General Approach for the Synthesis of Indole Alkaloids via the Asymmetric Pictet−Spengler Reaction: First Enantiospecific Total Synthesis of (−)-Corynantheidine as Well as the Enantiospecific Total Synthesis of (−)-Corynantheidol, (−)-Geissoschizol, and (+)-Geissoschizine

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Corynantheidine **1** was first isolated in 1944 by Janot et al. from the African plant *Pseudocinchona africana*,[1] and the structure was determined by the same group.[2] A number of partial and total syntheses of **1** have been reported, all of which resulted in racemates.[3] The related corynantheidol **2** was obtained from *Mitragyna parvifolia* (Roxb.) Korth. (Rubiaceae).[4a] Although several total syntheses of **2** have been realized,[5] only one approach was enantioselective (up to 86% ee); Meyers and co-workers completed this route in 1991 in excellent overall yield (16.4%).[6] Geissoschizol **3** has been isolated from *Hunteria zeylanica var. africana*,[7] and many elegant syntheses have been reported,[5b,8] at least one of which was enantioselective.[8a] Geissoschizine **4**, historically one of the most important intermediates in the biosynthesis of monoterpene indole alkaloids,[10a] has been obtained from a number of plants.[11] Because of the biosynthetic importance of **4**, its structural complexity, and the scarce availability from natural sources, there have been many important total syntheses of this natural product.[9,10] Among these, those of Winterfeldt, Overman, and Martin were enantioselective.[8a,10]

In this contribution, the first enantiospecific total synthesis of (−)-corynantheidine (**1**) as well as an efficient enantiospecific total synthesis of (−)-corynantheidol (**2**), (−)-geissoschizol (**3**), and (+)-geissoschizine (**4**) from a common intermediate are described (Figure 1). The stereochemical integrity of these natural products was guaranteed via the *trans* transfer of asymmetry via a new extension of the asymmetric[12] Pictet−Spengler reaction.

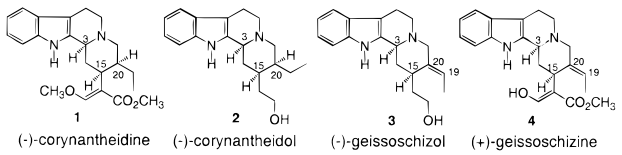
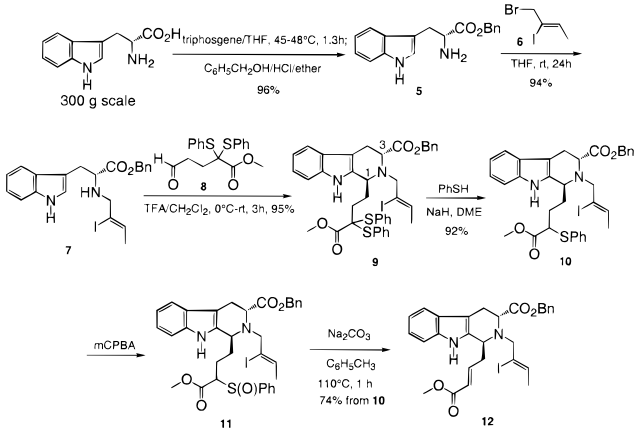


Figure 1. Structure of (−)-corynantheidine, (−)-corynantheidol, (−)-geissoschizol, and (+)-geissoschizine.

The synthesis of the common intermediate is outlined in Scheme 1. The benzyl ester of D-tryptophan (**5**) was prepared on 300 g scale in 96% yield according to a modified literature procedure.[13] Monoalkylation of the N_b-amino moiety with allylic

