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REVISED MANUSCRIPT

Synthesis of Alstoscholarisines A-E, Monoterpene Indole Alkaloids with Modulating Effects on Neural Stem Cells

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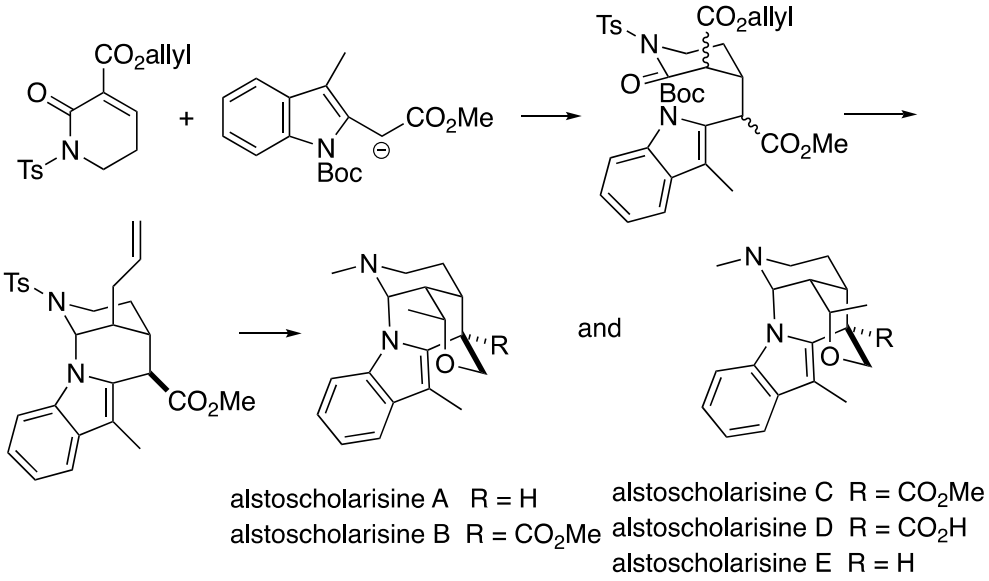
TOC Graphic



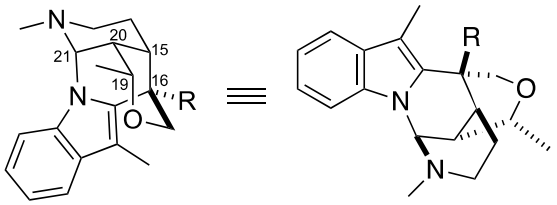
ABSTRACT: A divergent synthetic strategy has been developed for stereoselective total syntheses of alstoscholarisines A-E, monoterpenoid indole alkaloids which are modulators of adult neuronal stem cells. A pivotal step includes an intermolecular Michael addition of an indole-2-acetic acid methyl ester enolate to an α,β-unsaturated-*N*-sulfonyllactam to form the C15, C16 bond of the alkaloids. Other features of the strategy involve a selective partial reduction of an intermediate *N*-sulfonyllactam, followed by cyclization to a bridged aminal system which serves as a key precursor for all five of the alkaloids, as well as the use of an allyl group as a masked aldehyde equivalent.

INTRODUCTION AND BACKGROUND

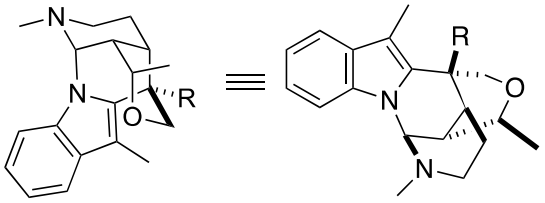
The development of therapies for treatment of neurodegenerative ailments has been a notoriously difficult and daunting challenge.[1] However, neural stem cells have shown promise for the invention of new CNS therapies. For example, several phase I/II clinical trials using stem cell strategies are currently underway for Alzheimer's disease.[2] In addition, many natural products are known to modulate stem cell fate and population, and such compounds may have a key role to play in the development of treatments for neurogenic disorders.[3]

In an ongoing search for biologically active natural products, the Luo group found in 2014 that the crude leaf extract of the Asian tree *Alstonia scholaris*, a plant with a long history of use in traditional medicine in China, India and Southeast Asia,[4] increases the proliferation of adult mouse hippocampal neural stem cells *in vitro*.[5] Upon chromatographic purification of the mixture, five novel, structurally related monoterpenoid indole alkaloids, (-)-alstoscholarisines A-E (**1**-**5**), were isolated (Figure 1). The structures of these metabolites were assigned by extensive NMR studies, as well as by X-ray crystallographic analysis of **1** and **3**. Each purified compound showed enhanced promotion of stem cell growth compared to the total alkaloid mixture, and alstoscholarisine A (**1**) was found to increase the propensity of neural stem cells to differentiate into neurons.

The structures of **1**-**5** are unusual among monoterpenoid indole alkaloids in that they lack one of the two sidechain carbons originating from tryptamine, one of the biogenetic building blocks.[6] Furthermore, the alkaloids all contain a unique pentacyclic ring system that includes five contiguous stereogenic centers incorporated into an interesting bridged aminal scaffold fused to a tetrahydropyran moiety. Alstoscholarisines A (**1**) and B (**2**) contain an equatorial methyl group at C19 of the tetrahydropyran ring, but differ in the nature of the substituent at C16 (i.e. H or CO_2Me). Alkaloids **3**-**5** include an axial methyl group at C19 of the tetrahydropyran and again differ in the C16 substituent (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 and stereochemistry of the alstoscholarisines.

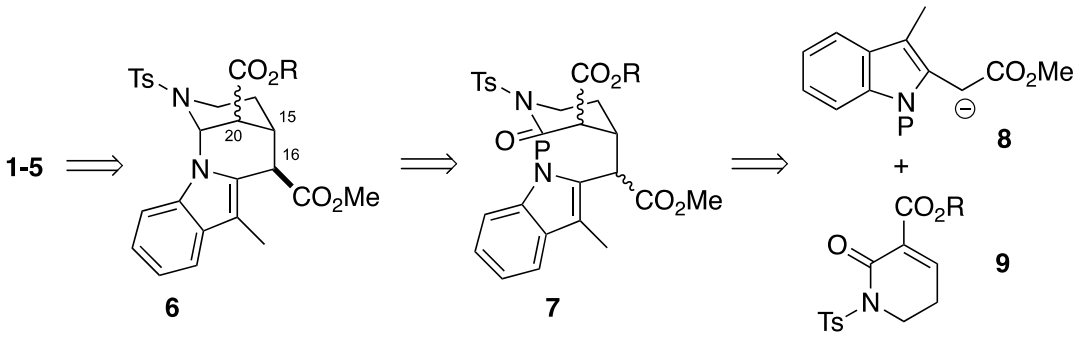
Alstoscholarisine A (**1**), the most biologically potent member of the class, has recently attracted interest from the synthetic community. Bihelovic and Ferjancic completed a total synthesis of racemic alkaloid **1** in 2016 by a twelve-step route which featured an intramolecular enamine Michael reaction/aminal formation domino sequence to construct the bridged core of the metabolite.[7] In the same year, Yang and coworkers completed an enantioselective synthesis of (−)-alstoscholarisine A through a twelve-step sequence that utilized a strategy based on an iridium-catalyzed intramolecular asymmetric Friedel-Crafts alkylation of an indole.[8] However, no synthetic work had been reported on the other four members of the class. We became interested in developing a divergent approach to the alstoscholarisines which would allow an efficient entry to all five alkaloids, and the details of this work are reported here.[9]

RESULTS AND DISCUSSION

Synthesis Plan. Our initial retrosynthetic analysis for construction of the alstoscholarisines **1**-**5** is depicted in Scheme 1. Thus, the general plan was to construct a bridged tetracyclic system **6**, which would act as a common intermediate to access all five of the alkaloids. Our intention was

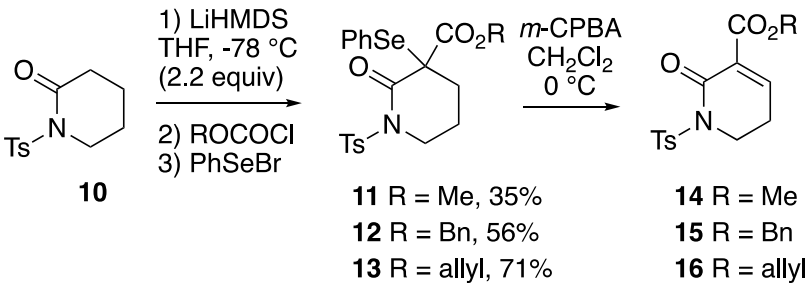
to utilize the C16 and C20 substituents in intermediate **6** as handles for subsequent formation of the requisite tetrahydropyran moieties of the metabolites. We surmised that such a compound could be produced from **7** by a selective partial reduction of the *N*-sulfonyllactam carbonyl group, followed by a ring closure involving the indole nitrogen to form the bridged aminal. It was expected that the configuration at C16 should be adjustable by epimerization of the ester to the more stable stereoisomer shown in **6**. In turn, we planned to produce tricycle **7** via a convergent, early-stage Michael coupling of an indole acetic ester enolate **8** and an α,β-unsaturated-*N*-sulfonyllactam **9** to form the C15,16 bond. These two fragments contain most of the carbons of the natural products.

