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A concise enantioselective synthesis of (+)-lentiginosine

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ABSTRACT

A high yielding enantioselective synthesis of the indolizidine alkaloid, (+)-lentiginosine, has been described based on asymmetric *aza*-Cope rearrangement and the L-proline catalyzed α-aminooxylation of aldehydes. The strategy also makes use of ring-closing metathesis for the construction of piperidine core.

1. Introduction

Polyhydroxylated alkaloids such as (+)-lentiginosine **1**, (−)-swainsonine **2** and (+)-catanospermine **3** constitute a class of aza-sugars exhibiting potent and selective glycosidase inhibitory activities and are found to be useful as anti-cancer, anti-diabetic and anti-viral agents and immune stimulants.[1] For instance, (+)-lentiginosine **1**, a dihydroxylated indolizidine alkaloid isolated from the leaves of *Astragalus lentiginosis*[2] was shown to be a selective inhibitor of amyloglucosidase, an enzyme that hydrolyses 1,4- and 1,6-α-glycosidic linkages.[3] Due to the enormous biological importance as well as structural complexities of this class of compounds, numerous reports describing the synthesis of these natural products and their analogues have been published.[4] Although the majority of the reported enantiospecific synthesis of (+)-lentiginosine relies mostly upon the chiral pool, the low-cost L-tartaric acid is the most widely employed since it allows the direct construction of the (1*S*,2*S*)-configuration of (+)-lentiginosine (Fig. 1).

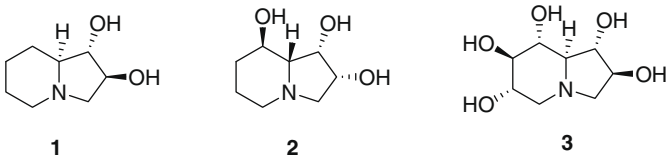

Figure 1. Structures of polyhydroxylated alkaloids.

2. Results and discussion

A retrosynthetic analysis of (+)-lentiginosine **1** is outlined in Scheme 1. Accordingly, (+)-lentiginosine **1** is envisaged to be prepared from α,β-unsaturated ester **4** via Os-catalyzed diastereoselective dihydroxylation. We further considered that the piperidine core in **4** could be constructed from **5** by ring-closing metathesis (RCM), which in turn may be obtained from the key intermediate **6**. The key intermediate **6** was planned to be synthesized by two routes involving proline-catalyzed α-aminooxylation[5] as well as via *aza*-Cope rearrangement.[6]

Firstly, our synthesis of (+)-lentiginosine **1** started with the protected aldehyde **7** prepared from the corresponding monoprotected 1,3-propanediol followed by selective oxidation with IBX in DMSO. The proline-catalyzed α-aminooxylation of aldehyde **7** involved a two-step reaction sequence: (i) reaction of aldehyde **7** with nitrosobenzene as electrophile in the presence of L-proline (25 mol %) in CH_3CN at −20 °C[5a] followed by treatment with $NaBH_4$ in MeOH to give crude aminooxy alcohol (ii) subsequent cleavage of aminooxy moiety with 30% $CuSO_4$[7] to yield chiral diol **9** in 54% yield. Selective protection of primary alcohol in **9** with mesyl chloride gave the corresponding mesylate which on treatment with K_2CO_3 in MeOH yielded the terminal epoxide **11**; $[\alpha]_D^{25} = -5.3$ (*c* 4.5, toluene). Regioselective ring opening of epoxide **11** with vinyl magnesium bromide in the presence of CuI (40 mol %)[8] in THF at −40 °C gave homoallylic alcohol **12**, which was converted into mesylate **13**. The nucleophilic displacement of mesylate **13** with NaN_3 in DMF at 80 °C yielded the corresponding azide **14** in 87% yield. The selective reduction of azide function in **14** using $LiAlH_4$ gave homoallylic amine **6** in 93% yield and >95% ee (by HPLC)[6]; $[\alpha]_D^{25} = +7.4$ (*c* 1, $CHCl_3$). Since the L-proline-based route for obtaining key intermediate **6** involved several steps, an alternative strategy was developed, which focused on asymmetric *aza*-Cope rearrangement[6] of aldehydes leading to the synthesis of homoallylic amines (Scheme 2).

In the second route, the synthesis of (+)-lentiginosine **1** commenced with benzyl-protected acetaldehyde **8**, which was subjected to an asymmetric *aza*-Cope rearrangement using the Kobayashi protocol[6] [(CSA (10 mol %), **20** (1 equiv), $NH_2OH{\cdot}AcOH$, 1,2-dichloroethane] to give exclusively (*S*)-homoallylic amine **6** in 87% yield and 96% ee (Scheme 3). Homoallylic amine **6** was protected as its Boc derivative **15** [$(Boc)_2O$, DMAP, Et_3N, and