Scheme 1. Preparation of the Common Intermediate **12**



bromide **6**, a building block prepared earlier by Ensley[14a] and employed by Bosch,[14b] Rawal,[8b,15] as well as Kuehne,[16] was achieved in excellent yield, employing **5** and **6** at high concentration in the presence of a slight excess of the benzyl ester **5**. The stereospecific, enantiospecific construction of the chiral center at C-1[12] in **9** was achieved by employing a modification of the asymmetric Pictet−Spengler reaction.[12] When a solution of aldehyde **8**[17] and 1 equiv of benzyl ester **7** was stirred in methylene chloride in the presence of TFA, this provided the tetrahydro-β-carboline **9** in 95% yield with complete *trans*-transfer of chirality[12] from C-3 to C-1. No *cis*-isomer was detected under these conditions. In Overman's elegant synthesis of (+)-geissoschizine,[10a] a similar reaction was attempted wherein the N_b-nitrogen atom in **7** was devoid of the alkyl substituent. In that case, a moderate (40%) yield was reported with a *trans*- to *cis*- ratio of approximately 1:4. The results (see **9**) described herein provide further evidence of the strong directing and accelerating effect of the large alkyl group[12] on the N_b-nitrogen atom on the stereoselectivity of the asymmetric Pictet−Spengler reaction.[12] This suggests that a bulky substituent on the N_b-nitrogen atom is the only requirement necessary to achieve 100% diastereoselectivity in the Pictet−Spengler reaction of carbonyl compounds with tryptophan alkyl esters. With tetrahydro-β-carboline **9** in hand, the desired α,β-unsaturated ester **12** was readily prepared in good yield via a series of standard transformations including removal of one equivalent of thiophenol from **9** followed by an oxidation (see **10** → **11**), sulfoxide elimination sequence (see Scheme 1).[17]

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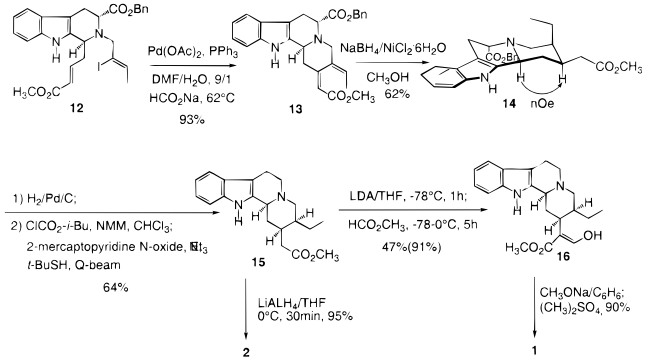
The synthesis of key intermediate **12** required six steps from D-(+)-tryptophan with an overall yield of 58%.

With the α,*β*-unsaturated ester **12** in hand, attention turned to the construction of the all *cis*-D-ring. Intramolecular Heck coupling of intermediate **12**, analogous to the coupling process in other systems[8b] provided α,*β*-*γ*,*δ*-unsaturated ester **13** in near quantitative yield. After a number of unsuccessful attempts, this ester **13** was successfully reduced with $NaBH_4$ in the presence of a catalytic amount of $NiCl_2 \cdot 6H_2O$[18] to provide **14** in 62% yield, with the partially reduced *β*,*γ*-unsaturated ester as the minor byproduct. The all *cis*-relationship among the hydrogen atoms at C-3, C-15, and C-20 was confirmed by nOe studies. In addition, removal of the carboxybenzyl group via catalytic debenzylation, followed by Barton−Crich decarboxylation[19] provided previously known ester **15** whose spectroscopic properties were in agreement in all respects to those reported earlier.[3c,e] Reduction of ester **15** with $LiAlH_4$ at 0 °C afforded (−)-corynantheidol **2** ($[\alpha]_D$ −102°; lit. −99°,[4b] −93° [6]) in 95% yield, the spectroscopic properties of which were identical in all respects to those reported in the literature.[6] The synthesis of **2** required 11 steps in 20% overall yield. Treatment of ester **15** with 3 equiv of LDA at −78 °C for 1 h followed by addition of excess methyl formate at −78 °C after which the mixture was allowed to warm to 0 °C over a period of 5 h furnished a 47% yield of the desired enol **16**. This ester was isolated as a mixture of the enol and the formyl tautomers, moreover the recovered starting material (48%) could be recycled if desired. The 91% yield depicted in Scheme 2 for this process

