Stereoselective Total Synthesis of (+)-Lentiginosine Using a Chiral Nitrone Intermediate†

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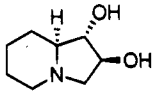
The indolizidine alkaloid lentiginosine (**1**), extracted from the leaves of *Astragalus lentiginosus*, is the first α-glucosidase inhibitor that has been found to possess only two hydroxyl groups.[1] The biosynthetic origin of **1**



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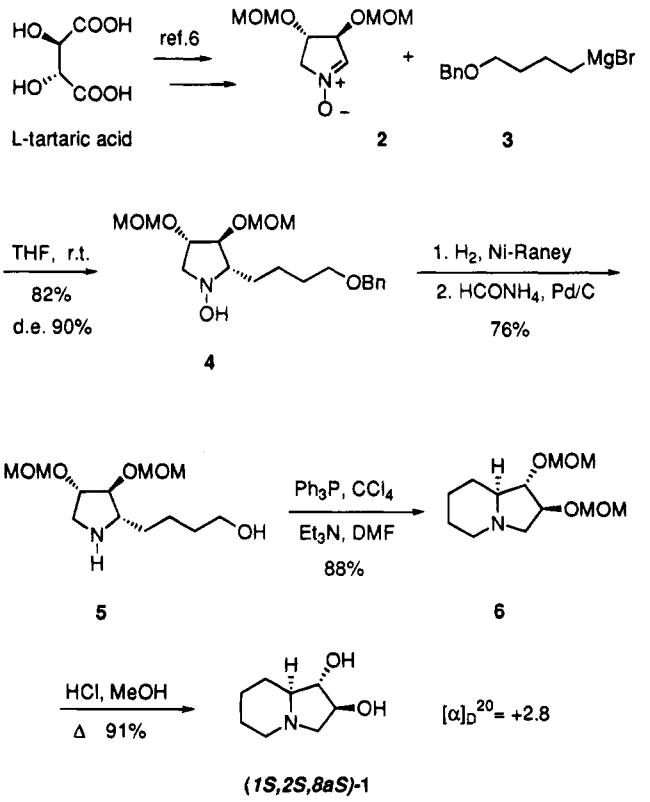
is related to other polyhydroxylated indolizidine metabolites, such as swainsonine and castanospermine[2] that have powerful glycosidase inhibitory and anti-HIV activities. The natural lentiginosine has a reported value $[\alpha]_D = -3.3$, and for biogenetic reasons, its absolute configuration has been proposed to be (1*S*,2*S*,8a*S*).[1] The first synthesis of this alkaloid Yoda *et al.*, realized starting from L-tartaric acid, gave a value of $[\alpha]_D = +0.19$. The apparent discrepancy with the value of natural **1** was attributed to some diastereomeric impurities in the natural product. However , a similar result has recently been obtained by Brandi *et al.* who report a value of $[\alpha]_D = +3.2$ for the compound prepared starting from L-tartaric acid.[4] The synthesis of both enantiomers of lentiginosine carried out by Gurjar *et al.*, starting from (*R*), and (*S*)-pipecolinic acid,[5] apparently proves that the natural lentiginosine has the (1*R*,2*R*,8a*R*) stereochemistry.

The stereochemical features of **1** suggest the possibility of using nitrone **2** as a precursor for the dihydroxylated portion of the molecule. This nitrone is readily available in five steps from L-tartaric acid[6] and has been previously used for the synthesis of other polyhydroxylated systems[7] as well as for lentiginosine itself.[4] Attack of organometallic reagents on nitrones usually produces α-substituted hydroxylamines that can be further reduced to the amino derivatives.[8] Following this strategy, we planned to create the third stereogenic center of the incoming indolizidine structure through the addition of a suitable organomagnesium reagent to nitrone **2**, followed by a ring

Scheme 1



closure to the desired bicyclic framework (Scheme 1). Addition of (4-(benzyloxy)butyl)magnesium bromide **3** to nitrone **2** in THF at rt was completely ineffective since the major product formed in this process was 4-(benzyloxy)butanol arising from the oxidation of **3** by the nitrone **2**.[9] After several trials, a simple reversal in the order of the reagents addition (i.e., nitrone **2** to 2 equiv of reagent **3** in THF) produced in 82% yield a chromatographically separable mixture of diastereomers (95:5) in which the 2,3-*trans* **4** predominates. This selectivity, compared to that observed in a foregoing procedure,[10] is quite surprising and can be explained by taking into account a possible coordination between the benzyloxy group and the magnesium atom of the reagent that would produce a six-membered ring structure endowed with a greater steric hindrance compared to a linear framework. The preparation of the amino alcohol **5** in 76% yield is best conducted in a two-stage process involving reduction of hydroxylamine **4** by hydrogenation (1 atm, rt) with Raney Ni catalyst in MeOH, followed by debenzylation using a catalytic transfer hydrogenolysis ($HCONH_4$, Pd/C).[11] Ring closure to the indolizidine **6** has been carried out by intramolecular displacement of the activated OH group by the $Ph_3P/CCl_4/Et_3N$ system in DMF (88% yield).

