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Synthesis of (−)-lentiginosine, its 8a-epimer and dihydroxylated pyrrolizidine alkaloid from D-glucose

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Abstract—The D-glucose derived α,β-unsaturated ester **5** on 1,2-acetonide deprotection, oxidative diol cleavage followed by treatment with *N*-benzylamine in the presence of $NaBH_3CN$ undergoes reductive amination and a concomitant intramolecular conjugate addition reaction leading to the formation of dihydroxypyrrolidine-ester **6a** and monohydroxypyrrolidine-γ-lactone **6b**. Intermediates **6a** and **6b** were efficiently converted to (−)-lentiginosine **3a**, its 8a-epimer **3b**, and pyrrolizidine azasugar **4** in good overall yield.

1. Introduction

Polyhydroxylated indolizidine alkaloids such as castanospermine **1**, swainsonine **2** and lentiginosine **3a** (Fig. 1) are known to be the potential glycosidase inhibitors.[1] Among these, the least hydroxylated lentiginosine **3a**, was found to be the selective inhibitor (IC_{50} 5 μg/mL) of amyloglucosidase enzyme and also exhibit anti-HIV activity.[2,3] (−)-Lentiginosine **3a** was isolated from the leaves of *Astragalus lentiginous* in 1990,[3a] however, its sign of rotation and the stereochemical assignments raised controversy[4] and therefore aroused synthetic interest in the past decade. The known synthetic strategies mainly involve asymmetric pathways starting from either chiral or achiral starting materials,[3,5] however, the use of carbohydrate substrates has received limited attention.[6] While working in the area of azasugars,[7] we have recently exploited D-glucose derived α,β-unsaturated ester **5** in the synthesis of trihydroxylated pyrrolidine alkaloids **A** and **B** (Scheme 1). Thus, opening of 1,2-acetonide group in **5** followed by oxidative cleavage afforded ethyl D-*threo*-hex-4-enoate, which on one pot reductive amination and intramolecular conjugate addition afforded hydroxy ester **6a** and γ-lactone **6b** in the ratio 42:58 (81%) that were converted to **A** and **B**, respectively.[7c] Now, we describe herein the utility of **6a/6b** in the synthesis of lentiginosine **3a**, its 8a-epimer **3b** and dihydroxylated pyrrolizidine alkaloid **4**.

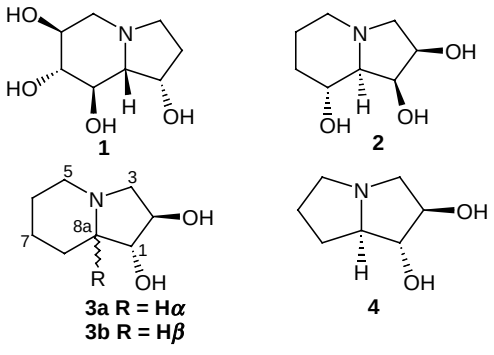
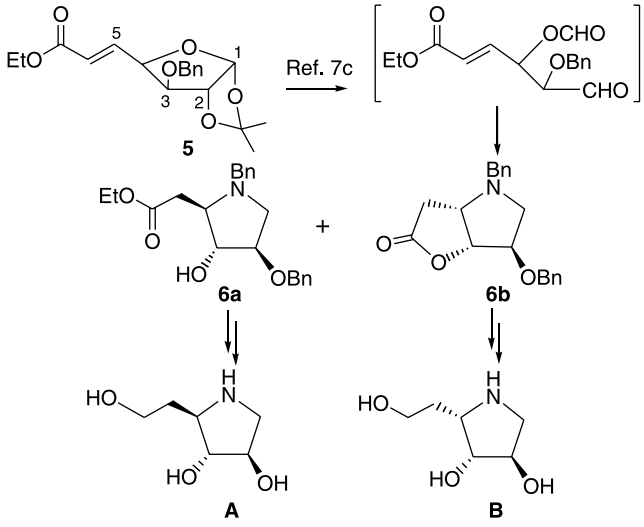


Figure 1. Indolizidine and pyrrolizidine alkaloids.



Scheme 1. Synthesis of pyrrolidine alkaloids.

Keywords: Alkaloids; Wittig olefination; Azasugars.
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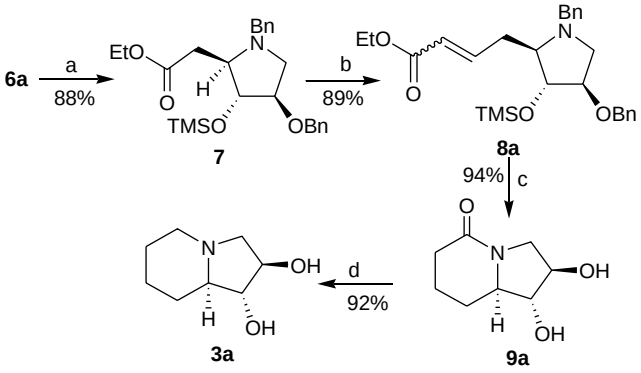
2. Results and discussion

