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**ENANTIOSELECTIVE TOTAL SYNTHESIS OF (-)-CHLOROTHRICOLIDE VIA THE  
TANDEM INTER- AND INTRAMOLECULAR DIELS-ALDER REACTION OF A  
HEXAENOATE INTERMEDIATE**

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SUPPORTING INFORMATION:

Complete experimental procedures for the total synthesis of (-)-chlorothricolide and  
<sup>1</sup>H NMR spectra of (-)-**1**, **19**, **21**, **22**, (E,E,E)-**24**, **41**, **42**, **44**, **45**, **52**, **58**, and **59**,  
and <sup>13</sup>C NMR spectra of **59** (31 pages).

**Experimental Section**

**General.** All reactions were conducted in flame-dried glassware under dry argon or nitrogen. All solvents were purified before use. Diethyl ether, THF and toluene were distilled from sodium benzophenone ketyl under a nitrogen atmosphere. Methylene chloride and acetonitrile were distilled from CaH<sub>2</sub>. Methanol was distilled from magnesium turnings. Other reagents and solvents were purified following standard procedures.<sup>2</sup>

<sup>1</sup>H NMR spectra were measured at 300 and 400 MHz on commercially available instruments. Chemical shifts are reported in  $\delta$  units; coupling constants are reported in Hz. Residual chloroform ( $\delta$  7.26) and benzene ( $\delta$  7.15) were used as internal references for spectra measured in these solvents. <sup>13</sup>C NMR spectra were measured at 100.6 MHz, and residual chloroform ( $\delta$  77.0) and benzene ( $\delta$  128.0) were used as internal references. Infrared spectra were recorded on a Perkin-Elmer Model 1420 Infrared Spectrophotometer. FT-IR spectra were recorded on Mattson Instruments 4020 Galaxy Series FT-IR Spectrophotometer. Low and high resolution mass spectra were measured at 70 eV. Optical rotations were measured on a Rudolph Autopol III polarimeter using a quartz cell with 1 mL capacity and a 10 cm path length. Elemental analyses were performed by Robertson Laboratories, Florham Park, NJ.

Preparative HPLC purifications were performed by using systems consisting of a Rheodyne 7125 injector, Waters 6000A pump and a Waters RI-401 RI detector, or a Rheodyne 7125 injector, Rainin HPXL pump and a Rainin UV-C detector at 254 nm. Analytical thin-layer chromatography (TLC) was performed by using 2.5 cm x 10 cm plates coated with a 0.25 mm thickness of silica gel containing PF 254 indicator (Analtech). Preparative thin-layer chromatography (PTLC) was performed by using 20 cm x 20 cm plates coated with 0.5 mm thickness of silica gel containing PF254 indicator (Analtech). Flash chromatography was performed as described by Still using of Kieselgel 60 silica gel (230-400 mesh).<sup>3</sup> Unless otherwise noted, all compounds purified by chromatography are sufficiently pure (>95% by <sup>1</sup>H NMR analysis) for use in subsequent reactions.

**(3S)-Methyl-1-trimethylsilyl-3-[(methoxymethyl)oxy]-hept-1-yn-7-oate (34).** The asymmetric reduction of **33**<sup>4</sup> was performed according to a literature procedure. Thus, a mixture of 9-BBN dimer (25.3 g, 104 mmol) and (-)- $\alpha$ -pinene (36.4 mL, 229 mmol) were heated without solvent at 65 °C for 5 h in a round bottom flask equipped with a reflux condenser. The solution was cooled to 0 °C and ketone **33** (23.5 g, 104 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred an additional 18 h. The mixture was then cooled to 0 °C and acetaldehyde (8 mL) was added to react with excess borane reagent. The mixture was stirred for 10 min, then was placed under high vacuum at 60 °C for 1 h. The crude product was diluted with Et<sub>2</sub>O (100 mL) and was cooled to 0 °C. Ethanolamine (104 mmol) was added and the solution was warmed to room temperature and stirred for 15 min. The solid was removed by filtration through a plug of Celite, which was subsequently washed with Et<sub>2</sub>O (4 x 150 mL). The filtrate was concentrated *in vacuo* and the crude alcohol was purified by flash chromatography (5:1 hexanes-Et<sub>2</sub>O gradient to 2:1 hexanes-Et<sub>2</sub>O), yielding the known propargyl alcohol (19.5 g, 82%).<sup>4</sup> The enantiomeric purity of this intermediate was determined to be 89% e.e. by Mosher ester analysis.<sup>5</sup> In other runs, e.e.'s as high as 94% e.e. were obtained.

To a 0 °C solution of the above propargyl alcohol (19.5 g, 85.2 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (180 mL) was added *i*-Pr<sub>2</sub>NEt (29.7 mL, 170 mmol) followed by slow addition of MOM-Cl (11.0 mL, 145 mmol). The reaction was stirred at room temperature for an additional 12 h. The mixture was then poured into sat. NaHCO<sub>3</sub> solution, and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 100 mL). The extracts were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo* to give the crude product that was purified by flash chromatography (4 : 1 hexanes-EtOAc), giving the MOM ether **34** (20.1 g, 87%), as a pale yellow oil: TLC R<sub>f</sub> = 0.46 (2 : 1 hexanes-Et<sub>2</sub>O); [ $\alpha$ ]<sub>D</sub><sup>25</sup> = -136° (*c* 1.1, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  4.92 (B of AB, *J* = 6.8 Hz, 1 H), 4.56 (A of AB, *J* = 6.8 Hz, 1 H), 4.30 (dd, *J* = 6.0, 5.6 Hz, 1 H), 3.66 (s, 3 H), 3.36 (s, 3 H), 2.36 (dd, *J* = 7.2, 6.8 Hz, 2 H), 1.77 (m, 4 H), 0.15 (s, 9 H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  173.7, 103.8, 94.0, 90.5, 65.5, 55.7, 51.5, 34.9, 33.6, 20.8, -0.2; IR (CCl<sub>4</sub>) 2950, 2770, 2165, 1740 cm<sup>-1</sup>; high resolution mass spectrum for C<sub>12</sub>H<sub>21</sub>O<sub>4</sub>Si (M<sup>+</sup> - CH<sub>3</sub>) calcd 257.1209, found 257.1199. *Anal.* Calcd for C<sub>13</sub>H<sub>24</sub>O<sub>4</sub>Si: C, 57.32; H, 8.88. Found: C, 57.46; H, 8.95.

**(3S)-7,7-Dimethoxy-3-[(methoxymethyl)oxy]-1-trimethylsilyl-1-heptyne (35).**

To a  $-78\text{ }^{\circ}\text{C}$  solution of ester **34** (10 g, 37 mmol) in  $\text{CH}_2\text{Cl}_2$  (370 mL) was added DIBAL-H (35 mL of a 1.0 M solution in  $\text{CH}_2\text{Cl}_2$ , 39 mmol) over a period of 30 min. The reaction mixture was stirred for 20 min at  $-78\text{ }^{\circ}\text{C}$ , then MeOH (2 mL) and sat. Rochelle's salt solution (100 mL) were added. The biphasic mixture stirred for 7 h at ambient temperature. The aqueous layer was separated and extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 100 mL). The combined extracts were dried over  $\text{Na}_2\text{SO}_4$  and concentrated *in vacuo*. The crude product was purified by flash chromatography (2 : 1 hexanes- $\text{Et}_2\text{O}$ ) to yield the aldehyde as a clear oil (8.5 g, 96% yield): TLC  $R_f = 0.3$  (2 : 1 hexanes- $\text{Et}_2\text{O}$ );  $[\alpha]_{\text{D}}^{25} = -190^{\circ}$  (*c* 1.3,  $\text{CH}_2\text{Cl}_2$ );  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.77 (t,  $J = 1.6$  Hz, 1 H), 4.93 (A of AB,  $J = 6.8$  Hz, 1 H), 4.57 (B of AB,  $J = 6.8$  Hz, 1 H), 4.32 (t,  $J = 6.0$  Hz, 1 H), 3.37 (s, 3 H), 2.49 (td,  $J = 7.2, 1.6$  Hz, 2 H), 1.88-1.72 (m, 4 H), 0.16 (s, 9 H);  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  202.1, 103.7, 94.1, 90.8, 65.6, 55.7, 43.4, 34.8, 18.0, -0.1; IR (neat)  $1730\text{ cm}^{-1}$ ; high resolution mass spectrum for  $\text{C}_{11}\text{H}_{19}\text{O}_3\text{Si}$  ( $\text{M}^+ - \text{CH}_3$ ) calcd 227.1103, found 227.1111.

To a  $0\text{ }^{\circ}\text{C}$  solution of the above aldehyde (8.1 g, 33 mmol) in MeOH (33 mL) was added trimethyl orthoformate (20 mL, 200 mmol) followed by *p*-TsOH (0.3 g, 1.7 mmol). The reaction mixture was stirred for 10 min, then poured into sat.  $\text{NaHCO}_3$  solution. The aqueous layer was extracted with  $\text{Et}_2\text{O}$  (3 x 50 mL) and the combined extracts were dried over  $\text{Na}_2\text{SO}_4$ . The extracts were concentrated *in vacuo* and the crude acetal was purified by flash chromatography (2 : 1 hexanes- $\text{Et}_2\text{O}$ ) to yield dimethyl acetal **35** as a clear oil (9.6 g, quantitative yield). All physical and spectroscopic data for **35** were identical to those previously reported<sup>6</sup> for racemic **35**, except for the optical rotation:  $[\alpha]_{\text{D}}^{25} = -111^{\circ}$  (*c* 1.3,  $\text{CH}_2\text{Cl}_2$ ).

**(1E)-(3S)-1-Iodo-7,7-dimethoxy-3-[(methoxymethyl)oxy]-1-trimethylsilyl-1-heptene (20).** To a solution of alkynyl silane **35** (4.7 g, 16 mmol) in  $\text{Et}_2\text{O}$  (180 mL) in a resealable Carius tube was added DIBAL-H (24 mL of a 1.0 M solution in cyclohexane, 24 mmol). The Carius tube was sealed and the reaction mixture was heated at  $60\text{ }^{\circ}\text{C}$  for 48 h. The reaction mixture was then cooled to  $-10\text{ }^{\circ}\text{C}$  and pyridine (2.7 mL, 33 mmol) was added. This mixture was stirred for 20 min., then was cooled to  $-50\text{ }^{\circ}\text{C}$  and NIS (7.3 g, 33 mmol) was added. The vigorously stirred mixture was allowed to warm to  $-10\text{ }^{\circ}\text{C}$  over a period of 1 h, then was poured into a cold 5% aqueous NaOH solution (100 mL). The biphasic mixture was stirred for 30 min at ambient temperature. The layers were separated and the aqueous layer was extracted with  $\text{Et}_2\text{O}$  (3 x 100 mL). The combined extracts were washed with water and sat. NaCl solution, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated *in vacuo*. The crude mixture was purified by flash chromatography (3 : 1 hexanes- $\text{Et}_2\text{O}$ ), giving vinyl iodide **20** (5.9 g, 82%) as a pale yellow oil. All spectroscopic and physical data for **20** were identical to those previously reported for the racemate,<sup>6</sup> except for the optical rotation:  $[\alpha]_{\text{D}}^{25} = -85^{\circ}$  (*c* 1.5,  $\text{CH}_2\text{Cl}_2$ ).

**(4Z)-4-[(*tert*-Butyldiphenylsilyloxy)methyl]-hexa-1,4-dien-3-ol (40).** To a -78 °C solution of known aldehyde **36**<sup>7</sup> (6.0 g, 18 mmol) in THF (90 mL) was added vinylmagnesium bromide (28 mL of a 1.0 M solution in THF, 27 mmol). The reaction mixture was stirred at -78 °C for 30 min then poured into sat. NH<sub>4</sub>Cl solution. The aqueous layer was extracted with Et<sub>2</sub>O (3 x 100 mL). The combined extracts were dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The crude product was purified by flash column chromatography (5 : 1 hexanes-Et<sub>2</sub>O), producing dienylic alcohol **40** (5.7 g, 88% yield) as a clear, viscous oil: TLC R<sub>f</sub> = 0.5 (2 : 1 hexanes-Et<sub>2</sub>O); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.75-7.72 (m, 4 H), 7.46-7.40 (m, 6 H), 5.98 (ddd, *J* = 17.2, 10.4, 5.2 Hz, 1 H), 5.67 (qtd, *J* = 7.2, 1.2, 0.8 Hz, 1 H), 5.42 (ddd, *J* = 17.2, 2.0, 1.6 Hz, 1 H), 5.22 (ddd, *J* = 10.4, 2.0, 1.6 Hz, 1 H), 4.77 (br t, *J* = 4.8 Hz, 1 H), 4.34 (s, 2 H), 3.43 (d, 6.0 Hz, 1 H), 1.46 (d, *J* = 7.2 Hz, 3 H), 1.07 (s, 9 H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 139.6, 138.1, 135.6, 132.7, 129.8, 127.8, 125.1, 114.6, 77.2, 60.4, 26.7, 19.0, 13.0; IR (CCl<sub>4</sub>) 3600, 3510 (broad) cm<sup>-1</sup>; high resolution mass spectrum for C<sub>23</sub>H<sub>29</sub>OSi (M<sup>+</sup> - OH) calcd 349.1988, found 349.1978. *Anal.* Calcd for C<sub>23</sub>H<sub>30</sub>O<sub>2</sub>Si: C, 75.36; H, 8.25. Found: C, 75.17; H, 8.55.

**Diethyl (2E,4Z)-4-[(*tert*-Butyldiphenylsilyloxy)methyl]-2,4-hexadienylphosphonate (22).** A solution of triphenylphosphine (1.87 g, 7.12 mmol) and 1,2-dibromotetrachloroethane (2.32 g, 7.12 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (40 mL) was stirred for 10 min.<sup>8</sup> The mixture was cooled to -5 °C, then a solution of dienylic alcohol **40** (1.93 g, 5.07 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was added over a period of 15 min. The reaction was stirred at 0 °C for 20 min. MeOH (288 μL, 7.10 mmol) and K<sub>2</sub>CO<sub>3</sub> (984 mg, 7.10 mmol) were then added and the resulting slurry was concentrated *in vacuo*. The semi-solid residue was dissolved in Et<sub>2</sub>O and filtered through Florisil. The mixture of allylic bromides **38** and **39** was diluted with a mixture of CH<sub>3</sub>CN (2.5 mL) and P(OEt)<sub>3</sub> (2.5 mL) and heated at 60 °C for 4 h. The reaction mixture was then concentrated *in vacuo* and the crude product purified by flash column chromatography (1 : 1 hexanes-EtOAc), affording a 5 : 1 mixture of dienyl phosphonate **22** and the (*E,E*)-isomer (1.40 g, 55% over two steps) as a clear viscous oil: TLC R<sub>f</sub> = 0.3 (1 : 1 hexanes-EtOAc); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.65 (m, 4 H), 7.40 (m, 6 H), 6.11 (dd, *J* = 16.0, 4.4 Hz, 1 H), 5.81 (ddt, *J* = 14.8, 7.6, 7.6 Hz, 1 H), 5.56 (dq, *J* = 0.4, 6.8 Hz, 1 H), 4.33 (d, *J* = 0.4 Hz, 2 H), 4.09 (m, 4 H), 2.66 (dd, *J* = 22.0, 7.6 Hz, 2 H), 1.46 (d, *J* = 7.2 Hz, 3 H), 1.29 (t, *J* = 6.8 Hz, 6 H), 1.04 (s, 9 H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 136.8, 135.6, 135.5, 133.6, 129.5, 128.6, 127.6, 116.5 (d, *J* = 12 Hz), 61.9, 61.8, 58.6, 31.1 (d, *J* = 139 Hz), 26.8, 19.2, 16.5, 16.4, 13.5; IR (CCl<sub>4</sub>) 3070, 3050, 2963, 2905, 2857, 1471, 1427, 1393, 1260 cm<sup>-1</sup>; high resolution mass spectrum for C<sub>27</sub>H<sub>39</sub>O<sub>4</sub>PSi (M<sup>+</sup>+1) calcd 487.2433, found 487.2428.

Partial data for minor (*E,E*)-isomer of **22**: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 6.46 (ddd, *J* = 15.6, 4.8, 0.8 Hz, 2 H), 5.73 (m, 1 H), 4.28 (s, 2 H), 1.75 (d, *J* = 6.0 Hz, 3 H), 1.05 (s, 9 H).

