Studies on the Synthesis of Quartromicins A_3 and D_3: Synthesis of the Vertical and Horizontal Bis-Spirotetronate Fragments

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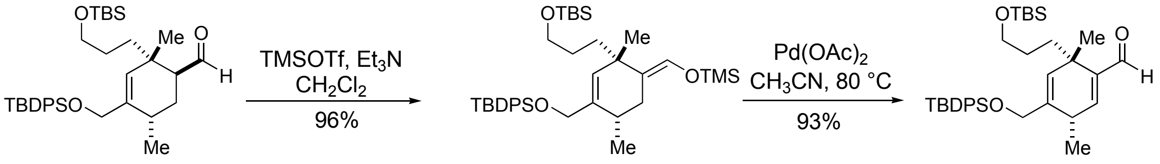
Supporting Information—Part 1

Experimental Procedures for Scheme 2 Intermediates

Supporting Information—Part 2

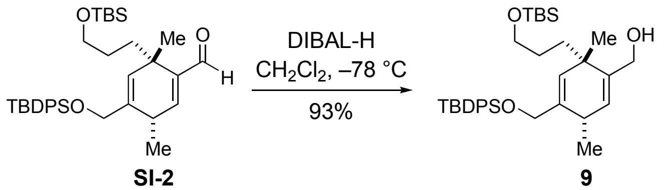
General Methods: All reaction solvents were purified before use. Tetrahydrofuran, dichloromethane, and toluene were purified by passing through a solvent column composed of activated A-1 alumina. Unless indicated, all chemicals were used as purchased without further purification.

NMR Measurements: Proton nuclear magnetic resonance (^{1}H NMR) spectra and carbon-13 (^{13}C NMR) spectra were recorded at 500 MHz and 125 MHz, respectively, or at 400 MHz and 100 MHz, respectively, on commercially available 500 MHz and 400 MHz NMR spectrometers. The proton signal of residual, non-deuterated solvent (δ 7.26 for $CHCl_3$) was used as an internal reference for ^{1}H spectra. For ^{13}C spectra, chemical shifts are reported relative to the δ 77.00 resonance of $CDCl_3$. Coupling constants are reported in Hz.

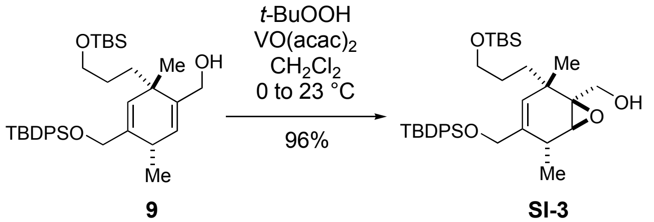


5 **SI-1** **SI-2**

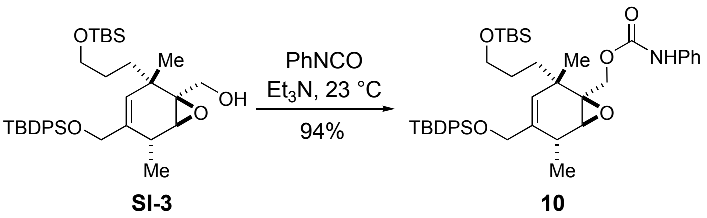
Enal SI-2. By following the literature procedure,[1] aldehyde **5** (4.90 g, 8.46 mmol) was converted to enol silane (5.28 g, 96% yield) as 3:1 mixture of alkene isomers. To a solution of enol silane **SI-1** (5.21 g, 8.00 mmol) in acetonitrile (150 mL) was added $Pd(OAc)_2$ (2.60 g, 11.6 mmol). The flask was fitted with a reflux condenser and was heated to ca. 80 °C for 1 h; additional $Pd(OAc)_2$ (1 g) was added. The reaction was judged complete after 20 h (TLC analysis). The reaction mixture was cooled to 23 °C and then was loaded directly onto a flash chromatography column (SiO_2, 750 g). Elution of the column with 10% EtOAc-hexane gave 4.32 g of **SI-2** (93%) as a clear light yellow oil: R_f 0.50 (20% EtOAc-hexane); $[\alpha]^{27}_{D}$ –0.3 (*c* 1.7, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.45 (s, 1H), 7.65 (m, 4H), 7.40 (m, 6H), 6.65 (d, *J*=3.7 Hz, 1H), 5.22 (s, 1H), 4.26 (AB, *J*=12.2 Hz, 1H), 4.13 (AB, *J*=13.2 Hz, 1H), 3.50 (m, 2H), 3.19 (m, 1H), 2.05 (m, 1H), 1.56 (app s, 1H), 1.28 (s, 3H), 1.27-1.20 (2H), 1.16 (d, *J*=7.3 Hz, 3H), 1.06 (s, 9H), 0.85 (s, 9H), –0.004 (s, 3H), –0.008 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.2, 156.2, 142.8, 135.5, 134.7, 133.6, 133.5, 130.83, 130.80, 129.7, 129.6, 127.7, 127.6, 65.4, 63.4, 38.2, 34.6, 32.4, 29.5, 27.5, 26.8, 25.9, 19.3, 19.2, 18.2, –5.3; FT-IR (neat) 2956, 2930, 2857, 1694, 1471, 1462, 1428, 1255, 1111, 836, 702 cm^{-1}; HRMS (ESI) calcd. for $C_{35}H_{52}O_3Si_2Na$ [M+Na]$^+$ 599.3353, found 599.3350 m/z.



Allylic alcohol 9. To a –78 °C solution of enal **SI-2** (13.3 g, 23.1 mmol) in CH_2Cl_2 (100 mL) was added DIBAL-H (31 mL, 1.5M solution in toluene) over 15 min. The reaction was judged complete after 30 min (TLC analysis) and MeOH (10 mL) was added slowly. The reaction mixture was allowed to warm to 23 °C, was treated with saturated aq. Rochelle's salt, and was stirred until both phases were clear and colorless (ca 2-3 h). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 200 mL). The organic extracts were washed with brine, dried with $MgSO_4$, filtered, and concentrated. Purification of the crude product by chromatography on SiO_2 (12 to 15% EtOAc-hexane) to afford allylic alcohol **9** (12.5 g, 93%) as a light yellow oil: R_f 0.38 (20% EtOAc-hexane); [□]$^{27}_{D}$ –6.4 (*c* 4.6, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) □ 7.75 (m, 4H), 7.41 (m, 6H), 5.81 (app d, *J*=3.6Hz, 1H), 5.28 (s, 1H), 4.28 (AB, *J*=12.9 Hz, 1H), 4.18 (AB, *J*=12.9 Hz, 1H), 4.16 (s, 2H), 3.52 (m, 1H), 3.56 (m, 1H), 2.94 (1H), 1.84 (1H), 1.66 (app dt, *J*=11.5, 3.2 Hz, 1H), 1.40-1.22 (3H), 1.19 (s, 3H), 1.10 (s, 9H), 1.09 (d, *J*=7.1 Hz, 3H), 0.92 (s, 9H), 0.071 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) □ 139.0, 137.0, 135.5, 135.4, 133.9, 133.7, 129.6, 129.5, 128.6, 127.6, 127.5, 65.6, 63.3, 62.5, 38.9, 36.0, 31.6, 31.3, 29.0, 28.9, 36.0, 31.6, 31.3, 29.0, 28.9, 26.8, 25.9, 22.6, 20.4, 19.3, 18.3, 14.1, –5.3; FT-IR (neat) 3412, 2956, 2930, 2930, 2857, 1649, 1462, 1471, 1428, 1255, 1111, 834, 774, 700, 612 cm^{-1}; HRMS (ESI) calcd. for $C_{35}H_{54}O_3Si_2Na$ [M+Na]$^+$ 601.3509, found 601.3503 m/z.

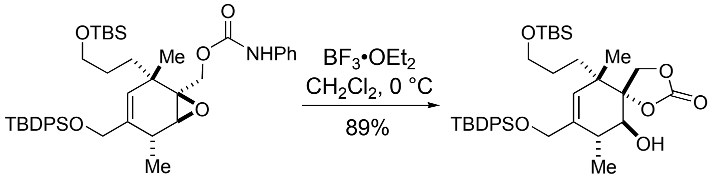


Epoxy alcohol SI-3. To a 0 °C solution of allylic alcohol **9** (12.5 g, 21.6 mmol) in CH_2Cl_2 (150 mL) was added $VO(acac)_2$ (210 mg, 0.79 mmol) in one portion. To this dark green solution was added *t*-BuOOH (3.60 mL, 6.0M in decane, 21.6 mmol). The solution turned dark purple, then the reaction mixture was allowed to warm to 23 °C and was stirred for 1 h at which point the solution was a clear orange/red color. The reaction mixture was diluted with EtOAc (500 mL) and 1M aq. HCl and the layers were separated. The aqueous layer was extracted with EtOAc (1 x 300 mL), the combined organic extracts were washed with saturated aq. $NaHCO_3$ (1 x), brine (1 x), saturated aq. $Na_2S_2O_3$, dried with $MgSO_4$, filtered, and concentrated. The crude product was partially purified by chromatography on SiO_2 (15 to 30% EtOAc-hexane). Some *t*-BuOOH contaminated the desired product so the residue was taken up in ca 150 mL 30% EtOAc-hexane, treated with 10% aq. tartaric acid (50 mL) and $FeSO_4$ (ca 2 g) and was stirred for 5 h. Separation of the layers, extraction of the aqueous layer with EtOAc (1 x 200 mL), drying of the combined organic extracts with $MgSO_4$, filtration, and concentration gave epoxy alcohol **SI-3** (12.4 g, 96%) as a clear viscous oil: R_f 0.49 (35% EtOAc-hexane); $[□]^{27}_{D}$ –18.7 (*c* 4.7, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) □ 7.70 (app t, 4H), 7.40 (m, 6H), 5.11 (s, 1H), 4.13 (m, 1H), 3.93 (dd, *J*=12.2, 2.9 Hz, 1H), 3.81 (dd, *J*=12.2, 9.7 Hz, 1H), 3.62 (m, 1H), 3.55 (m, 1H), 3.31 (s, 1H), 2.71 (q, *J*=14.6, 7.3 Hz, 1H), 2.00 (dd, *J*=10.7, 3.2 Hz, 1H), 1.56 (m, 1H), 1.46 (m, 2H), 1.35 (m, 1H), 1.17 (s, 3H), 1.10 (d, *J*=7.3 Hz, 3H), 1.07 (s, 9H), 0.91 (s, 9H), 0.061 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) □ 135.5, 135.4, 135.0, 133.6, 133.5, 129.6, 129.56, 127.6, 127.57, 126.6, 126.5, 65.8, 63.5, 63.1, 60.8, 60.7, 59.0, 37.8, 34.7, 30.2, 28.6, 25.9, 24.4, 19.2, 18.2, 16.7, –5.4; FT-IR (neat) 3468, 2955, 2930, 2857, 1471, 1462, 1428, 1255, 1111, 835, 702 cm^{-1}; HRMS (ESI) calcd. for $C_{35}H_{54}O_4Si_2Na$ $[M+Na]^+$ 617.3458, found 617.3461 m/z.



Urethane 10. To a solution of epoxy alcohol **SI-3** (3.56 g, 5.98 mmol) in CH_2Cl_2 (30 mL) was added Et_3N (1.10 mL, 7.78 mmol) and phenyl isocyanate (0.72 mL, 6.58 mmol). The reaction was judged complete after 1 h (TLC analysis), then was quenched with EtOAc (300 mL) and 1M aq. HCl. The layers were separated and the organic layer was washed with saturated aq. $NaHCO_3$ (1 x 100 mL), brine (1 x 100 mL), dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by chromatography on SiO_2 (15 to 20% EtOAc-hexane) giving urethane **10** (4.02 g, 94%) as a clear oil: R_f 0.40 (20% EtOAc-hexane); $[□]^{27}_{D}$ –14.9 (*c* 3.7, $CHCl_3$); ^1H NMR (500

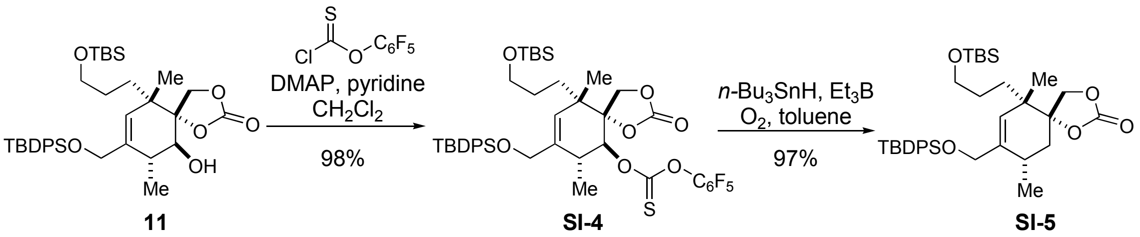
MHz, $CDCl_3$) 7.64 □ (dt, *J*=7.8, 1.7 Hz, 4H), 7.33 (m, 8H), 7.20 (t, *J*=8.6 Hz, 2H), 7.97 (t, *J*=8.4 Hz, 1H), 5.06 (s, 1H), 4.50 (AB, *J*=12.2 Hz, 1H), 4.36 (AB, *J*=12.2 Hz, 1H), 4.06 (app s, 2H), 3.60 (m, 1H), 3.54 (m, 1H), 3.17 (s, 1H), 2.63 (m, 1H), 1.66 (m, 1H), 1.50-1.36 (3H), 1.22 (1H), 1.20 (s, 3H), 1.02 (s, 12H), 0.87(s, 9H), 0.022 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) □ 153.0, 137.8, 135.4, 135.3, 134.6, 133.5, 133.3, 129.5, 128.8, 127.5, 127.4, 126.5, 126.4, 123.2, 118.6, 65.7, 63.2, 61.8, 61.7, 61.6, 38.2, 35.3, 31.4, 30.1, 28.6, 26.7, 25.8, 24.7, 22.5, 19.1, 18.2, 16.5, 14.0, –5.4; FT-IR (neat) 3323, 3050, 2956, 2930, 2857, 1740, 1601, 1541, 1255, 1218, 1111, 1055, 835, 702 cm^{-1}; HRMS (ESI) calcd. for $C_{42}H_{59}O_5Si_2NNa$ $[M+Na]^+$ 736.3830, found 736.3851 m/z.



10

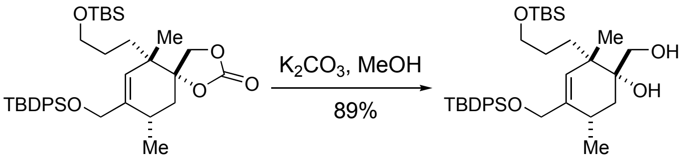
11

Hydroxyl carbonate 11: To a 0 °C solution of urethane **10** (5.68 g, 7.95 mmol) in CH_2Cl_2 (80 mL) was added $BF_3{\bullet}OEt_2$ (1.05 mL, 8.30 mmol). The 0 °C mixture was stirred for 40 min, at which point the reaction was judged complete by TLC analysis. The mixture was treated with 500 mL EtOAc and 100 mL 1M aq. H_2SO_4 and was stirred vigorously for 1.5 h. The layers were separated and the aqueous layer was extracted with EtOAc (1 x 200 mL), the combined organic extracts were washed with water (1 x), saturated aq. $NaHCO_3$ (1 x), brine (1 x), dried with $MgSO_4$, filtered, and concentrated. The residue was purified by chromatography on SiO_2 (15-25% EtOAc-hexane) to afford hydroxy carbonate **11** (4.50 g, 89%) as a white foam: R_f 0.23 (20% EtOAc-hexane); [□]$^{27}_{D}$ +18.5 (*c* 2.7, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) □ 7.63 (m, 4H), 7.45, (m, 2H), 7.39 (m, 4H), 5.30 (s, 1H), 4.35 (AB^1, *J*=8.5 Hz, 1H), 4.15 (AB^2, *J*=13.4 Hz, 1H), 4.09 (dd, *J*=8.8, 3.9 Hz, 1H), 4.06 (AB^2, *J*=12.7 Hz, 1H), 3.96 (AB^1, *J*=8.6 Hz, 1H), 3.58 (m, 1H), 3.52 (m, 1H), 2.44 (1H), 2.15 (m, 1H), 1.68-1.54 (2H), 1.15 (d, *J*=6.8 Hz, 3H), 1.06 (s, 9H), 1.04 (s, 3H), 0.88 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) □ 155.2, 138.9, 135.4, 133.4, 133.3, 129.8, 127.7, 127.3, 71.7, 66.5, 64.8, 63.3, 41.5, 36.9, 35.2, 27.4, 26.7, 25.9, 19.1, 18.5, 18.2, 16.0, –5.3; FT-IR (neat) 3445, 2956, 2930, 2857, 1807, 1471, 1255, 1112, 1071, 836, 775, 702, 611 cm^{-1}; HRMS (ESI) calcd. for $C_{36}H_{54}O_6Si_2Na$ $[M+Na]^+$ 661.3357, found 661.3359 m/z.