2.1. Synthesis of (−)-lentiginosine 3a

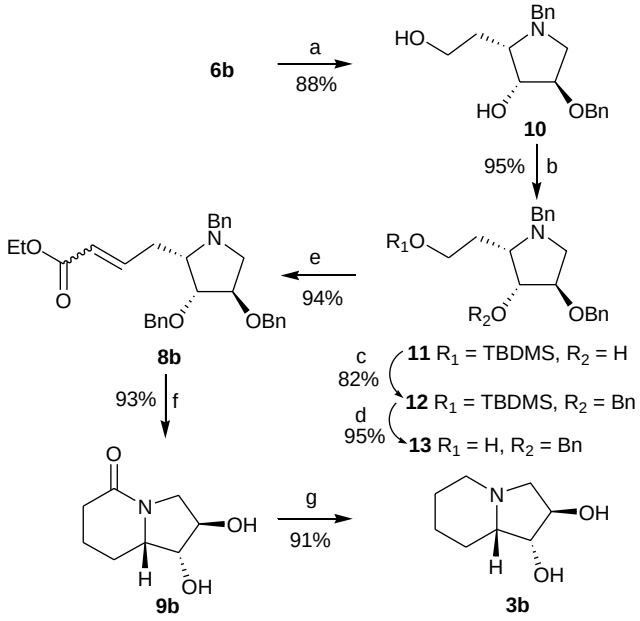
As shown in Scheme 2, treatment of hydroxy ester **6a** with hexamethyldisilazane in the presence of catalytic amount of both TMSCl and ammonium thiocyanate afforded 3-*O*-TMS protected ester **7**.[8] Reduction of the ester functionality in **7** with DIBAL-H followed by Wittig olefination (Ph_3P=CHCOOEt) gave α,β-unsaturated ester **8a** (*E*/*Z*=4:1 based on ^{1}H NMR). Hydrogenation of **8a** using ammonium formate, 10% Pd/C afforded bicyclic lactam **9a**. This one pot four-step process involves reduction of the double bond, hydrogenolysis of –*O*Bn and –*N*Bn groups, desilylation and concomitant cyclization to give δ-lactam **9a**. The products **7**, **8a** and **9a** were characterized by spectral and analytical techniques, and the data was found to be in agreement with the structures. In the next step, LAH reduction of **9a** in THF under reflux followed by column chromatography purification gave (−)-lentiginosine **3a** as white solid. This compound [observed $[\alpha]_D$ −3.5 (*c* 1.0, MeOH); lit.[3b,5c,g,o,6d] −1.6, −2.6, −3.05, −2.0, −4.5] had spectral and analytical data in agreement with that in the literature.[3,5,6]



Scheme 2. Reagents and conditions: (a) HMDS, cat. TMSCl, cat. NH_4SCN, CH_2Cl_2, 25 °C, 30 min; (b) (i) DIBAL-H, CH_2Cl_2, −50 °C, 2.5 h; (ii) $Ph_3PCHCOOEt$, CH_2Cl_2, 25 °C, 30 min; (c) $HCOONH_4$, 10% Pd/C, cat. AcOH, MeOH, reflux, 1 h; (d) LAH, THF, reflux, 8 h.

2.2. Synthesis of 1,2-epilentiginosine 3b

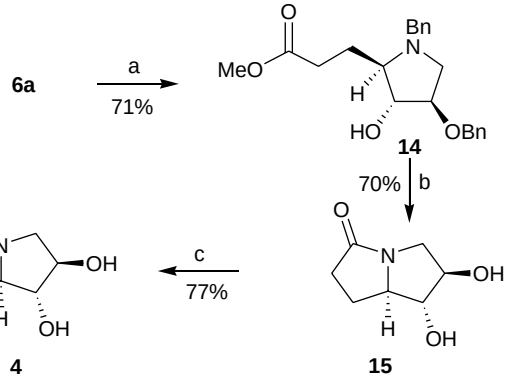
Similar methodology was attempted for the γ-lactone **6b**, however, DIBAL-H reduction afforded lactol, which on the Wittig olefination led to the formation of a diastereomeric mixture of an unexpected product.[9] As an alternative, reduction of γ-lactone **6b** with LAH in THF afforded diol **10** (Scheme 3). The primary hydroxy group in **10** was selectively protected using TBDMSCl to get **11** that on benzylation afforded **12**. Treatment of **12** with TBAF in THF furnished alcohol **13**, which on Swern oxidation and Wittig olefination gave α,β-unsaturated ester **8b** (*E*/*Z*=4:1 based on ^{1}H NMR). Hydrogenation of ester **8b** using ammonium formate and 10% Pd/C gave bicyclic lactam **9b**. Finally, reduction of **9b** with LAH afforded **3b**, an 8a-epimer of **3a**. This compound [observed $[\alpha]_D$+4.3 (*c* 0.5, MeOH); lit.[5k] +3.4 (*c* 0.41, MeOH)] had spectral and analytical data in agreement with that in the literature.[5k,10]



Scheme 3. Reagents and conditions: (a) LAH, THF, 0 °C, 30 min; (b) TBSCl, imidazole, CH_2Cl_2, 25 °C, 3 h; (c) NaH, BnBr, THF, 0 °C, 6 h; (d) TBAF, THF, 25 °C, 4 h; (e) (i) $(COCl)_2$, DMSO, NEt_3, −78 °C, 2 h; (ii) $PPh_3CHCOOEt$, CH_2Cl_2, 25 °C 1 h; (f) $HCOONH_4$, 10% Pd/C, MeOH, reflux, 1 h; (g) LAH, THF, reflux, 10 h.

2.3. Synthesis of dihydroxylated pyrrolizidine alkaloid 4

The hydroxyl ester **6a** was utilized in the synthesis of dihydroxylated pyrrolizidine alkaloid **4** (Scheme 4). Thus, hydrolysis of **6a** with lithium hydroxide and activation of carboxylate group using ethylchloroformate and triethyl amine afforded mixed anhydride, which on treatment with diazomethane in diethyl ether followed by Wolff rearrangement using silver benzoate in methanol furnished one carbon homologated methyl ester **14**.[7b] Treatment of methyl ester **14** with ammonium formate and 10% Pd/C afforded bicyclic lactam **15** that was reduced with LAH to give dihydroxylated pyrrolizidine alkaloid **4**. The spectral data and analytical data of **4** was found to be identical with that reported[5o] [observed $[\alpha]_D$ +6.5 (*c* 0.25, MeOH), lit.[5o] $[\alpha]_D$ +7.6 (*c* 1.3, MeOH)].



Scheme 4. Reagents and conditions: (a) (i) LiOH, methanol–water, 0–25 °C, 4 h; (ii) ClCOOEt, NEt_3, THF, 0–25 °C, 30 min; (iii) CH_2N_2, diethyl ether, 25 °C, 1.5 h; (iv) PhCOOAg, NEt_3, methanol, 25 °C, 3 h; (b) $HCOONH_4$, 10% Pd/C, methanol, reflux, 1 h; (c) LAH, THF, reflux, 10 h.

