

Article

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

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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/jo5016163 • Publication Date (Web): 23 Sep 2014

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General Strategy for the Synthesis of C-19 Methyl Substituted
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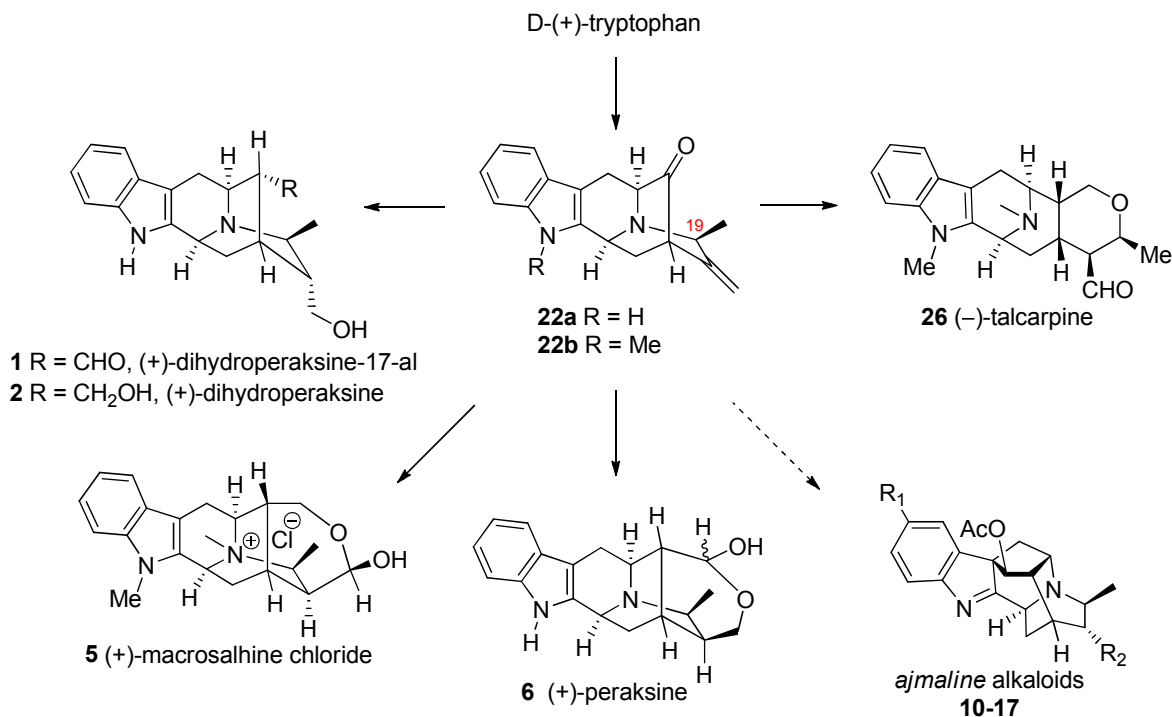
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TOC



ABSTRACT

A detailed account of the development of a general strategy for the synthesis of the C-19 methyl substituted alkaloids including the 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 macrosalpine 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. The synthesis of the advanced intermediate **32a** completes an improved formal total synthesis of talcarpine (**26**) and provides a starting point for the synthesis of *macroline*-related alkaloids **27-31**. Similarly extension of this synthetic strategy in the ring A oxygenated series should provide an easy access to the northern hemisphere **32b** of the bisindoles angusticraline, alstocraline and foliacraline (Figure 4).

INTRODUCTION

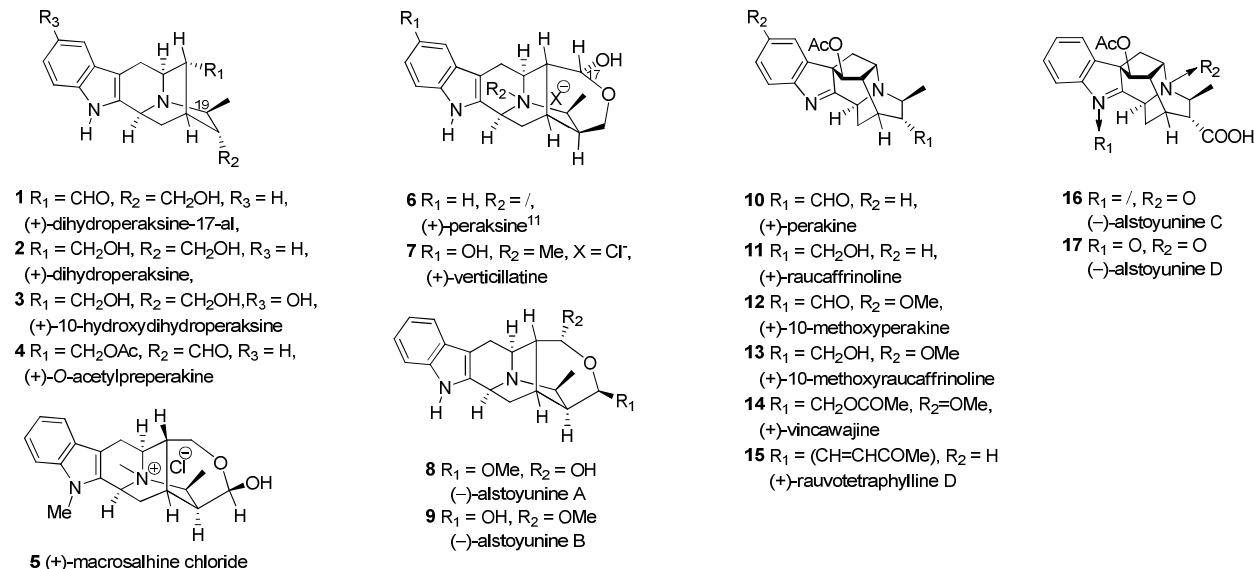
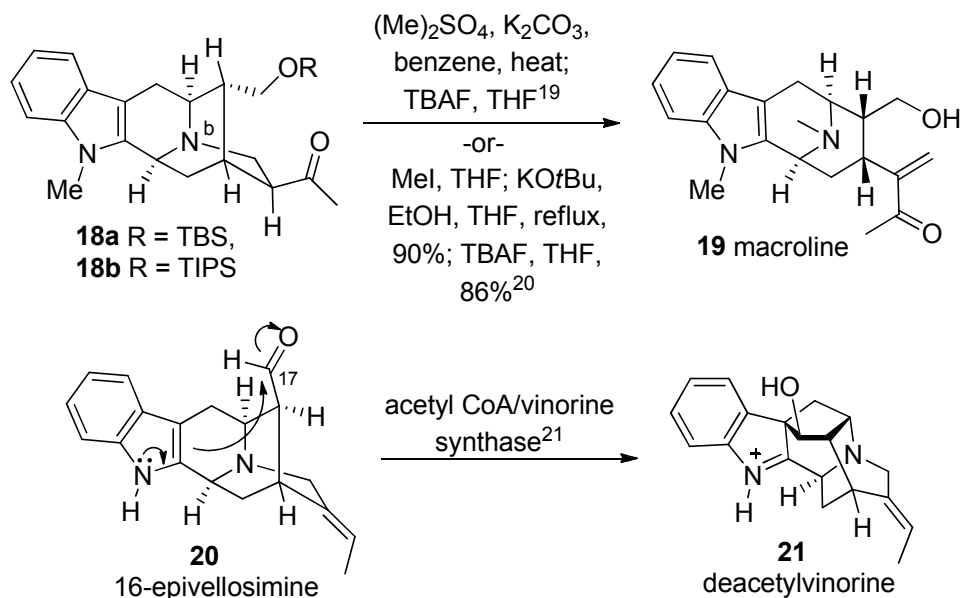


Figure 1. Sarpagine-ajmaline alkaloids containing a C-19(*S*) methyl group.

The C-19 methyl substituted indole alkaloids represented in Figure 1 are a relatively rare class of alkaloids belonging to the *sarpagine-ajmaline* series¹ with over seventeen 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.O.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 were not determined during isolation. The presence of a hexacyclic hemiacetal ring is a unique feature of the C-19 methyl substituted alkaloids macrosalpine 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.

Scheme 1. Biomimetic and Biosynthetic relationship between the *sarpagine*, *macroline* and *ajmaline* alkaloids.



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 elimination¹⁸ 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 *ajmaline* alkaloids was confirmed by the conversion of 16-epivellosimine **20** into deacetylvinorine **21** by Stöckigt et al. (Scheme 1).²¹

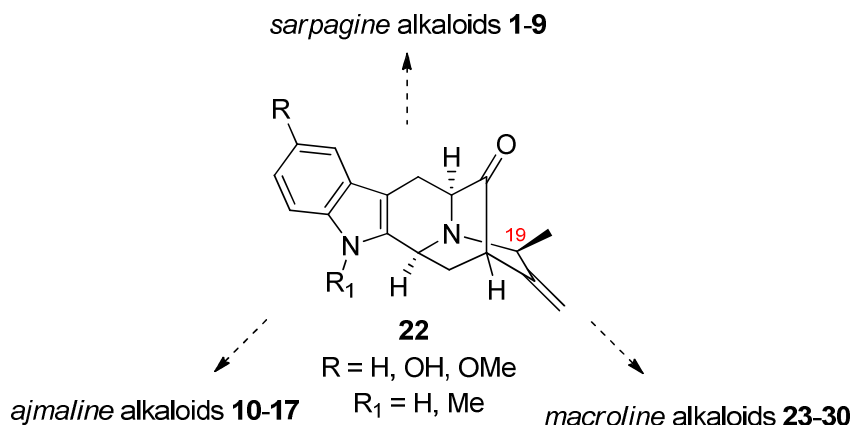
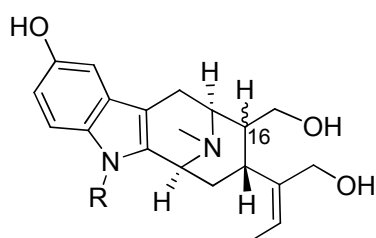


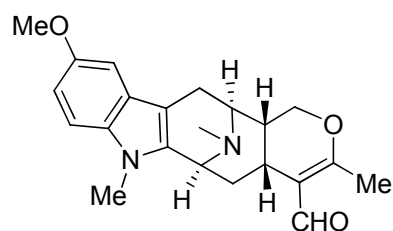
Figure 2. Pentacyclic intermediates **22**

Based on this, the C-19 methyl substituted basic *sarpagine* framework **22** (Figure 2) could serve as the key template for the synthesis of the *ajmaline* alkaloids **10-17** and the *macroline* bases **22-30** (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 bisindoles (+)-angusticaline, (+)-alstocraline and (+)-foliacraline (Figure 4).^{22b,23} Herein we would like to provide a detailed account of the development of a general strategy for the synthesis of the C-19 methyl substituted alkaloids including the total synthesis of (+)-19(*S*),20(*R*)-dihydroperaksine (**1**), (+)-19(*S*),20(*R*)-dihydroperaksine-17-al (**2**),²⁴ (+)-peraksine (**6**) and formal total synthesis of (–)-talcarpine (**25**) as well as the efforts directed toward the total synthesis of (+)-macrosalpine chloride (**5**).

