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General Strategy for Synthesis of C-19 Methyl-Substituted *Sarpagine/Macroline/Ajmaline* Indole Alkaloids Including Total Synthesis of 19(*S*),20(*R*)-Dihydroperaksine, 19(*S*),20(*R*)-Dihydroperaksine-17-al, and Peraksine

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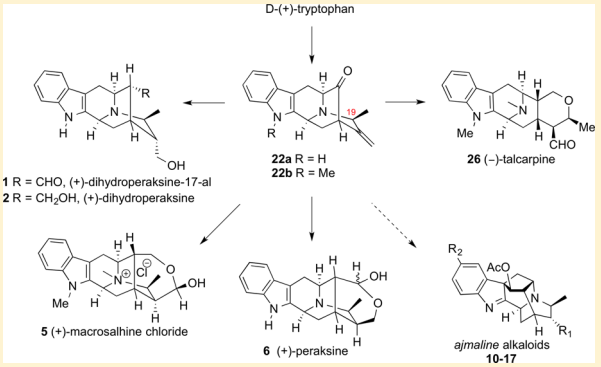
Supporting Information

ABSTRACT: A detailed account of the development of a general strategy for synthesis of the C-19 methyl-substituted alkaloids including total synthesis of 19(*S*),20(*R*)-dihydroperaksine-17-al (**1**), 19(*S*),20(*R*)-dihydroperaksine (**2**), and peraksine (**6**) is presented. Efforts directed toward the total synthesis of macrosalhine chloride (**5**) are also reported. Important to success is the sequence of chemical reactions which include a critical haloboration reaction, regioselective hydroboration, and controlled oxidation (to provide sensitive enolizable aldehydes at C-20). In addition, the all-important Pd-catalyzed α-vinylation reaction has been extended to a chiral C-19 alkyl-substituted substrate for the first time. Synthesis of the advanced intermediate **64** completes an improved formal total synthesis of talcarpine (**26**) and provides a starting point for synthesis of *macroline*-related alkaloids **27**−**31**. Similarly, extension of this synthetic strategy in the ring A oxygenated series should provide easy access to the northern hemisphere **32b** of the bisindoles angustricraline, alstocraline, and foliacraline (Figure 4).



INTRODUCTION

The C-19 methyl-substituted indole alkaloids represented in Figure 1 are a relatively rare class of alkaloids belonging to the *sarpagine*−*ajmaline* series[1] with over 17 members isolated to date.[2] In addition to the asymmetric centers at C-3(*S*), C-5(*S*), and C-15(*R*) of the *sarpagine*/*ajmaline* framework, these alkaloids share a distinctive feature which is the presence of a β-methyl group at C-19. The *sarpagine* indole alkaloids (+)-19(*S*),20(*R*)-dihydroperaksine-17-al (**1**), (+)-19(*S*),20(*R*)-dihydroperaksine (**2**), and (+)-10-hydroxydihydroperaksine (**3**) were isolated from the hairy root culture of *Rauwolfia serpentina* by Stöckigt et al.[3] The root of *Rauwolfia serpentina* Benth (N.0.Apocyanaciae) has been in use in India for hundreds of years for a host of unrelated ailments.[4] The plant has gained universal acclamation as a useful therapeutic agent in the treatment of high blood pressure.[5] The presence of high concentrations of alkaloids and other phytochemicals has provided a basis for the ethnomedical use of this plant in treating various medical conditions.[6] *O*-Acetyl preperakine (**4**) was isolated from the stem bark of *Rauwolfia volkensii* by Akinloye et al.[7] However, the stereochemistry of the C-19 methyl and C-20 aldehydic groups was not determined during isolation. The presence of a hexacyclic hemiacetal ring is a unique feature of the C-19 methyl-substituted alkaloids macrosalhine chloride **5** (isolated from *Alstonia macrophylla*),[8] peraksine **6** (isolated from *Rauwolfia perakensis*),[9] verticillatine **7** (isolated from *Rauwolfia verticillata*),[10] and alstoyunine A (**8**) and B **9** (isolated from *Alstonia yunnanensis*).[11] Perakine **10** (isolated from *Rauwolfia vomitoria*),[12] raucaffrinoline **11** (isolated from *Rauwolfia caffra*),[13] 10-methoxyperakine (**12**) and vincawajine **14** (isolated from *Vinca major*),[14] 10-methoxyraucaffrinoline **13** (isolated from *Vinca herbacea*),[15] rauvotetraphylline D **15** (isolated from *Rauwolfia tetraphylla*),[16] as well as alstoyunine C (**16**) and D **17** (isolated from *Alstonia yunnanensis*)[11] are the eight *ajmaline*-related alkaloids which also belong to this group.

The *sarpagine* group[1a] of alkaloids (represented by **18**) is the largest class of natural products related to the *macroline*[17] and *ajmaline*[1b] bases, and both series originate from common biogenetic intermediates. *Sarpagine* alkaloids can be converted to *macroline* **19** by a retro-Michael reaction or a Hoffmann elimination[18] reaction of the N_b-methyl intermediate of **18a**/**b**, as demonstrated by LeQuesne et al.[19] and latter confirmed in Milwaukee,[20] whereas a biogenetic connection between the *sarpagine* and the *ajmaline* alkaloids was confirmed by

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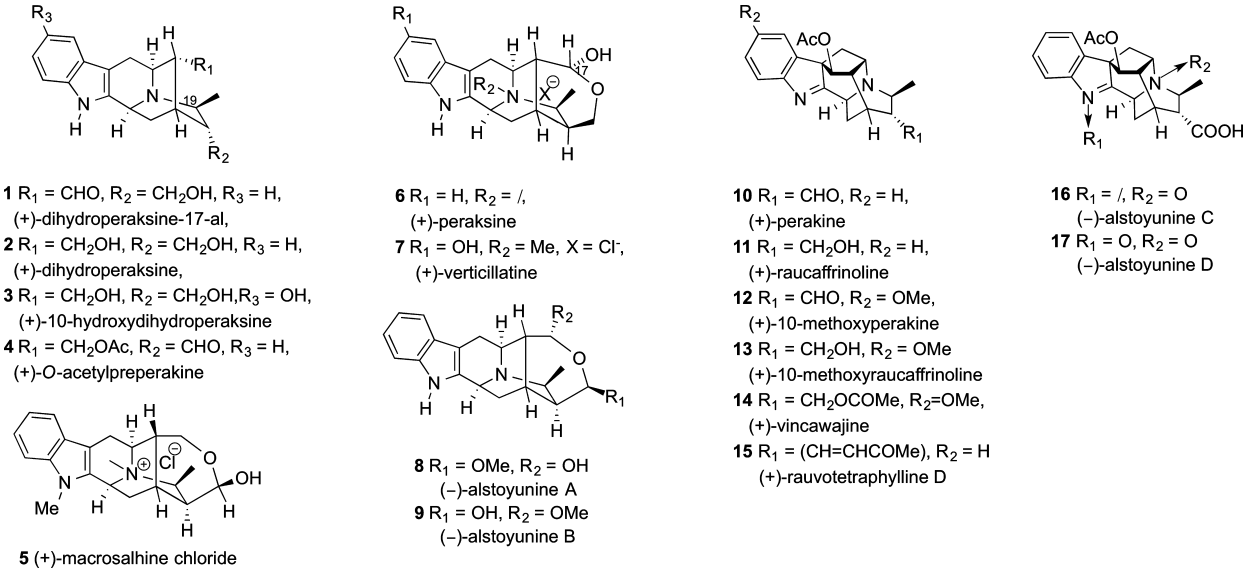
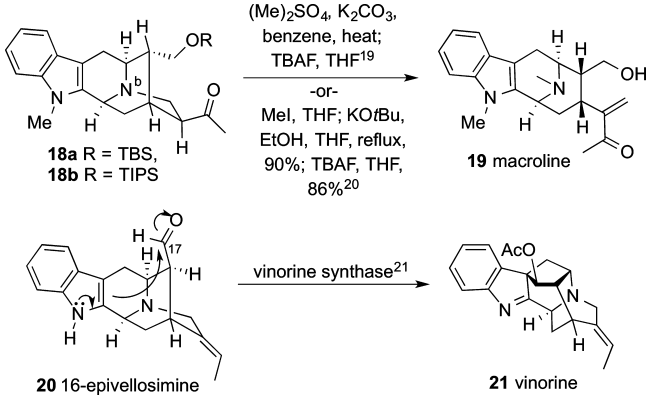


Figure 1. *Sarpagine-ajmaline* alkaloids containing a C-19(*S*) methyl group.

conversion of 16-epivellosimine **20** into vinorine **21** by Stöckigt et al. (Scheme 1).[21]

Scheme 1. Biomimetic and Biosynthetic Relationship between the *Sarpagine, Macroline,* and *Ajmaline* Alkaloids



Based on this, the C-19 methyl-substituted basic *sarpagine* framework **22** (Figure 2) could serve as the key template for synthesis of the *ajmaline* alkaloids **10**−**17** and the *macroline* bases **22**−**31** (Figure 3).[16,17,22] Extension of this synthetic strategy to the ring-A oxygenated series should provide the macroline intermediate **32b**, the northern hemisphere of the

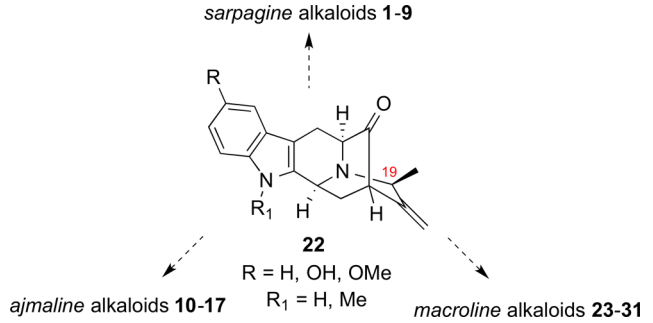


Figure 2. Pentacyclic intermediates **22**.

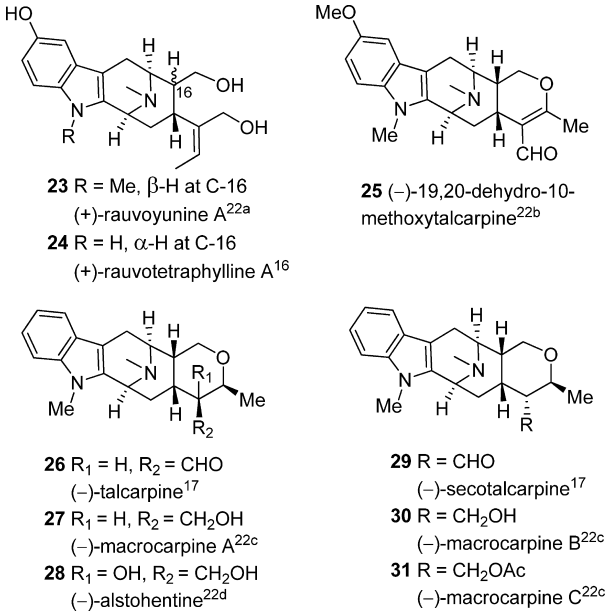


Figure 3. *Macroline*-related indole alkaloids.[16,17,22]

bisindoles (+)-angusticraline, (+)-alstocraline, and (+)-foliacraline (Figure 4).[22b,23] Herein we provide a detailed account of the development of a general strategy for synthesis of the C-19 methyl-substituted alkaloids including total synthesis of (+)-19-(*S*),20(*R*)-dihydroperaksine (**1**),[24] (+)-19(*S*),20(*R*)-dihydroperaksine-17-al (**2**),[24] (+)-peraksine (**6**), and formal total synthesis of (−)-talcarpine (**26**) as well as efforts directed toward total synthesis of (+)-macrosalhine chloride (**5**).

RESULTS AND DISCUSSION

As illustrated in Scheme 2, in a retrosynthetic sense, dihydroperaksine-17-al (**1**) and dihydroperaksine (**2**) could presumably be obtained from **36** by an oxidation/epimerization/reduction sequence. The β-primary alcohol in **36** could also serve as the precursor for peraksine (**6**) and can be expected to originate from the terminal olefinic moiety in aldehyde **35a** via a regioselective hydroboration process. The

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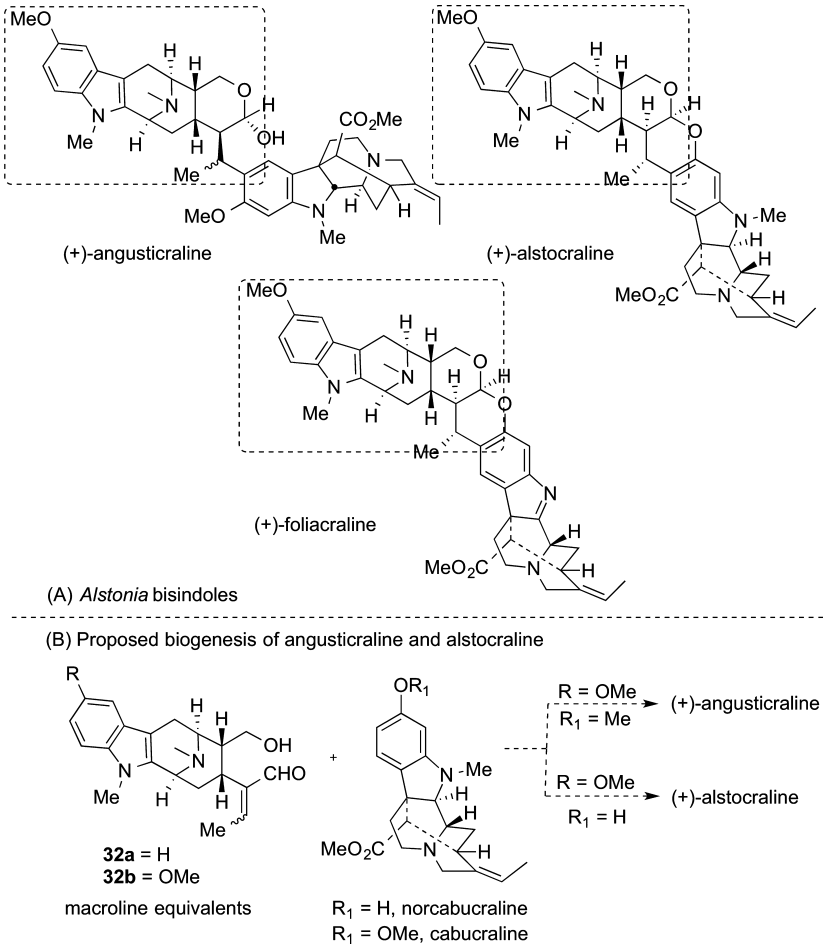
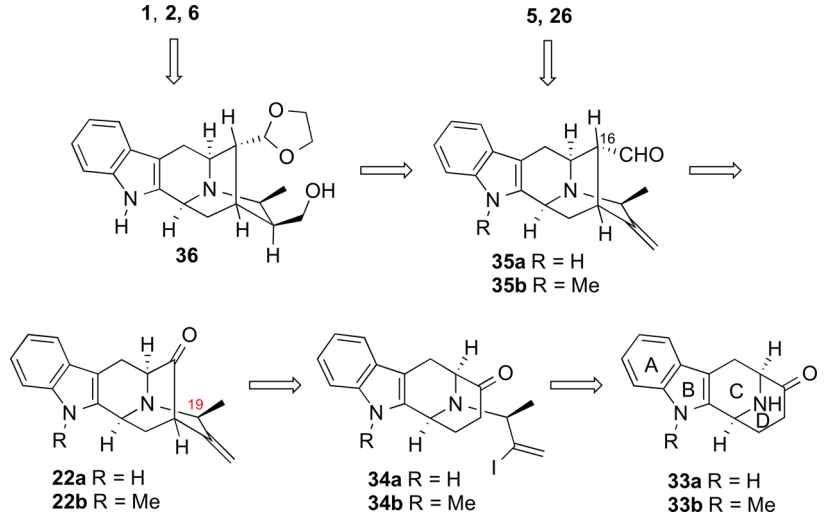


Figure 4. *Alstonia* bisindoles and their proposed biogenesis.

Scheme 2. Retrosynthetic Analysis



thermodynamically stable α-aldehydes at C-16 would arise via homologation of the pentacyclic ketones **22a/b**, which should be accessible via the recently modified α-vinylation process from iodides **34a/b**. The chiral methyl group could be introduced by alkylating the asymmetric N_b-H tetracyclic ketones **33a/b** with a suitably substituted optically active unit.

