Enantioselective Sulfonylation Reactions Mediated by a Tetrapeptide Catalyst

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Materials and Methods

Proton NMR spectra were recorded on a 400 or 500 MHz spectrometer. Proton chemical shifts were reported in ppm (δ) relative to internal tetramethylsilane (TMS, δ, 0.00 ppm), or with the solvent reference relative to TMS employed as the internal standard ($CDCl_3$, δ 7.26 ppm; CD_3OD, δ 3.30 ppm; CD_2Cl_2, δ 5.32 ppm). Spectral data are reported as follows: chemical shift (multiplicity [singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m)], coupling constants [Hz], integration). Carbon NMR spectra were recorded on a 400 (100) or 500 (125) MHz spectrometer with complete proton decoupling. Carbon chemical shifts are reported in ppm (δ) relative to the residual solvent signal ($CDCl_3$, δ 77.0 ppm; CD_3OD, δ 49.0 ppm; CD_2Cl_2, δ 53.8 ppm). When two peaks appear very close together, carbon chemical shifts are reported to two decimal places. NMR data were collected at ambient temperature unless otherwise indicated. Infrared spectra were obtained on a Nicolet 6700 FT-IR spectrometer, υ_{max} (cm^{-1}) are partially reported. Analytical thin-layer chromatography (TLC) was performed using Silica Gel 60 Å F254 pre-coated plates (0.25 mm thickness). TLC R_f values are reported and visualization was accomplished by irradiation with a UV lamp and/or staining with cerium ammonium molybdate

(CAM) or $KMnO_4$ solutions. Flash column chromatography was performed using Silica Gel 60 Å (32-63 micron). Optical rotations were recorded on a Rudolf Research Analytical Autopol IV Automatic polarimeter at the sodium D line (100 mm path length). High resolution mass spectra were acquired from the Mass Spectrometry Facility of the University of Illinois (Urbana-Champaign, IL) or at the Keck Center of Yale University. The method of ionization is given in parentheses. Chiral analytical normal phase HPLC was performed at a column temperature of 20 °C on a Hewlett-Packard 1100 Series chromatograph equipped with a diode array detector (210 nm, 230 nm or 254 nm).

All reactions were carried out under a nitrogen atmosphere employing oven- and flame-dried glassware. Solvents were purified using a Seca Solvent Purification System by GlassContour. All arenesulfonyl chlorides were recrystallized from Et_2O and petroleum ether and checked for purity by melting point analysis prior to use. All other chemicals were purchased commercially and used as received unless indicated otherwise.

Experimental Data

Experimental Procedures and Compounds Characterization

Preparation of 1,3-diol Substrates.

Synthesis of *myo*-Inositol-derived substrates.

2,4,6-Tribenzyl *myo*-inositol (**1**) was prepared in three steps from commercially available *myo*-inositol according to the method of Billington and coworkers.[1] 2,4,6-Tri-*O*-*para*-methoxybenzyl-*myo*-inositol (**12**) (Table 2, entry 2) was prepared in an analogous manner using a modified procedure.[2]

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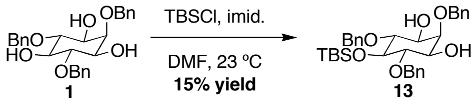
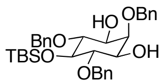
[1] Billington, D. C., Baker, R., Kulagowski, J. J., Mawer, I. M., Vacca, J. P., Jane deSolms, S. & Huff, J. R. The total synthesis of *myo*-inositol phosphates *via myo*-inositol orthoformate. *J. Chem. Soc., Perkin Trans. 1*, 1423–1429 (1989).

[2] (a) Lampe, D., Liu, C. & Potter, B. V. L. Synthesis of selective non-Ca^{2+} mobilizing inhibitors of D-myo-inositol 1,4,5-Trisphosphate 5-phosphatase. *J. Med. Chem.,* **37**, 907–912 (1994). (b) Xu, Y., Sculimbrene, B. R. & Miller, S. J. Streamlined synthesis of phosphatidylinositol (PI), PI3P, PI3,$5P_2$, and deoxygenated analogues as potential biological probes. *J. Org. Chem.*, **71**, 4919–4928 (2006).

2,4,6-Tri-*O*-benzyl-5-*O*-*tert*-butyldimethylsilyl-*myo*-inositol (13, Table 2, entry 3):





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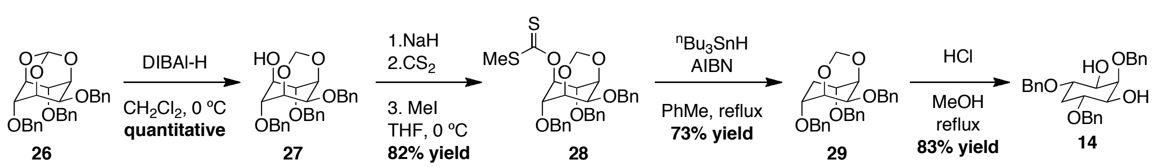
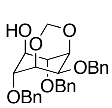
To an oven-dried 50 mL round bottom flask equipped with a stir bar was added 1.0 g (2.22 mmol) 2,4,6-tri-*O*-benzyl-*myo*-inositol (**1**) and 11 mL DMF. Imidazole (0.226 g, 3.33 mmol) and TBSCl (0.502 g, 3.33 mmol) were then added to the solution. After stirring at 23 ºC for 3 hours, 20 mL of deionized water was added, and the reaction mixture was transferred to a 125 mL separatory funnel containing 80 mL of Et_2O. After agitation and separation of the aqueous layer, the organic phase was washed with additional deionized water (3 x 20 mL), then 20 mL sat. aq. NaCl. The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure to provide a mixture of (mono)silylated and (bis)silylated regioisomers. The desired 5-silylated product was obtained by silica gel flash chromatography (gradient elution: 9:1→4:1 hexanes/EtOAC) of the crude reaction mixture to isolate the lowest R_f product spot as a colorless oil (190 mg, 15% yield). **TLC R_f** = 0.47 (2:1 hexanes/EtOAc); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.40-7.26 (m, 15H), 4.87 (d, *J* = 11.5 Hz, 2H), 4.72 (s, 2H), 4.71 (d, *J* = 11.5 Hz, 2H), 3.95 (t, *J* = 2.7 Hz, 1H), 3.62 (t, *J* = 9.1 Hz, 2H), 3.55-3.50 (m, 3H), 2.14 (d, *J* = 5.5 Hz, 2H), 0.95 (s, 9H), 0.07 (s, 6H) ppm; **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 138.60, 138.59, 128.5, 128.4, 127.99, 127.97, 127.8, 127.7, 82.4, 78.8, 75.5, 75.2, 75.1, 72.5, 26.1, 18.0, –4.0 ppm; **IR** (thin film) ν 3554, 2925, 2857, 1454, 1401, 1359, 1256, 1158, 1122, 1088, 1069, 1028, 837, 818 cm^{-1}; **HRMS** calcd for $[C_{33}H_{43}O_6Si\ H]^+$ requires *m/z* 565.2980; found 565.2981 (ESI+).

2,4,6-Tri-*O*-benzyl-5-deoxy-*myo*-inositol (14, Table 2, entry 4):

This substrate was prepared in 4 steps from the known orthoester.[1]





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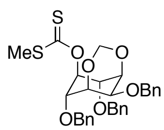
In a 100 mL round bottom flask, orthoester **26** (3.72 g, 8.10 mmol) was dissolved in 50 mL of CH_2Cl_2 and cooled to 0 ºC. To the cooled solution was added di-isobutyl aluminium hydride (1M solution in hexanes, 19.53 mL, 19.53 mmol) and the grey reaction mixture was stirred for 2.5 h. The reaction mixture was then transferred via cannula to a cooled solution (0 ºC) of potassium sodium tartrate (11.28 g) in 40 mL of water and 40 mL of sat. aq. NH_4Cl. The reaction mixture was allowed to stir overnight and then extracted with EtOAc three times, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the crude oil by silica gel flash chromatography (gradient elution: 85:15→4:1 hexanes/EtOAc) yielded a clear, colorless oil (3.73 g, 100%). The spectral data for this compound matched that which had been previously reported.[3]



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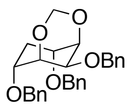
In a 50 mL round bottom flask, acetal **27** (250 mg, 0.54 mmol) was dissolved in THF (17 mL) and the solution was cooled to 0 ºC. NaH (25.92 mg, 1.08 mmol) was then added to the cooled solution and the mixture was allowed to stir for 30 minutes at 0 ºC. Then CS_2 (114.4 µL, 1.89 mmol) was added to the reaction mixture and it was allowed to stir at 0 ºC for 30 minutes. Finally, MeI (100.9 µL, 1.62 mmol) was added to the reaction mixture at 0 ºC and the mixture was allowed to stir overnight while gradually warming to room temperature. The yellow reaction mixture was then quenched with sat. aq. NH_4Cl and diluted with CH_2Cl_2 and water. The layers were extracted and the aqueous layer was washed with CH_2Cl_2 twice. The combined organic layers were washed with sat. aq. NaCl solution, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude yellow oil was purified by silica gel flash chromatography (10:1 hexanes/EtOAc) to provide a pale yellow oil (246 mg, 82%). **TLC R*f*** = 0.40 (5:1 hexanes/EtOAc); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.25-7.34 (m, 15H), 6.06 (s, 2H), 5.54 (d, *J* = 4.3 Hz, 1H), 4.77 (d, *J* = 12.0 Hz, 2H), 4.63-4.64 (m, 3H), 4.59 (d, *J* = 12.0 Hz, 2H), 4.37 (s, 2H), 4.34 (s, 1H), 3.99 (s, 2H), 2.49 (s, 3H) ppm; **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 214.3, 137.9, 137.8, 128.64, 128.56, 128.05, 128.00, 127.9, 127.8, 85.5, 79.1, 77.5, 77.3, 77.0, 76.8, 72.4, 71.0, 70.8, 70.2, 18.5 ppm; **IR** (thin film) ν 3089, 3060, 3028, 2917, 2852, 1957, 1875, 1720, 1601, 1581,

[3] Gilbert, I. H., Holmes, A. B., Pestchanker, M. J. & Young, R. C. Lewis acid-catalysed rearrangements of *myo*-inositol orthoformate derivatives. *Carbohydr. Res.*, **234**, 117–130 (1992).

1494, 1453, 1381, 1363, 1316, 1305, 1287, 1216, 1176, 1148, 1066, 1028, 888, 829, 805 cm^{-1}; **HRMS** calcd for $[C_{30}H_{32}O_6S_2\ Na]^+$ requires *m/z* 575.1533; found 575.1523 (ESI+).



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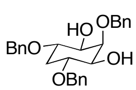
In a flame dried 250 mL round bottom flask, to a solution of the xanthate ester **28** (1.90 g, 3.44 mmol) in toluene (104 mL) was added Bu_3SnH (2.73 mL, 10.31 mmol) and AIBN (169.50 mg, 1.03 mmol). The yellow solution was brought to reflux and monitored by thin layer chromatography for disappearance of starting material. After approximately 1h the black reaction mixture was cooled to room temperature and concentrated under reduced pressure. The resulting black residue was partitioned between hexanes and acetonitrile to remove excess Bu_3Sn. Purification of the crude reaction mixture by silica gel flash chromatography (5:1 hexanes/EtOAc) provides the 5-deoxy acetal (1.12 g, 73%) as a pale yellow oil. **TLC R*f*** = 0.34 (25:1 toluene/acetone); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.27-7.35 (m, 15H), 5.61 (d, *J* = 4.5 Hz, 1H), 4.67 (d, *J* = 4.6 Hz, 2H), 4.64 (d, *J* = 11.9 Hz, 2H), 4.60 (s, 2H), 4.46 (d, *J* = 11.9 Hz, 2H), 4.43 (brs, 1H), 4.39 (br d, *J* = 3.4 Hz, 2H), 3.90 (dd, *J* = 2.9, 1.1 Hz, 2H), 2.24 (dt, *J* = 15.8, 4.2 Hz, 1H), 2.04 (brd, *J* = 15.8 Hz, 1H) ppm; **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 138.5, 138.0, 128.4, 128.3, 127.8, 127.7, 127.4, 85.1, 77.5, 71.4, 71.2, 70.4, 70.4, 23.4 ppm; **IR** (thin film) ν 3444, 3085, 3056, 3023, 2913, 2868, 1957, 1875, 1806, 1601, 1581, 1495, 1446, 1356, 1266, 1205, 1172, 1140, 1103, 1066, 1005, 731 cm^{-1}; **HRMS** calcd for $[C_{28}H_{30}O_5\ H]^+$ requires *m/z* 447.2171; found 447.2186 (ESI+).

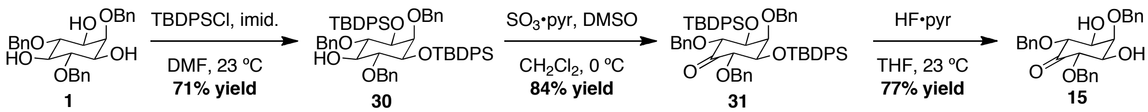


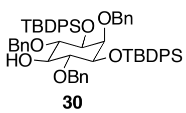
14

In a flame dried 100 mL round bottom flask, to a solution of the acetal (1.12 g, 2.53 mmol) in methanol (41.0 mL) was added concentrated HCl (6.15 mL). The cloudy white reaction mixture was brought to reflux and monitored by thin layer chromatography for disappearance of starting material. After approximately 4.5 h the solution was allowed to cool to room temperature and then diluted with ethyl acetate. The solution was neutralized to pH 7-8 with sat. aq. $NaHCO_3$, extracted twice with EtOAc, dried over Na_2SO_4, filtered, and concentrated under reduced pressure leaving a clear oil. Purification of the crude oil by silica gel flash chromatography (2:1 hexanes/EtOAc) provides 5-deoxy inositol **14** (911.2 mg, 83%) as a clear, colorless oil. **TLC R*f*** = 0.27 (2:1 hexanes/EtOAc); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.30-7.38 (m, 15H), 4.84 (s, 2H), 4.67 (d, J = 11.5 Hz, 2H), 4.58 (d, J = 11.0 Hz, 2H), 4.09 (t, J = 2.5 Hz, 1H), 3.70 (ddd, J = 11.3, 9.5, 4.5 Hz, 2H), 3.62 (ddd, J = 9.3, 5.3, 3.0 Hz, 2H), 2.52 (d, J = 4.5 Hz, 2H), 2.48 (dt, J = 12.5, 4.5 Hz, 1H), 1.29 (q, J = 11.8 Hz, 1H) ppm; **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 138.8, 138.3, 128.5, 128.4, 127.80, 127.78, 127.69, 79.3, 77.2, 76.7, 75.3, 74.9, 71.9, 31.3 ppm; **IR** (thin film) ν 3440 3060, 3023, 2921, 2872, 1716, 1605, 1495, 1450, 1389, 1348, 1270, 1205, 1115, 1091, 1066, 1033, 731 cm^{-1}; **HRMS** calcd for $[C_{27}H_{30}O_5\ Na]^+$ requires *m/z* 457.1985; found 457.1980 (ESI+).

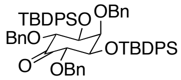
2,4,6-Tri-*O*-benzyl-5-keto-*myo*-inositol (15, Table 2, entry 5):

Prepared in 3 steps from 2,4,6-tri-*O*-benzyl-*myo*-inositol (**1**).





In a 50 mL round bottom flask, 2,4,6-tri-*O*-benzyl-*myo*-inositol (**1**) (2.0 g, 4.4 mmol) was dissolved in DMF (22 mL). Imidazole (1.51 g, 22.2 mmol) and *tert*-butyldiphenylsilyl chloride (5.77 mL, 22.2 mmol) were subsequently added and the reaction solution was allowed to stir for 48 hours. The solution was then diluted with Et_2O, washed with water four times, washed with sat. aq. NaCl, dried over Na_2SO_4, and concentrated under reduced pressure. Purification of the crude oil by silica gel flash chromatography (toluene) yielded the desired product as a thick, colorless oil (1.59 g, 71%). **TLC R_f** = 0.51 (5:1 hexanes/EtOAc); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.65 (dd, J = 8.0, 1.2 Hz, 4H), 7.55 (dd, J = 7.9, 1.2 Hz, 4H), 7.51 (d, J = 7.2 Hz, 2H), 7.44 (t, J = 7.6 Hz, 2H), 7.35-7.41 (m, 4H), 7.29 (t, J = 7.5 Hz, 4H), 7.21-7.25 (m, 10H), 7.04 (dd, J = 7.2, 2.2 Hz, 4H), 4.80 (s, 2H), 4.72 (d, J = 11.3 Hz, 2H), 4.59 (d, J = 11.3 Hz, 2H), 3.90 (t, J = 9.3 Hz, 2H), 3.53 (dd, J = 9.5, 2.2 Hz, 2H), 3.34 (t, J = 2.1 Hz, 1H), 3.29 (td, J = 9.0, 2.3 Hz, 1H), 2.20 (d, J = 2.4 Hz, 1H), 0.98 (s, 18H) ppm; **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 139.7, 139.0, 136.1, 135.9, 133.6, 133.3, 129.8, 129.4, 128.2, 128.1, 127.7, 127.5, 127.4, 127.1, 126.9, 81.9, 81.7, 76.1, 74.7, 74.4, 74.2, 27.2, 19.3 ppm; **IR** (thin film) ν 3571, 3473, 3088, 3069, 3049, 3031, 2999, 2959, 2930, 2891, 2858, 2296, 1957, 1883, 1822, 1773, 1659, 1606, 1587, 1567, 1495, 1470, 1453, 1425, 1388, 1357, 1263, 1209, 1151, 1108, 1026, 938, 842, 821, 802 cm^{-1}; **HRMS** calcd for $[C_{59}H_{66}O_6Si_2\ Na]^+$ requires *m/z* 949.4296; found 949.4341 (ESI+).



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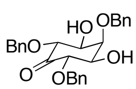
In a oven-dried 50 mL round bottom flask, 2,4,6-tri-*O*-benzyl-1,3-di-*O*-*tert*-butyldiphenylsilyl-*myo*-inositol **30** (1.68 g, 1.81 mmol) was dissolved in CH_2Cl_2 (12 mL). Triethylamine (5.05 mL, 36.2 mmol) was subsequently added and the reaction solution was cooled to 0 ºC. A solution of SO_3•pyridine (2.88 g, 18.1 mmol) in anhydrous DMSO (6 mL) was added over the course of 5 min at 0 ºC. The pale orange solution was allowed to warm gradually to room temperature and was stirred for 48 h. The reaction was then diluted with 1:1 hexanes/EtOAc (200 mL), washed with 1 N HCl (3 x 40 mL), sat. aq. $NaHCO_3$ (40 mL), then sat. aq. NaCl. The organic layer was dried over Na_2SO_4, and concentrated under reduced pressure. Purification of the crude oil by silica gel flash chromatography (toluene) yielded the desired product as white solid (1.41 g, 84%). **TLC R_f** = 0.41 (9:1 hexanes/EtOAc); **mp** = 163.5–165.5 ºC; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.57-7.54 (m, 4H), 7.48-7.31 (m, 13H), 7.26-7.20 (m, 10H), 7.19-7.14 (m, 4H), 7.13-7.09 (m, 4H), 4.85 (s, 2H), 4.66 (d, *J* = 10.2 Hz, 2H), 4.52 (d, *J* = 9.9 Hz, 2H), 4.17 (d, *J* = 10.2 Hz, 2H), 3.55 (dd, *J* = 9.9, 2.1 Hz, 2H), 3.49 (t, *J* = 2.1 Hz, 1H), 0.96 (s, 18H) ppm; **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 204.2, 139.2, 137.7, 136.1, 135.9, 133.4, 132.7, 129.8, 129.5, 128.4, 128.3, 127.8, 127.5, 127.33, 127.30, 82.7, 81.5, 75.7, 73.4, 72.8, 27.1, 19.3 ppm; **IR** (thin film) ν 3069, 3054, 3038, 2960, 2931, 2887, 2857, 1736, 1472, 1455, 1427, 1391, 1265, 1148, 1113, 1105, 1081, 1049, 1028, 1008, 945, 822, 808 cm^{-1}; **HRMS** calcd for $[C_{59}H_{64}O_6Si_2\ Na]^+$ requires *m/z* 947.4134; found 947.4138 (ESI+).



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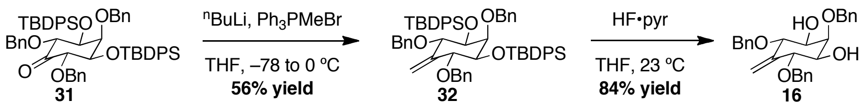
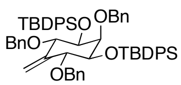
To a 50 mL polypropylene reaction vessel equipped with a stir bar were added 0.800 g (0.865 mmol) of bis(*tert*-butyldiphenylsilylated) ketone **31** and 10 mL of dry THF. The reaction was cooled to 0 ºC and 5.4 mL of HF•pyridine was added via a plastic graduated pipette. The mixture was allowed to warm slowly to room temperature. The reaction was monitored by TLC and two additional portions (2.0 mL each) of HF•pyridine were added to the reaction at 24 h and 48 h. After approximately 60 h, the reaction was cooled to 0 ºC and was quenched by adding sat. aq. $NaHCO_3$ dropwise until a pH of 8 was achieved. The mixture was transferred to a separatory funnel and extracted using EtOAc (2 x 200 mL). The combined organic layers were dried over Na_2SO_4, and concentrated under reduced pressure. Purification of the crude oil by silica gel flash chromatography (gradient elution: 4:1→1:1 hexanes/EtOAc) yielded desired product (**15**) as a white solid (0.300 g, 77%). **TLC R$_f$** = 0.36 (1:1 hexanes/EtOAc); **mp** = 133–135 ºC; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.45-7.42 (m, 4H), 7.40-7.30 (m, 11H), 4.96 (d, *J* = 11.0 Hz, 2H), 4.93 (s, 2H), 4.50 (d, *J* = 11.0 Hz, 2H), 4.42 (d, *J* = 9.9 Hz, 2H), 4.25 (t, *J* = 2.7 Hz, 1H), 3.79 (ddd, *J* = 9.9, 4.3, 2.7 Hz, 2H), 2.54 (d, *J* = 4.3 Hz, 2H) ppm; **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 202.9, 138.2, 137.3, 128.6, 128.5, 128.3, 128.1, 128.0, 127.9, 82.7, 77.9, 75.7, 73.4, 72.4 ppm; **IR** (thin film) ν 3578, 3416, 2905, 1736, 1454, 1359, 1214, 1128, 1081, 1038, 1028, 1003, 917 cm^{-1}; **HRMS** calcd for $[C_{27}H_{28}O_6\ Na]^+$ requires *m/z* 471.1778; found 471.1775 (ESI+).

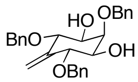
2,4,6-Tri-*O*-benzyl-1,3-di-*O*-*tert*-butyldiphenylsilyl-5-methylene-cyclohexane-1,2,3/4,6 pentol (16, Table 2, entry 6):





32

Methyltriphenylphosphonium bromide (0.568 g, 1.59 mmol), previously dried in vacuo at 70 ºC, was suspended in dry THF (5 mL) in a flame dried 20 mL round bottom flask under N_2 at –78 ºC. A 2.2 M solution of ^{n}BuLi in hexanes (0.69 mL, 1.51 mmol) was added and the reaction mixture was warmed to 0 ºC and the resulting yellow suspension was stirred for 20 min. A solution of ketone **31** (0.700 g, 0.757 mmol) in dry THF (3 mL) was added via cannula under N_2 pressure. The reaction was stirred at 0 ºC. After 7 h, TLC showed the reaction to be complete, and the solvent was removed by evaporation in vacuo. The residue was taken up in Et_2O and washed with water (20 mL), then sat. aq. NaCl (20 mL). The combined organic layers were dried over Na_2SO_4, and concentrated under reduced pressure. Purification of the crude oil by silica gel flash chromatography (gradient elution: 2:1→1:1 hexanes/toluene) yielded the desired product as viscous colorless oil (0.390 g, 56%). **TLC R$_f$** = 0.46 (9:1 hexanes/EtOAc); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.68 (d, *J* = 7.1 Hz, 4H), 7.58 (d, *J* = 7.2 Hz, 4H), 7.49 (d, *J* = 7.3 Hz, 2H), 7.43-7.32 (m, 7H), 7.28-7.21 (m, 14H), 7.06-7.02 (m, 4H), 5.16 (s, 2H), 4.78 (s, 2H) 4.51 (d, *J* = 11.1 Hz, 2H), 4.36 (d, *J* = 11.1 Hz, 2H), 4.30 (d, *J* = 9.3 Hz, 2H), 3.47 (d, *J* = 9.3 Hz, 2H), 3.39 (br s, 1H), 1.00 (s, 18H) ppm; **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 141.9, 139.8, 138.4, 136.1, 136.0, 134.1, 133.6, 129.6, 129.2, 128.1, 127.9, 127.6, 127.4, 127.24, 127.23, 127.17, 127.0, 81.8, 79.3, 76.4, 75.4, 72.2, 27.2, 19.3 ppm; **IR** (thin film) ν 3066, 3053, 3032, 2955, 2930, 2894, 2857, 1497, 1472, 1454, 1391, 1359, 1266, 1190, 1113, 1105, 1028, 1008, 963, 943, 840, 823 cm^{-1}; **HRMS** calcd for $[C_{60}H_{66}O_5Si_2\ K]^+$ requires *m/z* 961.4080; found 961.4074 (ESI+).

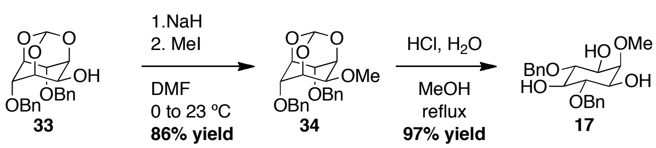


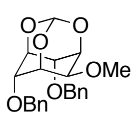
16

To a 50 mL polypropylene reaction vessel equipped with a stir bar were added 0.480 g (0.52 mmol) of bis(*tert*-butyldiphenylsilylated) alkene **32** and 6 mL dry THF. The reaction was cooled to 0 ºC and 3.0 mL of HF•pyridine was added via a plastic graduated pipette. The mixture was allowed to warm slowly to room temperature and the reaction was monitored by TLC. After approximately 48 h, the reaction was cooled to 0 ºC and was quenched by adding sat. aq. $NaHCO_3$ dropwise until a pH of 8 was achieved. The mixture was transferred to a separatory funnel and extracted using EtOAc (2 x 70 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the crude oil by silica gel flash chromatography (gradient elution: 2:1→1:1 hexanes/EtOAc) yielded desired product (**16**) as a white solid (0.196 g, 84%). **TLC** $\mathbf{R_f}$ = 0.52 (1:1 hexanes/EtOAc); **mp** = 88.5–90 ºC; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.42-7.30 (m, 15H), 5.41 (s, 2H), 4.85 (s, 2H) 4.79 (d, *J* = 11.5 Hz, 2H), 4.56 (d, *J* = 11.5 Hz, 2H), 4.14-4.10 (m, 3H), 3.65 (br s, 2H), 2.76 (br s, 2H) ppm; **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 140.4, 138.6, 138.0, 128.5, 128.4, 127.83, 127.78, 127.76, 127.69, 80.3, 77.6, 74.7, 74.6, 72.5 ppm; **IR** (thin film) ν 3530, 3459, 3030, 2908, 2883, 2872, 1497, 1454, 1390, 1361, 1210, 1122, 1087, 1072, 1042, 1028, 915 cm^{-1}; **HRMS** calcd for $[C_{28}H_{30}O_5\ Na]^+$ requires *m/z* 469.1985; found 469.1967 (ESI+).

2-*O*-methyl-4,6-di-*O*-benzyl-*myo*-inositol (17, Table 2, entry 7):

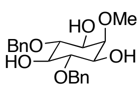
Prepared in 2 steps from the known dibenzyl orthoester.[2]





34

To a 50 mL flame-dried round bottom flask equipped with a stir bar were added dibenzyl orthoester **33** (0.400 g, 1.08 mmol) and DMF (11 mL). The solution was cooled to 0 ºC and NaH (95%, 41 mg, 1.62 mmol) was added. After the mixture was stirred at 0 ºC for 20 min, MeI was added and the reaction was allowed to warm to 23 ºC. After 1 h, the reaction was cooled to 0 ºC and 20 mL of deionized water was added to quench the remaining NaH. The mixture was transferred to a separatory funnel and extracted using Et_2O (100 mL). The combined organic layers were washed with water (3 x 20 mL) and sat. aq. NaCl (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification of the crude oil by silica gel flash chromatography (2:1 hexanes/EtOAc) yielded the desired product as viscous colorless oil (0.356 g, 86%). **TLC R$_f$** = 0.43 (2:1 hexanes/EtOAc); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.32-7.28 (m, 10H), 5.50 (d, *J* = 1.2 Hz, 1H), 4.71 (d, *J* = 11.6 Hz, 2H), 4.58 (d, *J* = 11.6 Hz, 2H), 4.48-4.44 (m, 1H), 4.38 (t, *J* = 3.8 Hz, 2H), 4.35-4.33 (m, 2H), 3.82-3.80 (m, 1H), 3.45 (s, 3H) ppm; **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 137.6, 128.5, 128.0, 127.7, 103.2, 74.0, 71.9, 69.8, 69.4, 68.0, 56.7 ppm; **IR** (thin film) ν 2965, 2884, 1497, 1454, 1396, 1368, 1307, 1276, 1198, 1166, 1138, 1116, 1095, 1001, 948, 897, 823 cm^{-1}; **HRMS** calcd for $[C_{22}H_{24}O_6\ H]^+$ requires *m/z* 385.1648; found 385.1646 (ESI+).