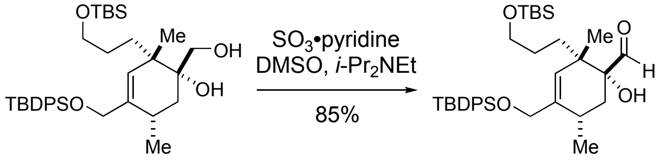
Carbonate SI-5. To a solution of hydroxy carbonate **11** (2.90 g, 4.54 mmol) in CH_2Cl_2 (9 mL) was added DMAP (1.66 g, 13.6 mmol), pyridine (3.67 mL, 45.4 mmol), then pentafluorophenyl chlorothionoformate (1.45 mL, 9.08 mmol) was added slowly. The red/orange solution was submersed in a 20 °C water bath as an exotherm was observed. The reaction was complete after 1h, white precipitate (pyridine-HCl) formed during the course of the reaction. Water then 1M aq HCl were added and after stirring for 10 min, then the layers were separated, the aqueous layer was extracted with CH_2Cl_2 (2 x). The combined organic extracts were washed with 1M aq. HCl, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by chromatography on SiO_2 (15% EtOAc-hexane) to afford the thionocarbonate **SI-4** (3.84 g, 98%) as a white foam.

To a solution of thionocarbonate **SI-4** (8.59 g, 9.93 mmol) in toluene (200 mL) was added Et_3B (1.5 mL, 1.0M in hexane, 1.5 mmol) and *n*-Bu_3SnH (4.0 mL, 14.9 mmol). Atmospheric air (50 mL) was slowly sparged into the solution to initiate the radical deoxygenation. The reaction was judged complete (TLC analysis) after 10 min. The reaction mixture was directly subjected to chromatography on SiO_2 (5, 10, 15, 20% EtOAc-hexane) to separate the residual *n*-Bu_3SnH. The crude material was subjected to a second round of purification by chromatography on SiO_2 (10 to 15% EtOAc-hexane) to afford the carbonate **SI-5** (6.70g, 97%) as an oil: R_f 0.33 (20% EtOAc-hexane); $[\alpha]^{27}_{D}$ +19.0 (*c* 5.8, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.63 (m, 4H), 7.44 (m, 2H), 7.38 (m, 4H), 5.33 (s, 1H), 4.19 (AB, *J*=14.6 Hz, 1H), 4.17 (app s, 1H), 4.09 (AB, *J*=9.1 Hz, 1H), 3.56 (m, 2H), 2.37 (q, *J*=14.6, 7.6 Hz, 1H), 2.08 (dd, *J*=13.4, 9.3 Hz, 1H), 1.93 (dd, *J*=1.35, 7.1 Hz, 1H), 1.53 (m, 3H), 1.26 (2H), 1.30 (app s, 12H), 0.99 (s, 3H), 0.88 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.7, 139.5, 135.3, 133.4, 133.3, 129.7, 127.6, 127.5, 87.0, 71.4, 65.0, 63.3, 40.2, 37.5, 34.5, 28.9, 27.4, 26.7, 25.8, 19.1, 18.1, –5.4; FT-IR (neat) 2956, 2930, 2857, 1807, 1471, 1428, 1255, 1111, 1066, 835, 702 cm^{-1}; HRMS (ESI) calcd. for $C_{36}H_{54}O_5Si_2Na$ $[M+Na]^+$ 645.3408, found 645.3407 m/z.



SI-5 **SI-6**

Diol SI-6. To a solution of carbonate **SI-5** (2.56 g, 4.11 mmol) in MeOH (60 mL) was added K_2CO_3 (1.10 g, 7.96 mmol) in one portion. The initial heterogeneous reaction mixture turned homogenous after a few hours. The reaction was quenched after 24 h by addition of 50% EtOAc-hexane (200 mL) and water (250 mL). The aqueous layer was extracted with 50% EtOAc-hexane (2 x 100 mL), the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by chromatography on SiO_2 (40 to 50% EtOAc-hexane) to afford the diol **SI-6** (2.22 g, 90%) as a sticky semi-solid: R_f 0.29 (35% EtOAc-hexane); []$^{27}_{D}$ +11.2 (*c* 12.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) 7.71 (m, 4H), 7.40 (m, 6H), 5.34 (s, 1H), 4.20 (AB, *J*=13.7 Hz, 1H), 4.11 (AB, *J*=12.9 Hz, 1H), 3.65 (app AB, *J*=11.3 Hz, 1H), 3.61 (2H), 3.45 (app AB, *J*=11.0 Hz, 1H), 2.32 (3H), 1.97 (dd, *J*=12.9, 6.1 Hz, 1H), 1.55 (m, 5H), 1.08 (s, 9H), 1.02 (d, *J*=6.8 Hz, 3H), 0.94 (s, 3H), 0.92 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) 138.1, 135.5, 135.4, 133.8, 133.7, 129.7, 129.6, 127.6, 127.5, 76.2, 65.5, 65.0, 64.1, 40.0, 36.8, 34.7, 30.1, 27.4, 26.8, 26.0, 19.7, 19.2, 19.1, 18.3, –5.3; FT-IR (neat) 3418, 2955, 2930, 2887, 1471, 1462, 1428, 1255, 1111, 1055, 835, 776, 702 cm^{-1}; HRMS (ESI) calcd. for $C_{35}H_{56}O_5Si_2Na$ $[M+Na]^+$ 619.3615, found 619.3613 m/z.



SI-6 **8b**

-Hydroxyaldehyde *exo*-8b. To a solution of diol **SI-6** (138 mg, 0.231 mmol) in CH_2Cl_2 (2.30 mL) was added sequentially DMSO (0.163 mL, 2.31 mmol), *i*-Pr_2NEt (0.20 mL, 1.56 mmol), and SO_3•pyridine (110 mg, 0.693 mmol). The reaction was judged complete in 15 min by TLC and was quenched by addition of EtOAc (20 mL) and 1M aq. HCl (5 mL). After layer separation the organic layer was washed with saturated aq. $NaHCO_3$, brine, dried with $MgSO_4$, filtered, concentrated, and was purified by chromatography on SiO_2 (10% EtOAc-hexane) to afford the known □-hydroxy aldehyde *exo*-**8b** (116 mg, 85%) as an oil: $[□]^{27}_{D}$ –1.5 (*c* 11.6, $CHCl_3$).[1]

References:

(1) Roush, W. R.; Barda, D. A.; Limberakis, C.; Kunz, R. K. *Tetrahedron* **2002**, *58*, 6433.

Studies on the Synthesis of Quartromicins A_3 and D_3: Synthesis of the Vertical and Horizontal Bis-Spirotetronate Fragments

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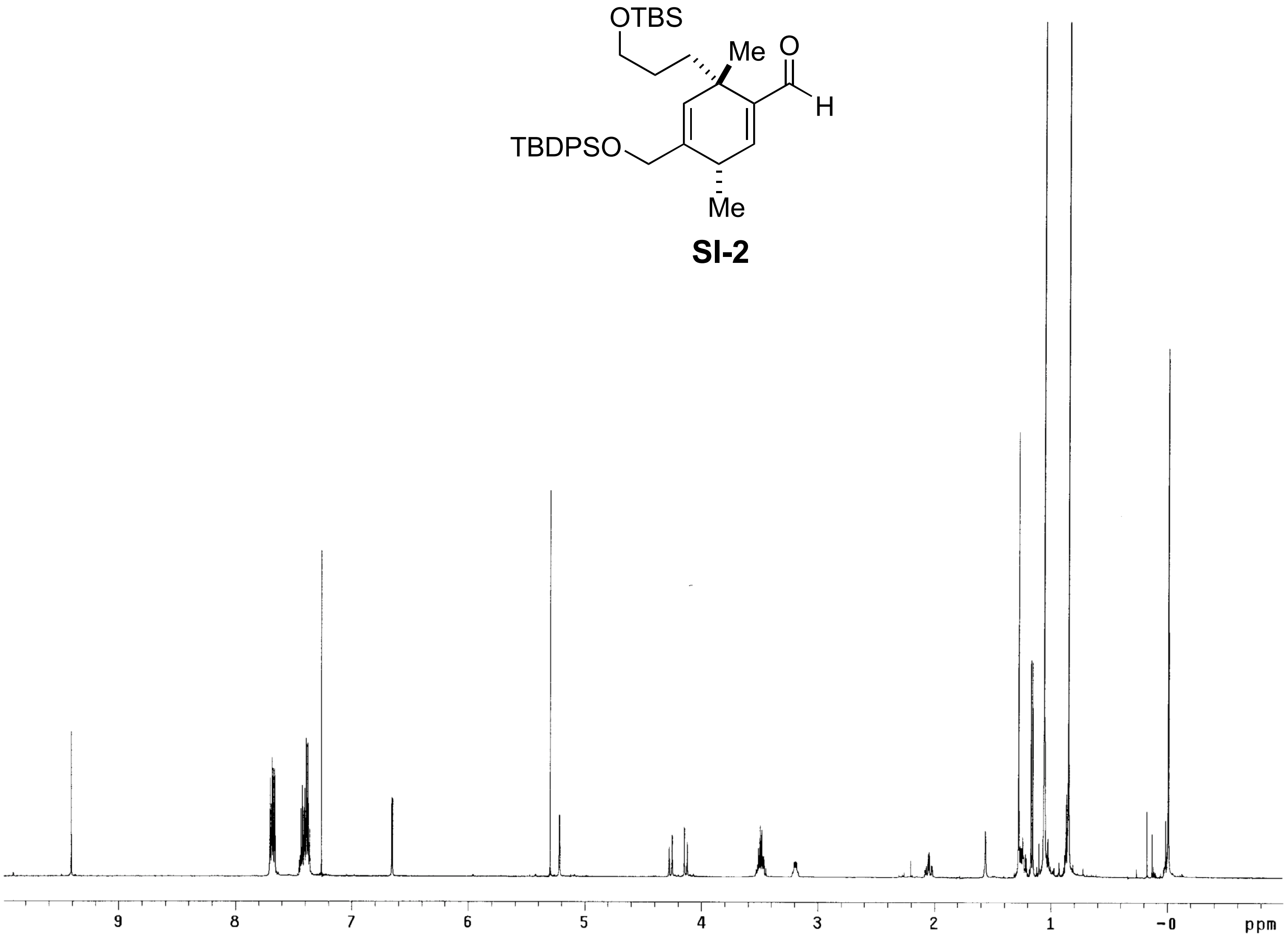
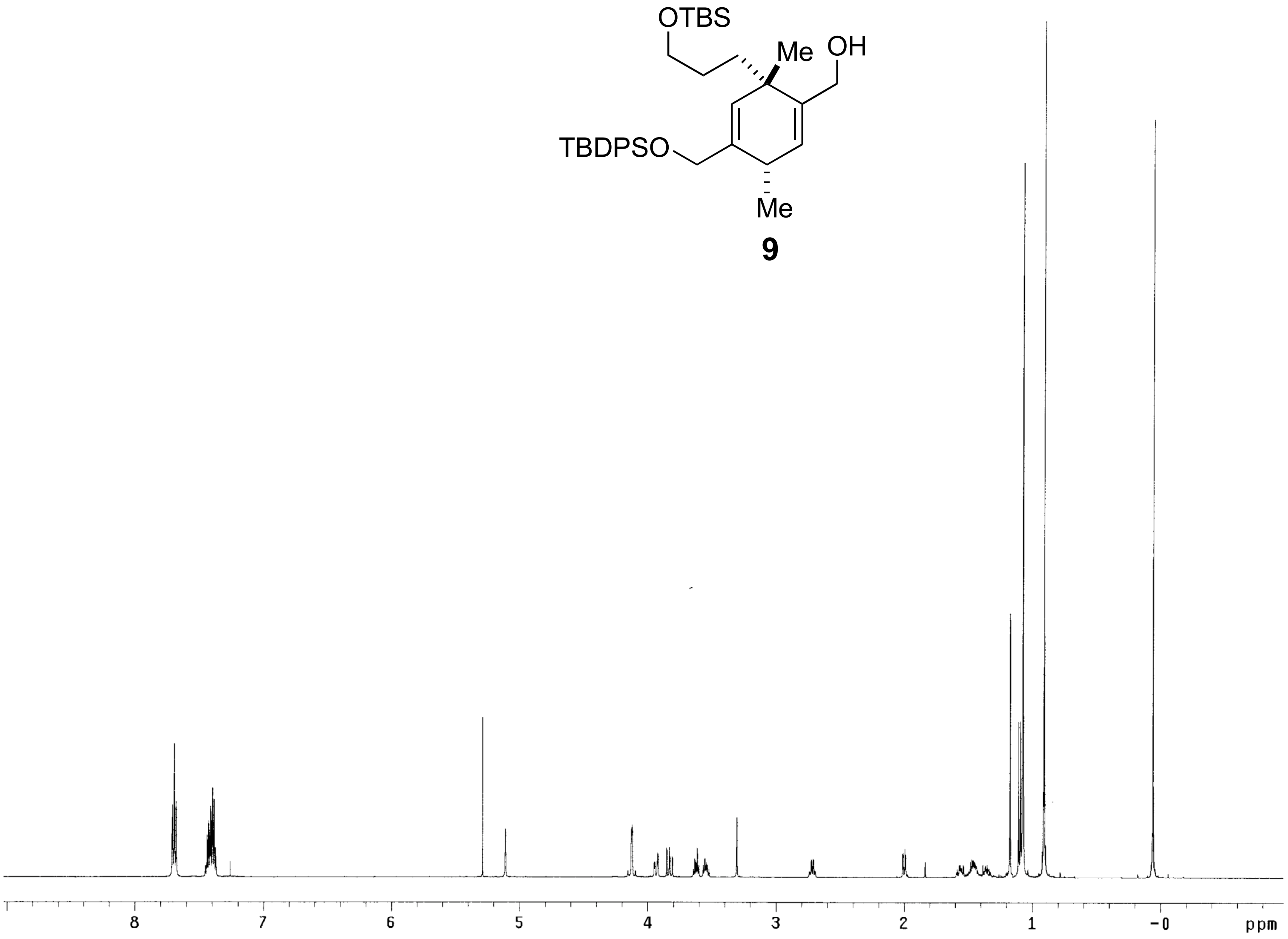
Supporting Information—Part 2

