Synthesis of Amino Carba Sugars and Conformationally Restricted Polyhydroxy γ-Amino Acids from (−)-Quinic Acid

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Dedicated to Professor José Luis Soto on the occasion of his retirement

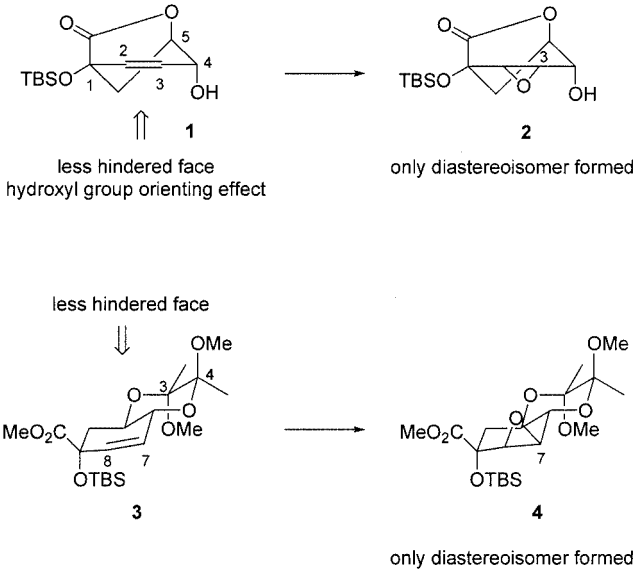
Keywords: Amino carba sugars / Polyhydroxy γ-amino acids / Regioselectivity / Glycosidase inhibitors

Efficient syntheses of two novel positional stereoisomers of valiolamine, a potent glycosidase inhibitor, and two polyhydroxy γ-amino acids are reported. The syntheses involve regio- and stereoselective azidolysis of epoxides by trimethylsilyl azide with $BF_3{\cdot}OEt_2$ as Lewis acid.

Introduction

Sugar analogues in which the ring oxygen atom has been replaced by a methylene group (carba sugars or pseudosugars[1]) have attracted considerable interest as inhibitors of glycosidase enzymes. Glycosidases are involved in numerous biological processes, and glycosidase inhibitors have enormous potential for the treatment of many diseases, including cancer, diabetes and viral infections. This is because they alter the glycosylation or catabolism of glycoproteins, or block the recognition of specific sugars.[2] Carba sugars also provide rigid systems that can be used to display pharmacophoric groups in well-defined spatial orientations.[3] Examples of naturally occurring carba sugars include carba-α-D-galactose,[4] valienamine,[5] validamine,[5b,6] and valiolamine.[1c,5b,7] On the other hand, in recent years considerable effort has been devoted to the synthesis of cyclic amino acids which can be incorporated into peptides and peptidomimetics to create conformationally restricted analogues that can be used to obtain important information about key structural features of receptor ligand complexes.[8] Also, recently, Granja et al. have used (1*R*,3*S*)-3-aminocyclohexanecarboxylic acid to develop new types of peptide nanotube with hydrophobic cavities.[9] Appropriate functionalization of this kind of cyclic amino acid should lead to nanotubes with greater selectivity as molecule containers, ion channels, receptors, etc.

We reported recently a practical route to a variety of polyhydroxycyclohexanes that involved stereocontrolled epoxide formation and hydrolysis: epoxidation of cyclohexenes **1** and **3** afforded **2** and **4**, respectively,[10] as the sole diastereoisomers (Scheme 1), while subsequent hydrolysis gave mainly ring opening on C-3 and C-7, respectively.[11] We now extend this strategy to the regio- and diastereoselective synthesis of the two novel amino carba sugars **5a** and **6a**, which are positional stereoisomers of valiolamine, and the corresponding polyhydroxy γ-amino acids **5b** and **6b**, that could be used to develop more selective nanotubes (Figure 1).



Scheme 1. Stereocontrolled epoxide formation

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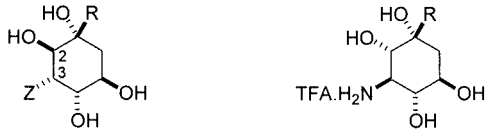


5a R = CH_2OH, Z = NH_2.TFA
5b R = CO_2H, Z = NHBoc

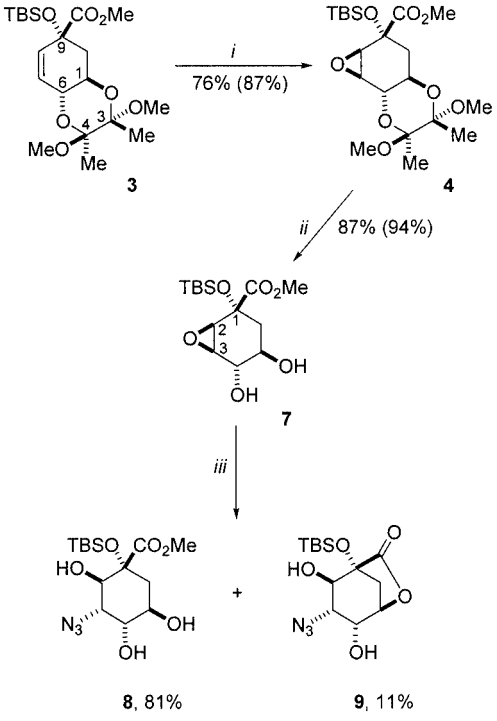
6a R = CH_2OH
6b R = CO_2H

Figure 1. Target compounds

Results and Discussion

Synthesis of Compounds 5

Compounds **5** were synthesized via epoxide **4**, which was prepared in 76% yield (87% taking into account the recovered starting material) by treatment of **3** with trifluoroperacetic acid that had been freshly prepared from urea−hydrogen peroxide (UHP) adduct and trifluoroacetic anhydride. This approach (Scheme 2) improves the previously reported protocol.[11]

