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Total synthesis of (−)-lentiginosine

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ABSTRACT

A simple and practical synthesis of (−)-lentiginosine **2** with good overall yield has been achieved from the commercially available diethyl D-tartarate. The key steps are a highly stereoselective Grignard reaction on an aldehyde and a Staudinger reduction.

1. Introduction

Polyhydroxylated indolizidine alkaloids, such as (+)-lentiginosine **1**, (−)-lentiginosine **2**, (−)-swainsonine **3** and (+)-castanospermine **4**, belong to the important class of iminosugars or azasugars (Fig. 1). They are mimics of monosaccharides in biological systems and are also excellent glycosidase inhibitors.[1] Glycosidases are enzymes which are involved in a wide range of metabolic pathways such as digestion, post-translational processing of glycoproteins and lysosomal catabolism of glycoconjugates.[2] Therefore iminosugars or azasugars are useful for the treatment of diabetes and viral infections, as well as being anticancer, anti-HIV and lysosomal storage disorder agents.[3]

(+)-Lentiginosine **1**, isolated in 1990 from the leaves of *Astragalus lentiginosus*,[4] is a well known selective inhibitor of natural amyloglucosidase,[4] and also found to be an inhibitor of ATPase and Heat shock protein 90 (Hsp90), which is a promising binding site for new classes of Hsp90 inhibitors with multi target anticancer potential.[5] (−)-Lentiginosine **2**, a synthetic iminosugar, acts as apoptosis inducer in U937 cells, naturally deficient in P53. Recent studies by Minutolo et al. on different tumour cell lines using compound **2**, showed interesting results. This compound exhibited glycosidase inhibitor activity and unexpected pro apoptotic activity.

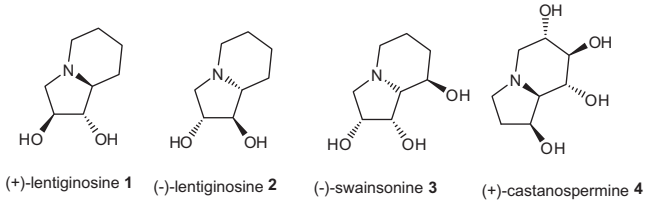

Figure 1.

Since these results were highly encouraging, analogues of compound **2** should have the potential to generate new anti cancer drugs.[6] Due to its biological importance, several approaches have been developed for the synthesis of (+)-lentiginosine **1**[7,8b] and its enantiomer (−)-lentiginosine **2**.[8] A good yielding approach which gives enantiomerically pure **2** is still desirable for further evaluation of its activity and preparation of analogues.

In continuation of our efforts in developing synthetic routes for iminosugars from nucleophilic additions on *N*-glycoslylamine derivatives,[9] we herein report a simple and practical synthesis of **2** using a highly stereoselective Grignard addition on an aldehyde.

2. Results and discussion

As per the retrosynthetic analysis shown in Scheme 1, (−)-lentiginosine **2** can be obtained by intramolecular dialkylation of the amino derivative, which in turn can be prepared by reduction of the azido compound **5**. Compound **5** can be obtained by stereoselective nucleophile addition of 4-bromo-1-butene on aldehyde **6** followed by simple transformations. Compound **6** can easily be synthesised from diethyl D-tartarate **7** using literature methods.[9a,10]

(−)-Diethyl D-tartrate **7** was converted into alcohol **8** using literature methods.[9a,10] Swern oxidation of alcohol **8** gave aldehyde **6**, which was subjected to a chelation controlled Grignard reaction (Fig. 2) using 4-bromo-1-butene and Mg in THF to give alcohols **9** and **10** (9:1) in 80% yield (over two steps),[11] which were separated by column chromatography. Hydroboration/oxidation of the terminal olefin in **9** using BH_3·DMS followed by NaOH and H_2O_2 furnished diol **11** in 85% yield.

The selective tosylation of the primary hydroxy group in **11** using TsCl, Et_3N in the presence of catalytic Bu_3SnO in dry DCM gave the tosylated compound which upon treatment with NaN_3 in DMF at 60 °C without any purification afforded the azido com-

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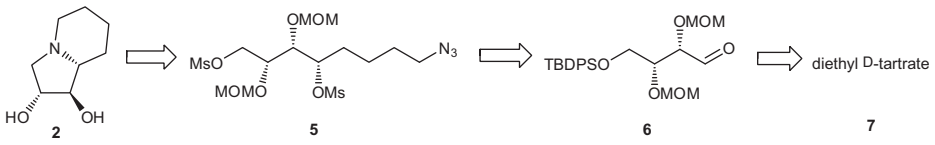


Scheme 1.

