Variable Strategy towards Carbasugars and Relatives. 6. Diastereoselective Synthesis of 2-Deoxy-2-amino-5a-carba-β-L-mannopyranuronic Acid and 2-Deoxy-2-amino-5a-carba-β-L-mannopyranose

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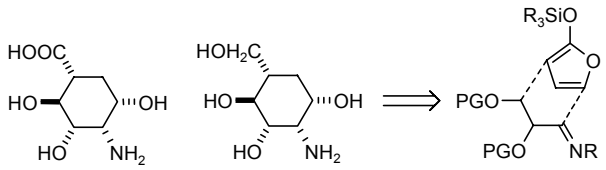


SUPPORTING INFORMATION

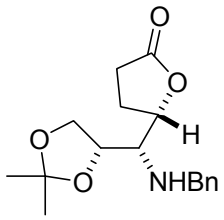
Experimental Section[1]

General. Flash chromatography was performed on 32-63 μm silica gel, using the indicated solvent mixtures. Analytical thin-layer chromatography was performed on silica gel 60 F_{254} plates (0.25 mm). The compounds were visualized by dipping the plates in an aqueous H_2SO_4 solution of cerium sulfate/ammonium molybdate or in an ethanolic solution of ninhydrin, followed by charring with a heat gun. Proton and carbon NMR spectra were recorded at 300 and 75 MHz, 400 and 100 MHz, and 600 and 150 MHz, respectively. Chemical shifts (δ) are reported in parts per million relative to tetramethylsilane (0.0 ppm) as an internal reference, with coupling constants in hertz (Hz). Connectivity was determined by ^{1}H-^{1}H COSY experiments. ^{13}C NMR assignments were obtained from ^{1}H-^{13}C HETCOR experiments. Optical rotations were measured at ambient temperature using a 100 mm cell with a 1 mL capacity and are given in units of 10^{-1} deg cm^2 g^{-1}. Melting points are uncorrected. All the solvents were distilled before use: THF over Na/benzophenone, Et_2O over $LiAlH_4$, CH_2Cl_2 over CaH_2.

Materials. 2-[(*tert*-Butyldimethylsilyl)oxy]furan (**3**, TBSOF) was prepared from 2-furaldehyde (Aldrich) according to a described protocol.[2] (2*S*)-2,3-*O*-Isopropylideneglyceraldehyde *N*-benzyl imine (**4**) was prepared by reacting 2,3-*O*-isopropylidene-D-glyceraldehyde with benzylamine in anhydrous diethyl ether at 0 °C in the presence of anhydrous $MgSO_4$. The crude material was used as such in the subsequent coupling process.

(1'*S*,4''*S*,5*S*)-5-[Benzylamino-(2,2-dimethyl-[1,3]dioxolan-4-yl)methyl]dihydrofuran-2-one (6). 2,3-*O*-Isopropylidene-D-glyceraldehyde *N*-benzyl imine **4** (3.30 g, 15.0 mmol) and TBSOF **3** (2.7 g, 13.5 mmol) were dissolved in dry CH_2Cl_2 (60 mL) under argon, and the mixture was cooled to –85 °C. *tert*-Butyldimethylsilyl trifluoromethanesulfonate (TBSOTf, 3.1 mL, 13.5 mmol), cooled to the same temperature, was added via cannula over 5 min, and the solution was allowed to stir for 3 h. A saturated aqueous $NaHCO_3$ solution was added at –85 °C and, after ambient temperature was reached, the mixture was extracted with CH_2Cl_2. The organic layer was washed with brine, dried ($MgSO_4$) and

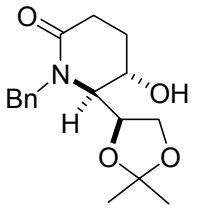
concentrated in vacuo to give lactone **5**, which was used without further purification in the next step. A solution of lactone **5** (3.80 g, 12.4 mmol) in 150 mL of absolute MeOH was cooled to 0 °C and treated with $NiCl_2 \cdot 6H_2O$ (737 mg, 3.1 mmol). The resulting mixture was stirred at the same temperature for 15 min before adding of $NaBH_4$ (234 mg, 6.2 mmol). After 30 min, further portion of $NaBH_4$ (117 mg, 3.1 mmol) was added, and the reaction was allowed to stir for additional 10 min. The reaction was then quenched with saturated NH_4Cl solution and extracted with CH_2Cl_2. The combined extracts were dried ($MgSO_4$) and concentrated under vacuum. Silica gel flash chromatographic purification (55:45 hexanes/EtOAc) afforded compound **6** (3.1 g, 68% two steps) as a colorless oil: $[\alpha]^{20}_D$ +21.5 (*c* 4.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.3-7.4 (m, 5H), 4.74 (td, *J* = 7.6, 3.6 Hz, 1H), 4.09 (m, 2H), 3.90 (d, *J* = 13.2 Hz, 1H), 3.82 (d, *J* = 13.2 Hz, 1H), 3.80 (m, 1H), 3.01 (dd, *J* = 7.2, 3.6 Hz, 1H), 2.4-2.6 (m, 2H), 2.2-2.3 (m, 2H), 1.53 (bs, 1H), 1.40 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.3, 139.9, 128.5 (2C), 128.2 (2C), 127.3, 109.4, 80.8, 75.3, 67.4, 61.0, 53.3, 28.6, 26.6, 25.1, 23.2. Anal. Calcd for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59. Found: C, 66.79; H, 7.67; N, 4.67.



