Total synthesis of (+)-gelsemine via an organocatalytic Diels–Alder approach

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The structurally complex alkaloid gelsemine was previously thought to have no significant biological activities, but a recent study has shown that it has potent and specific antinociception in chronic pain. While this molecule has attracted significant interests from the synthetic community, an efficient synthetic strategy is still the goal of many synthetic chemists. Here we report the asymmetric total synthesis of (+)-gelsemine, including a highly diastereoselective and enantioselective organocatalytic Diels–Alder reaction, an efficient intramolecular trans-annular aldol condensation furnishing the prolidine ring and establishing the configuration of the C20 quaternary carbon stereochemical centre. The entire gelsemine skeleton was constructed through a late-stage intramolecular S_N2 substitution. The enantiomeric excess of this total synthesis is over 99%, and the overall yield is around 5%.

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Although gelsemine was isolated\(^1\) in as early as 1876 from *Gelsemium Sempervirens* Ait., its structure was not determined until 1959 by means of nuclear magnetic resonance (NMR) spectroscopic techniques\(^2,3\) and X-ray crystallographic analysis\(^4\). This indole alkaloid contains a hexacyclic cage structure and seven contiguous chiral carbon centres (Fig. 1). The complex chemical structures of gelsemine and other members of the alkaloid family\(^5–8\) have attracted considerable attention from synthetic chemists. So far, in addition to the many synthetic efforts\(^9–37\), there are eight total syntheses reported in the literature\(^38–49\) (Fig. 2), two of which are asymmetric\(^44,48\). Although gelsemine was thought to have no particular biological activities, a recent report indicated that gelsemine exhibited potent and specific antinociception in chronic pain by acting at the three spinal glycine receptors\(^50\). Besides, gelsemine was nonaddictive, indicating that the mechanism of its action is different from that of morphine. The complex structure and the potential medicinal applications of gelsemine prompted us to initiate a more efficient organocatalytic total synthesis.

Herein we wish to report a 12-step, highly enantioselective organocatalytic total synthesis of (+)-gelsemine.

**Results**

**Retrosynthetic analysis.** Gelsemine may be synthesized from intermediate RS-1 and oxindole via the condensation of the hemiacetal with oxindole followed by an intramolecular SN\(_2\) displacement (Fig. 3). Although the condensation may result in four stereoisomers, only two of them may undergo the desired SN\(_2\) displacement. The other two isomers, however, may either stay intact or undergo an elimination followed by a Michael addition\(^31,52\) to regenerate the four stereoisomers. This equilibrium is shifted to form the desired product after the intramolecular SN\(_2\) displacement, which is irreversible under the reaction conditions (Figs 4 and 5). The SN\(_2\) displacement may result in two isomers, one of which is the desired product. Intermediate RS-1 may be obtained from RS-2 following a sequence of intramolecular aldol condensation, reduction of the carbonyl group, formation of the sulfonates and then elimination. The intramolecular aldol\(^53,54\) condensation deserves further discussion due to the fact that both the aldehyde and the ketone functionalities may undergo enolization under the reaction conditions, resulting in epimerization of both stereochemical centres attaching the carbonyl groups. Another issue is the direction of the aldol condensation. Since both of the carbonyl groups may be enolized, the aldol condensation from either one may be consequential. However, Cbz is a bulky functional group\(^55\) and it will play a significant role in preventing the aldehyde from being enolized prior to the ketone enolization. In this case, the potential epimerization of the ketone functionality is irrelevant. The third issue is the stereochemistry of the hydroxyl group even if aldol condensation occurs in the desired direction. This difficulty may be overcome when one realizes that the desired product has a more favourable internal hydrogen bond\(^56.57\) than the other isomer. Finally, formation of RS-3 and its conversion into RS-2 is straightforward.

**Synthesis of the (+)-gelsemine.** On the basis of the above analysis, the synthetic strategy seemed feasible. If intermediate 3 is made asymmetric, then gelsemine will be made asymmetric. Thus, after a brief literature search\(^38,59\), an asymmetric Diels–Alder reaction was designed and the synthesis began with dihydropropidine 1 (Fig. 6), which may be prepared from 4-methylpyridine in large scale\(^60\).

