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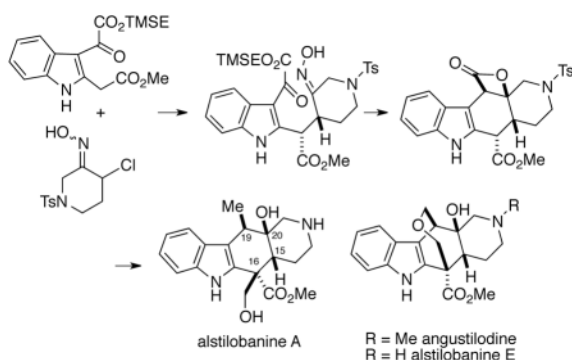
Total Syntheses of the Monoterpene Indole Alkaloids (±)-Alstilobanine A and E, and (±)-Angustilodine

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Abstract



A synthetic strategy has been developed culminating in stereoselective total syntheses of the small class of unusual monoterpene indole alkaloids exemplified by alstilobanine A (**3**) and E (**2**) and angustilodine (**1**). A pivotal step includes a novel intermolecular Michael-type addition of an indole ester dianion to a piperidine-derived nitrosoalkene to form the C15, C16 bond of the alkaloids. In addition, an application of the Romo protocol for effecting a stereoselective intramolecular nucleophile-assisted aldol-lactonization was employed, leading to a β -lactone incorporating the requisite *cis*-fused 2-azadecalin moiety and also setting the C15, C19, C20 relative stereochemistry of the metabolites. It was then possible to stereoselectively effect an aldolization of a dianion derived from this indole ester β -lactone intermediate with formaldehyde to introduce the requisite C16 hydroxymethyl group. Further manipulations of the system ultimately led to the three alkaloids in racemic form.

INTRODUCTION

Terpene-derived indole alkaloids are produced by several plant families, and are among the most abundant types of natural products with over 3000 such compounds currently known.¹ These alkaloids encompass an extraordinarily diverse array of structural motifs and

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[#]Dedicated to Professor Deukjoon Kim on the occasion of his retirement from Seoul National University

Notes

The authors declare no competing financial interest.

Supporting Information

 Proton and carbon NMR spectra of new compounds. Included also are X-ray data for compound **30**. This material is available free of charge on the Internet at <http://pubs.acs.org>.

complexity. About ten years ago, Kam and Choo isolated angustilodine (**1**), a new skeletal type of monoterpene indole alkaloid, from the leaves of the Malayan plant *Alstonia angustiloba* (Figure 1).² The structure of this unique metabolite was determined by detailed NMR spectroscopic analysis to be comprised of an indole appended to a *cis*-fused 2-azadecalin ring system bridged by an oxepane ether. In 2008, Morita and coworkers investigated alkaloids from the same plant and discovered the *N*-demethyl analog of angustilodine, alstilobanine E (**2**), along with alstilobanine A (**3**), which lacks the bridging oxepane ring found in compounds **1** and **2**.³ Based on NMR NOESY correlations, it was proposed that alstilobanine A has the conformation shown in Figure 1, where the piperidine ring is in a chair conformation. On the other hand, the Morita group proposed that alstilobanine E has the piperidine ring in a boat conformation as shown in **2**. Although the conformation of angustilodine was not explicitly discussed by Kam and Choo, it appears quite likely that this alkaloid has the same conformation as alstilobanine E. Alstilobanines A and E were found to possess moderate relaxant activity against phenylephrine-induced contractions of thoracic rat aortic rings. In a communication which appeared in 2012, we reported the first approach to these unusual alkaloids, resulting in a stereoselective total synthesis of racemic alstilobanine A (**3**).^{4,5} We now describe the details of our studies on alstilobanine A along with the extension of our synthetic strategy culminating in the first total syntheses of angustilodine and alstilobanine E.

RESULTS AND DISCUSSION

Synthesis Plan

Our initial retrosynthetic analysis for synthesis of alkaloids **1-3** is outlined in Scheme 1. Thus, the plan was to prepare a key intermediate β -lactone **4** which incorporates the *cis*-2-azadecalin moiety found in the metabolites, and subsequently elaborate such a species into the three natural products by suitable manipulations using the carboxylate groups at C16 and C19. The pentacyclic β -lactone **4** would be prepared via a Romo-type intramolecular nucleophile-assisted aldol-lactonization of keto acid **5** which would generate the required alkaloid relative stereochemistry at C15, C19, and C20.⁶ Prior to the outset of our work, studies by the Romo group had shown that in simpler, all-carbon systems structurally related to intermediate **5**, *cis*-decalins analogous to **4** can be formed with a high degree of stereoselectivity.^{6b} We envisaged that the acetic acid unit of intermediate **5** would be installed by appropriate manipulations of indole **6**. In turn, **6** would be produced via a conjugate addition of an indole-2-acetic ester enolate **7** with the *in situ*-generated nitrosoalkene **8** to form the C15, C16 bond of the natural products.⁷

Studies on Nitrosoalkene/Indole-2-acetic Ester Enolate Conjugate Additions

Our laboratory has recently been engaged in exploring the synthetic potential of conjugate additions of nucleophiles to transient, reactive nitrosoalkenes to effect the overall transformation of **9** to **11** as shown in Eq 1.⁸ There are presently two procedures normally used to generate nitrosoalkenes like **10**. The most common method involves a base-promoted 1,4-elimination of an α -chlorooxime **9** (R = H) to produce the nitrosoalkene. One drawback of this methodology is that it requires at least two equivalents of a nucleophile, one of which acts as the base for the initial elimination step. Such a procedure, however, is inefficient when using valuable nucleophiles. A second, but to date less widely used procedure for nitrosoalkene generation developed by Denmark, *et al.* relies on treatment of an *O*-silyl- α -chlorooxime **9** (R = SiR₃) with a fluoride source to form the nitrosoalkene **10**.⁹ In principle, the Denmark methodology alleviates the problem of using excess nucleophile in a conjugate addition, and towards this end we have recently developed a general experimental procedure for effecting both inter- and intramolecular reactions of

nitrosoalkenes formed *in situ* via this strategy with a variety of enolate nucleophile partners.^{8a-c}

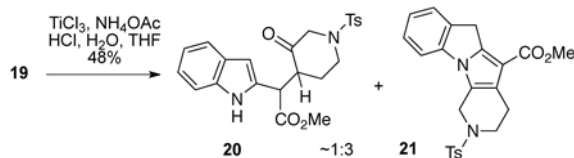


(1)

With the strategy in Scheme 1 in mind, we investigated the possibility of effecting the coupling of an ester enolate like **7** with piperidine-derived nitrosoalkene **8** to produce an intermediate such as **6**. Thus, *N*-Boc-protected indole **12**, prepared from methyl indole-2-acetate,¹⁰ was converted to the enolate **14** with lithium hexamethyldisilazide (Scheme 2). Using the Denmark-based protocol which we previously devised,^{8a-c} α -chloro-*O*-TBS-oxime **13**, prepared from the corresponding α -chloroketone,¹¹ was then added to this enolate, followed by tetrabutylammonium fluoride. Disappointingly, none of the adduct **16** resulting from addition of **14** to **8** was detected. As an alternative, the coupling was attempted by combining two equivalents of enolate **14** with one equivalent of the α -chlorooxime **15**. In this case, a small amount of the desired product **16** was generated, but only in very poor yield.

In view of these problems, it was decided to form a monoanion from 2 equivalents of unprotected methyl indole-2-acetate (**17**)¹⁰ and attempt to couple this intermediate with one equivalent of α -chlorooxime **15** (Scheme 3). We were pleased to find that this reaction led to formation of Michael adduct **19** in an acceptable 59% yield, along with recovered starting ester **17** (66%) which could be recycled. Compound **19** is about a 3:1 mixture of C15, C16 diastereomers, but appears to be a single oxime geometric isomer which is probably *E* (*vide infra*). We believe that the anion formed in the deprotonation step probably exists as an equilibrium mixture of **18a** and **18b**. However, the alkylation with the transient nitrosoalkene **8** occurs only at the carbon adjacent to the ester, and no products resulting from *N*-alkylation (which may in fact be reversible), or alkylation at the indole C3 position were detected. We are not aware of any precedent for this transformation. It might also be noted that the same reaction could be effected using one equivalent each of α -chloro-*O*-TBS-oxime **13** and anion **18** via the Denmark protocol, but led to product **19** only in low yield.

Having the coupled product **19** in hand, we next examined a number of different homologations of oxime-protected versions of this intermediate in attempts to introduce an acetic acid unit at C3 of the indole (Cf. **5**, Scheme 1). Unfortunately, none of these routes proved viable.⁵ However, one experiment performed on compound **19** did provide some useful information. Attempted reductive cleavage¹² of the oxime functionality in **19** led to some of the desired ketone **20** along with tetracyclic indolopyrrole **21** as the major product (Eq 2). Thus, it appeared that protection of the indole nitrogen would probably be necessary prior to generating the 3-piperidone (*vide infra*).



(2)

Since it was not possible to introduce the requisite acetate unit into indole **19**, we decided to explore a potentially more convergent route utilizing a C2, C3-disubstituted indole in the nitrosoalkene conjugate addition step. Therefore, indole **17** was first treated with oxalyl chloride, followed by addition of 2-trimethylsilylethanol/triethylamine to afford oxoacetate diester **22** in high yield having the two ester groups differentiated for later manipulations (Scheme 4).¹³ In order to improve the efficiency of our synthetic approach, we decided to explore a strategy which would potentially allow the use of equimolar equivalents of the coupling partners in the key nitrosoalkene conjugate addition step, thereby obviating the recovery/recycling of excess indole ester. Thus, indole oxoacetate derivative **22** (one equivalent) was first converted to the dianion **23** using two equivalents of lithium hexamethyldisilazide at low temperature. Subsequent addition of one equivalent of α -chlorooxime **15** to this dianion then led to the desired coupled product as a ~1.2:1 mixture (by NMR) of C15, C16 diastereomers **24a/b** in nearly quantitative yield. These isomers could be separated chromatographically for characterization purposes, and each seemed to be a single *E*-oxime geometric isomer. The stereochemistry of **24a** and **24b** was established at a later stage of the synthesis (*vide infra*).

We believe that this transformation proceeds via an initial dehydrohalogenation of the α -chlorooxime **15** by the dianion **6** to generate the transient nitrosoalkene **8** along with a monoanion derived from the indole ester **22**. As was observed with the anion **18** (Cf. Scheme 3), it seems likely that this intermediate is probably a similar equilibrium mixture of monoanions, but the conjugate addition to nitrosoalkene once again occurs exclusively at the carbon adjacent to the ester moiety to afford products **24a/b**.

Elaboration of Adducts **24a/b** to Ketoacid **34** and Subsequent Intramolecular Romo Cyclization

Since at this stage we believed that the C15, C16 stereochemistry was of no relevance to the synthesis, we opted to carry the mixture of diastereomers **24a/b** on to the next series of transformations, which was aimed to remove the C19 carbonyl group to produce an acetate ester chain on the indole. It was eventually found that the best way to effect this deoxygenation process was by use of a modification of a sequence developed by Hlasta, *et al.*¹⁴ Thus, the oxime moiety was first protected as the TBS ether **25** (Scheme 5). The keto group of the oxoacetate mixture **25** was then reduced with sodium borohydride, and the resulting crude alcohol mixture was acylated with acetic anhydride/pyridine to give the corresponding acetates as a complex mixture of stereoisomers. This mixture, however, could be easily separated by flash chromatography to give **26** as a ~3:1 mixture of acetate isomers (55% from keto esters **25**), and **28** as a ~2:1 mixture of acetates (36% from **25**).

Hlasta and coworkers had previously found that it was necessary to run the catalytic hydrogenation of an acetate like **26** with 10% Pd/C in a 1:9 TEA/EtOH solvent mixture for reduction to occur, presumably via an intermediate azafulvene.¹⁴ Thus, treatment of compound **26** under these hydrogenation conditions provided the desired reduction product **29**, albeit contaminated with an impurity which could not be separated by column

chromatography. We suspected from ^1H NMR analysis of the crude product that the impurity was ethoxy compound **27** resulting from the addition of ethanol to the azafulvene intermediate **A**. In fact, treatment of acetates **26** with ethanol/triethylamine indeed led to formation of **27** in good yield. We therefore investigated several other solvent combinations for the hydrogenation, and found that an alcohol is required for the reduction to occur. Ultimately it was determined that the reduction could be effected cleanly if carried out in *t*-butanol/triethylamine at 30 °C, although the hydrogenation is slow under these conditions, requiring four days to go to completion. However, using this approach, acetates **26** and **28** could be reduced to indole-3-acetates **29** and **30**, respectively, in high isolated yields.

Although our initial assumption was that the C15, C16 stereochemistry would have no effect on any of the planned transformations of intermediates **29** and **30**, the configuration at these centers in fact proved to have a critical role in the subsequent Romo cyclization (*vide infra*). Based on what was eventually learned in the work discussed below, it was determined that diastereomer **30** is the one required for the alkaloid synthesis. Fortunately, it was found that it is possible to easily equilibrate the undesired isomer **29** to **30**. Therefore, treatment of ester **29** with potassium hexamethyldisilazide at -78 °C, followed by slowly warming to room temperature and then acid quenching resulted in the formation of what is apparently the thermodynamically more stable diastereomer **30** in 70% isolated yield. This compound proved amenable to X-ray crystallographic analysis, thereby confirming its configuration and *E*-oxime geometry. Although fortuitous, it is not clear to us why isomer **30** is the thermodynamic product.

With substantial quantities of intermediate **30** now in hand, it was possible to convert this compound in high overall yield into the ketoacid **34** necessary for the key intramolecular Romo cyclization (Scheme 6). Therefore, indole **30** was first *N*-protected as the Cbz derivative **31** in order to avoid the cyclization problem shown in Eq 2. Removal of the *O*-TBS protecting group yielded the free oxime **32**, which could be hydrolyzed under acidic conditions to the piperidone **33**.¹⁵ Attempts were then made to convert the β -trimethylsilylethyl ester to the corresponding acid with various fluoride sources but to no avail. However, the TMSE-ester of ketoacid **34** could be removed selectively from compound **33** using trifluoroacetic acid in methylene chloride.¹⁶

The pivotal cyclization to form the *cis*-2-azadecalin system was then effected by applying the reaction conditions developed by Romo.⁶ Thus, treatment of ketoacid **34** with 4-pyrrolidinopyridine (PPY), 2-bromo-*N*-propylpyridinium triflate and diisopropylethylamine in methylene chloride, along with a small amount of acetic acid to suppress C16 ester epimerization, led to formation of an inseparable 97:3 mixture of the desired *cis*-azadecalin **35** and the *trans*-fused compound **37** in 93% total yield (Scheme 7). Hydrogenolysis of this mixture provided the unprotected indole β -lactones **36** (94%) and **38** (3%) which could be separated chromatographically.

Interestingly, the Romo cyclization takes a different and more complicated stereochemical course when conducted in the C15, C16-isomeric series derived from diastereomer **29** (Scheme 8). TMSE-ester **39** can be prepared via the sequence shown in Scheme 6 starting from indole **29**. However, when TMSE-ester **39** was treated under the same TFA cleavage conditions used to prepare ketoacid **34** from **33**, partial C16 epimerization resulted to produce a mixture of ketoacids **40** whose diastereomeric composition could not be determined. Subsequent exposure of this mixture to the standard Romo conditions led to a complex mixture of products **41** and **42** in high overall yield, each as a mixture of C16 epimers. Notably, in this case the major products **42** have the undesired *trans*-2-azadecalin configuration. Clearly the configuration at C16 in the precursors to the Romo cyclization

plays a key role in the stereochemical outcome of the process but at present we cannot assess exactly what factors are responsible for these results.

Introduction of the C17 Hydroxymethyl Group

At this stage of the synthesis we began to investigate introduction of the C16 hydroxymethyl group into the system via an ester enolate aldolization or alkylation. To examine this process, the mixture of inseparable Cbz-protected indole β -lactones **35** and **37** was first selectively reduced with diisobutylaluminum hydride to afford the 1,3-diol **43a** (66% isolated yield), which could be separated from a small amount of the corresponding diol produced from the *trans*-2-azadecalin (Scheme 9). Interestingly, extensive 2D NMR analysis (HMBC, HMQC, COSY and NOESY) indicated a conformation for the diol as shown in structure **43b**, which is actually the *cis*-2-azadecalin invertamer of alstilobanine A (**3**) (Cf. Figure 1). This diol **43a** could then be protected with acetaldehyde dimethyl acetal to afford acetal **44** as a single stereoisomer.

A number of attempts were made to deprotonate ester **44** using a wide variety of amide bases, followed by alkylation with monomeric formaldehyde^{17,18,19} and several other electrophiles such as BOM-Cl and MOM-Cl, but in all cases only unchanged starting material was recovered. Based on these experiments, it appeared that an ester enolate was not being formed from **44**. We attribute this problem to the indole Cbz protecting group, which for steric reasons may be causing the ester to assume a twisted conformation, precluding the proper alignment for deprotonation of the C16-H σ -bond with the carbonyl π -bond.

However, one experiment that was conducted pointed towards a possible solution to this enolization problem. Therefore, treatment of ester **44** with a mixture of sodium hydride and paraformaldehyde in DMF led to a high yield of the product **45** having the C16 hydroxymethyl moiety, but which also lacked the Cbz protecting group. Unfortunately, based on 2D NMR analysis, it was determined that **45** has the incorrect stereochemistry of the hydroxymethyl substituent at C16. We believe that in this transformation adventitious NaOH first promotes cleavage of the Cbz group, followed by subsequent ester deprotonation to afford a dianion **46**. This dianion can exist in conformation **46a** which is highly destabilized by A^{1,3}-strain, or in the more stable conformation **46b**. It appears that the reaction with formaldehyde probably occurs via the latter conformation from the face opposite to the bulky acetal ring.

Although these results indicated the feasibility of a C16 alkylation of a dianion derived from systems like **44**, our major concern at this point was to find a way to introduce the hydroxymethyl group with the requisite stereochemistry. We reasoned that one way to control the configuration at C16 would be to effect an intramolecular alkylation. Therefore, diol **43** was selectively silylated at the primary alcohol to afford TBS ether **47** and the Cbz protecting group was then removed by catalytic hydrogenolysis to yield the NH indole **48** (Scheme 10). Silylation of the tertiary alcohol functionality of **48** was effected with known chloromethyl(dimethyl)silyl chloride²⁰ to afford silyl ether **49**. Finkelstein exchange of the chlorine in **49** for iodine produced iodomethyl compound **50**.

We were gratified to find that treatment of intermediate **50** with three equivalents of potassium hexamethyldisilazide in THF at -78 °C and then warming to 0 °C resulted in an intramolecular alkylation of the ester enolate to produce the desired pentacyclic siloxane **51** in high yield. It was also possible to remove the TBS group from **51** to produce siloxane alcohol **52**. With these two siloxanes in hand, a wide variety of conditions were attempted in order to effect a Tamao-Fleming oxidation to produce the triol **53**.²¹ Under no

circumstances, however, were we able to access this product. In general, siloxanes **51** and **52** were resistant to ring opening under both acidic and basic conditions, and under more forcing conditions only led to the product where the C16 hydroxymethyl group was lost from **53**.⁵

In view of the problems discussed above we returned to the unprotected β -lactone ester **36** and explored its hydroxymethylation. We were pleased to find that intermediate **36** could indeed be deprotonated with two equivalents of lithium hexamethyldisilazide to generate the dianion **54**, followed by alkylation with monomeric formaldehyde^{17,18} to produce α -hydroxymethyl ester **55** as a single diastereomer that has the correct configuration at C16 for the alkaloids **1-3** (Scheme 11). The stereochemistry of compound **55** was established by 2D NMR analysis and by its eventual conversion to the natural products **1-3**. The β -lactone ring in dianion **54** appears to flatten the system sufficiently that the formaldehyde alkylation occurs exclusively from the desired face in this instance. The stereochemistry of **55** was further confirmed by the fact that the β -lactone, upon treatment with triethylamine in methylene chloride, underwent acyl migration to afford the bridged ϵ -lactone **57**. Since the hydroxymethyl group of **55** tends to be lost under a variety of reaction conditions (particularly basic ones) via a retro-aldol process, this functionality was protected as the TBS ether **56** for further use.

Synthesis of (\pm)-Alstilobanine A (**3**)

The synthesis of alstilobanine A (**3**) from the intermediates in hand basically required a deoxygenation sequence to produce the C19 methyl group of the metabolite. The first route which we explored involved an initial partial reduction of ϵ -lactone **57** with diisobutylaluminum hydride/boron trifluoride etherate to provide aldehyde diol **58**, albeit in only modest yield (Scheme 12). This compound was then converted to the dithiane **59** with 1,2-ethanedithiol promoted by boron trifluoride etherate. This dithiane could be directly reduced with W-2 Raney nickel to afford the desired methyl-containing compound **60**. This sequence, however, suffered from a number of serious problems including low and/or highly irreproducible yields and unstable intermediates due to a tendency of the hydroxymethyl group to be lost by a retro-aldol reaction.¹⁹

Thus, an alternative and much more efficient route to the alkaloid was devised. β -Lactone **56** was reduced with lithium borohydride to afford diol **61** (Scheme 13). Using a two-step sequence analogous to one reported by Huscroft, *et al.*²² diol **61** was first converted to iodo alcohol **62** via an Appel reaction. Catalytic hydrogenation of the iodomethyl compound **62** at atmospheric pressure using 10% Pd/C in a 1:1 mixture of ethyl acetate:*t*-butanol then led to the desired methyl compound **63**. The *N*-tosyl protecting group of intermediate **63** was cleaved using magnesium metal turnings in methanol under sonication to afford piperidine **64** in good yield.²³ The structure and stereochemistry of this intermediate were confirmed by 2D NMR analysis (see Supporting Information). Finally, removal of the TBS protecting group with HCl in methanol/chloroform afforded racemic alstilobanine A (**3**), isolated as its hydrochloride salt, having proton and carbon NMR spectra as reported for the alkaloid by Morita, *et al.*^{3,24}

Syntheses of (\pm)-Alstilobanine E (**2**) and (\pm)-Angustilodine (**1**)

The next goal of this project was to utilize one of the intermediates prepared for alstilobanine A to construct the bridging oxepane ring of alkaloids **1** and **2**, a task which proved considerably more difficult than originally envisioned. Towards this end, β -lactone **55** was reduced with DIBAL-H to afford diol **65** (Scheme 14). An attempt was then made to effect a Mitsunobu cyclization of this triol to generate the oxepane.²⁵ Treatment of **65** with triphenylphosphine and DIAD (1 equivalent) in benzene at room temperature, however, did

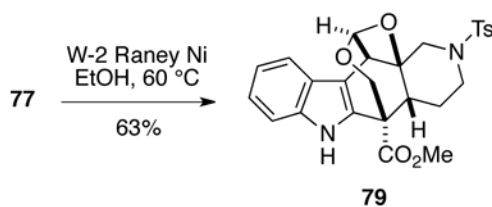
not afford any of the desired oxepane, but rather gave a chromatographically separable mixture of the tetrahydrofuranyl ether **67**²⁶ (51%) and oxetane **68**²⁷ (23%). Interestingly, using an excess of DIAD (5 equivalents) under the same reaction conditions produced the cyclopropane tetrahydropyranyl ether **66** in high yield.²⁸ If DEAD was used instead of DIAD, under refluxing conditions the major cyclization product was oxetane **68** along with traces of tetrahydrofuran **66** and cyclopropane **67**.

In another attempt to form an oxetane, intermediate iodomethyl compound **62**, which was used in the synthesis of alstilobanine A (Cf. Scheme 13), was exposed to silver fluoroborate or silver triflate.²⁹ In this case, however, only the cyclopropane **69** was formed in high yield (Scheme 15). Another variation which was tried with intermediate **62** was to treat it with tetrabutylammonium fluoride to promote cycloetherification. In this instance the only product formed was cyclopropane **70**, where the hydroxymethyl group has been lost.