As planned, the basic tetracyclic core of the N_a-H/N_a-Me tetracyclic ketones **33a/b**, which contained rings ABCD required for synthesis of the C-19 methyl-substituted *sarpagine* indole alkaloids, was constructed enantiospecifically and stereospecifically via the asymmetric Pictet–Spengler/Dieckmann protocol on a 400 g scale (from the commercially available D-(+)-tryptophan) following the procedure developed in Milwaukee.[25] Inclusion of the C-19 β-methyl group in the *sarpagine* skeleton required synthesis of a suitably protected *R*-acetylenic alcohol **40** in high optical purity (Scheme 3). Several

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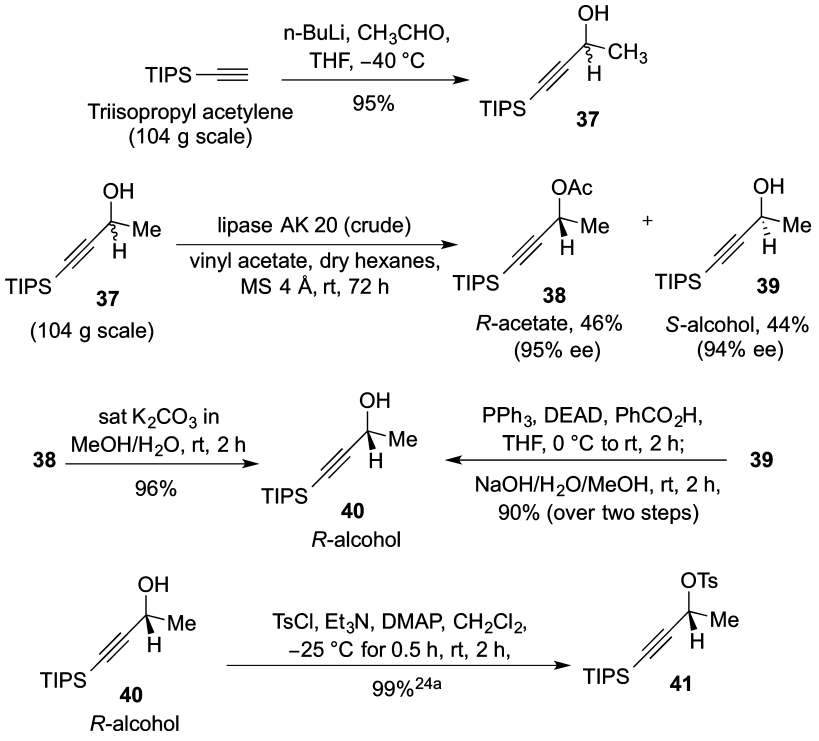
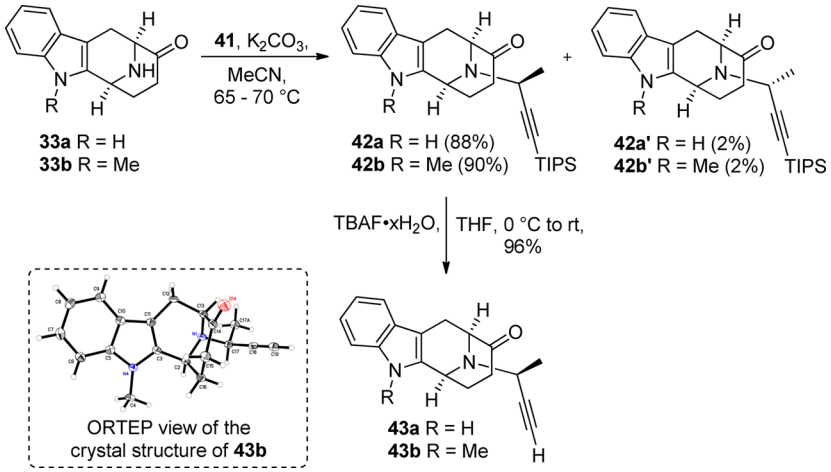
Scheme 3. Lipase-Mediated Kinetic Resolution of Racemic Alcohol 37



Scheme 4. Synthesis of the Acetylenic Ketones 43a/b



methods have been reported for synthesis of enantiomerically enriched alkynols.[26] However, many of these approaches are not completely satisfactory because of low or moderate chemical yields and/or enantioselectivity, especially those observed for the substrate, 1-alkyn-3-ol, which has been attributed to the small difference between the medium and the large substituents.[27] Although the enzymatic resolution of 1-alkyn-3-ols with a long alkyl chain was successful, this method was difficult to apply to short chain analogs such as 3-butyn-2-ol because of poor enantioselectivities.[26g] This prompted us to employ the 1-trialkylsilyl-1-alkyn-3-ols instead as the chiral unit for introduction of the C-19 methyl group into the *sarpagine* framework. The 1-trialkylsilyl-1-alkyn-3-ols have been synthesized in higher enantiomeric excess (ee) and high yield by lipase-mediated kinetic resolutions of the racemic alcohols[28] as well as by asymmetric reduction of the corresponding ketone.[24,26e,h,29] Because of the potential loss of material which results from the low volatility of the TMS-propargylic alcohols, it was decided to synthesize the more stable TIPS analog. Our initial report on synthesis of the optically active TIPS propargylic alcohol **40** began with the asymmetric Noyori hydrogenation, which when performed on a 25 g scale resulted in **40** with an erosion of ee (80% ee).[24] In this paper, the lipase-mediated kinetic resolution has been developed as an alternative approach for synthesis of **40**, which can be performed on a large scale with higher ee (>95%). As illustrated in Scheme 3, synthesis of **40** began with large-scale preparation of the racemic TIPS-acetylenic alcohol **37** from commercially available TIPS acetylene following the procedure of Jones et al.[30]

The racemic alcohol **37** on treatment with vinyl acetate in distilled hexanes under catalysis by crude lipase AK20 provided the desired (*R*)-acetate **38** in 95% ee and 46% yield. The unreacted (*S*)-alcohol **39** was also recovered in 94% ee in 44%

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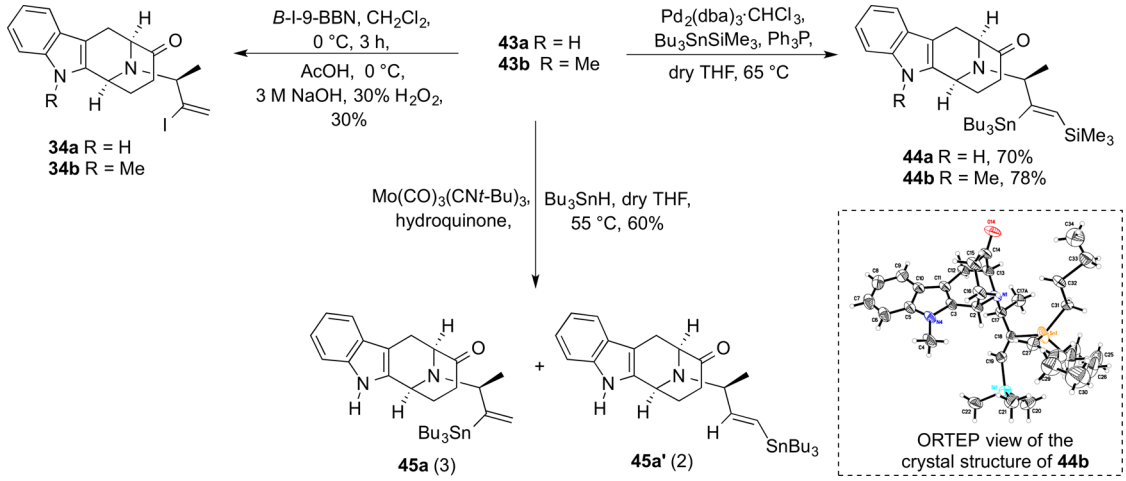
Scheme 5. Functionalization of the Acetylenic Tetracyclic Ketones 43a/b



yield. The reaction was found to be reproducible on a 104 g scale with no change in the ee's of the isolated products. To our knowledge this is the first report of a lipase-catalyzed resolution of the TIPS analog **37** on a large scale. The ee of the (*R*)-acetate **38** was determined by Eu(hcf)$_3$-aided analysis of the ^{1}H NMR spectrum.[28] Saponification of the acetoxy group in **38** with K_2CO_3/MeOH provided the (*R*)-alcohol **40** without loss of stereochemical integrity. The recovered (*S*)-alcohol **39** was recycled to the (*R*)-alcohol **40** by a Mitsunobu inversion (following the procedure of Crimmins et al.)[31] followed by saponification of the ester, thereby increasing the efficiency of the process. In order to perform the S_N2 reaction, the secondary alcohol in **40** was converted to propargyl tosylate **41**, which was employed for alkylation without any further purification.

The N_b-alkylation of the secondary amines **33a/b** (individually) with optically active (*R*)-tosylate **41** in THF/DMF/ethanol with K_2CO_3 resulted in very little conversion or complete consumption of **33a/b** accompanied by baseline impurities. Since it was well known that the nucleophilic strength was dependent on the solvent employed in the reaction,[32] accordingly acetonitrile proved to be the most suitable solvent for this process as the reaction went to completion in 12−14 h under refluxing conditions to give **42a** and **42b** (individually) along with the minor diastereomers **42a′/b′** in a combined yield of 90% and 92% in N_a-H and the N_a-Me series, respectively. Both diastereomers were completely separable in both the N_a-H and the N_a-Me series by silica gel column chromatography (Scheme 4).

Desilylation of **42a/b** with tetrabutylammonium fluoride (TBAF·xH$_2$O) at 0 °C in THF provided the acetylenic compounds **43a/b**, respectively, in 96% yield (Scheme 4). The "*S*" configuration at C-12 (C-19 for the *sarpagine* skeleton) was confirmed by X-ray crystal analysis in the N_a-Me series (Scheme 4). With successful introduction of the chiral methyl group into the developing *sarpagine* framework, attention now turned to the synthesis of ring E via the vinyl iodides **34a/b** (see Scheme 2).

The simplest method for converting terminal alkynes to vinyl iodides in a single step is by use of HI,[33] which is not useful especially for sensitive substrates. Although other methods are reported[34] there are very few reports on direct synthesis of α-vinyl iodides from terminal alkynes.[35] Suzuki et al.[36] reported a single-step conversion of terminal alkynes into 2-halo-1-alkenes in excellent yields and very high regioselectivity using B-bromo- or B-iodo-9-BBN [BBN = borabicyclo(3.3.1)nonane].

Initial attempts at haloboration of **43a/b** with B-I-9-BBN resulted in very little conversion. Attempts to improve this outcome included heating at reflux, excess reagent (1.2−8 equiv), use of freshly distilled reagent, and portionwise addition, but none of them provided any significant improvement on the outcome of the reaction. At best only 30% yield of the desired vinyl iodides **34a/b** could be achieved. It was felt that addition of the first few equivalents of the borane reagent resulted in complexation of the boron reagent to the ketone in **43a/b** and created a steric cloud, which prevented another molecule of B-I-9-BBN from approaching the acetylenic moiety. Due to less than satisfactory outcome of the key step, investigation of other haloborating agents was investigated. The order of reactivity[37] of the haloborating reagents commonly used is B-I-9-BBN, BBr_3 > BCl_3 > B-Br-9-BBN, B-Cl-9-BBN. Although BBr_3 is equivalent in reactivity to B-I-9-BBN, the propensity of the N_b-nitrogen in **43a/b** to form stable borane complexes with smaller boranes as observed earlier in a similar *sarpagine* framework[38] and possibly altering the course of the reaction at the terminal alkyne rendered it unsuitable. The consistently poor yields obtained during this process led us to two metal-catalyzed approaches to achieve this critical conversion. The Pd-catalyzed silastannation reaction as well as the Mo-catalyzed hydrostannation were employed to this effect (Scheme 5).

The Mo-catalyzed hydrostannation process reported by Kazmaier et al. is a useful method for synthesis of α-vinyl stannanes.[39] Secondary terminal propargylic systems are reported to give higher α-selectivities with good to excellent yields under these conditions. The acetylene **43a** on treatment with the catalyst Mo(CO)$_3$(CN*t*-Bu)$_3$ in the presence of Bu_3SnH in THF at 60 °C gave a mixture of both the desired α-stannylated product **45a** as well as the β-stannylated product **45a′** in a 3:2 ratio in 60% yield (Scheme 5). Formation of the β-stannylated alkenes **45a′** suggested that the isonitrile ligands were not bulky enough to impart regioselectivity in the system under study here. No further optimization was performed to improve the selectivity in the process.

The first examples of the Pd-catalyzed regioselective silastannation of alkynes were reported by the groups of Mitchell[40] and Chenard.[41] Terminal acetylenes on treatment with silylstannanes in the presence of catalytic amounts of

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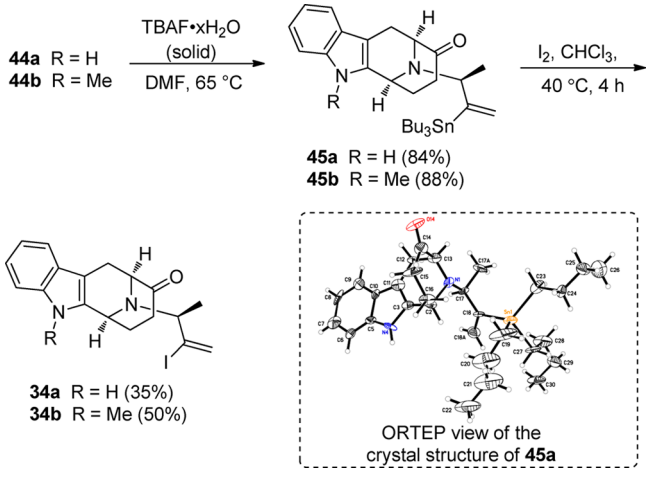
tetrakis(triphenylphosphine)palladium are reported to give highly regio- and stereoselective addition products (cis addition with tin always added to the internal position). Tanner et al.[42] reported the silastannation reaction of several secondary terminal propargylic alcohols (protected and unprotected) with palladium dibenzylidene chloroform adduct [$Pd_2(dba)_3$·$CHCl_3$] as the catalyst in combination with 1−2 equiv of Ph_3P per Pd, thereby improving the scope of this reaction. Both N_a-H and N_a-methyl acetylenic ketones **43a/b**, when subjected to the conditions of silastannation,[42] underwent complete conversion into the desired silastannanes **44a/b** in 3.5 h (Scheme 5). The silastannane reagent, trimethylsilyl tri-*n*-butylstannane ($Bu_3SnSiMe_3$), was prepared on large scale, according to the procedure of Rajanbabu et al.[43] Syn addition of the silastannane reagent to the alkyne was confirmed by X-ray analysis of **44b** (Scheme 5). Although efforts were continued to improve the haloboration approach, the poor selectivity obtained in the Mo-catalyzed hydrostannation process necessitated use of the lengthier silastannation method for synthesis of vinyl iodide **34a/b**.

Conversion of the silastannanes **44a/b** to the respective vinyl iodides required two additional steps. The first step of desilylation proved to be a challenging task. Vinyl silanes are known to undergo desilylation under conditions of nucleophilic catalysis specifically wherein good nucleophiles for silicon (i.e., F^- or alkoxide) are employed. Conditions tend to be harsh or prolonged for efficient desilylation unless other factors come into play. Additionally, due to the acid-sensitive nature of the substrate, protodesilylation was not a feasible option. Desilylation of **44a/b** with 1−1.5 equiv of TBAF in THF at room temperature (rt) resulted in yields consistently below 10% due to very little conversion. Due to the absence of stabilizing groups in the silastannane substrates **44a/b**, it was felt the protodesilylation would require harsher conditions. A large excess of TBAF·xH_2O (up to 25 equivalents at 70 °C for almost 20 h, 1.0 M solution in THF) was required for complete consumption of **44a/b** (Scheme 6). At best, only 65% conversion was observed in both N_a-H and N_a-Me substrates. It was then decided to increase the nucleophilicity of the fluoride ion by employing DMF as the co-solvent. A mixture of THF:DMF (3:2) improved the rate and yield of the reaction drastically. Upon further optimization it was found that performing the reaction in anhydrous DMF at 65 °C, with 13 (N_a-H series) and 4 (N_a-Me series) equiv of TBAF·xH_2O (solid), resulted in a much cleaner reaction with the desired vinyl stannanes **45a/b** obtained in 84% and 88% yield, respectively.

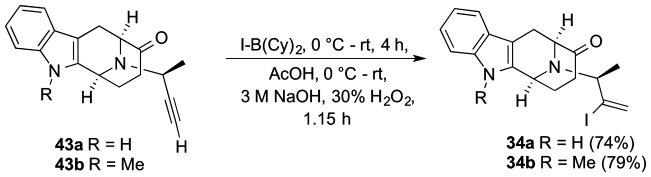
In order to obtain the iodo-olefins **34a/b**, the next step was to subject the vinyl stannanes **45a/b** to the conditions of halodestannation. Under the standard conditions for halodestannations, very low yields of the desired iodo-olefins **34a/b** were obtained. Addition of excess iodine or performing the reaction at reflux (in $CHCl_3$ with I_2/N-iodosuccinimide) were detrimental to the yield of the process. Although complete conversion was achieved after performing the reaction at 40 °C with 3.5 (for **45a**) to 2 (for **45b**) equivalents of iodine, the isolated yield of the process was still low at 35% (for **34a**) and 50% (for **34b**), Scheme 6.

Although the desired vinyl iodides **34a/b** were synthesized via the silastannation approach, efforts were made to make this approach more efficient. The haloboranes B-I-9-BBN and dicyclohexyliodoborane [I-B(Cy)$_2$] have been employed for synthesis of (*Z*)-enolborinates exclusively from various ethyl ketones.[44] I-B(Cy)$_2$ is a highly stereoselective reagent for executing enolboration of esters[45] and tertiary amides.[46] If all other parameters are kept the same, the inability of B-I-9-BBN to drive the haloboration reaction to completion was felt to be due to the rigid skeleton of the bicyclo ring of B-I-9-BBN as a major factor. In contrast, the two cyclohexyl rings of I-B(Cy)$_2$ are conformationally more flexible and should be able to adjust to the neighboring environment. This steric difference prompted substitution of the I-B(Cy)$_2$ for the B-I-9-BBN in the haloboration sequence. Moreover, the regioselectivity of the process should remain unchanged on making this switch. After numerous trials it was found that addition of 2.5 equiv of I-B(Cy)$_2$ (1.0 M solution in hexanes) and subsequent protonolysis with acetic acid provided the vinyl iodides **34a/b** in 74−79% yield with complete regioselectivity (Scheme 7).

Scheme 6. Synthesis of the Vinyl Iodides 34a/b via Halodestannation



Scheme 7. Haloboration of the Acetylenic Tetracyclic Ketones 43a/b



This was a huge improvement over the previous haloboration method and also provided a shorter and more efficient route to the core pentacyclic framework. To our knowledge, this is also the first example of haloboration on terminal acetylenes using I-B(Cy)$_2$ as the haloborating reagent. The silastannation, protodesilylation, and the halodestannation steps could now be avoided, and the acetylenic compounds **43a/b** (individually) could now be converted directly into the desired iodo-olefins **34a/b** in a single step in good yields.