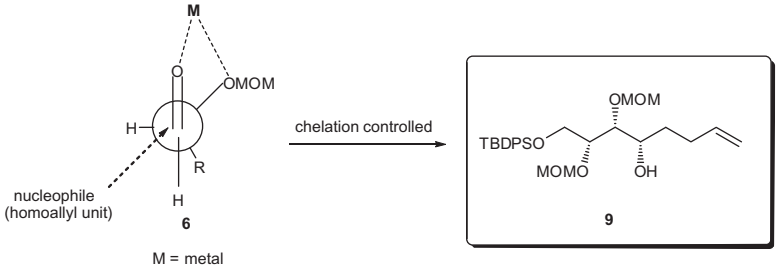


Figure 2. Chelation controlled addition of aldehyde **6**.

pound **12** in 80% yield. Cleavage of the silyl ether in **12** using TBAF yielded the primary alcohol 1**3** in 95% yield.

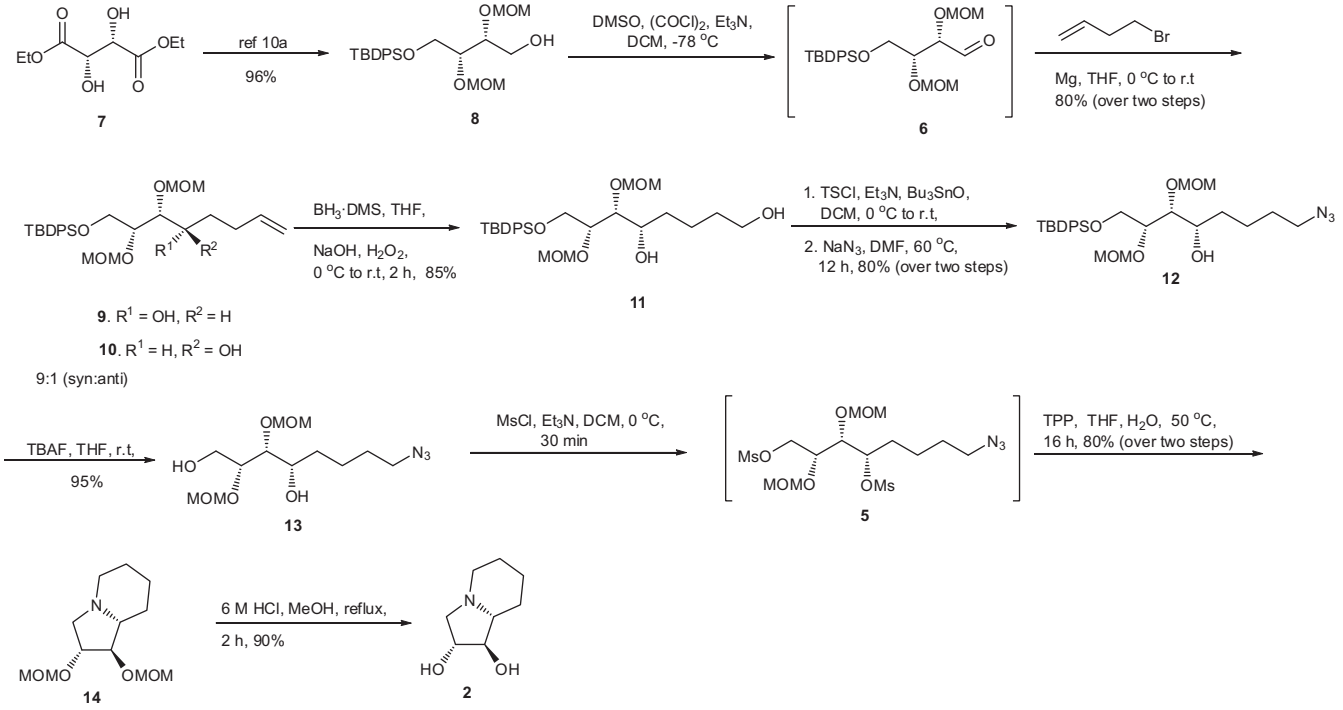
Compound **13** was treated with MsCl and Et_3N in DCM to afford the dimesylated compound **5**, which without further purification was subjected to a Staudinger protocol[12] (TPP, THF, H_2O) to afford the desired indolizidine ring **14** in 80% yield (over two steps) as shown in Scheme 2. Finally, treatment of **14** with 6 M HCl under reflux conditions followed by work-up gave the required final product (−)-lentiginosine **2** in 90% yield, whose spectroscopic and physical data were in good agreement with the reported values.[8j] The same strategy can be applied for the synthesis of (+)-lentiginosine **1** from diethyl L-tartarate.

