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An unexpected high *erythro*-selection in the Grignard reaction with an *N*,*O*-acetal: a concise asymmetric synthesis of indolizidine alkaloid (−)-2-*epi*-lentiginosine

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ABSTRACT

Starting from commercially available lactone **10**, a concise and highly diastereoselective synthesis of (−)-(1*S*,2*R*,8a*S*)-2-*epi*-lentiginosine (**2**) is described. The synthesis featured an unexpected highly *erythro*-selective reaction of Grignard reagent **7** with the protected *N*,*O*-acetal **8**. The stereochemical outcome of this reaction is contrary to the known results involving the reactions with *O*-benzyl protected aminofuranosides and aminoglycosides. Thus, this method constitutes an extension of the *threo*-diastereoselective C–C bond formation methodology.

1. Introduction

5-Substituted 3,4-*cis*-dihydroxypyrrolidine constitutes the key structural feature of a number of azasugars that exhibit a broad spectrum of bioactivities such as inhibition of glucosidases,[1] and are promising for the development of therapeutic agents against cancer, diabetes, or viral infections.[2] Among them, (+)-lentiginosine (**1**, Fig. 1) and its C-2 epimer (−)-2-*epi*-lentiginosine (**2**) were isolated from the leaves of *Astragalus lentiginosus*.[3] (+)-Lentiginosine **1** was found to be a powerful selective inhibitor of amyloglucosidase.[4] The first isolation of (−)-2-*epi*-lentiginosine was from the fungus *Rhizoctonia leguminicola*.[5a] The former has been shown to be a late intermediate in the biosynthesis of swainsonine in *R. leguminicola*.[5b] (−)-2-*epi*-Lentiginosine has shown to be a potent inhibitor of α-mannosidase with an IC_{50} value of 4.6 μM.[6] (−)-Swainsonine (**3**) is a well-known alkaloid first isolated from the fungus *R. leguminicola*,[5a,7] which exhibited α-mannosidase inhibitory properties and other promising biological acitivities.[8] A number of total syntheses of swainsonine (**3**) have been reported.[9] (−)-Steviamine (**4**), recently isolated from *Stevia rebaudiana* (Asteraceae) leaves,[10] was found to be a weak inhibitor of an α-galactosaminidase (GalNAcase).[11]

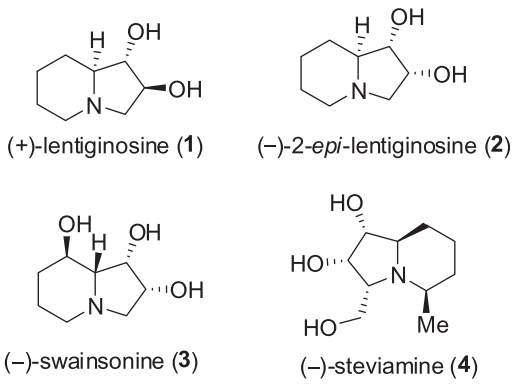

Fig. 1. Structures of some naturally occurring polyhydroxylated indolizidines.

Due to their remarkable bioactivities, the synthesis of lentiginosine and its stereoisomers has attracted much attention, which has accumulated in a number of enantioselective synthetic approaches[12] and some individual syntheses of (−)-2-*epi*-lentiginosine.[13] In connection with a program aiming at the asymmetric synthesis of bioactive alkaloids using malic acid[14] and tartaric acid[15] as the chiral sources, we were engaged in the synthesis of 3,4-*cis*-dihydroxypyrrolidine-containing azasugars starting from D-erythronolactone (**10**), and the results of this study are reported herein, which include an *erythro* (*anti*)-selective Grignard addition of reagent **7** to the *N*,*O*-acetal **8** and a concise synthesis of (−)-2-*epi*-lentiginosine **2**.

2. Results and discussion

Our initial target was **2a**, a stereoisomer of (−)-2-*epi*-lentiginosine, and the retrosynthetic analysis is depicted in Scheme 1. The key feature of the plan resided in the use of commercially available chiron **10** as the starting material and the *threo*(*syn*)-diastereoselective addition[16] of Grignard reagent **7** to *N*,*O*-acetal **8** as the key step to establish the third chiral center (C8a).

