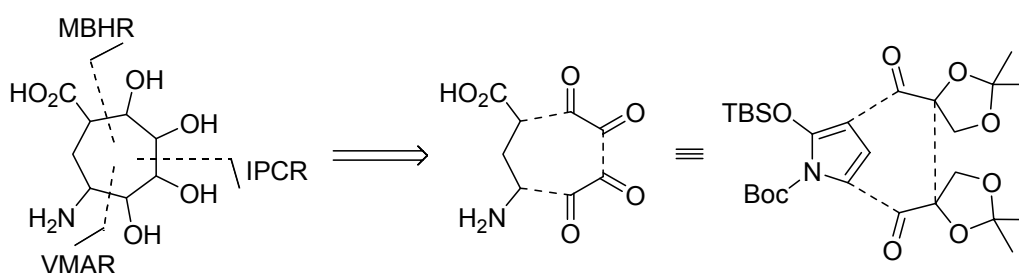


New Enantioselective Entry to Cycloheptane Amino Acid Polyols

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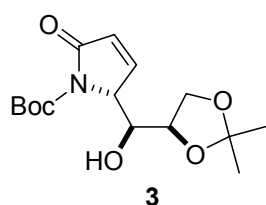
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General Experimental Procedures. All organic solvents were dried and freshly distilled before use according to literature procedures. All moisture sensitive reactions were carried out under a positive pressure of nitrogen or argon. TLC analysis was performed on silica gel 60 F₂₅₄ plates with visualization under short-wavelength UV light or by dipping the plates with molybdate reagent (aqueous H₂SO₄ solution of cerium sulfate/ammonium molybdate) followed by heating. Flash chromatography was performed on 40-63 μ m silica gel using the indicated solvent mixtures. Melting points were determined with an optical thermomicroscope and are uncorrected. Optical rotations were measured at ambient temperature using a 100-mm cell with a 1-mL capacity and are given in units of 10⁻¹ deg cm² g⁻¹. ¹H and ¹³C NMR spectra were recorded at 300/75 MHz or 600/150 MHz. Chemical shifts (δ) are given in parts per million (ppm) using chloroform-*d* (CHCl₃ δ _H 7.26, CDCl₃ δ _C 77.0), or deuterium oxide (DOH δ _H 4.75) as internal references. High-resolution mass spectrometry (HRMS) measurements were performed on a mass spectrometer equipped with an external electrospray ion source.

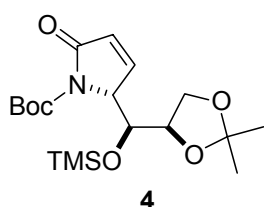
Materials. *N*-(*tert*-Butyloxycarbonyl)-2-[(*tert*-butyldimethylsilyl)oxy]pyrrole (**1**) was prepared from pyrrole according to a described protocol.¹ 2,3-*O*-Isopropylidene-D-glyceraldehyde (*R*-**2**) was prepared from D-mannitol according to a recently optimized protocol.² The preparation of 2,3-*O*-isopropylidene-L-glyceraldehyde (*S*-**2**) was carried out starting from 5,6-*O*-isopropylidene-L-gulonic acid 1,4-lactone following a known protocol.³ A samarium (II) iodide solution in THF was prepared as follows: samarium metal powder (0.15 g, 1.0 mmol) freshly obtained from an ingot of 99.9% pure samarium was added under a flow of argon to an oven-dried round-bottom flask containing a magnetic stirring bar and a septum inlet. The flask and the samarium had been flame-dried and cooled under a stream of argon. Anhydrous and deoxygenated THF (10 mL) was added and the resulting heterogeneous mixture was vigorously stirred and cooled to 0 °C. Neat diiodomethane (228 mg, 0.85 mmol) was added and the resulting dark green slurry was stirred at the same temperature for 15 min, then allowed to warm to 25 °C and vigorously stirred for an additional hour. The persistent deep blue solution of SmI₂ was titrated by a 0.1 M solution of iodine in THF and resulted to be 0.06 M.



(1'*S*,2*R*,4''*R*)-2-[(2,2-Dimethyl-[1,3]dioxolan-4-yl)hydroxymethyl]-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylic Acid *tert*-Butyl Ester (**3**). **Typical Procedure.**⁴ To a stirring solution of silyloxypyrrole **1** (700 mg, 2.35 mmol) in anhydrous Et₂O (20 mL) under argon atmosphere at -90 °C was added an ether

solution of aldehyde (*R*-**2**) (367 mg, 2.82 mmol dissolved in 8 mL of Et₂O). The resulting mixture was allowed to cool to -90 °C for 10 min, then SnCl₄ (3.06 mL of a 1.0 M solution in CH₂Cl₂, 3.06 mmol) was slowly added dropwise to the mixture at the same temperature over a period of 30 min. After 3 h, the reaction mixture was quenched at -90 °C with saturated aqueous NaHCO₃ (10 mL) and solid

NaHCO₃ (1.0 g) and temperature was allowed to reach ambient value (20 °C). Further portions of solid NaHCO₃ were added until neutral pH was achieved. The mixture was concentrated under vacuum to remove the ethereal phase. The water mixture was washed with hexanes (2 × 15 mL), and then extracted with EtOAc (3 × 15 mL). The combined organic layers were dried (MgSO₄) and concentrated in vacuum to give a solid crude residue which was crystallized from EtOAc/hexane to give unsaturated lactam **3** (604 mg, 82%, de > 98%) as a white solid: mp 138-140 °C; [α]_D²⁰ +197.6 (*c* 0.8, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.43 (dd, *J* = 6.3, 2.1 Hz, 1H), 6.13 (dd, *J* = 6.3, 1.5 Hz, 1H), 4.81 (dt, *J* = 5.7, 2.4 Hz, 1H), 4.09 (ddd, *J* = 6.0, 5.7, 3.9 Hz, 1H), 4.01 (q, *J* = 6.0 Hz, 1H), 3.94 (dd, *J* = 8.1, 6.0 Hz, 1H), 3.86 (dd, *J* = 8.1, 6.0 Hz, 1H), 3.63 (d, *J* = 3.9 Hz, 1H), 1.57 (s, 9H), 1.37 (s, 3H), 1.32 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 168.9, 150.9, 148.2, 126.9, 109.2, 83.8, 75.6, 72.6, 66.4, 65.6, 28.0 (3C), 26.4, 25.1. Anal. Calcd for C₁₅H₂₃NO₆: C, 57.50; H, 7.40; N, 4.47. Found: C, 57.31; H, 7.35; N, 4.32.

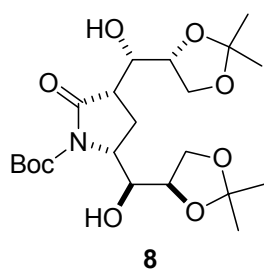


(1'S,2R,4''R)-2-[(2,2-Dimethyl-[1,3]dioxolan-4-

yl)(trimethylsilanyloxy)methyl]-5-oxo-2,5-dihydro-1H-pyrrole-1-carboxylic

Acid *tert*-Butyl Ester (4**). Typical Procedure.** To a stirring solution of unsaturated lactam **3** (604 mg, 1.93 mmol) in pyridine (5 mL), cooled to 0 °C under argon atmosphere, trimethylsilyl chloride (TMSCl, 0.49 mL, 3.85 mmol)

was added dropwise, and the resulting mixture was allowed to reach ambient value (20 °C). After 30 min, the reaction was quenched with distilled water and extracted with CH₂Cl₂ (3 × 5 mL). The combined organic layers were washed with water, dried over MgSO₄, filtered, and concentrated under reduced pressure to leave a crude product which was purified by silica gel flash chromatography (EtOAc/hexanes 6:4). Protected lactam **4** (729 mg, 98%) was obtained as a glassy solid: [α]_D²⁰ +168.9 (*c* 6.2, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.23 (dd, *J* = 6.2, 2.1 Hz, 1H), 6.12 (dd, *J* = 6.2, 1.7 Hz, 1H), 4.58 (dt, *J* = 4.8, 1.8 Hz, 1H), 4.50 (t, *J* = 5.1 Hz, 1H), 3.6-3.8 (m, 3H), 1.51 (s, 9H), 1.28 (s, 3H), 1.18 (s, 3H), 0.16 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 169.0, 149.4, 147.5, 128.3, 109.2, 83.1, 74.9, 71.2, 66.2, 65.3, 28.3 (3C), 26.4, 25.1, 0.3 (3C). Anal. Calcd for C₁₈H₃₁NO₆Si: C, 56.08; H, 8.10; N, 3.63. Found: C, 56.11; H, 8.16; N, 3.53.