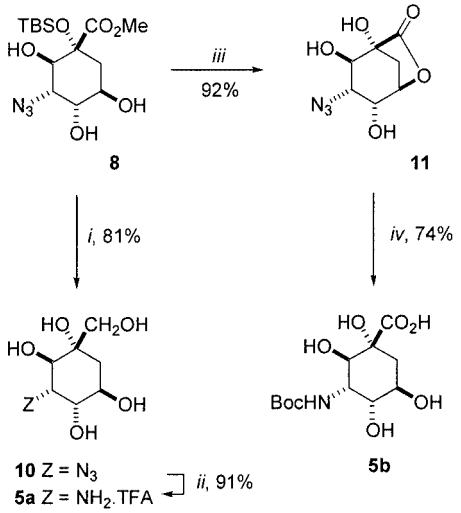


Scheme 2. Reagents and conditions: (i) UHP, TFAA, Na_2HPO_4, CH_2Cl_2, 0 °C; (ii) TFA (aq. 50%), room temp.; (iii) $TMSN_3$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, Δ

Attempts to azidolyse **4** using combinations of various azides (NaN_3, LiN_3, NaN_3/LiCl, $TMSN_3$), solvents (DMF, EtOH, MeOH/H_2O, H_2O, C_6H_6, CH_2Cl_2, $ClCH_2CH_2Cl$), Lewis acids [Ti(O*i*Pr)$_4$, $ZnCl_2$, $BF_3{\cdot}OEt_2$] and reaction temperatures all afforded mainly starting material. We reasoned that the poor reactivity of epoxide **4** might be due to conformational impediments to *trans*-diaxial opening and therefore removed its *trans*-diol protecting group, so that treatment of **4** with aqueous trifluoroacetic acid gave the diol **7** in good yield. Subsequent azidolysis of epoxide **7** by $TMSN_3$ with $BF_3{\cdot}OEt_2$ as Lewis acid, in refluxing dichloromethane, afforded a chromatographically separable mixture of the azido ester **8** (81%) and the azido carbolactone **9** (11%). X-ray crystallography was used to confirm the structure of compound **8** (Figure 2),[12] and the diaxial coupling constant between 2-H and 3-H ($J_{2,3}$ = 9.1 Hz) supports that of **9**.

Figure 2. X-ray structure of **8**

The desired amino carba sugar **5a** was obtained from azido ester **8** by the three-step reaction sequence shown in Scheme 3. Reduction of **8** with lithium borohydride in methanol afforded a mixture of alcohols because of a *cis*-1,2 migration of the silyl group from the tertiary hydroxy group to the primary hydroxy group. Treatment of this mixture with aqueous trifluoroacetic acid at 40 °C gave azido alcohol **10** in 81% yield from **8**. Finally, reduction of **10** by catalytic hydrogenolysis in an acid medium (to avoid decomposition of the free amine) afforded **5a** in 91% yield.



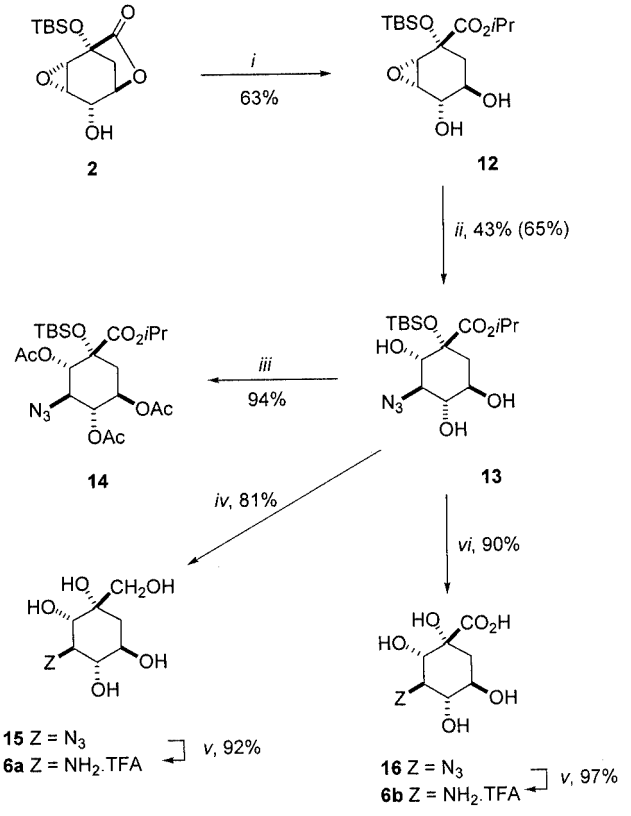
Scheme 3. Reagents and conditions: (i) 1) $LiBH_4$, MeOH, THF, 0 °C; 2) TFA (aq. 50%), 40 °C; (ii) H_2, Pd/C, MeOH, TFA, room temp.; (iii) TFA (aq. 50%), 80 °C; (iv) 1) H_2, Pd/C, Boc_2O, EtOAc, room temp.; 2) LiOH, room temp.; 3) Amberlite IR-120 (H^+), room temp.