Scheme 1. Retrosynthetic Plan for the Alstoscholarisines 1-5



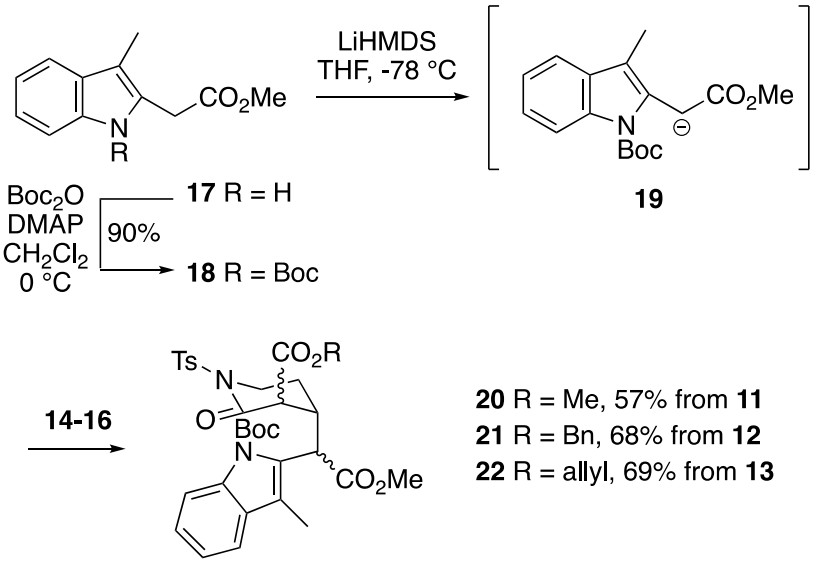
Michael Reactions. The components needed for the projected Michael reaction are readily available. Therefore, known α,β-unsaturated-*N*-sulfonyllactams **14** and **15** were prepared by a modification of the procedure described in the literature[10] starting from *N*-tosylvalerolactam (**10**) (Scheme 2). Deprotonation of **10** with 2.2 equivalents of LiHMDS, followed by sequential treatment with methyl chloroformate or benzyl chloroformate and then phenylselenyl bromide in a one-pot protocol led to the methyl and benzyl esters **11** and **12**, respectively. In addition, the same procedure was used to synthesize the analogous, previously unknown allyl ester **13**. Upon oxidation with *m*-chloroperbenzoic acid, the selenides **11-13** formed the corresponding selenoxides, which underwent spontaneous *in situ* elimination to produce the desired unsaturated lactams **14-16**. However, these compounds proved unstable to column chromatography and therefore were used in crude form for the Michael step.

Scheme 2. Preparation of Michael Acceptors 14-16



For the coupling reaction, known,[11] easily prepared 3-methylindole-2-acetic acid methyl ester (**17**) was first protected as the *N*-Boc derivative **18** (Scheme 3). This ester was deprotonated with LiHMDS at -78 °C, and to the resulting enolate **19** were added the crude α,β-unsaturated-*N*-sulfonyllactams **14**-**16**, leading to the Michael adducts **20**-**22**, respectively, in good yields (based on selenides **11**-**13**), each as a mixture of stereoisomers.

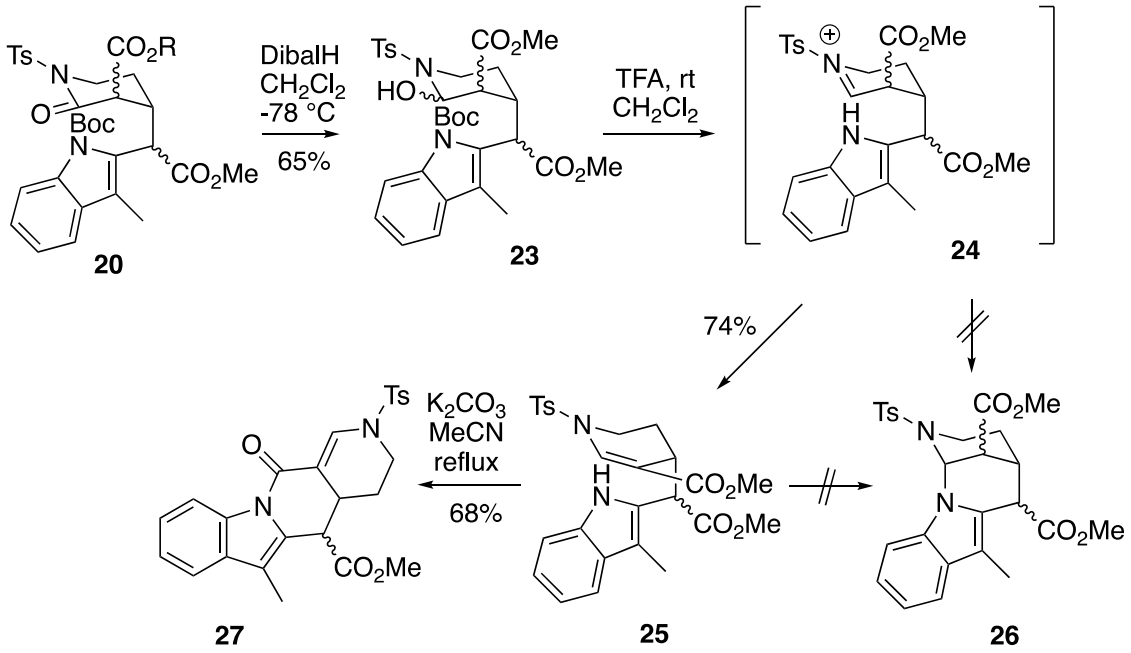
Scheme 3. Michael Addition of Indole Ester Enolate 19 to α,β-Unsaturated-*N*-sulfonyllactams 14-16



Studies on Formation of a Bridged Aminal System. With the Michael adducts in hand, studies were initiated to construct a bridged aminal intermediate like **6**, and our first experiments were conducted with the methyl ester **20**. We were pleased to find that the *N*-sulfonyllactam functionality of **20** could be selectively reduced with diisobutylaluminum hydride at low

temperature to afford *N,O*-hemiacetal **23** without affecting either of the ester groups (Scheme 4).[12] However, when exposed to trifluoroacetic acid, intermediate **23** was not converted to the desired bridged aminal **26**, but rather produced the vinylogous carbamate **25** in good yield. This transformation probably occurs via the *N*-sulfonyliminium intermediate **24**,[13] which, rather than closing to aminal **26**, tautomerizes to the conjugated system **25**. Compound **25** was found to be quite stable and resisted cyclization to the bridged aminal **26** under a variety of acidic conditions. Under basic conditions, only cyclization occurred to form a single diastereomeric lactam **27** (configuration not determined).

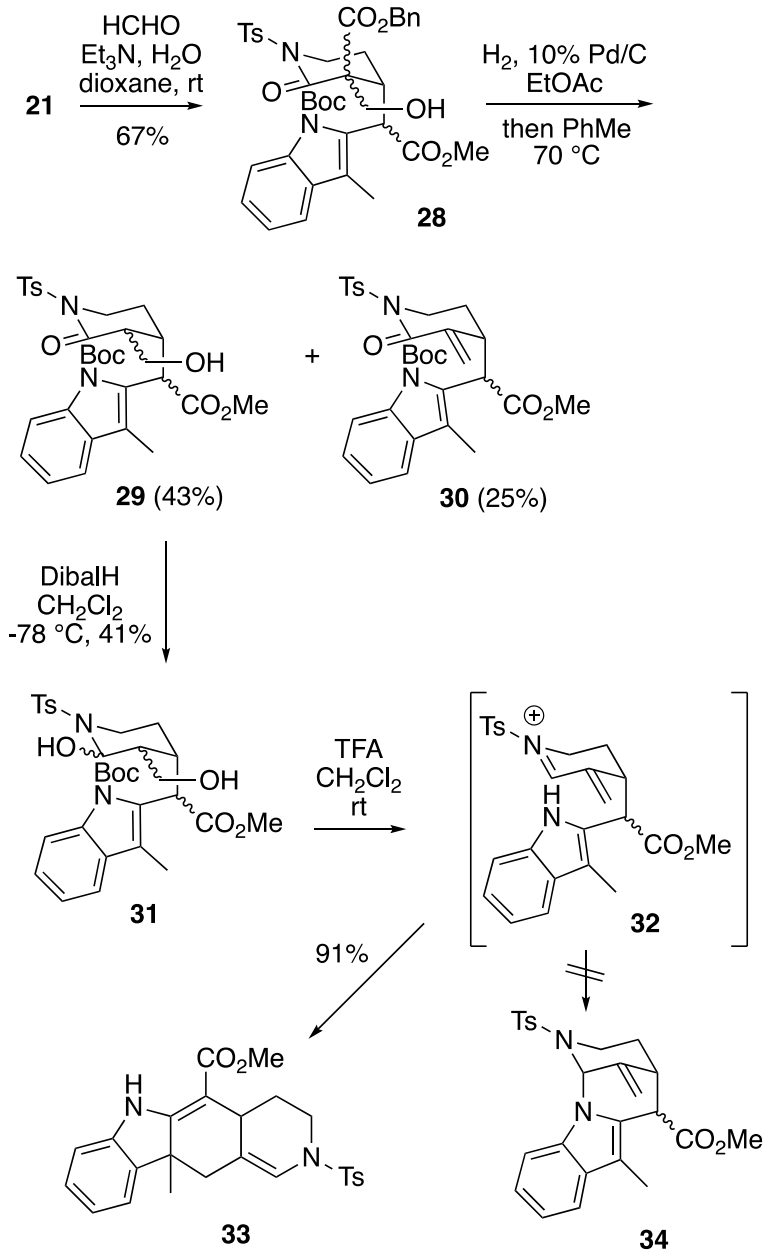
Scheme 4. Attempted Construction of a Bridged Aminal System



Since having a carbonyl group at C20 did not provide a viable pathway for construction of a bridged aminal, another type of functionalized one-carbon substituent was explored. Therefore, benzyl ester-containing Michael adduct **21** was first treated with aqueous formaldehyde in an aldol reaction promoted by trimethylamine, leading to hydroxymethyl compound **28** (mixture of stereoisomers) (Scheme 5). Subsequent catalytic hydrogenolysis of the benzyl ester resulted in decarboxylation to yield a mixture of hydroxymethyl lactam **29** along with the elimination product **30**. Partial reduction of the *N*-sulfonyllactam **29** with Dibal-H gave the corresponding *N,O*-hemiacetal **31** (41% unoptimized yield). However, subsequent treatment of this compound with