3. Conclusion

In conclusion, we have synthesised (−)-lentiginosine **2** from the commercially available starting material diethyl D-tartarate in 32% overall yield. The key steps involved in this synthesis are the highly diastereoselective Grignard addition on aldehyde **6** and a Staudinger reduction followed by in situ cyclisation to give the indolizidine ring. This strategy helps in making large quantities of compound **2** for further evaluation of its activity and in making analogues.

4. Experimental

Moisture and oxygen sensitive reactions were carried out under a nitrogen gas atmosphere in flame or oven dried glassware with magnetic stirring. All solvents and reagents were purified by standard techniques. Solutions were dried over Na_2SO_4 before concentration under reduced pressure. TLC was performed on Merck Kiesel gel 60, F254 plates (layer thickness 0.25 mm). Column chromatography was performed on silica gel (60–120 or 100–200 mesh) using ethyl acetate and hexane as eluants. Melting points were determined on a Fisher John's melting point apparatus and



Scheme 2.

are uncorrected. IR spectra were recorded on a Perkin–Elmer RX-1 FT-IR system. ^{1}H NMR in Bruker Avance-300 and Varian-400, 500 MHz and ^{13}C NMR spectra in 75 and 100 MHz were recorded. Chemical shifts were reported in ppm with respect to TMS as an internal standard. ^{1}H NMR data are expressed as chemical shifts in ppm followed by multiplicity (s-singlet; d-doublet; t-triplet; q-quartet; m-multiplet), number of proton(s) and coupling constants (*J*) which are quoted in Hz. Optical rotations were measured with JASCO digital polarimeter. Accurate mass measurements were performed on Q STAR mass spectrometer (Applied Biosystems, USA).

4.1. (2*R*,3*R*,4*S*)-1-(*tert*-Butyldiphenylsilyloxy)-2,3-bis(methoxymethoxy)oct-7-en-4-ol 9

To a stirred solution of oxalyl chloride (1.94 mL, 22.2 mmol) in dry DCM (20 mL) under a nitrogen atmosphere, was added DMSO (3.2 mL, 44.6 mmol) slowly at −78 °C and stirred for 30 min at the same temperature. Next, alcohol **8** (5.0 g, 11.1 mmol) in dry DCM (20 mL) was added slowly over 10 min and stirring was continued further for 2 h at −78 °C after which Et_3N (9.4 mL, 66.96 mmol) was added at −78 °C. The temperature was slowly raised to room temperature over 20 min and the reaction mixture was diluted with DCM (50 mL). The organic layer was sequentially washed with saturated aq NH_4Cl solution and brine, and dried over anhydrous Na_2SO_4. The solvent was removed on a rotary evaporator to give crude aldehyde **6**, which was used in the next step without purification.

