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

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Abstract: Total synthesis of (−)-lentiginosine was achieved from D-mannitol using highly stereoselective reactions. Similarly, (+)-lentiginosine was synthesized from L-tartaric acid.

(−)-Lentiginosine (−)-**1**, a dihydroxylated indolizidine alkaloid, was isolated in 1990 from the leaves of *Astragalus lentiginosus*.[1,2] It was reported to be a competitive inhibitor (IC_{50} 5 μg/mL) of the amyloglucosidase enzyme. The biosynthetic origin of **1** is related to other polyhydroxylated indolizidine metabolites that have powerful glycosidase inhibitory and anti-HIV activity.[3] The natural lentiginosine has a specific rotation of −3.3, and for biogenetic reasons, its absolute stereochemistry was assigned to be (1*S*,2*S*,8a*S*).[1] Early syntheses of this natural product created an ambiguity about its absolute stereochemistry.[4] This was later resolved after synthesis of both enantiomers of lentiginosine by Gurjar et al., starting from (*R*)- and (*S*)-pipecolinic acid.[5] Thus, natural lentiginosine (−)-**1** was corrected to have all (*R*)-stereochemistry (Figure 1). This assignment was further questioned by Brandi et al. who synthesized both the enantiomers of **1** and evaluated their inhibitory properties toward a wide range of glucosidases.[6] They observed IC_{50} values of 0.43 and 17 μg/mL for (+)- and (−)-lentiginosine, respectively. On the basis of the biological considerations where inhibitory activity obtained for a synthetic lentiginosine was closer to that of the value reported for natural lentiginosine, they concluded that the natural isomer is dextrorotatory, and not levorotatory as postulated by Elbein et al. The authors argued that the negative rotation obtained for the natural lentiginosine by Elbein and co-workers was due to impurities. This followed a series of papers[7] on total synthesis of (+)-**1** without having any unambiguous proof of whether

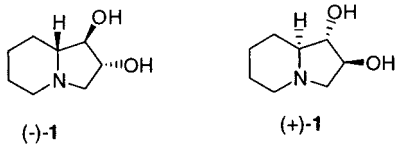

Figure 1.

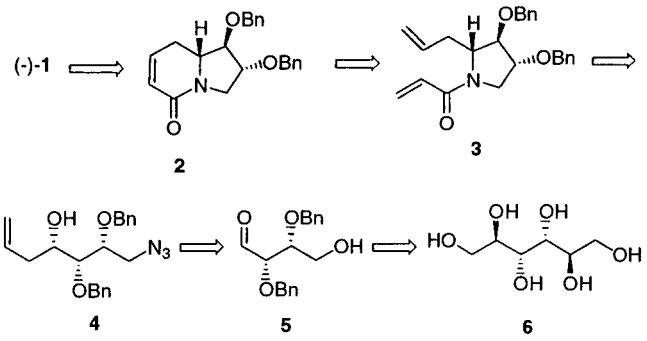

Figure 2. Retrosynthetic analysis.

it was really a natural one. While working on total synthesis of natural products from D-mannitol,[8] we envisioned that (−)-lentiginosine could easily be synthesized from the same precursor, which is very cheap and readily available. In this paper, we describe our synthetic strategy toward (−)-lentiginosine. We further report a synthesis of the (+)-isomer of the same natural product from L-tartaric acid using a similar strategy.

Retrosynthetic analysis of (−)-**1** is shown in Figure 2. We envisioned that the six-membered ring of the natural product could be synthesized from **3** via **2** using Grubbs cyclization.[9] The five-membered ring of the target can then be prepared by using an S_N2 reaction, where a nitrogen atom displaces a leaving group at the chiral center (C-8a). The strategy required an intermediate **4**, which can be mapped with D-mannitol **6**, an inexpensive starting material. In this strategy, the stereogenic centers C-1 and C-2 [both (*R*)-] of (−)-**1** were obtained from the two central chiral centers of D-mannitol without having any possibility of racemization, whereas the bridgehead carbon (C-8a) was obtained through a highly stereoselective reaction.

