Hydroxyl-Directed Cross-Coupling: A Scalable Synthesis of Debromohamigeran E and Other Targets of Interest

Thomas P. Blaisdell and James P. Morken

Department of Chemistry, Merkert Chemistry Center, Boston College, Chestnut Hill, MA 02467

Supporting Information

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A. General Information

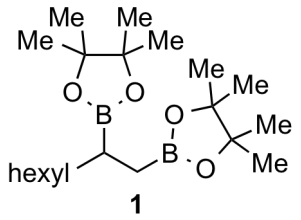
^{1}H NMR spectra were recorded on either a Varian Gemini-500 (500 MHz), or a Varian Inova-500 (500 MHz) spectrometer. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 7.26 ppm). Data are reported as follows: chemicalshift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, br = broad, m = multiplet, app = apparent), and coupling constants (Hz). ^{13}C NMR spectra were recorded on either a Varian Gemini-500 (125 MHz), or a Varian Inova-500 (125 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 77.0 ppm). Infrared (IR) spectra were recorded on a Bruker alpha spectrophotometer. Bands are characterized as broad (br), strong (s), medium (m), and weak (w) (ν max cm^{-1}). High resolution mass spectrometry (DART) was performed at the Mass Spectrometry Facility, Boston College.

Liquid Chromatography was performed using forced flow (flash chromatography) on silica gel (SiO_2, 230×450 Mesh) purchased from Silicycle. Thin Layer Chromatography was performed on 25 μm silica gel plates purchased from Silicycle. Visualization was performed using ultraviolet light (254 nm), potassium permanganate ($KMnO_4$) in water, ninhydrin with acetic acid in ethanol, phosphomolybdic acid (PMA) in ethanol, or phosphomolybdic acid and cerium(IV) sulfate in ethanol with sulfuric acid (Seebach). Analytical chiral supercritical fluid chromatography (SFC) was performed on a Thar Supercritical Chromatograph equipped with an auto sampler and a Waters photodiode array detector with isopropanol as the modifier.

All reactions were conducted in oven- or flame-dried glassware under an inert atmosphere of nitrogen or argon. Tetrahydrofuran, toluene, diethyl ether and dichloromethane were purified using Pure Solv MD-4 solvent purification system, from Innovative Technology, Inc., by passing the solvent through two activated alumina columns after being purged with argon.

B. EXPERIMENTAL PROCEDURES.

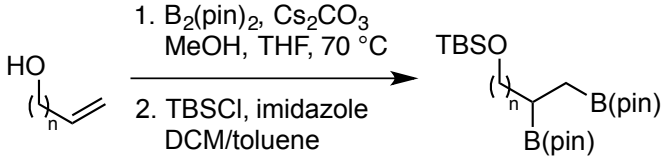
I. Preparation of Substrates



1

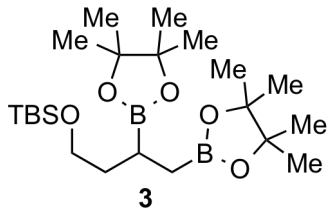
2,2'-(octane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (1). Prepared according to the literature procedure.[1] All spectral data are in accord with the literature.

Preparation of Bisboronates 3, 5, 7:



n=1 30% (2 steps)
n=2 84% (2 steps)
n=3 57% (2 steps)

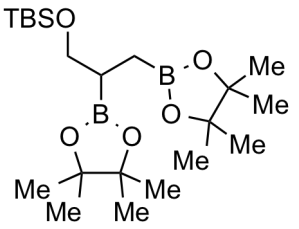
To an oven-dried 50 mL round bottom flask with magnetic stir bar was added $B_2(pin)_2$ (2.54 g, 10 mmol), Cs_2CO_3 (0.53 g, 1.50 mmol) and THF (10 mL). The alkenol (5.00 mmol) and methanol (3.44 mL, 85.0 mmol) were added sequentially to the reaction flask. The flask was sealed with a rubber septum and sealed with electrical tape. The flask was heated at 70 °C and allowed to stir for 6 hours. The reaction was cooled to room temperature and concentrated *in vacuo* (ensuring that all methanol has been removed from the residue). To the residue was added dichloromethane (23 mL) and imidazole (3.02 g, 44.4 mmol). The reaction mixture was cooled to 0 °C and a solution of TBSCl (2.24 g, 14.9 mmol) in toluene (5 mL). The reaction was sealed and allowed to warm to room temperature overnight. The reaction mixture was quenched with NH_4Cl (15 mL). The layers were allowed to separate and the aqueous layer was extracted with dichloromethane (3 x 30 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was purified on SiO_2.



3

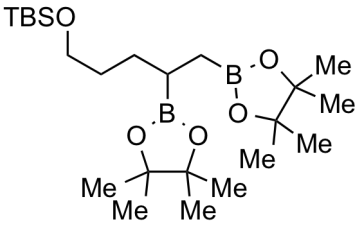
(3,4-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butoxy)(tert-butyl)dimethylsilane. (3) Prepared according to the general procedure using 3-buten-1-ol (0.43 mL, 5.00 mmol). The crude material was purified on SiO_2 (2.5% to 10% EtOAc/hexanes, stain with CAM) to afford the title compound as a colorless oil (1.86 g, 84% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.03 (6H, s), 0.88 (9H, s), 0.80-0.90 (2H, m), 1.13-1.19 (1H, m), 1.22 (24H, s), 1.51-1.58 (1H, m), 1.68-1.75 (1H, m), 3.57-3.66 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ -5.2, 18.4, 24.7, 24.8, 24.8, 24.9, 26.0, 36.6, 62.9, 82.8, 82.8; ^{11}B NMR (160 MHz, $CDCl_3$): δ 34.2; IR (neat): 2977.5 (w), 2928.8 (w), 2857.2 (w), 1470.9 (w), 1369.7 (s), 1311.1 (s), 1253.5 (m),

1140.6 (s), 1092.8 (s), 967.6 (m), 833.2 (s), 773.7 (s), 667.8 (m) cm^{-1}; HRMS-(DART-TOF) for $C_{22}H_{47}B_2O_5Si$ [M+H]: calculated: 441.3379, found: 441.3387.



5

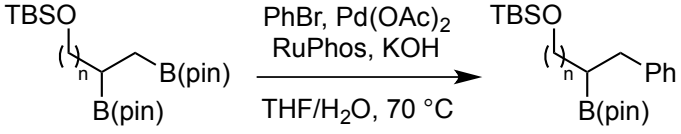
(2,3-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propoxy)(tert-butyl)dimethylsilane. (5) Prepared according to the general procedure using allyl alcohol (0.14 mL, 2.00 mmol). The crude material was purified on SiO_2 (2.5% to 10% EtOAc/hexanes, stain with CAM) to afford the title compound as a colorless oil (0.23 g, 30% yield). ^1H NMR (500 MHz, $CDCl_3$): δ 0.01 (6H, s), 0.86 (9H, s), 0.79-0.93 (2H, m), 1.22 (24H, s), 1.34-1.37 (1H, m), 3.64 (2H, d, J = 6.85 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ -5.4, 18.3, 24.7, 24.7, 24.8, 24.8, 24.8, 24.9, 26.0, 66.5, 82.8, 82.8; ^{11}B NMR (160 MHz, $CDCl_3$): δ 34.1; IR (neat): 2977.8 (w), 2929.0 (w), 2856.4 (w), 1470.6 (w), 1369.6 (s), 1313.3 (s), 1255.3 (m), 1214.0 (w), 1142.0 (s), 1087.2 (s), 1004.8 (s), 938.1 (m), 835.4 (s), 774.6 (m) cm^{-1}; HRMS-(DART-TOF) for $C_{21}H_{45}B_2O_5Si$ [M+H]: calculated: 427.3222, found: 427.3244.



7

((4,5-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentyl)oxy)(tert-butyl)dimethylsilane. (7) Prepared according to the general procedure using 4-penten-1-ol (0.52 mL, 5.00 mmol). The crude material was purified on SiO_2 (2.5% to 10% EtOAc/hexanes, stain with CAM) to afford the title compound as a colorless oil (1.30 g, 57% yield). ^1H NMR (500 MHz, $CDCl_3$): δ 0.03 (6H, s), 0.88 (9H, s), 0.77-0.90 (2H, m), 1.08-1.14 (1H, m), 1.22 (24H, s), 1.29-1.36 (1H, m), 1.41-1.48 (1H, m), 1.50-1.56 (1H, m), 3.57 (2H, t, J = 6.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ -5.2, 18.4, 24.7, 24.8, 24.8, 24.9, 26.0, 29.9, 32.3, 63.7, 82.8, 82.8; ^{11}B NMR (160 MHz, $CDCl_3$): δ 34.0; IR (neat): 2977.5 (w), 2929.1 (w), 2857.0 (w), 1470.7 (w), 1369.6 (s), 1311.1 (s), 1251.0 (m), 1141.1 (s), 1097.1 (s), 968.2 (m), 834.0 (s), 774.1 (s) cm^{-1}; HRMS-(DART-TOF) for $C_{23}H_{49}B_2O_5Si$ [M+H]: calculated: 455.3535, found: 455.3544.

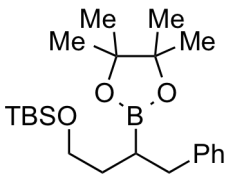
Procedure for Preparation of Substrates 9, 11, and 12:



n=1 61%
n=2 82%
n=3 80%

To an oven-dried 25 mL round bottom flask with magnetic stir bar in the dry box was added the 1,2-bis(boronate) (1.00 mmol), tetrahydrofuran (9.1 mL), potassium hydroxide (168 mg, 3.00 mmol), $Pd(OAc)_2$ (2.4 mg, 10 μmol), RuPhos (5.6 mg, 12 μmol) and bromobenzene (158 μL, 1.50 mmol). The flask was sealed with a rubber septum,

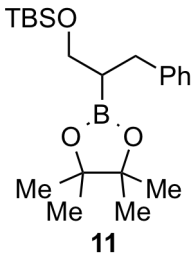
removed from the dry box, and heated to 70 ºC in an oil bath for 12 hours. The reaction mixture was cooled to room temperature and H_2O (10 mL) was added. The layers were allowed to separate and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude material was purified on SiO_2.



9

tert-butyldimethyl(4-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butoxy)silane. (9) Prepared according to the general procedure using (3,4-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butoxy)(tert-butyl)dimethylsilane (0.44 g, 1.00 mmol). The crude material was purified on SiO_2 (2.5% to 5% EtOAc/hexanes, stain with CAM) to afford the title compound as a colorless oil (0.32 g, 82% yield).

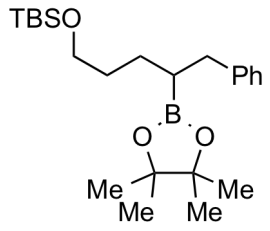
^{1}H NMR (500 MHz, $CDCl_3$): δ 0.02 (3H, s), 0.03 (3H, s), 0.88 (9H, s), 1.13 (6H, s), 1.16 (6H, s), 1.38-1.46 (1H, m), 1.58-1.71 (2H, m), 2.67 (1H, dd, J = 13.7 Hz, 7.8 Hz), 2.73 (1H, dd, J = 13.7 Hz, 8.3 Hz), 3.54-3.59 (1H, m), 3.62-3.67 (1H, m), 7.11-7.15 (1H, m), 7.19-7.24 (4H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ -5.3, -5.2, 18.4, 24.7, 24.8, 26.0, 34.1, 37.1, 62.9, 83.0, 125.6, 128.0, 128.9, 142.1; ^{11}B NMR (160 MHz, $CDCl_3$): δ 34.2; IR (neat): 2954.6 (w), 2928.1 (w), 2856.5 (w), 1471.2 (w), 1378.7 (m), 1318.5 (m), 1251.8 (m), 1143.3 (s), 1096.2 (s), 833.9 (s), 774.6 (s), 743.5 (w), 698.2 (m) cm^{-1}; HRMS-(DART-TOF) for $C_{22}H_{40}BO_3Si$ [M+H]: calculated: 391.2840, found: 391.2849.



11

tert-butyldimethyl(3-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propoxy)silane. (11) Prepared according to the general procedure using (3,4-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butoxy)(tert-butyl)dimethylsilane (87 mg, 0.20 mmol). The crude material was purified on SiO_2 (2.5% to 5% EtOAc/hexanes, stain with CAM) to afford the title compound as a colorless oil (46 mg, 61% yield).

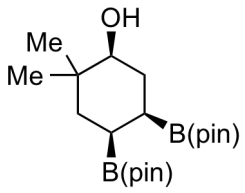
^{1}H NMR (500 MHz, $CDCl_3$): δ 0.02 (6H, s), 0.89 (9H, s), 1.16 (6H, s), 1.17 (6H, s), 1.57 (1H, quintet, J = 7.33 Hz), 2.72 (1H, dd, J = 13.7 Hz, 7.82 Hz), 2.79 (1H, dd, J = 13.7 Hz, 7.82 Hz), 3.62 (1H, dd, J = 9.78 Hz, 6.36 Hz), 3.67 (1H, dd, J = 9.78 Hz, 6.85 Hz), 7.12-7.15 (1H, m), 7.20-7.25 (4H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ -5.4, 18.3, 24.8, 24.8, 25.9, 33.2, 63.6, 83.1, 125.5, 128.0, 129.0, 142.0; ^{11}B NMR (160 MHz, $CDCl_3$): δ 33.8; IR (neat): 3027.3 (w), 2978.0 (w), 2953.9 (w), 2856.1 (w), 1471.1 (w), 1388.6 (m), 1369.4 (m), 1319.9 (m), 1143.4 (s), 1092.9 (s), 1004.8 (m), 832.7 (s), 773.5 (s), 743.7 (m), 697.5 (s) cm^{-1}; HRMS-(DART-TOF) for $C_{21}H_{38}BO_3Si$ [M+H]: calculated: 377.2683, found: 377.2683.



12

tert-butyldimethyl((5-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentyl)oxy)silane. (12) Prepared according to the general procedure using ((4,5-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentyl)oxy)(tert-butyl)dimethylsilane (0.45 g, 1.00 mmol). The crude material was purified on SiO_2 (2.5% to 5% EtOAc/hexanes, stain with CAM) to afford the title compound as a colorless oil (0.32 g, 80% yield).

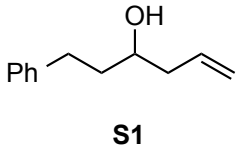
^{1}H NMR (500 MHz, $CDCl_3$): δ 0.03 (6H, s), 0.88 (9H, s), 1.13 (6H, s), 1.16 (6H, s), 1.36 (1H, q, J = 7.3 Hz), 1.43 (2H, q, J = 7.7 Hz), 1.48-1.61 (2H, m), 2.66 (1H, dd, J = 13.7 Hz, 7.3 Hz), 2.72 (1H, dd, J = 13.7 Hz, 8.3 Hz), 3.57 (2H, t, J = 6.6 Hz), 7.11-7.15 (1H, m), 7.18-7.24 (4H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ -5.3, 18.3, 24.7, 24.8, 26.0, 27.2, 32.4, 37.3, 63.4, 83.0, 125.5, 128.0, 128.8, 142.2; ^{11}B NMR (160 MHz, $CDCl_3$): δ 33.8; IR (neat): 2977.4 (w), 2928.5 (w), 2856.1 (w), 1495.0 (w), 1385.0 (m), 1318.8 (m), 1251.5 (m), 1143.0 (s), 1098.2 (s), 1005.6 (w), 832.9 (s), 773.6 (s), 743.3 (w), 697.7 (s) cm^{-1}; HRMS-(DART-TOF) for $C_{23}H_{42}BO_3Si$ [M+H]: calculated: 405.2996, found: 405.2991.



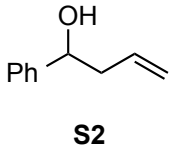
15

2,2-dimethyl-4,5-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohexan-1-ol. (15) Prepared according to the literature procedure.[2] All spectral data are in accord with the literature.

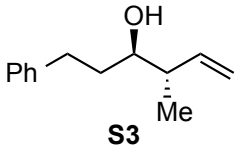
Preparation of Substrates used for Scheme 3:



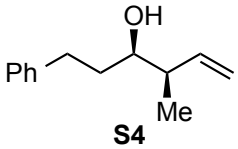
S1
*(used for **19-25** and **32-36**)*



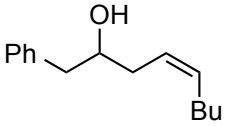
S2
*(used for **26**)*



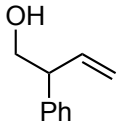
S3
*(used for **27**)*



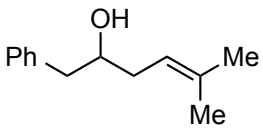
S4
*(used for **28**)*



S5
*(used for **29**)*



S6
*(used for **30**)*



S7
*(used for **31**)*

The substrates in Scheme 3 were prepared according to literature procedures.[2]

II. Experimental Procedure for Deprotection/Cross-Coupling/Oxidation (Table 1)

To an oven-dried 4-dram vial with magnetic stir bar was added the silyl ether (0.25 mmol), methanol (2 mL) and pTsOH (cat.). The reaction mixture was stirred at room temperature for 2 hours. The reaction was concentrated *in vacuo* (ensuring that all methanol has been removed from the residue). The flask was brought to a dry box and charged with solid potassium hydroxide (42 mg, 0.75 mmol), $Pd_2(dba)_3$/RuPhos (added as a 1:2 solution in THF (0.005 M); 0.25 mL for 0.5 mol% $Pd_2(dba)_3$), tetrahydrofuran (0.95 mL), toluene (1.2 mL) and bromobenzene (28 μL, 0.253 mmol). The vial was sealed, removed from the dry box, and H_2O (sparged with N_2 for 30 min, 0.23 mL) was added through the teflon septum cap. The vial was heated to 70 ºC and stirred for 12 h. The reaction mixture was transferred to a 25-mL round bottom flask and cooled to 0 ºC (ice/water) and charged with 3 M sodium hydroxide (0.5 mL), and 30% hydrogen peroxide (0.5 mL). The reaction was gradually warmed to room temperature and allowed to stir for 4 h at which time the vial was diluted with ethyl acetate and the aqueous and organic layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 10 mL) and the combined organics were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation.

III. Experimental Procedure for Diboration/Cross-Coupling/Oxidation (Table 1, Entry 8)

To an oven-dried 2-dram vial with magnetic stir bar was added homoallylic alcohol (0.25 mmol), Cs_2CO_3 (26 mg, 75 μmol), $B_2(pin)_2$ (95 mg, 0.38 mmol), tetrahydrofuran (1 mL, [substrate] = 0.25 M) and methanol (0.17 mL, 4.25 mmol). The vial was sealed with a teflon septum cap and heated to 70 ºC for 6 h. The reaction was cooled to room temperature and concentrated *in vacuo* (ensuring that all methanol has been removed from the residue). The flask was brought to a dry box and charged with solid potassium hydroxide (42 mg, 0.75 mmol), $Pd_2(dba)_3$/RuPhos (added as a 1:2 solution in THF (0.005 M); 0.25 mL for 0.5 mol% $Pd_2(dba)_3$), tetrahydrofuran (0.95 mL), toluene (1.2 mL) and electrophile (0.38 mmol). The vial was sealed, removed from the dry box, and H_2O (sparged with N_2 for 30 min, 0.23 mL) was added through the teflon septum cap. The vial was heated to 70 ºC and stirred for 12 h. The reaction mixture was transferred to a 25-mL round bottom flask and cooled to 0 ºC (ice/water) and charged with 3 M sodium hydroxide (0.5 mL), and 30% hydrogen peroxide (0.5 mL). The reaction was gradually warmed to room temperature and allowed to stir for 4 h at which time the vial was diluted with ethyl acetate and the aqueous and organic layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 10 mL) and the combined organics were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude material was purified on SiO_2.

IV. Experimental Procedure for Cross-Coupling of Bis(boronate) 15.

A oven-dried flask was brought to a dry box and charged with 2,2-dimethyl-4,5-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohexan-1-ol (95 mg, 0.25 mmol), solid potassium hydroxide (42 mg, 0.75 mmol), $Pd_2(dba)_3$/RuPhos (added as a 1:2 solution in THF (0.005 M); 0.25 mL for 0.5 mol% $Pd_2(dba)_3$), tetrahydrofuran (0.95 mL), toluene (1.2 mL) and bromobenzene (0.26 or 0.50 mmol). The vial was sealed, removed from the dry box, and H_2O (sparged with N_2 for 30 min, 0.23 mL) was added through the teflon septum cap. The vial was heated to 70 ºC and stirred for 12 h. The reaction mixture was cooled to room temperature and H_2O (5 mL) was added. The layers were allowed to separate and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude product was purified on silica gel (5% ethyl acetate in hexanes).

V. Experimental Procedure for Diboration/Cross-Coupling/Protection (Scheme 3)

To an oven-dried 2-dram vial with magnetic stir bar was added homoallylic alcohol (0.25 mmol), Cs_2CO_3 (26 mg, 75 μmol), $B_2(pin)_2$ (95.0 mg, 0.38 mmol), tetrahydrofuran (1 mL, [substrate] = 0.25 M) and methanol (0.17 mL, 4.25 mmol). The vial was sealed with a teflon septum cap and heated to 70 ºC for 6 h. The reaction was cooled to room temperature and concentrated *in vacuo* (ensuring that all methanol has been removed). The flask was brought to a dry box and charged with solid potassium hydroxide (42 mg, 0.75 mmol), $Pd_2(dba)_3$/RuPhos (added as a 1:2 solution in THF (0.005 M); 0.25 mL for 0.5 mol% $Pd_2(dba)_3$), tetrahydrofuran (0.95 mL), toluene (1.2 mL) and electrophile (39 μL, 0.38 mmol). The vial was sealed, removed from the dry box, and H_2O (sparged with N_2 for 30 min, 0.23 mL) was added through the teflon septum cap. The vial was heated to 70 ºC and stirred for 12 h. The reaction mixture was cooled to room temperature and H_2O (5 mL) was added. The layers were allowed to separate and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation in a 4-dram vial.

TBSCl Protection

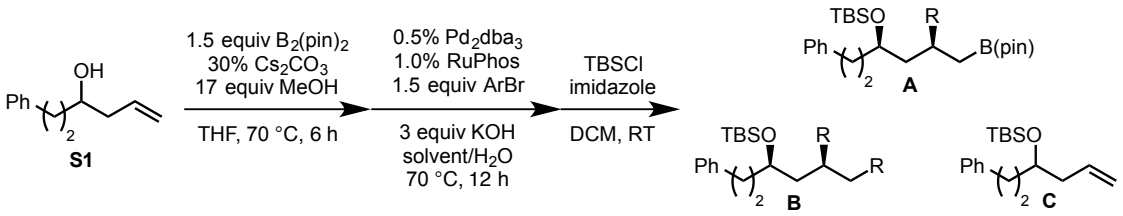
To the crude residue was added dichloromethane (1.2 mL) and imidazole (151 mg, 2.22 mmol). The reaction mixture was cooled to 0 °C and a solution of TBSCl (112 mg, 0.74 mmol) in toluene (0.25 mL). The reaction was sealed and allowed to warm to room temperature and stirred for 4 hours. The reaction mixture was quenched with aq. NH_4Cl (5 mL). The layers were allowed to separate and the aqueous layer was extracted with dichloromethane (3 x 5 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude material was purified on SiO_2.

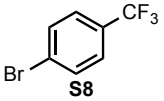
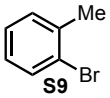
Ac_2O Protection

To the residue was added dichloromethane (1.2 mL), triethylamine (1.2 mL), and a single crystal of 4-(dimethylamino)pyridine under a nitrogen atmosphere. The reaction mixture was cooled to 0 °C and acetic anhydride (52 μL, 0.55 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 12 h. The reaction mixture was diluted with 1 M HCl. The organic layer was separated and washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude material was purified on SiO_2.

VI. Reaction Optimization

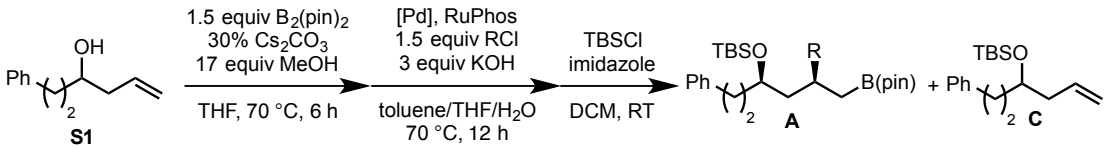
During reaction optimization, the couplings of electron-deficient (**S8**) and sterically hindered (**S9**) coupling partners were vulnerable to the formation of byproducts (**B** and **C**). The relative ratios of product and these byproducts were directly related to the solvent used in the reaction. The reactions shown below follow the general diboration/cross-coupling/protection procedure using 1-phenylhex-5-en-3-ol (44 mg, 0.25 mmol) as the substrate.

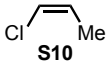


entry	ArX	solvent	conversion[a]	ratio of products[a] **(A : B : C)**
1	 **S8**	THF	>95%	56:20:24
2		Toluene	79%	42:58:–
3		THF/Toluene (1:1)	77%	78:22:–
4[b]		THF/Toluene (1:1)	84%	94:6:–
5	 **S9**	THF	>95%	73:8:19
6		Toluene	95%	24:76:–
7		THF/Toluene (1:1)	>95%	81:–:19

[a] Determined by ^{1}H NMR (conversion refers to unreacted 1,2-bis(boronate) observed). [b] Used 1.1 equivalents of ArBr

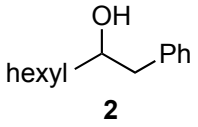
In the case of vinyl coupling partners, the use of $Pd(OAc)_2$, when compared to the use of Pd_2dba_3, minimized the formation of olefin byproduct (**C**). It is possible that free dibenzylideneacetone can compete for a coordination site on the palladium center, allowing for a more competitive β-deborylation pathway. Again, the reactions shown below follow the general diboration/cross-coupling/protection procedure using 1-phenylhex-5-en-3-ol (44 mg, 0.25 mmol) as the substrate.



entry	RCl	Catalyst	conversion[a]	ratio of products[a] **(A : C)**
1	 **S10**	Pd_2dba_3 (1.25%), RuPhos (2.5%)	83%	70:30
2		$Pd(OAc)_2$ (2.5%), RuPhos (3%)	92%	89:11
3	 **S11**	Pd_2dba_3 (1.25%), RuPhos (2.5%)	54%	79:21
4		$Pd(OAc)_2$ (10%), RuPhos (3%)	85%	95:5

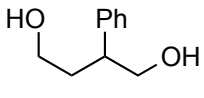
[a] Determined by ^{1}H NMR (conversion refers to unreacted 1,2-bis(boronate) observed).

VII. Full Characterization



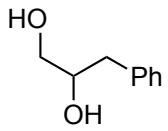
2

1-phenyloctan-2-ol. (2) Prepared according the general deprotection/cross-coupling/oxidation procedure using 2,2'-(octane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (92 mg, 0.25 mmol). The NMR yield was determined using 1,3,5-trimethoxybenzene as an internal standard. All spectral data are in accord with the literature.[3]



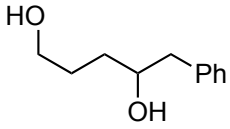
4

2-phenylbutane-1,4-diol. (4) Prepared according the general deprotection/cross-coupling/oxidation procedure using (3,4-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butoxy)(tert-butyl)dimethylsilane (110 mg, 0.25 mmol). The NMR yield was determined using 1,3,5-trimethoxybenzene as an internal standard. All spectral data are in accord with the literature.[4]



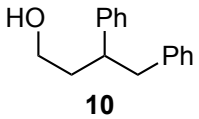
6

3-phenylpropane-1,2-diol. (6) Prepared according the general deprotection/cross-coupling/oxidation procedure using (2,3-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propoxy)(tert-butyl)dimethylsilane (87 mg, 0.20 mmol). The NMR yield was determined using 1,3,5-trimethoxybenzene as an internal standard. All spectral data are in accord with the literature.[5]



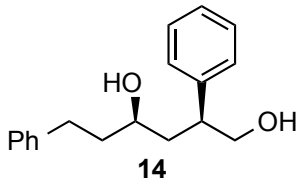
8

5-phenylpentane-1,4-diol. (8) Prepared according the general deprotection/cross-coupling/oxidation procedure using ((4,5-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentyl)oxy)(tert-butyl)dimethylsilane (114 mg, 0.25 mmol). The NMR yield was determined using 1,3,5-trimethoxybenzene as an internal standard. All spectral data are in accord with the literature.[6]



10

3,4-diphenylbutan-1-ol. (10) Prepared according the general deprotection/cross-coupling/oxidation procedure using tert-butyldimethyl(4-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butoxy)silane (49 mg, 0.13 mmol). The NMR yield was determined using 1,3,5-trimethoxybenzene as an internal standard. All spectral data are in accord with the literature.[7]



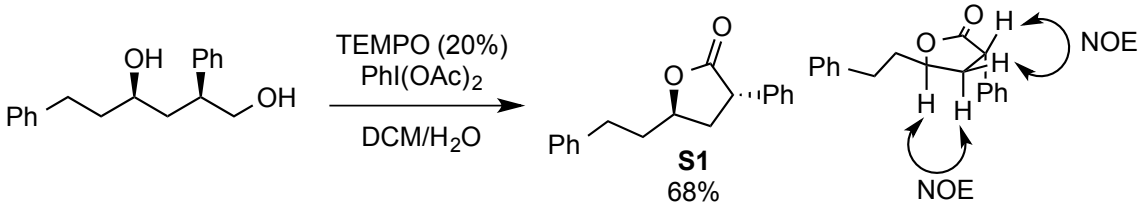
14

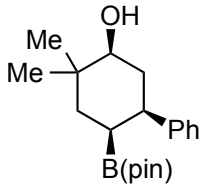
2,6-diphenylhexane-1,4-diol. (14) Prepared according the general diboration/cross-coupling/oxidation procedure using 1-phenylhex-5-en-3-ol (44 mg, 0.25 mmol) and bromobenzene (39 μL, 0.38 mmol). The crude product was purified on silica gel (40% ethyl acetate in hexaness) to afford the title compound as a colorless oil (45 mg, 67%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.75-1.88 (3H, m), 1.92-1.98 (1H, m), 2.60-2.66 (1H, m), 2.74-2.79 (1H, m), 3.01 (1H, quintet, J = 6.36 Hz), 3.71-3.80 (3H, m), 7.15-7.18 (3H, m),

7.20-7.22 (3H, m), 7.24-7.28 (2H, m), 7.30-7.33 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.8, 32.0, 38.8, 40.6, 44.9, 67.2, 69.5, 125.8, 126.9, 127.8, 128.4, 128.4, 128.8, 142.0, 142.6; IR (neat): 3330.5 (br), 3026.4 (w), 2928.8 (w), 1602.0 (w), 1493.9 (w), 1452.9 (w), 1265.3 (w), 1029.4 (m), 734.9 (s), 697.7 (s), 604.2 (m), 549.6 (m), 528.7 (m) cm^{-1}; HRMS-(DART-TOF) for $C_{18}H_{22}O_2$ [M+H]: calculated: 271.1698, found: 271.1699.

Proof of Stereochemistry: The relative stereochemistry was determined by NOESY NMR of the corresponding lactone derived from the 1,4-diol (as shown below).

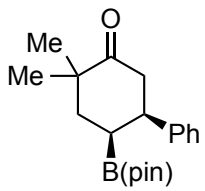




16

2,2-dimethyl-5-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohexan-1-ol. (16) Prepared according the procedure for cross-coupling of cyclic bis(boronate).

^{1}H NMR (600 MHz, $CDCl_3$): δ 0.90 (6H, s), 1.00 (3H, s), 1.02 (6H, s), 1.04 (3H, s), 1.65-1.71 (2H, m), 1.81 (1H, dd, J = 12.91 Hz, 1.76 Hz), 2.00 (1H, d, J = 12.32 Hz), 2.22 (1H, q, J = 11.74 Hz), 2.84 (1H, dt, J = 12.32 Hz, 3.52 Hz), 3.47 (1H, dd, J = 11.15 Hz, 4.11 Hz), 7.10-7.13 (1H, m), 7.21-7.24 (2H, m), 7.27-7.29 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.5, 24.1, 24.8, 29.3, 33.3, 35.7, 41.6, 42.8, 78.7, 82.6, 82.7, 125.4, 127.4, 127.5, 127.7, 145.3; IR (neat): 3398.0 (w), 2975.9 (m), 2946.0 (m), 2866.6 (m), 1388.6 (m), 1370.5 (m), 1316.3 (s), 1142.0 (s), 965.5 (m), 858.8 (m), 751.2 (m), 696.5 (s) cm^{-1}; HRMS-(DART-TOF) for $C_{20}H_{32}BO_3$ [M+H]: calculated: 331.2445, found: 331.2458.

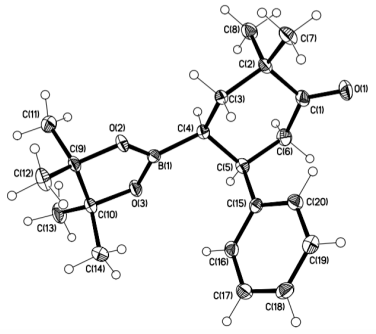


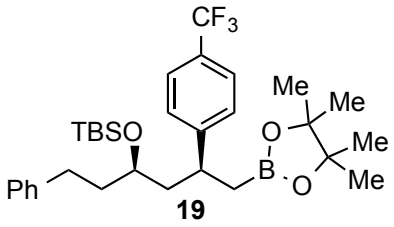
17

2,2-dimethyl-5-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohexan-1-one. (17) Prepared according the procedure for cross-coupling of cyclic bis(boronate).

^{1}H NMR (600 MHz, $CDCl_3$): δ 1.04 (6H, s), 1.14 (6H, s), 1.19 (3H, s), 1.22 (3H, s), 1.73 (1H, dd, J = 13.5 Hz, 2.93 Hz), 1.93-2.01 (2H, m), 2.71 (1H, dd, J = 14.67 Hz, 4.70 Hz), 2.83 (1H, dd, J = 14.68 Hz, 6.46 Hz), 3.61 (1H, q, J = 4.70 Hz), 7.13-7.17 (3H, m), 7.21-7.24 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.6, 25.0, 25.6, 26.0, 37.9, 43.5, 44.0, 45.1, 83.3, 126.4, 128.0, 128.3, 143.7, 217.2; IR (neat): 2975.3 (m), 2925.0 (w), 2866.2 (w), 1701.4 (s), 1371.6 (s), 1323.3 (s), 1111.5 (s), 967.1 (s), 851.9 (m), 694.4 (m) cm^{-1}; HRMS-(DART-TOF) for $C_{20}H_{30}BO_3$ [M+H]: calculated: 329.2288, found: 329.2304.

Proof of Stereochemistry: The relative stereochemistry was determined by crystal structure determination (as shown below).

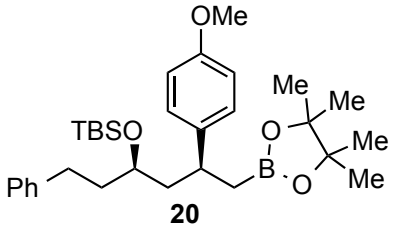




19

tert-butyldimethyl((1-phenyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(4-(trifluoromethyl)-phenyl)hexan-3-yl)oxy)silane. (19) Prepared according the general diboration/cross-coupling/protection procedure using 1-phenylhex-5-en-3-ol (44 mg, 0.25 mmol) and 4-bromobenzotrifluoride (39 μL, 0.275 mmol). The crude product was purified on silica gel (100% hexanes to 50% DCM in hexanes) to afford the title compound as a colorless oil (110 mg, 78%).

^{1}H NMR (500 MHz, $CDCl_3$): δ -0.08 (3H, s), -0.05 (3H, s), 0.88 (9H, s), 1.05-1.11 (1H, m), 1.09 (12H, s), 1.19 (1H, dd, J = 15.2 Hz, 6.4 Hz), 1.67-1.74 (1H, m), 1.78-1.84 (1H, m), 1.83 (2H, t, J = 6.4 Hz), 2.54 (1H, dd, J = 11.2 Hz, 5.9 Hz), 2.70 (1H, dd, J = 13.7 Hz, 5.4 Hz), 2.95 (1H, quintet, J = 7.8 Hz), 3.44 (1H, sextet, J = 4.4 Hz), 7.14-7.19 (3H, m), 7.25-7.28 (4H, m), 7.49-7.51 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ -4.5, -4.5, 18.1, 24.6, 24.7, 25.9, 31.1, 37.9, 38.4, 46.2, 69.5, 83.1, 125.1 (q, J = 3.9 Hz), 125.6, 127.7, 128.3, 128.3, 142.7, 151.3; ^{11}B NMR (160 MHz, $CDCl_3$): δ 33.5; IR (neat): 2977.9 (w), 2929.8 (w), 2857.1 (w), 1471.4 (m), 1370.2 (m), 1322.9 (s), 1254.3 (m), 1163.1 (m), A1123.2 (s), 1067.2 (s), 833.2 (s), 773.1 (s), 745.6 (m), 698.5 (m), 606.5 (m) cm^{-1}; HRMS-(DART-TOF) for $C_{31}H_{46}BF_3O_3Si$ [M+H]: calculated: 563.3340, found: 563.3345.

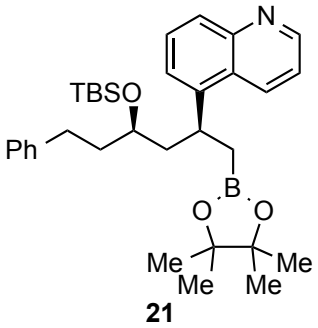


20

tert-butyl((-5-(4-methoxyphenyl)-1-phenyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexan-3-yl)oxy)-dimethylsilane. (20) Prepared according the general diboration/cross-coupling/protection procedure using 1-phenylhex-5-en-3-ol (44 mg, 0.25 mmol) and 4-bromoanisole (47 μL, 0.38 mmol). The crude product was purified on silica gel (100% hexanes to 50% DCM in hexanes) to afford the title compound as a colorless oil (101 mg, 77%).

^{1}H NMR (500 MHz, $CDCl_3$): δ -0.09 (3H, s), -0.05 (3H, s), 0.88 (9H, s), 1.06 (1H, dd, J = 15.7 Hz, 8.8 Hz), 1.10 (6H, s), 1.11 (6H, s), 1.15 (1H, dd, J = 15.2 Hz, 6.8 Hz), 1.66-1.73

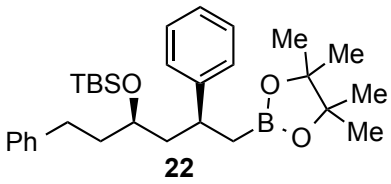
(1H, m), 1.79 (2H, t, J = 7.9 Hz), 1.78-1.87 (1H, m), 2.53 (1H, dd, J = 13.7 Hz, 4.9 Hz), 2.73 (1H, dd, J = 13.7 Hz, 5.4 Hz), 2.82 (1H, quintet, J = 7.3 Hz), 3.43 (1H, sextet, J = 3.9 Hz), 3.78 (3H, s), 6.79-6.80 (2H, m), 7.07-7.09 (2H, m), 7.16-7.19 (3H, m), 7.26-7.29 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ -4.6, -4.4, 18.1, 24.7, 24.7, 25.9, 31.2, 37.2, 38.2, 46.7, 55.3, 69.8, 82.9, 113.6, 125.5, 128.1, 128.3, 128.4, 139.0, 143.1, 157.7; ^{11}B NMR (160 MHz, $CDCl_3$): δ 33.6; IR (neat): 2977.0 (w), 2928.6 (w), 2855.9 (w), 1510.7 (m), 1462.2 (w), 1369.0 (s), 1318.6 (m), 1245.6 (s), 1143.6 (s), 967.2 (m), 830.5 (s), 807.6 (s), 772.8 (m), 698.4 (m) cm^{-1}; HRMS-(DART-TOF) for $C_{31}H_{50}BO_4Si$ [M+H]: calculated: 525.3571, found: 525.3589.



