Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Supplementary Information

Synthesis of (+)-DGDP and (-)-7-Epialexine

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^{1}H NMR spectra were recorded on a Bruker AVB500 (500 MHz) or DPX400 (400 MHz), and referenced to residual solvent peaks or to 1,4-Dioxane as an internal standard. Chemical shifts are quoted in ppm with signal splittings recorded as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), obscured (obs.) and broad (br.). Coupling constants, *J*, are measured to the nearest 0.1 Hz. ^{13}C NMR spectra were recorded on a Bruker AVB500 at 126 MHz, an AV400 at 101 MHz and were referenced to the solvent or 1,4-Dioxane as an internal standard.

Optical rotations were recorded on a Perkin Elmer 241 polarimeter (using the sodium D line, 589 nm) and $[\alpha]_D$ are given in units of 10^{-1} deg dm^2 g^{-1}.

Melting points were determined using a Leica hot stage microscope and are uncorrected.

Infra-red spectra were recorded on a Bruker Tensor 27 FTIR spectrometer. Spectra were analysed as thin films between NaCl plates or as KBr discs. Only structurally important absorption peaks are quoted. Absorption maxima (ν_{max}) are quoted in wavenumbers (cm^{-1}).

Mass spectra (MS) and accurate mass (HRMS) were recorded on Micro Mass LCT and GCT spectrometers under conditions of electrospray ionisation (ESI) and chemical ionisation (CI) respectively. Values are reported as a ratio of mass to charge in Daltons.

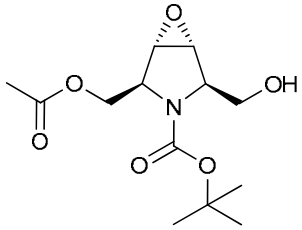
Flash column chromatography was performed using silica gel 60 (0.043-0.063mm, Merck) using head pressure by means of head bellows. TLC analyses were performed on Merck Kiesegel 60 F_{254} 0.25 mm pre-coated aluminium. Product spots were visualised under UV light (λ_{max} = 254 nm) and/or by staining with potassium permanganate.

Reagents obtained from Acros, Aldrich, Avocado, Fluka and Lancaster fine chemicals suppliers were used directly as supplied or following purification according to literature procedures.

Reactions were carried out under an inert atmosphere of argon if anhydrous conditions were required. Syringes and needles for the transfer of reagents, and flasks or other apparatus were dried in an oven before being cooled in a desiccator over self-indicating silica gel.

Tetrahydrofuran, pentane, dichloromethane and diethyl ether were purified by filtration through activated alumina columns. Other solvents were used as supplied (analytical or HPLC grade) without prior purification. Petroleum ether refers to the fraction of petroleum ether which boils in the range 40-60 °C.

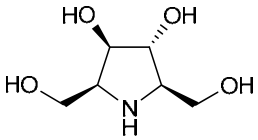
(1*S*,2*S*,4*R*,5*R*)-*tert*-Butyl-2-(acetoxymethyl)-4-(hydroxymethyl)-6-oxa-3-azabicyclo[3.1.0]hexane-3-carboxylate 2



To a solution of *alkene **(+)-1*** (230 mg, 0.85 mmol) in acetonitrile (10 cm^3) was added EDTA disodium salt (3 cm^3, 0.0004 mol dm^{-3}) followed by solid $NaHCO_3$ (1.43 g) in one portion at 0 ^oC. To this mixture was cautiously added 1,1,1-trifluroacetone (1.53 cm^3, 17.0 mmol) and Oxone (5.23 g) in 4 equal portions at 30 minute intervals with vigorous stirring . After which time, the mixture was filtered and the resulting solution diluted with dichloromethane (50 cm^3), washed with brine (20 cm^3), dried ($MgSO_4$) and the solvent removed under reduced pressure to give a colourless oil, which was purified by column chromatography on silica using diethyl ether:petrolem ether (3:7) as eluent to give the *title compound **2*** (229 mg, 94%) as a colourless oil.

$[\alpha]_D^{20}$ +20.2 (*c* 0.5, CH_2Cl_2); ν_{max}/cm^{-1} (film) 3469, 2976, 1746, 1697; ^1H NMR (500 MHz, DMSO-d_6, 373 K) δ_H 4.68 (1 H, br. s), 4.26 (1 H, dd, *J* = 10.8 and 4.3), 4.15 (1 H, dd, *J* = 10.8 and 6.8), 4.04 (1 H, t, *J* = 5.2), 3.87 (1 H, m), 3.71 (1 H, d, *J* = 3.0), 3.69 (1 H, d, *J* = 3.0), 3.64 (1 H, br. s), 3.46 (1 H, t, *J* = 8.6), 2.05 (3 H, s), 1.42 (9 H, s); ^{13}C NMR (126 MHz, DMSO-d_6, 373 K) δ_C 170.3, 154.6, 80.0, 62.8, 61.0, 60.7, 57.9, 57.5, 57.0, 28.6, 20.9; HRMS (ESI, *m/z*) 310.1256 $[M + Na]^+$, $C_{20}H_{27}NNaO_5$ requires 310.1267.

(2*S*,3*R*,4*R*,5*R*)-2,5-*bis*(Hydroxymethyl)pyrrolidine-3,4-diol, DGDP 4

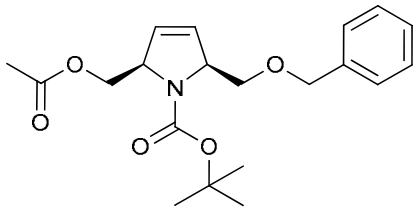


To a solution of *epoxide **2*** (190 mg, 0.66 mmol) in dichloromethane (10 cm^3) at -78 ^oC under N_2 was added $BF_3{\cdot}OEt_2$ (0.12 cm^3, 0.99 mmol) dropwise over 5 minutes. The resulting solution was then allowed to warm to room temperature over 4 hours before the

addition of methanol (10 cm^3). The reaction mixture was stirred at this temperature for a further 12 hours, after which time the solvent was removed under reduced to give a yellow oil, which was purified by column chromatography on silica using methanol:ethyl acetate:NH_4OH (4:5:1), DOWEX 50WX2-200 eluting with water then water NH_4OH:water (1:7) and finally dissolved in methanol:chloroform (1:7) and filtered through a short plug of Celite to give *DGDP* ***4*** (85 mg, 78%) as a colourless solid, the data was in good accordance to that in the literature.[1]

M.p 139-141 ^oC (MeOH); $[\alpha]_D^{25}$ +24.8 (*c* 1.0, H_2O), $[\alpha]_D^{Lit}$ +25.1 (*c* 1.5, H_2O); ν_{max}/cm^{-1} (KBr) 3356, 2934, 1653, 1559, 1419, 1057; ^1H NMR (400 MHz, D_2O) δ_H 4.05 (1 H, dd, *J* = 5.1 and 2.8), 3.80 (1 H, dd, *J* = 5.2 and 2.8), 3.72 (1 H, dd, *J* = 11.4 and 6.1), 3.67 (1 H, dd, *J* = 11.5 and 4.9), 3.61 (1 H, dd, *J* = 6.4 and 3.0), 3.58 (1 H, dd, *J* = 6.6 and 3.3), 3.26 (1 H, q, *J* = 6.2), 2.96 (1 H, q, *J* = 5.2); ^{13}C NMR (101 MHz, D_2O) δ_C 79.2, 77.5, 65.2, 62.3, 61.2, 60.2; HRMS (ESI, *m/z*) 164.0917 $[M + H]^+$, $C_6H_{14}NO_4$ requires 164.0923.

(2*R*,5*S*)-*tert*-Butyl-2-(acetoxymethyl)-5-(benzyloxymethyl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate 12

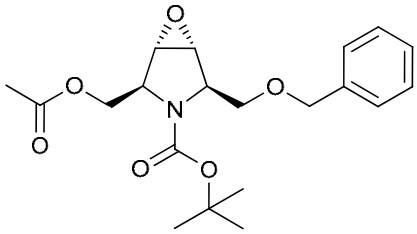


To a solution of *alkene* ***(+)-1*** (1.54 g, 5.71 mmol) in dichloromethane (30 cm^3) was added 4Å molecular sieves (200 mg), Ag_2O (6.60 g, 28.6 mmol) and benzyl bromide (2.72 cm^3, 22.8 mmol) at room temperature under N_2 and in the absence of light. The resulting mixture was stirred at room temperature for 12 hours, after which time the mixture was filtered through a pad of Celite eluting with diethyl ether to give a yellow oil, which was purified by column chromatography on silica eluting with diethyl ether:petroleum ether (2:8) to give the *title compound* ***12*** (1.50 g, 73%) as a colourless oil and *alkene* ***(+)-1*** (385 mg, 25%).

[1] Baxter, E. W.; Reitz, A. B. *J. Org. Chem.* **1994**, *59*, 3175.

$[\alpha]_D^{20}$ -23.2 (*c* 1.1, CH_2Cl_2); ν_{max}/cm^{-1} (film) 2977, 1745, 1699, 1477, 1454, 1177; ^1H NMR (500 MHz, DMSO-D_6, 373 K) δ_H 7.40-7.25 (5 H, m), 5.97 (1 H, dt, *J* = 6.5 and 1.9), 5.82 (1 H, dt, *J* = 6.3 and 1.7), 4.62 (1 H, ddd, *J* = 5.6, 3.7 and 1.9), 4.57 (1 H, obs. m), 4.54 (1 H, obs. d, *J* = 12.5), 4.50 (1 H, d, *J* = 12.5), 4.23 (1 H, dd, *J* = 10.9 and 3.9), 4.03 (1 H, dd, *J* = 10.7 and 5.7), 3.73 (1 H, dd, *J* = 9.1 and 3.8), 3.39 (1 H, dd, *J* = 9.1 and 7.1), 1.94 (3 H, s), 1.43 (9 H, s); ^{13}C NMR (126 MHz, DMSO-D_6, 373 K) δ_C 169.2, 153.0, 138.0, 129.3, 127.6, 126.9, 126.8, 126.7, 78.8, 72.1, 71.4, 64.0, 63.8, 63.0, 27.6, 19.8; HRMS (ESI, *m/z*) 384.1781 $[M + Na]^+$, $C_{20}H_{27}NNaO_5$ requires 384.1787.