†Dedicated to Professor Stephen Hanessian on the occasion of his 60th birthday.

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(10) Reaction of 4-(methoxybenzyl)magnesium chloride with **2** at 0 °C in THF produces a 2:3 mixture of diastereomers in which the 2,3 *cis* one predominates; see ref 6a.
(11) Only partial debenzylation (20%) is experienced with Raney Ni catalyst even using elevated pressures (5 atm) or a high amount (50% mol) of catalyst.

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Finally, removal of the methoxymethyl groups (HCl, MeOH) gave (1*S*,2*S*,8a*S*)-lentiginosine (**1**) as a white solid in 16% overall yield from L-tartaric acid . All recorded spectra are in full agreement with those reported for **1**[1,4] (see Experimental Section), and the value of $[\alpha]^{20}_D$ = +2.8, may lead to the erroneous attribution of the absolute configuration of natural lentiginosine made by Elbein *et al.*[1] It is also evident that only an X-ray structure determination on the natural lentiginosine could give a final answer to this problem.

Experimental Section

^{1}H NMR spectra were recorded at 300 MHz. Mass spectra were performed using the EI technique. All chemicals used are commercially available (Aldrich Co.). 4-(Benzyloxy)-1-bromobutane was prepared according to the literature.[12] Nitrone **2** was prepared according to a previously described method.[6] Flash chromatography was performed on Merck silica gel (0.040–0.063 mm).[13]

(2*S*,3*S*,4*S*)-1-Hydroxy-2-(4-(benzyloxy)butyl)-3,4-bis(methoxymethoxy) pyrrolidine (4). To a stirrred suspension of magnesium turnings (0.54 g, 22 mol) in THF (10 mL) was added 4-(benzyloxy)-1-bromobutane (4.62 g, 20 mmol) in THF (60 mL) dropwise, mantaining a gentle reflux. The solution was refluxed for a further 30 min after the addition was complete and then cooled to rt. Nitrone **2** (2.04 g, 10 mmol) in THF (40 mL) was then slowly added at rt. After the mixture was stirred for 2 h, saturated aqueous NH_4Cl (20 mL) was poured into the reaction mixture. The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The organic phases were dried over Na_2SO_4. After evaporation of the solvent the crude material was purified by flash chromatography over silica gel (hexane/ethyl acetate/ethanol (65:30:5)) affording 3.04 g (82%) as an oil: $[\alpha]^{20}_D$ −27.8 (*c* 0.9, $CHCl_3$); IR (cm^{-1}, neat) 3400; ^{1}H NMR ($CDCl_3$) δ 1.45–1.95 (m, 6H), 2.76–2.81 (m, 1H), 3.10 (dd, 1H, J = 11.2, 5.7 Hz), 3.25–3.35 (m, 1H), 3.36 (s, 6H), 3.48 (t, 3H, J = 6.2 Hz), 3.80 (d, 1H, J = 5.8 Hz), 4.08 (d, 1H, J = 5.6 Hz), 4.48 (s, 2H), 4.60–4.77 (m, 4H), 7.00 (bs, 1H), 7.22–7.35 (m, 5H); MS *m*/*z* 354 (M^+ − 16), 292, 262, 204, 190, 91. Anal. Calcd for $C_{19}H_{31}NO_6$: C, 61.77; H, 8.46; N, 3.79. Found: C, 61.71; H, 8.50; N, 3.76.

