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General Approach to the Total Synthesis of 9-Methoxy-Substituted Indole Alkaloids: Synthesis of Mitragynine, as well as 9-Methoxygeissoschizol and 9-Methoxy-N_b-methylgeissoschizol

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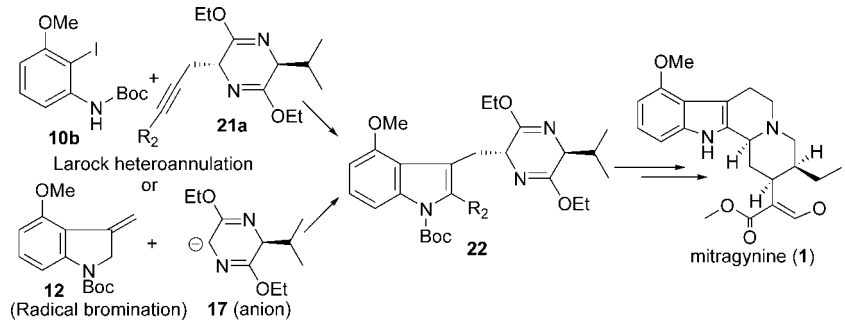

Herein, the full details of the synthesis of the 9-methoxy-substituted *Corynanthe* indole alkaloids mitragynine (**1**), 9-methoxygeissoschizol (**3**), and 9-methoxy-N_b-methylgeissoschizol (**4**) are described. Initially, an efficient synthetic route to the optically active 4-methoxytryptophan ethyl ester **20** on a multigram scale was developed via a Mori—Ban—Hegedus indole synthesis. The ethyl ester of D-4-methoxytryptophan **20** was obtained with a radical-mediated regioselective bromination of indoline **12** serving as a key step. Alternatively, the key 4-methoxytryptophan intermediate **22** could be synthesized by the Larock heteroannulation of aryl iodide **10b** with the internal alkyne **21a**. The use of the Boc-protected aniline **10b** was crucial to the success of this heteroannulation. The α,β-unsaturated ester **6** was synthesized via the Pictet—Spengler reaction as the pivotal step. This was followed by a $Ni(COD)_2$-mediated cyclization to set up the stereocenter at C-15. The benzyloxy group in **31** was removed to provide the intermediate ester **5**. This chiral tetracyclic ester **5** was employed to accomplish the first total synthesis of 9-methoxygeissoschizol (**3**) and 9-methoxy-N_b-methylgeissoschizol (**4**) as well as the opioid agonistic indole alkaloid mitragynine (**1**).

Introduction

Kratom is the common name of *Mitragyne speciosa Korth*, a plant native to Thailand, which has often been used as an opium substitute administrated by smoking, chewing, or drinking a broth form of the kratom leaves. The alkaloid content of the leaves of *Mitragyne speciosa* is about 0.5%, about half of which is comprised of mitragynine (**1**). Although the structure determination of **1** has a rich history,[1—4] the actual structure of **1** was unambiguously confirmed in 1964 when the X-ray crystal structure of mitragynine hydroiodide salt was completed by Zacharias.[5] The first formal study of the pharmacology of mitragynine (**1**) indicated that it was a central nervous system (CNS) stimulant.[6,7] Subsequent in vivo and in vitro studies indicated mitragynine primarily acted on μ-opioid receptors.[8,9] Although mitragynine was the major alkaloid in the extract of *Mitragyne speciosa*, it was not as active as the extract of

(1) Hooper, D. *Pharm. J.* **1907**, *78*, 453.
(2) Field, E. *J. Chem. Soc., Trans.* **1921**, *119*, 887.
(3) Hendrickson, J. B. *Chem. Ind. (London)* **1961**, 713.
(4) Joshi, B. S.; Raymond, H.; Taylor, W. I. *Chem. Ind. (London)* **1963**, 573.
(5) Zacharias, D. E.; Rosenstein, R. D.; Jeffrey, G. A. *Acta Crystallogr.* **1965**, *18*, 1039.
(6) Grewal, K. S. *J. Pharmacol.* **1932**, *46*, 251.
(7) Jansen, K. L.; Prast, C. J. *J. Ethnopharmacol.* **1988**, *23*, 115.
(8) Matsumoto, K.; Mizowaki, M.; Suchitra, T.; Murakami, Y.; Takayama, H.; Sakai, S.-i.; Aimi, N.; Watanabe, H. *Eur. J. Pharmacol.* **1996**, *317*, 75.
(9) Matsumoto, K.; Mizowaki, M.; Suchitra, T.; Takayama, H.; Sakai, S.-i.; Aimi, N.; Watanabe, H. *Life Sci.* **1996**, *59*, 1149.

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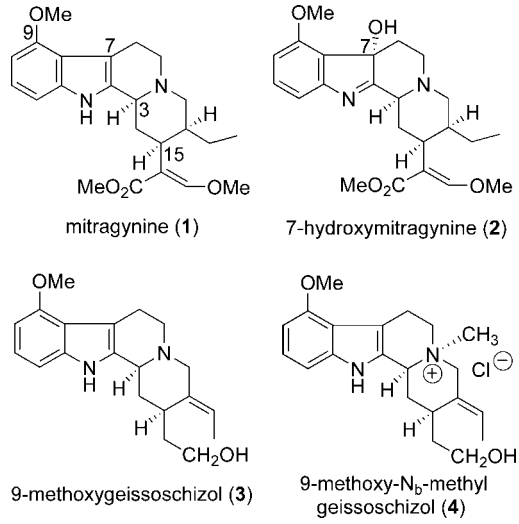
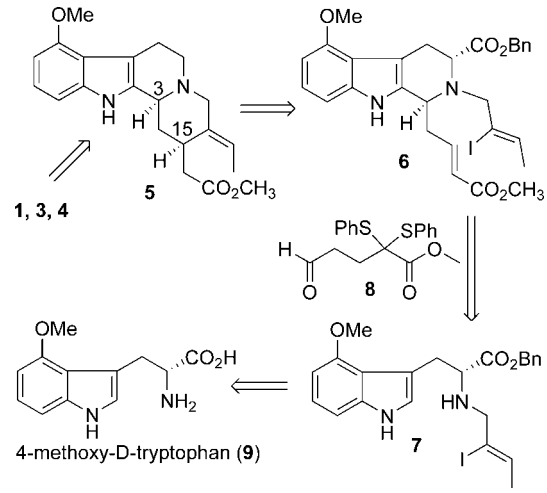


FIGURE 1. Structures of some 9-methoxy-substituted indole alkaloids.

SCHEME 1. Retrosynthetic Analysis



Mitragyne speciosa. This interesting behavior prompted a careful study and led to the discovery of another component, 7-hydroxymitragynine (**2**).[10,11] This alkaloid **2** could also be readily obtained by the oxidation of mitragynine with phenyliodine bis(trifluoroacetate) (PIFA).[12] This hydroxyl-substituted alkaloid was 46- and 17-fold higher in activity than mitragynine and morphine, respectively, on twitch contraction induced by electrical stimulation in the guinea pig ileum.[13,14] In vitro receptor binding studies revealed that 7-hydroxymitragynine (**2**) bound preferentially to μ-opioid receptors, although it also interacted with δ and κ receptors, albeit less potently.

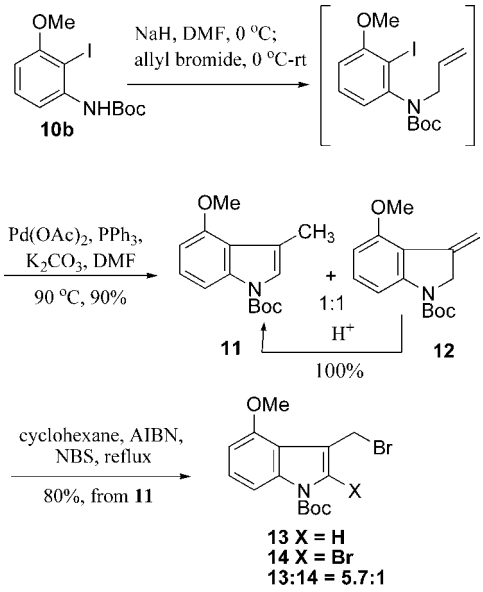
Interestingly, the demethoxy analogue of mitragynine, corynantheidine, did not exhibit opioid agonistic activity but reversed the morphine-inhibited twitch contraction. Therefore, corynantheidine is an opioid receptor antagonist.[14,15] When the methoxy group at C-9 was replaced with an ethoxy moiety or isopropoxy group, no opioid analgesic activity was observed. The 9-acetoxy analogue exhibited much less activity than mitragynine. In addition, the N_b-oxide derivative of mitragynine was not active. These results indicated the 9-methoxy group was a very important functional group for ligand binding to opioid receptors. It also demonstrated that the lone pair of electrons on the N_b nitrogen atom was indispensable in regard to opioid agonistic activity.[14,15] In summary, the mitragynine class of compounds are structurally different from morphine, and some of these indole alkaloids still exhibited high opioid agonistic activity primarily via μ-receptors similar to morphine. This renders these novel lead compounds for the design of new antinociceptive agents and tools with which to study opioid receptors.

