Enantiospecific Total Synthesis of the Sarpagine Related Indole Alkaloids Talpinine and Talcarpine as Well as the Improved Total Synthesis of Alstonerine and Anhydromacrosalhine-methine via the Asymmetric Pictet−Spengler Reaction

Peng Yu, Tao Wang, Jin Li, and James M. Cook*

Department of Chemistry, University of Wisconsin−Milwaukee, Milwaukee, Wisconsin 53201

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The enantiospecific total synthesis of talpinine **1** and talcarpine **2** has been accomplished from D-(+)-tryptophan in 13 steps (11 reaction vessels) in 10% and 9.5% overall yields, respectively. Moreover, this synthetic approach has been employed for the improved synthesis of alstonerine **3** and anhydromacrosalhine-methine **4** in 12% and 14% overall yield, respectively. A convenient synthetic route for the enantiospecific, stereospecific preparation of the key intermediate (−)-N_a-H, N_b-benzyl tetracyclic ketone **15a** via the asymmetric Pictet−Spengler reaction on a multihundred-gram scale has been developed. A diastereocontrolled (>30:1) anionic oxy-Cope rearrangement and the intramolecular rearrangement to form ring-E and an N_b-benzyl/N_b-methyl transfer reaction also served as key steps. This general approach can now be utilized for the synthesis of macroline/sarpagine related indole alkaloids and their antipodes for biological screening.

Introduction

During the last several decades, more than 90 macroline/sarpagine related indole alkaloids have been isolated from various species of *Alstonia*.[1−3] Interest in the macroline/sarpagine alkaloids originated as a result of folk tales, which described the medicinal properties of the plants from which these alkaloids were isolated.[4,5] A number of alkaloids from *Alstonia angustifolia* have been reported to possess antiprotozoal activity against *Entamoeba histolytica* or *Plasmodium falciparum* in vitro,[6] while other sarpagine alkaloids have been found to possess sedative, ganglionic blocking, hypoglycemic or antibacterial activity.[2] Studies were begun to evaluate these alkaloids for activity against cancer[7] and HIV;[7−9] however, the paucity of isolable material from these species has retarded biological screening.

Talpinine **1** is a typical representative of a seven-membered subgroup of talpinine-related alkaloids, which may exhibit pharmacological activity.[2] Unfortunately, to date, none of these bases has been synthesized or evaluated in vivo in detail. Talcarpine **2** is a related macroline/sarpagine indole alkaloid of which the total synthesis has also not yet been accomplished.[1,3] In addition, two closely related ring-A methoxylated derivatives of alstonerine **3** comprise southern portions of the bisindoles macralstonine **5** and alkaloid H.[1] Macralstonine **5** and its derivatives, in fact, have been found to exhibit potent hypotensive and antiamoebic activities, respectively.[10−13] The related monomer anhydromacrosalhine-methine **4** forms the northern portion of the bisindole (−)-macrocarpamine **6**. This alkaloid was found to be the most active antiamoebic agent against *E. histolytica* of the series [ED_{50}(95% CI) = 8.12(7.76−8.48) μM] isolated from *A. angustifolia*.[6,14] The results of these in vitro studies provide some basis for the traditional use of the plant extract from *A. angustifolia* for the treatment of amoebic dysentery and malaria by the people of the Malay Peninsula.[6] Moreover, anhydromacrosalhine-methine **4** and its ring-A methoxylated derivatives comprise portions of several other bisindoles, which may exhibit some degree of antiprotozoal activity because of their structural similarity to macrocarpamine **6**.[2] Therefore, development of an efficient approach to the synthesis of these alkaloids will not only permit biological screening of synthetic samples but will also provide a general route for the synthesis of other related alkaloids, or their antipodes.[1−3]

Talpinine **1**, which contains seven asymmetric centers, four heteroatoms, and six rings (Figure 1), was isolated from the stem bark and root bark of *Pleiocarpa talbotii* by Schmid[15] in 1972. The structure of **1** was elegantly

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(14) Mayerl, F.; Hesse, M. *Helv. Chim. Acta* **1978**, *61*, 337.

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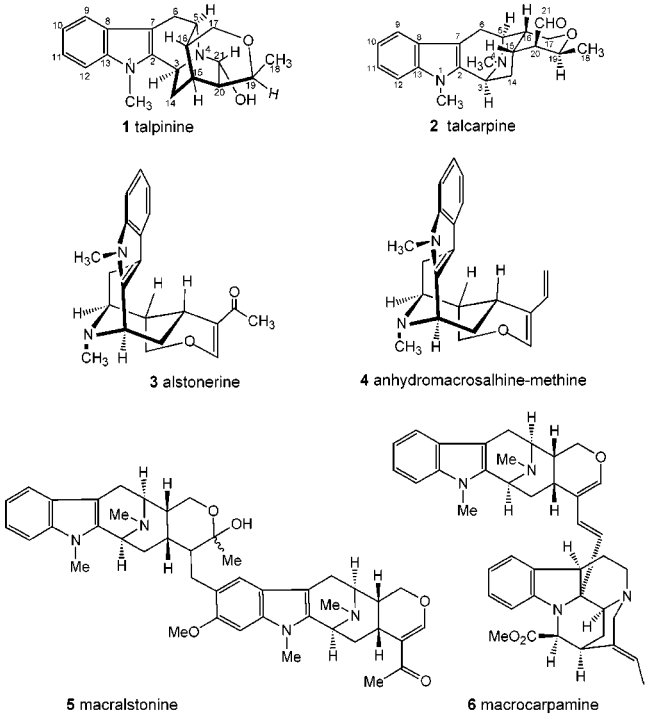
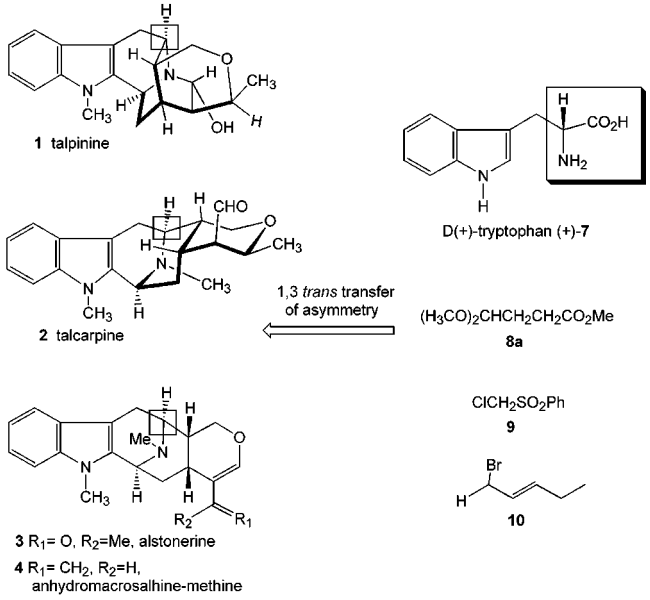


Figure 1.

determined originally by Schmid et al.[15] through chemical correlation and by analysis of the NMR and mass spectra of the base and its derivatives. Talcarpine **2**, which was first reported with **1**,[15] was also isolated recently from *Alstonia macrophylla* by Wong et al.[3] The proton assignments for **1** and **2** were made at all chiral centers with the exception of C(19), which remained ambiguous until the work of LeQuesne[16] and Sakai.[17] LeQuesne reported a series of interconversions between the *Alstonia* macroline-related alkaloids and **1** as well as **2**,[16] while Sakai[17] completed a partial synthesis of talcarpine **2** from ajmaline. At this time the assignment of the chirality of the C(19) methyl group was established in talcarpine **2** and then related chemically to that in talpinine **1**.[17]

From examination of the transformations carried out by LeQuesne,[16] it was clear the macroline alkaloids[1,2] are related biosynthetically to the two bases from *P. talbotii*. The stereogenic centers of the sarpagine alkaloids at C(3), C(5), C(15), and C(16) are identical to those in **1** and **2**, while both series are antipodal to ajmaline at C(16). We wish to report the first stereocontrolled entry into the correct chirality of the sarpagine alkaloids at C(3), C(5), C(15), and C(16), which resulted in the enantiospecific total synthesis of talpinine **1** and talcarpine **2** as well as the much improved total synthesis of alstonerine **3** and anhydromacrosalhinemethine **4**. This was accomplished via the trans transfer of chirality in the asymmetric Pictet−Spengler reaction[1,2,18−21] accompanied by a stereocontrolled anionic oxy-Cope rearrangement as the key steps.

Scheme 1



From a retrosynthetic point of view, D-(+)-tryptophan **7** was chosen to serve as the chiral auxiliary as well as the starting material. As illustrated in Scheme 1, the chirality of **7** was to be employed to introduce the correct stereogenic centers in the target compounds (seven stereocenters for **1** and six stereocenters for **2**) step by step. The important initial stereogenic centers would be established from the 1,3 trans transfer of chirality in the asymmetric Pictet−Spengler reaction.

More specifically, talpinine **1**, talcarpine **2**, alstonerine **3**, and anhydromacrosalhinemethine **4** might be available via a common intermediate, enol ether **12,** by either intramolecular rearrangements that involve ring-E or via functional group transformations. As illustrated in Scheme 2, enol ether **12** could arise from olefinic aldehyde **13/14** by oxidative cleavage of the olefinic unit (latent aldehyde). The synthesis of this aldehyde **13/14** can be approached from the tetracyclic ketone **15a/15b** via a number of pathways.[22] The ketone **15a/15b** should be available from D-(+)-tryptophan **7** on a large scale via the asymmetric Pictet−Spengler reaction and the Dieckmann reaction as key steps (Scheme 2).

Results and Discussion

The initial aim of this study was to develop a convenient synthetic route for large-scale diastereospecific preparation of N_a-H, N_b-benzyl tetracyclic ketone **15a** based on the following reasons: (1) Although several N_a-methyl macroline/sarpagine alkaloids have fallen to total synthesis,[1,2] the inability to synthesize stereospecifically the key intermediate **15a** in the N_a-H series has retarded efforts to prepare the N_a-H parent bases which represent about one-third of the isolated indole alkaloids.[1,2,23,24] (2)

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(16) Garnick, R. L.; LeQuesne, P. W. *J. Am. Chem. Soc.* **1978**, *100*, 4213.
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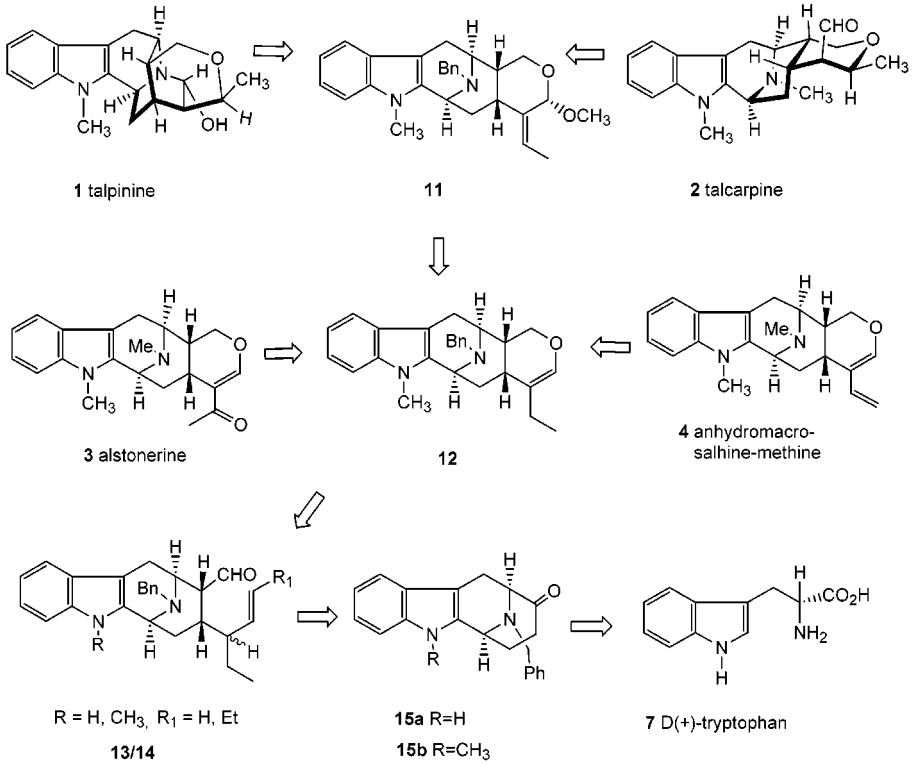
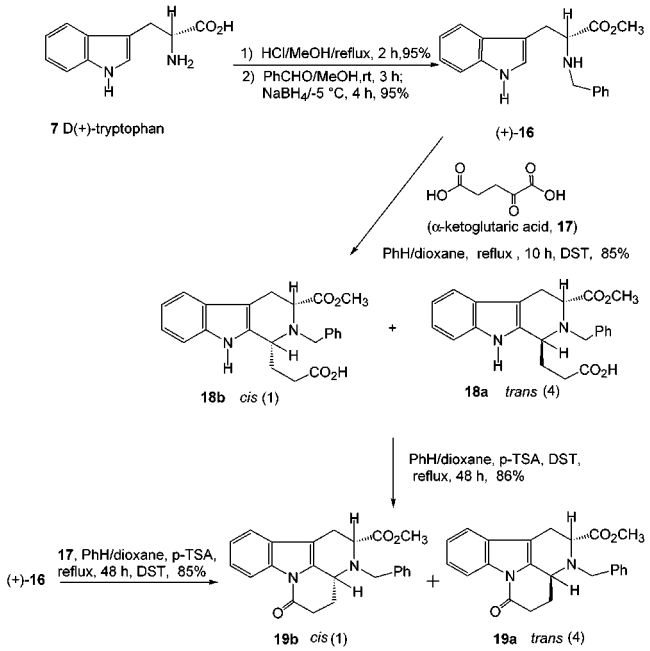
Scheme 2



Intermediates in the N_a-H series might well be converted into their N_a-methyl counterparts at a later stage to furnish the N_a-methyl alkaloids.[25,26] (3) This route would avoid the large-scale N_a-methylation in liquid ammonia previously required in the N_a-methyl series.[1,2,22] Due to the poor stereoselectivity encountered in the synthesis of the cis 1,3-disubstituted tetrahydro β-carbolines reported by Bailey,[27] Magnus,[28] Brossi, and others,[29] it was decided to fashion the correct chirality at the C(1) and C(3) stereocenters by employing the trans 1,3-transfer of chirality via the Pictet−Spengler reaction,[30−33] followed by inversion of the chiral center which remained at C(3) before the Dieckmann cyclization in the N_a-H series.

D-(+)-Tryptophan (+)-**7** was converted into its N_b-benzyl D-tryptophan methyl ester (+)-**16** in two steps in high yield with an improvement in the process of Sakai,[34] similar to the route utilized in the N_a-methyl series.[30,35] As illustrated in Scheme 3, Fisher esterification of (+)-**7** with methanolic hydrogen chloride gave the methyl ester. This was then converted into N_b-benzyl tryptophan methyl ester (+)-**16** on stirring with benzaldehyde at

Scheme 3



room temperature (2 h), followed by reduction of the imine, which resulted in situ with sodium borohydride at −5 °C (2−5 h, according to the scale). The temperature in the flask can be controlled by using an ice−salt bath; however, it was much easier to maintain the temperature between −10 and −5 °C by employing a dry ice bath (without solvent). If the temperature falls below −15 °C, a large amount of solid will form and it becomes too difficult to stir the reaction mixture. The slow addition of borohydride and low temperature of this process are critical to prevent racemization of the chiral center. The optical purity of the N_a-H, N_b-benzyl tryptophan methyl ester (+)-**16** prepared in this manner was found to be

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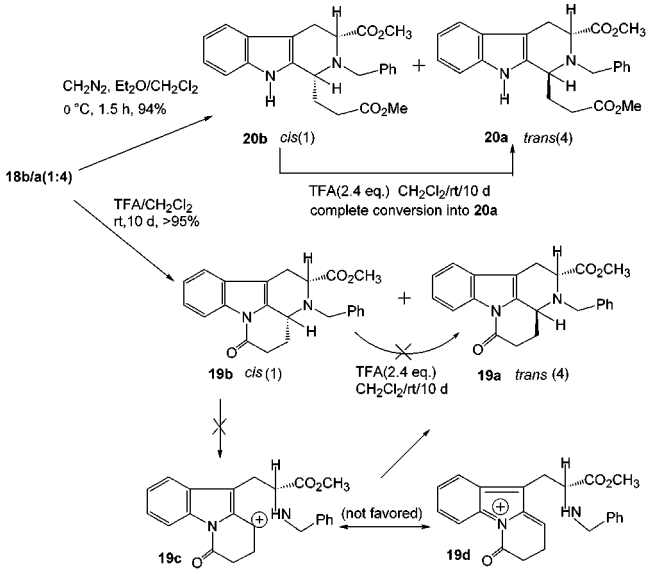
greater than 98% ee as determined by comparison to authentic samples.[30−33]

To introduce the desired stereocenter at the C(1) position with the same chirality as that of the natural macroline/sarpagine/ajmaline alkaloids, Soerens et al.[36] and Sakai et al.[34] have carried out the Pictet−Spengler condensation of N_a-H, N_b-benzyl tryptophan methyl ester **16** with α-ketoglutaric acid **17**. This process provided a mixture of ester acids (*trans*-**18a**/*cis*-**18b**) and δ-lactams (*trans*-**19a**/*cis*-**19b**) with good trans diastereoselectivity. The initial synthetic plan was to utilize this cheaper, commercially available **17** and adjust the Pictet−Spengler reaction conditions to achieve higher diastereoselectivity. Under the normal conditions of the Pictet−Spengler reaction in aprotic media (benzene/dioxane, Dean−Stark trap, reflux, 8 h), treatment of (+)-**16** with **17** provided the ester acids as a mixture of *trans*-**18a** and *cis*-**18b** (ratio = 4:1) diastereomers in 85% yield (Scheme 3).

In the presence of a catalytic amount of p-TSA on prolonged heating, the Pictet−Spengler reaction in aprotic media (benzene/dioxane, p-TSA, Dean−Stark trap, reflux, 60 h) afforded δ-lactams **19a**/**19b** in 86% yield in the ratio of trans/cis = 4:1 (Scheme 3). The mixture of trans and cis ester acids **18a**/**18b** could be gradually converted into δ-lactams **19a**/**19b** when the solution was heated to reflux for longer periods of time in the presence of a catalytic amount of p-TSA as expected (Scheme 3). The formation of the δ-lactam had been reported previously,[34,37,38] but it had been obtained either as a trace byproduct or as a component of a complex mixture.

