A Triple Diene-Transmissive Diels-Alder Strategy to Build the Quassinoid Framework

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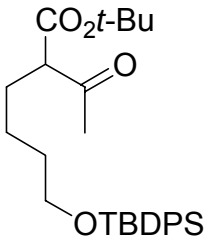
Supporting Information

Experimental procedures

GENERAL CONSIDERATIONS

All reactions were performed under an inert atmosphere of argon in glassware that had been flame dried. Solvents were distilled from potassium/benzophenone ketyl (Et_2O, tetrahydrofuran, benzene, toluene), from calcium hydride (CH_2Cl_2, $ClCH_2CH_2Cl$, triethylamine) or from potassium hydroxide (*N*,*N*,*N*,*N*-tetramethylethylenediamine) prior to use. Reagents were purchased from Aldrich and used without purification. Grignard and alkyl lithium reagents were titrated by the method of Love and Jones.[1] Flash chromatography was performed using Merck silica gel (230-400 Mesh ASTM) with solvents distilled prior to use. NMR spectra were recorded on a Bruker AC-300 spectrometer (^{1}H NMR at 300MHz, ^{13}C NMR at 75.5 MHz). The following abbreviations were used: s, singlet, d, doublet, t, triplet, q, quartet, qi, quintet, sx, sextet, sp, septet. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 7.26 ppm (^{1}H NMR), 77.0 ppm (^{13}C NMR); CD_2Cl_2: 5.33 (^{1}H NMR), 53.1 ppm (^{13}C NMR); acetone-d_6: 2.09 ppm (^{1}H NMR)). Infrared spectra were recorded on a Perkin Elmer 1600 FTIR spectrometer with a thin layer of the product on a NaCl disk. HPLC analyses were performed on a HP 1100 apparatus; GC analyses were performed on a Agilent 6890 series apparatus; GCMS analyses were performed on a HP 5890 serie II instrument (25 m length, 25μ OD, capillary Stabiliwax-DB5 column) coupled with a mass spectrometer (HP 5971). High-resolution spectrometry was performed on a ZAB-1F micromass spectrometer. Optical rotations $[\alpha]^{20}_D$ were measured on a Perkin Elmer 343 polarimeter.

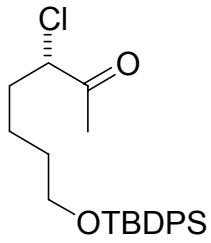
t-Butyl 2-acetyl-6-(*t*-butyldiphenylsilyloxy)hexanoate (8)



To a mixture of NaH (7.70 g, 194 mmol) in dry tetrahydrofuran (800 mL) at 0 ºC was added slowly *t*-butylacetoacetate (74.9 mL, 452 mmol). Then, a solution of **6**[2] (56.5 g, 129 mmol) in tetrahydrofuran (200 mL) was added at rt The reaction was heated to reflux and stirred for 60 h. After this time, the reaction was quenched with saturated NH_4Cl (400 mL), the two phases were separated, and the aqueous layer was extracted with Et_2O (3 x 400 mL). The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The excess *t*-butylacetoacetate was distilled under reduced pressure and the residue was purified by flash chromatography on silica gel (5 % ethyl acetate in hexanes) to afford 48.2 g (80%) of pure **8** as a yellow oil and 9.6 g (17%) of starting material. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.65 (dd, *J* =

7.4, 1.9 Hz, 4H), 7.45-7.34 (m, 6H), 3.64 (t, *J* = 6.1 Hz, 2H), 3.28 (t, *J* = 7.4 Hz, 1H), 2.20 (s, 3H), 1.86-1.72 (m, 2H), 1.57 (qt, *J* = 6.9 Hz, 2H), 1.45 (s, 9H), 1.42-1.24 (m, 2H), 1.03 (s, 9H); **IR** (neat): 3074, 1736, 1709, 1471; **LRMS** (m/z, relative intensity) : 486 ($(MNH_4)^+$, 55), 469 ($(MH)^+$, 5), 413 (65), 335 (100), 257 (50), 213 (50); **HRMS** calcd for $C_{28}H_{41}SiO_4$ $[MH]^+$: 469.2774, found: 469.2769.

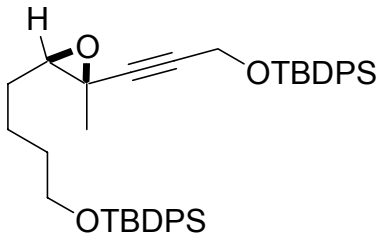
(3S*)-7-(*t*-Butyldiphenylsilyloxy)-3-chloroheptan-2-one (9)



To a solution of **8** (48.2 g, 103 mmol) in dry dichloromethane (890 mL) was added thionyl chloride (9.40 mL, 113 mmol) and the mixture was stirred at rt overnight. The reaction was quenched with water (200 mL), the two phases were separated and the aqueous layer was extracted with dichloromethane (3 x 300 mL). The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The crude α-chloro-β-ketoester was used without further purification.

To a solution of the α-chloro-β-ketoester (48.9 g, 97.0 mmol) in toluene (710 mL) was added *p*-toluenesulfonic acid (1.70 g, 9.0 mmol) and the reaction was heated to reflux. After 12 h, the reaction mixture was cooled to rt and diluted with a solution of saturated aqueous sodium bicarbonate (200 mL). The two phases were separated and the aqueous layer was extracted with diethyl ether (3 x 200 mL). The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. Flash chromatography on silica gel (2% ethyl acetate in hexanes) afforded 33.5 g (81% for 2 steps) of pure **9** as a colorless oil. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.66 (dd, *J* = 7.4, 1.8 Hz, 4H), 7.46-7.35 (m, 6H), 4.15 (dd, *J* = 8.8, 5.5 Hz, 1H), 3.66 (t, *J* = 6.1 Hz, 2H), 2.30 (s, 3H), 2.00-1.76 (m, 2H), 1.65-1.41 (m, 4H), 1.05 (s, 9H); **IR** (neat): 3065, 2939, 2862, 1718, 1466, 1430; **LRMS** (m/z, relative intensity) : 345 ($(M-C_4H_9)^+$, 10), 86 (100); **HRMS** calcd for $C_{19}H_{22}SiO_2Cl$ $[M-C_4H_9]^+$: 345.1078, found: 345.1081

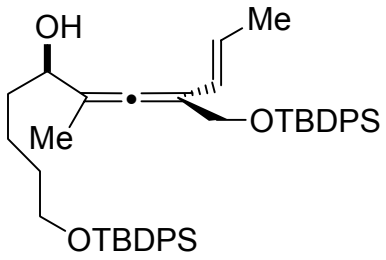
(4R*,5R*) 1,9-bis(t-Butyldiphenylsilyloxy)-4-methyl-4-nonen-2-yne, 4,5-oxide (11)



To a solution of 2-*t*-butyldiphenylsilyloxy-1-propyne (32.3 g, 110 mmol) in tetrahydrofuran (600 mL) was added *n*-butyllithium (2.3 M solution in hexanes,

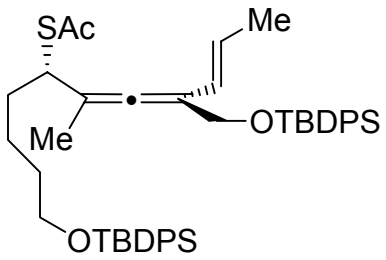
49.5 mL, 114 mmol) at -78 ºC and the mixture was stirred for 30 min. After this time, a solution of **9** (33.5 g, 83 mmol) in tetrahydrofuran (100 mL) was added. The mixture was warmed slowly to rt and stirred overnight. The reaction was quenched with saturated aquous ammonium chloride (200 mL) and the two phases were separated. The aqueous layer was extracted with diethyl ether (3 x 150 mL), and the combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. Flash chromatography on silica gel (5% ethyl acetate in hexanes) afforded 52.7 g (96%) of pure epoxide **11** as colorless oil. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.71-7.65 (m, 8H), 7.45-7.36 (m, 12H), 4.32 (s, 2H), 3.67 (t, *J* = 5.8 Hz, 2H), 2.97 (t, *J* = 5.8 Hz, 1H), 1.59-1.43 (m, 6H), 1.37 (s, 3H), 1.05 (s, 18H); **IR** (neat): 3069, 3050, 2933, 2859 1471; **LRMS** (m/z, relative intensity) : 678 ($(MNH_4)^+$, 100), 661($(MH)^+$, 30), 405, (77), 196 (52); **HRMS** calcd for $C_{42}H_{52}Si_2O_3$ $[MH]^+$: 661.3533, found: 661.3518.

(5R*,6S*)-1-(t-Butyldiphenylsilyloxy)-8-(t-Butyldiphenylsilyloxymethyl)-6-methyl-5-hydroxy-6,7,9-undecatriene (12)



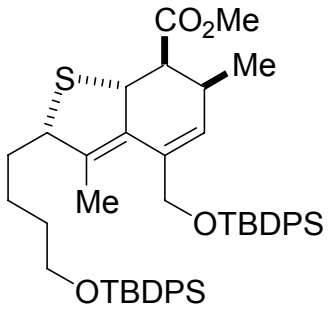
To a solution of *trans*-1-bromo-1-propene (8.7 mL, 102 mmol) in tetrahydrofuran (150 mL) was added *t*-butyllithium (1.7 M solution in pentane, 119 mL, 203 mmol) at -78 ºC and the reaction was stirred 30 min at -78 ºC. A dry 1 L tricol flask was charged with copper cyanide (4.5 g, 50.7 mmol) and tetrahydrofuran (150 mL) and the mixture was cooled at -78 ºC. Then, the mixture of *trans*-1-lithio-1-propene was transferred via cannula over a 15 min period to the mixture of copper cyanide at -78 ºC and the reaction was stirred for 25 min at that temperature. After this time, the reaction was cooled at -100 ºC and a solution of **11** (11.2 g, 17 mmol) in tetrahydrofuran (20 mL) was added. After 45 min, the reaction was warmed to 0 ºC and quenched with a solution of NH_4OH/NH_4Cl (9:1, 200 mL). The two-phase system was stirred overnight at rt, the two phases were separated, and the aqueous layer was extracted with diethyl ether (3 x 200 mL). The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The crude and unstable product **12** was used without further purification and used without further delay.

(5S*,6S*)-1-(t-Butyldiphenylsilyloxy)-8-(t-Butyldiphenylsilyloxymethyl)-6-methyl-5-thioacetyl-6,7,9-undecatriene (13)



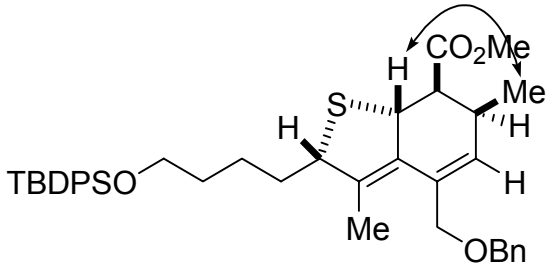
To a solution of triphenylphosphine (17.8 g, 68 mmol) in tetrahydrofuran (300 mL), was added diisopropyl azodicarboxylate (13.7 mL, 68 mmol) at 0 ºC. The reaction was stirred vigourously for 30 min. A mixture of thiolacetic acid (4.9 mL, 68 mmol) and **12** (12.0 g, 17 mmol) in tetrahydrofuran (170 mL) was added via cannula over a 20 min period at -20 ºC. The mixture was warmed to 0 ºC from -20 ºC for 0.5 h and allowed to stand at 0 ºC for 1 h. The mixture was then stirred overnight at rt and then poured into water (10 mL). The two phases were separated and the aqueous phase was extracted with diethyl ether (3 x 20 mL). The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Flash chromatography on silica gel (5% ethyl acetate in hexanes) afforded 9.7 g (74% for 2 steps) of pure **13** as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.69-7.63 (m, 8H), 7.43-7.34 (m, 12H), 5.81 (dd, *J* = 15.7, 1.4 Hz, 1H), 5.60 (dq, *J*= 15.9, 6.6 Hz, 1H), 4.28 (AB quartet, 2H), 3.96 (t, *J* = 7.1 Hz, 1H), 3.60 (t, *J* = 6.3 Hz, 1H), 3.59 (t, *J* = 6.1 Hz, 1H), 2.29 (s, 3H), 1.72 (s, 3H), 1.69 (dd, *J* = 6.3, 1.4 Hz, 3H), 1.67-1.24 (m, 6H), 1.03 (s, 18H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 202.9 (s), 195.7 (s), 135.6 (d), 134.1 (s), 133.7 (s), 129.5 (d), 127.5 (d), 126.2 (s), 125.1 (d), 106.5 (s), 102.1 (s), 63.8 (t), 62.6 (t), 47.6 (d), 34.0 (t), 30.5 (q), 26.8 (q), 23.4 (t), 19.2 (s), 18.6 (q), 17.6 (q); **IR** (neat): 3075, 2931, 2858, 1691; **LRMS** (m/z, relative intensity) : 760 ((M^+), 1), 742 (($M-H_2O$)$^+$, 5), 703 (($M-C_4H_9$)$^+$, 15), 199 (90), 136 (100); **HRMS** calcd for $C_{47}H_{60}Si_2O_3S$ [M]$^+$: 760.3801, found: 760.3795.

Diels-Alder adduct 14a.