In order to avoid cyclopropane formation, we decided to attenuate the reactivity of the indole at C3 by installing an electron withdrawing group on the nitrogen. Thus, indole β -lactone **56** was first protected as the Cbz derivative **71** (Scheme 16). The β -lactone could be reduced with lithium borohydride to give diol **72** which was then converted to bromomethyl compound **73** via an Appel reaction. Disappointingly, exposure of bromide **72** to silver triflate yielded only the oxetane **74** which was characterized by its conversion to oxetane **68**, previously prepared as shown in Scheme 14. It might also be noted that a number of attempts were made to effect similar cycloetherifications in systems where the tertiary alcohol was protected, but these sequences were not fruitful.

In light of these failures, we turned to a different strategy to build the oxepane ring. Diol **61** could be cleanly oxidized with IBX³⁰ to afford aldehyde **75** in excellent yield (Scheme 17). Removal of the TBS protecting group from **75** led to diol aldehyde **58** which had previously been prepared in low to moderate yield via partial reduction of ϵ -lactone **57** (Cf. Scheme 12). It was possible to convert compound **58** to dithioacetal diol **76** in high yield with ethanethiol catalyzed by titanium tetrachloride with no evidence of aldehyde epimerization.³¹ We were pleased to find that using a set of conditions developed by Nicolaou and coworkers for a related cyclization involving silver perchlorate catalysis,³² it was possible to cyclize dithioacetal alcohol **76** to the desired seven-membered ring hemithioacetals as a separable ~3:1 mixture of diastereomers **77** and **78** in high total yield. The stereochemistry of these hemithioacetals was established by 2D NMR NOESY analysis (see Supporting Information).

With a seven-membered ring finally in hand, we next surveyed a number of methods and reagents for reductively removing the thioethyl group from **77/78**. Raney nickel was investigated initially under several sets of conditions, but in general the major product from these reactions was the unusual oxetane acetal **79** along with only traces of the desulfurized product (Eq 3).³³ Various hydride (ZnBH_4 , $\text{NaCNBH}_3/\text{ZnCl}_2$, etc) and free radical-based reductions (Bu_3SnH , Ph_3SnH , etc) also failed to give any of the desired oxetane.



It was eventually found that reduction of hemithioacetals **77** and **78** with triethylsilane catalyzed by 10% Pd/C afforded the requisite oxepane **80** in excellent yield (Scheme 18).³⁴ The sulfonamide protecting group of **80** could then be removed with magnesium/methanol²³ as was done for alstilobanine A to give racemic alstilobanine E (**2**) which had NMR spectra as described in the literature.³ Finally, reductive *N*-methylation of alstilobanine E with paraformaldehyde/sodium borohydride³⁵ afforded racemic angustilodine (**1**) having proton and carbon NMR spectra identical to those provided by Professor Kam.^{2,24}

CONCLUSION

We have described the details of the first total syntheses of the structurally unique monoterpene indole alkaloids alstilobanine A (**3**), alstilobanine E (**2**) and angustilodine (**1**) from a common intermediate, indole β -lactone **56**. We have devised a convergent route to this intermediate which includes as key steps (1) an unprecedented conjugate addition of the dianion of indole-2-acetate ester **23** to the piperidine-derived nitrosoalkene **8** to form the C15, C16 bond in adducts **24a/b** and (2) a stereoselective intramolecular Romo nucleophile-assisted aldol-lactonization of ketoacid **34** to generate β -lactone **35** fused to the requisite *cis*-2-azadecalin needed for the alkaloid along with the attendant C15, C19, C20 relative stereochemistry. The vexing problem of introducing the C16 hydroxymethyl group needed for all three alkaloids was finally solved via an aldolization of a dianion derived from indole ester β -lactone intermediate **36** with monomeric formaldehyde. Some further manipulations eventually allowed conversion of the β -lactone carbonyl carbon into the C19 methyl group of alstilobanine A (**3**). Finally, a sequence was developed that allowed the silver-catalyzed cyclization of dithioacetal alcohol **76** into the seven-membered hemithioacetals **77/78**, which could be reductively desulfurized and then subsequently converted into alstilobanine E (**2**) and angustilodine (**1**).

EXPERIMENTAL SECTION

General Methods

All non-aqueous reactions were carried out in oven- or flame-dried glassware under an argon atmosphere. All chemicals were purchased from commercial vendors and used as is, unless otherwise specified. Anhydrous tetrahydrofuran (THF) and dichloromethane (CH_2Cl_2) were obtained from a solvent purification system. Reactions were magnetically stirred and monitored by thin layer chromatography (TLC) with 250 μm precoated silica gel plates. Flash column chromatography was performed using silica gel (230–400 mesh). Chemical shifts are reported relative to chloroform (δ 7.26), methanol (δ 3.31), or DMSO (δ 2.50) for ^1H NMR and chloroform (δ 77.2), methanol (δ 49.0), or DMSO (δ 39.5) for ^{13}C NMR. High resolution mass spectra were obtained on a time of flight instrument using electrospray ionization.

4-Chloro-1-tosylpiperidin-3-one Oxime (15)—To a stirred solution of 4-chloro-1-tosylpiperidin-3-one **11** (5.40 g, 18.8 mmol) in DMSO (50 mL) was added $\text{H}_2\text{NOH}\cdot\text{HCl}$ (1.46 g, 20.6 mmol) and the resulting solution was stirred at rt for 18 h. The reaction mixture was diluted with water (300 mL) and extracted repeatedly with CH_2Cl_2 . The combined organic layers were then washed with water, brine, and then dried over MgSO_4 . Removal of the solvent *in vacuo* provided α -chlorooxime **15** (5.49 g, 97%) as a white solid which was sufficiently pure for use without further purification. ^1H NMR (300 MHz, CDCl_3 , ~2:1 *E/Z* mixture of oxime isomers) δ 7.81–7.70 (m, 2H), 7.40–7.38 (d, J = 8.2 Hz, 2H), 5.53 (m, 0.33H), 5.15 (d, J = 14.2 Hz, 0.67H), 4.77 (t, J = 3.0 Hz, 0.67H), 4.30–4.27 (m, 0.33 H), 3.85–3.80 (m, 1H), 3.45 (d, J = 13.6 Hz, 0.33H), 3.23 (d, J = 14.5 Hz, 0.67H), 3.11 (td, J = 11.9, 3.0 Hz, 0.67H), 2.95 (m, 0.33H), 2.48 (m, 3H), 2.28–2.08 (m, 2H); ^{13}C NMR (75

MHz, CDCl₃) δ 150.9, 150.4, 144.7 (2C), 133.6, 133.2, 130.4, 128.2, 128.0, 66.4, 61.1, 55.9, 45.7, 44.6, 41.3, 41.0, 38.6, 33.9, 32.8, 22.0. The compound was unstable on attempted mass spectrometric analysis.

Methyl 2-(3-(Hydroxyimino)-1-tosylpiperidin-4-yl)-2-(1H-indol-2-yl)acetate (19)

—To a stirred solution of indole ester **17**¹⁰ (691 mg, 3.65 mmol) in THF (11 mL) at –78 °C was added LiHMDS (1.0 M in THF, 3.65 mL, 3.65 mmol). The resulting solution was stirred for 30 min and a solution of α-chlorooxime **15** (553 mg, 1.83 mmol, in 7 mL of THF) was added dropwise over 8 min. After stirring the mixture for an additional 90 min at –78 °C the reaction was quenched with aqueous NH₄Cl. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over MgSO₄ and concentrated *in vacuo* to give a residue which was purified by flash chromatography on silica gel (gradient 15–50% EtOAc/hexanes) to afford Michael adduct **19** (491 mg, 59%) as a ~3:1 mixture of diastereomers (foam) and recovered starting indole **17** (454 mg, 66%). ¹H NMR (400 MHz, CDCl₃, ~3:1 mixture of isomers) δ 8.83 (s, 1H), 8.60 (br s, 1H), 7.69-7.09 (m, 8H), 6.36 (s, 0.75 H), 6.29 (s, 0.25 H), 4.89 (d, *J* = 14.8 Hz, 0.75 H), 4.56 (d, *J* = 15.0 Hz, 0.25H), 3.98 (d, *J* = 10.3 Hz, 1 H), 3.69 (s, 0.75 H), 3.67 (s, 2.25 H), 3.60-3.46 (m, 1H), 3.20 (d, *J* = 14.4 Hz, 1H), 3.02 (td, *J* = 10.7, 4.7 Hz, 1H), 2.76-2.72 (m, 1H), 2.45-2.41 (m, 4H), 1.63-1.59 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 173.4, 153.4, 144.5, 136.7, 133.2, 132.5, 130.4, 130.3, 128.4, 128.1, 122.6, 120.7, 120.5, 111.5, 46.6, 46.5, 45.3, 42.3, 42.1, 28.1, 22.0; LRMS-ES+ *m/z* (relative intensity) 456; HRMS (*m/z*): [M+H]⁺ calcd for C₂₃H₂₆N₃O₅S 456.1593, found 456.1571.

2-(Trimethylsilyl)ethyl-2-(2-(2-methoxy-2-oxoethyl)-1H-indol-3-yl)-2-oxoacetate (22)

—To a stirred solution of indole ester **17**¹⁰ (3.50 g, 18.5 mmol) in Et₂O (310 mL) at 0 °C was added oxalyl chloride (1.84 mL, 21.4 mmol). The resultant orange solution was stirred at rt for 16 h and then cooled to 0 °C. 2-Trimethylsilylethanol (8.0 mL, 56 mmol) was added, followed by slow addition of triethylamine (6.4 mL, 47 mmol) over 5 min. The resulting red suspension was stirred at 0 °C for 1.5 h and then diluted with water. The organic layer was separated and the aqueous layer extracted with Et₂O. The combined organic layers were washed with water and brine, dried over MgSO₄, and concentrated *in vacuo* to give a viscous red oil which was purified by flash chromatography on silica gel (gradient 20–40% EtOAc/hexanes) to yield indole-3-oxoacetate **22** (purple solid, 6.03 g, 90%). ¹H NMR (300 MHz, CDCl₃) 10.50 (s, 1H), 7.83-7.78 (m, 1H), 7.45-7.40 (m, 1H), 7.30-7.23 (m, 2H), 4.56-4.50 (m, 2H), 4.32 (s, 2H), 3.82 (s, 3H), 1.22-1.16 (m, 2H), 0.10 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) 182.5; 171.3, 166.5, 142.3, 135.4, 126.1, 124.0, 123.4, 120.3, 112.3, 110.5, 65.2, 53.1, 32.9, 17.8, –1.1; LRMS-ES+ *m/z* (relative intensity) 362 (MH⁺, 80); HRMS (*m/z*): [M+H]⁺ calcd for C₁₈H₂₄NO₅Si 362.1424, found 362.1416.

Methyl 2-(3-(Hydroxyimino)-1-tosylpiperidin-4-yl)-2-(3-(2-oxo-2-(2-(trimethylsilyl)ethoxy)acetyl)-1H-indol-2-yl)acetate (24a/b)

—To a –78 °C solution of indole **22** (8.18 g, 22.6 mmol) was added LiHMDS (47.5 mL, 47.5 mmol, 1.0 M in THF) and the resulting solution was stirred for 30 min. A solution of α-chlorooxime **15** (9.6 g, 32 mmol) in THF (69 mL) was added via cannula over 10 min. The reaction mixture was stirred at –78 °C for 2 h and then diluted with aqueous NH₄Cl. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over MgSO₄ and concentrated *in vacuo* to give a residue which was purified by flash chromatography on silica gel (gradient 20–50% EtOAc/hexanes) to yield diastereomeric Michael adducts **24a** and **24b** (orange foam, 14.01 g, 99%, ~1.2:1 by ¹H NMR) which were carried on to the next step without separation. ¹H NMR (300 MHz, CDCl₃) δ 10.31 (s, 0.5H), 10.23 (s, 0.5H), 8.90 (s, 0.5H), 8.66 (s, 0.5H), 7.79-7.58 (m, 3H), 7.39-7.17 (m, 5H), 5.59 (d, *J* = 5.9 Hz, 0.5H), 5.13 (d, *J* = 8.6 Hz, 0.5H), 4.93 (d, *J* = 14.5

Hz, 0.5H), 4.60-4.50 (m, 2H), 3.69-4.47 (m, 4H), 3.37 (p, $J = 5.7$ Hz, 0.5H), 3.20 (d, $J = 14.6$ Hz, 0.5 H), 3.10 (q, $J = 7.3$ Hz, 0.5H), 2.97-2.85 (m, 1H), 2.44-2.28 (m, 3H), 2.08-2.03 (m, 0.5H), 1.78-1.76 (m, 0.5H), 1.41-1.31 (m, 0.5H), 0.11-0.07 (m, 9H); ^{13}C NMR (75 MHz, CDCl_3) δ 183.6, 183.0, 172.6, 171.9, 166.5, 166.5, 152.8, 152.7, 144.61, 144.57, 143.5, 143.4, 135.83, 135.80, 130.4, 130.3, 128.06, 127.96, 125.8, 125.6, 124.4, 124.2, 123.4, 123.2, 120.0, 119.6, 112.9, 112.7, 111.2, 111.1, 65.33, 65.29, 53.3, 53.2, 45.4, 44.9, 44.2, 43.4, 42.9, 42.7, 42.3, 41.9, 27.9, 27.8, 22.0, 21.9, 17.8, 14.6, 14.2, -1.1; LRMS-ES+ m/z (relative intensity) 666 ($\text{M}+\text{K}^+$, 100); HRMS (m/z): $[\text{M}+\text{NH}_4]^+$ calcd for $\text{C}_{30}\text{H}_{41}\text{N}_4\text{O}_8\text{SSi}$ 645.2414, found 645.2445.

For characterization of the isomers, a small amount of the mixture was separated by flash chromatography on silica gel (gradient 2–10% $\text{Et}_2\text{O}/\text{CH}_2\text{Cl}_2$) to afford **24a** (less polar) as an orange foamy solid. ^1H NMR (400 MHz, CDCl_3) δ 9.96 (s, 1H, NH), 7.91 (s, 1H), 7.62 (d, $J = 8.0$ Hz, 3H), 7.38 (m, 1H), 7.26-7.19 (m, 4H), 5.52 (d, $J = 6.1.1$ Hz, 1H), 4.87 (d, $J = 14.6$ Hz, 1H), 4.50 (t, $J = 8.2$ Hz, 2H), 3.64 (s, 3H), 3.30 (m, 1H), 3.18 (d, $J = 14.7$ Hz, 1H), 2.82 (m, 1H), 2.43 (m, 1H), 2.34 (s, 3H), 2.02 (dd, $J = 3.4, 12.8$ Hz, 1H), 1.38 (m, 1H), 1.15 (t, $J = 8.7$ Hz, 2H), 0.07 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3) δ 183.2, 171.5, 166.0, 153.1, 144.2, 135.3, 133.0, 130.0, 127.7, 125.3, 123.9, 122.9, 119.6, 112.4, 111.1, 64.9, 52.9, 45.0, 43.0, 42.6, 42.0, 27.5, 21.6, 17.5, -1.4. **24b** (more polar, brown foamy solid), ^1H NMR (300 MHz, CDCl_3) δ 9.84 (s, 1H), 7.97 (s, 1H), 7.61-7.57 (m, 3H), 7.29-7.23 (m, 2H), 1.17-7.14 (m, 3H), 5.00 (d, $J = 8.4$ Hz, 1H), 4.50-4.39 (m, 3H), 3.67 (s, 3H), 3.45-3.38 (m, 3H), 2.94 (m, 1H), 2.82 (m, 1H), 2.34 (s, 3H), 1.69 (m, 2H), 1.09-1.05 (m, 2H), 0.00 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3) δ 182.9, 172.8, 166.2, 152.9, 144.5, 143.5, 135.7, 133.3, 130.3, 128.1, 125.8, 124.4, 123.4, 120.2, 122.6, 111.2, 65.3, 53.3, 45.0, 44.1, 43.3, 42.0, 28.0, 22.0, 17.8, -1.1.

Methyl 2-(3-(((*tert*-Butyldimethylsilyl)oxy)imino)-1-tosylpiperidin-4-yl)-2-(3-(2-oxo-2-(2-(trimethylsilyl)ethoxy)acetyl)-1H-indol-2-yl)acetate (25)—To a solution of ester oxime mixture **24a/b** (5.66 g, 9.01 mmol) and imidazole (2.47 g, 36.3 mmol) in CH_2Cl_2 (240 mL) was added TBSCl (4.10 g, 27.2 mmol). The resulting suspension was stirred for 12 h at rt and then diluted with 1 M HCl. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 . The combined organic layers were dried over MgSO_4 and concentrated *in vacuo* to give a residue which was purified by flash chromatography on silica gel (30% $\text{EtOAc}/\text{hexanes}$) yielding *O*-TBS-oximes **25** (5.98 g, 89%) as an orange solid. ^1H NMR (300 MHz, CDCl_3) δ 9.91 (s, 0.5H), 9.79 (s, 0.5H), 7.77-7.61 (m, 3H), 7.41-7.21 (m, 5H) 5.56 (d, $J = 5.7$ Hz, 0.5H), 5.06-4.97 (m, 1H), 4.84 (d, $J = 15.0$ Hz, 0.5H), 4.54-4.45 (m, 2H), 3.69-3.60 (m, 4H), 3.41 (dt, $J = 7.1, 12.6$ Hz, 0.5H), 3.30 (d, $J = 15.0$ Hz, 0.5H), 3.18 (d, $J = 14.9$ Hz, 0.5H), 3.00-2.92 (m, 1H), 2.85-2.70 (m, 0.5H), 2.42 (s, 1.5H), 2.32 (s, 1.5H), 2.06-1.98 (m, 0.5H), 1.85-1.70 (m, 0.5H), 1.65-1.55 (m, 0.5H), 1.40-1.35 (m, 1H), 1.20-1.13 (m, 2H), 0.99 (m, 9H), 0.31-0.20 (m, 6H), 0.10-0.07 (m, 9H); ^{13}C NMR (75 MHz, CDCl_3) δ 183.4, 182.8, 172.6, 171.0, 166.3, 166.1, 157.9, 156.8, 144.40, 144.37, 143.6, 143.4, 135.5, 135.4, 133.9, 133.6, 130.20, 130.15, 128.0, 127.9, 126.0, 125.7, 124.4, 124.2, 123.5, 123.2, 120.6, 120.0, 112.4, 112.2, 111.3, 65.1, 53.2, 53.0, 45.2, 44.1, 43.5, 43.3, 42.9, 28.1, 27.7, 26.34, 26.28, 21.93, 21.85, 18.3, 18.2, 17.79, 17.76, -1.1, -4.2, -4.6, -4.8; LRMS-ES+ m/z (relative intensity) 780 ($\text{M}+\text{K}^+$, 100); HRMS (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{36}\text{H}_{52}\text{N}_3\text{O}_8\text{SSi}_2$ 742.3014, found 742.3005.

Methyl 2-(3-(((*tert*-Butyldimethylsilyl)oxy)imino)-1-tosylpiperidin-4-yl)-2-(3-(1-hydroxy-2-oxo-2-(2-(trimethylsilyl)ethoxy)ethyl)-1H-indol-2-yl)acetates (26 and 28)—To a stirred solution of α -ketoesters **25** (21.5 g, 29 mmol) in MeOH (55 mL) and THF (425 mL) cooled to 0 °C was added NaBH_4 (1.32 g, 34.7 mmol). The resulting solution was stirred for 1 h at 0 °C, and then diluted with aqueous NH_4Cl . The organic layer was

separated and the aqueous layer was extracted with CH_2Cl_2 . The combined organic layers were washed with water and brine and then dried over MgSO_4 . Removal of the solvent *in vacuo* provided the indole-3-hydroxyacetate products as a white powder.

Without further purification, this mixture was dissolved in a 1:1 (v/v) mixture of Ac_2O :pyridine (292 mL) and the solution was stirred at rt for 12 h. After removing the volatiles *in vacuo*, **26** and **28** were separated by flash chromatography on silica gel (gradient 15–40% EtOAc/hexanes). **26** (more polar isomer, orange foamy solid, 12.60 g, 55%, ~3:1 mixture of acetoxy diastereomers): ^1H NMR (400 MHz, CDCl_3) δ 9.07 (s, 0.75H), 9.03 (s, 0.25H), 7.75–7.71 (m, 1H), 7.64 (d, $J = 8.2$ Hz, 2H), 7.32–7.13 (m, 5H), 6.21 (s, 0.25H), 6.18 (s, 0.75H), 4.97–4.88 (m, 1H), 4.52 (d, $J = 5.9$ Hz, 0.25H), 4.48 (d, $J = 5.5$ Hz, 0.75H), 4.28–4.20 (m, 1H), 4.09–4.02 (m, 1H), 3.67–3.55 (m, 4H), 3.41–3.31 (m, 2H), 3.00–2.93 (m, 1H), 2.39–2.36 (m, 3H), 2.14 (s, 3H), 1.95–1.70 (m, 3H), 1.60–1.40 (m, 2H), 0.98 (s, 9H), 0.29–0.18 (m, 6H), 0.00–0.02 (m, 9H); ^{13}C NMR (90 MHz, CDCl_3) δ 171.0, 170.8, 170.6, 170.5, 169.1, 157.3, 144.0, 135.3, 135.2, 133.7, 133.5, 132.2, 131.7, 129.8, 127.6, 126.2, 126.1, 122.7, 120.3, 119.3, 111.2, 108.0, 107.8, 67.7, 64.2, 53.4, 52.5, 44.8, 43.2, 42.9, 42.7, 42.4, 42.1, 28.0, 26.0, 25.9, 21.5, 20.9, 20.7, 17.9, 17.3, –1.56, –1.59, –4.8, –5.1. **28** (less polar isomer, orange foamy solid, 8.29 g, 36%, ~2:1 mixture of acetoxy diastereomers): ^1H NMR (300 MHz, CDCl_3) δ 8.73–8.71 (m, 1H), 7.76 (d, $J = 7.6$ Hz, 1H), 7.66 (d, $J = 8.2$ Hz, 1H), 7.35–7.14 (m, 5H), 6.24–6.22 (m, 1H), 5.02 (t, $J = 7.1$ Hz, 1H), 4.34–4.07 (m, 3H), 3.66–3.53 (m, 4H), 3.15–3.07 (m, 2H), 2.72 (td, $J = 11.3, 3.2$ Hz, 1H), 2.45 (s, 3H), 2.20–2.18 (m, 3H), 1.58–1.39 (m, 2H), 1.00–0.89 (m, 12H), 0.26 (s, 3H), 0.20 (s, 3H), 0.02–0.04 (m, 9H); ^{13}C NMR (75 MHz, CDCl_3) δ 173.1, 173.0, 170.9, 170.8, 169.3, 169.2, 156.7, 144.4, 136.1, 136.0, 133.8, 133.6, 132.4, 132.2, 130.2, 128.1, 126.7, 123.5, 123.4, 121.1, 120.2, 111.5, 108.54, 108.50, 68.4, 68.0, 64.7, 64.5, 53.9, 53.0, 52.9, 45.4, 44.4, 44.1, 42.8, 42.6, 42.5, 28.5, 28.0, 26.4, 22.0, 21.2, 21.1, 18.4, 17.7, 17.6, –1.2, –4.75, –4.89, –4.92; LRMS-ES+ (mixture of diastereomers **26/28**) m/z (relative intensity) 824 ($\text{M}+\text{K}^+$, 25); HRMS (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{38}\text{H}_{56}\text{N}_3\text{O}_9\text{SSi}_2$ 786.3276, found 786.3286.

