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Novel and stereoselective synthesis of (+)-lentiginosine ☆

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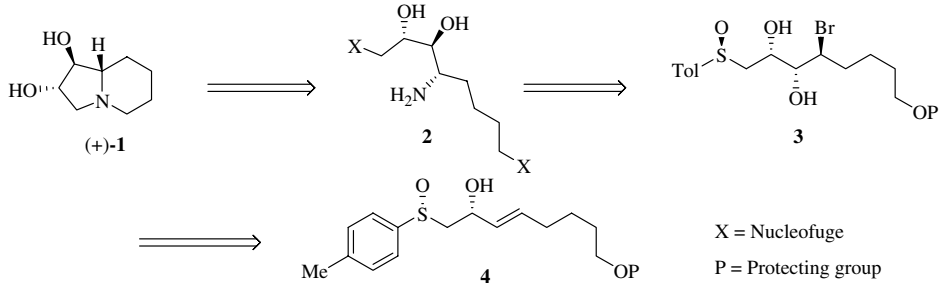
Abstract—The stereoselective synthesis of (+)-lentiginosine, a potent amyloglucosidase inhibitor, is disclosed exploiting the potential of the sulfinyl moiety as an internal nucleophile to regio- and stereoselectively functionalize an olefin.

1. Introduction

Lentiginosine **1**, a dihydroxy indolizidine alkaloid, was first isolated in 1990 from the leaves of *Astragalus lentiginosus*.[1] Lentiginosine is a strong and selective inhibitor of amyloglucosidase, an enzyme that hydrolyses 1,4- and 1,6-α-glucosidic linkages. The structure of lentiginosine was deduced from its NMR spectrum and was assigned as (1*S*,2*S*,8a*S*) absolute configuration based on biosynthetic considerations. The isolated compound was reported to be weakly leavorotatory $\{[\alpha]_D = -3.3$ in MeOH$\}$. Various syntheses[2] of all (*S*)-lentiginosine, however, have led to samples with small positive rotations. Based on the biological activity data[2g] of both (+)- and (−)-lentiginosine, it has been argued that the natural product is dextrorotatory and the negative rotation initially reported is due to impurities present in the natural product, which is evident from the published ^{1}H NMR spectrum.[1] Lentiginosine has attracted the attention of synthetic chemists as a popular synthetic target due to its biological activity. Despite significant advances in asymmetric synthesis, the vast majority of the reported enantioselective syntheses of lentiginosine rely on chiral pool starting materials. We recently disclosed a methodology[3] wherein the sulfinyl moiety was utilized as an intramolecular nucleophile to functionalize β-hydroxy-γ,δ-unsaturated sulfoxides, regio- and stereoselectively. As an extension of this methodology,[4] we herein report a novel and stereoselective synthesis of (+)-lentiginosine.

2. Results and discussion

By retrosynthetic analysis (Scheme 1), (+)-**1** can be derived from the retron **2**, which in turn can be obtained from the bromohydrin **3**. The bromohydrin **3** can be traced back to the unsaturated sulfoxide **4**.



Scheme 1.

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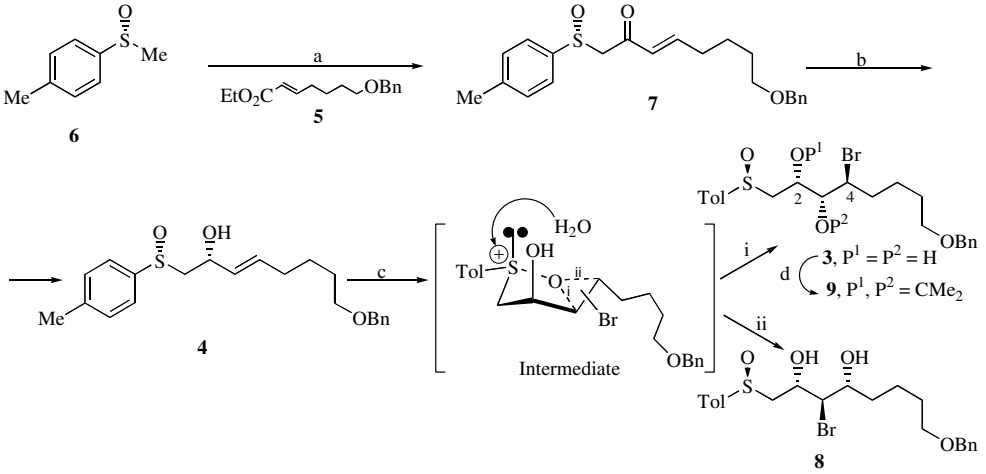


Scheme 2. Reaction conditions: (a) LDA, THF, −78 °C, 70%; (b) DIBAL, $ZnCl_2$, THF, −78 °C, 91%; (c) NBS, H_2O, toluene, rt, 85%; (d) 2,2-DMP, acetone, CSA (cat.), rt, 87%.