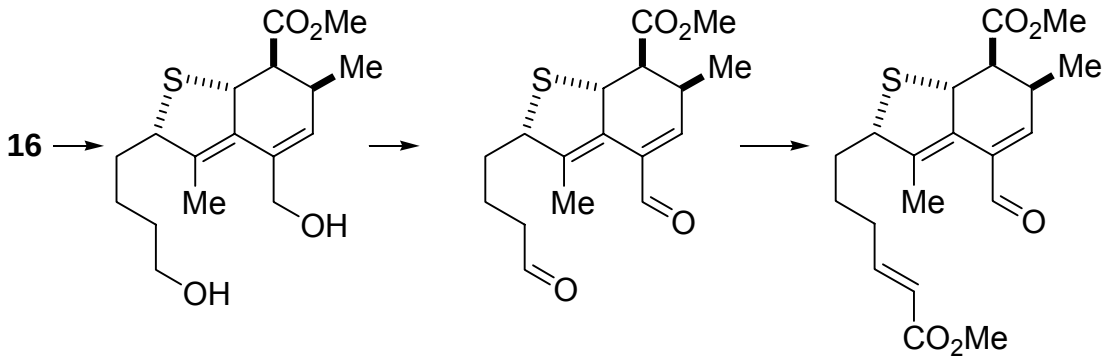


To a solution of **13** (9.7 g, 13 mmol) in acetonitrile (75 mL) was added a solution of hydrazine hydrate (1.0 M solution in acetonitrile, 37.4 mL, 37 mmol) and the mixture was stirred overnight at rt. After this time, acetonitrile and hydrazine were evaporated to dryness under reduced pressure and the residue was dissolved in dichloromethane (75 mL). Triethylamine (1.69 mL, 12.5 mmol) was added, the reaction was cooled to 0°C, and methyl propiolate (0.1 M solution in dichloromethane, 187 mL, 18.7 mmol) was added slowly. The mixture was warmed to rt and stirred at that temperature for 4 h. The dichloromethane was evaporated under reduced pressure and the crude product was purified by flash chromatography on silica gel (10% ethyl acetate in hexanes) affording 8.3 g (83%) of pure **14a** as a colorless oil. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.69-7.65 (m, 8H), 7.45-7.35 (m, 12H), 5.56 (d, 1H, *J* = 4.4 Hz), 4.58 (d, 1H, *J* = 13.2 Hz), 4.35 (d, 1H, *J* = 13.2 Hz), 4.26 (d, 1H, *J* = 12.1 Hz), 4.07 (br s, 1H), 3.72 (s, 3H), 3.66 (t, 2H, *J* = 6.3 Hz), 2.86 (dd, 1H, *J* = 12.1, 6.0 Hz), 2.67 (q, 1H, *J* = 6.6 Hz), 1.87 (s, 3H), 1.83-1.34 (m, 6H), 1.05 (s, 18H), 0.84 (d, 3H, *J* = 7.2 Hz); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 173.6 (s), 135.6 (d), 135.0 (s), 134.1 (s), 133.6 (s), 133.2 (s), 132.2 (d), 130.0 (s), 129.7 (d), 129.5 (d), 127.6 (d), 65.6 (t), 63.7 (t), 58.4 (q), 54.1 (d), 51.5 (q), 49.0 (d), 35.6 (t), 33.1 (d), 32.4 (d), 26.8 (q), 22.7 (t), 19.2 (q), 16.4 (t), 14.6 (s); **IR** (neat): 2939, 2857,1735; **LRMS** (m/z, (relative intensity)): 802 (M^+, 5), 745($(M-C_4H_9)^+$, 55), 489 (65), 290 (90), 199 (90), 86 (100); **HRMS** calcd for $C_{49}H_{62}Si_2O_4S$: 802.3907, found: 802.3890.

The benzyl ether analog **14b** was more amenable to 2D NMR spectral analysis. It was made the same way as per **14a**. Its stereochemistry was deduced from a key nOe enhancement as shown. Also, related structures made from similar Diels-Alder reactions are described in ref. 6a and 12. Copies of the COSY and NOESY spectra of this analog are included in this SI.



Aldehyde-ester 4



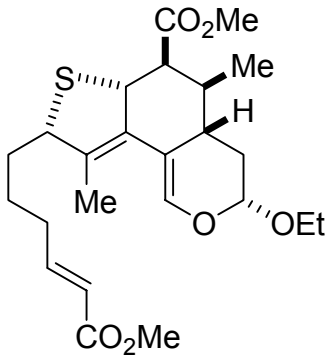
To a solution of **14a** (8.30 g, 10.3 mmol) in tetrahydrofuran (100 mL) was added tetra-*n*-butylammonium fluoride (1.0 M solution in tetrahydrofuran, 36.2 mL, 36.2 mmol) and the mixture was stirred overnight at rt. The reaction was quenched with saturated ammonium chloride (50 mL) and the two phases were separated. The aqueous layer was extracted with diethyl ether (3x 50 mL) and the combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. Flash chromatography on silica gel (70% ethyl acetate in hexanes) afforded 2.83 g (84%) of pure diol as a yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 5.76 (d, *J* = 5.0 Hz, 1H), 4.52 (br d, *J* = 12.6 Hz, 1H), 4.28 (br d, *J* = 12.1 Hz, 2H), 4.09 (br d, *J* = 7.2 Hz, 1H), 3.73 (s, 3H), 3.63 (t, *J* = 6.3 Hz, 2H), 2.87 (dd, *J* = 12.1, 6.6 Hz, 1H), 2.75 (st, *J* = 6.4 Hz, 1H), 1.93 (s, 3H), 1.93-1.76 (m, 2H), 1.63 -1.34 (m, 6H), 0.92 (d, *J* = 7.2 Hz, 3H); **IR** (neat): 3701-3099, 2939, 2874, 1735; **LRMS** (m/z, (relative intensity)): 326 (M^+, 10), 308 ($(M-H_2O)^+$, 25), 249 (60), 175 (50), 84 (100); **HRMS** calcd for $C_{17}H_{26}O_4S$: 326.1552, found: 326.1556.

To a solution of diol (500 mg, 1.53 mmol) in ethyl acetate (15 mL) was added IBX (1.72 g, 6.13 mmol). The mixture was heated to reflux for 3 h, cooled to rt and the IBX by-products were removed by filtration, washing with ethyl acetate. The solvent was evaporated under reduced pressure and the crude dialdehyde was used without further delay.

To a suspension of NaH (77 mg, 1.9 mmol) in tetrahydrofuran (10 mL) was added trimethylphosphonoacetate (300 μL, 1.84 mmol) at 0 ºC and the mixture was stirred 30 min. A solution of the dialdehyde (493 mg, 1.53 mmol) in tetrahydrofuran (5 mL) was added at -78 ºC. The reaction was stirred 7 h at this temperature and quenched with water (3 mL). The two phases were separated, the aqueous layer was extracted with diethyl ether (3x 5 mL) and the combined organic layers were washed with brine, dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Flash chromatography on silica gel (20% ethyl acetate in hexanes) afforded 370 mg (64%, 2 steps) of pure **4** as a colorless oil. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 9.52 (s, 1H), 6.93 (dt, *J* = 15.4, 7.3 Hz, 1H), 6.63 (d, *J* = 3.9 Hz, 1H), 5.81 (d, *J* = 15.4 Hz, 1H), 4.22-4.16 (m, 2H), 3.76 (s, 3H), 3.72 (s, 3H), 3.13-3.02 (m, 1H), 2.95 (dd, *J* = 11.8, 6.3 Hz, 1H), 2.25-2.17 (m, 2H), 1.88-1.78 (m, 1H), 1.72 (s, 3H), 1.64-1.36 (m, 3H), 1.01 (d, *J* = 7.7 Hz, 3H);

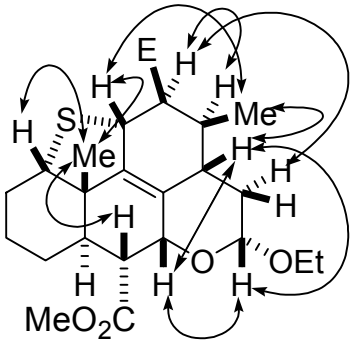
IR (neat): 2948, 2934, 2856, 1724, 1697, 1436; **LRMS** (m/z, (relative intensity)): 378 (M^+, 20), 346 (50), 163 (75), 84(100); **HRMS** calcd for $C_{20}H_{26}O_5S$: 378.1501, found: 378.1491.

Hetero Diels-Alder adduct 15

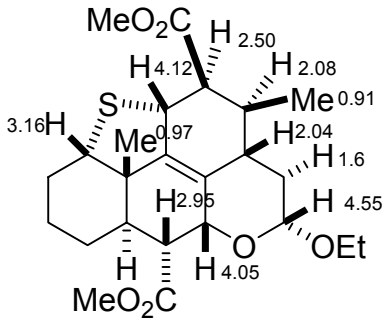


To a solution of **4** (370 mg, 0.98 mmol) in ethyl vinyl ether (6.2 mL) was added $Yb(fod)_3$ (74 mg, 20% w/w). The mixture was stirred three days under argon and after this time ethyl vinyl ether was evaporated under reduced pressure. Flash chromatography on silica gel (20% ethyl acetate in hexanes) afforded 334 mg (76%) of pure **15** as colorless oil. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 6.95 (dt, *J* = 15.4, 7.0 Hz, 1H), 6.57 (d, *J* = 1.7 Hz, 1H), 5.82 (d, *J* = 16.0 Hz, 1H), 5.00 (dd, *J* = 8.8, 2.2 Hz, 1H), 4.43 (br d, *J* = 9.9 Hz, 1H), 4.10 (br d, *J* = 7.1 Hz, 1H), 3.94 (dq, *J* = 9.6, 7.1 Hz, 1H), 3.72 (s, 3H), 3.70 (s, 3H), 3.59 (dq, *J* = 9.4, 7.1 Hz, 1H), 2.88 (t, *J* = 9.3 Hz, 1H), 2.51 (tdd, *J* = 10.6, 5.6, 1.7 Hz, 1H), 2.22 (br q, *J* = 7.0 Hz, 2H), 2.10 (ddd, *J* = 12.9, 5.8, 2.5 Hz, 1H), 1.96-1.81 (m, 2H), 1.77 (s, 3H), 1.58-1.43 (m, 4H), 1.25 (t, *J* = 7.2 Hz, 3H), 0.88 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 174.3 (s), 167.0 (s), 149.0 (d), 139.8 (d), 130.0 (s), 129.3 (s), 121.2 (d), 112.5 (s), 99.3 (d), 64.5 (t), 58.9 (d), 56.7 (d), 51.7 (d), 51.4 (q), 35.7 (d), 35.3 (t), 34.0 (d), 32.7 (t), 32.0 (t), 24.9 (q), 15.1 (q), 14.6 (q); **IR** (neat): 2922, 1727; **LRMS** (m/z, (relative intensity)): 450 (M^+, 70), 346 (50), 277 (50), 189 (75), 163 (100); **HRMS** calcd for $C_{24}H_{34}O_6S$: 450.2076, found: 450.2079.

Pentacycle 3.



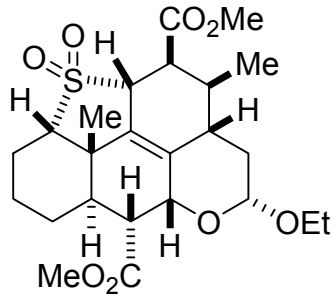
NOE



Value in ppm

A solution of **15** (150 mg, 0.33 mmol) in toluene (4.5 mL) was heated at 250 ºC for 17 h under N_2 in a sealed Schlenck tube. After this time, the tube was unsealed and the toluene was evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel (30% ethyl acetate in Hexanes) to afford **3** (75 mg, 50%) as a white solid. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 4.55 (dd, *J* = 9.4, 1.7 Hz, 1H), 4.12 (d, *J* = 9.9 Hz, 1H), 4.05 (dd, *J* = 6.1, 1.7 Hz, 1H), 3.78 (dq, *J* = 9.9, 7.2 Hz, 1H), 3.71 (s, 3H), 3.70 (s, 3H), 3.44 (dq, *J* = 9.6, 7.2 Hz, 1H), 3.16 (dd, *J* = 11.3, 5.8 Hz, 1H), 2.95 (dd, *J* = 12.4, 6.3 Hz, 1H), 2.50 (dd, *J* = 10.2, 3.6 Hz, 1H), 2.27 (dt, *J* = 12.4, 5.9 Hz, 1H), 2.14-2.01 (m, 3H), 1.90-1.76 (m, 3H), 1.65-1.53 (m, 2H), 1.50-1.31 (m, 1H), 1.24-1.05 (m, 1H), 1.18 (t, *J* = 7.2 Hz, 3H), 0.97 (s, 3H), 0.91 (d, *J* = 7.2 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 173.8 (s), 171.4 (s), 143.3 (s), 122.7 (s), 101.5 (d), 70.9 (d), 64.1 (t), 53.2 (d), 51.9 (q), 51.2 (q), 47.2 (d), 45.0 (s), 41.2 (d), 39.3 (t), 35.5 (d), 31.7 (d), 26.5 (t), 24.1 (q), 20.6 (t), 19.7 (t), 15.7 (q), 15.1 (q); **IR** (neat): 2949, 2869, 1736, 1435; **LRMS** (m/z, (relative intensity)): 450 (M^+, 1), 435 ($(M\text{-}CH_3)^+$, 1), 404 ($(M\text{-}C_2H_5OH)^+$, 100); **HRMS** calcd for $C_{24}H_{34}O_6S$: 450.2076, found: 450.2079; mp (°C): 164.3.

Pentacyclic sulfone 16.