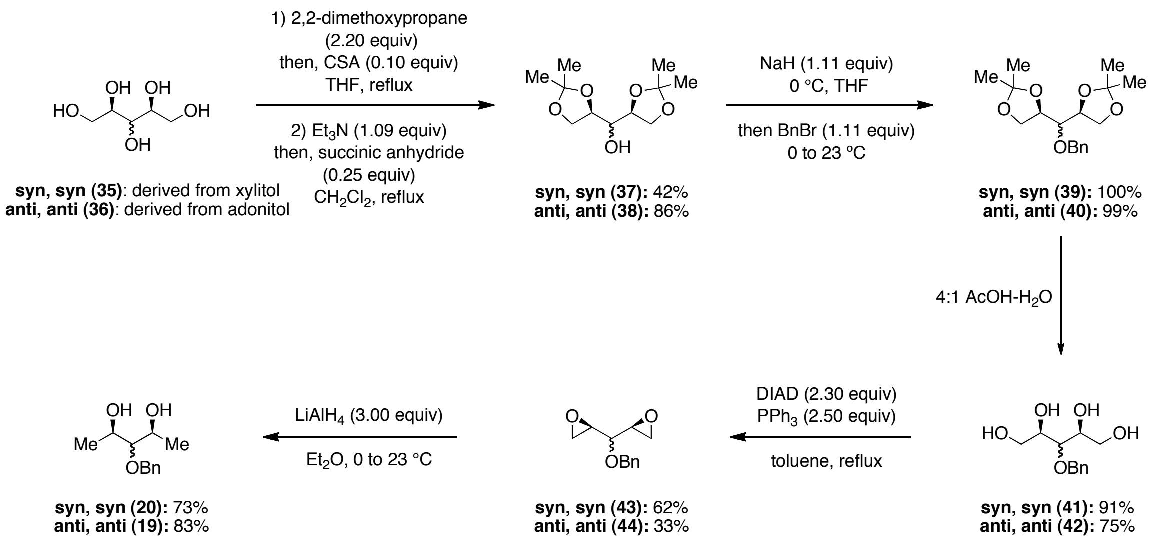


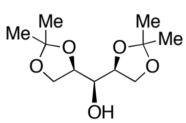
17

In a 100 mL round bottom flask, to a solution of orthoester **34** (0.353 g, 0.92 mmol) in methanol (12.0 mL) was added deionized water (0.27 mL) followed by concentrated HCl (0.54 mL). The cloudy white reaction mixture was brought to reflux and monitored by thin layer chromatography for disappearance of starting material. After approximately 2 h the solution was allowed to cool to room temperature and the solution was neutralized to pH 8 with sat. aq. NH_4OH. The reaction mixture was concentrated under reduced pressure and the resulting oil was dissolved in EtOAc. The insoluble white solid was removed by filtering through celite, and the resulting solution was concentrated under reduced pressure. Purification of the crude oil by silica gel flash chromatography (1:1 hexanes/EtOAc) provides **17** as a clear, colorless oil (334.5 mg, 97%). **TLC R$_f$** = 0.36 (1:2 hexanes/EtOAc); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.41-7.35 (m, 8H), 7.34-7.30 (m, 2H), 4.89 (d, *J* = 11.3 Hz, 2H), 4.85 (d, *J* = 11.3 Hz, 2H), 3.67 (t, *J* = 2.7 Hz, 1H), 3.65 (s, 3H), 3.61 (t, *J* = 9.3 Hz, 2H), 3.53-3.47 (m, 3H), 2.66 (d, *J* = 2.2 Hz, 1H), 2.58 (d, *J* = 5.8 Hz, 2H) ppm; **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 138.5, 128.5, 127.9, 127.8, 81.9, 81.2, 75.0, 74.8, 72.4, 61.8 ppm; **IR** (thin film) ν 3467, 3089, 3064, 3031, 2931, 2247, 1701, 1603, 1585, 1497, 1454, 1399, 1363, 1314, 1270, 1209, 1189, 1119, 1005, 911, 864, 829 cm^{-1}; **HRMS** calcd for $[C_{14}H_{19}O_5\ Na]^+$ requires *m/z* 397.1622; found 397.1618 (ESI+).

Synthesis of acyclic 1,3-diols (19 and 20, Table 2, entries 7 and 8):

The *syn,syn*- and *anti*,*anti*-acyclic 1,3-diols (**20** and **19**) were synthesized in 6 steps from xylitol and adonitol, respectively, using procedures adapted from Linclau and coworkers[4] and Miller and coworkers.[5]





37

In a flame dried 250 mL round bottom flask, 2,2-dimethoxypropane (8.87 mL, 72.4 mmol) was dissolved in 100 mL of THF and xylitol (5.0 g, 32.9 mmol) was added. The mixture was allowed to stir at reflux for 15 minutes and then L-(–)-camphorsulfonic acid (764.3 mg, 3.3 mmol) was added at refluxing temperature and pentaol **35** dissolved. After refluxing for another 5 minutes, the reaction was quenched at refluxing temperature with 2M NaOH (20 mL). The suspension was extracted with Et_2O and H_2O. The aqueous layer was further extracted three times with Et_2O. The organic layer was dried over Na_2SO_4, filtered, and concentrated to provide a colorless oil. After dissolving the oil in CH_2Cl_2 (100 mL), Et_3N (4.99 mL, 35.9 mmol) was added and the solution was brought to reflux. Succinic anhydride (823.1 mg, 8.2 mmol) was added to the reaction at refluxing temperature and the reaction was allowed to stir at reflux for an additional hour. The reaction was then quenched with sat. aq. $NaHCO_3$ (10 mL) at refluxing temperature

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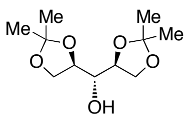
[4] Linclau, B., Boydell, A. J., Clarke, P. J., Horan, R. & Jacquet, C. Efficient desymmetrization of "*pseudo*"-C_2-symmetric substrates: illustration in the synthesis of a disubstituted butenolide from arabitol. *J. Org. Chem.*, **68**, 1821–1826 (2003).

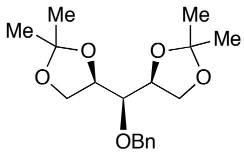
[5] Lewis, C. A., Sculimbrene, B. R., Xu, Y. & Miller, S. J. Desymmetrization of glycerol derivatives with peptide-based acylation catalysts. *Org. Lett.,* **7**, 3021–3023 (2005).

and the layers were separated once cool. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to yield a pale yellow oil. Purification of the crude oil by silica gel flash chromatography (gradient elution: 1:1→3:2 Et_2O/hexanes) provided the (bis)acetal as a clear, colorless oil (3.19 g, 42%). **TLC R$_f$** = 0.32 (3:2 Et_2O/hexanes); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 4.16 (q, *J* = 6.0 Hz, 2H), 4.06 (t, *J* = 7.4 Hz, 2H), 3.88 (t, *J* = 7.4 Hz, 2H), 3.58 (q, *J* = 5.4 Hz, 1H), 2.44 (dd, *J* = 6.1, 1.6 Hz, 1H), 1.44 (s, 6H), 1.37 (s, 6H) ppm; **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 109.5, 76.0, 71.6, 66.0, 26.4, 25.2 ppm; **IR** (thin film) ν 3481, 2983, 2934, 2893, 1368, 1250, 1209, 1152, 1066, 882, 854 cm^{-1}; **HRMS** calcd for $[C_{11}H_{20}O_5\ H]^+$ requires *m/z* 233.1384; found 233.1380 (ESI+).



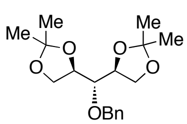
38

In a flame dried 100 mL round bottom flask, 2,2-dimethoxypropane (4.43 mL, 36.2 mmol) was dissolved in 25 mL of THF and adonitol (2.5 g, 16.4 mmol) was added. The mixture was allowed to stir at reflux for 15 minutes and then L-(–)-camphorsulfonic acid (381.7 mg, 1.6 mmol) was added at refluxing temperature and pentaol **36** dissolved. After refluxing for another 5 minutes, the reaction was quenched at refluxing temperature with 2M NaOH (10 mL). The suspension was extracted with Et_2O and H_2O. The aqueous layer was further extracted three times with Et_2O. The organic layer was dried over Na_2SO_4, filtered, and concentrated to provide a colorless oil. After dissolving the oil in CH_2Cl_2 (50 mL), Et_3N (2.49 mL, 17.9 mmol) was added and the solution was brought to reflux. Succinic anhydride (411.0 mg, 4.1 mmol) was added to the reaction at refluxing temperature and the reaction was allowed to stir at reflux for an additional hour. The reaction was then quenched with sat. aq. $NaHCO_3$ (5 mL) at refluxing temperature and the layers were separated once cool. The organic layer was dried over Na_2SO_4, filtered, and concentrated to yield a pale yellow oil. Purification of the crude oil by silica gel flash chromatography (1:1 to 3:2 Et_2O/hexanes) provided the (bis)acetal as a clear, colorless oil (3.26 g, 86%). **TLC R$_f$** = 0.41 (3:2 Et_2O/hexanes); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 4.09-4.13 (m, 2H), 4.07 (dd, *J* = 6.4, 1.5 Hz, 2H), 3.99 (dd, *J* = 6.0, 2.0 Hz, 2H), 3.84 (td, *J* = 5.3, 2.0 Hz, 1H), 2.22 (d, *J* = 2.1 Hz, 1H), 1.43 (s, 6H), 1.36 (s, 6H) ppm; **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 109.2, 75.8, 71.2, 65.5, 26.5, 25.1 ppm; **IR** (thin film) ν 3463, 2979, 2932, 2886, 1454, 1363, 1246, 1211, 1153, 1065, 915, 843, 793 cm^{-1}; **HRMS** calcd for $[C_{11}H_{20}O_5\ Na]^+$ requires *m/z* 255.1203; found 255.1203 (ESI+).



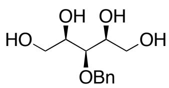
39

In a flame dried 250 mL round bottom flask (bis)acetal **37** (2.75 g, 11.8 mmol) was dissolved in THF (90 mL) and cooled to 0 ºC, then NaH (95%, 315.4 mg, 13.1 mmol) was added slowly and the mixture was allowed to stir at 0 ºC for 45 minutes. Then benzyl bromide (1.56 mL, 13.1 mmol) was added to the reaction and the mixture was allowed to warm up to room temperature. After stirring at room temperature overnight, the reaction was heated to 55 ºC and monitored by TLC for disappearance of starting material. The mixture was then quenched with sat. aq. $NaHCO_3$ and extracted with Et_2O and water. The aqueous layer was then extracted three more times with Et_2O and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to leave a clear oil. Purification of the crude oil by silica gel flash chromatography (1:1 Et_2O /hexanes) provides the (bis)acetal as a clear, colorless oil (3.80 g, 100%). **TLC** $\mathbf{R}_f$ = 0.53 (3:2 Et_2O/hexanes); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.33-7.38 (m, 4H), 7.27-7.30 (m, 1H), 4.79 (s, 2H), 4.24 (q, *J* = 6.5 Hz, 2H), 4.02 (dd, *J* = 6.6, 1.8 Hz, 2H), 3.82 (t, *J* = 7.9 Hz, 2H), 3.50 (t, *J* = 5.6 Hz, 1H), 1.43 (s, 6H), 1.35 (s, 6H) ppm; **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 138.4, 128.3, 128.0, 127.6, 109.1, 78.5, 78.0, 73.8, 66.1, 26.4, 25.3 ppm; **IR** (thin film) ν 2983, 2929, 2889, 2450, 1364, 1250, 1209, 1152, 1074, 1054, 890, 850, 731, 694, 662 cm^{-1}; **HRMS** calcd for $[C_{18}H_{26}O_5\ H]^+$ requires *m/z* 323.1853; found 323.1852 (ESI+).



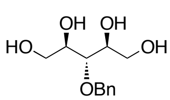
40

In a flame dried 250 mL round bottom flask (bis)acetal **38** (3.26 g, 14.1 mmol) was dissolved in THF (106 mL) and cooled to 0 ºC, then NaH (374.3 mg, 15.6 mmol) was added slowly and the mixture was allowed to stir at 0 ºC for 45 minutes. Then benzyl bromide (1.85 mL, 15.6 mmol) was added to the reaction and the mixture was allowed to warm up to room temperature. After stirring at room temperature overnight, the reaction was heated to 55 ºC and monitored by TLC for disappearance of starting material. The mixture was then quenched with sat. aq. $NaHCO_3$ and extracted with Et_2O and water. The aqueous layer was then extracted three more times with Et_2O and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to leave a clear oil. Purification of the crude oil by silica gel flash chromatography (1:1 Et_2O/hexanes) provides the (bis)acetal as a clear, colorless oil (4.50 g, 99%). **TLC R$_f$** = 0.79 (3:2 Et_2O/hexanes); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.32-7.38 (m, 4H), 7.27-7.31 (m, 1H), 4.79 (s, 2H), 4.16 (dt, *J* = 6.6, 5.0 Hz, 2H), 4.04 (dd, *J* = 6.6, 1.6 Hz, 2H), 3.92 (dd, *J* = 6.7, 1.4 Hz, 2H), 3.76 (t, *J* = 5.0 Hz, 1H), 1.44 (s, 6H), 1.35 (s, 6H) ppm; **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 138.3, 128.4, 128.0, 127.8, 109.2, 78.5, 76.1, 74.8, 65.8, 26.5, 25.1 ppm; **IR** (thin film) ν 2987, 2934, 2876, 1450, 1379, 1369, 1259, 1244, 1215, 1207, 1158, 1134, 1075, 1027, 857, 848, 748, 734, 698, 664 cm^{-1}; **HRMS** calcd for $[C_{18}H_{26}O_5\ H]^+$ requires *m/z* 323.1853; found 323.1855 (ESI+).



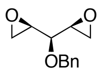
41

The (mono)benzyl-(bis)acetal **39** (3.49 g, 10.8 mmol) was dissolved in 181 mL of an 80% (v/v) acetic acid in water solution. The mixture was allowed to stir at room temperature while monitoring for the disappearance of starting material by TLC. After all starting material was consumed (approximately 24 h), the solution was concentrated under reduced pressure and purified by silica gel flash chromatography (9:1 CH_2Cl_2/MeOH) to yield a white solid (2.37 g, 91%). **TLC R$_f$** = 0.20 (9:1 CH_2Cl_2/MeOH); **mp =** 71–73°C; **^{1}H NMR** (CD_3OD, 500 MHz) δ 7.40 (d, *J* = 7.6 Hz, 2H), 7.32 (t, *J* = 7.5 Hz, 2H), 7.26 (t, *J* = 7.3 Hz, 1H), 4.70 (s, 2H), 3.86 (q, *J* = 5.1 Hz, 2H), 3.63-3.67 (m, 4H), 3.61 (t, *J* = 4.2 Hz, 1H) ppm; **^{13}C NMR** (CD_3OD, 125 MHz) δ 139.9, 129.3, 129.2, 128.7, 80.5, 75.5, 73.0, 64.2 ppm; **IR** (thin film) ν 3305, 2921, 2868, 1450, 1393, 1319, 1246, 1213, 1131, 1103, 1074, 1038, 1025, 980, 882, 862, 751, 731, 690 cm^{-1}; **HRMS** calcd for $[C_{12}H_{18}O_5\ H]^+$ requires *m/z* 243.1227; found 243.1223 (ESI+).



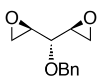
42

The (mono)benzyl-(bis)acetal **40** (4.91 g, 15.2 mmol) was dissolved in 245 mL of an 80% (v/v) acetic acid in water solution. The mixture was allowed to stir at room temperature while monitoring for the disappearance of starting material by TLC. After all starting material was consumed (approximately 20 h), the solution was concentrated and purified by silica gel flash chromatography (9:1 CH_2Cl_2/MeOH) to yield a clear, colorless thick oil (2.74 g, 75%). **TLC R$_f$** = 0.33 (9:1 CH_2Cl_2/MeOH); **^{1}H NMR** (CD_3OD, 500 MHz) δ 7.31-7.37 (m, 4H), 7.25-7.28 (m, 1H), 4.69 (s, 2H), 3.89 (dt, *J* = 6.0 Hz, *J* = 3.5 Hz, 2H), 3.76 (dd, *J* = 11.4, 3.7 Hz, 2H), 3.63 (dd, *J* = 6.4 , 5.0 Hz, 2H), 3.59 (t, *J* = 5.7 Hz, 1H) ppm; **^{13}C NMR** (CD_3OD, 125 MHz) δ 140.0, 129.3, 129.1, 128.7, 82.2, 74.9, 73.6, 64.4 ppm; **IR** (film) ν 3371, 2921, 2880, 1454, 1393, 1324, 1209, 1095, 1066, 907, 882, 747, 731, 694, 666 cm^{-1}; **HRMS** calcd for $[C_{12}H_{18}O_5\ H]^+$ requires *m/z* 243.1227; found 243.1224 (ESI+).



43

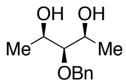
In a 100 mL round bottom flask, diisopropyl azodicarboxylate (1.85 mL, 9.6 mmol) and triphenylphosphine (2.73 g, 10.4 mmol) were added to a mixture of tetraol **41** (1.0 g, 4.2 mmol) in toluene (34 mL). The mixture was brought to reflux and monitored for disappearance of starting material by TLC (approximately 8 h). After the starting material was consumed, the excess diisopropyl azodicarboxylate was quenched with methanol and the mixture was concentrated under reduced pressure. Purification of the crude reaction mixture by silica gel flash chromatography (9:1 toluene/acetone) yielded a mixture containing the desired bis-epoxide. Further purification by silica gel flash chromatography (gradient elution: 10:1→6:1 hexanes/EtOAc) provided the bis-epoxide as a clear, colorless oil (524.6 mg, 62%). The spectral data for this compound matched that which had been previously reported.[6]



44

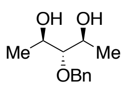
In a 250 mL round bottom flask, diisopropyl azodicarboxylate (5.06 mL, 26.2 mmol) and triphenylphosphine (7.48 g, 28.5 mmol) were added to a mixture of the tetraol **42** (2.74 g, 11.4 mmol) in toluene (92 mL). The mixture was brought to reflux and monitored for disappearance of starting material by TLC (approximately 8 h). After the starting material was consumed, the excess diisopropyl azodicarboxylate was quenched with methanol and the mixture was concentrated under reduced pressure. Purification of the crude reaction mixture by silica gel flash chromatography (9:1 toluene/acetone) yielded a mixture containing the desired bis-epoxide. Further purification by silica gel flash chromatography (gradient elution: 10:1→6:1 hexanes/EtOAc) provided the bis-epoxide as a clear, colorless oil (748.6 mg, 33%). The spectral data for this compound matched that which had been previously reported.[6]

[6] Kapitán, P. & Gracza, T. Stereocontrolled oxycarbonylation of 4-benzyloxyhepta-1,6-diene-3,5-diols promoted by chiral palladium(II) complexes. *Tetrahedron: Asymmetry*, **19**, 38–44 (2008).



20

In a 100 mL round bottom flask, bis-epoxide **43** (250 mg, 1.2 mmol) was dissolved in Et_2O (56 mL) and cooled to 0 ºC. Upon cooling of the solution to 0 ºC, $LiAlH_4$ (139.4 mg, 3.7 mmol) was slowly added and the mixture was allowed to stir while gradually warming to room temperature. The reaction mixture was monitored by TLC for disappearance of starting material (approximately 8 h) and then quenched with 2.2 mL of water, followed by 2.2 mL of a 10% NaOH in water solution, and finally another 6.6 mL of water. The reaction mixture was then separated and the organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the resulting oil by silica gel flash chromatography (1:1 hexanes/EtOAc) yielded diol **20** as a clear, colorless oil (187.5 mg, 73%). The spectral data for this compound matched that which had been previously reported.[5]



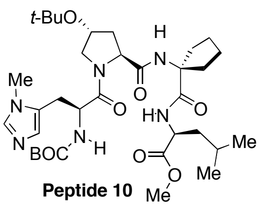
19

In a 100 mL round bottom flask, bis-epoxide **44** (250 mg, 1.2 mmol) was dissolved in Et_2O (56 mL) and cooled to 0 ºC. Upon cooling of the solution to 0 ºC, $LiAlH_4$ (139.4 mg, 3.7 mmol) was slowly added and the mixture was allowed to stir while gradually warming to room temperature. The reaction mixture was monitored by TLC for disappearance of starting material (approximately 8 h) and then quenched with 2.2 mL of water, followed by 2.2 mL of a 10% NaOH in water solution, and finally another 6.6 mL of water. The reaction mixture was then separated and the organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the resulting oil by silica gel flash chromatography (1:1 hexanes/EtOAc) yielded diol **19** as a clear, colorless oil (213 mg, 83%). The spectral data for this compound matched that which had been previously reported.[5]

Solid Phase Synthesis of Peptide Catalyst 10.

Peptide catalysts used for the reactions in Table 1 were synthesized on solid support using commercially available Wang polystyrene resin preloaded with the appropriate amino acid. Couplings were performed using 5.0 equiv of amino acid derivative, 5.0 equiv of HBTU, and 10.0 equiv of Hunig's base in DMF, for 3 h. Deprotections were performed using 20% piperidine in DMF for 20 min (to minimize diketopiperazine formation; dipeptides were deprotected using 50% piperidine in DMF for 5 min). Peptides were cleaved from solid support using 5.0 equiv of

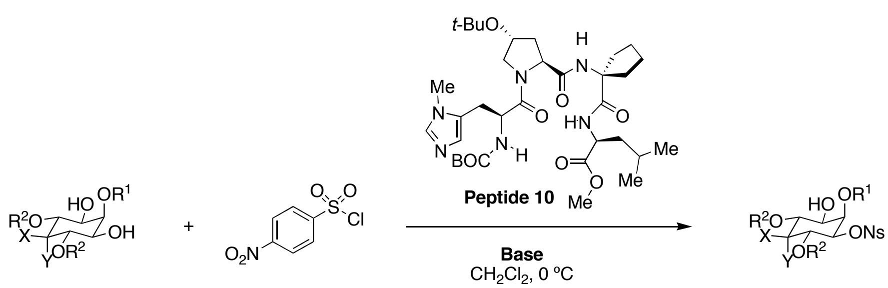
DBU in a mixture of MeOH:DMF (9:1) for 3 h. The peptides were passed through a plug of silica using 10:1 CH_2Cl_2/MeOH to remove the DBU, concentrated under reduced pressure, and then placed on high vacuum overnight. The resulting yellow residues were purified by reverse phase chromatography on a Biotage SP4 using C18 silica gel. The peptides were purified by a gradient of 40% MeOH/water to 75% MeOH/water over 30 column volumes.



Peptide 10

Pale yellow solid: **mp** = 95–100 °C; **^{1}H NMR** (major conformer) (CD_3OD, 500 MHz) δ 7.57 (s, 1H), 6.80 (s, 1H), 4.54 (dd, *J* = 9.7, 4.7 Hz, 1H), 4.50-4.41 (m, 3H), 3.73 (dd, *J* = 10.5, 5.0 Hz, 1H), 3.69 (s, 3H), 3.66 (s, 3H), 3.57 (dd, *J* = 10.5, 2.9, 1H), 2.98 (dd, *J* = 15.4, 4.6 Hz, 1H), 2.90 (dd, *J* = 15.4, 9.8 Hz, 1H), 2.25 (dt, *J* = 13.5, 7.1 Hz, 1H), 2.10-2.02 (m, 4H), 1.96 (dt, *J* = 13.2, 5.9 Hz, 1H), 1.79-1.63 (m, 8H), 1.34 (s, 9H), 1.19 (s, 9H), 0.91 (d, *J* = 10.0 Hz, 3H), 0.90 (d, *J* = 10.0 Hz, 3H) ppm; **^{13}C-NMR** (CD_3OD, 125 MHz) δ 176.2, 174.7, 174.3, 171.7, 157.4, 139.2, 129.1, 128.6, 80.6, 75.5, 71.2, 68.2, 60.9, 55.9, 52.6, 52.4, 41.7, 39.0, 38.3, 37.0, 31.8, 28.9, 28.7, 28.6, 27.2, 25.8, 25.6, 25.3, 23.2, 22.6 ppm; **IR** (thin film) ν 3316, 2973, 2872, 1743, 1643, 1507, 1443, 1391, 1366, 1324, 1252, 1171, 1109, 1054, 1025 cm^{-1}; **HRMS** calcd for $[C_{34}H_{56}N_6O_8\ H]^+$ requires *m/z* 677.4232; found 677.4217 (ESI+); **$[\alpha]^{25.0}_{D}$** = −23.4 (*c* 1.0, $CHCl_3$).

Catalytic Enantioselective Sulfonylation Reactions.



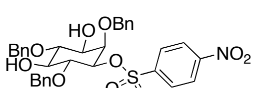
General procedure for initial screenings: To an oven-dried 1 dram vial equipped with a magnetic stir bar was added 2,4,6-tri-*O*-benzyl-*myo*-inositol (**1**) (45.1 mg, 0.10 mmol) and CH_2Cl_2 (0.4 mL). Solid $NaHCO_3$ (9.2 mg, 0.11 mmol) was then added followed by peptide catalyst **10** (3.4 mg, 0.005 mmol). The reaction was cooled to 0 °C and 4-nitrobenzenesulfonyl chloride (22.2 mg, 0.10 mmol) was added. The reaction was allowed to stir at 0 ºC for 24 h at which point it was diluted with CH_2Cl_2 (3 mL), filtered through celite, and concentrated under reduced pressure. The resulting yellow oil was purified by silica gel flash chromatography.

General procedure for sulfonylation using condition A (Table 2):

To an oven-dried 1 dram vial equipped with a magnetic stir bar was added diol substrate (0.10 mmol) and CH_2Cl_2 (0.4 mL). The peptide catalyst **10** (3.4 mg, 0.005 mmol) was then added and the reaction was cooled to 0 °C. 4-Nitrobenzenesulfonyl chloride (28.8 mg, 0.13 mmol) was added followed by 0.2 mL sat. aq. $NaHCO_3$ solution. The reaction was monitored by TLC for the disappearance of the sulfonyl chloride and allowed to stir at 0 ºC for 5-48 h. The biphasic reaction mixture was diluted with CH_2Cl_2 (2 mL) and sat. aq. $NaHCO_3$, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 2 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting yellow oil was purified by silica gel flash chromatography.

General procedure for sulfonylation using condition B (Table 2):

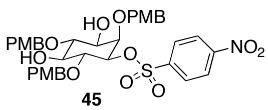
To an oven-dried 1 dram vial equipped with a magnetic stir bar was added diol substrate (0.10 mmol) and CH_2Cl_2 (0.4 mL). The peptide catalyst **10** (3.4 mg, 0.005 mmol) was then added and the reaction was cooled to 0 °C. 4-Nitrobenzenesulfonyl chloride (28.8 mg, 0.13 mmol) was added followed by 2,6-lutidine (17.5 µL, 0.15 mmol). The reaction was monitored by TLC for the disappearance of the sulfonyl chloride and allowed to stir at 0 ºC for 5-48 h. The reaction mixture was diluted with CH_2Cl_2 (2 mL), and 1M HCl (0.5 mL) was added. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 2 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting yellow oil was purified by silica gel flash chromatography.



2a

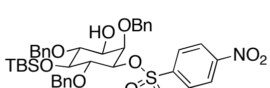
Purified by silica gel flash chromatography (gradient elution: 4:1→2:1 hexanes/EtOAc); pale yellow solid (49.8 mg, 78%): **TLC R$_f$** = 0.52 (2:1 hexanes/EtOAc); **mp** = 117–120 ºC; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 8.00-7.97 (m, 2H), 7.95-7.92 (m, 2H), 7.47-7.30 (m, 10H), 7.28-7.25 (m, 3H), 7.07-7.03 (m, 2H), 4.91 (d, J = 11.5 Hz, 1H), 4.83 (d, J = 11.4 Hz, 1H), 4.82 (d, J = 11.5 Hz, 1H), 4.81 (d, J = 11.4 Hz, 1H), 4.72 (d, J = 11.2 Hz, 1H), 4.46 (dd, J = 10.0, 2.6 Hz, 1H), 4.39 (d, J = 11.2 Hz, 1H), 4.27 (t, J = 2.6 Hz, 1H), 3.87 (t, J = 9.5 Hz, 1H), 3.65 (t, J = 9.5 Hz, 1H), 3.59

(ddd, J = 9.6, 6.2, 2.6 Hz, 1H), 3.51 (td, J = 9.1, 2.6 Hz, 1H), 2.38 (d, J = 2.6 Hz, 1H), 2.16 (d, J = 6.2 Hz, 1H) ppm; **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 150.4, 141.7, 138.2, 137.9, 137.6, 129.0, 128.7, 128.6, 128.3, 128.1, 128.0, 127.9, 127.0, 124.1, 82.5, 81.0, 78.9, 78.6, 75.8, 75.1, 75.04, 75.01, 71.7 ppm; **IR** (thin film) ν 3549, 3105, 3065, 2918, 1608, 1533, 1497, 1454, 1404, 1350, 1314, 1186, 1114, 1071, 1027, 966, 938, 858, 835 cm^{-1}; **HRMS** calcd for $[C_{33}H_{33}NO_{10}S\ Na]^+$ requires m/z 658.1717; found 658.1715 (ESI+); $[\alpha]_D^{25.0}$ = –14.0 (c 1.0, $CHCl_3$, 97:3 er); **HPLC** Chiracel AD; 35% ethanol/hexanes; flow rate = 0.5 mL/min.; t_r = 36.4 min. (major ent.), t_r = 31.6 min. (minor ent.).