3. Conclusion

In conclusion, a new synthetic protocol for (−)-lentiginosine **3a**, and its 8a-*epi*-analogue **3b** and dihydroxylated pyrrolizidine alkaloid **4** has been developed starting from D-glucose derived α,β-unsaturated ester **5**. With our methodology the hydroxylated C-3/C-4 carbons of D-glucose, both with the *R* configuration, are retained in the target molecule **3a**. It is therefore obvious that (−)-lentiginosine **3a** has (1*R*,2*R*,8a*R*) absolute configuration as reported earlier.[5c,o,6d]

4. Experimental

4.1. General

Melting points were recorded with Thomas Hoover melting point apparatus and are uncorrected. IR spectra were recorded with Shimadzu FTIR-8400 as a thin film or in Nujol mull or using KBr pellets and are expressed in reciprocal centimetre (cm^{-1}). ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded with Varian Mercury 300 using $CDCl_3$ or D_2O as a solvent. Chemical shifts were reported in δ unit (ppm) with reference to TMS as an internal standard and *J* values are given in Hertz. Elemental analyses were carried out with Elemental Analyser Flash 1112. Optical rotations were measured using a Bellingham Stanley-ADP digital polarimeter with sodium light (589.3 nm) at 25 °C. Thin-layer chromatography was performed on Merck pre-coated plates (0.25 mm, silica gel 60 F_{254}). Column chromatography was carried out with silica gel (100–200 mesh). The reactions were carried out in oven-dried glassware under dry N_2. Methanol, DMF, THF were purified and dried before use. Petroleum ether (PE) that was used is a distillation fraction between 40–60 °C. LAH, DIBAL-H, 10% Pd–C were purchased from Aldrich and/or Fluka. After decomposition of the reaction with water, the work-up involves—washing of combined organic layer with water, brine, drying over anhydrous sodium sulfate and evaporation of solvent at reduced pressure.

4.1.1. Ethyl 2-((2*R*,3*R*,4*R*)-1-benzyl-4-benzyloxy-3-trimethylsilyloxy-pyrrolidin-2-yl)acetate (7). To a solution of hydroxyester[7c] **6a** (1.00 g, 2.71 mmol) in dichloromethane (10 mL) was added HMDS (0.34 mL, 1.60 mmol) followed by catalytic amount of both TMSCl (0.04 mL, 0.30 mmol) and ammonium thiocyanate (0.01 g, 0.13 mmol) at 25 °C. The reaction mixture was stirred for 30 min and extracted with dichloromethane (2×30 mL). The combined organic layer was concentrated, adsorbed on neutral alumina and purification by column chromatography on neutral alumina (7% ethyl acetate/*n*-hexane) afforded **7** (1.10 g, 88%) as thick oil; [found: C, 67.82; H, 7.90. $C_{25}H_{35}NO_4Si$ requires C, 67.99; H, 7.99]; R_f (10% ethyl acetate/*n*-hexane) 0.47; $[\alpha]_D$ −4.0 (*c* 0.50, $CHCl_3$); ν_{max} (neat) 1728, 1217 cm^{-1}; δ_H (300 MHz, $CDCl_3$) δ 0.22 (s, 9H), 1.25 (t, *J*=7.1 Hz, 3H), 2.38 (dd, *J*=10.9, 6.3 Hz, 1H), 2.47 (d, *J*=5.7 Hz, 2H), 2.73 (dd, *J*=11.8, 5.7 Hz, 1H), 2.80 (dd, *J*=10.9, 1.9 Hz, 1H), 3.14 (d, *J*=13.1 Hz, 1H), 3.61–3.65 (m, 1H), 3.89 (d, *J*=13.1 Hz, 1H), 3.98 (dd, *J*=7.1, 4.6 Hz, 1H), 3.99 (q, *J*=7.1 Hz, 2H), 4.27 (ABq, *J*=11.8 Hz, 2H), 7.05–7.23 (m, 10H); δ_C (75 MHz, $CDCl_3$) δ 0.13 (s), 14.1, 36.6, 56.3, 58.3, 60.3, 66.9, 71.4, 80.9, 83.5, 126.8, 127.5, 127.6 (s), 128.1 (s), 128.2 (s), 128.6 (s), 138.0, 138.8, 171.9.

4.1.2. Ethyl(*E*)-4-((2*R*,3*R*,4*R*)-1-benzyl-4-benzyloxy-3-trimethylsilyloxy-pyrrolidin-2-yl)but-2-enoate (8a). To a solution of **7** (2.00 g, 4.50 mmol) in dichloromethane (20 mL) was added DIBAL-H (6.43 mL, 5.42 mmol) at −50 °C and stirred for 2.5 h. The reaction mixture was quenched with saturated solution of NH_4Cl (5 mL), filtered through Celite to afford aldehyde. To a solution of aldehyde (1.78 g, 4.29 mmol) in dichloromethane (10 mL) was added $PPh_3CHCOOEt$ (1.17 g, 5.15 mmol) at 25 °C and stirred for 30 min. Reaction mixture was adsorbed on neutral alumina and purified by column chromatography on neutral alumina (10% ethyl acetate/*n*-hexane) afforded **8a** (1.89 g, 89%) as a thick oil; [found: C, 69.42; H, 7.88. $C_{27}H_{37}NO_4Si$ requires C, 69.37; H, 7.97]; R_f (10% ethyl acetate/*n*-hexane) 0.43; $[\alpha]_D$ −36.4 (*c* 0.27, $CHCl_3$); ν_{max} (neat) 1718, 1259 cm^{-1}; δ_H (300 MHz, $CDCl_3$) δ 0.18 (s, 9H), 1.25 (t, *J*=7.1 Hz, 3H), 2.51–2.60 (m, 4H), 3.02 (br d, *J*=12.0 Hz, 1H), 3.29 (br d, *J*=13.1 Hz, 1H), 3.78 (dt, *J*=5.7, 2.4 Hz, 1H), 4.01 (dd, *J*=5.7, 3.2 Hz, 1H), 4.06 (d, *J*=13.1 Hz, 1H), 4.23 (q, *J*=7.1 Hz, 2H), 4.44 (ABq, *J*=11.2 Hz, 2H), 5.39 (d, *J*=15.6 Hz, 1H), 7.01–7.40 (m, 11H); δ_C (75 MHz, $CDCl_3$) δ 0.1 (s), 14.2, 33.4, 56.3, 58.0, 60.1, 68.8, 71.5, 81.0, 83.6, 123.1, 127.0, 127.5 (s), 127.7 (s), 128.2 (s), 128.3, 137.9, 138.4, 145.6, 166.2. Our attempt to isolate the *Z*-isomer in pure form was unsuccessful and the 89% yield reflects the total yield of *E* and *Z* mixtures.