The synthesis commences with a diol **7**,[8a] which was cleaved with lead tetraacetate to an aldehyde (Scheme 1). The crude aldehyde was reduced to an alcohol by using sodium borohydride.[8a] The alcohol, without any purification, was converted into an azide **8** by treating its tosylate with sodium azide in DMF. The acetonide group of the **8** was cleaved to a diol **9** by using trifluoroacetic acid in a mixture of THF and water in a quantitative yield. The

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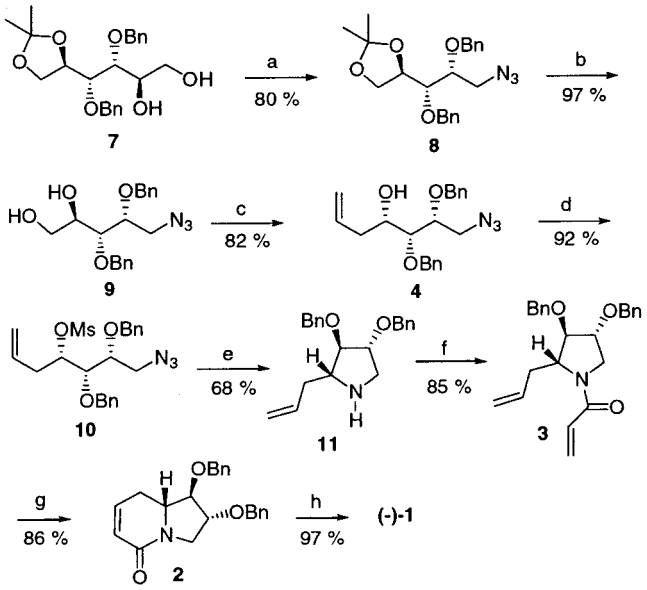
Scheme 1[a]



[a] Reaction conditions: (a) (i) $Pb(OAc)_4$, CH_2Cl_2, 3 h; (ii) $NaBH_4$, EtOH, 3 h; (iii) TsCl, Et_3N, CH_2Cl_2, 12 h; (iv) NaN_3, DMF, 80 °C, 8 h. (b) CF_3COOH, THF/H_2O (4:1), 65 °C, 8 h. (c) (i) $Pb(OAc)_4$, CH_2Cl_2, 3h; (ii) $SnCl_4$, allyltributyl tin, CH_2Cl_2, −78 °C, 1 h. (d) MsCl, Et_3N, CH_2Cl_2, 6 h. (e) $LiAlH_4$, THF, reflux, 65 °C, 12 h. (f) acryloyl chloride, Et_3N, CH_2Cl_2, 12 h. (g) Benzylidene-bis(tricyclohexyl phosphine)-dichlororuthenium (10 mol %), toluene reflux, 24 h. (h) (i) 10% Pd/C, H_2, 24 h; (ii) $LiAlH_4$, THF, reflux, 6 h.

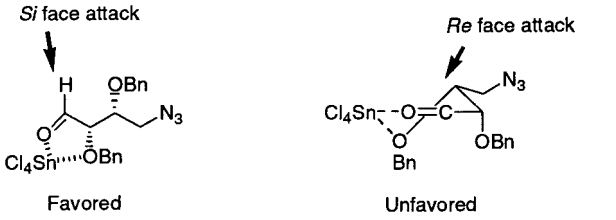
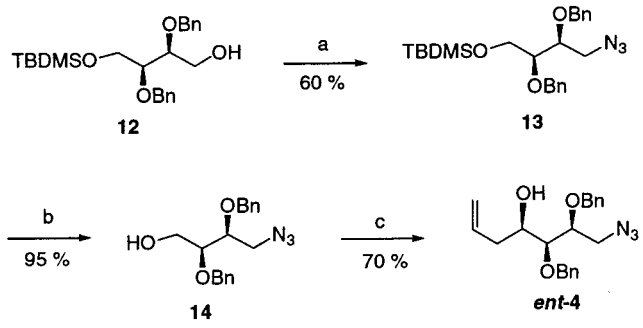