The unsaturated sulfoxide **4**, (P = Bn) was readily elaborated from the unsaturated ester **5**[5] by condensation with the lithium anion of (*R*)-methyl *p*-tolyl sulfoxide[6] **6** followed by a diastereoselective reduction[7] (dr > 95:<5) of the resulting β-ketosulfoxide **7** (Scheme 2). At the outset it was not clear if the bromohydration of **4** would afford 1,2-diol **3** via a 5-*exo* nucleophilic attack (pathway (i), Scheme 2) or 1,3-diol **8** via a 6-*endo* nucleophilic attack (pathway (ii), Scheme 2). The electron withdrawing inductive effect of the C2 hydroxy group and the electron releasing inductive effect of the alkyl chain at C4 was expected to promote the 6-*endo* nucleophilic attack by the sulfinyl group.

Treatment of **4** with *N*-bromosuccinimide in toluene in the presence of water afforded the bromohydrin **3**, via 5-*exo* nucleophilic attack. The regio- and stereochemistry of **3** was ascertained by its transformation into the acetonide **9**, whose ^{13}C NMR revealed[8] signals for the methyl group at δ 27.1, 27.4 and for the acetal carbon at δ 110. An overall *trans*-addition[9] of the electrophile and nucleophile across the double bond would predicate an *anti*-orientation of the C3 hydroxy and C4 bromine atom. Treatment of **3** with anhydrous potassium carbonate in methanol afforded the epoxide **10**. Further treatment of the epoxide **10** with sodium azide following Sharpless' protocol[10] afforded the azidodiol **11** as the only isolated product. Protection of the diol as its acetonide **12**,[11] and its subsequent treatment under Pummerer reaction conditions[12] afforded the intermediate **13**. One pot hydrolysis and reduction of the intermediate **13** afforded the alcohol **14**. Treatment of **14** with $Pd(OH)_2$/C under a hydrogen atmosphere in the presence of di-*tert*-butyl dicarbonate yielded the diol carbamate **15** by sequential reduction, carbamate formation and hydrogenolysis (Scheme 3). Further elaboration of **15** to the retron **2** required conversion of the diol into suitable leaving groups and deprotection of the acetonide. Thus, treatment of **15** with *p*-toluenesulfonyl chloride in the presence of triethylamine afforded the ditosyl derivative **16**, which upon further treatment with TFA/H_2O (95:5) overnight afforded the ammonium salt **17**, which without isolation was subjected to treatment with excess triethylamine in dichloromethane to afford (+)-lentiginosine after purification by passing through a Dowex column. The physical characteristics of (+)-lentiginosine were in excellent agreement to those reported in the literature.[2e]

3. Conclusion

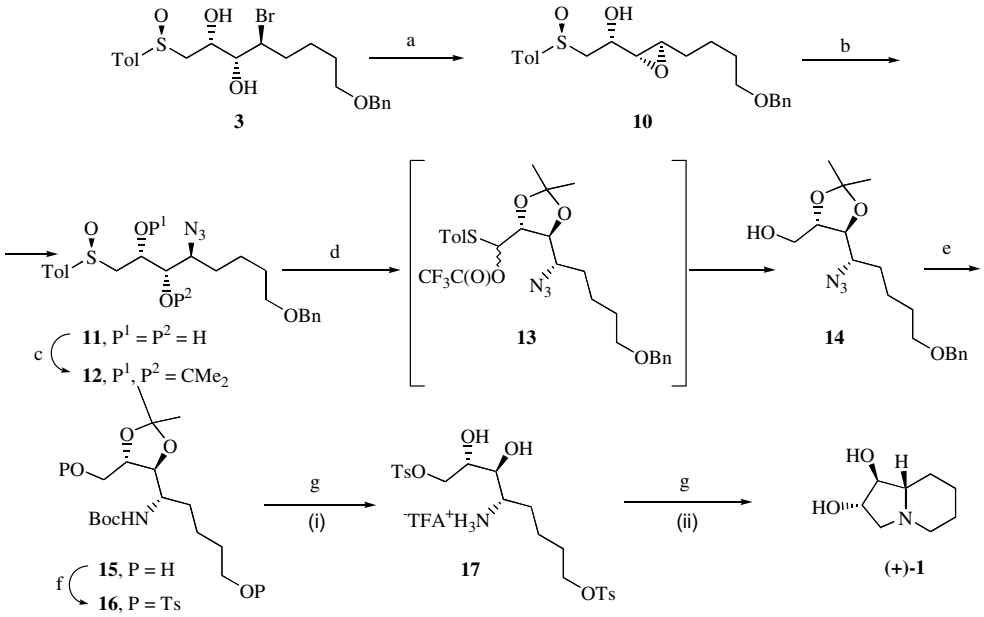
In summary we have disclosed a novel synthesis of lentiginosine, involving 12 steps in 10.7% overall yield that exploits the potential of the sulfinyl group as a nucleophile to functionalize an olefin stereo- and regioselectively.