The alkaloid 9-methoxygeissoschizol (**3**) (see Figure 1) was first isolated from the bark of *Strychnos guianensis*.[16] The crude extracts from the root and stem bark displayed muscle-relaxant activity.[17] The related 9-methoxy-N_b-methylgeissoschizol (**4**) as well as other quaternary indole alkaloids have also been identified.[18] These geissoschizol bases are biogenetically related to the C*orynanthe* alkaloids, which enables the design of a general approach to the synthesis of these 9-methoxy-substituted indole alkaloids. To date, many total syntheses of corynantheidine have been published.[19] However, few syntheses of mitragynine (**1**) have been reported.[20,21] Presumably, the difficulty in acquiring 4-methoxyindole starting materials has retarded other efforts in this area.

In this report, the details of the development of the recent syntheses of these 9-methoxy-substituted indole alkaloids are described. From a retrosynthetic perspective, it was felt the common 9-methoxy-substituted tetracyclic intermediate **5** could be transformed into the *Corynathe* indole alkaloids mitragynine (**1**), 9-methoxygeissoschizol (**3**), and 9-methoxy-N_b-methylgeissoschizol (**4**) in simple fashion (Scheme 1). The *cis* configuration at C-3 and C-15 could presumably be installed via a Ni(0)-mediated cyclization[22] of the vinyl iodide with the double bond of the α,β-unsaturated ester **6**, analogous to the previous work of Yu.[19f] An asymmetric Pictet−Spengler reaction[23] of the secondary N_b-alkylamine **7** and the aldehyde **8**[19f,24] would be employed to stereospecifically install the correct chirality at C-3. The N_b-allyl group of the secondary amine **7** would be required to direct the diastereoselectivity at C-3,[11] and presumably, this

(10) Ponglux, D.; Wongseripipatana, S.; Takayama, H.; Kikuchi, M.; Kurihara, M.; Kitajima, M.; Aimi, N.; Sakai, S.-i. *Planta Med.* **1994**, *60*, 580.
(11) Matsumoto, K.; Horie, S.; Ishikawa, H.; Takayama, H.; Aimi, N.; Ponglux, D.; Watanabe, K. *Life Sci.* **2004**, *74*, 2143.
(12) Ishikawa, H.; Takayama, H.; Aimi, N. *Tetrahedron Lett.* **2002**, *43*, 5637.
(13) Takayama, H. *Chem. Pharm. Bull.* **2004**, *52*, 916.
(14) Takayama, H.; Ishikawa, H.; Kurihara, M.; Kitajima, M.; Aimi, N.; Ponglux, D.; Koyama, F.; Matsumoto, K.; Moriyama, T.; Yamamoto, L. T.; Watanabe, K.; Murayama, T.; Horie, S. *J. Med. Chem.* **2002**, *45*, 1949.
(15) Matsumoto, K.; Takayama, H.; Ishikawa, H.; Aimi, N.; Ponglux, D.; Watanabe, K.; Horie, S. *Life Sci.* **2006**, *78*, 2265.
(16) Mavar-Manga, H.; Quetin-Leclercq, J.; Llabres, G.; Belem-Pinheiro, M.-L.; Imbiriba Da Rocha, A. F. *Phytochemistry* **1996**, *43*, 1125.
(17) West, R. *Arch. Int. Pharmacodyn. Ther.* **1937**, *56*, 81.
(18) Penelle, J.; Tits, M.; Christen, P.; Molgo, J.; Brandt, V.; Frederich, M.; Angenot, L. *Phytochemistry* **2000**, *53*, 1057.
(19) (a) Weisbach, J. A.; Kirkpatrick, J. L.; Williams, K. R.; Anderson, E. L.; Yim, N. C.; Douglas, B. *Tetrahedron Lett.* **1965**, *6*, 3457. (b) Autrey, R. L.; William, S. P. *J. Am. Chem. Soc.* **1968**, *90*, 4917. (c) Van Tamelen, E. E.; Hester, J. B., Jr. *J. Am. Chem. Soc.* **1969**, *91*, 7342. (d) Beard, R. L.; Meyers, A. I. *J. Org. Chem.* **1991**, *56*, 2091. (e) Lounasmaa, M.; Jokela, R.; Laine, C.; Hanhinen, P. *Tetrahedron Lett.* **1995**, *36*, 8687. (f) Yu, S.; Berner, O. M.; Cook, J. M. *J. Am. Chem. Soc.* **2000**, *122*, 7827.
(20) Takayama, H.; Maeda, M.; Ohbayashi, S.; Kitajima, M.; Sakai, S.-i.; Aimi, N. *Tetrahedron Lett.* **1995**, *36*, 9337.
(21) (a) Ma, J.; Yin, W.; Zhou, H.; Cook, J. M. *Org. Lett.* **2007**, *9*, 3491. (b) Ma, J. PhD Thesis, University of Wisconsin−Milwaukee, Milwaukee, WI, 2006.
(22) (a) Takayama, H.; Watanabe, F.; Kitajima, M.; Aimi, N. *Tetrahedron Lett.* **1997**, *38*, 5307. (b) Fornicola, R. S.; Subburaj, K.; Montgomery, J. *Org. Lett.* **2002**, *4*, 615.
(23) (a) Pictet, A.; Spengler, T. *Ber.* **1911**, *44*, 2030. (b) Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797.
(24) Massiot, G.; Mulamba, T. *J. Chem. Soc., Chem. Commun.* **1983**, *20*, 1147.

SCHEME 2. Initial Synthesis of Bromide 13

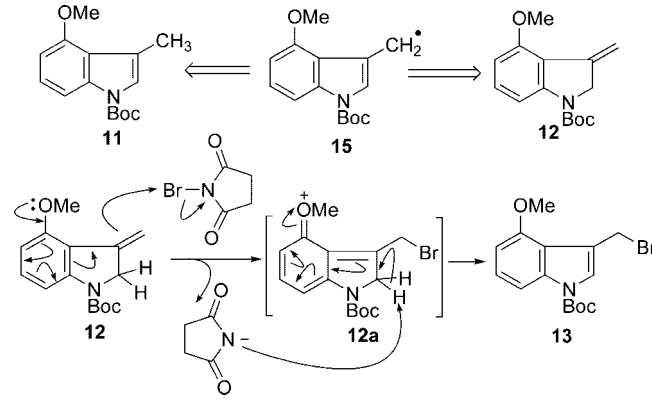


amine **7** could be obtained from monoalkylation of 4-methoxy-D-tryptophan **9**.

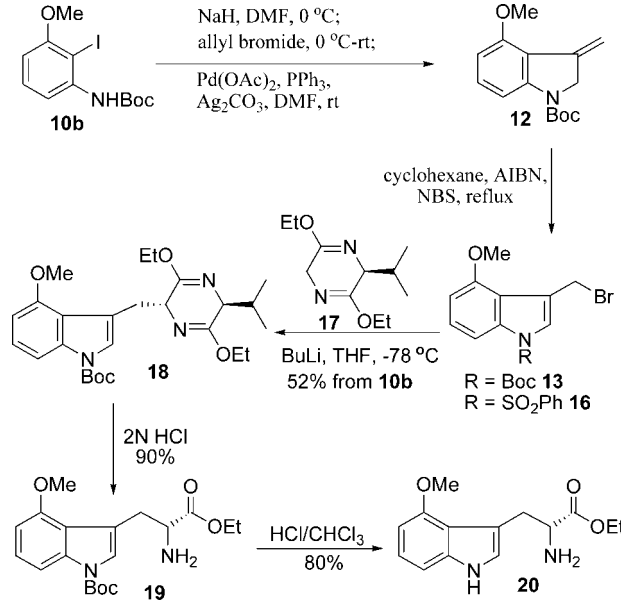
Results and Discussion

A key obstacle in the preparation of **1**, **3**, and **4** stems from the general lack of availability of 4-methoxytryptophans. Extensive efforts by Ley et al.[25] led to a synthesis of 4-methoxytryptophan (**9**) in high optical purity by the process of enzymatic kinetic resolution employing immobilized penicillin G acylase. The initial strategy here was to use the Mori−Ban−Hegedus indole synthesis to synthesize 4-methoxy-3-methylindole (**11**), which could undergo regioselective bromination and coupling with the anion of the Schöllkopf chiral auxiliary[26] to provide 4-methoxyindole derivative **18** (Scheme 4). This process had previously been successfully employed to synthesize 5-methoxytryptophan[27] in a regiospecific fashion. The protection of the indole N_a−H function with an electron-withdrawing group such as a Boc moiety to decrease the electron density of the 2,3-indole double bond was essential to decrease the nucleophilicity at the C-2 position. Thus, the readily available aryl iodide **10b**[28] was subjected to the conditions of allylic alkylation followed by the Mori−Ban−Hegedus indole synthesis, to give a 1:1 mixture of 3-methylindoline **12** and 3-methylindole **11**; the latter compound was presumably formed from the isomerization of the 3-methylindoline **12** under the reaction conditions (Scheme 2). The 3-methylindoline **12** was found to isomerize rapidly to the thermodynamically more stable 3-methylindole **11** during chromatography on silica gel.[21b] Alternatively, the crude mixture of **11** and **12** could be stirred under acidic conditions to provide the 4-methoxy-3-methylindole **11** in 90% overall yield from aryl iodide **10b**. Unfortunately, the radical-mediated bromination of the methyl indole **11** gave both the

SCHEME 3. Possible Pathway for Synthesis of Bromide 13



SCHEME 4. Improved Synthesis of Bromide 13 and Its Application in 4-Methoxytryptophan Synthesis



desired 3-bromomethyl indole **13**, as well as the dibromide **14**. Although the successful radical bromination of the electron-rich 5-methoxy-3-methylindole had been reported,[27] the difficulty in achieving the regioselective bromination of the 4-methoxy-3-methylindole was not unexpected. Presumably, the methoxy substituent at the C-4 position not only enhanced the nucleophilicity at the C-2 position but also increased the steric hindrance at C-3 due to its proximity to the benzylic methyl group.