To a stirred solution of aldehyde **6** (3 g, 6.73 mmol) in dry THF (20 mL) at 0 °C, were added dropwise homoallyl magnesium bromide [prepared in situ from Mg (0.64 g, 26.9 mmol) and homoallyl bromide (1.02 g, 10.0 mmol)] in dry THF (5 mL) over a period of 5 min. The solution was then gradually allowed to room temperature, and stirring was continued for another 5 h after which the reaction mixture was quenched by adding saturated aq NH_4Cl solution at 0 °C. The mixture was extracted with ethyl acetate (3 × 50 mL) and the combined organic extracts were washed with water and brine, and dried over anhydrous Na_2SO_4. The solvent was removed on a rotary evaporator and the residue was purified through silica gel column chromatography (ethyl acetate/hexane = 1:9) to give compound **9** (2.70 g, 80%) as a colourless oil. $[\alpha]_D^{25} = -11.3$ (*c* 0.7, $CHCl_3$); IR (neat): 3472, 3071, 2927, 2892, 2855, 1468, 1427, 1107, 1025 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74–7.60 (m, 4H), 7.49–7.39 (m, 6H), 5.87 (m, 1H), 5.06 (dd, *J* = 16.9 Hz, 1.1 Hz, 1H), 4.98 (dd, *J* = 9.8 Hz, 1.8 Hz, 1H), 4.71, 4.69 (ABq, J_{AB} = 6.7 Hz, 2H), 4.63 (d, *J* = 6.7 Hz, 1H), 4.55 (d, *J* = 6.7 Hz, 1H), 3.88–3.74 (m, 4H), 3.63 (m, 1H), 3.40 (s, 3H), 3.28 (s, 3H), 3.14 (d, *J* = 4.1 Hz, 1H), 2.39–2.11 (m, 2H), 1.75–1.50 (m, 2H), 1.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.4, 135.59, 135.53, 133.0, 129.8, 127.75, 127.71, 114.7, 98.7, 96.6, 82.6, 77.6, 69.8, 62.8, 56.2, 55.8, 32.6, 29.8, 26.8, 19.1; ESIMS (*m*/*z*): 525 [M+Na]$^+$; HRMS (ESI) [M+Na]$^+$: Anal. Calcd for $C_{28}H_{42}O_6NaSi$ 525.26429 Found 525.26417.

4.2. (2*R*,3*R*,4*R*)-1-(*tert*-Butyldiphenylsilyloxy)-2,3-bis(methoxymethoxy)oct-7-en-4-ol 10

$[\alpha]_D^{25} = -4.4$ (*c* 0.9, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72–7.63 (m, 4H), 7.47–7.36 (m, 6H), 5.83 (m, 1H), 5.05 (dd, *J* = 17.0 Hz, 1.6 Hz, 1H), 4.96 (dd, *J* = 10.2 Hz, 1.8 Hz, 1H), 4.75 (d, *J* = 6.7 Hz, 1H), 4.67 (d, *J* = 6.7 Hz, 1H), 4.65, 4.63 (ABq, J_{AB} = 7.0 Hz, 2H), 3.93 (m, 1H), 3.81–3.74 (m, 3H), 3.59 (dd, *J* = 6.4 Hz, 3.2 Hz, 1H), 3.50 (d, *J* = 5.6 Hz, 1H), 3.36 (s, 3H), 3.28 (s, 3H), 2.34 (m, 1H), 2.15 (m, 1H), 1.75–1.50 (m, 2H), 1.05 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.6, 135.56, 135.54, 133.05, 133.01, 129.7, 127.7, 114.6, 98.1, 97.6, 81.8, 78.3, 70.0, 63.6, 56.1, 32.1, 30.0, 26.7, 19.1; ESIMS (*m*/*z*): 525 [M+Na]$^+$; HRMS (ESI) [M+Na]$^+$: Anal. Calcd for $C_{28}H_{42}O_6NaSi$ 525.26429 Found 525.26411.

4.3. (5*S*,6*R*,7*R*)-8-(*tert*-Butyldiphenylsilyloxy)-6,7-bis(methoxymethoxy)octane-1,5-diol 11