(1*S*,2*S*,4*R*,5*R*)-*tert*-Butyl-2-(acetoxymethyl)-4-(benzyloxymethyl)-6-oxa-3-azabicyclo[3.1.0]hexane-3-carboxylate 5

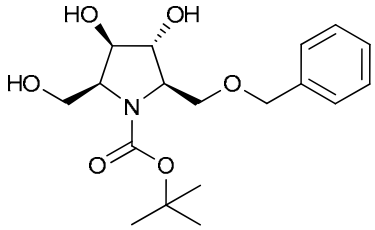


To a solution of *alkene* ***12*** (660 mg, 1.83 mmol) in acetonitrile (20 cm^3) was added aqueous EDTA disodium salt (7.0 cm^3, 0.0004 mol dm^{-3}) followed by solid $NaHCO_3$ (3.0 g) in one portion at 0 ^oC. To this mixture was cautiously added 1,1,1-trifluroacetone (3.3 cm^3, 36.6 mmol) and Oxone (11.2 g, 18.3 mmol) in 4 equal portions at 30 minute intervals with vigorous stirring . After which time, the mixture was filtered and the resulting solution diluted with dichloromethane (40 cm^3), washed with brine (20 cm^3), dried ($MgSO_4$) and the solvent removed under reduced pressure to give a colourless oil, which was purified by column chromatography on silica using diethyl ether:petrolem ether (4:6) as eluent to give the *title compound* ***5*** (662 mg, 96%) as a colourless oil.

$[\alpha]_D^{20}$ -14.6 (*c* 1.3, CH_2Cl_2); ν_{max}/cm^{-1} (film) 2974, 1746, 1699, 1420 1177; ^1H NMR (500 MHz, DMSO-d_6, 373 K) δ_H 7.41-7.23 (5 H, m), 4.59 (1 H, d, *J* = 12.2), 4.55 (1 H, d, *J* = 12.3), 4.19 (1 H, dd, *J* = 10.6 and 4.2), 4.12 (1 H, dd, *J* = 11.0 and 6.6), 4.06 (1 H, m), 4.02 (1 H, m), 3.72 (1 H, d, *J* = 2.8), 3.68 (1 H, d, *J* = 2.7), 3.64 (1 H, dd, *J* = 9.8 and 3.5), 3.54 (1 H, dd, *J* = 9.6 and 6.9), 1.99 (3 H, s), 1.39 (9 H, s); ^{13}C NMR (126 MHz, DMSO-d_6, 373 K) δ_C 169.2, 153.4, 137.6, 127.6, 126.9, 126.8, 79.1, 72.2, 68.1, 61.7,

57.9, 56.9, 56.3, 55.8, 27.5, 19.8; HRMS (ESI, *m/z*) 400.1731 $[M + Na]^+$, $C_{20}H_{27}NNaO_6$ requires 400.1736.

(2*R*,3*R*,4*R*,5*S*)-*tert*-Butyl-2-(benzyloxymethyl)-3,4-dihydroxy-5-(hydroxymethyl)pyrrolidine-1-carboxylate 6

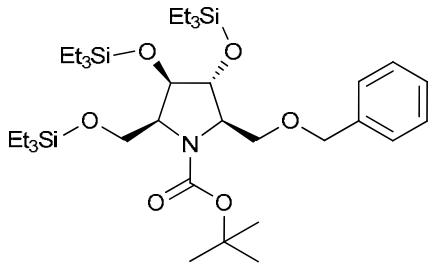


To a solution of *epoxide* ***5*** (746 mg, 1.98 mmol) in dichloromethane (20 cm^3) was added dropwise $BF_3{\cdot}OEt_2$ (0.27 cm^3, 2.18 mmol) at -50 ^oC under N_2 and the resulting solution was stirred at this temperature for 14 hours. After which time, saturated aqueous $NaHCO_3$ solution was added and the resulting mixture was allowed to warm to room temperature. The mixture was extracted with ethyl acetate (3 x 50 cm^3) and the combined organic extracts were dried ($MgSO_4$) and the solvent removed under reduced pressure to give a yellow oil. The crude mixture was dissolved in methanol (20 cm^3) and K_2CO_3 (500 mg) was added and the resulting mixture was stirred at room temperature for 2 hours. After which time silica was added and the solvent reduced under reduced pressure. The compound was purified by column chromatography on silica eluting with ethyl acetate to give the *title compound* ***6*** (509 mg, 73%) as a white solid.

M.p. 127-129 ^oC (EtOAc); $[\alpha]_D^{20}$ -34.4 (*c* 0.5, CH_2Cl_2); ν_{max}/cm^{-1} (KBr) 3484, 3300, 1683, 1383, 1117; ^1H NMR (500 MHz, DMSO-d_6, 373 K)[2] δ_H 7.36-7.26 (5 H, m), 4.52 (2 H, s), 4.05-4.03 (2 H, m), 3.83 (1 H, q, *J* = 5.5), 3.74-3.60 (5 H, m), 1.40 (9 H, s); ^{13}C NMR (126 MHz, DMSO-d_6, 373 K) δ_C 154.5, 138.1, 127.5, 126.7, 126.7, 78.4, 75.9, 75.7, 71.9, 69.0, 64.0, 61.1, 59.8, 27.6; HRMS (ESI, *m/z*) 376.1731 $[M + Na]^+$, $C_{18}H_{27}NNaO_6$ requires 376.1736.

[2] The chemical shifts of hydroxyl protons were too broad to be observed in the ^1H-NMR spectrum at this temperature

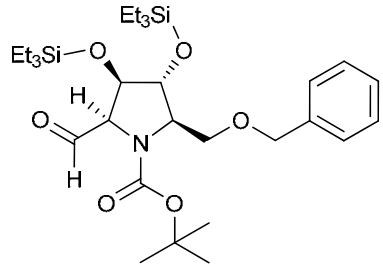
(2*R*,3*R*,4*R*,5*S*)-*tert*-Butyl-2-(benzyloxymethyl)-3,4-*bis*(triethylsilyloxy)-5-((triethylsilyloxy)methyl)pyrrolidine-1-carboxylate 13



To a solution of *triol* ***6*** (600 mg, 1.70 mmol) in dichloromethane (20 cm^3) was added DMAP (1.04 g, 8.50 mmol), triethylamine (0.94 cm^3, 10.2 mmol) and chlorotriethylsilane (1.43 cm^3, 8.50 mmol) and the reaction stirred at room temperature for 16 hours. After which time, 1M hydrochloric acid (20 cm^3) was added and the organic extract separated and dried ($MgSO_4$). The solvent was removed under reduced pressure to give a yellow oil, which was purified by column chromatography on silica eluting with diethyl ether:petroleum ether (5:95) to give the *title compound* ***13*** (992 mg, 84%) as a yellow oil. $[\alpha]_D^{25}$ +36.5 (*c* 0.5, CH_2Cl_2); ν_{max}/cm^{-1} (film) 2955, 2877, 1701, 1388, 1175; ^{1}H NMR (500 MHz, $CDCl_3$)[3] δ_H 7.35-7.23 (5 H, m), 4.60-4.42 (2 H, m), 4.20-3.52 (8 H, m), 1.41 (9 H, br. s), 1.04-0.85 (27 H, m), 0.67-0.49 (18 H, m); ^{13}C NMR (126 MHz, $CDCl_3$)[4] δ_C 155.8, 138.8, 128.1, 127.3, 127.2, 79.2, 78.2, 76.4, 72.8, 70.2, 66.6, 62.5, 59.2, 28.5, 6.9, 6.8, 6.7, 6.4, 4.8, 4.4; HRMS (ESI, *m/z*) 718.4325 $[M + Na]^+$, $C_{36}H_{69}NNaO_6Si_3$ requires 718.4330.

[3] Peaks in ^{1}H-NMR spectrum broad and split due to the presence of *N*-Boc rotamers, compound **13** was unstable to high temperature NMR.
[4] Peaks in ^{13}C-NMR spectrum broad and split due to the presence of *N*-Boc rotamers, compound **13** was unstable to high temperature NMR. Several peaks missing due to overlap of *O*-TES carbons.