4.1.3. (1*R*,2*R*,8a*R*)-Hexahydro-1,2-dihydroxyindolizidin-5(1*H*)-one (9a). A solution of **8a** (0.50 g, 1.10 mmol), ammonium formate (0.22 g, 7.49 mmol), 10% Pd/C (0.20 g) and acetic acid (0.02 mL, 0.34 mmol) in methanol (10 mL) was refluxed for 1 h. The solution was filtered, concentrated and purified by column chromatography (10% methanol/chloroform) to afford **9a** (0.17 g, 94%) as a white solid, mp 122–124 °C; [found: C, 56.21; H, 7.54. $C_8H_{13}NO_3$ requires C, 56.13; H, 7.65]; R_f (10% methanol/chloroform) 0.34; $[\alpha]_D$ +12.0 (*c* 0.25, MeOH); ν_{max} (KBr) 3357, 1720, 1656.7, 1452, 1028 cm^{-1}; δ_H (300 MHz, D_2O) δ 1.30–1.47 (m, 1H), 1.60–1.76 (m, 1H), 1.90–2.00 (m, 1H), 2.13–2.20 (m, 1H); 2.21–2.43 (m, 2H), 3.31 (dd, *J*=12.6, 6.8 Hz, 1H), 3.39 (ddd, *J*=15.3, 11.5, 3.5 Hz, 1H), 3.65–3.72 (m, 2H), 4.19 (dd, *J*=15.3, 7.1 Hz, 1H); δ_C (75 MHz, D_2O) δ 19.3, 25.5, 29.8, 48.6, 61.5, 72.7, 79.7, 172.4.

4.1.4. (1*R*,2*R*,8a*R*)-(−)-1,2-Dihydroxyindolizidine (3a). To an ice-cooled suspension of LAH (0.06 g, 1.50 mmol) in THF (3 mL) was added lactam **9a** (0.07 g, 0.41 mmol) in THF (7 mL). The reaction mixture was warmed to room temperature, refluxed for 8 h and quenched with ethyl acetate (2 mL) and aq NH_4Cl (0.3 mL). Filtration through Celite, the filtrate was adsorbed on silica gel and column chromatography (20% methanol/chloroform) gave **3a** (0.06 g, 92%) as a white solid, mp 106–108 °C; lit.[3b,5g] 106–107 °C; [found: C, 61.08; H, 9.59. $C_8H_{15}NO_2$ requires C, 61.12; H, 9.62]; R_f (20% methanol/chloroform) 0.30; [observed $[\alpha]_D$ −3.5 (*c* 1.0, MeOH); lit.[3b,5c,g,o,6d] −1.6, −2.6, −3.05, −2.0, −4.5]; ν_{max} (neat) 3578, 2929, 1134 cm^{-1}; δ_H (300 MHz, D_2O) δ 1.14–1.25 (m, 2H), 1.34–1.41 (m, 1H), 1.52–1.60 (m, 1H), 1.73–1.74 (m, 1H);

1.85–1.91 (m, 2H), 1.98 (ddd, J=14.0, 11.5, 2.7 Hz, 1H), 2.56 (dd, J=11.2, 7.6 Hz, 1H), 2.76 (dd, J=11.2, 1.6 Hz, 1H), 2.87 (d, J=10.9 Hz, 1H), 3.56 (dd, J=8.7, 3.8 Hz, 1H), 4.00 (ddd, J=7.6, 3.8, 1.6 Hz, 1H); δ_C (75 MHz, D_2O) δ 25.3, 26.3, 29.9, 54.9, 62.5, 70.8, 77.9, 85.2.

4.1.5. (2*S*,3*R*,4*R*)-1-Benzyl-4-benzyloxy-2-(2-hydroxyethyl)pyrrolidin-3-ol (10). To an ice-cooled suspension of LAH (0.19 g, 4.76 mmol) in THF (4 mL) was added a solution of γ-lactone **6b** (0.50 g, 2.46 mmol) in THF (10 mL) and stirred for 30 min at 25 °C. Work up as described for **3a** and purification by column chromatography (30% ethyl acetate/*n*-hexane) afforded **10** (0.44 g, 88%) as thick oil; [found: C, 73.41; H, 7.71. $C_{20}H_{25}NO_3$ requires C, 73.37; H, 7.70]; R_f (50% ethyl acetate/*n*-hexane) 0.43; $[\alpha]_D$ +84.8 (*c* 0.33, $CHCl_3$); ν_{max} (neat) 3300–3600 (broad) cm^{-1}; δ_H (300 MHz, $CDCl_3$) δ 1.90–1.97 (m, 2H), 2.18 (dd, J=10.8, 6.4 Hz, 1H), 2.73–2.79 (m, 1H), 3.22 (d, J=12.8 Hz, 1H), 3.24 (dd, J=10.8, 6.3 Hz, 1H), 3.56 (br s, exchangeable with D_2O, 2H), 3.67–3.75 (m, 1H), 3.81–3.86 (m, 1H), 3.89 (dt, J=6.4, 2.6 Hz, 1H), 4.00 (d, J=12.8 Hz, 1H), 4.19 (dd, J=5.8, 2.6 Hz, 1H), 4.52 (ABq, J=11.7 Hz, 2H), 7.22–7.36 (m, 10H); δ_C (75 MHz, $CDCl_3$) δ 28.9, 57.2, 58.3, 59.8, 66.4, 71.6, 76.7, 83.5, 127.2, 127.6, 127.7 (s), 128.3 (s), 129.0 (s), 137.7, 137.9.

