Supplementary Information

The case for a Diels-Alderase-free, bis-pericyclic, [4+2] dimerization in the biosynthesis of (±)-paracaseolide A

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I. General Experimental Protocols

NMR (^{1}H and ^{13}C) spectra were recorded on Bruker Avance 500 (500 MHz) or Varian Inova 500 (500 MHz) spectrometers. ^{1}H NMR chemical shifts ($CDCl_3$, CD_3OD) are referenced to TMS (0.00 ppm) and CHD_2OD (3.31 ppm), respectively. The designation "nfom" is used to denote non-first order multiplets. ^{13}C NMR chemical shifts are referenced to chloroform (77.23 ppm) and methanol (49.15 ppm). The following format is used to report each resonance: chemical shift in ppm (multiplicity, *J* values (coupling constant(s)) in Hz, integral value, and assignment). Coupling constant analysis was aided by protocols we have reported elsewhere.[1] The skeleton of some of the more complex structures are numbered to simplify identification of the proton assignment.

Infrared (IR) spectra were recorded of thin film samples on a ZnSe plate (ATR) on a Prospect MIDAC FT-IR spectrometer. Bands are reported in cm^{-1}.

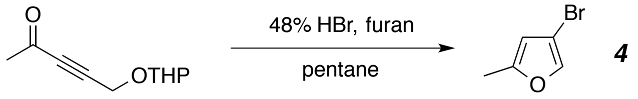
MPLC refers to medium pressure liquid chromatography (50-200 psi) using hand-packed silica gel columns (25-35 µm, 60 Å pores) and a Waters HPLC pump outfitted with a Waters R401 differential refractive index detector. Flash chromatography was carried out on columns packed with E. Merck silica gel (40-63 µm).

Mass spectrometric measurements were made: i) at low resolution on an Agilent 5975 GC-MS instrument using an electron impact ionization method at 70 eV and ii) at high resolution on a Bruker BioTOF II instrument using electrospray ionization and PEG as an internal calibrant.

Optical rotation values were measured on a Rudolph Research Analytical (Autopol III) instrument.

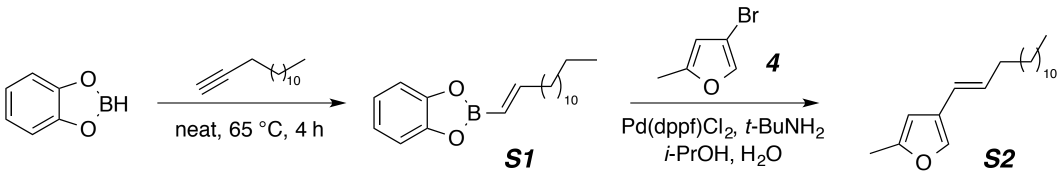
Reactions needing anhydrous conditions were carried out under an atmosphere of argon or nitrogen in flame- or oven-dried glassware. Anhydrous diethyl ether, THF, toluene, and methylene chloride were collected after being passed through a column of activated alumina immediately prior to use.

II. Preparation procedures and characterization data for all key compounds



Preparation of 4-bromo-2-methylfuran (4)

Furan (2 mL) was added to a solution of 5-(tetrahydro-2*H*-pyran-2-yloxy)pent-3-yn-2-one[1] (495 mg, 2.72 mmol) in pentane (8 mL). The solution was cooled to 0 °C in an ice bath and concentrated aqueous hydrobromic acid (48%, 0.4 mL) was added. The reaction mixture was stirred at room temperature for 18 h and a solution of saturated aqueous $NaHCO_3$ was added. The resulting mixture was extracted with pentane (5 mL x 2). The combined organic layers were directly applied to a silica gel column and eluted with pentane. The eluent was concentrated on a rotary evaporator in an ambient temperature bath to a volume of ca. 0.3 mL. NMR analysis of this colorless solution allowed estimation of the percent content of 4-bromo-2-methylfuran **4** (est. 286 mg, 1.78 mmol, 65%). The ^{1}H NMR and MS data were consistent with the structure of this known compound.[1] This material was carried forward into the next reaction.



Preparation of (*E*)-2-methyl-4-(tetradec-1-enyl)furan (S2) via (*E*)-2-(tetradec-1-enyl)benzo[d][1,3,2]dioxaborole (S1)

Under an Ar atmosphere, a 20 mL vial was charged with catecholborane (2.3 mL, 19.2 mmol) and tetradecyne (4.7 mL, 19.1 mmol) and then sealed with a Teflon cap. The mixture was heated to 55 °C for 15 h. The resulting colorless liquid sample of **S1** was used directly without further purification.

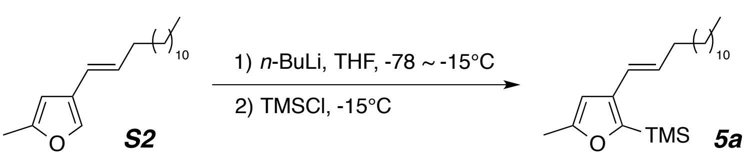
To a solution of 4-bromo-2-methylfuran (**4**, 0.58 g, 3.6 mmol) in *i*-PrOH/H_2O (11.5 mL/5.6 mL) was added Pd(dppf)Cl_2 (53.5 mg, 0.07 mmol, 2 mol%) and *t*-BuNH_2 (1.15 mL, 10.9 mmol). (*E*)-2-(Tetradec-1-enyl)benzo[d][1,3,2]dioxaborole (**S1**, 3.8 mL) was added dropwise. The headspace was flushed with N_2 and the vessel was sealed with a Teflon cap. The mixture was heated to 80 °C for 26 h. The resulting mixture was directly filtered through a short plug of Celite® (EtOAc elution), the filtrate concentrated, and the residue chromatographed on silica (pure hexanes) to afford (*E*)-2-methyl-4-(tetradec-1-enyl)furan (**S2**, 0.95 g, 3.44 mmol, 96%) as a colorless oil.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.19 (d, J = 0.4 Hz, 1H, *H5*), 6.16 (dt, J = 15.7, 1.6 Hz, 1H, ArC*H*=CHCH$_2$), 6.10 (dq, J = 0.4 and 1.0 Hz, 1H, *H3*), 5.86 (dt, J = 15.7, 6.9 Hz, 1H, ArCH=C*H*CH$_2$), 2.25 (d, J = 1.0 Hz, 3H, Ar-C*H*$_3$), 2.12 (ddt, J = 7.0, 1.5, 7.0 Hz, 2H, ArCH=CHC*H*$_2$), 1.41 (br quintet, 2H, CH=CHCH$_2$C*H*$_2$), 1.34–1.19 (m, 18H), and 0.88 (t, J = 7.0 Hz, 3H, CH$_2$C*H*$_3$).

^{13}C NMR (125 MHz, $CDCl_3$) δ 153.1, 137.9, 130.5, 125.7, 119.8, 103.7, 33.1, 32.2, 29.9 (4C), 29.8, 29.7, 29.6, 29.5, 22.9, 14.3, and 13.8.

IR (neat): 2924, 2853, 1687, 1606, 1544, 1464, 1381, 1126, 959, 917, 797, and 735 cm^{-1}.

GC-LRMS (ES, 70 eV): t_R = 10.08 min. *m/z*: 276 (M^+), 135 (M^+-$C_{10}H_{21}$) and 121 (M^+-$C_{11}H_{23}$).



S2 **5a**

Preparation of (*E*)-trimethyl(5-methyl-3-(tetradec-1-enyl)furan-2-yl)silane (5a)

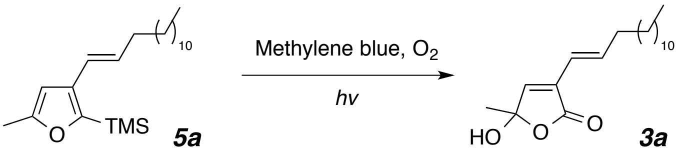
To a dry 100 mL flask was added (*E*)-2-methyl-4-(tetradec-1-enyl)furan (**S2**, 0.95 g, 3.44 mmol) and THF (20 mL). The headspace was flushed with N_2 and the mixture was cooled to -78 °C in a dry ice-acetone acetone bath. *n*-BuLi (2.7 mL, 6.75 mmol, 2.5 M solution in hexanes) was added dropwise. The mixture was allowed to warm to -10 °C over 40 min, and freshly distilled TMSCl (0.74 g, 6.8 mmol) was added. The mixture was allowed to stir at room temperature for 1 h and saturated aqueous NH_4Cl was added. The water layer was extracted with diethyl ether. The combined organic phase was dried over Na_2SO_4, filtered, and concentrated to give (*E*)-trimethyl(5-methyl-3-(tetradec-1-enyl)furan-2-yl)silane (**5a**, 1.0 g, 3.0 mmol, 86%) as a colorless oil that was used without further purification.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.31 (ddt, *J* = 15.6, 0.3, 1.5 Hz, 1H, ArC*H*=CH), 6.12 (br s, 1H, Ar*H*), 5.86 (dt, *J* = 15.5, 7.0 Hz, 1H, ArCH=C*H*), 2.27 (d, *J* = 0.9 Hz, 3H, Ar-CH_3), 2.13 (ddt, *J* = 7.0, 1.6, 7.0 Hz, 2H, CH=CHCH_2), 1.45–1.35 (m, 2H, CH=CHCH_2CH_2), 1.34–1.20 (m, 18H), 0.88 (t, *J* = 6.9 Hz, 3H, CH_2CH_3), and 0.29 (s, 9H, Si(CH_3)$_3$).

^{13}C NMR (125 MHz, $CDCl_3$) *δ* 156.4, 154.3, 135.5, 130.7, 121.1, 104.0, 33.3, 32.2, 29.9 (2C), 29.8, 29.7 (2C), 29.6, 29.4 (2C), 22.9, 14.4, 13.9, and 0.6.

IR (neat): 2954, 2923, 2853, 1248, 957, 841, 794, and 758 cm^{-1}.

GC-LRMS (ES, 70 eV): t_R = 10.90 min. *m/z*: 348 (M^+), 333 (M^+-CH_3), 275 (M^+-TMS), and 73 (TMS^+).



5a **3a**

Preparation of (±)-(*E*)-5-hydroxy-5-methyl-3-(tetradec-1-enyl)furan-2(5*H*)-one (3a)

Methylene blue (1 mg) was added to a solution of (*E*)-trimethyl(5-methyl-3-(tetradec-1-enyl)furan-2-yl)silane (**5a**, 0.90 g, 2.59 mmol) in CH_2Cl_2 (50 mL) in a round bottomed flask. The mixture was cooled to -40 °C in a dry ice-acetone bath. O_2 was introduced into the solution via a fritted glass tube. A 175 W mercury lamp was placed directly above the reaction flask (distance < 5 cm). After 1.5 h full consumption of furan **5a** was confirmed by TLC analysis. The mixture was concentrated and purified by flash column chromatography to give (*E*)-5-hydroxy-5-methyl-3-(tetradec-1-enyl)furan-2(5H)-one (**3a**) as a colorless waxy solid (602 mg, 1.95 mmol, 76%), whose spectral data closely matched those reported for this butenolide.[2,3,4,5,6]

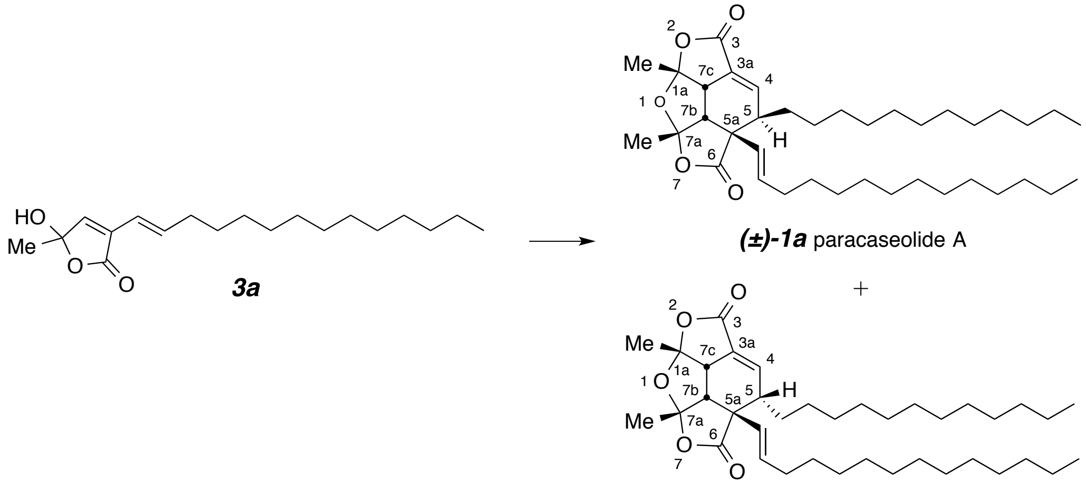
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.84 (br dt, *J* = 15.8, 7.1 Hz, 1H, CH=C*H*CH$_2$), 6.83 (br s, 1H, C(OH)(CH$_3$)C*H*=C), 6.07 (dt, *J* = 15.8, 1.7 Hz, 1H, C*H*=CHCH$_2$), 2.87 (br s, 1H, -O*H*), 2.17 (ddt, *J* = 1.6, 7.1, 7.4 Hz, 2H, CH=CHCH_2), 1.71 (s, 3H, C(OH)-CH_3), 1.47–1.40 (m, 2H, CH=CHCH$_2$CH_2), 1.35–1.21 (m, 18H), and 0.88 (t, *J* = 7.0 Hz, 1H, CH$_2$CH_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1, 144.0, 141.4, 131.1, 118.0, 104.1, 33.7, 32.1, 29.9 (3C), 29.8, 29.7, 29.6, 29.5, 28.9, 25.1, 22.9, and 14.3.

IR (neat): 3356, 2924, 2853, 1746, 1662, 1463, 1414, 1372, 1260, 1170, 1106, 1056, 971, and 931 cm^{-1}.

HRMS (ESI-TOF): Calcd for $(C_{19}H_{33}O_3)^+$ 309.2424. Found: 309.2412

mp 36–42 °C.



3a

(±)-1a paracaseolide A

(±)-S3 5-*epi*-paracaseolide A

Preparation of (±)-paracaseolide A (1a*R*,5*R*,5a*S*,7a*S*,7b*R*,7c*S*)-rel-(±)-5-dodecyl-1a,5,5a,7a,7b,7c-hexahydro-1a,7a-dimethyl-5a-(1*E*)-1-tetradecen-1-yldifuro[2,3,4-cd:4',3',2'-hi]isobenzofuran-3,6-dione [(±)-1a] and its C5-epimer (1a*R*,5*S*,5a*S*,7a*S*,7b*R*,7c*S*)-rel-(±)-5-dodecyl-1a,5,5a,7a,7b,7c-hexahydro-1a,7a-dimethyl-5a-(1*E*)-1-tetradecen-1-yldifuro[2,3,4-cd:4',3',2'-hi]isobenzofuran-3,6-dione [(±)-S3]

(±)-(*E*)-5-Hydroxy-5-methyl-3-(tetradec-1-enyl)furan-2(5H)-one (**3a**, 33.2 mg, 0.11 mmol) was placed in a 1 mL vial with a Teflon cap. The headspace was flushed with Ar. The reaction vial was heated to 110 °C for 43 h. The crude mixture was directly subjected to flash column chromatography on silica gel (hexanes:ethyl acetate = 12:1, then 5:1, then 3:1) to give (±)–paracaseolide A (**1a**, 13.4 mg, 42%) and (±)–5-*epi*-paracaseolide A (**S3,** 2.0 mg, 7%), each as a white powder.

(±)–paracaseolide A (1a):[2,3,4,5,6,7]

^{1}**H NMR** (CDCl$_3$, 500 MHz): δ 7.25 (dd, J = 7.6, 3.2 Hz, 1H, *H*4), 5.83 (dt, J = 15.7, 6.9 Hz, 1H, HC=C*H*CH$_2$), 5.49 (dt, J = 15.8, 1.5 Hz, 1H, *H*C=CHCH$_2$), 3.37 (dd, J = 9.5, 3.3 Hz, 1H, *H*7c), 3.30 (d, J = 9.6 Hz, 1H, *H*7b), 3.04 (ddd, J = 11.6, 7.6, 3.7 Hz, 1H, *H*5), 2.11 (ddt, J = 1.3, 7, 7 Hz, 2H, HC=CHC*H*$_2$), 1.76 [s, 3H, C(1a)C*H*$_3$], 1.71–1.64 [m, 1H, C(5)C*H*$_a$H$_b$], 1.62 [s, 3H, C(7a)C*H*$_3$], 1.45–1.34 (m, 2H, HC=CHCH$_2$C*H*$_2$), 1.34–1.16 (m, many H), 1.20–1.05 [m, 1H, C(5)CH$_a$*H*$_b$], and 0.88 [t, J = 7.0 Hz, 6H, (C*H*$_3$CH$_2$)$_2$].

^{13}**C NMR** (125 MHz, CDCl$_3$) δ 175.3, 166.4, 144.9, 135.3, 129.5, 126.5, 115.6, 114.0, 58.5, 50.5, 46.9, 45.3, 32.9, 32.1 (2x), 29.91, 29.88 (2x), 29.87 (2x), 29.86 (2x), 29.84 (2x), 29.77, 29.64 (2x), 29.58 (2x), 29.3, 29.2, 28.4, 28.2, 26.8, 25.9, 22.9 (2x), and 14.3 (2x).

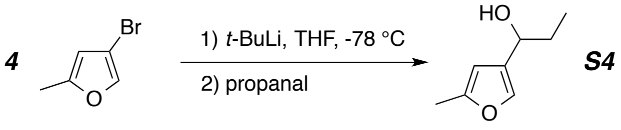
IR (neat): 2923, 2853, 1774, 1465, 1390, 1312, 1272, 1129, 1056, and 913 cm^{-1}.

HRMS (ESI-TOF): Calcd for (C$_{38}$H$_{62}$NaO$_5$)$^+$ 621.4489, Found: 621.4499.

mp 59–64 °C.

(±)–5-*epi*-paracaseolide A (S3):[4,5]

^{1}**H NMR** (CDCl$_3$, 500 MHz): δ 6.98 (dd, J = 4.2, 3.5 Hz, 1H, *H*4), 5.69 (dt, J = 15.7, 6.9 Hz, 1H, HC=C*H*CH$_2$), 5.43 (dt, J = 15.7, 1.4 Hz, 1H, *H*C=CHCH$_2$), 3.27 (ddd, J = 9.9, 3.3, 2.0, *H*7c), 3.20 (d, J = 9.9 Hz, 1H, *H*7b), 2.20–2.07 (m, 3H, *H*5, CH=CHC*H*$_2$), 2.01 [dddd, J = 13.8, 12.1, 10.2, 4.6 Hz, 1H, C(5)HC*H*$_a$H$_b$], 1.75 (dddd, J = 13.6, 10.6, 6.0, 3.0 Hz, 1H, C(5)HCH$_a$*H*$_b$] 1.74 [s, 3H, C(1a)C*H*$_3$], 1.59 [s, 3H, C(7a)C*H*$_3$], 1.53–1.45 (m, 1H), 1.41–1.35 (m, 2H), 1.35–1.17 (m, many H), and 0.88 [t, J = 7.0 Hz, 6H, (C*H*$_3$CH$_2$)$_2$].



Preparation of 1-(5-methylfuran-3-yl)propan-1-ol (S4)

An oven-dried 250 mL round bottom flask was charged with dry THF (75 mL). The flask was cooled to -78 °C before dropwise addition of a solution of *t*-BuLi (38 mL, 1.7 M, in hexanes; 65 mmol). 4-Bromo-2-methylfuran (**4**) containing ca. 5 wt% of pentane (4.98 g, 29 mmol) was added dropwise at -78 °C to form an orange solution. This mixture was stirred at -78 °C for 10 min before dropwise addition of dry propionaldehyde (6 mL, 84 mmol). The reaction mixture was allowed to warm to room temperature, quenched with aqueous NH_4Cl solution, and extracted with ethyl acetate The organic layer was washed with brine, dried with Na_2SO_4, filtered, concentrated, and subjected to flash column chromatography on silica gel (hexanes:ethyl acetate = 5:1) to give 1-(5-methylfuran-3-yl)propan-1-ol (**S4**, 3.8 g, 95% yield) as a colorless liquid.

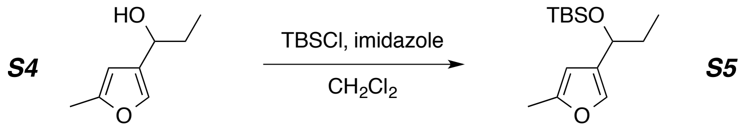
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (br s, 1H, *H2*), 5.98 (br s, 1H, *H4*), 4.49 (br t, *J* = 6.5 Hz, 1H, C*H*(OH)CH_2), 2.27 (s, 3H, ArC*H₃*), 1.75 (ddq, *J* = 14, 7.4, 7.4 Hz, 1H, $CH_aH_bCH_3$), 1.71 (ddq, *J* = 14, 7.2, 7.2 Hz, 1H, $CH_aH_bCH_3$), 1.71 (br s, 1H, OH), and 0.93 (t, *J* = 7.5 Hz, 3H, CH_2CH_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 153.1, 137.4, 129.9, 104.6, 68.8, 30.8, 13.8, and 10.2.

IR (neat): 3384, 2964, 2933, 2877, 1555, 1452, 1381, 1266, and 1208 cm^{-1}.

HRMS (ESI-TOF): Calcd for $(C_{19}H_{33}O_3)^+$ 309.2424. Found: 309.2412.

GC-LRMS (ES, 70 eV): t_R = 4.08 min. *m/z*: 140 (M^+), 111 (M^+-CH_2CH_3), and 83 (M^+-$COCH_2CH_3$).



Preparation of *tert*-butyldimethyl(1-(5-methylfuran-3-yl)propoxy)silane (S5)

To a CH_2Cl_2 (150 mL) solution of 1-(5-methylfuran-3-yl)propan-1-ol (**S4**, 3.6 g, 26 mmol) was added TBSCl (8.8 g, 58 mmol) and imidazole (3.9 g, 58 mmol) at room temperature. The reaction mixture was stirred for 20 h, and the resulting slurry was filtered through a cotton plug, using DCM to wash the solid filter cake. The filtrate was concentrated and the residue redissolved in ethyl acetate. This solution was washed with deionized water, dried over Na_2SO_4, filtered, and concentrated. The residue was purified using flash column chromatography on silica gel (hexanes:ethyl acetate = 12:1) to give *tert*-butyldimethyl(1-(5-methylfuran-3-yl)propoxy)silane (**S5**, 5.9 g, 90% yield) as a colorless liquid.

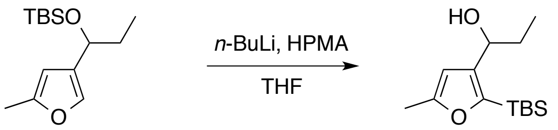
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.11 (br s, 1H, *H2*), 5.90 (br s, 1H, *H4*), 4.51 (t, *J* = 6.0 Hz, 1H, C*H*(OTBS)CH_2CH_3), 2.25 (s, 3H, ArC*H₃*), 1.67 (ddq, *J* = 6.7, 13.9, 7.4 Hz, 1H, $CH_aH_bCH_3$), 1.61 (ddq, *J* = 5.8, 13.9, 7.6 Hz, 1H, $CH_aH_bCH_3$), 0.88 (s, 9H, $SiC(CH_3)_3$), 0.86 (t, *J* = 7.4 Hz, 3H, CH_2CH_3), 0.04 (s, 3H, $SiMe_aMe_b$), and –0.04 (s, 3H, $SiMe_aMe_b$).

^{13}C NMR (125 MHz, $CDCl_3$) δ 152.4, 137.1, 130.8, 105.0, 69.3, 32.4, 26.1, 18.5, 13.9, 9.9, –4.4, and –4.7.

IR (neat): 2958, 2930, 2858, 1473, 1255, 1059, 1017, 836, and 776 cm^{-1}.

GC-LRMS (ES, 70 eV): t_R = 6.09 min. *m/z*: 239 (M^+-CH_3), 225 (M^+-CH_2CH_3), and 197 (M^+-$C(CH_3)_3$).

S5



S6

Preparation of 1-(2-(*tert*-butyldimethylsilyl)-5-methylfuran-3-yl)propan-1-ol (S6)

To a solution of *tert*-butyldimethyl(1-(5-methylfuran-3-yl)propoxy)silane (**S5**, 5.4 g, 21 mmol) in dry THF (330 mL) was added HPMA (4.2 mL, 24 mmol) at room temperature. The reaction flask was then cooled to 0 °C followed by dropwise addition of *n*-BuLi solution (15 mL, 2.5 M in hexanes). The reaction solution was allowed to warm to room temperature and stirred for 45 min before being quenched by the addition of Et_2O and aqueous NH_4Cl solution. The organic layer was washed with brine, dried with Na_2SO_4, and concentrated. The residue was purified using flash column chromatography on silica gel (hexanes:ethyl acetate = 5:1) to give 1-(2-(*tert*-butyldimethylsilyl)-5-methylfuran-3-yl)propan-1-ol (**S6**, 4.67 g, 86% yield) as an off-white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.05 (s, 1H, Ar-*H*), 4.58 (dt, J = 2.4, 6.9 Hz, 1H, C*H*(OH)), 2.28 (s, 3H, ArCH_3), 1.82 (ddq, J = 7.3, 14.3, 7.3 Hz, 1H, CH(OH)CH_aH$_b$), 1.66 (ddq, J = 7.3, 14.3, 7.3 Hz, 1H, CH(OH)CH_aH$_b$), 0.92 (s, 9H, SiC(CH_3)$_3$), 0.91 (t, J = 7.3 Hz, 3H, CH$_2$CH_3), 0.27 (s, 3H, SiMe_aMe$_b$), and 0.25 (s, 3H, SiMe$_a$$Me_b$).

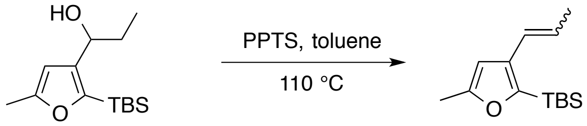
^{13}C NMR (125 MHz, $CDCl_3$) δ 156.9, 152.7, 140.9, 104.2, 68.6, 31.2, 26.7, 17.4, 14.1, 10.83, –4.84 and –5.14.

IR (neat): 3366, 2956, 2930, 2858, 1606, 1523, 1471, 1463, 1249, 836, and 826 cm^{-1}.

HRMS (ESI-TOF): Calcd for $(C_{14}H_{26}NaO_2Si)^+$ 277.1594. Found: 277.1596.

mp 52.1–56.5 °C .

S6



5b

Preparation of *E*- and *Z*-*tert*-butyldimethyl(5-methyl-3-(prop-1-en-1-yl)furan-2-yl)silanes (5b)

To a solution of 1-(2-(*tert*-butyldimethylsilyl)-5-methylfuran-3-yl)propan-1-ol (**S6**, 1.0 g, 4 mmol) in dry toluene (80 mL) was added *p*-toluenesulfonic acid (15 mg, 0.08 mmol) and 4 Å molecular sieves (ca. 1 g) at room temperature. A reflux condenser was attached and the reaction flask was placed in a 110 °C oil bath and stirred for 2 h. The reaction mixture was then cooled to room temperature and filtered through Celite. The filtrate was concentrated and the residue purified with flash column chromatography on silica gel (pure hexanes) to give a coeluting, 5:1 *E*/*Z* mixture of *tert*-butyldimethyl(5-methyl-3-(prop-1-en-1-yl)furan-2-yl)silane (**5b**, 0.73 g, 78% yield) as a colorless liquid. If the reaction mixture was quenched and worked-up by partitioning between aqueous and organic layers, the resulting crude material showed a decided tendency to decompose (to a red-colored non-elutable material) when subjected to silica gel. The following data were extracted from the spectra of the mixture.

(*E*)-*tert*-Butyldimethyl(5-methyl-3-(prop-1-en-1-yl)furan-2-yl)silane (*E*-5b):

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.33 (ddq, J = 0.6, 15.5, 1.7 Hz, 1H, C*H*=CHCH$_3$), 6.11 (dq, J = 0.5, 1.0 Hz, 1H, Ar-*H*), 5.87 (dq, J = 15.5, 6.6 Hz, 1H, CH=C*H*CH$_3$), 2.26 (d, J = 0.9 Hz, 3H, Ar-CH_3), 1.81 (dd, J = 1.7, 6.7 Hz, 3H, CH=CHCH_3), 0.90 (s, 9H, SiC(CH_3)$_3$), and 0.27 (s, 6H, Si(CH_3)$_2$).

^{13}C NMR (125 MHz, $CDCl_3$) δ 156.5, 152.9, 136.5, 124.9, 122.9, 103.9, 26.7, 18.8, 17.8, 13.9, and –5.29.

GC-LRMS (ES, 70 eV): t_R = 6.35 min. *m/z*: 236 (M^+), and 179 (M^+-C(CH$_3$)$_3$).

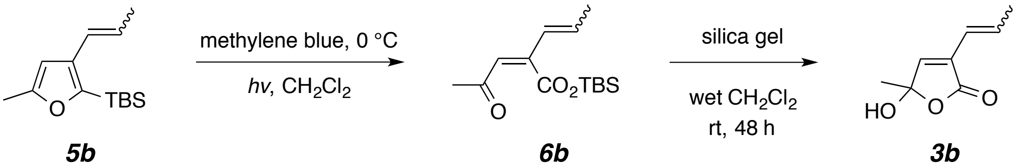
(*Z*)-*tert*-Butyldimethyl(5-methyl-3-(prop-1-en-1-yl)furan-2-yl)silane (*Z*-5b):

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.33 (ddq, *J* = 0.5, 11.4, 1.8 Hz, 1H, C*H*=CHCH$_3$), 6.18 (dq, *J* = 0.5, 0.9 Hz, 1H, Ar-*H*), 5.57 (dq, *J* = 7.1, 11.5 Hz, 1H, CH=C*H*CH$_3$), 2.30 (d, *J* = 0.9 Hz, 3H, Ar-C*H$_3$*), 1.84 (dd, *J* = 1.8, 7.1 Hz, 3H, CH=CHC*H$_3$*), 0.90 (s, 9H, SiC(C*H$_3$*)$_3$), and 0.25 (s, 6H, Si(C*H$_3$*)$_2$).

^{13}C NMR (125 MHz, $CDCl_3$) δ 156.5, 152.9, 136.5, 125.2, 122.1, 107.3, 26.7, 18.8, 17.8, 14.9, and –5.29.

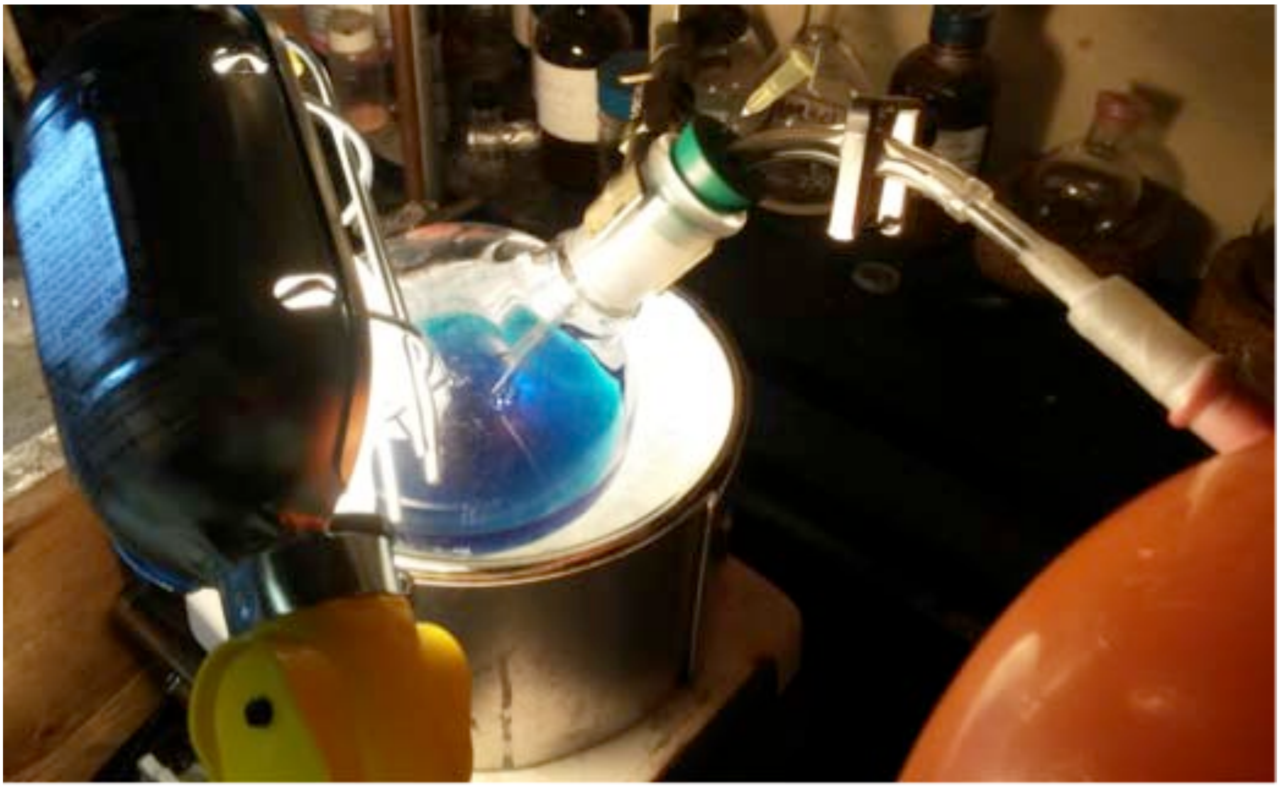
GC-LRMS (ES, 70 eV): t_R = 6.22 min. *m/z*: 236 (M^+), and 179 (M^+-$C(CH_3)_3$).

