

Supporting Information

A Flexible Strategy for the Synthesis of Pyrrolizidine Alkaloids

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¹H NMR spectra were recorded on a Bruker AVB500 (500 MHz), Avance AV400 (400 MHz), DPX400 (400 MHz), DPX250 (250 MHz) and DPX200 (200 MHz) and referenced to residual solvent peaks or to sodium 3-(trimethylsilyl)propionate (TSP) as an internal standard. Chemical shifts are quoted in ppm with signal splittings recorded as singlet (s), doublet (d), triplet (t), quartet (q) and multiplet (m). Coupling constants, *J*, are measured to the nearest 0.1 Hz. ¹³C NMR spectra were recorded on a Bruker AVB500 at 126 MHz, the AV400 at 101 MHz and on a Bruker DPX200 at 50 MHz and were referenced to the solvent.

Optical rotations were recorded on a Perkin Elmer 241 polarimeter (using the sodium D line, 589 nm) and [α]_D are given in units of 10⁻¹ deg dm² 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.

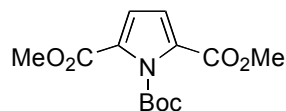
Flash column chromatography was performed using silica gel 60 (0.043-0.063mm, Merck) and silica gel 100 C₁₈-reversed phase (0.040-0.063mm, Merck) using head pressure by means of head bellows. TLC analyses were performed on Merck Kiesegel 60 F₂₅₄ 0.25 mm pre-coated aluminium. Product spots were visualised under UV light (λ_{\max} = 254 nm) and/or by staining with potassium permanganate or anisaldehyde.

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. Light petroleum refers to the fraction of petroleum ether which boils in the range 40-60 °C.

1-*tert*-Butyl-2,5-dimethyl 1*H*-pyrrole-1,2,5-tricarboxylate 25

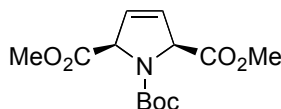


To a solution of 2,2,6,6-tetramethyl piperidine (27 mL, 0.16 mol) in tetrahydrofuran (200 mL) under an atmosphere of argon at -78 °C was added *n*-butyllithium (100 mL of a 1.6 M solution in hexanes) dropwise *via* cannula. To this reaction mixture was then added a solution of *N*-Boc pyrrole **7** (10.7 mL, 0.064 mol) in tetrahydrofuran (45 mL) dropwise *via* cannula. The reaction was stirred at -78 °C for 3 h before being transferred dropwise *via* a cooled

cannula into a stirred solution of methyl chloroformate (14.8 mL, 0.19 mol) in tetrahydrofuran (20 mL) under an atmosphere of argon at $-78\text{ }^{\circ}\text{C}$. After 30 mins the reaction was quenched by addition of saturated ammonium chloride solution (20 mL) and warmed to room temperature. Water (150 mL) and diethyl ether (200 mL) were added and the layers separated. The aqueous layer was extracted with diethyl ether (4 x 100 mL) and then the combined organic layers were washed with hydrochloric acid (1 M, 100 mL) followed by brine (100 mL). The combined organic layers were dried over magnesium sulfate, filtered and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography [SiO_2 , diethyl ether-light petroleum, 20:80] to afford a pale yellow solid, which was then recrystallised from cyclohexane to afford the title compound **25** as a white crystalline solid (14.1 g, 78%). ^1H and ^{13}C NMR were consistent with previously reported data.

M.p. $107\text{--}109\text{ }^{\circ}\text{C}$ (Lit. $112\text{--}114\text{ }^{\circ}\text{C}$); ^1H NMR (400 MHz, CDCl_3) δ_{H} 6.84 (2 H, s), 3.87 (6 H, s), 1.67 (9 H, s); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 159.9, 148.9, 126.7, 115.8, 86.3, 52.0, 27.3.

(2*R*,5*S*)-1-*tert*-Butyl-2,5-dimethyl 1*H*-pyrrole-1,2,5(2*H*,5*H*)-tricarboxylate **8**

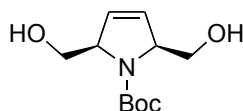


A solution of di-*tert*-butyl biphenyl (7.02 g, 26.0 mmol) in tetrahydrofuran (300 mL) was cooled to $0\text{ }^{\circ}\text{C}$ under an atmosphere of argon. Lithium wire (2.94 g, 424 mmol), which had been washed in pentane was rapidly cut into small pieces (approx. 2 mm length) and added to the tetrahydrofuran solution under an atmosphere of argon. After approximately 5 mins a blue/green colour was observed. The LiDBB solution was stirred at $0\text{ }^{\circ}\text{C}$ for 3 h before being cooled to $-78\text{ }^{\circ}\text{C}$. Pyrrole **25** (15 g, 53.0 mmol) in tetrahydrofuran (100 mL) was added dropwise causing the blue colour to be replaced by a brown colour. The reaction mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 16 h. 2,6-Di-*tert*-butyl phenol (43.7 g, 212 mmol) in tetrahydrofuran (100 mL) was added dropwise and the reaction mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 30 mins. Saturated ammonium chloride solution (100 mL) was added and the reaction vessel removed from the ice-bath. After 20 mins, the reaction mixture was poured into water (250 mL) *via* a Buchner funnel to remove any unreacted lithium wire, and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 400 mL). The combined organic layers were then dried over magnesium sulfate, filtered and the solvent removed *in vacuo*. The

crude product was purified by flash column chromatography [SiO₂, diethyl ether:light petroleum, 40:60] to afford *cis*-dihydropyrrole **8** (13.3 g, 88%) as a pale yellow oil. ¹H and ¹³C NMR were consistent with previously reported data.

¹H NMR (400 MHz, CDCl₃) δ_H 5.93 (2 H, ddt, *J* = 18.0, 6.0 and 2.1), 5.09 (2 H, app. dq, *J* = 27.5 and 2.3), 3.78 (6 H, s), 1.46 (9 H, s); ¹³C NMR (101 MHz, CDCl₃) δ_C 169.2, 153.1, 127.6, 127.5, 81.1, 66.9, 66.6, 52.5, 52.4, 28.2.

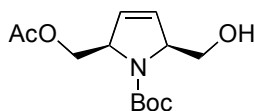
(2*R*,5*S*)-*tert*-Butyl-2,5-bis(hydroxymethyl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate **26**



Red-Al[®] (63 mL, 0.21 mol, 65% solution in toluene) was syringed into tetrahydrofuran (500 mL) at 0 °C under an atmosphere of argon. Diester *cis*-**8** (12.0 g, 0.042 mol) in tetrahydrofuran (50 mL) was added dropwise and the reaction mixture stirred for 2 h. Following careful addition of sodium hydroxide (2 M, 75 mL), the reaction mixture was warmed to room temperature. Saturated Rochelle's solution (250 mL) was added and the resulting layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 200 mL) and then the combined organic extracts were washed with brine (200 mL). These were dried over magnesium sulfate, filtered and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography [SiO₂, ethyl acetate-light petroleum, 70:30] to afford the title compound **26** as a white solid (9.64 g, 84%). ¹H and ¹³C NMR were consistent with previously reported data.

M.p. 108-109 °C (Lit. 105-109 °C); ¹H NMR (400 MHz, CDCl₃) δ_H 5.74-5.81 (2 H, m), 4.70 (1 H, br s), 4.58 (1 H, br s), 3.96-4.08 (4 H, m), 3.63-3.69 (2 H, m), 1.49 (9 H, s); ¹³C NMR (101 MHz, CDCl₃) δ_C 155.1, 128.6, 80.7, 67.2, 66.9, 64.1, 63.5, 28.5.

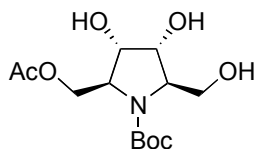
(2*R*,5*S*)-*tert*-Butyl-2-(acetoxymethyl)-5-(hydroxymethyl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate (+)-9****



Vinyl acetate (31 mL, 341 mmol) and lipoprotein lipase from *Pseudomonas sp.* (150 mg) were added to a solution of *diol* **26** (7.81 g, 34.1 mmol) in tetrahydrofuran (300 mL). The mixture was incubated at 37 °C for 30 h (shaken at 150 rpm). The enzyme was removed by filtration and the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography [SiO₂, ethyl acetate-light petroleum, 20:80 then 40:60 then 80:20] to yield *(+)*-pyrroline **9** as a pale yellow oil (7.38 g, 80%, e.e. >98%), ¹H and ¹³C NMR were consistent with previously reported data.

[α]_D²⁰ +71.1 (*c* 1.0, CH₂Cl₂), ¹H NMR (400 MHz, CDCl₃) δ _H 5.94 (1 H, td, *J* = 4.1 and 1.8), 5.79 (1 H, td, *J* = 4.1 and 1.8), 4.59-4.61 (1 H, m), 4.40-4.44 (2 H, m), 4.22 (1 H, dd, *J* = 10.9 and 3.9), 4.04 (1 H, dd, *J* = 10.8 and 5.5), 3.68 (1 H, br d, *J* = 10.1), 3.30-3.37 (1 H, m), 1.99 (3 H, s), 1.43 (9 H, s); ¹³C NMR (101 MHz, CDCl₃) δ _C 170.6, 154.4, 130.5, 127.7, 79.9, 67.1, 65.1, 64.1, 64.0, 28.6, 28.4, 21.0, 20.8.

(2*S*,3*S*,4*R*,5*R*)-tert-Butyl-2-(acetoxymethyl)-3,4-dihydroxy-5-(hydroxymethyl)pyrrolidine-1-carboxylate **27**

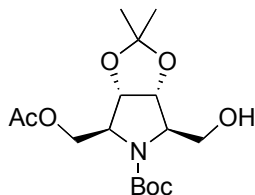


Osmium tetroxide (345 mg, 1.36 mmol) and trimethylamine *N*-oxide (9.04 g, 81.3 mmol) were added to a solution of *pyrroline* **9** (7.36 g, 27.1 mmol) in dichloromethane (370 mL) causing the reaction mixture to turn bright yellow in colour. After stirring overnight, saturated sodium sulfite solution (110 mL) was added and the resulting heterogeneous mixture was vigorously stirred for 30 mins. The layers were then separated and the aqueous layer extracted with ethyl acetate (3 x 100 mL). The combined organic layers were dried over magnesium sulfate, filtered and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography [SiO₂, ethyl acetate] to afford the title compound **27** as a white solid (7.20 g, 87%). ¹H and ¹³C NMR were consistent with previously reported data.

M.p. 102-104 °C (Lit. 84-86 °C); [α]_D +8.6 (*c* 1, CHCl₃) (Lit., +12 (*c* 1, CH₂Cl₂)); ¹H NMR (500 MHz, DMSO-*D*₆, 363 K) δ _H 4.61 (1 H, d, *J* = 5.5), 4.52 (1 H, d, *J* = 4.9), 4.42 (1 H, t, *J* = 5.4), 4.24 (1 H, dd, *J* = 11.2 and 6.15), 4.08 (1 H, dd, *J* = 11.2 and 3.8), 4.03 (1 H, q, *J* = 4.4), 3.96 (1 H, q, *J* = 4.6), 3.66-3.70 (1 H, m), 3.55 (1 H, q, *J* = 4.5), 3.46-3.52 (2 H, m),

2.00 (3 H, s), 1.42 (9 H, s); ^{13}C NMR (126 MHz, DMSO- D_6 , 363 K) δ_{C} 170.4, 155.1, 79.4, 72.1, 71.4, 65.9, 62.9, 62.3, 60.8, 28.6, 20.9.

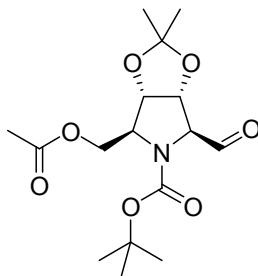
(3a*S*,4*S*,6*R*,6a*R*)-*tert*-Butyl-4-(acetoxymethyl)-6-(hydroxymethyl)-2,2-dimethyldihydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrole-5(4*H*)-carboxylate **10**



To a solution of *triol* **27** (5 g, 16.4 mmol) in anhydrous DMF (125 mL) under an atmosphere of argon was added 2-methoxy-propene (3.1 mL, 32.8 mmol) and *para*-toluene sulfonic acid (300 mg, 1.66 mmol). The reaction mixture was stirred at room temperature for 16 h, after which time diethyl ether (15 mL) was added. The reaction mixture was poured into water (100 mL) and extracted with diethyl ether (3 x 50 mL). The combined organic layers were dried over magnesium sulfate, filtered and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography [SiO_2 , ethyl acetate-light petroleum, 50:50] to afford the title compound **10** as a colourless oil (5.31 g, 94%). ^1H and ^{13}C NMR were consistent with previously reported data.

$[\alpha]_{\text{D}}^{20} +9.6$ (c 1, CH_2Cl_2) (Lit., +12 (c 1, CH_2Cl_2)); ^1H NMR (500 MHz, DMSO- D_6 , 363 K) δ_{H} 4.74 (1 H, t, $J = 5.1$), 4.68 (1 H, d, $J = 5.8$), 4.58 (1 H, d, $J = 5.7$), 4.13 (1 H, dd, $J = 10.7$ and 5.0), 4.00-4.08 (2 H, m), 3.88-3.93 (1 H, br s), 3.55 (1 H, td, $J = 7.5$ and 4.2), 3.36-3.40 (1 H, m), 2.04 (3 H, s), 1.43 (9 H, s), 1.39 (3 H, s), 1.29 (3 H, s); ^{13}C NMR (126 MHz, DMSO- D_6 , 363 K) δ_{C} 170.3, 154.1, 111.3, 82.3, 79.8, 66.5, 63.9, 63.8, 61.6, 55.1, 28.5, 27.6, 25.7, 20.9.

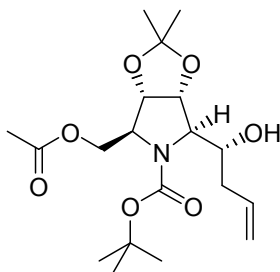
tert*-Butyl-4-(acetoxymethyl)-6-formyl-2,2-dimethyl-tetrahydro-[1,3]dioxolo[4,5-*c*]pyrrole-5-carboxylate **28*



Pyrrolidine **10** (828 mg, 2.40 mmol) was dissolved in DCM (15 mL) and added to a suspension of Dess-Martin periodinane (1.2 g, 2.60 mmol) in DCM (15 mL). The mixture was stirred for 2 hours. The solvent was then removed *in vacuo* and the crude product was purified by flash column chromatography [SiO₂, ethyl acetate-light petroleum, 20:80] to afford the title compound **28** a pale yellow oil (712 mg, 86%).

$[\alpha]_D^{20}$ -16 (*c* 1, CH₂Cl₂); $\nu_{\max}/\text{cm}^{-1}$ (film): 2966, 1749, 1700; ¹H NMR (500 MHz, DMSO-D₆, 363K) δ_{H} : 9.55 (1H, br s), 4.93 (1H, dd, *J* = 5.8 and 2.2), 4.64 (1H, d, *J* = 5.8), 4.31 (1H, br s), 4.26 (1H, m), 4.15 (1H, dd, *J* = 11.3 and 3.6), 4.05 (1H, dd, *J* = 11.3 and 5.0), 1.97 (3H, s), 1.44 (9H, s), 1.43 (3H, s), 1.32 (3H, s); ¹³C NMR (126 MHz, CDCl₃) δ_{C} : 199.4, 199.2, 170.3, 170.2, 154.2, 153.4, 112.3, 112.3, 82.7, 81.9, 81.5, 81.0, 79.9, 73.1, 72.4, 64.9, 64.6, 62.8, 62.2, 28.2, 28.1, 27.9, 27.0, 26.9, 25.0, 20.8; Analysis by mass spectrometry was not possible.

tert*-Butyl-4-acetoxymethyl-6-(1-hydroxy-but-3-enyl)-2,2-dimethyl-tetrahydro-[1,3]dioxolo[4,5-*c*]pyrrole-5-carboxylate **11*

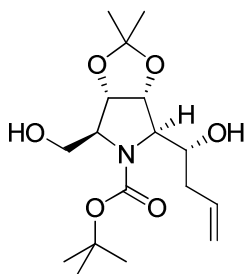


Aldehyde **28** (662 mg, 1.9 mmol) was dissolved in a 5:1 mixture of saturated aqueous ammonium chloride solution and tetrahydrofuran (60 mL). Zinc (627 mg, 9.7 mmol) and allyl bromide (840 μL , 9.7 mmol) were added and the mixture was stirred for 30 minutes. The crude reaction mixture was extracted into Et₂O (2 x 30 mL) and washed with brine (30 mL).

The combined organics were dried over Na₂SO₄ and concentrated *in vacuo* to furnish the title compound **11** as a colourless solid (678 mg, 93%).

$[\alpha]_D^{20}$ -7.5 (*c* 1, CH₂Cl₂); m.p.: 74-78 °C; $\nu_{\max}/\text{cm}^{-1}$ (film): 3420, 2978, 1736, 1695; ¹H NMR (500 MHz, DMSO-D₆, 363K) δ_{H} : 5.85 (1H, ddt, *J* = 17.2, 10.2, 6.9), 5.10 (1H, ddt, *J* = 17.2, 2.1, 1.5), 5.05 (1H, ddt, *J* = 10.2, 2.3, 1.2), 4.78 (1H, dd, *J* = 5.9 and 1.3), 4.53 (1H, dd, *J* = 5.9 and 1.5), 4.17-4.00 (3H, m), 3.87 (1H, dd, *J* = 3.7 and 0.8), 3.64 (1H, td, *J* = 6.8 and 3.9), 2.23 (2H, tt, *J* = 6.9 and 1.3), 2.03 (3H, s), 1.43 (9H, s), 1.37 (3H, s), 1.29 (3H, s); ¹³C NMR (126 MHz, DMSO-D₆, 363K) δ_{C} : 170.4, 154.3, 135.7, 117.1, 111.2, 82.5, 80.4, 79.8, 70.6, 68.9, 39.4, 28.6, 28.5, 27.6, 25.8, 21.0; HRMS (ESI, *m/z*) 408.1992 [M + Na]⁺, C₁₉H₃₁NO₇Na requires 408.1998.

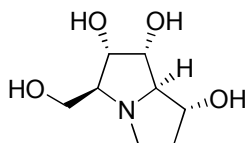
(3a*R*,4*R*,6*S*,6a*S*)-tert-Butyl 4-((*R*)-1-hydroxybut-3-enyl)-6-(hydroxymethyl)-2,2-dimethyldihydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrole-5(4*H*)-carboxylate **29**



To a stirred solution of *acetate 11* (512 mg, 1.3 mmol) in MeOH (30 mL) was added K₂CO₃ (918 mg, 6.6 mmol) at room temperature. The reaction mixture was stirred for 2 h, after which time silica was added and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography [SiO₂, diethyl ether] to afford the title compound **29** as a yellow oil (429 mg, 94%).

$[\alpha]_D^{20}$ -4.1 (*c* 1.0, CH₂Cl₂); $\nu_{\max}/\text{cm}^{-1}$ (film) 3378, 2980, 2936; 1697, 1671, 1370, 1171, 1067; ¹H NMR (500 MHz, DMSO-D₆, 363 K) δ_{H} 5.85 (1 H, ddt, *J* = 17.2, 10.3, and 6.9), 5.10 (1 H, dd, *J* = 17.2 and 2.0), 5.04 (1 H, dt, *J* = 10.2 and 1.1), 4.86 (1 H, d, *J* = 5.0), 4.75 (2 H, m), 4.62 (1 H, dd, *J* = 5.8 and 1.4), 3.87 (1 H, m), 3.81 (1 H, m), 3.71 (1 H, m), 3.54 (2 H, m), 2.22 (2 H, t, *J* = 6.8). 1.43 (9 H, s), 1.38 (3 H, s), 1.29 (3 H, s); ¹³C NMR (126 MHz, DMSO-D₆, 363 K) δ_{C} 154.9, 136.2, 117.3, 11.3, 82.8, 80.6, 79.9, 71.2, 69.4, 67.3, 62.4, 39.7, 29.0, 28.2, 26.3; HRMS (ESI, *m/z*) 366.1887 [M + Na]⁺, C₂₀H₃₅NO₈Na requires 366.1893.

(1*R*,2*S*,3*S*,7*R*,7*aR*)-3-(Hydroxymethyl)hexahydro-1*H*-pyrrolizine-1,2,7-triol; (-)-2,3,7-triepiaustraline **2**



To a stirred solution of *allylic alcohol* **29** (200 mg, 0.58 mmol), in DCM (10 mL) O₂ was bubbled through for 10 minutes at -78 °C. After this time, O₃ was bubbled through this solution for 30 minutes until the reaction maintained a blue colour. At this point, O₂ was bubbled through the solution until the blue colour was discharged. PPh₃ (765 mg, 2.92 mmol) was then added and the reaction left to warm to room temperature overnight; after which time the solvent removed *in vacuo*. The crude product was rapidly purified by flash column chromatography [SiO₂, diethyl ether-light petroleum, 30:70] to afford *aldehyde* **12** as a colourless oil (167 mg, 83%), which was carried on to the next step without further purification.