Transformation of **8** into the amino acid **5b** was more difficult because treatment of **8** with aqueous trifluoroacetic

acid at 80 °C afforded exclusively the 1,5-carbolactone **11**. In order to proceed to **5b**, it was necessary firstly to transform the azide group in the corresponding Boc derivative and then hydrolyse the lactone under basic conditions. Catalytic hydrogenolysis in the presence of Boc_2O gave the desired Boc-amino carbolactone, and subsequent reaction with lithium hydroxide, followed by treatment with Amberlite IR-120 (H^+) ion exchange resin and lyophilization, gave the desired amino acid derivative **5b** in 74% yield from **11**.

Synthesis of Compounds 6

For preparation of compounds **6** we employed the epoxide **2**[11] (Scheme 4). Since this substrate was practically inert when direct azidolysis was attempted (presumably because the nucleophile must attack from the more hindered face), we tried to open the lactone to the corresponding methyl ester. However, attempts using NaOMe/MeOH, K_2CO_3/MeOH, $Ti(OMe)_4$/MeOH and $Ti(OiPr)_4$/MeOH all afforded very low conversion rates, probably due to relactonization to **2**. Finally, reaction with 2-propanol and $Ti(OiPr)_4$ gave the isopropyl ester **12** in 63% yield, and azidolysis of **12** by treatment with $TMSN_3$ and $BF_3{\cdot}OEt_2$ in refluxing dichloromethane afforded the azido alcohol **13** in 43% yield (65% taking into account the recovered starting material). The regiochemistry of the azidolysis reaction was confirmed by studying its acetylated derivative **14** (obtained by treatment of **13** with acetic anhydride). The ^1H NMR spectrum of **14** showed that 2-H and 3-H are axial ($J_{2,3}$ = 10.4, $J_{3,4}$ = 10.0 Hz).



Scheme 4. Reagents and conditions: (i) $Ti(OiPr)_4$, *i*PrOH, C_6H_6, Δ; (ii) $TMSN_3$, $BF_3{\cdot}OEt_2$, DCM, Δ; (iii) Ac_2O, Et_3N, DMAP, DCM, room temp.; (iv) 1) $LiBH_4$, MeOH, THF, 0 °C; 2) TFA (aq. 50%), 40 °C; (v) H_2, Pd/C, TFA, MeOH, room temp.; (vi) TFA (aq. 50%), 90 °C

The desired amino carba sugar **6a** was obtained from azido ester **13** by a similar method to that for compound **5a** from **8**. Reduction of **13** with lithium borohydride in methanol, followed by treatment with aqueous trifluoroacetic acid at 40 °C, gave an 81% yield of azido alcohol **15**, which upon catalytic hydrogenolysis in an acidic medium afforded the desired amino derivative **6a** in 92% yield.

Finally, azido ester **13** was transformed into amino acid **6b** in 87% overall yield by treatment with aqueous trifluoroacetic acid at 80 °C, which afforded carboxylic acid **16** in 90% yield followed by catalytic hydrogenolysis in an acidic medium.

Conclusion

In conclusion, epoxide azidolysis with $TMSN_3$ and $BF_3{\cdot}OEt_2$ allows the regio- and stereoselective synthesis of the novel 3-amino carba sugars **5a** and **6a**, positional stereoisomers of valiolamine, and the new conformationally restricted polyhydroxy γ-amino acids **5b** and **6b**, from inexpensive commercially available (−)-quinic acid. Conformation seems to have an important influence on the efficiency of the ring opening reaction.

Experimental Section

General Remarks: All starting materials and reagents were obtained from commercial sources and used without further purification. FT-IR spectra were recorded from films sandwiched between NaCl plates. $[\alpha]_D$ values are given in 10^{-1} deg·cm^2·g^{-1}. ^1H NMR spectra (250, 300, 400, and 500 MHz), ^{19}F NMR spectra (282 MHz), and ^{13}C NMR spectra (63, 75, 100, and 125 MHz) were measured in deuterated solvents. *J* values are given in Hz. NMR assignments were made using a combination of 1 D, COSY, and DEPT-135 experiments. All procedures involving the use of ion exchange resins were carried out at room temperature and using Milli-Q deionized water. Amberlite IR-120 (H^+) (cation exchanger) was washed alternately with water, 10% HCl, water, 10% NaOH, 10% HCl, and finally water before use.

Methyl (1*R*,3*S*,4*S*,6*S*,7*R*,8*R*,9*R*)-9-(*tert*-Butyldimethylsilyloxy)-7,8-epoxy-3,4-dimethoxy-3,4-dimethyl-2,5-dioxabicyclo[4.4.0]decane-9-carboxylate (4): Freshly distilled trifluoroacetic anhydride (2.14 mL, 15.12 mmol) was added to a suspension of urea−hydrogen peroxide adduct (UHP) (1.22 g, 12.98 mmol) in dry dichloromethane (10 mL) at 0 °C and under an inert gas. The resultant solution was stirred at this temperature for 2 h and then was added to a suspension of anhydrous Na_2HPO_4 (84 g, 28.08 mmol) in dry dichloromethane (10 mL) at 0 °C and under an inert gas. After 30 min, a solution of alkene **3**[11] (0.9 g, 2.16 mmol) in dry dichloromethane (12 mL) was added dropwise and the resulting solution was stirred at this temperature for 72 h. Powdered K_2CO_3 was added and after 15 min, the suspension was filtered and washed with dichloromethane. The filtrate and washings were concentrated to give a white solid which was purified by flash chromatography elut-

ing with 15% diethyl ether/hexanes, to yield 0.71 g of epoxide **4**[11] (76%) and 0.12 g of starting material (13%).