21

5-(4-((tert-butyldimethylsilyl)oxy)-6-phenyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexan-2-yl)quinolone. (21) Prepared according the general diboration/cross-coupling/protection procedure using 1-phenylhex-5-en-3-ol (44 mg, 0.25 mmol) and 5-bromoquinoline (78 μL, 0.38 mmol). The crude product was purified on silica gel (2% MeOH in DCM) to afford the title compound as a colorless oil (90 mg, 66%).

^{1}H NMR (500 MHz, $CDCl_3$): δ -0.03 (3H, s), 0.04 (3H, s), 0.88 (6H, s), 0.93 (9H, s), 0.96 (6H, s), 1.24-1.29 (1H, m), 1.35 (1H, dd, J = 15.7 Hz, 5.38 Hz), 1.69-1.79 (2H, m), 1.86 (1H, quintet, J = 6.35 Hz), 2.00 (1H, quintet, J = 6.85 Hz), 2.46-2.52 (1H, m), 2.56-2.63 (1H, m), 3.64 (1H, quintet, J = 5.87 Hz), 3.85 (1H, app s), 7.07 (2H, d, J = 7.5 Hz), 7.15 (1H, t, J = 7.0 Hz), 7.23 (2H, t, J = 7.0 Hz), 7.39 (1H, dd, J = 9.0 Hz, 4.0 Hz), 7.50 (1H, d, J = 7.0), 7.66 (1H, t, J = 7.5 Hz), 7.95 (1H, d, J = 8.5 Hz), 8.63 (1H, d, J = 8.5 Hz), 8.90 (1H, dd, J = 4.0 Hz, 1.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ -4.4, -4.4, 18.1, 24.4, 24.5, 24.7, 26.0, 31.1, 39.2, 46.6, 69.8, 82.9, 120.4, 123.7, 125.6, 126.8, 127.6, 128.2, 128.3, 129.0, 132.5, 142.5, 144.3, 148.6, 149.7; ^{11}B NMR (160 MHz, $CDCl_3$): δ 33.5; IR (neat): 3063.6 (w), 3027.1 (w), 2976.0 (w), 2951.8 (m), 2928.3 (m), 2856.1 (w), 1594.9 (m), 1572.5 (m), 1499.3 (m), 1470.8 (m), 1361.3 (s), 1323.6 (m), 1252.5 (m), 1142.9 (s), 1060.6 (m), 832.9 (s), 800.0 (s), 773.0 (s), 739.2 (m), 698.4 (m) cm^{-1}; HRMS-(DART-TOF) for $C_{33}H_{49}BNO_3Si$ [M+H]: calculated: 546.3575, found: 546.3598.

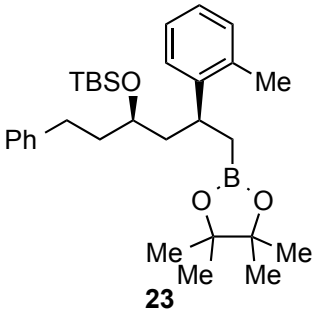


22

tert-butyl((-1,5-diphenyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexan-3-yl)oxy)dimethylsilane. (22) Prepared according the general diboration/cross-coupling/protection procedure using 1-phenylhex-5-en-3-ol (44 mg, 0.25 mmol) and bromobenzene (39 μL, 0.38 mmol). The crude product was purified on silica gel (100% hexanes to 50% DCM in hexanes) to afford the title compound as a colorless oil (57 mg, 85%).

^{1}H NMR (500 MHz, $CDCl_3$): δ -0.11 (3H, s), -0.06 (3H, s), 0.87 (9H, s), 1.09 (6H, s), 1.10 (6H, s), 1.07-1.12 (1H, m), 1.18 (1H, dd, J = 15.2 Hz, 6.85 Hz), 1.67-1.74 (1H, m), 1.78-1.88 (3H, m), 2.53 (1H, dd, J = 11.3 Hz, 5.38 Hz), 2.73 (1H, dd, J = 13.7 Hz, 5.38

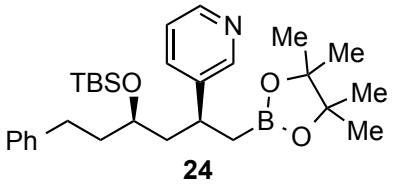
Hz), 2.86 (1H, quintet, J = 8.32 Hz), 3.43 (1H, quintet, J = 6.36 Hz), 7.13-7.18 (6H, m), 7.22-7.29 (4H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ -4.6, -4.4, 18.1, 24.7, 24.7, 25.9, 31.2, 38.1, 38.2, 46.6, 69.8, 82.9, 125.5, 125.9, 127.3, 128.2, 128.3, 128.4, 143.0, 146.9; ^{11}B NMR (160 MHz, $CDCl_3$): δ 33.4; IR (neat): 2977.1 (w), 2928.3 (w), 2856.2 (w), 1453.7 (w), 1369.4 (s), 1318.4 (s), 1253.5 (m), 1143.9 (s), 1066.4 (s), 967.1 (m), 881.5 (m), 832.9 (s), 772.4 (s), 697.8 (s) cm^{-1}; HRMS-(DART-TOF) for $C_{30}H_{48}BO_3Si$ [M+H]: calculated: 495.3466, found: 495.3477.



23

tert-butyldimethyl((1-phenyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(o-tolyl)hexan-3-yl)oxy)silane. (23) Prepared according the general diboration/cross-coupling/protection procedure using 1-phenylhex-5-en-3-ol (44 mg, 0.25 mmol) and 2-bromotoluene (45 μL, 0.38 mmol). The crude product was purified on silica gel (100% hexanes to 50% DCM in hexanes) to afford the title compound as a colorless oil (92 mg, 72%).

^{1}H NMR (500 MHz, $CDCl_3$): δ -0.05 (3H, s), 0.00 (3H, s), 0.90 (9H, s), 1.04 (12H, s), 1.05 (1H, dd, J = 15.2 Hz,, 9.3 Hz), 1.16 (1H, dd, J = 15.7 Hz, 6.4 Hz), 1.67-1.86 (4H, m), 2.35 (3H, s), 2.56 (1H, dd, J = 11.3 Hz, 4.9 Hz), 2.68 (1H, dd, J = 13.7 Hz, 5.9 Hz), 3.24 (1H, quintet, J = 6.8 Hz), 3.58 (1H, quintet, J = 5.9 Hz), 7.02-7.09 (2H, m), 7.14-7.18 (4H, m), 7.22-7.28 (3H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ -4.5, -4.5, 18.1, 19.9, 24.5, 24.7, 25.9, 31.3, 32.1, 39.3, 46.3, 69.8, 82.8, 125.4, 125.5, 126.0, 126.0, 128.3, 128.3, 130.0, 135.5, 142.9, 145.5; ^{11}B NMR (160 MHz, $CDCl_3$): δ 33.4; IR (neat): 2976.4 (w), 2952.2 (w), 2928.1 (w), 2856.3 (w), 1461.9 (w), 1367.0 (s), 1317.8 (s), 1254.0 (m), 1144.1 (s), 1066.3 (m), 967.6 (m), 833.2 (s), 772.6 (s), 698.1 (m) cm^{-1}; HRMS-(DART-TOF) for $C_{31}H_{50}BO_3Si$ [M+H]: calculated: 509.3622, found: 509.3641.

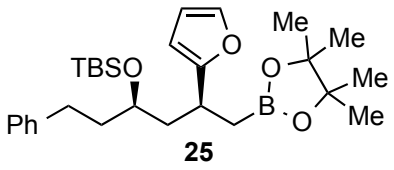


24

3-(4-((tert-butyldimethylsilyl)oxy)-6-phenyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexan-2-yl)pyridine. (24) Prepared according the general diboration/cross-coupling/protection procedure using 1-phenylhex-5-en-3-ol (44 mg, 0.25 mmol) and 3-bromopyridine (36 μL, 0.38 mmol). The crude product was purified on silica gel (2% MeOH in DCM) to afford the title compound as a colorless oil (64 mg, 52%).

^{1}H NMR (500 MHz, $CDCl_3$): δ -0.08 (3H, s), -0.06 (3H, s), 0.87 (9H, s), 1.09 (12H, s), 1.04-1.12 (1H, m), 1.21 (1H, dd, J = 15.6 Hz, 6.36 Hz), 1.68-1.75 (1H, m), 1.79-1.87 (3H, m), 2.51-2.57 (1H, m), 2.67-2.73 (1H, m), 2.92 (1H, quintet, J = 7.72 Hz), 3.46 (1H, quintet, J = 5.87 Hz), 7.15-7.20 (4H, m), 7.25-7.28 (2H, m), 7.49-7.50 (1H, m), 8.41-8.44 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ -4.5, -4.5, 18.0, 24.7, 24.7, 25.9, 31.1, 35.4, 38.5, 46.2, 69.6, 83.1, 123.2, 125.6, 128.3, 134.4, 142.2, 142.7, 147.5, 149.6; ^{11}B NMR (160 MHz, $CDCl_3$): δ 34.2; IR (neat): 3026.6 (w), 2977.1 (w), 2928.8 (m), 2856.2 (w), 1369.7 (s), 1317.3 (m), 1252.3 (m), 1143.2 (s), 1068.2 (m), 833.2 (s), 772.9 (s), 715.1

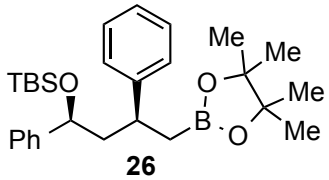
(m), 698.6 (m) cm^{-1}; HRMS-(DART-TOF) for $C_{29}H_{47}BNO_3Si$ [M+H]: calculated: 496.3418, found: 496.3435.



25

tert-butyl((5-(furan-2-yl)-1-phenyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexan-3-yl)oxy)dimethylsilane. (25) Prepared according the general diboration/cross-coupling/protection procedure using 1-phenylhex-5-en-3-ol (44 mg, 0.25 mmol) and 2-bromofuran (33 μL, 0.38 mmol). The crude product was purified on silica gel (100% hexanes to 50% DCM in hexanes) to afford the title compound as a colorless oil (62 mg, 51%).

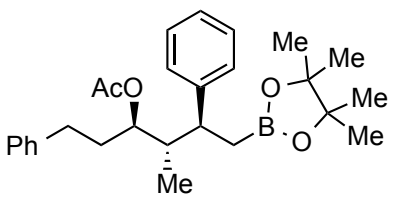
^{1}H NMR (500 MHz, $CDCl_3$): δ -0.02 (3H, s), 0.00 (3H, s), 0.89 (9H, s), 1.12 (2H, t, J = 6.36 Hz), 1.17 (6H, s), 1.17 (6H, s), 1.67-1.76 (2H, m), 1.81-1.94 (2H, m), 2.57 (1H, dd, J = 11.2 Hz, 4.89 Hz), 2.73 (1H, dd, J = 13.7 Hz, 5.37 Hz), 3.02 (1H, quintet, J = 7.83 Hz), 3.59 (1H, quintet, J = 5.37 Hz), 5.93 (1H, d, J = 2.93 Hz), 6.23 (1H, t, J = 2.45 Hz), 7.15-7.19 (3H, m), 7.25-7.28 (3H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ -4.6, -4.5, 18.1, 24.7, 24.8, 25.9, 31.3, 31.4, 38.5, 44.0, 69.8, 83.0, 104.0, 109.7, 125.5, 128.3, 128.4, 140.4, 142.9, 160.0; ^{11}B NMR (160 MHz, $CDCl_3$): δ 33.6; IR (neat): 2977.3 (w), 2950.9 (w), 2928.7 (w), 2856.3 (w), 1461.5 (w), 1368.3 (s), 1318.5 (m), 1253.7 (m), 1143.9 (s), 1068.0 (m), 1006.3 (m), 967.5 (m), 833.3 (s), 773.1 (s), 728.0 (m), 698.2 (m) cm^{-1}; HRMS-(DART-TOF) for $C_{28}H_{46}BO_4Si$ [M+H]: calculated: 485.3258, found: 485.3274.



26

tert-butyl(1,3-diphenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butoxy)dimethylsilane. (26) Prepared according the general diboration/cross-coupling/protection procedure using 1-phenylbut-3-en-1-ol (44 mg, 0.25 mmol) and bromobenzene (39 μL, 0.38 mmol). The crude product was purified on silica gel (100% hexanes to 50% DCM in hexanes) to afford the title compound as a colorless oil (80 mg, 68%).

^{1}H NMR (500 MHz, $CDCl_3$): δ -0.27 (3H, s), -0.08 (3H, s), 0.81 (9H, s), 1.03 (6H, s), 1.05 (6H, s), 1.02-1.07 (1H, m), 1.17 (1H, dd, J = 15.2 Hz, 6.36 Hz), 1.96 (1H, quintet, J = 6.85 Hz), 2.12 (1H, quintet, J = 6.16 Hz), 2.73 (1H, quintet, J = 7.33 Hz), 4.39 (1H, t, J = 6.36 Hz), 7.13-7.16 (1H, m), 7.18-7.19 (2H, m), 7.21-7.24 (4H, m), 7.25-7.29 (3H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ -5.0, -4.7, 18.1, 24.6, 24.7, 25.8, 37.5, 49.9, 73.3, 82.8, 125.8, 126.9, 127.9, 128.1, 145.3, 147.0; ^{11}B NMR (160 MHz, $CDCl_3$): δ 33.2; IR (neat): 2977.1 (w), 2954.5 (w), 2928.5 (w), 2856.2 (w), 1453.8 (w), 1369.0 (s), 1318.9 (m), 1252.7 (m), 1144.2 (s), 1068.9 (m), 967.8 (m), 834.1 (s), 774.0 (s), 697.6 (s) cm^{-1}; HRMS-(DART-TOF) for $C_{28}H_{42}BO_3Si$ [M+H]: calculated: 465.2996, found: 466.3014.

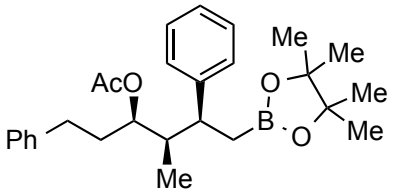


27

(3R,4S,5S)-4-methyl-1,5-diphenyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexan-3-yl acetate. (27) Prepared according the general diboration/cross-coupling/protection procedure using (3R,4S)-4-methyl-

1-phenylhex-5-en-3-ol (48 mg, 0.25 mmol) and bromobenzene (29 μL, 0.28 mmol). The crude product was purified on silica gel (100% hexanes to 50% DCM in hexanes) to afford the title compound as a white solid (80 mg, 73%).

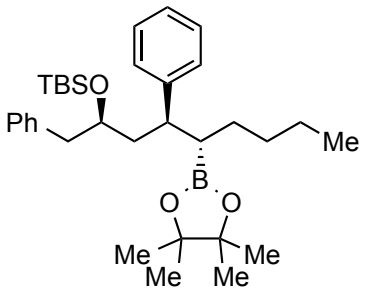
^{1}H NMR (500 MHz, $CDCl_3$): δ 0.95 (3H, d, J = 6.85 Hz), 0.98 (6H, s), 0.99 (6H, s), 1.04 (1H, dd, J = 15.2 Hz, 11.2 Hz), 1.24 (1H, dd, J = 15.2 Hz, 4.40 Hz), 1.76-1.81 (2H, m), 1.99 (3H, s), 2.02-2.08 (1H, m), 2.29-2.35 (1H, m), 2.48-2.54 (1H, m), 2.68-2.73 (1H, m), 4.59 (1H, quintet, J = 4.41 Hz), 7.07-7.08 (2H, m), 7.13-7.17 (4H, m), 7.23-7.26 (4H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 11.7, 21.2, 24.5, 24.6, 24.6, 30.6, 32.3, 43.2, 43.7, 75.9, 82.9, 125.8, 126.1, 127.9, 128.1, 128.3, 128.3, 141.9, 144.9, 170.6; ^{11}B NMR (160 MHz, $CDCl_3$): δ 33.5; IR (neat): 3027.0 (w), 2975.9 (m), 2931.7 (w), 1732.0 (s), 1495.1 (w), 1453.4 (m), 1365.8 (s), 1319.4 (m), 1234.8 (s), 1143.6 (s), 988.4 (m), 966.6 (m), 846.6 (m), 747.8 (m), 698.0 (s) cm^{-1}; HRMS-(DART-TOF) for $C_{27}H_{38}BO_4$ [M+H]: calculated: 437.2863, found: 437.2853.



28

(3R,4R,5S)-4-methyl-1,5-diphenyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexan-3-yl acetate. (28) Prepared according the general diboration/cross-coupling/protection procedure using (3R,4R)-4-methyl-1-phenylhex-5-en-3-ol (48 mg, 0.25 mmol) and bromobenzene (39 μL, 0.38 mmol). The crude product was purified on silica gel (100% hexanes to 50% DCM in hexanes) to afford the title compound as a white solid (83 mg, 76%).

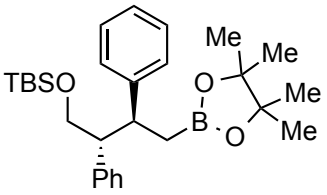
^{1}H NMR (500 MHz, $CDCl_3$): δ 0.75 (3H, d, J = 6.85 Hz), 0.97 (6H, s), 0.99 (6H, s), 1.11 (1H, dd, J = 15.16 Hz, 10.76 Hz), 1.33 (1H, dd, J = 15.16 Hz, 4.89 Hz), 1.80-1.90 (2H, m), 1.99 (3H, s), 1.96-2.04 (1H, m), 2.58-2.65 (2H, m), 2.72-2.77 (1H, m), 5.19 (1H, septet, J = 2.93 Hz), 7.09-7.15 (3H, m), 7.17-7.24 (5H, m), 7.26-7.30 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 11.8, 21.2, 24.5, 24.6, 32.2, 34.3, 42.8, 44.0, 74.7, 82.8, 125.9, 125.9, 128.0, 128.1, 128.2, 128.3, 128.3, 128.4, 141.7, 145.4, 170.9; ^{11}B NMR (160 MHz, $CDCl_3$): δ 33.4; IR (neat): 3060.4 (w), 3027.6 (w), 2976.9 (w), 2931.1 (w), 1731.1 (s), 1368.2 (s), 1320.8 (m), 1237.0 (s), 1143.4 (s), 966.3 (m), 908.8 (m), 846.8 (m), 735.2 (s), 698.7 (s) cm^{-1}; HRMS-(DART-TOF) for $C_{27}H_{38}BO_4$ [M+H]: calculated: 437.2863, found: 437.2868.



29

tert-butyl((1,4-diphenyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nonan-2-yl)oxy)dimethylsilane. (29) Prepared according the general diboration/cross-coupling/protection procedure using (Z)-1-phenylnon-4-en-2-ol (55 mg, 0.25 mmol) and bromobenzene (39 μL, 0.38 mmol). The crude product was purified on silica gel (100% hexanes to 50% DCM in hexanes) to afford the title compound as a colorless oil (85 mg, 63%).

^{1}H NMR (500 MHz, $CDCl_3$): δ -0.71 (3H, s), -0.40 (3H, s), 0.68 (9H, s), 0.75 (3H, t, J = 6.35 Hz), 1.01-1.14 (3H, m), 1.14-1.22 (3H, m), 1.26-1.29 (1H, m), 1.29 (12H, s), 1.76 (1H, ddd, J = 13.7 Hz, 10.3 Hz, 3.42 Hz), 1.90 (1H, td, J = 12.7 Hz, 2.93 Hz), 2.35 (1H, dd, J = 13.7 Hz, 9.29 Hz), 2.67 (1H, td, J = 13.7 Hz, 3.43 Hz), 2.99 (13.7 Hz, 1.96 Hz), 3.27 (1H, t, J = 9.78), 7.00-7.01 (2H, m), 7.09-7.12 (1H, m), 7.16-7.21 (5H, m), 7.29-7.32 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ -5.7, -5.1, 13.9, 17.8, 22.7, 25.0, 25.1, 25.8, 29.3, 31.3, 42.5, 44.7, 45.4, 72.2, 83.2, 125.7, 126.1, 127.8, 128.0, 128.3, 129.9, 140.1, 144.7; ^{11}B NMR (160 MHz, $CDCl_3$): δ 34.6; IR (neat): 2954.6 (w), 2927.2 (m), 2856.0 (w), 1454.1 (w), 1405.0 (m), 1317.5 (m), 1254.1 (m), 1142.6 (s), 1079.8 (m), 1066.5 (m), 830.4 (s), 809.2 (m), 773.9 (s), 698.9 (s) cm^{-1}; HRMS-(DART-TOF) for $C_{33}H_{54}BO_3Si$ [M+H]: calculated: 537.3935, found: 537.3924.

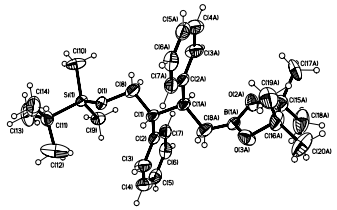


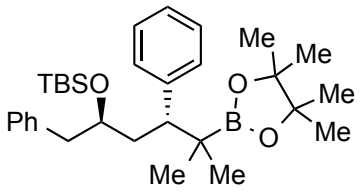
30

tert-butyl(2,3-diphenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butoxy)dimethylsilane. (30) Prepared according the general diboration/cross-coupling/protection procedure using 2-phenylbut-3-en-1-ol (37 mg, 0.25 mmol) and bromobenzene (39 μL, 0.38 mmol). The crude product was purified on silica gel (100% hexanes to 50% DCM in hexanes) to afford the title compound as a white solid (62 mg, 53%).

^{1}H NMR (500 MHz, $CDCl_3$): δ -0.28 (3H, s), -0.24 (3H, s), 0.73 (9H, s), 0.89 (6H, s), 0.92 (6H, s), 0.89-0.97 (2H, m), 2.81 (1H, quintet, J = 4.89 Hz), 3.24 (1H, sextet, J = 5.38 Hz), 3.48-3.51 (2H, m), 7.14-7.21 (2H, m), 7.23-7.28 (8H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ -5.8, -5.7, 18.2, 24.3, 24.6, 25.8, 42.8, 56.5, 65.5, 82.7, 126.0, 126.1, 127.8, 127.9, 128.3, 129.2, 142.9, 145.4; ^{11}B NMR (160 MHz, $CDCl_3$): δ 33.5; IR (neat): 3028.1 (w), 2977.0 (w), 2954.0 (w), 2928.0 (m), 2895.9 (w), 2856.1 (w), 1601.8 (w), 1494.2 (w), 1470.3 (w), 1452.8 (w), 1361.3 (m), 1322.4 (m), 1252.1(m), 1144.5 (m), 1105.5 (s), 834.1 (s), 773.4 (m), 756.2 (m), 698.1 (s) cm^{-1}; HRMS-(DART-TOF) for $C_{28}H_{44}BO_3Si$ [M+H]: calculated: 467.3153, found: 467.3156.

Proof of Stereochemistry: The relative stereochemistry was determined by crystal structure determination (as shown below).

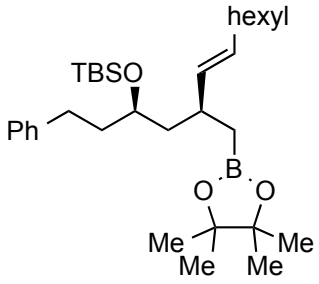




31

tert-butyldimethyl((5-methyl-1,4-diphenyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexan-2-yl)oxy)-silane. (31) Prepared according the general diboration/cross-coupling/protection procedure using 5-methyl-1-phenylhex-4-en-2-ol (48 mg, 0.25 mmol) and bromobenzene (39 μL, 0.38 mmol). The crude product was purified on silica gel (100% hexanes to 50% DCM in hexanes) to afford the title compound as a white solid (58 mg, 46%).

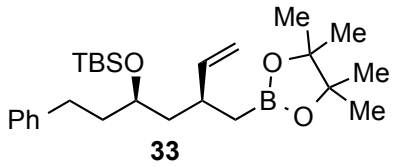
^{1}H NMR (500 MHz, $CDCl_3$): δ -0.13 (3H, s), -0.10 (3H, s), 0.72 (3H, s), 0.76 (3H, s), 0.91 (9H, s), 1.14 (6H, s), 1.17 (6H, s), 1.50-1.54 (1H, m), 1.97 (1H, td, J = 13.2 Hz, 1.96 Hz), 2.54 (1H, dd, J = 13.2 Hz, 7.82 Hz), 2.70 (1H, dd, J = 13.2 Hz, 4.4 Hz), 2.86 (1H, dd, J = 12.2 Hz, 1.95 Hz), 3.49 (1H, m), 6.88-6.89 (2H, m), 7.02-7.03 (2H, m), 7.12-7.15 (3H, m), 7.15-7.18 (1H, m), 7.20-7.23 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ -4.6, -4.1, 18.1, 20.7, 24.2, 24.6, 24.8, 26.0, 38.3, 45.3, 48.6, 71.9, 82.9, 125.7, 125.8, 127.2, 128.0, 129.7, 130.1, 138.9, 141.6; ^{11}B NMR (160 MHz, $CDCl_3$): δ 34.2; IR (neat): 3027.3 (w), 2953.2 (m), 2928.5 (m), 2889.4 (w), 2856.3 (w), 1471.2 (m), 1370.7 (m), 1343.8 (m), 1306.1 (m), 1252.8 (m), 1135.3 (s), 1083.2 (s), 1063.6 (s), 964.5 (m), 832.8 (s), 772.9 (s), 743.2 (s), 698.7 (s) cm^{-1}; HRMS-(DART-TOF) for $C_{31}H_{50}BO_3Si$ [M+H]: calculated: 509.3622, found: 509.3610.



32

tert-butyldimethyl(((E)-1-phenyl-5-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) methyl)tridec-6-en-3-yl)oxy)-silane. (32) Prepared according the general diboration/cross-coupling/protection procedure using 1-phenylhex-5-en-3-ol (44 mg, 0.25 mmol) and (E)-1-chlorooct-1-ene (63 μL, 0.38 mmol). Cross-coupling run with 2.5 mol% $Pd(OAc)_2$ and 3 mol% RuPhos. The crude product was purified on silica gel (100% hexanes to 50% DCM in hexanes) to afford the title compound as a colorless oil (71 mg, 54%).

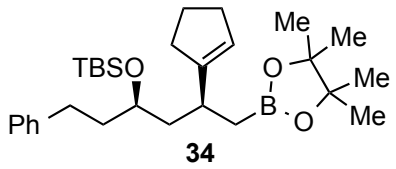
^{1}H NMR (500 MHz, $CDCl_3$): δ 0.05 (6H, s), 0.77-0.90 (2H, m), 0.89 (3H, t, J = 6.8 Hz), 0.91 (9H, s), 1.22 (12H, s), 1.24-1.34 (8H, m), 1.43-1.56 (2H, m), 1.67 (1H, sextet, J = 5.9 Hz), 1.81-1.87 (1H, m), 1.93-1.95 (2H, m), 2.21-2.27 (1H, m), 2.57 (1H, td, J = 13.7 Hz, 4.9 Hz), 2.76 (1H, td, J = 13.7 Hz, 5.4 Hz), 3.71 (1H, septet, J = 3.9 Hz), 5.22 (1H, dd, J = 15.2 Hz, 8.3 Hz), 5.33 (1H, dt, J = 15.2 Hz, 6.9 Hz), 7.15-7.20 (3H, m), 7.26-7.29 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$): -4.4, -4.2, 14.1, 18.1, 22.6, 24.8, 24.9, 24.9, 25.0, 26.0, 28.9, 29.6, 31.4, 31.8, 32.5, 35.5, 38.2, 45.2, 70.2, 82.9, 125.5, 128.2, 128.4, 129.3, 135.5, 143.1; ^{11}B NMR (160 MHz, $CDCl_3$): δ 33.5; IR (neat): 2954.5 (w), 2926.0 (m), 2855.3 (w), 1461.7 (w), 1369.6 (m), 1317.2 (m), 1253.6 (m), 1144.3 (m), 1079.2 (m), 1059.8 (m), 967.7 (m), 833.3 (s), 772.6 (s), 697.9 (m) cm^{-1}; HRMS-(DART-TOF) for $C_{32}H_{58}BO_3Si$ [M+H]: calculated: 529.4248, found: 529.4262.



33

tert-butyldimethyl((1-phenyl-5-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)hept-6-en-3-yl)oxy)-silane. (33) Prepared according the general diboration/cross-coupling/protection procedure using 1-phenylhex-5-en-3-ol (44 mg, 0.25 mmol) and 1,2-dichloroethane (59 μL, 0.75 mmol). KOtBu (168 mg, 1.5 mmol) was used instead of KOH. Cross-coupling run with 2.5 mol% $Pd(OAc)_2$ and 3 mol% RuPhos. The crude product was purified on silica gel (100% hexanes to 50% DCM in hexanes) to afford the title compound as a colorless oil (83 mg, 75%).

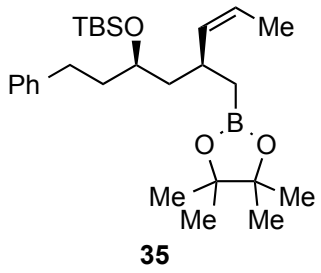
^{1}H NMR (500 MHz, $CDCl_3$): δ 0.05 (6H, s), 0.79-0.91 (2H, m), 0.91 (9H, s), 1.22 (12H, s), 1.49-1.58 (2H, m), 1.64-1.71 (1H, m), 1.80-1.87 (1H, m), 2.33 (1H, q, J = 6.9 Hz), 2.59 (1H, td, J = 13.7 Hz, 5.4 Hz), 2.75 (1H, td, J = 13.2 Hz, 5.4 Hz), 3.72 (1H, quintet, J = 6.4 Hz), 4.89 (1H, dd, J = 10.3 Hz, 1.5 Hz), 4.93 (1H, d, J = 17.1 Hz), 5.67 (1H, quintet, J = 9.2 Hz), 7.15-7.20 (3H, m), 7.26-7.29 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ -4.4, -4.3, 18.1, 24.9, 26.0, 31.3, 36.6, 38.3, 44.5, 70.0, 83.0, 113.1, 125.5, 128.2, 128.4, 143.1, 144.1; ^{11}B NMR (160 MHz, $CDCl_3$): δ 33.4; IR (neat): 2977.4 (w), 2952.9 (w), 2928.1 (m), 2856.4 (w), 1471.2 (w), 1368.3 (s), 1318.6 (m), 1254.4 (m), 1144.2 (s), 1061.3 (s), 967.6 (m), 833.8 (s), 772.9 (s), 698.1 (m) cm^{-1}; HRMS-(DART-TOF) for $C_{26}H_{46}BO_3Si$ [M+H]: calculated: 445.3309, found: 445.3320.



34

tert-butyl((5-(cyclopent-1-en-1-yl)-1-phenyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexan-3-yl)oxy)dimethylsilane. (34) Prepared according the general diboration/cross-coupling/protection procedure using 1-phenylhex-5-en-3-ol (44 mg, 0.25 mmol) and 1-chlorocyclopent-1-ene (37 μL, 0.38 mmol). Cross-coupling run with 10 mol% $Pd(OAc)_2$ and 12 mol% RuPhos. The crude product was purified on silica gel (100% hexanes to 50% DCM in hexanes) to afford the title compound as a colorless oil (62 mg, 51%).

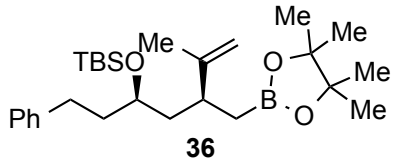
^{1}H NMR (500 MHz, $CDCl_3$): δ 0.03 (3H, s), 0.04 (3H, s), 0.90 (9H, s), 0.83-0.94 (2H, m), 1.20 (12H, s), 1.48-1.53 (1H, m), 1.59-1.70 (2H, m), 1.77-1.87 (3H, m), 2.23 (2H, t, J = 7.8 Hz), 2.14-2.27 (2H, m), 2.52-2.60 (1H, m), 2.59 (1H, td, J = 11.7 Hz, 4.9 Hz), 2.74 (1H, td, J = 13.2 Hz, 4.9 Hz), 3.61 (1H, septet, J = 4.9 Hz), 5.30 (1H, s), 7.15-7.19 (3H, m), 7.25-7.28 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$): -4.5, -4.3, 18.1, 23.4, 24.8, 24.8, 26.0, 31.1, 31.2, 32.0, 33.6, 38.2, 43.4, 70.2, 82.9, 123.6, 125.5, 128.2, 128.4, 143.1, 148.6; ^{11}B NMR (160 MHz, $CDCl_3$): δ 33.6; IR (neat): 2976.9 (w), 2928.1 (w), 2855.3 (w), 1461.7 (w), 1368.6 (s), 1313.4 (m), 1252.9 (m), 1144.2 (m), 1031.1 (w), 967.7 (w), 938.5 (w), 808.4 (s), 772.5 (s), 746.7 (w), 698.1 (m) cm^{-1}; HRMS-(DART-TOF) for $C_{29}H_{50}BO_3Si$ [M+H]: calculated: 485.3622, found: 485.3627.



35

tert-butyldimethyl(((Z)-1-phenyl-5-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)oct-6-en-3-yl)oxy)silane. (35) Prepared according the general diboration/cross-coupling/protection procedure using 1-phenylhex-5-en-3-ol (44 mg, 0.25 mmol) and (Z)-1-chloroprop-1-ene (31 μL, 0.38 mmol). Cross-coupling run with 2.5 mol% $Pd(OAc)_2$ and 3 mol% RuPhos. The crude product was purified on silica gel (100% hexanes to 50% DCM in hexanes) to afford the title compound as a colorless oil (78 mg, 68%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.05 (3H, s), 0.06 (3H, s), 0.75 (1H, dd, J = 15.7 Hz, 8.3 Hz), 0.86 (1H, dd, J = 15.2 Hz, 5.7 Hz), 0.91 (9H, s), 1.21 (12H, s), 1.43-1.49 (1H, m), 1.56 (1H, t, J = 3.9 Hz), 1.59 (3H, dd, J = 6.9 Hz, 1.5 Hz), 1.67 (1H, sextet, J = 5.4 Hz), 1.79-1.86 (1H, m), 2.56 (1H, td, J = 11.7 Hz, 4.9 Hz), 2.62 -2.69 (1H, m), 2.76 (1H, td, J = 13.7 Hz, 5.4 Hz), 3.65 (1H, septet, J = 4.4 Hz), 5.17 (1H, td, J = 10.3 Hz, 1.5 Hz), 5.34-5.40 (1H, m), 7.15-7.19 (3H, m), 7.26-7.29 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$): -4.4, -4.2, 13.2, 18.1, 24.8, 24.9, 26.0, 29.6, 31.6, 38.7, 45.5, 70.3, 82.9, 122.3, 125.5, 128.3, 128.4, 136.6, 143.1; ^{11}B NMR (160 MHz, $CDCl_3$): δ 33.6; IR (neat): 2977.5 (w), 2952.4 (w), 2928.5 (m), 2856.6 (w), 1461.9 (w), 1405.7 (s), 1362.2 (m), 1320.3 (m), 1253.9 (m), 1144.2 (s), 1062.9 (s), 967.8 (m), 833.5 (s), 772.4 (s), 730.7 (m), 697.7 (m) cm^{-1}; HRMS-(DART-TOF) for $C_{27}H_{48}BO_3Si$ [M+H]: calculated: 459.3466, found: 459.3489.



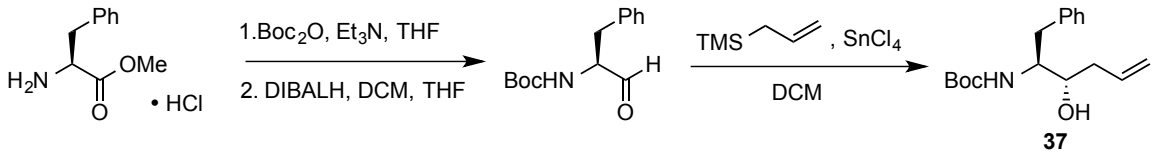
36

tert-butyldimethyl((6-methyl-1-phenyl-5-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)hept-6-en-3-yl)oxy)silane. (36) Prepared according the general diboration/cross-coupling/protection procedure using 1-phenylhex-5-en-3-ol (44 mg, 0.25 mmol) and 2-chloroprop-1-ene (32 μL, 0.38 mmol). Cross-coupling run with 10 mol% $Pd(OAc)_2$ and 12 mol% RuPhos. The crude product was purified on silica gel (100% hexanes to 50% DCM in hexanes) to afford the title compound as a colorless oil (80 mg, 70%).

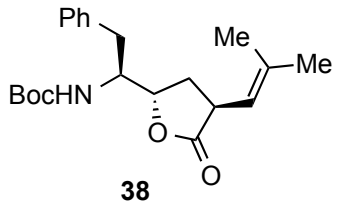
^{1}H NMR (500 MHz, $CDCl_3$): δ 0.04 (3H, s), 0.05 (3H, s), 0.91 (9H, s), 0.82-0.93 (2H, m), 1.21 (12H, s), 1.47-1.52 (1H, m), 1.57-1.64 (1H, m), 1.66 (3H, s), 1.69 (1H, quintet, J = 5.9 Hz), 1.80-1.87 (1H, m), 2.36-2.43 (1H, m), 2.58 (1H, td, J = 11.7 Hz, 4.9 Hz), 2.75 (1H, td, J = 12.7 Hz, 5.2 Hz), 3.61-3.65 (1H, m), 4.66 (1H, s), 4.68 (1H, s), 7.15-7.19 (3H, m), 7.26-7.28 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$): -4.4, -4.3, 18.1, 18.2, 24.8, 24.9, 25.9, 31.1, 38.2, 39.5, 42.8, 70.1, 83.0, 110.4, 125.5, 128.2, 128.4, 143.2, 149.1; ^{11}B NMR (160 MHz, $CDCl_3$): δ 33.5; IR (neat): 2977.3 (w), 2928.8 (w), 2856.5 (w), 1461.5 (w), 1361.9 (m), 1317.1 (m), 1253.5 (m), 1144.1 (s), 1061.5 (m), 967.7 (m), 833.0 (s), 772.3 (s), 697.9 (m) cm^{-1}; HRMS-(DART-TOF) for $C_{27}H_{48}BO_3Si$ [M+H]: calculated: 459.34658, found: 459.34576.