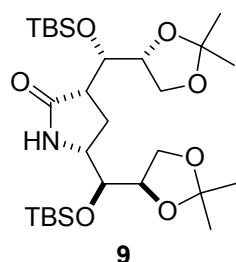


(1'S,1'''S,3S,4''R,4''R,5R)-3,5-Bis[(2,2-dimethyl-[1,3]dioxolan-4-

yl)hydroxymethyl]-2-oxopyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (8**).**

Typical Procedure. To a solution of lactam **7** (280 mg, 0.54 mmol) in methanol (15 mL), solid citric acid (311 mg, 1.62 mmol) was added and the resulting

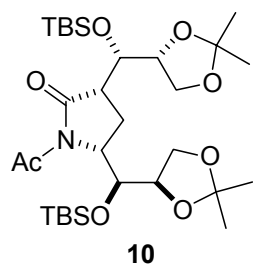
mixture was allowed to stir at room temperature for 6 h, while further portions of citric acid (6×311 mg, 9.72 mmol) were added. The reaction mixture was then diluted with water and treated with saturated aqueous NaHCO_3 solution. Extraction with EtOAc (3×10 mL), drying over MgSO_4 and concentration under reduced pressure afforded a crude residue which was purified by silica gel flash chromatography (EtOAc/hexanes 75:25). Pure diol **8** was obtained (228 mg, 95%) as a white solid: mp 125-130 °C; $[\alpha]_D^{20} +10.2$ (c 1.0, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 4.89 (bs, 1H, OH), 4.37 (ddd, $J = 9.6, 5.0, 2.5$ Hz, 1H, H5), 4.35 (bs, 1H, OH), 4.0-4.2 (m, 4H, H5^{II}a, H1', H5^{IV}a, H5^{VI}b), 3.99 (m, 1H, H4^{IV}), 3.90 (m, 2H, H5^{II}b, H4^{II}), 3.73 (bt, $J = 6.1$ Hz, 1H, H1^{III}), 2.98 (ddd, $J = 12.1, 4.4, 1.5$ Hz, 1H, H3), 2.32 (ddd, $J = 13.8, 12.4, 9.9$ Hz, 1H, H4a), 2.03 (ddd, $J = 13.9, 4.4, 2.8$ Hz, 1H, H4b), 1.47 (s, 9H, Boc), 1.41 (s, 3H, Me), 1.39 (s, 3H, Me), 1.33 (s, 3H, Me), 1.32 (s, 3H, Me); ^{13}C NMR (75 MHz, CDCl_3) δ 177.2 (C2), 150.8 (Boc), 109.6 (CMe_2), 109.3 (CMe_2), 83.6 (Boc), 76.9, 76.4, 76.3, 70.9 (C4^{II}, C1', C4^{IV}, C1^{III}), 67.5, 67.4 (C5^{II}, C5^{IV}), 58.0 (C5), 45.6 (C3), 27.8 (3C, Boc), 26.9 (Me), 26.7 (Me), 25.4 (Me), 25.3 (Me), 21.2 (C4). Anal. Calcd for $\text{C}_{21}\text{H}_{35}\text{NO}_9$: C, 56.62; H, 7.92; N, 3.14. Found: C, 56.74; H, 8.02; N, 2.99.



(1'S,1'''S,3S,4''R,4''R,5R)-3,5-Bis[(*tert*-butyldimethylsilyloxy)(2,2-dimethyl-[1,3]dioxolan-4-yl)methyl]pyrrolidin-2-one (9**). Typical Procedure.**

Deprotected lactam **8** (228 mg, 0.51 mmol) was dissolved in anhydrous CH_2Cl_2 (10 mL) at ambient temperature under argon and 2,6-lutidine (365 μL , 3.06 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf, 234 μL , 1.0 mmol) were sequentially added under stirring. After 2 h, the reaction mixture was quenched with saturated NH_4Cl solution, diluted with distilled water and extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were dried over MgSO_4 , filtered, and concentrated under reduced pressure to furnish a crude product which was dissolved in 30 mL of acetonitrile, warmed to 80 °C, and the resulting mixture was treated with ammonium cerium (IV) nitrate (CAN, 56 mg, 0.10 mmol). After 3 h, the reaction was quenched with 10% aqueous $\text{Na}_2\text{S}_2\text{O}_3$ solution and extracted with EtOAc (3×20 mL). The combined organic layers were dried (MgSO_4), filtered and concentrated under reduced pressure furnishing a crude residue which was purified by silica gel flash chromatography (EtOAc/hexanes 1:1). *N*-deprotected lactam **9** (234 mg, 80%) was recovered as a white solid: mp 108-112 °C; $[\alpha]_D^{20} -4.8$ (c 5.3, CHCl_3); ^1H NMR (600 MHz, CDCl_3) δ 5.63 (s, 1H), 4.25 (d, $J = 7.8$ Hz, 1H), 4.09 (m, 2H), 3.92 (m, 2H), 3.83 (m, 2H), 3.70 (dd, $J = 8.4, 3.6$ Hz, 1H), 3.43 (td, $J = 9.0, 6.6$ Hz, 1H), 2.87 (dd, $J = 10.2, 9.6$ Hz, 1H), 2.11 (ddd, $J = 12.6, 8.4, 7.2$ Hz, 1H), 2.05 (td, $J = 12.0, 10.2$ Hz, 1H), 1.45 (s, 3H), 1.42 (s, 3H), 1.37 (s, 3H), 1.35 (s, 3H), 0.93 (s, 9H), 0.88 (s, 9H), 0.15 (s, 9H), 0.09 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 176.8, 109.3, 109.0, 77.3, 76.3, 76.0, 70.8, 67.9, 64.6, 55.9, 45.3, 26.7, 26.4, 26.0 (3C), 25.9 (3C), 25.4, 25.1,

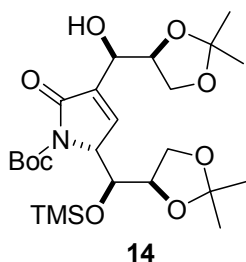
23.5, 18.3, 18.4, -3.9 (2C), -4.0, -4.9. Anal. Calcd for C₂₈H₅₅NO₇Si₂: C, 58.60; H, 9.66; N, 2.44. Found: C, 58.54; H, 9.59; N, 2.35.