Copies of ^{1}H NMR spectra for new compounds



SI-2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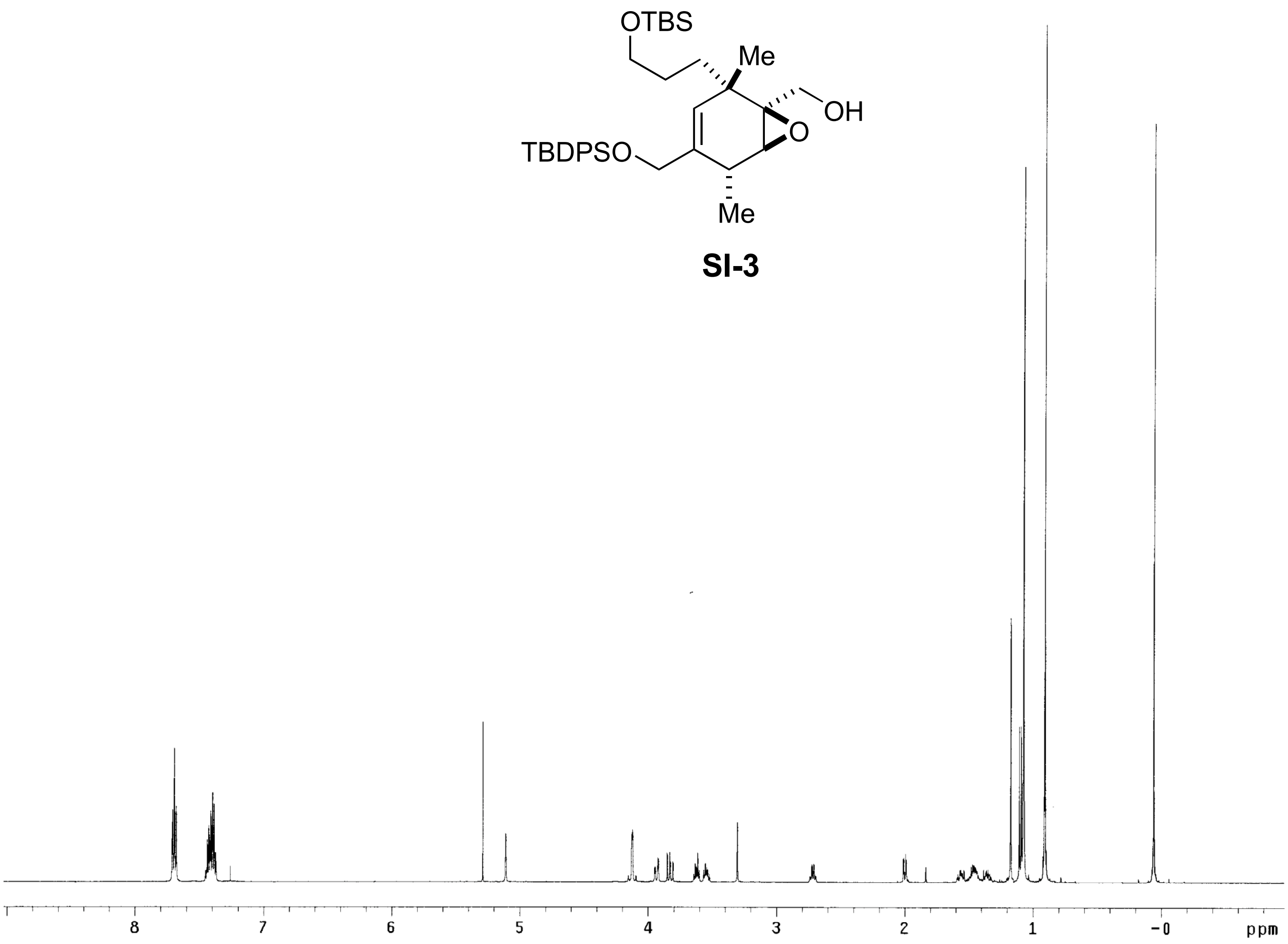

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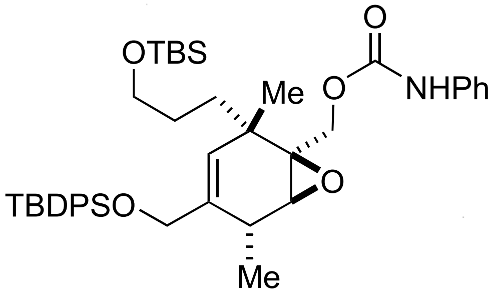

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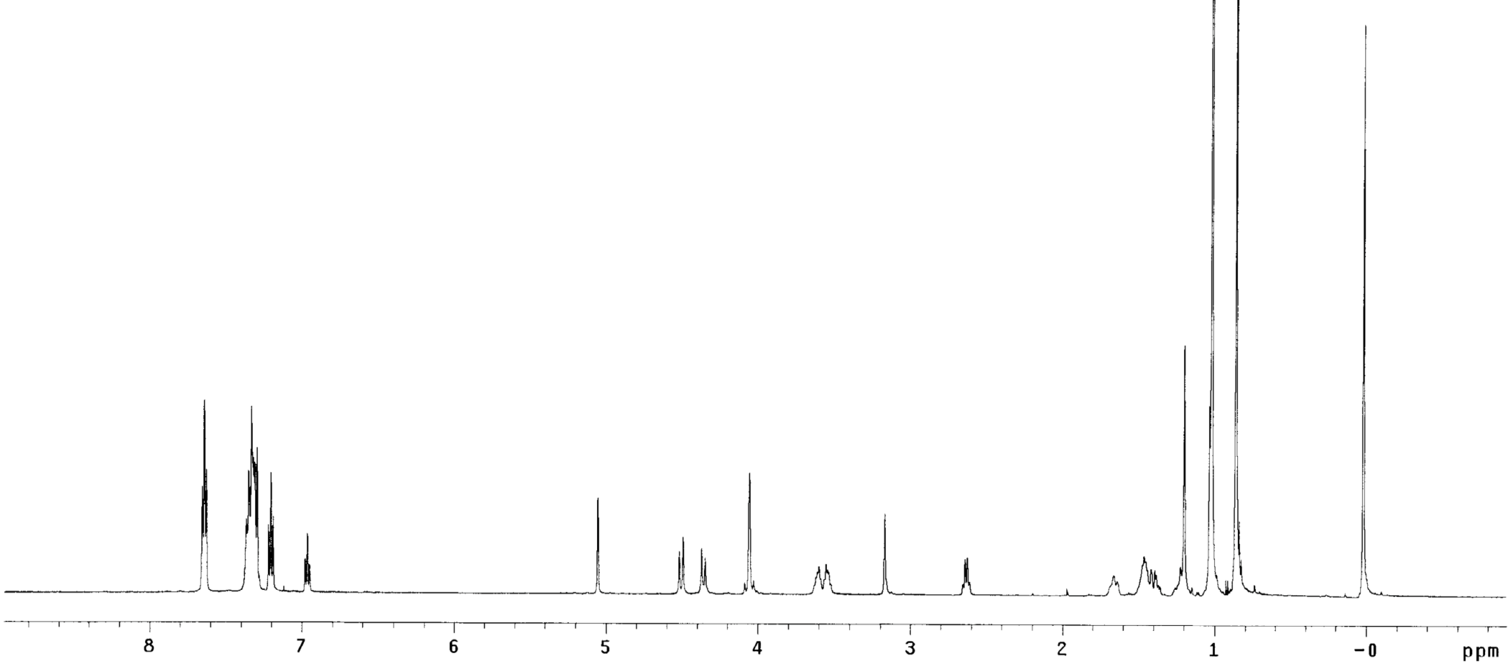

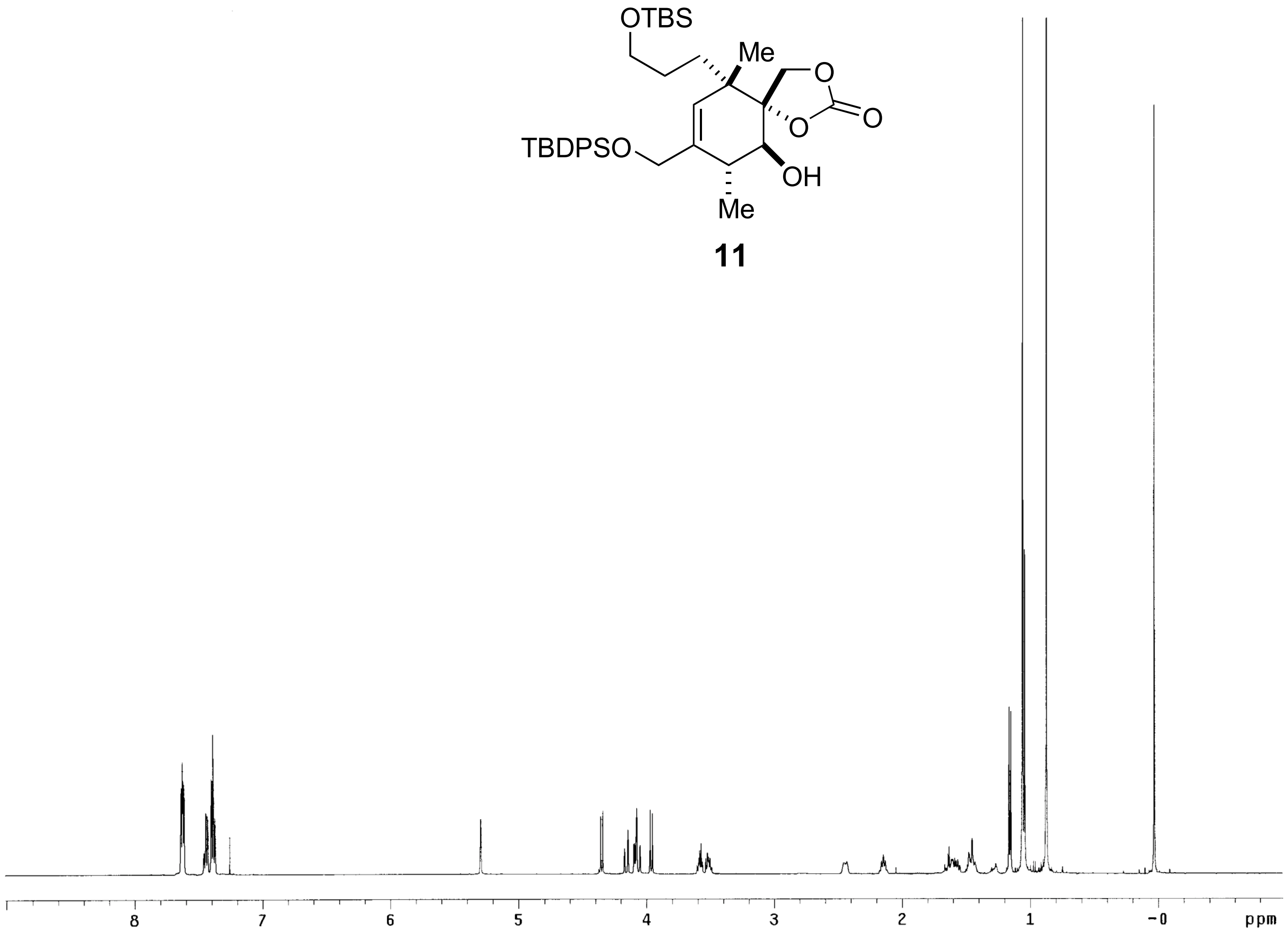

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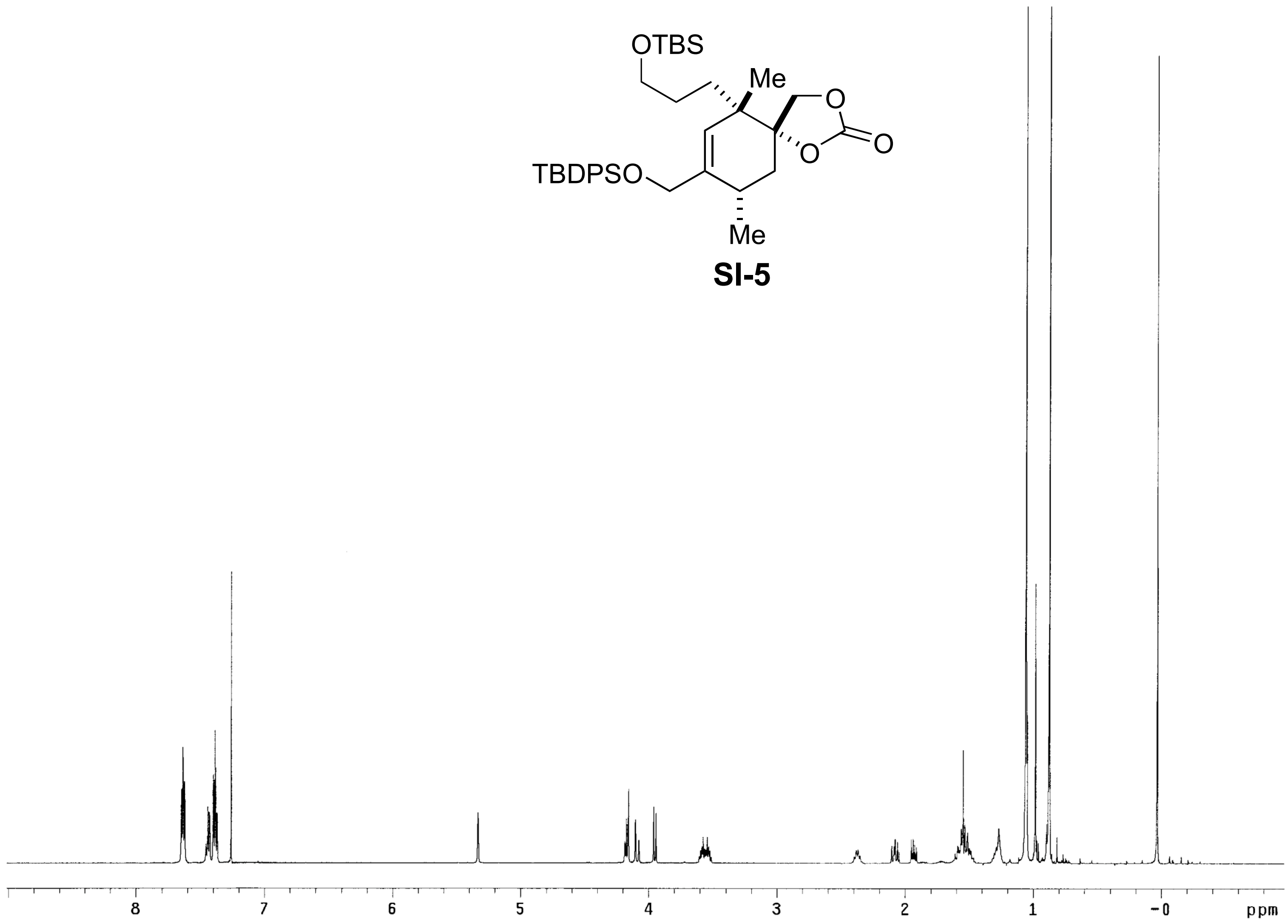