**(E)-1-Hydroxy-6-heptenyl-7-boronic acid (21).** 6-Heptyn-1-ol<sup>9</sup> (2.0 g, 18 mmol) was placed in a resealable Carius tube and cooled to 0 °C. Freshly double-distilled catechol borane (3.9 mL, 36 mmol) was added slowly allowing for H<sub>2</sub> evolution.<sup>10</sup> The mixture was stirred until gas evolution ceased. The Carius tube was sealed under an argon atmosphere and the reaction mixture was heated to 75 °C for 14 h. The mixture was cooled to room temperature and diluted with EtOAc (10 mL). The reaction mixture was carefully treated with distilled water (15 mL) and stirred for 1 h. The aqueous layer was extracted with EtOAc (8 x 20 mL); then the combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. The crude product was purified by flash chromatography (2 : 1 hexanes-EtOAc gradient to 19 : 1 CH<sub>2</sub>Cl<sub>2</sub>-MeOH), yielding **21** (2.0 g, 71%) as a clear glass: TLC R<sub>f</sub> = 0.3 (2:1 hexanes-Et<sub>2</sub>O); <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 6.53 (dt, *J* = 17.2, 6.8 Hz, 1 H), 5.56 (dt, *J* = 17.2, 1.2 Hz, 1 H), 3.53 (t, *J* = 6.8 Hz, 2 H), 2.16 (ddt, *J* = 7.2, 7.2, 1.6 Hz, 2 H), 1.57-1.31 (m, 6 H); <sup>13</sup>C NMR (100 MHz, CD<sub>3</sub>OD) δ 153.8, 62.9, 36.9, 33.5, 29.6, 26.5.

**(6Z,8E)-(5S)-1,1-Dimethoxy-5-[(methoxymethyl)oxy]-7-trimethylsilyl-tetradeca-6,8-dien-14-ol.** A solution of vinyl iodide **20** (5.8 g, 14 mmol) in degassed THF (140 mL) was treated with Pd(PPh<sub>3</sub>)<sub>4</sub> (2.6 g, 2.2 mmol). This mixture was stirred for 10 min, then a solution of vinyl boronic acid **21** (2.9 g, 18 mmol) in degassed aqueous TIOH (61 mL of a 0.3 M solution, 18 mmol) was added.<sup>11</sup> The reaction mixture was stirred for 30 min then was filtered through a pad of Celite. The aqueous layer was extracted with EtOAc (2 x 100 mL) and the combined extracts were dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The crude product was purified by flash chromatography (1 : 1 hexanes-Et<sub>2</sub>O gradient to 1:2 hexanes-Et<sub>2</sub>O), giving the 1,3-diene alcohol (5.2 g, 92%) as a colorless oil: TLC R<sub>f</sub> = 0.2 (1 : 1 hexanes-Et<sub>2</sub>O); [ $\alpha$ ]<sub>D</sub><sup>25</sup> = -65° (*c* 1.8, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 6.01 (dd, *J* = 15.2, 0.8 Hz, 1 H), 5.89 (d, *J* = 9.6 Hz, 1 H), 5.56 (dt, *J* = 15.2, 6.8 Hz, 1 H), 4.67 (B of AB, *J* = 6.4 Hz, 1 H), 4.47 (A of AB, *J* = 6.4 Hz, 1 H), 4.36 (dd, *J* = 6.0, 5.6 Hz, 1 H), 4.29 (dt, *J* = 9.6, 4.4 Hz, 1 H), 3.64 (dd, *J* = 6.8, 6.4 Hz, 2 H), 3.35 (s, 3 H), 3.31 (s, 6 H), 2.06 (dt, *J* = 7.2, 6.8 Hz, 2 H), 1.59 (m, 6 H), 1.39 (m, 7 H), 0.18 (s, 9 H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 142.3, 142.1, 134.5, 130.2, 104.5, 93.2, 73.8, 62.9, 55.2, 52.7, 35.8, 32.9, 32.6, 32.5, 29.3, 25.3, 20.7, 0.6; IR (CCl<sub>4</sub>) 3638, 3508 cm<sup>-1</sup>; high resolution mass spectrum for C<sub>21</sub>H<sub>42</sub>O<sub>5</sub>Si (M<sup>+</sup>) calcd 402.2801, found 402.2810. *Anal.* Calcd for C<sub>21</sub>H<sub>42</sub>O<sub>5</sub>Si: C, 62.64; H, 10.51. Found: C, 62.75; H, 10.54.

**(6Z,8E)-(5S)-1,1-Dimethoxy-5-[(methoxymethyl)oxy]-7-trimethylsilyl-tetradeca-6,8-dien-14-al (41).** To a -78 °C solution of oxalyl chloride (0.80 mL, 9.2 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (58 mL) was slowly added dimethyl sulfoxide (1.42 mL, 18.4 mmol).<sup>12</sup> The reaction mixture was stirred 10 min and then a solution of the diene alcohol prepared in the preceding experiment (2.40 g, 6.13 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) was added dropwise over a period of 15 min. The mixture was stirred 40 min at -78 °C, then triethylamine (3.80 mL, 27.6 mmol) was added. The reaction mixture was then

allowed to warm to room temperature over a period of 1 h. It was then diluted with Et<sub>2</sub>O (100 mL) and washed with sat. NaHCO<sub>3</sub> solution. The aqueous layer was extracted with Et<sub>2</sub>O (3 x 50 mL), then the combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. The crude aldehyde was purified by silica gel flash column chromatography (3 : 1 hexanes-Et<sub>2</sub>O), giving **41** (2.25 g, 94%; 86% from **20**) as a pale yellow oil: TLC R<sub>f</sub> = 0.3 (1 : 1 hexanes-Et<sub>2</sub>O);  $[\alpha]_D^{25} = -67^\circ$  (*c* 1.7, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.76 (t, *J* = 2.0 Hz, 1 H), 6.02 (ddt, *J* = 15.2, 2.4, 1.2 Hz, 1 H), 5.89 (dd, *J* = 9.6, 1.2 Hz, 1 H), 5.54 (dt, *J* = 15.2, 7.2 Hz, 1 H), 4.67 (B of AB, *J* = 7.2 Hz, 1 H), 4.48 (A of AB, *J* = 7.2 Hz, 1 H), 4.36 (t, *J* = 5.6 Hz, 1 H), 4.29 (ddd, *J* = 9.6, 8.4, 4.4 Hz, 1 H), 3.35 (s, 3 H), 3.31 (s, 6 H), 2.44 (dt, *J* = 7.2, 2.0 Hz, 2 H), 2.07 (ddd, *J* = 14.8, 7.2, 1.6 Hz, 2 H), 1.66-1.38 (m, 10 H), 0.18 (s, 9 H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 202.5, 142.3, 142.2, 135.0, 129.5, 104.5, 93.2, 73.7, 55.2, 52.7, 43.7, 35.8, 32.6, 32.5, 28.9, 21.5, 20.7, 0.5; IR (CCl<sub>4</sub>) 2940, 2710, 1725 cm<sup>-1</sup>; high resolution mass spectrum for C<sub>21</sub>H<sub>41</sub>O<sub>5</sub>Si (M<sup>+</sup>+1) calcd 401.2732, found 401.2703.

**(6Z,8E,14E,16E,18Z)-(5S)-18-[(*tert*-Butyldiphenylsilyloxy)methyl]-1,1-dimethoxy-5-[(methoxymethyl)oxy]-7-trimethylsilyl-6,8,14,16,18-icosapentaene (**42**).**

A -78 °C solution of dienyl phosphonate **22** (2.01 g, 4.48 mmol; a 5 : 1 mixture of trisubstituted olefin isomers) in THF (6 mL) was treated with *n*-BuLi (1.80 mL of a 2.48 M solution in THF, 4.48 mmol).<sup>13</sup> This solution was stirred at -78 °C for 1 h, then a -78 °C solution of aldehyde **41** (1.63 g, 4.07 mmol) in THF (3 mL) was added dropwise over a period of 20 min. The mixture was stirred for an additional 1 h at -78 °C, then HMPA (1.40 mL, 7.32 mmol) was added and the solution was allowed to warm to room temperature over a period of 1.5 h. The reaction mixture was stirred for an additional 6 h at room temperature. It was then poured into sat. NH<sub>4</sub>Cl solution (25 mL) and extracted with Et<sub>2</sub>O (3 x 15 mL). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. The crude pentaene was purified by flash chromatography (3 : 1 hexanes-Et<sub>2</sub>O) yielding **42** (2.52 g, 84%) as a 5 : 1 mixture of trisubstituted olefin isomers: TLC R<sub>f</sub> = 0.6 (2 : 1 hexanes-Et<sub>2</sub>O);  $[\alpha]_D^{25} = -35^\circ$  (*c* 1.4, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.70 (m, 4 H), 7.40 (m, 6 H), 6.36 (dd, *J* = 15.2, 10.4 Hz, 1 H), 6.07 (d, *J* = 15.6 Hz, 1 H), 6.06 (d, *J* = 15.2 Hz, 1 H), 6.02 (dd, *J* = 15.6, 1.6 Hz, 1 H), 5.91 (dd, *J* = 9.6, 1.2 Hz, 1 H), 5.60 (m, 3 H), 4.69 (B of AB, *J* = 6.8 Hz, 1 H), 4.48 (A of AB, *J* = 6.8 Hz, 1 H), 4.36 (s, 2 H), 4.30 (m, 2 H), 3.36 (s, 3 H), 3.32 (s, 6 H), 2.09 (m, 4 H), 1.63 (m, 4 H), 1.55 (d, *J* = 7.2 Hz, 3 H), 1.42 (m, 6 H), 1.05 (s, 9 H), 0.20 (s, 9 H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 142.4, 142.1, 137.7, 135.7, 135.5, 134.5, 133.8, 132.6, 131.2, 130.3, 129.5, 128.3, 128.1, 127.6, 104.5, 93.2, 73.8, 58.5, 55.2, 52.7, 35.8, 32.9, 32.6, 32.5, 29.1, 28.9, 26.8, 20.8, 19.3, 13.8, 0.6; IR (CCl<sub>4</sub>) 3134, 3071, 2900, 1590 cm<sup>-1</sup>; high resolution mass spectrum for C<sub>44</sub>H<sub>69</sub>O<sub>5</sub>Si<sub>2</sub> (M<sup>+</sup>+1) calcd 733.4683, found 733.4648.

**Allyl 2-Diethylphosphonopropionate (**23**).** To a 25 °C solution of triethyl 2-phosphonopropionate **43** (2.5 g, 11 mmol) in THF (20 mL) was added NaOH (12 mL of a 1.0 M

solution, 12 mmol). The reaction mixture was stirred 12 h at room temperature. The mixture was then acidified to pH 1 (10% aqueous HCl) and saturated with NaCl. The aqueous layer was extracted with EtOAc (3 x 20 mL). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, then concentrated *in vacuo* to give the crude carboxylic acid which was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (20 mL). To this solution was added allyl alcohol (1.0 mL, 14 mmol), DCC (4.7 g, 23 mmol), and catalytic DMAP. The reaction was stirred for 12 h at 23 °C, then was filtered through glass wool and concentrated *in vacuo*. The crude product was purified by flash column chromatography (1 : 1 hexanes-EtOAc gradient to 1 : 2 hexanes-EtOAc), affording allyl ester **23** (2.3 g, 88%) as a clear oil: TLC R<sub>f</sub> = 0.2 (1 : 1 hexanes-EtOAc); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.89 (ddt, *J* = 17.2, 10.4, 6.0 Hz, 1 H), 5.34 (ddt, *J* = 17.2, 1.6, 1.6 Hz, 1 H), 5.22 (ddt, *J* = 10.2, 1.6, 1.0 Hz, 1 H), 4.62 (m, 2 H), 4.13 (m, 4 H), 3.04 (dq, *J* = 23.2, 7.2 Hz, 1 H), 1.43 (dd, *J* = 18.0, 7.2 Hz, 3 H), 1.30 (dt, *J* = 7.2, 2.0 Hz, 6 H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 169.4 (d, *J* = 4.6 Hz), 131.6, 118.4, 65.9, 62.6 (d, *J* = 6.8 Hz), 39.3 (d, *J* = 133 Hz), 16.3 (d, *J* = 5 Hz), 11.6 (d, *J* = 6 Hz); IR (CCl<sub>4</sub>) 1740, 1456, 1260 cm<sup>-1</sup>; high resolution mass spectrum for C<sub>10</sub>H<sub>20</sub>O<sub>5</sub>P (M<sup>+</sup>+1) calcd 251.1048, found 251.1041. *Anal.* Calcd for C<sub>10</sub>H<sub>19</sub>O<sub>5</sub>P: C, 48.00; H, 7.65. Found: C, 47.56; H, 7.92.

**Allyl (2E,8Z,10E,16E,18E,20Z)-(7S)-18-[(tert-Butyldiphenylsilyloxy)-methyl]-7-[(methoxymethyl)oxy]-2-methyl-9-trimethylsilyl-2,8,10,16,18,20-docosaenoate (19).** A solution of pentaene dimethyl acetal **42** (1.13 g, 1.54 mmol) in CH<sub>3</sub>CN (5 mL) was slowly added to a 0 °C solution of LiBF<sub>4</sub> (191 mg, 1.70 mmol) in 2% aqueous CH<sub>3</sub>CN (15 mL, 0.1 M).<sup>14</sup> The reaction mixture was warmed to room temperature, then allowed to stir for an additional 2 h. At this time the mixture was poured into sat. NaHCO<sub>3</sub> solution (15 mL) and extracted with Et<sub>2</sub>O (3 x 10 mL). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. The crude product was purified by flash chromatography (4 : 1 hexanes-Et<sub>2</sub>O) to yield the pentaene aldehyde (1.03 g, 97%) as a clear oil: TLC R<sub>f</sub> = 0.6 (2 : 1 hexanes-Et<sub>2</sub>O); [α]<sub>D</sub><sup>25</sup> = -41° (*c* 1.5, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.78 (t, *J* = 1.6 Hz, 1 H), 7.71 (m, 4 H), 7.40 (m, 6 H), 6.38 (dd, *J* = 15.6, 10.4 Hz, 1 H), 6.10 (d, *J* = 15.2 Hz, 1 H), 6.07 (d, *J* = 15.2 Hz, 1 H), 6.04 (dd, *J* = 15.2, 1.2 Hz, 1 H), 5.92 (dd, *J* = 9.6, 1.2 Hz, 1 H), 5.61 (m, 3 H), 4.70 (B of AB, *J* = 6.8 Hz, 1 H), 4.49 (A of AB, *J* = 6.8 Hz, 1 H), 4.38 (s, 2 H), 4.32 (m, 1 H), 3.37 (s, 3 H), 2.48 (dt, *J* = 7.2, 1.6 Hz, 2 H), 2.10 (m, 4 H), 1.90-1.60 (m, 3 H), 1.56 (d, *J* = 7.2 Hz, 3 H), 1.50-1.38 (m, 5 H), 1.06 (s, 9 H), 0.21 (s, 9 H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 202.3, 142.8, 141.5, 137.7, 135.7, 135.5, 134.3, 133.8, 132.6, 131.2, 130.5, 129.5, 128.3, 128.1, 127.6, 93.2, 76.7, 73.5, 58.5, 55.3, 43.7, 35.4, 32.9, 32.6, 29.0, 26.8, 19.3, 18.2, 13.8, 0.6; IR (CCl<sub>4</sub>) 2714, 1730, 1550 cm<sup>-1</sup>; high resolution mass spectrum for C<sub>38</sub>H<sub>53</sub>O<sub>4</sub>Si<sub>2</sub> (M<sup>+</sup>-C<sub>4</sub>H<sub>9</sub>) calcd 629.3482, found 629.3504.