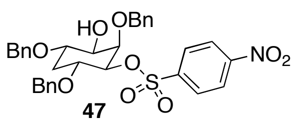
45

Purified by silica gel flash chromatography (gradient elution: 3:1→1:1 hexanes/EtOAc); viscous yellow oil (54.5 mg, 75%): **TLC R_f** = 0.46 (1:1 hexanes/EtOAc); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 8.04-8.02 (m, 2H), 7.97-7.94 (m, 2H), 7.31-7.25 (m, 14H), 7.00-6.97 (m, 2H), 6.94-6.91 (m, 2H), 6.90-6.87 (m, 2H), 6.80-6.77 (m, 2H), 4.83 (d, J = 11.2 Hz, 1H), 4.75 (d, J = 11.1 Hz, 1H), 4.74 (d, J = 10.8 Hz, 1H), 4.72 (d, J = 11.1 Hz, 1H), 4.65 (d, J = 11.2 Hz, 1H), 4.42 (dd, J = 10.0, 2.7 Hz, 1H), 4.34 (d, J = 10.8 Hz, 1H), 4.23 (t, J = 2.7 Hz, 1H), 3.84 (t, J = 9.4 Hz, 1H), 3.84 (s, 3H), 3.82 (s, 3H), 3.80 (s, 3H), 3.60 (t, J = 9.4 Hz, 1H), 3.53 (ddd, J = 9.4, 6.4, 2.7 Hz, 1H), 3.51 (td, J = 9.1, 2.3 Hz, 1H), 2.36 (d, J = 2.3 Hz, 1H), 2.12 (d, J = 6.4 Hz, 1H) ppm; **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 159.54, 159.52, 159.3, 150.4, 141.8, 130.4, 130.0, 129.9, 129.7, 129.6, 129.1, 128.8, 124.1, 114.1, 114.0, 113.7, 82.6, 80.8, 78.5, 78.4, 75.4, 75.0, 74.8, 74.7, 71.7, 55.29, 55.28, 55.24 ppm; **IR** (thin film) ν 3547, 3467, 2952, 2937, 2839, 1612, 1586, 1532, 1514, 1465, 1442, 1404, 1350, 1314, 1303, 1249, 1186, 1110, 1074, 1035, 965, 938, 834 cm^{-1}; **HRMS** calcd for $[C_{36}H_{39}NO_{13}S\ Na]^+$ requires m/z 748.2034; found 748.2037 (ESI+); $[\alpha]_D^{25.0}$ = –1.6 (c 1.0, $CHCl_3$, 97:3 er); **HPLC** Chiracel AD; 35% ethanol/hexanes; flow rate = 1.0 mL/min.; t_r = 46.3 min. (major ent.), t_r = 37.4 min. (minor ent.).



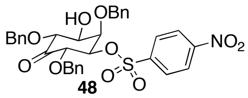
46

Purified by silica gel flash chromatography (gradient elution: 9:1→4:1 hexanes/EtOAc); viscous colorless oil (48.2 mg, 64%): **TLC R_f** = 0.43 (2:1 hexanes/EtOAc); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.92-7.90 (m, 2H), 7.85-7.82 (m, 2H), 7.40-7.30 (m, 10H), 7.21-7.18 (m, 3H), 7.00-6.97 (m, 2H), 4.85 (d, *J* = 11.6 Hz, 1H), 4.79 (d, *J* = 10.9 Hz, 1H), 4.75 (d, *J* = 10.9 Hz, 1H), 4.73 (d, *J* = 12.0 Hz, 1H), 4.67 (d, *J* = 11.6 Hz, 1H), 4.54 (dd, *J* = 9.7, 2.8 Hz, 1H), 4.46 (d, *J* = 12.0 Hz, 1H), 4.25 (t, *J* = 2.7 Hz, 1H), 3.82 (t, *J* = 9.1 Hz, 1H), 3.65 (t, *J* = 9.1 Hz, 1H), 3.57-3.53 (m, 2H), 1.97 (d, *J* = 5.6 Hz, 1H), 0.84 (s, 9H), 0.05 (s, 3H), –0.09 (s, 3H) ppm; **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 150.3, 141.7, 138.3, 138.1, 137.8, 128.7, 128.6, 128.4, 128.0, 127.9, 127.2, 125.9, 124.1, 82.9, 81.3, 79.4, 78.4, 75.6, 75.5, 74.7, 74.6, 71.6, 25.9, 17.8, –4.07, –4.13 ppm; **IR** (thin film) ν 3556, 3033, 2927, 2855, 1608, 1534, 1497, 1455, 1404, 1350, 1313, 1258, 1208, 1187, 1158, 1113, 1094, 1071, 1029, 971, 937, 829 cm^{-1}; **HRMS** calcd for $[C_{39}H_{47}NO_{10}SSi\ Na]^+$ requires *m/z* 775.2582; found 775.2575 (ESI+); **$[\alpha]_D^{25.0}$** = –14.1 (*c* 1.0, $CHCl_3$, 95.5:4.5 er); **HPLC** Chiracel AD; 10% ethanol/hexanes; flow rate = 1.0 mL/min.; t_r = 8.7 min. (major ent.), t_r = 7.0 min. (minor ent.).



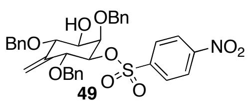
47

Purified by silica gel flash chromatography (gradient elution: 4:1→2:1 hexanes/EtOAc); pale yellow oil (37.8 mg, 61%): **TLC R_f** = 0.83 (1:1 hexanes/EtOAc); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.93 (s, 4H), 7.24-7.38 (m, 13H), 7.03 (dd, *J* = 7.7, 1.4 Hz, 2H), 4.86 (AB quartet, *J*= 11.3, 8.6 Hz, 2H) 4.65 (d, *J* = 11.5 Hz, 1H), 4.55 (d, *J* = 11.5 Hz, 1H), 4.45 (dd, *J* = 9.6, 2.8 Hz, 1H), 4.44 (d, *J* = 10.8 Hz, 1H), 4.33 (t, *J* = 2.7 Hz, 1H), 4.14 (d, *J* = 10.8 Hz, 1H), 3.88 (ddd, *J* = 11.4, 9.7, 5.1 Hz, 1H), 3.69 (ddd, *J* = 11.2, 9.4, 4.6 Hz, 1H), 3.62 (ddd, *J* = 9.4, 4.8, 2.6 Hz, 1H), 2.50 (dt, *J* = 12.8, 4.9 Hz, 1H), 2.40 (d, *J* = 4.8 Hz, 1H), 1.22 (q, *J* = 11.9 Hz, 1H) ppm; **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 150.3, 142.0, 138.2, 138.0, 137.3, 129.1, 128.6, 128.5, 128.3, 128.1, 127.96, 127.93, 127.90, 127.8, 127.6, 123.9, 84.7, 79.1 75.9, 75.5, 74.4, 73.5, 72.1, 71.8, 31.5 ppm; **IR** (thin film) 3555, 3105, 3060, 3028, 2921, 2864, 1605, 1528, 1495, 1450, 1401, 1348, 1307, 1181, 1111, 1091, 1070, 1052, 968, 910, 837, 735, 694, 617 cm^{-1}; **HRMS** calcd for $[C_{33}H_{33}O_9NS\ Na]^+$ requires *m/z* 642.1768; found 642.1766 (ESI+); **$[\alpha]_D^{25.0}$** = –11.5 (*c* 1.0, $CHCl_3$, 96:4 er); **HPLC** Chiracel AD; 25% 2-propanol/hexanes; flow rate = 1.0 mL/min.; t_r = 20.4 min. (major ent.), t_r = 15.9 min. (minor ent.).



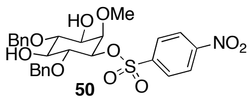
48

Purified by silica gel flash chromatography (gradient elution: 4:1→3:1 hexanes/EtOAc); white solid (49.7 mg, 78%): **TLC R*f*** = 0.52 (2:1 hexanes/EtOAc); **mp** = 147–148 ºC (decomp.); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.89 (s, 4H), 7.47-7.52 (m, 13H), 7.13-7.11 (m, 2H), 4.99 (s, 2H), 4.94 (d, *J* = 11.1 Hz, 1H), 4.73 (d, *J* = 10.1 Hz, 1H), 4.54 (t, *J* = 2.5 Hz, 1H), 4.51 (dd, *J* = 10.7, 1.1 Hz, 1H), 4.49-4.45 (m, 3H), 4.09 (d, *J* = 10.2 Hz, 1H), 3.77 (dt, *J* = 10.2, 2.9 Hz, 1H), 2.52 (d, *J* = 3.3 Hz, 1H) ppm; **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 201.1, 150.3, 141.2, 137.6, 137.0, 136.5, 129.2, 128.6, 128.5, 128.4, 128.30, 128.26, 128.19, 128.12, 128.0, 123.9, 82.1, 80.9, 80.1, 77.9, 76.4, 73.6, 73.5, 71.4 ppm; **IR** (thin film) ν 3550, 3107, 3062, 2920, 2897, 2872, 1743, 1608, 1533, 1497, 1455, 1405, 1350, 1315, 1187, 1147, 1120, 1081, 1028, 1014, 979, 943, 912, 857, 830 cm^{-1}; **HRMS** calcd for $[C_{33}H_{31}NO_{10}S\ Na]^+$ requires *m/z* 656.1561; found 656.1558 (ESI+); **$[\alpha]_D^{25.0}$** = –2.3 (*c* 1.0, $CHCl_3$, 96:4 er); **HPLC** Chiracel OD; 35% ethanol/hexanes; flow rate = 1.0 mL/min.; t_r = 9.5 min. (major ent.), t_r = 12.1 min. (minor ent.).



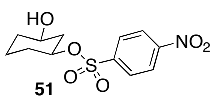
49

Purified by silica gel flash chromatography (gradient elution: 6:1→2:1 hexanes/EtOAc); pale yellow oil (50.0 mg, 79%): **TLC R*f*** = 0.53 (2:1 hexanes/EtOAc); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.92 (s, 4H), 7.38-7.26 (m, 13H), 7.10-7.06 (m, 2H), 5.45 (d, *J* = 1.1 Hz, 1H), 5.40 (d, *J* = 1.1 Hz, 1H), 4.90 (d, *J* = 11.2 Hz, 1H), 4.87 (d, *J* = 11.2 Hz, 1H), 4.77 (d, *J* = 11.5 Hz, 1H), 4.59 (d, *J* = 11.1 Hz, 1H), 4.53 (d, *J* = 11.5 Hz, 1H), 4.37 (dd, *J* = 9.5, 2.8 Hz, 1H), 4.35 (t, *J* = 2.8 Hz, 1H), 4.30 (d, *J* = 9.5 Hz, 1H), 4.24 (d, *J* = 11.1 Hz, 1H), 4.13 (d, *J* = 9.2 Hz, 1H), 3.55-3.51 (m, 1H), 2.46 (t, *J* = 1.7 Hz, 1H) ppm; **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 150.2, 141.8, 139.4, 138.0, 137.7, 137.2, 129.0, 128.6, 128.4, 128.2, 128.00, 127.98, 127.92, 127.85, 127.83, 127.1, 123.9, 110.2, 84.0, 79.0, 78.2, 76.7, 76.0, 74.2, 73.0, 72.7 ppm; **IR** (thin film) ν 3572, 2884, 2871, 1532, 1497, 1454, 1404, 1350, 1314, 1187, 1119, 1097, 1086, 1027, 976, 949, 856, 836 cm^{-1}; **HRMS** calcd for $[C_{34}H_{33}NO_9S\ Na]^+$ requires *m/z* 654.1768; found 654.1770 (ESI+); **$[\alpha]_D^{25.0}$** = –11.1 (*c* 1.0, $CHCl_3$, 96.5:3.5 er); **HPLC** Chiracel OD; 30% ethanol/hexanes; flow rate = 1.0 mL/min.; t_r = 11.4 min. (major ent.), t_r = 20.2 min. (minor ent.).



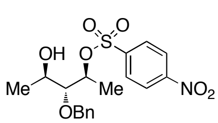
50

Purified by silica gel flash chromatography (gradient elution: 4:1→2:1 hexanes/EtOAc); colorless oil (32.5 mg, 58%): **TLC R_f** = 0.36 (2:1 hexanes/EtOAc); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 8.01-7.99 (m, 2H), 7.96-7.94 (m, 2H), 7.38-7.29 (m, 5H), 7.26-7.22 (m, 3H), 7.05-7.02 (m, 2H), 4.85 (d, *J* = 11.4 Hz, 1H), 4.83 (d, *J* = 11.4 Hz, 1H), 4.72 (d, *J* = 11.2 Hz, 1H), 4.42 (dd, *J* = 10.0, 2.6 Hz, 1H), 4.37 (d, *J* = 11.2 Hz, 1H), 4.01 (t, *J* = 2.6 Hz, 1H), 3.79 (t, *J* = 9.6 Hz, 1H), 3.70 (s, 3H), 3.62-3.55 (m, 2H), 3.47 (td, *J* = 9.0, 2.5 Hz, 1H), 2.40 (br s, 1H), 2.36 (br d, *J* = 4.0 Hz, 1H) ppm; **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 150.4, 141.7, 138.3, 137.7, 129.0, 128.6, 128.3, 128.0, 127.93, 127.91, 127.0, 124.1, 82.7, 81.2, 80.9, 78.5, 75.2, 75.04, 74.96, 71.7, 62.3 ppm; **IR** (thin film) ν 3557, 3476, 2931, 1608, 1533, 1498, 1454, 1404, 1351, 1314, 1292, 1267, 1187, 1110, 1071, 1015, 965, 937, 858, 836 cm^{-1}; **HRMS** calcd for $[C_{27}H_{29}NO_{10}S\ Na]^+$ requires *m/z* 397.1622; found 397.1618 (ESI+); **$[\alpha]_D^{25.0}$** = –17.5 (*c* 1.0, $CHCl_3$, 88:12 er); **HPLC** Chiracel AD; 45% ethanol/hexanes; flow rate = 1.0 mL/min.; t_r = 19.8 min. (major ent.), t_r = 8.1 min. (minor ent.).



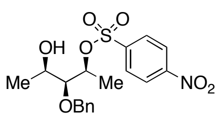
51

Purified by silica gel flash chromatography (gradient elution: 3:1→1:1 hexanes/EtOAc); colorless oil (19.8 mg, 66%): **TLC R_f** = 0.33 (1:1 hexanes/EtOAc); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 8.42-8.38 (m, 2H), 8.13-8.09 (m, 2H), 4.58 (tt, *J* = 10.7, 4.5 Hz, 1H), 3.65-3.57 (m, 1H), 2.22-2.20 (m, 1H), 1.95-1.78 (m, 3H), 1.60 (br s, 1H), 1.53 (dt, *J* = 11.7, 10.7 Hz, 1H), 1.49-1.40 (m, 1H), 1.29-1.19 (m, 2H) ppm; **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 150.6, 143.2, 128.9, 137.7, 124.5, 80.9, 68.1, 41.3, 33.8, 31.6, 19.6 ppm; **IR** (thin film) ν 3396, 2945, 2861, 1608, 1532, 1454, 1404, 1352, 1312, 1184, 1096, 1064, 928, 905, 855, 825 cm^{-1}; **HRMS** calcd for $[C_{12}H_{15}NO_6S\ Na]^+$ requires *m/z* 324.0693; found 324.0511 (ESI+); **HPLC** Chiracel OJ-H; 20% 2-propanol/hexanes; flow rate = 1.0 mL/min.; t_r = 28.0 min., t_r = 33.1 min.



52

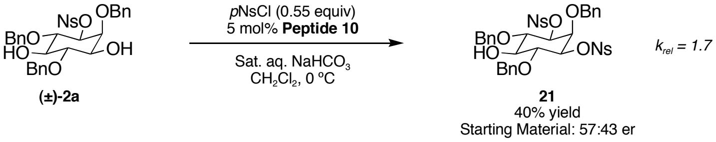
Purified by silica gel flash chromatography (gradient elution: 5:1→1:1 hexanes/EtOAc); pale yellow solid (29.3 mg, 74%): **TLC R_f** = 0.66 (1:1 hexanes/EtOAc); **mp** = 56–58°C; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 8.34 (dt, *J* = 8.9, 2.3 Hz, 2H), 8.07 (dt, *J* = 8.8, 2.1 Hz, 2H), 7.29-7.36 (m, 5H), 5.12 (qd, J = 6.6, 2.3 Hz, 1H), 4.74 (d, J = 11.4 Hz, 1H), 4.59 (d, J = 11.4 Hz, 1H), 3.72-3.78 (m, 1H), 3.48 (dd, J = 6.7, 2.3 Hz, 1H), 1.56 (d, J = 5.3 Hz, 1H), 1.37 (d, J = 6.6 Hz, 3H), 1.22 (d, J = 6.3 Hz, 3H) ppm; **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 150.6, 143.0, 137.6, 129.0, 128.5, 128.0, 127.9, 124.4, 84.2, 82.0, 74.1, 67.6, 20.1, 15.7 ppm; **IR** (thin film) ν 3551, 3448, 3105, 3068, 3036, 2962, 2929, 1601, 1532, 1450, 1401, 1348, 1307, 1258, 1181, 1091, 1050, 1025, 907, 850, 796, 735, 698, 682, 613 cm^{-1}; **HRMS** calcd for $[C_{18}H_{21}NO_7S\ H]^+$ requires m/z 396.1111; found 396.1111 (ESI+); $[\alpha]_D^{25.0}$ = 0 (c 2.0, $CHCl_3$, 89:11 er); **HPLC** Chiracel AD; 10% 2-propanol/hexanes; flow rate = 1.0 mL/min.; t_r = 14.3 min. (major ent.), t_r = 17.2 min. (minor ent.).



53

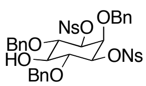
Purified by silica gel flash chromatography (gradient elution: 5:1→1:1 hexanes/EtOAc); pale yellow oil (20.2 mg, 51%): **TLC R$_f$** = 0.57 (1:1 hexanes/EtOAc); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 8.15 (dt, J = 9.0, 2.1 Hz, 2H), 8.00 (dt, J = 8.9, 2.2 Hz, 2H), 7.29 (dd, J = 4.5, 2.0 Hz, 3H), 7.14-7.16 (m, 2H), 4.94 (p, J = 6.6 Hz, 1H), 4.60 (d, J = 11.3 Hz, 1H), 4.53 (d, J = 11.3 Hz, 1H), 3.79-3.86 (m, 1H), 3.25 (dd, J = 7.1, 2.9 Hz, 1H), 1.80 (d, J = 8.9 Hz, 1H), 1.44 (d, J = 6.5 Hz, 3H), 1.21 (d, J = 6.4 Hz, 3H) ppm; **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 150.4, 142.7, 137.2, 128.9, 128.4, 128.1, 127.3, 124.2, 83.9, 82.2, 75.2, 66.7, 20.4, 17.8 ppm; **IR** (thin film) ν 3555, 3428, 3105, 3064, 3023, 2974, 2921, 2876, 1610, 1528, 1450, 1401, 1348, 1307, 1181, 1136, 1087, 1062, 1009, 915, 894, 850, 788, 735, 698, 682, 613 cm^{-1}; $[\alpha]_D^{25.0}$ = –1.4 (c 1.0, $CHCl_3$, 70:30 er); **HRMS** calcd for $[C_{18}H_{21}NO_7S\ H]^+$ requires m/z 396.1111; found 396.1113 (ESI+); **HPLC** Chiracel AD; 10% 2-propanol/hexanes; flow rate = 1.0 mL/min.; t_r = 23.5 min. (major ent.), t_r = 21.2 min. (minor ent.).

Kinetic Resolution of Racemic (Mono)sulfonate 2a.



To an oven-dried 1 dram vial equipped with a magnetic stir bar was added (mono)nosylate **2a** (32.0 mg, 0.05 mmol) and CH_2Cl_2 (0.2 mL). The peptide catalyst **10** (1.7 mg, 0.0025 mmol) was then added and the reaction was cooled to 0 °C. 4-Nitrobenzenesulfonyl chloride (6.1 mg, 0.276

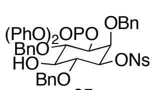
mmol) was added followed by 0.1 mL sat. aq. $NaHCO_3$ solution. The reaction was monitored by TLC for the disappearance of the sulfonyl chloride and allowed to stir at 0 ºC for 4 h. The biphasic reaction mixture was diluted with CH_2Cl_2 (2 mL) and sat. aq. $NaHCO_3$, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 2 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting yellow oil was purified by silica gel flash chromatography (gradient elution: 4:1→2:1 hexanes/EtOAc) to obtain the starting material as pale yellow solid (16.6 mg, 52%) and the bis(nosylate) as a pale yellow solid (18.2 mg, 44%)



21

TLC R*f* = 0.54 (4:1 hexanes/EtOAc); **mp** = 189–192 ºC; **^{1}H NMR** (CD_2Cl_2, 500 MHz) δ 8.07-8.04 (m, 4H), 7.99-7.96 (m, 4H), 7.41-7.34 (m, 5H), 7.26-7.23 (m, 6H), 7.06-7.04 (m, 4H), 4.86 (s, 2H), 4.67 (d, *J* = 11.3 Hz, 2H), 4.52 (dd, *J* = 10.0, 2.6 Hz, 2H), 4.46 (t, *J* = 2.6 Hz, 1H), 4.40 (d, *J* = 11.3 Hz, 2H), 3.85 (t, *J* = 9.6 Hz, 2H), 3.52 (td, *J* = 9.5, 3.2 Hz, 1H), 2.42 (d, *J* = 3.2 Hz, 1H) ppm; **^{13}C NMR** (CD_2Cl_2, 125 MHz) δ 151.0, 141.8, 138.0, 137.9, 129.4, 128.8, 128.6, 128.4, 128.2, 128.1, 127.5, 124.7, 81.4, 81.0, 78.9, 78.2, 76.8, 75.4, 75.3 ppm; **IR** (thin film) ν 3559, 3107, 2917, 2878, 1608, 1533, 1498, 1455, 1405, 1351, 1314, 1292, 1188, 1118, 1095, 1028, 1014, 977, 940, 858, 841, 821 cm^{-1}; **HRMS** calcd for $[C_{39}H_{36}N_2O_{14}S_2\ Na]^+$ requires *m/z* 843.1500; found 843.1509 (ESI+).

Determination of Absolute Stereochemistry

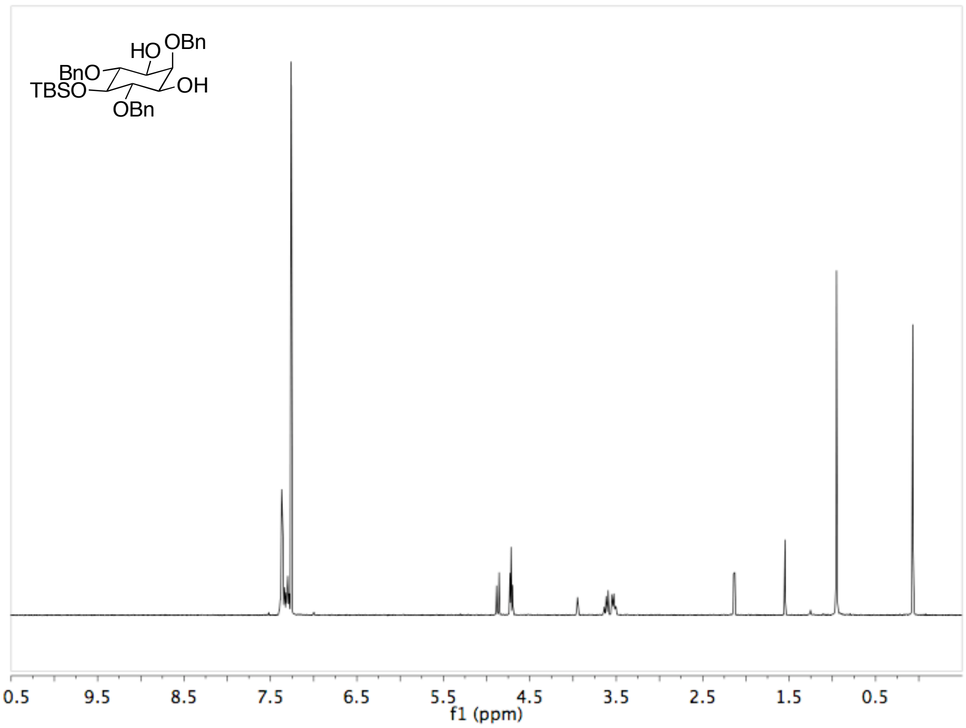


25

Monophosphate **24** (40.0 mg, 0.059 mmol) was dissolved in 236.0 µL of CH_2Cl_2 and *N,N*-dimethyl-4-aminopyridine (7.2 mg, 0.059 mmol), solid $NaHCO_3$ (10.9 mg, 0.13 mmol), and 4-nitrobenzenesulfonyl chloride (25.9 mg, 0.117 mmol) were added respectively. The reaction mixture was allowed to stir for 48 h and then the mixture was run through a short plug of celite and concentrated under reduced pressure. Purification of the crude oil by silica gel flash chromatography (gradient elution: 4:1→2:1 hexanes/EtOAc) provided **25** as a light yellow oil (20.0 mg, 39%). **TLC R*f*** = 0.56 (2:1 hexanes/EtOAc); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.94 (dd, *J* = 8.9, 1.3 Hz, 2H), 7.89 (dd, *J* = 8.8, 1.4 Hz, 2H), 7.14-7.39 (m, 23H), 7.02-7.03 (m, 2H), 4.79 (d,

J = 11.4 Hz, 1H), 4.73 (dd, J = 11.2, 2.2 Hz, 2H), 4.61 (dd, J = 6.4, 4.2 Hz, 3H), 4.48 (s, 1H), 4.41 (dd, J = 8.3, 1.8 Hz, 1H), 4.33 (d, J = 11.2 Hz, 1H), 3.92 (t, J = 9.6 Hz, 1H), 3.86 (t, J = 9.5 Hz, 1H), 3.52 (t, J = 9.3 Hz, 1H), 2.30 (d, J = 2.0 Hz, 1H) ppm; **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 150.6, 138.0, 137.9, 137.7, 129.95, 129.85, 129.1, 128.5, 128.4, 128.3, 128.0, 127.9, 127.8, 127.5, 127.2, 125.69, 125.66, 125.5, 124.1, 120.1, 120.02, 119.98, 119.9, 81.5, 79.34, 79.30, 78.71, 78.65, 78.5, 78.1, 76.0, 75.3, 75.1, 74.8 ppm; **^{31}P NMR** ($CDCl_3$, 202 MHz) δ -12.44 ppm; **IR** (thin film) ν 3567, 3424, 3105, 3064, 3028, 2921, 2868, 2844, 1949, 1867, 1806, 1720, 1588, 1531, 1488, 1454, 1347, 1311, 1288, 1217, 1188, 1163, 1115, 1091, 1070, 1024, 960, 829, 737, 686, 615 cm^{-1}; $[\alpha]_D^{25.0}$ = –20.6 (c 1.0, $CHCl_3$, 99:1 er); **HRMS** calcd for $[C_{45}H_{42}O_{13}NPS\ Na]^+$ requires m/z 868.2187; found 868.2162 (ESI+); **HPLC** Chiracel OD; 15% ethanol/hexanes; flow rate = 0.75 mL/min.; t_r = 20.6 min. (major ent.), t_r = 16.2 min. (minor ent.).