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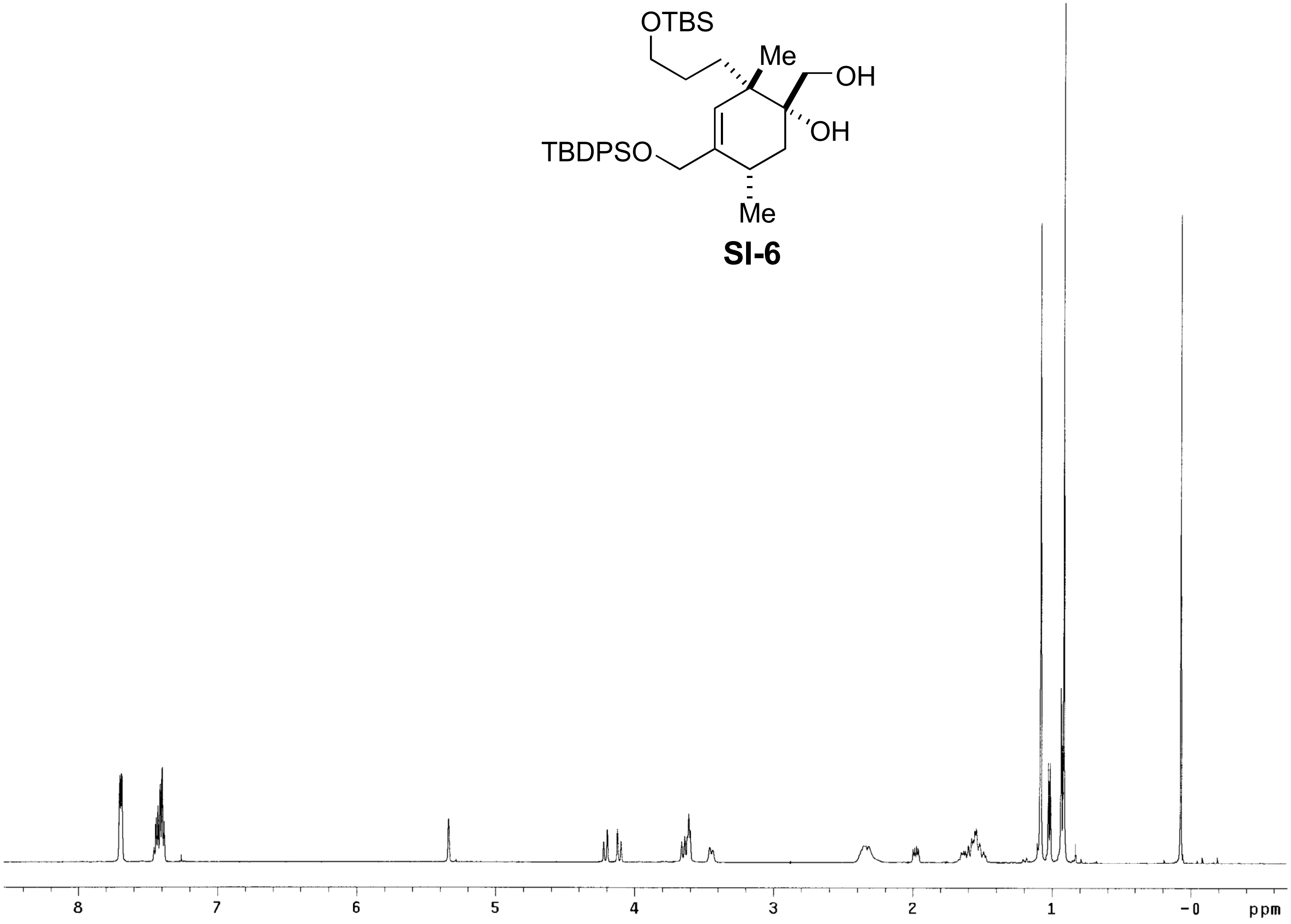
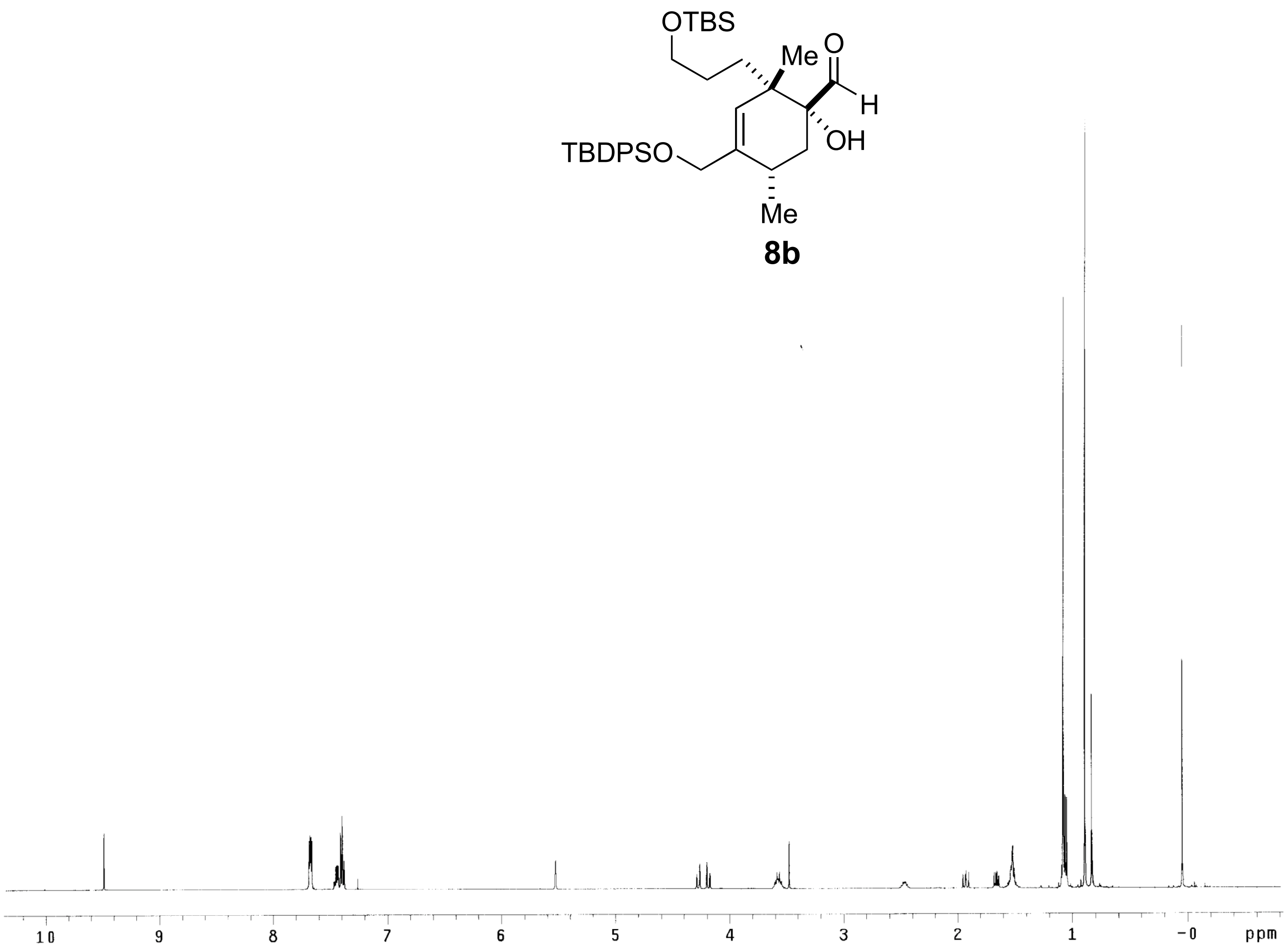
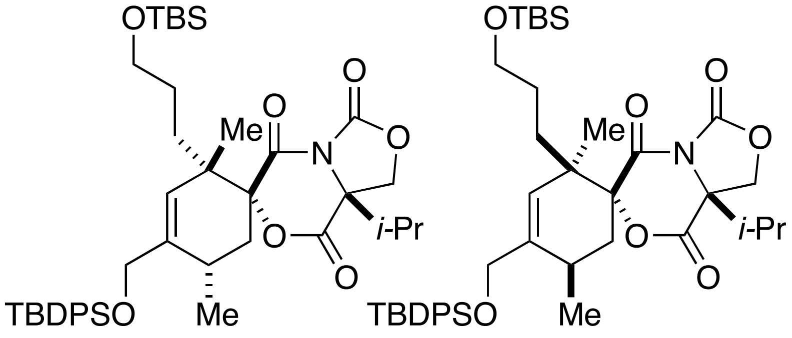


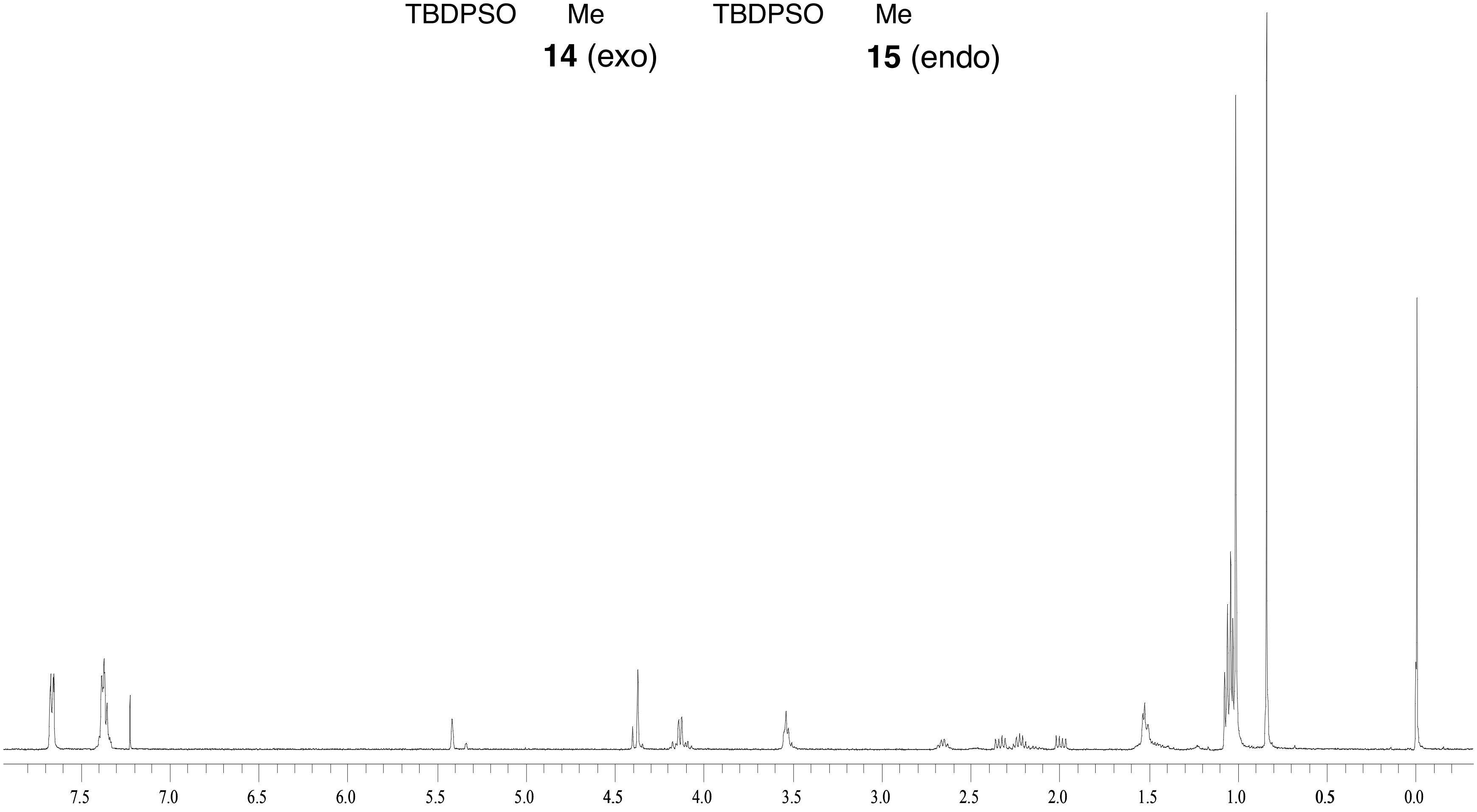
SI-6

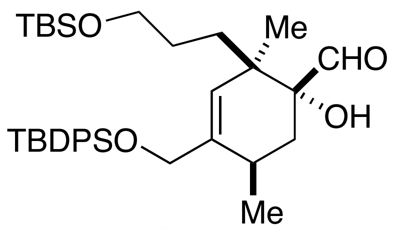


8b

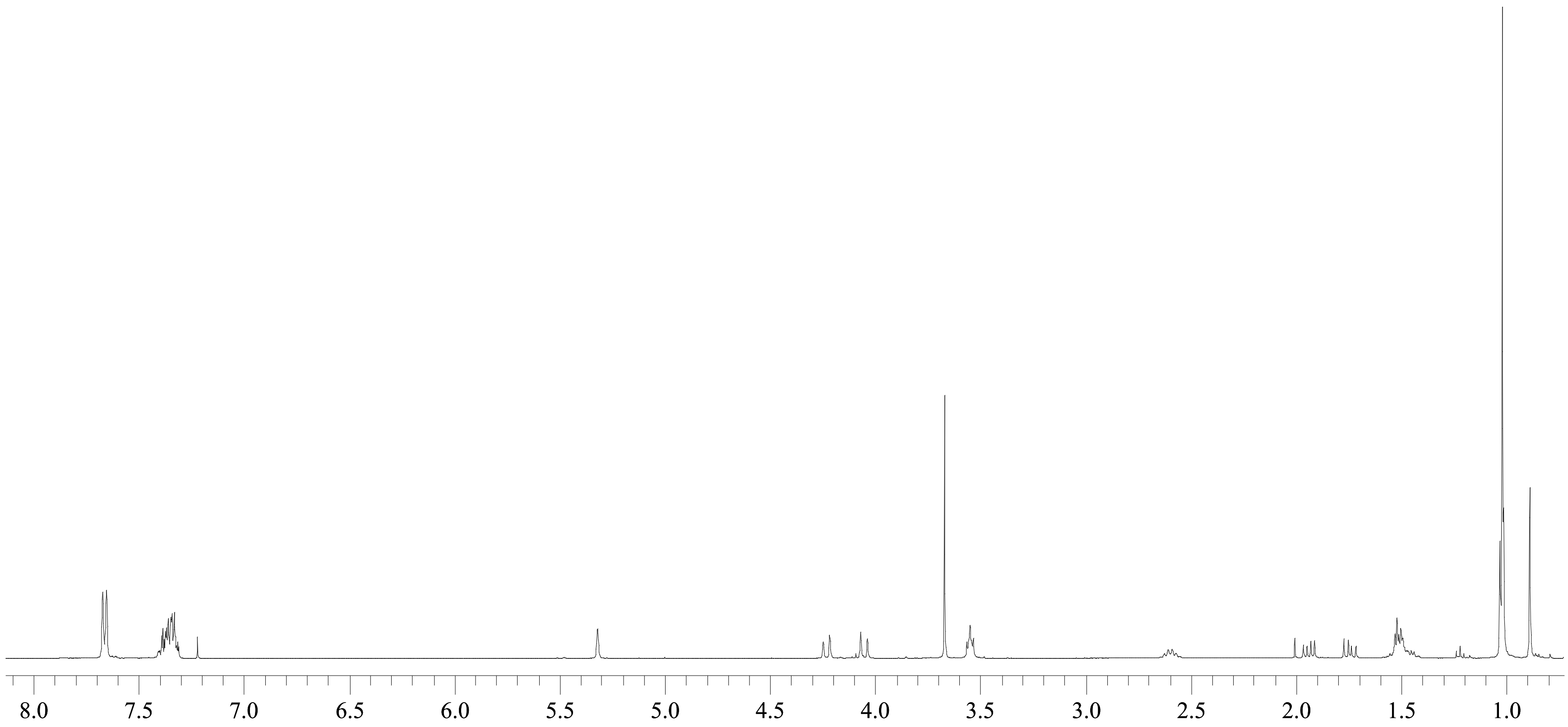


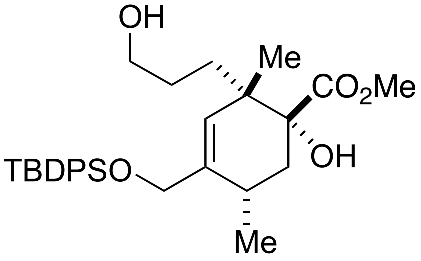
14 (exo) **15** (endo)