Figure 3. Chelation-controlled transition state models.

diastereoselective addition of allyltributylstannane to the crude aldehyde, obtained from an oxidative cleavage of the diol **9** with lead tetraacetate, was carried out at −78 °C using $SnCl_4$ as a Lewis acid to give a homoallylic alcohol **4** in a very highly diastereoselective manner (ratio of syn vs anti diastereomer by HPLC = 99:1). The formation of syn diastereomer **4** can be explained by a chelation-controlled addition of the allyl group to the aldehyde with two alkoxy groups at α and *β* positions.[10] The formation of a more rigid five-membered transtion state is favored over a flexible six-membered half-chair analogue (Figure 3). To construct a pyrrolidine ring, it was envisaged that the reduction of the azide group should trigger the cyclization if the alcohol is activated to a good leaving group. This was indeed the case. The azido mesylate **10**, on treatment with LAH in THF at reflux temperature, gave the cyclized amine **11** where an amine produced by reduction of the azide displaced the mesylate via an S_N2 mechanism. Thus, an inversion of configuration took place during the cyclization reaction. The secondary amine of the **11** was converted into an acrylamide **3** using standard conditions. Formation of the

Scheme 2[a]



[a] Reaction conditions: (a) (i) TsCl, Et_3N, CH_2Cl_2, 12 h; (ii) NaN_3, DMF, 80 °C, 12 h; (b) TBAF, THF, 8 h; (c) (i) NCS, DMS, CH_2Cl_2, Et_3N, −25 °C, 4 h; (ii) $SnCl_4$, allyltributyl tin, CH_2Cl_2, −78 °C, 1 h.

six-membered ring was accomplished using a Grubbs catalyst in toluene at 110 °C. Thus, the cyclized product **2** was obtained in 85% yield. Hydrogenation of **2** followed by reduction of the crude amide with LAH gave (−)-**1** in quantitative yield.

The other enantiomer of lentiginosine was prepared from **12**, which was easily procured from L-(+)-tartaric acid using a literature procedure[11] (Scheme 2). Compound **12** was converted into an azide **13** following the above procedure. The TBDMS group of the **13** was desilylated using tetrabutylammonium fluoride to provide an alcohol **14**. Conversion of **14** into *ent*-**4** required oxidation to an aldehyde followed by allylic addition. Various methods were tried for oxidation of **14** to the aldehyde. The reaction was not clean with Swern oxidation. Mild methods such as Ag_2CO_3/Celite and Dess−Martin reagent were also unsuccessful. Use of PCC under buffer conditions did give the aldehyde, but with partial racemization[12] as the subsequent addition of allyltributyl under the above condition gave *ent*-**4** in a diastereomeric ratio of 74:26 (HPLC). Finally, it was observed that there was virtually no racemization if the alcohol **14** was oxidized by the Corey−Kim method.[13] Thus, the alcohol **14** was treated with NCS and dimethyl sulfide at −25 °C to obtain the aldehyde,[14] which was allylated under the above conditions to provide *ent*-**4** in a diastereomeric ratio of 96:4 (HPLC). Since the conversion of **4** into (−)-**1** has already been done above, the *ent*-**4** was left at this stage, and thus it completes the formal synthesis of (+)-**1**.

In conclusion, we have completed total synthesis of (−)- and (+)-lentiginosine from readily available starting materials. The controversy, whether natural lentiginosine is dextrorotatory or levorotatory, can only be solved by the X-ray structure of the natural product.

Experimental Section

(2*R*,3*S*,4*R*)-5-Azido-3,4-bis-benzyloxy-1,2-*O*-isopropylidene Pentane (8). A solution of 3,4-di-*O*-benzyloxy-5,6-*O*-isopropylidene-D-mannitol **7** (1 g, 2.49 mmol) in dry DCM (10 mL) was treated with lead tetraacetate (1.3 g, 2.98 mmol) at 0 °C and further stirred for 4 h (from 0 °C to rt). The reaction

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(12) ^{1}H NMR of the crude aldehyde showed two peaks in the aldehydic region (*δ* 9.72 and 9.67) in a ratio of 3:1.