Numerous attempts to optimize the reaction conditions failed to avoid electrophilic aromatic substitution at C-2 of the indole **11**. It was later decided the 3-methyleneindoline **12** might actually serve as a better substrate for the radical bromination since the electrophilic attack at the C-2 position in **12** would not occur. Moreover, the allylic radical intermediate generated from the 3-methyleneindoline **12** should aromatize rapidly to the lower energy indolic radical **15** (Scheme 3), which could undergo the radical bromination to give the desired 3-bromomethylindole **13**. Alternatively, the electrophilic addition of the NBS to the 3-methyleneindoline **12** to provide the cationic intermediate might occur and this could be followed by loss of a H^+ to regenerate the indole ring and provide the bromide **13**. Presumably, this ionic process was slow compared with the radical process.

(25) (a) Ley, S. V.; Priour, A. *Eur. J. Org. Chem.* **2002**, *23*, 3995. (b) Ley, S. V.; Priour, A.; Heusser, C. *Org. Lett.* **2002**, *4*, 711. (c) Siu, J. B.; Baxendale, I. R.; Ley, S. V. *Org. Biomol. Chem.* **2004**, *2*, 160.

(26) Schöllkopf, U.; Groth, U.; Deng, C. *Angew. Chem.* **1981**, *93*, 793.

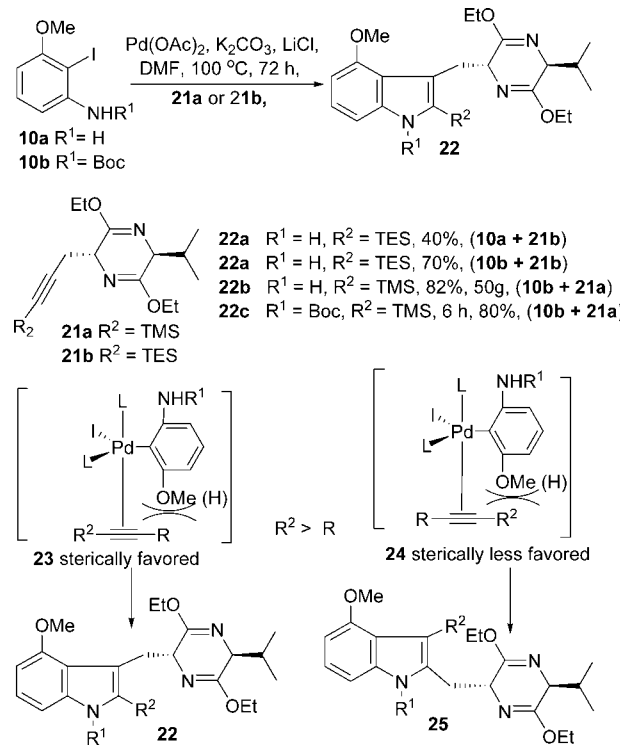
(27) (a) Zhang, P.; Cook, J. M. *Synth. Commun.* **1995**, *25*, 3883. (b) Zhao, S.; Liao, X.; Cook, J. M. *Org. Lett.* **2002**, *4*, 687. (c) Zhao, S.; Liao, X.; Wang, T.; Flippen-Anderson, J.; Cook, J. M. *J. Org. Chem.* **2003**, *68*, 6279. (d) Sarma, S. P. V. V.; Cook, J. M. *Org. Lett.* **2006**, *8*, 1017.

(28) Kondo, Y.; Kojima, S.; Sakamoto, T. *J. Org. Chem.* **1997**, *62*, 6507.

To minimize the isomerization of the 3-methyleneindoline **12** to the 3-methylindole **11** in the Mori−Ban−Hegedus indole synthesis, it was necessary to switch the base from potassium carbonate to silver carbonate. This silver salt is known to minimize the isomerization of the double bond effected by the HPdX species in the Heck coupling, and it has been previously employed as the base in the Mori−Ban−Hegedus indole synthesis.[29] Gratifyingly, when silver carbonate was employed in the Heck reaction, the process was much faster, and the reaction could be carried out at room temperature (Scheme 4). The desired 3-methyleneindoline **12** was obtained, accompanied by a small amount of the 3-methylindole **11**. The subsequent NBS-mediated radical reaction of **12** then gave bromide selectively, and the reaction conversion was increased from 80% to 90%. The dibromide byproduct **14** was observed only in trace amounts by NMR analysis of the crude material. The process could also be scaled up to the 50 g level without loss of selectivity or yield, although the workup was more tedious and extra care was required to avoid isomerization. It had been reported by Ley[25a] that the instability of a similar intermediate **16** led to the failure of its coupling with the anion of the Schöllkopf chiral auxiliary **17**. Indeed, the reaction mixture of **13** was initially yellow in CCl_4 or cyclohexane solution, but on removal of solvent the reaction mixture rapidly decomposed to a black solid which is no longer soluble in CCl_4 or cyclohexane. Moreover, the coupling of this crude material in THF with the anion of the Schöllkopf chiral auxiliary **17** provided bislactim **18**, albeit in very low yields. Consequently, after removal of the excess NBS and *N*-succinimide by filtration, most of the cyclohexane was removed while a small portion of cyclohexane remained to avoid decomposition. This cyclohexane solution of the bromide **13** was directly used to couple with the anion of the Schöllkopf chiral auxiliary **17** in THF to furnish the desired bislactim **18** in 52% overall yield for the four steps. With the bislactim **18** in hand, the thermal deprotection of the Boc moiety in **18** was attempted in refluxing xylene; unfortunately, this gave the desired product in only 80% yield, accompanied by a minor product, which was believed to be the epimerized product at the chiral auxiliary. Other alternative methods for removal of the Boc group under various conditions, including TMSOTf/lutidine, silica gel-mediated[30] deprotection of the Boc moiety (under reduced pressure), and KOtBu/Et_2O,[31] were attempted, but the epimerization was observed in all cases. To circumvent this problem, the Schöllkopf chiral auxiliary was removed under acidic conditions (90%), and this was followed by the acid-mediated cleavage of the indole N_a-Boc group by stirring in a saturated solution of anhydrous HCl in chloroform (80%).

The initial development of the synthesis of the optically active 4-methoxytryptophan ethyl ester (**20**) had involved a Mori−Ban−Hegedus indole synthesis and the regioselective bromination of the 3-methylene indole **12**. However, a tedious workup process and skillful experimental techniques were required in this process to obtain good yields. This prompted a study of

SCHEME 5. Larock Heteroannulation



the Larock heteroannulation.[32] Since its development in 1991, the Larock heteroannulation had been used extensively in the synthesis of indoles. The strength of the Larock process stems from the facile construction the indole ring from halide-substituted aniline and alkyne. Good regioselectivity in most cases can be achieved when a bulky silyl-substituted internal alkyne was employed as a substrate. The steric interactions between the ortho aromatic H atom and the substituent on the alkyne (see intermediates **23** and **24** in Scheme 5) are the key factors controlling the regioselectivity.[32b,33] In the case of 4-methoxyindole derivatives, this steric effect was even more demanding because the aromatic hydrogen atom was now replaced by a methoxyl group in the Larock heteroannulation. Analogous to the successful synthesis of 6- and 7-methoxy indoles,[34] the Larock heteroannulation of aniline **10a**[28] and the TES propargyl-substituted Schöllkopf chiral auxiliary **21b**[34] was attempted. Unfortunately, this provided only 40% of the desired bislactim **22a**. It was observed that the reaction rate of the Larock heteroannulation in the 4-methoxyindole series was slower than the corresponding 6- and 7-methoxy analogues. It was felt that the 4-methoxyl group in the aromatic ring substantially decreased the reaction rate of the oxidative addition step both for electronic and steric reasons. An electron-withdrawing group such as a Boc group on the aniline nitrogen atom might speed up the oxidative addition step in the catalytic cycle. Gratifyingly, the Boc-protected 2-iodo-3-methoxyaniline **10b** and the TMS alkyne **21a**[34] underwent the Larock heteroannulation at a much faster rate to afford the N_a-Boc-protected indole derivative **22c** in 80% yield in 6 h. Moreover, the removal

(29) Sakamoto, T.; Kondo, Y.; Uchiyama, M.; Yamanaka, H. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1941.

(30) Apelqvist, T.; Wensbo, D. *Tetrahedron Lett.* **1996**, *37*, 1471.

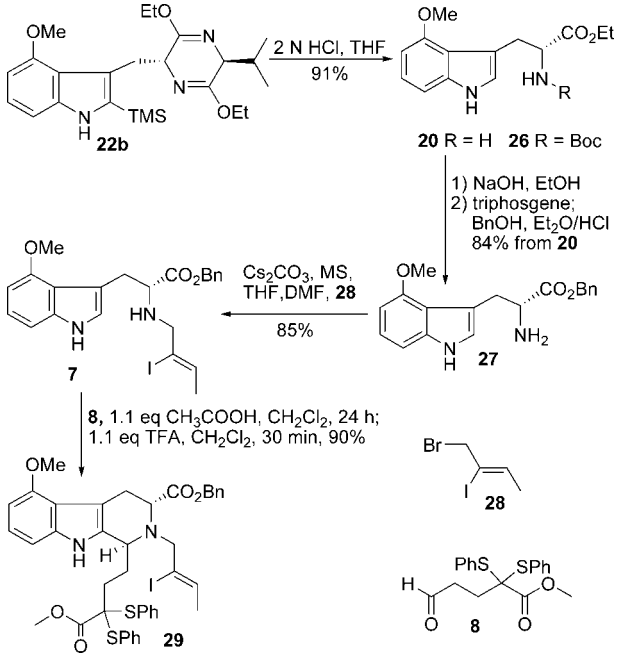
(31) (a) Gassman, P. G.; Hodgson, P. K. G.; Balchunis, R. J. *J. Am. Chem. Soc.* **1976**, *98*, 1275. (b) Gassman, P. G.; Schenk, W. N. *J. Org. Chem.* **1977**, *42*, 918.

