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Total synthesis of (−)-lentiginosine

S. Chandrasekhar,* B. V. D. Vijaykumar and T. V. Pratap

Organic Division-I, Indian Institute of Chemical Technology, Hyderabad 500 007, India

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Abstract—The total synthesis of (−)-lentignosine is achieved from D-glyceraldehyde in good yields involving a Sharpless asymmetric epoxidation and a one-pot indolizidine construction strategy.

1. Introduction

The design and synthesis of glycosidase inhibitors has been a topic of current research among various research groups. Most glycosidase inhibitors fall under 'sugar mimics', typically represented by polyhydroxylated piperidines, pyrrolidines, indolizidines and nortropane alkaloids. These mimics have been used as potential therapeutic agents in antidiabetic therapy, tumour metastasis, viral infections (mainly as anti-HIV agents)[1] and genetic disorders.[2] As a result of these properties, all of the hydroxylated alkaloids (more than 100 of these have already been isolated from both plants and microorganisms) have attracted special attention from both biologists and chemists. The large number of synthetic efforts has culminated in the total synthesis of several of these natural products and their analogues.[3,4] (+)-Lentiginosine **2** has attracted much attention from synthetic chemists and work involved with this target has recently been reviewed.[5]

(−)-Lentiginosine **1** has shown a selective inhibition of amyloglucosidases that hydrolyze 1,4- and 1,6-α-glucosidic linkages.[3a,6] Herein, we report a new chiron approach towards the synthesis of **1** (Fig. 1) starting from dioxa-spiro derivative **4**, which was obtained from glyceraldehyde derivative **3**[7] (Scheme 1).

2. Results and discussion

Aldehyde **3** was subjected to a Corey–Fuchs protocol[8] using TPP, CBr_4 and *n*-BuLi to furnish acetylenic intermediate **4** in over 90% yield. The 4-(*p*-methoxybenzyl) butyl iodide **5** was prepared by following the literature procedure.[9] The acetylenic anion in **4** was treated with **5** to give the alkylated 3-octyne derivative **6** in 52% yield.[10]

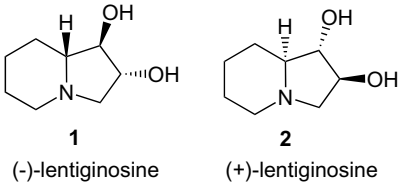

Figure 1. Structures of (−) and (+)-lentiginosine.

The deprotection of the cyclohexylidene protection in **6** was straightforward in the presence of dilute HCl to furnish 1,2-diol **7**. By taking advantage of the propargylic alcohol, compound **7** was subjected to $LiAlH_4$ reduction in ether at 0 °C to rt for 4 h to furnish (*E*)-allylic alcohol **8** whose geometry was proven by NMR spectroscopy (^{1}H NMR chemical shift on C-4: δ 5.74, dtd, $J = 0.9, 6.8, 15.5$ Hz; ^{1}H NMR chemical shift on C-3: δ 5.43, tdd, $J = 1.3, 6.6, 15.5$ Hz). The required additional stereogenic centres were derived by Sharpless asymmetric epoxidation using (+)-diisopropyl L-tartrate, which is in accordance with the existing chirality[11] to realize mismatched epoxy diol **9** in about 65% yield. The chiral HPLC of this compound confirmed the enantiomeric purity to be greater than 95%, whereas simple epoxidation with *m*-CPBA ended up with 6:4 non-separable diastereomeric mixture. The selective tosylation of the 1° alcohol group in **9** was achieved using *p*-toluenesulfonylchloride, pyridine and catalytic Bu_2SnO in 90% yield. The displacement of the tosyl group by azide was achieved using NaN_3 in DMF at 80 °C to furnish the azido-alcohol **10**. The

* Corresponding author. Tel.: +91 40 27193210; fax: +91 40 27160512; e-mail: srivaric@iict.res.in

