Supplementary Material for Organic & Biomolecular Chemistry

ELECTRONIC SUPPLEMENTARY INFORMATION

Synthesis of naturally occurring iminosugars from D-fructose by the use of a zinc-mediated fragmentation reaction

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(2*R*,3*R*,4*R*)-*N*-Trifluoroacetyl-1,3,4-tris(benzyloxy)-2-(but-3-enylamino)-hex-5-ene (8)

To a solution of **7R** (0.224 g, 0.475 mmol) in dry CH_2Cl_2 (20 mL) was added Et_3N (0.64 mL, 4.6 mmol) and the mixture was cooled to 0 °C. TFAA (0.32 mL, 2.26 mmol) was added and the solution was warmed to room temterature over 30 min. The mixture was diluted with CH_2Cl_2 (20 mL), washed with saturated aqueous $NaHCO_3$ (2 × 30 mL), dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (hexane–EtOAc, 7:1) to give **8** (0.220 g, 82%) which showed a mixture of rotamers by NMR. R_f 0.55 (hexane–Et_2O, 3:1); $[\alpha]_D$ +5.5 (*c* 2, $CHCl_3$); ν_{max}(neat)/cm^{-1}: 2868, 1688, 1208, 1147, 1095; δ_H (300 MHz, $CDCl_3$): 7.35-7.27 (m, 15H), 6.07-5.25 (m, 4H), 4.98-4.88 (m, 2H), 4.75-4.36 (m, 6H), 4.19-3.67 (m, 5H), 3.62-3.15 (m, 2H), 2.54-2.42 (m, 1H), 2.32-2.20 (m, 1H); δ_C (75 MHz, $CDCl_3$): 157.6, 157.1, 138.1, 138.0, 137.9 (2C), 137.8, 137.7, 135.4, 134.9, 134.5, 134.1, 128.5 (7C), 128.4, 128.2, 128.1, 128.0 (2C), 127.8 (3C), 127.7 (2C), 127.6, 120.6, 119.7, 118.3, 117.1, 116.7, 114.5, 83.3, 82.9, 80.4, 80.0, 75.2, 75.1, 73.2, 73.0, 70.6 (2C), 67.1, 66.7, 62.6, 57.4, 49.3, 44.5, 33.7, 31.4; HRMS calcd. for $C_{33}H_{37}F_3NO_4$ $[M+H]^+$ *m/z* 568.2675, found *m/z* 568.2675.

(2*R*,3*R*,4*R*)-*N*-Trifluoroacetyl-3,4-bis(benzyloxy)-2-benzyloxymethyl-5,6-didehydro-azocane (9)

A solution of **8** (0.930 g, 1.64 mmol) in dry CH_2Cl_2 (80 mL) was degassed under N_2 for 3 min and Grubbs 2nd generation catalyst (0.028 g, 0.033 mmol) was added. The mixture was stirred overnight at room temperature followed by addition of a 1.5 M solution of $P(CH_2OH)_3$ in isopropanol (2.4 mL) and stirring for an additional 24 h. H_2O

(60 mL) was added and the phases were separated. The organic layer was washed with H_2O (40 mL), dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (hexane–EtOAc, 4:1) to give the title compound (0.630 g, 71%). $[\alpha]_D$ +45.4 (*c* 2, $CHCl_3$); ν_{max}(neat)/cm^{-1}: 3030, 2930, 1694, 1455, 1190, 1146, 1102; δ_H (300 MHz, $CDCl_3$): 7.39-7.25 (m, 15H), 5.84-5.79 (m, 2H), 4.83 (d, *J* = 11.3 Hz, 1H), 4.66 (d, *J* = 11.6 Hz, 1H), 4.57-4.43 (m, 5H), 4.32-4.25 (m, 2H), 3.94-3.82 (m, 2H), 3.59-3.53 (m, 1H), 3.34-3.27 (m, 1H), 2.55 (br s, 1H), 2.32-2.28 (m, 1H); δ_C (75 MHz, $CDCl_3$): 157.4, 156.9, 138.5, 138.3, 138.1, 128.5, 128.4 (3C), 128.2, 127.9, 127.7, 127.6 (3C), 80.3, 76.1, 74.9, 73.2, 71.6, 67.0, 64.4, 49.4, 27.0; HRMS calcd. for $C_{31}H_{32}F_3NO_4Na$ $[M+Na]^+$ *m/z* 562.2181, found *m/z* 562.2188.

(2*R*,3*R*,4*R*)-*N*-Trifluoroacetyl-3,4-bis(benzyloxy)-2-benzyloxymethyl-5,6-epoxy-azocane (10)

A solution of **9** (0.045 g, 0.083 mmol) in CH_2Cl_2 (1 mL) was cooled to 0 °C and *m*-CPBA (0.056 g, 0.32 mmol) was added. The reaction mixture was stirred at ambient temperature for 6 h followed by addition of 10% aqueous Na_2SO_3 (2.5 mL) and stirring for an additional 10 min. The mixture was diluted with CH_2Cl_2 (5 mL), washed with saturated aqueous $NaHCO_3$ (3 mL) and brine (3 mL). The organic phase was dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (hexane–EtOAc, 5:1) to afford **10** (0.026 g, 56%) as a 1:1 diastereomeric mixture. R_f 0.18 (heptane–Et_2O, 3:1); ν_{max}(neat)/cm^{-1}: 3031, 2866, 1693, 1455, 1201, 1141, 1106; δ_H (300 MHz, $CDCl_3$): 7.30-7.07 (m, 30H), 4.84 (dd, *J* = 10.1, 5.5 Hz, 2H), 4.61 (d, *J* = 7.8 Hz, 1H), 4.51-4.29 (m, 10H), 4.19-4.07 (m, 3H), 3.94-3.83 (m, 4H), 3.66 (dd, *J* = 9.9, 3.8 Hz, 1H), 3.45-2.92 (m, 11H), 2.25-2.13 (m, 2H); δ_C (75 MHz, $CDCl_3$): 138.3 (2C), 138.1, 138.0, 137.5, 137.3, 128.7, 128.5 (2C), 128.4 (2C), 128.3 (2C), 128.2, 128.1, 128.0, 127.8 (4C), 127.6 (2C), 84.7, 76.4, 74.7, 73.7 (2C), 73.5, 73.4 (2C), 73.2, 67.6, 67.3, 66.1, 62.8, 57.1, 54.2, 53.1, 51.8, 48.3, 46.6, 30.2, 26.4; HRMS calcd. for $C_{31}H_{33}F_3NO_5$ $[M+H]^+$ *m/z* 556.2311, found *m/z* 556.2323.

The diastereomeric mixture of **10** (0.088 g, 0.158 mmol) and $LiOH•H_2O$ (0.067 g, 1.6 mmol) were dissolved in EtOH–H_2O (25 mL, 1:1) and the mixture was stirred at reflux for 24 h. The solution was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (15 mL), dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (CH_2Cl_2–MeOH, 23:2) to give 22 mg (30%) of the unreacted diastereomer of **10** and 30 mg (41%) of (1*S*,5*R*,6*R*,7*R*,7a*R*)-6,7-bis(benzyloxy)-5-benzyloxymethyl-hexahydro-1*H*-pyrrolizidin-1-ol. R_f 0.48 (CH_2Cl_2–MeOH, 9:1); $[\alpha]_D$ +4.8 (*c* 1, $CHCl_3$); ν_{max}(neat)/cm^{-1}: 3400, 2862, 2454, 1114, 735, 699; δ_H (300 MHz, $CDCl_3$): 7.37-7.24 (m, 15H), 4.66 (d, *J* = 11.7 Hz, 1H), 4.57-4.46 (m, 5H), 4.30 (t, *J* = 4.5 Hz, 1H), 4.16 (t, *J* = 5.6 Hz, 1H), 4.09 (m, 1H), 3.63-3.56 (m, 3H), 3.31 (br s, 1H), 3.13 (q, *J* = 6.0 Hz, 1H), 2.86-2.78 (m, 1H), 2.02-1.86 (m, 2H); δ_C (75 MHz, $CDCl_3$): 138.4, 138.1, 137.7, 128.6 (2C), 128.4, 128.0, 127.9, 127.8, 127.7, 85.3, 81.1, 73.4, 73.0, 72.7, 72.3, 71.5, 69.9, 53.1, 36.9; HRMS calcd. for $C_{29}H_{34}NO_4$ $[M+H]^+$ *m/z* 460.2488, found *m/z* 460.2489. Hydrogenolysis over $Pd(OH)_2/C$ in MeOH furnished australine with spectral data in accordance with literature values.

(2*R*,3*R*,4*R*)-*N*-Benzyloxycarbonyl-1,3,4-tris(benzyloxy)-2-(but-3-enylamino)-hex-5-ene (11)

To a solution of **7R** (0.302 g, 0.640 mmol) in CH_2Cl_2 (23 mL) and H_2O (20 mL) was added $KHCO_3$ (0.44 g, 4.4 mmol) and the solution was cooled to 0 °C. CbzCl (0.1 mL, 0.71 mmol) was added over 2 min and the mixture was stirred at room temperature for 1 h. The two phases were separated and the organic phase was washed with H_2O (30 mL), dried (K_2CO_3), and concentrated. The residue was purified by flash chromatography (hexane–Et_2O, 3:1) to give the title compound (0.312 g, 80%). R_f 0.56 (hexane–Et_2O, 3:1); $[\alpha]_D$ +10.9 (*c* 2.1, CH_2Cl_2); ν_{max}(neat)/cm^{-1}: 3031, 2864, 1697, 1454, 1096, 735, 699; δ_H (300 MHz, $CDCl_3$): 7.38-7.25 (m, 20H), 6.03-5.58 (m, 2H), 5.35-5.12 (m, 4H), 5.02-4.73 (m, 3H), 4.61-4.25 (m, 6H), 4.02-3.63 (m, 4H), 3.42-3.12 (m, 2H), 2.40-2.27 (m, 2H); δ_C (75 MHz, $CDCl_3$): 156.1, 138.3, 137.0, 136.6, 135.8, 128.5, 128.4, 128.1, 128.0, 127.7, 127.5, 119.2, 116.1, 82.9, 82.5, 82,1, 75.0, 73.0, 68.3, 67.2, 58.7, 47.1, 33.0; Anal. calcd. for $C_{39}H_{43}NO_5$: C, 77.33; H, 7.15; N, 2.31. Found: C, 77.04; H, 7.21; N, 2.34%.