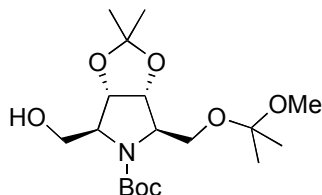
To a stirred solution of *aldehyde* **12** (160 mg, 0.46 mmol) in DCM (5 mL) was added ZnBr₂ (512 mg, 2.32 mmol) and the reaction was stirred for 12 h at room temperature. After which time water (1 mL) and the reaction stirred for a further 1 h. The solvent was then removed *in vacuo* and the crude product was passed through a short plug of Dowex 50X8-100 (eluting with water, then 7:1 H₂O:NH₄OH) to give *aminol* **13** which was used in the next step without further purification.

To *aminol* **13** was added dichloroethane (2 mL), trifluoroacetic acid (2 mL) and Et₃SiH (0.37 mL, 2.32 mmol) and this mixture was heated to 70 °C for 5h. The reaction was then allowed to cool to room temperature before the solvent was removed *in vacuo*. The crude product was purified by flash chromatography [SiO₂, NH₄OH:MeOH:EtOAc, 1:3:6], followed by reversed-phase silica gel [C₁₈, MeOH:CHCl₃ 1:7] and finally Dowex 50X8-100 (eluting with water then 7:1 H₂O:NH₄OH) to give (-)-2,3,7-triepiaustraline **2** as a colourless oil (57 mg, 65% yield over two steps).

$[\alpha]_D^{20}$ -51 (*c* 0.51, H₂O), (Lit for enantiomer, +60, *c* 0.58, H₂O); $\nu_{\max}/\text{cm}^{-1}$ (film) 3334, 2980, 2927; 1568, 1418, 1105; ¹H NMR (500 MHz, D₂O (TSP)) δ_{H} 4.14 (1 H, ddd, *J* = 8.0, 6.2, and 6.0), 4.06 (1 H, dd, *J* = 5.2 and 2.4), 3.95 (1 H, dd, *J* = 9.5 and 5.4), 3.87 (2 H, d), 3.21 (1 H, m), 3.19 (1 H, dd, *J* = 5.5 and 2.4), 3.00 (1 H, ddd, *J* = 10.1, 7.3 and 3.5), 2.90 (1 H, ddd, *J* = 10.3, 10.1 and 6.3), 2.14 (1 H, m), 1.76 (1 H, m); ¹³C NMR (126 MHz, D₂O (TSP)) δ_{C} 78.6,

77.0, 76.5, 73.8, 67.3, 61.8, 47.7, 36.3; HRMS (ESI, m/z) 190.1074 $[M + H]^+$, $C_8H_{16}NO_4$ requires 190.1079.

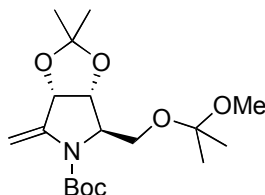
3a*S*,4*S*,6*R*,6a*R*)-tert-Butyl-4-(hydroxymethyl)-6-[(2-methoxypropan-2-yloxy)methyl]-2,2-dimethyldihydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrole-5(4*H*)-carboxylate **14**



Alcohol 10 (100 mg, 0.289 mmol) was dissolved in 2-methoxypropene (5 mL) under an atmosphere of argon and cooled to 0 °C over activated 4Å molecular sieves (1 g). Pyridinium *p*-toluenesulfonate (7 mg, 0.029 mmol) was added and the reaction was allowed to warm to room temperature overnight. Following addition of triethylamine (40 µL, 0.289 mmol) the reaction mixture was stirred for 5 mins. Potassium carbonate (60 mg, 0.434 mmol) was added in one portion followed by methanol (5 mL) and the resulting reaction mixture was stirred for 1 h. The reaction mixture was then filtered through filter paper and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography [SiO_2 , diethyl ether-light petroleum, 30:70] to afford the title compound **14** as a pale yellow oil (76 mg, 70%).

$[\alpha]_D^{20}$ -2.8 (c 1, CH_2Cl_2); ν_{max}/cm^{-1} (film) 3444, 2986, 1697; 1H NMR (500 MHz, Toluene- D_8 , 373 K) δ_H 4.72 (1 H, dd, $J = 5.6$ and 2.1), 4.57 (1 H, d, $J = 5.4$), 4.25 (1 H, br. s), 4.17-4.21 (1 H, m), 3.86 (1 H, dd, $J = 11.2$ and 3.7), 3.79-3.89 (1 H, m), 3.62 (1 H, dd, $J = 11.2$ and 3.7), 3.50 (1 H, dd, $J = 9.9$ and 2.7), 3.09 (3 H, s), 1.42 (3 H, s), 1.40 (9 H, s), 1.24-1.25 (6 H, m), 1.23 (3 H, s); ^{13}C NMR (126 MHz, Toluene- D_8 , 373 K) δ_C 154.6, 111.2, 100.4, 82.3, 82.2, 79.4, 67.2, 65.5, 64.0, 61.0, 48.1, 28.0, 27.2, 25.3, 23.9, 23.6; HRMS (ESI, m/z) 398.2155 $[M + Na]^+$, $C_{18}H_{33}NO_7Na$ requires 398.2149.

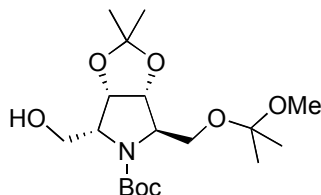
(3a*R*,4*R*,6a*S*)-tert-Butyl-4-[(2-methoxypropan-2-yloxy)methyl]-2,2-dimethyl-6-methylenedihydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrole-5(4*H*)-carboxylate **15**



To a stirred solution of *alcohol* **14** (951 mg, 2.53 mmol) and DMAP (774 mg, 6.33 mmol) in dichloromethane (50 mL) under an atmosphere of argon was added methanesulfonic anhydride (882 mg, 5.07 mmol). The reaction mixture was stirred at room temperature for 18 h. Water (30 mL) was added and the resulting layers separated. The aqueous layer was extracted with dichloromethane (3 x 30 mL) and then the combined organic extracts were washed with brine (20 mL). The organic layer was dried over magnesium sulfate, filtered and the solvent removed *in vacuo* yielding the crude mesylate. This was dissolved in dimethoxyethane (50 mL) under an atmosphere of argon and sodium iodide (3.77 g, 25.2 mmol) and DBU (1.88 mL, 12.6 mmol) were added to the resulting solution. The reaction mixture was heated at reflux for 72 h. Upon cooling the reaction was quenched with water (50 mL) and diethyl ether (50 mL). The resulting layers were separated and the aqueous layer was extracted with dichloromethane (3 x 50 mL) and then the combined organic extracts were washed with brine (50 mL). These were dried over magnesium sulfate, filtered and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography [SiO₂ doped with 1% triethylamine, light petroleum] to afford the title compound **15** as a colourless oil (710 mg, 79%).

$[\alpha]_D^{20}$ -117 (*c* 1, CH₂Cl₂); $\nu_{\max}/\text{cm}^{-1}$ (film) 1726, 1697, 1663; ¹H NMR (250 MHz, CDCl₃) δ_{H} 5.25-5.70 (1 H, m), 4.99 (1 H, d, *J* = 5.6), 4.61 (1 H, br s), 4.50 (1 H, d, *J* = 5.6), 4.28 (1 H, br s), 3.65-3.78 (1 H, m), 3.47 (1 H, dd, *J* = 10.1 and 2.4), 3.12 (3 H, s), 1.53 (9 H, s), 1.46 (3 H, s), 1.38 (3 H, s), 1.31 (3 H, s), 1.27 (3 H, s); ¹³C NMR (63 MHz, CDCl₃) δ_{C} 152.5, 146.8, 111.9, 100.5, 94.1, 81.6, 78.8, 77.6, 64.4, 60.7, 48.9, 28.7, 28.0, 26.6, 24.8, 24.4; HRMS (ESI, *m/z*) 358.2224 [*M* + *H*]⁺; C₁₈H₃₂NO₆ requires 358.2224.

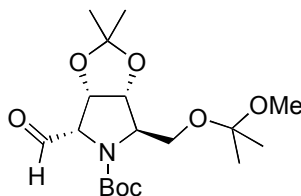
(3a*S*,4*R*,6*R*,6a*R*)-tert-Butyl-4-(hydroxymethyl)-6-[(2-methoxypropan-2-yloxy)methyl]-2,2-dimethyldihydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrole-5(4*H*)-carboxylate **16**



To a stirred solution of *enamine* **15** (703 mg, 1.97 mmol) in tetrahydrofuran (50 mL) under an atmosphere of argon was added borane solution (3.93 mL, 1 M solution in tetrahydrofuran) dropwise. The reaction mixture was stirred for 3 h before careful addition of hydrogen peroxide (35% aqueous solution, 10 mL) and sodium hydroxide solution (2 M, 10 mL). After stirring for 30 mins the reaction mixture was diluted with a saturated solution of potassium carbonate (50 mL) and ethyl acetate (50 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over magnesium sulfate, filtered and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography [SiO₂ doped with 1% triethylamine, diethyl ether-light petroleum, 20:80] to afford the title compound **16** as a colourless oil which became a white crystalline solid upon standing (658 mg, 89%).

M.p. 102-104 °C; $[\alpha]_D^{20}$ -42.9 (*c* 0.9, CH₂Cl₂); $\nu_{\max}/\text{cm}^{-1}$ (film) 3427, 2987, 1677; ¹H NMR (400 MHz, CDCl₃) δ_{H} 5.31 (1 H, dd, *J* = 10.9 and 2.5), 4.75 (1 H, t, *J* = 6.1), 4.58 (1 H, d, *J* = 6.2), 4.07 (1 H, t, *J* = 2.7), 3.87-3.92 (2 H, m), 3.77 (1 H, ddd, *J* = 13.1, 7.4 and 2.3), 3.66 (1 H, dd, *J* = 9.8 and 3.5), 3.42 (1 H, dd, *J* = 9.7 and 2.3), 3.14 (3 H, s), 1.48 (9 H, s), 1.45 (3 H, s), 1.32 (6 H, s), 1.30 (3 H, s); ¹³C NMR (101 MHz, CDCl₃) δ_{C} 155.9, 111.0, 100.1, 81.2, 80.9, 80.5, 66.3, 63.5, 63.0, 61.0, 48.7, 28.4, 26.1, 24.7, 24.4, 24.2; HRMS (ESI, *m/z*) 398.2150 [*M* + Na]⁺, C₁₈H₃₃NO₇Na requires 398.2149.

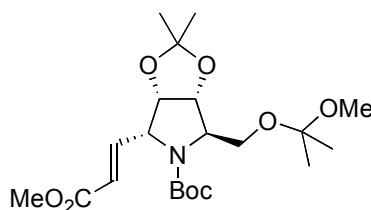
(3a*S*,4*S*,6*R*,6a*R*)-tert-Butyl-4-formyl-6-[(2-methoxypropan-2-yloxy)methyl]-2,2-dimethyldihydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrole-5(4*H*)-carboxylate **17**



To a stirred solution of *alcohol* **16** (1.29 g, 3.43 mmol) in freshly distilled dichloromethane (300 mL) under an atmosphere of argon was added 4Å molecular sieves (15 g) followed by NMO (702 mg, 5.99 mmol) and TPAP (120 mg, 0.34 mmol). The reaction mixture was stirred overnight at room temperature then filtered through Celite®. The crude reaction mixture was then purified *via* flash column chromatography [SiO₂ doped with 1% triethylamine, diethyl ether-light petroleum, 25:75] to afford the title compound **17** as a colourless oil (1.33 g, 100%).

$[\alpha]_{\text{D}}^{20} -139$ (*c* 0.6, CHCl₃); $\nu_{\text{max}}/\text{cm}^{-1}$ (film) 2987, 1741, 1695; ¹H NMR (400 MHz, CDCl₃) δ_{H} 9.32 (1 H, dd, *J* = 17.1 and 3.9), 4.95 (1 H, dt, *J* = 12.5 and 6.3), 4.70 (1 H, t, *J* = 5.5), 4.36 (1 H x 0.6, br s), 4.19-4.21 (2 H x 0.4, m), 4.11 (1 H x 0.6, dd, *J* = 7.0 and 4.0), 3.94 (1 H x 0.6, dd, *J* = 9.9 and 2.6), 3.73 (1 H x 0.4, dd, *J* = 9.8 and 2.8), 3.42 (1 H, ddd, *J* = 16.0, 9.9 and 1.8), 3.12 (3 H, s), 1.46-1.49 (3 H + 9 H x 0.4, m), 1.40 (9 H x 0.6, s), 1.27-1.33 (9 H, m); ¹³C NMR (101 MHz, CDCl₃) δ_{C} 199.0, 198.6, 154.5, 153.3, 112.1, 112.0, 100.2, 100.1, 83.2, 82.3, 81.7, 81.6, 81.2, 80.5, 69.0, 68.9, 63.1, 62.9, 61.1, 60.1, 48.8, 48.6, 28.3, 28.1, 25.8, 25.7, 24.4, 24.2, 24.0; HRMS (ESI, *m/z*) 396.1993 [M + Na]⁺, C₁₈H₃₁NO₇Na requires 396.1993.

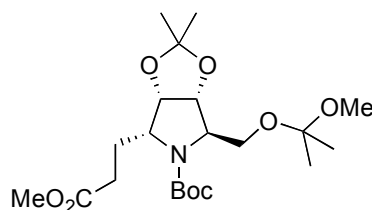
(3a*S*,4*R*,6*R*,6a*R*)-tert-Butyl-4-[(*E*)-3-methoxy-3-oxoprop-1-enyl]-6-[(2-methoxypropan-2-yloxy)methyl]-2,2-dimethyldihydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrole-5(4*H*)-carboxylate **18**



To a stirred solution of *aldehyde* **17** (134 mg, 0.359 mmol) in anhydrous toluene under an atmosphere of argon was added methyl(triphenylphosphoranylidene) acetate (360 mg, 1.076 mmol). The reaction mixture was heated at reflux and stirred for 24 h, after which another portion of methyl(triphenylphosphoranylidene) acetate (240 mg, 0.717 mmol) was added. The reaction was heated for another 24 h at reflux then cooled to room temperature and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography [SiO₂ doped with 1% triethylamine, diethyl ether-light petroleum, 10:90] to afford the title compound **18** as a colourless oil (111 g, 72%).

$[\alpha]_D^{20} -96.5$ (c 1, CHCl_3); $\nu_{\text{max}}/\text{cm}^{-1}$ (film) 2986, 1717, 1698, 1644; ^1H NMR (400 MHz, CDCl_3) δ_{H} 6.74-6.84 (1 H, m), 5.83 (1 H, app. dd, $J = 23.6$ and 15.9), 4.74 (1 H, q, $J = 7.1$), 4.63 (1 H, d, $J = 5.8$), 4.43 (1 H x 0.4, t, $J = 7.3$), 4.34 (1 H x 0.6, t, $J = 7.5$), 4.23 (1 H x 0.6, br s), 4.11 (1 H x 0.4, br s), 3.90 (1 H x 0.6, dd, $J = 9.6$ and 2.2), 3.64-3.74 (3 H and 1 H x 0.4, m), 3.36-3.42 (1 H, m), 3.12 (3 H, s), 1.45 (3 H, s), 1.42 (3 H, s), 1.33 (3 H, s), 1.30 (3 H, s), 1.28 (9 H, s); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 166.5, 153.9, 148.2, 147.4, 120.3, 111.8, 111.7, 100.0, 82.5, 82.0, 81.8, 81.2, 80.5, 80.3, 63.7, 62.5, 62.5, 61.1, 59.9, 51.5, 51.4, 48.8, 48.5, 28.3, 28.2, 25.8, 24.8, 24.4, 24.2; HRMS (ESI, m/z) 452.2249 $[\text{M} + \text{Na}]^+$, $\text{C}_{21}\text{H}_{35}\text{NO}_8\text{Na}$ requires 452.2255.

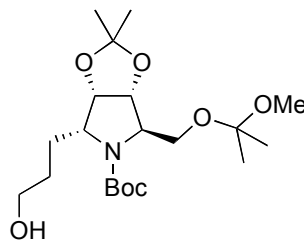
(3a*S*,4*R*,6*R*,6a*R*)-tert-Butyl-4-(3-methoxy-3-oxopropyl)-6-[(2-methoxypropan-2-yl)oxy)methyl]-2,2-dimethyldihydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrole-5(4*H*)-carboxylate
30



To a stirred solution of *ester 18* (483 mg, 1.13 mmol) in methanol (10 mL) was added PtO_2 (26 mg, 0.112 mmol). The reaction mixture was stirred under a balloon of hydrogen for 18 h and then filtered through Celite[®]. The solvent was removed *in vacuo* to afford the title compound **30** as a colourless oil (454 mg, 94%) which was used without further purification.

$[\alpha]_D^{20} -65.7$ (c 0.82, CHCl_3); $\nu_{\text{max}}/\text{cm}^{-1}$ (film) 2987, 2943, 1740, 1696; ^1H NMR (400 MHz, CDCl_3) δ_{H} 4.67 (1 H, t, $J = 6.25$), 4.59 (1 H, d, $J = 6.19$), 4.14 (1 H x 0.4, br s), 4.04 (1 H x 0.6, br s), 3.86-3.97 (1 H x 0.4, m), 3.58-3.77 (4 H + 1 H x 0.6, m), 3.30-3.44 (1 H, m), 3.13 (3 H, s), 2.58-2.73 (1 H x 0.6, m), 2.30-2.52 (2 H + 1 H x 0.4, m), 1.86-2.00 (1 H, m), 1.49 (3 H, s), 1.44 (9 H, s), 1.32 (3 H, s), 1.29 (3 H, s), 1.27 (3 H, s); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 174.1, 154.5, 111.0, 100.0, 81.8, 81.3, 80.6, 79.9, 62.9, 62.1, 61.5, 61.1, 59.9, 51.4, 48.8, 30.9, 29.7, 28.4, 25.8, 24.8, 24.4, 24.3, 24.1; HRMS (ESI, m/z) 454.2413 $[\text{M} + \text{Na}]^+$, $\text{C}_{21}\text{H}_{37}\text{NO}_8\text{Na}$ requires 454.2411.

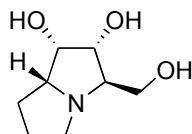
(3a*S*,4*R*,6*R*,6a*R*)-tert-Butyl-4-(3-hydroxypropyl)-6-[(2-methoxypropan-2-yloxy)methyl]-2,2-dimethyldihydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrole-5(4*H*)-carboxylate **19**



To a stirred solution of *ester 30* (200 mg, 0.463 mmol) in tetrahydrofuran (20 mL) under an atmosphere of argon was added lithium borohydride (20 mg, 0.926 mmol) and methanol (0.5 mL). The reaction mixture was stirred for 1.5 h and then quenched carefully with water (20 mL). Ethyl acetate (20 mL) was added and the layers separated. The aqueous layer was extracted with ethyl acetate (2 x 20 mL) and then the combined organic layers were washed with brine (20 mL), dried over magnesium sulfate, filtered and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography [SiO₂ doped with 1% triethylamine, diethyl ether-light petroleum, 20:80 then 50:50] to afford the title compound **19** as a colourless oil (156 mg, 84%).

M.p. 92-95 °C; $[\alpha]_D^{20}$ -77.5 (*c* 1.1, CH₂Cl₂); $\nu_{\max}/\text{cm}^{-1}$ (film) 3455, 2939, 1689; ¹H NMR (400 MHz, CDCl₃) δ_{H} 4.71 (1 H, t, *J* = 6.3), 4.62 (1 H, d, *J* = 6.3), 4.02-4.18 (1 H, m), 3.88-3.96 (1 H x 0.2, m), 3.71-3.80 (1 H x 0.8, m), 3.58-3.70 (3 H, m), 3.32-3.44 (1 H, m), 3.14 (3 H, s), 2.21-2.43 (1 H, m), 1.50-1.78 (3 H, m), 1.52 (3 H, s), 1.45 (9 H, s), 1.35 (3 H, s), 1.31 (3 H, s), 1.29 (3 H, s); ¹³C NMR (101 MHz, CDCl₃) δ_{C} 154.8, 111.0, 100.0, 81.9, 79.9, 79.9, 62.8, 62.5, 62.5, 61.1, 48.8, 29.3, 28.4, 25.9, 24.9, 24.4, 24.3, 24.1; ESI HRMS (*m/z*) 426.2463 [M + Na]⁺, C₂₀H₃₇NO₇Na requires 426.2462.

(1*S*,2*R*,3*R*,7a*R*)-3-(Hydroxymethyl)hexahydro-1*H*-pyrrolizine-1,2-diol, (+)-Hyacinthacine A₁ **6**



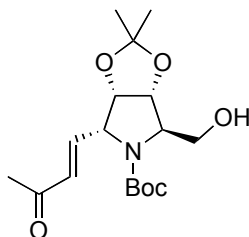
Alcohol 19 (119 mg, 0.296 mmol) was dissolved in anhydrous pyridine (1 mL) under an atmosphere of argon and cooled to 0 °C. Methanesulfonic anhydride (83 mg, 0.474 mmol)

was added and the reaction mixture was stirred for 10 mins before being warmed to room temperature. After stirring at room temperature for 1 h the pyridine was removed *in vacuo* and the resulting residue taken up in ethyl acetate (5 mL) and water (5 mL). The two layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 5 mL). The combined organic layers were washed with brine (5 mL), dried over magnesium sulfate, filtered and the solvent removed *in vacuo* to give *mesylate* **31** (136 mg) as a colourless oil which was used without further purification.