Methyl 2-(3-(((*tert*-Butyldimethylsilyl)oxy)imino)-1-tosylpiperidin-4-yl)-2-(3-(2-oxo-2-(2-(trimethylsilyl)ethoxy)ethyl)-1H-indol-2-yl)acetate (29**)**—To a solution of acetates **26** (2.94 g, 3.75 mmol) in *t*-BuOH (80 mL) was added 10% Pd/C (1.20 g). The resulting mixture was evacuated and backfilled with H_2 from a balloon and TEA (10.0 mL) was then added. The mixture was warmed to 30 °C and stirred for 4 days until all the starting material was consumed as judged by TLC. The reaction mixture was then diluted with EtOAc, filtered through a pad of Celite and concentrated *in vacuo* to give a residue which was purified by flash chromatography on silica gel (gradient 10–25% EtOAc/hexanes) to afford indole **29** (2.47 g, 91%) as an off-white foam. ^1H NMR (360 MHz, CDCl_3) δ 8.74 (br s, 1H), 7.62 (d, $J = 7.2$ Hz, 2H), 7.57 (d, $J = 7.8$ Hz, 1H), 7.28–7.24 (m, 3H), 7.17 (dd, $J = 7.1, 7.5$ Hz, 1H), 7.09 (dd, $J = 7.3, 7.4$ Hz, 1H), 4.82 (d, $J = 15.1$ Hz, 1H), 4.33 (d, $J = 6.0$ Hz, 1H), 4.11–4.07 (m, 2H), 3.64 (s, 3H), 3.60 (d, $J = 4.4$ Hz, 2H), 3.58–3.55 (m, 1H), 3.36 (d, $J = 15.2$ Hz, 1H), 3.30–3.25 (m, 1H), 2.90 (td, $J = 4.0, 11.9$ Hz, 1H), 2.36 (s, 3H), 1.89–1.84 (m, 1H), 1.59–1.54 (m, 1H), 0.94 (s, 9H), 0.21 (s, 3H), 0.15 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 171.7, 171.6, 157.2, 144.0, 135.4, 133.7, 130.0, 129.9, 129.5, 128.9, 127.7 (2C), 122.3, 119.7, 118.9, 111.0, 107.6, 63.2, 52.5, 44.7, 43.0, 42.7, 42.3, 30.8, 27.6, 26.0, 21.6, 18.0, 17.4, –1.4, –4.8, –5.0; LRMS-ES+ m/z (relative intensity) 766 ($\text{M}+\text{K}^+$, 75); HRMS (m/z): $[\text{M}+\text{NH}_4]^+$ calcd for $\text{C}_{36}\text{H}_{57}\text{N}_4\text{O}_7\text{SSi}_2$ 745.3487, found 745.3478.

Synthesis of Indole Diester **30**

Following a similar procedure described for preparation of **29**, acetates **28** (3.95 g, 5.03 mmol) were reduced by catalytic hydrogenation to afford indole diester **30** as an off white foamy solid (3.16 g, 86%). Slow evaporation of this compound from EtOAc gave crystals

suitable for X-ray crystallography (see Supporting Information).³⁶ Mp 128–130 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.19 (s, 1H), 7.65 (d, *J* = 8.5 Hz, 2H), 7.57 (d, *J* = 7.7 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.26 (d, *J* = 7.6 Hz, 1H), 7.17 (dd, *J* = 7.0, 7.1 Hz, 1H), 7.11 (dd, *J* = 7.1, 7.2 Hz, 1H), 5.03 (d, *J* = 14.4 Hz, 1H), 4.17–4.13 (m, 2H), 4.06 (d, *J* = 10.7 Hz, 1H), 3.64 (app. s, 2H), 3.62 (s, 3H), 3.57 (m, 1H), 3.06–3.00 (m, 2H), 2.66 (td, *J* = 3.8, 11.5 Hz, 1H), 2.44 (s, 3H), 1.46 (m, 1H), 1.39 (m, 1H), 0.97 (s, 9H), 0.23 (s, 3H), 0.16 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 173.0, 171.4, 156.5, 144.0, 135.7, 133.4, 129.8, 128.0 (2C), 127.8, 122.7, 120.1, 119.2, 111.0, 108.3, 63.3, 52.5, 45.2, 43.8, 42.5, 42.0, 30.6, 27.8, 26.1, 25.9, 21.7, 18.1, 17.5, –1.4, –5.1, –5.2; HRMS (*m/z*): [M+H]⁺ calcd for C₃₆H₅₄N₃O₇SSi₂ 728.3221, found 728.3224.

Epimerization of Ester 29 to Ester 30

To a solution of diester **29** (4.45 g, 6.12 mmol) in THF (81 mL) cooled to –78 °C was added dropwise KHMDS solution (0.5 M in toluene, 13.5 mL, 6.73 mmol, 1.1 equiv.). After the addition was complete, the cooling bath was removed and the reaction mixture was stirred at rt for 30 min. To the resulting olive green solution was added glacial acetic acid (0.40 mL) followed by aqueous NH₄Cl. The mixture was extracted with EtOAc. The organic phase washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by flash chromatography on silica gel (30 % EtOAc/hexanes) to afford diester **30** as a light yellow foam (3.23 g, 73%), which was identical to material prepared from hydrogenation of **28**.

Benzyl 2-(1-(3-(((*tert*-Butyldimethylsilyl)oxy)imino)-1-tosylpiperidin-4-yl)-2-methoxy-2-oxoethyl)-3-(2-oxo-2-(2-(trimethylsilyl)ethoxy)ethyl)-1H-indole-1-carboxylate (31)—A stirred solution of indole **30** (1.05 g, 1.45 mmol) in acetonitrile (40 mL) was heated to 90 °C. Dibenzyl dicarbonate (2.07 g, 7.24 mmol) was added, followed immediately by DMAP (0.53 g, 4.33 mmol). After gas evolution stopped (~1 min), the reaction mixture was heated at 90 °C for another 2 min, and cooled to rt. The solvent was removed *in vacuo* to give a pale brown residue, which was purified by flash chromatography on silica gel (gradient 5–20% EtOAc/hexanes) to afford **31** as a white foam (1.23 g, 99%, ~2:1 Cbz rotamers). ¹H NMR (400 MHz, CDCl₃) δ 8.11 (d, *J* = 7.6 Hz, 0.7H), 8.00 (m, 0.3H), 7.64 (d, *J* = 6.9 Hz, 2H), 7.57 (d, *J* = 6.4 Hz, 0.7H), 7.46–7.26 (m, 9H), 5.68 (d, *J* = 10.1 Hz, 0.3H), 5.17 (d, *J* = 11.7 Hz, 0.7H), 5.52–5.46 (m, 0.7H), 5.29 (d, *J* = 13.1 Hz, 0.7H), 5.16 (d, *J* = 9.3 Hz, 1.7H), 4.14–4.10 (m, 2H), 3.90 (d, *J* = 15.90 Hz, 0.3H), 3.65–3.53 (m, 2.7H), 3.48 (s, 3H), 3.11 (m, 1H), 2.90 (d, *J* = 13.2 Hz, 0.3H), 2.68 (d, *J* = 13.2 Hz, 0.7H), 2.60 (m, 0.3H), 2.49–2.44 (m, 3H), 2.17 (m, 0.7H), 1.40 (m, 0.3H), 1.12 (m, 1.7H), 0.98 (m, 9H), 0.22 (s, 2H), 0.19–0.17 (m, 4H), 0.02 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 171.7, 171.1, 170.8, 170.1, 155.8, 155.6, 151.8, 151.3, 143.8, 135.9, 135.6, 134.8, 133.4, 132.5, 132.2, 129.8, 129.4, 129.2, 129.0, 128.8, 127.9, 125.3, 123.5, 119.3, 118.9, 118.6, 117.2, 115.8, 69.3, 68.6, 63.6, 63.4, 52.1, 45.7, 42.8, 42.4, 42.0, 41.3, 40.7, 30.9, 30.2, 28.6, 27.5, 26.2, 25.6, 21.7, 18.3, 17.5, –1.5, –5.1; LRMS-ES+ *m/z* (relative intensity) 862 (MH⁺, 90); HRMS (*m/z*): [M+H]⁺ calcd for C₄₄H₆₀N₃O₉SSi₂ 862.3589, found 862.3585.

Benzyl 2-(1-(3-(Hydroxyimino)-1-tosylpiperidin-4-yl)-2-methoxy-2-oxoethyl)-3-(2-oxo-2-(2-(trimethylsilyl)ethoxy)ethyl)-1H-indole-1-carboxylate (32)—To a stirred solution of *O*-TBS-oxime **31** (12.9 g, 14.9 mmol) in THF (600 mL) was added AcOH (6.6 mL) followed by a solution of TBAF in THF (1 M, 22.1 mL, 22.1 mmol). The resulting solution was stirred at rt overnight and then diluted with aqueous NH₄Cl. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over MgSO₄ and concentrated *in vacuo* to give a residue which was purified by flash column chromatography on silica gel (30% EtOAc/hexanes) to yield free oxime **32** as a white foam (11.1 g, 100%, ~2:1 Cbz rotamers). ¹H NMR (400 MHz, CDCl₃) δ 8.10 (m, 0.7H), 8.0–7.8 (m, 1.3H), 7.65 (d, *J* = 7.1 Hz, 2H), 7.54 (m, 0.7H), 7.45 (m,

3.5H), 7.35-7.26 (m, 6H), 5.68 (m, 0.3H), 5.57 (d, $J = 11.5$ Hz, 0.7H), 5.47 (s, 0.7H), 5.18 (m, 1.4H), 5.07 (m, 1H), 4.13 (m, 2H), 3.87 (m, 0.3H), 3.65-3.59 (m, 3H), 3.48 (s, 3H), 3.09 (m, 1H), 2.91 (0.3H), 2.68 (d, $J = 13.1$ Hz, 0.7H), 2.60 (m, 0.3H), 2.48-2.44 (m, 3H), 2.19 (m, 0.7H), 1.64 (m, 0.4H), 1.40 (m, 0.3H), 1.17 (m, 1.6H), 0.94 (t, $J = 8.8$ Hz, 2H), 0.01 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3) δ 172.0, 171.5, 170.8, 170.5, 152.9, 151.8, 151.4, 143.9, 135.8, 135.5, 134.7, 133.0, 132.3, 132.0, 129.8, 129.4, 129.2, 129.1, 129.0, 128.8, 128.6, 127.9, 127.8, 127.1, 125.3, 124.9, 123.5, 123.2, 119.3, 118.6, 117.2, 116.1, 115.9, 69.5, 68.7, 65.4, 64.5, 63.8, 63.4, 52.6, 52.3, 45.7, 42.4, 41.8, 41.0, 40.7, 40.5, 31.0, 30.7, 30.3, 28.5, 27.6, 21.6, 21.1, 19.2, 17.3, 13.8, -1.5; LRMS-ES+ m/z (relative intensity) 748 (MH^+ , 75); HRMS (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{38}\text{H}_{46}\text{N}_3\text{O}_9\text{SSi}$ 748.2724, found 748.2718.

Benzyl 2-(2-Methoxy-2-oxo-1-(3-oxo-1-tosylpiperidin-4-yl)ethyl)-3-(2-oxo-2-(2-(trimethylsilyl)ethoxy)ethyl)-1H-indole-1-carboxylate (33)—Oxime **32** (11.14 g, 14.9 mmol) was added to a mixture of levulinic acid and 1 M HCl (334 g, 9:1 v/v) and the mixture was stirred at 30 °C for 4.5 h. The reaction mixture was diluted with water (1 L), and was extracted with dichloromethane. The organic layer was washed with aqueous NaHCO_3 , water and brine, dried over Na_2SO_4 , and concentrated. The residue was purified by flash column chromatography on silica gel (gradient, 20–30% EtOAc/hexanes) to afford ketone **33** as a slightly pink foam (10.04 g, 92%). ^1H NMR (400 MHz, CDCl_3) δ 8.06 (d, $J = 7.6$ Hz, 1H), 7.62 (d, $J = 8.1$ Hz, 2H), 7.55-7.26 (m, 10H), 5.54 (d, $J = 11.8$ Hz, 1H), 5.20 (d, $J = 11.6$ Hz, 1H), 4.91 (d, $J = 6.6$ Hz, 1H), 4.18-4.07 (m, 2H), 4.21 (d, $J = 13.6$ Hz, 1H), 3.62 (s, 2H), 3.48 (s, 3H), 3.32 (q, $J = 9.3$ Hz, 1H), 3.20 (d, $J = 13.6$ Hz, 1H), 2.48 (s, 3H), 2.46 (m, 1H), 1.46-1.42 (m, 2H), 0.95 (t, $J = 8.6$ Hz, 2H), 0.02 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3) δ 201.6, 171.2, 170.2, 151.5, 144.3, 135.4, 134.7, 132.2, 131.7, 130.0, 129.3, 129.1, 128.9, 128.0, 125.4, 123.7, 119.3, 117.4, 115.9, 68.9, 63.8, 56.1, 52.4, 48.8, 45.3, 40.0, 30.8, 27.5, 21.7, 17.4, -1.5; LRMS-ES+ m/z (relative intensity) 750 ($\text{M}+\text{NH}_4^+$, 75); HRMS (m/z): $[\text{M}+\text{NH}_4]^+$ calcd for $\text{C}_{38}\text{H}_{48}\text{N}_3\text{O}_9\text{SSi}$ 750.2881, found 750.2878.

2-(1-((Benzyloxy)carbonyl)-2-(2-methoxy-2-oxo-1-(3-oxo-1-tosylpiperidin-4-yl)ethyl)-1H-indol-3-yl)acetic Acid (34)—To a stirred solution of TMSE-ester **33** (3.95 g, 5.38 mmol) in CH_2Cl_2 (138 mL) was added TFA (34 mL). The resulting solution was stirred at rt for 9 h and the solvent was removed *in vacuo* to give a residue which was purified by flash column chromatography on silica gel (40% EtOAc/hexanes + 1% AcOH) to give keto acid **34** as an off-white foam (3.39 g, 100%). ^1H NMR (300 MHz, CDCl_3) δ 8.07 (d, $J = 6.9$ Hz, 1H), 7.62 (d, $J = 8.0$ Hz, 2H), 7.50-7.16 (m, 10H), 5.54 (d, $J = 11.8$ Hz, 1H), 5.21 (d, $J = 11.1$ Hz, 1H), 4.87 (d, $J = 6.2$ Hz, 1H), 4.00 (13.4 Hz, 1H), 3.68 (s, 2H), 3.46 (s, 3H), 3.36-3.29 (m, 1H), 3.18 (d, $J = 13.9$ Hz, 1H), 2.48 (s, 3H), 1.41 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 201.6, 175.3, 171.1, 151.4, 144.3, 137.9, 135.4, 134.5, 132.2, 131.9, 129.9, 129.3, 129.1, 128.8, 128.2, 127.9, 125.5, 125.3, 123.7, 119.1, 116.6, 115.9, 68.9, 56.0, 52.4, 48.7, 45.2, 40.0, 30.0, 27.5, 21.6; LRMS-ES+ m/z (relative intensity) 633 (MH^+ , 100); HRMS (m/z): $[\text{M}+\text{NH}_4]^+$ calcd for $\text{C}_{33}\text{H}_{36}\text{N}_3\text{O}_9\text{S}$ 650.2172, found 650.2142.

8-Benzyl 7-Methyl 1-Oxo-4-tosyl-3,4,5,6,6a,7-hexahydro-1H-oxeto[2,3-c]pyrido[4,3-b]carbazole-7,8(12cH)-dicarboxylate (35) and trans-2-Azadecaline **37**—To a stirred suspension of 4-pyrrolidinopyridine (1.09 g, 7.35 mmol), 2-bromo-*N*-propylpyridinium triflate (2.57 g, 7.35 mmol) and DIPEA (1.7 mL, 9.8 mmol) in CH_2Cl_2 (79 mL) at rt was added a solution of ketoacid **34** (3.00 g, 4.90 mmol) and glacial acetic acid (0.35 mL, 6.1 mmol) in CH_2Cl_2 over 1 h via a syringe pump. The resulting orange solution was stirred for another 3 h at rt. Solvent was then removed *in vacuo* to give a residue which was purified by flash chromatography on silica gel (gradient 30–40% EtOAc/hexanes) affording an inseparable mixture of β -lactones **35** and **37** as an off white solid (2.71 g, 93%). FTIR (film) 1835 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3 , ~97:3 mixture of diastereomers

determined by ^1H NMR, only the major diastereomer peaks are reported) δ 8.02 (d, $J = 7.2$ Hz, 1H), 7.66 (d, $J = 7.8$ Hz, 2H), 7.60 (d, $J = 7.4$ Hz, 1H), 7.45 (m, 2H), 7.42-7.31 (m, 7H), 5.46 (d, $J = 10.8$ Hz, 1H), 5.32 (d, $J = 12.0$ Hz, 1H), 4.76 (s, 1H), 4.41 (d, $J = 5.7$ Hz, 1H), 3.88 (d, $J = 12.0$ Hz, 1H), 3.50 (m, 1H), 3.50 (s, 3H), 2.95 (d, $J = 11.8$ Hz, 1H), 2.55 (dd, $J = 7.3, 14.5$ Hz, 1H), 1.60 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 170.7, 165.4, 151.8, 144.5, 136.6, 134.5, 132.3, 130.1, 129.9, 129.0, 128.9, 128.8, 127.8, 126.9, 125.8, 123.8, 118.8, 115.6, 110.6, 75.6, 69.4, 53.0, 52.2, 50.9, 44.8, 43.3, 38.5, 25.1, 21.7; LRMS-ES+ m/z (relative intensity) 615 (MH+, 100); HRMS (m/z): $[\text{M}+\text{NH}_4]^+$ calcd for $\text{C}_{33}\text{H}_{34}\text{N}_3\text{O}_8\text{S}$ 632.2067, found 632.2053.

Methyl 1-Oxo-4-tosyl-3,4,5,6,6a,7,8,12c-octahydro-1H-oxeto[2,3-c]pyrido[4,3-b]carbazole-7-carboxylate (36) and trans-2-Azadecalin 38—10% Pd/C (0.54 g) was suspended in a solution of the mixture of *N*-Cbz β -lactones **35** and **37** (2.71 g, 4.41 mmol) in EtOAc (280 mL). One drop of glacial acetic acid was added to the mixture, followed by three evacuation-backfill cycles with hydrogen gas from a balloon. The reaction mixture was stirred under a balloon of H_2 for 1.5 h at rt. The mixture was filtered through a pad of Celite, concentrated and the residue was purified by flash chromatography on silica gel (gradient 2–5% $\text{Et}_2\text{O}/\text{CH}_2\text{Cl}_2$) to afford β -lactone **36** (1.99 g, 94%) as a white solid: ^1H NMR (400 MHz, CDCl_3) δ 9.50 (br s, 1H), 7.66 (d, $J = 8.0$ Hz, 2H), 7.62 (d, $J = 7.6$ Hz, 1H), 7.42 (d, $J = 7.8$ Hz, 1H), 7.36 (d, $J = 8.0$ Hz, 2H), 7.25-7.18 (m, 2H), 4.86 (s, 1H), 4.21 (d, $J = 4.5$ Hz, 1H), 4.09 (d, $J = 11.6$ Hz, 1H), 3.86 (s, 3H), 3.72 (dd, $J = 2.0, 9.6$ Hz, 1H), 2.78 (d, $J = 11.6$ Hz, 1H), 2.71 (dt, $J = 4.5, 12.6$ Hz, 1H), 2.46 (s, 3H), 2.30 (td, $J = 2.5, 12.0$ Hz, 1H), 1.58 (m, 1H), 1.40 (qd, $J = 4.5, 13.0$ Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 171.5, 166.1, 144.5, 136.1, 132.6, 130.1, 129.1, 127.9, 125.7, 122.8, 120.7, 118.3, 111.7, 101.4, 53.6, 53.0, 51.7, 45.4, 39.5, 39.1, 24.5, 21.7; HRMS (m/z): $[\text{M}+\text{NH}_4]^+$ calcd for $\text{C}_{25}\text{H}_{28}\text{N}_3\text{O}_6\text{S}$, 498.1699; found 498.1693. β -Lactone **38** (65 mg, 3%) was obtained as a white solid: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.69 (d, $J = 8.1$ Hz, 2H), 7.61 (d, $J = 7.8$ Hz, 1H), 7.45 (d, $J = 8.1$ Hz, 2H), 7.40 (d, $J = 8.0$ Hz, 1H), 7.15 (dd, $J = 7.1, 7.4$ Hz, 1H), 7.08 (dd, $J = 7.4, 7.5$ Hz, 1H), 4.84 (s, 1H), 4.03-4.00 (m, 2H), 3.51 (br s, 4H), 2.94 (dd, $J = 3.6, 12.6$ Hz, 1H), 2.88 (d, $J = 11.6$ Hz, 1H), 2.46-2.43 (m, 1H), 2.41 (s, 3H), 1.95 (br d, $J = 10.1$ Hz, 1H), 1.08 (qd, $J = 4.3, 12.9$ Hz, 1H); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$) δ 170.9, 166.9, 143.9, 136.2, 132.6, 130.0, 127.5, 125.4, 121.6, 119.3, 117.9, 111.5, 100.2, 76.8, 52.4, 52.1, 50.7, 44.8, 42.8, 38.8, 30.7, 28.7, 21.0; HRMS (m/z): $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{25}\text{H}_{25}\text{N}_2\text{O}_6\text{S}$, 481.1428; found 481.1426.

6-Benzyl 5-Methyl 11a-Hydroxy-11-(hydroxymethyl)-2-tosyl-3,4,4a,5,11,11a-hexahydro-1H-pyrido[4,3-b]carbazole-5,6(2H)-dicarboxylate (43a)—To a 0 °C solution of a mixture of β -lactones **35** and **37** (62.8 mg, 0.102 mmol) was added DIBAL-H (1.0 M in PhMe, 511 μL , 0.511 mmol). The resulting solution was stirred for 1.5 h, then poured into a stirring solution of aqueous NH_4Cl and the mixture was stirred for an additional 2 h. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over MgSO_4 and concentrated *in vacuo* to give a residue which was purified by preparative thin layer chromatography on silica gel (50% EtOAc/hexanes) to afford 1,3-diol **43a** (white foam, 41.8 mg, 66%) and the corresponding diol derived from the *trans*-2-azadecalin **37** (5.6 mg, 9%). **1,3-diol 43a**: ^1H NMR (400 MHz, CDCl_3) δ 8.17 (d, $J = 7.8$ Hz, 1H), 7.67-7.64 (m, 3H), 7.49-7.47 (m, 2H), 7.43-7.28 (m, 7H), 5.47 (d, $J = 12.0$ Hz, 1H), 5.29 (d, $J = 12.1$ Hz, 1H), 4.80-4.75 (m, 1H), 4.68 (d, $J = 4.0$ Hz, 1H), 4.50-4.45 (m, 1H), 3.77 (br s, 1H), 3.65 (s, 1H), 3.50 (s, 3H), 2.47 (s, 3H), 2.30-2.22 (m, 2H), 2.15-2.10 (m, 1H), 1.99 (br s, 1H), 1.67 (s, 1H), 1.60-1.54 (m, 1H), 1.30-1.26 (m, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 172.9, 152.0, 144.3, 137.1, 135.1, 133.3, 130.3, 130.2, 129.2, 129.1, 128.5, 128.1, 128.0, 125.2, 123.8, 119.4, 116.4, 114.0, 73.1, 69.3, 60.7, 54.3, 52.1, 46.1, 44.6, 43.6, 36.7, 24.9, 22.0; LRMS-ES+ m/z (relative

intensity) 619 (MH⁺, 100); HRMS-ES⁺ (C₃₃H₃₅N₂O₈S) calcd 619.2114 (MH⁺), found 619.2111. **Minor 1,3-diol** (white foam): ¹H NMR (400 MHz, CDCl₃) δ 8.18 (d, *J* = 7.9 Hz, 1H), 7.67-7.55 (m, 3H), 7.48-7.28 (m, 9H), 5.43 (q, *J* = 8.4 Hz, 2H), 4.65-4.53 (m, 2H), 4.33-4.30 (m, 1H), 4.10 (br s, 1H), 3.54 (s, 2H), 3.51 (s, 3H), 2.46-2.43 (m, 4H), 2.42-2.38 (m, 2H), 2.36-2.26 (m, 1H), 1.81-1.76 (m, 1H), 1.70-1.65 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 173.6, 151.9, 144.3, 137.0, 135.1, 133.3, 130.3, 129.30, 129.25, 129.2, 128.3, 128.2, 128.0, 125.4, 123.9, 119.5, 116.6, 72.5, 71.1, 69.3, 61.3, 57.5, 54.2, 52.7, 45.4, 25.7, 22.0; LRMS-ES⁺ *m/z* (relative intensity) 619 (MH⁺, 100); HRMS-ES⁺ (C₃₃H₃₅N₂O₈S) calcd 619.2114 (MH⁺), found 619.2138.