To a 0 °C solution of phosphonate **23** (770 mg, 3.06 mmol) in CH<sub>3</sub>CN (10 mL) was added LiCl (129 mg, 3.06 mmol) and DBU (411 μL, 2.75 mmol).<sup>15</sup> This mixture was stirred for 10 min at 0 °C, then a solution of the above pentaene aldehyde (1.05 g, 1.53 mmol) in CH<sub>3</sub>CN (5 mL) was added. The

reaction mixture was stirred for 2.5 h, then was poured into sat.  $\text{NH}_4\text{Cl}$  solution and extracted with  $\text{Et}_2\text{O}$  (3 x 10 mL). The combined extracts were dried over  $\text{Na}_2\text{SO}_4$  and concentrated *in vacuo*. The crude product was purified by flash chromatography (4 : 1 hexanes- $\text{Et}_2\text{O}$ ), affording hexaenoate **19** (953 mg, 80%) as a clear viscous oil: TLC  $R_f = 0.3$  (5 : 1 hexanes- $\text{Et}_2\text{O}$ );  $[\alpha]_D^{25} = -30^\circ$  (*c* 1.4,  $\text{CH}_2\text{Cl}_2$ );  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.70 (m, 4 H), 7.40 (m, 6 H), 6.80 (tq,  $J = 7.6, 1.6$  Hz, 1 H), 6.36 (dd,  $J = 15.6, 10.4$  Hz, 1 H), 6.08 (d,  $J = 14.8$  Hz, 1 H), 6.07 (dd,  $J = 15.2, 8.8$  Hz, 1 H), 6.02 (dt,  $J = 15.2, 1.2$  Hz, 1 H), 5.96 (ddt,  $J = 17.2, 10.8, 5.2$  Hz, 2 H), 5.90 (dd,  $J = 10, 1$  Hz, 1 H), 5.61 (partially obscured dt, 1 H), 5.59 (q,  $J = 6.4$  Hz, 1 H), 5.58 (dt,  $J = 15.2, 6.8$  Hz, 1 H), 5.33 (ddt,  $J = 17.2, 1.6, 1.6$  Hz, 1 H), 5.23 (ddt,  $J = 10.4, 1.6, 1.2$  Hz, 1 H), 4.68 (B of AB,  $J = 6.8$  Hz, 1 H), 4.64 (dt, 5.6, 1.6 Hz, 1 H), 4.48 (A of AB,  $J = 6.8$  Hz, 1 H), 4.36 (s, 2 H), 4.31 (m, 1 H), 3.35 (s, 3 H), 2.21 (dt,  $J = 7.2, 6.4$  Hz, 2 H), 2.08 (m, 4 H), 1.85 (d,  $J = 1.6$  Hz, 3 H), 1.62 (m, 2 H), 1.55 (d,  $J = 7.2$  Hz, 3 H), 1.51-1.38 (m, 6 H), 1.04 (s, 9 H), 0.19 (s, 9 H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  167.7, 142.5, 142.3, 141.8, 137.7, 135.7, 135.5, 134.4, 133.8, 133.7, 132.5, 131.2, 130.4, 129.5, 128.2, 128.1, 127.7, 127.5, 117.7, 93.2, 73.6, 65.0, 58.5, 55.2, 35.7, 32.8, 32.6, 29.0, 28.9, 28.7, 26.8, 24.6, 19.2, 13.7, 12.4, 0.6; IR ( $\text{CCl}_4$ ) 3072, 3060, 3050, 2931, 2858, 1713, 1550  $\text{cm}^{-1}$ ; high resolution mass spectrum for  $\text{C}_{48}\text{H}_{70}\text{O}_5\text{Si}_2$  ( $\text{M}^+$ ) calcd 782.4762, found 782.4739.

**(1R,2R,4aS,5S,8aR)-2-Propenyl 2-(5E)-[6-(2R,5S,6R,9R)-[2-(1,1-Dimethylethyl)-8-[[[(1,1-dimethylethyl)diphenylsilyl]oxy]methyl]-9-methyl-4-oxo-1,3-dioxaspiro[4,5]dec-7-en-6-yl]-5-hexenyl]-1,2,4a,6,7,8,8a-octahydro-5-(methoxymethoxy)-1-methyl-4-(trimethylsilyl)-1-naphthalenecarboxylate (44).** A solution of hexaenoate **19** (410 mg, 0.52 mmol) in degassed toluene (350  $\mu\text{L}$ , 1.5 M) was added to a Carius tube that had been pre-silylated with *bis*-trimethylsilylacetamide (BSA). Dienophile (*R*)-**12**<sup>16</sup> (165 mg, 1.05 mmol) and a crystal of *tert*-butylhydroxytoluene (BHT) were then added to the Carius tube which was sealed and heated at 120  $^\circ\text{C}$  for 20 h. The cooled reaction mixture was concentrated *in vacuo*. HPLC analysis of the crude reaction mixture revealed that four major double cycloadducts were produced in the ratio of 67 : 13 : 5 : 5 (average of several runs). The HPLC trace also contained several other minor bands that presumably represent minor diastereomers expected from the Diels-Alder reaction of (*R*)-**12** and ent-**19** (present at the ca. 3-5% level in **19**). Separation of this mixture by flash chromatography (7 : 1 hexanes- $\text{Et}_2\text{O}$ ) provided the desired cycloadduct **44** (220 mg, 45%; ca. 90% isomeric purity) plus a mixture of isomeric double Diels-Alder adducts (91 mg, 19%) and the IMDA adduct (*E,E,E*)-**24** with an isomerized C(20-21) trisubstituted olefin (107 mg, 26%). An analytically pure sample of **44** was obtained by preparative HPLC purification (4% EtOAc-hexanes, 18 mL/min, 20 mm Whatman M9 silica gel column, retention time: **24**, 14 min; **44**, 22 min; **46**, 26 min; **47**, 27 min; **45**, 39 min).

**Recycle of (*E,E,E*)-24 via Diels-Alder reaction with (*R*)-12** (for this particular run): A solution of (*E,E,E*)-**24** (107 mg, 0.14 mmol) in trichloroethylene (140  $\mu\text{L}$ , 1.0 M), that had been

neutralized by elution through basic alumina, was added to a pre-silylated (BSA) Carius tube. To this solution was then added dienophile (*R*)-**12**<sup>16</sup> (43 mg, 0.27 mmol) and a crystal of BHT. The Carius tube was sealed and the mixture heated at 120 °C for 23 h. The reaction mixture was concentrated *in vacuo* and the crude product purified by flash chromatography (7 : 1 hexanes-Et<sub>2</sub>O), giving cycloadduct **44** (48 mg, 38%) as well as recovered (*E,E,E*)-triene **24** (48 mg, 45%), which was further recycled. A small amount (ca. 3%) of **46** was also obtained by HPLC separation of mixed fractions.

Better conditions for the recycle of (*E,E,E*)-**24** are as follows: A solution of (*E,E,E*)-**24** (248 mg, 0.32 mmol), (*R*)-**12** (89 mg, 0.58 mmol), and a crystal of BHT in trichloroethylene (215  $\mu$ L, 1.5 M; purified by elution through basic alumina) in a sealed, pre-silylated (BSA) Carius tube was heated at 125 °C for 36 h. The reaction mixture was concentrated *in vacuo* and the crude product purified by flash chromatography (7 : 1 hexanes-Et<sub>2</sub>O). This provided the desired cycloadduct **44** (172 mg, 58%) as well as recovered (*E,E,E*)-triene **24** (56 mg, 22%).

**Data for 44:** TLC R<sub>f</sub> = 0.45 (4 : 1 hexanes-Et<sub>2</sub>O); [ $\alpha$ ]<sub>D</sub><sup>25</sup> = -95.3° (*c* 1.66, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.65 (m, 4 H), 7.40 (m, 6 H), 6.13 (dd, *J* = 5.6, 1.6 Hz, 1 H), 5.90 (ddt, *J* = 16.8, 10.8, 5.2 Hz, 1 H), 5.60 (dt, *J* = 15.6, 6.4 Hz, 1 H), 5.41 (d, *J* = 0.4 Hz, 1 H), 5.33 (d, *J* = 15.6 Hz, 1 H), 5.33 (dd, *J* = 15.6, 8 Hz, 1 H), 5.31 (ddt, *J* = 17.2, 1.6, 1.6 Hz, 1 H), 5.21 (ddt, *J* = 10.8, 1.6, 1.2 Hz, 1 H), 5.11 (s, 1 H), 4.70 (B of AB, *J* = 7.2 Hz, 1 H), 4.65 (A of AB, *J* = 7.2 Hz, 1 H), 4.55 (m, 2 H), 4.23 (B of AB, *J* = 13.2 Hz, 1 H), 4.14 (A of AB, *J* = 13.2 Hz, 1 H), 3.35 (s, 3 H), 3.23 (dt, *J* = 10.0, 4.0 Hz, 1 H), 3.13 (d, *J* = 8.4 Hz, 1 H), 2.59 (m, 1 H), 2.41 (m, 1 H), 2.11 (dd, *J* = 14.0, 7.2 Hz, 1 H), 1.97 (m, 4 H), 1.74 (m, 4 H), 1.41-1.19 (m, 8 H), 1.12 (d, *J* = 7.2 Hz, 3 H), 1.10 (s, 3 H), 1.06 (s, 9 H), 0.93 (s, 9 H), 0.06 (s, 9 H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  175.9, 175.7, 140.8, 140.4, 137.9, 135.6, 135.3, 133.7, 133.6, 132.3, 129.6, 127.6, 127.1, 120.7, 117.9, 109.9, 96.1, 83.5, 81.2, 65.8, 64.6, 55.5, 48.0, 47.7, 45.9, 45.6, 39.1, 36.7, 34.9, 33.2, 32.5, 29.4, 28.5, 27.8, 27.2, 26.8, 24.4, 23.4, 19.6, 19.3, 17.5, 1.4; IR (CCl<sub>4</sub>) 3065, 3045, 2950, 1795, 1727 cm<sup>-1</sup>; high resolution mass spectrum for C<sub>54</sub>H<sub>77</sub>O<sub>6</sub>Si<sub>2</sub> (M<sup>+</sup>-C<sub>2</sub>H<sub>5</sub>O<sub>2</sub>) calcd 877.5258, found 877.5230. *Anal.* Calcd for C<sub>56</sub>H<sub>82</sub>O<sub>8</sub>Si<sub>2</sub>: C, 71.60; H, 8.80. Found: C, 71.33; H, 8.56.

**Data for (*E,E,E*)-24:** TLC R<sub>f</sub> = 0.56 (4 : 1 hexanes-Et<sub>2</sub>O); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.65 (m, 4 H), 7.40 (m, 6 H), 6.40 (d, *J* = 15.2 Hz, 1 H), 6.18-6.04 (m, 3 H), 5.91 (ddt, *J* = 17.2, 6.4, 5.6 Hz, 1 H), 5.78 (q, *J* = 6.8 Hz, 1 H), 5.62 (dt, *J* = 14.8, 6.8 Hz, 1 H), 5.30 (dq, *J* = 17.2, 1.6 Hz, 1 H), 5.21 (ddt, *J* = 10.4, 1.6, 1.2 Hz, 1 H), 4.70 (B of AB, *J* = 6.8 Hz, 1 H), 4.65 (A of AB, *J* = 6.8 Hz, 1 H), 4.55 (d, *J* = 5.6 Hz, 2 H), 4.33 (m, 2 H), 3.35 (s, 3 H), 3.23 (dt, *J* = 9.6, 4.0 Hz, 1 H), 2.41 (m, 1 H), 2.06 (m, 2 H), 1.96 (m, 2 H), 1.78 (d, *J* = 7.2 Hz, 3 H), 1.72 (m, 2 H), 1.44-1.20 (m, 10 H), 1.10 (s, 3 H), 1.07 (s, 9 H), 0.06 (s, 9 H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  175.8, 140.5, 137.8, 135.7, 135.5, 135.3, 134.6, 133.7, 132.3, 131.3, 129.5, 128.5, 127.6, 124.9, 123.5, 117.9, 96.1, 83.5, 64.9, 64.6, 55.5, 48.0, 47.7, 46.0, 39.1, 34.9, 33.2, 32.6, 29.5, 28.5, 26.8, 24.4, 19.3,

17.5, 13.1, 1.4; IR (CCl<sub>4</sub>) 3088, 3065, 3028, 2960, 2940, 2860, 1730, 1606 cm<sup>-1</sup>; high resolution mass spectrum for C<sub>44</sub>H<sub>61</sub>O<sub>5</sub>Si<sub>2</sub> (M<sup>+</sup>-C<sub>4</sub>H<sub>9</sub>) calcd 725.4057, found 725.4063.

**Data for 45 (the second most predominant double cycloadduct):** TLC R<sub>f</sub> = 0.38 (4 : 1 hexanes-Et<sub>2</sub>O); [α]<sub>D</sub><sup>27</sup> = -82.1° (c 1.92, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.65 (m, 4 H), 7.40 (m, 6 H), 6.12 (dd, *J* = 4.4, 2.8 Hz, 1 H), 5.88 (ddt, *J* = 18.8, 6.8, 5.6 Hz, 1 H), 5.64 (dt, *J* = 15.2, 6.8 Hz, 1 H), 5.42 (d, *J* = 0.8 Hz, 1 H), 5.35 (dd, *J* = 15.2, 8.8 Hz, 1 H), 5.31 (dq, *J* = 17.2, 1.6 Hz, 1 H), 5.19 (ddt, *J* = 10.4, 1.6, 1.2 Hz, 1 H), 5.12 (s, 1 H), 4.65 (B of AB, *J* = 7.2 Hz, 1 H), 4.63 (A of AB, *J* = 7.2 Hz, 1 H), 4.53 (ddd, *J* = 5.6, 1.6, 1.2 Hz, 2 H), 4.24 (B of AB, *J* = 12.8 Hz, 1 H), 4.14 (A of AB, *J* = 12.8 Hz, 1 H), 4.10 (d, *J* = 2.8 Hz, 1 H), 3.35 (s, 3 H), 3.14 (d, *J* = 8.8 Hz, 1 H), 2.68 (m, 1 H), 2.60 (m, 1 H), 2.36 (m, 2 H), 2.12 (dd, *J* = 14.0, 7.2 Hz, 1 H), 2.04 (m, 2 H), 1.77 (dd, *J* = 14.0, 2.4 Hz, 1 H), 1.66-1.24 (m, 12 H), 1.23 (s, 3 H), 1.13 (d, *J* = 7.6 Hz, 3 H), 1.06 (s, 9 H), 0.94 (s, 9 H), 0.09 (s, 9 H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 177.6, 175.9, 141.5, 140.8, 135.5, 134.4, 133.6, 132.3, 129.6, 127.6, 127.1, 120.7, 118.0, 109.9, 94.0, 81.2, 73.9, 65.8, 65.1, 55.0, 48.2, 45.6, 42.0, 40.5, 37.7, 36.6, 34.9, 32.7, 31.6, 31.0, 29.6, 29.0, 27.8, 27.4, 23.4, 20.9, 20.5, 19.6, 19.3, 15.3, 14.1, -.03; IR (CCl<sub>4</sub>) 3073, 3052, 2934, 2861, 1796, 1728 cm<sup>-1</sup>; high resolution mass spectrum for C<sub>53</sub>H<sub>77</sub>O<sub>7</sub>Si<sub>2</sub> (M<sup>+</sup>-C<sub>3</sub>H<sub>5</sub>O) calcd 881.5208, found 881.5207.

**(1*R*,2*R*,4*aS*,5*S*,8*aR*)-2-Propenyl 2-(5*E*)-[6-(1*R*,4*R*,6*S*)-[3-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]methyl]-6-(methoxycarbonyl)-4-methyl-6-hydroxy-2-cyclohexen-1-yl]-5-hexenyl]-1,2,4*a*,6,7,8,8*a*-octahydro-5-(methoxymethoxy)-1-methyl-4-(trimethylsilyl)-1-naphthalenecarboxylate.** To a 25 °C solution of **44** (278 mg, 0.30 mmol) in a 4 : 1 mixture of MeOH and THF (3 mL) was added K<sub>2</sub>CO<sub>3</sub> (18 mg, 0.13 mmol). The reaction mixture was stirred for 9 h, then was diluted with Et<sub>2</sub>O and washed with sat. NH<sub>4</sub>Cl solution. The aqueous layer was extracted with Et<sub>2</sub>O (3 x 10 mL). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. The crude product was purified by flash chromatography (2 : 1 hexanes-Et<sub>2</sub>O) producing the α-hydroxy ester (242 mg, 97%) as a clear viscous oil: TLC R<sub>f</sub> = 0.14 (4 : 1 hexanes-Et<sub>2</sub>O); [α]<sub>D</sub><sup>25</sup> = -92.7° (c 1.1, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.65 (m, 4 H), 7.40 (m, 6 H), 6.13 (dd, *J* = 5.6, 2.0 Hz, 1 H), 5.90 (ddt, *J* = 17.2, 10.4, 6.0 Hz, 1 H), 5.48 (ddt, *J* = 15.6, 6.4, 0.8 Hz, 1 H), 5.45 (broad s, 1 H), 5.33 (broad d, *J* = 15.6 Hz, 1 H), 5.31 (ddt, *J* = 17.2, 1.6, 1.6 Hz, 1 H), 5.21 (ddt, *J* = 10.4, 1.6, 1.2 Hz, 1 H), 4.70 (B of AB, *J* = 7.2 Hz, 1 H), 4.65 (A of AB, *J* = 7.2 Hz, 1 H), 4.55 (dt, *J* = 5.2, 1.6 Hz, 2 H), 4.25 (B of AB, *J* = 13.2 Hz, 1 H), 4.12 (A of AB, *J* = 13.2 Hz, 1 H), 3.76 (s, 3 H), 3.35 (s, 3 H), 3.23 (m, 2 H), 2.69 (broad s, 1 H), 2.54 (m, 1 H), 2.41 (m, 1 H), 2.19 (dd, *J* = 13.2, 6.8 Hz, 1 H), 1.97 (m, 3 H), 1.71 (m, 6 H), 1.41-1.16 (m, 8 H), 1.12 (d, *J* = 7.2 Hz, 3 H), 1.09 (s, 3 H), 1.05 (s, 9 H), 0.05 (s, 9 H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 176.5, 175.8, 140.5, 137.8, 135.5, 134.8, 133.8, 132.3, 129.6, 127.8, 127.6, 127.5, 121.4, 117.9, 96.1, 83.5, 77.2, 66.0, 64.6, 55.5, 52.6, 48.0, 47.7, 46.1, 45.7, 39.1, 38.0, 34.9,

33.3, 32.6, 29.7, 28.5, 28.4, 27.2, 26.8, 24.4, 19.9, 19.3, 17.5, 1.4; IR (CCl<sub>4</sub>) 3536, 3073, 3052, 2934, 2859, 1730 cm<sup>-1</sup>; high resolution mass spectrum for C<sub>48</sub>H<sub>67</sub>O<sub>8</sub>Si<sub>2</sub> (M<sup>+</sup>-C<sub>4</sub>H<sub>9</sub>) calcd 827.4374, found 827.4407. *Anal.* Calcd for C<sub>52</sub>H<sub>76</sub>O<sub>8</sub>Si<sub>2</sub>: C, 70.55; H, 8.65. Found: C, 70.74; H, 8.81.

**(1*R*,2*R*,4*aS*,5*S*,8*aR*)-2-Propenyl 2-(5*E*)-[6-(1*R*,4*R*,6*S*)-[3-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]methyl]-6-(methoxycarbonyl)-4-methyl-6-[(2-propenyloxy)acetyl]oxy]-2-cyclohexen-1-yl]-5-hexenyl]-1,2,4*a*,6,7,8,8*a*-octahydro-5-(methoxymethoxy)-1-methyl-4-(trimethylsilyl)-1-naphthalenecarboxylate (50).** A mixture of the  $\alpha$ -hydroxy ester prepared above (85 mg, 0.10 mmol), DCC (119 mg, 0.58 mmol), allyloxyacetic acid **49**<sup>17</sup> (68 mg, 0.58 mmol), and catalytic DMAP in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) was stirred at ambient temperature for 9 h. The reaction mixture was then filtered through a plug of glass wool and concentrated *in vacuo*. The crude product was purified by flash chromatography (3 : 1 hexanes-Et<sub>2</sub>O), thereby providing ester **50** (88 mg, 94%) as a clear viscous oil: TLC R<sub>f</sub> = 0.4 (2 : 1 hexanes-Et<sub>2</sub>O); [ $\alpha$ ]<sub>D</sub><sup>27</sup> = -155° (*c* 1.5, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.65 (m, 4 H), 7.40 (m, 6 H), 6.12 (dd, *J* = 6.0, 1.2 Hz, 1 H), 5.91 (ddt, *J* = 17.2, 10.4, 5.6 Hz, 1 H), 5.90 (ddt, *J* = 17.2, 10.4, 5.6 Hz, 1 H), 5.48 (m, 1 H), 5.45 (dt, *J* = 15.2, 6.8 Hz, 1 H), 5.302 (ddt, *J* = 17.2, 1.6, 1.6 Hz, 1 H), 5.300 (ddt, *J* = 17.2, 1.6, 1.6 Hz, 1 H), 5.23 (ddt, *J* = 9.6, 1.6, 1.2 Hz, 1 H), 5.20 (ddt, *J* = 9.2, 1.6, 1.2 Hz, 1 H), 5.17 (d, *J* = 8.8 Hz, 1 H), 4.70 (B of AB, *J* = 6.8 Hz, 1 H), 4.65 (A of AB, *J* = 6.8 Hz, 1 H), 4.55 (ddt, *J* = 5.6, 1.6, 0.8 Hz, 2 H), 4.21 (B of AB, *J* = 12.8 Hz, 1 H), 4.08 (B of AB, *J* = 16.8 Hz, 1 H), 4.07, (m, 2 H), 4.05 (A of AB, *J* = 12.8 Hz, 1 H), 3.98 (A of AB, *J* = 16.8 Hz, 1 H), 3.71 (s, 3 H, superimposed on m, 1 H), 3.35 (s, 3 H), 3.22 (dt, *J* = 6.4, 4.0 Hz, 1 H), 2.37 (m, 2 H), 2.15 (ddd, *J* = 13.2, 5.6, 0.8 Hz, 1 H), 1.94 (m, 4 H), 1.84 (dd, *J* = 12.8, 10.4 Hz, 1 H), 1.78-1.68 (m, 3 H), 1.39-1.15 (m, 9 H), 1.09 (s, 3 H), 1.04 (d, *J* = 6.8 Hz, 3 H), 1.03 (s, 9 H), 0.05 (s, 9 H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  175.7, 171.4, 169.3, 140.4, 138.5, 137.9, 135.5, 135.4, 133.85, 133.7, 133.6, 132.3, 129.6, 127.6 (two resonances), 127.4, 123.2, 118.1, 117.9, 96.1, 83.5, 81.8, 72.2, 66.8, 65.5, 65.6, 55.5, 52.4, 48.0, 47.7, 46.0, 43.7, 39.1, 36.1, 34.9, 33.3, 32.5, 29.8, 28.9, 28.5, 27.4, 26.7, 24.4, 19.3, 18.6, 17.5, 1.4; IR (CCl<sub>4</sub>) 3052, 3073, 2934, 2861, 1761, 1730 cm<sup>-1</sup>; high resolution mass spectrum for C<sub>54</sub>H<sub>77</sub>O<sub>9</sub>Si<sub>2</sub> (M<sup>+</sup>-OC<sub>3</sub>H<sub>5</sub>) calcd 925.5144, found 925.5106. *Anal.* Calcd for C<sub>57</sub>H<sub>82</sub>O<sub>10</sub>Si<sub>2</sub>: C, 69.62; H, 8.40. Found: C, 69.40; H, 8.60.

**(1*R*,2*R*,4*aS*,5*S*,8*aR*)-2-Propenyl 2-(5*E*)-[6-(2*R*,6*R*,9*R*)-8-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]methyl]-4-(methoxymethoxy)-9-methyl-2-oxo-3-(2-propenyloxy)-1-oxaspiro[4,5]deca-3,7-dien-6-yl]-5-hexenyl]-1,2,4*a*,6,7,8,8*a*-octahydro-5-(methoxymethoxy)-1-methyl-4-(trimethylsilyl)-1-naphthalene-carboxylate (51).** To a -78 °C solution of allyloxy ester **50** (315 mg, 0.32 mmol) in THF (3.2 mL) was added LiN(TMS)<sub>2</sub> (703  $\mu$ L of a 0.98 M solution in hexanes, 0.70 mmol). The reaction mixture was stirred for 1 h at -78 °C then was allowed to warm to 0 °C over a period of 30 min. Next, HMPA (100  $\mu$ L, 0.58

mmol) and MOM-Cl (73  $\mu$ L, 0.96 mmol) were added to the reaction mixture, which was then warmed to room temperature and stirred for an additional 3 h. The reaction mixture was then poured into sat.  $\text{NH}_4\text{Cl}$  solution and extracted with  $\text{Et}_2\text{O}$  (3 x 15 mL). The combined extracts were dried over  $\text{Na}_2\text{SO}_4$ , then concentrated *in vacuo*. The crude product was purified by flash chromatography (4 : 1 hexanes- $\text{Et}_2\text{O}$  gradient to 2 : 1 hexanes- $\text{Et}_2\text{O}$ ) to afford (300 mg, 94%) allyl tetronate **51** as a viscous oil: TLC  $R_f = 0.3$  (4 : 1 hexanes- $\text{Et}_2\text{O}$ );  $[\alpha]_D^{25} = -73.5^\circ$  (*c* 1.5,  $\text{CH}_2\text{Cl}_2$ );  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.65 (m, 4 H), 7.40 (m, 6 H), 6.13 (dd,  $J = 6.0, 2.4$  Hz, 1 H), 5.97 (ddt,  $J = 10.0, 7.2, 6.4$  Hz, 1 H), 5.90 (ddt,  $J = 10.4, 6.8, 5.6$  Hz, 1 H), 5.46 (B of AB,  $J = 5.2$  Hz, 1 H, superimposed on m, 1 H), 5.42 (m, 1 H), 5.41 (A of AB,  $J = 5.2$  Hz, 1 H), 5.33 (dq,  $J = 17.2, 1.6$  Hz, 1 H), 5.30 (dq,  $J = 17.2, 1.6$  Hz, 1 H), 5.23 (dq,  $J = 10.4, 1.2$  Hz, 1 H), 5.20 (dq,  $J = 10.4, 1.2$  Hz, 1 H), 5.16 (dd,  $J = 15.6, 8.8$  Hz, 1 H), 4.70 (B of AB,  $J = 7.2$  Hz, 1 H), 4.65 (A of AB,  $J = 7.2$  Hz, 1 H), 4.55 (m, 4 H), 4.23 (B of AB,  $J = 13.2$  Hz, 1 H), 4.13 (A of AB,  $J = 13.2$  Hz, 1 H), 3.52 (s, 3 H), 3.35 (s, 3 H), 3.22 (dt,  $J = 10.0, 4.0$  Hz, 1 H), 3.12 (br d,  $J = 8.8$  Hz, 1 H), 2.60 (m, 1 H), 2.41 (m, 1 H), 2.23 (dd,  $J = 14.4, 7.2$  Hz, 1 H), 1.92 (m, 4 H), 1.73 (m, 4 H), 1.61 (dd,  $J = 14.4, 1.6$  Hz, 1 H), 1.42-1.18 (m, 8 H), 1.13 (d,  $J = 7.6$  Hz, 3 H), 1.09 (s, 3 H), 1.06 (s, 9 H), 0.05 (s, 9 H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  175.7, 168.4, 159.3, 140.5, 140.4, 137.8, 135.5, 135.0, 133.5, 133.2, 132.3, 129.6, 127.6, 125.8, 121.7, 121.2, 118.8, 117.9, 96.3, 96.1, 83.5, 80.8, 72.5, 65.9, 64.6, 57.3, 55.5, 48.0, 47.7, 46.0, 43.6, 39.1, 37.4, 34.9, 33.3, 32.5, 29.8, 28.5, 27.9, 27.3, 26.9, 24.3, 20.0, 19.3, 17.5, 1.4; IR ( $\text{CCl}_4$ ) 3072, 2932, 2859, 1765, 1726, 1686  $\text{cm}^{-1}$ . *Anal.* Calcd for  $\text{C}_{58}\text{H}_{82}\text{O}_{10}\text{Si}_2$ : C, 69.98; H, 8.30. Found: C, 69.53; H, 7.99.

**(1R,2R,4aS,5S,8aR)-2-(5E)-[6-(2R,6R,9R)-8-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]methyl]-3-hydroxy-4-(methoxymethoxy)-9-methyl-2-oxo-1-oxaspiro[4,5]deca-3,7-dien-6-yl]-5-hexenyl]-1,2,4a,6,7,8,8a-octahydro-5-(methoxymethoxy)-1-methyl-4-(trimethylsilyl)-1-naphthalenecarboxylic Acid (52).** A 25  $^\circ\text{C}$  mixture of allyl tetronate **51** (52 mg, 0.06 mmol),  $\text{Pd}(\text{PPh}_3)_4$  (2 mg, 3 mol %) and dimedone (18 mg, 0.13 mmol) in degassed THF (520  $\mu$ L) was stirred for 45 min. The reaction mixture was concentrated *in vacuo*, and the crude seco acid was purified by preparative thin layer chromatography (2 : 1 hexanes- $\text{EtOAc}$ ), yielding **52** (45 mg, 94%) as a white foam: TLC  $R_f = 0.60$  (1 : 1 hexanes- $\text{EtOAc}$ );  $[\alpha]_D^{25} = -73.0^\circ$  (*c* 1.1,  $\text{CH}_2\text{Cl}_2$ );  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.65 (m, 4 H), 7.40 (m, 6 H), 6.03 (dd,  $J = 6.0, 2.0$  Hz, 1 H), 5.59 (B of AB,  $J = 5.6$  Hz, 1 H), 5.47 (A of AB,  $J = 5.6$  Hz, 1 H), 5.44 (s, 1 H), 5.32 (ddd,  $J = 15.2, 9.6, 4.0$  Hz, 1 H), 5.02 (ddd,  $J = 15.6, 8.8, 1.6$  Hz, 1 H), 4.68 (B of AB,  $J = 7.2$  Hz, 1 H), 4.64 (A of AB,  $J = 7.2$  Hz, 1 H), 4.21 (B of AB,  $J = 12.8$  Hz, 1 H), 4.13 (A of AB,  $J = 12.8$  Hz, 1 H), 3.56 (s, 3 H), 3.34 (s, 3 H), 3.15 (m, 2 H), 2.57 (m, 1 H), 2.40 (m, 1 H), 2.28 (dd,  $J = 14.4, 7.2$  Hz, 1 H), 2.23 (m, 1 H), 1.90-1.18 (m, 14 H), 1.12 (d,  $J = 6.8$  Hz, 3 H), 1.12 (s, 3 H), 1.06 (s, 9 H), 1.02-0.82 (m, 2 H), 0.05 (s, 9 H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  180.6, 172.6, 153.9, 141.9, 140.4, 135.8, 135.5, 133.6, 129.6, 127.7, 127.6, 126.0, 120.8, 120.6, 96.4, 96.1, 83.5,

82.6, 65.9, 57.4, 55.5, 48.0, 47.2, 46.2, 43.6, 38.7, 36.4, 34.8, 32.8, 32.3, 29.3, 29.0, 27.9, 27.6, 26.9, 24.2, 20.1, 19.3, 17.1, 1.5; IR (CCl<sub>4</sub>) 3165 (br), 3073, 2932, 2860, 1744, 1703 cm<sup>-1</sup>; low resolution mass spectrum (FAB) for C<sub>52</sub>H<sub>74</sub>O<sub>10</sub>Si<sub>2</sub>Na (M<sup>+</sup> + Na) calcd 937.5, found 937.9.

**20-Decarboxy-20-[[[(1,1-dimethylethyl)diphenylsilyl]oxy]methyl]-7,24-O-(methoxymethoxy)-9-(trimethylsilyl)chlorothricolide (57).** A solution of seco acid **52** (19.0 mg, 0.02 mmol) in toluene (2 mL, 0.01 M) was treated with triethylamine (13 μL, 0.08 mmol) and BOP-Cl (11 mg, 0.04 mmol).<sup>18</sup> The reaction mixture was heated at 100 °C for 1 h. The mixture was cooled to room temperature, then diluted with EtOAc and washed with 1.0 M NaHSO<sub>4</sub> solution (5 mL). The aqueous layer was extracted with EtOAc (3 x 2 mL) and the extracts were dried over Na<sub>2</sub>SO<sub>4</sub>. The extracts were concentrated *in vacuo* then the crude mixture was purified by silica gel flash column chromatography (5 : 1 hexanes-Et<sub>2</sub>O gradient to 1 : 1 hexanes-EtOAc), affording macrolactone **57** (9.3 mg, 50%) plus recovered seco acid **52** (6.0 mg, 31%).

Data for **57**: TLC R<sub>f</sub> = 0.69 (3 : 1 hexanes-EtOAc); [α]<sub>D</sub><sup>25</sup> = +9.3 ° (c 0.3, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.65 (m, 4 H), 7.40 (m, 6 H), 6.06 (dd, *J* = 6.0, 2.0 Hz, 1 H), 5.47 (d, *J* = 0.4 Hz, 1 H), 5.35 (m, 1 H), 5.32 (B of AB, *J* = 5.6 Hz, 1 H), 5.19 (A of AB, *J* = 5.6 Hz, 1 H), 5.07 (m, 1 H), 4.69 (B of AB, *J* = 6.8 Hz, 1 H), 4.65 (A of AB, *J* = 6.8 Hz, 1 H), 4.22 (B of AB, *J* = 13.2 Hz, 1 H), 4.14 (A of AB, *J* = 13.2 Hz, 1 H), 3.52 (s, 3 H), 3.35 (s, 3 H), 3.19 (m, 2 H), 2.61 (m, 1 H), 2.43 (m, 1 H), 2.35 (dd, *J* = 14.0, 6.8 Hz, 1 H), 2.18 (m, 1 H), 2.11 (m, 1 H), 1.95 (m, 1 H), 1.78 (m, 2 H), 1.75 (t, *J* = 14.0 Hz, 1 H), 1.53-1.30 (m, 5 H), 1.26 (s, 3 H), 1.15 (d, *J* = 7.2 Hz, 3 H), 1.12-0.90 (m, 5 H), 1.06 (s, 9 H), 0.72 (m, 1 H), 0.05 (s, 9 H); IR (CCl<sub>4</sub>) 3073, 3052, 2934, 2861, 1779, 1753, 1686 cm<sup>-1</sup>; high resolution mass spectrum for C<sub>48</sub>H<sub>63</sub>O<sub>9</sub>Si<sub>2</sub> (M<sup>+</sup>-C<sub>4</sub>H<sub>9</sub>) calcd 839.4010, found 839.4024. *Anal.* Calcd for C<sub>52</sub>H<sub>72</sub>O<sub>9</sub>Si<sub>2</sub>: C, 69.60; H, 8.09. Found: C, 69.34; H, 8.25.