6

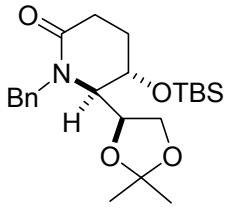
(4'*S*,5*S*,6*S*)-1-Benzyl-6-(2,2-dimethyl-[1,3]dioxolan-4-yl)-5-hydroxypiperidin-2-one (7). 1,8-Diaza-bicyclo[5.4.0]undec-7-ene (DBU, 4.0 mL, 9.8 mmol) was added to saturated lactone **6** (3.0 g, 9.8 mmol) and the resulting mixture was stirred at 140 °C for 12 h. The resulting syrup was purified by flash chromatography over silica gel (EtOAc/MeOH 95:5) to afford 2.87 g (96%) of lactam **7** as a glassy solid: $[\alpha]^{20}_D$ +33.7 (*c* 3.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.2-7.4 (m, 5H), 5.41 (d, *J* = 15.2 Hz, 1H), 4.21 (m, 1H), 4.10 (bq, *J* = 7.6 Hz, 1H), 4.02 (dd, *J* = 8.0, 6.4 Hz, 1H), 3.92 (d, *J* = 15.2 Hz, 1H), 3.72 (t, *J* = 7.6 Hz, 1H), 3.40 (m, 1H), 2.65 (ddd, *J* = 18.0, 9.2, 7.6 Hz, 1H), 2.45 (ddd, *J* = 18.0, 7.6, 4.4 Hz, 1H), 2.08 (m, 1H), 1.89 (m, 1H), 1.70 (bs, 1H), 1.40 (s, 3H), 1.31 (s, 3H); ^{13}C NMR

(100 MHz, $CDCl_3$) δ 170.6, 136.8, 128.6 (2C), 127.9 (2C), 127.5, 109.2, 76.5, 67.2, 64.7, 63.5, 48.7, 27.2, 26.3, 25.3, 25.1. Anal. Calcd for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59. Found: C, 66.97; H, 7.63; N, 4.48.



7

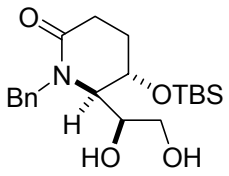
(4'*S*,5*S*,6*S*)-1-Benzyl-5-(*tert*-butyldimethylsilanyloxy)-6-(2,2-dimethyl-[1,3]dioxolan-4-yl)piperidin-2-one (8). TBSOTf (2.3 mL, 10.1 mmol) and 2,6-lutidine (3.5 mL, 30.4 mmol) were sequentially added to a stirred solution of compound **7** (2.85 g, 9.3 mmol) in anhydrous CH_2Cl_2 (100 mL) under argon atmosphere at 0 °C. The reaction was concentrated under vacuum to afford a crude residue that was purified by silica gel flash chromatography (hexanes/EtOAc 1:1). Pure lactam **8** (3.59 g, 92%) was obtained as a colorless oil: $[\alpha]^{20}_D$ +50.0 (*c* 3.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.2-7.3 (m, 5H), 5.45 (d, *J* = 15.6 Hz, 1H), 4.25 (dt, *J* = 4.0, 2.0 Hz, 1H), 4.0-4.1 (m, 2H), 3.87 (d, *J* = 15.6 Hz, 1H), 3.69 (m, 1H), 3.75 (m, 1H), 2.71 (ddd, *J* = 18.0, 12.0, 7.6 Hz, 1H), 2.44 (ddd, *J* = 18.0, 7.2, 2.0 Hz, 1H), 2.01 (dddd, *J* = 14.0, 11.6, 7.2, 2.4 Hz, 1H), 1.80 (m, 1H), 1.39 (s, 3H), 1.33 (s, 3H), 0.81 (s, 9H), 0.02 (s, 3H), –0.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 136.7, 128.4 (2C), 127.8 (2C), 127.1, 108.8, 77.0, 67.5, 65.2, 64.4, 48.5, 26.9, 26.2, 25.7 (3C), 25.3, 25.1, 17.9, –4.9, –5.0. Anal. Calcd for $C_{23}H_{37}NO_4Si$: C, 65.83; H, 8.89; N, 3.34. Found: C, 65.87; H, 8.80; N, 3.41.



8

(1'*S*,5*S*,6*S*)-1-Benzyl-5-(*tert*-butyldimethylsilanyloxy)-6-(1,2-dihydroxyethyl)piperidin-2-one (9).