A solution of **3** (258 mg, 0.57 mmol) in CH_2Cl_2 (6 mL) was cooled at 0 ºC and m-CPBA (564 mg, 2.29 mmol) was added. The reaction was warmed to rt, stirred for 2 h, and the reaction was then quenched with saturated $Na_2S_2O_3$. The two phases were separated and the organic layer was washed with saturated $NaHCO_3$. The combined aqueous layers were extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (60% ethyl acetate in Hexanes) to afford the sulfone **16** (271 mg, 99%) as a white solid. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 4.56 (dd, *J* = 9.3, 2.2 Hz, 1H), 4.18 (dd, *J* = 9.9, 2.2 Hz, 1H), 4.05 (dd, *J* = 6.0, 2.2 Hz, 1H), 3.80-3.72(m, 1H), 3.77 (s, 3H), 3.69 (s, 3H), 3.42 (dq, *J* = 9.4, 7.2 Hz, 1H), 3.12-3.06 (m, 2H), 2.93 (dd, *J* = 12.6, 6.1 Hz, 1H), 2.34-2.17 (m, 2H), 2.10-2.01 (1.97-1.89, m, 3H), 1.70-1.59 (m, 3H), 1.50-1.41 (m, 1H), 1.39-1.06 (m, 1H), 1.17 (t, *J* = 7.2 Hz, 3H), 1.17 (s, 3H), 0.90 (d, *J* = 7.2 Hz, 3H); **IR** (neat): 2952, 2874, 1742, 1444; **LRMS** (m/z, (relative intensity)): 481 ($(M-H)^+$, 1), 437 ($(M-C_2H_5OH)^+$, 10), 418 ($(M-SO_2)^+$, 20), 344 (60), 313 (55), 269 (60), 225, (100), 169 (55); **HRMS** calcd for $C_{24}H_{33}O_8S$ $[M-H]^+$: 481.1896, found: 481.1899.

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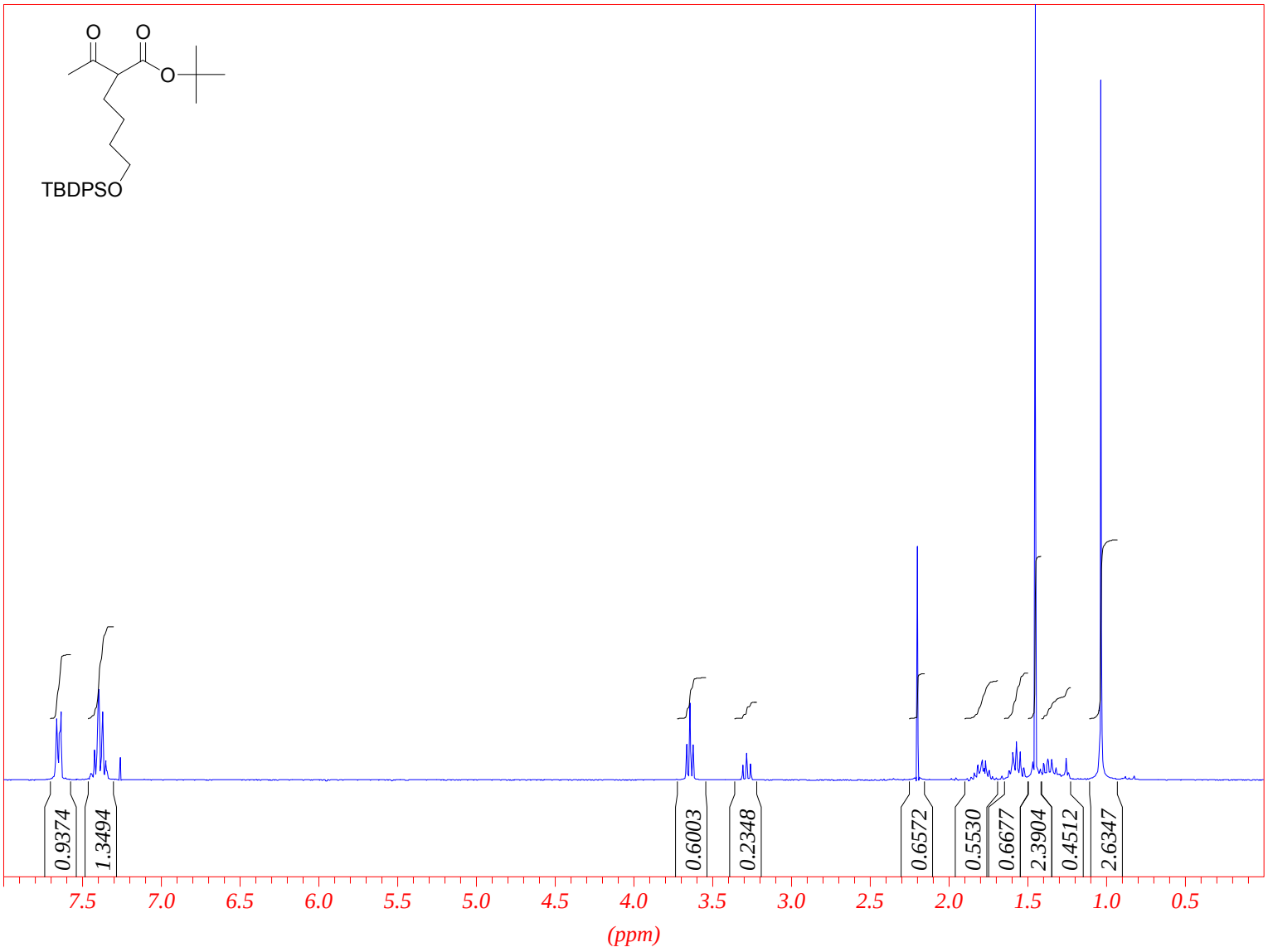
[1] Love, B. E.; Jones, E. G. *J. Org. Chem.* **1999**, *64*, 3755-3756.

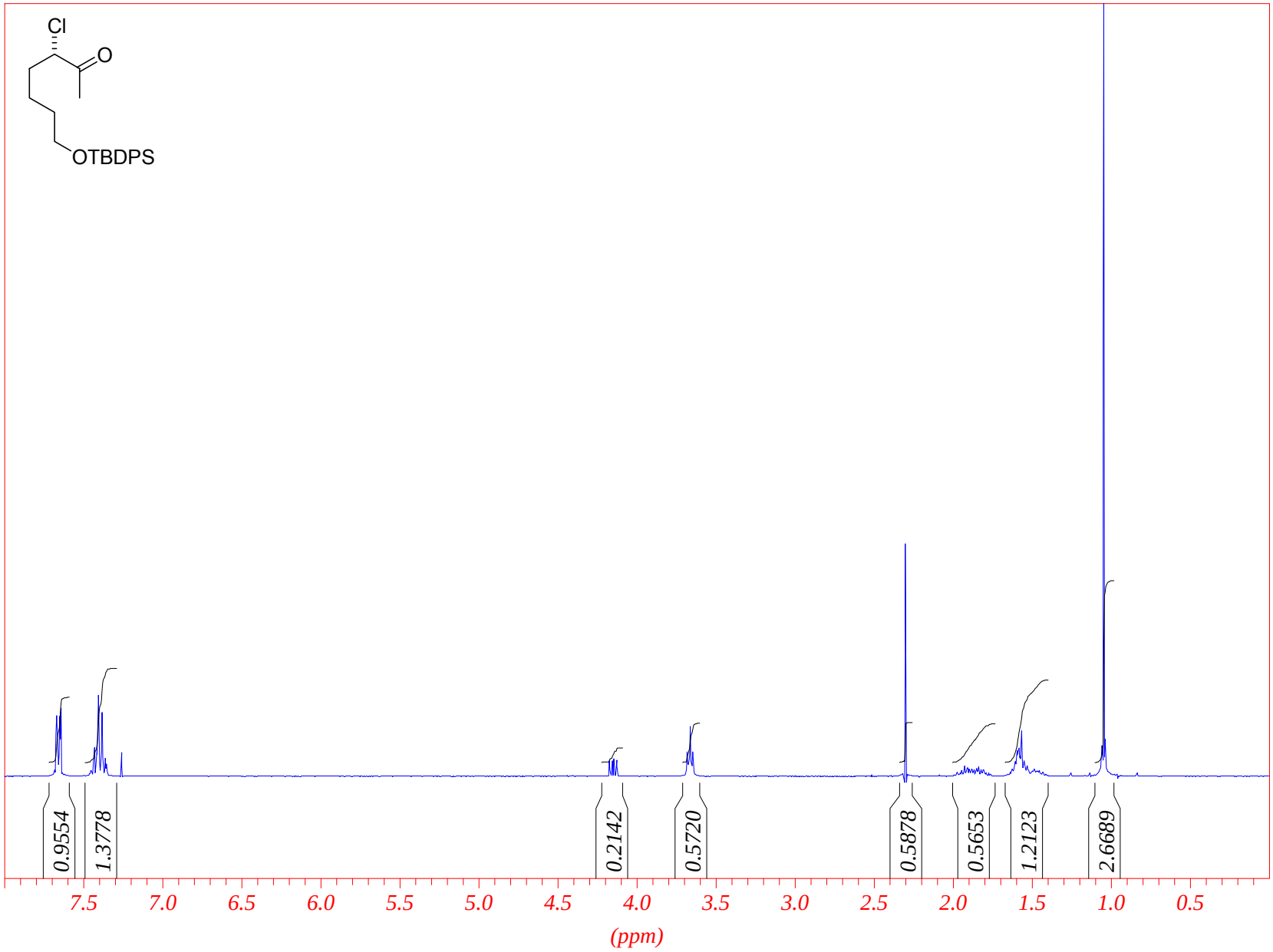
[2] The 4-iodobutanol was synthesized from tetrahydrofuran following this procedure: L. H. Long, G. F. Freeguard, *Nature*, **1965**, *207*, 403. Protection of 4-iodobutanol with TBDPS followed standard procedure.

Copies of ^{1}H NMR

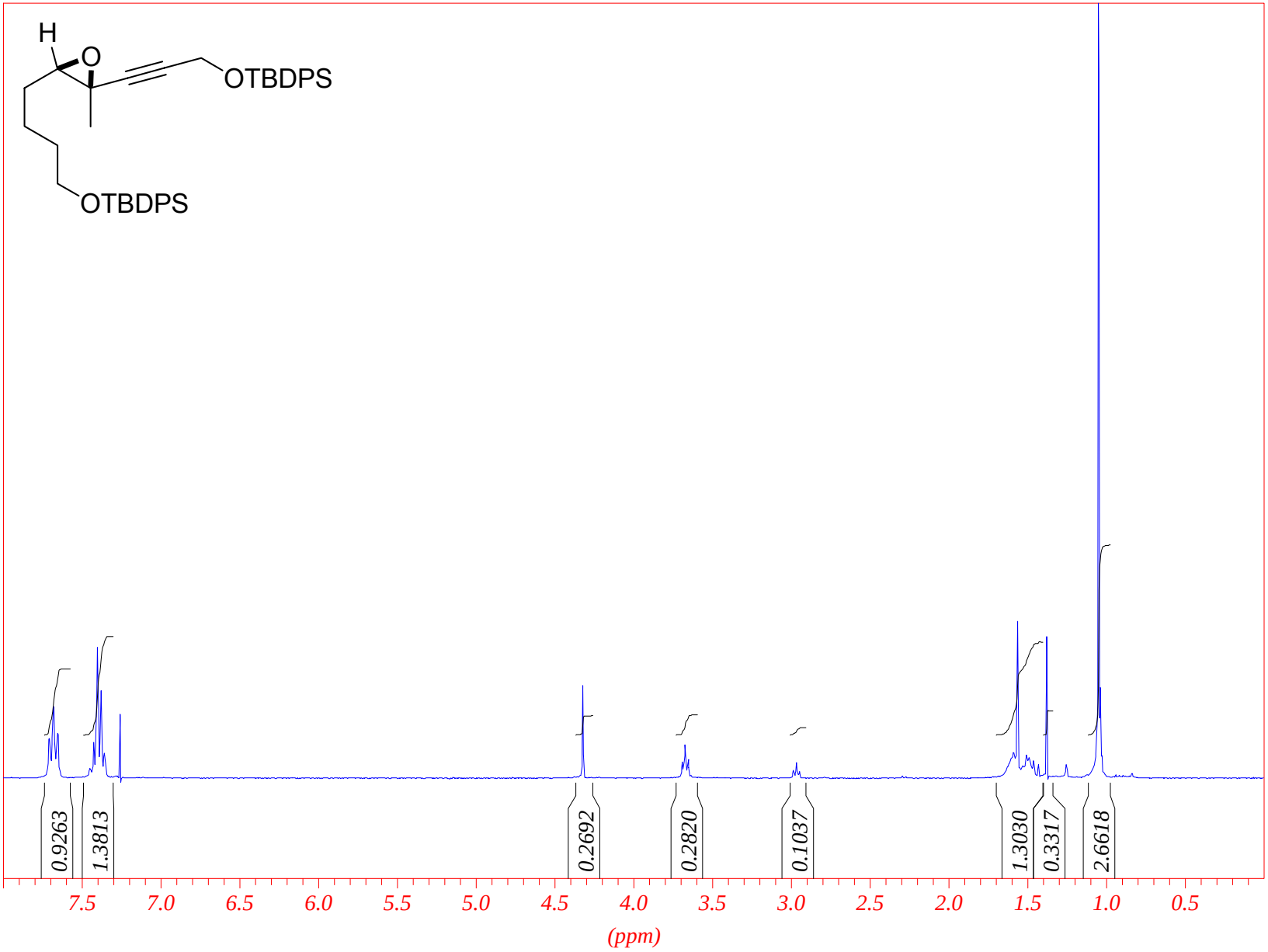
t-Butyl 2-acetyl-6-(*t*-butyldiphenylsilyloxy)hexanoate (8)



