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A Concise, Stereoselective Synthesis of (±)-Geissoschizine

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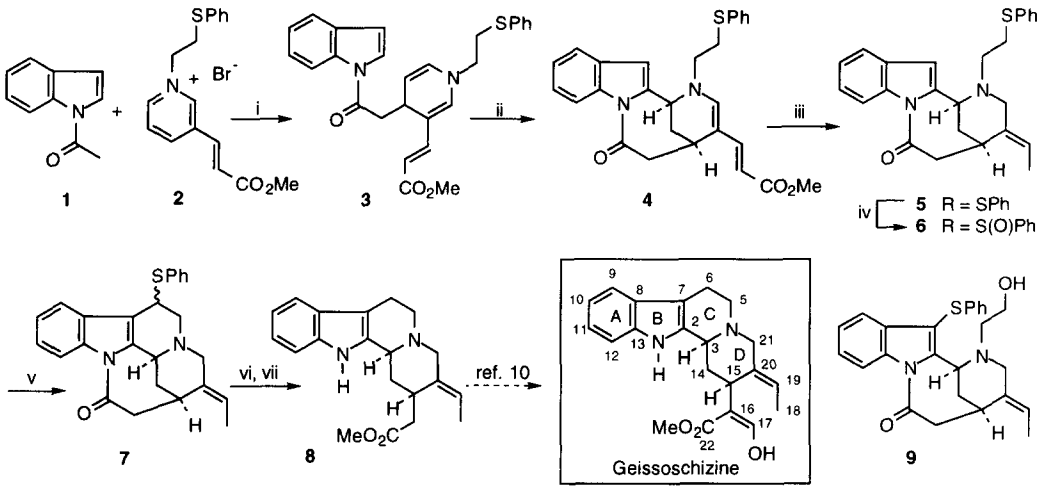
Abstract: A stereocontrolled synthesis of (±)-geissoschizine, involving the addition of the enolate derived from 1-acetylindole to pyridinium salt **2**, cyclization of the resultant 1,4-dihydropyridine, stereoselective elaboration of the *E*-ethylidene substituent, closure of C ring by Pummerer reaction, and methanolysis of the resulting pentacyclic lactam, is reported.

Geissoschizine, a pivotal early intermediate in indole alkaloid biosynthesis, has received considerable attention from the synthetic standpoint.[1] However, most of the reported syntheses of this alkaloid suffer from some stereochemical problems, as they usually lead to C-3/C-15 *trans* indoloquinolizidine derivatives and/or to the unnatural *Z* configuration (or *Z*/*E* mixtures) for the ethylidene double bond. Consequently, additional steps to promote epimerization at C-3 and/or *Z*–*E* isomerization are required.[2]

We present here a concise, stereocontrolled synthesis of (±)-geissoschizine, in which the required C-3/C-15 *cis*-relationship is secured from the bridgehead character of these carbons in the intermediates **4**-**7**, which embody an extra seven-membered bridged ring that acts as an element of stereochemical control. (Scheme 1). On the other hand, the *E*-configurated ethylidene substituent is stereoselectively formed taking advantage of the β-(tetrahydropyridyl)acrylate moiety of tetracycle **4**. Interestingly, the C-16/C-22 two-carbon fragment of the final intermediate **8** comes from the acetyl group of the starting *N*-substituted indole **1**. The synthesis is based on the general methodology for indole alkaloid synthesis involving the nucleophilic addition of indole-containing enolates to *N*-alkylpyridinium salts, with subsequent elaboration of the resulting 1,4-dihydropyridines.[3]

Interaction of the enolate derived from acetylindole **1** with pyridinium salt **2**, followed by acid-induced cyclization of the resulting 1,4-dihydropyridine **3** in the presence of lithium iodide,[4] led to tetracycle **4**,[5] which was stereoselectively elaborated into the (*E*)-ethylidene derivative **5** (30% yield) by the known[6] one-pot sequence consisting of treatment with refluxing aqueous HCl and subsequent sodium borohydride reduction. Sulfide **5** was then chemoselectively oxidized at the sulfur atom with *m*-CPBA to give sulfoxide **6** (80% yield) as a mixture of stereoisomers. Pummerer cyclization[7] of amino sulfoxides **6** was effected with trimethylsilyl triflate in the presence of diisopropylethylamine to give a 3:1 epimeric mixture of pentacyclic sulfides **7**[8] in 64% yield.[9] The opening of the seven-membered lactam ring by methanolysis, followed by desulfurization, gave the known indoloquinolizidine **8** (50% overall yield from **7**), which had previously been converted into (±)-geissoschizine.[10]



Scheme 1. *Reagents and Conditions:* i) LDA, THF; ii) TsOH-C_6H_6, LiI, THF, rt, 1.5 h; iii) 2.5 N HCl, 100 °C, 2 h, then $NaBH_4$, MeOH, 0 °C, 1 h; iv) TFA (1 eq), then *m*-CPBA, -70 °C, 15 min; v) TMSOTf, DIPEA, CH_2Cl_2, rt, 1.5 h; vi) MeONa (1.5 eq), 4:1 MeOH-THF, rt, 3 h; vii) Bu_3SnH, AIBN, C_6H_6, reflux, 4 h.

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8. **7** (major epimer): ^{1}H-NMR (500 MHz, $CDCl_3$) 1.60 (dd, *J* = 6.8, 2 Hz, 18-H), 2.11 (dt, *J* = 14.3, 4.2 Hz, 14-H), 2.39 (dd, *J* = 14.5, 4.4 Hz, 16-H), 2.53 (dt, *J* = 14.3, 2.7 Hz, 14-H), 3.07 (dd, *J* = 14.5, 11.6 Hz, 16-H), 3.10 (d, *J* = 13.2 Hz, 21-H), 3.39 (m, 15-H), 3.50 (d, *J* = 15.0 Hz, 5-H), 3.86 (dd, *J* = 15.0, 6.5 Hz, 5-H), 4.03 (br d, *J* = 13.2 Hz, 21-H), 4.25 (br s, 3-H), 4.55 (dd, *J* = 6.5, 2.2 Hz, 6-H), 5.40 (q, *J* = 6.8 Hz, 19-H), 7.25-7.40 (m, 5H), 7.50 (m, 2H), 7.81 (dm, *J* = 7.1 Hz, 9-H), 7.93 (dm, *J* = 7.9 Hz, 12-H). ^{13}C-NMR (75 MHz) 12.5 (C-18), 25.9 (C-15), 30.5 (C-14), 39.8 (C-6), 45.4 (C-16), 51.9 (C-21), 53.6 (C-3), 58.0 (C-5), 114.2 (C-12), 117.9 (C-7), 120.0 (C-9), 120.9 (C-19), 123.3 (C-10), 124.9 (C-11), 128.5 (C-8), 136.2 (C-2, C-20), 137.4 (C-13), 174.1 (C-22).
9. When the reaction was carried out with TFAA/TFA or TFAA/BF_3.Et_2O, the tetracyclic sulfide **9** was isolated in 50% yield. For precedents of this abnormal Pummerer reaction, see: (a) Pyne, S. G.; Hajipour, A. R. *Tetrahedron* **1994**, *50*, 13501-13510. (b) Arnone, A.; Bravo, P.; Bruché, L.; Cruacianelli, M.; Vichi, L.; Zanda, M. *Tetrahedron Lett.* **1995**, *36*, 7301-7304. (c) Amat, M.; Bennasar, M.-L.; Hadida, S.; Sufi, B. A.; Zulaica, E.; Bosch, J. *Tetrahedron Lett.* **1996**, *29*, 5217-5220.
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