4. Experimental section

All air or moisture sensitive reactions were carried out under nitrogen atmosphere. Solvents were distilled freshly over Na/benzophenone ketyl for THF, over P_2O_5 followed by CaH_2 for DCM and over P_2O_5 for toluene. Commercially available reagents were used without further purification except NBS, which was freshly recrystallized from hot water before use. Thin layer chromatography was performed with precoated silica gel plates. Column chromatography was carried out using silica gel (60–120 mesh). NMR spectra were recorded on a 200, 300 or 400 MHz spectrometer. ^1H NMR and ^{13}C NMR samples were internally referenced to TMS (0.00 ppm).

4.1. 8-Benzyloxy-1-(R_S)-(4-methylbenzylsulfinyl)-*E*-3-octen-2-one 7

A solution of (*R*)-(+)-methyl *p*-tolylsulfoxide (2.77 g, 18 mmol) in THF was added dropwise to a solution of



Scheme 3. Reaction conditions: (a) K_2CO_3, MeOH, 0 °C, 83%; (b) NaN_3, NH_4Cl, MeOH/H_2O (8:1), reflux, 85%; (c) 2,2-DMP, acetone, CSA (cat.), rt, 87%; (d) TFAA, Et_3N, CH_2Cl_2, 0 °C then aq $NaHCO_3$, $NaBH_4$, 75% for two steps; (e) H_2, $Pd(OH)_2$, $(Boc)_2O$, ethanol, rt, 82%; (f) TsCl, Et_3N, DMAP (cat.), DCM, 75%; (g) (i) TFA/H_2O (95:5), DCM, 0 °C to rt; (ii) Et_3N, DCM, rt, 70% for two steps.

LDA (18.0 mmol), prepared from diisopropylamine (2.5 mL, 18.0 mmol) and *n*-BuLi (11.3 mL, 1.6 M/hexanes, 18.0 mmol), in THF (25 mL) and cooled at −78 °C. The mixture was stirred at −78 °C for 1 h and then added dropwise via a canula to a solution of ester **5** (2.46 g, 9 mmol) in THF (56 mL) cooled at −78 °C. After 3 h at −78 °C, the reaction mixture was decomposed with aq saturated NH_4Cl solution (100 mL). The reaction mixture was diluted with ether (100 mL), the organic layer separated and the aq layer extracted with EtOAc (3×25 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure to yield a residue, which was purified by column chromatography using EtOAc/petroleum ether (2:3 v/v) as the eluent to afford **7** (4.66 g, 12.6 mmol) in 70% yield. Viscous liquid. R_f: 0.32 (40% EtOAc/petroleum ether). $[\alpha]_D^{25} = +145.0$ (*c* 1, acetone). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.53 (d, $J = 8.2$ Hz, 2H), 7.38–7.25 (m, 7H), 6.82 (dt, $J = 15.6$, 6.7 Hz, 1H), 6.10 (d, $J = 15.6$ Hz, 1H), 4.52 (s, 2H), 4.0 (d, $J = 13.0$ Hz, 1H), 3.82 (d, $J = 13.0$ Hz, 1H), 3.48 (t, $J = 5.6$ Hz, 2H), 2.42 (s, 3H), 2.30–2.16 (m, 2H), 1.68–1.58 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.2, 24.3, 28.9, 32.2, 69.5, 72.7, 123.9, 127.3, 127.34, 128.1, 129.8, 130.2, 138.2, 139.7, 141.8, 151.1, 190.5. *m*/*z* FAB: 371 $[M+H]^+$. Anal. Calcd for $C_{22}H_{26}O_3S$: C, 71.32; H, 7.07; S, 8.65. Found: C, 70.91; H, 7.11; S, 8.46.

