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Chivosazole A – Elucidation of the absolute configuration

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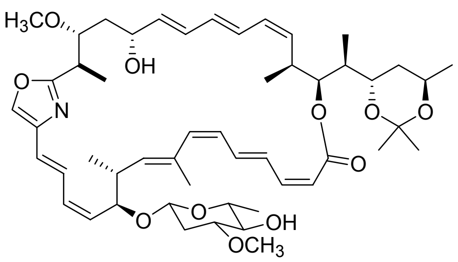
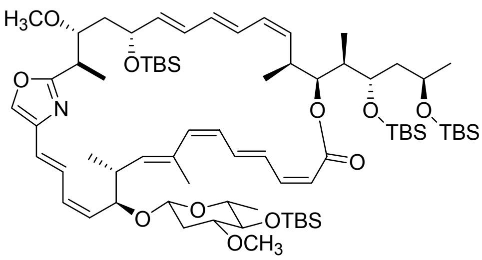
Acetonide 8



To a solution of chivosazole A (50 mg, 0.06 mmol) in acetone (5 mL) *p*-TsOH (2 mg, 0.01 mmol) was added. The solution was stirred for 4 h at r.t. Then Et_3N (3 mL) was added and the solvent was removed *in vacuo*. Flash column chromatography delivered acetonide **8** (17 mg, 0.02 mmol, 34%). R_f = 0.31 (CH_2Cl_2/MeOH 50:1); $[\alpha]^{23}_D$ = -13.5 (*c* 1.60, $CHCl_3$); ^{1}H-NMR (400 MHz, MeOD) δ 7.75 (s, 1H), 7.19 (dd, *J* = 15.2, 11.8 Hz, 1H), 7.08 (dd, *J* = 14.8, 11.5 Hz, 1H), 6.86 (dd, *J* = 14.9, 10.8 Hz, 1H), 6.54-6.13 (m, 6H), 5.95-5.84 (m, 3H), 5.77 (dd, *J* = 15.2, 3.6 Hz, 1H), 5.56 (t, *J* = 10.3 Hz, 1H), 5.41 (d, *J* = 11.5 Hz, 1H), 5.24-5.14 (m, 3H), 4.78 (dd, *J* = 9.3, 5.9 Hz, 1H), 4.43 (d, *J* = 7.8 Hz, 1H), 4.34 (bd, J = 9.7 Hz, 1H), 3.95-3.93 (m, 2H), 3.60 (s, 3H), 3.57 (s, 3H), 3.49 (s, 3H), 3.42-3.36 (m, 2H), 3.24-3.21 (m, 1H), 3.13-3.08 (m, 1H), 3.03-3.00 (m, 3H), 2.90 (t, *J* = 8.0 Hz, 3H), 1.89 (s, 3H), 1.73-1.66 (m, 2H), 1.60-1.55 (m, 1H), 1.37 (d, *J* = 7.2 Hz, 3H), 1.29 (s, 3H), 1.20-1.14 (m, 11H), 1.08

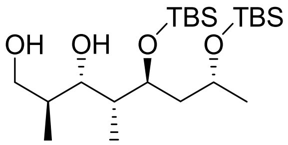
(d, J = 6.8 Hz, 3H), 1.01-0.97 (m, 6H); ^{13}C-NMR (100 MHz, MeOD) δ 167.9, 167.4, 144.6, 140.1, 139.5, 139.2, 138.5, 137.7, 135.8, 135.5, 134.4, 134.2, 131.9, 130.9, 130.6, 130.1, 129.3, 129.0, 128.5, 127.3, 122.4, 118.4, 103.3, 101.8, 87.5, 85.4, 80.1, 79.0, 76.7, 76.3, 73.1, 68.5, 68.1, 64.1, 61.2, 61.0, 58.2, 41.0, 40.4, 39.7, 37.9, 36.6, 35.7, 25.2, 24.8, 21.8, 18.0, 17.6, 17.2, 14.8, 11.0, 8.9; ESI-HRMS [M+Na]$^+$ Calcd. for $C_{52}H_{75}NO_{12}Na$: 928.5187, Found: 928.5176

TBS protected chivosazole 1a



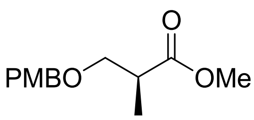
To a solution of chivosazole A (100 mg, 0.12 mmol) in CH_2Cl_2 (5 mL) 2,6-lutidine (201 μL, 1.16 mmol) and TBSOTf (265 μL, 1.16 mmol) were added successively. The solution was stirred for 4 h at r.t. and then sat. aq. $NaHCO_3$ (2 mL) was added. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2x10 mL). The combined organic layers were washed with sat. aq. NH_4Cl (2 x 20 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and flash column chromatography delivered the TBS protected chivosazole **1a** (35 mg, 26 μmol, 23%). R_f = 0.30 (EtOAc/hexanes 1:8) ; $[\alpha]^{23}_D$ = -8.5 (c 1.10, $CHCl_3$); ^{1}H-NMR (400 MHz, MeOD) δ 7.71 (s, 1H), 7.16 (dd, J = 15.1, 11.9 Hz, 1H), 7.03 (dd, J = 14.9, 11.5 Hz, 1H), 6.86 (dd, J = 14.9, 9.7 Hz, 1H), 6.50-6.10 (m, 6H), 5.96-5.81 (m, 3H), 5.74 (dd, J = 15.1, 5.4 Hz, 1H), 5.55 (t, J = 10.3 Hz, 1H), 5.39 (d, J = 11.6 Hz, 1H), 5.17-5.04 (m, 3H), 4.83-4.79 (m, 1H), 4.47 (d, J = 7.7 Hz, 1H), 4.40 (bd, J = 5.1 Hz, 1H), 3.97-3.91 (m, 2H), 3.81-3.77 (m, 1H), 3.60 (s, 3H), 3.54 (s, 3H), 3.45 (s, 3H), 3.28-3.24 (m, 1H), 3.13-2.91 (m, 6H), 1.98-1.95 (m, 1H), 1.92 (s, 3H), 1.74-1.67 (m, 1H), 1.65-1.58 (m, 1H), 1.51-1.47 (m, 1H), 1.33 (d, J = 7.0 Hz, 3H), 1.16 (d, J = 6.3 Hz, 3H), 1.13 (d, J = 6.0 Hz, 3H), 1.10-1.07 (m, 6H) 1.04 (d, J = 6.5 Hz, 3H), 0.96 (s, 9H), 0.90 (s, 9H), 0.89 (s, 9H), 0.88 (s, 9H), 0.12-0.03 (m, 24H); ^{13}C-NMR (100 MHz, MeOD) δ 166.3, 165.7, 142.7, 138.9, 138.0, 137.7, 137.6, 135.5, 134.4, 134.0, 133.7, 133.4, 130.3, 130.0, 129.9, 129.1, 128.5, 126.8, 126.6, 120.9, 118.4, 102.3, 86.7, 85.2, 78.1, 77.5, 77.4, 76.3, 76.2, 73.7, 72.6, 67.9, 66.7, 61.2, 60.5, 56.7, 44.8, 40.6, 39.6, 36.6, 35.9, 34.3, 29.9, 26.2, 26.1, 25.0, 18.4, 18.3, 18.3, 18.2, 18.2, 18.1, 16.9, 14.2, 9.7, 9.7, -3.7, -3.8, -3.9, -3.9, -3.9, -4.1, -4.5, -4.9; ESI-HRMS [M-Na]$^+$ Calcd. for $C_{73}H_{127}NO_{12}Si_4Na$: 1344.8333, Found: 1344.8289.

Isolated fragment 9



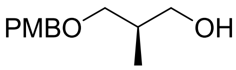
Ozone was passed through a solution of compound 1a (60 mg, 0.05 mmol) in CH_2Cl_2 (5 mL) at -78 °C until the solution turned slightly blue. Then Oxygen was passed through until the colour disappeared again. Next $NaBH_4$ (10 mg, 0.26 mmol) was added at -78 °C and the solution was warmed to r.t. After stirring the solution for 16 h at r.t. aq. phosphate solution (pH7, 0.1 M, 3 mL) was added. The layers were separated and the organic layer was washed with sat. aq. NaCl (2x5 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and flash column chromatography delivered the fragment **9** (10 mg, 23 µmol, 46%). R_f = 0.22 (EtOAc/hexanes 1:5); $[\alpha]^{23}_D$ = +5.1 (*c* 0.39, $CHCl_3$); CD (0.3 mM, CH_3CN) nm (mdeg) 196.5 (+4.9), 209.5 (-3.3), 226.5 (-3.0), 250.0 (-0.7); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.96 (d, *J* = 9.7 Hz, 1H), 3.85-3.77 (m, 2H), 3.70 (dd, *J* = 10.9, 8.4 Hz, 1H), 3.61 (dd, *J* = 10.9, 3.3 Hz, 1H), 2.04-1.97 (m, 1H), 1.91-1.84 (m, 1H), 1.67-1.61 (m, 2H), 1.13 (d, *J* = 6.0 Hz, 3H), 1.03 (d, *J* =7.0 Hz, 3H), 0.9 (s, 18H), 0.73 (d, *J* = 6.9 Hz, 3H), 0.11-0.06 (m, 12H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 77.8, 77.4, 69.5, 66.6, 45.5, 37.5, 37.0, 26.0, 25.9, 24.0, 18.2. 18.0, 13.5, 11.6, -4.1, -4.1, -4.3, -4.7; ESI-HRMS [M+Na$^+$] Calcd. for $C_{22}H_{50}O_4Na$: 457.3145, Found: 457.3156.

Ester 13a



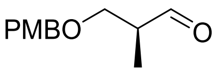
Camphersulfonic acid (1.8 g, 6.0 mmol) was added to a solution of (+)-methyl L-β-hydoxy-isobutyrate (8.5 mL, 77 mmol) and *p*-methoxybenzyl-trichloroacetimidate (28 mL, 32.5 g, 115 mmol) in CH_2Cl_2 (150 mL). After stirring for 16 h sat. aq. $NaHCO_3$ (100 mL) was added and the layers were separated. The organic layer was washed with sat. aq. NaCl (100 mL) and dried over $MgSO_4$. Filtration, removal of the solvent *in vacuo* and flash column chromatography (EtOAc/hexanes 1:4) delivered the ester **13a** (16.7 g, 70 mmol, 91%) as a yellow oil. R_f= 0.45 (EtOAc/hexanes 1:1); $[\alpha]^{23}_D$ = +7.4 (*c* 1.04, $CHCl_3$) ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.5 Hz, 2 H), 6.88 (d, *J* = 8.5 Hz, 2 H), 4.46 (s, 2 H), 3.79 (s, 3 H), 3.70 (s, 3 H), 3.65 (dd, *J* = 9.1, 7.3 Hz, 1 H), 3.48 (dd, *J* = 9.1, 6.0 Hz, 1 H), 2.83-2.74 (m, 1 H), 1.19 (d, *J* = 7.2 Hz, 3 H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 175.3, 159.2, 130.2, 129.2, 113.7, 72.7, 71.6, 55.2, 51.6, 40.2, 14.0; ESI-HRMS [$M+Na^+$] Calcd. for $C_{13}H_{18}O_4Na$: 261.1103, Found: 261.1108.

Alcohol 13b



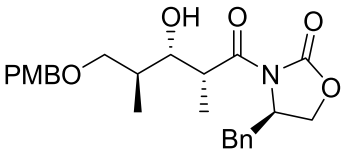
A solution of DIBAL-H in toluene (49 mL, 74 mmol) was added at -78 °C drop wise during 30 min to the ester 13a (7.0 g, 29 mmol) dissolved in CH_2Cl_2 (70 mL). The solution was stirred at -78 °C for 30 min, diluted with MTBE (70 mL) and warmed to r.t. After 60 min water (10 mL) was added and the solution was stirred until a gel formed. Following addition of aq. 2 M NaOH (15 mL) and water (8 mL), the gel dissolved and a white solid precipitated. The solution was dried over $MgSO_4$ and the solid was filtered. The solvent was removed *in vacuo* and flash column chromatography (EtOAc/hexanes 1:2) provided alcohol **13b** (4.6 g, 22 mmol, 76%). R_f = 0.33 (EtOAc/hexanes 1:1); $[\alpha]^{23}_D$ = +15.7 (*c* 1.38, $CHCl_3$); ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.4 Hz, 2 H), 6.87 (d, *J* = 8.4 Hz, 2 H), 4.42 (s, 2 H), 3.77 (s, 3 H), 3.56 (d, *J* = 5.9 Hz, 2 H), 3.49-3.34 (m, 2 H), 3.06 (bs, 1 H), 2.09-1.93 (m, 1 H), 0.88 (d, *J* = 6.7 Hz, 3 H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 159.2, 130.2, 129.1, 113.7, 74.4, 72.9, 66.9, 55.1, 35.7, 13.6; ESI-HRMS [$M+CH_3CN+Na^+$] Calcd. for $C_{14}H_{21}NO_3Na$: 274.1419, Found: 274.1422.

Aldehyd 13c



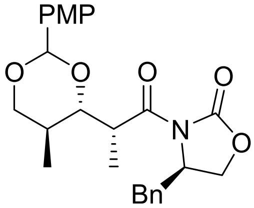
DMSO (6.1 mL, 85.6 mmol) was added to a solution of oxalyl chloride (4.9 mL, 57.1 mmol) in CH_2Cl_2 (100 mL) at -78 °C. The solution was stirred for 15 min and subsequently treated with a solution of the alcohol **13b** (6.0 g, 28.5 mmol) in CH_2Cl_2 (35 mL). After further 15 min the solution was warmed to -45 °C and stirred 60 min at this temperature. Then NEt_3 (19.8 mL, 14.4 g, 142.7 mmol) was added to the solution and warmed to 0 °C and stirred for 15 min at this temperature. The reaction mixture was poured into a mixture of MTBE and sat. aq. NH_4Cl (1:1, 150 mL). The layers were separated and the aqueous layer was extracted with MTBE (2x50 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$, dried over $MgSO_4$ and filtered. The solvents were removed *in vacuo* and flash column chromatography (EtOAc/hexanes 1:4) provided the product (5.6 g, 27.1 mmol, 95%). R_f= 0.58 (EtOAc/hexanes 1:1); $[\alpha]^{23}_D$ = +26.7 (*c* 1.17, $CHCl_3$); ^{1}H-NMR (200 MHz, $CDCl_3$) δ 9.70 (d, *J* = 1.5 Hz, 1H), 7.23 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 4.44 (s, 2H), 7.23 (s, 3H), 3.63 (d, J = 3.1 Hz, 1H), 3.60 (d, J = 2.0 Hz, 1H), 2.72-2.54 (m, 1H), 1.25 (d, J = 7.2 Hz, 3H) ; ^{13}C-NMR (50 MHz, $CDCl_3$) δ 203.9, 159.4, 130.1, 129.3, 113.9, 73.0, 69.9, 55.3, 46.8, 10.8; ESI-HRMS [M+Na$^+$] Calcd. for $C_{12}H_{16}O_3Na$: 231.0997, Found: 231.0997.

Aldol Product 14



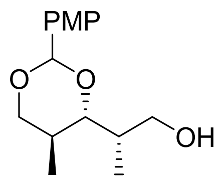
Bu_2BOTf solution in CH_2Cl_2 (15.0 mL) and NEt_3 (2.7 mL, 19.0 mmol) were added at -78 °C to a solution of 4-*R*-Benzyl-3-propionyl-oxazolidin-2-one (3.2 g, 13.6 mmol) in CH_2Cl_2 (30 mL). The mixture was stirred for 45 min at 0 °C and cooled to -78 °C. Then aldehyde **13c** (3.4 g, 16.3 mmol) dissolved in CH_2Cl_2 (15 mL) was added to the solution. After stirring at -78 °C the reaction mixture was warmed to 0 °C and stirred at this temperature for 60 min. Aq. phosphate solution (pH7, 0.1 M, 17 mL), MeOH (50 mL) and MeOH/35%-H_2O_2 (50 mL, 2:1) were added successively to the solution which was stirred for 60 min at 0 °C. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with sat. aq. NaCl (100 mL) and dried over $MgSO_4$. After filtration the solvent was removed *in vacuo*. Flash column chromatography (EtOAc/hexanes 1:2) delivered the product (5.1 g, 12.0 mmol, 85%) as a white oil. R_f = 0.46 (EtOAc/hexanes 1:1); $[\alpha]^{23}_D$ = -23.8 (*c* 0.94, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.37-7.24 (m, 7 H), 6.90 (d, J = 8.9 Hz, 2 H), 4.74-4.68 (m, 1 H), 4.48 (s, 2 H), 4.20-4.17 (m, 2 H), 4.02-3.96 (m, 1 H), 3.93-3.87 (m, 2 H), 3.83 (s, 3 H), 3.63-3.55 (m, 2 H), 3.34 (dd, J = 13.3, 2.7 Hz, 1 H), 2.05-1.98 (m, 1 H), 1.30 (d, J = 6.8 Hz, 3 H), 0.99 (d, J = 7.2 Hz, 3 H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 176.2, 159.3, 153.2, 135.4, 129.6, 129.5, 129.4, 129.0, 127.4, 113.9, 75.5, 74.7, 73.2, 66.2, 55.6, 55.3, 40.7, 37.6, 36.0, 13.6, 9.7; ESI-HRMS [M+Na$^+$] Calcd. for $C_{25}H_{31}NO_6Na$: 464.2049, Found: 464.2047.

Acetal 14a



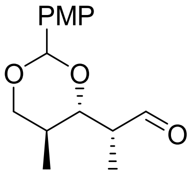
A solution of DDQ (2.7 g, 12.0 mmol) in CH_2Cl_2 (200 mL) was added to molecular sieve (11 g, 4 Å) and cooled to 0 °C. To the cooled suspension a solution of aldol product **14** (4.8 g, 11.0 mmol), in CH_2Cl_2 (20 mL), which was pre-dried over mol sieve (3 g, 4 Å), was added and stirred for 90 min at 0 °C. Subsequently the solution was treated with sat. aq. $NaHCO_3$ and Na_2SO_3 and stirred until the accrued precipitate dissolved again. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (100 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ and sat. aq. NaCl and dried over $MgSO_4$. After filtration the solvent was removed *in vacuo*. Flash column chromatography (EtOAc/hexanes 1:2) delivered the acetal **14a** (3.5 g, 8.0 mmol, 73%). R_f = 0.59 (EtOAc/hexanes 1:1); $[\alpha]^{23}_D$ = +25.2 (*c* 1.32, $CHCl_3$); ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.8 Hz, 2 H), 7.37-7.23 (m, 5 H), 6.92 (d, *J* = 8.8 Hz, 2 H), 5.48 (s, 1 H), 4.72-4.61 (m, 1 H), 4.22-4.10 (m, 4 H), 3.92 (dd, *J* = 9.9, 2.9 Hz, 1 H), 3.83 (s, 3 H), 3.58 (t, *J* = 11.1 Hz, 1 H), 3.37 (dd, *J* = 13.3, 3.1 Hz, 1 H), 2.82 (dd, *J* = 13.2, 9.5 Hz, 1 H), 2.19-2.03 (m, 1 H), 1.38 (d, *J* = 6.9 Hz, 3 H), 0.90 (d, *J* = 6.8 Hz, 3 H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 174.0, 159.9, 153.4, 135.4, 131.1, 129.5, 129.0, 127.3, 113.6, 100.7, 82.1, 72.8, 66.3, 55.9, 55.3, 40.2, 37.7, 31.5, 11.9, 10.1; ESI-HRMS $[M+Na^+]$ Calcd. for $C_{25}H_{29}NO_6Na$: 462.1895, Found: 462.1893.