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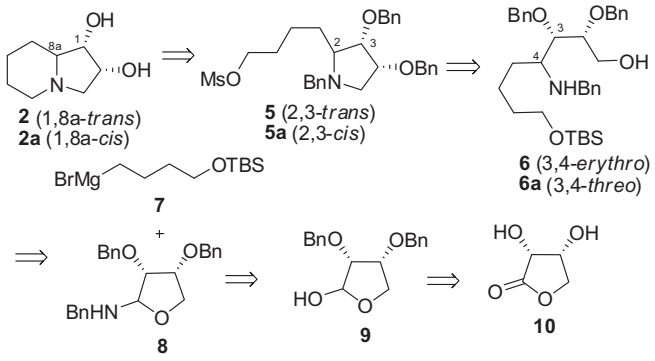
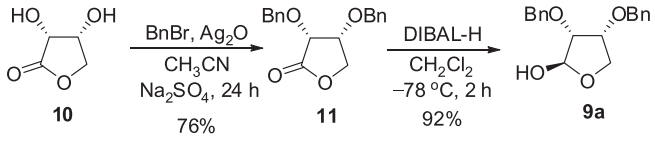


Scheme 1. Retrosynthetic analysis of 3,4-*cis*-dihydroxypyrrolidine-containing indolizidines **2**/**2a**.

As described in Scheme 2, Ag_2O-catalyzed dibenzylation (BnBr, MeCN)[18] of D-erythronolactone (**10**), which is commercially available or easily prepared from D-isoascorbic acid,[17] gave the protected lactone **11** in 76% yield. Compound **11** was treated with DIBAL-H at −78 °C in CH_2Cl_2 to afford the β-D-erythrofuranose (2,3-*trans* hemiacetal) **9a** as the only isolable diastereomer in 92% yield. The 2,3-*trans* relationship was determined by NOESY experiments (Fig. 2). The observed high diastereoselectivity is attributable to a chelation-directed *cis* delivery of a hydride to the carbonyl group of **11** to provide *trans*-diastereomer **9a**.



Scheme 2. Preparation of the β-D-erythrofuranose **9a**.

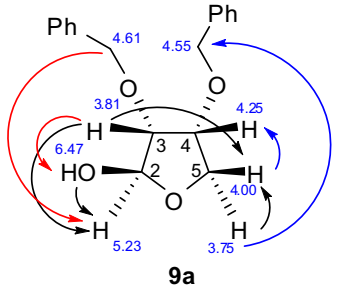
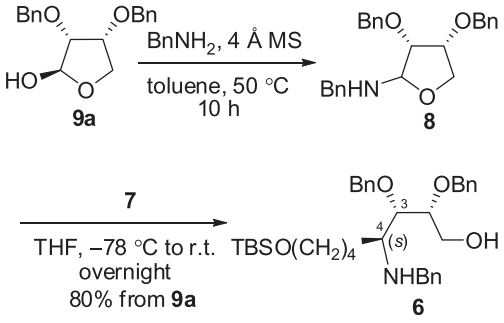


Fig. 2. Observed correlations (in part) in the NOESY of compound **9a**.

The addition of organometallic reagents to *N*,*O*-acetals has been shown to be an efficient and versatile method for the synthesis of azasugars[16a,16d] and functionalized pyrrolidines.[19] The reactions are considered to pass through imine or iminium intermediates.[20] In this context, nucleophilic addition with α-*O*-benzyl protected *N*,*O*-acetals has been shown to be *threo*-selective.[16,21] Only 2,3-*O*-isopropylidene protected derivatives gave major 1,2-*erythro*-diastereomers.[22] Our interest in the chemistry of *N*,*O*- and *N*,*S*-acetals[15,23] led us to examine the addition of Grignard reagent to *N*,*O*-acetal derivative **8**. Thus, *N*,*O*-acetal **8** was prepared from β-D-erythrofuranose (**9a**) by reaction with benzylamine in the presence of 4 Å molecular sieve. The resultant diastereomeric mixture **8** was used in the subsequent step without further separation. After removal of the solvent under reduced pressure, the residual *N*,*O*-acetal **8** was dissolved in THF, and treated with an excess of Grignard reagent $BrMg(CH_2)_4OTBS$[24] (**7**) (−78 °C to rt, overnight) to produce a single diastereomer **6** (yield: 80% over two steps) as indicated in the ^1H NMR spectrum of the crude product (Scheme 3). To our surprise, the expected *threo*-diastereomer (**6a**) was not observed.[16] In the consideration of this fact, the adduct **6** was then converted into known natural product (−)-2-*epi*-lentiginosine (**2**) (vide infra). Thus, the addition of Grignard reagent **7** with *N*,*O*-acetal **8** turned out to be *erythro*-selective.



Scheme 3. Synthesis of amino alcohol **6**.