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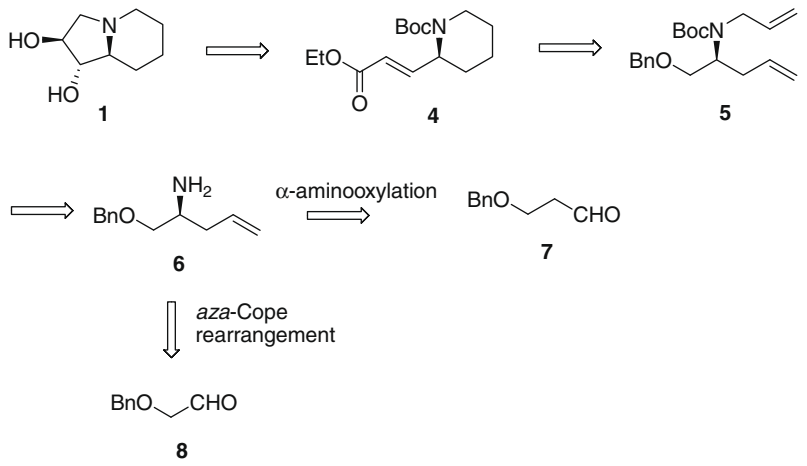
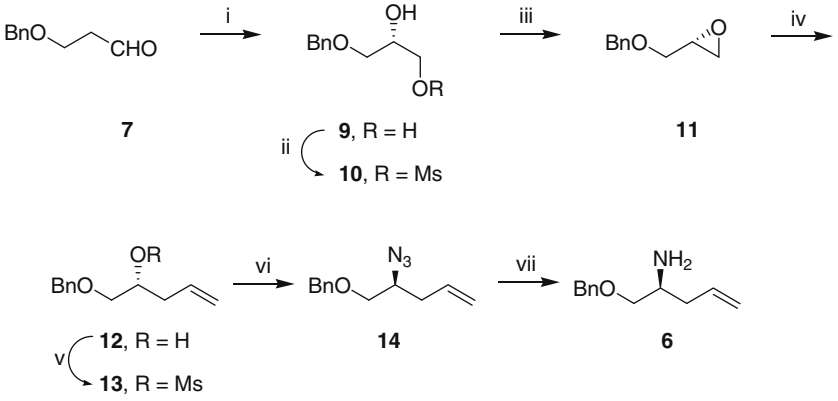
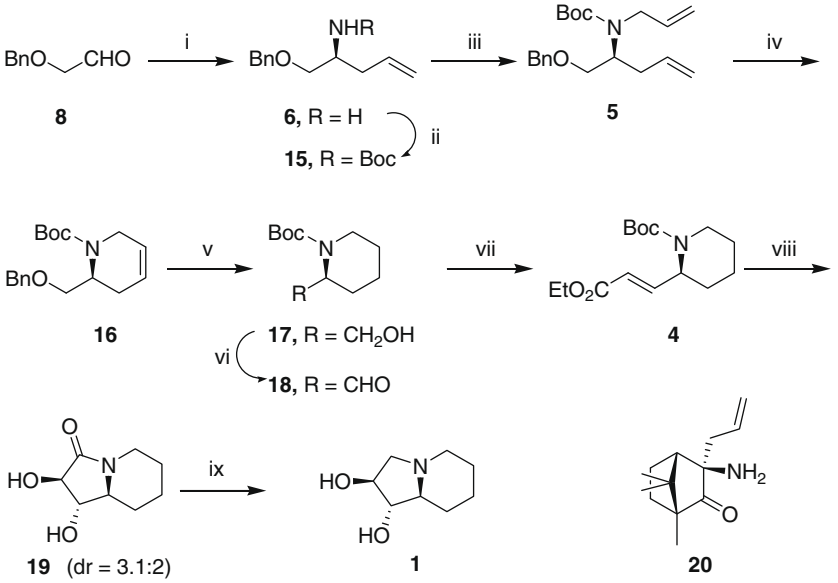


Scheme 1. Retrosynthetic analysis of (+)-lentiginosine.



Scheme 2. Reagents and conditions: (i) (a) L-Proline (25 mol %), PhNO, CH_3CN, −23 °C, 24 h; then $NaBH_4$, MeOH, 0 °C, 1 h; (b) $CuSO_4$ (30 mol %), MeOH, 12 h, 54%; (ii) MsCl, Et_3N, CH_2Cl_2, 0 °C; (iii) K_2CO_3, MeOH, 91% for two steps; (iv) CH_2=CHMgBr, CuI (40 mol %), THF, −40 °C, 92%; (v) (a) MsCl, Et_3N, CH_2Cl_2, 45 min, 94%; (vi) NaN_3, DMF, 85 °C, 87%; (vii) $LiAlH_4$, THF, 0–25 °C, 93%.



Scheme 3. Reagents and conditions: (i) Camphorsulfonic acid (10 mol %), (1*R*,3*R*,4*S*)-3-allyl-3-amino-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one **20** (1 equiv), 1,2-dichloroethane, $NH_2OH{\cdot}AcOH$, 25 °C, 24 h, 87%; (ii) $(Boc)_2O$, DMAP (10 mol %), Et_3N, CH_2Cl_2, 25 °C, 10 h, 95%; (iii) NaH, allylbromide, dry DMF, 0–25 °C, 5 h, 88%; (iv) Grubbs' 2nd generation catalyst (10 mol %), dry CH_2Cl_2, 20 h, reflux, 78%; (v) 10% Pd/C, H_2 (20 psi), MeOH, 25 °C, 8 h, 88%; (vi) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 93%; (vii) Ph_3P=$CHCO_2Et$, benzene, 50 °C, 14 h, 90%; (viii) OsO_4, NMO, ^tBuOH:H_2O, 25 °C, 24 h; then TFA, 18 h, EtOH, reflux, 58%; (ix) $LiAlH_4$, THF, reflux, 12 h, 82%.

CH_2Cl_2] followed by N-allylation with allylbromide and NaH to give the RCM precursor **5** in 88% yield. Ring-closing metathesis[9] of **5** using Grubbs' 2nd generation catalyst, (10 mol %) in refluxing dichloromethane proceeded smoothly to give dihydropyridine **16** in 78% yield. Catalytic hydrogenation of the resulting olefin coupled with the removal of the benzyl group resulted in piperidine alcohol **17** in 88% yield. The enantiomeric purity of **17** was determined to be 98% ee by HPLC analysis. The Swern oxidation of piperidine alcohol **17** produced piperidine carboxaldehyde **18** in 93% yield, which underwent Wittig olefination with stabilized salt ($Ph_3P{=}CHCO_2Et$) to give α,β-unsaturated ester **4** in 90% yield. The Os-catalyzed diastereoselective dihydroxylation[10] of α,β-unsaturated ester **4** furnished the corresponding diol in 87% yield, which on in situ Boc deprotection followed by refluxing the crude mixture in EtOH produced indolizidinone **19** (dr = 60:40) which was purified by chromatography followed by recrystallization[4o] to give a single diastereomer **19** in 58% yield. Finally, $LiAlH_4$ reduction of indolizidinone carbonyl in **19** was carried out that produced (+)-lentiginosine **1** in 82% yield, whose stereogenic values (mp, ^1H and ^{13}C NMR, $[\alpha]_D$, etc.) are in complete agreement with the reported synthesis.[4c,h,p,x,y]