4.1.6. (2*S*,3*R*,4*R*)-1-Benzyl-4-benzyloxy-2-(2-*tert*-butyldimethysilyloxyethyl)pyrrolidin-3-ol (11). To a solution of diol **10** (0.40 g, 1.22 mmol), in dichloromethane (15 mL) was added TBDMSCl (0.22 g, 1.46 mmol) followed by imidazole (1.00 g, 1.46 mmol) and stirred for 3 h at 25 °C. Water was added to the reaction mixture and extracted with (3×10 mL) dichloromethane. The combined organic layer was concentrated, adsorbed on silica gel and purified by column chromatography (20% ethyl acetate/*n*-hexane) afforded **11** (0.81 g, 95%) as thick oil; [found: C, 70.65; H, 8.93. $C_{26}H_{39}NO_3Si$ requires C, 70.70; H, 8.90]; R_f (20% ethyl acetate/*n*-hexane) 0.23; $[\alpha]_D$ +65.5 (*c* 0.58, $CHCl_3$); ν_{max} (neat) 3429, 2930, 1460, 1254 cm^{-1}; δ_H (300 MHz, $CDCl_3+D_2O$) δ 0.20 (s, 6H), 0.82 (s, 9H), 1.90–2.15 (m, 2H), 2.25 (dd, J=10.1, 6.5 Hz, 1H), 2.73–2.79 (m, 1H), 3.29 (d, J=13.1 Hz, 1H), 3.32 (dd, J=10.1, 6.8 Hz, 1H), 3.73 (ddd, J=12.0, 9.3, 3.0 Hz, 1H), 3.91–3.99 (m, 2H), 4.03 (d, J=13.1 Hz, 1H), 4.23 (dd, J=5.7, 2.4 Hz, 1H), 4.6 (ABq, J=11.8 Hz, 2H), 7.13–7.21 (m, 10H); δ_C (75 MHz, $CDCl_3$) δ 18.1, 25.8 (s), 29.5, 57.5, 58.1, 61.2, 67.3, 71.6, 76.8, 83.3, 127.0, 127.5, 127.7 (s), 128.2 (s), 128.3 (s), 128.9 (s), 137.9, 138.1.

4.1.7. (2*S*,3*R*,4*R*)-1-Benzyl-3,4-bis(benzyloxy)-2-(2-*tert*-butyldimethysilyloxyethyl)pyrrolidine (12). To a hexane washed sodium hydride (0.03 g, 1.25 mmol) was added a solution of alcohol **11** (0.43 g, 0.97 mmol) in THF (8 mL) dropwise at 0 °C and stirred for 30 min. A solution of benzyl bromide (0.13 mL, 1.07 mmol) in THF (2 mL) was added dropwise, followed by addition of TBAI (0.02 g, 0.05 mmol) and stirred for 5 h at 25 °C. The reaction mixture was neutralized with water concentrated under vaccum, extracted using (3×10 mL) dichloromethane. The combined organic layer was concentrated, adsorbed on silica gel and purified using column chromatography (10% ethyl acetate/*n*-hexane) afforded **12** (0.41 g, 82%) as a thick liquid; [found: C, 74.52; H, 8.43. $C_{33}H_{45}NO_3Si$ requires C, 74.53; H, 8.53]; R_f (20% ethyl acetate/*n*-hexane) 0.75; $[\alpha]_D$ +48.6 (*c* 0.7, $CHCl_3$); ν_{max} (neat) 2926, 1456, 1252, 1092 cm^{-1}; δ_H (300 MHz, $CDCl_3$) δ 0.02 (s, 6H), 0.88 (s, 9H), 1.69–1.91 (m, 2H), 2.02–2.09 (m, 1H), 2.18–2.56 (m, 1H), 2.91 (m, 1H), 3.43–3.48 (m, 1H), 3.54–5.56 (m, 1H), 3.67–3.74 (m, 1H), 3.90 (dd, J=6.0, 2.1 Hz, 1H), 3.99 (ddd, J=7.6, 6.0, 2.1 Hz, 1H), 4.06 (d, J=13.1 Hz, 1H), 4.44 (s, 2H), 4.45 (d, J=12.0 Hz, 1H), 4.63 (d, J=12.0 Hz, 1H), 7.25–7.38 (m, 15H); δ_C (75 MHz, $CDCl_3$) δ 18.2, 25.9 (s), 30.2, 57.3, 58.4, 60.7, 63.3, 71.4, 81.5, 82.9, 127.1, 127.6 (s), 127.7 (s), 128.0 (s), 128.2 (s), 128.3 (s), 128.4 (s), 129.3, 138.0.