NMR Data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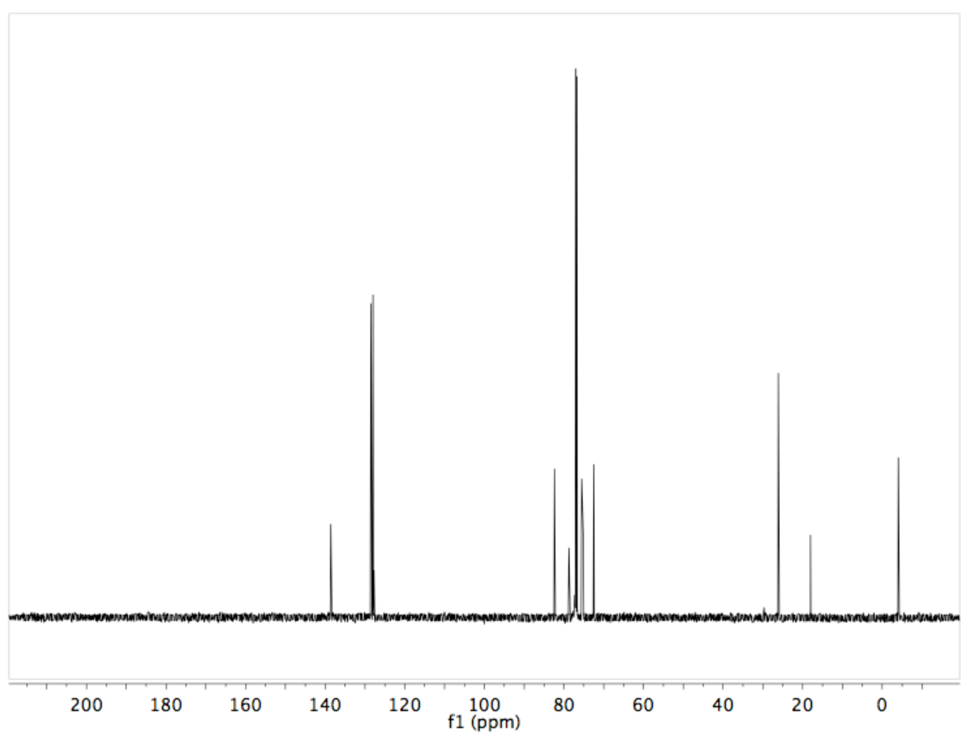
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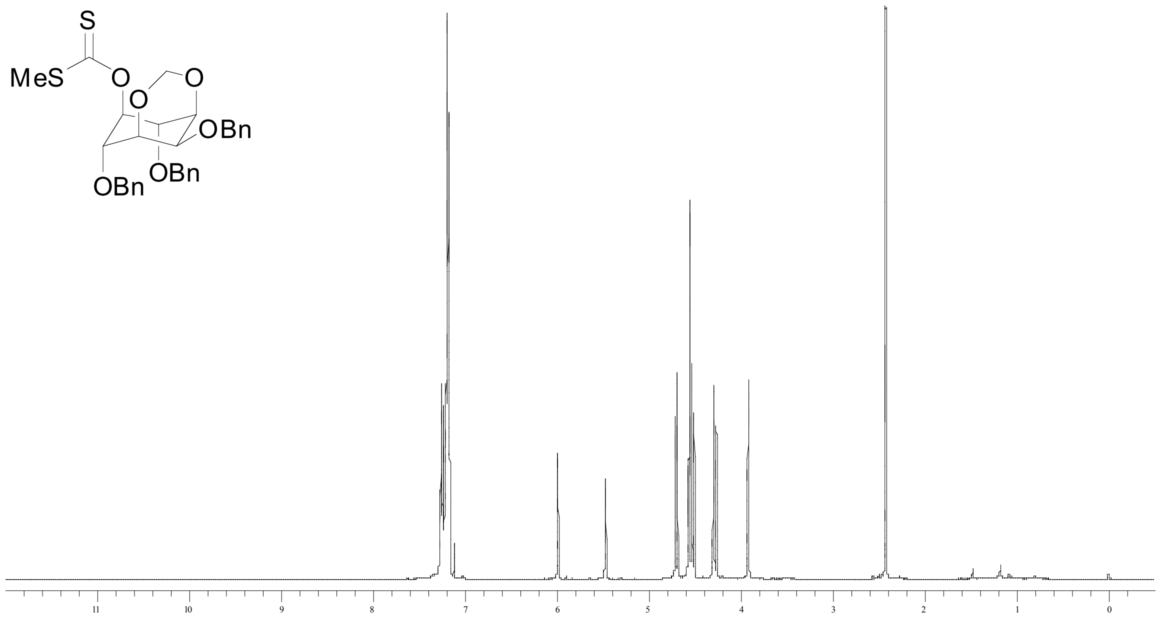
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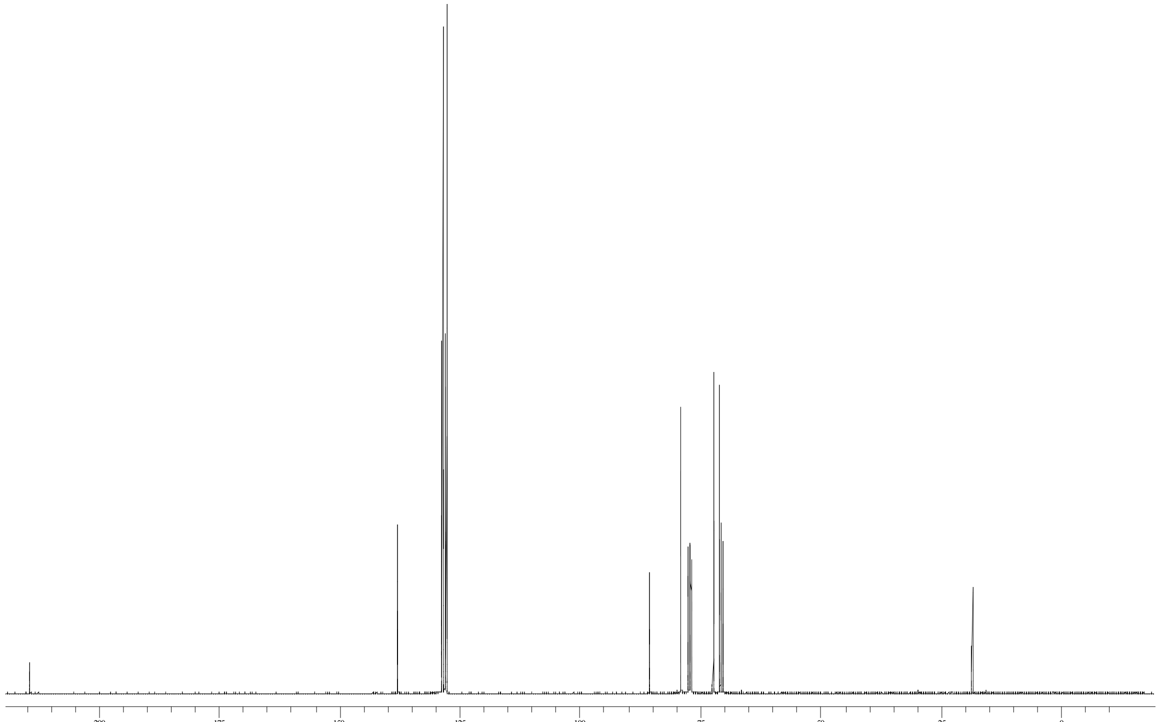
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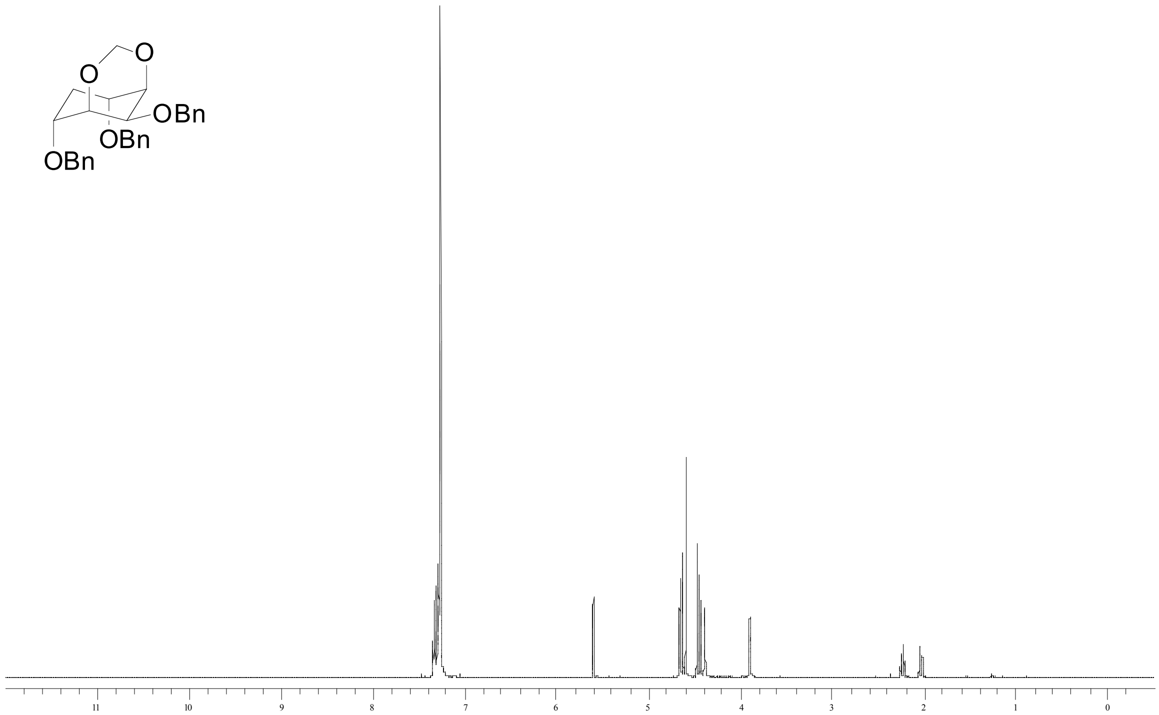
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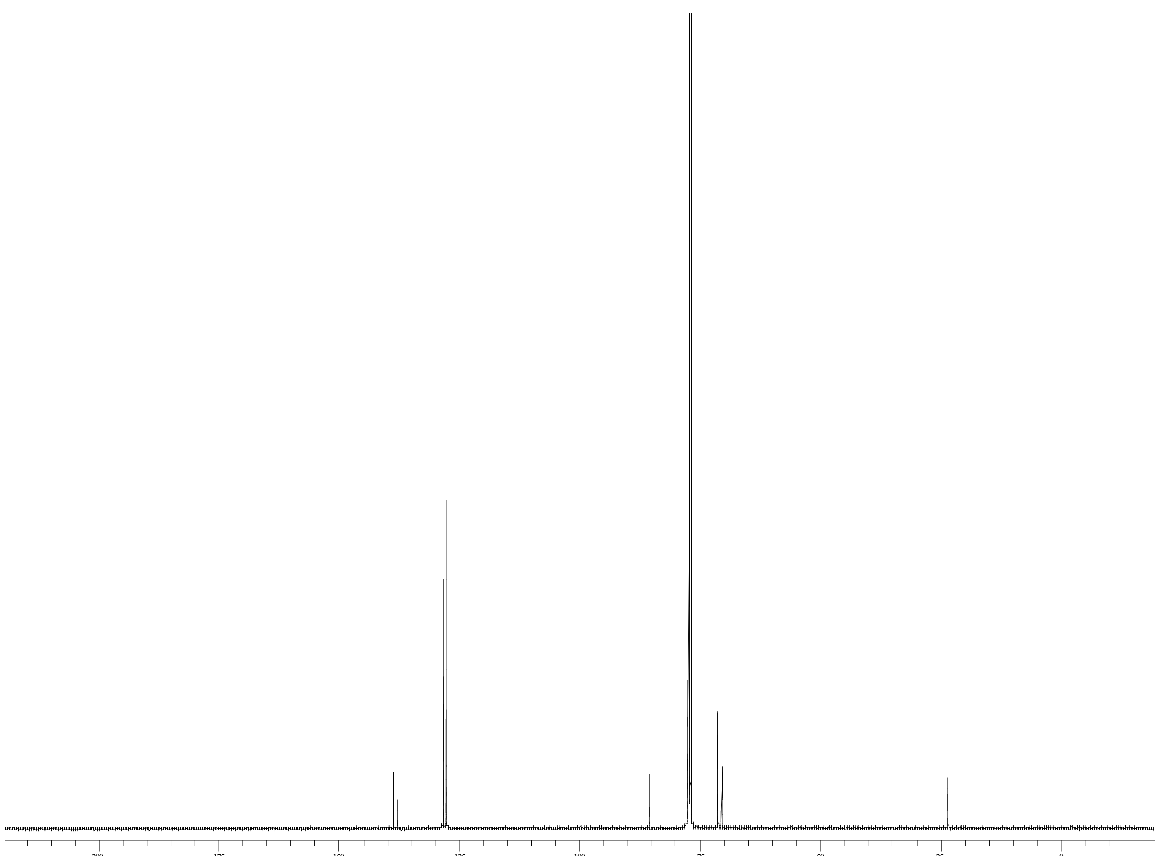

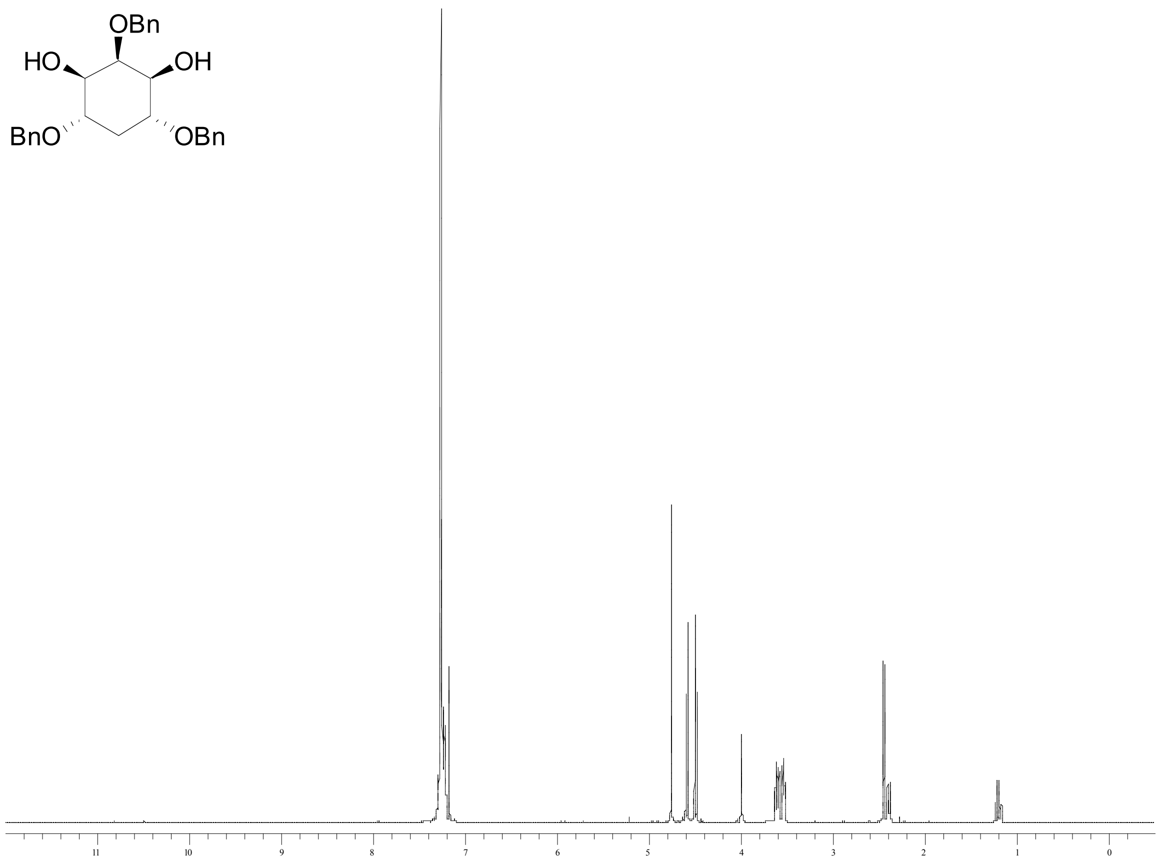
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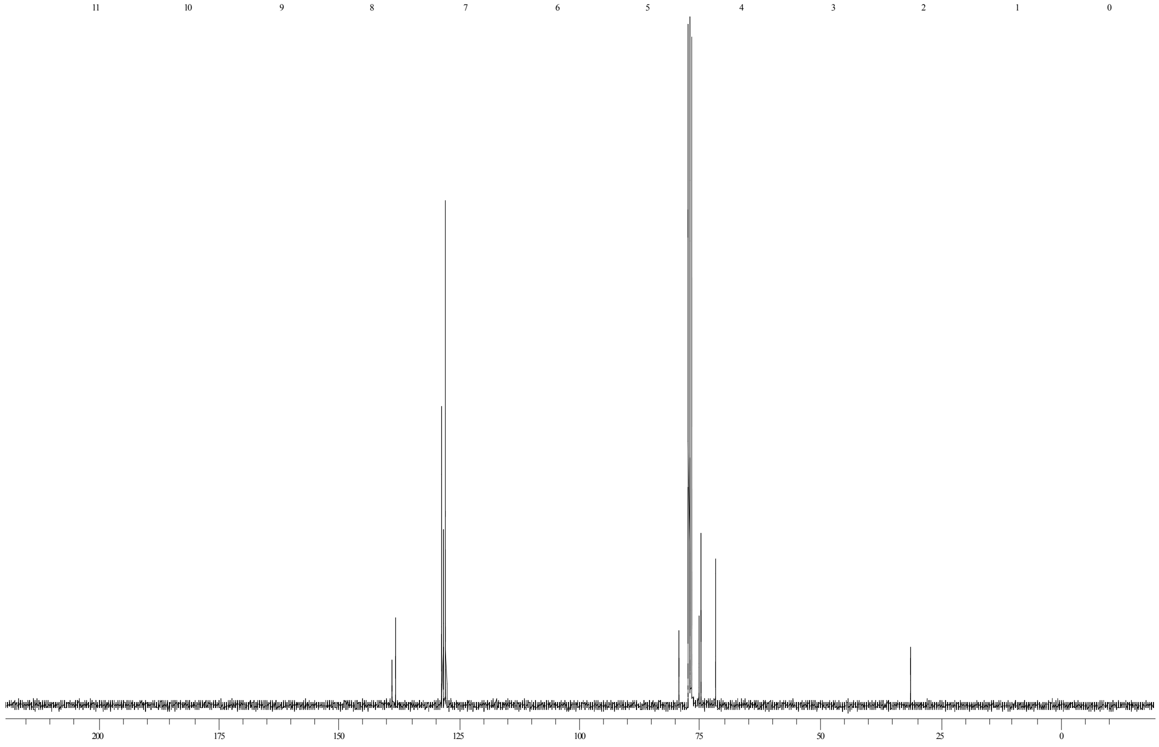
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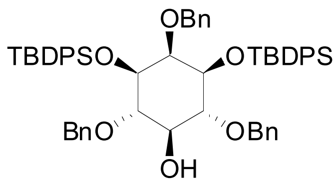
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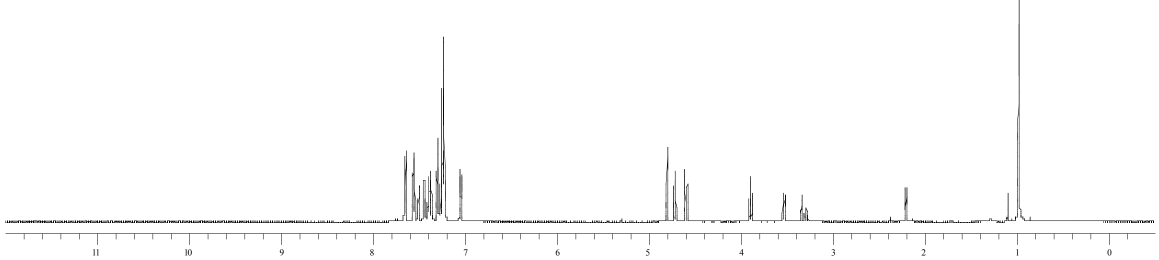
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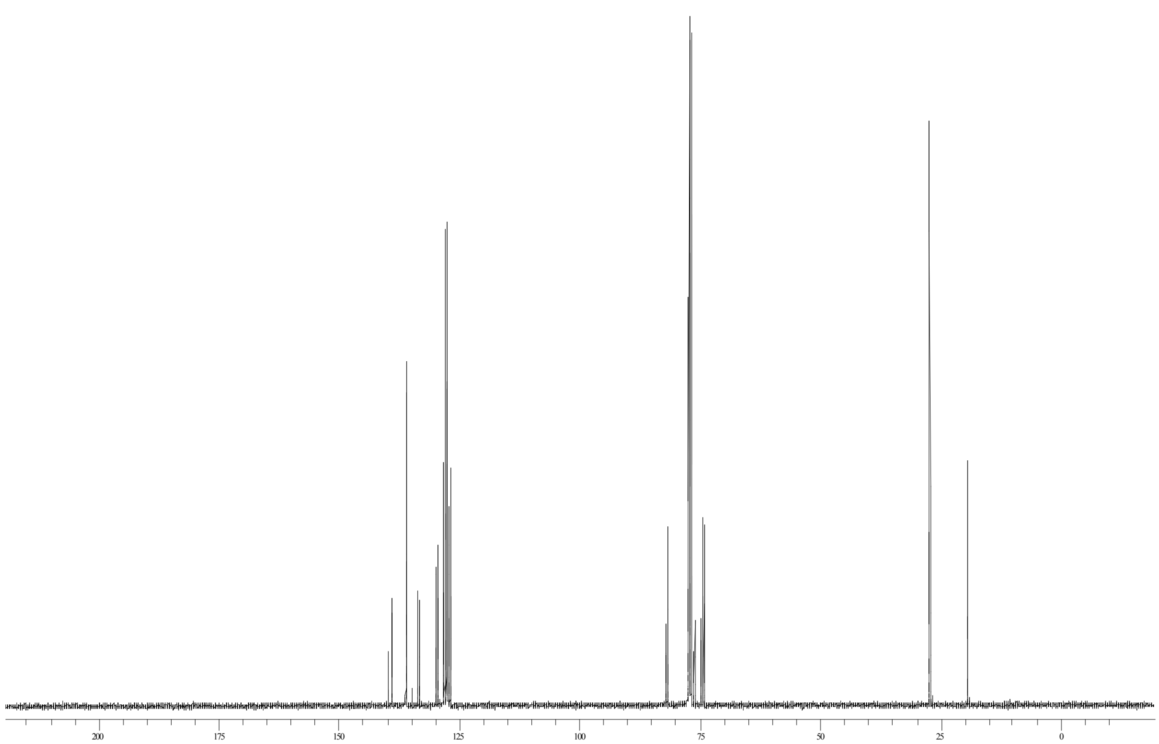
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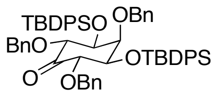
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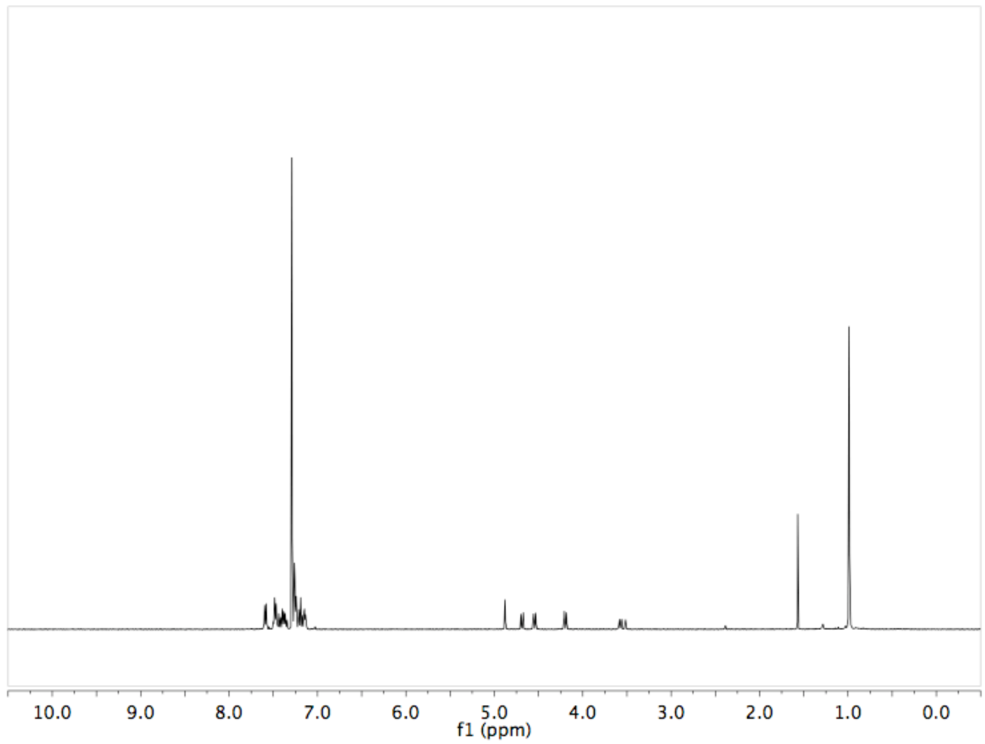
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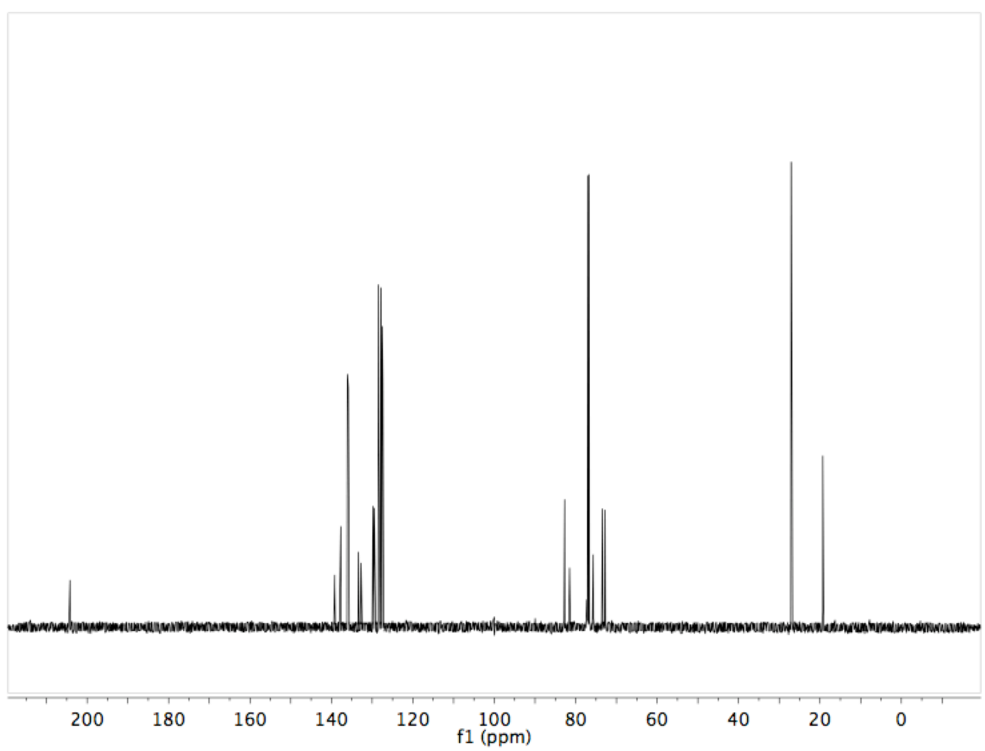
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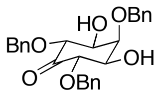
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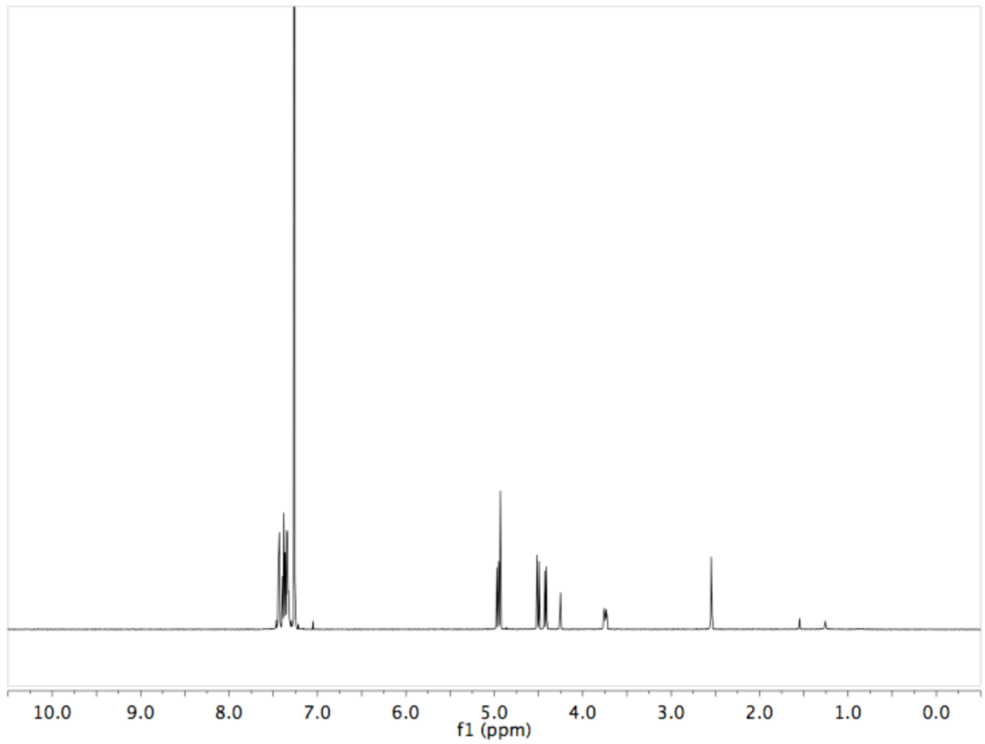
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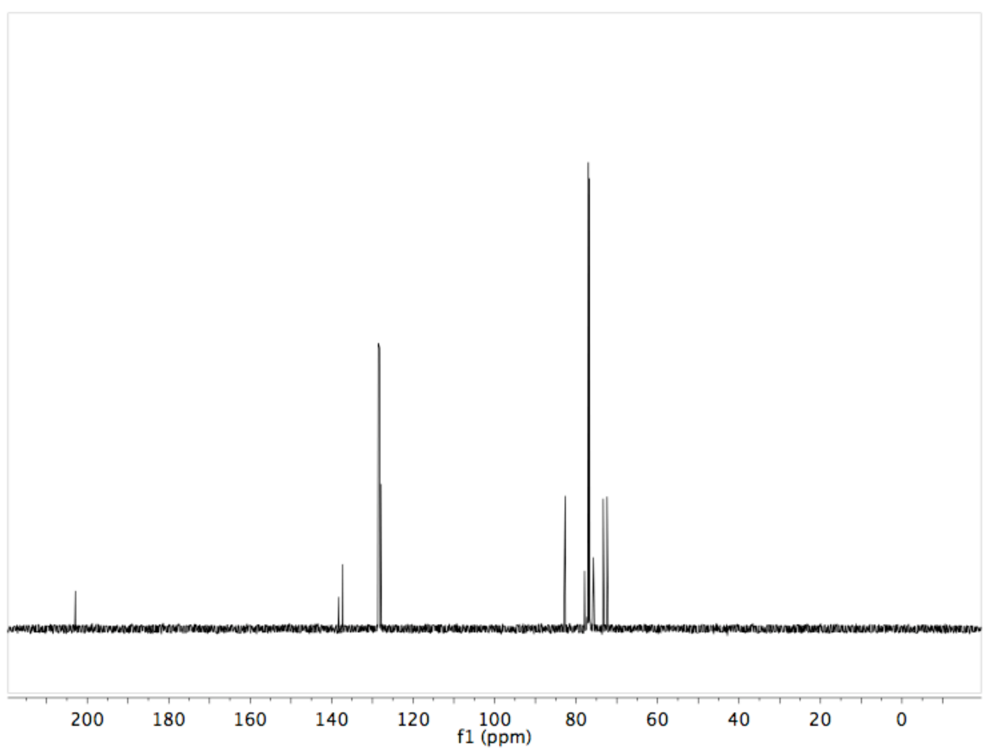
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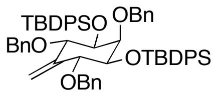
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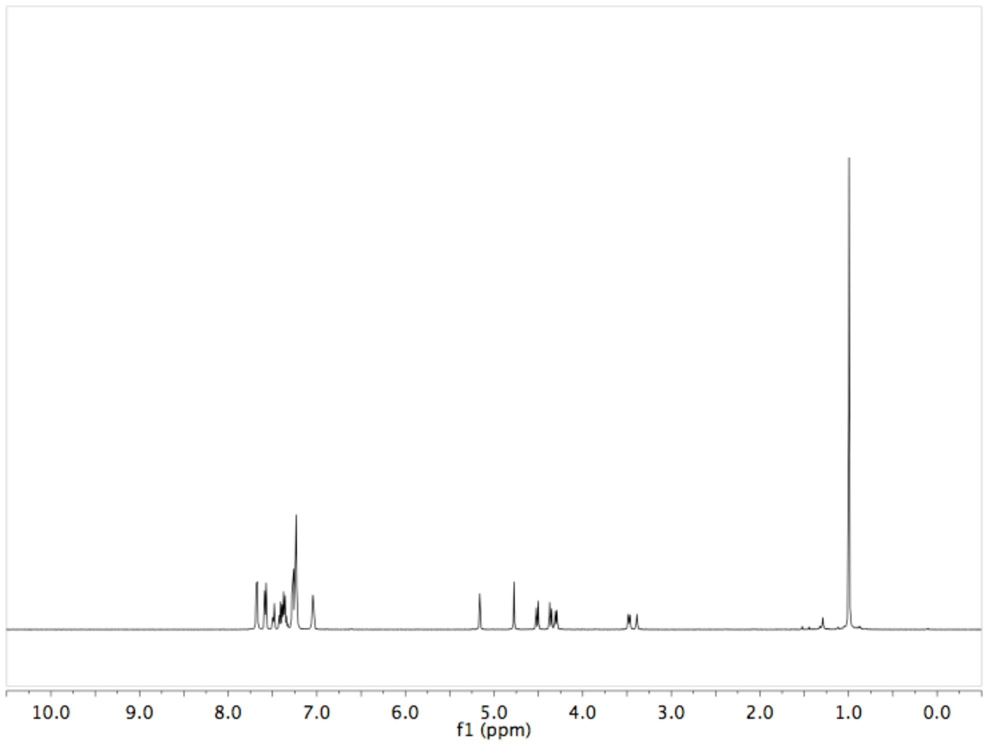
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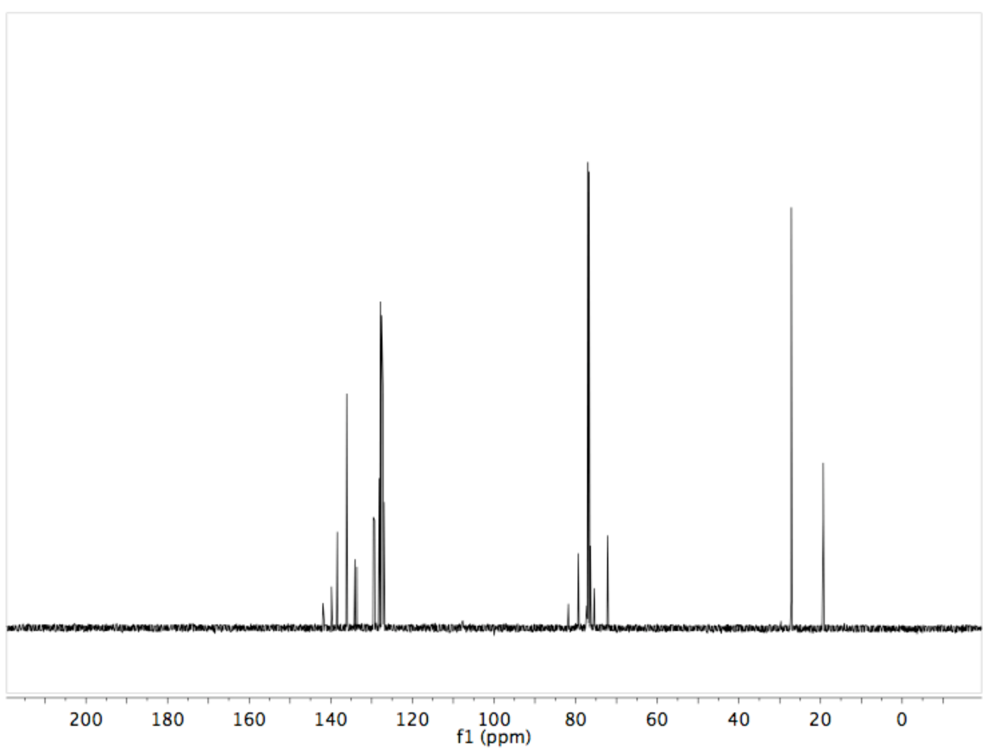
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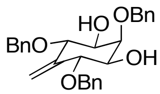
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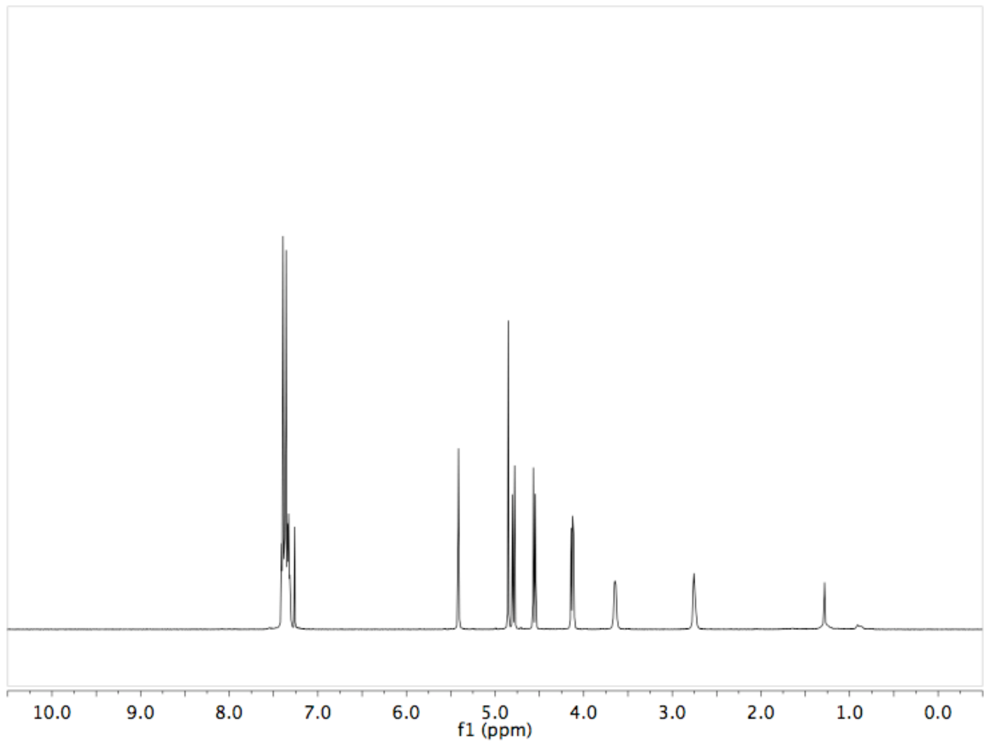
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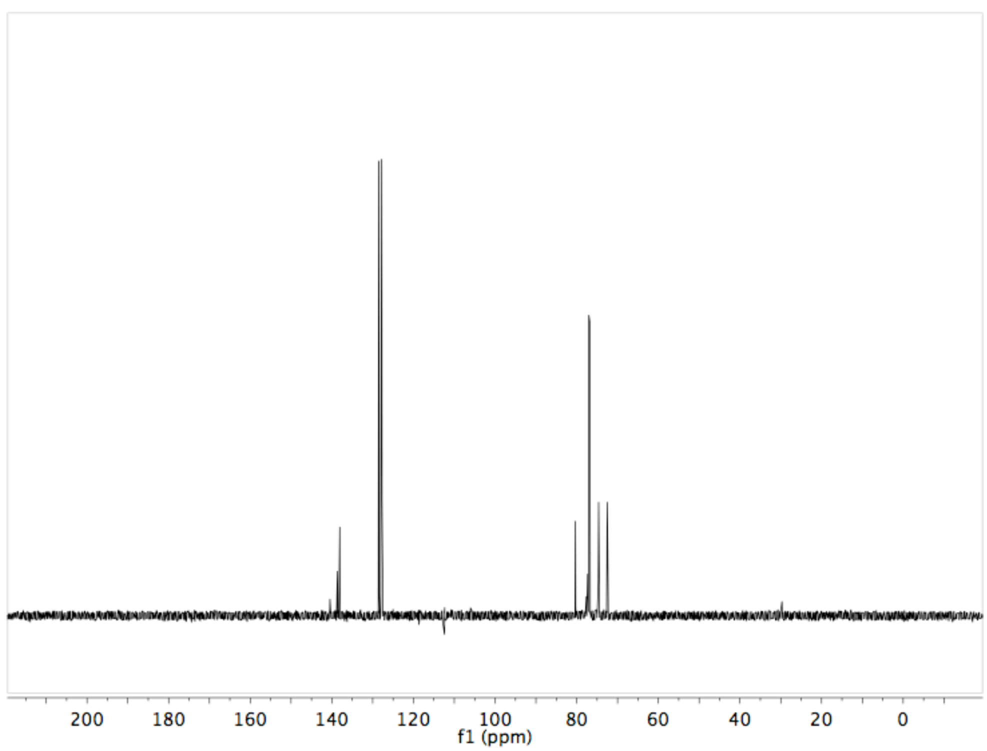
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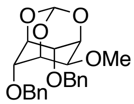
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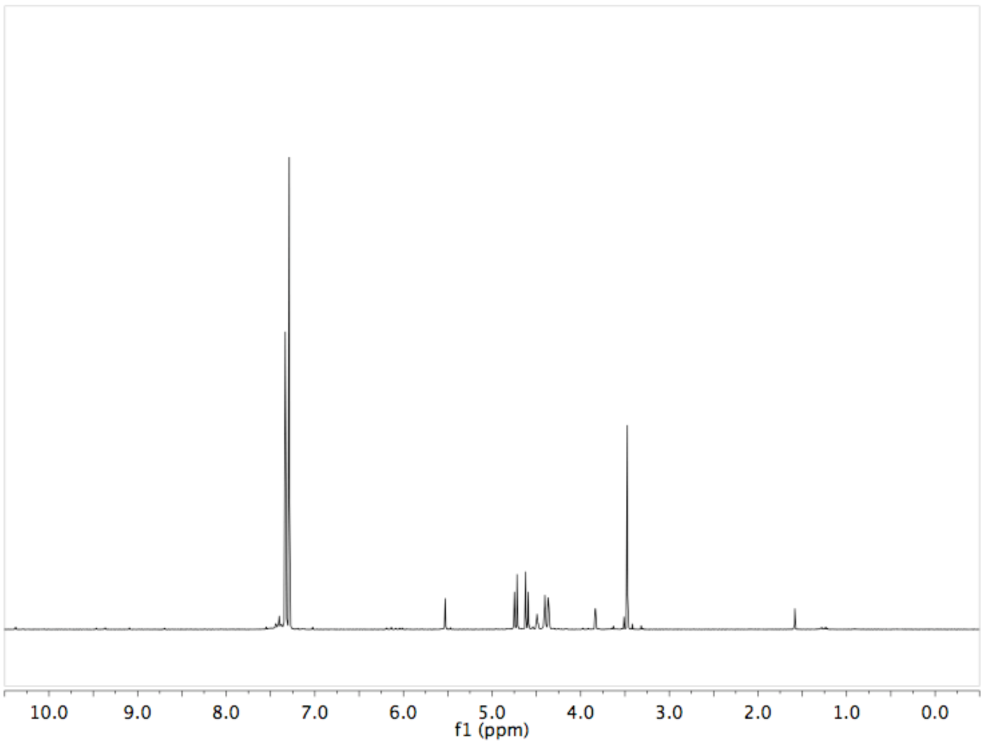
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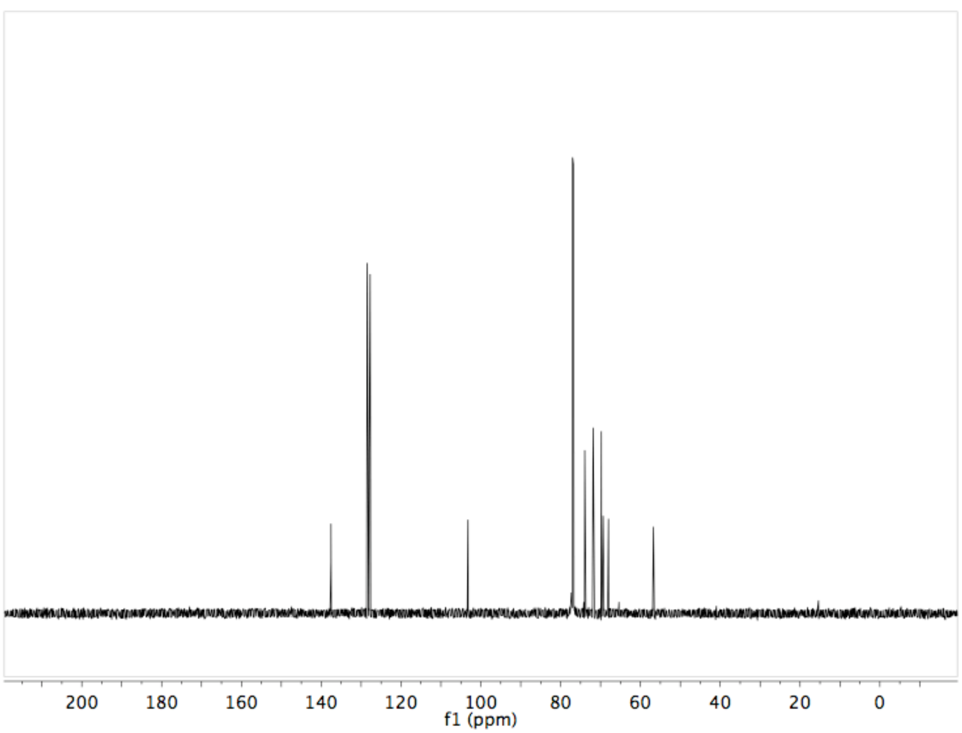
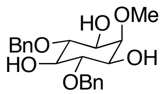
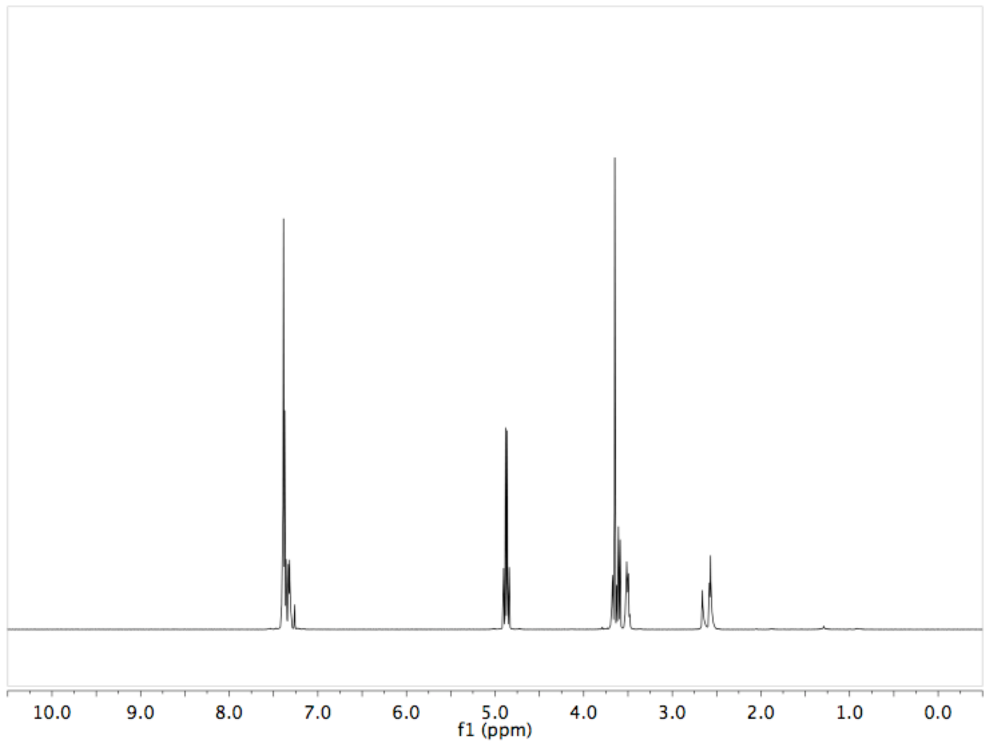
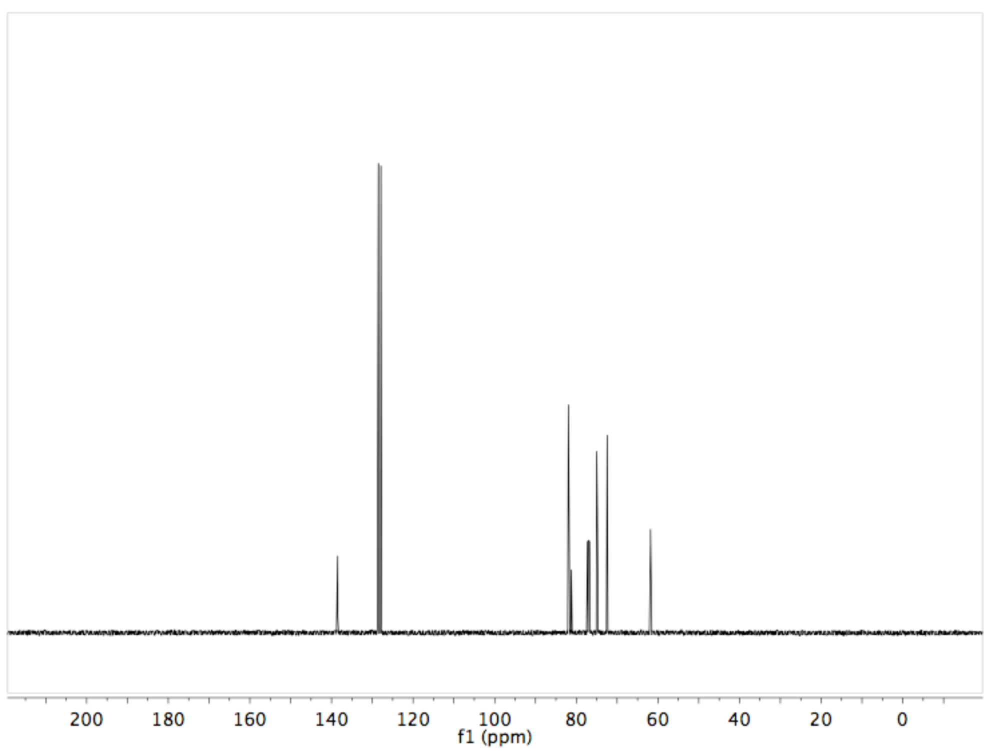
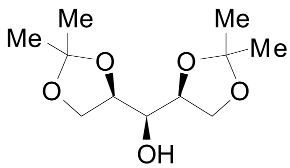
f1 (ppm)