(32) (a) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689. (b) Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem.* **1998**, *63*, 7652. (c) Castle, S. L.; Srikanth, G. S. C. *Org. Lett.* **2003**, *5*, 3611. (d) Gathergood, N.; Scammells, P. J. *Org. Lett.* **2003**, *5*, 921. (e) Larock, R. C. *J. Organomet. Chem.* **1999**, *576*, 111.

(33) Dussault, D. D. MS Thesis, Massachusetts Institute of Technology, Cambridge, MA, 2003.

(34) (a) Ma, C.; Liu, X.; Li, X.; Flippen-Anderson, J.; Yu, S.; Cook, J. M. *J. Org. Chem.* **2001**, *66*, 4525. (b) Liu, X.; Cook, J. M. *Org. Lett.* **2002**, *4*, 3339. (c) Zhou, H.; Liao, X.; Cook, J. M. *Org. Lett.* **2004**, *6*, 249. (d) Yu, J.; Wearing, X.; Cook, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 1358. (e) Lewis, S. E. *Tetrahedron* **2006**, *62*, 8655.

SCHEME 6. Establishment of Stereochemistry at C-3



of the Boc moiety was achieved after the reaction mixture continued to stir for 3 days to afford the desired 4-methoxy N_a-H indole **22b** in 82% yield. This was carried out on a 50 g scale. A switch from the TMS- to the TES-substituted alkyne **21b** resulted in a lower yield (70%) of indole **22a**. Presumably, the oxidative addition of Pd(0) to the Boc-protected iodoaniline **10b** was more facile than in the free aniline **10a**. Furthermore, the TMS-substituted alkyne was bulky enough to achieve the regioselectivity while binding more rapidly to the Pd catalyst than the corresponding TES substituted analogue. Overall, excellent regioselectivity and reaction rate in the Larock heteroannulation was a delicate balance between electronic and steric effects.

The hydrolysis of the Schöllkopf chiral auxiliary and concomitant loss of the indole-2-silyl group of **22b** smoothly took place in aqueous 2 N HCl in THF to provide 4-methoxy-D-tryptophan ethyl ester (**20**) in a single step in 91% yield (Scheme 6). The enantiomer, 4-methoxy-L-tryptophan ethyl ester, was also synthesized (from D-valine) by the same route. With both enantiomers in hand, the optical purity of the 4-methoxytryptophan ethyl ester **20** could be determined by chiral HPLC [an (*S*,*S*)-WHELK-01 chiral column was employed]. However, the separation of the enantiomers **20** was not acceptable. Consequently, the N_b nitrogen atom of **20** was protected by heating with Boc anhydride (THF) to afford the N_b-Boc-protected derivative **26**. The enantiomer of **26** was also prepared, and both were successfully separated on the HPLC when the (*S*,*S*)-WHELK-01 chiral column was employed. The optical purity of indole **20** was found to be >95% ee. The desired ethyl ester **20** was hydrolyzed in ethanolic NaOH solution and then converted into the benzyl ester **27** in 84% yield.[19f] Cesium carbonate[35] was then employed as the base, and the monoalkylation of primary amine **27** with allylic bromide **28** was successfully executed when THF/DMF (1:1) was used as a mixed solvent system to give secondary amine **7** in 85% yield. When DMF was used as the only solvent, dialkylation was observed. When THF was used as the only solvent the reaction was very slow. It had been established that a bulky group on the N_b-nitrogen atom was required to achieve 100% trans diastereoselectivity in the asymmetric Pictet−Spengler reaction.[36] The Pictet−Spengler reaction of the aldehyde **8**[24] and the secondary amine **7** was then attempted in TFA/CH_2Cl_2.[19f] Unfortunately, decomposition of 4-methoxyindole **7** was observed under these conditions. A switch to weaker acids such as trichloroacetic acid or chloroacetic acid resulted in decomposition as well. Finally, acetic acid was employed to initially provide a mixture of *cis* and *trans* isomers in a 1:3 ratio. When this solution was allowed to stir for 5 days, the epimerization of the *cis* isomer to provide the desired *trans*-tetrahydro-β-carboline **29** went to completion, and an overall yield of 90% was obtained. Alternatively, the *cis* and *trans* mixture could be stirred in dilute TFA/CH_2Cl_2 solution for 30 min, although this should be monitored by TLC carefully to avoid the decomposition of the 4-methoxyindole system.

With the *trans*-tetrahydro-β-carboline **29** in hand, the desired α,β-unsaturated ester **6** was readily prepared in good yield (Scheme 7).[19f,24] The removal of 1 equiv of thiophenol from **29** was achieved in the presence of thiophenol and a catalytic amount of NaH to furnish the monosulfide **30** in 92% yield. Selective oxidation of the second phenyl sulfide moiety in the presence of the N_b nitrogen atom was accomplished with *m*-CPBA at −78 °C to give the sulfoxide. This material was heated to reflux in toluene in the presence of sodium carbonate to afford the α,β-unsaturated ester **6** in 72% yield over the three steps. The α,β-unsaturated ester **6** was then subjected to the Ni(COD)$_2$-mediated cyclization, analogous to the work reported by Yu[19f] and Takayama[22a] to afford the C*orynanthe* skeleton in **31** in 75% yield. The hydrogenolysis of the benzyl ester **31** was mediated by Et_3SiH in the presence of $PdCl_2$[37] to afford the corresponding carboxylic acid. (The catalytic debenzylation had been attempted with Pd/C/H_2, and the simultaneous reduction of the double bond had been observed.) The acid was then activated via the mixed anhydride and converted into the selenoester, which underwent the Martin modification of a Barton−Crich decarboxylation[38] to give the tetracyclic system **5** in 59% yield. The reduction of the ester **5** with lithium aluminum hydride in THF at rt furnished the synthetic 9-methoxygeissoschizol (**3**) in 90% yield. Methylation of **3** with methyl iodide was followed by the exchange of the iodide anion to chloride anion employing AgCl to provide the 9-methoxy-N_b-methylgeissoschizol (**4**). The ^{13}C NMR spectral data of 9-methoxygeissoschizol (**3**) and 9-methoxy-N_b-methylgeissoschizol (**4**) are in excellent agreement with the literature (see the Supporting Information for details).[16,18]

Efforts then turned to the synthesis of mitragynine from the common intermediate, α,β-unsaturated ester **6**, analogous to the work reported by Yu.[19f] The vinyl iodide **6** was subjected to the Pd(OAc)$_2$-catalyzed intramolecular Heck coupling in DMF at 80 °C for 18 h to afford diene **32** in 92% yield (Scheme 8). The reduction of the conjugated diene system was achieved with

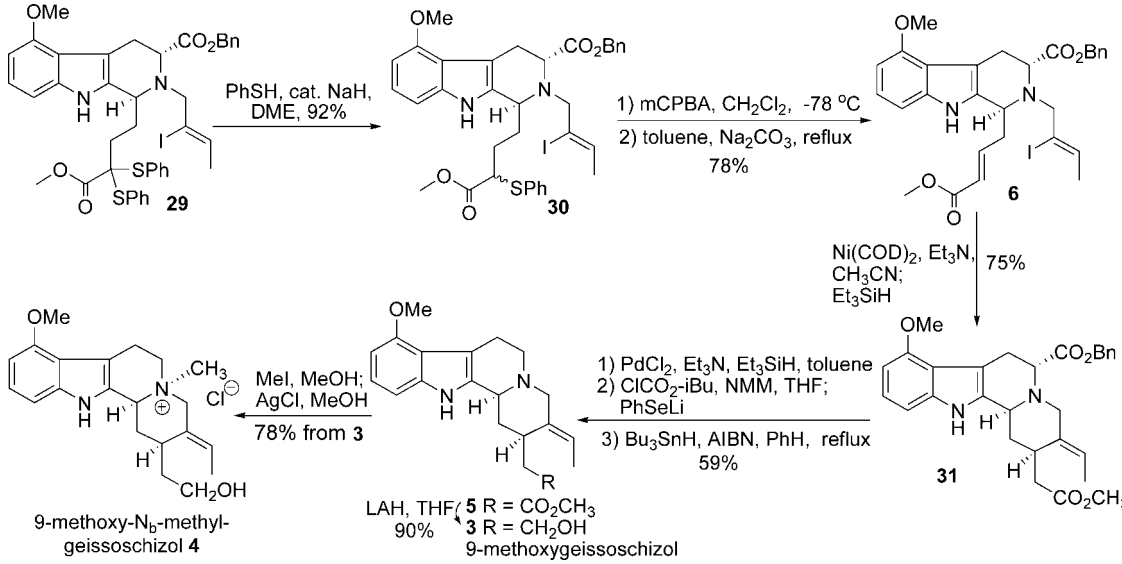
(35) Salvatore, R. N.; Nagle, A. S.; Schmidt, S. E.; Jung, K. W. *Org. Lett.* **1999**, *1*, 1893.

