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Total Synthesis of the Opioid Agonistic Indole Alkaloid Mitragynine and the First Total Syntheses of 9-Methoxygeissoschizol and 9-Methoxy-N_b-methylgeissoschizol

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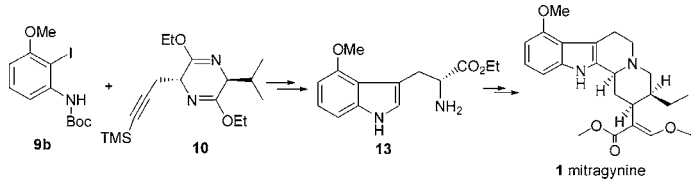
ABSTRACT



An enantiospecific method for the synthesis of 4-methoxytryptophan has been developed via a regiospecific Larock heteroannulation and employed for the first total syntheses of 9-methoxygeissoschizol and 9-methoxy-N_b-methylgeissoschizol, as well as the total synthesis of the opioid agonistic alkaloid mitragynine. The asymmetric Pictet–Spengler reaction and a Ni(COD)$_2$-mediated cyclization served as key steps.

Mitragynine (**1**) was isolated from *Mitragyne speciosa* Korth[1] and has been employed as a substitute for opioids in the treatment of pain in Thailand. The X-ray crystal structure of the hydroiodide salt of mitragynine was determined in 1965.[2] Although mitragynine was the major alkaloid from the extract of *Mitragyne speciosa*, a more careful study indicated that a more potent alkaloid, 7-hydroxymitragynine (**2**), was present in the mature leaves of *M. speciosa* (Thailand). This hydroxyl derivative could also be obtained from the oxidation of mitragynine with iodobenzene diacetate.[3] The interesting analgesic activity and relatively complex structure of mitragynine prompted Takayama et al. to carry out the first total synthesis of mitragynine[4] and an SAR study.[5] Interestingly, the methoxyl functional group was found essential for the analgesic acitivity.[5d] Mitragynine itself was a full opioid agonist and primarily acted on μ- and δ-opioid receptors, whereas the desmethyl mitragynine exhibited high affinity for μ-opioid receptors; however, it was only a partial agonist. Furthermore, the desmethoxy analogue of mitragynine, corynantheidine, did not exhibit any opioid agonistic activity at all, but it reversed the morphine-inhibited twitch contraction. Therefore, corynantheidine is an opioid receptor antagonist.[5d] The alkaloid 9-methoxy-geissoschizol (**3**) was first isolated from the bark

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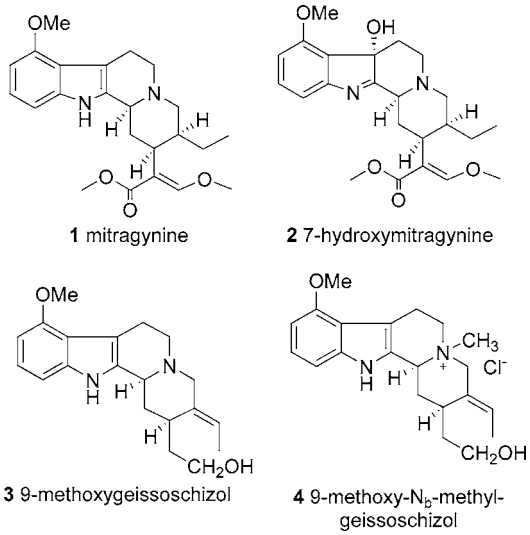


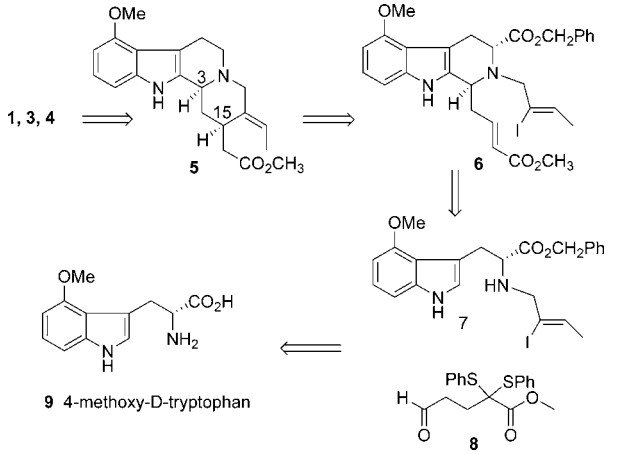
Figure 1. Examples of 9-methoxy indole alkaloids.