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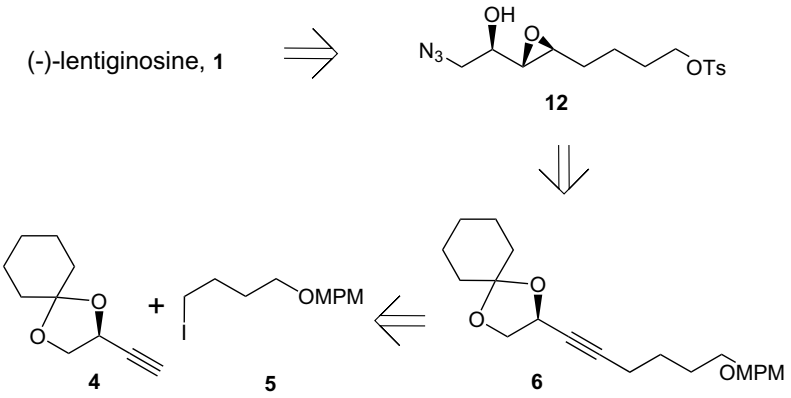
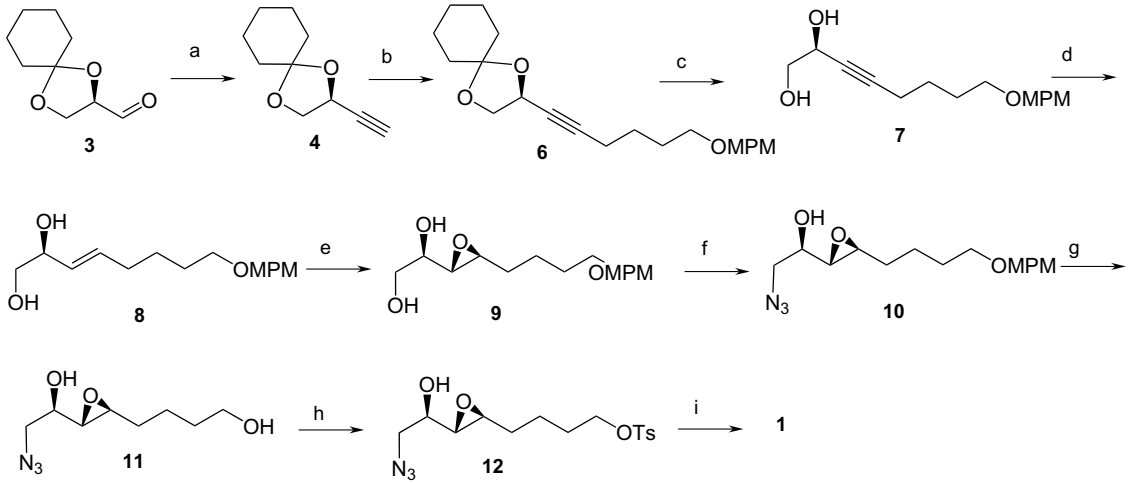


Scheme 1. Retrosynthesis of (−)-lentiginosine.



Scheme 2. Reagents and conditions: (a) TPP, CBr_4, CH_2Cl_2, 0 °C to rt, 90%; (ii) *n*-BuLi, Et_2O, 0 °C to rt, 79%; (b) *n*-BuLi, THF, **5**, −78 °C, 52%; (c) 1:1 CH_3CN/1 M HCl, rt, 98%; (d) $LiAlH_4$, Et_2O, 0 °C to rt, 70%; (e) (+)-DIPT, $Ti(^iOPr)_4$, TBHP, CH_2Cl_2, −20 °C, 72 h, 65%; (f) (i) TsCl, Py, Bu_2SnO, rt, 84%; (ii) NaN_3, DMF, 80 °C, 90%; (g) DDQ, THF/H_2O (1:1) 62%; (h) TsCl,Py, 0 °C, 57%; (i) 10 mol % Lindlar's catalyst, MeOH, rt, 3 h then two drops methanolic KOH, 39%.

deprotection of the MPM group was achieved using DDQ to form the primary alcohol **11**, which was again tosylated to give **12** using 1 equiv of *p*-toluenesulfonylchloride and pyridine as solvent. The reduction of azido group using Lindlar's catalyst in MeOH resulted in the one-pot reduction, a double intramolecular nitrogen triggered epoxide opening (a *5-endo-tet* ring closure)[12] and tosyl displacement in a clean indolizidine construction (Scheme 2). This allowed us to complete the total synthesis of (−)-lentiginosine, whose analytical data were in complete agreement with the reported ones.[3]

3. Conclusions

In conclusion, we have achieved a higly efficient stereoselective synthesis of (−)-lentiginosine. The key steps being 'mismatched Sharpless asymmetric epoxidation' and one-pot indolizidine construction by Lindlar's catalytic hydrogenation.