A solution of *mesylate* **31** (50 mg, 0.104 mmol) in dichloromethane (3.75 mL) was added dropwise to a solution of ZnBr₂ (117 mg, 0.520 mmol) in dichloromethane (2.5 mL). The reaction mixture was stirred for 18 h. Water (2.5 mL) was added and the reaction mixture was vigorously stirred for 30 mins. The layers were separated and the organic layer was extracted with water (3 x 2 mL). The combined aqueous layers were concentrated *in vacuo* to give an orange oil. Purification on Dowex 50X8-100 (eluted with water followed by 2 M NH₄OH solution) resulted in formation of (+)-*Hyacinthacine A₁* **6** as a colourless oil (15 mg, 79% over two steps).

$[\alpha]_D^{22} +43.5$ (*c* 0.23, H₂O) (Lit., +38.2 (*c* 0.23, H₂O)); ¹H NMR (400 MHz, Methanol-D₄) δ_H 3.90 (1 H, m), 3.88 (1 H, m), 3.81 (1 H, dd, *J* = 11.2 and 3.3), 3.60 (1 H, dd, *J* = 11.2 and 6.6), 3.52 (1 H, ddd, *J* = 7.8, 6.6 and 3.5), 3.10 (1 H, ddd, *J* = 10.4, 5.6 and 5.6), 2.81 (1 H, m), 2.69 (1 H, ddd, *J* = 10.0, 8.1 and 6.2), 2.11 (1 H, m), 1.96 (1 H, m), 1.78 (1 H, m), 1.70 (1 H, m); ¹³C NMR (101 MHz, Methanol-D₄) δ_C 76.6, 72.9, 71.2, 67.4, 64.2, 57.0, 28.1, 25.3; ESI HRMS (*m/z*) 174.1127 [*M* + *H*]⁺, C₈H₁₆NO₃ requires 174.1125.

(3a*R*,4*R*,6*R*,6a*S*)-tert-Butyl-4-(hydroxymethyl)-2,2-dimethyl-6-[(*E*)-3-oxobut-1-enyl]dihydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrole-5(4*H*)-carboxylate **32**

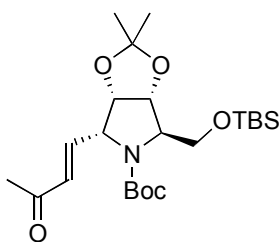


A stirred suspension of sodium hydride (161 mg, 6.69 mmol) in tetrahydrofuran (65 mL) was cooled to 0 °C under an atmosphere of argon. To this suspension was added a solution of diethyl 2-oxopropylphosphonate **21** (1.40 g, 7.23 mmol) in tetrahydrofuran (15 mL). The

reaction mixture was warmed to room temperature and stirred for 30 mins before being cooled to 0 °C and stirred for a further 30 mins. A solution of *aldehyde 17* (1.00 g, 2.68 mmol) was added dropwise in tetrahydrofuran (15 mL) and the reaction was allowed to warm to room temperature over 18 h. The reaction mixture was quenched with hydrochloric acid (1 M, 25 mL) and then stirred for 30 mins. Diethyl ether (100 mL) was added and the resulting layers were separated. The aqueous layer was extracted with diethyl ether (3 x 50 mL) and then the combined organic extracts were washed with brine (100 mL), dried over magnesium sulfate, filtered and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography [SiO₂, diethyl ether-light petroleum, 60:40 then 80:20] to afford the title compound **32** as a colourless solid (719 mg, 79%).

M.p. 143-145 °C; $[\alpha]_D^{19}$ -81.0 (*c* 1, CH₂Cl₂); $\nu_{\max}/\text{cm}^{-1}$ (film) 3418, 2978, 1693, 1668, 1457, 1397, 1368 cm; ¹H NMR (500 MHz, DMSO-D₆, 373 K) δ_{H} 6.58 (1 H, dd, *J* = 16.1 and 7.9), 6.03 (1 H, d, *J* = 16.1), 4.79 (1 H, t, *J* = 6.3), 4.73 (1 H, d, *J* = 5.9), 4.60-4.66 (1 H, m), 4.44 (1 H, t, *J* = 7.3), 3.92-3.95 (1 H, m), 3.58-3.67 (2 H, m), 2.20 (3 H, s), 1.40 (3 H, s), 1.38 (9 H, s), 1.28 (3 H, s); ¹³C NMR (126 MHz, DMSO-D₆, 373 K) δ_{C} 197.6, 154.1, 146.5, 130.1, 111.4, 81.9, 81.6, 79.9, 64.9, 63.3, 60.7, 28.5, 27.2, 26.3, 25.3; HRMS (ESI, *m/z*) 364.1726 [M + Na]⁺, C₁₇H₂₇NO₆Na requires 364.1731.

(3a*R*,4*R*,6*R*,6a*S*)-tert-Butyl-4-[(*tert*-butyldimethylsilyloxy)methyl]-2,2-dimethyl-6-[(*E*)-3-oxobut-1-enyl]dihydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrole-5(4*H*)-carboxylate 22

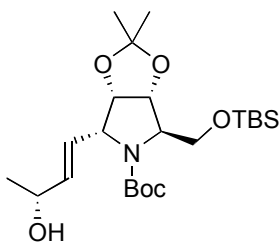


Enone 32 (684 mg, 2.00 mmol) was dissolved in DMF (1.5 mL) under an atmosphere of argon. Imidazole (546 mg, 8.01 mmol) and DMAP (24 mg, 0.20 mmol) were added followed by TBSCl (604 mg, 4.01 mmol). The reaction mixture was stirred for 18 h then more TBSCl (302 mg, 2.01 mmol) and imidazole (273 mg, 4.01 mmol) were added. The reaction mixture was stirred for a further 6 h. Saturated ammonium chloride solution (50 mL) and diethyl ether (50 mL) were added and the layers separated. The aqueous layer was extracted with diethyl ether (2 x 50 mL) and then the combined organic layers were washed with brine (50 mL),

dried over magnesium sulfate, filtered and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography [SiO₂, diethyl ether-light petroleum, 10:90] to afford the title compound **22** as a colourless oil (728 mg, 80%).

$[\alpha]_D^{21}$ -99.8 (*c* 1.3, CH₂Cl₂); $\nu_{\max}/\text{cm}^{-1}$ (film) 2931, 2858, 1698, 1678, 1634, 1472, 1377; ¹H NMR (500 MHz, DMSO-D₆, 373 K) δ_{H} 6.58 (1 H, dd, *J* = 16.1 and 7.9), 6.01 (1 H, dd, *J* = 16.1 and 0.9), 4.76 (1 H, t, *J* = 6.3), 4.69 (1 H, dd, *J* = 5.9 and 0.5), 4.39-4.42 (1 H, m), 3.96-3.98 (1 H, m), 3.91 (1 H, dd, *J* = 10.2 and 4.2), 3.74 (1 H, dd, *J* = 10.3 and 2.4), 2.20 (3 H, s), 1.40 (3 H, s), 1.37 (9 H, s), 1.28 (3 H, s), 0.91 (9 H, s), 0.08 (3 H, s), 0.07 (3 H, s); ¹³C NMR (126 MHz, DMSO-D₆, 373 K) δ_{C} 197.6, 153.9, 146.3, 130.1, 111.5, 82.1, 81.5, 80.1, 64.6, 63.7, 62.4, 28.5, 27.3, 26.2, 26.2, 25.2, 18.2; HRMS (ESI, *m/z*) 478.2588 [M + Na]⁺, C₂₃H₄₁NO₆SiNa requires 478.2595.

(3a*R*,4*R*,6*R*,6a*S*)-tert-Butyl-4-[(*tert*-butyldimethylsilyloxy)methyl]-6-[(*R,E*)-3-hydroxybut-1-enyl]-2,2-dimethyldihydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrole-5(4*H*)-carboxylate (*S*)-24

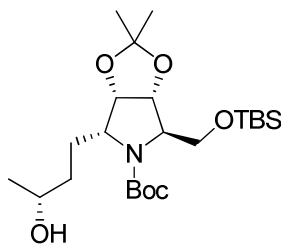


To a stirred solution of borane (1.84 mL, 1M solution in tetrahydrofuran) in tetrahydrofuran (84 mL) was added *tert*-Bu-(*S*)-CBS reagent (3.2 mL, 0.0985M solution in toluene) dropwise under an atmosphere of argon. The solution was cooled to -15 °C and *enone* **22** (775 mg, 1.70 mmol) in tetrahydrofuran (15 mL) was added dropwise. The resulting reaction mixture was stirred at -15 °C for 18 h, then anhydrous methanol (7 mL) was added dropwise and the reaction stirred for 15 mins. Saturated sodium hydrogen carbonate solution (50 mL) was added and the reaction mixture warmed to room temperature. The layers were separated and the aqueous layer was extracted with diethyl ether (3 x 100 mL). The combined organic layers were washed with brine (50 mL), dried over magnesium sulfate, filtered and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography [SiO₂, diethyl ether-light petroleum, 40:60] to afford the title compound **24** as a colourless oil (708 mg, 91%) as a >20:1 mixture of diastereomers.

$[\alpha]_D^{21} -94.9$ (c 1, CH_2Cl_2); $\nu_{\text{max}}/\text{cm}^{-1}$ (film) 3454, 2956, 2931, 2859, 1691, 1472, 1379; ^1H NMR (500 MHz, Toluene- D_8 , 373 K) δ_{H} 5.75 (1 H, dd, $J = 15.6$ and 8.1), 5.59 (1 H, dd, $J = 15.6$ and 5.7), 4.68 (1 H, d, $J = 6.1$), 4.63 (1 H, t, $J = 6.2$), 4.34 (1 H, t, $J = 7.2$), 4.19-4.27 (1 H, m), 4.17 (1 H, br s), 4.08 (1 H, dd, $J = 10.0$ and 3.5), 3.63 (1 H, dd, $J = 10.1$ and 1.9), 1.45 (3 H, s), 1.43 (9 H, s), 1.21-1.24 (6 H, m), 0.92 (9 H, s), 0.05 (3 H, s), 0.04 (3 H, s); ^{13}C NMR (126 MHz, Toluene- D_8 , 373 K) δ_{C} 153.9, 134.9, 111.3, 82.0, 81.7, 78.9, 67.7, 64.6, 64.5, 62.6, 28.2, 25.8, 25.6, 24.7, 22.9, 17.9, -5.9 , -6.0 ; HRMS (ESI, m/z) 516.3463 $[\text{M} + \text{MeCN} + \text{NH}_4]^+$, $\text{C}_{25}\text{H}_{50}\text{N}_3\text{O}_6\text{Si}$ requires 516.3463.

[C-6 carbon peak missing due to overlap with toluene signals]

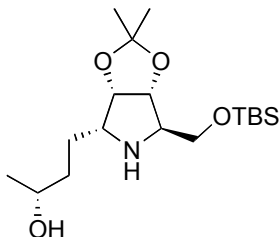
(3a*R*,4*R*,6*R*,6a*S*)-*tert*-Butyl-4-[(*tert*-butyldimethylsilyloxy)methyl]-6-[(*R*)-3-hydroxybutyl]-2,2-dimethyldihydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrole-5(4*H*)-carboxylate
33



To a stirred solution of *allylic alcohol* (*S*)-**24** (655 mg, 1.43 mmol) in ethyl acetate (20 mL) was added PtO_2 (33 mg, 0.143 mmol). The reaction mixture was stirred under a balloon of hydrogen for 18 h, then filtered through Celite[®] and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography [SiO_2 , diethyl ether-light petroleum, 20:80 then 40:60] to afford the title compound **33** as a colourless oil (554 mg, 84%).

$[\alpha]_D^{22} -88.8$ (c 1.0, CH_2Cl_2); $\nu_{\text{max}}/\text{cm}^{-1}$ (film) 3452, 2957, 2932, 2859, 1688, 1472, 1380, 1252, 1109; ^1H NMR (500 MHz, Toluene- D_8 , 363 K) δ_{H} 4.64-4.69 (2 H, m), 4.09-4.12 (1 H, m), 3.95-4.02 (1 H, m), 3.86 (1 H, ddd, $J = 10.2$, 5.4 and 2.9), 3.77-3.83 (1 H, m), 3.60 (1 H, dd, $J = 10.1$ and 2.3), 2.44-2.58 (1 H, m), 1.97-2.04 (1 H, m), 1.61-1.68 (1 H, m), 1.48-1.57 (1 H, m), 1.46 (3 H, s), 1.45 (9 H, s), 1.25 (3 H, s), 1.06 (3 H, d, $J = 6.1$), 0.92 (9 H, s), 0.05 (3 H, s), 0.04 (3 H, s); ^{13}C NMR (126 MHz, Toluene- D_8 , 363 K) δ_{C} 154.3, 111.0, 81.8, 80.3, 78.9, 67.2, 65.0, 62.9, 62.8, 36.1, 28.2, 25.8, 25.5, 25.1, 24.6, 23.1, 17.8, -5.8 , -6.0 ; HRMS (ESI, m/z) 482.2917 $[\text{M} + \text{Na}]^+$; $\text{C}_{23}\text{H}_{45}\text{NO}_6\text{SiNa}$ requires 482.2908.

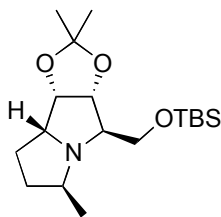
(R)-4-[(3a*S*,4*R*,6*R*,6a*R*)-6-[(*tert*-Butyldimethylsilyloxy)methyl]-2,2-dimethyltetrahydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrol-4-yl]butan-2-ol **34**



Alcohol 33 (62 mg, 0.135 mmol) in dichloromethane (1.5 mL) was added dropwise to a solution of ZnBr₂ (152 mg, 0.674 mmol) and *p*-cresol (146 mg, 1.35 mmol) in dichloromethane (11 mL). The reaction mixture was stirred for 20 h then quenched with a saturated solution of Rochelle's salt (15 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (2 x 10 mL). The combined organic layers were dried over sodium sulfate, filtered and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography [SiO₂, methanol-dichloromethane, 2:98 then 5:95] to afford the title compound **34** as a colourless oil (39 mg, 80%).

$[\alpha]_D^{21}$ -5.2 (c 1.0, CH₂Cl₂); $\nu_{\max}/\text{cm}^{-1}$ (film) 3357, 2931, 2858, 1463, 1373, 1256; ¹H NMR (400 MHz, Methanol-D₄) δ_{H} 4.68 (1 H, d, J = 5.7), 4.58-4.61 (1 H, m), 3.72-3.79 (1 H, m), 3.68 (1 H, dd, J = 10.5 and 5.4), 3.60 (1 H, dd, J = 10.5 and 6.3), 3.11-3.20 (2 H, m), 1.65-1.77 (1 H, m), 1.45-1.65 (3 H, m), 1.47 (3 H, s), 1.32 (3 H, s), 1.18 (3 H, d, J = 6.2), 0.93 (9 H, s), 0.11 (3 H, s), 0.10 (3 H, s); ¹³C NMR (101 MHz, Methanol-D₄) δ_{C} 111.1, 83.9, 82.0, 67.6, 65.4, 63.8, 62.2, 36.4, 25.4, 25.4, 25.3, 23.3, 22.5, 18.1, -6.3 , -6.3 ; HRMS (ESI, m/z) 360.2576 $[\text{M} + \text{H}]^+$, C₁₈H₃₈NO₄Si requires 360.2570.

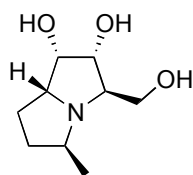
(3a*R*,4*R*,6*S*,8a*R*,8b*S*)-4-[(*tert*-Butyldimethylsilyloxy)methyl]-2,2,6-trimethylhexahydro-3a*H*-[1,3]dioxolo[4,5-*a*]pyrrolizine **35**



Amino alcohol 34 (61 mg, 0.170 mmol) was dissolved in dichloromethane (5 mL) and the solution was cooled to 0 °C in an ice/water bath. Triethylamine (0.12 mL, 0.848 mmol) was added dropwise, followed by methanesulfonyl chloride (14 µL, 0.178 mmol). The reaction was stirred at 0 °C for 10 mins then warmed to room temperature and stirred for a further 48 h. Water (5 mL) was added and the layers separated. The aqueous layer was extracted with dichloromethane (2 x 5 mL). The combined organic layers were dried over sodium sulfate, filtered and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography [SiO₂, methanol-dichloromethane, 1:99 then 2:98] to afford the title compound **35** as a colourless oil (48 mg, 83%).

$[\alpha]_D^{21} +14.9$ (*c* 1.0, CH₂Cl₂); $\nu_{\max}/\text{cm}^{-1}$ (film) 2930, 1463, 1372, 1257; ¹H NMR (400 MHz, CDCl₃) δ_{H} 4.77 (1 H, d, *J* = 5.9), 4.53 (1 H, t, *J* = 5.4), 3.67 (1 H, dt, *J* = 8.8 and 4.4), 3.61 (1 H, dd, *J* = 10.1 and 5.1), 3.39-3.45 (1 H, m), 3.26 (1 H, dq, *J* = 16.1 and 6.0), 3.15-3.20 (1 H, m), 2.06-2.17 (1 H, m), 1.96-2.05 (1 H, m), 1.83-1.93 (1 H, m), 1.40-1.51 (1 H, m), 1.47 (3 H, s), 1.30 (3 H, s), 1.03 (3 H, d, *J* = 6.0), 0.89 (9 H, s), 0.06 (3 H, s), 0.05 (3 H, s); ¹³C NMR (101 MHz, CDCl₃) δ_{C} 111.5, 86.2, 83.5, 67.8, 67.6, 65.5, 60.1, 34.8, 26.8, 26.0, 23.7, 22.7, 21.2, 18.3, -5.4; HRMS (ESI, *m/z*) 342.2460 [*M* + *H*]⁺, C₁₈H₃₆NO₃Si requires 342.2464.

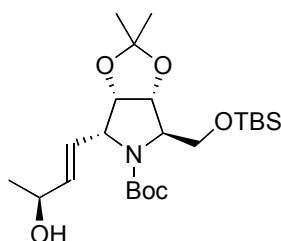
(1*S*,2*R*,3*R*,5*S*,7*aR*)-3-(Hydroxymethyl)-5-methylhexahydro-1*H*-pyrrolizine-1,2-diol, (+)-Hyacinthacine A₇ **3**



Pyrrolizidine 35 (36 mg, 0.105 mmol) was dissolved in anhydrous methanol (1 mL) under an atmosphere of argon. Oxalyl chloride (0.05 mL) was added dropwise and the resulting reaction mixture stirred for 18 h. A further portion of oxalyl chloride (0.05 mL) was added dropwise and the reaction mixture stirred for 24 h before being concentrated *in vacuo*. Purification was achieved by flash column chromatography [SiO₂, NH₄OH (35% aq solution)-*i*-PrOH-ethyl acetate, 10:50:40] and then dissolving the title compound in 6:1 chloroform:methanol followed by filtration through a short plug of Celite[®] to afford the title compound as a colourless crystalline solid (18 mg, 92%).

M.p. 93-95 °C; $[\alpha]_D^{20} +52.5$ (c 0.45, H₂O) (Lit., -51.8 (c 0.45, H₂O)); ¹H NMR (500 MHz, D₂O) δ_H 4.10 (1 H, dd, J = 9.3 and 4.1), 4.02 (1 H, t, J = 4.0), 3.81 (1 H, dd, J = 11.9 and 4.7), 3.76 (1 H, dd, J = 11.9 and 5.0), 3.70 (1 H, ddd, J = 8.4, 7.0 and 3.9), 3.08 (1 H, m), 2.96 (1 H, ddd, J = 9.5, 4.8 and 4.8), 2.10 (1 H, m), 2.04 (1 H, m), 1.87 (1 H, m), 1.55 (1 H, m), 1.18 (3 H, d, J = 6.4); ¹³C NMR (126 MHz, D₂O) δ_C 78.5, 74.5, 71.4, 69.3, 67.2, 64.9, 37.5, 25.0, 21.4; HRMS (ESI, m/z) 188.1278 [M + H]⁺, C₉H₁₈NO₃ requires 188.1281.

(3a*R*,4*R*,6*R*,6a*S*)-tert-Butyl-4-[(tert-butyldimethylsilyloxy)methyl]-6-[(*S,E*)-3-hydroxybut-1-enyl]-2,2-dimethyldihydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrole-5(4*H*)-carboxylate (*R*)-23



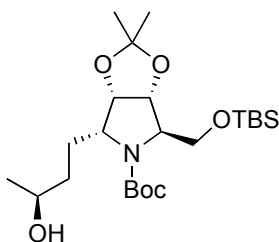
To a stirred solution of borane (1.6 mL, 1M solution in tetrahydrofuran) in tetrahydrofuran (72 mL) was added *tert*-Bu-(*R*)-CBS reagent (3.2 mL, 0.0985M solution in toluene) dropwise under an atmosphere of argon. The solution was cooled to -17 °C and *enone* **22** (725 mg, 1.59 mmol) in tetrahydrofuran (15 mL) was added dropwise. The resulting reaction mixture was stirred at -17 °C for 18 h, then anhydrous methanol (6 mL) was added dropwise and the reaction stirred for 15 mins. Saturated sodium hydrogen carbonate solution (50 mL) was added and the reaction mixture warmed to room temperature. The layers were separated and the aqueous layer was extracted with diethyl ether (3 x 80 mL). The combined organic layers were washed with brine (50 mL), dried over magnesium sulfate, filtered and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography [SiO₂, diethyl ether-light petroleum, 30:70 then 50:50] to afford the title compound **23** as a colourless oil (677 mg, 93%) as a >20:1 mixture of diastereomers.