VIII. Synthesis of Chemokine Antagonist

Tert-butyl (S)-(1-oxo-3-phenylpropan-2-yl)carbamate and tert-butyl ((2S,3S)-3-hydroxy-1-phenylhex-5-en-2-yl)carbamate (**37)** were prepared following literature procedures (shown below).[8] All spectral data are in accord with the literature.[8]



37

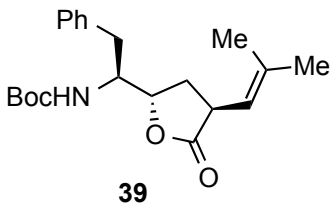


38

tert-butyl ((S)-1-((2S,4S)-4-(2-methylprop-1-en-1-yl)-5-oxotetrahydrofuran-2-yl)-2-phenylethyl)carbamate. (38) To an oven-dried 2-dram vial with magnetic stir bar was added tert-butyl ((2S,3S)-3-hydroxy-1-phenylhex-5-en-2-yl)carbamate (73 mg, 0.25 mmol), Cs_2CO_3 (26 mg, 75 μmol), $B_2(pin)_2$ (95 mg, 0.38 mmol), tetrahydrofuran (1 mL, [substrate] = 0.25 M) and methanol (0.17 mL, 4.25 mmol). The vial was sealed with a teflon septum cap and heated to 70 ºC for 12 h. The reaction was cooled to room temperature and concentrated *in vacuo* (ensuring that all methanol has been removed from the residue). The flask was brought to a dry box and charged with solid potassium hydroxide (42 mg, 0.75 mmol), $Pd(OAc)_2$/RuPhos (added as a 1:1.2 solution in THF (0.025 M); 0.25 mL for 2.5 mol% $Pd(OAc)_2$), tetrahydrofuran (0.95 mL), toluene (1.2 mL) and 1-chloro-2-methylpropene (37 μL, 0.38 mmol). The vial was sealed, removed from the dry box, and H_2O (sparged with N_2 for 30 min, 0.23 mL) was added through the teflon septum cap. The vial was heated to 70 ºC and stirred for 12 h. The reaction mixture was transferred to a 25-mL round bottom flask and cooled to 0 ºC (ice/water) and charged with 3 M sodium hydroxide (0.5 mL), and 30% hydrogen peroxide (0.5 mL). The reaction was gradually warmed to room temperature and allowed to stir for 4 h at which time the vial was diluted with ethyl acetate and the aqueous and organic layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 10 mL) and the combined organics were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation into 20 mL vial. To the residue was added DCM (2.8 mL), H_2O (0.83 mL), $PhI(OAc)_2$ (0.36 g, 1.10 mmol), and TEMPO (8 mg, 0.05 mmol). The reaction was allowed to stir for 4 h at room temperature. The reaction mixture was quenched with sat. $NaHCO_3$ (4 mL). The layers were allowed to separate and the aqueous layer was extracted with DCM (3 x 10 mL). The combined organic layers were washed with brine, dried with Na_2SO_4, filtered and concentrated with rotatory evaporation. The crude material was purified on SiO_2 (5% to 15% EtOAc/hexanes, stain with $KMnO_4$) to afford the title compound as a colorless oil (60 mg, 67% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.39 (9H, s), 1.69 (3H, s), 1.73 (3H, s), 1.92-1.98 (1H, m), 2.40-2.46 (1H, m), 2.86-2.94 (2H, m), 3.52 (1H, q, J = 8.80 Hz), 4.03 (1H, q, J = 7.83 Hz), 4.50 (1H, t, J = 6.85 Hz), 4.56 (1H, d, J = 9.29 Hz), 5.04 (1H, d, J = 8.80 Hz), 7.23-7.26 (3H, m), 7.29-7.32 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 18.3, 25.6, 28.0, 28.2, 32.0, 39.2, 39.6, 54.6, 78.1, 80.0, 119.7, 126.7, 128.6, 129.3, 137.1, 137.8, 155.8, 178.7; IR (neat): 3330.1 (br), 2975.5 (w), 2931.3 (w), 1767.7 (s), 1691.6 (s), 1517.3 (m), 1365.1

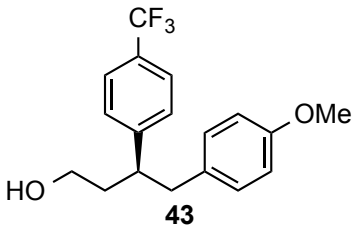
(m), 1246.4 (m), 1159.8 (s), 1060.9 (m), 960.9 (w), 736.5 (w), 699.4 (s) cm^{-1}; HRMS-(DART-TOF) for $C_{21}H_{33}N_2O_4$ [M+NH_4]: calculated: 377.2440, found: 377.2438.



39

tert-butyl ((S)-1-((2S,4R)-4-isobutyl-5-oxotetrahydrofuran-2-yl)-2-phenylethyl)-carbamate. (39) To an oven-dried 10 mL round bottom flask was added Pd/C (4.2 mg). A solution of tert-butyl ((S)-1-((2S,4S)-4-(2-methylprop-1-en-1-yl)-5-oxotetrahydrofuran-2-yl)-2-phenylethyl)carbamate (14 mg, 39 μmol) and methanol (1.5 mL) were added to the flask and it was sealed with a rubber septum. The flask was evacuated and refilled with H_2 gas three times and allowed to stir for 1 h at room temperature under 1 atm of H_2. The reaction mixture was filtered through a plug of celite and washed with EtOAc. The solution was concentrated with rotatory evaporation to afford the title compound cleanly as a colorless oil (13.8 mg, 98% yield). All spectral data are in accord with the literature.[9]

IX. Synthesis of Vitronectin Receptor Antagonist



43

(S)-4-(4-methoxyphenyl)-3-(4-(trifluoromethyl)phenyl)-butan-1-ol. (43) To an oven-dried 16-mL vial with magnetic stir bar in the dry box was added $Pt(dba)_3$ (4.5 mg, 5.0 μmol), (S,S)-3,5-di-iso-propylphenylTADDOLPPh (5.5 mg, 6.0 μmol), $B_2(pin)_2$ (133 mg, 525 μmol) and tetrahydrofuran (0.5 mL). The vial was sealed with a teflon septum cap, removed from the dry box, and heated to 80 °C in an oil bath for 20 minutes. The vial was cooled to room temperature, returned to the dry box and charged with (but-3-en-1-yloxy)(tert-butyl)dimethylsilane (115 μL, 500 μmol). The vial was sealed, removed from the dry box and stirred at 60 °C for 3 h. The vial was cooled to room temperature, returned to the dry box and charged with solid potassium hydroxide (84 mg, 1.50 mmol), $Pd(OAc)_2$ (1.1 mg, 5.0 μmol)/RuPhos (2.3 mg, 6.0 μmol) (added as a 1:1.2 solution in THF (1 mL)), tetrahydrofuran (3.05 mL) and 4-bromoanisole (66 μl, 525 μmol). The vial was sealed, removed from the dry box, and H_2O (sparged with N_2 for 30 min, 0.45 mL) was added through the teflon septum cap. The vial was heated to 70 °C and stirred for 12 h. The reaction mixture was cooled to room temperature and water (4 mL) was added. The layers were allowed to separate and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation in a 4-dram vial. The crude boronate was dissolved in MeOH (4 mL) and *p*-TsOHxH_2O (5 mg). The vial was capped and stirred at room temperature for 1 hour and concentrated, ensuring all the methanol was removed. The crude deprotected intermediate was returned to the dry box and charged with solid potassium hydroxide (84.0 mg, 1.50 mmol), $Pd_2(dba)_3$/RuPhos (added as a 1:2 solution in THF (0.01 M); 0.25 mL for 0.5 mol% $Pd_2(dba)_3$, tetrahydrofuran (2.0 mL), toluene (2.3 mL) and 4-bromobenzotrifluoride (77 μL, 0.55 mmol). The vial was sealed, removed from the dry box, and H_2O (sparged with N_2 for 30 min, 0.45 mL) was added through the teflon septum cap. The vial was heated to 70 ºC and stirred for 16 h. The reaction mixture was cooled to room temperature and sat. NH_4Cl (aq.) (3 mL) was added. The layers were allowed to separate and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude material was purified on SiO_2 (10% to 25% EtOAc/hexanes, stain with CAM) to afford the title compound as a colorless oil (101 mg, 62% yield).

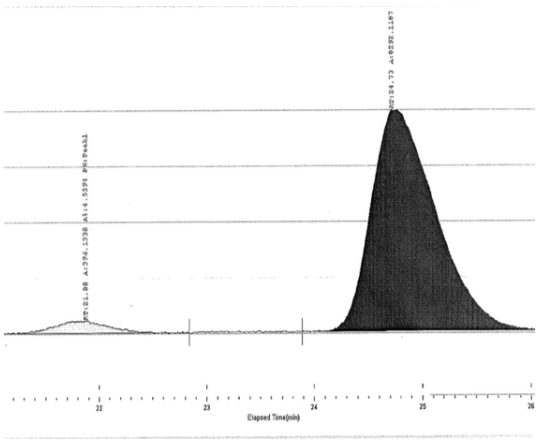
^{1}H NMR (600 MHz, $CDCl_3$): δ 1.82 – 1.88 (1H, m), 1.98 – 2.04 (1H, m), 2.83 (1H, dd, J = 13.5 Hz, 8.22 Hz), 2.88 (1H, dd, J = 14.1 Hz, 7.04 Hz), 3.04 – 3.09 (1H, m), 3.38 – 3.42 (1H, m), 3.51 – 3.55 (1H, m), 3.76 (3H, s), 6.75 (2H, d, J = 8.22 Hz), 6.92 (2H, d, J = 8.80 Hz), 7.23 (2H, d, J = 8.22), 7.51 (2H, d, J = 8.22 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): 38.0, 42.6, 44.3, 55.2, 60.7, 113.6, 125.3, 125.3, 125.3, 125.3, 128.1, 130.0, 131.6, 148.6, 157.9; ^{19}F NMR (564 MHz, $CDCl_3$): -62.3; IR (neat): 3365.8 (w), 2935.4 (m), 2837.7 (w), 1613.8 (m), 1511.3 (s), 1323.3 (s), 1244.9 (s), 1161.4 (s), 1113.9 (s), 1068.1 (s), 1035.2 (s), 1017.1 (s), 837.6 (m) cm^{-1}; HRMS-(DART-TOF) for $C_{18}H_{23}F_3NO_2$

[M+NH_4]: calculated: 342.1681, found: 342.1667. $[\alpha]_D^{20}$ = -33.4 (c = 1.02, $CHCl_3$, l= 50 nm).

Analysis of Stereochemistry: The title compound was compared to the racemic analogue derived from the racemic diboration of (but-3-en-1-yloxy)(tert-butyl)dimethylsilane. The resulting racemic diboron was transformed into 4-(4-methoxyphenyl)-3-(4-(trifluoromethyl)phenyl)butan-1-ol. as described for the enantioenriched variant.

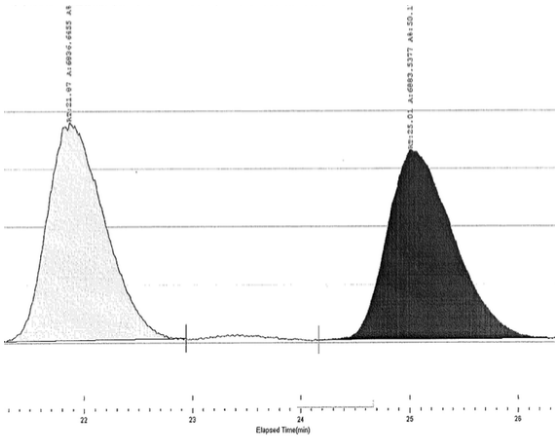
Chiral SFC (Chiracel, OD-H, 35 °C, 3 mL/min, 5% Isopropanol, 100 bar, 210-270nm) – analysis of (S)-4-(4-methoxyphenyl)-3-(4-(trifluoromethyl)phenyl)butan-1-ol.

Reaction Products



Peak No	% Area	Area	RT (min)
1	4.5594	396.1338	21.88
2	95.4406	8292.1187	24.73
Total:	100	8688.2525	

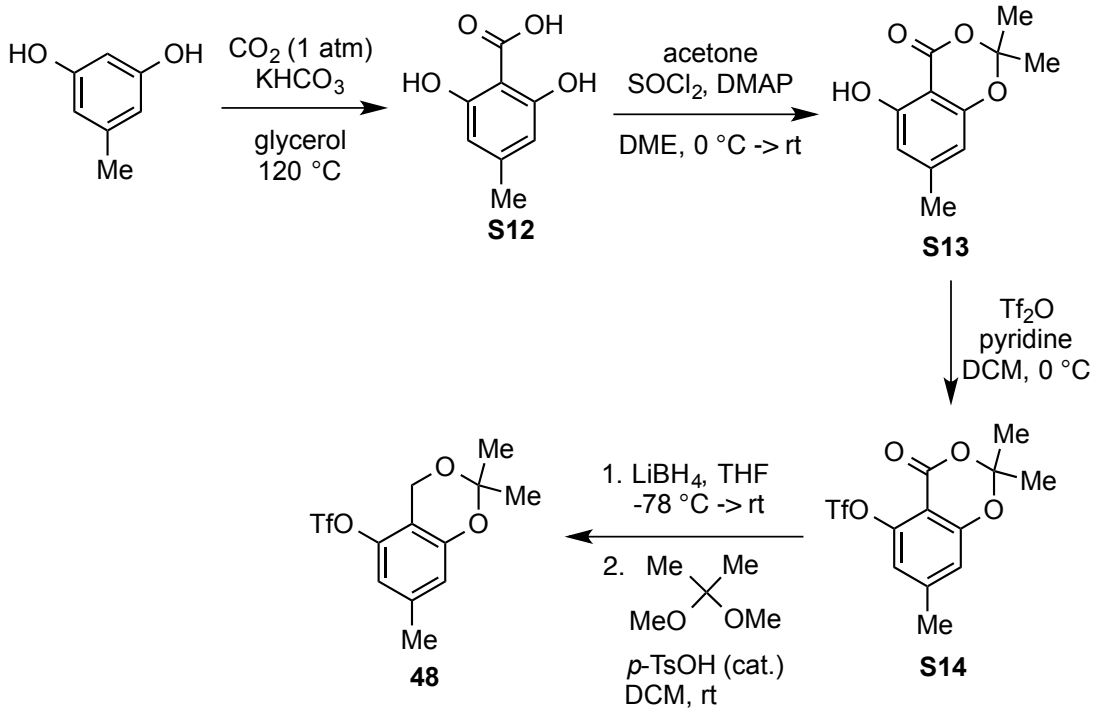
Racemic

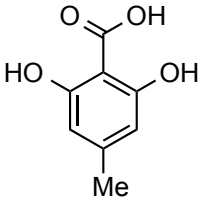


Peak No	% Area	Area	RT (min)
1	49.8291	6836.6455	21.87
2	50.1709	6883.5377	25.01
Total:	100	13720.1832	

X. Synthesis of Debromohamigeran E

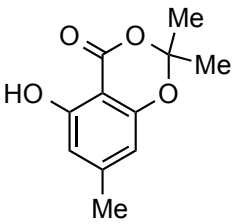
2,2,7-trimethyl-4H-benzo[d][1,3]dioxin-5-yl trifluoromethanesulfonate (**48**) was synthesized using the route shown below.





2,6-dihydroxy-4-methylbenzoic acid. Prepared following literature procedures.[10] All spectral data are in accord with the literature.

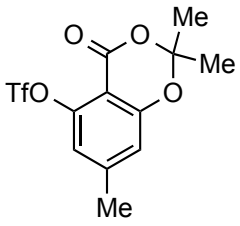
S12



S13

5-hydroxy-2,2,7-trimethyl-4H-benzo[d][1,3]dioxin-4-one. To an oven-dried vial with magnetic stir bar and a teflon septum cap was added 2,6-dihydroxy-4-methylbenzoic acid (5.80 g, 34.5 mmol), DMAP (0.21 g, 1.72 mmol) and 1,2-dimethoxyethane (26 mL, [substrate] = 1.33 M) under N_2. The vial was cooled to 0 ºC and added acetone (3.29 mL, 44.8 mmol) and $SOCl_2$ (3.26 mL, 44.8 mmol). Stir at 0 ºC for 1 hour and allowed to warm to room temperature. Stir at room temperature for 23 hours. Quench the reaction with sat. $NaHCO_3$. The layers were allowed to separate and the aqueous layer was extracted with Et_2O (3 x 40 mL). The combined organic layers was dried with $MgSO_4$, filtered and concentrated with rotatory evaporation. The crude material was purified on SiO_2 (2.5% to 10% EtOAc in hexanes, stained with CAM) to afford the title

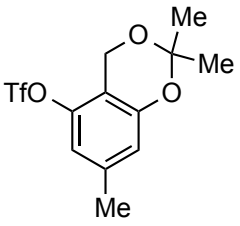
compound as a white solid (5.06 g, 71% yield). All spectral data are in accord with the literature.[11]



S14

2,2,7-trimethyl-4-oxo-4H-benzo[d][1,3]dioxin-5-yl trifluoromethanesulfonate. To an oven-dried vial with magnetic stir bar and a teflon septum cap was added 5-hydroxy-2,2,7-trimethyl-4H-benzo[d][1,3]dioxin-4-one (5.71 g, 27.4 mmol) and dichloromethane (27.4 mL, [substrate] = 1.0 M) under N_2. The vial was cooled to 0 ºC and added pyridine (7.95 mL, 98.7 mmol) and Tf_2O (7.50 mL, 32.91 mmol). Stir at 0 ºC for 1.5 hours. Quench the reaction with H_2O. The layers were allowed to separate and the aqueous layer was extracted with Et_2O (3 x 30 mL). The combined organic layers was dried with $MgSO_4$, filtered and concentrated with rotatory evaporation. The crude material was purified on SiO_2 (5% to 10% EtOAc in hexanes, stained with CAM) to afford the title compound as a white solid (8.86 g, 95% yield).

^{1}H NMR (600 MHz, $CDCl_3$): δ 1.71 (6H, s), 2.41 (3H, s), 6.78 (1H, s), 6.84 (1H, s); ^{13}C NMR (150 MHz, $CDCl_3$): 22.0, 25.4, 105.5, 106.7, 117.4, 118.0, 118.7 (q, J = 321 Hz), 148.4, 148.7, 157.2; IR (neat): 1744.4 (s), 1630.0 (s), 1425.0 (s), 1282.9 (s), 1197.4 (s), 1159.5 (s), 1135.9 (s), 1048.8 (s), 987.0 (s), 854.8 (s), 600.2 (s) cm^{-1}; ^{19}F NMR (564 MHz, $CDCl_3$): -73.2; HRMS-(DART-TOF) for $C_{12}H_{12}F_3O_6S$ [M+H]: calculated: 341.03067, found: 341.03106.



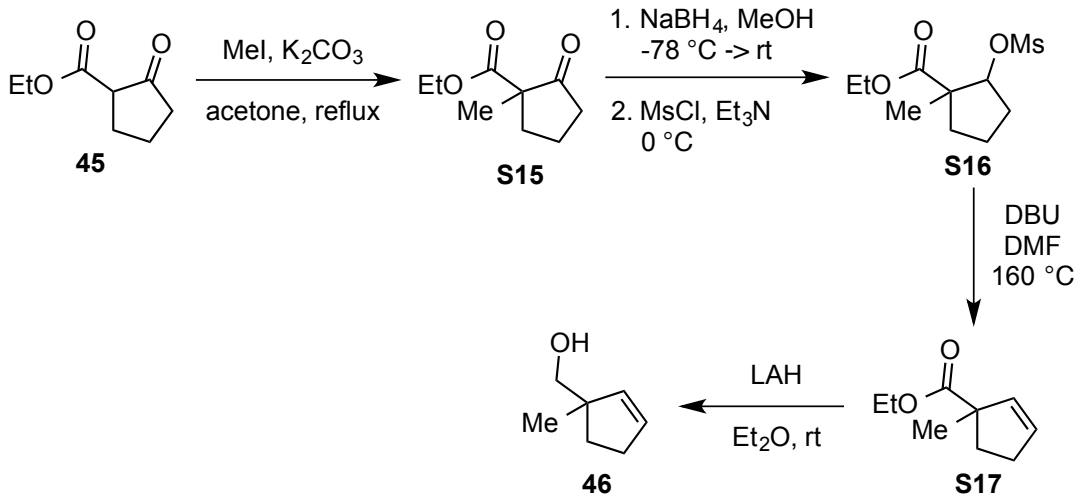
48

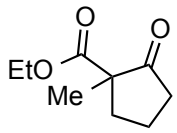
2,2,7-trimethyl-4H-benzo[d][1,3]dioxin-5-yl trifluoromethanesulfonate. (48) To an oven-dried vial with magnetic stir bar and a teflon septum cap was added 2,2,7-trimethyl-4-oxo-4H-benzo[d][1,3]dioxin-5-yl trifluoromethanesulfonate (8.65 mg, 25.4 mmol) and THF (150 mL) under N_2. The vial was cooled to -78 ºC and added 2M $LiBH_4$ in THF (50.8 mL, 102 mmol). Slowly warm the reaction to room temperature and stir overnight. Quench the reaction 1M HCl (aq.). The layers were allowed to separate and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layers was dried with Na_2SO_4, filtered and concentrated with rotatory evaporation. The crude material was put through a plug of SiO_2 and wash with EtOAc. To an oven-dried vial with magnetic stir bar and a teflon septum cap was added the crude alcohol and DCM (254 mL, [substrate] = 0.1 M) under N_2. Add 2,2-dimethoxypropane (15.57 mL, 127.1 mmol) and *p*-TsOH (cat.). Stir the reaction at room temperature for 1 hour. Quench the reaction with sat. $NaHCO_3$. The layers were allowed to separate and the aqueous layer was extracted with DCM (3 x 30 mL). The combined organic layers was dried with Na_2SO_4, filtered and concentrated with rotatory evaporation. The crude material was purified on SiO_2 (2.5% to 10% EtOAc in hexanes, stained with CAM) to afford the title compound as a colorless oil (3.90 g, 47% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.54 (3H, s). 1.55 (3H, s), 2.32 (3H, s), 4.86 (2H, s), 6.68 (2H, s); ^{13}C NMR (150 MHz, $CDCl_3$): 21.3, 24.5, 57.1, 100.1, 110.1, 113.4, 117.5, 118.6 (q, J = 320 Hz), 139.4, 145.0, 152.5; ^{19}F NMR (470 MHz, $CDCl_3$): -73.7; IR (neat):

1635.2 (w), 1578.1 (w), 1455.3 (m), 1207.3 (s), 1138.0 (s), 975.0 (m), 842.3 (m), 824.6 (m), 610.9 (m) cm^{-1}; HRMS-(DART-TOF) for $C_{12}H_{13}F_3O_5S$ [M]: calculated: 326.04358, found: 326.04474.

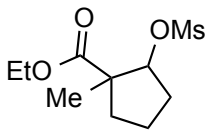
(1-methylcyclopent-2-en-1-yl)methanol (**46**) was synthesized using the route shown below.





S15

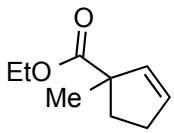
ethyl 1-methyl-2-oxocyclopentane-1-carboxylate. To an oven-dried round-bottomed flask with magnetic stir bar and septum was added ethyl 2-oxocyclopentanecarboxylate (4.45 mL, 30 mmol) and acetone (99 mL). Add potassium carbonate (8.29 g, 60.0 mmol) and MeI (3.74 mL, 60.0 mmol) to the flask. Heat the reaction to reflux for 4 hours. Add MeI (3.74 mL, 60.0 mmol). Stir the reaction overnight at reflux. Cool the flask to room temperature and filter the reaction mixture through a plug of SiO_2 and wash with acetone. The collected organic fraction was concentrated with rotatory evaporation. The crude material was purified on SiO_2 (2.5% to 10% EtOAc in hexanes, stained with CAM) to afford the title compound as a colorless oil (4.44 g, 87% yield). All spectral data are in accord with the literature.[12]



S16

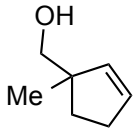
ethyl 1-methyl-2-((methylsulfonyl)oxy)cyclopentane-1-carboxylate. To an oven-dried round-bottomed flask with magnetic stir bar and septum was added MeOH (31 mL) and $NaBH_4$ (1.18 g, 31.3 mmol). Cool the flask to -78 ºC and add ethyl 1-methyl-2-oxocyclopentane-1-carboxylate (4.44 g, 26.1 mmol) in MeOH (51 mL). Slowly warm the reaction to room temperature and stir for two hours. Quench the reaction with brine. The layers were allowed to separate and the aqueous layer was extracted with DCM (3 x 60 mL). The combined organic layers was dried with Na_2SO_4, filtered and concentrated with rotatory evaporation. The crude alcohol was taken up in DCM (57 mL) and cooled to 0 ºC. Add Et_3N (10.9 mL, 78.3 mmol) and MsCl (2.63 mL, 33.9 mmol) to the flask dropwise. Allow the reaction to stir at 0 ºC for two hours. Quench the reaction with water. The layers were allowed to separate and the aqueous layer was extracted with

DCM (3 x 30 mL). The combined organic layers was dried with Na_2SO_4, filtered and concentrated with rotatory evaporation. The crude material was purified on SiO_2 (15% to 30% EtOAc in hexanes, stained with CAM) to afford the title compound as a colorless oil (4.54 g, 74% yield). All spectral data are in accord with the literature.[12]



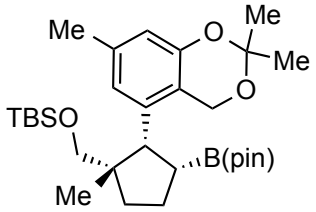
S17

ethyl 1-methylcyclopent-2-ene-1-carboxylate. Prepared following literature procedures from ethyl 1-methyl-2-((methylsulfonyl)oxy)cyclopentane-1-carboxylate.[12] All spectral data are in accord with the literature. [12]



46

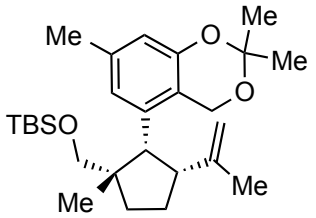
(1-methylcyclopent-2-en-1-yl)methanol. (46) Prepared following literature procedures from ethyl 1-methylcyclopent-2-ene-1-carboxylate.[12] All spectral data are in accord with the literature. [12]



49

tert-butyldimethyl((1-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(2,2,7-trimethyl-4H-benzo[d][1,3]-dioxin-5-yl)cyclopentyl)methoxy)silane. (49) To an oven-dried 2-dram vial with magnetic stir bar was added (1-methylcyclopent-2-en-1-yl)methanol (1.34 g, 12.0 mmol), Cs_2CO_3 (1.17 g, 3.58 mmol), $B_2(pin)_2$ (4.55 g, 17.9 mmol), tetrahydrofuran (23.9 mL, [substrate] = 0.5 M) and methanol (8.23 mL, 203 mmol). The vial was sealed with a teflon septum cap and heated to 70 ºC for 12 h. The reaction was cooled to room temperature and concentrated *in vacuo* (ensuring that all methanol has been removed from the residue). The flask was brought to a dry box and charged with solid potassium hydroxide (2.01 g, 35.9 mmol), $Pd_2(dba)_3$ (274 mg, 0.30 mmol), RuPhos (279 mg, 0.60 mmol), tetrahydrofuran (54 mL), toluene (54 mL) and 2,2,7-trimethyl-4H-benzo[d][1,3]dioxin-5-yl trifluoromethane-sulfonate (3.90 g, 12.0 mmol). The vial was sealed, removed from the dry box, and H_2O (sparged with N_2 for 30 min, 10.8 mL) was added through the teflon septum cap. The vial was heated to 70 ºC and stirred for 12 h. The reaction mixture was cooled to room temperature and sat. NH_4Cl (aq.) (15 mL) was added. The layers were allowed to separate and the aqueous layer was extracted with dichloromethane (3 x 40 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation in a 4-dram vial. To the residue was added dichloromethane (54 mL) and imidazole (7.22 g, 106 mmol). The reaction mixture was cooled to 0 °C and a solution of TBSCl (5.35 g, 35.5 mmol) in toluene (12 mL). The reaction was sealed and allowed to warm to room temperature overnight. The reaction mixture was quenched with sat. NH_4Cl (20 mL). The layers were allowed to separate and the aqueous layer was extracted with dichloromethane (3 x 30 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude material was purified on SiO_2 (1% to 2% EtOAc in hexanes, stained with CAM) to afford the title compound as a white solid (2.70 g, 43% yield).

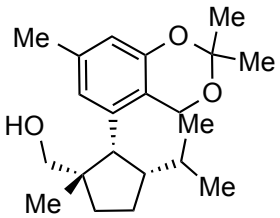
^{1}H NMR (600 MHz, $CDCl_3$): δ -0.14 (3H, s), -0.14 (3H, s), 0.79 (9H, s), 0.84 (6H, s), 0.96 (6H, s), 1.13 (3H, s), 1.46 (3H, s), 1.50 (3H, s), 1.70 – 1.76 (1H, m), 1.99 – 2.05 (1H, m), 2.09 – 2.17 (2H, m), 2.21 (3H, s), 2.82 (1H, d, J = 7.63 Hz), 3.08 (2H, s), 4.84 (1H, d, J = 14.7 Hz), 5.00 (1H, d, J = 14.1 Hz), 6.39 (1H, s), 6.40 (1H, s); ^{13}C NMR (150 MHz, $CDCl_3$): -5.8, -5.8, 18.4, 21.5, 23.0, 24.5, 24.6, 24.8, 25.8, 26.0, 26.2, 35.3, 49.4, 50.8, 60.3, 68.7, 82.6, 98.0, 114.8, 115.7, 120.4, 136.6, 141.2, 150.7; IR (neat): 3344.9 (m), 2953.2 (w), 2855.8 (w), 1618.9 (m), 1582.1 (m), 1375.9 (m), 1315.4 (m), 1250.8 (w), 1135.3 (m), 1079.1 (m), 1061.3 (m), 833.7 (s), 775.0 (s), 668.1 (m) cm^{-1}; HRMS-(DART-TOF) for $C_{30}H_{52}BO_5Si$ [M+H]: calculated: 531.36771, found: 531.36760.



50

tert-butyldimethyl((1-methyl-3-(prop-1-en-2-yl)-2-(2,2,7-trimethyl-4H-benzo[d][1,3]dioxin-5-yl)cyclopentyl)-methoxy)silane. (50) To an oven-dried 2-dram vial with magnetic stir bar was added Et_2O (21 mL) and 2-bromopropene (675 µL, 7.63 mmol). Cool to -78 ºC and add *t*BuLi (11.8 mL, 1.30 M) dropwise. Allow the reaction to stir at -78 ºC for two hours. Allow the reaction to warm to room temperature and stir for 15 minutes. Once again, cool the flask to -78 ºC and add a solution of tert-butyldimethyl((1-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(2,2,7-trimethyl-4H-benzo[d][1,3]dioxin-5-yl)cyclopentyl)methoxy)silane (2.70 g, 5.09 mmol) in Et_2O (24 mL) dropwise. Allow the reaction to stir at -78 ºC for 45 minutes and 15 minutes at 0 ºC. At 0 ºC, add a solution of I_2 (1.94 g, 7.63 mmol) and MeOH (41 mL) and stir for 15 minutes. Add NaOMe (824 mg, 15.26 mmol) in MeOH (17 mL) dropwise and allow the reaction mixture to warm to room temperature and continue to stir for three hours. Concentrate the reaction mixture by rotary evaporation. Take up the crude mixture in Et_2O and wash organic layer with 5% $Na_2S_2O_3$, 5% NaOH, 5% NaOH (with 10% H_2O_2), 5% $Na_2S_2O_3$, and brine, sequentially. The combined organics were dried over $MgSO_4$, filtered, and concentrated by rotary evaporation. The crude material was purified on SiO_2 (1% to 2% EtOAc in hexanes, stained with CAM) to afford the title compound as a yellow oil (2.10 g, 93% yield).

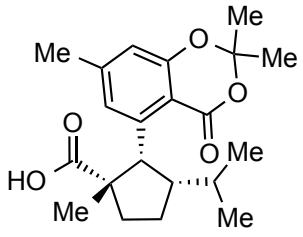
^{1}H NMR (600 MHz, $CDCl_3$): δ -0.15 (3H, s), -0.14 (3H, s), 0.80 (9H, s), 1.25 (3H, s), 1.39 (3H, s), 1.43 (3H, s), 1.51 (3H, s), 1.48 – 1.55 (1H, m), 1.71 – 1.77 (1H, m), 1.98 – 2.04 (1H, m), 2.13 – 2.19 (1H, m), 2.20 (3H, s), 2.79 (1H, d, J = 7.63 Hz), 3.03 (1H, d, J = 9.98 Hz), 3.08 (1H, d, J = 9.39 Hz), 3.20 (1H, q, J = 9.39 Hz), 4.64 (1H, s), 4.69 (1H, s), 4.75 (1H, d, J = 14.7 Hz), 5.01 (1H, d, J = 14.7 Hz), 6.29 (1H, s), 6.44 (1H, s); ^{13}C NMR (150 MHz, $CDCl_3$): -5.8, -5.8, 18.4, 21.6, 22.8, 23.0, 26.0, 26.1, 26.7, 27.1, 34.2, 49.5, 49.8, 50.1, 60.4, 69.1, 98.0, 110.1, 115.1, 115.5, 122.0, 136.1, 137.0, 145.7, 150.7; IR (neat): 2952.9 (m), 2928.6 (m), 2855.6 (m), 1581.8 (m), 1462.4 (m), 1370.3 (m), 1318.5 (m), 1203.8 (m), 1133.6 (m), 1085.0 (m), 833.9 (s), 775.2 (s) cm^{-1}; HRMS-(DART-TOF) for $C_{27}H_{45}O_3Si$ [M+H]: calculated: 445.31380, found: 445.31174.



51

(3-isopropyl-1-methyl-2-(2,2,7-trimethyl-4H-benzo[d][1,3]-dioxin-5-yl)cyclopentyl)methanol. (51) To an oven-dried round-bottomed flask with magnetic stir bar was added tert-butyldimethyl((1-methyl-3-(prop-1-en-2-yl)-2-(2,2,7-trimethyl-4H-benzo[d][1,3]dioxin-5-yl)cyclopentyl)methoxy)silane (1.12 g, 2.52 mmol), PtO_2 (30 mg) and EtOAc (133 mL). Evacuate and refill the flask with H_2 (10x). The reaction was stirred at room temperature for 3 hours under a H_2 atmosphere. The reaction mixture was put through a plug of celite and washed with EtOAc. The combined organics were concentrated by rotary evaporation. The crude silyl ether and THF (32) was added to an oven-dried round-bottomed flask with magnetic stir bar. Add TBAF (7.6 mL, 1M) was added dropwise to the reaction mixture at room temperature and stirred overnight. The reaction mixture was quenched with water. The layers were allowed to separate and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude material was purified on SiO_2 (1% to 5% EtOAc in hexanes, stained with CAM) to afford the title compound as a colorless oil (593 mg, 71% yield).

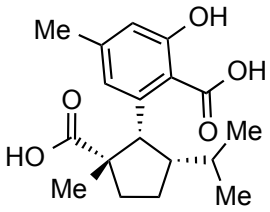
^{1}H NMR (600 MHz, $CDCl_3$): δ 0.59 (3H, d, J = 6.46 Hz), 0.88 (3H, d, J = 7.05 Hz), 1.01 (1H, t, J = 5.28 Hz), 1.23 (3H, s), 1.39 – 1.47 (2H, m), 1.48 (3H, s), 1.51 (3H, s), 1.67 – 1.79 (2H, m), 2.11 – 2.22 (2H, m), 2.27 (3H, s), 2.62 (1H, d, J = 6.46 Hz), 3.08 (1H, dd, J = 10.6 Hz, 5.87 Hz), 3.12 (1H, dd, J = 10.6 Hz, 3.53 Hz), 4.80 (1H, d, J = 14.7 Hz), 5.03 (1H, d, J = 14.7 Hz), 6.41 (1H, s), 6.51 (1H, s); ^{13}C NMR (150 MHz, $CDCl_3$): 21.7, 22.2, 24.3, 24.9, 26.5, 29.5, 29.9, 33.7, 49.6, 49.8, 51.3, 60.7, 69.3, 98.3, 115.3, 115.8, 122.0, 136.6, 137.6, 151.2; IR (neat): 3467.8 (w), 2952.7 (m), 2868.0 (m), 1617.3 (w), 1579.7 (m), 1453.2 (m), 1382.6 (m), 1313.9 (m), 1281.6 (m), 1159.8 (s), 1026.5 (s), 864.3 (s), 737.7 (s) cm^{-1}; HRMS-(DART-TOF) for $C_{21}H_{31}O_2$ [M+H-H_2O]: calculated: 315.23240, found: 315.23312.



52

3-isopropyl-1-methyl-2-(2,2,7-trimethyl-4-oxo-4H-benzo[d]-[1,3]dioxin-5-yl)cyclopentane-1-carboxylic acid. (52) To a round-bottomed flask with magnetic stir bar was added (3-isopropyl-1-methyl-2-(2,2,7-trimethyl-4H-benzo[d][1,3]dioxin-5-yl)cyclopentyl)methanol (61.6 mg, 185 μmol), MeCN (1.54 mL) and EtOAc (1.54 mL). The reaction mixture was cooled to 0 ºC. A solution of $NaIO_4$ (0.28 g, 1.30 mmol) and $RuCl_3$ (4.2 mg, 18.5 μmol) in H_2O (2.5 mL) was added dropwise to the reaction at 0 ºC over 1 hour. The reaction was allowed to stir at 0 ºC for 2 hours and at room temperature for 12 hours. The reaction was quench with 6M HCl (0.4 mL) and diluted with water (4 mL). The aqueous layer was extracted with EtOAc (5 x 5 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude material was purified on SiO_2 (10% to 30% EtOAc in hexanes, stained with CAM) to afford the title compound as a clear oil (27 mg, 41% yield).

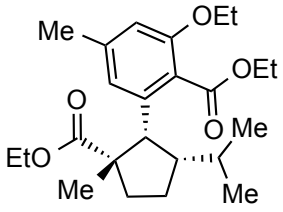
^{1}H NMR (600 MHz, $CDCl_3$): δ 0.62 (3H, d, J = 6.45 Hz), 0.84 (3H, d, J = 6.45 Hz), 1.15 – 1.20 (1H, m), 1.54 (3H, s), 1.62 (3H, s), 1.69 (3H, s), 1.70 – 1.78 (2H, m), 2.09 – 2.14 (1H, m), 2.21 – 2.27 (1H, m), 2.32 (3H, s), 2.65 – 2.71 (1H, m), 4.66 (1H, d, J = 7.04 Hz), 6.63 (1H, s), 6.68 (1H, s), 9.56 (1H, br s); ^{13}C NMR (150 MHz, $CDCl_3$): 21.7, 21.9, 22.3, 24.9, 25.8, 28.3, 29.0, 29.9, 33.5, 49.3, 51.3, 57.1, 105.0, 111.7, 116.2, 125.6, 145.3, 146.1, 156.8, 162.3, 179.3; IR (neat): 2956.3 (w), 2871.2 (w), 1730.1 (s), 1696.6 (s), 1616.2 (m), 1571.3 (m), 1265.3 (s), 1210.5 (m), 1157.0 (m), 1045.1 (m), 735.8 (s) cm^{-1}; HRMS-(DART-TOF) for $C_{21}H_{29}O_5$ [M+H]: calculated: 361.2015, found: 361.2014.



debromohamigeran E. To a round-bottomed flask with magnetic stir bar was added 3-isopropyl-1-methyl-2-(2,2,7-trimethyl-4-oxo-4H-benzo[d][1,3]dioxin-5-yl)cyclopentane-1-carboxylic acid (23.0 mg, 63.8 μmol), DMSO (4 mL) and 48% aqueous KOH (0.95 mL). The reaction flask was heated to 60 ºC and stirred for 1 hour. The reaction is cool to room temperature and 2M HCl (aq.) is added dropwise until a pH of 2 is reached. The aqueous layer was extracted with EtOAc (8 x 2 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The residue is heated at 35 ºC under hi-vac until the DMSO is distilled away from the product. ^{1}H NMR showed product contaminated with DMSO. The determined yield of the reaction accounts for the DMSO present. (18.9 mg, 93% yield).