(2*R*,3*R*,4*R*)-*N*-Benzyloxycarbonyl-3,4-bis(benzyloxy)-2-benzyloxymethyl-5,6-didehydro-azocane (12)

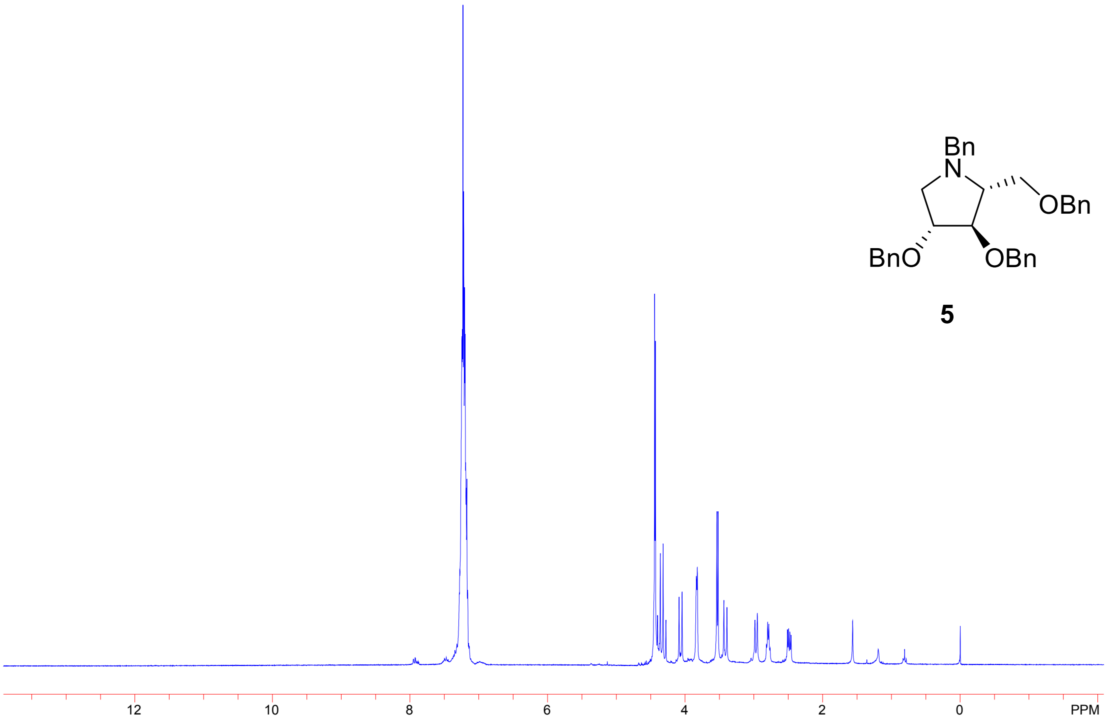
A solution of **11** (0.431 g, 0.711 mmol) in dry CH_2Cl_2 (35 mL) was degassed under N_2 for 5 min followed by addition of Grubbs 2nd generation catalyst (0.03 g, 0.035 mmol). The mixture was stirred at room temperature for 24 h. A 1.5 M solution of $P(CH_2OH)_3$ in isopropanol (0.6 mL) was added and the stirring was continued for an additional 5 h. H_2O (15 mL) was added and the phases were separated. The organic phase was washed with H_2O (15 mL), dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (hexane–Et_2O, 3:1) to give **12** (0.320 g, 78%). R_f 0.28 (heptane–EtOAc, 3:1); $[\alpha]_D$ +62.0 (*c* 1.0, $CHCl_3$); ν_{max}(neat)/cm^{-1}: 3019, 2863, 1698, 1454, 1210, 1104; δ_H (300 MHz, $CDCl_3$): 7.23-7.18 (m, 20H), 5.79-5.48 (m, 2H), 4.96-3.63 (m, 13H), 3.22-3.21 (m, 1H), 2.87-2.82 (m, 1H), 2.36-2.32 (m, 1H), 2.10-2.00 (m, 1H); δ_C (75 MHz, $CDCl_3$): 138.7, 138.5, 138.4, 138.2, 137.0, 128.6, 128.5, 128.4, 128.2, 127.9, 127.8, 127.6, 127.5, 78.3, 77.4, 74.8, 73.1, 73.0, 71.5, 69.8, 69.0, 67.3, 66.5, 61.4, 27.1; HRMS calcd. for $C_{37}H_{40}NO_5$ $[M+H]^+$ *m/z* 578.2906, found *m/z* 578.2951.

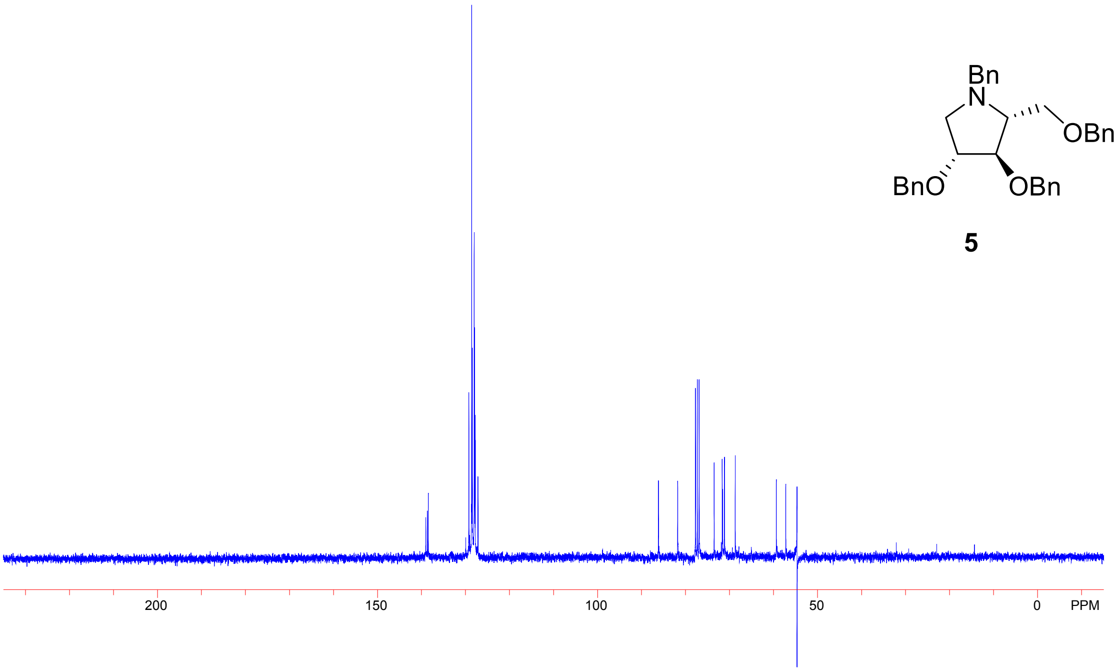
(9*R*,10*R*,10a*R*)-9,10-Bis(benzyloxy)-1,5,6,9,10,10a-hexahydro[1,3]oxazolo[3,4-*a*]azocin-3-one (13)

To an ice-cooled solution of carbamate **12** (0.320 g, 0.554 mmol) in dry CH_2Cl_2 (9 mL) and Ac_2O (9 mL) was added a 0.5 M solution of TMSOTf in CH_2Cl_2 (0.3 mL, 0.15 mmol). The reaction mixture was stirred at 0 °C for 30 min. Saturated aqueous $NaHCO_3$ (20 mL) was added and the stirring was continued for 1 h. The organic phase was isolated and the aqueous phase extracted with CH_2Cl_2 (2 × 20 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. The residue was dissolved in MeOH (7.5 mL) and a 1 M solution of NaOMe in MeOH (0.37 mL) was added. The mixture was stirred for 6 h and then neutralized with 1 M HCl and concentrated to remove MeOH. The residue was dissolved in EtOAc (20 mL), washed with brine (10 mL), dried ($MgSO_4$), concentrated and purified by flash chromatography (hexane–EtOAc, 2:1) to give oxazolidinone **13** (0.090 g, 43%). R_f 0.45 (CH_2Cl_2–MeOH, 49:1); $[\alpha]_D$ +21.8 (*c* 1, $CHCl_3$) (lit.[1] $[\alpha]_D^{23}$ +22.8 (*c* 1.33, $CHCl_3$)); ν_{max}(neat)/cm^{-1}: 3028, 2870, 1749, 1419, 1209, 1076, 742; δ_H (300 MHz, $CDCl_3$): 7.38-7.26 (m, 10H), 5.83-5.70 (m, 2H), 5.13 (d, *J* = 10.7 Hz, 1H), 4.72 (d, *J* = 11.7 Hz, 1H), 4.58 (d, *J* = 11.1 Hz, 1H), 4.50 (d, *J* = 11.8 Hz, 1H), 4.33-4.26 (m, 2H), 4.17 (d, *J* = 9.0 Hz, 1H), 3.76 (dt, *J* = 12.8, 5.4 Hz, 1H), 3.53-3.42 (m, 2H), 3.12 (dq, *J* = 13.4, 3.1 Hz, 1H), 2.43-2.36 (m, 1H), 2.33-2.24 (m, 1H); δ_C (75 MHz, $CDCl_3$): 159.9, 138.1, 137.9, 133.1, 128.7, 128.5, 128.4, 128.2, 128.1, 127.9, 127.8, 81.5, 78.8, 75.9, 71.2, 68.5, 58.7, 43.9, 27.0; HRMS calcd. for $C_{23}H_{26}NO_4$ $[M+H]^+$ *m/z* 380.1862, found *m/z* 380.1861.

Reference

1) J. D. White and P. Hrnciar, *J. Org. Chem.*, 2000, **65**, 9129-9142.





