h and was diluted with satd NH_4Cl (20 mL). The mixture was extracted with CH_2Cl_2 (2 × 20 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (gradient 30% to 35% EtOAc in hexanes) to afford lactol acetate **242** (18.1 mg, 34%) as a pale yellow solid and acetate sulfonamide **236** (19.6 mg, 37%) as a pale yellow foam.

Lactol acetate **242**: IR (neat) 2924, 1754, 1462, 1352, 1182 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.2 Hz, 2H), 7.54-7.41 (m, 2H), 7.29-7.09 (m, 4H), 6.61 (s, 1H), 5.80 (d, *J* = 2.9 Hz, 1H), 3.84 (s, 2H), 3.23 (dd, *J* = 6.3, 14.5 Hz, 1H), 3.14 (s, 1H), 2.49-2.34 (m, 5H), 2.21 (s, 3H), 2.19 (s, 3H), 2.17-2.08 (m, 1H), 2.00-1.84 (m, 1H), 1.67 (d, *J* = 14.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3, 143.8, 137.7, 135.3, 133.4, 129.9, 127.2, 121.8, 120.5, 118.5, 110.6, 106.1, 93.0, 71.3, 60.4, 39.6, 38.4, 33.3, 32.6, 28.6, 21.6, 21.2, 8.1; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{26}H_{29}N_2O_5S$ 481.1797; found 481.1781.

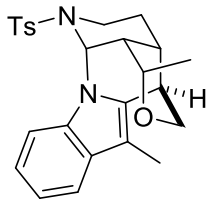
Sulfonamide **236:** IR (neat) 3274, 3058, 1738, 1660, 1465, 1323, 1151 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.49 (s, 1H), 7.87 (s, 1H), 7.75 (d, *J* = 8.2 Hz, 2H), 7.57-7.42 (m, 2H), 7.39-7.26 (m, 4H), 5.80 (dd, *J* = 4.0, 9.0 Hz, 1H), 4.01 (dd, *J* = 7.5, 10.9 Hz, 1H), 3.86 (dd, *J* = 8.3, 10.9 Hz, 1H), 3.39 (t, *J* = 7.6 Hz, 1H), 3.20 (dd, *J* = 4.1, 10.7 Hz, 1H), 3.14-3.00 (m, 1H), 2.60-2.45 (m, 1H), 2.43 (s, 3H), 2.31 (s, 3H), 1.85-1.67 (m, 1H), 1.41-1.28 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.5, 170.8, 143.2, 139.5, 137.4, 134.4, 131.3, 129.7, 128.9, 128.9, 127.1, 124.3, 123.4, 121.4, 119.5, 117.6, 109.0, 64.4, 40.4, 36.6, 34.8, 27.7, 21.6, 21.0, 8.6; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{26}H_{29}N_2O_5S$ 481.1797; found 481.1788.

Method B: Internal alkene **260** (173.2 mg, 0.384 mmol) was dissolved in a mixture of THF (5.5 mL) and H_2O (2.7 mL), and NMO (225 mg, 1.92 mmol) was added followed by a solution of OsO_4 (4% in H_2O, 0.05 mL, 2.0 mg of OsO_4, 0.008 mmol). The reaction mixture was stirred at rt for 4 h and quenched by addition of satd Na_2SO_3 (10 mL). The mixture was stirred for 10 min and extracted with EtOAc (2 × 30 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, and concentrated *in vacuo* to yield the crude triol as a colorless oil.

The triol was dissolved in EtOAc (110 mL) and $Pb(OAc)_4$ (255 mg, 0.58 mmol) was added. The reaction mixture was stirred at rt for 1 h. The orange solution was filtered through a silica gel pad and the filtrate was concentrated *in vacuo* to provide the crude aldehyde as a colorless oil.

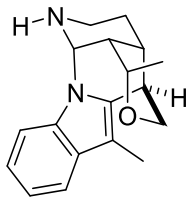
The aldehyde was dissolved in $CHCl_3$ (6.7 mL) and DBU (0.11 mL, 117 mg, 0.77 mmol) was added. The mixture was stirred at rt for 15 min, after which Ac_2O (0.36 mL, 392 mg, 3.84 mmol) was added. The reaction was stirred at rt for 1 h and diluted with satd NH_4Cl (30 mL). The mixture was extracted with CH_2Cl_2 (2 × 30 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (gradient 30% to 35% EtOAc in hexanes) to provide lactol acetate **242** (57.6 mg, 31%) as a

pale yellow solid, as well as acetate sulfonamide **236** (60.2 mg, 33%) as a pale yellow foam. Both compounds had spectroscopic data identical to the ones prepared by Method A.