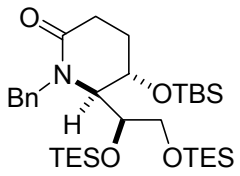
Protected lactam **8** (3.50 g, 8.3 mmol) was treated with 30 mL of 80% aqueous acetic acid, and the resulting mixture was allowed to react at 80 °C. The reaction was monitored by TLC and was judged complete after 7 h. The solution was then diluted with H_2O and extracted with CH_2Cl_2 and EtOAc; the extracts were separated and treated with saturated $NaHCO_3$ solution, and the combined organic layers were dried ($MgSO_4$) and concentrated to give a crude residue that was purified by flash chromatography (EtOAc/MeOH 9:1). Pure terminal diol **9** (2.49 g, 79%) was obtained as a white solid: mp 123-124 °C; $[\alpha]^{20}_D$ +47.0 (*c* 5.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.2-7.3 (m, 5H), 5.55 (d, J = 15.2 Hz, 1H), 5.25 (bs, 1H), 4.16 (m, 1H), 4.05 (m, 1H), 3.86 (d, J = 15.2 Hz, 1H), 3.58 (m, 2H), 3.24 (m, 1H), 3.01 (bs, 1H), 2.64 (m, 1H), 2.39 (m, 2H), 1.72 (m, 1H), 0.79 (s, 9H), –0.01 (s, 3H), –0.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 136.4, 128.5 (2C), 127.8 (2C), 127.2, 69.7, 64.5, 64.3, 63.7, 47.2, 26.8, 26.4, 25.7 (3C), 17.9, –4.9, –5.0. Anal. Calcd for $C_{20}H_{33}NO_4Si$: C, 63.29; H, 8.76; N, 3.69. Found: C, 63.38; H, 8.86; N, 3.58.



9

(1'*S*,5*S*,6*S*)-1-Benzyl-6-(1,2-bis-triethylsilanyloxyethyl)-5-(*tert*-butyldimethylsilanyloxy)piperidin-2-one (10). To a solution of lactam **9** (2.43 g, 6.4 mmol) in dry pyridine (20 mL) under argon at room temperature triethylsilyltriflate (TESOTf, 4.3 mL, 19.2 mmol) and 4-dimethylaminopyridine (DMAP, 118 mg, 0.96 mmol) were added. After 1 h the reaction was quenched by adding a saturated aqueous NH_4Cl solution, and the resulting mixture was extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was subjected to silica gel flash chromatographic purification (hexanes/EtOAc 9:1) to give fully protected lactam **10** (3.74 g, 96% yield) as a white solid: mp 54-56 °C; $[\alpha]^{20}_D$ +34.0 (*c* 5.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.2-7.3 (m, 5H), 5.60 (d, J = 14.8 Hz, 1H), 4.17 (m, 1H), 4.03 (ddd, J = 8.4, 5.6, 2.4 Hz, 1H),

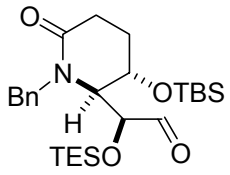
3.71 (d, J = 14.8 Hz, 1H), 3.61 (dd, J = 10.4, 5.6 Hz, 1H), 3.50 (m, 2H), 2.66 (m, 1H), 2.37 (m, 2H), 1.67 (m, 1H), 0.93 (m, 18H), 0.78 (s, 9H), 0.58 (m, 12H), –0.01 (s, 3H), –0.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 137.0, 128.3 (2C), 128.2 (2C), 126.9, 70.7, 63.9, 63.8, 62.7, 46.6, 27.1, 26.8, 25.6 (3C), 17.8, 6.8 (3C), 6.7 (3C), 4.8 (3C), 4.2 (3C), –5.0 (2C). Anal. Calcd for $C_{32}H_{61}NO_4Si_3$: C, 63.21; H, 10.11; N, 2.30. Found: C, 63.33; H, 9.98; N, 2.40.