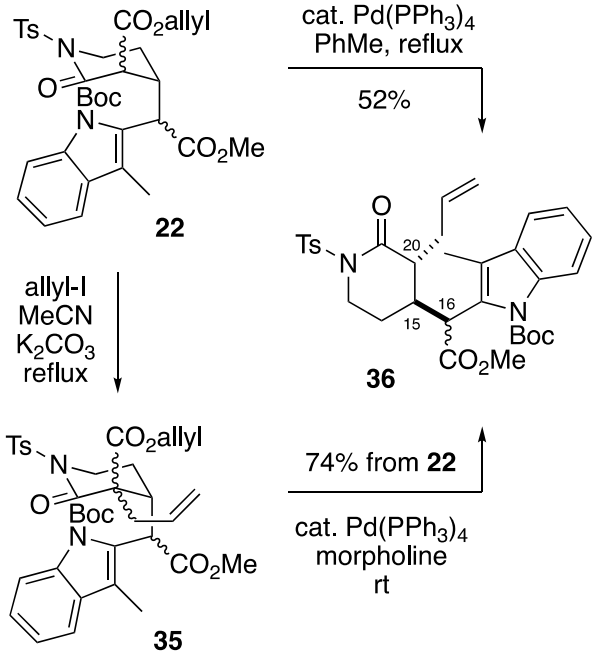
TFA to our surprise cleanly produced the tetracyclic indole **33** in good yield. It seems reasonable that TFA promotes Boc removal and concurrent dehydration of the hydroxymethyl *N*,*O*-hemiacetal **31** to generate the α,β-unsaturated-*N*-tosyliminium ion **32**. Rather than cyclize onto the indole nitrogen to form the bridged aminal **34**, this intermediate undergoes a conjugate addition of the unsaturated *N*-sulfonyliminium moiety with C3 of the indole to yield the observed product **33**.

Scheme 5. Another Attempt at Bridged Aminal Formation



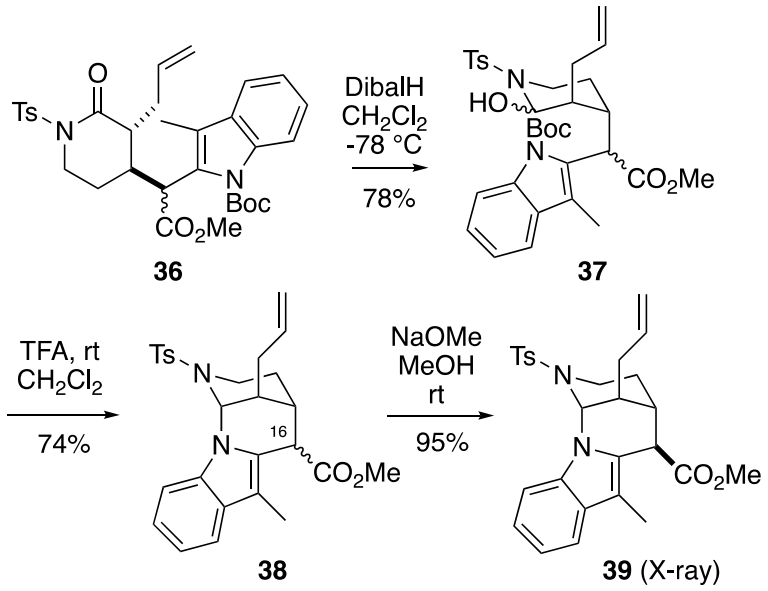
Faced with the problems described above, we considered other possible substitutents that (1) could be conveniently installed at C20, (2) would not interfere with formation of the bridged aminal and (3) could easily be transformed into an aldehyde group. We believed that an allyl group might meet these requirements and act as a suitable aldehyde equivalent. Towards this end, in order to effect a direct O- to C-allyl transfer, Michael adduct **22** was treated with a catalytic amount of $Pd(PPh_3)_4$, leading to the desired C20 allyl compound **36** in 52% yield along with some of the decarboxylated starting lactam (Scheme 6).[14] Since the yield here was only moderate, a more efficient procedure for synthesis of **36** was investigated. Thus, an alternative one-pot protocol was developed whereby lactam ester **22** could first be C-allylated using allyl iodide/K_2CO_3 in acetonitrile to form **35**, which was not isolated, followed by *in situ*-addition of $Pd(PPh_3)_4$/morpholine to promote decarboxylation of the allyl ester, leading to the desired C-allylated lactam **36** in 74% overall yield for the two steps. Interestingly, in both approaches to **36**, this product was exclusively the more stable C15, C20 *trans* isomer shown, but as mixtures of stereoisomers at the C16 ester-bearing center.[15]

Scheme 6. C20 Allylation of Michael Adduct 22



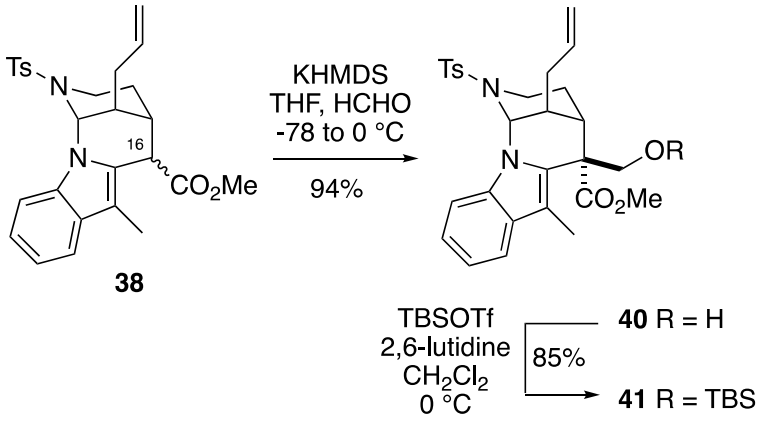
To continue the synthesis, *N*-sulfonyllactam **36** was partially reduced to the isolable *N,O*-hemiacetal **37** using DibalH (Scheme 7). Exposure of this material to trifluoroacetic acid at room temperature resulted in removal of the Boc group on the indole nitrogen and subsequent closure via an *N*-sulfonyliminium ion to afford the desired bridged aminal **38** in good yield as a mixture of C16 ester stereoisomers. We were pleased to find that this mixture could be epimerized under mild conditions with sodium methoxide/methanol to yield exclusively the more stable ester isomer **39**, allowing this compound to be fully characterized, including an X-ray analysis, as well as establishing the requisite functionality and stereochemistry at C16 for eventual conversion to alstoscholarisines A and E (vide infra).

Scheme 7. Synthesis of Bridged Aminal 39



Syntheses of (±)-Alstoscholarisines B, C and D. We initially focused on completing total syntheses of the three alstoscholarisines bearing a C16 carboxyl group. Thus, a mixture of ester epimers **38** was converted to the corresponding enolate with potassium hexamethyldisilazide at -78 °C, followed by an aldol reaction with anhydrous monomeric formaldehyde[16] that occurred from the least hindered face, leading to hydroxymethyl compound **40** as a single stereoisomer in excellent yield (Scheme 8).[17] The alcohol **40** could then be protected as the TBS ether **41**.

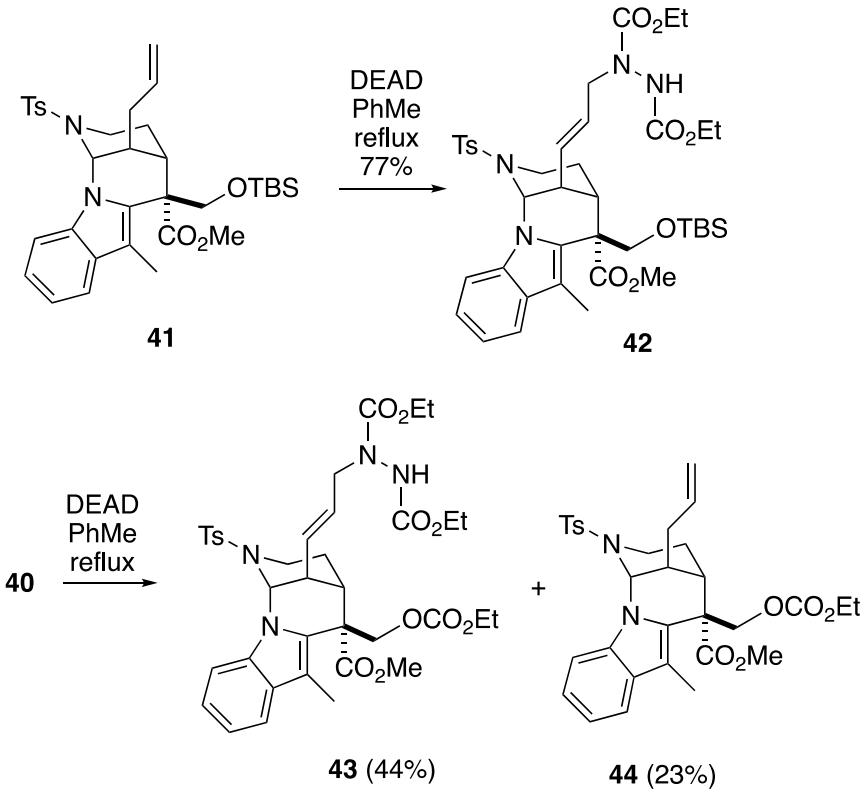
Scheme 8. Hydroxymethylation of Ester 38