(2*R*,3*R*,4*R*,5*R*)-*tert*-Butyl-2-(benzyloxymethyl)-5-formyl-3,4-*bis*(triethylsilyloxy)pyrrolidine-1-carboxylate 7



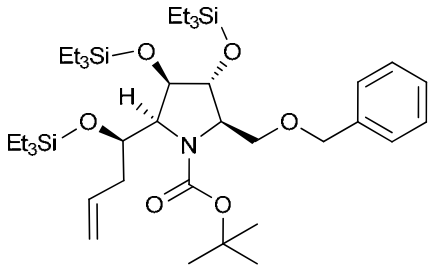
To a solution of oxalyl chloride (0.12 cm^3, 1.47 mmol) in dichloromethane (20 cm^3) at -78 ^oC under N_2 was added dimethyl sulfoxide (0.21 cm^3, 2.94 mmol) dropwise over 10 minutes and the resulting solution was stirred at this temperature for a further 20 minutes. After which time, *tris-silylether **13*** (510 mg, 0.73 mmol) as a solution in dichloromethane (15 cm^3) was added dropwise over 10 minutes and the resulting solution was stirred at -78 ^oC for 1 hour. Triethylamine (0.61 cm^3, 4.40 mmol) was then added dropwise over 10 minutes and the resulting solution was stirred at -78 ^oC for 1 hour, after which time the reaction was allowed to warm to room temperature and water (10 cm^3) was added. The organic layer was separated, washed with 1M hydrochloric acid (10 cm^3), dried ($MgSO_4$) and the solvent removed under reduced pressure to give a yellow oil which was purified by column chromatography on silica eluting with diethyl ether:petroleum ether (5:95) to give the *title compound 7* (387 mg, 91%) as a colourless oil.

$[\alpha]_D^{25}$ -27.2 (*c* 0.6, CH_2Cl_2); ν_{max}/cm^{-1} (film) 2957, 2878, 1739, 1711, 1457, 1367, 1107; ^{1}H NMR (500 MHz, $CDCl_3$)[5] δ_H 9.44 (0.5 H, d, *J* = 3.0), 9.40 (0.5 H, d, *J* = 3.3), 7.38-7.25 (5 H, m), 4.60 (0.5 H, d, *J* = 11.8), 4.57 (0.5 H, d, *J* = 12.1), 4.53 (0.5 H, obs. d), 4.50 (0.5 H, d, *J* = 11.8), 4.31 (1 H, m), 4.23 (1.5H, m), 4.12 (0.5 H, t, *J* = 3.9), 4.07 (0.5 H, dd, *J* = 10.6 and 4.8), 3.90 (1 H, m), 3.78 (1.5 H, m), 1.45 (4.5 H, s), 1.42 (4.5 H, s), 0.97-0.89 (18 H, m), 0.65-0.51 (12 H, m); ^{13}C NMR (126 MHz, $CDCl_3$)[6] δ_C 202.6, 201.5, 155.8, 154.8, 138.6, 138.4, 128.3, 128.2, 127.5, 127.4, 127.3, 127.3, 81.2, 81.1, 80.8,

[5] Peaks in ^{1}H-NMR spectrum split as a 1:1 mixture due to the presence of *N*-Boc rotamers. Compound **7** was unstable to high temperature NMR. Both rotamers are described.
[6] Peaks in ^{13}C-NMR spectrum split as a 1:1 mixture due to the presence of *N*-Boc rotamers. Compound **7** was unstable to high temperature NMR. Both rotamers are described. Several peaks missing due to overlap of *O*-TES carbons.

79.9, 78.0, 77.2, 73.0, 73.0, 69.4, 69.2, 69.1, 69.1, 66.9, 66.8, 28.3, 28.2, 6.7, 6.6, 6.6, 4.6, 4.5; HRMS (ESI, *m/z*) 602.3304 $[M + Na]^+$, $C_{30}H_{53}NNaO_6Si_2$ requires 603.3309.

(2*R*,3*R*,4*R*,5*S*)-*tert*-Butyl-2-(benzyloxymethyl)-3,4-*bis*(triethylsilyloxy)-5-((*R*)-1-(triethylsilyloxy)but-3-enyl)pyrrolidine-1-carboxylate 8



To a solution of *aldehyde 7* (350 mg, 0.60 mmol) in tetrahydrofuran (20 cm^3) at -78 ^oC under N_2 was added allylmagnesium bromide (1 mol dm^{-3}, 0.66 cm^3, 0.66 mmol) dropwise and the solution stirred at this temperature for 1 hour. After which time, saturated aqueous NH_4Cl (10 cm^3) was added and the mixture was allowed to warm to room temperature. The mixture was diluted with diethyl ether (20 cm^3), separated and dried ($MgSO_4$). The solvent was removed under reduced pressure to give a yellow oil.

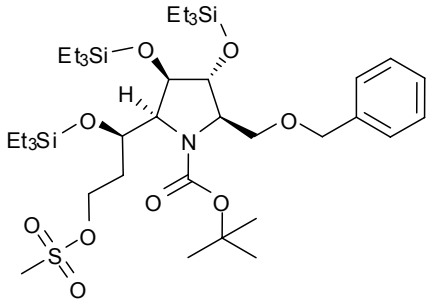
To a solution of the crude product in dichloromethane (20 cm^3) was added DMAP (147 mg, 1.21 mmol), triethylamine (0.23 cm^3, 1.81 mmol) and chlorotriethylsilane (0.20 cm^3, 1.21 mmol) and the reaction stirred at room temperature for 16 hours. After which time, 1M hydrochloric acid (10 cm^3) was added, the organic extract separated and dried ($MgSO_4$). The solvent was removed under reduced pressure to give the *title compound* ***8*** as a 6:1 mixture of diastereomers, which was purified by column chromatography on silica eluting with diethyl ether:petroleum ether (3:97) to give the *title compound* ***8*** (381 mg, 86%) as a yellow oil.

$[\alpha]_D^{20}$ +17.3 (*c* 1.5, CH_2Cl_2); ν_{max}/cm^{-1} (film) 2955, 2878, 1700, 1457, 1366, 1240, 1098, 1006, 741; ^1H NMR (500 MHz, Toluene-d_8, 373K)[7] δ_H 7.39-7.05 (5 H, m), 6.06 (1 H, ddt, *J* = 17.6, 10.3 and 7.2), 5.17 (1 H, d, *J* = 17.2), 5.05 (1 H, d, *J* = 10.3), 4.76 (1 H, m), 4.53 (1 H, d, *J* = 11.8), 4.38 (1 H, m), 4.25 (1 H, m), 4.20 (1 H, obs. t, *J* = 5.2), 4.17 (1 H, obs. m), 3.97 (1 H, t, *J* = 9.4), 3.90 (1 H, dd, *J* = 8.8 and 5.0), 2.73-2.60 (2 H, m), 1.44 (9

[7] Compound **8** generated as a 6:1 mixture of diastereomers which could be partially purified by silica gel chromatography, only major isomer is described.

H, s), 1.11-1.00 (27 H, m), 0.80-0.68 (18 H, m); ^{13}C NMR (126 MHz, Toluene-d^{8}, 373K)[8] δ_C 156.5, 139.6, 138.3, 116.1, 80.8, 79.8, 78.6, 73.8, 72.7, 71.6, 68.1, 64.8, 38.6, 28.8, 7.4, 7.3, 7.0, 6.1, 5.8; HRMS (ESI, *m/z*) 758.4638 $[M + Na]^+$, $C_{39}H_{73}NNaO_6Si_3$ requires 758.4643.

(2*R*,3*R*,4*R*,5*S*)-2-Benzyloxymethyl-5-((*R*)-3-methanesulfonyloxy-1-triethylsilanyloxy-propyl)-3,4-*bis*-triethylsilanyloxy-pyrrolidine-1-carboxylic acid *tert*-butyl ester 9



To a solution of *alkene **8*** (210 mg, 0.29 mmol) at -78 °C was bubbled through O_2 for 10 minutes before O_3 was bubbled though this solution for 20 minutes, after which time the solution formed a light blue colour. O_2 was then bubbled through this solution until the blue colour was dissipated. PPh_3 (374 mg, 1.43 mmol)was then added and the solution allowed to warm to room temperature overnight. The solvent was removed under reduced pressure and the crude product subjected to rapid column chromatography on silica eluting with diethyl ether:petroleum ether (1:9) to give the crude product as a colourless oil.

The crude product was dissolved in dichloromethane:methanol (5:1, 10 cm^3) at 0 °C and $NaBH_4$ (12 mg, 0.31 mmol) was added in one portion and the reaction stirred for 10 minutes. After which time, brine (10 cm^3) was added and the organic layer separated, dried ($MgSO_4$) and the solvent removed under reduced pressure to give a yellow oil, which was carried on to the next step without further purification.

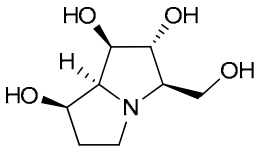
The crude product was dissolved in dichloromethane (10 cm^3) at room temperature under N_2 and DMAP (129 mg, 0.86 mmol) and 2,6-lutidine (0.20 cm^3, 1.71 mmol) were added in one portion, followed by methane sulfonic anhydride (149 mg, 0.86 mmol) and the

[8] Compound **8** generated as a 6:1 mixture of diastereomers which could be partially purified by silica gel chromatography, only major isomer is described. Several peaks missing due to overlap of *O*-TES carbons and overlap of benzyl peaks with toluene-d_8.

resulting mixture was stirred at this temperature overnight. After which time, saturated aqueous $NaHCO_3$ solution (10 cm^3) was added, the organic layer separated, dried ($MgSO_4$) and the solvent removed under reduced pressure to give a yellow oil, which was purified by column chromatography on silica eluting with diethyl ether:petroleum ether (1:9) to give the *title compound* ***9*** (233 mg, 74%) as a yellow oil.

