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The Enantiospecific, Stereospecific Total Synthesis of the Ring-A Oxygenated Sarpagine Indole Alkaloids (+)-Majvinine, (+)-10-Methoxyaffinisine, and (+)-N_a-Methylsarpagine, as Well as the Total Synthesis of the *Alstonia* Bisindole Alkaloid Macralstonidine

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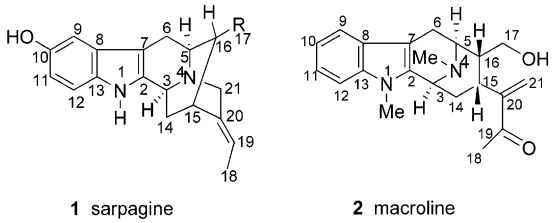
The first stereospecific, enantiospecific total synthesis of the ring-A oxygenated sarpagine indole alkaloids (+)-N_a-methylsarpagine (**8**), (+)-majvinine (**14**), and (+)-10-methoxyaffinisine (**49**), as well as the first total synthesis of the *Alstonia* bisindole alkaloid macralstonidine (**9**), has been accomplished. This approach employed the Schöllkopf chiral auxiliary for the stereospecific construction of the desired D-(+)-tryptophan unit required for the asymmetric Pictet−Spengler reaction. In addition, the strategy was doubly convergent for the enolate-mediated Pd^0 coupling process and the asymmetric Pictet−Spengler reaction can be employed to synthesize both macroline (**2**) and N_a-methylsarpagine (**8**), the coupling of which provides macralstonidine (**9**). This approach to ring-A substituted alkoxyindole alkaloids should find wide application for the synthesis of other alkaloids for it is stereospecific and either enantiomer can be prepared with ease.

Introduction

The sarpagine[1] alkaloids (Figure 1) are the largest class of natural products related to the macroline bases and both series originate from common biogenetic intermediates. Macroline[2] has not been isolated as a natural product but is believed to be a biomimetic precursor to many *Alstonia* alkaloids. During the last several decades more than 100 macroline/sarpagine related indole alkaloids have been isolated from *Alstonia macrophylla* Wall, *Alstonia muelleriana* Domin, *Alstonia angustifolia*, and other *Alstonia* species.[3,4] Among these alkaloids, at least 21 are bisindoles, including macrocarpamine **3a**, villalstonine **4a**, and macralstonine **5a** (Figure 2). Interest in the macroline/sarpagine alkaloids isolated from *Alstonia* species originated as a result of folk tales which described the medicinal properties of these plants.[5,6] For example,



1 sarpagine **2** macroline

FIGURE 1. The numbering system of the sarpagine skeleton.

the base macralstonine **5a**, isolated from *Alstonia macrophylla* Wall,[7,8] was reported to exhibit potent hypotensive activity by Elderfield[9] and Manalo[7] many years ago.

With respect to the macroline/sarpagine alkaloids, more recently, Wright *et al.*[10] reported on the antiprotozoal activity of nine alkaloids from *Alstonia angustifolia* against *Entamoeba histolytica* and *Plasmodium falciparum in vitro*. Of the nine alkaloids tested, macrocarpamine **3a**, villalstonine **4a**, and macralstonine *O*-acetate **5b** (Figure 2) were found to possess significant activity against both protozoa. Macrocarpamine **3a** was found to be the most active antiamoebic compound against *Entamoeba histolytica* of the series [ED_{50}(95% C.I.) = 8.12(7.76−

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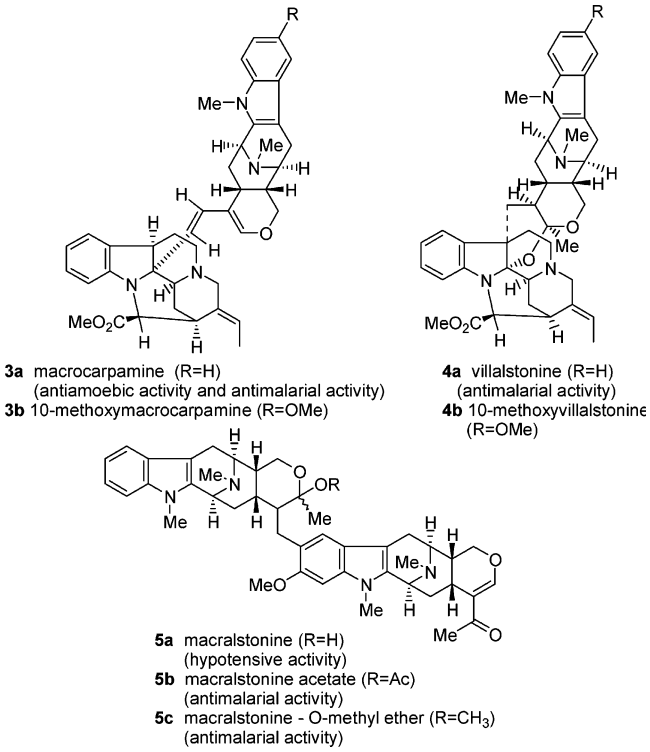
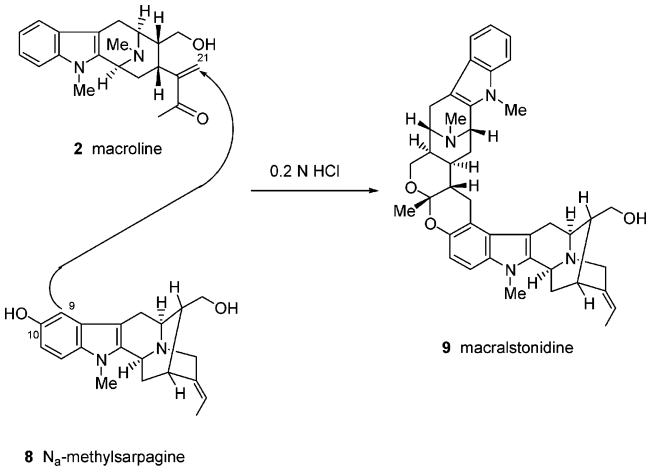


FIGURE 2. Biological activity of macrocarpamine **3a**, villalstonine **4a**, and macralstonine **5a**.

8.48) μM] although it was only one-fourth as potent as the standard drug emetine.[10] Villalstonine **4a** was found to be the most potent alkaloid against *Plasmodium falciparum* [ED_{50}(95% C.I.) = 2.92(1.11−3.14) μM] of the alkaloids tested. The results of these *in vitro* studies provide some basis for the traditional use of the plant extract from *Alstonia angustifolia* for the treatment of amoebic dysentery and malaria by the people of the Malay peninsula.[10] In addition, the studies by Wright *et al.* coupled with the ethanopharmacological reports indicated these bisindoles are orally active.[10] It has also been reported that the monomeric alkaloids exhibited very little antiprotozoal activity.[10] This suggests that at least part of both of the ring systems present in the dimeric alkaloids are essential for potent activity. The structural studies via molecular modeling of the standard antiamoebic drug emetine and the base usambarensine also support this suggestion.[11] The cytotoxic activity of villalstonine **4a** against KB cells was also evaluated and found to be similar to its antiamoebic activity.[10] However, the standard antiamoebic drug emetine is highly toxic to KB cells but is three times less toxic to amoebae than to KB cells. Therefore, villalstonine **4a** appears to have a more favorable antiamoebic/cytotoxic ratio as compared to emetine.[10,11]

Recent interest in synthetic chemistry in this series has grown considerably in an enantiospecific sense to permit comparison of the biological properties of the unnatural alkaloids to those of the natural products.[12−14]

SCHEME 1



Importantly, a number of active bisindole alkaloids from *Alstonia* species belong to the macroline/sarpagine family. The biomimetic interconversions of *Alstonia* alkaloids and the coupling reactions of monomeric indoles into bisindoles were pioneered by LeQuesne et al.[2,15−17]

The biomimetic synthesis of *Alstonia* alkaloids usually involves the addition of a monomeric alkaloid to C-21 of the α,β-unsaturated enone moiety of (+)-macroline.[18] The total synthesis of (+)-macroline **2** has been completed and coupled with natural pleiocarpamine, consequently a partial synthesis of villalstonine **4a** has been achieved.[19] In addition, the synthesis of geissoschizine[20] coupled with its previous conversion into epipleiocarpamine[21]/pleiocarpamine[22] by Sakai constituted a formal total synthesis of pleiocarpamine **6** and villastonine **4a**.[22]

A number of ring-A parent(H) macroline/sarpagine indole alkaloids have been previously synthesized including macroline,[23−26] in which a ring-A unsubstituted tetracyclic azabicyclo[3.3.1]nonane **7** (Scheme 2) was employed as a common template. Since the total synthesis of (+)-macroline **2** has been completed, the synthesis of the ring-A oxygenated alkaloid N_a-methylsarpagine **8** would result in the total synthesis of the bisindole alkaloid macralstonidine **9**. The total synthesis of these bisindoles in optically active form, therefore, requires the enantiospecific preparation of the monomeric indole alkaloid N_a-methylsarpagine **8**. As illustrated in Scheme

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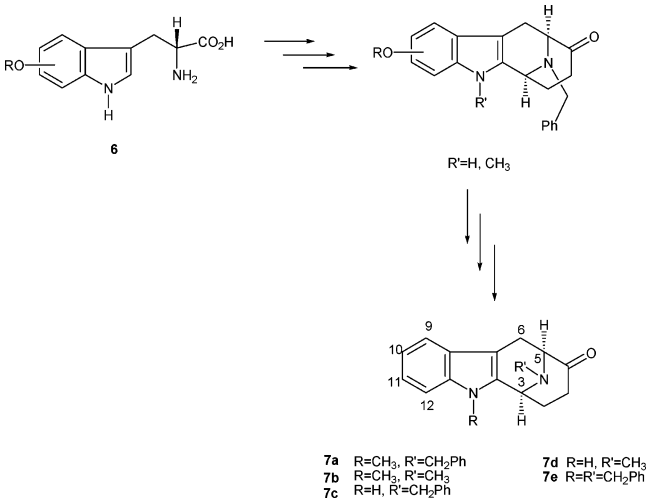
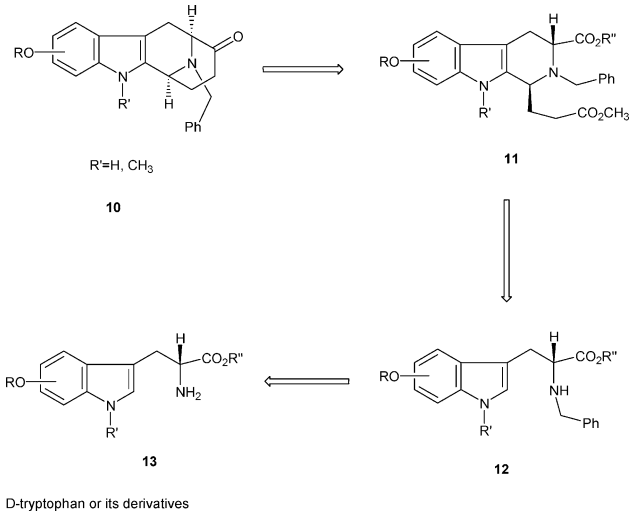
SCHEME 2



SCHEME 3



1, macralstonidine **9** could be constructed from condensation of macroline **2** (northern unit) and N_a-methylsarpagine **8** (southern unit) *via* the biomimetic coupling process of LeQuesne.[2,16]

With the recent completion of the enantiospecific synthesis of (+)-macroline **2** as well as the improved route to (+)-macroline **2** (from D-tryptophan)[27] and the antipode, (−)-macroline (from L-tryptophan),[28] a broader search for antiprotozoal activity can be initiated that may lead to more selective antimalarial agents in the future. The syntheses of ring-A oxygenated indole alkaloids are rare in comparison to the synthesis of the unsubstituted (parent) bases. This stems from the difficulty in incorporation of the oxygen functionality into ring-A during the latter stages of the synthetic sequence.[29] Therefore, an enantiospecific, regiospecific synthetic route to such alkaloids might require the installation of the oxygen functionality early in the sequence. A synthetic route to ring-A oxygenated tryptophans would provide material that could be employed in the total synthesis of these ring-A oxygenated alkaloids. The synthetic route should also be capable of scale-up to provide large quantities of intermediates which could be employed for other synthetic routes as well as for biological screening.

The total synthesis of sarpagine indole alkaloids [from D-(+)-tryptophan] *via* the trans 1,3-transfer of asymmetry during the Pictet−Spengler reaction[23,26,30,31] has prompted the development of an enantiospecific route to ring-A oxygenated D-(+)- or L-(−)-tryptophans and their derivatives. For the approach to these indole-substituted amino acids, the Schöllkopf auxiliary[32] has been chosen since this provided a route to either D-(+)- (from L-valine) or L-(−)- (from D-valine) tryptophans on large scale.[33] The substituted indoles could then be converted into ring-A substituted azabicyclo[3.3.1]nonanes required for the total synthesis of ring-A substituted sarpagine alkaloids (Scheme 2).[34]

The initial goal was to develop a general route to ring-A oxygenated indole alkaloids. Consequently, an ideal approach to these bases might rest on the multigram synthesis of a common, optically active intermediate that could be employed for the synthesis of many related natural products. This common intermediate would, at the very least, contain the requisite stereochemistry and tetracyclic ring system which could be readily functionalized for further elaboration. In 1988, an enantiospecific synthesis of the (−)-N_b-benzyltetracyclic ketone **7a** (Scheme 2) was reported and extended to multihundred gram scale.[26,35−39] This intermediate has been employed for the total synthesis of (−)-alstonerine,[40] (−)-suaveoline,[25] (+)-macroline,[19,27,28] and anhydromacrosalhinemethine[41] as well as the ajmaline-related alkaloids (−)-raumacline, (−)-N_b-methylraumacline,[24,25] ajmaline, and alkaloid G.[42,43,44]

To apply the same approach to the synthesis of ring-A oxygenated indole alkaloids, a route to the ring-A oxygenated tetracyclic ketone **12** would be required that was capable of scale-up to multigram levels. Retrosynthetically, the ring-A oxygenated tetracyclic ketone **10** (Scheme 3) could be envisaged to arise *via* a regiospecific Dieckmann condensation. This intermediate could originate from trans diester **11**, which would be available from the asymmetric Pictet−Spengler reaction of an optically active ring-A alkoxylated D-tryptophan analogue (Scheme

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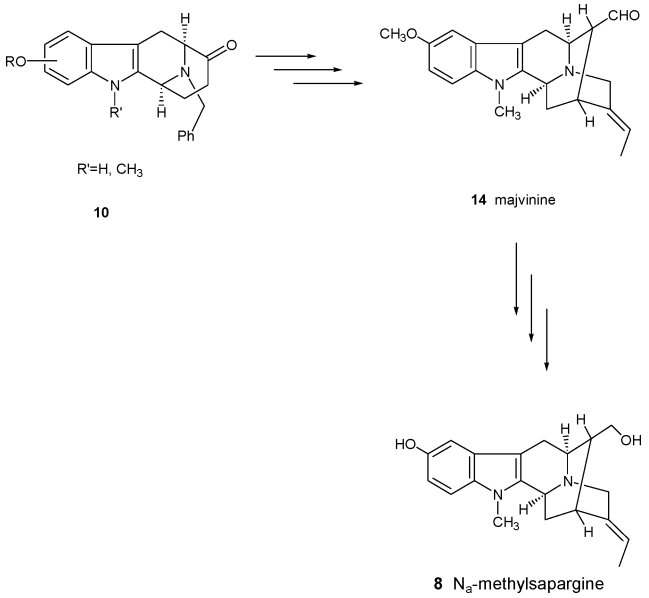
SCHEME 4



3). This approach would also require the base-catalyzed epimerization at C(5) in trans diester **11** followed by ring closure of the cis-fused system to provide the tetracyclic ketone **10**. Precedent for this originates from the previous work of Soerens, Zhang, and Trudell.[36,44−48]

This ketone **10** could be employed to prepare the stable ring-A oxygenated sarpagine indole alkaloid, (+)-majvinine **14** (Scheme 4). It was felt the development of a synthetic route to (+)-majvinine **14** would also lead to the synthesis of a series of ring-A oxygenated sarpagine indole alkaloids. Furthermore, (+)-majvinine **14**, presumably, could be converted into the ring-A oxygenated indole alkaloid N_a-methylsarpagine **8** (Scheme 4), a key monomeric unit of the bisindole alkaloid macralstonidine **9** (see Scheme 1). This 10-hydroxysarpagine base was susceptible to oxidation, consequently its isolation from plants was problematic.