Our initial plan had been to isomerize the allyl group of **40/41** to the corresponding propenyl systems using transition-metal catalysis, followed by oxidative double bond cleavage to the aldehyde. As discussed below, preliminary experiments aimed at effecting this transformation were rather discouraging. Therefore, a strategy was explored for isomerizing the allylic double bond by an ene reaction of intermediates **40/41**. Indeed, heating silyl-protected substrate **41** with DEAD in toluene at reflux overnight led to the desired ene product **42**, formed exclusively as the (*E*)-geometric isomer, in good yield (Scheme 9).[18]

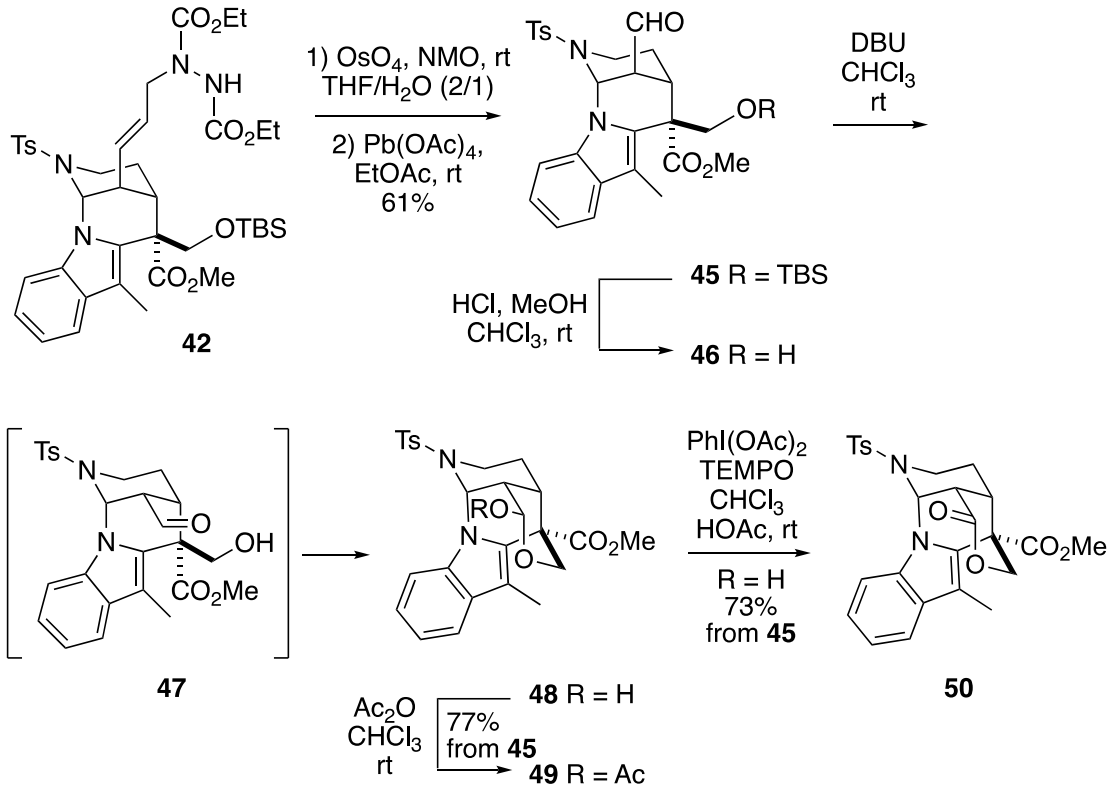
Interestingly, if the unprotected alcohol **40** was used in this reaction, the major product formed was ene product-carbonate **43**, along with allyl compound **44**, which had not undergone an ene reaction (Scheme 9). Since attempted removal of the carbonate group of the ene product **43** by basic hydrolysis led to partial retro-aldol loss of formaldehyde, the latter sequence was not optimized, and the TBS-protected series was used for subsequent work.

Scheme 9. Thermal Ene Reactions with DEAD



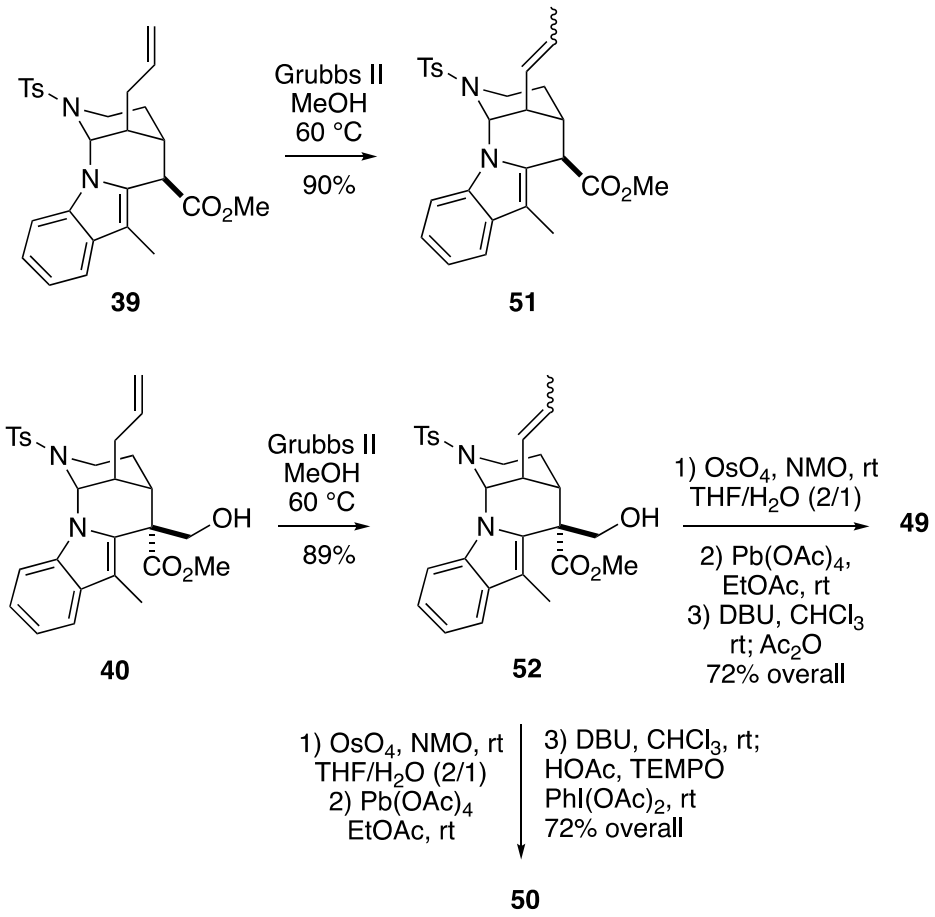
It was found that cleavage of the double bond in the allylic hydrazine derivative **42** could be effected by a two-step procedure involving an initial dihydroxylation with osmium tetraoxide/NMO, followed by exposure of the diol to lead tetraacetate to afford the axial aldehyde **45** (Scheme 10). The TBS group of **45** could then be removed under acidic conditions using HCl to produce alcohol **46**. Utilizing a strategy similar to one used in the Bihelovic/Ferjancic synthesis of alstoscholarisine A,[7] aldehyde **46** was treated with DBU in chloroform at room temperature, resulting in epimerization to the equatorial hydroxyl aldehyde **47**, which subsequently cyclizes to the isolable lactol **48**. This lactol could be O-acylated with acetic anhydride to produce acetate **49**, and, in addition, could be oxidized with iodobenzene diacetate/TEMPO[19] to yield the δ-lactone **50**.

Scheme 10. Preparation of Lactol Acetate 49 and δ-Lactone 50



As mentioned above, we had initially aimed at degrading the allyl group of an intermediate such as **39** to an aldehyde by first effecting a transition-metal catalyzed isomerization to a propenyl system like **51** (Scheme 11). However, some early preliminary experiments towards this end were not promising. Initially discouraged by these results, we moved on to investigate the alternative ene strategy shown in Scheme 9 for degradation of the allyl group. However, at this stage we decided to return to the double bond isomerization to see if we could develop a shorter route to aldehyde **46** which would not require protection of the hydroxymethyl group. Thus, exposing allyl compound **39** to the Grubbs II ruthenium catalyst in methanol at 60 °C (10 mol % of catalyst, 12 hours)[20] indeed led to the desired propenyl derivative **51** in 90% isolated yield (~2.8:1 *E/Z* mixture).

Scheme 11. Ru-Catalyzed Allyl to Propenyl Isomerizations



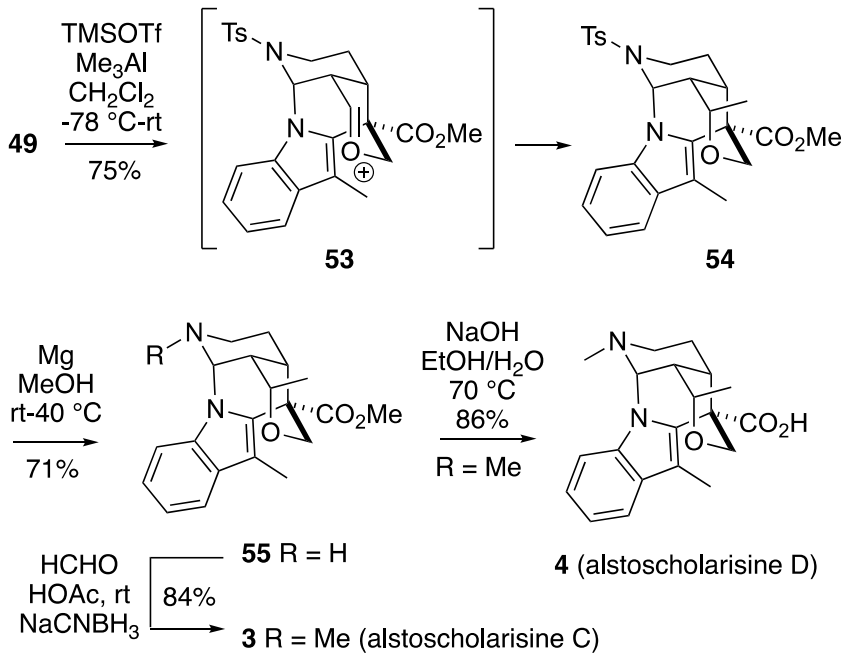
Similarly, the allyl group in the unprotected hydroxymethyl compound **40** could be isomerized to the requisite propenyl intermediate **52** in 89% yield as a ~3.6:1 mixture of *E/Z* isomers (Scheme 11). Oxidative cleavage of alkene **52** by the usual two-step protocol then led to the corresponding aldehyde, which without purification was epimerized with DBU and the resulting lactol was acetylated to produce acetate **49** (72% overall yield from **52**). In addition, lactone **50** could be obtained from alkene **52** in a four-step sequence via TEMPO/PhI(OAc)$_2$ oxidation[19] of the crude intermediate lactol (72% overall yield).