$[\alpha]_D^{25}$ -41.6 (*c* 0.3, CH_2Cl_2); ν_{max}/cm^{-1} (film) 2956, 2878, 1697, 1457, 1365, 1242, 1365, 1242, 1177, 1103, 1007, 742; ^{1}H NMR (500 MHz, $CDCl_3$)[9] δ_H 7.37-7.24 (5 H, m), 4.59-4.42 (3 H, m), 4.37-4.05 (4 H, m), 3.91 (1 H, m), 3.82-3.62 (3 H, m), 2.99 (3 H, s), 2.21-1.95 (2 H, m), 1.40 (9 H, br. s), 1.03-0.88 (27 H, m), 0.72-0.55 (18 H, m); ^{13}C NMR (126 MHz, $CDCl_3$)[10] δ_C 156.2, 138.6, 128.2, 127.4, 127.3, 79.2, 72.9, 70.4, 68.3, 67.2, 66.4 62.9, 37.3, 36.6, 28.4, 7.0, 4.8; HRMS (ESI, *m/z*) 840.4363 $[M + Na]^+$, $C_{39}H_{75}NNaO_9SSi_3$ requires 840.4368.

(1*R*,2*R*,3*R*,7*R*,7a*S*)-3-(Hydroxymethyl)hexahydro-1*H*-pyrrolizine-1,2,7-triol, 7-*epi*-alexine 11



To a solution of *mesylate* ***9*** (204 mg, 0.25 mmol) in dichloromethane (10 cm^3) was added 2,6-lutidine (0.17 cm^3, 1.50 mmol) followed by triethylsilyl triflate (0.28 cm^3, 1.24 mmol) at room temperature under N_2 and the solution was stirred at this temperature for 4 hours. After which time, methanol was added and the solution was stirred overnight. The solvent was then removed under reduced pressure to give the crude product, which was carried on to the next step without further purification.

The crude product was dissolved in methanol (10 cm^3) and palladium on carbon (300 mg) was added in one portion at room temperature followed by concentrated hydrochloric acid (5 drops) and the reaction was stirred under 1 atmosphere of hydrogen for 6 hours.

[9] Peaks in ^{1}H-NMR spectrum broad and split due to the presence of *N*-Boc rotamers, compound **9** was unstable to high temperature NMR.
[10] Peaks in ^{13}C-NMR spectrum broad and split due to the presence of *N*-Boc rotamers, compound **9** was unstable to high temperature NMR. Several peaks missing due to overlap of *O*-TES carbons and overlap with $CDCl_3$.

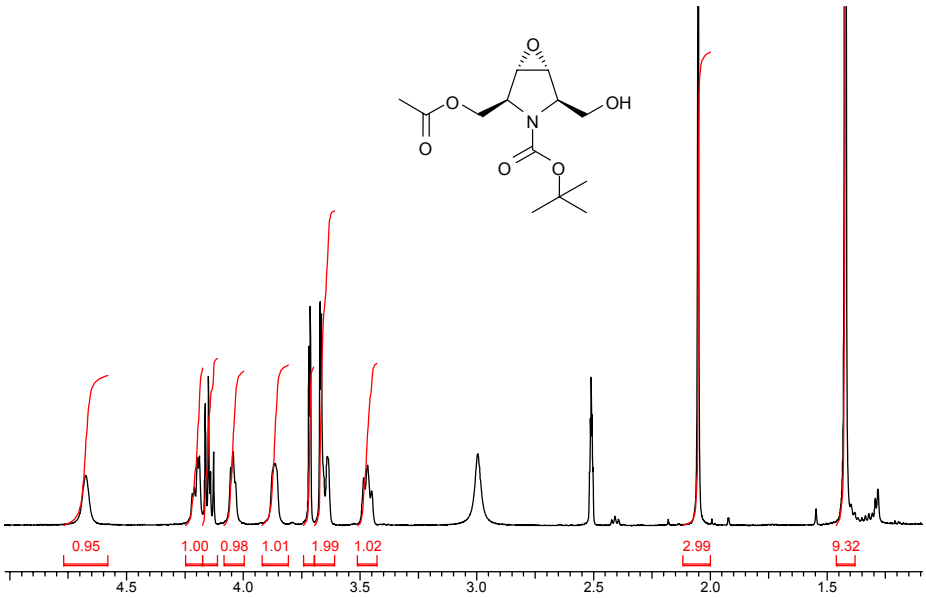
After which time, the reaction was filtered through a short plug of Celite eluting with methanol. The solvent was then removed under reduced pressure to give a yellow oil, which was purified by column chromatography on silica eluting with methanol:ethyl acetate:NH_4OH (4:5:1), DOWEX 50WX2-200 eluting with water then NH_4OH:water (1:7) and finally dissolved in methanol:chloroform (1:7) and filtered through a short plug of Celite to give *7-epialexine **11*** (42 mg, 89%) as a colourless oil, the data was in good accordance to that in the literature.[11]

$[\alpha]_D^{25}$ -8.0 (*c* 1.0, H_2O), $[\alpha]_D^{Lit}$ -10.6 (*c* 0.6, H_2O); ν_{max}/cm^{-1} (film) 3354, 2929, 1046; ^1H NMR (500 MHz, D_2O) δ_H 4.38 (1 H, br. t, J = 3.9), 4.14 (1 H, t, J = 8.1), 3.80 (3 H, m), 3.38 (1 H, dd, J = 8.0 and 3.9), 3.10 (1 H, m), 2.85 (2 H, m), 1.75 (2 H, m); ^{13}C NMR (126 MHz, D_2O (1,4-Dioxane as internal standard δ_C 67.4)) δ_C 78.6, 76.2, 73.0, 66.6, 64.3, 60.1, 46.3, 34.6; HRMS (ESI, *m/z*) 190.1074 $[M + H]^+$, $C_8H_{16}NO_4$ requires 190.1079.

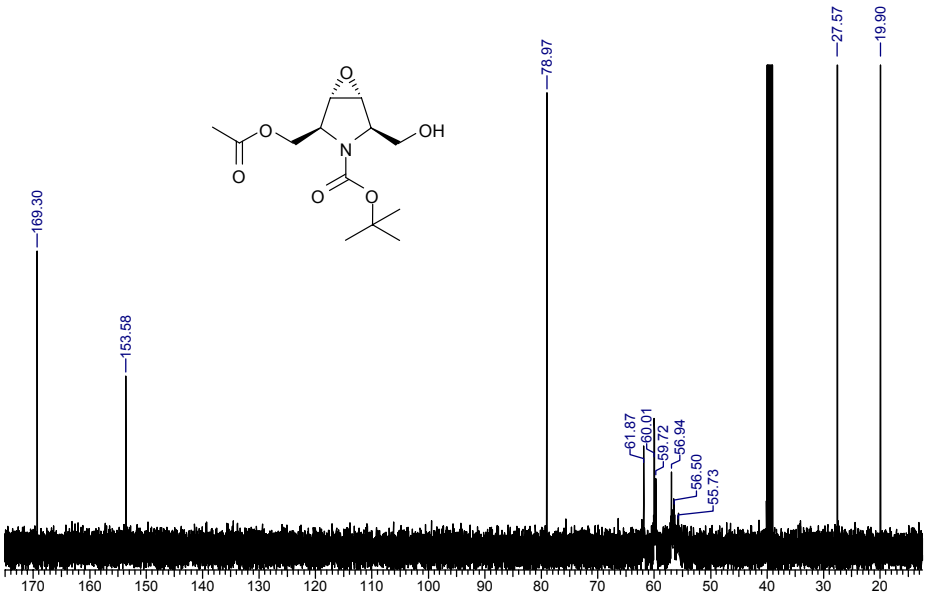
[11] Pearson, W. H.; Hines, J. V. *J. Org. Chem.* **2000**, *65*, 5785; Fleet, G. W. J.; Haraldson, M.; Nash, R. J.; Fellows, L. E. *Tetrahedron Lett.* **1988**, *29*, 42, 5441.

(1*S*,2*S*,4*R*,5*R*)-*tert*-Butyl-2-(acetoxymethyl)-4-(hydroxymethyl)-6-oxa-3-azabicyclo[3.1.0]hexane-3-carboxylate 2

^{1}H-NMR (500 MHz, DMSO-d$_6$, 373K)

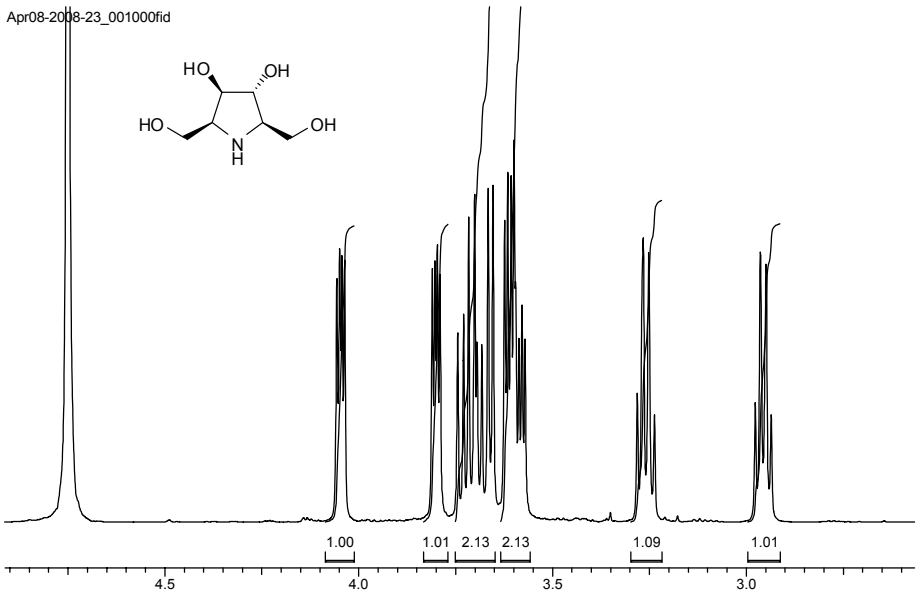


^{13}C-NMR (126 MHz, DMSO-d$_6$, 373K)

