Total Synthesis

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Enantioselective Total Synthesis of (−)-Stenine**

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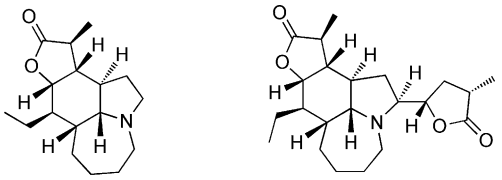
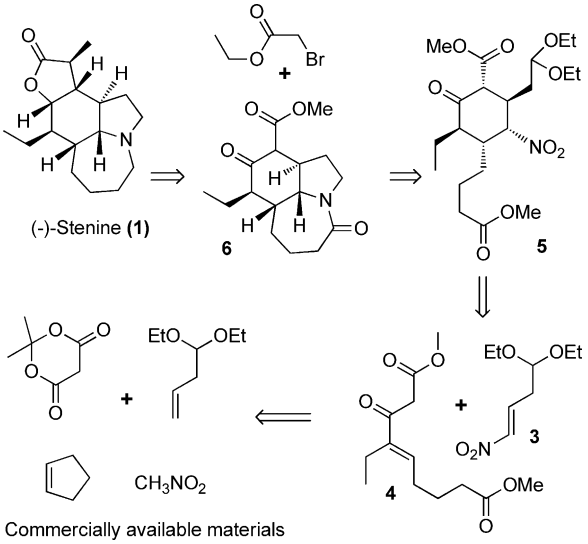
The roots of *Stemonaceae* plants are used in traditional Chinese medicines for the treatment of various respiratory ailments. The structure of (−)-stenine (**1**; Scheme 1), an



Scheme 1. (−)-stenine and (−)-tuberostemonine.

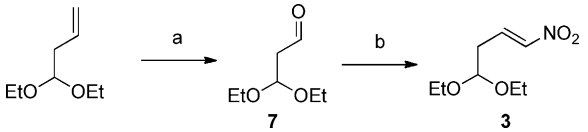
alkaloid that is isolated from the roots of *Stemona* species, is unique among *Stemona* alkaloids; it has a pyrrolo[*1,2-a*]azepine nucleus and a highly substituted perhydroindole ring system.[1] The polycyclic system and the seven contiguous stereogenic centers in (−)-stenine as well as (−)-tuberostemonine (**2**) present a challenge for asymmetric organic synthesis. Previous efforts to synthesize (−)-stenine have resulted in a number of elegant total syntheses.[2] However, only two asymmetric syntheses have been reported; these involve 25[2c] and 30 synthetic steps.[2d] Most of the synthetic strategies rely on a Diels–Alder reaction as the key step in assembling the core cyclohexane ring.[3] Herein, we report an alternative, efficient approach for the enantioselective synthesis of (−)-stenine.

With the aim of developing efficient and flexible synthetic strategies for bioactive natural products and their analogues, we studied the synthesis of (−)-stenine and (−)-tuberostemonine. Our retrosynthetic analysis is outlined in Scheme 2. We anticipated that the densely substituted cyclohexane core could be assembled by using a sequential double Michael addition, and that the key azepinoindole intermediate **6** could be obtained by reductive amination and subsequent amidation. The key issue in this new approach is the enantioselective Michael addition of nitroolefin **3** to β-ketoester **4**. Although asymmetric Michael additions of nitroolefins have been intensively studied in recent years,[4] the development of a practical method for the proposed carbocyclization, which is initiated by a Michael addition and builds up five consecutive stereogenic centers in the newly formed cyclohexane ring, remains a challenge. Furthermore, few nitroalkene-based strategies have been developed for the synthesis of polycyclic natural products.[5]



Scheme 2. Retrosynthetic analysis of (−)-stenine.

Nitroolefin **3** was prepared in two steps in 81% yield by the oxidative cleavage of commercially available diethoxybutene,[6] and then a Henry reaction (Scheme 3) and subsequent dehydration with trifluoroacetic anhydride (TFAA) in the presence of triethylamine. Although relatively unstable, pure **3** can be kept at −80 °C for several months.



Scheme 3. Synthesis of **3**: a) O_3, CH_2Cl_2, −78 °C, then Me_2S; b) $MeNO_2$, EtOH, NaOH. The crude product was then treated with Et_3N and TFAA in THF, 81% yield over two steps.