For the synthesis of alstoscholarisine C (**3**), lactol acetate **49** was first treated with a mixture of trimethylsilyl triflate and trimethylaluminum[21,22] to afford α-methyl tetrahydropyran **54** as a single stereoisomer having the configuration shown (Scheme 12). This transformation probably involves initial formation of an intermediate oxocarbenium ion **53**, followed by methyl group transfer from the aluminum reagent onto the least encumbered face. It should be noted that a

similar methylation was also attempted with lactol **48**, but in this case the major product formed was the corresponding O-silylated lactol along with only small amounts of tetrahydropyran **54** (~10%).

To complete synthesis of the alkaloid, the *N*-Ts group of intermediate **54** was removed reductively with magnesium metal in methanol,[23] providing amine **55**, followed by N-methylation with formalin and sodium cyanoborohydride,[24] to give (±)-alstoscholarisine C (**3**) having proton and carbon NMR spectra identical with those reported for the natural metabolite (see Supporting Information).[5a]

Scheme 12. Coversion of Lactol Acetate 49 to Alstoscholarisines C and D

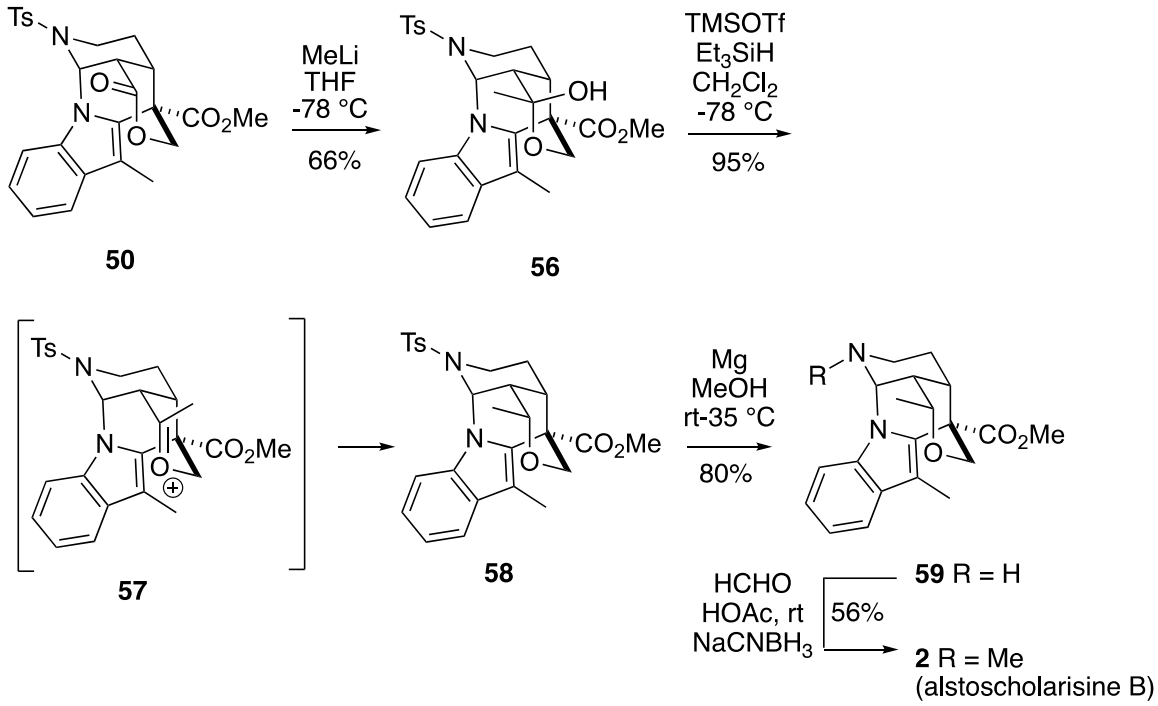


A basic hydrolysis of the methyl ester with sodium hydroxide in aqueous ethanol at 70 °C served to convert alstoscolarisine C (**3**) to alstoscholarisine D (**4**) in good yield. Purification of this amino acid by silica gel chromatography proved rather troublesome, but pure material could be obtained by reverse phase preparative TLC. Synthetic (±)-alstoscholarisine D (**4**) had proton and carbon NMR spectra that matched those described for the natural alkaloid.[5a]

The synthesis of alstoscholarisine B (**2**) made use of the δ-lactone **50** (Scheme 13). Thus, methyllithium could be added selectively to the lactone carbonyl group of **50** at -78 °C to afford

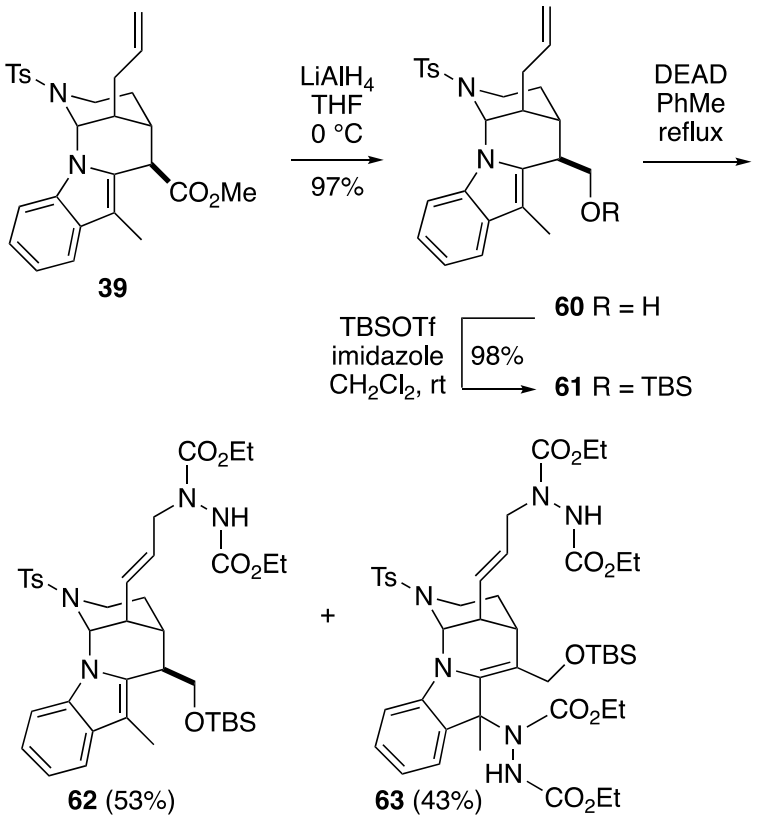
hemiketal **56** as a single stereoisomer (configuration not determined). Treatment of this compound with TMS-triflate and triethylsilane[7,25] at -78 °C presumably generates oxocarbenium species **57**, which is then reduced from the less hindered face to afford the equatorial α-methyl tetrahydropyran **58** as a single stereoisomer. Removal of the tosyl group from **58** with Mg/MeOH[23] and subsequent N-methylation[24] of the resulting secondary amine **59** led to (±)-alstoscholarisine B (**2**) whose NMR spectra matched those reported for the natural product.[5a]

Scheme 13. Synthesis of Alstoscholarisine B From δ-Lactone 50



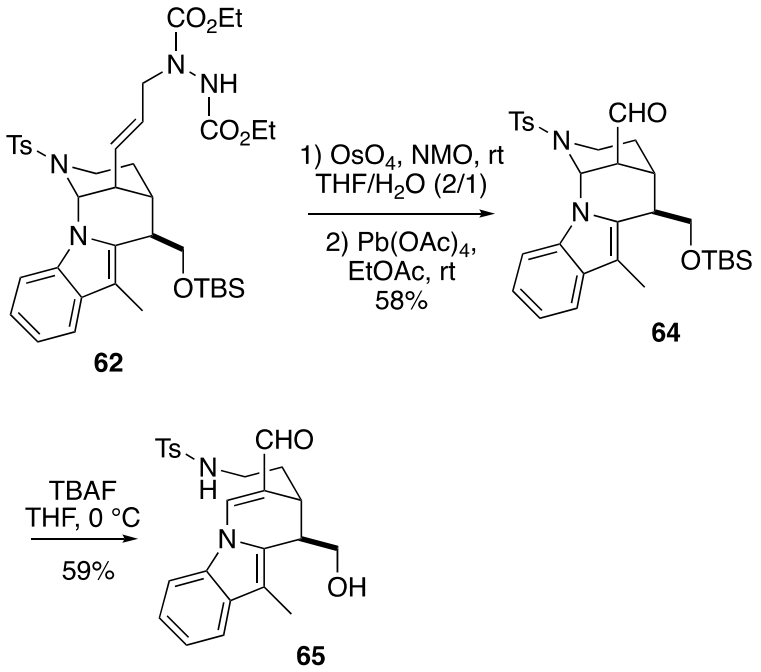
Syntheses of (±)-Alstoscholarisines A and E. The total syntheses of the remaining two alstoscholarsines lacking the C16 carboxyl group utilized the key bridged intermediate ester **39**. In our first approach, reduction of the methyl ester with lithium aluminum hydride cleanly provided alcohol **60**, which was then protected as the TBS ether **61** (Scheme 14). This compound underwent an ene reaction with DEAD in refluxing toluene to afford the desired (*E*)-allylic hydrazine derivative **62** in 53% yield, along with some of the compound **63** (43%) where reaction with the DEAD had also occurred at C3 of the indole (3.8:1 mixture of diastereomers). Attempts to convert **63** to the desired ene product **62** by heating in xylenes only led to decomposition.