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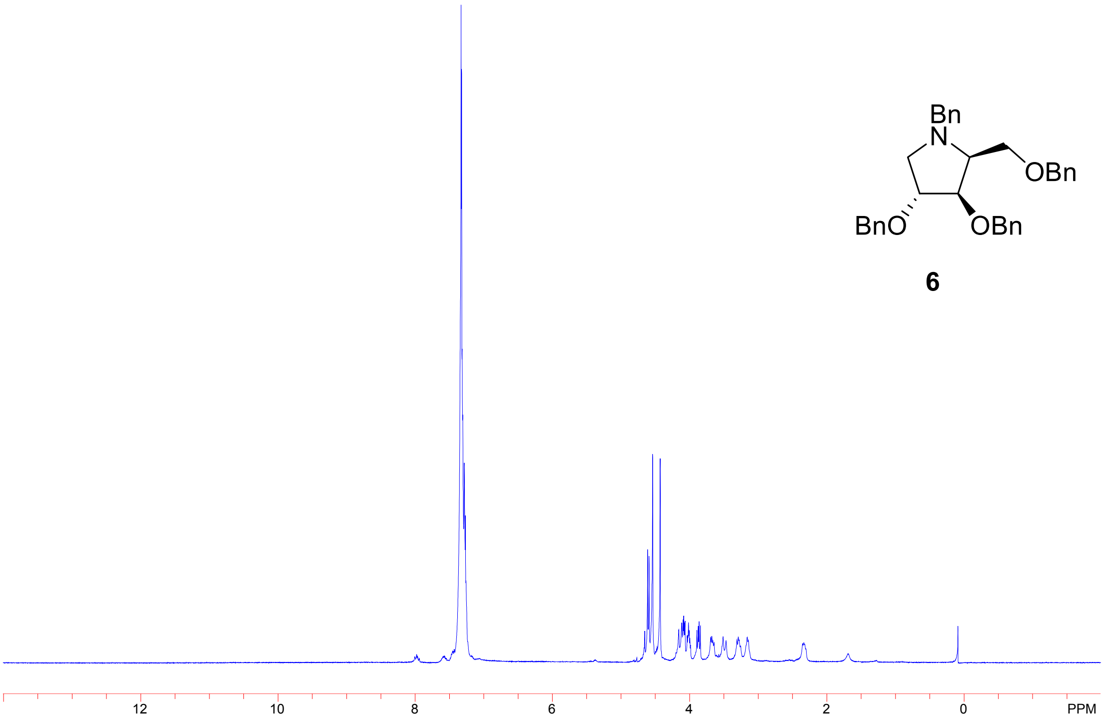
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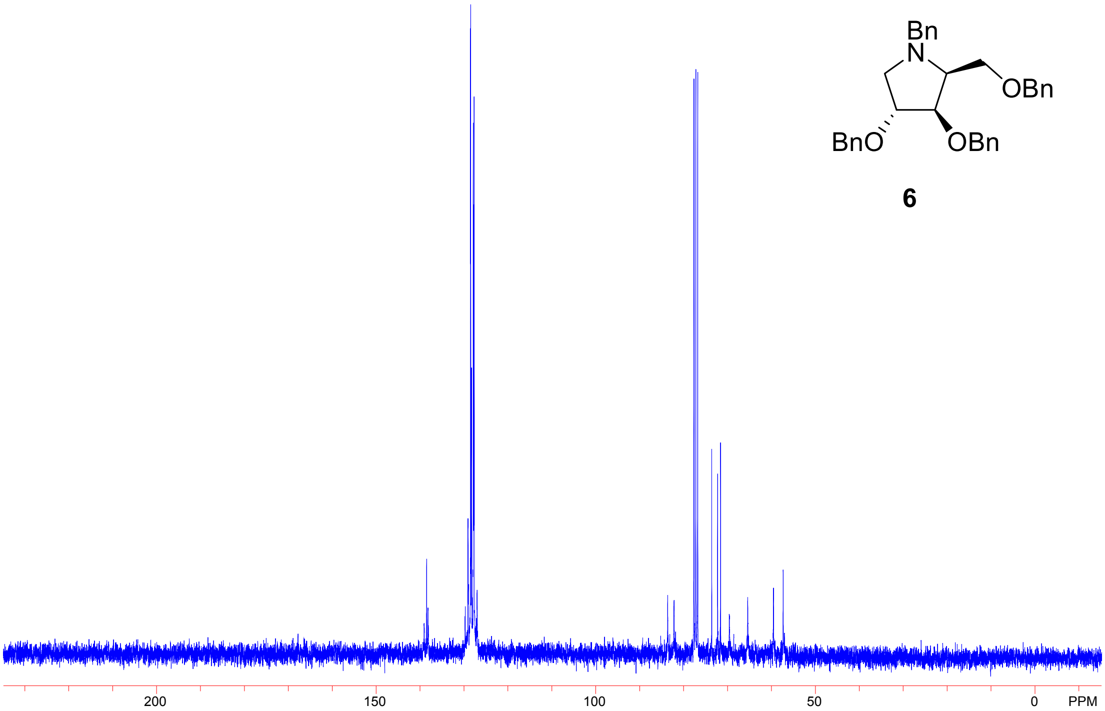
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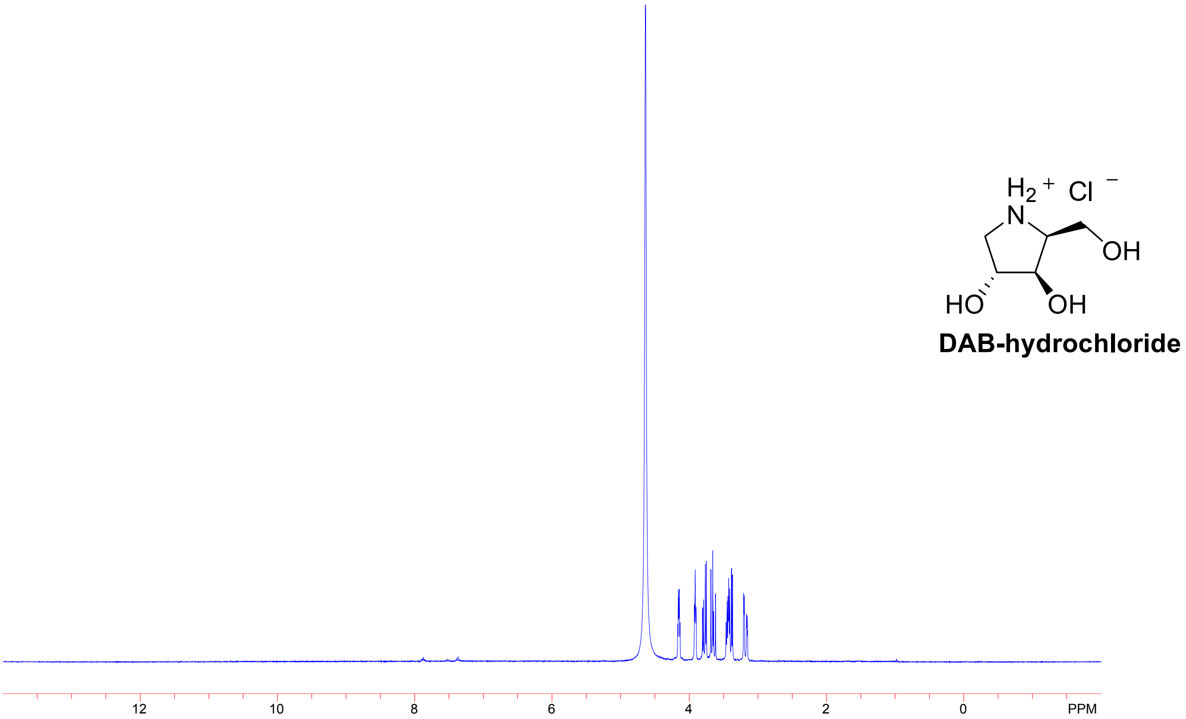
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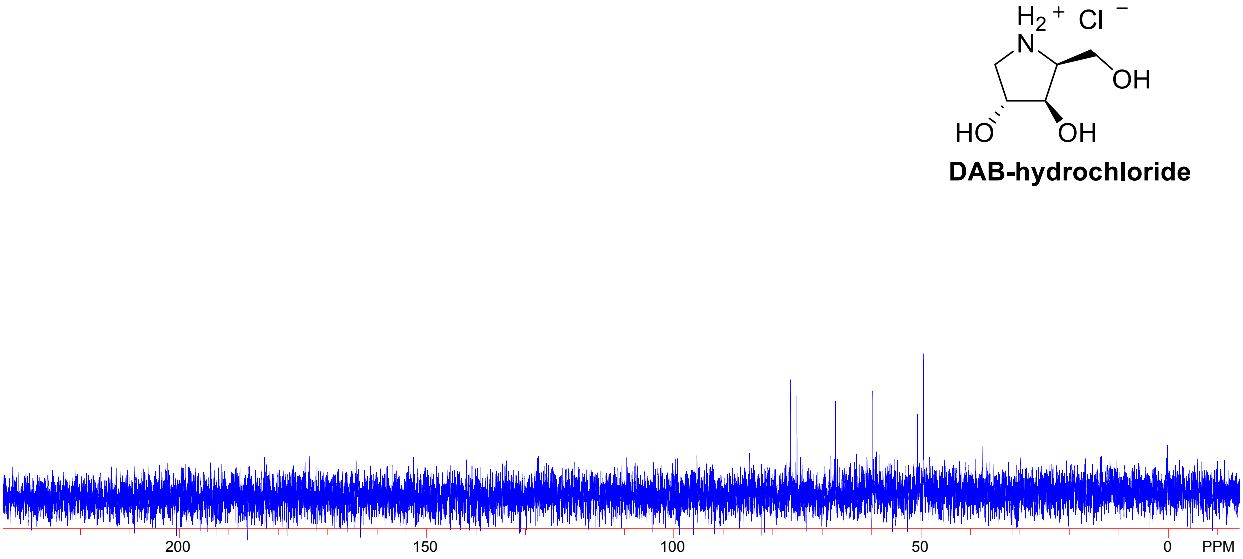
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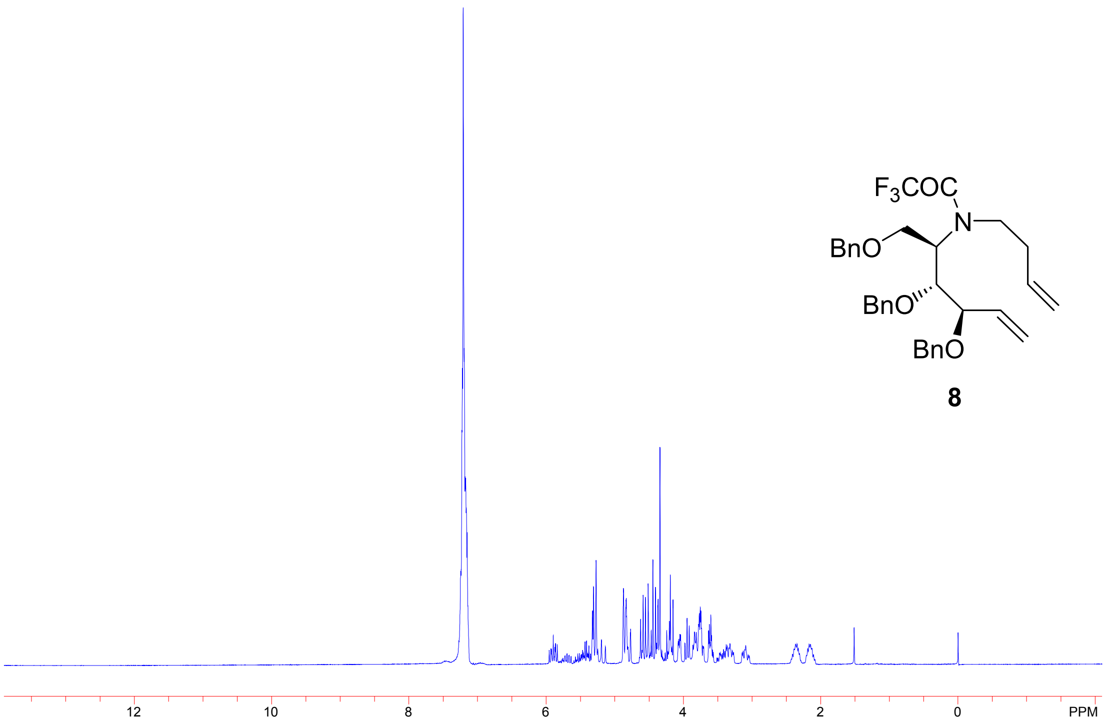

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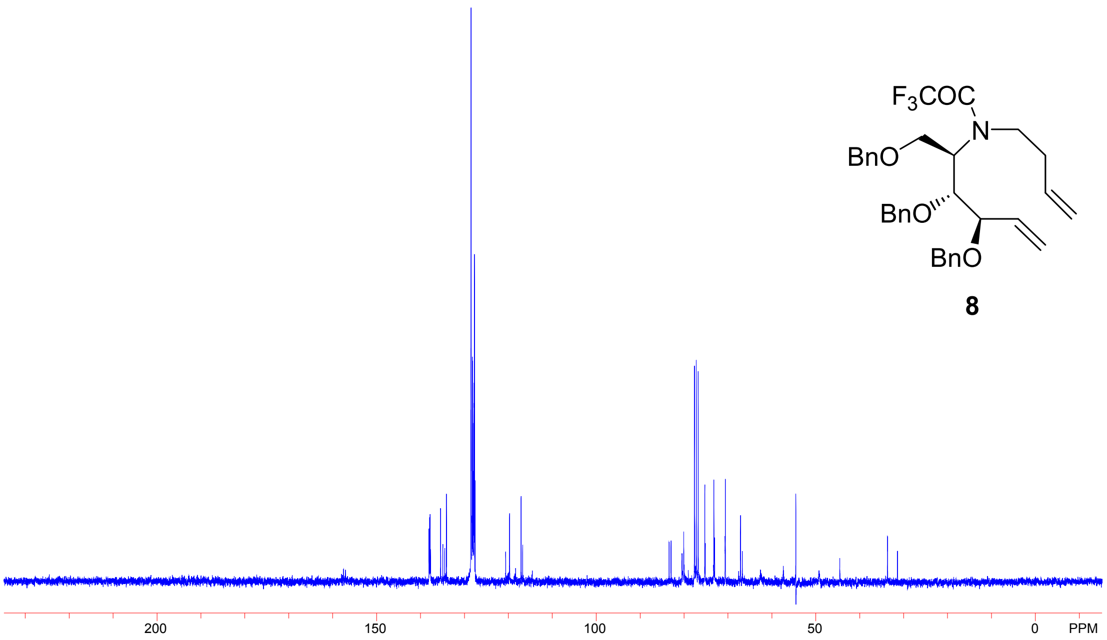