IR (neat, of the *E/Z* mixture of alkenes): 2954, 2928, 2857, 1604, 1502, 1463, 1249, 1111, and 957 cm^{-1}.



Preparation of 5-hydroxy-5-methyl-3-(prop-1-en-1-yl)furan-2(5H)-one (3b) via (2*Z*)-*tert*-butyldimethylsilyl 4-oxo-2-(prop-1-en-1-yl)pent-2-enoate (6b).

Methylene blue (5 mg) was added to a solution of *tert*-butyldimethyl(5-methyl-3-(prop-1-en-1-yl)furan-2-yl) silane (**5b**, 1.83 g, 7.7 mmol) in CH_2Cl_2 (250 mL) in a round bottomed flask. The mixture was cooled to 0 °C in an ice-water bath. O_2 was introduced into the solution by slow bubbling through a fritted glass tube fitted into a stopper or septum that contained a vent needle. A common 75 W incandescent light bulb was placed directly above the reaction flask (distance < 5 cm). (See photo below of a typical set-up for the experiment.) Ice was periodically added to maintain sub-ambient temperature. After 7 h full consumption of furan **5b** was confirmed by TLC analysis. The mixture was concentrated through a short plug of silica gel with CH_2Cl_2 elution to give a 6:1 *E*/*Z* crude mixture of (2*Z*)-*tert*-butyldimethylsilyl 4-oxo-2-(prop-1-en-1-yl)pent-2-enoate (**6b**) as a pale yellow liquid (2.55 g, 123% mass recovery). Because of the propensity of this silyl ester to undergo desilylation during attempts at more careful chromatographic treatments, this crude mixture was directly used for dimerization studies without further purification.



(2*E*)-*tert*-butyldimethylsilyl 4-oxo-2-((1*E*)-prop-1-en-1-yl)pent-2-enoate (*Z*-6b):

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.12 (ddq, *J* = 0.6, 15.7, 6.2 Hz, 1H, C*H*CH_3), 6.08 (br d, *J* = 15.7 Hz, 1H, C*H*=$CHCH_3$), 5.97 (br s, 1H, C*H*C(=O)CH_3), 2.23 (s, 3H, C(=O)C*H*$_3$), 1.88 (br d, *J* = 5.2 Hz, 3H, CHC*H*$_3$), 0.94, (s, 9H, $SiMe_2C(CH_3)_3$), and 0.42 (s, 6H, $Si(CH_3)_2C(CH_3)_3$).

^{13}C NMR (125 MHz, $CDCl_3$) δ 196.3, 168.2, 147.0, 138.2, 128.6, 122.6, 30.5, 25.7, 19.3, 17.9, and -4.7.

GC-LRMS (ES, 70 eV): t_R = 7.54 min. *m/z*: 268 (M^+), 253 ($M^+ – CH_3$) and 211 ($M^+ – C(CH_3)_3$).

(2*Z*)-*tert*-butyldimethylsilyl 4-oxo-2-((1*Z*)-prop-1-en-1-yl)pent-2-enoate (*Z*-6b):

^{1}H NMR (500 MHz, $CDCl_3$) δ obscured under resonances of major isomer between 6.06–6.16 (1H, C*H*C(=O)CH_3), 5.96 (ddq, *J* = 0.6, 11.7, 6.9 Hz, 1H, C*H*CH_3), 5.92 (br d, *J* = 11.8 Hz, 1H, C*H*=$CHCH_3$), 2.25 (s, 3H, C(=O)C*H*$_3$), 1.85 (br d, *J* = 5.9 Hz, 3H, CHC*H*$_3$), 0.93, (s, 9H, $SiMe_2C(CH_3)_3$), and 0.41 (s, 6H, $Si(CH_3)_2C(CH_3)_3$).

^{13}C NMR (125 MHz, $CDCl_3$) δ 196.8, 169.0, 143.6, 135.4, 127.7, 125.9, 30.6, 25.6, 17.9, 14.8, and -5.0.

GC-LRMS (ES, 70 eV): t_R = 7.39 min. *m/z*: 268 (M^+), 253 ($M^+ – CH_3$), and 211 ($M^+ – C(CH_3)_3$).

IR (neat, of the *E/Z* mixture of alkenes): 2956, 2932, 2859, 1716, 1689, 1582, 1384, 1375, 1253, 1191, and 961 cm^{-1}.

Hydrolysis of TBS-esters 6b to butenolides 3b.

A sample of the crude mixture of 3*E*- and 3*Z*-(2*Z*)-*tert*-butyldimethylsilyl 4-oxo-2-(prop-1-en-1-yl)pent-2-enoates (**6b**, 156 mg, 0.58 mmol) and wet CH_2Cl_2 (12 mL, 1 drop of water was added) were combined in 20 mL glass vial. Silica gel (500 mg) and a stir bar were added, and the slurry was stirred at room temperature for 48 h. This mixture was filtered. The residue was washed with CH_2Cl_2 three times, and combined with the filtrate. This combined solution was then concentrated and purified using column chromatography on silica gel (hexanes:ethyl acetate = 5:1 to 3:1 to 1:1) to give a 7:1 *E*:*Z* mixture of 5-hydroxy-5-methyl-3-(prop-1-en-1-yl)furan-2(5H)-one (**3b**, 52 mg, 58% yield) as a pale yellow oil. The following NMR data were extracted from this mixture.

(*E*)-5-Hydroxy-5-methyl-3-(prop-1-en-1-yl)furan-2(5H)-one (*E*-3b):

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.83 (d, *J* = 0.6 Hz, 1H, *H4*), 6.81 (dq, *J* = 15.5, 6.9 Hz, 1H, *H2'*), 6.08 (ddq, *J* = 0.6, 15.9, 1.8 Hz, 1H, *H1'*), 1.86 (ddd, *J* = 0.6, 1.7, 6.8 Hz, 3H, *H3'*), and 1.69 (s, 3H, C5-C*H*$_3$).

^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2, 144.1, 136.0, 130.9, 119.4, 104.2, 25.0, and 19.3.

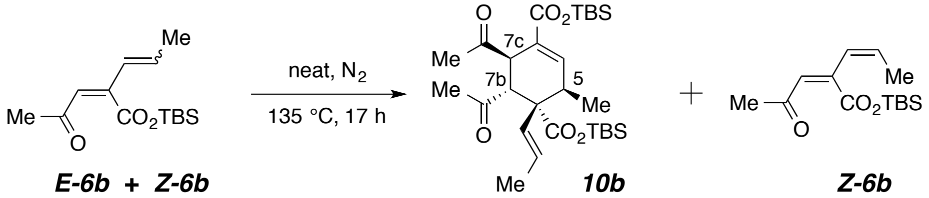
(*Z*)-5-Hydroxy-5-methyl-3-(prop-1-en-1-yl)furan-2(5H)-one (*Z*-3b):

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.01 (br s, 1H, *H4*), 6.14 (ddq, *J* = 0.5, 11.5, 7.0 Hz, 1H, *H2'*), 6.07 (ddq, *J* = 0.9, 12.0, 1.7 Hz, 1H, *H1'*), 1.86 (ddd, *J* = 0.6, 1.5, 6.9 Hz, 3H, *H3'*), and 1.74 (s, 3H, C5-C*H*$_3$).

^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5, 146.4, 135.9, 129.8, 117.3, 104.9, 25.1, and 16.0.

HRMS (ESI-TOF): Calcd for $(C_8H_{10}NaO_3)^+$ 177.0522. Found: 177.0524.

IR (neat, of the *E/Z* mixture of alkenes): 3370, 2994, 2939, 1742, 1665, 1445, 1414, 1167, 1114, 1055, 967, and 925 cm^{-1}.



E-6b* + *Z-6b **10b** ***Z-6b***

Preparation of bis(tert-butyldimethylsilyl) (3R,4S,5R,6R)-5,6-diacetyl-3-methyl-4-((E)-prop-1-en-1-yl)cyclohex-1-ene-1,4-dicarboxylate (10b).

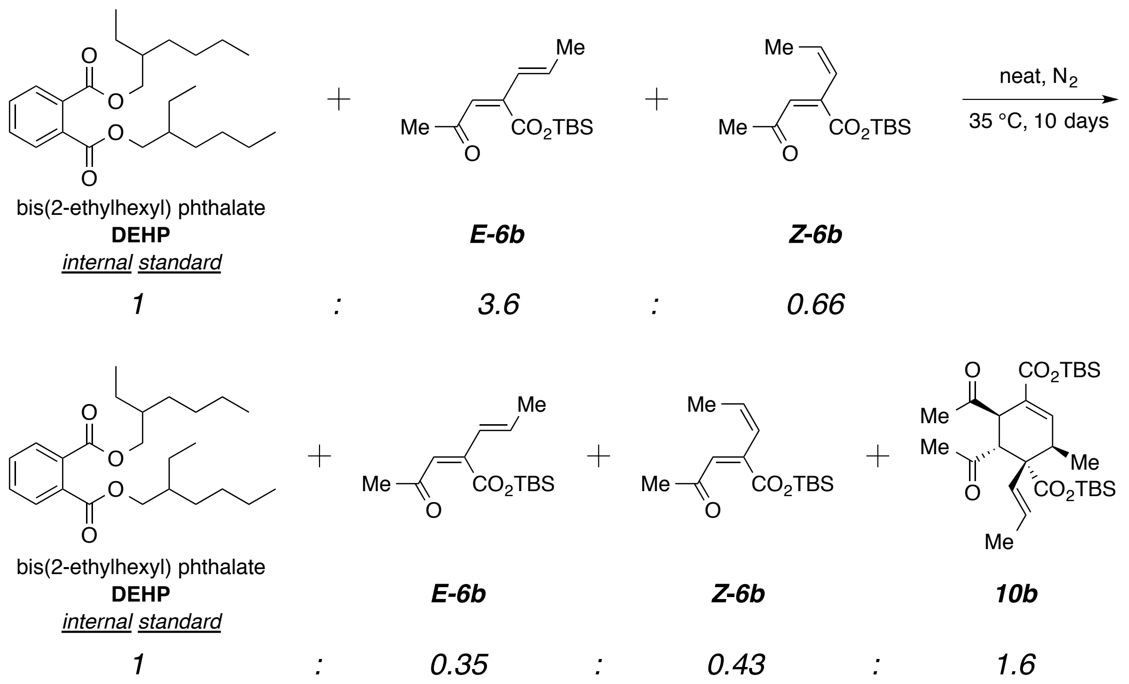
To a small glass vial was added the crude mixture of *E/Z* isomers of (2*Z*)-*tert*-butyldimethylsilyl 4-oxo-2-(prop-1-en-1-yl)pent-2-enoates (**6b**, 158 mg, 0.59 mmol). The headspace was flushed with N$_2$ and the vial was sealed with a Teflon-lined cap. The reaction mixture was placed in a 135 °C oil bath for 17 h to produce a mixture of 151 mg of bis(tert-butyldimethylsilyl) (3R,4S,5R,6R)-5,6-diacetyl-3-methyl-4-((*E*)-prop-1-en-1-yl)cyclohex-1-ene-1,4-dicarboxylate (**10b**) and *tert*-butyldimethylsilyl (*Z*)-4-oxo-2-((*Z*)-prop-1-en-1-yl)pent-2-enoate (***Z*-6b**). The small mass loss was due to the fact that some of the ***Z*-6b** vaporized and re-condensed on the cap and was not collected). This crude mixture was used directly without purification.

^{1}**H NMR** (500 MHz, CDCl$_3$) δ 6.92 [dd, *J* = 3.1, 1.1 Hz, 1H, =C*H*CH(CH$_3$)], 5.56 (dq, *J* = 15.9, 6.5 Hz, 1H, CH=C*H*CH$_3$), 5.23 (dq, *J* = 15.8, 1.7 Hz, 1H, C*H*=CHCH$_3$), 3.75 (ddd, *J* = 2.0, 2.0, 1.3 Hz, 1H, *H*7c), 3.70 (d, *J* = 2.2 Hz, 1H, *H*7b), 3.38 [ddq, *J* = 3.0, 1.9, 7.4 Hz, 1H, *H*5], 2.27 (s, 3H, C$_a$(=O)C*H$_3$*), 2.26 (s, 3H, C$_b$(=O)C*H$_3$*), 1.60 (dd, *J* = 6.5, 1.6 Hz, 3H, CH=CHC*H$_3$*), 1.28 [d, *J* = 7.4, 3H, C5(C*H$_3$*)], 0.95 [s, 9H, -Si$_a$Me$_2$C(C*H$_3$*)$_3$], 0.94 [s, 9H, -Si$_b$Me$_2$C(C*H$_3$*)$_3$], 0.29, 0.274, 0.272, and 0.26 (four singlets, 4 × 3H, Si(C*H$_3$*)$_2$C(CH$_3$)$_3$).

^{13}**C NMR** (125 MHz, CDCl$_3$) δ 207.2, 206.3, 174.2, 166.5, 147.9, 129.2, 127.8, 125.8, 58.3, 52.3, 48.7, 34.7, 29.1, 28.1, 25.9, 25.8, 18.2, 18.0, 17.9, 16.7, -4.6, -4.7, -4.79, and -4.80.

IR (neat) 2922, 2354, 2320, 1767, 1712, 1454, 1387, 1250, 1196, 1164, 1056, 1021, 973, 919, and 836 cm^{-1}**.**

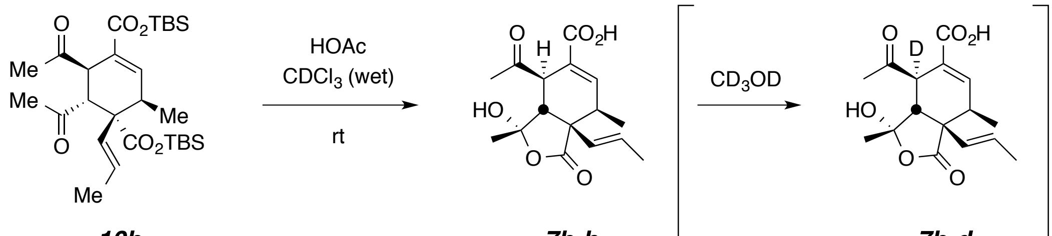
HRMS (ESI-TOF): Calcd for $(C_{28}H_{48}NaO_6Si_2)^+$ 559.2882. Found: 559.2895.



DEHP *internal standard* — ***E-6b*** — ***Z-6b*** — ***10b***

Dimerization experiment of (2*Z*)-*tert*-butyldimethylsilyl 4-oxo-2-(prop-1-en-1-yl)pent-2-enoate (6b) at ambient temperature (35 °C)

To a small glass vial was added a DCM solution of the crude mixture of *E/Z* isomers (ca. 5.5:1) of (2*Z*)-*tert*-butyldimethylsilyl 4-oxo-2-(prop-1-en-1-yl)pent-2-enoates (**6b**) and bis(2-ethylhexyl) phthalate (DEHP) as an internal standard. The DCM was evaporated. The relative initial quantity of the three components in the resulting neat mixture was measured by ^{1}H NMR spectroscopic analysis of an aliquot. The headspace of the vial was flushed with N_2 and the vial was sealed with a Teflon-lined cap. The reaction mixture was placed in a 35 °C oil bath for 10 days. The crude reaction mixture was directly subjected to ^{1}H NMR analysis. The relative amount of the four components was calculated relative to the DEHP proton resonances. The crude ^{1}H NMR spectra at t = 0 and t = 10 days as well as expansions are provided on pages S66-S69.



10b ***7b-h*** ***7b-d***

Preparation of (3S,4R,7R,7aS)-4-acetyl-3-hydroxy-3,7-dimethyl-1-oxo-7a-((E)-prop-1-en-1-yl)-1,3,3a,4,7,7a-hexahydroisobenzofuran-5-carboxylic acid (7b-h).

To a 20 mL glass vial was added the bis(tert-butyldimethylsilyl) ester **10b** (75 mg, 0.14 mmol), $CDCl_3$ (5 mL), and HOAc (1 mL). The reaction mixture was stirred at room temperature for 24 h. The solution was concentrated and the residue purified by flash column chromatography (hexanes:ethyl acetate:acetic acid = 50:50:1) to give (3S,4R,7R,7aS)-4-acetyl-3-hydroxy-3,7-dimethyl-1-oxo-7a-((E)-prop-1-en-1-yl)-1,3,3a,4,7,7a-hexahydroisobenzofuran-5-carboxylic acid (**7b-h**, 31 mg, 72% yield) as an off-white solid. This material showed marginal solubility in $CDCl_3$, but the NMR spectra in that solvent were relatively sharp. They also indicated the presence of at least three distinct species, the major of which comprised >90% of the spectral intensity.

Presumably this reflects the presence of epimeric acylals and/or open and closed species among the various ketoacids. The sample was much more soluble in CD_3OD, but the spectra were quite broad, suggestive of dynamic processes.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.07 [dd, *J* = 2.1, 2.1 Hz, 1H, C=C*H*CH(CH_3)], 5.76 (dq, *J* = 16.0, 6.3 Hz, 1H, CH=C*H*CH_3), 5.30 (dq, *J* = 15.7, 1.8 Hz, 1H, C*H*=CHCH_3), 3.70 (br s, 1H, *H*7c), 2.99-2.90 (m, 2H, *H*7b and O*H*], 2.57 (br s, 1H, *H*5), 2.29 (s, 3H, C(=O)CH_3), 1.81 (s, 3H, C(OH)CH_3), 1.67 (dd, *J* = 6.4, 1.6 Hz, 3H, CH=CHCH_3), and 1.21 [d, *J* = 7.5, 3H, C5(CH_3)].

^{1}H NMR (500 MHz, CD_3OD) δ 6.89 [br s, 1H, C=C*H*CH(CH_3)], 5.68 (dq, *J* = 15.7, 6.3 Hz, 1H, CH=C*H*CH_3), 5.31 (br dq, *J* = 15.9, 1.7 Hz, 1H, C*H*=CHCH_3), 3.68 (br s, 1H, *H*7c), 2.94 (br s, 1H, *H*7b), 2.56 (br s, 1H, *H*5), 2.28 (br s, 3H, C(=O)CH_3), 1.75 (br s, 3H, C(OH)CH_3), 1.63 (dd, *J* = 6.5, 1.2 Hz, 3H, CH=CHCH_3), and 1.17 [br d, *J* = 7.3, 3H, C5(CH_3)].

^{13}C NMR (125 MHz, $CDCl_3$, chemical shifts taken from the HSQC data) δ 147 (*C*4), 128 (=*C*HCH_3), 127 (H*C*=CHCH_3), 51 (*C*5), 44 (*C*7c), 34 (*C*7b), 28 (C(=O)CH_3), 27 C(OH)*C*H_3), 18 (=CH*C*H_3), and 15 (and C5*C*H).

^{13}C NMR (125 MHz, CD_3OD) δ 209.9 (br s), 178.9, 169.6, 145.2 (br s), 129.8 (br s), 129.1 (br s), 128.9, 106.5, 53.3 (br s), 50.9 (br s), 46.2, 35.7, 28.9 (br s), 26.7 (br s), 18.5, and 15.6 (br s).

IR (neat): 2956, 2923, 2854, 2358, 1751, 1699, 1654, 1457, 1355, 1246, 1191, 1163, 1057, 1017, 971, and 914 cm^{-1}.

HRMS (ESI-TOF): Calcd for $(C_{16}H_{20}NaO_6)^+$ 331.1152 Found: 331.1153.

mp 170–174 °C (accompanied by sweating; NMR spectrum of material upon cooling was that of dimer **1b**.

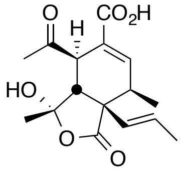
Deuterium exchange of H7c in CD_3OD

The solution of **7b-h** in CD_3OD was observed to lose signal intensity in the ^{1}H NMR spectrum for proton H7c at ambient temperature. The half-life for this exchange was ca. 3.2 days at ambient temperature (ca. 21 °C).

X-ray structure determination of 7b

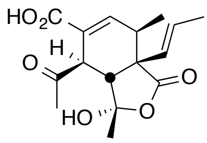
A single crystal used for X-ray analysis was prepared by dissolving a portion of this purified product in CH_2Cl_2 (containing ~5% residual EtOAc). This solution was transferred to a small vial, which was then placed inside a larger capped vial containing pentane. Upon standing at room temperature for 3 days white crystals of suitable quality were formed.

The crystallographic data (excluding structure factors) for this structure have been deposited into the Cambridge Crystallographic Data Centre (CCDC). The deposition number is CCDC 1042989. Copies of the data can be obtained (, free of charge) by contacting the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, or by linking to http://www.ccdc.cam.ac.uk/pages/Home.aspx.



7b-h

≡



7b-h

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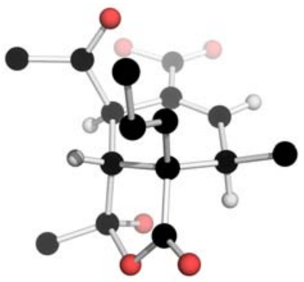
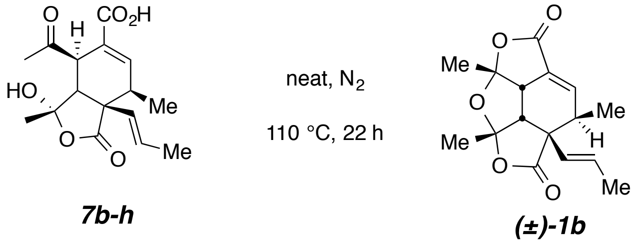
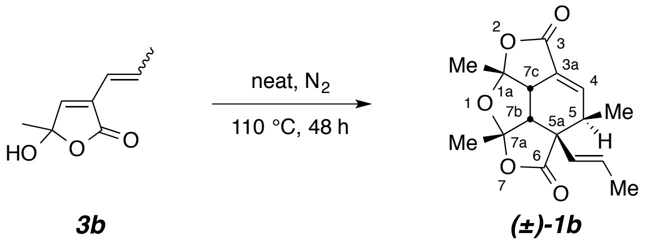




Preparation of truncated paracaseolide A (1a*R*,5*R*,5a*S*,7a*S*,7b*R*,7c*S*)-rel-(±)-1a,5,5a,7a,7b,7c-hexahydro-1a,5,7a-trimethyl-5a-(1*E*)-1-propen-1-yl difuro[2,3,4-cd:4',3',2'-hi]isobenzofuran-3,6-dione [(±)-1b]

The acid (**7b-h**, 1.0 mg, 3.2 μmol) was added to a glass vial. The headspace was flushed with N_2. The vial was sealed with a Teflon-lined cap and placed in a 110 °C oil bath. After 22 h the ^1H NMR spectrum of the sample showed that clean conversion had occurred to give the truncated (±)-paracaseolide A (**1b**, 0.7 mg, after re-evaporation of the NMR solvent). The overall cleanliness of this reaction can be seen from inspection of the ^1H NMR spectrum, a copy of which is included later in this Supplementary Information.



Preparation of truncated paracaseolide A (1a*R*,5*R*,5a*S*,7a*S*,7b*R*,7c*S*)-rel-(±)-1a,5,5a,7a,7b,7c-hexahydro-1a,5,7a-trimethyl-5a-(1*E*)-1-propen-1-yl difuro[2,3,4-cd:4',3',2'-hi]isobenzofuran-3,6-dione [(±)-1b]

5-Hydroxy-5-methyl-3-(prop-1-en-1-yl)furan-2(5H)-one (**3b**, 35 mg, 0.23 mmol) was placed in a 2 mL vial with a Teflon cap. The headspace was flushed with N_2. The reaction vial was capped and heated to 110 °C for 48 h. The crude mixture was directly subjected to MPLC (hexanes:ethyl acetate = 1:1) to give unreacted 5-hydroxy-5-methyl-3-(prop-1-en-1-yl)furan-2(5H)-ones (**3b**, 8 mg, *E*:*Z* = 3:4) followed by the truncated paracaseolide A analog **(±)-1b** (13.9 mg, 42%) as a white powder.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.26 (dd, *J* = 7.6, 3.3 Hz, 1H, *H4*), 5.87 (dq, *J* = 15.7, 6.5 Hz, 1H, =C*H*CH$_3$), 5.53 (dq, *J* = 15.7, 1.6 Hz, 1H, *H*C=CHCH$_3$), 3.38 (dd, *J* = 9.5, 3.3 Hz, 1H, *H7c*), 3.30 (d, *J* = 9.5 Hz, 1H, *H7b*), 3.11 (dq, *J* = 7.4, 7.4 Hz, 1H, *H5*), 1.80 (dd, *J* = 6.5, 1.7 Hz, 3H, =CHC*H$_3$*), 1.76 (s, 3H, (C1a)C*H$_3$*), 1.63, (s, 3H, (C7a)C*H$_3$*), and 1.05 (d, *J* = 7.3 Hz, 3H, H(C5)C*H$_3$*).

^{13}C NMR (125 MHz, $CDCl_3$) δ 175.3, 166.4, 144.7, 130.0, 129.5, 127.5, 115.6, 114.1, 58.7, 50.4, 46.5, 39.3, 26.9, 25.9, 18.4, and 12.1.

IR (neat): 2923, 2854, 1771, 1390, 1312, 1050, and 911 cm^{-1}.

HRMS (ESI-TOF): Calcd for $(C_{16}H_{18}NaO_5)^+$ 313.1046. Found: 313.1062.

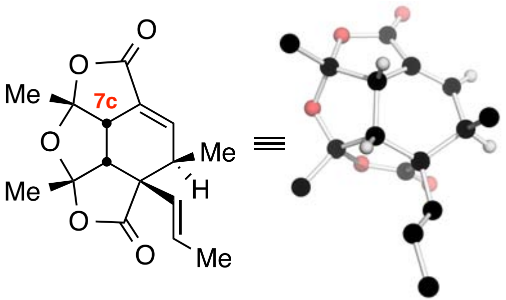
mp 200-201 °C.

X-ray structure determination of (±)-1b

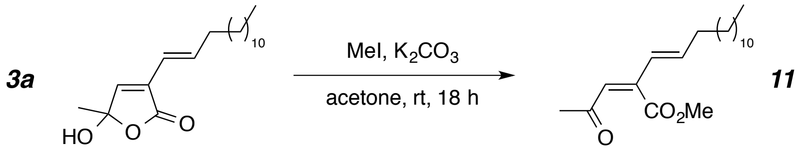
A single crystal used for X-ray analysis was prepared by dissolving a portion of this purified product in CH_2Cl_2. This solution was transferred to a small vial, which was then placed inside a larger capped vial containing pentane. Upon standing at room temperature for several days white crystals of suitable quality were formed.

The crystallographic data (excluding structure factors) for this structure have been deposited into the

Cambridge Crystallographic Data Centre (CCDC). The deposition number is CCDC 1042994. Copies of the data can be obtained (, free of charge) by contacting the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, or by linking to http://www.ccdc.cam.ac.uk/pages/Home.aspx.



1b



Preparation of methyl (2*Z*,3*E*)-2-(2-oxopropylidene)hexadec-3-enoate (11)

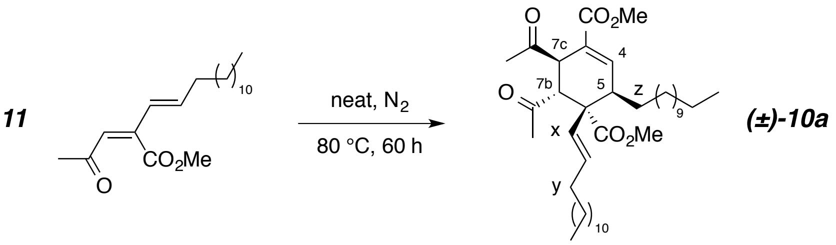
(±)-(*E*)-5-Hydroxy-5-methyl-3-(tetradec-1-enyl)furan-2(5H)-one (**3a**, 18.3 mg, 0.059 mmol) was placed in a 14x45 mm (1dram) vial. Acetone (2 mL), MeI (25 μL, 0.08 mmol), and K_2CO_3 (15 mg, 0.10 mmol) were added. The vial was sealed with a Teflon cap and stirred at room temperature for 18 h. The reaction mixture was partitioned between ethyl acetate and brine. The organic layer was washed again with brine, filtered through a plug of Na_2SO_4, concentrated, and purified using MPLC on silica gel (hexanes:ethyl acetate = 4:1) to give methyl (2*Z*,3*E*)-2-(2-oxopropylidene)hexadec-3-enoate (**11**) as a colorless oil (10.4 mg, 55%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.12-6.04 (m, 3H, =C*H*s), 3.90 (s, 3H, CO_2CH_3), 2.24 (s, 3H, $COCH_3$), 2.21-2.16 (nfom, 2H, =$CHCH_2CH_2$), 1.42 (br pentet, *J* = 7.3 Hz, 2H, =$CHCH_2CH_2$), 1.32-1.22 (m, 18H, -$(CH_2)_9$), and 0.88, (t, *J* = 6.9 Hz, 3H, CH_2CH_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 196.5, 168.9, 145.7, 144.5, 126.7, 124.0, 52.8, 33.6, 32.1, 30.7, 29.87, 29.84 (br), 29.7, 29.60, 29.56, 29.4, 28.6, 22.9, and 14.3.

IR (neat): 2924, 2853, 1740, 1690, 1585, 1378, 1250, 1198, 1175, and 963 cm^{-1}.

HRMS (ESI-TOF): Calcd for $(C_{20}H_{34}NaO_3)^+$ 345.2400 Found: 345.2397.



Preparation of (±)-dimethyl (3*R*,4*S*,5*R*,6*R*)-5,6-diacetyl-3-dodecyl-4-((*E*)-tetradec-1-en-1-yl)cyclohex-1-ene-1,4-dicarboxylate [(±)-10a]

(±)-Methyl (2*Z*,3*E*)-2-(2-oxopropylidene)hexadec-3-enoate (**11**, 5 mg, 16 μmol) was placed in a 2 mL vial with a Teflon cap. The headspace was flushed with N_2. The reaction vial was heated to 80 °C for 60 h. The crude material was directly purified by flash column chromatography (hexanes: ethyl acetate = 5:1 ~ 3:1) to give of (±)-dimethyl (3*R*,4*S*,5*R*,6*R*)-5,6-diacetyl-3-dodecyl-4-((*E*)-tetradec-1-en-1-yl)cyclohex-1-ene-1,4-dicarboxylate (**(±)-10a**, 5 mg, 100 %) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 [dd, *J* = 3.1, 1.1 Hz, 1H, =C*H*CH(CH_2CH_2)], 5.43 (dt, *J* = 15.9, 6.8 Hz, 1H, CH=C*H*CH_2), 5.18 (dt, *J* = 15.9, 1.2 Hz, 1H, C*H*=$CHCH_3$), 3.77 (br dt, *J* = 1.2, 2.0 Hz, 1H, *H*7c), 3.75 (s, 3H, $C_aO_2CH_3$), 3.73 (d, *J* = 2.2 Hz, 1H, *H*7b), 3.70 (s, 3H, $C_bO_2CH_3$), 3.08 (br ddt, *J* = 11.1, 2.7, 2.1 Hz, 1H, *H*5), 2.28 [s, 3H, C_a(=O)CH_3], 2.27 [s, 3H, C_b(=O)CH_3], 1.96-1.83 (m, 3H), 1.62-1.52 (m, 1H), 1.49-1.40 (m, 1H), 1.40-1.09 (m, 39H), 0.883 (t, *J* = 7.0 Hz, 3H,CH_2CH_3), and 0.880 (t, *J* = 7.0 Hz, 3H,CH_2CH_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 207.3, 206.3, 174.3, 167.0, 145.1, 133.2, 127.9, 124.2, 57.6, 52.3, 51.9, 48.4, 40.0, 32.8, 32.2, 31.0, 29.95, 29.94, 29.90 (br), 29.87, 29.65, 29.61, 29.4, 29.1, 28.8, 28.40, 28.36, 22.9, and 14.4.

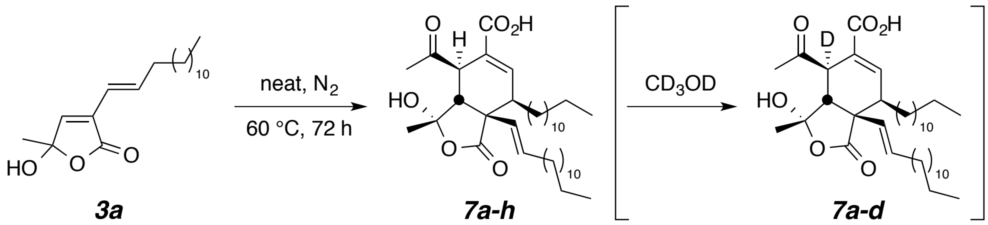
IR (neat): 2923, 2853, 1770, 1748, 1715, 1436, 1356, 1268, 1241, 1170, and 1048 cm^{-1}.

HRMS (ESI-TOF): Calcd for $(C_{40}H_{68}NaO_6)^+$ 667.4908 Found: 667.4941

NMR-based assignment of the relative configuration (i.e., as an *exo* adduct) of (±)-10a

Difference NOE experiments (carried out in C_6D_6 for better chemical shift dispersion) gave several key enhancements that were consistent with the assignment of the relative configuration shown above for **(±)-10a**. Namely: irradiation of Hx enhanced H7b, Hy, one of the diastereotopic protons Hz, and one of the two methyl ketone resonance, although we did not make a definitive assignment of which resonance was associated with which methyl group (and it did not enhance H7c or H5) and irradiation of either H7c or H7b enhanced both sets of methyl ketone protons.