4.1.8. 2-((2*S*,3*R*,4*R*)-1-Benzyl-3,4-bis(benzyloxy)pyrrolidin-2-yl)ethanol (13). To a solution of **12** (0.15 g, 0.29 mmol), in THF (10 mL) was added TBAF (0.18 g, 0.58 mmol) and stirred for 4 h at 25 °C. The reaction mixture was concentrated under vaccum and extracted with (3×15 mL) dichloromethane. The combined organic layers were concentrated, adsorbed on silica gel and purified by column chromatography (10% ethyl acetate/*n*-hexane) afforded **13** (0.12 g, 95%) as thick oil; [found: C, 77.63; H, 7.50. $C_{27}H_{31}NO_3$ requires C, 77.67; H, 7.48]; R_f (20% ethyl acetate/*n*-hexane) 0.19; $[\alpha]_D$ +21.4 (*c* 0.28, $CHCl_3$); ν_{max} (neat) 3494, 2922, 1377, 1217 cm^{-1}; δ_H (300 MHz, $CDCl_3+D_2O$) δ 1.81–1.86 (m, 1H), 1.92–2.03 (m, 1H), 2.30–2.35 (m, 1H), 3.13–3.14 (m, 1H), 3.24 (dd, J=10.4, 5.5 Hz, 1H), 3.39 (br d, J=12.6 Hz, 1H), 3.68–3.75 (m, 1H), 3.81–3.88 (m, 1H), 4.02–4.11 (m, 3H), 4.46 (s, 2H), 4.35 (d, J=11.8 Hz, 1H), 4.64 (d, J=11.8 Hz, 1H), 7.22–7.34 (m, 15H); δ_C (75 MHz, $CDCl_3$) δ 29.3, 55.4, 59.5, 61.4, 64.8, 71.8, 72.0, 82.3, 83.9, 127.2, 127.5 (s), 127.6 (s), 128.3 (s), 129.0 (s), 137.7, 137.8.

4.1.9. Ethyl (*E*)-4-((2*S*,3*R*,4*R*)-1-benzyl-3,4-bis(benzyloxy)pyrrolidin-2-yl)but-2-enoate (8b). To a solution of oxalyl chloride (0.03 mL, 0.31 mmol) in dichloromethane (1 mL) at −78 °C was added slowly a solution of DMSO (0.04 mL, 0.58 mmol) in dichloromethane (1 mL). After 10 min, a solution of alcohol **13** (0.11 g, 0.26 mmol) in dichloromethane (2 mL) was added and the reaction was stirred at −78 °C for 2 h. Triethylamine (0.18 mL, 1.31 mmol) was added and the mixture was stirred at −78 °C for 30 min. Usual work up afforded aldehyde as a thick liquid. To the solution of aldehyde (0.11 g, 0.30 mmol) in dichloromethane (10 mL) was added PPh_3-CHCOOEt (0.12 g, 0.36 mmol) and stirred for 1 h at 25 °C. The reaction mixture was adsorbed on silica gel and purification by column chromatography (10% ethyl acetate/*n*-hexane) afforded **8b** (0.12 g, 94%) as thick oil; [found: C, 76.61; H, 7.18. $C_{31}H_{35}NO_4$ requires C, 76.67; H, 7.26]; R_f (10% ethyl acetate/*n*-hexane) 0.73; $[\alpha]_D$ +44.0 (*c* 0.25, $CHCl_3$); ν_{max} (neat) 1724, 1244 cm^{-1}; δ_H (300 MHz, $CDCl_3$) δ 1.20 (t, J=7.1 Hz, 3H), 2.19 (dd, J=9.9, 5.7 Hz, 1H), 2.36–2.41 (m, 1H), 2.56–2.58 (m, 1H), 2.80–2.81 (m, 1H), 3.19–3.27 (m, 2H), 3.82 (dd, J=6.0, 2.4 Hz, 1H), 3.89 (d, J=12.9 Hz, 1H), 3.87–3.89 (m, 1H), 4.08 (q, J=7.1 Hz, 2H), 4.33 (s, 2H), 4.36 (d, J=11.8 Hz, 1H), 4.51 (d, J=11.8 Hz, 1H), 5.75 (d, J=15.6 Hz, 1H), 6.90 (dt, J=15.6, 7.1 Hz, 1H), 7.19–7.25 (m, 15H); δ_C (75 MHz, $CDCl_3$) δ 14.4, 30.9, 57.3, 58.6, 60.1, 65.2, 71.4, 71.7, 81.4, 83.3, 122.5, 126.9, 127.4 (s), 127.5 (s), 127.6 (s), 127.9 (s), 128.1 (s), 137.7, 146.7, 166.3. Our attempt to isolate the *Z*-isomer

in pure form was unsuccessful, 94% yield reflects the total yield of *E* and *Z* isomer.

4.1.10. (1*R*,2*R*,8a*S*)-Hexahydro-1,2-dihydroxyindolizin-5(1*H*)-one (9b). The reaction of **8b**, (0.12 g, 0.25 mmol) with 10% Pd/C (0.08 g) and ammonium formate (0.11 g, 1.73 mmol) as described for the synthesis of **9a** afforded **9b** (0.04 g, 93%) as a white solid, mp 174–176 °C; [found: C, 56.10; H, 7.59. $C_8H_{13}NO_3$ requires C, 56.13; H, 7.65]; R_f (10% methanol/chloroform) 0.34; $[\alpha]_D$ −19.0 (*c* 0.42, MeOH); ν_{max} (KBr) 3441, 2926, 1711, 1653, 1212 cm^{-1}; δ_H (300 MHz, D_2O) δ 1.46 (m, 1H), 1.74–1.82 (m, 1H), 1.94–2.04 (m, 2H), 2.19–1.45 (m, 2H), 3.32 (d, J=13.7 Hz, 1H), 3.74–3.84 (m, 2H), 4.08–4.09 (m, 1H), 4.23 (dd, J= 4.9, 0.8 Hz, 1H); δ_C (75 MHz, D_2O) δ 20.0, 21.6, 30.1, 51.6, 60.8, 72.1, 76.1, 173.18.