Dissatisfied with the 80% diastereoselectivity, it was decided to epimerize the cis ester acid **18b** and the cis δ-lactam **19b** into the trans diastereomers **18a** and **19a**, respectively. As illustrated in Scheme 4, when the ester

Scheme 4

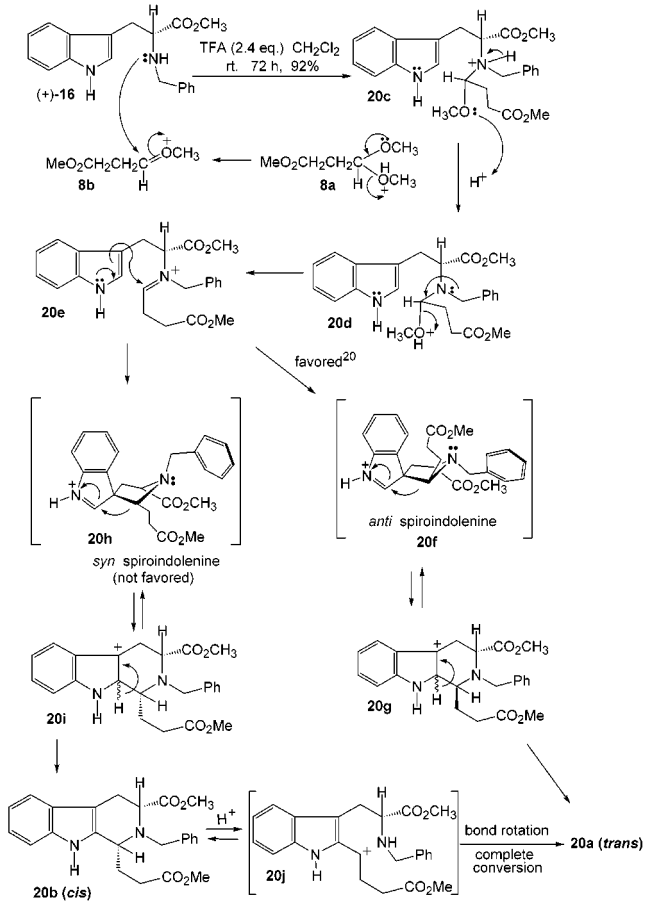


acids **18a/18b** were stirred with TFA, the trans and cis mixture was converted into the δ-lactams **19a**/**19b** rather than into the trans diastereomer **18a**. Moreover, the cis δ-lactam **19b** could not be converted into the corresponding trans isomer **19a** even when stirred under strongly acidic conditions for 10 days (Scheme 4).

To improve the diastereoselectivity of this sequence, esterification of the ester acids **18a**/**18b** with diazomethane under neutral conditions was carried out to avoid the formation of the δ-lactams. As illustrated in Scheme 4, the N_a-H, N_b-benzyl diesters **20a**/**20b** were obtained in 94% yield. The cis diester **20b** was separated from the trans isomer by flash chromatography and then treated with TFA at room temperature for 10 days in CH_2Cl_2 (Scheme 4). After workup, it was found that the cis diester **20b** had been completely converted into the trans diastereomer **20a**.

After study of the epimerization process, it was felt the Pictet−Spengler cyclization could be carried out under the conditions of the isomerization process (TFA in CH_2Cl_2 at room temperature) wherein two reactions could be combined in a one-pot process. To do this, the acid function of α-ketoglutaric acid **17** required protection to avoid the formation of the δ-lactams **19a**,**b** (Scheme 3). It was decided to employ methyl 4,4-dimethoxybutyrate **8a**, which could be prepared very cheaply on a large scale,[39] directly for the modified Pictet−Spengler reaction.[40] This successful process is detailed below.

Scheme 5



As illustrated in Scheme 5, the lone pair of electrons of the N_b-nitrogen atom of **16** presumably attacked the

(36) Soerens, D.; Sandrin, J.; Ungemach, F.; Mokry, P.; Wu, G. S.; Yamanaka, E.; Hutchins, L.; DiPierro, M.; Cook, J. M. *J. Org. Chem.* **1979**, *44*, 535.

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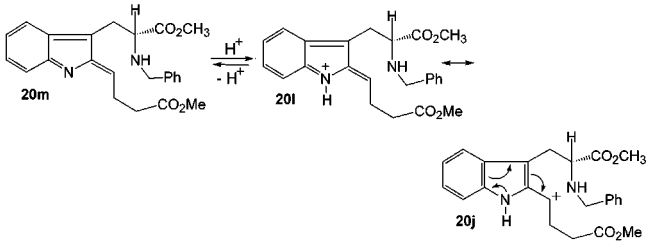
(40) Czerwinski, K. M.; Deng, L.; Cook, J. M. *Tetrahedron Lett.* **1992**, *33*, 4721.

oxonium ion **8b** to form the intermediate **20c**. Protonation of the oxygen atom of the methoxyl group of **20c** generated the intermediate **20d**. The elimination of the protonated methoxyl group provided the iminocation **20e**, which could be converted into the trans diester **20a** via two mechanistic pathways outlined for the Pictet−Spengler cyclization/isomerization process. Attack of the iminium ion at the indole C-(3) position could form either the anti spiroindolenine **20f** or the syn spiroindolenine **20h**. The intermediate **20f** can rearrange directly into the desired trans diester **20a** via the intermediate **20g** (Scheme 5). However, in the case of the disfavored syn spiroindolenine,[34] it is felt the rearrangement to the cis diester **20b** would occur first (Scheme 5), followed by the acid-catalyzed isomerization at C(1) to afford the more stable trans diester **20a**. Consequently, during the process of this Pictet−Spengler reaction, the cis diester **20b** derived from **20h** was indeed detected by TLC but was converted entirely into the trans diester **20a**. Presumably via the carbocationic intermediate **20j** as planned. After workup, the trans diester **20a** was obtained as the only diastereomer.

Examination of these results suggests the following: (1) Kinetically, the trans isomers are preferred in this Pictet−Spengler reaction; consequently, the trans isomers were formed predominantly in a ratio of 4:1 in both the acid ester (**18a**/**18b**) and δ-lactam series (**19a**/**19b**). (2) Thermodynamically, the trans isomer is also favored; moreover, any cis diester **20b** formed from the γ-ester can be completely converted into the more stable trans diester **20a** in the presence of TFA. (3) Formation of the δ-lactam is faster than epimerization of the cis ester acid into the trans ester acid in the process catalyzed by *p*-TSA or TFA (Schemes 3 and 4). (4) The substitution of an electron-withdrawing group (amide) on the N_a-H function to provide the δ-lactam **19b** destabilizes the proposed cationic intermediate **19c** necessary for the epimerization. The free energy of the intermediate **19c**/**19d** is too high to overcome even in the presence of the strong acid TFA. Consequently, epimerization of **19b** into **19a** was not observed. (5) No racemization at the C-(1) position occurred when this modified Pictet−Spengler reaction was executed with a benzyl group at the N_b-nitrogen function in the N_a-H series, in agreement with a similar case in the N_a-methyl series.[31] Earlier, Harrison,[41] Hino,[42] and Bailey[43] had reported that execution of the Pictet−Spengler reaction in nonacidic aprotic media with optically active N_b-H tryptophan methyl esters resulted in racemization to varying degrees. In contrast, it is felt that the enantiospecific nature of this modified Pictet−Spengler reaction was due to the presence of the N_b-benzyl group. Its presence resulted in a more reactive iminium ion **20e**, which underwent cyclization rather than racemization; moreover, this group also promoted trans diastereoselectivity. (6) The unique nature of the N_a-H function resulted in a faster rate not only for the modified Pictet−Spengler condensation but also for the cis to trans epimerization in the N_a-H series in comparison to that in the N_a-methyl series. The latter process required heating in TFA/$CHCl_3$ for 24 h to provide an initial 9:1 trans/cis selective cyclization, which could later be converted entirely into the trans isomer.[22] Not only was the spiroindolenine intermediate **20f** formed more easily from iminium ion **20e** in the N_a-H case as compared to the N_a-methyl series, but the formation of carbocationic intermediate **20j** can be stabilized (in part) by loss of a proton from **20l** (Scheme 6) during the

Scheme 6



formation of intermediate **20m**. This cannot take place readily in the N_a-methyl series. These results are entirely consistent with the proposed mechanism of C−N bond cleavage for epimerization of *cis*-N_b-benzyltetrahydro β-carbolines into their trans counterparts recently reported from our laboratory.[20−22,31]

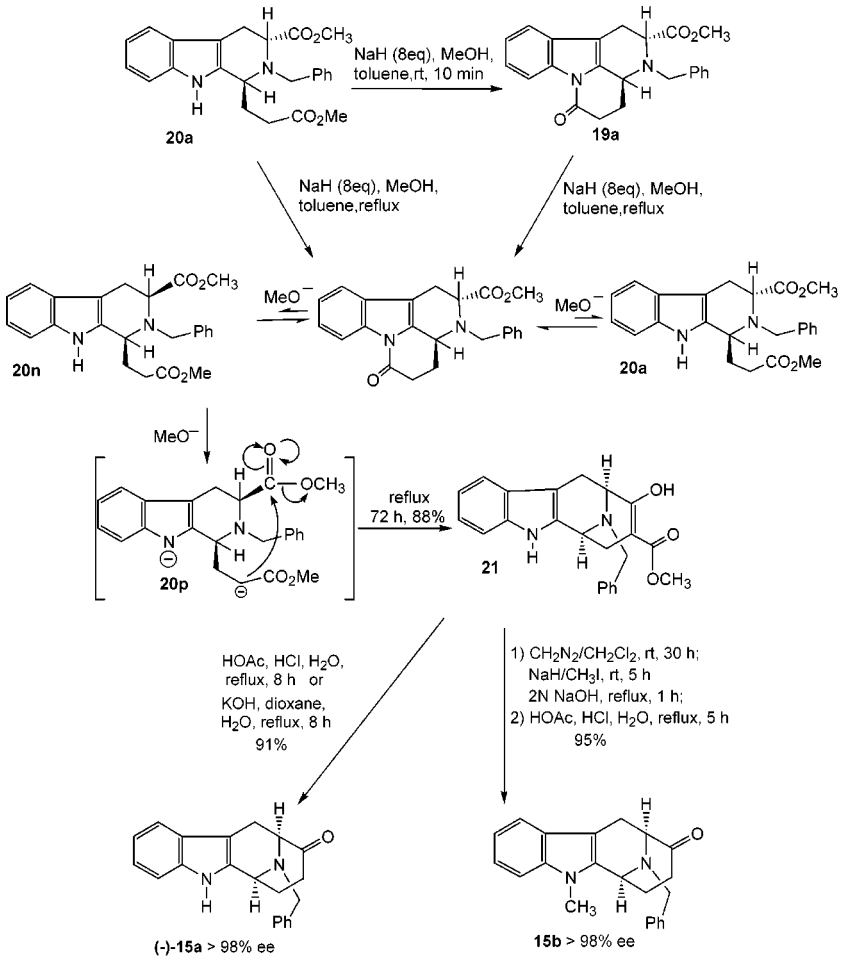
When the diester **20a** was treated with sodium hydride in the presence of excess methanol in refluxing toluene[31] for 1 h, the trans diester **20a** was converted almost entirely into trans δ-lactam **19a** (Scheme 7). However, when **20a** was treated under these same reaction conditions for an extended period (72 h), the desired Dieckmann product **21** was produced in 88% yield. Presumably, the δ-lactam **19a** formed and then underwent ring opening to provide **20n** under these conditions, which was eventually converted entirely into β-ketoester **21** via the Dieckmann process**.** It was felt the δ-lactam **19a** was favored in the equilibrium with diesters **20a** and **20n**; however, the irreversible formation of the enolate in the Dieckmann cyclization gradually promoted completion of the process to provide the β-ketoester **21**, exclusively.

At least 4 equiv of sodium hydride were required in this Dieckmann cyclization process for facile reaction (Scheme 7). Hydrolysis of the β-ketoester **21** and decarboxylation under acidic conditions were achieved in one step to provide the template (−)-N_a-H, N_b-benzyltetracyclic ketone[(−)-9-oxo-12-benzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indole] (−)-**15a** in 91% yield. The enantiomeric purity of β-ketoester **21** was shown to be greater than 98% ee by ^{1}H NMR spectroscopy in the presence of the chiral shift reagent (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol and by converting it into (−)-N_a-methyl, N_b-benzyl tetracyclic ketone (−)-**15b,** whose enantiomeric purity had been determined previously by Zhang.[31]

Recently, a much improved route to the key tetracyclic intermediate **15a** was developed. D-(+)-Tryptophan methyl ester **22** was diastereospecifically converted (via **20a**) into azabicyclononone **15a** in greater than 98% ee in a two-pot process on a multihundred gram scale. More specifically, after N_b-benzylation of **22** with benzaldehyde and sodium borohydride in methanol, trifluoroacetic acid was added to the reaction vessel at 0 °C to neutralize the reaction mixture. After removal of the solvent, CH_2Cl_2, TFA, and **8a** were added to the vessel at 0 °C, and the modified Pictet−Spengler reaction was carried out in the same vessel to provide the trans diester **20a** in 83% overall yield. This diester **20a** was purified by

(41) Harrison, D. M.; Sharma, R. B. *Tetrahedron Lett.* **1986**, *27*, 521.
(42) Nakagawa, M.; Fukushima, H.; Kawate, T.; Hongu, M.; Kodato, S.; Une, T.; Taniguchi, M.; Hino, T. *Tetrahedron Lett.* **1986**, *27*, 3235.
(43) Bailey, P. D.; Hollinshead, S. P.; Mclay, N. R. *Tetrahedron Lett.* **1987**, *28*, 5177.

Scheme 7



crystallization. In the second sequence, after Dieckmann cyclization was completed, the reaction solution was cooled to 0 °C and carefully quenched with glacial acetic acid. After removal of the solvent, concentrated glacial acetic acid, aqueous hydrochloric acid, and water were added to the residue at 0 °C and the acidic hydrolysis of **21** and decarboxylation was executed in the same vessel to provide **15a** in 82% overall yield.

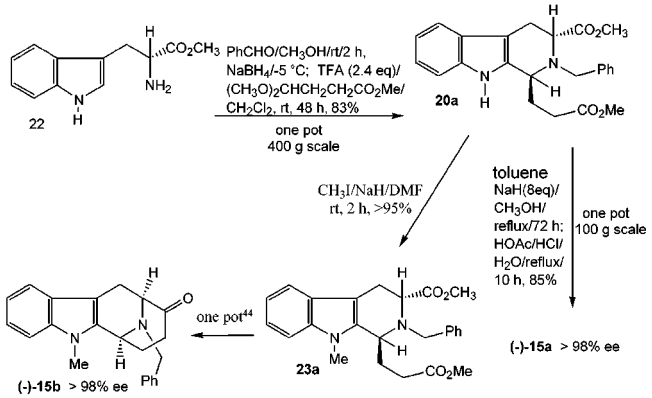
The methylated version of the key intermediate **15a**, N_a-methyl, N_b-benzyl tetracyclic ketone **15b**, has been employed as a key building block for the synthesis of numerous N_a-methyl-substituted indole alkaloids.[1,2] In 1988, Zhang[31] executed the first asymmetric Pictet−Spengler reaction for the synthesis of the key diester [*trans*-(−)-**23a**]. A mixture of trans and cis diesters **23a**,**b** in a ratio of 72:28 (81% yield) had been obtained, and the cis diester **23b** was isomerized to its trans diastereomer under acidic conditions.[31] The trans diester **23a** was converted into the ketone **15b** in good yield. Recently, the preparation of the N_a-methyl trans diester (+)-**23a** was improved by employing the modified conditions of the asymmetric Pictet−Spengler reaction;[44] however, some difficulty arose when the N_a-methyl trans diester **23a** could not be readily crystallized. Although any residual cis diester **23b** could be separated and then epimerized into the trans diastereomer **23a** under mildly acidic conditions,[31] the separation and epimerization would result in a decreased yield. The reaction could be carried out to provide only the trans diester on longer heating; however, yields were slightly lower as well in this case.

An initial attempt was made to execute the direct N_a-methylation of **15a**. This process was carried out under various conditions, but 5,8-dimethylation could not be avoided.[45] The N_a-methylation of ketoester **21**, however, was realized in a one-pot two-step process in high yield. β-Ketoester **21** was carefully treated with freshly prepared diazomethane to protect the ketone function and prevent α-methylation, followed by N_a-methylation with NaH/CH_3I. This was followed by hydrolysis of the ester that resulted, and acid-mediated decarboxylation afforded the desired **15b** in 90% yield. However, the utilization of diazomethane limited the scale of this route because of safety issues.

With the availability of the N_a-H trans diester **20a** on a multihundred-gram scale that could be easily purified by crystallization, it was decided to methylate the N_a-H function of *trans*-**20a**. The process took place readily in DMF to yield the N_a-methyl trans diester **23a** (Scheme 8) in 95% yield. When the analogous reaction was executed in THF, the N_a-methyl trans diester **23a** was obtained accompanied by some byproducts. It was felt the more polar solvent (DMF) stabilized the necessary N_a-anionic intermediate resulting from **20a** better than THF. This process gave **23a** in excellent yield in the former case on a multihundred gram scale very conveniently (Scheme 8), which could be easily converted into **15b**. Conversion of the carbonyl function of (−)-**15a** into

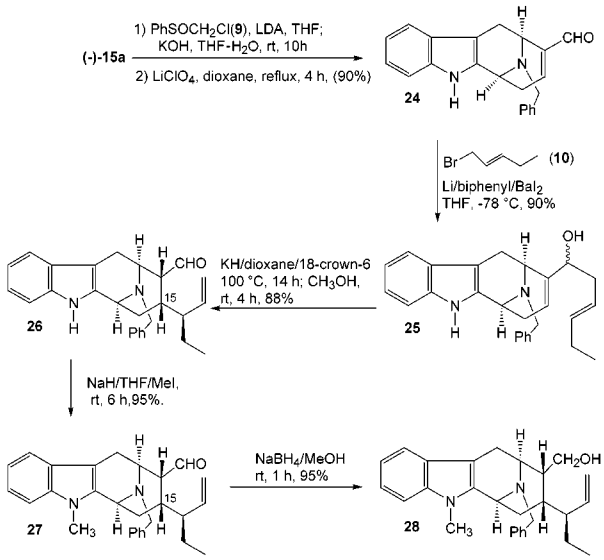
(44) Li, J. Ph.D. Thesis, University of Wisconsin-Milwaukee, 1999.