6-Benzyl 5-Methyl 11a-Hydroxy-11-(hydroxymethyl)-2-tosyl-3,4,4a,5,11,11a-hexahydro-1H-pyrido[4,3-*b*]carbazole-5,6(2H)-dicarboxylate (44)—To a solution of 1,3-diol **43a** (12.0 mg, 0.019 mmol) in MeCH(OMe)₂ (1 mL) was added a catalytic amount of *p*-TsOH·H₂O (<1 mg) and the resulting mixture was placed in a preheated oil bath at 80 °C. After stirring for 30 min, the solution was concentrated *in vacuo* to give a residue which was purified by column chromatography on silica gel (30% EtOAc/hexanes) to yield the acetal **44** (pale gum, 11.6 mg, 93%). ¹H NMR (300 MHz, CDCl₃) δ 8.12 (br d, *J* = 6.1 Hz, 1H), 7.71 (d, *J* = 8.2 Hz, 2H), 7.52-7.48 (m, 3H), 7.46-7.38 (5H), 7.31-7.27 (m, 2H), 5.50 (d, *J* = 12.1 Hz, 1H), 5.34 (d, *J* = 10.3 Hz, 1H), 5.07 (q, *J* = 5.0 Hz, 1H), 4.78-4.66 (m, 3H), 4.36 (dd, *J* = 12.3, 3.0 Hz, 1H), 3.84-3.80 (m, 1H), 3.52 (s, 3H), 3.40 (br s, 1H), 2.49 (s, 3H), 2.27 (td, *J* = 12.2, 2.9 Hz, 1H), 2.19-2.06 (m, 2H), 1.70-1.55 (m, 1H), 1.31-1.23 (m, 1H), 1.20 (d, *J* = 4.9 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 172.9, 152.3, 144.5, 135.4, 133.5, 131.5, 130.4, 129.3, 129.13, 129.06, 128.3, 127.9, 124.8, 123.4, 119.5, 116.5, 116.3, 93.3, 72.5, 69.1, 65.3, 53.9, 52.1, 50.4, 46.2, 44.5, 43.3, 29.7, 23.7, 22.0, 21.6; LRMS-ES⁺ *m/z* (relative intensity) 645 (MH⁺, 50).

Methyl 10-(Hydroxymethyl)-3-methyl-7-tosyl-3,4,6,7,8,9,9a,10,11,15c-decahydro-1H-[1,4]dioxepino[5,6-*c*]pyrido[4,3-*b*]carbazole-10-carboxylate (45)—To a stirred suspension of paraformaldehyde (4.3 mg, 0.140 mmol) and ester **44** (6.0 mg, 0.009 mmol) in DMF (0.5 mL) was added NaH (60% dispersion on mineral oil, 1.9 mg, 0.005 mmol) and the resulting mixture was stirred for 2 h at rt. The reaction mixture was diluted with brine and EtOAc. The organic layer was separated and washed with water and then brine. The organic layer was dried over MgSO₄ and concentrated *in vacuo* to give a residue which was purified by flash column chromatography on silica gel (75% EtOAc/hexanes) to give hydroxymethyl ester **45** (foam, 4.7 mg, 93%). ¹H NMR (400 MHz, CDCl₃) δ 8.91 (s, 1H), 7.70 (d, *J* = 6.1 Hz, 2H), 7.57 (d, *J* = 6.0 Hz, 1H), 7.40-7.36 (m, 3H), 7.20 (t, *J* = 5.5 Hz, 1H), 7.12 (t, *J* = 5.8 Hz, 1H), 5.03 (q, *J* = 3.7 Hz, 1H), 4.83 (d, *J* = 9.0 Hz, 1H), 4.67 (d, *J* = 8.1 Hz, 1H), 4.37 (dd, *J* = 9.1, 2.1 Hz, 1H), 3.86-3.78 (m, 2H), 3.68 (s, 3H), 3.39-3.37 (m, 1H), 2.49 (s, 3H), 2.39-2.26 (m, 2H), 2.21-2.16 (m, 2H), 1.54-1.41 (m, 2H), 1.10 (d, *J* = 3.7 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 175.9, 144.5, 137.3, 133.3, 132.8, 130.3, 128.0, 126.0, 122.3, 119.7, 119.4, 111.8, 108.2, 93.1, 73.6, 68.7, 65.8, 52.8, 50.4, 49.5, 47.7, 46.2, 30.0, 22.7, 22.0, 21.3; LRMS-ES⁺ *m/z* (relative intensity) 541 (MH⁺, 30); HRMS-ES⁺ (C₂₈H₃₆N₃O₇S) calcd 558.2274 (M+NH₄⁺), found 558.2265.

6-Benzyl 5-Methyl 11-(((*tert*-Butyldimethylsilyl)oxy)methyl)-11a-hydroxy-2-tosyl-3,4,4a,5,11,11a-hexahydro-1H-pyrido[4,3-*b*]carbazole-5,6(2H)-dicarboxylate (47)—To a solution of 1,3-diol **43** (39.7 mg, 0.0642 mmol) and 2,6-lutidine (75 μL, 0.64 mmol) in CH₂Cl₂ (3 mL) at 0 °C was added TBSOTf (61 μL, 0.32 mmol). The resulting mixture was stirred for 1 h and then washed with 1 M HCl. The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried over MgSO₄ and concentrated *in vacuo* to give a residue which was purified by flash chromatography on silica gel (30% EtOAc/hexanes) to afford *O*-TBS-ether **47** (white

foam, 45 mg, 96%). ^1H NMR (300 MHz, CDCl_3) δ 8.14 (d, $J = 9.2$ Hz, 1H), 7.70-7.67 (m, 2H), 7.59-7.56 (m, 1H), 7.48-7.34 (m, 7H), 7.30-7.25 (m, 2H), 5.50 (d, $J = 7.8$ Hz, 1H), 5.29 (d, $J = 12.2$ Hz, 1H), 4.73-4.69 (m, 2H), 4.51 (dd, $J = 11.2, 1.7$ Hz, 1H), 4.15 (d, $J = 10.2$ Hz, 1H), 3.77 (br d, $J = 11.6$ Hz, 1H), 3.66-3.64 (m, 1H), 3.50 (s, 3H), 2.47 (s, 3H), 2.22-2.17 (m, 2H), 2.10-2.03 (m, 1H), 1.63-1.53 (m, 2H), 0.60 (s, 9H), 0.04-0.03 (m, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 173.1, 152.0, 144.3, 135.4, 130.2, 129.1, 129.0, 128.9, 128.6, 128.0, 124.7, 123.1, 119.9, 116.1, 115.6, 72.8, 69.0, 61.5, 54.7, 52.0, 46.2, 45.1, 43.5, 36.1, 30.1, 26.1, 25.7, 24.7, 22.0, 18.0, 1.4, -5.2, -5.7; LRMS-ES+ m/z (relative intensity) 733 (MH^+ , 100); HRMS-ES+ ($\text{C}_{39}\text{H}_{49}\text{N}_2\text{O}_8\text{SSi}$) calcd 733.2979 (MH^+), found 733.2961.

Methyl 11-(((*tert*-Butyldimethylsilyloxy)methyl)-11a-(((chloromethyl)dimethylsilyloxy)-2-tosyl-2,3,4,4a,5,6,11,11a-octahydro-1H-pyrido[4,3-b]carbazole-5-carboxylate (49)—To a solution of *N*-Cbz-indole **47** (45.0 mg, 0.061 mmol) in MeOH (1.5 mL) and EtOAc (1.5 mL) under an argon atmosphere was added 10% Pd/C (6.5 mg). The resulting mixture was evacuated and backfilled three times with H_2 from a balloon and the resulting suspension was stirred for 2.5 h. The reaction mixture was then filtered through a pad of Celite with EtOAc and the filtrate was concentrated *in vacuo* to give NH indole **48** (colorless gum), which was used in the next step without further purification. ^1H NMR (400 MHz, CDCl_3) δ 9.14 (s, 1H), 7.69 (d, $J = 8.2$ Hz, 2H), 7.56 (d, $J = 7.8$ Hz, 1H), 7.40-7.33 (m, 3H), 7.18 (t, $J = 6.2$ Hz, 1H), 7.13 (t, $J = 8.1$ Hz, 1H), 5.70 (s, 1H), 4.64-4.52 (m, 3H), 4.19 (dd, $J = 11.4, 1.7$ Hz, 1H), 3.80 (s, 3H), 3.77-3.68 (m, 1H), 3.69-3.67 (m, 1H), 2.48 (s, 3H), 2.31-2.18 (m, 3H), 1.54-1.41 (m, 2H), 0.67 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H); LRMS-ES+ m/z (relative intensity) 599 (MH^+ , 75); HRMS-ES+ ($\text{C}_{31}\text{H}_{43}\text{N}_2\text{O}_6\text{SSi}$) calcd 599.2611 (MH^+), found 599.2585.

To a solution of crude alcohol **48** and 2,6-lutidine (270 μL , 1.23 mmol) in CH_2Cl_2 (2.5 mL) was added chloromethyl(dimethyl)silyl triflate (289 μL , 2.47 mmol). The resulting mixture was stirred for 1.5 h at rt and then washed with 1 M HCl. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 . The combined organic layers were dried over MgSO_4 and concentrated *in vacuo* to afford a residue, which was purified by flash chromatography on silica gel (20% EtOAc/hexanes) to give chloromethyl(dimethyl)silyl ether **49** (colorless gum, 32.9 mg, 76% from **47**). ^1H NMR (400 MHz, CDCl_3) δ 9.16 (s, 1H), 7.67-7.62 (m, 3H), 7.40-7.33 (m, 3H), 7.20-7.12 (m, 2H), 4.73 (dd, $J = 10.1, 1.5$ Hz, 1H), 4.45-4.39 (m, 2H), 3.89 (t, $J = 10.1$ Hz, 1H), 3.82 (s, 3H), 3.78-3.70 (m, 2H), 2.79 (d, $J = 13.8$ Hz, 1H), 2.74 (d, $J = 13.8$ Hz, 1H), 2.48 (s, 3H), 2.26-2.17 (m, 3H), 1.51-1.42 (m, 1H), 1.37-1.26 (m, 1H), 1.04 (s, 9H), 0.32-0.28 (m, 12H); ^{13}C NMR (75 MHz, CDCl_3) δ 173.4, 144.1, 136.8, 133.4, 130.1, 128.7, 128.1, 127.0, 121.9, 119.81, 119.78, 111.8, 108.2, 76.2, 64.0, 60.8, 56.8, 52.9, 47.7, 46.4, 39.8, 31.5, 26.8, 24.2, 22.0, 21.5, 19.2, 14.6, 0.2, -0.1, -4.6, -5.0; LRMS-ES+ m/z (relative intensity) 705 (MH^+ , 50).

Methyl 11-(((*tert*-Butyldimethylsilyloxy)methyl)-11a-(((iodomethyl)dimethylsilyloxy)-2-tosyl-2,3,4,4a,5,6,11,11a-octahydro-1H-pyrido[4,3-b]carbazole-5-carboxylate (50)—A sealed tube was charged with chloride **49** (77.4 mg, 0.110 mmol), acetone (5 mL) and then NaI (411 mg, 2.74 mmol). The vessel was sealed and the resulting mixture was heated at reflux and stirred for 15 h. After cooling to rt, the reaction mixture was diluted with ether and the organic phase was washed with water followed by aqueous $\text{Na}_2\text{S}_2\text{O}_3$. The aqueous layers were extracted with ether and the combined organic layers were dried over MgSO_4 and concentrated *in vacuo* to give a residue. This material was purified by flash chromatography on silica gel (20% EtOAc/hexanes) to give iodide **50** (colorless gum, 84.4 mg, 97%). ^1H NMR (300 MHz, CDCl_3) δ 9.17 (s, 1H), 7.69-7.64 (m, 3H), 7.40-7.47 (m, 3H), 7.21-7.11 (m, 2H), 4.73 (d, $J = 9.9$ Hz, 1H), 4.48-4.42 (m, 2H), 3.92 (t, $J = 9.8$ Hz, 1H), 3.82 (s, 3H), 3.78-3.70 (m, 2H), 2.48 (s,

3H), 2.28-2.16 (m, 3H), 2.03 (q, $J = 8.7$ Hz, 2H), 1.50-1.28 (m, 3H), 1.05 (s, 9H), 0.38-0.28 (m, 12H); ^{13}C NMR (75 MHz, CDCl_3) δ 173.4, 144.1, 136.8, 133.4, 130.1, 128.7, 128.1, 127.0, 121.8, 119.8, 111.7, 108.2, 76.2, 64.0, 56.8, 52.8, 47.8, 46.4, 39.9, 39.8, 26.8, 24.2, 22.0, 19.2, 1.3, 0.7, -4.5, -4.9, -12.4; LRMS-ES+ m/z (relative intensity) 797 (MH^+ , 40).

Methyl 11-(((*tert*-Butyldimethylsilyloxy)methyl)-13,13-dimethyl-2-tosyl-1,2,3,4,4a,5,6,11-octahydro-11a,5-(epoxysilanomethano)pyrido[4,3-b]carbazole-5-carboxylate (51)—To a solution of indole iodo ester **50** (36.9 mg, 0.0463 mmol) at -78 °C was added KHMDS (0.1 M solution in THF, 1.39 mL, 0.139 mmol). The resulting mixture was stirred for 1 h at -78 °C, then transferred to a ice bath and stirred for an additional 15 min. The reaction mixture was diluted with aqueous NH_4Cl , the organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over MgSO_4 and concentrated *in vacuo* to give a residue, which was purified by flash chromatography on silica gel (25% EtOAc/hexanes) to afford pentacycle **51** (white foam, 31.0 mg, 97%). ^1H NMR (300 MHz, CDCl_3) δ 9.00 (s, 1H), 8.06 (d, $J = 7.08$ Hz, 1H), 7.72 (d, $J = 8.2$ Hz, 2H), 7.39-7.34 (m, 3H), 7.21 (t, $J = 7.7$ Hz, 1H), 7.11 (t, $J = 7.3$ Hz, 1H), 4.50 (d, $J = 10.7$ Hz, 1H), 5.60 (dd, $J = 10.4, 4.8$ Hz, 1H), 4.17 (dd, $J = 10.5, 5.1$ Hz, 1H), 3.80-3.72 (m, 5H), 2.47 (s, 3H), 2.34-2.26 (m, 1H), 2.08 (d, $J = 11.1$ Hz, 1H), 1.91-1.86 (m, 1H), 1.53-1.41 (m, 3H), 1.06 (s, 9H), 0.97-0.85 (m, 2H), 0.29 (s, 3H), 0.27 (s, 3H), 0.10 (s, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 176.1, 143.8, 137.8, 133.6, 132.1, 130.0, 128.4, 127.1, 122.4, 121.8, 119.6, 111.5, 110.4, 75.5, 63.8, 55.6, 52.8, 49.9, 46.9, 46.7, 40.5, 30.1, 28.0, 26.7, 25.5, 22.0, 19.1, 2.23, 2.16, -4.8, -4.9; LRMS-ES+ m/z (relative intensity) 669 (MH^+ , 30); HRMS-ES+ ($\text{C}_{34}\text{H}_{49}\text{N}_2\text{O}_6\text{SSi}_2$) calcd 669.2850 (MH^+), found 669.2857.

Methyl 7-(Hydroxymethyl)-1-oxo-4-tosyl-3,4,5,6,6a,7,8,12c-octahydro-1H-oxeto[2,3-c]pyrido[4,3-b]carbazole-7-carboxylate (55)—To a solution of indole β -lactone **36** (255 mg, 0.531 mmol) in THF (25 mL) cooled to -78 °C was added a solution of LiHMDS (1.0 M in THF, 1.60 mL, 1.60 mmol) dropwise with stirring. The resulting orange red solution was stirred at -78 °C for another 30 min. A solution of freshly distilled monomeric formaldehyde¹⁵ in THF (~0.5 M, 10.6 mL, 5.3 mmol) was added dropwise. The resulting brownish red solution was stirred at -78 °C for 5 min, then warmed to -40 °C and stirred for another 15 min. The reaction mixture was then quenched at -40 °C by addition of glacial acetic acid (0.10 mL, 1.6 mmol). The bright yellow solution was diluted with dichloromethane, quickly washed with ice cold water and dried over Na_2SO_4 . After concentration of the solution, the residue was purified by column chromatography on silica gel (5% $\text{Et}_2\text{O}/\text{CH}_2\text{Cl}_2$, then 50% EtOAc/hexanes) to afford α -hydroxymethyl ester **55** as an off-white solid (160 mg, 59%). FT-IR (film) 3403, 1824 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 9.43 (s, 1H, NH), 7.62-7.66 (m, 4H), 7.34-7.42 (m, 4H), 7.16-7.25 (m, 2H), 4.86 (s, 1H), 3.97-4.02 (m, 3H), 3.83 (s, 3H), 3.68 (app. d, $J = 15.6$ Hz, 1H), 2.74 (d, $J = 15.7$ Hz, 1H), 2.57 (dd, $J = 6.4, 15.9$ Hz, 1H), 2.46 (s, 3H), 2.26 (td, $J = 4.2, 15.7$ Hz, 1H), 2.13 (t, $J = 8.2$ Hz, 1H), 1.43-1.58 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 172.4, 167.1, 144.7, 136.6, 132.9, 131.6, 130.2, 128.0, 125.7, 123.2, 120.8, 118.6, 111.8, 101.0, 69.5, 55.4, 54.1, 53.1, 51.7, 45.3, 40.7, 26.8, 21.8; ESI MS (m/z): $[\text{M} + \text{H}]^+$ 511.3; HRMS-ES (m/z): $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{26}\text{H}_{27}\text{N}_2\text{O}_7\text{S}$, 511.1539; found, 511.1538.

Methyl 11a-Hydroxy-12-oxo-2-tosyl-2,3,4,4a,5,6,11,11a-octahydro-1H-5,11-(methanooxymethano)pyrido[4,3-b]carbazole-5-carboxylate (57)—To a solution of β -lactone **55** (200 mg, 0.39 mmol) in dichloromethane (2.6 mL) at rt was added triethylamine (10.6 mL, excess). The resulting slightly yellow solution was stirred at rt for 2 h, evaporated to dryness and the residue was purified by flash column chromatography on silica gel (5% $\text{Et}_2\text{O}/\text{CH}_2\text{Cl}_2$, then 50% EtOAc/hexanes) to afford ϵ -lactone **57** as an off white solid (65 mg, 33%). The recovered β -lactone **55** was subjected to another

translactonization under the same conditions. After 2 runs, 40 mg of β -lactone **55** was recovered and ϵ -lactone **57** was isolated by chromatography on silica gel (gradient 20–50% EtOAc/hexanes) as an off white foam (92 mg, BRSM, 58%). FT-IR (neat) 3407, 1725 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 9.61 (s, 1H, NH), 7.61 (d, $J = 8.2$ Hz, 2H), 7.53 (d, $J = 7.5$ Hz, 1H), 7.41 (d, $J = 8.0$ Hz, 1H), 7.25–7.27 (m, 4H), 7.21 (t, $J = 7.4$ Hz, 1H), 7.15 (t, $J = 7.5$ Hz), 4.90 (d, $J = 11.7$ Hz, 1H), 4.37 (d, $J = 11.7$ Hz, 1H), 4.16 (s, 1H), 3.93 (s, 3H), 3.65 (br s, 1H), 3.58 (d, $J = 13.5$ Hz, 1H), 3.52–3.58 (m, 1H), 3.01 (m, 1H), 2.81 (dd, $J = 3.8, 13.6$ Hz, 1H), 2.59 (d, $J = 13.6$ Hz, 1H), 2.37 (s, 3H), 1.40 (m, 1H), 0.76 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.0, 167.8, 144.2, 135.9, 134.4, 132.0, 130.2, 127.4, 124.9, 122.8, 120.9, 118.0, 113.7, 112.1, 107.0, 76.0, 73.6, 53.7, 53.0, 52.8, 52.2, 50.6, 42.4, 23.8, 21.7; ESI MS (m/z): $[\text{M} + \text{H}]^+$ 511.3; HRMS (m/z): $[\text{M} + \text{NH}_4]^+$ calcd for $\text{C}_{26}\text{H}_{30}\text{N}_3\text{O}_7\text{S}$ 528.1804; found 528.1797.

Methyl 7-(((tert-Butyldimethylsilyl)oxy)methyl)-1-oxo-4-tosyl-3,4,5,6,6a,7,8,12c-octahydro-1H-oxeto[2,3-c]pyrido[4,3-b]carbazole-7-carboxylate (56)—To a solution of hydroxymethyl compound **55** (100 mg, 0.196 mmol) in CH_2Cl_2 (15 mL) at 0 °C was added 2,6-lutidine (226 μL , 1.95 mmol) and freshly distilled TBSOTf (225 μL , 0.98 mmol) with stirring. The colorless reaction mixture was stirred at 0 °C and monitored by TLC. Once the reaction was complete (~40 min), the solvent was removed *in vacuo*. The residue was purified by flash chromatography on silica gel (gradient 5–30% EtOAc/hexanes) to afford *O*-TBS ether **56** as a white foam (105 mg, 86%). ^1H NMR (400 MHz, CDCl_3) δ 9.32 (br s, 1H, NH), 7.66–7.63 (m, 3H), 7.40 (d, $J = 8.0$ Hz, 1H), 7.36 (d, $J = 7.7$ Hz, 2H), 7.23 (m, 1H), 7.19 (dd, $J = 7.5, 7.6$ Hz, 1H), 4.84 (s, 1H), 4.03 (d, $J = 10.1$ Hz, 1H), 4.00 (d, $J = 12.4$ Hz, 1H), 3.88 (d, $J = 9.2$ Hz, 1H), 3.81 (s, 3H), 3.70 (m, 1H), 2.74 (d, $J = 11.6$ Hz, 1H), 2.55 (dd, $J = 4.7, 12.1$ Hz, 1H), 2.46 (s, 3H), 2.27 (td, $J = 3.0, 11.8$ Hz, 1H), 1.55–1.47 (m, 2H), 0.80 (s, 9H), -0.17 (s, 3H), -0.33 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 172.5, 167.4, 144.8, 136.4, 132.7, 132.4, 130.4, 128.2, 125.7, 123.1, 120.7, 118.7, 111.7, 100.4, 70.3, 55.8, 54.4, 53.0, 51.9, 45.5, 41.3, 27.1, 26.1, 25.9, 22.0, 18.4, -5.6 ; HRMS (m/z): $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{32}\text{H}_{41}\text{N}_2\text{O}_7\text{SSi}$, 625.2404; found 625.2390.