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(14) ^{1}H NMR of the crude aldehyde showed only one peak (*δ* 9.73) in the aldehydic region.

mixture was cooled (ice bath), and the reaction was quenched by an addition of saturated aqueous sodium bicarbonate. The solids were filtered through a Celite pad, and the filtrate was extracted with dichloromethane. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and concentrated in vacuo to give an aldehyde. The crude aldehyde was taken into ethanol (10 mL), and the solution was treated with $NaBH_4$ (188 mg, 4.98 mmol) in portions at 0 °C for 1 h. Most of the ethanol was removed in vacuo, and the crude was partitioned between EtOAc and water. The organic layer was separated out, washed with water and brine, dried over anhydrous sodium sulfate, and concentrated in vacuo to give an alcohol as a colorless liquid (920 mg). A solution of the alcohol (900 mg, 2.41 mmol) and triethylamine (1.3 mL, 9.64 mmol) in DCM (5 mL) was treated with tosyl chloride (600 mg, 3.13 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 12 h. The mixture was diluted with ether and washed with water and brine. The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo. The crude tosylate was taken in DMF (8 mL) and treated with NaN_3 (626 mg, 9.64 mmol) at 80 °C for 12 h. The reaction mixture was taken in water and extracted with ether several times. The combined organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and concentrated in vacuo. The crude material was chromatographed over silica gel to give the azide **8** as a colorless oil: yield 864 mg (80%); R_f 0.65 (10% EtOAc in petroleum ether); $[\alpha]^{25}_D$ −11.5 (*c* 1, $CHCl_3$); IR (thin film) 2987, 2882, 2098, 1374 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.36 (s, 3H), 1.45 (s, 3H), 3.41 (d, J = 6.0 Hz, 2H), 3.70 (m, 1H), 3.76 (dd, J = 4.0, 4.0 Hz, 1H), 3.93 (dd, J = 8.0, 6.8 Hz, 1H), 4.02 (dd, J = 8.0, 6.4 Hz, 1H), 4.23 (m, 1H), 4.58−4.80 (m, 4H), 7.3 (m, 10 H);^{13}C NMR (100 MHz, $CDCl_3$) δ 25.03, 26.44, 51.25, 66.09, 73.41, 74.61, 76.01, 78.60, 108.55, 127.83, 128.01, 128.08, 128.34, 137.55, 137.83; MS (FAB) 398 (M^++1). Anal. Calcd for $C_{22}H_{27}N_3O_4$: C, 66.50; H, 6.80; N, 10.58. Found: C, 66.48; H, 6.83; N, 10.51.

(2*R*,3*R*,4*R*)-5-Azido-3,4-bis-benzyloxy-pentane-1,2-diol (9). A solution of **8** (800 mg, 2.01 mmol) in THF/H_2O (4:1; 10 mL) was treated with trifluoroacetic acid (310 μL, 4.03 mmol) at room temperature and further refluxed for 8 h. The solvent was removed in vacuo, and the residue was taken in water and extracted with EtOAc. The organic layer was washed with aqueous sodium bicarbonate, water, and brine, dried over anhydrous sodium sulfate, concentrated in vacuo, and chromatographed over silica gel to give a diol **9** as a low-melting solid: yield 700 mg (97%), R_f 0.45 (40% EtOAc in petroleum ether); $[\alpha]^{25}_D$ −38.7 (*c* 2.9, $CHCl_3$); IR (thin film) 3450, 2101, 1266, 1072 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.56 (bs, O*H*), 3.42 (dd, J = 13.0, 4.4 Hz, 1H), 3.48 (dd, J = 13.0, 7.3 Hz, 1H), 3.57 (m, 1H), 3.59 (dd, J = 9.7, 4.1 Hz, 1H), 3.66 (dd, J = 11.7, 3.4, Hz, 1H), 3.74 (m, 2H), 4.49 (d, J = 11.5 Hz, 1H), 4.53 (d, J = 11.5, 1H), 4.54 (d, J = 11.2 Hz, 1H), 4.63 (d, J = 11.2 Hz, 1H), 7.28 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 51.09, 63.18, 71.34, 73.39, 73.70,76.06, 78.38, 128.14, 128.27, 128.50, 128.56, 136.91, 137.34; MS (FAB): 358 (M^+ + 1). Anal. Calcd for $C_{19}H_{23}N_3O_4$: C, 63.86; H, 6.44; N, 11.76. Found: C, 63.90; H, 6.48; N, 11.81.