10

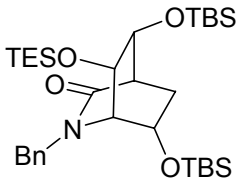
(2*S*,2'*S*,3'*S*)-[1-Benzyl-3-(*tert*-butyldimethylsilanyloxy)-6-oxopiperidin-2-yl]triethylsilanyloxy-acetaldehyde (11). To a solution of oxalyl chloride (5.3 mL, 61.0 mmol) in CH_2Cl_2 (35 mL) at –80 °C under argon a solution of dimethylsulfoxide (DMSO, 8.6 mL, 122 mmol) in CH_2Cl_2 (35 mL) was added dropwise. After 10 min, a solution of protected lactam **10** (3.71 g, 6.1 mmol) in CH_2Cl_2 (21 mL) was added dropwise. After 20 min at –80 °C, the mixture was allowed to rise to –10 °C and was stirred at this temperature for 1 h. The mixture was then cooled again to –80 °C and Et_3N (30.6 mL, 219.6 mmol) was added dropwise. The reaction mixture was stirred at –80 °C for 15 min and then warmed to 25 °C over a period of 2 h. Toluene (60 mL) was added to the mixture, and the solution was filtered and concentrated under vacuum. The residue was dissolved in hexanes (60 mL), filtered again, and concentrated under reduced pressure to give a crude residue that was subjected to flash chromatographic purification (hexanes/EtOAc 85:15). Pure aldehyde **11** (2.73 g, 91%) was recovered as a glassy solid: $[\alpha]_D^{20}$ +5.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.70 (s, 1H), 7.2-7.3 (m, 5H), 5.61 (d, J = 11.4 Hz, 1H), 4.32 (d, J = 2.8 Hz, 1H), 3.89 (m, 1H), 3.70 (d, J = 11.4 Hz, 1H), 3.61 (bs, 1H), 2.68 (m, 1H), 2.41 (m, 2H), 1.72 (m, 1H), 0.95 (t, J = 8.2 Hz, 9H), 0.77 (s, 9H), 0.64 (q, J = 8.2 Hz, 6H), –0.04 (s, 3H), –0.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.0, 170.7, 136.5, 128.6 (2C), 128.0 (2C), 127.4, 76.1, 65.5, 64.7, 46.8, 27.2, 26.9, 25.6 (3C), 17.8, 6.6 (3C), 4.6 (3C), –5.0, –5.1. Anal. Calcd for

$C_{26}H_{45}NO_4Si_2$: C, 63.50; H, 9.22; N, 2.85. Found: C, 63.57; H, 9.34; N, 2.72.



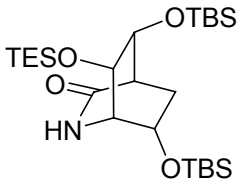
11

(1*S*,4*R*,5*S*,6*S*,7*S*)-2-Benzyl-5,7-bis-(*tert*-butyldimethylsilanyloxy)-6-triethylsilanyloxy-2-azabicyclo-[2.2.2]octan-3-one (12). To a solution of DIPEA (2.9 mL, 16.5 mmol) in anhydrous CH_2Cl_2 (190 mL) at 25 °C under argon atmosphere TBSOTf (3.8 mL, 16.5 mmol) was added. The resulting solution was stirred at the same temperature for 10 min and then aldehyde **11** (2.70 g, 5.5 mmol) dissolved in anhydrous CH_2Cl_2 (95 mL) was added dropwise. After 2 h, the reaction mixture was quenched with a saturated NH_4Cl aqueous solution, and extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The oily residue was purified by flash chromatography (hexanes/EtOAc 9:1) to give **12** (2.97 g, 89%) as a white solid: mp 103-106 °C: $[\alpha]^{20}_D$ +16.7 (*c* 1.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.2-7.3 (m, 5H, CH_2*Ph*), 4.85 (d, *J* = 15.3 Hz, 1H, *CH*$_2$Ph), 4.32 (d, *J* = 15.3 Hz, 1H, *CH*$_2$Ph), 4.00 (dt, *J* = 8.0, 2.7 Hz, 1H, H-1), 3.84 (dt, *J* = 3.4, 1.7 Hz, 1H, H-4), 3.47 (t, *J* = 1.9 Hz, 1H, H-3), 3.30 (t, *J* = 2.1 Hz, 1H, H-2), 2.64 (q, *J* = 3.0 Hz, 1H, H-5), 2.38 (ddd, *J* = 13.7, 8.3, 2.6 Hz, 1H, H5aβ), 1.46 (dtd, *J* = 13.8, 3.1, 1.5 Hz, 1H, H5aα), 0.91 (s, 9H, Bu^t), 0.88 (t, *J* = 7.7 Hz, 9H, *CH*$_3$CH$_2$Si), 0.87 (s, 9H, Bu^t), 0.46 (q, *J* = 7.7 Hz, 6H, CH$_3$*CH*$_2$Si), 0.11 (s, 6H, Me), 0.05 (s, 3H, Me), 0.04 (s, 3H, Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6 (C-6), 137.5 (CH_2*Ph*), 128.5 (2C, CH_2*Ph*), 128.2 (2C, CH_2*Ph*), 127.0 (CH_2*Ph*), 77.4 (C-3), 76.4 (C-4), 68.1 (C-1), 67.3 (C-2), 51.0 (*CH*$_2$Ph), 46.0 (C-5), 29.1 (C-5a), 25.8 (3C, Bu^t), 25.7 (3C, Bu^t), 18.0 (Bu^t), 17.9 (Bu^t), 6.8 (3C, *CH*$_3$CH$_2$Si), 4.6 (3C, CH$_3$*CH*$_2$Si), –4.2 (Me), –4.7 (Me), –4.8 (Me), –5.0 (Me). Anal. Calcd for $C_{32}H_{59}NO_4Si_3$: C, 63.42; H, 9.81; N, 2.31. Found: C, 63.29; H, 9.90; N, 2.43.