Scheme 14. Synthesis of Ene Product 62



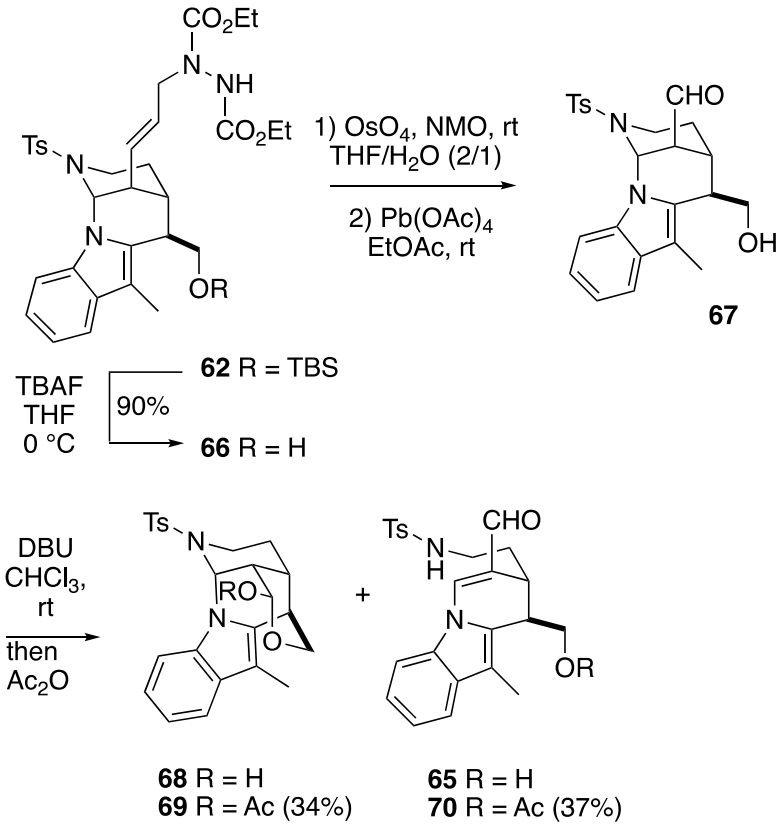
Cleavage of the double bond of **62** using the previously applied two-step sequence was uneventful and provided the requisite axial aldehyde **64** (Scheme 15). However, at this stage an unforeseen problem arose: all attempts to remove the TBS protecting group of **64** using TBAF inexplicably led to the exclusive formation of the ring-opened product **65**. A similar result was observed on attempting to remove the TBS group with HCl. It is notable that the compound analogous to **65** was never detected in the system bearing a C16 carbomethoxyl group (Cf. Scheme 11).

Scheme 15. Unexpected Bridged Aminal Ring Opening



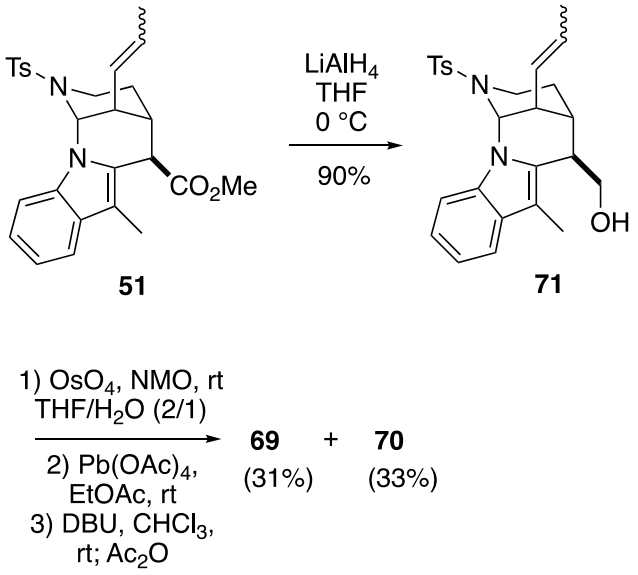
This problem could be mitigated by simply changing the order of steps. Therefore, the TBS group in ene product **62** was first removed with TBAF to yield alcohol **66** (Scheme 16). Cleavage of the alkene could then be effected by the usual two-step dihydroxylation/oxidative cleavage protocol, leading to the desired axial aldehyde **67**. Upon treatment with DBU, this aldehyde was transformed to lactol **68** along with some of the ring-opened product **65**. Without purification, this mixure was converted to lactol acetate **69** using acetic anhydride (34% yield from axial aldehyde **67**) along with the acetylated ring-opened product **70** (37%). It should be noted that in the Bihelovic/Ferjancic synthesis of alstoscholarisine A,[7] treatment of an axial aldehyde like **67**, but bearing an *N*-methyl rather than an *N*-tosyl group, with DBU led to the lactol corresponding to **68** in a similar yield (35%). However, no mention was made by these authors regarding the formation of a ring-opened product such as **65**.

Scheme 16. Conversion of Ene Product 62 to Lactol Acetate 69



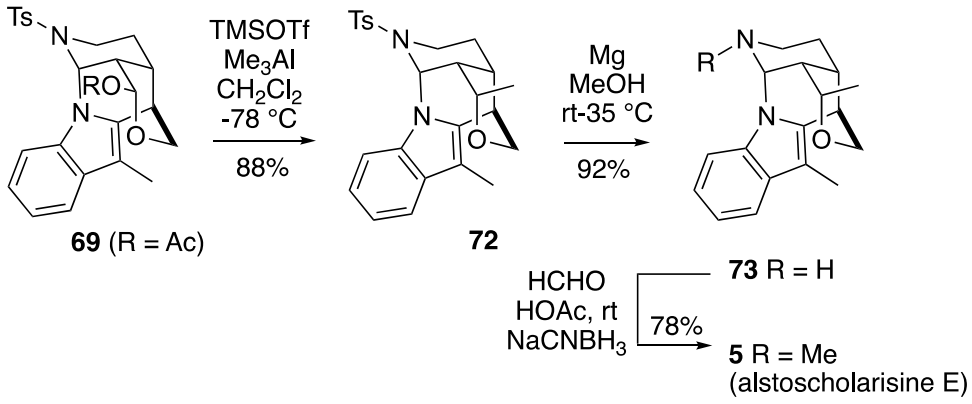
In a similar vein, the ester group in propenyl compound **51** could be reduced with lithium aluminum hydride to afford the corresponding alcohol **71** (Scheme 17). The double bond in this intermediate could then be cleaved as usual to afford the axial aldehyde, which without purification was converted to lactol acetate **69** (31%) along with the ring-opened derivative **70** (33%).

Scheme 17. Formation of Lactol Acetate 69 from Propenyl Compound 51



A synthesis of alstoscholarisine E (**5**) could be executed from lactol acetate **69**, which was first exposed to TMS-triflate and trimethylaluminum in methylene chloride at -78 °C, affording tetrahydropyran **72** in good yield as a single stereoisomer (Scheme 18). It should be pointed out that to effect a clean reaction, this step requires a lower temperature than the methylation of the corresponding lactol acetate substrate **49** bearing an ester moiety at C16, which is done at room temperature (Cf. Scheme 12). The tosyl group could be removed from intermediate **72** using Mg/MeOH, and the resulting amine **73** was N-methylated to afford (±)-alstoscholarisine E (**5**) which had proton and carbon NMR spectra as described for natural material.[5a]

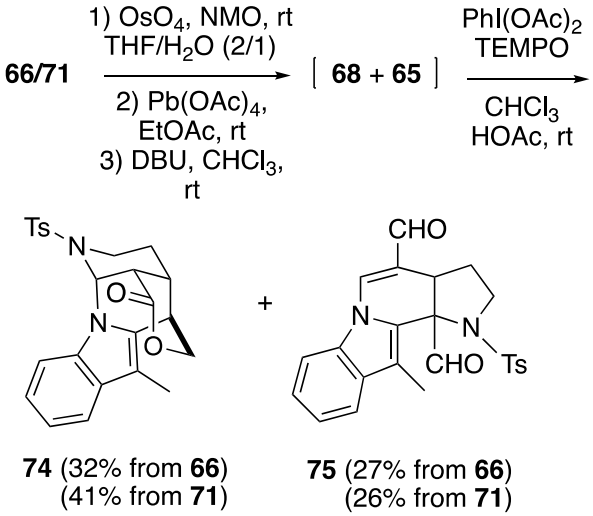
Scheme 18. Coversion of Lactol Acetate 69 to Alstoscholarisine E



The construction of alstoscholarisine A (**1**) utilized δ-lactone **74**. Thus, using ene product **66**, it was possible to effect double bond cleavage as usual, followed by aldehyde epimerization with DBU to produce a mixture of lactol **68** and ring-opened product **65**, which was not purified (Scheme 19). Further oxidation of this crude mixture with TEMPO/$PhI(OAc)_2$,[19] as had previously been done with the lactol **48** which contains a carbomethoxyl group (Cf. Scheme 10), indeed gave the desired lactone **74** (32% from alkene **66**) but also produced some of the unexpected tetracyclic dialdehyde **75** as one stereoisomer (27% from **66**, stereochemistry not determined). However, lactone **74** could be obtained in somewhat better yield by effecting the same sequence with propenyl derivative **71** (see Experimental Section).