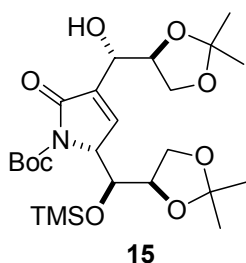
10

(1'S,1'''S,3S,4''R,4''R,5R)-1-Acetyl-3,5-bis[(tert-butyl)dimethylsilanyloxy](2,2-dimethyl-[1,3]dioxolan-4-yl)methylpyrrolidin-2-one (10). Typical Procedure. To a stirring solution of lactam **9** (234 mg, 0.41 mmol) in acetonitrile (20 mL) under argon, Et₃N (114 μL, 0.82 mmol), acetic anhydride (39 μL, 0.41 mmol), and 4-dimethylaminopyridine (DMAP, 100 mg, 0.82 mmol) were sequentially added. The resulting mixture was warmed to 70 °C and further portions of Et₃N (3 × 114 μL, 2.46 mmol), acetic anhydride (3 × 39 μL, 1.23 mmol), and DMAP (3 × 100 mg, 2.46 mmol) were added. After 24 h, the reaction mixture was quenched with saturated NH₄Cl solution, diluted with distilled water and extracted with CH₂Cl₂ (3 × 10 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated under vacuum. After flash chromatographic purification (EtOAc/hexanes 1:4) pure acetylated lactam **10** was recovered (225 mg, 89%) as a glassy solid: ¹H NMR (600 MHz, CDCl₃) δ 4.62 (dd, *J* = 8.4, 4.8 Hz, 1H, H1'''), 4.30 (m, 2H, H1', H5), 4.10 (m, 2H, H5''a, H4'''), 4.02 (dd, *J* = 9.0, 6.6 Hz, 1H, H5''a), 3.95 (dt, *J* = 7.8, 5.4 Hz, 1H, H4''), 3.91 (m, 2H, H5''b, H5''b), 2.93 (ddd, *J* = 11.4, 9.6, 1.2 Hz, 1H, H3), 2.47 (s, 3H, Ac), 2.16 (td, *J* = 12.6, 10.2 Hz, 1H, H4a), 2.02 (ddd, *J* = 13.8, 10.2, 8.4 Hz, 1H, H4b), 1.44 (s, 3H, Me), 1.37 (s, 3H, Me), 1.31 (s, 3H, Me), 1.30 (s, 3H, Me), 0.93 (s, 9H, TBS), 0.91 (s, 9H, TBS), 0.21 (s, 3H, TBS), 0.19 (s, 3H, TBS), 0.18 (s, 3H, TBS), 0.08 (s, 3H, TBS); ¹³C NMR (150 MHz, CDCl₃) δ 176.2 (C2), 173.0 (Ac), 109.5 (CMe₂), 109.3 (CMe₂), 76.9 (C4''), 73.8 (C4''), 70.8 (C1'), 69.8 (C1'''), 67.2 (2C, C5'', C5''), 57.2 (C5), 45.5 (C3), 26.8 (Me), 26.0 (Me), 25.9 (3C, TBS), 25.8 (Ac), 25.7 (3C, TBS), 25.6 (Me), 25.2 (Me), 18.3 (TBS), 17.9 (TBS), 16.4 (C4), -3.7 (TBS), -4.2 (TBS), -4.9 (TBS), -5.2 (TBS). Anal. Calcd for C₃₀H₅₇NO₈Si₂: C, 58.50; H, 9.33; N, 2.27. Found: C, 58.44; H, 9.25; N, 2.20.

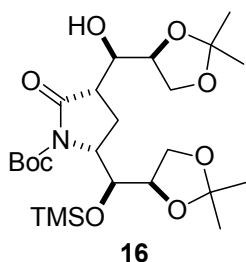
(1'R,1'''S,4''S,4''R,5R)-3-[(2,2-Dimethyl-[1,3]dioxolan-4-yl)hydroxymethyl]-5-[(2,2-dimethyl-[1,3]dioxolan-4-yl)(trimethylsilyloxy)methyl]-2-oxo-2,5-dihydro-1H-pyrrole-1-carboxylic Acid *tert*-Butyl Ester (14) and (1'S,1'''S,4''S,4''R,5R)-3-[(2,2-Dimethyl-[1,3]dioxolan-4-yl)hydroxymethyl]-5-[(2,2-dimethyl-[1,3]dioxolan-4-yl)(trimethylsilyloxy)methyl]-2-oxo-2,5-dihydro-1H-pyrrole-1-carboxylic Acid *tert*-Butyl Ester (15). The title compounds were prepared from butenolide **4** (364 mg, 0.94 mmol) and L-gliceraldehyde (*S*)-**2** (245 mg, 1.88 mmol) according to the typical procedure described for **5** and **6**. After flash chromatographic purification (EtOAc/hexanes 35:65), adducts **14** (300 mg, 62%) and **15** (78 mg, 16%) were recovered in 78% combined yield.



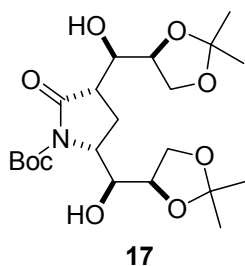
Compound 14: a colorless oil, $[\alpha]_D^{20} +75.3$ (c 2.2, CHCl_3); ^1H NMR (600 MHz, CDCl_3) δ 7.28 (dd, $J = 2.4, 1.8$ Hz, 1H, H4), 4.64 (ddt, $J = 5.4, 4.2, 1.8$ Hz, 1H, H1'), 4.62 (dt, $J = 4.2, 1.8$ Hz, 1H, H5), 4.58 (bq, $J = 6.0$ Hz, 1H, H4''), 4.48 (dd, $J = 7.2, 4.2$ Hz, 1H, H1'''), 3.99 (dd, $J = 7.8, 6.6$ Hz, 1H, H5''a), 3.94 (dd, $J = 8.4, 6.0$ Hz, 1H, H5''b), 3.92 (dd, $J = 8.4, 6.6$ Hz, 1H, H5''a), 3.75 (dd, $J = 7.8, 6.0$ Hz, 1H, H5''b), 3.71 (dt, $J = 7.2, 6.0$ Hz, 1H, H4''), 3.07 (d, $J = 4.2$ Hz, 1H, OH), 1.60 (s, 9H, Boc), 1.49 (s, 3H, Me), 1.39 (s, 3H, Me), 1.36 (s, 3H, Me), 1.27 (s, 3H, Me), 0.25 (s, 9H, TMS); ^{13}C NMR (75 MHz, CDCl_3) δ 168.2 (C2), 149.4 (Boc), 142.0 (C4), 138.3 (C3), 109.7 (CMe_2), 109.5 (CMe_2), 83.2 (Boc), 75.9, 75.6 (C4'', C4''), 71.2 (C1'''), 67.3, 67.1 (C1', C5), 64.8, 64.0 (C5'', C5''), 28.2 (3C, Boc), 25.2 (Me), 25.1 (Me), 25.0 (Me), 24.9 (Me), 0.2 (3C, TMS). Anal. Calcd for $\text{C}_{24}\text{H}_{41}\text{NO}_9\text{Si}$: C, 55.90; H, 8.01; N, 2.72. Found: C, 55.78; H, 8.07; N, 2.84.



Compound 15: a colorless oil, $[\alpha]_D^{20} +70.8$ (c 1.5, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 7.22 (bs, 1H), 4.58 (m, 1H), 4.46 (m, 3H), 4.0-4.2 (m, 3H), 3.92 (m, 1H), 3.71 (m, 1H), 2.98 (bs, 1H), 1.56 (s, 9H), 1.48 (s, 3H), 1.43 (s, 3H), 1.32 (s, 3H), 1.23 (s, 3H), 0.2 (s, 9H). Anal. Calcd for $\text{C}_{24}\text{H}_{41}\text{NO}_9\text{Si}$: C, 55.90; H, 8.01; N, 2.72. Found: C, 56.01; H, 8.05; N, 2.62.