In keeping with the retrosynthetic analysis, the iodo-olefins **34a/b** were subjected to the conditions of the recently developed palladium-catalyzed intramolecular cross-coupling reaction.[47] The iodo-olefins **34a/b** were stirred (individually) with $Pd_2(dba)_3$, DPEPhos, and NaO*t*-Bu in refluxing THF to provide the desired pentacyclic ketones **22a/b** in 60−68% yield (Scheme 8). The key N_a-H pentacyclic ketone **22a** could now

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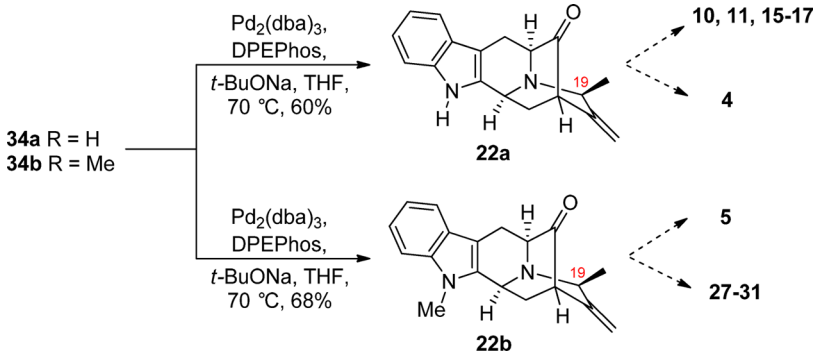
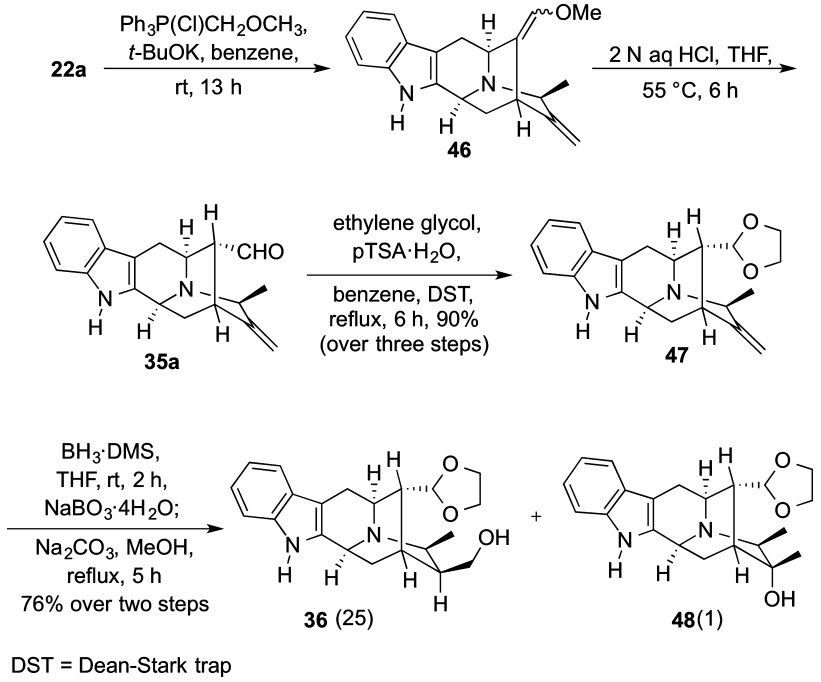
Scheme 8. Synthesis of the Key Pentacyclic Ketones 22a/b



Scheme 9. Synthesis of the C-20 Primary Alcohol 48



be used for synthesis of the C-19 methyl-substituted *sarpagine* and *ajmaline* alkaloids. The N_a-Me intermediate **22b**, on the other hand, could now be employed for synthesis of *macroline* and *sarpagine* alkaloids as discussed earlier (see Figure 2). The following sections detail the further functionalization of the ketones **22a/b** toward achieving synthesis of the target alkaloids.

With the C-19 methyl pentacyclic ketones **22a/b** now available in gram quantities, **22a** was subjected to a one carbon atom homologation process to provide the C-16 aldehyde in **35a**. Execution of a Wittig reaction followed by acid hydrolysis of the corresponding two stereoisomeric enol methyl ethers **46** afforded the thermodynamically stable α-aldehyde. The aldehyde at C-16 was located in the more stable configuration even with the presence of the C-19 methyl group in the β-position. The aldehydic group in **35a** was protected as the cyclic acetal **47** with 1,3-dioxolane in the presence of para toluenesulfonic acid monohydrate (pTSA·H_2O) in refluxing benzene (Scheme 9). The hydroboration−oxidation sequence to generate the desired primary alcohol **36** was achieved under kinetic control;[38] 9 equiv of borane dimethylsulfide complex was added at rt in one portion to a solution of the acetal **47** in THF to minimize the Markovnikov alcohol **48** and facilitate formation of the anti-Markovnikov (kinetic) monol **36** (Scheme 9). The primary and tertiary alcohols existed as N_b-BH_3 complexes (in a ratio of 25:1) because of the highly basic (highly exposed) nature of the N_b-nitrogen atom. The presence of the N_b-borane complex was felt to be the reason for formation of a small amount of tertiary alcohol **48**. Inverse addition of the acetal **47** to a solution of borane dimethylsulfide complex in THF did not eliminate formation of **48**. Decomplexation of the N_b-borane complexes of **36** and **48** was achieved by stirring the mixture with 5 equiv of Na_2CO_3 in refluxing methanol for 5 h, after which the desired primary alcohol **36** along with tertiary alcohol **48** were obtained with the free nitrogen function in 76% yield. Clearly hydroboration of the C20−C21 terminal olefin bond had taken place from the α-face and supported its hindered nature from the β-face.

With the all important primary alcohol **36** in hand, the next step was oxidation[48] to obtain the β-aldehyde followed by epimerization. The basicity of the N_b-nitrogen function in the sarpagine framework and the electron-rich character of the indole nucleus (especially with the indole N_a-H function) contributed in making oxidation of the primary alcohol in **36**

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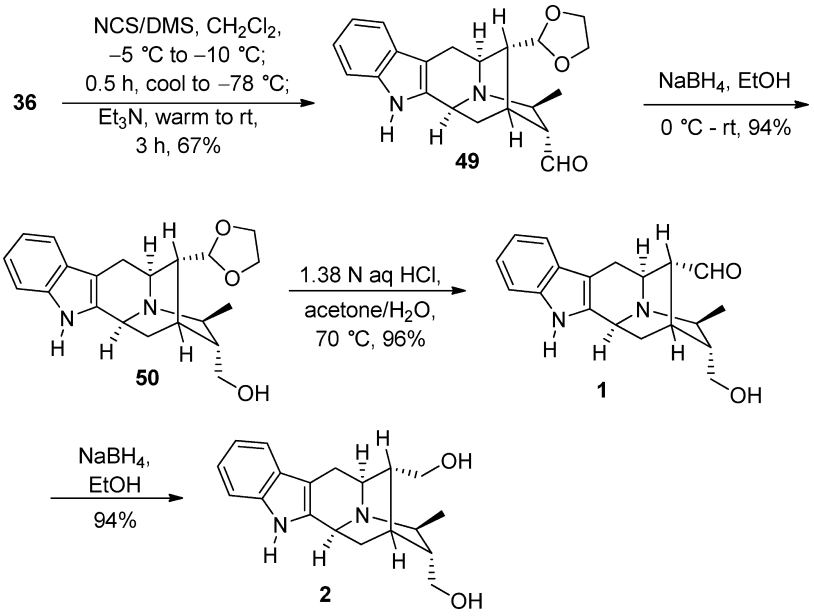
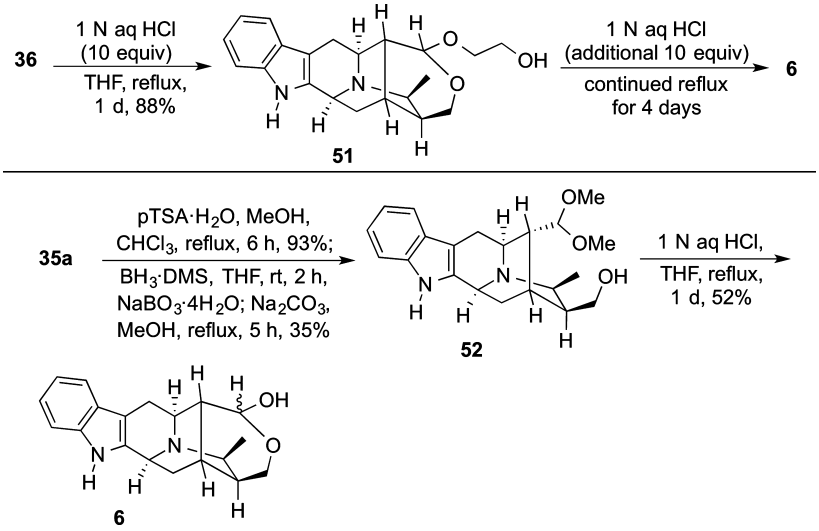
Scheme 10. Completion of the Total Synthesis of 1 and 2



Scheme 11. Completion of the Total Synthesis of Peraksine (6)



more problematic. Swern oxidation gave a complex mixture of products, whereas Dess–Martin periodinane (DMP) oxidation led to aldehyde N_b-oxide formation and some overoxidized byproduct as identified by mass spectrometry. Because of the susceptibility of the N_b-nitrogen atom in the monol **36** to overoxidation, attention focused on the much milder Corey–Kim oxidation. During initial attempts, addition of the alcohol **36** in CH_2Cl_2 at rt to 5 equiv of the Corey–Kim salt at −78 °C generated a small amount of the aldehyde N_b-oxide (not shown). Reduction of the equivalents of the Corey–Kim reagent from 5 to 3.5 accompanied by addition of the cooled solution (−78 °C) of **36** in CH_2Cl_2 to the reagent at −78 °C resulted in a much cleaner reaction and completely eliminated formation of any overoxidized byproduct. The reaction mixture was then treated with 16 equiv of triethylamine and allowed to stir at −78 °C for 1 h and rt for 1 h. Since an epimeric mixture of aldehydes was obtained (^{1}H NMR spectrum), it was decided to carry out complete epimerization in the same reaction vessel by allowing the reaction mixture to stir at rt for an additional 2 h. Chromatographic purification of the crude material furnished the α-aldehyde **49** as a colorless oil (Scheme 10).

Reduction of the stable α-aldehyde **49** with $NaBH_4$ in ethanol for 3 h at rt furnished the α-alcohol **50** in 94% yield (Scheme 10). This was followed by hydrolysis of the acetal group in **50** under acidic conditions (1.38 N aqueous HCl) in refluxing acetone to provide 19(*S*),20(*R*)-dihydroperaksine-17-al **1** in 96% yield. A modified workup which took advantage of the basicity of the N_b-nitrogen function was sufficient to remove all the hydrocarbon impurities, and the product **1** thus obtained required no further purification. Signals in the ^{1}H and ^{13}C NMR spectra of **1** were in excellent agreement with the literature values.[3] The 19(*S*),20(*R*)-dihydroperaksine-17-al (**1**) was then further subjected to reduction with $NaBH_4$ to complete the total synthesis of 19(*S*),20(*R*)-dihydroperaksine **2** (Scheme 10). The synthetic **1** and **2** were also identical on silica gel thin layer chromatography (TLC) including a mixed TLC sample to the sample of natural 19(*S*),20(*R*)-dihydroperaksine-

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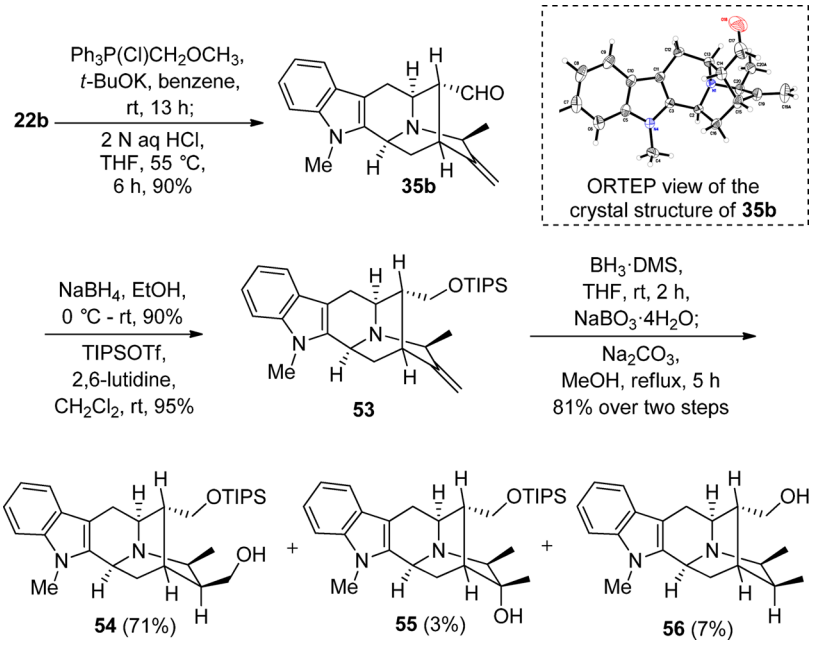
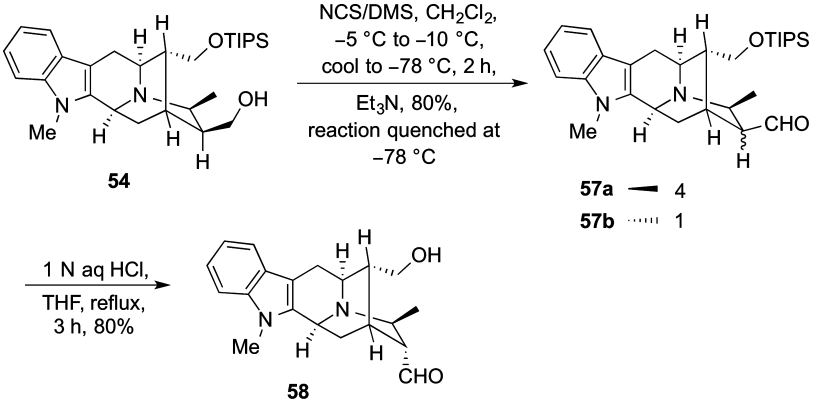
Scheme 12. Synthesis of C-20 Primary Alcohol 54



Scheme 13. Corey–Kim Oxidation



17-al (**1**) and natural 19(*S*),20(*R*)-dihydroperaksine (**2**) kindly supplied by Professor Joachim Stöckigt.[49]

To effect formation of the hemiacetal ring in peraksine (**6**), the monol **36** was heated to reflux for 24 h in THF in the presence of 10 equiv of 1 N aq HCl. Examination of the ^{1}H NMR spectrum of the crude material after 24 h indicated formation of the hemiacetal ring, but the cyclic acetal ring opened only half way to give an ether linkage (see **51**) as a single diastereomer (Scheme 11). The same result was obtained upon heating the material in THF:H_2O (1:1), at reflux for 24 h. Eventually, continued heating of ether **51** with an additional 10 equiv of 1 N aqueous HCl for 4 days resulted in formation of trace amount of **6**.

Because of the resistance of the ethereal linkage in **51** to hydrolysis due to reversible formation of the 1,3-dioxolane ring, the cyclic acetal was converted into the dimethoxy acetal. The dimethoxy acetal group was not as stable as the 1,3-dioxolane group to the hydroboration reaction conditions and resulted in only 35% yield of the desired monol **52**. The monol **52** when subjected to reflux in acidic conditions effected the hemicacetal ring formation and thus provided peraksine **6** as an epimeric mixture at C-17 in 52% yield (Scheme 11) analogous to Arthur et al.[9c]

Studies Directed toward Total Synthesis of Macrosalhine Chloride (5) as Well as Partial Total Synthesis of Talcarpine (26). With the successful synthesis of the C-19 methyl-functionalized *sarpagine* alkaloids **1**, **2** and **6** in the N_a-H series, synthesis of the hemiacetal alkaloid (in the N_a-methyl series) macrosalhine chloride **5** was next attempted. Macrosalhine **5** was isolated from the stem bark of *Alstonia macrophylla* WALL. by Schmid et al. in small amounts as the chloride or the thiocyanate salt. The structure of this alkaloid was determined on the basis of NMR and by X-ray analysis of its bromide salt.[8] With the key pentacyclic template **22b** in hand, attention was focused on synthesis of the hemiacetal ring formation in **5**. It was decided to first reduce the aldehyde at C-16 into an alcohol, protect it with a suitable acid-labile group, and then functionalize the terminal olefin to the least stable *β*-aldehyde by a hydroboration–oxidation sequence. Cyclization of this *β*-aldehyde with the protected primary alcohol under acidic conditions would then enable hemiacetal ring formation in **5**.

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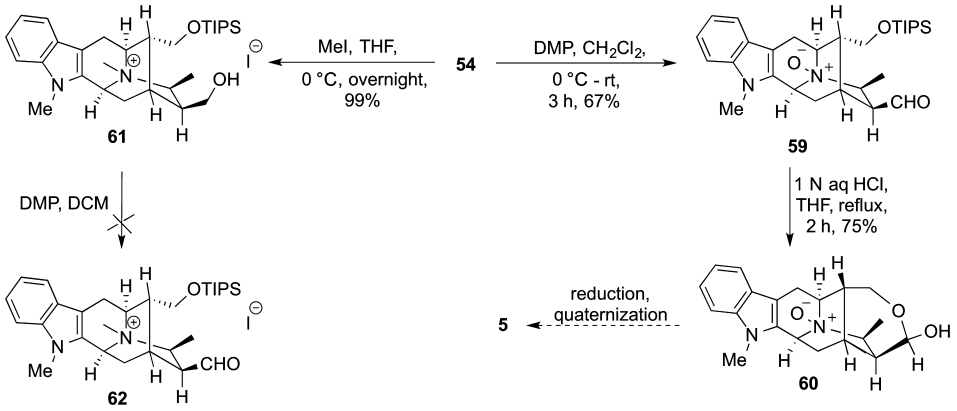
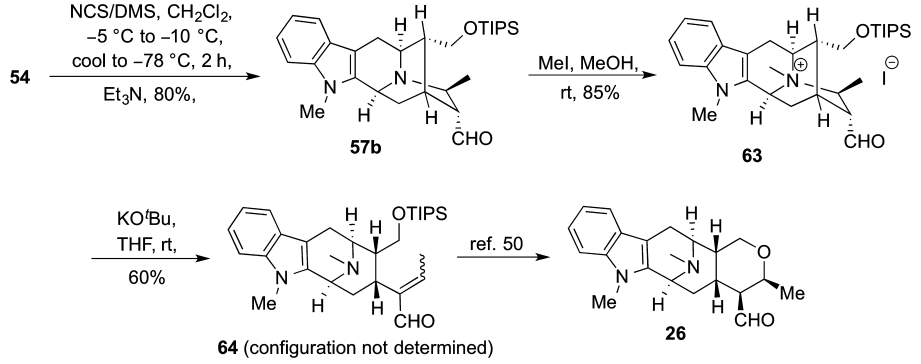
Scheme 14. DMP Oxidation and Acid-Mediated Hemiacetal Ring Formation



Scheme 15. Formal Total Synthesis of Talcarpine (26)



The pentacyclic ketone **22b** was thus converted to the aldehyde **35b** by a Wittig–hydrolysis sequence. The α-position of the aldehyde at C-16 was confirmed by X-ray analysis (Scheme 12). Reduction of **35b** with $NaBH_4$ afforded the alcohol (95%), which was then protected as its silyl ether to give **53**. Hydroboration of the terminal olefin in **53** provided the desired monol **54**, accompanied by the expected tertiary alcohol **55** and the unusual protodeboronation byproduct **56** (Scheme 12).

Due to the susceptibility of the more basic N_b-nitrogen to form *N*-oxides, as observed in the N_a-H series, it was decided to employ the milder Corey–Kim oxidation to carry out the oxidation, although it was felt some of the more stable α-aldehyde **57b** might form in this process. The oxidation was carried out under identical conditions developed in the N_a-H series and resulted in a mixture of aldehydes **57a/b** (reaction mixture was not allowed to warm to rt after addition of Et_3N). The ratio of the two aldehydes as determined by ^1H NMR was 4:1 in favor of the β-aldehyde **57a**. The mixture of aldehydes **57a/b** was then heated at reflux under mild acidic conditions to attempt formation of the cyclic hemiacetal. However, upon stirring in acidic media, complete epimerization to the α-aldehyde accompanied by desilylation of the TIPS ether was observed (Scheme 13). Reduction of the equivalents of Et_3N (from 16 to 3) failed to improve the outcome of the process. Thus, the inability to prevent formation of the α-aldehyde in the Corey–Kim oxidation was detrimental to hemiacetal ring formation.