The observed stereochemical outcome of the Grignard addition with *N*,*O*-acetal **8** is in contrast with the reported cases using benzyl as the hydroxyls protecting group,[16,21] where the reactions of all furanosylamines (derived from protected D-arabinose, D-ribose or L-xylose, and primary or secondary amines) and D-glucopyranosylamines produced uniformly *threo*-adducts as the major diastereomers. For a typical example, aldose **12** was transformed into the corresponding glycosylamine **13**, which is then reacted with Grignard reagent to give *threo*-adduct **14** via a α-chelation transition state[16f,16g] (Fig. 3a). Moreover, the diastereoselectivity of the addition reaction depends on the protecting group of 1,2-diol. Further results from a very recent report by Behr and co-workers[22] led them to conclude that, in the ribose series, the Grignard reagent additions with 2,3-*O*-isopropylidene protected derivatives mainly give rise to 3,4-*erythro*-diastereomers (Fig. 3b). Notably, the reaction of organometallic reagents with furanoses and pyranoses derived open-chain nitrone–hydroxylamine mixtures gave a mixture of *threo*/*erythro*-diastereoisomers, and the good to high 1,2-*erythro*-diastereoselectivities were observed depending on the carbon stereocenter adjacent to the nitrone group.[25]

In the case of the *N*,*O*-acetal **8**, quoting the α-chelation control model[16f] fails to interpret the formation of the *erythro*-adduct. Instead, a postulated seven-membered chelating structure[26] (**18**) was proposed. Grignard reagent would approach from the *Si*-face of the iminium ion **18** to avoid steric hindrance with the *O*-benzyl groups, which results in the formation of the *erythro*-diastereomer **6** (Fig. 4). In addition, the *erythro*-selectivity in this Grignard reaction seems to be ascribed to the transition state involving either a Felkin–Anh or Cornforth model,[27] although we prefer the seven-membered structure for the case of *N*,*O*-acetal **8**.

The formation of seven-membered chelating structure afforded a reaction with an iminium ion species suitable for a nucleophilic addition. That can explain why an excess of Grignard reagent and much longer reaction time (warmed up to rt and stirred overnight for **8**; 10 min to 1 h for **12**[16c,16h] in Fig. 3a) are required for the completion of the reaction. It is worthy of mentioning that the reaction of the dianion of 4-PSBA (4-(phenylsulfonyl)butanic acid) with a *N*,*O*-acetal derived from malic acid produced exclusively the *threo*-diastereomer in only 29% yield.[28]

With these valuable results in hand, we reoriented our target, and switched to the synthesis of 2-*epi*-lentiginosine (**2**) (Scheme 4). Intramolecular cyclization of amino alcohol **6** using Appel reaction[29] with $PPh_3/CBr_4/Et_3N$ system in CH_2Cl_2 for 2 h yielded 2-substituted pyrrolidine **19** in 95% yield. Desilylation of **19** with TBAF in THF gave alcohol **20** in 90% yield. Treatment of alcohol **20** with MsCl (DMAP, Et_3N, rt) afforded mesylate **5**, which, without

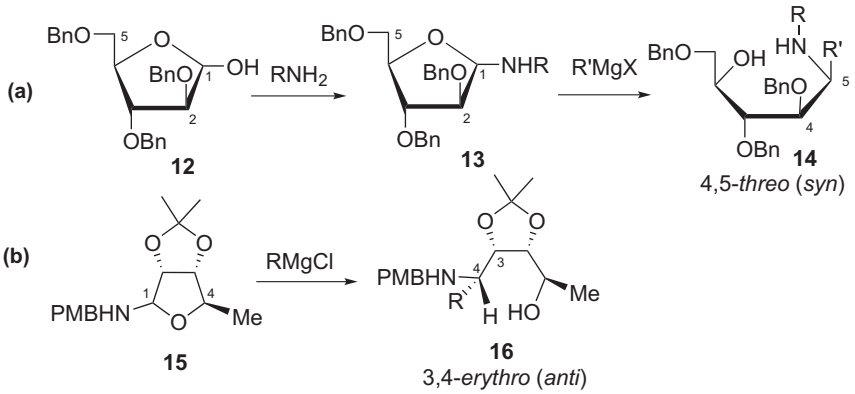


Fig. 3. Plausible mechanism for the formation of 4,5-*threo*- and 3,4-*erythro*-diastereomers **14**/**16** via Grignard addition.

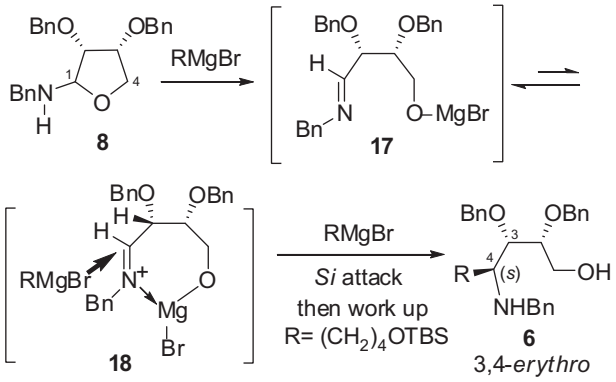


Fig. 4. Proposed mechanism for the formation of the *erythro*-diastereomer **6**.