3. Conclusion

In conclusion, a short enantioselective synthesis of (+)-lentiginosine **1** has been described based on asymmetric *aza*-Cope rearrangement and L-proline-catalyzed α-aminooxylation of aldehydes. Our route to (+)-lentiginosine emphasizes on an organocatalytic and metal-free approach demonstrating a shortest route to key intermediate homoallylic amine **6** and should hold promise for the synthesis of similar such alkaloids. The synthesis also involves RCM strategy for the construction of piperidine core.

4. Experimental

4.1. (*R*)-3-(Benzyloxy)propane-1,2-diol 9

To a pre-cooled (−20 °C) acetonitrile (50 mL) solution of aldehyde **7** (5.0 g, 30.4 mmol) and nitrosobenzene (1.68 g, 15.7 mmol) was added L-proline (0.49 g, 25 mol %). The reaction mixture was allowed to stir at the same temperature for 24 h, followed by the addition of MeOH (20 mL) and $NaBH_4$ (2.31 g, 60.9 mmol), which was stirred for 20 min. After the addition of saturated aq NH_4Cl, the resulting mixture was extracted with EtOAc (3 × 60 mL) and the combined organic phases were dried over anhyd Na_2SO_4 and concentrated to give the crude aminooxy alcohol, which was directly used for the next step without purification. To a MeOH (50 mL) solution of the crude aminooxyalcohol was added $CuSO_4{\cdot}5H_2O$ (1.28 g, 5.1 mmol) at 0 °C. The reaction mixture was allowed to stir for 10 h at this temperature. After the addition of the phosphate buffer, the resulting mixture was extracted with $CHCl_3$ (3 × 60 mL) and the combined organic phases were dried over anhyd Na_2SO_4 and concentrated to give the crude diol, which was then purified by column chromatography over silica gel using petroleum ether/EtOAc (6:4) to give diol **9** (1.5 g, 54%) as a colourless oil. $[\alpha]_D^{25} = +5.5$ (*c* 10, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 2.19–2.25 (dd, *J* = 5.4, 1.2 Hz, 1H), 2.69–2.72 (d, *J* = 4.8 Hz, 1H), 3.59–3.60 (m, 2H), 3.62–3.74 (m, 2H), 3.83–3.95 (m, 1H), 4.55 (s, 2H), 7.29–7.39 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 63.7, 70.7, 71.3, 73.2, 127.7, 128.3, 137.5; IR ($CHCl_3$ cm^{-1}): 3684, 3615, 3472, 3020, 2927, 2400, 1602, 1521, 1455, 1424, 1216, 1094, 1051, 929, 850, 770, 660. Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.89, H, 7.68.

4.2. (*R*)-2-(Benzyloxymethyl)oxirane 11

A solution of diol **9** (1.5 g, 8.2 mmol) in CH_2Cl_2 (40 mL) was treated with methane sulfonyl chloride (0.98 mL, 12.3 mmol) and Et_3N (2.29 mL, 16.48 mmol) at 0 °C. After being stirred for 35 min, the mixture was extracted with CH_2Cl_2 (3 × 100 mL), washed with water and the combined organic phases were dried over anhyd Na_2SO_4 and concentrated to give the crude mesylate **10**, which was subjected to epoxidation without further purification. To a solution of mesylate **10** (1.96 g, 7.5 mmol) in MeOH (40 mL) was added anhyd K_2CO_3 (1.03 g, 7.5 mmol) and the mixture was stirred at 25 °C for 1 h. After the reaction was completed (monitored by TLC), the mixture was evaporated and the residue was extracted with diethyl ether (3 × 80 mL). The combined organic phases were dried over anhyd Na_2SO_4 and concentrated to give the crude product, which was then purified by column chromatography over silica gel using petroleum ether/EtOAc (8:2) to give epoxide **11** (1.6 g, 91%) as a colourless oil. $[\alpha]_D^{25} = -5.3$ (*c* 4.5, toluene) ^1H NMR (200 MHz, $CDCl_3$): δ 2.60–2.63 (dd, *J* = 2.6, 5.0 Hz, 1H), 2.77–2.82 (dd, *J* = 4.2, 1.0 Hz, 1H), 3.15–3.22 (m, 1H), 3.39–3.47 (dd, *J* = 5.8, 5.5 Hz, 1H), 3.73–3.80 (dd, *J* = 2.9, 8.5 Hz, 1H), 4.51–4.65 (d, *J* = 3.8 Hz, 2H), 7.27–7.36 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 44.1, 50.7, 70.6, 73.2, 127.6, 127.9, 128.3, 137.8; IR ($CHCl_3$ cm^{-1}): 877, 985, 1216, 1387, 1452, 1476, 3018, 3435. Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 73.20, H, 7.29.