4. Experimental

4.1. General

All solvents and reagents were purified by standard techniques. Crude products were purified by column chromatography on silica gel of 60–120 mesh. IR spectra were recorded on Perkin–Elmer 683 spectrometer. Optical rotations were obtained on Jasco Dip 360 digital polarimeter. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution on a Varian Gemini 200 and Brucker Avance 300. Chemical shifts were reported in parts per million with respect to internal TMS. Coupling constants (*J*) are quoted in Hertz. Mass spectra were obtained on an Agilent Technologies LC/MSD Trap SL.

4.1.1. (*S*)-1,2-Cyclohexylidenedioxybut-3-yne 4. Triphenyl phosphine (9.18 g, 35.0 mmol) was dissolved in CH_2Cl_2 (85 mL) and cooled to 0 °C. To the cooled solution was

added CBr_4 (5.85 g, 17.6 mmol) in one portion, and the mixture was stirred for 1 h, after which a solution of **3** (2.52 g, 14.9 mmol) in 20 mL of CH_2Cl_2 was added in one portion, and the mixture was stirred for 1 h. The solution was concentrated in vacuo, and the residual solid was purified via silica gel column chromatography eluted with hexanes/EtOAc (9:1) to give dibromoalkene (4.378 g, 90% yield) as a light brownish oil.

This vinyldibromide (1.21 g, 3.7 mmol) was dissolved in THF (20 mL) and subsequently cooled to −78 °C. To this was added a solution of *n*-BuLi (2.5 M in hexanes) (3.6 mL, 9.0 mmol) over 15 min via a syringe. The reaction was then allowed to proceed at −78 °C for 30 min, after which the solution was warmed to room temperature and stirred for 1 h. The mixture was then cooled to 0 °C, quenched with H_2O (100 mL) and extracted into EtOAc (100 mL × 2). The combined organic layers were dried with $MgSO_4$, filtered and concentrated in vacuo. Purification via silica gel chromatography eluted with hexanes/Et_2O (9.5:0.5) gave **4** (0.49 g, 79% yield) as a low boiling light yellow liquid; $[\alpha]_D^{25} = +39.0$ (*c* 1.0, $CHCl_3$); IR (neat): *v* 3440, 2923, 1636, 1216, 1045, 761 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 4.71–4.67 (m, 1H), 4.17 (dd, $J = 8.3$, 6.8 Hz, 1H), 4.15 (dd, $J = 8.3$, 6.0 Hz, 1H), 2.48 (d, $J = 2.2$ Hz, 1H), 1.76 (m, 2H), 1.63 (m, 6H), 1.42 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 111.2, 81.6, 73.7, 69.5, 64.9, 36.4, 36.1, 25.1, 23.8; ESIMS: *m*/*z* 167 $(M+H)^+$ detected in APCI-scan only.