Methyl 11a-Hydroxy-5-(hydroxymethyl)-11-methyl-2-tosyl-2,3,4,4a,5,6,11,11a-octahydro-1H-pyrido[4,3-b]carbazole-5-carboxylate (60)—To a stirred solution of aldehyde **58** (10 mg, 0.020 mmol) in CH_2Cl_2 (1.5 mL) at rt was added $\text{BF}_3 \cdot \text{OEt}_2$ (2.5 μL , 0.020 mmol) and 1,2-ethanedithiol (3.5 μL , 0.042 mmol). The reaction mixture was stirred at rt for 12 h, then diluted with CH_2Cl_2 and phosphate buffer (pH 7). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 . The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to give a residue which was purified by column chromatography on silica gel (gradient 30–50% EtOAc/hexanes) to afford dithiane **59** as a white foam (10 mg, 87%) which was used directly in the next step. ^1H NMR (400 MHz, CDCl_3) δ 9.05 (br s, 1H), 7.68–7.60 (m, 3H), 7.44 (d, $J = 7.8$ Hz, 1H), 7.38 (d, $J = 8.9$ Hz, 2H), 7.23–7.12 (m, 2H), 5.87 (br s, 1H), 4.88 (s, 1H), 4.28 (d, $J = 11.2$ Hz, 1H), 4.17–4.02 (m, 3H), 3.87 (s, 3H), 3.70 (m, 1H), 3.05 (m, 1H), 2.78 (d, $J = 11.7$ Hz, 1H), 2.45 (s, 3H), 2.30 (m, 3H); LRMS-ES+ m/z (relative intensity) 589 (MH^+).

To a slurry of freshly prepared W-2 Raney nickel (large excess) in ethanol was added a solution of dithiane **59** (12.0 mg, 0.020 mmol) in ethanol (5 mL). The reaction mixture was heated at 60 °C until TLC indicated consumption of the starting material (~45 min). The Raney nickel was filtered off through a pad of Celite, and the filtrate was evaporated to dryness *in vacuo* to give essentially pure methyl compound **60** as a white powder (7.5 mg, 74%). ^1H NMR (400 MHz, CDCl_3) δ 8.64 (br s, 1H), 7.72 (d, $J = 7.8$ Hz, 1H), 7.67 (d, $J = 8.1$ Hz, 2H), 7.35 (m, 3H), 7.20 (dd, $J = 7.2, 7.2$ Hz, 1H), 7.12 (dd, $J = 7.2, 7.2$ Hz, 1H), 4.11 (d, $J = 11.2$ Hz, 1H), 4.01 (d, $J = 11.2$ Hz, 1H), 3.93 (d, $J = 10.6$ Hz, 1H), 3.75 (s, 3H),

3.67 (q, $J = 7.1$ Hz, 1H), 2.45 (s, 3H), 2.27 (m, 1H), 2.13 (dd, $J = 3.7, 12.5$ Hz, 1H), 2.08 (d, $J = 11.6$ Hz, 1H), 1.56 (d, $J = 7.0$ Hz, 3H), 0.83 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 174.1, 137.9, 133.3, 130.2, 128.1, 122.5, 120.9, 120.0, 111.9, 78.8, 72.7, 53.0, 47.8, 46.1, 31.0, 30.1, 26.8, 22.0, 13.3.

Methyl 5-(((*tert*-Butyldimethylsilyl)oxy)methyl)-11a-hydroxy-11-(hydroxymethyl)-2-tosyl-2,3,4,4a,5,6,11,11a-octahydro-1H-pyrido[4,3-b]carbazole-5-carboxylate (61)—To a solution of *O*-TBS β -lactone **56** (120 mg, 0.193 mmol) in THF at rt was added LiBH_4 (22 mg, 1.0 mmol). The reaction mixture was stirred at rt for 12 h, diluted with aqueous NH_4Cl and extracted with CH_2Cl_2 . The extract was dried over Na_2SO_4 and the solvent was removed *in vacuo* to give a residue which was purified by flash chromatography on silica gel (gradient 2–5% $\text{Et}_2\text{O}/\text{CH}_2\text{Cl}_2$) affording diol **61** as a white solid (90 mg, 75%). ^1H NMR (400 MHz, CDCl_3) δ 8.76 (br s, 1H), 7.69–7.66 (m, 3H), 7.39 (d, $J = 7.9$ Hz, 1H), 7.34 (d, $J = 7.7$ Hz, 2H), 7.22 (dd, $J = 7.6, 7.8$ Hz, 1H), 7.14 (dd, $J = 7.1, 7.4$ Hz, 1H), 4.87 (d, $J = 12.2$ Hz, 1H), 4.44 (d, $J = 12.9$ Hz, 1H), 4.23 (d, $J = 8.7$ Hz, 1H), 4.08 (d, $J = 9.5$ Hz, 2H), 3.71 (s, 3H), 3.67 (m, 1H), 2.45 (s, 3H), 2.25 (dd, $J = 10.5, 10.8$ Hz, 1H), 2.17 (d, $J = 11.8$ Hz, 1H), 1.92 (d, $J = 12.2$ Hz, 1H), 1.59 (m, 1H), 1.40 (m, 1H), 0.87 (s, 9H), -0.05 (s, 3H), -0.11 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 173.4, 144.3, 137.0, 135.0, 133.2, 130.2, 128.1, 125.8, 122.3, 120.2, 119.2, 111.9, 103.8, 74.5, 71.8, 61.0, 55.8, 54.9, 52.5, 47.6, 46.1, 37.4, 26.4, 26.2, 22.0, 18.5, -5.2 , -5.5 ; HRMS (m/z): $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{32}\text{H}_{45}\text{N}_2\text{O}_7\text{SSi}$, 629.2717; found 629.2717.

Methyl 5-(((*tert*-Butyldimethylsilyl)oxy)methyl)-11a-hydroxy-11-(iodomethyl)-2-tosyl-2,3,4,4a,5,6,11,11a-octahydro-1H-pyrido[4,3-b]carbazole-5-carboxylate (62)—To a solution of PPh_3 (229 mg, 0.87 mmol) and I_2 (222 mg, 0.87 mmol) in CH_2Cl_2 (9 mL) at rt was added imidazole (99 mg, 1.48 mmol). The resulting yellow suspension was stirred at rt for 10 min. A solution of diol **61** (122 mg, 0.195 mmol) in CH_2Cl_2 (15 mL) was added dropwise, and the bright yellow suspension was stirred at rt for 5 h. The mixture was diluted with CH_2Cl_2 and washed with 5% aqueous $\text{Na}_2\text{S}_2\text{O}_3$. The aqueous layer was extracted with CH_2Cl_2 . The combined organic layers were washed with brine, dried over Na_2SO_4 , and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (2% $\text{Et}_2\text{O}/\text{CH}_2\text{Cl}_2$) to afford iodo alcohol **62** as a white foamy solid (133 mg, 93%). ^1H NMR (400 MHz, CDCl_3) δ 8.80 (br s, 1H), 7.67 (d, $J = 8.1$ Hz, 2H), 7.63 (d, $J = 7.7$ Hz, 1H), 7.37–7.33 (m, 3H), 7.20 (dd, $J = 7.1, 7.5$ Hz, 1H), 7.14 (dd, $J = 7.4, 7.4$ Hz, 1H), 4.17–4.09 (m, 2H), 4.00–3.96 (m, 1H), 3.90–3.88 (m, 2H), 3.68 (s, 3H), 3.30 (s, 1H), 2.44 (s, 3H), 2.30 (m, 1H), 2.18 (m, 1H), 2.08 (dd, $J = 3.1, 11.5$ Hz, 1H), 1.63 (m, 1H), 1.43 (m, 1H), 0.84 (s, 9H), -0.08 (s, 3H), -0.10 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 172.9, 144.0, 136.5, 132.7, 132.3, 132.1, 129.9, 128.7, 127.9, 126.0, 122.0, 119.6, 111.4, 108.9, 72.9, 71.0, 54.8, 54.3, 52.3, 45.6, 36.4, 25.8, 21.6, 18.2, 4.8, 1.1, -5.6 , -5.7 ; HRMS (m/z): $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{32}\text{H}_{44}\text{IN}_2\text{O}_6\text{SSi}$, 739.1734; found 739.1764.

Methyl 5-(((*tert*-Butyldimethylsilyl)oxy)methyl)-11a-hydroxy-11-methyl-2-tosyl-2,3,4,4a,5,6,11,11a-octahydro-1H-pyrido[4,3-b]carbazole-5-carboxylate (63)—10% Pd/C (158 mg) was suspended in a stirred solution of iodide **62** (29 mg, 0.039 mmol) in *t*-BuOH/EtOAc (1:1 v/v, 30 mL). The reaction mixture was evacuated and backfilled with H_2 three times from a balloon and stirred under a H_2 atmosphere at rt. After 3.5 h, another portion of 10% Pd/C (32 mg) was added and the reaction mixture was stirred under H_2 at rt for another 12 h. The Pd/C was filtered off through a pad of Celite, and the solvent was removed *in vacuo* to afford a yellow foamy solid. This material was purified by flash column chromatography on silica gel (CH_2Cl_2 , then 2% $\text{Et}_2\text{O}/\text{CH}_2\text{Cl}_2$) to afford methyl compound **63** as a white solid (23 mg, 96%). ^1H NMR (400 MHz, CDCl_3) δ 8.51 (br s, 1H), 7.72 (d, $J = 7.9$ Hz, 1H), 7.67 (d, $J = 8.1$ Hz, 2H), 7.34–7.32 (m, 3H), 7.17 (dd, $J =$

7.1, 7.6 Hz, 1H), 7.08 (dd, $J = 7.2, 7.4$ Hz, 1H), 4.13 (d, $J = 9.4$ Hz, 1H), 4.00 (d, $J = 9.4$ Hz, 1H), 3.96 (d, $J = 11.8$ Hz, 1H), 3.72 (s, 3H), 3.66 (q, $J = 7.0$ Hz, 1H), 3.09 (s, 1H), 2.45 (s, 3H), 2.26 (t, $J = 10.4$ Hz, 1H), 2.04 (d, $J = 13.0$ Hz, 1H), 2.00 (dd, $J = 3.7, 12.6$ Hz, 1H), 1.63 (qd, $J = 4.4, 12.9$ Hz, 1H), 1.57 (d, $J = 6.9$ Hz, 3H), 0.80 (s, 3H), -0.07 (s, 3H), -0.12 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 173.3, 143.9, 137.1, 133.0, 130.0, 129.9, 129.8, 127.9, 126.7, 121.7, 120.5, 119.1, 111.4, 111.2, 72.5, 70.7, 55.1, 53.4, 52.3, 48.2, 46.0, 30.5, 26.5, 25.8, 25.7, 21.7, 18.1, 12.8, -5.7, -5.8; HRMS (m/z): $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{32}\text{H}_{45}\text{N}_2\text{O}_6\text{SSi}$, 613.2768; found 613.2772.

Methyl 5-(((*tert*-Butyldimethylsilyloxy)methyl)-11a-hydroxy-11-methyl-2,3,4,4a,5,6,11,11a-octahydro-1*H*-pyrido[4,3-*b*]carbazole-5-carboxylate (64)—Magnesium turnings (399 mg, excess) were added to a solution of sulfonamide **63**

(21.6 mg, 0.035 mmol) in anhydrous methanol, and the mixture was sonicated at rt until all the magnesium turnings dissolved (~45 min). The reaction mixture was then poured into aqueous NH_4Cl at 0 °C, and extracted with CHCl_3 . The organic extract was dried over Na_2SO_4 , and evaporated to dryness *in vacuo* to give a white foamy solid. This material was purified by flash chromatography on silica gel (gradient 2–5% MeOH/ CHCl_3 , then 1% NEt_3 in 5% MeOH/ CHCl_3) to afford piperidine **64** as a white solid (15.6 mg, 96%). ^1H NMR (400 MHz, CD_3OD) δ 7.90 (br s, 1H), 7.66 (d, $J = 7.8$ Hz, 1H), 7.33 (d, $J = 8.0$ Hz, 1H), 7.08 (dd, $J = 7.2, 7.4$ Hz, 1H), 6.98 (dd, $J = 7.2, 7.3$ Hz, 1H), 4.34 (d, $J = 9.3$ Hz, 1H), 4.20 (d, $J = 9.4$ Hz, 1H), 3.77 (s, 3H), 3.42 (q, $J = 6.7$ Hz, 1H), 3.28 (m, 1H), 3.03 (q, $J = 7.2$ Hz, 1H), 2.94 (br d, $J = 12.6$ Hz, 1H), 2.69 (m, 1H), 2.50 (d, $J = 12.7$ Hz, 1H), 2.29 (m, 1H), 1.49 (d, $J = 6.7$ Hz, 3H), 0.83 (s, 9H), -0.02 (s, 3H), -0.10 (s, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 175.1, 138.6, 131.7, 127.9, 122.2, 120.8, 119.4, 112.7, 112.0, 79.6, 72.4, 71.6, 56.9, 54.0, 52.7, 47.8, 45.4, 32.1, 26.4, 19.2, 14.5, -5.4, -5.5; HRMS (m/z): $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{25}\text{H}_{39}\text{N}_2\text{O}_4\text{Si}$, 459.2674; found 459.2676.

Synthesis of (\pm)-Alstilobanine A (3)

A solution of *O*-TBS indole **64** (16.5 mg, 0.036 mmol) in CHCl_3 (3.3 mL) at 0 °C was treated with a solution of hydrogen chloride in MeOH (1.25 M, 3.3 mL). The resultant colorless solution was stirred at rt for 2 h, and the volatiles were removed under high vacuum to afford (\pm)-alstilobanine A (**3**) hydrochloride salt as a white solid (12.2 mg, 100%). ^1H NMR (400 MHz, CD_3OD) δ 7.55 (d, $J = 7.9$ Hz, 1H), 7.34 (d, $J = 8.0$ Hz, 1H), 7.08 (dd, $J = 7.4, 7.5$ Hz, 1H), 6.98 (dd, $J = 7.4, 7.5$ Hz, 1H), 4.14 (d, $J = 10.9$ Hz, 1H), 4.04 (d, $J = 10.8$ Hz, 1H), 3.78 (s, 3H), 3.54 (d, $J = 12.5$ Hz, 1H), 3.26 (q, $J = 7.1$ Hz, 1H), 3.09 (m, 1H), 2.93 (m, 1H), 2.87 (d, $J = 12.6$ Hz, 1H), 2.52 (m, 1H), 2.06 (m, 1H), 1.87 (m, 1H), 1.43 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 174.9, 138.9, 130.9, 127.2, 122.5, 119.6, 119.5, 113.3, 112.2, 71.0, 68.7, 55.2, 53.0, 50.5, 42.4 (2C), 34.4, 22.6, 15.7; HRMS (m/z): $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{19}\text{H}_{25}\text{N}_2\text{O}_4$, 345.1809; found 345.1809.

Methyl 11a-Hydroxy-5,11-bis(hydroxymethyl)-2-tosyl-2,3,4,4a,5,6,11,11a-octahydro-1*H*-pyrido[4,3-*b*]carbazole-5-carboxylate (65)—To a solution of β -lactone alcohol **55** (10.0 mg, 0.020 mmol) in THF (1.7 mL) at rt was added dropwise a solution of DIBAL-H in toluene (1.5 M, 0.15 mL, 0.22 mmol). The reaction mixture was stirred at rt for 2 h, was then diluted with aqueous NH_4Cl and 10% Rochelle's salt and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and evaporated *in vacuo* to give a brown residue which was purified by flash chromatography on silica gel (gradient 30–50% EtOAc/hexanes) to afford triol **65** as a slightly brown gum (4.9 mg, 53%). ^1H NMR (400 MHz, CDCl_3) δ 8.94 (br s, 1H), 7.66 (d, $J = 8.1$ Hz, 3H), 7.41 (d, $J = 8.1$ Hz, 1H), 7.35 (d, $J = 8.0$ Hz, 2H), 7.22 (app t, $J = 7.4$ Hz, 1H), 7.14 (app t, $J = 7.2$ Hz, 1H), 5.11 (app br s, 1H), 4.78 (d, $J = 12.9$ Hz, 1H), 4.47 (t, $J = 9.7$ Hz, 1H), 4.19 (dd, $J = 4.2, 11.1$ Hz, 1H), 4.13-4.06 (m, 2H), 3.76 (s, 3H), 3.69 (m, 2H), 2.71 (m, 1H), 2.45 (s, 3H), 2.27 (m, 1H), 2.21

(d, $J = 12.0$ Hz, 1H), 2.10 (dd, $J = 3.7, 12.2$ Hz, 2H), 1.44 (m, 1H), 0.87 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.1, 144.3, 133.2, 130.2, 128.0, 122.6, 120.5, 119.3, 117.6, 112.1, 111.2, 74.4, 71.3, 70.8, 61.2, 55.1, 55.0, 52.9, 45.8, 30.1, 26.5, 22.0; LRMS-ES+ m/z (relative intensity) 515 (MH^+ , 100); HRMS (m/z): $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{26}\text{H}_{31}\text{N}_2\text{O}_7\text{S}$, 515.1852; found 515.1851.

Methyl 11-(Hydroxymethyl)-2-tosyl-1,2,3,4,4a,5,6,11-octahydro-11a,5-(epoxymethano)pyrido[4,3-b]carbazole-5-carboxylate (67) and Methyl 7-(Hydroxymethyl)-4-tosyl-3,4,5,6,6a,7,8,12c-octahydro-1H-oxeto[2,3-c]pyrido[4,3-b]carbazole-7-carboxylate (68)—To a solution of PPh_3 (8.5 mg, 0.032 mmol) and triol **65** (12.0 mg, 0.024 mmol) in THF (5 mL) at rt was added dropwise DIAD (5 μL , 0.016 mmol). The resulting orange solution was stirred at rt for 1 h. The volatiles were then removed *in vacuo* to give an orange residue which was purified by flash chromatography on silica gel (gradient 20–30% EtOAc/hexanes) to afford tetrahydrofuranyl ether **67** as the major product (white foam, 6.1 mg, 51%). ^1H NMR (400 MHz, CDCl_3) δ 9.04 (br s, 1H), 7.69 (d, $J = 7.7$ Hz, 2H), 7.60 (d, $J = 7.6$ Hz, 1H), 7.36 (m, 1H), 7.18 (dd, $J = 7.1, 7.8$ Hz, 1H), 7.13 (dd, $J = 7.1, 7.8$ Hz, 1H), 4.97 (d, $J = 4.0$ Hz, 1H), 4.73 (d, $J = 10.8$ Hz, 1H), 4.38 (d, $J = 11.7$ Hz, 1H), 4.21–4.18 (m, 3H), 3.97 (d, $J = 9.9$ Hz, 1H), 3.86 (s, 3H), 3.72 (d, $J = 5.1$ Hz, 1H), 2.45 (s, 3H), 2.41 (m, 1H), 2.29 (d, $J = 12.0$ Hz, 1H), 1.69–1.54 (m, 1H), 1.49 (dd, $J = 4.3, 12.8$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.4, 144.0, 136.1, 134.3, 132.8, 130.0, 127.5, 126.6, 122.1, 120.2, 119.6, 113.9, 111.7, 106.9, 106.1, 83.1, 81.3, 62.1, 54.7, 54.0, 53.2, 51.8, 45.7, 39.4, 29.9, 22.8, 21.8; LRMS-ES+ m/z (relative intensity) 497 (MH^+ , 100); HRMS (m/z): $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{26}\text{H}_{29}\text{N}_2\text{O}_6\text{S}$, 497.1746; found 497.1729.

Oxetane **68** (white solid, 2.8 mg, 23%). ^1H NMR (400 MHz, CDCl_3) δ 9.24 (br s, 1H), 7.69–7.23 (m, 8H), 5.13 (t, $J = 6.1$ Hz, 1H), 4.42 (m, 1H), 4.31 (m, 1H), 4.12 (m, 1H), 4.04 (dd, $J = 3.5, 6.4$ Hz, 1H), 3.96 (dd, $J = 3.3, 5.5$ Hz, 1H), 3.83 (s, 3H), 3.60 (m, 1H), 2.45 (s, 3H), 2.39 (d, $J = 11.4$ Hz, 1H), 2.23–2.00 (m, 2H), 1.39 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 173.7, 144.2, 136.8, 133.2, 132.7, 132.4, 131.7, 130.3, 128.7, 128.0, 126.1, 122.7, 120.0, 116.1, 110.4, 85.1, 75.3, 71.7, 55.7, 54.2, 52.9, 45.6, 43.0, 33.8, 26.0, 21.8; HRMS (m/z): $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{26}\text{H}_{29}\text{N}_2\text{O}_6\text{S}$, 497.1746; found 497.1752.

Oxetane **68** could be formed as the major product using the following procedure: to a solution of PPh_3 (4.3 mg, 0.016 mmol) and triol **65** (6.5 mg, 0.013 mmol) in benzene at 0 °C was added dropwise a solution of DEAD in toluene (40 wt %, 6.5 μL , 0.014 mmol). The reaction mixture was stirred at 0 °C for 5 min, and then heated at reflux for 1 h. The mixture was cooled to rt and concentrated *in vacuo* to give a residue which was purified by preparative TLC (30% EtOAc/hexanes, plate developed 4 times) to afford oxetane **68** as a white solid (4.4 mg, 70%), together with small amounts of cyclopropane **66** (<0.5 mg, <8%) and tetrahydrofuranyl ether **67** (<0.5 mg, <8%).

Methyl 3-Tosyl-1,1a,2,3,4,5,5a,6-octahydro-1b,6-(epoxymethano)cyclopropa[d]pyrido[4,3-b]carbazole-6-carboxylate (66)—To a solution of PPh_3 (21 mg, 0.080 mmol) and triol **65** (8.4 mg, 0.016 mmol) in THF (1.5 mL) at 0 °C was added dropwise DIAD (16 μL , 0.050 mmol). The resulting orange solution was stirred at 0 °C for 10 min, then allowed to warm to rt and stirred for 5 h. The volatiles were removed *in vacuo* to give an orange residue which was purified by flash chromatography on silica gel (gradient 20–30% EtOAc/hexanes) to afford cyclopropane **66** as a white foam (6.6 mg, 86%). ^1H NMR (400 MHz, CDCl_3) δ 7.73 (d, $J = 7.8$ Hz, 1H), 7.68 (m, 2H), 7.63 (d, $J = 8.4$ Hz, 2H), 7.47 (m, 3H), 4.25 (d, $J = 9.2$ Hz, 1H), 4.21 (d, $J = 10.2$ Hz, 1H), 4.08 (d, $J = 9.5$ Hz, 1H), 3.86 (s, 3H), 3.81 (m, 1H), 3.17 (dd, $J = 5.6, 8.5$ Hz, 1H), 2.64 (t, $J = 5.4$ Hz,

1H), 2.47 (d, $J = 10.5$ Hz, 1H), 2.44 (s, 3H), 2.21 (m, 1H), 2.15 (dd, $J = 3.2, 12.7$ Hz, 1H), 2.06 (m, 1H), 1.93 (m, 1H), 0.95 (m, 1H), 0.77 (m, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 170.2, 132.4, 132.3, 132.2, 130.1, 128.8, 128.7, 127.7, 127.2, 125.2, 121.8, 119.0, 116.6, 112.8, 107.9, 106.3, 78.9, 72.8, 60.5, 58.6, 53.5, 53.0, 46.0, 42.2, 24.3, 22.0, 21.8; LRMS-ES+ m/z (relative intensity) 479 (MH^+ , 100); HRMS (m/z): $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{26}\text{H}_{27}\text{N}_2\text{O}_5\text{S}$, 479.1641; found 479.1631.