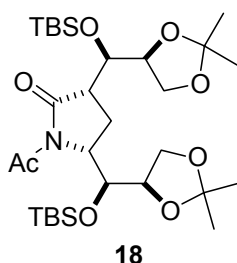


(1'R,1'''S,3S,4''S,4''R,5R)-3-[(2,2-Dimethyl-[1,3]dioxolan-4-yl)hydroxymethyl]-5-[(2,2-dimethyl-[1,3]dioxolan-4-yl)(trimethylsilyloxy)methyl]-2-oxopyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (16). The title compound was prepared from **14** (300 mg, 0.58 mmol) according to the typical procedure described for lactam **7**. After flash chromatographic purification (EtOAc/hexanes 6:4), compound **16** was obtained (294 mg, 98%) as a glassy solid: $[\alpha]_D^{20} +25.7$ (c 1.0, CHCl_3); ^1H NMR (600 MHz, CDCl_3) δ 4.27 (dd, $J = 7.2, 4.2$ Hz, 1H, H1'''), 4.24 (d, $J = 3.6$ Hz, 1H, OH), 4.18 (dt, $J = 7.8, 6.0$ Hz, 1H, H4''), 4.15 (ddd, $J = 9.0, 6.6, 4.2$ Hz, 1H, H5), 4.11 (dd, $J = 9.0, 6.0$ Hz, 1H, H5''a), 4.09 (q, $J = 7.2$ Hz, 1H, H4''), 4.03 (dd, $J = 7.8, 6.0$ Hz, 1H, H5''a), 4.01 (dd, $J = 9.0, 5.4$ Hz, 1H, H5''b), 3.74 (dd, $J = 7.8, 6.6$ Hz, 1H, H5''b), 3.69 (td, $J = 7.2, 3.0$ Hz, 1H, H1'), 2.72 (ddd, $J = 10.8, 9.0, 7.2$ Hz, 1H, H3), 2.25 (ddd, $J = 14.4, 11.4, 9.0$ Hz, 1H, H4a), 2.02 (ddd, $J = 14.4, 9.0, 6.6$ Hz, 1H, H4b), 1.53 (s, 9H, Boc), 1.40 (s, 3H, Me), 1.34 (s, 3H, Me), 1.32 (s, 3H, Me), 1.28 (s, 3H, Me), 0.15 (s, 9H, TMS); ^{13}C NMR (75 MHz, CDCl_3) δ 176.1 (C2), 149.8 (Boc), 109.5 (CMe_2), 109.4 (CMe_2), 83.2 (Boc), 77.9, 74.7, 73.6, 71.8 (C4'', C1', C4'', C1'''), 67.7, 67.2 (C5'', C5''), 58.4 (C5), 45.0 (C3), 28.1 (3C, Boc), 26.6 (Me), 26.3 (Me), 25.3 (Me), 25.2 (Me), 20.8 (C4), 0.3 (3C, TMS). Anal. Calcd for $\text{C}_{24}\text{H}_{43}\text{NO}_9\text{Si}$: C, 55.68; H, 8.37; N, 2.71. Found: C, 55.83; H, 8.21; N, 2.62.



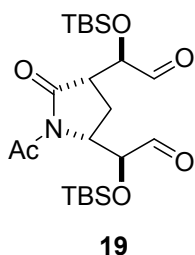
(1'*R*,1'''*S*,3*S*,4''*S*,4''*R*,5*R*)-3,5-Bis[(2,2-dimethyl-[1,3]dioxolan-4-yl)hydroxymethyl]-2-oxopyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (17).

The title compound was prepared from lactam **16** (294 mg, 0.57 mmol) according to the procedure described for **8**. After flash chromatographic purification (EtOAc/hexanes 7:3), lactam **17** was obtained (229 mg, 90%) as a light white solid: $[\alpha]_D^{20} +23.7$ (*c* 1.2, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 4.2-4.4 (m, 3H), 4.0-4.2 (m, 3H), 3.9-4.0 (m, 3H), 3.78 (m, 1H), 3.70 (dd, *J* = 7.2, 4.8 Hz, 1H), 2.88 (dt, *J* = 11.1, 5.7 Hz, 1H), 2.49 (ddd, *J* = 14.1, 11.4, 9.3 Hz, 1H), 2.06 (ddd, *J* = 14.1, 6.0, 4.8 Hz, 1H), 1.54 (s, 9H), 1.41 (s, 3H), 1.40 (s, 3H), 1.36 (s, 3H), 1.35 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 175.3, 151.4, 109.4, 109.3, 83.8, 76.7, 76.6, 75.6, 74.4, 67.3, 67.2, 58.6, 45.1, 27.9 (3C), 26.7, 26.5, 25.3, 25.2, 25.1. Anal. Calcd for C₂₁H₃₅NO₉: C, 56.62; H, 7.92; N, 3.14. Found: C, 56.70; H, 7.99; N, 3.02.



(1'*R*,1'''*S*,3*S*,4''*S*,4''*R*,5*R*)-1-Acetyl-3,5-bis[(*tert*-butyldimethylsilanyloxy)(2,2-dimethyl-[1,3]dioxolan-4-yl)methyl]pyrrolidin-2-one (18).

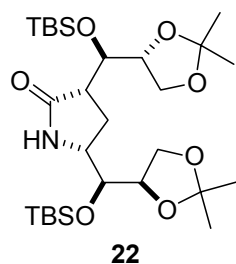
The title compound was prepared from **17** (229 mg, 0.51 mmol) by adopting the two-step typical procedure to **10**. After flash chromatographic purification (EtOAc/hexanes 1:4), protected lactam **18** was recovered (242 mg, 77%) as a glassy solid: $[\alpha]_{578}^{20} +26.0$ (*c* 1.0, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 4.63 (dd, *J* = 7.5, 4.8 Hz, 1H), 4.1-4.3 (m, 5H), 4.02 (dd, *J* = 8.3, 6.5 Hz, 1H), 3.92 (m, 1H), 3.89 (dd, *J* = 8.3, 6.6 Hz, 1H), 2.73 (ddd, *J* = 12.0, 10.2, 2.4 Hz, 1H), 2.43 (s, 3H), 2.04 (m, 2H), 1.38 (s, 3H), 1.32 (s, 6H), 1.29 (s, 3H), 0.92 (s, 9H), 0.89 (s, 9H), 0.18 (s, 3H), 0.16 (s, 3H), 0.14 (s, 3H), 0.13 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 174.5, 173.1, 109.7, 109.1, 75.9, 74.1, 72.9, 70.1, 67.9, 67.0, 56.9, 47.8, 26.0, 25.9, 25.8 (2C), 25.7 (3C), 25.6 (3C), 25.1, 18.5, 18.0, 17.9, -4.3, -4.4, -4.6, -4.9. Anal. Calcd for C₃₀H₅₇NO₈Si₂: C, 58.50; H, 9.33; N, 2.27. Found: C, 58.37; H, 9.39; N, 2.38.



(2*S*,2'*R*,2''*R*,4''*S*)-2,2'-(1-Acetyl-5-oxopyrrolidine-2,4-diyl)bis(*tert*-butyldimethylsilyloxyacetaldehyde) (19).

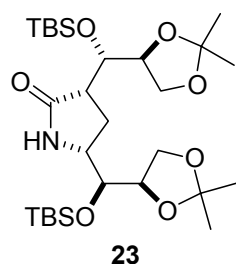
The title compound was prepared from lactam **18** (242 mg, 0.39 mmol) according to the typical procedure described for compound **11**. Aldehyde **19** was obtained (170 mg, 94%) as a colorless oil: $[\alpha]_{578}^{20} +52.0$ (*c* 1.0, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 9.86 (s, 1H, H1), 9.52 (s, 1H, H1'), 4.27 (m, 3H, H2', H2, H2''), 3.17 (ddd, *J* = 12.6, 9.0, 3.5 Hz, 1H, H4''), 2.50 (s, 3H, Ac), 2.28 (ddd, *J* = 12.6, 9.0, 6.9 Hz, 1H, H3''a), 1.90 (td, *J* = 12.4, 10.2 Hz, 1H, H3''b), 0.95 (s, 9H, TBS), 0.93 (s, 9H, TBS), 0.14 (s, 3H, TBS), 0.13 (s, 3H, TBS), 0.11 (s, 6H, TBS); ¹³C NMR (75 MHz, CDCl₃) δ 203.5, 201.6, 173.4, 172.4,

75.5 (2C), 57.9, 48.2, 25.8 (3C), 25.6 (3C), 25.2, 23.6, 18.2, 17.9, -4.5, -4.7, -4.8, -4.9. Anal. Calcd for C₂₂H₄₁NO₆Si₂: C, 56.01; H, 8.76; N, 2.97. Found: C, 55.93; H, 8.65; N, 3.08.