Chemical shift arguments are also consistent with the assignment. There are close similarities of the shifts and multiplicity of key protons in **(±)-10a** vis-a-vis the bis-TBS ester of the truncated analog **10b**. The relative configuration of that latter compound is secure because it was desilylated to produce **1b**, for which a single crystal X-ray structure had been obtained. Namely, resonances for the following protons had nearly identical chemical shifts and multiplicities in the ^{1}H NMR spectra ($CDCl_3$) of **(±)-10a** and **10b**: H7c, H7b, and both methyl ketone Me's.



Preparation of (±)-(3*S*,3a*R*,4*R*,7*R*,7a*S*)-4-acetyl-7-dodecyl-3-hydroxy-3-methyl-1-oxo-7a-((*E*)-tetradec-1-en-1-yl)-1,3,3a,4,7,7a-hexahydroisobenzofuran-5-carboxylic acid [(±)-7a]

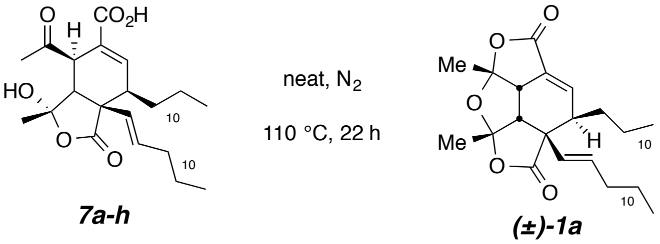
(±)-(*E*)-5-Hydroxy-5-methyl-3-(tetradec-1-enyl)furan-2(5H)-one (**3a**, 64 mg, 0.21 mmol) was placed in a 2 mL vial with a Teflon cap. The headspace was flushed with N_2. The reaction vial was heated to 60 °C for 72 h. The crude material was directly purified by flash column chromatography (hexanes:ethyl acetate:acetic acid = 50:50:1) to give recovered starting material (**3a**, 23 mg) and (±)-(3*S*,3a*R*,4*R*,7*R*,7a*S*)-4-acetyl-7-dodecyl-3-hydroxy-3-methyl-1-oxo-7a-((*E*)-tetradec-1-en-1-yl)-1,3,3a,4,7,7a-hexahydroisobenzofuran-5-carboxylic acid [**(±)-7a**, 29 mg, 45 %] as a colorless sticky oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 [br s, 1H, C=C*H*CH(CH_2)], 5.69 (br dt, *J* = 15.7, 6.4 Hz, 1H, CH=C*H*CH_2), 5.26 (br d, *J* = 15.9 Hz, 1H, C*H*=CHCH_2), 3.72 (br s, 1H, *H*7c), 2.71 (br s, 1H, *H*7b), 2.61 (br s, 1H, *H*5), 2.25 (very br s, 3H, C(=O)CH_3), 1.97 (br dt, *J* = 7, 7 Hz, 1H, =CHCH_2), 1.79 (very br s, 3H, C(OH)CH_3), 1.51 (br s, 1H), 1.35-1.16 (m, ~41H), and 0.88 [t, *J* = 7.0 Hz, 6H,CH_2CH_3 (2x)]

^{13}C NMR (125 MHz, $CDCl_3$) δ 133.8, 126.6, 52 (br), 50 (br), 44.8 (br), 40.6 (br), 32.9, 32.1, 29.91 (br), 29.89, 29.87, 29.84, 29.80 (br), 29.7, 29.6, 29.4, 22.9, and 14.4. [Because this compound appears to exist as an equilibrating mixture of pseudo-acids and/or hemiketals (^{1}H NMR), many resonances in the core of this structure were either broad of not observed in this ^{13}C NMR spectrum.]

IR (neat): 2923, 2853, 1770, 1758, 1696, 1464, 1246, 1056, and 911 cm^{-1}.

HRMS (ESI-TOF): Calcd for $(C_{38}H_{64}NaO_6)^+$ 639.4595 Found: 639.4595.



Preparation of (±)-paracaseolide A

(1a*R*,5*R*,5a*S*,7a*S*,7b*R*,7c*S*)-rel-(±)-5-dodecyl-1a,5,5a,7a,7b,7c-hexahydro-1a,7a-dimethyl-5a-(1*E*)-1-tetradecen-1-yldifuro[2,3,4-cd:4',3',2'-hi]isobenzofuran-3,6-dione [(±)-1a]

In a glass vial was added the acid **7a-h** (4.7 mg, 7.6 µmol). The headspace was flushed with N_2. The vial was sealed with a Teflon-lined cap and placed in a 110 °C oil bath. After 22 h the ^{1}H NMR spectrum of the sample showed that clean conversion had occurred to give (±)-paracaseolide A (**1a**, 4.3 mg, after re-evaporation of the NMR solvent). The overall cleanliness of this reaction can be seen from inspection of the ^{1}H NMR spectrum, a copy of which is included later in this Supplementary Information.

III. Computational Methods

DFT calculations were carried out using Gaussian 09.[8] Geometries were optimized using the M06-2X functional developed by Truhlar et al[9] or the B3LYP[10] functional. The double-ζ 6-31G(d), cc-pVDZ, or triple-ζ 6-311+G(d,p) basis sets were used. The SMD continuum solvation model[11] was used with 2-butanol as the solvent, chosen to mimic the medium for the neat reaction conditions, during the frequency calculation and the geometry optimization (unless otherwise indicated). The "grid=ultrafine" option was applied during the numerical integrations. The harmonic vibrational frequency calculations were carried out using 298 K as the thermal correction for the free energies. Every optimized transition state structure geometry showed only one imaginary frequency.

First, we used DFT calculations to evaluate the relative energies of transition state (TS) structures corresponding to the exo vs. the endo modes of dimerization of **3b** [SMD/M06-2X/6-31G(d) in 2-butanol]. The TS structures for both of these modes of addition are shown on following pages. Both homochiral and heterochiral possibilities (i.e., dimerization of two copies of the same enantiomer or one copy of each enantiomer of **3b**) as well as approaches of the two molecules with inward vs. outward orientations of the hydroxyl groups were examined. The two heterochiral-TS structures for the *exo* mode of addition converged to the same (bis-pericyclic) structure (**TS$_{exo}$-2**) during the optimization.

	G$_{rel}$ (kcal•mol^{-1})	
TS$_{endo}$-1	4.7	Homochiral: hydroxyls in on diene and out on dienophile
TS$_{endo}$-2	2.9	Heterochiral: hydroxyls in on both diene and dienophile (lowest G, *endo* TS)
TS$_{endo}$-3	8.1	Heterochiral: hydroxyls out on both the diene and dienophile
TS$_{endo}$-4	3.7	Homochiral: hydroxyls out on diene and in on dienophile
TS$_{exo}$-1	4.6	Homochiral: hydroxyls out on both diene and dienophile
TS$_{exo}$-2	2.3	Heterochiral: hydroxyls in on diene and out on dienophile
TS$_{exo}$-3	0	Homochiral: hydroxyls in on both diene and dienophile (lowest G, *exo* TS)

Second, we optimized the lowest energy *endo* and *exo* TS structures (i.e., **TS$_{endo}$-2** and **TS$_{exo}$-3**) with several other combinations of functional and basis set. A gas-phase calculation (i.e., no SMD) was also performed. Specifically, the following combinations were used: SMD/M06-2X/6-311+G(d,p), SMD/M06-2X/cc-pVDZ, SMD/B3LYP/6-311+G(d,p) in 2-butanol, and M06-2X/6-311+G(d,p) without SMD solvation. All of the resulting TS geometries were very similar; the TS energies are given in Table S1 (below). The optimized structure of **TS$_{endo}$-2** and **TS$_{exo}$-3** at the SMD/M06-2X/6-311+G(d,p) level are those given in the manuscript (as "**TS$_{endo}$**" and "**TS$_{exo}$**").

Third, we examined a conformational analog of **TS$_{endo}$-2** in which the dienophile has an s-trans geometry at the SMD/M06-2X/6-311+G(d,p) level. The resulting **TS$_{endo}$-2$_{s\text{-}trans}$** had a G$_{rel}$ 0.8 kcal•mol^{-1} higher than the energy of the s-cis-containing **TS$_{endo}$-2**.

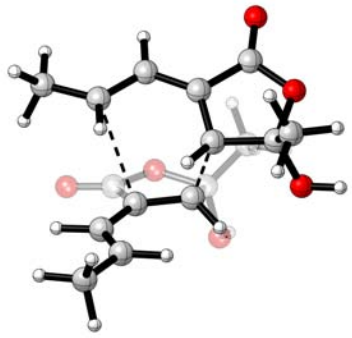
Last, we optimized monomer **3b** and the product structure **PD** (co-ordinates for both below) from an *exo* DA dimerization at the SMD/M06-2X/6-311+G(d,p) level to determine the computed free energy of reaction (-14.0 kcal•mol^{-1}), which is also now given in the manuscript.

Table S1. Energies of $\mathbf{TS_{exo}}$ and $\mathbf{TS_{endo}}$ with different functional/basis set/solvation combinations

Method	**Structure**	**H (Hartree/Particle)**	**G (Hartree/Particle)**	**H_{rel} (kcal•mol^{-1})**	**G_{rel} (kcal•mol^{-1})**
SMD/M06-2X/6-31G(d) in 2-butanol	$\mathbf{TS_{exo}}$	-1072.262291	-1072.333059	0.0	0.0
	$\mathbf{TS_{endo}}$	-1072.258385	-1072.328436	2.5	2.9
SMD/M06-2X/6-311+G(d,p) in 2-butanol [a]	$\mathbf{TS_{exo}}$	-1072.595731	-1072.666831	0.0	0.0
	$\mathbf{TS_{endo}}$	-1072.590218	-1072.660629	3.5	3.9
SMD/M06-2X/6-311+G(d,p) in gas phase	$\mathbf{TS_{exo}}$	-1072.558434	-1072.629637	0.0	0.0
	$\mathbf{TS_{endo}}$	-1072.548248	-1072.619829	6.4	6.2
SMD/M06-2X/cc-pVDZ in 2-butanol	$\mathbf{TS_{exo}}$	-1072.384888	-1072.455101	0.0	0.0
	$\mathbf{TS_{endo}}$	-1072.379505	-1072.450097	3.4	3.1
SMD/B3LYP/6-311+G(d,p) in 2-butanol	$\mathbf{TS_{exo}}$	-1073.029730	-1073.103066	0.0	0.0
	$\mathbf{TS_{endo}}$	-1073.023419	-1073.096053	4.0	4.4

[a] These are the TS structures (and energies) presented in the manuscript.

TS structure for TS$_{endo}$-1



Imaginary frequency: -411.3425 cm^{-1}

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---------------------------------------------------------------------
 Center     Atomic      Atomic             Coordinates (Angstroms)
 Number     Number       Type             X           Y           Z
 ---------------------------------------------------------------------
      1          6           0       -1.588845    0.048150   -0.541480
      2          6           0       -2.529889    1.083225   -0.188519
      3          6           0       -2.293487    2.401553   -0.316568
      4          6           0       -1.147341   -0.538479    2.148195
      5          6           0        0.143990   -0.953094    1.993001
      6          6           0       -0.295266    0.178270   -1.056084
      7          1           0       -3.478186    0.743661    0.228515
      8          1           0       -1.392579    0.495934    1.923016
      9          1           0        0.460493   -1.920718    2.380553
     10          1           0       -0.022201    1.026521   -1.678114
     11          1           0       -1.355849    2.737189   -0.762081
     12          6           0       -1.956040   -1.372415   -0.558222
     13          8           0       -2.998762   -1.903819   -0.238641
     14          6           0        0.047589   -1.191751   -1.661607
     15          8           0       -0.916731   -2.089388   -1.067252
     16          6           0        1.082586   -0.201397    1.260247
     17          6           0        0.829857    0.855803    0.386021
     18          6           0        2.189289    1.339714   -0.120805
     19          1           0        0.098608    1.635463    0.609687
     20          6           0        2.504547   -0.571508    1.133589
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    21          8           0        3.101844   -1.480727    1.663170
    22          8           0        3.115518    0.303596    0.302665
    23          6           0       -2.212860   -1.359285    2.786517
    24          1           0       -1.845620   -2.350671    3.065388
    25          1           0       -2.601076   -0.857085    3.680732
    26          1           0       -3.058326   -1.484637    2.097928
    27          6           0       -3.261721    3.468133    0.080660
    28          1           0       -2.815391    4.147519    0.816676
    29          1           0       -3.538222    4.083188   -0.784238
    30          1           0       -4.172630    3.041883    0.510050
    31          6           0        1.414722   -1.815211   -1.482833
    32          1           0        1.486055   -2.684648   -2.145536
    33          1           0        2.193179   -1.100335   -1.756731
    34          1           0        1.566519   -2.169791   -0.463336
    35          8           0       -0.259502   -1.034519   -3.018515
    36          1           0       -0.041166   -1.864789   -3.476463
    37          8           0        2.209254    1.417124   -1.504260
    38          1           0        3.017284    1.886905   -1.775126
    39          6           0        2.621987    2.639097    0.532466
    40          1           0        3.641292    2.883813    0.215941
    41          1           0        1.947730    3.443645    0.227383
    42          1           0        2.602408    2.543989    1.620953
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```

TS structure for TS$_{endo}$-2

Imaginary frequency: -429.9500 cm^{-1}

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	1.570973	0.038078	0.559134
2	6	0	2.690384	0.870674	0.170578
3	6	0	2.638739	2.208067	0.061772
4	6	0	1.251333	-0.764880	-2.005612
5	6	0	-0.042965	-1.173654	-1.857347
6	6	0	0.296531	0.420849	0.983080
7	1	0	3.616027	0.343864	-0.061957
8	1	0	1.473603	0.296807	-1.938029
9	1	0	-0.328829	-2.197970	-2.091930
10	1	0	0.125469	1.406655	1.406859
11	1	0	1.710910	2.726119	0.309033
12	6	0	1.711434	-1.403216	0.793344
13	8	0	2.666644	-2.130230	0.620369
14	6	0	-0.275391	-0.781374	1.749186
15	8	0	0.552964	-1.875593	1.336995
16	6	0	-1.016269	-0.335306	-1.285986
17	6	0	-0.817856	0.857030	-0.595866
18	6	0	-2.199480	1.352867	-0.163676
19	1	0	-0.095626	1.611585	-0.907642
20	6	0	-2.427796	-0.734525	-1.120064

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     21          8           0       -2.986387   -1.734188   -1.502470
     22          8           0       -3.094228    0.263633   -0.488301
     23          6           0       -0.120783   -0.581829    3.250722
     24          1           0       -0.756179    0.247209    3.577863
     25          1           0       -0.430987   -1.495895    3.764022
     26          1           0        0.917510   -0.352816    3.506129
     27          8           0       -1.574954   -1.176534    1.435448
     28          1           0       -2.163831   -0.444323    1.699246
     29          6           0        2.358542   -1.654812   -2.453629
     30          1           0        2.045849   -2.701861   -2.485497
     31          1           0        2.706811   -1.356841   -3.450565
     32          1           0        3.215805   -1.568906   -1.776253
     33          6           0        3.789747    3.063997   -0.359690
     34          1           0        3.539884    3.645284   -1.255503
     35          1           0        4.043307    3.789395    0.422756
     36          1           0        4.677090    2.461896   -0.575014
     37          6           0       -2.654888    2.579991   -0.927557
     38          1           0       -3.684977    2.824874   -0.649002
     39          1           0       -2.005489    3.425439   -0.686304
     40          1           0       -2.615418    2.390741   -2.003078
     41          8           0       -2.242485    1.550008    1.218475
     42          1           0       -3.076912    2.000224    1.440408
 ---------------------------------------------------------------------
```
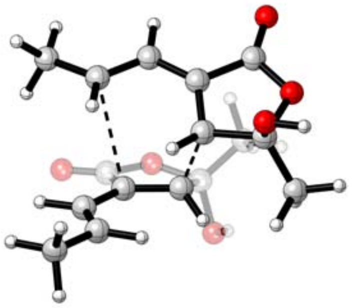

TS structure for TS_{endo}-3

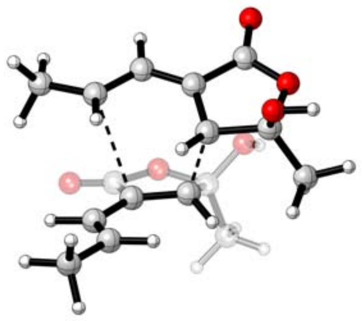


Imaginary frequency: -407.7633 cm^{-1}

```
 ---------------------------------------------------------------------
 Center     Atomic      Atomic             Coordinates (Angstroms)
 Number     Number       Type             X           Y           Z
 ---------------------------------------------------------------------

      1          6           0       -1.598563    0.085071   -0.535560
      2          6           0       -2.503460    1.143660   -0.157200
      3          6           0       -2.228920    2.456701   -0.258707
      4          6           0       -1.133849   -0.598582    2.131792
      5          6           0        0.157553   -1.007112    1.961511
      6          6           0       -0.301551    0.178052   -1.045874
      7          1           0       -3.459621    0.823864    0.257306
      8          1           0       -1.380255    0.441856    1.937232
      9          1           0        0.474683   -1.985838    2.319945
     10          1           0       -0.024709    1.024150   -1.669215
     11          1           0       -1.284802    2.775488   -0.703051
     12          6           0       -2.028864   -1.315018   -0.600136
     13          8           0       -3.094408   -1.807307   -0.293543
     14          6           0        0.009292   -1.198660   -1.660654
     15          8           0       -1.030176   -2.060112   -1.143633
     16          6           0        1.094636   -0.233335    1.249135
     17          6           0        0.843212    0.846436    0.406186
     18          6           0        2.208576    1.359815   -0.058301
     19          1           0        0.114787    1.623705    0.641735
     20          6           0        2.515779   -0.604557    1.100212
```

```
     21          8           0        3.114065   -1.530541    1.595659
     22          8           0        3.118493    0.281171    0.269556
     23          6           0       -2.196602   -1.440870    2.746289
     24          1           0       -1.819506   -2.430723    3.017453
     25          1           0       -2.604510   -0.955266    3.640679
     26          1           0       -3.031062   -1.569403    2.044303
     27          6           0       -3.162398    3.542017    0.169780
     28          1           0       -2.692331    4.184581    0.923849
     29          1           0       -3.420160    4.190016   -0.676505
     30          1           0       -4.085504    3.132741    0.589484
     31          8           0        2.491149    2.450592    0.764439
     32          1           0        3.329756    2.846440    0.469126
     33          6           0        2.399133    1.700236   -1.520625
     34          1           0        1.741392    2.532339   -1.787823
     35          1           0        3.437478    2.008393   -1.679774
     36          1           0        2.185559    0.849412   -2.171044
     37          6           0        1.319580   -1.915020   -1.407529
     38          1           0        1.352755   -2.796725   -2.057095
     39          1           0        2.171008   -1.275407   -1.649271
     40          1           0        1.394828   -2.266618   -0.378884
     41          8           0       -0.197582   -0.999156   -3.029325
     42          1           0        0.026559   -1.823195   -3.495587
 ---------------------------------------------------------------------
```

TS structure for TS_{endo}-4

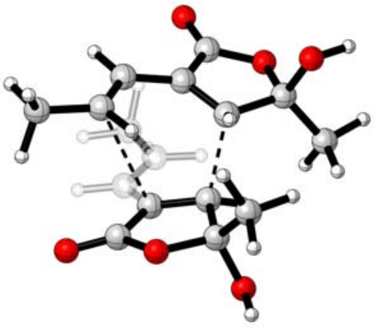


Imaginary frequency: -426.9161 cm^{-1}

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	1.580038	0.033963	0.565672
2	6	0	2.614079	0.980567	0.211805
3	6	0	2.463838	2.315956	0.230073
4	6	0	1.214578	-0.637520	-2.061478
5	6	0	-0.075428	-1.059673	-1.907216
6	6	0	0.286723	0.285716	1.036596
7	1	0	3.560940	0.549192	-0.113416
8	1	0	1.437153	0.417465	-1.924463
9	1	0	-0.367005	-2.064191	-2.210806
10	1	0	0.076614	1.200099	1.587160
11	1	0	1.520140	2.743367	0.572618
12	6	0	1.832694	-1.407023	0.658687
13	8	0	2.842865	-2.033322	0.410192
14	6	0	-0.196916	-1.021193	1.670556
15	8	0	0.724910	-2.016673	1.161784
16	6	0	-1.035609	-0.260738	-1.263797
17	6	0	-0.818279	0.873675	-0.486382
18	6	0	-2.200898	1.394861	-0.086012
19	1	0	-0.088038	1.640889	-0.744780
20	6	0	-2.454044	-0.648010	-1.115844

```
    21          8           0       -3.022365   -1.622099   -1.549558
    22          8           0       -3.100072    0.309202   -0.411130
    23          6           0       -0.054571   -0.991024    3.184137
    24          1           0       -0.732274   -0.243529    3.605929
    25          1           0       -0.306719   -1.975217    3.592118
    26          1           0        0.972328   -0.744664    3.466239
    27          8           0       -1.482461   -1.355957    1.285105
    28          1           0       -1.804916   -2.074350    1.856348
    29          6           0        2.307697   -1.488982   -2.607133
    30          1           0        1.996452   -2.532739   -2.702283
    31          1           0        2.620291   -1.120097   -3.592277
    32          1           0        3.188275   -1.446481   -1.955845
    33          6           0        3.528553    3.286436   -0.168739
    34          1           0        3.187891    3.926044   -0.991792
    35          1           0        3.779436    3.955240    0.663420
    36          1           0        4.439505    2.771162   -0.486334
    37          8           0       -2.457444    2.465123   -0.945951
    38          1           0       -3.306855    2.864415   -0.688952
    39          6           0       -2.440329    1.768959    1.360503
    40          1           0       -1.775201    2.589350    1.644321
    41          1           0       -3.476762    2.104175    1.472185
    42          1           0       -2.277484    0.913860    2.018498
 ---------------------------------------------------------------------
```

TS structure for TS_{exo}-1

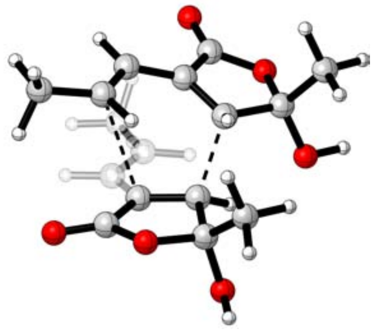


Imaginary frequency: -382.0468 cm^{-1}

```
---------------------------------------------------------------------
 Center     Atomic      Atomic             Coordinates (Angstroms)
 Number     Number       Type             X           Y           Z
 ---------------------------------------------------------------------
      1          6           0        1.196264   -0.515698   -0.888305
      2          6           0        0.475684   -1.610503   -1.434422
      3          6           0       -0.808807   -1.491957   -1.848309
      4          6           0        0.808808   -1.491951    1.848310
      5          6           0       -0.475683   -1.610501    1.434424
      6          6           0        0.737420    0.784610   -0.689977
      7          1           0        0.957528   -2.587143   -1.416437
      8          1           0        1.255087   -0.499359    1.917244
      9          1           0       -0.957525   -2.587142    1.416438
     10          1           0        0.092961    1.256933   -1.421455
     11          1           0       -1.255089   -0.499366   -1.917241
     12          6           0        2.582652   -0.604096   -0.407316
     13          8           0        3.332221   -1.555350   -0.392820
     14          6           0        1.960908    1.611363   -0.273670
     15          8           0        2.971919    0.620735    0.034667
     16          6           0       -1.196265   -0.515698    0.888307
     17          6           0       -0.737421    0.784611    0.689977
     18          6           0       -1.960910    1.611363    0.273668
     19          1           0       -0.092963    1.256935    1.421454
     20          6           0       -2.582652   -0.604096    0.407316
```

```
     21          8           0       -3.332221   -1.555352    0.392822
     22          8           0       -2.971919    0.620733   -0.034669
     23          6           0        1.657973   -2.634913    2.287153
     24          1           0        2.544901   -2.711137    1.642944
     25          1           0        2.025753   -2.482259    3.308770
     26          1           0        1.112125   -3.581332    2.244505
     27          6           0       -1.657969   -2.634921   -2.287150
     28          1           0       -2.544890   -2.711156   -1.642933
     29          1           0       -2.025760   -2.482264   -3.308763
     30          1           0       -1.112114   -3.581336   -2.244514
     31          6           0       -1.872667    2.541628   -0.918495
     32          1           0       -2.807960    3.106019   -0.993985
     33          1           0       -1.045803    3.245396   -0.787501
     34          1           0       -1.739997    1.990694   -1.851911
     35          8           0       -2.334396    2.298275    1.430482
     36          1           0       -3.092013    2.870326    1.216213
     37          8           0        2.334393    2.298276   -1.430484
     38          1           0        3.092008    2.870329   -1.216216
     39          6           0        1.872666    2.541629    0.918493
     40          1           0        2.807959    3.106019    0.993983
     41          1           0        1.045801    3.245396    0.787499
     42          1           0        1.739997    1.990695    1.851909
 ---------------------------------------------------------------------
```

TS structure for TS$_{exo}$-2

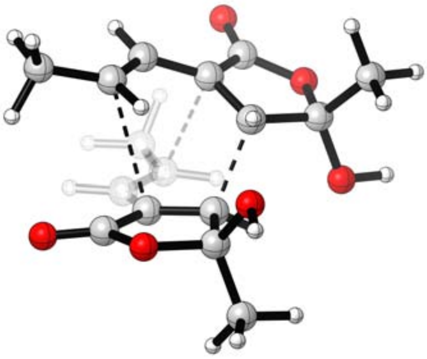


Imaginary frequency: -385.5927 cm^{-1}

```
 ---------------------------------------------------------------------
 Center     Atomic      Atomic             Coordinates (Angstroms)
 Number     Number       Type             X           Y           Z
 ---------------------------------------------------------------------
      1          6           0        1.199783   -0.533092   -0.858853
      2          6           0        0.495490   -1.642720   -1.393504
      3          6           0       -0.782015   -1.534880   -1.833272
      4          6           0        0.766763   -1.498703    1.878439
      5          6           0       -0.515118   -1.603144    1.451787
      6          6           0        0.722263    0.767316   -0.693374
      7          1           0        0.978921   -2.617623   -1.345788
      8          1           0        1.229153   -0.512987    1.938803
      9          1           0       -1.010095   -2.573242    1.438254
     10          1           0        0.063610    1.223998   -1.424564
     11          1           0       -1.227725   -0.544582   -1.931280
     12          6           0        2.574883   -0.598563   -0.342469
     13          8           0        3.334384   -1.540583   -0.288199
     14          6           0        1.941226    1.612432   -0.303840
     15          8           0        2.938145    0.639356    0.090199
     16          6           0       -1.210369   -0.505185    0.880806
     17          6           0       -0.720211    0.787265    0.681052
     18          6           0       -1.912955    1.627589    0.211926
     19          1           0       -0.076870    1.238918    1.427954
     20          6           0       -2.576686   -0.579209    0.347959
```

21	8	0	-3.343274	-1.518176	0.320393
22	8	0	-2.931912	0.646859	-0.115884
23	6	0	1.595611	-2.649873	2.334515
24	1	0	2.480944	-2.748938	1.691012
25	1	0	1.966478	-2.490754	3.353978
26	1	0	1.034238	-3.587662	2.303463
27	6	0	-1.622429	-2.688827	-2.259141
28	1	0	-2.515844	-2.754442	-1.622418
29	1	0	-1.980568	-2.557042	-3.287064
30	1	0	-1.074823	-3.632879	-2.192299
31	8	0	2.348591	2.212951	-1.498316
32	1	0	3.114549	2.782353	-1.308028
33	6	0	1.823269	2.629476	0.811492
34	1	0	2.749887	3.210649	0.861883
35	1	0	0.992391	3.308426	0.598883
36	1	0	1.673953	2.155829	1.783879
37	6	0	-2.460681	2.507261	1.322692
38	1	0	-1.714863	3.257555	1.598561
39	1	0	-3.367170	3.012825	0.974491
40	1	0	-2.707137	1.905019	2.200723
41	8	0	-1.616649	2.356970	-0.929073
42	1	0	-2.356248	2.962703	-1.110682

TS structure for TS$_{exo}$-3

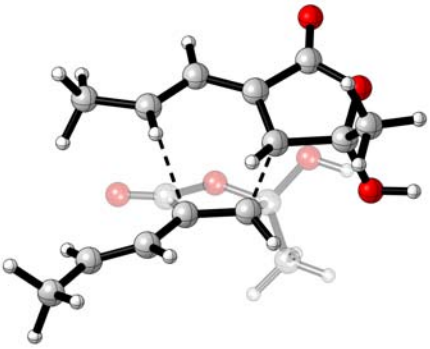


Imaginary frequency: -394.7486 cm^{-1}

Center	Atomic	Atomic	Coordinates (Angstroms)		
Number	Number	Type	X	Y	Z
1	6	0	1.184355	-0.512468	-0.894271
2	6	0	0.461789	-1.600844	-1.446535
3	6	0	-0.826603	-1.476693	-1.850053
4	6	0	0.826584	-1.476690	1.850061
5	6	0	-0.461803	-1.600841	1.446530
6	6	0	0.714612	0.786740	-0.676606
7	1	0	0.942169	-2.578355	-1.440275
8	1	0	1.270485	-0.482856	1.911701
9	1	0	-0.942186	-2.578350	1.440276
10	1	0	0.064338	1.266644	-1.401473
11	1	0	-1.270499	-0.482858	-1.911706
12	6	0	2.565777	-0.607517	-0.407642
13	8	0	3.319925	-1.557458	-0.410942
14	6	0	1.927740	1.603581	-0.212657
15	8	0	2.954716	0.610904	0.047044
16	6	0	-1.184360	-0.512464	0.894251
17	6	0	-0.714605	0.786740	0.676593
18	6	0	-1.927724	1.603598	0.212651
19	1	0	-0.064325	1.266630	1.401465
20	6	0	-2.565779	-0.607498	0.407614
21	8	0	-3.319940	-1.557429	0.410916

```
    22          8           0       -2.954699    0.610924   -0.047083
    23          6           0       -2.438651    2.525969    1.304431
    24          1           0       -1.681372    3.284309    1.521047
    25          1           0       -3.357533    3.018225    0.969628
    26          1           0       -2.651834    1.959749    2.214553
    27          6           0        2.438657    2.525990   -1.304409
    28          1           0        1.681366    3.284324   -1.521003
    29          1           0        3.357528    3.018253   -0.969588
    30          1           0        2.651851    1.959801   -2.214548
    31          8           0        1.675205    2.288661    0.967359
    32          1           0        2.425182    2.882657    1.144644
    33          8           0       -1.675185    2.288715   -0.967342
    34          1           0       -2.425042    2.882909   -1.144463
    35          6           0        1.681575   -2.614928    2.289660
    36          1           0        2.561211   -2.694958    1.635646
    37          1           0        2.061335   -2.453393    3.305527
    38          1           0        1.137008   -3.562661    2.261027
    39          6           0       -1.681601   -2.614936   -2.289622
    40          1           0       -2.561223   -2.694961   -1.635588
    41          1           0       -2.061384   -2.453415   -3.305482
    42          1           0       -1.137032   -3.562669   -2.260990
 ---------------------------------------------------------------------
```

Structure for TS$_{endo}$-**2**$_{s\text{-}trans}$

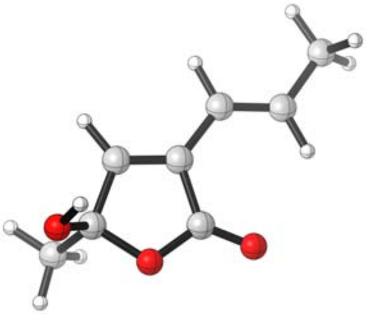


Imaginary frequency: -457.5097 cm^{-1}