12

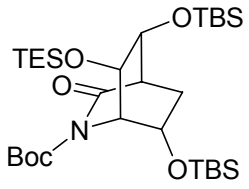
(1*S*,4*R*,5*S*,6*S*,7*S*)-5,7-Bis-(*tert*-butyldimethylsilanyloxy)-6-triethylsilanyloxy-2-azabicyclo-[2.2.2]octan-3-one (13). Anhydrous ammonia (70 mL) was condensed into a two-necked flask containing a solution of **12** (2.91 g, 4.8 mmol) in anhydrous THF (70 mL) mantained at –78 °C. Sodium metal was added to the mixture until the blue color persisted. The reaction was stirred for 30 min at –78 °C monitoring by TLC, and then quenched by careful addition of solid NH_4Cl. The ammonia was evaporated, and the residue was treated with saturated NH_4Cl aqueous solution and extracted with EtOAc. The organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuum. Purification by flash chromatography (85:15 hexanes /EtOAc) gave *N*-deprotected bicyclic compound **13** (2.40 g, 97%) as an oil; $[\alpha]_D^{20}$ +16.1 (*c* 3.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.75 (d, J = 4.8 Hz, 1H), 3.94 (dt, J = 8.4, 2.0 Hz, 1H), 3.80 (dt, J = 3.3, 1.6 Hz, 1H), 3.50 (t, J = 2.0 Hz, 1H), 3.21 (dt, J = 5.6, 2.0 Hz, 1H), 2.50 (bq, J = 3.0 Hz, 1H), 2.38 (ddd, J = 14.0, 8.4, 3.2 Hz, 1H), 1.42 (dtd, J = 14.0, 2.8, 1.6 Hz, 1H), 0.95 (t, J = 8.0 Hz, 9H), 0.89 (s, 9H), 0.87 (s, 9H), 0.60 (q, J = 8.0 Hz, 6H), 0.08 (s, 3H), 0.07 (s, 3H), 0.06 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 77.3, 76.2, 67.2, 62.2, 46.2, 29.0, 25.7 (6C), 18.0, 17.8, 6.8 (3C), 4.9 (3C), –4.5, –4.6, –4.7, –5.0. Anal. Calcd for $C_{25}H_{53}NO_4Si_3$: C, 58.20; H, 10.35; N, 2.71. Found: C, 58.33; H, 10.39; N, 2.59.



13

(1*S*,4*R*,5*S*,6*S*,7*S*)-5,7-Bis-(*tert*-butyldimethylsilanyloxy)-3-oxo-6-triethylsilanyloxy-2-azabicyclo-[2.2.2]octane-2-carboxylic acid *tert*-butyl ester (14). To a solution of compound **13** (2.37 g, 4.6 mmol) in MeCN (25 mL) di-*tert*-butyldicarbonate (1.0 g, 4.6 mmol) and DMAP (55 mg) were sequentially

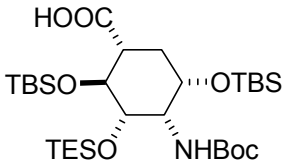
added under argon atmosphere. The reaction mixture was stirred at room temperature for 12 h, then the solvent was evaporated under reduced pressure and the crude residue was purified by silica gel flash chromatography (hexanes/EtOAc 9:1) to furnish 2.46 g (87%) of *N*-Boc protected lactam **14** as a colorless oil: $[\alpha]^{20}_{D}$ +19.3 (*c* 1.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.47 (t, *J* = 2.4 Hz, 1H, H-2), 3.98 (dt, *J* = 8.8, 2.4 Hz, 1H, H-1), 3.83 (dt, *J* = 3.2, 1.6 Hz, 1H, H-4), 3.54 (t, *J* = 2.0 Hz, 1H, H-3), 2.58 (q, *J* = 3.2 Hz, 1H, H-5), 2.35 (ddd, *J* = 14.0, 8.4, 2.4 Hz, 1H, H-5aβ), 1.46 (dtd, *J* = 14.0, 2.8, 1.6 Hz, 1H, H-5aα), 1.51 (s, 9H, Bu^t), 0.95 (t, *J* = 8.0 Hz, 9H, CH_3CH_2Si), 0.88 (s, 9H, Bu^t), 0.86 (s, 9H, Bu^t), 0.61 (q, *J* = 8.0 Hz, 6H, CH_3CH_2Si), 0.07 (s, 12H, Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 151.3, 82.6, 76.1, 75.3, 65.9, 63.1, 48.1, 28.0 (3C), 27.9, 25.7 (6C), 18.0, 17.9, 6.8 (3C), 4.7 (3C), –4.5, –4.9, –5.0, –5.1. Anal. Calcd for $C_{30}H_{61}NO_6Si_3$: C, 58.49; H, 9.98; N, 2.27. Found: C, 58.37; H, 9.90; N, 2.39.



