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Studies toward the total synthesis of (+)-gelsemine and synthesis of spirocyclopentaneoxindole through intramolecular Michael cyclization

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ABSTRACT

During the approach to the total synthesis of (+)-gelsemine, two novel spirocyclopentaneoxindole compounds **2** and **3** were obtained. Starting from compound **9**, spirocyclopentaneoxindole **3** was efficiently and unexpectedly obtained through a Boc migration–intramolecular Michael cyclization cascade procedure. This intramolecular Michael addition strategy allows conveniently access to complex spirooxindole and spirocyclopentaneoxindole derivatives.

Heterocyclic compounds play important roles in the drug discovery process. Polycyclic spirooxindoles are commonly occurring heterocyclic ring systems found in a range of natural products and pharmaceuticals.[1–5] Among them, spirocyclopentaneoxindole scaffolds are widely embodied in natural alkaloids such as paraherquamide A, notoamide B, and sclerotiamide (Fig. 1).[6,7] Spirocyclopentaneoxindole, bearing a critical quaternary carbon at the joint point, remains a challenging motif for synthetic chemists. Because of the intriguing structure and potential biological activity, the synthetic methodologies of spirocyclopentaneoxindole framework have received significant attention around the world. To date, many elegant strategies concerning the synthesis of spirocyclopentaneoxindole framework have been reported.[8–11] Recently, two new spirocyclopentaneoxindole derivatives compounds **2** and **3** were efficiently constructed through an intramolecular Michael addition and an unexpected Boc migration–intramolecular Michael cyclization cascade procedure, respectively.

(+)-Gelsemine **1** was first isolated in 1876 and its elusive structure was elucidated in 1959 by NMR spectroscopy and X-ray crystallographic analysis,[12–14] which has attracted numerous synthetic efforts in the chemical community.[15] During our research on asymmetric total synthesis of (+)-gelsemine,[16] to our surprise, two new spirocyclopentaneoxindole derivatives **2** and **3** were achieved (Fig. 2). In this Letter, we will have a further discussion on studies toward the total synthesis of (+)-gelsemine and formation of the spirocyclopentaneoxindole skeleton.

As shown in the retrosynthetic analysis of (+)-gelsemine (Scheme 1), we envisioned that (+)-gelsemine could be synthesized

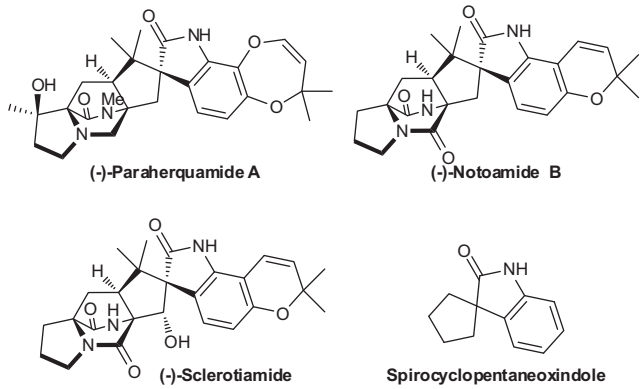

Figure 1. Natural products containing the spirocyclopentaneoxindole scaffold.

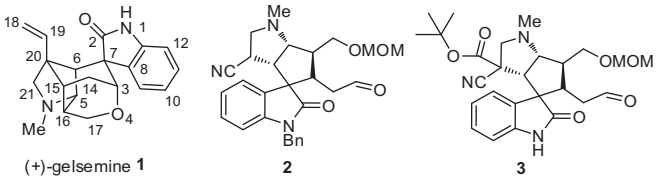

Figure 2. Structures of (+)-gelsemine and compounds **2** and **3**.