4.2. 8-Benzyloxy-1-(R_S)-(4-methylphenylsulfinyl)-(2*R*,3*E*)-3-octen-2-ol 4

A solution of the β-ketosulfoxide **7** (2.59 g, 7 mmol) in anhydrous THF (61.5 mL) was added to a solution of $ZnCl_2$ (1.14 g, 8.4 mmol) in anhydrous THF (8.5 mL) and stirred at rt for 15 min. The reaction mixture was cooled to −78 °C and DIBAL-H (5.25 mL, 2 M/toluene, 10.5 mmol) added dropwise over a period of 10 min. After 30 min of stirring at the same temperature, methanol (70 mL) was added and the reaction mixture allowed to return to rt. The solvent was evaporated under reduced pressure and the residue diluted with 5% aq HCl solution and extracted into CH_2Cl_2. The organic layer was washed with 5% aq NaOH solution, brine and dried over Na_2SO_4. The crude product was purified by column chromatography using 40% EtOAc/petroleum ether as the eluent to afford the hydroxysulfoxide **4** (2.34 g, 6.33 mmol) essentially as a single diastereomer in 91% yield as a pale yellow liquid. R_f: 0.27 (40% EtOAc/petroleum ether). $[\alpha]_D^{25} = +90.5$ (*c* 1, acetone). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.51 (d, $J = 8.2$ Hz, 2H), 7.34–7.20 (m, 7H), 5.74 (dt, $J = 15.6$, 6.7 Hz, 1H), 5.42 (dd, $J = 15.6$, 5.9 Hz, 1H), 4.75–4.66 (m, 1H), 4.44 (s, 2H), 3.56 (br s, 1H), 3.42 (t, $J = 6.9$ Hz, 2H), 2.94 (dd, $J = 13.0$, 9.7 Hz, 1H), 2.70 (dd, $J = 13.0$, 3.0 Hz, 1H), 2.41 (s, 3H), 2.14–1.96 (m, 2H), 1.62–1.40 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.4, 25.5, 29.2, 31.8, 62.9, 69.4, 70.1, 72.8, 123.9, 127.4, 127.5, 128.2, 130.0, 130.2, 133.1, 137.5, 140.0, 141.8. *m*/*z* FAB: 373 $[M+H]^+$. Anal. Calcd for $C_{22}H_{28}O_3S$: C, 70.93; H, 7.58; S, 8.61. Found: C, 70.72; H, 7.31; S, 8.56.

4.3. 8-Benzyloxy-4-bromo-1-(S_S)-(4-methylphenylsulfinyl)-(2*R*,3*R*,4*S*)-octane-2,3-diol 3

To a solution of the sulfoxide **4** (2.24 g, 6.02 mmol) in dry toluene (24 mL) was added water (216 mg, 12.04 mmol), followed by *N*-bromosuccinimide (1.27 g, 7.22 mmol) and the reaction mixture stirred at room temperature for 15 min. The reaction was quenched by the addition of aq saturated $NaHCO_3$ solution. The layers were separated and the aqueous layer extracted with ethylacetate (3×25 mL). The combined organic

layers were successively washed with water, brine and dried over Na_2SO_4. Evaporation of the solvent afforded the crude product, which was purified by column chromatography using EtOAc/hexane (2:3 v/v) as the eluent to yield bromohydrin **3** (2.4 g, 5.11mmol) in 85% yield. Colourless solid. Mp 147–148 °C. R_f: 0.27 (40% EtOAc/petroleum ether). $[\alpha]_D^{25} = -58.5$ (*c* 1.0, acetone). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.52 (d, $J = 8.2$ Hz, 2H), 7.36–7.24 (m, 7H), 4.80 (br s, 1H), 4.50–4.46 (m, 3H), 4.0 (t, $J = 6.8$ Hz, 1H), 3.88–3.78 (m, 1H), 3.44 (m, 3H), 3.15 (m, 2H), 2.44 (s, 3H), 1.74–1.40 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.4, 51.0, 61.1, 67.9, 71.4, 73.3, 74.7, 124.1, 127.7, 127.8, 128.4, 130.1, 137.4, 139.7, 142.0. *m/z* FAB: 471 $[M+H]^+$. Anal. Calcd for $C_{22}H_{29}O_4BrS$: C, 56.29; H, 6.23; S, 6.83. Found: C, 56.21; H, 6.15; S, 6.70.

4.4. 4-[5-Benzyloxy-1-bromo-(1*S*)-pentyl]-2,2-dimethyl-5-(S_S)-(4-methylphenylsulfinylmethyl)-(4*R*,5*R*)-1,3-dioxolane 9

To a solution of the bromohydrin (0.093 g, 0.2 mmol) in a mixture of acetone and 2,2-dimethoxypropane (3:1, 0.8 mL) was added a catalytic amount of CSA (3 mg) and the reaction mixture then stirred at ambient temperature for 1 h. Et_3N, enough to neutralize CSA, was added and the volatiles removed under reduced pressure. The residue was purified by column chromatography using EtOAc/hexane (1:4 v/v) as the eluent to yield acetonide **9** (0.088 g, 0.17 mmol) in 87% yield. Pale yellow solid. Mp 96–97 °C. R_f: 0.5 (30% EtOAc/petroleum ether). $[\alpha]_D^{25} = -116.5$ (*c* 0.6, acetone). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.52 (d, $J = 8.2$ Hz, 2H), 7.36–7.20 (m, 7H), 4.51–4.44 (m, 3H), 3.88 (m, 2H), 3.45 (t, $J = 5.7$ Hz, 2H), 3.35 (dd, $J = 13.2$, 2.3 Hz, 1H), 2.80 (dd, $J = 13.2$, 10.2 Hz, 1H), 2.42 (s, 3H), 2.16–2.04 (m, 1H), 1.80–1.56 (m, 5H), 1.44 (s, 3H), 1.43 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.3, 23.5, 27.1, 27.4, 28.9, 34.9, 55.9, 63.7, 69.9, 72.8, 75.3, 82.9, 110.0, 123.9, 127.3, 127.5, 128.2, 129.9, 138.4, 139.4, 141.4. *m/z* FAB: 513 $[M+H]^+$. Anal. Calcd for $C_{25}H_{33}BrO_4S$: C, 58.94; H, 6.53; S, 6.29. Found: C, 58.59; H, 6.32; S, 6.09.