Scheme 8



the α,β-unsaturated aldehyde moiety of **24** via the spirooxiranophenylsulfoxide[18,19] was accomplished in 87% overall yield by modification of the procedure of Fu.[20] The compound (−)-**24** contains the desired absolute configuration at C(3) as well as C(5) and serves as the key intermediate for the total synthesis of the targets **1**, **2**, **3**, and **4** (see Scheme 1). From the beginning, an intramolecular sigmatropic rearrangement was envisaged to generate the correct chirality at C(15) for this series of alkaloids. An anionic oxy-Cope rearrangement would be expected to occur by the preferred chair transition state[46,47] from the bottom face of the azabicyclononene ring system (from **24**) to generate the correct chirality at C(15). However, the allylic carbanion required to provide allylic alcohol **25** would be expected to undergo an allylic rearrangement when stabilized as either the magnesium or lithium species. This obstacle was overcome by an important modification of the barium chemistry of Yamamoto et al.[48] Addition of a mixture of trans 1-bromo-2-pentene **10** and aldehyde **24** to freshly pre-

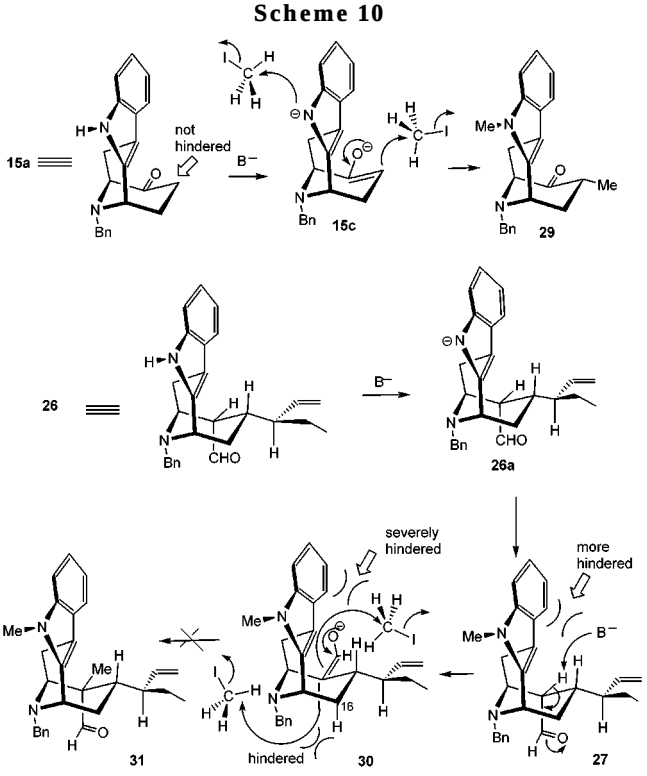
Scheme 9



pared barium metal at −78 °C generated the desired allylic carbanion in 90% yield. This barium-stabilized species added in situ at −78 °C in a 1,2-fashion to **24** in high yield without allylic rearrangement. The anionic oxy-Cope rearrangement took place in the N_a-H azabicyclononene system **25** almost exclusively from the desired bottom face of the C(15)−C(16) olefinic bond. The diastereoselectivity at C(15) was greater than 30:1 in this system to provide the correct chirality at C(15). Although the major diastereomer **26** (76%) contained the correct chirality at C(15) and C(16), it was accompanied by a minor diastereomer (12%) epimeric at the aldehydic carbon atom at C(16). This isomer, however, was completely converted into **26** on addition of methanol to the reaction mixture with continued stirring at room temperature for 2 h. The desired stereochemistry in **26** was obtained with high diastereoselectivity from **25** in 88% overall yield. The stereoselectivity of the oxy-anion Cope rearrangement here was increased significantly in comparison to the previously reported heptenyl[44] and pentenyl series in the N_a-methyl cases. The purpose of adding methanol to the above mixture was to epimerize the aldehydic function at C(16) of the minor isomer into the more stable configuration present in **26**. This sequence of reactions provides the first stereocontrolled entry into the correct chirality of the sarpagine alkaloids at C(3), C(5), C(15), and C(16). The N_a-H aldehydic olefin **26** was regiospecifically N_a-methylated in 95% yield to provide **27,** which was reduced with sodium borohydride in 95% yield to furnish alcohol **28**.

As mentioned previously, numerous attempts to N_a-methylate the N_a-H function of the (−)-N_a-H, N_b-benzyl tetracyclic ketone **15a** always provided some of the 5,8-dimethylated material **29**. As illustrated in Scheme 10,

Scheme 10



the α-position of **15a** was not severely hindered; therefore, it was felt that the strong base deprotonated both the N_a-H proton and the proton at the C(8) position to provide the 5,8-dimethylated ketone **29**.

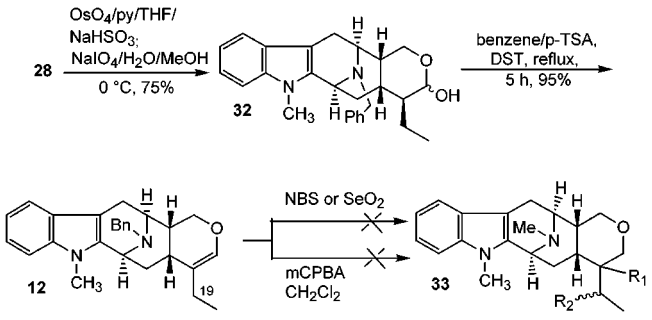
Unlike the N_a-H function of **15a**, alkylation of the α-position of the aldehyde in **26** (C-16) was much more

(45) Yu, P. Ph.D. Thesis, University of Wisconsin-Milwaukee, 1999.
(46) Paquette, L. A. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 609.
(47) Paquette, L. A.; Maynard, G. D. *J. Am. Chem. Soc.* **1992**, *114*, 5018.
(48) Yanagisawa, A.; Habaue, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1991**, *113*, 8955.

hindered from the top and bottom faces of the enolate. As illustrated in Scheme 10, deprotonation of the C(16) position of **27** would generate the enolate **30**. Methylation of this intermediate **30** would be expected to be hindered from the top face by the indolomethylene bridge and from the bottom face by the C(16)-proton and the N_b-benzyl group.

To selectively cleave the olefinic bond in the presence of an indole moiety in **28**, it was felt that ozone might be more active at the double bond at C(21) than the indole double bond at C(2)−C(7) since the indole double bond was contained in an aromatic π system. Numerous attempts to oxidatively cleave the double bond in **28** by ozonization under different conditions were executed.[45] However, none of these attempts were successful; the indole double bond was destroyed in all cases. As illustrated in Scheme 11, when the olefin **28** was stirred

Scheme 11



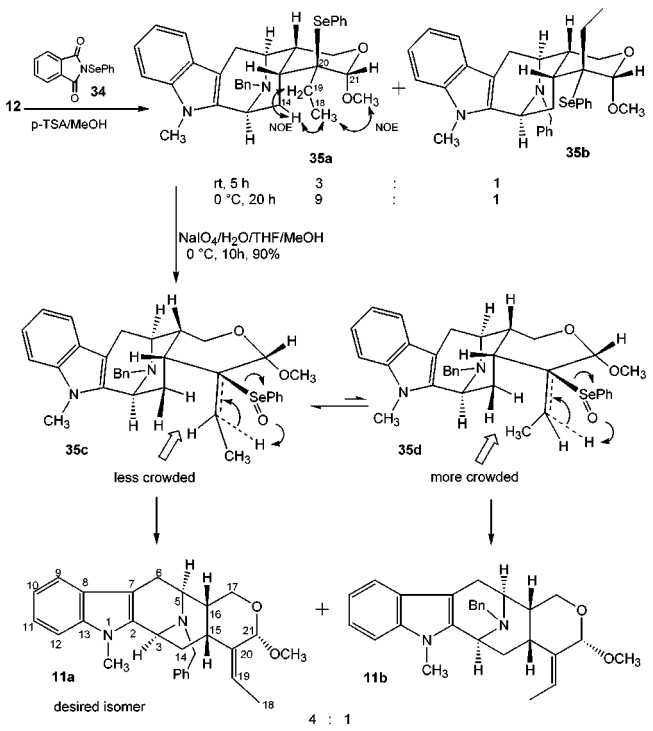
with a prepared solution of OsO_4−pyridine[49] in THF at 0 °C for 8 h followed by treatment with $NaIO_4$, oxidative cleavage of the olefinic unit (latent aldehyde) in **28** occurred followed by cyclization to form the E-ring without affecting the stereochemistry at C(15) and C(16). The hemiacetal **32** was converted into a single pure enol ether **12** on dehydration with *p*-TSA in refluxing benzene.

With the desired N_b-benzyl enol ether **12** in hand, several attempts to introduce a functional group at the C-19 position of **12** were made including allylic bromination with NBS,[50] allylic oxidation with various reagents including SeO_2,[51] and epoxidation with *m*-CPBA. Unfortunately, all of these reactions failed or gave mixtures of inseparable material (Scheme 11).

The regiospecific oxyselenation of the olefin **12** was carried out with *N*-phenylselenophthalimide **34**, according to the procedure of Nicolaou et al.,[52] in CH_2Cl_2−MeOH in the presence of *p*-toluenesulfonic acid at 0 °C to provide selenoacetals **35a**/**35b** in a ratio of 9:1 in high yield. This mixture was directly treated with $NaIO_4$ in THF−MeOH−H_2O solution at 0 °C for 10 h without separation to afford **11a**,**b** in 90% yield (Scheme 12).

As illustrated in Scheme 12, examination of the data from the NOESY spectrum of the major isomer **35a** clearly indicated there were NOE interactions between the proton located at C(14) and the protons at C(19) as well as the protons at C(18). Consequently, the configuration of C(20) in **35a** was assigned as S. Moreover, the NOE interactions between the protons located at C(18)

Scheme 12



and the protons of the C(21)-methoxyl group indicated that the C(21)-methoxyl group of **35a** existed in the α-orientation (Scheme 12). This was confirmed by analysis of the structure of the elimination product **11a** (Scheme 13) since the stereochemistry at C(21) should not be altered during that transformation.

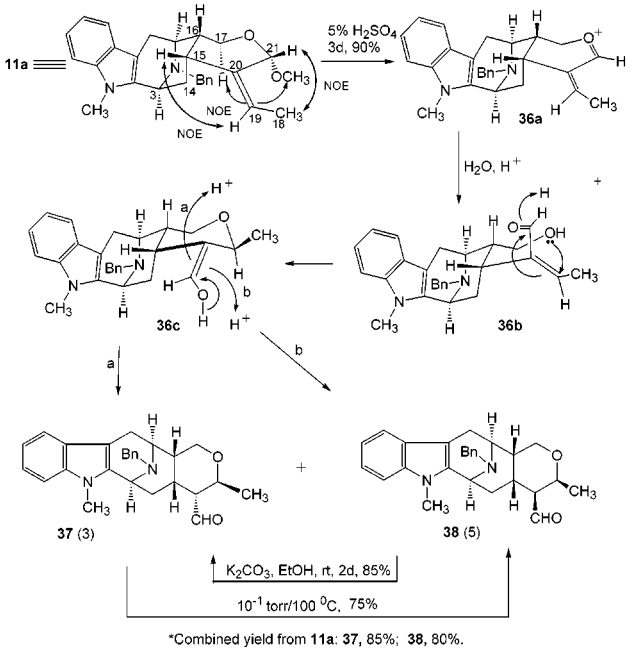
It was well-known that selenoxide elimination takes place by a syn elimination. As illustrated in Scheme 12, the selenoacetal **35a** was oxidized with $NaIO_4$ to generate the selenoxide intermediates **35c**,**d**. There are at least two possible transition states for the elimination. Transition state **35d** should be less favored because the terminal methyl group is believed to be oriented toward ring-D and should experience severe repulsive interactions between this methyl group and the protons at C(14). In comparison to **35d**, the transition state **35c** is not as crowded because the terminal methyl group is farther removed from the protons at C(14) and C(15). Consequently, it is felt the selenoacetal **35a** underwent the selenoxide elimination via transition state **35c** to provide the desired olefin **11a** predominating in a ratio of 4:1 (Scheme 12).

The minor isomer (selenoacetal **35b**) should undergo the selenoxide elimination via a similar low energy transition state to provide the undesired olefin **11b** as the major isomer. The structure of the desired olefin **11a** was determined by NMR experiments [COSY, DEPT, HSQC (H−C correlation), ^1H and ^{13}C spectra].

As illustrated in Scheme 13, examination of the data from the NOESY spectrum of olefin **11a** clearly indicated there were NOE interactions between the protons located at C(17)−H_α and those on the OCH_3 group at C(21). The vinyl proton at C(19) experienced an NOE with the proton at C(15) and the protons at C(18) interacted with the proton at C(21). Consequently, it can be concluded that the geometry of this desired olefinic acetal **11a** was *Z* and the C(21)-methoxyl group existed in the α-orientation.

(49) Fu, X.; Cook, J. M. *J. Org. Chem.* **1993**, *58*, 661.
(50) Gan, T.; Cook, J. M. *J. Org. Chem.* **1998**, *63*, 1478.
(51) Gan, T. Ph.D. Thesis, University of Wisconsin−Milwaukee, 1997.
(52) Nicolaou, K. C.; Claremon, D. A.; Barnette, W. E.; Seitz, S. P. *J. Am. Chem. Soc.* **1979**, *101*, 3704.

Scheme 13



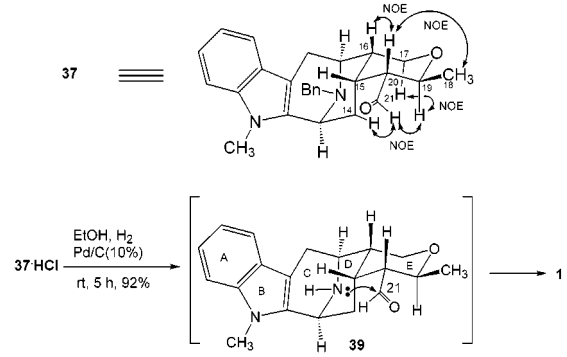
Acid-catalyzed[15,17] hydrolysis of acetal **11a** was followed by the Michael addition of the C(17) hydroxyl group to the α,β-unsaturated aldehyde **36b** which resulted. This process provided a mixture of N_b-benzyl, N_b-21-secotalpinine **37** and N_b-benzyltalcarpine **38** via the intermediate **36c** in a ratio of 3:5 in 90% yield. Both compounds obtained in this process are important, for aldehyde **37** was required for the synthesis of talpinine, while aldehyde **38** was necessary for the preparation of talcarpine. As shown in Scheme 13, the mixture of **37** and **38** was converted completely into the desired secotalpinine **37** on stirring in methanol in the presence of K_2CO_3.[15,17] This provided the secotalpinine **37** required for the synthesis of **1** in 85% overall yield from **11a**.

Conversely, aldehyde **37** could be separated from **38** via flash chromatography and the secotalpinine **37**, which remained, pyrolyzed[15] to provide aldehyde **38** (75%, accompanied by 20% starting **37**). In this fashion, the overall yield of the necessary secotalcarpine **38** was increased to 80% (from **11a**). The process outlined in Scheme 13 is unique for either aldehyde **37** or aldehyde **38** can be prepared in greater than 80% yield from **11a**, when desired, and in greater than 98% ee.

The mechanism for the epimerization of aldehyde **38** into its thermodynamically more stable isomer **37** is straightforward; however, the mechanism for the pyrolysis (from **37** to **38**) is not yet clear, formation of **36b** followed by the Michael addition to regenerate the E-ring is part of this pathway. The medium and temperature under which the two epimerization/protonation processes were carried out are entirely different, which complicates the comparison of these two reactions.

The structures of the desired aldehyde **37** and secotalcarpine **38** were determined by NMR experiments [COSY, DEPT, HSQC (H−C correlation), ^1H and ^{13}C spectra].[45] As illustrated in Scheme 14, examination of the data from the NOESY experiment on **37** clearly indicated that the protons at C(18) on the methyl function underwent an NOE interaction with the β proton located at C(20), which in turn interacted with the β proton at C(16). Because the configuration of C(16) of the starting

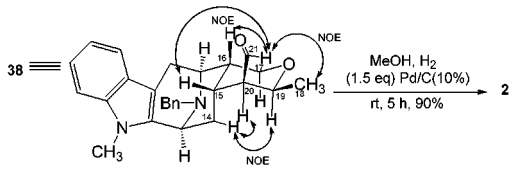
Scheme 14



acetal **11a** had been confirmed previously (Scheme 13) and the stereochemistry should not be affected during this transformation, the above evidence suggested that the C(18)-methyl group should exist in the β-orientation. This was confirmed by the observation of NOE interactions between protons located at C(17)-H_α and C(19)-Hα. The configuration of C(20) in **37** was assigned as R based on the observation of NOE interactions between the β proton located at C(20) and the β proton at C(16). In addition, NOEs were observed between the proton at C(19) and the one located at C(21) as well as between the proton at C(14) and the one at C(21), respectively.

Examination of the data from the NOESY experiments on secotalcarpine **38** (Scheme 15) indicated that the

Scheme 15



configuration at C(19) in **38** was also *S*, similar to that in N_b-benzyl, N_b-21-secotalpinine **37** (Scheme 14). NOE interactions were observed between the protons located at C(18) and the one at C(15). In addition, the protons at C(18) and the one at C(21) experienced an NOE and the proton at C(21) in turn interacted with the proton located at C(15) as well as with the proton at C(16). The proton at C(19) also experienced an NOE with the one at C(14), respectively. Analysis of these NOEs indictated that the C(18)-methyl group in **38** should exist in the β-orientation, as shown in Scheme 15. In contrast to the structure of N_b-benzyl, N_b-21-secotalpinine **37** (Scheme 14), the configuration of C(20) in **38** was assigned as *S* based on examination of the NOE interactions between the proton located at C(20) and the one at C(14). This proton at C(14) in turn interacted with the one at C(19). The proton at C(21) interacted with the one at C(15); furthermore, the protons at C(18) experienced an NOE with the one at C(21), respectively.

When N_b-benzyl, N_b-21-secotalpinine **37** as the hydrochloride salt was subjected to the conditions of catalytic debenzylation (10% Pd/C, H_2)[31] in ethanol, a 92% yield of talpinine **1** was realized, as shown in Scheme 14. It was believed the debenzylation of **37** to provide **1** went through the intermediate N_b-H, N_b-21-secotalpinine **39**, as expected. The lone pair of electrons of the N_b-nitrogen atom of **39** then immediately attacked the aldehyde group at C(21) to form the F-ring of talpinine **1** (Scheme 14).

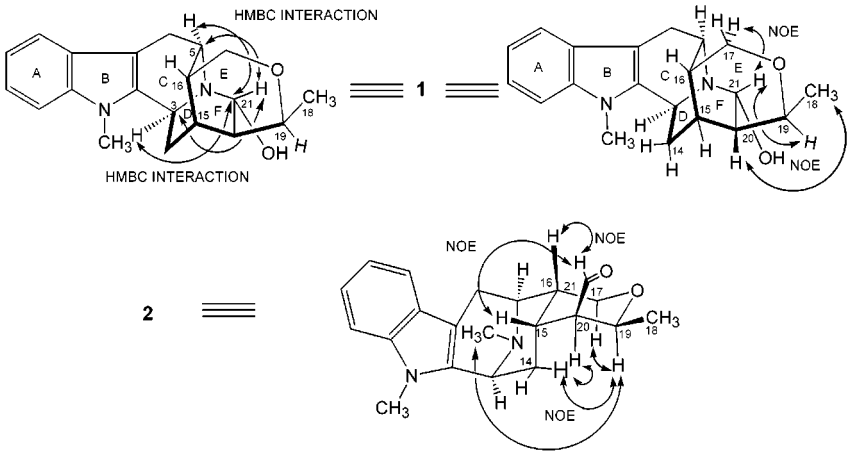


Figure 2.

To confirm the formation of the F-ring of **1**, it was decided to execute a 2D $^1H/^{13}C$ multiple bond correlation (HMBC) experiment. As illustrated in Figure 2, analysis of this experiment clearly indicated HMBC interactions occurred between the carbon atom at C(21) and the protons at C(3) and C(5) as well as the interactions between the proton at C(21) and the carbon atoms at C(3) and C(5) in **1**. Because HMBC interactions only occur within a range of 2−3 bonds, the above evidence indicated that the cyclization of **39** (Scheme 14) did occur to generate a nitrogen(4) bridge between C(21) and C(3) as well as between C(21) and C(5). Otherwise, the bond range between C(21) and C(3) as well as between C(21) and C(5) would be too long (five bonds) to have observed the HMBC interactions.

To elucidate the configurations at C(19), C(20), and C(21) in **1**, a NOSEY experiment was executed. As illustrated in Figure 2, examination of the data from the NOESY spectrum of **1** clearly indicated the methyl protons at C(18) underwent an NOE enhancement with the proton at C(15). Because the configuration of C(15) in the starting material **37** had been confirmed previously (Scheme 14), the above evidence suggested that the C(18)-methyl group should exist in a β-orientation. This was confirmed by the NOE observed between the proton located at C(19) and the one at C(21), which in turn interacted with the proton at C(17)-Hα. The configuration of C(20) in **1** was assigned as *R* based on the NOE interaction between the proton located at C(21) and the one at C(19). This was confirmed by analysis of the splitting pattern of the peak for the proton at C(19) in the ^1H NMR spectrum [δ 4.03 ppm (1H, q, $J = 6.8$ Hz)] of **1**. The lack of coupling observed between the proton at C(20) and the one at C(19) indicated there was no interaction between these two hydrogen atoms. Therefore, the C−H bond at C(20) and the one at C(19) should be located in **1** with a torsional angle of about 90°. The observation that the proton at C(21) underwent NOE interactions with the protons at C(19) and at C(17) coupled with the observation that there was no NOE interaction between the proton at C(14) and the one at C(21) (Figure 2), suggested that the configuration of C(21) should be *R*. This was confirmed by the small coupling constant between C(20)-H (δ 1.25 ppm) and C(21)-H [δ 4.49 ppm (1H, d, $J = 1.8$ Hz)], which indicated they were trans (a, e) to each other with a bond angle of about 95°.