4.1.2. (2*S*)-2-{6-[(4-Methoxybenzyl)oxy]-1-hexynyl}-1,4-dioxaspiro[4.5]decane 6. To a cold (−78 °C), stirred solution of 1-alkyne (1.99 g, 12.0 mmol) in THF (50 mL) was added *n*-BuLi (1.6 M in hexanes) (6.87 mL, 11 mmol). The solution was allowed to warm to room temperature before adding alkyl halide (3.2 g, 10 mmol). The reaction mixture was heated at gentle reflux and stirred until all of the alkyl halide was consumed (TLC, 9 h). The mixture was cooled to 0 °C and quenched with saturated NH_4Cl (70 mL). Standard work-up with ether (50 mL × 2) provided a crude material, which was purified by flash chromatography eluted with hexanes/EtOAc (95:5) to give alkylated 3-octyne derivative **6** (1.88 g, 52% yield) as a light yellowish oily liquid; $[\alpha]_D^{25} = +24.5$ (*c* 1.2, $CHCl_3$); IR (neat): *v* 3449, 2930, 2857, 2368, 1614, 1513, 1246, 1102, 926, 821, 765 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.25 (d, $J = 8.7$ Hz, 2H), 6.86 (d, $J = 8.7$ Hz, 2H), 4.72–4.66 (m, 1H), 4.42 (s, 2H), 4.10 (dd, $J = 7.8$, 6.2 Hz, 1H), 3.81 (m, 4H), 3.44 (t, $J = 6.2$ Hz, 2H), 2.23 (dt, $J = 6.9$, 1.9 Hz, 2H), 1.74–1.52 (m, 14H) ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.1, 130.6, 129.1, 113.7, 110.5, 86.3, 77.6, 72.5, 69.8, 69.4, 65.4, 55.2, 35.7, 35.4, 28.8, 25.1, 25.0, 23.8, 18.5. (ESI-MS): *m*/*z* 381 $(M+Na)^+$; HRMS calcd for $C_{22}H_{30}O_4Na$: 381.2041 $(M+Na)^+$, found: 381.2043.

4.1.3. (2*S*)-8-[(4-Methoxybenzyl)oxy]-3-octyne-1,2-diol 7. Into a 250 mL round-bottom flask were added cyclohexylidene acetal (3.4 g, 9.5 mmol) and 20 mL of 1:1 CH_3CN/1 M HCl and stirred at room temperature for about 20 min. The reaction was quenched with solid sodiumbicarbonate (5 g, till neutralization) at room temperature. The CH_3CN in the reaction mixture was removed under vacuum. Then, it was diluted with ethyl acetate (50 mL) and after separation of the layers, the aqueous layer was further extracted into ethyl acetate (30 mL × 3). The combined organic layers were washed with brine (30 mL) and dried over anhydrous Na_2SO_4. After the evaporation of the solvent, the residue was purified on silica gel column eluted with hexanes/EtOAc (1:1) to give diol **8** (2.32 g, 98% yield) as a viscous liquid; $[\alpha]_D^{25} = +11.0$ (*c* 1.2, $CHCl_3$): IR (neat): *v* 3434, 2924, 2857, 1623, 1514, 1246, 1084, 1032 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.18 (d, $J = 8.3$ Hz, 2H), 6.82 (d, $J = 8.3$ Hz, 2H), 4.39 (s, 2H), 4.34–4.30 (m, 1H), 3.79 (s, 3H), 3.65–3.50 (m, 2H), 3.42 (t, $J = 6.0$ Hz, 2H), 2.22 (dt, $J = 6.7$, 1.5 Hz, 2H), 2.10 (br s, 1H), 2.01 (br s, 1H), 1.72–1.53 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.1, 130.4, 129.2, 113.7, 86.6, 78.2, 72.5, 69.3, 66.7, 63.3, 55.2, 28.7, 25.2, 18.4; ESIMS: *m*/*z* 301 $(M+Na)^+$; HRMS calcd for $C_{22}H_{30}O_4Na$: 301.1415 $(M+Na)^+$, found: 301.1417.