14

(1*R*,2*S*,3*S*,4*S*,5*S*)-4-*tert*-Butoxycarbonylamino-2,5-bis-(*tert*-butyldimethylsilanyloxy)-3-triethylsilanyloxycyclohexanecarboxylic acid (15). A solution of bicyclic adduct **14** (2.47 g, 4.0 mmol) in THF (30 mL) at room temperature was treated with 958 mg (40 mmol) of LiOH dissolved in 10 mL of H_2O. After 24 h the reaction mixture was quenched with saturated NH_4Cl solution and extracted with CH_2Cl_2 and EtOAc. The combined organic extracts were dried, filtered and concentrated to leave a residue which was purified by silica gel flash chromatography (hexanes/EtOAc 8:2) to give partially protected carbasugar **15** (2.36 g, 93%) as a colorless oil: $[\alpha]^{20}_{D}$ –10.3 (*c* 0.7, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.70 (bs, 1H), 5.03 (d, *J* = 10.0 Hz, 1H), 4.24 (t, *J* = 2.8 Hz, 1H), 4.14 (q, *J* = 3.2 Hz, 1H), 3.95 (dt, *J* = 10.0, 3.8 Hz, 1H), 3.73 (t, *J* = 3.6 Hz, 1H), 2.78 (dt, *J* = 6.0, 2.8 Hz, 1H), 2.22 (ddd, *J* = 15.6, 6.0, 3.6 Hz, 1H), 2.09 (dt, *J* = 15.6, 3.2 Hz, 1H), 1.45 (s, 9H), 0.99 (t, *J* = 8.0 Hz, 9H),

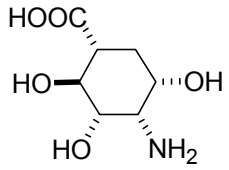
0.95 (s, 9H), 0.89 (s, 9H), 0.65 (q, J = 8.0 Hz, 6H), 0.17 (s, 3H), 0.16 (s, 3H), 0.12 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 154.5, 79.4, 73.0, 72.2, 69.3, 47.9, 45.5, 28.4 (3C), 27.4, 25.8 (3C), 25.7 (3C), 18.3, 17.8, 6.7 (3C), 4.9 (3C), –4.7, –5.0, –5.1 (2C). Anal. Calcd for $C_{30}H_{63}NO_7Si_3$: C, 56.83; H, 10.01; N, 2.21. Found: C, 56.94; H, 9.86; N, 2.29.



15

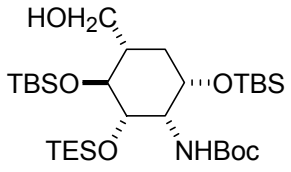
(1*R*,2*S*,3*S*,4*S*,5*S*)-4-Amino-2,3,5-trihydroxycyclohexanecarboxylic acid (1). Partially protected carbasugar **15** (2.30 g, 3.6 mmol) was treated with a mixture of 6N aqueous HCl/THF/MeOH (1:2:1) (20 mL) at room temperature for 3 h. The reaction mixture was then concentrated under vacuum, diluted with water and washed with CH_2Cl_2. The aqueous layer was evaporated under reduced pressure and the residue was passed through DOWEX 50W × 8 ion-exchange resin. Elution of the resin with 1.5% aqueous NH_4OH furnished amino acid **1** (674 mg, 98%) as a glassy solid: $[\alpha]^{20}_D$ –2.0 (*c* 0.5, MeOH); ^{1}H NMR (400 MHz, D_2O) δ 4.10 (dt, J = 12.4, 4.0 Hz, 1H, H-1), 3.78 (t, J = 10.0 Hz, 1H, H-4), 3.75 (dd, J = 10.2, 4.0 Hz, 1H, H-3), 3.69 (t, J = 4.0 Hz, 1H, H-2), 2.27 (ddd, J = 12.8, 10.0, 4.0 Hz, 1H, H-5), 2.07 (dt, J = 12.8, 4.0 Hz, 1H, H-5aβ), 1.67 (q, J = 12.8 Hz, 1H, H-5aα); ^{13}C NMR (100 MHz, D_2O) δ 180.6 (C-6), 70.4 (C-3), 70.2 (C-4), 65.5 (C-1), 56.7 (C-2), 48.1 (C-5), 30.0 (C-5a). Anal. Calcd for $C_7H_{13}NO_5$: C, 43.98; H, 6.85; N, 7.33. Found: C, 43.88; H, 6.91; N, 7.38.

HCl salt: $[\alpha]^{20}_D$ –4.5 (*c* 0.9, MeOH/H_2O 2:1); ^{1}H NMR (400 MHz, D_2O) δ 4.17 (dt, J = 12.0, 4.3 Hz, 1H, H-1), 3.84 (t, J = 10.3 Hz, 1H, H-4), 3.82 (dd, J = 10.3, 4.0 Hz, 1H, H-3), 3.77 (t, J = 4.0 Hz, 1H, H-2), 2.50 (ddd, J = 12.6, 10.3, 4.6 Hz, 1H, H-5), 2.17 (dt, J = 12.6, 4.6 Hz, 1H, H-5aβ), 1.77 (q, J = 12.6 Hz, 1H, H-5aα); ^{13}C NMR (100 MHz, D_2O) δ 176.6 (C-6), 69.6 (C-3), 69.5 (C-4), 64.7 (C-1), 56.6 (C-2), 45.3 (C-5), 29.3 (C-5a).