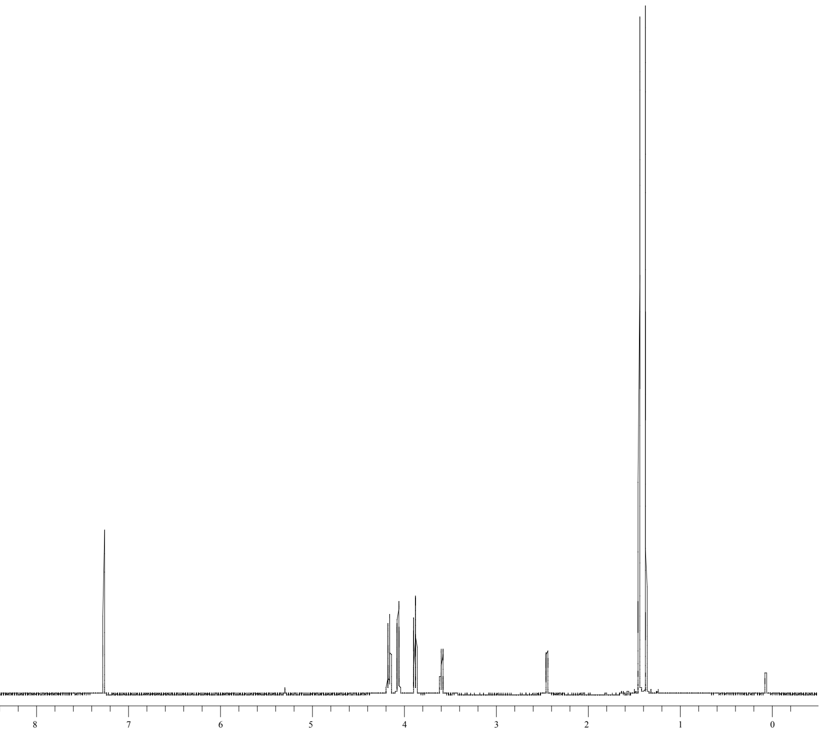

200 180 160 140 120 100 80 60 40 20 0
f1 (ppm)

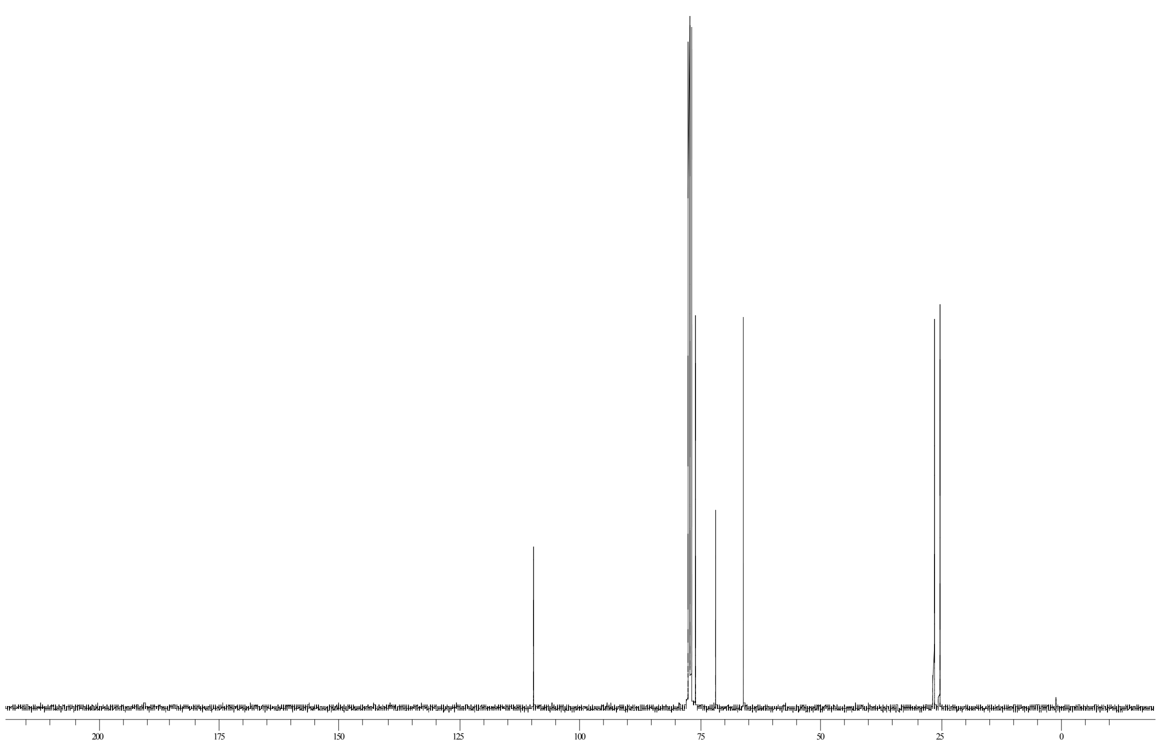

HO OMe
BnO
HO
OH
OBn

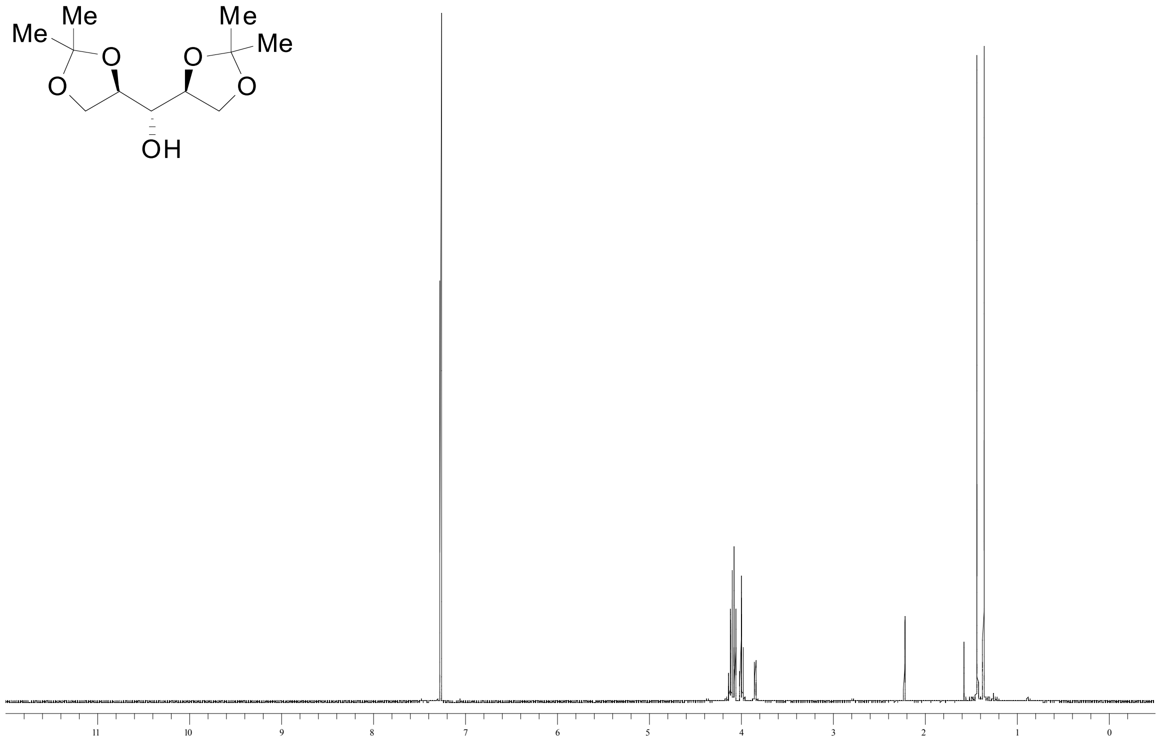

10.0 9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0.0
f1 (ppm)

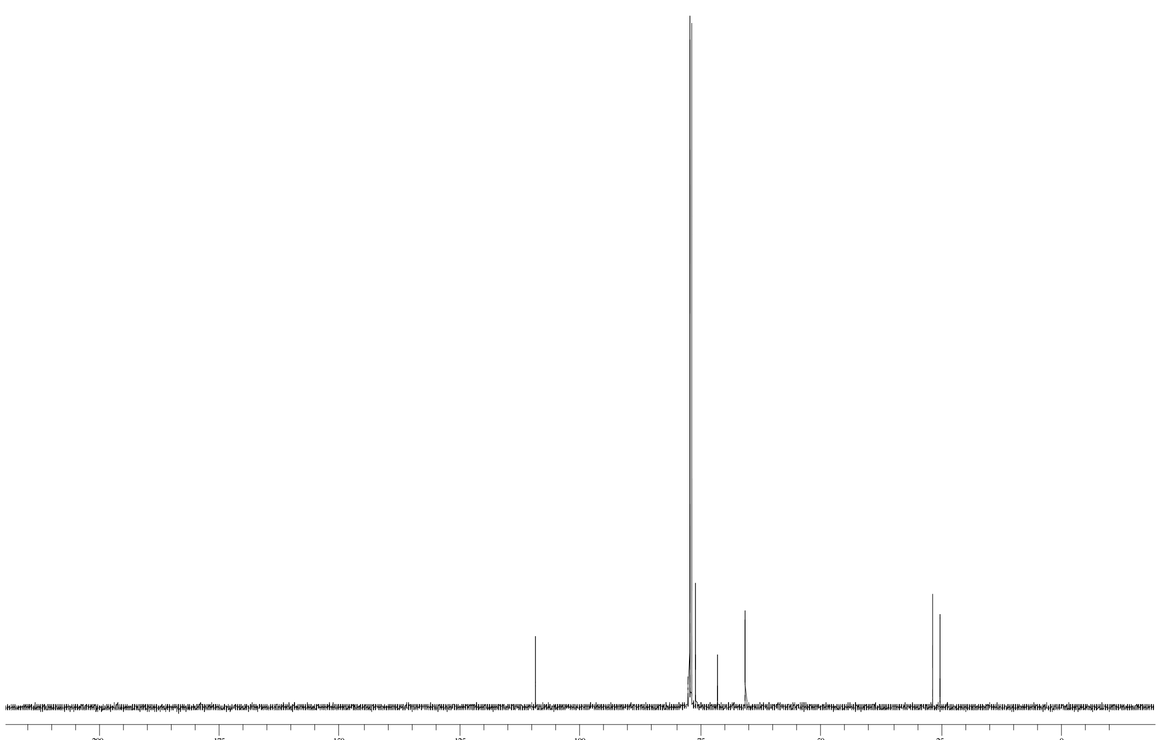

200 180 160 140 120 100 80 60 40 20 0
f1 (ppm)