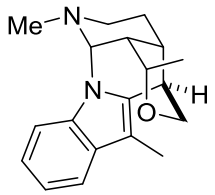
244

(1R,5R*,6R*,15S*,16S*)-7,15-Dimethyl-2-tosyl-1,2,3,4,5,6-hexahydro-1,5,6-(epiethane[1,1,2]triyloxymethano)[1,3]diazocino[1,8-a]indole (**244**).* Trimethylaluminum (2.0 M in hexanes, 0.23 mL, 0.46 mmol) and TMSOTf (0.04 mL, 51 mg, 0.23 mmol) were added to a -78 °C solution of lactol acetate **242** (22.1 mg, 0.046 mmol) in CH_2Cl_2 (0.92 mL). The mixture was stirred at -78 °C for 20 min and quenched by pouring into satd Rochelle's salt (30 mL). The mixture was extracted with CH_2Cl_2 (2 × 30 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (gradient 25% to 30% EtOAc in hexanes) to provide tetrahydropyran **244** (17.6 mg, 88%) as a white foam. IR (neat) 2919, 1461, 1348, 1157 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.1 Hz, 2H), 7.50-7.45 (m, 1H), 7.34-7.30 (m, 1H), 7.21 (d, *J* = 8.1 Hz, 2H), 7.13-7.07 (m, 2H), 6.33 (d, *J* = 2.0 Hz, 1H), 4.20 (q, *J* = 6.7 Hz, 1H), 3.94 (dd, *J* = 1.6, 10.7 Hz, 1H), 3.54 (dd, *J* = 2.0, 10.4 Hz, 1H), 3.17 (dd, *J* = 6.2, 14.3 Hz, 1H), 3.09 (s, 1H), 2.62-2.56 (m, 1H), 2.39 (s, 3H), 2.20 (s, 3H), 2.18-2.13 (m, 1H), 2.13-2.09 (m, 1H), 2.01-1.92 (m, 1H), 1.64 (d, *J* = 14.0 Hz, 1H), 1.34 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.7, 137.7, 135.4, 134.9, 130.1, 129.8, 127.3, 121.5, 120.3, 118.3, 110.3, 105.7, 71.2, 67.2, 64.8, 41.6, 38.4, 34.3, 29.3, 28.2, 21.6, 17.8, 8.1; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{25}H_{29}N_2O_3S$ 437.1899; found 437.1888.



245

(1S,5R*,6R*,15S*,16S*)-7,15-Dimethyl-1,2,3,4,5,6-hexahydro-1,5,6-(epiethane[1,1,2]triyloxymethano)[1,3]diazocino[1,8-a]indole (**245**).* Sulfonamide **244** (24.6 mg, 0.065 mmol) was dissolved in MeOH (5.6 mL) and Mg ribbon (684 mg, 28.2 mmol) was added. The mixture was sonicated for 30 min, as the bath temperature was increased from rt to 35 °C. The reaction was quenched by pouring into satd NH_4Cl (30 mL) and was extracted with EtOAc (2 × 30 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by preparative thin-layer chromatography on silica gel (EtOAc) to provide secondary amine **245** (14.6 mg, 92%) as a colorless film. IR (neat) 3327, 2921, 1460, 1342, 1155 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.6 Hz, 1H), 7.29-7.24 (m, 1H), 7.15 (t, *J* = 7.3 Hz, 1H), 7.11 (t, *J* = 7.3 Hz, 1H), 5.36 (d, *J* = 1.7 Hz, 1H), 4.12 (q, *J* = 6.7 Hz, 1H), 3.97 (dd, *J* = 2.0, 10.4 Hz, 1H), 3.57 (dd, *J* = 2.2, 10.4 Hz, 1H), 3.08 (s, 1H), 2.58-2.52 (m, 1H), 2.44 (dd, *J* = 6.1, 11.7 Hz, 1H), 2.23 (s, 3H), 2.17 (s, 1H), 2.02-1.94 (m, 1H), 1.80 (td, *J* = 3.5, 12.5 Hz, 1H), 1.72 (d, *J* = 13.6 Hz, 1H), 1.36 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.9, 134.8, 130.3, 120.7, 119.4, 118.7, 108.5, 103.4, 72.1, 67.5, 66.3, 41.9, 37.6, 34.6, 30.1, 28.5, 18.3, 8.1; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{23}N_2O$ 283.1810; found 283.1797.