When secotalcarpine **38** was stirred with 1.5 equiv (excess) of Pd/C (10%) in methanol in the presence of hydrogen (Scheme 15), analogous to the procedure of Fu,[49] the important N_b-benzyl/N_b-methyl transfer reaction took place to provide talcarpine **2** in 90% yield. This N_b-benzyl/N_b-methyl transfer reaction, which may involve formaldehyde formation, was observed in the suaveoline as well as the raumacline series[49] and may have some utility in the synthesis of other N_b-methyl azabicyclo-[3.3.1]nonane functionalized alkaloids. The spectral and physical properties, including the optical rotation, of **2** were in good agreement with the published values for the natural product and also with those of talcarpine **2** obtained from the degradation of ajmaline.[17]

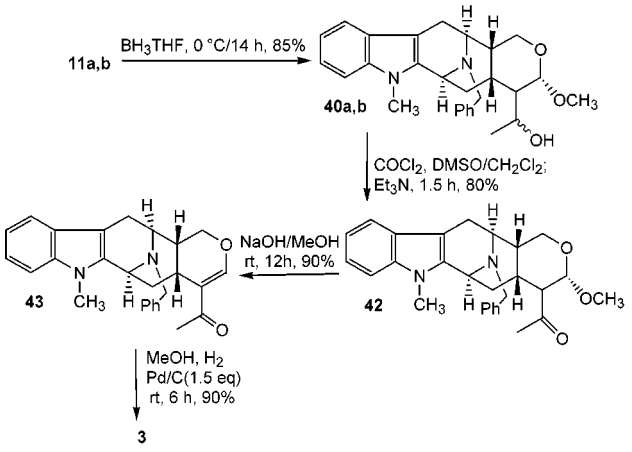
The stereochemistry of **2** at C(19) and C(20) was determined by Sakai et al.[17] during the partial synthesis of **2** from the degradation of ajmaline. This was confirmed by NMR experiments carried out on synthetic **2**. As illustrated in Figure 2, examination of the data from the NOESY spectrum of **2** clearly indicated NOE interactions between the proton at C(19) and the protons located at C(17)-Hα, C(14), and the N_b-methyl group. The α proton at C(20) underwent an NOE interaction with one of the protons at C(14), which in turn interacted, with the proton located at C(19). The above evidence confirmed that the C(18)-methyl group in **2** should exist in a β-orientation, as previously found in **38** previous to the debenzylation process. The configuration at C(20) was also maintained as *S* (Figure 2) since an NOE was observed between the C(21)-H atom and the protons at C(15) and C(16). Examination of the data from the COSY and HSQC NMR experiments was in agreement with the ^{13}C NMR assignments for talcarpine **2** by Sakai except for the assignment reversal of the carbon atoms at C(3) and C(5), as well as those between C(19) and C(20) (Table 15) from the earlier report.[17]

The COSY spectrum clearly indicated that the proton at C(3) should be located at δ 3.92 ppm which underwent COSY interactions with the proton at C(14) (δ 1.36 ppm). The proton at C(5) actually appeared at δ 2.82 ppm and underwent COSY interactions with the protons located at C(6) (δ 3.33 ppm) and C(16) (δ 2.06 ppm). The proton at C(19) was found at δ 3.95 ppm and the COSY interaction was observed with the protons at C(18) (δ 1.32 ppm). The proton at C(20) was observed at δ 1.78 ppm and experienced a COSY interaction with the protons at C(15) (δ 2.20 ppm). With the proton NMR values of C(3), C(5), C(19), and C(20) available, the ^{13}C NMR values were easily assigned as C(3), 53.68; C(5), 54.63; C(19), 69.51; C(20), 54.72, respectively, by examination of the HSQC

data. The above assignments were confirmed by comparison with the ^{13}C and ^{1}H NMR assignments of talcarpine **2** by Wong,[3] who obtained **2** recently during isolation work.

With the availability of the key enol ether **12** (Scheme 11) and **11a**,**b** (Scheme 12), a much improved route to prepare the indole alkaloids alstonerine **3** and anhydromacrosalhine-methine **4** was carried out. As illustrated in Scheme 16, treatment of the mixture of olefins **11a**,**b**

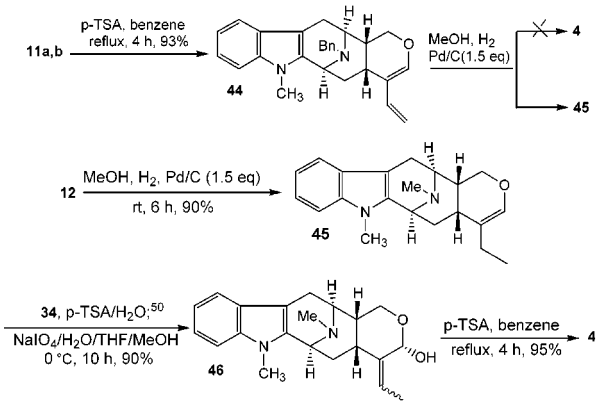
Scheme 16



with the BH_3·THF complex in THF at 0 °C for 14 h provided the alcohol represented by **40** as a mixture of diastereomers. Treatment of the alcohol **40** with the modified Swern oxidation conditions of Zhang[25] (−78 to −10 °C, 1.5 h) gave the ketoacetal **42** in 80% yield. This was followed by base-mediated elimination of the elements of methanol to generate the N_b-benzyl alstonerine **43** in 90% yield. When **43** was stirred with an excess of Pd/C in methanol for 6 h in the presence of hydrogen,[49] here again the N_b-benzyl/N_b-methyl transfer reaction took place to provide alstonerine **3** in 90% yield (Scheme 16).

To execute an improved synthesis of anhydromacrosalhinemethine **4**, attempts were first made to employ the intermediates **11a**,**b** to generate N_b-benzylanhydromacrosalhinemethine **44** via the elimination of the elements of methanol to provide the diene **44**. This was readily accomplished (Scheme 17); however, the N_b-benzyl/N_b-

Scheme 17



methyl transfer reaction (excess of 10% Pd/C in methanol in the presence of hydrogen)[49] to provide the desired anhydromacrosalhinemethine **4** took place but was accompanied by reduction of the terminal olefin to furnish **45** (Scheme 17).

Unable to execute the N_b-benzyl/N_b-methyl transformation without olefin reduction, it was decided to execute this functional group exchange at an earlier stage. As illustrated in Scheme 17, the N_b-benzyl/N_b-methyl transfer reaction readily took place with the N_b-benzyl enol ether **12** to provide N_b-methyl enol ether **45** in 90% yield. This material was converted into anhydromacrosalhinemethine **4** via the intermediate **46** available from selenoxide formation and elimination with **34** in high yield by following the procedure developed earlier.[50]

Conclusion

The enantiospecific total synthesis of **1** and **2** has been accomplished in 13 steps (11 reaction vessels) in 10% and 9.5% overall yields, respectively. Moreover, this synthetic approach has been employed for the improved synthesis of alstonerine **3** and anhydromacrosalhinemethine **4** in 14 reaction vessels (12% overall yield) and 12 vessels (14% overall yield), respectively. D-(+)-Tryptophan **7** has served here both as the chiral auxiliary and the starting material which provides a facile route [from L-(−)-tryptophan] to the antipodes of these alkaloids, if desired. The stereospecific conversion of **7** into **15a**/**b** on a multihundred-gram scale carried out in only two reaction vessels constitutes a significant advance over previous work in this area. The addition of the barium stabilized carbanion to the aldehyde **24** in a 1,2-fashion without allylic rearrangement should provide a route to other sarpagine or suaveoline related alkaloids via the diastereocontrolled (>30:1) anionic oxy-Cope rearrangement. Finally, the N_b-benzyl to N_b-methyl transfer reaction in the presence of excess Pd/C permits one to carry the N_b-benzyl group throughout the route and remove it at the very end without loss of valuable alkaloidal material.

Experimental Section

Microanalyses were performed on a Perkin-Elmer 240C carbon, hydrogen, and nitrogen analyzer. All samples submitted for CHN analyses were first dried under high vacuum for a minimum of 6 h using a drying pistol with methylene chloride or isopropyl alcohol as the solvent with phosphorus pentoxide in the drying bulb. Proton and carbon high-resolution nuclear magnetic resonance spectra were obtained on a Bruker 250-MHz multiple probe NMR instrument, GE 500-MHz NMR spectrometer, or a Bruker 300-MHz NMR spectrometer. The low-resolution mass spectra (EI/CI) were obtained on a Hewlett-Packard 5985B gas chromatograph−mass spectrometer, while high-resolution spectra were recorded on a VG AutoSpec (Manchester, England) mass spectrometer.

Analytical thin-layer chromatography plates used were E. Merck Brinkmann UV-active silica gel (Kieselgel 60 F254) on plastic. Silica gel 60A, grade 60 for flash and gravity chromatography, was purchased from E. M. Laboratories.

Alkaloids were visualized with Dragendorf's reagent or a saturated solution of ceric ammonium sulfate in 50% sulfuric acid or with an aqueous solution of 2,4-dinitrophenylhydrazine in 30% sulfuric acid. Methanol (MeOH) and ethanol (EtOH) were dried by distillation over magnesium metal and iodine. Tetrahydrofuran (THF), benzene, toluene, dioxane, and diethyl ether were dried by distillation from sodium−benzophenone ketyl. Methylene chloride was dried over $MgSO_4$ and then distilled over P_2O_5. Dimethyl sulfoxide was dried by distillation under vacuum over CaH_2. Triethylamine, diisopropylamine, and pyridine were dried by distillation over KOH. All other chemicals were purchased from Aldrich Chemical Co.

D-(+)-N_b-Benzyltryptophan Methyl Ester (16). To a round-bottom flask (5000 mL) that contained a freshly saturated solution of methanolic hydrogen chloride (2500 mL) was

added D-(+)-tryptophan **7** (400 g). The mixture that resulted was heated to reflux for 3.5 h and then allowed to cool to room temperature. The crystalline product that formed upon cooling was collected by filtration and washed with cold ether to provide D-tryptophan methyl ester·HCl, which was treated with aqueous NH_4OH (10%) followed by extraction with CH_2Cl_2 in methanol (8:2). After removal of the solvent, the free base that resulted was placed in a round-bottom flask (3000 mL). To this vessel were added dry CH_3OH (1500 mL) and benzaldehyde (260.0 g, 2.3 mol). The solution that resulted was stirred for 2 h at 22 °C, until examination by TLC indicated the disappearance of the starting free base. The mixture was then cooled in an ice−salt bath to −5 °C [It was much easier to maintain the inside temperature between −10 and −5 °C by the employment of a dry ice bath (without solvent)]. If the temperature falls below −15 °C, a large amount of solid will appear, and it is too difficult to stir the reaction mixture. Sodium borohydride (42 g, 1.1 mol) was then added portionwise at −5 °C over a period of 2.5 h [the slow addition and lower temperature of this process were critical to avoid racemization of the chiral center at C(3)]. The solution was allowed to stir for 3 h and then followed by the addition of ice−water (50 mL). The solvent was removed under reduced pressure. The residue was dissolved in $CHCl_3$ and washed with brine. The organic layer was dried (K_2CO_3), and the solvent was removed under reduced pressure to give the D-(+)-N_b-benzyl tryptophan methyl ester **16**. (525 g, 90%), which could be further purified by crystallization from EtOH.

16: mp 109−110 °C; $[\alpha]^{22}_D = +12.5°$ (*c* 1.0 in $CHCl_3$), [lit.[34] $[\alpha]^{12}_D = +8.65°$ (*c* 1.0 in CH_3OH); IR (film) 1745 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.88 (1 H, s), 3,15 (2 H, m), 3.65 (3 H, s), 3.75 (3 H, s), 3.80 (3 H, m), 6.90 (1 H, s), 7.10 (1 H, t, J = 8.2 Hz), 7.25 (7 H, m), 7.55 (1 H, d, J = 8.2 Hz), 8.12 (1H, bs); ^{13}C NMR ($CDCl_3$) δ 29.4, 51.7, 52.2, 61.4, 111.2, 111.4, 118.8, 119.5, 122.1, 122.9, 127.0, 127.6, 128.2, 128.3, 136.3, 139.8, 175.4; EIMS (*m*/*e*, relative intensity) 308 (M, 28), 249 (22), 178 (57), 130 (100).

Anal. Calcd for $C_{19}H_{20}O_2N_2$: C, 74.03; H, 6.49; N, 9.08. Found: C, 73.99; H, 6.56; N, 8.99.

Diastereoselective Pictet−Spengler Reaction To Provide *trans*-(1*S*,3*R*)-(−)-2-Benzyl-3-methoxycarbonyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-propionic Acid (18a) and *cis*-(1*R*,3*R*)-(+)-2-Benzyl-3-methoxycarbonyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-propionic Acid (18b). Optically active N_b-benzyl-D-tryptophan methyl ester **16** (50 g, 162 mmol) was dissolved in C_6H_6 (500 mL) and dioxane (500 mL) in a round-bottom flask (2000 mL) that was equipped with a Dean−Stark trap (DST) and a reflux condenser. To this solution was added 2-ketoglutaric acid **17** (26 g, 178 mmol). The reaction mixture was heated to reflux for 3 h and then allowed to cool to room temperature. The solution was diluted with EtOAc (300 mL). The aqueous layer was separated and extracted with EtOAc. The combined organic layers were washed with brine and dried (K_2CO_3), and then the solvent was removed under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc/hexane, 50/50, v/v) to provide the ester acids as a mixture of *cis*-**18b** and *trans*-**18a** diastereomers (49.9 g, 85%). The pure trans diastereomer **18a** was obtained by crystallization from the above mixture with EtOAc−hexane as colorless prisms. The mixture of **18a** and **18b** was used for a later reaction without separation.

18a: mp 174−175 °C (lit.[29] mp 174−176 °C); $[\alpha]^{22}_D = -17.5°$ (*c* 1.0 in $CHCl_3$), [lit.[34] $[\alpha]^{17}_D = -18.0°$ (*c* 1.0 in $CHCl_3$)]; IR (film) 1710, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.90−2.10 (1 H, m), 2.11−2.38 (1 H, m), 2.40−2.52 (1 H, m), 3.01−3.21 (2 H, m), 3.66 (1 H, d, J = 13.2 Hz), 3.80 (3 H, s), 4.01 (1 H, d, J = 13.5 Hz), 4.03−4.09 (2 H, m), 7.03−7.40 (8 H, m), 7.55 (1 H, d, J = 7.7 Hz), 8.04 (1 H, s); ^{13}C NMR ($CDCl_3$) δ 21.3, 28.4, 31.1, 52.0, 53.6, 55.6, 56.6, 107.6, 111.02, 118.3, 119.8, 122.1, 126.9, 127.6, 128.5, 129.5, 133.2, 136.5, 138.1, 172.7, 177.3; CIMS (*m*/*e*, relative intensity) 393 (M + 1, 100).

Anal. Calcd for $C_{23}H_{24}N_2O_4$: C, 70.39; H, 6.16; N, 7.14. Found: C, 70.12; H, 6.01; N, 6.97.

***p*-TSA-Catalyzed Diastereoselective Pictet−Spengler Reaction To Provide *trans*-(1*S*,3*R*)-(+)-Methyl 3-Benzyl-1,2,3,3a,4,5-hexahydro-6-oxocanthine-2-carboxylate (19a) and *cis*-(1*R*,3*R*)-(+)-Methyl 3-Benzyl-1,2,3,3a,4,5-hexahydro-6-oxocanthine-2-carboxylate (19b).** Optically active N_b-benzyl-D-tryptophan methyl ester **16** (50 g, 162 mmol) was dissolved in C_6H_6 (500 mL) and dioxane (500 mL) in a round-bottom flask (2000 mL) that was equipped with a Dean−Stark trap (DST) and a reflux condenser. To this solution were added **17** (26 g, 178 mmol) and *p*-toluenesulfonic acid (1.85 g, 9.7 mmol). The reaction mixture was heated to reflux for 48 h and then allowed to cool to room temperature. The solution was then diluted with EtOAc (300 mL), and the aqueous layer was separated and extracted with EtOAc. The combined organic layers were washed with brine and dried (K_2CO_3), and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc/hexane, v/v, 20/80) to afford the trans δ−lactam **19a** (42 g, 70%) and the cis δ-lactam **19b** (10 g, 16%).

19a: $[\alpha]^{28}_D = +37.5°$ (*c* 1.0, $CHCl_3$) [lit.[34] $[\alpha] = +37.0°$ (*c* 1.0, $CHCl_3$)]; mp 168−169 °C; IR (film) 1715, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.72−1.85 (1 H, m), 2.41−2.47 (1 H, m), 2.82 (1 H, t, J = 14.4 Hz), 2.85 (1 H, d, J = 13.7 Hz), 2.98 (1 H, ddd, J = 2.8, 6.6, 16.8 Hz), 3,10 (1 H, dt, J = 1.8, 16.4 Hz), 3.89 (1 H, dd, J = 1.4, 16.8 Hz), 3.96 (1 H, d, J = 14.4 Hz), 4.26 (1 H, d, J = 14.4 Hz), 4.53 (1 H, dt, J = 2.0, 12.2 Hz), 7.18−7.41 (8 H, m), 8.39 (1 H, d, J = 13.4 Hz); ^{13}C NMR ($CDCl_3$) δ 24.1, 28.4, 33.1, 51.7, 52.2, 54.9, 57.8, 111.0, 116.3, 118.0, 123.7, 124.5, 127.3, 128.2, 128.5, 129.2, 134.8, 135.0, 139.2, 168.3, 173.0; CIMS (*m*/*e*, relative intensity) 375 (M + 1, 100).

Anal. Calcd for $C_{23}H_{22}N_2O_3$: C, 73.78; H, 5.92; N, 7.48. Found: C, 73.83; H, 5.81; N, 7.38.

19b: $[\alpha]^{28}_D = +9.8°$ (*c* 1.0, $CHCl_3$) [lit.[34] $[\alpha]^{17}_D = +5.3°$ (*c* 1.0, $CHCl_3$); mp 165−166 °C; IR (film) 1700, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.87 (1 H, dq, J = 4.5, 12.7 Hz), 1.90−2.25 (1 H, m), 2.63 (1 H, dq, J = 4.5, 13.0 Hz), 2.73 (1 H, dt, J = 3.5, 17.3 Hz), 2.97 (1 H, dq, J = 2.5, 16.3 Hz), 3,13 (1 H, dd J = 9.2, 16.3 Hz), 3.68 (3 H, s), 3.87 (2 H, s), 3.99 (1 H, q, J = 5.0 Hz), 4.12 (1 H, dt, J = 2.3, 12.3 Hz), 7.27−7.49 (8 H, m), 8.40 (1 H, d, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 22.8, 27.7, 33.4, 52.2, 53.2, 56.4, 62.9, 111.6, 116.2, 118.1, 124.0, 124.6, 127.1, 128.1, 128.3, 129.0, 133.8, 134.8, 139.5, 168.0, 172.8; CIMS (*m*/*e*, relative intensity) 375 (M + 1, 100).