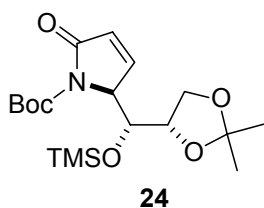
(1'R,1''S,3S,4''R,4''R,5R)-3,5-Bis[(*tert*-butyldimethylsilanyloxy)(2,2-dimethyl-[1,3]dioxolan-4-yl)methyl]pyrrolidin-2-one (22). The title compound was prepared from **6** (92 mg, 0.18 mmol) by adopting the three-step typical procedure described for **9**. After flash chromatographic purification (EtOAc/hexanes 1:1), lactam **22** was recovered (91 mg, 88%) as a glassy solid: ¹H

NMR (600 MHz, CDCl₃) δ 5.69 (bs, 1H, NH), 4.54 (dt, *J* = 7.8, 6.0 Hz, 1H, H4''), 4.07 (dd, *J* = 7.8, 6.6 Hz, 1H, H5''a), 4.05 (m, 1H, H4''), 3.98 (t, *J* = 7.2 Hz, 1H, H5''a), 3.93 (dd, *J* = 5.4, 3.6 Hz, 1H, H1'), 3.85 (t, *J* = 7.8 Hz, 1H, H5''b), 3.78 (dd, *J* = 8.4, 4.2 Hz, 1H, H1''), 3.68 (t, *J* = 7.8 Hz, 1H, H5''b), 3.46 (q, *J* = 8.4 Hz, 1H, H5), 2.64 (td, *J* = 9.6, 3.6 Hz, 1H, H3), 2.27 (m, 1H, H4a), 2.19 (m, 1H, H4b), 1.43 (s, 6H, Me), 1.38 (s, 3H, Me), 1.36 (s, 3H, Me), 0.94 (s, 9H, TBS), 0.93 (s, 9H, TBS), 0.16 (s, 3H, TBS), 0.15 (s, 3H, TBS), 0.14 (s, 3H, TBS), 0.13 (s, 3H, TBS); ¹³C NMR (75 MHz, CDCl₃) δ 175.5, 109.2, 109.1, 77.3, 76.6, 76.0, 71.9, 66.2, 65.4, 55.8, 46.2, 26.6, 26.5, 26.4, 26.0 (3C), 25.9 (3C), 25.8, 25.3, 18.3, 18.1, -3.9, -4.0, -4.2, -4.7. Anal. Calcd for C₂₈H₅₅NO₇Si₂: C, 58.60; H, 9.66; N, 2.44. Found: C, 58.71; H, 9.80; N, 2.31.



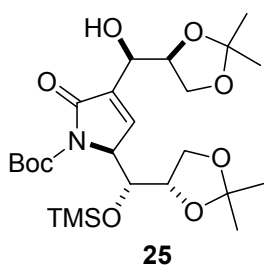
(1'S,1''S,3S,4''S,4''R,5R)-3,5-Bis[(*tert*-butyldimethylsilanyloxy)(2,2-dimethyl-[1,3]dioxolan-4-yl)methyl]pyrrolidin-2-one (23). The title compound was prepared from **15** (78 mg, 0.15 mmol) in three steps according to the typical procedures described for **9**. After flash chromatographic purification (EtOAc/hexanes 1:1), lactam **23** was obtained (77 mg, 90%) as a glassy solid:

[α]_D²⁰ -14.5 (*c* 0.6, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 5.66 (bs, 1H, NH), 4.33 (dd, *J* = 6.8, 1.2 Hz, 1H, H1'), 4.06 (td, *J* = 6.2, 3.8 Hz, 1H, H4''), 4.02 (q, *J* = 6.7 Hz, 1H, H4''), 3.96 (m, 2H, H5''a, H5''b), 3.90 (t, *J* = 7.7 Hz, 1H, H5''a), 3.71 (t, *J* = 7.0 Hz, 1H, H5''b), 3.69 (dd, *J* = 8.9, 4.0 Hz, 1H, H1''), 3.42 (td, *J* = 9.2, 6.8 Hz, 1H, H5), 2.42 (ddd, *J* = 10.4, 9.4, 1.0 Hz, 1H, H3), 2.0-2.2 (m, 2H, H4a, H4b), 1.45 (s, 3H, Me), 1.43 (s, 3H, Me), 1.37 (s, 6H, Me), 0.93 (s, 9H, TBS), 0.90 (s, 9H, TBS), 0.15 (s, 6H, TBS); 0.14 (s, 3H, TBS), 0.12 (s, 3H, TBS); ¹³C NMR (150 MHz, CDCl₃) δ 176.2 (C2), 109.5 (CMe₂), 109.1 (CMe₂), 78.3 (C4''), 76.5 (C1''), 76.2 (C4''), 70.5 (C1'), 65.5 (C5''), 64.8 (C5''), 56.0 (C5), 44.9 (C3), 26.5 (Me), 26.3 (Me), 26.0 (3C, TBS), 25.9 (3C, TBS), 25.3 (Me), 25.2 (Me), 23.9 (C4), 18.3 (TBS), 18.1 (TBS), -3.9 (TBS), -4.0 (TBS), -4.4 (TBS), -4.9 (TBS). Anal. Calcd for C₂₈H₅₅NO₇Si₂: C, 58.60; H, 9.66; N, 2.44. Found: C, 58.52; H, 9.55; N, 2.51.

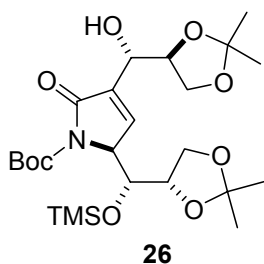


(1'*R*,2*S*,4''*S*)-2-[(2,2-Dimethyl-[1,3]dioxolan-4-yl)(trimethylsilyloxy)methyl]-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylic Acid *tert*-Butyl Ester (24). The title compound was prepared from silyloxypyrrole **1** (700 mg, 2.35 mmol) and L-glyceraldehyde (*S*)-**2** (367 mg, 2.82 mmol) in two steps, according to the typical procedures described for **4**. Flash chromatographic purification (EtOAc/hexanes 6:4) afforded lactam **24** (721 mg, 80%) as a glassy solid: $[\alpha]_D^{20} -171.1$ (c 2.1, CHCl₃); ¹H and ¹³C NMR: see enantiomeric compound **4**. Anal. Calcd for C₁₈H₃₁NO₆Si: C, 56.08; H, 8.10; N, 3.63. Found: C, 56.00; H, 8.18; N, 3.57.

(1'*R*,1'''*R*,4''*S*,4'*VS*,5*S*)-3-[(2,2-Dimethyl-[1,3]dioxolan-4-yl)hydroxymethyl]-5-[(2,2-dimethyl-[1,3]dioxolan-4-yl)(trimethylsilyloxy)methyl]-2-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylic Acid *tert*-Butyl Ester (25) and (1'*S*,1'''*R*,4''*S*,4'*V**S*,5*S*)-3-[(2,2-Dimethyl-[1,3]dioxolan-4-yl)hydroxymethyl]-5-[(2,2-dimethyl-[1,3]dioxolan-4-yl)(trimethylsilyloxy)methyl]-2-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylic Acid *tert*-Butyl Ester (26).** The title compounds were prepared from lactam **24** (360 mg, 0.93 mmol) and L-glyceraldehyde (*S*)-**2** (242 mg, 1.86 mmol) according to the typical procedure described for **5** and **6**. After flash chromatographic purification (EtOAc/hexanes 35:65) adducts **25** (297 mg, 62%) and **26** (86 mg, 18%) were recovered in a 80% global yield.



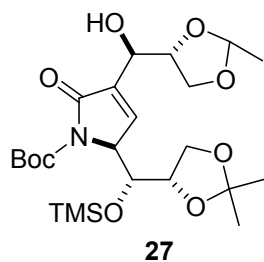
Compound 25: a glassy solid, $[\alpha]_D^{20} -101.7$ (c 1.4, CHCl₃); ¹H and ¹³C NMR: see enantiomer **5**. Anal. Calcd for C₂₄H₄₁NO₉Si: C, 55.90; H, 8.01; N, 2.72. Found: C, 55.83; H, 7.92; N, 2.88.



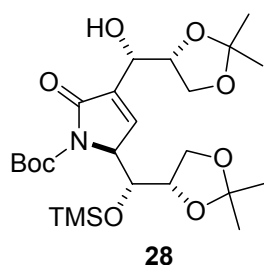
Compound 26: a glassy solid, ¹H and ¹³C NMR: see enantiomer **6**. Anal. Calcd for C₂₄H₄₁NO₉Si: C, 55.90; H, 8.01; N, 2.72. Found: C, 56.01; H, 8.12; N, 2.64.