Alcohol 14b



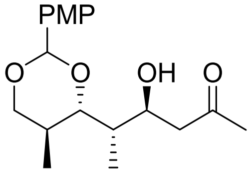
At 0 °C ethanol (124 µL, 2.1 mmol) and a 2 M solution of $LiBH_4$ in THF (1.1 mL, 2.1 mmol) were added to a solution of acetal **14a** (851 mg, 1.9 mmol) in THF (30 mL) and subsequently warmed to r.t.. The solution was stirred for 2 h at r.t. and treated again with ethanol (124 µL, 2.1 mmol) and a 2 M solution of $LiBH_4$ in THF (1.1 mL, 2.1 mmol). After further 2 h the solution was treated with aq. 2 M NaOH (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2x30 mL). The combined organic layers were washed with sat. aq. NaCl, dried over $MgSO_4$ and filtered. The solvents were removed *in vacuo* and flash column chromatography provided the product (484 mg, 1.8 mmol, 96%). R_f = 0.28 (EtOAc/hexanes 1:1); $[\alpha]^{23}_D$ = +40.6 (*c* 1.17, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.7 Hz, 2 H), 6.87 (d, *J* = 8.8 Hz, 2 H), 5.47 (s, 1 H), 4.10 (dd, *J* = 11.2, 4.7 Hz, 1 H), 3.79 (s, 3 H), 3.71-3.68 (m, 3 H), 3.51 (t, *J* = 11.1 Hz, 1 H), 2.12-2.05 (m, 1 H), 1.99-1.94 (m, 1 H), 1.03 (d, *J* = 7.0 Hz, 3 H), 0.76 (d, *J* = 6.8 Hz, 3 H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 160.0, 131.3, 127.4, 113.7, 101.2, 84.7, 73.3, 66.7, 55.4, 35.8, 30.5, 12.0, 9.8; ESI-HRMS $[M+Na^+]$ Calcd. for $C_{15}H_{22}O_4Na$: 289.1416, Found: 289.1425.

Aldehyde 15



DMSO (1.7 mL, 24.3 mmol) was added to a solution of oxalyl chloride (1.4 mL, 16.2 mmol) in CH_2Cl_2 (30 mL) at -78 °C. The solution was stirred for 15 min and subsequently treated with a solution of the alcohol **14b** (2.2 g, 8.1 mmol) in CH_2Cl_2 (10 mL). After further 15 min the solution was warmed to -45 °C and stirred 60 min at this temperature. Then NEt_3 (5.7 mL, 40.5 mmol) was added to the solution and warmed to 0 °C and stirred for 15 min at this temperature. The reaction mixture was poured into a mixture of MTBE and sat. aq. NH_4Cl (1:1, 50 mL). The layers were separated and the aqueous layer was extracted with MTBE. The combined organic layers were washed with sat. aq. $NaHCO_3$, dried over $MgSO_4$ and filtered. The solvents were removed *in vacuo* and flash column chromatography (EtOAc/hexanes 1:4) provided the product (2.1 mg, 8.0 mmol, 99%). R_f = 0.58 (EtOAc/hexanes 1:1); $[\alpha]^{23}_D$ = +22.9 (*c* 1.03, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.76 (d, *J* = 0.5 Hz, 1H), 7.34 (d, *J* = 8.5 Hz, 2 H), 6.86 (d, *J* = 8.9 Hz, 2 H), 5.49 (s, 1 H), 4.15 (dd, *J* = 11.4, 4.8 Hz, 1 H), 4.07 (dd, *J* = 10.2, 2.6 Hz, 1 H), 3.79 (s, 3 H), 3.6 (t, *J* = 11.1 Hz, 1 H), 2.58 (dq, *J* = 7.0, 2.5 Hz, 1 H), 2.20-2.03 (m, 1 H), 1.25 (d, *J* = 7.2 Hz, 3 H), 0.82 (d, *J* = 6.7 Hz, 3 H) ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 204.1, 160.0, 127.4, 113.58, 101.0, 81.7, 81.6, 72.9, 55.3, 47.5, 30.4, 12.0, 7.1; ESI-HRMS [M+H$^+$] Calcd. for $C_{15}H_{21}O_4$: 265.1440, Found: 265.1454.

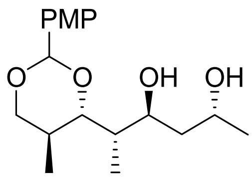
Aldol Product 16



A solution of isopropenyloxy-trimethyl-silane (902 μL, 5.4 mmol) and aldehyde **15** (714 mg, 2.7 mmol) in toluene (15 mL) was treated with bortrifluoride-ethyletherate (342 μL, 0.09 mmol) at -78 °C. After 10 s a saturated solution of sodium carbonate in methanol (5 mL) was added and the mixture was diluted with CH_2Cl_2 (10 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2x10 mL). The combined organic layers were washed with sat. aq. NaCl, dried over $MgSO_4$ and filtered. The solvents were removed *in vacuo*. The product was processed without further purification (745 mg, 2.31 mmol, 86%). R_f

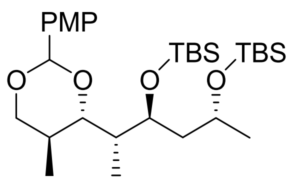
= 0.24 (EtOAc/hexanes 1:1); $[\alpha]^{23}_{D}$ = +20.3 (*c* 1.20, $CHCl_3$) ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.9 Hz, 2 H), 6.86 (d, *J* = 8.5 Hz, 2 H), 5.45 (s, 1 H), 4.08 (dd, *J* = 11.1, 5.3 Hz, 2 H), 3.84 (dd, *J* = 10.2, 1.4 Hz, 1 H), 3.77 (s, 3 H), 3.50 (t, *J* = 11.1 Hz, 1 H), 3.26 (bs, 1 H), 2.74 (dd, *J* = 17.1, 3.1 Hz, 1 H), 2.56 (dd, *J* = 17.1, 9.2 Hz, 1 H), 2.10-2.02 (m, 1 H), 1.87-1.80 (m, 1 H), 0.97 (d, *J* = 7.2 Hz, 3 H), 0.73 (d, *J* = 6.8 Hz, 3 H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 209.9, 159.9, 131.3, 127.3, 113.6, 101.0, 82.1, 73.2, 69.6, 55.3, 48.2, 38.5, 30.9, 30.3, 12.0, 9.7; ESI-HRMS [M+Na$^+$] Calcd. for $C_{18}H_{26}O_5Na$: 345.1678, Found: 345.1675.

Diol 17



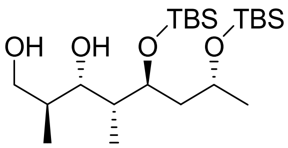
The β-hydroxyketone **16** (2.3 g, 7.0 mmol) was dissolved in acetonitrile (50 mL) and added at -30 °C to a solution of $(AcO)_3BHNMe_4$ (8.9 g, 33.7 mmol) in a mixture of acetonitrile and glacial acetic acid (1:1, 150 mL). The mixture was stirred at -30 °C for 16 h. Then sat. aq. Rochelle salt (100 mL) was added. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2x100 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and filtered. The solvents were removed *in vacuo* and flash column chromatography provided the product (1.3 g, 4.0 mmol, 57%). R_f= 0.36 (EtOAc/hexanes 3:1); $[\alpha]^{23}_{D}$ = +32.1 (*c* 1.03, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.5 Hz, 2 H), 6.86 (d, *J* = 8.5 Hz, 2 H), 5.48 (s, 1 H), 4.09 (dd, *J* = 11.4, 4.6 Hz, 1 H), 3.95-3.87 (m, 2 H), 3.78 (s, 3 H), 3.51 (t, *J* = 11.1 Hz, 1 H), 3.10 (bs, 2 H), 2.13-2.05 (m, 1 H), 1.83-1.76 (m, 1 H), 1.72-1.57 (m, 2 H), 1.22 (d, *J* = 6.5 Hz, 3 H), 1.03 (d, *J* = 6.8 Hz, 3 H), 0.73 (d, *J* = 6.8 Hz, 3 H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 160.0, 131.1, 127.4, 113.7, 101.1, 82.8, 73.3, 71.5, 65.4, 55.4, 42.9, 38.5, 30.4, 23.8, 12.0, 10.9; ESI-HRMS [M+CH_3CN+Na$^+$] Calcd. for $C_{20}H_{31}NO_5Na$: 388.2100, Found: 388.2090.

Acetal 17a



Diol **17** (300 mg, 0.93 mmol) and 2,6-lutidine (542 µL, 4.7 mmol) were dissolved in CH_2Cl_2 (15 mL). Then the solution was treated with TBSOTf (471 µL , 2.1 mmol) at 0 °C to and stirred at r.t. for 16 h. Sat. aq. $NaHCO_3$ (10 mL) was added to the solution. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2x20 mL). The combined organic layers were washed with sat. aq. NH_4Cl (1x50 mL) and sat. aq. NaCl (1x50 mL), dried over $MgSO_4$ and filtered. The solvents were removed *in vacuo* and flash column chromatography provided the product (370 mg, 0.67 mmol, 72%). R_f = 0.32 (EtOAc/hexanes 1:9); $[\alpha]^{23}_D$ = +11.4 (*c* 0.96, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.7 Hz, 2 H), 6.86 (d, *J* = 8.8 Hz, 2 H), 5.41 (s, 1 H), 4.11 (dd, *J* = 11.0, 4.7 Hz, 1 H), 3.98-3.91 (m, 2 H), 3.80 (s, 3 H), 3.58 (dd, *J* = 10.0, 0.7 Hz, 1 H), 3.48 (dd, *J* = 11.2, 11.2 Hz, 1 H), 2.05-1.97 (m, 1 H), 1.92 (ddd, *J* = 14.4, 9.0 , 2.1 Hz, 1 H), 1.88-1.84 (m, 1 H), 1.42 (ddd, *J* = 14.3, 7.9, 3.0, 1 H), 1.15 (d, *J* = 5.9 Hz, 3 H), 0.95 (d, *J* = 7.2 Hz, 3 H), 0.89 (s, 9 H), 0.85 (s, 9 H), 0.74 (d, *J* = 6.8 Hz, 3 H), 0.04 (s, 12 H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 159.8, 131.7, 127.5, 113.5, 100.7, 83.5, 73.4, 73.4, 66.8, 55.4, 45.1, 40.6, 30.7, 26.2, 26.1, 25.3, 18.3, 18.2, 12.5, 7.9, -3.2, -3.8, -4.0, -4.2; ESI-HRMS [M+Na^+] Calcd. for $C_{30}H_{56}O_5NaSi_2$: 575.3564, Found: 575.3577.

Synthesized fragment 9



$Pd(OH)_2$/C (2 mg) was added to a solution of the acetale **17a** (5 mg, 9 nmol) in *i*-PrOH (1 mL). The suspension was stirred for 16 h under a H_2 atmosphere and was then filtered through a plug of celite. The solvent was removed *in vacuo* and flash column chromatography delivered fragment **9** (2.9 mg, 7 nmol, 74 %). R_f = 0.63 (EtOAc/hexanes 1:1); $[\alpha]^{23}_D$ = +8.3 (*c* 0.29, $CHCl_3$); CD (0.3 mM, CH_3CN) nm (mdeg) 195.0 (+3.8), 209.0 (-3.6), 226.0 (-3.1), 253.0 (-0.6); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.96 (dd, *J* = 8.6, 1.0 Hz, 1 H), 3.83 (ddd, *J* = 8.9, 4.1, 1.5 Hz, 1 H), 3.79 (dd, *J* = 12.6, 6.4 Hz, 1 H), 3.69 (dd, *J* = 10.4, 8.4 Hz, 1 H), 3.60 (dd, *J* = 10.8, 2.9 Hz, 1 H), 2.00 (ddd, *J* = 14.2, 8.4, 6.3 Hz, 1 H), 1.92-1.82 (m, 1H), 1.67-1.61 (m, 2H), 1.14 (d, *J* = 6.2 Hz, 3 H), 1.034 (d, *J* = 7.2 Hz, 3 H), 0.89 (s, 9 H), 0.88 (s, 9 H), 0.73 (d, *J* = 6.8 Hz, 3 H), 0.11 (s, 6 H), 0.06 (s, 6 H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 77.8, 77.4, 69.5, 66.6, 45.5, 37.5, 37.0, 26.0, 25.9, 24.0, 18.2. 18.0, 13.5, 11.6, -4.1, -4.1, -4.3, -4.7; ESI-HRMS [M+Na^+] Calcd. for $C_{22}H_{50}O_4Na$: 457.3145, Found: 457.3144.

II. Copies of 1D, 2D NMR and CD spectra

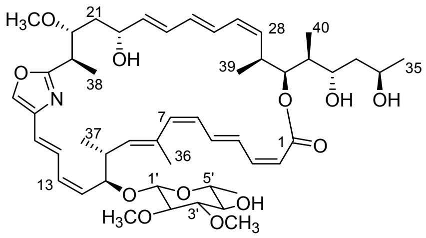
Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker DRX 500 spectrometer equipped with a 5mm $^{1}H/^{13}C/^{15}N$ TCI CryoProbe. The ROESY experiments were acquired with spin-lock times of 50, 100 and 150ms in CD_3OD and $CDCl_3$. To suppress the coherent magnetisation transfer by TOCSY the T-ROESY[i] pulse sequence was used.

Table2. Coupling constants in chivosazole A from ^{1}H-NMR data (500 MHz, CD_3OD) and based on calculations with MacroModel 8.0

	Compound		
	10L-11L-19D-20D-22L-29D-30D		**Chivosazole A**
(Hi,Hj)	Torsion angle [°]	^{3}J(Hi,Hj) (calculated)	observed coupling constant [Hz]
H9-H10	-155.5	9.5	8.8
H10-H11	-61.3	**3.1**	5.6
H11-H12	160.4	9.5	9.4
H19-H20	66.7	2.5	3.8
H20-H21a	-171.8	11.0	10.6
H20-H21b	69.6	1.3	1.7
H21a-H22	67.8	1.5	2.4
H21b-H22	-174.4	11.2	10.4
H22-H23	-49.2	2.9	3.7
H28-H29	-158.9	9.9	10.3
H29-H30	174.2	9.6	10.3
H30-H31	61.1	1.6	1.1

[i] Hwang, T.-L; Shaka, A. J., *J. Am. Chem. Soc.* **1992,** *114,* 3157-3159.

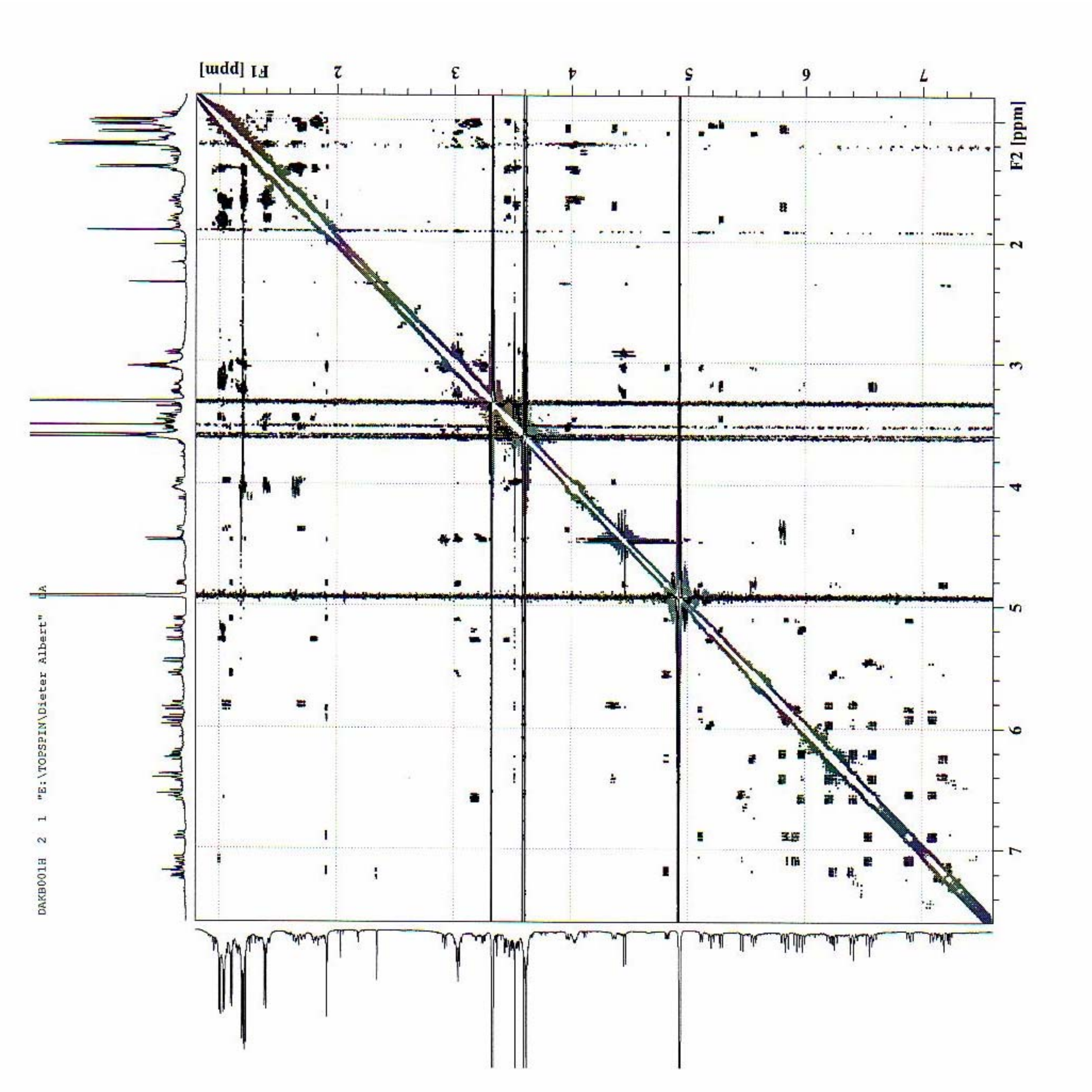
Table2. [1]H-NMR data and ROESY correlations for chivosazole A (500 MHz, CD_3OD)[ii]