Common structural features of the sarpagine indole alkaloids include the *E*-ethylidene double bond at C(19)−C(20) and the asymmetric centers at C-3(*S*), C-5(*R*), C-15(*R*), and C-16(*R*) (see Figure 1 for the numbering system of the sarpagine skeleton). These stereocenters provided much of the interest in the design of a general approach to these alkaloids. Sakai[49] earlier reported the partial synthesis of (−)-koumidine, which contained a similar skeleton to that of the sarpagine series; however, the double bond in (−)-koumidine was present in the *Z*-configuration and the chirality at C(16) was *S* rather than *R*. Establishment of the stereochemistry of the C(19)−C(20) double bond in (−)-koumidine by Sakai *via* an elimination process yielded the more stable *Z*-configuration required for koumidine in a 5:1 ratio. This is opposite to the characteristic *E*-configuration required for the C(19)−C(20) double bond in the sarpagine alkaloids. Magnus[50] reported the total synthesis of the antipode of (−)-koumidine (from L-tryptophan); however, establishment of the double bond (*Z*:*E* 1:1) was still not stereospecific. Several other groups have encountered a similar problem during the synthesis of the C(19)−C(20) double bond in the related alkaloid geissoschizine; the ratio of *E* to *Z* was very good but not reported as stereospecific.[51−53] Recently, Martin's total synthesis of geissoschizine with stereoselective establishment of the double bond was carried out by an elimination process.[54] Rawal and Bosch reported the total synthesis of *Strychnos* alkaloids with stereocontrolled establishment of the double bond by a Heck coupling reaction,[55−57] and this novel method has been applied toward the enantiospecific total synthesis of the *Corynanthe* indole alkaloids.[20] However, no total synthesis of members of the ring-A substituted sarpagine series has appeared to date.

Enantiospecific Synthesis of 5-Methoxylated D(+)-Tryptophans for Indole Alkaloid Total Synthesis. A number of synthetic routes to substituted tryptophans have been considered earlier (Scheme 5).[58,59] However, attempts to execute these in a practical sense met with only limited success. The principal reason for the failure of the second and fourth approaches, as represented in Scheme 5, originated from the inability of the chiral auxiliary to tolerate the harsh conditions of the Fischer-indole cyclization.[60] The third approach in Scheme 5 provided a poor yield of indole with low stereoselectivity.[60] Consequently, the Schöllkopf chiral auxiliary[61] was chosen here for the preparation of the desired D-(+)-tryptophan would be available from L-valine, while the L-(−)-isomer would originate from D-valine. This chiral auxiliary had been employed earlier for the preparation of 1-benzenesulfonyl-6-methoxy-D-(−)-tryptophan ethyl ester.[61] The success of this sequence rested on the ability to scale-up the first few steps to multihundred gram levels.

The Japp−Klingmann/Fischer-Indole Process. The well-known Fischer-indole cyclization,[62] *via* a thermally mediated [3,3]sigmatropic rearrangement, was chosen as the means to generate (from *p*-anisidine **15**) large quantities of 5-methoxy-3-methylindole **17** (Scheme 6). The synthesis of 5-methoxy-D-tryptophan *via* this route could

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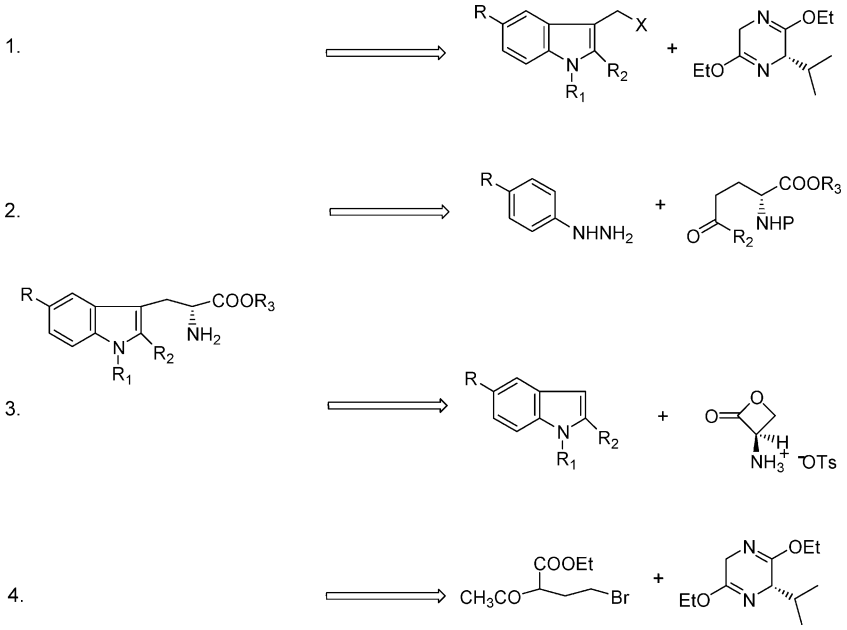
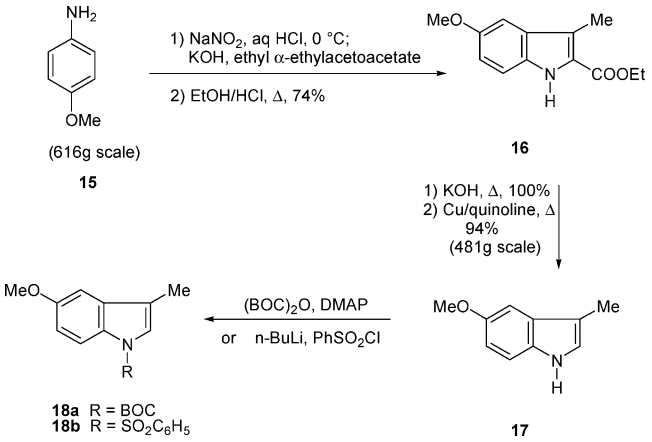
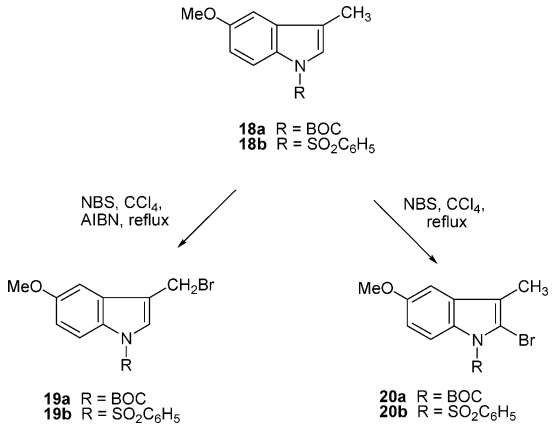
SCHEME 5



SCHEME 6



SCHEME 7



also be employed for the L(−)-isomer from the antipode of the Schöllkopf auxiliary.[60]

Ethyl 5-methoxy-3-methylindole-2-carboxylate **16** was prepared on a large scale from *p*-anisidine **15** and ethyl α-ethylacetoacetate by the Fischer-indole cyclization *via* a Japp−Klingemann azo-ester intermediate (Scheme 6).[63] This process was developed by Abramovitch and Shapiro as well as reviewed.[32,64] Alkaline hydrolysis of ester **16** and subsequent copper/quinoline-mediated decarboxylation of the carboxylic acid that resulted furnished the 5-methoxy-3-methylindole **17** in excellent yield. Care must be exercised on decarboxylation of the corresponding acid on a large scale. The best yields were obtained when the carboxylic acid was fully dried and the decarboxylation was executed at reflux in a well-stirred minimum amount of distilled quinoline (1.5−2 equiv of quinoline with respect to the carboxylic acid). Only a catalytic amount of copper powder was required to ensure yields of **16** in excess of 90% (Scheme 6). To carry out the regiospecific bromination in high yield, protection/deactivation of the indole N(H) group was required. This was accomplished by stirring **16** with either BOC anhydride or benzenesulfonyl chloride. A detailed study of the electrophilic *vs* free radical bromination of various 3-methylindoles follows here.

Regiospecific Bromination of 3-Methylindoles. With the N_a-protected 3-methylindoles **18a** and **18b** in hand, the bromination of 3-methylindoles with NBS was carried out under two sets of conditions (Scheme 7). In the electrophilic bromination process, 3-methylindoles were simply heated with NBS in refluxing carbon tetrachloride in the absence of the radical initiator (AIBN) to provide **20a** and **20b**, respectively, in high yield. In the radical bromination process, 3-methylindoles were heated in refluxing CCl_4 and then treated with NBS and AIBN to provide **19a** and **19b**; in this process, NBS was admixed with AIBN. This mixture was then added to the refluxing solution of 3-methylindole in CCl_4. After 5 min, AIBN was added again, if necessary. The competition between electrophilic and free radical bromination has been studied[65,66] in methyl-substituted anisoles on treatment with NBS. The regiospecific bromination of 3-me-

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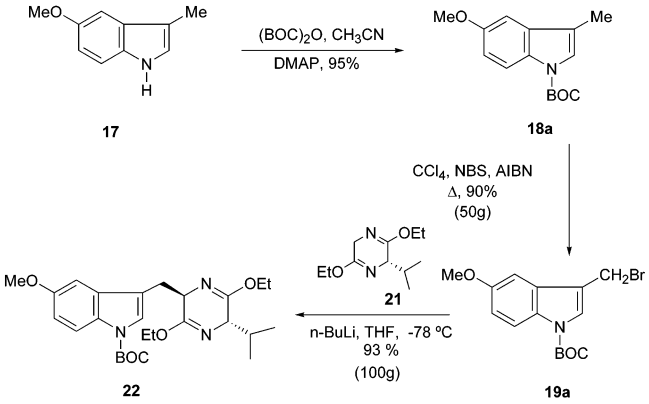
(64) Abramovitch, R. A.; Shapiro, D. S. *J. Chem. Soc., Perkin Trans.1* **1956**, 4589.

SCHEME 8



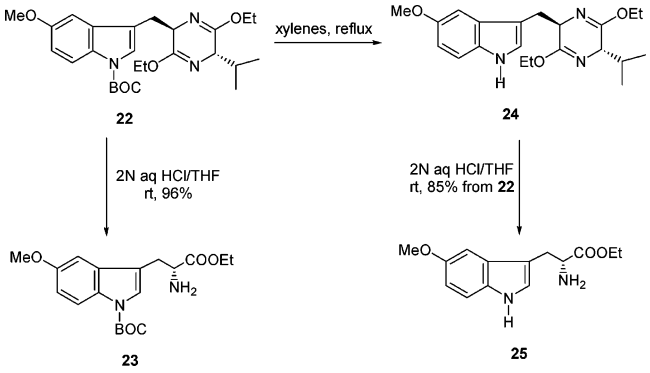
thylindoles at either the C(3) alkyl group (radical bromination) or the indole 2-position *via* electrophilic attack also has been investigated and the details have been reported.[60,67]

Although the presence of an electron-withdrawing group at the N(1) position of **18a** or **18b** should deactivate the C(2) position, the electrophilic bromination of indoles **18a** and **18b** occurred readily at C(2) when they were stirred with NBS in the absence of a radical initiator (Scheme 8). In the case of **18a** and **18b**, two contrasting factors were involved in the electrophilic vs free radical process. Even though indoles are reactive aromatic systems, the presence of an electron-withdrawing group at the N(1) position would be expected to deactivate them to electrophilic attack at C(2). However, since the methoxyl group has been employed to promote the electrophilic bromination of methyl-substituted anisoles,[65] it plays the same role in the bromination of indoles **18a** and **18b** at the C(2) position. Consequently, deactivation of the indole 2,3-double bond by the N(1) protecting group and activation by the methoxyl group at the C(5) position of indoles **18a** and **18b** are delicately balanced. A slight change in reaction conditions in the bromination process promoted the reaction in the direction of either the electrophilic or free radical bromination process.

Examination of these results demonstrated that the regiospecific bromination of 3-methyl-5-methoxyindoles can be controlled by judicious choice of the reaction conditions and the choice of the protecting group at the N(1) position. In the presence of an activating group such as a methoxyl moiety, the protection of indoles at the N(1) position should be accomplished before the bromination is carried out. The 3-methylindoles protected in this fashion (e.g. **18a** and **18b**) should lead to either 3-bromomethylindoles or 2-bromo-3-methylindoles based on the choice of the reaction conditions (free radical *vs* electrophilic). In the absence of ring-A oxygenated activating groups, free radical bromination at the 3-methyl group should be facilitated by the electron-withdrawing group at the N(1) position of the 3-methylindole. On the other hand, to brominate 3-methylindoles at the C(2) position even when they lack the ring-A activating substituent, the bromination should proceed before the protection sequence is executed.

(65) Gruter, G. M.; Akkerman, O. S.; Bickelhaupt, F. *J. Org. Chem.* **1994**, *59*, 4473 and references therein.
(66) Goldberg, Y.; Bensimon, C.; Alper, H. *J. Org. Chem.* **1992**, *57*, 6374.
(67) Zhang, P.; Liu, R.; Cook, J. M. *Tetrahedron Lett.* **1995**, *36*, 3103.

SCHEME 9



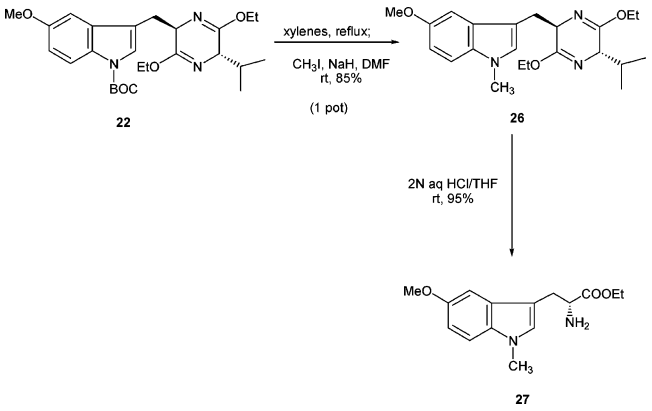
Enantiospecific Synthesis of 5-Methoxytryptophans *via* the Schöllkopf Chiral Auxiliary. The approach to the preparation of the desired 5-methoxylated D(+)-tryptophans for indole alkaloid synthesis was based on the regiospecific bromination at C(3) of the N(1) BOC-protected derivative of 3-methylindole **18a**. Since the BOC group can be removed under different conditions, in comparison to the benzenesulfonyl group, this extended the use of the Schöllkopf/Fischer-indole protocol employed previously.[68] In practice, 5-methoxy-3-methylindole **17** was protected with the BOC group at the N(1) position to afford 1-*tert*-butyloxycarbonyl-3-methylindole **18a**. With indole **18a** in hand, the AIBN-initiated regiospecific bromination[67] of 3-methyl-indole **18a** at the 3-methyl group was accomplished by using NBS as the brominating agent in cyclohexane or carbon tetrachloride (Scheme 8). The 3-bromomethylindole **19a** was very labile and not stable to chromatographic purification and could not be readily crystallized. In most cases it was dried and used in the next step as crude material without further purification (see the Experimental Section for details). However, it was also converted into the 3-hydroxymethylindole (see the Experimental Section) for characterization. The crude 3-bromoalkylindole **19a** was treated with the anion derived from the Schöllkopf chiral auxiliary **21** at −78 °C to afford a single diastereomer **22** (Scheme 8) in 93% yield.

As illustrated in Scheme 8, the pyrazine chiral auxiliary was stable to strongly alkaline conditions, consequently it served as an excellent protecting group for the amino acid ester function. The pyrazine group (see Scheme 9) could be removed under acidic conditions to provide the BOC-protected 5-methoxy-D-tryptophan ethyl ester **23** in high yield. In contrast, the BOC could be removed initially (xylenes, reflux) to provide intermediate **24**, which could be hydrolyzed to afford 5-methoxy-D-tryptophan ethyl ester **25**. Introduction of the methyl group at N(1) was carried out by removal of the BOC protecting group under thermal conditions and N_a-methylation in a one-pot process (Scheme 10) to provide N_a-methyl D-(+)-tryptophan ethyl ester **27**. In this fashion N_a-H-5-methoxy- and N_a-methyl- 5-methoxytryptophans were available in optically active form for the total synthesis of indole alkaloids.