(36) 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.

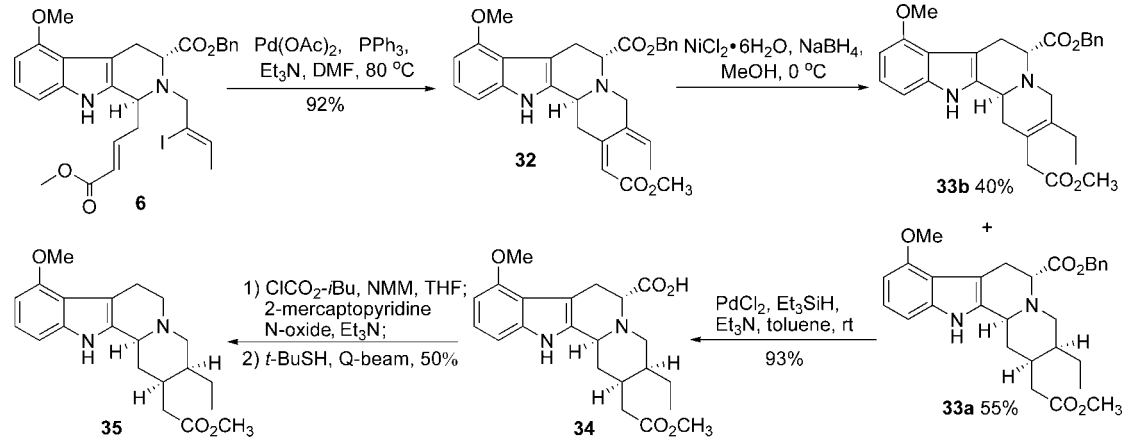
(37) Birkofer, L.B. E.; Ritter, A. *Chem. Ber.* **1961**, *94*, 821.

(38) (a) Barton, D. H. R.; Crich, D.; Potier, P. *Tetrahedron Lett.* **1985**, *41*, 5943. (b) Martin, S. F.; Chen, K. X.; Eary, C. T. *Org. Lett.* **1999**, *1*, 79. (c) Boger, D. L.; Mathvink, R. J. *J. Org. Chem.* **1992**, *57*, 1443.

SCHEME 7. Synthesis of 9-Methoxygessisoschizol (3) and 9-Methoxy-N_b-methylgeissoschizol (4)



SCHEME 8. Initial Synthesis of Tetracycle 35



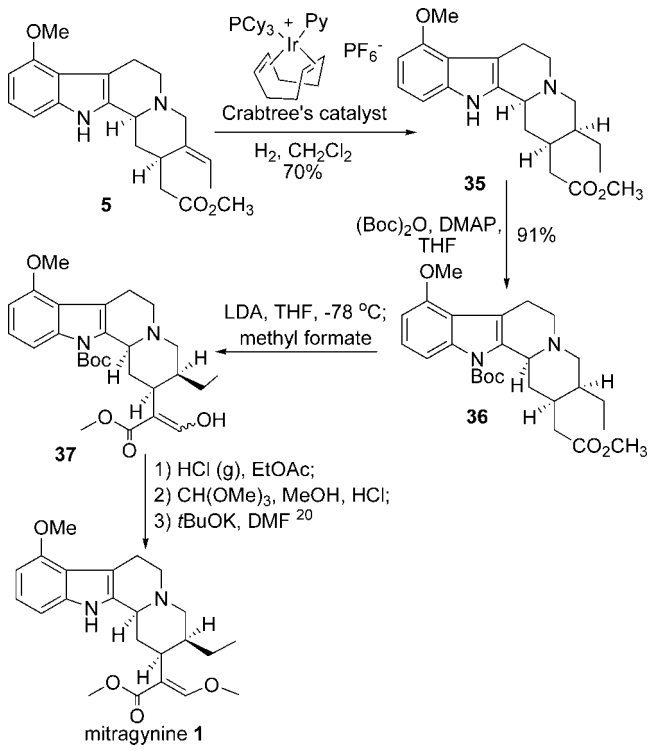
$NaBH_4$ in the presence of $NiCl_2 \cdot 6H_2O$[39] to provide the desired *cis* system **33a** in 55% yield, accompanied by the partially reduced β,γ-unsaturated ester **33b**, as a byproduct (40% yield). In this process, $NaBH_4$ was added in portions at 0 °C into a mixture of the α,β-unsaturated ester **32** in MeOH and solid $NiCl_2 \cdot 6H_2O$. This step was exothermic, and the reaction was carried out at 0 °C to avoid the hydrolysis of the methyl ester moiety. The removal of the benzyl function of ester **33a** was again achieved with $PdCl_2$ in the presence of Et_3SiH[37] to afford the acid **34**, which then underwent the Barton−Crich decarboxylation to provide *cis* intermediate **35** in 50% yield. The acid **34** was activated by isobutyl chloroformate to provide the mixed anhydride as the intermediate in the presence of NMM. This process was followed by the addition of the 2-mercaptopyridine *N*-oxide and Et_3N to provide the Barton ester. This intermediate was then subjected to irradiation with a Q-beam in the presence of *t*-BuSH until the disappearance of the intermediate (TLC), to furnish the key intermediate **35** for mitragynine. Unfortunately, this decarboxylation process gave inconsistent yields. Attempts to use the radical mediated decarboxylation of the selenoester analogous to the synthesis of **5** furnished very low yields of **35**. This prompted development of an alternative route for the synthesis of this key tetracycle **35**.

Due to the inconsistent yields, as mentioned, during the decarboxylation of the acid **34**, efforts were then directed toward the synthesis of the tetracyclic intermediate **35** from the stereoselective reduction of olefin **5**, which had been employed in the synthesis of 9-methoxygeissoschizol (**3**). Reduction of the double bond in olefin **5** turned out to be problematic. The reduction of **5** with $Pd/C/H_2$ or PtO_2/H_2 was very slow at both 1 atm pressure and at 50 psi, returning mostly starting material. Some isomerization of the double bond in **5** was also observed. This isomerization took place, presumably, because of the slow rate of the reduction. Finally, the reduction of olefin **5** to **35** was effected in 70% yield using Crabtree's catalyst[40a] (Scheme 9), which has been widely employed in the reduction of tri- and tetrasubstituted alkenes.[40] With tetracycle **35** in hand, the indole N_a nitrogen atom in **35** was protected with a Boc group to facilitate the formylation to provide the enol **37** accompanied by its aldehydic tautomer. This enol/aldehyde mixture was then treated with HCl (g) in EtOAc to remove the Boc group, and

(39) Jacobi, P. A.; Craig, T. A.; Walker, D. G.; Arrick, B. A.; Frechette, R. F. *J. Am. Chem. Soc.* **1984**, *106*, 5585.

(40) (a) Crabtree, R. H. *Acc. Chem. Res.* **1979**, *12*, 331. (b) Cui, X.; Burgess, K. *Chem. Rev.* **2005**, *105*, 3272.

SCHEME 9. Synthesis of Mitragynine (1)



this was followed by treatment with anhydrous methanolic hydrogen chloride solution in the presence of trimethyl orthoformate to afford the corresponding acetal intermediate. Analogous to the route of Takayama et al.,[20] the acetal was dissolved in DMF and treated with *t*-BuOK to furnish mitragynine (**1**).

Conclusion

An efficient synthesis of optically active D- or L-4-methoxytryptophan ethyl ester (**20**) has been developed. Both the 4-methoxy-3-methylindole (**11**) and the isomeric indoline derivative **12** could be obtained via the Mori−Ban−Hegedus indole synthesis. The regioselective radical bromination of indoline **12** gave better yields of the bromide **13** than the indole **11**. The bromide **13** was successfully converted into 4-methoxy tryptophan ethyl ester (**20**) after coupling with the anion of the Schöllkopf chiral auxiliary **17**, followed by hydrolysis of the chiral auxiliary. Alternatively, the Larock heteroannulation was successfully employed to synthesize tryptophan derivative **20** in a more efficient way. Importantly, the Boc protection of the aniline was crucial to the success of this heteroannulation. The synthetic 4-methoxytryptophan ethyl ester (**20**) was transformed into the tetracycle **5**. The stereocenter at C-3 was installed by the Pictect−Spengler reaction, and the *cis* configuration at C-3 and C-5 was achieved by the $Ni(COD)_2$-mediated cyclization. The total syntheses of mitragynine (**1**), 9-methoxygeissoschizol (**3**), and 9-methoxy-N_b-methylgeissoschizol (**4**) were accomplished from the common intermediate **5**.