4.1.4. (2*S*,3*E*)-8-[(4-Methoxybenzyl)oxy]-3-octene-1,2-diol 8. In a clean and dry round-bottom flask, $LiAlH_4$ (0.27 g, 7.1 mmol) was dissolved in dry ether (5 mL) and cooled to 0 °C. To it was added diol **7** (1.0 g, 3.6 mmol) in Et_2O (10 mL). The mixture was stirred for 2 h and quenched with saturated aq Na_2SO_4 (3 mL) and stirred for 3 h. Then it was filtered through Celite and washed with ethyl acetate (20 mL × 2). The combined organic layers were washed with water (25 mL), brine (20 mL), dried over Na_2SO_4 and the solvent was evaporated in vacuo. The residue obtained was purified by column chromatography on silica gel eluted with hexanes/EtOAc (1:1) to give the allylic diol **8** (0.70 g, 70% yield) as a yellowish oily liquid; $[\alpha]_D^{25} = +7.2$ (*c* 1.0, $CHCl_3$); IR (neat): *v* 3423, 2925, 2856, 2364, 1742, 1621, 1513, 1457, 1247, 1087, 1030, 761 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.24 (d, $J = 8.7$ Hz, 2H), 6.88 (d, $J = 8.7$ Hz, 2H), 5.74 (dtd, $J = 0.9$, 6.8, 15.5 Hz, 1H), 5.43 (tdd, $J = 1.3$, 6.6, 15.5 Hz, 1H), 4.42 (s, 2H), 4.19–4.13 (m, 1H), 3.8 (s, 3H), 3.60 (dd, $J = 3.6$, 11.1 Hz, 1H), 3.48–3.41 (m, 2H), 3.02 (t, $J = 7.5$ Hz, 1H), 2.45 (br s, 2H), 2.04 (q, $J = 7.1$ Hz, 2H), 1.68–1.38 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.1, 133.9, 130.6, 129.2, 128.6, 113.7, 73.1, 72.5, 69.8, 66.5, 55.2, 32.0, 29.2, 25.6; ESIMS: *m*/*z* 303 $(M+Na)^+$; HRMS calcd for $C_{16}H_{24}O_4Na$: 303.1572 $(M+Na)^+$, found: 303.1566.

4.1.5. (1*R*)-1-{(2*S*,3*S*)-3-4-[(4-Ethylbenzyl)oxy]butyloxiran-2-yl}ethane-1,2-diol 9. To a stirred suspension of vaccum-dried and powdered molecular sieves (4 Å) (2.0 g) in CH_2Cl_2 (40 mL) were added $Ti(O^iPr)_4$ (1.1 mL, 3.6 mmol) and (+)-diisopropyl L-tartrate (DIPT) (0.98 g, 4.2 mmol) in CH_2Cl_2 (6 mL) at −20 °C. After stirring for 30 min at the same temperature, diol **8** (0.98 g, 3.5 mmol) was added to the mixture and kept stirring for 1 h at the same temperature. A solution of *tert*-butyl hydroperoxide (TBHP) (4 M in toluene) (960 μL, 3.84 mmol) was added to the mixture and the mixture was stirred for 72 h at −20 °C. The reaction was quenched by the addition of water (10 mL) followed by acetone (50 mL), and the mixture was filtered using Celite. The Celite was washed with THF (100 mL × 2) and the combined filtrate was dried over anhydrous Na_2SO_4, evaporated under reduced pressure

to leave the residue which was purified by silica gel column chromatography eluted with hexanes/Et_2O (4:1) to afford epoxide **9** (0.67 g, 65% yield) as a light yellow viscous liquid; $[\alpha]_D^{25} = -12.8$ (*c* 1.0, $CHCl_3$); IR (neat): *v* 3425, 2924, 2857, 1706, 1610, 1253, 1098, 1032, 762 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.26 (d, $J = 8.3$ Hz, 2H), 6.86 (d, $J = 8.3$ Hz, 2H), 4.42 (s, 2H), 3.79 (s, 3H), 3.7–3.61 (m, 3H), 3.44 (t, $J = 6.0$ Hz, 2H), 3.20 (br s, 2H), 2.95 (br s, 1H), 2.82 (br s, 1H), 1.66–1.54 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.0, 130.4, 129.2, 113.7, 72.5, 70.9, 69.6, 64.3, 58.9, 55.6, 55.1, 31.1, 29.3, 22.5. (ESI-MS): *m/z* 313 $(M+Na)^+$; HRMS calcd for $C_{16}H_{24}O_5Na$: 319.1516 $(M+Na)^+$, found: 319.1515.