Methyl (1*R*,2*R*,3*R*,4*S*,5*R*)-1-(*tert*-Butyldimethylsilyloxy)-2,3-epoxy-4,5-dihydroxycyclohexane-1-carboxylate (7): A solution of the epoxide **4** (0.5 g, 1.16 mmol) in aqueous TFA (50%, 12 mL) was stirred at room temperature for 15 min. Powdered K_2CO_3 was added and the solvent was evaporated. The crude reaction mixture was purified by flash chromatography eluting with 80% diethyl ether/hexanes to yield 318 mg of the diol **7** (87%) as white needles, and 38 mg of starting material (7%). M.p. 95−97 °C (hexane). $[\alpha]_D^{20} = -31$ (c = 1.1 in $CHCl_3$). IR (film): $\tilde{\nu}$ = 1742 (C=O), 3478 (O−H) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 0.10 (s, 3 H), 0.14 (s, 3 H), 0.88 (s, 9 H), 1.77 (dd, J = 13.6, 11.5 Hz, 1 H), 1.91 (ddd, J = 1.2, 3.7, 13.6 Hz, 1 H), 2.42 (s, 1 H, OH), 2.89 (s, 1 H, OH), 3.20 (d, J = 3.3 Hz, 1 H), 3.28 (d, J = 3.3 Hz, 1 H), 3.78 (m, 2 H), 3.79 (s, 3 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = −3.5 ($SiCH_3$), −3.4 ($SiCH_3$), 18.4 [$C(CH_3)_3$], 25.7 [$C(CH_3)_3$], 34.8 (CH_2), 52.5 (OCH_3), 55.9 (CH), 56.5 (CH), 69.4 (CH), 72.1 (CH), 76.3 (C), 172.1 (C) ppm. MS (CI): m/z = 319 [MH^+]. HRMS: calcd. for $C_{14}H_{27}O_6Si$ [MH^+] 319.1577; found 319.1577.

Methyl (1*R*,2*R*,3*S*,4*R*,5*R*)-3-Azido-1-(*tert*-butyldimethylsilyloxy)-2,4,5-trihydroxycyclohexane-1-carboxylate (8) and (1*R*,2*R*,3*S*,4*R*,5*R*)-3-Azido-1-(*tert*-butyldimethylsilyloxy)-2,4-dihydroxycyclohexane-1,5-carbolactone (9): $TMSN_3$ (0.44 mL, 3.3 mmol) and $BF_3{\cdot}OEt_2$ (0.57 mL, 4.5 mmol) were added to a stirred solution of the epoxide **7** (320 mg, 1.01 mmol) in dry dichloromethane (10 mL). The resultant solution was heated under reflux for 1.5 h. The mixture was diluted with dry dichloromethane and then poured into saturated K_2CO_3 at 0 °C. The organic phase was separated and the aqueous phase was extracted twice with dichloromethane. The combined organic extracts were dried (anhydrous Na_2SO_4), filtered and the solvents evaporated. The residue was purified by flash chromatography eluting with diethyl ether giving azido ester **8** (293 mg, 81%) as white prisms and azido carbolactone **9** (37 mg, 11%) as white needles.

8: M.p. 126−128 °C (10% diethyl ether/hexane). $[\alpha]_D^{20} = -23$ (c = 1.4 in $CHCl_3$). IR (film): $\tilde{\nu}$ = 1715 (C=O), 2121 (N=N), 3358 (O−H) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 0.09 (s, 3 H), 0.10 (s, 3 H), 0.88 (s, 9 H), 2.26−2.10 (m, 2 H), 2.93 (d, J = 5.5 Hz, 1 H), 3.79 (s, 3 H), 4.10−3.94 (m, 3 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = −3.6 ($SiCH_3$), −3.2 ($SiCH_3$), 18.3 [$C(CH_3)_3$], 25.6 [$C(CH_3)_3$], 37.0 (CH_2), 52.5 (OCH_3), 63.1 (CH), 68.1 (CH), 72.5 (CH), 75.4 (CH), 79.6 (C), 175.0 (C) ppm. MS (CI): m/z = 362 [MH^+]. HRMS: calcd. for $C_{14}H_{28}N_3O_6Si$ [MH^+] 362.1747; found, 362.1760.

9: M.p. 89−90 °C (hexane). $[\alpha]_D^{20} = -24$ (c = 1.5 in $CHCl_3$). IR (film): $\tilde{\nu}$ = 1790 (C=O), 2110 (N=N), and 3520 (O−H) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 0.13 (s, 3 H), 0.22 (s, 3 H), 0.91 (s, 9 H), 2.37 (dd, J = 5.9, 11.9 Hz, 1 H), 2.50 (d, J = 11.9 Hz, 1 H), 2.66 (d, J = 1.9 Hz, 1 H, OH), 2.96 (d, J = 1.3 Hz, 1 H, OH), 3.58 (dd, J = 4.5, 9.1 Hz, 1 H), 3.98 (dd, J = 1.1, 9.1 Hz, 1 H), 4.21 (ddd, J = 1.3, 4.6, 4.5 Hz, 1 H), 4.71 (dd, J = 5.9, 4.6 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = −3.4 ($SiCH_3$), −3.3 ($SiCH_3$), 18.1 [$C(CH_3)_3$], 25.6 [$C(CH_3)_3$], 35.1 (CH_2), 64.3 (CH), 66.9 (CH), 74.5 (CH), 75.7 (CH), 76.8 (C), 173.0 (C) ppm. MS (CI): m/z = 330 [MH^+]. HRMS: calcd. for $C_{13}H_{24}N_3O_5Si$ [MH^+] 330.1485; found, 330.1486.