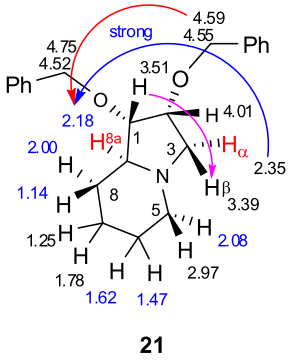
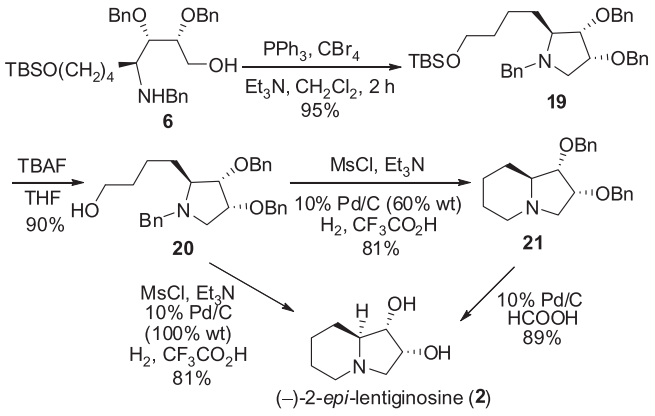


Fig. 5. Observed correlations (in part) in the NOESY of indolizidine **21**.

purification, was subjected to catalytic hydrogenolysis conditions [10% Pd/C (60% wt), H_2, 5 atm, 5% CF_3CO_2H in MeOH, rt] to give the protected 2-*epi*-lentiginosine **21** in 81% yield from **20**.



Scheme 4. Synthesis of (−)-2-*epi*-lentiginosine (**2**).

At this stage, NOESY experiments were undertaken on indolizidine **21** (Fig. 5). The strong NOE correlation between H-8*a* (δ_H 2.18) and H-3α (δ_H 2.35) indicated that C-1 and C-8a are in a *trans* relationship. Thus, the stereochemistry at C-4 of compound **6** was deduced to be *S*.

Finally, protected 2-*epi*-lentiginosine **21** was converted into (−)-2-*epi*-lentiginosine (**2**) in 89% yield under transfer hydrogenation reaction conditions (10% Pd/C, CH_3OH, HCO_2H). Alternatively, direct conversion of compound **20** to (−)-2-*epi*-lentiginosine (**2**) was achieved by increasing the amount of 10% Pd/C to 100% (weight based on **20**) in the catalytic hydrogenolysis conditions, which directly produced (−)-2-*epi*-lentiginosine (**2**) in 81%. The physical {$[\alpha]_D^{20}$ −33.6 (*c* 0.25, H_2O); lit.[6] $[\alpha]_D^{20}$ −31.7 (*c* 0.25, H_2O)} and spectral data of the synthetic (−)-2-*epi*-lentiginosine (**2**) are identical with those reported for the natural product.[6]

3. Conclusions

In summary, a six-step stereoselective synthesis of (−)-2-*epi*-lentiginosine (**2**) from commercially available chiron D-erythronolactone (**10**) has been achieved with an overall yield of 39%. The synthesis features an unexpected *erythro*-diastereoselective addition reaction and two highly efficient cyclization reactions to construct the pyrrolidine and piperidine moieties, respectively. This unambiguous asymmetric synthesis of (−)-2-*epi*-lentiginosine revealed that the addition of Grignard reagent **7** with the protected *N*,*O*-acetal **8** is *erythro*-stereoselective. The observed highly diastereoselective addition reaction of a Grignard reagent with the *O*,*O*′-dibenzyl group protected *N*,*O*-acetal **8** extended the scope of the powerful *threo*-diastereoselective C–C bond formation methodology, which would be useful for the synthesis of azasugars and others *N*-containing heterocycles.

4. Experimental

4.1. General

Melting points were determined on a X-4 digital micro melting point apparatus and were uncorrected. Infrared spectra were measured with a Nicolet Avatar 330 FT-IR spectrometer using film

KBr pellet technique. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Bruker AV400 with tetramethylsilane as an internal standard. Chemical shifts are expressed in δ (ppm) units downfield from TMS. Mass spectra were recorded by a Bruker Dalton Esquire 3000 plus LC–MS apparatus. Optical rotations were measured with a Perkin–Elmer 341 automatic polarimeter. THF was distilled over sodium, and dichloromethane was distilled over P_2O_5 prior to use. Flash column chromatography was carried out on silica gel (300–400 mesh) with eluent ethyl acetate/petroleum ether (60–90 °C) (EtOAc/PE).