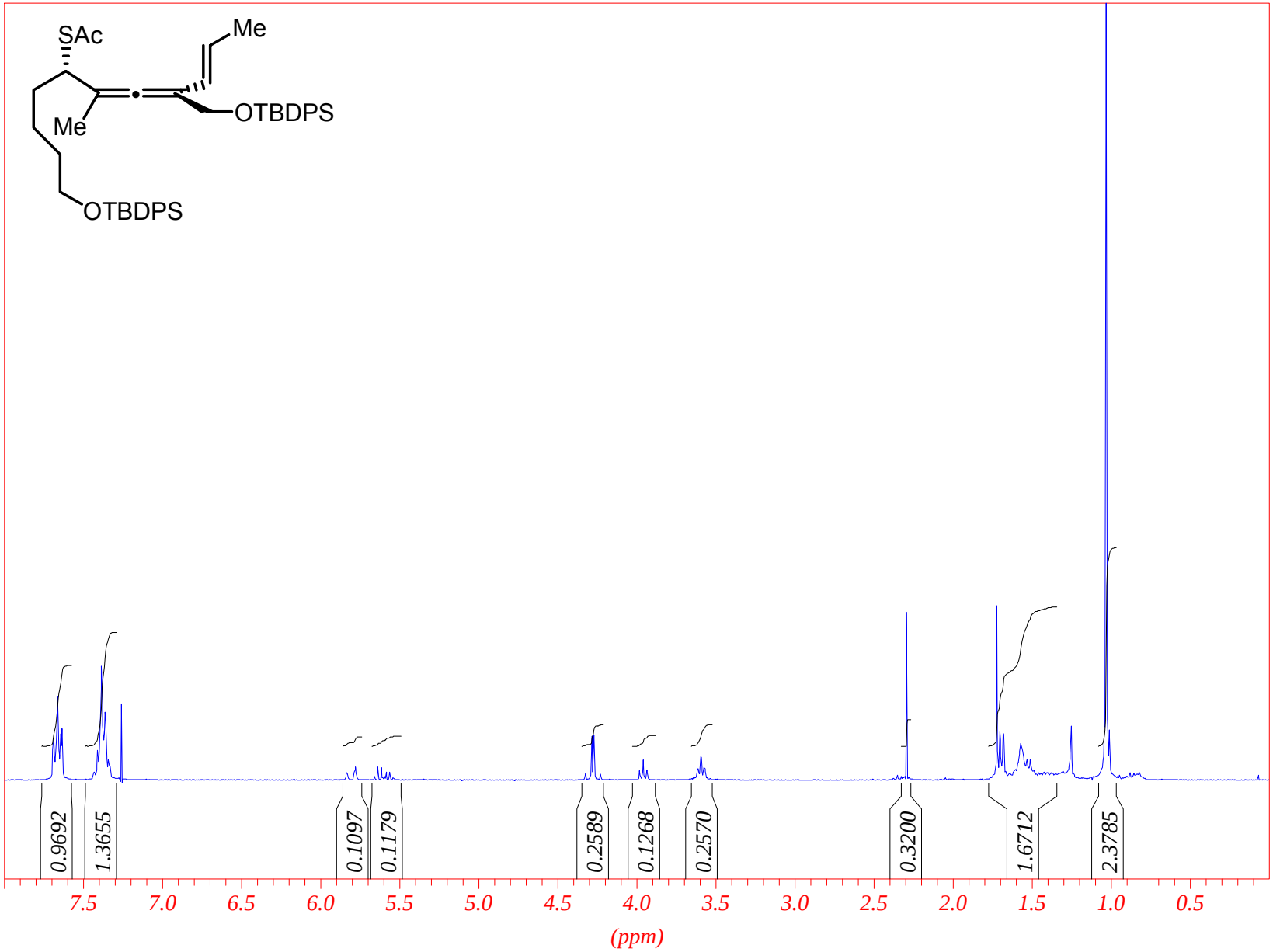
(3S*)-7-(*t*-Butyldiphenylsilyloxy)-3-chloroheptan-2-one (9)



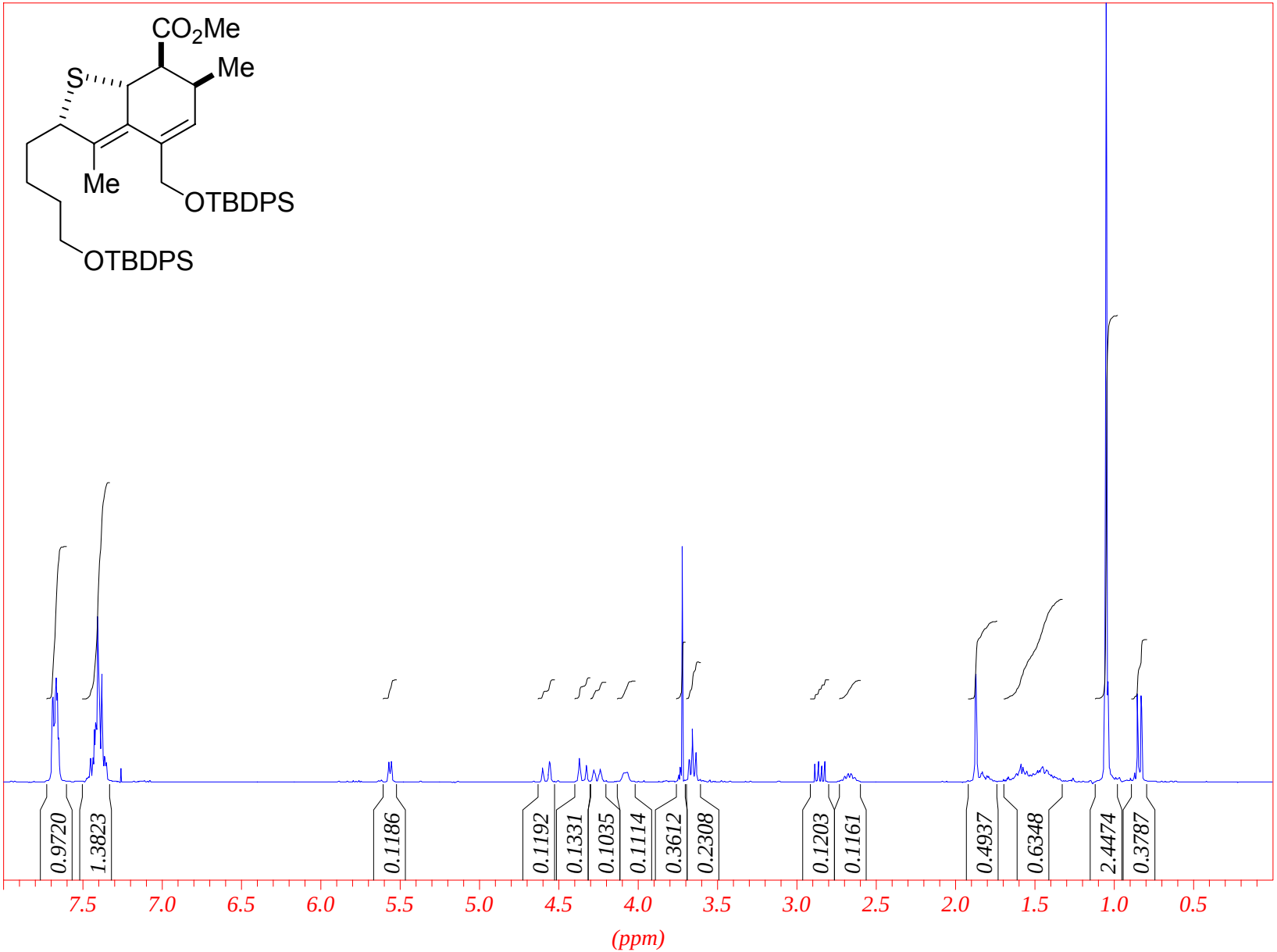
(4R*,5R*) 1,9-bis(t-Butyldiphenylsilyloxy)-4-methyl-4-nonen-2-yne, 4,5-oxide (11)



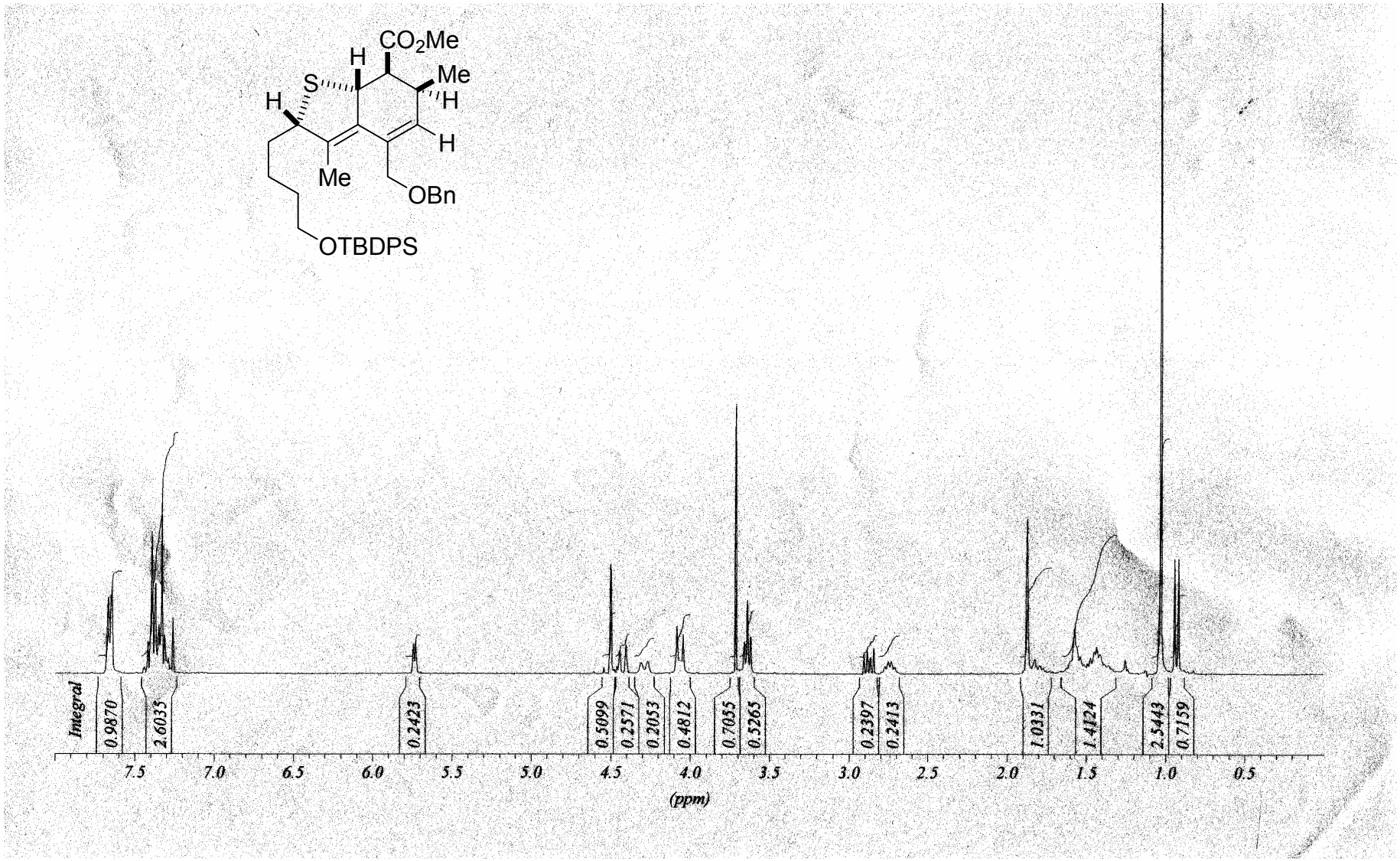
(5S*,6S*)-1-(t-Butyldiphenylsilyloxy)-8-(t-Butyldiphenylsilyloxymethyl)-6-methyl-5-thioacetyl-6,7,9-undecatriene (13)



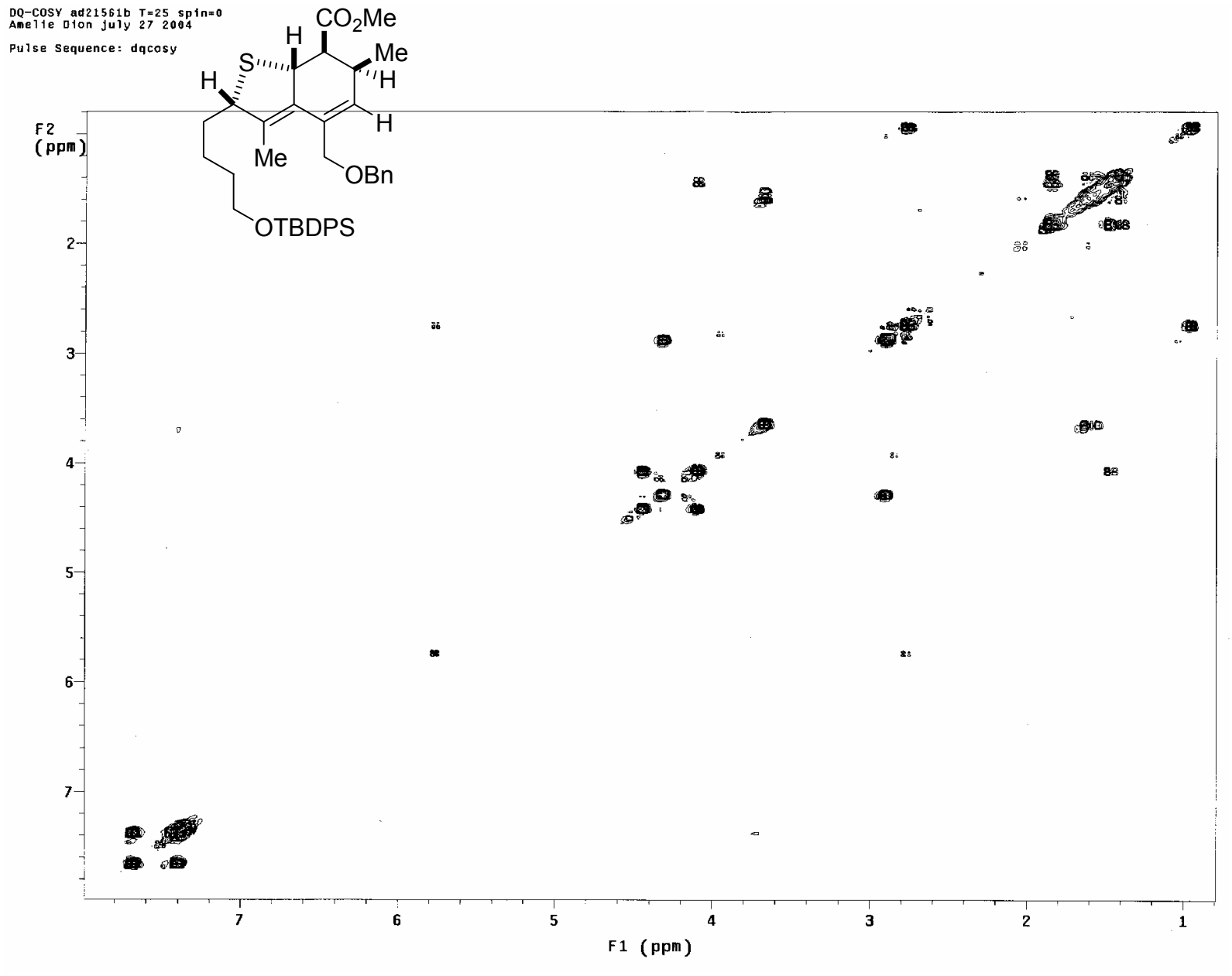
Diels-Alder adduct 14a



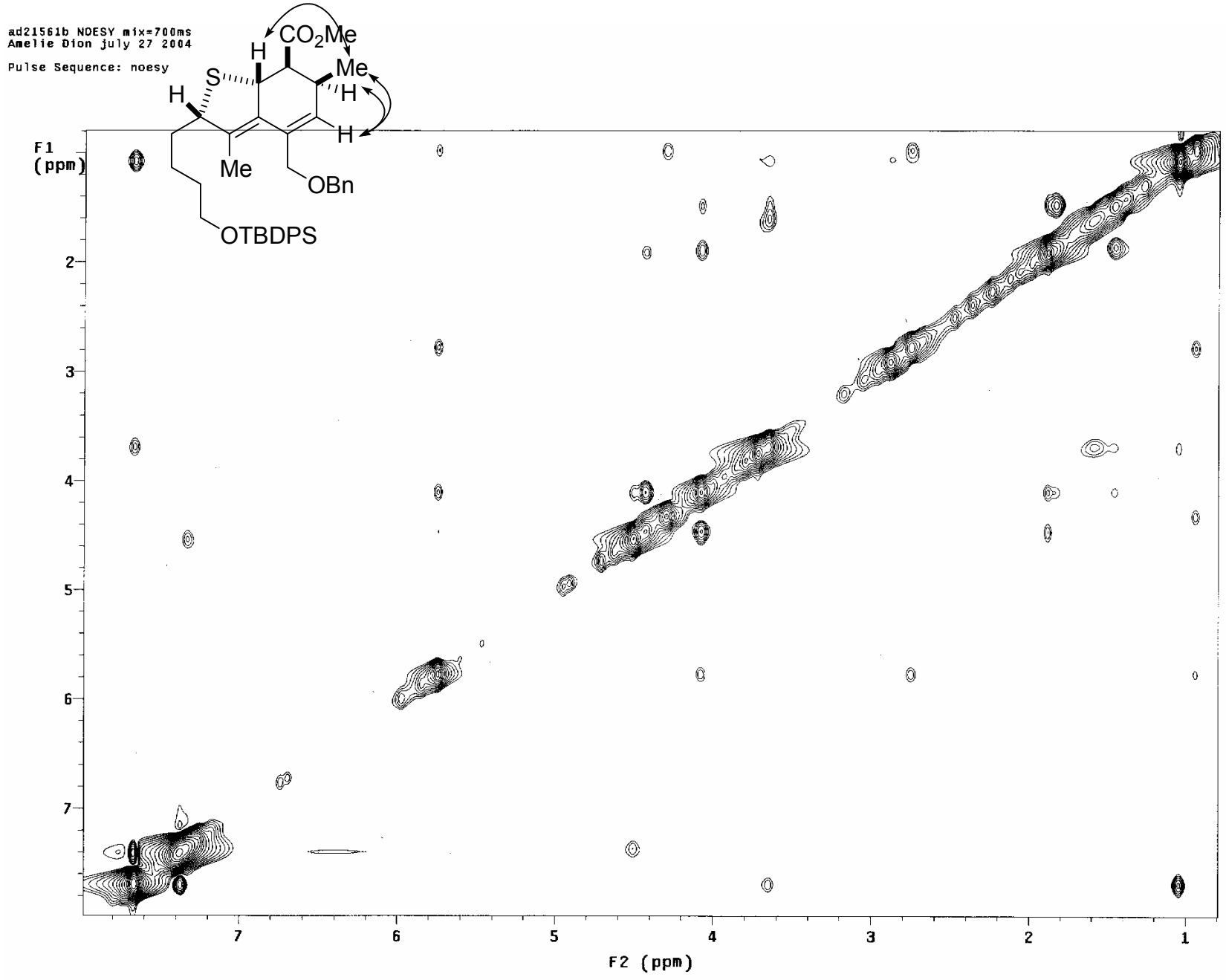
Benzyl ether 14b



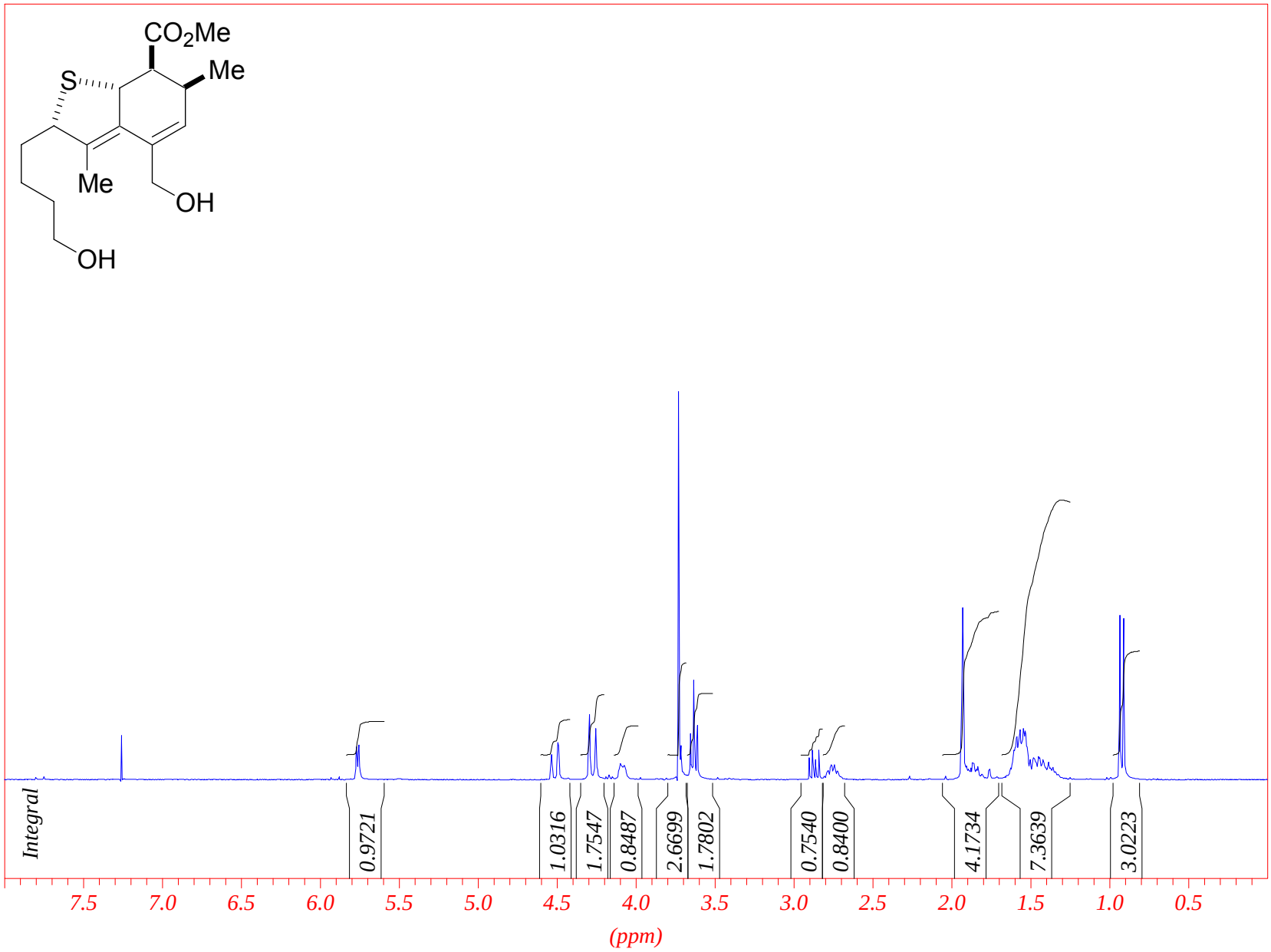
COSY 14b


DQ-COSY ad21561b T=25 spin=0
Amelie Dion july 27 2004
Pulse Sequence: dqcosy
CO2Me
H
Me
S
H
H
H
Me
OBn
OTBDPS
F2 (ppm)
F1 (ppm)

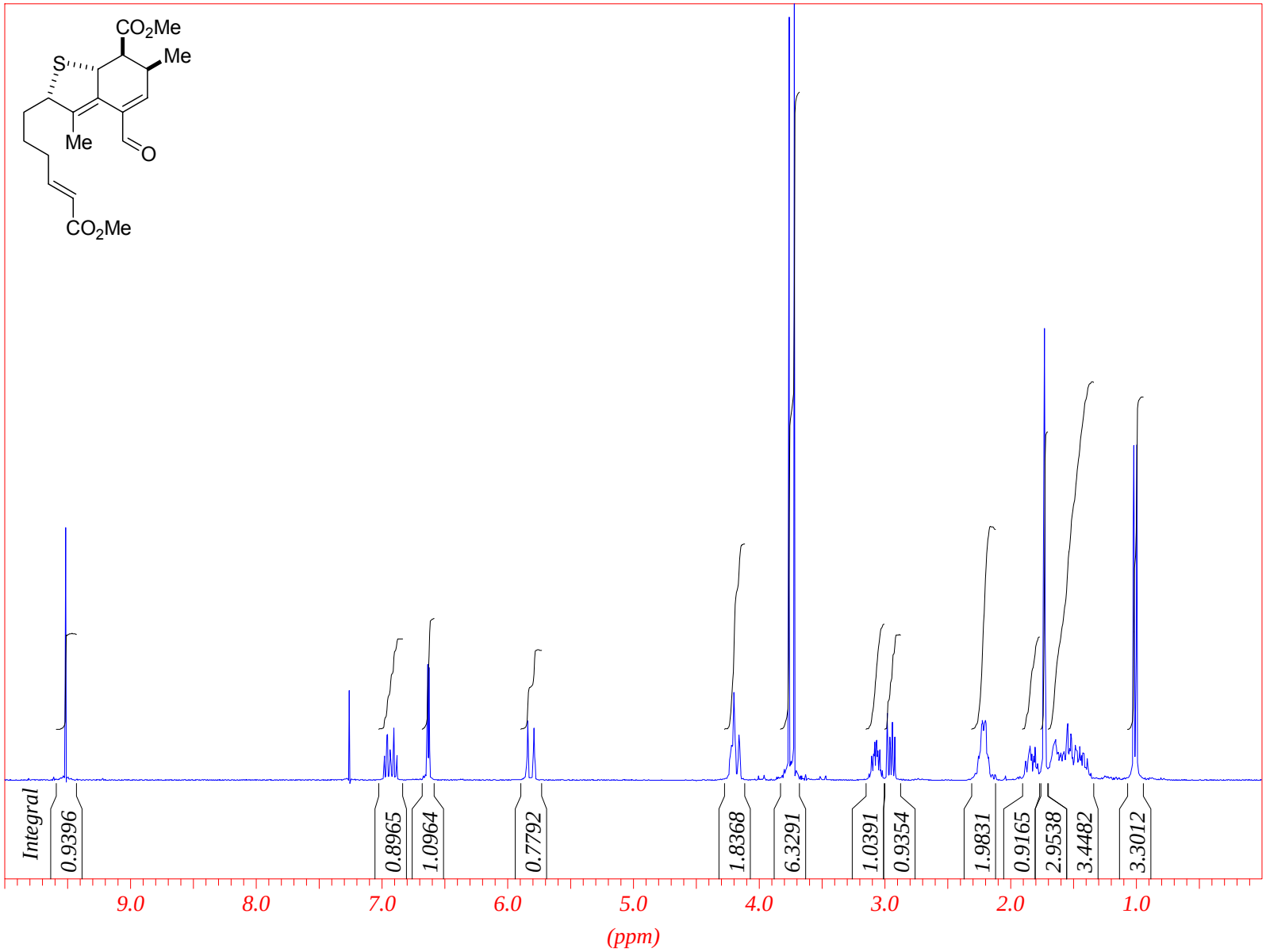
NOESY 14b


ad21561b NOESY mix=700ms
Amelie Dion july 27 2004
Pulse Sequence: noesy
H
CO2Me
Me
S
H
H
H
Me
OBn
OTBDPS
F1 (ppm)
2
3
4
5
6
7
7
6
5
4
3
2
1
F2 (ppm)