(1'*R*,1'''*R*,4''*R*,4'*VS*,5*S*)-3-[(2,2-Dimethyl-[1,3]dioxolan-4-yl)hydroxymethyl]-5-[(2,2-dimethyl-[1,3]dioxolan-4-yl)(trimethylsilyloxy)methyl]-2-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylic Acid *tert*-Butyl Ester (27) and (1'*S*,1'''*R*,4''*R*,4'*V**S*,5*S*)-3-[(2,2-Dimethyl-[1,3]dioxolan-4-yl)hydroxymethyl]-5-[(2,2-dimethyl-[1,3]dioxolan-4-yl)(trimethylsilyloxy)methyl]-2-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylic Acid *tert*-Butyl Ester (28).** The title compounds were prepared from unsaturated lactam **24** (360 mg, 0.93 mmol) and D-glyceraldehyde (*R*)-**2** (242 mg, 1.86 mmol)

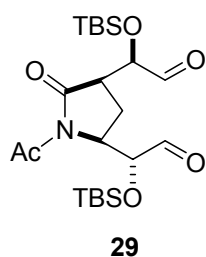
according to the typical procedure described for **5** and **6**. Flash chromatographic purification (EtOAc/hexanes 35:65) of the residue furnished 67 mg of compound **27** (14%) and 302 mg of **28** (63%).



Compound 27: a colorless oil, $[\alpha]_D^{20} -67.9$ (c 1.6, CHCl_3); ^1H NMR: see enantiomeric counterpart **15**. Anal. Calcd for $\text{C}_{24}\text{H}_{41}\text{NO}_9\text{Si}$: C, 55.90; H, 8.01; N, 2.72. Found: C, 55.76; H, 8.13; N, 2.78.

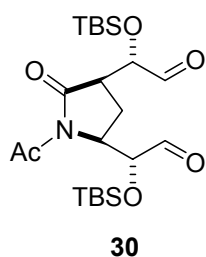


Compound 28: a colorless oil, $[\alpha]_D^{20} -76.2$ (c 0.9, CHCl_3); ^1H and ^{13}C NMR: see enantiomeric counterpart **14**. Anal. Calcd for $\text{C}_{24}\text{H}_{41}\text{NO}_9\text{Si}$: C, 55.90; H, 8.01; N, 2.72. Found: C, 55.99; H, 7.89; N, 2.84.



(2*R*,2'*R*,2''*S*,4''*R*)-2,2'-(1-Acetyl-5-oxopyrrolidine-2,4-diyl)bis(tert-

butyldimethylsilanyloxyacetaldehyde) (29). The title compound was prepared from lactam **25** (297 mg, 0.58 mmol) in five steps, according to the typical procedures described for **11**. Flash chromatographic purification (EtOAc/hexanes 6:4) of the residue afforded aldehyde **29** (180 mg, 66%) as a colorless oil: $[\alpha]_D^{20} +54.3$ (c 0.6, CHCl_3); ^1H and ^{13}C NMR: see enantiomer **11**. Anal. Calcd for $\text{C}_{22}\text{H}_{41}\text{NO}_6\text{Si}_2$: C, 56.01; H, 8.76; N, 2.97. Found: C, 56.10; H, 8.87; N, 2.82.



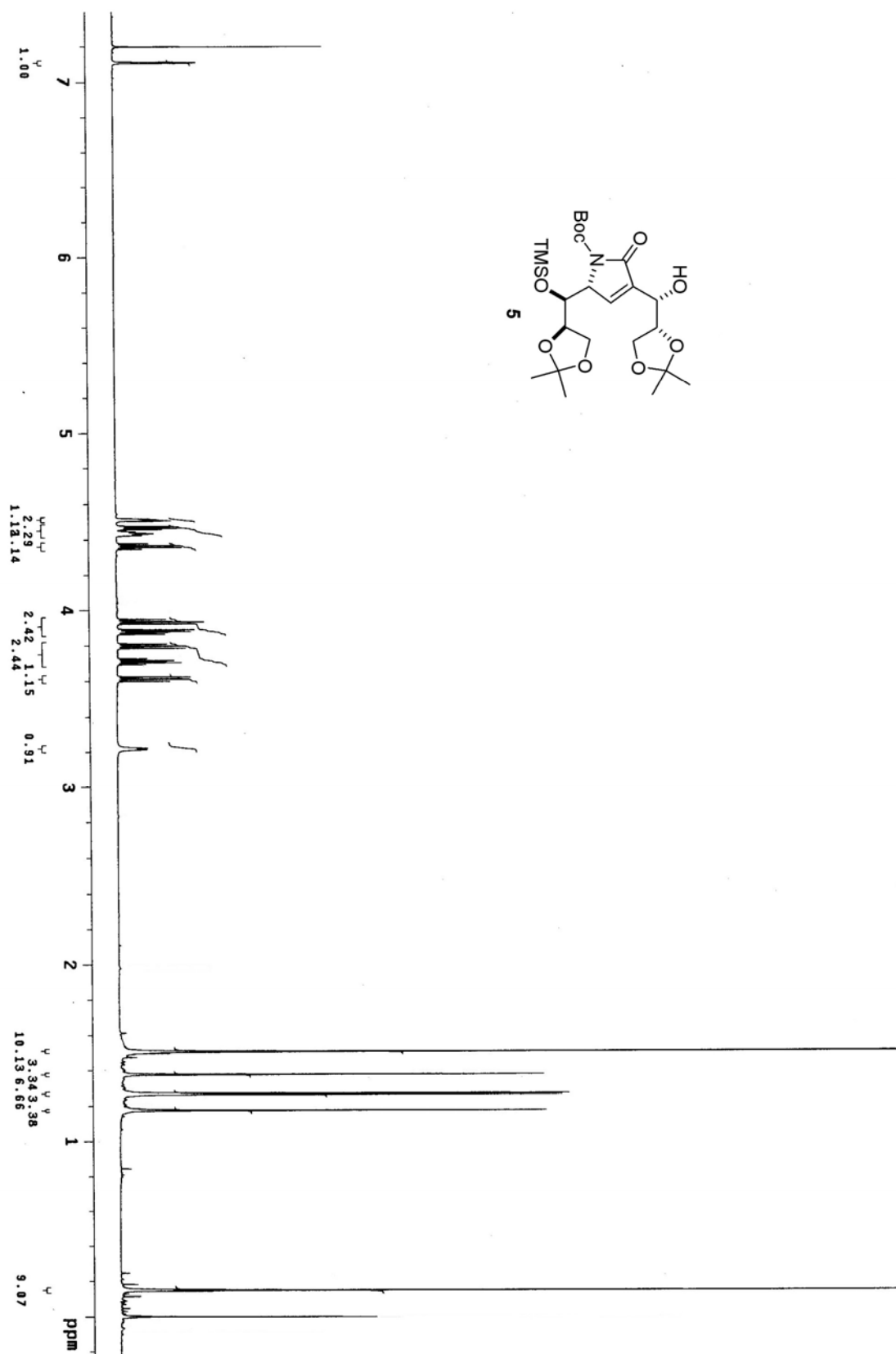
(2*R*,2'*S*,2''*S*,4''*R*)-2,2'-(1-Acetyl-5-oxopyrrolidine-2,4-diyl)bis(tert-
butyldimethylsilanyloxyacetaldehyde) (30). The title compound was prepared from

lactam **28** (302 mg, 0.59 mmol) in five steps, according to the typical procedures described for **11**. Flash chromatographic purification (EtOAc/hexanes 6:4) of the residue afforded aldehyde **30** (180 mg, 65%) as a colorless oil: $[\alpha]_D^{20} -50.9$ (c 1.0, CHCl_3); ^1H and ^{13}C NMR: see enantiomer **19**. Anal. Calcd for $\text{C}_{22}\text{H}_{41}\text{NO}_6\text{Si}_2$: C, 56.01; H, 8.76; N, 2.97. Found: C, 56.10; H, 8.87; N, 2.82.