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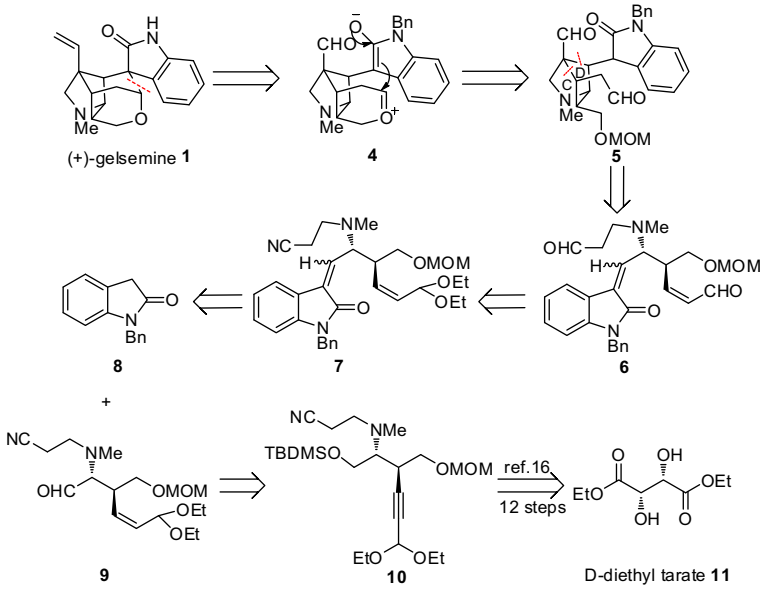
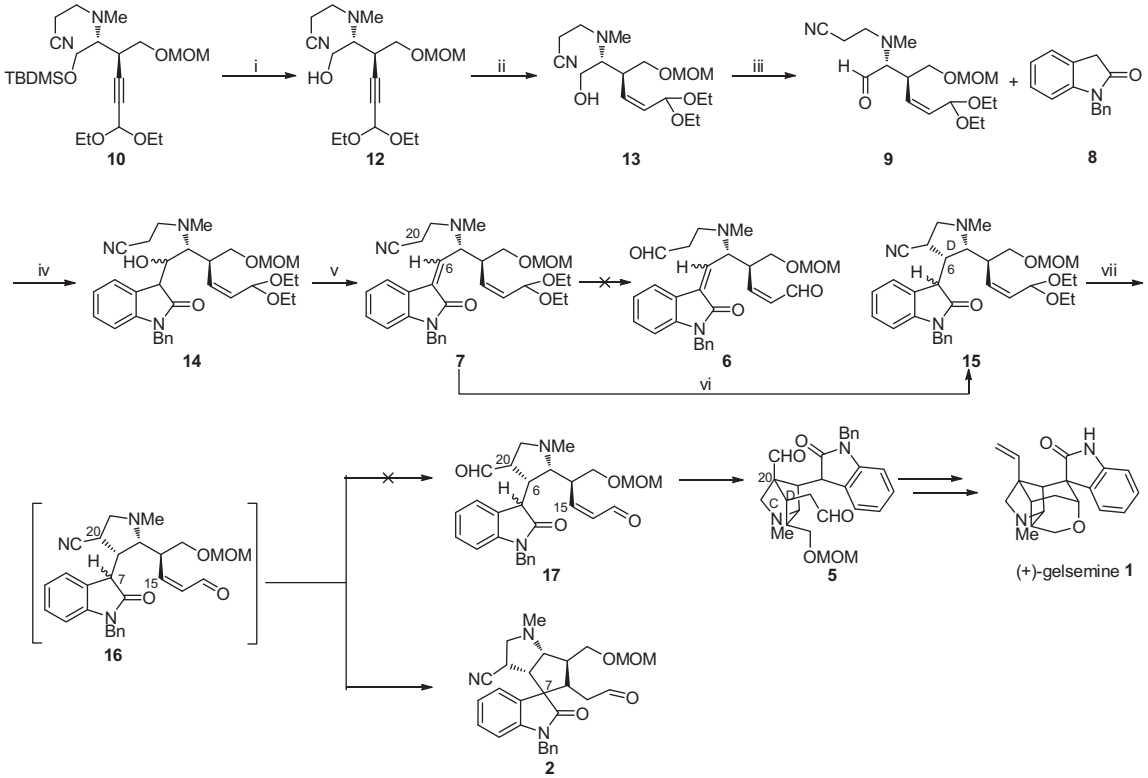