1

(1*S*,2*S*,3*S*,4*S*,6*S*)-[3,6-Bis-(*tert*-butyldimethylsilanyloxy)-4-hydroxymethyl-2-triethylsilanyloxycyclohexyl]carbamic acid *tert*-butyl ester (16). To a solution of compound **15** (500 mg, 0.8 mmol) in 4.5 mL of THF a 2M solution in THF of borane-methyl sulfide complex (3.2 mL, 6.4 mmol) was added dropwise, and the mixture was stirred at room temperature for 2 h. The reaction mixture was quenched by careful addition of 7 mL of MeOH. The solvent was then removed under vacuum and the residue was dissolved in CH_2Cl_2, washed with water, dried, filtered, and concentrated to afford a residue that was purified by silica gel flash chromatography (hexanes/EtOAc 9.2:0.8). Partially protected amino alcohol **16** (426 mg, 86%) was obtained as an oil: $[\alpha]^{20}_D$ +18.0 (*c* 2.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.03 (d, *J* = 10.0 Hz, 1H), 4.03 (ddd, *J* = 10.0, 7.6, 6.4 Hz, 1H), 3.8-4.0 (m, 4H), 3.70 (t, *J* = 3.6 Hz, 1H), 2.00 (ddd, *J* = 14.4, 5.6, 3.2 Hz, 1H), 1.83 (m, 1H), 1.67 (bd, *J* = 14.4 Hz, 1H), 1.44 (s, 9H), 1.38 (t, *J* = 6.0 Hz, 1H), 0.98 (t, *J* = 8.0 Hz, 9H), 0.90 (s, 9H), 0.88 (s, 9H), 0.63 (q, *J* = 8.0 Hz, 6H), 0.08 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 78.7, 73.8, 71.5, 69.0, 64.2, 49.6, 42.0, 28.7, 28.4 (3C), 25.8 (3C), 25.7 (3C), 18.0, 17.9, 6.9 (3C), 4.7 (3C), –4.4, –4.6, –4.9, –5.3. Anal. Calcd for $C_{30}H_{65}NO_6Si_3$: C, 58.11; H, 10.57; N, 2.26. Found: C, 58.19; H, 10.65; N, 2.12.

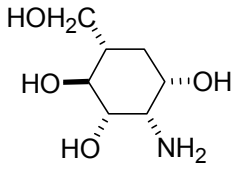


16

(1*S*,2*S*,3*S*,4*S*,6*S*)-3-Amino-6-hydroxymethylcyclohexane-1,2,4-triol (2). The partially protected carbasugar **16** (420 mg, 0.68 mmol) was treated with a mixture of 6N aqueous HCl/THF/MeOH (1:2:1) (5 mL) at room temperature for 3 h. The reaction mixture was then concentrated under vacuum,

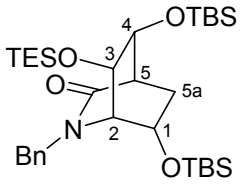
diluted with water and washed with CH_2Cl_2. The aqueous layer was evaporated under reduced pressure and the residue was passed through DOWEX 50W × 8 ion-exchange resin. Elution with 1.5% aqueous NH_4OH furnished amino alcohol **2** (116 mg, 96%) as an oil: $[\alpha]^{20}_D$ –7.0 (*c* 1.3, MeOH); ^{1}H NMR (400 MHz, D_2O) δ 3.3-4.2 (m, 6H), 1.7-2.0 (m.1H), 1.3-1.6 (m, 2H); ^{13}C NMR (100 MHz, D_2O) δ 73.5, 69.5, 68.0, 62.5, 55.9, 40.6, 28.7. Anal. Calcd for $C_7H_{15}NO_4$: C, 47.45; H, 8.53; N, 7.90. Found: C, 47.39; H, 8.55; N, 7.94.

HCl salt: $[\alpha]^{20}_D$ –7.0 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, D_2O) δ 4.13 (dt, *J* = 12.4, 4.4 Hz, 1H, H-1), 3.79 (dd, *J* = 10.0, 4.4 Hz, 1H, H-3), 3.77 (dd, *J* = 11.2, 4.0 Hz, 1H, H-6), 3.74 (bt, *J* = 4.0 Hz, 1H, H-2), 3.63 (dd, *J* = 11.2, 6.0 Hz, 1H, H-6'), 3.45 (t, *J* = 10.8 Hz, 1H, H-4), 1.99 (dtd, *J* = 13.0, 4.0, 0.8 Hz, 1H, H-5aβ), 1.60 (dddt, *J* = 12.8, 10.8, 6.0, 4.3 Hz, 1H, H-5), 1.43 (q, *J* = 12.8 Hz, 1H, H-5aα); ^{13}C NMR (150 MHz, D_2O) δ 71.1 (C-3), 70.0 (C-4), 65.7 (C-1), 62.6 (C-6), 57.7 (C-2), 40.6 (C-5), 29.6 (C-5a).