β-Ketoester **4** was synthesized from commercially available Meldrum's acid. Treatment of Meldrum's acid with butyryl chloride gave ketal **8**, and the reaction of **8** with diethyl chlorophosphite in the presence of a base furnished the dioxenone phosphonate **9** in 80% yield in two steps

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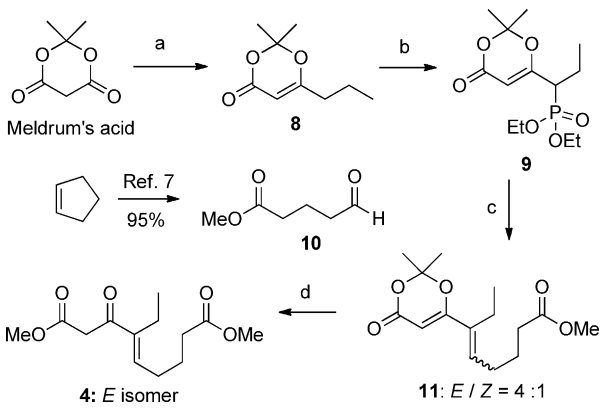
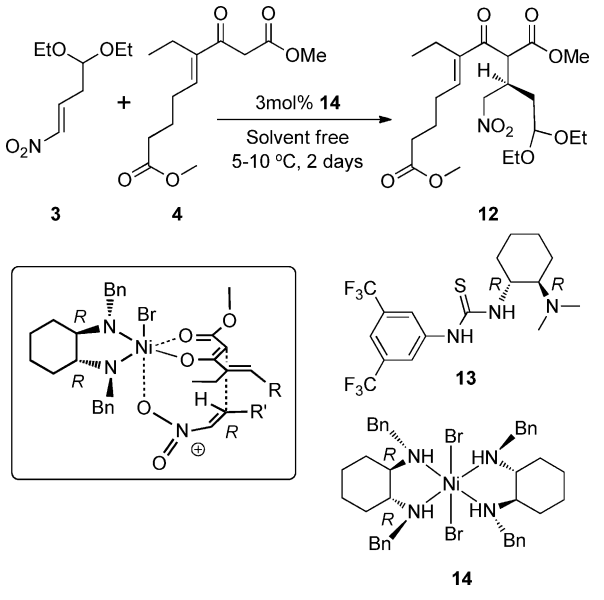


Scheme 4. Synthesis of **4**: a) Pyridine, CH_2Cl_2, butyryl chloride, 93% yield; b) $[(CH_3)_3Si]_2NLi$, THF, −78°C, diethyl chlorophosphite; then 30% H_2O_2, 86% yield; c) LDA, THF, −78°C, Hexamethylphosphoramide (HMPA), then **10**, 85% yield; d) MeOH, NaH, THF, 80% yield.

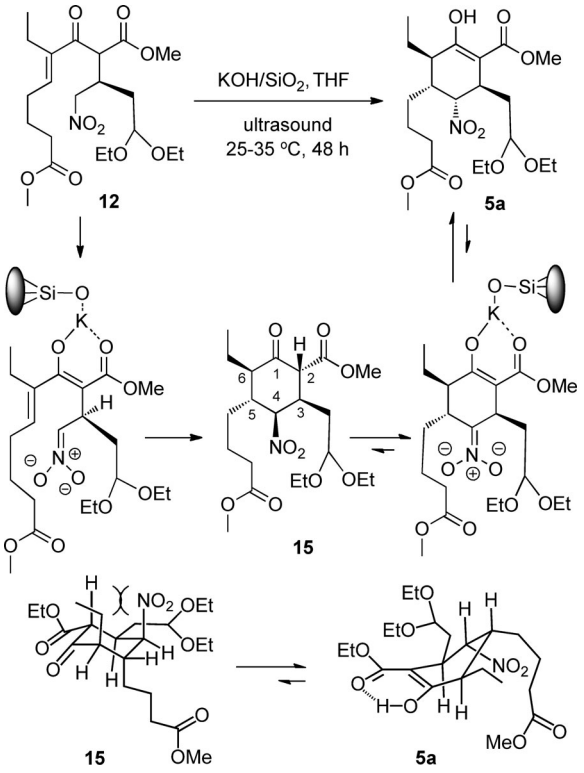
(Scheme 4).[7] Aldehyde **10** was prepared by the oxidative cleavage of cyclopentene in methanol[8] and a Horner–Wadsworth–Emmons reaction with **10** and **9** gave olefin **11** as a mixture of geometrical isomers (*E*/*Z* ratio = 4:1) in 85% yield (Scheme 4). Treatment of **11** with methanol in the presence of sodium hydride afforded the desired *E* olefin **4** in 80% yield. Compound **4** is an unsaturated β-ketoester with the ethyl group that is required for the synthesis of (−)-stenine.

The double Michael addition is the key stage in the synthesis. The challenge is to secure the required configuration with a high enantioselectivity and diasteroselectivity. To gain some insight into the stereoselectivity of the Michael addition (Scheme 2), two catalysts were tested (**13** and **14**, Scheme 5). Although the bifunctional thiourea catalyst **13** has been used for similar asymmetric conjugate additions,[5h,9] it was not effective with substrate **4**. Only trace amounts (less than 5%) of the Michael addition product **12** were obtained. However, the reaction with the Evans catalyst (**14**), which is derived from (1*R*,2*R*)-(−)-1,2-diaminocyclohexane,[10] gave **12** in 96% yield under solvent-free conditions. Although the first Michael addition was achieved, catalysts **13** and **14** did not catalyze the second Michael addition. The enantioselectivity for the first Michael addition was not determined at this stage because our efforts were focused on the promotion of the second Michael addition, which is the pivotal step in the synthesis.



Scheme 5. Investigation of the asymmetric Michael addition. Inset: prediction of the absolute configuration of **12** from the first Michael addition of **3** and **4** based on Evans' model. Bn = benzyl.

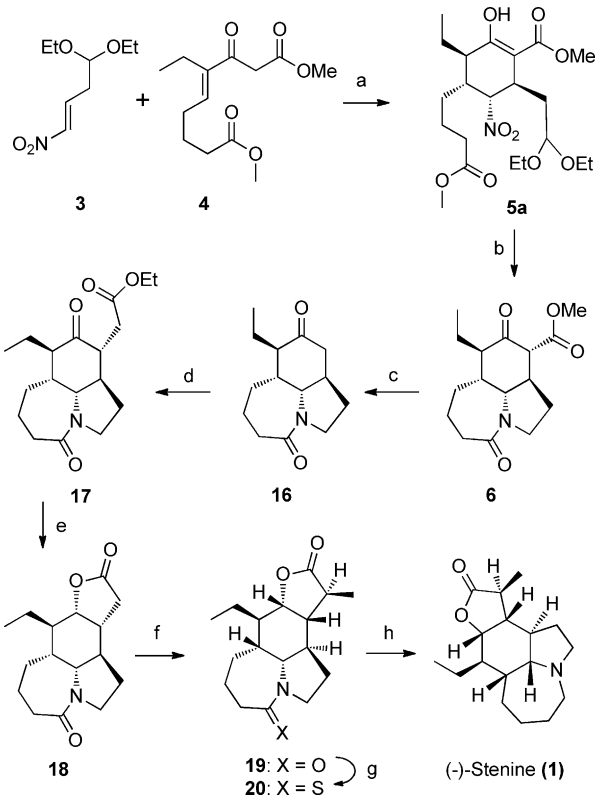
A number of base and solvent combinations, such as K_2CO_3 in methanol, KOH in ethanol, NaH in THF, or Triton B in methanol, were tested for the desired transformation of **12** into **5a**. Unfortunately, these conditions yielded a complex mixture of products. After some experimentation, a heterogeneous process for the second Michael addition was developed; the cyclization was achieved in the presence of potassium hydroxide that was supported on silica gel (KOH/SiO_2, see the Supporting Information) in anhydrous THF with ultrasound. KOH/SiO_2 mediated the second Michael addition with high diastereoselectivity. The keto form of cyclohexanone derivative **15**, which contains five continuous stereogenic centers, was isolated as a single diastereomer in high yield (Scheme 6).[11] When the reaction time was extended under application of ultrasound, the key intermediate **5a** was obtained in 80% yield together with β-ketoester **15** in 11% yield. Compound **5a** was in the enol form and had the correct relative configuration for the synthesis of (−)-stenine. The inversion of the configuration of the nitro group at the C4-position was also concomitantly achieved in



Scheme 6. Michael addition promoted by potassium hydroxide supported on silica gel.

this one-pot, heterogeneous reaction. After the one-pot double Michael addition and the subsequent inversion of the configuration at the C4-position, the *ee* value for compound **5a** was determined to be 87% by HPLC on a chiral stationary phase (Chiralcel OJ-H column).[12]

The reductive aminocyclization and subsequent intramolecular amidation of **5a** gave the tricyclic amide **6** in 81% yield (Scheme 7). Amide **6** was then treated with lithium chloride and water in dimethyl sulfoxide to give ketone **16** in



Scheme 7. Enantioselective synthesis of (−)-stenine: a) **14**, 5 °C; then KOH/SiO_2, THF, sonicated in a water bath at 35 °C, 80% yield; b) acetic acid, H_2O, 90 °C, then Zn powder. The crude product was then heated to 90 °C in toluene, 81% yield; c) LiCl, H_2O, DMSO, 155 °C, 89% yield; d) $[(CH_3)_3Si]_2NLi$, THF, −78 °C, ethyl bromoacetate, 78% yield; e) $NaBH_4$, MeOH, 0 °C, 51% yield after recrystallization; f) $[(CH_3)_3Si]_2NLi$, THF, −78 °C, MeI, 65% yield; g) Lawesson's reagent, CH_2Cl_2; h) Raney Ni, EtOH, 25 °C, 90% yield over two steps.

89% yield. By using the elegant procedure developed by Zeng and Aubé,[2i] the treatment of ketone **16** with ethyl bromoacetate in the presence of lithium bis(trimethylsilyl)-amide in THF gave ester **17** in 78% yield. After reduction of **17** with sodium borohydride in methanol, lactone **18** was obtained in 62% yield. After recrystallization, the isomeric purity of lactone **18** was greater than 98%, as determined by HPLC analysis. Lactone **18** was treated with methyl iodide in the presence of lithium bis(trimethylsilyl)amide in THF to give oxostenine **19** as white, platelike crystals in 65% yield ($[\alpha]_D = -136.3°$, $c = 0.40$, CH_2Cl_2, literature $[\alpha]_D = -84.7°$, $c = 0.37$, CH_2Cl_2[2c]). The absolute configuration of **19** was

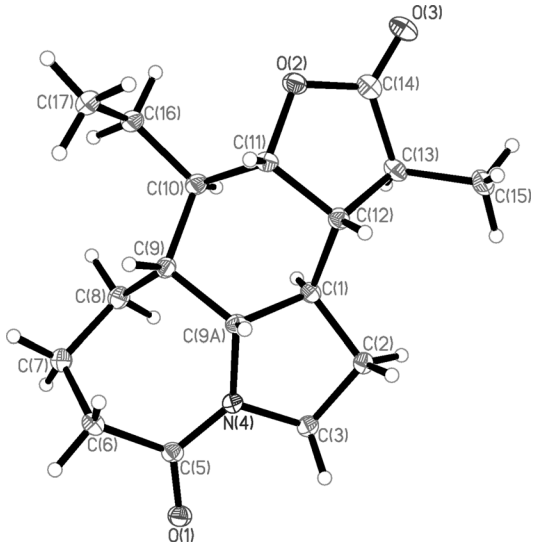


Figure 1. Absolute configuration of (−)-oxostenine.

confirmed by X-ray crystallography (Figure 1) with Cu-K_α radiation.

The conversion of amide **19** into the thioamide **20**: $[\alpha]_D = -87.0°$, $c = 0.5$, CH_2Cl_2; literature $[\alpha]_D = -54.3°$, $c = 0.4$, CH_2Cl_2[2c]) with Lawesson's reagent and subsequent desulfurization with Raney nickel[2a] gave (−)-stenine in 90% yield in two steps (Scheme 7, $[\alpha]_D = -30.3°$, $c = 0.5$, MeOH, literature $[\alpha]_D = -30.2°$, MeOH[1a]). The NMR spectra of our synthetic sample were in complete agreement with the reported spectra.[2]

In summary, we have developed a catalytic, enantioselective strategy for the synthesis of (−)-stenine. This route, which features a highly stereocontrolled, one-pot cyclization to establish the required stereogenic centers, gives (−)-stenine in 14 steps from commercially available materials (11 steps from known starting materials) in an overall yield of 5.9%. This strategy is flexible and could be used for the synthesis of stenine analogues, which are of interest in medicinal chemistry. The application of this method to the catalytic asymmetric synthesis of (−)-tuberostemonine (**2**), which is a more complex target, is currently under investigation.

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[11] The relative stereochemistry of β-ketoester **15** was established by a NOE NMR experiment and also by the characteristic coupling constant ($J = 12.6$ Hz) between the H3 atom and the H2 atom (C2-H: 4.51 ppm, d, $J = 12.6$ Hz).

[12] After the first Michael addition, the resulting mixture was diluted with anhydrous THF and treated with KOH/SiO_2 under sonication at 25–35 °C for 48 h (see the Supporting Information).