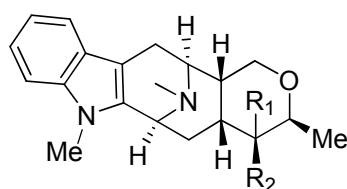


23 R = Me, β -H at C-16
(+)-rauvoyunine A^{22a}

24 R = H, α -H at C-16
(+)-rauvotetraphylline A¹⁶



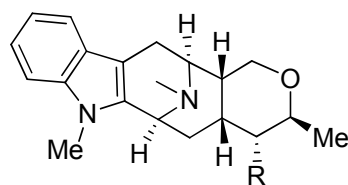
25 (-)-19,20-dehydro-10-methoxytalcarpine^{22b}



26 R₁ = H, R₂ = CHO
(-)-talcarpine¹⁷

27 R₁ = H, R₂ = CH₂OH
(-)-macrocarpine A^{22c}

28 R₁ = OH, R₂ = CH₂OH
(-)-alstohentine^{22d}

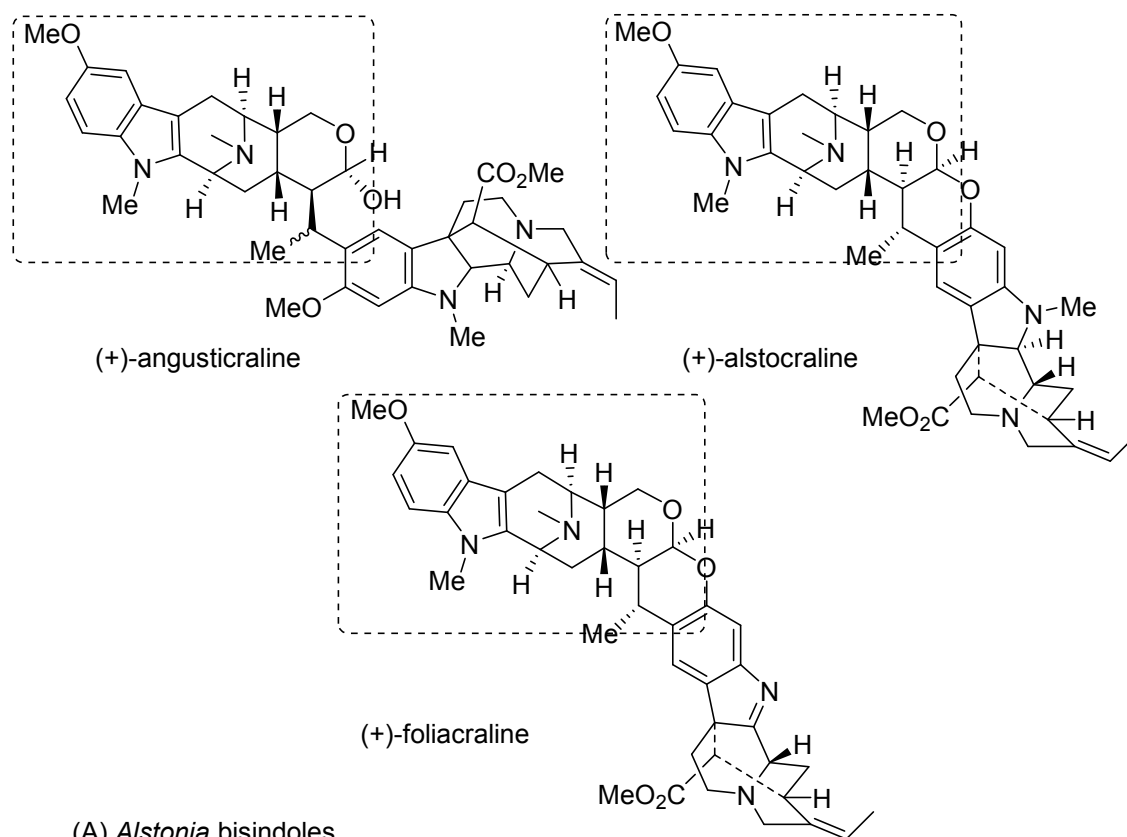


29 R = CHO
(-)-secotalcarpine¹⁷

30 R = CH₂OH
(-)-macrocarpine B^{22c}

31 R = CH₂OAc
(-)-macrocarpine C^{22c}

Figure 3. *Macroline*-related indole alkaloids^{16,17,22}



(A) *Alstonia bisindoles*

(B) Proposed biogenesis of angusticraline and alstocraline

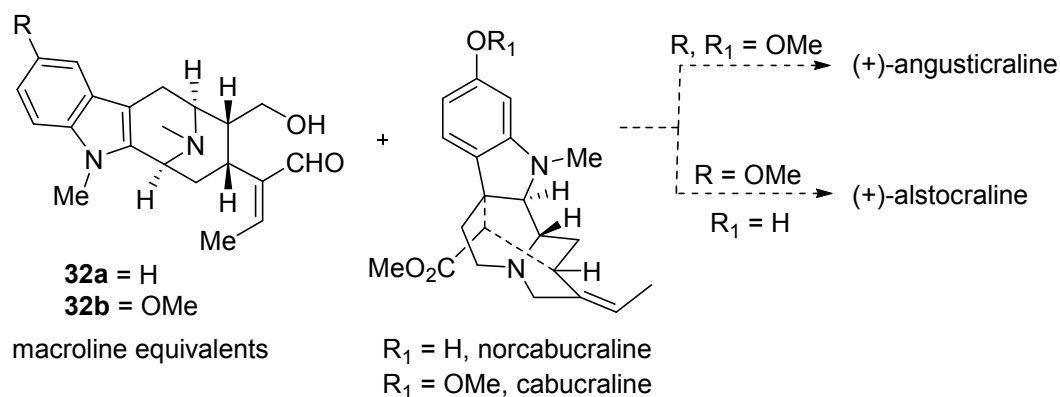
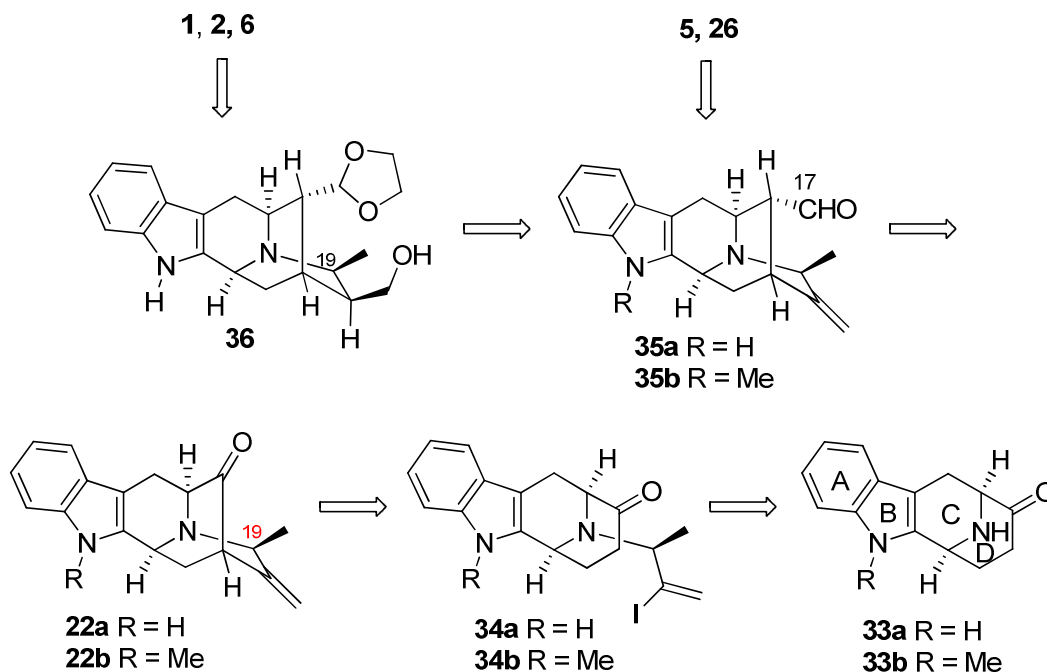


Figure 4. *Alstonia* bisindoles and their proposed biogenesis.

RESULTS AND DISCUSSION

Scheme 2. Retrosynthetic Analysis



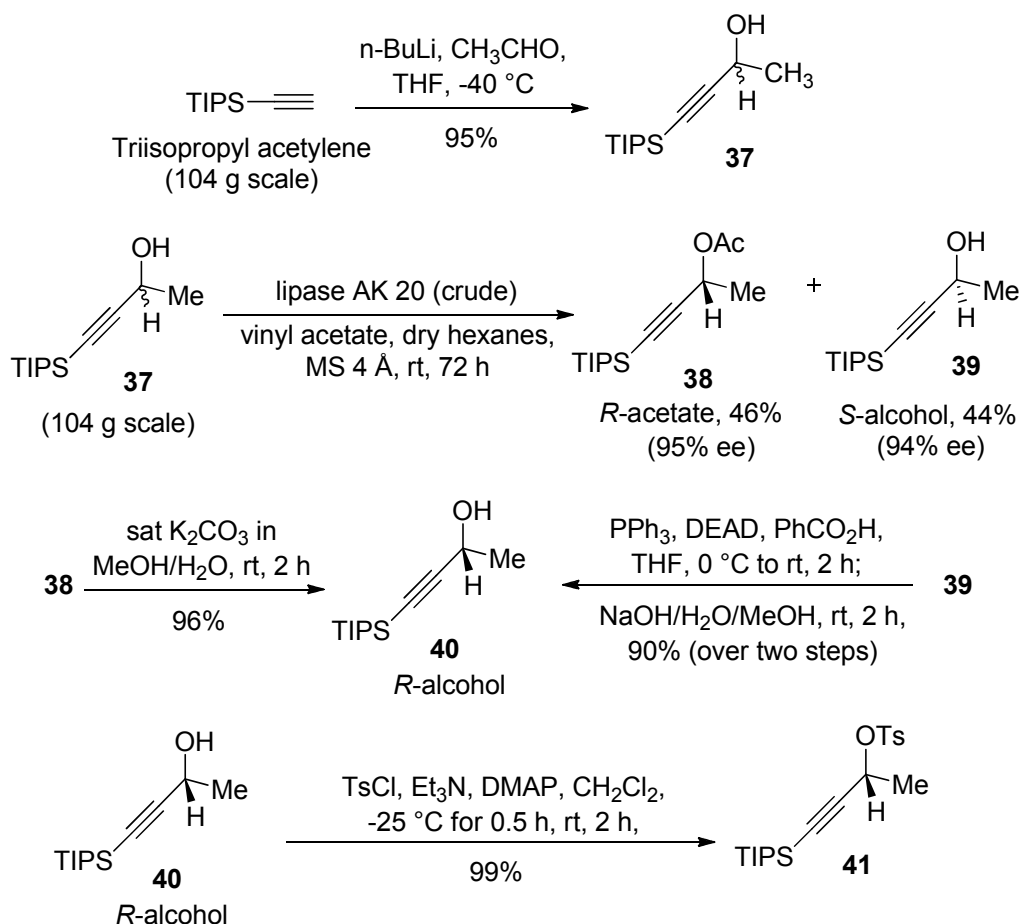
As illustrated in Scheme 2, in a retrosynthetic sense, dihydroperaksine-17-al (**1**), and dihydroperaksine (**2**) could presumably be obtained from **36** by an oxidation/epimerization/reduction sequence. The β -primary alcohol in **36** could also serve as the precursor for peraksine (**6**) and can be expected to originate from the terminal olefinic moiety in aldehyde **35a** via a regioselective hydroboration process. The thermodynamically stable α -aldehydes at C-17 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 the 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 The inclusion of the C-19 β -methyl group in the *sarpagine* skeleton required the synthesis of a suitably protected *R*-acetylenic alcohol **40** in high optical purity (Scheme 3). Several methods have been reported for the 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 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-butyne-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. Our initial report on the 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 the synthesis of **40** which can be performed on a large scale with higher ee (>95%). As illustrated in Scheme 3, the synthesis of **40** began with the large scale

