ORGANIC LETTERS

1999
Vol. 1, No. 1
79−81

An Enantioselective Total Synthesis of (+)-Geissoschizine†

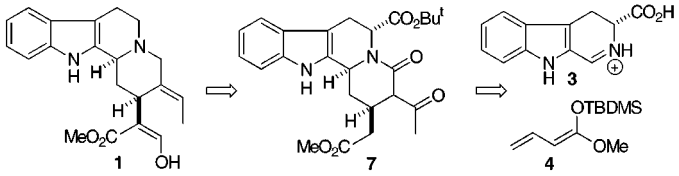
Stephen F. Martin,* Kevin X. Chen, and C. Todd Eary

Department of Chemistry and Biochemistry, University of Texas at Austin, Austin, Texas 78712

sfmartin@mail.utexas.edu

Received April 1, 1999

ABSTRACT



A concise asymmetric synthesis of the indole alkaloid (+)-geissoschizine (1) has been completed. The synthesis features the highly diastereoselective vinylogous Mannich reaction of 3 with 4 to give 5, which is elaborated into the key tetracyclic intermediate 7 in two steps. Following the stereoselective introduction of the ethylidene moiety to give 9, reduction of the lactam and radical decarboxylation via an acyl selenide gave 12, which was converted into (+)-geissoschizine by formylation. The synthesis requires only 11 chemical operations and proceeds in an overall yield of 17%.

The corynantheoid alkaloid geissoschizine (**1**),[1] which has been isolated from a number of plant species, is a pivotal intermediate in the biosynthesis of the monoterpenoid indole alkaloids of the *Corynantheine-Yohimbine, Aspidosperma, Iboga, Strychnos, Sarpagine, Picraline,* and *Ajmaline* families.[2,3] The solution structure of **1** has been studied extensively (Figure 1),[4] and recent work suggests that the preferred

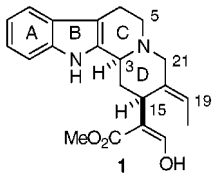


Figure 1. Geissoschizine.

conformation is one in which the CD ring is a *trans*-quinolizidine with a twist-boat D-ring and an intramolecular hydrogen bond between the enol hydroxyl group and the nitrogen lone pair.[4e] Its structure, coupled with its importance as a key biosynthetic intermediate and lack of availability, has inspired numerous synthetic investigations. Since the first total synthesis of racemic geissoschizine by van Tamelen, a

† Dedicated to the memory of Dr. Ta-shue Chou (1950−1999).

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10.1021/ol990554a CCC: $18.00
Published on Web 05/17/1999

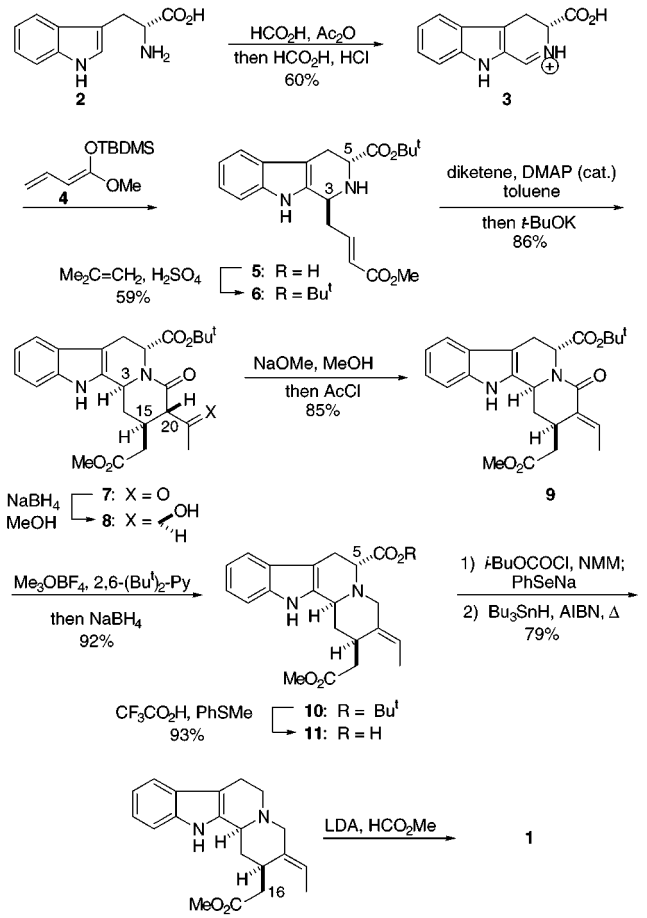
number of syntheses have been completed,[5] but only two asymmetric syntheses of **1** have been reported by the Winterfeldt and Overman groups.[6]

We were attracted some years ago to geissoschizine (**1**) as a consequence of our interest in designing general strategies for the synthesis of indole alkaloids, and we developed one facile entry to this target in which a vinylogous Mannich reaction and an intramolecular hetero Diels–Alder reaction were exploited as key constructions.[5e,g,7] In that synthesis, the relative stereochemistry between C(3) and C(15) and the geometry of the ethylidene side chain were controlled, thereby addressing two of the standing problems in the area. However, this route to geissoschizine could not be readily modified for an asymmetric synthesis of **1**, and it could not be adapted to provide intermediates related to geissoschizine that could be transformed along biogenetic pathways into the more complex indole alkaloids of the *Sarpagine*, *Ajmaline*, and *Picraline* groups.[8] We now report a novel entry to geissoschizine that provides a concise solution to these two problems.