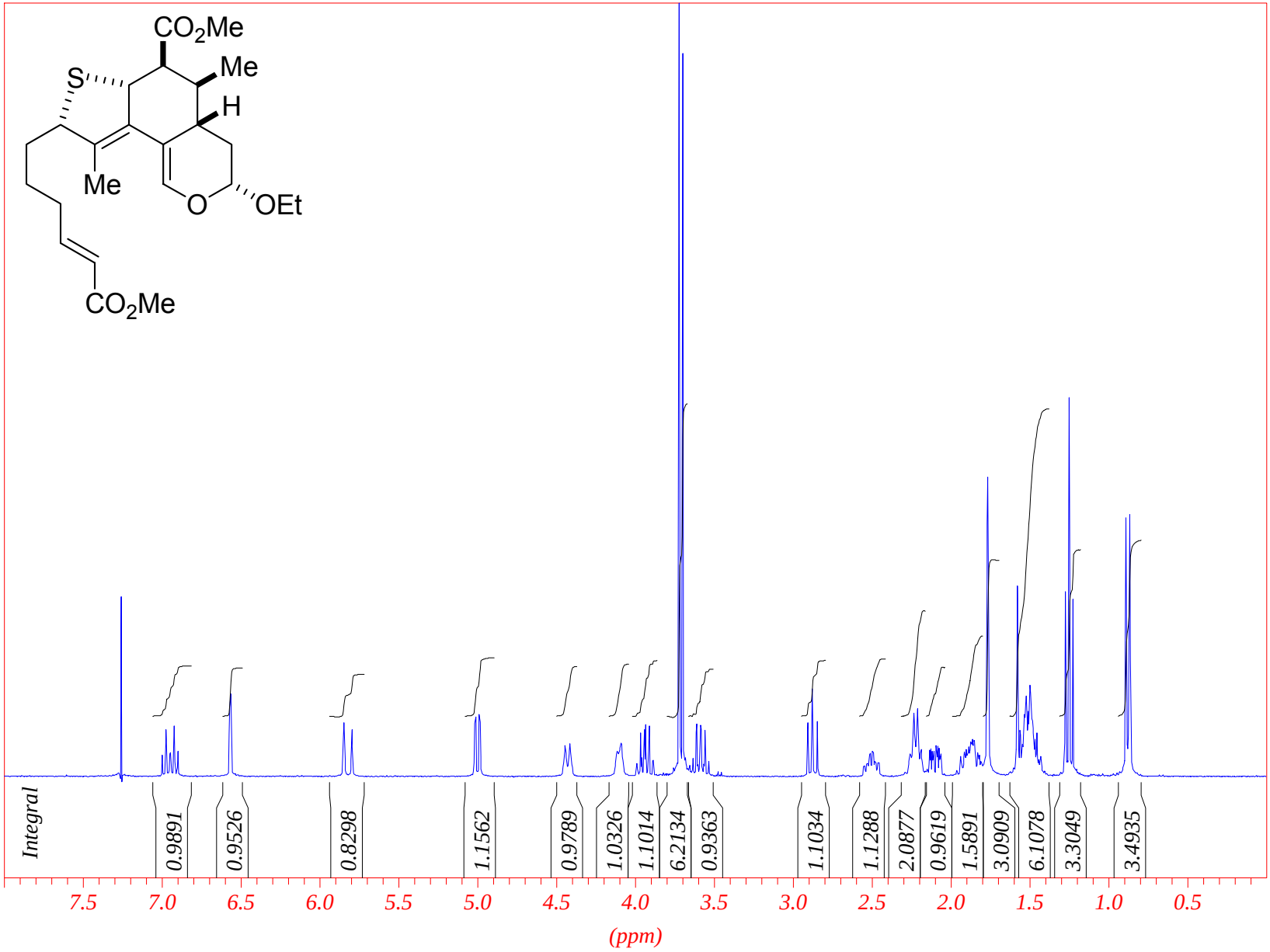
Diol, from the deprotection of 14a



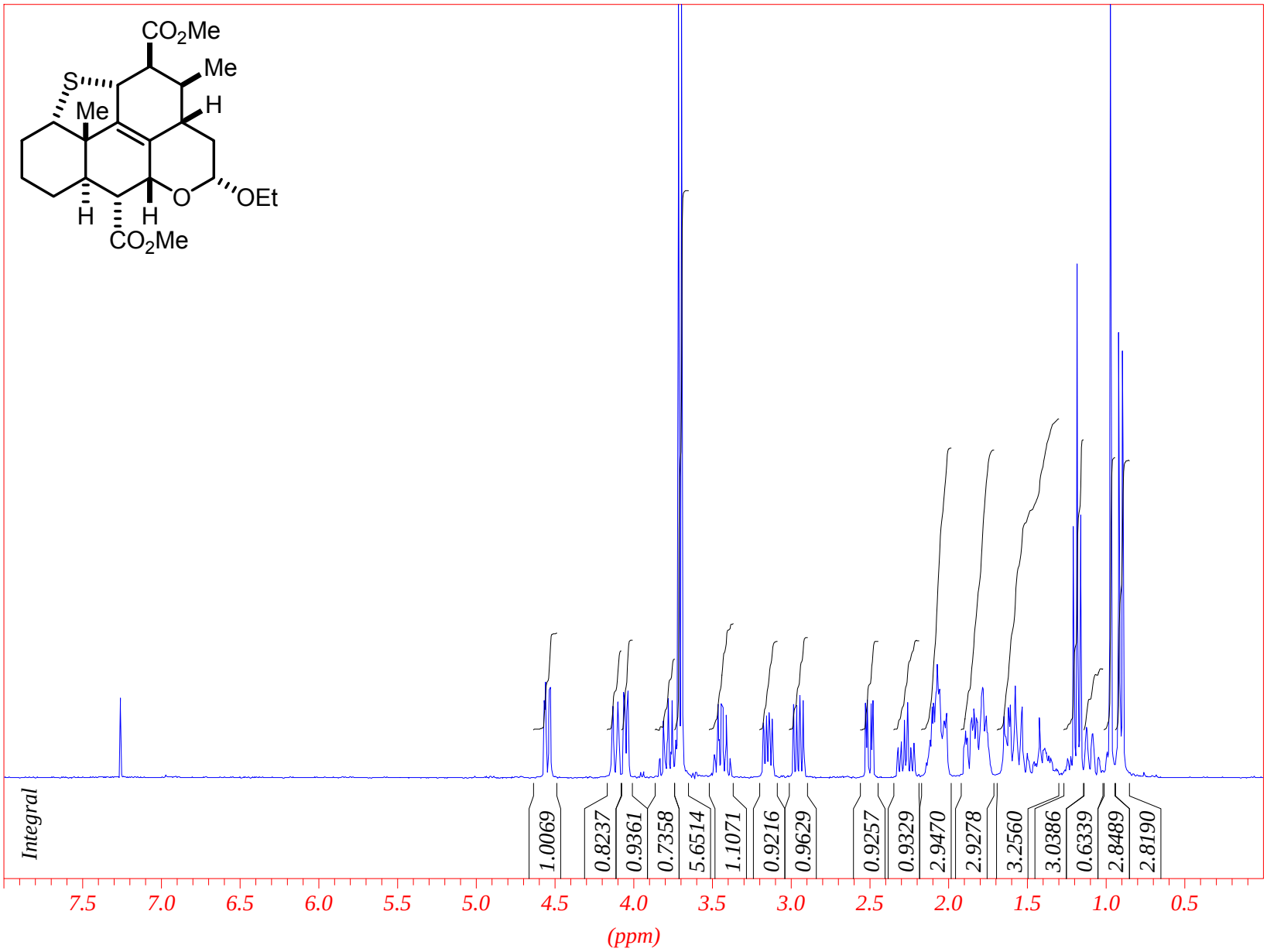
Aldehyde-ester 4



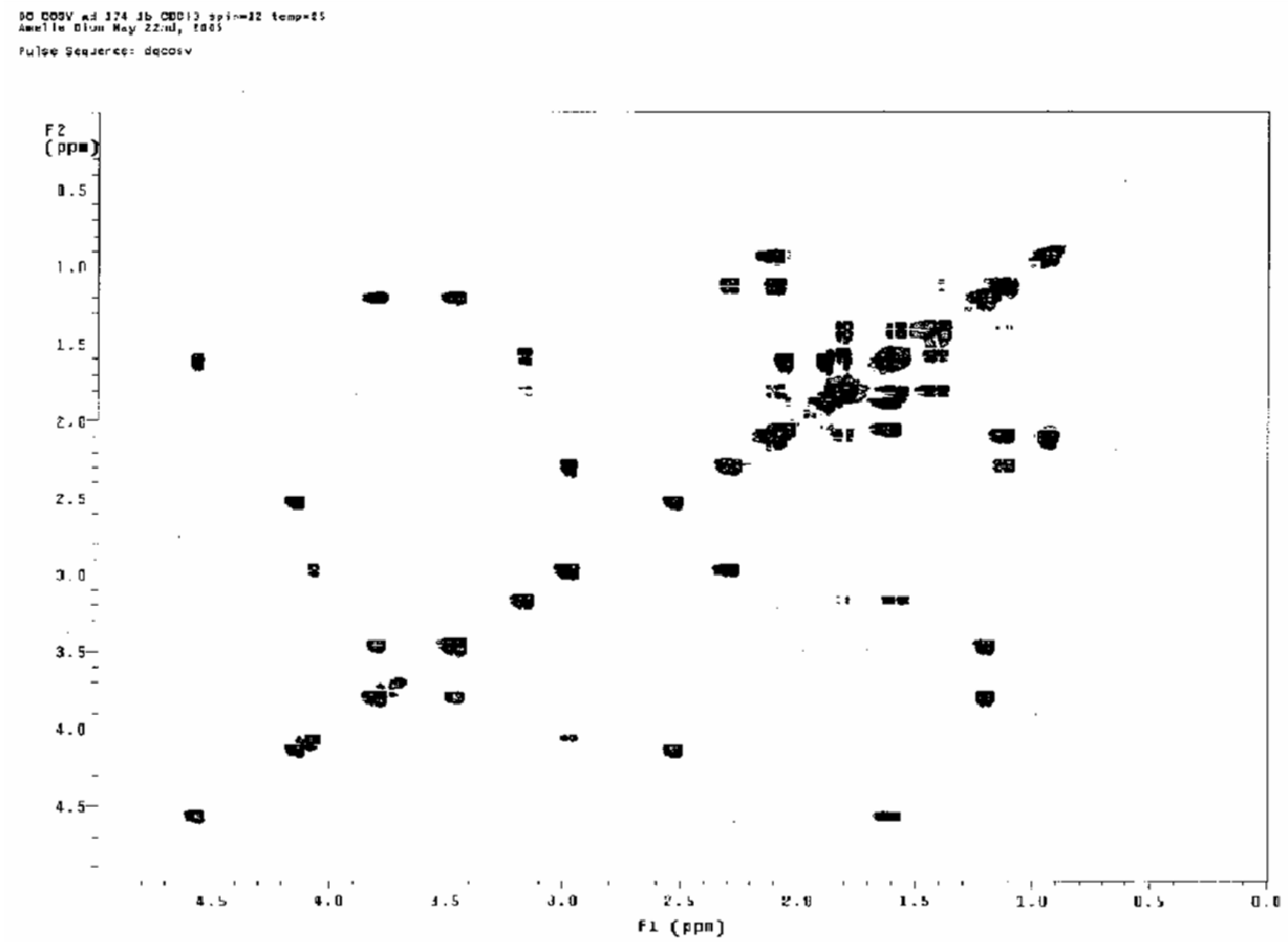
Hetero Diels-Alder adduct 15



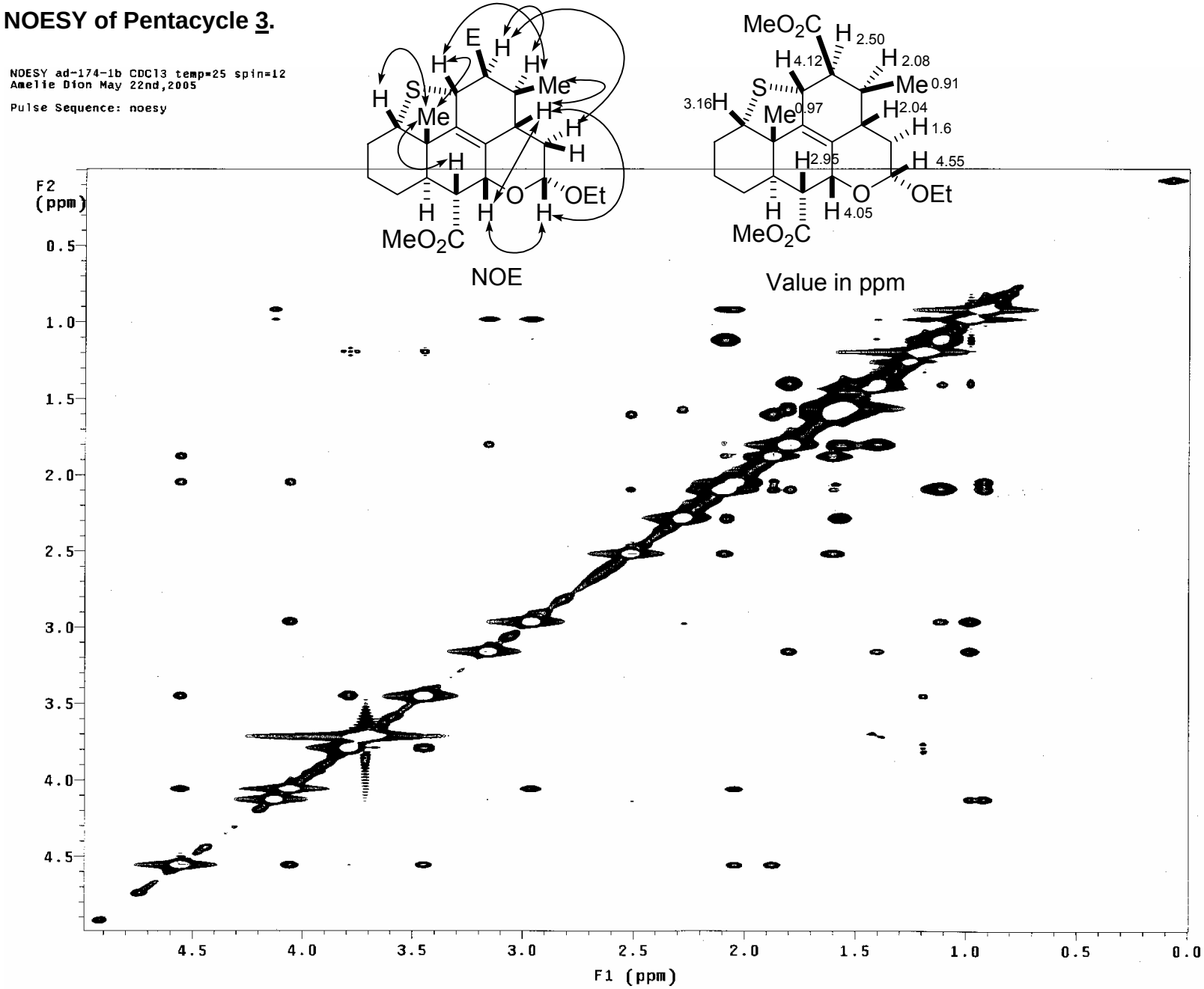
Pentacycle 3.



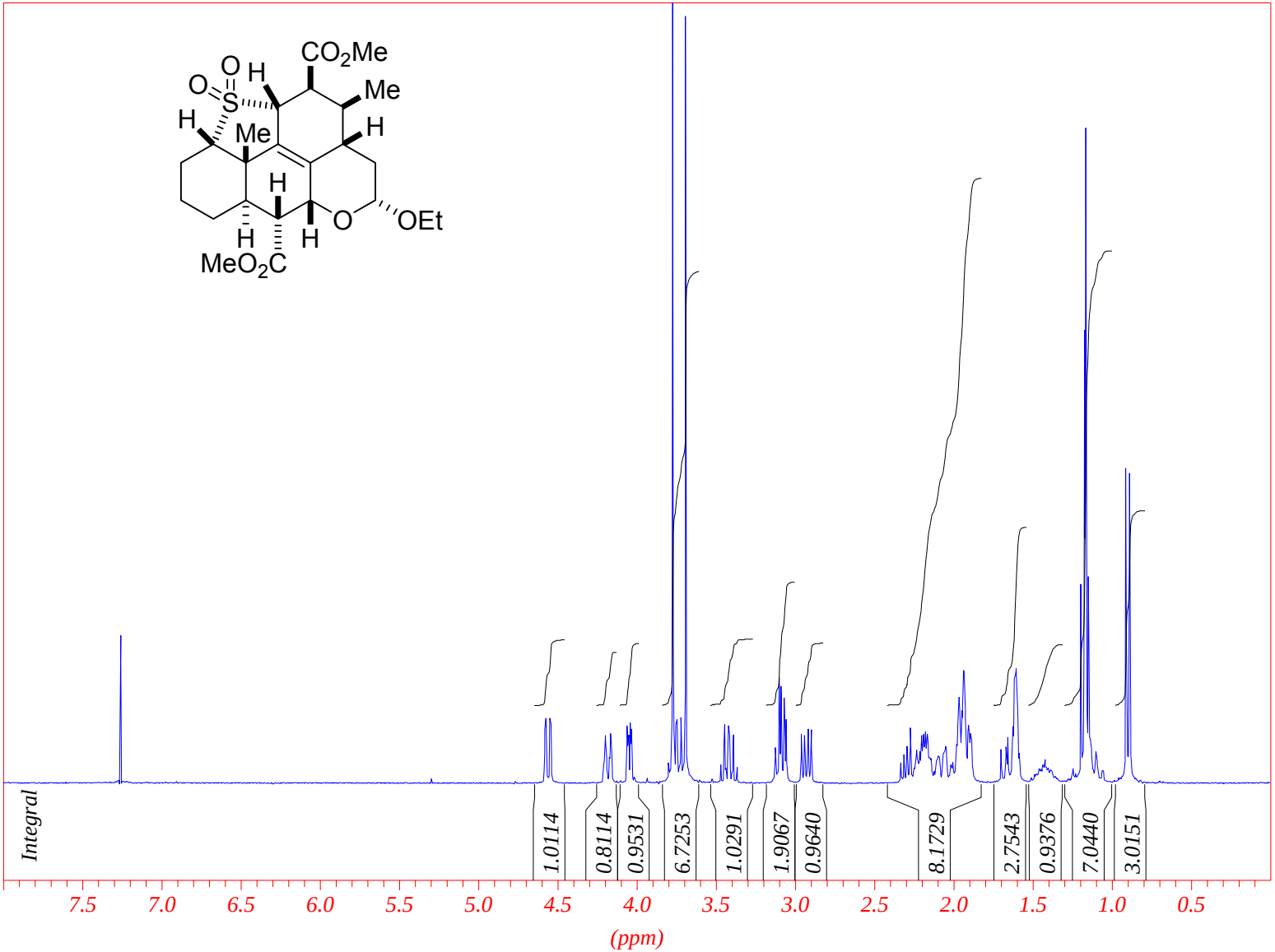
COSY of Pentacycle 3.



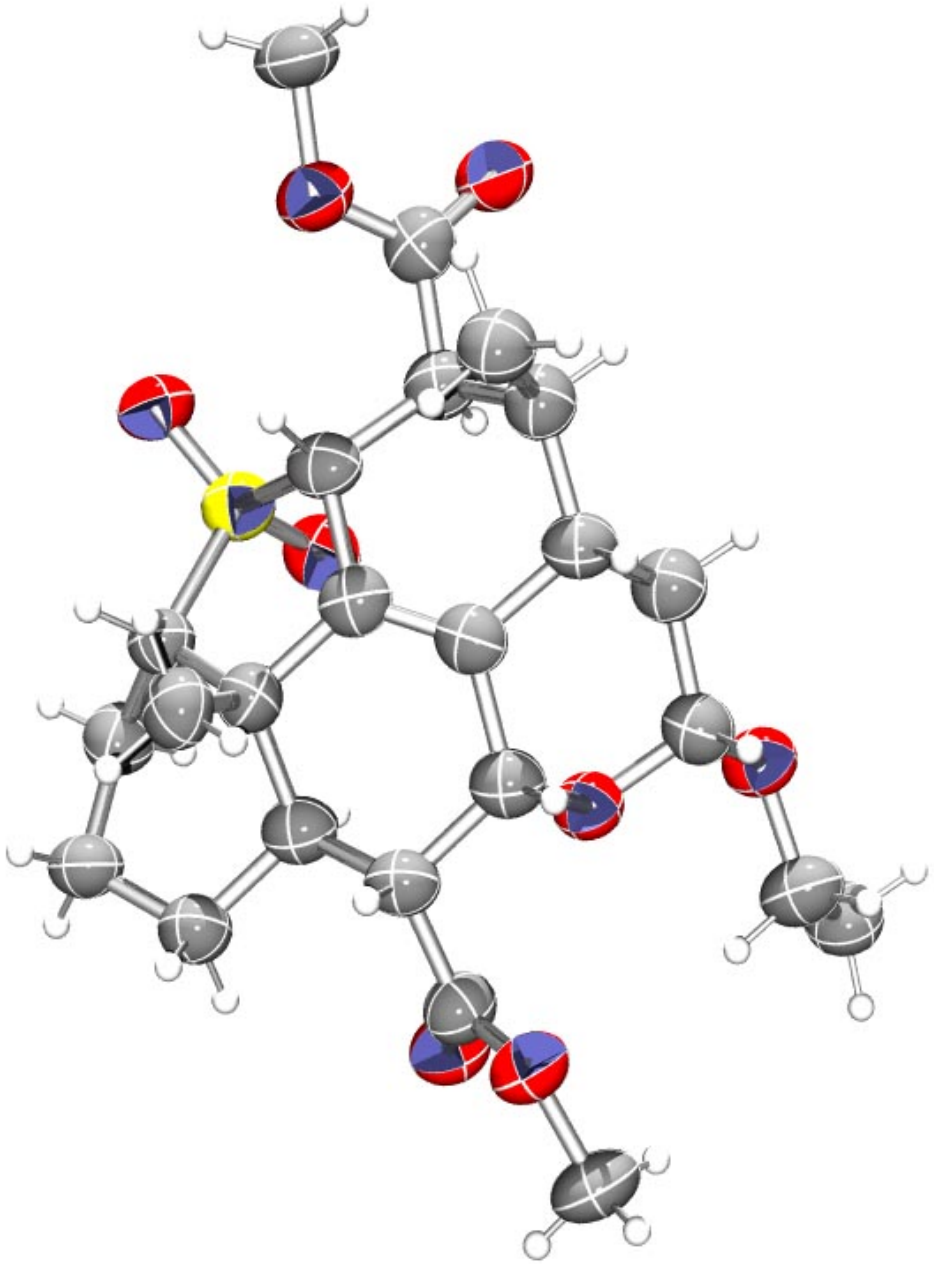
NOESY of Pentacycle 3.



Pentacyclic sulfone <u>16</u>.



ORTEP of pentacyclic sulfone 16.



X-ray data of pentacyclic sulfone 16.

Crystallography:

Experimental : The crystals were grown by slow evaporation of an ethyl acetate solution at room temperature**.** One single crystal of 0.4 X 0.3 X 0.3 mm was mounted in Paratone oil using a glass fiber on the goniometer at 183(2) K. Data were collected on an Enraf-Nonius CAD-4 automatic diffractometer at the Université de Sherbrooke using ω scans. The