of *Strychnos guianensis*,[6] which was found in the basin of the middle and upper Rio Orinoco rivers and throughout the Amazon basin. The crude extracts from the root and stem bark displayed muscle relaxant activity.[7] The related 9-methoxy-N_b-methylgeissoschizol (**4**), a quaternary indole alkaloid, was identified later.[8] To our knowledge, no total syntheses of **3** and **4** have appeared to date, in part due to the difficulty in regiospecific formation of the 4-methoxyindole unit. Herein is reported the first enantiospecific total syntheses of **3** and **4**, as well as the total synthesis of mitragynine.

It was envisioned that these *Corynathe* indole alkaloids mitragynine (**1**), 9-methoxygeissoschizol (**3**), and 9-methoxy-N_b-methylgeissoschizol (**4**) could be synthesized from the same 9-methoxy-substituted tetracyclic intermediate **5** (see Scheme 1). Analogous to the previous work of Yu,[9] the C(3) and C(15) cis configuration might be generated via Ni(0)[10] mediated cyclization of the vinyl iodide with the double bond of the α,β-unsaturated ester in intermediate **6**. The C(3) configuration could be set up stereospecifically by the asymmetric Pictet−Spengler reaction[11] of the secondary N_b-alkyl amine **7** and the aldehyde **8**.[9,12] The N_b-alkyl group of the secondary amine **7** would direct the diastereoselectivity at C(3)[11] and, presumably, could be obtained from monoalkylation of 4-methoxy-D-tryptophan **9**.

A key obstacle in the preparation of **1**, **3** and **4** stems from the availability, or lack thereof, of 4-methoxytryptophan. To

Scheme 1. Retrosynthetic Analysis of Intermediate **5**



date, 4-methoxytryptophan could be obtained in high optical purity only by the use of immobilized penicillin G acylase, in a kinetic resolution reported by Ley et al.[13] However, the Larock heteroannulation[14] is a powerful method for the synthesis of ring-A substituted indole derivatives and has been employed for the regiospecific synthesis of both 11- and 12-methoxy-substituted indole alkaloids.[15] The strength of the Larock process stems from the regioselectivity that can be achieved when a bulky silyl-substituted internal alkyne is employed as a substrate. This regioselectivity is due, in large part, to steric interactions between the ortho aromatic H atom and the substituent on the alkyne.[14b,16] This steric effect is even more demanding when the aromatic hydrogen atom is replaced by a methoxyl group in the Larock heteroannulation, as required in the synthesis of 4-methoxy indole derivatives. Initial attempts of the Larock heteroannulation with aniline **9a** and the TES propargyl-substituted Schöllkopf chiral auxiliary **10b**,[18] under conditions analogous to those successfully employed to prepare 11- and 12-methoxy indoles, gave only 40% of the desired indole **11a**. Gratifyingly, the Larock heteroannulation process between Boc-protected 2-iodo-3-methoxyaniline[17] **9b** and the TMS alkyne **10a**[18] gave the N_a-Boc-protected indole derivative **12** in 80% yield in 6 h. Moreover, when the Boc-protected indole **12** was allowed to stir for 3 days, the desired 4-methoxy N_a-H indole **11b** could be obtained in 82% yield. This was carried out on 50 g scale. When the TES-substituted alkyne **10b** and the Boc-protected aniline **9b** were subjected