Anal. Calcd for $C_{23}H_{22}N_2O_3$: C, 73.78; H, 5.92; N, 7.48. Found: C, 73.73; H, 5.82; N, 7.30.

***p*-TSA-Catalyzed Conversion of Ester Acids 18a,b into δ-Lactams 19a,b.** The diastereomeric mixture of trans and cis ester acids **18a** and **18b** (4.7 g, 12 mmol) was dissolved in C_6H_6 (100 mL) and dioxane (100 mL) in a round-bottom flask (500 mL) that was equipped with a Dean−Stark trap (DST) and a reflux condenser. To this solution was added *p*-toluenesulfonic acid (0.3 g, 1.6 mmol). The reaction mixture was heated to reflux for 36 h and then allowed to cool to room temperature. After the solution was diluted with EtOAc (30 mL), water was added. The aqueous layer was separated and extracted with EtOAc. The combined organic layers were washed with brine and dried (K_2CO_3), and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc/hexane, v/v, 20/80) to afford the trans δ-lactam **19a** (4.0 g, 70%) and the *cis* δ−lactam **19b** (0.9 g, 16%), which were spectrometrically identical to that of authentic samples (see above) including the optical rotations.

Attempt To Epimerize the *cis*-(1*R*,3*R*)-(+)-2-Benzyl-3-methoxycarbonyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-propionic Acid (18b) into *trans*-(1*S*,3*R*)-(−)-2-Benzyl-3-methoxycarbonyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-propionic Acid (18a) with TFA. To the diastereomeric mixture of trans and cis ester acids **18a** and **18b** (20 mg, 0.05 mmol) in dry CH_2Cl_2 (1.0 mL) was added CF_3COOH (10 μL, 0.12 mmol, 2.4 equiv) via syringe. The solution was allowed to stir at room temperature under N_2 [examination of the TLC (silica gel, EtOAc/hexane, v/v, 20/80) indicated the gradual formation of trans δ-lactam **19a** and the cis δ−lactam **19b**]. After stirring for 10 days, the reaction mixture was worked up (analysis by TLC indicated the trans and cis ester acids **18a** and **18b** had disappeared). The solution was cooled

in an ice bath, after which the mixture was diluted with CH_2Cl_2 (10 mL) and brought to pH = 8 with an aqueous solution of $NaHCO_3$ (10%). The aqueous layer was separated and extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried (K_2CO_3), and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc/hexane, v/v, 20/80) to afford the trans δ-lactam **19a** (13 mg, 70%) and the cis δ-lactam **19b** (3 mg, 16%), which were spectrometrically identical to that of authentic samples including the optical rotations.

Attempt To Epimerize the *cis*-(1*R*,3*R*)-(+)-Methyl 3-Benzyl-1,2,3,3a,4,5-hexahydro-6-oxocanthine-2-carboxylate 19b into the *trans*-(1*S*,3*R*)-(+)-Methyl 3-Benzyl-1,2,3,-3a,4,5-hexahydro-6-oxocanthine-2-carboxylate 19a with TFA. To the cis δ-lactam **19b** (20 mg, 0.05 mmol) in dry CH_2Cl_2 (1.0 mL) was added CF_3COOH (10 μL, 0.12 mmol, 2.4 equiv) via syringe. The solution was allowed to stir at room temperature under N_2 and monitored by TLC (silica gel, EtOAc/hexane, v/v, 20/80). After being stirred for 10 days, the reaction mixture (analysis by TLC indicated that no trans isomer **19a** had been formed) was cooled in an ice bath. The mixture was then diluted with CH_2Cl_2 (10 mL) and brought to pH = 8 with an aqueous solution of $NaHCO_3$ (10%). The aqueous layer was separated and extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried (K_2CO_3), and the solvent was removed under reduced pressure. The oil that resulted was purified by flash chromatography (silica gel, EtOAc/hexane, v/v, 20/80) to provide **19b** (18 mg) as white crystals in 90% yield. This material was spectrometrically identical to that of an authentic sample of *cis*-**19b** including the optical rotation.

Esterification of Ester Acids (18a,b) To Provide the *trans*-(1*S*,3*R*)-(−)-2-Benzyl-3-methoxycarbonyl-1-methoxycarbonylethyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (20a) and *cis*-(1*R*,3*R*)-(+)-2-Benzyl-3-methoxycarbonyl-1-methoxycarbonylethyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (20b). The diastereomeric mixture of trans and cis ester acids **18a**/**18b** (4.7 g, 12 mmol) was dissolved in CH_2Cl_2 (50 mL), and the solution that resulted was cooled to −20 °C. To this stirred solution was added an excess of ethereal diazomethane (60 mmol) over a 10 min period at −20 °C. The mixture, which resulted, was then stirred at room temperature for an additional 1.5 h. After removal of solvent under reduced pressure, the residue was separated by flash chromatography (silica gel, EtOAc/hexane, 10/90, v/v) to provide the trans diester **20a** (3.8 g, 83% from ester acid) and the cis diester **20b** (0.5 g, 12% from ester acid).

trans-**20a**: mp 152−153 °C [lit.[34] mp 150−151 °C); $[\alpha]^{28}_D$ = −35.5° (*c* 1.09, $CHCl_3$) [lit.[34] $[\alpha]^{17}_D$ = −38.0° (*c* 1.0, $CHCl_3$)]; IR (KBr) 1707, 1731, 3310 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.85−2.15 (2H, m), 2.20−2.50 (2H, m), 3.03 (1H, dd, *J* = 5.3, 15.8 Hz), 3.12 (1H, dd, *J* = 8.8, 15.8 Hz), 3.48 (3H, s), 3.75 (3H, s), 3.59 (1H, d, *J* = 13.6 Hz), 3.84 (1H, d, *J* = 13.6 Hz), 3.87−3.93 (1H, m), 3.98 (1H, dd, *J* = 5.3, 8.8 Hz), 7.07−7.35 (8H, m), 7.43 (1H, d, *J* = 7.2 Hz), 7.98 (1H, bs); ^{13}C NMR ($CDCl_3$) δ 21.4, 29.0, 29.9, 51.5, 51.9, 53.5, 54.8, 56.8, 107.5, 111.0, 118.2, 119.5, 121.8, 127.1, 127.1, 128.3, 129.1, 134.3, 136.5, 139.4, 173.4, 174.2; EIMS (*m*/*e*, relative intensity) 406 (M^+, 60), 347 (45), 319 (100), 169 (50).

Anal. Calcd for $C_{24}H_{26}N_2O_4$: C, 70.91; H, 6.45; N, 6.89. Found: C, 70.88; H, 6.47; N, 6.91.

cis-**20b**: $[\alpha]^{28}_D$ = +0.58 (*c* 2.5, $CHCl_3$) [lit.[34] $[\alpha]^{17}_D$ = −1.3 (*c* 1.0, $CHCl_3$)]; IR (KBr) 1730, 3470 cm^{-1}, ^1H NMR ($CDCl_3$) δ 1.74−1.90 (1H, m), 1.90−2.01 (1H, m), 2.43−2.56 (2H, m), 2.99 (1H, dd, *J* = 6.3, 15.8 Hz), 3.24 (1H, dd, *J* = 3.6, 15.8 Hz), 3.56 (3H, s), 3.62 (3H, s), 3.76−3.94 (1H, m), 3.84 (1H, d, *J* = 14.0 Hz), 3.94 (1H, d, *J* = 14.0 Hz), 7.02−7.44 (8H, m), 7.52 (1H, d, *J* = 7.2 Hz), 8.01 (1H, bs); ^{13}C NMR ($CDCl_3$) δ 20.0, 29.4, 30.4, 51.5, 51.8, 56.4, 58.8, 59.4, 107.4, 110.9, 118.2, 119.4, 121.8, 127.3, 127.3, 128.4, 129.0, 133.5, 136.5, 139.1, 173.9, 174.6; EIMS (*m*/*e*, relative intensity) 406 (M^+,15), 347 (14), 319 (100), 259 (13), 169 (25).

Anal. Calcd for $C_{24}H_{26}N_2O_4$: C, 70.91; H, 6.45; N, 6.89. Found: C, 70.87; H, 6.32; N, 6.75.

Acid-Catalyzed Epimerization of *cis*-(1*R*,3*R*)-(+)-2-Benzyl-3-methoxycarbonyl-1-methoxycarbonylethyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (20b) into *trans*-(1*S*,3*R*)-(−)-2-Benzyl-3-methoxycarbonyl-1-methoxycarbonylethyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (20a). To the cis diastereomer **20b** (20 mg, 0.05 mmol) in dry CH_2Cl_2 (1.0 mL) was added CF_3COOH (10 μL, 0.12 mmol, 2.4 equiv) via syringe. The solution was allowed to stir at room temperature under N_2 and monitored by TLC (silica gel, EtOAc/hexane, v/v, 20/80). After stirring for 10 days, the reaction mixture (analysis by TLC indicated that all cis isomer **20b** had been consumed) was cooled in an ice bath. The mixture was then diluted with CH_2Cl_2 (10 mL) and brought to pH = 8 with an aqueous solution of $NaHCO_3$ (10%). The aqueous layer was separated and extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried (K_2CO_3), and the solvent was removed under reduced pressure to furnish an oil. The oil that resulted was purified by flash chromatography(silica gel, EtOAc/hexane, v/v, 20/80) to furnish pure *trans*-**20a** (18 mg) as white crystals in 90% yield. This ester **20a** was spectrometrically identical to that of an authentic sample of *trans*-**20a** including the optical rotation.

Preparation of Methyl 4,4-Dimethoxybutyrate (8a). To a round-bottom flask (1000 mL) that contained a solution of methyl acrylate (107.5 g) and nitromethane (76.25 g) in CH_2Cl_2 (250 mL) was added a solution of NaOH (6 g) in water (250 mL) at 20 °C. The mixture, which resulted, was stirred at 20 °C for 24 h. The organic layer was separated, washed with brine, and dried ($MgSO_4$). The solvent was then removed under reduced pressure, and the residue was distilled under vacuum (95−100 °C/8 mm of Hg) to give the pure methyl γ-nitro butyrate (54 g, 30%).[39] This was dissolved in methanolic sodium methoxide (800 mL, 0.5 N, freshly made from sodium hydride), and the solution that resulted was added dropwise at a rate of 1 drop per second to a round-bottom flask (3000 mL) that contained a solution of sulfuric acid (400 mL) in methanol (1500 mL) at −20 to −30 °C. After the addition was completed, the reaction mixture was poured into CH_2Cl_2 (3000 mL). The organic layer was separated, washed with ice−water and aqueous NaOH, and dried (K_2CO_3). The solvent was removed under reduced pressure, and the residue was distilled (110−115 °C/8 mm of Hg) to provide methyl 4,4-dimethoxybutyrate **8a** (48 g, 90%). The spectral properties of **8a** were identical to the reported values.[39]

8a: ^1H NMR ($CDCl_3$) δ 1.92 (2 H, q, *J* = 7.5 Hz), 2.37 (2 H, t, *J* = 7.5 Hz), 3.31 (6 H, s), 3.66 (3 H, s), 4.38 (1 H, t, *J* = 15.8 Hz); ^{13}C NMR ($CDCl_3$) δ 27.9, 29.1, 51.5, 53.1, 103.1; CIMS (*m*/*e*, relative intensity) 375 (M + 1, 100).

Diastereospecific Preparation of the *trans*-(1*S*,3*R*)-(−)-2-Benzyl-3-methoxycarbonyl-1-methoxycarbonylethyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (20a) via the Asymmetric Pictet−Spengler Reaction on a Large Scale. To a round-bottom flask (5000 mL) that contained a solution of optically active N_b-benzyl-D-tryptophan methyl ester **16** (400 g, 1.3 mol) in CH_2Cl_2 (2500 mL) was added methyl 4,4-dimethoxybutyrate **8a** (227 g, 1.4 mol) and TFA (180 g, 2.4 equiv) at 0 °C. The reaction mixture that resulted was stirred at room temperature for 72 h and then cooled in an ice bath and brought to pH = 8 with an aqueous solution of $NaHCO_3$ (10%). The aqueous layer was separated and extracted with CH_2Cl_2. After the combined organic layers were washed with brine and dried (K_2CO_3), EtOAc (100 mL) and hexane (300 mL) were added to the above solution. The volume of the solution was reduced to 300 mL, and the solution was cooled to −20 °C. The trans diester **20a** (402 g, 76%) precipitated out as white crystals, and the mother liquor was concentrated. The residue that resulted was purified by flash chromatography (silica gel, EtOAc/hexane, 20/80) to provide additional **20a** (83 g, 16%). The combined yield of **20a** (485 g) was 92% and the material was identical to the trans diester **20a** obtained from trans ester acid **18a**.

Dieckmann Cyclization of the N_a-H Diester (20a) To Provide (6*S*,10*S*)-(−)-Methyl-9-oxo-12-benzyl-6,7,8,9,10,-11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indole-8-carboxylate (−)-(21). To a round-bottom flask (2000 mL) that

contained a suspension of sodium hydride (5.1 g, 0.21 mol) in dry toluene (100 mL) was added a solution of N_a-H, trans diester **20a** (40.6 g, 0.10 mol) in toluene (650 mL) that had been predried by azeotropic removal of H_2O by a DST (reflux for 3 h). The reaction mixture that resulted was heated to reflux for 10 min under Ar, after which a solution of dry CH_3OH (4 mL) in toluene (16 mL) was added dropwise over 1 h. The solution was held at reflux for an additional 72 h. Glacial acetic acid (15 mL) was added to the solution carefully, and this was followed by neutralization with a saturated aqueous solution of $NaHCO_3$. The mixture was extracted with toluene, and the combined organic extracts were washed with brine and dried (K_2CO_3). Removal of the solvent under reduced pressure followed by purification by flash chromatography (silica gel, EtOAc/hexane, 20/80) provided the N_a-H, β-ketoester (−)-**21** (33.8 g, 88%).

21: mp 149−150 °C; $[\alpha]^{22}_D = -177.4°$ (*c* 1.0, $CHCl_3$); IR (KBr) 1630, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.30 (1H, d, J = 15.6 Hz), 2.82 (1H, dd, J = 15.5, 5.6 Hz), 2.90 (1H, d, J = 15.3 Hz), 3.18 (1H, dd, J = 15.9, 5.9 Hz), 3.66 (3H, s), 3.71 (1H, d, J = 13.4 Hz), 3.77 (1H, d, J = 5.3 Hz), 3.82 (1H, d, J = 13.4 Hz), 3.98 (1H, d, J = 5.4 Hz), 7.11 (1H, t, J = 7.1 Hz), 7.16 (1H, t, J = 7.0 Hz), 7.24−7.39 (6H, m), 7.50 (1H, d, J = 7.1 Hz), 7.63 (1H, s), 11.98 (1H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.2, 28.6, 49.7, 51.3, 55.2, 55.9, 94.3, 106.2, 110.8, 118.1, 119.5, 121.6, 127.0, 127.2, 128.4, 128.7, 133.4, 135.7, 138.3, 171.6, 172.5; CIMS (*m*/*e*, relative intensity) 374 (M + 1, 100).

Anal. Calcd for $C_{23}H_{22}N_2O_3$: C, 73.78; H, 5.92; N, 7.48. Found: C, 74.19; H, 6.23; N, 7.35.

Preparation of (6*S*,10*S*)-(−)-9-Oxo-12-benzyl-6,7,8,9,10,-11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indole (−)-15a via Hydrolysis of the N_a-H, β-Ketoester (−)-21. To a round-bottom flask (500 mL) that contained the N_a-H, β-ketoester (−)-**21** (45.0 g, 0.12 mol) were added glacial acetic acid (167 mL), aqueous hydrochloric acid (245 mL, concentrated), and water (65 mL). The solution, which resulted, was heated at reflux for 8 h. After removal of the solvent under reduced pressure, the residue was brought to pH = 9 with an aqueous solution of NaOH (3 N). The mixture, which resulted, was extracted with CH_2Cl_2, and the combined organic extracts were washed with a saturated aqueous solution of NH_4Cl and brine and dried (K_2CO_3). Removal of the solvent under reduced pressure afforded an oil. After a short wash column on silica gel, the N_a-H, N_b-benzyl tetracyclic ketone (−)-**15a** (24.5 g, 64%) was crystallized from EtOAc/hexane (2:8, 30 mL). The mother liquor was concentrated under reduced pressure, and the residue was chromatographed on silica gel with EtOAc/hexane (20:80) to provide additional (−)-**15a** (10.5 g, 27%). The combined yield of (−)-**15a** (35.0 g) was 91%.

15a: $[\alpha]^{25}_D = -240.2°$ (*c* 1.0, $CHCl_3$); IR (KBr):1715 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.02(1H, m), 2.15 (1H, m), 2.49 (2H, m), 2.71 (1H, d, J = 16.9 Hz), 3.27 (1H, dd, J = 16.9, 6.8 Hz), 3.78 (2H, s), 3.80 (1H,s), 4.02 (1H, s), 7.17 (1H, dt, J = 7.3, 1.0 Hz), 7.23 (1H, dt, J = 7.6, 1.0 Hz), 7.30−7.38 (5H,m), 7.54 (1H, d, J = 7.6 Hz), 7.81 (1H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.4, 30.4, 34.5, 49.4, 56.1, 65.2, 106.7, 110.9, 118.2, 119.7, 122.0, 126.9, 127.4, 128.4, 128.6, 132.0, 135.9, 138.3, 210.4; CIMS (*m*/*e*, relative intensity) 317 (M + 1).

Anal. Calcd for $C_{21}H_{20}N_2O$: C, 79.72; H, 6.37; N, 8.85. Found: C, 79.51; H, 6.37; N, 8.85.

One-Pot Process for Stereospecifically Converting D-(−)-Tryptophan Methyl Ester (22) into *trans*-(1*S*,3*R*)-(−)-2-Benzyl-3-methoxycarbonyl-1-methoxycarbonylethyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (20a). To a round-bottom flask (12000 mL) that contained a solution of D-(−)-tryptophan methyl ester **22** (400 g, 1.83 mol) in CH_3OH (5000 mL) was added benzaldehyde (230 g, 2.2 mol). The solution, which resulted, was stirred for 2 h at room temperature. The mixture was then cooled to −10 °C, and sodium borohydride (55 g, 1.3 mol) was added portionwise over a period of 4 h. The internal pot temperature was kept between −10 and −5 °C with a dry ice bath. After analysis by TLC (silica gel, EtOAc/hexane, 1/1) indicated the completion of the reaction, the mixture was allowed to stir for an additional 0.5 h followed by the slow addition of CF_3COOH (260 mL) at 0 °C. The solvent was removed under reduced pressure, and the residue was dissolved in CH_2Cl_2 (3000 mL). After the solution that resulted was cooled to 0 °C, methyl 4,4-dimethoxybutyrate acetal **8a** (324 g, 2.0 mol) and TFA (500 g, 2.4 equiv) were added to this vessel at 0 °C. The reaction mixture was stirred at room temperature for 72 h, after which it was cooled in an ice bath and brought to pH = 8 with an aqueous solution of $NaHCO_3$ (10%). The aqueous layer was separated and extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried (K_2CO_3). EtOAc (100 mL) and hexane (300 mL) were added to the above solution. The volume was reduced to 400 mL, and the solution was cooled to −20 °C. The trans diester **20a** (510 g, 69%) precipitated out as white crystals, the mother liquor was concentrated, and the residue that resulted was purified by flash chromatography (silica gel, EtOAc/hexane, 20/80) to provide additional **20a** (114 g, 14%). The combined yield of **20a** (624 g) was 83% and the solid was identical to the trans diester **20a** obtained above from N_b-benzyl-D-tryptophan methyl ester **16**.