DIFRAC[(1)] program was used for centering, indexing, and data collection. Two standard reflections were measured every 100 reflections, no intensity decay was observed during data collection. The data were corrected for absorption by numerical methods and reduced with the NRCVAX[(2)] programs. They were solved using SHELXS-97[(3)] and refined by full-matrix least squares on F^2 with SHELXL-97[(4)]. The non-hydrogen atoms were refined anisotropically. The hydrogen atoms were placed at idealized calculated geometric position and refined isotropically using a riding model. The crystal was twinned with a BASF parameter of 0.47(6). For this reason, the final absolute structure[(5)] could not be determined by anomalous dispersion effects.

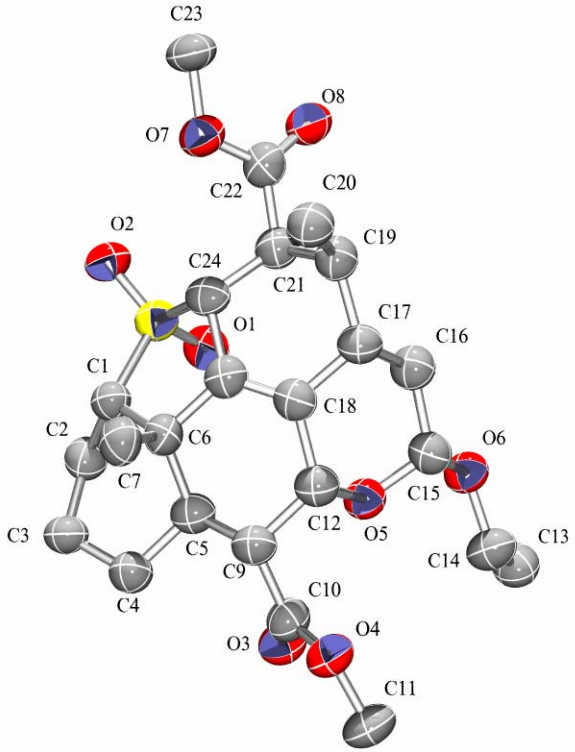
(1) H.D. Flack, E. Blanc and D. Schwarzenbach (1992), *J. Appl. Cryst.*, **25**, 455-459.