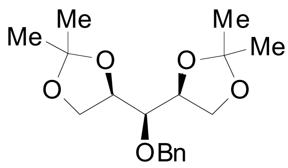

Me
Me
O
O
Me
Me
O
O
OH

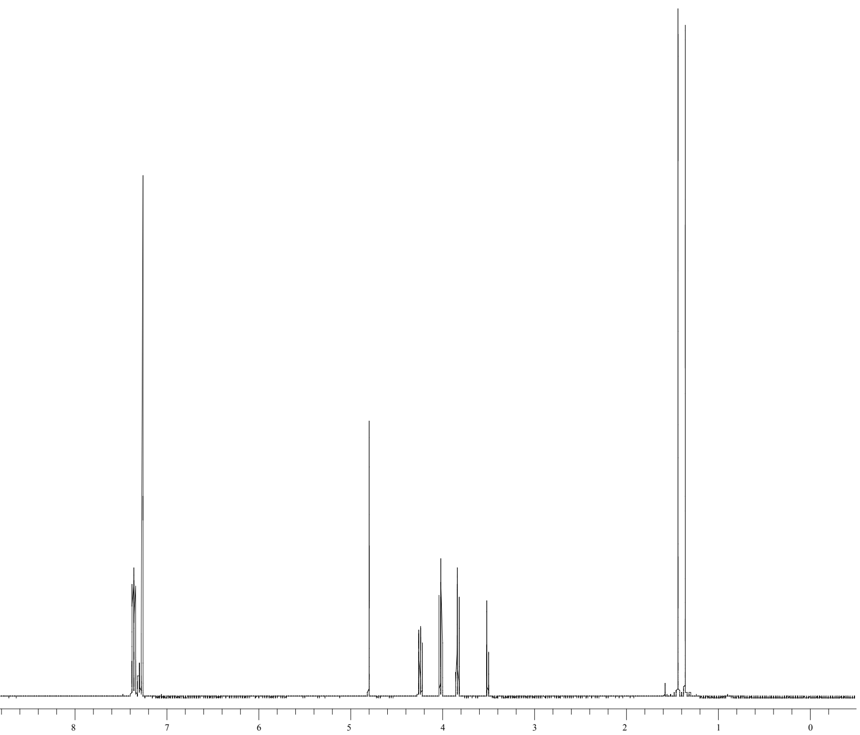


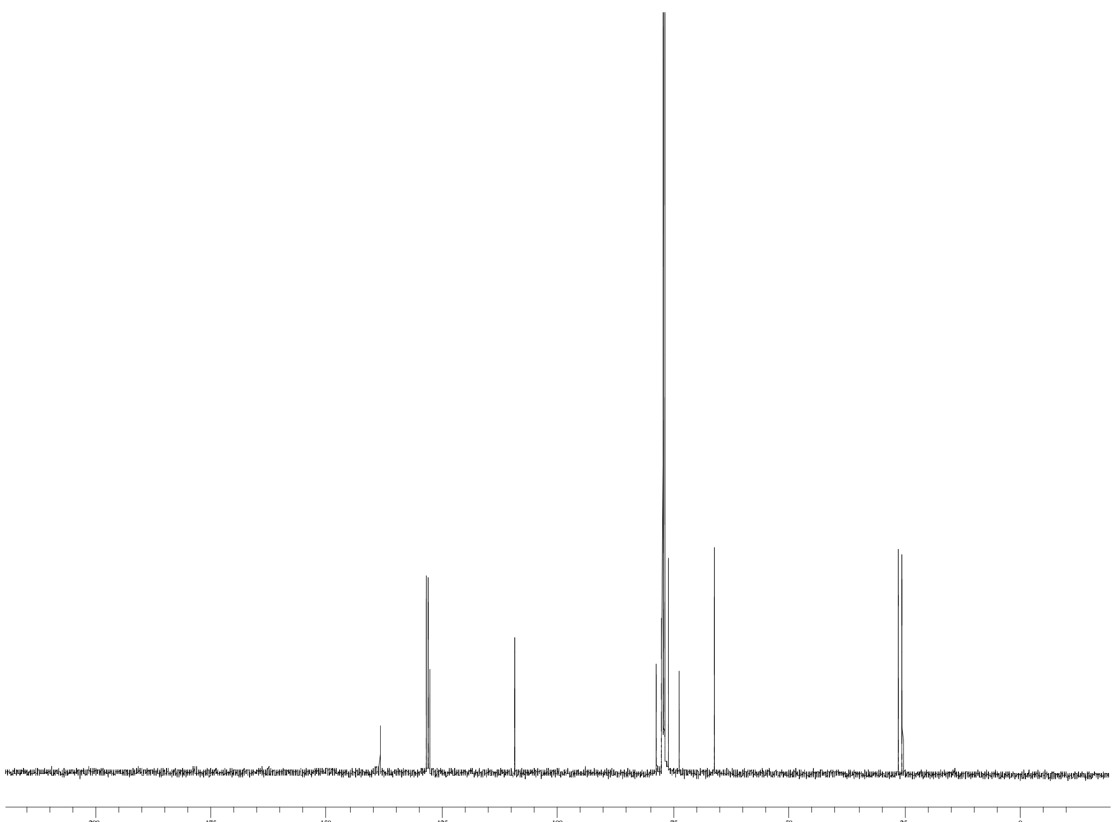


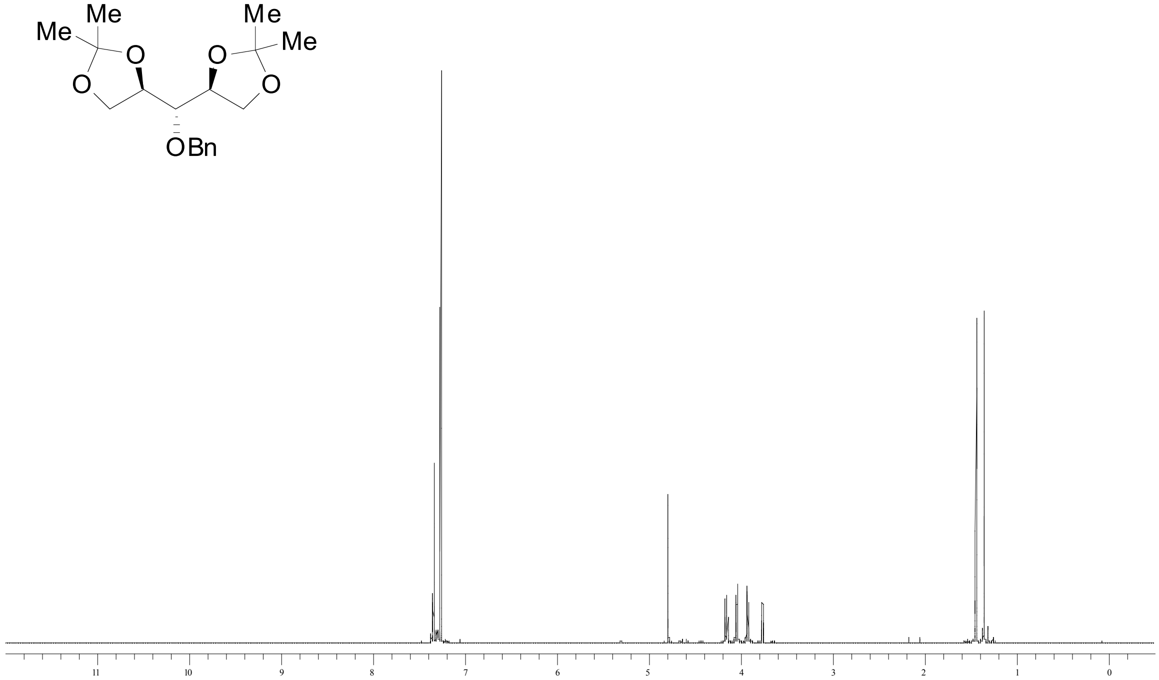

Me
Me
O
O
Me
Me
O
O
OH
11
10
9
8
7
6
5
4
3
2
1
0

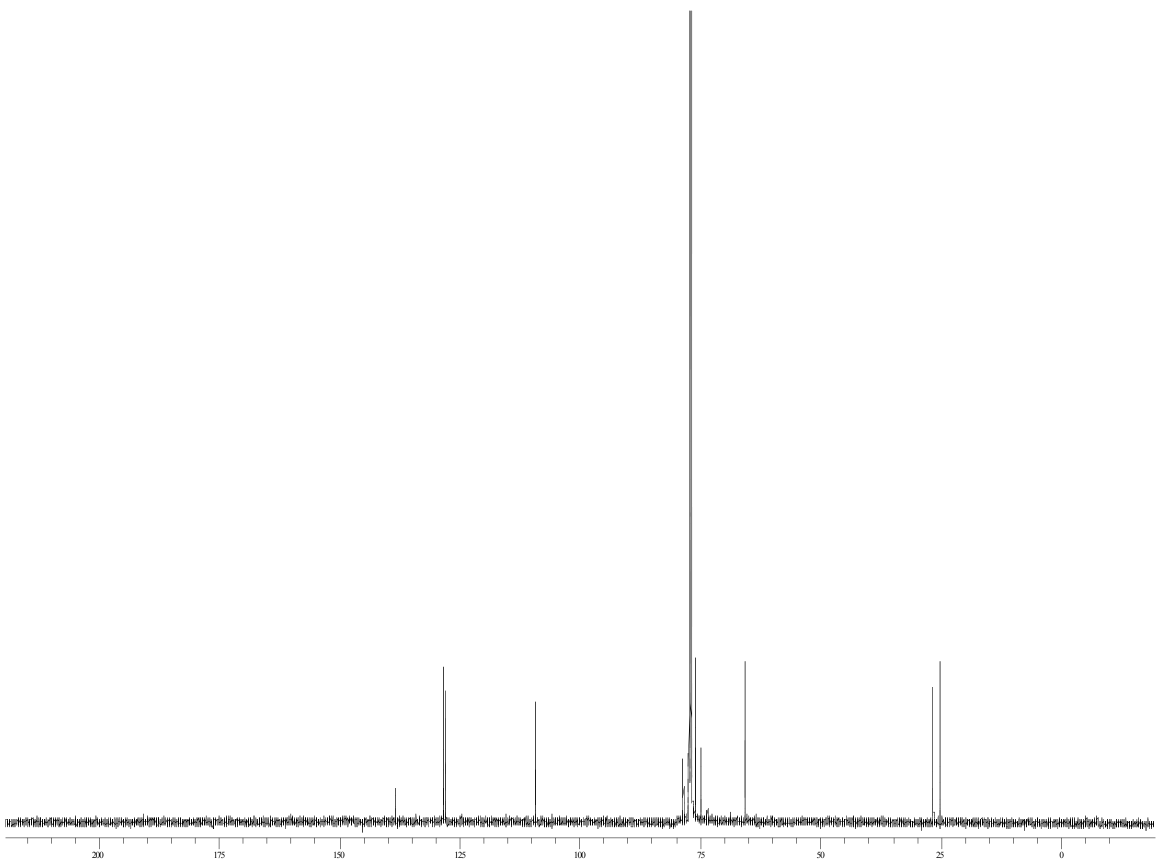

200
175
150
125
100
75
50
25
0

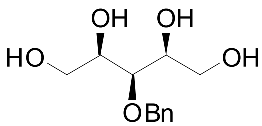

Me
Me
O
O
Me
Me
O
O
OBn

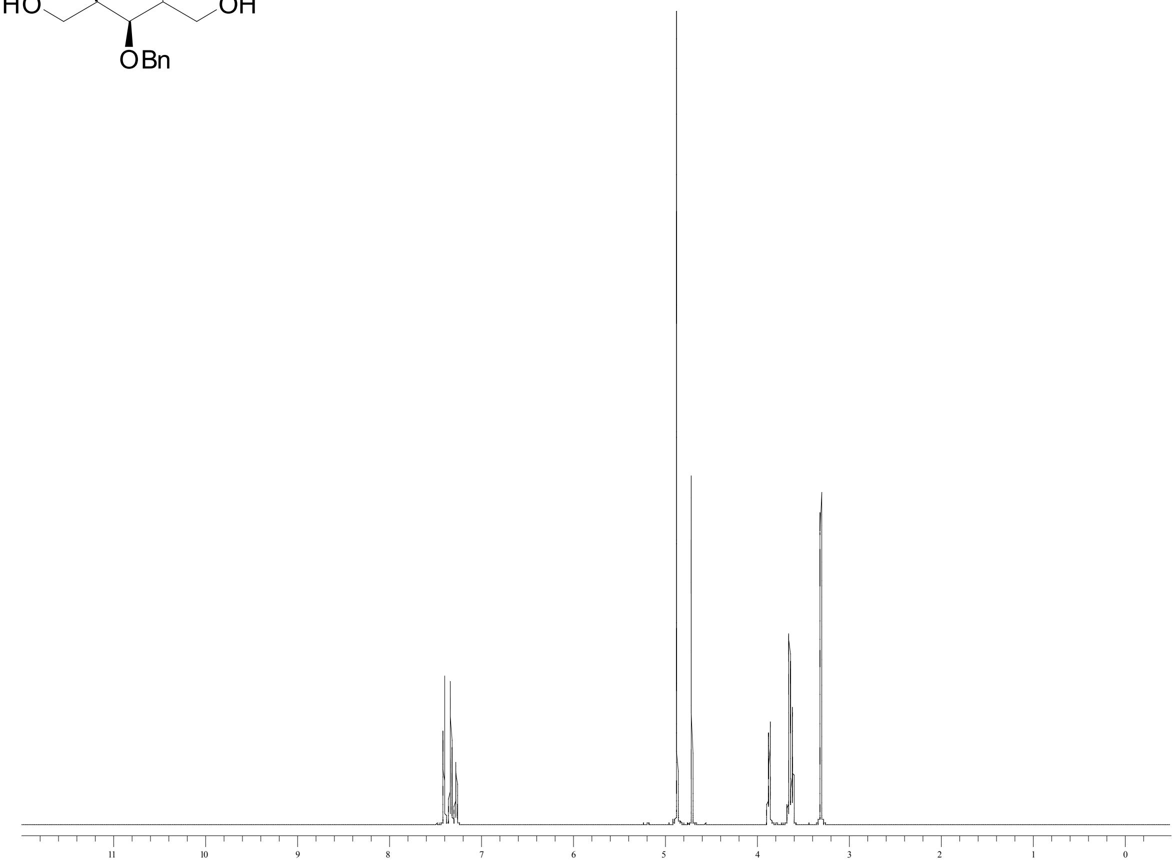

11 10 9 8 7 6 5 4 3 2 1 0

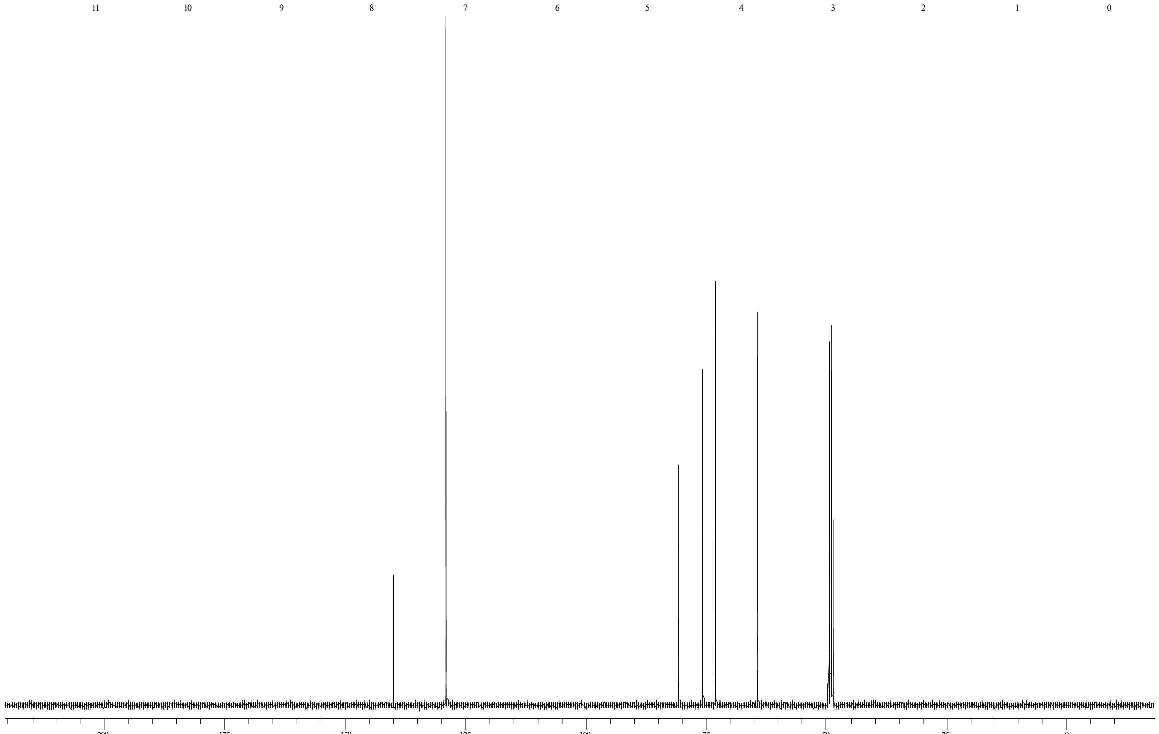

200 175 150 125 100 75 50 25 0

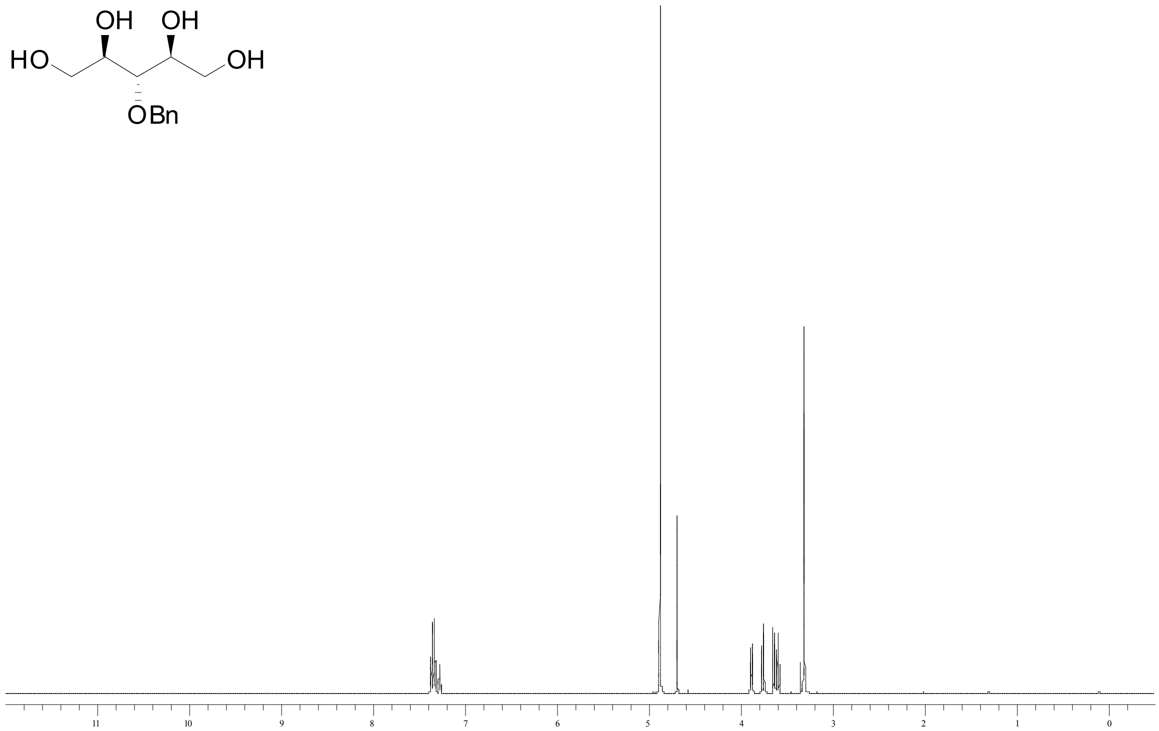

Me
Me
O
O
O
O
Me
Me
OBn
11
10
9
8
7
6
5
4
3
2
1
0

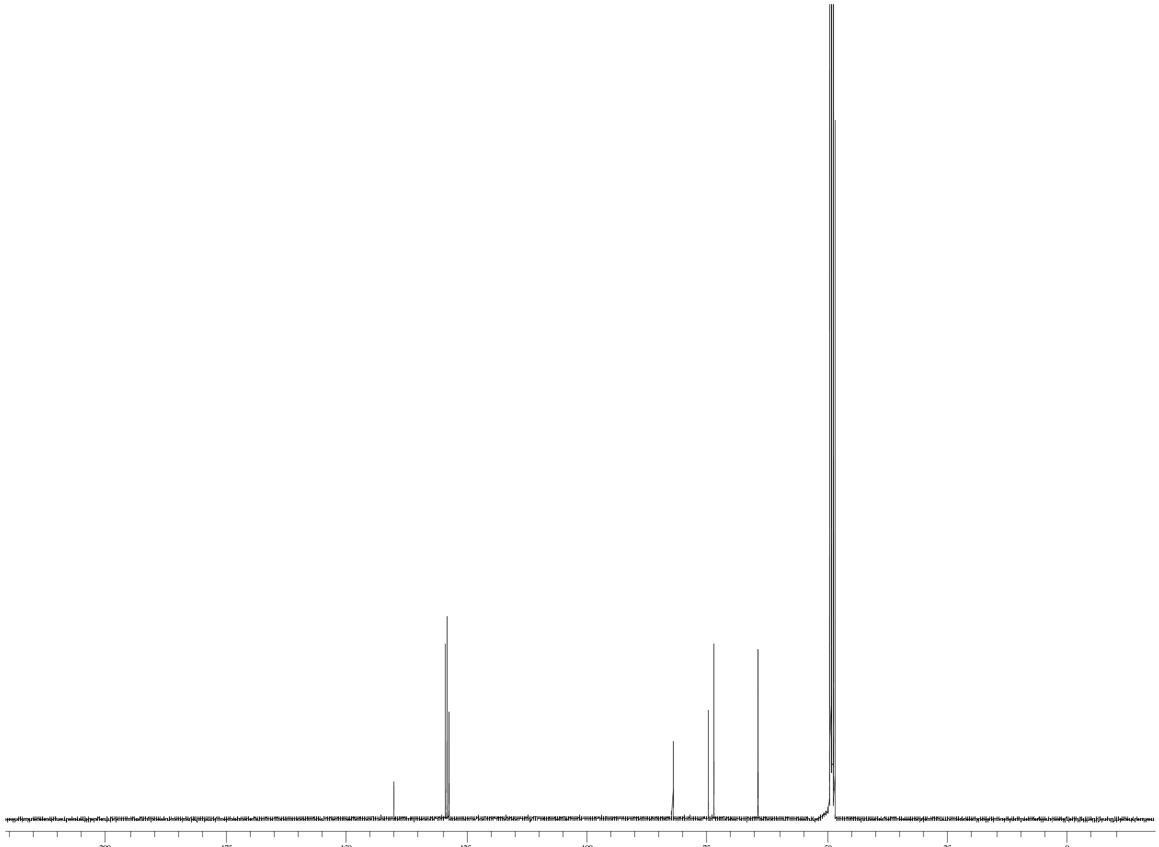

200
175
150
125
100
75
50
25
0

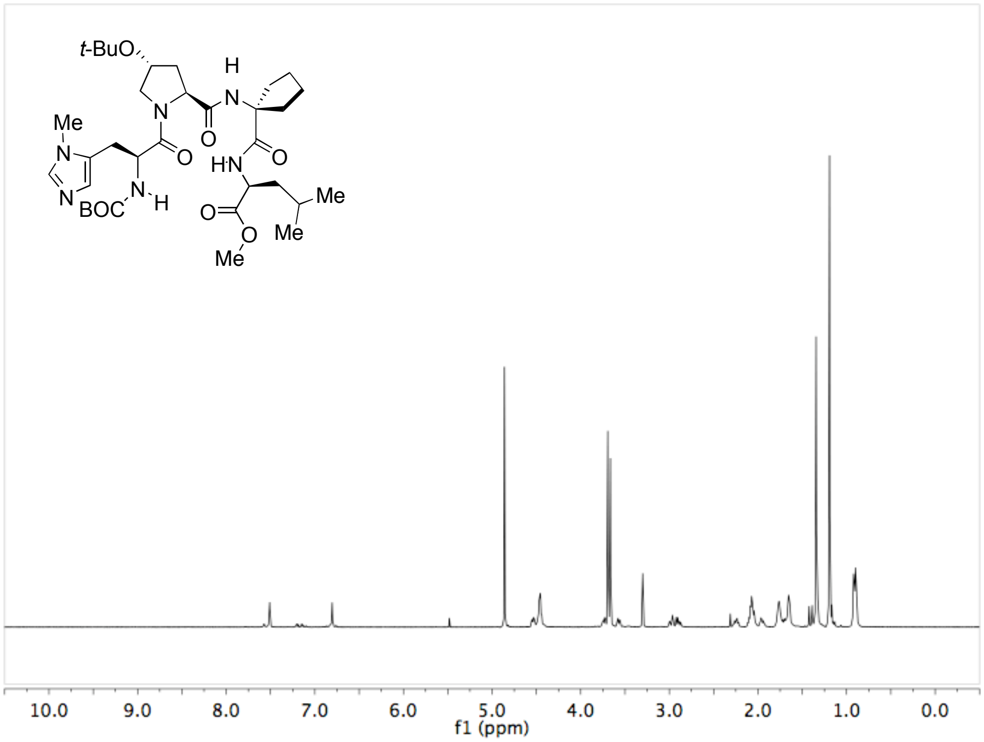

OH
OH
HO
OH
OBn

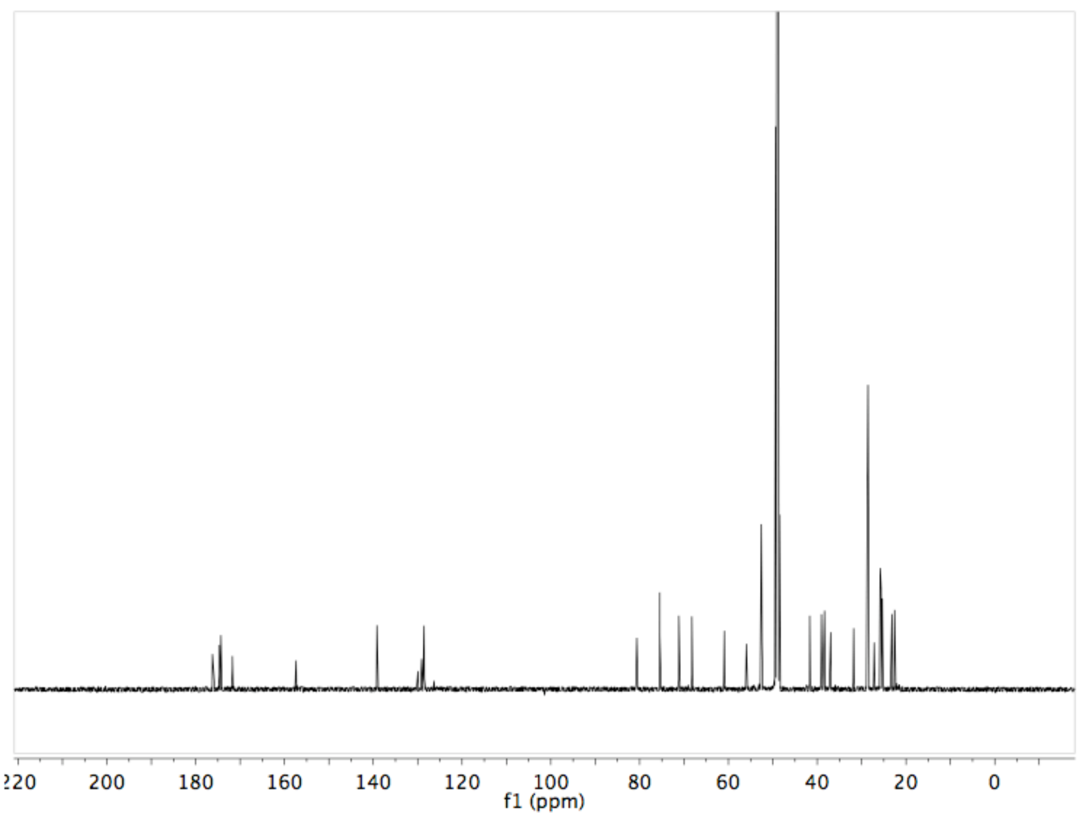

11
10
9
8
7
6
5
4
3
2
1
0

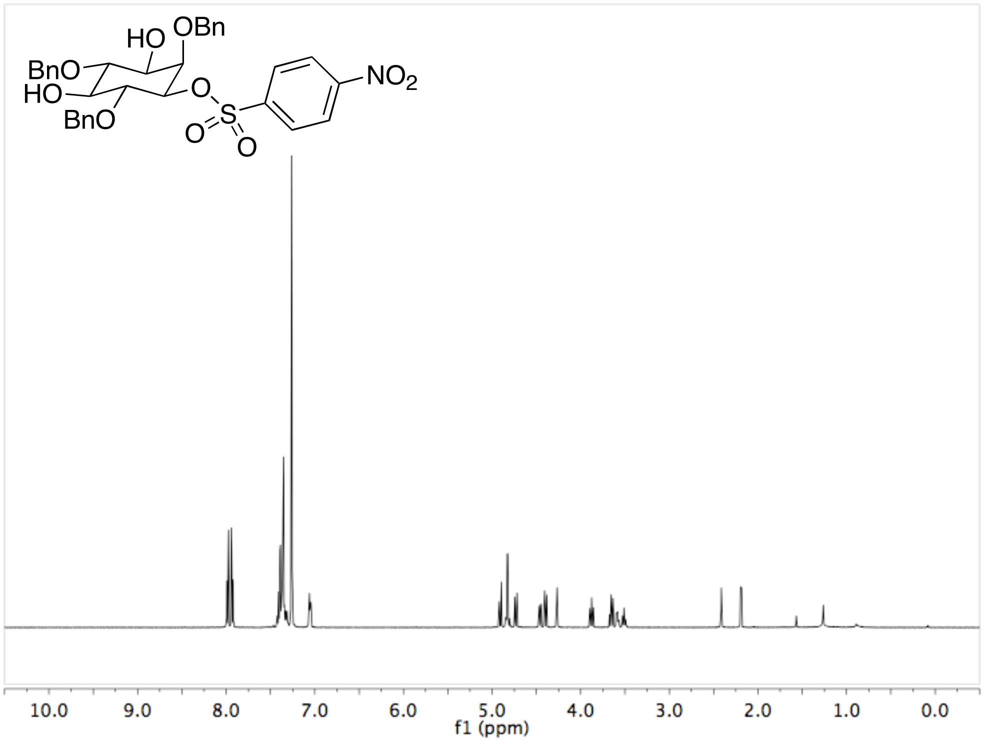

200
175
150
125
100
75
50
25
0

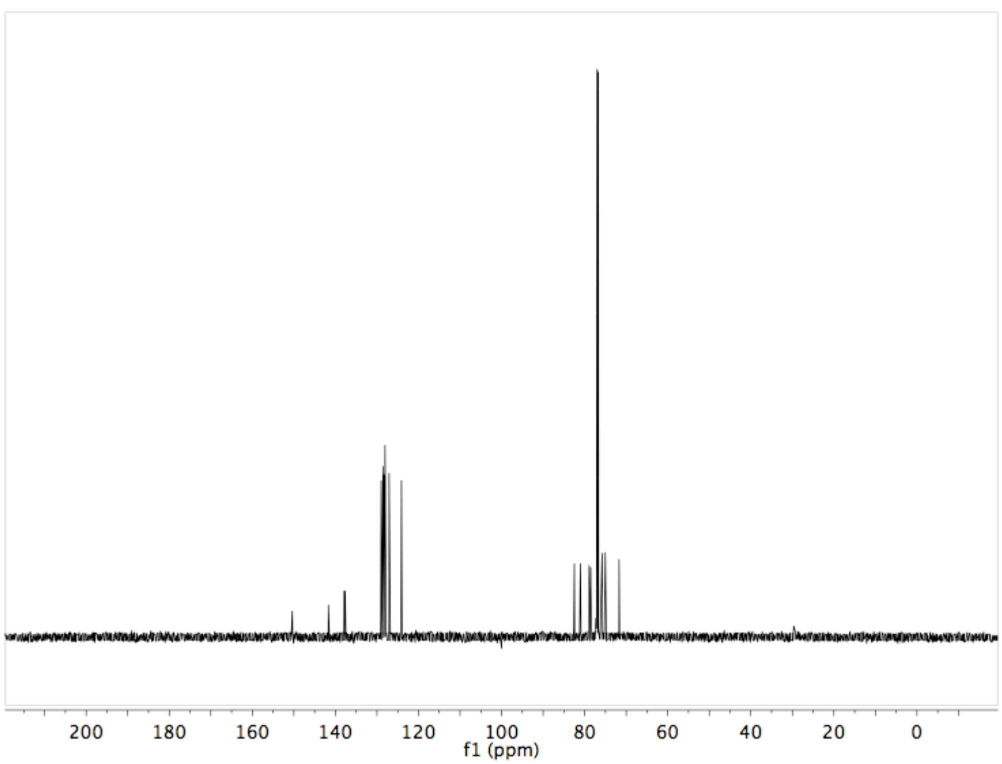

OH OH
HO OH
OBn
11 10 9 8 7 6 5 4 3 2 1 0

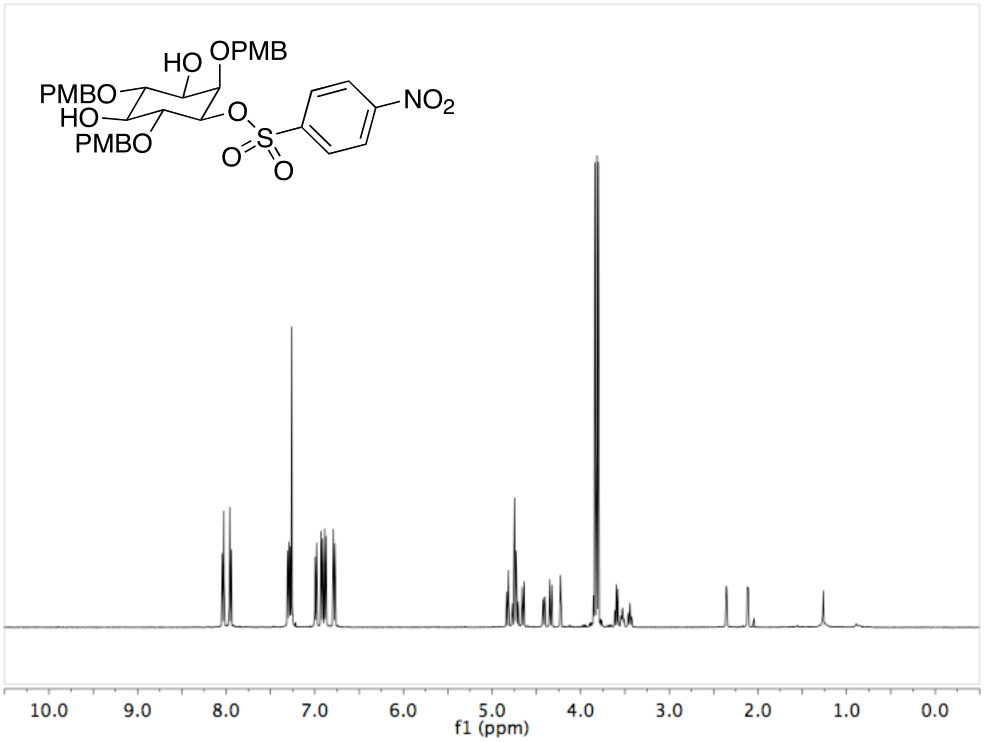

200 175 150 125 100 75 50 25 0

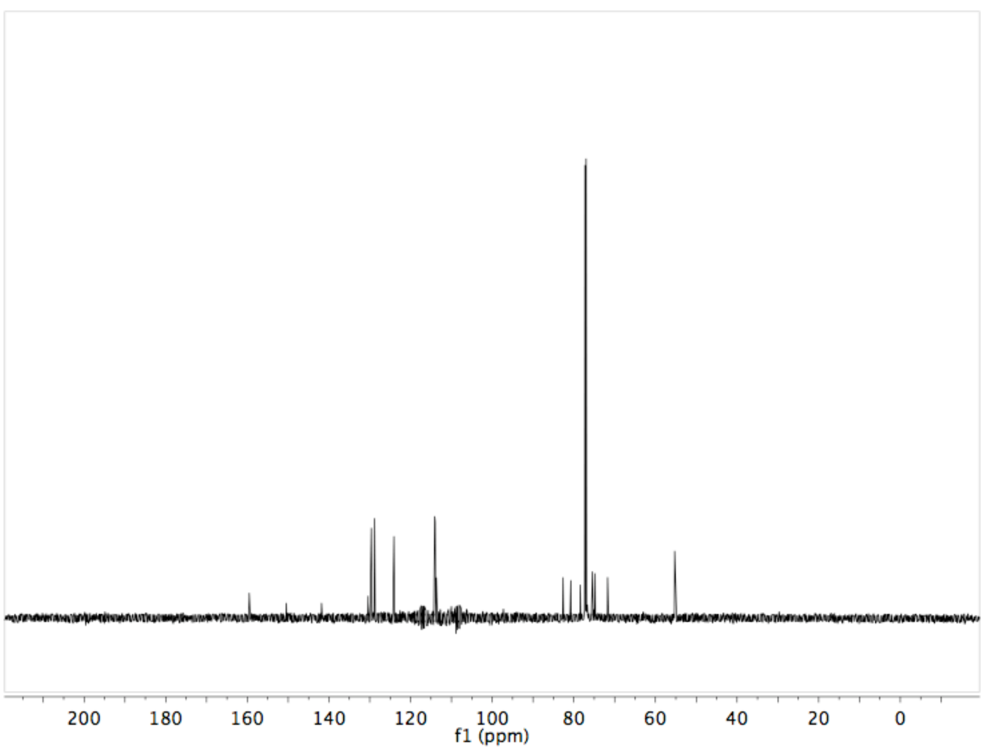

t-BuO
H
N
Me
N
O
HN
O
N
Me
N
BOC
N
H
O
O
Me
Me
O
Me