4.3. (*R*)-1-(Benzyloxy)pent-4-en-2-ol 12

Vinyl bromide (6.44 M in THF, 6 mL, 38.36 mmol) was added slowly to Mg (0.4 g, 19.1 mmol) in THF (20 mL) at 0 °C and the mixture was stirred for 10 min; then cooled to −40 °C and CuI (0.52 g, 30 mol %) was added. The resulting reaction mixture was stirred for 30 min at −40 °C and a solution of epoxide **11** (1.5 g, 9.14 mmol) in THF (25 mL) was added. After being stirred for 3 h, the mixture was quenched with saturated aq NH_4Cl solution, extracted with diethyl ether (3 × 80 mL), washed with brine and the combined organic phases were dried over anhyd Na_2SO_4 and concentrated to give the crude product, which was then purified by column chromatography over silica gel using petroleum ether/EtOAc (7:3) to give alcohol **12** (1.6 g, 92%) as a colourless oil. $[\alpha]_D^{25} = -2$ (*c* 1, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 2.21–2.29 (m, 1H), 2.34 (br s, 1H), 3.31–3.34 (dd, *J* = 7.3, 2.0 Hz, 1H), 4.5 (s, 2H), 5.06–5.16 (m, 2H), 5.71–5.92 (m, 1H), 7.27–7.38 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 37.8, 69.5, 73.2, 73.8, 117.5, 127.6, 128.3, 134.2, 137.8; IR ($CHCl_3$ cm^{-1}): 1243, 1670, 2930, 3010, 3415. Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.88, H, 8.27.

4.4. (*R*)-1-(Benzyloxy)pent-4-en-2-yl methanesulfonate 13

To a stirred solution of alcohol **12** (2.5 g, 13 mmol) in CH_2Cl_2 (40 mL) was added Et_3N (3.6 g, 26.0 mmol) at 0 °C. After 10 min, methanesulfonyl chloride (1.5 g, 19.5 mmol) was added dropwise. The reaction mixture was then stirred for another 1 h at 0 °C and brought to room temperature. After completion of the reaction as monitored by TLC, it was quenched with water and extracted with CH_2Cl_2 (3 × 50 mL) washed with water, brine and dried over anhyd Na_2SO_4. The combined organic layer was concentrated under reduced pressure to obtain crude mesylate **13**, which was purified by column chromatography using petroleum ether/ethyl acetate (6:4) to give pure mesylate **13** (3.3 g, 94%) as a viscous liquid. $[\alpha]_D^{25} = -4.8$ (*c* 0.84, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 2.47–2.50 (t, *J* = 6.6, 13.3 Hz, 2H), 3.0 (s, 3H), 3.60–3.62 (t, *J* = 3.7 Hz, 2H), 4.51–4.58 (q, *J* = 11.7 Hz, 2H), 4.80–4.85 (m, 1H), 5.14–5.18 (m, 2H), 5.74–5.82 (m, 1H), 7.28–7.36 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 36.2, 38.4, 70.8, 73.2, 81.0, 119.1, 127.6, 127.7, 128.3,

131.7, 137.2; IR ($CHCl_3$ cm^{-1}): 3085, 3031, 2867, 2360, 1647, 1456, 1357, 1174, 1116, 910, 781, 705, 649. Anal. Calcd for $C_{13}H_{18}O_4S$: C, 57.76; H, 6.71; S, 11.86. Found: C, 57.80, H, 6.69; S, 11.79.

4.5. 1-{[(*S*)-2-Azidopent-4-enyloxy]methyl} benzene 14

To a stirred mixture of crude methane sulfonate ester **13** (2 g, 7.3 mmol) in DMF (30 mL) was added sodium azide (2.4 g, 37 mmol), and the reaction mixture was heated at 80 °C for 15 h. After completion of the reaction as monitored by TLC, it was extracted with EtOAc (3 × 50 mL), washed with water, brine and dried over anhyd Na_2SO_4. The combined organic layer was concentrated under reduced pressure to give the crude homoallylic azide, which was purified by column chromatography using petroleum ether/ethyl acetate (9:1) to give **14** (1.4 g, 87%). $[\alpha]_D^{25} = -7.3$ (*c* 1.1, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.26–2.33 (m, 2H), 3.48–3.61 (m, 3H), 4.56 (s, 2H), 5.08–5.18 (m, 2H), 5.68–5.89 (m, 1H), 7.28–7.36 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 35.2, 60.9, 72.06, 73.2, 118.1, 127.4, 127.6, 128.3, 133.4, 137.7; IR ($CHCl_3$ cm^{-1}): 2959, 2112, 1650, 1216, 640. Anal. Calcd for $C_{12}H_{15}N_3O$: C, 66.34; H, 6.96; N, 19.34. Found: C, 66.29, H, 6.89; N, 19.30.

4.6. Proline route: (*S*)-1-(benzyloxy)pent-4-en-2-amine 6

To a stirred mixture of $LiAlH_4$ (0.350 g, 9.21 mmol) in anhyd THF (20 mL) was added homoallylic azide **14** (1 g, 4.60 mmol) in THF (10 mL) at 0 °C. The reaction mixture was stirred at 25 °C for 10 h. After completion of the reaction as monitored by TLC, it was quenched with ice-cold water and 20% aq NaOH. This crude mixture was passed through anhyd Na_2SO_4 and washed thoroughly with EtOAc (3 × 50 mL) and the solvent was evaporated under reduced pressure to give the crude homoallylic amine, which was purified by column chromatography using $CHCl_3$/MeOH (9:1) to give **6** (0.820 g, 93%) as colourless oil. $[\alpha]_D^{25} = +7.4$ (*c* 1, $CHCl_3$) {lit.[6] $[\alpha]_D^{25} = +7.1$ (*c* 1.14, $CHCl_3$)}.