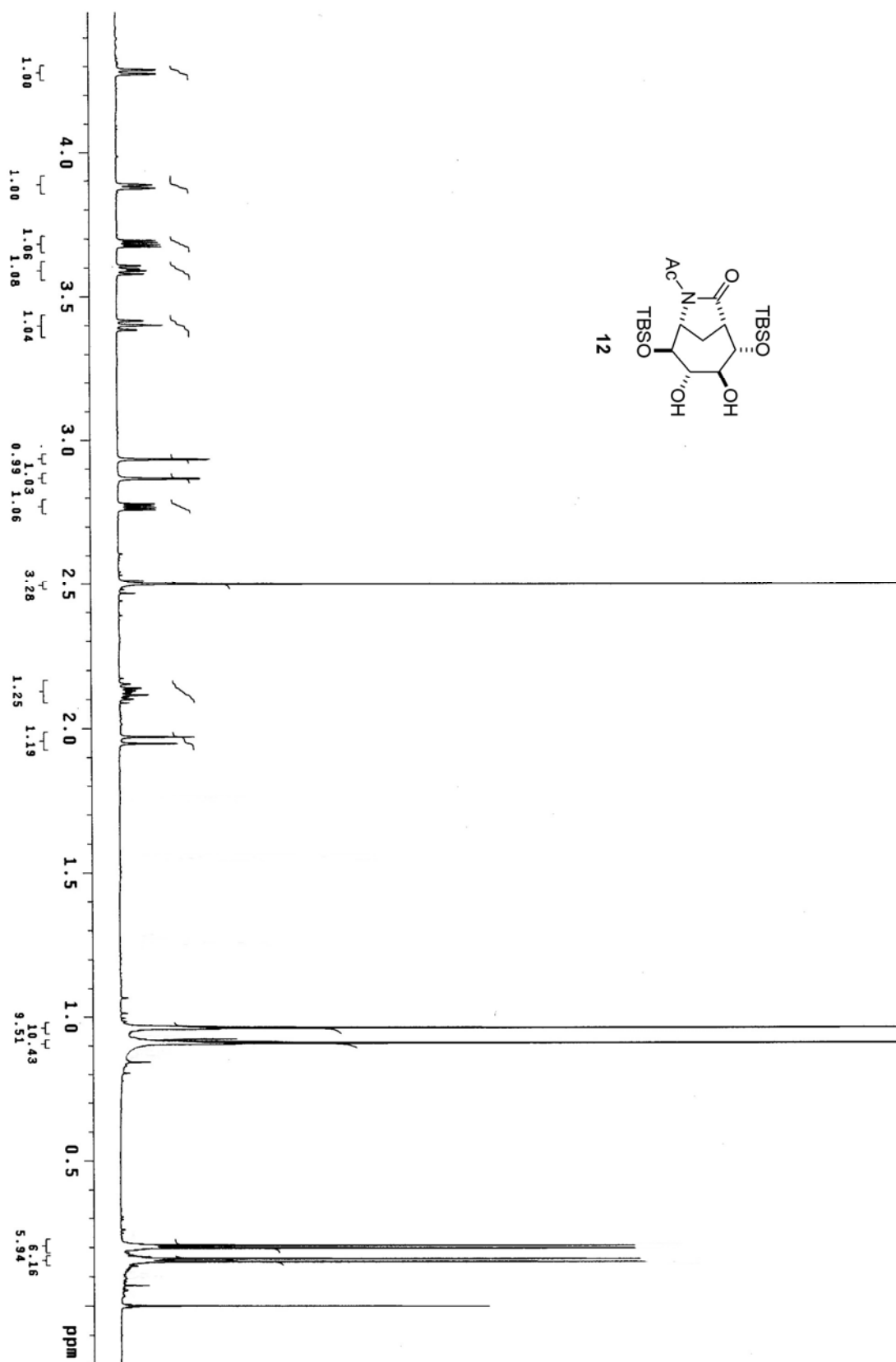
References

- (1) Rassa, G.; Zanardi, F.; Battistini, L.; Gaetani, E.; Casiraghi, G. *J. Med. Chem.* **1997**, *40*, 168-180.
- (2) Zanardi, F.; Battistini, L.; Rassa, G.; Auzzas, L.; Pinna, L.; Marzocchi, L.; Acquotti, D.; Casiraghi, G. *J. Org. Chem.* **2000**, *65*, 2048-2064.
- (3) Hubschwerlen, C.; Specklin, J.-L.; Higelin, J. *Org. Synth.* **1995**, *72*, 1-5.
- (4) The experimental procedure and spectroscopic data for compound **3** have been reported before (see Ref. 10 in the text). However, they are included again here since the original experimental procedure has been optimized.

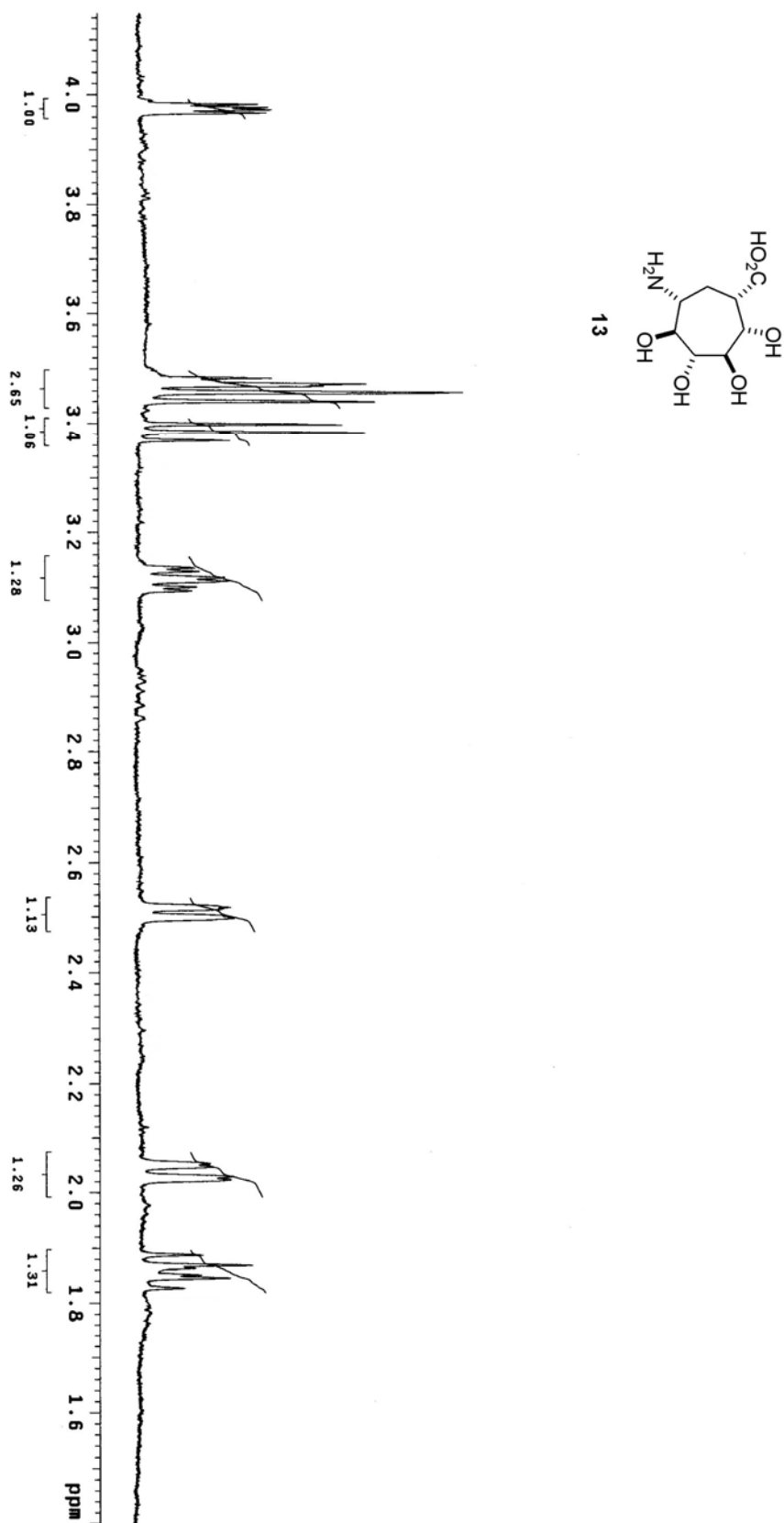
^1H NMR spectrum (600 MHz, CDCl_3) of lactam **5**