As performed in the N_a-H series, the Dess–Martin periodinane (DMP) oxidation was next attempted. As expected, the *N*-oxide of the desired β-aldehyde **59** was obtained as the only stereoisomer (Scheme 14), in spite of efforts to prevent overoxidation by either using fewer equivalents of DMP or performing the reaction at lower temperature. While attempts at using trifluoroacetic acid (TFA) [equivalents varied from 1.5 to 1.1 equiv] in the above case (to protonate the N_b-nitrogen) failed to prevent *N*-oxide formation, oxidation with IBX/DMSO resulted in no reaction. Since macrosalhine chloride **5** is a quaternary salt, the N_b nitrogen in amine **54** was quaternized with excess methyl iodide to give salt **61**. However, oxidation of alcohol **61** with DMP resulted in a complex mixture with no evidence of aldehyde **62** formation. In all the above processes strict anhydrous conditions were maintained.

Since the β-aldehyde **59** was obtained as the sole product during the above oxidation process, it was decided to first attempt hemiacetal ring formation and then perform a reduction of the *N*-oxide to complete synthesis of **5**. Thus, refluxing the aldehyde **59** in 1 N aqueous HCl for 24 h furnished the cyclic hemiacetal **60**. At this point with only limited material left in hand, efforts to reduce the *N*-oxide with Zn/AcOH failed to produce the free N_b-nitrogen. Further work toward attempting this key step is necessary to complete the total synthesis of **5**.

Although the Corey–Kim oxidation could not be utilized for synthesis of **5**, it provided a much milder method for synthesis of the epimeric aldehydes **57a/b** (Scheme 13) and then to the thermodynamically stable α-aldehyde **57b** (Scheme 15) in a one-pot process. Further quaternization of the N_b-nitrogen atom in **57b** with excess MeI provided salt **63**, which when subjected to a retro-Michael reaction provided the *macroline* framework in olefin **64** as a single isomer (configuration not determined). Desilylation of the TIPS group in olefin **64** to the

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free alcohol would generate the all-important macroline equivalent **32a** (Figure 4b), which was the intermediate involved in partial synthesis of talcarpine **26** by Sakai et al.[50] This resulted in the formal total synthesis of **26** here. The macroline intermediate **64** would also serve as the precursor for potential synthesis of the *macroline*-related alkaloids **27**−**31**. Additionally, **32b** the 10-methoxy equivalent of **32a** and the northern hemisphere of the Alstonia bisindoles (+)-angusticraline, (+)-alstocraline, and (+)-foliacraline (Figure 4A) could be synthesized from 5-methoxy-D-tryptophan ethyl ester[51] via the route developed here.

CONCLUSION

The first enantiospecific, stereospecific total synthesis of 19(*S*),20(*R*)-dihydroperaksine (**1**), 19(*S*),20(*R*)-dihydroperaksine-17-al (**2**), and peraksine (**6**) has been accomplished. A stereospecific approach toward synthesis of macrosalhine chloride (**5**) was also developed. Commercially available D-(+)-tryptophan has served both as the chiral auxiliary and as the starting material. Moreover, this is the first synthesis which sets the stereochemistry of the methyl group at C-19 in a stereospecific fashion. The acetylenic moiety **43a/b** was modified to the key vinyl iodide **34a/b** by silyl-stannation and haloboration approaches. Initial attempts at haloboration were accompanied by inconsistent reproducibility, purification problems, and very low yield, which were circumvented by modification of the reaction conditions and use of a superior haloborating agent [I-B(Cy)$_2$]. It is important to point out that the palladium-catalyzed α-vinylation has been extended to the C-19 chiral methyl series which make it a process of more general applicability. The key N_a-H pentacyclic ketone **22a** could now be used for synthesis of the C-19 methyl-substituted *ajmaline* alkaloids **10**, **11**, and **15**−**17** (Figure 1), and a route amenable to the synthesis of *macroline*−related alkaloids **27**−**31** (Figure 3) is now possible due to the efficient synthesis of the advanced intermediate **64** via a general strategy for synthesis of C-19 methyl-substituted indole alkaloids. This process provides a general entry into a whole series of biosynthetically important monoterpene C-19-substituted indole alkaloids.

EXPERIMENTAL SECTION

Experimental details and spectral data for synthesis of alkaloids **1** and **2** and compounds **22a**, **34a** (from **43a**), **36**, **41**, **42a**, **43a**, **47**, **49**, and **50** are contained in the Supporting Information of ref 24a. For general experimental considerations see the Supporting Information.

Lipase-Catalyzed Kinetic Resolution of 4-Triisopropylsilyl-3-butyn-2-ol (37). A 5 L round-bottom flask, which had been flame dried, was equipped with an overhead mechanical stirrer and charged with 69.0 g of ground activated 4 Å molecular sieves and 50 g (0.5 mass equiv) of the lipase (crude) Amano AK20. To this were added 4 L of distilled hexanes, 158.2 g (1.83 mmol) of vinyl acetate (dried over $MgSO_4$), and the racemic alcohol **37** (104 g, 0.46 mol). This suspension was stirred at 25 °C for 5 days, after which analysis by NMR spectroscopy indicated 50% conversion to the *R*-acetate **38**. The solution was filtered and concentrated under reduced pressure, and the crude product was purified by column chromatography (silica gel) with 2−10% EtOAc/hexanes as the eluant to afford the *R*-acetate **38** (63.0 g, 46%) and the *S*-alcohol **39** (46.0 g, 44%).

*R-Acetate **38**.* R_f 0.59 (silica gel, EtOAc/hexanes, 1:7). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.49 (q, 1H, J = 6.8 Hz), 2.10 (s, 3H), 1.51 (d, 3H, J = 6.8 Hz), 1.09 (s, 21H). The % ee of the *R*-acetate **38** was determined as 95% by Eu(hcf)$_3$-aided ^{1}H NMR analysis. The acetate was not subjected to any further characterization and used in the next step as is.

*S-Alcohol **39**.* R_f 0.33 (silica gel, EtOAc/hexanes, 1:7). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.54 (q, 1H, J = 6.6 Hz), 1.91 (s, 1H), 1.47 (d, 3H, J = 6.6 Hz), 1.07 (s, 21H) [^{1}H NMR was identical to that reported for *R*-alcohol **40** herein]. HRMS (APCI-TOF) m/z: [M + H]$^+$ calcd for $C_{13}H_{27}OSi$ 227.1826, found 227.1828.

This material was employed directly in the next step without any further characterization.

Hydrolysis of the *R*-Acetate 38 to the *R*-Alcohol 40. The *R*-acetate **38** (10 g, 37.2 mmol) was dissolved in a saturated solution (100 mL) of K_2CO_3 in MeOH:H_2O (15:1). The solution, which resulted, was stirred at rt for 2 h until disappearance of the starting material **38** as monitored by TLC (silica gel). The solvent was then removed under reduced pressure, and the mixture, which resulted, was extracted with ether. The organic layer was separated and dried over anhydrous Na_2SO_4 and concentrated to give the *R*-alcohol **40** as a clear oil (8.1 g, 96%). R_f 0.33 (silica gel, EtOAc/hexanes, 1:7). $[\alpha]^{20}_D$ + 23.38° (c 2.01 $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.56 (q, 1H, J = 6.4 Hz), 2.06 (br s, 1H), 1.49 (d, 3H, J = 6.4 Hz), 1.09 (s, 21H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 109.8, 84.4, 58.8, 24.6, 18.6, 11.1. HRMS (APCI-TOF) m/z: [M + H]$^+$ calcd for $C_{13}H_{27}OSi$ 227.1826, found 227.1826.

Mitsunobu Inversion of the *S*-Alcohol 39 to the *R*-Alcohol 40. To a stirred solution of *S*-alcohol **39** (28.0 g, 0.124 mol) in dry THF (2.1 L) at rt was added triphenylphosphine (64.85 g, 0.247 mol) and benzoic acid (30.2 g, 0.247 mol). The mixture, which resulted, was then cooled to 0 °C, and to it was added diethyl azodicarboxylate (41 g, 0.235 mol). The reaction mixture was allowed to warm to rt and stirred for an additional 2.5 h. The solution was then concentrated, and the residue was dissolved in ethyl acetate and filtered through a pad of Celite topped with silica gel. The filtrate was concentrated, and the residue was dissolved in a solution of MeOH (200 mL), THF (70 mL), H_2O (70 mL), and 15 g of NaOH. This mixture was stirred for 2 h, and solvents were removed under reduced pressure. The aq residue was extracted with diethyl ether (3 × 100 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated to give the *R*-alcohol **40** (25.2 g, 90%). Spectral data of **40** were identical in all respects to that reported above for **40** (obtained from **38**). HRMS (APCI-TOF) m/z: [M + H]$^+$ calcd for $C_{13}H_{27}OSi$ 227.1826, found 227.1826.

(6*S*,10*S*)-12-((*S*)-4-(Triisopropylsilyl)but-3-yn-2-yl)-7,8,10,11-terahydro-5*H*-6,10-epiminocycloocta[*b*]indol-9(6*H*)-one (42a) and (6*S*,10*S*)-12-((*R*)-4-(Triisopropylsilyl)but-3-yn-2-yl)-7,8,10,11-terahydro-5*H*-6,10-epiminocycloocta[*b*]indol-9(6*H*)-one (42a′). An oven-dried 500 mL flask cooled under argon was charged with optically active N_a-H, N_b-H tetracyclic ketone **33a** (5.0 g, 22.1 mmol), freshly distilled acetonitrile (150 mL), (*R*)-4-triisopropylsilyl-3-butyn-2-ol tosylate **41** (13.5 g, 35.4 mmol) in dry acetonitrile (50 mL), and anhydrous potassium carbonate (6.1 g, 44.2 mmol). The mixture which resulted was allowed to stir at 75 °C (outside oil bath temperature) for 12 h under argon. Analysis by TLC (silica gel, $CHCl_3$/EtOH, 9:1) indicated the absence of tetracyclic ketone **33a** after 12 h. The reaction mixture was cooled to rt, and the K_2CO_3 was filtered off by passing the solution through a bed of Celite using EtOAc as the eluent. After removal of the solvent under reduced pressure, the crude product was purified by flash chromatography (silica gel, EtOAc/hexanes) to provide the major (*S*)-N_a-H, TIPS acetylenic tetracyclic ketone **42a** as a light yellow-colored solid (8.4 g) in 88% yield and a small amount of the (*R*)-N_a-H, TIPS acetylenic tetracyclic ketone **42a′** as a buff-colored solid (0.2 g, 2%). A small amount of **42a′** was obtained because of the 95% ee of the starting tosylate **41**.

*Major [C(12)-S] Diastereomer **(42a)**.* For spectral data see the Supporting Information of ref 24a.

*Minor [C(12)-R] Diastereomer **(42a′)**.* Mp 135−137 °C. $[\alpha]^{20}_D$ −4.30 (c 0.93 $CHCl_3$). IR (KBr): 3376, 2944, 2166, 1698, 1450 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.81 (s, 1H), 7.49 (d, 1H, J = 7.6 Hz), 7.35 (d, 1H, J = 7.9 Hz), 7.19 (td, 1H, J = 7.1, 1.2 Hz), 7.13 (td, 1H, J = 10.7, 1.1 Hz), 4.37−4.34 (m, 2H), 3.73 (q, 1H, J = 6.5 Hz), 3.31 (dd, 1H, J = 16.7, 6.5 Hz), 2.72 (d, 1H, J = 16.8 Hz), 2.62−2.44 (m, 2H), 2.19−2.01 (m, 2H), 1.47 (d, 3H, J = 6.5 Hz), 1.06 (s, 21H). ^{13}C

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NMR (75 MHz, $CDCl_3$): δ 210.3 (C), 135.8 (C), 131.9 (C), 126.8 (C), 122.0 (CH), 119.7 (CH), 118.2 (CH), 110.8 (CH), 107.9 (C), 107.5 (C), 85.3 (C), 63.3 (CH), 48.4 (CH), 47.3 (CH), 34.5(CH_2), 29.9 (CH_2), 21.6 (CH_2), 21.0 (CH_3), 18.5 (6 × CH_3), 11.1 (3 × CH). EIMS (*m*/*e*, relative intensity): 434 (M^+, 5), 378 (24), 225 (9), 197 (6), 183 (18), 169 (100), 139 (7), 115 (10), 83 (16), 59 (18). Anal. Calcd for $C_{27}H_{38}N_2OSi$: C, 74.60; H, 8.81; N, 6.44. Found: C, 74.22; H, 9.09; N, 6.24.

(6*S*,10*S*)-5-Methyl-12-((*S*)-4-(triisopropylsilyl)but-3-yn-2-yl)-7,8,10,11-tetrahydro-5*H*-6,10-epiminocycloocta[*b*]indol-9(6*H*)-one (42b) and (6*S*,10*S*)-5-Methyl-12-((*R*)-4-(triisopropylsilyl)-but-3-yn-2-yl)-7,8,10,11-tetrahydro-5*H*-6,10-epiminocycloocta[*b*]indol-9(6*H*)-one (42b′). An oven-dried 1 L flask cooled under argon was charged with optically active N_a-Me, N_b-H tetracyclic ketone **33b** (15.0 g, 0.062 mol). The solid **33b** was dissolved in freshly distilled acetonitrile (1 L), after which a solution of (*R*)-4-triisopropylsilyl-3-butyn-2-ol tosylate **41** (47.57 g, 0.116 mol) in dry acetonitrile (50 mL) was added. Anhydrous potassium carbonate (17.27 g, 0.125 mol) was added, and the mixture which resulted was allowed to stir at 75 °C (outside oil bath temperature) for 12 h under argon. Analysis by TLC (silica gel, $CHCl_3$/EtOH, 9:1) indicated the absence of tetracyclic ketone **33b** after 12 h. The reaction mixture was cooled to rt, and the K_2CO_3 was filtered off by passing the solution through a bed of Celite using EtOAc as eluent. After removal of the solvent under reduced pressure, the crude product was purified by flash chromatography (silca gel, EtOAc/hexanes) to provide the (*S*)-N_a-Me, TIPS-protected acetylenic tetracyclic ketone **42b** as a light yellow-colored solid (25.3 g, 90%) and a small amount of the (*R*)-N_a-Me, TIPS-protected acetylenic tetracyclic ketone **42b′** as a buff-colored solid (0.51 g, 2%) in a combined yield of 92%. A small amount of **42b′** was obtained because of the 95% ee of starting tosylate **41**.

*Major [C(12)-S] Diastereomer (**42b**).* Mp 92.5−94.5 °C. R_f 0.51 (silica gel, ethyl acetate/hexane, 6:2). IR (KBr): 2939, 2862, 2168, 1701, 1471, 738 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.48 (d, 1H, *J* = 7.7 Hz), 7.32 (d, 1H, *J* = 8.1 Hz), 7.24 (td, 1H, *J* = 7.0, 1.1 Hz), 7.12 (ddd, 1H, *J* = 7.8, 6.9, 1.0 Hz), 4.93−4.90 (m, 1H), 3.98 (d, 1H, *J* = 6.4 Hz), 3.69 (s, 3H), 3.66 (q, 1H, *J* = 6.5 Hz), 3.16 (dd, 1H, *J* = 16.7, 6.6 Hz), 2.71 (d, 1H, *J* = 16.7 Hz), 2.65−2.44 (m, 2H), 2.19−2.01 (m, 2H), 1.48 (d, 3H, *J* = 6.6 Hz), 1.05 (s, 21H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 209.9 (C), 137.1 (C), 133.5 (C), 126.3 (C), 121.4 (CH), 119.1 (CH), 118.1 (CH), 108.7 (C), 108.7 (CH), 106.2 (C), 84.6 (C), 61.6 (CH), 48.7 (CH), 47.6 (CH), 34.3 (CH_2), 29.2 (CH_3), 29.1 (CH_2), 20.9 (CH_2), 20.5 (CH_3), 18.5 (6 × CH_3), 11.1 (3 × CH). EIMS (*m*/*e*, relative intensity): 448 (M^+, 83), 420 (14), 391 (100), 338 (24), 239 (20), 197 (14), 183 (97), 168 (26), 144 (11). Anal. Calcd for $C_{28}H_{40}N_2OSi$: C, 74.95; H, 8.99; N, 6.24. Found: C, 74.81; H, 9.26; N, 6.12.

*Minor [C(12)-R] Diastereomer (**42b′**).* Mp 92−94 °C. R_f 0.22 (silica gel, ethyl acetate/hexane, 6:2). IR (KBr): 2938, 2862, 2168, 1707, 1470, 740 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.50 (d, 1H, *J* = 7.7 Hz), 7.32 (d, 1H, *J* = 8.1 Hz), 7.24 (td, 1H, *J* = 7.0, 1.2 Hz), 7.12 (ddd, 1H, *J* = 7.9, 6.8, 1.1 Hz), 4.51 (d, 1H, *J* = 2.8 Hz), 4.31 (d, 1H, *J* = 6.7 Hz), 3.72 (q, 1H, *J* = 6.4 Hz), 3.70 (s, 3H), 3.30 (dd, 1H, *J* = 16.7, 6.8 Hz), 2.73 (d, 1H, *J* = 16.7 Hz), 2.65−2.54 (m, 1H), 2.48 (dd, 1H, *J* = 15.8, 6.5 Hz), 2.22−2.00 (m, 2H), 1.48 (d, 3H, *J* = 6.5 Hz), 1.07 (s, 21 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 210.3 (C), 137.2 (C), 133.1 (C), 126.3 (C), 121.5 (CH), 119.1 (CH), 118.2 (CH), 108.7 (CH), 107.5 (C), 106.8 (C), 85.3 (C), 63.0 (CH), 47.4 (CH), 47.2 (CH), 34.3 (CH_2), 29.2 (CH_3), 29.1 (CH_2), 22.0 (CH_2), 21.0 (CH_3), 18.5 (6 x CH_3), 11.1 (3 × CH). EIMS (*m*/*e*, relative intensity): 448 (M^+, 100), 420 (24), 391 (80), 338 (15), 239 (25), 197 (12), 183 (64), 168 (35), 144 (21), 83 (11). Anal. Calcd for $C_{28}H_{40}N_2OSi$: C, 74.95; H, 8.99; N, 6.24. Found: C, 74.81; H, 9.20; N, 6.14.