^{1}H NMR (600 MHz, $CDCl_3$): δ 0.59 (3H, d, J = 6.46 Hz), 0.81 (3H, d, 6.46 Hz), 1.03-1.08 (1H, m), 1.55 (3H, s), 1.72-1.78 (1H, m), 1.82-1.87 (1H, m), 2.11-2.24 (2H, m), 2.29 (3H, s), 2.63-2.71 (1H, m), 3.66 (1H, d, J = 6.45 Hz), 6.47 (1H, s), 6.67 (1H, s); IR (neat): 3414.7 (w), 2956.5 (w), 2925.5 (w), 2870.4 (w), 1612.6 (m), 1263.1 (m), 1218.3 (m), 1192.4 (m), 1010.4 (m), 949.7 (m), 876.3 (m), 735.9 (s) cm^{-1}; HRMS-(DART-TOF) for $C_{18}H_{25}O_5$ [M+H]: calculated: 321.1702, found: 321.1716.

The purification of debromohamigeran E proved to be difficult and full characterization could not be performed. Instead, similar to isolation studies [13], the crude debromohamigeran E was subjected to alkylation conditions to form triethyldebromohamigeran E.



triethyldebromohamigeran E. To an oven-dried vial with magnetic stir bar was added debromohamigeran E (10 mg, 31.2 μmol) and acetone (5 mL). To the vial was added potassium carbonate (1.00 g) and MeI (1.00 mL). The vial was sealed and heated to 55 ºC overnight. Cool the flask to room temperature and filter the reaction mixture through a plug of SiO_2 and wash with EtOAc. The collected organic fraction was concentrated with rotatory evaporation. The crude material was purified on SiO_2 (5% to 10% EtOAc in hexanes, stained with CAM) to afford the title compound as a clear oil (8.1 mg, 64% yield). All spectral data are in accord with the literature.[13]

Triethyldebromohamigeran E: Comparison of ^{1}H and ^{13}C NMR Shifts			
^{1}H NMR (ppm)	***Reported ^{1}H NMR (ppm)***	***^{13}C NMR (ppm)***	***Reported ^{13}C NMR (ppm)***
0.77	0.77	13.5	13.5
0.81	0.81	14.3	14.3
0.85	0.85	14.7	14.7
1.32	1.32	22.1	22.1
1.34	1.33	22.1	22.1
1.37	1.36	22.2	22.2
1.40	1.40	28.3	28.3
1.56	1.58	29.2	29.2
1.81	1.81	29.8	29.8
2.04	2.05	34.1	34.1
2.10	2.10	51.8	51.8
2.29	2.29	54.7	54.7
2.73	2.73	56.3	56.3
3.15	3.14	60.0	60.0
3.62	3.62	60.6	60.6
3.75	3.75	64.2	64.2
3.97	3.97	110.9	110.9
3.98	3.98	121.9	121.9
4.33	4.34	123.6	123.6
4.38	4.37	138.9	138.9
6.49	6.49	139.1	139.1
6.53	6.53	155.7	155.6
		168.5	168.6
		175.8	175.8

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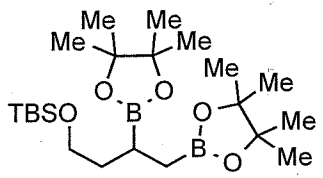

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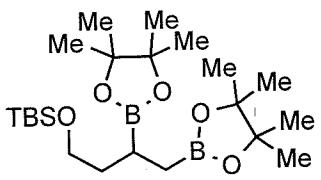
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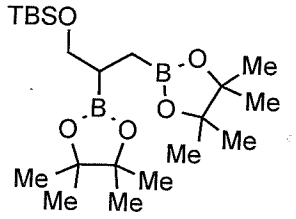

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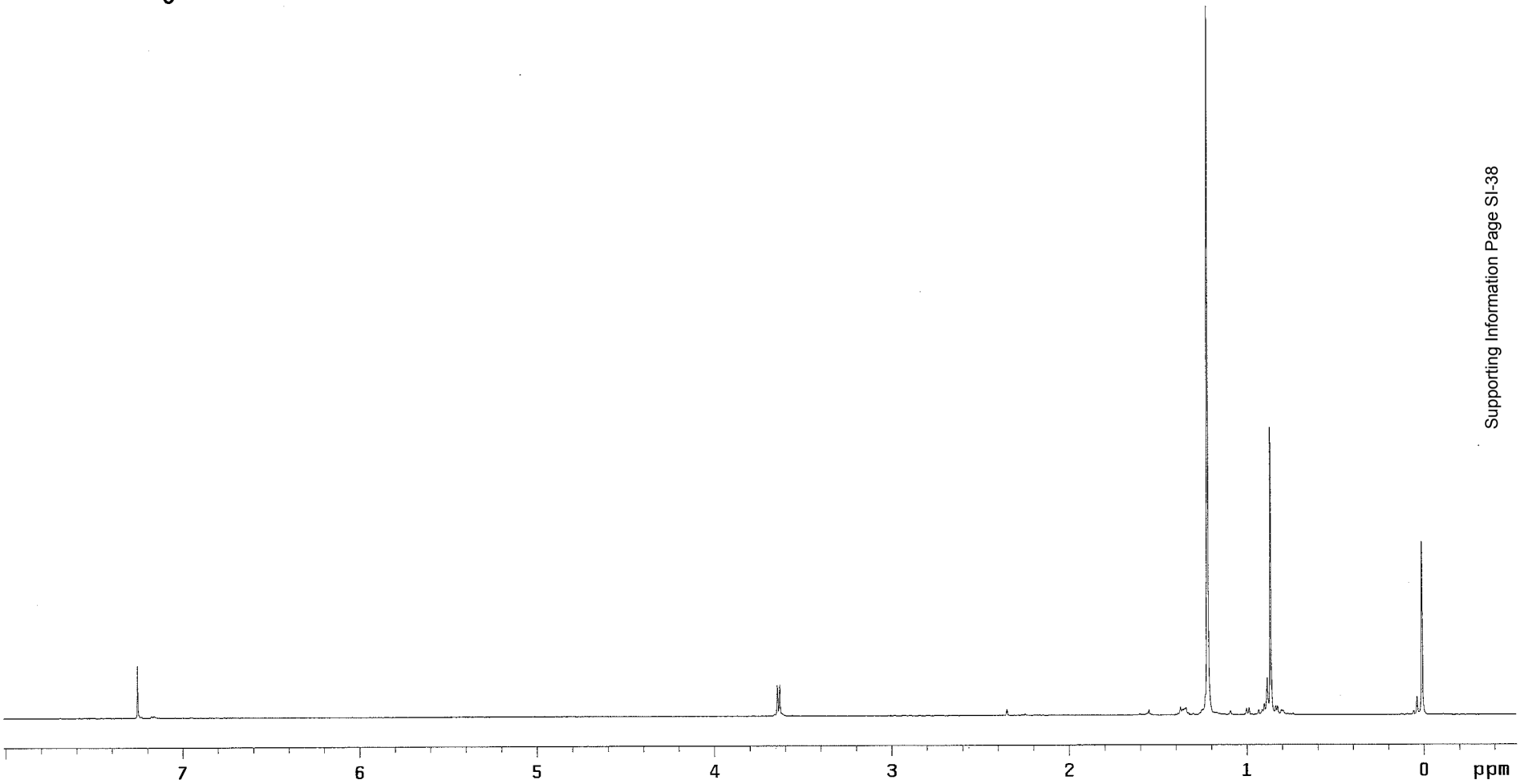

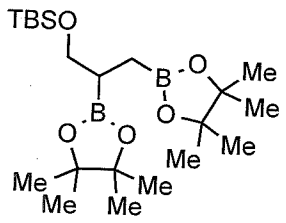
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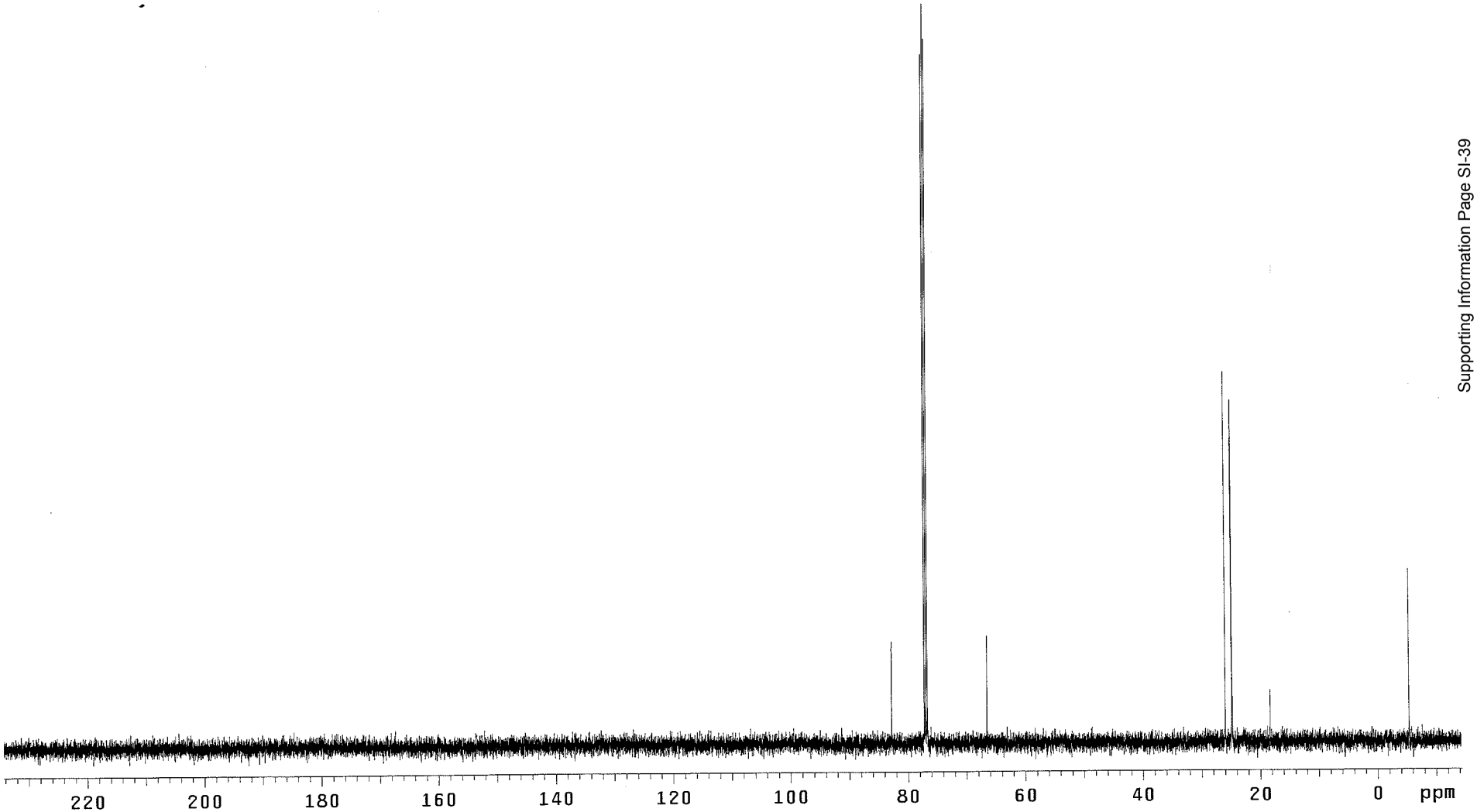
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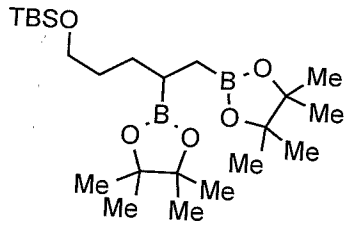

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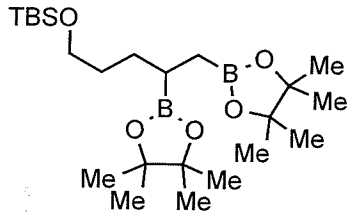
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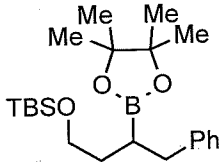

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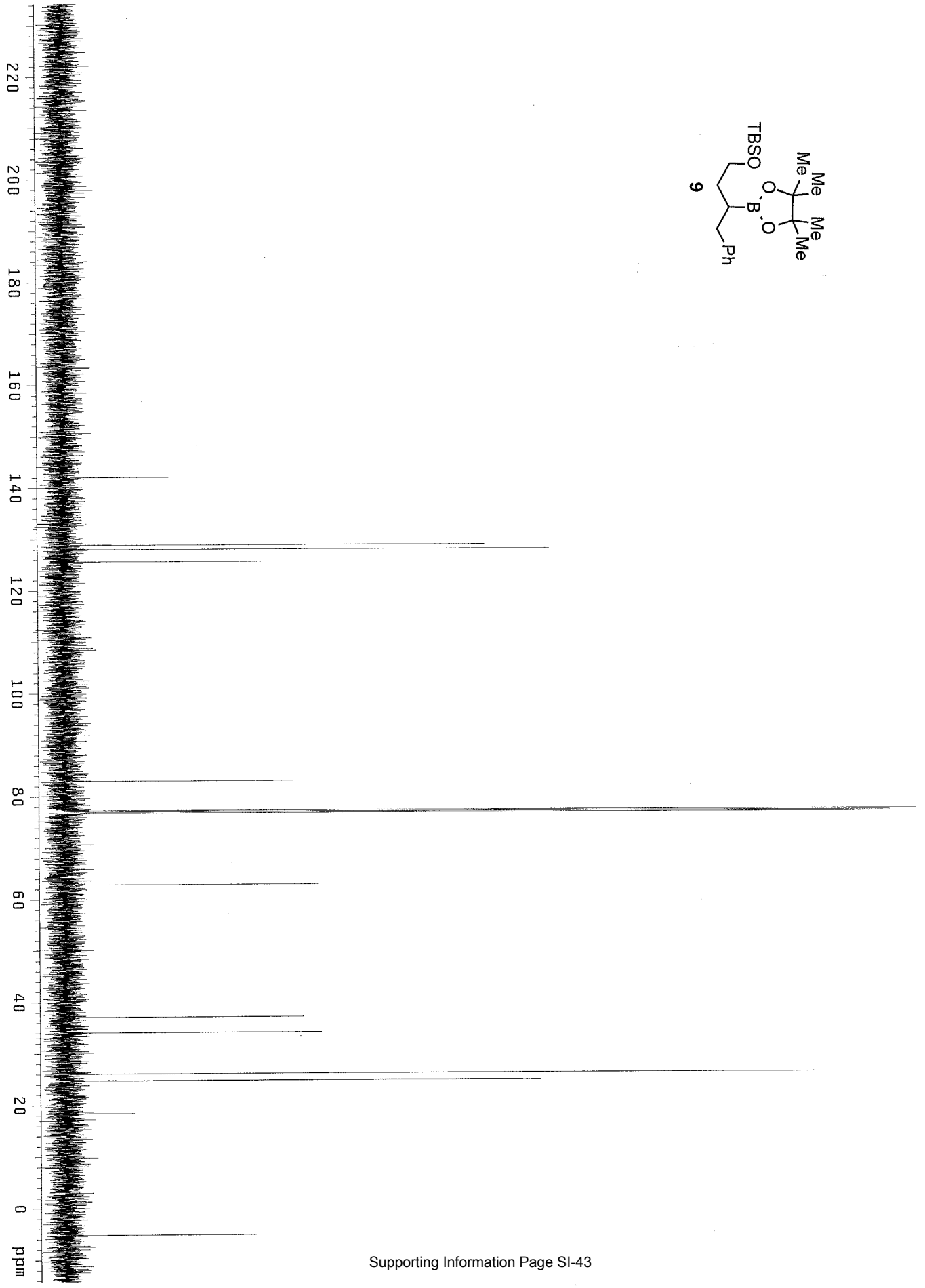
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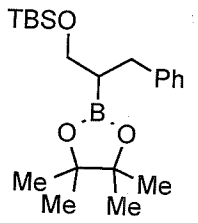

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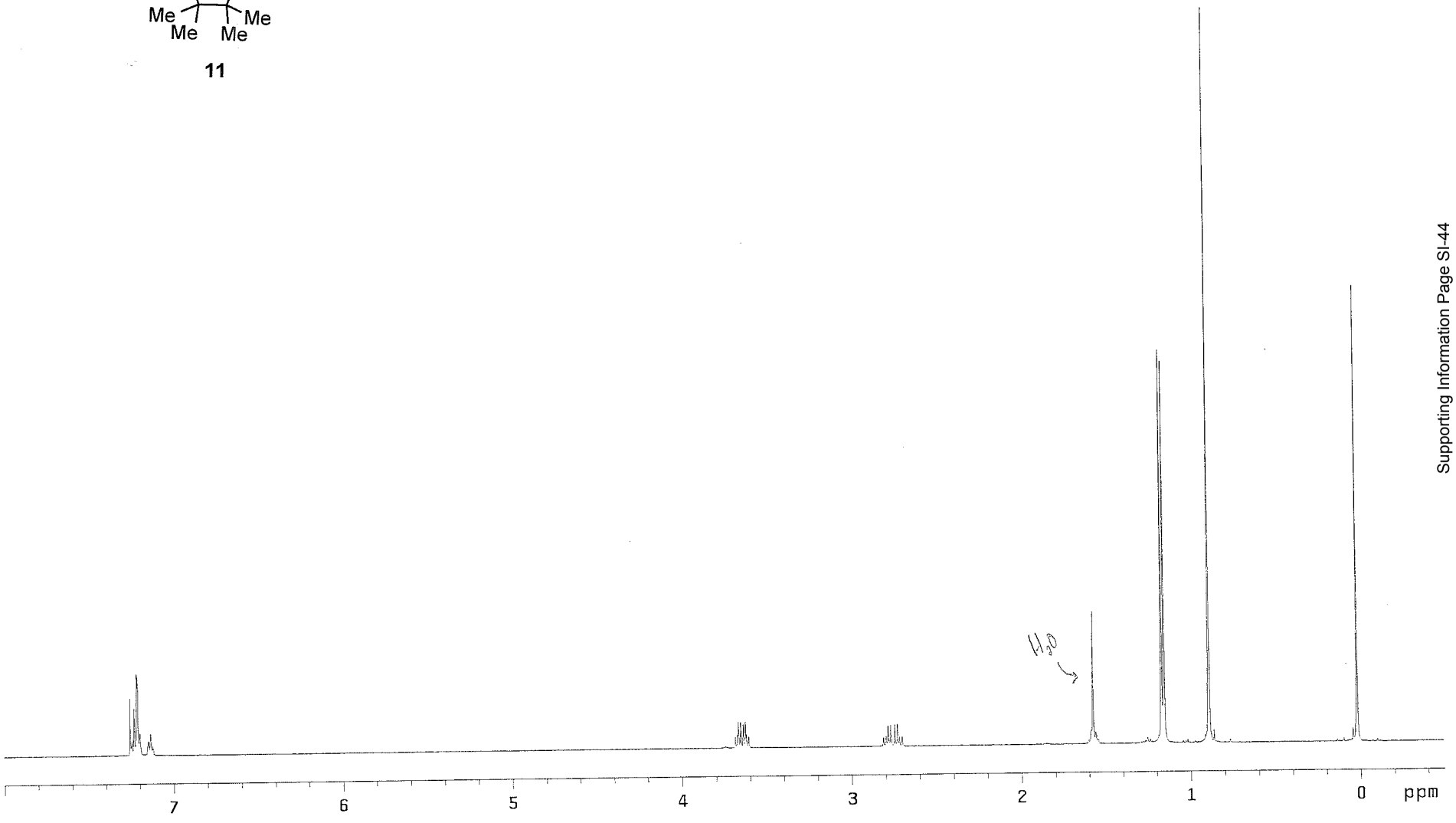

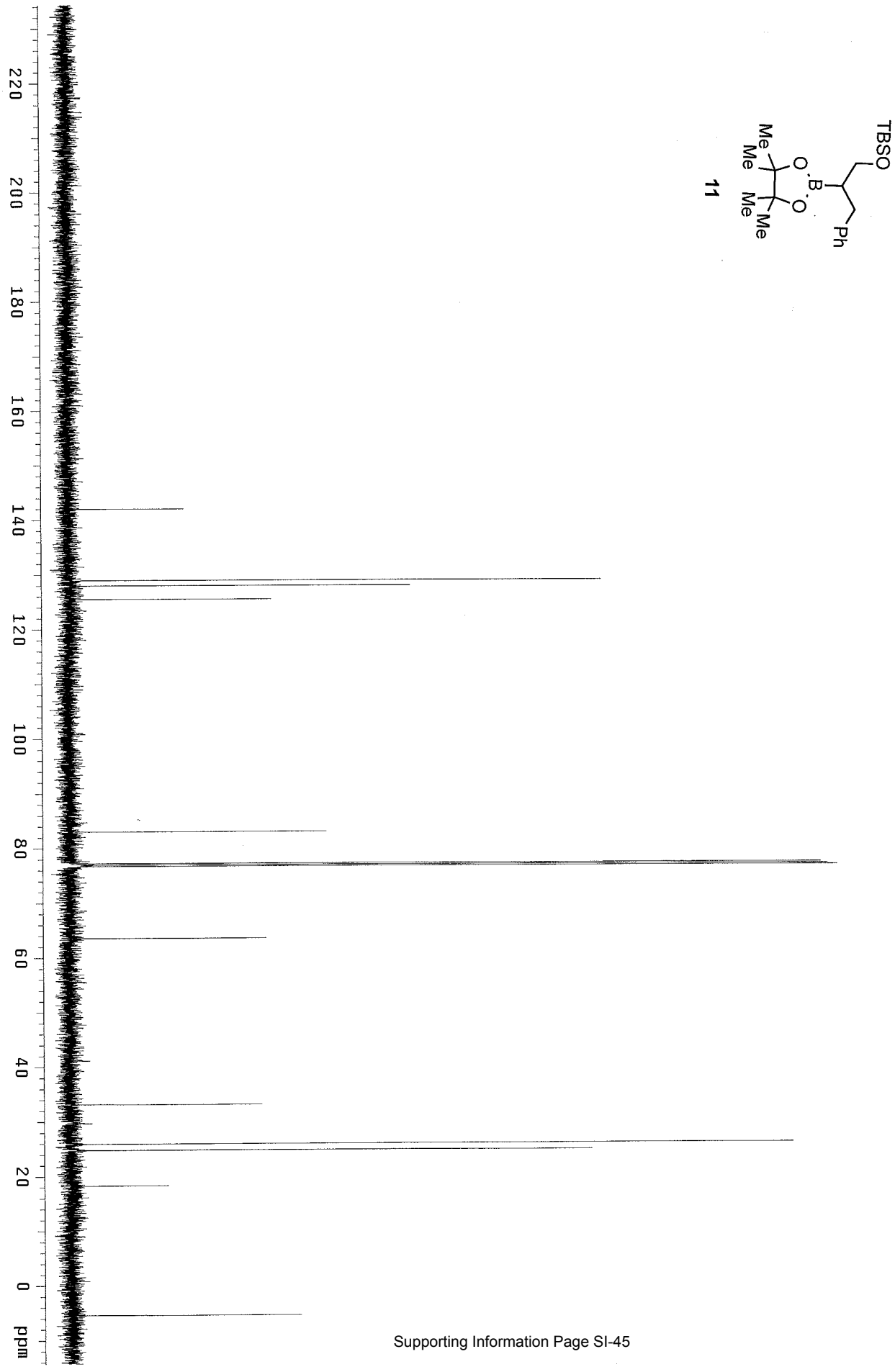
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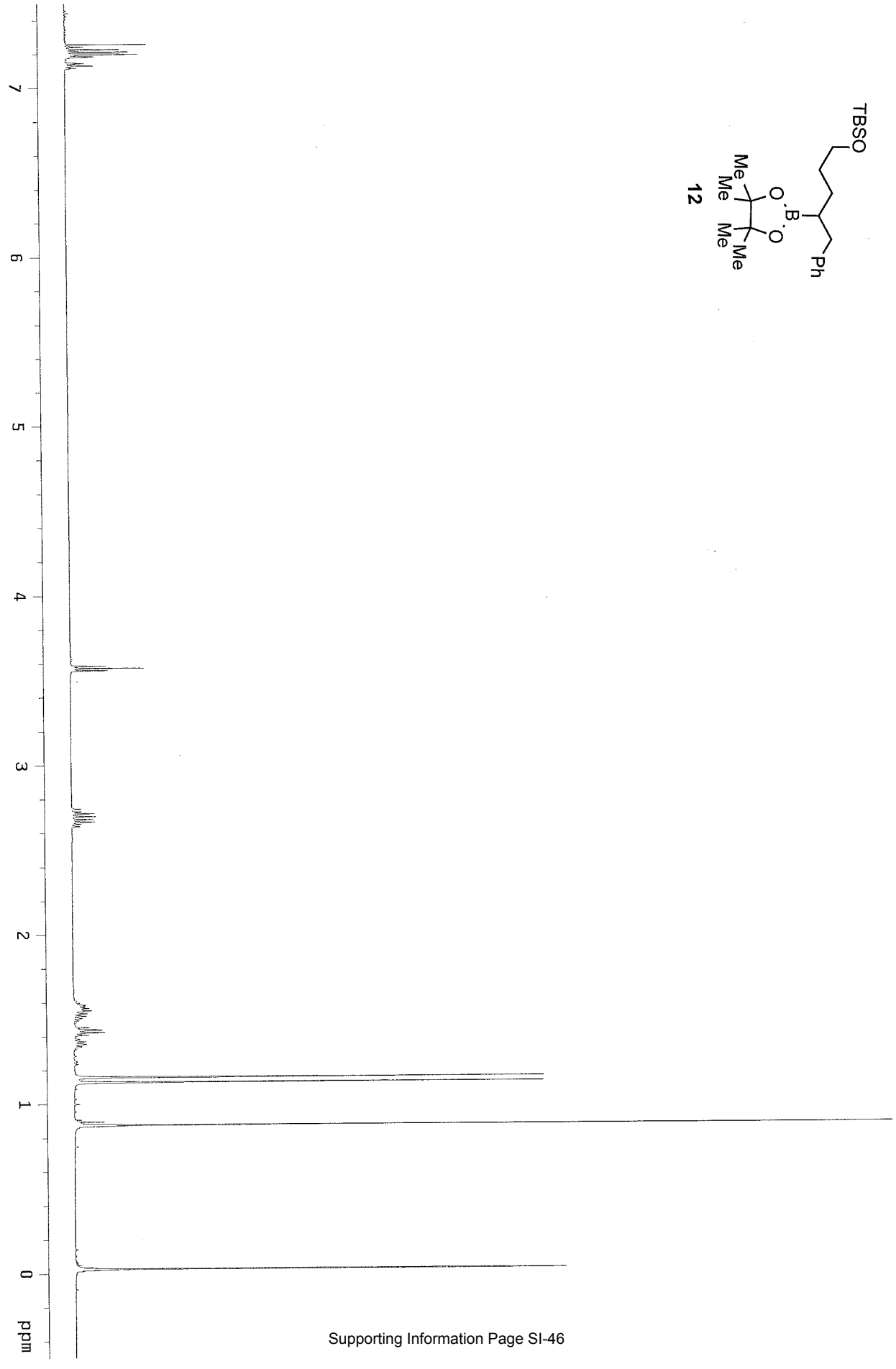
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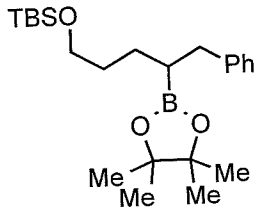
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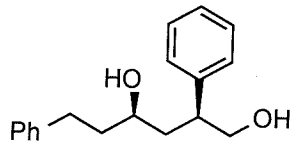

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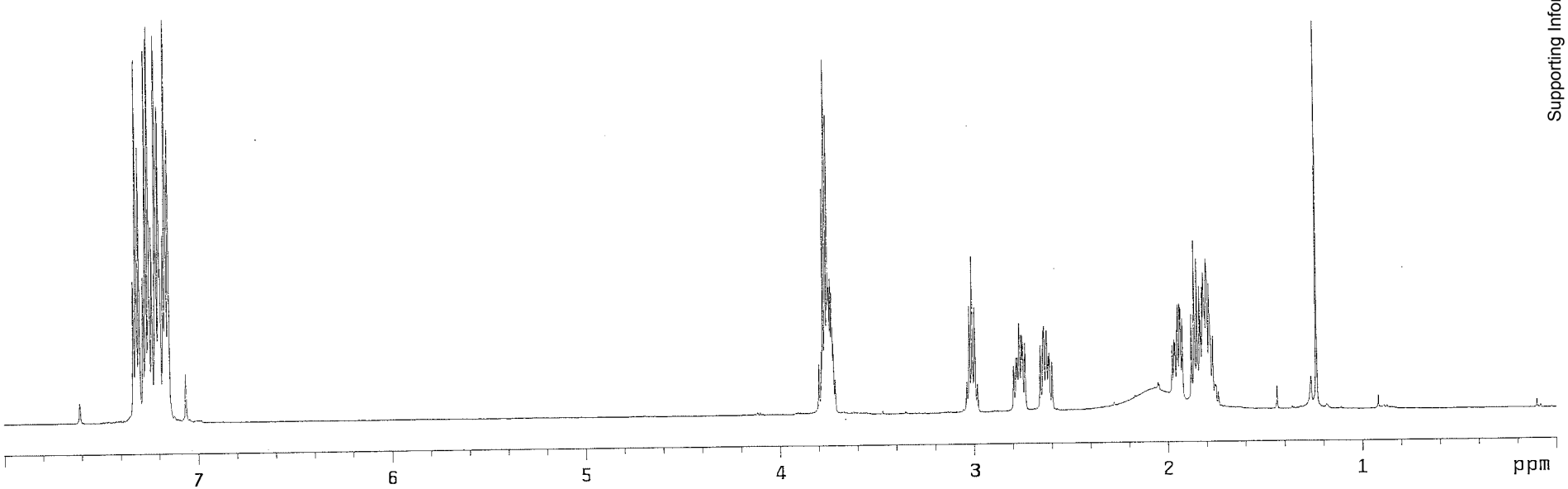

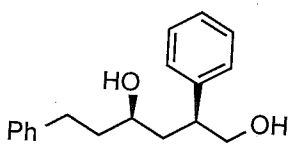

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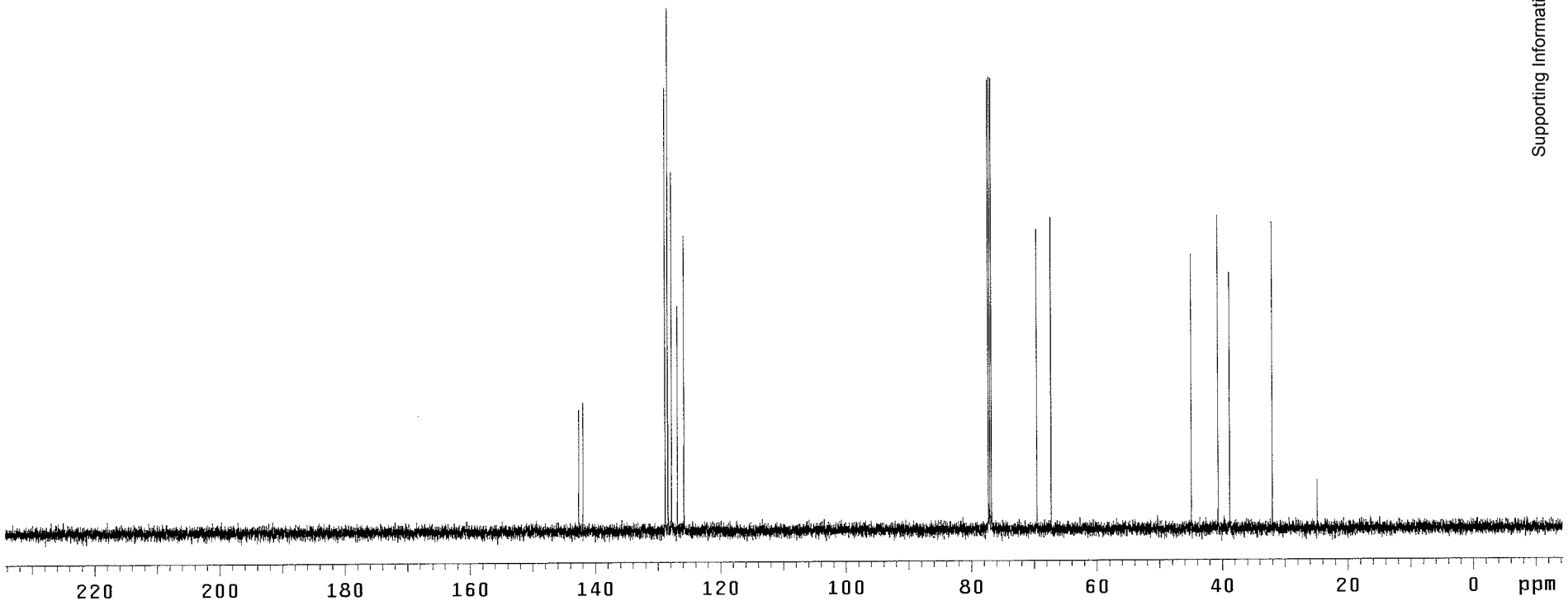

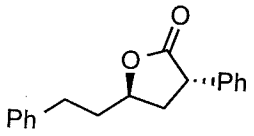

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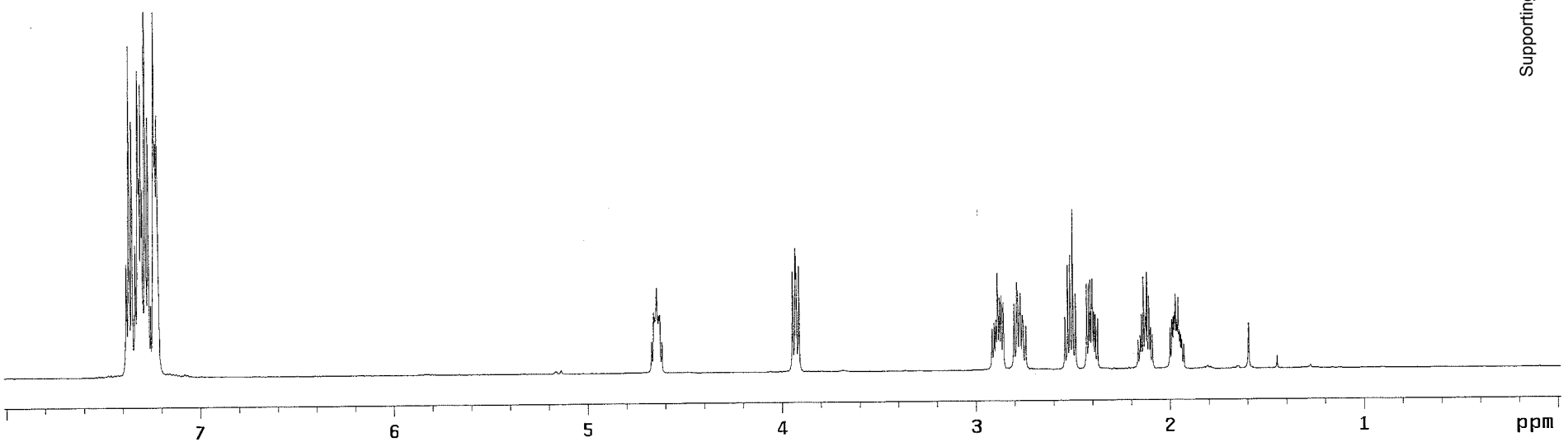
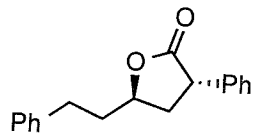
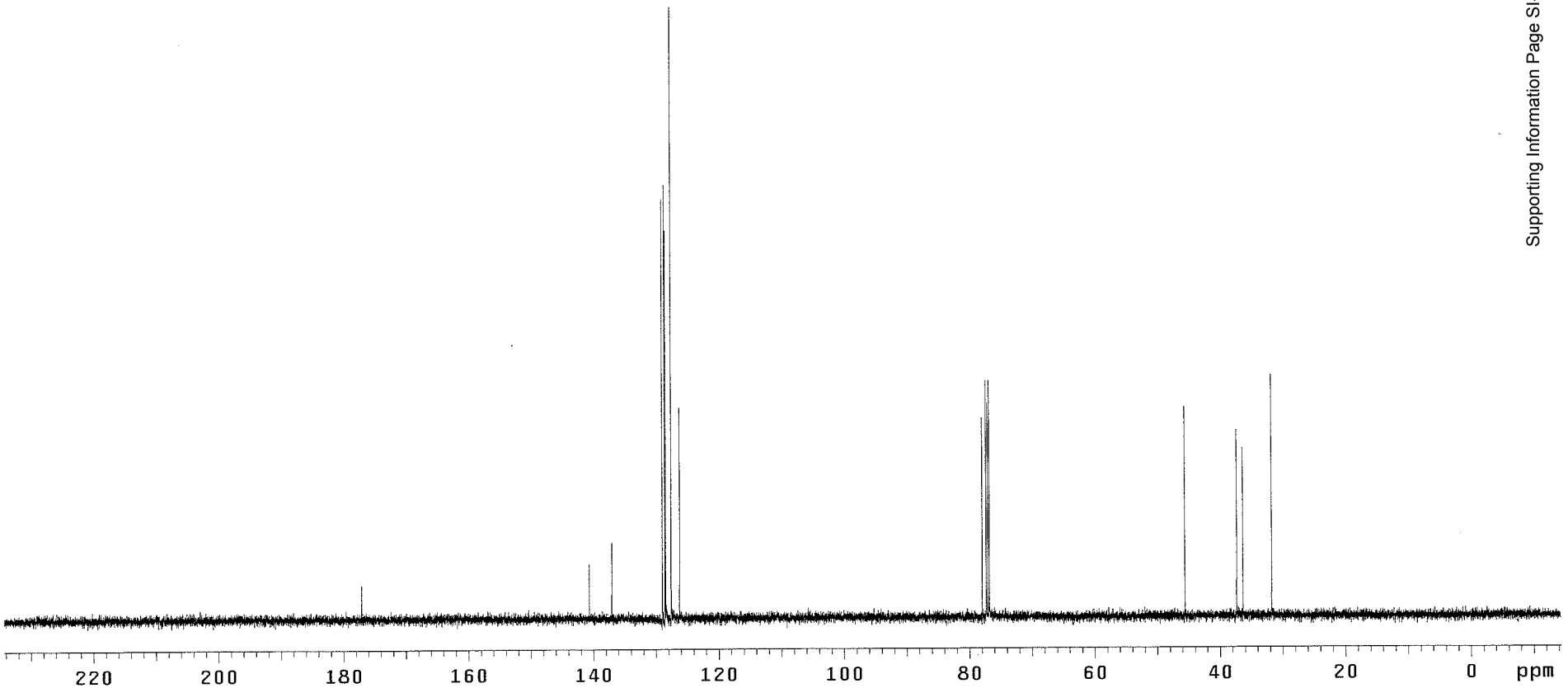
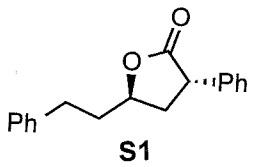