4.5. 1-[(3*S*)-(4-benzyloxybutyl(2*S*)-oxiranyl]-2-(S_S)-(4-methylphenylsulfinyl)-(1*R*)-ethan-1-ol 10

To a solution of **3** (1.88 g, 4.0 mmol) in methanol (16 mL) was added K_2CO_3 (0.61g, 4.40 mmol) at 0 °C. The reaction mixture was stirred and gradually allowed to return to rt over a period of 45 min. After stirring for another 1 h at rt, TLC revealed the complete conversion of the starting material. Diethylether (15 mL) was added to the reaction mixture, and after 10 min, when the inorganic salts had settled, the reaction mixture was filtered and the filtrate evaporated under reduced pressure to afford the epoxide **10** (1.28 g, 3.32 mmol) in 83% yield, which was taken ahead to the next step without further purification. White solid. Mp 124–125 °C. R_f: 0.24 (40% EtOAc/petroleum ether). $[\alpha]_D^{25} = -102.0$ (*c* 0.8, acetone). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.51 (d, $J = 8.2$ Hz, 2H), 7.40–7.24 (m, 7H), 4.46 (s, 2H), 4.18 (m, 1H), 3.42 (t, $J = 5.6$ Hz, 2H), 3.03–2.89 (m, 2H), 2.78–2.70 (m, 2H), 2.44 (s, 3H), 1.76–1.40 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.4, 22.6, 29.6, 31.1, 55.9, 60.4, 65.7, 69.9, 72.9, 74.0, 123.9, 124.8, 127.6, 128.3, 130.1, 137.9, 139.6, 141.8. *m/z* FAB: 389 $[M+H]^+$. Anal. Calcd for $C_{22}H_{28}O_4S$: C, 68.01; H, 7.26; S, 8.25. Found: C, 67.85; H, 7.21; S, 8.05.

4.6. 4-Azido-8-benzyloxy-1-(S_S)-(4-methylphenylsulfinyl)-(2*R*,3*S*,4*S*)-octane-2,3-diol 11

To a solution of the epoxide **10** (120 g, 3.1 mmol) in a solvent mixture of MeOH/H_2O (8:1, 18 mL) was added NH_4Cl (0.50 g, 9.3 mmol) followed by NaN_3 (1.21 g, 18.6 mmol) and the mixture refluxed for 6 h. The reaction mixture allowed to attain rt and the solvent then evaporated under reduced pressure. The residue was extracted with ethylacetate (2×30 mL), washed successively with water and brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to yield the crude product, which was purified by column chromatography using EtOAc/hexane (2:3 v/v) to afford the azidodiol **11** (1.13 g, 2.64 mmol) in 85% yield. White solid. Mp 119–120 °C. R_f: 0.28 (40% EtOAc/petroleum ether). $[\alpha]_D^{25} = -90.5$ (*c* 0.8, acetone). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.51 (d, $J = 8.2$ Hz, 2H), 7.34–7.22 (m, 7H), 5.50 (br s, OH, 1H), 4.42 (s, 2H), 4.40 (m, 1H), 3.51–3.33 (m, 3H), 3.18 (dd, J = 13.4, 10.0 Hz, 1H), 3.05–3.0 (m, 1H), 2.70 (d, $J = 13.4$ Hz, 1H), 2.41 (s, 3H), 1.68–1.52 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.4, 22.5, 29.5, 31.0, 59.9, 63.7, 65.2, 70.0, 72.9, 74.8, 124.1, 127.5, 127.7, 128.4, 130.2, 138.5, 138.8, 142.0. *m/z* FAB: 432 $[M+H]^+$. Anal. Calcd for $C_{22}H_{29}N_3O_4S$: C, 61.23; H, 6.77; N, 9.74; S, 7.43. Found: C, 61.0; H, 6.52; N, 9.60; S, 7.23.