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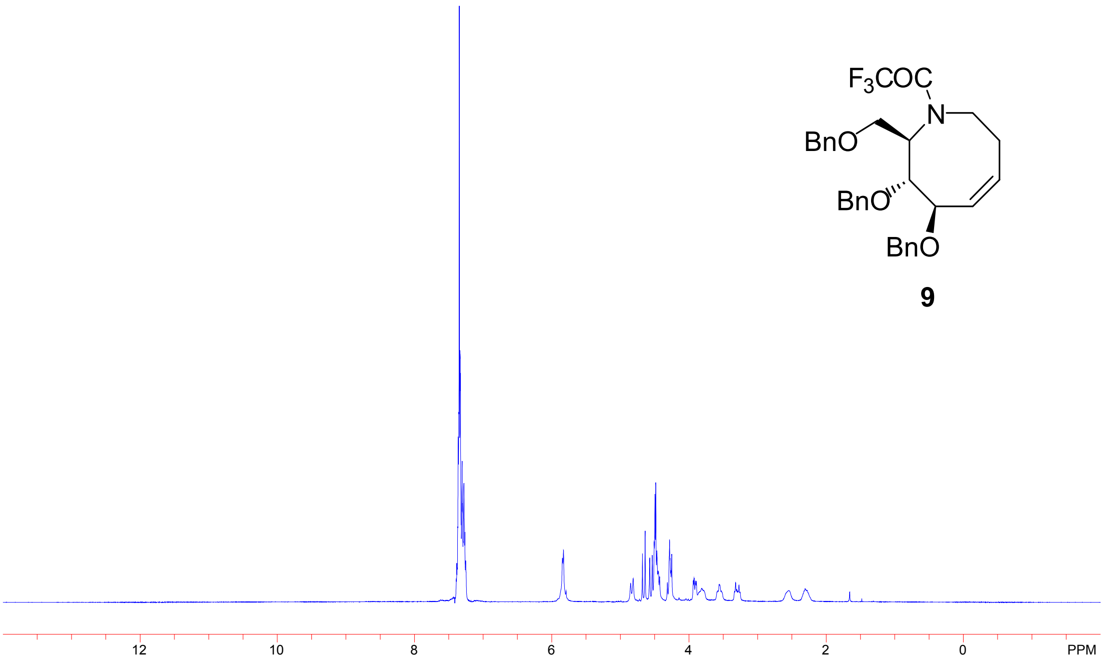

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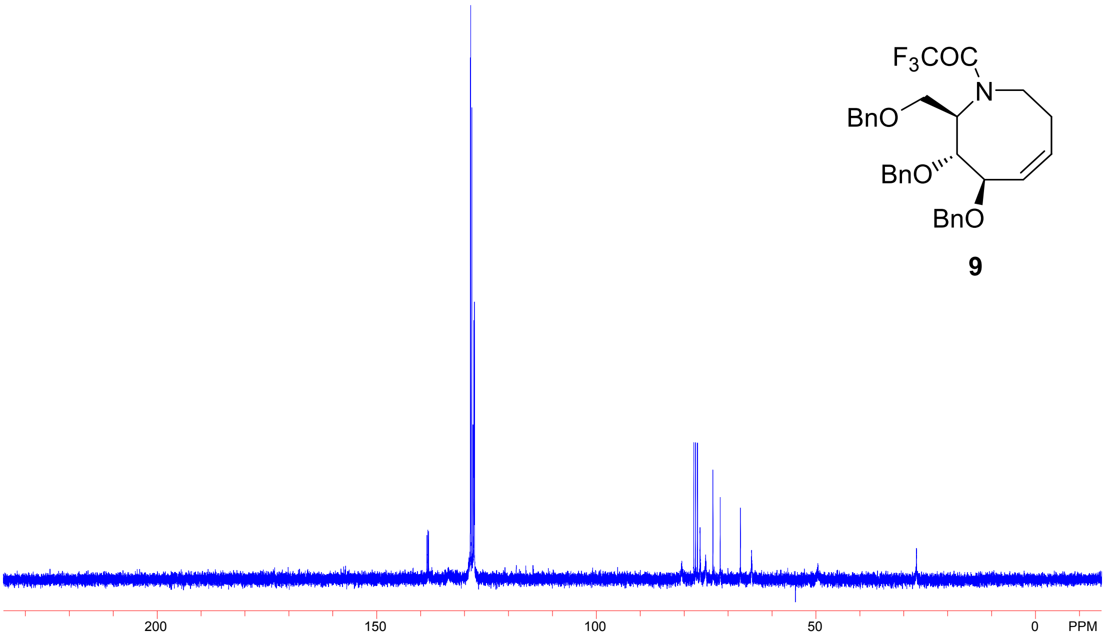

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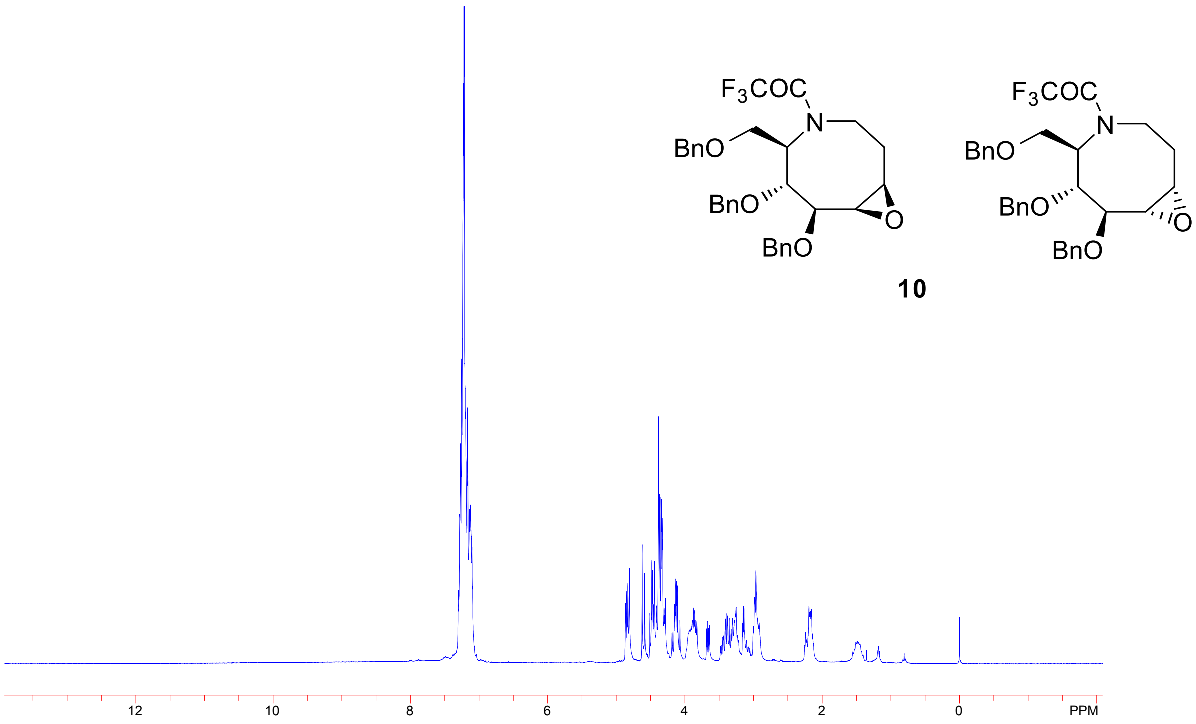