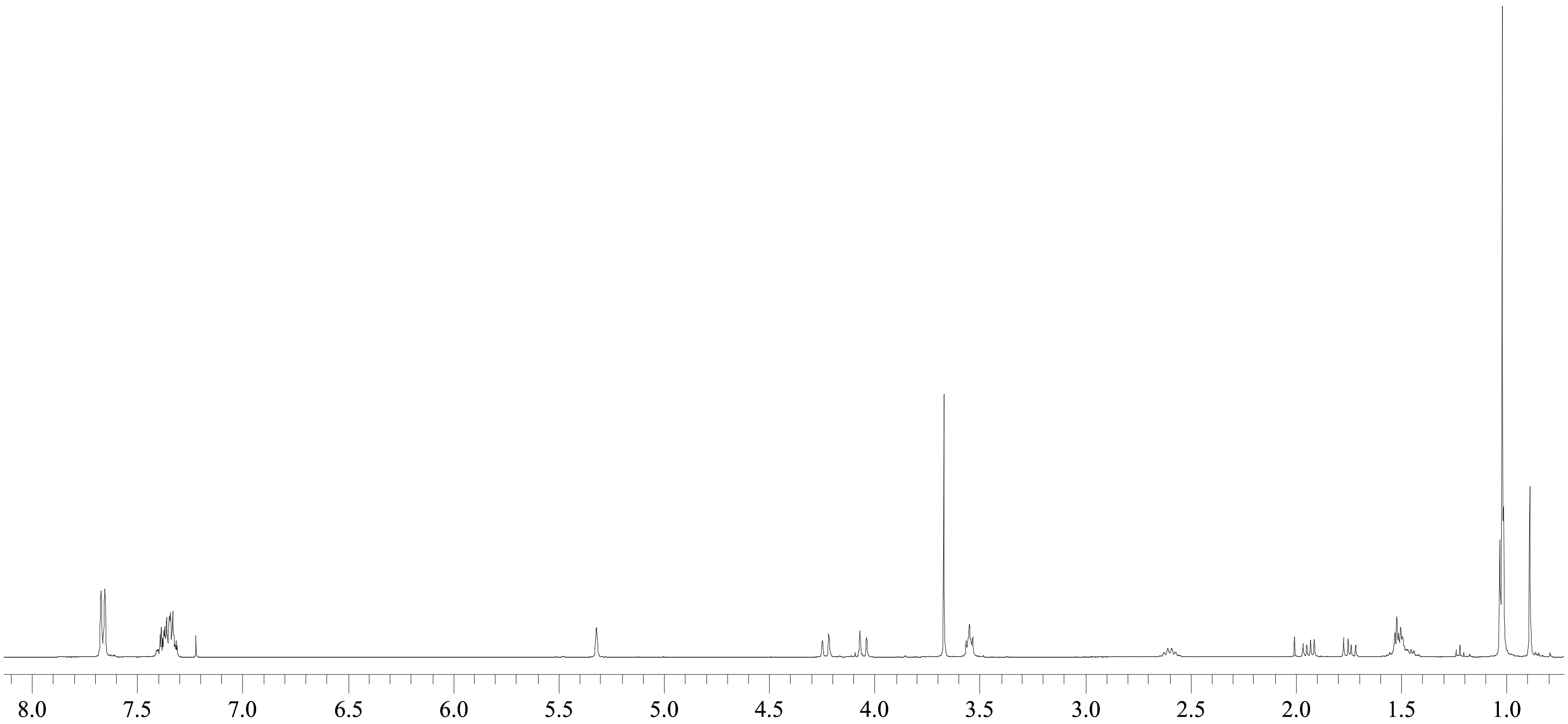


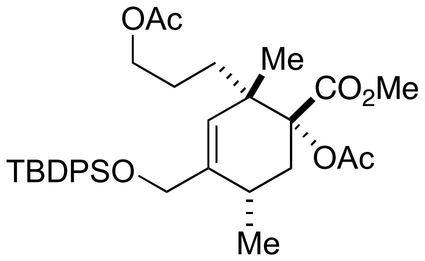
endo-**6**



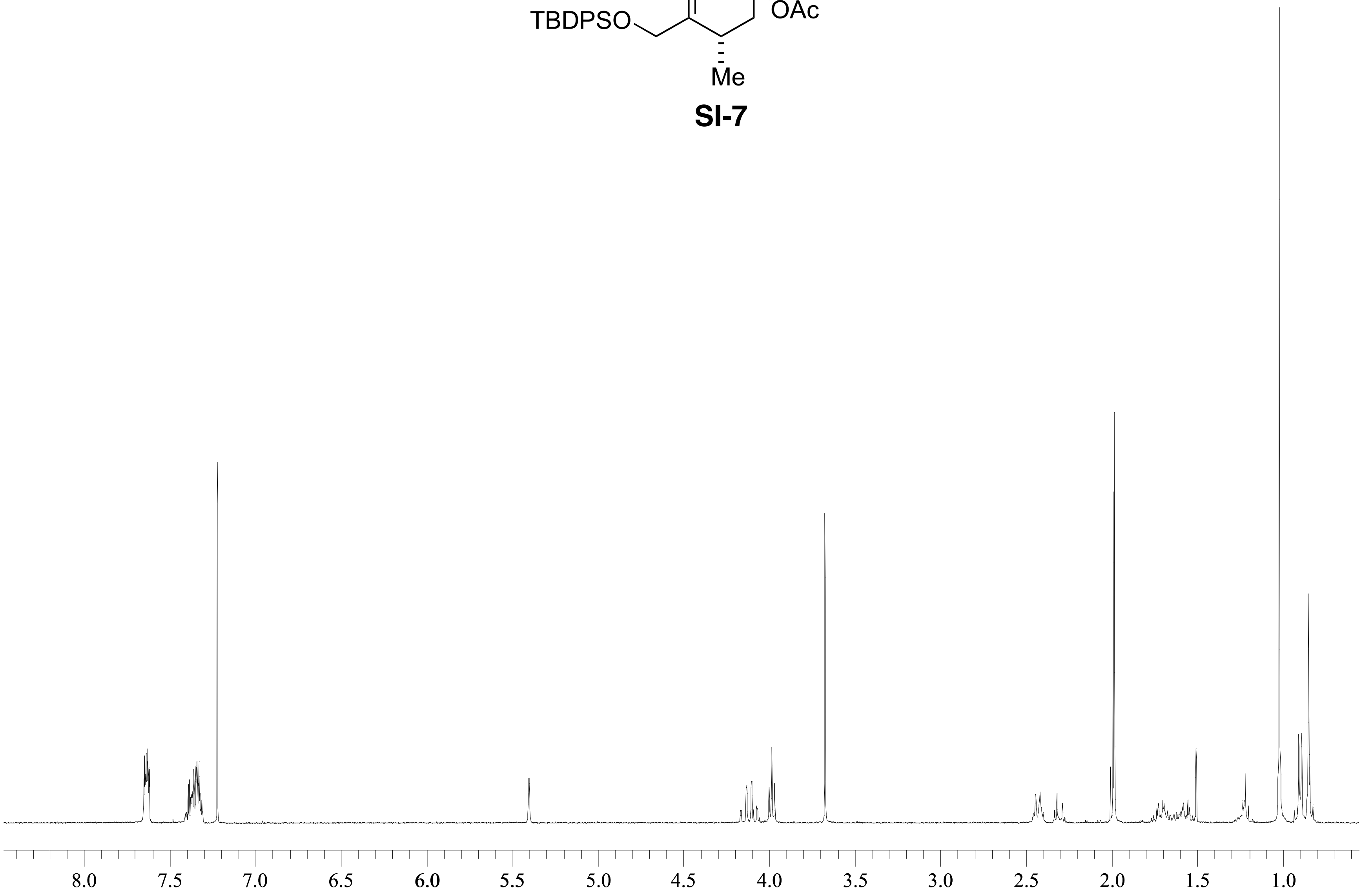


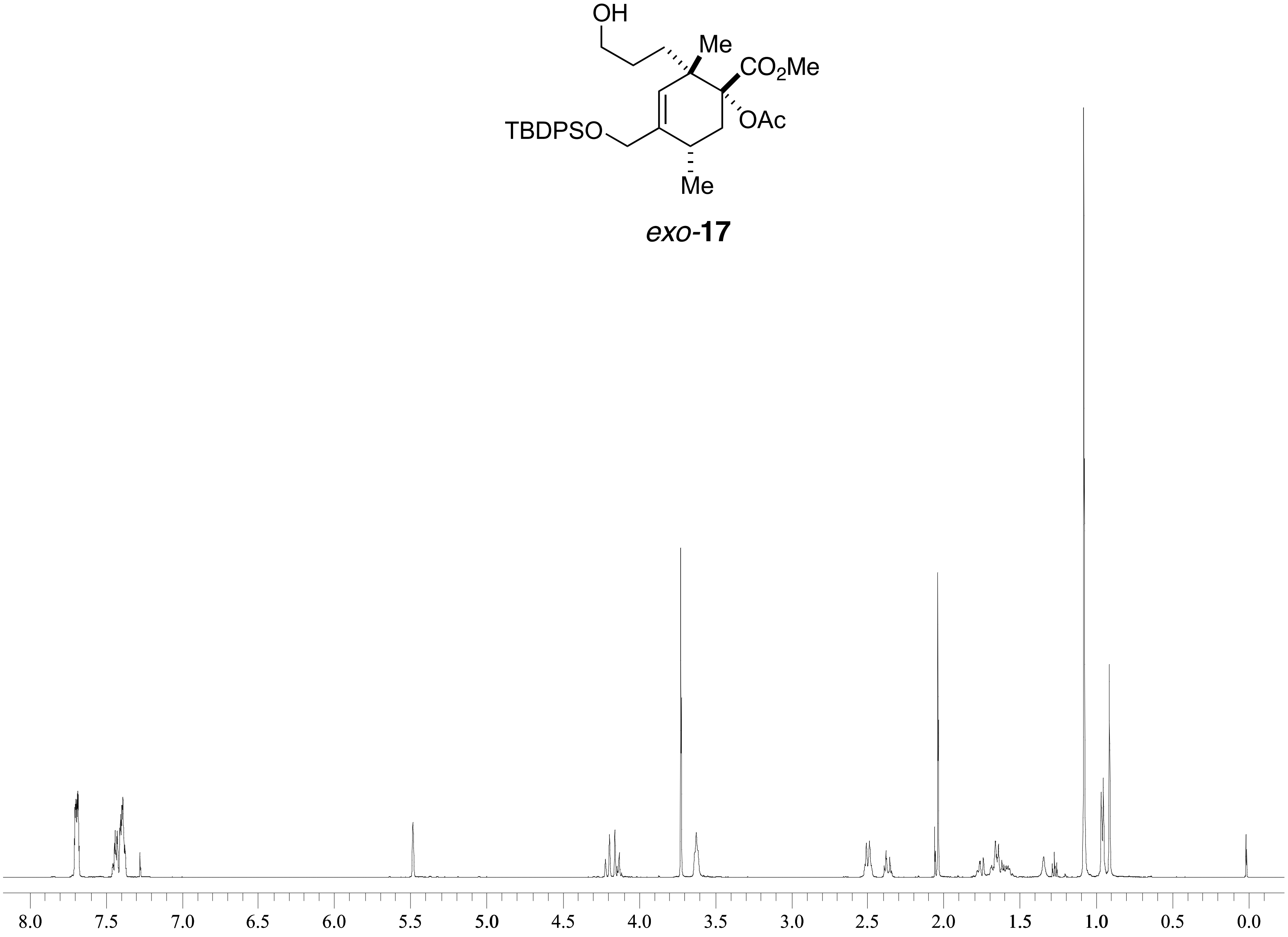
exo-**16**




OAc
Me
CO2Me
OAc
TBDPSO
Me

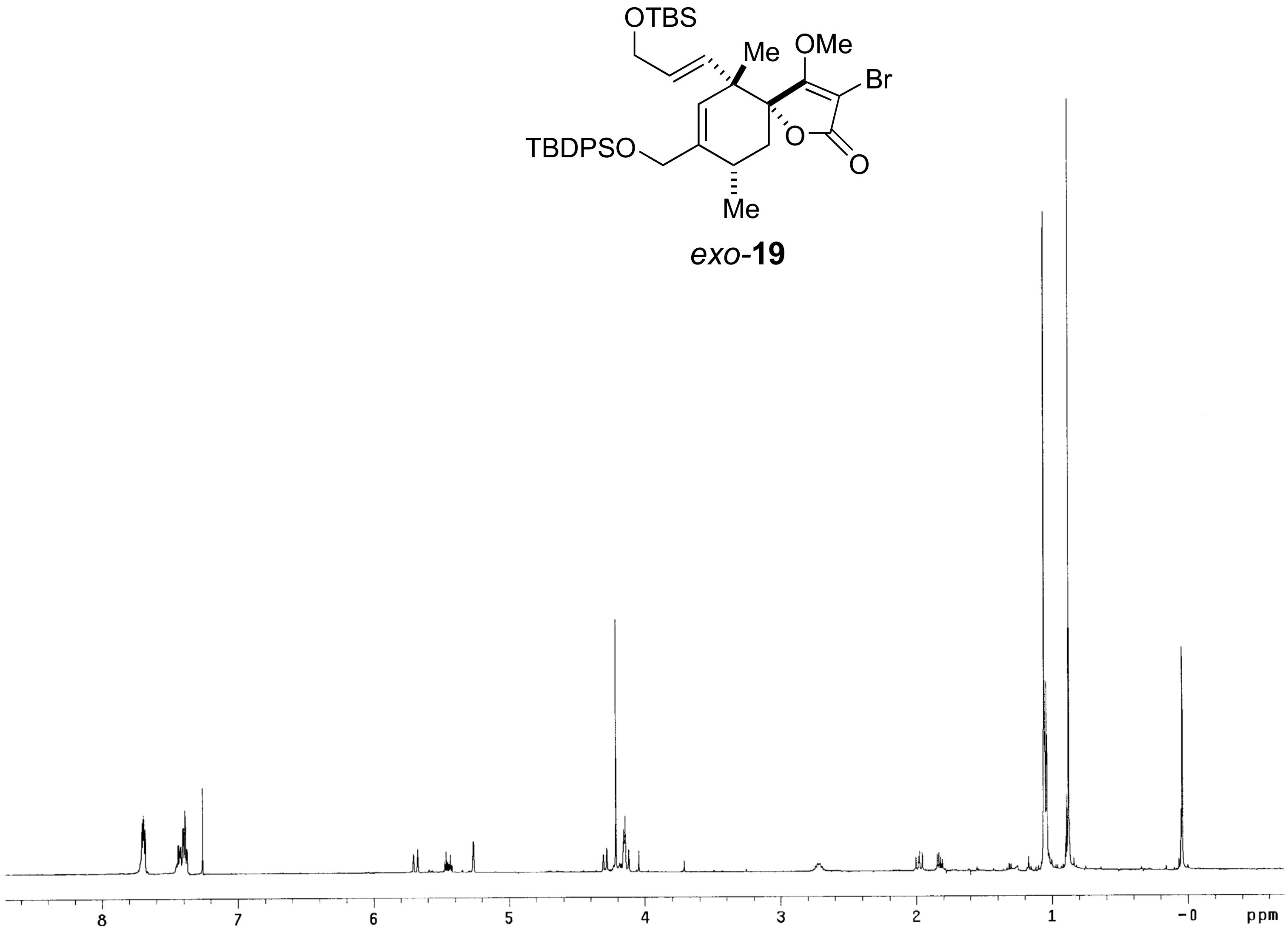
SI-7

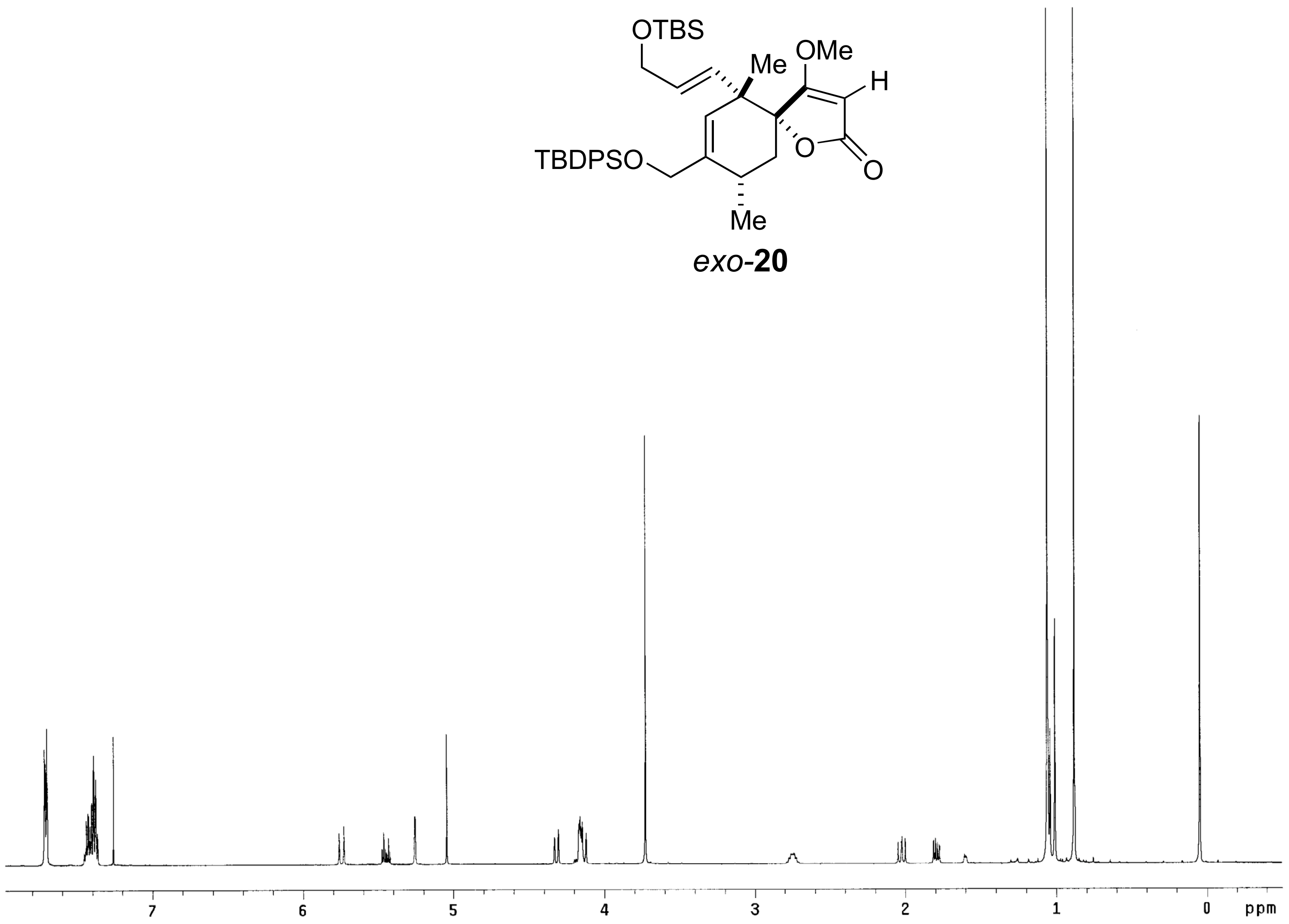

8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0