(1*S*,2*R*,3*S*,4*R*,5*R*)-3-Azido-1-hydroxymethyl-1,2,4,5-cyclohexanetetrol (10): Lithium borohydride (5 mg, 0.22 mmol) was added to a stirred solution of the ester **8** (73 mg, 0.20 mmol) in a dry solution of methanol in tetrahydrofuran (2 mL, 1:20 v/v) under argon and at 0 °C. The reaction mixture was stirred at room temperature for 45 min and then ethyl acetate (1 mL) and water (2 mL) were added. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (4 × 3 mL). The combined organic extracts were dried (anhydrous Na_2SO_4), filtered and concentrated under reduced pressure. The crude reaction mixture was purified by flash chromatography [eluent: 1. dichloromethane, 2. methanol/dichloromethane (2%)] to yield 54 mg of a mixture of hydroxysilyl ethers. A solution of the crude reaction mixture (54 mg) in aqueous TFA (1.7 mL, 50%) was heated at 40 °C for 1h. The solvent was evaporated and the residue was purified by flash chromatography eluting with 10% methanol/ethyl acetate to yield azido alcohol **10** (37 mg, 81%) as a white foam. $[\alpha]_D^{20} = -4$ (c = 1.5 in MeOH). IR (film): $\tilde{\nu}$ = 2120 (N=N), 3377 (O−H) cm^{-1}. ^1H NMR (500 MHz, CD_3OD): δ = 1.74 (dd, J = 6.2, 14.0 Hz, 1 H), 1.86 (dd, J = 3.4, 14.0 Hz, 1 H), 3.59 (d, J = 11.2 Hz, 1 H), 3.69 (d, J = 11.2 Hz, 1 H), 3.73 (dd, J = 2.7, 7.6 Hz, 1 H), 3.83−3.83 (m, 2 H), 3.91 (d, J = 7.6 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, CD_3OD): δ = 37.3 (CH_2), 65.7 (CH), 67.5 (CH_2), 69.3 (CH), 74.0 (CH), 74.5 (CH), 76.0 (C) ppm. MS (CI): m/z = 194 [$MH^+ - N_2$]. HRMS: calcd. for $C_7H_{16}NO_5$ [$MH^+ - N_2$] 194.1028; found 194.1025.

(1*S*,2*R*,3*S*,4*R*,5*R*)-3-Amino-1-hydroxymethyl-1,2,4,5-cyclohexanetetrol, Trifluoroacetic Acid Salt (5a): A suspension of the azide **10** (16 mg, 0.07 mmol) and 10% palladium on carbon (2 mg) in methanol (0.75 mL) and TFA (17 μL) was shaken under hydrogen at room temperature for 1 h. The mixture was filtered through Fluorosil, which was then washed with methanol. The filtrate and washings were concentrated under reduced pressure to yield ammonium salt **5a** (22 mg, 91%) as a colourless oil. $[\alpha]_D^{20} = -5$ (c = 1.1 in MeOH). IR (film): $\tilde{\nu}$ = 3398 (O−H) cm^{-1}. ^1H NMR (250 MHz, CD_3OD): δ = 1.83−1.70 (m, 2 H), 3.43 (m, 2 H), 3.62 (d, J = 11.5 Hz, 1 H), 3.90−3.83 (m, 3 H) ppm. ^{13}C NMR (125 MHz, CD_3OD): δ = 36.6 (CH_2), 56.3 (C), 56.8 (CH), 67.2 (CH_2), 68.5 (CH), 71.0 (CH), 76.6 (CH), 118.1 (C, $J_{C,F}$ = 290 Hz), 163.3 (C, $J_{C,F}$ = 34 Hz) ppm. MS (CI): m/z = 194 [MH^+ − TFA]. HRMS: calcd. for $C_7H_{16}NO_5$ [MH^+ − TFA] 194.1028; found 194.1019.

(1*R*,2*R*,3*S*,4*R*,5*R*)-3-Azido-1,2,4-trihydroxycyclohexan-1,5-carbolactone (11): A solution of the silyl ether **8** (60 mg, 0.17 mmol) in aqueous TFA (1.7 mL, 50%) was heated at 80 °C for 5 h. The solvent was evaporated and the residue was purified by flash chromatography eluting with 5% methanol/dichloromethane to afford hydroxy carbolactone **11** (33 mg, 92%) as a colourless oil. $[\alpha]_D^{20}$ = +7 (c = 1.5 in MeOH). IR (film): $\tilde{\nu}$ = 1784 (C=O), 2116 (N=N), 3410 (O−H) cm^{-1}. ^1H NMR (250 MHz, CD_3OD): δ = 2.11 (dd, J = 5.6, 12.0 Hz, 1 H), 2.24 (d, J = 12.0 Hz, 1 H), 3.03 (dd, J = 4.6, 9.6 Hz, 1 H), 3.69 (d, J = 9.6 Hz, 1 H), 4.00 (dd, J = 4.6, 4.5 Hz, 1 H), 4.42 (t, J = 5.3 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, CD_3OD): δ = 36.1 (CH_2), 66.0 (CH), 68.5 (CH), 74.8 (CH), 76.2 (C), 77.1 (CH), 176.9 (C) ppm. MS (CI): m/z = 216 [MH^+]. HRMS: calcd. for $C_7H_{10}N_3O_5$ [MH^+] 216.0620; found 216.0616.