(6*S*,10*S*)-12-((*S*)-but-3-yn-2-yl)-5-Methyl-7,8,10,11-tetrahydro-5*H*-6,10-epiminocycloocta[*b*]indol-9(6*H*)-one (43b). TBAF·xH_2O (84 mL, 0.084 mol, 1.0 M solution in THF) was added to a solution of the N_a-Me, TIPS-protected acetylenic tetracyclic ketone **42b** (25 g, 0.056 mol) in THF (420 mL) at 0 °C. The solution which resulted was allowed to stir at 0 °C for 0.5 h, after which the ice bath was removed and the mixture was stirred at rt for 3 h until analysis by TLC indicated disappearance of the starting material **42b**. The reaction solution was then quenched with H_2O (150 mL) at rt, followed by dilution with EtOAc (500 mL). The two layers were separated. The organic layer was washed with water, brine, and dried (Na_2SO_4). The EtOAc was removed under reduced pressure, and the residue was passed through a small pad of silica gel to give the N_a-Me acetylenic tetracyclic ketone **43b** as an off-white-colored solid (15.7 g, 96% yield). Part of the solid was crystallized using EtOAc to give **43b** as white crystals for X-ray analysis. IR (KBr): 3266, 2983, 2099, 1708, 1469, 756, 662 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.48 (d, 1H, *J* = 7.3 Hz), 7.34 (d, 1H, *J* = 8.1 Hz), 7.25 (td, 1H, *J* = 7.0, 1.1 Hz), 7.13 (ddd, 1H, *J* = 7.8, 6.9, 1.1 Hz), 4.78−4.77 (m, 1H), 3.97 (d, 1H, *J* = 6.6 Hz), 3.72 (s, 3H), 3.64 (qd, 1H, *J* = 6.7, 2.2 Hz), 3.16 (dd, 1H, *J* = 16.8, 6.7 Hz), 2.72 (d, 1H, *J* = 16.8 Hz), 2.67−2.58 (m, 1H), 2.54−2.47 (m, 1H), 2.31 (d, 1H, *J* = 2.2 Hz), 2.20−2.02 (m, 2H), 1.48 (d, 3H, *J* = 6.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.1 (C), 137.1 (C), 133.5 (C), 126.2 (C), 121.5 (CH), 119.2 (CH), 118.1 (CH), 108.9 (CH), 106.1 (C), 84.7 (C), 72.4 (CH), 61.3 (CH), 49.2 (CH), 47.1 (CH), 34.3 (CH_2), 29.2 (CH_3), 28.9 (CH_2), 21.4 (CH_2), 20.4 (CH_3). EIMS (*m*/*e*, relative intensity) 292 (M^+, 81), 235 (100), 196 (24), 183 (46), 168 (26). HRMS (EI-trisector) *m*/*z*: calcd for $C_{19}H_{20}N_2O$ 292.1576, found 292.1570.

(6*S*,10*S*)-12-((*S*,*Z*)-3-(Tributylstannyl)-4-(trimethylsilyl)but-3-en-2-yl)-7,8,10,11-tetrahydro-5*H*-6,10-epiminocycloocta[*b*]-indol-9(6*H*)-one (44a). An oven-dried three-neck flask was cooled under argon and charged with terminal alkyne **43a** (9.2 g, 33.1 mmol), which had been dissolved in freshly distilled THF (55 mL), Ph_3P (347 mg, 1.32 mmol), and $Bu_3SnSiMe_3$ (15.6 g, 43 mmol). The system was degassed under reduced pressure at rt and backfilled with argon (3 times). To the above solution, tris(dibenzylideneacetone)dipalladium(0) chloroform adduct (1.03 g, 0.99 mmol) was added along with dry THF (3 mL), and the system was again degassed under reduced pressure at rt and backfilled with argon (4 times). The mixture, which resulted, was then heated to 65 °C (oil bath temperature) under an atmosphere of argon for 4.5 h. Analysis by TLC (silica gel, EtOAc/hexanes, 3:5) indicated the absence of terminal alkyne **43a** and the presence of a new indole component of higher R_f. The reaction mixture was cooled to rt and passed through a bed of Celite. Ether (1 L) was used for elution. The ether layer was concentrated and purified by flash chromatography (silica gel, EtOAc/hexane, 1:9, 1% Et_3N) to give silastannane tetracyclic ketone **44a** as a white colored solid (14.9 g, 70% yield). ^1H NMR (300 MHz, $CDCl_3$): δ 7.92, (s, 1H), 7.51 (d, 1H, *J* = 7.5 Hz), 7.36 (d, 1H, *J* = 7.8 Hz), 7.24−7.13 (m, 2H), 6.41 (s, 1H), 4.27 (br, s, 1H), 4.02 (d, 1H, *J* = 6.2 Hz), 3.27 (q, 1H, *J* = 6.3 Hz), 3.14 (dd, 1H, *J* = 16.7, 6.5 Hz), 2.69 (d, 1H, *J* = 16.7 Hz), 2.48 (dd, 1H, *J* = 15.9, 5.6 Hz), 2.41−2.31 (m, 1H), 2.20−2.09 (m, 1H), 2.05−1.99 (m, 1H), 1.63−1.47 (m, 6H), 1.35 (sex, 6H, *J* = 7.1 Hz), 1.21 (d, 3H, *J* = 6.5 Hz), 1.14−1.00 (m, 6H), 0.95−0.91 (m, 9H), 0.16 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 210.7 (C), 170.8 (C), 143.1 (CH), 135.8 (C), 132.4 (C), 126.9, (C), 121.7 (CH), 119.5 (CH), 118.1 (CH), 110.8 (CH), 107.6 (C), 70.0 (CH), 61.3 (CH), 48.7 (CH), 34.6 (CH_2), 30.1 (CH_2), 29.2 (3 x CH_2), 27.5 (3 × CH_2), 21.1 (CH_2), 19.1 (CH_3), 13.5 (3 × CH_3), 12.4 (3 × CH_2), 0.21 (3 × CH_3). CIMS (*m*/*e*, relative intensity): 643 (M^+ + 1, 30), 585 (100), 351 (51), 335 (23), 283 (14), 253 (95), 210 (10), 169 (14). HRMS (ESI-TOF) *m*/*z*: $(M + H)^+$ calcd for $C_{33}H_{55}N_2OSi^{120}Sn$, 643.3106, found 643.3100.

(6*S*,10*S*)-5-Methyl-12-((*S*,*Z*)-3-(tributylstannyl)-4-(trimethylsilyl)but-3-en-2-yl)-7,8,10,11-tetrahydro-5*H*-6,10-epiminocycloocta[*b*]indol-9(6*H*)-one (44b). The reaction was performed following the same procedure employed for **44a**. Terminal alkyne **43b** (8 g, 27.38 mmol), freshly distilled THF (38 mL), Ph_3P (287 mg, 1.09 mmol), $Bu_3SnSiMe_3$ (15.9 g, 43.8 mmol), and tris(dibenzylideneacetone)dipalladium(0) chloroform adduct (850 mg, 0.82 mmol) were added together. The silastannane tetracyclic ketone **44b** (14 g, 78%) was obtained as an oil. Part of the oil was crystallized using EtOAc to give **44b** as white crystals for X-ray analysis. Mp 82−84 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 7.50 (d, 1H, *J* = 7.7 Hz), 7.33 (d, 1H, *J* = 8.1 Hz), 7.24 (td, 1H, *J* = 8.1, 1.1 Hz), 7.14 (ddd, 1H, *J* = 7.9, 6.8, 1.1 Hz), 6.29 (s, 1H), 4.35 (br, s, 1H), 3.99 (d, 1H, *J* = 6.5

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Hz), 3.60 (s, 3H), 3.16 (q, 1H, J = 6.9 Hz), 3.10 (d, 1H, J = 6.7 Hz), 2.65 (d, 1H, J = 16.8 Hz), 2.47−2.29 (m, 2H), 2.21−2.10 (m, 1H), 1.98−1.92 (m, 1H), 1.56−1.55 (m, 6H), 1.35 (sex, 6H, J = 7.1 Hz), 1.17 (d, 3H, J = 6.5 Hz), 1.05−0.99 (m, 6H), 0.91 (t, 9H, J = 7.2 Hz), 0.12 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 210.0 (C), 170.6 (C), 143.3 (CH), 137.0 (C), 133.3 (C), 126.5 (C), 121.2 (CH), 119.1 (CH), 118.1 (CH), 108.8 (CH), 106.6 (C), 70.5 (CH), 60.9 (CH), 47.2 (CH), 34.3 (CH_2), 29.6 (CH_2), 29.3 (3 × CH_2), 28.9 (CH_3), 27.4 (3 × CH_2), 20.8 (CH_2), 18.8 (CH_3), 13.5 (3 × CH_3), 12.5 (3 × CH_2), 0.1 (3 × CH_3). CIMS (m/e, relative intensity): 657 (M^+ + 1, 46), 599 (100), 367 (82), 349 (27), 297 (27), 269 (84), 224 (17), 183 (17). Anal. Calcd for $C_{34}H_{56}N_2OSiSn$: C, 62.29; H, 8.61; N, 4.27. Found: C, 62.19; H, 8.70; N, 4.19.

(6*S*,10*S*)-12-((*S*)-3-(Tributylstannyl)but-3-en-2-yl)-7,8,10,11-tetrahydro-5*H*-6,10-epiminocycloocta[*b*]indol-9(6*H*)-one (45a). To a solution of the silylstannane **44a** (4.54 g, 7.1 mmol) in DMF (123 mL) was added solid TBAF·xH$_2$O (14.80 g, 57 mmol) at rt. The mixture which resulted was heated to 65 °C (oil bath temperature). After heating for 3 h, an additional 9.25 g (5 equiv) of solid TBAF·xH$_2$O was added at 65 °C in three portions of 3.7 (2 equiv), 3.7 (2 equiv), and 1.85 g (1 equiv) in intervals of 2, 2, and 1 h. After heating for 10 h, analysis by TLC indicated the disappearance of the silylstannane **44a**. The reaction mixture was brought to rt and diluted with water (123 mL). The mixture was stirred for 5 min, and this was followed by addition of EtOAc (500 mL). The two layers were separated, and the aq layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with water (5 × 50 mL) and brine (5 × 40 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by chromatography on basic alumina to yield the vinylstannane **45a** as a white-colored solid (4.0 g, 84%). Part of the oil was crystallized using EtOAc to give **45a** as white crystals for X-ray analysis. Mp 99−101 °C, $[\alpha]^{20}_D$ −70.36 (c 1.12 $CHCl_3$). R_f 0.4 (hexanes/EtOAc, 6:2). IR (KBr): 1692 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.78 (s, 1H), 7.50 (d, 1H, J = 7.6 Hz), 7.35 (d, 1H, J = 7.8 Hz), 7.23−7.11 (m, 2H), 5.64 (d, 1H, J = 2.3 Hz), 5.17 (d, 1H, J = 2.3 Hz), 4.27 (s, 1H), 4.02 (d, 1H, J = 6.4 Hz), 3.36 (q, 1H, J = 9.5, 3.2 Hz), 3.14 (dd, 1H, J = 16.8, 6.6 Hz), 2.67 (d, 1H, J = 16.8 Hz), 2.49−2.39 (m, 1H), 2.37−2.29 (m, 1H), 2.20−2.10 (m, 1H), 2.03−1.97 (m, 1H), 1.58−1.46 (m, 6H), 1.35 (sex, 6H, J = 7.4 Hz), 1.19 (d, 3H, J = 6.4 Hz), 1.00−0.90 (m, 15H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 210.6 (C), 161.0 (C), 135.7 (C), 132.3 (C), 126.9 (C), 125.6 (CH_2), 121.8 (CH), 119.6 (CH), 118.0 (CH), 110.8 (CH), 107.6 (C), 64.2 (CH), 61.2 (CH), 48.7 (CH), 34.5 (CH_2), 30.1 (CH_2), 29.0 (3 × CH_2), 27.3 (3 × CH_2), 20.8 (CH_2), 19.8 (CH_3), 13.6 (3 × CH_3), 10.6 (3 × CH_2). CIMS (m/e, relative intensity) 571 (M^+ + 1, 36), 513 (100), 281 (37), 263 (17), 169 (11). HRMS (ESI-TOF) m/z: (M + H)$^+$ calcd for $C_{30}H_{47}N_2O^{120}Sn$ 571.2711, found 571.2705.

Molybdenum-Catalyzed Functionalization of Acetylene 43a To Provide 45a and (6*S*,10*S*)-12-((*S*,*E*)-4-(Tributylstannyl)but-3-en-2-yl)-5,6,7,8,10,11-hexahydro-9*H*-6,10-epiminocycloocta-[*b*]indol-9-one (45a′). In an oven-dried flask were dissolved the N_a-*H*, acetylenic tetracyclic ketone **43a** (451 mg, 1.6 mmol), hydroquinone (10 mg, 0.1 mmol), and $Mo(CO)_3(CN$*t*$-Bu)_3$ (230 mg, 0.28 mmol) under argon in THF (5 mL). Then Bu_3SnH (1.4 g, 4.9 mmol) was added slowly, and the mixture was warmed to 55 °C and held at the same temperature for 9 h until all the starting material **43a** was consumed on analysis by TLC (silica gel). After cooling to rt, the reaction mixture was concentrated under reduced pressure and subjected to flash chromatography on silica gel. The excess Bu_3SnH was removed using hexanes as eluent. The stannylated products **45a** (360 mg) and **45a′** (190 mg) were obtained using hexanes/ethyl acetate containing 1% triethylamine as the eluent in a yield of 60%.

Major Diastereomer (45a). The spectral and physical properties of vinyl stannane **45a** were identical to those described in the above experiment.

Minor Diastereomer (45a′). R_f 0.58 (hexanes/EtOAc, 6:2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.75 (s, 1H), 7.49 (d, 1H, J = 7.6 Hz), 7.35 (d, 1H, J = 7.9 Hz), 7.22−7.11 (m, 2H), 6.04−5.78 (m, 2H), 4.42 (br, 1H), 4.04 (d, 1H, J = 6.3 Hz), 3.25 (t, 1H, J = 6.3 Hz), 3.14 (dd, 1H, J = 16.7, 6.6 Hz), 2.68 (d, 1H, J = 16.7 Hz), 2.52−2.36 (m, 2H), 2.19−2.00 (m, 2H), 1.58−1.47 (m, 6H), 1.34 (sex, 6H, J = 7.3), 1.25 (d, 3H, J = 6.4 Hz), 0.97−0.87 (m, 15H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 210.8 (C), 152.2 (CH), 135.7 (C), 132.5 (C), 129.4 (CH), 126.9 (C), 121.8 (CH), 119.6 (CH), 118.1 (CH), 110.7 (CH), 107.7 (C), 61.6 (CH), 61.1 (CH), 48.7 (CH), 34.5 (CH_2), 29.9 (CH_2), 29.1 (3 × CH_2), 27.1 (3 × CH_2), 20.8 (CH_2), 19.3 (CH_3), 13.7 (3 × CH_3), 9.4 (3 × CH_2). EIMS (m/e, relative intensity) 570 (M^+, 9), 513 (68), 279 (32), 251 (59), 223 (24), 210 (16), 182 (26), 169 (100), 156 (16), 121 (9). HRMS (ESI-TOF) m/z: (M + H)$^+$ calcd for $C_{30}H_{47}N_2O^{120}Sn$ 571.2711, found 571.2705.

(6*S*,10*S*)-5-Methyl-12-((*S*)-3-(tributylstannyl)but-3-en-2-yl)-7,8,10,11-tetrahydro-5*H*-6,10-epiminocycloocta[*b*]indol-9(6*H*)-one (45b). To a solution of the silylstannane **44b** (12 g, 18.30 mmol) in DMF (70 mL) was added TBAF·xH$_2$O (73.2 mL g, 73.2 mmol, 1.0 M solution in THF) at rt. The mixture which resulted was heated to 68 °C (oil bath temperature). After 2 h of heating the reaction mixture was brought to rt and diluted with water (123 mL). The mixture was stirred for 5 min, and this was followed by addition of EtOAc (500 mL). The two layers were separated, and the aq layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with water (5 × 50 mL) and brine (5 × 40 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by chromatography on basic alumina to yield the vinylstannane **45b** as a yellow oil (9.39 g, 88%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51 (d, 1H, J = 7.7 Hz), 7.34 (d, 1H, J = 8.1 Hz), 7.25 (td, 1H, J = 7.0, 1.2 Hz), 7.14 (td, 1H, J = 7.4, 1.0 Hz), 5.62 (d, 1H, J = 2.4 Hz), 5.17 (dd, 1H, J = 2.5 Hz), 4.36−4.35 (m, 1H), 4.03 (d, 1H, J = 6.6 Hz), 3.63 (s, 3H), 3.31 (q, 1H, J = 6.3 Hz), 3.16 (dd, 1H, J = 16.8, 6.8 Hz), 2.67 (d, 1H, J = 16.8 Hz), 2.48−2.32 (m, 2H), 2.22−2.08 (m, 1H), 2.02−1.92 (m, 1H), 1.62−1.48 (m, 6H), 1.36 (sex, 6H, J = 7.3 Hz), 1.9 (d, 3H, J = 6.4 Hz), 1.02−0.88 (m, 15H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 210.3 (C), 160.9 (C), 137.0 (C), 133.4 (C), 126.4 (C), 125.5 (CH_2), 121.2 (CH), 119.0 (CH), 118.0 (CH), 108.8 (CH), 106.5 (C), 64.2 (CH), 61.0 (CH), 47.4 (CH), 34.3 (CH_2), 29.5 (CH_2), 29.1 (3 × CH_2), 29.0 (CH_3), 27.3 (3 × CH_2), 20.6 (CH_2), 19.8 (CH_3), 13.6 (3 × CH_3), 10.6 (3 × CH_2). CIMS (m/e, relative intensity): 585 (M^+ + 1, 29), 527 (100), 293 (12).; HRMS (ESI-TOF) m/z: (M + H)$^+$ calcd for $C_{31}H_{49}N_2O^{120}Sn$ 585.2861, found 585.2883.

(6*S*,10*S*)-12-((*S*)-3-Iodobut-3-en-2-yl)-7,8,10,11-tetrahydro-5*H*-6,10-epiminocycloocta[*b*]indol-9(6*H*)-one (34a). An oven-dried single neck flask was cooled under argon and charged with the vinylstannane **45a** (1.0 g, 1.76 mmol) dissolved in CH_2Cl_2 (25 mL). Iodine (0.67 g, 2.63 mmol) was dissolved in CH_2Cl_2 (20 mL) and this solution was added in one portion to the vinylstannane **45a**, and the mixture was placed and stirred in a preheated oil bath (40−45 °C) for 1 h. After 1 h of heating, another 1.5 equiv of iodine solution (0.67 g dissolved in 20 mL of CH_2Cl_2) was added to the reaction mixture after which it was allowed to stir at 40−45 °C for 2 h. The reaction mixture was then quenched with solutions of 5% aq sodium bisulfite (100 mL) and 5% KF in methanol (100 mL), and the mixture which resulted was stirred vigorously for 10 min. The reaction mixture was diluted with additional CH_2Cl_2 (50 mL), and the two layers were separated. The aq layer was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic layers were washed with brine (2 × 50 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue was purified by silica gel chromatography to give the vinyl iodide **34a** as a white-colored solid (285 mg, 35%).

Spectral data for **34a** was identical to that reported in the communication.[24a]

(6*S*,10*S*)-12-((*S*)-3-Iodobut-3-en-2-yl)-5-methyl-7,8,10,11-tetrahydro-5*H*-6,10-epiminocycloocta[*b*]indol-9(6*H*)-one (34b). Procedure with iodine: The reaction was performed following the same procedure as for **34a** except the reaction was performed on a relatively smaller scale. Vinyl stannane **45b** (407 mg, 0.697 mmol) was dissolved in $CHCl_3$ (25 mL). Iodine (354 mg, 1.39 mmol) was dissolved in $CHCl_3$ (46 mL) and added to the solution of **45b**. Vinyl iodide **34b** was obtained as a white-colored solid (150 mg, 50%). Mp 63 °C. Procedure with I-B(Cy)$_2$: An oven-dried flask fitted with an addition funnel was cooled under argon and charged with N_a-Me acetylenic tetracyclic ketone **43b** (2.10 g, 7.55 mmol) dissolved in

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freshly distilled CH_2Cl_2 (52.5 mL) and hexanes (7.0 mL). The flask was cooled to 0 °C with ice, and I-B(Cy)$_2$ (30.2 mL, 15.1 mmol, 0.5 M solution in hexanes) was added dropwise every 0.5 h in three portions, over a total period of 1.5 h. After the last addition the reaction mixture was allowed to stir at 0 °C for another 0.5 h, after which the ice bath was removed and the mixture was stirred at rt for 2 h. After stirring at rt for 2 h, another 0.5 equiv of I-B(Cy)$_2$ (7.6 mL, 3.78 mmol) was added dropwise at rt and the mixture was allowed to stir for another 2 h. The mixture was then treated with glacial acetic acid (4.8 mL, 83.1 mmol) at 0 °C and stirred at rt for 1.15 h. At this point the flask was again cooled to 0 °C, a solution of cold aq 3 M NaOH (40.3 mL, 121 mmol) and 30% H_2O_2 (2.6 mL, 23 mmol) was added, and the stirring was maintained for 1 h at rt. The biphasic solution which resulted was transferred to a bigger flask, diluted with CH_2Cl_2 (400 mL) and water (50 mL), after which the two layers were separated. The original reaction flask still had some residual solid attached to the bottom of the flask. The solid was dissolved in acetone (50 mL). The acetone was evaporated under reduced pressure to 3/4th the volume, and the mixture was diluted with CH_2Cl_2 (50 mL). Again, the two layers were separated, and the combined CH_2Cl_2 layers were treated with solutions of 5% KF in methanol (160 mL) and 5% aq sodium bisulfite (160 mL) under vigorous stirring for 5 min. The aq layer was separated, extracted with CH_2Cl_2 (2 × 80 mL), after which the combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification by chromatography on silica gel (EtOAc/hexanes, 1:4) afforded vinyl iodide **34b** as a white solid (79%, 2.3 g). Mp 63−65 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50 (d, 1H, J = 7.7 Hz), 7.35−7.22 (m, 2H), 7.14 (ddd, 1H, J = 7.9, 7.8, 1.1 Hz), 6.22 (d, 1H, J = 0.8 Hz), 5.87 (d, 1H, J = 1.3 Hz), 4.26−4.25 (m, 1H), 4.02 (d, 1H, J = 6.5 Hz), 3.65 (s, 3H), 3.14 (dd, 1H, J = 16.9, 6.5 Hz), 2.78 (d, 1H, J = 16.3 Hz), 2.62 (q, 1H, J = 6.2 Hz), 2.59−2.51 (m, 2H), 2.20−1.95 (m, 2H), 1.95 (d, 3H, J = 6.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 210.1 (C), 137.1 (C), 132.9 (C), 126.3 (C), 125.7 (CH_2), 122.5 (C), 121.5 (CH), 119.2 (CH), 118.1 (CH), 108.9 (CH), 106.5 (C), 62.3 (CH), 60.7 (CH), 47.6 (CH), 34.3 (CH_2), 29.6 (CH_2), 29.2 (CH_3), 21.1 (CH_2), 19.7 (CH_3). EIMS (m/e, relative intensity): 420 (M^+, 78), 363 (100), 293 (46), 265 (34), 239 (32), 211 (15), 196 (27), 183 (78), 168 (42), 154 (17), 128 (14). Anal. Calcd for $C_{19}H_{21}IN_2O$: C, 54.30; H, 5.04; N, 6.67. Found: C, 54.09; H, 5.00; N, 6.26.

(6*S*,8*S*,11*R*,11a*S*)-11-(1,3-Dioxolan-2-yl)-8-methyl-9-methylene-5,6,8,9,10,11,11a,12-octahydro-6,10-methanoindolo[3,2-*b*]quinolizine (47). A mixture of anhydrous potassium *tert*-butoxide (1.82 g, 16.2 mmol) and methoxy-methyltriphenylphosphonium chloride (5.13 g, 15.0 mmol) in dry benzene (82.1 mL) was allowed to stir at rt for 1 h. The pentacyclic ketone **22a** (570 mg, 2.05 mmol) in THF (23 mL) was then added to the above red-colored solution dropwise at 0 °C. The mixture which resulted was stirred at rt for 12 h. After 12 h at rt, analysis of the mixture by TLC (silica gel, CH_2Cl_2:MeOH, 4.7:0.3, R_f 0.58) indicated the absence of starting material **22a**. The mixture was then diluted with EtOAc (100 mL), and the reaction solution was quenched with water (50 mL). The aq layer was extracted with EtOAc (2 × 15 mL), and the combined organic layers were washed with brine (2 × 30 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford a mixture of enol ethers **46** as an oil. The baseline materials (silica gel, TLC) were removed by percolation through a wash column. This material was employed directly in the next step without any further characterization and purification.

The crude compound **46** was dissolved in a solution of THF/H_2O (1:1, 10 mL). To the above solution was added 12 N aq conc HCl (1.65 mL) and the mixture which resulted was stirred at 55 °C (oil bath temperature) for 6 h. The reaction mixture was then cooled to 0 °C and extracted with ethyl ether (4 × 15 mL) to remove the phosphorus byproducts, after which the aq layer was then brought to pH 8 with an ice-cold solution of 14% aq NH_4OH. The aq layer was extracted with EtOAc (3 × 15 mL), and the combined organic layers were washed with brine (2 × 15 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford the α-aldehyde **35a** as an oil, which was subjected to the next step without any further purification and characterization.

The crude alkenic aldehyde **35a** (2.0 g, 6.84 mmol) was dissolved in dry benzene (233 mL), and this was followed by addition of dry ethylene glycol (4.67 g, 75 mmol) and *p*-toluenensulfonic acid monohydrate (1.43 g, 7.52 mmol). The mixture which resulted was heated to reflux for 6 h followed by removal of water via a DST. Analysis of the mixture by TLC (silica gel, CH_2Cl_2:MeOH) indicated the absence of starting material **35a**. The mixture was allowed to cool to rt, diluted with EtOAc, and at 0 °C brought to pH 8−9 with 14% aq NH_4OH. The aq layer was separated and then extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (2 × 20 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure and chromatographed [silica gel, CH_2Cl_2/MeOH, (10:0.3) to provide the ethylene acetal **47** (620 mg, 90% yield over 3 steps from **22a**). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.90 (s, 1H), 7.51 (d, 1H, J = 7.4 Hz), 7.32 (d, 1H, J = 7.3 Hz), 7.15 (td, 1H, J = 7.1, 1.3 Hz), 7.10 (td, 1H, J = 7.2, 1.1 Hz), 4.98 (d, 1H, J = 2.4 Hz), 4.91 (d, 1H, J = 1.5 Hz), 4.82, (d, 1H, J = 8.0 Hz), 4.21 (d, 1H, J = 8.9 Hz), 3.97−3.80 (m, 4H), 3.64−3.57 (m, 1H), 3.36 (t, 1H, J = 6.0 Hz), 3.02 (dd, 1H, J = 15.6, 5.1 Hz), 2.85 (dd, 1H, J = 14.7, 1.1 Hz), 2.54 (t, 1H, J = 1.8 Hz), 2.10 (ddd, 1H, J = 12.3, 10.2, 2.0 Hz), 1.77−1.66 (m, 2H), 1.44 (d, 3H, J = 6.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 151.8 (C), 137.7 (C), 136.3 (C), 127.8 (C), 121.3 (CH), 119.2 (CH), 118.2 (CH), 110.7 (CH), 107.7 (CH_2), 106.1 (CH), 105.2 (C), 64.7 (CH_2), 64.4 (CH_2), 57.9 (CH), 51.8 (CH), 47.0 (CH), 45.6 (CH), 35.6 (CH), 33.5 (CH_2), 27.0 (CH_2), 16.8 (CH_3). EIMS (m/e, relative intensity): 336.5 (M^+, 100), 293.5 (14), 263.5 (98), 207.4 (12), 169.4 (71), 115.3 (18), 91.3 (12). HRMS (EI) calcd for $C_{21}H_{24}N_2O_2$ 336.1838, found 336.1831.

(6*S*,8*S*,11a*S*)-5,8-Dimethyl-9-methylene-5,6,8,9,10,11,11a,12-octahydro-6,10-methanoindolo[3,2-*b*]-quinolizine-11-carbaldehyde (35b). A mixture of N_a-Me vinyl iodo tetracyclic ketone **34b** (1.78 g, 4.23 mmol), DPEPhos (88.4 mg, 0.164 mmol), and *t*-BuONa (610 mg, 6.35 mmol) in a solution of freshly distilled THF (48 mL) was degassed under reduced pressure at rt and backfilled with argon (3 times). $Pd_2(dba)_3$ (77.5 mg, 0.08 mmol) along with dry THF (3 mL) was introduced into the reaction mixture, and the system was again degassed under reduced pressure at rt and backfilled with argon (4 times). The mixture was then heated to 70 °C (oil bath temperature) under argon for 3.5 h. The mixture was then cooled to rt and quenched with ice−water. The THF volume was reduced to one-half under reduced pressure, and the mixture was diluted with EtOAc (70 mL). The aq layer was extracted with EtOAc (2 × 15 mL), and the combined organic layers were washed with brine (2 × 30 mL) and dried (Na_2SO_4). The EtOAc was then removed under reduced pressure, and the residue was flash chromatographed with CH_2Cl_2 on basic alumina to provide the cross-coupled pentacyclic ketone **22b** as a light brown-colored solid (842 mg, 68%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50 (d, 1H, J = 7.7 Hz), 7.26 (d, 1H, J = 7.2 Hz), 7.20 (ddd, 1H, J = 7.5, 6.9, 1.1 Hz), 7.10 (t, 1H, J = 7.3 Hz), 5.14 (d, 1H, J = 2.7 Hz), 5.03 (d, 1H, J = 2.3 Hz), 4.43 (dd, 1H, J = 9.4, 2.1 Hz), 3.96−3.89 (m, 1H), 3.74 (d, 1H, J = 5.5 Hz), 3.62 (s, 3H), 3.36 (dd, 1H, J = 15.6, 1.4 Hz), 3.07 (dd, 1H, J = 3.7, 2.0 Hz), 2.93 (dd, 1H, J = 15.5, 6.1 Hz), 2.62 (ddd, 1H, J = 12.3, 9.9, 1.9 Hz), 2.15 (ddd, 1H, J = 12.7, 3.8, 2.7 Hz), 1.51 (d, 3H, J = 6.8 Hz). EIMS (m/e, relative intensity): 292 (M^+, 34), 263 (100), 249 (15), 183 (91), 168 (31). The pentacylic ketone **22b** was not subjected to any further characterization. It was used directly in the next experiment.

A mixture of anhydrous potassium *tert*-butoxide (4.85 g, 43.2 mmol) and methoxy-methyltriphenylphosphonium chloride (13.69 g, 39.9 mmol) in dry benzene (82.1 mL) was allowed to stir at rt for 1 h. The pentacyclic ketone **22b** (1.7 g, 5.47 mmol) in THF (20 mL) was then added to the above red-colored solution dropwise at 0 °C. The mixture which resulted was stirred at rt for 12 h. After 12 h at rt analysis of the mixture by TLC (silica gel, CH_2Cl_2:MeOH, 4.7:0.3, R_f = 0.58) indicated the absence of starting material **22b**. The mixture was then diluted with EtOAc (100 mL), and the reaction was quenched with water (50 mL). The aq layer was extracted with EtOAc (2 × 15 mL), and the combined organic layers were washed with brine (2 × 30

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mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford the mixture of enol ethers as a brownish red oil. The baseline materials (silica gel, TLC) were removed by percolation through a wash column (silica gel). The solvent was removed under reduced pressure, and the residue was dissolved (without further purification) in a solution of THF/H_2O (1:1, 28 mL). To the above mixture aq 12 N conc HCl (4.7 mL) was added, and the mixture which resulted was stirred at 55 °C (oil bath temperature) for 6 h. The reaction mixture was then cooled to 0 °C and extracted with ethyl ether (4 × 15 mL) to remove the phosphorus byproducts, after which the aq layer was then brought to pH 8 with an ice-cold solution of 14% aq NH_4OH. The aq layer was extracted with EtOAc (3 × 15 mL), and the combined organic layers were washed with brine (2 × 15 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford **35b** as a solid (1.5 g, 90%). Part of the solid was crystallized using CH_2Cl_2:MeOH to give white crystals of **35b** for X-ray analysis. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.64 (s, 1H), 7.49 (d, 1H, J = 7.7 Hz), 7.30 (d, 1H, J = 12.8 Hz), 7.21 (td, 1H, J = 7.0 Hz), 7.11 (ddd, 1H, J = 7.8, 6.9, 1.0 Hz), 4.94 (d, 1H, J = 2.7 Hz), 4.90 (d, 1H, J = 2.3 Hz), 4.34 (d, 1H, J = 8.8 Hz), 3.83 (t, 1H, J = 6.3 Hz), 3.67 (s, 4H), 3.10 (dd, 1H, J = 15.6, 5.1 Hz), 2.86 (t, 1H, J = 1.8 Hz), 2.64 (dd, 1H, J = 15.7, 0.96 Hz), 2.43 (d, 1H, J = 7.6 Hz), 2.24 (ddd, 1H, J = 12.3, 10.0, 2.0 Hz), 1.77 (dt, 1H, J = 12.4, 3.2 Hz), 1.44 (d, 3H, J = 6.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.8 (CH), 150.3 (C), 138.8 (C), 137.3 (C), 127.1 (C), 121.0 (CH), 118.9 (CH), 118.1 (CH), 108.7 (CH), 108.4 (CH_2), 103.6 (C), 57.9 (CH), 54.9 (CH), 50.8 (CH), 44.4 (CH), 34.9 (CH), 32.4 (CH_2), 29.3 (CH_3), 27.3 (CH_2), 16.6 (CH_3). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{22}N_2O$ 306.1732, found 306.1729.

((6*S*,8*S*,9*S*,11*R*,11a*S*)-11-(1,3-Dioxolan-2-yl)-8-methyl-5,6,8,9,10,11,11a,12-octahydro-6,10-methanoindolo[3,2-*b*]-quinolizin-9-yl)methanol (36) and (6*S*,8*S*,9*R*,11*R*,11a*S*)-11-(1,3-Dioxolan-2-yl)-8,9-dimethyl-5,6,8,9,10,11,11a,12-octahydro-6,10-methanoindolo[3,2-*b*]quinolizin-9-ol (48). Procedure is reported in the Supporting Information of ref 24a.

Primary Alcohol (36). For spectral data see the Supporting Information of ref 24a.

Tertiary Alcohol (48). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.07 (s, 1H), 7.50 (d, 1H, J = 7.3 Hz), 7.32 (d, 1H, J = 7.6 Hz), 7.17−7.07 (m, 2H), 4.97 (d, 1H, J = 7.5 Hz), 4.13 (d, 1H, J = 8.8 Hz), 3.93−3.74 (m, 4H), 3.37 (d, 1H, J = 7.1 Hz), 3.02−2.91 (m, 3H), 2.60 (t, 1H, J = 11.5 Hz), 1.97 (t, 1H, J = 1.7 Hz), 1.88 (t, 1H, J = 8.2 Hz), 1.38 (s, 4H), 1.27 (d, 3H, J = 7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.4 (C), 136.3 (C), 127.8 (C), 121.2 (CH), 119.1 (CH), 118.2 (CH), 110.8 (CH), 106.2 (CH), 104.9 (C), 70.4 (C), 64.8 (CH_2), 64.2 (CH_2), 63.8 (CH), 52.4 (CH), 46.4 (CH), 44.4 (CH), 39.3 (CH), 30.1 (CH_2), 26.5 (CH_3), 26.3 (CH_2), 13.0 (CH_3). EIMS (m/e, relative intensity): 354.6 (M^+, 97), 337.6 (15), 311.5 (37), 282.5 (56), 265.5 (15), 239.5 (34), 209.4 (52), 169.4 (100), 143.3 (35), 130.3 (22), 73.2 (54). HRMS (EI-trisector) m/z: calcd for $C_{21}H_{26}N_2O_3$ 354.1943, found 354.1921.

*Conversion of **36** into Ether **51**.* To a solution of **36** (9 mg, 0.03 mmol) in THF (2 mL) was added 1 N aq HCl (0.3 mL, 0.3 mmol). The mixture which resulted was heated to reflux for 24 h, after which it was cooled to rt and brought to pH = 7 with 10% aq NH_4OH. The mixture was extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with brine, dried (Na_2SO_4), and removed under reduced pressure to provide **51** (8 mg) as an oil in 88% yield. ^{1}H NMR (300 MHz, CD_3OD): δ 7.92 (s, 1H), 7.41 (d, 1H, J = 7.7 Hz), 7.30 (d, 1H, J = 8.0 Hz), 7.07 (t, 1H, J = 6.9 Hz), 6.99 (t, 1H, J = 6.8 Hz), 4.71 (br, s, 1H), 4.19 (d, 1H, J = 8.2 Hz), 3.90 (dd, 1H, J = 11.9, 2.7 Hz), 3.80−3.73 (m, 2H), 3.69 (dd, 2H, J = 5.1, 4.0 Hz), 3.59−3.51 (m, 2H), 3.01 (dd, 1H, J = 15.7, 5.7 Hz), 2.68 (d, 1H, J = 15.6 Hz), 2.32 (m, 1H), 2.11−2.04 (m, 1H), 1.73 (d, 1H, J = 9.9 Hz), 1.58−1.52 (m, 2H), 1.46 (d, 3H, J = 7.1 Hz) (one proton is embedded in the solvent peak). ^{13}C NMR (75 MHz, $CDCl_3$): δ 120.6, 118.3, 117.1, 110.4, 99.8, 68.7, 60.8, 59.7, 55.4, 51.5, 39.6, 34.0, 32.2, 26.3, 22.7, 12.3 (quaternary carbons are not shown). EIMS (m/e, relative intensity): 354 (M^+, 95), 353 (100), 323 (7), 309 (33), 290 (69), 221 (24), 207 (72), 182 (41), 169 (51), 168 (51), 156 (24), 43 (36). HRMS (EI-trisector) m/z: calcd for $C_{21}H_{26}N_2O_3$ 354.1943, found 354.1928.