The synthesis commenced with the conversion of D-tryptophan (**2**) into the dihydrocarboline **3** in a single operation by a modification of a known procedure[9] to set the stage for the key vinylogous Mannich reaction (Scheme 1).[7b,10] In the event, reaction of **3** with the vinyl ketene acetal **4** proceeded with a high degree of stereoselectivity via attack at C(3) from the face opposite the carboxyl group at C(5) to give **5** as the only observed product.[11] Although it was not necessary to esterify the acid function in **3** prior to this addition, subsequent transformations required protection of the carboxyl group; therefore, **5** was treated with isobutylene in the presence of acid to give **6** in 59% overall yield from **3**. *N*-Acylation of **6** with diketene followed by a base-induced, intramolecular Michael reaction gave **7** (86%), in which the correct relative and absolute stereochemistries at C(3) and C(15) have been established. The equatorial orientation of the two substituents at C(15) and C(20) is presumably subject to thermodynamic control, but this issue has not been explicitly addressed.

Having assembled the requisite skeletal framework, it then remained to refunctionalize **7** to give geissoschizine. Hydride reduction of the ketone moiety in **7** gave the alcohol **8**, which was characterized by X-ray crystallographic analysis, as the only product. The stereochemical outcome of this reduction is consistent with that observed in closely related systems.[7b,12] Treatment of **8** with sodium methoxide in methanol induced β-elimination and stereoselective introduction of the (*E*)-ethylidene side chain. The resulting acid was esterified with acetyl chloride, producing **9** in 85% overall yield from **7**. The lactam function was selectively reduced by the Borch protocol to furnish the ester **10** in 92% yield.[13]

Scheme 1



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(11) The numbering of all synthetic intermediates corresponds to that shown in **1** for geissoschizine. The structure assigned to each compound was in accord with its spectral (^{1}H and ^{13}C NMR, IR, MS) characteristics. Analytical samples of all new compounds were obtained by distillation, recrystallization, or preparative HPLC or TLC and gave satisfactory combustion analysis (C, H) and/or identification by high-resolution mass spectrometry. All yields are based on isolated, purified materials.

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Acid-catalyzed cleavage of the *tert*-butyl ester in the presence of thioanisole,[14] an essential additive, provided the acid **11**. Removal of the carboxyl group at C(5) proved to be more difficult than anticipated. For example, application of the classical Barton radical decarboxylation procedures to **11** provided **12** in low and inconsistent yields (0−15%).[15] Radical decarboxylation of the benzophenone oxime ester derived from **11** was also examined without reward.[16] Methods involving generation and reduction of the iminium ion generated by the reaction of **11** with phosphorus oxychloride were also unsuccessful.[17] Ultimately we found that the acyl selenide derived from **11**, which was best prepared by sequential reaction with isobutyl chloroformate and then sodium phenylselenide,[18] underwent facile and efficient radical decarbonylation to give **12** in 79% overall yield from **11**.[19] Formylation of **12** according to the procedure of Winterfeldt then delivered (+)-geissoschizine (**1**) in 48% yield; 50% of starting **12** was also recovered. The synthetic geissoschizine thus obtained was spectroscopically identical with an authentic sample of racemic geissoschizine prepared independently in our group,[5g] and the optical rotation compared favorably with naturally obtained material.[20]

In summary, a concise and practical asymmetric synthesis of geissoschizine (**1**) has been developed that involves only 11 chemical operations from commercially available D-tryptophan and proceeds in 17% overall yield, based upon recovered **12** in the last step. In this synthesis the relative stereochemistries at C(3) and C(15) and the geometry of the ethylidene array are controlled completely. The approach highlights the utility of vinylogous Mannich reactions as key constructions in alkaloid synthesis. The utility of acyl selenides as intermediates for efficient radical decarboxylation has also been further validated.

Acknowledgment. We thank the National Institutes of Health and The Robert A. Welch Foundation for their generous support of this research.

Supporting Information Available: Complete characterization data (^{1}H and ^{13}C NMR and mass spectral data) for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL990554A

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(20) The optical rotation for synthetic geissoschizine was $[\alpha]^{21}_D = +109°$ ($c = 0.58$, EtOH), and the value for a previous asymmetric synthesis of geissoschizine was $[\alpha]^{25}_D = +113°$ ($c = 0.43$, EtOH).[6b]