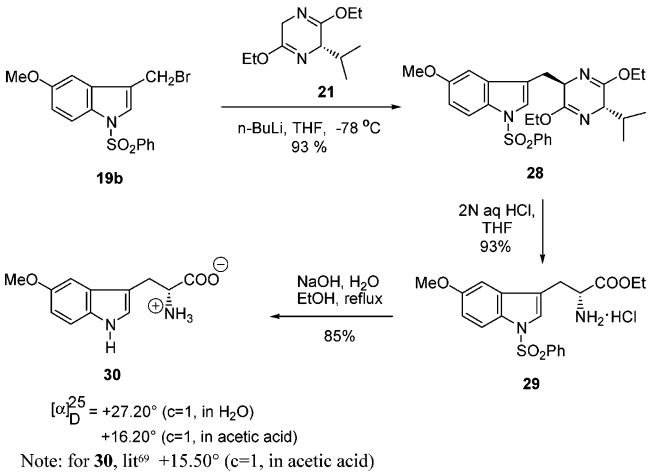
As illustrated in Scheme 11, hydrolysis of the tryptophan ethyl ester **29** provided 5-methoxy-D-(+)-tryp-

(68) Allen, M. S.; Hamaker, L. K.; La Loggia, A. J.; Cook, J. M. *Synth. Commun.* **1992**, *22*, 2077.

SCHEME 10



SCHEME 11



tophan **30**. The optical rotation of **30** in acetic acid was in good agreement with the reported value.[69] The racemization of the chiral center of the amino acid **30** was not observed under the conditions of hydrolysis (8 h). Treatment of **29** under the same conditions of hydrolysis for an additional 72 h returned the same amino acid **30** with the same optical rotation observed on hydrolysis of **29** for only 8 h. This provided an enantiospecific entry into either 5-methoxy-D-(+)- or L-(−)-tryptophan and their derivatives.[70,71]

Studies of the Asymmetric Pictet−Spengler Reaction and Its Application to Ring-A Oxygenated D-(+)-Tryptophan Systems. With 5-methoxylated D-(+)-tryptophans **23**, **25**, and **27** in hand (Schemes 9 and 10), the conversion of D-tryptophan **27** into the natural alkaloids turned to the enantiospecific trans transfer of chirality observed in the asymmetric Pictet−Spengler reaction.[40,72]

As illustrated in Scheme 12, tryptophan **27** was treated with benzaldehyde at 0 °C, followed by sodium borohydride reduction (at −5 °C) to afford N_b-benzyl-N_a-methyltryptophan ethyl ester **31** (greater than 98% ee) in 92% yield. The optical purity of **31** was verified by ^{1}H NMR spectroscopy with the chiral shift reagent {tris-[3-(trifluoro-methylhydroxymethylene)-(+)-camphorate]-europium(III)} employed in the work of Zhang on the parent tetracyclic ketone **7a**.[26] Racemic material of **31** was obtained from the intended racemization of the benzylation process by warming the imine formation/reduction step to room temperature. This process provided a racemic sample of **31** as a control for the chiral shift experiment. The enantiomeric purity of **31** proved to be greater than 98% with use of this NMR technique. The benzylation of the N_b-nitrogen function could be carried out without racemization if care was taken to keep the imine intermediate cold during the reduction and to limit the reaction time (3 h). At the very beginning, tryptophan **27** was treated with benzaldehyde at room temperature and the tetrahydro-β-carbolines **35a**,**b** were also obtained. Activation of the indole ring was affected by the 5-methoxyl group and the Pictet−Spengler cyclization of the intermediate N_b-benzylidene imine **34** took place at 25 °C (Scheme 13).[73] This problem was overcome by lowering the reaction temperature to 0 °C. Under these conditions, only N_b-benzyl derivative **31** was observed after sodium borohydride reduction and in excellent yield.

If the Pictet−Spengler cyclization was carried out in CH_2Cl_2/TFA, decomposition of the 5-methoxyindole **31** took place, which resulted in a low yield of trans diester **33** (<40%). However, since it was known that the trans diester **33** was the thermodynamically more stable isomer, advantage could be taken of the carbocation-mediated isomerization of the cis isomer into the desired trans isomer **33**.[38,39,74] The Pictet−Spengler reaction was carried out under modified conditions. N_b-Benzyltryptophan **31** was stirred with aldehyde **32** in acetic acid and CH_2Cl_2, which provided a mixture of both diastereomers. TFA was then added to epimerize at C(1) all of the cis isomer into the desired trans diester **33**. The stereochemistry of the trans diester **33** was later confirmed by single-crystal X-ray analysis (Figure 3).[75]

Synthesis of Ring-A Oxygenated Tetracyclic Ketones and Their Application to the Total Synthesis of Ring-A Oxygenated Indole Alkaloids. When trans diester **33** was treated with at least 2 equiv of sodium hydride in the presence of excess methanol (Scheme 13), a regiospecific Dieckmann cyclization occurred as developed by Zhang.[39] The first equivalent of sodium hydride epimerized the stereocenter at position C(3) of **33** and the second equivalent was employed in the Dieckmann condensation. The base-mediated epimerization occurred only at C(3) in agreement with previous results.[23] The best results for this process were realized when 3 equiv of NaH and 3.5 equiv of CH_3OH were employed in refluxing toluene. Hydrolysis of the β-ketoester **36** and decarboxylation under basic conditions were then achieved in one step to provide the ring-A oxygenated tetracyclic ketone **37** (Scheme 13). Furthermore, N_a-H tetracyclic ketone **44** was also prepared *via* this approach as the template for the synthesis of ring-A oxygenated N_a-H indole alkaloids including sarpagine **1**.

(69) Porter, J.; Dykert, J.; Rivier, J. *Int. J. Peptide Protein Res.* **1987**, *30*, 13.
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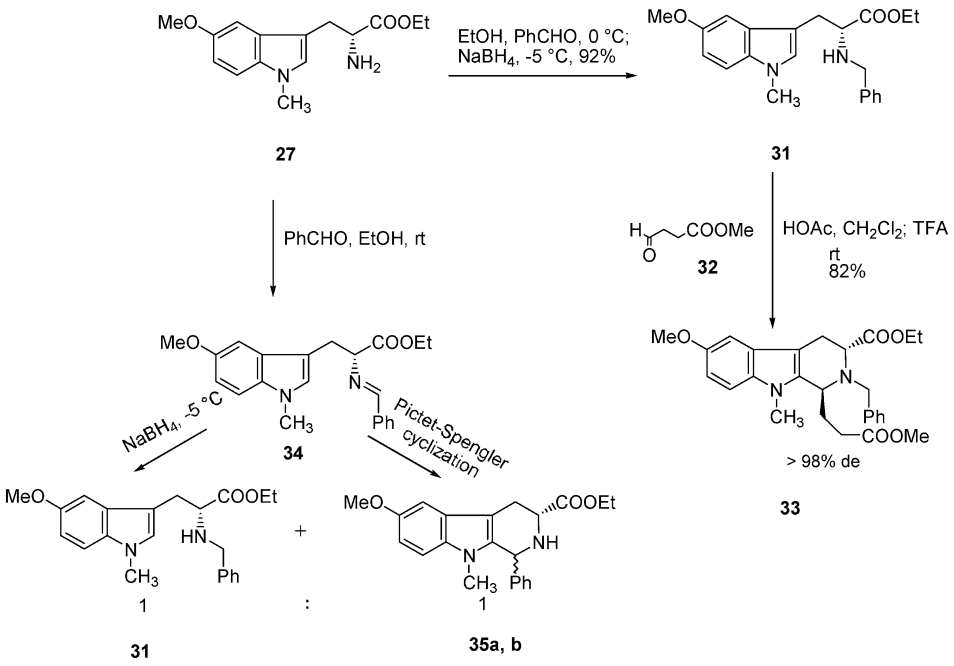
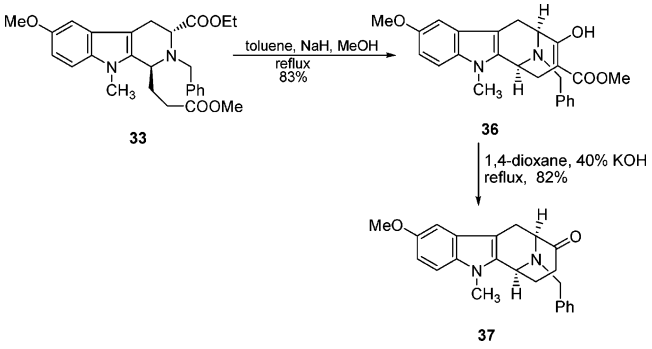
(73) Zhao, S. Ph.D. Thesis, University of Wisconsin−Milwaukee, 2001.
(74) Cox, E. D.; Hamaker, L. K.; Li, J.; Yu, P.; Czerwinski, K. M.; Deng, L.; Bennett, D. W.; Cook, J. M.; Watson, W. H.; Krawiec, M. *J. Org. Chem.* **1997**, *62*, 44.
(75) Flippen-Anderson, J.; Deschamps, J. Laboratory for the Structure of Matter, Naval Research Laboratory, Washington, DC.

SCHEME 12



SCHEME 13



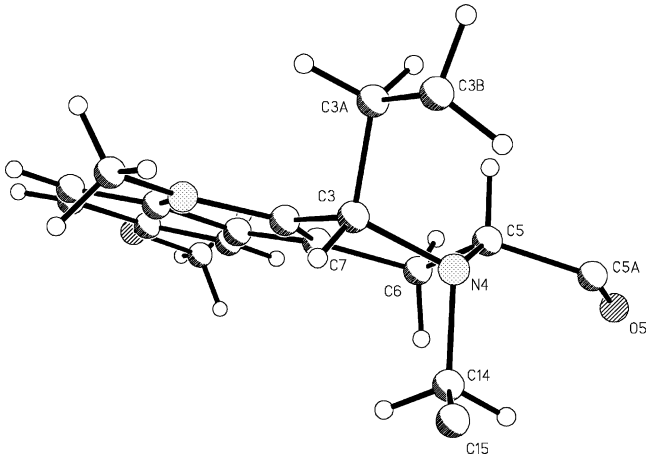


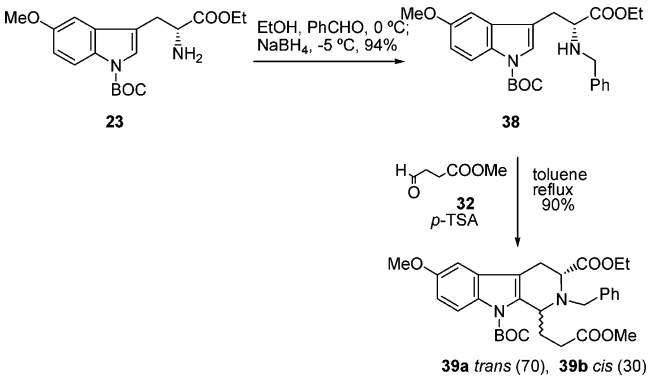
FIGURE 3. X-ray crystal structure (some of the atoms have been removed for clarity) of trans diester **33** showing labeling of the non-hydrogen atoms. Thermal ellipsoids are at the 20% probability level, and hydrogen atoms are shown as small balls of an arbitrary radius. It is clear the C3−C3A and N4−C14 bonds are axial while the C5−C5A bond is equatorial.

As illustrated in Scheme 14, N_a-BOC-protected tryptophan **23** was treated with benzaldehyde at room temperature, followed by sodium borohydride reduction (at −5 °C) to afford N_a-BOC-protected N_b-benzyltryptophan ethyl ester **38** in 94% yield. The N_a-BOC-protected tryptophan ethyl ester **38** was then stirred with methyl 3-formylpropionate **32** in the presence of *p*-TSA in refluxing toluene. This process provided both the trans and cis diastereomers in a ratio of 7:3 (trans:cis). The structures of these isomers were assigned by 2D NMR spectroscopy as well as by analogy to other systems of known stereochemistry.[38,39,74] Because of the presence of the N_a-BOC group, the cis isomer **39b** cannot be converted into the desired trans isomer **39a**. Presumably, electron withdrawal by the BOC group decreased the stability of the carbocationic intermediate **40** (Scheme 15), consequently the C(1)−N(2) bond cleavage/isomerization does not occur.

An alternate route to **44** was then explored (Scheme 16). The N_a-BOC-substituted tryptophan ethyl ester **38** was stirred with acetal **41** in TFA and $CHCl_3$ at reflux to execute the Pictet−Spengler reaction. After the excess TFA and the solvent were removed, the crude reaction product was heated in toluene. This sequence provided a route to the trans lactam **42**, stereospecifically and in high yield. The Dieckmann condensation (10 equiv of NaH, 10 equiv of CH_3OH) with lactam **42** was then carried out, followed by hydrolysis to provide the N_a-H tetracyclic ketone **44**. This provided the required building block for the synthesis of N_a-H ring-A oxygenated (C-10) indole alkaloids.

In summary, the tetracyclic ketones **37** and **44** in the important ring-A oxygenated series were diastereospecifically prepared *via* the asymmetric Pictet−Spengler/Dieckmann protocol. In addition, this new process can be carried out on multihundred gram scale because the intermediate trans diester **33** and target tetracyclic ketones **37** and **44** can be purified by crystallization. Therefore, the tetracyclic ketones **37** and **44** can now be used as key templates for the synthesis of optically pure ring-A oxygenated sarpagine and macroline indole alka-

SCHEME 14



loids. This route can also be employed for the synthesis of ring-A oxygenated (C-10) L-tryptophan alkyl esters permitting entry into both antipodes of the natural products for biological screening.

The Enantiospecific, Stereospecific Total Synthesis of (+)-Majvinine (14) and (+)-10-Methoxyaffinisine (49). As illustrated in Scheme 17, the N_a-Me-N_b-benzyltetracyclic ketone **37** was stirred with palladium on carbon under 1 atm of hydrogen under acidic conditions, during which the benzyl group was successfully removed. The control of the acidity of the reaction solution was critical. Tetracyclic ketone **37** was first mixed with EtOH, after which a saturated solution of HCl/EtOH was added dropwise until ketone **37** completely dissolved. The solvent was then removed under reduced pressure. Dry EtOH was added into the flask to dissolve the HCl salt of **37**. This process eliminated the excess HCl. If too much HCl(g) were present, **37** would form a ketal on reaction with EtOH. Alkylation of the N_a-Me-N_b-H tetracyclic ketone **45** with *Z*-1-bromo-2-iodo-2-butene **46** under basic conditions smoothly took place to provide the N_a-Me-N_b-*Z*-2′-iodo-2′-butenyl tetracyclic ketone **47** in 80% yield. The *Z*-1-bromo-2-iodo-2-butene **46** had been synthesized in three steps by following the procedure of Corey[76] and Ensley.[77] This bromide **46** had been employed by several groups in the total syntheses of geissoschizine and strychnine.[20,55,56,78] The last step in Scheme 17 was the key intramolecular cyclization catalyzed by Pd^0. This was the first time, in a stereospecific manner, the *E*-ethylidene function has been incorporated into any of the ring-A alkoxylated indoles in the sarpagine/macroline series (81% yield).

With the key *E*-ethylidene intermediate **48** in hand, the next step rested on the simple transformation of ketone **48** to aldehyde **14** *via* addition of a Wittig reagent. This could be followed by hydrolysis to afford the natural product (+)-majvinine **14**. When **48** was stirred with $CH_3OCH_2PPh_3Cl$ in the presence of t-BuO^-K^+, the enol ether was formed. Since the C-17 aldehydo function in **14** was known to be in the more stable position, this material was directly hydrolyzed to provide the aldehyde **14** in 90% yield. Both transformations were carried out in the same reaction vessel. The spectral data (^{1}H NMR, IR, MS, mp) for this base were identical with those reported for the natural product.[79] The overall yield of the two steps was finally improved to 90% by a modified workup procedure. The troublesome $Ph_3P{=}O$ was removed by extracting the aqueous layer [**14** was present as the hydrochloride salt and still soluble in H_2O (before neutralization)] with Et_2O after which basification/extraction provided **14**. A second sarpagine alkaloid, (+)-10-methoxyaffinisine **49**, was synthesized in enantiospecific fashion by this route. The aldehyde **14** was reduced with sodium borohydride to provide (+)-10-methoxyaffinisine **49** in over 90% yield (Scheme 18). The spectral data (^{1}H NMR, ^{13}C NMR, IR, and MS) for (+)-10-methoxyaffinisine **49** were identical with those reported for the natural product and the optical rotations (±2°) were within experimental error {$[\alpha]^{26}_D$ +78 (*c* 0.2, $CHCl_3$); lit.[80] $[\alpha]_D$ +75 (*c* 0.62, $CHCl_3$)}. The stereochemistry of (+)-majvinine **14** was later confirmed by single-crystal X-ray analysis (Figure 4).[75]

This represented the first total synthesis of ring-A alkoxylated indole alkaloids in the sarpagine/macroline series. It is noteworthy for it is both enantiospecific and stereospecific. The stereocontrolled intramolecular palladium-mediated cross-coupling reaction provided the first stereospecific solution to the problem of the stereochemistry of the C(19)−C(20) *E*-ethylidene function in the ring-A oxygenated sarpagine indole alkaloids. The synthesis of **14** (from tryptophan ethyl ester **27**) was accomplished in 10 steps (8 reaction vessels) and in 28% overall yield.