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)

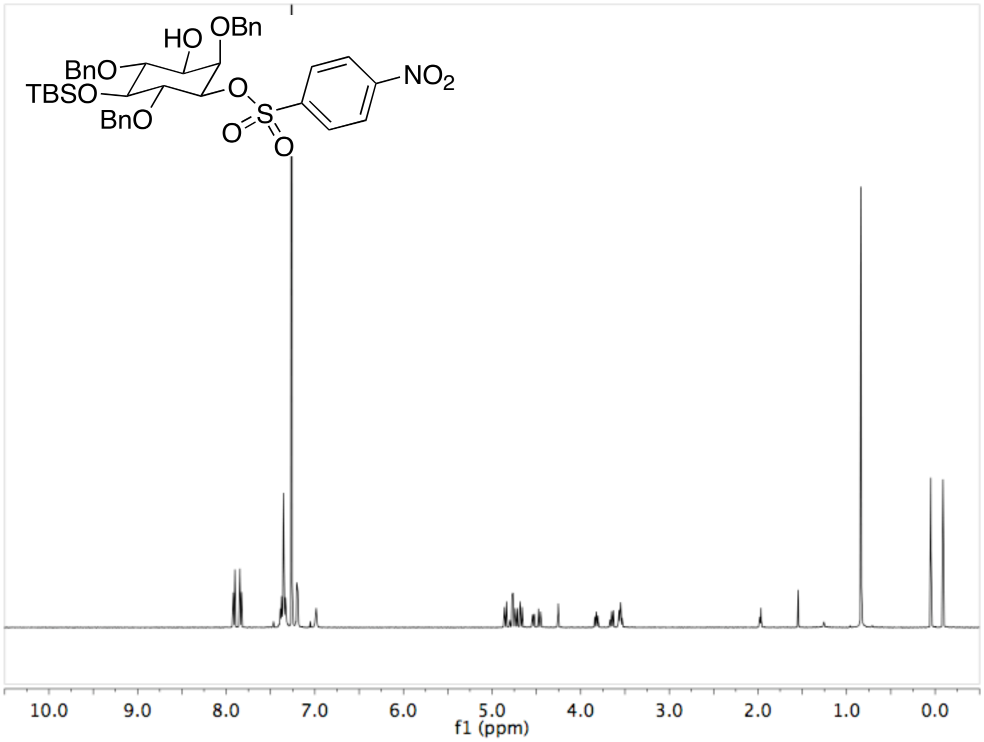

220
200
180
160
140
120
100
80
60
40
20
0
f1 (ppm)

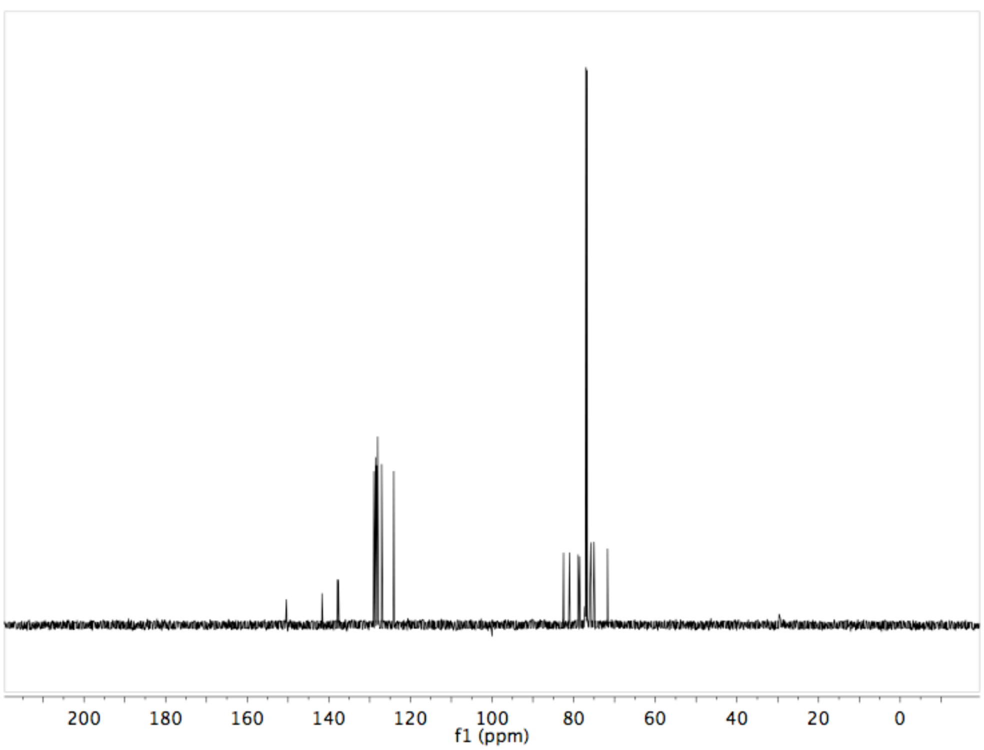

HO
OBn
BnO
HO
BnO
O
S
O
O
NO2
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)

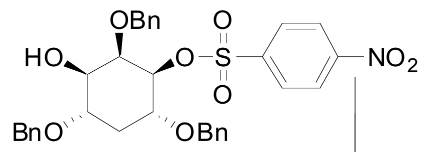

200
180
160
140
120
100
80
60
40
20
0
f1 (ppm)

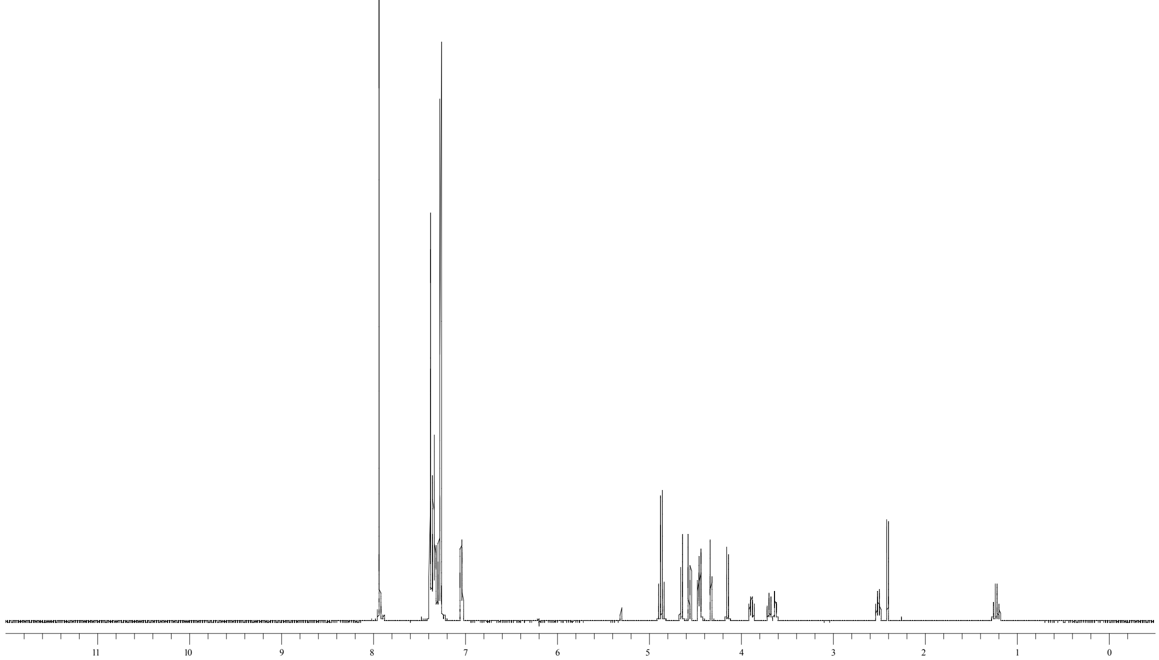

HO
OPMB
PMBO
HO
PMBO
O
S
O
O
NO_2
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)

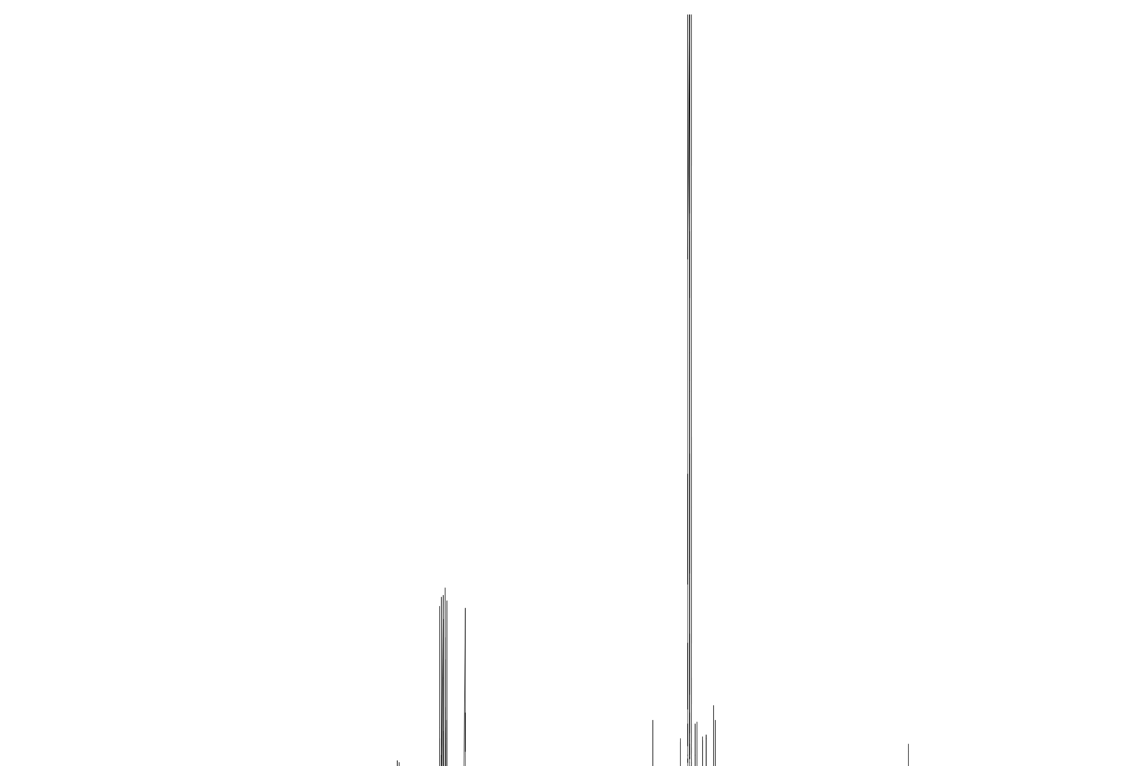

200
180
160
140
120
100
80
60
40
20
0
f1 (ppm)

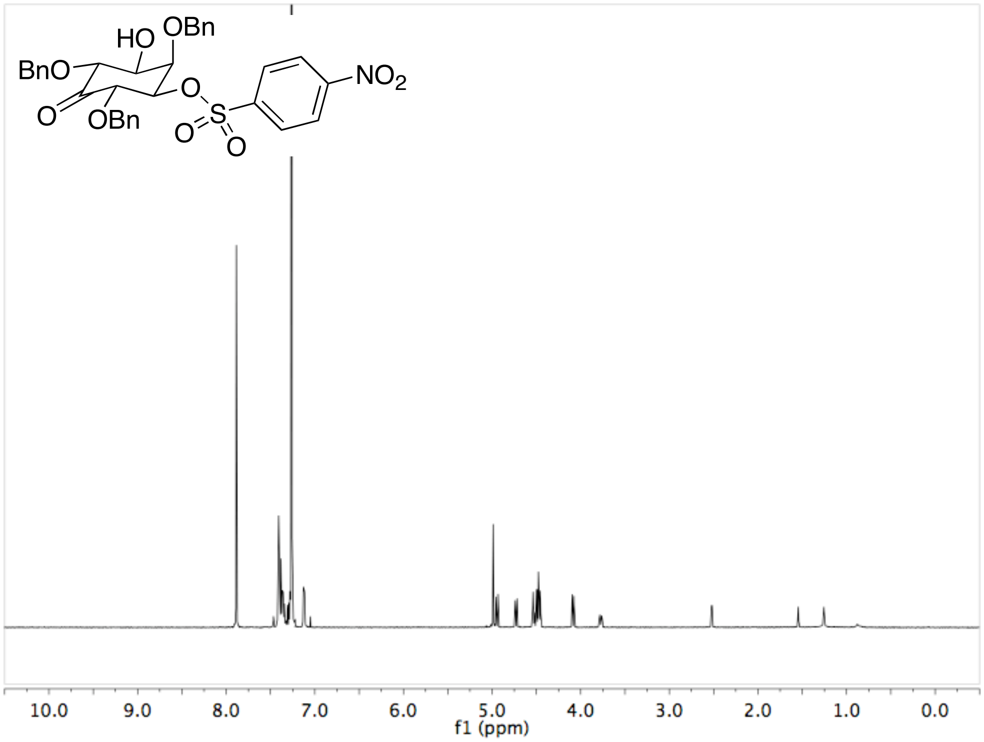

HO
OBn
BnO
TBSO
BnO
O
S
O
O
NO2
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)

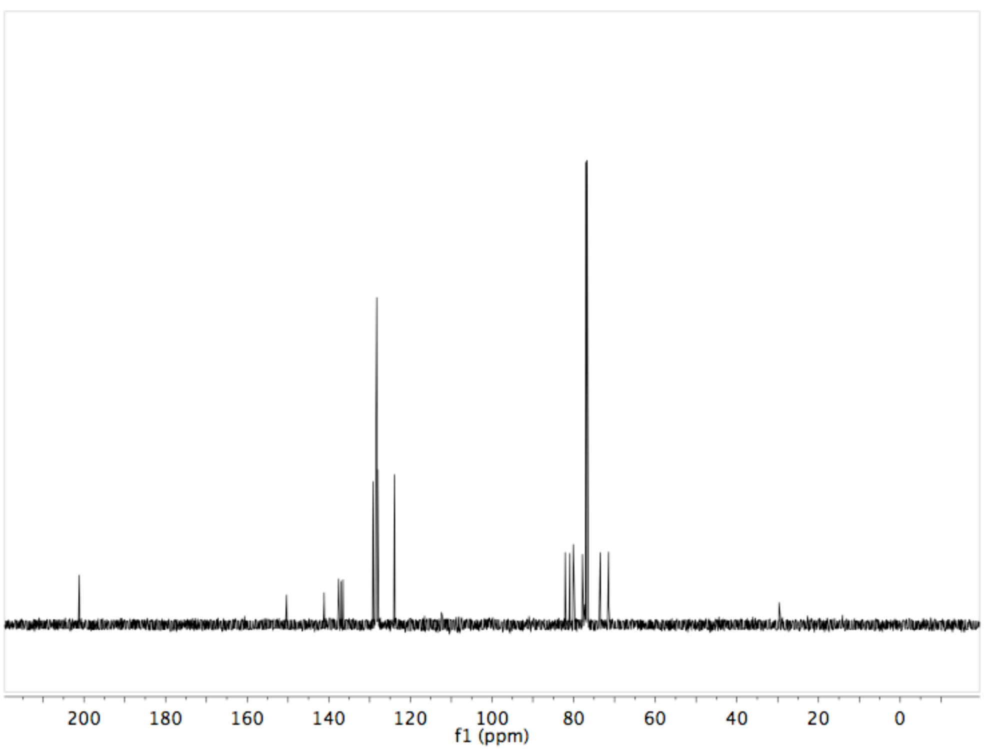

200
180
160
140
120
100
80
60
40
20
0
f1 (ppm)

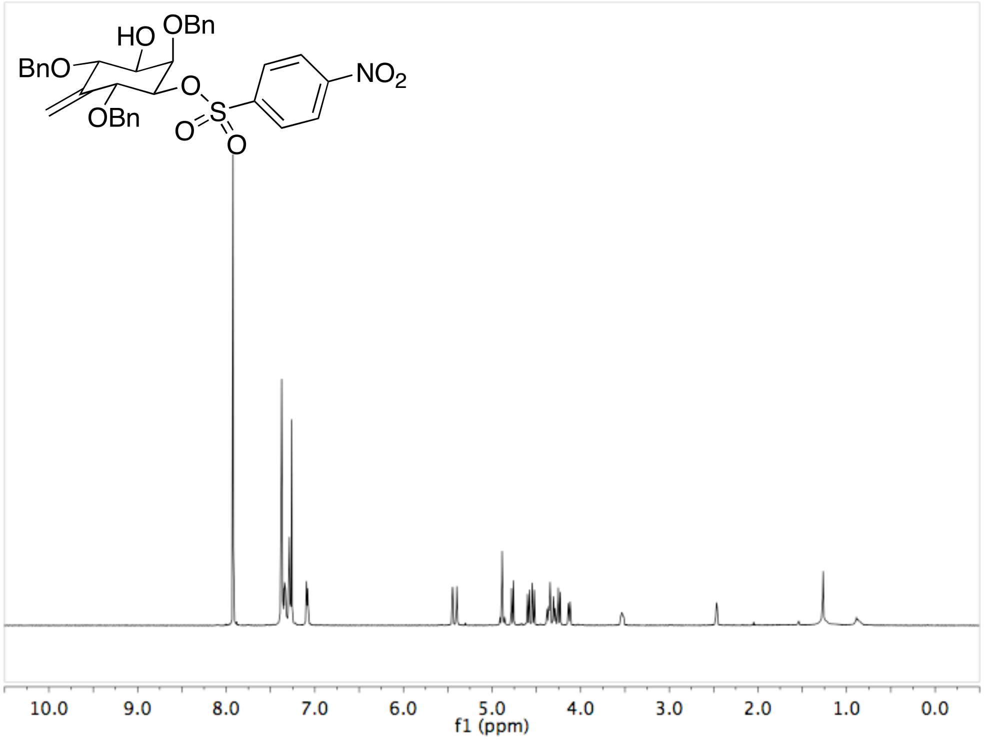

OBn
HO
O
S
O
O
NO2
BnO
OBn

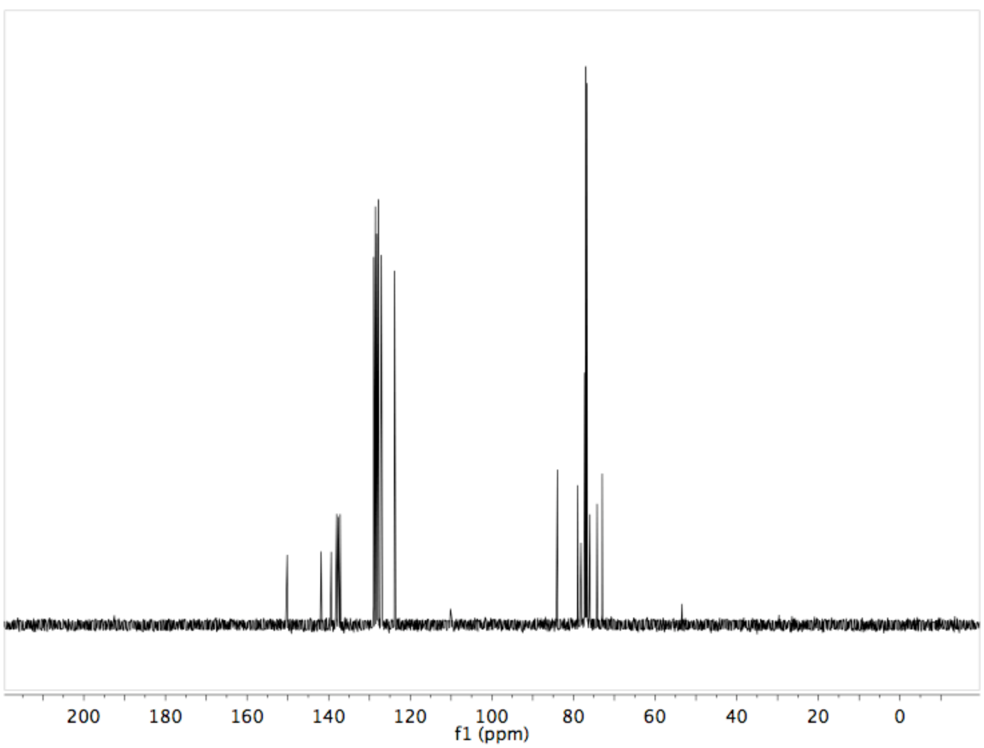

11
10
9
8
7
6
5
4
3
2
1
0

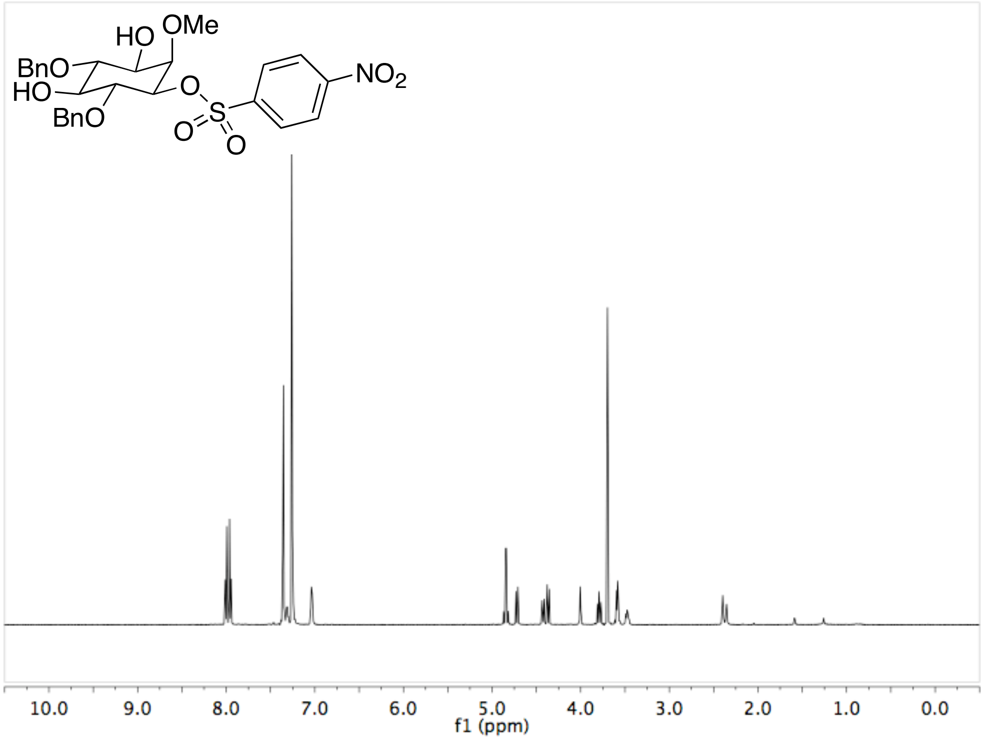

200
175
150
125
100
75
50
25
0

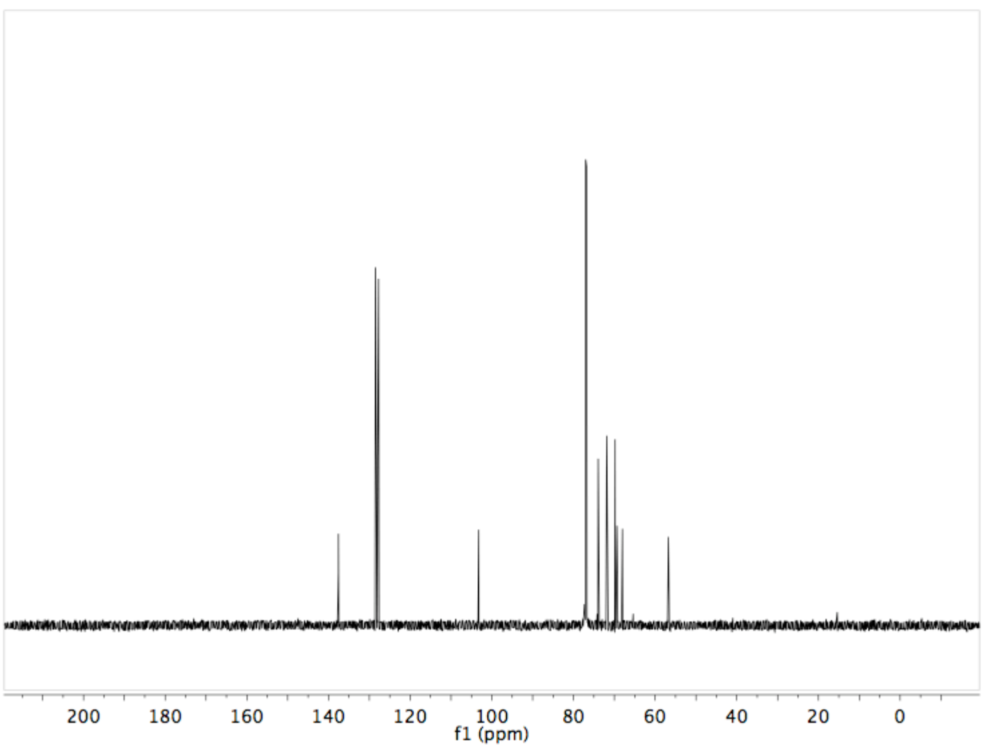

HO
OBn
BnO
NO2
O
OBn
O
S
O
O
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)