**7,24-O-(Methoxymethoxy)-9-(trimethylsilyl)chlorothricolide (58).** A mixture of macrocycle **57** (18 mg, 0.02 mmol), Et<sub>3</sub>N•HF<sup>19</sup> (15 mg, 0.12 mmol) and CH<sub>3</sub>CN (300 μL, 0.1 M) in a sealed Carious tube was heated at 55 °C for 15 h. The reaction mixture was then diluted with Et<sub>2</sub>O and washed with sat. NH<sub>4</sub>Cl solution. The aqueous layer was extracted with EtOAc (3 x 2 mL). The combined extracts were dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The crude product was purified by flash chromatography (2 : 1 hexanes-EtOAc), giving the allylic alcohol (11 mg, 85%) as a white foam: TLC R<sub>f</sub> = 0.25 (2 : 1 hexanes-EtOAc); [α]<sub>D</sub><sup>25</sup> = +25° (c 0.8, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 6.06 (dd, *J* = 6.0, 2.0 Hz, 1 H), 5.51 (dd, *J* = 2.0, 0.8 Hz, 1 H), 5.37 (ddd, *J* = 15.2, 9.2, 3.6 Hz, 1 H), 5.31 (B of AB, *J* = 5.6 Hz, 1 H), 5.17 (A of AB, *J* = 5.6 Hz, 1 H), 5.10 (ddd, *J* = 15.6, 8.8, 1.2 Hz, 1 H), 4.69 (B of AB, *J* = 7.6 Hz, 1 H), 4.64 (A of AB, *J* = 7.6 Hz, 1 H), 4.19 (B of AB, *J* = 12.8 Hz, 1 H), 4.12 (A of AB, *J* = 12.8 Hz, 1 H), 3.51 (s, 3 H), 3.35 (s, 3 H), 3.20 (dt, *J* = 10.0, 4.0 Hz, 1 H), 2.63 (m, 1 H), 2.42 (m, 1 H), 2.39 (dd, *J* = 14.0, 7.2 Hz, 1 H), 2.19 (m, 1 H), 2.10

(m, 1 H), 1.95 (t,  $J=10.0$  Hz, 1 H), 1.82-1.28 (m, 8 H), 1.26 (s, 3 H), 1.26 (partially obscured d,  $J=6.8$  Hz, 3 H), 1.21-0.80 (m, 8 H), 0.05 (s, 9 H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  174.7, 166.9, 162.5, 142.0, 141.1, 136.0, 135.2, 125.6, 122.1, 115.2, 97.5, 96.3, 83.3, 81.9, 65.2, 57.7, 55.5, 47.4, 47.0, 44.0, 39.3, 36.0, 34.8, 32.3, 31.5, 29.7, 29.4, 28.0, 27.8, 27.0, 24.2, 20.0, 16.5, 1.3; IR ( $\text{CCl}_4$ ) 3630, 3440, 2936, 1779, 1752, 1686  $\text{cm}^{-1}$ ; high resolution mass spectrum for  $\text{C}_{36}\text{H}_{55}\text{O}_9\text{Si}$  ( $\text{M}^++\text{H}$ ) calcd 659.3615, found 659.3590.

A solution of the above allylic alcohol (29 mg, 0.045 mmol; combined from several runs) in  $\text{CH}_2\text{Cl}_2$  (0.56 mL, 0.08 M) was treated with activated  $\text{MnO}_2$  (55 mg, 1.4 mmol). The mixture was stirred for 4 h, then was filtered through a plug of Celite and the filtrate was concentrated *in vacuo*. A solution of the crude aldehyde (29 mg, 0.045 mmol) and 2-methyl-2-butene (0.18 mL, 1.4 mmol) in *tert*-butanol (0.450 mL, 0.1 M) was treated with a solution of  $\text{NaClO}_2$  (40 mg, 0.045 mmol) and  $\text{NaH}_2\text{PO}_4$  (42 mg) in 0.70 mL of  $\text{H}_2\text{O}$ .<sup>20,21</sup> The heterogeneous mixture was stirred for 2 h, then was diluted with saturated  $\text{NaCl}$  solution and extracted with  $\text{EtOAc}$  (4 x 1 mL). The combined extracts were concentrated *in vacuo* and the crude acid was purified by flash chromatography (1 : 1 hexanes- $\text{EtOAc}$ ), giving the carboxylic acid **58** (27 mg, 88% overall) as a white foam: TLC  $R_f = 0.39$  (1 : 1 hexanes- $\text{EtOAc}$ );  $[\alpha]_D^{25} = -1.4^\circ$  ( $c$  0.7,  $\text{CH}_2\text{Cl}_2$ );  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.89 (dd,  $J = 2.4, 1.6$  Hz, 1 H), 6.06 (dd,  $J = 6.0, 2.0$  Hz, 1 H), 5.44 (ddd,  $J = 15.2, 8.8, 3.6$  Hz, 1 H), 5.34 (B of AB,  $J = 5.6$  Hz, 1 H), 5.18 (A of AB,  $J = 5.6$  Hz, 1 H), 5.15 (ddd,  $J = 15.6, 9.2, 0.8$  Hz, 1 H), 4.69 (B of AB,  $J = 6.8$  Hz, 1 H), 4.65 (A of AB,  $J = 6.8$  Hz, 1 H), 3.51 (s, 3 H), 3.35 (s, 3 H), 3.33 (dt,  $J = 9.2, 2.0$  Hz, 1 H), 3.20 (dt,  $J = 9.6, 4.0$  Hz, 1 H), 2.98 (m, 1 H), 2.42 (m, 1 H), 2.37 (dd,  $J = 14.0, 6.8$  Hz, 1 H), 2.22 (m, 1 H), 2.11 (t,  $J = 7.2$  Hz, 1 H), 1.96 (t,  $J = 10.0$  Hz, 1 H), 1.80 (m, 4 H), 1.46-0.7 (m, 10 H), 1.33 (d,  $J = 7.2$  Hz, 3 H), 1.26 (s, 3 H), 0.05 (s, 9 H); IR ( $\text{CCl}_4$ ) 3200 (broad), 2938, 2861, 1782, 1753, 1690  $\text{cm}^{-1}$ ; high resolution mass spectrum for  $\text{C}_{36}\text{H}_{53}\text{O}_{10}\text{Si}$  ( $\text{M}^++1$ ), calcd 673.3408, found 673.3378.

**(-)-Chlorothricolide (1)**. A mixture of carboxylic acid **58** (6.9 mg, 10  $\mu\text{mol}$ ) and ethanethiol (6  $\mu\text{L}$ , 82  $\mu\text{mol}$ ) in  $\text{CH}_2\text{Cl}_2$  (150  $\mu\text{L}$ ) was treated with  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  (5  $\mu\text{L}$ , 41  $\mu\text{mol}$ ).<sup>22</sup> The reaction mixture was stirred for 3.5 h, then was diluted with sat.  $\text{NH}_4\text{Cl}$  solution (300  $\mu\text{L}$ ). The aqueous layer was extracted with  $\text{EtOAc}$  (4 x 1 mL) and the extracts were concentrated *in vacuo*. The crude product was purified by flash chromatography (1 : 2 hexanes- $\text{EtOAc}$  gradient to 24 : 74 : 2 hexanes- $\text{EtOAc}$ -acetic acid), giving (-)-chlorothricolide **1** (4.6 mg, 91%) as a white glass: TLC  $R_f = 0.12$  (1:3 hexanes- $\text{EtOAc}$ );  $[\alpha]_D^{25} = -23^\circ$  ( $c$  0.23,  $\text{CH}_2\text{Cl}_2$ );  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  10.14 (s, 1 H), 6.84 (dd,  $J = 2.4, 1.6$  Hz, 1 H), 5.87 (d,  $J = 10.0$  Hz, 1 H), 5.61 (ddd,  $J = 10.0, 4.8, 2.4$  Hz, 1 H), 5.42 (ddd,  $J = 15.2, 10.8, 3.2$  Hz, 1 H), 5.17 (ddd,  $J = 15.2, 9.6, 2.0$  Hz, 1 H), 3.32 (m, 2 H), 2.97 (m, 1 H), 2.38 (dd,  $J = 14.4, 7.2$  Hz, 1 H), 2.28 (m, 1 H), 2.09 (m, 2 H), 1.89-1.40 (m, 10 H), 1.36 (s, 3 H), 1.33 (d,  $J = 6.8$  Hz, 3 H), 1.28-0.80 (m, 6 H); IR ( $\text{CHCl}_3$ ) 3684, 3621, 3038, 2976, 2930, 1769, 1707,

1688  $\text{cm}^{-1}$ ; FAB mass spectrum (low resolution), calcd for  $\text{C}_{29}\text{H}_{35}\text{O}_8\text{Na}_2$  ( $\text{M}^+ + 2 \text{Na} - \text{H}$ ), calcd. 557.2, found 556.9.

**(-)-24-O-Methyl Chlorothricolide Methyl Ester (59).** A solution of (-)-chlorothricolide **1** (4.0 mg; 7.7  $\mu\text{mol}$ ) in  $\text{Et}_2\text{O}$  (1 mL) was treated with an ethereal solution of diazomethane (230  $\mu\text{mol}$ ). The reaction mixture was allowed to stand 1 h then it was concentrated *in vacuo*. The mixture was purified by flash chromatography (2 : 1 hexanes-EtOAc), yielding (-)-24-O-methyl chlorothricolide methyl ester **59** (3.3 mg; 80%): TLC  $R_f = 0.40$  (1 : 1 hexanes-EtOAc); ( $[\alpha]_D^{25} -29.3^\circ$  ( $c$  0.95,  $\text{CHCl}_3$ ), mp 228.5-229  $^\circ\text{C}$ ; lit.<sup>23</sup>  $[\alpha]_D^{20} -30^\circ$  ( $c$  1,  $\text{CHCl}_3$ ), lit.<sup>23</sup> mp 230  $^\circ\text{C}$ );  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.73 (dd,  $J = 2.8, 1.2$  Hz, 1 H), 5.85 (d,  $J = 10.0$  Hz, 1 H), 5.65 (ddd,  $J = 10.0, 5.2, 2.4$  Hz, 1 H), 5.44 (ddd,  $J = 15.6, 8.8, 4.0$  Hz, 1 H), 5.17 (ddd,  $J = 15.6, 8.8, 0.8$  Hz, 1 H), 4.03 (s, 3 H), 3.76 (s, 3 H), 3.34 (dt,  $J = 9.6, 4.0$  Hz, 1 H), 3.25 (dt,  $J = 9.2, 2.4$  Hz, 1 H), 2.97 (m, 1 H), 2.30 (dd,  $J = 14.4, 7.2$  Hz, 1 H), 2.25-2.04 (m, 3 H), 1.89-1.65 (m, 5 H), 1.46 (m, 3 H), 1.35 (s, 3 H), 1.28 (d,  $J = 7.2$  Hz, 3 H), 1.12-0.70 (m, 6 H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  174.8, 166.8, 165.9, 137.2, 137.1, 134.2, 131.0, 123.6, 122.7, 114.2, 80.7, 73.5, 59.8, 51.7, 47.9, 45.8, 44.6, 38.5, 36.3, 35.5, 33.0, 31.2, 27.8, 27.2, 26.9, 24.3, 20.7, 16.3; IR ( $\text{CHCl}_3$ ) 3684, 3621, 3038, 3009, 2976, 2938, 1763, 1711, 1684  $\text{cm}^{-1}$ ; high resolution mass spectrum for  $\text{C}_{31}\text{H}_{41}\text{O}_8$  ( $\text{M}^++1$ ) calcd 541.2801, found 541.2776.

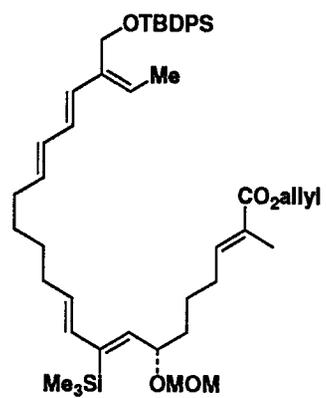
Synthetic (-)-**59** was identified by comparison with a sample of racemic **59** kindly by Prof. Yoshii.<sup>24</sup> The two samples were identical in all respects, with the exception of optical rotation and melting point.

**Data for Racemic 24-O-Methyl Chlorothricolide Methyl Ester:**<sup>24</sup> TLC  $R_f = 0.40$  (1 : 1 hexanes-EtOAc); mp 195-197  $^\circ\text{C}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.73 (dd,  $J = 2.8, 1.2$  Hz, H(13)), 5.85 (d,  $J = 10.0$  Hz, H(5)), 5.64 (ddd,  $J = 10.0, 5.2, 2.4$  Hz, H(6)), 5.44 (ddd,  $J = 15.6, 8.4, 4.0$  Hz, H(11)), 5.17 (ddd,  $J = 15.6, 8.8, 0.8$  Hz, H(12)), 4.03 (s,  $\text{CH}_3\text{O}-$ ), 3.76 (s,  $\text{CO}_2\text{CH}_3$ ), 3.34 (dt,  $J = 10.0, 4.0$  Hz, H(4)), 3.25 (dt,  $J = 8.8, 2.0$  Hz, H(12a)), 2.97 (m, H(15)), 2.30 (dd,  $J = 14.0, 7.2$  Hz, H(16 $_{\text{ax}}$ )), 2.25-2.04 (m, 3 H), 1.89-1.65 (m, 5 H), 1.46 (m, 3 H), 1.35 (s, C(21)- $\text{CH}_3$ ), 1.28 (d,  $J = 7.2$  Hz, C(15)- $\text{CH}_3$ ), 1.12-0.70 (m, 6 H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  174.8, 166.8, 165.9, 137.2, 137.1, 134.2, 131.0, 123.6, 122.7, 114.2, 80.7, 73.5, 59.8, 51.7, 47.9, 45.8, 44.6, 38.5, 36.3, 35.5, 33.0, 31.2, 27.8, 27.2, 26.9, 24.3, 20.7, 16.3; IR ( $\text{CHCl}_3$ ) 3684, 3621, 3038, 3009, 2976, 2940, 1763, 1711, 1684  $\text{cm}^{-1}$ .

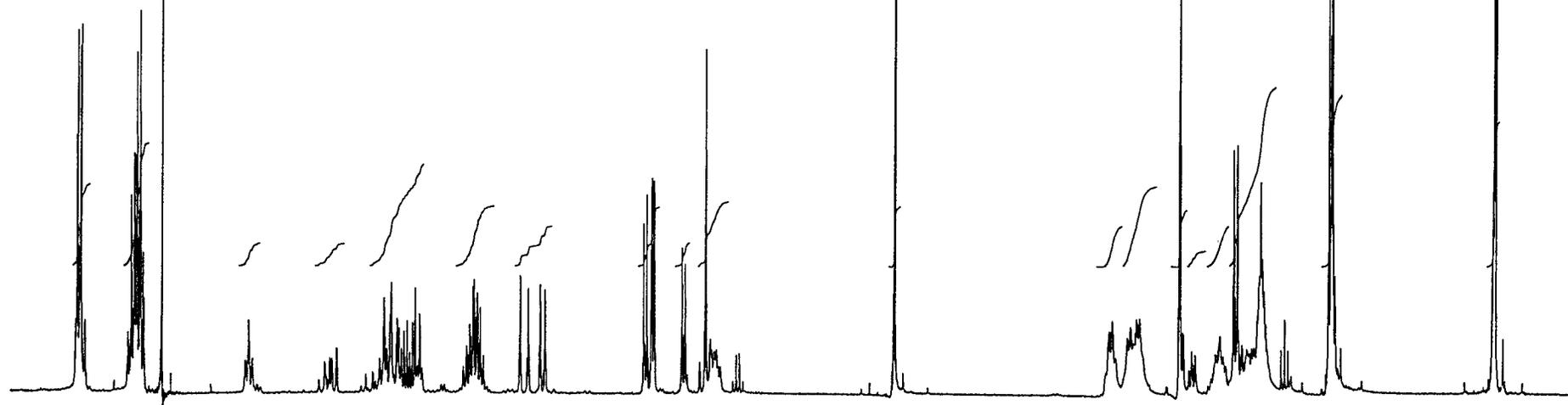
### References

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- (2) Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*; Pergamon Press: New York, 1988.
- (3) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
- (4) Chemin, D.; Linstumelle, G. *Tetrahedron* **1992**, *48*, 1943.
- (5) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.
- (6) Roush, W. R.; Kageyama, M.; Riva, R.; Brown, B. B.; Warmus, J. S.; Moriarty, K. J. *J. Org. Chem.* **1991**, *56*, 1192.
- (7) Roush, W. R.; Brown, B. B. *J. Org. Chem.* **1993**, *58*, 2151.
- (8) Bringmann, G.; Schneider, S. *Synthesis* **1983**, 139.
- (9) Marshall, J. A.; Andersen, M. W. *J. Org. Chem.* **1993**, *58*, 3912.
- (10) Lane, C. F.; Kabalka, G. W. *Tetrahedron* **1976**, *32*, 981.
- (11) Uenishi, J.-i.; Beau, J.-M.; Armstrong, R. W.; Kishi, Y. *J. Am. Chem. Soc.* **1987**, *109*, 4756.
- (12) Mancusco, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.
- (13) Thomas, E. J.; Whitehead, J. W. F. *J. Chem. Soc., Perkin Trans. I* **1989**, 499.
- (14) Lipshutz, B. H.; Harvey, D. F. *Synth. Commun.* **1982**, *12*, 267.
- (15) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essensfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.
- (16) Roush, W. R.; Brown, B. B. *J. Org. Chem.* **1992**, *57*, 3380.
- (17) Manhas, M.; Amin, S.; Chawla, H. P. S.; Bose, A. K. *J. Heterocycl. Chem.* **1978**, *15*, 601.
- (18) Corey, E. J.; Hua, D. H.; Pan, B.-C.; Seitz, S. P. *J. Am. Chem. Soc.* **1982**, *104*, 6818.
- (19) Hünig, S.; Wehner, G. *Synthesis* **1975**, 180.
- (20) Kraus, G. A.; Taschner, M. J. *J. Org. Chem.* **1980**, *45*, 1175.
- (21) Lindgren, B. O.; Nilsson, T. *Acta Chem. Scand.* **1973**, *27*, 888.
- (22) Fuji, K.; Ichikawa, K.; Node, M.; Fujita, E. *J. Org. Chem.* **1979**, *44*, 1661.
- (23) Muntwyler, R.; Keller-Schierlein, W. *Helv. Chim. Acta* **1972**, *55*, 2071.
- (24) Takeda, K.; Igarashi, Y.; Okazaki, K.; Yoshii, E.; Yamaguchi, K. *J. Org. Chem.* **1990**, *55*, 3431.