Experimental Section

***tert*-Butyl 4-Methoxy-3-methyleneindoline-1-carboxylate (12).** Carbamate **10b** (54.7 g, 0.157 mol) in DMF (1 L) was cooled with an ice bath and stirred at 0 °C for 10 min. To this cold solution was added NaH (60% dispersion in mineral oil, 6.91 g, 0.172 mol), and the mixture was stirred at 0 °C for 30 min. Allyl bromide (16.2 mL, 0.188 mol) was injected via a syringe, and the mixture was warmed to rt and stirred for 5 h, after which aq NH_4Cl solution (10 mL) was carefully added dropwise to destroy the excess NaH at 0 °C. The mixture which resulted was poured into EtOAc (2.2 L) and H_2O (300 mL), and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with H_2O and dried (Na_2SO_4). The solvent was removed to afford the crude allylation product, which was used directly in the next step. To the crude allylation product (58.0 g, 0.149 mol) were added palladium(II) acetate (836 mg, 3.73 mmol), silver carbonate (49.34 g, 0.180 mol, 90% purity), triphenylphosphine (1.955 g, 7.454 mmol), and DMF (320 mL, anhydrous). The reaction mixture was degassed under vacuum and stirred at rt under a slow stream of argon for 8 h. The reaction mixture was poured into EtOAc (1 L) and filtered through a pad of Celite to remove the Pd black and inorganic salts. The solution which resulted was diluted with additional EtOAc (1 L) and was then washed with water and brine and dried (Na_2SO_4). The solvent was removed under reduced pressure. This residue contained a trace amount of DMF which was subsequently removed under vacuum at rt (**heat should not be used to avoid isomerization**) overnight to provide the desired 3-methyleneindoline **12** as a yellow solid: IR (film) 2974, 2929, 1712, 1635, 1597, 1469, 1382, 1348, 1269, 1150, 1096, 903, 860, 791, 753, 695, 609 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 1.40 (9H, s), 3.25 (3H, s), 4.30 (2H, b), 4.97 (1H, t, $J = 0.7$ Hz), 6.06 (1H, t, $J = 2.4$ Hz), 6.12 (1H, d, $J = 8.3$ Hz), 7.02 (1H, t, $J = 8.2$ Hz), 8.14 (1H, b); EIMS (*m*/*e*, relative intensity) 261 (M^+, 72), 205 (100), 188 (21), 160 (80), 146 (34). This material was used directly in the next step.

***tert*-Butyl 3-(Bromomethyl)-4-methoxy-1*H*-indole-1-carboxylate (13).** To a three-neck round-bottom flask (5 L) equipped with an overhead stirrer was added cyclohexane (2.5 L, not distilled), and it was heated to reflux. The *N*-Boc 4-methoxy-3-methyleneindoline **12** was added in one portion, and this was followed by addition of *N*-bromosuccinimide (25.2 g, 0.142 mol) as well as AIBN (750 mg, 4.567 mmol). After being heated at reflux for 30 min, the slurry was cooled in an ice bath and then filtered through a pad of Celite to remove the succinimide. The filtrate was dried (Na_2SO_4), and most of the solvent was removed to provide the 3-bromomethyl 4-methoxyindole **13** as a yellow solution (around 100 mL in volume). **Caution: the product will rapidly decompose if all the solvent is removed.** This yellow solution was diluted with anhydrous THF (180 mL), cooled to −78 °C, and used directly in the next step: ^1H NMR (300 MHz, $CDCl_3$) δ 1.70 (9H, s), 3.99 (3H, s), 4.86 (2H, s), 6.65 (1H, d, $J = 8.0$ Hz), 7.21 (1H, t, $J = 8.1$ Hz), 7.52 (1H, s), 7.76 (1H, d, $J = 8.2$ Hz). This material was employed immediately in the next step.

***tert*-Butyl 3-(((2*R*,5*S*)-3,6-Diethoxy-5-isopropyl-2,5-dihydropyrazin-2-yl)methyl)-4-methoxy-1*H*-indole-1-carboxylate (18).** To a solution of (3*S*)-3,6-dihydro-6-isopropyl-2,5-diethoxypyrazine (**17**) (37.93 g, 0.179 mol) in anhydrous THF (500 mL) under argon at −78 °C was added dropwise *n*-BuLi (2.5 M in hexane, 89.6 mL, 0.224 mol). This solution was stirred for 30 min at −78 °C, and the solution of 3-bromomethyl 4-methoxyindole **13** from the previous step was added slowly over a period of 15 min via a cannula at −78 °C. The mixture was stirred at −78 °C for 6 h, slowly warmed to rt, and then quenched with a saturated aqueous $NaHCO_3$ solution (80 mL). The mixture was poured into EtOAc (1.5 L) and water (200 mL). The aqueous layer was extracted with EtOAc. The organic layer was combined and washed with water and brine and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue was purified by flash chromatography (100% hexane gradient to 5% EtOAc in hexane) to afford the desired indole **18** as a yellow oil: IR (film) 3206, 2974, 2871, 2838, 1731, 1692, 1603, 1567, 1494, 1465, 1434, 1368 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.72 (3H, d, $J = 6.8$ Hz), 1.05 (3H, d, $J = 6.8$ Hz), 1.17−1.34 (6H, m), 1.66 (9H, s), 2.20−2.37 (1H, m), 3.01 (1H, dd, $J = 8.2$, 14.3 Hz), 3.59 (1H, dd, $J = 4.2$, 14.1 Hz), 3.82 (1H, t, $J = 3.3$ Hz), 3.92 (3H, s), 4.00−4.12 (4H, m), 4.24−4.33 (1H, m), 6.64 (1H, d, $J = 8.1$ Hz), 7.19 (1H, t, $J = 8.4$

Hz), 7.30 (1H, s), 7.77 (1H, d, $J = 8.4$ Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.2 (2 carbons), 16.6, 19.0, 28.1 (3 carbons), 31.4, 31.6, 55.0, 56.4, 60.3, 60.4 (2 carbons), 82.9, 103.0, 108.1, 117.4, 120.3, 122.8, 124.6, 136. 8, 149.6, 154.4, 163.0, 163.4. Anal. Calcd for $C_{26}H_{37}N_3O_5$: C, 66.22; H, 7.91, N, 8.91. Found: C, 66.04; H, 8.01; N, 9.18.

3-(((2S,5*R*)-3,6-Diethoxy-5-isopropyl-2,5-dihydropyrazin-2-yl)-methyl)-4-methoxy-2-trimethyl-silyl)-1*H*-indole (22b). To carbamate **10b** (51.20 g, 0.176 mol) were added the internal alkyne **21a** (56.80 g, 0.159 mol), palladium acetate (650 mg, 2.90 mmol), potassium carbonate (50.42 g, 0.365 mol), lithium chloride (6.365 g, 0.150 mol), and DMF (300 mL). The mixture was degassed under vacuum (argon) and then heated at 100 °C under a slow stream of argon for 72 h. The mixture was cooled to rt, and EtOAc (400 mL) was added and then filtered through Celite to remove the Pd black and inorganic salts. The solution which resulted was diluted with additional EtOAc (1.2 L), and it was then washed with water and brine and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue was purified on silica gel (gradient elution from hexane to 10% EtOAc in hexane) to give the 4-methoxyindole **22b** as a yellow oil (53.43 g, 82%): IR (film) 3426, 2956, 1688, 1582, 1505, 1365 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.39 (9H, s), 0.73 (3H, d, $J = 6.8$ Hz), 1.11 (3H, d, $J = 6.8$ Hz), 1.17 (3H, t, $J = 7.1$ Hz), 1.24 (3H, t, $J = 7.1$ Hz), 2.35 (1H, m), 3.00 (1H, dd, $J = 10.2$, 13.4 Hz), 3.54 (1H, dd, $J = 4.7$, 13.4 Hz), 3.87 (3H, s), 3.94 (3H, m), 4.08 (1H, m), 4.21 (1H, m), 4.43 (1H, m), 6.42 (1H, d, $J = 7.6$ Hz), 6.96 (1H, d, $J = 8.0$ Hz), 7.06 (1H, t, $J = 7.8$ Hz), 7.89 (1H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 0.4, 14.2, 16.5, 19.2, 28.2, 30.9, 32.8, 54.6, 58.6, 60.0, 60.1, 60.3, 98.7, 104.0, 119.3, 122.7, 122.8, 129.5, 140.0, 154.6, 162.6, 164.8; EIMS (*m*/*e*, relative intensity) 443 (M^+, 19), 232 (100), 212 (27), 169 (27); HRMS *m*/*z* $C_{24}H_{38}N_3O_3Si$ $(M + H)^+$ calcd 444.2682, found 444.2686.

(2*R*,6*R*,12b*S*,*E*)-Benzyl 3-Ethylidene-8-methoxy-2-(2-methoxy-2-oxoethyl)-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine-6-carboxylate (31). To a solution of α,β-unsaturated ester **6** (1.8 g, 2.93 mmol) in freshly distilled CH_3CN (80 mL) was added Et_3N (1.9 mL), and this was followed by addition of Ni[COD]$_2$ (1.51 g, air sensitive, weighed under argon) at rt. The reaction mixture gradually turned red, and the starting material was completely consumed after 40 min (TLC). To the above solution was added Et_3SiH (2.0 mL), and the mixture was stirred for 30 min. The reaction mixture was then poured into a saturated aqueous solution of Na_2CO_3 (30 mL) and EtOAc (150 mL). The mixture was filtered through a pad of Celite, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue was subjected to flash column chromatography (gradient elution from hexane to 30% EtOAc in hexane) to afford the tetracycle **31** (1.07 g) in 75% yield: IR (film) 3380, 2948, 2834, 1730, 1571, 1508, 1435, 1352 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.65 (3H, d, $J = 6.9$ Hz), 1.98−2.05 (1H, m), 2.16−2.22 (1H, m), 2.25−2.36 (2H, m), 3.13- 3.19 (1H, m), 3.22 (1H, d, $J = 12.2$ Hz), 3.37−3.42 (1H, m), 3.48 (1 H, s), 3.50−3.56 (1H, m), 3.67 (3H, s), 3.85−3.90 (1 H, m), 3.87 (3 H, s), 4.54 (1H, t, $J = 5.6$ Hz), 5.07 (1H, d, $J = 12.4$ Hz), 5.16 (1H, d, $J = 12.4$ Hz), 5.43 (1H, q, $J = 6.9$ Hz), 6.47 (1H, d, $J = 7.5$ Hz), 6.93 (1H, d, $J = 7.7$ Hz), 7.02 (1H, t, $J = 7.8$ Hz), 7.24−7.29 (5 H, m), 8.23 (1 H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.6, 21.0, 31.4, 32.3, 37.9, 48.9, 51.6, 54.8, 55.1, 61.0, 66.1, 99.6, 104.2, 105.0, 117.4, 120.8, 122.3, 127.8 (2 carbons), 128.3 (2 carbons), 128.5, 131.9, 135.5, 135.9, 137.3, 154.2, 172.3, 173.7; EIMS (*m*/*e*, relative intensity) 488 (M^+, 54.0), 397 (19.5), 353 (100), 279 (19.2), 199 (12.0); HRMS *m*/*z* $C_{29}H_{32}N_2O_5$ $(M + H)^+$ calcd 489.2389, found 489.2368.