preparation of the racemic TIPS-acetylenic alcohol **37** from commercially available TIPS acetylene, following the procedure of Jones et al.³⁰

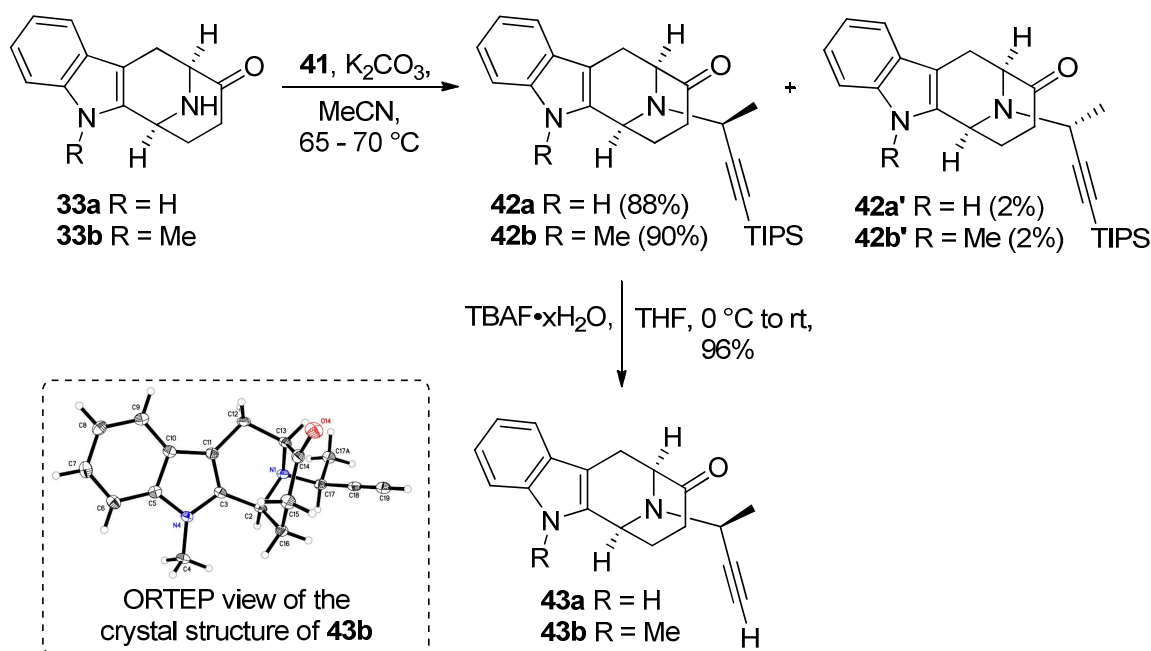
Scheme 3. Lipase mediated kinetic resolution of racemic alcohol **37**



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% 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 ¹H-

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.

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



The N_b -alkylation of the secondary amines **33a/b** (individually) with optically active (*R*)-tosylate **41** either 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

their minor diastereomers **42a'/b'** in a combined yield of 89% and 94% in N_a -H and the N_a -Me series, respectively. Both diastereomers (major vs minor) were completely separable both in the N_a -H and N_a -Me series by silica gel column chromatography.

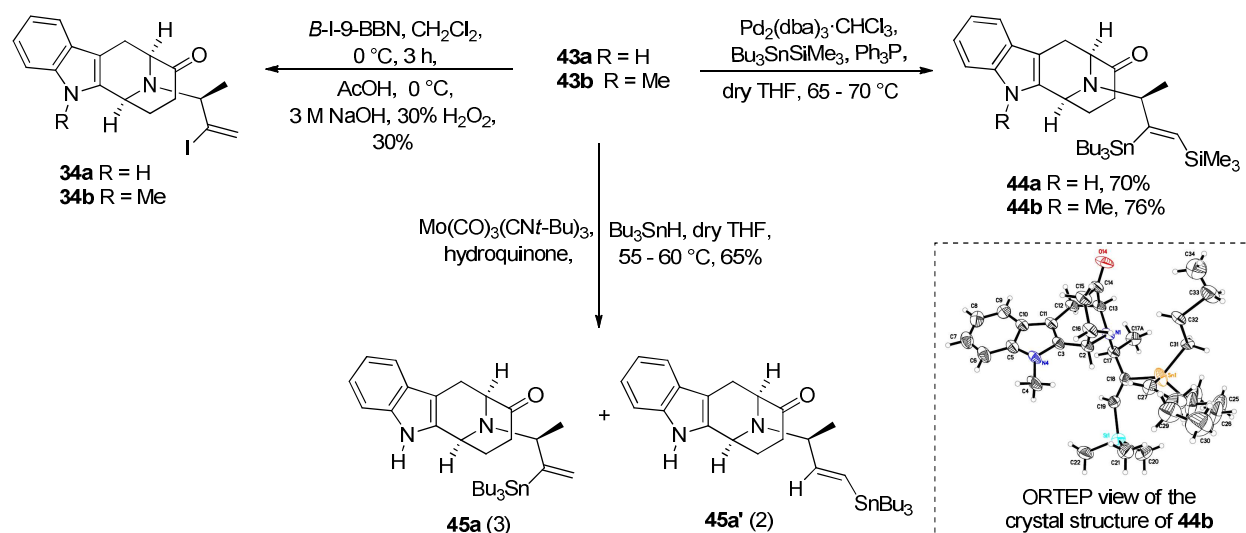
Desilylation of **42a/b** with tetrabutylammonium fluoride (TBAF·xH₂O) at 0 °C in THF provided the acetylenic compounds **43a/b**, respectively, in 96% yield (Scheme 4). The 'S' configuration at C-12 (C-19 for the *sarpagine* skeleton) was confirmed by X-ray crystal analysis in the N_a -Me series (Scheme 4). With the 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**.

The simplest method for converting terminal alkynes to vinyl iodides in a single step is by the use of HI³³ which is not useful especially for sensitive substrates. Although other methods are reported³⁴ there are very few reports on the 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 by 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 included: heating it to reflux, or increasing the equivalents of the reagent (1.2 to 8 eq), use of freshly distilled reagent, portion wise 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 the less than satisfactory outcome of the key step,

investigation of other haloborating agents was investigated. The order of reactivity³⁷ of the haloborating reagents commonly used is: B-I-9-BBN, $\text{BBr}_3 > \text{BCl}_3 > \text{B-Br-9-BBN}$. 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* framework³⁸ 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).

Scheme 5. Functionalization of the acetylenic tetracyclic ketones **43a/b**



The Mo-catalyzed hydrostannation process reported by Kazmaier et al. is a useful method for the 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 system **43a** on treatment with the catalyst $\text{Mo(CO)}_3(\text{CN}t\text{-Bu})_3$ 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 6 : 4 ratio in 60% yield (Scheme 5). The formation of the β -

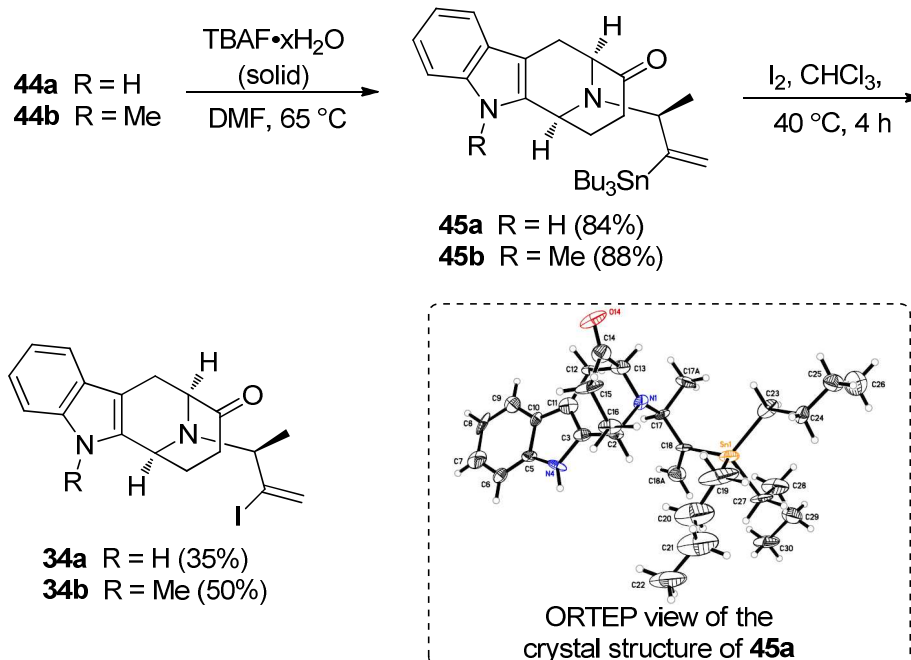
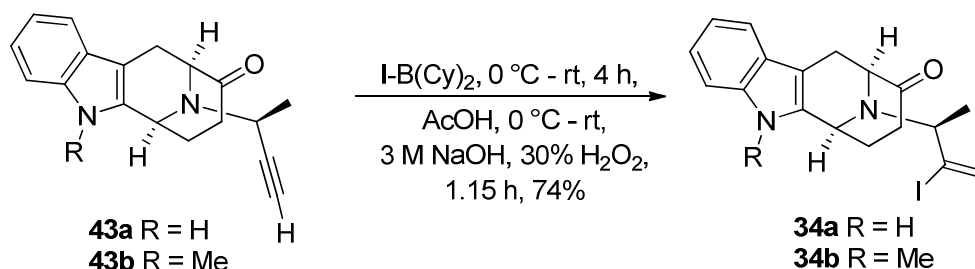
stannylated alkenes **45a'** suggested that the isonitrile ligands were not bulky enough to impart regioselectivity in the system under study here. No further optimization was performed to improve the selectivity in the process.