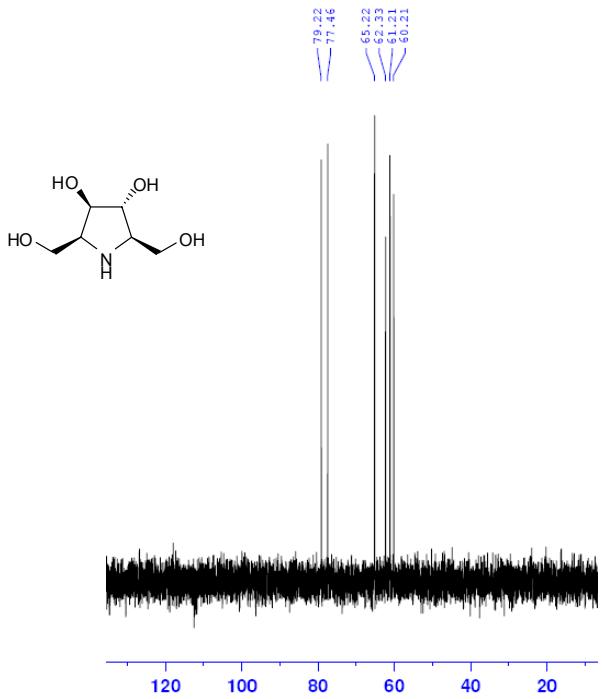


(2*S*,3*R*,4*R*,5*R*)-2,5-*bis*(Hydroxymethyl)pyrrolidine-3,4-diol, DGDP 4

^{1}H-NMR (400 MHz, D_2O)

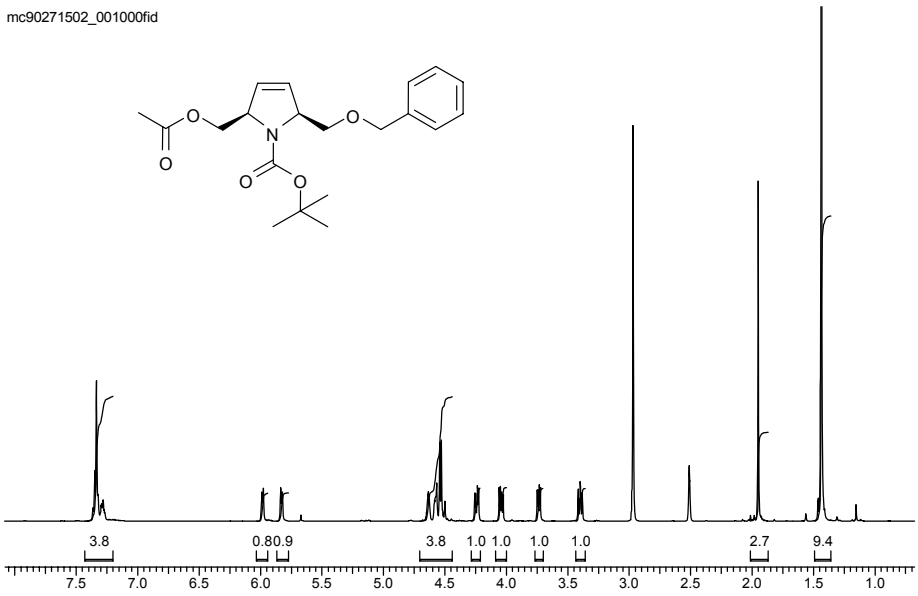


^{13}C (101 MHz, D_2O)

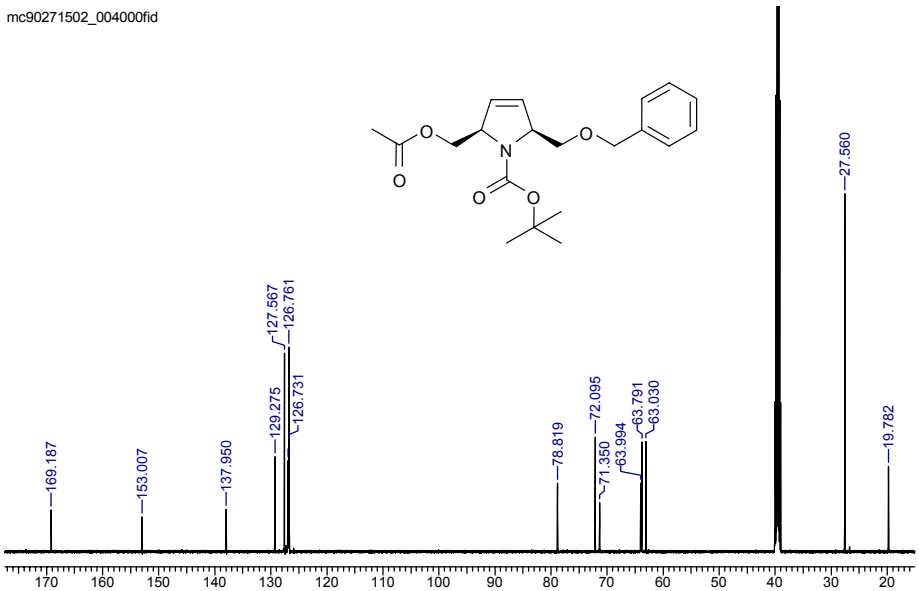


(2*R*,5*S*)-*tert*-Butyl-2-(acetoxymethyl)-5-(benzyloxymethyl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate 12

^{1}H-NMR (500 MHz, DMSO-d_6, 373K)

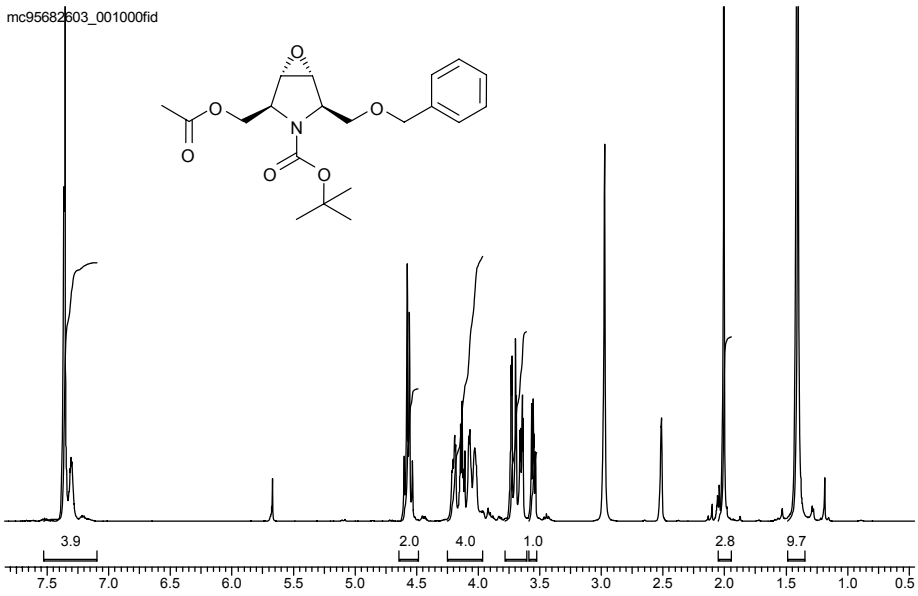


^{13}C-NMR (126 MHz, DMSO-d_6, 373K)

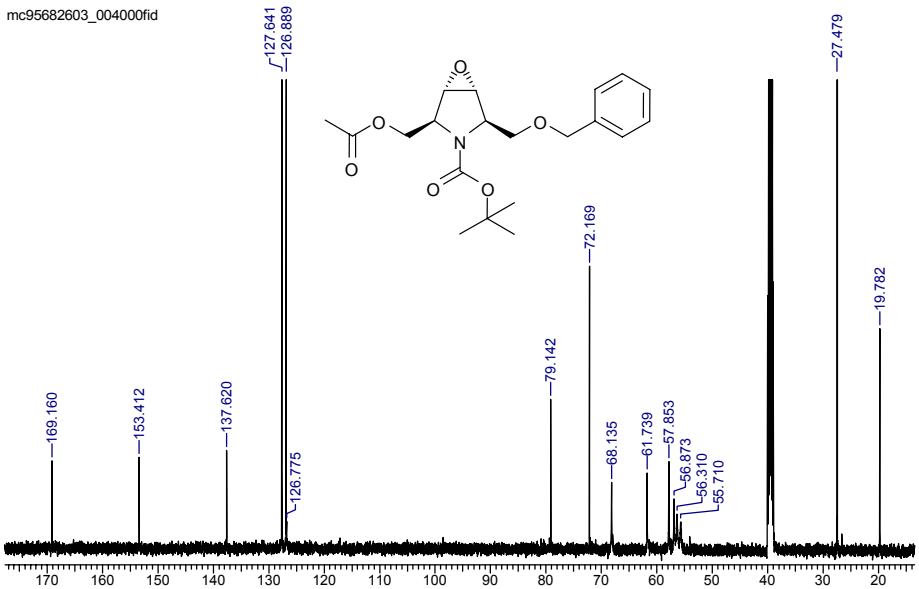


(1*S*,2*S*,4*R*,5*R*)-*tert*-Butyl-2-(acetoxymethyl)-4-(benzyloxymethyl)-6-oxa-3-azabicyclo[3.1.0]hexane-3-carboxylate 5

^{1}H-NMR (500 MHz, DMSO-d$_6$, 373K)