4.1.6. (*R*)-2-Azido-1-((2*S*,3*S*)-3-(4-(4-methoxybenzyloxy) butyl)oxiran-2-yl)ethanol 10. To a solution of **9** (0.27 g, 0.9 mmol) in CH_2Cl_2 (10 mL) were added Et_3N (280 μL, 2.0 mmol) and *p*-toluenesulfonylchloride (0.19 g, 1.0 mmol) at 0 °C and allowed to stir for 3 h at room temperature. After the completion of the reaction, the reaction mixture was quenched with saturated solution of aq NH_4Cl (20 mL) and extracted into CH_2Cl_2 (30 mL × 2). The combined organic layers were washed with water (50 mL), brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography on silica gel eluted with hexanes/EtOAc (9:1) to afford mono tosyl product of **9** (0.34 g, 84% yield) as a yellow viscous liquid; $[\alpha]_D^{25} = -6.6$ (*c* 1.0, $CHCl_3$); IR (neat): *v* 3434, 2924, 2856, 2353, 2102, 1730, 1620, 1520, 1171, 1025, 760 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.81 (d, $J = 8.3$ Hz, 2H), 7.37 (d, $J = 8.3$ Hz, 2H), 7.22 (d, $J = 9.0$ Hz, 2H), 6.85 (d, $J = 9.0$ Hz, 2H), 4.42 (s, 2H), 4.04 (d, $J = 6.0$ Hz, 2H), 3.88–3.82 (m, 1H), 3.81 (s, 3H), 3.44 (t, $J = 6.0$ Hz, 2H), 2.95–2.89 (m, 1H), 2.83–2.80 (m, 1H), 2.48 (s, 3H) 2.25 (br s, 1H), 1.69–1.46 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.1, 145.1, 130.6, 129.9, 129.2, 128.7, 128.0, 113.8, 72.5, 70.6, 69.6, 67.8, 57.6, 55.5, 55.2, 31.1, 29.7, 29.4, 22.6; ESIMS: *m/z* 473 $(M+Na)^+$, HRMS calcd for $C_{23}H_{30}O_7SNa$: 473.1609 $(M+Na)^+$, found: 473.1620.

The above compound (0.34 g, 0.7 mmol) was dissolved in dry DMF (2 mL), after which was added NaN_3 (0.05 g, 0.8 mmol). The mixture was stirred at 80 °C for 3 h. After the completion of the reaction it was cooled to room temperature and cold water (5 mL) added. Then the compound was extracted into ether (10 mL × 2). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography on silica gel to afford azidoalcohol **10** (0.20 g, 82% yield) as an oily yellow liquid; $[\alpha]_D^{25} = -8.0$ (*c* 0.5, $CHCl_3$); IR (neat): *v* 3424, 2923, 2854, 1624, 1462, 1216, 760 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.24 (d, $J = 8.6$ Hz, 2H), 6.87 (d, $J = 8.6$ Hz, 2H), 4.43 (s, 2H), 3.88–3.72 (m, 4H), 3.50–3.35 (m, 4H), 3.0–2.91 (m, 1H), 2.83 (dd, $J = 2.3$, 3.9 Hz, 1H), 2.0 (br s, 1H), 1.68–1.50 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.1, 130.6, 129.2, 113.7, 72.5, 69.6, 69.3, 58.6, 55.9, 55.2, 54.3, 31.1, 29.4, 22.6; ESIMS: 344 $(M+Na)^+$; HRMS calcd for $C_{16}H_{23}N_3O_4Na$: 344.1586 $(M+Na)^+$, found: 344.1575.

4.1.7. 4-((2*S*,3*S*)-3-((*R*)-2-Azido-1-hydroxyethyl)oxiran-2-yl)butan-1-ol 11. In a 100 mL round bottom flask azidoalcohol **10** (212 mg, 0.66 mmol) was dissolved in 5:1 mixture of CH_2Cl_2/H_2O (10 mL) and DDQ (165 mg, 0.72 mmol) added at 0 °C and allowed to stir at rt for 3 h. The reaction was quenched with saturated $NaHCO_3$ and extracted into CH_2Cl_2 (10 mL × 2). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude residue was purified by silica gel column chromatography to afford azidodiol **11** (82 mg, 62% yield) as a viscous yellow liquid; $[\alpha]_D^{25} = -11.0$ (*c* 0.25, $CHCl_3$); IR (neat): *v* 3420, 2924, 2855, 2353, 2102, 1742, 1644, 1515, 1459, 1217, 1173, 1020 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 3.89–3.72 (m, 3H), 3.57–3.38 (m, 2H), 3.09–2.96 (m, 1H), 2.9–2.8 (m, 1H), 2.2 (br s, 2H), 1.75–1.45 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 69.6, 62.8, 58.9, 56.1, 54.5, 31.1, 29.4, 22.6; ESIMS: *m/z* 224 $(M+Na)^+$; HRMS calcd for $C_8H_{15}N_3O_3Na$: 224.1005 $(M+Na)^+$, found: 224.1004.