One-Pot Process for Converting *trans*-(1*S*,3*R*)-(−)-2-Benzyl-3-methoxycarbonyl-1-methoxycarbonylethyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (20a) into (6*S*,-10*S*)-(−)-9-Oxo-12-benzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indole (−)-15a. The trans diester **20a** (100 g, 246 mmol) was dissolved in dry toluene (3000 mL) in a round-bottom flask (5000 mL) that was equipped with a DST and a reflux condenser. The solution, which resulted, was heated to reflux for 3 h. After removal of the DST and cooling to 0 °C, sodium hydride (100 g of 60% NaH in mineral oil) was added to the above vessel under an atmosphere of Ar. Dry CH_3OH (170 mL) was added carefully (a large amount of H_2 was evolved at this point). The mixture was stirred at room temperature for 0.5 h and then heated to reflux for an additional 72 h. After analysis by TLC (silica gel, EtOAc/hexane, 20/80) indicated the reaction was complete, the reaction mixture was cooled to 0 °C and then quenched carefully with glacial acetic acid (200 mL). The solvent was removed under reduced pressure, and glacial acetic acid (320 mL), aqueous hydrochloric acid (500 mL, concentrated), and water (130 mL) were added to the above vessel. The mixture that resulted was heated at reflux for 8 h. After removal of the solvent under reduced pressure, the residue was brought to pH = 9 by addition of an aqueous solution of cold NaOH (3 N). The mixture that resulted was extracted with CH_2Cl_2, and the combined organic extracts were washed with brine and dried (K_2CO_3). Removal of the solvent under reduced pressure afforded an oil that was chromatographed on silica gel with EtOAc/hexane (3:7) to provide the tetracyclic ketone **15a** (65 g, 85%), which was identical to the ketone obtained above from ketoester **21**.

One-Pot Process for Converting N_a-H, N_b-Benzyl, β-Ketoester (−)-21 into (6*S*,10*S*)-(−)-5-Methyl-9-oxo-12-benzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]-indole (−)-15b. To a round-bottom flask (250 mL) that contained a stirred solution of the N_a-H, β-ketoester (−)-**21** (3.9 g, 10 mmol) in CH_2Cl_2 (50 mL) was added an excess of ethereal diazomethane (50 mmol) over a 10 min period at −20 °C. The mixture, which resulted, was then stirred at room temperature for an additional 1.5 h. After removal of the solvent under reduced pressure, THF (50 mL) was added to this reaction vessel, and the solution was cooled to −5 °C. Then NaH (260 mg, 11 mmol) was added to this solution, and the mixture that resulted was allowed to stir at room temperature for 1 h before it was cooled to 0 °C. Methyl iodide (1.2 g, 12.5 mmol) was added to the above solution at 0 °C, and the reaction mixture that resulted was stirred at 0 °C for 5 h. The reaction was quenched by careful addition of CH_3OH (5 mL), and an aqueous solution of NaOH (2 N, 30 mL) was added to this reaction vessel. The mixture that resulted was heated to reflux for 1 h and then cooled to 0 °C. Glacial acetic acid (15 mL), aqueous hydrochloric acid (20 mL, concentrated), and H_2O (6 mL) were added to this reaction vessel, and the mixture that resulted was heated to reflux for 5 h. After removal of the solvent under reduced pressure, the residue was brought to pH = 9 with an aqueous solution of NaOH (3 N). The

mixture, which resulted, was extracted with CH_2Cl_2, and the combined organic extracts were washed with a saturated aqueous solution of NH_4Cl and brine and dried (K_2CO_3). The solvent was removed under reduced pressure, and the residue that resulted was chromatographed (silica gel, EtOAc/hexane, 20/80) to provide the N_a-methyl, N_b-benzyl tetracyclic ketone (−)-**15b** (3.1 g, 90%), the properties of which were identical to the published values including the optical rotation.[31]

***N*$_a$-Methylation of the *trans*-*N*$_a$-H, *N*$_b$-Benzyldiester (20a) To Provide *trans*-(1*S*,3*R*)-(−)-2-Benzyl-3-methoxycarbonyl-1-methoxycarbonylethyl-9-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (23a).** To a round-bottom flask (100 mL) that was equipped with a reflux condenser were added N_a-H trans diester **20a** (2 g, 5 mmol), CH_3I (0.5 g, 5.5 mmol), and dry DME (30 mL) and then the mixture cooled to 0 °C. To this solution was added NaH (130 mg, 5.5 mmol) at 0 °C. The slurry, which resulted, was allowed to stir at room temperature for 2 h until analysis by TLC indicated the disappearance of **20a**. The reaction solution was quenched by careful addition of CH_3OH (1 mL) and then was neutralized with an aqueous solution of NH_4Cl and extracted with EtOAc. The combined organic layers were washed with brine and dried (K_2CO_3). The solvent was removed under reduced pressure, and the residue was subjected to a short wash column (silica gel, EtOAc/hexane, 20/80) to provide the N_a-methyl, N_b-benzyldiester (−)-**23a** (2.1 g, 99%), the properties of which were identical to the published values including the optical rotation.[31]

(6*S*,10*S*)-(−)-9-Formyl-12-benzyl-6,7,10,11-tetrahydro-6,10-imino-5*H*-cyclooct[*b*]indole (24) and (6*S*,10*S*)-5-9-(1′-Hydroxylhex-3′-enyl)-12-benzyl-6,7,10,11-tetrahydro-6,-10-imino-5*H*-cycooct[*b*]indole (25) were prepared following the procedure in ref 22.

One-Pot Oxyanion−Cope Rearrangement/Epimerization To Convert Allylic Alcohol (25) into (6*S*,10*S*)-8-(1′-Ethyl-2′-propenyl)-12-benzyl-6,7,8,9,10,11-hexahydro-6,-10-imino-5*H*-cyclooct[*b*]indolyl-9-carbaldehyde (26). A solution of the allylic alcohol **25** (1.20 g, 3.0 mmol) and 18-crown-6-ether (1.3 g, 4.8 mmol) in dry dioxane (100 mL) was added to a suspension of KH (2.4 g, 62 mmol) and dry dioxane (100 mL). The light yellow-colored mixture that resulted was stirred at room temperature for 8 h and then was heated to reflux for 16 h. Analysis of the mixture by TLC (silica gel, EtOAc/hexane, 20/80) indicated the presence of two new components and the disappearance of starting material. The reaction mixture was allowed to cool to room temperature and was quenched by careful addition of CH_3OH (20 mL). The reaction mixture that resulted was allowed to stir at room temperature until analysis by TLC (silical gel, EtOAc/hexane, 20/80) indicated the disappearance of the minor of the two components formed during the rearrangement (6 h). The reaction mixture was brought to pH = 8 with an aqueous solution of NH_4Cl and extracted with EtOAc. The combined organic layers were washed with water and brine and dried (K_2CO_3). After the solvent was removed under reduced pressure, the residue was chromatographed (silical gel, EtOAc/hexane, 20/80) to provide the olefinic aldehyde **26** (1.02 g, 85%) as the single isolable isomer, the properties of which were identical to the published values.[22]

***N*$_a$-Methylation of Olefinic Aldehyde (26) To Provide (6*S*,10*S*)-5-Methyl-8-(1′-ethyl-2′-propenyl)-12-benzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indolyl-9-carboxaldehyde (27).** A solution of the olefinic aldehyde **26** (600 mg, 1.5 mmol) in dry THF (25 mL) was added to a suspension of NaH (41 mg, 1.8 mmol) and dry THF (25 mL) in a round-bottom flask (100 mL) at 0 °C. The slurry, which resulted, was allowed to stir at room temperature for 1 h before it was cooled to 0 °C. Methyl iodide (300 mg, 2.1 mmol) was added to the above solution at 0 °C, and the reaction mixture that resulted was stirred at 0 °C for 2 h and then at room temperature for 6 h. The reaction was quenched by careful addition of CH_3OH (2 mL) and then was neutralized with an aqueous solution of NH_4Cl and extracted with EtOAc. The combined organic layers were washed with brine and dried (K_2CO_3). After the solvent was removed under reduced pressure, the residue was chromatographed (silica gel, EtOAc/hexane, 20/80) to provide the N_a-methyl olefinic aldehyde **27** (587 mg, 95%).

27: IR (KBr) 1722 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.75 (3H, t, J = 7.1 Hz), 0.85 (1H, m), 1.51 (1H, m), 1.65 (1H, t, J = 11.5 Hz), 1.83 (1H, d, J = 12.7 Hz), 2.34 (1H, dd, J = 9.8, 3.2 Hz), 2.51 (1H, m), 2.52 (1H, d, J = 16.8 Hz), 3.36 (1H, dd, J = 16.8, 7.5 Hz), 3.60 (2H, s), 3.69 (1H, dd, J = 7.3, 1.7 Hz), 4.13 (1H, s), 4.95 (1H, dd, J = 16.9, 2.2 Hz), 5.04(1H, dd, J = 10.1, 2.2 Hz), 5.26 (1H, dt, J = 16.8, 10.0 Hz), 7.17−7.39 (8H, m), 7.59 (1H, d, J = 7.7 Hz), 9.99 (1H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 11.6, 21.8, 24.4, 28.9, 31.0, 32.7, 46.9, 50.8, 53.4, 55.6, 57.7, 106.4, 108.9, 116.8, 118.0, 118.9, 120.9, 126.4, 127.1, 128.3, 128.6, 134.3, 136.9, 138.8, 140.5, 204.6; EIMS (*m*/*e*, relative intensity) 412 (M, 30), 315 (15), 273 (100), 182 (750), 144 (40).

Anal. Calcd for $C_{28}H_{32}N_2O$: C, 81.35; H, 7.99; N, 6.78. Found: C, 81.25; H, 8.03; N, 6.57.

$NaBH_4$ Reduction of Aldehyde (27) To Provide (6*S*,-10*S*)-5-Methyl-8-(pent-2′-enyl)-12-benzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]-indolyl-9-hydroxymethane (28). To a stirred solution of the N_a-methyl olefinic aldehyde **27** (450 mg, 1.1 mmol) in MeOH (10 mL) in a round-bottom flask (25 mL) was added $NaBH_4$ (60 mg, 1.6 mmol) at room temperature. After 20 min, examination of the TLC (silica gel, EtOAc/hexane, 40/60) indicated the disappearance of the starting material, and the reaction was quenched by careful addition of ice−water (10 mL). The mixture was neutralized with an aqueous solution of NH_4Cl. The reaction solution was extracted with $CHCl_3$. The combined organic layers were dried (K_2CO_3), and the solvent was removed under reduced pressure. The residue was chromatographed (silica gel, $CHCl_3$/MeOH, 90:10) to provide the N_a-methyl olefinic alcohol **28** (432 mg, 96%).

28: IR (KBr) 2935 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.71 (3H, t, J = 7.1 Hz), 0.80 (1H, m), 1.48 (1H, m), 1.52−1.72 (2H, m), 2.08 (1H, dt, J = 9.5, 3.2 Hz), 2.16 (1H, dt, J = 12.4, 4.6 Hz), 2.51 (1H, d, J = 16.8 Hz), 3.35 (1H, dd, J = 16.8, 7.6 Hz), 3.54 (1H, d, J = 12.5 Hz), 3.55 (2H, s), 3.60 (1H, d, J = 7.4 Hz), 3.72 (1H, d, J = 12.6 Hz), 3.9 (1H, dd, J = 11.1, 3.3 Hz), 4.05 (1H, s), 4.12 (1H, dd, J = 11.0, 2.5 Hz), 4.97 (1H, dd, J = 13.1, 2.1 Hz), 5.03 (1H, dd, J = 6.9, 2.1 Hz), 5.27 (1H, dt, J = 16.8, 9.7 Hz), 7.13−7.39 (8H, m), 7.56 (1H, d, J = 7.6 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 11.4, 22.8, 24.1, 28.9, 32.0, 32.9, 43.5, 47.2, 49.8, 57.5, 58.6, 66.0, 106.5, 109.0, 116.0, 118.1, 118.9, 121.0, 126.3, 127.5, 128.6, 129.2, 133.4, 137.0, 137.8, 141.3; EIMS (*m*/*e*, relative intensity) 414 (M, 60), 273 (60), 251 (40), 182 (100), 144 (55).

Anal. Calcd for $C_{28}H_{34}N_2O$: C, 80.96; H, 8.43; N,6.74. Found: C, 81.03; H, 8.03; N, 6.57.

Oxidative Cleavage of Olefinic Alcohol (28) To Provide Hemiacetal (32). To a round-bottom flask (100 mL) was charged a lightly yellow-colored solution of OsO_4 (190 mg, 0.74 mmol) in dry THF (5 mL) and pyridine (freshly distilled, 2 mL) that had been prestirred at room temperature for 2 h. To the above mixture was added the solution of N_a-methyl olefinic alcohol **28** (420 mg, 1.0 mmol) in dry THF (20 mL) and pyridine (freshly distilled, 1.5 mL) at 0 °C. The black-colored mixture that resulted was stirred at 0 °C for 16 h under an atmosphere of Ar. An aqueous solution of $NaHSO_3$ (0.6 g dissolved in 3 mL of H_2O) was then added, and the slurry was stirred at room temperature for 2 h. The mixture was diluted with CH_2Cl_2 (50 mL), and the aqueous layer was separated and then extracted with CH_2Cl_2−MeOH (9:1). The combined organic layers were dried (K_2CO_3), and the solvent was removed under reduced pressure. The residue was dissolved in distilled CH_3OH (10 mL) in a round-bottom flask that was coated with aluminum foil to exclude light. The solution, which resulted, was cooled to 0 °C, and an aqueous solution of $NaIO_4$ (255 mg, 1.2 mmol, in 10 mL of H_2O) was added to the chilled solution. The mixture was stirred at 0 °C for 16 h. Methanol was removed under reduced pressure, and the residue that resulted was dissolved in EtOAc/water (2:1). The two layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with water and brine and

dried (K_2CO_3). The solvent was removed under reduced pressure, and the residue was chromatographed (silica gel, EtOAc/hexane, 20/80) to provide the hemiacetal **32** (323 mg, 78%).

32 [two (OH) diastereomers]: FTIR (KBr) 1460, 3505 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.77 (3H, t, J = 7.6 Hz), 1.02−1.27 (2H, m), 1.49 (1H, m), 1.63 (1H, m), 1.98 (1H, m), 2.45 (2H, t, 16.3 Hz), 3.07 (2H, t, 6.4 Hz), 3.27 (2H, d, J = 16.4 Hz), 3.43 (1H, m), 3.56 (3H, s), 3.74 (1H, m), 3.97 (1H, s), 4.70 (1H, t, J = 11.3 Hz), 5.05−5.15 (1H, m), 7.05−7.35 (8H, m), 7.53 (1H, d, J = 6.8 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.7, 13.1, 13.8, 18.1, 22.6, 23.0, 23.1, 25.2, 28.9, 29.1, 30.8, 31.1, 32.1, 37.6, 38.2, 43.2, 44.3, 51.2, 51.6, 52.6, 53.2, 57.6, 59.8, 67.0, 94.8, 95.0, 107.0, 107.1, 108.8, 118.0, 118.1, 118.7, 118.8, 120.7, 120.8, 125.5, 126.5, 126.9, 128.2, 128.5, 132.8, 133.1, 137.0, 138.8, 139.7; CIMS (*m/e*, relative intensity) 417 (M + 1, 100), 399 (40).

Anal. Calcd for $C_{27}H_{32}N_2O_2$: C, 77.89; H, 7.69; N, 6.73. Found: C, 77.74; H, 7.91; N, 6.65.

Dehydration of Hemiacetal (32) with *p*-TSA To Provide Enol Ether (12). A solution of hemiacetal **32** (300 mg, 0.71 mmol) and *p*-toluenesulfonic acid (185 mg, 0.97 mmol) in dry benzene (10 mL) was heated to reflux with a DST under N_2 for 3 h. The reaction mixture was then allowed to cool and was diluted with EtOAc and brought to alkaline pH with an aqueous solution of NH_4OH (10%) at 0 °C. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with brine and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (silica gel, EtOAc/hexane, 20/80) to afford enol ether **12** (270 mg, 95%).

12: mp 166−167 °C; IR (KBr) 1470, 1670 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.73 (3H, t, J = 7.6 Hz), 1.63−1.72 (2H, m), 1.77 (1H, d, J = 9.2 Hz), 1.92−2.11 (2H, m), 2.45 (1H, d, 16.5 Hz), 3.07 (1H, d, 7.0 Hz), 3.21 (1H, dt, J = 16.5, 7.0 Hz), 3.48 (3H, s), 3.51 (1H, d, J = 3.0 Hz), 3.91−3.97 (2H, m), 4.43 (1H, t, J = 10.8 Hz), 6.07 (1H, s), 7.07 (1H, t, J = 7.7 Hz), 7.13 (1H, t, J = 7.7 Hz), 7.28−7.35 (6H, m), 7.47 (1H, d, J = 7.7 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.4, 23.7, 24.0, 27.9, 29.5, 33.6, 40.8, 51.6, 53.8, 57.9, 66.6, 107.2, 109.3, 118.0, 118.5, 119.3, 121.3, 127.1, 127.4, 128.7, 128.9, 134.4, 137.5, 138.3, 140.4; EIMS (*m/e*, relative intensity) 398 (M, 80), 307 (20), 273 (60), 170 (100), 146 (90).

Anal. Calcd for $C_{27}H_{30}N_2O$: C, 81.37; H, 7.54; N, 7.04. Found: C, 81.00; H, 7.69; N, 7.03.

Oxyselenation of Enol Ether (12) with *N*-Phenylselenophthalimide (34) To Provide Selenoacetals (35a) and (35b). To a solution of enol ether **12** (120 mg, 0.30 mmol) in CH_2Cl_2 (5 mL) were added *N*-phenylselenophthalimide **34**[52] (122 mg, 0.41 mmol), *p*-toluenesulfonic acid (65 mg, 0.34 mmol), and CH_3OH (0.5 mL). The reaction mixture was stirred at 0 °C for 20 h. It was then diluted with CH_2Cl_2 (10 mL) and brought to an alkaline pH with an aqueous solution of NH_4OH (10%) at 0 °C. The aqueous layer was separated and extracted with CH_2Cl_2. The combined organic layers were dried (K_2CO_3) and concentrated under vacuum. The residue was purified by flash chromatography (silica gel, EtOAc−hexane, 2:8) to provide selenoacetal **35a** (135 mg, 82%) as an amorphous powder accompanied by **35b** (16 mg, 9%).

35a: ^1H NMR (300 MHz, $CDCl_3$) δ 0.66 (3H, t, J = 7.5 Hz), 1.41−1.49 (1H, m), 1.74 (1H, d, J = 11.9 Hz), 1.86−1.91 (1H, m), 2.05−2.13 (1H, m), 2.39 (1H, d, J = 16.7 Hz), 2.32−2.53 (1H, m), 3.00 (1H, d, J = 7.1 Hz), 3.24 (1H, dd, J = 16.7, 7.2 Hz), 3.45 (2H, s), 3.50 (3H, s), 3.82 (1H, dd, J = 11.7, 4.6 Hz), 4.00 (1H, t, 2.9 Hz), 4.46 (1H, t, 11.9 Hz), 5.25 (1H, s), 6.68−7.46 (14H, m); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 10.5, 22.9, 25.0, 29.6, 31.0, 34.9, 42.4, 53.3, 54.6, 58.8, 59.3, 61.4, 68.5, 107.7, 108.9, 110.9, 120.1, 120.8, 122.9, 128.5, 129.1, 130.0, 130.2, 130.3, 130.5, 135.0, 139.1, 139.5, 141.4; CIMS (*m/e*, relative intensity) 572 (M + 1, 100).