$[\alpha]_D^{22} -89.5$ (c 1.05, CH₂Cl₂); $\nu_{\max}/\text{cm}^{-1}$ (film) 3447, 2957, 2932, 2859, 1690, 1473, 1378, 1254; ¹H NMR (500 MHz, Toluene-D₈, 373 K) δ_H 5.73 (1 H, dd, J = 15.6 and 8.0), 5.59 (1 H, dd, J = 15.6 and 5.8), 4.68 (1 H, dd, J = 6.0 and 0.8), 4.62 (1 H, t, J = 6.3), 4.34 (1 H, t, J = 7.3), 4.21-4.27 (1 H, m), 4.15-4.19 (1 H, m), 4.05-4.11 (1 H, m), 3.61 (1 H, dd, J = 10.1 and 2.2), 1.45 (3 H, s), 1.44 (9 H, s), 1.21-1.24 (6 H, m), 0.92 (9 H, s), 0.05 (3 H, s), 0.04 (3 H, s);

^{13}C NMR (126 MHz, Toluene- D_8 , 373 K) δ_{C} 153.9, 135.0, 111.2, 81.9, 81.7, 79.0, 67.9, 64.6, 64.6, 62.6, 28.2, 25.8, 25.6, 24.7, 23.1, 17.9, -5.6, -6.0; HRMS (ESI, m/z) 480.2751 $[\text{M} + \text{Na}]^+$, $\text{C}_{23}\text{H}_{43}\text{NO}_6\text{SiNa}$ requires 480.2752.

[C-6 carbon peak missing due to overlap with toluene signals]

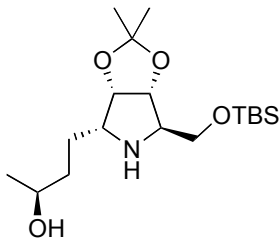
(3a*R*,4*R*,6*R*,6a*S*)-*tert*-Butyl-4-[(*tert*-butyldimethylsilyloxy)methyl]-6-[(*S*)-3-hydroxybutyl]-2,2-dimethyldihydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrole-5(4*H*)-carboxylate
36



To a stirred solution of *allylic alcohol* (*R*)-**23** (675 mg, 1.48 mmol) in ethyl acetate (20 mL) was added PtO_2 (33 mg, 0.147 mmol). The reaction mixture was stirred under a balloon of hydrogen for 18 h, then filtered through Celite[®] and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography [SiO_2 , diethyl ether-light petroleum, 20:80 then 50:50] to afford the title compound **36** as a colourless oil (623 mg, 92%).

$[\alpha]_{\text{D}}^{23}$ -79.9 (c 1, CH_2Cl_2); $\nu_{\text{max}}/\text{cm}^{-1}$ (film) 3445, 2957, 2932, 2859, 1688, 1380, 1252; ^1H NMR (500 MHz, Toluene- D_8 , 373 K) δ_{H} 4.64-4.71 (2 H, m), 4.08-4.13 (1 H, m), 3.94-4.03 (1 H, m), 3.81-3.87 (1 H, m), 3.71-3.77 (1 H, m), 3.61 (1 H, dd, J = 10.1 and 2.4), 2.48-2.60 (1 H, m), 1.89-1.98 (1 H, m), 1.61-1.68 (1 H, m), 1.41-1.56 (13 H, m), 1.25 (3 H, s), 1.14 (3 H, d, J = 6.1), 0.92 (9 H, s), 0.05 (3 H, s), 0.04 (3 H, s); ^{13}C NMR (126 MHz, Toluene- D_8 , 373 K) δ_{C} 154.2, 110.9, 81.8, 80.5, 78.9, 67.7, 65.1, 63.3, 62.8, 36.3, 28.2, 25.8, 25.5, 25.5, 24.6, 23.1, 17.8, -5.8, -6.0; HRMS (ESI, m/z) 482.2893 $[\text{M} + \text{Na}]^+$, $\text{C}_{23}\text{H}_{45}\text{NO}_6\text{SiNa}$ requires 482.2908.

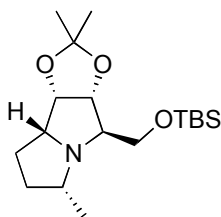
(S)-4-[(3a*S*,4*R*,6*R*,6a*R*)-6-[(*tert*-Butyldimethylsilyloxy)methyl]-2,2-dimethyltetrahydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrol-4-yl]butan-2-ol **37**



Alcohol 36 (179 mg, 0.389 mmol) in dichloromethane (4 mL) was added dropwise to a solution of zinc bromide (438 mg, 1.95 mmol) and *p*-cresol (421 mg, 3.89 mmol) in dichloromethane (31 mL). The reaction mixture was stirred for 20 h then quenched with a saturated solution of Rochelle's salt (50 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (2 x 40 mL). The combined organic layers were dried over sodium sulfate, filtered and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography [SiO₂, methanol-dichloromethane, 2:98 then 5:95] to afford the title compound **37** as a colourless oil (105 mg, 75%).

$[\alpha]_D^{22} +5.5$ (*c* 1, CH₂Cl₂); $\nu_{\max}/\text{cm}^{-1}$ (film) 3385, 2955, 2931, 2858, 1463, 1372, 1257; ¹H NMR (400 MHz, Methanol-D₄) δ_{H} 4.68 (1 H, d, *J* = 5.7), 4.60 (1 H, dd, *J* = 5.6 and 4.3), 3.70-3.77 (1 H, m), 3.68 (1 H, dd, *J* = 10.4 and 5.4), 3.60 (1 H, dd, *J* = 10.4 and 6.3), 3.10-3.20 (2 H, m), 1.49-1.69 (4 H, m), 1.47 (3 H, s), 1.32 (3 H, s), 1.18 (1 H, d, *J* = 6.3), 0.93 (9 H, s), 0.11 (3 H, s), 0.10 (3 H, s); ¹³C NMR (101 MHz, Methanol-D₄) δ_{C} 111.1, 83.9, 82.1, 67.6, 65.4, 63.8, 62.2, 36.6, 25.8, 25.5, 25.4, 23.3, 22.6, 18.1, -6.3; HRMS (ESI, *m/z*) 360.2558 [*M* + *H*]⁺, C₁₈H₃₈NO₄Si requires 360.2565.

(3a*R*,4*R*,6*R*,8a*R*,8b*S*)-4-[(*tert*-Butyldimethylsilyloxy)methyl]-2,2,6-trimethylhexahydro-3a*H*-[1,3]dioxolo[4,5-*a*]pyrrolizine **38**

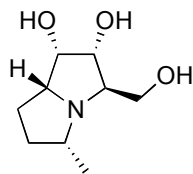


Amino alcohol 37 (84 mg, 0.234 mmol) was dissolved in dichloromethane (8 mL) and the solution was cooled to 0 °C in an ice/water bath. Triethylamine (0.16 mL, 1.17 mmol) was

added dropwise, followed by methanesulfonyl chloride (20 μ L, 0.257 mmol). The reaction was stirred at 0 $^{\circ}$ C for 15 mins then warmed to room temperature and stirred for a further 18 h. Water (10 mL) was added and the layers separated. The organic layer was dried over magnesium sulfate, filtered and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography [SiO_2 , methanol-dichloromethane, 1:99] to afford the title compound **38** as a colourless oil (60 mg, 75%).

$[\alpha]_{\text{D}}^{19}$ -9.0 (c 1.0, CH_2Cl_2); $\nu_{\text{max}}/\text{cm}^{-1}$ (film) 2957, 2931, 2857, 1463, 1380, 1257, 1206; ^1H NMR (400 MHz, Methanol- D_4) δ_{H} 4.65 (1 H, dd, $J = 6.1$ and 2.4), 4.55 (1 H, t, $J = 5.6$), 3.67-3.72 (1 H, m), 3.64 (1 H, dd, $J = 10.1$ and 5.1), 3.53 (1 H, dd, $J = 10.1$ and 6.5), 3.25-3.31 (2 H, m), 1.99-2.07 (1 H, m), 1.89-1.96 (1 H, m), 1.58-1.73 (2 H, m), 1.50 (3 H, s), 1.32 (3 H, s), 1.17 (3 H, d, $J = 6.7$), 0.94 (9 H, s), 0.11 (6 H, s); ^{13}C NMR (101 MHz, Methanol- D_4) δ_{C} 112.0, 86.5, 81.3, 68.2, 65.9, 64.3, 57.0, 34.6, 25.5, 25.5, 23.9, 23.6, 18.2, 17.3, -6.2 ; HRMS (ESI, m/z) 342.2459 $[\text{M} + \text{H}]^+$, $\text{C}_{18}\text{H}_{36}\text{NO}_3\text{Si}$ requires 342.2459.

(1*S*,2*R*,3*R*,5*R*,7*aR*)-3-(Hydroxymethyl)-5-methylhexahydro-1*H*-pyrrolizine-1,2-diol, (+)-Hyacinthacine A₆ **20**

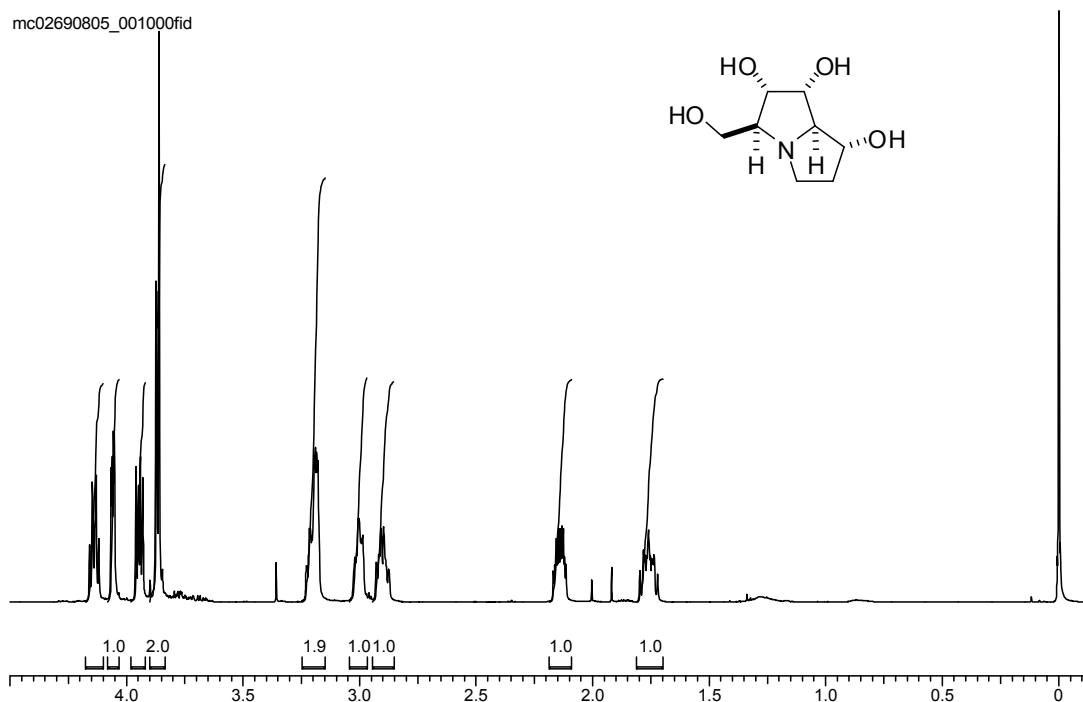


Pyrrolizidine **38** (45 mg, 0.132 mmol) was dissolved in anhydrous methanol (1.5 mL) under an atmosphere of argon. The solution was cooled to 0 $^{\circ}$ C in an ice/water bath and then oxalyl chloride (75 μ L) was added dropwise. The resulting reaction mixture was allowed to warm to room temperature and stirred for 18 h. A further portion of oxalyl chloride (75 μ L) was added dropwise and the reaction mixture stirred for 2 h before being concentrated *in vacuo*. Purification was achieved by flash column chromatography [SiO_2 , NH_4OH (35% aq solution) i PrOH-ethyl acetate, 10:50:40] and then dissolving the title compound in 6:1 chloroform:methanol followed by filtration through a short plug of Celite[®] to afford Hyacinthacine A₆ **20** as a colourless crystalline solid (23 mg, 93%).

M.p. 106-109 $^{\circ}$ C; $[\alpha]_{\text{D}}^{18}$ $+17.7$ (c 0.22, H_2O) (Lit., $+16.3$ (c 0.22, H_2O)); ^1H NMR (500 MHz, D_2O) δ_{H} 4.25-4.33 (3 H, m), 3.98 (1 H, dd, $J = 13.0$ and 3.1), 3.89 (1 H, dd, $J = 13.0$ and 3.6),

3.88 (1 H, m), 3.57 (1 H, ddd, $J = 9.5, 3.2$ and 3.2), 2.25 (1 H, m), 2.16 (1 H, m), 1.97 (1 H, m), 1.41 (3 H, d, $J = 6.8$); ^{13}C NMR (126 MHz, D_2O) δ_{C} 74.5, 73.0, 72.1, 64.5, 64.3, 59.2, 35.6, 25.3, 16.4; HRMS (ESI, m/z) 188.1281 $[\text{M} + \text{H}]^+$, $\text{C}_9\text{H}_{18}\text{NO}_3$ requires 188.1281.

(-)-2,3,7-Trieptiaustraline (D₂O, 500 MHz, TSP) ¹H-NMR Spectrum¹

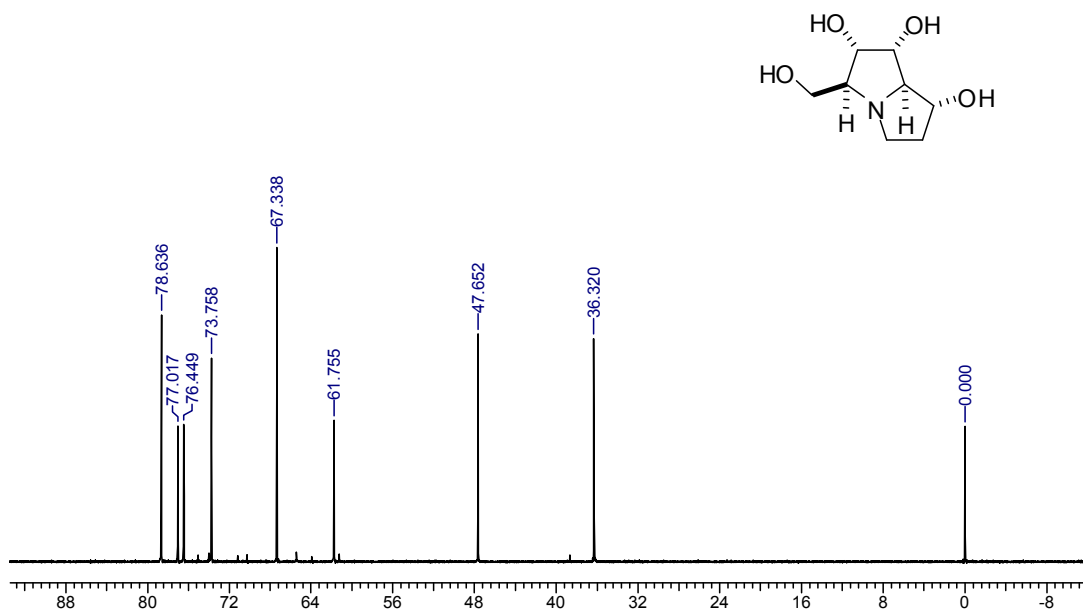


Entry	Natural	Synthetic
1	4.14 (1H, ddd, J = 8.0, 5.9 and 5.9)	4.14 (1H, ddd, J = 8.0, 6.2 and 6.0)
2	4.06 (1H, dd, J = 5.3 and 2.5)	4.06 (1H, dd, J = 5.2 and 2.4)
3	3.95 (1H, dd, J = 9.3 and 5.3)	3.95 (1H, dd, J = 9.5 and 5.4)
4	3.87 (2H, d)	3.87 (2H, d)
5	3.21 (1H, ddd, J = 9.3, 6.0 and 6.0)	3.21 (1H, m)
6	3.19 (1H, dd, J = 5.9 and 2.5)	3.19 (1H, dd, J = 5.5 and 2.4)
7	3.01 (1H, ddd, J = 10.3, 6.8 and 3.4)	3.00 (1H, ddd, J = 10.1, 7.3 and 3.5)
8	2.90 (1H, ddd, J = 10.6, 10.3 and 5.8)	2.90 (1H, ddd, J = 10.3, 10.1 and 6.3)
9	2.14 (1H, m)	2.14 (1H, m)
10	1.76 (1H, m)	1.76 (1H, m)

¹ Minor impurities present appeared upon addition of TSP reference to NMR sample

(-)-2,3,7-Triepiaustraline (D₂O, 126 MHz, TSP) ¹³C-NMR Spectrum¹

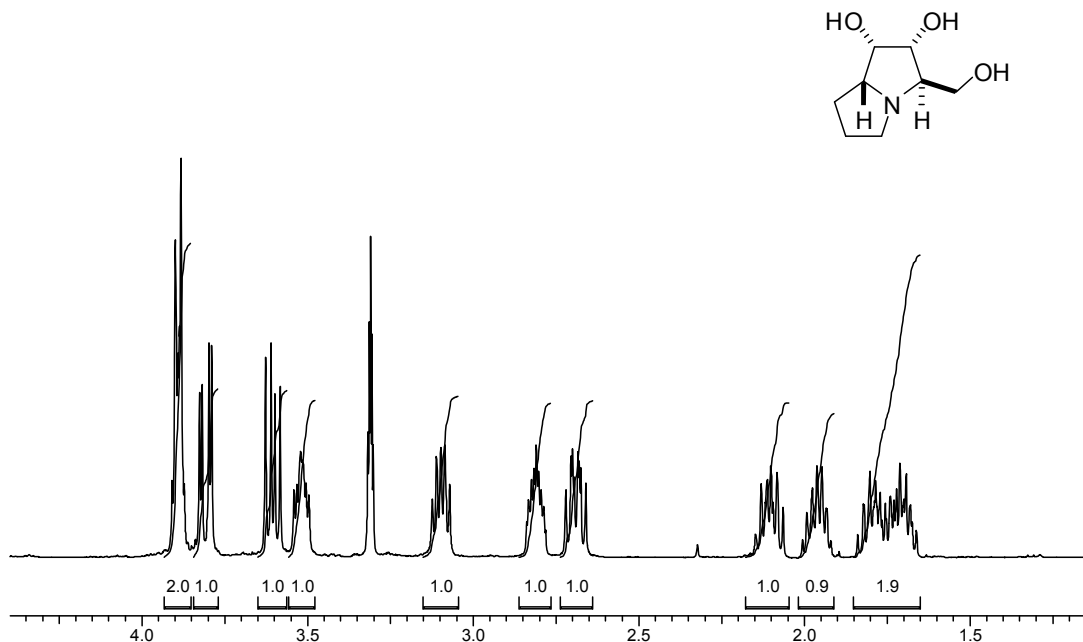
mc02690805_002000fid



Entry	Natural	Synthetic
1	78.7	78.6
2	77.0	77.0
3	76.4	76.5
4	73.8	73.8
5	67.4	67.3
6	61.8	61.8
7	47.7	47.7
8	36.3	36.3