((6*S*,8*S*,9*S*,11*R*,11a*S*)-11-(Dimethoxymethyl)-8-methyl-5,6,8,9,10,11,11a,12-octahydro-6,10-methanoindolo[3,2-*b*]-quinolizin-9-yl)methanol (52). A mixture of **35a** (100 mg, 0.34 mmol), pTSA·H_2O (75 mg, 0.39 mmol), methanol (132 mg, 4.04 mmol), and trimethyl orthoformate (109 mg, 1.03 mmol) was refluxed in $CHCl_3$ (8 mL) for 6 h. The reaction mixture was brought to pH 7 with 10% aq NH_4OH. The layers were separated. The $CHCl_3$ layer was washed with brine, dried (Na_2SO_4), and removed under reduced pressure to provide dimethoxy acetal (114 mg) as an oil in 93% yield. EIMS (m/e, relative intensity): 338 (M^+, 100), 323 (63), 307 (36), 291 (13), 277 (16), 263 (78), 216 (64), 201 (89), 169 (39). This material was employed directly in the next step without any further characterization.

To a solution of the dimethoxy acetal (114 mg, 0.38 mmol) in dry THF (4 mL) was added BH_3·DMS (2.0 M solution in THF, 1.5 mL, 3.0 mmol) at rt. The mixture which resulted was stirred at rt for 2 h. The reaction mixture was then quenched by careful addition of ice cold water (4 mL) at 0 °C (initial addition of water results in a large amount of effervescence). At this point $NaBO_3$·$4H_2O$ (1.2 g, 7.76 mmol) was added to the mixture in one portion at 0 °C. The mixture which resulted was allowed to stir at rt for 2 h, after which EtOAc (100 mL) and H_2O (15 mL) were added. The organic layer was separated, washed with water (2 × 20 mL), brine (2 × 20 mL), and dried (Na_2SO_4). The EtOAc was then removed under reduced pressure to provide the N_b-BH_3 complex as a mixture of isomers at [C(20)], the majority of which was the primary alcohol. This material was used in the next step without any further purification. The above mixture of isomers was dissolved in freshly distilled MeOH (10 mL), and Na_2CO_3 (178 mg, 1.7 mmol) was added. The mixture was then warmed to 60 °C (oil bath) for 5 h under vigorous stirring. The reaction mixture which resulted was cooled to rt, followed by filtration through a bed of Celite. The filtrate was concentrated under reduced pressure to provide a turbid oil, which was redissolved in CH_2Cl_2. The CH_2Cl_2 layer was washed with H_2O (1 × 10 mL), brine (4 × 10 mL), and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford a crude solid, which was purified by flash chromatography [silica gel, CH_2Cl_2/MeOH (v/v 10:1)] to furnish the primary alcohol **52** (43 mg, 35%). The other impurities were not characterized.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.41 (br, s, 1H), 7.50 (d, 1H, J = 7.5 Hz), 7.36 (d, 1H, J = 7.8 Hz), 7.18−7.08 (m, 2H), 4.65 (d, 1H, J = 8.9 Hz), 4.19 (d, 1H, J = 8.4 Hz), 3.79−3.67 (m, 2H), 3.61 (s, 3H), 3.33−3.20 (m, 2H), 3.14 (s, 3H), 2.94−2.93 (m, 2H), 2.08 (br, s, 1H), 1.96 (t, 2H, J = 11.0 Hz), 1.87 (t, 1H, J = 8.6 Hz), 1.67 (dt, 1H, J = 12.2, 3.0 Hz), 1.29 (d, 3H, J = 7.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.1 (C), 136.3 (C), 127.6 (C), 121.3 (CH), 119.1 (CH), 118.2 (CH), 111.0 (CH), 105.8 (CH), 104.8 (C), 62.2 (CH_2), 54.6 (CH_3), 54.0 (CH), 52.3 (CH), 49.2 (CH_3), 48.7 (CH), 39.8 (CH), 39.1 (CH), 36.5 (CH_2), 26.8 (CH_2), 24.7 (CH), 12.8 (CH_3). EIMS (m/e, relative intensity): 356 (M^+, 34), 341 (66), 323 (100), 293 (13), 281 (26), 207 (28), 169 (17), 129 (170). HRMS (EI-trisector) m/z: calcd for $C_{21}H_{28}N_2O_3$ 356.2100, found 356.2110.

Peraksine (6). To a solution of **52** (8 mg, 0.03 mmol) in THF (2 mL) was added 1 N aq HCl (0.8 mL, 0.6 mmol). The mixture which resulted was heated to reflux for 4 days, after which it was cooled to rt and brought to pH = 7 with 10% aq NH_4OH. The mixture was extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with brine, dried (Na_2SO_4), and removed under reduced pressure to afford an oil. Peraksine (1 mg) was isolated by preparative TLC (silica gel) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.85 (br, s, 1H), 7.47 (t, 1H, J = 6.8 Hz), 7.35−7.32 (m, 1H), 7.18−7.07 (m, 2H), 5.10 (d, 1/2H, J = 2.0 Hz), 4.71 (d, 1/2H, J = 1.2 Hz), 4.21 (d, 1H, J = 10.9 Hz), 4.04 (dd, 1H, J = 11.8, 2.4 Hz), 3.82 (t, 1H, J = 4.6 Hz), 3.75 (d, 1H, J = 11.1 Hz), 3.56 (t, 1H, J = 5.3 Hz), 3.50 (dd, 1H, J = 12.2, 2.5 Hz), 3.28−3.02 (m, 2H), 2.70 (d, 1H, J = 16.0 Hz), 2.61 (d, 1H, J = 16.0 Hz), 2.30 (br, s, 1H), 2.06−1.94 (m, 2H), 1.47 (d, 3H, J = 7.2 Hz) (The compound is a epimeric mixture as reported).[9c] EIMS (m/e, relative intensity): 310 (M^+, 100), 309 (69), 293 (11), 279 (13), 263 (16), 223 (16), 209 (59), 195 (22), 182 (41), 168 (47), 156 (36), 115 (24).

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HRMS (EI-trisector) m/z: calcd for $C_{19}H_{22}N_2O_2$ 310.1681, found 310.1664. No further characterization was carried out.

(6*S*,8*S*,11*R*,11a*S*)-5,8-Dimethyl-9-methylene-11-(((triisopropylsilyl)oxy)methyl)-5,6,8,9,10,11,11a,12-octahydro-6,10-methanoindolo[3,2-*b*]quinolizine (53). The aldehyde **35b** (530 mg, 1.72 mmol) was dissolved in EtOH (10 mL). $NaBH_4$ (98 mg, 2.59 mmol) was added to the above solution in one portion at 0 °C and allowed to stir at 0 °C for 8 h. The reaction mixture was diluted with CH_2Cl_2 (300 mL) and poured into cold water (50 mL). The aq layer was extracted with additional CH_2Cl_2 (3 × 80 mL), and the combined organic layer was washed with brine (80 mL) and dried (K_2CO_3). The solvent was removed under reduced pressure to afford the crude product, which was purified by chromatography on silica gel (CH_2Cl_2/CH_3OH = 10:1) to provide the primary alcohol (480 mg, 90%) as a yellow oil (see S1 in Supporting Information). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44 (d, 1H, J = 7.8 Hz), 7.34 (d, 1H, J = 8.2 Hz), 7.23 (t, 1H, J = 7.6 Hz), 7.12 (t, 1H, J = 7.6 Hz), 4.95 (d, 2H, J = 3.0 Hz), 4.27 (d, 1H, J = 9.8 Hz), 3.68 (s, 4H), 3.57−3.49 (m, 2H), 3.05 (t, 1H, J = 6.2 Hz), 2.99 (dd, 1H, J = 15.3, 5.1 Hz), 2.66 (d, 1H, J = 15.3 Hz), 2.39 (br, s, 1H), 2.17−2.11 (m, 2H), 1.69 (q, 1H, J = 6.8 Hz), 1.60−1.58 (m, 1H), 1.44 (d, 3H, J = 6.8 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.0, 139.8, 137.8, 127.8, 121.3, 119.2, 118.6, 109.1, 108.3, 104.4, 65.3, 58.6, 51.4, 48.6, 45.0, 36.6, 33.6, 29.8, 27.5, 17.3. EIMS (m/e, relative intensity): 308 (M^+, 100), 293 (12), 277 (41), 196 (12), 183 (69), 168 (24): HRMS (ESI-TOF) m/z: $(M + H)^+$ calcd for $C_{20}H_{25}N_2O$, 309.1967, found 309.1976.

A solution of the primary alcohol (520 mg, 1.68 mmol) in dry CH_2Cl_2 (40 mL) was cooled to 0 °C, after which 2,6-lutidine (0.587 mL, 5.05 mmol) was added, and this was followed by addition of TIPSOTf (774 mg, 2.52 mmol) to the stirred solution. The mixture was then allowed to stir for an additional 2 h at 0 °C, after which cold water (2 mL) was added to quench the reaction. The reaction mixture was diluted with CH_2Cl_2 (100 mL) and the layers separated. The aq layer was extracted with additional CH_2Cl_2 (2 × 50 mL), and the combined organic layer was washed with brine (30 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford the crude product, which was dried in vacuo to remove the extra 2,6-lutidine before the solid was purified by chromatography on silica gel (CH_2Cl_2/CH_3OH = 20:1) to provide the *O*-TIPS ether as a white-colored solid **53** (744 mg, 95%). R_f 0.53 (silica gel, hexanes/EtOAc, 1:4). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49 (d, 1H, J = 7.6 Hz), 7.30 (d, 1H, J = 7.7 Hz), 7.19 (td, 1H, J = 7.0, 1.1 Hz), 7.09 (ddd, 1H, J = 14.7, 6.9, 1.1 Hz), 4.93−4.90 (m, 2H), 4.26 (d, 1H, J = 7.9 Hz), 3.66 (s, 4H), 3.62−3.61 (m, 2H), 3.02−2.94 (m, 2H), 2.73 (d, 1H, J = 14.0 Hz), 2.44 (t, 1H, J = 1.8 Hz), 2.16 (ddd, 1H, J = 12.7, 10.1, 2.0 Hz), 1.80 (q, 1H, J = 7.5 Hz), 1.71−1.64 (m, 1H), 1.42 (d, 3H, J = 6.8 Hz), 1.06 (s, 21H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.0 (C), 139.3 (C), 137.2 (C), 127.4 (C), 120.7 (CH), 118.6 (CH), 118.1 (CH), 108.6 (CH), 107.7 (CH_2), 104.2 (C), 65.5 (CH_2), 58.3 (CH), 51.1 (CH), 48.7 (CH), 44.4 (CH), 35.6 (CH), 33.2 (CH_2), 29.2 (CH_3), 27.2 (CH_2), 18.0 (6 × CH_3), 16.8 (CH_3), 11.9 (3 × CH). EIMS (m/e, relative intensity): 464 (M^+, 100), 421 (12), 277 (50), 196 (21), 183 (52), 161 (20). Anal. Calcd for $C_{29}H_{44}N_2OSi$: C, 74.94; H, 9.54; N, 6.03. Found: C, 74.74; H, 9.45; N, 6.06.

((6*S*,8*S*,9*S*,11*R*,11a*S*)-5,8-Dimethyl-11-(((triisopropylsilyl)oxy)methyl)-5,6,8,9,10,11,11a,12-octahydro-6,10-methanoindolo[3,2-*b*]quinolizin-9-yl)methanol (54), (6*S*,8*S*,9*S*,11*R*,11a*S*)-5,8,9-Trimethyl-11-(((triisopropylsilyl)oxy)methyl)-5,6,8,9,10,11,11a,12-octahydro-6,10-methanoindolo[3,2-*b*]quinolizin-9-ol (55), and (6*S*,8*S*,9*S*,11*R*,11a*S*)-5,8,9-Trimethyl-11-(((triisopropylsilyl)oxy)methyl)-5,6,8,9,10,11,11a,12-octahydro-6,10-methanoindolo[3,2-*b*]quinolizine (56). To a solution of the alkenic TIPS-protected alcohol **53** (208 mg, 0.447 mmol) in dry THF (9.3 mL) was added BH_3·DMS (2.0 M solution in THF, 2.05 mL, 4.11 mmol) at rt. The mixture which resulted was stirred at rt for 2 h. The reaction mixture was then quenched by careful addition of ice cold water (8.5 mL) at 0 °C (initial addition of water results in a large amount of effervescence). At this point $NaBO_3$·$4H_2O$ (1.85 g, 12 mmol) was added to the mixture in one portion at 0 °C. The mixture which resulted was allowed to stir at rt for 2 h, after which EtOAc (200 mL) and H_2O (25 mL) were added. The organic layer was separated, washed with water (2 × 20 mL), brine (2 × 20 mL), and dried (Na_2SO_4). The EtOAc was then removed under reduced pressure to provide the N_b-BH_3 complex as a mixture of isomers at [C(20)], the major of which was the primary alcohol. This material was used in the next step without any further purification. The above mixture of isomers was dissolved in freshly distilled MeOH (20 mL), and Na_2CO_3 (237 mg, 2.23 mmol) was added. The mixture was then warmed to 60 °C (oil bath) for 5 h under vigorous stirring. The reaction mixture which resulted was cooled to rt, followed by filtration through a bed of Celite. The filtrate was concentrated under reduced pressure to provide a turbid oil which was redissolved in CH_2Cl_2. The CH_2Cl_2 layer was washed with H_2O (1 × 10 mL) and brine (4 × 10 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford a crude solid, which was purified by flash chromatography [silica gel, CH_2Cl_2/MeOH (v/v 10:1)] and furnished the primary alcohol **54** (153 mg, 71%) and the tertiary alcohol **55** (6.48 mg, 3%) along with the desilylated by product **56** (10 mg, 7%) in a combined yield of 81%.

Primary Alcohol ***54***. R_f 0.29 (silica gel, EtOAc/EtOH 4.2:0.8). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48 (d, 1H, J = 7.6 Hz), 7.31 (d, 1H, J = 8.1 Hz), 7.20 (td, 1H, J = 7.0, 1.0 Hz), 7.10 (t, 1H, J = 7.3 Hz), 4.18 (dd, 1H, J = 9.6, 1.7 Hz), 3.91 (dd, 1H, J = 10.3, 8.3 Hz), 3.81 (d, 1H, J = 8.8 Hz), 3.74 (d, 1H, J = 10.0 Hz), 3.70−3.66 (m, 4H), 3.42−3.33 (m, 2H), 3.20 (dd, 1H, J = 8.0, 4.9 Hz), 2.98 (dd, 1H, J = 15.3, 5.1 Hz), 2.70 (d, 1H, J = 15.3 Hz), 2.24 (br, s, 1H), 2.07−1.80 (m, 3H), 1.60−1.53 (m, 1H), 1.33 (d, 3H, J = 7.3 Hz), 1.05 (s, 21H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.3 (C), 137.2 (C), 127.5 (C), 120.6 (CH), 118.6 (CH), 118.0 (CH), 108.6 (CH), 103.9 (C), 67.0 (CH_2), 63.1 (CH_2), 54.1 (CH), 51.2 (CH), 48.7 (CH), 41.2 (CH), 40.0 (CH), 36.4 (CH_2), 29.2 (CH_3), 27.6 (CH_2), 25.0 (CH), 17.9 (6 × CH_3), 13.2 (CH_3), 11.8 (3 × CH). EIMS (m/e, relative intensity): 482 (M^+, 100), 451 (27), 409 (10), 295 (13), 253 (10), 210 (24), 182 (52). HRMS (ESI-TOF) m/z: $(M + H)^+$ calcd for $C_{29}H_{47}N_2O_2Si$ 483.3401, found 483.3410.

Tertiary Alcohol ***55***. R_f 0.59 (silica gel, EtOAc/EtOH 4.2:0.8). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45 (d, 1H, J = 7.7 Hz), 7.28 (d, 1H, J = 8.0 Hz), 7.17 (td, 1H, J = 7.0, 1.1 Hz), 7.07 (t, 1H, J = 7.3 Hz), 4.23 (dd, 1H, J = 9.8, 2.0 Hz), 3.83 (dd, 1H, J = 9.8, 7.9 Hz), 3.73 (dd, 1H, J = 9.8, 6.9 Hz), 3.65 (s, 3H), 3.15−3.11 (m, 1H), 3.03 (q, 1H, J = 7.2 Hz), 2.93−2.92 (m, 2H), 2.66 (ddd, 1H, J = 10.8, 10.3, 1.8 Hz), 2.03−1.95 (m, 1H), 1.78 (t, 1H, J = 1.5 Hz), 1.35 (s, 3H), 1.32 (d, 1H, J = 2.9 Hz), 1.28 (d, 3H, J = 7.2 Hz), 1.05 (s, 21H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.5 (C), 137.1 (C), 127.6 (C), 120.4 (CH), 118.5 (CH), 118.0 (CH), 108.5 (CH), 104.1 (C), 70.9 (C), 67.3 (CH_2), 64.1 (CH), 51.4 (CH), 48.9 (CH), 43.1 (CH), 39.9 (CH), 30.4 (CH_2), 29.2 (CH_3), 27.1 (CH_2), 26.7 (CH_3), 18.0 (6 × CH_3), 13.4 (CH_3), 11.9 (3 × CH). EIMS (m/e, relative intensity): 482 (M^+, 76), 464 (100), 463 (65), 449 (13), 410 (13), 409 (23), 277 (47), 183 (82), 182 (71). HRMS (ESI-TOF) m/z: $(M + H)^+$ calcd for $C_{29}H_{47}N_2O_2Si$, 483.3401, found 483.3407.