We believe that compound **75** arises from cyclization of sulfonamide **65** via a Hofmann-Loffler-Freytag process, which has precedent in related systems, but not with this combination of reagents.[26] An interesting question here is how an initial sulfonamide radical derived from substrate **65** is produced under these conditions. We speculate that the TEMPO is first oxidized by $PhI(OAc)_2$ to form an oxoammonium species[27] that undergoes nucleophilic attack at oxygen by the sulfonamide nitrogen. The resulting intermediate could then undergo N-O bond homolysis to reform TEMPO along with the sulfonamide radical.

Scheme 19. Formation of δ-Lactone 74

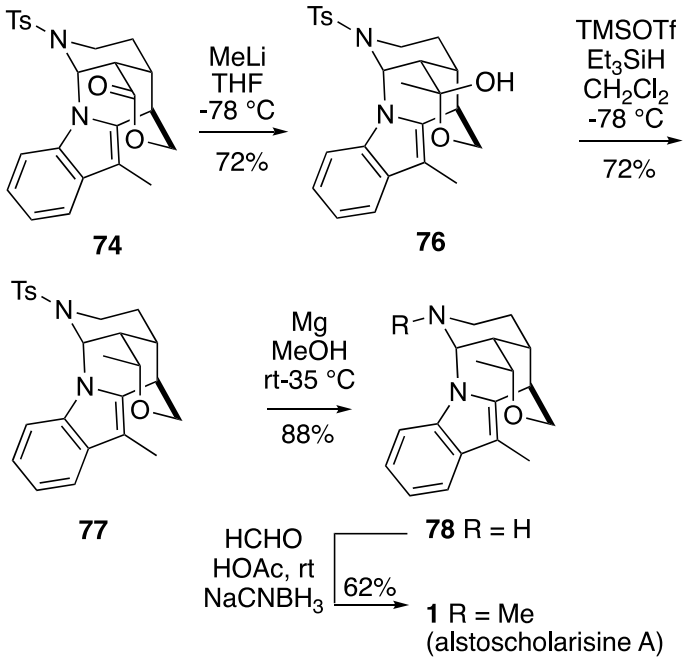


74 (32% from **66**)
(41% from **71**)

75 (27% from **66**)
(26% from **71**)

Reaction of lactone **74** with methyllithium afforded hemiketal **76**, which upon treatment with trimethylsilyl triflate/triethylsilane in methylene chloride at -78 °C led to the tetrahydropyran **77** as a single stereoisomer in 72% yield (Scheme 20). Finally, removal of the tosyl group of **77** produced amine **78** and subsequent N-methylation yielded (±)-alstoscholarisine A (**1**) having spectra as reported for the natural product.[5a]

Scheme 20. Conversion of δ-Lactone 74 to Alstoscholarisine A



CONCLUSION

In summary, we have devised a divergent strategy[28] for construction of alstoscholarisines A-E. Bridged aminal ester **38**, which acts as a pivotal intermediate in this approach, is prepared in five steps via an initial Michael addition of the readily available indole-2-acetic acid methyl ester enolate **19** with the α,β-unsaturated-*N*-sulfonyllactam **16** to form the C15, C16 bond of the alkaloids. This step is followed by a one-pot C-allylation/decarboxylation at C20 and then a selective partial reduction of the *N*-acylsulfonamide functionality to a *N,O*-hemiacetal **37** that can be cyclized under acidic conditions via an *N*-sulfonyliminium ion to form aminal **38**. This intermediate proved to be central for the construction of the five alkaloids.

EXPERIMENTAL SECTION

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 **10** 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 sat. 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.

*Methyl 2-Oxo-3-(phenylselanyl)-1-tosylpiperidine-3-carboxylate (**11**).* Prepared by the general procedure using the following quantities: lactam **10** (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 **11** (1.378 g, 35%) as a pale yellow solid. IR

(neat) 2952, 1729, 1688, 1351, 1167 cm^{-1}; ^1H 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.

*Benzyl 2-Oxo-3-(phenylselanyl)-1-tosylpiperidine-3-carboxylate (**12**).* Prepared by the general procedure using the following quantities: lactam **10** (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 **12** (1.810 g, 56%) as white needles. IR (neat) 2980, 1727, 1692, 1352, 1168 cm^{-1}; ^1H 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.

*Allyl 2-Oxo-3-(phenylselanyl)-1-tosylpiperidine-3-carboxylate (**13**).* Prepared by the general procedure using the following quantities: lactam **10** (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 **13** (22.10 g, 71%) as pale yellow needles. IR (neat) 2956, 1728, 1699, 1353, 1170 cm^{-1}; ^1H 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%, 2.0 equiv)

was added and the reaction mixture was stirred at 0 °C for 1 h, and was diluted with sat. $Na_2S_2O_3$. The organic layer was washed sequentially with sat. $NaHCO_3$ 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 was purified by flash chromatography on silica gel.

*Methyl 2-Oxo-1-tosyl-1,2,5,6-tetrahydropyridine-3-carboxylate (**14**).* Prepared by the general procedure using the following quantities: selenide **11** (981 mg, 2.10 mmol) and *m*-CPBA (73%, 1.04 g, 725 mg of *m*-CPBA, 4.20 mmol) provided crude Michael acceptor **14** (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 **14** 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.

*Benzyl 2-Oxo-1-tosyl-1,2,5,6-tetrahydropyridine-3-carboxylate (**15**).* Prepared by the general procedure using the following quantities: selenide **12** (2.54 g, 4.68 mmol) and *m*-CPBA (73%, 2.21 g, 1.62 g of *m*-CPBA, 9.36 mmol) provided crude Michael acceptor **15** (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 **15** 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.

*Allyl 2-Oxo-1-tosyl-1,2,5,6-tetrahydropyridine-3-carboxylate (**16**).* Prepared by the general procedure using the following quantities: selenide **13** (13.17 g, 26.74 mmol) and *m*-CPBA (73%, 12.00 g, 9.23 g of *m*-CPBA, 53.5 mmol) provided crude Michael acceptor **16** (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 **16** 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.

*tert-Butyl 2-(2-Methoxy-2-oxoethyl)-3-methyl-1H-indole-1-carboxylate (**18**).* Indole ester **17**[11] (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 **18** (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 **18** (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 sat. 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.

*tert-Butyl 2-(1-(3-((Methyloxy)carbonyl)-2-oxo-1-tosylpiperidin-4-yl)-2-methoxy-2-oxoethyl)-3-methyl-1H-indole-1-carboxylate (**20**).* Prepared by the general procedure using the following quantities: LiHMDS (1.0 M in THF, 0.46 mL, 0.46 mmol), indole ester **18** (127 mg,

0.418 mmol), and crude Michael acceptor **14** (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 **20** (121 mg, 57%) as a colorless oil (complex mixture of inseparable stereoisomers). IR (neat) 2951, 1724, 1455, 1356, 1168, 1134 cm^{-1}; ^{1}H 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.

*tert-Butyl 2-(1-(3-((Benzyloxy)carbonyl)-2-oxo-1-tosylpiperidin-4-yl)-2-methoxy-2-oxoethyl)-3-methyl-1H-indole-1-carboxylate (**21**).* Prepared by the general procedure using the following quantities: LiHMDS (1.0 M in THF, 0.81 mL, 0.81 mmol), indole ester **18** (244 mg, 0.805 mmol), and crude Michael acceptor **15** (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 **21** (316 mg, 68%) as a colorless oil (complex mixture of inseparable stereoisomers). IR (neat) 2975, 1725, 1358, 1327, 1162 cm^{-1}; ^{1}H 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.

*tert-Butyl 2-(1-(3-((Allyloxy)carbonyl)-2-oxo-1-tosylpiperidin-4-yl)-2-methoxy-2-oxoethyl)-3-methyl-1H-indole-1-carboxylate (**22**).* Prepared by the general procedure using the following quantities: LiHMDS (1.0 M in THF, 35.5 mL, 35.5 mmol), indole ester **18** (9.73 g, 32.1 mmol), and crude Michael acceptor **16** (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 **22** (11.80 g, 69%) as a white foam (complex mixture of inseparable stereoisomers). IR (neat) 2976, 2939, 1725, 1452, 1357, 1162, 1131 cm^{-1}; ^1H 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.

*tert-Butyl 2-(1-(2-Hydroxy-3-(methoxycarbonyl)-tosylpiperidin-4-yl)-2-methoxy-2-oxoethyl)-3-methyl-1H-indole-1-carboxylate (**23**).* 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 **20** (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 **23** (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.

*Methyl 4-(2-Methoxy-1-(3-methyl-1H-indol-2-yl)-2-oxoethyl)-1-tosyl-1,4,5,6-tetrahydropyridine-3-carboxylate (**25**).* Hemiaminal **23** (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 sat. $NaHCO_3$ (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 **25** (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.

*Methyl 6-Methyl-12-oxo-2-tosyl-2,3,4,4a,5,12-hexahydroindolo[1,2-b][2,7]naphthyridine-5-carboxylate (**27**).* Vinylogous carbamate **25** (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 **27** (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.

*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 (**28**).* Michael adduct **21** (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 sat. 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 **21** (423 mg, 67%) as a white foam (complex mixture of inseparable stereoisomers). IR (neat) 3514, 2977, 1723, 1455, 1357, 1328, 1164 cm^{-1}; ^1H 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.