(+)-Hyacinthacine A₁ (MeOD, 400 MHz,) ¹H-NMR Spectrum

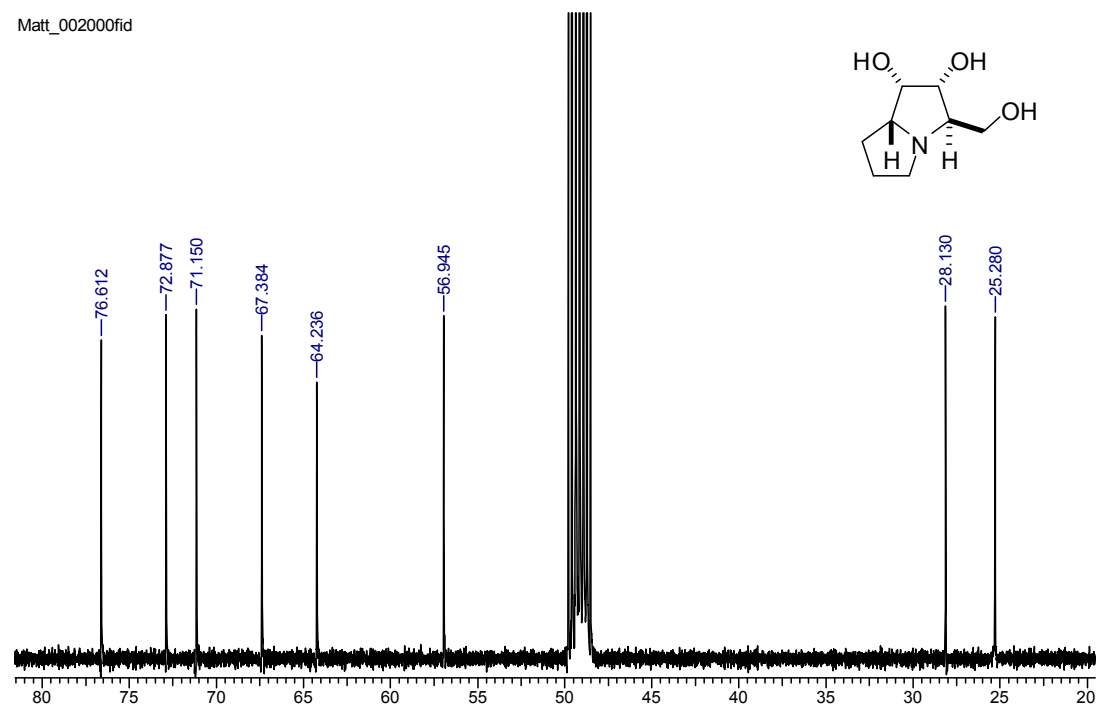
1 1_000000fid



Entry	Natural	Synthetic
1	3.88 (1H, dd, $J = 9.0$ and 4.0)	3.90 (1H, m)
2	3.87 (1H, t, $J = 4.0$)	3.88 (1H, m)
3	3.78 (1H, dd, $J = 11.3$ and 3.4)	3.81 (1H, dd, $J = 11.2$ and 3.3)
4	3.58 (1H, dd, $J = 11.3$ and 6.4)	3.60 (1H, dd, $J = 11.2$ and 6.6)
5	3.47 (1H, ddd, $J = 8.1, 6.6$ and 4.0)	3.52 (1H, ddd, $J = 7.8, 6.6,$ and 3.5)
6	3.05 (1H, ddd, $J = 10.0, 6.4$ and 4.9)	3.10 (1H, ddd, $J = 10.4, 5.6$ and 5.6)
7	2.76 (1H, ddd, $J = 9.0, 6.4$ and 3.4)	2.81 (1H, m)
8	2.65 (1H, ddd, $J = 10.0, 8.1$ and 6.1)	2.69 (1H, ddd, $J = 10.0, 8.1$ and 6.2)
9	2.08 (1H, m)	2.11 (1H, m)
10	1.93 (1H, m)	1.96 (1H, m)
11	1.74 (1H, m)	1.78 (1H, m)
12	1.68 (1H, m)	1.70 (1H, m)

(+)-Hyacinthacine A₁ (MeOD, 101 MHz,) ¹³C-NMR Spectrum

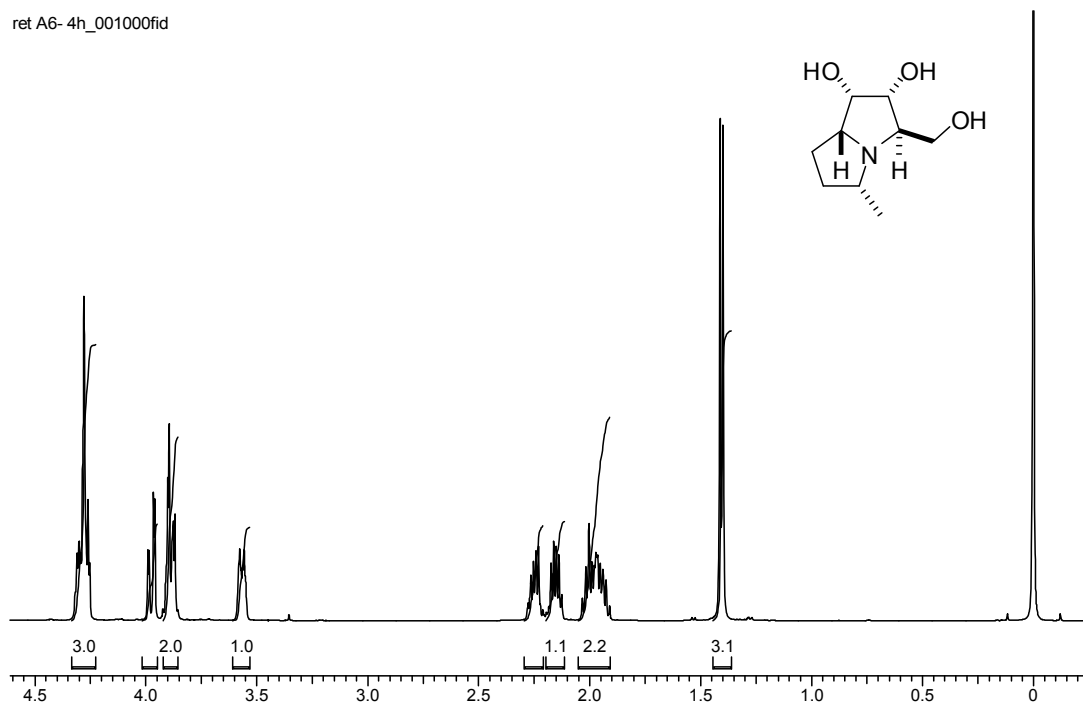
Matt_002000fid



Entry	Natural	Synthetic
1	77.5	76.6
2	73.7	72.9
3	71.9	71.2
4	67.9	67.4
5	65.2	64.2
6	57.5	57.0
7	28.8	28.1
8	26.0	25.3

(+)-Hyacinthacine A₆ (D₂O, 500 MHz, TSP) ¹H-NMR Spectrum

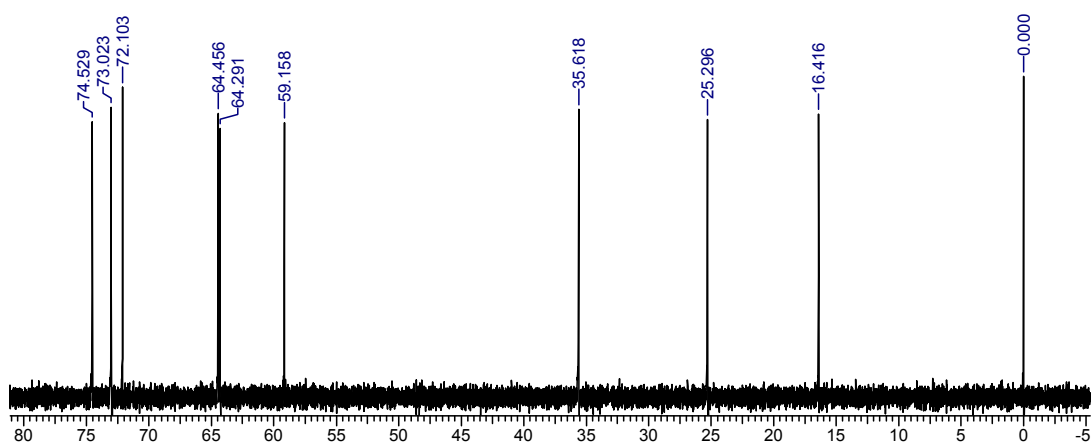
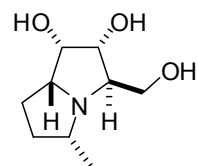
ret A6- 4h_001000fid



Entry	Natural	Synthetic
1	4.23 (1H, dd, $J = 4.5$ and 4.0)	
2	4.22 (1H, dd, $J = 9.5$ and 4.0)	4.25-4.33 (3H, m)
3	4.14 (1H, ddd, $J = 8.5, 5.5$ and 4.4)	
4	3.92 (1H, dd, $J = 12.7$ and 3.5)	3.98 (1H, dd, $J = 13.0$ and 3.1)
5	3.84 (1H, dd, $J = 12.7$ and 4.0)	3.89 (1H, dd, $J = 13.0$ and 3.6)
6	3.77 (1H, m)	3.88 (1H, m)
7	3.48 (1H, ddd, $J = 9.5, 4.0$ and 3.5)	3.57 (1H, ddd, $J = 9.5, 3.2$ and 3.2)
8	2.18 (1H, m)	2.25 (1H, m)
9	2.10 (1H, m)	2.16 (1H, m)
10	1.91 (1H, m)	1.97 (1H, m)
11	1.35 (3H, d, $J = 7.0$)	1.41 (3H, d, $J = 6.8$)

(+)-Hyacinthacine A₆ (D₂O, 126 MHz, TSP) ¹³C-NMR Spectrum

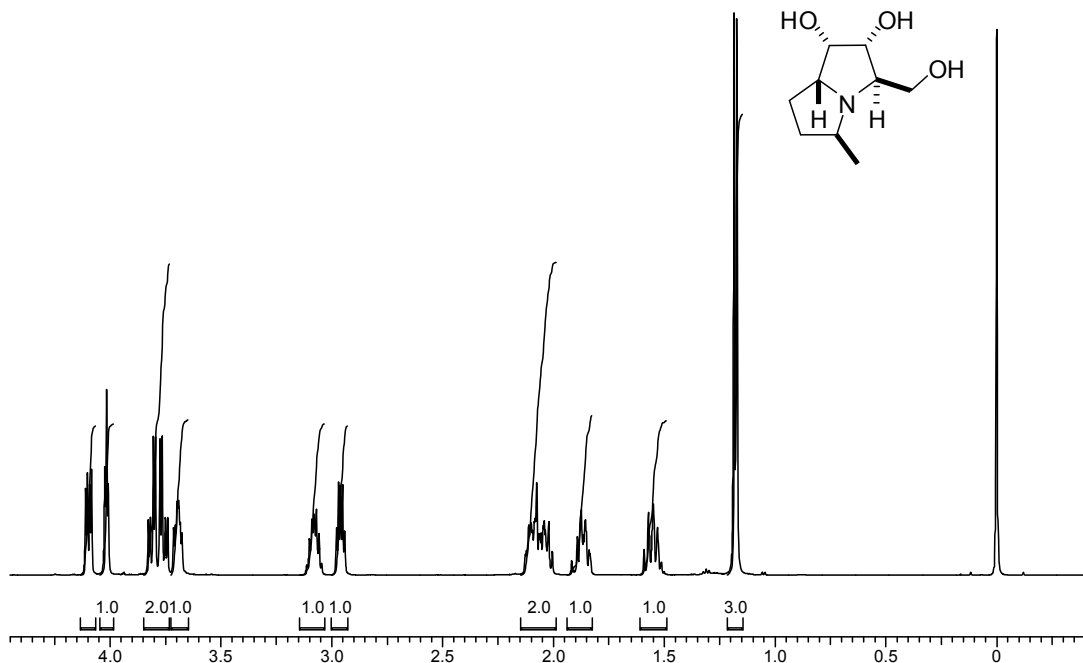
ret A6-carbon_001000fid



Entry	Natural	Synthetic
1	75.4	74.5
2	72.4	73.0
3	72.2	72.1
4	64.3	64.5
5	63.2	64.3
6	60.6	59.2
7	35.7	35.6
8	25.2	25.3
9	16.7	16.4

(+)-Hyacinthacine A₇ (D₂O, 500 MHz, TSP) ¹H-NMR Spectrum

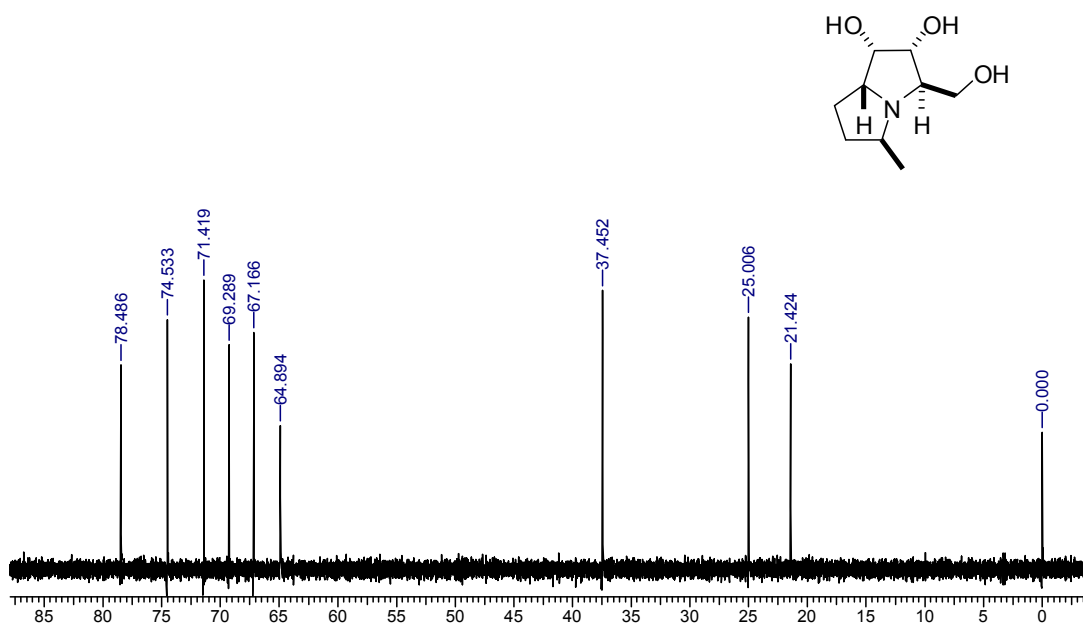
ret A7-1 h- H and C_002000fid



Entry	Natural	Synthetic
1	4.19 (1H, dd, $J = 9.5$ and 4.0)	4.10 (1H, dd, $J = 9.3$ and 4.1)
2	4.13 (1H, t, $J = 4.0$)	4.02 (1H, t, $J = 4.0$)
3	3.98 (1H, ddd, $J = 8.6, 7.0$ and 4.0)	3.70 (1H, ddd, $J = 8.4, 7.0$ and 3.9)
4	3.92 (1H, dd, $J = 12.5$ and 3.9)	3.81 (1H, dd, $J = 11.9$ and 4.7)
5	3.82 (1H, dd, $J = 12.5$, and 4.9)	3.76 (1H, dd, $J = 11.9$ and 5.0)
6	3.35 (1H, m)	3.08 (1H, m)
7	3.22 (1H, ddd, $J = 9.5, 4.9$ and 3.9)	2.96 (1H, ddd, $J = 9.5, 4.8$ and 4.8)
9	2.21 (1H, m)	2.10 (1H, m)
10	2.17 (1H, m)	2.04 (1H, m)
11	1.98 (1H, m)	1.87 (1H, m)
12	1.69 (1H, m)	1.55 (1H, m)
13	1.31 (3H, d, $J = 6.5$)	1.18 (3H, d, $J = 6.4$)

(+)-Hyacinthacine A₇ (D₂O, 126 MHz, TSP) ¹³C-NMR Spectrum

ret A7-1 h- H and C_003000fid



Entry	Natural	Synthetic
1	77.1	78.5
2	73.6	74.5
3	71.3	71.4
4	70.7	69.3
5	68.5	67.2
6	62.6	64.9
7	37.0	37.5
8	24.8	25.0
9	20.0	21.4

Crystals of **3**, **11**, **19** and **20** were grown by slow evaporation. Single crystal X-ray diffraction data were collected using graphite monochromated Mo K α radiation ($\lambda = 0.71073$ Å) on an Enraf-Nonius KappaCCD diffractometer. The diffractometer was equipped with a Cryostream N₂ open-flow cooling device,² 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.³ The structures of were all solved by direct methods⁴ and refined by full-matrix least squares on F² using the CRYSTALS suite.⁵ Intensities were corrected for absorption effects by the multi-scan method, based on multiple scans of identical and Laue equivalent reflections. All non-hydrogen atoms were refined with anisotropic displacement parameters. For structures **11** and **19** anisotropic displacement parameters for atoms were slightly anomalous which was thought to be the result of a small amount of disorder. Efforts were made to model this but were unsuccessful. 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 3: C₉ H₁₇ N₁ O₃, M_r = 187.24, orthorhombic (P2(1) 2(1) 2(1)), a = 5.9500(2) Å, b = 6.4395(2) Å, c = 24.5151(9) Å, $\alpha = \beta = \gamma = 90^\circ$, V = 939.30 (6) Å³, Z = 4, μ = not measured D_{calc} = N/A, T = 150(2) K, 1909 reflections collected, 1228 independent [R(int) = 0.021], R₁ = 0.0407 wR₂ = 0.0751 [I>3sigma(I)].

Single Crystal X-ray Diffraction Data for 11: C₁₉ H₃₁ N₁ O₇, M_r = 385.46, monoclinic (C1 2 1), a = 17.2428(3) Å, b = 8.4360(2) Å, c = 14.8099(4) Å, $\alpha = 90^\circ$, $\beta = 106.7653^\circ$, $\gamma = 90^\circ$, V = 2062.68(8) Å³, Z = 4, μ = not measured D_{calc} = N/A, T = 150(2) K, 4354 reflections collected, 2491 independent [R(int) = 0.014], R₁ = 0.0386, wR₂ = 0.0813 [I>3sigma(I)].

Single Crystal X-ray Diffraction Data for 19: C₂₀ H₃₇ N₁ O₇, M_r = 403.52, triclinic (P(-1)), a = 8.8245(3) Å, b = 10.8106(6) Å, c = 12.2027(7) Å, $\alpha = 89.835(3)^\circ$, $\beta = 86.545(3)^\circ$, $\gamma = 75.493(3)^\circ$, V = 1124.86(10) Å³, Z = 2, μ = not measured D_{calc} = N/A, T = 150(2) K, 8442 reflections collected, 5069 independent [R(int) = 0.031], R₁ = 0.0440, wR₂ = 0.1021 [I>3sigma(I)].

Single Crystal X-ray Diffraction Data for 20: C₁₈ H₃₁ N O₆ Si, M_r = 385.53, orthorhombic (P2(1)2(1)2(1)), a = 7.25550(10) Å, b = 11.1317(2) Å, c = 23.8058(3) Å, $\alpha = \beta = \gamma = 90^\circ$, V = 1922.70(5) Å³, Z = 8, μ = not measured D_{calc} = N/A, T = 150(2) K, 8675 reflections collected, 2523 independent [R(int) = 0.029], R₁ = 0.0301, wR₂ = 0.0698 [I>3sigma(I)].

² J. Cosier and A. M. Glazer, *J. Appl. Cryst.*, 1986, **19**, 105.

³ 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.

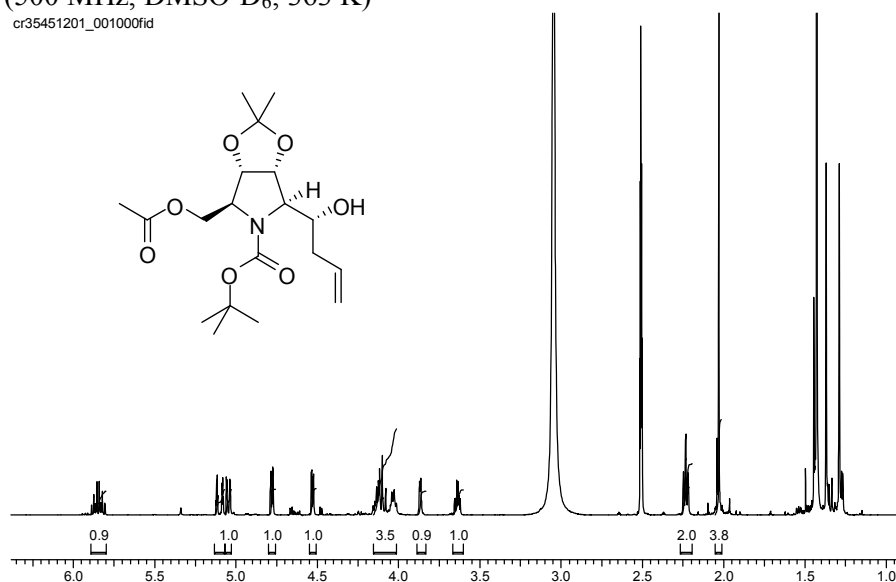
⁴ A. Altomare, G. Cascarano, G. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori and M. Camalli, *J. Appl. Cryst.*, 1994, 27, 435.