The first examples of the Pd catalyzed regioselective silastannation of alkynes was reported by the groups of Mitchell⁴⁰ and Chenard.⁴¹ Terminal acetylenes on treatment with silylstannanes in the presence of catalytic amounts of tetrakis(triphenylphosphine)palladium gave 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 [Pd₂(dba)₃·CHCl₃] as the catalyst in combination with 1-2 equivalents of Ph₃P 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 the silastannation,⁴⁰ underwent complete conversion into the desired silastannanes **44a/b** in 3.5 h (Scheme 5). The silastannane reagent, trimethylsilyl tri-*n*-butylstannane (Bu₃SnSiMe₃), was prepared on large scale, according to the procedure of Rajanbabu et al.⁴³ The 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 the use of the lengthier silastannation method for the 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 eq. of TBAF in THF at room temperature 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·xH₂O (up to 25 eq 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 solvent. A mixture of THF : DMF (3 : 2) improved the rate and the 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) equivalents of TBAF·xH₂O (solid), resulted in a much cleaner reaction with the desired vinyl stannanes **45a/b** obtained in 84% and 88% yield, respectively.

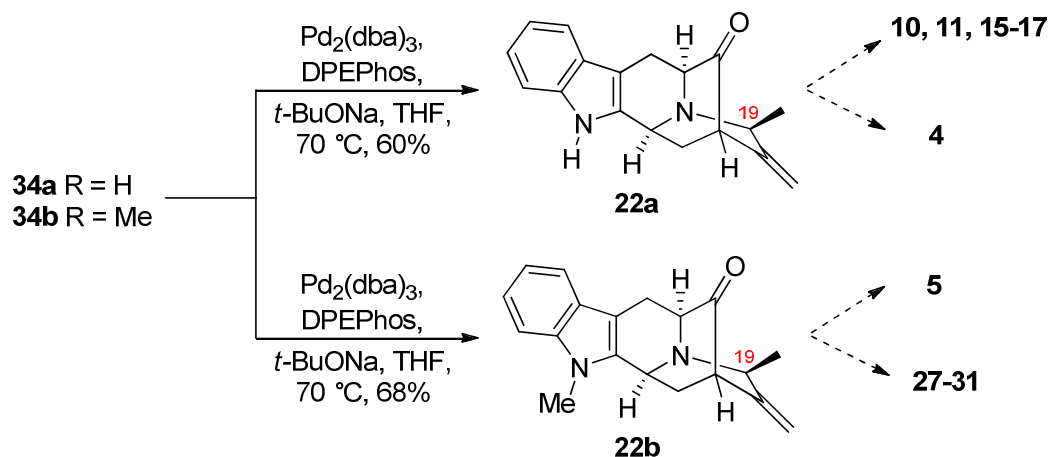
In order to obtain the iodo-olefins **34a/b**, the next step was to subject the vinyl stannanes **45a/b** to the conditions of halodestannation. Under the standard conditions for halodestannations, very low yields of the desired iodo-olefins **34a/b** were obtained. Addition of excess iodine or performing the reaction at reflux (in CHCl₃ with I₂/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 35% (for **34a**) and 50% (for **34b**).

Scheme 6. Synthesis of the vinyl iodides **34a/b** via halodestannylationScheme 7. Haloboration of the acetylenic tetracyclic ketones **43a/b**

Although the desired vinyl iodides **34a/b** were synthesized via the silastannylation approach, effort were made to make this approach more efficient. The haloboranes B-I-9-BBN and dicyclohexyliodoborane [I-B(Cy)₂] have been employed for the synthesis of (*Z*)-enolborinates exclusively from various ethyl ketones.⁴⁴ I-B(Cy)₂ is a highly stereoselective reagent for executing enolboration of esters⁴⁵ 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 the 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 eq of dicyclohexyliodoborane (1.0 M solution in hexanes) and subsequent protonolysis with acetic acid provided the vinyl iodides **34a/b** in 74% yield with complete regioselectivity. 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 in a single step in good yields.

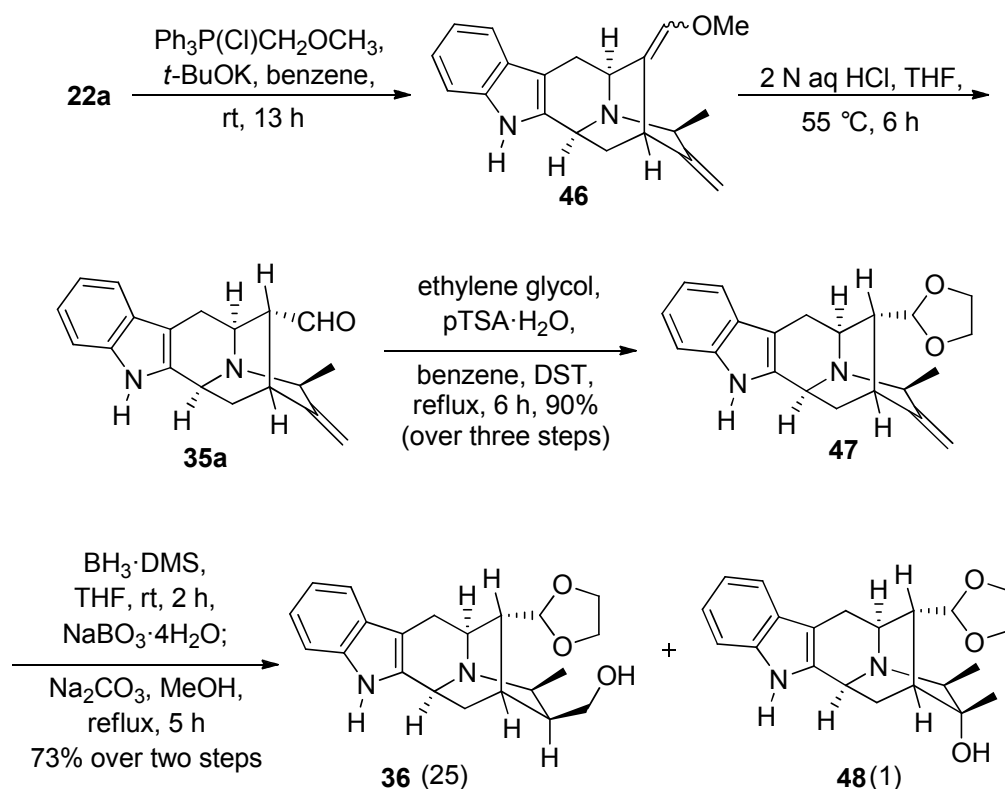
Scheme 8. Synthesis of the Key Pentacyclic Ketones **22a/b**



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 $\text{Pd}_2(\text{dba})_3$, DPEPhos and

NaOt-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 be used for both the 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 the synthesis of *macroline* and *sarpagine* alkaloids as discussed earlier. The following sections detail the further functionalization of the ketones **22a/b**, toward achieving the synthesis of the target alkaloids.

Scheme 9. Synthesis of the C-20 primary alcohol **48**



DST = Dean-Stark trap

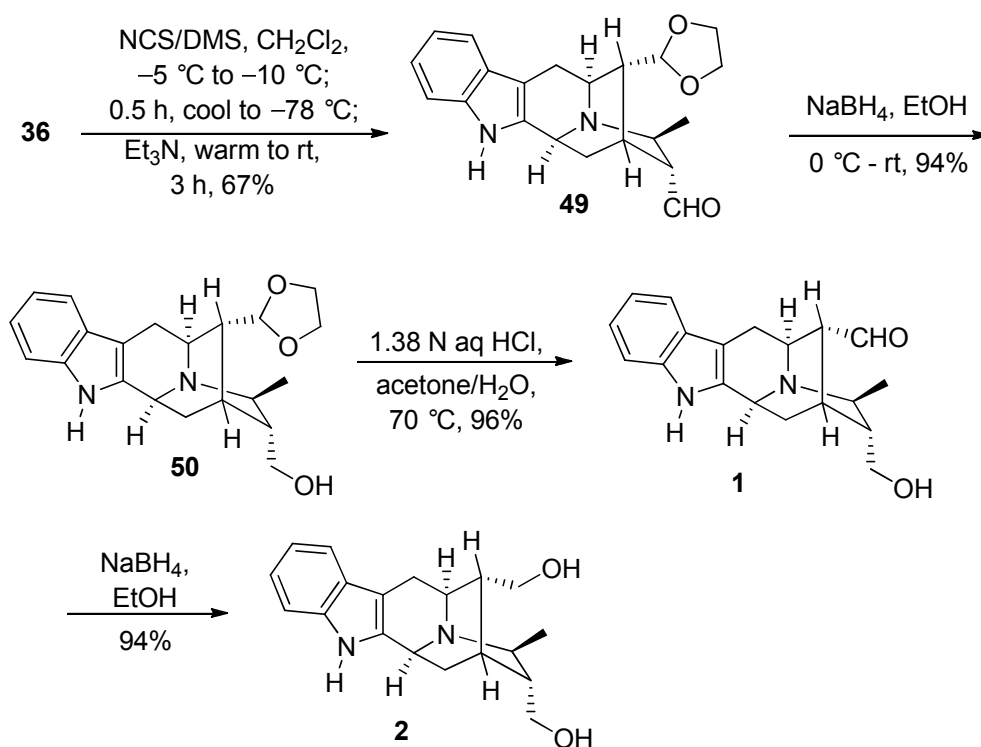
With the C-19 methyl pentacyclic ketone's **22a/b** now available in gram quantities; **22a** was subjected to a one carbon atom homologation process to provide the C-17 aldehyde in **35a**. Execution of a Wittig reaction, followed by acid hydrolysis of the corresponding two stereoisomeric enol methyl ethers **46** afforded the thermodynamically stable α -aldehyde. The

aldehyde at C-17 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** in 93% yield with 1,3-dioxolane in the presence of para toluenesulfonic acid monohydrate (pTSA·H₂O) in refluxing benzene (Scheme 9). The hydroboration-oxidation sequence to generate the desired primary alcohol **36**, was achieved under kinetic control;⁴³ 9 equivalents of borane dimethylsulfide complex were added at room temperature in one portion to a solution of the acetal **47** in THF, to minimize the Markovnikov alcohol **49** and to facilitate the formation of the anti-Markovnikov (kinetic) monol **36** (Scheme 9). The primary and tertiary alcohols existed as *N_b*-BH₃ complexes (in the 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 the 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 the formation of **48**. Decomplexation of the *N_b*-borane complexes of **36** and **48** was achieved by stirring the mixture with 5 eq. of Na₂CO₃ in refluxing methanol for 5 h, after which the desired primary alcohol **36** along with tertiary alcohol **48** was obtained with the free nitrogen function in 88% yield. Clearly the 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 oxidation⁴⁸ 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 the oxidation of the primary alcohol in **36** 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 over oxidized

byproduct as identified by mass spectrometry. Because of the susceptibility of the N_b -nitrogen atom in the monol **36** to over oxidation, attention focused on the much milder Corey-Kim oxidation. During initial attempts, the addition of the alcohol **36** in CH_2Cl_2 at room temperature to 5 equivalents 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 over oxidized byproduct. The reaction mixture was then treated with 16 eq. of triethylamine and allowed to stir