35b: ^1H NMR (300 MHz, $CDCl_3$) δ 0.86 (3H, m), 1.45−1.5 (2H, m), 1.85−1.86 (1H, m), 2.49 (1H, d, J = 16.5 Hz), 2.60 (1H, td, J = 16.6, 3.8 Hz), 2.86−2.96 (1H, m), 3.06 (1H, d, J = 6.5 Hz), 3.36 (2H, s), 3.44 (3H, s), 3.53 (1H, dd, J = 11.7, 4.3 Hz), 3.62 (1H, s), 3.91 (1H, s), 4.39 (1H, t, 11.6 Hz), 4.46 (1H, s), 6.72 (2H, t, J = 7.7 Hz), 7.02 (1H, t, J = 7.7 Hz), 7.14−7.30 (10H, m), 7.57(1H, d, J = 6.4 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 8.9, 22.9, 25.2, 28.6, 29.0, 33.1, 51.6, 53.5, 55.5, 57.3, 60.3, 60.5, 101.7, 107.3, 108.8, 118.1, 118.9, 120.7, 126.6, 126.9, 127.3, 128.3, 128.4, 128.5, 133.3, 137.8, 139.6; CIMS (*m/e*, relative intensity) 572 (M + 1, 100).

One-Pot Oxyselenation of Enol Ether (12) with *N*-Phenylselenophthalimide (34) Followed by Selenoxide Elimination with $NaIO_4$ To Provide Olefins (11a) and (11b). To a solution of enol ether **12** (240 mg, 0.60 mmol) in CH_2Cl_2 (10 mL) were added *N*-phenylselenophthalimide **34**[52] (244 mg, 0.81 mmol), *p*-toluenesulfonic acid (130 mg, 0.68 mmol), and CH_3OH (1 mL). The reaction mixture was stirred at 0 °C for 20 h. It was then diluted with CH_2Cl_2 and brought to an alkaline pH with an aqueous solution of NH_4OH (10%) at 0 °C. The aqueous layer was separated and extracted with CH_2Cl_2. The combined organic layers were dried (K_2CO_3) and concentrated in vacuo. The residue was dissolved in THF (11 mL) at 0 °C, and a solution of $NaIO_4$ (82 mg, 0.384 mmol) in H_2O (2.4 mL) was added. The reaction mixture was allowed to stir at room temperature for 5 h. The precipitate that formed was removed by filtration, and the reaction mixture was concentrated under reduced pressure, after which it was brought to alkaline pH with an aqueous solution of NH_4OH (10%) at 0 °C. The aqueous layer was extracted with $CHCl_3$. The organic extracts were washed with brine, dried (K_2CO_3), and then concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc−hexane, 2:8) to provide olefin **11a** (185 mg, 72%) as an amorphous powder accompanied by **11b** (46 mg, 18%).

11a: ^1H NMR (300 MHz, $CDCl_3$) δ 1.32 (1H, dq, J = 12.9, 2.5 Hz), 1.50 (3H, d, J = 13.0 Hz), 1.60 (1H, dt, J = 12.8, 4.8 Hz), 1.90 (1H, dt, J = 11.8, 4.1 Hz), 2.37 (1H, d, J = 16.6 Hz), 2.72 (1H, dt, J = 12.9, 4.2 Hz), 2.96 (1H, d, J = 7.1 Hz), 3.18 (1H, dd, J = 16.6, 7.1 Hz), 3.39 (1H, dd, J = 10.2, 4.5 Hz), 3.41 (3H, s), 3.48 (3H, s), 3.52 (2H, s), 3.88 (1H, t, 3.1 Hz), 4.48 (1H, t, 11.5 Hz), 5.09 (1H, q, J = 7.0 Hz), 5.17 (1H, s), 7.06 (1H, t, J = 7.3 Hz), 7.15−7.25 (7H, m), 7.46 (1H, d, J = 7.5 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.7, 22.7, 29.0, 33.2, 34.4, 43.7, 51.6, 52.6, 55.0, 57.7, 60.1, 96.5, 107.0, 108.9, 118.1, 118.8, 120.8, 123.6, 127.1, 127.4, 128.7, 128.9, 134.1, 136.5, 137.0, 139.6; EIMS (*m/e*, relative intensity) 428 (M, 90), 397 (20), 305 (15), 273 (85), 181 (40),170 (95).

Anal. Calcd for $C_{28}H_{32}N_2O_2$: C, 78.50; H, 7.48; N, 6.54. Found: C, 78.26; H, 7.88; N, 6.58.

11b: ^1H NMR (300 MHz, $CDCl_3$) δ 1.21 (3H, d, J = 13.0 Hz), 1.40−1.60 (2H, m), 1.93 (1H, dt, J = 11.8, 4.1 Hz), 2.45 (1H, d, J = 16.6 Hz), 2.70−2.80 (1H, m), 2.96 (1H, d, J = 7.1 Hz), 3.18 (1H, dd, J = 16.6, 7.1 Hz), 3.39 (1H, dd, J = 10.2, 4.5 Hz), 3.41 (3H, s), 3.48 (3H, s), 3.52 (2H, s), 3.88 (1H, t, 3.1 Hz), 4.48 (1H, t, 11.5 Hz), 4.71 (1H, s), 5.40 (1H, q, J = 7.0 Hz), 7.06 (1H, t, J = 7.3 Hz), 7.15−7.25 (7H, m), 7.46 (1H, d, J = 7.5 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 11.9, 22.7, 26.9, 28.9, 30.9, 42.8, 51.6, 52.6, 54.7, 57.7, 60.1, 103.5, 107.0, 108.9, 118.1, 118.8, 120.8, 123.6, 126.7, 127.0, 128.3, 128.6, 133.8, 136.5, 137.0, 139.6; EIMS (*m/e*, relative intensity) 428 (M, 100), 297 (30), 273 (90), 170 (100), 146 (70).

Anal. Calcd for $C_{28}H_{32}N_2O_2$: C, 78.50; H, 7.48; N, 6.54. Found: C, 78.16; H, 7.87; N, 6.47.

Acid-Catalyzed Rearrangement of 11a Followed by Epimerization To Provide N_b-Benzyl, N_b-21-Secotalpinine (37). A suspension of olefin **11a** (50 mg) in aqueous 5% H_2SO_4 (5 mL) was stirred at room temperature for 30 h under Ar. Then CH_2Cl_2 (10 mL) was added to the reaction mixture, and it was brought to alkaline pH with an aqueous solution of NH_4OH (10%) at 0 °C. The aqueous layer was extracted with $CHCl_3$, and the organic extracts were concentrated under reduced pressure. The residue was dissolved in a solution of K_2CO_3 (20 mg) in EtOH (10 mL), and the reaction mixture, which resulted, was stirred at room temperature for 24 h. After removal of the solvent under reduced pressure, CH_2Cl_2 (10 mL) was added to the reaction mixture, and it was neutralized with an aqueous solution of NH_4Cl at 0 °C. The aqueous layer was separated and extracted with $CHCl_3$. The organic extracts were washed with brine, dried (K_2CO_3), and then concentrated

under reduced pressure. The residue that resulted was purified by flash chromatography (silica gel, EtOAc−hexane, 2:8) to provide N_b-benzyl, N_b-21-secotalpinine **37** (42 mg, 84%).

37: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (1H, dt, J = 6.7, 1.4 Hz), 1.31 (3H, d, J = 6.4 Hz), 2.03 (1H, m), 2.04−2.06 (1H, m), 2.28−2.31 (1H, m), 2.47 (1H, d, J = 16.0 Hz), 2.48 (1H, m), 2.98 (1H, d, J = 6.9 Hz), 3.27 (1H, dd, J = 16.1, 6.9 Hz), 3.54 (3H, s), 3.57 (2H, s), 3.86 (1H, dd, J = 11.7, 4.5 Hz), 4.00 (1H, t, J = 6.8 Hz), 4.02 (1H, m), 4.30 (1H, t, J = 11.6 Hz), 7.14 (1H, t, J = 5.7 Hz), 7.21 (1H, t, J = 5.7 Hz), 7.23−7.29 (5H, m), 7.30 (1H, d, J = 6.25 Hz), 7.51 (1H, d, J = 6.25 Hz), 9.95 (1H, d, J = 3.3 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 19.2, 23.0, 27.7, 29.0, 30.2, 39.6, 51.0, 52.9, 54.7, 57.6, 66.7, 69.5, 107.2, 108.9, 116.2, 119.0, 121.1, 126.6, 127.1, 128.4, 128.6, 133.2, 137.1, 139.5, 204.6; EIMS (*m*/*e*, relative intensity) 414 (M, 40), 386 (100), 273 (90), 146 (90).

Anal. Calcd for $C_{27}H_{30}N_2O_2$: C, 78.26; H, 7.25; N, 6.76. Found: C, 78.30; H, 7.47; N, 6.56.

Acid-Catalyzed Rearrangement of 11a Followed by Pyrolysis To Provide N_b-Benzyltalcarpine (38). A suspension of olefin **11a** (50 mg) in an aqueous solution of H_2SO_4 (5%, 5 mL) was stirred at room temperature for 30 h under Ar. Then CH_2Cl_2 (10 mL) was added to the reaction mixture, and it was brought to alkaline pH with an aqueous solution of NH_4OH (10%) at 0 °C. The aqueous layer was extracted with $CHCl_3$. The organic extracts were washed with brine, dried (K_2CO_3), and then concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, EtOAc−hexane, 2:8) to provide N_b-benzyl, N_b-21-secotalpinine **37** (16 mg, 34%) and N_b-benzyltalcarpine **38** (28 mg, 54%). The secotalpinine **37** (16 mg) was dissolved in $CHCl_3$ (5 mL) in a round-bottom flask (10 mL), and the solvent was removed so that **37** coated the sides of the flask. The above flask was evacuated to 10^{-1} Torr and kept in a oil bath at 120 °C for 6 h. The residue was purified by flash column chromatography (silica gel, EtOAc−hexane, 2:8) to provide **38** (12 mg, 75% from **37**) and 20% of **37**. The combined yield of **38** was 40 mg (80% from **11a**).

38: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13 (3H, d, J = 6.2 Hz), 1.18 (1H, d, J = 2.7 Hz), 1.85−1.90 (1H, m), 2.30−2.37 (3H, m), 2.44 (1H, d, J = 16.8 Hz), 2.97 (1H, d, J = 6.9 Hz), 3.25 (1H, dd, J = 16.1, 6.9 Hz), 3.54 (3H, s), 3.57 (2H, s), 3.66 (1H, dd, J = 12.0, 5.4 Hz), 3.82−3.91 (1H, m), 3.91 (1H, m), 4.16 (1H, t, J = 12.0 Hz), 7.09 (1H, t, J = 7.1 Hz), 7.15 (1H, t, J = 6.6 Hz), 7.23−7.29 (5H, m), 7.25 (1H, d, J = 7.8 Hz), 7.47 (1H, d, J = 7.5 Hz), 9.33 (1H, d, J = 1.2 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.4, 23.0, 26.9, 29.0, 42.8, 50.8, 53.4, 57.6, 58.1, 67.2, 68.9, 107.3, 109.0, 118.1, 119.1, 121.2, 126.3, 127.1, 128.3, 128.5, 133.4, 137.3, 139.3, 202.9; EIMS (*m*/*e*, relative intensity) 414 (M, 80), 385 (20), 273 (60), 146 (100).

Anal. Calcd for $C_{27}H_{30}N_2O_2$: C, 78.26; H, 7.25; N, 6.76. Found: C, 78.30; H, 7.48; N, 6.54.

Catalytic Debenzylation of N_b-Benzyl, N_b-21-Secotalpinine (37) To Provide Talpinine (1). The N_b-benzyl, N_b-21-secotalpinine hydrochloride salt was prepared from the corresponding free base **37** (15 mg, 0.033 mmol) and ethanolic hydrogen chloride. The solvent was removed under reduced pressure, and the residue was dissolved in absolute EtOH (3 mL). The 10% Pd/C (5 mg) was added, and the slurry was allowed to stir at room temperature under 1 atm of H_2 (benchtop) for 1 h. Examination of the mixture by TLC (silica gel, EtOAc−hexane, 30/70) indicated the disappearance of starting material and the appearance of a new component. The catalyst was filtered from the medium and washed with EtOH (5 × 10 mL). The solvent was removed under reduced pressure. The residue, which resulted, was dissolved in a mixture of $CHCl_3$ (5 mL) and aqueous NH_4OH (5%, 5 mL). The aqueous layer was extracted with $CHCl_3$. The combined organic layers were dried (K_2CO_3), and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (silica gel, EtOAc/hexane, 30/70) to provide **1** (11 mg, 92%).

1: $[\alpha]^{25}_D = -31.6°$ (*c* 1.0, $CHCl_3$) [lit.[15] $[\alpha]^{25}_D = -30°$ (*c* 0.302, $CHCl_3$)]; IR (KBr) 1140, 1470, 3410 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27 (3H, d, J = 5.8 Hz), 1.81 (1H, d, J = 10.6 Hz), 1.87 (1H, d, J = 3.0 Hz), 2.03 (1H, s), 2.60 (1H, s), 3.20 (1H, dd, J = 15.8, 5.8 Hz), 3.42 (1H, d, J = 11.4 Hz), 3.50 (1H, t, J = 6.35 Hz), 3.56 (3H, s), 3.65 (1H, t, J = 7.6 Hz), 4.03 (1H, q, J = 6.8 Hz), 4.39(1H, d, J = 8.1 Hz), 4.69 (1H, d, J = 1.8 Hz), 7.07 (1H, t, J = 7.9 Hz), 7.17 (1H, t, J = 7.8 Hz), 7.27 (1H, d, J = 8.0 Hz), 7.45 (1H, d, J = 7.7); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 15.7, 23.5, 26.4, 29.2, 32.2, 35.4, 40.3, 43.9, 50.0, 60.3, 64.0, 72.7, 88.1, 103.2, 108.7, 118.3, 119.0, 121.0, 127.5, 137.7 (The ^{1}H NMR spectral data are in agreement with that reported for talpinine.[15] There were no ^{13}C NMR signals reported from that reference.); EIMS (*m*/*e*, relative intensity) 325 (M + 1, 100), 307 (20), 283 (10); MS (EI) *m*/*z* 324 (M, 60), 323 (100), 183 (90).

N_b-Benzyl/N_b-Methyl Transfer Reaction To Convert N_b-Benzyltalcarpine 38 into Talcarpine (2). N_b-Benzyltalcarpine **38** (20 mg, 0.031 mmol) was dissolved in freshly distilled dry CH_3OH (10 mL), and 10% Pd/C (15 mg) was added to the solution. The mixture, which resulted, was allowed to stir at room temperature for 12 h under 1 atm of H_2 (benchtop). Analysis of the reaction by TLC (silica gel, EtOAc/hexane, 30/70) indicated the disappearance of starting material. The catalyst was filtered from the medium and washed with methanol (5 × 20 mL). The combined methanol extracts were concentrated under reduced pressure. The residue, which resulted, was dissolved in a mixture of $CHCl_3$ and an aqueous solution of NH_4OH (10%). The aqueous layer was extracted with $CHCl_3$. The combined $CHCl_3$ layers were dried (K_2CO_3) and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc/hexane, 30/70) to provide **2** (15 mg, 90%).

2: $[\alpha]^{25}_D = -49.7°$ (*c* 0.35, $CHCl_3$) [lit.[3] $[\alpha]^{25}_D = -49°$ (*c* 0.302, $CHCl_3$)]; IR (KBr) 1722, 2901 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (1H, m), 1.32 (3H, d, J = 6.7 Hz), 1.36 (1H,dt, J = 8.9, 4.8 Hz), 1.78 (1H, s), 2.06 (1H, m), 2.20 (1H, dt, J = 8.0, 5.0 Hz), 2.32 (3H, s), 2.45 (1H, d, J = 16.7 Hz), 2.49 (1H, m), 2.82 (1H, d, J = 5.7 Hz), 3.33 (1H, dd, J = 16.5, 7.0 Hz), 3.63 (3H, s), 3.92 (1H, dd, J = 11.5, 5.0 Hz), 3.95−4.03 (2H, m), 7.07 (1H, t, J = 7.3 Hz), 7.17 (1H, t, J = 7.9 Hz), 7.27 (1H, d, J = 8.1 Hz), 7.46 (1H, t, J = 7.8 Hz), 9.94 (1H, d, J = 3.2 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 19.2, 22.5, 27.1, 28.9, 30.3, 39.6, 41.8, 53.5, 54.6, 54.7, 68.9, 69.5, 106.6, 108.7, 118.2, 119.0, 121.1, 126.4, 132.7, 137.2, 204.3 (The ^{1}H NMR and ^{13}C NMR data are in agreement with that reported for talcarpine.[3]); EIMS (*m*/*e*, relative intensity) 339 (M + 1, 100); MS (EI) *m*/*z* 338 (M, 60), 310 (20), 197 (100), 149 (40).

Hydroboration of Olefins 11a,b with BH_3·THF To Provide the Alcohol 40. To a round-bottom flask (25 mL) that contained a stirred solution of olefins **11a**,**b** (214 mg, 0.5 mmol) in dry THF (10 mL) was added BH_3·THF (1 M in THF, 3 mL) at 0 °C. The solution, which resulted, was stirred at 0 °C for 12 h, and then an additional quantity of BH_3·THF (1 M in THF, 1.5 mL) was added. The solution was stirred at 0 °C for an additional 20 h, after which H_2O (2 mL) was added to quench the excess borane. An aqueous solution of NaOH (3 N, 5.5 mL, 16.5 mmol) was added to the solution at 0 °C, and this was followed by dropwise addition of H_2O_2 (30%, 1.2 mL, 12 mmol). The reaction mixture that resulted was stirred at 0 °C for 1 h and then heated to reflux for 1 h. The reaction mixture was cooled to room temperature, saturated with NaCl, and extracted with $CHCl_3$. The combined organic layers were washed with brine and dried (K_2CO_3), and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (silica gel, EtOAc/hexane, 3:7; EtOAc; MeOH/ $CHCl_3$, 1:10) to afford the diastereomers **40a**,**b** (190 mg, 85%) as pure compounds.

40a: IR (KBr) 3345 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96 (3H, d, J = 6.3 Hz), 1.49−1.54 (1H, m), 1.83−1.88 (2H, m), 2.07−2.13 (1H, m), 2.43 (1H, d, J = 6.5 Hz), 2.60 (1H, td, J = 13.1, 4.1 Hz), 3.01 (1H, d, J = 6.9 Hz), 3.25 (1H, dd, J = 16.5, 7.1 Hz), 3.39−3.43 (1H, m), 3.43 (3H, s), 3.54 (3H, s), 3.55 (2H, d, J = 3.1 Hz), 3.83 (1H, t, 6.3 Hz), 3.95 (1H, t, appears brs), 4.41 (1H, t, J = 12.5 Hz), 4.59 (1H, d, J = 3.5 Hz), 7.11 (1H, t, J = 7.1 Hz), 7.19 (1H, t, J = 7.0 Hz), 7.23−7.34 (6H, m), 7.51 (1H, d, J = 7.5 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.7, 22.8, 25.0, 28.5, 29.0, 43.2, 47.7, 51.6, 53.2, 55.2, 57.5, 60.0, 66.5, 100.9, 107.0, 109.0, 117.9, 118.7, 120.6, 126.6, 126.9,

128.2, 128.6, 134.0, 137.0, 139.6; CIMS (*m/e*, relative intensity) 447 (M + 1, 100).