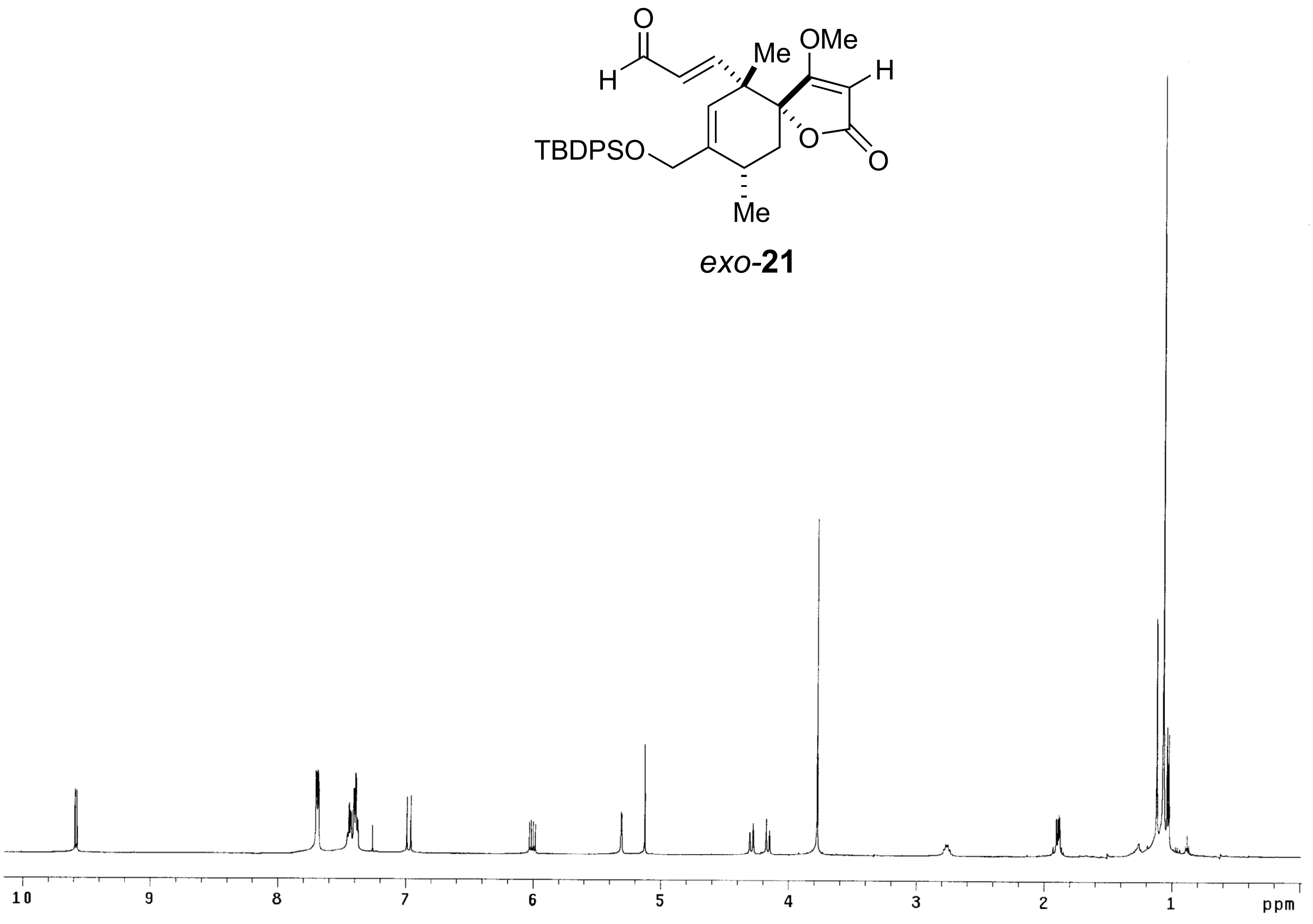
exo-**17**

OH
Me
CO2Me
OAc
TBDPSO
Me
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

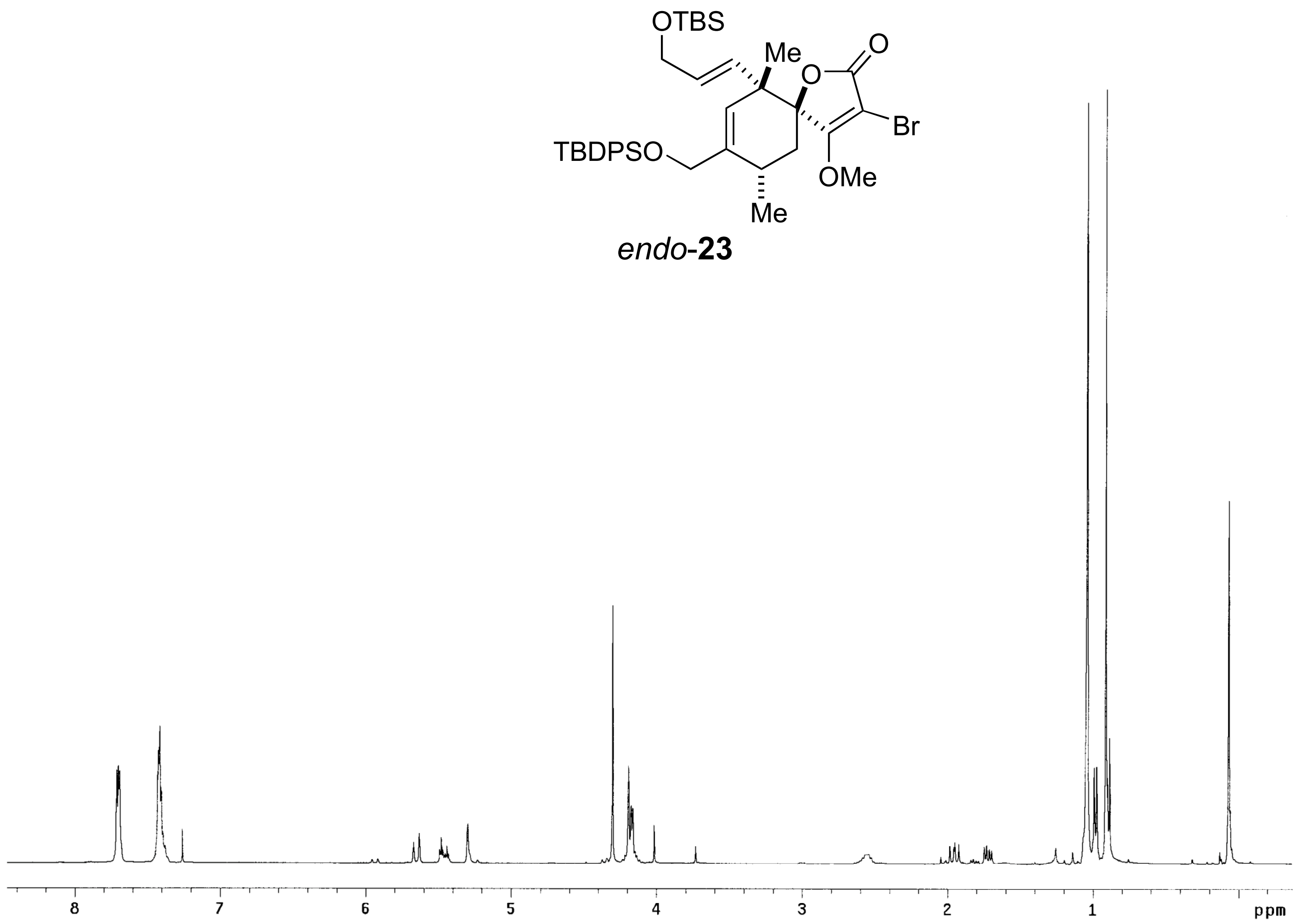

OTBS
Me
OMe
Br
TBDPSO
O
O
Me
exo-19
8
7
6
5
4
3
2
1
-0
ppm



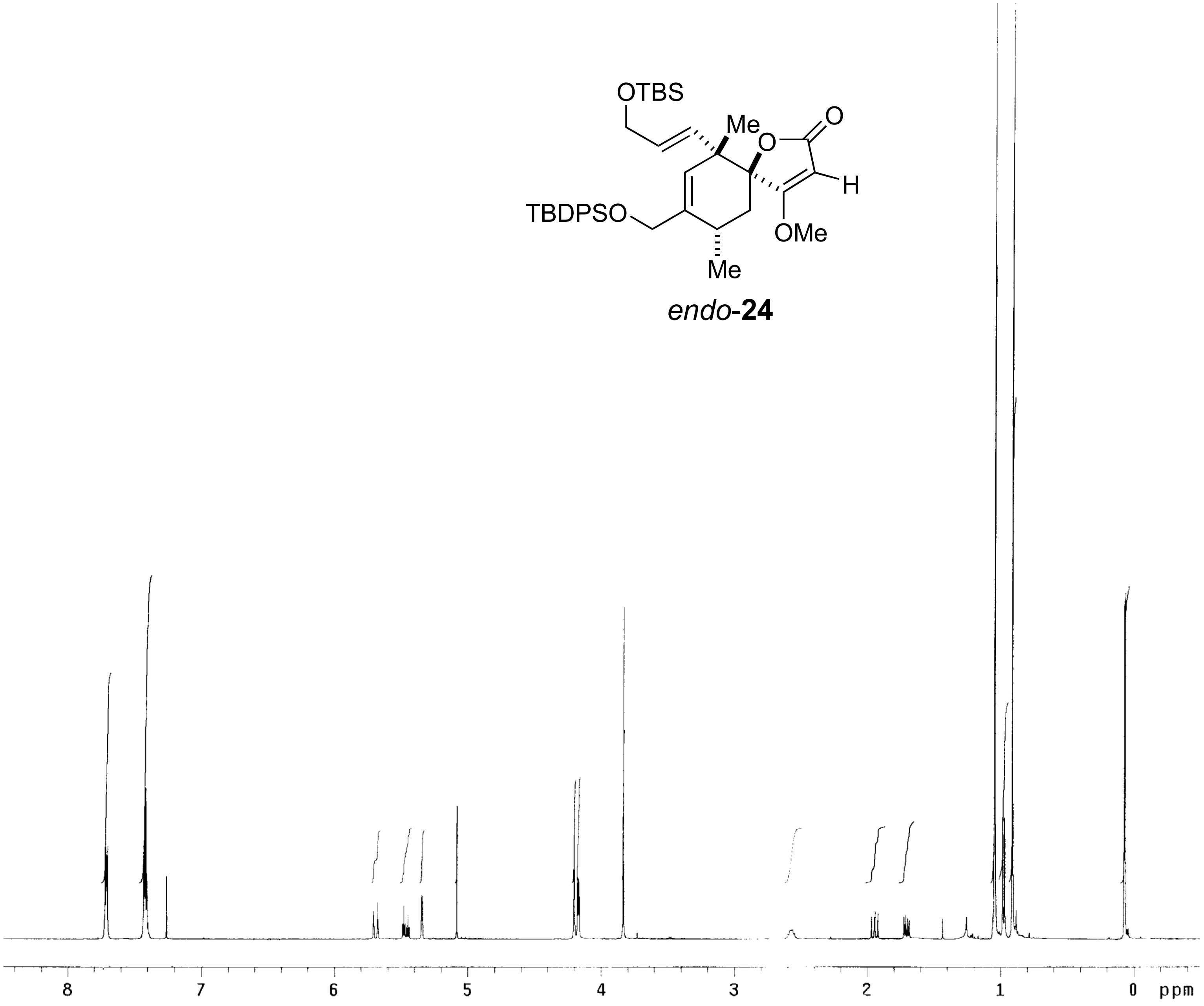
exo-**20**



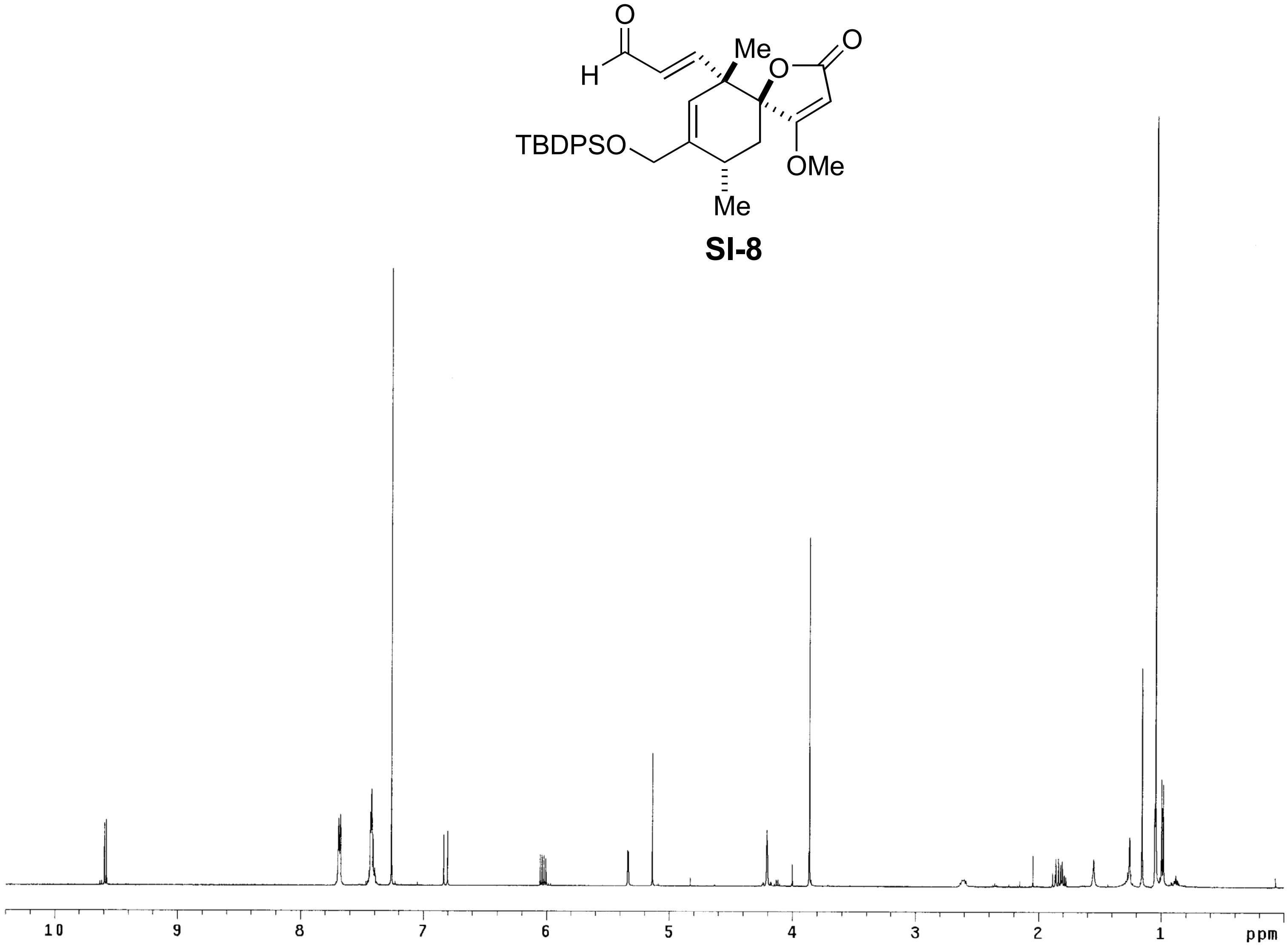
exo-**21**



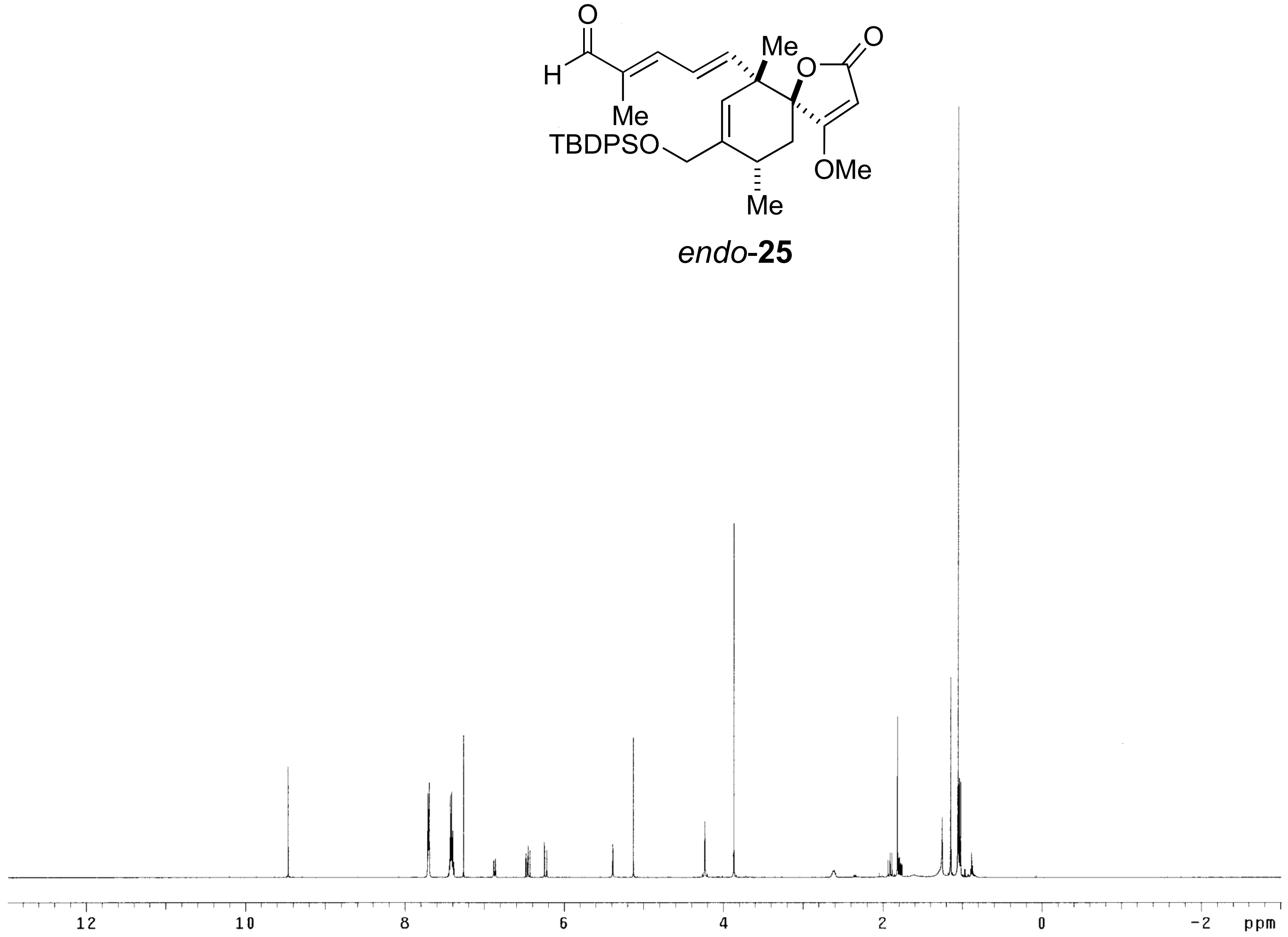