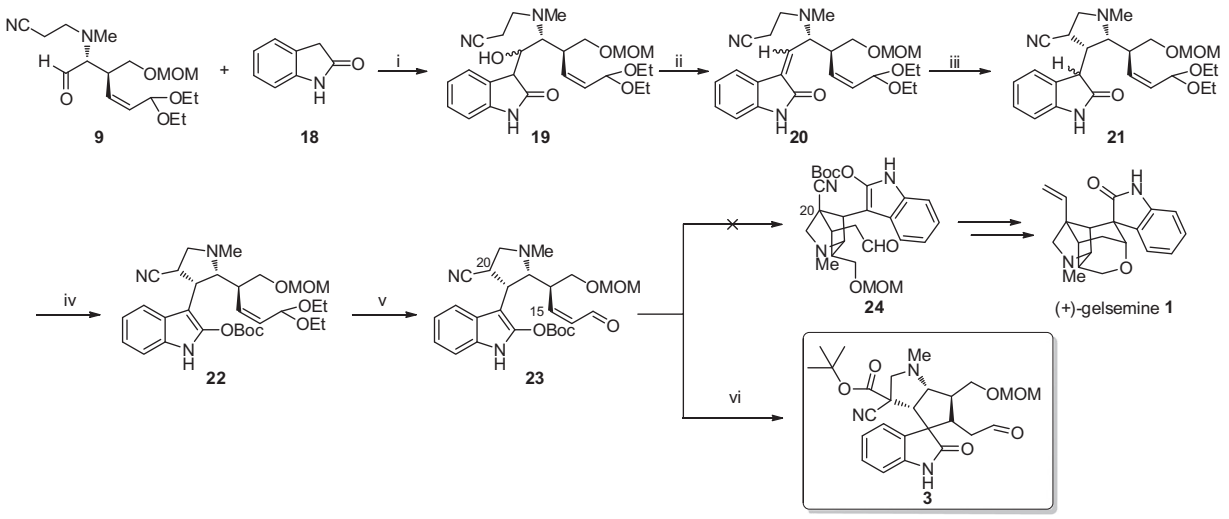
Scheme 1. Retrosynthetic analysis of (+)-gelsemine.

from the intermediate **5** through an acid-catalyzed enol-oxonium cyclization. We reasoned that the C-ring and D-ring of compound **5** could be constructed by two continuous intramolecular Michael additions due to the nucleophilicity of α position of aldehyde group in **6**. Compound **6** could be achieved through cyano reduction and deprotection of acetal from compound **7**. Compound **7** was synthesized by intermolecular aldol condensation of *N*-benzyloxindole **8** and aldehyde **9**. Cis alkene **9** could be conveniently generated from compound **10**, which was easily prepared from D-diethyl tartrate in 12 steps according to our reported synthetic route.[16]

According to the retrosynthetic analysis, our total synthesis of (+)-gelsemine commenced with converting **10** to **12** (Scheme 2). Removal of *t*-butyldimethylsilyl (TBDMS) with tetrabutylammonium fluoride in **10** provided alcohol **12** in 93% yield, which followed by the partial hydrogenation of triple bond in **12** with Lindlar catalyst ($Pd/CaCO_3$) at 1 atm of hydrogen pressure in MeOH for 3 h gave the expected *Z*-conformation alkene **13** in excellent



Scheme 2. The first route toward (+)-gelsemine. Reagents and conditions: (i) $Bu_4N^+F^-$, THF, rt, 93%; (ii) Lindlar Cat., H_2, CH_3OH, rt, 95%; (iii) Swern oxidation, 95%; (iv) LDA, THF, −78 °C, 70%; (v) $SOCl_2$/pyridine, 0 °C, 85%, *E*/*Z* = 3:5; (vi) LDA, THF, −78 °C, 70%; (vii) PPTS, acetone–H_2O, rt., 80%.