Scheme 10. Completion of the total synthesis of **1** and **2**



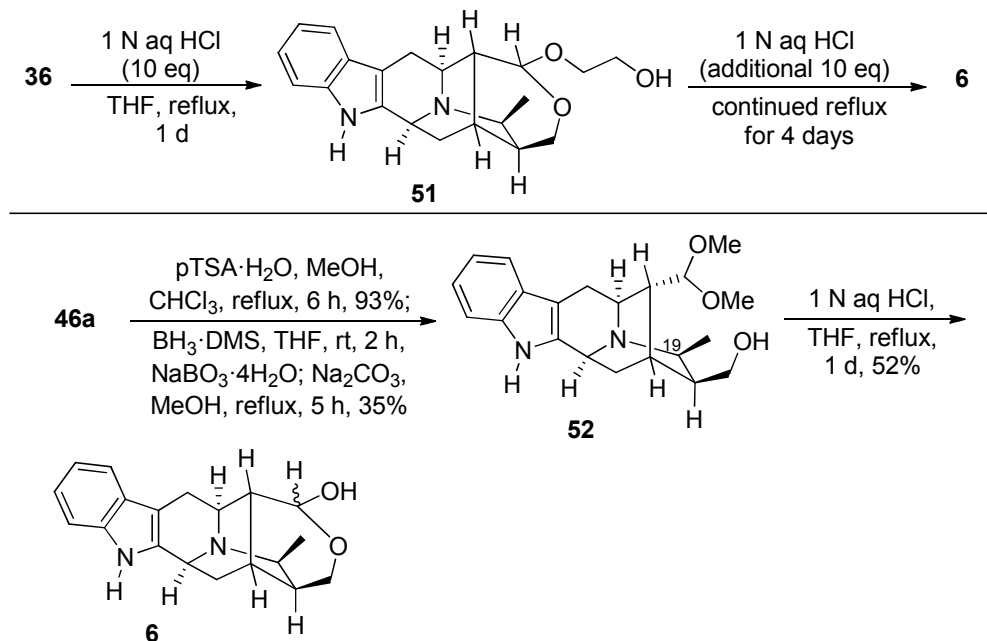
at -78°C for 1 h and at rt for 1 h. Since an epimeric mixture of aldehydes were obtained (^1H NMR spectrum), it was decided to carry out complete epimerization in the same reaction vessel

by allowing the reaction mixture to stir at rt for an additional 2 h. Column chromatography purification of the crude furnished the α -aldehyde **49** as a colorless oil (Scheme 10).

Reduction of the stable α -aldehyde **49** with NaBH₄ in ethanol for 3 h at room temperature furnished the α -alcohol **50** in 95% 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. The signals in the ¹H and ¹³C 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 NaBH₄ to complete the first total synthesis of 19(*S*),20(*R*)-dihydroperaksine **2** (Scheme 10). The synthetic **1** and **2** were also identical on TLC including a mixed TLC sample to the sample of natural 19(*S*),20(*R*)-dihydroperaksine-17-al (**1**) and natural 19(*S*),20(*R*)-dihydroperaksine (**2**) kindly supplied by Professor Joachim Stöckigt.⁴⁹

To effect the 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 eq. of 1 N aq HCl. Examination of the ¹H NMR spectrum of the crude material after 24 h indicated the formation of the hemiacetal ring but the cyclic acetal ring had opened only half way to give an ether linkage (see **51**) as a single diastereomer (Scheme 11). To overcome this problem the reaction was also carried out in THF : H₂O (1:1), but this also resulted in the formation of ether **51** after 1 day at reflux. The continued heating of ether **51** with an additional 10 eq of 1 N aqueous HCL for 4 days resulted in the formation of a trace amount of **6**.

Scheme 11. Completion of the total synthesis of peraksine (6)



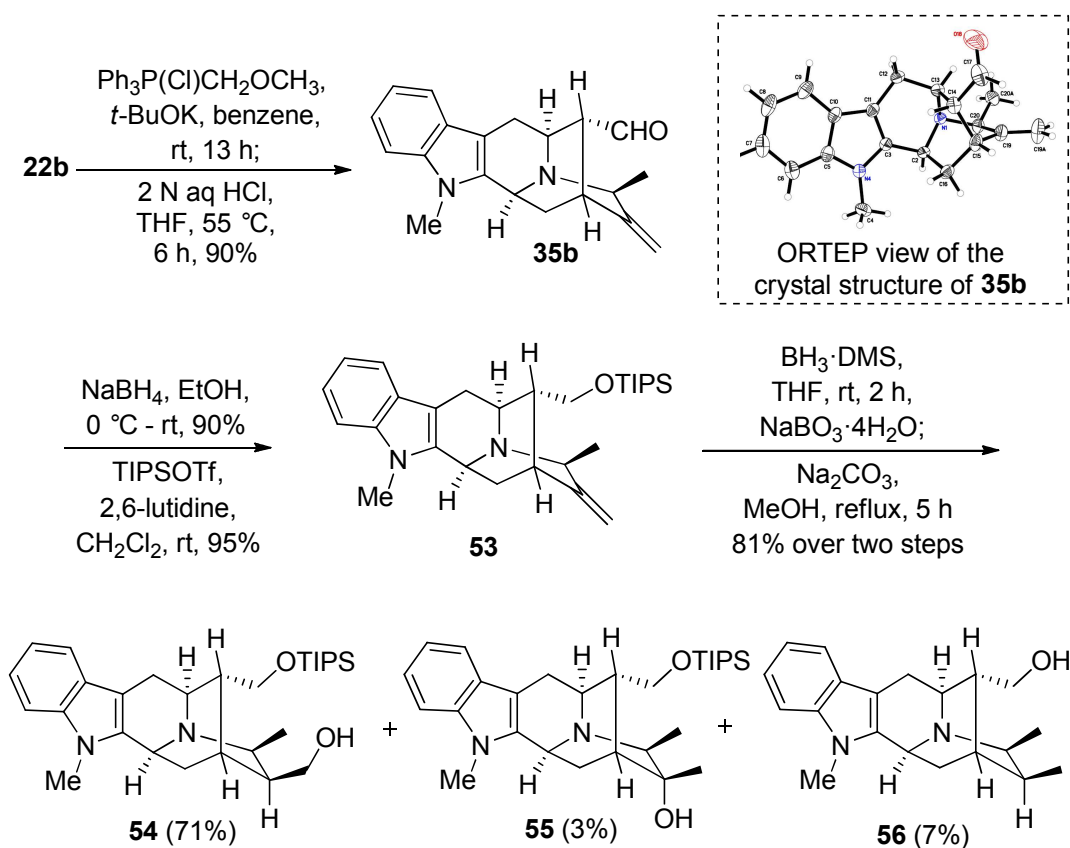
Because of the resistance of the ethereal linkage in **51** to hydrolysis due to reversible formation of the 1,3-dioxolane ring, the cyclic acetal was converted into the dimethoxy acetal. The dimethoxy acetal group was not as stable as the 1,3-dioxolane group to the hydroboration reaction conditions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

Studies directed toward the total synthesis of macrosalpine chloride (5) as well as the partial total synthesis of talcarpine (26).

With the successful synthesis of the C-19 methyl functionalized *sarpagine* alkaloids **1** and **2** in the *N*_a-H series, synthesis of the hemiacetal alkaloid (in the *N*_a-methyl series) macrosalpine chloride **5**, was next attempted. Macrosalpine **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 **31b** in hand, attention was focused on the 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 the hemiacetal ring formation in **5**.

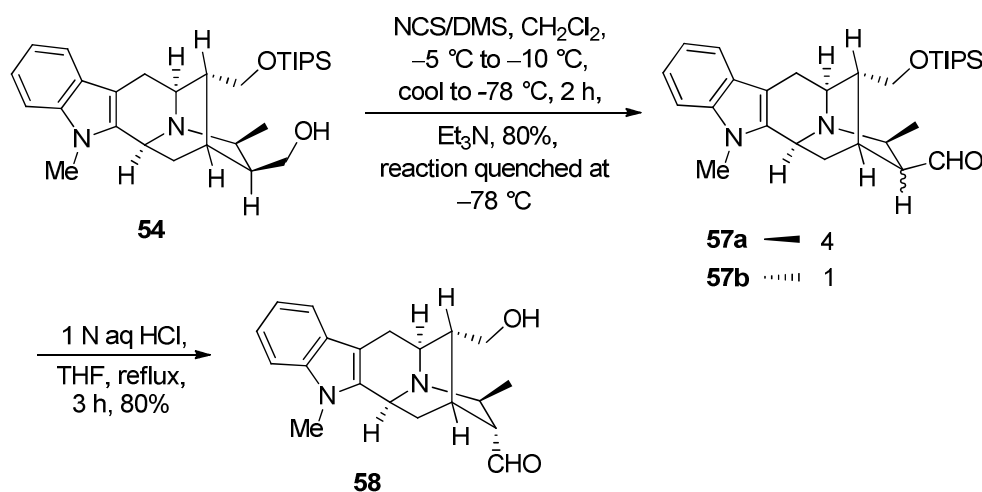
Scheme 12. Synthesis of C-20 primary alcohol **54**



The pentacyclic ketone **22b** was thus converted to the aldehyde **35b** by a Wittig-hydrolysis sequence. The α -position of the aldehyde at C16 was confirmed by X-ray analysis (Scheme 12). Reduction of **35b** with NaBH_4 afforded the alcohol (95%), which was then