4.7. Aza-Cope rearrangement: (*S*)-1-(benzyloxy)pent-4-en-2-amine 6

To a solution of chiral amine **20**[6] (2.072 g, 10 mmol) and aldehyde **8** (1.5 g, 10 mmol) in 1,2-dichloroethane (20 mL) was added camphorsulfonic acid (0.232 g, 10 mol %) at 0 °C. The mixture was stirred at the 0 °C for 24 h. Then, a solution of $HONH_2$·AcOH in methanol [0.5 M, 2 mL, prepared from $HONH_2$·HCl, NaOH (solid, 1 equiv), and AcOH (1 equiv) in methanol] was added to the solution. After being stirred at 50 °C for 3 h, the mixture was cooled to 25 °C, acidified with 1 N aq HCl (pH 1). The mixture was washed with dichloromethane (3 × 50 mL), basified with 6 N aq NaOH (pH 10), and extracted with dichloromethane (3 × 50 mL). The combined solvent layers were dried over anhyd Na_2CO_3, filtered, and evaporated to give amine **6**. The crude product was purified by column chromatography (petroleum ether/EtOAc = 1:1) to give pure amine **6** (1.65 g, 87%). $[\alpha]_D^{25} = +7.1$ (*c* 1.46, $CHCl_3$), {lit.[6] $[\alpha]_D^{25} = +7.1$ (*c* 1.14, $CHCl_3$)}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.6 (s, 2H), 1.96–2.10 (m, 1H), 2.16–2.30 (m, 1H), 3.0–3.12 (m, 1H), 3.23–3.31 (t, *J* = 3.0 Hz, 1H), 3.42–3.48 (dd, *J* = 4.3, 4.8 Hz, 1H), 4.52 (s, 1H), 4.97–5.13 (t, *J* = 10.3 Hz, 2H), 5.67–5.87 (m, 1H), 7.31–7.38 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 38.6, 50.2, 73.1, 75.1, 117.3, 127.5, 128.2, 135.0, 138.1; IR ($CHCl_3$ cm^{-1}): 3418, 3297, 3020, 1618, 761, 670. Anal. Calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.29, H, 8.91, N, 7.28.

4.8. *tert*-Butyl (*S*)-1-(benzyloxy)pent-4-en-2-ylcarbamate 15

To a solution of amine **6** (4 g, 20.9 mmol) in dry CH_2Cl_2 (40 mL) were added dry Et_3N (4.3 mL, 31.38 mmol, $(Boc)_2O$ (5.47 g, 25.2 mmol) and DMAP (0.255 g, 10 mol %), and the reaction mixture was stirred for 10 h. After completion of the reaction as monitored by TLC, it was extracted with CH_2Cl_2 (3 × 60 mL), washed with brine and dried over anhyd Na_2SO_4 and concentrated to give the crude product, which was then purified by column chromatography over silica gel using petroleum ether/EtOAc (7:3) to give carbamate **15** (5.8 g, 95%) as a colourless oil. $[\alpha]_D^{25} = -5.8$ (*c* 0.86, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.42 (s, 9H), 1.64 (br s, 1H), 2.29–2.36 (m, 2H), 3.40–3.53 (m, 2H), 4.49–4.51 (d, *J* = 2.4 Hz, 2H), 5.01–5.12 (m, 2H), 5.65–5.86 (m, 1H), 7.27–7.35 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 28.2, 36.3, 49.8, 71.0, 73.0, 79.1, 117.5, 127.5, 128.2, 134.4, 138.0, 155.4; IR ($CHCl_3$ cm^{-1}): 3750, 3690, 3021, 2928, 2357, 1708, 1425, 1216, 764, 670. Anal. Calcd for $C_{17}H_{25}NO_3$: C, 70.07; H, 8.65; N, 4.81. Found: C, 70.11, H, 8.59; N, 4.78.

4.9. *tert*-Butyl allyl-(*S*)-1-(benzyloxy)pent-4-en-2-ylcarbamate 5

To a solution of NaH (0.494 g, 12.35 mmol) in dry DMF (30 mL) was added Boc-protected amine **15** (3 g, 10.29 mmol) at 0 °C. After 15 min, allylbromide (1 mL, 12.35 mmol) was added dropwise. The reaction mixture was then stirred for 6 h at 25 °C. After completion of the reaction as monitored by TLC, it was extracted with CH_2Cl_2 (3 × 50 mL), washed with brine and dried over anhyd Na_2SO_4 and concentrated to give the crude product, which was then purified by column chromatography over silica gel using petroleum ether/EtOAc (9:1) to give **5** (3 g, 88%) as a colourless oil. $[\alpha]_D^{25} = +2.05$ (*c* 1.46, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.43 (s, 9H), 2.29–2.37 (t, *J* = 7.0 Hz, 2H), 3.44–3.61 (m, 2H), 3.71–3.81 (m, 2H), 4.05–4.31 (m, 1H), 4.46–4.48 (d, *J* = 5.0 Hz, 2H), 4.99–5.11 (m, 4H), 5.63–5.88 (m, 2H), 7.30 (s, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 28.2, 34.1, 47.2, 55.1, 70.9, 72.7, 79.2, 115.1, 116.1, 127.3, 128.1, 135.0, 136.0, 138.1, 155.4; IR ($CHCl_3$ cm^{-1}): 3780, 3697, 3633, 3019, 2932, 2361, 1682, 1216, 1104, 762, 670. Anal. Calcd for $C_{20}H_{29}NO_3$: C, 72.47; H, 8.82; N, 4.23. Found: C, 72.50, H, 8.79; N, 4.19.