```
---------------------------------------------------------------------
 Center     Atomic      Atomic             Coordinates (Angstroms)
 Number     Number       Type             X           Y           Z
 ---------------------------------------------------------------------
      1          6           0       -1.439597    0.515449    0.265325
      2          6           0       -2.456018    0.218633    1.259751
      3          6           0       -3.771392    0.083558    1.036697
      4          6           0       -1.154699   -2.018970   -0.378062
      5          6           0        0.080143   -1.897034   -0.950805
      6          6           0       -0.143181    0.964106    0.541788
      7          1           0       -2.080863    0.110891    2.276988
      8          1           0       -1.233673   -1.937676    0.701333
      9          1           0        0.235180   -2.157873   -1.994595
     10          1           0        0.080093    1.408695    1.505594
     11          1           0       -4.156332    0.207179    0.028840
     12          6           0       -1.692044    0.732960   -1.165669
     13          8           0       -2.684152    0.539795   -1.827999
     14          6           0        0.324033    1.725145   -0.706936
     15          8           0       -0.582890    1.286723   -1.727617
     16          6           0        1.136452   -1.299946   -0.248878
     17          6           0        1.054632   -0.583286    0.940619
     18          6           0        2.469993   -0.129229    1.289577
     19          1           0        0.421390   -0.879015    1.769976
     20          6           0        2.495822   -1.123292   -0.795574
     21          8           0        2.953006   -1.518676   -1.837289
```

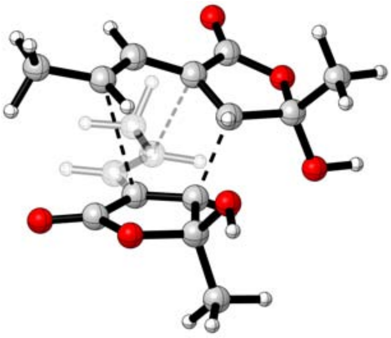
```
     22          8           0        3.250224   -0.462129    0.110640
     23          6           0        0.166743    3.223899   -0.504285
     24          1           0        0.861957    3.560951    0.268362
     25          1           0        0.391742    3.735857   -1.441488