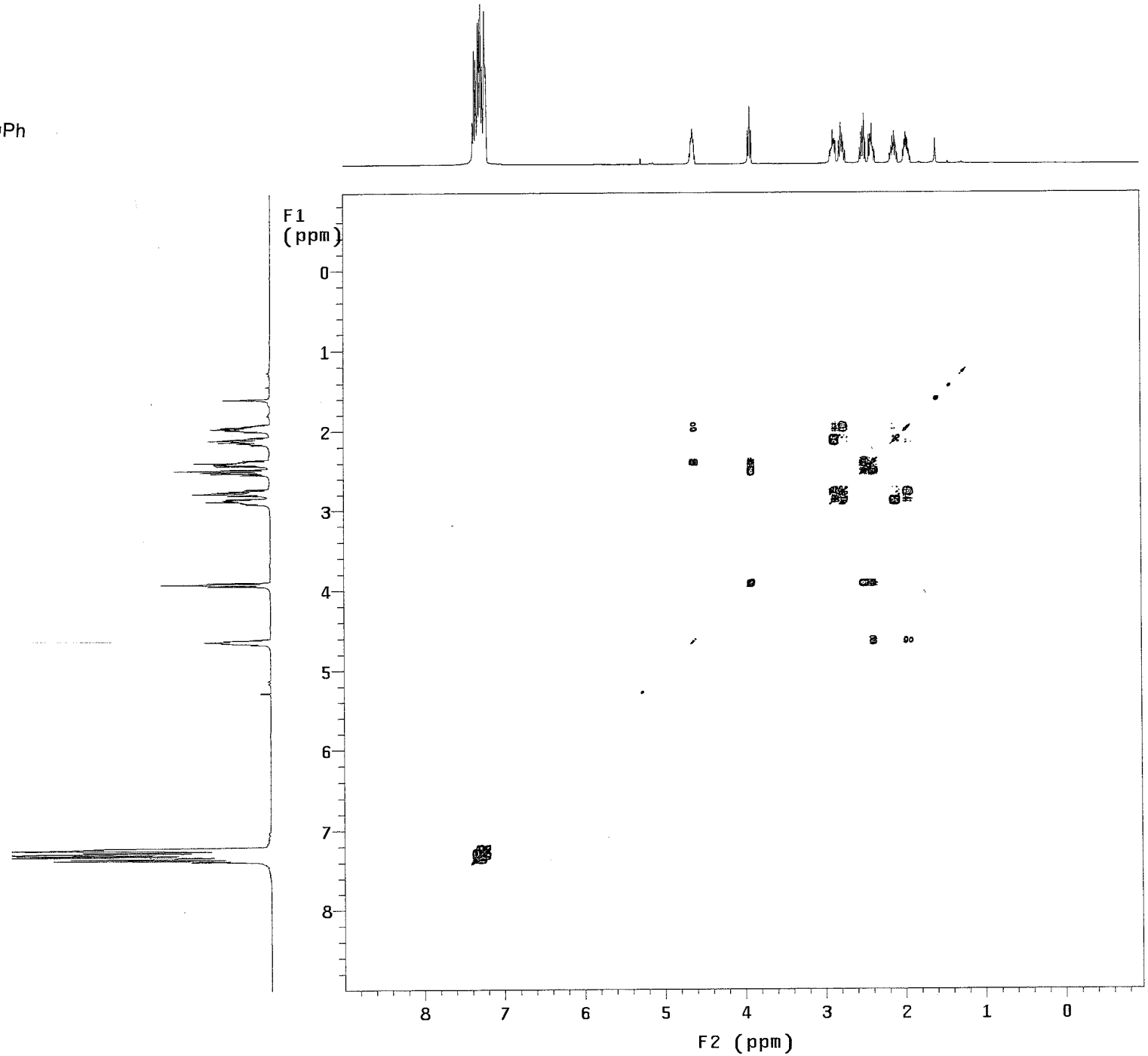


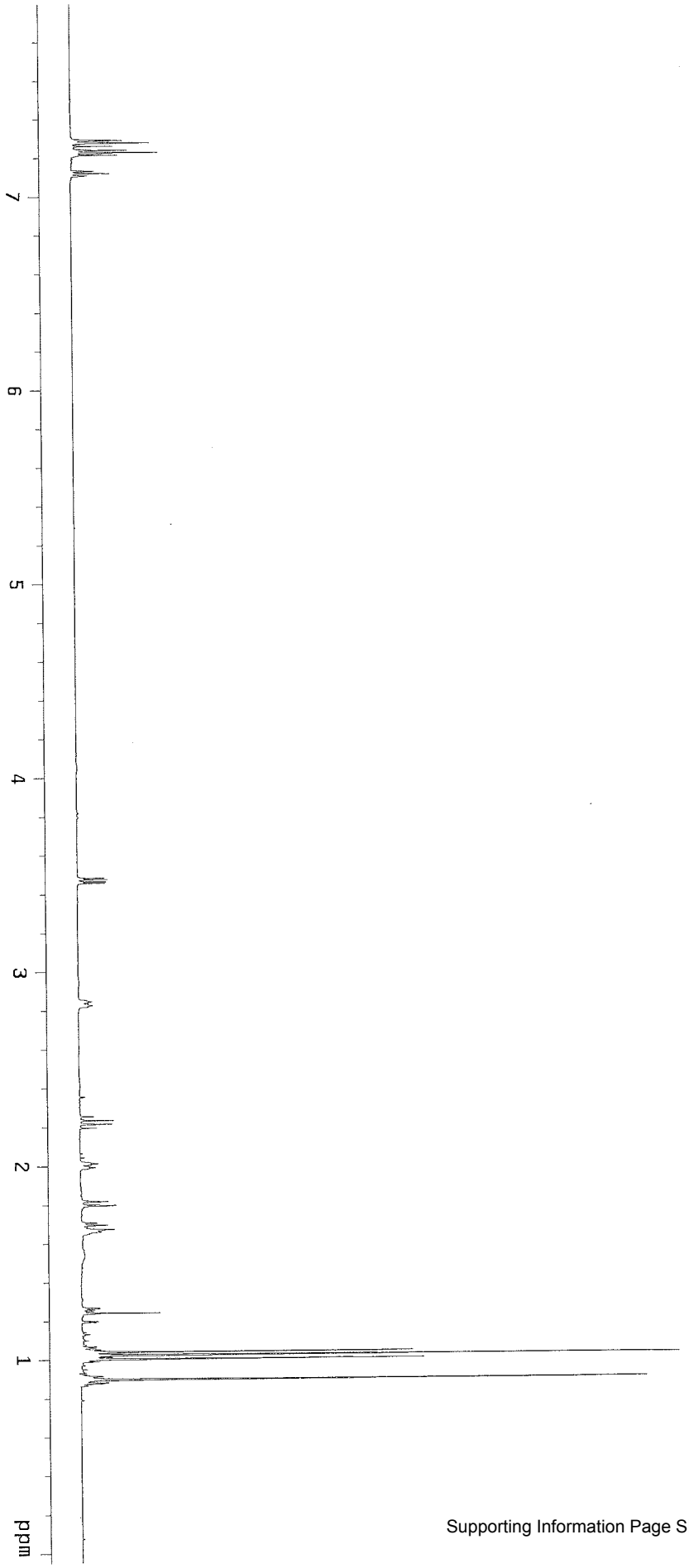
S1

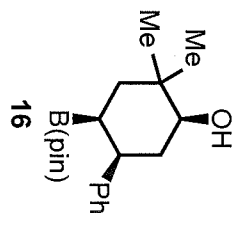




S1







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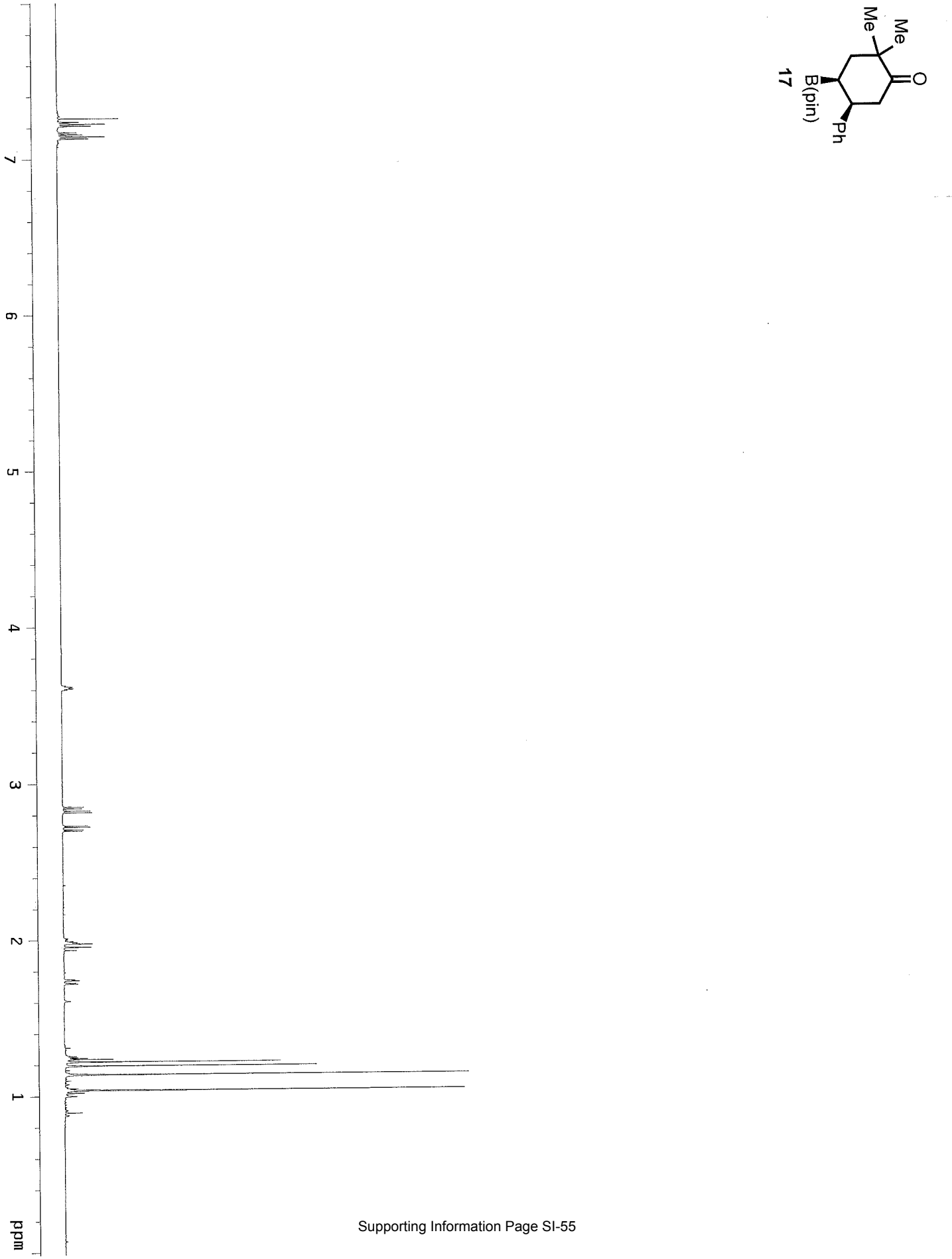
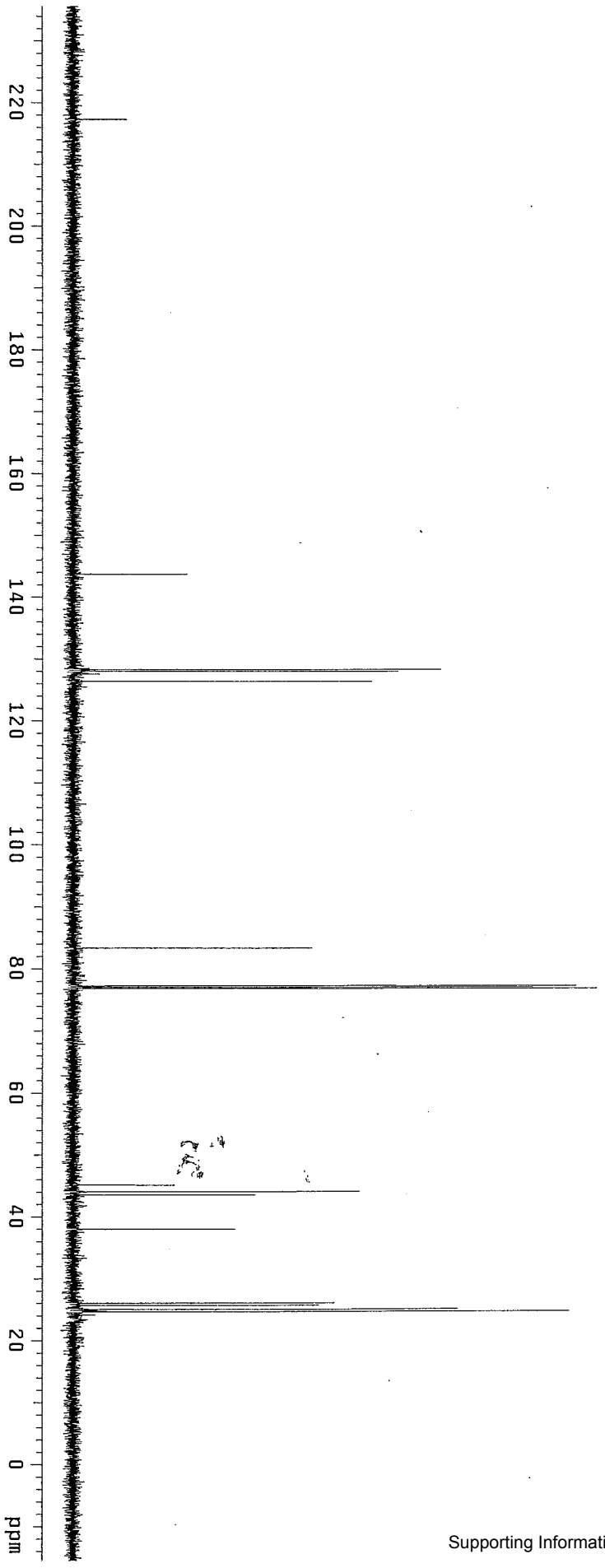
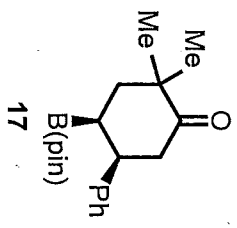

Me
Me
O
B(pin)
Ph
17
7
6
5
4
3
2
1
ppm





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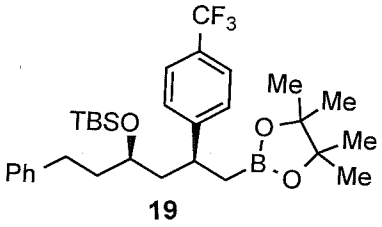

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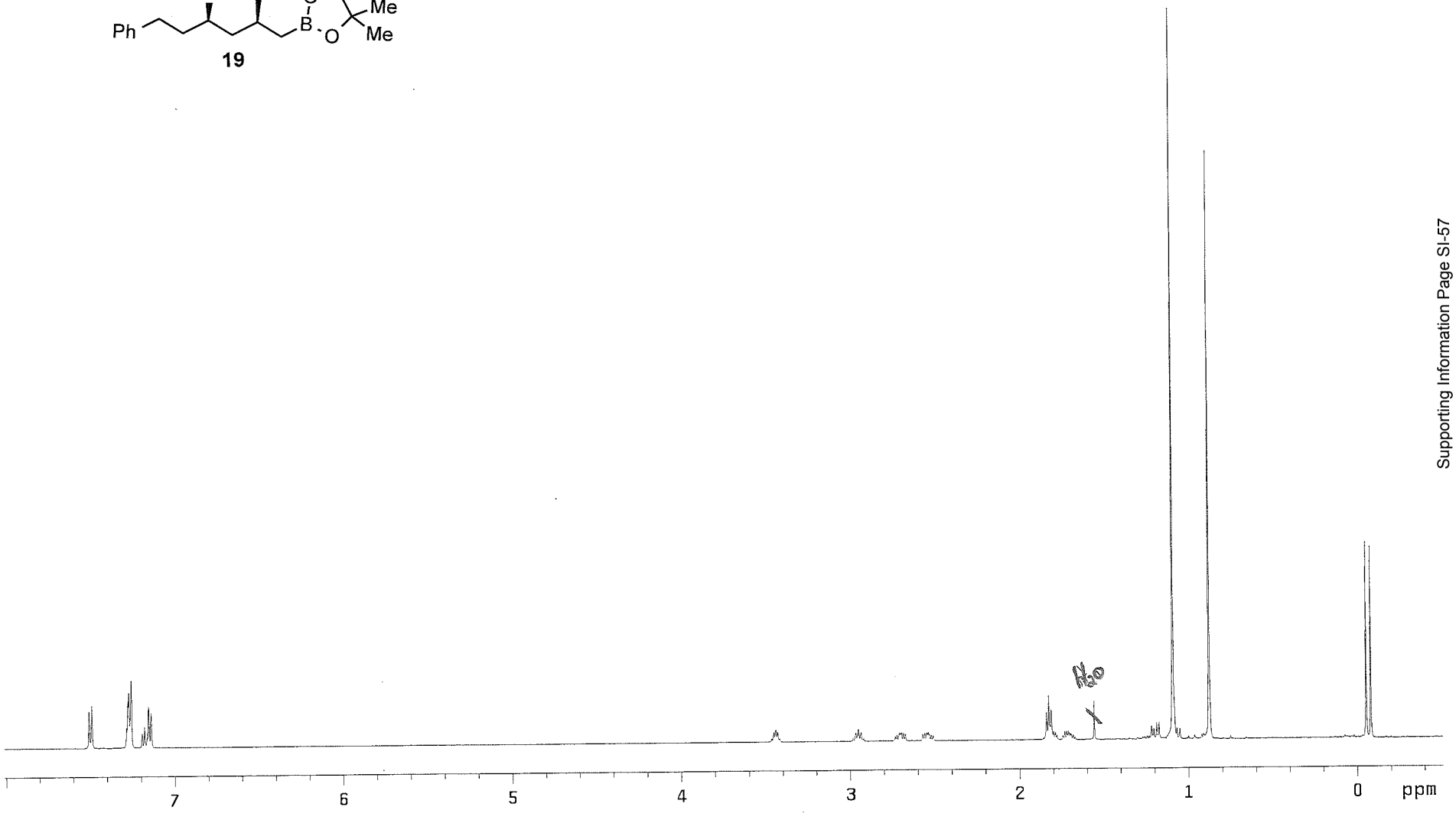

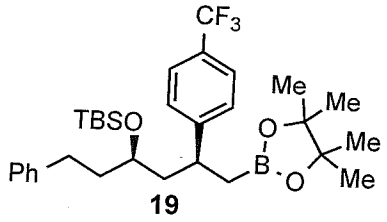
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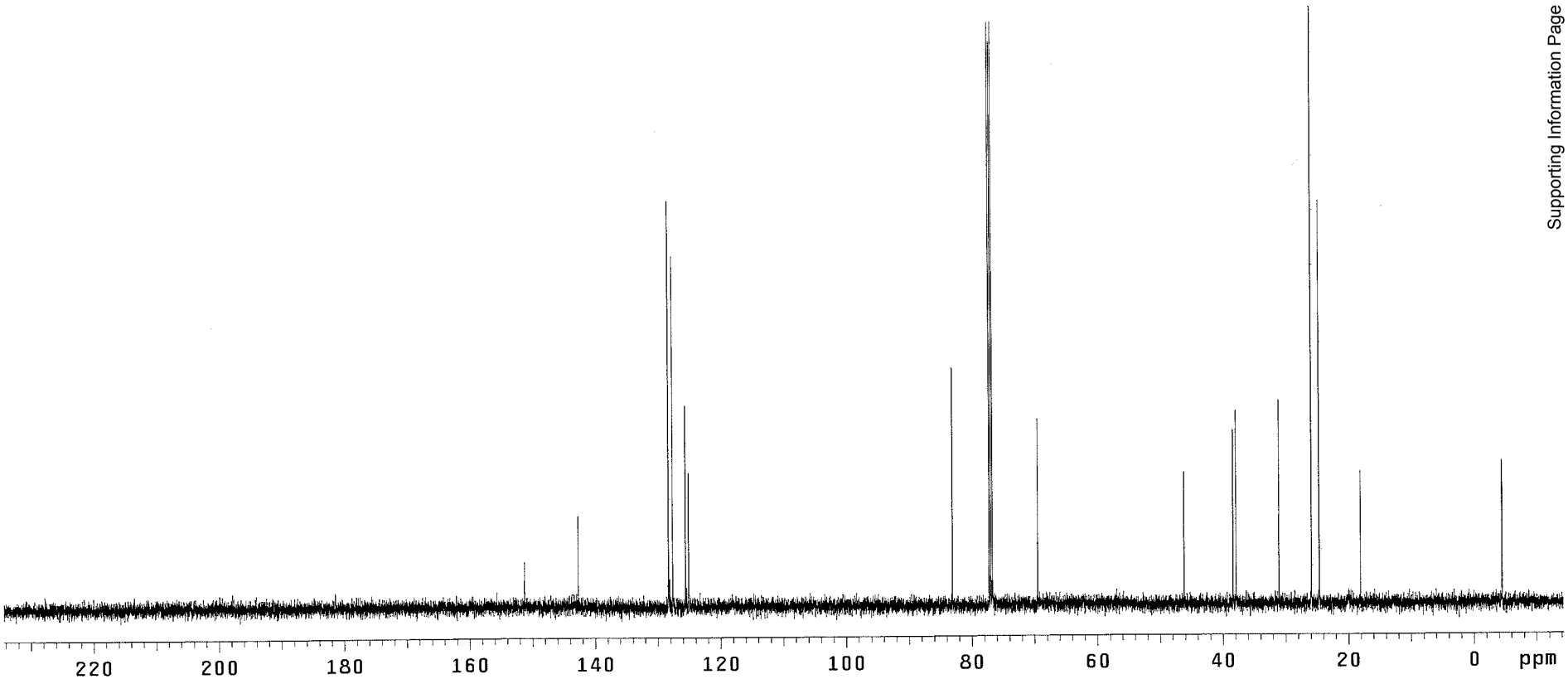
Me
Ph
B
O
Me

19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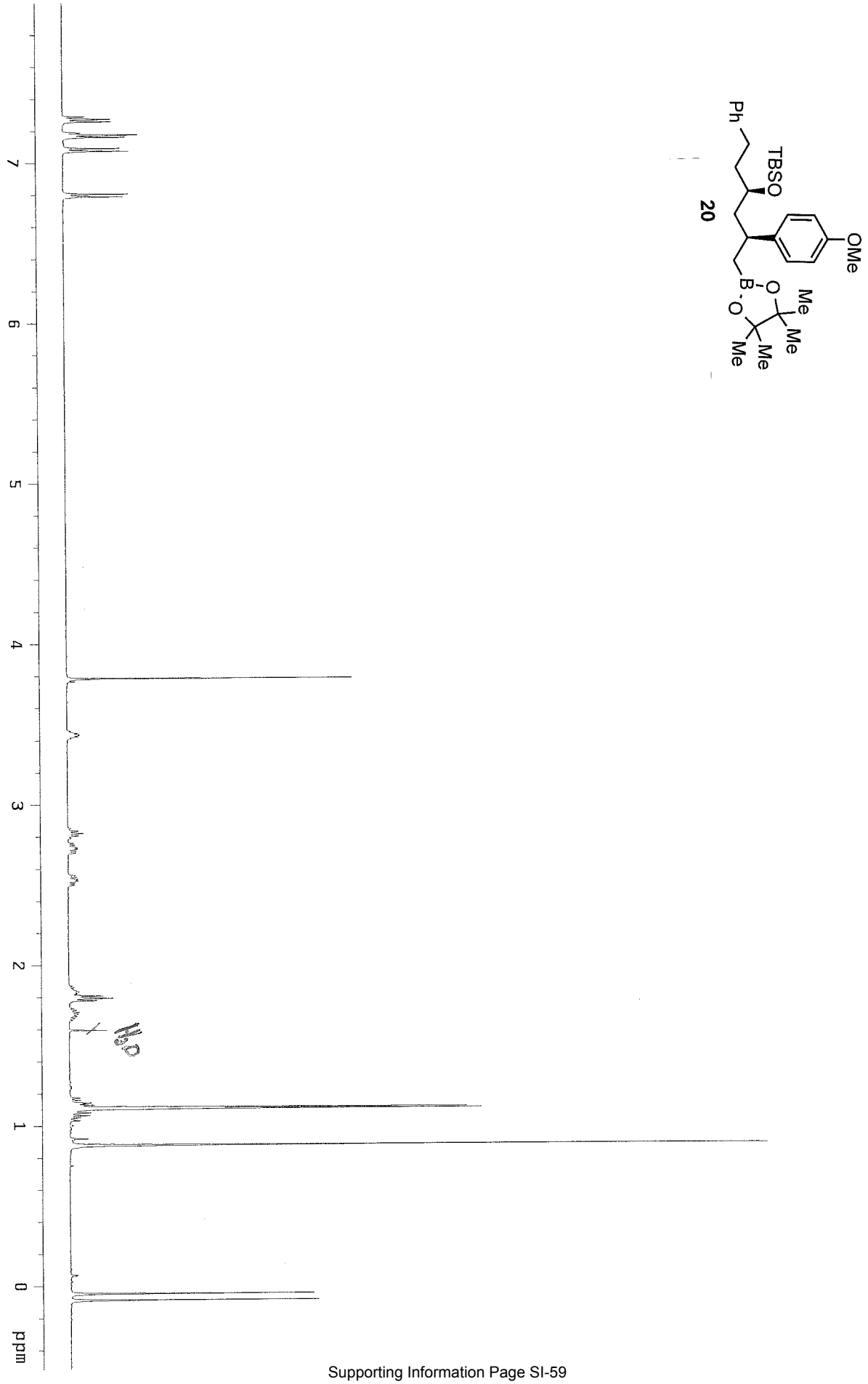
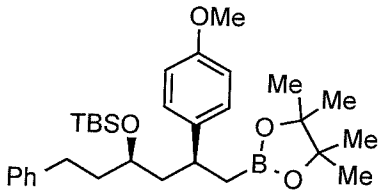
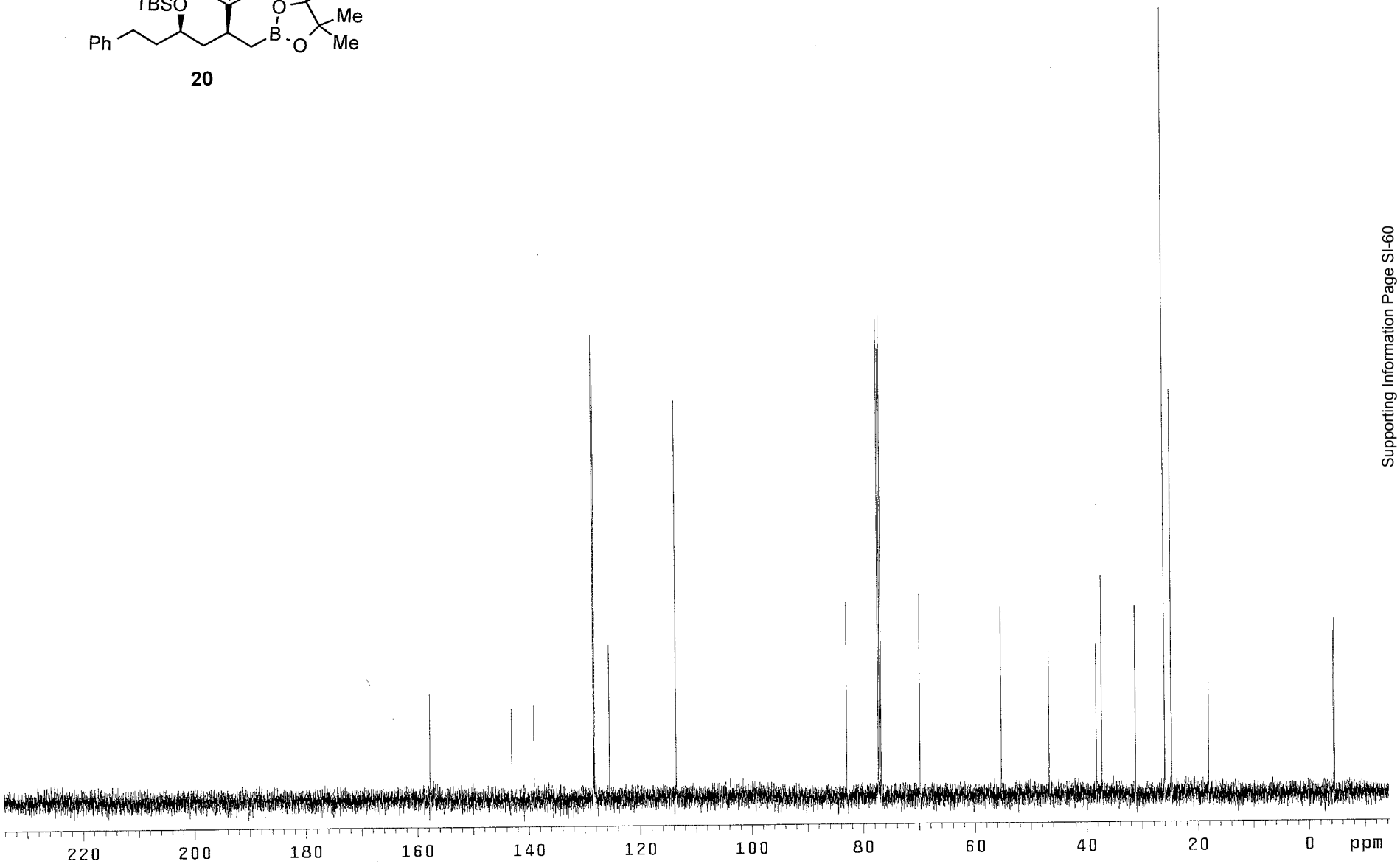
ppm


Ph
TBSO
OMe
B
O
O
Me
Me
Me
Me
20
7
6
5
4
3
2
1
0
ppm


OMe
Me
Me
TBSO
O
Me
Ph
B
O
Me

20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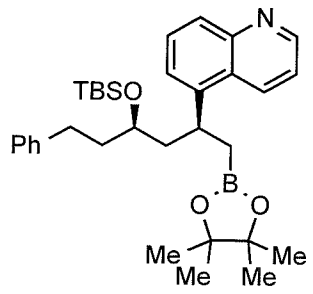

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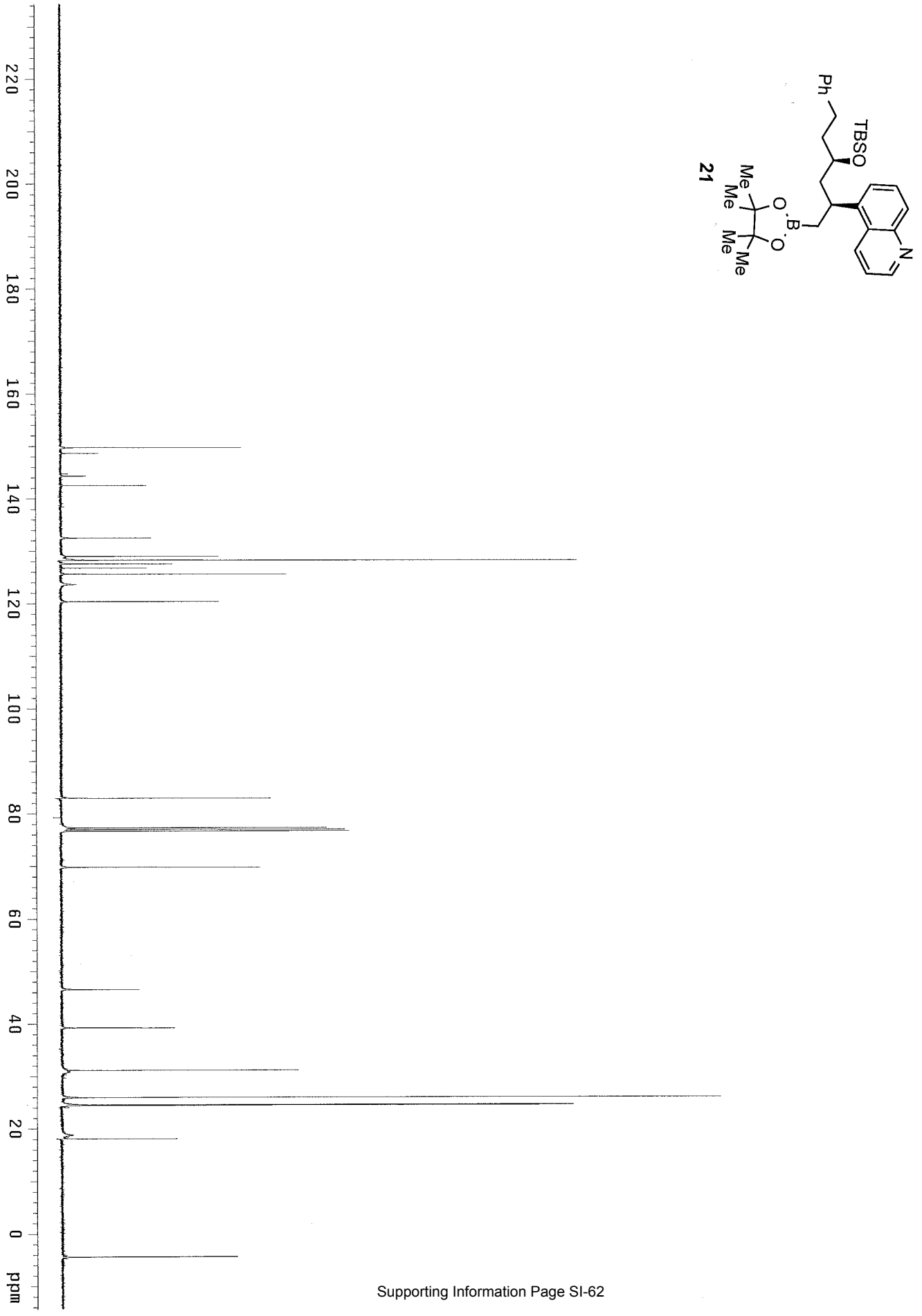
Ph
TBSO
Me
Me
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B
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Me
N
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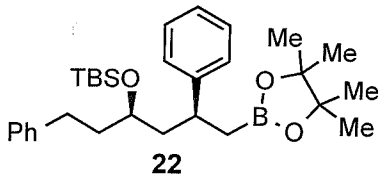
40
20
0
ppm