4.10. (*S*)-*tert*-Butyl-6-(benzyloxymethyl)-5,6-dihydropyridine-1(2*H*)-carboxylate 16

Olefin **5** (1 g, 3 mmol) was dissolved in dry CH_2Cl_2 (40 mL) and the solution was degassed by bubbling with argon for 10 min. Then, Grubbs' 2nd generation ruthenium catalyst (256 mg, 0.30 mmol) was added. The reaction mixture was stirred for 22 h at 50 °C and then cooled and the solvent was evaporated to give the residue, which was then directly purified by column chromatography over silica gel using petroleum ether/EtOAc (8:2) to give dihydropyridine **16** (0.720 g, 78%) as a colourless oil. $[\alpha]_D^{25} = +20$ (*c* 1, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.45 (s, 9H), 1.66–1.70 (m, 1H), 2.01–2.16 (m, 1H), 2.31–2.48 (m, 1H), 3.34–3.50 (m, 3H), 4.05-.24 (m, 1H), 4.49–4.53 (d, *J* = 5.4 Hz, 2H), 5.56–5.74 (m, 2H), 7.29–7.32 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 25.2, 28.2, 40.4, 45.9, 68.7, 72.5, 72.9, 79.4, 122.4, 123.1, 127.3, 128.1, 128.9, 138.1, 155.0; IR ($CHCl_3$ cm^{-1}): 3443, 2978, 1685, 1413, 1227, 1115, 1028, 909, 698, 648. Anal. Calcd for $C_{18}H_{25}NO_3$: C, 71.26; H, 8.31; N, 4.62. Found: C, 71.30, H, 8.29; N, 4.58.

4.11. (*S*)-*tert*-Butyl 2-(hydroxymethyl)piperidine-1-carboxylate 17

Dihydropyridine **16** (0.5 g, 1.65 mmol) was dissolved in MeOH (25 mL), 10% Pd/C (38 mg) was added and the mixture was stirred under H_2 (20 psi) atmosphere for 8 h. The mixture was then filtered over Celite, washed with MeOH (2 × 20 mL) and the solvent was evaporated under reduced pressure to afford alcohol **17**, which was then purified by column chromatography over silica gel using petroleum ether/EtOAc (7:3) to give **17** (0.320 g, 88%).

Chiral column: CHIRALCEL OD-H, length 25 cm, wavelength: 230 nm, flow rate 1.0 mL/min. Mobile phase: 5% isopropyl alcohol in hexane; ee = 98.4%; $[\alpha]_D^{25} = -40.1$ (*c* 1, $CHCl_3$), {lit.[11] $[\alpha]_D^{25} = -40.5$ (*c* 1, $CHCl_3$)}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.45 (s, 9H), 1.51–1.76 (m, 6H), 2.11 (br s, 1H), 2.78–2.92 (m, 1H), 3.5–3.6 (m, 1H), 3.74–3.96 (m, 2H), 4.23–4.34 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 18.9, 24.4, 24.9, 28.0, 39.5, 51.7, 60.0, 79.1, 155.5; IR ($CHCl_3$ cm^{-1}): 3442, 2940, 2890, 1655, 1422, 1370, 1280, 1170, 1150, 1060, 1050, 870. Anal. Calcd for $C_{11}H_{21}NO_3$: C, 61.37; H, 9.83, N, 6.51. Found: C, 61.40, H, 9.79, N, 6.49.

4.12. (*S*)-*tert*-Butyl 2-[*E*-2-(ethoxycarbonyl)vinyl] piperidine-1-carboxylate 4

To a stirred solution of oxalyl chloride (0.825 g, 6.48 mmol) in CH_2Cl_2 (20 mL) at −78 °C was added a solution of DMSO (0.760 g, 9.72 mmol). The reaction mixture was stirred for 20 min. followed by the addition of a solution of alcohol **17** (0.7 g, 3.24 mmol) in CH_2Cl_2 (10 mL). After stirring for 1 h at −78 °C, the reaction was quenched by the addition of Et_3N (1.8 mL, 12.96 mmol). The reaction mixture was then stirred for 20 min. followed by the addition of water (20 mL). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL), dried over anhyd Na_2SO_4 and concentrated to give the corresponding crude aldehyde **18** in 0.650 g (93%), which was subjected to Wittig olefination without purification as follows. To a solution of aldehyde **18** in dry benzene (20 mL) was added $Ph_3P{=}CHCO_2Et$ (1 g, 3.0 mmol) and the reaction mixture was heated at 50 °C for 12 h. After completion of the reaction as monitored by TLC, it was cooled to 25 °C, extracted with EtOAc (3 × 50 mL), washed with water, brine and dried over anhyd Na_2SO_4 and concentrated to give the crude product, which was then purified by column chromatography over silica gel using petroleum ether/EtOAc (8:2) to give the unsaturated ester **4** (0.6 g, 90%) as a gum. $[\alpha]_D^{25} = -77.5$ (*c* 1.3, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.25–1.32 (t, *J* = 7.0 Hz, 3H), 1.44 (s, 9H), 1.50–1.84 (m, 6H), 2.73–2.87 (m, 1H), 3.94–4.0 (d, *J* = 12.0 Hz, 1H), 4.12–4.23 (q, *J* = 7.0 Hz, 2H), 4.92 (s, 1H), 5.73–5.82 (dd, *J* = 2.1, 13.7 Hz, 1H), 6.79–6.89 (dd, *J* = 4.0, 12.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0, 19.6, 25.0, 28.1, 28.7, 39.8, 51.5, 60.2, 79.6, 121.8, 147.2, 154.8, 160.0; IR ($CHCl_3$ cm^{-1}): 2940, 2862, 1730, 1700, 1665, 1440, 1410, 1370, 1310, 1280, 1270, 1160, 1050, 870, 770. Anal. Calcd for $C_{15}H_{25}NO_4$: C, 63.58; H, 8.89; N, 4.94. Found: C, 63.60, H, 8.90, N, 4.89.