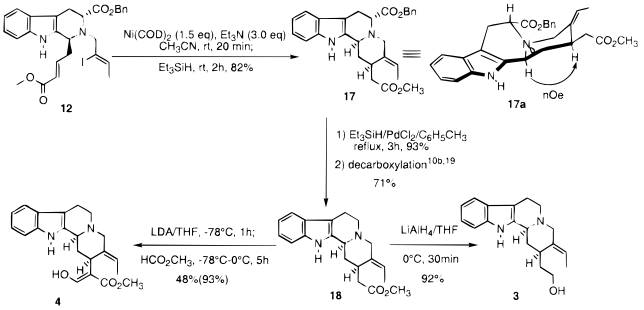
Scheme 2. Synthesis of Corynantheidol and Corynantheidine



is based on recovered starting **15**. Enol ester **16** was directly methylated using 1 equiv of sodium methoxide and 1 equiv of dimethyl sulfate to provide (−)-corynantheidine **1**. The optical rotation ($[\alpha]_D$ −166°, lit. −171°,[2] −155° [3c]) and spectroscopic properties of synthetic (−)-**1** agree in all respects to those of natural (−)-corynantheidine.[3] The route employed 12 steps with a overall yield of 18%. To the best of our knowledge, this is the first enantiospecific total synthesis of (−)-**1**.

To construct the molecular framework of geissoschizol/geissoschizine from **12**, a stereoselective Michael reaction was proposed. Unfortunately, this seemingly simple transformation turned out to be difficult. Because the construction of the D-ring in the synthesis of racemic geissoschizol/geissoschizine had employed transition-metal chemistry, (see the work of Rawal[8b,15] and Takayama[9]), it was felt a nickel-mediated process related to the work of Takayama[9] might provide a solution. Indeed, when vinyl iodide **12** was treated with 1.5 equiv of $Ni[COD]_2$ and 3.0 equiv of triethylamine in acetonitrile and this was followed by the addition of 2 equiv of Et_3SiH,[9,14b,20] an 82% yield of the desired *Corynanthe* skeleton **17** was isolated. The important *cis*-relationship between the hydrogen atoms at C-3 and C-15 was confirmed by nOe studies, while the E-configuration of the double bond in **17** was felt to be maintained[9,14b−16] and later demonstrated (see below). Removal of the benzyl group mediated by Et_3SiH in the presence of $PdCl_2$[21] afforded the corresponding carboxylic acid which was converted into the known optically active ester **18** in 71% yield by a Barton-Crich decarboxylation.[19] This intermediate **18** was converted into the two natural products (−)-geissoschizol **3** and (+)-geissoschizine **4** (see Scheme 3). Treatment of **18** with

Scheme 3. Synthesis of Geissoschizine



$LiAlH_4$ at 0 °C for 30 min afforded (−)-**3** whose optical rotation ($[\alpha]_D$: −68°; lit.: −70°,[11a] −54° [8a]) and spectroscopic properties were in full agreement with the reported values.[5b,8b] This synthesis was completed in 10 steps with an overall yield of 29%. Formylation of **18** under similar conditions to those employed for **15** gave (+)-geissoschizine **4** in 48% yield (93% based on recovered starting material[10]). The spectroscopic properties and optical rotation($[\alpha]_D$ +113°; lit. +114°,[11a] +114°,[8a] +113°, [10a] +109° [10b]) of synthetic (+)-**4** agree in all respects with those reported for the natural product.[9−11] This synthesis required 10 steps from D-tryptophan and was completed in an overall yield of 29%. To the best of our knowledge, this is most efficient total synthesis of (+)-geissoschizine reported, to date.

In summary, the first enantiospecific total synthesis of (−)-corynantheidine **1** was achieved (18% overall yield) as well as the enantiospecific synthesis of (−)-corynantheidol, (−)-geissoschizol, and (+)-geissoschizine. A facile entry into key intermediate **12** (the branching point of corynantheidine and geissoschizine) from D-tryptophan was developed in six steps with an overall yield of 58%. This approach extends the scope of the asymmetric Pictet−Spengler reaction while providing a simple route to the enantiomer (from L-tryptophan) of these alkaloids for biological screening. The transition metal mediated formation of **17** will provide an efficient solution to the stereospecific formation of *E*-ethylidene moieties for a number of indole alkaloids in this series.

Supporting Information Available: Experimental procedures for **1**, **2**, **3**, **4**, **5**, **7**, **9**, **12**, **13**, **14**, **15**, **17**, and **18** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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