4.1.11. (1*R*,2*R*,8a*S*)-(+)-1,2-Dihydroxyindolizidine (3b). The reaction of lactam **15** (0.07 g, 0.04 mmol) with LAH (0.06 g, 1.50 mmol) as described for the synthesis of **3a** afforded **3b** (0.06 g, 91%) as a sticky solid; [found: C, 56.21; H, 7.68. $C_8H_{15}NO_2$ requires C, 56.13; H, 7.65]; R_f (20% methanol/chloroform) 0.30; [observed $[\alpha]_D$ +4.3 (*c* 0.5, MeOH); lit.[5k] +3.4 (*c* 0.41, MeOH)]; ν_{max} (neat) 3355, 2934, 1121 cm^{-1}; δ_H (300 MHz, D_2O) δ 1.57–1.79 (m, 3H), 1.95–2.08 (m, 3H), 2.90 (dd, J=13.2, 3.0 Hz, 1H), 3.02–3.10 (m, 1H), 3.36 (d, J=11.8 Hz, 1H), 3.66 (d, J=12.1 Hz, 1H), 4.03 (dd, J=12.1, 6.3 Hz, 1H), 4.18 (d, J=3.0 Hz, 1H), 4.31 (dd, J=6.3, 3.0 Hz, 1H); δ_C (75 MHz, D_2O) δ 22.9, 24.7, 25.2, 53.1, 62.2, 66.9, 77.8, 81.1.

4.1.12. Methyl 3-((2*R*,3*R*,4*R*)-1-benzyl-4-benzyloxy-3-hydroxypyrrolodin-2-yl)propanoate (14). To an ice-cooled solution of **6a** (0.63 g, 1.30 mmol) in methanol–water (5 mL, 4/1) was added lithium hydroxide monohydrate (0.30 g, 5.22 mmol) and stirred for 4 h at 25 °C. The solution was neutralized and worked up to afford the acid. To a solution of an acid in THF (5 mL) was added triethylamine (0.28 mL, 2.02 mmol) and ethylchloroformate (0.19 mL, 2.02 mmol). After 15 min, the suspension was allowed to warm to 25 °C and filtered. The filtrate was cooled to 0 °C and a freshly prepared solution of diazomethane in diethyl ether (0.24 g, 5.80 mmol) was added dropwise and stirred for 3 h at 25 °C. The solvent was evaporated to afford thick oil. To a solution of diazoketone in methanol (8 mL) was added dropwise a solution of silver benzoate (0.11 g, 0.49 mmol) in triethylamine (0.50 mL) and stirred for 3 h at 25 °C. The solvent was evaporated and the residue was purified by column chromatography (20% ethyl acetate/*n*-hexane) to give **14** (0.45 g, 71%) as a thick liquid; [found: C, 71.46; H, 7.46. $C_{22}H_{27}NO_4$ requires C, 71.52; H, 7.37]; R_f (25% ethyl acetate/*n*-hexane) 0.68; $[\alpha]_D$ −24.0 (*c* 0.5, $CHCl_3$); ν_{max} (neat) 3345, 1728, 1457, 1134 cm^{-1}; δ_H (300 MHz, $CDCl_3+D_2O$): δ 1.25–1.28 (m, 2H), 2.56–2.76 (m, 3H), 2.90–3.33 (m, 2H), 2.98 (br d, J= 13.1 Hz, 1H), 3.72 (s, 3H), 3.87 (d, J=6.8 Hz, 1H), 3.96 (br d, J=13.1 Hz, 1H), 4.11 (d, J=3.8 Hz, 1H), 4.33 (ABq, J= 12.0 Hz, 2H), 7.26–7.34 (m, 10H); δ_C (75 MHz, $CDCl_3$) δ 29.5, 36.7, 52.0, 57.0, 57.8, 67.1, 71.0, 82.5, 82.8, 127.2, 127.5, 127.7 (s), 128.3 (s), 128.6 (s), 128.8 (s), 137.7, 138.0, 173.9.

4.1.13. (6*R*,7*R*,7a*R*)-Hexahydro-6,7-dihydroxypyrrolizin-3-one (15). The reaction of **14** (0.20 g, 0.54 mmol) with 10% Pd/C (0.10 g) and ammonium formate (0.23 g, 3.70 mmol) as described for the synthesis of **9a** afforded **15** (0.06 g, 70%) as a sticky gum; [found: C, 53.51; H, 7.03. $C_7H_{11}NO_3$ requires C, 53.49; H, 7.05]; R_f (10% methanol/chloroform) 0.35; $[\alpha]_D$ −15.3 (*c* 0.5, MeOH); ν_{max} (neat) 3335, 1723, 1659, 1433, 1214 cm^{-1}; δ_H (300 MHz, D_2O) δ 1.54–1.79 (m, 2H), 2.58 (dd, J=10.7, 0.8 Hz, 1H), 3.16–3.24 (m, 2H), 3.42–3.58 (m, 2H); 3.82 (dd, J=5.7, 1.8 Hz, 1H), 4.12–4.16 (m, 1H); δ_C (75 MHz, D_2O) δ 32.4, 49.7, 58.3, 63.2, 74.1, 78.6, 180.5.

4.1.14. (1*R*,2*R*,7a*R*)-(+)-1,2-Dihydroxypyrrolizidine (4). The reaction of lactam **15** (0.10 g, 0.63 mmol) with LAH (0.10 g, 2.54 mmol) as described for **3b** afforded **4** (0.07 g, 77%) as thick oil; [found: C, 58.68; H, 9.19. $C_7H_{13}NO_2$ requires C, 58.72; H, 9.15]; R_f (20% methanol/chloroform) 0.32; [observed $[\alpha]_D$ +6.5 (*c* 0.25, MeOH), lit.[5o] $[\alpha]_D$ +7.6 (*c* 1.3, MeOH)]; ν_{max} (neat) 3300–3600 (broad) cm^{-1}; δ_H (300 MHz, D_2O) δ 1.76–1.91 (m, 1H); 1.95–2.16 (m, 1H), 2.18–2.27 (m, 2H), 2.86–2.98 (m, 2H), 3.11 (dd, J=11.2, 4.9 Hz, 1H), 3.23 (dd, J=11.2, 3.8 Hz, 1H), 3.35–3.41 (m, 1H), 3.92–4.04 (m, 1H), 4.17–4.25 (m, 1H); δ_C (75 MHz, D_2O) δ 28.7, 32.4, 59.8, 62.2, 72.1, 80.2, 82.3.