To a stirred solution of **9** (2.0 g, 3.98 mmol) in dry THF (20 mL), $BH_3{\cdot}Me_2S$ (0.7 mL, 8.76 mmol) was added dropwise at −10 °C. Stirring was then continued for 3 h at room temperature. The reaction mixture was quenched by the addition of 10% NaOH (10 mL) followed by 30% H_2O_2 (15 mL) at 0 °C and allowed to warm to room temperature, and stirred for another 2 h. The reaction mixture was extracted with ethyl acetate (2 × 100 mL). The combined organic layers were washed with brine, separated and dried over anhydrous Na_2SO_4. The solvent was removed on rotary evaporator. The residue was purified by column chromatography on silica gel using ethyl acetate/hexane (3:2) as the eluant to give pure compound **11** (1.76 g, 85%) as a colourless oil. $[\alpha]_D^{25} = -2.1$ (*c* 0.9, $CHCl_3$); IR (neat): 3435, 2927, 2855, 1466, 1427, 1213, 1108, 1028 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69–7.63 (m, 4H), 7.47–7.37 (m, 6H), 4.71, 4.69 (ABq, J_{AB} = 6.7 Hz, 2H), 4.62 (d, *J* = 6.7 Hz, 1H), 4.54 (d, *J* = 6.7 Hz, 1H), 3.85–3.75 (m, 4H), 3.67 (t, *J* = 5.9 Hz, 1H), 3.62 (dd, *J* = 5.6 Hz, 2.8 Hz, 1H), 3.40 (s, 3H), 3.29 (s, 3H), 3.25 (m, 1H), 1.68–1.46 (m, 6H), 1.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 135.56, 135.50, 133.0, 132.9, 129.8, 127.74, 127.72, 98.7, 96.6, 82.9, 77.6, 70.2, 62.69, 62.62, 56.2, 55.8, 32.59, 32.56, 26.7, 21.6, 19.1; ESIMS (*m*/*z*): 543 [M+Na]$^+$; HRMS (ESI) [M+Na]$^+$: Anal. Calcd for $C_{28}H_{44}O_7NaSi$ 543.27485 Found 543.27436.

4.4. (2*R*,3*R*,4*S*)-8-Azido-1-(*tert*-butyldiphenylsilyloxy)-2,3-bis-(methoxymethoxy) octan-4-ol 12

To a stirred solution of **11** in DCM (1.5 g, 6.7 mmol) were added Et_3N (0.4 mL, 2.88 mmol), Bu_2SnO (0.71 g, 2.88 mmol) and *p*-toluenesulfonylchloride in DCM (0.54 g, 2.88 mmol) at 0 °C under a nitrogen atmosphere. After stirring for 1 h at room temperature, the reaction mixture was extracted with $CHCl_3$ (100 mL). The organic extract was washed with water (30 mL) and brine (30 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure afforded the tosylated compound as a liquid, which was used in the next step without further purification.

To the above tosylated derivative in dry DMF (20 mL) was added NaN_3 (1.12 g, 17.28 mmol) under a nitrogen atmosphere at room temperature. The reaction was slowly heated to 90 °C and stirred for 12 h, after which the reaction mixture was allowed to cool to room temperature, poured into ice cold water (40 mL) and extracted with diethyl ether (3 × 80 mL). The combined organic extracts were washed with water (50 mL) and brine (30 mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure and purified by column chromatography (ethyl acetate/hexane 1:8) to afford **12** (1.25 g, 80% for two steps) as a liquid. $[\alpha]_D^{25} = -6.5$ (*c* 1.1, $CHCl_3$); IR (neat): 2923, 2853, 2094, 1465, 1428, 1108, 1028 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.71–7.61 (m, 4H), 7.47–7.35 (m, 6H), 4.71, 4.69 (ABq, J_{AB} = 6.7 Hz, 2H), 4.62 (d, *J* = 6.7 Hz, 1H), 4.54 (d, *J* = 6.7 Hz, 1H), 3.85–3.73 (m, 4H), 3.61 (dd, *J* = 5.6 Hz, 2.6 Hz, 1H), 3.40 (s, 3H), 3.33–3.23 (m, 2H), 3.29 (s, 3H), 1.68–1.46 (m, 6H), 1.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 135.56, 135.51, 132.9, 129.8, 127.76, 127.73, 98.7, 96.6, 82.9, 77.5, 70.0, 62.6, 56.2, 55.8, 51.3, 32.5, 28.8, 26.7, 22.7, 19.1; ESIMS (*m*/*z*): 568 [M+Na]$^+$; HRMS (ESI) [M+Na]$^+$: Anal. Calcd for $C_{28}H_{43}O_6N_3NaSi$ 568.28133 Found 568.28086.