The alkaloid (+)-majvinine **14** was then employed for the synthesis of (+)-N_a-methylsarpagine **8**. As illustrated in Scheme 18, (+)-majvinine **14** was treated with 6 equiv of dry BBr_3 in CH_2Cl_2 at −78 °C for 1 h, after which the solution was allowed to warm to room temperature and stirring continued for 2 h. The reaction mixture was degassed carefully before adding the BBr_3 because the phenol **50** would readily undergo air (O_2) oxidation. After the reaction was completed on analysis by TLC (silica gel), cold, concentrated aq NH_4OH was added to adjust the pH to 8. The mixture was then admixed with silica gel (see the Experimental Section) and directly passed through a wash column to provide **50**. This compound was then treated (without further purification) with sodium borohydride in ethanol. Reduction of aldehyde **50** by sodium borohydride in EtOH provided N_a-methylsarpagine **8** in 90% yield. The spectral data and optical rotation for **8** were in excellent agreement with the natural product.

In agreement with the doubly convergent approach to these bisindole alkaloids, the total synthesis of (+)-macroline **2** (from D-tryptophan) or the antipode [(−)-macroline (from L-tryptophan)] can be accomplished now in 12.3% overall yield *via* the improved route of Liu.[27,28] The key features of this route will be presented here.[23,27,28,81] The ketone **51**, available in 27% overall yield from the asymmetric Pictet−Spengler reaction and enolate driven Pd^0-mediated coupling process, was converted into the desired aldehyde **52** *via* the Wittig/hydrolysis process (illustrated in Scheme 19). This aldehyde **52** was

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(77) Ensley, H. E.; Buescher, R. R.; Lee, K. *J. Org. Chem.* **1982**, *47*, 404.
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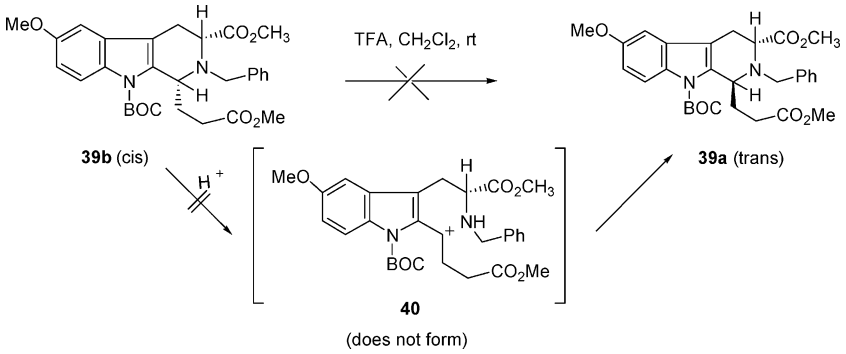
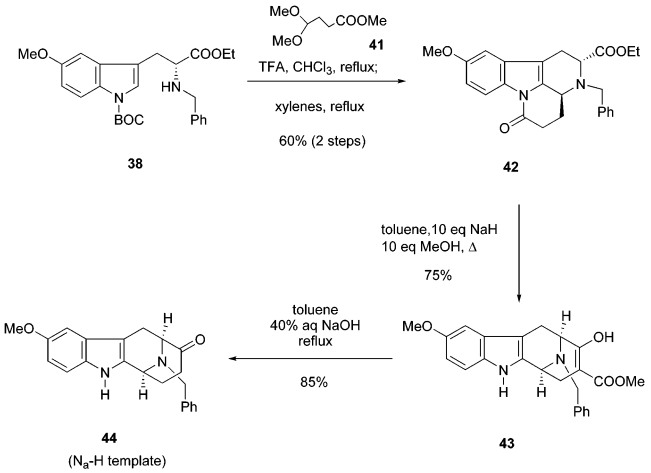
(80) Kam, T. S.; Iek, I. H.; Choo, Y. M. *Phytochemistry* **1999**, *51*, 839.
(81) Liu, X.; Deschamps, J. R.; Cook, J. M. *Org. Lett.* **2002**, *4*, 3339.

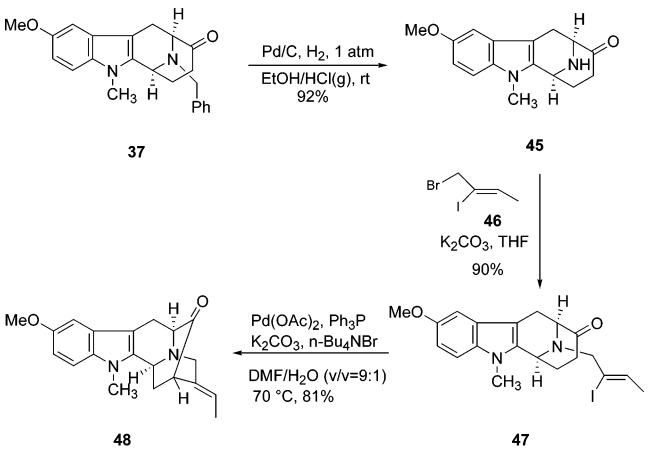
SCHEME 15



SCHEME 16

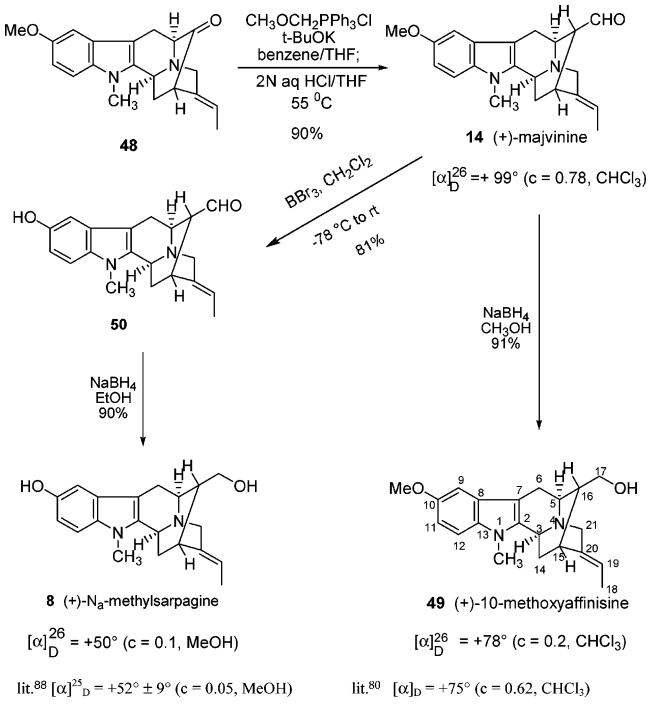


SCHEME 17



reduced with sodium borohydride and the alcohol that resulted was converted into a triisopropylsilyl ether **53** with imidazole serving as the base. The triisopropylsilyl ether **53** was then subjected to the conditions of hydroboration (9 equiv of BH_3·THF, rt, 3 h; H_2O_2/OH^- oxidation) to provide **54** obtained as a mixture of the two N_b-borane complexes. The alcohol that resulted was converted into the methyl ketone by a Swern oxidation followed by treatment with 1 equiv of HCl (1 N aq) to completely cleave the N_b-borane moieties to provide ketone **55** as the sole product (76% overall yield from **54**). Methylation of **55** with methyl iodide followed by removal of the silyl group with TBAF furnished macroline **2** in excellent yield.

SCHEME 18



Since the enantiospecfic total synthesis of macroline **2** had been accomplished by Bi *et al.* and the enantiomer completed by Liu,[19,23,82] this work culminated in the total synthesis of macralstonidine **9**, the first *Alstonia* bisindole to fall to total synthesis (see Scheme 1).

Conclusion

The macroline/sarpagine related ring-A oxygenated indole alkaloids, as well as the corresponding bisindoles, exhibit important biological activity.[10,83−86] Furthermore, bisindoles are of special significance because they exhibit more potent antimalarial activity than the monomeric units which comprise them.[10,87] The first enantiospecific total synthesis of the *Alstonia* bisindole alkaloid macra-

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(85) Harada, M.; Ozaki, Y. *Chem. Pharm. Bull.* **1976**, *24*, 211.
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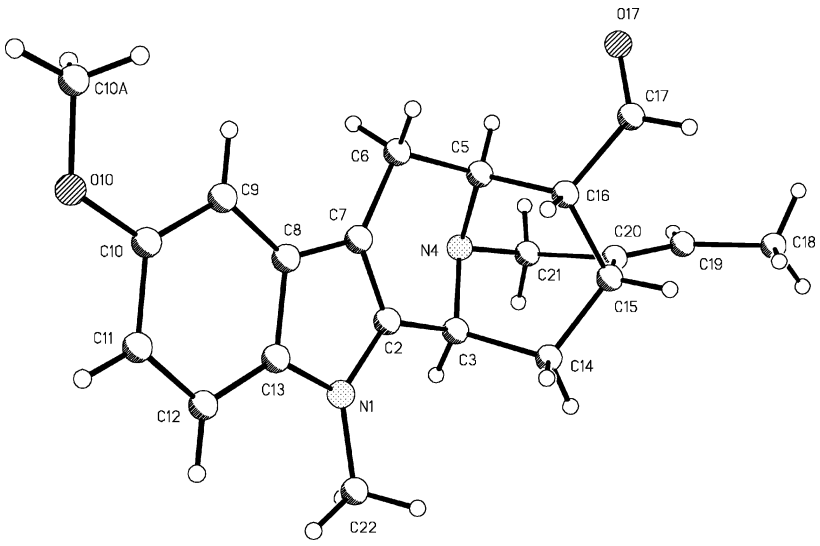
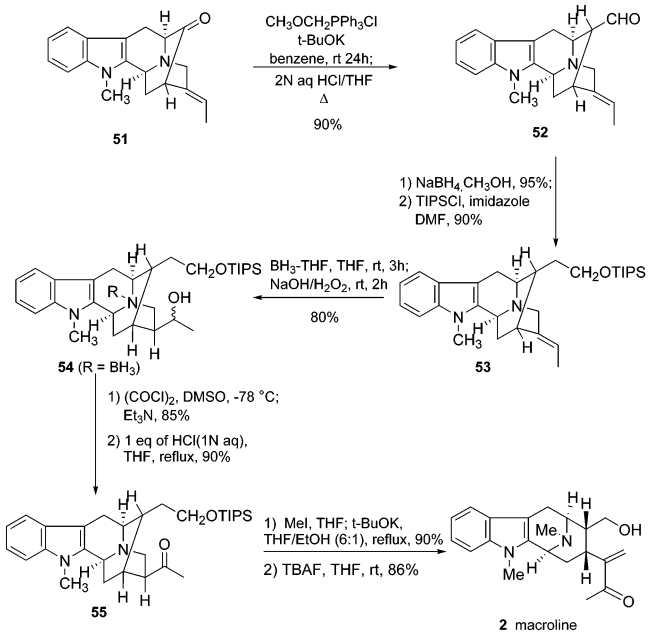


FIGURE 4. X-ray crystal structure of (+)-majvinine **14** showing labeling of the non-hydrogen atoms. Thermal ellipsoids are at the 20% probability level, and hydrogen atoms are shown as small balls of an arbitrary radius.

SCHEME 19



lstonidine **9** has been accomplished. Since only small amounts of **9** have been isolated from plants, this alkaloid has not been evaluated in regard to biological activity to the authors' knowledge. The route described above could be employed to prepare **9** for screening as well as its enantiomers. This work also culminated in the first regiospecifc, enantiospecific, stereospecific total synthesis of the ring-A oxygenated indole alkaloids (+)-majvinine **14**, (+)-10-methoxyaffinisine **49**, and (+)-N_a-methylsarpagine **8** in the sarpagine/macroline series. In this approach the key template, N_b-benzyltetracyclic ketone **37**, as well as **44**, was synthesized in stereospecific fashion by the asymmetric Pictet−Spengler reaction and a stereocontrolled Dieckmann cyclization. An intramolecular palladium (enolate-mediated) coupling reaction was employed to introduce the C(19)−C(20) *E*-ethylidene function in the ring-A oxygenated sarpagine alkaloids in stereospecific fashion, as well as macroline **2**. The total synthesis of (+)-majvinine **14** was completed (from 5-methoxytryptophan **27**) in eight reaction vessels and an overall yield of 27.5%. Many macroline/sarpagine related ring-A oxygenated indole alkaloids have not fallen to total synthesis to date due to the difficulty of incorporating an oxygen moiety regiospecifically into ring-A in the latter stages of the synthetic route. Hence, the synthetic route developed here can be employed for the total synthesis of a number of macroline/sarpagine related ring-A oxygenated indole alkaloids in both the N_a-Me and N_a-H series, as well as bisindoles. The total synthesis of the bisindole described here is doubly convergent for both N_a-methylsarpagine **8** and (+)-macroline **2** were prepared *via* the same stereospecific chemical processes including the asymmetric Pictet−Spengler reaction and the enolate-driven Pd°-coupling process.

Experimental Section

General Method. Reagent and solvent purification, workup procedures, and analyses were in general performed as described previously.[33]

Ethyl 5-Methoxy-3-methylindole-2-carboxylate (16). To a mixture of *p*-anisidine **15** (91 g, 0.74 mol), concentrated aq HCl (185 mL), and water (350 mL) was added a solution of $NaNO_2$ [(53.6 g, 0.77 mol) in 100 mL of water] in a dropwise manner at −5 °C. After addition, the mixture was stirred at 0 °C for 15 min and brought to pH 3−4 by addition of sodium acetate (60 g, 0.74 mol). In a separate flask, a solution of ethyl α-ethylacetoacetate (100 g, 0.64 mol) in ethanol (500 mL) at 0 °C was treated with an aq solution of KOH (0.64 mol in 50 mL of H_2O), followed by addition of ice (1000 g). The diazonium salt prepared above was immediately added to this alkaline solution. The mixture was then adjusted to pH 5−6 and stirred at 0 °C for 3 h. After the solution was kept for a further 12 h at 4 °C, the mixture was extracted with ethyl acetate (4 × 200 mL). The combined extracts were washed with brine and dried ($MgSO_4$). Most of the solvent was removed under reduced pressure and the liquid residue was added dropwise to a solution of 14.5% ethanolic HCl previously heated to 70 °C. This reaction is exothermic! After addition, the mixture was held at 78 °C for 2 h. The solvent was removed under reduced pressure and the residue was treated with water (100 mL) and CH_2Cl_2 (300 mL). The aq layer was extracted with CH_2Cl_2 (3

× 100 mL) and the combined organic layers were washed with brine and dried (Na_2SO_4). Purification on a short wash column (silica gel, ethyl acetate/hexane, 1:3) gave **16** as a white solid (110 g, 74%): mp 151.0−152.5 °C (lit.[70] mp 151−152 °C); IR (KBr) 3331, 2929, 1668 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.40 (t, 3H, J = 7.2 Hz), 2.61 (s, 3H), 3.90 (5, 3H), 4.42 (q, 2H, J = 7.3 Hz), 7.01 (m, 2H), 7.30 (d, 1H, J = 7.6 Hz). EIMS *m/e* (rel intensity) 233 (M^+, 37 0.8), 187 (100), 172 (20.7), 140 (10). Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.84; H, 6.48; N, 6.02.