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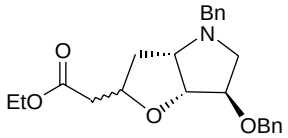
References and notes

1. Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645.
2. Review: Burgess, K.; Henderson, I. *Tetrahedron* **1992**, *48*, 4045.
3. (a) Isolation: Pastuszak, I.; Molyneux, R. J.; James, L. F.; Elbein, A. D. *Biochemistry* **1990**, *29*, 1886. (b) Activity: Brandi, A.; Cicchi, S.; Cordero, F. M.; Frignoli, R.; Goti, A.; Picasso, S.; Vogel, P. *J. Org. Chem.* **1995**, *60*, 6806.
4. The natural lentiginosine with all *S* configurations is reported to have $[\alpha]_D$ −3.3, while Yoda et al. and Brandi et al. have reported the synthesis of lentiginosine starting from L-tartaric acid and gave a value $[\alpha]_D$ +0.19 and +3.2, respectively. The synthesis of both enantiomers of lentiginosine was reported by Gurjar et al., starting from (*R*) and (*S*)-pipecolinic acid and showed that the (−)-lentiginosine has the all *R* stereochemistry. However, the subsequent report of Brandi et al. claim that natural lentiginosine is not levorotatory but dextrorotatory and this has the (1*S*,2*S*,8a*S*) configuration.
5. (a) Yoda, H.; Kitayama, H.; Katagiri, T.; Tkabe, K. *Tetrahedron: Asymmetry* **1993**, *4*, 1455. (b) Cordero, F. M.; Cicchi, S.; Goti, A.; Brandi, A. *Tetrahedron Lett.* **1994**, *35*, 949. (c) Gurjar, M. K.; Ghosh, L.; Syamala, M.; Jayasree, V. *Tetrahedron Lett.* **1994**, *35*, 8871. (d) Giovannini, R.; Marcantoni, E.; Petrini, M. *J. Org. Chem.* **1995**, *60*, 5706. (e) Goti, A.; Cardona, F.; Brandi, A. *Synlett* **1996**, 761. (f) Goti, A.; Cardona, F.; Brandi, A. *Tetrahedron: Asymmetry*

1996, *7*, 1659. (g) McCaig, A. E.; Meldrum, K. P.; Wightman, R. H. *Tetrahedron* **1998**, *54*, 9429. (h) Ha, D.-C.; Yun, C.-S.; Lee, Y. *J. Org. Chem.* **2000**, *65*, 621. (i) Klitzke, C. F.; Pilli, R. C. *Tetrahedron Lett.* **2001**, *42*, 5605. (j) Yoda, H.; Katoh, H.; Ujihara, Y.; Takabe, K. *Tetrahedron Lett.* **2001**, *42*, 2509. (k) Nakui, S.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *J. Org. Chem.* **1995**, *69*, 398. (l) Rasmussen, M. O.; Delair, P.; Greene, A. E. *J. Org. Chem.* **2001**, *66*, 5438. (m) Lim, S. H.; Ma, S.; Beak, P. *J. Org. Chem.* **2001**, *66*, 9056. (n) Feng, Z.-X.; Zhou, W.-S. *Tetrahedron Lett.* **2003**, *44*, 497. (o) Ayad, T.; Genisson, Y.; Baltas, M.; Gorrichon, L. *Chem. Commun.* **2003**, 582. (p) Sha, C.-K.; Chau, C.-M. *Tetrahedron Lett.* **2003**, *44*, 499–501. (q) Raghavan, S.; Sreekanth, T. *Tetrahedron: Asymmetry* **2004**, *15*, 565.

6. (a) Yoda, H.; Kawauchi, M.; Takabe, K. *Synlett* **1998**, 137. (b) Paolucci, P.; Mattioli, L. *J. Org. Chem.* **2001**, *66*, 4787. (c) Rabiczako, Z.; Urbanczyk-Lipkowska, Z.; Chmielewski, M. *Tetrahedron* **2002**, *58*, 1433. (d) Chandra, K. L.; Chandrasekar, M.; Singh, V. K. *J. Org. Chem.* **2002**, *67*, 4630.
7. (a) D-Glucose derived α,β-unsaturated ester was utilized by us in the synthesis of azasugars see: (a) Desai, V. N.; Saha, N. N.; Dhavale, D. D. *J. Chem. Soc., Chem. Commun.* **1999**, 1719. (b) Patil, N. T.; Tilekar, J. N.; Dhavale, D. D. *J. Org. Chem.* **2001**, *66*, 1065. (c) Chaudhari, V. D.; Ajish Kumar, K. S.; Dhavale, D. D. *Tetrahedron Lett.* **2004**, *45*, 8363. (d) Dhavale, D. D.; Matin, M. M.; Sharma, T.; Sabharwal, S. G. *Bioorg. Med. Chem.* **2003**, *11*, 3295. (e) Dhavale, D. D.; Markad, S. D.; Karanjule, N. S.; Prakashareddy, J. *J. Org. Chem.* **2004**, *69*, 4760. . For other references on azasugars see: Karanjule, N. S.; Markad, S. D.; Sharma, T.; Sabharwal, S. G.; Puranik, V. G.; Dhavale, D. D. *J. Org. Chem.* **2005**, *70*, 1356 and references cited therein.
8. This is an unpublished work from our laboratory. For details see: Chiron approaches to polyhydroxylated pyrrolidine, indolizidine, pyrrolizidine alkaloids and sphingolipids, Chaudhari, V. D. Ph. D. dissertation, University of Pune, October 2005.
9. Reaction of γ-lactone **6b** with DIBAL-H afforded corresponding lactol, which on the Wittig olefination led to the formation of inseparable diastereomeric mixture of unexpected conjugate addition adduct **X**.



X

10. For enantiomer of **3b** see: Paolucci, C.; Musiani, L.; Venturelli, F.; Fava, V. *Synthesis* **1997**, 1415.