4.5. (2*R*,3*R*,4*S*)-8-Azido-2,3-bis(methoxymethoxy)octane-1,4-diol 13

To a stirred solution of compound **12** (1.0 g, 1.83 mmol) in dry THF (10 mL) was added TBAF (3.7 mL, 1 M solution in THF) at room temperature and stirred for 1 h. The solvent was removed on a rotary evaporator and the residue was purified by column

chromatography on silica gel (ethyl acetate/hexane, 3:2) to give pure compound **13** (0.53 g, 95%) as a colourless liquid. $[\alpha]_D^{25}$ = +8.7 (*c* 1.2, $CHCl_3$); IR (neat): 3415, 2922, 2852, 2093, 1459, 1213, 1149, 1021 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.80–4.68 (m, 4H), 3.88–3.73 (m, 4H), 3.56 (m, 1H), 3.44 (s, 3H), 3.43 (s, 3H), 3.30 (t, *J* = 6.4 Hz, 2H), 2.79 (br s, 1H), 1.71–1.46 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 98.2, 97.0, 81.1, 79.8, 69.5, 61.3, 56.2, 55.9, 51.3, 33.5, 28.7, 23.0; ESIMS (*m*/*z*): 330 $[M+Na]^+$; HRMS (ESI) $[M+Na]^+$: Anal. Calcd for $C_{12}H_{25}O_6N_3NaSi$ 330.16356 Found 330.16331.

4.6. (1*R*,2*R*,8a*R*)-1,2-Bis(methoxymethoxy)octahydroindolizine 14

To an ice-cold solution of **13** (0.5 g, 1.63 mmol) in dry DCM (10 mL) was added Et_3N (0.4 mL, 2.45 mmol) under a nitrogen atmosphere. After stirring for 5 min methane sulfonylchloride (0.2 mL, 1.79 mmol) and catalytic DMAP were added to the reaction mixture and allowed to stir at room temperature for 30 min. The reaction mixture was then extracted with $CHCl_3$ (2 × 50 mL). The organic extract was washed with brine (20 mL), separated and dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure afforded the dimesylated compound **5** as a liquid, which was used in the next step without further purification. To the crude mesylated compound **5** in THF (10 ml), triphenyl phosphine (0.64 g, 2.45 mmol) and water (0.2) were added at room temperature. The reaction mixture was stirred for 16 h at 50 °C. After completion of the reaction (by monitoring TLC) the solvent was removed on a rotary evaporator and the residue was purified by column chromatography on silica gel (dichloromethane/methanol 40:1) to give pure compound **14** (0.32 g, 80%) as a colourless liquid. $[\alpha]_D^{25}$ = +27.7 (*c* 0.8, $CHCl_3$); IR (neat): 2925, 2853, 1515, 1213, 1035 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 4.80–4.65 (m, 4H), 4.01 (dd, *J* = 5.6 Hz, 1.8 Hz, 1H), 3.77 (dd, *J* = 7.9 Hz, 1.8 Hz, 1H), 3.39 (s, 6H), 3.05–2.98 (m, 2H), 2.42 (dd, *J* = 9.7 Hz, 6.0 Hz, 1H), 2.01–1.19 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 95.8, 95.2, 87.4, 79.5, 68.7, 59.6, 55.5, 55.4, 53.2, 28.9, 24.6, 24.0; ESIMS (*m*/*z*): 246 $[M+H]^+$; HRMS (ESI) $[M+H]^+$: Anal. Calcd for $C_{12}H_{24}O_4N$ 246.16998 Found 246.16971.

4.7. (1*R*,2*R*,8a*R*)-Octahydroindolizine-1,2-diol 2

To compound **14** (0.1 g, 0.41 mmol), in MeOH (2 mL) was added 6 M HCl, and the resulting solution was stirred for 12 h at room temperature. The solvent was concentrated in vacuo, the crude product obtained was neutralised with 2 M NaOH and purified by an acid resin column (DOWEX 50 W X 8, 100–200 mesh), by eluting with 1 N NH_4OH to give **2** as a white solid (0.057 g, 90%). Observed $[\alpha]_D^{25}$ = −2.9 (*c* 0.5, MeOH), mp 105–108 °C (dec); {lit.[8j,n,r,t] −3.05, −2.0, −2.6, −3.5, mp 106–108 °C (dec)}; IR (neat): 3315, 2943, 2831, 1449, 1414, 1020 cm^{-1}; ^1H NMR (300 MHz, D_2O): δ 4.00 (m, 1H), 3.56 (dd, *J* = 8.6 Hz, 3.9 Hz, 1H), 2.87 (d, *J* = 11.3 Hz, 1H), 2.76 (dd, *J* = 11.3 Hz, 1.7 Hz, 1H), 2.56 (dd, *J* = 11.3 Hz, 7.5 Hz, 1H), 2.05–1.81 (m, 3H), 1.73 (m, 1H), 1.56 (m, 1H), 1.37 (m, 1H), 1.24–1.14 (m, 2H); ^{13}C NMR (125 MHz, D_2O): δ 85.1, 77.9, 70.9, 62.5, 54.9, 29.7, 26.2, 25.3; ESIMS (*m*/*z*): 158 $[M+H]^+$; HRMS (ESI) $[M+H]^+$: Anal. Calcd for $C_8H_{16}O_2N$ 158.11756 Found 158.11752.