*4.1.1. (2R,3R)-2,3-Bis(benzyloxy)-4-hydroxybutanoic acid 1,4-lactone (**11**).* To a solution of D-erythronolactone (**10**)[17] (2.51 g, 21.2 mmol) in anhydrous acetonitrile (125 mL) at room temperature was added benzyl bromide (15.1 mL, 127 mmol). Anhydrous sodium sulfate (15.0 g, 106 mmol) was then added and the resulting mixture was stirred for 5 min. Silver (I) oxide (9.83 g, 42.4 mmol) was added in three portions over 5 min. The mixture was vigorously stirred at room temperature for 12 h in the dark, and a second portion of silver (I) oxide (9.83 g, 42.4 mmol) was added. After stirring for another 12 h, the reaction mixture was filtered through a plug of Celite to remove the solids, washed with acetonitrile (3×60 mL). The combined organic phases were concentrated, and the residue was purified by flash column chromatography on silica gel (EtOAc/PE=1:4) to yield compound **11** (4.81 g, yield: 76%) as a white solid. Mp 90–93 °C (hexane) [lit.[30] mp 89–90 °C (hexane)]. $[\alpha]_D^{20}$ +6.0 (*c* 0.5, $CHCl_3$) {lit.[30] $[\alpha]_D^{20}$ +5.9 (*c* 0.5, $CHCl_3$)}; IR (film): 3033, 1774, 1167 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.15–4.22 (m, 3H), 4.33 (dd, *J*=1.0, 10.3 Hz, 1H), 4.64 (d, *J*=12.0 Hz, 1H, OC*H*$_2$Ph), 4.71 (d, *J*=12.0 Hz, 1H, OC*H*$_2$Ph), 4.81 (d, *J*=12.1 Hz, 1H, OC*H*$_2$Ph), 4.93 (d, *J*=12.1 Hz, 1H, OC*H*$_2$Ph), 7.28–7.38 (m, 10H, Ar-*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 69.5, 71.9, 72.4, 73.9, 74.2, 128.5, 128.4, 128.1, 128.0, 127.9, 127.8, 136.6, 137.1, 173.2; MS (ESI): *m*/*z* 321 (M+Na$^+$, 100).

*4.1.2. (2R,3R,4R)-3,4-Bis(benzyloxy)-tetrahydrofuran-2-ol (**9a**).* To a stirring solution of compound **11** (1.49 g, 5.0 mmol) in CH_2Cl_2 (65 mL) was added dropwise a 1.0 M THF solution of DIBAL-H (6.5 mL, 6.5 mmol) at −78 °C. The solution was stirred at −78 °C for 2 h. Then MeOH (2 mL) was added and the solution was stirred at room temperature overnight. EtOAc (7 mL) and saturated $NaHCO_3$ (3.5 mL) were added, and the mixture was continued to be stirred for another 6 h. After addition of anhydrous Na_2SO_4 (2.0 g), the mixture was filtered and the filtrate was concentrated. The residue was purified by chromatography on silica gel (EtOAc/PE=1:3) to afford compound **9a** (1.44 g, yield: 92%) as a colorless oil. $[\alpha]_D^{20}$ −9.6 (*c* 1.0, $CHCl_3$); IR (film): 3415, 3063, 3031, 2883, 1454, 1141, 1080 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 3.73 (dd, *J*=4.9, 9.0 Hz, 1H, OC*H*$_2$CHOBn), 3.79 (dd, *J*=2.5, 4.6 Hz, 1H, CHC*H*OBn), 3.98 (dd, *J*=5.6, 9.0 Hz, 1H, OC*H*$_2$-CHOBn), 4.23 (ddd, *J*=4.6, 4.9, 5.6 Hz, 1H, CH$_2$C*H*OBn), 4.56 (d, *J*=9.8 Hz, 1H, OC*H*$_2$Ph), 4.57 (d, *J*=10.5 Hz, 1H, OC*H*$_2$Ph), 4.59 (d, *J*=10.5 Hz, 1H, OC*H*$_2$Ph), 4.62 (d, *J*=9.8 Hz, 1H, OC*H*$_2$Ph), 5.20 (dd, *J*=2.5, 5.2 Hz, 1H, C*H*OH), 6.45 (d, *J*=5.2 Hz, 1H, O*H*), 7.25–7.36 (m, 10H, Ar-*H*); ^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ 68.8, 71.5, 71.7, 77.3, 82.6, 100.2, 127.9 (2C), 128.1 (2C), 128.6 (2C), 138.8 (2C); MS (ESI): *m*/*z* 323 (M+Na$^+$, 100). Anal. Calcd for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 71.78; H, 6.64.