(4*S*,5*R*,6*R*)-7-Azido-5,6-bis-benzyloxy-hept-1-en-4-ol (4). A solution of the azido diol **9** (430 mg, 1.20 mmol) in dry DCM (6 mL) was treated with lead tetraacetate at 0 °C and further stirred for 3 h (0 °C − rt). The reaction mixture was cooled (ice bath), and the reaction was quenched with aqueous $NaHCO_3$. The solids were filtered through a Celite pad, and the filtrate was extracted with dichloromethane. The organic layer was washed with water and brine and dried over anhydrous sodium sulfate before being concentrated in vacuo to provide an aldehyde. A solution of this crude aldehyde in dry DCM (5 mL) was cooled to −78 °C under a N_2 atmosphere, and to this was added $SnCl_4$ (155 μL, 1.32 mmol, in 1.2 mL of DCM). Then, a solution of allyltributyl stannane (405 μL, 1.32 mmol) in DCM (1.2 mL) was added dropwise at the same temperature. The reaction mixture was stirred for 1 h, and then the reaction was quenched by an addition of 1 N NaOH in wet MeOH. The cooling bath was removed, and the flask was brought to room temperature. The solvent was removed in vacuo, and the residue was taken in water and extracted with DCM. The organic layer was washed with water and brine, dried (anhydrous sodium sulfate), and concentrated to provide a residue, which was chromatographed over silica gel to give a diastereomerically pure homoallylic alcohol **4**: diastereomeric ratio 99:1 (HPLC, silica gel column 100 × 4.6 mm, solvent 99:1 *n*-hexanes/2-propanol, flow rate 1.25 mL/min, UV 254 nm, R_T 3.04 min for major and 2.52 min for minor diastereomers); yield 362 mg (82%); R_f 0.70 (30% EtOAc in petroleum ether); $[\alpha]^{25}_D$ −28.7 (*c* 1.08, $CHCl_3$); IR (thin film) 3450, 2877, 2096, 1068 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.05 (d, 1H, −O*H*), 2.19 (m, 2H), 3.44 (m, 3H), 3.73 (m, 2H), 4.52 (dd, J = 13.9, 11.5 Hz, 2H), 4.64 (dd, J = 18.3, 11.5 Hz, 2H), 5.01 (m, 2H), 5.69 (m,1H), 7.3 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.31, 51.56, 69.52, 73.22, 74.41, 78.99, 117.86, 128.13, 128.48, 134.47, 137.70, 137.74. Anal. Calcd for $C_{21}H_{25}N_3O_3$: C, 68.66; H, 6.81; N, 11.44. Found: C, 68.70; H, 6.78; N, 11.42.

(4*S*,5*S*,6*R*)-7-Azido-5,6-bis-benzyloxy-hept-1-en-4-methanesulfonate (10). A solution of the homoallylic alcohol **4** (183 mg, 0.5 mmol) and triethylamine (210 μL, 1.5 mmol) in dry DCM (5 mL) was treated with methanesulfonyl chloride (60 μL, 0.75 mmol) at 0 °C under a N_2 atmosphere. The reaction mixture was stirred for 6 h (from 0 °C to rt). It was diluted with diethyl ether and washed with water and brine. After drying (anhydrous sodium sulfate) and concentration in vacuo, the residue was purified over silica gel to give a pure mesylated product **10**: yield 205 mg (92%); R_f 0.65 (EtOAc in petroleum ether); $[\alpha]^{25}_D$ −14.3 (*c* 2.3, $CHCl_3$); IR (thin film) 2931, 2100, 1346, 917 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.34 (m, 1H), 2.58 (m, 1H), 2.93 (s, 3H), 3.48 (m, 2H), 3.69 (m, 2H), 4.57 (d, J = 11.5 Hz, 1H), 4.68 (m, 3H), 4.79 (q, J = 5.6 Hz, 1H), 5.06 (dd, J = 17.1, 1.0 Hz, 1H), 5.13 (dd, J = 10.2, 1.0 Hz, 1H), 5.71 (m, 1H), 7.34 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.75, 38.73, 50.60, 73.08, 75.07, 77.43, 77.95, 80.92, 119.35, 128.12, 128.21, 128.22, 128.30, 128.52, 128.56, 132.18, 137.27, 137.39. Anal. Calcd for $C_{22}H_{27}N_3O_5S$: C, 59.32; H, 6.07; N, 9.44; S, 7.19. Found: C, 59.37; H, 6.10; N, 9.48; S, 7.21.