Methyl 6-(((*tert*-Butyldimethylsilyloxy)methyl)-1b-hydroxy-3-tosyl-1a,1b,2,3,4,5,5a,6-octahydro-1*H*-cyclopropa[d]pyrido[4,3-*b*]carbazole-6-carboxylate (69)—To a stirred solution of AgOTf (2.6 mg, 0.010 mmol) in CH_2Cl_2 (0.8 mL) at rt was added dropwise a solution of iodide **62** (4.0 mg, 0.0054 mmol) in CH_2Cl_2 (0.2 mL). After 15 min, the colorless solution became a yellow suspension. The reaction mixture was then filtered through a pad of Celite. The filtrate was concentrated *in vacuo* to give cyclopropane **69** as a white solid (3.0 mg, 92%). ^1H NMR (400 MHz, CDCl_3) δ 7.65 (d, $J = 7.7$ Hz, 1H), 7.57 (d, $J = 8.1$ Hz, 2H), 7.36 (dd, $J = 7.5, 7.6$ Hz, 1H), 7.30 (d, $J = 8.1$ Hz, 2H), 7.23 (m, 1H), 7.06 (d, $J = 7.4$ Hz, 1H), 4.16 (d, $J = 9.7$ Hz, 1H), 3.99 (d, $J = 9.9$ Hz, 1H), 3.52 (m, 2H), 3.48 (br s, 1H), 2.83 (s, 3H), 2.72-2.70 (m, 2H), 2.62 (t, $J = 7.9$ Hz, 1H), 2.37 (s, 3H), 2.30 (m, 1H), 1.77 (dd, $J = 4.8, 8.0$ Hz, 1H), 0.82 (m, 1H), 0.75 (s, 9H), -0.05 (s, 3H), -0.15 (s, 3H); LRMS-ES+ m/z (relative intensity) 611 (MH^+ , 100); HRMS (m/z): $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{32}\text{H}_{42}\text{N}_2\text{O}_6\text{SSi}$, 611.2611; found 611.2602.

Methyl 1b-Hydroxy-3-tosyl-1a,1b,2,3,4,5,5a,7-octahydro-1*H*-cyclopropa[d]pyrido[4,3-*b*]carbazole-6-carboxylate (70)—To a stirred solution of OTBS iodomethyl indole **62** (28 mg, 0.038 mmol) in CH_2Cl_2 (5.6 mL) at rt was added a solution of TBAF in THF (1.0 M, 71 μL , 0.071 mmol). The reaction mixture was stirred at rt for 1.5 h, diluted with aqueous NH_4Cl and extracted with CH_2Cl_2 . The organic layer was washed with brine, dried over Na_2SO_4 , and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (gradient 20–50% EtOAc/hexanes) to afford cyclopropane indoline **70** as a white solid (17 mg, 97%). ^1H NMR (400 MHz, CDCl_3) δ 9.57 (br s, 1H), 7.56 (d, $J = 8.0$ Hz, 2H), 7.27 (m, 2H), 7.17 (dd, $J = 7.5, 7.6$ Hz, 1H), 6.93 (dd, $J = 7.5, 7.6$ Hz, 1H), 6.85 (d, $J = 7.7$ Hz, 2H), 3.70 (s, 3H), 3.59 (d, $J = 11.4$ Hz, 1H), 3.47 (d, $J = 11.9$ Hz, 1H), 3.18 (s, 1H), 2.98 (d, $J = 14.5$ Hz, 1H), 2.56 (br s, 1H), 2.40 (s, 3H), 2.37-2.32 (m, 2H), 2.23-2.13 (m, 2H), 2.06 (m, 1H), 1.40 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 169.2, 162.5, 144.2, 143.9, 133.6, 131.0, 130.1, 127.7, 127.6, 121.2, 118.7, 116.7, 114.0, 111.5, 109.4, 85.9, 69.4, 51.7, 50.8, 42.7, 34.4, 32.6, 32.5, 29.8, 23.4, 21.7, 20.6; LRMS-ES+ m/z (relative intensity) 467 (MH^+ , 100); HRMS (m/z): $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{25}\text{H}_{27}\text{N}_2\text{O}_5\text{S}$, 467.1641; found 467.1671.

8-Benzyl 7-Methyl 7-(((*tert*-Butyldimethylsilyloxy)methyl)-1-oxo-4-tosyl-3,4,5,6,7-hexahydro-1*H*-oxeto[2,3-*c*]pyrido[4,3-*b*]carbazole-7,8(12*cH*)-dicarboxylate (71)—To a solution of NH indole- β -lactone **56** (28 mg, 0.045 mmol) in THF (2.5 mL) cooled to -78 $^\circ\text{C}$ was added a solution of KHMDS in toluene (0.5 M, 0.14 mL, 0.070 mmol). After the resulting yellow solution was stirred at -78 $^\circ\text{C}$ for 30 min, CbzCl (neat, 51 μL , 0.36 mmol) was added dropwise. The reaction mixture was allowed to warm to rt, stirred for another 5 h, and then diluted with CH_2Cl_2 . The organic phase was washed with aqueous NH_4Cl , dried over Na_2SO_4 , and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (CH_2Cl_2) to afford the *N*-Cbz- β -lactone **71** as a colorless gum (31 mg, 91%). ^1H NMR (400 MHz, CDCl_3) δ 7.98-7.95 (m, 1H), 7.66 (m, 3H), 7.48 (m, 2H), 7.42-7.29 (m, 6H), 5.46 (d, $J = 12.0$ Hz, 1H), 5.35 (d, $J = 12.0$ Hz, 1H), 4.71 (m, 2H), 4.41 (d, $J = 10.1$ Hz, 1H), 3.97 (d, $J = 10.1$ Hz, 1H), 3.82 (m, 1H), 3.47 (m, 1H), 3.39 (s, 3H), 2.95 (m, 2H), 2.46 (s, 3H), 2.43 (m, 1H), 1.64-1.59 (m, 1H), 0.73 (s, 9H), -0.04 (s, 3H), -0.11 (s, 3H).

6-Benzyl 5-Methyl 5-(((*tert*-Butyldimethylsilyl)oxy)methyl)-11a-hydroxy-11-(hydroxymethyl)-2-tosyl-3,4,4a,5,11,11a-hexahydro-1*H*-pyrido[4,3-*b*]carbazole-5,6(2*H*)-dicarboxylate (72)—To a solution of *N*-Cbz-indole- β -lactone **71** (10.0 mg, 0.013 mmol) in THF (2.0 mL) at rt was added solid LiBH₄ (2.0 mg, 0.091 mmol). The reaction mixture was stirred at rt for 3 h, diluted with aqueous NH₄Cl, and extracted with CH₂Cl₂. The organic layer was dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (gradient 2–5% Et₂O/CH₂Cl₂) to afford diol **72** as a white solid (6.4 mg, 64%). ¹H NMR (400 MHz, CDCl₃) δ 8.02 (br m, 1H), 7.87 (m, 1H), 7.65 (m, 2H), 7.46 (m, 2H), 7.40–7.30 (m, 7H), 5.46 (d, *J* = 13.2 Hz, 1H), 5.37 (d, *J* = 12.0 Hz, 1H), 4.71 (s, 1H), 4.43 (m, 1H), 4.35 (m, 1H), 4.22 (m, 2H), 3.78 (m, 1H), 3.56 (s, 1H), 3.36 (s, 3H), 2.44 (s, 3H), 2.12 (m, 2H), 0.65 (s, 9H), –0.03 (s, 3H), –0.20 (s, 3H); LRMS-ES+ *m/z* (relative intensity) 763 (MH⁺, 100); HRMS (*m/z*): [M + H]⁺ calcd for C₄₀H₅₁N₂O₉SSi, 763.3085; found 763.3121.

6-Benzyl 5-Methyl 11-(Bromomethyl)-11a-hydroxy-5-(hydroxymethyl)-2-tosyl-3,4,4a,5,11,11a-hexahydro-1*H*-pyrido[4,3-*b*]carbazole-5,6(2*H*)-dicarboxylate (73)—To a solution of PPh₃ (39 mg, 0.15 mmol) and CBr₄ (45 mg, 0.14 mmol) in CH₂Cl₂ at rt was added dropwise a solution of *N*-Cbz diol **72** (41 mg, 0.054 mmol) in CH₂Cl₂ (8.2 mL). The resulting cloudy reaction mixture was stirred at rt for 20 h. The mixture was evaporated *in vacuo* to give a residue which was purified by preparative TLC on silica gel (5% Et₂O/CH₂Cl₂) to afford the bromo alcohol **73** as a white solid (10 mg, 26%). ¹H NMR (400 MHz, CDCl₃) δ 8.05 (m, 1H), 7.67 (m, 3H), 7.48 (d, *J* = 7.6 Hz, 2H), 7.43–7.30 (m, 7H), 5.48 (d, *J* = 12.0 Hz, 1H), 5.35 (d, *J* = 12.0 Hz, 1H), 4.41 (br s, 2H), 4.22–4.11 (m, 2H), 4.03 (d, *J* = 6.6 Hz, 1H), 3.97 (d, *J* = 11.2 Hz, 1H), 3.66 (m, 1H), 3.33 (s, 3H), 2.45 (s, 3H), 2.28–2.14 (m, 2H), 1.49 (m, 1H), 1.00–0.86 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 175.0, 144.4, 135.0, 133.0, 130.2, 129.4, 129.3, 129.2, 128.4, 128.2, 125.7, 123.8, 120.2, 116.4, 112.3, 110.0, 70.9, 69.5, 54.9, 52.0, 31.2, 27.3, 22.0; HRMS (*m/z*): [M + H]⁺ calcd for C₃₄H₃₆N₂O₈SBr, 711.1376; found 711.1417.

8-Benzyl 7-Methyl 7-(Hydroxymethyl)-4-tosyl-3,4,5,6,6a,7-hexahydro-1*H*-oxeto[2,3-*c*]pyrido[4,3-*b*]carbazole-7,8(12*cH*)-dicarboxylate (74)—To a solution of bromide **73** (1.6 mg, 0.0023 mmol) in CH₂Cl₂ (0.8 mL) was added activated 4Å molecular sieves (5.2 mg), silica gel (5.2 mg), solid NaHCO₃ (3.0 mg, 0.036 mmol) and solid AgOTf (12.2 mg, 0.047 mmol). The reaction mixture was stirred at rt for 2 h, then diluted with CH₂Cl₂ and filtered through a pad of Celite. The filtrate was concentrated *in vacuo* to afford oxetane **74** as a white solid (1.2 mg, 84%). ¹H NMR (400 MHz, CDCl₃) δ 8.05 (d, *J* = 10.8 Hz, 1H), 7.67 (d, *J* = 7.2 Hz, 2H), 7.55–7.15 (m, 10H), 5.51 (d, *J* = 14.4 Hz, 1H), 5.37 (d, *J* = 14.4 Hz, 1H), 5.13 (m, 1H), 4.52 (d, *J* = 11.0 Hz, 1H), 4.43 (d, *J* = 11.0 Hz, 1H), 4.31 (t, *J* = 7.2 Hz, 1H), 3.98 (m, 1H), 3.86 (m, 2H), 3.66 (m, 1H), 3.37 (s, 3H), 2.46 (s, 3H), 2.35 (t, *J* = 7.2 Hz, 1H), 2.17–2.07 (m, 2H).

For characterization, *N*-Cbz-indole oxetane **74** (1.2 mg) and glacial HOAc (1.0 μ L) were dissolved in EtOAc (1.0 mL) and hydrogenated with 10% Pd/C (5 mg) under H₂ from a balloon at rt for 1.5 h. The reaction mixture was then filtered through a pad of Celite and the filtrate was evaporated to dryness *in vacuo* to give a white solid (0.8 mg, 85%), which was identical to oxetane **68**.

Methyl 5-(((*tert*-Butyldimethylsilyl)oxy)methyl)-11-formyl-11a-hydroxy-2-tosyl-2,3,4,4a,5,6,11,11a-octahydro-1*H*-pyrido[4,3-*b*]carbazole-5-carboxylate (75)—Freshly prepared IBX³⁷ (46 mg, 0.16 mmol) was added to a solution of diol **61** (97 mg, 0.16 mmol) in dry DMSO (5.3 mL) and the mixture was stirred at rt for 20 h. The reaction mixture was diluted with water and extracted with ether. The organic phase was

washed with aqueous NaHCO₃, brine, and dried over MgSO₄. The solvent was removed *in vacuo* to give a residue which was purified by flash chromatography on silica gel (gradient 20–40% EtOAc/hexanes) to afford aldehyde **75** as a white solid (91 mg, 94%). ¹H NMR (300 MHz, CDCl₃) δ 10.26 (s, 1H), 8.74 (br s, 1H, NH), 7.68 (d, *J* = 8.0 Hz, 2H), 7.42–7.32 (m, 4H), 7.21 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.11 (dd, *J* = 7.5, 7.5 Hz, 1H), 4.70 (br s, 1H), 4.42 (s, 1H), 4.20 (d, *J* = 9.5 Hz, 1H), 4.13–4.08 (m, 1H), 4.02 (d, *J* = 9.5 Hz, 1H), 3.74 (s, 3H), 3.70 (m, 1H), 2.44 (s, 3H), 2.29 (m, 1H), 2.23 (m, 1H), 2.00 (dd, *J* = 3.8, 11.5 Hz, 1H), 1.54 (dd, *J* = 4.2, 12.8 Hz, 1H), 1.43 (m, 1H), 0.79 (s, 9H), –0.09 (s, 3H), –0.14 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 203.6, 172.8, 144.0, 136.9, 133.0, 131.4, 129.9, 127.9, 125.8, 122.4, 120.0, 119.4, 111.5, 103.7, 72.4, 70.5, 55.2, 55.1, 52.6, 48.9, 48.5, 45.7, 26.4, 25.7, 21.7, 18.1, –5.7, –5.8; HRMS (*m/z*): [M + H]⁺ calcd for C₃₂H₄₃N₂O₇SSi, 627.2560; found 627.2542.

Methyl 11-Formyl-11a-hydroxy-5-(hydroxymethyl)-2-tosyl-2,3,4,4a,5,6,11,11a-octahydro-1H-pyrido[4,3-b]carbazole-5-carboxylate (58)

Method A: To a solution of ε-lactone **57** (5.5 mg, 0.011 mmol) in CH₂Cl₂ (0.2 mL) at –78 °C was added BF₃·OEt₂ (2.7 μL, 0.022 mmol), followed by dropwise addition of a DIBAL-H solution in toluene (1.5 M, 14 μL, 0.022 mmol). The reaction mixture was stirred at –78 °C for 1 h, and then quenched by addition of 10% Rochelle's salt and Na₂HPO₄/KH₂PO₄ buffer (pH 7). The mixture was extracted with CH₂Cl₂. The organic layer was washed with brine and dried over Na₂SO₄. The solvent was removed *in vacuo* to give a residue which was purified by flash chromatography on silica gel (gradient 30–50% EtOAc/hexanes) to afford aldehyde **58** as an off-white foam (1.2 mg, 22%). ¹H NMR (400 MHz, CDCl₃) δ 10.3 (s, 1H), 8.94 (s, 1H), 7.67 (m, 3H), 7.41 (d, *J* = 8.2 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.24 (m, 1H), 7.14 (dd, *J* = 7.4, 7.5 Hz, 1H), 4.51 (s, 1H), 4.19 (d, *J* = 11.1 Hz, 1H), 4.15–4.00 (m, 3H), 3.78 (s, 3H), 3.70 (m, 2H), 2.46 (s, 3H), 2.26 (m, 2H), 2.11 (td, *J* = 4.2, 11.4 Hz, 1H), 1.00–0.86 (m, 2H); ¹³C NMR δ (75 MHz, CDCl₃) δ 203.1, 173.4, 144.5, 137.4, 133.2, 130.8, 130.3, 128.2, 126.4, 123.1, 120.5, 120.0, 112.1, 105.2, 72.5, 69.4, 55.5, 55.2, 53.2, 49.6, 48.7, 45.9, 26.8, 22.0; HRMS (*m/z*): [M + H]⁺ calcd for C₂₆H₂₉N₂O₇S, 513.1695; found 513.1696.

Method B: OTBS aldehyde **75** (233 mg, 0.36 mmol) was dissolved in a solution of HCl in EtOAc (1.0 M, 5 mL) and the mixture was stirred at rt for 1 h. The volatiles were removed *in vacuo* to afford hydroxy aldehyde **58** as a red solid (183 mg, 100%), which was used in the next step without further purification.

Methyl 11-(bis(Ethylthio)methyl)-11a-hydroxy-5-(hydroxymethyl)-2-tosyl-2,3,4,4a,5,6,11,11a-octahydro-1H-pyrido[4,3-b]carbazole-5-carboxylate (76)

—To a solution of hydroxymethyl aldehyde **58** (16 mg, 0.032 mmol) and ethanethiol (69 μL, 0.96 mmol) in CH₂Cl₂ (2.5 mL) at –50 °C was added a solution of TiCl₄ in CH₂Cl₂ (1.0 M, 0.10 mL, 0.10 mmol). The resulting dark orange-brown mixture was stirred while allowed to warm slowly to rt over 15 h. The reaction mixture was then diluted with CH₂Cl₂, treated with aqueous NaHCO₃, and extracted with CH₂Cl₂. The organic layers were washed with aqueous NH₄Cl and brine, and dried over Na₂SO₄. The solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel (gradient 10–50% EtOAc/hexanes) to afford dithioacetal **76** as a pink solid (18 mg, 94%). ¹H NMR (300 MHz, CDCl₃) δ 9.09 (br s, 1H), 8.15 (d, *J* = 6.3 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 2H), 7.36–7.33 (m, 3H), 7.22–7.12 (m, 2H), 4.70 (s, 1H), 4.19 (s, 3H), 4.13 (m, 1H), 3.63 (br m, 3H), 2.91 (m, 1H), 2.73 (q, *J* = 7.2 Hz, 4H), 2.44 (s, 3H), 2.23–2.12 (m, 3H), 1.31 (t, *J* = 7.2 Hz, 3H), 1.20 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 174.2, 144.5, 137.1, 132.7, 132.2, 130.2, 128.5, 127.0, 122.6, 122.0, 119.9, 111.8, 109.2, 77.7, 70.1, 56.1, 54.5, 52.9, 52.5, 28.7, 27.4,

22.0, 14.7 (2C); HRMS (m/z): $[M + Na]^+$ calcd for $C_{30}H_{38}N_2O_6S_3Na$, 641.1790; found 641.1792.

Methyl 12-(Ethylthio)-11a-hydroxy-2-tosyl-2,3,4,4a,5,6,11,11a-octahydro-1H-5,11-(methanooxymethano)pyrido[4,3-b]carbazole-5-carboxylate (77) and Methyl 12-(Ethylthio)-11a-hydroxy-2-tosyl-2,3,4,4a,5,6,11,11a-octahydro-1H-5,11-(methanooxymethano)pyrido[4,3-b]carbazole-5-carboxylate (78)—To a solution of dithioacetal **76** (130 mg, 0.21 mmol) in nitromethane (10 mL) at rt was added a mixture of 4Å MS and flame dried silica gel (1:1 wt. mixture, 390 mg), followed by solid $NaHCO_3$ (79 mg, 0.94 mmol). The mixture was stirred at rt for 40 min and then was treated dropwise with a solution of anhydrous $AgClO_4$ (131 mg, 0.63 mmol) in nitromethane (1.7 mL). The resulting brown suspension was stirred at rt until TLC indicated completion of the reaction (~30 min). The mixture was diluted with CH_2Cl_2 and EtOAc, filtered through a pad of Celite, and the filtrate was evaporated to dryness *in vacuo* to give a yellow powder. This powder was stirred with 10 mL of CH_2Cl_2 at rt for 10 min and filtered to give the major C18 diastereomer **77** as a white solid (77 mg, 66%). 1H NMR (400 MHz, DMSO-*d6*) δ 10.84 (br s, 1H), 7.44 (d, $J = 7.5$ Hz, 3H), 7.37 (d, $J = 7.6$ Hz, 1H), 7.17 (d, $J = 7.9$ Hz, 2H), 7.04 (app t, $J = 7.0$ Hz, 1H), 6.98 (app t, $J = 7.4$ Hz, 1H), 5.49 (d, $J = 3.1$ Hz, 1H), 5.26 (br s, 1H), 4.07 (d, $J = 11.4$ Hz, 1H), 3.89 (d, $J = 11.4$ Hz, 1H), 3.78 (s, 3H), 3.30 (d, $J = 12.2$ Hz, 2H), 3.22 (d, $J = 3.1$ Hz, 1H), 3.07 (t, $J = 12.7$ Hz, 1H), 2.46–2.36 (m, 3H), 2.30 (s, 3H), 2.37 (d, $J = 12.5$ Hz, 1H), 1.51 (d, $J = 11.0$ Hz, 1H), 1.10 (t, $J = 7.4$ Hz, 3H), 0.57 (m, 1H); ^{13}C NMR (100 MHz, DMSO-*d6*) δ 172.2, 143.6, 136.6, 136.3, 135.8, 130.2, 127.6, 126.9, 121.2, 119.9, 118.1, 113.1, 111.7, 110.2, 82.4, 77.5, 68.3, 54.9, 53.5, 51.9, 48.3, 47.5, 42.2, 25.7, 25.4, 21.8, 16.0.

The filtrate was concentrated to give a residue which was purified by flash chromatography on silica gel (gradient 20–50% EtOAc/hexanes) to afford the minor C18 diastereomer **78** as an off-white solid (23 mg, 20%). 1H NMR (400 MHz, $CDCl_3$) δ 9.48 (s, 1H), 7.63 (d, $J = 8.1$ Hz, 2H), 7.43 (d, $J = 8.0$ Hz, 1H), 7.36 (d, $J = 7.2$ Hz, 1H), 7.20 (d, $J = 8.0$ Hz, 2H), 7.11–7.16 (m, 2H), 5.58 (d, $J = 4.4$ Hz, 1H), 4.44 (d, $J = 11.3$ Hz, 1H), 4.02 (d, $J = 11.3$ Hz, 1H), 3.85 (s, 3H), 3.59 (d, $J = 13.5$ Hz, 1H), 3.30–3.36 (m, 2H), 3.28 (d, $J = 4.5$ Hz, 1H), 2.65 (d, $J = 13.5$ Hz, 1H), 2.62 (dd, $J = 4.6, 13.0$ Hz, 1H), 2.41–2.48 (m, 2H), 2.37 (s, 3H), 1.52 (m, 1H), 1.16 (t, $J = 7.4$ Hz, 3H), 0.97 (dd, $J = 5.7, 13.5$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 143.3, 136.0, 135.5, 135.2, 129.6, 127.5, 126.6, 121.9, 120.4, 117.9, 115.6, 112.8, 111.8, 109.9, 83.5, 77.9, 66.9, 54.6, 53.0, 50.5, 49.8, 46.8, 41.9, 25.4, 25.1, 21.6, 15.3; HRMS (m/z): $[M + H]^+$ calcd for $C_{28}H_{33}N_2O_6S_2$, 557.1775; found 557.1780.

Methyl 4-Tosyl-3,4,5,6,6a,7,8,12c-octahydro-1H-1,7-(epoxymethano)oxeto[2,3-c]pyrido[4,3-b]carbazole-7-carboxylate (79)—The major hemithioacetal **77** (1.8 mg, 0.0032 mmol) was heated with a slurry of freshly prepared W-2 Raney nickel in ethanol (~0.5 mL, excess) at 60 °C for 1 h. The reaction mixture was diluted with CH_2Cl_2 and filtered through a pad of Celite. The filtrate was concentrated to give oxetane acetal **79** as a colorless gum (1.0 mg, 63%). 1H NMR (360 MHz, $CDCl_3$) δ 9.49 (br s, 1H), 7.63 (d, $J = 7.2$ Hz, 2H), 7.44 (d, $J = 7.0$ Hz, 1H), 7.39 (d, $J = 7.2$ Hz, 1H), 7.17 (m, 3H), 6.80 (m, 1H), 4.36 (m, 1H), 4.17 (d, $J = 11.0$ Hz, 1H), 4.03 (m, 2H), 3.85 (s, 3H), 3.58 (m, 2H), 3.32 (m, 2H), 3.06 (app s, 1H), 2.68 (d, $J = 12.0$ Hz, 1H), 2.60 (m, 1H), 2.38 (s, 3H), 1.44 (m, 2H); HRMS (m/z): $[M + H]^+$ calcd for $C_{26}H_{27}N_2O_6S$, 495.1590, found 495.1572.