*4.1.3. (2R,3S,4S)-4-(Benzylamino)-2,3-bis(benzyloxy)-8-(tert-butyldimethylsilyloxy)octan-1-ol (**6**).* A solution of compound **9a** (700 mg, 2.3 mmol) in anhydrous toluene (10 mL) was added successively 4 Å molecular sieve (70 mg) and $BnNH_2$ (320 μL, 2.8 mmol) at room temperature with stirring under nitrogen. The mixture was stirred at 50 °C for 10 h. After cooling to room temperature, the mixture was filtered and the solvent was removed under reduced pressure to afford the crude product **8** as a pale yellow oil. The crude product **8**, without further purification, was dissolved in 35 mL of THF and a 0.4 M THF solution of $BrMg(CH_2)_4OTBS$[24] (35 mL, 14 mmol) was added dropwise at −78 °C. The mixture was allowed to warm slowly to room temperature and stirred overnight. The reaction was quenched with a saturated NH_4Cl aqueous solution (25 mL), and the aqueous layer was extracted with CH_2Cl_2 (5×20 mL). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (EtOAc/PE=1:5) to provide compound **6** (1.07 g, yield: 80%) as a colorless oil. $[\alpha]_D^{20}$ +1.4 (*c* 1.0, $CHCl_3$); IR (film): 3302, 3063, 3029, 2930, 1253, 1098, 1029 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 6H, OSi(C*H*$_3$)$_2$), 0.89 (s, 9H, OSiC(C*H*$_3$)$_3$), 1.08–1.56 (m, 6H, CH(C*H*$_2$)$_3$CH$_2$OSi), 2.86–2.91 (m, 1H, C*H*NHBn), 3.51 (t, *J*=6.4 Hz, 2H, C*H*$_2$OH), 3.60–3.68 (m, 2H, C*H*$_2$OTBS), 3.68 (d, *J*=12.9 Hz, 1H, PhC*H*$_2$N), 3.77 (dd, *J*=2.1, 4.3 Hz, 1H, CHC*H*OBn), 3.82 (d, *J*=12.9 Hz, 1H, PhC*H*$_2$N), 3.93 (dd, *J*=8.0, 11.0 Hz, 1H, CH$_2$C*H*OBn), 4.51 (d, *J*=12.0 Hz, 1H, PhC*H*$_2$O), 4.56 (d, *J*=11.8 Hz, 1H, PhC*H*$_2$O), 4.65 (d, *J*=12.0 Hz, 1H, PhC*H*$_2$O), 4.76 (d, *J*=11.8 Hz, 1H, PhC*H*$_2$O), 7.22–7.32 (m, 15H, Ar-*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.3 (2C), 18.3, 22.1, 26.0 (3C), 29.8, 32.9, 51.7, 57.7, 58.7, 62.7, 71.6, 73.3, 79.0, 81.4, 127.2, 127.6 (2C), 127.7, 127.8, 128.2, 128.3 (2C), 128.5, 138.4, 138.6, 139.3; MS (ESI): *m*/*z* 578 (M+H$^+$, 100). Anal. Calcd for $C_{35}H_{51}NO_4Si$: C, 72.75; H, 8.90. Found: C, 73.01; H, 8.63.

*4.1.4. (2S,3S,4R)-1-Benzyl-3,4-bis(benzyloxy)-2-(4-(tert-butyldimethylsilyloxy)butyl) pyrrolidine (**19**).* To a solution of the protected amino alcohol **6** (130 mg, 0.22 mmol) in anhydrous CH_2Cl_2 (2 mL) at 0 °C were added Et_3N (1.2 mL, 8.8 mmol), PPh_3 (474 mg, 1.8 mmol), and CBr_4 (596 mg, 1.8 mmol). After stirring at 0 °C for 2 h, the mixture was diluted with water (10 mL). The aqueous phase was separated and extracted with CH_2Cl_2 (2×20 mL). The combined organic phases were washed with brine, dried over anhydrous K_2CO_3, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (EtOAc/PE=1:5) to give compound **19** (117 mg, yield: 95%) as a pale yellow oil. $[\alpha]_D^{20}$ +12.8 (*c* 1.0, $CHCl_3$); IR (film): 3063, 3030, 2926, 2856, 1100, 1028 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 6H, OSi(C*H*$_3$)$_2$), 0.89 (s, 9H, OSiC(C*H*$_3$)$_3$), 1.24–1.58 (m, 6H, CH(C*H*$_2$)$_3$CH$_2$OSi), 2.56 (dd, *J*=7.5, 9.2 Hz, 1H, CHC*H*$_2$NBn), 2.76–2.81 (m, 1H, CHC*H*NBn), 3.09 (dd, *J*=5.8, 9.2 Hz, 1H, CHC*H*$_2$NBn), 3.40 (d, *J*=12.9 Hz, 1H, PhC*H*$_2$N), 3.56 (t, *J*=6.4 Hz, 2H, C*H*$_2$OH), 3.65 (dd, *J*=4.9, 4.9 Hz, 1H, CHC*H*OBn), 3.91 (ddd, *J*=4.9, 5.8, 7.5 Hz, 1H, CH$_2$C*H*OBn), 3.95 (d, *J*=12.9 Hz, 1H, PhC*H*$_2$N), 4.48 (d, *J*=12.0 Hz, 1H, PhC*H*$_2$O), 4.54 (2d superposed, each *J*=12.1 Hz, 2H, PhC*H*$_2$O), 4.69 (d, *J*=12.0 Hz, 1H, PhC*H*$_2$O), 7.22–7.36 (m, 15H, Ar-*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.3 (2C), 18.3, 21.7, 25.9 (3C), 32.6, 33.1, 56.0, 59.5, 63.0, 68.0, 71.5, 71.7, 76.3, 81.2, 126.8, 127.5 (2C), 127.6, 127.9, 128.1, 128.2 (2C), 128.8, 138.3, 138.5, 139.3; MS (ESI): *m*/*z* 560 (M+H$^+$, 100). Anal. Calcd for $C_{35}H_{49}NO_3Si$: C, 75.09; H, 8.82. Found: C, 75.34; H, 8.41.