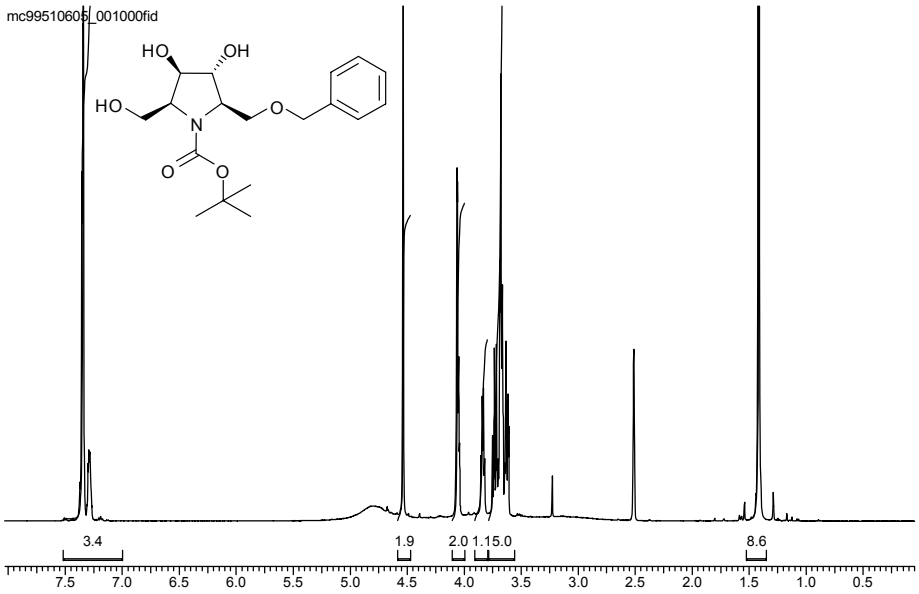


^{13}C-NMR (126 MHz, DMSO-d$_6$, 373K)

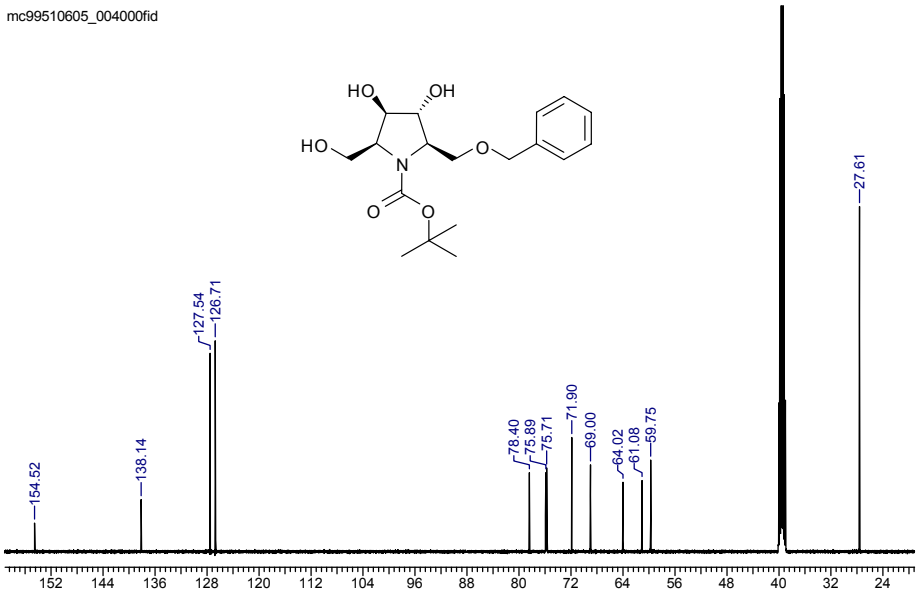


(2*R*,3*R*,4*R*,5*S*)-*tert*-Butyl-2-(benzyloxymethyl)-3,4-dihydroxy-5-(hydroxymethyl)pyrrolidine-1-carboxylate 6

^{1}H-NMR (500 MHz, DMSO-d_6, 373K)

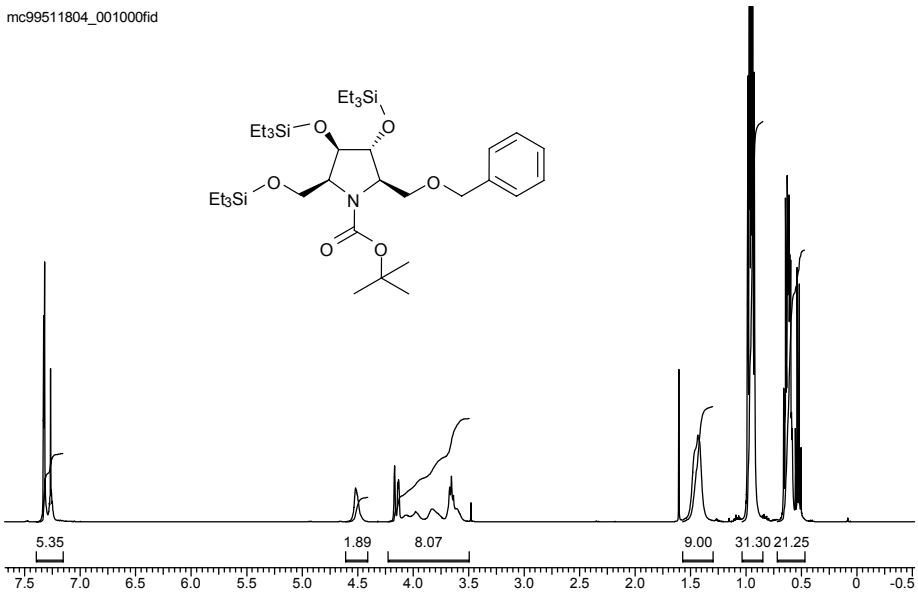


^{13}C-NMR (126 MHz, DMSO-d_6, 373K)

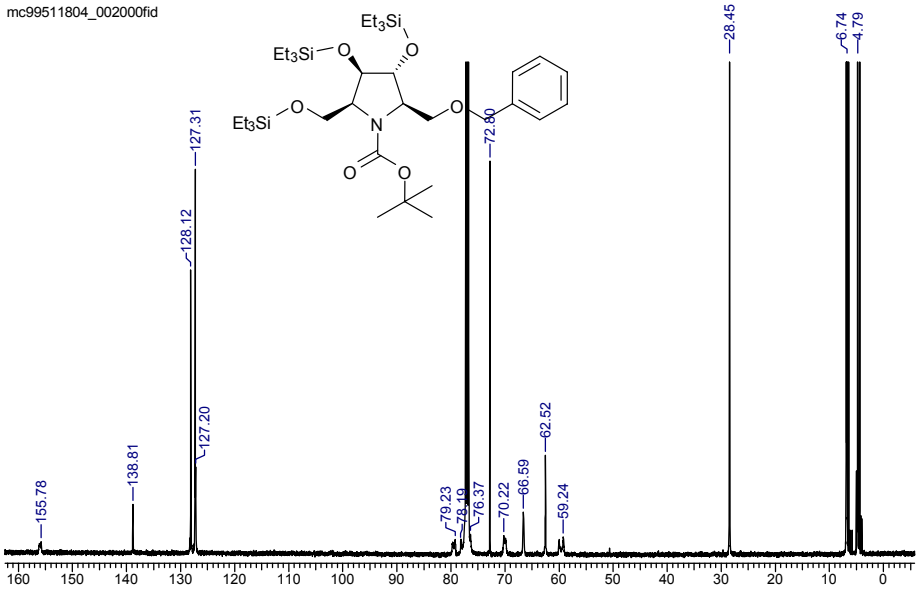


(2*R*,3*R*,4*R*,5*S*)-*tert*-Butyl-2-(benzyloxymethyl)-3,4-*bis*(triethylsilyloxy)-5-((triethylsilyloxy)methyl)pyrrolidine-1-carboxylate 13

^{1}H-NMR (500 MHz, $CDCl_3$)

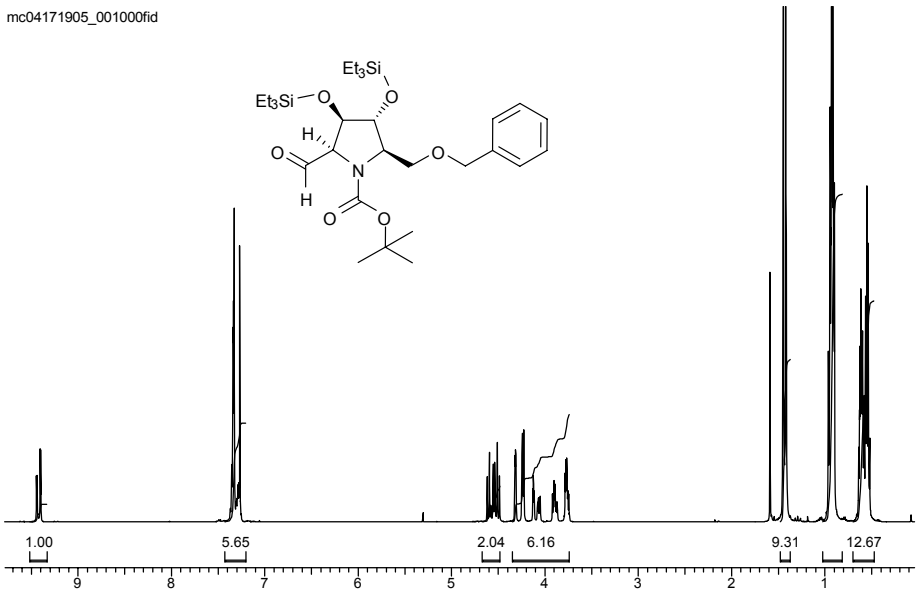


^{13}C-NMR (126 MHz, $CDCl_3$)