(1*S*,2*R*,3*S*,4*R*,5*R*)-3-(*tert*-Butoxycarbonylamino)-1,2,4,5-tetrahydroxycyclohexane-1-carboxylic Acid (5b): A suspension of the azide **11** (30 mg, 0.14 mmol), Boc_2O (39 mg, 0.18 mmol), and 10% palladium on carbon (3 mg) in ethyl acetate (1.5 mL) was shaken under hydrogen at room temperature for 24 h. The mixture was filtered through Fluorosil, which was then washed with methanol. The filtrate and washings were concentrated under reduced pressure. A solution of the crude reaction products (30 mg) in THF (1 mL) was treated at 0 °C with aqueous lithium hydroxide (0.3 mL, 0.5 M) and stirred at room temperature for 25 min. THF was removed under reduced pressure, and the remaining aqueous solution was diluted with water and treated with Amberlite IR-120 until

pH = 6 was reached. The resin was filtered and washed with water. The filtrate was washed with diethyl ether (× 2) and then lyophilized to afford amino acid **5b** (32 mg, 74%) as an amorphous white solid. M.p. 201−203 °C. $[\alpha]_D^{20} = -2$ (c = 0.8 in MeOH). IR (film): $\tilde{\nu}$ = 1655 (C=O), 1691 (C=O), 3398 (O−H and N−H) cm^{-1}. ^1H NMR (250 MHz, D_2O): δ = 1.26 (s, 9 H), 1.66 (m, 2 H), 3.55 (d, J = 8.2 Hz, 1 H), 3.67 (dd, J = 5.3, 10.4 Hz, 1 H), 3.71 (m, 1 H), 3.98 (dd, J = 3.0, 7.9 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, D_2O): δ = 28.0 [C(CH_3)$_3$], 29.9 [C(CH_3)$_3$], 35.4 (CH_2), 68.4 (C), 72.4 (CH), 73.4 (CH), 77.9 (CH), 81.4 (C), 157.9 (C), 179.8 (C) ppm. MS (CI): m/z = 208 [MH^+ − Boc]. HRMS: calcd. for $C_7H_{14}O_6N$ [MH^+ − Boc] 208.0821; found 208.0816.

Isopropyl (1*R*,2*S*,3*S*,4*S*,5*R*)-1-(*tert*-Butyldimethylsilyloxy)-2,3-epoxy-4,5-dihydroxycyclohexane-1-carboxylate (12): Titanium(IV) isopropoxide (3.13 mL, 10.60 mmol) and 2-propanol (0.74 mL, 9.72 mmol) were added to a stirred solution of the lactone **2**[11] (2.53 g, 8.84 mmol) in dry benzene (88 mL) under argon. The resulting mixture was heated at 75 °C for 5 h. After cooling to room temperature, diethyl ether and 5% H_2SO_4 were added. The resulting suspension was stirred until two clear phases were obtained. The organic layer was separated and the aqueous phase was extracted with diethyl ether (× 3). The combined organic extracts were dried (anhydrous Na_2SO_4), filtered and concentrated under reduced pressure. The crude reaction mixture was purified by flash chromatography eluting with diethyl ether to yield the ester **12** as white needles (1.93 g, 63%). M.p. 108−109 °C (diethyl ether). $[\alpha]_D^{20} = +1$ (c = 1.0 in $CHCl_3$). IR (nujol): $\tilde{\nu}$ = 1728, 1742 (C=O), 3460 (O−H) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 0.14 (s, 3 H), 0.15 (s, 3 H), 0.90 (s, 9 H), 1.28 (d, J = 6.3 Hz, 3 H), 1.29 (d, J = 6.3 Hz, 3 H), 1.92 (m, 2 H), 2.24 (d, J = 3.3 Hz, 1 H), 2.37 (d, J = 7.4 Hz, 1 H), 2.51 (br. s, 2 H, OH), 3.50 (dd, J = 3.9, 2.2 Hz, 1 H), 3.54 (d, J = 3.9 Hz, 1 H), 3.91−3.75 (m, 2 H), 5.07 (sept, J = 6.3 Hz, 1 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = −3.2 (SiMe), −3.2 (SiMe), 18.5 [C(CH_3)$_3$], 21.6 (CH_3), 21.6 (CH_3), 25.8 [C(CH$_3$)$_3$], 41.2 (CH_2), 57.5 (CH), 58.0 (CH), 67.4 (CH), 69.5 (CH), 72.9 (CH), 75.1 (C), 172.6 (C) ppm. MS (CI): m/z = 347 [MH^+]. HRMS: calcd. for $C_{16}H_{31}O_6Si$ [MH^+] 347.1890; found 347.1896.

Isopropyl (1*R*,2*S*,3*R*,4*R*,5*R*)-3-Azido-1-(*tert*-butyldimethylsilyloxy)-2,4,5-trihydroxycyclohexane-1-carboxylate (13): $TMSN_3$ (0.31 mL, 2.31 mmol) and $BF_3{\cdot}OEt_2$ (0.33 mL, 2.6 mmol) were added to a stirred solution of the epoxide **12** (200 mg, 0.58 mmol) in dry dichloromethane (2 mL). The resulting solution was heated under reflux for 2.6 h. The mixture was diluted with dry dichloromethane and then poured into saturated K_2CO_3 at 0 °C. The organic layer was separated and the aqueous phase was extracted twice with dichloromethane. The combined organic extracts were dried (anhydrous Na_2SO_4), filtered and the solvents evaporated. The residue was purified by flash chromatography eluting with 50% diethyl ether/hexanes to yield 96 mg of azido ester **13** (43%) as a colourless oil, and 67 mg of starting material (34%). $[\alpha]_D^{20} = -2$ (c = 2.2 in $CHCl_3$). IR (film): $\tilde{\nu}$ = 1748 (C=O), 2115 (N=N), 3419 (O−H) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 0.14 (s, 3 H), 0.20 (s, 3 H), 0.91 (s, 9 H), 1.25 (d, J = 6.3 Hz, 6 H), 1.74 (dd, J = 13.7, 11.6 Hz, 1 H), 2.14 (dd, J = 4.8, 13.7 Hz, 1 H), 2.59 (d, J = 8.5 Hz, 1 H), 3.24 (dd, J = 9.3, 9.5 Hz, 1 H), 3.41 (t, J = 9.9 Hz, 1 H), 3.85 (m, 3 H), 5.03 (m, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = −3.2 ($SiCH_3$), −2.6 ($SiCH_3$), 19.0 [C(CH_3)$_3$], 21.6 (2 × CH_3), 26.3 [C(CH$_3$)$_3$], 38.4 (CH_2), 67.0 (CH), 68.7 (CH), 70.1 (CH), 75.7 (CH), 75.9 (CH), 79.2 (C), 171.5 (C) ppm. MS (CI): m/z = 390 [MH^+]. HRMS: calcd. for $C_{16}H_{32}N_3O_6Si$ [MH^+] 390.2060; found 390.2056.