*4.1.5. 4-[(2S,3S,4R)-1-Benzyl-3,4-bis(benzyloxy)pyrrolidin-2-yl]butan-1-ol (**20**).* To a solution of compound **19** (260 mg, 0.5 mmol) in THF (2.0 mL) was added dropwise a 1.0 M THF solution of TBAF (1.5 mL, 1.5 mmol) under nitrogen. The mixture was stirred at room temperature overnight. Then H_2O (5.0 mL) was added, and the aqueous layer was extracted with $CHCl_3$ (5×5 mL). The combined organic phases were washed with brine and the solvent was removed. The residue was purified by flash column chromatography on silica gel (EtOAc/PE=1:3) to give compound **20** (200 mg, yield: 90%) as a pale yellow oil. $[\alpha]_D^{20}$ +2.0 (*c* 1.0, $CHCl_3$); IR (film): 3416, 3061, 3028, 2930, 2861, 1453, 1364, 1208, 1140 cm^{-1}; ^{1}H NMR

(400 MHz, $CDCl_3$) δ 1.26–1.58 (m, 6H, CH(CH_2)$_3$$CH_2$OH), 2.57 (dd, J=7.2, 9.5 Hz, 1H, CHCH_2NBn), 2.78–2.82 (m, 1H, CHCHNBn), 3.11 (dd, J=5.7, 9.5 Hz, 1H, CHCH_2NBn), 3.42 (d, J=12.9 Hz, 1H, PhCH_2N), 3.56 (t, J=6.4 Hz, 2H, CH_2OH), 3.69 (dd, J=5.1, 5.1 Hz, 1H, CHCHOBn), 3.92 (ddd, J=5.1, 5.7, 7.2 Hz, 1H, CH_2CHOBn), 3.95 (d, J=12.9 Hz, 1H, PhCH_2N), 4.48 (d, J=12.0 Hz, 1H, PhCH_2O), 4.53 (d, J=11.8 Hz, 2H, PhCH_2O), 4.56 (d, J=11.8 Hz, 1H, PhCH_2O), 4.71 (d, J=12.0 Hz, 1H, PhCH_2O), 7.21–7.33 (m, 15H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 32.4, 33.0, 56.1, 59.6, 62.8, 67.9, 71.7, 71.9, 76.3, 81.4, 126.9, 127.6 (2C), 127.7, 128.0, 128.2, 128.3 (2C), 128.8, 138.4, 138.6, 139.3; MS (ESI): m/z 446 ($M+H^+$, 100). Anal. Calcd for $C_{29}H_{35}NO_3$: C, 78.17; H, 7.92. Found: C, 77.79; H, 8.10.