⁵ Betteridge, P.W., Carruthers, J.R., Cooper, R.I., Prout, K. & Watkin, D.J. (2003). *J. Appl. Cryst.* **36**, 1487

***tert*-Butyl-4-acetoxymethyl-6-(1-hydroxy-but-3-enyl)-2,2-dimethyl-tetrahydro-[1,3]dioxolo[4,5-*c*]pyrrole-5-carboxylate 11**

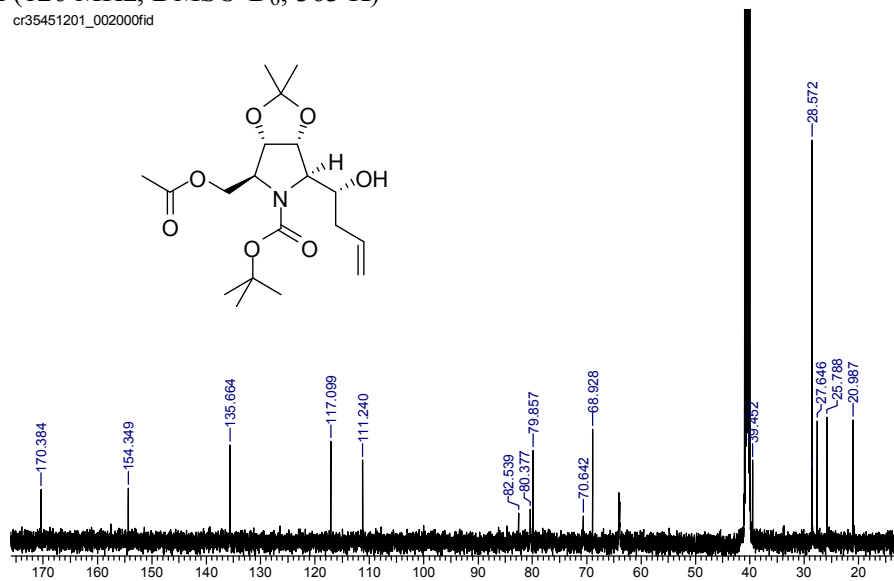
¹H NMR (500 MHz, DMSO-D₆, 363 K)

cr35451201_001000fid



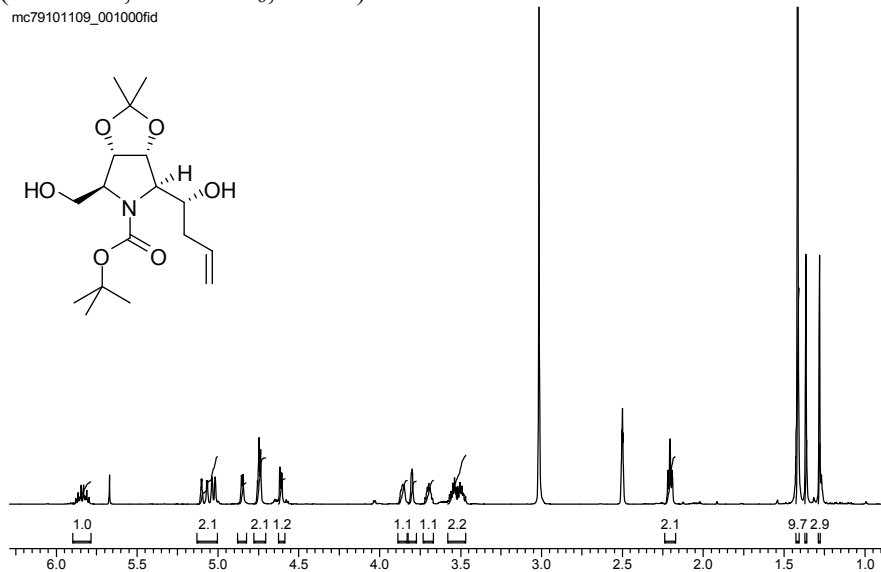
¹³C NMR (126 MHz, DMSO-D₆, 363 K)

cr35451201_002000fid

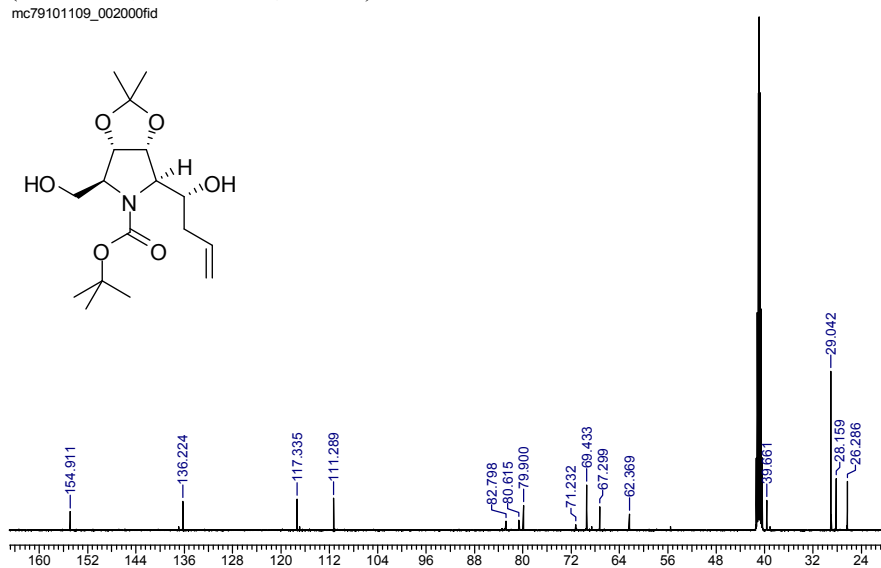


(3a*R*,4*R*,6*S*,6a*S*)-*tert*-Butyl 4-((*R*)-1-hydroxybut-3-enyl)-6-(hydroxymethyl)-2,2-dimethyldihydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrole-5(4*H*)-carboxylate 29

¹H NMR (500 MHz, DMSO-D₆, 363 K)

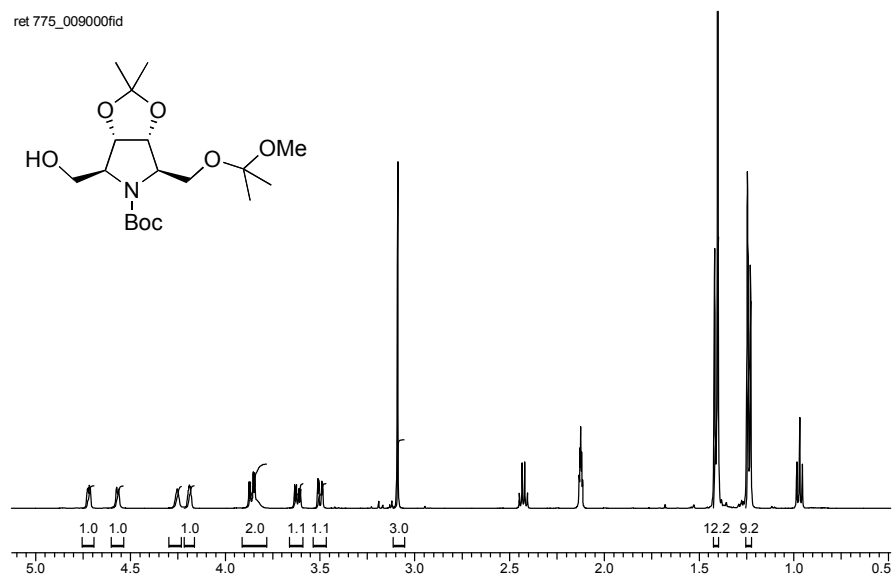


¹³C NMR (126 MHz, DMSO-D₆, 363 K)

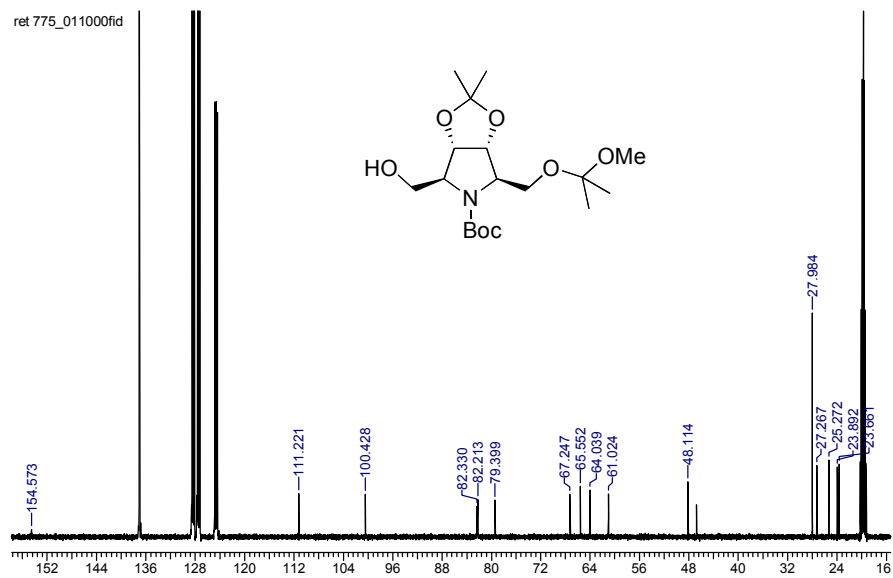


3a*S*,4*S*,6*R*,6a*R*)-*tert*-Butyl-4-(hydroxymethyl)-6-[(2-methoxypropan-2-yloxy)methyl]-2,2-dimethyldihydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrole-5(4*H*)-carboxylate 14

¹H NMR (500 MHz, Toluene-D₈, 373 K)

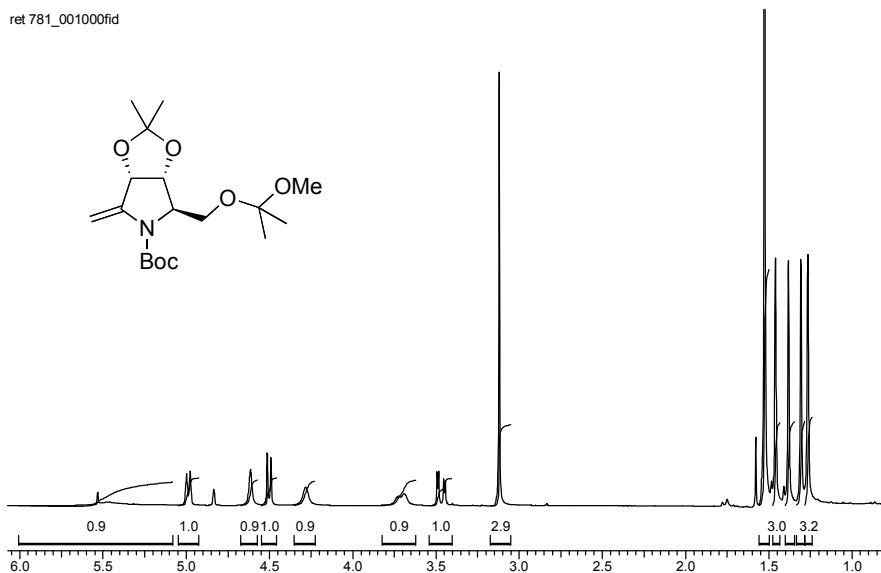


¹³C NMR (126 MHz, Toluene-D₈, 373 K)

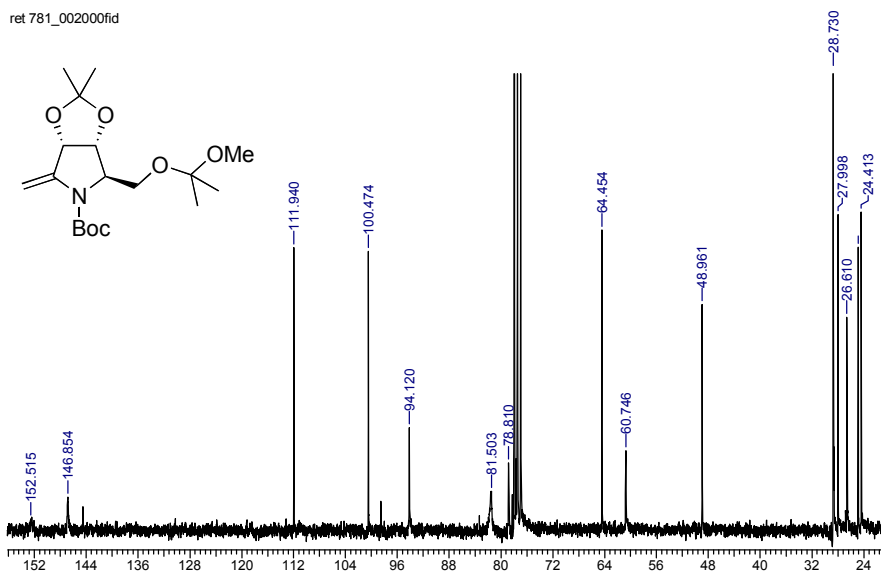


(3a*R*,4*R*,6a*S*)-*tert*-Butyl-4-[(2-methoxypropan-2-yloxy)methyl]-2,2-dimethyl-6-methylenedihydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrole-5(4*H*)-carboxylate 15

¹H NMR (250 MHz, CDCl₃)

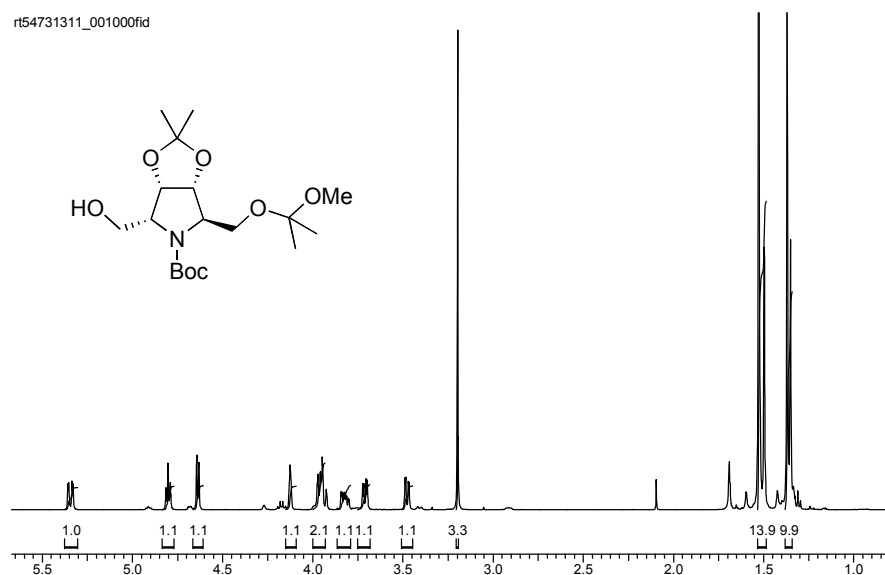


¹³C NMR (63 MHz, CDCl₃)

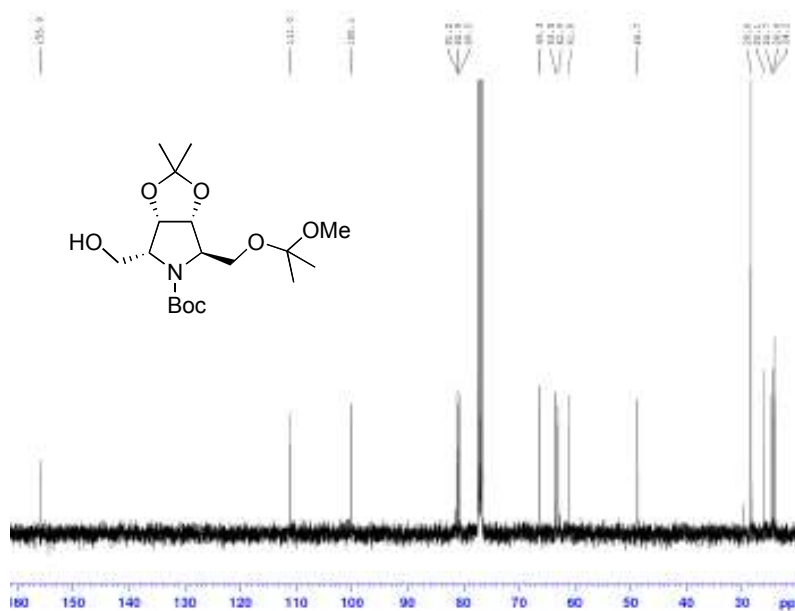


(3a*S*,4*R*,6*R*,6a*R*)-*tert*-Butyl-4-(hydroxymethyl)-6-[(2-methoxypropan-2-yloxy)methyl]-2,2-dimethyldihydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrole-5(4*H*)-carboxylate 16

^1H NMR (400 MHz, CDCl_3)

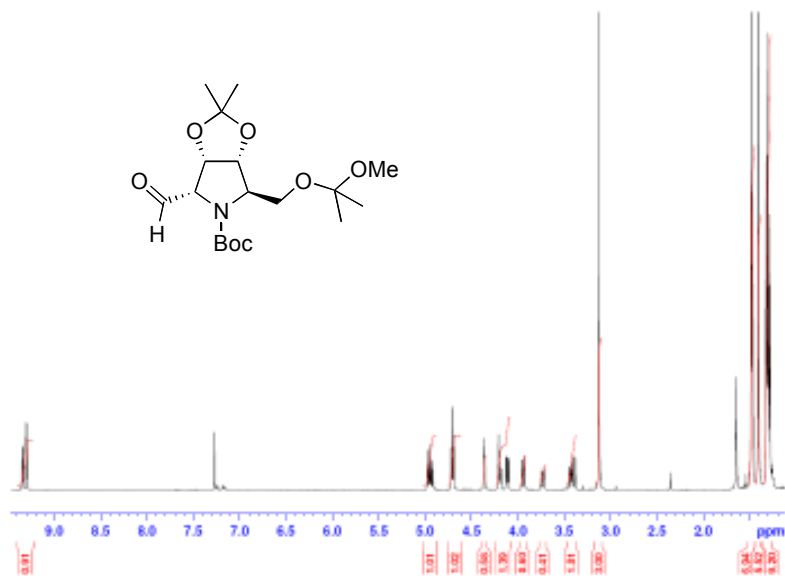


^{13}C NMR (101 MHz, CDCl_3)

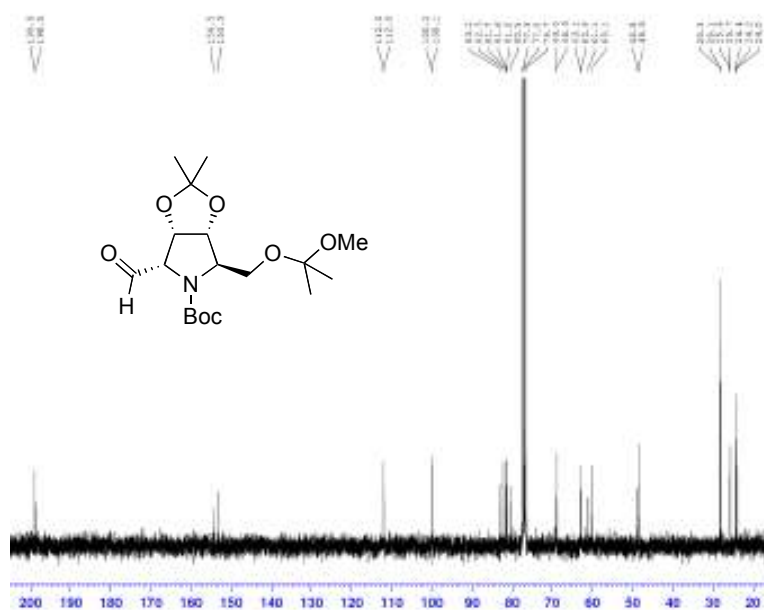


(3a*S*,4*S*,6*R*,6a*R*)-*tert*-Butyl-4-formyl-6-[(2-methoxypropan-2-yloxy)methyl]-2,2-dimethyldihydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrole-5(4*H*)-carboxylate 17

^1H NMR (400 MHz, CDCl_3)

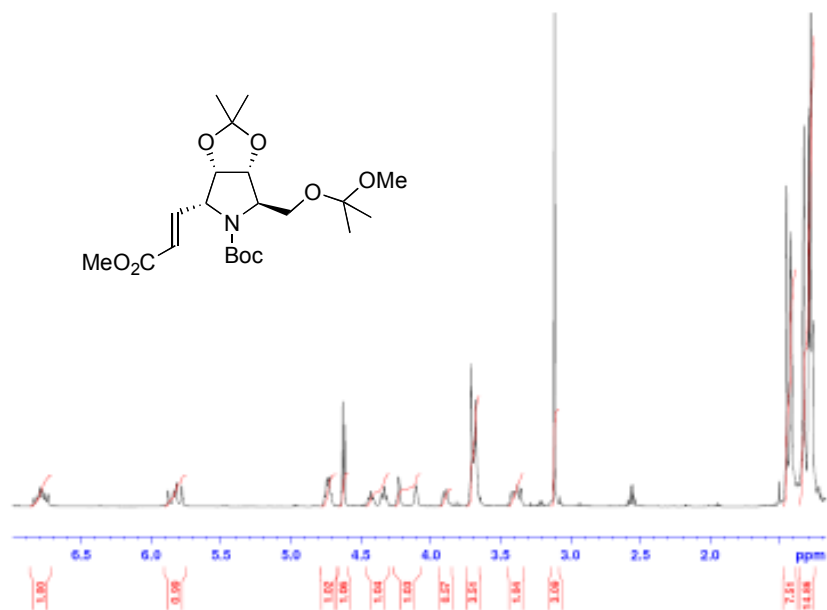


^{13}C NMR (101 MHz, CDCl_3)