(2) E.J. Gabe, Y. Le Page, J.-P. Charland, F.L. Lee, and P.S. White, (1989) *J. Appl. Cryst.*, **22**, 384-387.

(3) G. M. Sheldrick, SHELXS-97, G.M. Sheldrick, University of Göttingen, Germany, 1997, Release 97-2.

(4) G. M. Sheldrick, SHELXL-97, G.M. Sheldrick, University of Göttingen, Germany, 1997, Release 97-2.

(5) Flack H D (1983), Acta Cryst. A39, 876-881.



Ellipsoid probability set at 50%

Table 1. Crystal data and structure refinement for ad451a.

Identification code	ad451a	
Empirical formula	C24 H34 O8 S	
Formula weight	482.59	
Temperature	183(2) K	
Wavelength	1.54176 Å	
Crystal system	Orthorhombic	
Space group	P212121	
Unit cell dimensions	a = 7.848(6) Å	α= 90°.
	b = 15.969(5) Å	β= 90°.
	c = 18.794(6) Å	γ = 90°.
Volume	2355(2) $Å^3$	
Z	4	
Density (calculated)	1.361 Mg/m^3	
Absorption coefficient	1.627 mm^{-1}	
F(000)	1032	
Crystal size	0.4 x 0.3 x 0.3 mm^3	
Theta range for data collection	3.63 to 69.89°.	
Index ranges	0<=h<=9, 0<=k<=19, 0<=l<=22	
Reflections collected	2457	
Independent reflections	2457 [R(int) = 0.0000]	
Completeness to theta = 69.89°	96.1 %	
Absorption correction	Numerical	
Max. and min. transmission	0.5209 and 0.4819	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2457 / 0 / 305	
Goodness-of-fit on F^2	1.071	
Final R indices [I>2sigma(I)]	R1 = 0.0747, wR2 = 0.1997	
R indices (all data)	R1 = 0.0926, wR2 = 0.2210	

Absolute structure parameter	0.47(6)
Extinction coefficient	0.053(5)
Largest diff. peak and hole	0.392 and -0.523 e.Å^{-3}

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for ad451a. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	6237(8)	8476(4)	6746(3)	61(1)
C(2)	6105(9)	9216(4)	6227(4)	67(2)
C(3)	4222(9)	9369(4)	6045(4)	68(2)
C(4)	3170(9)	9592(4)	6694(3)	69(2)
C(5)	4065(8)	9351(4)	7393(3)	62(1)
C(6)	4859(9)	8472(4)	7339(3)	62(1)
C(7)	3552(9)	7775(4)	7180(4)	69(2)
C(8)	5779(8)	8261(4)	8030(3)	62(1)
C(9)	2903(8)	9399(4)	8044(3)	62(1)
C(10)	2131(8)	10262(3)	8159(3)	64(1)
C(11)	72(12)	11015(4)	8804(5)	89(2)
C(12)	3841(9)	9186(4)	8726(4)	66(2)
C(13)	5729(10)	12133(4)	9940(4)	78(2)
C(14)	4870(10)	11300(4)	9907(4)	79(2)
C(15)	5438(9)	9872(4)	9648(4)	68(2)
C(16)	6857(9)	9236(3)	9632(4)	69(2)
C(17)	6187(8)	8396(3)	9339(3)	62(1)
C(18)	5270(8)	8546(3)	8654(3)	61(1)
C(19)	7561(9)	7734(4)	9273(3)	64(2)
C(20)	6833(10)	6849(3)	9289(4)	69(2)
C(21)	8622(8)	7891(3)	8584(3)	63(1)
C(22)	10121(9)	7335(4)	8585(4)	67(2)
C(23)	11349(10)	6068(4)	8184(4)	83(2)
C(24)	7473(8)	7831(3)	7924(3)	63(2)

O(1)	8753(6)	9215(3)	7422(3)	69(1)
O(2)	9461(6)	7937(3)	6763(3)	72(1)
O(3)	2627(6)	10898(3)	7893(3)	75(1)
O(4)	827(5)	10208(3)	8624(3)	70(1)
O(5)	4618(5)	9948(2)	8974(2)	61(1)
O(6)	6121(6)	10658(2)	9803(2)	68(1)
O(7)	10025(6)	6693(3)	8141(3)	74(1)
O(8)	11358(6)	7444(3)	8986(3)	75(1)
S(1)	8247(2)	8398(1)	7174(1)	63(1)

Table 3. Bond lengths [Å] and angles [°] for ad451a.

C(1)-C(2)	1.536(8)
C(1)-C(6)	1.554(9)
C(1)-S(1)	1.775(6)
C(2)-C(3)	1.536(9)
C(3)-C(4)	1.514(9)
C(4)-C(5)	1.540(9)
C(5)-C(9)	1.527(9)
C(5)-C(6)	1.540(8)
C(6)-C(8)	1.523(9)
C(6)-C(7)	1.543(9)
C(8)-C(18)	1.320(9)
C(8)-C(24)	1.510(8)
C(9)-C(12)	1.518(9)
C(9)-C(10)	1.520(8)
C(10)-O(3)	1.196(7)
C(10)-O(4)	1.349(7)
C(11)-O(4)	1.459(8)
C(12)-O(5)	1.438(7)
C(12)-C(18)	1.523(9)
C(13)-C(14)	1.493(9)
C(14)-O(6)	1.432(8)
C(15)-O(6)	1.396(7)
C(15)-O(5)	1.427(7)
C(15)-C(16)	1.507(9)
C(16)-C(17)	1.542(8)
C(17)-C(18)	1.494(9)
C(17)-C(19)	1.515(8)

C(19)-C(20)	1.525(8)
C(19)-C(21)	1.559(9)
C(21)-C(22)	1.474(9)
C(21)-C(24)	1.537(9)
C(22)-O(8)	1.242(8)
C(22)-O(7)	1.323(7)
C(23)-O(7)	1.443(7)
C(24)-S(1)	1.782(6)
O(1)-S(1)	1.440(4)
O(2)-S(1)	1.431(5)

C(2)-C(1)-C(6)	114.4(5)
C(2)-C(1)-S(1)	113.7(5)
C(6)-C(1)-S(1)	107.0(4)
C(3)-C(2)-C(1)	109.2(6)
C(4)-C(3)-C(2)	112.5(6)
C(3)-C(4)-C(5)	112.3(5)
C(9)-C(5)-C(6)	109.9(5)
C(9)-C(5)-C(4)	113.5(5)
C(6)-C(5)-C(4)	110.9(5)
C(8)-C(6)-C(5)	109.7(5)
C(8)-C(6)-C(7)	108.8(5)
C(5)-C(6)-C(7)	113.7(6)
C(8)-C(6)-C(1)	106.4(5)
C(5)-C(6)-C(1)	109.0(5)
C(7)-C(6)-C(1)	109.1(5)
C(18)-C(8)-C(24)	122.7(6)
C(18)-C(8)-C(6)	122.5(6)
C(24)-C(8)-C(6)	113.9(5)

C(12)-C(9)-C(10)	106.1(5)
C(12)-C(9)-C(5)	112.1(5)
C(10)-C(9)-C(5)	113.4(5)
O(3)-C(10)-O(4)	124.8(6)
O(3)-C(10)-C(9)	125.5(6)
O(4)-C(10)-C(9)	109.7(5)
O(5)-C(12)-C(9)	106.8(5)
O(5)-C(12)-C(18)	106.5(5)
C(9)-C(12)-C(18)	115.6(5)
O(6)-C(14)-C(13)	109.5(6)
O(6)-C(15)-O(5)	106.4(5)
O(6)-C(15)-C(16)	109.1(5)
O(5)-C(15)-C(16)	111.9(5)
C(15)-C(16)-C(17)	110.0(6)
C(18)-C(17)-C(19)	112.6(5)
C(18)-C(17)-C(16)	109.5(5)
C(19)-C(17)-C(16)	113.2(5)
C(8)-C(18)-C(17)	124.4(6)
C(8)-C(18)-C(12)	122.2(6)
C(17)-C(18)-C(12)	112.6(5)
C(17)-C(19)-C(20)	112.2(6)
C(17)-C(19)-C(21)	109.6(5)
C(20)-C(19)-C(21)	111.5(5)
C(22)-C(21)-C(24)	115.5(5)
C(22)-C(21)-C(19)	109.2(5)
C(24)-C(21)-C(19)	110.3(5)
O(8)-C(22)-O(7)	122.4(6)
O(8)-C(22)-C(21)	122.7(5)
O(7)-C(22)-C(21)	114.9(6)

C(8)-C(24)-C(21)	112.4(5)
C(8)-C(24)-S(1)	100.0(4)
C(21)-C(24)-S(1)	114.0(4)
C(10)-O(4)-C(11)	113.7(5)
C(15)-O(5)-C(12)	114.0(4)
C(15)-O(6)-C(14)	114.1(5)
C(22)-O(7)-C(23)	117.4(6)
O(2)-S(1)-O(1)	117.2(3)
O(2)-S(1)-C(1)	112.5(3)
O(1)-S(1)-C(1)	109.2(3)
O(2)-S(1)-C(24)	113.1(3)
O(1)-S(1)-C(24)	107.4(3)
C(1)-S(1)-C(24)	95.2(3)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for ad451a. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	66(3)	54(3)	64(3)	-5(2)	-1(3)	2(3)
C(2)	75(4)	59(3)	68(4)	3(3)	0(3)	6(3)
C(3)	70(4)	61(3)	75(4)	2(3)	-6(3)	6(3)
C(4)	69(3)	63(3)	73(4)	-2(3)	-8(3)	2(3)
C(5)	60(3)	54(3)	71(4)	2(2)	-2(3)	2(3)
C(6)	70(3)	57(3)	60(3)	-3(2)	-5(3)	-2(3)
C(7)	80(4)	61(3)	67(3)	-2(3)	-3(3)	-4(3)
C(8)	63(3)	51(3)	71(3)	-3(3)	0(3)	-4(3)
C(9)	61(3)	55(3)	71(3)	6(3)	0(3)	-3(3)
C(10)	68(4)	54(3)	69(3)	5(3)	1(3)	-1(3)
C(11)	99(5)	66(4)	103(5)	-8(4)	10(5)	17(4)
C(12)	69(4)	58(3)	70(4)	0(3)	-1(3)	0(3)
C(13)	83(5)	60(3)	92(4)	0(3)	-4(4)	12(3)
C(14)	77(4)	63(3)	97(5)	-8(3)	-3(4)	8(4)
C(15)	70(4)	61(3)	73(3)	3(3)	-9(3)	-1(3)
C(16)	74(4)	54(3)	78(4)	-1(3)	-7(3)	2(3)
C(17)	66(3)	50(3)	70(3)	4(2)	-2(3)	3(3)
C(18)	68(3)	45(3)	68(3)	1(2)	-2(3)	-8(3)
C(19)	80(4)	54(3)	59(3)	2(2)	3(3)	-5(3)
C(20)	82(4)	53(3)	72(4)	3(2)	1(4)	2(3)
C(21)	71(3)	46(3)	71(3)	-1(2)	5(3)	1(3)
C(22)	72(4)	55(3)	74(4)	-2(3)	1(3)	-9(3)
C(23)	92(5)	60(3)	97(5)	-4(3)	-9(4)	26(4)
C(24)	67(3)	40(2)	81(4)	0(2)	-9(3)	0(3)

O(1)	70(2)	54(2)	83(3)	5(2)	-5(2)	-10(2)
O(2)	70(2)	64(2)	80(3)	3(2)	2(2)	14(2)
O(3)	79(3)	63(2)	83(3)	4(2)	5(2)	8(2)
O(4)	65(2)	58(2)	86(3)	-4(2)	7(2)	4(2)
O(5)	65(2)	49(2)	68(2)	-2(2)	-3(2)	0(2)
O(6)	71(3)	53(2)	78(3)	-7(2)	-6(2)	0(2)
O(7)	78(3)	57(2)	88(3)	-11(2)	-11(3)	13(2)
O(8)	72(3)	65(2)	88(3)	-7(2)	-5(2)	8(2)
S(1)	63(1)	53(1)	74(1)	2(1)	0(1)	-1(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for ad451a.

	x	y	z	U(eq)
H(1)	6082	7964	6466	73
H(2A)	6589	9714	6442	81
H(2B)	6738	9093	5796	81
H(3A)	4144	9820	5701	82
H(3B)	3754	8868	5828	82
H(4A)	2081	9307	6667	82
H(4B)	2951	10190	6693	82
H(5)	4997	9750	7467	74
H(7A)	2736	7747	7560	104
H(7B)	4131	7248	7139	104
H(7C)	2975	7897	6741	104
H(9)	1974	8996	7981	75
H(11A)	-250	11302	8375	134
H(11B)	886	11347	9060	134
H(11C)	-919	10929	9095	134
H(12)	3020	8989	9082	79
H(13A)	6441	12203	9529	118
H(13B)	6414	12164	10362	118
H(13C)	4884	12567	9950	118
H(14A)	4253	11198	10346	95
H(14B)	4059	11292	9517	95
H(15)	4601	9717	10012	81
H(16A)	7300	9154	10109	82

H(16B)	7777	9438	9334	82
H(17)	5345	8185	9680	74
H(19)	8329	7794	9681	77
H(20A)	5971	6795	8930	104
H(20B)	6342	6742	9748	104
H(20C)	7728	6453	9200	104
H(21)	9046	8468	8608	75
H(23A)	11193	5739	8606	124
H(23B)	12441	6339	8200	124
H(23C)	11293	5711	7773	124
H(24)	7293	7242	7796	75