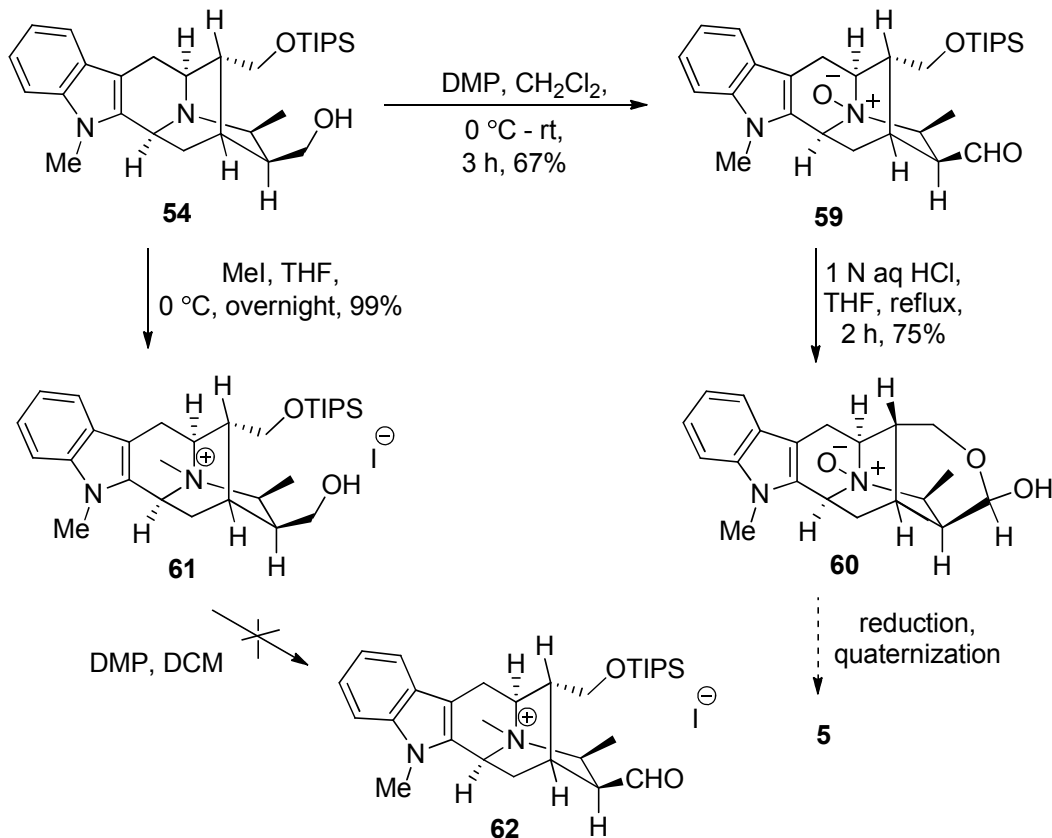
protected as its silyl ether to give **53**. Hydroboration of the terminal olefin in **53** provided the desired monol **54**, accompanied by the expected tertiary alcohol **55** and the unusual protodeboronation byproduct **56** (Scheme 12).

Scheme 13. Corey-Kim oxidation



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 Et₃N). 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 Et₃N from 16 to 3 failed to improve the outcome of the process. Thus the inability to prevent the formation of the α-aldehyde in the Corey-Kim oxidation was detrimental to the hemiacetal ring formation.

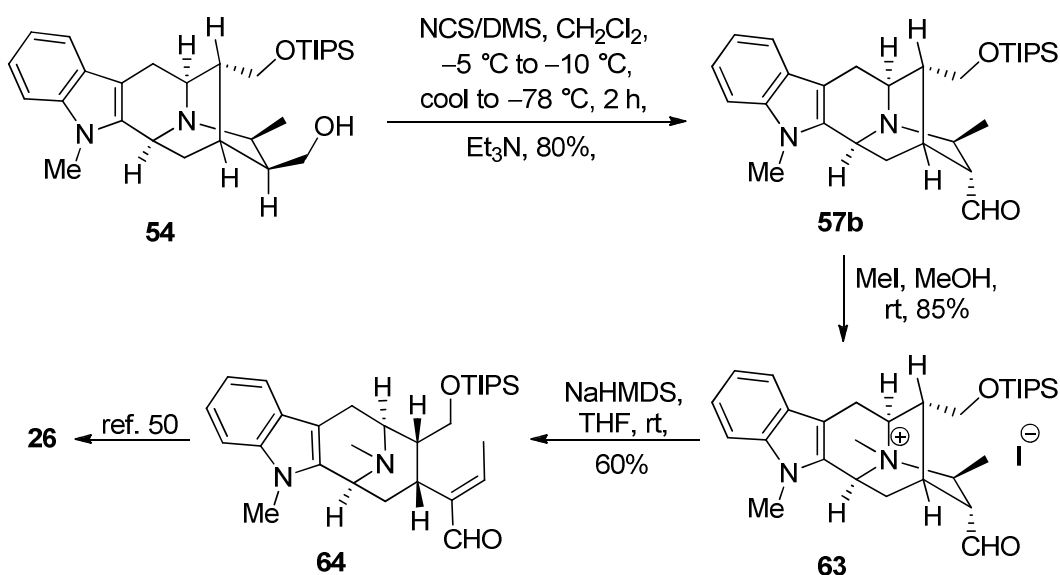
Scheme 14. DMP Oxidation and Acid Mediated Hemiacetal Ring Formation



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 over oxidation by either using fewer equivalents of DMP or performing the reaction at lower temperature. Attempts at using TFA (equivalents varied from 1.5 to 1.1 eq.) in the above case (to protonate the N_b -nitrogen) or IBX/DMSO to carry out the oxidation also gave similar results along with recovered starting material **52**. Since macrosalpine 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 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 the hemiacetal ring formation and then perform a reduction of the *N*-oxide to complete the 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 this is necessary to complete the total synthesis of **5**.

Scheme 15. Formal total synthesis of talcarpine



Although the Corey-Kim oxidation could not be utilized for the synthesis of **5**, it provided a much milder method for the 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** (Scheme 15). Desilylation of the TIPS group in olefin **64** to the free alcohol would generate the all-important *macroline* equivalent **32a** (Figure 4b), which was the intermediate involved in the

partial synthesis of talcarpine **25** by Sakai et. al.⁵⁰ This resulted in the formal total synthesis of **25** here. The macroline intermediate **64** would also serve as the precursor for the potential synthesis of the *macroline* related alkaloids **26**, **29** and **30**. Additionally **32b**, with the 10-methoxy equivalent of **32a** and the northern hemisphere of the *Alstonia* bisindoles (+)-angusticaline, (+)-alstocraline and (+)-foliacraline (Figure 4A) could be synthesized from 5-methoxy-D-tryptophan ethyl ester⁵¹ 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 towards the synthesis of macrosalpine chloride (**5**) was also developed. Commercially available D-(+)-tryptophan has served both as the chiral auxiliary and 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 the use of a superior haloborating agent (dicyclohexyliodoborane). 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 the synthesis of the C-19 methyl substituted *ajmaline* alkaloids **10**, **11**, **14-17** and a route amenable to the synthesis of *macroline*-related alkaloids **27-31** is now possible due to the efficient synthesis of the advanced intermediate **64** via a general strategy for the synthesis of C-

19 methyl substituted indole alkaloids. This process provides a general entry; it is felt, into a whole series of biosynthetically important monoterpene C-19 substituted indole alkaloids.

EXPERIMENTAL SECTION

The experimental details for the synthesis of alkaloids **1**, **2** and compounds **22a**, **34a**, **36**, **41**, **42a**, **43a**, **47**, **49** and **50** are contained in the SI of reference 24a. For general experimental considerations see SI.

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 was charged with 69.0 g of ground activated 4Å 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 MgSO₄) 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 purified by column chromatography (silica gel) with 2-10% EtOAc/hexanes as the eluant to afford the *R*-acetate **38** (63.0 g, 45.8%) and the *S*-alcohol **39** (46.0 g, 44%).

R-acetate **38**: *R_f* 0.59 (silica gel, EtOAc/hexanes, 1:7); ¹H NMR (400 MHz, CDCl₃) 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 ¹H NMR analysis. The acetate was not subjected to any further characterization and was used in the next step as is.

S-alcohol **39**: *R_f* 0.33 (silica gel, EtOAc/hexanes, 1:7); ¹H NMR (300 MHz, CDCl₃) 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) [¹H 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) 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 the 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); $[\alpha]_D^{20} + 23.38^\circ$ (c 2.01 $CHCl_3$); 1H 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 NaOH. This mixture was stirred for 2 h and the solvents were removed under reduced pressure. The aq residue was extracted with diethyl ether (3 x 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%). The 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-tetrahydro-5*H*-6,10-epimino-cycloocta[*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-tetrahydro-5*H*-6,10-epimino-cycloocta[*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 SI of reference 24a.

Minor [C(12)-*R*] diastereomer (**42a'**): mp 135-137 °C; $[\alpha]_D^{20}$ -4.30 (c 0.93 $CHCl_3$); IR (KBr) 3376, 2944, 2166, 1698, 1450 cm^{-1} ; 1H 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 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(CH₂), 29.9 (CH₂), 21.6 (CH₂), 21.0 (CH₃), 18.5 (6 x CH₃), 11.1 (3 x 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 $\text{C}_{27}\text{H}_{38}\text{N}_2\text{OSi}$: 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 (42*b*) and (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 (42*b'*). 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, $\text{CHCl}_3/\text{EtOH}$, 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 (silica 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 x CH_3), 11.1 (3 x 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 $\text{C}_{28}\text{H}_{40}\text{N}_2\text{OSi}$: 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 x 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). The TBAF·xH₂O (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 the disappearance of the starting material **42b**. The reaction solution was then quenched with H₂O (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 (Na₂SO₄). 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 (14.67 g, 90% yield). Part of the solid was crystallized by 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, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 (CH₂), 29.2 (CH₃), 28.9 (CH₂), 21.4 (CH₂), 20.4 (CH₃); EIMS (*m/e*, relative intensity) 292 (M⁺, 81), 235 (100), 196 (24), 183 (46), 168 (26); HRMS (EI-trisector) *m/z*: Calcd for C₁₉H₂₀N₂O 292.1576, Found 292.1570.