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References

1. (a) Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 139; (b) Michael, J. P. *Nat. Prod. Rep.* **2007**, *24*, 191; (c) Cardona, F.; Goti, A.; Brandi, A. *Eur. J. Org. Chem.* **2007**, 1551. and references cited therein.
2. (a) Cipolla, L.; La Ferla, B.; Gregori, M. *Comb. Chem. High Throughput Screening* **2006**, *9*, 571; (b) Watson, A. A.; Fleet, G. W. J.; Asano, N.; Molyneux, R. J.; Nash, R. J. *Phytochemistry* **2001**, *56*, 265.
3. (a) Mehta, A.; Ziztmann, N.; Rudd, P. M.; Block, T. M.; Dwek, R. A. *FEBS Lett.* **1998**, *430*, 17; (b) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645; (c) Asano, N. *Glycobiology* **2003**, *13*, 93R.
4. Pastuszack, I.; Molyneux, R. J.; James, L. F.; Elbein, A. D. *Biochemistry* **1990**, *29*, 1886.
5. From Piaz, F.; Vassallo, A.; MG, Chini; Cordero, FM; Cardona, F.; Pisano, C.; Bifulco, G.; De Tommasi, N.; Brandi, A. *PLoS ONE* **2012**, *7*, e43316.
6. (a) Cordero, M. F.; Bonanno, P.; Khairnar, B. B.; Cardona, F.; Brandi, A.; Macchi, B. *Chem Plus Chem* **2012**, *77*, 9; (b) Minutolo, A.; Grelli, S.; Marino-Merlo, F.; Cordero, F. M.; Brandi, A.; Macchi, B.; Mastino, A. *Cell Death Dis.* **2012**, *3*, e358; (c) Macchi, B.; Minutolo, A.; Grelli, S.; Mastino, A.; Cardona, F.; Cordero, F. M.; Brandi, A. *Glycobiology* **2010**, *20*, 500.
7. (a) Alam, M. A.; Vankar, Y. D. *Tetrahedron Lett.* **2008**, *49*, 5534. Recent publications of (+)-lentinginosine: For more details see review Ref.[1c];; (b) Prasad, K. R.; Pawar, A. B. *ARKIVOC* **2010**, 39; (c) Lauzon, S.; Tremblay, F.; Gagnon, D.; Godbout, C.; Chabot, C.; Mercier-Shanks, C.; Perreault, S.; DeSève, H.; Spino, C. *J. Org. Chem.* **2008**, *73*, 6239; (d) Chen, M.-J.; Tsai, Y.-M. *Tetrahedron Lett.* **2007**, *48*, 6271; (e) Raghavan, S.; Sreekanth, T. *Tetrahedron: Asymmetry* **2004**, *15*, 565.
8. (a) Ansari, A. A.; Vankar, Y. D. *RSC Adv.* **2014**, *4*, 12555; (b) Kim, G.-W.; Jin, T.; Kim, J.-S.; Park, S.-H.; Lee, K.-H.; Kim, S.-S.; Myeong, I.-S.; Ham, W.-H. *Tetrahedron: Asymmetry* **2014**, *25*, 87; (c) Shao, J.; Yang, J.-S. *J. Org. Chem.* **2012**, *77*, 7891; (d) Kamal, A.; Reddy, V. S. *Tetrahedron* **2011**, *67*, 1341; (e) Liu, S.-W.; Hsu, H.-C.; Chang, C.-H.; Tsai, H.-H. G.; Hou, D.-R. *Eur. J. Org. Chem.* **2010**, 4771; (f) Chandrasekhar, S.; Vijaykumar, B. V. D.; Pratap, T. V. *Tetrahedron: Asymmetry* **2008**, *19*, 746; (g) Azzouz, R.; Fruit, C.; Bischoff, L.; Marsais, F. *J. Org. Chem.* **2008**, *73*, 1154; (h) Angle, S. R.; Bensa, D.; Belanger, D. S. *J. Org. Chem.