(±)-alstoscholarisine E (**5**)

*(±)-Alstoscholarisine E (**5**).* Secondary amine **245** (6.0 mg, 21.2 μmol) was dissolved in a mixture of glacial acetic acid (0.47 mL) and 37% aqueous formaldehyde (0.08 mL, 32 mg of formaldehyde, 1.07 mmol), and $NaBH_3CN$ (8.0 mg, 0.13 mmol) was added. The reaction mixture was stirred at rt for 1 h and was poured into satd Na_2CO_3 (25 mL). The resulting mixture was extracted with CH_2Cl_2 (2 × 25 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by preparative thin-layer chromatography on silica gel (90% EtOAc in hexanes) to provide (±)-alstoscholarisine E (**5**) (4.9 mg, 78%) as a white solid. IR (neat) 2922, 1649, 1458, 1346, 1317, 1123, 1072, 742 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 7.51 (d, *J* = 8.1 Hz, 1H), 7.43 (d, *J* = 7.8 Hz, 1H), 7.07 (t, *J* = 8.1 Hz, 1H), 7.00 (t, *J* = 7.8 Hz, 1H), 5.49 (s, 1H), 4.07 (q, *J* = 6.8 Hz, 1H), 3.96 (dd, *J* = 1.6, 10.4 Hz, 1H), 3.41 (dd, *J* = 2.5, 10.4 Hz, 1H), 3.15 (br s, 1H), 2.59-2.54 (m, 1H), 2.44 (dd, *J* = 6.1, 11.9 Hz, 1H), 2.35 (s, 3H), 2.23 (s, 3H), 2.24-2.21 (m, 1H), 2.14-2.05 (m, 1H), 1.95 (td, *J* = 3.9, 12.4 Hz, 1H), 1.87 (br d, *J* = 13.6 Hz, 1H), 1.35 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 138.6, 136.9, 130.4, 121.5, 120.1, 118.7, 111.5, 105.6, 73.2, 72.5, 68.8, 47.2, 45.1, 43.0, 36.0, 30.6, 28.4, 18.3, 8.0; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{25}N_2O$ 297.1967; found 297.1962.

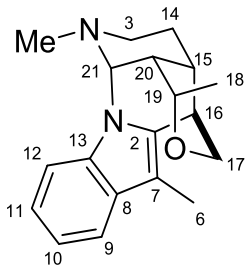
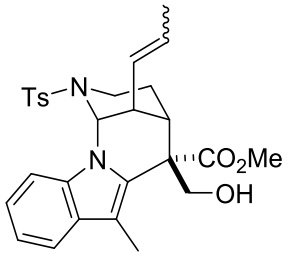


Table 15. Comparison of ^{1}H NMR Spectra of Natural and Synthetic Alstoscholarisine E (**5**) in CD_3OD

	natural (600 MHz)[5]	synthetic (500 MHz)
H-3	1.85 (td, *J* = 4.0, 11.3 Hz)	1.95 (td, *J* = 3.9, 12.4)
	2.33 (dd, *J* = 6.8, 11.3 Hz)	2.44 (dd, *J* = 6.1, 11.9 Hz)
H-6	2.21 (s)	2.23 (s)
H-9	7.41 (d, *J* = 8.0 Hz)	7.43 (d, *J* = 7.8 Hz)
H-10	6.99 (t, *J* = 8.0 Hz)	7.00 (t, *J* = 7.8 Hz)
H-11	7.04 (t, *J* = 8.0 Hz)	7.07 (t, *J* = 8.1 Hz)
H-12	7.49 (d, *J* = 8.0 Hz)	7.51 (d, *J* = 8.1 Hz)
H-14	1.81 (m)	1.87 (br d, *J* = 13.6 Hz)
	2.03 (m)	2.14-2.05 (m)
H-15	2.50 (m)	2.59-2.54 (m)
H-16	3.09 (br s)	3.16 (br s)
H-17	3.37 (dd, *J* = 2.6, 10.2 Hz)	3.41 (dd, *J* = 2.5, 10.4 Hz)
	3.92 (dd, *J* = 1.9, 10.2 Hz)	3.96 (dd, *J* = 1.6, 10.4 Hz)
H-18	1.32 (d, *J* = 6.8 Hz)	1.35 (d, *J* = 6.8 Hz)
H-19	4.04 (q, *J* = 6.8 Hz)	4.07 (q, *J* = 6.8 Hz)
H-20	2.16 (br s)	2.24-2.21 (m)
H-21	5.37 (d, *J* = 2.3 Hz)	5.49 (s)
NCH_3	2.26 (s)	2.35 (s)

