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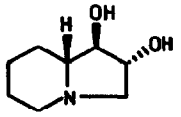
Stereoselective Synthesis of (+)- and (−)-Lentiginosine

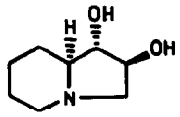
M K Gurjar*, Lakshmi Ghosh, M Syamala, V Jayasree
Indian Institute of Chemical Technology, Hyderabad 500 007, India

Abstract : Simple routes to (1R,2R,8aR)- and (1S,2S,8aS)-lentiginosine have been described, based on Sharpless asymmetric dihydroxylation, starting from (R)- and (S)-pipecolinic acids.

Interest in pyrrolizidine and indolizidine alkaloids is considerable due to their potent glycosidase inhibitory and anti-HIV activities[1] and castanospermine[2], a plant polyhydroxylated alkaloid, is presently undergoing advanced clinical trials for anti-AIDS activity. Recently, lentiginosine (1), a dihydroxylated indolizidine alkaloid, with potent amyloglucosidase inhibitory activity, was isolated from the leaves of Astragalus lentiginosus and its absolute stereochemistry - (1S,2S,8aS)-**1b**, was assigned on the basis of biogenetic considerations[3]. Stereospecific



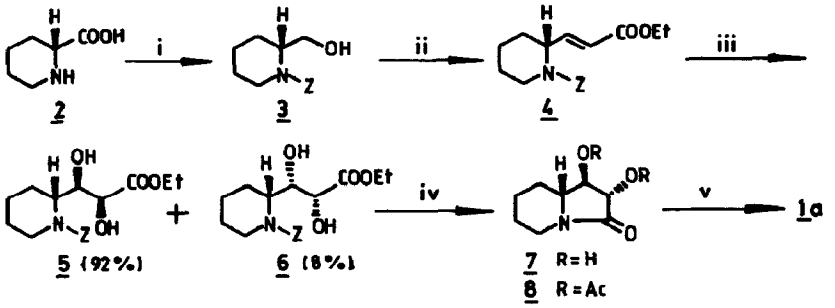
1a



1b

syntheses of (1S,2S,8aS)-**1b** from (+)-tartaric acid were reported by Yoda et al[4] and Cordiro et al[5]. The specific optical rotation of the synthetic **1b** { $[\alpha]_D$ + 0.19° (c 6, MeOH)[4], $[\alpha]_D$ +3.2° (c 0.27, MeOH)[5] } , however, did not correlate with those of the natural product { $[\alpha]_D$ -3.3° (c 0.33, MeOH) } . This discrepancy led us to believe that a synthesis of (1R,2R,8aR)-isomer **1a** was required for comparison with the natural product. In both the previous syntheses[4,5], the stereogenic centers C-1 and C-2 of **1b** were obtained from (+)-tartaric acid whereas the bridgehead carbon (C-8a) was derived by either deoxygenation of the quarternary α-hydroxylactam or by thermal rearrangement of a spiro-oxazolidine precursor. We focused our attention on the synthesis of **1a** and **1b** from pipecolinic acid, available in both enantiomeric forms. The stereogenic center (C-2) of pipecolinic acid correlated with the bridgehead carbon (C-8a) whilst the trans-diol (C_1-C_2) segment was realised by the Sharpless asymmetric dihydroxylation[6].

(R)-Pipecolinic acid (**2**) was transformed into the N-Z-alcohol (**3**), oxidised with Py:SO_3 in DMSO and olefinated with Ph_3P=CHCOOEt to afford (E)-ester (**4**). Subsequent dihydroxylation with AD-mix-β at 0°-RT for 24 h provided a mixture of diols (**5** and **6**) in the ratio of 92:8 (HPLC). In order to obtain the enantiomerically pure **5** { $[\alpha]_D$ -55° (c 1.1, MeOH), lit.[4] +58° (c 1.36, MeOH) of its antipode} , the mixture was converted into the acetonide derivatives, separated by chromatography and hydrolysed. Hydrogenolysis of **5** over Pd-C gave the cyclic product **7**. The derived diacetate **8** showed in its ^{1}H NMR spectrum, the characteristic doublet



i) (a) CbzCl, 4(N) NaOH, RT, 6 h; (b) 2M BH_3:SMe_2, THF, 0°-RT, 10 h; ii) (a) Py:SO_3, DMSO, 0°-RT, 30 min, (b) Ph_3P=CHCOOEt, C_6H_6, RT, 10 h; iii) AD-mix-β , (1:1), t-BuOH-H_2O, RT, 24 h; iv) a) 10% Pd-C, NaOAc, MeOH, H_2, 1 atm, 12 h; b) Ac_2O, Py, RT, 8 h; v) 2M BH_3:SMe_2, THF, RT, 12 h.

at δ 5.36 (H-8) and a triplet at δ 5.02 (H-7) with coupling constants $J_{6,7}$=$J_{7,8}$=5.3 Hz establishing trans-trans relationship. Reduction of 7 with 2M BH_3:Me_2S in THF gave **1a** { $[\alpha]_D$ -2.6° (c 1.0, MeOH)}whose ^{1}H NMR spectrum was superimposable on the reported spectrum[3]. Similarly (S)-pipecolinic acid was transformed into (1S,2S,8aS)-lengtiginosine (**1b**) { $[\alpha]_D$+3.2° (c 0.33, MeOH)}. Our results clearly implicated the structure **1a** for natural lengtiginosine and apparently confirmed the earlier proposal of Cordiro et al[5].

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