     26          1           0       -0.851809    3.462891   -0.192349
     27          8           0        1.586331    1.418650   -1.213987
     28          1           0        2.245554    1.773399   -0.599876
     29          6           0       -2.369934   -2.484737   -1.092235
     30          1           0       -2.236407   -2.474209   -2.174807
     31          1           0       -2.624849   -3.501759   -0.773436
     32          1           0       -3.225751   -1.853112   -0.829045
     33          6           0       -4.766665   -0.217891    2.109956
     34          1           0       -5.516447    0.576823    2.176386
     35          1           0       -5.310892   -1.140277    1.882685
     36          1           0       -4.287197   -0.328137    3.084589
     37          6           0        3.057485   -0.878737    2.467095
     38          1           0        4.099893   -0.580352    2.604782
     39          1           0        2.490984   -0.642627    3.369389
     40          1           0        3.017180   -1.953853    2.286629
     41          8           0        2.522969    1.253311    1.466376
     42          1           0        3.365715    1.487037    1.878846
 ---------------------------------------------------------------------
```

Structure for 3b



Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.391688	-0.369921	-0.012026
2	6	0	-0.708362	-1.131312	-0.031929
3	6	0	-1.952141	-0.282238	-0.037791
4	1	0	-0.762440	-2.214706	-0.043272
5	6	0	1.784803	-0.799366	0.004154
6	1	0	1.931830	-1.879032	0.006914
7	6	0	2.849695	0.012000	0.017400
8	1	0	2.700884	1.088868	0.014197
9	6	0	4.262214	-0.476648	0.036685
10	1	0	4.812047	-0.104053	-0.835711
11	1	0	4.788854	-0.101442	0.922182
12	1	0	4.311312	-1.569348	0.039112
13	8	0	-1.426581	1.069329	-0.033945
14	6	0	-0.075367	1.051043	-0.007615
15	8	0	0.569246	2.071514	0.017564
16	8	0	-2.742024	-0.461255	-1.167824
17	1	0	-2.167805	-0.429284	-1.952890
18	6	0	-2.831789	-0.457979	1.181283
19	1	0	-3.669326	0.242534	1.123671
20	1	0	-3.218460	-1.479636	1.209287