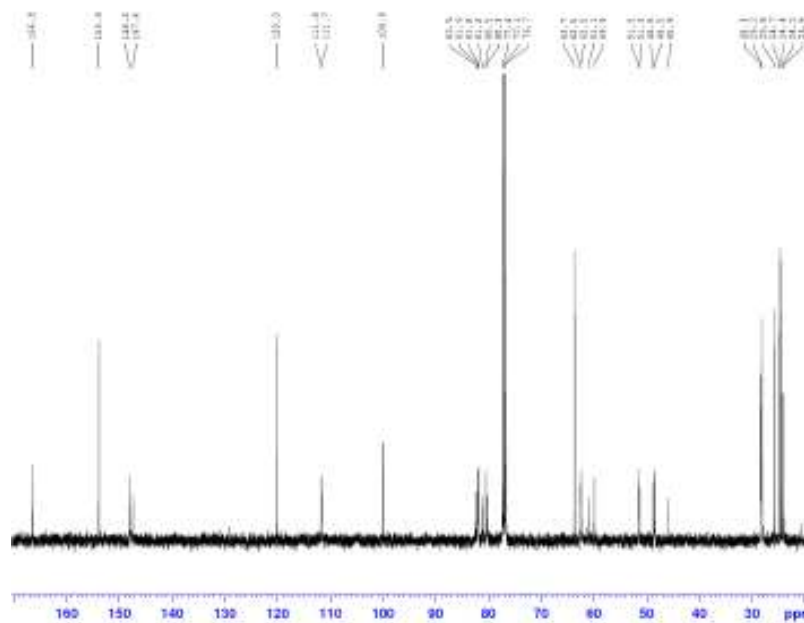


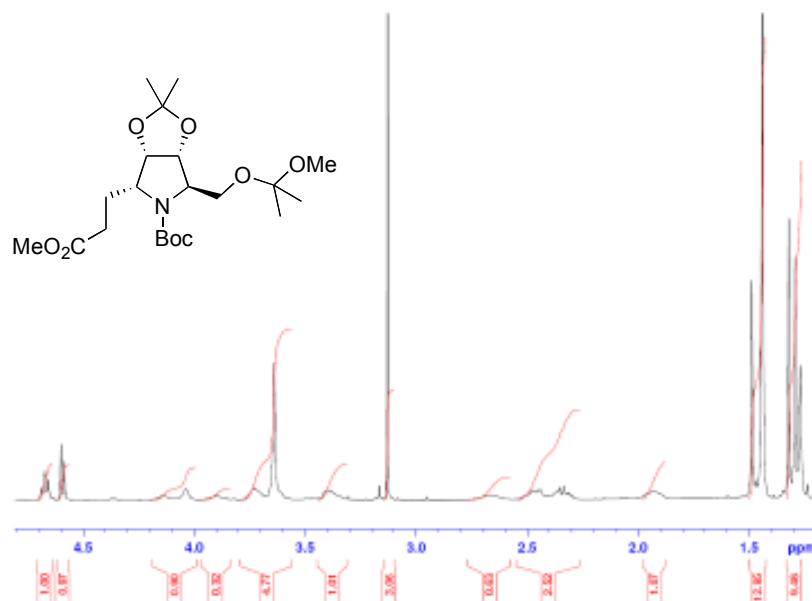
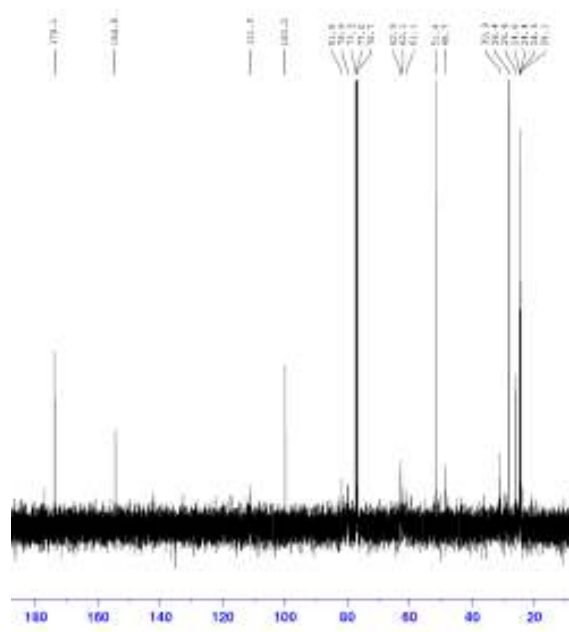
(3a*S*,4*R*,6*R*,6a*R*)-*tert*-Butyl-4-[(*E*)-3-methoxy-3-oxoprop-1-enyl]-6-[(2-methoxypropan-2-yloxy)methyl]-2,2-dimethyldihydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrole-5(4*H*)-carboxylate
18

¹H NMR (400 MHz, CDCl₃)



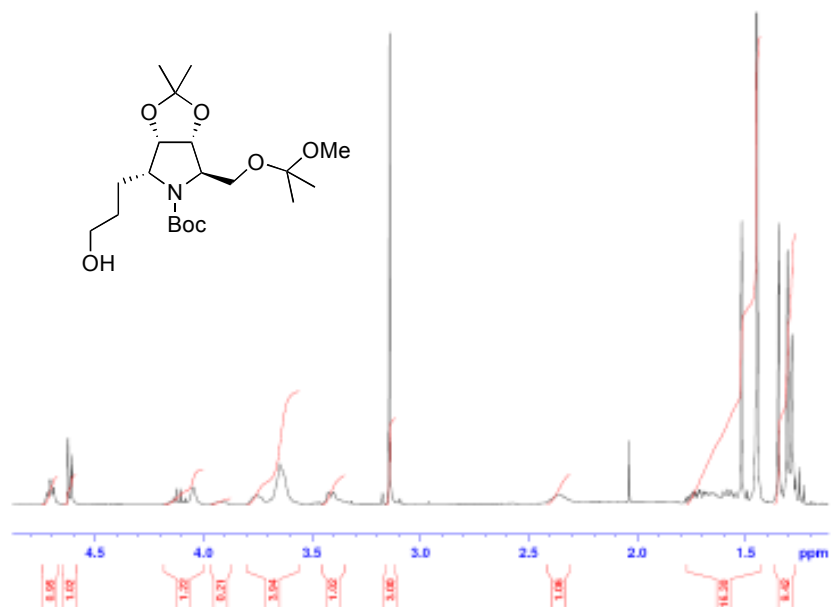
¹³C NMR (101 MHz, CDCl₃)



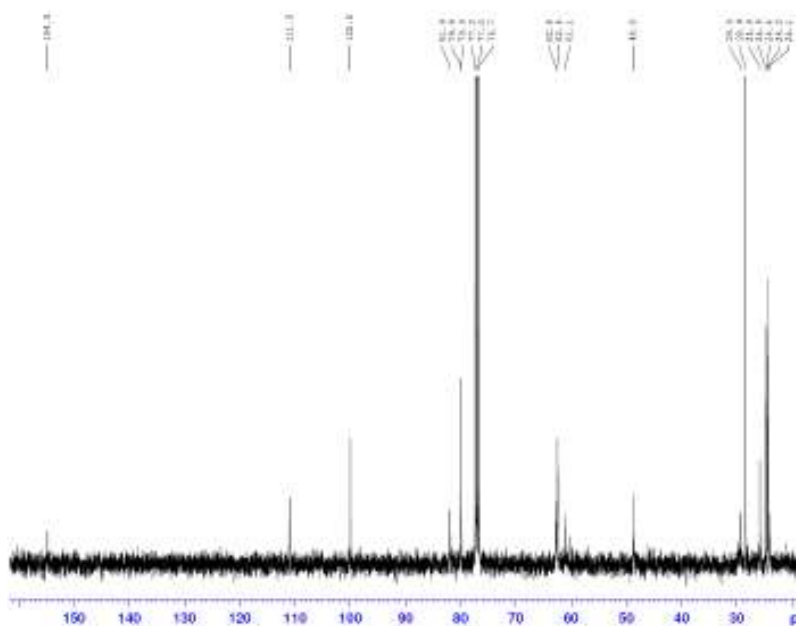
¹H NMR (400 MHz, CDCl₃) ^{13}C NMR (101 MHz, CDCl_3)

(3a*S*,4*R*,6*R*,6a*R*)-*tert*-Butyl-4-(3-hydroxypropyl)-6-[(2-methoxypropan-2-yloxy)methyl]-2,2-dimethyldihydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrole-5(4*H*)-carboxylate 19

^1H NMR (400 MHz, CDCl_3)

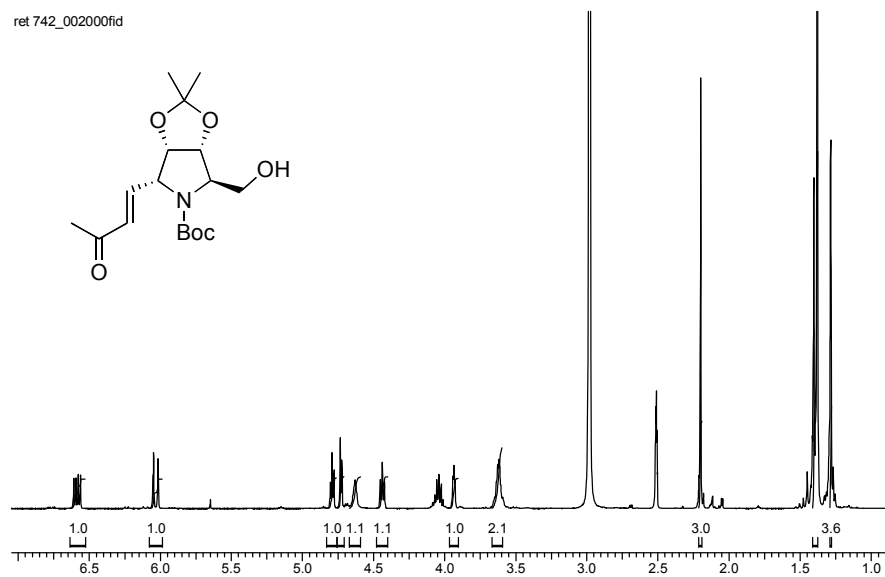


^{13}C NMR (101 MHz, CDCl_3)

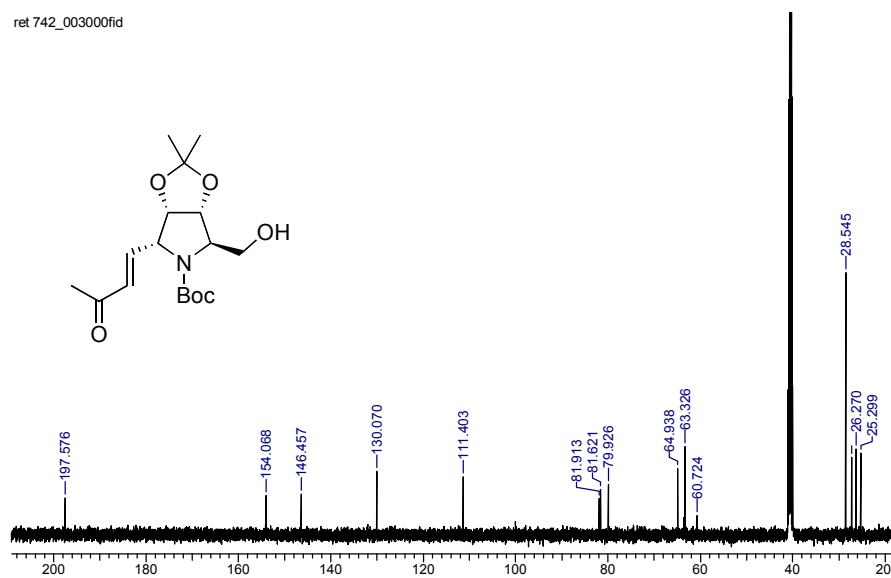


(3a*R*,4*R*,6*R*,6a*S*)-*tert*-Butyl-4-(hydroxymethyl)-2,2-dimethyl-6-[(*E*)-3-oxobut-1-enyl]dihydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrole-5(4*H*)-carboxylate 32

¹H NMR (500 MHz, DMSO-D₆, 373 K)

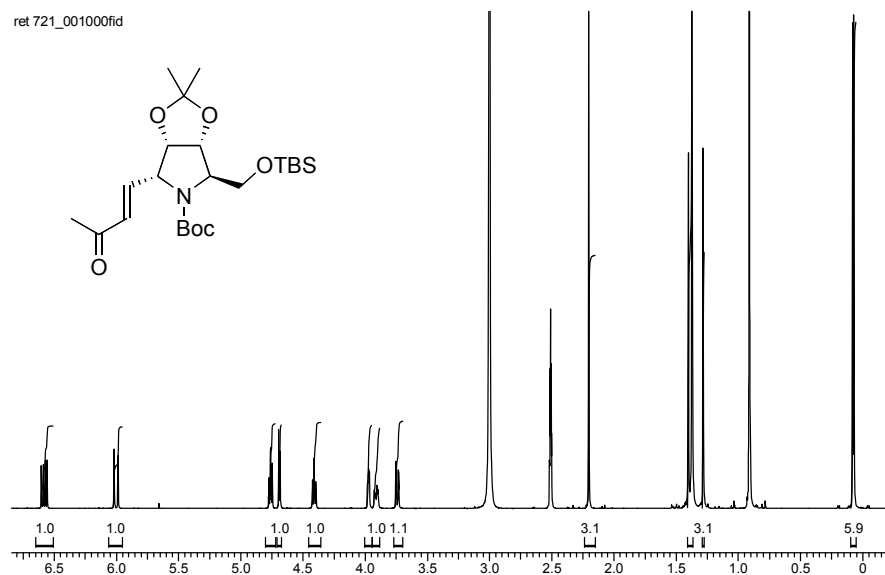


¹³C NMR (126 MHz, DMSO-D₆, 373 K)

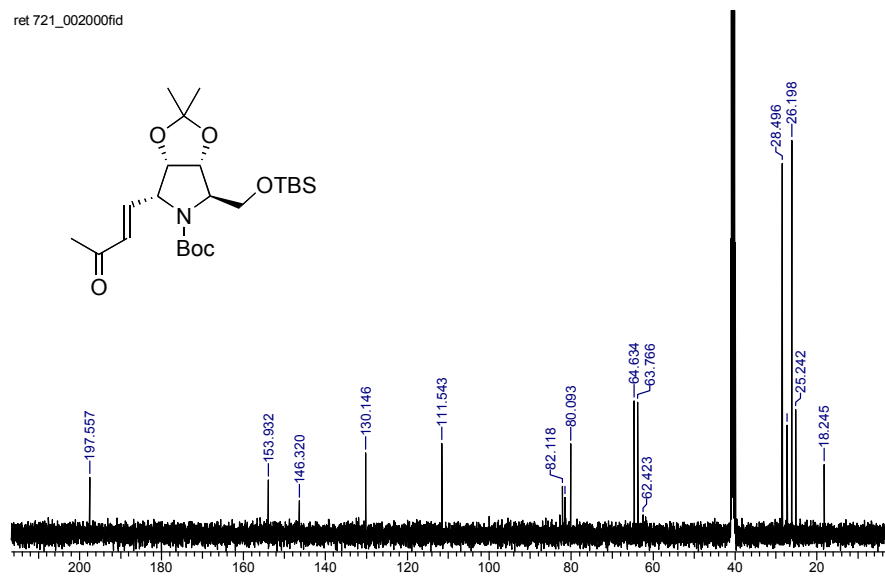


(3a*R*,4*R*,6*R*,6a*S*)-*tert*-Butyl-4-[(*tert*-butyldimethylsilyloxy)methyl]-2,2-dimethyl-6-[(*E*)-3-oxobut-1-enyl]dihydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrole-5(4*H*)-carboxylate 22

^1H NMR (500 MHz, DMSO- D_6 , 373 K)

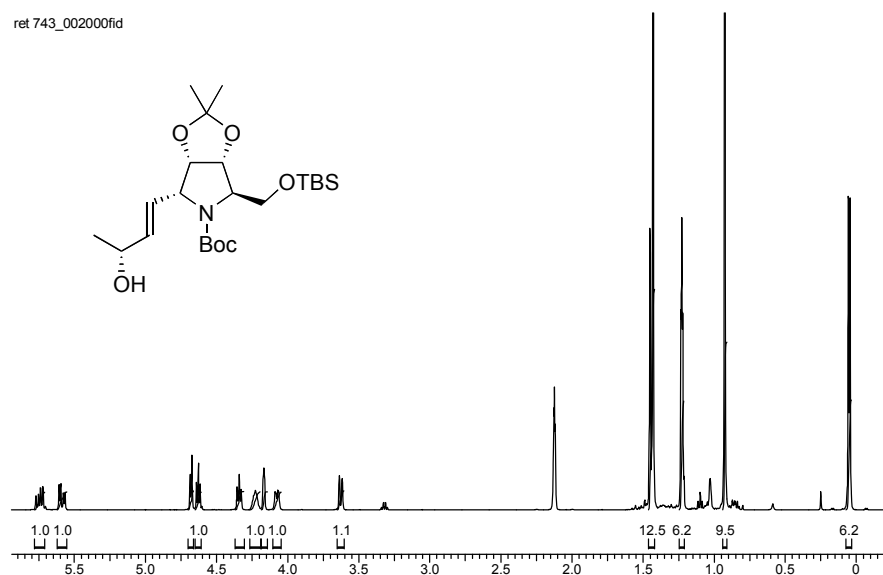


^{13}C NMR (126 MHz, DMSO- D_6 , 373 K)

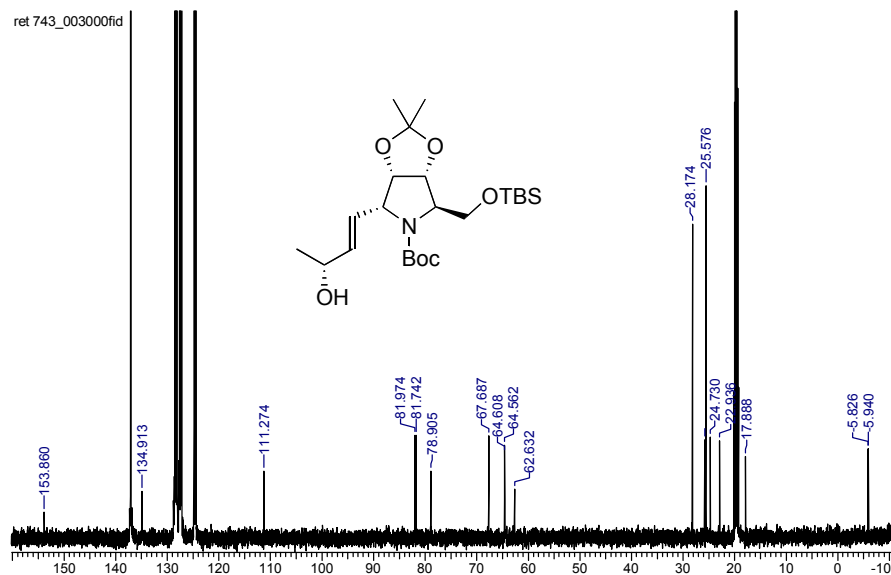


(3*aR*,4*R*,6*R*,6*aS*)-*tert*-Butyl-4-[(*tert*-butyldimethylsilyloxy)methyl]-6-[(*R,E*)-3-hydroxybut-1-enyl]-2,2-dimethyldihydro-3*aH*-[1,3]dioxolo[4,5-*c*]pyrrole-5(4*H*)-carboxylate (*S*)-24

¹H NMR (500 MHz, Toluene-D₈, 373 K)

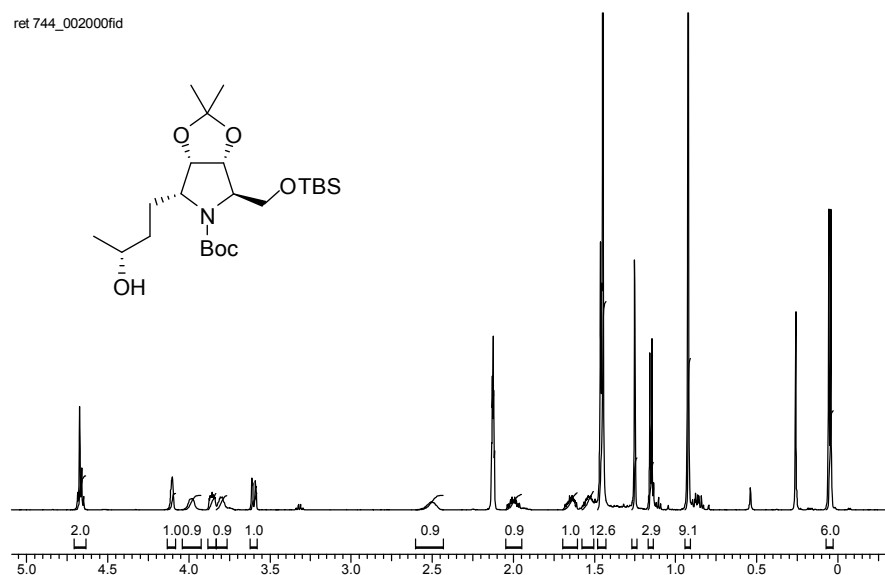


¹³C NMR (126 MHz, Toluene-D₈, 373 K)

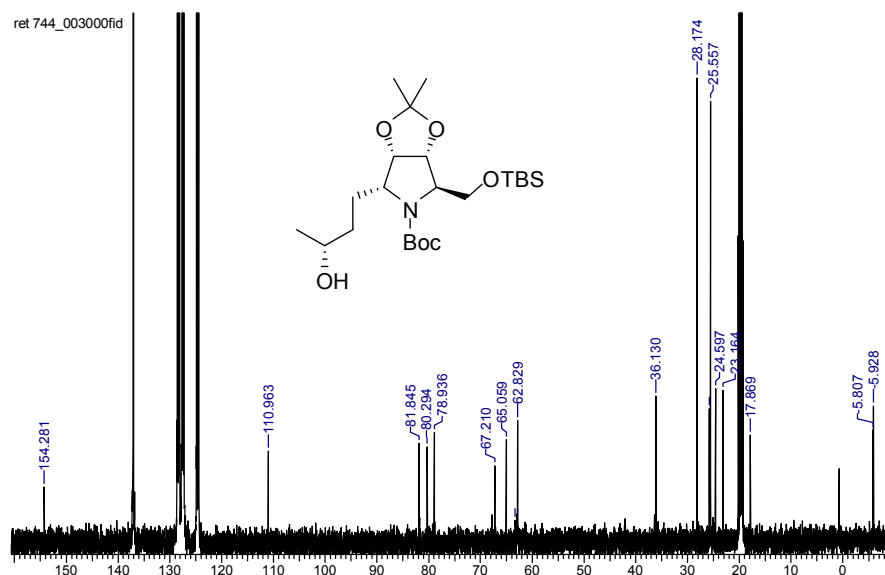


(3a*R*,4*R*,6*R*,6a*S*)-*tert*-Butyl-4-[(*tert*-butyldimethylsilyloxy)methyl]-6-[(*R*)-3-hydroxybutyl]-2,2-dimethyldihydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrole-5(4*H*)-carboxylate
33