(6*S*,10*S*)-12-((*S*,*Z*)-3-(Tri-butylstannyl)-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), Ph₃P (347 mg, 1.32 mmol) and Bu₃SnSiMe₃ (15.6 g, 43 mmol). The system was degassed under reduced pressure at rt and back filled 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 back filled 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. Cyclohexane (1 L) was used for elution. After complete elution by cylcohexane, the Celite bed was eluted with ether and finally with EtOAc. All the eluents were kept separate (The EtOAc layer usually contained all the palladium residue but if you see any product after concentrating it and analyzing it by TLC, combine it with the ether layer). The cyclohexane layer was concentrated. A precipitate was obtained after diluting the concentrated oil with hexanes. The precipitate was removed by filtration and the hexane layer was concentrated in vacuuo to give a light reddish colored oil which was purified by flash chromatography (silica gel, EtOAc/hexane, 1:9, 1% Et₃N) to afford silastannane tetracyclic ketone **44a** as a yellow oil. The combined ether and EtOAc layer were also concentrated and purified by flash chromatography on silica gel to give silastannane tetracyclic ketone **44a** as a white colored solid. The combined yield was 70% (14.9 g). ¹H NMR (300 MHz, CDCl₃) 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 (CH₂), 30.1 (CH₂), 29.2 (3 x CH₂), 27.5 (3 x CH₂), 21.1 (CH₂), 19.1 (CH₃), 13.5 (3 x CH₃), 12.4 (3 x CH₂), 0.21 (3 x CH₃); CIMS (m/e , relative intensity) 643 ($\text{M}^+ + 1$, 30), 585 (100), 351 (51), 335 (23), 283 (14), 253 (95), 210 (10), 169 (14); HRMS (ESI-TOF) m/z : ($\text{M} + \text{H}$)⁺ Calcd for $\text{C}_{33}\text{H}_{55}\text{N}_2\text{OSi}^{120}\text{Sn}$, 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), $\text{Bu}_3\text{SnSiMe}_3$ (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 by 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, $J = 6.5$ 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 (CH₂), 29.6 (CH₂), 29.3 (3 x CH₂), 28.9 (CH₃), 27.4 (3 x CH₂), 20.8 (CH₂), 18.8 (CH₃), 13.5 (3 x CH₃), 12.5 (3 x CH₂), 0.1 (3 x CH₃); 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 C₃₄H₅₆N₂OSiSn: 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·xH₂O (14.80 g, 57 mmol) at rt. The mixture which resulted was heated to 68 °C (oil bath temperature). After heating for 3 h, an additional 9.25 g (5 eq) of solid TBAF·xH₂O was added at 68 °C in three portions of 3.7 g (2 eq), 3.7 g (2 eq) and 1.85g (1 eq) in intervals of 2 h, 2 h and 1h. After heating for 10 h, analysis by TLC indicated the disappearance of the silylstannane. 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 the addition of EtOAc (500 mL). The two layers were separated and the aq layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with water (5 x 50 mL), brine (5 x 40 mL), dried (Na₂SO₄) 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 by using EtOAc to give **45a** as white crystals for X-ray analysis. mp 99-101 °C; [α]_D²⁰ -70.36 (c 1.12 CHCl₃); R_f 0.4 (hexanes/EtOAc, 6 : 2); IR (KBr) 1692 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) 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 x CH_2), 27.3 (3 x CH_2), 20.8 (CH_2), 19.8 (CH_3), 13.6 (3 x CH_3), 10.6 (3 x CH_2); CIMS (m/e , relative intensity) 571 ($\text{M}^+ + 1$, 36), 513 (100), 281 (37), 263 (17), 169 (11); HRMS (ESI-TOF) m/z : ($\text{M} + \text{H}$) $^+$ Calcd for $\text{C}_{30}\text{H}_{47}\text{N}_2\text{O}^{120}\text{Sn}$ 571.2711, Found 571.2705.

The 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 $\text{Mo}(\text{CO})_3(\text{CN}t\text{-Bu})_3$ (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 there 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); ^1H 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 x CH_2), 27.1 (3 x CH_2), 20.8 (CH_2), 19.3 (CH_3), 13.7 (3 x CH_3), 9.4 (3 x 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 : ($\text{M} + \text{H}$) $^+$ Calcd for $\text{C}_{30}\text{H}_{47}\text{N}_2\text{O}^{120}\text{Sn}$ 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· $x\text{H}_2\text{O}$ (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 the addition of EtOAc (500 mL). The two layers were separated and the aq layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with water (5 x 50 mL), brine (5 x 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%). ^1H 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 (CH₂), 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 (CH₂), 29.5 (CH₂), 29.1 (3 x CH₂), 29.0 (CH₃), 27.3 (3 x CH₂), 20.6 (CH₂), 19.8 (CH₃), 13.6 (3 x CH₃), 10.6 (3 x CH₂); CIMS (*m/e*, relative intensity) 585 (M⁺+1, 29), 527 (100), 293 (12); HRMS (ESI-TOF) *m/z*: (M + H)⁺ Calcd for C₃₁H₄₉N₂O¹²⁰Sn, 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 CH₂Cl₂ (25 mL). Iodine (0.67 g, 2.63 mmol) was dissolved in CH₂Cl₂ (20 mL). The iodine solution was added in one portion to the vinylstannane **45a** and the mixture was placed and stirred in a pre-heated oil bath (40 – 45 °C) for 1 h. After 1 h of heating, another 1.5 eq of iodine solution (0.67 g dissolved in 20 mL CH₂Cl₂) was added to the reaction mixture after which it was allowed to stand 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 CH₂Cl₂ (50 mL) and the two layers were separated. The aq layer was extracted with CH₂Cl₂ (3 x 20 mL) and the combined organic layers were washed with brine (2 x 50 mL) and dried (Na₂SO₄). 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%).

The 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 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 2.0 h. After stirring at rt for 2.0 h, another 0.5 eq 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 2.0 h. After this 2.0 h, the mixture was 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 and 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 1.0 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 $\frac{3}{4}$ th 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 x 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; ^1H 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 $\text{C}_{19}\text{H}_{21}\text{IN}_2\text{O}$: 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*,11*aS*)-11-(1,3-dioxolan-2-yl)-8-methyl-9-methylene-5,6,8,9,10,11,11*a*,12-octahydro-6,10-methano-indolo[3,2-*b*]quinolizine (47)

A mixture of anhydrous potassium *tert*-butoxide (1.82 g, 16.2 mmol) and methoxymethyltriphenylphosphonium 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 x 15 mL), and the combined organic layers were washed with brine (2 x 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.

The crude compound **46** was dissolved (without further purification) in a solution of THF/H₂O (1:1, 28 mL). To the above solution, a solution of aq 12 N conc HCl 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 x 15 mL) to remove the phosphorous byproducts, after which the aq layer was then brought to pH 8 with an ice-cold solution of 14% aq NH₄OH. The aq layer was extracted with EtOAc (3 x 15 mL), and the combined organic layers were washed with brine (2 x 15 mL) and dried (Na₂SO₄). The solvent was removed under reduced pressure to afford the α -aldehyde **35a** as an oil, which was directly 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 the addition of dry ethylene glycol (4.67 g, 75 mmol) and p-toluenesulfonic 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, CH₂Cl₂ : MeOH) indicated the absence of starting material **35a**. The mixture was allowed to cool to rt, diluted with EtOAc and at 0 °C was brought to pH 8-9 with 14% aq NH₄OH. The aq layer was separated and then extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (2 x 20 mL) and dried (Na₂SO₄). The solvent was removed under reduced pressure and chromatographed [silica gel, CH₂Cl₂/MeOH, (10 : 0.3) to provide the ethylene acetal **47** (620 mg, 90% yield over 3 steps from **22a**). ¹H NMR (300 MHz, CDCl₃) 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 $\text{C}_{21}\text{H}_{24}\text{N}_2\text{O}_2$ 336.1838, found 336.1831.

(6*S*,8*S*,11*aS*)-5,8-Dimethyl-9-methylene-5,6,8,9,10,11,11*a*,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 back filled with argon (3 times). The $\text{Pd}_2(\text{dba})_3$ (77.5 mg, 0.08 mmol) catalyst along with dry THF (3 mL) was introduced into the reaction mixture and the system was again degassed under reduced pressure at rt and back filled with argon (4 times). The mixture was then heated to 70 - 75 °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 half under reduced pressure and the mixture was diluted with EtOAc (70 mL). The aq layer was extracted with EtOAc (2 x 15 mL) and the combined organic layers were washed with brine (2 x 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%): ^1H 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 pentacyclic 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 methoxymethyltriphenylphosphonium 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, CH₂Cl₂: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 x 15 mL), and the combined organic layers were washed with brine (2 x 30 mL) and dried (Na₂SO₄). 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/H₂O (1:1, 28 mL). To the above mixture a solution of aq 12 N conc HCl (0.24 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 x 15 mL) to remove the phosphorous byproducts, after which the aq layer was then brought to pH 8 with an ice-cold solution of 14% aq NH₄OH. The aq layer was extracted with EtOAc (3 x 15 mL), and the

combined organic layers were washed with brine (2 x 15 mL) and dried (Na₂SO₄). The solvent was removed under reduced pressure to afford **35b** as a solid (1.5 g, 90%). Part of the solid was crystallized by using CH₂Cl₂:MeOH to give white crystals of **35b** for X-ray analysis: ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 (CH₂), 103.6 (C), 57.9 (CH), 54.9 (CH), 50.8 (CH), 44.4 (CH), 34.9 (CH), 32.4 (CH₂), 29.3 (CH₃), 27.3 (CH₂), 16.6 (CH₃); HRMS (ESI-TOF) *m/z*: [M+H]⁺ Calcd for C₂₀H₂₂N₂O 306.1732, Found 306.1729.

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

Primary alcohol **(36)**: For spectral data see SI of reference 24a.

Tertiary alcohol **(48)**: ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 (CH₂), 64.2 (CH₂), 63.8 (CH), 52.4 (CH), 46.4 (CH),

44.4 (CH), 39.3 (CH), 30.1 (CH₂), 26.5 (CH₃), 26.3 (CH₂), 13.0 (CH₃); 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 C₂₁H₂₆N₂O₃ 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 NH₄OH. The mixture was extracted with CH₂Cl₂. The CH₂Cl₂ layer was washed with brine, dried (Na₂SO₄) and removed under reduced pressure to provide **51** (8 mg) as an oil in 88% yield. ¹H NMR (300 MHz, CD₃OD) 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); ¹³C NMR (75 MHz, CDCl₃) 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 C₂₁H₂₆N₂O₃ 354.1943, found 354.1928.

((6*S*,8*S*,9*S*,11*R*,11*aS*)-11-(Dimethoxymethyl)-8-methyl-5,6,8,9,10,11,11*a*,12-octahydro-6,10-methanoindolo[3,2-*b*]quinolizin-9-yl)methanol (52). A mixture of **35a** (100 mg, 0.34 mmol), *p*TSA.H₂O (75 mg, 0.39 mmol), methanol (132 mg, 4.04 mmol) and trimethyl orthoformate (109 mg, 1.03 mmol) was refluxed in CHCl₃ (8 mL) for 6 h. The reaction mixture was brought to pH

7 with 10% aq NH_4OH . Two 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 $\text{BH}_3\cdot\text{DMS}$ (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 $\text{NaBO}_3\cdot 4\text{H}_2\text{O}$ (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 x 20 mL), brine (2 x 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 (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 to remove the solids. 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 x 10 mL), brine (4 x 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, $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (v/v 10:1)] and furnished the primary alcohol **52** (43 mg, 35%). The other impurities were not characterized.

¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 (CH₂), 54.6 (CH₃), 54.0 (CH), 52.3 (CH), 49.2 (CH₃), 48.7 (CH), 39.8 (CH), 39.1 (CH), 36.5 (CH₂), 26.8 (CH₂), 24.7 (CH), 12.8 (CH₃); 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 C₂₁H₂₈N₂O₃ 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 d after which it was cooled to rt and brought to pH = 7 with 10% aq NH₄OH. The mixture was extracted with CH₂Cl₂. The CH₂Cl₂ layer was washed with brine, dried (Na₂SO₄) and removed under reduced pressure to afford an oil. Peraksine (1 mg) was isolated by preparative TLC (silica gel) as an oil. ¹H NMR (300 MHz, CDCl₃) 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)^{9b}; 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); HRMS (EI-trisector) *m/z*: Calcd for C₁₉H₂₂N₂O₂ 310.1681, Found 310.1664. No further characterization was carried out.

(6*S*,8*S*,11*R*,11*aS*)-5,8-Dimethyl-9-methylene-11-(((triisopropylsilyl)oxy)methyl)-

5,6,8,9,10,11,11*a*,12-octahydro-6,10-methanoindolo[3,2-*b*]quinolizine (53). The aldehyde **35b**

(530 mg, 1.72 mmol) was dissolved in EtOH (10 mL). Then NaBH₄ (98 mg, 2.59 mmol) was

added to the above solution in one portion at 0 °C. The mixture was then stirred at 0 °C for 8 h.

The reaction mixture was diluted with CH₂Cl₂ (300 mL) and poured into cold water (50 mL).

The aq layer was extracted with additional CH₂Cl₂ (3 × 80 mL), and the combined organic layer

was washed with brine (80 mL) and dried (K₂CO₃). The solvent was removed under reduced

pressure to afford the crude product, which was purified by chromatography on silica gel

(CH₂Cl₂/CH₃OH = 10:1) to provide the primary alcohol (480 mg, 93%) as a yellow oil (see S1 in

Supporting Information). ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₂₀H₂₅N₂O, 309.1967, Found

309.1976.

A solution of the primary alcohol (520 mg, 1.68 mmol) in dry CH₂Cl₂ (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 CH₂Cl₂ (100 mL) and poured into cold water (20

mL). The aq layer was extracted with additional CH₂Cl₂ (2 × 50 mL), and the combined organic layer was washed with brine (30 mL) and dried (Na₂SO₄). 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 (CH₂Cl₂/CH₃OH = 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); ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 (CH₂), 104.2 (C), 65.5 (CH₂), 58.3 (CH), 51.1 (CH), 48.7 (CH), 44.4 (CH), 35.6 (CH), 33.2 (CH₂), 29.2 (CH₃), 27.2 (CH₂), 18.0 (6 × CH₃), 16.8 (CH₃), 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 C₂₉H₄₄N₂OSi: 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*,11*aS*)-5,8-Dimethyl-11-(((triisopropylsilyl)oxy)methyl)-5,6,8,9,10,11,11*a*,12-octahydro-6,10-methanoindolo[3,2-*b*]quinolizin-9-yl)methanol (54), (6*S*,8*S*,9*S*,11*R*,11*aS*)-5,8,9-trimethyl-11-(((Triisopropylsilyl)oxy)methyl)-5,6,8,9,10,11,11*a*,12-octahydro-6,10-methanoindolo[3,2-*b*]quinolizin-9-ol (55), and (6*S*,8*S*,9*S*,11*R*,11*aS*)-5,8,9-Trimethyl-11-(((triisopropylsilyl)oxy)methyl)-5,6,8,9,10,11,11*a*,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 BH₃·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 $\text{NaBO}_3 \cdot 4\text{H}_2\text{O}$ (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 x 20 mL), brine (2 x 20 mL) and dried (Na_2SO_4). The EtOAc was then removed under reduced pressure to provide the $N_b\text{-BH}_3$ 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 to remove the solids. 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 x 10 mL), brine (4 x 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, $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (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); ^1H 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 (CH₂), 63.1 (CH₂), 54.1 (CH), 51.2 (CH), 48.7 (CH), 41.2 (CH), 40.0 (CH), 36.4 (CH₂), 29.2 (CH₃), 27.6 (CH₂), 25.0 (CH), 17.9 (6 x CH₃), 13.2 (CH₃), 11.8 (3 x 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 C₂₉H₄₇N₂O₂Si, 483.3401, Found 483.3410.

Tertiary alcohol **55**: R_f 0.59 (silica gel, EtOAc/EtOH 4.2 : 0.8); ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 (CH₂), 64.1 (CH), 51.4 (CH), 48.9 (CH), 43.1 (CH), 39.9 (CH), 30.4 (CH₂), 29.2 (CH₃), 27.1 (CH₂), 26.7 (CH₃), 18.0 (6 x CH₃), 13.4 (CH₃), 11.9 (3 x 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 C₂₉H₄₇N₂O₂Si, 483.3401, Found 483.3407.

Reduced ethylidene byproduct **56**: R_f 0.1 (silica gel, EtOAc/EtOH 4.2 : 0.8); ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 (CH₂),

55.0 (CH), 51.5 (CH), 49.0 (CH), 42.5 (CH), 37.4 (CH₂), 32.1 (CH), 31.8 (CH), 29.2 (CH₃), 27.7 (CH₂), 16.8 (CH₃), 14.3 (CH₃); 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 C₂₀H₂₆N₂O 310.2045, Found 310.2055.

(6*S*,8*S*,9*R*,11*R*,11*aS*)-5,8-Dimethyl-11-((triisopropylsilyl)oxy)-methyl)-5,6,8,9,10,11,,11*a*,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 CH₂Cl₂ (1.5 mL) 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 CH₂Cl₂ (1.0 mL) was also cooled at –78 °C and then added via canula to the white complex, and the 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 CH₂Cl₂ and H₂O. The organic layer was separated, washed with brine and dried (Na₂SO₄). 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 the 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 to 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 ¹H NMR spectrum of the residue indicated the 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 the 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, 70%). ^1H 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 x CH_3), 11.8 (3 x CH); HRMS (EI-trisector) m/z : Calcd for $\text{C}_{29}\text{H}_{44}\text{N}_2\text{O}_2\text{Si}$ 480.3172, Found 480.3175.

(6*S*,8*S*,9*R*,11*R*,11*aS*)-11-(Hydroxymethyl)-5,8-dimethyl-5,6,8,9,10,11,11*a*,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, $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (v/v 10:1) with 1% NH_4OH (14%)]. ^1H 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.

Macrosalpine N_b -oxide (60). The 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 sat solution of aq $NaHCO_3$ (9 mL) and a sat 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 X 20 mL), and the combined organic layer was washed with brine (20 mL) and dried (K_2CO_3). 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%). 1H 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 : Calcd 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 d, after which it was cooled to rt

and brought to pH = 7 with 10% aq NH₄OH. The mixture was extracted with CH₂Cl₂. The CH₂Cl₂ layer was washed with brine, dried (Na₂SO₄) and removed under reduced pressure to afford an oil. Macrosalpine N_b-oxide **60** (2.6 mg, 75%) was isolated by preparative TLC (silica gel) as an oil. ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 C₂₀H₂₄N₂O₃ 340.1787, Found 340.1779; HRMS (ESI-TOF) *m/z*: (M + H)⁺ Calcd for C₂₀H₂₅N₂O₃ 341.1860, Found 341.1837.

(6*S*,8*S*,9*S*,11*R*,11*aS*)-9-(Hydroxymethyl)-5,7,8-trimethyl-11-(((triisopropylsilyl)oxy)methyl)-6,7,8,9,10,11,11*a*,12-octahydro-5*H*-6,10-methanoindolo[3,2-*b*]quinolizin-7-ium iodide (61**).**

To a solution of the monol **54** (10 mg, 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, dried overnight under high vacuum, to provide the N_b-methyl salt **61** (mg, 85%). ¹H NMR (300 MHz, CDCl₃) 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 x CH_3), 11.7 (3 x CH), 10.6 (CH_3); HRMS (ESI-TOF) m/z : (M) $^+$ Calcd for $\text{C}_{30}\text{H}_{49}\text{N}_2\text{O}_2\text{Si}$ 497.3563, Found 497.3561.

(6*S*,8*S*,9*R*,11*R*,11*aS*)-9-Formyl-5,7,8-trimethyl-11-(((triisopropylsilyl)oxy)methyl)-

6,7,8,9,10,11,11*a*,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, 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); ^1H 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 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 x CH_3), 16.8 (CH_3), 11.8 (3 x CH); HRMS (ESI-TOF) m/z : (M) $^+$ Calcd for $\text{C}_{30}\text{H}_{47}\text{N}_2\text{O}_2\text{Si}$ 495.3401, Found 495.3410.

(*E*)-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, NaHMDS (4 mg, 0.020 mmol) was added at rt, after which the mixture was allowed to stir overnight. In the next morning analysis by LCMS indicated the disappearance of **63**. The 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. ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 (CH₂), 53.9 (CH), 53.4 (CH), 46.7 (CH), 42.1(CH₃), 29.7 (CH₂), 29.0 (CH), 28.9 (CH₃), 22.2 (CH₂), 18.1 (6 x CH₃), 13.0 (CH₃), 12.0 (3 x CH); HRMS (ESI-TOF) *m/z*: (M + H)⁺ Calcd for C₃₀H₄₇N₂O₂Si 495.3401, Found 495.3408.

ASSOCIATED CONTENTS

ACKNOWLEDGEMENTS

We wish to acknowledge NIH, MH-046851 (in part) and the Lynde and Harry Bradley Foundation for support of this work. X-ray crystallographic studies were supported by NIDA-NRL Interagency Agreement Number Y1-DA1101. We wish to thank Professor Joachim Stöckigt for kindly providing authentic samples of 19(*S*),20(*R*)-dihydroperaksine-17-al (**1**), 19(*S*),20(*R*)-dihydroperaksine (**2**) for TLC comparison.

Supporting Information

¹H and ¹³C NMR spectra for all new compounds **22b**, **34b**, **35b**, **42a'**, **42b-45b**, **42b'**, **44a**, **45a/a'**, **48**, **51-56**, **57b**, **58**, **60-61**, **63-64** and 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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