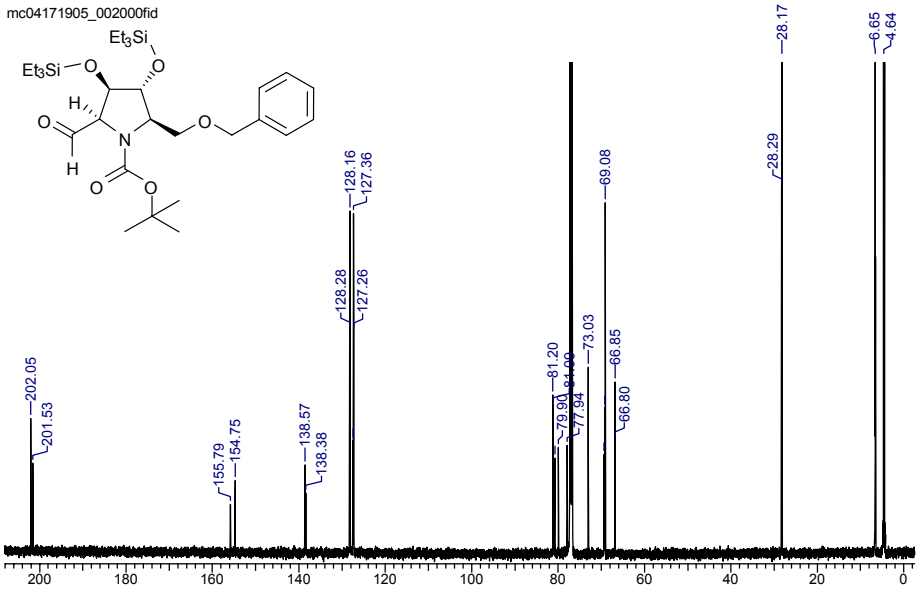


(2*R*,3*R*,4*R*,5*R*)-*tert*-Butyl-2-(benzyloxymethyl)-5-formyl-3,4-*bis*(triethylsilyloxy)pyrrolidine-1-carboxylate 7

^{1}H-NMR (500 MHz, $CDCl_3$)

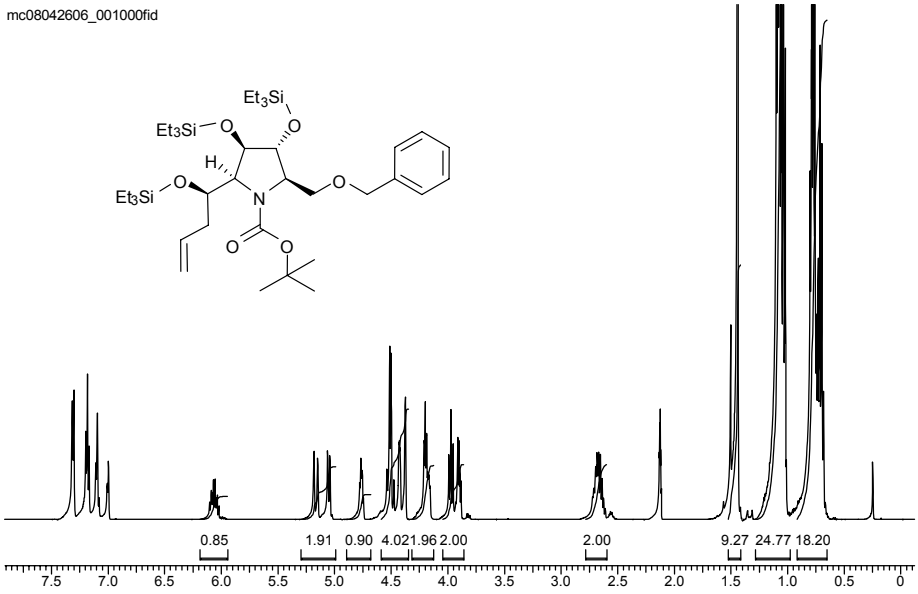


^{13}C-NMR (126 MHz, $CDCl_3$)

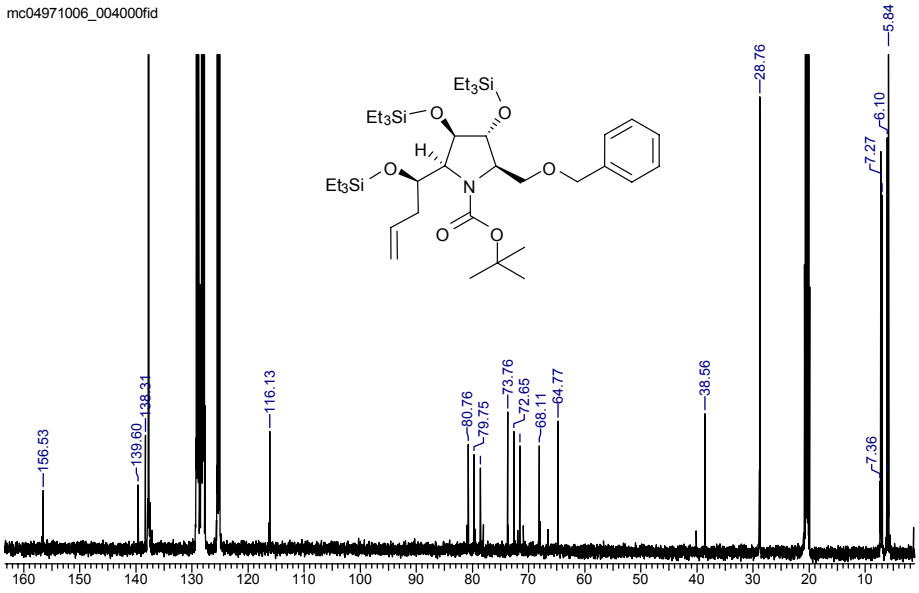


(2*R*,3*R*,4*R*,5*S*)-*tert*-Butyl-2-(benzyloxymethyl)-3,4-*bis*(triethylsilyloxy)-5-((*R*)-1-(triethylsilyloxy)but-3-enyl)pyrrolidine-1-carboxylate 8

^{1}H-NMR (500 MHz, Toluene-d$_8$, 373K)

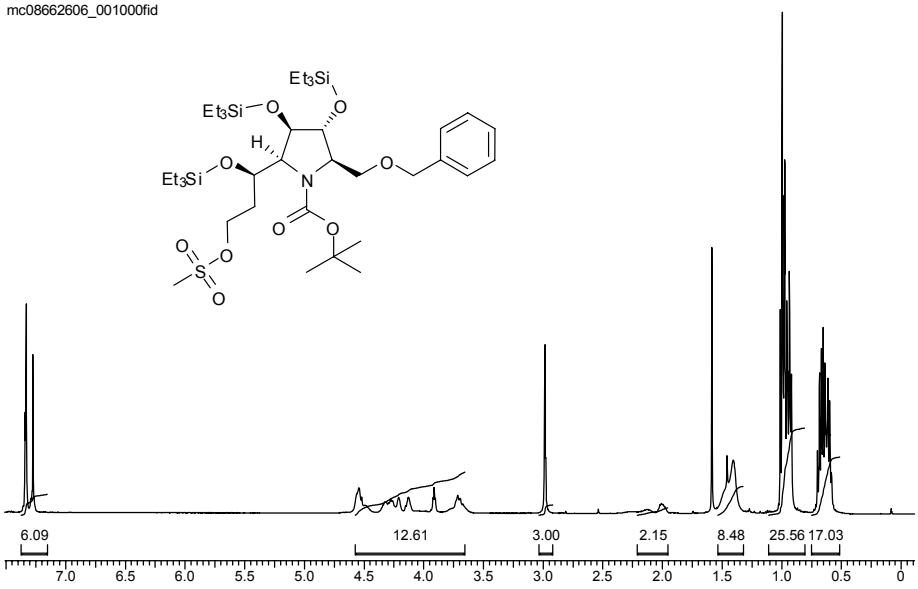


^{13}C-NMR (126 MHz, Toluene-d$_8$, 373K)

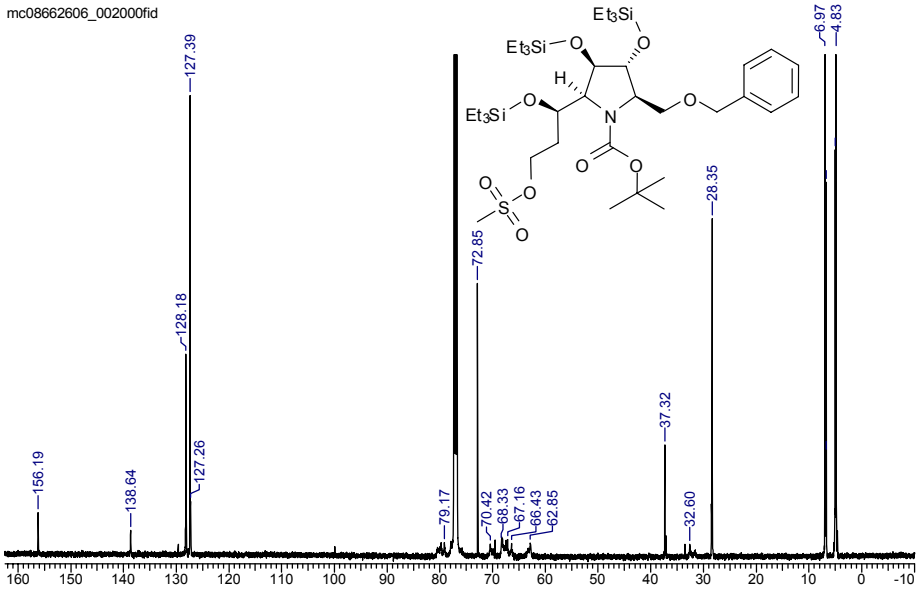


(2*R*,3*R*,4*R*,5*S*)-2-Benzyloxymethyl-5-((*R*)-3-methanesulfonyloxy-1-triethylsilanyloxy-propyl)-3,4-*bis*-triethylsilanyloxy-pyrrolidine-1-carboxylic acid *tert*-butyl ester 9