4.7. 4-[1-Azido-5-benzyloxy-(1*S*)-pentyl]-2,2-dimethyl-5-(S_S)-(4-methylphenylsulfinylmethyl)-(4*S*,5*R*)-1,3-dioxolane 12

To a solution of the azidodiol **11** (1.07 g, 2.5 mmol) in a mixture of 2,2-dimethoxypropane and acetone (1:3, 10 mL) was added CSA (24 mg, 0.1 mmol) and the reaction mixture stirred at ambient temperature for 1 h. A few drops of Et_3N were added to neutralize CSA and the volatiles removed under reduced pressure to afford the crude product, which was purified by column chromatography using EtOAc/hexane (1:4 v/v) as the eluent to yield acetonide **12** (1.02 g, 2.17 mmol) in 87% yield. Viscous liquid. R_f: 0.48 (30% EtOAc/petroleum ether). $[\alpha]_D^{25} = -116.5$ (*c* 0.6, acetone). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.52 (d, $J = 8.2$ Hz, 2H), 7.36–7.20 (m, 7H), 4.50 (s, 2H), 4.44–4.38 (m, 1H), 3.56 (t, $J = 6.7$, Hz, 1H), 3.50–3.36 (m, 3H), 3.01 (dd, $J = 13.4$, 2.2 Hz, 1H), 2.73 (dd, $J = 13.4$, 10.4 Hz, 1H), 2.41 (s, 3H), 1.58–1.32 (m, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.2, 22.5, 26.6, 27.0, 29.1, 30.7, 62.8, 63.3, 69.6, 72.7, 72.8, 81.4, 110.1, 123.7, 127.3, 127.4, 128.1, 129.9, 138.3, 140.9, 141.6 *m/z* FAB: 472 $[M+H]^+$. Anal. Calcd for $C_{25}H_{33}N_3O_4S$: C, 63.67; H, 7.05; N, 8.91; S, 6.80. Found: C, 63.51; H, 6.89; N, 8.80; S, 6.76.

4.8. 5-[1-Azido-5-benzyloxy-(1*S*)-pentyl]-2,2-dimethyl-(4*S*,5*S*)-1,3-dioxolan-4-ylmethanol 14

To a solution of azido acetonide **12** (0.89 g, 1.9 mmol) in dry DCM (9 mL) was added Et_3N (0.79 mL, 5.7 mmol) followed by TFAA (0.79 mL, 5.7 mmol) under N_2 at 0 °C and stirred for 15 min. $NaBH_4$ (0.28 g, 7.6 mmol) dissolved in an aqueous solution of 5% $NaHCO_3$ (12 mL) was then added to the reaction mixture at 0 °C and stirred for another 20 min at the same temperature. The reaction mixture was then extracted into DCM. The combined organic layers were washed successively with water, brine and dried over anhydrous Na_2SO_4. The solvent was evaporated in vacuo and the residue on column chromatography over silica gel using a mixture of EtOAc/petroleum ether (1:4 v/v) as the eluent afforded **14** (0.50 g, 1.42 mmol) in 75% yield. Viscous liquid. R_f: 0.5 (25% EtOAc/petroleum ether). $[\alpha]_D^{25} = -30.5$ (*c* 0.6, acetone). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.38–7.22 (m, 5H), 4.50 (s, 2H), 4.04 (m, 1H), 3.90–3.72 (m, 2H), 3.66–3.41 (m, 4H), 1.76–1.48 (m, 6H), 1.45 (s, 3H), 1.41 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.9, 26.8, 27.1, 29.3, 30.8, 62.7, 63.9, 69.8, 72.8, 72.9, 78.2, 109.4, 127.5, 127.6, 128.3, 138.3. *m*/*z* FAB: 350 $[M+H]^+$. Anal. Calcd for $C_{18}H_{27}N_3O_4$: C, 61.87; H, 7.79; N, 12.03. Found: C, 61.75; H, 7.68; N, 11.85.

4.9. 5-[1-*tert*-Butyloxycarbonylamido-5-benzyloxy-(1*S*)-pentyl]-2,2-dimethyl-(4*S*,5*S*)-1,3-dioxolan-4-ylmethanol 15

To a mixture of azido acetonide **14** (0.45 g, 1.3 mmol) and $(Boc)_2O$ (0.56 g, 2.6 mmol) in absolute ethanol (2.6 mL) was added $Pd(OH)_2$ (45 mg, 10% by wt). The reaction mixture was evacuated, subsequently filled with H_2 and stirred for 16 h at atmospheric pressure. The reaction mixture was filtered through a small pad of Celite and repeatedly washed with ethanol. Evaporation of the solvent afforded the crude product, which was purified by column chromatography using EtOAc/petroleum ether (4:6) as the eluent to yield **15** (0.35 g, 1.06 mmol) in 82% yield. Solid. Mp 75–76 °C. $[\alpha]_D^{25} = -6.9$ (*c* 0.6, acetone). ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.90 (d, $J = 9$ Hz, 1H), 3.98 (m, 1H), 3.64–3.52 (m, 6H), 2.04 (d, $J = 3.4$ Hz, 1H), 1.64–1.52 (m, 6H), 1.44 (s, 9H), 1.38 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6, 26.9, 27.0, 28.3, 31.0, 32.2, 52.6, 62.3, 62.6, 79.4, 79.5, 79.6, 109.0, 156.0. *m*/*z* FAB: 334 $[M+H]^+$. Anal. Calcd for $C_{16}H_{31}NO_6$: C, 57.64; H, 9.37; N, 4.20;. Found: C, 57.49; H, 9.19; N, 4.10.