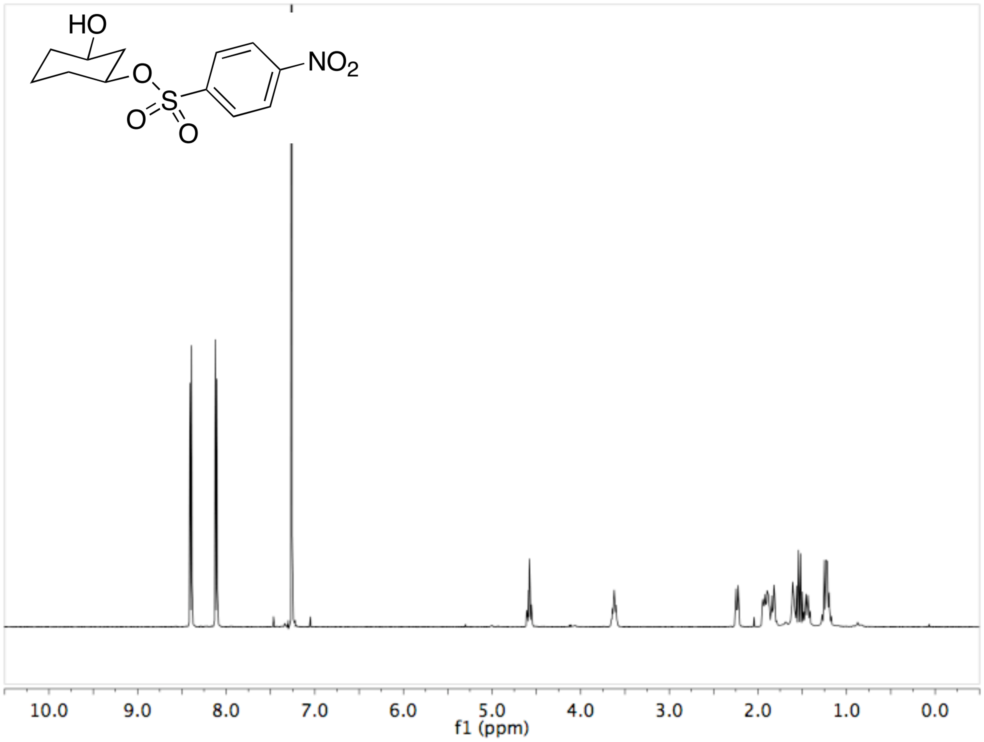

200
180
160
140
120
100
80
60
40
20
0
f1 (ppm)

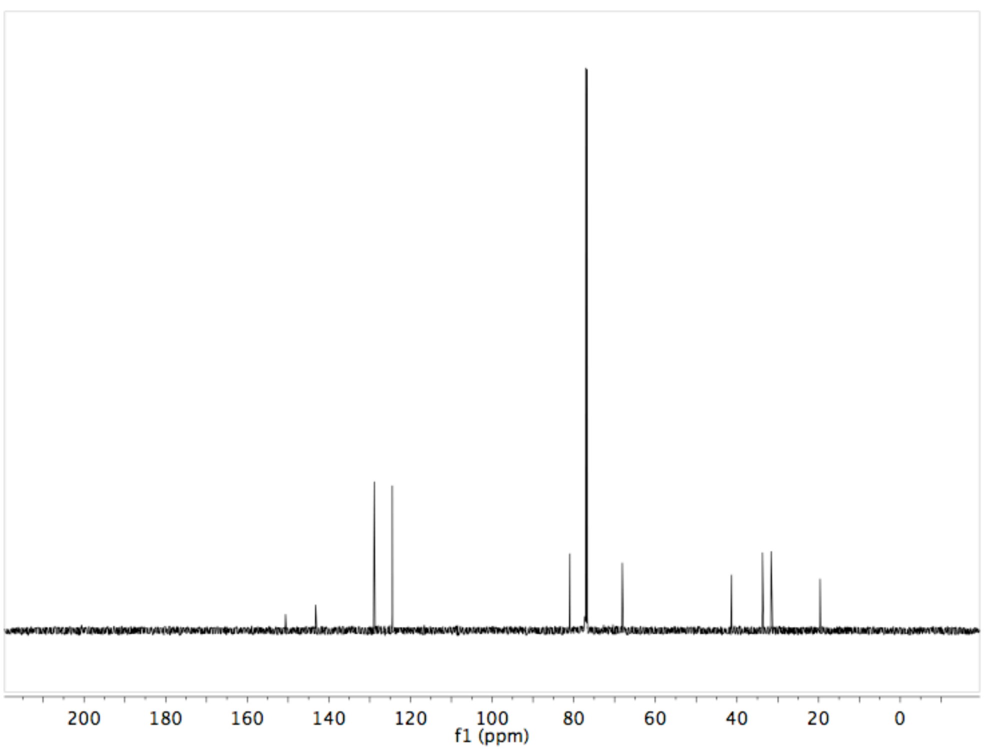

HO
OBn
BnO
O
S
O
O
NO2
OBn
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)

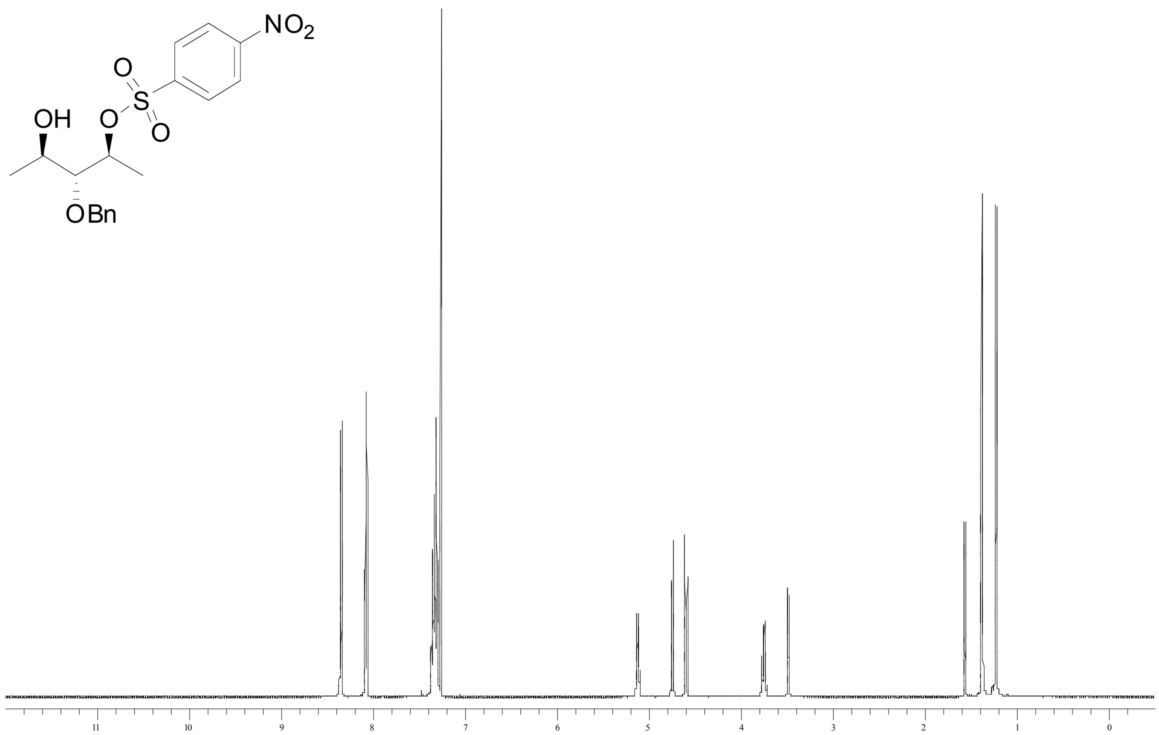

200
180
160
140
120
100
80
60
40
20
0
f1 (ppm)

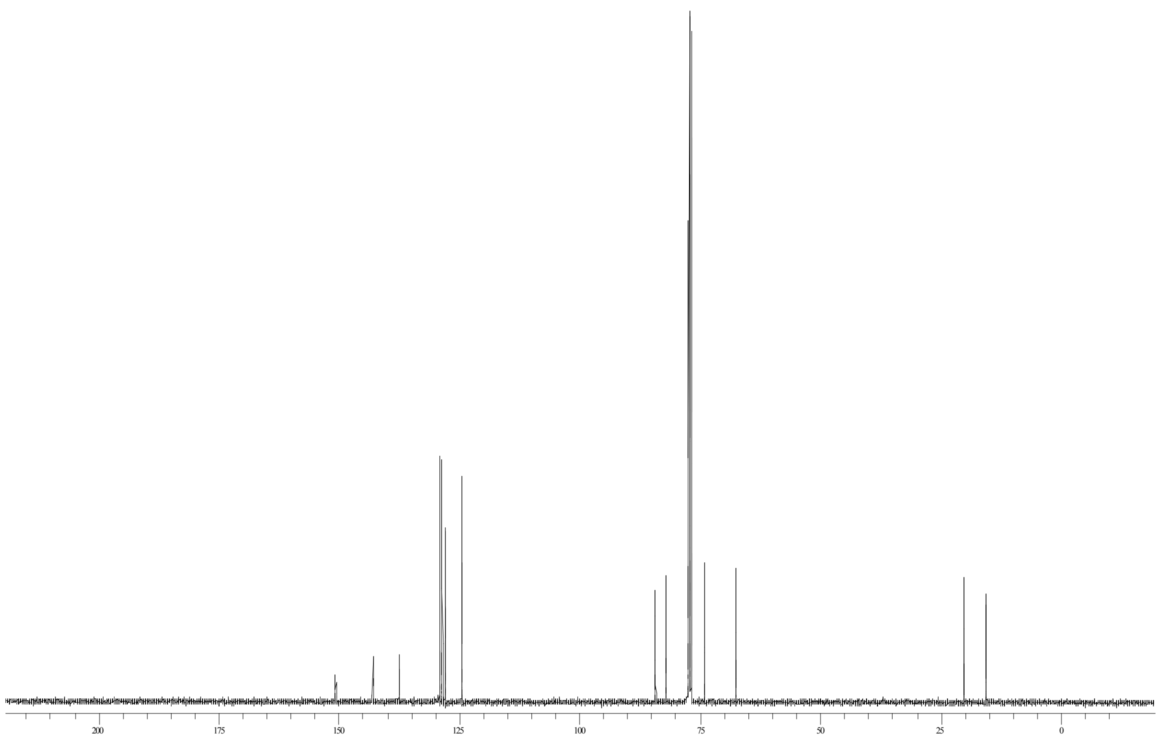

HO OMe
BnO
HO
BnO
O
S
O
O
NO2
10.0 9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0.0
f1 (ppm)

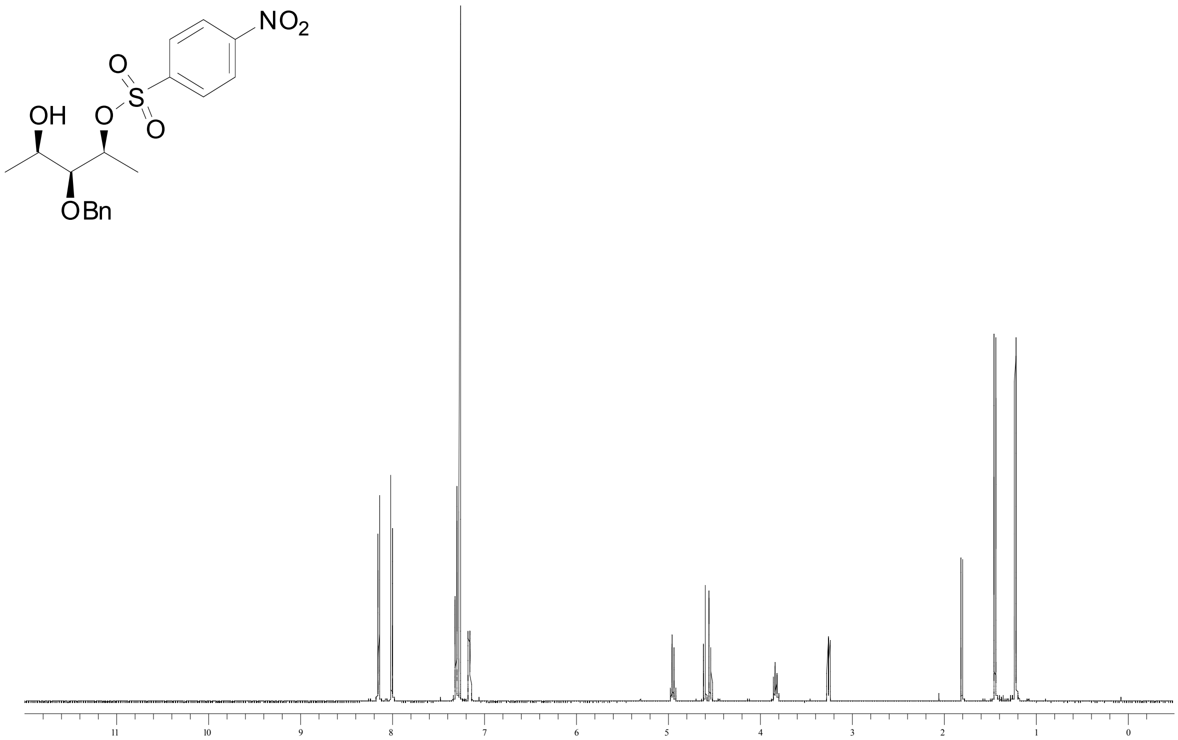

200 180 160 140 120 100 80 60 40 20 0
f1 (ppm)

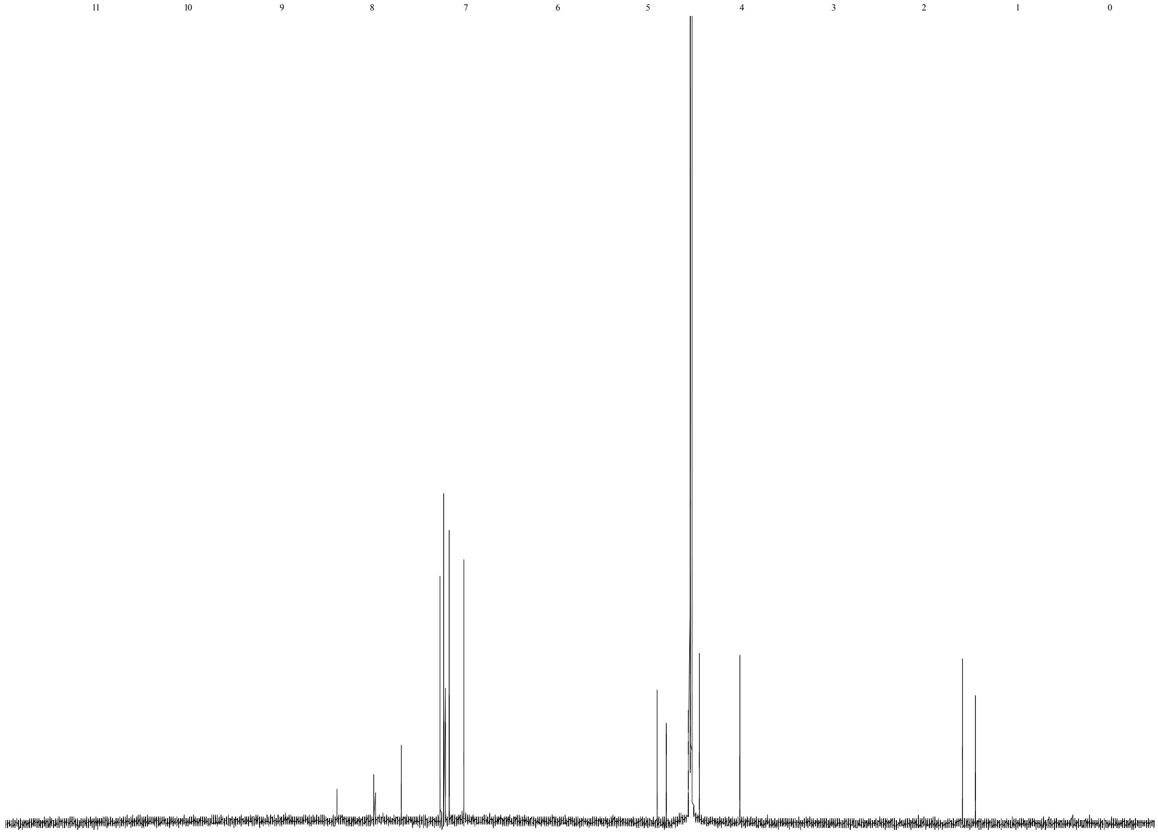

HO
O
S
O
O
NO2
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)

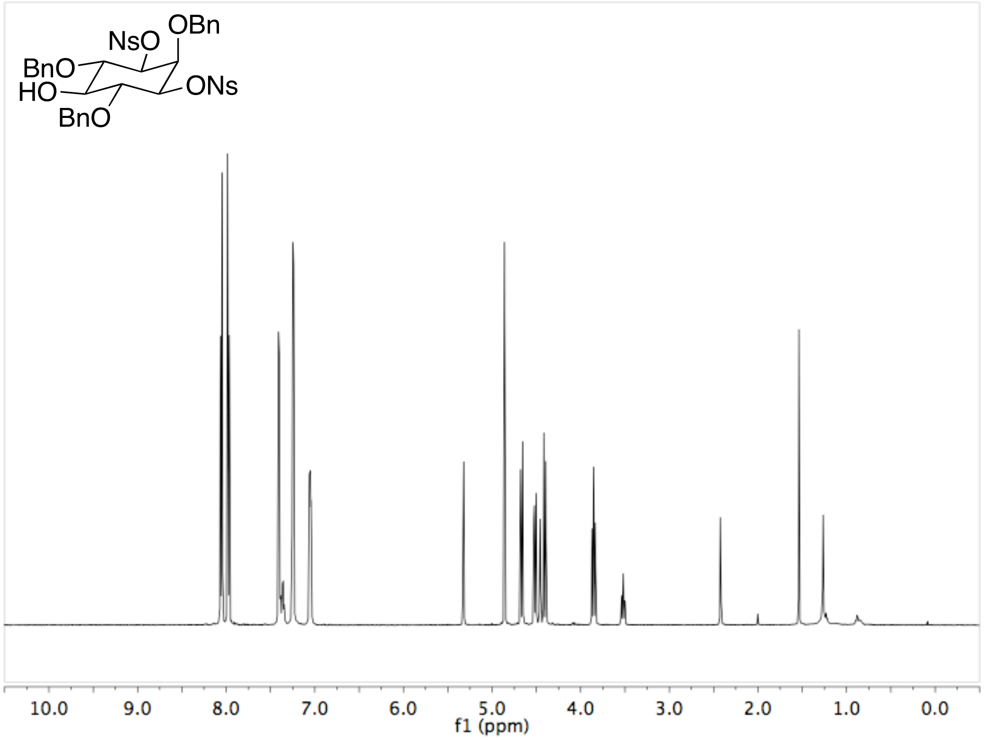

200
180
160
140
120
100
80
60
40
20
0
f1 (ppm)

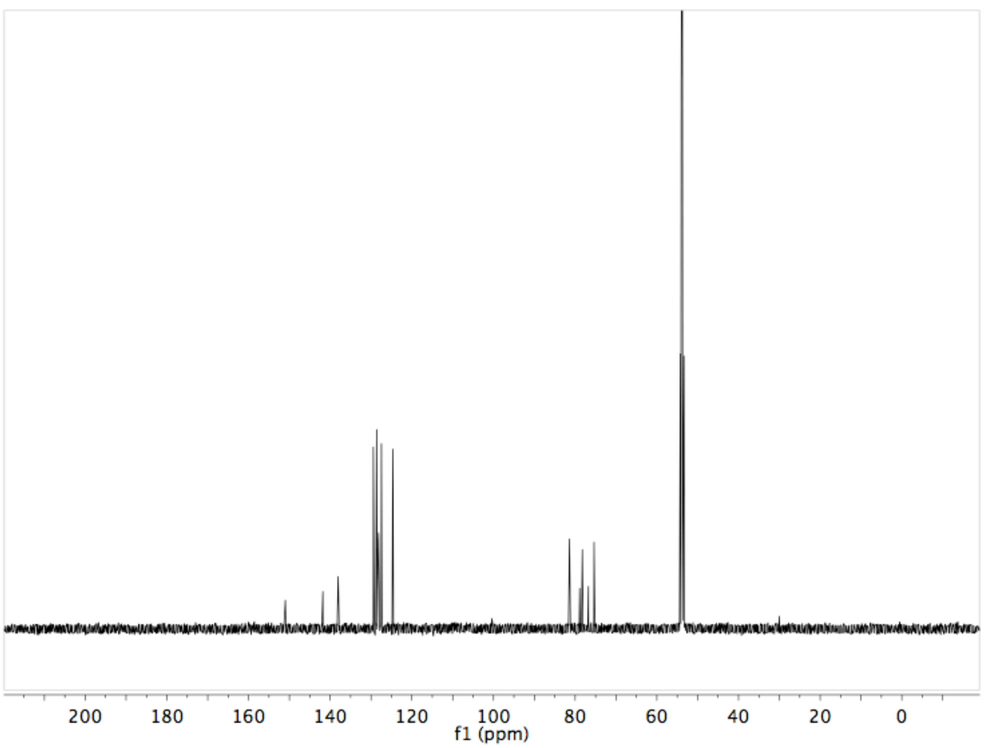

NO2
O
S
O
OH
O
OBn
11
10
9
8
7
6
5
4
3
2
1
0

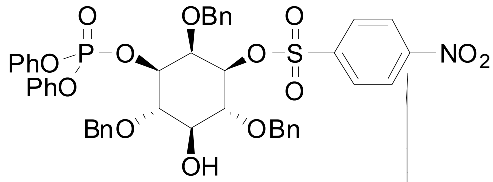

200
175
150
125
100
75
50
25
0

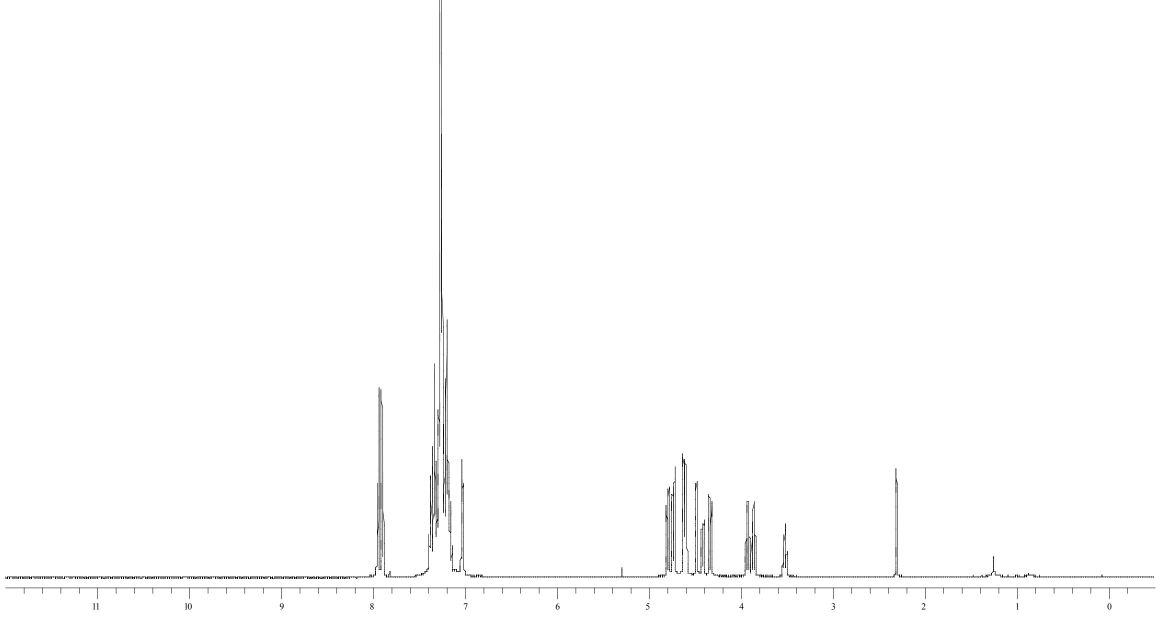

NO2
O
S
O
OH
O
OBn

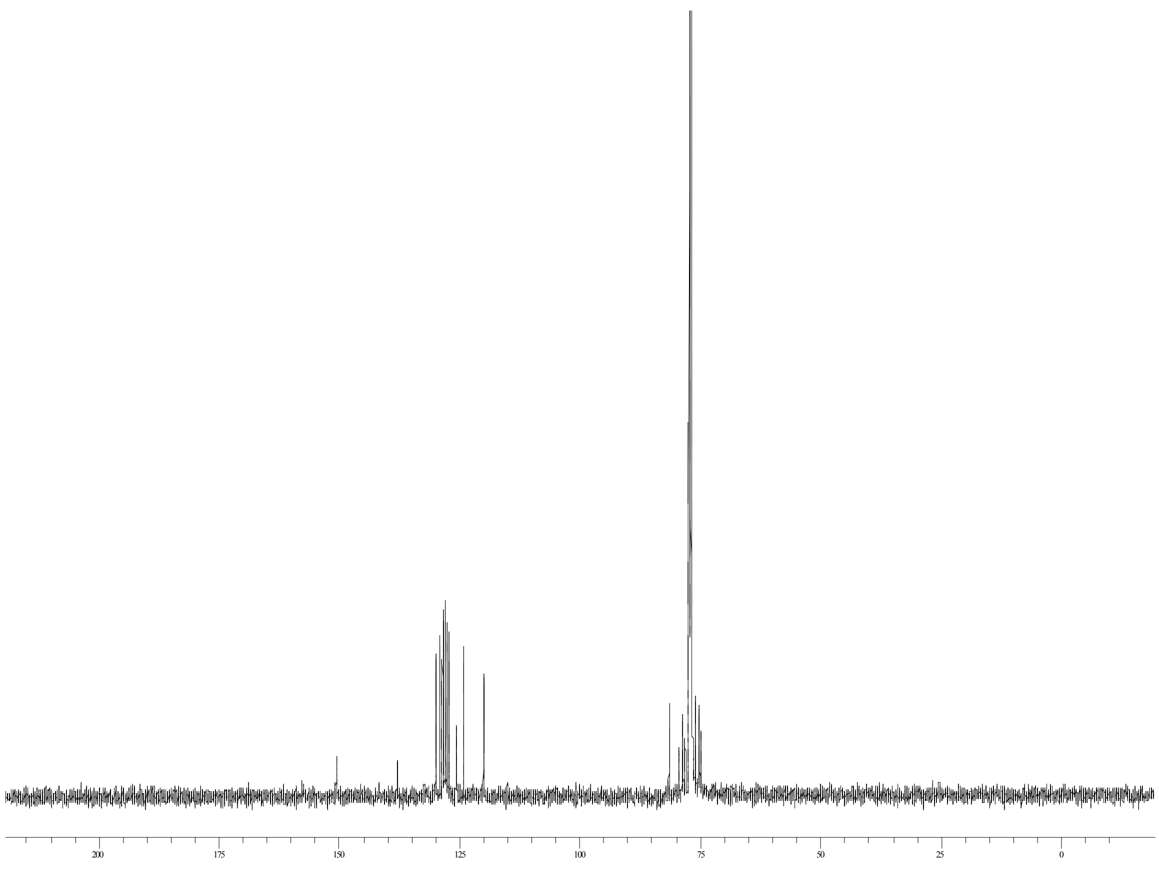



NsO
OBn
BnO
HO
ONs
BnO
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)


200
180
160
140
120
100
80
60
40
20
0
f1 (ppm)


O
OBn
O
PhO
P
O
O
S
NO2
PhO
O
BnO
OBn
OH





^{31}P NMR: