A Unified Total Synthesis of Isocyclocapitelline and Cyclocapitelline

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Abstract
A facile and concise synthesis of β-carboline alkaloids, such as (-)-isocyclocapitelline and (+)-cyclocapitelline, has been achieved from commercially available geraniol through a unified strategy. The key steps involved in this synthesis are Sharpless epoxidation, intramolecular ring opening of epoxide, Pictet-Spengler reaction, and dehydrogenative aromatization using 10% palladium/carbon in xylene under neutral conditions.

Keywords
β-carboline alkaloids, sharpless epoxidation, intramolecular epoxide opening, pictet-spengler reaction

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Substituted tetrahydrofuran (THF) ring containing natural products possess a highly complex structure with a diverse range of biological properties.1,2 The tetrahydrofuran ring is frequently found in natural products, as well as in many biologically and pharmaceutically active compounds.3,4 In particular, 2,5-disubstituted THFs is a key structure for a variety of biologically active natural products.5,6 On the other hand, THFs are the synthons for the synthesis of complex natural products such as pheromones, pharmaceutical agents, polymer antibiotics, and marine toxins.7,8 These fascinating structural features and intrinsic biological activities attracted many scientists toward the total synthesis of these natural products.9-11

β-Carboline alkaloids (Figure 1), such as (-)-isocyclocapitelline (8a) and (+)-cyclocapitelline (8b), were first isolated from the Rubiaceae family plant Hedyotis capitella (used as a folk medicine in China and Vietnam) by Gunter Adam et al in 1999.26 Voltz et al reported the first total synthesis of these alkaloids (8a) and (8b) from α-hydroxyallenes through a gold-catalyzed cycloisomerization.26,27 Subsequently, a modular approach has been reported for the synthesis of (-)-isocyclocapitelline (8a) and (+)-cyclocapitelline (8b) from cis-arbuscone and trans-arbuscone, respectively.28 Herein, we have established a synthetic route which permits access to the synthesis of (-)-isocyclocapitelline (8a) and (+)-cyclocapitelline (8b) in a unified fashion, from commercially available terpene, geraniol, as a key precursor. The present synthesis is a highly concise and protection group free process to construct the β-carboline skeleton under mild conditions.

Results and Discussion
Our synthesis commenced with a familiar transformation in organic synthesis, which is Sharpless asymmetric epoxidation of the readily available monoterpene geraniol (1). The vital strategy in our synthesis is the preparation of chiral 2-((2R,5,5)-5-(2-hydroxypropan-2-yl)-2-methyltetrahydrofuran-2-yl)acetaldheyde (5a), a key intermediate in our synthesis, which was prepared by a sequence of transformations. Gignaniol (1) was subjected to Sharpless epoxidation29-31 using (R)- and (S)-diisopropyl tartarate, Ti(OPr)4, and tert-butyl hydroperoxide in dichloromethane (CH2Cl2) to afford the epoxy alcohol 2 in 95% yield. The reductive opening of epoxide 2 was accomplished by using sodium bis(2-methoxyethoxy)aluminum hydride (3.5 M in toluene, 1.1 equiv.), to give the diol 3, with 90% yield. The diol 3 was further treated with meta-chloroperbenzoic acid in CH2Cl2 to afford the functionalized THF core as a mixture of diastereomers 4a and 4b in a 1:1 ratio, which was separated by column chromatography and obtained as pure compounds. Treatment of diol 3 with a chiral Shibata's ketone A (derived from fructose) in the presence of oxone, potassium carbonate in acetonitrile and water over 8 hours gave the chiral THF core 4a.

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as a single isomer. Disappearance of the signal (dd) at δ 5.11 ppm and the presence of signals at δ 131.5, 121.4 ppm in the ¹H and ¹³C nuclear magnetic resonance (NMR) spectra confirmed the formation of 4a and 4b from 3. The spectroscopic data of 4a are in agreement with that of the product formed with Shi ketone, which was further confirmed by its stereochemistry. Compound 4a was further oxidized to aldehyde 5 under a nitrogen atmosphere, using pyridinium chlorochromate (PCC) as an oxidant in CH₂Cl₂ (60% yield) (Scheme 1). The characteristic triplet ¹H signal at δ 9.85 ppm and ¹³C signal at δ 202.2 ppm confirmed the formation of aldehyde 5.

Coupling of Aldehyde 5a and 5b With Tryptamine (6)

Aldehyde 5a was treated with tryptamine (6) in the presence of TFA in CH₂Cl₂ under Pictet-Spengler³³ conditions to give tetrahydrocarboline 7, which was further subjected to dehydrogenation with palladium (Pd)/carbon (C) in xylene under reflux conditions to furnish (−)-isocyclocapitelline (7a) in 75% yield over 2 steps, as shown in Scheme 2. The ¹H and ¹³C NMR spectra of the synthesized product 8a were in full agreement with those of the reported natural product.³⁴ The specific rotation of our synthesized compound was [α]²⁵ = −72 (c 0.5, CHCl₃), which correlated with the natural product [α]²⁵ = −72 (c 0.5, CHCl₃).

Similarly, synthesis of (+)-cyclocapitelline (8b) was achieved from the aldehyde 5b by adopting the above reaction conditions, as shown in Scheme 3.

The ¹H and ¹³C NMR spectra of the synthesized product 8b correlated with those of the reported natural product.³⁴ The specific rotation of our synthesized compound was [α]D²⁵ = +42.8 (c 0.5, CHCl₃), which was in agreement with the natural product [α]D²⁵ = +43 (c 0.5, CHCl₃).

General experimental details and spectroscopic data have been included in Supplementary Material 1.

Figure 1. Representative examples of β-carboline alkaloids.

Scheme 2. Reagents and conditions: (f) tryptamine (6), trifluoroacetic acid, dichloromethane, 78 °C, 3 hours; (g) palladium/carbon, xylene, reflux, 8 hours, 75%.

Scheme 3. Reagents and conditions: (h) tryptamine (6), trifluoroacetic acid, dichloromethane, 78 °C, 3 hours; (i) palladium/carbon, xylene, reflux, 8 hours, 70% over 2 steps.
Conclusion
In summary, we have successfully established a unified strategy for the total synthesis of *Hedyotis* plant alkaloids (−)-isocyclocapitelline (8a) and (+)-cyclocapitelline (8b) from readily available geraniol (I). The vital reactions involved in this approach are the Sharpless asymmetric epoxidation, reductive cleavage of epoxide, intramolecular ring opening of epoxide, and Pictet-Spengler reaction. The overall strategy is a very facile, scalable, and protection group-free synthesis, which makes it a concise synthesis.

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