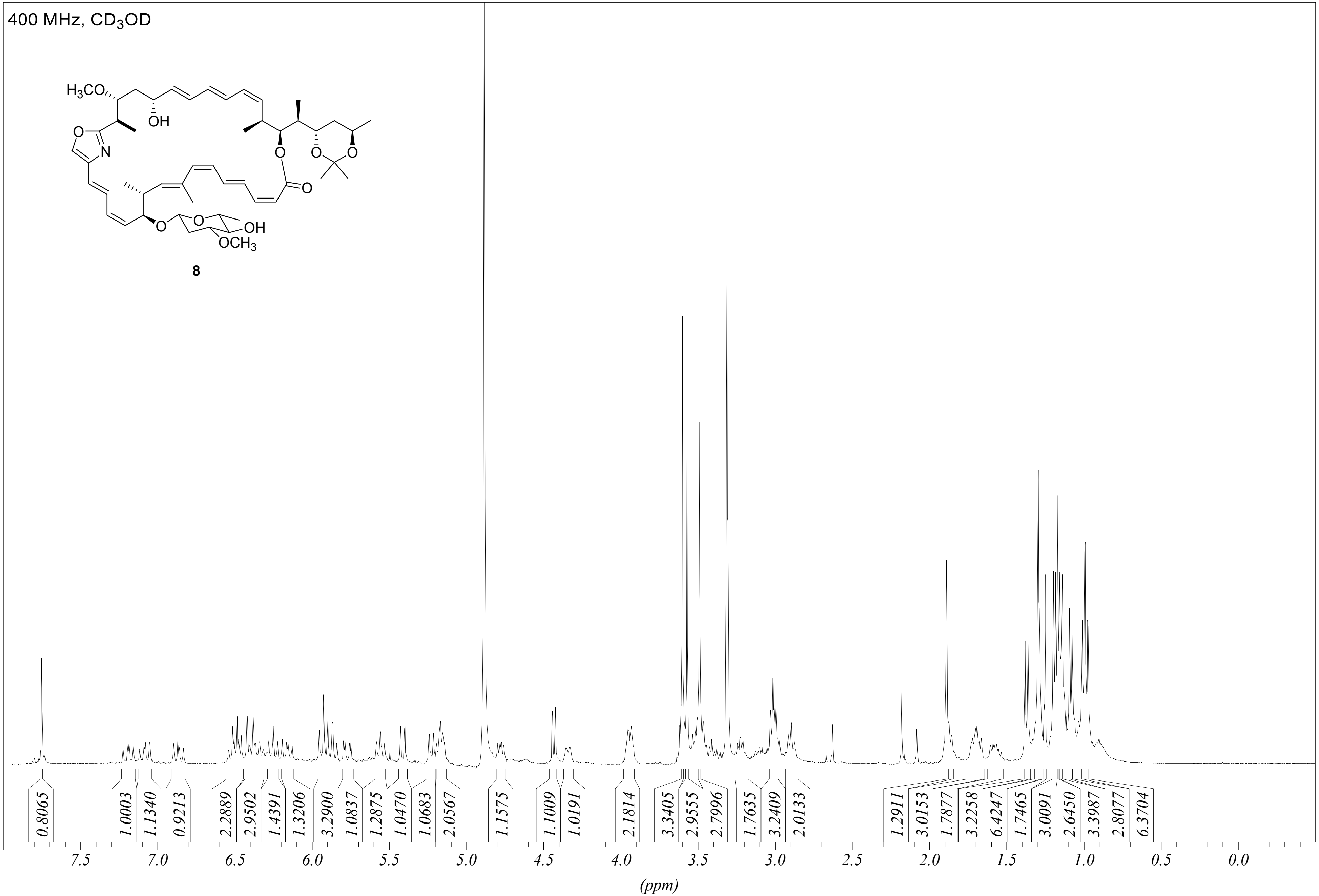


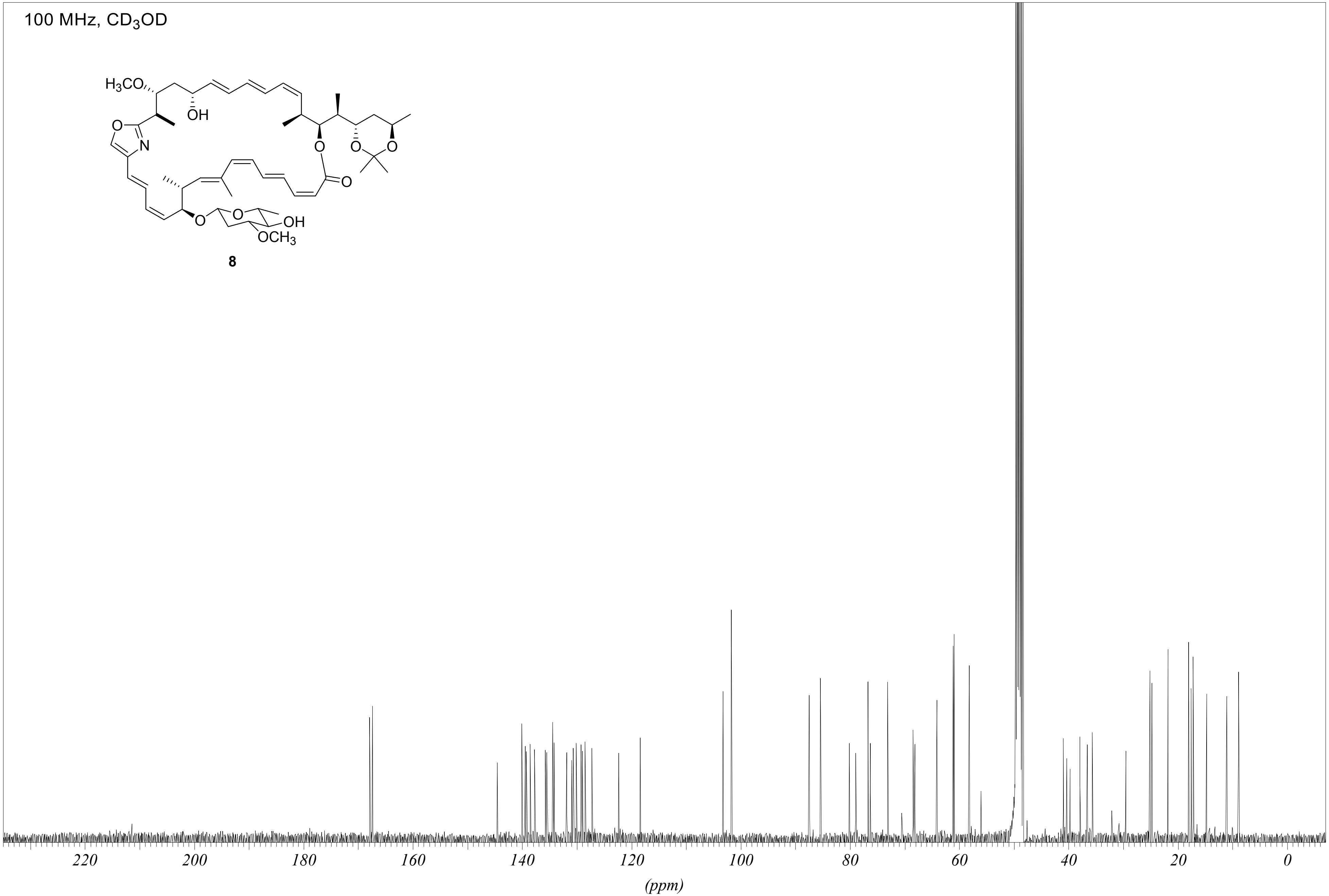
Proton	δ [ppm], mult., *J* [Hz]	ROESY correlations[iii]
H2	5.44; d; 11.6	H3 (s)
H3	6.52; t; 11.7	H2 (s), H5 (s)
H4	7.07; dd; 14.9, 11.7	H6 (m), Me40 (m)
H5	6.87; dd; 14.8, 11.1	H3 (s), H9 (m), Me36 (w)
H6	5.91; t; 11.1	H4 (m)
H7	5.82; d; 11.3	H9 (w), H21b (m), Me36 (m)
H9	5.10; d; 8.8	H5 (m), H7 (w), Me37 (m)
H10	3.02; m	H11 (s), H12 (m), Me36(s), Me37 (s)
H11	4.80; dd; 9.5, 5.6	H10 (s), H12 (w), H14 (s), Me36 (m), H1’ (m)
H12	5.54; dd; 10.1, 10.0	H10 (m), H11 (w), H13 (s), Me37 (m)
H13	6.23; t; 11.1	H12 (s)
H14	7.16; dd; 15.3, 11.7	H11 (s)
H15	6.37; d; 15.2	H17 (m)
H17	7.73, s	H15 (m)
H19	3.52; m	H20 (s), OMe-20 (s), Me38 (s)
H20	3.95; ddd, 10.6; 3.8; 1.7	OMe-20 (s), H21b (s)
H21a	1.68; ddd; 14.2; 10.8; 2.4	H21b (s), H22 (m), H23 (m), Me38 (s)
H21b	1.06; m	H7 (m), H20 (s), H21a (s), Me38 (m)
H22	4.35; d; 9.8	H21a (m), H23 (m), H24 (w)
H23	5.79; dd; 15.2; 3.7	H21a (m), H22 (m), H25 (s)
H24	6.40; ddd; 15.3, 10.7, 1.6	H22 (w), H26 (m)
H25	6.18; dd; 14.8, 10.7	H23 (s), H27 (s)
H26	6.57; d; 11.4	H24 (m), H29 (s)
H27	5.95; t; 10.8	H25 (s), H28 (s)
H28	5.18; t; 10.3	H27 (s), H30 (w), Me39 (s)
H29	3.17; m	H26 (s), Me39 (s), Me40 (s)
H30	5.26; dd; 10.3, 1.2	H28 (w), H31 (m), H32 (m), Me39 (m)
H31	1.78; m	H30 (m), H32 (m), H33a (m), H33b (s), Me39 (s), Me40 (s)
H32	3.44; m	H30 (m), H31 (m), H33a (s), Me40 (m)
H33a	1.63; ddd; 14.2, 9.8, 2.0	H31 (m), H32 (s), Me35 (s), Me40 (s)
H33b	1.39; ddd; 14.2, 10.2, 2.5	H31 (s), H34 (s), Me35 (s), Me40 (m)
H34	4.02; m	H33b (s), Me35
Me35	1.17; d; 6.3	H33a (s), H33b (s), H34
Me36	1.89; s	H5 (w), H7 (m), H10 (s), H11 (m), Me38 (m), H1’ (w)
Me37	1.08; d; 6.7	H9 (m), H10 (s), H12 (m)
Me38	1.37; d; 7.2	H19 (s), H21a (s), H21b (m), Me36 (m)
Me39	1.02; d; 6.6	H28 (s), H29 (s), H30 (m), H31 (s)
Me40	0.98; d; 6.9	H4 (m), H29 (s), H31 (s), H32 (m), H33a (s), H33b (m)
OMe-20	3.50; s	H19 (s), H20 (s)
H1’	4.43; d; 7.8	H11 (m), Me36 (w) H3’ (s), H5’ (s)
H2’	2.90; dd; 8.7; 8.1	H5’ (s), OMe-2’ (m)
H3’	3.03; m	H1’ (s), OMe-3’ (s)
H4’	3.00; m	-
H5’	3.23; dd; 8.9; 6.1	H1’ (s)
Me6’	1.19; d; 6.1	-
OMe-2’	3.57; s	H2’ (m)
OMe-3’	3.60; s	H3’ (s)

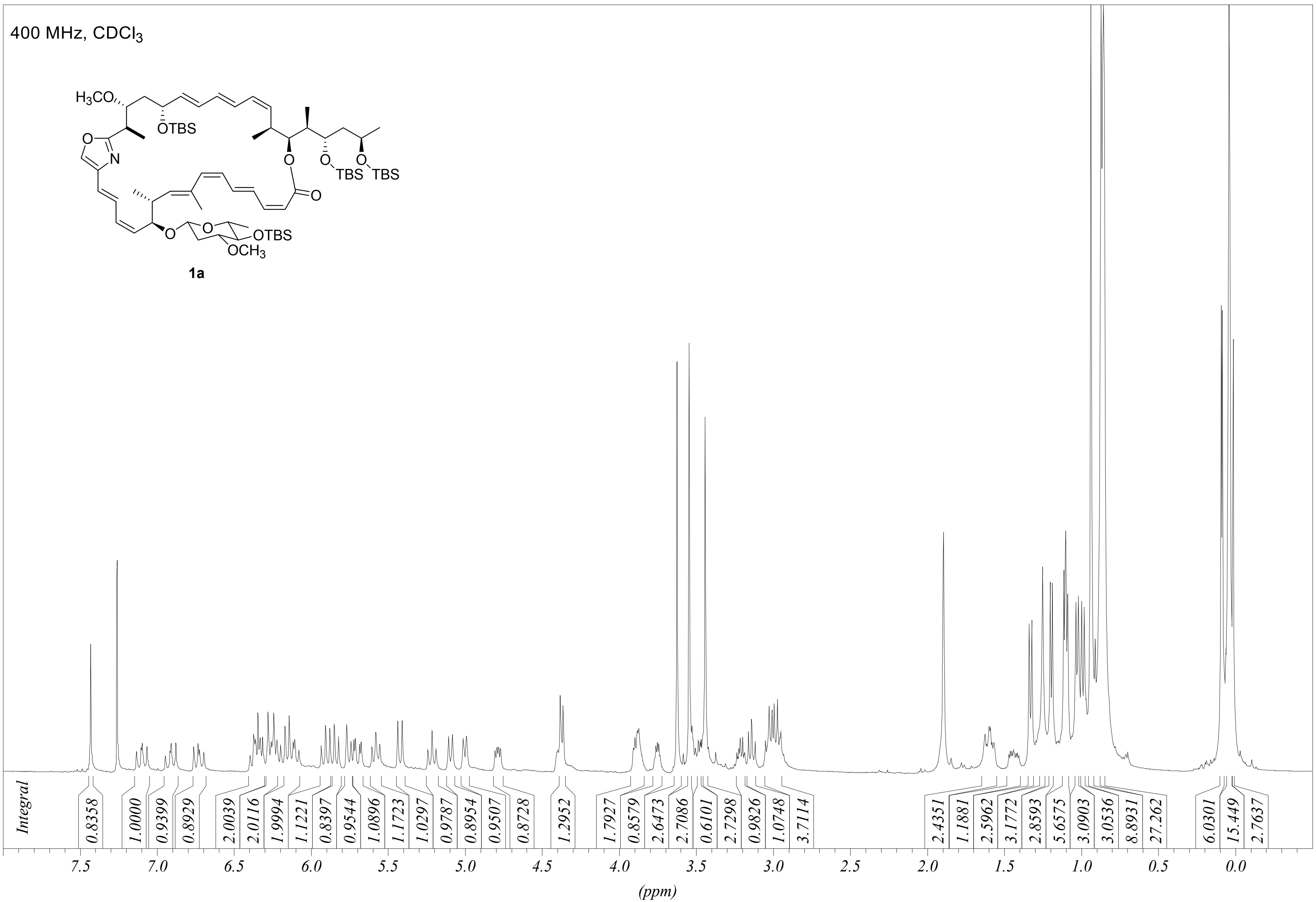
[ii] The coupling constants are the same in $CDCl_3$.
[iii] definitions: (s) = strong, (m) = medium, (w) = weak.

ROESY spectrum of chivosazole A (1) in CD_3OD (500 MHz)

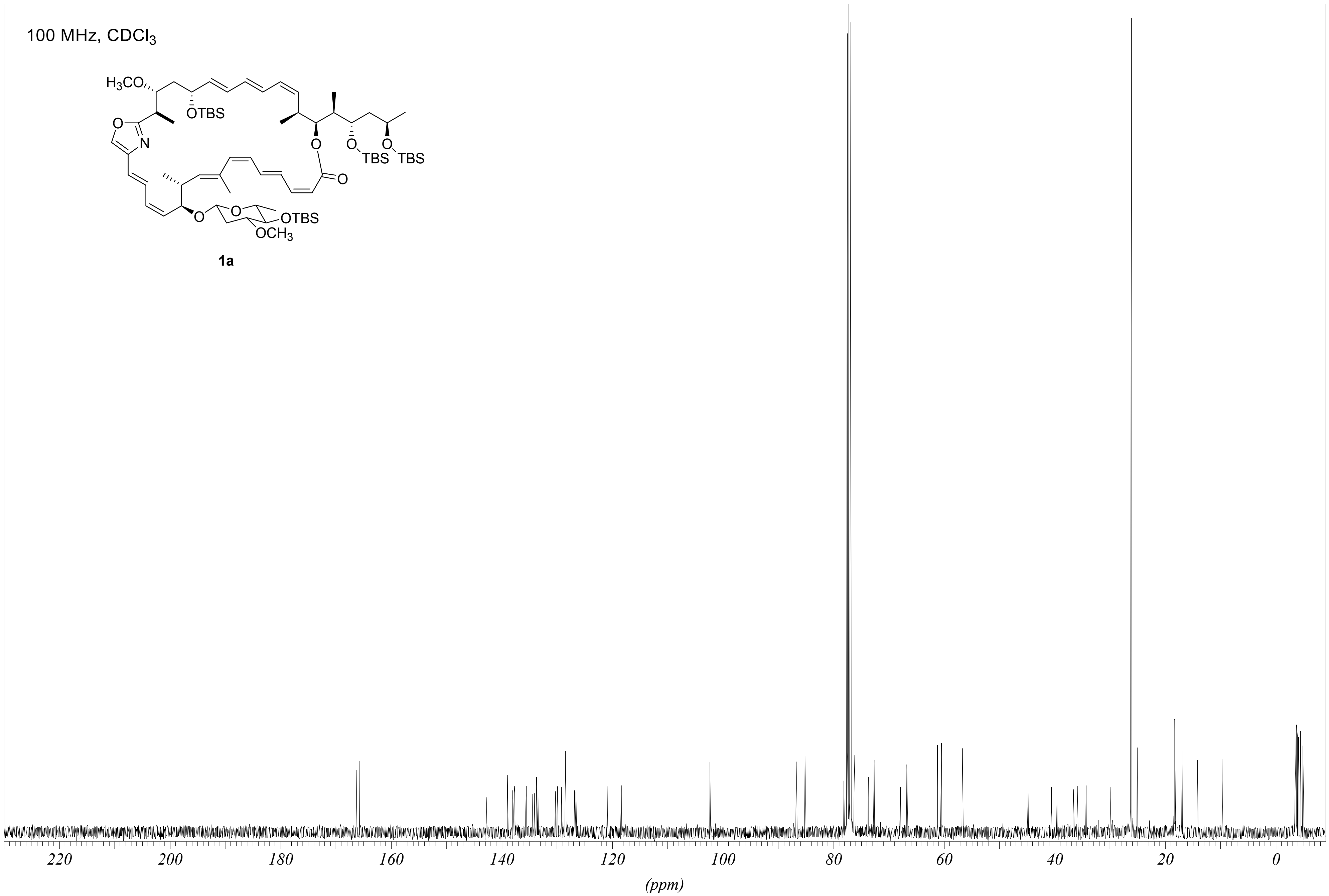



400 MHz, CD3OD
H3CO
OH
O
N
O
O
O
O
O
O
OH
OCH3
8
0.8065
1.0003
1.1340
0.9213
2.2889
2.9502
1.4391
1.3206
3.2900
1.0837
1.2875
1.0470
1.0683
2.0567
1.1575
1.1009
1.0191
2.1814
3.3405
2.9555
2.7996
1.7635
3.2409
2.0133
1.2911
3.0153
1.7877
3.2258
6.4247
1.7465
3.0091
2.6450
3.3987
2.8077
6.3704
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)