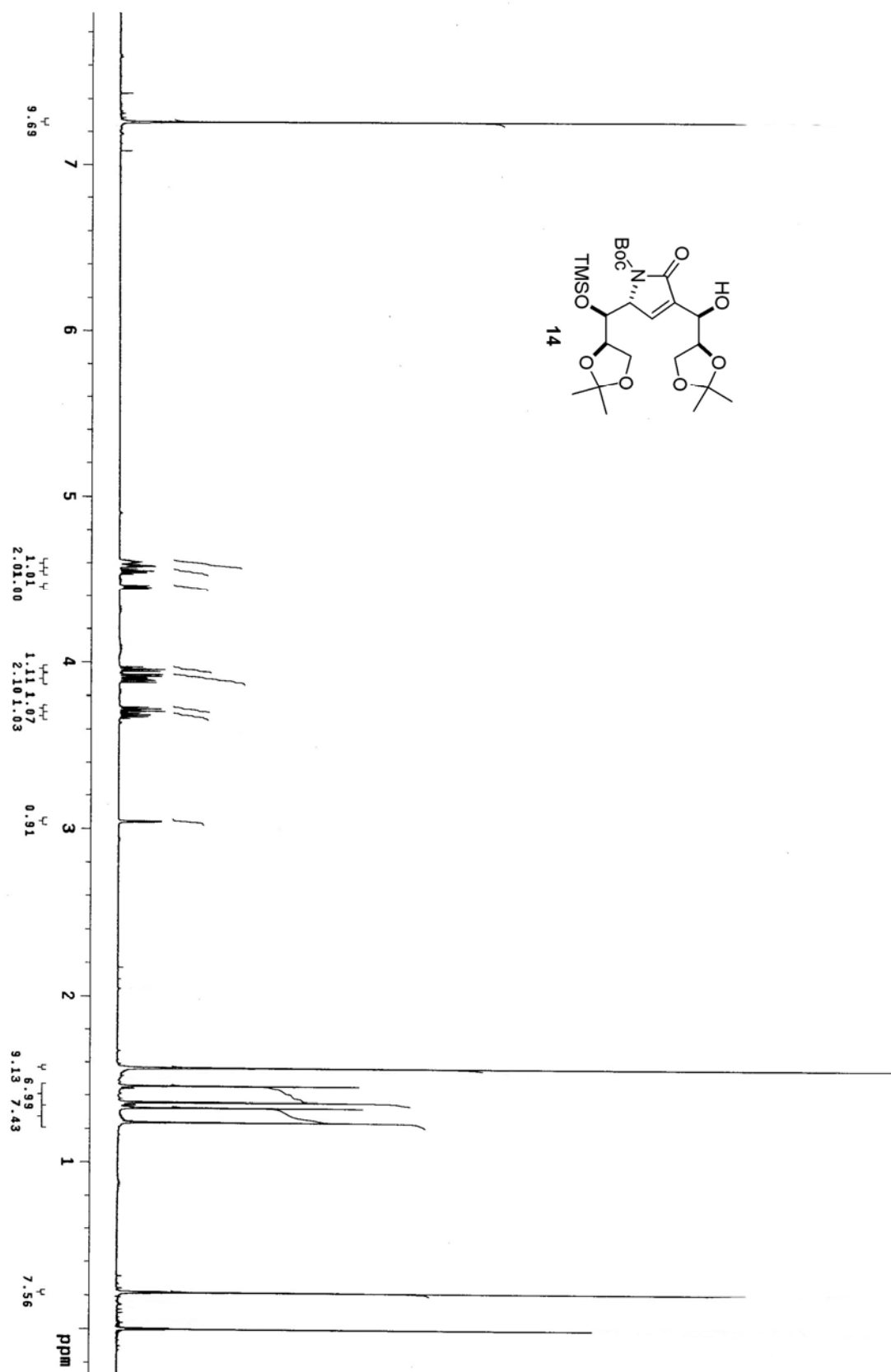
^1H NMR spectrum (600 MHz, CDCl_3) of bicycle **12**



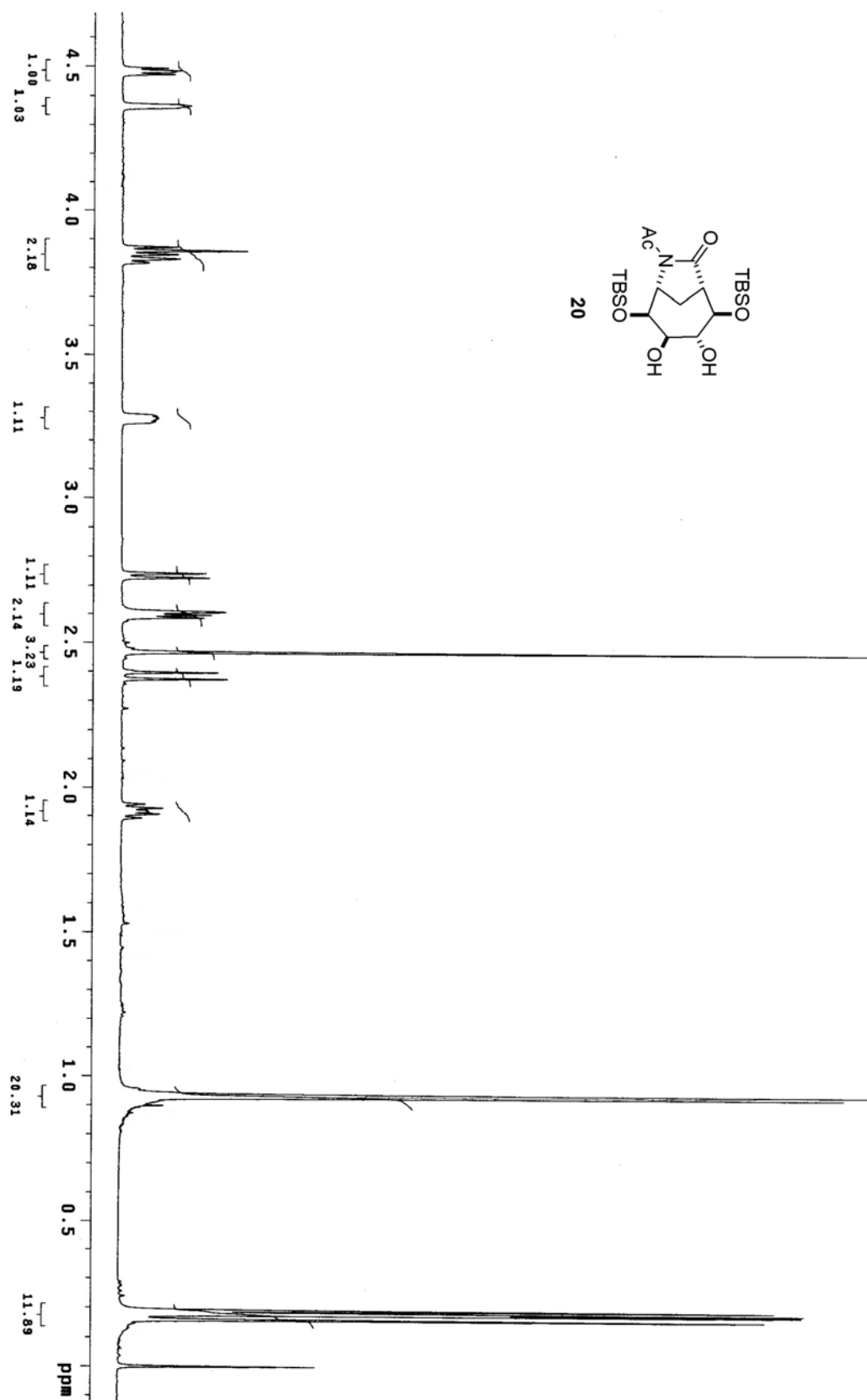
^1H NMR spectrum (600 MHz, D_2O) of amino acid **13**



^1H NMR spectrum (600 MHz, CDCl_3) of lactam **14**



^1H NMR spectrum (600 MHz, CDCl_3) of bicycle **20**



^1H NMR spectrum (600 MHz, D_2O) of amino acid **21**