Ethyl 5-Methoxy-3-methylindole-2-carboxylate (16), Large Scale. A solution (1300 mL) of concentrated aq HCl was diluted to 3000 mL. This solution was then used to dissolve *p*-anisidine **15** (616 g, 5 mol). After the anisidine was dissolved, the acidic solution was transferred into a 12-L, three-neck flask, cooled in an ice−water bath, while sodium nitrite (414 g, 6 mol) was dissolved in 1000 mL of H_2O, then cooled in an ice bath to ∼0 °C. This solution (sodium nitrite) was then placed in an addition funnel, and added into the acidic anisidine solution slowly at 0 °C with stirring (overhead stir). After the addition, the solution was stirred for 3 h at 0 °C. The solution was brought to pH 3−4 by addition of sodium acetate (328 g, 4 mol) in portions.

KOH (85% pellet, 365 g, 5.5 mol) was dissolved in 500 mL of H_2O, then cooled to 0 °C. In a 22-L, three-necked flask, ice (5000 g) was added into EtOH (5000 mL), after which ethyl α-ethylacetoacetate (869 g, 5.5 mol) was added to this ice cold alcohol solution. The mixture was stirred with an overhead stirrer, after which the above cold KOH solution was added quickly. The mixture was stirred for 15 min, after which the diazonium salt solution was poured in. The whole mixture was kept at 0 °C with stirring overnight. The mixture was kept at 0 °C for another 10 h before $CHCl_3$ was used to extract the solution. The black organic layer was washed with H_2O, and then dried (Na_2SO_4). The solvent was removed under reduced pressure.

A 3.3-L sample of 3 N HCl in EtOH was preheated to 65 °C in a 5-L flask equipped with an overhead stirrer, reflux condenser, and an addition funnel. The above black residue was added at a rate rapid enough to keep the solution at reflux due to the exotherm. [**Caution**: At first, the reaction is slow, consequently do not add too much hydrazone, otherwise this will effect a very fast reaction and blow out the solution.] After finishing the addition, turn on the heating mantle again to keep the mixture at reflux for 30 min more. Cease heating at this point and put the flask in the cold room (2−4 °C) overnight. The solid that formed was filtered and washed with H_2O until pH 6−7. The filtrate was collected and the solvent was removed under reduced pressure. The residue was treated with H_2O (500 mL) and CH_2Cl_2 (2000 mL). The aq layer was extracted with CH_2Cl_2 (3 × 500 mL) and the combined organic layers were washed with brine and dried (Na_2SO_4). After the solvent was removed under reduced pressure, the solid residue was combined with the above solid that had been filtered from the reaction mixture. Purification by recrystallization provided a white solid (864 g, 74%). The physical and spectral properties of **16** were identical with those reported immediately above.

5-Methoxy-3-methylindole (17). A mixture of **16** (72 g, 0.3 mol), EtOH (150 mL), KOH pellets (85%, 60 g, 0.9 mol), and water (100 mL) was heated to reflux for 1 h. The volume was reduced to 100 mL under reduced pressure and brought to acidic pH with an aq solution of 3 N HCl. The precipitate that resulted was collected on a filter, washed with distilled water, and dried in a vacuum oven at 80 °C to afford 5-methoxy-3-methylindole-2-carboxylic acid as a white solid (61.5 g, 100%): mp 202−203 °C (lit.[70] mp 200−201 °C). This acid (59.5 g, 0.29 mol) was then heated to reflux in a well-stirred (mechanical stirrer) mixture of distilled quinoline (125 mL) and copper powder (2.5 g) under nitrogen for 2.5 h. The copper powder was removed by filtration, after which the filtrate was brought to pH 2−3 with an aq solution of 6 N HCl and the solution that resulted was extracted with diethyl ether (4 × 100 mL). The combined organic layers were washed with brine and dried ($MgSO_4$). The solvent was removed under reduced pressure to afford **17** as a brown solid (43.7 g, 93.6%): mp 68−69 °C (lit.[70] mp 66 °C); IR (KBr) 2930, 1609, 1380, 1218, 820 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.30 (s, 3H), 3.91 (s, 3H), 6.85 (dd, 1H, J = 8.8,2.5 Hz), 6.95 (s, 1H), 7.01 (d, 1H, J = 2.3 Hz), 7.25 (d, 1H, J = 8.8 Hz), 7.80 (br, 1H, D_2O exchangeable). Anal. Calcd: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.70; H, 6.78; N, 8.72.

5-Methoxy-3-methylindole (17), Large Scale. A mixture of **16** (481 g, 2.06 mol), EtOH (1000 mL), KOH pellets (85%, 401 g, 7.16 mol), and water (670 mL) was heated to reflux for 1 h. The volume was reduced to 670 mL under reduced pressure and brought to acidic pH with an aq solution of 3 N HCl. The precipitate that resulted was collected on a filter, washed with distilled water, and dried in a vacuum oven at 80 °C to afford 5-methoxy-3-methyl-indole-2-carboxylic acid as a white solid (398 g, 1.93 mol). This acid was then heated to 185 °C in a well-stirred (mechanical stirrer) mixture of quinoline (710 mL) and copper powder (17 g) under nitrogen for 2.5 h (monitored by TLC). The copper powder was removed by filtration, after which the filtrate was brought to pH 2−3 with an aq solution of 6 N HCl and the resulting solution was extracted with diethyl ether (4 × 650 mL). The combined organic layers were washed with brine and dried ($MgSO_4$). The solvent was removed under reduced pressure to afford **17** as a brown solid (246 g, 74%). The physical and spectral properties of **17** were identical with those reported immediately above.

1-*tert*-Butyloxycarbonyl-5-methoxy-3-methylindole (18a). A solution of 5-methoxy-3-methylindole **17** (384 g, 2.39 mol) in acetonitrile (3000 mL) under nitrogen was stirred at room temperature with di-*tert*-butyl dicarbonate (558 g, 2.49 mol) and DMAP (15 g, 0.12 mol). The resulting mixture was stirred at room temperature for 12 h and the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate (3000 mL), washed with an aq solution of 1 N HCl (2 × 900 mL) and brine (1500 mL), and dried (Na_2SO_4). After removal of the solvent under reduced pressure, the residue solidified to afford **18a** as a white solid (595 g, 95%): mp 58−60 °C; IR (KBr) 2974, 1721, 1452 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.67 (s, 9H), 2.23 (s, 3H), 3.87 (s, 3H), 6.92 (dd, 1H, J = 8.5, 2.6 Hz), 7.25 (s, IH), 7.33 (br, 1H), 7.98 (d, 1H, J = 8.4 Hz); EIMS *m/e* (rel intensity) 261 (M^+, 21.2), 205 (100.0), 161 (63.6), 146 (63.3). Anal. Calcd for $Cl_5H_{19}NO_3 \cdot {}^1/_4H_2O$: C, 67.92; H, 7.35; N, 5.28. Found: C, 68.12; H, 7.17; N, 5.26.

1-Benzenesulfonyl-5-methoxy-3-methylindole (18b). A solution of **17** (39 g, 0.24 mol) in dry THF (800 mL) was treated at −78 °C with *n*-butyllithium (2.5 M in hexane, 107 mL, 0.266 mol) under nitrogen. The mixture was stirred at −78 °C for 20 min and then allowed to slowly warm to room temperature. After 2 h, a clear solution was obtained, which was cooled to −78 °C and treated with benzenesulfonyl chloride (36 mL, 0.28 mol). The reaction mixture was stirred at −78 °C for 30 min and then at room temperature for 4 h. The solvent was removed under reduced pressure to give a yellow solid that was recrystallized from a mixture of ethyl acetate and hexane to afford **18b** as a yellow solid (68 g, 94%): mp 137−138 °C; IR (KBr) 3100, 2924, 1609 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.20 (s, 3H), 3.80 (s, 3H), 6.88 (d, 1H, J = 2.3 Hz), 6.92 (dd, 1H, J = 9.0, 2.4 Hz), 7.27 (s, 1H), 7.4 (t, 2H, J = 7.2 Hz), 7.50 (d, 1H, J = 7.2 Hz), 7.85 (m, 3H). Anal. Calcd for $C_{16}H_{15}NSO_3$: C, 63.77; H, 5.02; N, 4.65. Found: C, 63.54; H, 4.98; N, 4.32.

1-*tert*-Butyloxycarbonyl-3-bromomethyl-5-methoxyindole (19a). To a boiling solution of 1-*tert*-butyloxycarbonyl-5-methoxy-3-methylindole **18a** (50 g, 0.192 mol) in CCl_4 (4000 mL) was added a mixture of *N*-bromosuccinimide (38 g, 0.211 mol) and AIBN (500 mg) in one portion. After 2 min, another portion of AIBN (350 mg) was added. The mixture was heated to reflux for 40 min. The succinimide was removed by filtration and washed with CCl_4 (2 × 150 mL). The solvent was removed

under reduced pressure to afford 3-bromo-methylindole **19a** as a brown oil (64 g, 87%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.66 (s, 9H), 3.89 (s, 3H), 4.66 (s, 2H), 6.97 (dd, 1H, J = 9.1, 2.6 Hz), 7.12 (d, 1H, J = 2.5 Hz), 7.13 (s, 1H), 8.04 (d, 1H, J = 8.9 Hz). EIMS *m/e* 341 (M^+, 14), 339 (M^+, 15), 283 (10), 238 (10), 204 (70), 160 (100), 144 (20). 3-Bromomethylindole **19a** is very labile and could not be purified by chromatography or distillation. It was characterized by converting 3-bromomethylindole **19a** into 3-hydroxymethylindole as follows. A solution of 3-bromomethylindole **19a** (100 mg) in a mixture of THF (5 mL) and water (5 mL) was treated with a saturated aq solution of $NaHCO_3$ (2 mL). The mixture was stirred for 30 min and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine and dried (Na_2SO_4). After removal of solvent under reduced pressure, purification of the residue by flash chromatography (silica gel, EtOAc) afforded 1-*tert*-butyloxycarbonyl-3-hydroxymethyl-5-methoxyindole as white crystals: mp 145−146 °C; IR (KBr) 3138, 2931, 1720, 1478 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.52 (t, 1H, J = 5.7 Hz, D_2O exchangeable), 1.66 (s, 9H), 3.87 (s, 3H), 4.81 (d, 2H, J = 5.7 Hz), 6.96 (dd, 1H, J = 9.0, 2.6 Hz), 7.12 (d, 1H, J = 2.4 Hz), 7.55 (5, 1H), 8.02 (d, 1H, J = 9.0 Hz); EIMS *m/e* 277 (M^+, 18.7), 221 (100.0), 177 (29.4), 160 (84.8), 133 (42.4). Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.98; H, 6.86; N 5.05. Found: C, 64.81; H, 7.00; N, 5.00. The crude product of 3-bromomethylindole **19a** was flash evaporated under reduced pressure with dry THF three times and used in the next step without further purification.

CCl_4 has been replaced by cyclohexane to carry out this bromination at reflux. This provided **19a** in the same yield.

1-Benzenesu1fonyl-3-bromomethyl-5-methoxyindole (19b). A solution of **18b** (35.5 g, 0.118 mol) in CCl_4 (500 mL) was heated to reflux after which a mixture of *N*-bromosuccinimide (22.2 g, 0.123 mol) and AIBN (500 mg) was carefully added portionwise over 5 min. After completion of the addition, three additional portions of AIBN (3 × 200 mg) were added every 30 min. After 3 h the mixture was cooled to room temperature and the succinimide that resulted was filtered off and washed with CCl_4 (3 × 50 mL). The solvent was removed under reduced pressure to yield a brown solid. A further purification by recrystallization from diethyl ether afforded **19b** as off-white crystals (37 g, 82.5%): mp 116−118 °C; IR (KBr) 3103, 2856, 1607 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.85 (s, 3H), 4.60 (s, 2H), 6.95 (dd, 1H, J = 8.7, 2.4 Hz), 7.05 (d, 1H, J = 2.3 Hz), 7.45 (t, 2H, J = 7.6 Hz), 7.55 (d, 1H, J = 8.0 Hz), 7.65 (s, 1H), 7.85 (m, 3H); EIMS *m/e* (rel intensity) 381 (M^+, 21.4), 379 (M^+, 18.3), 240 (51.1), 238 (53.4), 160 (39.1), 159 (100), 116 (77). Anal. Calcd for $C_{16}H_{14}BrNO_3S$: C, 50.54; H,3.71; N, 3.68. Found: C, 50.36; H, 3.47; N, 4.01.

1-*tert*-Butyloxycarbonyl-2-bromo-5-methoxy-3-methylindole (20a). A mixture of 3-methylindole **18a** (1.31 g, 5 mmol) and NBS (0.98 g, 5.5 mmol) in anhydrous CCl_4 (10 mL) was heated to reflux under nitrogen. When all of the NBS had been converted into succinimide, which floated on the surface of the CCl_4, the reaction solution was cooled to room temperature. The succinimide was removed by filtration and washed with CCl_4 (2 × 2 mL). The combined filtrates were concentrated under reduced pressure to afford **20a** as a brown solid (1.61 g, 95%). The residue was crystallized from a mixture of CCl_4 and hexane to afford 1-*tert*-butyloxycarbonyl-2-bromo-5-methoxy-3-methylindole (**20a**) as a white solid: mp 82−84 °C. ^{1}H NMR (250 MHz, DMSO-d_6) δ 1.62 (s, 9H), 2.18 (s, 3H), 3.79 (s, 3H), 6.91 (dd, 1H, J = 9.0, 2.5 Hz), 7.07 (d, 1H, J = 2.4 Hz), 7.38 (d, 1H, J = 9.1 Hz). EIMS *m/e* (rel intensity) 341 (M^+, 18.9), 339 (M^+, 21.0), 285 (27.4), 283 (28.6), 241 (92.1), 239 (100.0), 226 (38.3), 224 (43.4). Anal. Calcd for $C_{15}H_{18}BrNO_3$: C, 52.94; H, 5.29; N, 4.12. Found: C, 52.72; H, 5.41; N, 3.87.

1-Benzenesulfonyl-2-bromo-5-methoxy-3-methylindole (20b) was isolated as a byproduct with **19b** when a mixture of **18b**, *N*-bromosuccinimide, AIBN, and CCl_4 was heated to reflux without continuous addition of AIBN. In the absence of AIBN, a mixture of **18b**, *N*-bromosuccinimide, and CCl_4 was heated to reflux for 3 h and afforded exclusively **20b**: mp 148−150 °C; IR (KBr) 3064, 2839, 1609 cm^{-1}; ^{1}H NMR (250, MHz, $CDCl_3$) δ 2.15 (s, 3H), 3.85 (s, 3H), 6.80 (d, 1H, J = 2.1 Hz), 6.95 (dd, 1H, J = 8.6, 2.2 Hz), 7.40 (t, 2H, J = 8.2 Hz), 7.50 (t, 1H, J = 8.6 Hz), 7.81 (d, 2H, J = 8.5 Hz), 8.17 (d, 1H, J = 8.5 Hz); EIMS *m/e* 381 (M^+, 30.6), 379 (M^+, 26.4), 240 (74.0), 238 (71.9), 159 (100). Anal. Calcd for $C_{16}H_{14}BrNSO_3 \cdot {}^1/_2H_2O$: C, 49.37; H, 3.88; N, 3.60. Found: C, 49.20; H, 3.52; N, 3.34.