hexaenolate



19



8 7 6 5 4 3 2 1 0 ppm

3.60

5.40

1.01

1.00

4.51

2.64

1.75

2.61

1.83

2.84

2.63

3.51

1.79

0.68

2.47

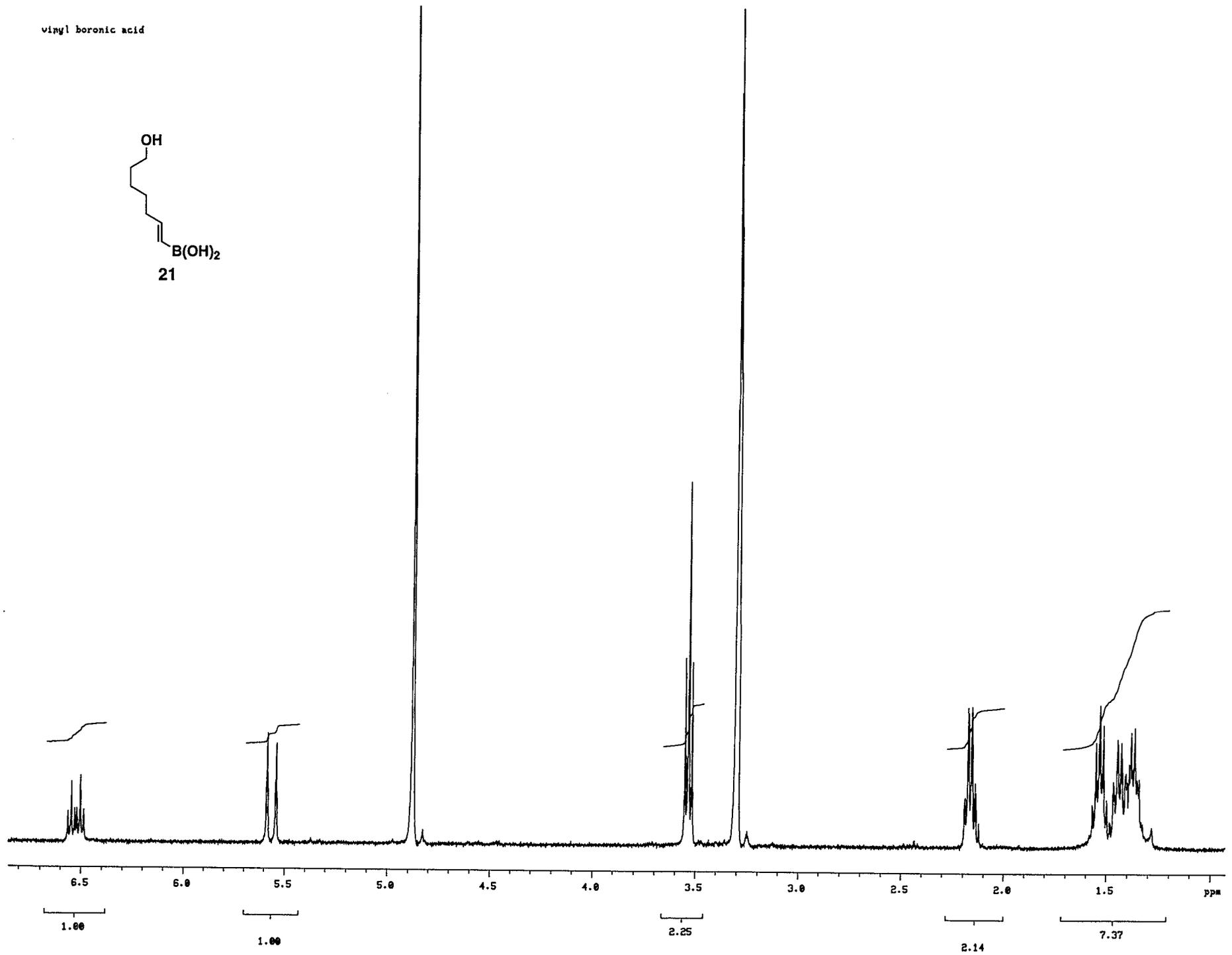
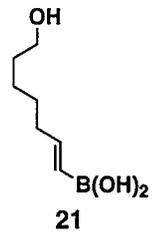
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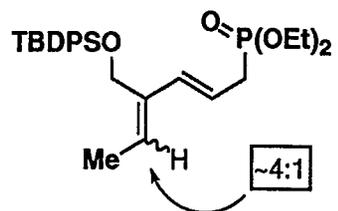
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7.61

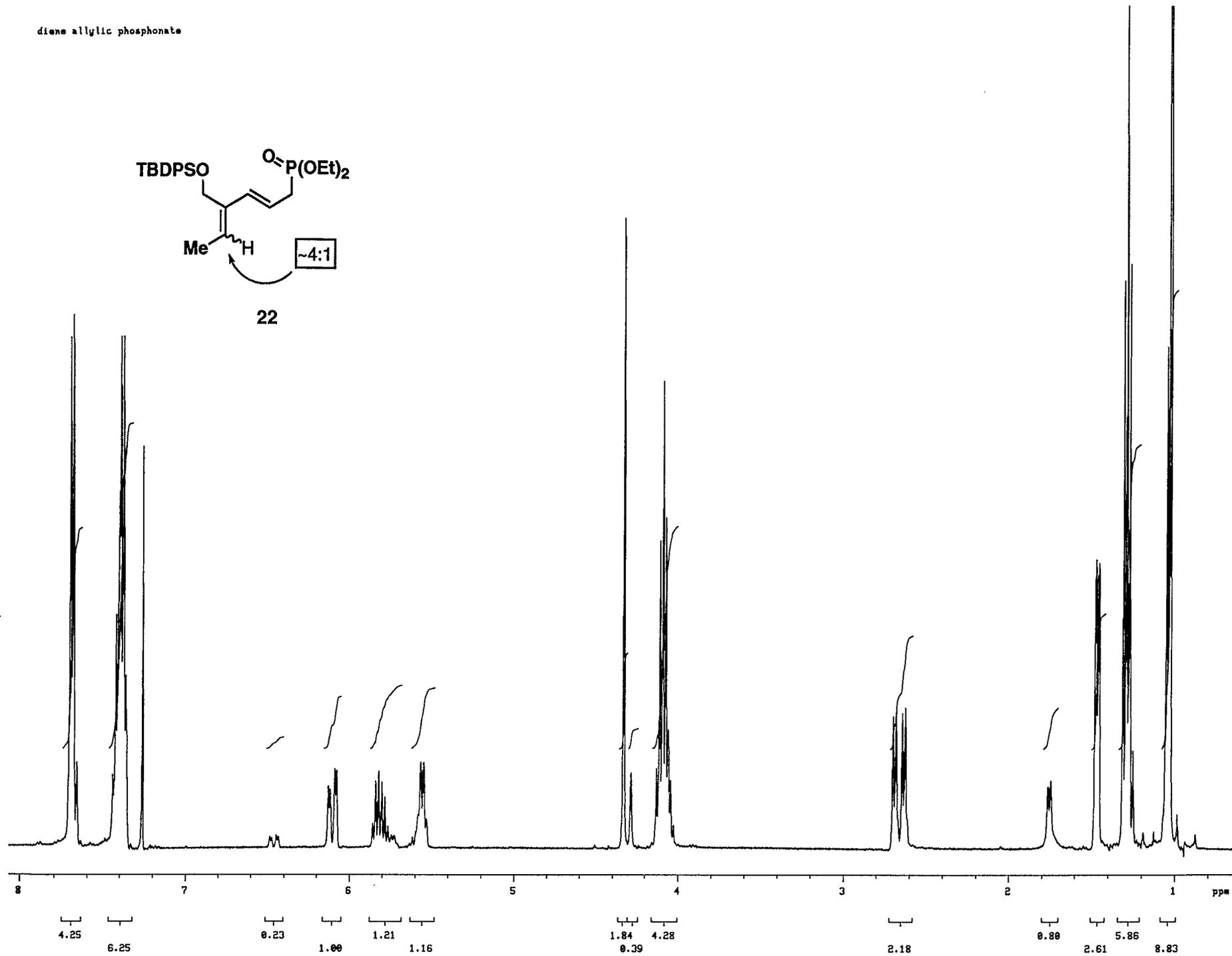
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vinyl boronic acid

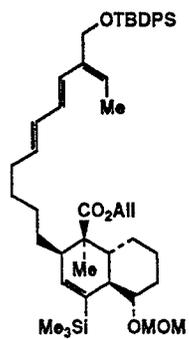




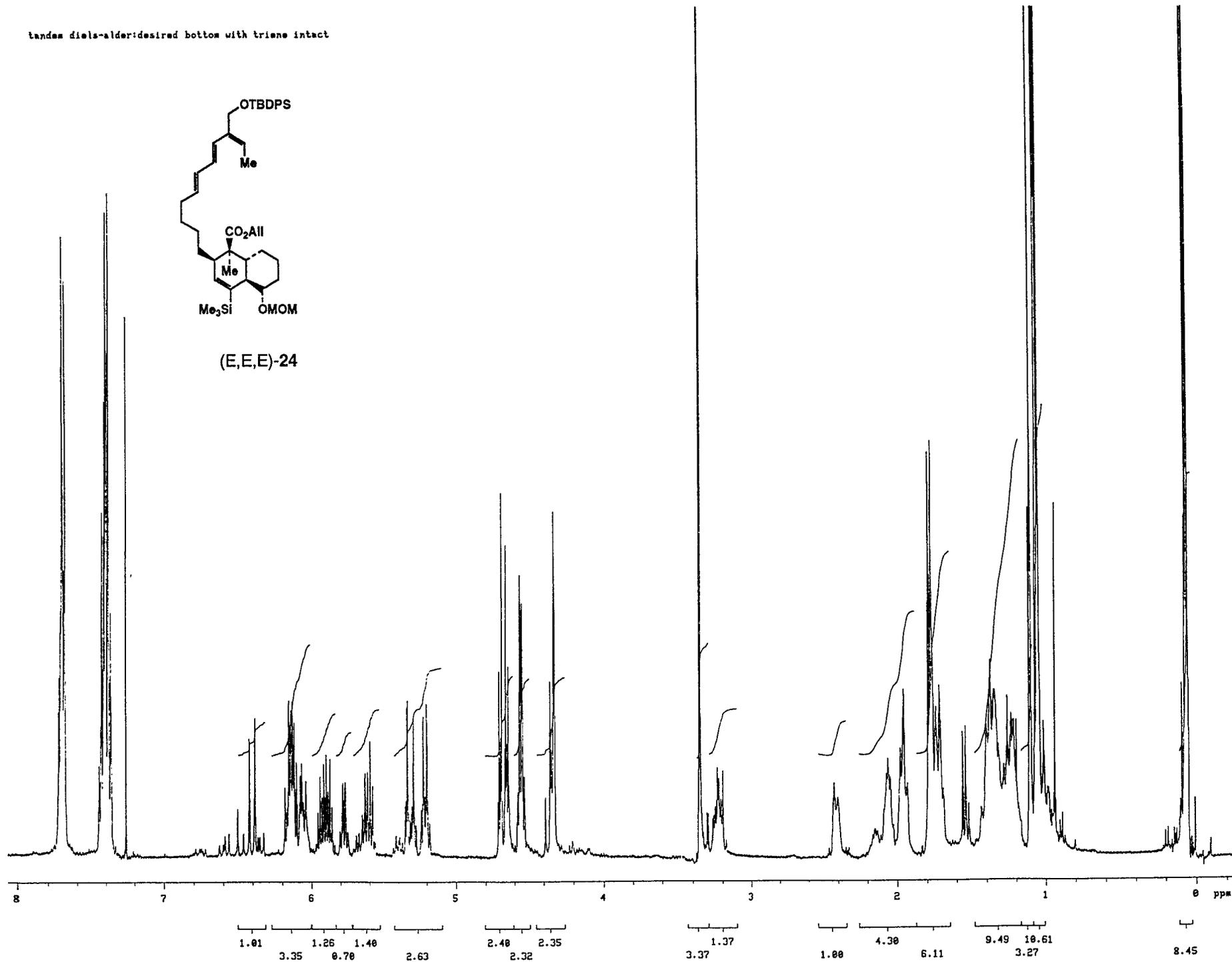
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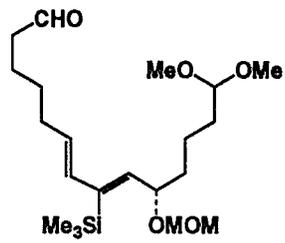


tandem diels-alder:desired bottom with triene intact

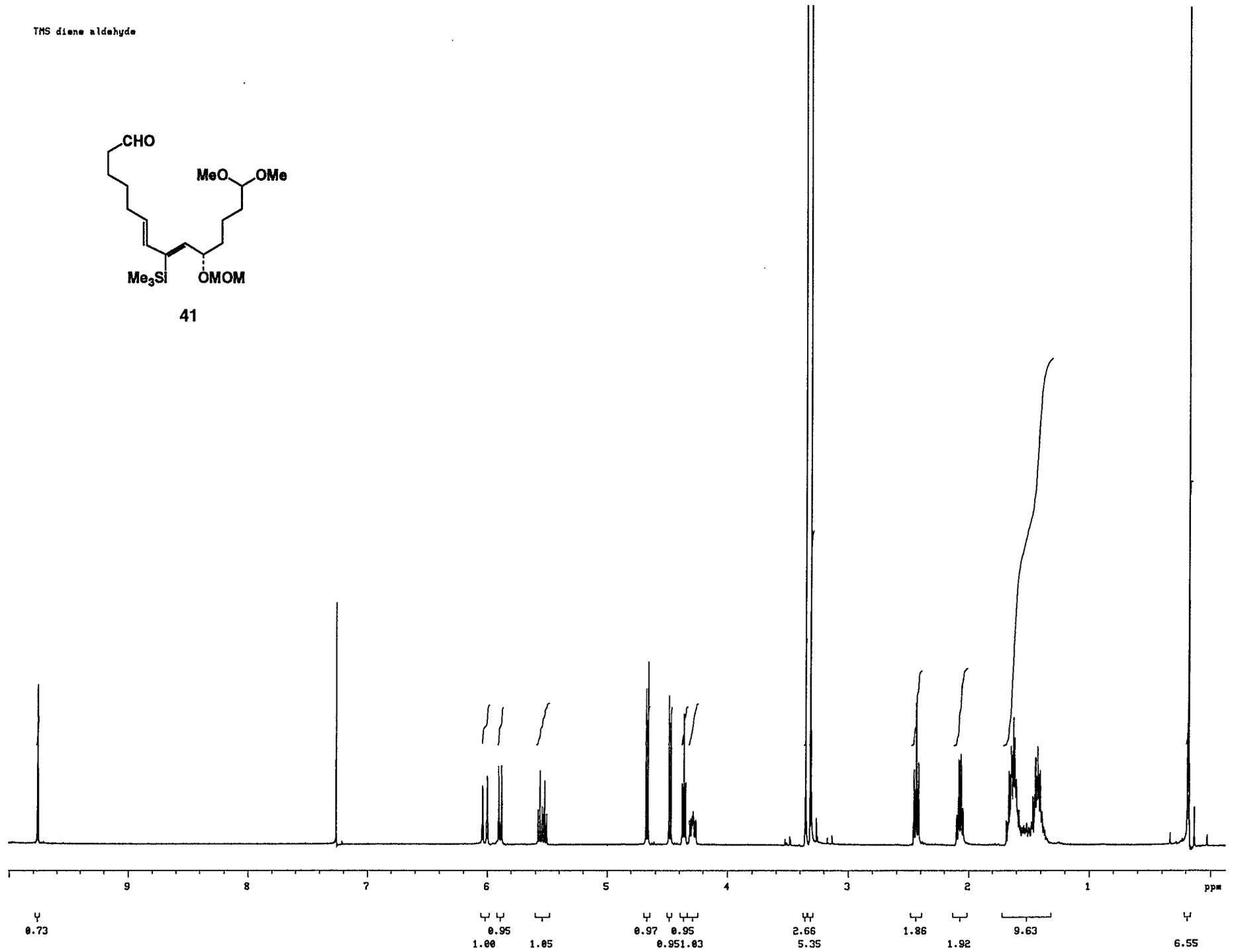


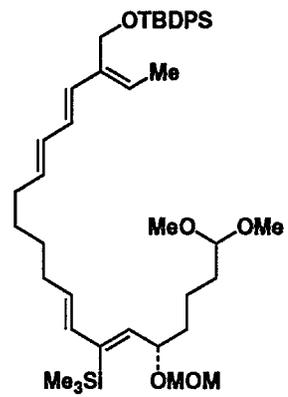
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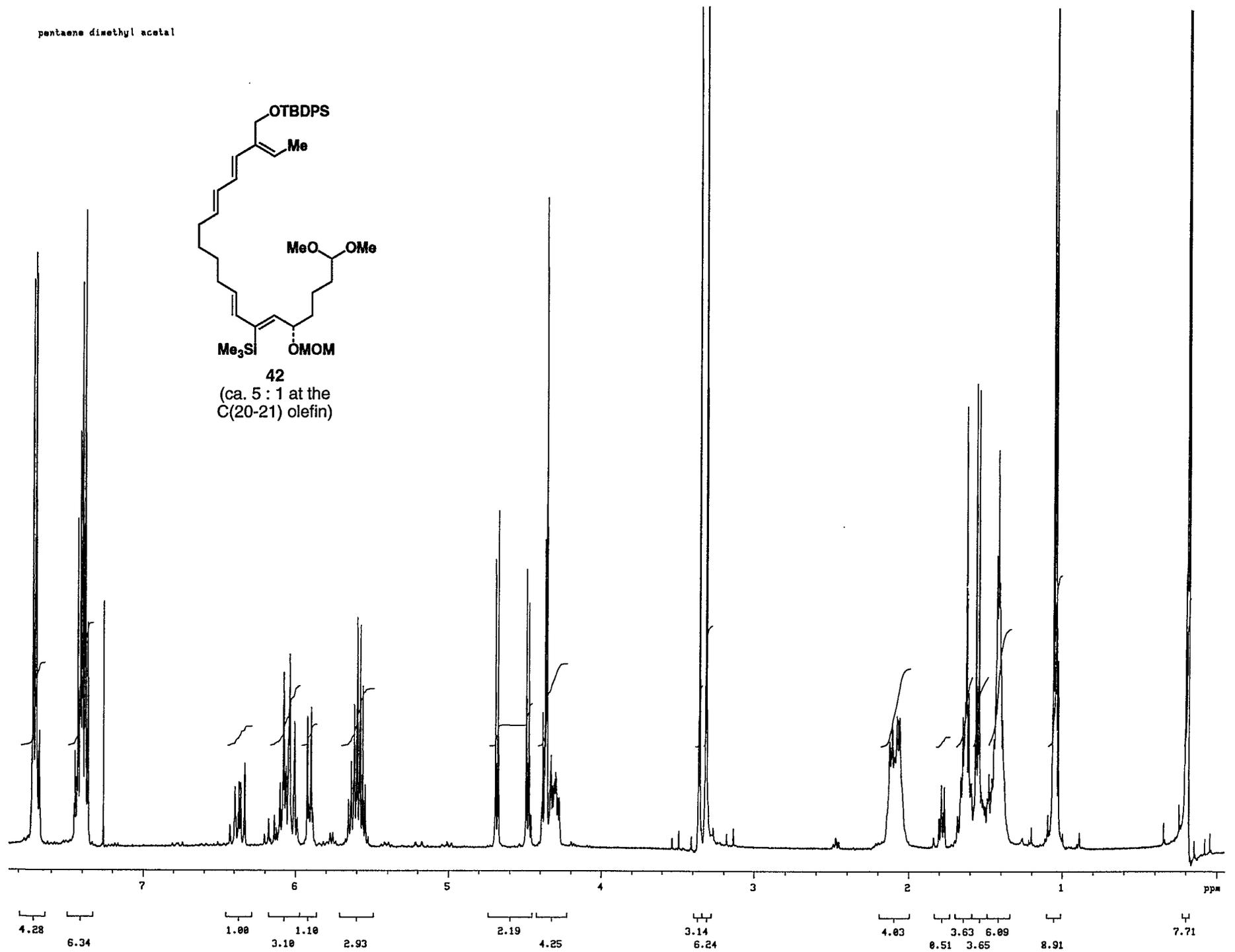


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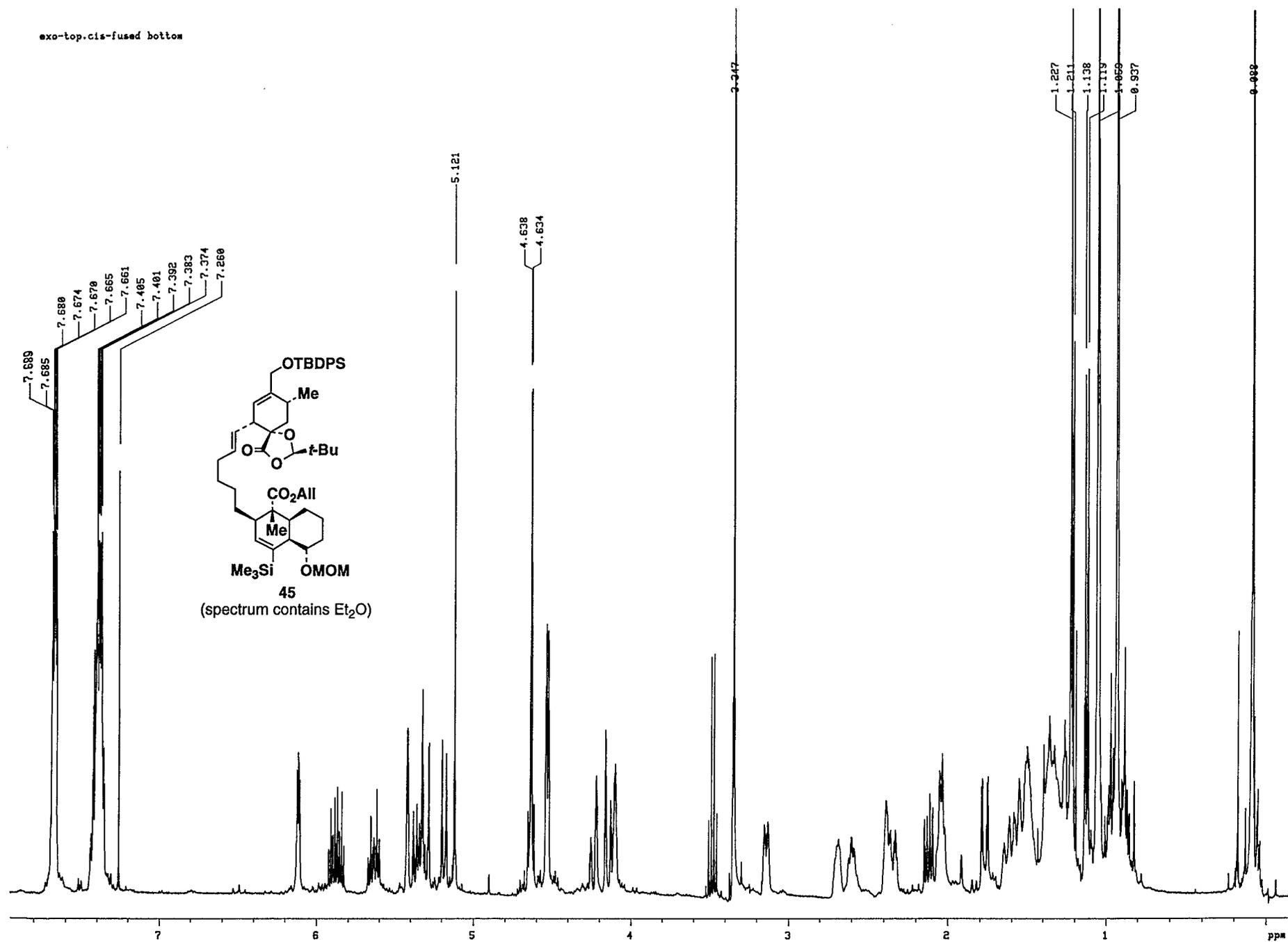


42  
(ca. 5 : 1 at the  
C(20-21) olefin)

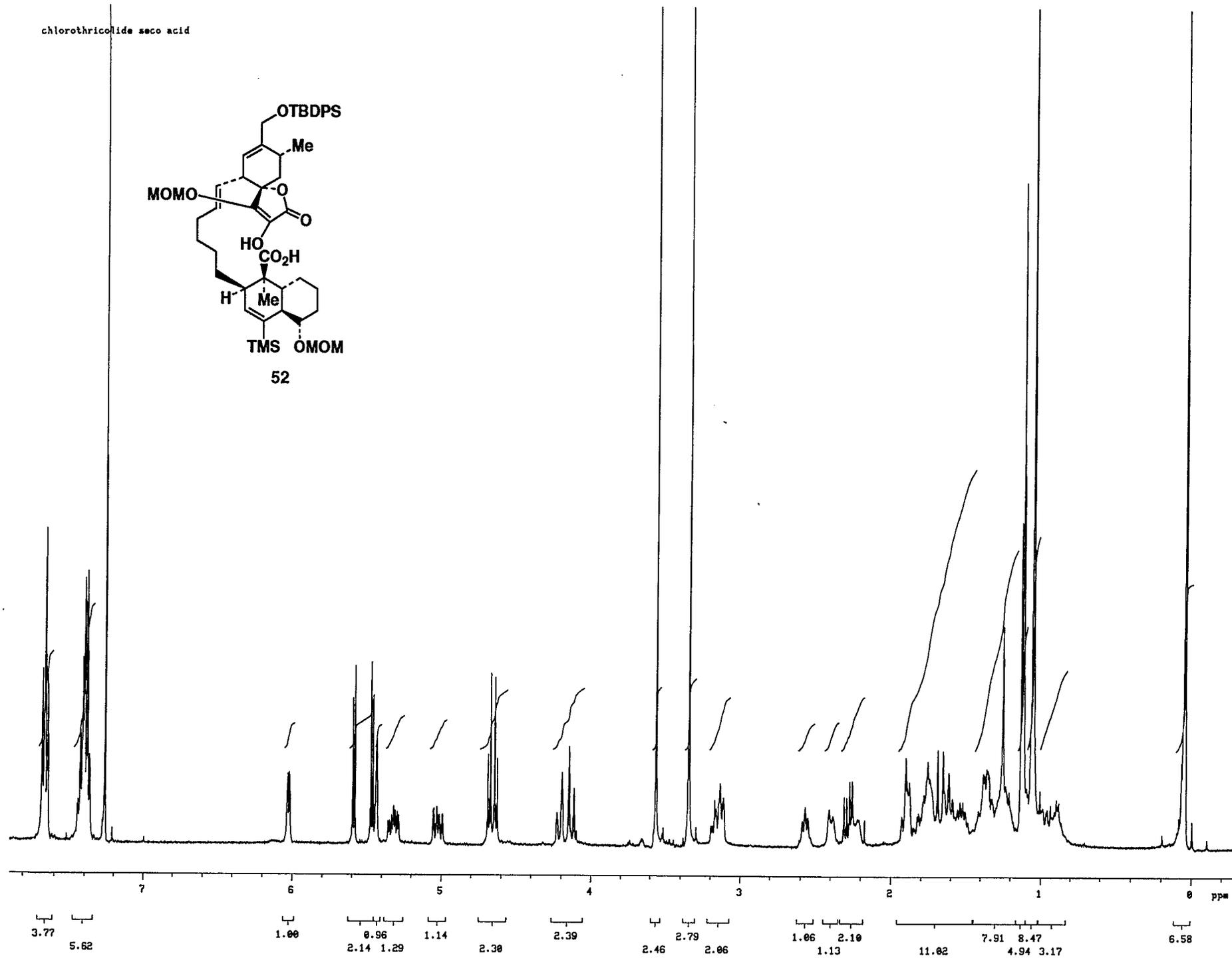
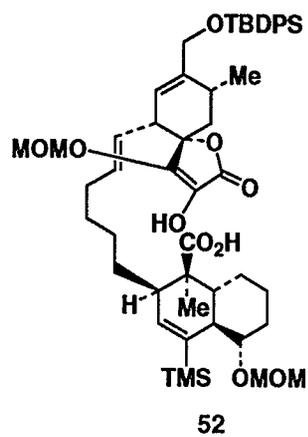




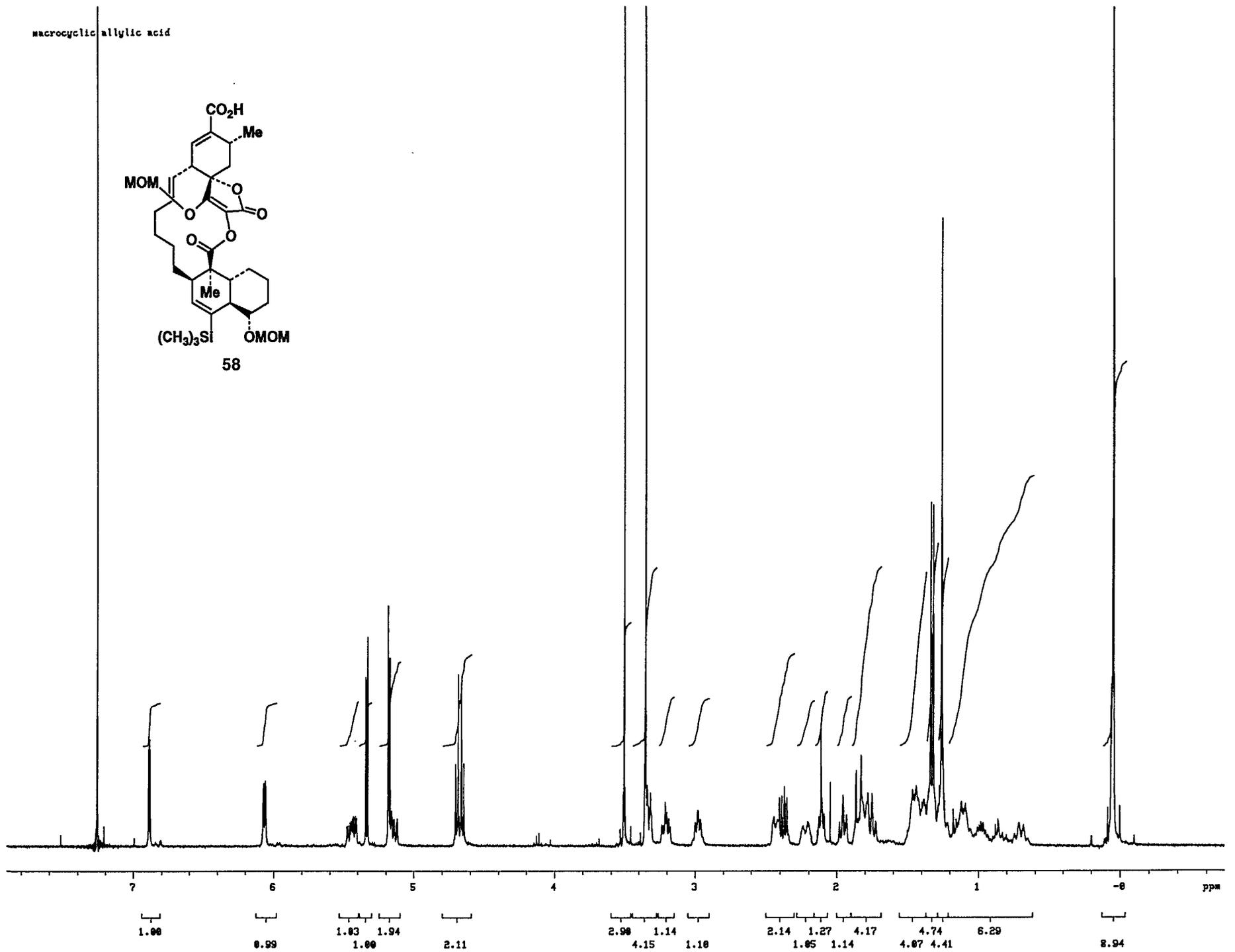
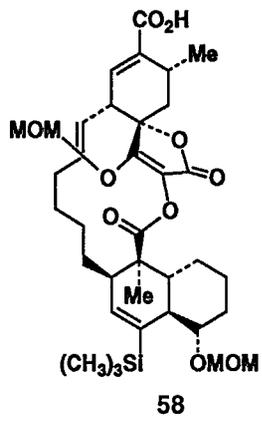
exo-top.cis-fused bottom