Reduced Ethylidene Byproduct ***56***. R_f 0.1 (silica gel, EtOAc/EtOH 4.2:0.8). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46 (d, 1H, J = 7.6 Hz), 7.28 (d, 1H, J = 8.0 Hz), 7.17 (td, 1H, J = 7.0, 1.1 Hz), 7.08 (t, 1H, J = 7.7 Hz), 4.17 (d, 1H, J = 9.8 Hz), 3.82−3.70 (m, 2H), 3.65 (s, 3H), 3.34 (dd, 1H, J = 10.4, 7.3 Hz), 3.26 (dd, 1H, J = 8.7, 4.9 Hz), 2.95 (dd, 1H, J = 15.3, 4.9 Hz), 2.76 (d, 1H, J = 15.2 Hz), 2.01−1.90 (m, 2H), 1.84 (br, s, 1H), 1.72 (q, 1H, J = 1.57 (ddd, 1H, J = 12.0, 4.2, 2.5 Hz), 1.28 (d, 3H, J = 7.1 Hz), 1.09 (d, 3H, J = 7.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.5 (C), 137.1 (C), 127.5 (C), 120.5 (CH), 118.6 (CH), 118.0 (CH), 108.5 (CH), 104.4 (C), 67.2 (CH_2), 55.0 (CH), 51.5 (CH), 49.0 (CH), 42.5 (CH), 37.4 (CH_2), 32.1 (CH), 31.8 (CH), 29.2 (CH_3), 27.7 (CH_2), 16.8 (CH_3), 14.3 (CH_3). EIMS (m/e, relative intensity): 310 (M^+, 100), 309 (87), 295 (28), 279 (14), 253 (18), 237 (14), 183 (44). HRMS (EI-trisector) m/z: calcd for $C_{20}H_{26}N_2O$ 310.2045, found 310.2055.

(6*S*,8*S*,9*R*,11*R*,11a*S*)-5,8-Dimethyl-11-((triisopropylsilyl)oxy)-methyl)-5,6,8,9,10,11,11a,12-octahydro-6,10-methanoindolo-[3,2-*b*]quinolizine-9-carbaldehyde (57b). To a stirred solution of *N*-chlorosuccinimide (8.3 mg, 0.062 mmol) in dry CH_2Cl_2 (1.5 mL)

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was added dimethyl sulfide (7.6 μL, 0.103 mmol) at −5 to −15 °C (outside bath temperature) under argon. A white precipitate appeared immediately after addition of the sulfide, which was stirred for an additional 0.5 h at the above-mentioned temperature range. After 0.5 h, the temperature of the reaction mixture was lowered to −78 °C (EtOAc−dry ice bath). The alcohol **54** (10 mg, 0.02 mmol) in dry CH_2Cl_2 (1.0 mL) was also cooled at −78 °C and then added via cannula to the white complex, and stirring was continued for 2 h at −78 °C. A solution of distilled triethylamine (11 μL, 0.08 mmol) was then added to the above mixture dropwise (neat) and the stirring was continued for an additional 1 h at −78 °C. Upon completion of the reaction, the reaction mixture was quenched at −78 °C by addition of excess CH_2Cl_2 and H_2O. The organic layer was separated, washed with brine, and dried (Na_2SO_4). The solvent was removed under reduced pressure to provide the mixture of crude aldehydes **57a/b**. Addition of EtOAc from the sides of the flask resulted in formation of a white insoluble precipitate. The precipitate was filtered, and the EtOAc layer was concentrated under reduced pressure. The same process was repeated 4−5 times until one no longer sees any formation of a precipitate after addition of EtOAc to the residue to remove the Corey−Kim sulfur impurities. Analysis of the ^{1}H NMR spectrum of the residue indicated formation of the epimeric aldehydes (**57a**:**57b**) in the ratio of 4:1. The epimeric mixture of aldehydes **57a/b** was dissolved in a solution of MeOH (3 mL) and triethylamine (0.17 mL), and the mixture was stirred overnight at rt to effect complete epimerization. The methanol was then removed under reduced pressure to give an oil, which was further purified by flash column chromatography (basic alumina, EtOAc:EtOH, 9:0.1) to give the α-aldehyde **57b** as a colorless oil (6.97 mg, 80%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.85 (s, 1H), 7.50 (d, 1H, *J* = 7.7 Hz), 7.30 (d, 1H, *J* = 8.1 Hz), 7.20 (ddd, 1H, *J* = 7.5, 7.0, 1.1 Hz), 7.11 (t, 1H, *J* = 7.3 Hz), 4.20 (d, 1H, *J* = 8.1 Hz), 3.87−3.78 (m, 2H), 3.62 (s, 3H), 3.50−3.41 (m, 1H), 3.23 (t, 1H, *J* = 6.1 Hz), 3.00 (dd, 1H, *J* = 15.4, 5.0 Hz), 2.74 (d, 1H, *J* = 14.7 Hz), 2.53 (d, 1H, *J* = 8.5 Hz), 2.46 (d, 1H, *J* = 2.0 Hz), 1.92 (dd, 1H, *J* = 11.8, 1.7 Hz), 1.78 (dd, 1H, *J* = 14.1, 6.7 Hz), 1.46−1.39 (m, 1H), 1.36 (d, 3H, *J* = 6.8 Hz), 1.10 (s, 21H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.5 (CH), 139.1 (C), 137.2 (C), 127.3 (C), 120.8 (CH), 118.7 (CH), 118.0 (CH), 108.6 (CH), 104.3 (C), 64.3 (CH_2), 52.2 (CH), 51.3 (CH), 51.0 (CH), 47.6 (CH), 42.4 (CH), 29.5 (CH_2), 29.2 (CH_3), 26.9 (CH_2), 26.6 (CH), 19.3 (CH_3), 18.0 (6 × CH_3), 11.8 (3 × CH). HRMS (EI-trisector) *m*/*z*: calcd for $C_{29}H_{44}N_2O_2Si$ 480.3172, found 480.3175.

(6*S*,8*S*,9*R*,11*R*,11a*S*)-11-(Hydroxymethyl)-5,8-dimethyl-5,6,8,9,10,11,11a,12-octahydro-6,10-methanoindolo[3,2-*b*]quinolizine-9-carbaldehyde (58). The aldehydes **57a/b** were synthesized following the above procedure for the Corey−Kim oxidation. To a solution of **57a/b** (15 mg, 0.03 mmol) in THF (10 mL) was added 1 N aq HCl (1.6 mL, 0.6 mmol). The mixture which resulted was heated to reflux for 3 h, after which it was cooled to rt and brought to pH = 7 with cold 10% aq NH_4OH. The mixture was extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with brine, dried (Na_2SO_4), and removed under reduced pressure to afford **58** as a brown oil (8 mg, 80%), which was purified by preparative TLC [silica gel, CH_2Cl_2/MeOH (v/v 10:1) with 1% NH_4OH (14%)]. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.87 (s, 1H), 7.48 (d, 1H, *J* = 7.7 Hz), 7.29 (d, 1H, *J* = 7.8 Hz), 7.20 (m, 1H), 7.09 (m, 1H), 4.18 (d, 1H, *J* = 12.4 Hz), 3.80−3.75 (m, 2H), 3.62 (s, 3H), 3.51−3.41 (m, 1H), 3.12−3.08 (m, 1H), 3.00 (dd, 1H, *J* = 15.6, 4.9 Hz), 2.71 (d, 1H, *J* = 15.0 Hz), 2.47 (br, s, 1H), 2.38 (d, 1H, *J* = 8.5 Hz), 1.98−1.90 (m, 1H), 1.79 (q, 1H, *J* = 7.6 Hz), 1.44−1.43 (m, 1H), 1.34 (d, 3H, *J* = 6.8 Hz). EIMS (*m*/*e*, relative intensity): 324 (M^+, 91), 306 (11), 295 (77), 281 (20), 253 (15), 223 (30), 209 (21), 196 (37), 183 (100), 168 (41), 144 (28), 115 (14). HRMS (EI-trisector) *m*/*z*: calcd for $C_{20}H_{24}N_2O_2$ 324.1838, found 324.1818. No further characterization was carried out.

Macrosalhine N_b-Oxide (60). Dess−Martin periodinane (184 mg, 0.434 mmol) was added to a solution of the primary alcohol **54** (100 mg, 0.207 mmol) in CH_2Cl_2 (30 mL) in one portion at 0 °C. The reaction mixture was then allowed to warm to rt and stirred for 2 h at this temperature. The reaction mixture was quenched with a saturated solution of aq $NaHCO_3$ (9 mL), and a saturated solution of aq $Na_2S_2O_3$ (9 mL) was added, after which the mixture was stirred for 10 min at 0 °C. The aq layer was extracted with additional amounts of CH_2Cl_2 (3 × 20 mL), and the combined organic layer was washed with brine (20 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure to provide the crude product, which was separated by preparative TLC [silica gel, CH_2Cl_2/MeOH (v/v 20:1) with 1% NH_4OH(14%)] to provide the aldehyde N_b-oxide **59** (69 mg, 67%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.1 [(s, 1H (CHO)]. EIMS (*m*/*e*, relative intensity): 496 (M^+, 100), 467 [25 (M − CHO)], 451 (15), 437 (24), 409 (12), 308 (17), 279 (14), 248 (23), 211 (43), 183 (97), 170 (71), 75 (20). HRMS (EI-trisector) *m*/*z*: clcd for $C_{29}H_{44}N_2O_3Si$ 496.3121, found 496.3097.HRMS (ESI-TOF) *m*/*z*: $(M + H)^+$ calcd for $C_{29}H_{45}N_2O_3Si$ 497.3199, found 497.3193. No further characterization was carried out.

To a solution of **59** (5 mg, 0.01 mmol) in THF (2 mL) was added 1 N aq HCl (0.8 mL, 0.6 mmol). The mixture which resulted was heated to reflux for 2 days, after which it was cooled to rt and brought to pH = 7 with 10% aq NH_4OH. The mixture was extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with brine, dried (Na_2SO_4), and removed under reduced pressure to afford an oil. Macrosalhine N_b-oxide **60** (2.6 mg, 75%) was isolated by preparative TLC (silica gel) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48 (d, 1H, *J* = 7.7 Hz), 7.30 (d, 1H, *J* = 9.5 Hz), 7.19 (t, 1H, *J* = 7.9 Hz), 7.09 (t, 1H, *J* = 7.7 Hz), 5.10 (s, 1H), 4.28 (d, 1H, *J* = 8.7 Hz), 4.03 (d, 1H, *J* = 10.5 Hz), 3.66−3.61 (m, 4H), 3.45 (dd, 1H, *J* = 10.9, 1.9 Hz), 3.22−3.05 (m, 2H), 2.67−2.51 (m, 3H), 2.07−2.05 (m, 2H), 1.56 (d, 2H, *J* = 5.2 Hz), 1.40 (d, 3H, *J* = 7.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 120.8, 118.7, 118.0, 108.6, 92.8, 69.9, 63.5, 61.8, 49.6, 46.1, 38.3, 31.4, 29.1, 26.5, 25.2, 12.1 (the quaternary carbons are not reported). EIMS (*m*/*e*, relative intensity): 340 (M^+, 82), 339 (91), 322 (40), 296 (32), 265 (19), 239 (15), 221 (18), 196 (13), 183 (100), 168 (18), 97 (18), 83 (14), 57 (14). HRMS (EI-trisector) *m*/*z*: calcd for $C_{20}H_{24}N_2O_3$ 340.1787, found 340.1779. HRMS (ESI-TOF) *m*/*z*: $(M + H)^+$ calcd for $C_{20}H_{25}N_2O_3$ 341.1860, found 341.1837.

(6*S*,8*S*,9*S*,11*R*,11a*S*)-9-(Hydroxymethyl)-5,7,8-trimethyl-11-(((triisopropylsilyl)oxy)methyl)-6,7,8,9,10,11,11a,12-octahydro-5*H*-6,10-methanoindolo[3,2-*b*]quinolizin-7-ium Iodide (61). To a solution of the monol **54** (10 mg, 0.02 mmol) in MeOH (0.8 mL) was added an excess of MeI (0.3 mL) at 0 °C, after which the mixture was allowed to stir in the dark at 0 °C overnight. Upon completion of the reaction, the solvent was removed under reduced pressure and dried overnight under high vacuum to provide the N_b-methyl salt **61** (10.2 mg, 99%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45 (d, 1H, *J* = 7.8 Hz), 7.38 (d, 1H, *J* = 8.1 Hz), 7.32 (t, 1H, *J* = 7.0 Hz), 7.18 (t, 1H, *J* = 7.5 Hz), 6.20 (d, 1H, *J* = 9.7 Hz), 5.16−5.10 (m, 1H), 3.99−3.86 (m, 2H), 3.82 (s, 3H), 3.80−3.68 (m, 3H), 3.43 (d, 1H, *J* = 15.5 Hz), 3.21 (s, 3H), 2.90 (t, 1H, *J* = 11.4 Hz), 2.82−2.69 (m, 1H), 2.35 (br, s, 1H), 2.28−2.21 (m, 1H), 1.96 (dd, 1H, *J* = 13.3, 3.4 Hz), 1.76 (d, 3H, *J* = 7.0 Hz), 1.05 (s, 21H). ^{13}C NMR (75 MHz, $CDCl_3$): 137.7(C), 133.7 (C), 125.7 (C), 122.6 (CH), 120.1 (CH), 118.2 (CH), 109.6 (CH), 100.1 (C), 67.0 (CH), 66.1 (CH_2), 61.4 (CH_2), 61.0 (CH), 60.7 (CH), 44.6 (CH_3), 42.8 (CH), 42.4 (CH), 34.6 (CH_2), 30.7 (CH_3), 25.9 (CH), 25.0 (CH_2), 18.0 (6 × CH_3), 11.7 (3 × CH), 10.6 (CH_3). HRMS (ESI-TOF) *m*/*z*: $(M)^+$ calcd for $C_{30}H_{49}N_2O_2Si$ 497.3563, found 497.3561.

(6*S*,8*S*,9*R*,11*R*,11a*S*)-9-Formyl-5,7,8-trimethyl-11-(((triisopropylsilyl)oxy)methyl)-6,7,8,9,10,11,11a,12-octahydro-5*H*-6,10-methanoindolo[3,2-*b*]quinolizin-7-ium Iodide (63). To a solution of the aldehyde **57b** (10 mg, 0.02 mmol) in MeOH (0.8 mL) was added an excess of MeI (0.3 mL) at 0 °C, after which the mixture was allowed to stir in the dark at 0 °C overnight. Upon completion of the reaction the solvent was removed under reduced pressure and dried overnight under high vacuum to provide the N_b-methyl salt **63** (8.76 mg, 85%). R_f 0.5 (basic alumina, DCM/MeOH, 2.4:0.1). ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.93 (s, 1H), 7.51 (d, 1H, *J* = 6.0 Hz), 7.39 (d, 1H, *J* = 12.0 Hz), 7.33 (t, 1H, *J* = 6.0 Hz), 7.20 (t, 1H, *J* = 6.0 Hz), 6.52 (d, 1H, *J* = 12.0 Hz), 5.31−5.28 (m, 1H), 4.05−4.03 (m, 1H), 3.96 (d, 2H, *J* = 6.0 Hz), 3.83 (s, 3H), 3.40 (s, 3H), 3.33 (dd, 1H, *J* = 18.0, 6.0 Hz), 3.14 (d, 2H, *J* = 12 Hz), 2.75−2.72 (m, 2H), 2.24−2.21 (q, 1H, *J* = 6.0 Hz), 1.88 (d, 1H, *J* = 6.0 Hz), 1.74 (d, 3H, *J* = 6.0

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Hz), 1.10 (s, 21H). ^{13}C NMR (150 MHz, $CDCl_3$): 198.1 (CH), 137.9 (C), 132.8 (C), 125.6 (C), 123.0 (CH), 120.4 (CH), 118.4 (CH), 110.0 (CH), 100.2 (C), 63.7 (CH_2), 63.7 (CH), 61.0 (CH), 59.0 (CH), 52.2 (CH), 44.9 (CH_3), 42.3 (CH), 31.0 (CH_3), 29.2 (CH_2), 25.8 (CH), 24.2 (CH_2), 18.1 (6 × CH_3), 16.8 (CH_3), 11.8 (3 × CH). HRMS (ESI-TOF) m/z: $(M)^+$ calcd for $C_{30}H_{47}N_2O_2Si$ 495.3401, found 495.3410.

2-((6*S*,8*R*,9*R*,10*S*)-5,12-Dimethyl-9-(((triisopropylsilyl)oxy)-methyl)-6,7,8,9,10,11-hexahydro-5*H*-6,10-epiminocycloocta-[*b*]indol-8-yl)but-2-enal (64). To a solution of N_b-Me salt **63** (5 mg, 0.010 mmol) in THF, KO^{t}Bu (2.3 mg, 0.020 mmol) was added at rt, after which the mixture was allowed to stir overnight. Analysis by LCMS indicated the disappearance of **63**. THF was removed under reduced pressure, and the residue was purified by flash chromatography [silica gel, DCM/methanol (v/v 1:1)] to provide the macroline equivalent **64** (3 mg) in 60% yield. ^{1}H NMR (400 MHz, $CDCl_3$): 10.05 (s, 1H), 7.54 (d, 1H, J = 8 Hz), 7.26 (d, 1H, J = 8 Hz), 7.17 (t, 1H, J = 8.0 Hz), 7.10 (t, 1H, J = 8.0 Hz), 6.34 (q, 1H, J = 8.0 Hz), 4.01 (br, s, 1H), 3.91 (t, 1H, J = 8.0 Hz), 3.60 (s, 3H), 3.47−3.42 (m, 2H), 3.30 (dd,1H, J = 16.0, 8.0 Hz), 2.91 (d, 1H, J = 16.0 Hz), 2.62 (d, 1H, J = 16.5 Hz), 2.31 (s, 3H), 2.16 (t, 1H, J = 4.0 Hz), 2.07 (d, 4H, J = 8.0 Hz), 1.33 (d, 1H, J = 12.0 Hz), 1.04 (s, 21H). ^{13}C NMR (100 MHz, $CDCl_3$): 190.1 (CH), 141.7(C), 141.4 (CH), 137.0 (C), 133.3 (C), 126.7 (C), 120.6 (CH), 118.7 (CH), 118.4 (CH), 108.6 (CH), 107.5, 62.0 (CH_2), 53.9 (CH), 53.4 (CH), 46.7 (CH), 42.1(CH_3), 29.7 (CH_2), 29.0 (CH), 28.9 (CH_3), 22.2 (CH_2), 18.1 (6 × CH_3), 13.0 (CH_3), 12.0 (3 × CH). HRMS (ESI-TOF) m/z: $(M + H)^+$ calcd for $C_{30}H_{47}N_2O_2Si$ 495.3401, found 495.3408.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra for all new compounds **22b**, **34b**, **35b**, **42a′**, **42b−45b**, **42b′**, **44a**, **45a/a′**, **48**, **51−56**, **57b**, **58**, **60**, **61**, **63**, and **64**; X-ray data for compounds **35b**, **43b**, **44b**, and **45a** in CIF. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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