21	1	0	-2.256478	-0.264075	2.089182

Structure for TS_{exo}



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    8          1           0        1.220415    0.526828   -1.953415
    9          1           0       -0.988941    2.596166   -1.393816
   10          1           0        0.059254   -1.221752    1.415662
   11          1           0       -1.220175    0.528073    1.953598
   12          6           0        2.572609    0.586932    0.347926
   13          8           0        3.342720    1.518537    0.319088
   14          6           0        1.903649   -1.620452    0.228570
   15          8           0        2.931532   -0.642978   -0.093889
   16          6           0       -1.200931    0.523339   -0.863815
   17          6           0       -0.709227   -0.771202   -0.674723
   18          6           0       -1.904247   -1.620055   -0.228261
   19          1           0       -0.059772   -1.222316   -1.415436
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     32          1           0        2.350205   -2.983615   -1.067527
     33          8           0       -1.631400   -2.355920    0.916175
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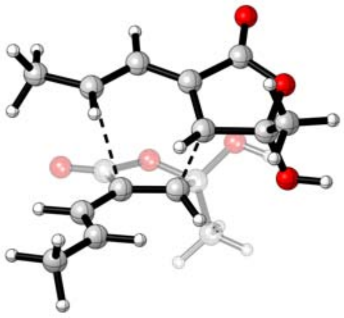
Structure for TS_{endo}



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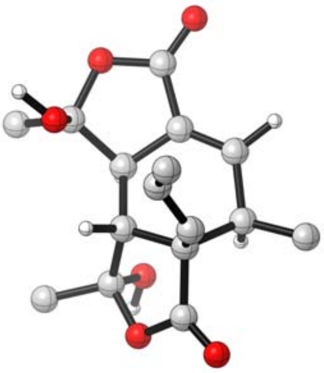
Structure for PD



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IV. References for Supplementary Information

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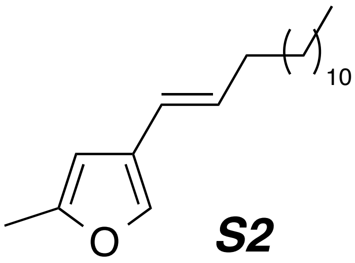

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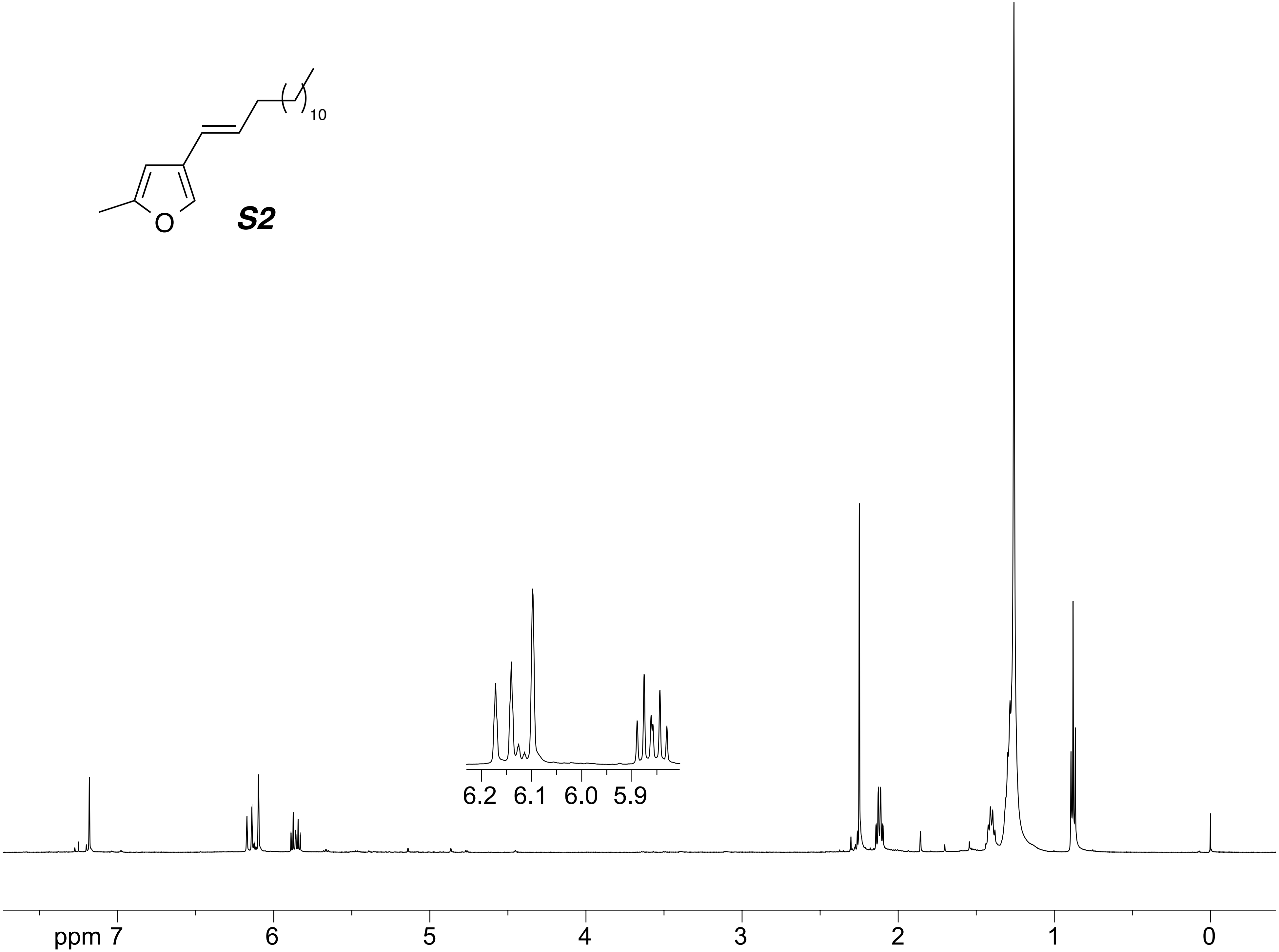

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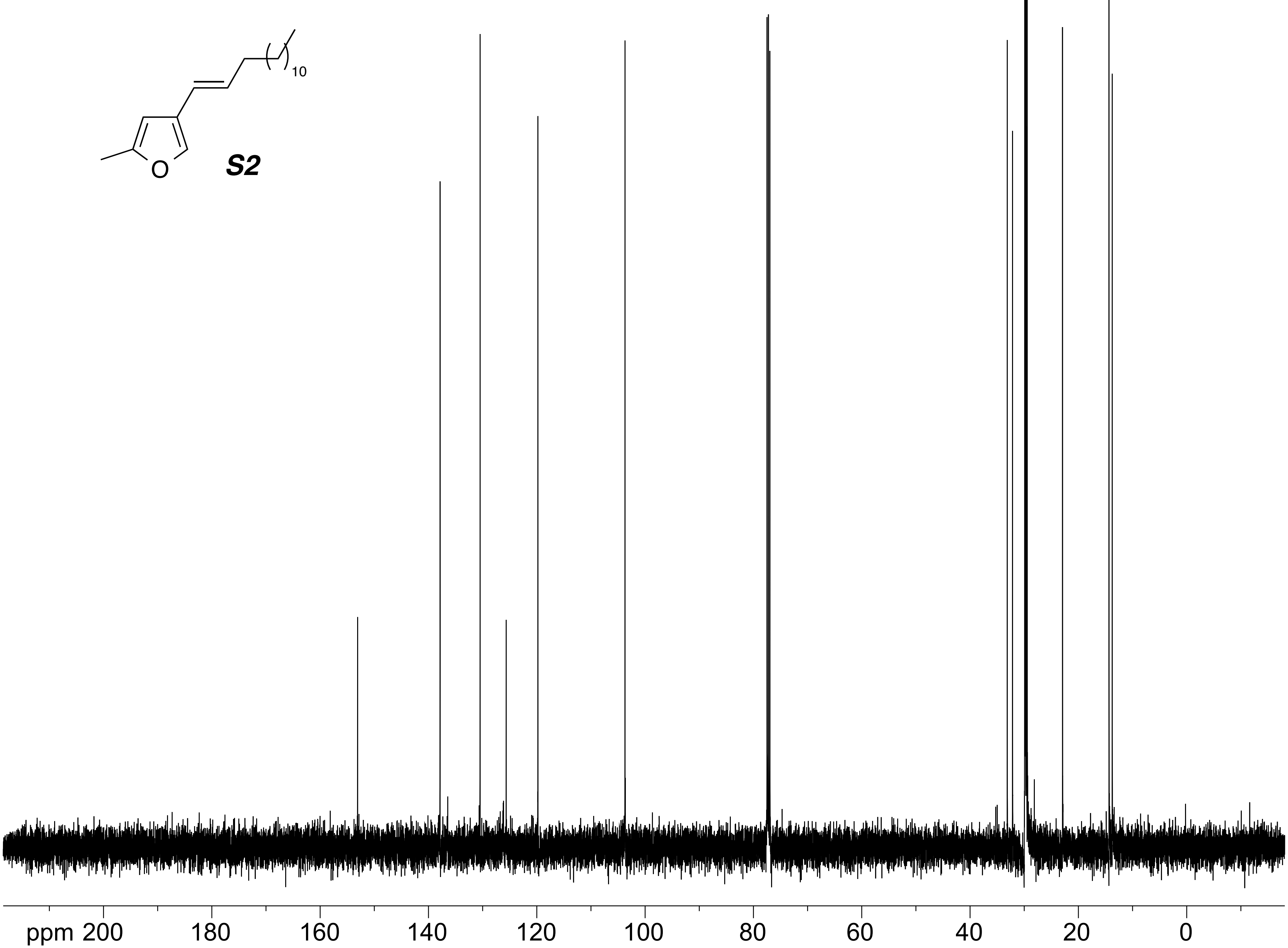

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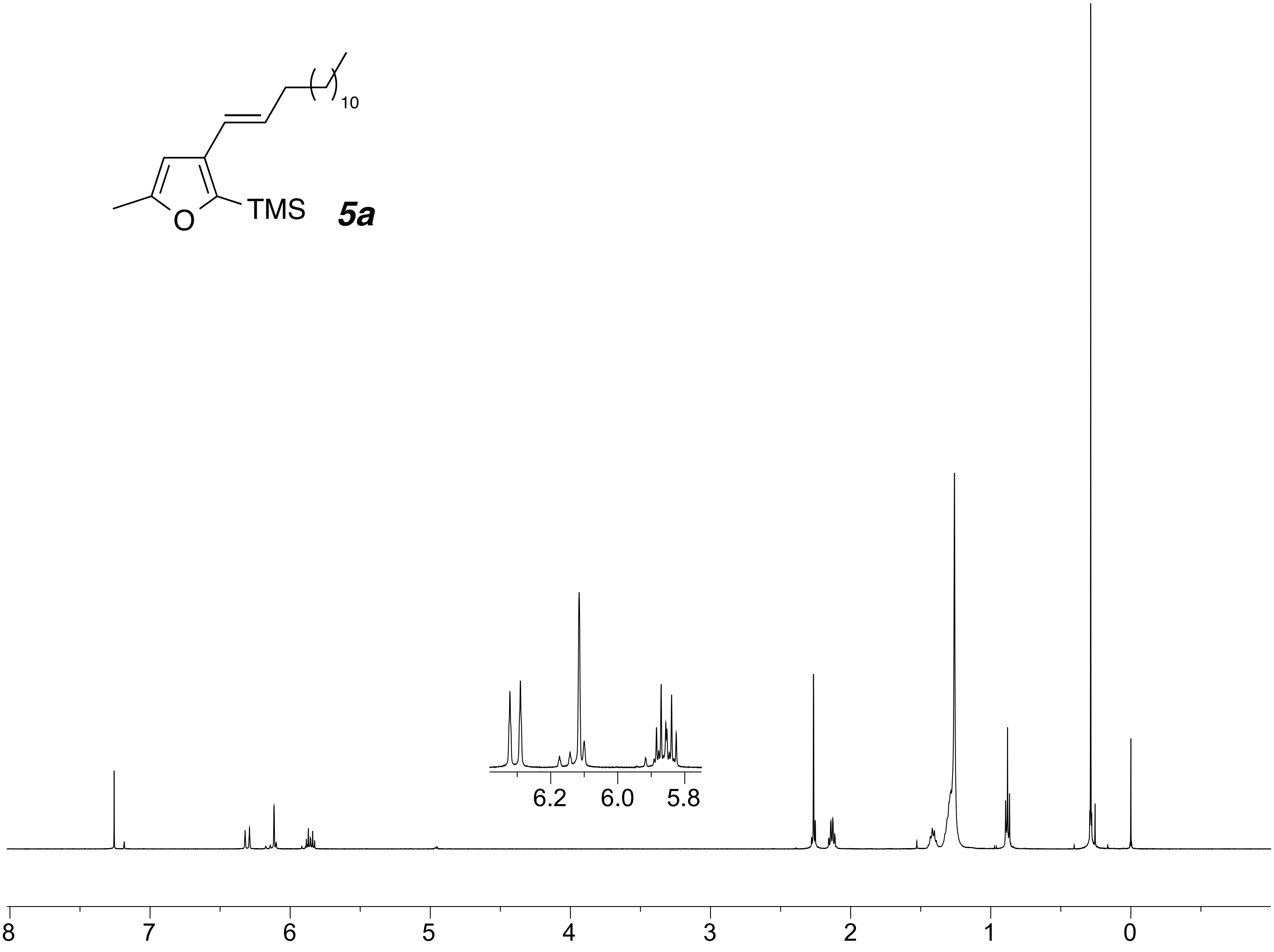

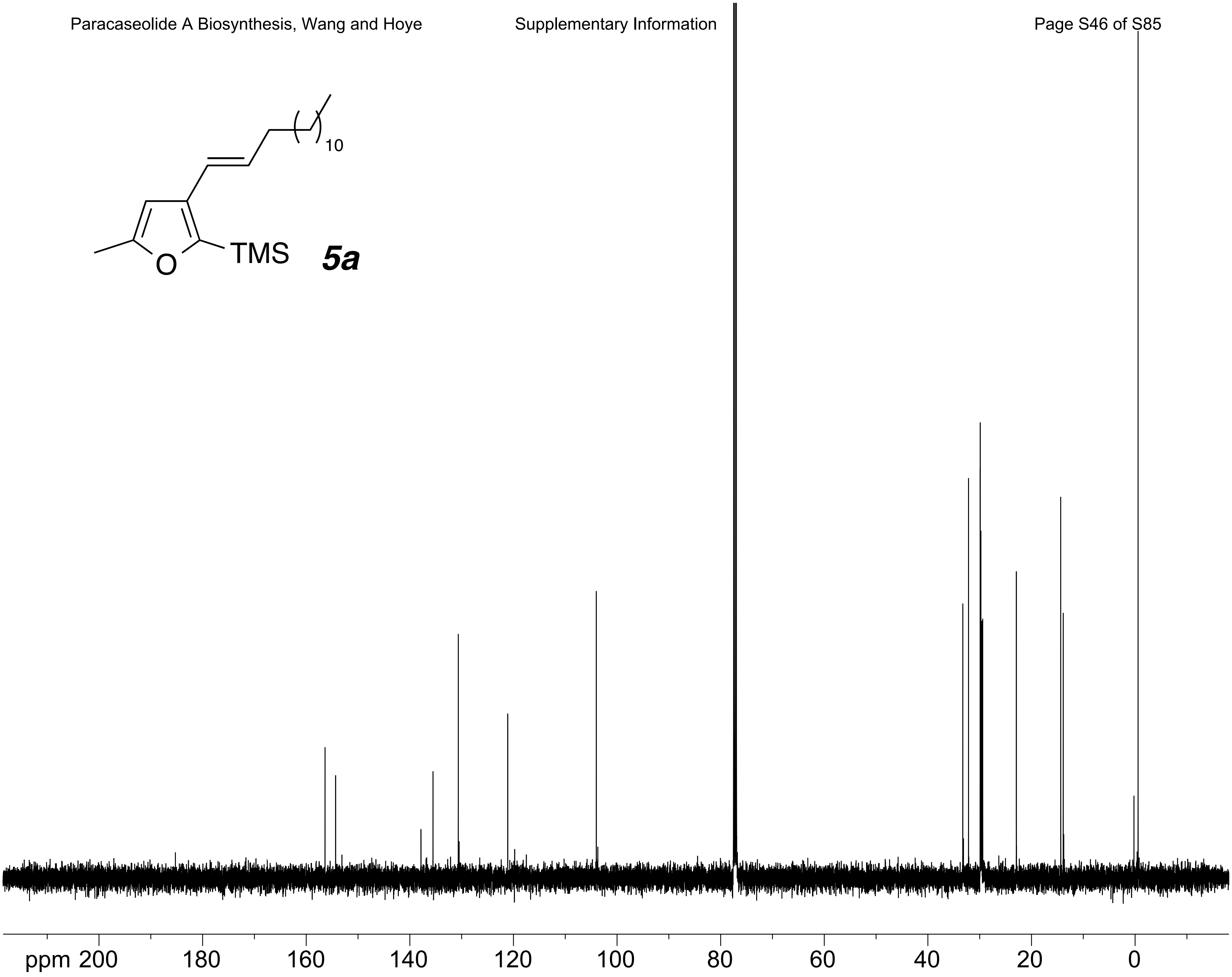

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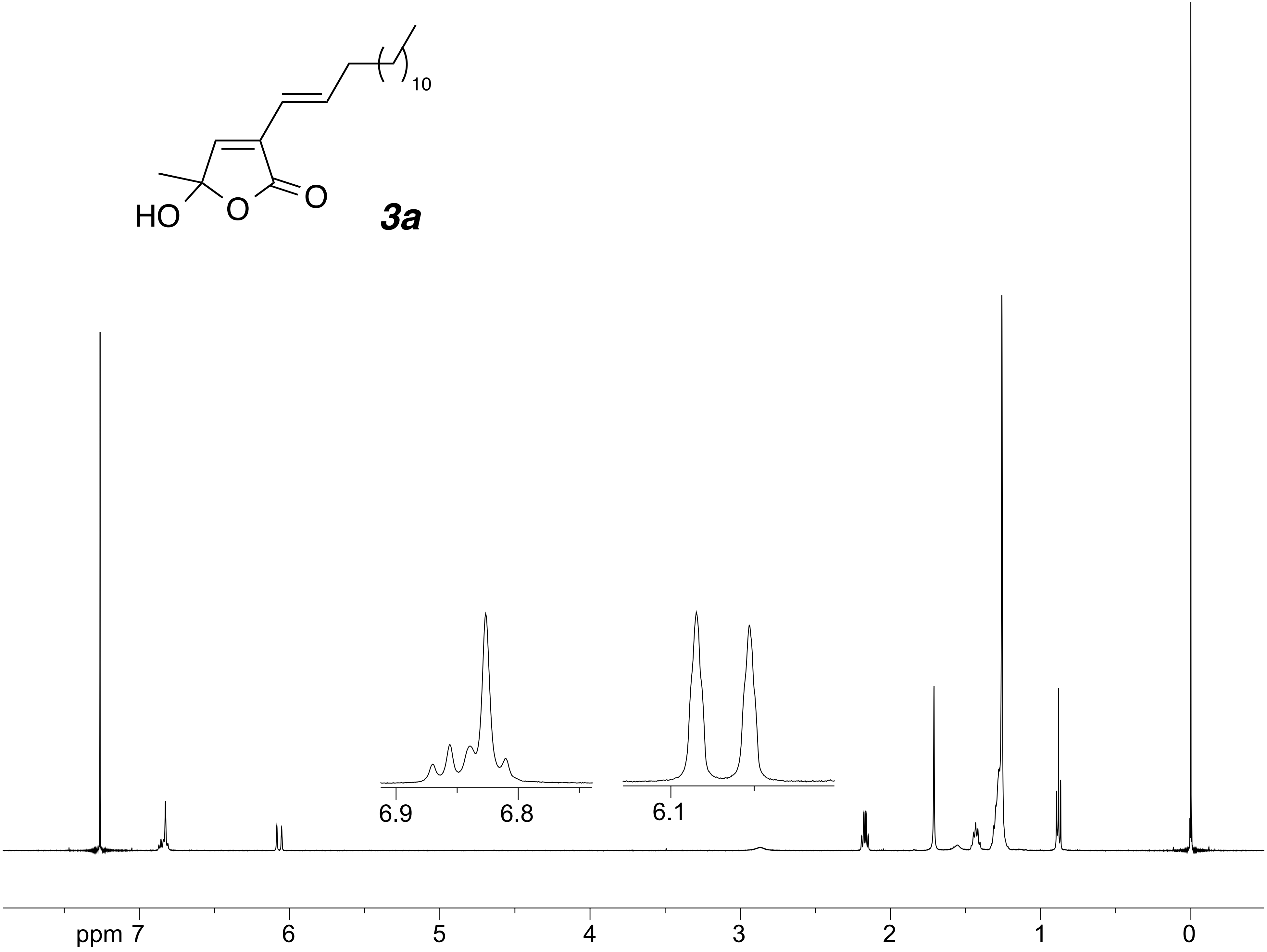

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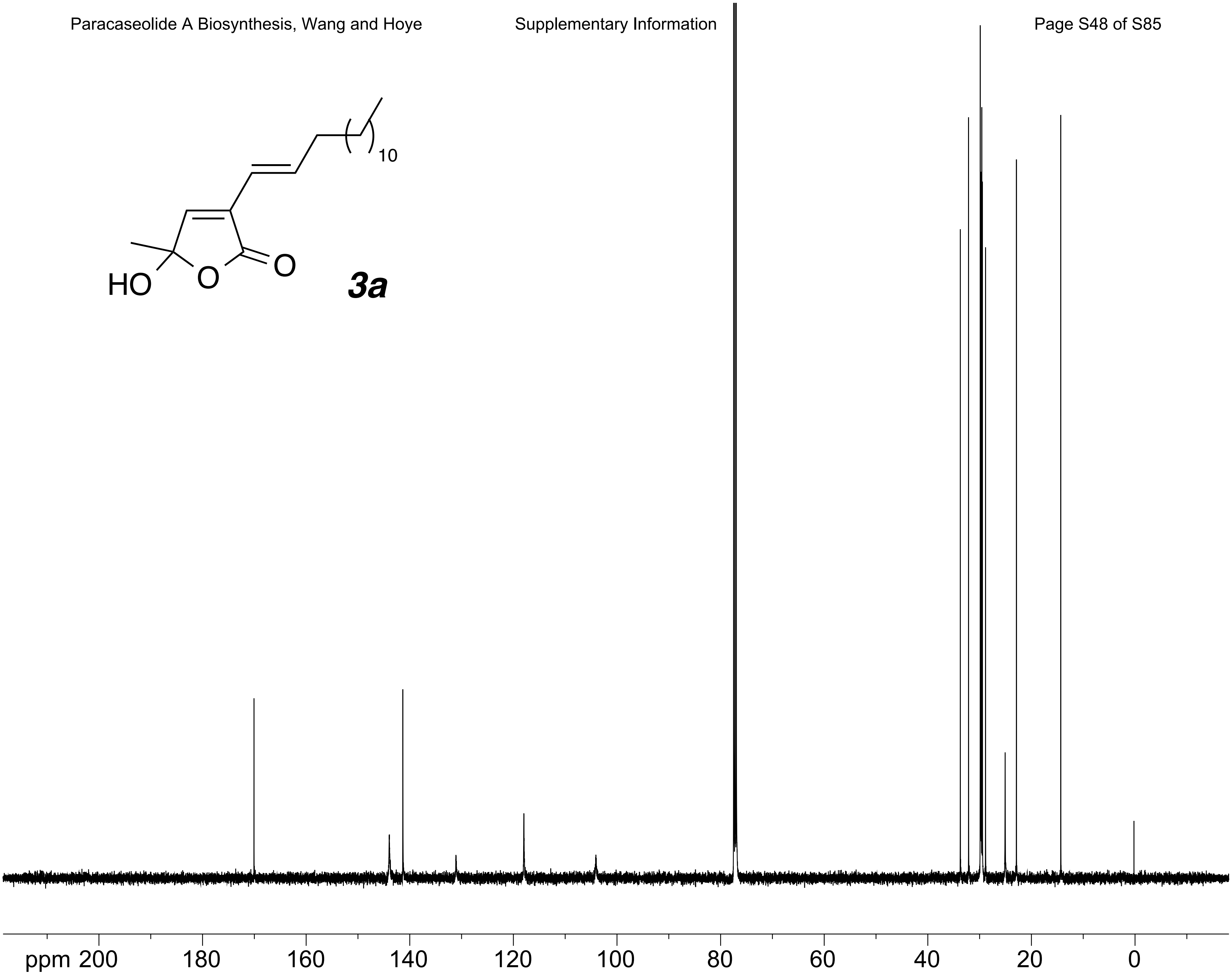