Methyl 11a-Hydroxy-2-tosyl-2,3,4,4a,5,6,11,11a-octahydro-1H-5,11-(methanooxymethano)pyrido[4,3-b]carbazole-5-carboxylate (80)—To a solution of major hemithioacetal **77** (13.6 mg, 0.0245 mmol) in acetone (5.0 mL) was added 10% Pd/C (75 mg) and triethylsilane (0.7 mL, excess). The reaction mixture was heated at reflux.

Additional Pd/C and triethylsilane were added every 2 h until TLC indicated completion of the reaction (6 additions of 10% Pd/C and Et₃SiH were required in total). The reaction mixture was then filtered through a pad of Celite and the filtrate was concentrated *in vacuo* to give a residue which was purified by flash column chromatography on silica gel (gradient 5–10% EtOAc/hexanes, then 30% EtOAc/hexanes, then 5% Et₂O/CH₂Cl₂, then 50% EtOAc/hexanes) to afford oxepane **80** as a white foamy solid (11.4 mg, 94%). ¹H NMR (400 MHz, CDCl₃) δ 9.49 (s, 1H), 7.62 (d, *J* = 8.1 Hz, 2H), 7.44 (d, *J* = 7.6 Hz, 1H), 7.39 (d, *J* = 7.9 Hz, 1H), 7.21 (d, *J* = 8.1 Hz, 2H), 7.11–7.17 (m, 2H), 4.38 (dd, *J* = 3.7, 11.4 Hz, 1H), 4.17 (d, *J* = 11.4 Hz, 1H), 3.84 (s, 3H), 3.83 (d, *J* = 11.4 Hz, 1H), 3.58 (d, *J* = 13.4 Hz, 1H), 3.54 (dd, *J* = 1.8, 11.3 Hz, 1H), 3.25–3.37 (m, 2H), 3.06 (t, *J* = 1.8 Hz, 1H), 2.67 (d, *J* = 13.3 Hz, 1H), 2.60 (dd, *J* = 4.5, 13.1 Hz, 1H), 2.36 (s, 3H), 1.48 (m, 1H), 0.95 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 173.0, 143.7, 135.8, 135.6, 135.4, 130.0, 127.8, 125.5, 122.0, 120.3, 117.9, 114.4, 112.5, 112.0, 74.2, 68.0, 55.4, 53.2, 52.7, 51.6, 42.4, 42.3, 25.5, 21.9, 18.4; HRMS (*m/z*): [*M* + *H*]⁺ calcd for C₂₆H₂₉N₂O₆S, 497.1746; found 497.1753. The minor hemithioacetal **78** could be converted to oxepane **80** under the same reaction conditions in essentially identical yield.

Synthesis of (±)-Alstilobanine E (2)

Magnesium turnings (451 mg, excess) were added to a solution of sulfonamide-protected oxepane **80** (20 mg, 0.040 mmol) in anhydrous methanol and the mixture was sonicated at rt until all the magnesium had dissolved (~45 min). The reaction mixture was then poured into aqueous NH₄Cl at 0 °C, and extracted with CHCl₃. The organic extract was dried over Na₂SO₄, and evaporated to dryness *in vacuo*. The residue was purified by flash chromatography on silica gel (gradient 1–5% MeOH/CH₂Cl₂, then 1% NEt₃ in 5% MeOH/CH₂Cl₂, then 1% NEt₃ in 10% MeOH/CH₂Cl₂) to afford racemic alstilobanine E (**2**) as an off-white solid (13 mg, 95%). ¹H NMR (400 MHz, CD₃OD, 1 μL of TFA added) δ 7.90 (s, 1H), 7.47 (d, *J* = 8.6 Hz, 1H), 7.43 (d, *J* = 9.0 Hz, 1H), 7.10 (dd, *J* = 7.0, 7.4 Hz, 1H), 7.03 (dd, *J* = 7.0, 7.3 Hz, 1H), 4.31 (dd, *J* = 3.0, 11.4 Hz, 1H), 4.14 (d, *J* = 11.4 Hz, 1H), 3.90 (s, 3H), 3.84 (d, *J* = 11.4 Hz, 1H), 3.57 (dd, *J* = 3.0, 11.6 Hz, 1H), 3.24 (m, 1H), 3.20 (m, 1H), 2.96 (d, *J* = 13.0 Hz, 1H), 2.74 (dd, *J* = 5.2, 13.0 Hz, 1H), 2.61 (d, *J* = 13.1 Hz, 1H), 1.69–1.74 (m, 1H), 1.19 (dddd, *J* = 5.9, 13.1, 13.3, 13.9 Hz, 1H); ¹³C NMR (100 MHz, CD₃OD) δ 172.9, 137.8, 135.3, 126.4, 122.4, 120.6, 118.0, 113.0, 112.5, 75.6, 75.4, 67.2, 56.1, 53.2, 51.5, 49.0, 43.9, 39.8, 23.3; HRMS (*m/z*): [*M* + *H*]⁺ calcd for C₁₉H₂₃N₂O₄, 343.1652; found 343.1658.

Synthesis of (±)-Angustilodine (1)

Alstilobanine E (**2**) (10.4 mg, 0.0304 mmol) and paraformaldehyde (6.4 mg, ~7 equiv.) were stirred in methanol (3.0 mL) and treated with glacial acetic acid (7.5 μL) at rt. The resulting white suspension was stirred at rt for another 30 min, and solid NaBH₄ was added every 60 min (4.0 mg, 0.105 mmol in each portion, 3 h total) until TLC (1% NEt₃ in 5% MeOH/CH₂Cl₂) indicated completion of the reaction. The reaction mixture was treated with aqueous NH₄Cl, and was extracted with CHCl₃. The combined organic layers were washed with aqueous NaHCO₃, brine, and dried over Na₂SO₄. The solvent was removed *in vacuo* to give a residue which was purified by flash chromatography on silica gel (gradient 1–5% MeOH/CH₂Cl₂, then 1% NEt₃ in 5% MeOH/CH₂Cl₂) to afford racemic angustilodine (**1**) as an off-white gum (8.8 mg, 81%). ¹H NMR (400 MHz, CDCl₃) δ 9.55 (s, 1H), 7.47 (d, *J* = 7.6 Hz, 1H), 7.42 (d, *J* = 7.8 Hz, 1H), 7.17 (app t, *J* = 8.0 Hz, 1H), 7.12 (app t, *J* = 7.6 Hz, 1H), 4.39 (dd, *J* = 2.1, 11.3 Hz, 1H), 4.12 (d, *J* = 11.4 Hz, 1H), 3.86 (d, *J* = 11.4 Hz, 1H), 3.84 (s, 3H), 3.55 (dd, *J* = 3.3, 11.3 Hz, 1H), 3.06 (app t, *J* = 3.0 Hz, 1H), 3.03 (m, 1H), 2.66 (dd, *J* = 4.4, 13.1 Hz, 1H), 2.36 (d, *J* = 11.9 Hz, 1H), 2.31 (d, *J* = 11.3 Hz, 1H), 2.28 (m, 1H), 2.26 (s, 3H), 1.32 (m, 1H), 0.98 (m, 1H); ¹³C NMR (212.5 MHz, CDCl₃) δ 173.3, 135.5, 135.0, 125.6, 121.2, 119.7, 117.4, 111.7, 111.3, 76.5, 72.9, 66.2, 61.0, 55.2, 52.6,

52.3, 49.9, 45.4, 41.9, 24.8; HRMS (m/z): $[M + H]^+$ calcd for $C_{20}H_{25}N_2O_4$, 357.1809, found 357.1806.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

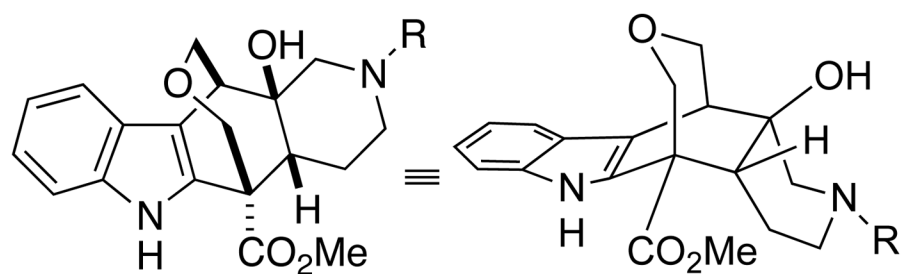
Acknowledgments

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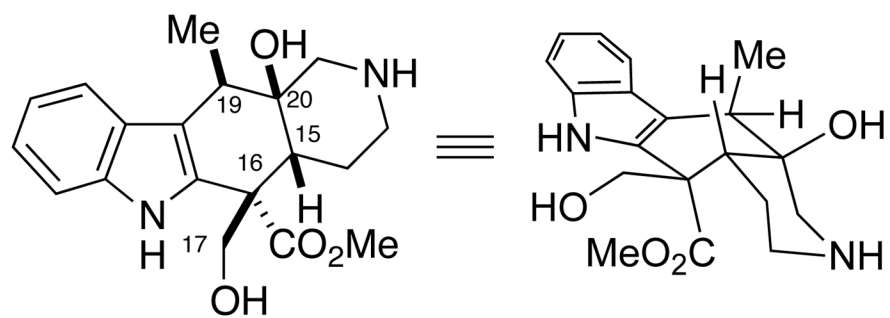
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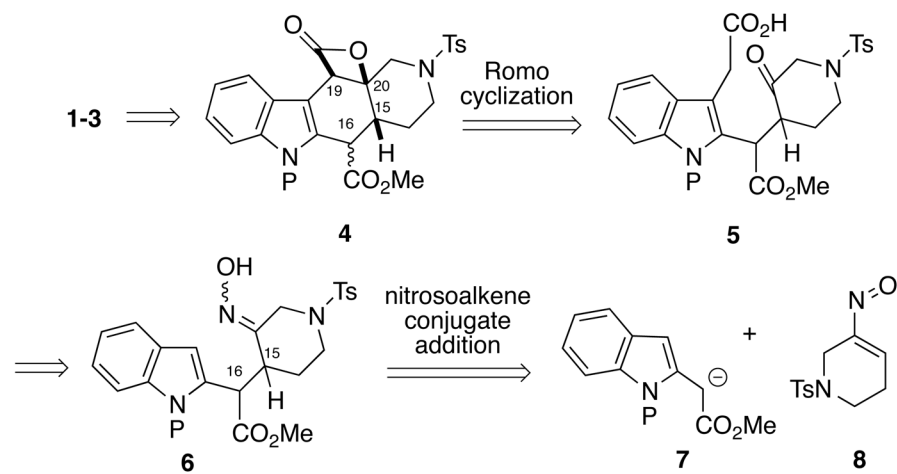


1 R = Me angustilodine
2 R = H alstilobanine E

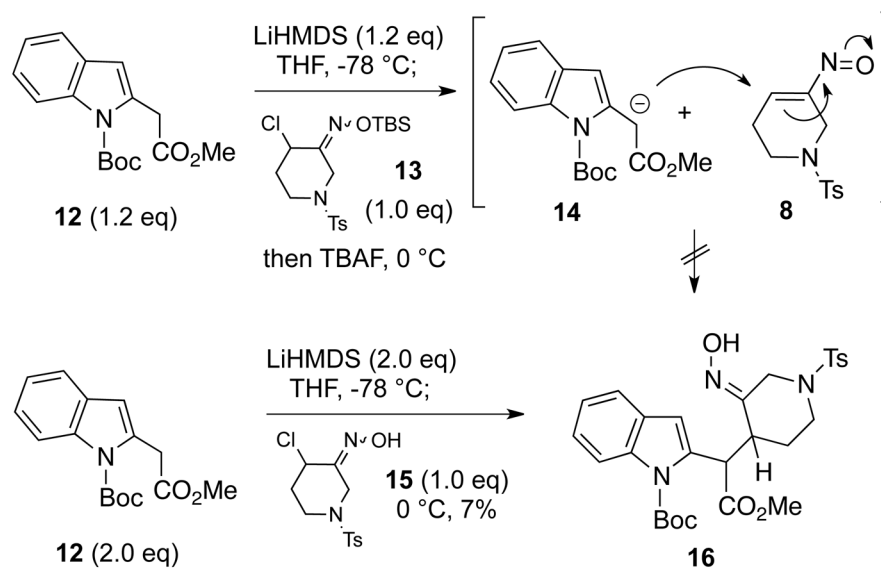


3 alstilobanine A

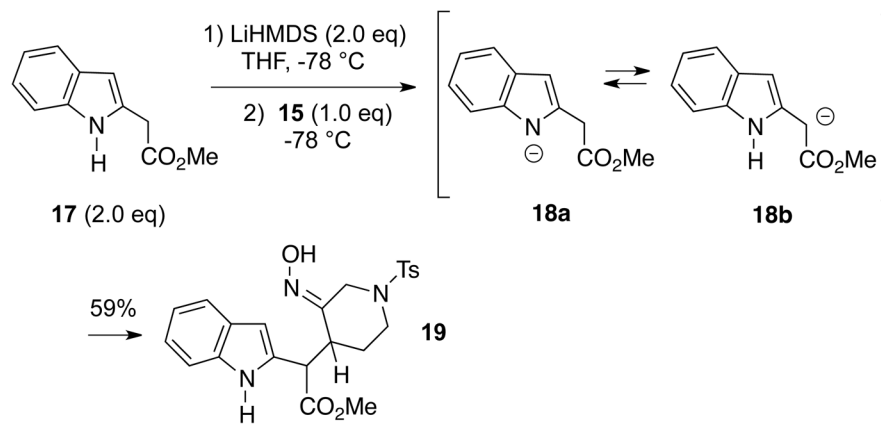
Figure 1. Structures and conformations of the alstilobanine/angustilodine alkaloids.



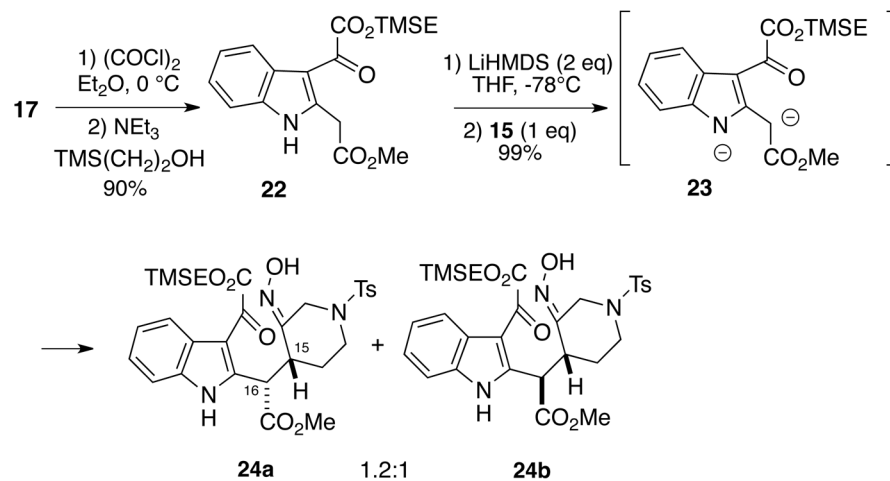
Scheme 1.
First Generation Retrosynthetic Analysis of Alkaloids 1-3



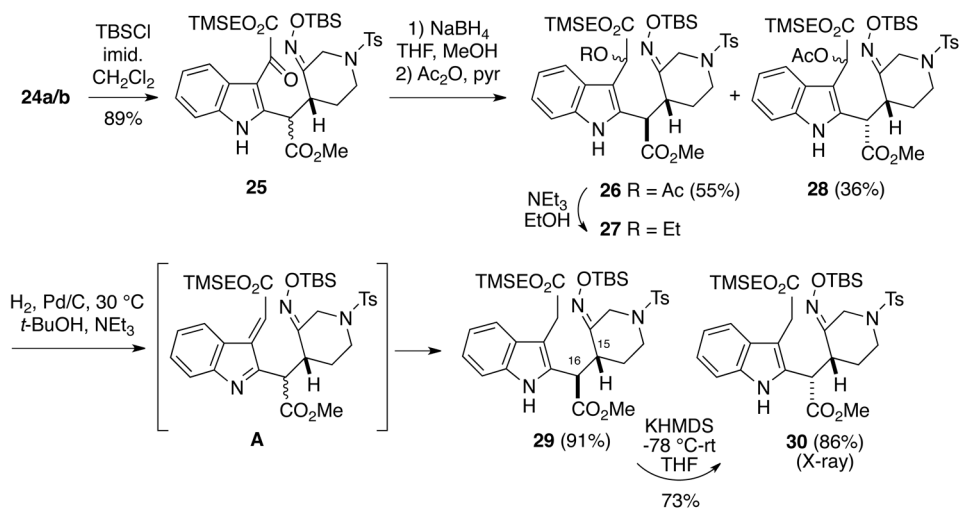
Scheme 2.
Attempted Enolate/Nitrososalkene Conjugate Addition



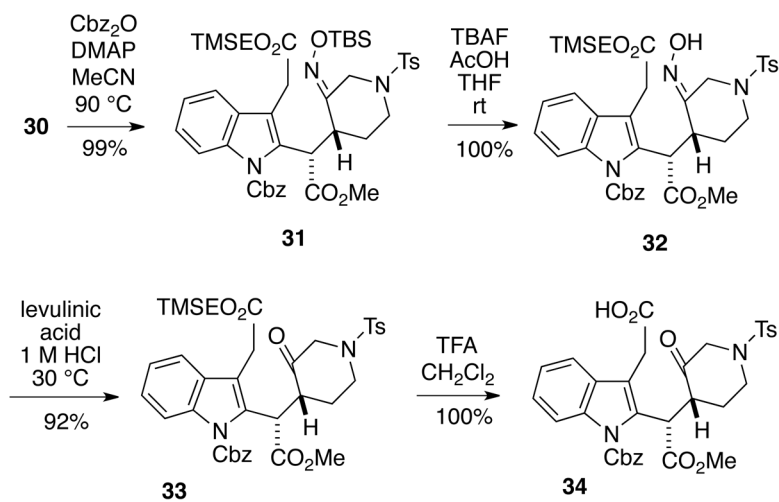
Scheme 3.
Successful Enolate/Nitrososalkene Conjugate Addition



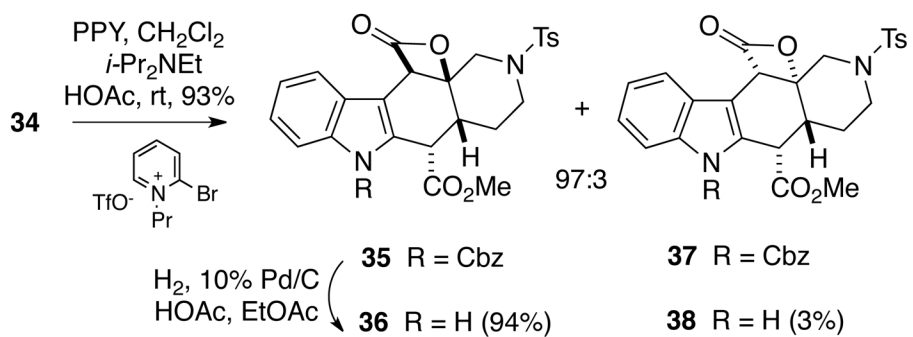
Scheme 4.
Efficient Nitrosoalkene Conjugate Addition to Form Adducts **24a/b**



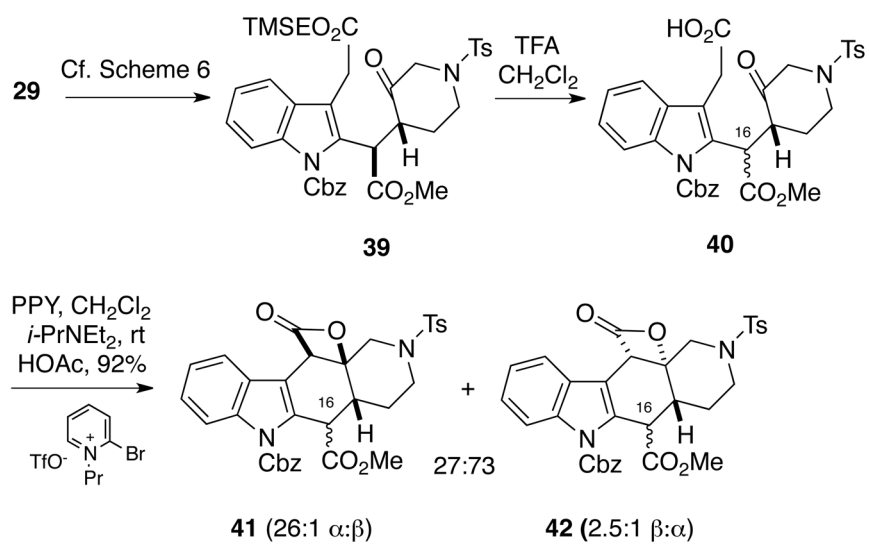
Scheme 5.
Elaboration of Adducts **24a/b** into Intermediate **30**



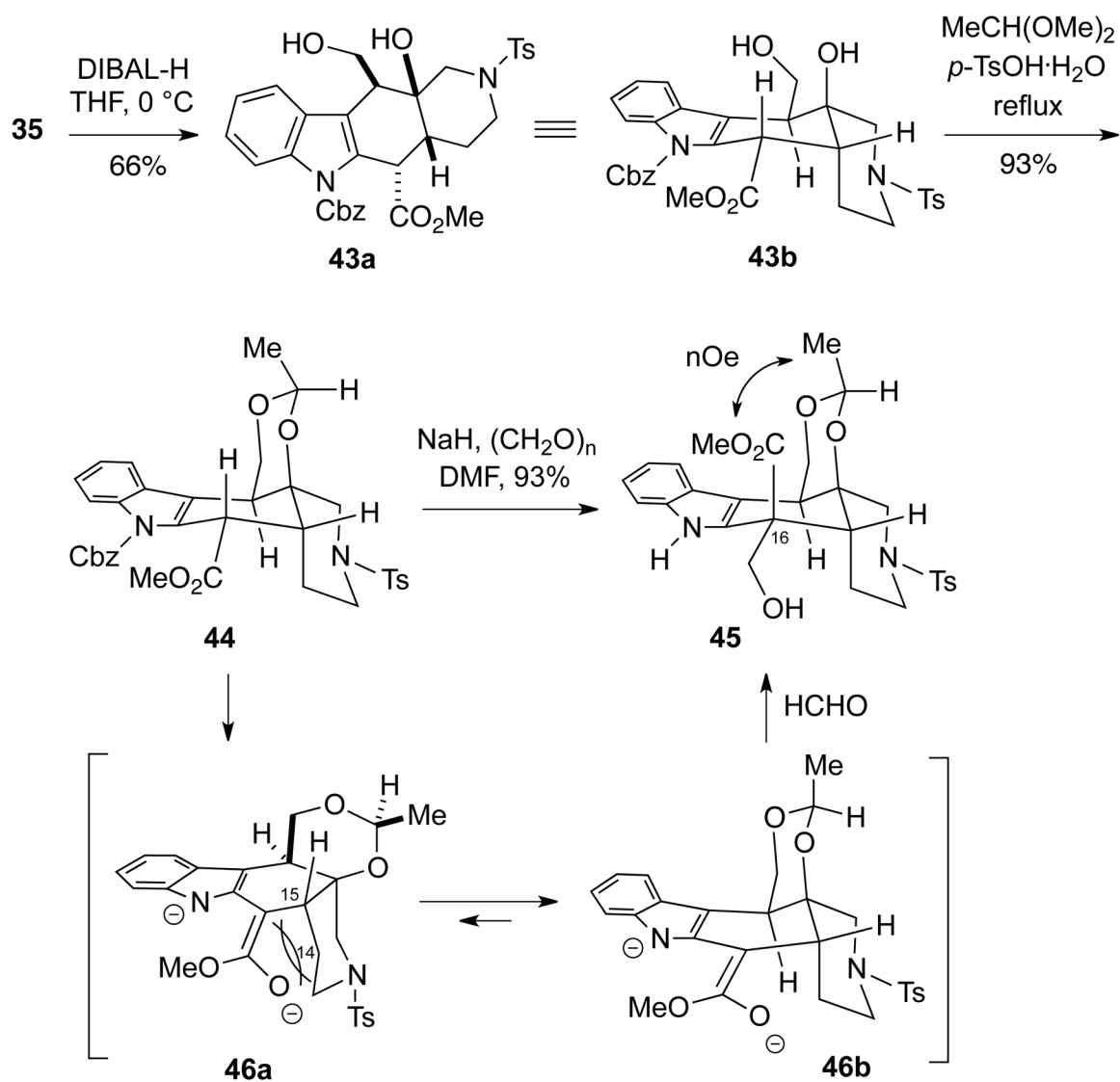
Scheme 6.
Preparation of Ketoacid **34** for the Romo Cyclization