(2*S*,3*S*,4*S*)-2-(4-Hydroxybutyl)-3,4-bis(methoxymethoxy)pyrrolidine (5). Hydroxylamine **4** (3.0 g, 8.4 mmol) was dissolved in MeOH (70 mL) and hydrogenated at 1 atm in the presence of Raney Ni W2 (0.40 g) for 18 h at rt. The catalyst was removed by filtration and washed thoroughly with methanol. After evaporation of the solvent the crude product was dissolved in EtOH (80 mL), and $HCONH_4$ (4.0 g, 32 mmol) and 10% Pd on carbon (1.0 g) were added. The mixture was refluxed for 2 h and then cooled to rt. The catalyst was removed by filtration through a Celite pad and washed with EtOH. After evaporation of the solvent the crude product was purified by flash chromatography on silica gel ($CHCl_3$/MeOH/30% NH_4OH (80:19:1)) to afford 1.68 g (76%) of a waxy solid: $[\alpha]^{20}_D$ −8.7 (*c* 0.7, $CHCl_3$); IR (cm^{-1}, neat) 3300; ^{1}H NMR ($CDCl_3$) δ 1.45–1.75 (m, 6H), 2.60 (bs, 1H), 2.86–2.98 (m, 1H), 3.02 (d, 2H, J = 3.5 Hz), 3.35 (s, 3H), 3.45 (s, 3H), 3.56–3.68 (m, 2H), 3.72 (dd, 1H, J = 4.5, 1.3 Hz), 4.04–4.10 (m, 1H), 4.61–4.75 (m, 2H); MS *m*/*z* M^+ 263, 202, 190, 114, 114, 85, 70, 56. Anal. Calcd for $C_{12}H_{25}NO_5$: C, 54.73; H, 9.57; N, 5.32. Found: C, 54.78; H, 9.54; N, 5.36.

(1*S*,2*S*,8a*S*)-1,2-Bis(methoxymethoxy)indolizidine (6). Amino alcohol **5** (1.6g, 6 mmol) was dissolved in dry DMF (20 mL), and then Ph_3P (3.14 g, 12 mmol), CCl_4 (1.84 g, 1.16 mL, 12 mmol) and Et_3N (1.2 g, 1.66 mL, 12 mmol) were sequentially added. The suspension was strirred for 2 h, and then DMF was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane/ethyl acetate/ethanol/30% NH_4OH (65:25:9:1)) affording 1.3 g (88%) of a yellow oil: $[\alpha]^{20}_D$ −31 (*c* 1.52, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.10–1.45 (m, 2H), 1.50–1.68 (m, 2H), 1.70–1.84 (m, 2H), 1.85–2.00 (m, 2H), 2.38 (dd, 1H, J = 10.5, 6.0 Hz), 2.98 (d, 2H, J = 10.5 Hz), 3.35 (s, 6H), 3.73 (dd, 1H, J = 7.8, 2.2 Hz), 3.98 (dd, 1H, J = 5.7, 2.2 Hz), 4.62–4.83 (m, 2H); MS *m*/*z* M^+ 245, 214, 200, 184, 156, 128, 124, 97. Anal. Calcd for $C_{12}H_{23}NO_4$: C, 58.75; H, 9.45; N, 5.71. Found: C, 58.70; H, 9.49; N, 5.75.

(1*S*,2*S*,8a*S*)-1,2-Dihydroxyindolizidine ((+)-Lentiginosine, 1). Indolizidine **6** (1,2 g, 4.9 mmol) was dissolved in MeOH (15 mL), and 37% HCl (0.75 mL) was added. The solution was gently refluxed for 3 h, and after the solution was cooled to rt, 30% NH_4OH (15 mL) was added. The solid residue obtained after evaporation of the solvent was purified by flash chromatography over silica gel (CH_2Cl_2/MeOH/30% NH_4OH (80:19:1)) to afford 0.7 g (91%) of a white solid: mp 107 °C (lit.[4] mp 106–107 °C); $[\alpha]^{20}_D$ +2.8 (*c* 0.28, MeOH); ^{1}H NMR (D_2O) δ 1.12–1.80 (m, 5H), 1.81–2.01 (m, 2H), 2.06 (dd, 1H, J = 11.3, 2.9 Hz), 2.60 (dd, 1H, J = 11.4, 7.4 Hz), 2.79 (dd, 1H, J = 11.4, 2.0 Hz), 2.90 (dd, 1H, J = 11.2, 2.0 Hz), 3.59 (dd, 1H, J = 8.8, 4.0 Hz), 4.03 (ddd, 1H, J = 7.5, 4.0, 1.9 Hz); ^{13}C NMR (D_2O) δ 25.1, 25.9, 29.5, 54.7, 62.9, 71.4, 77.8, 85.1; MS *m*/*z* M^+ 157, 140, 97, 84, 69, 55. Anal. Calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.20; H, 9.57; N, 8.97.

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