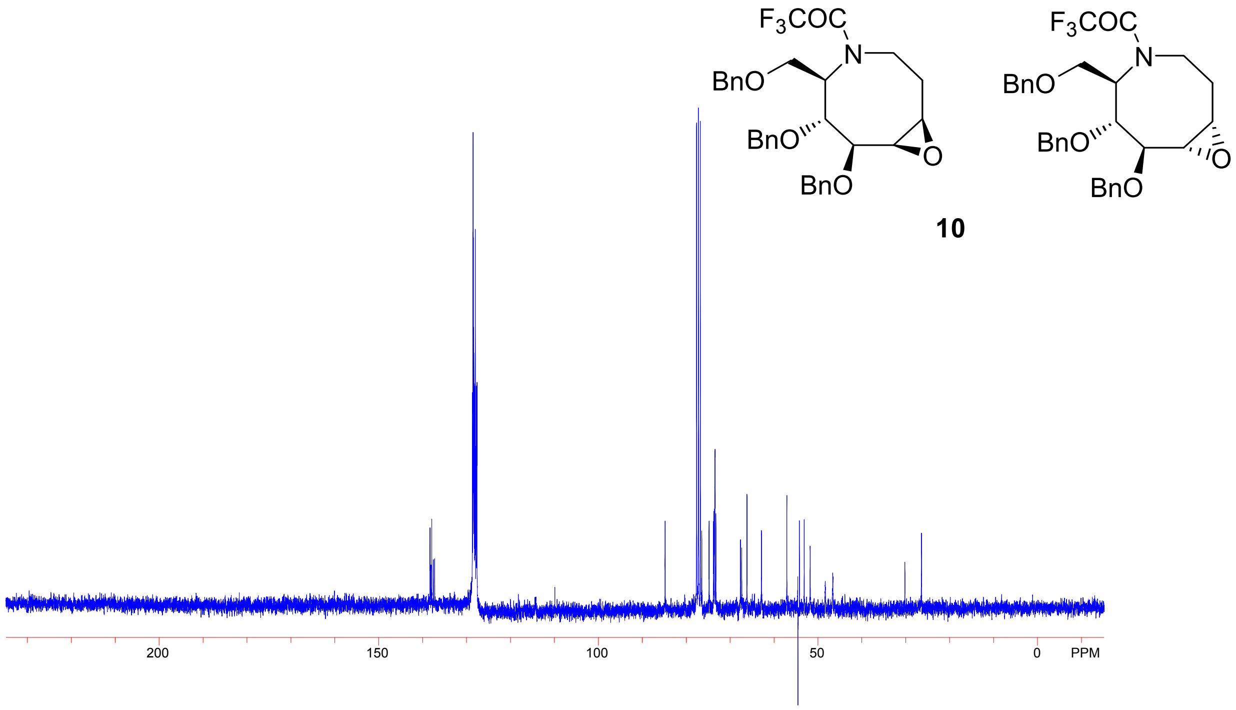

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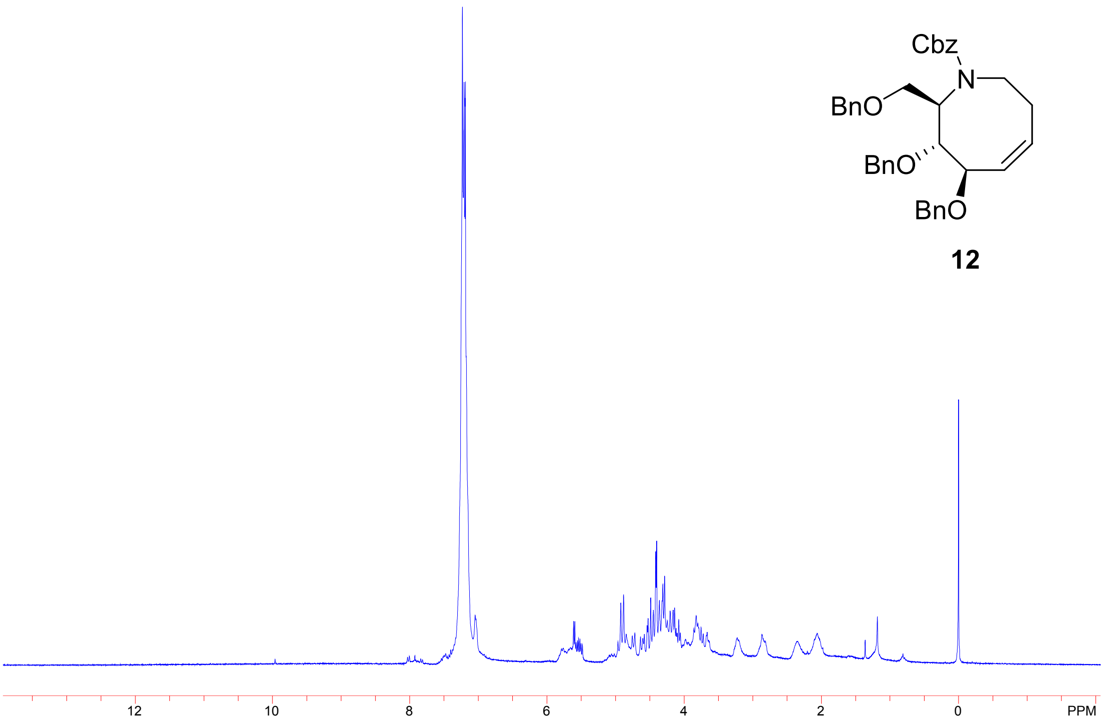
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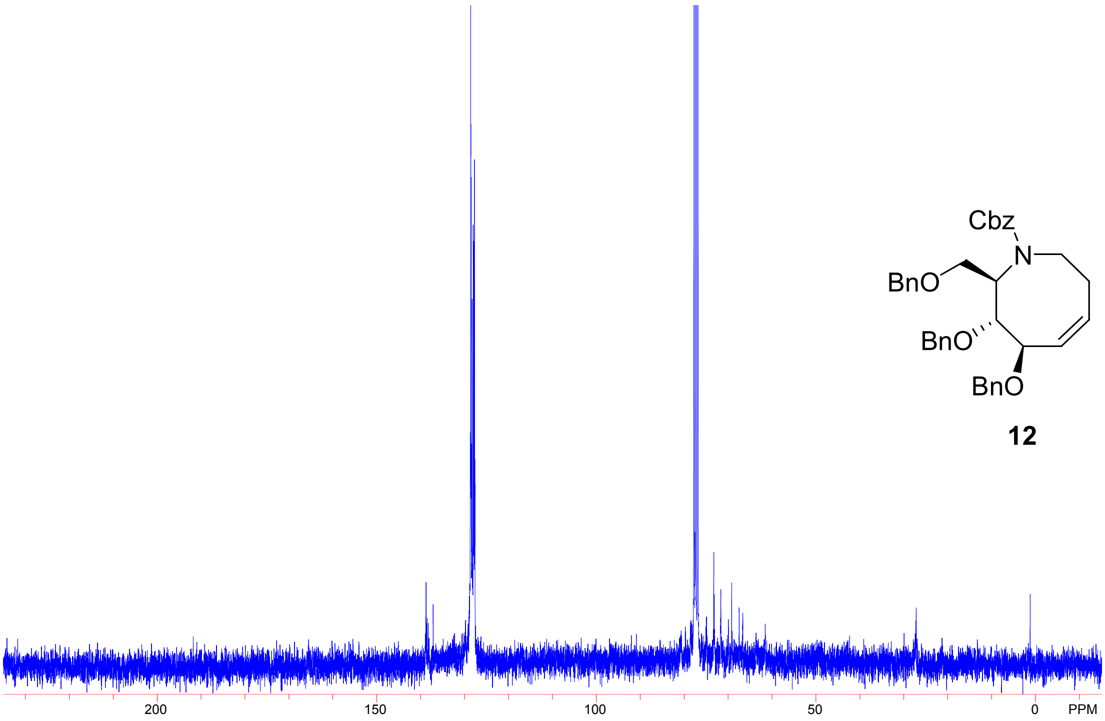
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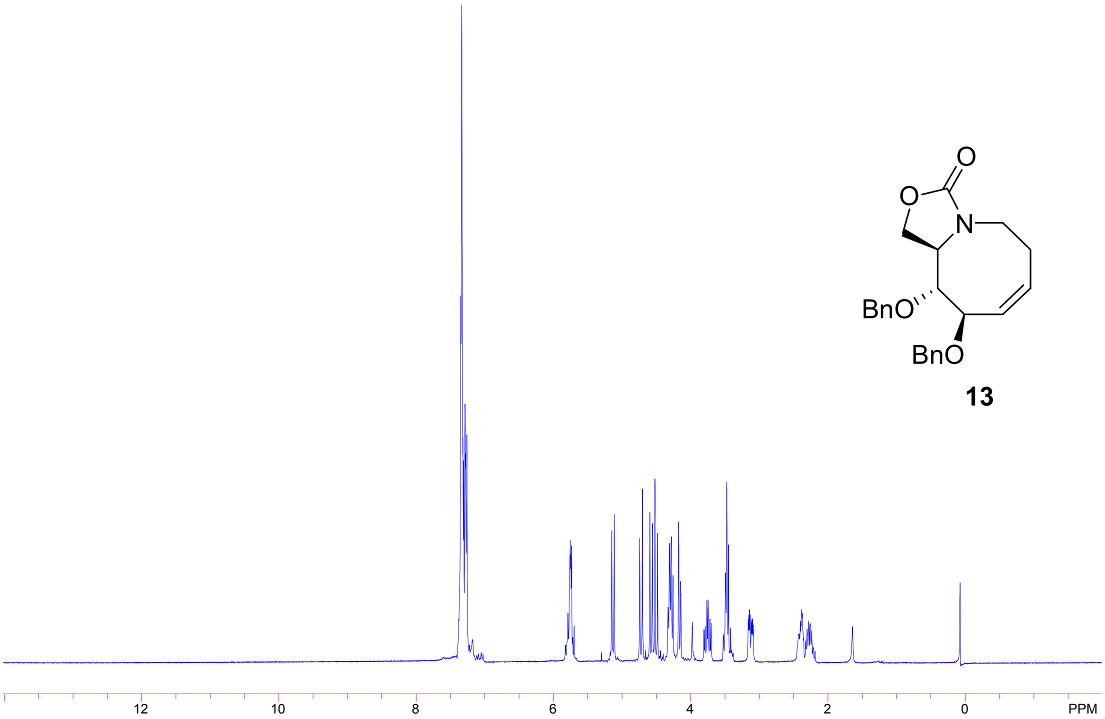

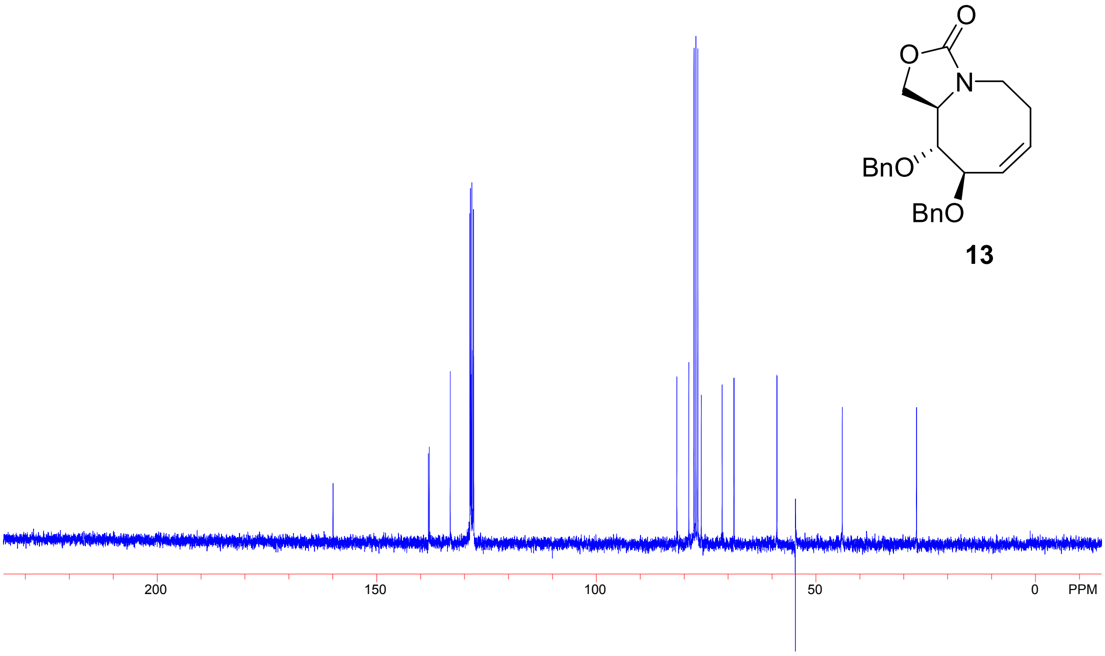

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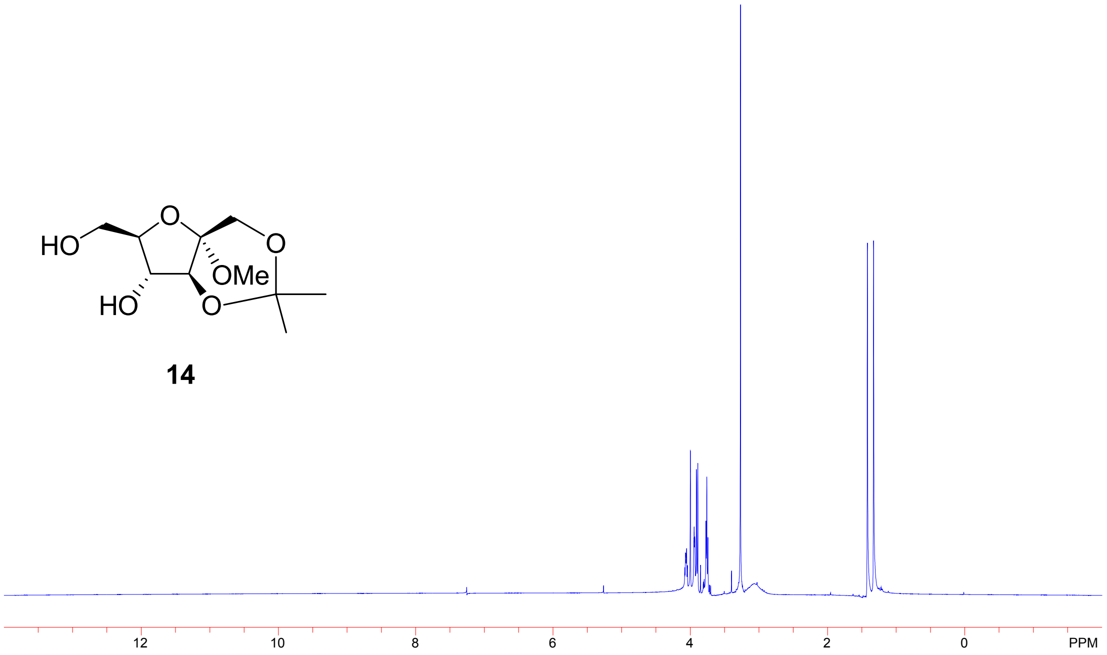