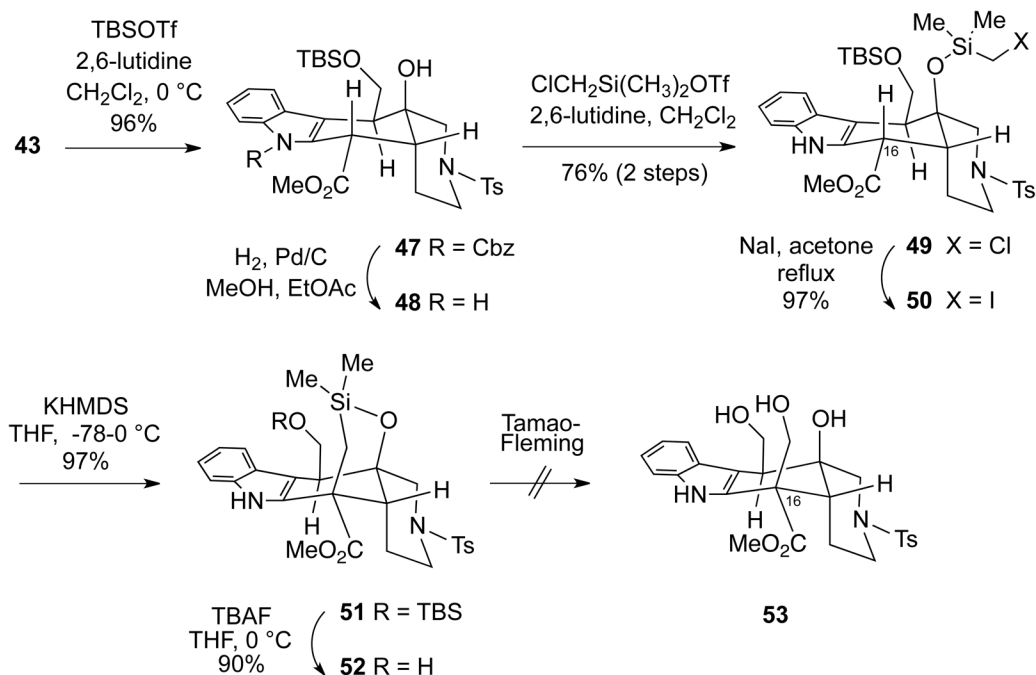
Scheme 7.
Intramolecular Romo Cyclization of Ketoacid **34**



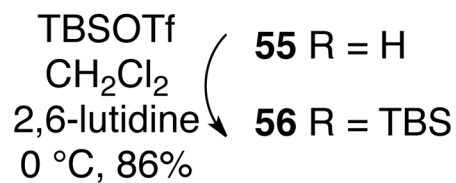
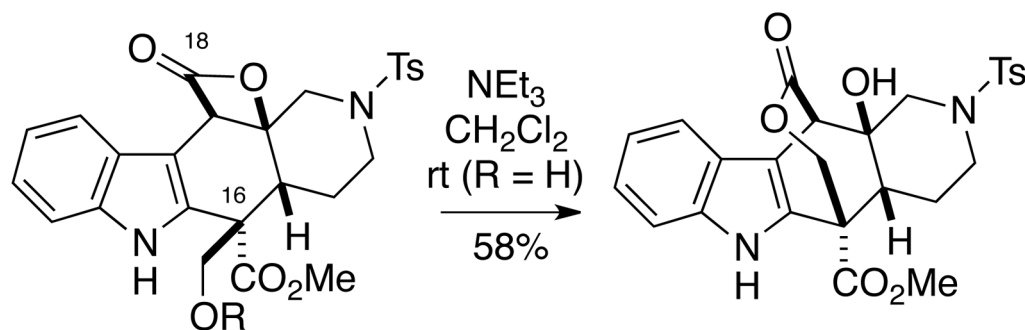
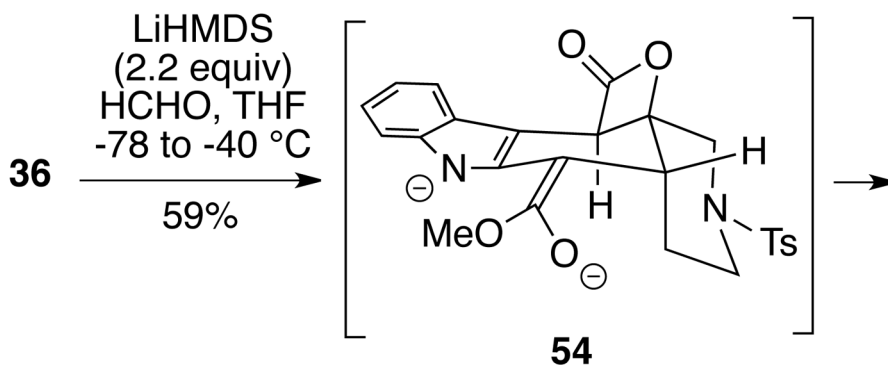
Scheme 8.
Romo Cyclization of the Ketoacid Diastereomer



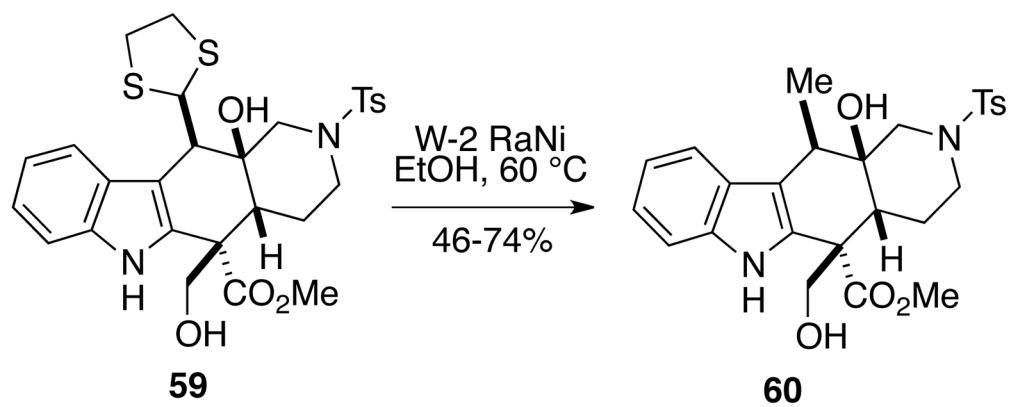
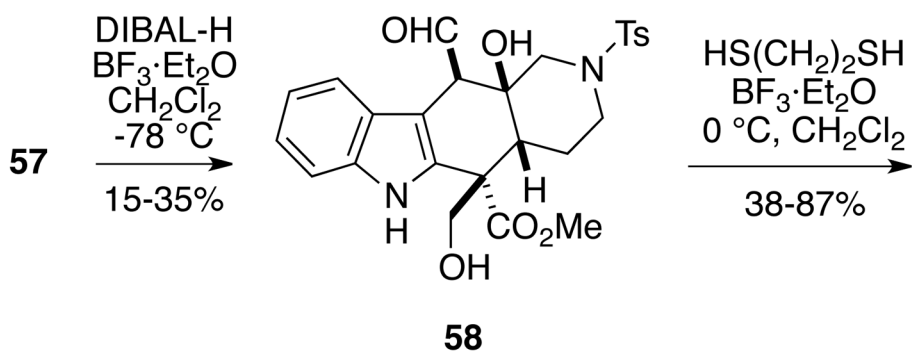
Scheme 9.
Hydroxymethylation of Dianion **46** to the Undesired Stereoisomer **45**



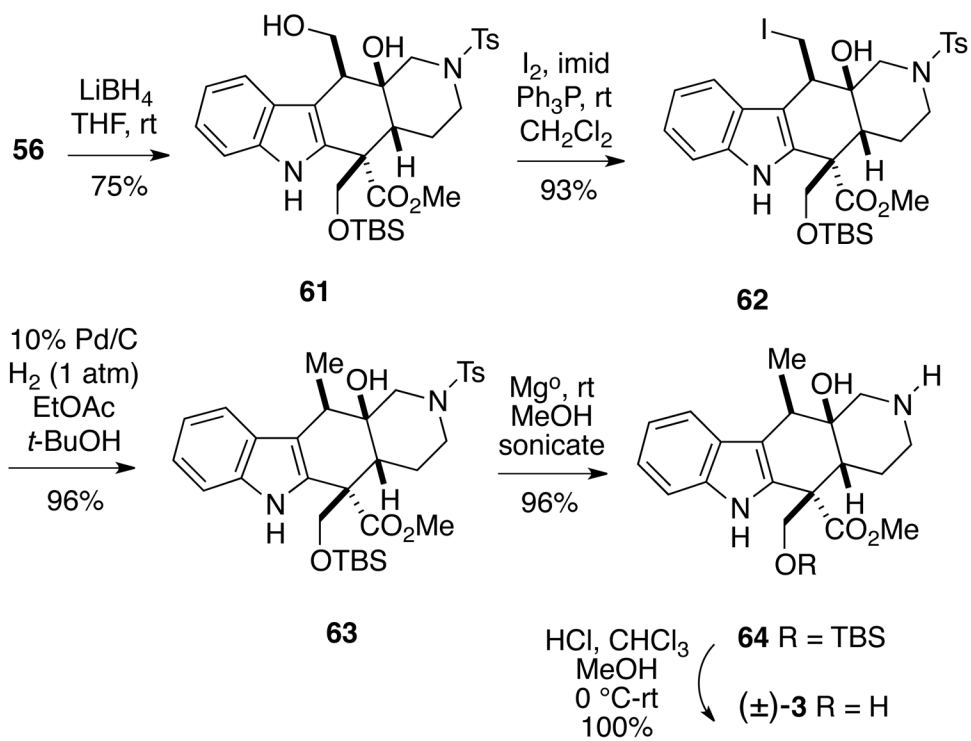
Scheme 10.
Intramolecular Alkylation of a Silicon-Tethered Iodomethyl Compound



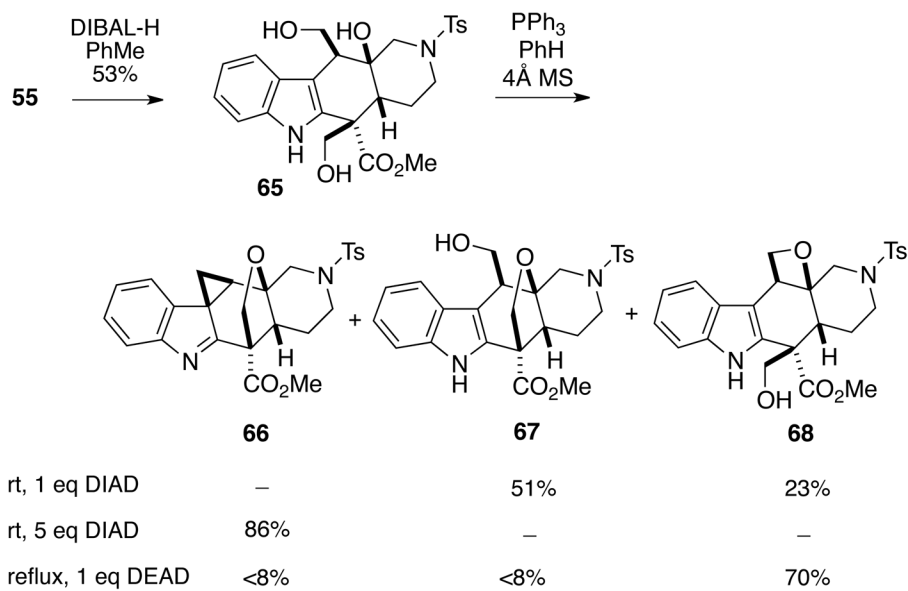
Scheme 11.
Stereoselective Hydroxymethylation of Dianion **54**



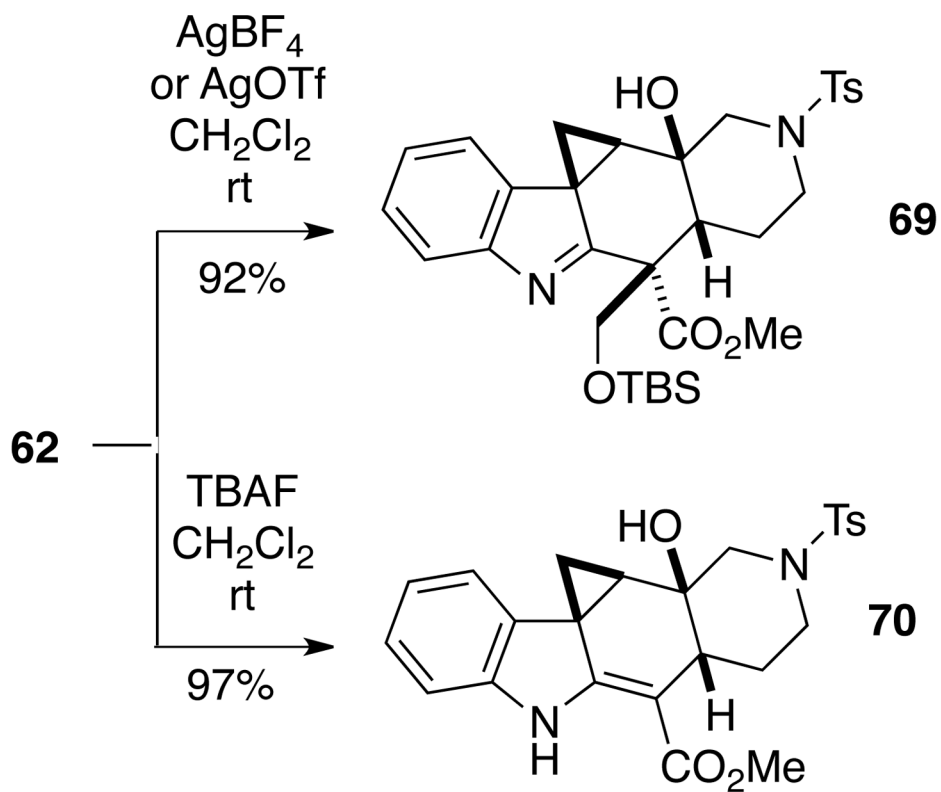
Scheme 12.
Formation of a C18 Methyl Group



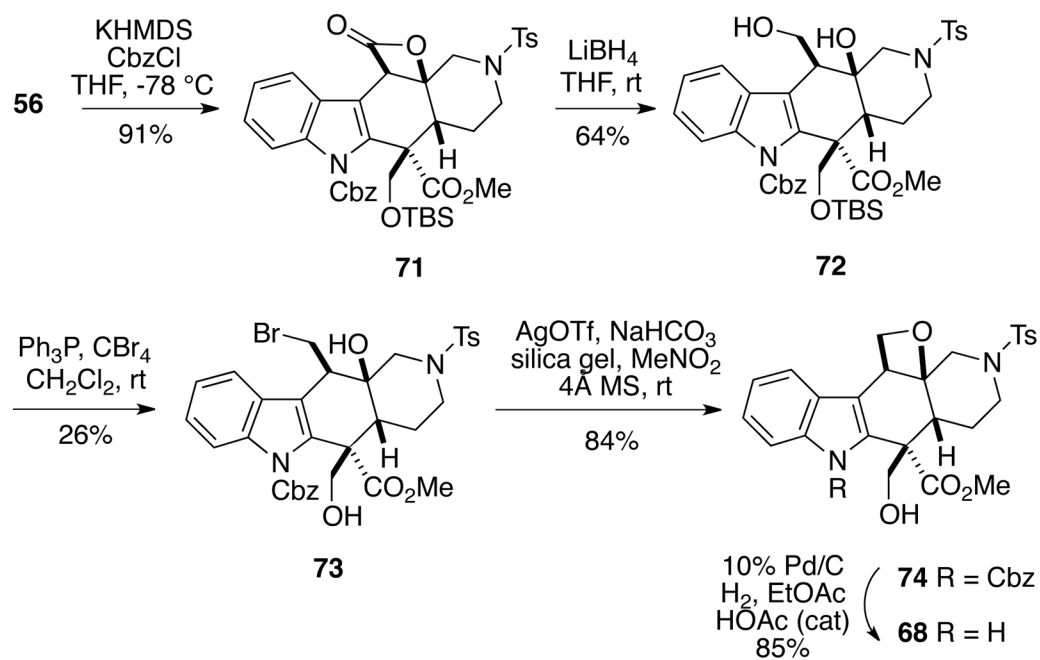
Scheme 13.
Completion of the Total Synthesis of Alstilobanine A



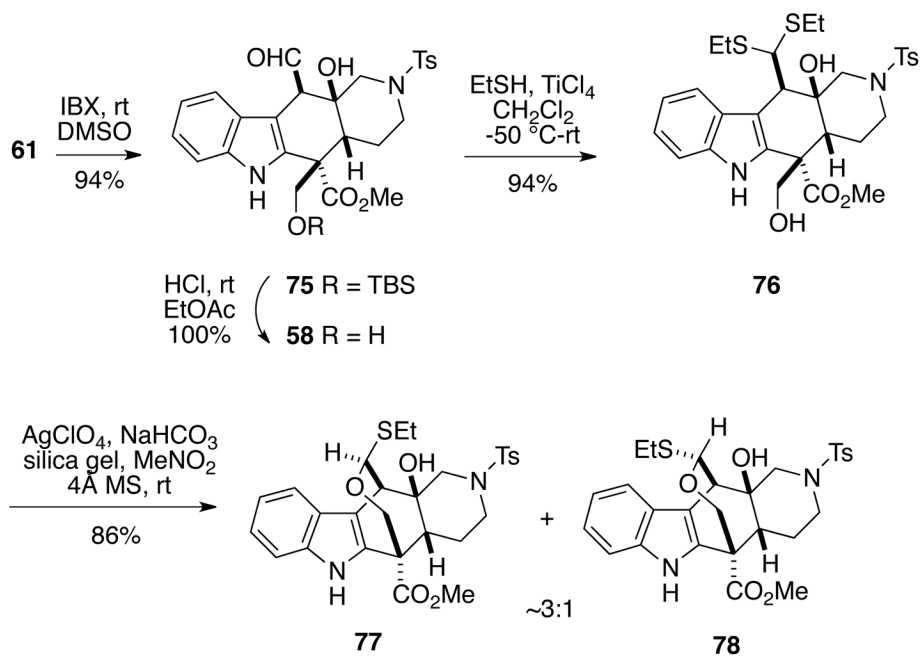
Scheme 14.
Attempts to Form an Oxepane via a Mitsunobu Process



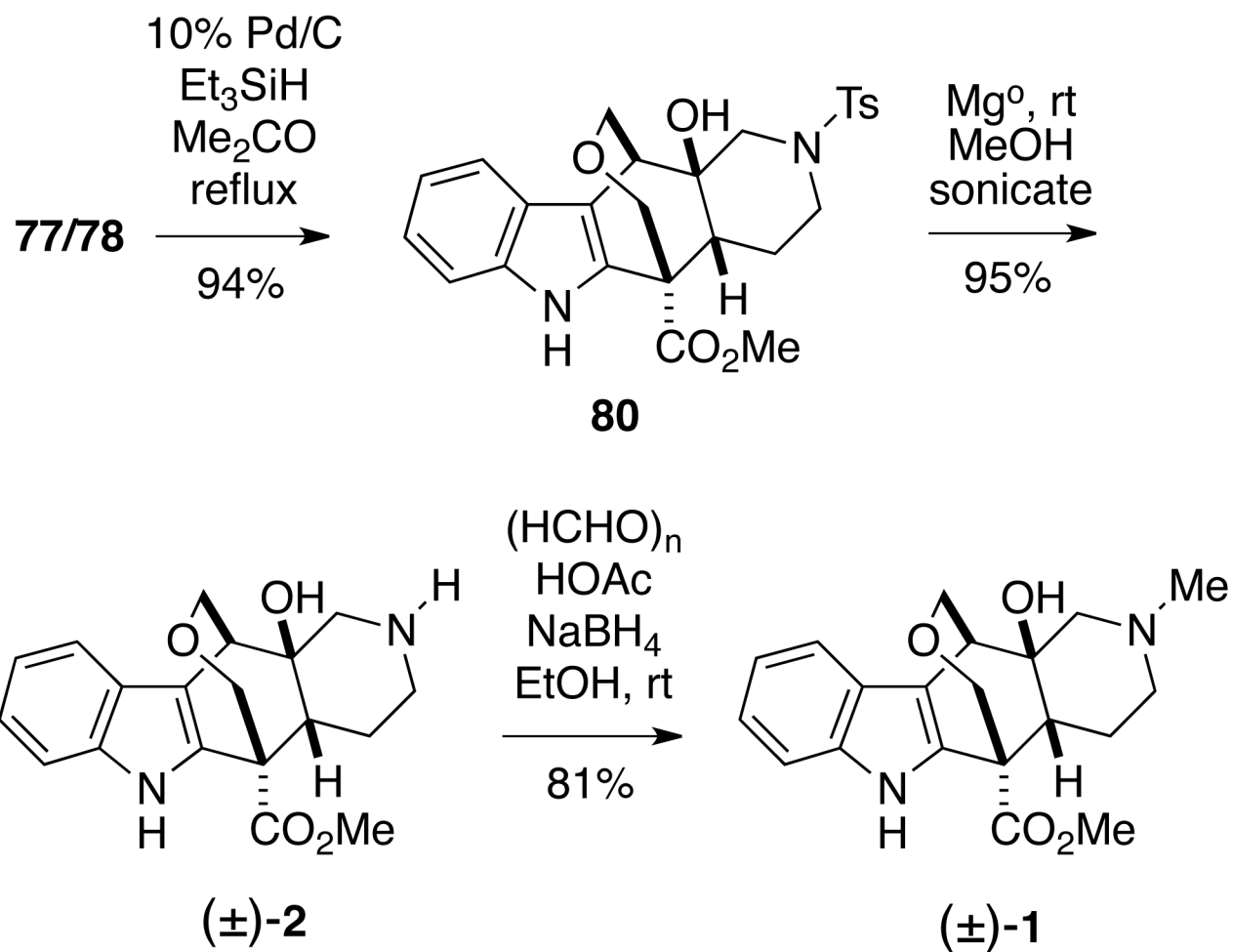
Scheme 15.
Additional Attempts at Oxepane Formation



Scheme 16.
Oxetane Formation from Bromomethyl Alcohol **73**



Scheme 17.
Formation of a Seven-Membered Hemithioacetal



Scheme 18.
Completion of the Total Syntheses of Alstilobanine E and Angustilodine