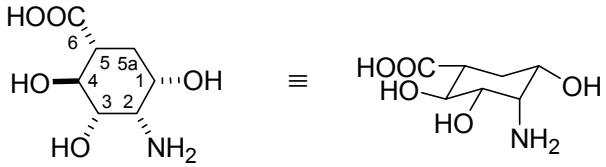
2

Table S1. Diagnostic ^{1}H NMR data (300 MHz) of compound **12** in $CDCl_3$, δ in ppm, J in Hz. NOE intensities: w, weak; m, medium; s, strong.



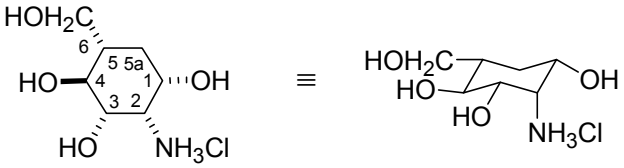
H-1	4.00 (dt)	$^{3}J_{1,2}$	2.5
H-2	3.30 (t)	$^{3}J_{2,3}$	2.0
H-3	3.47 (t)	$^{3}J_{3,4}$	2.0
H-4	3.84 (dt)	$^{3}J_{4,5}$	3.2
H-5	2.64 (q)	$^{3}J_{5,5a\alpha}$	3.0
H-5aβ	2.38 (ddd)	$^{3}J_{5,5a\beta}$	3.0
H-5aα	1.46 (dtd)	$^{3}J_{1,5a\beta}$	8.0
		$^{3}J_{1,5a\alpha}$	3.0
NOEs		$^{2}J_{5a\alpha,5a\beta}$	13.8
H-1–H-3 (m)	H-1–H-5aβ (s)	$^{4}J_{4,5a\alpha}$	1.6
H-3–H-5 (m)			

Table S2. Diagnostic ^{1}H NMR data (400 MHz) of compound **1** in D_2O, δ in ppm, J in Hz. NOE intensities: w, weak; m, medium; s, strong.



H-1	4.10 (dt)	$^{3}J_{1,2}$	4.0
H-2	3.69 (t)	$^{3}J_{2,3}$	4.0
H-3	3.75 (dd)	$^{3}J_{3,4}$	10.0
H-4	3.78 (t)	$^{3}J_{4,5}$	10.0
H-5	2.27 (ddd)	$^{3}J_{5,5a\beta}$	4.0
H-5aβ	2.07 (dt)	$^{3}J_{5,5a\alpha}$	12.8
H-5aα	1.67 (q)	$^{3}J_{1,5a\beta}$	4.0
		$^{3}J_{1,5a\alpha}$	12.8
NOEs		$^{2}J_{5a\alpha,5a\beta}$	12.8
H-1–H-3 (m)	H-3–H-5 (m)		
H-1–H-5 (w)	H-4–H-5aα (w)		

Table S3. Diagnostic ^{1}H NMR data (400 MHz) of compound **2**·HCl in D_2O, δ in ppm, J in Hz. NOE intensities: w, weak; m, medium; s, strong.



H-1	4.13 (dt)	$^{3}J_{1,2}$	4.3
H-2	3.74 (bt)	$^{3}J_{2,3}$	4.0
H-3	3.79 (dd)	$^{3}J_{3,4}$	10.8
H-4	3.45 (t)	$^{3}J_{4,5}$	10.8
H-5	1.60 (dddt)	$^{3}J_{5,6}$	4.0
H-6	3.77 (dd)	$^{3}J_{5,6'}$	6.0
H-6'	3.63 (dd)	$^{3}J_{5,5a\beta}$	4.4
H-5aβ	1.99 (dtd)	$^{3}J_{5,5a\alpha}$	12.8
H-5aα	1.43 (q)	$^{3}J_{1,5a\beta}$	4.0
		$^{3}J_{1,5a\alpha}$	12.4
NOEs		$^{2}J_{5a\alpha,5a\beta}$	12.8
H-1–H-3 (m)	H-3–H-5 (m)	$^{2}J_{6,6'}$	11.2
H-1–H-5 (w)	H-4–H-5aα (w)	$^{4}J_{2,5a\beta}$	0.8

Supporting Information References and Notes

1. Throughout the experimental section, IUPAC nomenclature for all compounds has been adopted. This criterion has encountered some discrepancies in formulae numbering in the text. Where indicated, the spectral assignments follow the numbering adopted in the text.

2. Rassu, G.; Zanardi, F.; Battistini, L.; Gaetani, E.; Casiraghi, G. *J. Med. Chem.* **1997**, *40*, 168-180.