9-Methoxygeissoschizol (3). The tetracyclic ester **5** (12 mg, 0.034 mmol) was dissolved in THF (2 mL), and the solution was cooled to 0 °C. Then $LiAlH_4$ (3 mg, 0.079 mmol) was added, and the mixture was stirred at 0 °C for 1 h until the disappearance of the starting ester **5** (TLC). Aqueous 10% NaOH solution (0.5 mL) was added, and the mixture stirred for 10 min. Some white precipitate formed during this time, and the mixture was poured into EtOAc (20 mL) and H_2O (5 mL). The mixture which resulted was then filtered through a pad of Celite, and the aqueous layer was extracted with EtOAc. The organic layers were combined, washed with brine, and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue was purified on a short wash column (5% methanol in ethyl acetate) to provide the 9-methoxygeissoschizol (**3**) (10 mg) as a light yellow foam in 90% yield: IR (film) 3253, 2932, 1668, 1511, 1436, 1355 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42−1.58 (2H, m), 1.64 (3H, dd, $J = 1.2$, 7.0 Hz), 2.10−2.40 (2H, m), 2.90 (2H, s), 2.91−3.12 (2H, m), 3.13−3.27 (2H, m), 3.47−3.70 (3H, m), 3.90 (3H, s), 4.23 (1H, t, $J = 5.3$ Hz), 5.52 (1H, q, $J = 6.8$ Hz), 6.48 (1H, d, $J = 7.5$ Hz), 6.97 (1H, t, $J = 8.0$ Hz), 7.03 (1H, t, $J = 7.9$ Hz), 8.03 (1H, s), 8.56 (1H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.8, 20.0, 31.4, 32.4, 35.7, 51.2, 51.3, 53.5, 55.1, 61.5, 99.6, 104.5, 106.9, 117.3, 121.3, 122.0, 131.8, 136.0, 137.3, 154.2; EIMS (*m*/*e*, relative intensity) 326 (M^+, 77.0), 325 (82.1), 309 (10.0), 279 (22.5), 199 (63.8), 55 (100). The signals in the ^{13}C NMR spectrum were in excellent agreement with the literature values (see the Supporting Information).[3]

9-Methoxy-N_b-methylgeissoschizol (4). The 9-methoxygeissoschizol (**3**) (3.1 mg), MeI (0.05 mL), and freshly distilled MeOH (2 mL) were stirred at rt for 24 h until disappearance of the starting material (TLC). The solvent and excess MeI was removed under reduced pressure, and the residue was dissolved in freshly distilled MeOH (2 mL). This was followed by addition of AgCl (6 mg). The mixture was covered with aluminum foil and allowed to stir at rt for 2 d. The mixture was filtered through Celite, and the solvent was removed under reduced pressure to afford 9-methoxy-N_b-methylgeissoschizol **4** (2.8 mg) in 78% yield: ^{1}H NMR (300 MHz, CD_3OD) δ 1.32−1.44 (1H, m), 1.46−1.61 (1H, m), 1.75 (1H, dd, $J = 1.3$, 7.0 Hz), 2.14−2.33 (1H, m), 2.47−2.64 (1H, m), 3.09 (3H, s), 3.10−3.20 (2H, m), 3.42 (2H, t, $J = 6.2$ Hz), 3.62 (1H, d, $J = 12.6$ Hz), 3.65−3.78 (2H, m), 3.81 (3H, s), 4.26 (1H, d, $J = 12.8$ Hz), 4.50−4.60 (1H, m), 5.90 (1H, q, $J = 7.0$ Hz), 6.44 (1H, d, $J = 7.7$ Hz), 6.88 (1H, d, $J = 8.0$ Hz), 6.99 (1H, t, $J = 7.9$ Hz); ^{13}C NMR (75.5 MHz, CD_3OD) δ 12.6, 18.8, 29.8, 30.8, 35.3, 48.3, 54.1, 58.5, 59.6, 62.5, 64.4, 99.2, 103.9, 104.3, 116.4, 123.3, 126.3, 128.8, 131.8, 138.4, 154.3. The signals in the ^{13}C NMR spectra of **4** are in good agreement with the literature values (see the Supporting Information).[3]

(2Z,3E,6*R*,12bS)-Benzyl 3-Ethylidene-8-methoxy-2-(2-methoxy-2-oxoethylidene)-1,2,3,4,6,7,12,12 b-octahydroindolo[2,3-*a*]quinolizine-6-carboxylate (32). To the solution of α,β-unsaturated ester **6** (860 mg, 1.40 mmol) in DMF (10 mL) were added $Pd(OAc)_2$ (30 mg, 0.133 mmol), PPh_3 (75 mg, 0.286 mmol), and Et_3N (0.5 mL). The mixture was degassed (under vacuum and then argon) and then heated to 80 °C for 24 h. The mixture was diluted with EtOAc (20 mL) and then filtered through a pad of Celite to remove the inorganic salts. The filtrate was poured into EtOAc (150 mL) and H_2O (20 mL), and the aq layer was extracted with EtOAc. The organic layers were combined, washed with H_2O and brine, and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue was purified on a short wash column (gradient elution from hexane to 25% EtOAc in hexane) to give the Heck coupling product **32** (626 mg) in 92% yield: IR (film) 3372, 2947, 2835, 1722, 1710, 1440, 1355, 1257 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.76 (3H, d, $J = 6.9$ Hz), 2.38 (1H, t, $J = 11.8$ Hz), 3.39−3.45 (2H, m), 3.54 (1H, d, $J = 16.2$ Hz), 3.75−3.80 (1H, m), 3.77 (3H, s), 3.86−3.92 (1H, m), 3.87 (3H, s), 4.14 (1H, dd, $J = 2.6$, 13.8 Hz), 4.48 (1H, d, $J = 9.8$ Hz), 5.07 (2H, ABq, $J = 12.6$ Hz), 5.59 (1H, q, $J = 7.0$ Hz), 5.78 (1H, d, $J = 1.4$ Hz), 6.47 (1H, d, $J = 7.7$ Hz), 6.92 (1H, d, $J = 7.9$ Hz), 7.04 (1H, t, $J = 7.8$ Hz), 7.18−7.32 (5H, m), 7.98 (1H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.5, 26.4, 35.4, 51.1, 53.8, 55.1, 60.3, 60.8, 65.8, 99.6, 104.3, 105.3, 116.9, 117.0, 122.2, 123.5, 127.6 (2 carbons), 127.9, 128.5 (2 carbons), 131.5, 135.8, 136.0, 137.5, 154.2, 154.3, 167.2, 172.3; HRMS *m*/*z* $C_{29}H_{31}N_2O_5$ $(M + H)^+$ calcd 487.2233, found

487.2237. Anal. Calcd for $C_{29}H_{30}N_2O_5$: C, 71.59; H, 6.21; N, 5.76. Found: C, 71.38; H, 6.03; N, 5.52.

(2*R*,3*S*,6*R*,12b*S*)-Benzyl 3-Ethyl-8-methoxy-2-(2-methoxy-2-oxoethyl)-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine-6-carboxylate (33a). To a solution of the unsaturated ester **32** (326 mg, 0.67 mmol) in CH_3OH (10 mL) was added $NiCl_2 \cdot 6H_2O$ (24 mg, 0.10 mmol) at 0 °C. After the solution was stirred at 0 °C for 15 min, $NaBH_4$ (195 mg, 5.10 mmol) was added, and the mixture was stirred at 0 °C for 2 h. The reaction mixture was quenched by addition of water (0.5 mL) at 0 °C. The mixture was filtered through a pad of Celite and poured into EtOAc (100 mL) and H_2O (10 mL). The aqueous layer was extracted with EtOAc, the combined organic layers were washed with brine and dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was purified on a flash column (gradient elution from hexane to 20% EtOAc in hexane) to provide the saturated ester **33a** (180 mg) as the first fraction in 55% yield: IR (film) 3388, 2955, 1734, 1718, 1558, 1510, 1434, 1354 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.83−0.94 (1H, m), 0.85 (3H, t, J = 7.1 Hz), 1.13−1.25 (1H, m), 1.38−1.55 (2H, m), 1.85 (1H, d, J = 14.6 Hz), 2.28−2.41 (3H, m), 2.94 (1H, d, J = 13.9 Hz), 3.13 (1H, d, J = 11.3 Hz), 3.25−3.60 (2H, m), 3.73 (3H, s), 3.66−3.79 (1H, m), 3.89 (3H, s), 4.24 (1H, d, J = 12.2 Hz), 5.08 (2H, s), 6.48 (1H, d, J = 7.7 Hz), 6.90 (1H, d, J = 8.1 Hz), 7.01 (1H, t, J = 7.9 Hz), 7.13−7.32 (5H, m), 7.80 (1H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.5, 17.3, 26.8, 33.5, 36.9, 38.2, 39.9, 51.5, 53.6, 54.9, 55.1, 61.8, 65.6, 99.6, 104.1, 105.3, 117.2, 122.1, 127.3 (2 carbons), 127.6, 128.3 (2 carbons), 133.0, 136.1, 137.4, 154.3, 172.9, 173.4; EIMS (*m*/*e*, relative intensity) 490 (M^+, 28), 399 (29), 355 (100), 281 (12), 199 (32), 91 (55); HRMS *m*/*z* $C_{29}H_{35}N_2O_5$ $(M + H)^+$ calcd 491.2546, found 491.2535.