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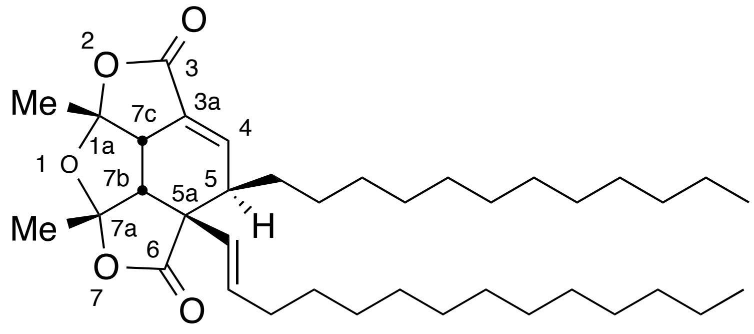

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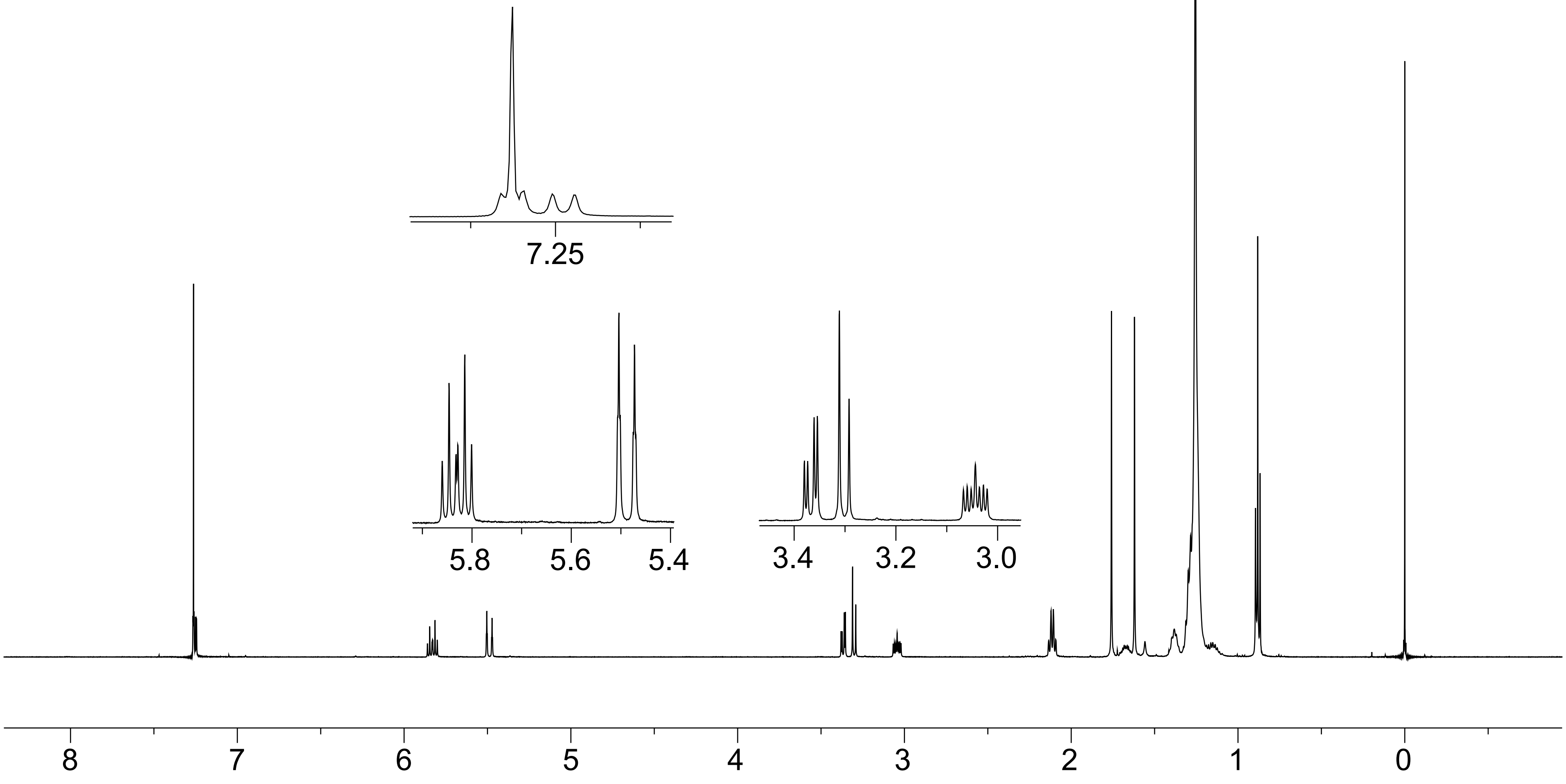

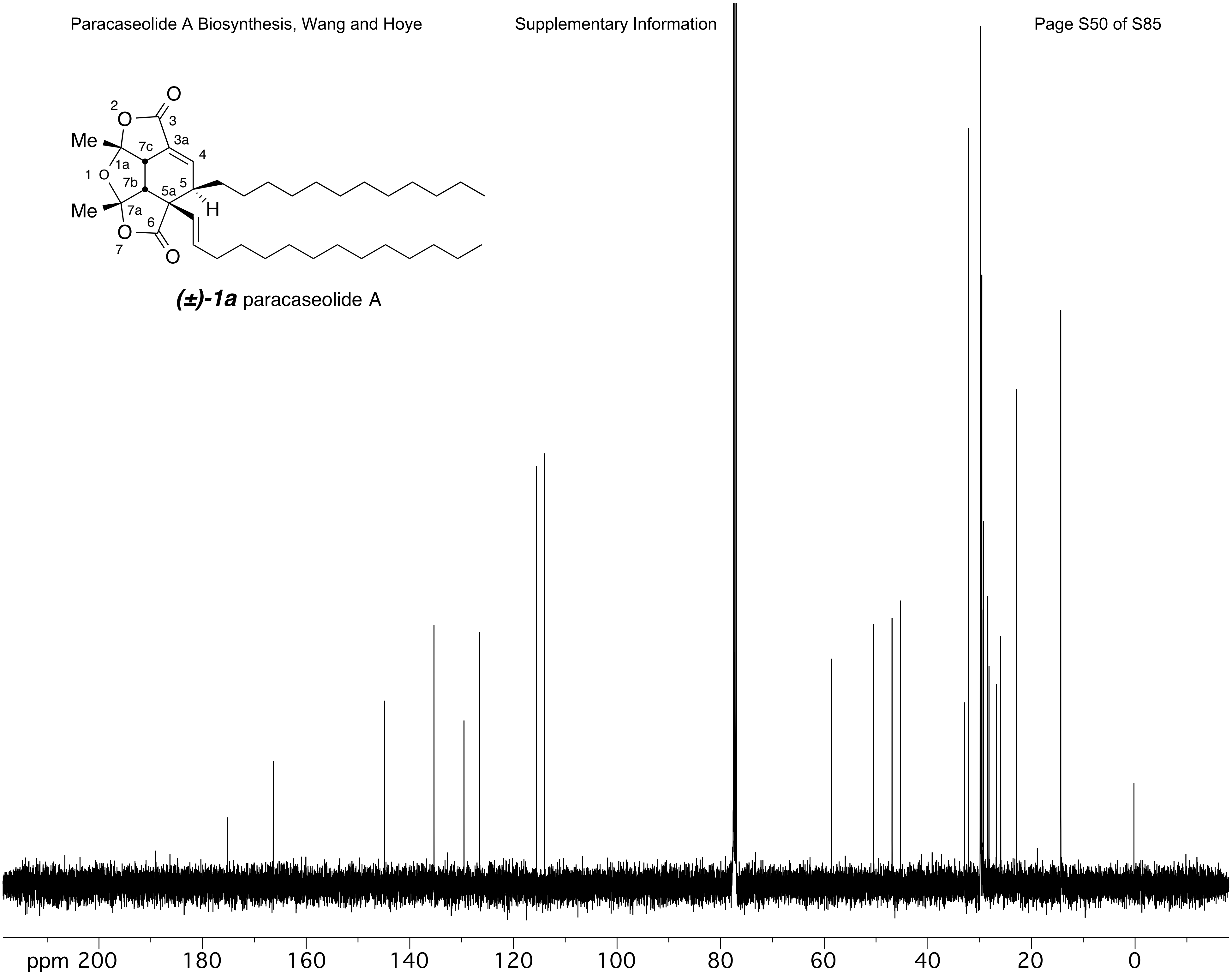

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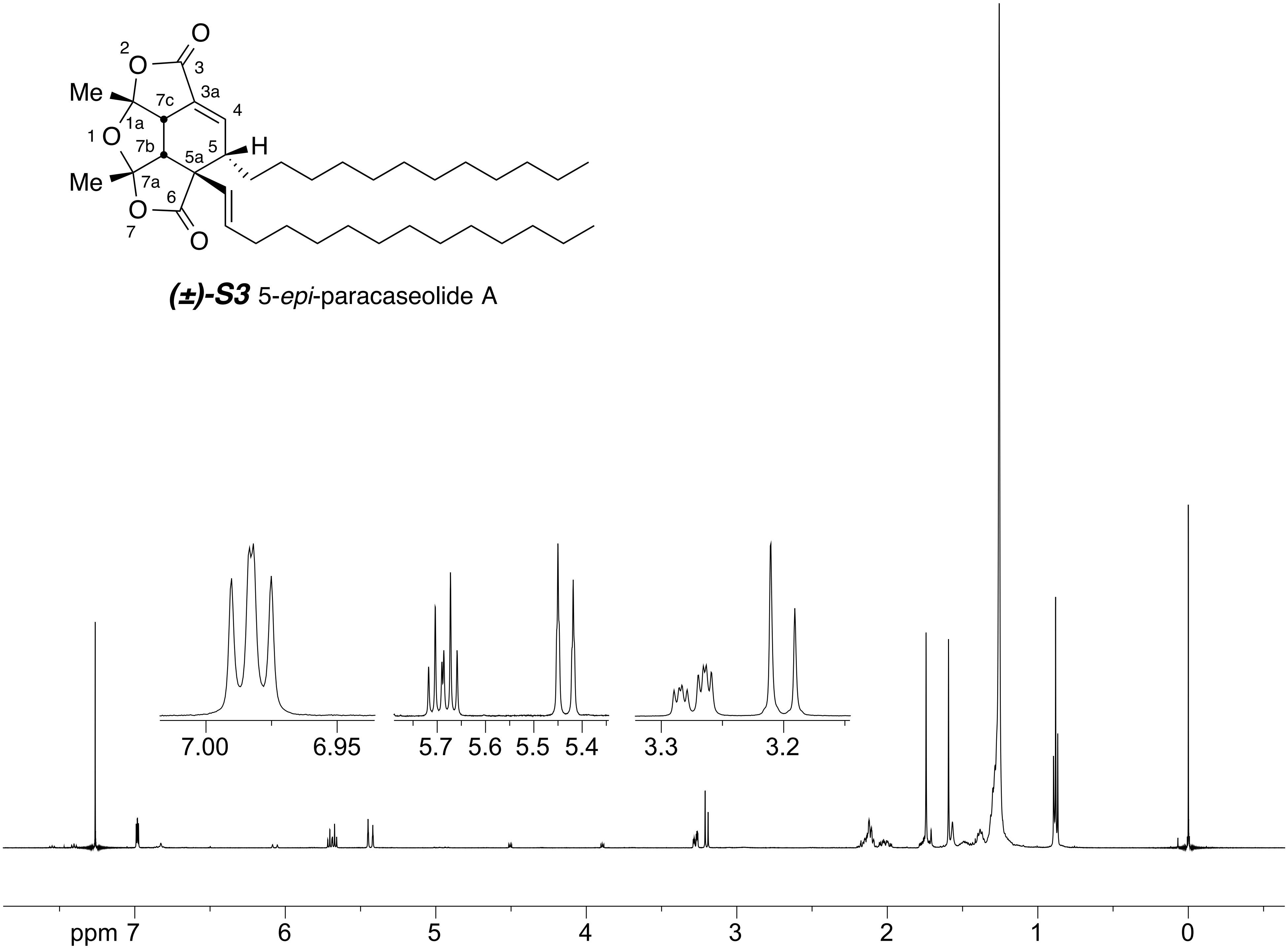

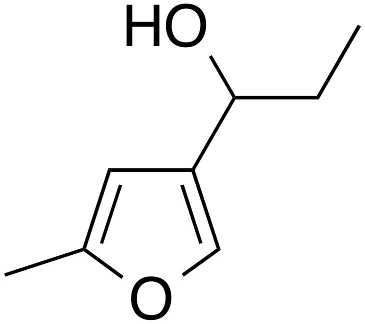

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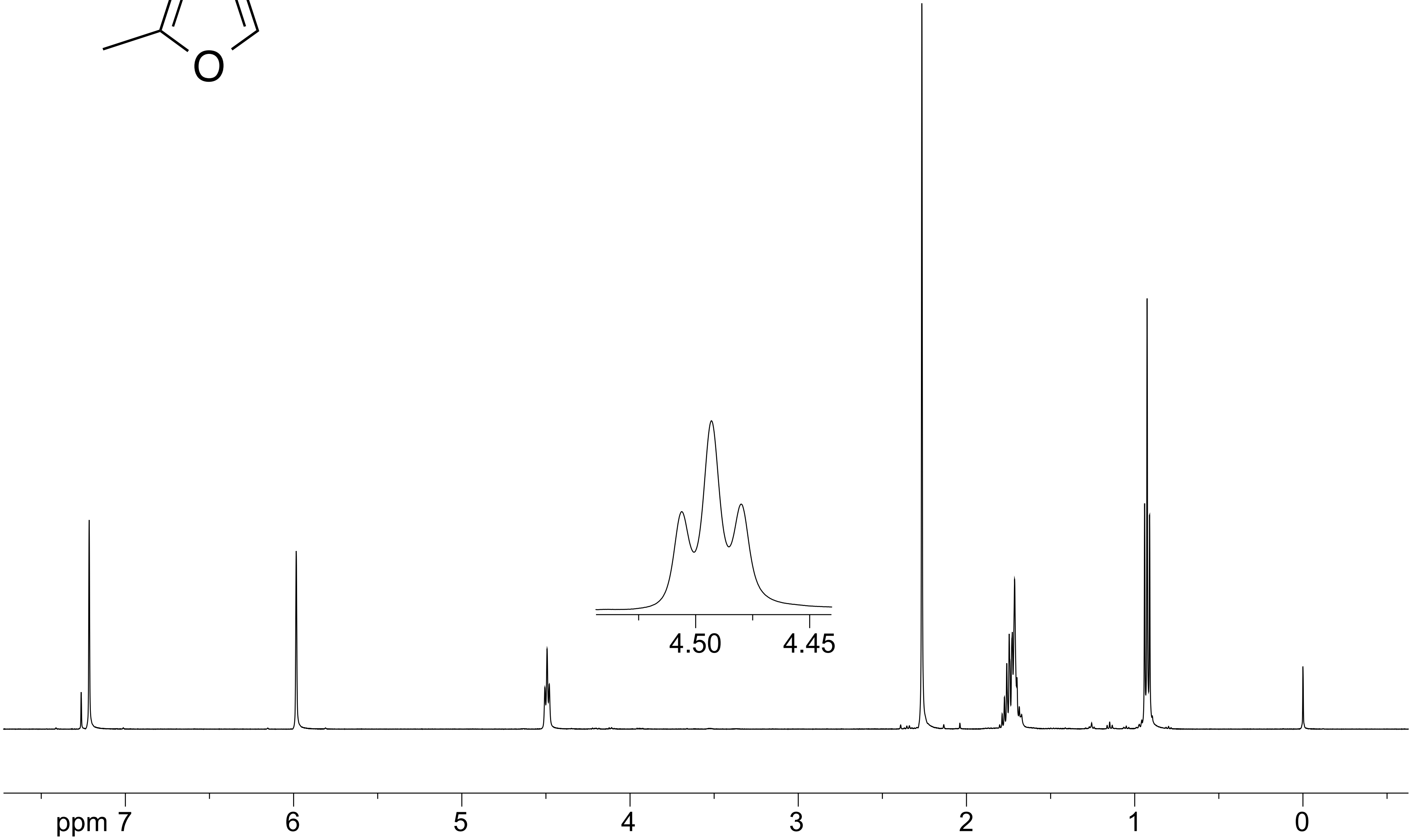

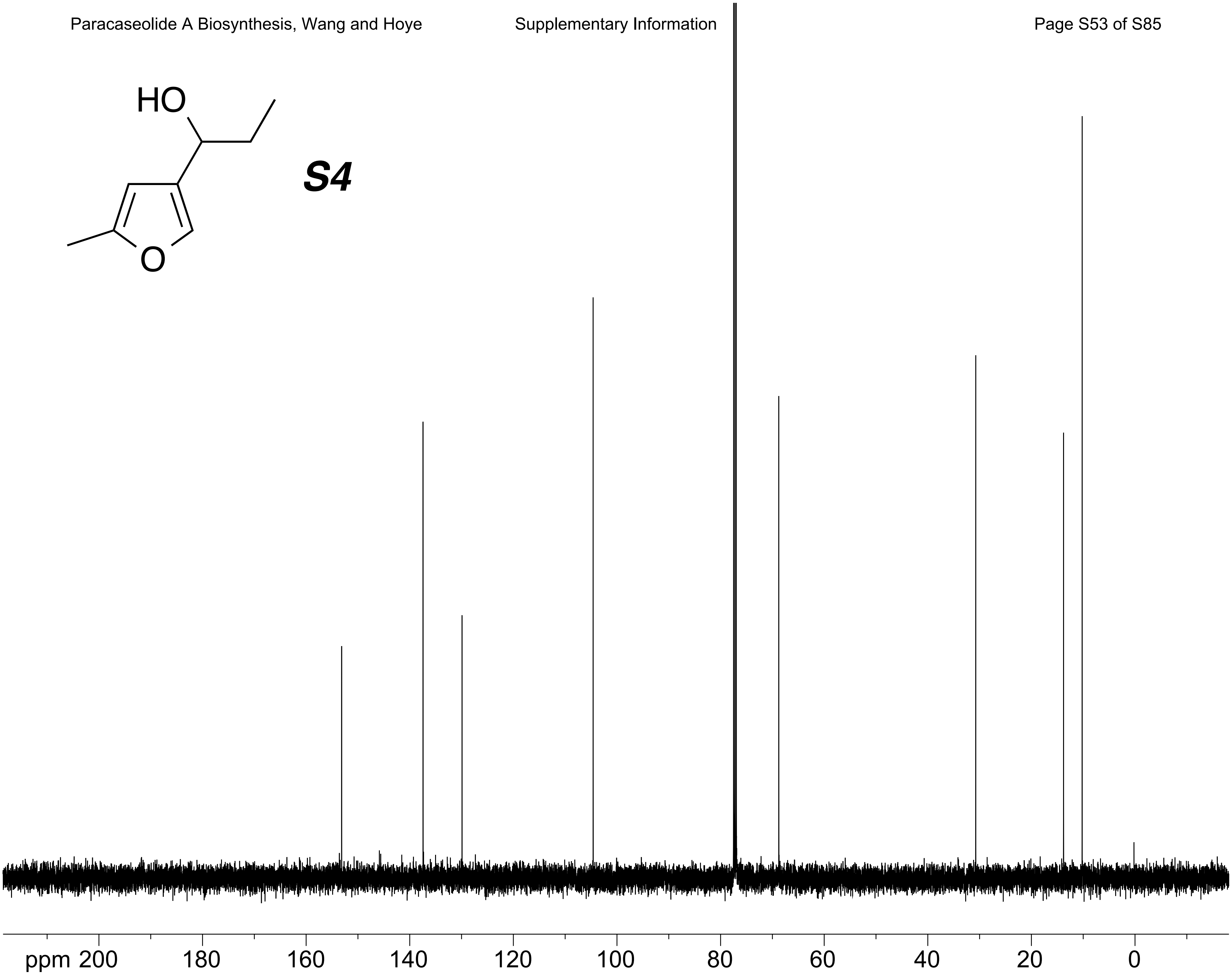

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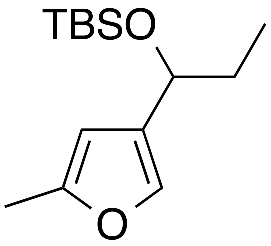

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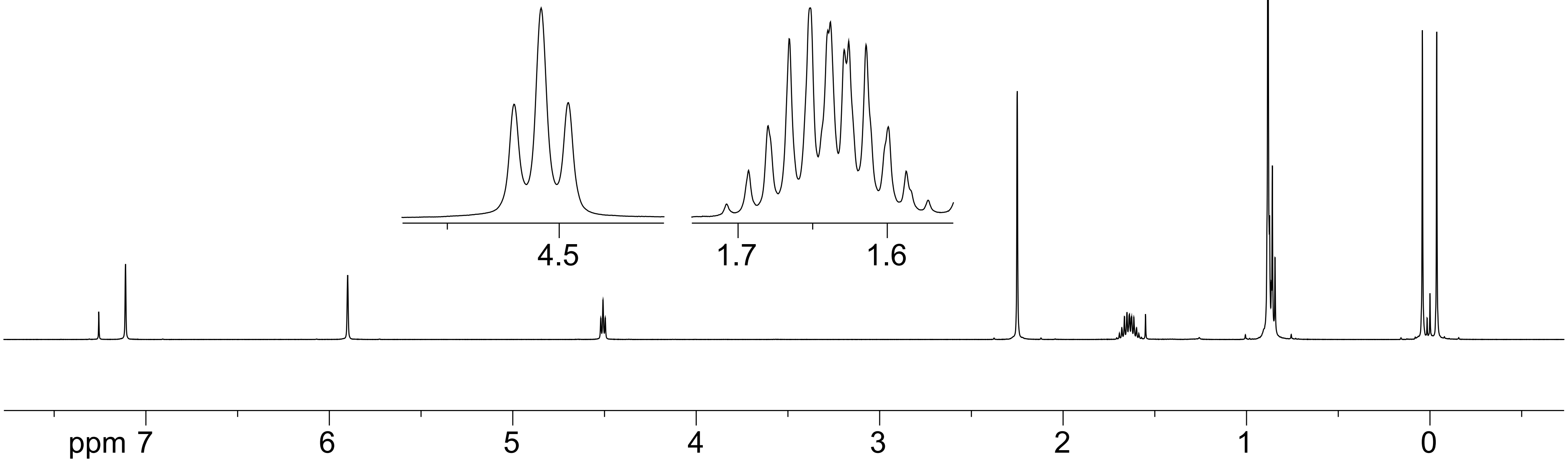

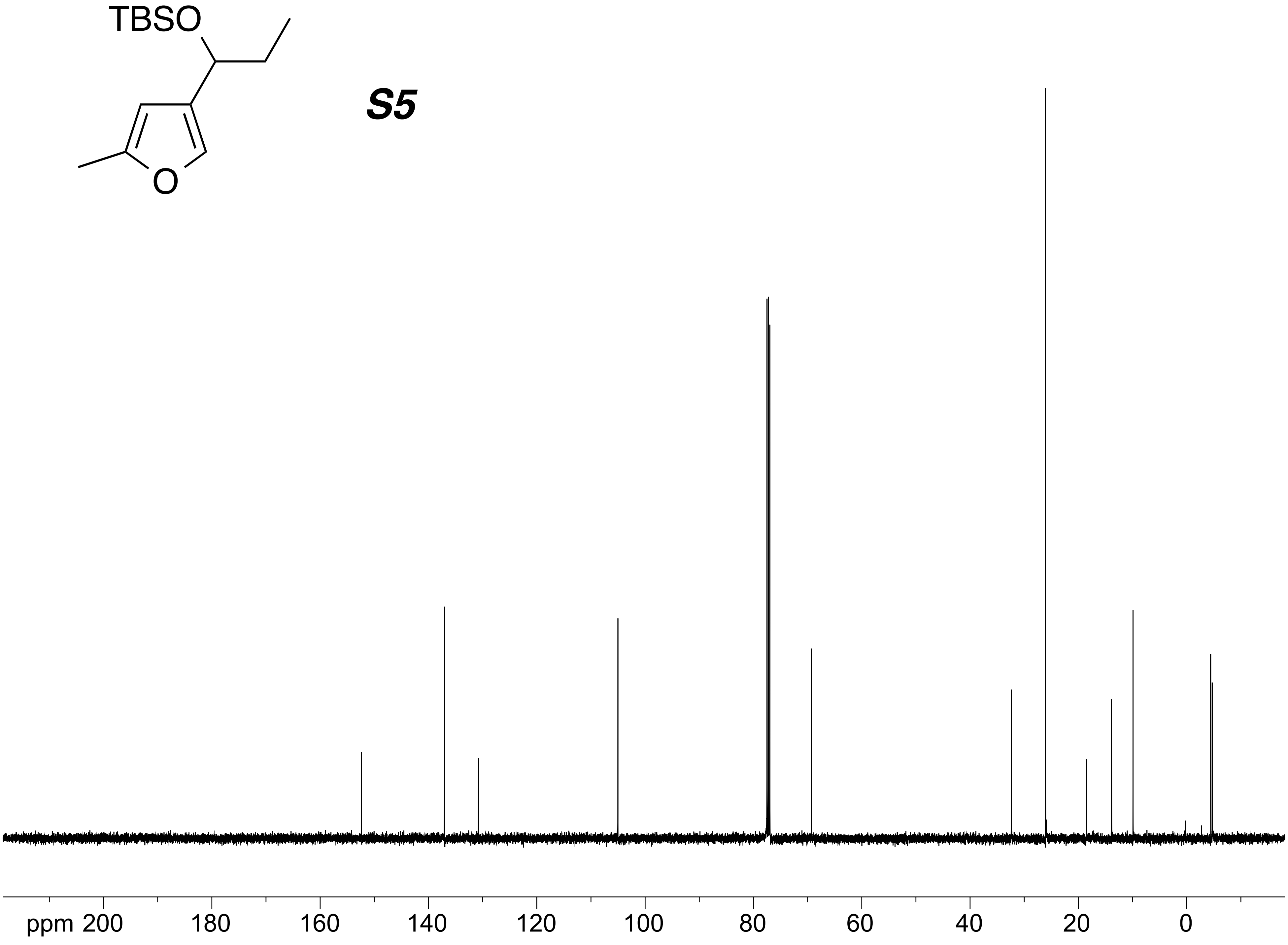
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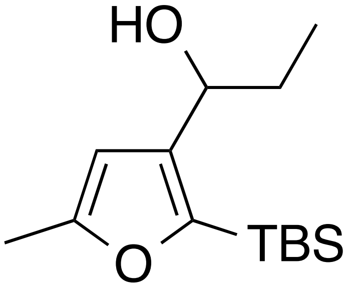

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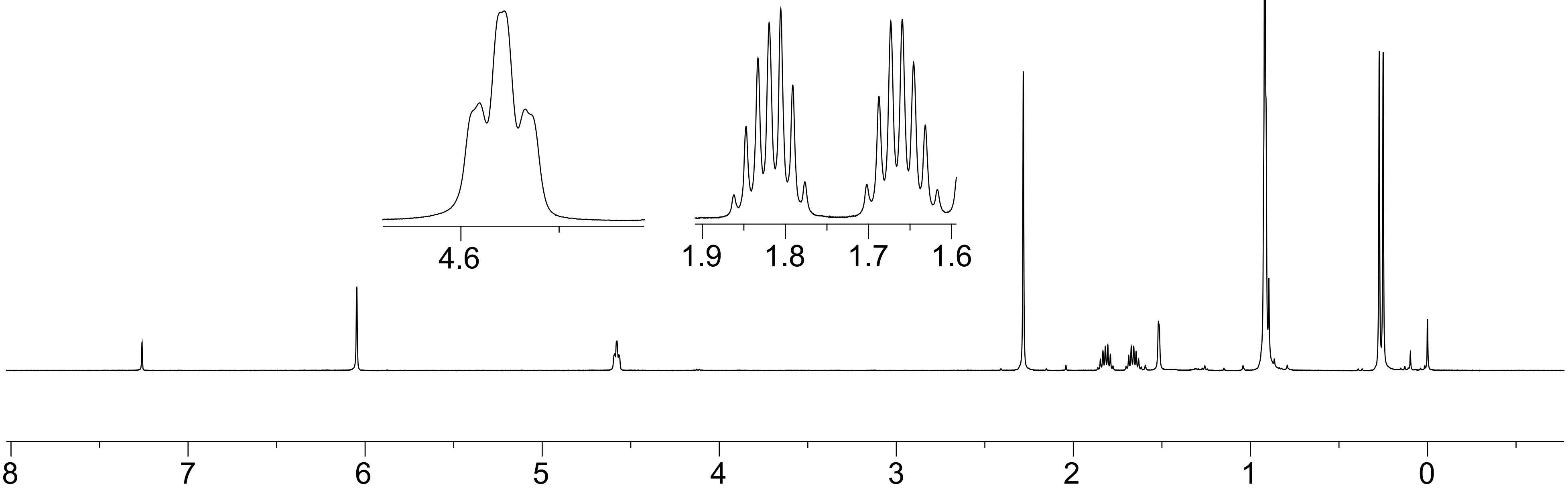

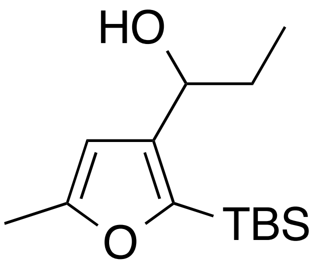

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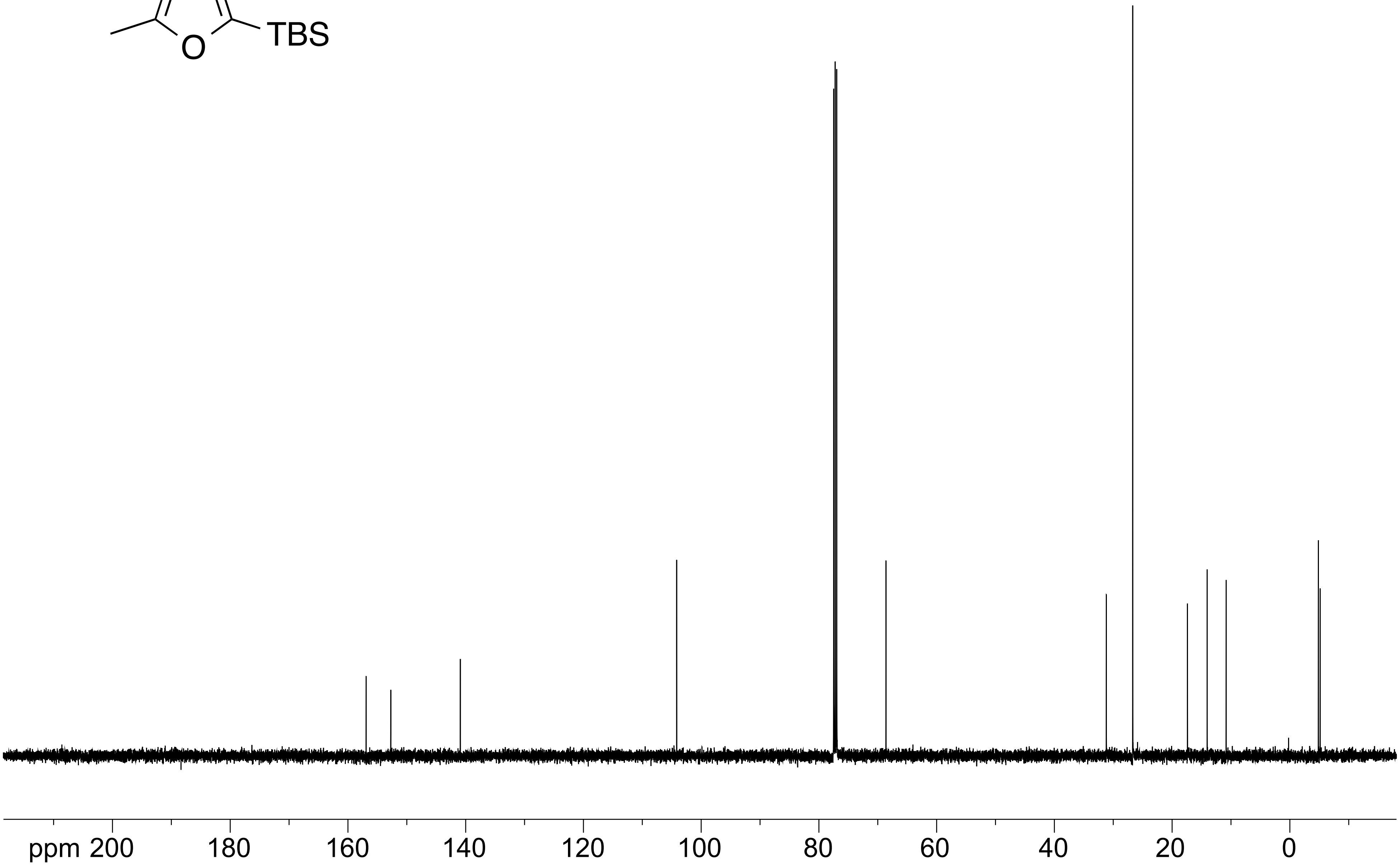

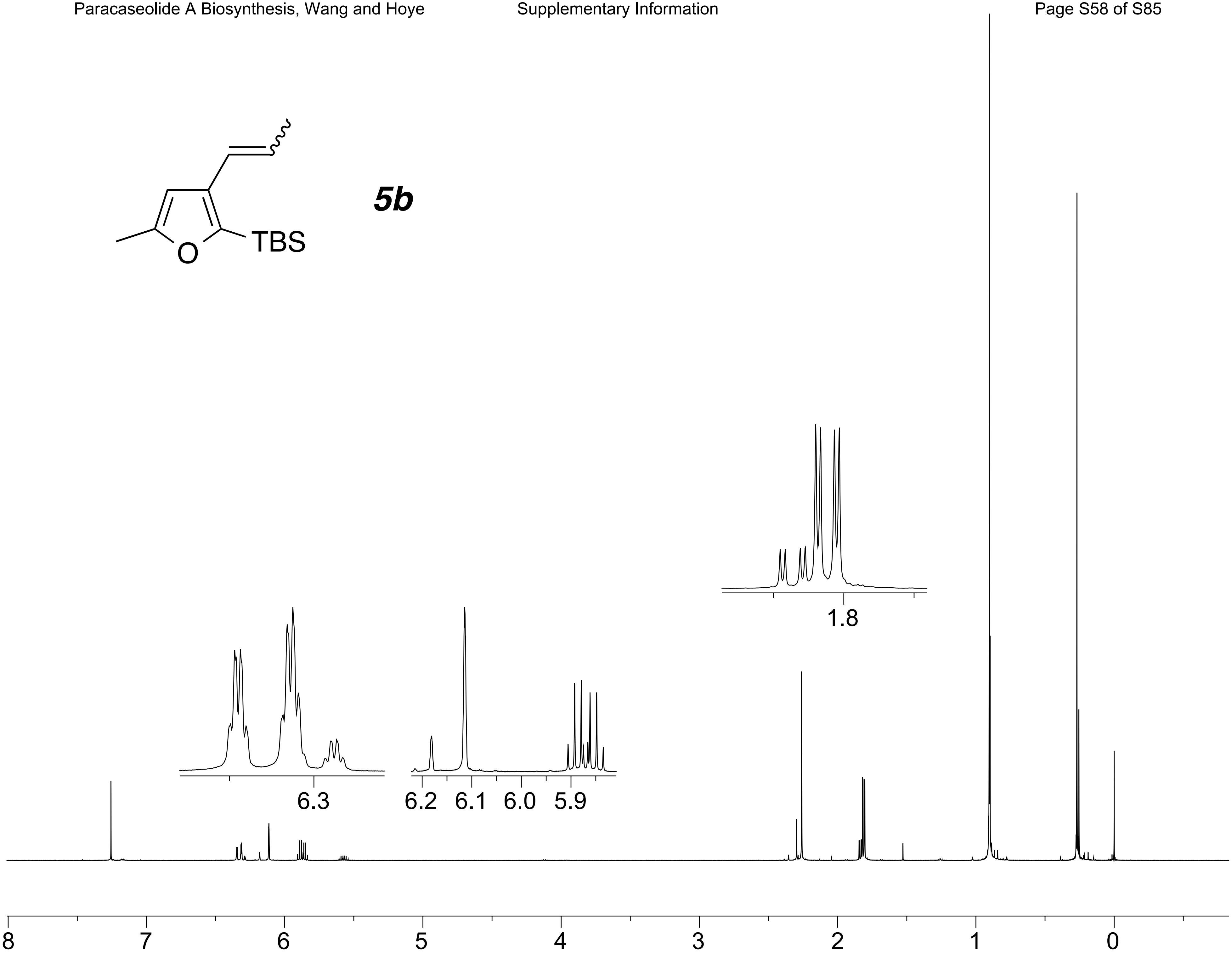
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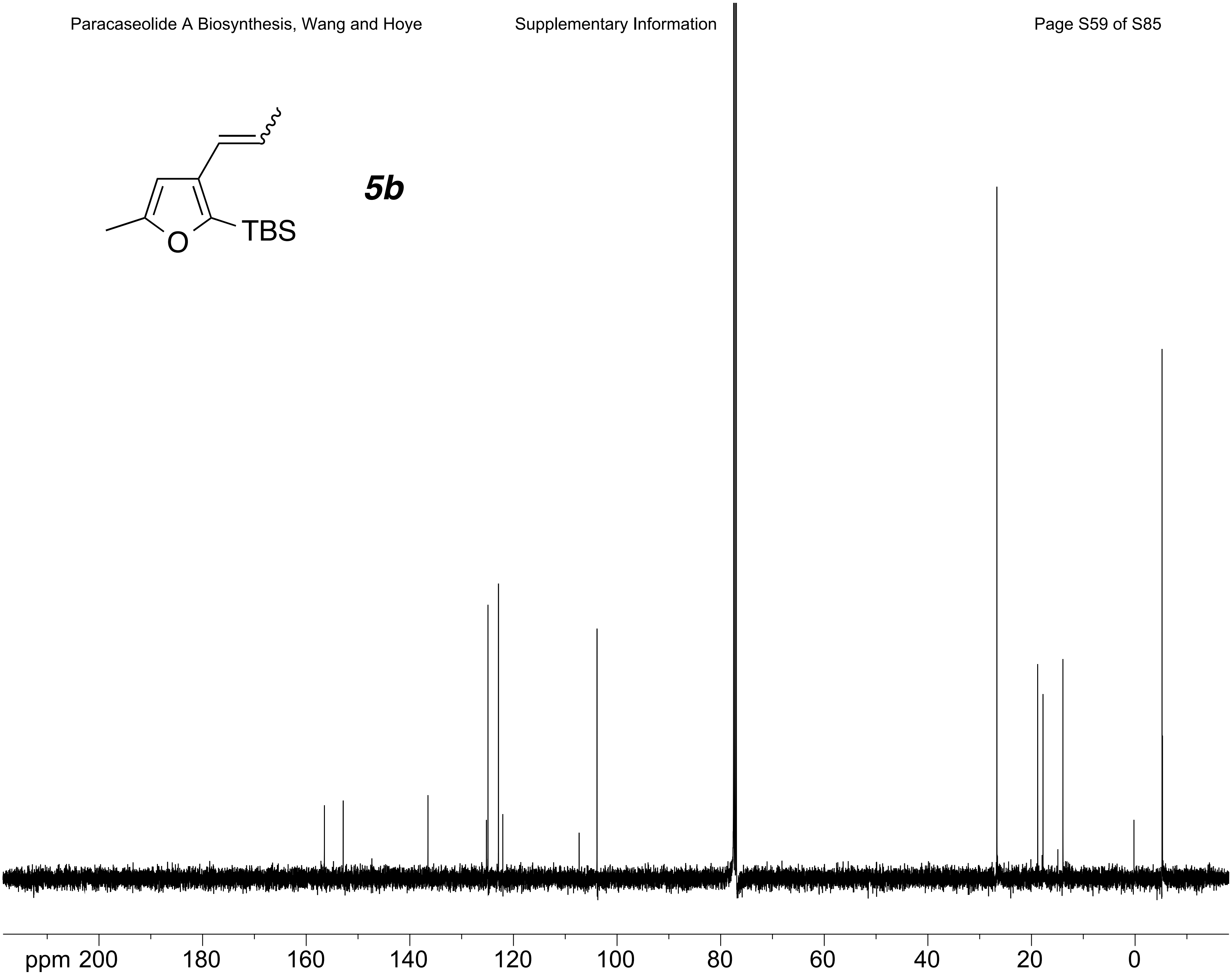
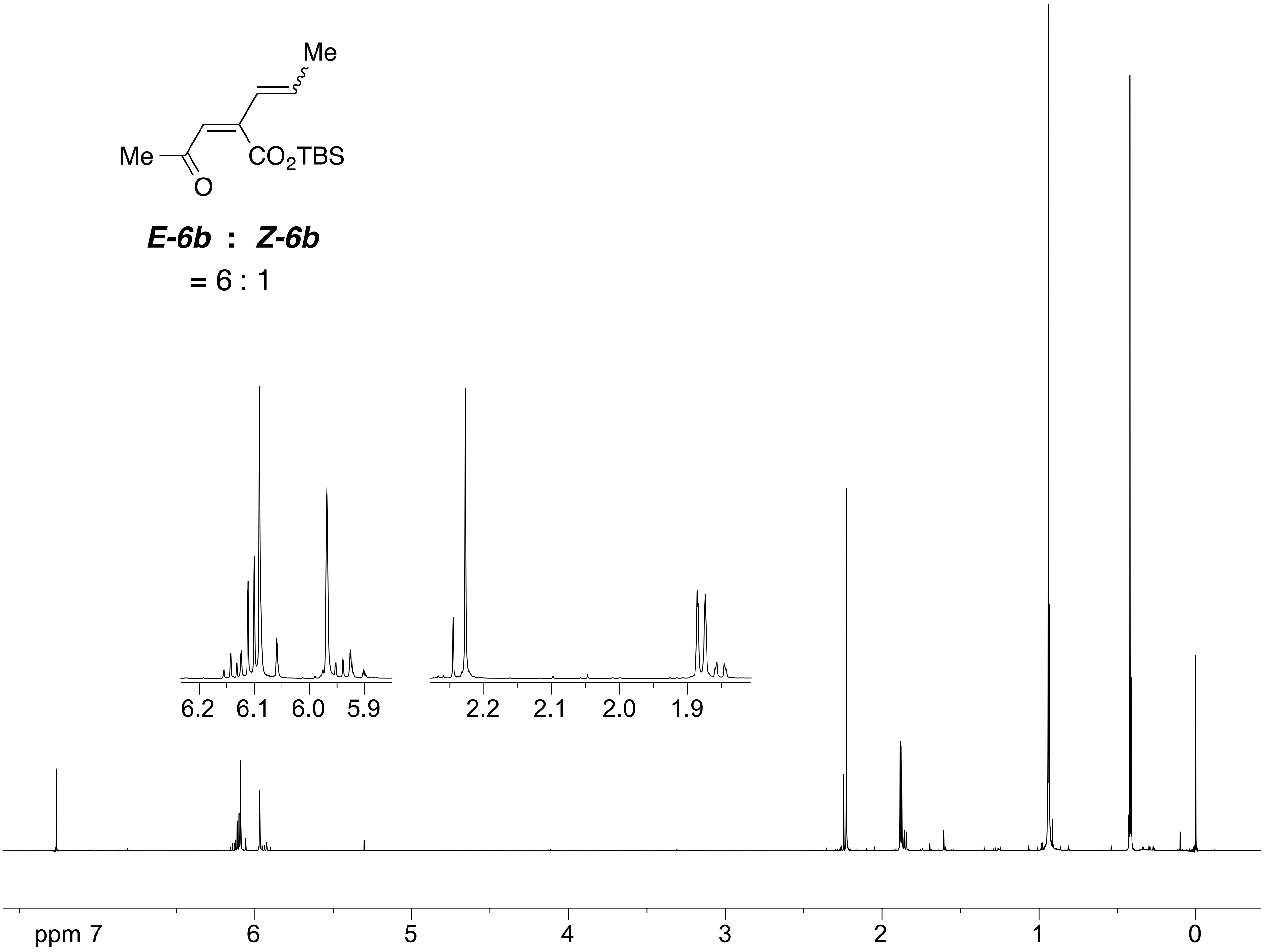
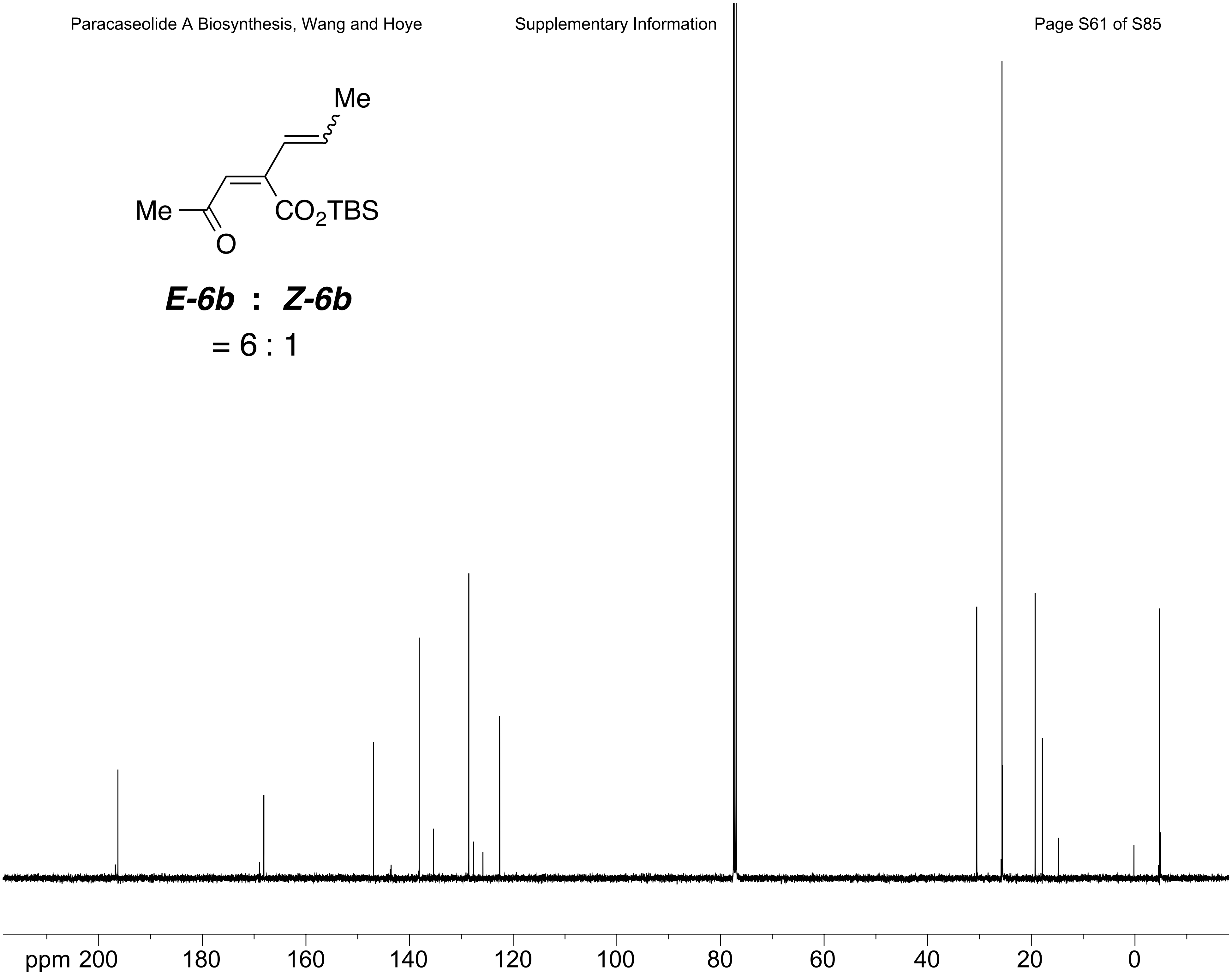


5b



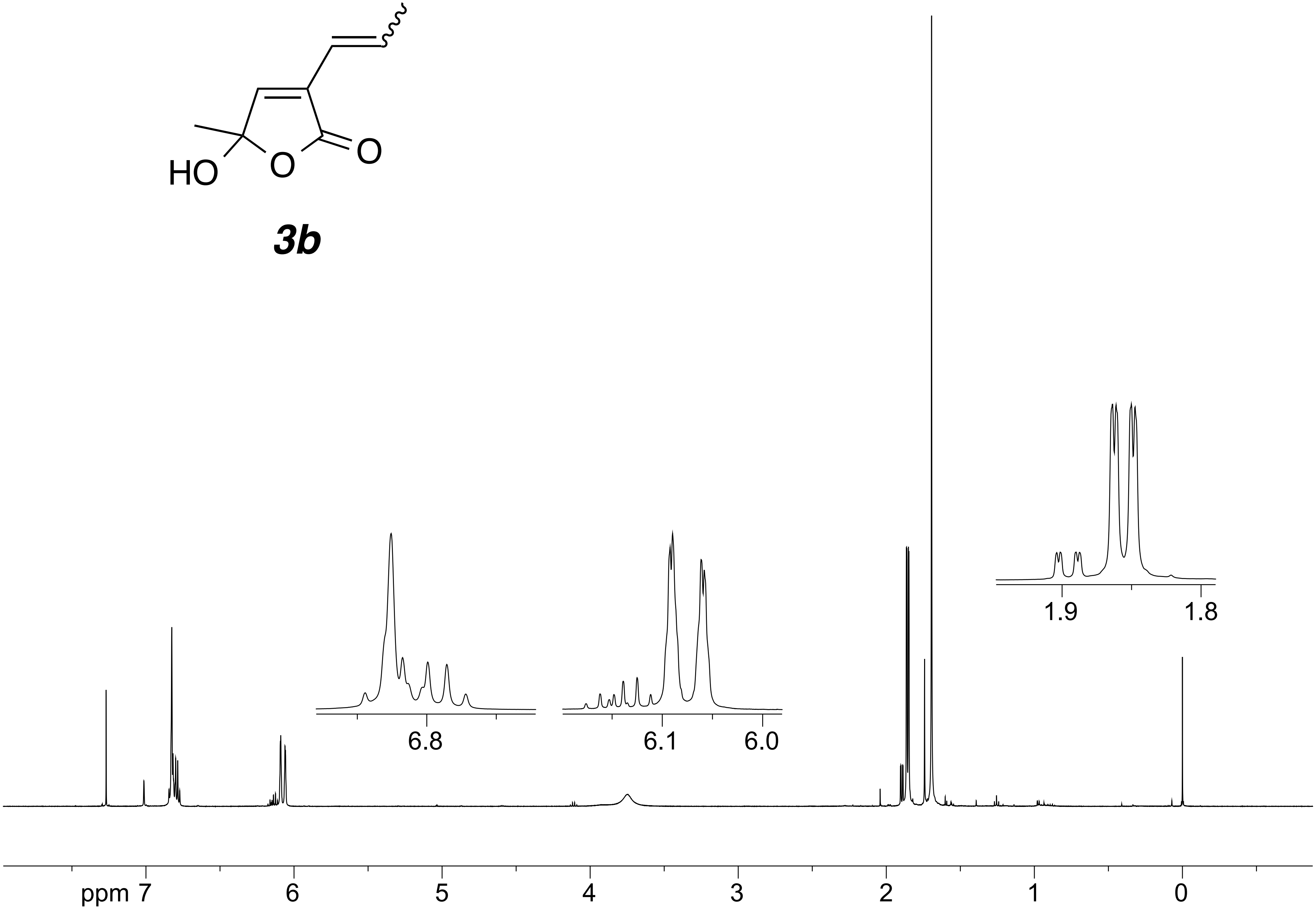
E-6b* : *Z-6b
= 6 : 1

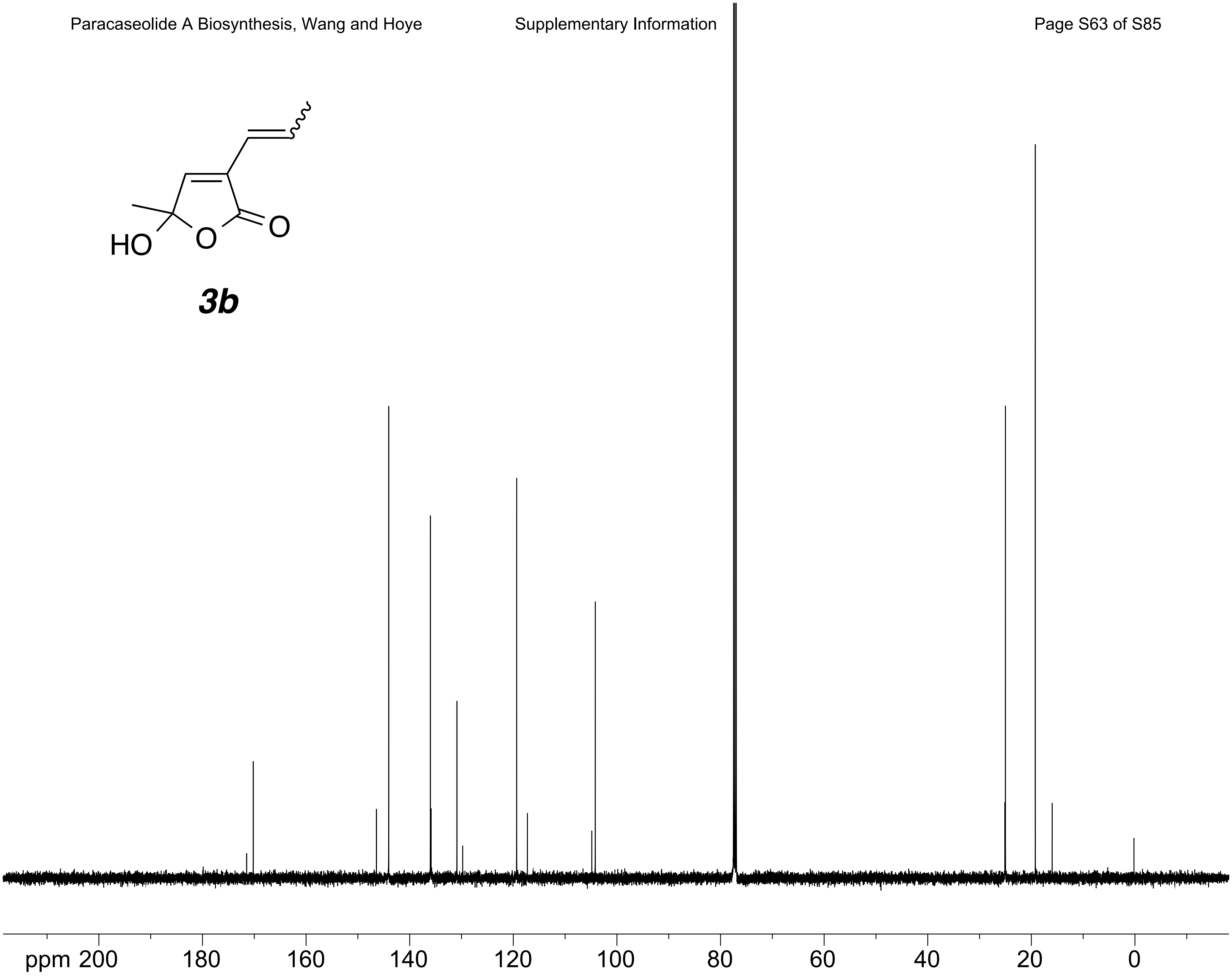


***E*-6b : *Z*-6b**

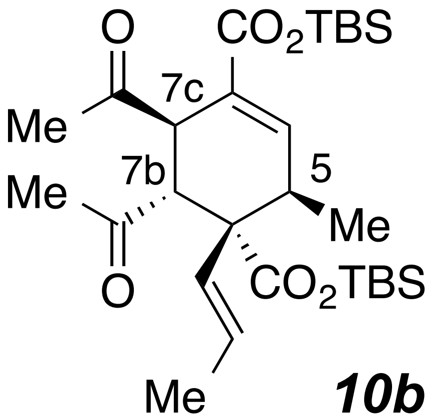
= 6 : 1

3b

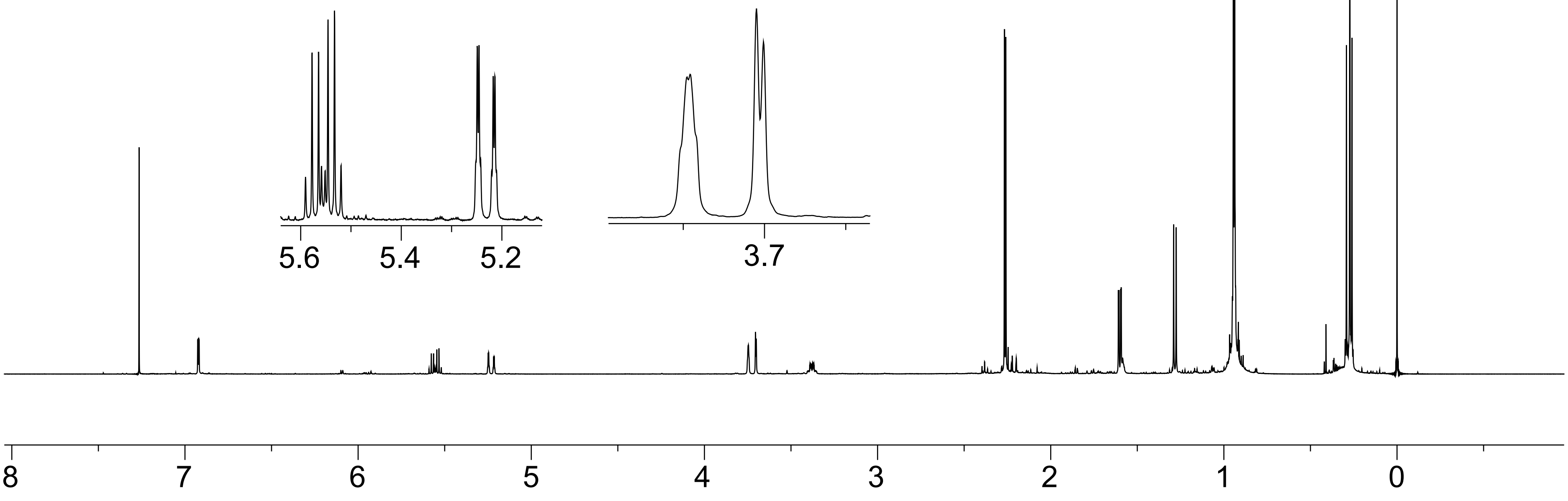


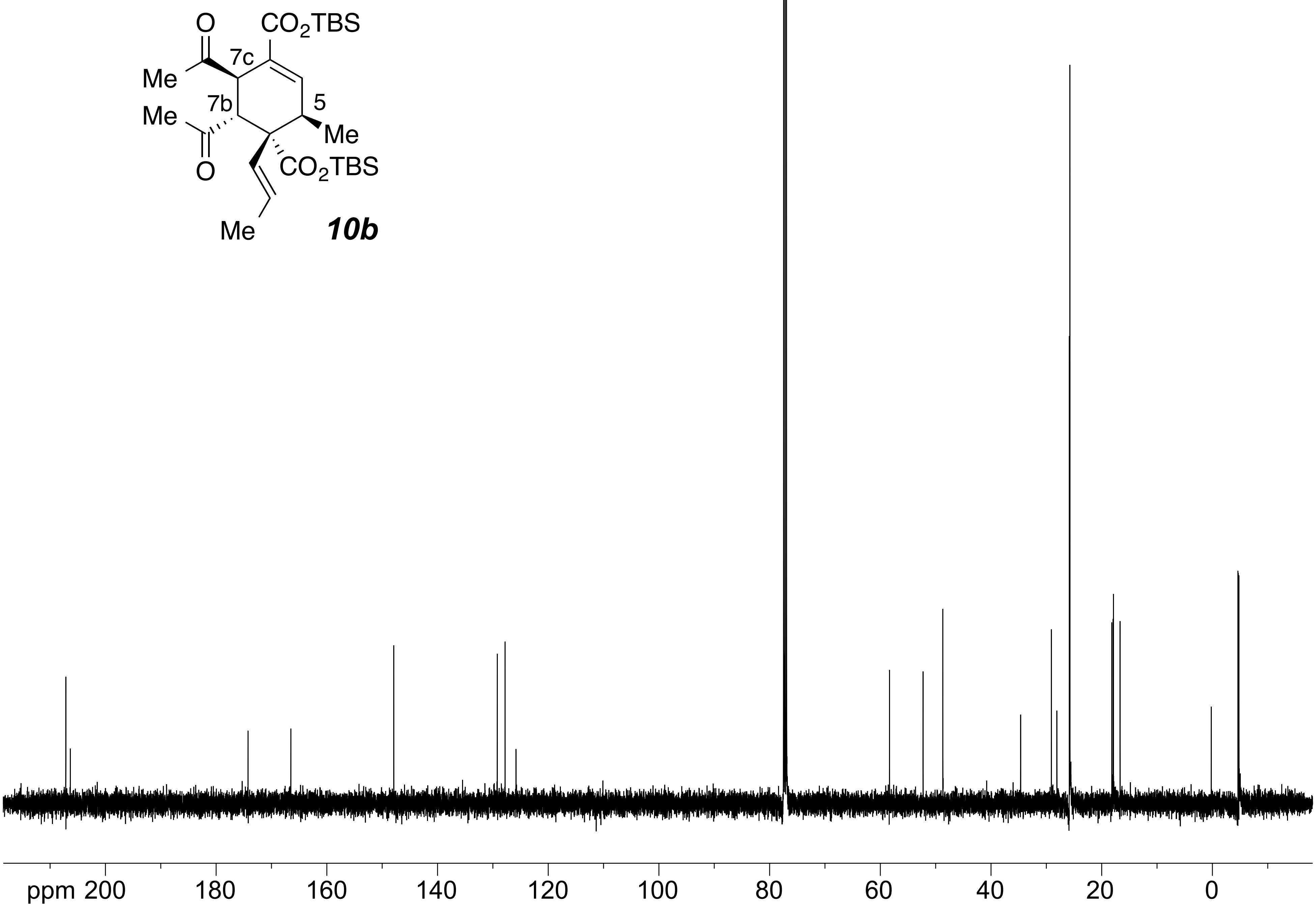


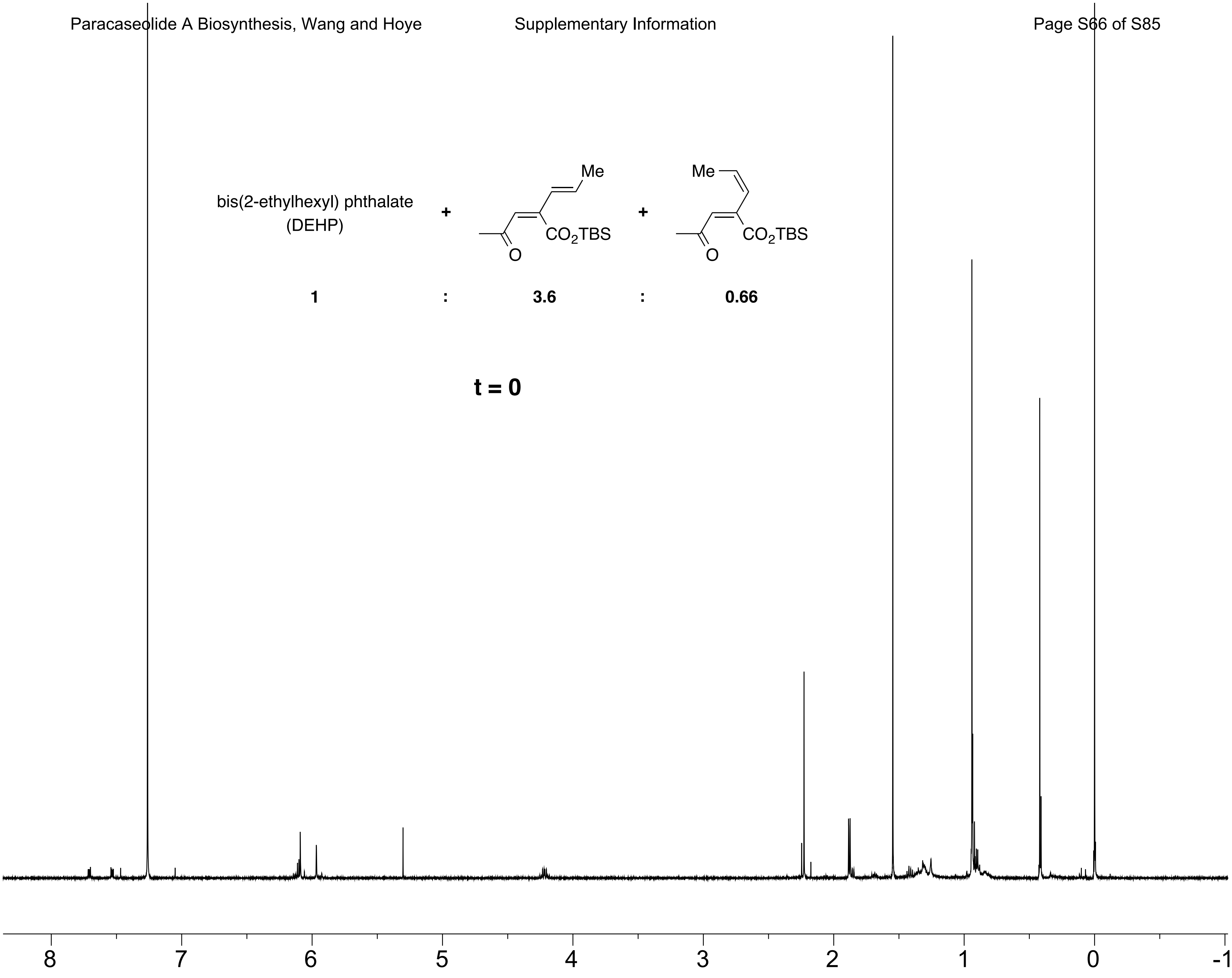
3b

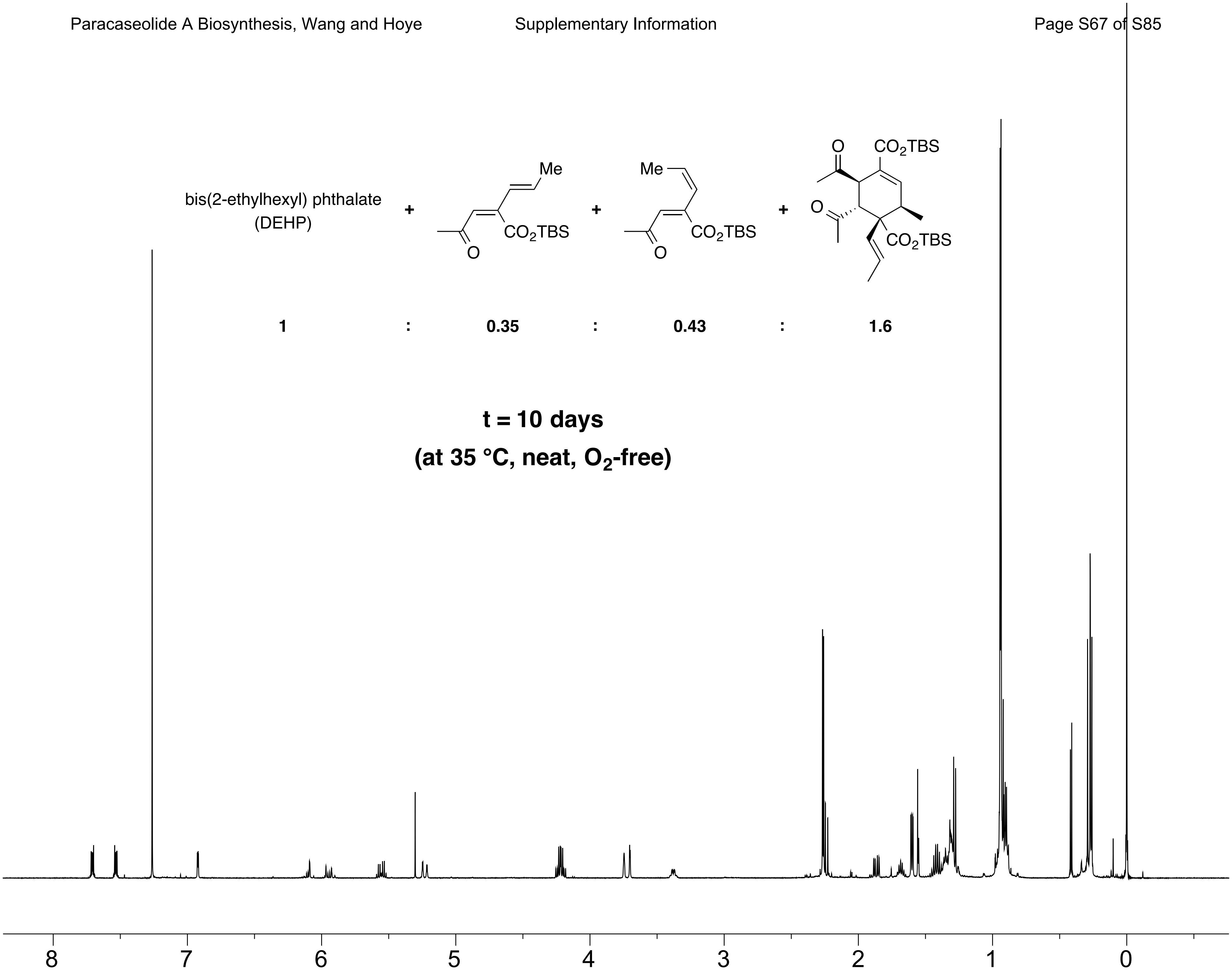


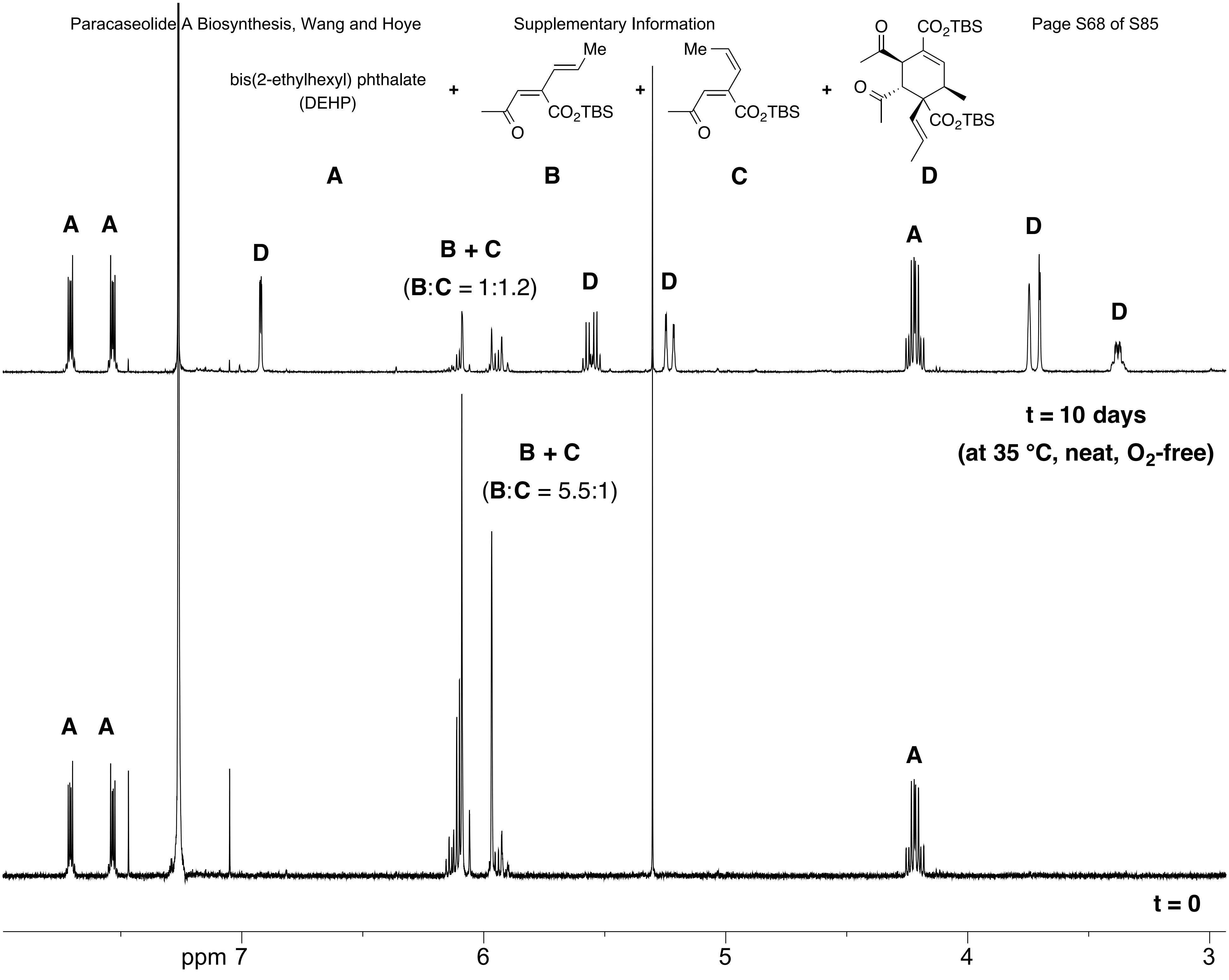
10b

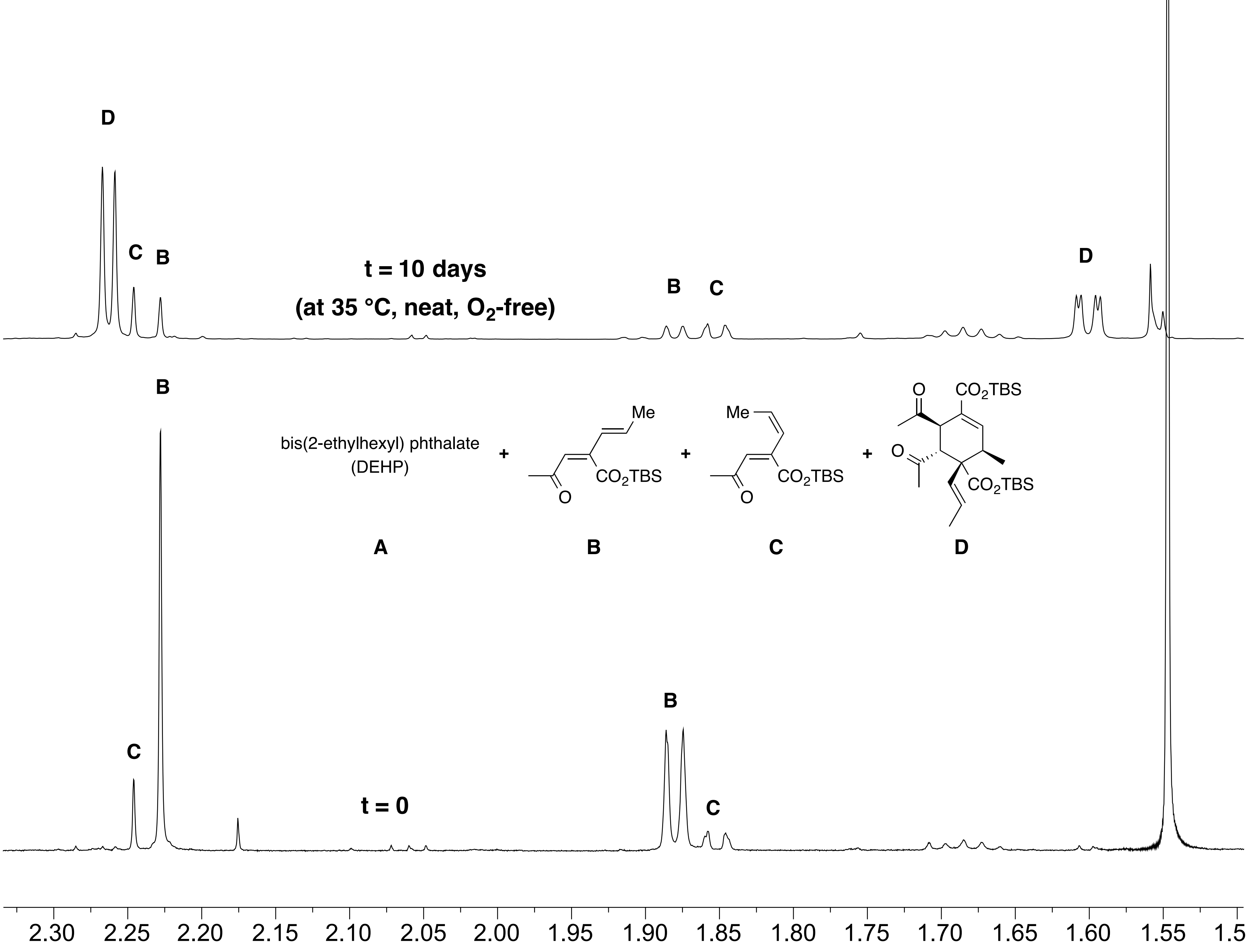


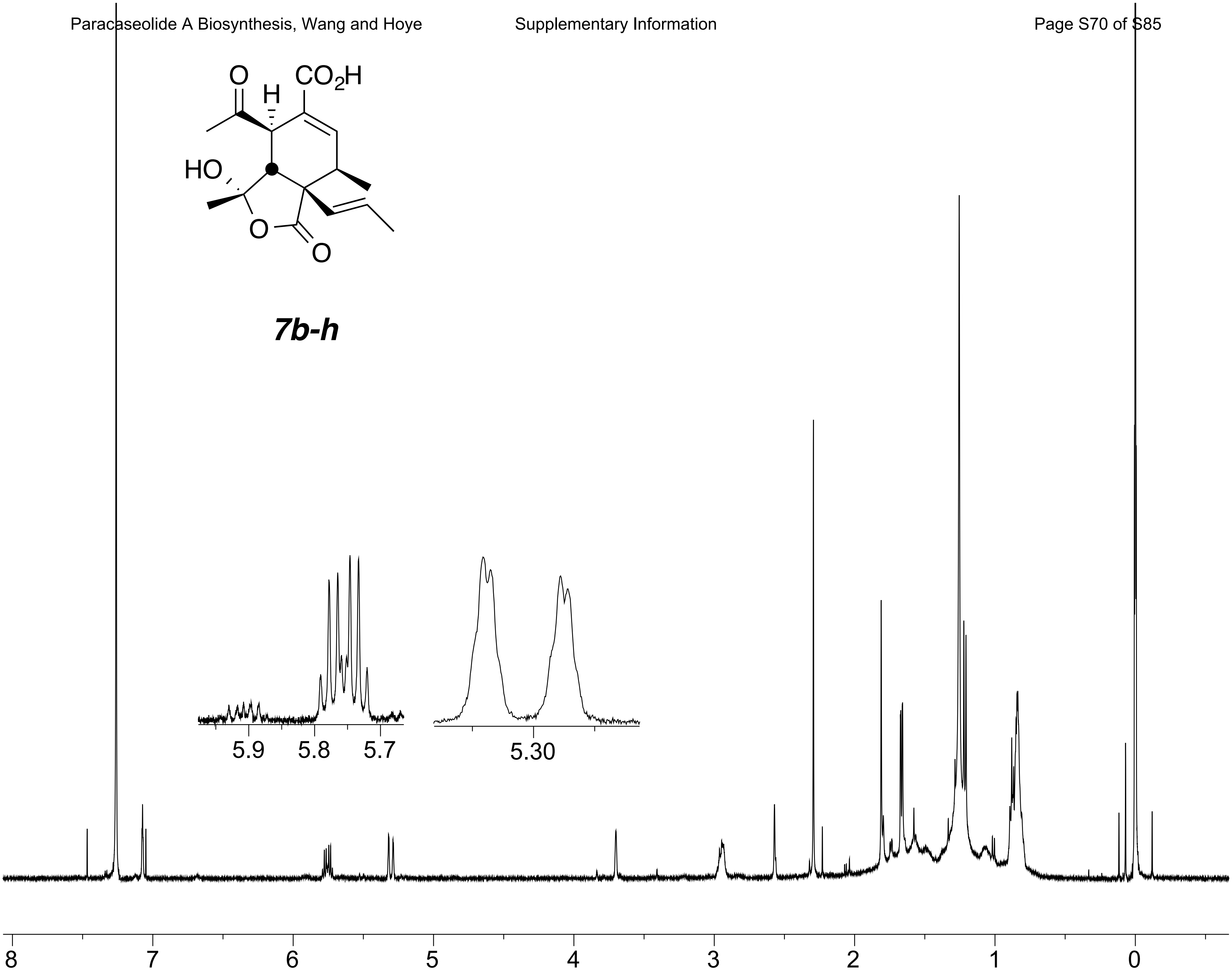

O
CO$_2$TBS
7c
Me
7b
Me
5
Me
O
CO$_2$TBS
Me
10b
ppm 200
180
160
140
120
100
80
60
40
20
0


bis(2-ethylhexyl) phthalate
(DEHP)
+
Me
CO2TBS
O
+
Me
CO2TBS
O
1
:
3.6
:
0.66
t = 0
8
7
6
5
4
3
2
1
0
-1


bis(2-ethylhexyl) phthalate
(DEHP)
+
Me
CO2TBS
O
+
Me
CO2TBS
O
+
O
CO2TBS
O
CO2TBS
1
:
0.35
:
0.43
:
1.6
t = 10 days