Isopropyl (1*R*,2*S*,3*R*,4*R*,5*R*)-2,4,5-Triacetoxy-3-azido-1-(*tert*-butyldimethylsilyloxy)cyclohexane-1-carboxylate (14): Triethylamine (115 μL, 0.81 mmol), acetic anhydride (70 μL, 0.73 mmol) and DMAP (3 mg, 3 μmol) were added to a stirred solution of the triol **13** (60 mg, 0.16 mmol) in dry dichloromethane (0.8 mL) under an inert gas at 0 °C. The resulting solution was stirred at room temperature for 12 h. Dichloromethane and then water were added. The organic layer was separated and the aqueous phase was extracted twice with dichloromethane. The combined organic extracts were dried (anhydrous Na_2SO_4), filtered and the solvents evaporated. The residue was purified by flash chromatography eluting with 50% diethyl ether/hexanes to yield the triacetoxy azide **14** (78 mg, 94%) as a colourless oil. $[\alpha]_D^{20} = -21$ (c = 3.8 in $CHCl_3$). IR (film): $\tilde{\nu}$ = 1753 (C=O), 2105 (N=N) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.18 (s, 3 H), 0.19 (s, 3 H), 0.96 (s, 9 H), 1.20 (d, J = 6.5 Hz, 3 H), 1.22 (d, J = 6.5 Hz, 3 H), 1.91 (dd, J = 11.6, 13.5 Hz, 1 H), 1.98 (s, 3 H), 2.08 (s, 3 H), 2.09 (s, 3 H), 2.21 (dd, J 5 and 13.5 Hz, 1 H), 3.82 (dd, J = 10.4, 10.0 Hz, 1 H), 4.91 (m, 1 H), 5.08 (t, J = 10.0 Hz, 1 H), 5.2 (ddd, J = 5, = 10.0, 11.6 Hz, 1 H), 5.24 (d, J = 10.4 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = −3.2 ($SiCH_3$), −2.8 ($SiCH_3$), 19.0 [C(CH_3)$_3$], 20.6 (CH_3), 20.7 (CH_3), 21.3 (CH_3), 21.5 (CH_3), 26.2 [C(CH$_3$)$_3$], 37.1 (CH_2), 62.5 (CH), 69.1 (CH), 70.4 (CH), 72.7 (CH), 73.8 (CH), 77.7 (C), 168.8 (C), 169.7 (C), 169.6 (C), 169.8 (C) ppm. MS (CI): m/z = 516 [MH^+]. HRMS: calcd. for $C_{22}H_{38}N_3O_9Si$ [MH^+] 516.2373; found 516.2400.

(1*S*,2*S*,3*R*,4*R*,5*R*)-3-Azido-1-hydroxymethyl-1,2,4,5-cyclohexanetetrol (15): Lithium borohydride (3 mg, 0.12 mmol) was added to a stirred solution of the ester **13** (44 mg, 0.11 mmol) in a dry solution of methanol in tetrahydrofuran (1.1 mL, 1:20 v/v) under argon and at 0 °C. The reaction mixture was stirred at room temperature for 45 min and then ethyl acetate (1 mL) and water (2 mL) were added. The organic layer was separated and the aqueous phase was extracted with ethyl acetate (4 × 3 mL). The combined organic extracts were dried (anhydrous Na_2SO_4), filtered and concentrated under reduced pressure. The crude reaction mixture was purified by flash chromatography eluting with diethyl ether giving 31 mg of a mixture of hydroxysilyl ethers. A solution of the crude reaction products (31 mg) in aqueous TFA (1 mL, 50%) was heated at 40 °C for 2 h. The solvent was evaporated and the residue was purified by flash chromatography eluting with 5% methanol/dichloromethane to yield azido alcohol **15** (20 mg, 81%) as a colourless oil. $[\alpha]_D^{20} = -13$ (c = 0.8 in MeOH). IR (film): $\tilde{\nu}$ = 2118 (N=N), 3363 (O−H) cm^{-1}. ^1H NMR (250 MHz, CD_3OD): δ = 1.41 (dd, J = 11.8, 13.8 Hz, 1 H), 1.82 (dd, J = 4.9, 13.8 Hz, 1 H), 1.95 (s, 1 H), 2.09 (s, 1 H), 3.03 (t, J = 9.2 Hz, 1 H), 3.26 (d, J = 10.8 Hz, 1 H), 3.40 (dd, J = 9.8, 9.2 Hz, 1 H), 3.50 (d, J = 10.8 Hz, 1 H), 3.70 (ddd, J = 4.9, 9.2, 11.8 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, CD_3OD): δ = 38.4 (CH_2), 67.1 (CH_2), 69.6 (CH), 70.2 (CH), 73.5 (CH), 74.7 (C), 77.9 (CH) ppm. MS (CI): m/z = 220 [MH^+]. HRMS: calcd. for $C_7H_{14}N_3O_5$ [MH^+] 220.0934; found 220.0933.