Table 16. Comparison of ^{13}C NMR Spectra of Natural and Synthetic Alstoscholarisine E (**5**) in CD_3OD

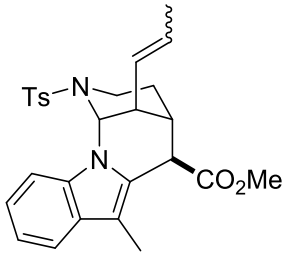
	natural (150 MHz)[5]	synthetic (125 MHz)
C-2	137.0	136.9
C-3	47.1	47.2
C-6	8.0	8.0
C-7	105.0	105.6
C-8	130.2	130.4
C-9	118.6	118.7
C-10	119.8	120.1
C-11	121.3	121,5
C-12	111.6	111.5
C-13	138.7	138.6
C-14	31.0	30.6
C-15	28.5	28.4
C-16	36.0	36.0
C-17	68.8	68.8
C-18	18.3	18.3
C-19	73.3	73.2
C-20	43.4	43.0
C-21	72.4	72.5
NCH_3	45.5	45.1



259 (3.6:1 *E*/*Z*)

Methyl (1R,5S*,6S*,13R*)-6-(Hydroxymethyl)-7-methyl-13-((E/Z)-prop-1-en-1-yl)-2-tosyl-1,2,3,4,5,6-hexahydro-1,5-methano[1,3]diazocino[1,8-a]indole-6-carboxylate* ***(259).*** Terminal alkene **178** (352.7 mg, 0.693 mmol) was dissolved in MeOH (14 mL) and the solution was heated to 60 °C. Grubbs second-generation ruthenium metathesis catalyst (58.8 mg, 0.069 mmol) was added and the resulting mixture was heated at 60 °C for 12 h. The reaction mixture

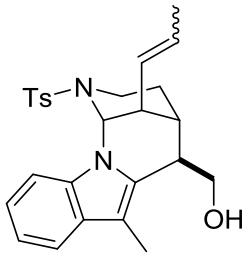
was cooled to rt and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (35% EtOAc in hexanes) to provide internal alkene **259** (314.3 mg, 89%) as a white foam (3.6:1 mixture of inseparable *E*/*Z* isomers). IR (neat) 3528, 2949, 1705, 1460, 1323, 1154 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.1 Hz, 0.8H), 7.72 (d, *J* = 7.4 Hz, 0.2H), 7.63 (d, *J* = 8.1 Hz, 2H), 7.51 (d, *J* = 7.7 Hz, 1H), 7.25-7.09 (m, 4H), 6.43 (s, 1H), 5.93-5.70 (m, 2H), 4.15 (d, *J* = 11.9 Hz, 1H), 3.77 (s, 3H), 3.61 (t, *J* = 11.7 Hz, 1H), 3.47 (d, *J* = 11.2 Hz, 1H), 3.23 (dd, *J* = 5.3, 13.3 Hz, 1H), 3.12-2.86 (m, 3H), 2.37 (s, 3H), 2.16 (s, 3H), 2.21-2.10 (m, 1H), 1.79 (d, *J* = 5.3 Hz, 3H), 1.21 (d, *J* = 14.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.2, 143.4, 137.0, 134.2, 129.9, 129.5, 129.0, 128.9, 127.9, 127.5, 122.3, 120.2, 118.2, 64.9, 62.5, 52.5, 52.3, 39.5, 38.1, 33.2, 23.0, 21.5, 18.3, 9.7; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{28}H_{33}N_2O_5S$ 509.2110; found 509.2092.