¹H NMR (500 MHz, Toluene-D₈, 363 K)

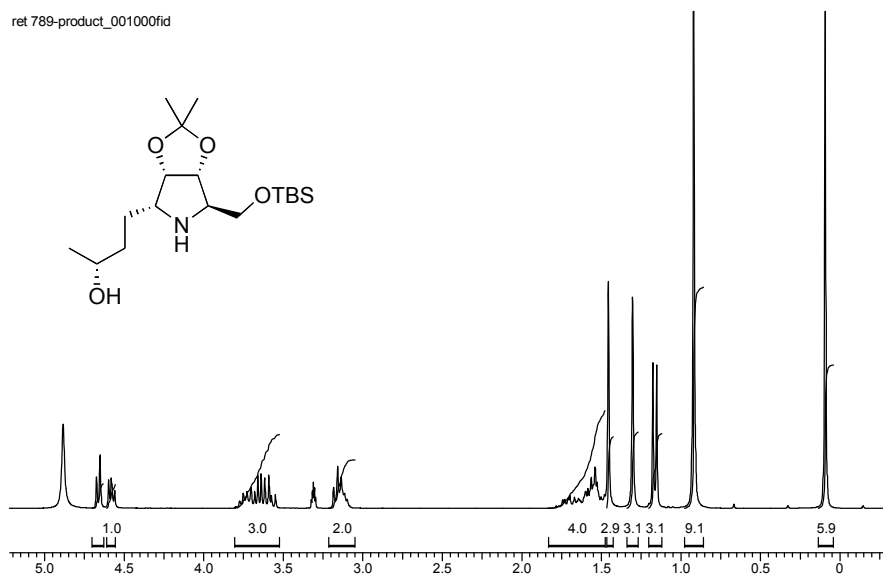


¹³C NMR (126 MHz, Toluene-D₈, 363 K)

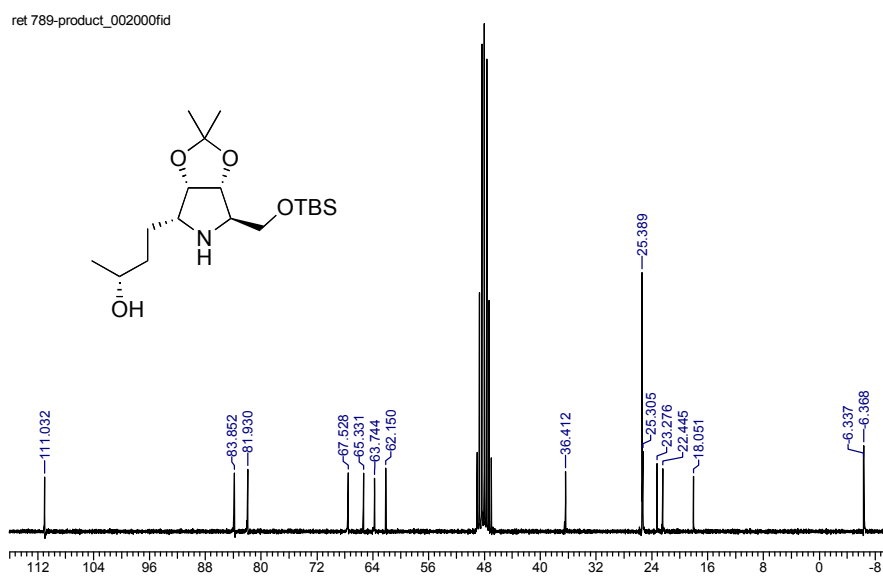


(*R*)-4-[(3*aS*,4*R*,6*R*,6*aR*)-6-[(*tert*-Butyldimethylsilyloxy)methyl]-2,2-dimethyltetrahydro-3*aH*-[1,3]dioxolo[4,5-*c*]pyrrol-4-yl]butan-2-ol 34

¹H NMR (250 MHz, Methanol-D₄)

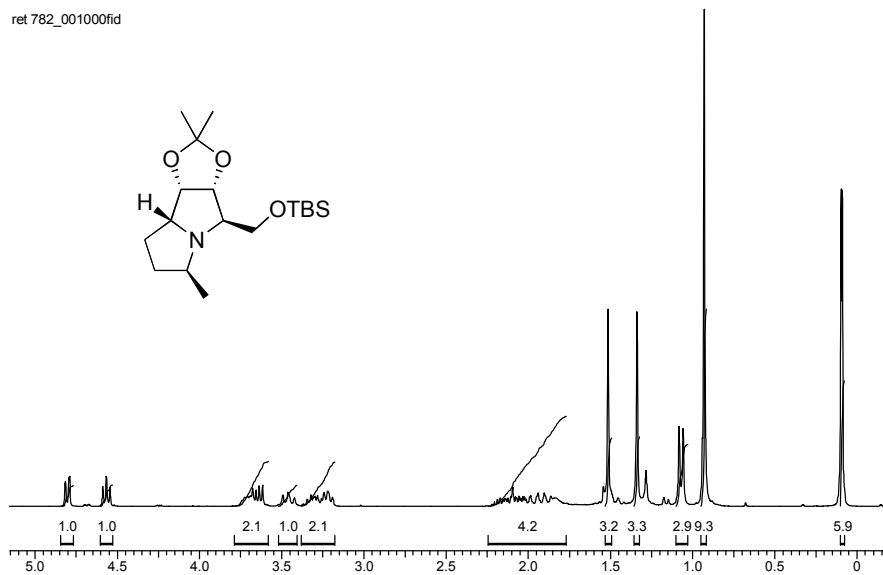


¹³C NMR (63 MHz, Methanol-D₄)

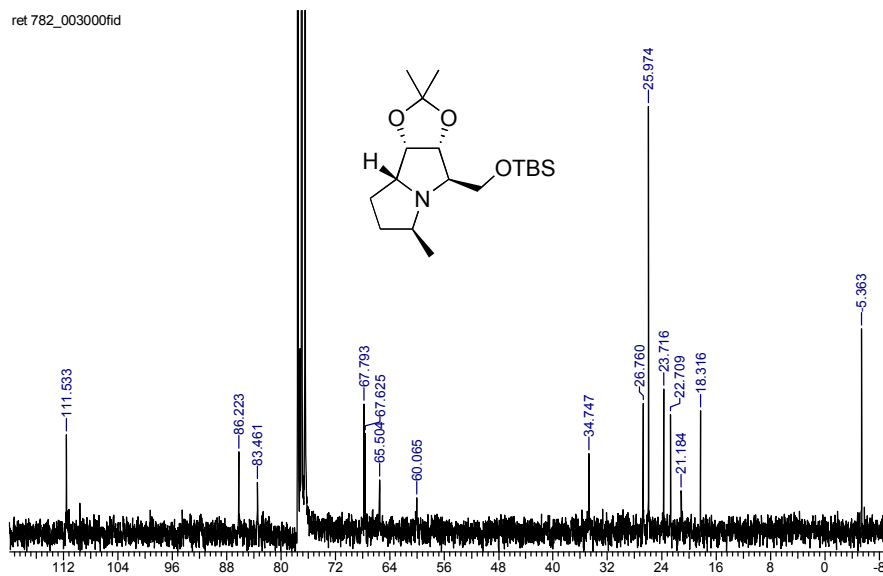


(3a*R*,4*R*,6*S*,8a*R*,8b*S*)-4-[(*tert*-Butyldimethylsilyloxy)methyl]-2,2,6-trimethylhexahydro-3a*H*-[1,3]dioxolo[4,5-*a*]pyrrolizine 35

¹H NMR (250 MHz, CDCl₃)

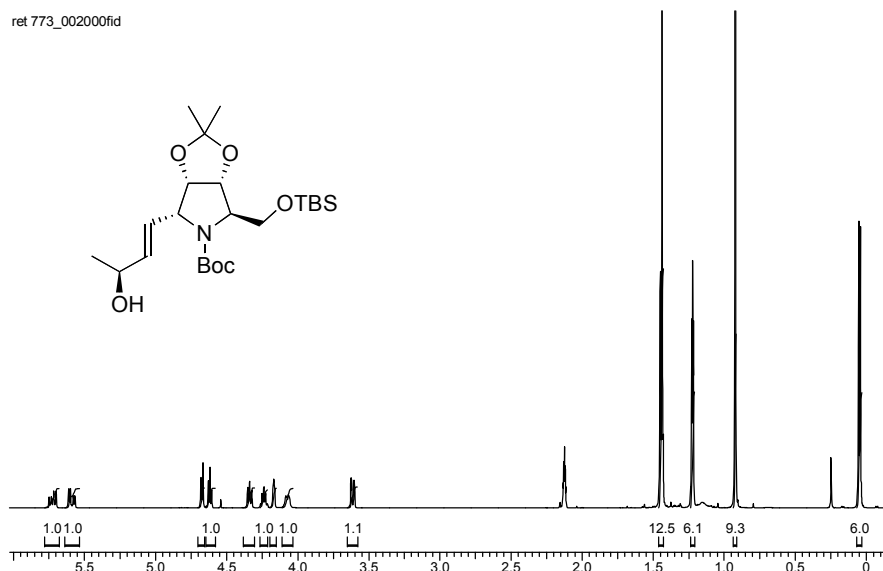


¹³C NMR (63 MHz, CDCl₃)

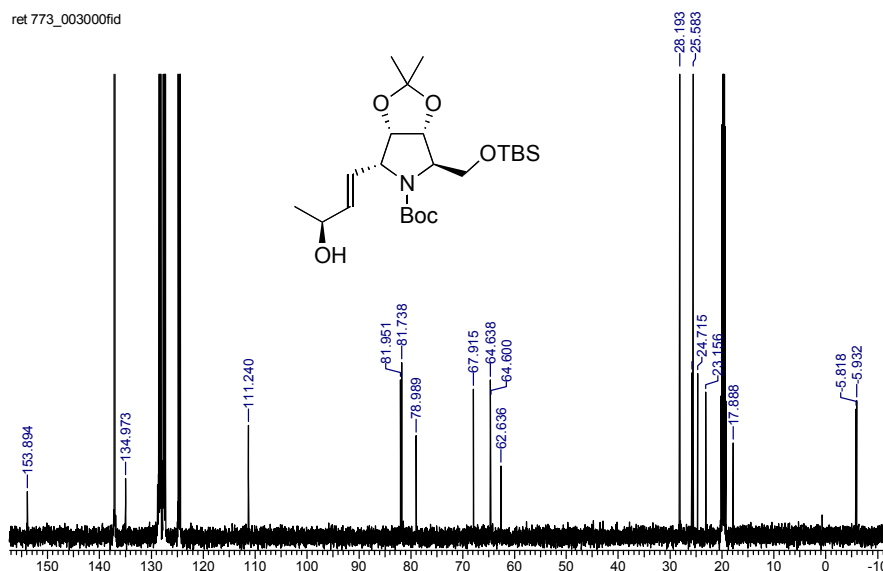


(3a*R*,4*R*,6*R*,6a*S*)-*tert*-Butyl-4-[(*tert*-butyldimethylsilyloxy)methyl]-6-[(*S,E*)-3-hydroxybut-1-enyl]-2,2-dimethyldihydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrole-5(4*H*)-carboxylate (*R*)-23

¹H NMR (500 MHz, Toluene-D₈, 373 K)

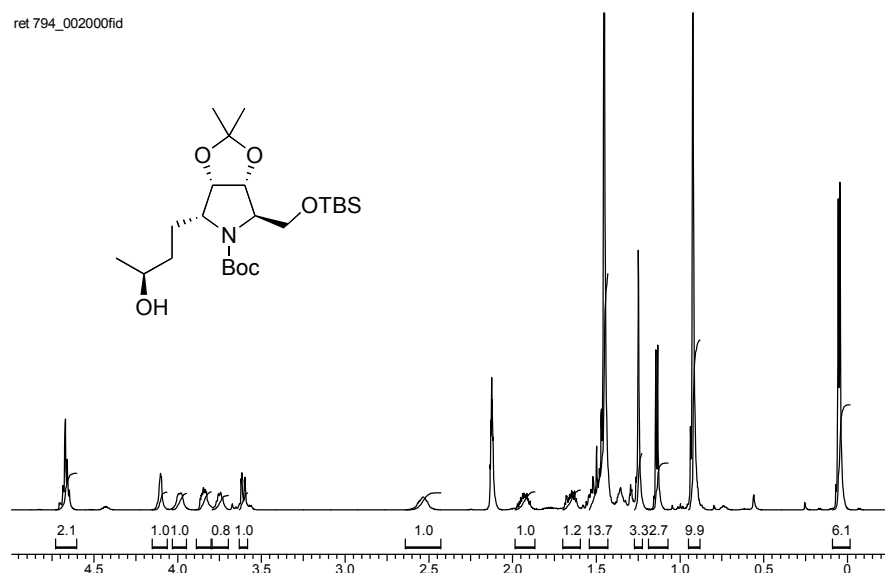


¹³C NMR (126 MHz, Toluene-D₈, 373 K)

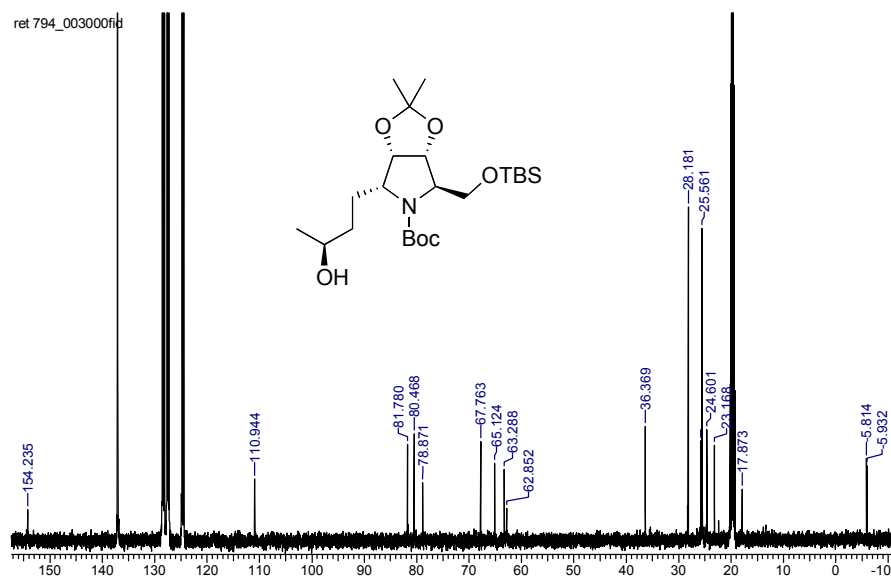


(3a*R*,4*R*,6*R*,6a*S*)-*tert*-Butyl-4-[(*tert*-butyldimethylsilyloxy)methyl]-6-[(*S*)-3-hydroxybutyl]-2,2-dimethyldihydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrole-5(4*H*)-carboxylate
36

¹H NMR (500 MHz, Toluene-D₈, 373 K)

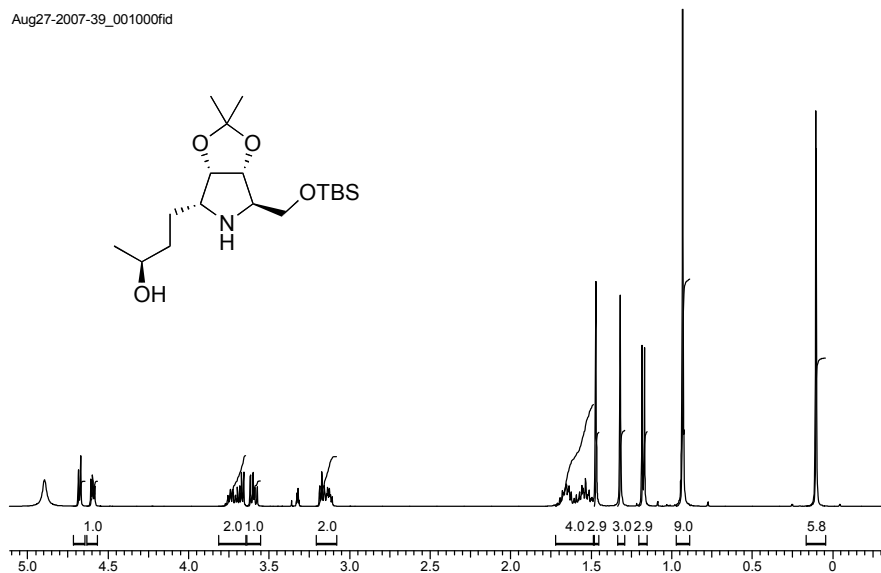


¹³C NMR (126 MHz, Toluene-D₈, 373 K)

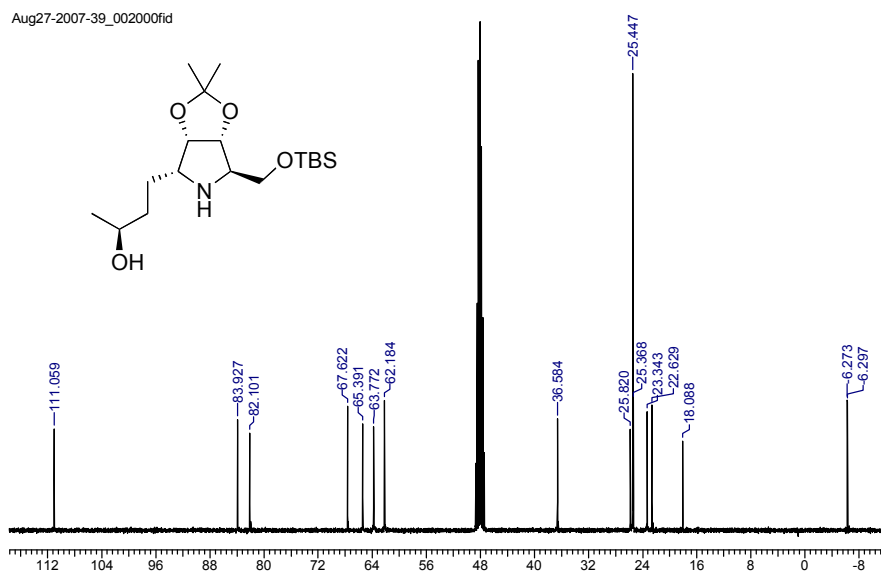


(S)-4-[(3a*S*,4*R*,6*R*,6*aR*)-6-[(*tert*-Butyldimethylsilyloxy)methyl]-2,2-dimethyltetrahydro-3*aH*-[1,3]dioxolo[4,5-*c*]pyrrol-4-yl]butan-2-ol 37

¹H NMR (400 MHz, Methanol-D₄)

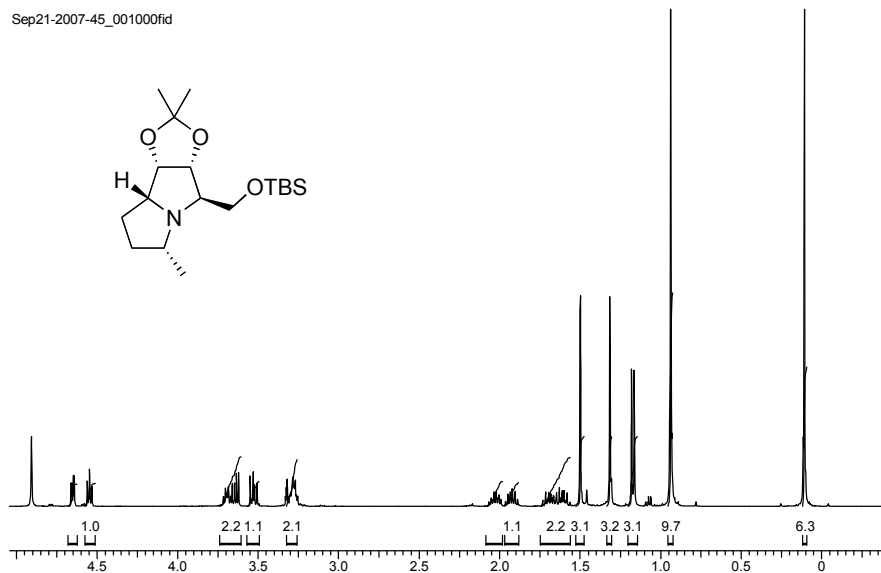


¹³C NMR (101 MHz, Methanol-D₄)



3a*R*,4*R*,6*R*,8a*R*,8b*S*)-4-[(*tert*-Butyldimethylsilyloxy)methyl]-2,2,6-trimethylhexahydro-3a*H*-[1,3]dioxolo[4,5-*a*]pyrrolizine 38

¹H NMR (400 MHz, Methanol-D₄)



¹³C NMR (101 MHz, Methanol-D₄)