(2*R*,3*R*,4*R*)-2-Allyl-3,4-bis-benzyloxy-pyrrolidine (11). A solution of the azido mesylate **10** (190 mg, 0.43 mmol) in dry THF (3 mL) was treated with lithium aluminum hydride solution (850 μL, 1.0 M) at 0 °C. The reaction mixture was refluxed for 12 h, and the reaction was quenched by the addition of EtOAc and water (3−4 drops). The solids were filtered through a Celite pad, and the filtrate was concentrated in vacuo. The crude material was chromatographed over silica gel to give the pure cyclized product **11**: yield 94 mg (68%); R_f 0.70 (10% MeOH in CH_2Cl_2); $[\alpha]^{25}_D$ +10.2 (*c* 2.1, $CHCl_3$); IR (thin film) 2922, 1368, 1075, 738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.29 (m, 2H), 2.65 (bs, −N*H*), 3.03 (m, 3H), 3.60 (d, J = 4.4 Hz, 1H), 3.91 (m, 1H), 4.45 (m, 4H), 5.01 (m, 2H), 5.73 (m, 1H), 7.30 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.60, 50.76, 63.87, 71.04, 71.86, 83.93, 87.88, 117.35, 127.67, 127.75, 128.39, 128.43, 134.94, 137.93; MS (FAB) 324 (M^+ + 1). Anal. Calcd for $C_{21}H_{25}NO_2$: C, 78.02; H, 7.74; N, 4.33. Found: C, 78.16; H, 7.70; N, 4.28.

(2*R*,3*R*,4*R*)-1-(2-Allyl-3,4-bis-benzyloxy-pyrrolidin-1-yl)-propenone (3). A solution of the cyclized amine **11** (106 mg, 0.33 mmol) and triethylamine (180 μL, 1.31 mmol) in dry DCM (1 mL) was treated with acryloyl chloride (40 μL, 0.49 mmol) at 0 °C under a N_2 atmosphere. The reaction mixture was stirred for 12 h (from 0 °C to rt) and then diluted with diethyl ether and washed with water and brine. The mixture was dried over anhydrous sodium sulfate, concentrated in vacuo and chromatographed over silica gel to give the pure amide **3**: yield 105 mg (85%); R_f 0.65 (50% EtOAc in petroleum ether); ^1H NMR (400 MHz, $CDCl_3$) δ 2.32 (m, 1H), 2.53 (m, 0.5H, rotamer), 2.75 (m, 0.5H, rotamer), 3.64 (m, 1H), 3.84 (dd, J = 11.2, 5.6 Hz, 0.5H, rotamer), 3.95 (m, 3H), 4.25 (dd, J = 10.7, 3.9 Hz, 0.5H, rotamer), 4.45 (m, 4H), 5.02 (m, 2H), 5.62 (m, 1H), 5.75 (m, 1H), 6.34 (m, 2H), 7.28 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.84, 37.60, 50.48, 51.65, 61.82, 62.49, 71.09, 71.34, 71.50, 71.60, 79.72, 81.11, 81.74, 83.89, 117.75, 118.56, 127.52, 127.56, 127.63, 127.75, 127.80, 127.86, 127.94, 128.04, 128.41, 128.48, 128.53, 133.58, 134.85, 137.35, 137.51, 164.72 (most of the carbons are showing two peaks because of the presence of rotamers). Anal. Calcd for $C_{24}H_{27}NO_3$: C, 76.39; H, 7.16; N, 3.71. Found: C, 76.34; H, 7.20; N, 3.68.