(3*R*,6*S*)-3-(1-*tert*-Butyloxycarbonyl-5-methoxy-3-indoyl)-methyl-3,6-di-hydro-6-isopropyl-2,5-diethoxypyrazine (22). To a solution of (3*S*)-3,6-di-hydro-6-isopropyl-2,5-diethoxypyrazine **21** (38.5 g, 0.182 mol) in dry THF (770 mL) under nitrogen was added n-BuLi (2.5 M in THF, 50.8 mL, 0.127 mol) dropwise at −78 °C. The resulting solution was stirred at −78 °C for 30 min and a solution of crude 3-bromomethylindole **19a** (64 g, about 0.17 mol) in THF (490 mL) was slowly added. The resulting mixture was stirred at −78 °C for 20 h, allowed to slowly warm to room temperature, and then treated with a saturated aq solution of $NaHCO_3$ (80 mL). The THF was removed under reduced pressure and the residue was partitioned between brine (240 mL) and CH_2Cl_2 (900 mL). The aq layer was washed with CH_2Cl_2 (3 × 170 mL). The combined organic layers were washed with brine (240 mL) and dried (Na_2SO_4). After removal of solvent under reduced pressure, the residue was purified by chromatography (hexane/ethyl acetate, 6/1) to afford **22** as a colorless oil (75 g, 93%) that was crystallized from hexane to yield **22** as white needles: mp 74−76 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.68 (d, 3H, J = 6.7 Hz), 0.96 (d, 3H, J = 6.9 Hz), 1.22 (t, 3H, J = 7.1 Hz), 1.32 (t, 3H, J = 7.1 Hz), 1.89 (s, 9H), 2.18 (m, 1H), 3.13 (m, 2H), 3.58 (t, 1H, J = 3.4 Hz), 3.85 (s, 3H), 4.02−4.20 (m, 4H), 4.28 (q, 1H, J = 8.8 and 4.6 Hz), 6.88 (dd, 1H, J = 9.0 and 2.6 Hz), 7.04 (d, 1H, J = 2.5 Hz), 7.34 (s, 1H), 7.97 (d, 1H, J = 8.9 Hz); ^{13}C NMR ($CDCl_3$) 14.27, 16.65, 28.26, 29.42, 31.74, 55.78, 56.16, 60.45, 60.53, 60.80, 82.82, 102.90, 112.42, 115.55, 116.68, 124.91, 130.05, 132.37, 149.61, 155.71, 162.31, 163.50; EIMS *m/e* (rel intensity) 471 (M^+, 5.4), 212 (33.9), 204 (49.7), 160 (100.0), 159 (25.3). Anal. Calcd for $C_{26}H_{37}N_3O_5$: C, 66.24; H, 7.86; N 8.92. Found: C, 66.18; H, 8.07; N, 8.84.

1-*tert*-Butyloxycarbonyl-5-methoxytryptophan Ethyl Ester (23). To a solution of pyrazine **22** (75 g, 0.16 mol) in THF (450 mL) at 0 °C was added an aq solution of 2 N HCl (380 mL). After the solution was allowed to warm to room temperature, the mixture was stirred for 40 min and then poured into a cold aq solution of NH_4OH to a final pH of ca. 9. The resulting solution was concentrated under reduced pressure and CH_2Cl_2 (1500 mL) was added. The aq layer was extracted with CH_2Cl_2 (2 × 570 mL). The combined organic layers were washed with brine and dried (Na_2SO_4). After removal of solvent under reduced pressure, valine ethyl ester, which resulted from hydrolysis of the chiral auxiliary, was removed by high-vacuum distillation. This valine ethyl ester could be reused. The residue that remained was purified by flash chromatography (ethyl acetate/hexane, 1/4, followed by ethyl acetate) to afford **23** (56 g, 96%) as a clear oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.22 (t, 3H, J = 7.1 Hz), 1.60 (br, 2H), 1.64 (s, 9H), 2.93 (dd, 1H, J = 14.4, 7.7 Hz), 3.18 (dd, 1H, J = 14.5, 5.1 Hz), 3.80 (m, 1H), 3.83 (5, 3H), 4.18 (q, 2H, J = 71. Hz), 6.91 (dd, 1H, J = 8.9, 2.5 Hz), 7.01 (d, 1H, J = 2.5 Hz), 7.43 (5, 1H), 7.98 (d, 1H, J = 8.7 Hz); EIMS *m/e* (rel intensity) 362 (M^+, 3.7), 204 (21.6), 161 (11.4), 160 (100.0), 103 (15.6). This material was employed in a later experiment.

D-(−)-5-Methoxytryptophan Ethyl Ester (25) and Its HCl Salt. A solution of pyrazine **22** (50 g, 0.106 mo1) in xylenes (2000 mL) was degassed and kept at reflux for 48 h. Examination of the reaction mixture by TLC (silica gel; hexane:EtOAc 5:1) indicated the disappearance of starting **22** and the appearance of a new component (lower R_f). After removal of solvent *in vacuo*, a small portion of the residue was purified by flash chromatography (silica gel; hexane:EtOAc 5:1)

to afford (3*R*,6*S*)-3-(5-methoxy-3-indoyl)-methyl-3,6-di-hydro-6-isopropyl-2,5-diethoxypyrazine **24**. ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.63 (d, 3H, J = 6.8 Hz), 0.92 (d, 3H, J = 6.9 Hz), 1.24 (t, 3H, J = 7.0 Hz), 1.34 (t, 3H, J = 7.1 Hz), 2.18 (m, 1H), 3.23 (d, 2H, J = 4.7 Hz), 3.36 (t, 1H, J = 3.4 Hz), 3.85 (s, 3H), 4.1 (m, 4H), 4.32 (q, 1H, J = 4.5 Hz), 6.79 (d, 1H, J = 8.7 Hz), 6.91 (d, 1H, J = 2.3 Hz), 7.11 (d, 1H, J = 2.4 Hz), 7.18 (d, 1H, J = 8.7 Hz), 7.86 (br, 1H, D_2O exchangeable). ^{13}C NMR ($CDCl_3$) δ 14.28, 14.41, 16.54, 19.02, 29.60, 31.36, 55.95, 56.81, 60.34, 60.42, 101.63, 111.32, 111.91, 123.56, 123.68, 129.97, 131.10, 153.90, 162.64, 163.34. This material was not further characterized but was hydrolyzed in the next step. The above crude residue was dissolved in THF (350 mL) and treated at 0 °C with an aq solution of 2 N HCl (300 mL). The mixture was allowed to warm to room temperature, after which it was stirred for 2 h and treated with a cold aq solution of NH_4OH (to pH ca. 9). The resulting solution was concentrated and extracted with EtOAc (3 × 600 mL). The combined organic layers were washed with brine and dried (Na_2SO_4). The solvent was removed under reduced pressure and the valine ethyl ester that resulted from hydrolysis of the chiral auxiliary was removed by Kugelrohr distillation *in vacuo*. Purification of the residue by flash chromatography (silica gel; $CHCl_3$/MeOH/Et_3N, 25/10/1) afforded **25** as an oil (24 g, 85% for the two steps), which was converted into the HCl salt in methanolic hydrogen chloride: mp 204−206 °C. $[\alpha]^{26}_D$ −4.4 (*c* 1, in methanol); ^{1}H NMR (free base, 250 MHz, $CDCl_3$) δ 1.22 (t, 3H, J = 7.2 Hz), 1.61 (br, 2H, D_2O exchangeable), 3.02 (dd, 1H, J = 14.5, 7.8 Hz), 3.24 (dd, 1H, J = 14.5, 5.0 Hz), 3.81 (dd, 1H, J = 7.7, 5.0 Hz), 3.82 (s, 3H), 4.18 (q, 2H, J = 7.2 Hz), 6.84 (dd, 1H, J = 8.8, 2.4 Hz), 7.02 (d, 1H, J = 2.3 Hz), 7.07 (d, 1H, J = 2.4 Hz), 7.22 (d, 1H, J = 8.8 Hz), 8.21 (br, 1H, D_2O exchangeable). EIMS (free base) *m/e* (rel intensity) 262 (M^+, 4.6), 189 (4.7), 161 (12.2), 160 (100.0), 145 (12.3). Anal. Calcd for $C_{14}H_{18}N_2O_3$·HCl: C, 56.29; H, 6.37; N 9.38. Found: C, 56.12; H, 6.62; N, 9.10.

5-Methoxy-1-methyl-(D)-tryptophan Ethyl Ester (27) and Its HCl Salt. A solution of pyrazine **22** (50 g, 0.106 mol) in toluene (2000 mL) was degassed and held at reflux for 48 h. Examination of the reaction mixture by TLC (silica gel; hexane:EtOAc 5:1) indicated the disappearance of starting **22** and the appearance of a new component (lower R_f). After removal of the solvent *in vacuo*, dry THF (1000 mL) was added to dissolve the residue. The NaH (5.1 g, 60% in mineral oil, 0.127 mol) was added slowly at 0 °C. The mixture was allowed to stir for 30 min, after which it was treated with methyl iodide (18.0 g, 0.127 mol) and stirred for 18 h. The THF was then removed under reduced pressure and the residue was partitioned between brine (150 mL) and CH_2Cl_2 (600 mL). The aq layer was washed with CH_2Cl_2 (3 × 120 mL). The combined organic layers were washed with brine (150 mL) and dried (Na_2SO_4). After removal of the solvent under reduced pressure, the residue was purified by passing it through a short wash column (silica gel; hexane:ethyl acetate 10:1) to afford (3*R*,6*S*)-3-(1-methyl-5-methoxy-3-indoyl)methyl-3,6-dihydro-6-isopropyl-2,5-diethoxy-pyrazine (**26**) as an oil (35 g, 85%): ^{1}H NMR ($CDCl_3$) δ 0.63 (d, 3H, J = 6.8 Hz), 0.93 (d, 3H, J = 6.9 Hz), 1.25 (t, 3H, J = 7.1 Hz), 1.31 (t, 3H, J = 7.0 Hz), 2.15 (m, 1H), 3.21 (d, 2H, J = 4.7 Hz), 3.33 (t, 1H, J = 3.3 Hz), 3.68 (s, 3H), 3.86 (s, 3H), 4.01−4.42 (m, 5H), 6.80 (dd, 1H, J = 8.8, 2.4 Hz), 6.92 (d, 1H, J = 2.3 Hz), 7.15 (d, 1H, J = 8.7 Hz), 7.18 (s, 1H). This material was not further characterized but was used in the next step. The solution of the above pyrazine in THF (200 mL) was stirred with an aq solution of 2 N HCl (180 mL). After the mixture was allowed to stir at room temperature for 40 min, the THF was removed under reduced pressure and the aq residue was brought to alkaline pH with cold aq NH_4OH at 0 °C. The solution was extracted with ethyl acetate (3 × 80 mL). The combined organic layers were washed with brine and dried (Na_2SO_4). The solvent was removed under reduced pressure and the valine ethyl ester that resulted from hydrolysis of the chiral auxiliary was removed by Kugelrohr distillation. The resulting residue was then purified by flash chromatography (ethyl acetate:hexane 1:4, followed by ethyl acetate) to afford **27** (24 g, 95%) as a clear oil: mp of (HCl salt), 207−209 °C; ^{1}H NMR ($CDCl_3$) δ 1.25 (t, 3H, J = 7.1 Hz), 1.65 (br, 2H), 2.98 (dd, 1H, J = 14.3, 7.6 Hz), 3.21 (dd, 1H, J = 14.4, 4.8 Hz), 3.71 (s, 3H), 3.76 (dd, 1H, J = 7.6, 5.0 Hz), 3.85 (s, 3H), 4.18 (q, 2H, J = 7.2 Hz), 6.86 (dd, 1H, J = 8.8, 2.4 Hz), 6.89 (s, 1H), 7.05 (d, 1H, J = 2.4 Hz), 7.17 (d, 1H, J = 8.9 Hz); EIMS *m/e* 276 (M^+, 5.2), 203 (6.0), 174 (100.0). Anal. Calcd for $C_{15}H_{21}N_2O_3Cl$·$^1/_2H_2O$: C, 56.07; H, 6.85; N, 8.72. Found: C, 56.05; H, 6.84; N, 9.05.

(3*R*,6*S*)-3-(1-Benzenesulfonyl-5-methoxy-3-indoyl)methyl-3,6-dihydro-6-isopropyl-2,5-diethoxypyrazine (28). To a solution of (3*S*)-isopropyl-2,5-di-ethoxypyrazine **21** (11.8 g, 0.056 mol) in THF (200 mL) was added *n*-butyllithium (2.5 M in hexane, 24 mL, 0.06 mol) at −78 °C under nitrogen. The resulting solution was stirred at −78 °C for 30 min after which a solution of **19b** (20.2 g, 0.053 mol) in THF (100 mL) under nitrogen was added dropwise. After the mixture was allowed to stir at −78 °C for 20 h, the reaction solution was slowly warmed to room temperature and treated with a saturated aq solution of $(NH_4)_2CO_3$ (50 mL). Most of the THF was removed under reduced pressure and the residue that resulted was treated with diethyl ether to furnish two layers. The organic layer was separated and the aq layer was extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed with brine and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford **28** as a brown oil (25.2 g, 93%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.60 (d, 3H, J = 6.9 Hz), 0.84 (d, 3H, J = 6.7 Hz), 1.20 (t, 3H, J = 7.1 Hz), 1.28 (t, 3H, J = 7.1 Hz), 2.10 (m, 1H), 3.1 (m, 2H), 3.20 (t, 1H, J = 3.4 Hz), 3.80 (s, 3H), 3.95 (m, 1H), 4.10 (m, 3H), 4.25 (q, 1H, J = 4.1 Hz), 6.85 (dd, 1H, J = 9.0, 2.4 Hz), 6.96 (d, 1H, J = 2.0 Hz), 7.38 (t, 2H, J = 8.0 Hz), 7.46 (t, 1H, J = 7.7 Hz), 7.75 (d, 2H, J = 8.6 Hz), 7.8 (d, 2H, J = 8.6 Hz); ^{13}C NMR ($CDCl_3$) δ 14.28, 14.33, 16.56, 18.95, 29.20, 31.55, 55.67, 60.53, 103.09, 113.16, 114.28, 119.08, 125.41, 126.51, 129.05, 129.70, 132.86, 133.34, 138.57, 156.34, 161.79, 163.59. EIMS *m/e* (rel intensity) 511 (M^+, 5.2), 301 (18.8), 300 (70.9), 211 (9.5), 160 (26.0), 159 (100), 144 (29.6). The pyrazine **28** was employed in the next step without further purification.

Ethyl 1-Benzenesulfonyl-5-methoxy-D-(−)-tryptophan Hydrochloride (29). A mixture of **28** (7.5 g, 0.0147 mol), THF (40 mL), and 2 N aq HCl (60 mL) was stirred at room temperature for 2 h. The resulting precipitate was collected by filtration to furnish the first crop of **29** as its hydrochloride salt. The filtrate was concentrated *in vacuo* and the precipitate that formed was collected to afford the second crop of **29** (combined yield 6.0 g, 93%): mp 243.5−245.0 °C; $[\alpha]^{26}_D$ −20.20 (*c* 1, in methanol); IR (KBr) 3465, 3423, 2832, 2400−3500, 1735, 1602 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.15 (t, 3H, J = 7.1 Hz), 1.65 (br, 3H), 2.90 (dd, 1H, J = 14.5, 7.3 Hz), 3.10 (dd, 1H, J = 14.5, 5.3 Hz), 3.70 (m, 1H), 3.75 (s, 3H), 4.10 (dq, 2H, J = 7.1, 1.8 Hz), 6.90 (dd, 1H, J = 8.1, 2.5 Hz), 6.95 (s, 1H), 7.35−7.6 (m, 4H), 7.85 (m, 3H). Anal. Calcd for $C_{20}H_{22}N_2SO_5$·HCl: C, 54.79; H, 5.25; N, 6.39. Found: C, 55.16; H, 5.41; N, 6.12.

5-Methoxy-D-(+)-tryptophan (30). A mixture of **29** (2.0 g, 0.0046 mol), H_2O (20 mL), EtOH (30 mL), and NaOH (1.8 g) was heated at reflux for 8 h. The ethanol was removed under reduced pressure. After the aq solution of residue that remained was brought to pH 2−3 with aq 6 N HCl and extracted with CH_2Cl_2 (3 × 50 mL) to remove byproducts, the water layer was then brought to a final pH of 6−7 with aq 3 N NaOH. The water was then removed under reduced pressure. The white solid residue that resulted was ground, placed on a pad of silica gel, and eluted with a solution of CH_3OH, $CHCl_3$, and concentrated aq NH_4OH (18.5:28.5:3 by volume). The solvent was concentrated to afford **30** as a white solid. Further crystallization of **30** in a mixture of ethanol and water afforded 5-methoxy-D-(+)-tryptophan **30** as white crystals (0.91 g, 85%): mp 238−240 °C; $[\alpha]^{25}_D$ +27.20 (*c* 1, in H_2O) and

+16.20 (*c* 1, in acetic acid); lit[69] $[\alpha]^{22}_D$ +15.5 (*c* 1, in acetic acid); IR (KBr) 3575, 3462, 3382, 3043, 2950, 2831, 1629, 1602 cm^{-1}; ^1H NMR (D_2O) δ 3.15−3.35 (m, 2H), 3.70 (s, 3H), 4.10 (t, IH, J = 5.8 Hz), 6.78 (dd, 1H, J = 8.9,2.3 Hz), 7.05 (d, 1H, J = 2.3 Hz), 7.15 (s, 1H), 7.27 (d, 1H, J = 8.9 Hz). EIMS *m/e* (rel intensity) 234 (M^+, 7.4), 161 (14.0), 160 (100), 145 (16.7), 117 (18.8). Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 61.53; H, 6.02; N, 11.96. Found: C, 61.15; H, 5.91; N, 11.89.