^{1}H-NMR (500 MHz, $CDCl_3$)

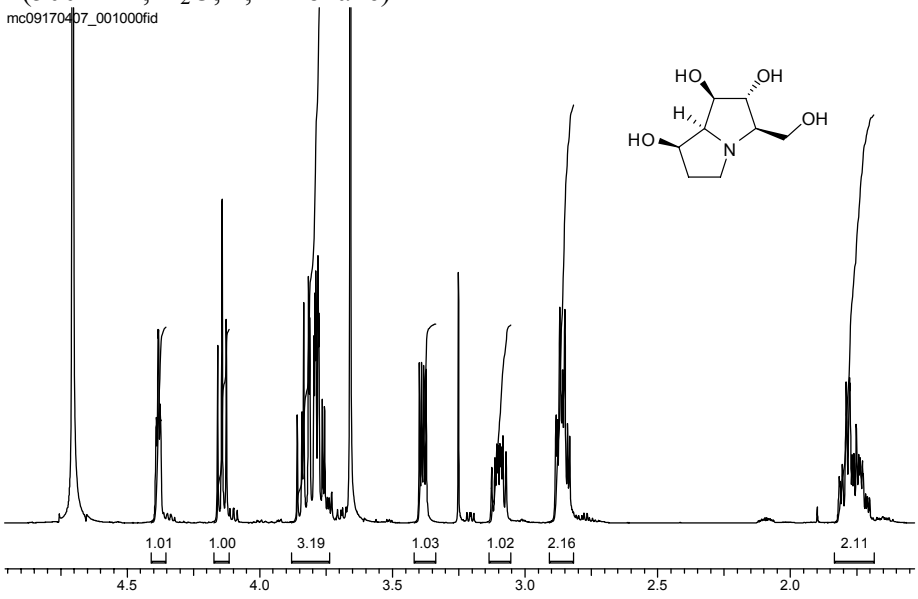


^{13}C-NMR (126 MHz, CDCl3)



(1*R*,2*R*,3*R*,7*R*,7a*S*)-3-(hydroxymethyl)hexahydro-1*H*-pyrrolizine-1,2,7-triol, 7-*epi*alexine 11

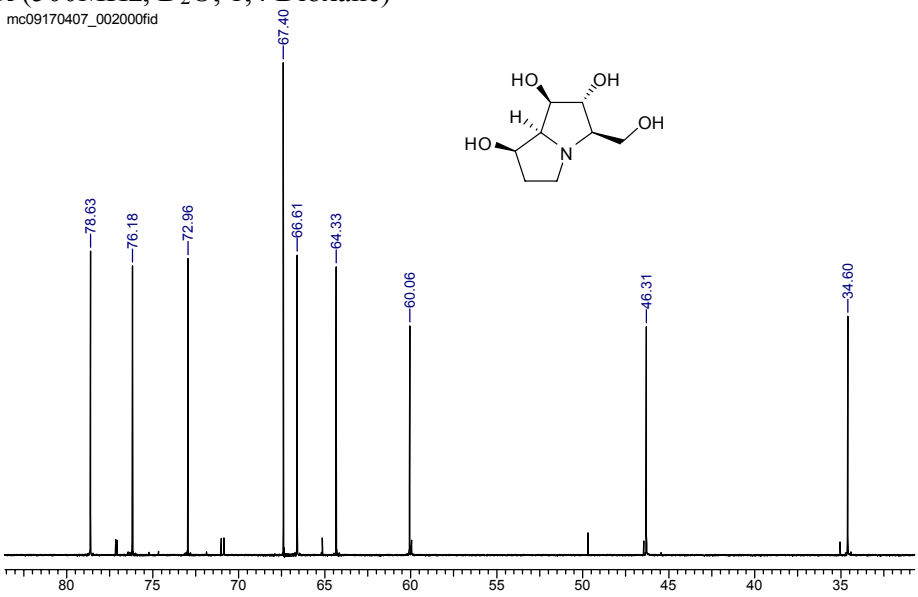
^{1}H-NMR (500MHz, D_2O, 1,4 Dioxane)



Entry	*Synthesis*	*Literature*[12]
1	4.38 (1 H, br. t, J = 3.9)	4.32 (1 H, br. t, J = 3.0)
2	4.14 (1 H, t, J = 8.1)	4.09 (1 H, t, J = 8.0)
3	3.80 (3 H, m)	3.75 (3 H, m)
4	3.38 (1 H, dd, J = 8.0 and 3.9)	3.39 (1 H, dd, J = 8.0 and 4.0)
5	3.10 (1 H, m)	3.08 (1 H, m)
6	2.85 (2 H, m)	2.85 (2 H, m)
7	1.75 (2 H, m)	1.71 (2 H, m)

[12] Pearson, W. H.; Hines, J. V. *J. Org. Chem.* **2000**, *65*, 5785.

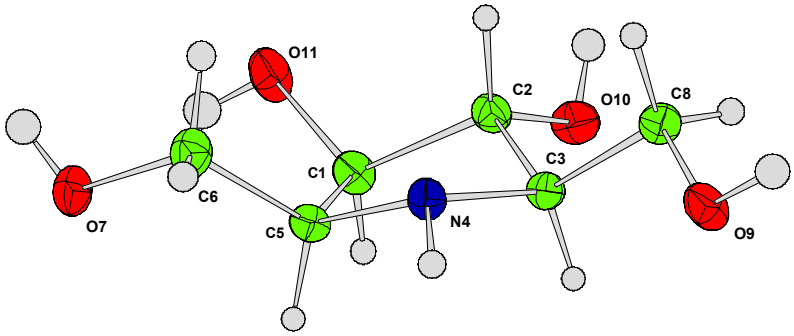
^{1}H-NMR (500MHz, D_2O, 1,4 Dioxane)



Entry	*Synthesis*	*Literature*[13]
1	78.6	77.5
2	76.2	75.2
3	73.0	72.4
4	66.6	67.1
5	64.3	64.2
6	60.0	59.2
7	46.3	46.9
8	34.6	34.2

[13] Fleet, G. W. J.; Haraldson, M.; Nash, R. J.; Fellows, L. E. *Tetrahedron Lett.* **1988**, *29*, 42, 5441.

Single-crystal X-ray diffraction report for compound 4



A typical clear, colourless crystal of **4** was chosen (0.1 × 0.2 × 0.6 mm) for single crystal X-ray analysis. Single crystal X-ray diffraction data were collected using graphite monochromated Mo K_α radiation (λ = 0.71073 Å) on an Enraf-Nonius KappaCCD diffractometer. The diffractometer was equipped with a Cryostream N_2 open-flow cooling device,[14] and the data were collected at 150(2) K. Series of ω-scans were performed in such a way as to cover a sphere of data to a maximum resolution of 0.77 Å. Cell parameters and intensity data were processed using the DENZO-SMN package.[15] The structures of were all solved by direct methods[16] and refined by full-matrix least squares on F^2 using the CRYSTALS suite.[17] Intensities were corrected for absorption effects by the multi-scan method, based on multiple scans of identical and Laue

[14] J. Cosier and A. M. Glazer, *J. Appl. Cryst.*,1986, **19**, 105.
[15] Z. Otwinowski, W. Minor, Processing of X-ray Diffraction Data Collected in Oscillation Mode, Methods Enzymol. 1997, 276, Eds C. W. Carter, R. M. Sweet, Academic Press.
[16] A. Altomare, C. Cascarano, G. Giacovazzo, A. Guagliardi ,M. C. Burla, G. Polidori and M. Camalli, *J. Appl. Cryst.,* 1994, 27, 435.
[17] Betteridge, P.W., Carruthers, J.R., Cooper, R.I., Prout, K. & Watkin, D.J. (2003). *J. Appl. Cryst.* **36**, 1487

equivalent reflections. All non-hydrogen atoms were refined with anisotropic displacement parameters. The H atoms were all located in a difference map, but those attached to carbon atoms were repositioned geometrically. The H atoms were initially refined with soft restraints on the bond lengths and angles to regularise their geometry (C-H in the range 0.93-0.98; N-H in the range 0.86-0.89; N-H to 0.86; O-H = 0.82 Å) and U_{iso}(H) (in the range 1.2-1.5 times U_{eq} of the parent atom), after which the positions were refined with riding constraints.

Single Crystal X-ray Diffraction Data for **4**: $C_6H_{13}NO_4$; M_r = 163.17; orthorhombic (P 2_1 2_1 2_1); *a* = 5.9247(2), *b* = 7.2417(3), *c* = 17.4475(9) Å; $\alpha = \beta = \gamma = 90$ ºC; V = 748.58(6) $Å^3$; T = 150(2) K; Z = 4; μ = 0.121 mm^{-1}; D_{calc} = 1.448 g cm^{-3}; Reflections collected = 1703; independent reflections = 1018 (R_{int} = 0.031); R values [I >2σ(I), 796 reflections]: R_1 = 0.0382, wR_2 = 0.0911.