179 (2.8:1 *E*/*Z*)

Methyl (1R,5S*,6R*,13R*)-7-Methyl-13-((E/Z)-prop-1-en-1-yl)-2-tosyl-1,2,3,4,5,6-hexahydro-1,5-methano[1,3]diazocino[1,8-a]indole-6-carboxylate (**179**).* Terminal alkene **163** (450.2 mg, 0.941 mmol) was dissolved in MeOH (18.5 mL) and the solution was heated to 60 °C. Grubbs second-generation ruthenium metathesis catalyst (80.0 mg, 0.094 mmol) was added and the resulting mixture was heated at 60 °C for 12 h. The reaction mixture was cooled to rt and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (15% EtOAc in hexanes) to provide internal alkene **179** (404.0 mg, 90%) as a white solid (2.8:1 mixture of inseparable *E*/*Z* isomers). IR (neat) 2917, 1732, 1459, 1319, 1154 cm^{-1}; ^{1}H NMR (500

MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.1 Hz, 0.75H), 7.67 (d, *J* = 7.8 Hz, 0.25H), 7.57 (d, *J* = 8.2 Hz, 1.5H), 7.54-7.48 (m, 1.5H), 7.23-7.12 (m, 4H), 6.43 (d, *J* = 2.1 Hz, 1H), 5.93-5.77 (m, 1.25H), 5.72 (dd, *J* = 7.3, 16.5 Hz, 0.75H), 4.06 (s, 0.25H), 4.05 (s, 0.75H), 3.72 (s, 3H), 3.35 (d, *J* = 7.0 Hz, 0.75H), 3.22 (dd, *J* = 6.0, 13.6 Hz, 1H), 2.54 (td, *J* = 3.1, 13.6 Hz, 2H), 2.35 (s, 2.25H), 2.32 (s, 0.75H) 2.22 (s, 3H), 2.05-2.18 (m, 1H), 1.78 (d, *J* = 6.1 Hz, 2.25H), 1.76 (dd, *J* = 1.3, 6.9 Hz, 0.75H), 1.52 (br d, *J* = 13.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.7, 143.4, 137.3, 137.0, 135.0, 129.6, 129.5, 129.4, 128.5, 128.3, 128.0, 127.8, 127.5, 127.4, 122.0, 120.4, 118.3, 111.2, 109.0, 108.9, 63.2, 62.4, 52.5, 44.9, 40.4, 38.2, 35.3, 33.8, 33.6, 26.4, 26.2, 21.6, 18.5, 13.5, 8.7; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{27}H_{31}N_2O_4S$ 479.2005; found 479.1999.



260

((1R,5S*,6R*,13R*)-7-Methyl-13-((E)-prop-1-en-1-yl)-2-tosyl-1,2,3,4,5,6-hexahydro-1,5-methano[1,3]diazocino[1,8-a]indol-6-yl)methanol* ***(260).*** Powdered $LiAlH_4$ (45.3 mg, 1.19 mmol) was added to a 0 °C solution of ester **179** (380.4 mg, 0.795 mmol) in THF (3.2 mL) and the mixture was stirred at 0 °C for 1 h. The reaction mixture was quenched by sequential dropwise addition of H_2O (0.05 mL), 15% NaOH (0.05 mL), and H_2O (0.15 mL) and was warmed to rt. $MgSO_4$ was added and the suspension was filtered through a Celite pad. The filtrate was concentrated *in vacuo* and the residue was purified by flash chromatography on silica gel (35% EtOAc in hexanes) to provide alcohol **260** (324.0 mg, 90%) as a white powder. (2.8:1 mixture of *E*/*Z* isomers). IR (neat) 3528, 2925, 1461, 1322, 1155 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.0 Hz, 0.75H), 7.62 (d, *J* = 7.0 Hz, 0.25H), 7.54-7.45 (m, 3H), 7.19-7.04 (m, 4H), 6.36 (d,

J = 2.4 Hz, 1H), 5.81-5.72 (m, 2H), 3.89 (dd, *J* = 4.6, 11.0 Hz, 1H), 3.71 (t, *J* = 10.2 Hz, 1H), 3.26 (dd, *J* = 4.5, 9.3 Hz, 1H), 3.17 (dd, *J* = 5.9, 13.6 Hz, 1H), 3.10-3.06 (m, 1H), 2.54 (td, *J* = 3.5, 13.6 Hz, 1H), 2.46 (br s, 1H), 2.34 (s, 3H), 2.27 (s, 3H), 2.28-2.16 (m, 2H), 1.78 (d, *J* = 5.4 Hz, 2.25H), 1.75 (dd, *J* = 1.7, 6.9 Hz, 0.75H), 1.42 (br d, *J* = 13.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.3, 137.4, 134.9, 131.5, 129.6, 129.5, 129.1, 129.0, 127.5, 121.8, 120.3, 117.9, 111.1, 107.3, 64.3, 63.3, 41.7, 39.7, 38.7, 31.6, 26.5, 21.5, 18.4, 9.1; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{26}H_{31}N_2O_3S$ 451.2055; found 451.2057.

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