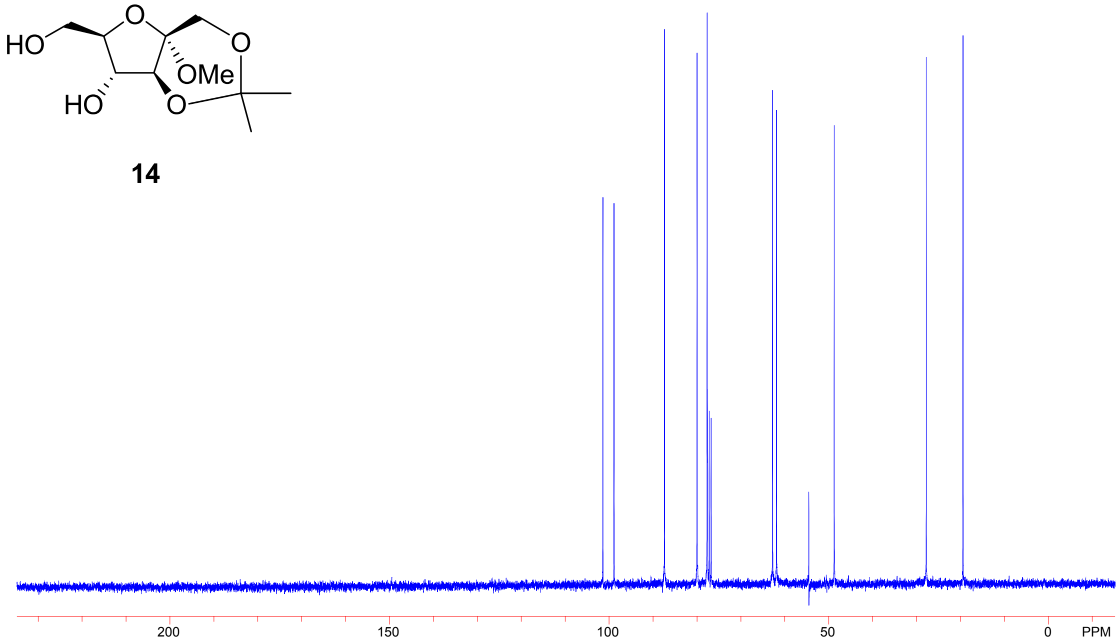

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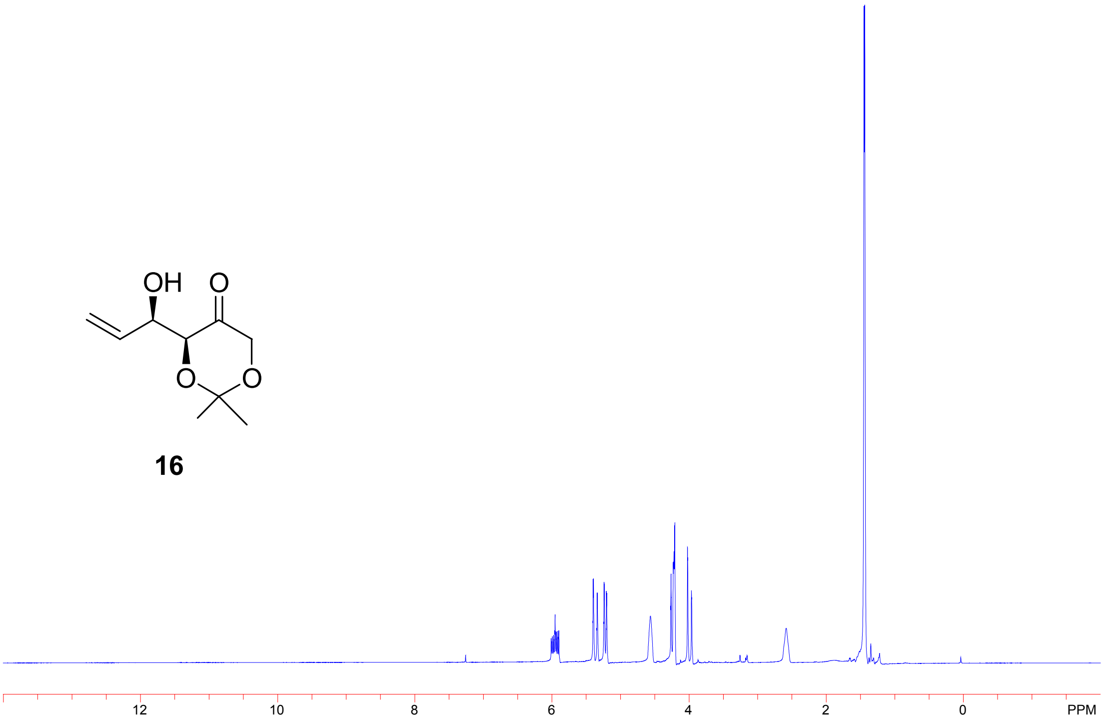
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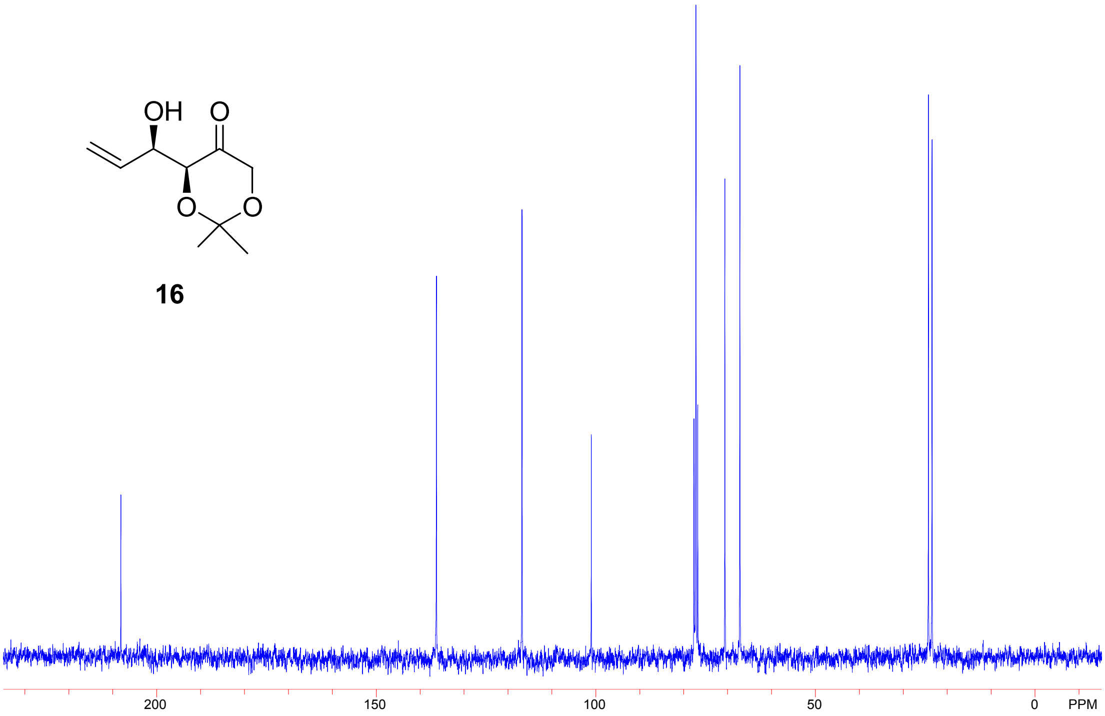
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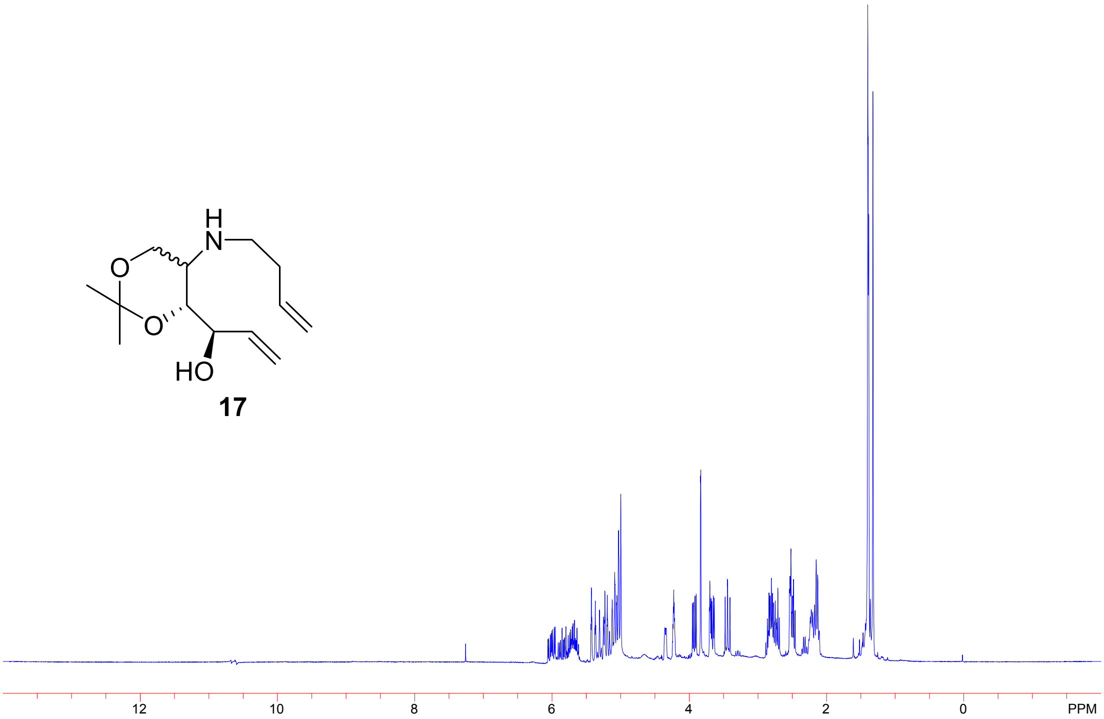

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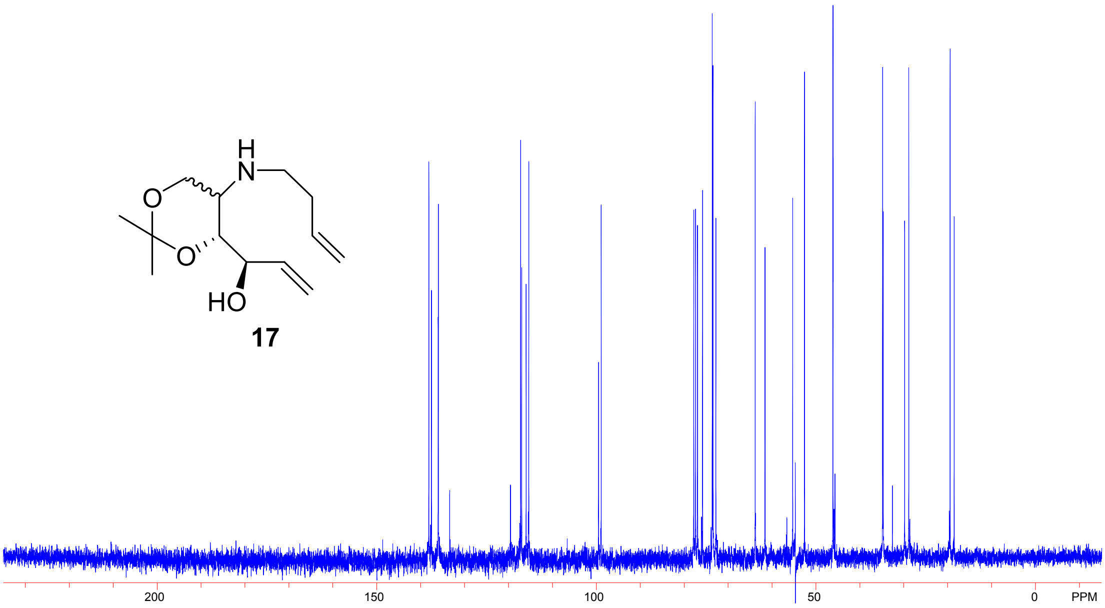

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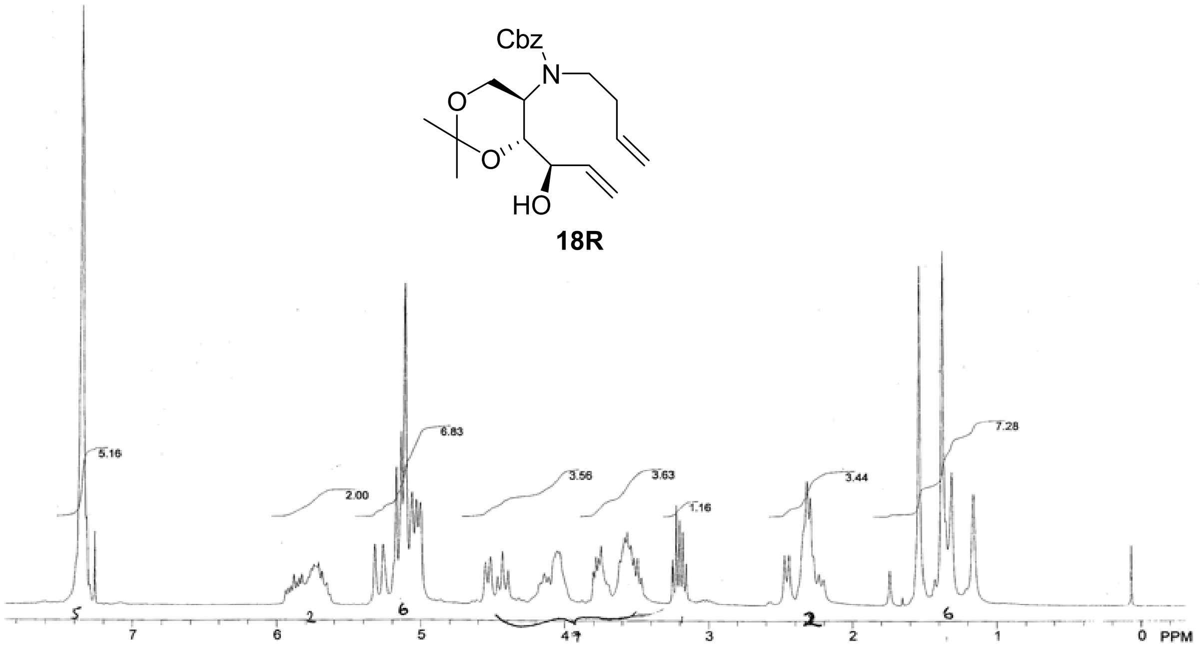