(1*R*,2*R*,8a*R*)-1,2-Bis-benzyloxy-2,3,8,8a-tetrahydro-1*H*-indolizidin-5-one (2). Grubbs catalyst (13 mg, 0.0154 mmol) was added to a solution of **3** (58 mg, 0.15 mmol) in toluene (20 mL) and refluxed for 24 h. The solvent was evaporated, and the

residue was chromatographed over silica gel to give the pure product **2**: yield 46 mg (86%); R_f 0.35 (50% EtOAc in petroleum ether); $[\alpha]^{25}_D$ +48.5 (*c* 3.65, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.16 (m, 1H), 2.43 (m, 1H), 3.67 (m, 3H), 3.84 (dd, J = 7.1, 5.4 Hz, 1H), 4.04 (td, J = 6.8, 5.1 Hz, 1H), 4.43 (d, J = 11.7 Hz, 1H), 4.52 (d, J = 8.76 Hz, 1H), 4.55 (d, J = 8.8 Hz, 1H), 4.65 (d, J = 11.7 Hz, 1H), 5.85 (dd, J = 10.0, 2.9 Hz, 1H), 6.42 (ddd, J = 7.6, 5.6, 2.2 Hz, 1H), 7.26 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.31, 47.09, 59.11, 72.01, 72.40, 80.17, 87.38, 125.36, 127.71, 127.77, 127.93, 127.95, 128.45, 128.49, 137.36, 137.63, 138.42, 163.20. Anal. Calcd for $C_{22}H_{23}NO_3$: C, 75.64; H, 6.59; N, 4.01. Found: C, 75.59; H, 6.63; N, 3.97.

(1*R*,2*R*,8a*R*)-(−)-Lentiginosine (1). A solution of the **2** (46 mg, 0.13 mmol) in ethanol (2 mL) was treated with a catalytic amount of 10% Pd/C. The reaction mixture was purged with H_2 gas and stirred for 24 h with a H_2 balloon connected to the flask. The reaction mixture was filtered through a Celite pad and concentrated in vacuo. The crude product was taken in THF (2 mL) and treated with lithium aluminum hydride (260 μL, 1.0 M) at 0 °C under a N_2 atmosphere. The reaction mixture was refluxed for 12 h. It was worked up as above, and the residue was chromatographed over silica gel to give the pure (−)-lentiginosine **1** in quantitative yield: mp 105 °C (lit.[7d] 106−107 °C); $[\alpha]^{25}_D$ −4.5 (*c* 0.8, MeOH) (lit.[7d] $[\alpha]^{25}_D$ −3.05 (*c* 1, MeOH)); IR (thin film) 3740, 3058, 1265, 740 cm^{-1}; ^{1}H NMR (400 MHz, D_2O) δ 1.19 (m, 2H), 1.35 (m, 1H), 1.55 (m, 1H), 1.68 (m, 1H), 1.83 (m, 1H), 2.15 (m, 2H), 2.73 (dd, J = 11.4, 7.6 Hz, 1H), 2.83 (d, J = 11.7 Hz, 1H), 2.95 (d, J = 10.8 Hz, 1H), 3.57 (dd, J = 8.8, 3.7 Hz, 1H), 3.99 (ddd, J = 7.3, 3.9, 2.0, 1H); ^{13}C NMR (100 MHz, D_2O) δ 25.78, 26.72, 30.14, 55.76, 63.00, 71.82, 78.30, 85.30.