4.13. (1*S*,2*R*,8a*S*)-Hexahydro-1,2-dihydroxyindolizin-3(5*H*)-one 19

To a solution of *tert*-butyl alcohol (5.0 mL) and water (5.0 mL) in THF (5 mL), 4-methylmorpholine N-oxide (0.39 g, 3.34 mmol) and OsO_4 (0.02 g, 0.1 M solution in toluene, 5 mol %) were added and the mixture was stirred at room temperature for 15 min. A solution of ester **4** (0.5 g, 1.76 mmol) in THF (3.0 mL) was added. After 24 h, the reaction mixture was treated with Florisil (2.0 g), and $NaHSO_3$ (1.0 g) and stirring was continued for 1 h. The reaction mixture was diluted with EtOAc (20 mL), filtered through Celite and the filtrate was distilled in vacuo to give a mixture of diols. This crude mixture of diol was stirred in 10 mL of TFA for (Boc deprotection) 10 h and evaporated solvent in vacuo followed by refluxing this mixture in ethanol for 6 h gave indolizidinone **19** as 60:40 ratio (80% combine yield, determined by ^{1}H and ^{13}C NMR). These compounds were separated by repeated recrystallization followed by flash column chromatographic purification on silica gel ($CHCl_3$/MeOH/Et_3N, 30:68:2) to give pure indolizidinone **19** in 58% yield. $[\alpha]_D^{25} = +55.2$ (*c* 1, MeOH), {lit.[4h] $[\alpha]_D^{21} = +52.3$ (*c* 1.99, MeOH)}; ^{1}H NMR (200 MHz, CD_3OD): δ 0.94–1.09 (m, 1H), 1.12–1.22 (m, 2H), 1.28–1.56 (m, 2H), 1.57–1.91 (m, 1H), 2.55–3.08 (m, 1H), 2.55–3.08 (m, 1H), 3.41–3.47 (t, *J* = 7.0 Hz, 1H), 3.78–3.94 (m, 2H); ^{13}C NMR (50 MHz, CD_3OD): δ 25.0, 25.9, 30.4, 41.8, 64.2, 71.2, 72.5, 172.0; IR ($CHCl_3$ cm^{-1}): 1685, 1450, 1365, 1280, 640. Anal. Calcd for $C_8H_{13}NO_3$: C, 56.13; H, 7.65; N, 8.18. Found: C, 56.20, H, 7.59, N, 8.20.

4.14. (+)-Lentiginosine 1

To a stirred solution of (0.1 g, 0.584 mmol) of indolizidinone **19** in THF (10 mL) at 0 °C was added lithium aluminum hydride (0.044 g, 1.16 mmol). The suspended mixture was stirred at 65 °C for 12 h, cooled to 0 °C, diluted with 2 mL of THF, and then carefully treated successively with water, 10% aq NaOH. The resulting mixture was stirred for 1 h and filtered through pad of sodium sulfate and filtrate was concentrated under reduced pressure. The crude residue was then purified by column chromatography on silica gel ($CHCl_3$/MeOH, 8:2) to give 0.075 g of pure lentiginosine **1** as a colourless solid 82%. Mp 103–105 °C [lit.[4p] mp 103–104 °C]; $[\alpha]_D^{25} = +3.0$ (*c* 0.4, MeOH) {lit.[4j] $[\alpha]_D^{24} = +3.1$ (*c* 0.31, MeOH); ^{1}H NMR (200 MHz, D_2O): δ 1.15–1.89 (m, 7H), 1.99–2.07 (m, 1H), 2.48–2.62 (dd, *J* = 11.0, 7.4 Hz, 1H), 2.68–2.79 (dd, *J* = 11.0, 2.0 Hz, 1H), 2.90–2.93 (br d, *J* = 11.0 Hz, 1H), 3.46–3.60 (dd, *J* = 8.0, 4.0 Hz, 1H), 4.03–4.20 (m, 1H); ^{13}C NMR (50 MHz, D_2O): δ 23.9, 24.8, 28.4, 53.5, 61.1, 69.4, 76.5, 83.8; IR ($CHCl_3$ cm^{-1}): 3525, 3515, 3021, 3012, 2932, 2857, 1443, 1210, 1130. 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, 8.78.