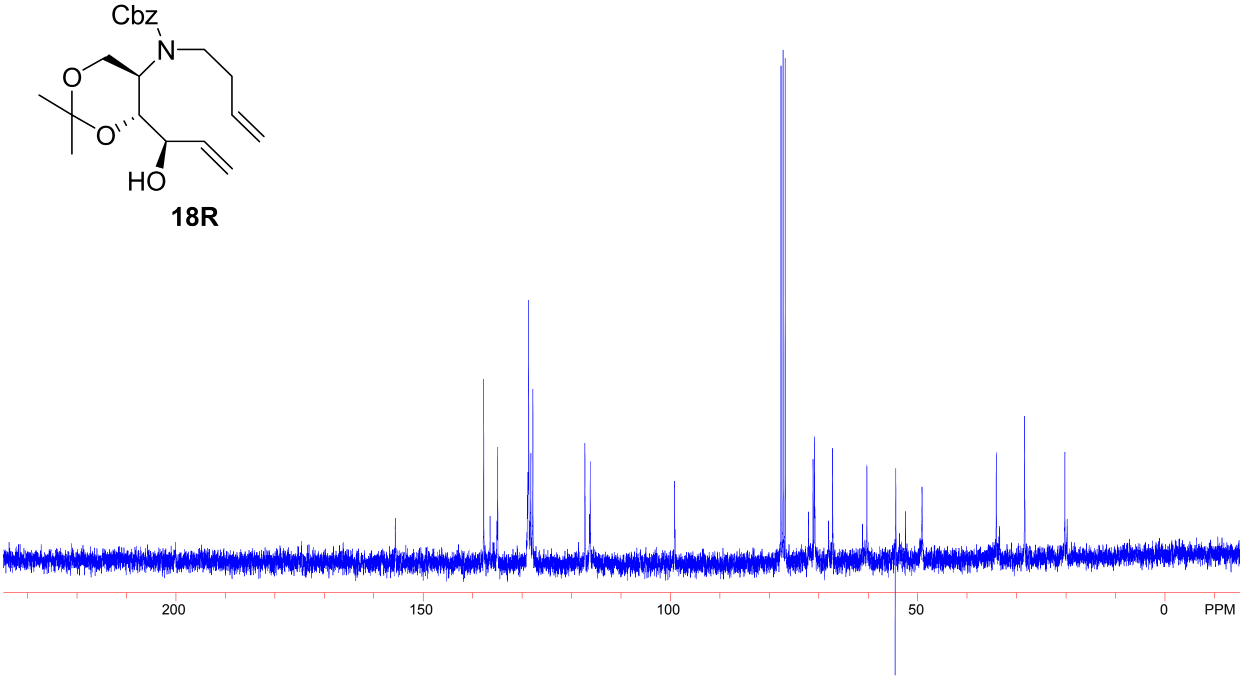

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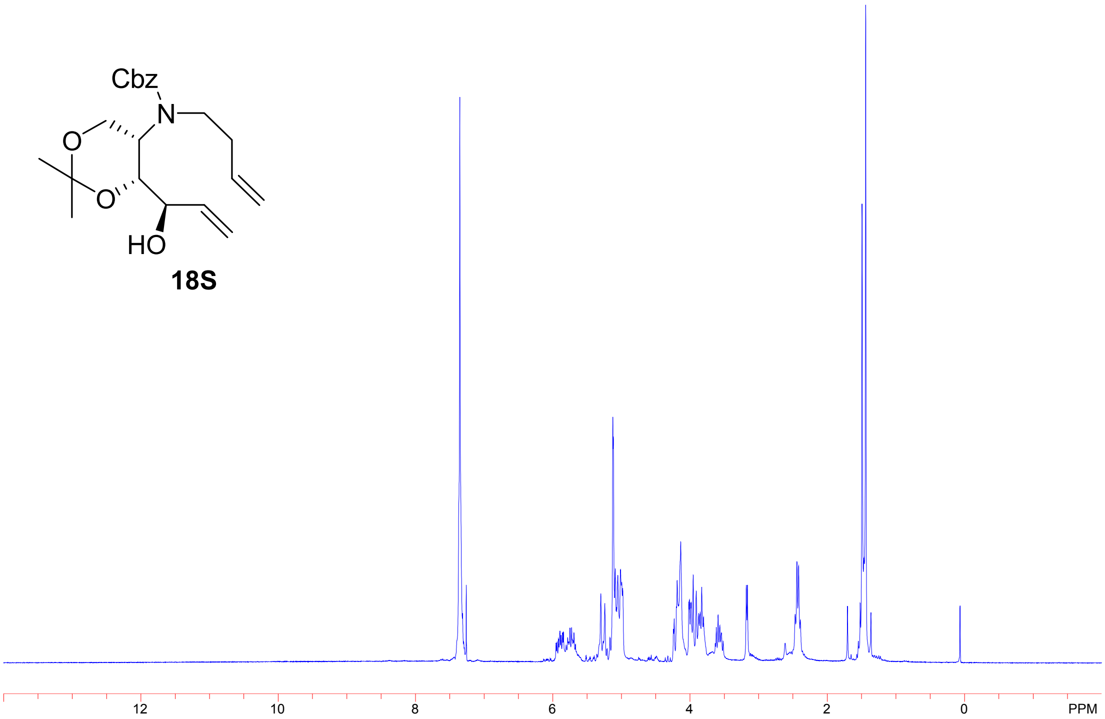

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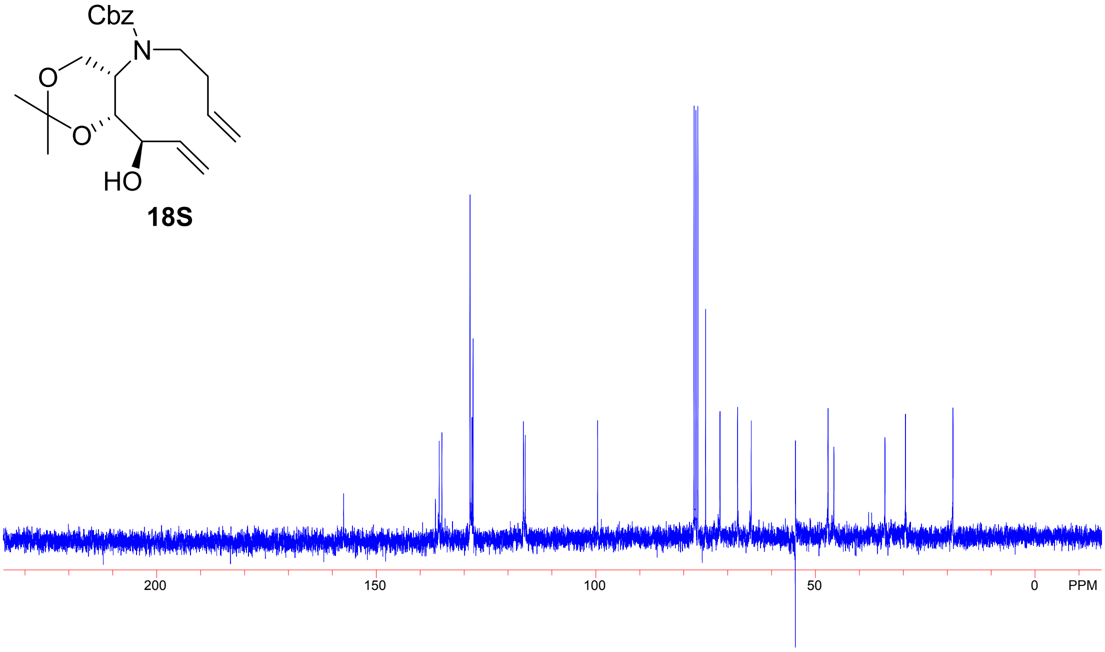