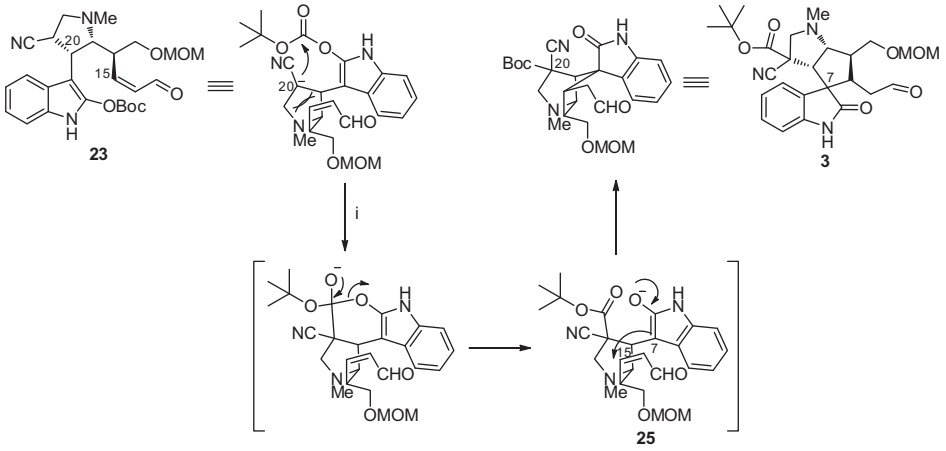
Scheme 3. The second route toward (+)-gelsemine. Reagents and conditions: (i) LDA, THF, −78 °C, 70%; (ii) $SOCl_2$/pyridine, 0 °C, 85%; (iii) LDA, THF, −78 °C, 70%; (iv) $(Boc)_2O$, Et_3N, CH_2Cl_2, rt, 40%; (v) PPTS, acetone–H_2O, rt, 80%; (vi) LiHMDS, THF, −78 °C → −40 °C.

yield. Oxidation of the hydroxy group in **13** provided aldehyde **9**. Aldol condensation of the resulting aldehyde **9** with *N*-benzyloxindole **8** in the presence of LDA at −78 °C, followed by dehydration with $SOCl_2$/pyridine delivered compound **7** (*E*/*Z* = 3:5). With **7** in hand, we began to synthesize the key compound **6**. Perhaps, due to the instability of **6**, numerous efforts for converting compound **7** to **6** failed, which declared the failure of our initial plan to assemble the C/D rings, and C20 quaternary stereocenter of gelsemine via two continuous intramolecular Michael additions. Based on the above results, we have to construct the C/D rings of gelsemine, respectively. Starting from compound **7**, the pyrrolidine ring (D ring) was easily prepared through the first intramolecular Michael addition of C20 to C6 in the presence of LDA at −78 °C to provide **15** in 70% yield. However, our attempt to construct the C-ring via a second intramolecular Michael addition of C20 to C15 in compound **17** was failed. Although the anticipated α,β-unsaturated aldehyde **16** was achieved after the deprotection of the acetal, compound **17** was unable to be prepared from compound **16** because **16** was directly converted into an enantiomerically pure spirocyclopentaneoxindole derivative **2**[19] via an intramolecular Michael addition of C7 to C15 (Scheme 2).

α,β-Unsaturated aldehyde **16** was easily converted into spirooxindole **2** via the spontaneous attack of oxindole enolate on the electrophilic C15 under acidic condition.[17,18] However, the C-ring of gelsemine was more difficult to form, as a strong base was usually needed to active the α position of cyano. Based on the above analysis, in order to construct C-ring smoothly, the nucleophilicity of C7 should be weakened at first. Therefore, we designed compound **23** to avoid the cyclization of C7 to C15. Adopting the above procedure, compound **21** was obtained successfully in three steps from **9** including Aldol condensation, Lindlar reduction, and Michael addition. Protection of **21** with ditertbutyl-dicarbonate in the presence of Et_3N gave the O-protected indole **22** in 40% yield. Removal of acetal in **22** provided the stable α,β-unsaturated aldehyde **23** in 80% yield. It is anticipated that the key precursor **24** of (+)-gelsemine could be synthesized by intramolecular Michael addition between C20 and C15. Surprisedly, treatment of α,β-unsaturated aldehyde **23** with LiHMDS yielded an enantiomerically pure spirocyclopentaneoxindole compound **3**[19] rather than the desired **24** (Scheme 3).

The data of ^1H and ^{13}C NMR spectra, together with further ^1H–^1H, direct ^1H–^{13}C, and long range ^1H–^{13}C scalar connectivities as measured from 2D experiments, allowed the determination of the structure of **3** as shown in Figure 2.

The unexpected novel spirocyclopentaneoxindole derivative compound **3** was assumed to be obtained through a tandem



Scheme 4. Plausible mechanism for the formation of **3**. Reagents and conditions: (i) LiHMDS, THF, −78 °C → −40 °C.

procedure of Boc migration–intramolecular Michael cyclization. The plausible mechanism for the unexpected cascade reaction is proposed in Scheme 4. After deprotonation of C20, the formed anion is unreactive toward the α,β-unsaturated aldehyde, probably because of the strong steric exclusion involved in the formation of C20 quaternary stereocenter and cage-like structure. However, the C20 anion is enough to attack the adjacent enol-Boc group to form compound **25**. After Boc migrated to C20, the spirocyclopentaneoxindole skeleton was immediately formed via a spontaneous intramolecular Michael addition of C7 to C15.