N_b-Benzyl-5-methoxy-1-methyl-(D)-tryptophan Ethyl Ester (31). To a solution of tryptophan ethyl ester **27** (20 g, 72 mmol) in dry ethanol (430 mL) at 0 °C under nitrogen was added benzaldehyde (9.2 g, 87 mmol). The solution was stirred at 0 °C for 5 h, cooled to −10 °C, and treated portionwise with $NaBH_4$ (3.3 g, 87 mmol) to keep the temperature below −5 °C (about 3 h). After the mixture was allowed to stir for an additional 1 h, ice water (15 mL) was added and the mixture was allowed to warm to room temperature. The ethanol was removed under reduced pressure and the aq residue was extracted with EtOAc (3 × 360 mL). The combined organic layers were washed with brine and dried (Na_2SO_4). After removal of the solvent under reduced pressure, the residue was purified by flash chromatography (ethyl acetate:hexane 3:1) to afford **31** as an oil (25 g, 94%). ^1H NMR ($CDCl_3$) δ 1.12 (t, 3H, J = 7.1 Hz), 1.82 (br, 2H), 3.10 (m, 2H), 3.61 (m, 2H), 3.67 (s, 3H), 3.79 (s, 3H), 3.81 (d, 1H, J = 15.5 Hz), 4.12 (q, 2H, J = 7.1 Hz), 6.83 (s, 1H), 6.87 (dd, 1H, J = 8.9, 2.4 Hz), 7.01 (d, 1H, J = 2.3 Hz), 7.18 (d, 1H, J = 8.9 Hz), 7.28 (m, 4H), 7.48 (m, 1H). CIMS *m/e* 367 ($M^+ + 1$, 100). This material was employed directly in the next step.

***trans*-N_b-Benzyl-3-(ethoxycarbonyl)-6-methoxy-9-methyltetrahydro-β-carboline-1-propionoic Acid Methyl Ester (33).** To a round-bottom flask (500 mL) that contained a solution of optically active N_a-methyl-N_b-benzyl-D-tryptophan ethyl ester **31** (20 g, 0.055 mol) in dry CH_2Cl_2 (120 mL) was added aldehyde **32** (9.6 g, 0.083 mol) and HOAc (6.6 g, 0.011 mol) at 0 °C. The resulting reaction mixture was stirred at room temperature overnight. TFA (9.5 g, 0.083 mol) was then added at 0 °C. The resulting reaction mixture was stirred at room temperature for 10 d and then cooled in an ice bath and brought to pH 8 with an aq solution of NH_4OH. The aq layer was separated and extracted with CH_2Cl_2 (3 × 200 mL). After the combined organic layers were washed with brine and dried (K_2CO_3), the solvent was removed under reduced pressure. The crude product was dissolved in EtOH on heating to reflux. The solution was then cooled and stored in the refrigerator for 1 day. Most of the trans diester **33** (18 g, 70%) precipitated out as white crystals. The mother liquor was concentrated under reduced pressure and the residue that resulted was purified by flash chromatography (silica gel, EtOAc:hexane 1:4) to provide additional **33** (3 g, 12%). The combined yield of **33** (21 g) was 82%: mp 155−156 °C; $[\alpha]^{23}_D$ −43.9 (*c* 1.13, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.39 (t, 3H, J = 7.1 Hz), 1.98 (m, 2H), 2.41 (dt, 1H, J = 17.5, 5.6 Hz), 2.57 (m, 1H), 3.08 (m, 2H), 3.40 (d, 1H, J = 13.2 Hz) 3.49 (s, 3H), 3.76 (s, 3H), 3.79 (m, 2H), 3.90 (s, 3H), 4.08 (dd, 1H, J = 10.8, 5.3 Hz), 4.32 (m, 2H), 6.9 (dd, 1H, J = 8.8, 2.4 Hz), 7.05 (d, 1H, J = 2.4 Hz), 7.21 (d, 1H, J = 8.8 Hz), 7.26−7.38 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.3, 20.3, 28.0, 29.6, 29.9, 51.3, 52.8, 53.4, 56.1, 56.2, 61.0, 100.4, 105.9, 109.6, 111.3, 126.8, 127.0, 128.2, 129.4, 132.8, 136.3, 139.2, 154.0, 172.9, 174.0. EIMS *m/e* 464 (M^+, 5.6), 378 (25.2), 377 (100.0), 213 (34.8). Anal. Calcd for $C_{27}H_{32}N_2O_5$: C, 69.81; H, 6.94; N, 6.03. Found: C, 69.87; H, 6.94; N, 5.98.

(6*S*,10*S*)-Methyl-2-methoxy-5-methyl-9-oxo-12-benzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indole-8-carboxylate (36). To a solution of trans diester **33** (5 g, 0.010 mol) in dry toluene (10 mL) under argon was added sodium hydride (1.2 g of 60% NaH in mineral oil, 0.030 mol). Dry methanol (1.0 mL) was added carefully to the above mixture (a large amount of H_2 was evolved at this point). The resulting mixture was stirred at room temperature for 0.5 h, and heated to reflux for an additional 4 h. The reaction mixture was then allowed to cool to room temperature, and treated with a saturated aq solution of $NaHCO_3$ (10 mL). The organic layer was separated, washed with brine, and dried (Na_2SO_4). After removal of solvent under reduced pressure, the residue was purified by flash chromatography (hexane/ethyl acetate, 3/1) to afford **36** (3.5 g, 83%) as a yellow solid: mp 165−166 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 2.31 (d, 1H, J = 15.4 Hz), 2.88 (m, 2H), 3.17 (m, 1H), 3.05 (s, 3H), 3.15 (5, 3H), 3.18−3.30 (m, 3H), 3.34 (s, 3H), 4.10 (m, 1H), 6.88 (d, 1H, J = 8.6 Hz), 7.01 (d, 1H, J = 2.1 Hz), 7.18 (d, 1H, J = 8.8 Hz), 7.31−7.50 (m, 5H), 11.97 (s, 1H); EIMS *m/e* 418 (M^+, 46.4), 303 (100.0), 271 (23.9), 213 (53.6), 212 (43.9), 197 (51.2), 170 (23.2). The β-ketoester **36** was used in the next step without further characterization.

(6*S*,10*S*)-Methyl-2-methoxy-5-methyl-9-oxo-12-benzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indole-8-carboxylate (37). A solution of β-ketoester **36** (4 g, 9.6 mmol) was dissolved in 1,4-dioxane (40 mL). The 40% aq KOH was then added to the above solution. The resulting reaction mixture was heated to reflux for 48 h. The solution was allowed to cool to room temperature and the 1,4-dioxane was removed under reduced pressure. The mixture that remained was extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was separated, washed with brine, and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was purified by flash chromatography (hexane/ethyl acetate, 3/1) to afford **37** as white crystals (2.8 g, 82%): mp 167−168 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.89 (m, 1H), 2.02 (m, 1H), 2.31−2.43 (m, 2H), 2.58 (d, 1H, J = 16.8 Hz), 3.15 (dd, 1H, J = 16.8, 6.8 Hz), 3.50 (s, 3H), 3.70 (m, 3H), 3.80 (s, 3H), 3.96 (t, 1H, J = 4 Hz), 6.82 (dd, 1H, J = 8.8, 2.4 Hz), 6.89 (d, 1H, J = 2.4 Hz), 7.14 (d, 1H, J = 8.8 Hz), 7.19−7.27 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.5, 29.4, 29.8, 34.4, 49.0, 56.0, 56.2, 64.9, 100.3, 105.3, 109.6, 111.4, 126.7, 127.3, 128.4, 128.6, 132.4, 133.8, 138.3, 154.1, 210.1; EIMS *m/e* 360 (M^+, 30.0), 304 (33.0), 303 (100.0), 212 (19.2), 197 (19.2). Anal. Calcd for $C_{23}H_{24}N_2O_2$: C, 76.64; H, 6.71; N, 7.77. Found: C, 76.66; H, 6.68; N, 7.76.

1-*tert*-Butyloxycarbonyl-N_b-benzyl-5-methoxytryptophan Ethyl Ester (38). To a solution of tryptophan ethyl ester **23** (2.5 g, 6.9 mmol) in ethanol (20 mL) was added benzaldehyde (0.81 g, 7.7 mmol). The resulting solution was stirred at room temperature for 4.5 h after which it was cooled to −10 °C, and then treated portionwise with $NaBH_4$ (0.2 g, 5.0 mmol). After the mixture was stirred for an additional 1 h, ice water (2 mL) was added and the mixture was allowed to warm to room temperature. The ethanol was removed under reduced pressure and the aq residue was extracted with CH_2Cl_2 (3 × 50 mL). 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 chromatography (hexane/ethyl acetate, 2/1) to afford **38** as an oil (2.9 g, 94%). ^1H NMR (300 MHz, $CDCl_3$) δ 1.17 (t, 3H, J = 7.1 Hz), 1.65 (s, 9H), 3.03 (m, 2H), 3.65 (m, 2H), 3.87 (s, 3H), 3.87 (d, 1H, J = 14.8), 4.11 (q, 2H, J = 7.1 Hz), 6.90 (dd, 1H, J = 8.9, 2.4 Hz), 6.95 (d, J = 2.4 Hz), 7.26 (m, 5H), 7.38 (d, 1H, J = 2.4 Hz), 7.98 (br, 1H). HRMS $C_{26}H_{32}N_2O_5$: calcd 452.2311, found 452.2276.

2-Ethoxycarbonyl-3-benzyl-9-methoxy-1,2,3,3a,4,5-hexahydrocanthin-6-one (42). To a round-bottom flask (250 mL) that contained a solution of tryptophan ethyl ester **38** (5 g, 11 mmol) in dry $CHCl_3$ (30 mL) was added methyl 4,4-dimethoxybutyrate **41** (2.67 g, 16.5 mmol) and TFA (3.76 g, 33 mmol) at 0 °C. The resulting reaction mixture was heated to reflux and then kept at reflux overnight. After removal of the $CHCl_3$ and excess TFA under reduced pressure, a mixture of xylenes (150 mL) was added into the same flask. The reaction mixture was degassed and then heated to reflux for 2 d. After removal of the solvent, CH_2Cl_2 (30 mL) was added into the flask. The mixture was then cooled in an ice bath and brought to pH 8 with an aq solution of NH_4OH. The aq layer was separated and extracted with CH_2Cl_2 (3 × 30 mL). After

the combined organic layers were washed with brine and dried (K_2CO_3), the solvent was removed under reduced pressure. The crude product was then purified by a wash column (silica gel, EtOAc:hexane 1:4) to provide only **42** (2.8 g, 60%). The base **42** is the trans diastereomer, which was determined by observing that the proton at C(1) underwent a long-range coupling with the α proton at C(4) by $^1H-^1H$ COSY experiments. **42**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.26 (t, 3H, J = 7.1 Hz), 1.79 (m, 1H), 2.41 (m, 1H), 2.81 (m, 2H), 2.96 (ddd, 1H, J = 16.4, 6.8, 2.8 Hz), 3.06 (dt, 1H, J = 16.4, 1.8 Hz), 3.85 (s, 3H), 3.88 (dd, 1H, J = 6.8, 1.3 Hz), 3.97 (d, 1H, J = 14.3 Hz), 4.07−4.22 (m, 2H), 4.26 (d, 1H, J = 14.3 Hz), 4.54 (dd, 1H, J = 10.1, 2.1 Hz), 6.87−6.91 (m, 2H), 7.25−7.38 (m, 5H), 8.25 (dd, 1H, J = 8.3, 0.83 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.21, 24.00, 28.31, 32.80, 52.00, 54.68, 55.62, 57.38, 60.44, 101.64, 110.81, 111.88, 116.74, 127.16, 128.20, 128.40, 129.50, 130.23, 135.59, 139.15, 156.73, 167.80, 172.44; EIMS *m/e* 418 (M^+, 18.8), 345 (20.8), 328 (19.8), 327 (100), 253 (12.5), 198 (13.5). HRMS $C_{25}H_{26}N_2O_4$: calcd 418.2018, found 418.2009.

(6*S*,10*S*)-Methyl-2-methoxy-9-oxo-12-benzyl-6,7,8,9,10,-11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indole-8-carboxylate (43). To a solution of trans lactam **42** (2 g, 4.8 mmol) in dry toluene (55 mL), which had been predried by azeotropic removal of H_2O by a DST (reflux for 3 h), was added sodium hydride (1.92 g of 60% NaH in mineral oil, 48 mmol) at room temperature. Dry methanol (3.3 mL) was added to the above mixture dropwise (a large amount of H_2 was evolved at this point) under Ar. The resulting mixture was stirred at room temperature for 0.5 h and heated to reflux for an additional 72 h until analysis by ^1H NMR spectroscopy indicated the disappearance of the trans lactam **42**. The reaction mixture was then poured into an ice-cold mixture of H_2O and CH_2Cl_2 (20 mL). The aq layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with brine and dried (K_2CO_3). The solvent was removed under reduced pressure and the mineral oil was separated by decantation. The resulting residue was purified by flash chromatography (silica gel, EtOAc:hexane 1:4) to provide the N_a-H, β-ketoester **43** (1.5 g, 75%). ^1H NMR (300 MHz, $CDCl_3$) δ 2.28 (d, 1H, J = 15.6), 2.80 (dd, 1H, J = 15.6, 5.5 Hz), 2.87 (dd, 1H, J = 16.0, 0.78 Hz), 3.14 (dd, 1H, J = 16.0, 5.9 Hz), 3.65 (s, 3H), 3.70 (d, 1H, J = 13.4 Hz), 3.76 (d, 1H, J = 5.7 Hz), 3.81 (d, 1H, J = 13.3 Hz), 3.85 (s, 3H), 3.94 (d, 1H, J = 5.1 Hz), 6.80 (dd, 1H, J = 8.7, 2.5 Hz), 6.95 (d, 1H, J = 2.4 Hz), 7.16 (d, 1H, J = 8.7 Hz), 7.26−7.36 (m, 5H), 7.54 (s, 1H), 11.99 (s, 1H); EIMS *m/e* 404 (M^+, 100), 372 (42), 289 (95), 281 (52), 253 (18), 199 (38). HRMS $C_{24}H_{24}N_2O_4$: calcd 404.1736, found 404.1683.

(6*S*,10*S*)-Methyl-2-methoxy-9-oxo-12-benzyl-6,7,8,9,10,-11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indole-8-carboxylate (44). A solution of β-ketoester **43** (1.0 g, 2.5 mmol) was dissolved in 1,4-dioxane (10 mL). A mixture of 40% aq KOH was then added into the above solution. The resulting reaction mixture was heated to reflux for 48 h. The solution was then allowed to cool to room temperature. The 1,4-dioxane was removed under reduced pressure. The remaining mixture was extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was separated, washed with brine, and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was purified by flash chromatography (hexane/ethyl acetate, 3/1) to afford **44** as a white solid (0.73 g, 85%). ^1H NMR (300 MHz, $CDCl_3$) δ 1.90−1.97 (m, 1H), 2.03−2.14 (m, 1H), 2.34−2.47 (m, 2H), 2.63 (d, 1H, J = 16.7 Hz), 3.19 (dd, 1H, J = 16.7, 6.7 Hz), 3.73 (m, 3H), 3.85 (s, 3H), 3.94 (m, 1H), 6.83 (dd, 1H, J = 8.7, 2.5 Hz), 6.94 (d, 1H, J = 2.4 Hz), 7.19 (d, 1H, J = 8.7 Hz), 7.20−7.36 (m, 5H), 7.80 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.40, 30.32, 34.50, 49.98, 55.89, 56.06, 64.93, 100.29, 106.37, 111.60, 111.76, 127.22, 127.28, 128.39, 128.57, 130.84, 132.88, 138.22, 154.15, 210.50. EIMS *m/e* 346 (M^+, 32.7), 318 (9.6), 290 (36.5), 289 (100), 199 (11.5), 183 (9.6). HRMS $C_{22}H_{22}N_2O_2$: calcd 346.1681, found 346.1628. Anal. Calcd for $C_{22}H_{22}N_2O_2$: C, 76.28; H, 6.40; N, 8.09. Found: C, 76.46; H, 6.68; N, 7.86.