(1*S*,2*S*,3*R*,4*R*,5*R*)-3-Amino-1-hydroxymethyl-1,2,4,5-cyclohexanetetrol, Trifluoroacetic Acid Salt (6a): A suspension of the azide **15** (24 mg, 0.11 mmol) and 10% palladium on carbon (3 mg) in methanol (1.1 mL) and TFA (25 μL) was shaken under hydrogen at room temperature for 1 h. The mixture was filtered through Fluorosil, which was then washed with methanol. The filtrate and washings were concentrated under reduced pressure to yield the ammonium salt **6a** (31 mg, 92%) as a colourless oil. $[\alpha]_D^{20} = -9$ (c = 1.5 in MeOH). IR (film): $\tilde{\nu}$ = 1681 (C=O), 3386 (O−H) cm^{-1}. ^1H NMR (250 MHz, CD_3OD): δ = 1.45 (dd, J = 12.2, 14.0 Hz, 1 H), 1.96 (dd, J = 4.8, 14.0 Hz, 1 H), 3.19 (dd, J = 10.6, 10.5 Hz,

1 H), 3.35 (dd, J = 9.3, 10.5 Hz, 1 H), 3.40 (d, J = 11.5 Hz, 1 H), 3.48 (d, J = 11.5 Hz, 1 H), 3.61 (d, J = 10.6 Hz, 1 H), 3.71 (ddd, J = 4.8, 9.3, 12.2 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, D_2O): δ = 39.2 (CH_2), 58.7 (CH), 68.0 (CH_2), 71.8 (CH), 72.5 (CH), 76.3 (CH), 76.6 (C), 119.4 (C, $J_{C,F}$ = 290 Hz), 166.2 (C, $J_{C,F}$ = 36 Hz) ppm. MS (CI): m/z = 194 [MH^+ − TFA]. HRMS: calcd. for $C_7H_{16}NO_5$ [MH^+ − TFA] 194.1028; found 194.1019.

(1*R*,2*S*,3*R*,4*R*,5*R*)-3-Azido-1,2,4,5-tetrahydroxycyclohexane-1-carboxylic Acid (16): A solution of the ester **13** (50 mg, 0.13 mmol) in aqueous TFA (1.2 mL, 50%) was heated at 90 °C for 12 h. The solvent was evaporated and the residue was redissolved in water. The aqueous solution was washed twice with ethyl acetate and lyophilized to afford hydroxyacid **16** (27 mg, 90%) as an amorphous white solid. M.p. 175−177 °C. $[\alpha]_D^{20}$ = −1 (c = 1.0 in MeOH). IR (film): $\tilde{\nu}$ = 1608 (C=O), 2119 (N=N), 3389 (O−H) cm^{-1}. ^{1}H NMR (400 MHz, D_2O): δ = 1.65 (dd, J = 11.9, 13.7 Hz, 1 H), 1.88 (dd, J = 4.9, 13.7 Hz, 1 H), 3.23 (dd, J = 9.4, 10.0 Hz, 1 H), 3.36 (t, J = 10.0 Hz, 1 H), 3.63 (ddd, J = 4.9, 9.4, 11.9 Hz, 1 H), 3.68 (d, J = 10.1 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 40.8 (CH_2), 70.2 (CH), 72.0 (CH), 76.9 (CH), 78.7 (CH), 80.0 (C), 181.2 (C) ppm. MS (CI): m/z = 234 [MH^+]. HRMS: calcd. for $C_7H_{12}N_3O_6$ [MH^+] 234.0726; found 234.0724.

(1*R*,2*S*,3*R*,4*R*,5*R*)-3-Amino-1,2,4,5-tetrahydroxycyclohexane-1-carboxylic Acid, Trifluoroacetic Acid Salt (6b): A suspension of the azide **16** (27 mg, 0.12 mmol) and 10% palladium on carbon (3 mg) in methanol (1.2 mL) and TFA (35 μL) was shaken under hydrogen at room temperature for 1 h. The mixture was filtered through Fluorosil, which was then washed with methanol and water. The filtrate and washings were concentrated under reduced pressure and then lyophilized to yield amino acid **6b** as a colourless oil (36 mg, 97%). $[\alpha]_D^{20}$ = −11 (c = 1.9 in MeOH). IR (film): $\tilde{\nu}$ = 1633 (C=O), 1680 (C=O), 3389 (O−H) cm^{-1}. ^{1}H NMR (400 MHz, D_2O): δ = 1.73 (dd, J = 11.8, 13.9 Hz, 1 H), 2.03 (dd, J = 4.9, 13.9 Hz, 1 H), 3.15 (t, J = 10.6 Hz, 1 H), 3.19 (s, 1 H), 3.41 (t, J = 9.2 Hz, 1 H), 3.67 (ddd, J = 4.9, 9.1, 11.8 Hz, 1 H), 3.97 (d, J = 10.6 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 40.2 (CH_2), 58.4 (CH), 71.6 (CH), 74.1 (CH), 76.1 (CH), 79.4 (C), 119.3 (C, $J_{C,F}$ = 290 Hz), 166.0 (C, $J_{C,F}$ = 35 Hz), 178.8 (C) ppm. ^{19}F NMR (282 MHz, CD_3OD): δ = −73.7 (s, 3 F) ppm. MS (CI): m/z = 208 [MH^+ − TFA]. HRMS: calcd. for $C_7H_{14}NO_6$ [MH^+ − TFA] 208.0821; found 208.0825.

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