(2*S*,3*S*)-4-Azido-2,3-bis-benzyloxy-1-*tert*-butyl-dimethyl-siloxybutane (13). A solution of the TBDMS alcohol **12** (1.8 g, 4.32 mmol) and triethylamine (2.3 mL, 17.28 mmol) in dry DCM (15 mL) was treated with *p*-toluenesulfonyl chloride (1.09 g, 5.7 mmol) at 0 °C and stirred for 12 h. The solution was diluted with diethyl ether and washed with water and brine. The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo. The crude tosylate was taken in DMF (5 mL) and treated with NaN_3 (570 mg, 8.77 mmol) at 80 °C for 12 h. The reaction mixture was taken in water and extracted with ether. The organic layer was washed with water and brine and finally dried over anhydrous sodium sulfate before being concentrated in vacuo and chromatographed over silica gel to give the azide **13** as a colorless oil: yield 1.1 g (60%); R_f 0.65 (10% EtOAc in petroleum ether); $[\alpha]^{25}_D$ +27.8 (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.01 (s, 6H), 0.85 (s, 9H), 3.34 (d, J = 5.6 Hz, 2H), 3.53 (m, 1H), 3.67 (m, 3H), 4.59 (m, 4H), 7.25 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.50, 18.10, 25.80, 51.46, 62.01, 73.04, 73.45, 78.22, 79.21, 127.64, 127.72, 127.91, 128.03, 128.26, 128.28, 137.86, 138.25. Anal. Calcd for $C_{24}H_{35}N_3O_3Si$: C, 65.31; H, 7.94; N, 9.52. Found: C, 65.28; H, 7.89; N, 9.54.

(2*S*,3*S*)-4-Azido-2,3-bis-benzyloxy-butan-1-ol (14). A solution of the TBDMS azide **13** (807 mg, 1.76 mmol) in dry THF (6 mL) was treated with TBAF (2.1 mL, 1.0 M) at 0 °C under a N_2 atmosphere. The reaction mixture was stirred for 8 h. The solvent was evaporated, and the residue was taken in water and extracted with ethyl acetate. The organic layer was washed with water and brine, dried (anhydrous sodium sulfate), concentrated in vacuo, and purified by silica gel chromatography to give **14** as an oil: yield 568 mg (95%); R_f 0.65 (40% EtOAc in petroleum ether); $[\alpha]^{25}_D$ +22.7 (*c* 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.33 (dd, J = 13.0, 6.8 Hz, 1H), 3.39 (dd, J = 13.0, 3.7 Hz, 1H), 3.56 (m, 2H), 3.70 (m, 2H), 4.54 (m, 3H), 4.63 (d, J = 11.4 Hz, 1H), 7.28 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 51.11, 61.04, 72.89, 73.22, 78.33, 78.49, 127.97, 128.49, 137.51, 137.77. Anal. Calcd for $C_{18}H_{21}N_3O_3$: C, 66.05; H, 6.42; N, 12.84. Found: C, 66.08; H, 6.48; N, 12.88.

(4*R*,5*S*,6*S*)-7-Azido-5,6-bis-benzyloxy-hept-1-en-4-ol (*ent*-4). A solution of *N*-chlorosuccinimide (95.5 mg, 0.72 mmol) in toluene (3 mL) was treated with Me_2S at 0 °C. As a result, a white precipitate appeared, which was cooled to −25 °C. A solution of azido alcohol (117 mg, 0.36 mmol) in toluene (1 mL) was added dropwise. After the reaction mixture was stirred for 4 h at the same temperature, Et_3N (100 μL, 0.72 mmol) was added and the cooling bath was removed. The reaction mixture was stirred at room temperature for 5 min and extracted with Et_2O. The organic layer was washed with 1% aqueous HCl solution, water, and brine, dried over anhydrous sodium sulfate, and concentrated in vacuo, and the crude aldehyde was subjected to allylation as it was done above in the case of **4** to provide *ent*-**4** (90 mg, 70% yield) in a diastereomeric ratio of 96:4 (HPLC, silica gel column 100 × 4.6 mm, solvent 99:1 *n*-hexanes/2-propanol, flow rate 1.25 mL/min, UV 254 nm, R_T 3.06 min for major and 2.52 min for minor diastereomers); $[\alpha]^{25}_D$ +25.9 (*c* 1, $CHCl_3$).

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