*tert-Butyl 2-(1-(3-(Hydroxymethyl)-2-oxo-1-tosylpiperidin-4-yl)-2-methoxy-2-oxoethyl)-3-methyl-1H-indole-1-carboxylate (**29**) and tert-Butyl 2-(2-Methoxy-1-(3-methylene-2-oxo-1-tosylpiperidin-4-yl)-2-oxoethyl)-3-methyl-1H-indole-1-carboxylate (**30**).* Benzyl ester **28** (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 alcohols **29** (118.2 mg, 43%) and α-methylene lactam **30** (67.1 mg, 25%, inseparable mixture of stereoisomers) as white foams. For characterization purposes, a sample of the two isomers of alcohol **29** was separated by flash chromatography on silica gel (30% EtOAc in hexanes).

Less polar isomer **29**: 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 **29**: 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 **30:** 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.

*tert-Butyl 2-(1-(2-Hydroxy-3-(hydroxymethyl)-1-tosylpiperidin-4-yl)-2-methoxy-2-oxoethyl)-3-methyl-1H-indole-1-carboxylate (**31**).* 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 **29** (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 **31** (31.7 mg, 41%) as a colorless oil (complex mixture of inseparable stereoisomers). IR (neat) 3509, 2931, 1725, 1456, 1328, 1161 cm^{-1}; ^{1}H 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.

*Methyl 10b-Methyl-2-tosyl-3,4,4a,6,10b,11-hexahydro-2H-pyrido[4,3-b]carbazole-5-carboxylate (**33**).* Trifluoroacetic acid (0.32 mL) was added to a solution of hemiaminal **31** (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 sat. $NaHCO_3$ (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 **33** (13.3 mg, 91%) as a white powder. IR (neat) 3357, 2924, 1674, 1604, 1466, 1356, 1165 cm^{-1}; ^{1}H 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.

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 (**36**).* Method A: 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 **22** (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 **36** (7.09 g, 74%) as an off-white solid (inseparable mixture of stereoisomers). IR (neat) 2976, 2947, 1723, 1452, 1354, 1326, 1163 cm^{-1}; ^{1}H 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: Allyl ester **22** (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 **36** (96.7 mg, 52%). Material prepared by this procedure had spectroscopic data identical to that prepared by Method A.

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 (**37**).* 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 **36** (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 **37** (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}; ^1H 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.

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 (**38**).* TFA (25 mL) was added to a solution of hemiaminal **37** (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 **38** (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.

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 (**39**).* The mixture of ester epimers **38** 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 sat. 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 **39** (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 (see Supporting Information). 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.

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 (**40**).* Ester **38** (2.486 g, 5.194 mmol, 1:4.5 mixture of epimers) was dissolved in a solution of monomeric formaldehyde in THF[16] (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 sat. 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 **40** (2.483 g, 94%) as a white powder. IR (neat) 3525, 2925, 1709, 1459, 1319, 1154 cm^{-1}; ^1H 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.

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 (**41**).* A solution of alcohol **40** (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 **41** (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.

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 (**42**).* DEAD (40% in PhMe, 5.2 mL, 1.97 g of DEAD, 11.3 mmol) was added to a solution of terminal olefin **41** (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 **42** (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.

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 (**43**) and 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 (**44**).* Terminal alkene alcohol **40** (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 hydrazine **43** (86.8 mg, 44%) as a white powder and carbonate **44** (35.0 mg, 23%) as a colorless oil.

Hydrazine **43**: IR (neat) 3334, 2981, 1744, 1461, 1258 cm^{-1}; ^1H 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.

Carbonate **44**: Colorless oil IR (neat) 2954, 1742, 1460, 1319, 1156 cm^{-1}; ^1H 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.

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 (**45**).* Ene

adduct **42** (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 sat. 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 **45** (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.

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 (**49**).* Method A: Silyl ether **45** (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 sat. $NaHCO_3$ (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 sat. 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 **49** (99.6 mg, 77% from **45**) 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 **52** (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 sat. 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 sat. 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 **49** (187.7 mg, 72%) as a white solid. This material had spectral data identical to that prepared by Method A.

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 (**50**).* Method A: Silyl ether **45** (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 sat. $NaHCO_3$ (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 sat. $Na_2S_2O_3$ (20 mL) and sat. $NaHCO_3$ (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 **50** (169.6 mg, 73% from **45**) 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 **52** (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 sat. 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 sat. $Na_2S_2O_3$ (10 mL) and sat. $NaHCO_3$ (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 **50** (36.9 mg, 72% from **52**) as a pale yellow foam. This material had spectroscopic data identical to that prepared using Method A.

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 (**51**).* Terminal alkene **39** (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 **51** (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}; ^1H 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.

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 (**52**).* Terminal alkene **40** (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 **52** (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}; ^1H 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.

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 (**54**).* Lactol acetate **49** (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 **54** (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.

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 (**55**).* Sulfonamide **54** (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 sat. 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 **55** (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**).* Secondary amine **55** (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 sat. 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.

*(±)-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.

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 (**56**).* Lactone **50** (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 sat. 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 **56** (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.

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 (**58**).* 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 **56** (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 **58** (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.

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 (**59**).* Sulfonamide **58** (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 sat. 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 **59** (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**).* Secondary amine **59** (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 sat. 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.

((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 (**60**).* Powdered $LiAlH_4$ (125 mg, 3.30 mmol) was added to a 0 °C solution of ester **39** (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 **60** (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.

(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* ***(61).*** Alcohol **60** (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 sat. 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 **61** (340.9 mg, 98%) as a white foam. IR (neat) 2929, 1460, 1322, 1155, 1088 cm^{-1}; ^{1}H 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.

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* ***(62)*** *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* ***(63).*** DEAD (40% in PhMe, 1.1 mL, 431 mg of DEAD, 2.48 mmol) was added to a solution of terminal olefin **61** (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 **62** (193.8 g, 53%) as a white foam and bis-hydrazine **63** (192.8 mg, 43%, 3.8:1 mixture of inseparable stereoisomers) as a pale yellow solid.

Ene adduct **62**: IR (neat) 3309, 2930, 1709, 1460, 1319, 1207, 1154, 1087 cm^{-1}; ^1H 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 **63**: IR (neat) 3297, 2933, 1708, 1463, 1324, 1256, 1090 cm^{-1}; ^1H 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.

(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* ***(64).*** Ene adduct **62** (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 sat. 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 **64** (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.

N-(2-((8R,9R*)-7-Formyl-9-(hydroxymethyl)-10-methyl-8,9-dihydropyrido[1,2-a]indol-8-yl)ethyl)-4-methylbenzenesulfonamide (**65**).* Silyl ether **64** (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 sat. 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 **65** (8.7 mg, 59%) as a pale yellow solid. IR (neat) 3463, 3272, 2923, 1657, 1606, 1464, 1318, 1154 cm^{-1}; ^1H 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.

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 (**66**).* A solution of silyl ether **62** (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 sat. 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 **66** (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.

(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 (**69**) and ((8R*,9R*)-7-Formyl-10-methyl-8-(2-((4-methylphenyl)sulfonamide)ethyl)-8,9-dihydropyridol[1,2-a]indol-9-yl)methyl Acetate (**70**).* 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 **66** (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 sat. 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 1 h 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 sat. 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 **69** (18.1 mg, 34%) as a pale yellow solid and acetate sulfonamide **70** (19.6 mg, 37%) as a pale yellow foam.

Lactol acetate **69**: 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 **70:** IR (neat) 3274, 3058, 1738, 1660, 1465, 1323, 1151 cm^{-1}; ^1H 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 **71** (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 sat. 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 sat. 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 **69** (57.6 mg, 31%) as a pale yellow solid, as well as acetate sulfonamide **70** (60.2 mg, 33%) as a pale yellow foam. Both compounds had spectroscopic data identical to the ones prepared by Method A.

((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 (**71**).* Powdered $LiAlH_4$ (45.3 mg, 1.19 mmol) was added to a 0 °C solution of ester **51** (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 **71** (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.

(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 (**72**).* 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 **69** (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 sat. 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 **72** (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.

(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 (**73**).* Sulfonamide **72** (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 sat. 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 **73** (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**).* Secondary amine **73** (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 sat. 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.

(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 (**74**) and 11-Methyl-1-tosyl-1,2,3,3a-tetrahydro-11bH-pyrrolo[2',3',3,4]pyrido[1,2-a]indole-4-11b-dicarbaldehyde (**75**).* Method A: Ene adduct **66** (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 sat. 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 sat. $Na_2S_2O_3$ (10 mL) and sat. $NaHCO_3$ (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 **74** (28.5 mg, 32%) as a pale yellow foam and bis-aldehyde **75** (24.3 mg, 27%) as a pale yellow powder.

Lactone **74**: 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 **75**: 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 **71** (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 sat. 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 sat. $Na_2S_2O_3$ (10 mL) and sat. $NaHCO_3$ (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 **74** (59.8 mg, 41%) as a pale yellow foam and bis-aldehyde **75** (37.5 mg, 26%) as a pale yellow powder. Both compounds had spectroscopic data identical to material prepared by Method A.

(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 (**76**).* Lactone **74** (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 sat. 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 **76** (10.8 mg, 72%) as a colorless oil. IR (neat) 3472, 2927, 1461, 1327, 1157, 1092 cm^{-1}; ^1H 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.

(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 (**77**).* 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 **76** (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. Sat. $NaHCO_3$ (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 **77** (22.3 mg, 72%) as a colorless film. IR (neat) 2916, 1462, 1348, 1326, 1139, 1095 cm^{-1}; ^1H 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.

(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 (**78**).* Sulfonamide **77** (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 sat. 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 **78** (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**).* Secondary amine **78** (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 sat. 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.

ASSOCIATED CONTENT

Supporting Information

Proton and carbon NMR spectra of compounds and X-ray data (CIF) for compound **39**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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