In conclusion, the synthetic strategy using two continuous intramolecular Michael additions to construct C/D-ring and C20 quaternary stereocenter of (+)-gelsemine was studied. Although the key skeleton of (+)-gelsemine failed to be synthesized, interesting chemistry ensued from our exploration. Two novel enantiomerically pure spirocyclopentaneoxindole derivatives **2** and **3** were achieved, and the research of their possible bioactivities is now in progress. The spirocyclopentaneoxindole skeleton of **3** was efficiently and unexpectedly prepared through a Boc migration–intramolecular Michael cyclization cascade procedure. This work demonstrates the intramolecular Michael addition strategy which will be useful for the synthesis of complex spirooxindole and spirocyclopentaneoxindole derivatives.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.08.048. These data include MOL files and InChiKeys of the most important compounds described in this article.

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19. *Analytical data*
Compound **2**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.58 (s, 1H), 7.36 (d, J = 7.6 Hz, 1H), 7.34–7.24 (m, 5H), 7.22 (t, J = 7.6 Hz, 1H), 7.08 (t, J = 7.6 Hz, 1H), 6.72 (d, J = 7.6 Hz, 1H), 4.98 (d, J = 15.6 Hz, 1H), 4.75 (d, J = 15.6 Hz, 1H), 4.65(s, 2H), 3.78–3.63 (m, 4H), 3.38 (s, 3H), 3.28 (t, J = 11.6 Hz, 1H), 3.20 (dt, J = 12.0, 3.2 Hz, 1H), 3.04 (t, J = 11.6 Hz, 1H), 2.96 (d, J = 10.8 Hz, 1H), 2.78 (dd, J = 16.0, 3.2 Hz, 1H), 2.45 (s, 3H), 2.29–2.22 (m, 1H), 2.05–1.98 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.9, 177.3, 142.7, 135.5, 131.1, 128.7, 128.6, 128.5, 127.6, 127.5, 127.3, 123.1, 122.6, 119.3, 109.8, 96.7, 72.5, 66.9, 65.3, 61.9, 55.6, 50.8, 50.6, 46.4, 45.5, 44.1, 41.9, 23.5; IR (KBr) 2960, 2933, 2896, 2247, 1720, 1705, 1638, 1486, 1379, 1191, 1168, 1120, 1097, 923, 768, 701 cm^{-1}; HRMS (M+Na$^+$) calcd for $C_{28}H_{31}N_3NaO_4$ 496.2207, found 496.2211.
Compound **3**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.13 (s, 1H), 7.86 (s, 1H), 7.18 (t, J = 7.6 Hz, 1H), 7.04 (d, J = 7.6 Hz, 1H), 6.96 (t, J = 7.6 Hz, 1H), 6.85 (d, J = 7.6 Hz, 1H), 4.62 (s, 2H), 3.97 (d, J = 11.2 Hz, 1H), 3.87–3.84 (m, 1H), 3.70–3.65 (m, 2H), 3.44–3.32 (m, 1H), 3.35 (s, 3H), 3.29 (d, J = 12.4 Hz, 1H), 3.22 (d, J = 11.2 Hz, 1H), 2.92 (dd, J = 18.8, 10.8 Hz, 1H), 2.79 (dd, J = 18.8, 4.0 Hz, 1H), 2.51 (s, 3H), 2.04–2.01 (m, 1H), 1.11 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.1, 178.1, 166.2, 141.7, 128.7, 128.2, 124.6, 121.8, 116.5, 110.0, 96.5, 84.4, 72.6, 71.3, 69.3, 63.0, 55.5, 50.8, 46.8, 46.2, 44.2, 41.8, 27.7, 27.4, 27.2; IR (KBr) 3002, 2985, 2876, 2246, 1718, 1707, 1624, 1485, 1374, 1205, 1145, 1107, 1072, 923, 720, 697 cm^{-1}; HRMS (M+Na$^+$) calcd for $C_{26}H_{33}N_3NaO_6$ 506.2267, found 506.2272.