100 MHz, CD_3OD
H_3CO
OH
O
N
O
O
O
O
O
O
OH
OCH_3
8
220
200
180
160
140
120
100
80
60
40
20
0
(ppm)



400 MHz, $CDCl_3$
H_3CO
OTBS
O
N
O
O
TBS
TBS
O
O
O
OTBS
OCH_3
1a
Integral
0.8358
1.0000
0.9399
0.8929
2.0039
2.0116
1.9994
1.1221
0.8397
0.9544
1.0896
1.1723
1.0297
0.9787
0.8954
0.9507
0.8728
1.2952
1.7927
0.8579
2.6473
2.7086
0.6101
2.7298
0.9826
1.0748
3.7114
2.4351
1.1881
2.5962
3.1772
2.8593
5.6575
3.0903
3.0536
8.8931
27.262
6.0301
15.449
2.7637
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)


100 MHz, CDCl3
H3CO
OTBS
O
N
O
O
TBS
TBS
O
OTBS
OCH3
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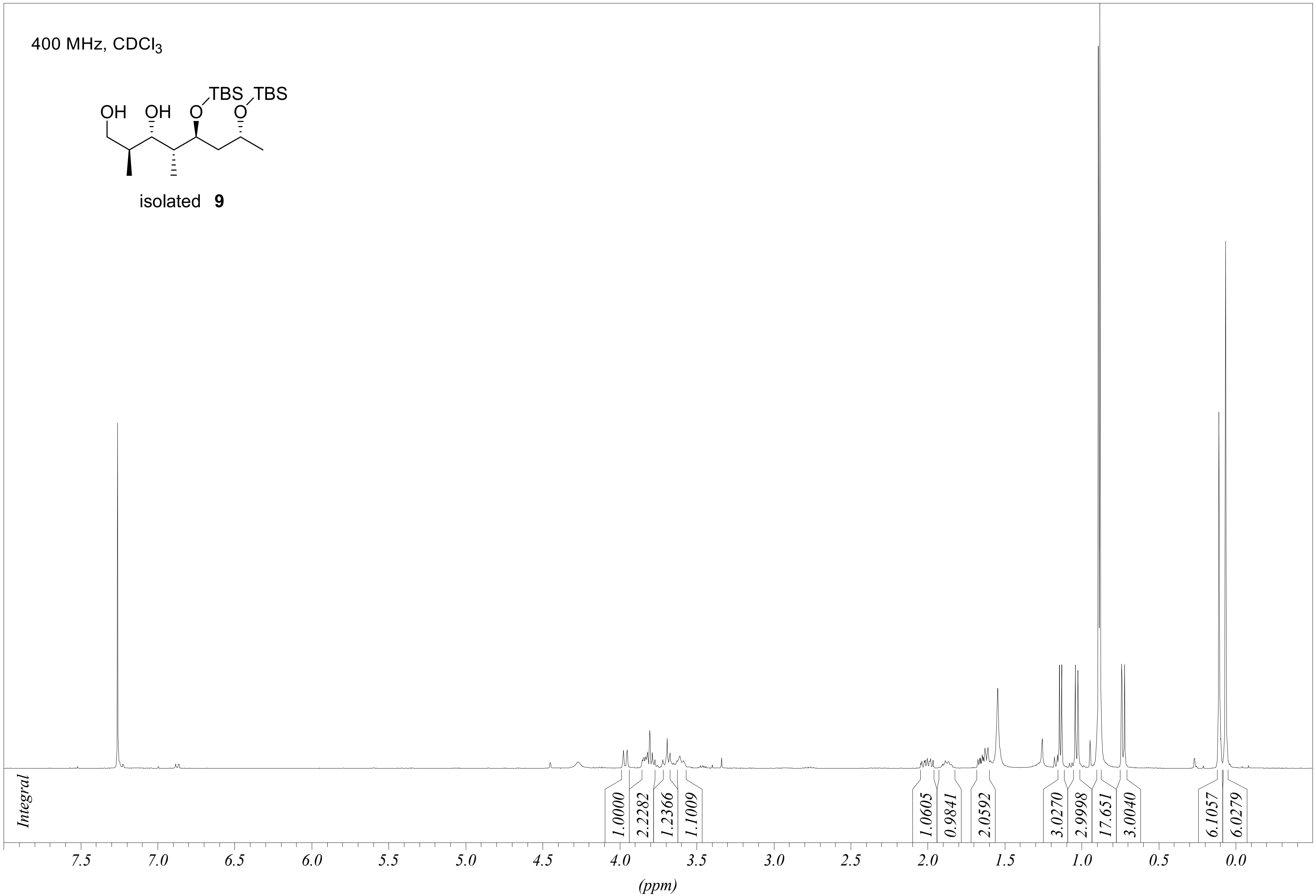
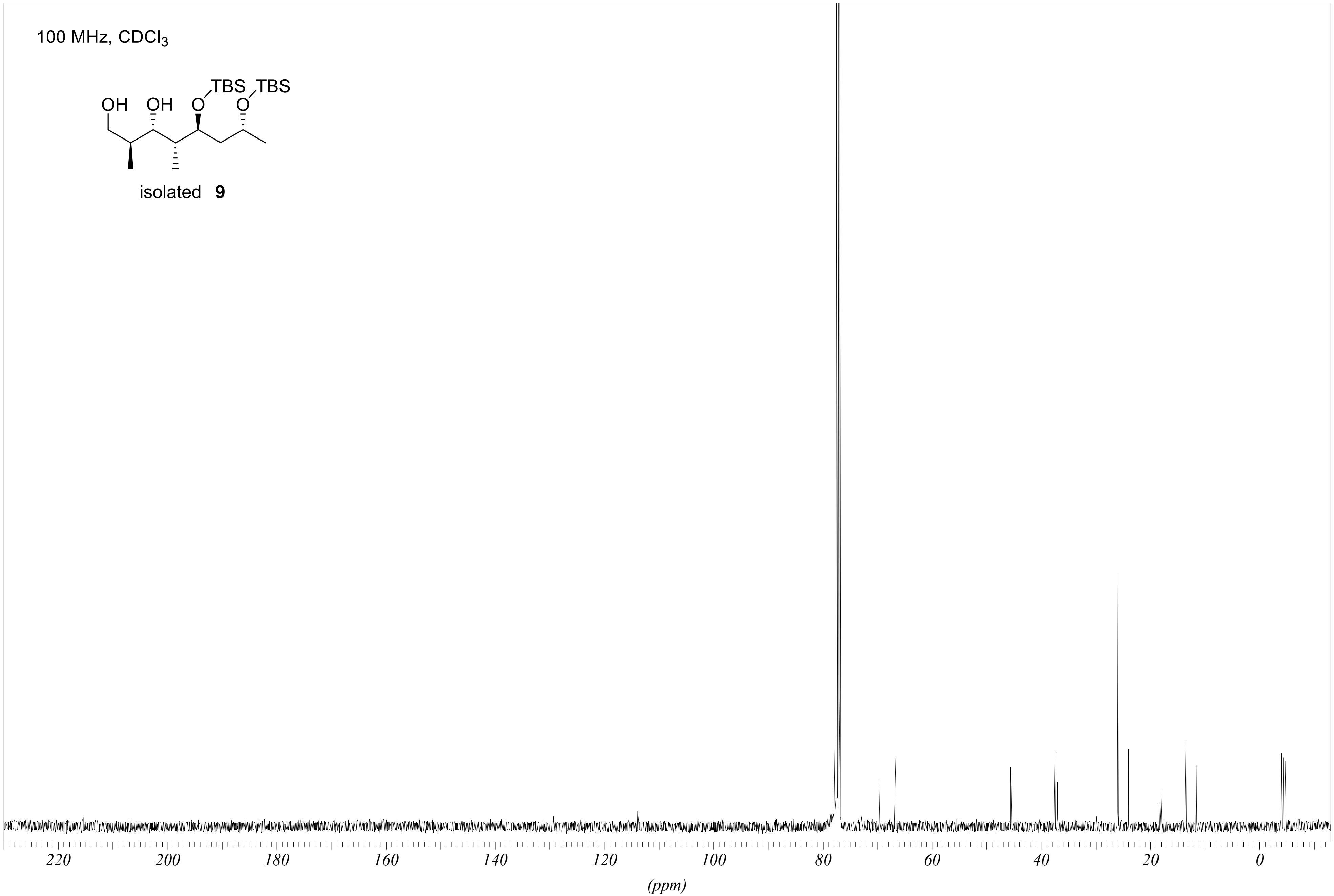
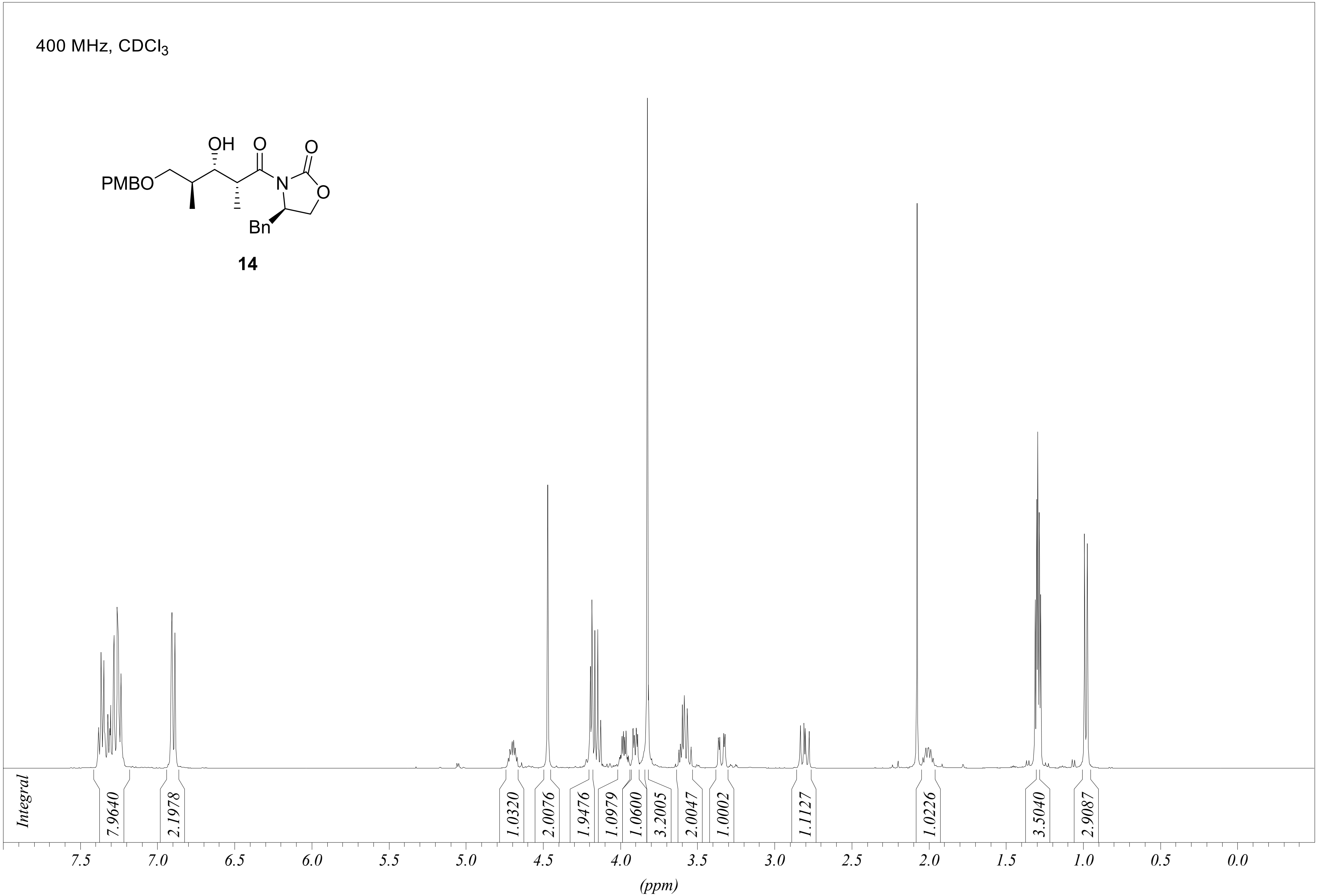
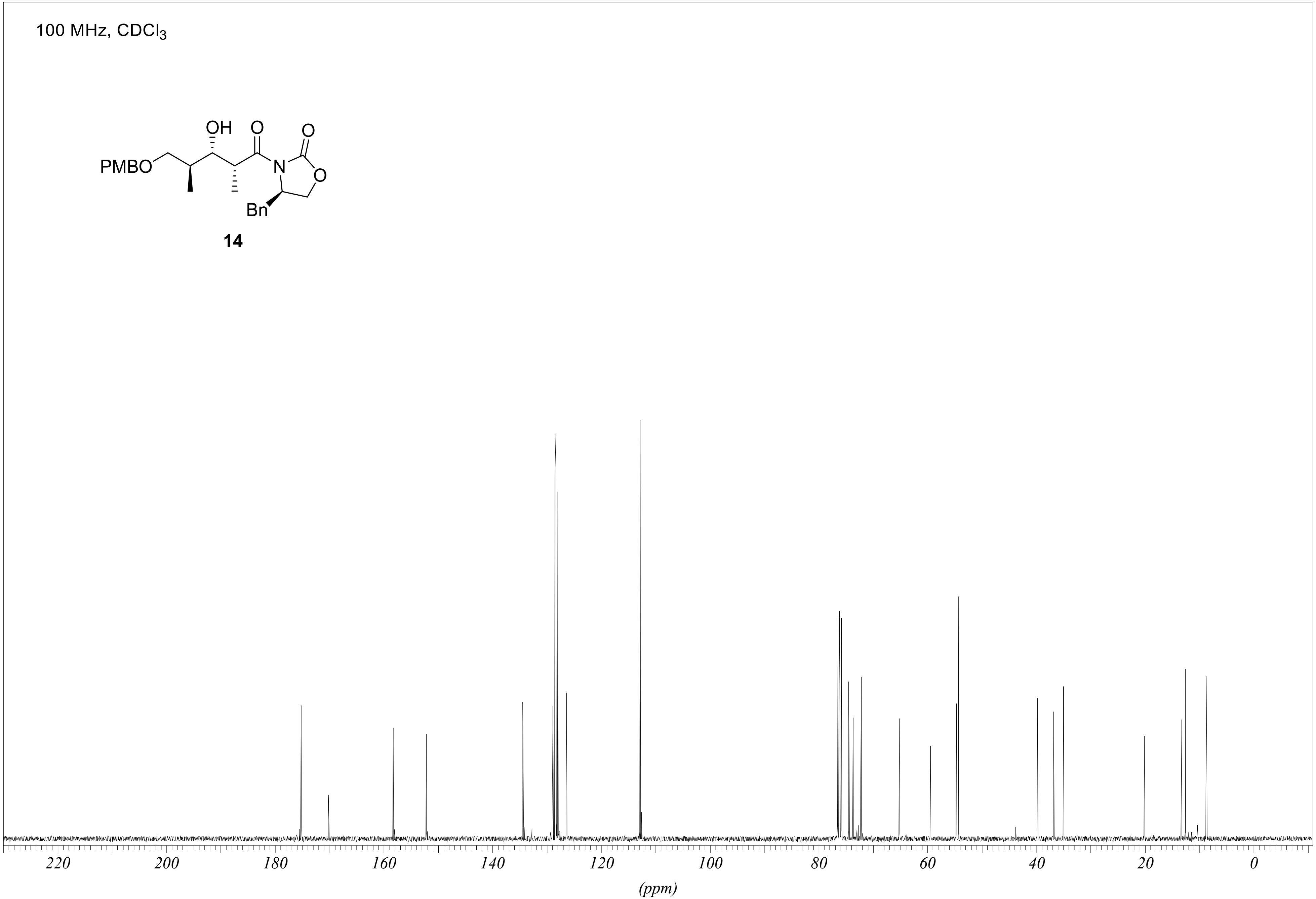
220
200
180
160
140
120
100
80
60
40
20
0
(ppm)

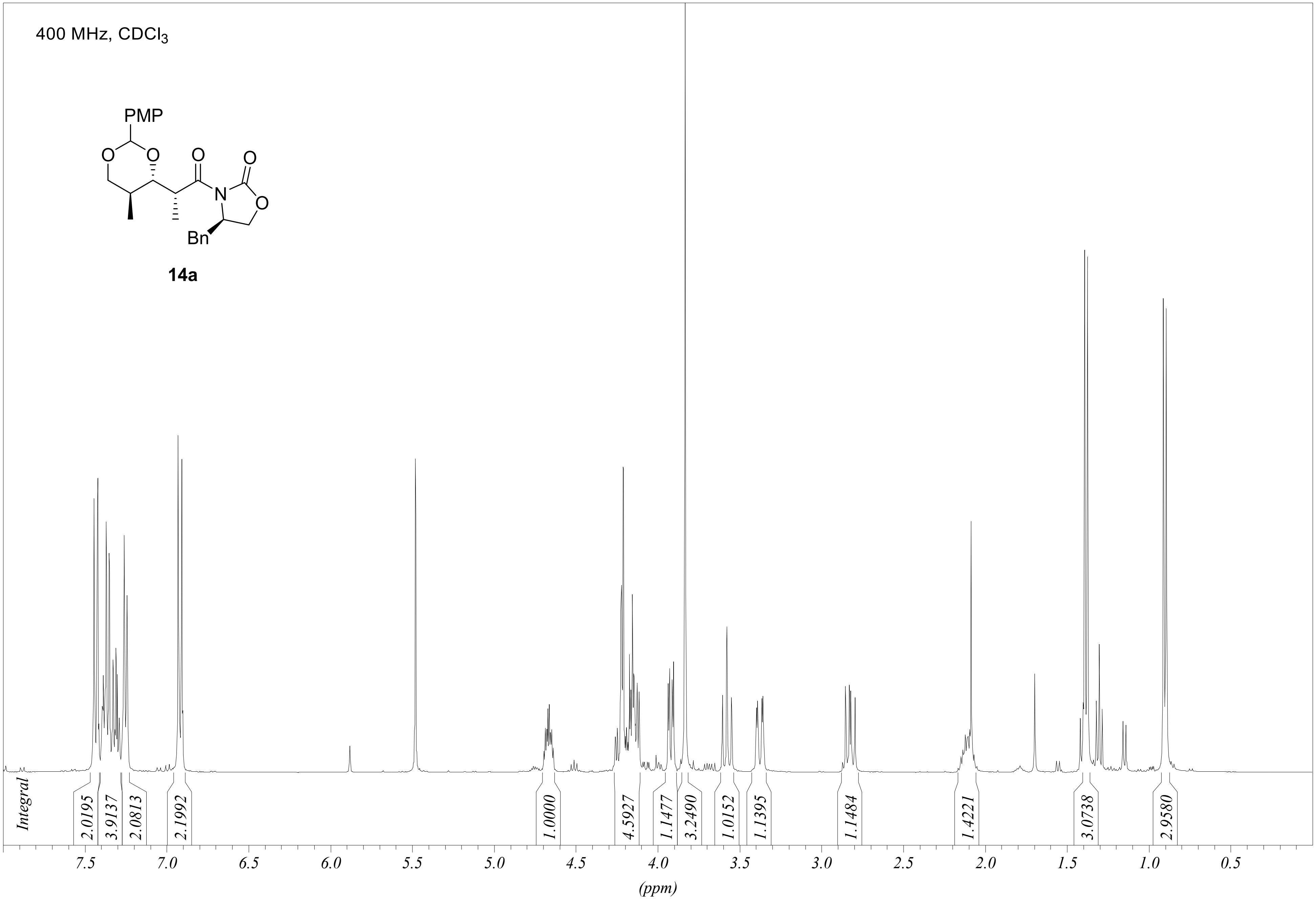

400 MHz, $CDCl_3$
OH OH O TBS O TBS
isolated **9**
Integral
1.0000 2.2282 1.2366 1.1009 1.0605 0.9841 2.0592 3.0270 2.9998 17.651 3.0040 6.1057 6.0279
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
(ppm)



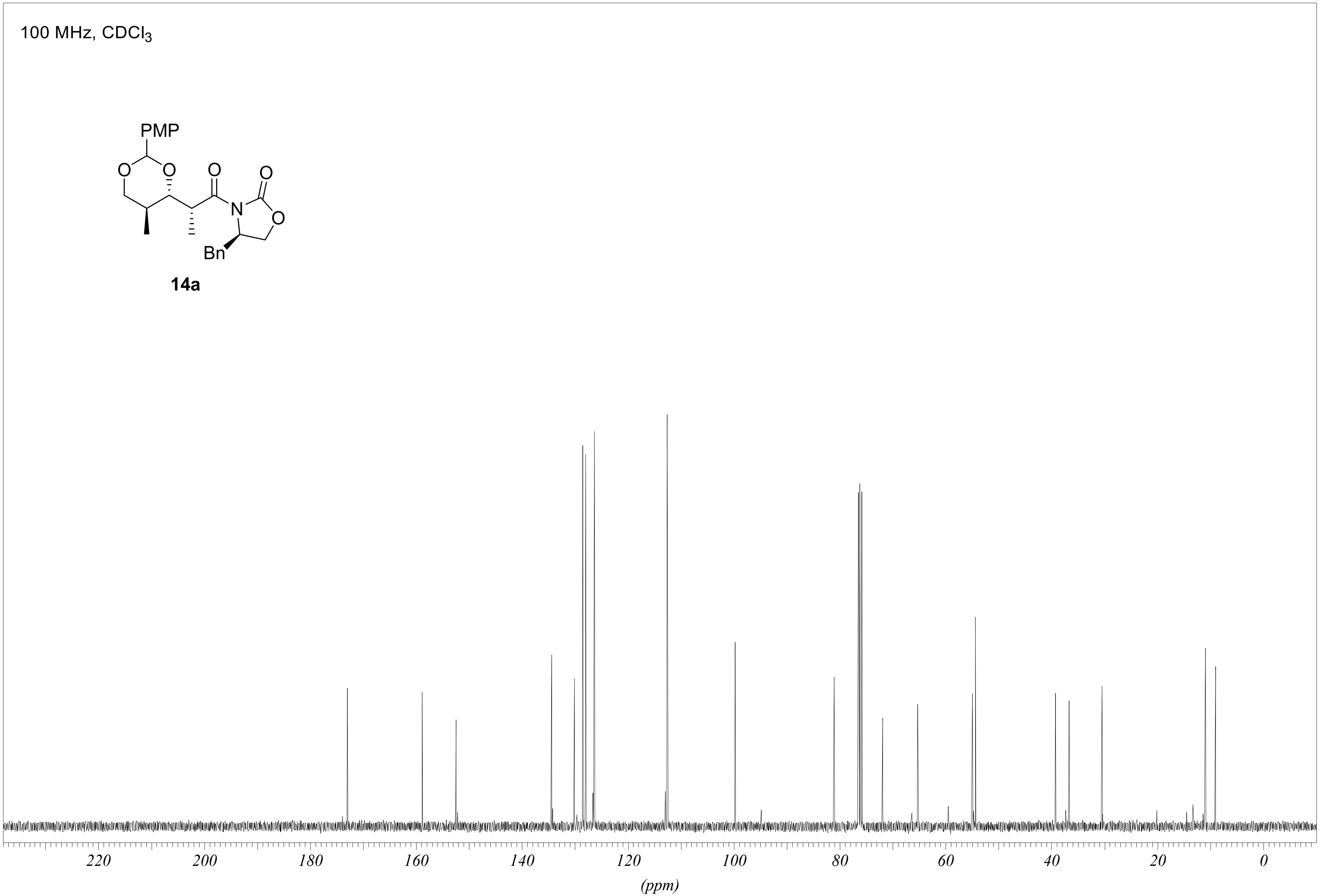
100 MHz, CDCl3
OH
OH
O
TBS
O
TBS
isolated 9
220
200
180
160
140
120
100
80
60
40
20
0
(ppm)

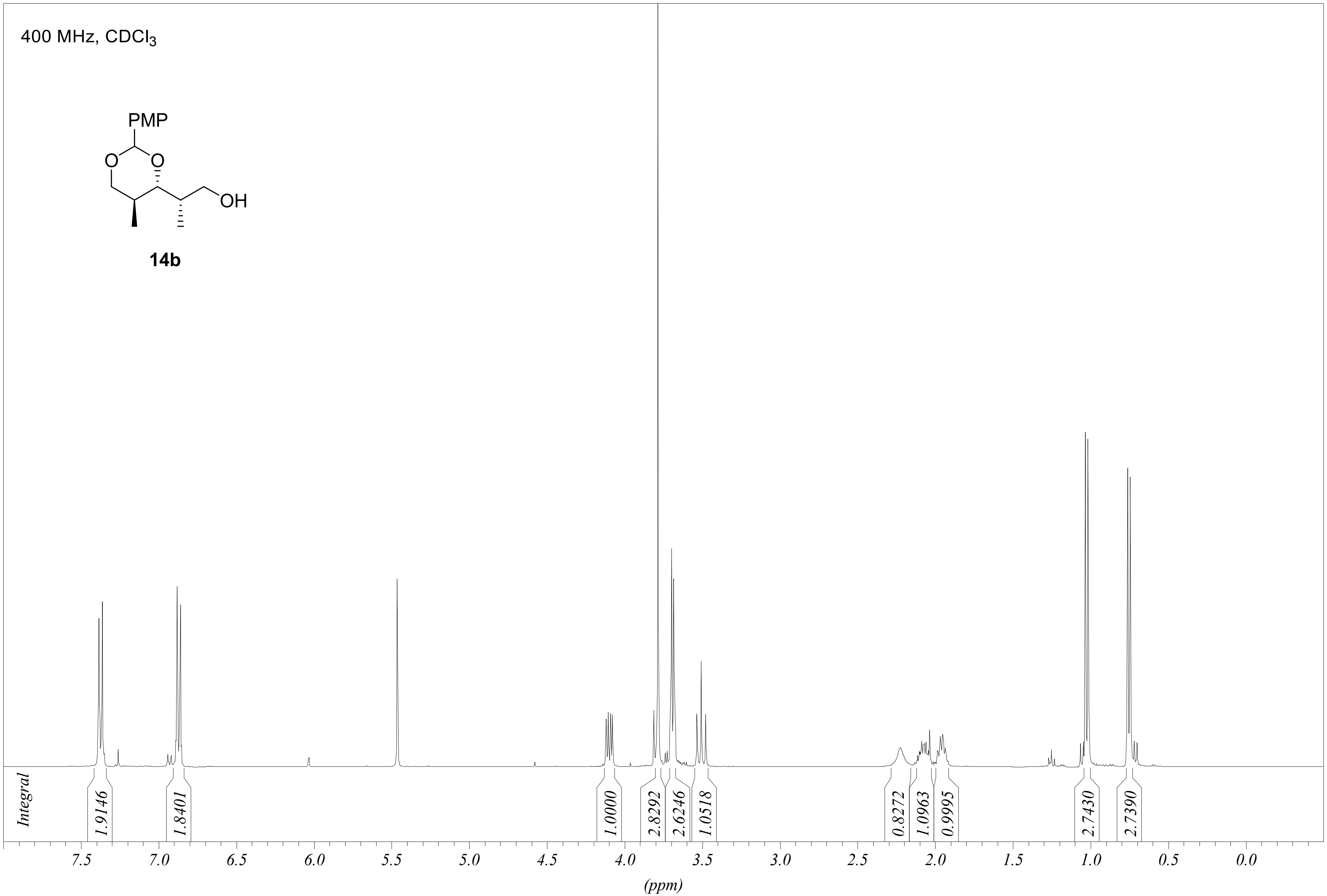

400 MHz, CDCl3
PMBO
OH
O
O
N
O
Bn
14
Integral
7.9640
2.1978
1.0320
2.0076
1.9476
1.0979
1.0600
3.2005
2.0047
1.0002
1.1127
1.0226
3.5040
2.9087
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
(ppm)


100 MHz, $CDCl_3$
OH
O
O
PMBO
N
O
Bn
14
220
200
180
160
140
120
100
80
60
40
20
0
(ppm)



400 MHz, CDCl3
PMP
O
O
O
O
N
O
Bn
14a
Integral
2.0195
3.9137
2.0813
2.1992
1.0000
4.5927
1.1477
3.2490
1.0152
1.1395
1.1484
1.4221
3.0738
2.9580
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)


100 MHz, $CDCl_3$
PMP
O
O
O
O
N
O
Bn
14a
220
200
180
160
140
120
100
80
60
40
20
0
(ppm)



400 MHz, CDCl3
PMP
O
O
OH
14b
Integral
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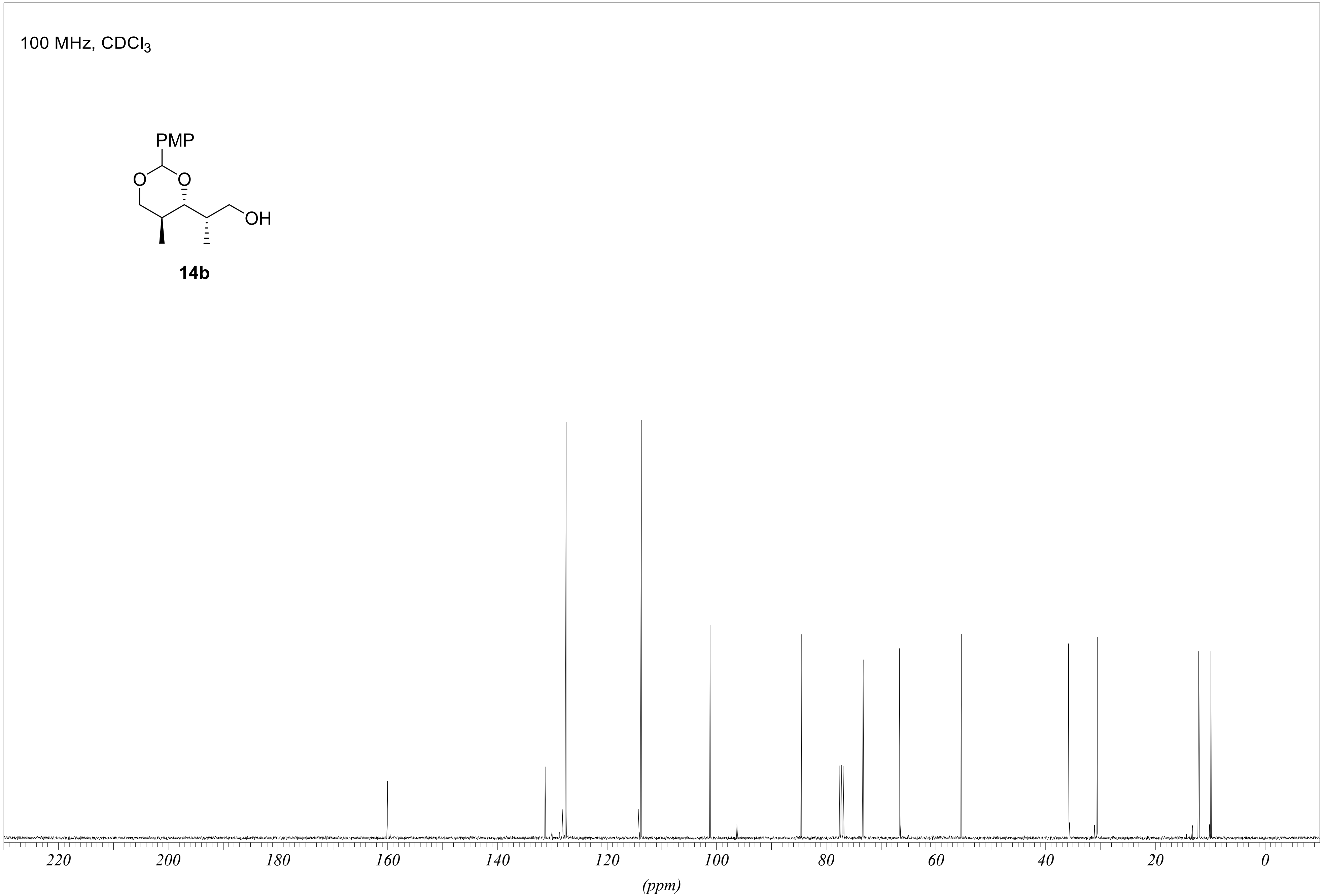
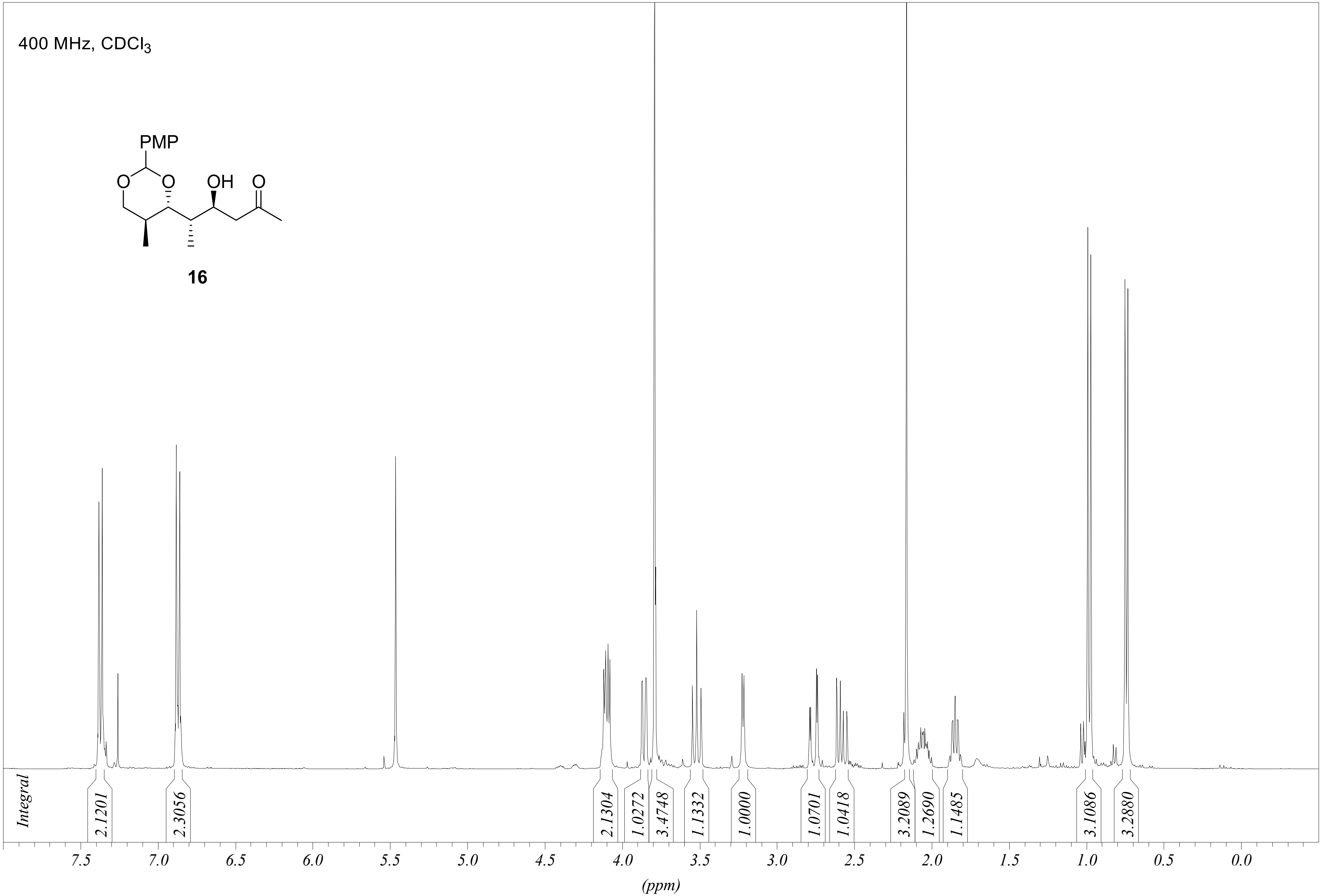
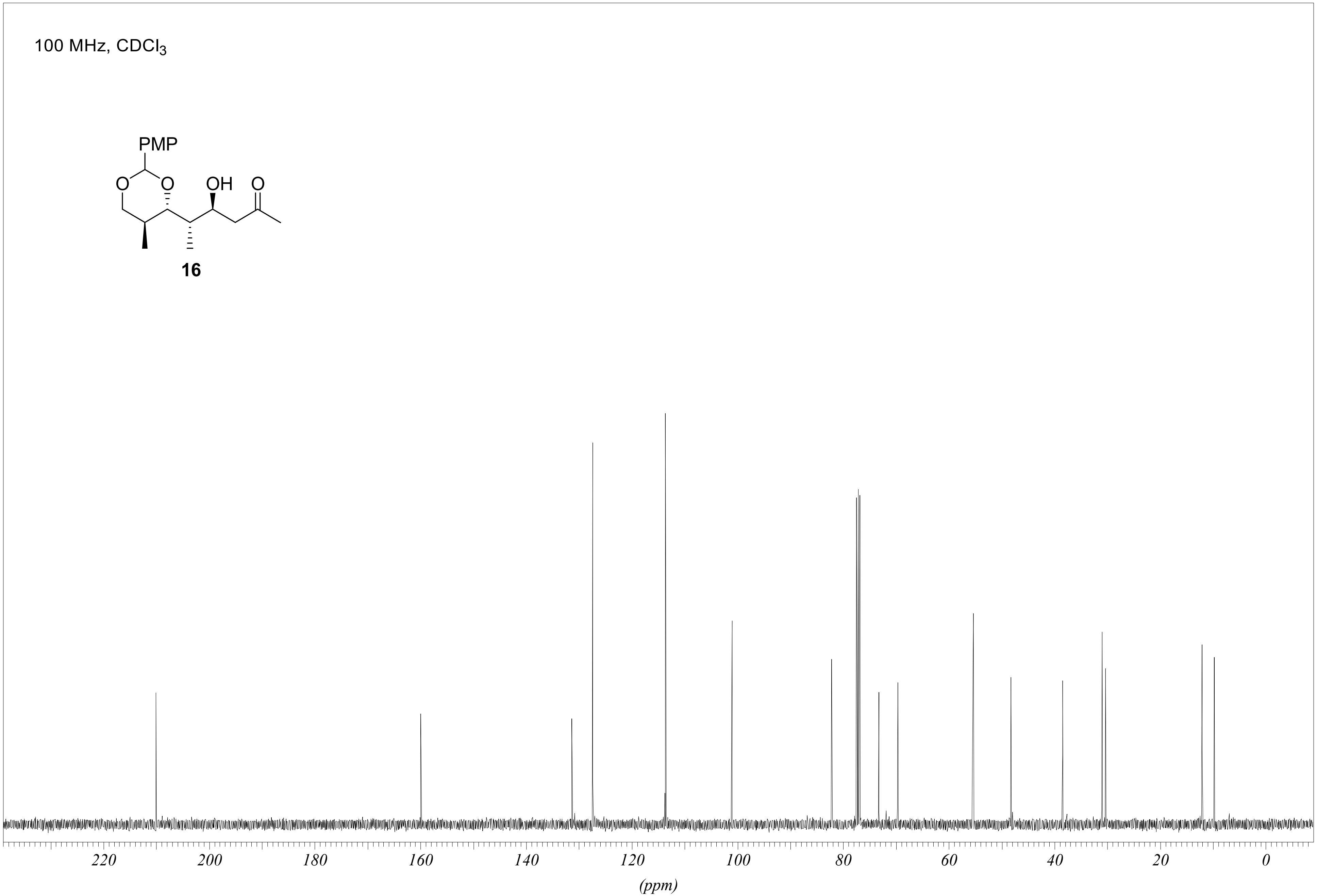
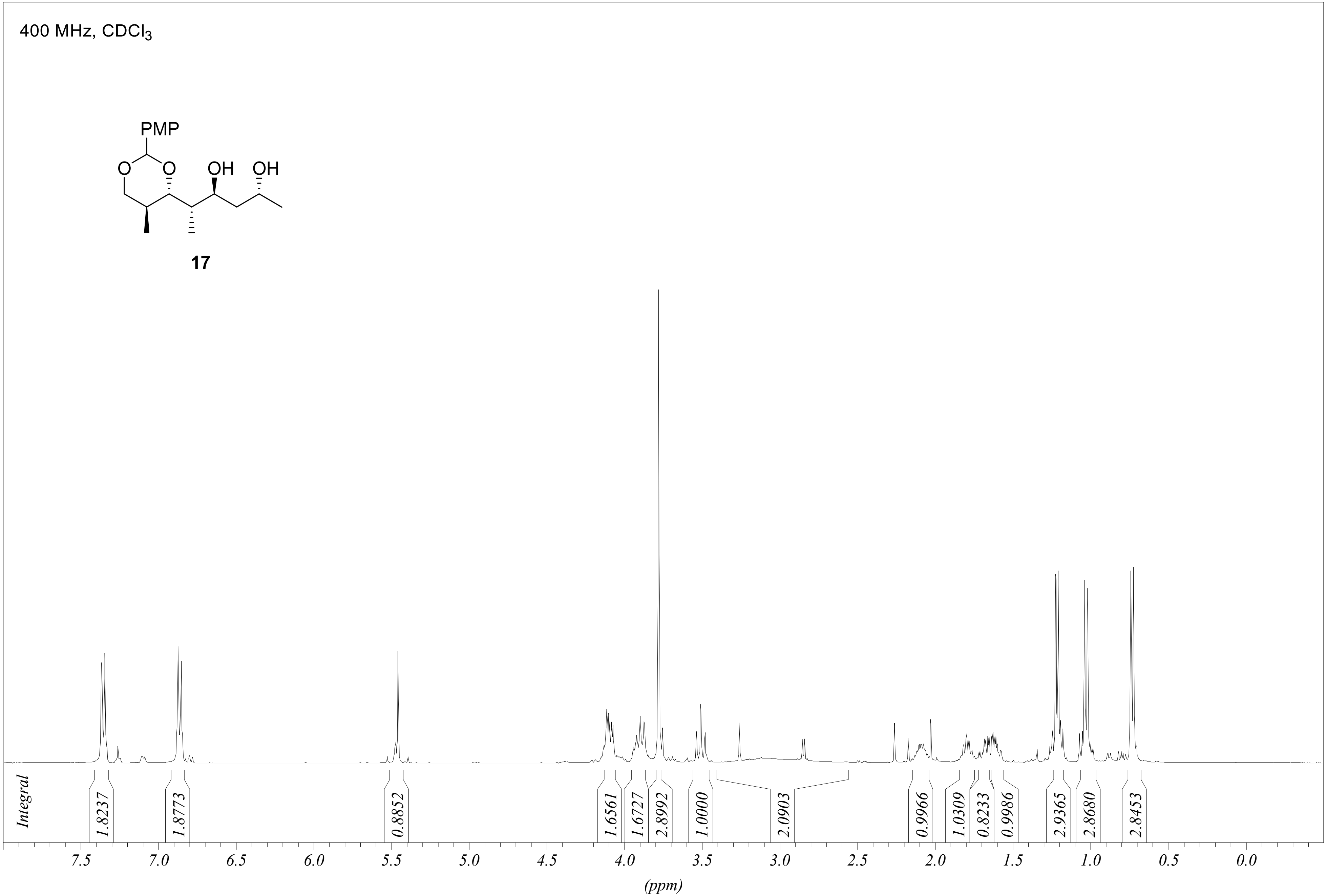
1.8401
1.0000
2.8292
2.6246
1.0518
0.8272
1.0963
0.9995
2.7430
2.7390
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
(ppm)


100 MHz, $CDCl_3$
PMP
O
O
OH
14b
220
200
180
160
140
120
100
80
60
40
20
0
(ppm)

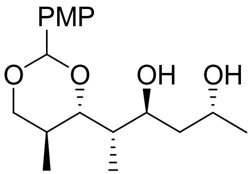

400 MHz, $CDCl_3$
PMP
O
O
OH
O
16
Integral
2.1201
2.3056
2.1304
1.0272
3.4748
1.1332
1.0000
1.0701
1.0418
3.2089
1.2690
1.1485
3.1086
3.2880
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
(ppm)


100 MHz, CDCl3
PMP
O
O
OH
O
16
220
200
180
160
140
120
100
80
60
40
20
0
(ppm)

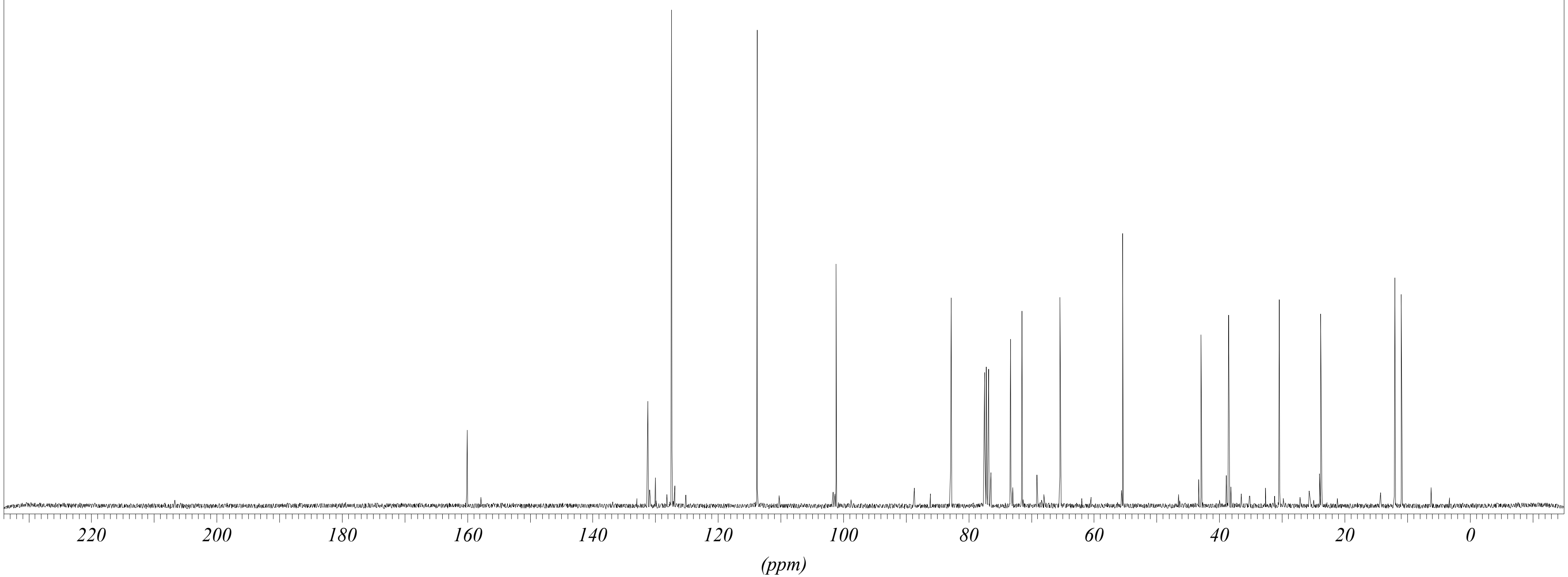


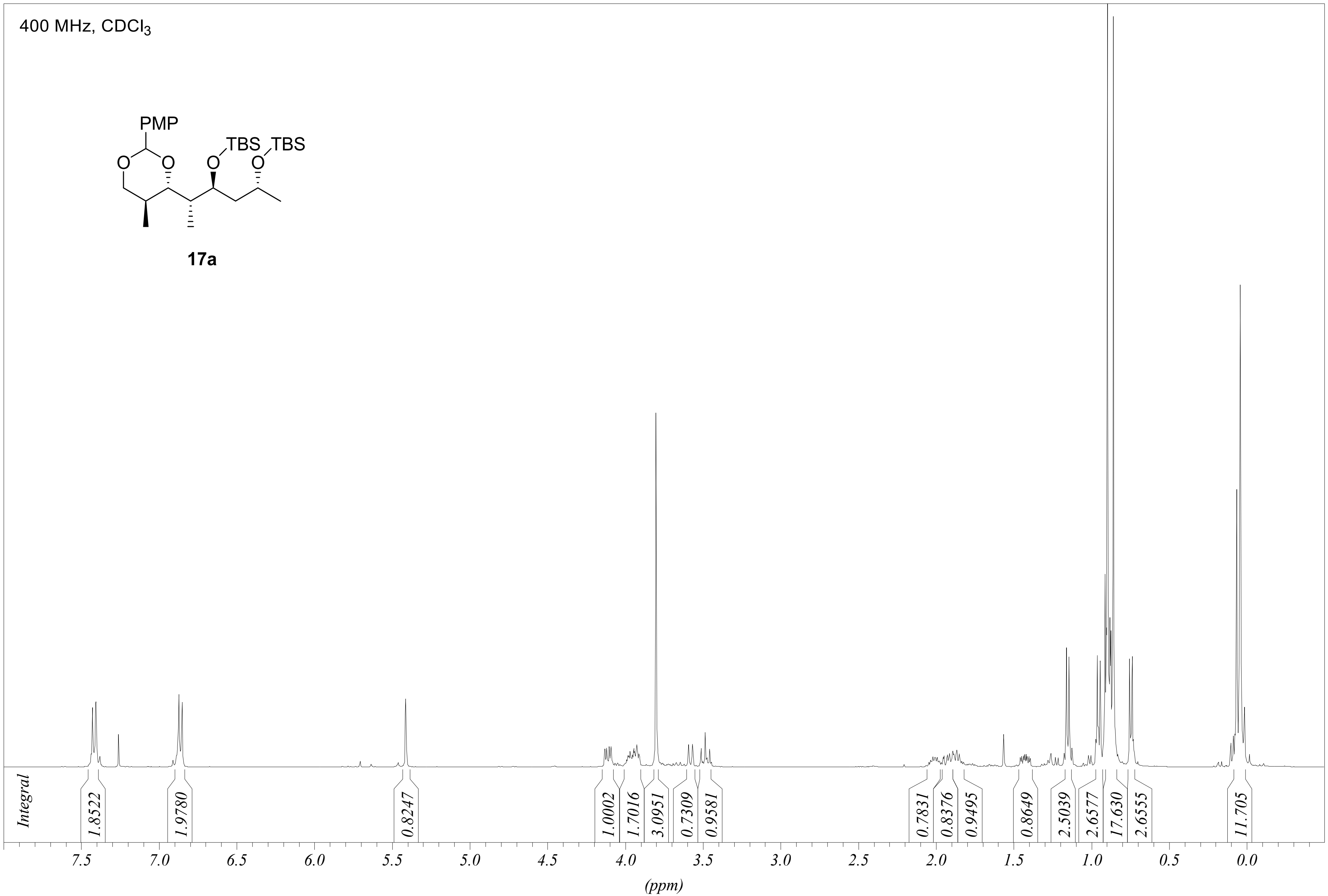
400 MHz, $CDCl_3$
PMP
O O OH OH
17
Integral
1.8237
1.8773
0.8852
1.6561
1.6727
2.8992
1.0000
2.0903
0.9966
1.0309
0.8233
0.9986
2.9365
2.8680
2.8453
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
(ppm)

100 MHz, $CDCl_3$



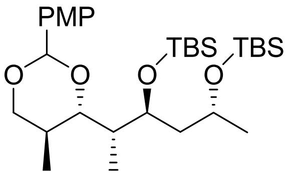
17



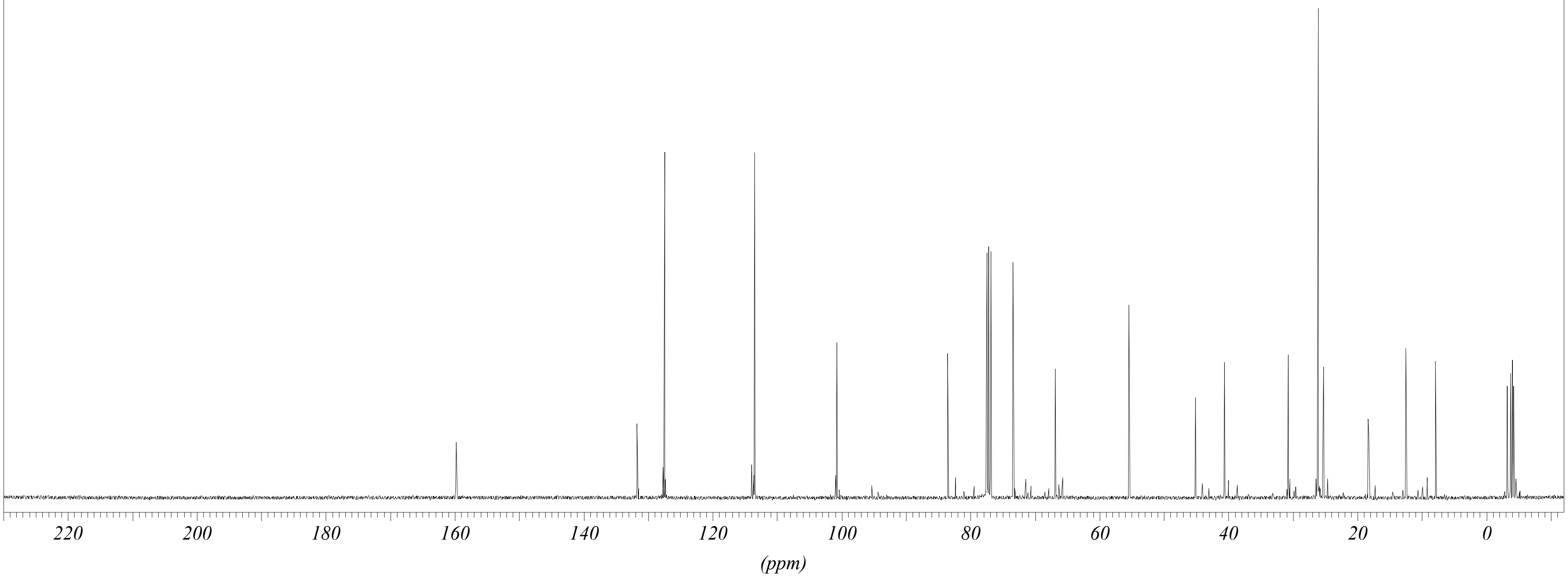


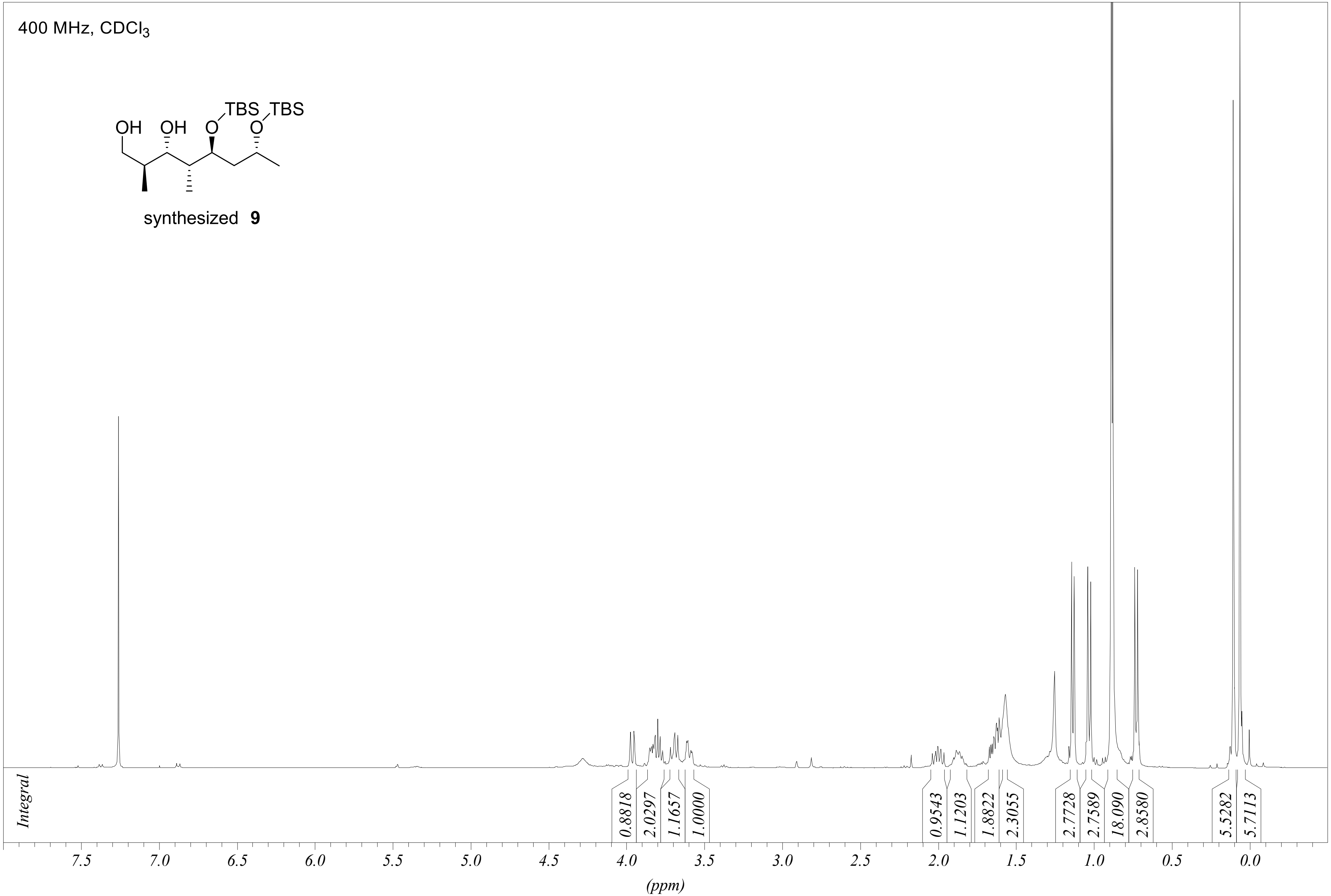
400 MHz, CDCl3
PMP
TBS
TBS
O
O
O
O
17a
Integral
1.8522
1.9780
0.8247
1.0002
1.7016
3.0951
0.7309
0.9581
0.7831
0.8376
0.9495
0.8649
2.5039
2.6577
17.630
2.6555
11.705
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)

100 MHz, $CDCl_3$

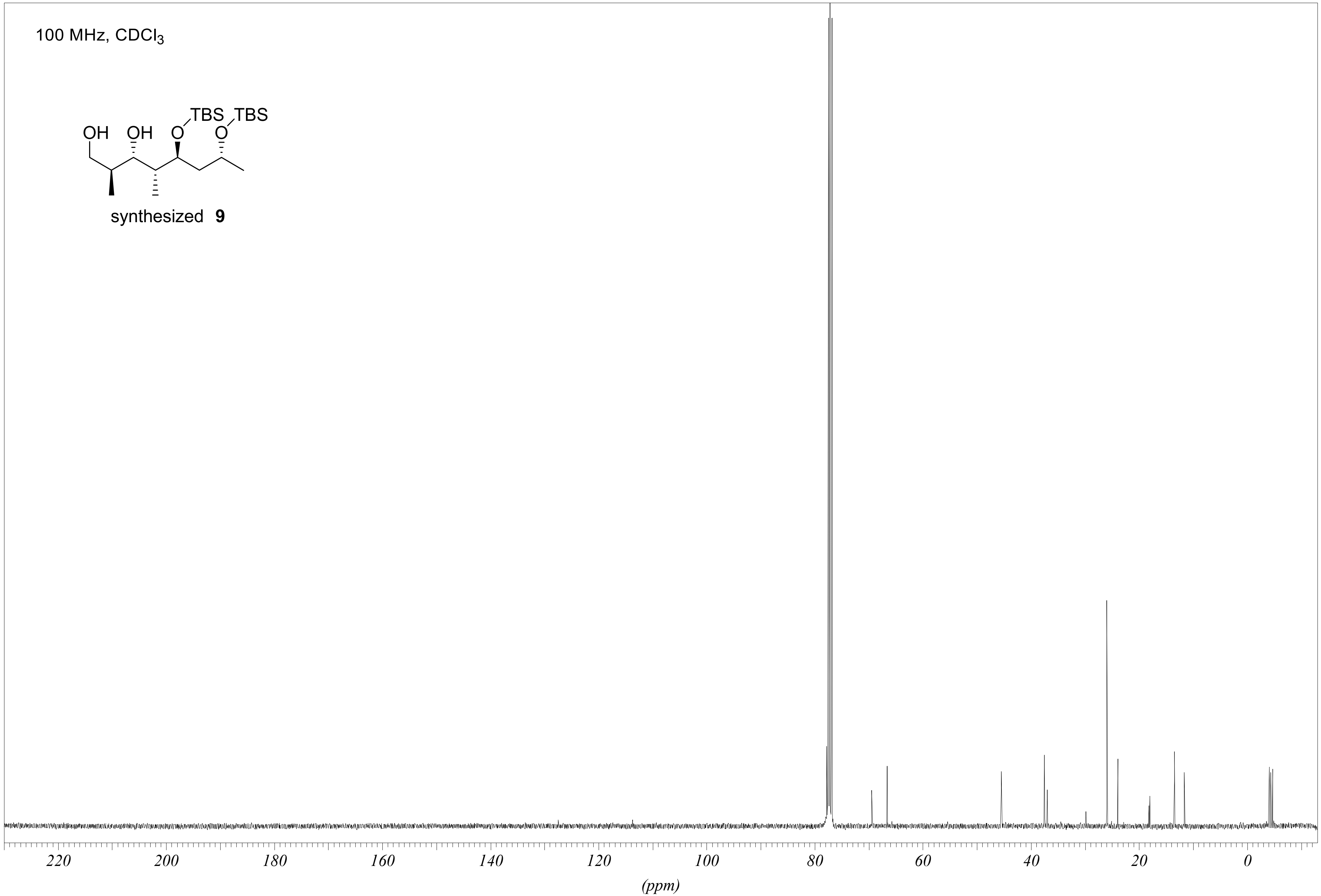


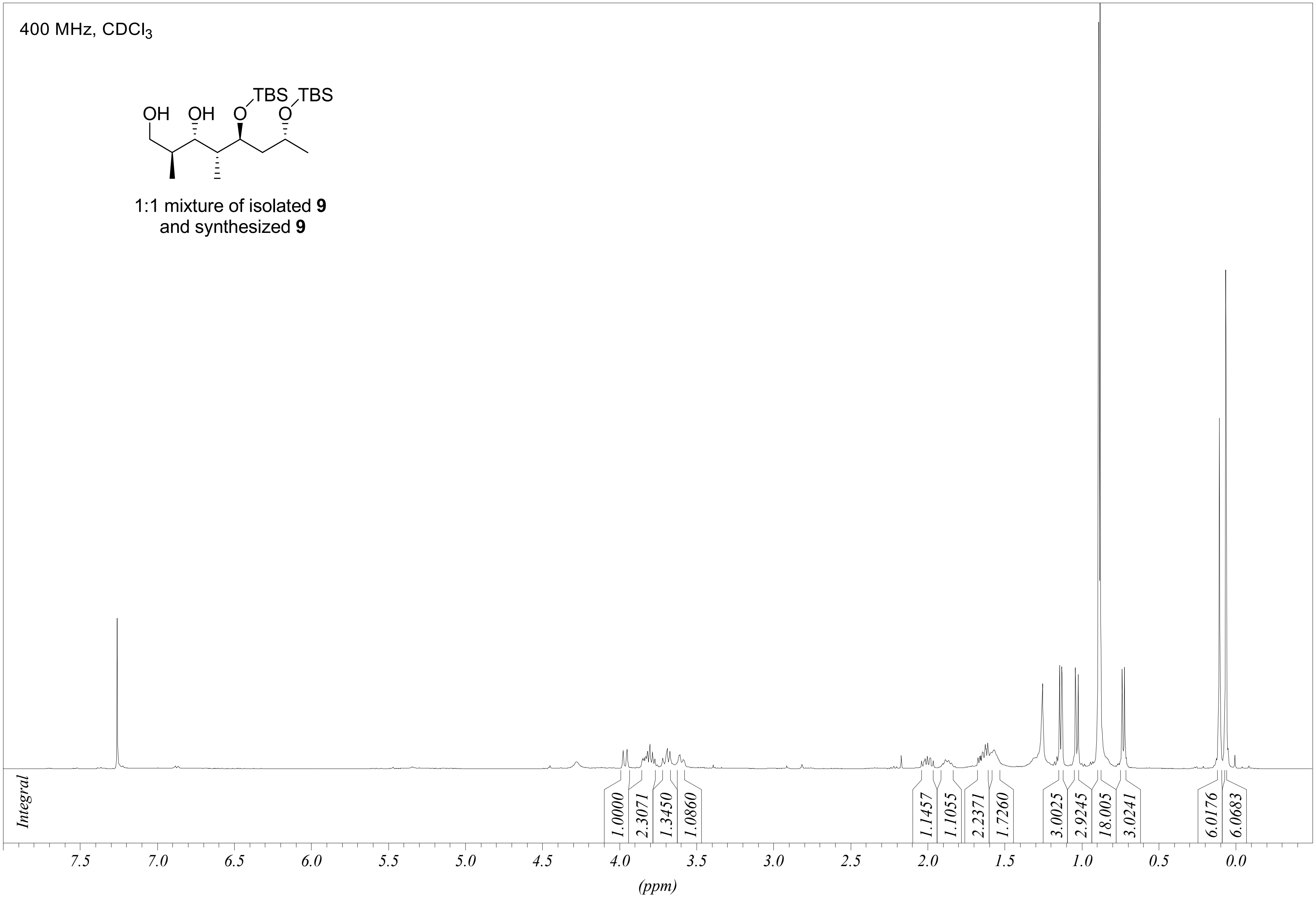
17a

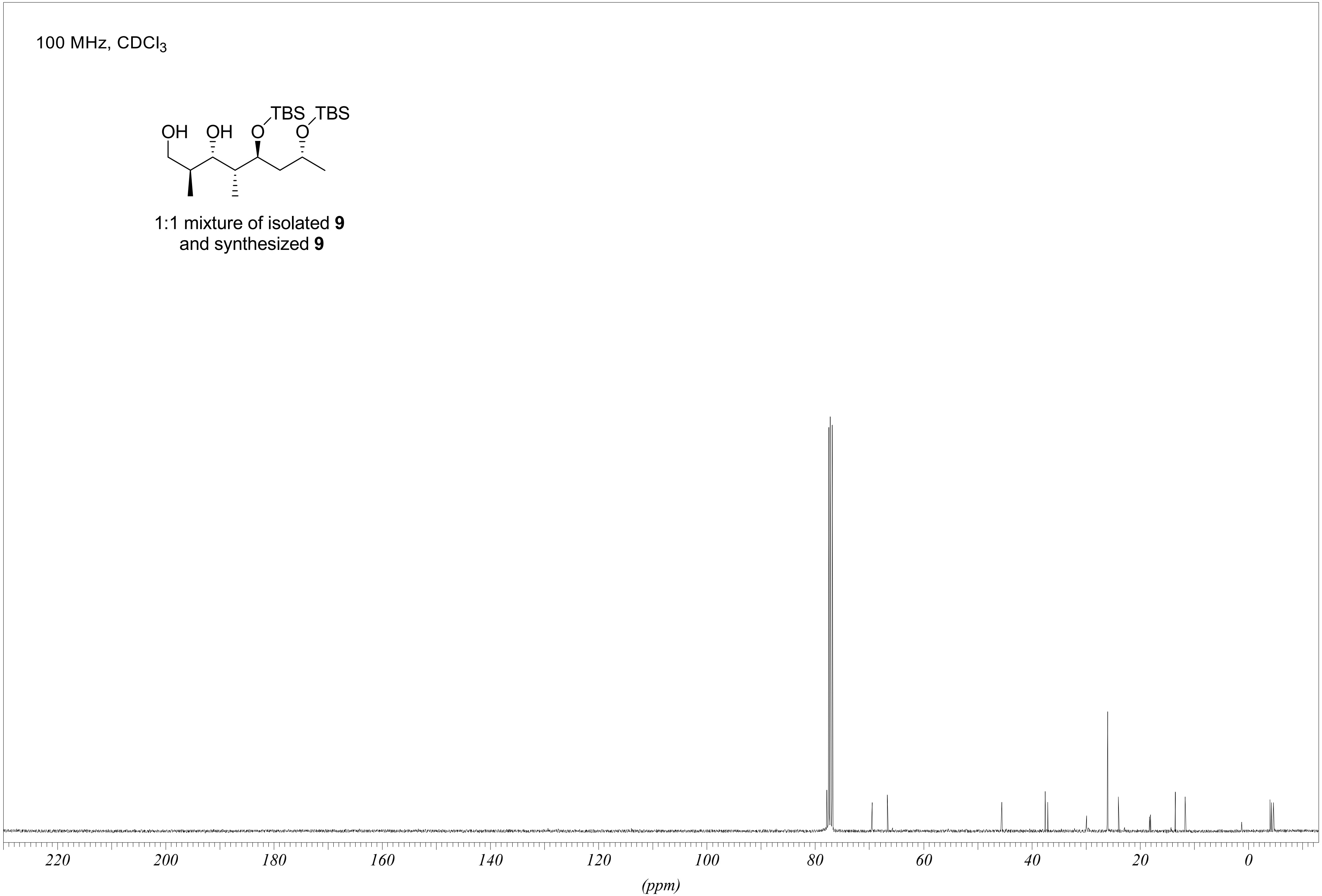


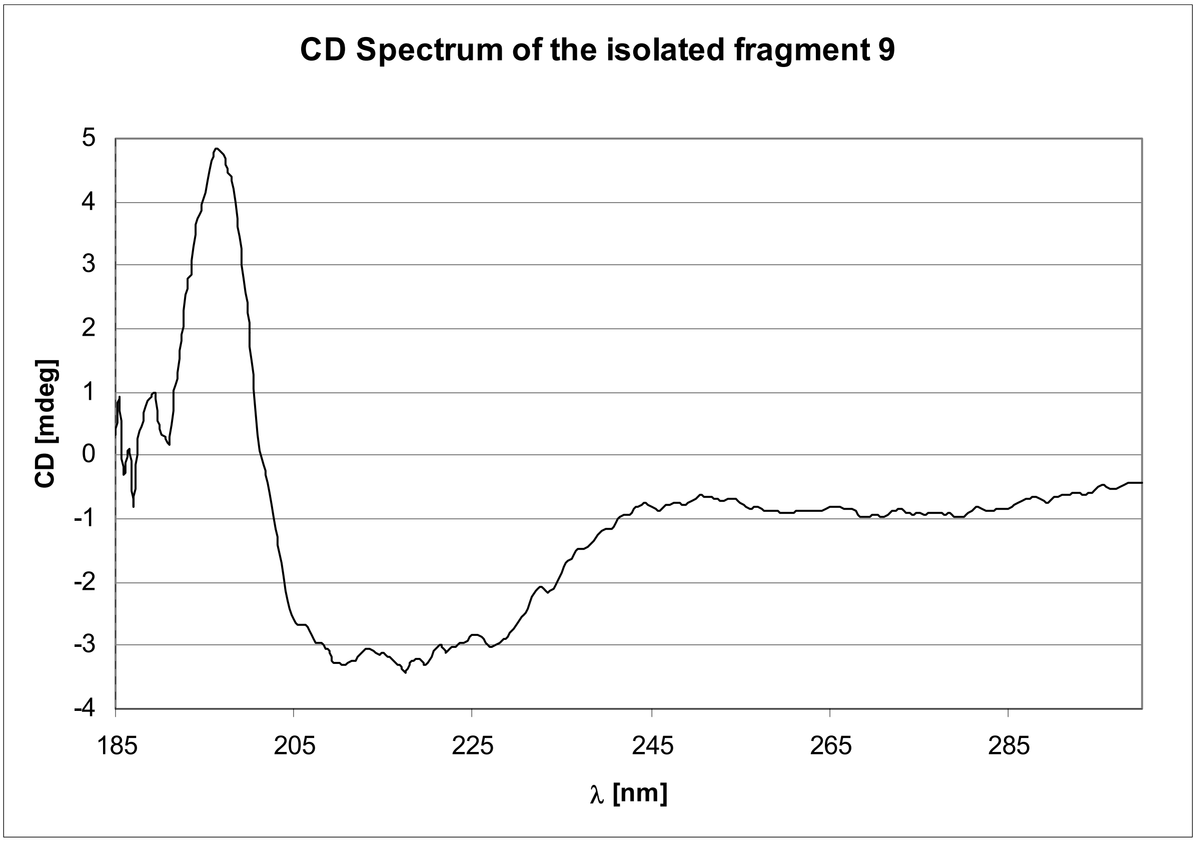


400 MHz, $CDCl_3$
OH OH O TBS O TBS
synthesized **9**
Integral
0.8818
2.0297
1.1657
1.0000
0.9543
1.1203
1.8822
2.3055
2.7728
2.7589
18.090
2.8580
5.5282
5.7113
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
(ppm)

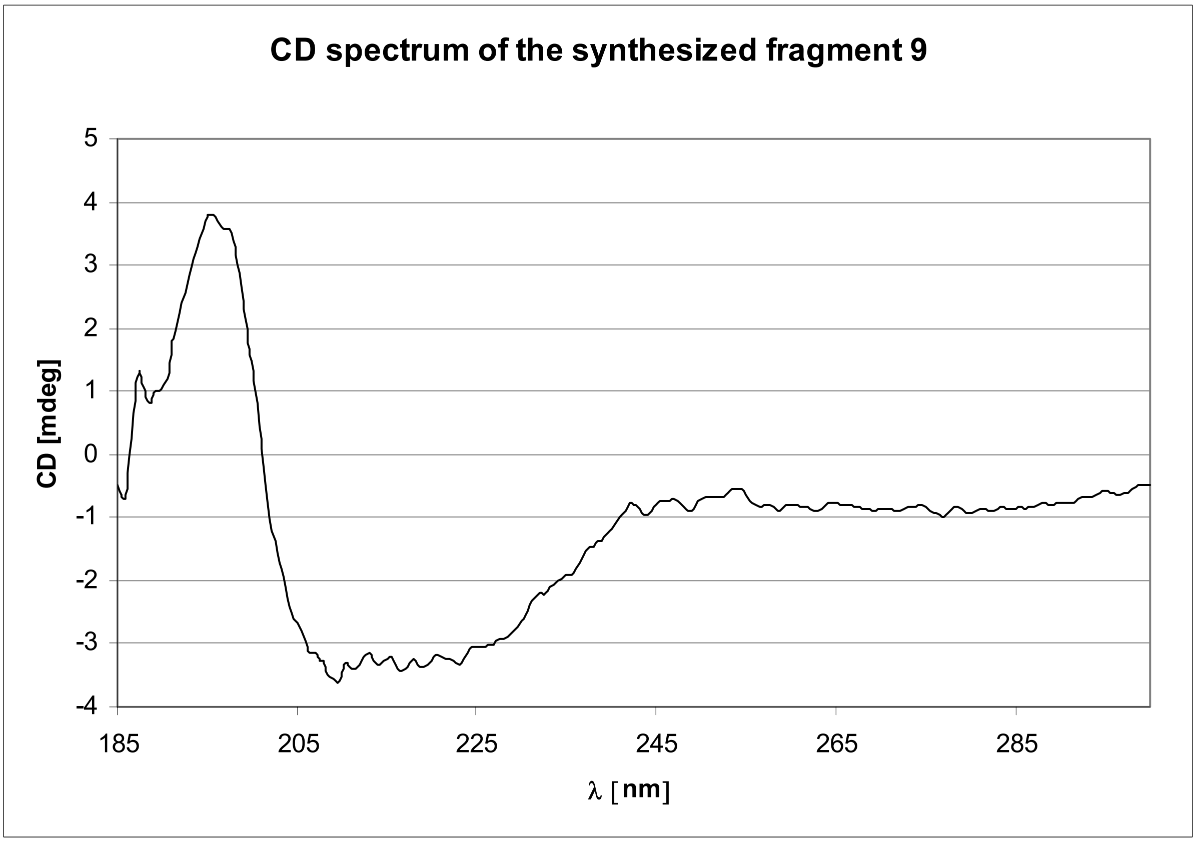

100 MHz, CDCl3
OH
OH
O
TBS
O
TBS
synthesized 9
220
200
180
160
140
120
100
80
60
40
20
0
(ppm)


400 MHz, CDCl3
OH
OH
O
TBS
O
TBS
1:1 mixture of isolated 9
and synthesized 9
Integral
1.0000
2.3071
1.3450
1.0860
1.1457
1.1055
2.2371
1.7260
3.0025
2.9245
18.005
3.0241
6.0176
6.0683
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)


100 MHz, CDCl3
OH
OH
O
TBS
O
TBS
1:1 mixture of isolated 9
and synthesized 9
220
200
180
160
140
120
100
80
60
40
20
0
(ppm)



CD Spectrum of the isolated fragment 9
5
4
3
2
1
0
-1
-2
-3
-4
CD [mdeg]
185
205
225
245
265
285
λ [nm]



CD spectrum of the synthesized fragment 9
5
4
3
2
1
0
-1
-2
-3
-4
CD [mdeg]
185
205
225
245
265
285
λ [nm]

III. Molecular Modeling

Perspective drawing of the global minimum of the conformational search of chivosazole A generated by Macromodel 8.0

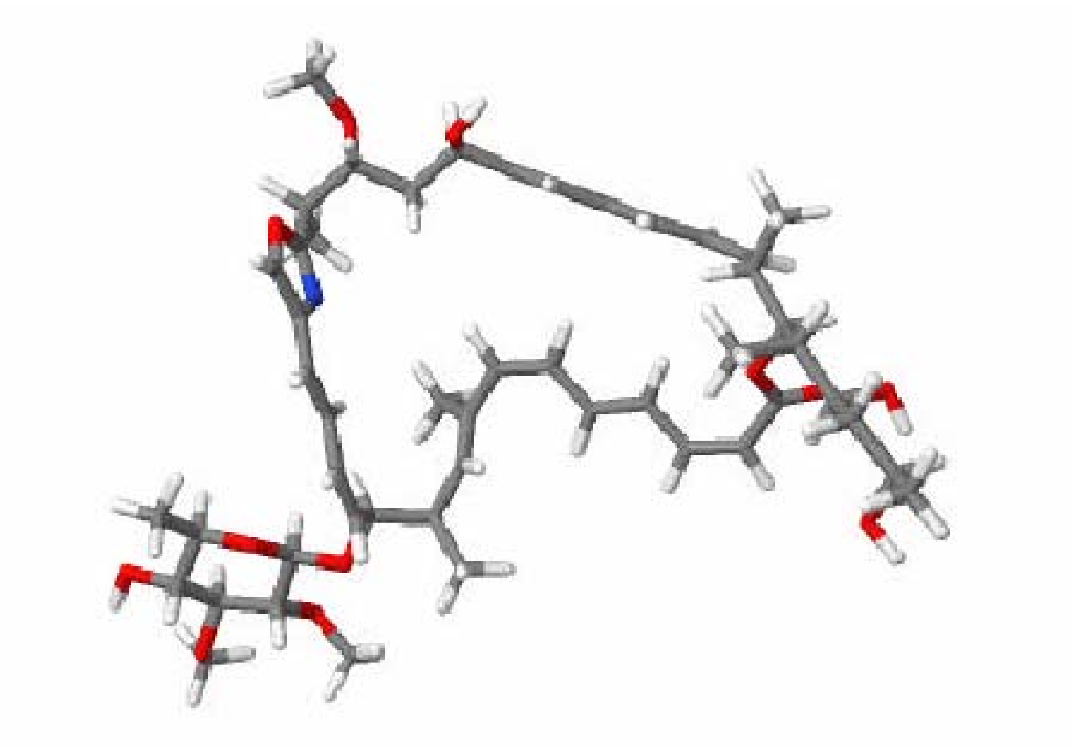


Table 2. Torsion angles resulted from molecular modeling

Compound	10L-11L-19D-20D-22L-29D-30D	10D-11D-19L-20L-22D-29L-30L	10L-11L-19L-20L-22D-29L-30L	10L-11L-19D-20L-22D-29L-30L	10L-11L-19D-20L-22D-29L-30L	10D-11D-19L-20D-22L-29D-30D	10L-11D-19D-20L-22D-29L-30L	10L-11L-19L-20D-22L-29D-30D
Force field	MMFF	MMFF	MMFF	MMFF	MMFF	MMFF	MMFF	MMFF
Energy [kJ mol-1][a]	579.630	604.198	626.566	637.536	591.998	610.873	603.238	642.117
Torsion angles [°]								
H9-H10	-150	162	34	34	-157	153	-170	30
H10-H11	-60	66	-66	-72	-66	67	85	-73
H11-H12	163	-156	166	153	163	-158	146	156
H19-H20	68	-68	-55	-63	-72	71	60	56
H20-H21a	-171	172	-168	-180	171	-173	-173	-177
H20-H21b	71	-69	-51	-62	-70	69	68	65
H21a-H22	70	-71	-52	-60	-70	71	67	66
H21b-H22	-173	172	-168	-176	172	-172	-176	-177
H22-H23	-52	53	68	53	51	-56	-54	-57
H28-H29	-159	172	162	169	159	-174	-158	171
H29-H30	174	-180	-170	180	-172	179	175	159
H30-H31	61	-53	-63	-53	-63	53	61	65

[a] In chloroform (GB/SA) as solvent

PDB output-file the global minimum of the conformational search of chivosazole A

```
HEADER    ALBERT1.MOL                                E =   620.3     kJ/mol
COMPDN    Mi 7 Dez 2005 13:54:02
SOURCE    from CHIVOSAZOLALBERT1.MOL (Sybyl 2) by Mol2Mol 3.50
HETATM    1  O   UNK     1       5.662   6.884  -1.450  1.00  0.00           O
HETATM    2  C   UNK     1       4.489   6.094  -1.706  1.00  0.00           C
HETATM    3  C   UNK     1       4.006   6.392  -3.108  1.00  0.00           C
HETATM    4  C   UNK     1       2.745   6.628  -3.504  1.00  0.00           C
HETATM    5  C   UNK     1       1.567   6.603  -2.665  1.00  0.00           C
HETATM    6  C   UNK     1       0.329   6.856  -3.118  1.00  0.00           C
HETATM    7  C   UNK     1      -0.842   6.822  -2.314  1.00  0.00           C
HETATM    8  N   UNK     1      -0.827   6.440  -0.996  1.00  0.00           N
HETATM    9  C   UNK     1       4.864   4.605  -1.487  1.00  0.00           C
HETATM   10  C   UNK     1       4.114  -1.671  -2.216  1.00  0.00           C
HETATM   11  C   UNK     1       2.904  -0.899  -2.032  1.00  0.00           C
HETATM   12  C   UNK     1       4.237  -2.966  -2.541  1.00  0.00           C
HETATM   13  C   UNK     1       2.926   0.390  -1.654  1.00  0.00           C
HETATM   14  C   UNK     1       1.727   1.175  -1.447  1.00  0.00           C
HETATM   15  C   UNK     1       1.662   2.450  -1.029  1.00  0.00           C
HETATM   16  C   UNK     1       2.772   3.339  -0.712  1.00  0.00           C
HETATM   17  C   UNK     1       3.665   3.695  -1.656  1.00  0.00           C
HETATM   18  C   UNK     1       2.760   3.845   0.703  1.00  0.00           C
HETATM   19  C   UNK     1       3.166  -3.945  -2.818  1.00  0.00           C
HETATM   20  O   UNK     1       3.257  -5.112  -2.463  1.00  0.00           O
HETATM   21  O   UNK     1       2.179  -3.392  -3.565  1.00  0.00           O
HETATM   22  C   UNK     1      -2.119   7.146  -2.700  1.00  0.00           C
HETATM   23  C   UNK     1      -2.088   6.554  -0.629  1.00  0.00           C
HETATM   24  O   UNK     1      -2.933   6.982  -1.620  1.00  0.00           O
HETATM   25  C   UNK     1      -2.714   6.285   0.701  1.00  0.00           C
HETATM   26  C   UNK     1      -3.530   4.967   0.680  1.00  0.00           C
HETATM   27  C   UNK     1      -2.654   3.694   0.634  1.00  0.00           C
HETATM   28  C   UNK     1      -3.494   2.424   0.408  1.00  0.00           C
HETATM   29  C   UNK     1      -2.660   1.177   0.571  1.00  0.00           C
HETATM   30  C   UNK     1      -2.328   0.313  -0.401  1.00  0.00           C
HETATM   31  C   UNK     1      -1.578  -0.902  -0.159  1.00  0.00           C
HETATM   32  C   UNK     1      -1.240  -1.753  -1.139  1.00  0.00           C
HETATM   33  C   UNK     1      -0.543  -2.997  -0.899  1.00  0.00           C
HETATM   34  C   UNK     1      -0.127  -3.872  -1.829  1.00  0.00           C
HETATM   35  C   UNK     1      -0.219  -3.736  -3.339  1.00  0.00           C
HETATM   36  C   UNK     1       1.089  -4.246  -4.009  1.00  0.00           C
HETATM   37  C   UNK     1      -1.457  -4.495  -3.823  1.00  0.00           C
HETATM   38  C   UNK     1       1.091  -4.239  -5.572  1.00  0.00           C
HETATM   39  C   UNK     1       6.018   4.125  -2.380  1.00  0.00           C
HETATM   40  C   UNK     1      -1.679   6.340   1.828  1.00  0.00           C
HETATM   41  O   UNK     1      -4.330   4.877   1.871  1.00  0.00           O
HETATM   42  O   UNK     1      -4.090   2.499  -0.885  1.00  0.00           O
HETATM   43  C   UNK     1      -5.590   5.523   1.753  1.00  0.00           C
HETATM   44  C   UNK     1       5.387   8.144  -0.818  1.00  0.00           C
HETATM   45  C   UNK     1       6.735   8.785  -0.454  1.00  0.00           C
HETATM   46  O   UNK     1       4.656   9.006  -1.689  1.00  0.00           O
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HETATM	47	C	UNK	1	4.322	10.251	-1.079	1.00	0.00	C
HETATM	48	C	UNK	1	6.530	10.189	0.135	1.00	0.00	C
HETATM	49	O	UNK	1	7.369	7.973	0.544	1.00	0.00	O
HETATM	50	O	UNK	1	7.794	10.872	0.177	1.00	0.00	O
HETATM	51	C	UNK	1	5.602	11.022	-0.755	1.00	0.00	C
HETATM	52	O	UNK	1	5.265	12.231	-0.079	1.00	0.00	O
HETATM	53	C	UNK	1	3.429	11.013	-2.052	1.00	0.00	C
HETATM	54	C	UNK	1	8.379	10.894	1.472	1.00	0.00	C
HETATM	55	C	UNK	1	8.493	7.259	0.050	1.00	0.00	C
HETATM	56	C	UNK	1	0.857	-2.830	-6.136	1.00	0.00	C
HETATM	57	C	UNK	1	2.408	-4.855	-6.131	1.00	0.00	C
HETATM	58	C	UNK	1	2.420	-4.978	-7.667	1.00	0.00	C
HETATM	59	H	UNK	1	5.246	4.512	-0.461	1.00	0.00	H
HETATM	60	H	UNK	1	-3.408	7.113	0.895	1.00	0.00	H
HETATM	61	H	UNK	1	-4.191	4.966	-0.198	1.00	0.00	H
HETATM	62	H	UNK	1	-4.310	2.381	1.139	1.00	0.00	H
HETATM	63	H	UNK	1	3.729	6.355	-0.962	1.00	0.00	H
HETATM	64	H	UNK	1	4.778	6.433	-3.875	1.00	0.00	H
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HETATM	66	H	UNK	1	1.702	6.355	-1.617	1.00	0.00	H
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HETATM	68	H	UNK	1	5.043	-1.132	-2.032	1.00	0.00	H
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HETATM	77	H	UNK	1	2.909	3.017	1.405	1.00	0.00	H
HETATM	78	H	UNK	1	-2.589	7.485	-3.611	1.00	0.00	H
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HETATM	83	H	UNK	1	-1.306	-1.120	0.871	1.00	0.00	H
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HETATM	87	H	UNK	1	-0.334	-2.675	-3.583	1.00	0.00	H
HETATM	88	H	UNK	1	1.251	-5.279	-3.675	1.00	0.00	H
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HETATM	95	H	UNK	1	6.912	4.740	-2.234	1.00	0.00	H
HETATM	96	H	UNK	1	-2.145	6.159	2.802	1.00	0.00	H
HETATM	97	H	UNK	1	-0.878	5.606	1.689	1.00	0.00	H

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HETATM   98  H   UNK     1      -1.204   7.328   1.867  1.00  0.00           H
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HETATM  100  H   UNK     1       7.373   8.858  -1.347  1.00  0.00           H
HETATM  101  H   UNK     1       6.112  10.129   1.150  1.00  0.00           H
HETATM  102  H   UNK     1       6.126  11.294  -1.680  1.00  0.00           H
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HETATM  104  H   UNK     1       3.101  11.970  -1.635  1.00  0.00           H
HETATM  105  H   UNK     1       3.951  11.201  -2.997  1.00  0.00           H
HETATM  106  H   UNK     1       2.542  10.419  -2.297  1.00  0.00           H
HETATM  107  H   UNK     1       6.098  12.686   0.134  1.00  0.00           H
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HETATM  110  H   UNK     1       8.555   9.882   1.843  1.00  0.00           H
HETATM  111  H   UNK     1       8.898   6.652   0.864  1.00  0.00           H
HETATM  112  H   UNK     1       8.206   6.595  -0.770  1.00  0.00           H
HETATM  113  H   UNK     1       9.269   7.956  -0.283  1.00  0.00           H
HETATM  114  H   UNK     1       0.268  -4.884  -5.903  1.00  0.00           H
HETATM  115  H   UNK     1      -6.123   5.407   2.701  1.00  0.00           H
HETATM  116  H   UNK     1      -5.472   6.591   1.553  1.00  0.00           H
HETATM  117  H   UNK     1      -6.186   5.055   0.964  1.00  0.00           H
HETATM  118  H   UNK     1       3.261  -4.249  -5.804  1.00  0.00           H
HETATM  119  O   UNK     1       2.558  -6.160  -5.568  1.00  0.00           O
HETATM  120  H   UNK     1       0.729  -2.853  -7.222  1.00  0.00           H
HETATM  121  H   UNK     1      -0.056  -2.380  -5.736  1.00  0.00           H
HETATM  122  H   UNK     1       1.695  -2.164  -5.907  1.00  0.00           H
HETATM  123  C   UNK     1       3.665  -5.679  -8.229  1.00  0.00           C
HETATM  124  H   UNK     1       1.532  -5.533  -7.993  1.00  0.00           H
HETATM  125  H   UNK     1       2.367  -3.974  -8.104  1.00  0.00           H
HETATM  126  H   UNK     1       3.491  -6.415  -5.660  1.00  0.00           H
HETATM  127  H   UNK     1       3.734  -6.702  -7.844  1.00  0.00           H
HETATM  128  O   UNK     1       4.828  -4.970  -7.813  1.00  0.00           O
HETATM  129  C   UNK     1       3.632  -5.722  -9.751  1.00  0.00           C
HETATM  130  H   UNK     1       5.602  -5.438  -8.171  1.00  0.00           H
HETATM  131  H   UNK     1       3.629  -4.710 -10.172  1.00  0.00           H
HETATM  132  H   UNK     1       2.750  -6.257 -10.115  1.00  0.00           H
HETATM  133  H   UNK     1       4.526  -6.220 -10.140  1.00  0.00           H
CONECT    1    2   44
CONECT    2    1    3    9   63
CONECT    3    2    4   64
CONECT    4    3    5   65
CONECT    5    4    6   66
CONECT    6    5    7   67
CONECT    7    6    8   22
CONECT    8    7   23
CONECT    9    2   17   39   59
CONECT   10   11   12   68
CONECT   11   10   13   69
CONECT   12   10   19   70
CONECT   13   11   14   71
CONECT   14   13   15   72
CONECT   15   14   16   73
```

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CONECT   16   15   17   18
CONECT   17    9   16   74
CONECT   18   16   75   76   77
CONECT   19   12   20   21
CONECT   20   19
CONECT   21   19   36
CONECT   22    7   24   78
CONECT   23    8   24   25
CONECT   24   22   23
CONECT   25   23   26   40   60
CONECT   26   25   27   41   61
CONECT   27   26   28   79   80
CONECT   28   27   29   42   62
CONECT   29   28   30   81
CONECT   30   29   31   82
CONECT   31   30   32   83
CONECT   32   31   33   84
CONECT   33   32   34   85
CONECT   34   33   35   86
CONECT   35   34   36   37   87
CONECT   36   21   35   38   88
CONECT   37   35   90   91   92
CONECT   38   36   56   57  114
CONECT   39    9   93   94   95
CONECT   40   25   96   97   98
CONECT   41   26   43
CONECT   42   28   89
CONECT   43   41  115  116  117
CONECT   44    1   45   46   99
CONECT   45   44   48   49  100
CONECT   46   44   47
CONECT   47   46   51   53  103
CONECT   48   45   50   51  101
CONECT   49   45   55
CONECT   50   48   54
CONECT   51   47   48   52  102
CONECT   52   51  107
CONECT   53   47  104  105  106
CONECT   54   50  108  109  110
CONECT   55   49  111  112  113
CONECT   56   38  120  121  122
CONECT   57   38   58  118  119
CONECT   58   57  123  124  125
CONECT   59    9
CONECT   60   25
CONECT   61   26
CONECT   62   28
CONECT   63    2
CONECT   64    3
CONECT   65    4
CONECT   66    5
```

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CONECT   67    6
CONECT   68   10
CONECT   69   11
CONECT   70   12
CONECT   71   13
CONECT   72   14
CONECT   73   15
CONECT   74   17
CONECT   75   18
CONECT   76   18
CONECT   77   18
CONECT   78   22
CONECT   79   27
CONECT   80   27
CONECT   81   29
CONECT   82   30
CONECT   83   31
CONECT   84   32
CONECT   85   33
CONECT   86   34
CONECT   87   35
CONECT   88   36
CONECT   89   42
CONECT   90   37
CONECT   91   37
CONECT   92   37
CONECT   93   39
CONECT   94   39
CONECT   95   39
CONECT   96   40
CONECT   97   40
CONECT   98   40
CONECT   99   44
CONECT  100   45
CONECT  101   48
CONECT  102   51
CONECT  103   47
CONECT  104   53
CONECT  105   53
CONECT  106   53
CONECT  107   52
CONECT  108   54
CONECT  109   54
CONECT  110   54
CONECT  111   55
CONECT  112   55
CONECT  113   55
CONECT  114   38
CONECT  115   43
CONECT  116   43
CONECT  117   43
```

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CONECT  118   57
CONECT  119   57  126
CONECT  120   56
CONECT  121   56
CONECT  122   56
CONECT  123   58  127  128  129
CONECT  124   58
CONECT  125   58
CONECT  126  119
CONECT  127  123
CONECT  128  123  130
CONECT  129  123  131  132  133
CONECT  130  128
CONECT  131  129
CONECT  132  129
CONECT  133  129
END
```