*4.1.6. (1S,2R,8aS)-1,2-Bis(benzyloxy)-octahydroindolizine (**21**).* To a stirring solution of compound **20** (500 mg, 1.12 mmol) in CH_2Cl_2 (10 mL) at 0 °C were added Et_3N (0.20 mL, 1.34 mmol) and methylsulfonyl chloride (0.10 mL, 1.34 mmol). The mixture was stirred for 3 h. To the resulting mixture was added 10 mL of saturated $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2 (2×10 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to give crude product, which was dissolved in a solution of 5% CF_3CO_2H in MeOH (10 mL). To the resulting solution was added 10% Pd/C (300 mg). The reaction mixture was stirred under 5 atm of H_2 at room temperature for 24 h. The catalyst was filtered off through Celite, and the solvent was removed in vacuo. The residue was purified by flash column chromatography (EtOAc/PE=1/6) to give compound **21** (306 mg, yield: 81%) as a white solid. Mp 43–46 °C (EtOAc/PE); $[\alpha]_D^{20}$ −60.0 (c 0.95, $CHCl_3$); IR (film): 3029, 2932, 2853, 1453, 1321, 1147 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.15–1.26 (m, 2H, H-7, H-8β), 1.41–1.48 (m, 1H, H-6), 1.60–1.63 (m, 1H, H-6), 1.75–1.78 (m, 1H, H-7), 1.98–2.18 (m, 1H, H-8α), 2.04–2.10 (m, 1H, H-5α), 2.15–2.20 (m, 1H, H-8a), 2.35 (dd, J=5.5, 9.6 Hz, 1H, H-3α), 2.94–2.98 (m, 1H, H-5β), 3.39 (dd, J=6.6, 9.6 Hz, 1H, H-3β), 3.51 (dd, J=7.1, 8.4 Hz, 1H, H-1), 4.01 (ddd, J=5.5, 6.6, 7.1 Hz, 1H, H-2), 4.52 (d, J=11.8 Hz, 1H, OCH_2Ph), 4.55 (d, J=11.8 Hz, 1H, OCH_2Ph), 4.59 (d, J=11.8 Hz, 1H, OCH_2Ph), 4.75 (d, J=11.8 Hz, 1H, OCH_2Ph), 7.25–7.36 (m, 10H, Ar-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.8, 25.4, 29.4, 53.1, 60.3, 66.2, 71.9, 72.5, 73.7, 82.3, 127.5, 127.6, 127.9, 128.2 (2C), 128.3, 138.3, 138.4; MS (ESI): m/z 338 ($M+H^+$, 100). Anal. Calcd for $C_{22}H_{27}NO_2$: C, 78.30; H, 8.06. Found: C, 77.91; H, 8.10.

*4.1.7. (−)-2-epi-Lentiginosine (**2**).* To a stirring solution of compound **20** (500 mg, 1.12 mmol) in CH_2Cl_2 (10 mL) at 0 °C were added successively Et_3N (0.20 mL, 1.34 mmol) and methylsulfonyl chloride (0.10 mL, 1.34 mmol). The mixture was stirred for 3 h. To the resulting mixture was added 10 mL of saturated $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2 (2×10 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to give the crude product **5**, which was dissolved in a solution of 5% CF_3CO_2H in MeOH (10 mL). To the resulting solution was added 10% Pd/C (500 mg). The reaction mixture was stirred under 5 atm of H_2 at room temperature for 24 h. The catalyst was filtered off through Celite and the solvent was removed in vacuo. The residue was dissolved in deionized water (10 mL) and passed through a column of ion-exchange resin (Dowex 1×8-100, OH form) eluting with deionized water (15 mL). The eluent was concentrated in vacuo to give (−)-2-*epi*-lentiginosine (**2**) as a colorless oil (141 mg, yield: 81%). $[\alpha]_D^{20}$ −33.6 (c 0.25, H_2O) {lit.[6] $[\alpha]_D^{20}$ −31.7 (c 0.25, H_2O)}; IR (film): 3361, 2933, 1144, 1061 cm^{-1}; ^{1}H NMR (400 MHz, D_2O) δ 1.14–1.50 (m, 3H, H-8, H-7, H-6), 1.64–1.70 (m, 1H, H-6), 1.82–1.85 (m, 1H, H-7), 1.97–2.01 (m, 1H, H-8), 2.02–2.07 (m, 1H, H-5α), 2.08–2.15 (m, 1H, H-8a), 2.16 (dd, J=5.2, 10.1 Hz, 1H, H-3α), 2.96–3.00 (m, 1H, H-5β), 3.42 (dd, J=6.8, 10.1 Hz, 1H, H-3β), 3.60 (dd, J=7.0, 8.9 Hz, 1H, H-1), 4.18 (ddd, J=5.2, 6.8, 7.0 Hz, 1H, H-2); ^{13}C NMR (100 MHz, D_2O) δ 25.9, 27.2, 30.7, 55.2, 63.1, 69.2, 69.7, 77.4; MS (ESI): m/z 158 ($M+H^+$, 100).

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Supplementary data

Supplementary data (^{1}H and ^{13}C NMR spectra of compounds **2**, **6**, **9a**, **11**, **19**, **20**, and **21**; NOESY spectra of compounds **9a** and **19**). Supplementary data related to this article can be found online at doi:10.1016/j.tet.2011.12.063.

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