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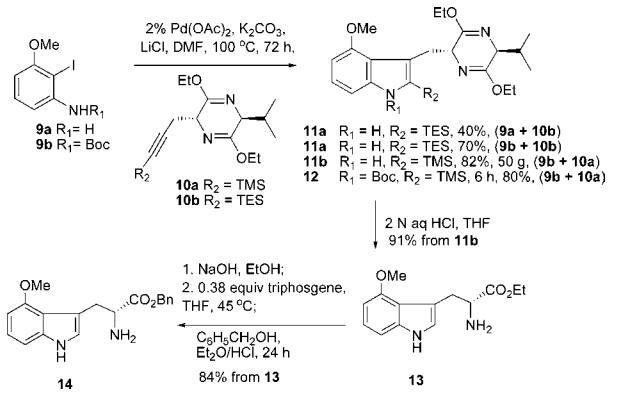
to the same conditions, the yield of indole decreased to 70%. Presumably, the Boc-protected iodoaniline **9b** increased the reaction rate by accelerating the oxidative addtion of Pd(0) to the aryl iodide. Furthermore, since the steric demands of the methoxyl function are greater than the corresponding aromatic H atom, the TMS substituted alkyne is bulky enough to promote the regioselectivity while binding more rapidly to the Pd catalyst than the corresponding TES-substituted analogue. The hydrolysis of the Schöllkopf chiral auxiliary was accompanied by concomitant loss of the indole-2-silyl group of **11b**. This smoothly took place in aqueous 2 N HCl in THF to provide 4-methoxy-D-tryptophan ethyl ester (**13**) in a single step in 91% yield. The valine ethyl ester could be removed by Kugelrohr distillation and reused. The ethyl ester **13** was hydrolyzed in ethanolic NaOH solution and then converted into the benzyl ester **14** by a literature procedure in high yield, analogous to the process employed in the synthesis of corynantheidine (Scheme 2).[9,19]

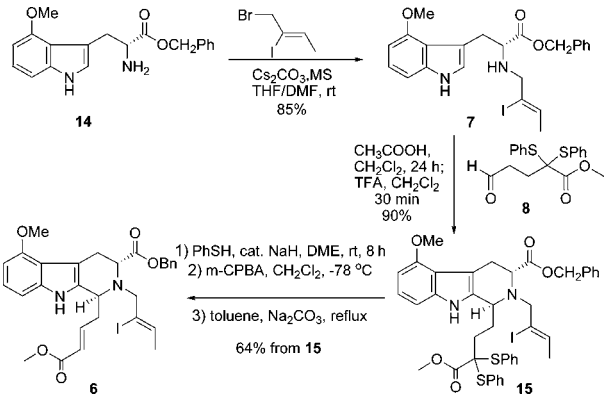
Scheme 2



The monoalkylation of benzyl ester **14** with the allylic bromide[20] afforded the secondary amine **7** in 85% yield when Cs_2CO_3[21] was used as the base in a mixture of DMF and THF (Scheme 3). The desired stereocenter at C-3 was achieved via the asymmetric Pictet−Spengler reaction[11] between the secondary amine **7** and the aldehyde[12] **8** to furnish the tetrahydro-β-carboline **15**. This diester **15** was converted into the desired α,β-unsaturated ester **6** in 64% overall yield via a series of standard transformations including removal of 1 equiv of thiophenol from **15**, followed by an oxidation with *m*-CPBA and a sulfoxide elimination sequence (Scheme 3).[9,12]

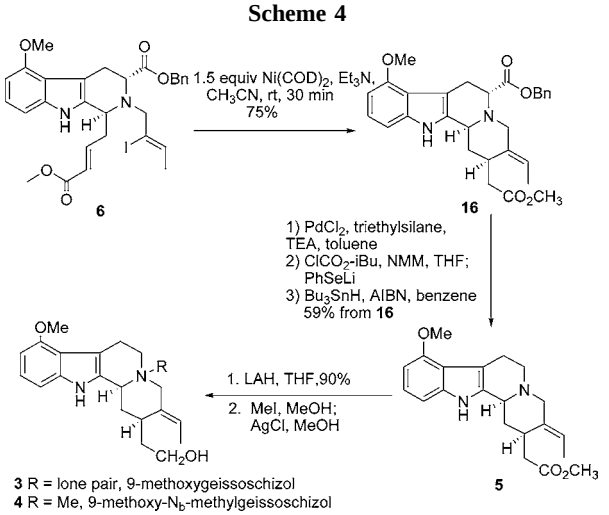
The α,β-unsaturated ester **6** was then subjected to the Ni(COD)$_2$-mediated cyclization[9,10] to provide the desired *Corynanthe* skeleton **16** in 75% yield. Removal of the benzyl group of the benzyl ester **16** was achieved when **16** was treated with $PdCl_2$ in the presence of Et_3SiH,[9,22] and the