(6*S*,10*S*)-2-Methoxy-9-oxo-12-(*Z*-2′-iodo-2′-butenyl)-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indole (47). Tetracyclic ketone **37** (2.05 g, 5.5 mmol) was mixed with dry EtOH (15 mL). A saturated solution of EtOH/HCl(g) was then added dropwise into the above mixture until the solid completely dissolved. The solvent was removed under reduced pressure to furnish an HCl salt. The residue was then dissolved in dry EtOH (15 mL), after which Pd/C (10%, 0.35 g) was added. The resulting mixture was allowed to stir at room temperature under an atmosphere of hydrogen for 12 h. After analysis by TLC (silica gel plate was exposed to NH_3 vapors) indicated the absence of starting material **37**, the catalyst was removed by filtration and washed with EtOH (3 × 15 mL). The solvent was removed under reduced pressure to provide N_b-H tetracyclic ketone **45** (1.36 g, 92%). ^1H NMR (300 MHz, $CDCl_3$) δ 1.15−1.28 (m, 2H), 1.55−1.80 (m, 2H), 2.01−2.12 (m, 1H), 2.82 (dd, 1H, J = 17.0, 6.7 Hz), 2.95 (d, 1H, J = 17.0 Hz), 3.50 (t, 1H, J = 5.8 Hz), 3.81 (m, 1H), 3.85 (s, 3H), 4.03 (br s, 1H), 4.10 (m, 1H), 6.80 (dd, 1H, J = 8.7, 2.4 Hz), 6.96 (d, 1H, J = 2.3 Hz), 7.20 (d, 1H, J = 8.7 Hz), 8.16 (br s, 1H); CIMS *m/e* 271 (M^+ + 1, 100). This material was not further characterized but was used directly in the next step. The above crude residue **45** and *Z*-1-bromo-2-iodo-2-butene **46**[76,77] (2.0 g, 7.7 mmol) were dissolved in THF (25 mL) and K_2CO_3 (0.5 g) was added. The resulting reaction mixture was stirred at room temperature for 24 h, and then heated to 60 °C for 24 h. The reaction solution was cooled to room temperature, and stirred at room temperature for 24 h. Analysis by TLC (silica gel, $CHCl_3$:C_2H_5OH 4:1) indicated the absence of tetracyclic ketone **45**. The K_2CO_3 was removed by filtration and was washed with EtOAc (3 × 10 mL). After removal of the solvent under reduced pressure, the crude product was purified by flash chromatography (silica gel, EtOAc:hexane 1:9) to provide N_b-*Z*-2′-iodo-2′-butenyl, tetracyclic ketone **47** (1.3 g, 80%). IR (NaCl) 1708 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.81 (d, 3H, J = 6.4 Hz), 1.90−2.09 (m, 2H), 2.48−2.53 (m, 2H), 2.67 (d, 1H, J = 16.8 Hz), 3.10 (dd, 1H, J = 16.8, 6.7 Hz), 3.35 (br s, 2H), 3.62 (s, 3H), 3.71 (d, 1H, J = 6.6 Hz), 3.85 (s, 3H), 4.06 (br s, 1H), 5.83 (br q, 1H, J = 6.3 Hz), 6.88 (dd, 1H, J = 8.8, 2.5 Hz), 6.93 (d, 1H, J = 2.4 Hz), 7.18 (d, 1H, J = 8.7 Hz); CIMS *m/e* 451 (M^+ + 1, 100). Anal. Calcd for $C_{20}H_{23}N_2O_2I\cdot{}^1/_2H_2O$: C, 52.30; H, 5.27; N, 6.10. Found: C, 52.43; H, 5.50; N, 6.06.

Palladium-Catalyzed Cyclization of (6*S*,10*S*)-2-Methoxy-9-oxo-12-(*Z*-2′-iodo-2′-butenyl)-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indole (47) To Provide Pentacyclic Ketone (48). A mixture of N_b-*Z*-2′-iodo-2′-butenyl, tetracyclic ketone **47** (100 mg, 0.22 mmol), $Pd(OAc)_2$ (4.93 mg, 0.022 mmol), Bu_4NBr (77 mg, 0.24 mmol), PPh_3 (21.9 mg, 0.084 mmol), and K_2CO_3 (117 mg, 0.84 mmol) in a solution of DMF−H_2O (9:1, 2.2 mL) was degassed under reduced pressure. The mixture was then heated to 70 °C (oil bath temperature) under an atmosphere of argon for 5 h. Analysis by TLC (silica gel, EtOAc:hexane 3:2) indicated the absence of N_b-*Z*-2′-iodo-2′-butenyl, tetracyclic ketone **47** and the presence of a new indole component of lower R_f value. The mixture was cooled to room temperature, diluted with EtOAc (220 mL), washed with H_2O (5 × 50 mL), and dried (K_2CO_3). The solvent was removed under reduced pressure and the resulting oil was chromatographed (silica gel, EtOAc:hexane 3:7) to provide pentacyclic ketone **48** (57.5 mg, 81%). ^1H NMR (300 MHz, $CDCl_3$) δ 1.69 (d, 3H, J = 6.8 Hz), 2.10−2.14 (m, 1H), 2.65−2.69 (m, 1H), 3.29 (s, 3H), 3.32−3.5 (m, 3H), 3.85 (s, 3H), 3.93−4.25 (m, 3H), 5.02 (m, 1H), 5.64 (br q, 1H, J = 6.8 Hz), 6.80−6.90 (m, 2H), 7.05 (d, 1H, J = 8.6 Hz). CIMS *m/e* 323 (M^+ + 1, 100). HRMS $C_{20}H_{22}N_2O_2$: calcd 322.1681, found 322.1677. This material was used directly in a later step.

Palladium-Catalyzed Cyclization of (6*S*,10*S*)-2-Methoxy-9-oxo-12-(*Z*-2′-iodo-2′-butenyl)-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indole (47) To Provide Pentacyclic Ketone (48), Gram Scale. A mixture of N_b-*Z*-2′-iodo-2′-butenyl, tetracyclic ketone **47** (1.1 g, 2.42 mmol),

$Pd(OAc)_2$ (27.1 mg, 0.121 mmol), Bu_4NBr (0.85 g, 2.64 mmol), PPh_3 (120 mg, 0.462 mmol), and K_2CO_3 (1.29 g, 9.24 mmol) in a solution of DMF−H_2O (9:1, 24 mL) was degassed under reduced pressure. The mixture was then heated to 70 °C (oil bath temperature) under an atmosphere of argon for 5 h. Analysis by TLC (silica gel, EtOAc:hexane 4:1) indicated the absence of N_b-*Z*-2′-iodo-2′-butenyl, tetracyclic ketone **47** and the presence of a new indole component of lower R_f value. The mixture was cooled to room temperature, diluted with EtOAc (2 L), washed with H_2O (5 × 500 mL), and dried (K_2CO_3). The solvent was removed under reduced pressure and the resulting oil was chromatographed (silica gel, EtOAc:hexane 3:7) to provide pentacyclic ketone **48** (624 mg, 80%). The ^{1}H NMR spectrum of **48** was identical with that reported immediately above. This material was used directly in a later step.

(+)-Majvinine (14). A mixture of anhydrous potassium *tert*-butoxide (276 mg, 2.45 mmol) and methoxymethyl triphenylphosphonium chloride (775 mg, 2.26 mmol) in dry benzene (11 mL) was allowed to stir at room temperature for 1 h. The pentacyclic ketone **48** (100 mg, 0.31 mmol) in THF (3.5 mL) was then added into the above orange solution dropwise at room temperature. The resulting mixture was stirred at room temperature for 24 h (the reaction progress was monitored by ^{1}H NMR spectroscopy of a sample from the process). The mixture was diluted with EtOAc (3 × 15 mL), washed with H_2O (3 × 1 mL) and brine (1 mL), and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was dissolved (without further purification) in a solution of aq 2 N HCl in H_2O/THF (30 mL). The resulting solution was stirred at 55 °C (oil bath temperature) under an atmosphere of argon for 6 h (the reaction progress was monitored by analysis of the crude product by ^{1}H NMR spectroscopy). After the reaction was completed, THF was removed under reduced pressure. The reaction mixture was washed with H_2O (10 mL) and extracted with diethyl ether (6 × 10 mL) to remove PPh_3═O. The aq layer was then brought to pH 8 with an aq solution of NH_4OH. The resulting aq layer was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic layers were washed with H_2O (3 × 1 mL) and brine (1 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford an oil that was chromatographed (silica gel, EtOAc:hexane 3:2) to provide pure (+)-majvinine **14** (94 mg, 90%). $[\alpha]^{26}_D$ 99 (*c* 0.78, $CHCl_3$). IR (NaCl) 2700, 1718 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.63 (dt, 3H, J = 6.8, 2.0 Hz), 1.80 (dt, 1H, J = 10, 2.0 Hz), 2.21 (br t, 1H, J = 10 Hz), 2.57 (m, 2H), 3.22 (m, 2H), 3.50 (s, 3H), 3.73 (d, 3H, J = 2.0 Hz), 3.85 (s, 3H), 4.38 (d, 1H, J = 9.1 Hz), 5.40 (br q, 1H, J = 6.8 Hz), 6.86 (dd, 1H, J = 8.8, 2.3 Hz), 6.92 (d, 1H, J = 2.3 Hz), 7.17 (d, 1H, J = 8.8 Hz), 9.63 (d, 1H, J = 0.87 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.7, 26.4, 26.8, 29.4, 31.9, 49.5, 50.8, 54.5, 55.7, 55.9, 100.4, 102.4, 109.8, 111.3, 118.2, 127.1, 132.2, 132.7, 138.3, 154.0, 201.5. EIMS *m*/*e* 336 (M$^+$, 53.8), 226 (13.2), 307, (100), 293 (10.3), 213 (71.8), 212 (75.6), 198 (23.1), 197 (33.3). HRMS $C_{21}H_{24}N_2O_2$: calcd 336.1838, found 336.1841. The spectral data were in good agreement with those of the natural product.[79] The structure was later confirmed by single-crystal X-ray analysis.

(+)-10-Methoxyaffinisine (49). The (+)-majvinine **14** (5 mg, 0.015 mmol) was dissolved in MeOH (1 mL). The $NaBH_4$ (0.57 mg, 0.015 mmol) was added to the above solution in one portion. The mixture was then stirred at 0 °C for 8 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and poured into cold water (2 mL). The aq layer was extracted with additional CH_2Cl_2 (3 × 4 mL), and the combined organic layers were washed with brine (2 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford the crude product, which was chromatographed (with use of a pipet as a column) to provide (+)-10-methoxyaffinisine **49** (4.6 mg, 90%). $[\alpha]^{26}_D$ +78 (*c* 0.2, $CHCl_3$) {lit.[80] $[\alpha]_D$ +75 (*c* 0.62, $CHCl_3$)}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.65 (d, 3H, J = 6.8 Hz), 1.72 (m, 1H), 1.85 (m, 2H), 2.10 (t, 1H, J = 10), 2.63 (d, 1H, J = 15 Hz), 2.85 (m, 2H), 3.09 (dd, 1H, J = 15, 5.3 Hz), 3.54 (m, 2H), 3.55 (m, 2H), 3.60 (s, 3H), 3.86 (s, 3H), 4.24 (d, 1H, J = 8.4 Hz), 5.43 (br q, 1H, J = 6.8 Hz), 6.84 (dd, 1H, J = 8.8, 2 Hz), 6.94 (d, 1H, J = 2 Hz), 7.18 (d, 1H, J = 8.8 Hz); ^{13}C NMR (75.7 MHz, $CDCl_3$) δ 12.8, 27.0, 27.5, 29.5, 32.8, 44.1, 49.6, 54.4, 56.0, 56.3, 65.0, 100.5, 103.2, 109.5, 110.7, 117.0, 127.5, 132.6, 135.4, 139.8, 153.8. EIMS *m*/*e* 338 (M$^+$, 78.3), 337 (69.6), 323 (13.0), 307 (39.1), 293 (10.9), 226 (10), 213 (91.3), 212 (100), 198 (29.3), 197 (30.4). HRMS $C_{21}H_{26}N_2O_2$: calcd 338.1994, found 338.1982. The spectral data for **49** were identical with those reported in the literature.[80]

(+)-N_a-Methylsarpagine (8). To a solution (degassed at −78 °C) of (+)-majvinine **14** (10 mg, 0.0297 mmol) in dry methylene chloride (1 mL) at −78 °C was added a solution of BBr_3 (0.178 mL of a 1.0 M solution of BBr_3 in dry CH_2Cl_2, 0.178 mmol) dropwise under Ar. The mixture was kept at −78 °C for 1 h and slowly warmed to room temperature. After an additional 2 h of stirring, the reaction solution was cooled with a dry ice bath and treated with a concentrated aq solution of NH_4OH to pH 8. Silica gel was added directly into the above mixture. After removal of solvent, the well-packed silica gel was then put into a small column. The column of silica gel was eluted with $CHCl_3$/EtOH (v/v 9:1). Removal of $CHCl_3$/EtOH provided the aldehyde **50** (7.8 mg, 81%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.64 (d, 3H, J = 6.9 Hz), 1.83 (d, 1H, J = 11.9 Hz), 2.21 (t, 1H, J = 11.9 Hz), 2.47−2.57 (m, 2H), 3.16 (dd, 1H, J = 15.5, 5.1 Hz), 3.27 (br s, 1H), 3.59 (s, 3H), 3.74 (m, 3H), 4.40 (d, 1H, J = 9.4 Hz), 5.42 (br q, 1H, J = 6.9 Hz), 6.76 (dd, 1H, J = 8.6, 2.3 Hz), 6.81 (d, 1H, J = 2.3 Hz), 7.10 (d, 1H, J = 8.6 Hz), 9.64 (s, 1H). CIMS *m*/*e* 323 (M$^+$ + 1, 100). This aldehyde **50** was used directly in the next step without further characterization. The above aldehyde **50** (5.0 mg, 0.0155 mmol) was dissolved in EtOH (1 mL). The $NaBH_4$ (0.59 mg, 0.0155 mmol) was added to the above solution in one portion. The mixture was then stirred at 0 °C for 4 h. The resulting reaction mixture was then treated with acetic acid to bring the pH to 5−6. The solvent was removed under reduced pressure to afford the crude product, which was chromatographed [silica gel, $CHCl_3$/MeOH (v/v 9:1)] to provide (+)-N_a-methylsarpagine **8** (4.5 mg, 90%). $[\alpha]^{26}_D$ 50 (*c* 0.1, MeOH) {lit.[88] $[\alpha]^{25}_D$ 52 ± 9 (*c* 0.05, MeOH)}. ^{1}H NMR (300 MHz, CD_3OD) δ 1.55 (d, 3H, J = 6.8 Hz), 1.61 (m, 1H), 1.76 (m, 2H), 2.08 (dt, 1H, J = 10, 2.1 Hz), 2.53 (d, 1H, J = 15 Hz), 2.69 (br t, 1H, J = 7 Hz), 2.88 (dd, 1H, J = 15, 5.2 Hz), 3.48 (m, 4H), 3.51 (s, 3H), 4.33 (d, 1H, J = 10 Hz), 5.38 (br q, 1H, J = 6.8 Hz), 6.59 (dd, 1H, J = 8.7, 2.3 Hz), 6.70 (d, 1H, J = 2.3 Hz), 7.05 (d, 1H, J = 8.7 Hz); ^{13}C NMR (CD_3OD) δ 13.3, 27.2, 28.0, 30.0, 33.0, 45.0, 51.6, 56.2, 57.5, 64.6, 103.0, 103.7, 110.8, 112.7, 120.8, 128.8, 132.0, 134.4, 138.0, 152.1. EIMS *m*/*e* 324 (M$^+$, 38), 323 (23), 293 (24), 199 (100), 198 (85), 184 (47). HRMS $C_{20}H_{24}N_2O_2$: calcd 324.1838, found 324.1820. The EIMS data were identical with those reported in the literature.[88]

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Supporting Information Available: X-ray data for compounds **14** and **33**. This material is available free of charge via the Internet at http://pubs.acs.org.

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