endo-**23**

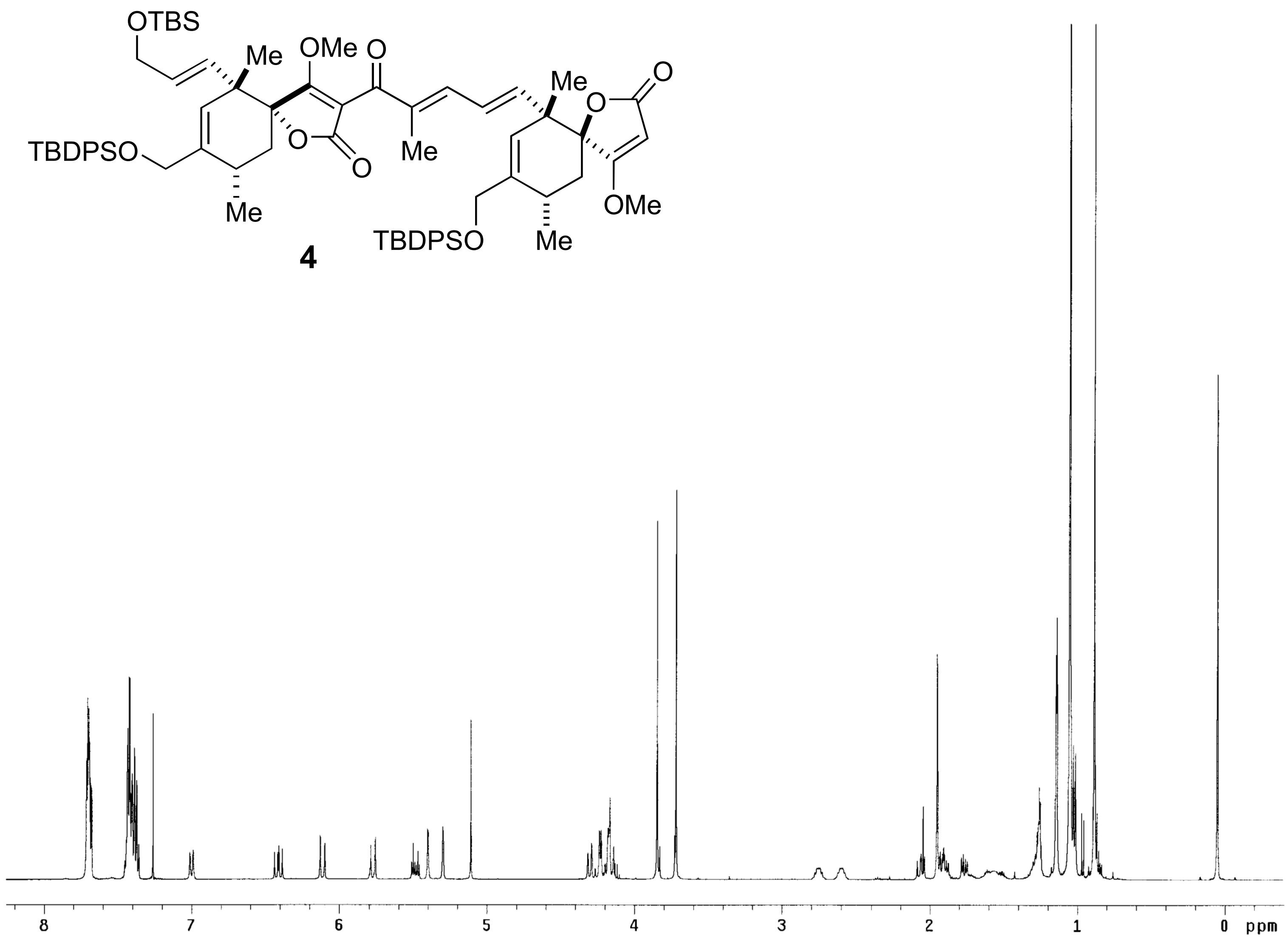


endo-**24**

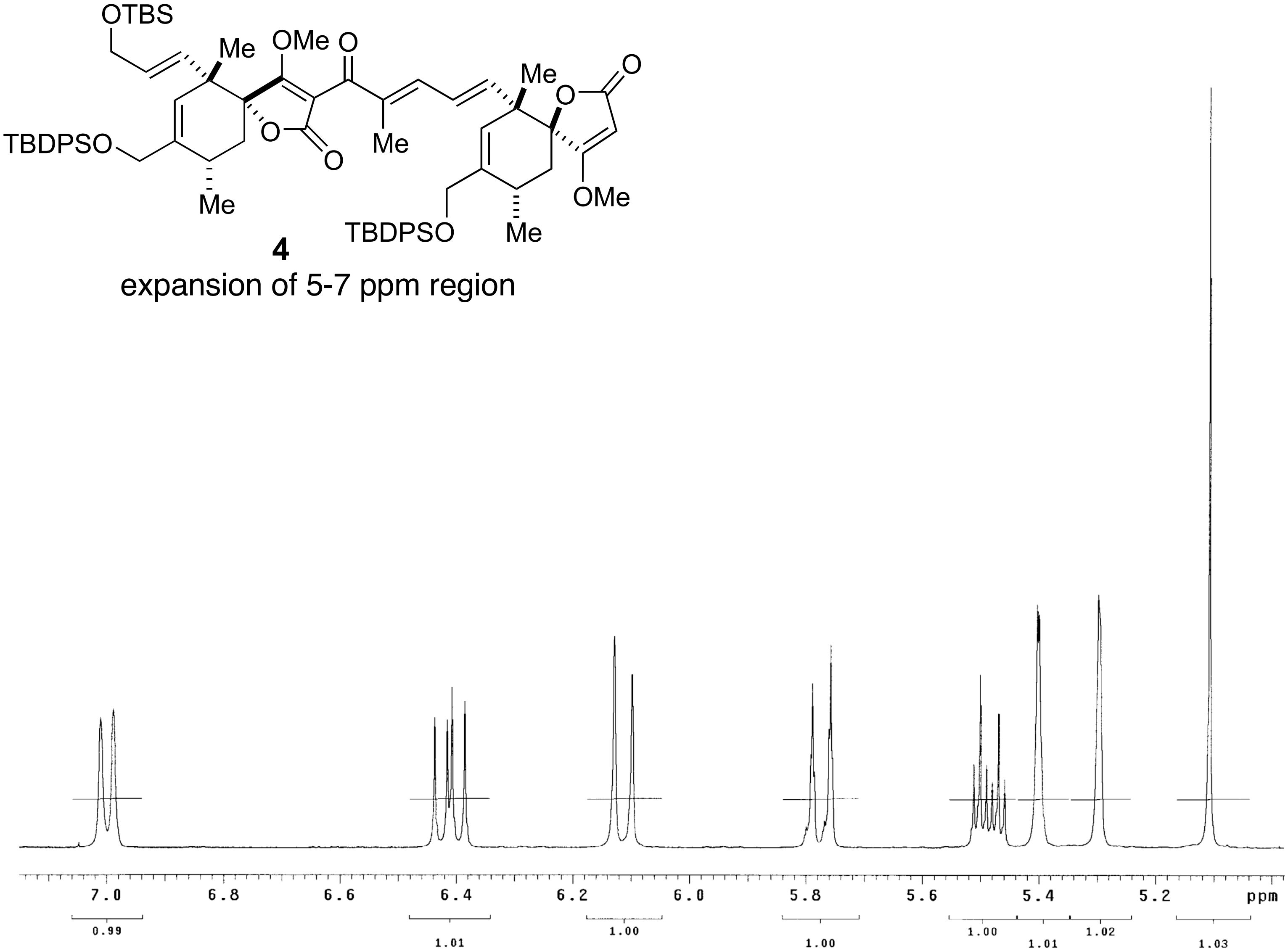


SI-8


endo-**25**

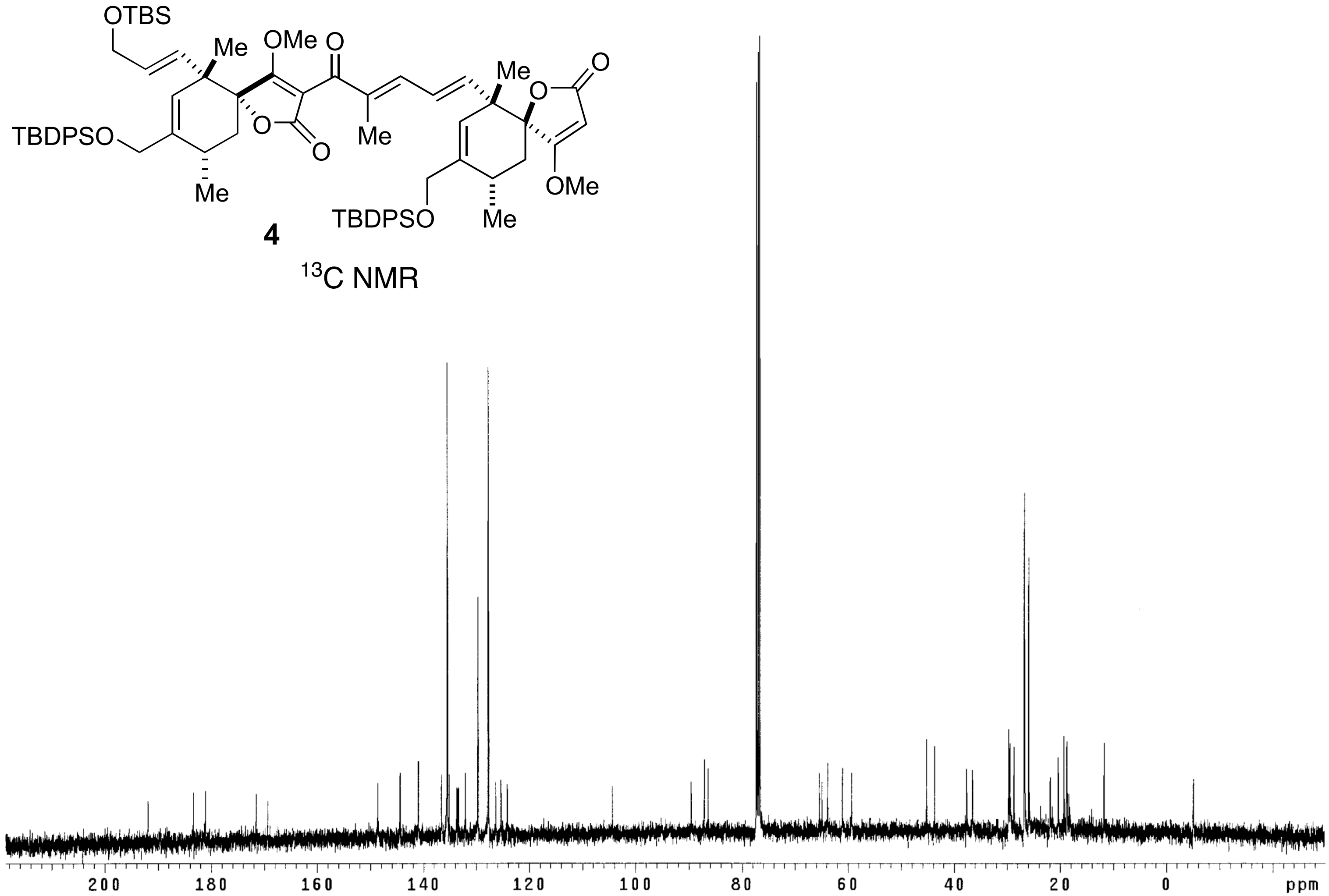

OTBS
Me
OMe
O
Me
O
TBDPSO
O
O
Me
Me
O
O
OMe
TBDPSO
Me
8
7
6
5
4
3
2
1
0
ppm

4



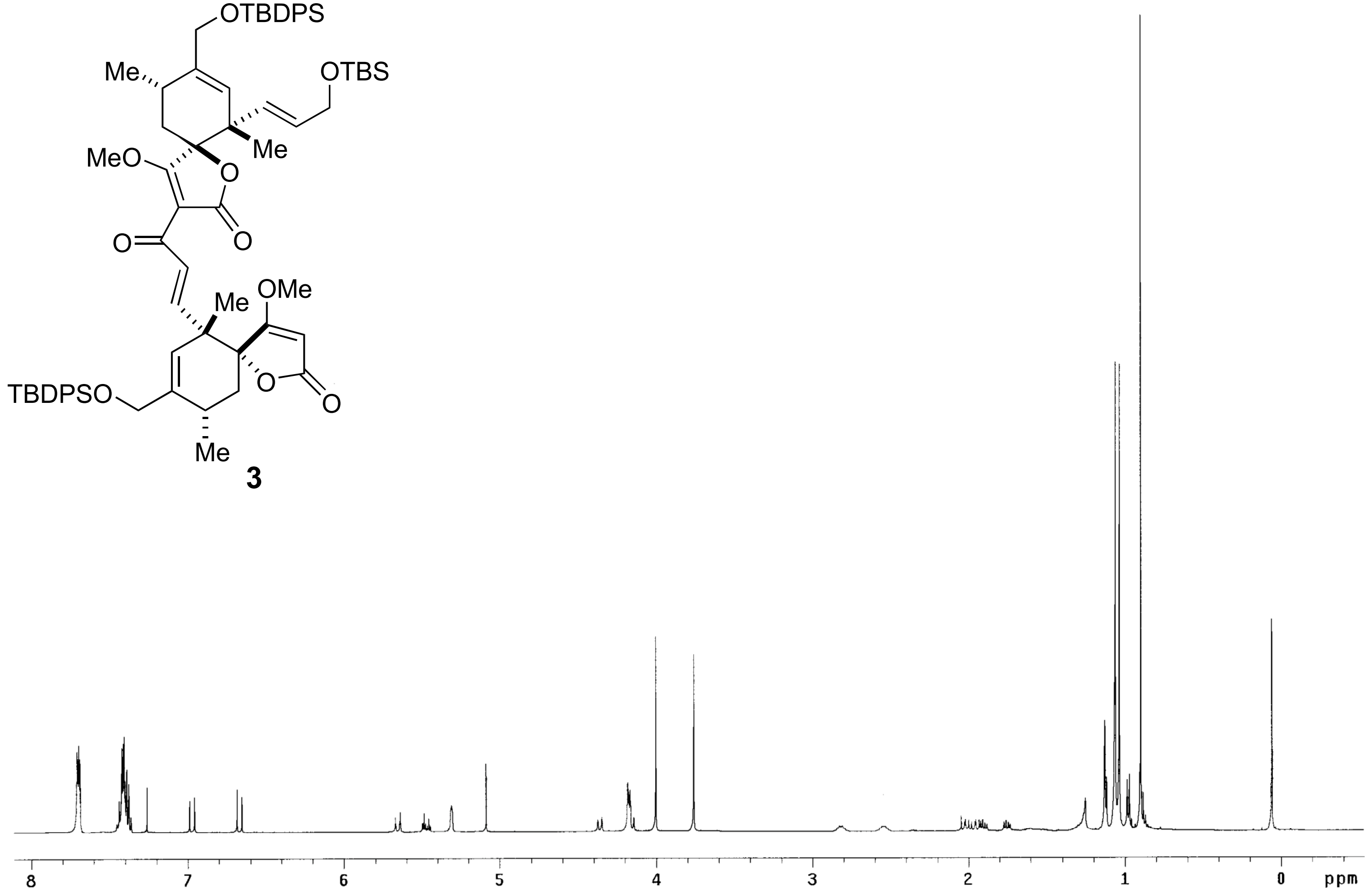
4

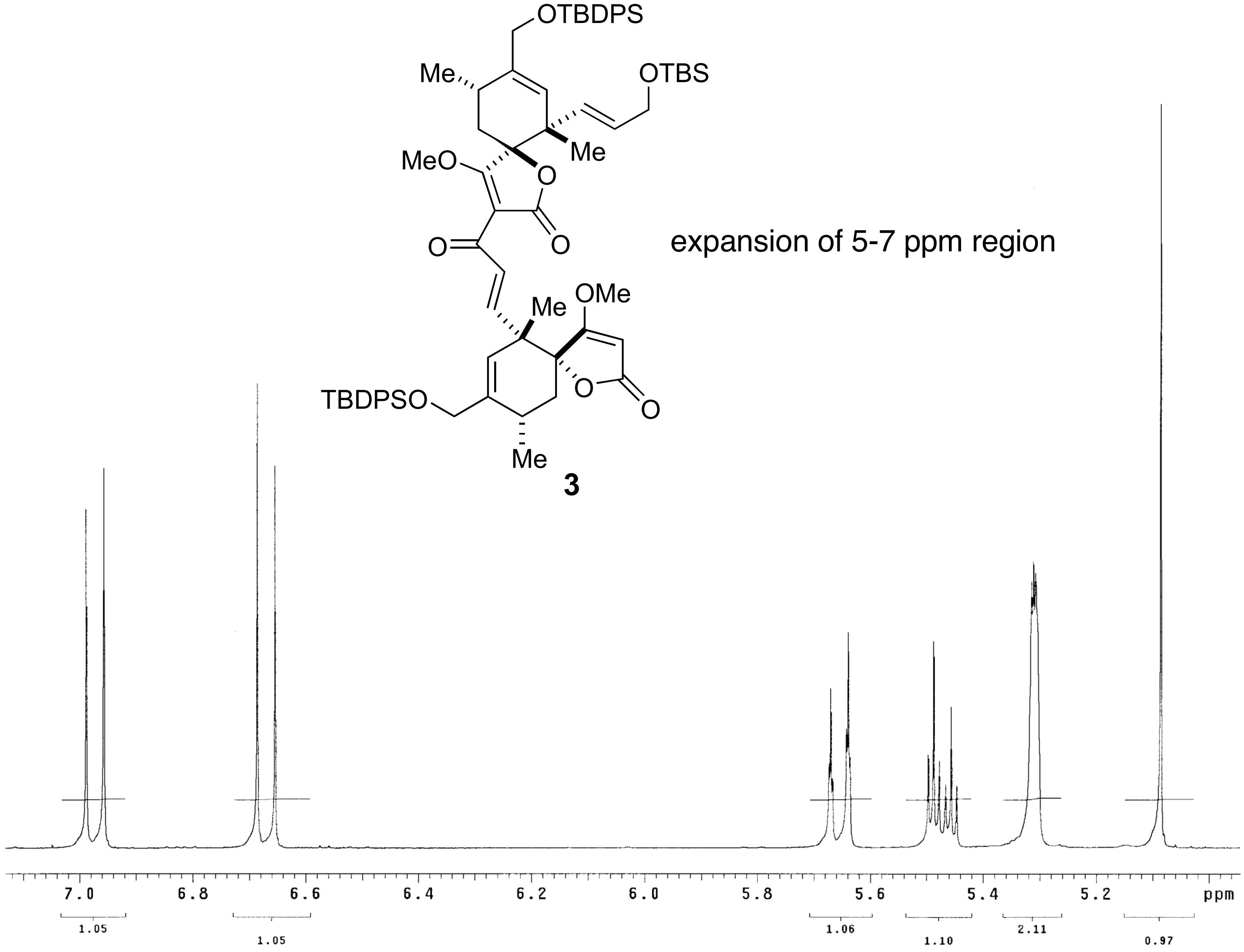
expansion of 5-7 ppm region