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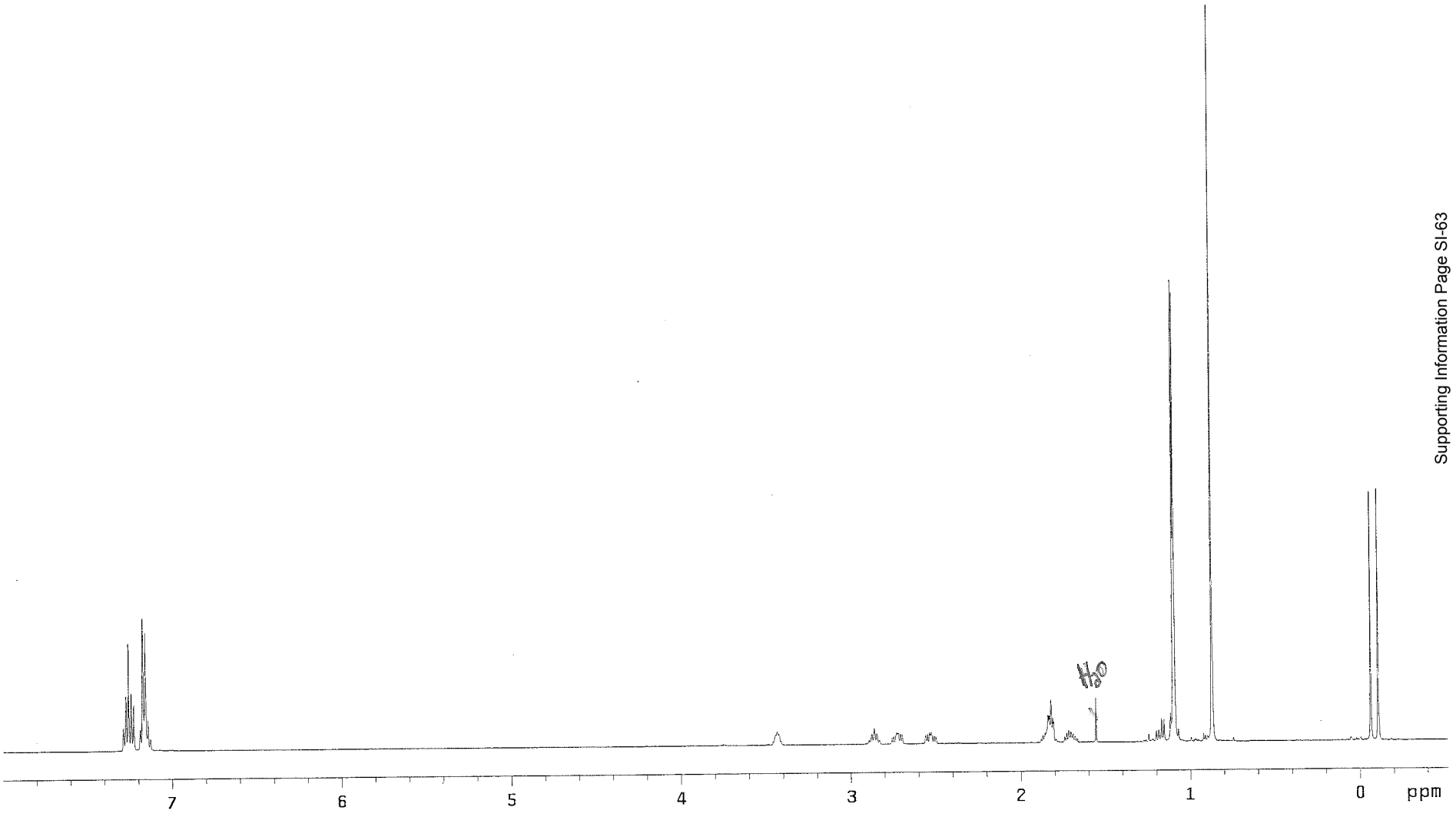
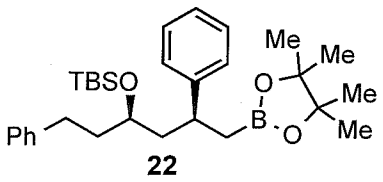
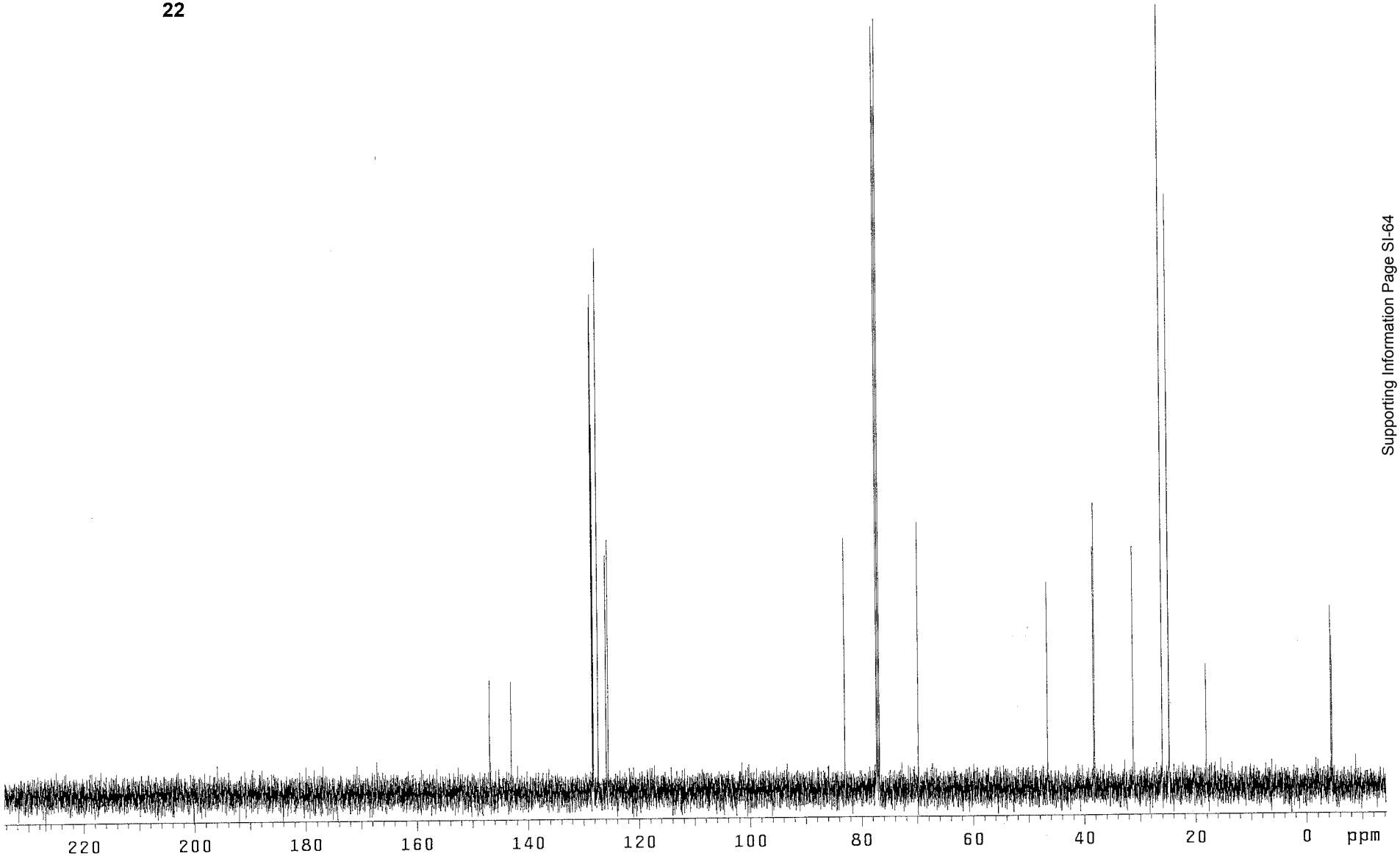



TBSO
Ph
Me
Me
O
B
O
Me
Me

22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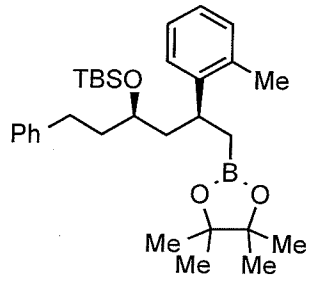
ppm



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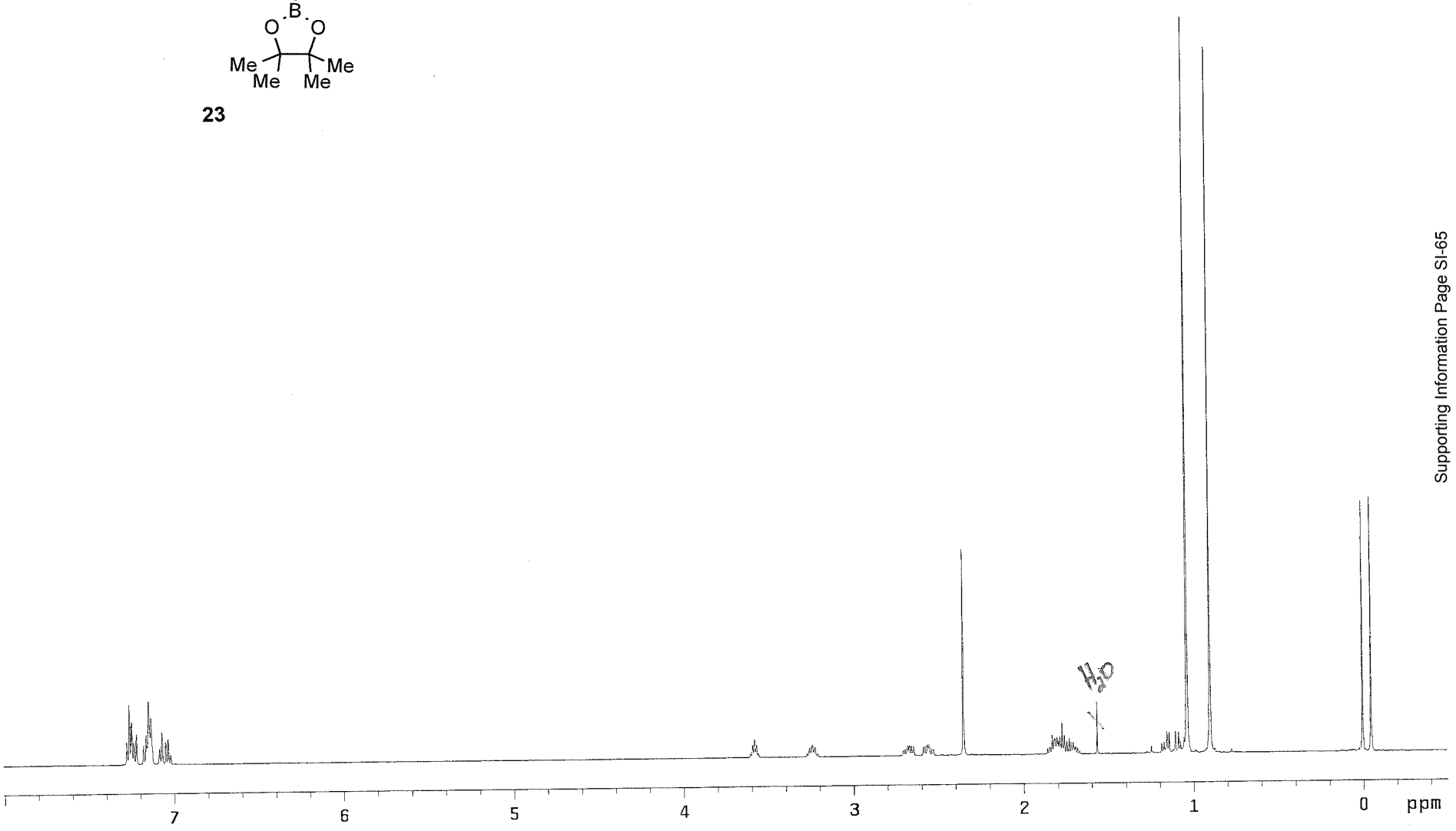
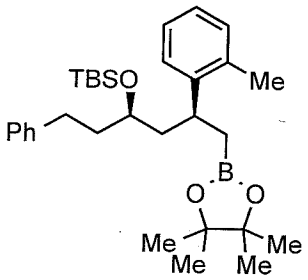
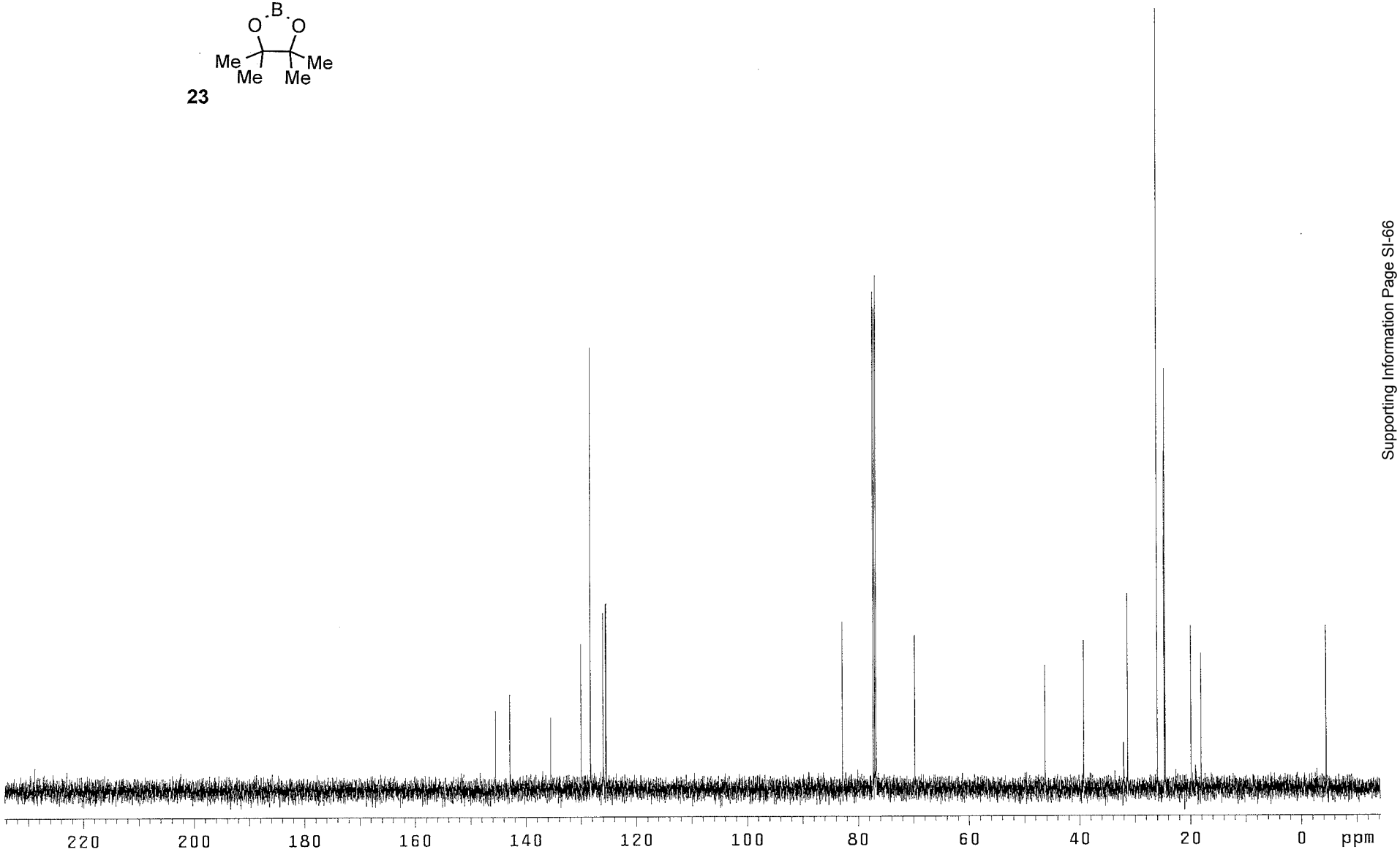



TBSO
Me
Ph
B
O
O
Me
Me
Me
Me

23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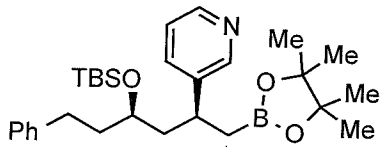
ppm



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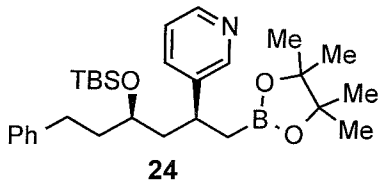
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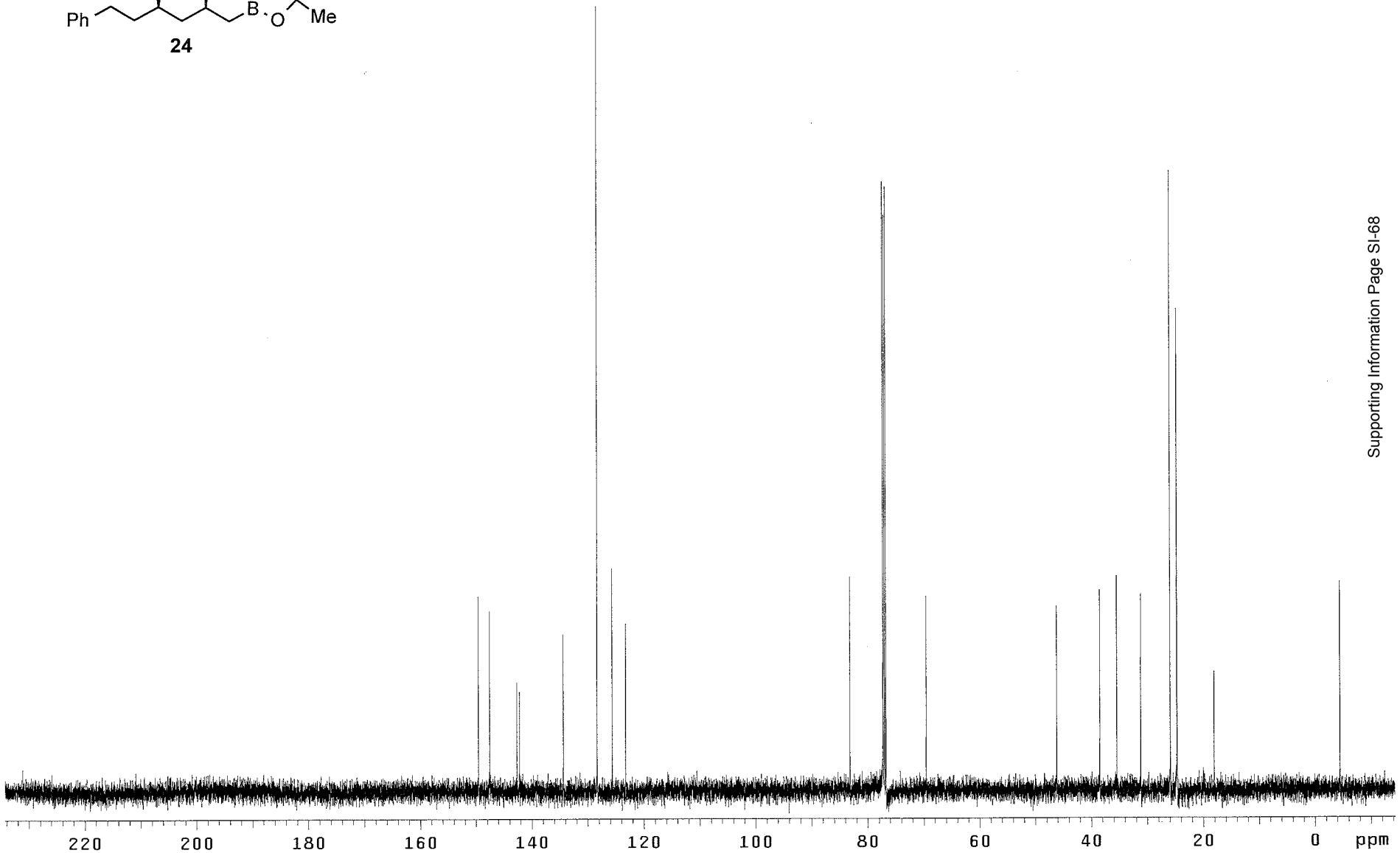
Me
Me
TBSO
O
Me
B
O
Me
Ph

24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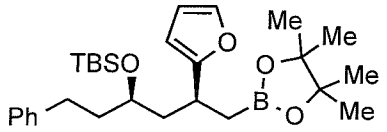
120
100
80
60
40
20
0
ppm



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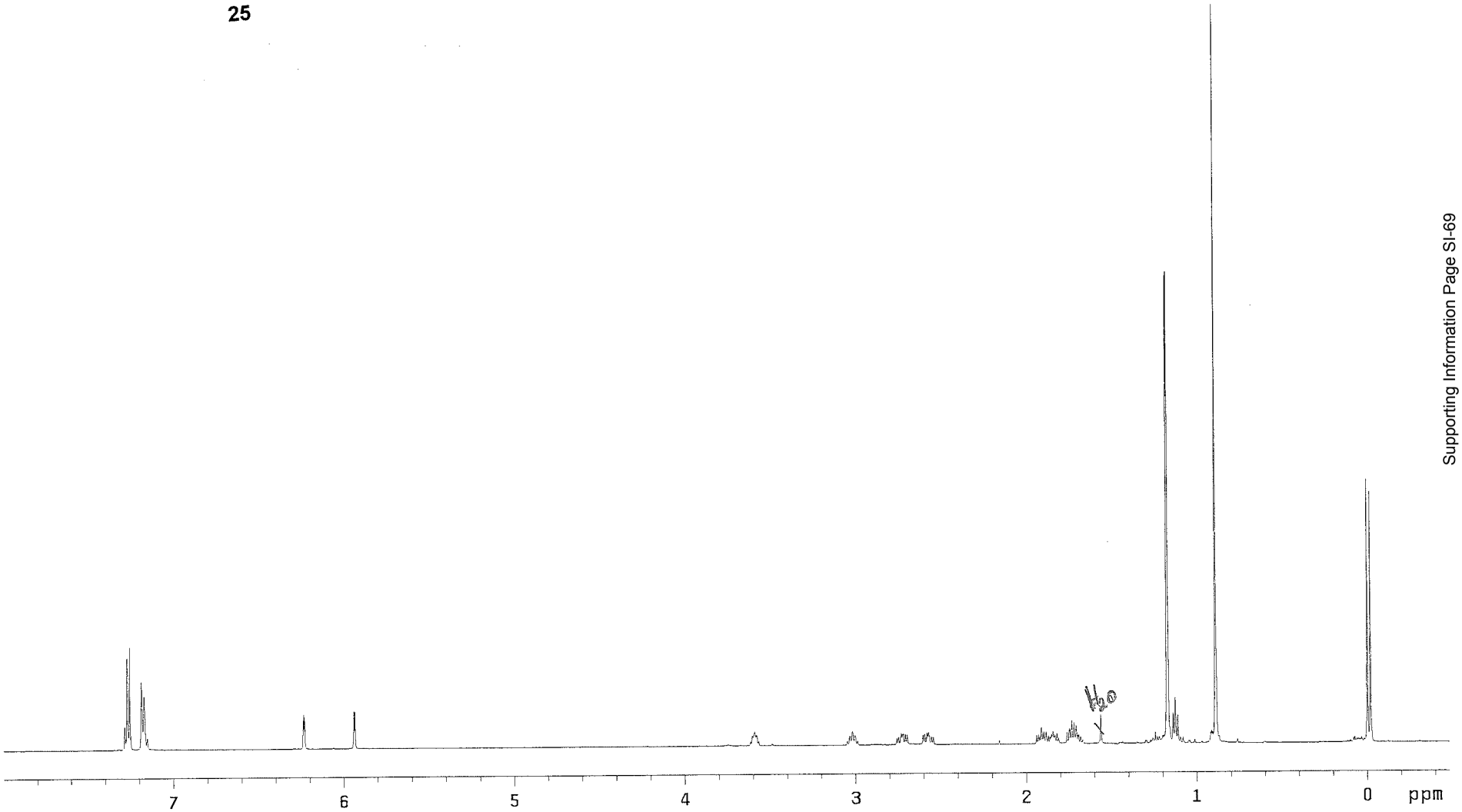

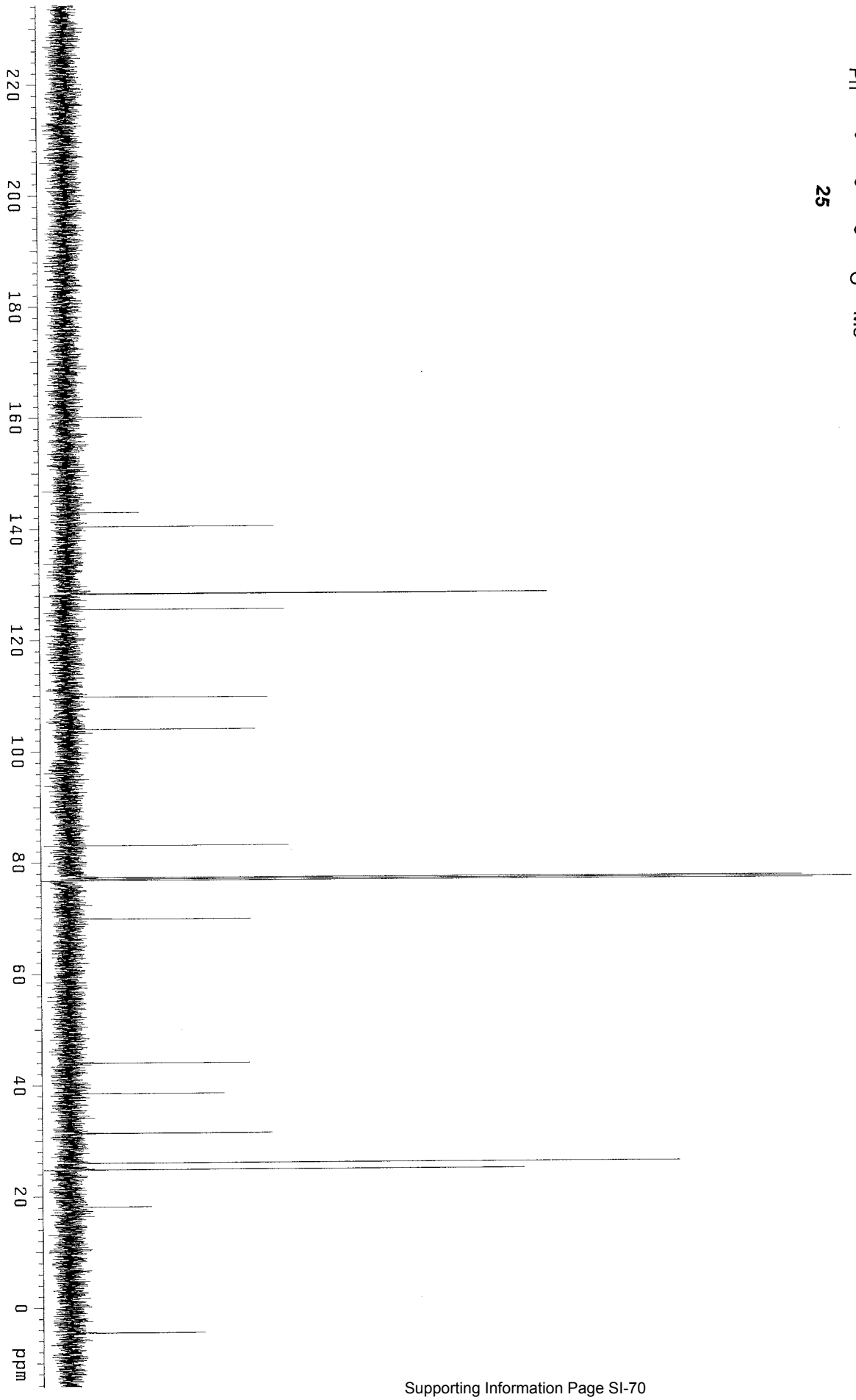
Ph
TBSO
O
B
O
O
Me
Me
Me
Me
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220
200
180
160
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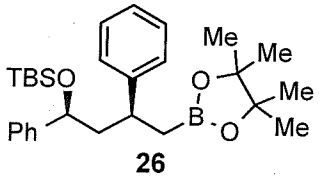
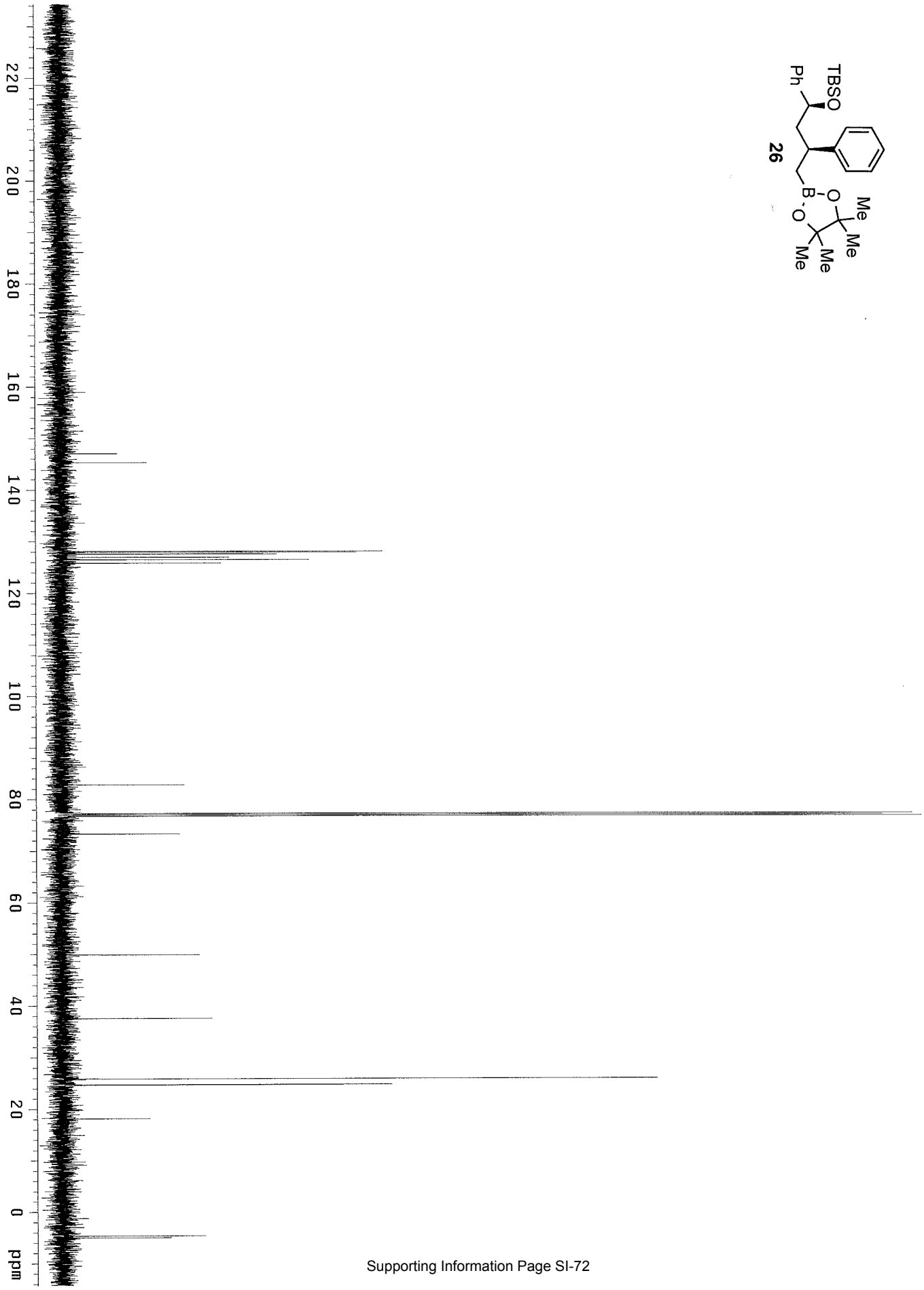
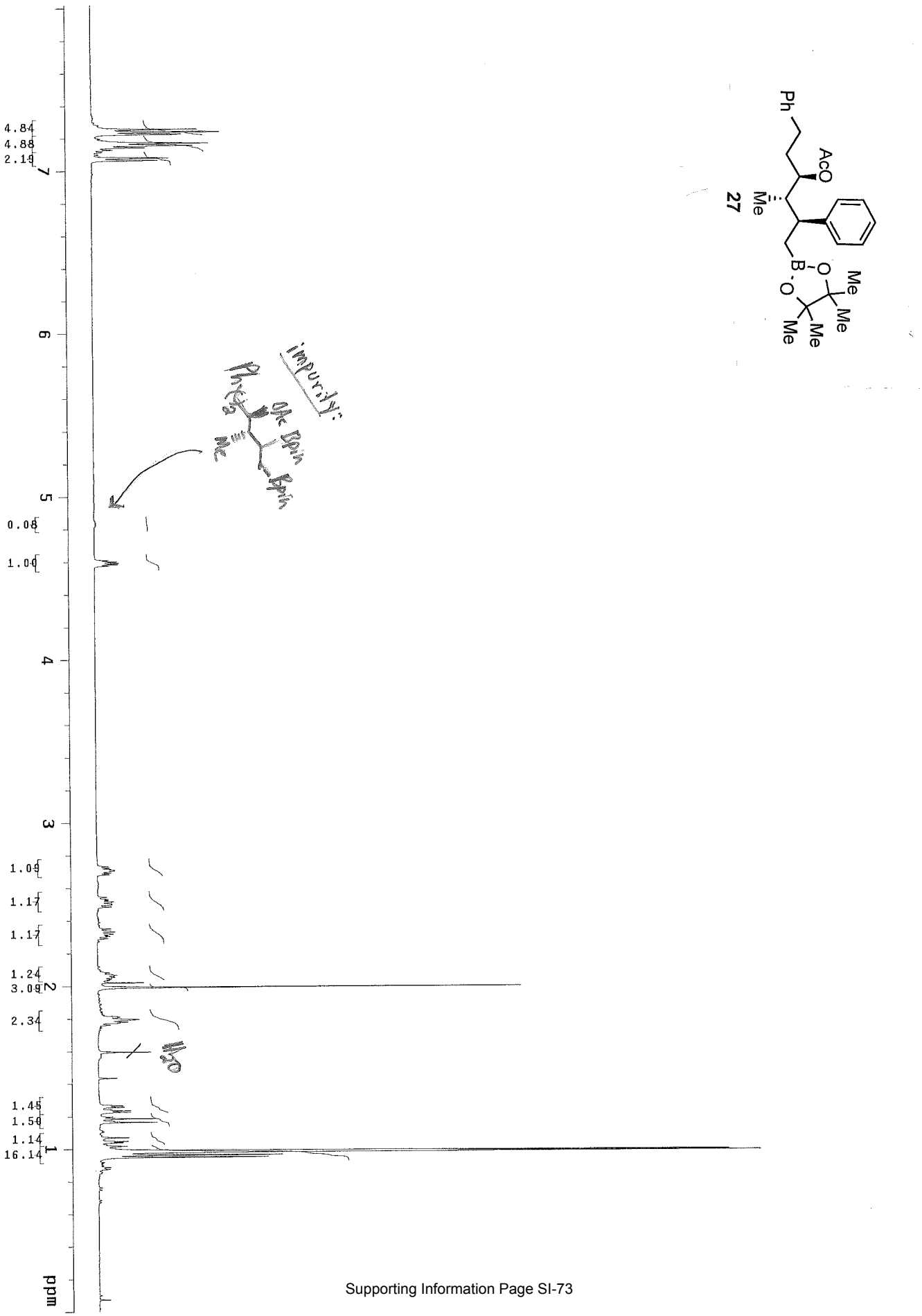
120
100
80
60
40
20
0
ppm


TBSO
Ph
Me
Me
Me
Me
O
O
B
26

H6
7
6
5
4
3
2
1
0
ppm


TBSO
Ph
26
B
O
O
Me
Me
Me
Me
220
200
180
160
140
120
100
80
60
40
20
0
ppm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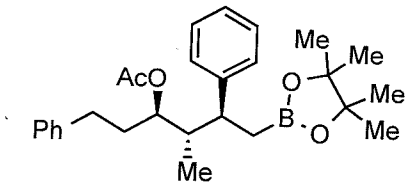
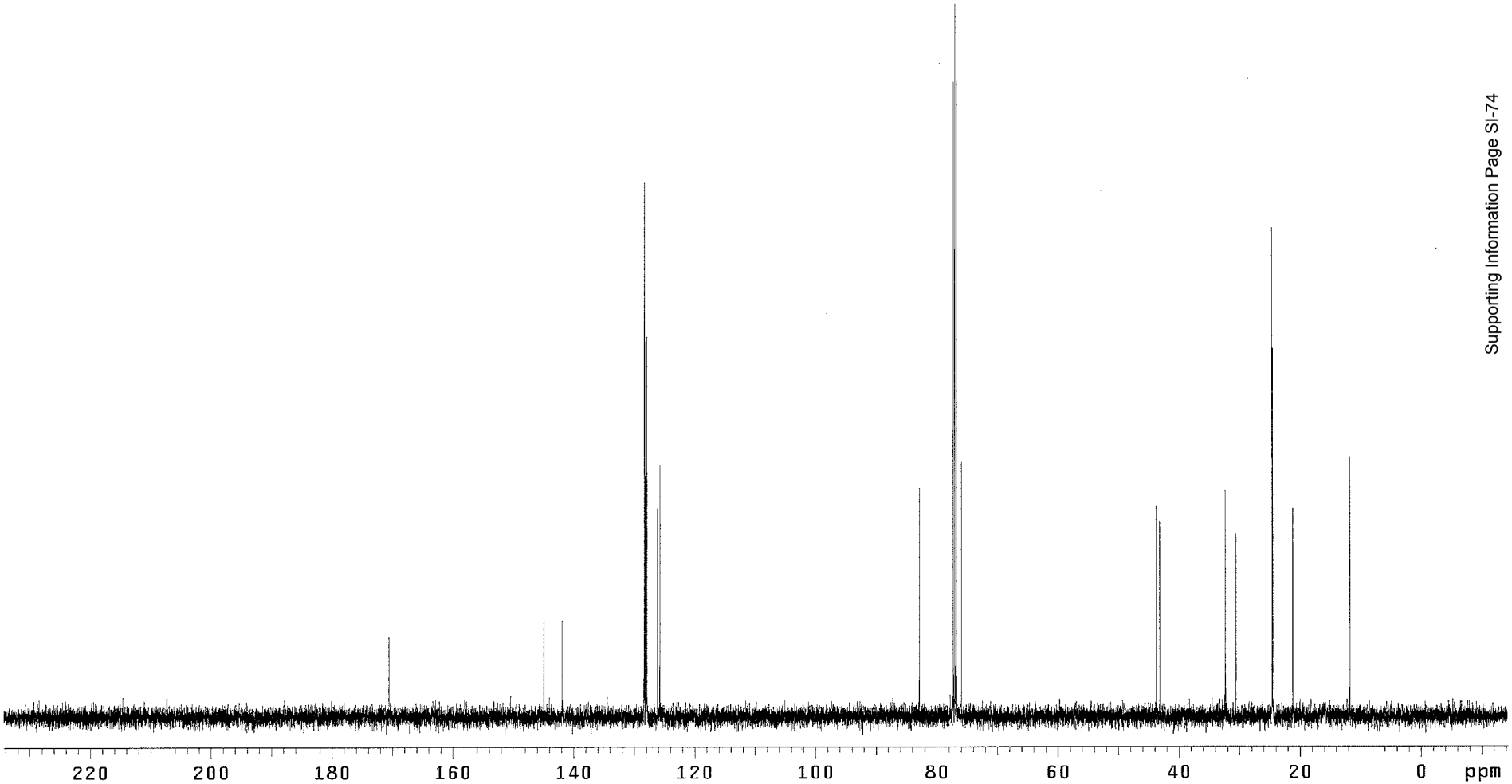
4.88
2.19
0.08
1.00
1.09
1.17
1.17
1.24
3.09
2.34
1.45
1.50
1.14
16.14
7
6
5
4
3
2
1
ppm
impurity:
H2O
Ph
AcO
Me
27
B
O
Me
Me
Me
Me


Me
Me
AcO
O
Me
Ph
B
O
Me
Me

27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200
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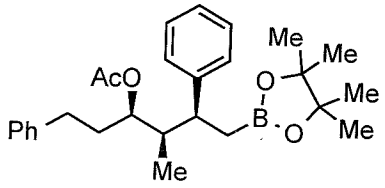
160
140
120
100
80
60
40
20
0
ppm



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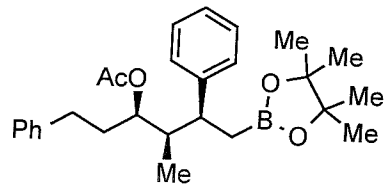
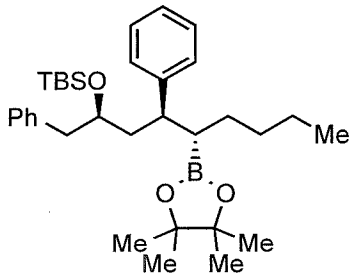