4.10. 4-[1-*tert*-Butyloxycarbonylamido-5-benzyloxy-(1*S*)-pentyl]-2,2-dimethyl-5-(4-methylphenylsulfonyloxy-methyl)-(4*S*,5*S*)-1,3-dioxolane 16

To a solution of diol **15** (0.33 g, 1.0 mmol) in dichloromethane (5 mL) was added triethylamine (0.62 mL, 4.5 mmol) followed by *p*-toluenesulfonyl chloride (0.42 g, 2.2 mmol) and the mixture stirred under nitrogen for 1 h. The reaction mixture was quenched with 10% citric acid solution. The aqueous layer was then extracted with DCM (2 × 5 mL). The combined organic layer was successively washed with water, brine and dried over Na_2SO_4. Evaporation of the solvent afforded the crude product, which was purified by column chromatography using EtOAc/petroleum ether (3:7 v/v) as the eluent to afford **16** (0.47 g, 0.75 mmol) in 75% yield. Solid. Mp 96–97 °C. $[\alpha]_D^{25} = -14.3$ (*c* 0.6, acetone). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.80 (m, 4H), 7.36–7.32 (m, 4H), 4.38 (d, $J = 9.4$ Hz, 1H), 4.14–3.98 (m, 5H), 3.71–3.64 (m, 2H), 2.47 (s, 6H), 1.72–1.62 (m, 4H), 1.48 (s, 9H), 1.33 (s, 3H), 1.30 (s, 3H), 1.28–1.25 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.3, 21.6, 26.7, 26.9, 28.2, 28.4, 31.4, 52.7, 69.3, 70.1, 78.8, 79.8, 109.7, 127.8, 127.9, 129.8, 129.82, 132.7, 133.0, 144.7, 145.0, 155.6. *m*/*z* FAB: 642 $[M+H]^+$. Anal. Calcd for $C_{30}H_{43}NO_{10}S_2$: C, 56.14; H, 6.75; N, 2.18; S, 9.99. Found: C, 56.11; H, 6.69; N, 2.17; S, 9.89.

4.11. (1*S*,2*S*,8a*S*)-Perhydro-1,2-indolizinediol 1

To a solution of the acetonide **16** (0.38 g, 0.6 mmol) in DCM (0.6 mL) was added a solution of TFA/water (95:5, 1.2 ml) at 0 °C after which the mixture was gradually allowed to attain rt for 16 h. The solvent was evaporated under reduced pressure with any traces of water in the residue removed as an azeotrope with benzene. The residue was dissolved in DCM (3 mL) and triethylamine (0.5 mL, 3.6 mmol) added. The reaction mixture was stirred at rt for 6 h. The solvent was evaporated and the residue dissolved in the minimum amount of water and purified by ion-exchange chromatography (Dowex resin) using 2% ammonia solution to afford **1** (65 mg, 0.42 mmol) in 70% yield. Solid. Mp 103–104 °C. $[\alpha]_D^{25} = +2.9$ (*c* 0.28, MeOH). ^{1}H NMR (300 MHz, D_2O) δ 4.02 (ddd, $J = 7.4$, 4.0, 1.9 Hz, 1H), 3.57 (dd, $J = 8.8$, 4.0 Hz, 1H), 2.90 (dd, $J = 11.2$, 2.0Hz, 1H), 2.79 (dd, $J = 11.4$, 2.0 Hz, 1H), 2.60 (dd, $J = 11.4$, 7.4 Hz, 1H), 2.06 (dd, $J = 11.3$, 2.9 Hz, 1H), 2.01–1.12 (m, 7H). ^{13}C NMR (75 MHz, D_2O dioxane internal standard) δ 23.8, 24.8, 28.4, 53.4, 61.1, 69.3, 76.4, 83.8. *m*/*z* FAB: 158 $[M+H]^+$. HRMS-FAB (*m*/*z*) $[M+H]^+$ calcd for $C_8H_{15}NO_2$ 158.1180, found 158.1190.

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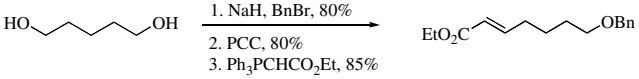
References and notes

1. Pastuszak, I.; Molyneux, R. J.; James, L. F.; Elbein, A. D. *Biochemistry* **1990**, *29*, 1886.
2. (a) McCaig, A. E.; Wightman, R. H. *Tetrahedron Lett.* **1993**, *34*, 3939; (b) Cordero, F. M.; Cicchi, S.; Goti, A.;