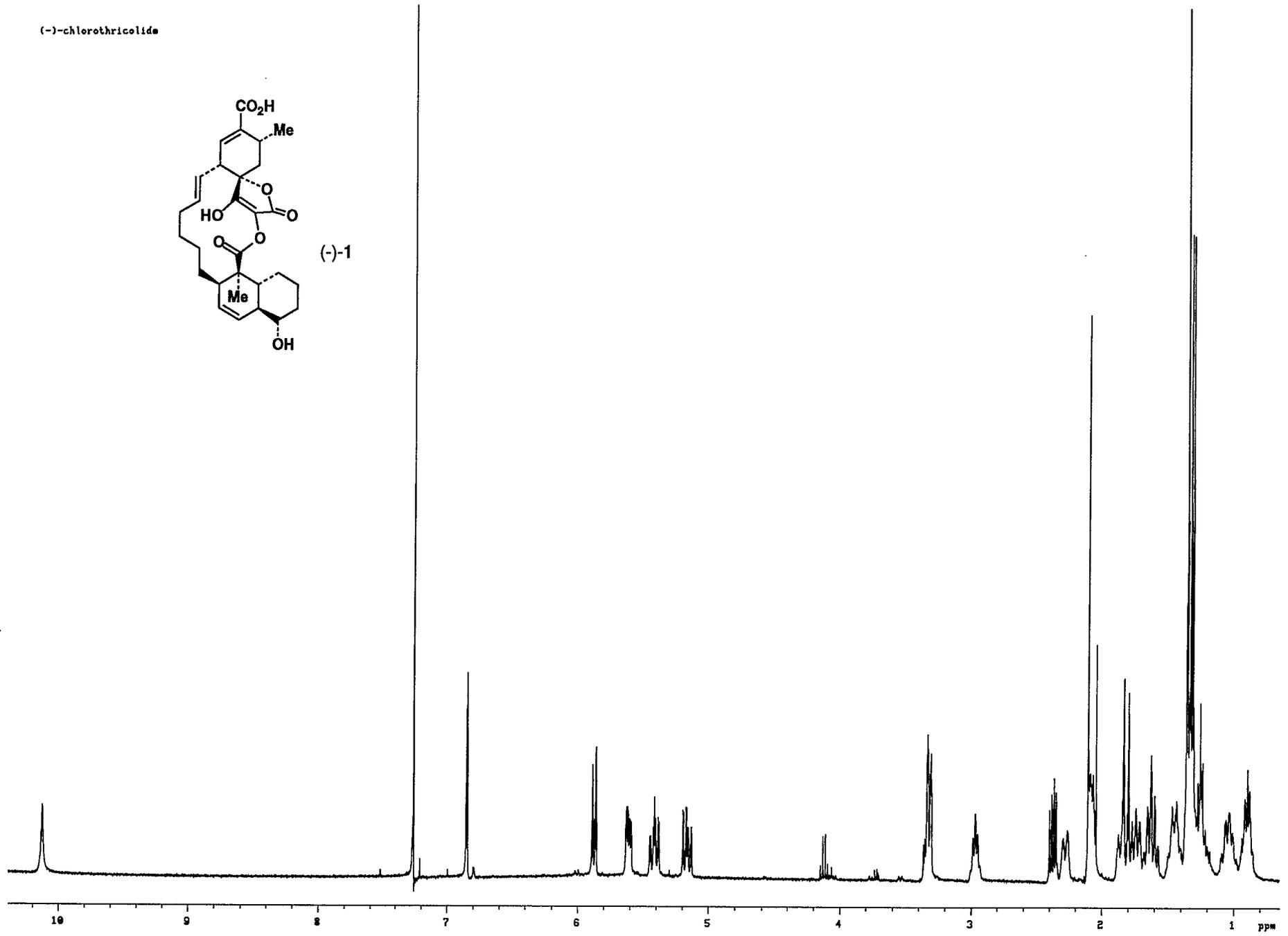
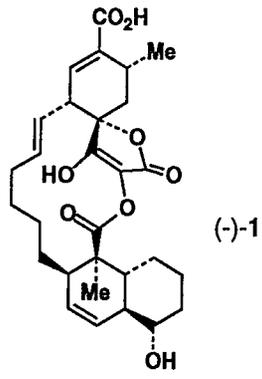
chlorothricolide seco acid



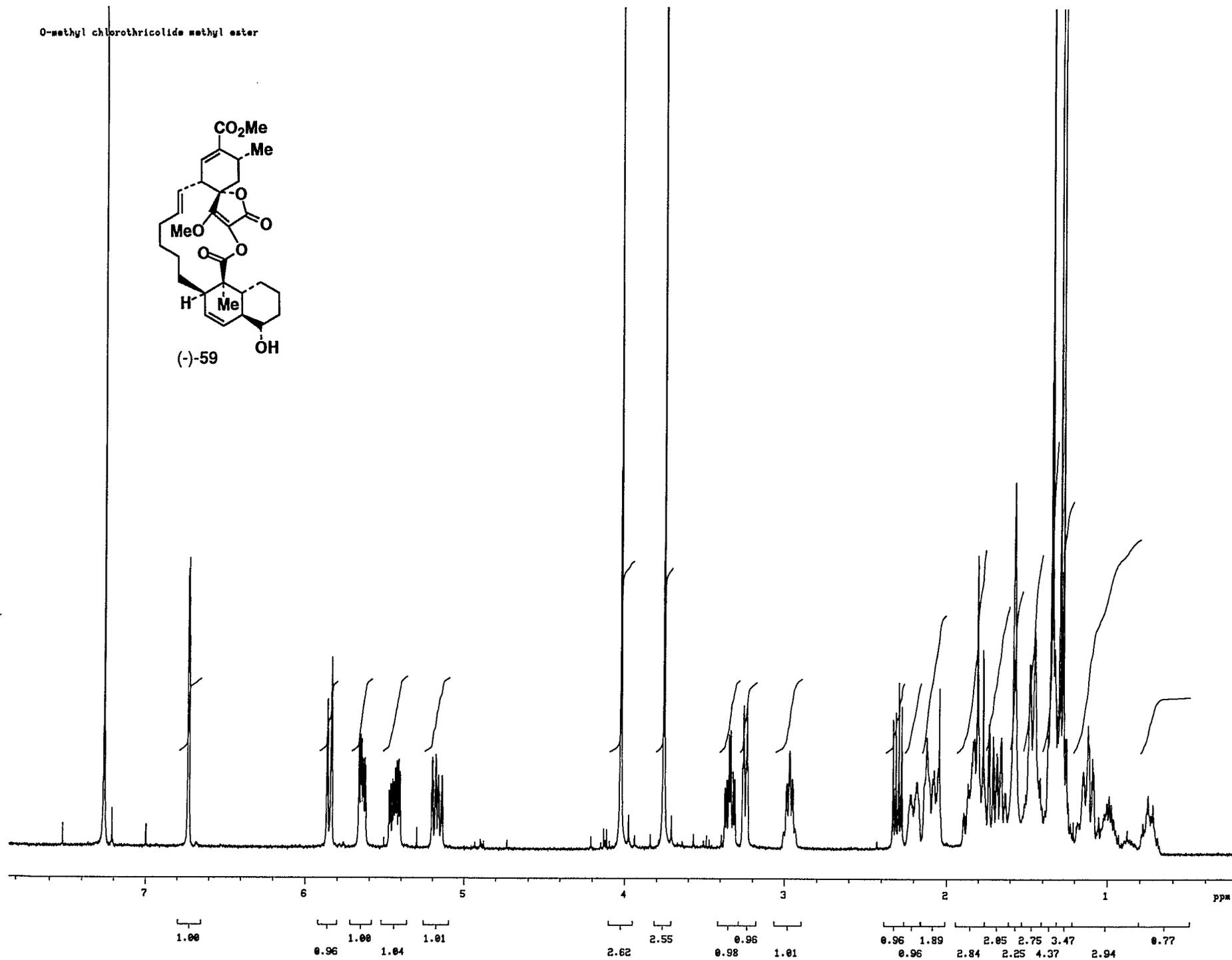
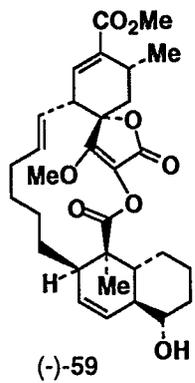
macrocyclic allylic acid

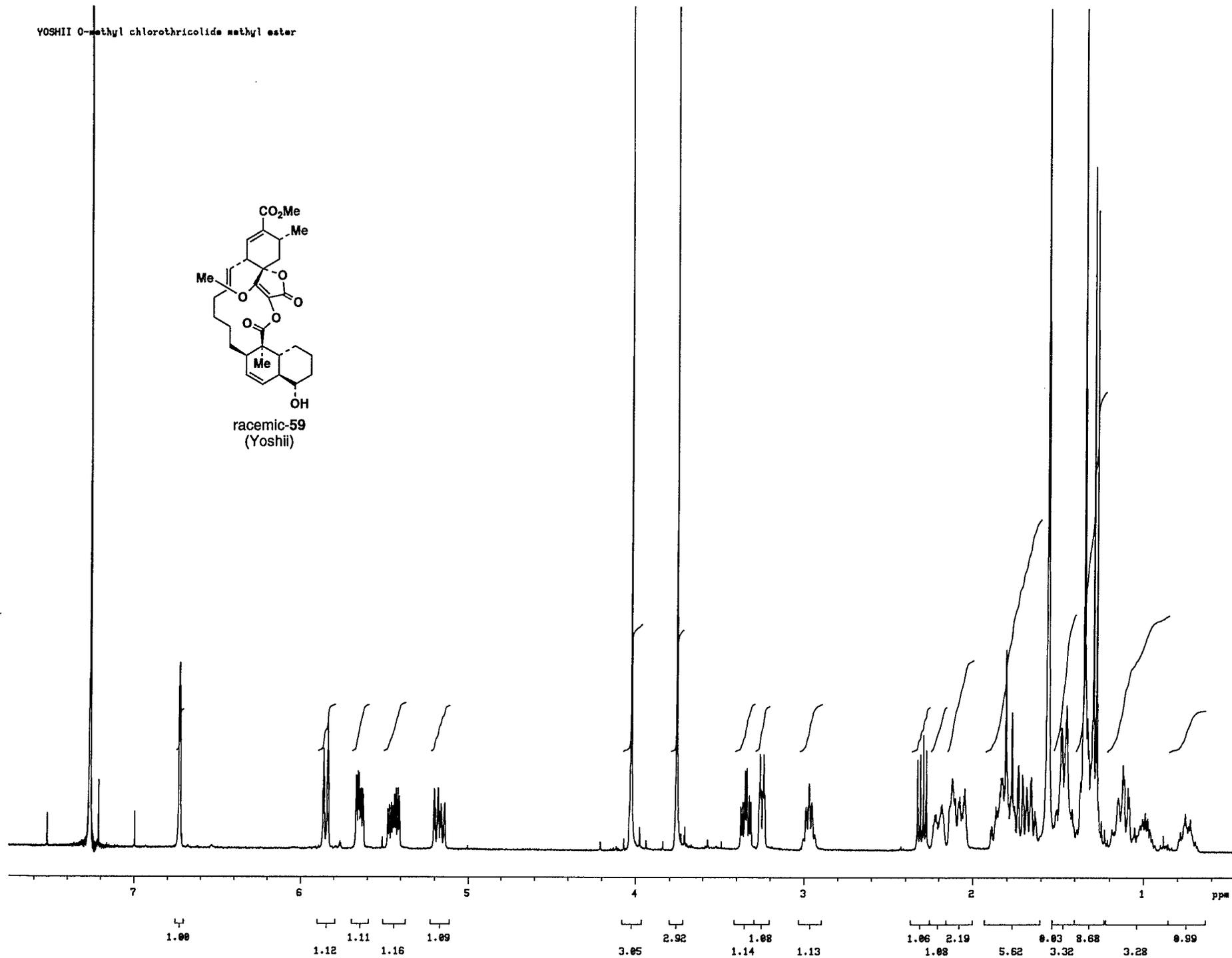
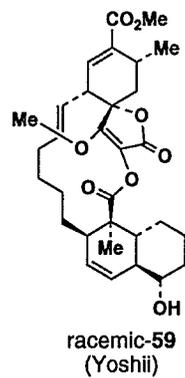


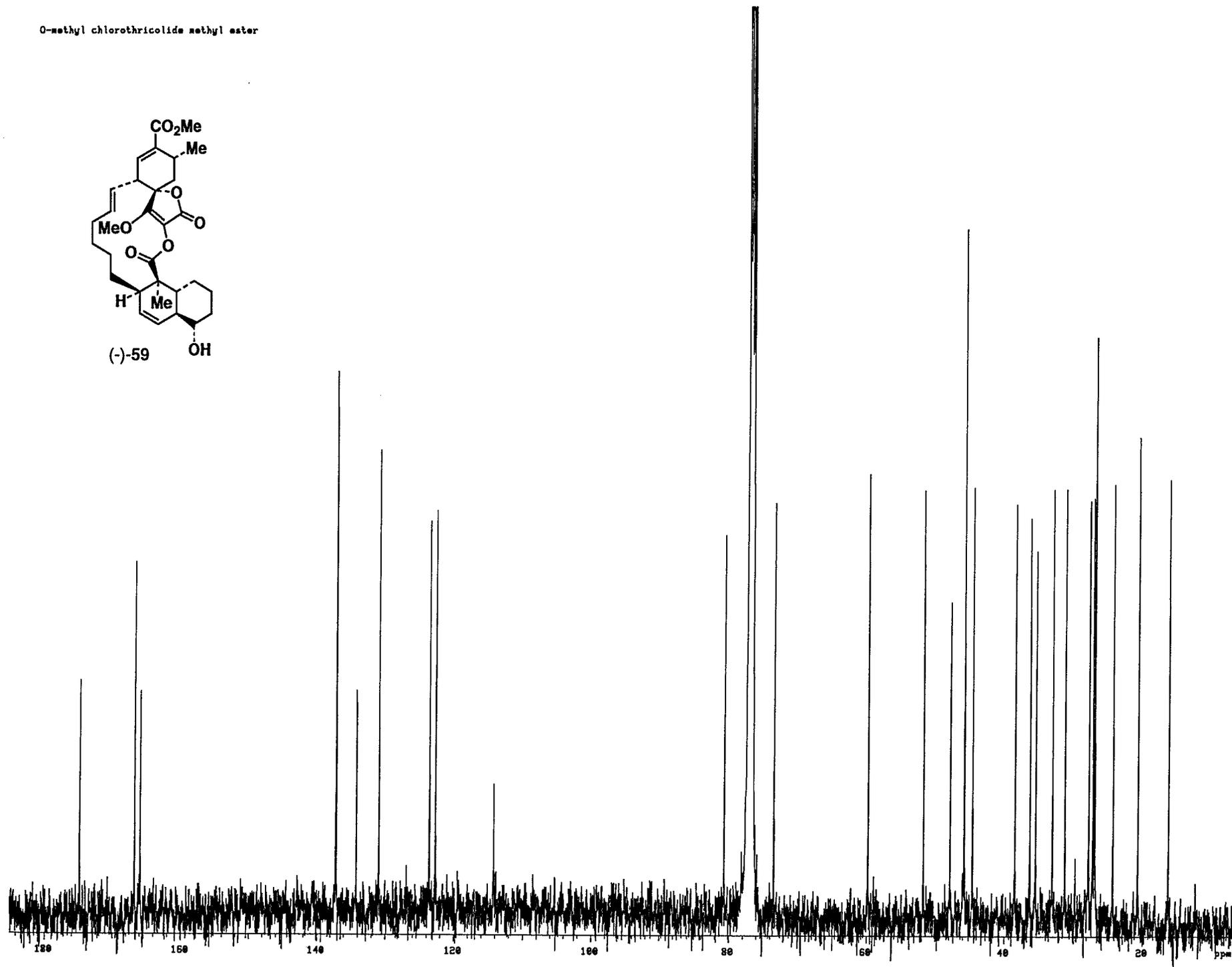
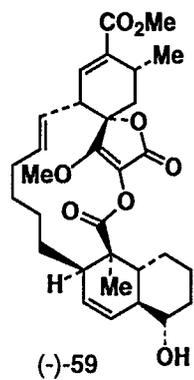
(-)-chloroethrionide

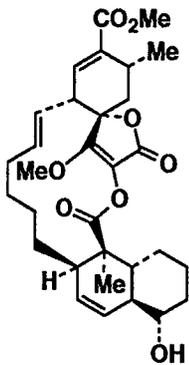


O-methyl chlorothricolide methyl ester









Yoshii's Chlorothricolide  
racemic 59