AcO
Ph
Me
Me
Me
Me
O
B
O
Me

28

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



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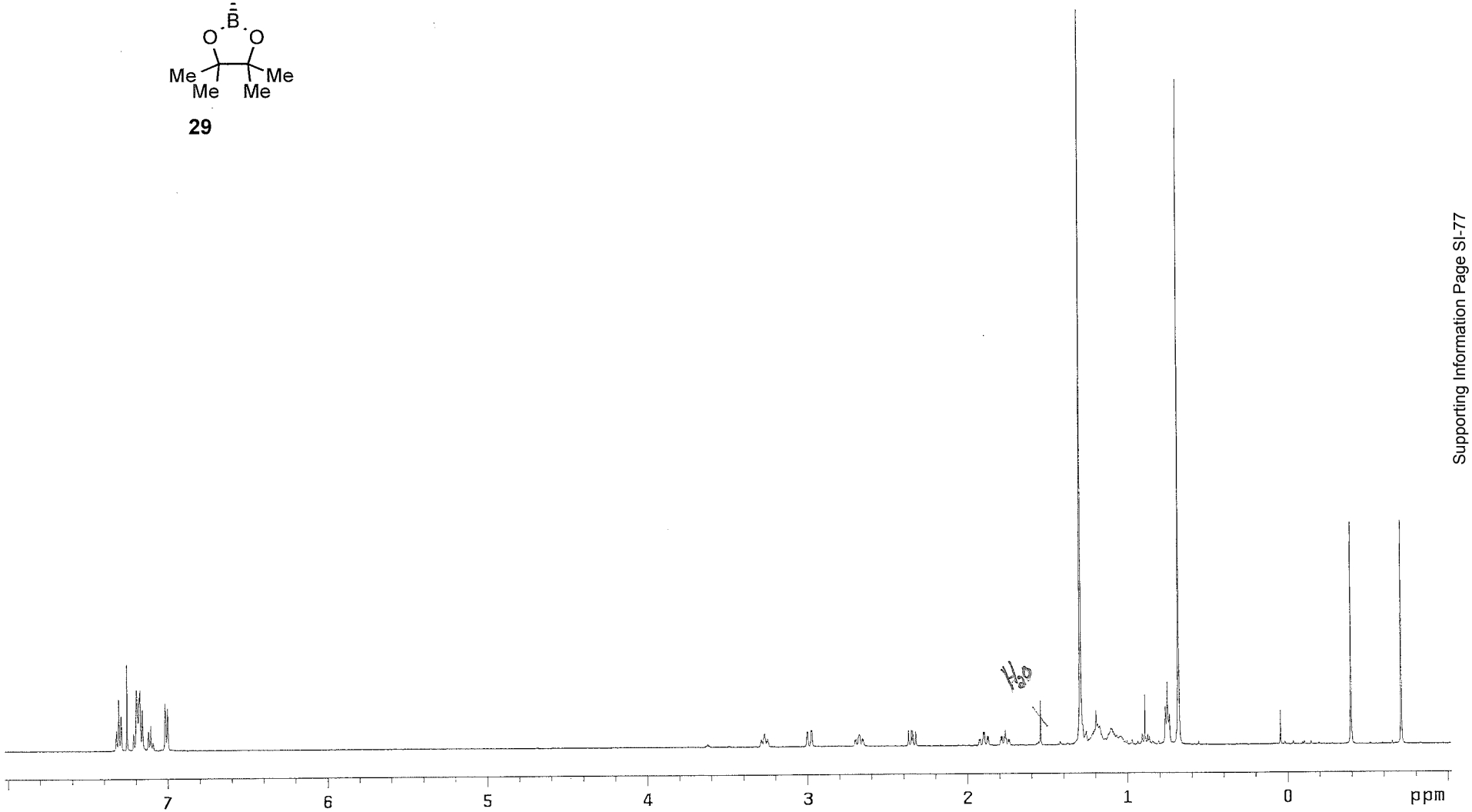
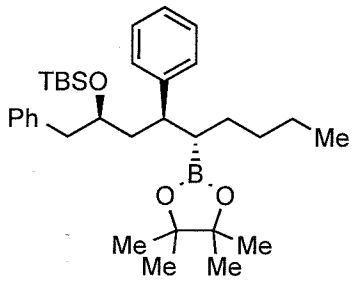
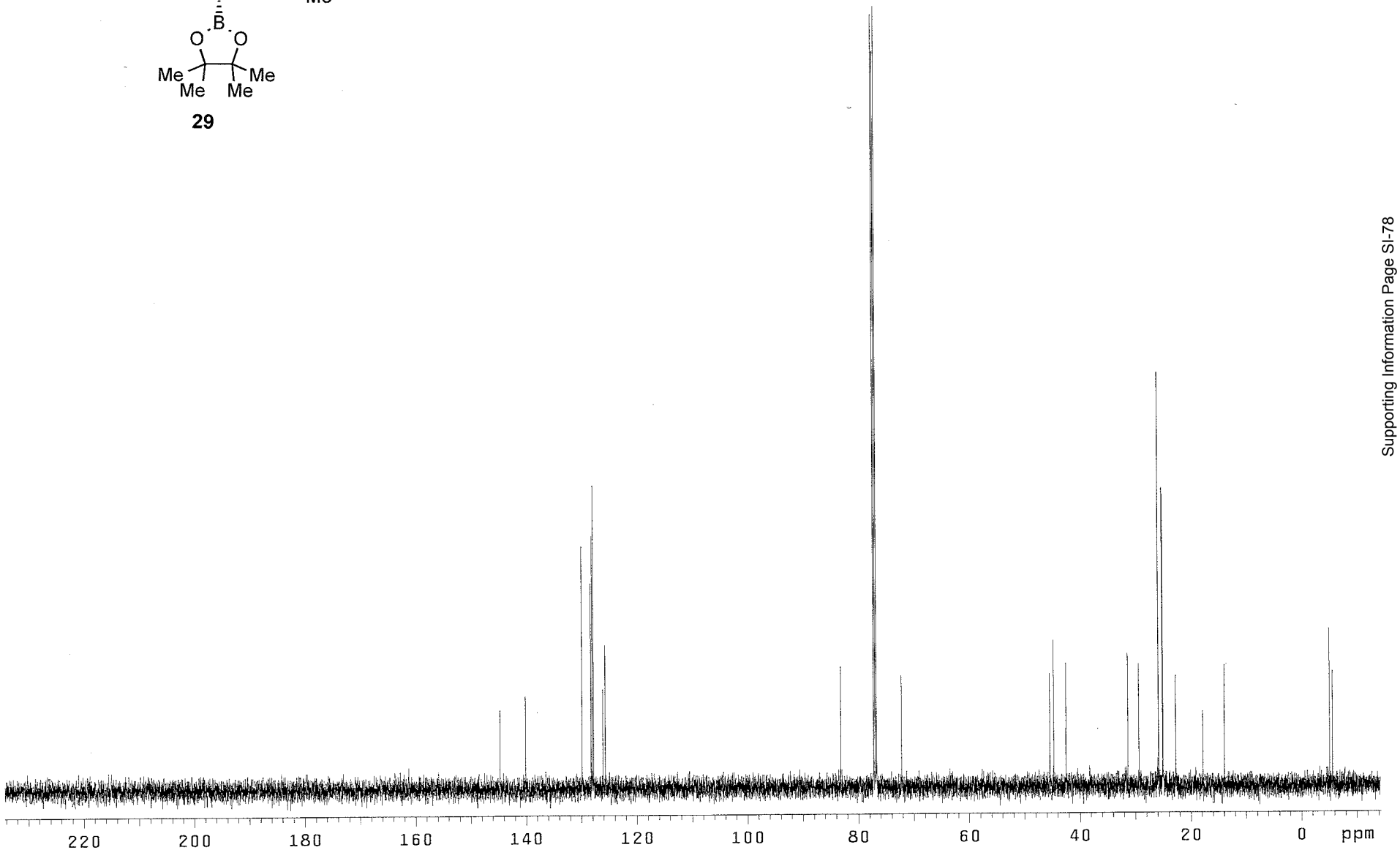



TBSO
Ph
Me
B
O
O
Me
Me
Me
Me

29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200
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160
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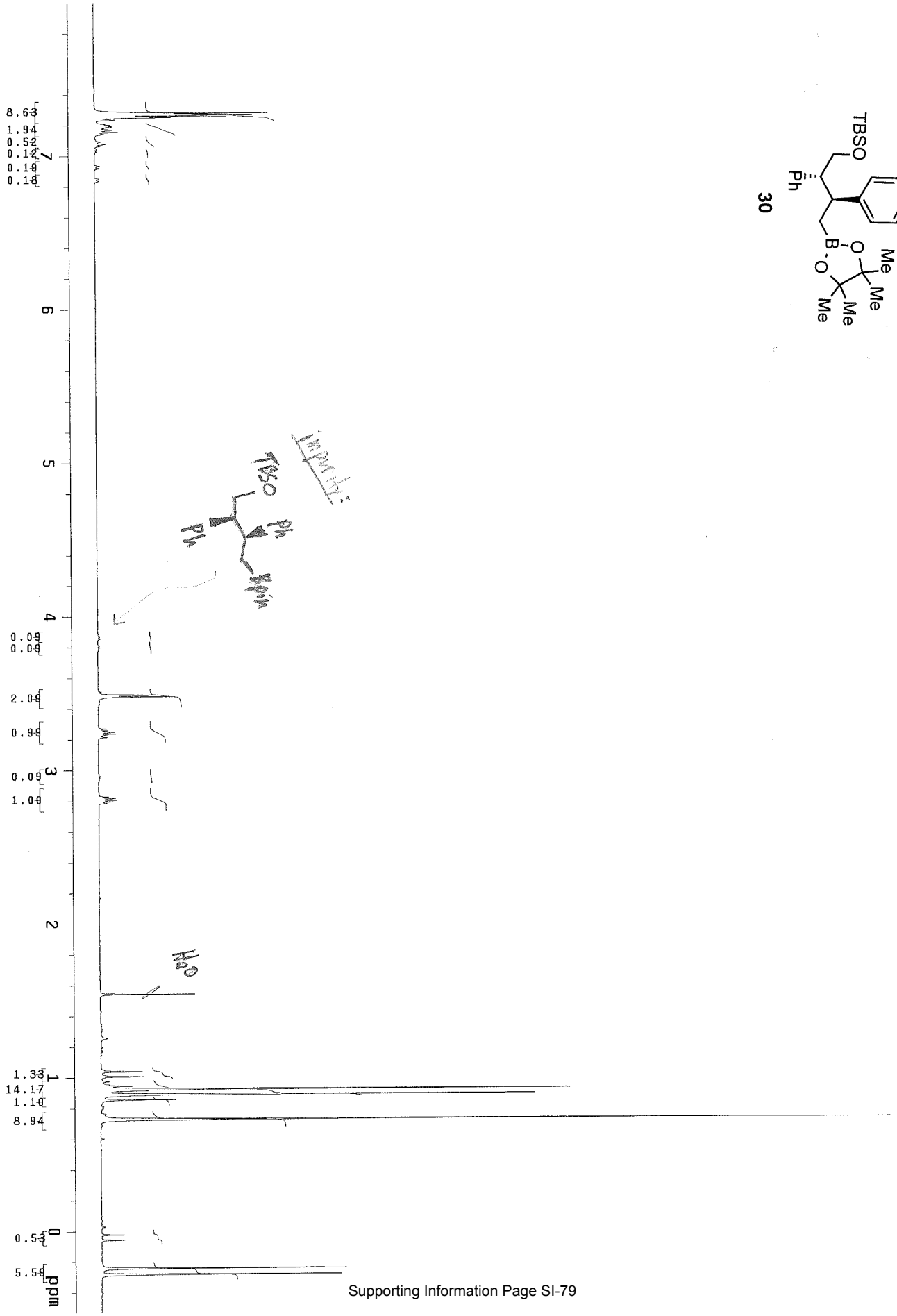
120
100
80
60
40
20
0
ppm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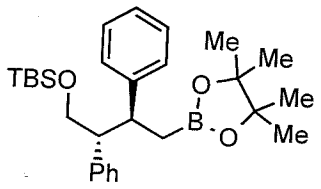
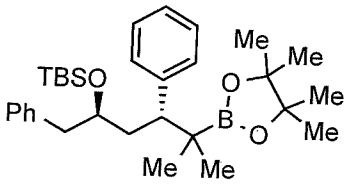
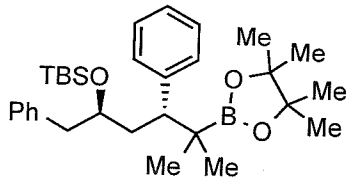
0.19
0.18
0.09
0.09
2.09
0.99
0.09
1.00
1.33
14.17
1.10
8.94
0.53
5.59
ppm
TBSO
Ph
Ph
Bpin
H2O
TBSO
Ph
B
O
O
Me
Me
Me
Me
30



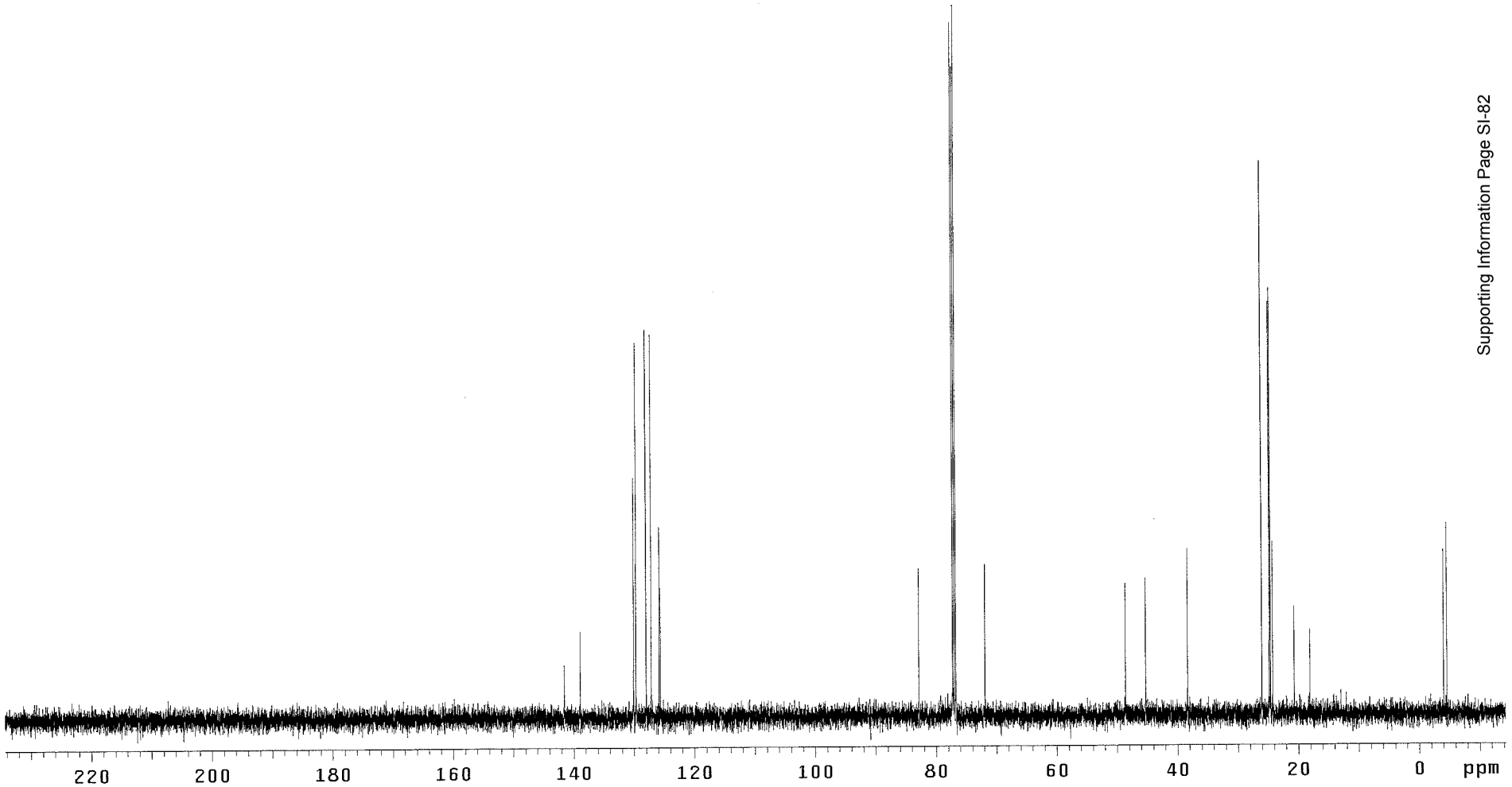
30



31


TBSO
Ph
Me
Me
O
B
O
Me
Me
Me
Me

31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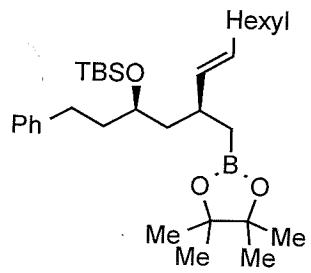

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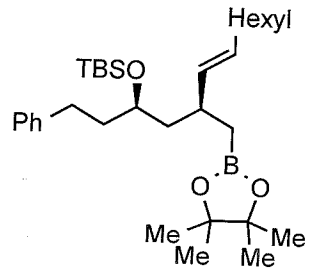
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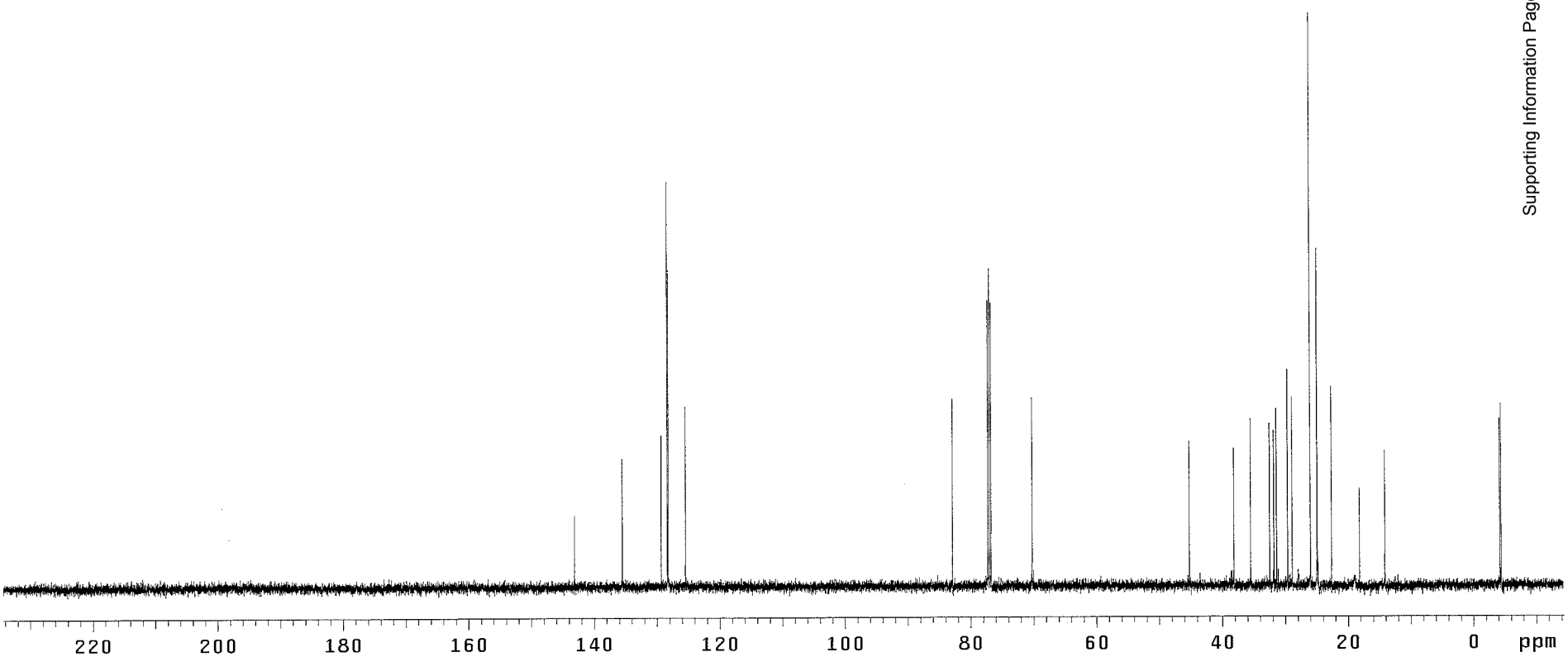
Me

32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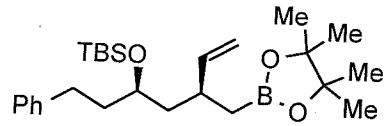

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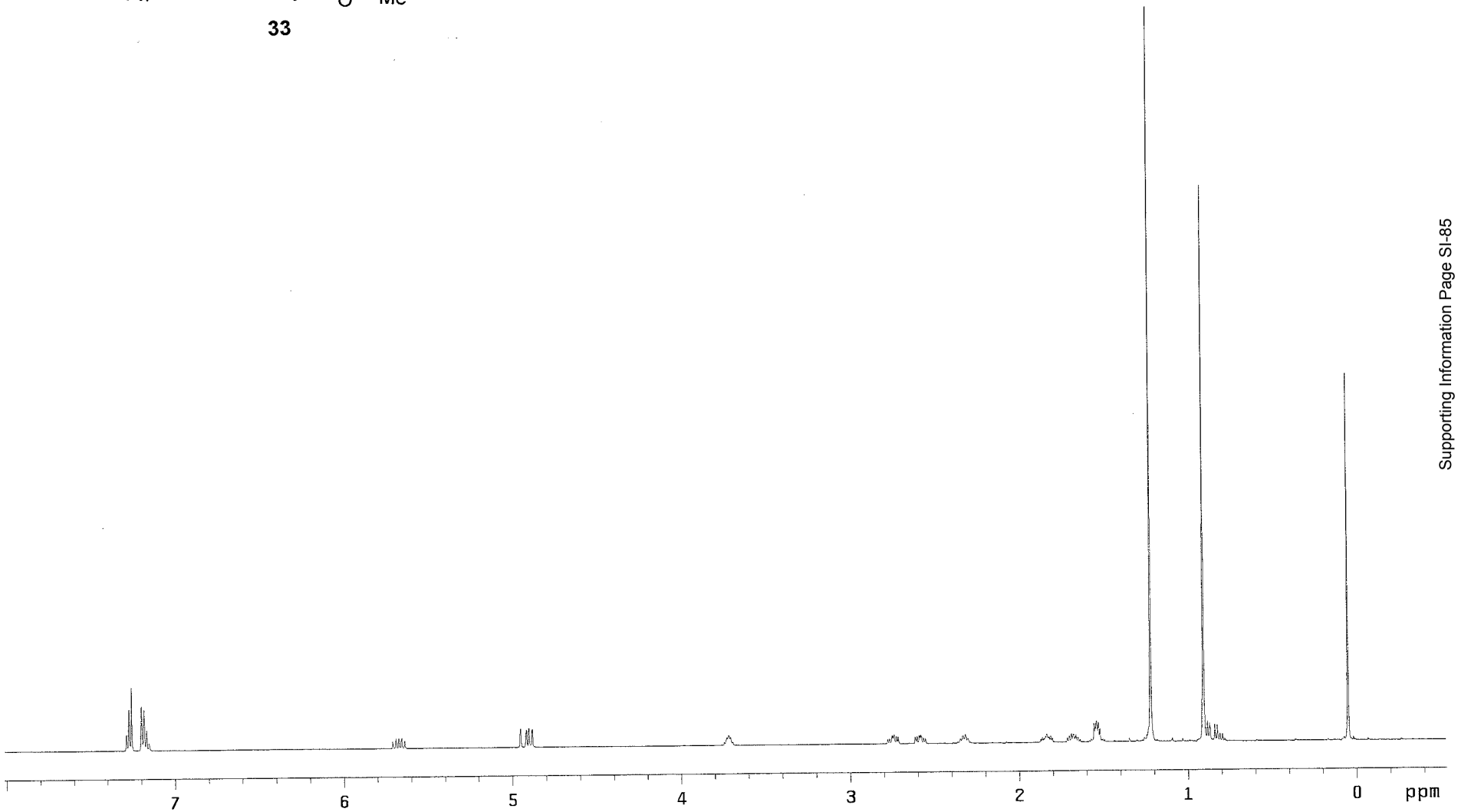

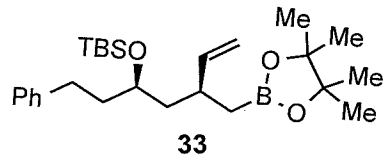
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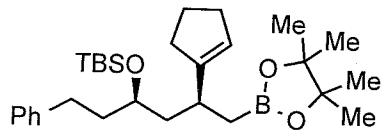

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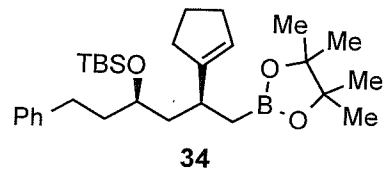
TBSO
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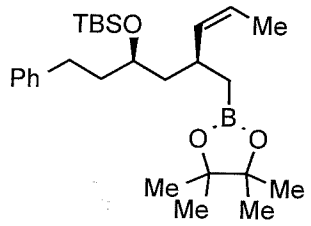
ppm



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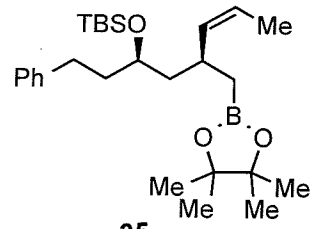
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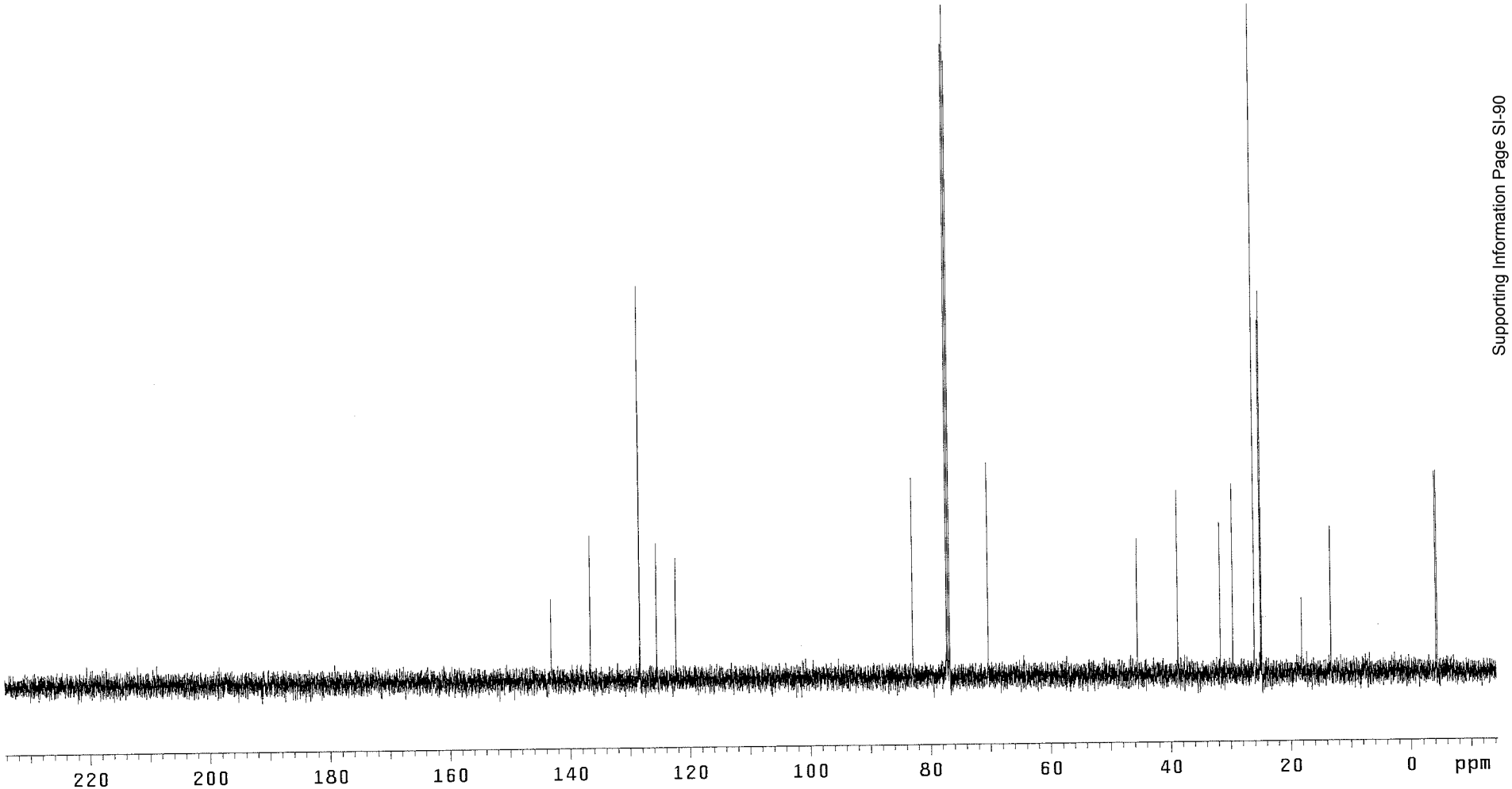
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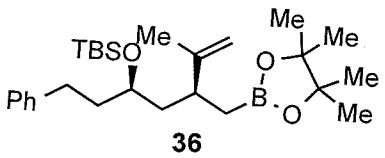

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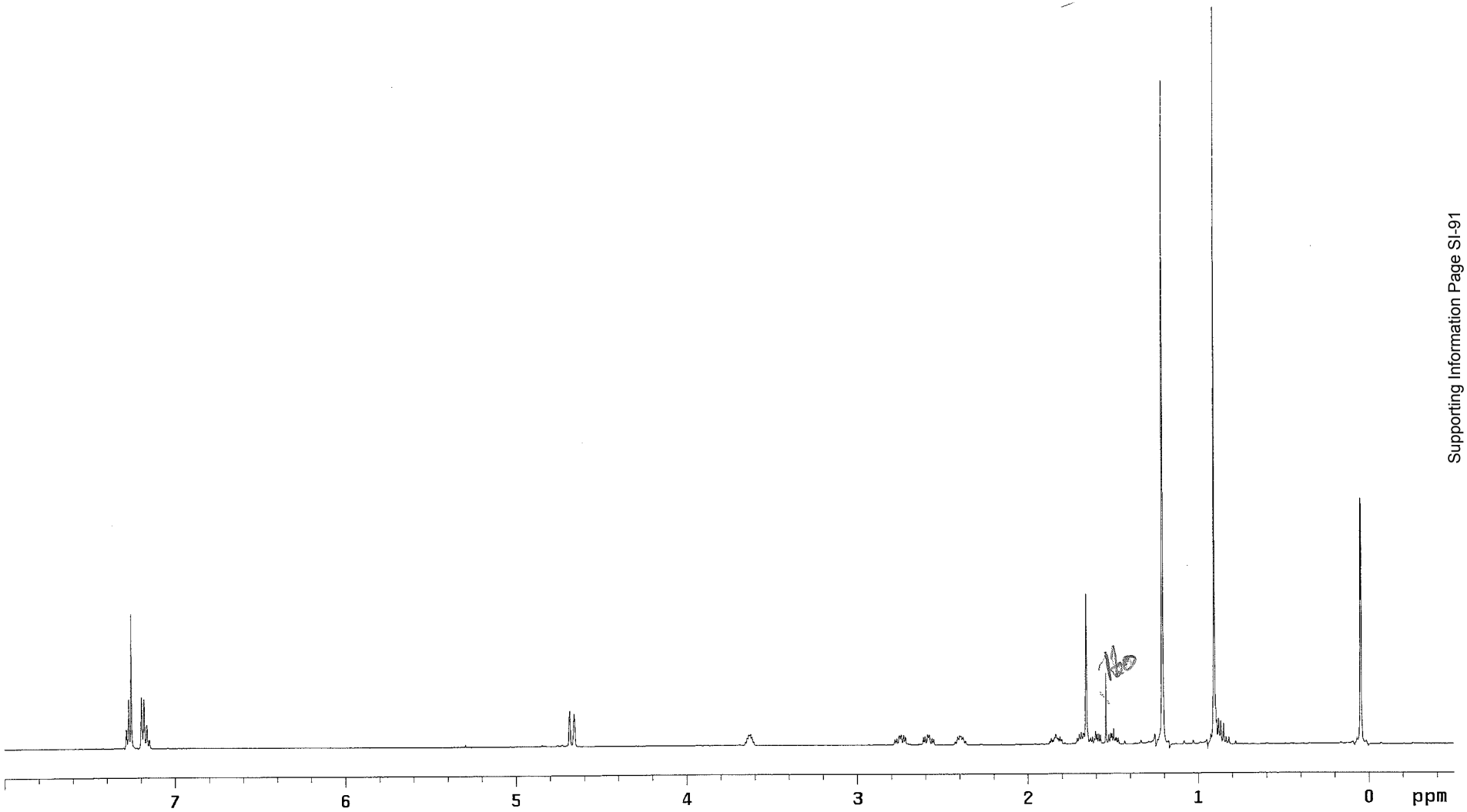

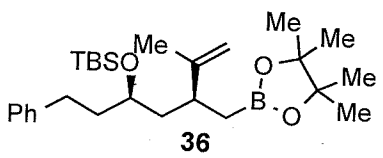
Me
Me
TBSO
Me
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Ph
B
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Me

36

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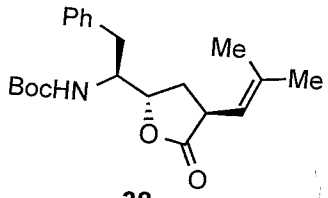
0
ppm



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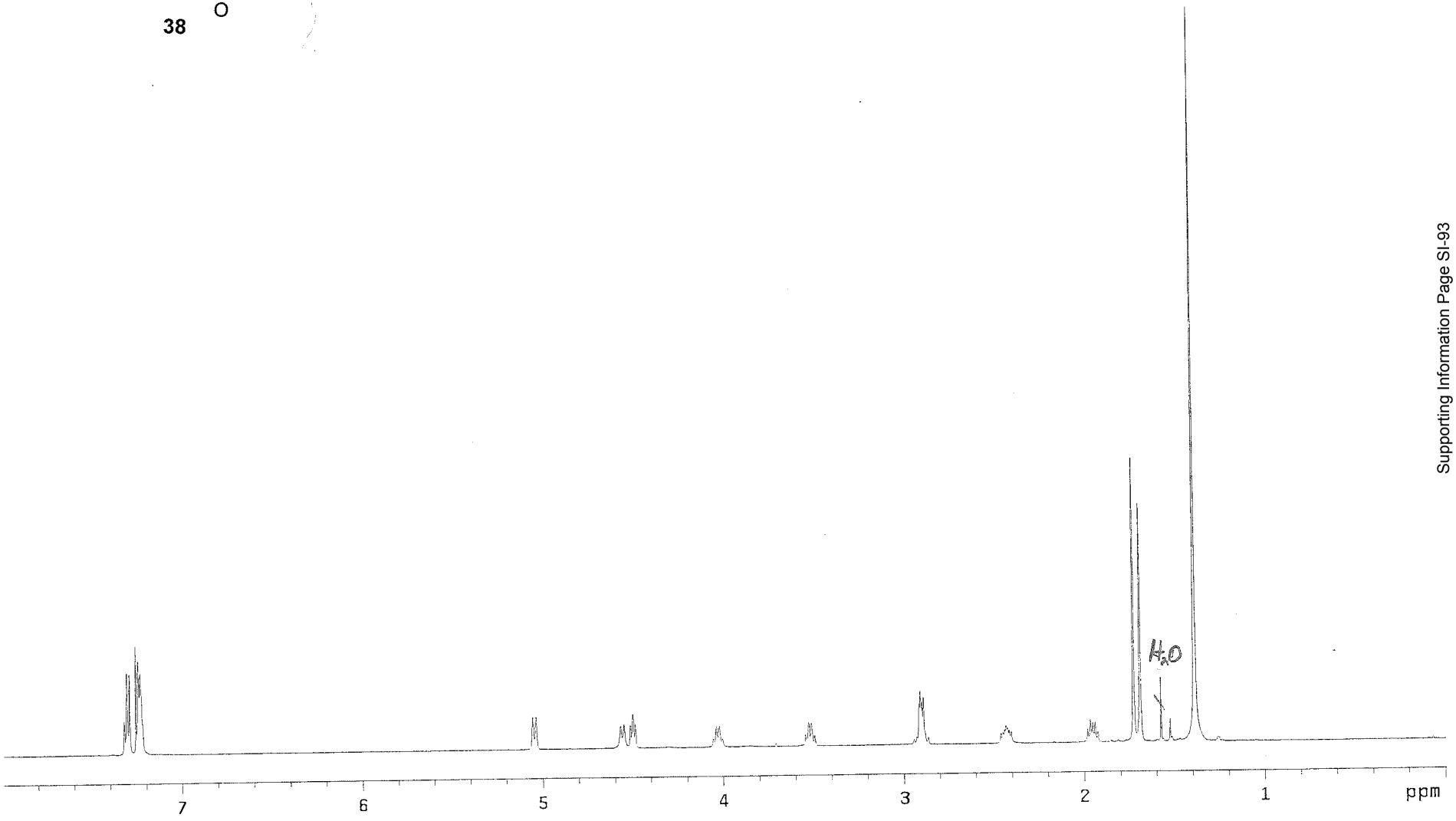