(6*R*,12b*S*)-Benzyl 3-Ethyl-8-methoxy-2-(2-methoxy-2-oxoethyl)-1,4,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine-6-carboxylate (33b). The tetrasubstituted olefin **33b** was obtained as the second fraction (30% EtOAc in hexane) in 40% yield (131 mg): ^1H NMR (300 MHz, $CDCl_3$) δ 1.01 (3H, t, J = 7.6 Hz), 1.94−2.19 (2H, m), 2.24 (1H, d, J = 13.9 Hz), 2.48 (1H, d, J = 15.9 Hz), 2.98 (1H, d, J = 15.0 Hz), 3.20 (1H, d, J = 15.0 Hz), 3.27 (1H, d, J = 15.7 Hz), 3.50 (2H, m), 3.67 (3H, s), 3.73 (1H, m), 3.86 (3H, s), 3.95 (1H, d, J = 6.6 Hz), 4.50 (1H, d, J = 10.3 Hz), 5.05 (2H, s), 6.46 (1H, d, J = 7.9 Hz), 6.89 (1H, d, J = 8.2 Hz), 7.02 (1H, t, J = 8.1 Hz), 7.10−7.23 (5H, m), 7.83 (1H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.9, 24.0, 26.8, 36.6, 37.6, 50.4, 51.8, 54.1, 55.1, 59.8, 65.6, 99.6, 104.2, 105.0, 117.1, 120.6, 122.1, 127.4 (2 carbons), 127.8, 128.3 (2 carbons), 132.6, 135.0, 135.5, 137.6, 154.3, 172.0, 172.6; EIMS (*m*/*e*, relative intensity) 488 (M^+, 26), 397 (21), 353 (73), 199 (100), 155 (22), 91 (84); HRMS *m*/*z* $C_{29}H_{33}N_2O_5$ $(M + H)^+$ calcd 489.2390, found 489.2411.

Methyl 2-((2*R*,3*S*,12b*S*)-3-Ethyl-8-methoxy-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizin-2-yl)acetate (35). Method A: A mixture of benzyl ester **33a** (26 mg, 0.053 mmol) and $PdCl_2$ (3 mg, 0.0168 mmol) in a solution of Et_3SiH (0.5 mL) and freshly distilled toluene (5 mL) was stirred at rt for 5 h until the disappearance of the starting benzyl ester **33a** by TLC. The mixture was filtered through a pad of Celite, and the solvent was removed under reduced pressure. The residue was purified on a short wash column to give the acid (20 mg) in 93% yield. To this acid were added freshly distilled CH_2Cl_2 (3 mL), isobutyl chloroformate (20 uL), and NMM (18 uL). The reaction mixture was stirred at rt for 1 h, at which time it was observed that the carboxylic acid was completely consumed (TLC). The reaction vessel was covered with aluminum foil, and to the above solution were added 2-mercaptopyridine *N*-oxide (14 mg) and Et_3N (30 uL). The mixture was stirred at rt for 2 h until the disappearance of the mixed anhydride. To the above solution was added *t*-BuSH (0.2 mL), and the aluminum foil was removed. The solution was then irradiated with a Q-beam light for 2 h. The solution was poured into a mixture of EtOAc (30 mL) and dilute aq NH_4OH (5 mL). The aq layer was extracted with EtOAc. The combined organic layers were washed with brine and dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was subjected to flash chromatography (gradient elution from hexane to 80% EtOAc in hexane) to yield the tetracyclic ester **35** (9 mg) in 50% yield.

Method B: To a solution of trisubstituted olefin **5** (24 mg, 0.067 mmol) was added (1,5-cyclooctadiene) (pyridine)(tricycle-hexylphosphine)iridium(I) hexafluorophosphate (Crabtree's catalyst, 8 mg, 0.010 mmol) and CH_2Cl_2 (3 mL). The solution was degassed and filled with H_2. A balloon filled with H_2 was connected to the round-bottom flask via a needle. This solution was stirred at rt for 24 h, after which the balloon was removed and the solvent was removed under reduced pressure. The residue was purified on a flash column (gradient elution from hexane to 80% EtOAc in hexane) to provide the desired saturated ester **35** (17 mg) in 70% yield: IR (film) 3386, 2924, 2799, 2751, 1730, 1569, 1507, 1436, 1353 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.91 (3H, t, J = 7.3 Hz), 1.20−1.30 (1H, m), 1.40−1.74 (3H, m), 1.89 (1H, td, J = 2.7, 12.8 Hz), 2.19−2.43 (4H, m), 2.56 (1H, dt, J = 4.4, 11.5 Hz), 2.85−3.33 (5H, m), 3.72 (3H, s), 3.87 (3H, s), 6.45 (1H, d, J = 7.7 Hz), 6.88 (1H, d, J = 8.0 Hz), 6.99 (1H, t, J = 7.9 Hz), 7.76 (1H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.4, 18.2, 23.6, 31.6, 36.5, 37.9, 39.8, 51.5, 53.3, 55.2, 59.5, 60.0, 99.6, 104.2, 107.8, 117.4, 121.8, 132.5, 133.0, 137.2, 154.4; EIMS (*m*/*e*, relative intensity) 356 (M^+, 90.0), 325 (13.2), 299 (23.5), 283 (21.6), 255 (23.2), 220 (100), 199 (17.0), 156 (61.2).

Mitragynine 1. Diisopropylamine (0.053 mL, 0.37 mmol) and THF (3 mL) were added to a round-bottom flask (10 mL), and the solution which resulted was cooled to −78 °C and stirred for 10 min. This was followed by addition of *n*-BuLi (0.1 mL, 0.248 mmol, 2.5 M in hexane). The solution was stirred at −78 °C for 30 min, and the tetracyclic ester **36** (30 mg, 0.062 mmol) in anhydrous THF (2.5 mL) was added to this solution. The mixture was stirred at −78 °C for 2 h and then warmed to 0 °C and stirred for 30 min. The reaction mixture was quenched with an aqueous solution of $NaHCO_3$ (1 mL), and the mixture was poured into EtOAc (20 mL) and H_2O (5 mL). The aq layer was extracted with EtOAc, and the organic layers were combined, washed (brine), and dried (Na_2SO_4). The solvent was removed under reduced pressure to provide the enol **37** together with its aldehyde tautomers (22.1 mg). Part of this mixture (6 mg, 0.0165 mmol) was dissolved in a saturated solution of hydrogen chloride (g) in EtOAc and stirred at rt for 8 h. The solvent was then removed under reduced pressure, and the residue was dissolved in anhydrous methanol. To this mixture were added methanolic HCl (1 drop) and trimethyl orthoformate (0.1 mL), and the solution which resulted was stirred at rt for 5 h. It was then heated to reflux for 12 h. The solvent was removed under reduced pressure, and the residue was dissolved in DMF (2 mL). To this solution was added *t*-BuOK (3 mg), and the mixture was stirred at rt for 8 h. The mixture was poured into EtOAc (20 mL) and aq $NaHCO_3$ (5 mL).The aq layer was extracted with EtOAc. The organic layers were combined, washed with H_2O and brine, and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue was purified on a short wash column (alumina, gradient elution from hexane to 40% EtOAc in hexane) to give mitragynine **1** (1.0 mg): ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (3H, t, J = 7.5 Hz), 1.58−1.70 (2H, m), 1.72−1.85 (2H, m), 2.40−2.60 (4H, m), 2.92 (1H, dd, J = 5.5, 10.8 Hz), 2.96−3.08 (3H, m), 3.16 (1H, d, J = 11.6 Hz), 3.70 (3H, s), 3.73 (3H, s), 3.88 (3H, s), 6.46 (1H, d, J = 7.8 Hz), 6.90 (1H, d, J = 8.0 Hz), 7.00 (1H, t, J = 7.9 Hz), 7.43 (1H, s), 7.67 (1H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.9, 19.1, 23.9, 30.0, 39.9, 40.7, 51.3, 53.8, 55.3, 57.8, 61.3, 99.8, 104.2, 107.9, 111.3, 121.8, 133.7, 137.2, 154.5, 160.5; EIMS (*m*/*e*, relative intensity) 398 (M^+, 100), 383 (43.5), 269 (14.3), 214 (74.5). The synthetic mitragynine was identical on TLC to mitragynine kindly supplied by Professor Takayama at Chiba University, and the ^1H NMR and ^{13}C NMR

are in good agreement with the data kindly supplied by Professor Takayama.

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Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra for the intermediates and final products and chiral HPLC chromatograms of the N_b-Boc-4-methoxytryptophan ethyl ester (**26**). This material is available free of charge via the Internet at http://pubs.acs.org.

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