(at 35 °C, neat, O2-free)
8
7
6
5
4
3
2
1
0


bis(2-ethylhexyl) phthalate
(DEHP)
+
Me
CO2TBS
O
+
Me
CO2TBS
O
+
O
CO2TBS
O
CO2TBS
A
B
C
D
A
A
D
B + C
(B:C = 1:1.2)
D
D
A
D
D
t = 10 days
(at 35 °C, neat, O2-free)
B + C
(B:C = 5.5:1)
A
A
A
t = 0
ppm 7
6
5
4
3

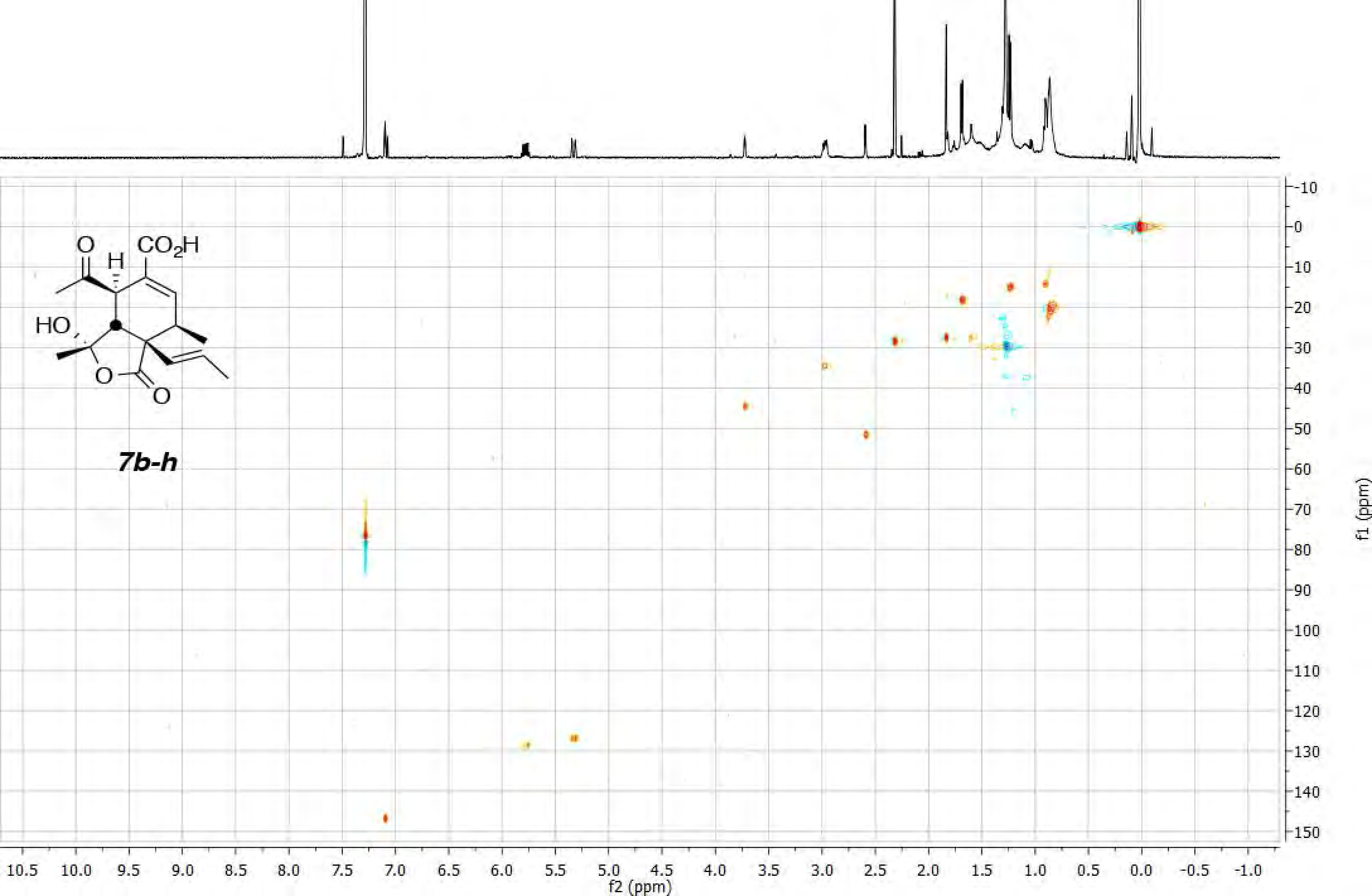

D
C
B
t = 10 days
(at 35 °C, neat, O2-free)
B
C
D
B
bis(2-ethylhexyl) phthalate
(DEHP)
+
Me
CO2TBS
O
+
Me
CO2TBS
O
+
O
CO2TBS
O
CO2TBS
A
B
C
D
C
t = 0
B
C
2.30
2.25
2.20
2.15
2.10
2.05
2.00
1.95
1.90
1.85
1.80
1.75
1.70
1.65
1.60
1.55

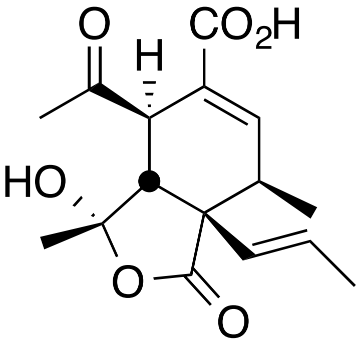


7b-h

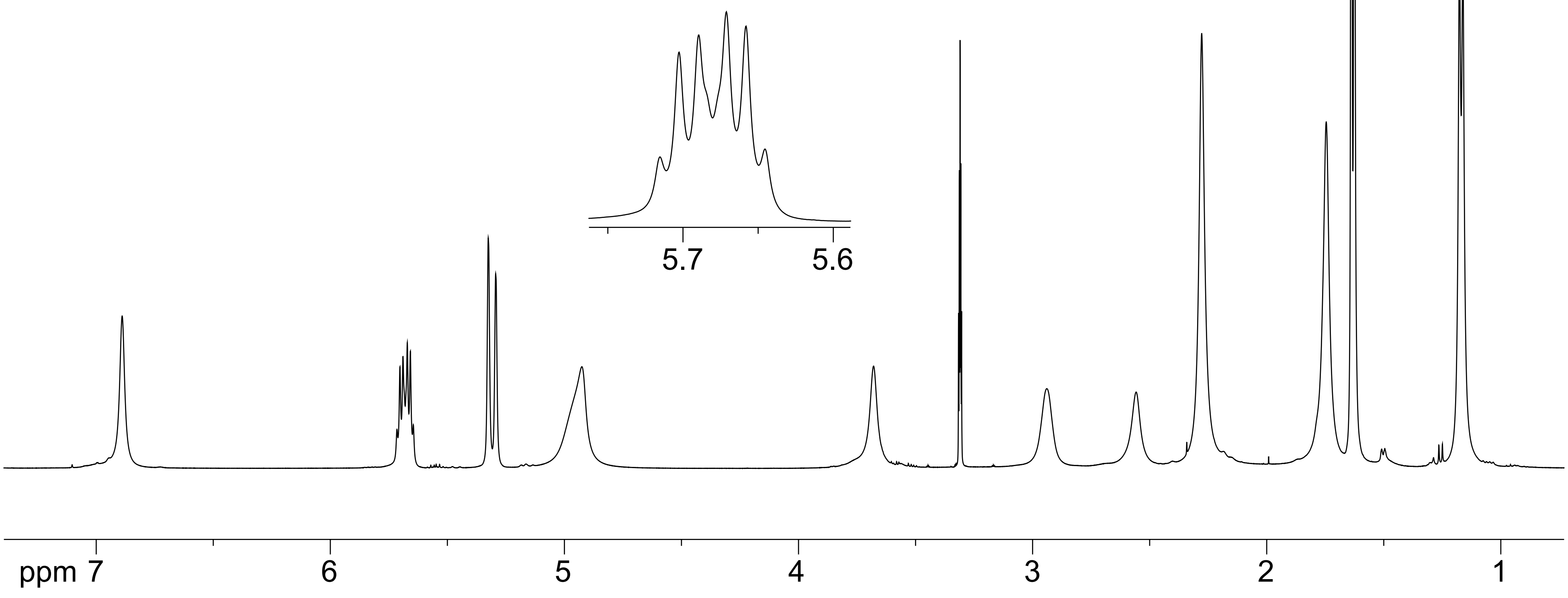
O
CO2H
H
HO
O
O

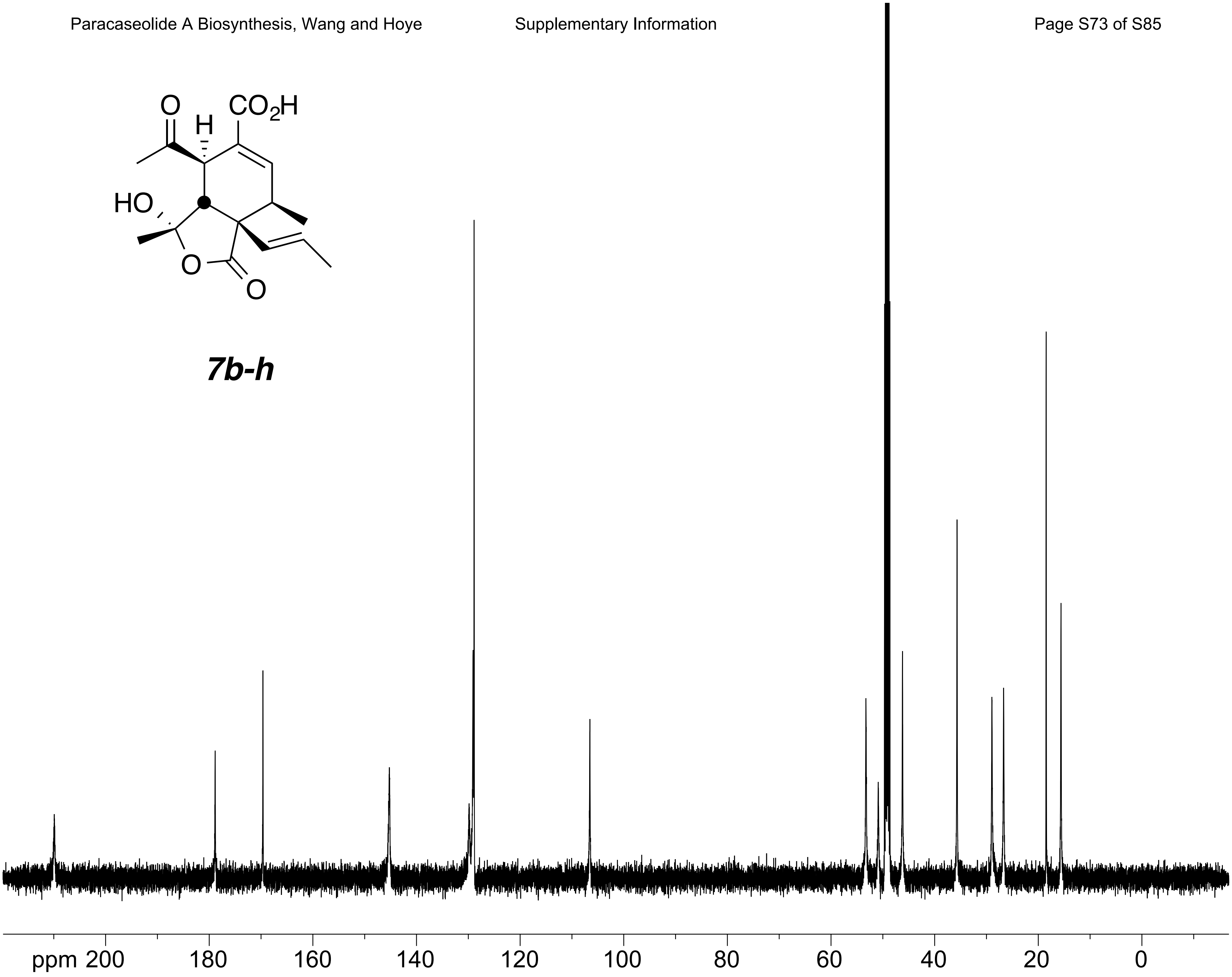
7b-h


10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f2 (ppm)
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
f1 (ppm)

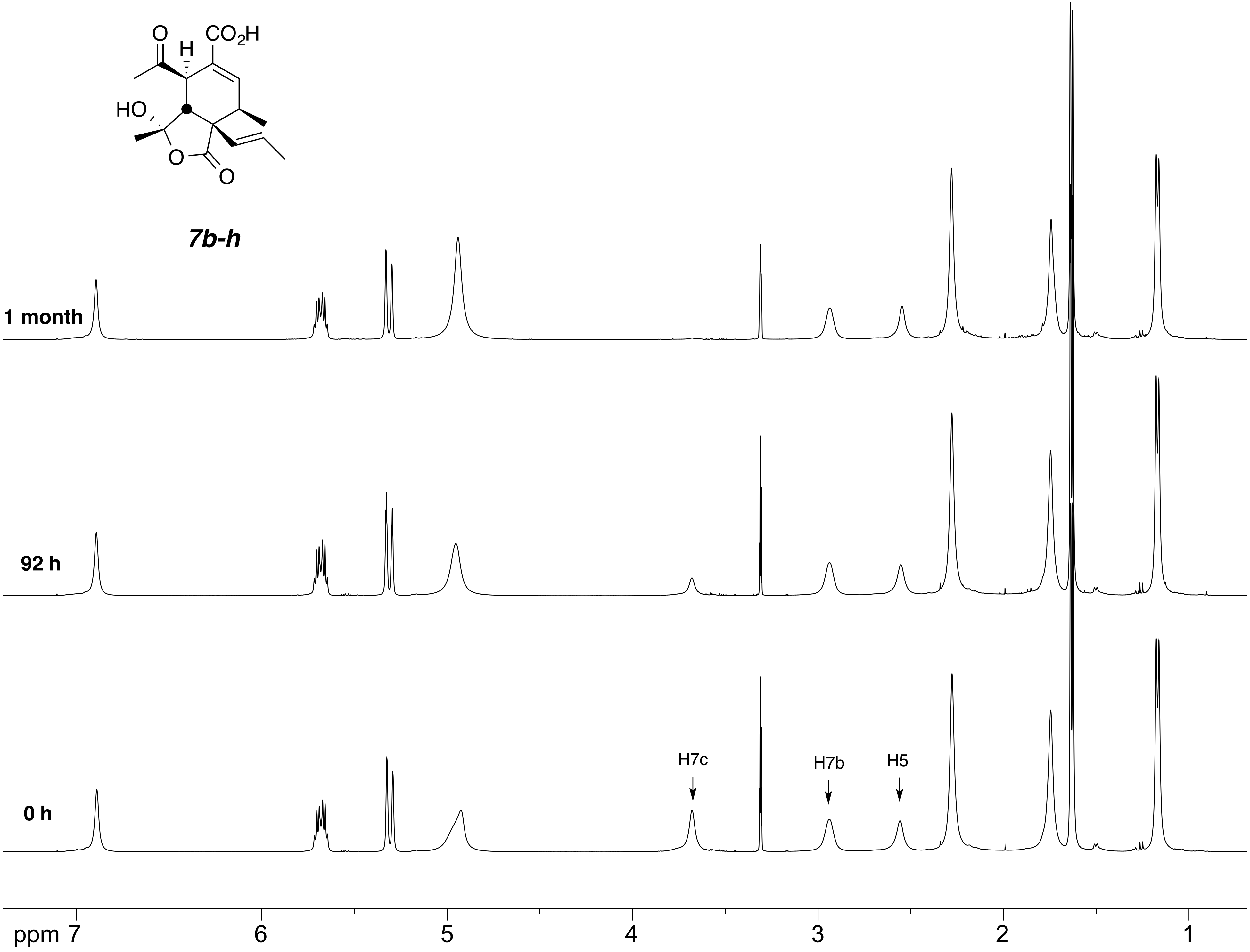


7b-h

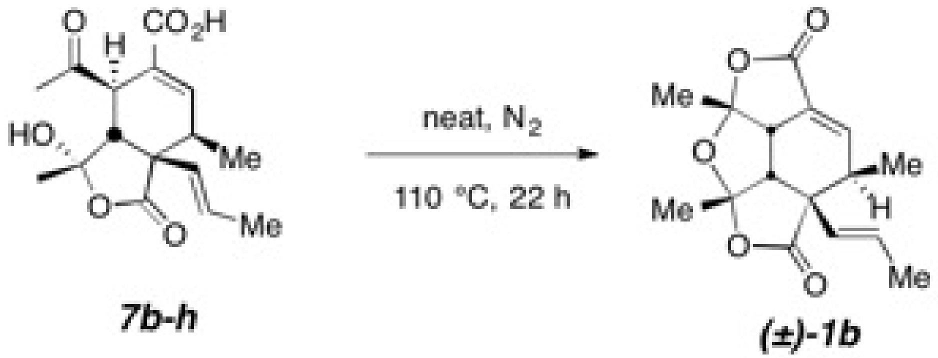




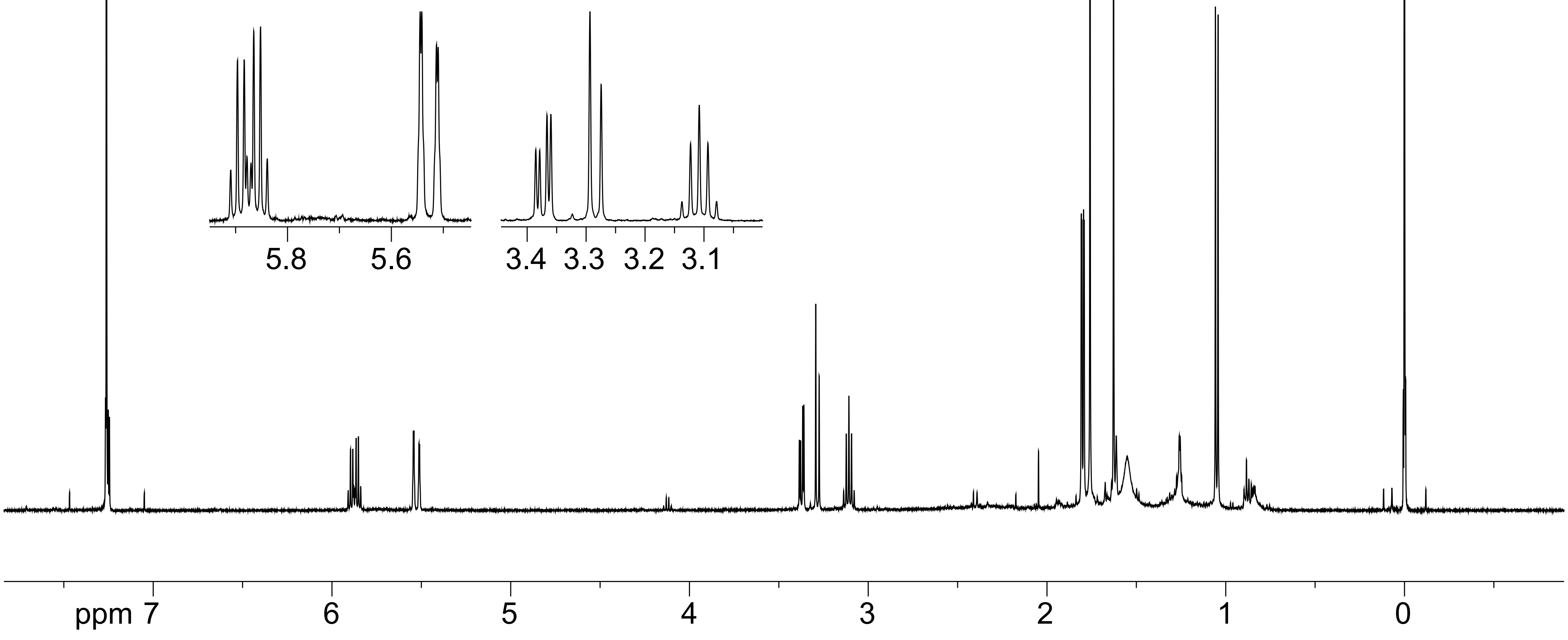
7b-h

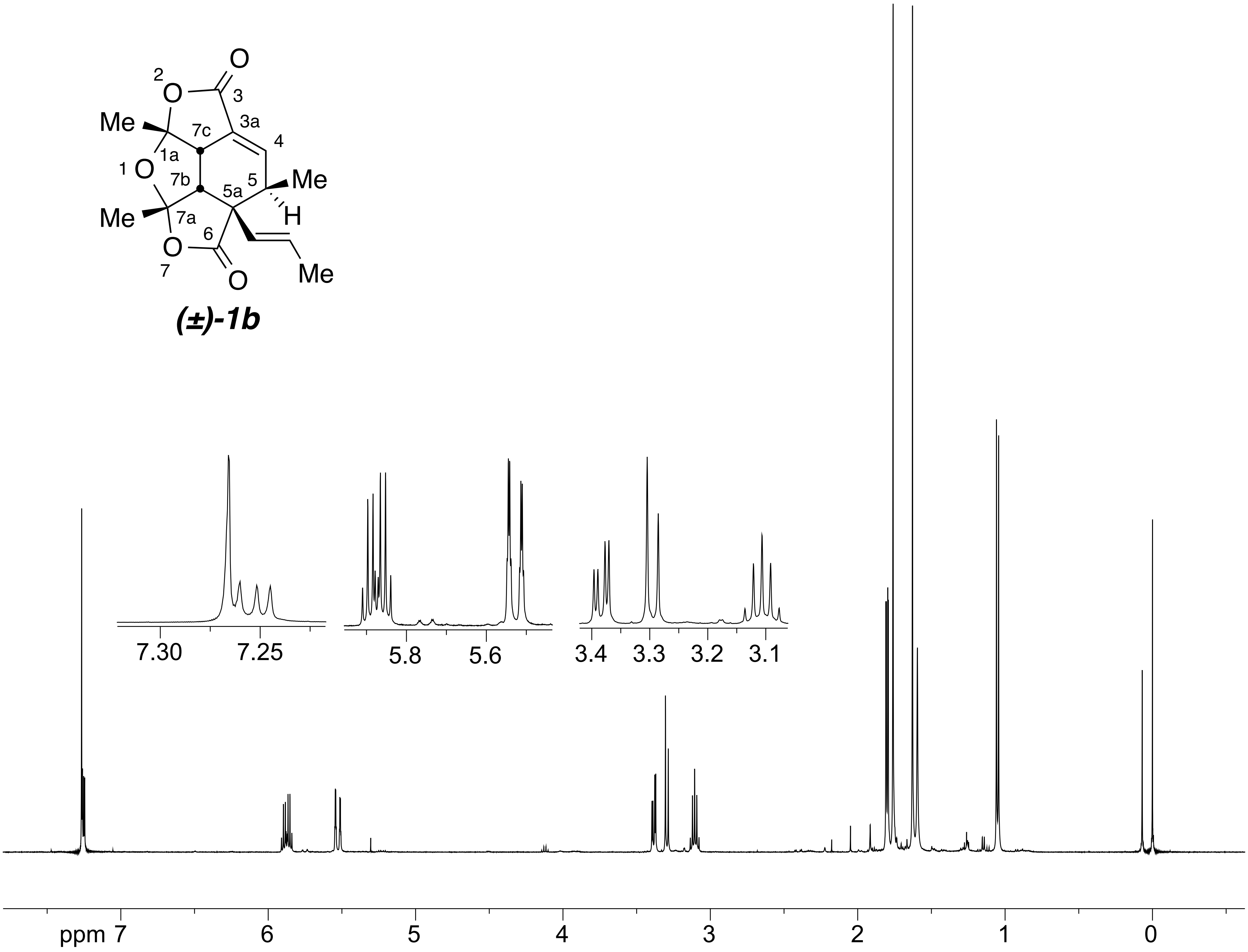


7b-h



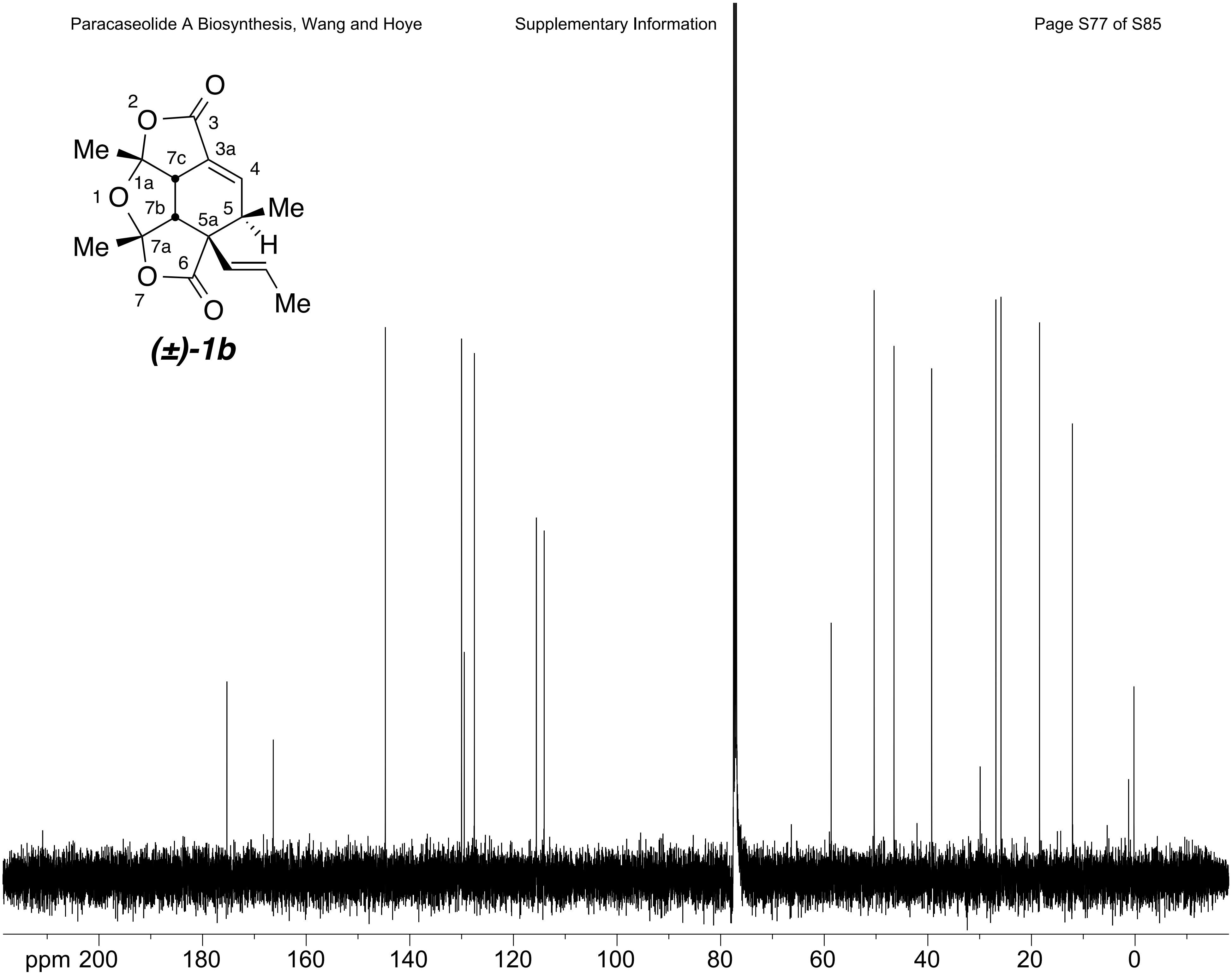
NMR spectrum of crude product mixture





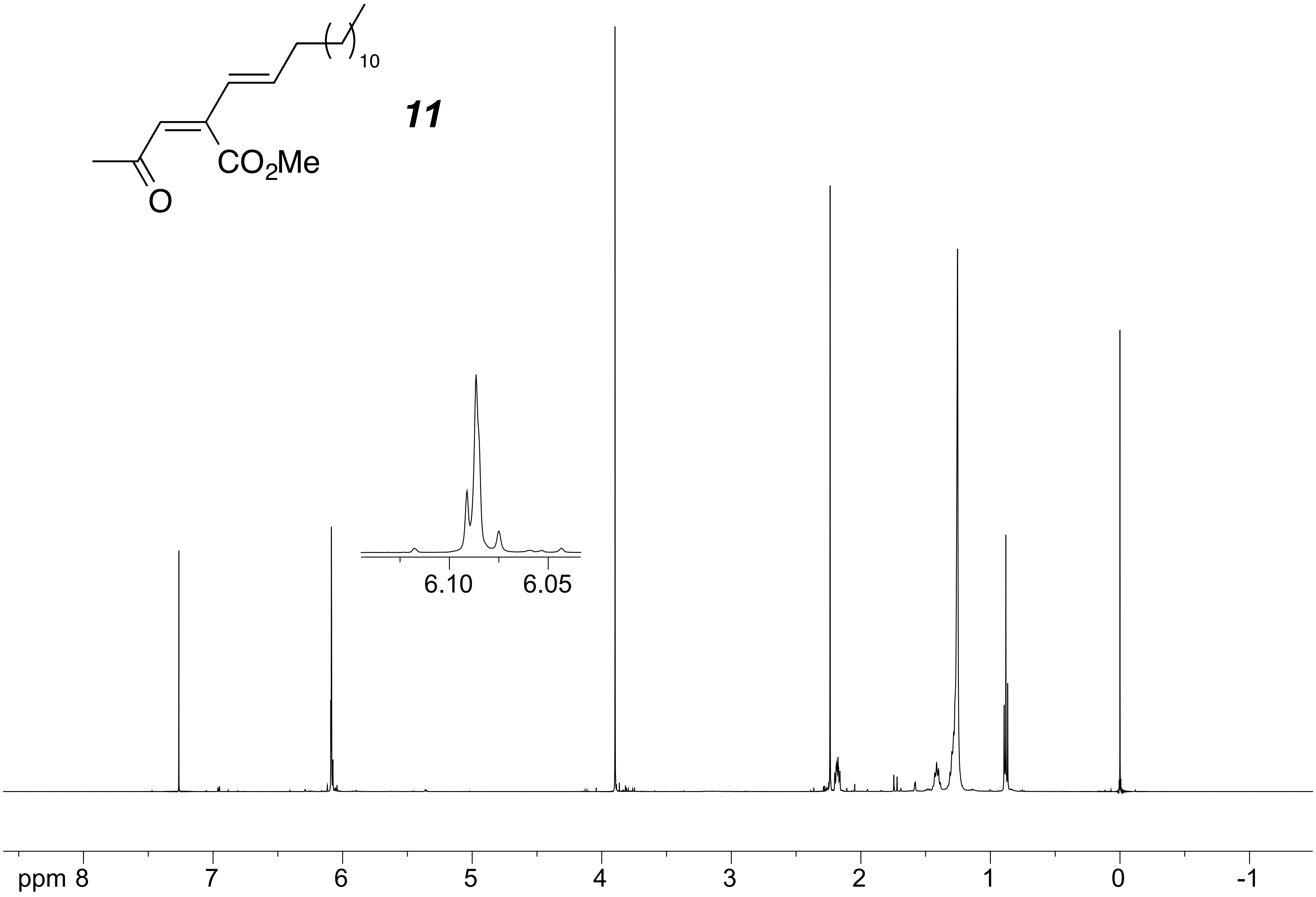
O
2
O
3
Me
7c
3a
4
1a
1
O
7b
5a
5
Me
H
Me
7a
6
O
7
O
Me
7.30
7.25
5.8
5.6
3.4
3.3
3.2
3.1
ppm 7
6
5
4
3
2
1
0

(±)-1b

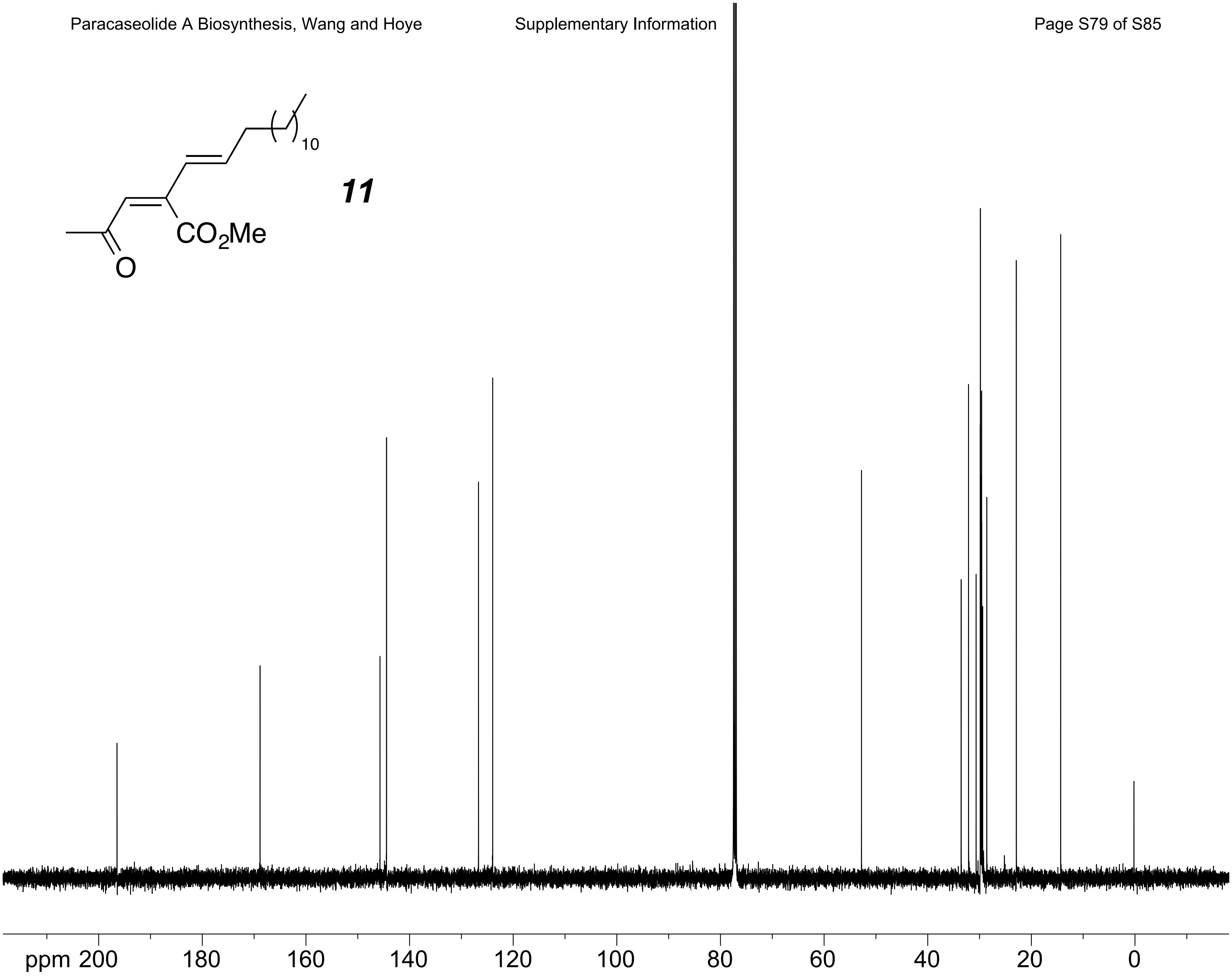

O
2
O
3
Me
3a
7c
4
1a
1 O
7b
5
Me
5a
H
Me
7a
6
O
7
O
Me

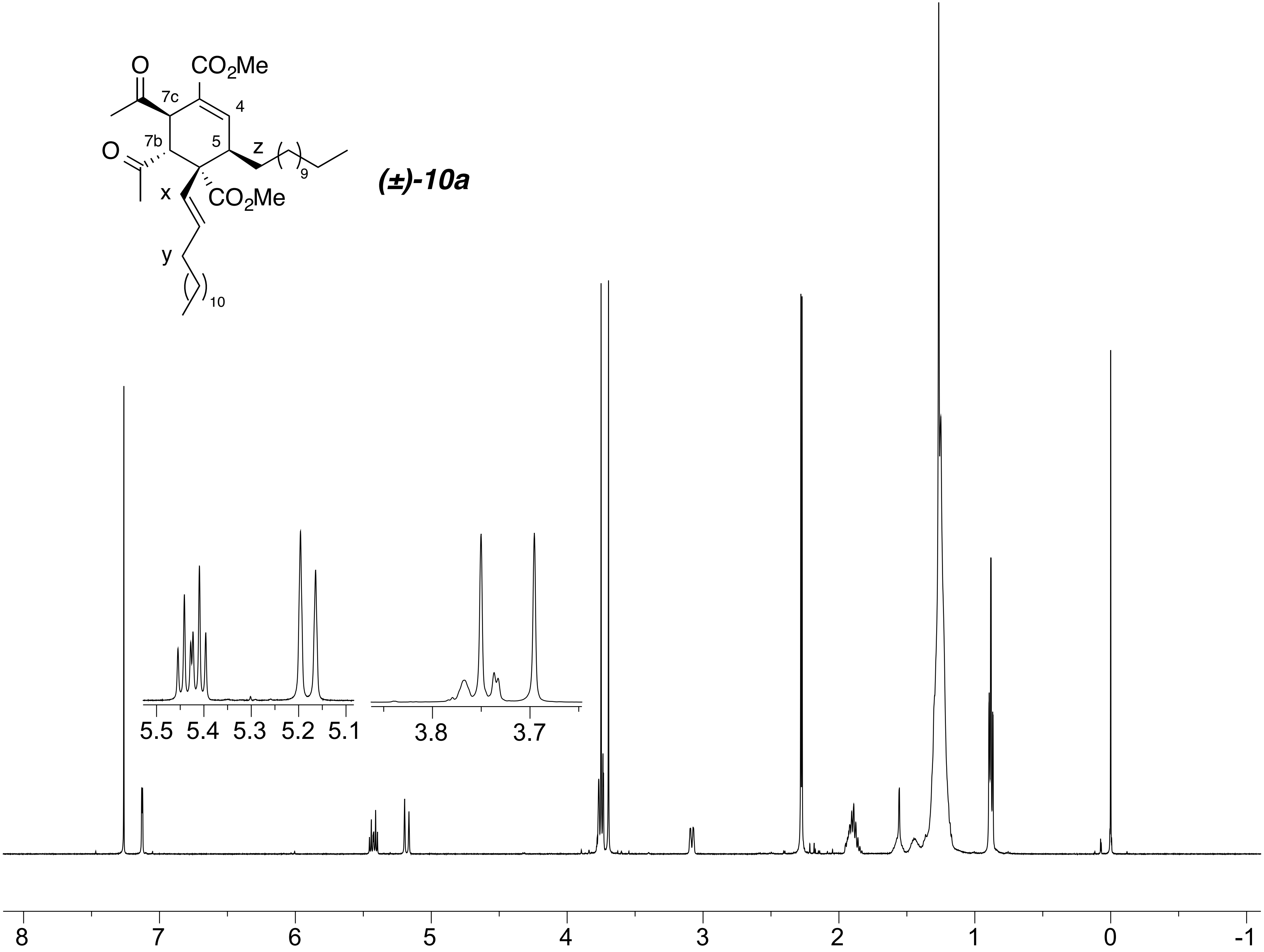
(±)-1b

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


11

11

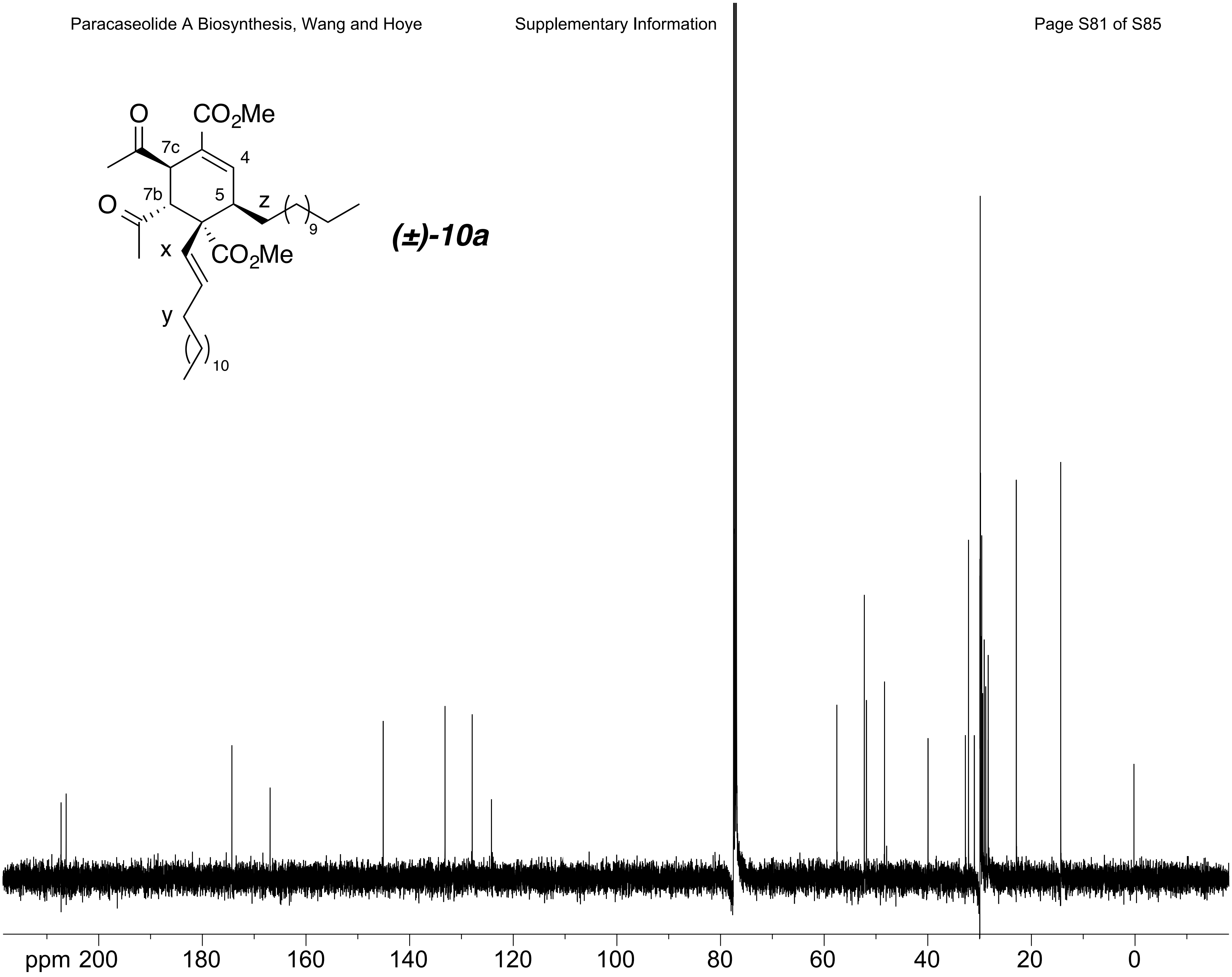




(±)-10a

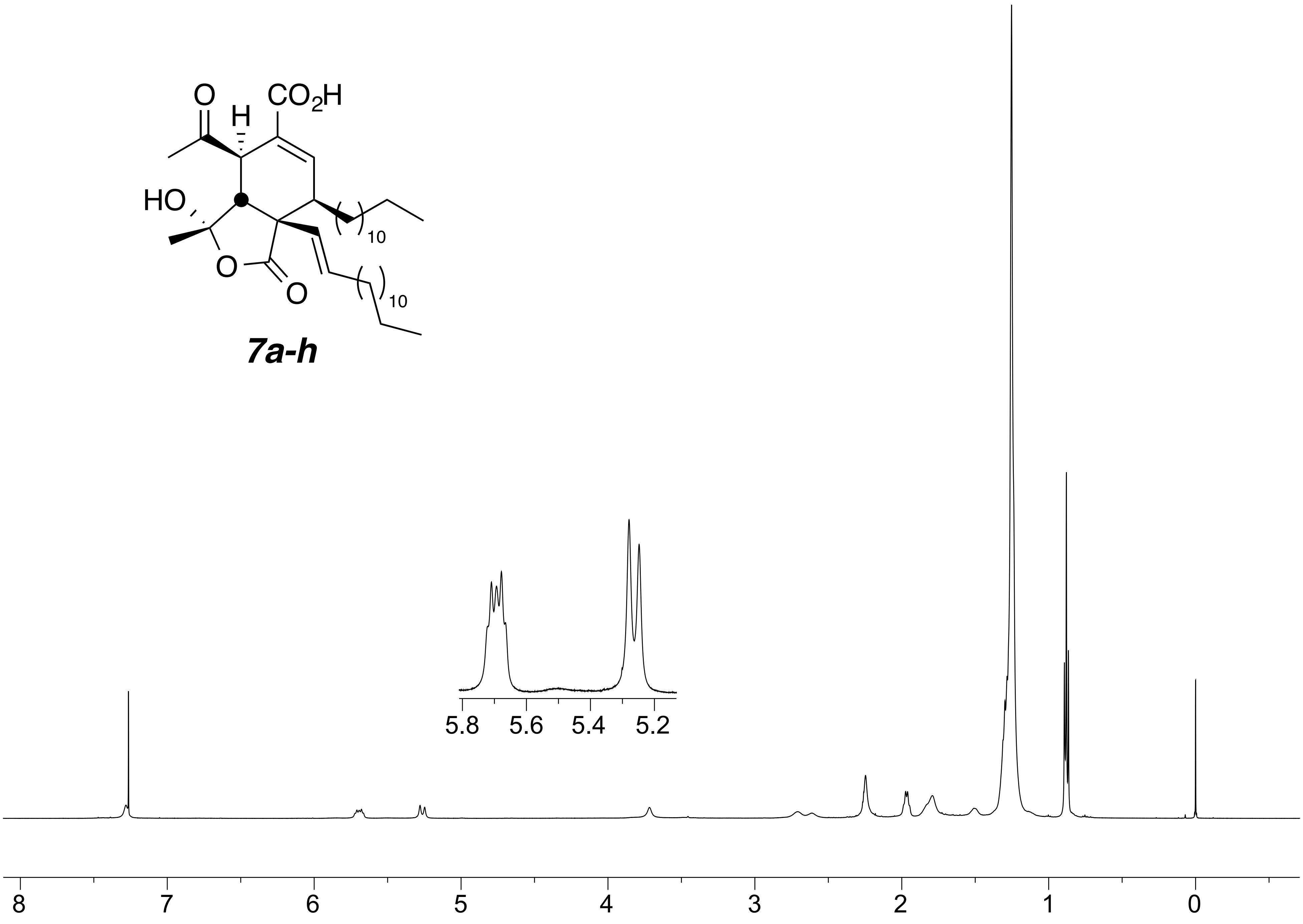
O
CO2Me
7c
4
7b
5
z
9
O
x
CO2Me
y
10

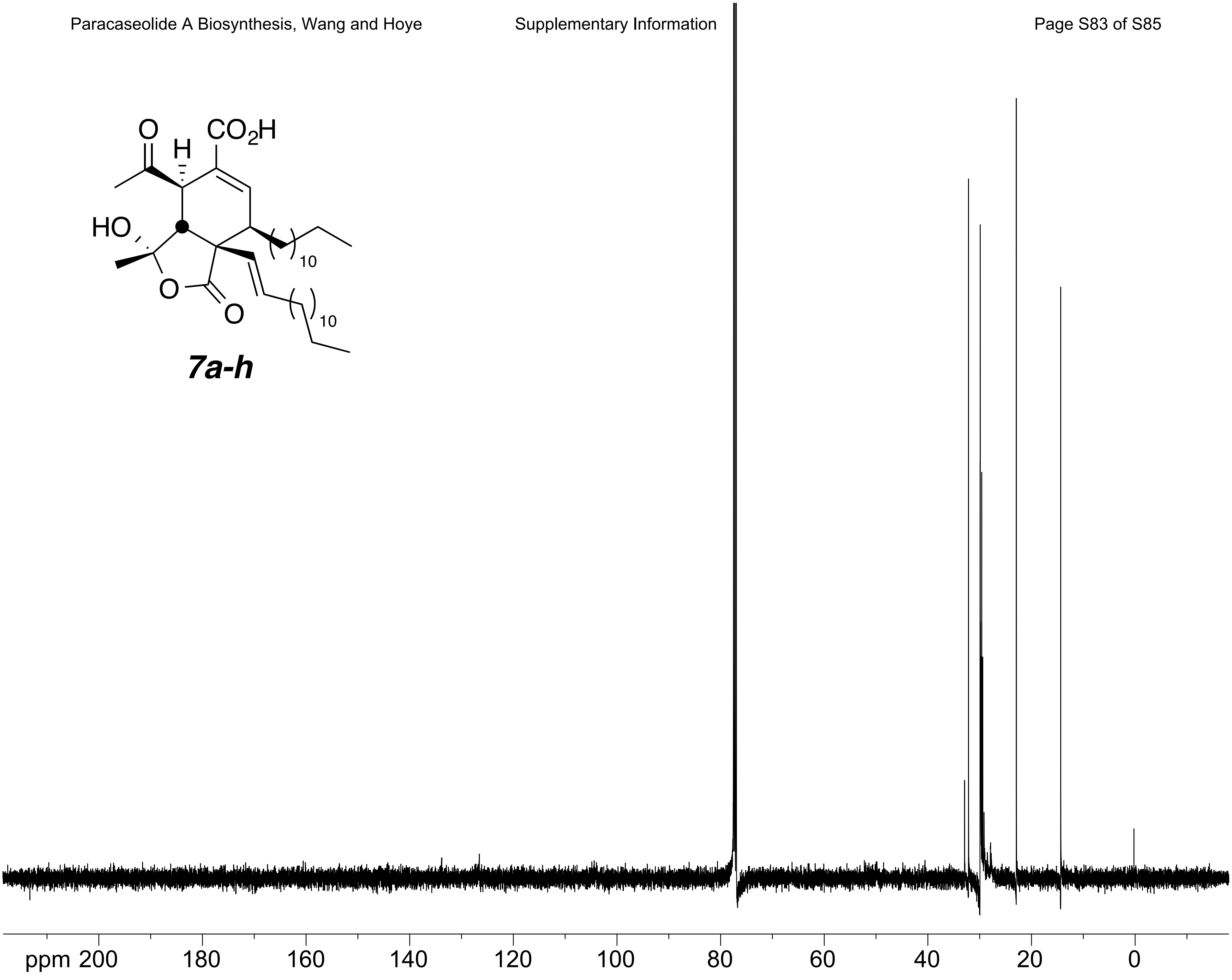
(±)-10a

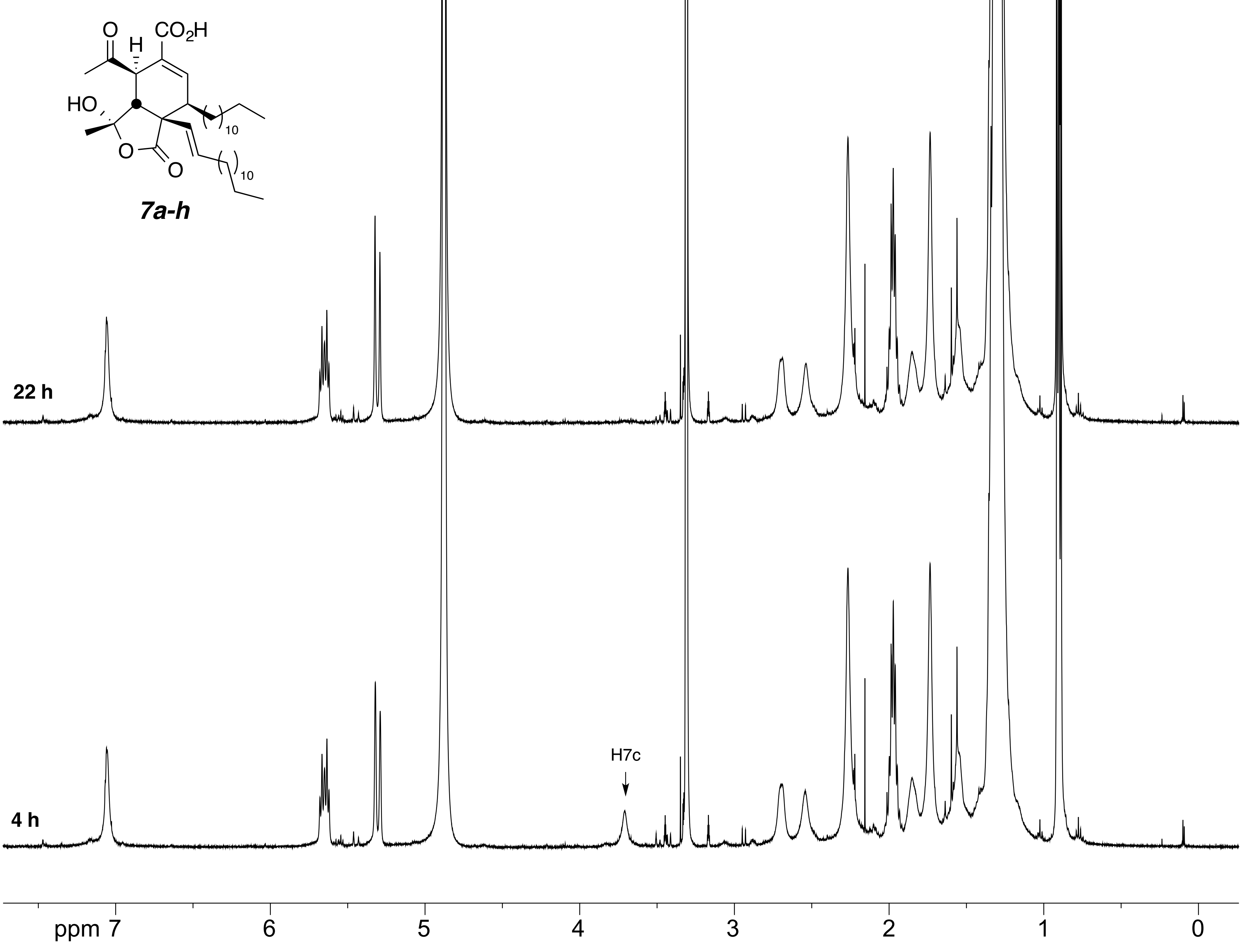


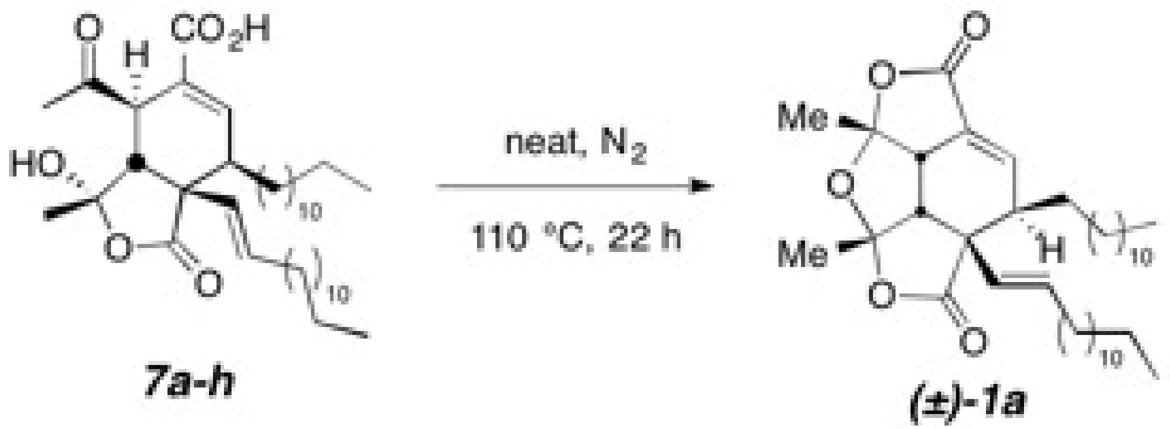
ppm 200
180
160
140
120
100
80
60
40
20
0

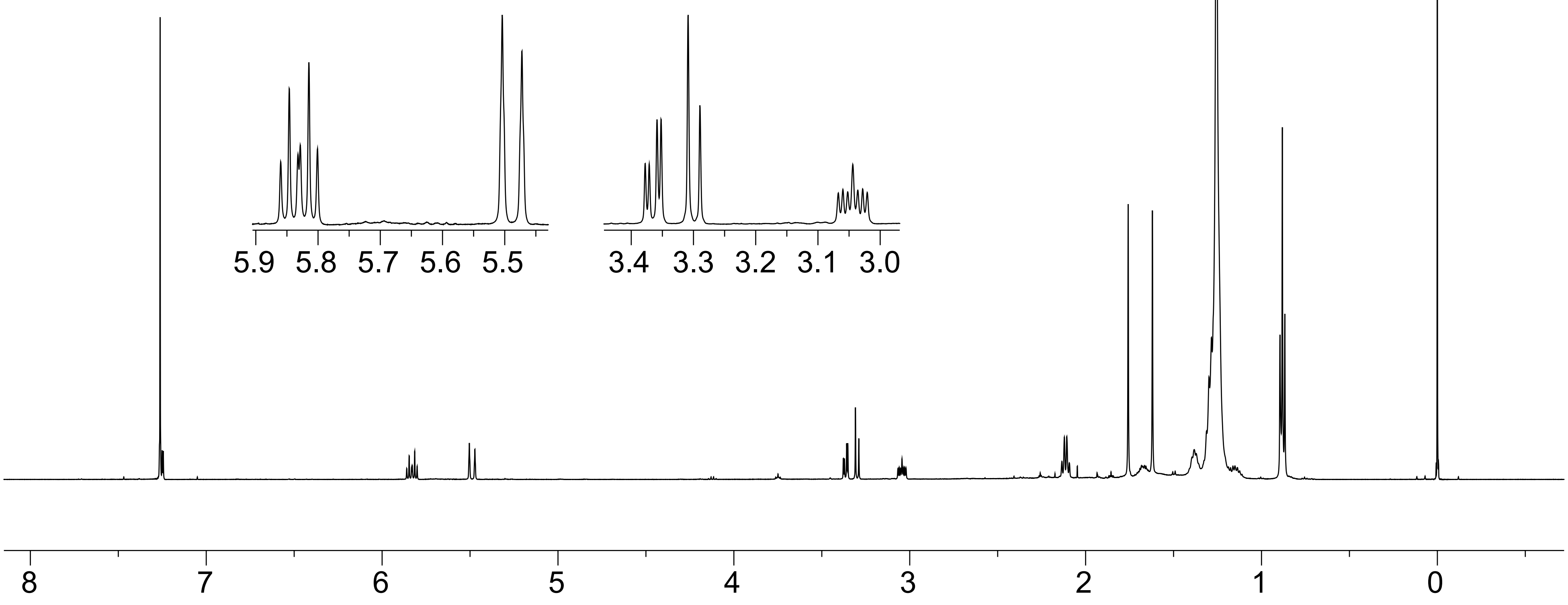
7a-h




O
CO2H
H
HO
10
O
O
10
7a-h
ppm 200
180
160
140
120
100
80
60
40
20
0


O
CO2H
H
HO
O
O
10
10
7a-h
22 h
4 h
H7c
ppm 7
6
5
4
3
2
1
0


CO2H
H
HO
10
10
7a-h
neat, N2
110 °C, 22 h
Me
Me
H
10
10
(±)-1a


5.9
5.8
5.7
5.6
5.5
3.4
3.3
3.2
3.1
3.0
8
7
6
5
4
3
2
1
0