4.1.8. 4-((2*S*,3*S*)-3-((*R*)-2-Azido-1-hydroxyethyl)oxiran-2-yl)butyl 4-methylbenzenesulfonate 12. To a stirred solution of azidodiol **11** (55 mg, 0.27 mmol) in dry pyridine (218 μL, 2.7 mmol) was added *p*-toluenesulfonylchloride (55 mg, 0.28 mmol) portionwise and stirred for 30 min. After the completion of the reaction, the mixture was quenched with a saturated solution of aq $CuSO_4$ (5 mL) and extracted into CH_2Cl_2 (5 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude product obtained was purified by flash column chromatography to afford compound **12** (55 mg, 57% yield) as yellowish viscous liquid; $[\alpha]_D^{25} = +19.0$ (*c* 1.0, $CHCl_3$); IR (neat): *v* 3420, 2924, 2855, 2353, 2102, 1742, 1644, 1515, 1459, 1217, 1173, 1020, 759, 667 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.78 (d, $J = 8.3$ Hz, 2H), 7.37 (d, $J = 8.3$ Hz, 2H), 4.03 (t, $J = 6.3$ Hz, 2H), 3.74 (br s, 1H), 3.43–3.38 (m, 2H), 2.93 (s, 1H), 2.82 (d, $J = 3.9$ Hz, 1H), 2.46–2.55 (m, 4H), 1.75–1.49 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 145.0, 133.1, 130.0, 128.0, 70.2, 69.5, 58.8, 55.7, 54.3, 30.8, 28.6, 22.0, 21.7; ESIMS: *m/z* 378 $(M+Na)^+$; HRMS calcd for $C_{15}H_{21}N_3O_5SNa$: 378.1099 $(M+Na)^+$, found: 378.1093.

4.1.9. (1*R*,2*R*,8*aR*)-1,2-Dihydroxyindolizidine 1, [(−)-lentiginosine]. To a solution of monotosylate **12** (36 mg, 0.1 mmol) in MeOH (5 mL), Lindlar's catalyst (0.01 mmol) was added and stirred under a H_2 atmosphere for 3 h. The reaction mixture was filtered through Celite and washed with MeOH (5 mL × 2). The filterate was basified (if necessary) with methanolic KOH (2 drops) and then MeOH was removed under reduced pressure. The crude residue was dissolved in H_2O (1 mL) and purified by ion-exchange chromatography (Dowex resin) using 2% ammonia solution to afford **1** (6 mg, 39% yield) as a white crystalline solid: mp 106–108 °C (lit.[3c] 106–107 °C); $[\alpha]_D^{25} = -3.1$ (*c* 0.5, MeOH); IR (neat): *v* 3423, 2924, 1638, 1019, 758 cm^{-1}. ^1H NMR (D_2O, 300 MHz): δ 4.05 (ddd, $J = 7.6$, 3.8, 1.6 Hz, 1H), 3.66 (dd, $J = 8.7$, 3.8 Hz, 1H), 3.01 (br d, $J = 10.9$ Hz, 1H), 2.85–2.58 (m, 2H), 2.2–2.12 (m, 2H), 1.91–1.85 (m, 1H), 1.73–1.74 (m, 1H), 1.60–1.52 (m, 1H), 1.41–1.27 (m, 1H), 1.25–1.14 (m, 2H); ^{13}C NMR (D_2O, 75 MHz): δ 81.8, 75.0, 69.0, 59.8, 52.9, 26.8,

23.5, 22.6; (ESI-MS): m/z 158 ($M+H^+$); HRMS ($M+H^+$) calcd for $C_8H_{16}NO_2$: 158.1181, found: 158.1180.

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