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References

1. (a) Pearson, M. S. M.; Mathe-Allainmat, M.; Fargeas, V.; Lebreton, J. *Eur. J. Org. Chem.* **2005**, 2159–2191; (b) Stutz, A. E. *Iminosugars as Glycosidase Inhibitors: Nojirimycin and Beyond*; Wiley, 1999; (c) Lillielund, V. H.; Jensen, H. H.; Liang, X.; Bols, M. *Chem. Rev.* **2002**, *102*, 515–554; (d) Dwek, R. A.; Butters, T. D.; Platt, F. M.; Zitzmann, N. *Nat. Rev.* **2002**, *1*, 65–75; (e) Asano, N. *Glycobiology* **2003**, *13*, 93R; (f) Watson, A. A.; Fleet, G. W. J.; Asano, N.; Molyneux, R. J.; Nash, R. J. *Phytochemistry* **2001**, *56*, 265–295; (g) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645–1680; (h) Mehta, G.; Ramesh, S. *Can. J. Chem.* **2005**, *83*, 581; (i) Laventine, D. M.; Jenkins, P. R.; Cullis, P. M. *Tetrahedron Lett.* **2005**, *46*, 2295–2298; (j) Robinson, K. M.; Begovic, M. E.; Rhinehart, B. L.; Heineke, E. W.; Ducep, J.-B.; Kastner, P. R.; Mashall, F. N.; Danzin, C. *Diabetes* **1991**, *40*, 825–830.
2. Pastuszak, I.; Molyneux, R. J.; James, L. F.; Elbein, A. D. *Biochemistry* **1990**, *29*, 1886–1891.
3. (a) Walker, B. D.; Kowalski, M.; Goh, W. C.; Kowarsky, K.; Krieger, M.; Rosen, W. C.; Rohrschneider, L. R.; Haseltine, W. A.; Sodroski, J. *Proc. Natl. Acad. Sci.* **1987**, *84*, 8120–8124; (b) Karpas, A.; Fleet, G. W. J.; Dwek, R. A.; Petursson, S.; Namgoong, S. K.; Ramsden, N. G.; Jacob, G. S.; Rademacher, T. W. *Proc. Natl. Acad. Sci.* **1988**, *85*, 9229–9233; (c) Winkler, D. A.; Holan, G. *J. Med. Chem.* **1989**, *32*, 2084–2089.
4. (a) Yoda, H.; Kitayama, H.; Katagiri, T.; Takabe, K. *Tetrahedron: Asymmetry* **1993**, *4*, 1455–1456; (b) Gurjar, M. K.; Ghosh, L.; Syamala, M.; Jayasree, V. *Tetrahedron Lett.* **1994**, *35*, 8871–8872; (c) Brandi, A.; Cicchi, S.; Cordero, F. M.; Frignoli, R.; Goti, A.; Picasso, S.; Vogel, P. *J. Org. Chem.* **1995**, *60*, 6806–6812; (d) Giovannini, R.; Marcantoni, E.; Petrini, M. *J. Org. Chem.* **1995**, *60*, 5706–5707; (e) Nukui, S.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 398–404; (f) McCaig, A. E.; Meldrum, K. P.; Wightman, R. H. *Tetrahedron* **1998**, *54*, 9429–9446; (g) Yoda, H.; Kawauchi, M.; Takabe, K. *Synlett* **1998**, 137–138; (h) Ha, D.-C.; Yun, C-S.; Lee, Y. *J. Org. Chem.* **2000**, *65*, 621–623; (; (i) Yoda, H.; Katoh, H.; Ujihara, Y.; Takabe, K. *Tetrahedron Lett.* **2001**, *42*, 2509–2512; (j) Rasmussen, M. O.; Delair, P.; Greene, A. E. *J. Org. Chem.* **2001**, *66*, 5438–5443; (k) Chandra, K. L.; Chandrashekhar, M.; Singh, V. K. *J. Org. Chem.* **2002**, *67*, 4630–4633; (l) El-Nezhawy, A. O. H.; El-Diwani, H. I.; Schmidt, R. R. *Eur. J. Org. Chem.* **2002**, 4137–4142; (m) Rabiczko, J.; Urbanczyk, L. Z.; Chmielewski, M. *Tetrahedron* **2002**, *58*, 1433–1441; (n) Sha, C-K.; Chau, C-M. *Tetrahedron Lett.* **2003**, *44*, 499–501; (o) Feng, Z.-X.; Zhou, W.-S. *Tetrahedron Lett.* **2003**, *44*, 497–498; (p) Raghavan, S.; Sreekanth, T. *Tetrahedron: Asymmetry* **2004**, *15*, 565–570; (q) Ayad, T.; Genisson, Y.; Baltas, M. *Org. Biomol. Chem.* **2005**, *3*, 2626–2631; (r) Cardona, F.; Moreno, G.; Guarna, F.; Vogel, P.; Schuetz, C.; Merino, P.; Goti, A. *J. Org. Chem.* **2005**, *70*, 6252–6255; (s) Kim, I. S.; Zee, O. P.; Jung, Y. H. *Org. Lett.* **2006**, *8*,

4101–4104; (t) Chaudhari, V. D.; Kumar, K. S. A.; Dhavale, D. D. *Tetrahedron* **2006**, *62*, 4349–4354; (u) Cardona, F.; Goti, A.; Brandi, A. *Eur. J. Org. Chem.* **2007**, 1551–1565; (v) Chen, M.-J.; Tsai, Y.-M. *Tetrahedron Lett.* **2007**, *48*, 6271–6274; (w) Chandrashekhar, S.; Vijaykumar, B. V. D.; Pratap, T. V. *Tetrahedron: Asymmetry* **2008**, *19*, 746–750; (x) Alam, M. A.; Vankar, Y. D. *Tetrahedron Lett.* **2008**, *49*, 5534–5536; (y) Lauzon, S.; Tremblay, F.; Gagnon, D.; Godbout, C.; Chabot, C.; Mercier-Shanks, C.; Perreault, S.; DeSeve, H.; Spino, C. *J. Org. Chem.* **2008**, *73*, 6239–6250; (z) Shi, G.-F.; Li, J.-Q.; Jiang, X.-P.; Cheng, Y. *Tetrahedron* **2008**, *64*, 5005–5012.

5. (a) Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Shoji, M. *Tetrahedron Lett.* **2003**, *44*, 8293; (b) Zhong, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4247; (c) Hayashi, Y.; Yamaguchi, J.; Sumiya, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2003**, *43*, 1112; (d) Brown, S. P.; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 10808; (e) Cordova, A.; Sunden, H.; Bøgevig, A.; Johansson, M.; Himo, F. *Chem. Eur. J.* **2004**, *10*, 3673.
6. Sugiura, M.; Mori, C.; Kobayashi, S. *J. Am. Chem. Soc.* **2006**, *128*, 11038.
7. Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2003**, *125*, 6038.
8. Felpin, F.; Lebreton, J. *J. Org. Chem.* **2002**, *67*, 9192.
9. (a) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446; (b) Davies, S. G.; Iwamoto, K.; Smethrust, C. A. P.; Smith, A. D.; Rodriguez-Solla, H. *Synlett* **2002**, 1146–1148; (c) Pandit, U. K.; Overkleeft, H. S.; Borer, B. C.; Bieraugel, H. *Eur. J. Org. Chem.* **1999**, *5*, 959; (d) Wright, D. L. *Curr. Org. Chem.* **1999**, *3*, 211; (e) Phillips, A. J.; Abell, A. D. *Aldrichim. Acta* **1999**, *32*, 75; (f) Maier, M. E. *Angew. Chem., Int. Ed.* **2000**, *39*, 2073.
10. Dondoni, A.; Merino, P.; Perrone, D. *Tetrahedron* **1993**, *49*, 2939.
11. Sanchez-Sancho, F.; Herradon, B. *Tetrahedron: Asymmetry* **1998**, *9*, 1951–1965.