**Figure 1 | The structures of gelsemium alkaloids.** The difference between the members of the gelsemium alkaloids is the presence of the functional groups in the unique carbon skeleton. The major difference appeared in C-19 and C-21.
Gratifyingly, the yield of the desired endo product was 47% after reduction of the aldehyde carbonyl group with sodium borohydride, and its enantio excess was determined using chiral high-performance liquid chromatography (HPLC) to be 99.7%, while the exo product was not detected. It was surprising that intermediate 3a was also produced in 30% yield. Since intermediate 3 was stable under the reaction conditions, 3a may be a result of the double-bond isomerization of the enal during the catalytic process\(^6\), and the rate of the double-bond isomerization was comparable to that of the Diels–Alder cyclization through the ketone carbonyl group enolization can provide the desired product, which is thermodynamically more stable than the other isomer.

Figure 5 | The aldol condensation and possible complications. Enolization of both the aldehyde and the ketone carbonyl groups is possible, while only the cyclization through the ketone carbonyl group enolization can provide the desired product, which is thermodynamically more stable than the other isomer.
the synthesis of gelsemine. As expected, the condensation of intermediate 11 with oxindole in refluxing methanol and a catalytic amount of piperidine afforded the desired product 12 (85%) as an inseparable mixture of all four possible isomers. The seemed straightforward intramolecular SN2 substitution reaction turned out to be problematic. Many reaction conditions were tested (NaH/THF; NaOCH3/CH3OH; KOTBu/THF; KOTBu/THF/BuOH; LDA/THF; CsF/DMF; LiHMDS/THF; LiHMDS/HMPA/THF; LiHMDS/LiCl/THF; LiHMDS/ZnCl2/THF; LiHMDS/DMSO; LDA/Et2AlCl/THF; LiHMDS/Me3AlCl/toluene; NaHMDS/Me2AlCl/THF; NaH/DMF) but all turned into a complex product mixture. However, when intermediate 12 was treated with LDA and then diethylaluminum chloride in toluene at 90°C, the reaction furnished the desired product in 32% yield as a single isomer. Finally, acid hydrolysis of the methyl group from the methoxymethyl protective group and removal of the resulting hydroxymethyl with triethylamine converted 13 into (+)-gelsemine in 70% combined yield. The synthetic material is identical to the natural product in terms of carbon and proton NMR spectra and optical rotation (see Supplementary Fig. 15).

Discussion
The total synthesis of (+)-gelsemine is completed in a highly enantioselective manner from readily accessible starting materials. This synthesis features an enantioselective organocatalytic Diels–Alder reaction, a formidable intramolecular aldol
The rapid assembly of polycyclic systems containing quaternary centers. A new strategy involving the isatylideneacetic esters and cinnamyl derivatives was employed. The combination of all these features resulted in exceptional cyclization and a challenging intramolecular $S_N2$ displacement. The experimental procedures and spectroscopic and physical data of compounds and the crystallographic data of compound 8, see Supplementary Methods.

Methods

General. All reagents were reagent grade and used without purification, unless otherwise noted. All reactions involving air- or moisture-sensitive reagents or intermediates were performed under an inert atmosphere of argon in glassware that was oven dried. Reaction temperatures referred to the temperature of the cooling/heating bath. Chromatography was performed using forced flow (flash chromatography) of the indicated solvent system on 230–400 mesh silica gel (Silicycle flash F60), unless otherwise noted. $^1$H NMR and $^{13}$C NMR spectra were referenced to the deuterated solvent (for example, for CDCl$_3$, $^1$H NMR $d_2$CDCl$_3$ $d_1$): 7.26 p.p.m. for $^1$H and 77.0 p.p.m. for $^{13}$C NMR, respectively) and reported in parts per million (ppm) and indicated as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), or complex (comp) with their coupling constant ($J$). For $^1$H NMR and $^{13}$C NMR, $J$ was reported in Hz and the splitting abbreviations used were: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; comp, overlapping multiplets of magnetically non-equivalent protons; br, broad; app, apparent. Reactions were monitored using thin-layer chromatography carried out on 0.25-mm E. Merck silica gel plates (60F-254) using ultraviolet light as the visualizing agent or an ethanolic solution of phosphomolybdic acid, cerium sulfate and heat as developing agents. Optical rotations were measured on a PerkinElmer 341 polarimeter. Enantiomeric compositions were determined by chiral HPLC using a chiralpak AD-H (amylese tris (3,5-di-t-butylbenzoylcamphor) coated on 5-µm silica gel) with hexane and i-PrOH as eluents. Tetrahydrofuran, benzene, toluene and diethyl ether were distilled from calcium hydride, while methanol was distilled from dry magnesium turnings immediately before use.

For $^1$H and $^{13}$C NMR spectra of compounds, see Supplementary Figs 1–14. For the comparisons of $^1$H spectra of the natural and synthetic gelsemine, see Supplementary Fig. 15. For the HPLC of 3, see Supplementary Fig. 16. For the 

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