OTBS
Me
OMe
O
TBDPSO
O
O
Me
Me
Me
O
O
OMe
TBDPSO
Me
200
180
160
140
120
100
80
60
40
20
0
ppm

4

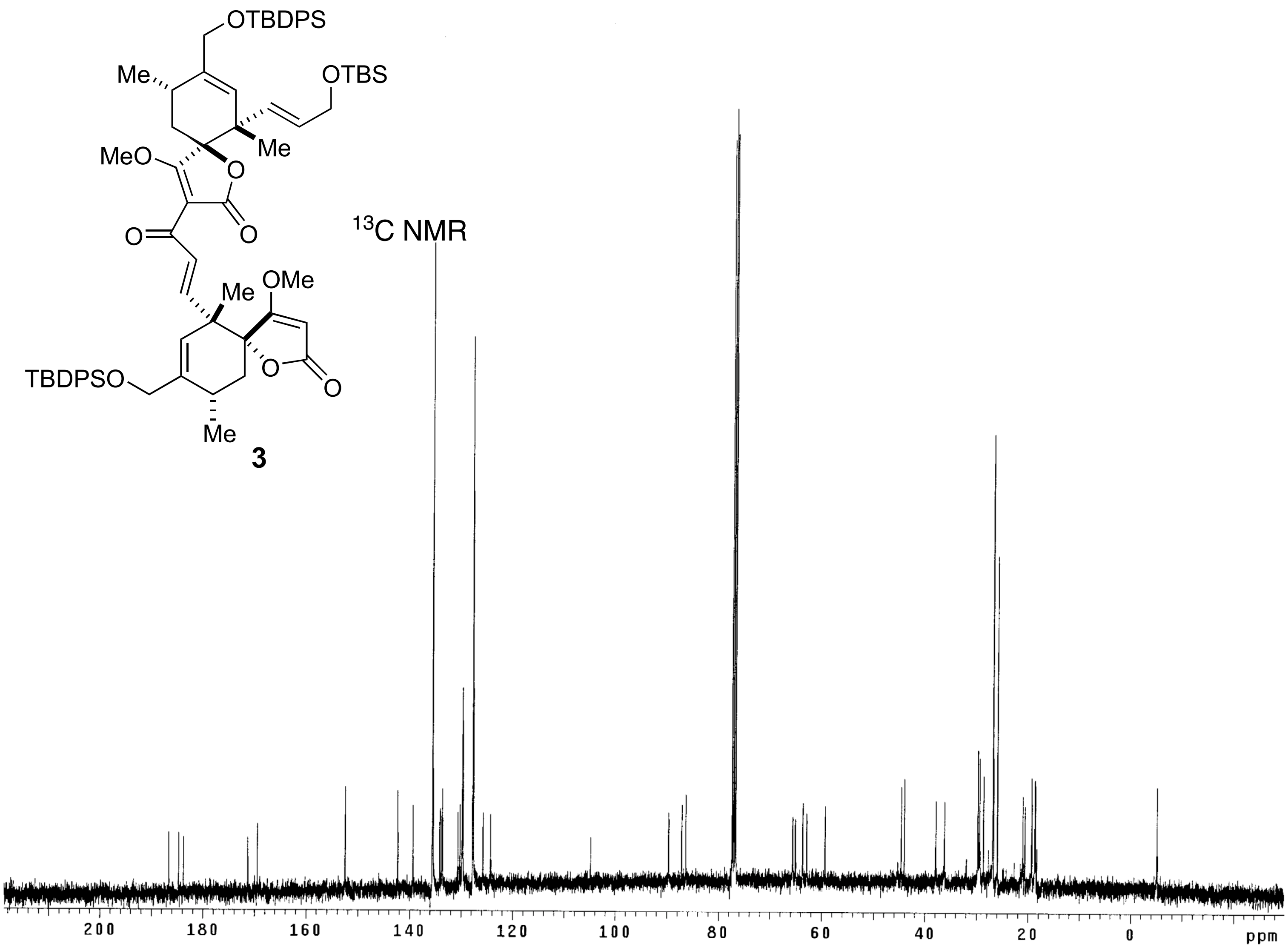
^{13}C NMR


OTBDPS
Me
OTBS
Me
MeO
O
O
O
Me
OMe
TBDPSO
O
O
Me
3
8
7
6
5
4
3
2
1
0
ppm



3

expansion of 5-7 ppm region



3

OTBDPS
OTBS
Me
Me
MeO
O
O
O
Me
OMe
TBDPSO
O
O
Me
13C NMR
200
180
160
140
120
100
80
60
40
20
0
ppm