Anal. Calcd for $C_{28}H_{34}N_2O_3$: C, 75.34; H, 7.62; N, 6.28. Found: C, 75.04; H, 7.79; N, 6.00.

40b: IR (KBr) 3335 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.84 (3H, d, J = 6.3 Hz), 1.21 (1H, s), 1.50−1.62 (2H, m), 1.80 (1H, m), 2.14 (1H, d, J = 6.5 Hz), 2.38 (1H, d, J = 16.5 Hz), 2.59 (1H, td, J = 16.5, 4.8 Hz), 2.97 (1H, d, J = 7.1 Hz), 3.19 (1H, dd, J = 16.4, 6.3 Hz), 3.34−3.40 (1H, m), 3.40 (3H, s), 3.49 (3H, s), 3.50 (2H, d, J = 6.9 Hz), 3.62−3.67 (1H, m), 3.90 (1H, s), 4.32 (1H, t, J = 11.3 Hz), 4.82 (1H, d, J = 3.5 Hz), 7.06 (1H, t, J = 7.5 Hz), 7.12−7.35 (7H, m), 7.47 (1H, d, J = 7.5 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 8.2, 22.9, 27.7, 28.0, 29.0, 34.0, 43.5, 50.3, 57.8, 58.6, 59.0, 66.8, 75.2, 75.6, 106.6, 108.9, 118.2, 118.9, 120.8, 126.6, 127.3, 128.3, 130.0, 133.9, 137.1, 138.4; CIMS (*m/e*, relative intensity) 447 (M + 1, 100).

Anal. Calcd for $C_{28}H_{34}N_2O_3$: C, 75.34; H, 7.62; N, 6.28. Found: C, 75.39; H, 7.75; N, 6.30.

Swern Oxidation of the Alcohols 40a,b To Provide the Ketoacetal 42. To a round-bottom flask (10 mL) that contained a stirred solution of oxalyl chloride (2.0 M, 0.15 mL, 0.3 mmol) in CH_2Cl_2 (3 mL) was added a solution of dry DMSO (0.04 mL, 0.6 mmol) in CH_2Cl_2 (1 mL) at −78 °C under Ar. The mixture, which resulted, was stirred at −78 °C for 15 min followed by dropwise addition of a solution of alcohols **40a,b** (45 mg, 0.1 mmol) in CH_2Cl_2 (1 mL) over a 2 min period. The mixture, which resulted, was stirred for 1 h and 15 min at a temperature that ranged from −78 to −10 °C. Et_3N (0.2 mL) was then added, and the mixture which resulted was allowed to warm to room temperature with stirring over a 45 min period. Water (3 mL) was added to the reaction mixture, and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with brine and dried (Na_2SO_4). The solvent was removed under reduced pressure to provide an oil which was chromatographed (silica gel, EtOAc/hexane, 3:7) to provide the ketoacetal **42** (35 mg, 80%).

42: IR (KBr) 1705 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.87 (1H, dt, J = 12.5, 3.6 Hz), 1.89 (1H, s), 2.25−2.48 (2H, m), 2.60 (1H, dt, J = 12.8, 3.9 Hz), 3.02 (1H, d, J = 5.5 Hz), 3.27 (1H, dd, J = 16.5, 7.1 Hz), 3.44 (1H, dd, J = 11.4, 4.3 Hz), 3.47 (3H, s), 3.57 (3H, s), 3.58 (2H, d, J = 4.8 Hz), 3.95 (1H, t, J = 3.2 Hz), 4.39 (1H, t, J = 11.5 Hz), 5.07 (1H, q, J = 3.4 Hz), 7.11 (1H, t, J = 7.8 Hz), 7.20 (1H, t, J = 7.8 Hz), 7.23−7.35 (6H, m), 7.50 (1H, d, J = 7.8 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.8, 26.3, 27.5, 28.2, 28.9, 43.0, 51.8, 53.0, 54.8, 55.5, 57.5, 59.8, 98.4, 106.8, 109.0, 117.8, 118.7, 120.7, 126.2, 126.9, 128.2, 128.5, 133.9, 136.9, 139.7, 205.1; CIMS (*m/e*, relative intensity) 445 (M + 1, 100).

Anal. Calcd for $C_{28}H_{32}N_2O_3$: C, 75.68; H, 7.21; N, 6.31. Found: 75.50; H, 7.01; N, 6.51%

Base-Mediated Elimination of the Elements of Methanol from the Ketoacetal 42 To Provide N_b-Benzylalstonerine 43. To a round-bottom flask (10 mL) that contained a stirred solution of **t**he ketoacetal **42** (22 mg, 0.05 mmol) in CH_3OH (3 mL) was added an aqueous solution of NaOH (2 N, 2 mL) at 0 °C. The reaction mixture which resulted was allowed to stir at room temperature for 12 h and then was cooled to 0 °C. The above solution was brought to pH = 9 with an aqueous solution of saturated NH_4Cl (3 mL), and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with brine and dried (Na_2SO_4). After the solvent was removed under reduced pressure, the residue was purified by flash chromatography (silica gel, EtOAc/hexane, 2:8) to provide N_b-benzylalstonerine **43** (18 mg, 90%).

43: IR (KBr) 1625, 1655 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.79 (1H, dd, J = 12.0, 3.9 Hz), 1.85−1.95 (1H, m), 2.09 (3H, s), 2.40 (1H, m), 2.53 (1H, d, J = 16.6 Hz), 2.67 (1H, m), 3.12 (1H, d, J = 7.0 Hz), 3.30 (1H, dd, J = 16.5, 6.9 Hz), 3.45 (1H, d, J = 7.8 Hz), 3.56 (3H, s), 3.57 (2H, s), 3.86 (1H, t, J = 3.2 Hz), 4.55 (1H, t, J = 11.4 Hz), 7.10 (1H, t, J = 7.9 Hz), 7.20−7.33 (7H, m), 7.49 (1H, d, J = 7.5 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 23.2, 23.3, 25.0, 29.0, 32.5, 38.5, 51.5, 52.7, 57.5, 67.7, 106.4, 109.0, 117.9, 118.8, 120.9, 121.2, 126.6, 127.0, 128.3, 128.5, 133.7, 137.5, 139.4, 157.4, 195.4; CIMS (*m/e*, relative intensity) 413 (M + 1, 100).

Anal. Calcd for $C_{27}H_{28}N_2O_2$: C, 78.64; H, 6.80; N, 6.80. Found: C, 79.01; H, 7.05; N, 6.90.

N_b-Benzyl/N_b-Methyl Transfer Reaction To Convert N_b-Benzylalstonerine 43 into Alstonerine 3. To a round-bottom flask (10 mL) that contained a solution of N_b-benzylalstonerine (10 mg, 0.025 mmol) in CH_3OH (freshly distilled, 5 mL) was added 10% Pd/C (10 mg). The slurry which resulted was allowed to stir at room temperature for 12 h under 1 atm of H_2. Analysis of the reaction by TLC (silica gel, EtOAc/hexane, 3/7) indicated the disappearance of starting material. The catalyst was filtered from the medium and washed with CH_3OH (5 × 10 mL). The combined organic layers were concentrated under reduced pressure. The residue, which resulted, was dissolved in a mixture of $CHCl_3$ and an aqueous solution of NH_4OH. The aqueous layer was separated and extracted with $CHCl_3$. The combined organic layers were dried (K_2CO_3), and the solvent was removed under reduced pressure. The residue that resulted was purified by flash chromatography (silica gel, EtOAc/hexane, 30/70) to provide **3** (7.1 mg, 90%), the spectral data of which were identical to the published values.[30]

3: $[\alpha]^{25}_D$ = −190° (*c* 0.35, EtOH) [lit.[30] $[\alpha]^{25}_D$ = −195° (*c* 0.60, EtOH)]; IR (NaCl) 1621, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ.1.77 (1H, dd, J = 12.2, 4.2 Hz), 1.89 (1H, ddd, J = 12.2, 11.4, 1.5 Hz), 2.10 (3H, s), 2.11 (1H, ddd, J = 11.2, 4.6, 4.0 Hz), 2.30 (3H, s), 2.49 (1H, d, J = 16.4 Hz), 2.60 (1H, ddd, J = 12.4, 4.6, 4.6 Hz), 3.08 (1H, d, J = 6.8 Hz), 3.31 (1H, dd, J = 16.4, 6.8 Hz), 3.63 (3H, s), 3.86 (1H, t, J = 1.5 Hz), 4.15 (1H, ddd, J = 11.2, 4.0, 1.5 Hz), 4.39 (1H, t, J = 11.2 Hz), 7.10 (1H, t, J = 8.1 Hz), 7.18 (1H, t, J = 7.0 Hz), 7.30 (1H, d, J = 8.1 Hz), 7.45 (1H, d, J = 7.6 Hz,), 7.52 (1H, s); ^{13}C NMR ($CDCl_3$) δ 22.8, 22.9, 25.1, 29.1, 32.4, 38.5, 41.8, 53.8, 54.7, 67.8, 105.9, 109.0, 117.8, 118.7, 120.8, 126.5, 129.7, 133.2, 137.2, 157.4, 195.5; EIMS (*m/e*, relative intensity) 337 (M^+ + 1, 26.2), 336 (M^+, 100), 197 (70.5), 181 (35.9), 170 (50.7); HRMS (*m/e*, relative intensity) required for $C_{21}H_{24}N_2O_2$ 336.1846, found 336.1838.

The 1,4-Elimination of the Elements of Methanol from the Olefins 11a,b with *p*-TSA To Provide N_b-Benzylanhydromacrosalhinemethine 44. To a round-bottom flask (50 mL) that contained a solution of the olefins **11a**,**b** (21 mg, 0.05 mmol) in dry benzene (20 mL) was added *p*-toluenesulfonic acid (13 mg, 0.068 mmol). The solution, which resulted, was heated to reflux for 4 h. The reaction mixture was cooled to room temperature and then brought to pH = 10 with an aqueous solution of NH_4OH (10%). The aqueous layer was separated and extracted with $CHCl_3$, and the combined organic extracts were dried (K_2CO_3). After the solvent was removed under reduced pressure the residue which resulted was purified by flash chromatography (silica gel, EtOAc−hexane, 3:2) to afford N_b-benzylanhydromacrosalhinemethine **44** (18.3 mg, 93%).

44: IR (KBr) 1630, 2890, 3420 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.26 (1H, s), 1.90−2.13 (3H, m), 2.46 (1H, dt, J = 11.9, 5.8 Hz), 2.56 (1H, d, J = 16.5 Hz), 3.18 (1H, d, J = 6.8 Hz), 3.35 (1H, dd, J = 16.4, 6.9 Hz), 3.58 (3H, s), 3.62 (2H, s), 3.96−4.02 (2H, m), 4.40 (1H, d, J = 17.5 Hz), 4.54 (1H, d, J = 11.0 Hz), 7.14 (1H, t, J = 7.3 Hz), 7.20−7.34 (7H, m), 7.54 (1H, d, J = 7.5 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 23.2, 23.9, 29.0, 32.4, 39.0, 51.5, 53.1, 57.5, 66.9, 106.4, 107.0, 108.9, 117.0, 118.1, 118.9, 120.9, 126.7, 127.0, 128.3, 128.5, 133.8, 134.2, 137.1, 139.5, 145.4; CIMS *m/e* (relative intensity) 397 (M + 1, 100).

Anal. Calcd for $C_{27}H_{28}N_2O$: C, 81.82; H, 7.07; N, 8.07. Found: C, 81.41; H, 7.37; N, 7.70.

Attempt To Convert N_b-Benzylanhydromacrosalhinemethine 44 into Anhydromacrosalhine-methine 4 via the N_b-Benzyl/N_b-Methyl Transfer Reaction. To a round-bottom flask (10 mL) that contained a solution of N_b-benzylanhydromacrosalhinemethine **44** (8 mg, 0.02 mmol) in CH_3OH (freshly distilled, 5 mL) was added 10% Pd/C (10 mg). The slurry, which resulted, was allowed to stir at room temperature for 12 h under 1 atm of H_2 (benchtop). Analysis of the reaction

by TLC (silica gel, EtOAc/hexane, 30/70) indicated the disappearance of starting material. The catalyst was filtered from the medium and washed with CH_3OH (5 × 10 mL). The combined organic layers were concentrated under reduced pressure. The residue, which remained, was dissolved in a mixture of $CHCl_3$ and an aqueous solution of NH_4OH. The aqueous layer was separated and extracted with $CHCl_3$. The combined organic layers were dried (K_2CO_3) and the solvent was removed under reduced pressure. The residue that resulted was purified by flash chromatography (silica gel, EtOAc/hexane, 30/70) to provide enol ether **45** (5.0 mg, 78%) instead of the desired anhydromacrosalhinemethine **4**.

***N*b-Benzyl/*N*b-Methyl Transfer Reaction of Enol Ether (12) To Provide *N*b-Methyl Enol Ether 45.** To a round-bottom flask (25 mL) that contained a solution of *N*b-benzyl enol ether **12** (21 mg, 0.05 mmol) in CH_3OH (freshly distilled, 10 mL) was added 10% Pd/C (25 mg). The mixture, which resulted, was allowed to stir at room temperature for 12 h under 1 atm of H_2. Analysis of the reaction by TLC (silica gel, EtOAc/hexane, 30/70) indicated the disappearance of **12**. The catalyst was filtered from the medium and washed with CH_3OH (5 × 20 mL). The combined methanol washes were concentrated under reduced pressure, and the residue, which resulted, was dissolved in a mixture of $CHCl_3$ and an aqueous solution of NH_4OH. The aqueous layer was extracted with $CHCl_3$ and the combined organic layers were dried (K_2CO_3). The solvent was removed under reduced pressure, and the residue that resulted was purified by flash chromatography (silica gel, EtOAc/hexane, 3/7) to provide *N*b-methyl enol ether **45** (14.5 mg, 90%).

45: IR (KBr) 1380, 1470, 1670, 2900 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.81 (3H, t, J = 7.5 Hz), 1.65−2.04 (3H, m), 2.33 (3H, s), 2.49 (1H, d, J = 16.5 Hz), 3.08 (1H, d, J = 6.9 Hz), 3.30 (1H, dd, J = 16.5, 6.9 Hz), 3.64 (3H, s), 3.90−3.95 (3H, m), 4.19 (1H, t, J = 10.9 Hz), 6.14 (1H, s), 7.11 (1H, t, J = 7.8 Hz), 7.20 (1H, td, J = 7.8, 0.9 Hz), 7.31 (1H, d, J = 8.0 Hz), 7.51 (1H, d, J = 7.9 Hz); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 12.9, 23.0, 23.5, 27.1, 29.0, 33.1, 40.6, 41.9, 53.8, 55.3, 66.3, 106.5, 108.8, 117.4, 118.0, 118.8, 120.8, 126.7, 133.6, 137.2, 138.1; CIMS (CH_4) *m*/*e* (relative intensity) 323 (M + 1, 100); EIMS *m*/*e* (relative intensity) 322 (M^+, 100), 307 (12.5) 279 (33.0), 253 (45.1), 224 (26.9), 212 (21.3), 197 (69.7), 182 (29.7), 170 (67.8), 149 (47.9).

Anal. Calcd for $C_{21}H_{26}N_2O \cdot 1/3H_2O$: C, 76.79; H, 8.18; N, 8.53. Found: C, 76.73; H, 7.95; N, 8.47. The spectral properties of **45** were identical to those of **45** prepared above.

Oxyselenation/Selenoxide Elimination of Enol Ether (45) Followed by 1,4-Elimination of the Elements of Water To Provide Anhydromacrosalhine-methine (4).[50] To a round-bottom flask (25 mL) that contained a solution of enol ether **45** (200 mg, 0.62 mmol) in CH_2Cl_2 (10 mL) were added *N*-phenylselenophthalimide **34** (244 mg, 0.81 mmol),[52] *p*-toluenesulfonic acid (130 mg, 0.68 mmol), and 1 drop of H_2O. The reaction mixture, which resulted, was stirred at room temperature for 5 h and then diluted with CH_2Cl_2. This solution was brought to alkaline pH with an aqueous solution of NH_4OH (15%) at 0 °C, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried (K_2CO_3) and concentrated under reduced pressure. The residue, which resulted, was purified by flash chromatography (silica gel, EtOAc) to afford a mixture of hydroxyselenides. This mixture was used directly in the next step. To a stirred solution of hydroxyselenides (130 mg, 0.262 mmol) in THF (11 mL) at 0 °C was added a solution of $NaIO_4$ (82 mg, 0.384 mmol) in H_2O (2.4 mL). The reaction mixture, which resulted, was allowed to stir at room temperature for 5 h. The precipitate which formed was removed by filtration and the reaction mixture was concentrated under reduced pressure after which it was brought to alkaline pH with an aqueous solution of NH_4OH (15%) at 0 °C. The aqueous layer was extracted with $CHCl_3$, and the organic extracts were washed with brine, dried (K_2CO_3), and then concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, MeOH−$CHCl_3$, 1:9) to provide a mixture of allylic alcohols which was charged to a solution of *p*-toluenesulfonic acid (80 mg, 0.41 mmol) in dry THF (10 mL). The reaction mixture, which resulted, was stirred at room temperature for 5 h, brought to alkaline pH with an aqueous solution of NH_4OH (10%) and then extracted with $CHCl_3$. The combined organic extracts were dried (K_2CO_3) and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc−hexane, 3:2) to afford anhydromacrosalhine-methine **4** (68 mg, 85%).

4: mp 146−150 °C (from EtOAc); IR (KBr) 1470, 1630, 2890, 3420 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.03−1.96 (2H, m), 2.12 (1H, dt, J = 13.1, 3.8 Hz), 2.34 (3H, s), 2.40−2.30 (1H, m), 2.52 (1H, d, J = 16.5 Hz), 3.10 (1H, d, J = 6.7 Hz), 3.33 (1H, dd, J = 16.5, 6.9 Hz), 3.64 (1H, s), 3.91 (1H, s), 4.02 (1H, dd, J = 10.9, 3.2 Hz), 4.38 (1H, d, J = 17.4 Hz), 4.39 (1H, t, J = 11.3 Hz), 4.54 (1H, d, J = 10.8 Hz), 5.99 (1H, dd, J = 17.5, 10.9 Hz), 6.45 (1H, s), 7.10 (1H, t, J = 7.4 Hz), 7.20 (1H, t, J = 7.5 Hz), 7.31 (1H, d, J = 8.2 Hz), 7.50 (1H, d, J = 7.7 Hz); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 22.9, 23.6, 27.0, 32.4, 39.3, 41.9, 54.0, 55.1, 87.1, 106.4, 106.7, 108.8, 116.9, 118.1, 119.0, 120.9, 126.8, 133.5, 134.3, 137.3, 145.5; CIMS *m*/*e* (relative intensity) 321 (M^+, 100); EIMS *m*/*e* (relative intensity) 320 (M + 1, 100), 251 (38.0), 222 (15.9), 197 (64.6), 181 (34.8), 170 (64.1). The spectral data for **4** were identical to those reported by Hesse et al in ref 14.

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