Brandi, A. *Tetrahedron Lett.* **1994**, *35*, 949; (c) Yoda, H.; Kitayama, H.; Katagiri, T.; Takabe, K. *Tetrahedron: Asymmetry* **1994**, *5*, 1455; (d) Gurjar, M. K.; Ghosh, L.; Syamala, M.; Jayasree, V. *Tetrahedron Lett.* **1994**, *35*, 8871; (e) Nukui, S.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 398; (f) Giovannini, R.; Marcantoni, E.; Petrini, M. *J. Org. Chem.* **1995**, *60*, 5706; (g) Brandi, A.; Cicchi, S.; Cordero, F. M.; Frignoli, R.; Goti, A.; Picasso, S.; Vogel, P. *J. Org. Chem.* **1995**, *60*, 6806; (h) Goti, A.; Cordona, F.; Brandi, A. *Synlett* **1996**, 761; (i) Paolucci, C.; Musiani, L.; Venturelli, F.; Fava, A. *Synthesis* **1997**, 1415; (j) Yoda, H.; Kawauchi, M.; Takabe, K. *Synlett* **1998**, 137; (k) Wightman, R. H.; Meldrum, K. P.; McCaig, A. E. *Tetrahedron* **1998**, *54*, 9429; (l) Ha, D.-C.; Yun, C.-S.; Lee, Y. *J. Org. Chem.* **2000**, *65*, 621; (m) Cordona, F.; Goti, A.; Picasso, S.; Vogel, P. *J. Carbohydr. Chem.* **2000**, *19*, 585; (n) Yoda, H.; Katoh, H.; Ujihara, Y.; Takabe, K. *Tetrahedron Lett.* **2001**, *42*, 2509; (o) Klitzke, C. F.; Pill, R. A. *Tetrahedron Lett.* **2001**, *42*, 5605; (p) Rasmussen, M. O.; Delair, P.; Greene, A. E. *J. Org. Chem.* **2001**, *66*, 5438; (q) Chandra, K. L.; Chandrasekhar, M.; Singh, V. K. *J. Org. Chem.* **2002**, *67*, 4630; (r) Feng, Z.-X.; Zhou, W.-S. *Tetrahedron Lett.* **2003**, *44*, 497; (s) Sha, C.-K.; Chan, C.-M. *Tetrahedron Lett.* **2003**, *44*, 499.

3. Raghavan, S.; Rasheed, M. A.; Joseph, S. C.; Rajender, A. *J. Chem. Soc.* **1999**, 1845.
4. (a) Raghavan, S.; Joseph, S. C. *Tetrahedron: Asymmetry* **2003**, *14*, 101; (b) Raghavan, S.; Rasheed, M. A. *Tetrahedron: Asymmetry* **2003**, *14*, 1371; (c) Raghavan, S.; Rajender, A.; Yadav, J. S. *Tetrahedron: Asymmetry* **2003**, *14*, 2093; (d) Raghavan, S.; Rajender, A. *J. Org. Chem.* **2003**, *68*, 7094; (e) Raghavan, S.; Joseph, S. C. *Tetrahedron Lett.* **2003**, *44*, 7613; (f) Raghavan, S.; Rasheed, M. A. *Tetrahedron* **2003**, *59*, 0000; (g) Raghavan, S.; Joseph, S. C. *Tetrahedron Lett.* **2003**, *44*, 8237.
5. The ester **5** was readily obtained in three steps from 1,5-pentanediol.



6. Komatsu, N.; Hashizume, M.; Sugita, T.; Uemura, S. *J. Org. Chem.* **1993**, *58*, 4529.
7. (a) Solladie, G.; Demailly, G.; Greck, C. *Tetrahedron Lett.* **1985**, *26*, 435; (b) Solladie, G.; Frechou, C.; Demailly, G.; Greck, C. *J. Org. Chem.* **1986**, *51*, 1912; (c) Carreno, M. C.; Garcia Ruano, J. L.; Martin, A. M.; Pedregal, C.; Rodriguez, J. H.; Rubio, A.; Sanchez, J.; Solladie, G. *J. Org. Chem.* **1990**, *55*, 2120.
8. For the assignment of the relative configurations of 1,2-acetonides using ^{13}C data refer: Dana, G.; Danechpajouh, H. *Bull. Soc. Chim. Fr.* **1980**, 395.
9. Chamberlin, A. R.; Dezube, M.; Dussault, P.; McMills, M. C. *J. Am. Chem. Soc.* **1983**, *105*, 5819.
10. Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1557.
11. The ^{13}C spectrum of **12** confirms the assigned structure. The methyl groups of the acetonide resonate at δ 26.6, 27.0 and the ketal carbon resonates at δ 110.1. A *syn*-1,3-acetonide is expected from a regioisomeric opening of the epoxide **10** by sodium azide, which is not observed.
12. (a) Pummerer, R. *Chem. Ber.* **1909**, *42*, 2282; (b) Sugihara, H.; Tanikaga, R.; Kaji, A. *Synthesis* **1978**, 881; (c) Padwa, A.; Gunn, D. E., Jr, Osterhout, M. H. *Synthesis* **1997**, 1353.