* **2007**, *72*, 5592; (i) Kim, I. S.; Zee, O. P.; Jung, Y. H. *Org. Lett.* **2006**, *8*, 4101; (j) Chaudhari, V. D.; Kumar, K. S. A.; Dhavale, D. D. *Tetrahedron* **2006**, *62*, 4349; (k) Ayad, T.; Genisson, Y.; Baltas, M. *Org. Biomol. Chem.* **2005**, *3*, 2626; (l) Nukui, S.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 398; (m) Ichikawa, Y.; Ito, T.; Isobe, M. *Chem. Eur. J.* **2005**, *11*, 1949; (n) Ayad, T.; Génisson, Y.; Baltas, M.; Gorrichon, L. *Chem. Commun.* **2003**, 582; (o) Chandra, K. L.; Chandrashekhar, M.; Singh, V. K. *J. Org. Chem.* **2002**, *67*, 4630; (p) Azzouz, R.; Fruit, C.; Bischoff, L.; Marsais, F. *J. Org. Chem.* **2002**, *67*, 1154; (q) Cardona, F.; Goti, A.; Picasso, S.; Vogel, P.; Brandi, A. J. *Carbohydr. Res.* **2000**, *19*, 585; (r) McCaig, A. E.; Meldrum, K. P.; Wightman, R. H. *Tetrahedron* **1998**, *54*, 9429; (s) Brandi, A.; Cicchi, S.; Cordero, F. M.; Frignoli, R.; Goti, A.; Picasso, S.; Vogel, P. *J. Org. Chem.* **1995**, *60*, 6806; (t) Gurjar, M. K.; Ghosh, L.; Syamala, M.; Jayasree, V. *Tetrahedron Lett.* **1994**, *35*, 8871.
9. (a) Lingamurthy, M.; Rajender, A.; Rao, B. V. *Tetrahedron Lett.* **2013**, *54*, 6189; (b) Rajender, A.; Rao, J. P.; Rao, B. V. *Eur. J. Org. Chem.* **2013**, 1749; (c) Rajender, A.; Rao, B. V. *Tetrahedron Lett.* **2013**, *54*, 2329; (d) Chandrasekhar, B.; Rao, B. V. *Tetrahedron: Asymmetry* **2009**, *20*, 1217; (e) Jagadeesh, Y.; Chandrasekhar, B.; Rao, B. V. *Tetrahedron: Asymmetry* **2010**, *21*, 2314; (f) Rao, J. P.; Rao, B. V.; Swarnalatha, J. L. *Tetrahedron Lett.* **2010**, *51*, 3083; (g) Rajender, A.; Rao, J. P.; Rao, B. V. *Tetrahedron: Asymmetry* **2011**, *22*, 1306; (h) Rao, M. V.; Chandrasekhar, B.; Rao, B. V. *Tetrahedron: Asymmetry* **2011**, *22*, 1342; (i) Rao, G. S.; Rao, B. V. *Tetrahedron Lett.* **2011**, *52*, 4861; (j) Rao, G. S.; Chandrasekhar, B.; Rao, B. V. *Tetrahedron: Asymmetry* **2012**, *23*, 564; (k) Rao, G. S.; Rao, B. V. *Tetrahedron Lett.* **2011**, *52*, 6076.
10. (a) Lee, J.; Kim, K.-H.; Jeong, S. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 4203; (b) Zhong, H. M.; Suhn, J.-H.; Rawal, V. H. *J. Org. Chem.* **2007**, *72*, 386; (c) Suhn, J.-H.; Waizumi, N.; Zhong, H. M.; Rawal, V. H. *J. Am. Chem. Soc.* **2005**, *127*, 7290; (d) Dulphy, H.; Gras, J.-L.; Lejon, T. *Tetrahedron* **1996**, *52*, 8517.
11. (a) Iida, H.; Yamazaki, N.; Kibayashi, C. *Tetrahedron Lett.* **1985**, *36*, 3255; (b) Gautam, D.; Rao, B. V. *Tetrahedron Lett.* **2010**, *51*, 4199.
12. Takahata, H.; Kubota, M.; Takahashi, S.; Mamose, T. *Tetrahedron: Asymmetry* **1996**, *7*, 3047.