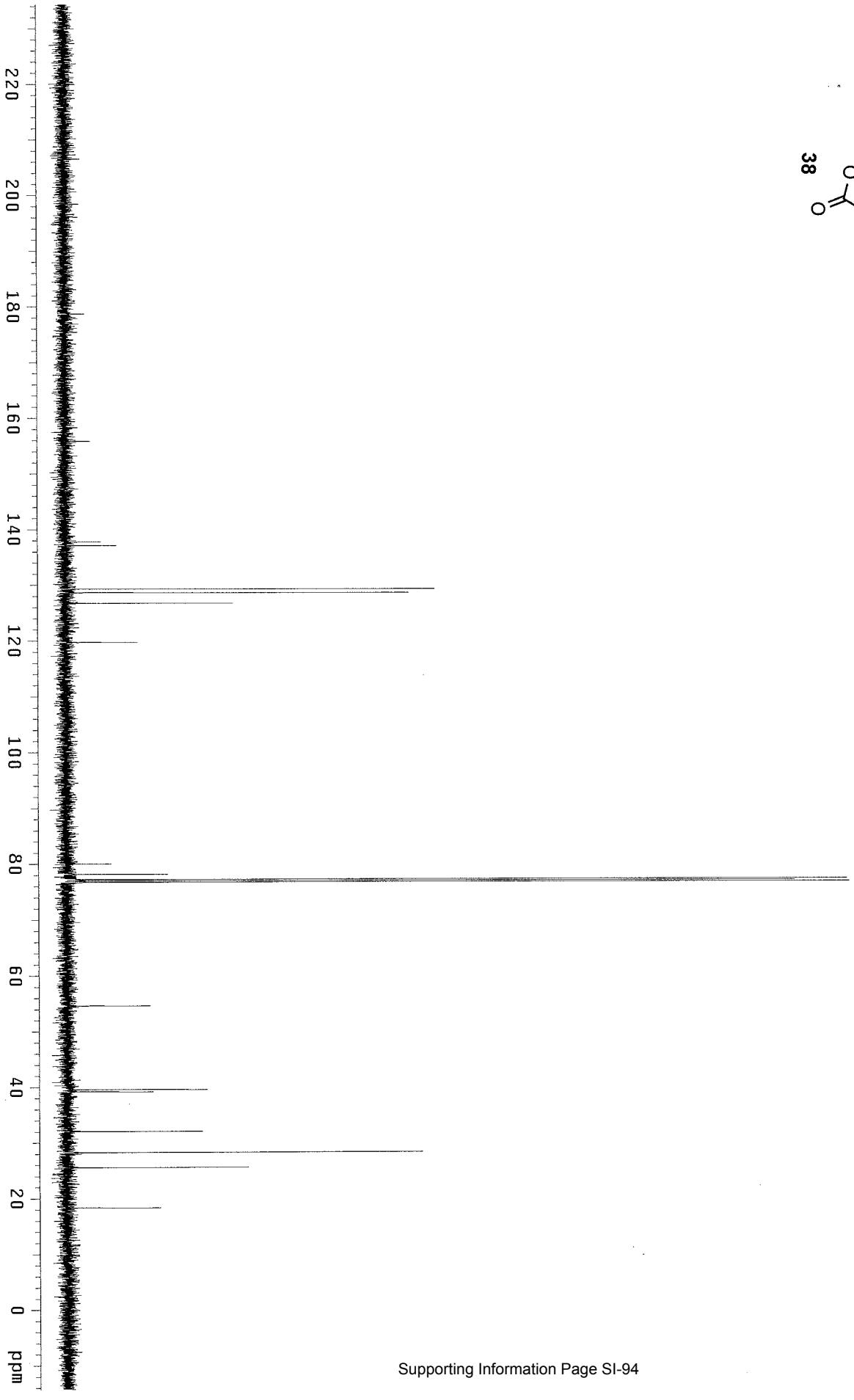

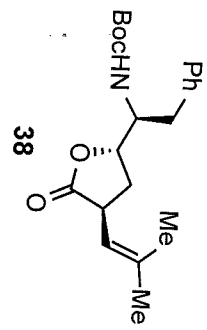

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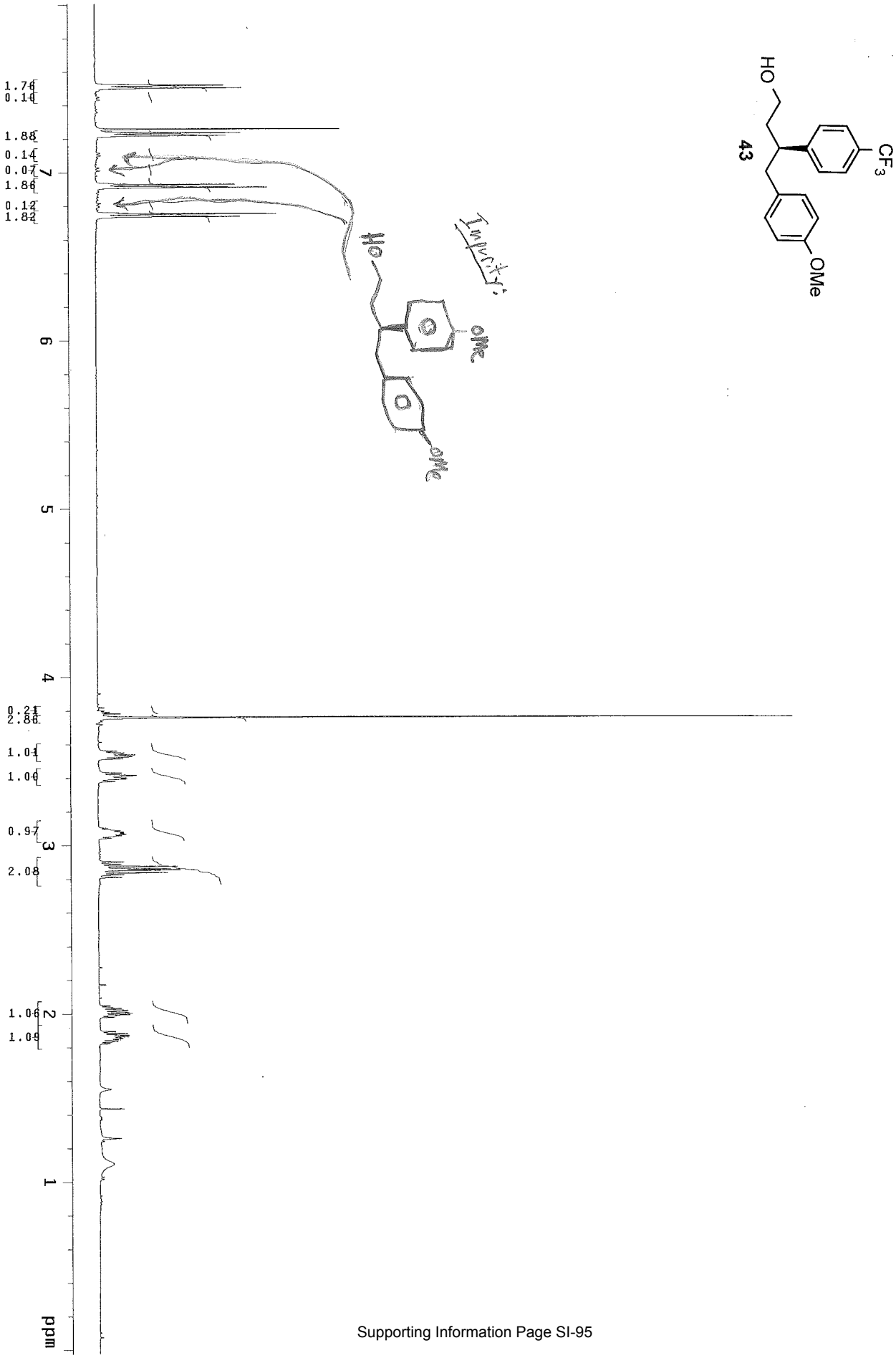
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CF3
43
OMe
Impurity:
HO
OMe
OMe
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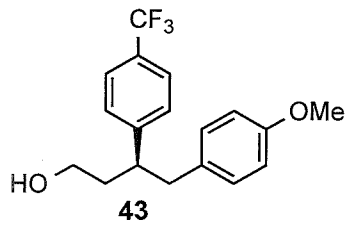
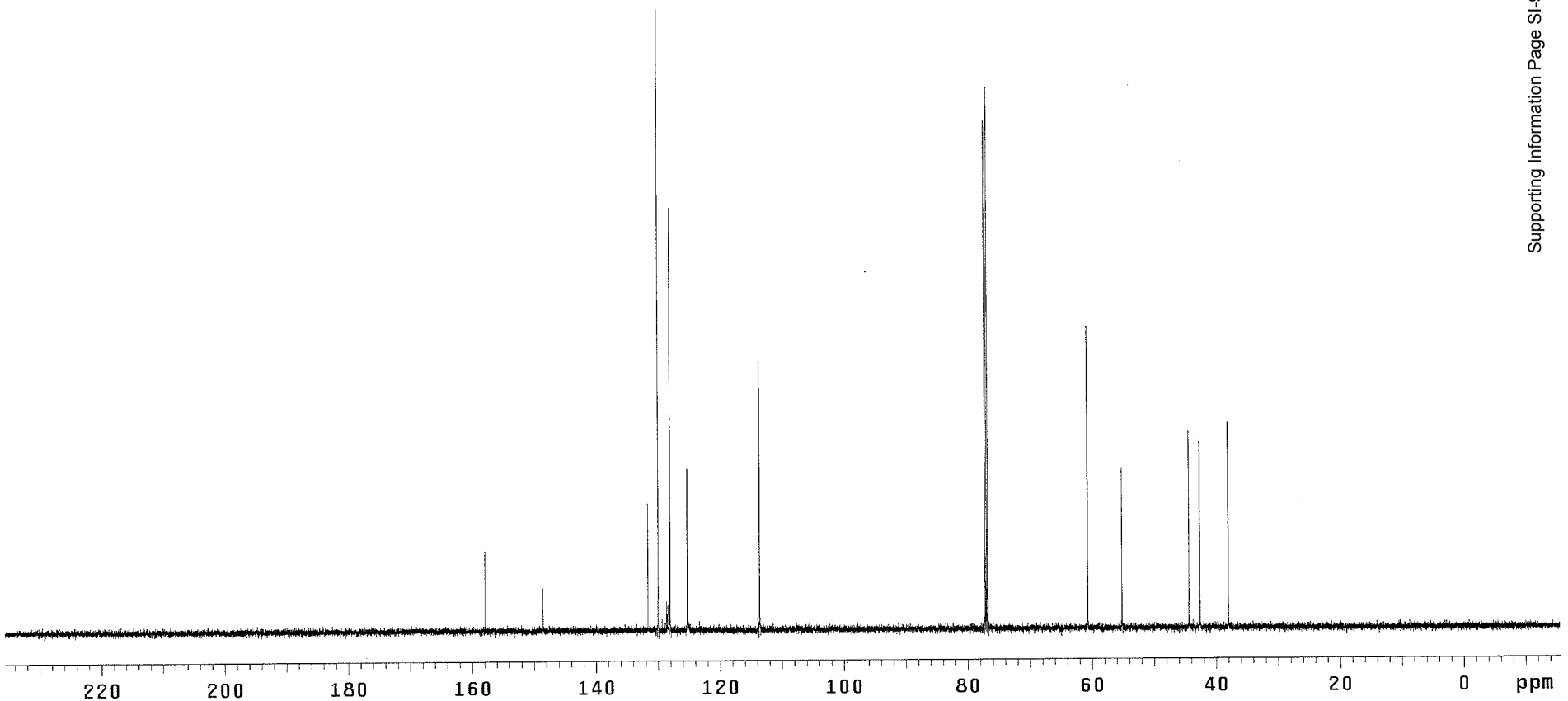
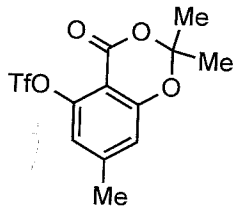
0.14
1.88
0.14
0.07
1.86
0.12
1.82
0.21
2.86
1.01
1.00
0.97
2.08
1.06
1.09
7
6
5
4
3
2
1
ppm



43





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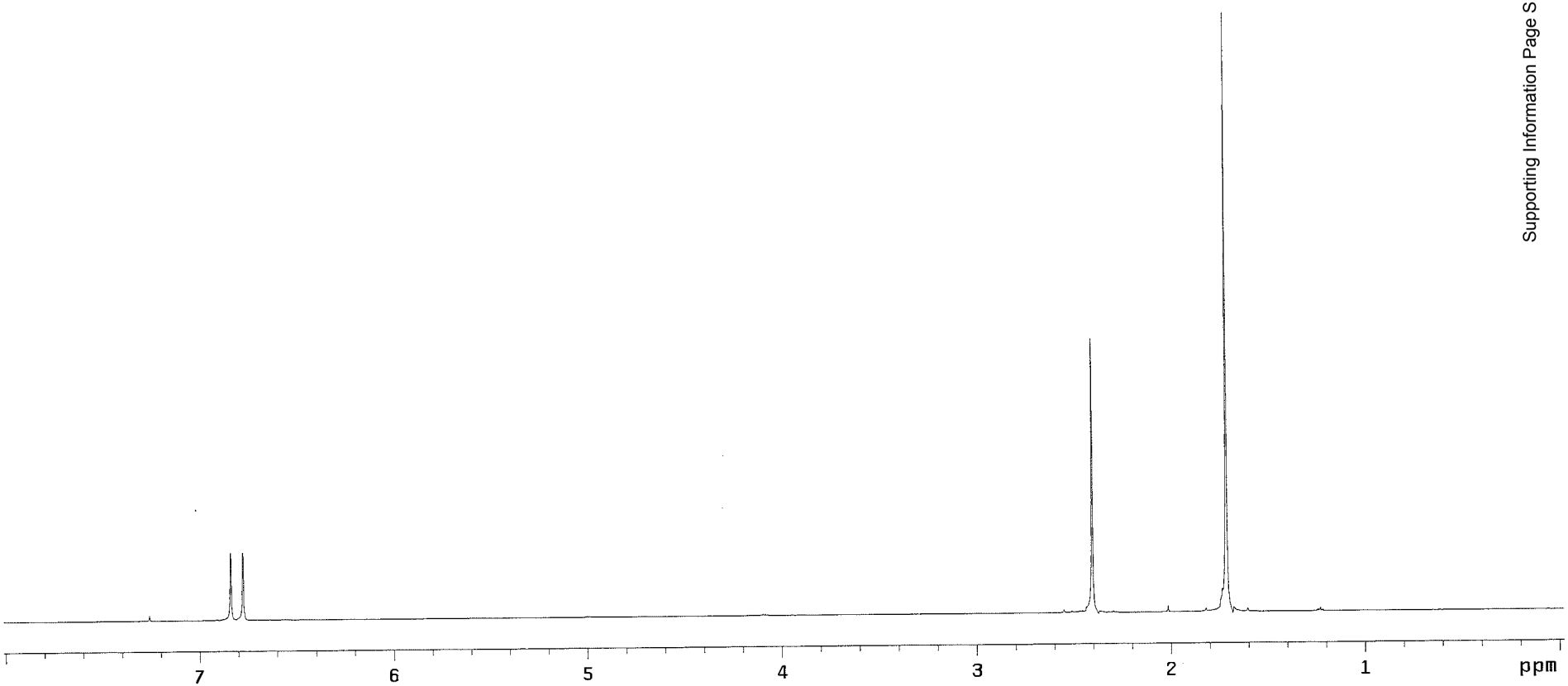

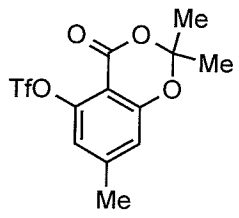

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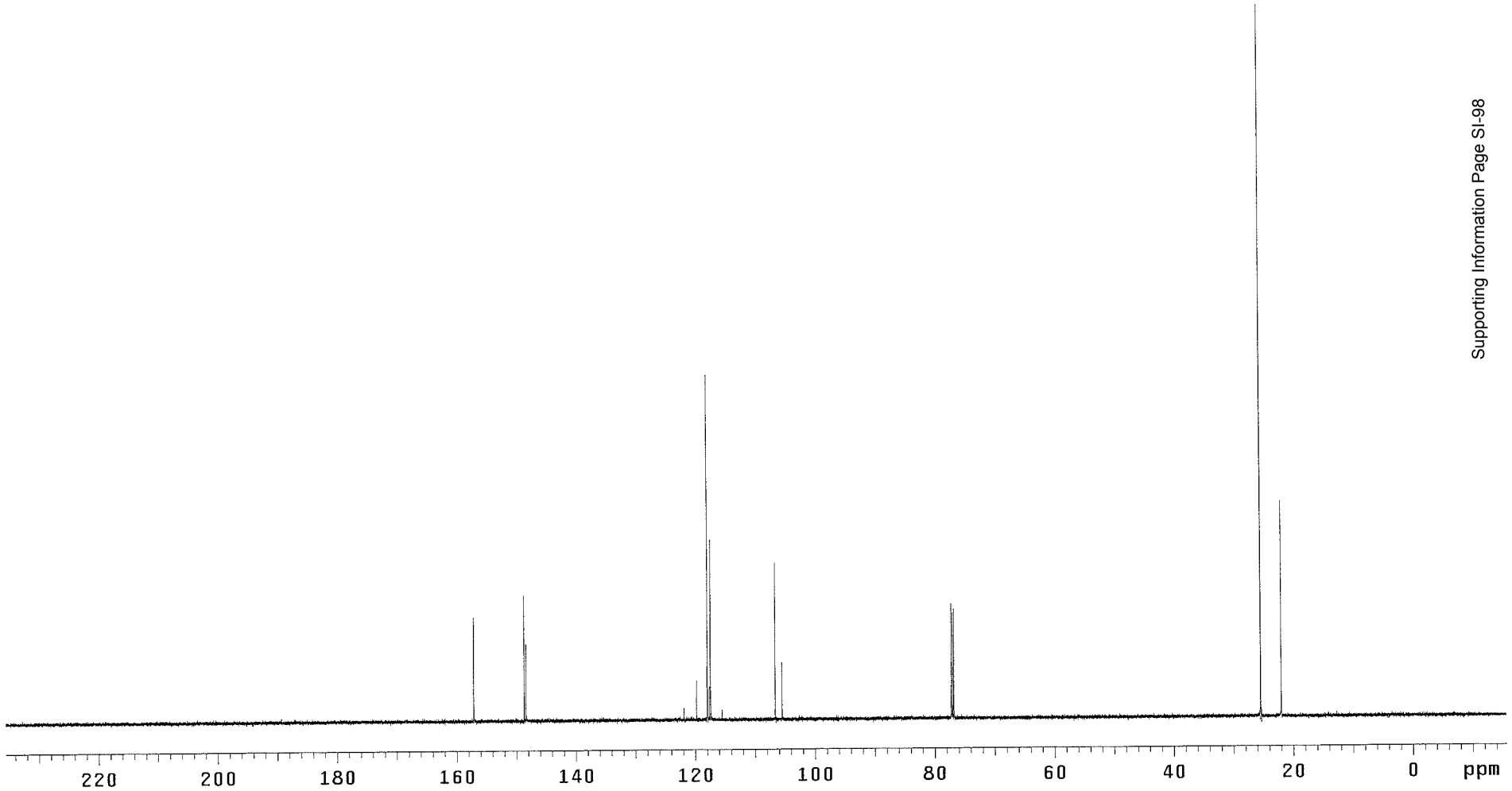

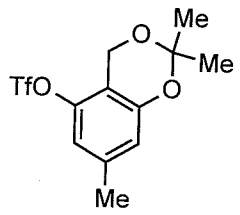

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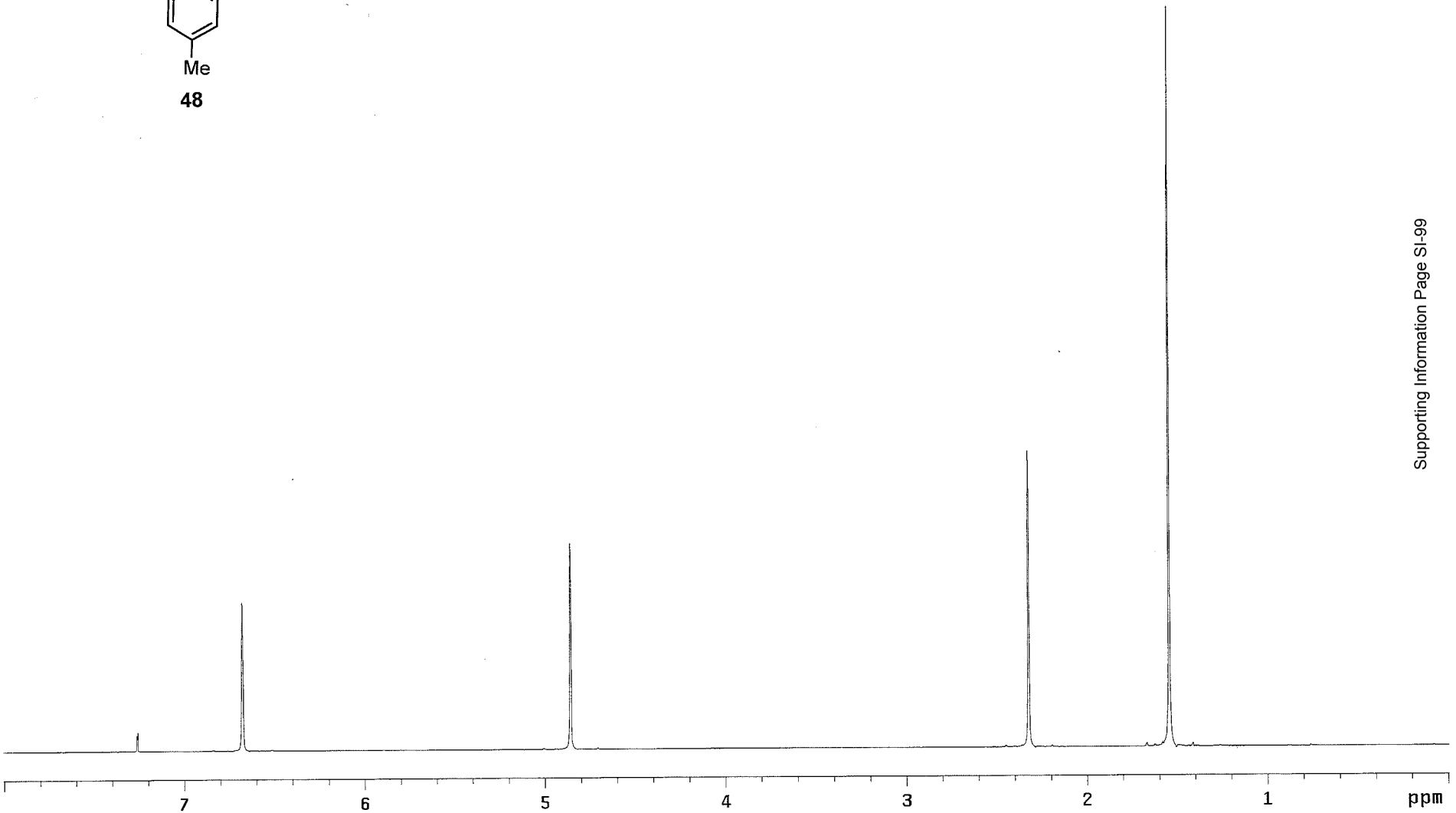

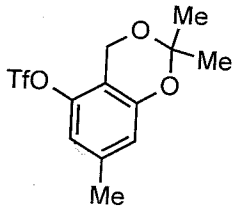

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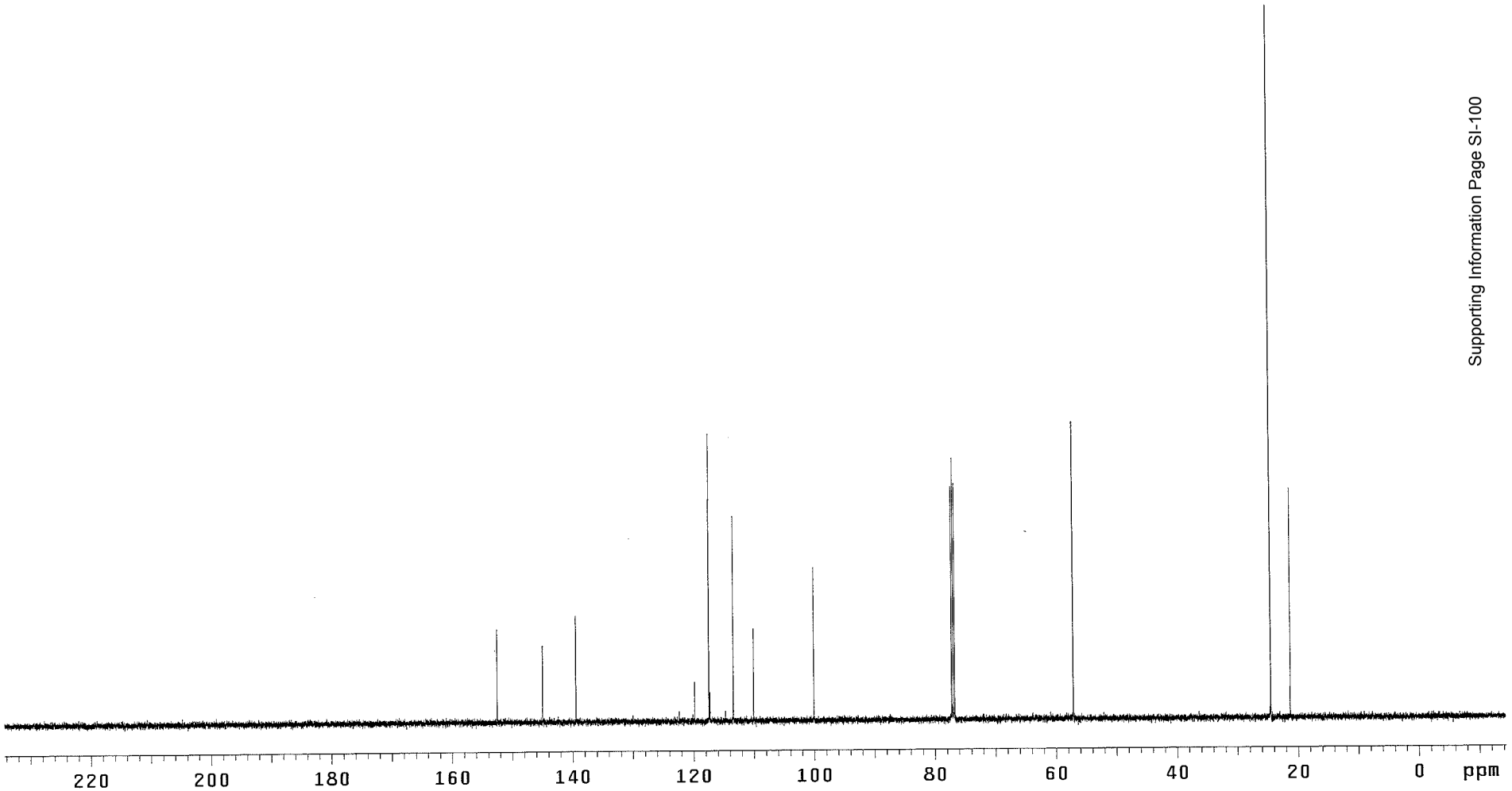

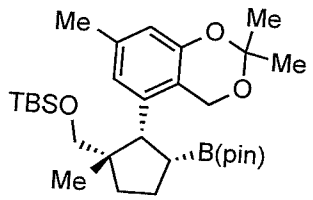

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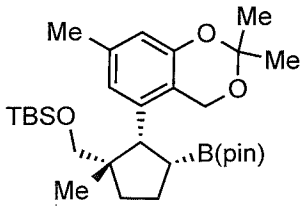

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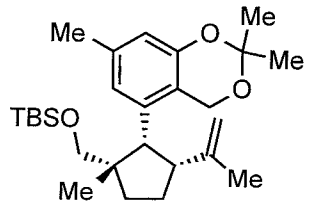

50

TBSO
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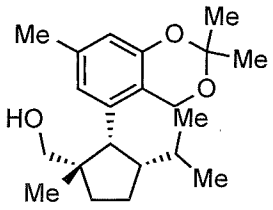

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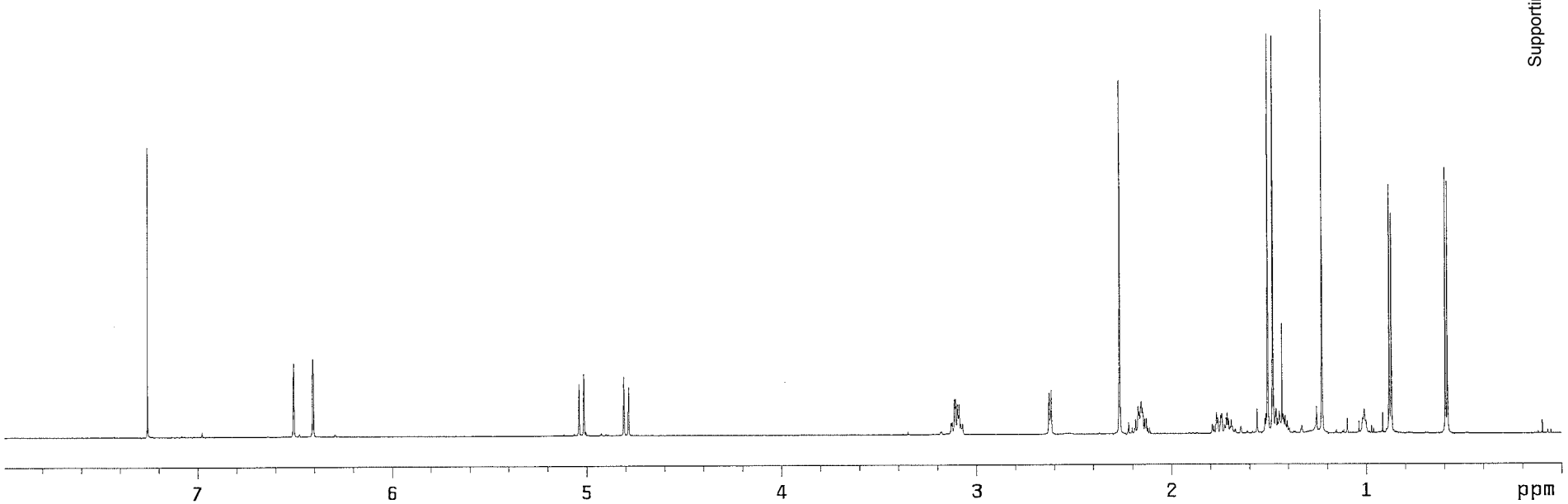

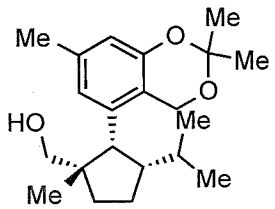

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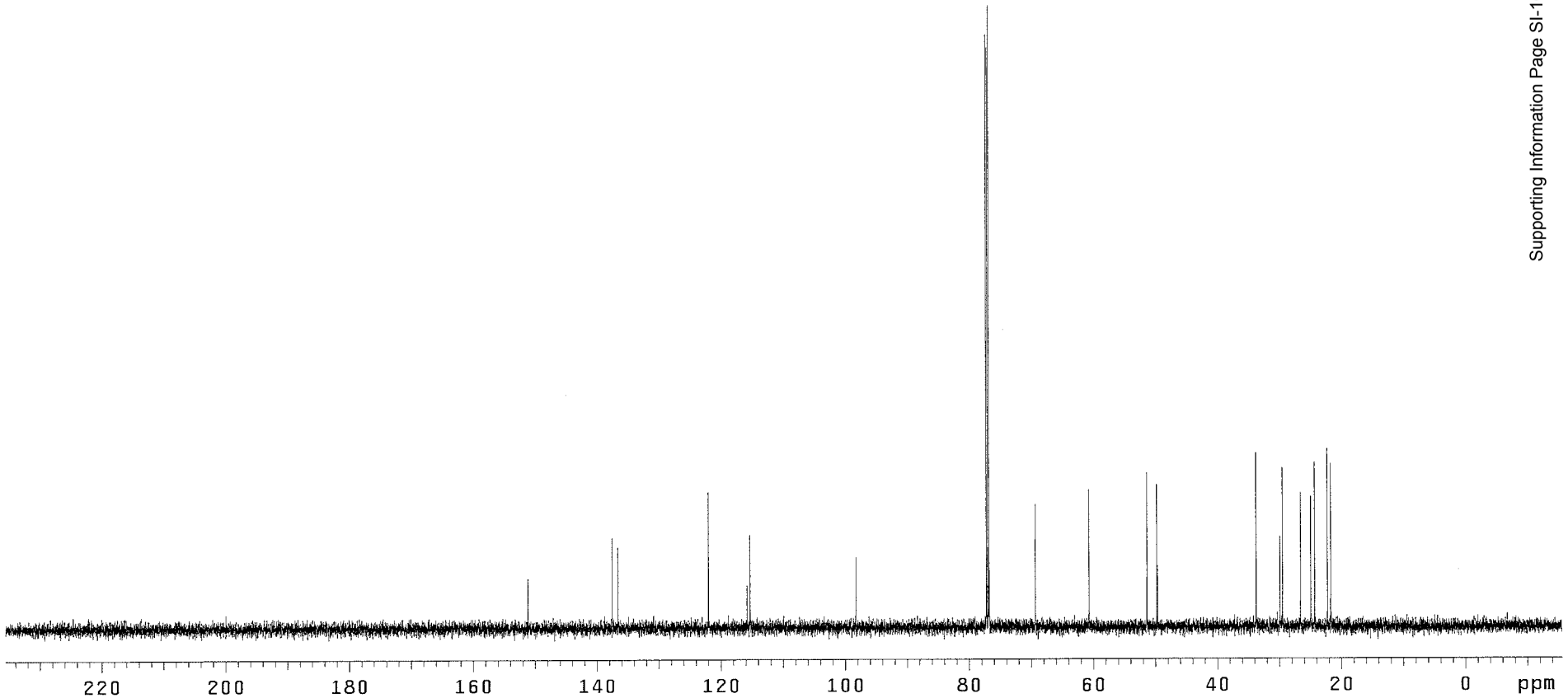

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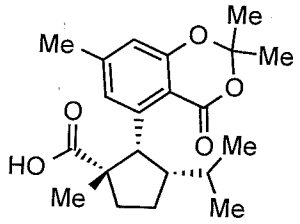
Me
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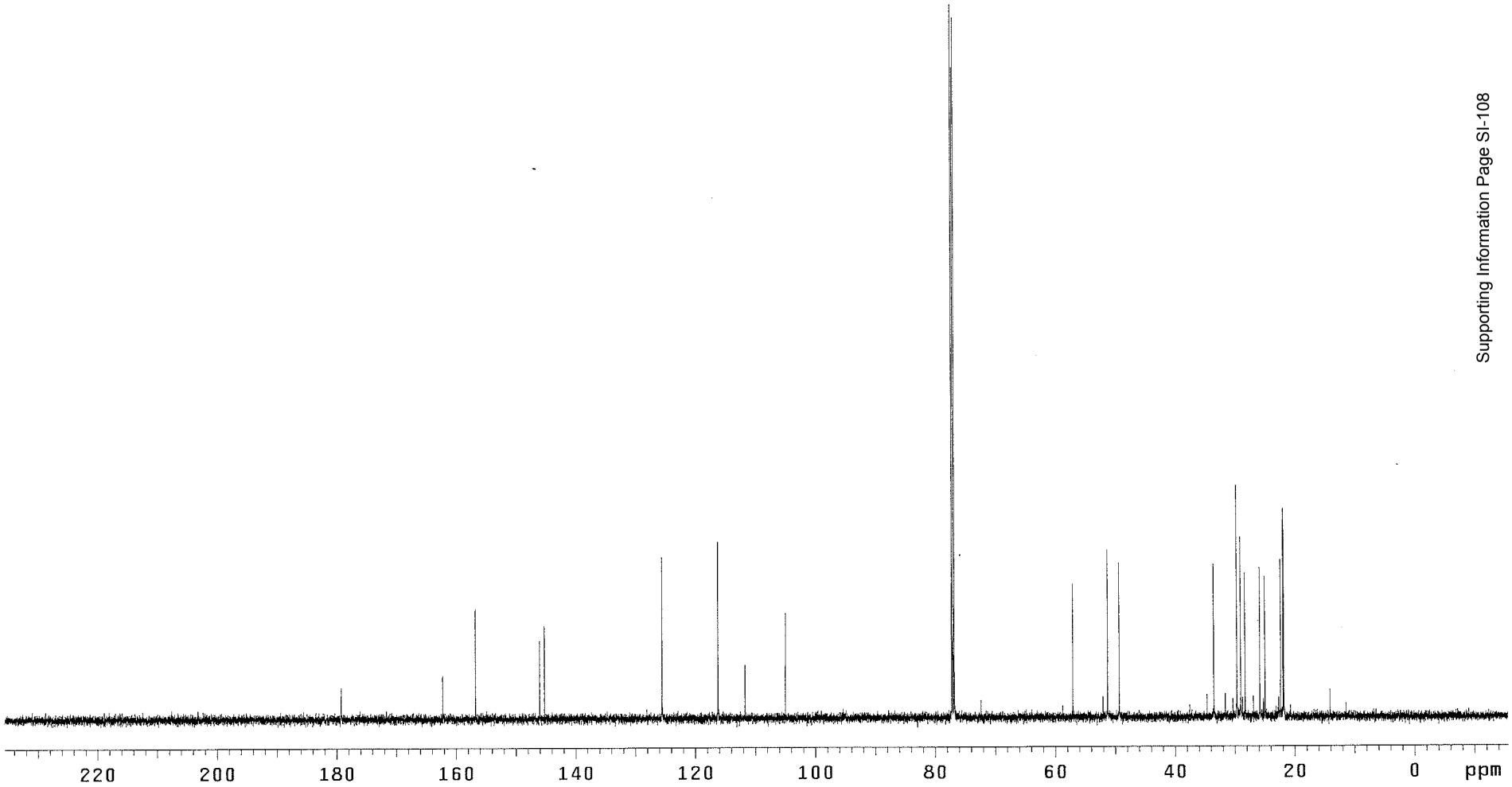
Me
Me
Me

52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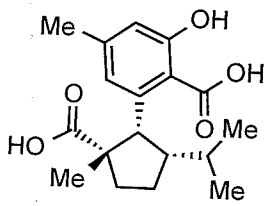
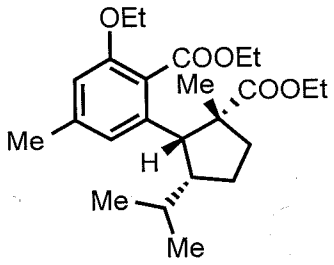
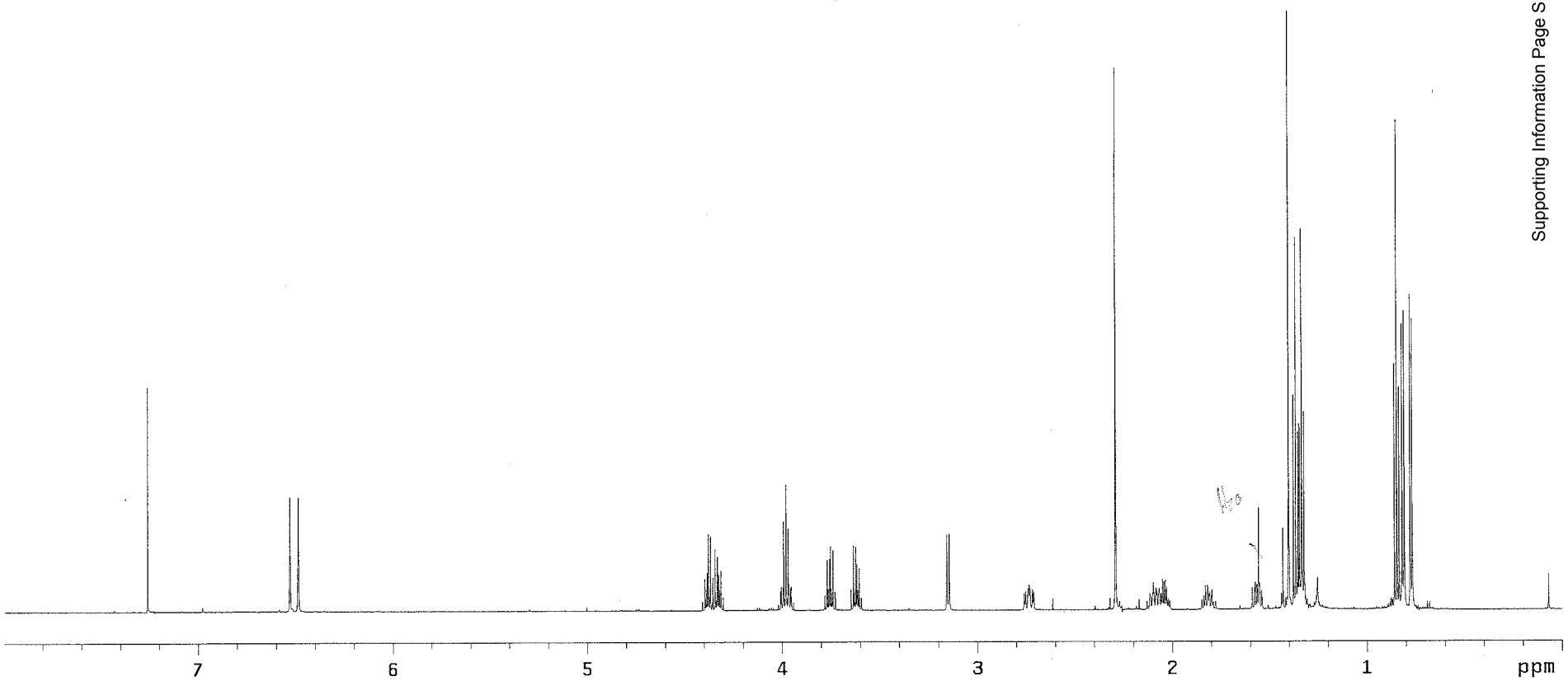
ppm

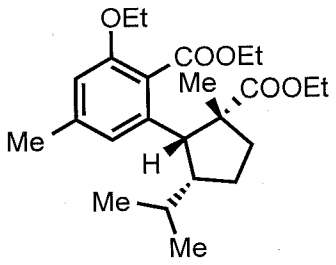


Debromohamigeran E
(crude)



Triethyldebromohamigeran E





Triethyldebromohamigeran E