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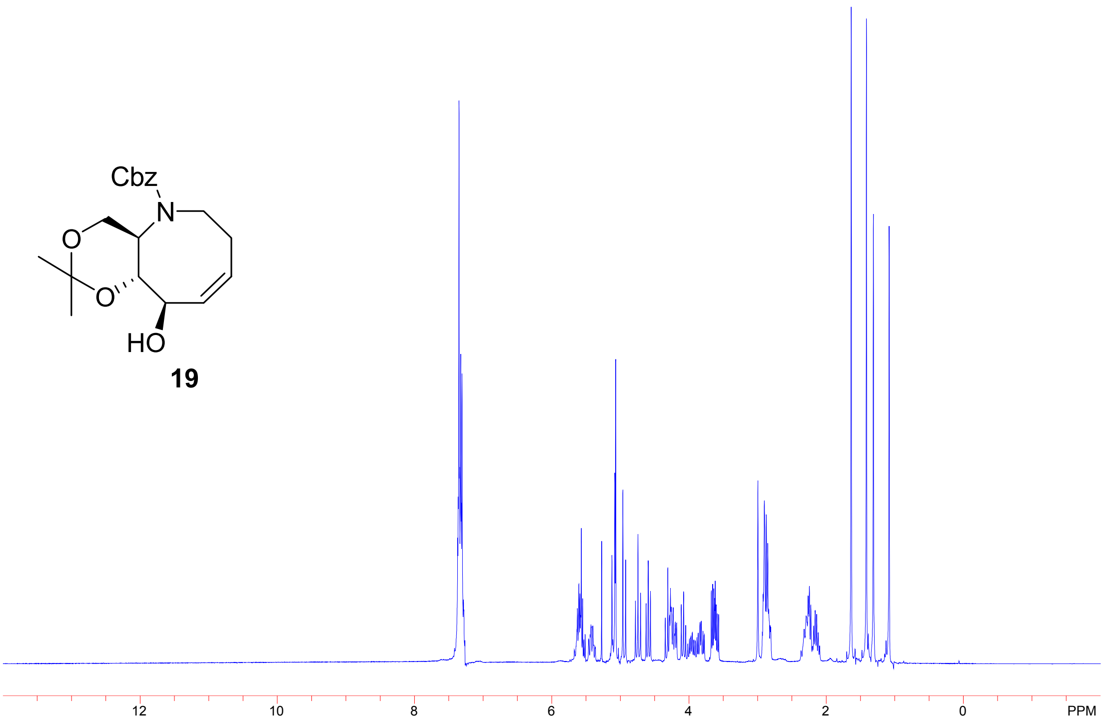
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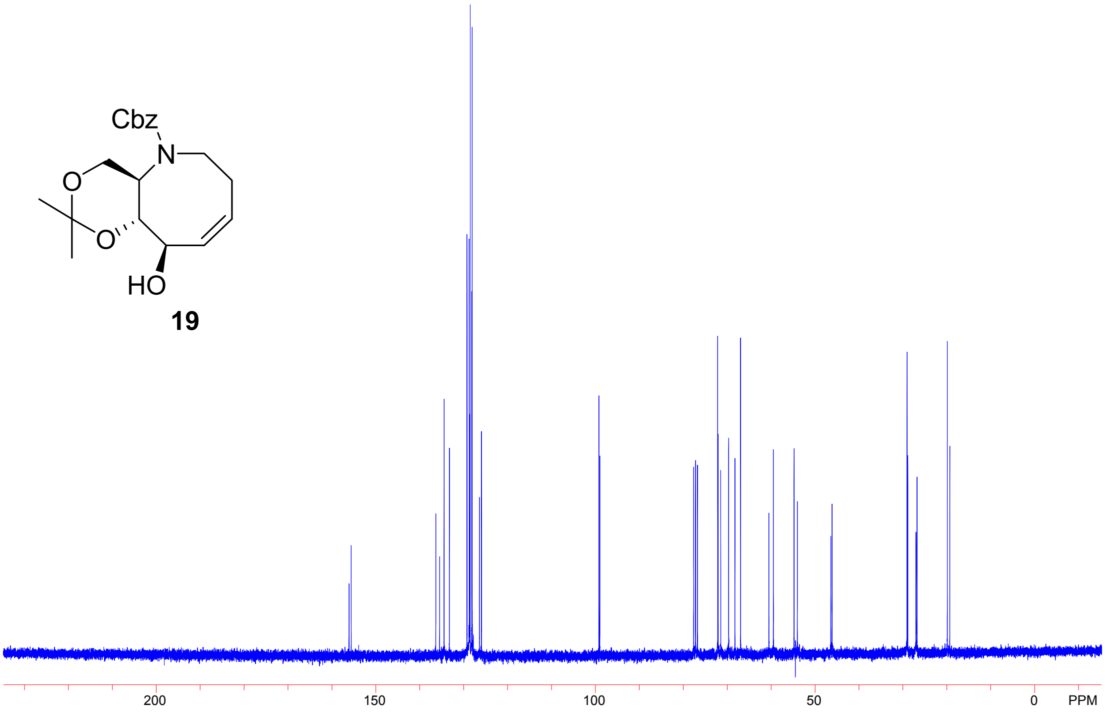
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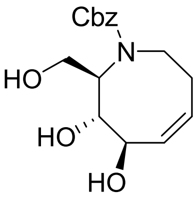
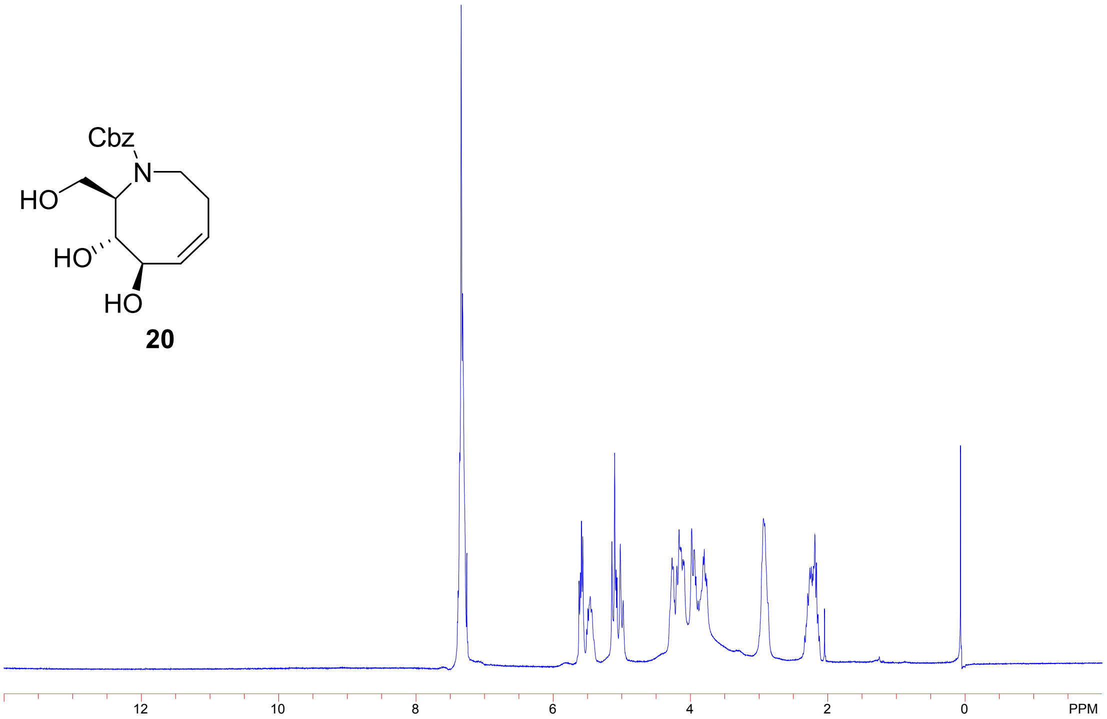
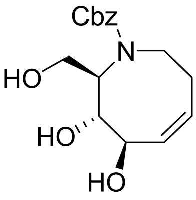


20





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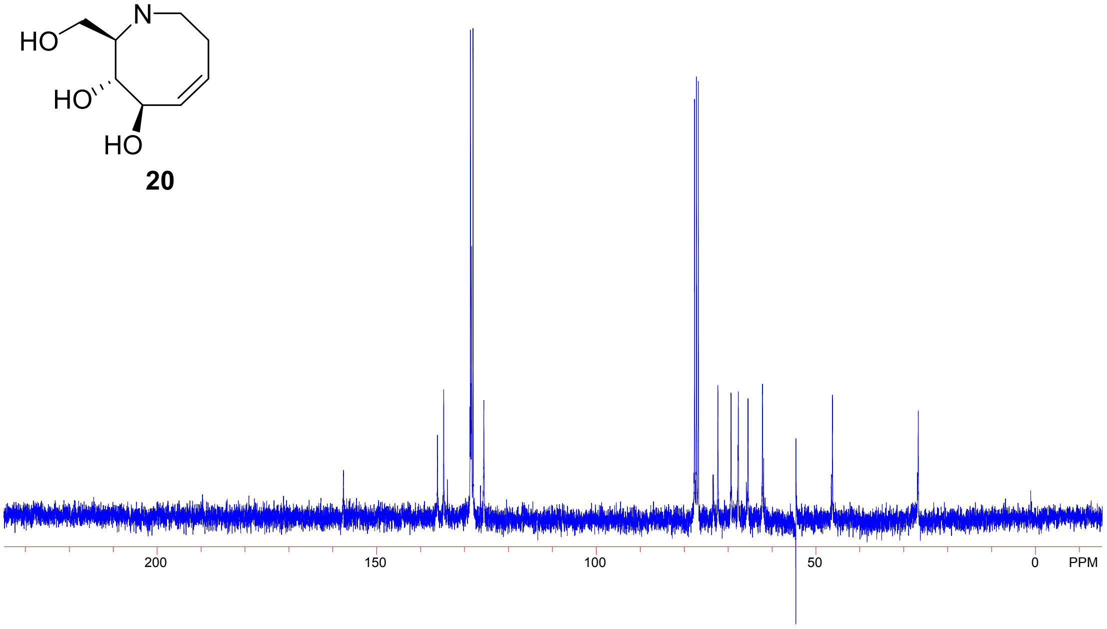
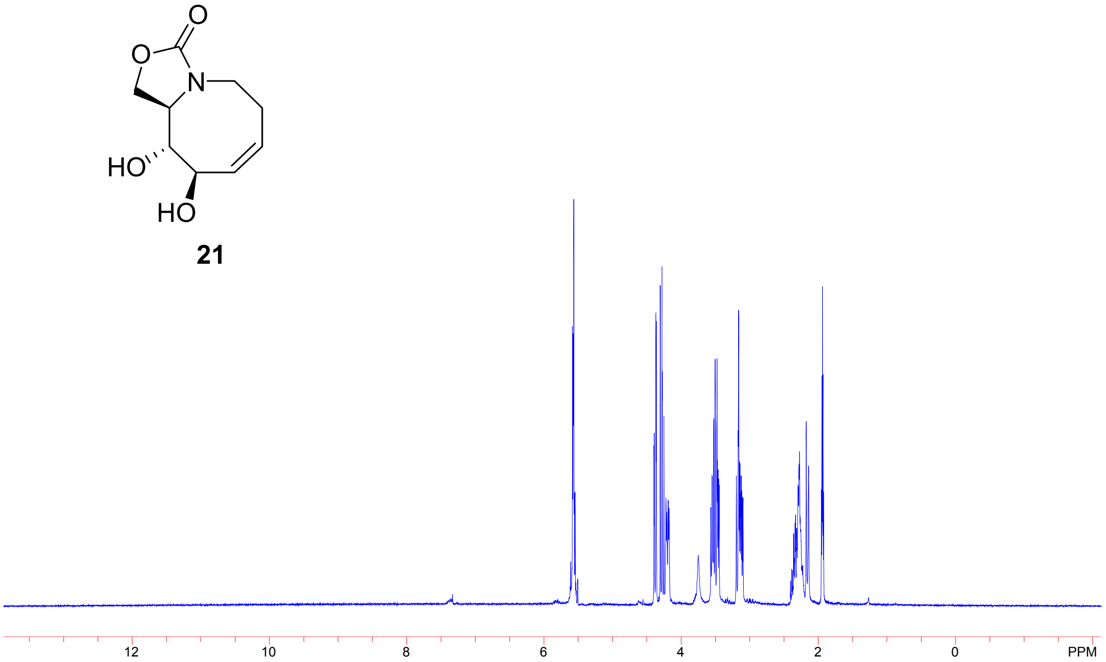


Artifact at 54ppm



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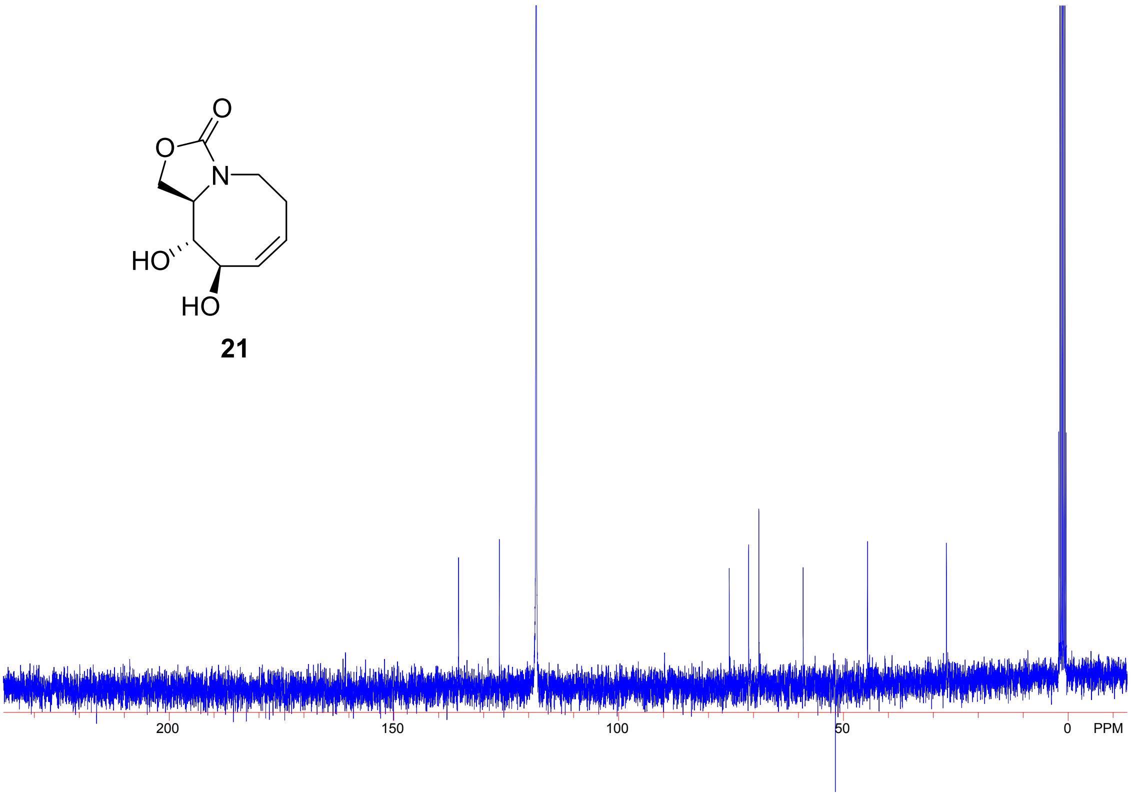

21

Artifact at 54ppm