Scheme 3



corresponding carboxylic acid was converted into the tetracyclic ester **5** via the Barton−Crich decarboxylation process.[9,23] Although one hates to remove a carboxylic acid function during total synthesis, this function originated from glycine employed in the Schöllkopf chiral auxiliary. The ester **5** was reduced with LAH to give 9-methoxygeissoschizol (**3**) in 90% yield. 9-Methoxy-N_b-methylgeissoschizol (**4**) was then synthesized via the N_b methylation of **3** with methyl iodide followed by exchange of the iodide to the chloride using AgCl (Scheme 4). To the best of our knowledge, this

Scheme 4



is the first total synthesis of 9-methoxygeissoschizol (**3**) and 9-methoxy-N_b-methylgeissoschizol (**4**). The ^{13}C NMR data of synthetic (+)-**4** agree in all respects with those reported for the natural product.[6,8]

To prepare **1**, reduction of the olefin bond in **5** was required. The reduction of this double bond turned out to be difficult. Many attempts with PtO_2 or Pd/C reduction with H_2 were unsuccessful. However, when Crabtree's catalyst[24]

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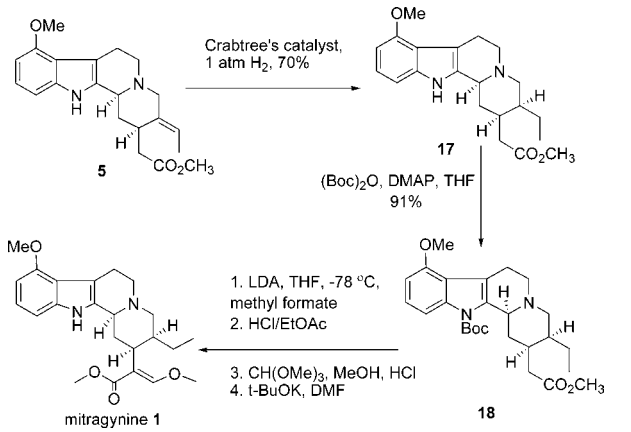
Scheme 5



was employed, the desired ester **17** was obtained in 70% yield. With the tetracycle **17** in hand, it was then treated with $(Boc)_2O$ in the presence of a catalytic amount of DMAP to provide the Boc derivative **18** in 91% yield. The ester **18** was then subjected to formylation, and the Boc group was removed in EtOAc that had been saturated with HCl gas. This was followed by acetal formation and *t*-BuOK mediated elimination of MeOH to provide mitragynine **1**, analogous to the final steps reported by Takayama et al.[4] The synthetic mitragynine **3** was identical on TLC to the sample of mitragynine kindly supplied by Professor Takayama (Chiba University), and the ^1H NMR data were in excellent agreement with the data kindly supplied by Professor Takayama.

In summary, the 4-methoxy-D-tryptophan ethyl ester **13** was prepared via Larock heteroannulation, and the Boc-substituted aniline **9b** provided much better yields of indole than the iodoaniline **9a** itself. This process could be employed for the synthesis of 4-methoxy-D-tryptophan on large scale, and 4-methoxy-L-tryptophan could also be synthesized in a similar manner by employing D-valine.[25] The first total syntheses of 9-methoxygeissoschizol (**3**) and 9-methoxy-N_b-methylgeissoschizol (**4**), as well as the total synthesis of mitragynine (**1**), was achieved from 4-methoxy-D-tryptophan. The asymmetric Pictet−Spengler reaction and $Ni(COD)_2$-mediated cyclization served as key steps to set up the stereochemistry at C(3) and C(15) in these indole alkaloids.

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