

Supporting Information

“Synthesis of the Cytotrienin A Core *via* Metal Catalyzed C-C Coupling”

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Experimental Procedures

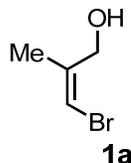
General

All reactions were run under an atmosphere of argon under anhydrous conditions unless otherwise indicated. Dichloromethane (DCM), 1,2-dichloroethane (DCE), diethyl ether (Et₂O), tetrahydrofuran (THF), and toluene (PhMe) were obtained from a Pure-Solv MD-5 Solvent Purification System (Innovative Technology, inc). Anhydrous solvents were transferred using oven-dried syringes. All other commercial reagents were used directly without further purification. Analytical thin-layer chromatography (TLC) was carried out using 0.2-mm commercial silica gel plates (DC-Fertigplatten Kieselgel 60 F254). Visualization of the chromatograms was accomplished using UV light and vanillin, anisaldehyde, permanganate, or cerium molybdate stain with heating. Preparative column chromatography using silica gel was performed according to the method of Still.¹ Infrared spectra were recorded on a Nicolet 380 FTIR. Analytical high performance liquid chromatography (HPLC) spectra were obtained using an Agilent Technologies 1200 series HPLC. Analytical Gas Chromatography (GC) spectra were obtained using an Agilent Technologies 7890A GC system. High-resolution mass spectra (HRMS) were obtained on a Waters Micromass Autospec or a Varian FTICR as m/z (relative intensity). Accurate masses are reported for the molecular ion (M+1, M or M-1) or a suitable fragment ion. Melting points were obtained on a Stuart[®] melting point apparatus SMP3. Proton nuclear magnetic resonance spectra (¹H NMR) were recorded with a Varian spectrometer (400 MHz or 500 MHz) and reported in parts per million (ppm) referenced to the residual protio solvent signal as an internal standard. Coupling constants are reported in Hertz (Hz). Carbon nuclear magnetic resonance spectra (¹³C NMR) were recorded with a Varian spectrometer (100 MHz or 125 MHz) and reported in parts per million (ppm) referenced to the residual solvent signal as an internal standard. Optical rotations were measured on an ATAGO AP-300 automatic polarimeter at a path length of 1 dm.

Preparation of (S)-Ir-complex

To a mixture of [Ir(cod)Cl]₂ (520 mg, 0.774 mmol, 100 mol%), (S)-SEGPHOS (945 mg, 1.55 mmol, 200 mol %), Cs₂CO₃ (1.010 g, 3.10 mmol, 400 mol %), 4-CN-3-NO₂BzOH² (595 mg, 3.10 mmol, 400 mol %) and allyl acetate (387 mg, 3.87 mmol, 500 mol %) in a sealed tube under a N₂ atmosphere was added THF (15.5 mL, 0.05 M). The reaction mixture was stirred for 30 min at 70 °C and heated for 1.5 hours at 80 °C, at which point the reaction mixture was allowed to cool to 25 °C. The reaction mixture was filtered and the filter cake was washed with THF (100 mL). The filtrate was concentrated under reduced pressure and hexanes (350 mL) were added. The precipitate collected by filtration and dried under vacuum to furnish the title compound (S)-Ir-complex (1.52 g, 1.47 mmol) as a yellow precipitate in 95% yield.

(Z)-3-Bromo-2-methylprop-2-ene-1-ol (1a)



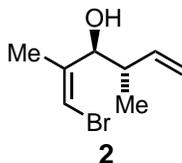
A solution of MeMgBr (52 mL, 160 mmol, 220 mol %, 3 M in Et₂O) was added dropwise to a stirred suspension of freshly distilled propargylalcohol (4.00 g, 71.4 mmol, 100 mol %) and CuI (1.36 g, 7.14 mmol, 10 mol %) in THF (70 mL, 1 M) at -10°C. After addition the cooling bath was removed and the dark suspension was stirred for a further 16 h at 25 °C. The suspension was cooled to -78 °C and trimethylborate (9.7 mL, 8.9 g, 86 mmol, 120 mol %) was added. The reaction mixture was stirred for an additional 30 min at 25 °C after the cooling bath was removed. The reaction mixture was transferred to a separatory funnel containing HCl (aq.) (100 mL, 2 M). The organic layer was washed and separated and the aqueous layer was extracted with Et₂O (3 x 50 mL). The combined organic extracts were concentrated under reduced pressure to roughly half their initial volume. The organic layer was transferred to a separatory funnel and was extracted with NaOH (aq.) (4 x 25 mL, 8 M). The combined aqueous layers were washed with Et₂O (2 x 25 mL), then acidified with aq. HCl (approx. 140 mL, 6 M) so that color change (from yellow to colorless) occurred. The acidic aqueous layer was then extracted with Et₂O (6 x 40 mL) and the combined organic extracts were dried (Na₂SO₄), filtered and concentrated under reduced pressure. The crude residue (4.1 g) was dissolved in MeOH (82 mL, 0.5 M) and a solution of CuBr₂ (28.1 g, 126 mmol, 300 mol %) in water (82 mL) was added. The dark solution was stirred under reflux for 22 h. Brine (80 mL) was added at 25 °C and the aqueous layer was extracted with Et₂O (6 x 80 mL). The combined organic extracts were dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, 10–50% DCM/hexanes) to furnish the title compound **1a** as a light yellow oil (3.74 g, 24.8 mmol) in 35% yield.³

R_f = 0.34 (SiO₂, DCM).

¹H NMR (400 MHz, CDCl₃): δ 5.98 (s, 1H), 4.29 (s, 2H), 1.97 (s, 1H), 1.89 (s, 3H) ppm.

¹³C NMR (100 MHz, CDCl₃): δ 140.5, 101.9, 63.6, 20.1 ppm.

(Z,3S,4S)-1-Bromo-2,4-dimethyl-3-hydroxyhexa-1,5-diene (2)



(S)-Ir-complex (103 mg, 0.099 mmol, 5 mol %), vinylbromide **1a** (300 mg, 1.99 mmol, 100 mol %), and Na₂CO₃ (105 mg, 0.994 mmol, 50 mol %) were suspended in THF (1.0 mL, 2 M) at 25 °C in a resealable pressure tube (13 x 100 mm). α -Methyl allyl acetate (454 mg, 3.97 mmol, 200 mol %) and degassed water (180 mg, 9.94 mmol, 500 mol %) were added and the mixture was stirred under an atmosphere of argon at 70 °C for 6 d. The reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography (SiO₂, 5–10% EtOAc /hexanes) to furnish the title compound **2** (267 mg, 1.30 mmol, *dr* = 12:1, *anti:syn*, 94% *ee*) in 66% yield as pale yellow oil.

R_f = 0.38 (SiO₂, hexanes/EtOAc = 5 : 1).

$[\alpha]_{26}^D = +178^\circ$ (c = 0.37, CHCl₃ 96% *ee*).

¹H NMR (400 MHz, CDCl₃): δ 6.07 (qd, *J* = 1.5 Hz, 0.5 Hz, 1H), 5.80 (ddd, *J* = 17.1 Hz, 10.3 Hz, 8.6 Hz, 1H), 5.20 (ddd, *J* = 17.1 Hz, 1.8 Hz, 0.9 Hz, 1H), 5.19 (ddd, *J* = 10.3 Hz, 1.8 Hz, 0.5 Hz, 1H), 4.49 (d, *J* = 9.0 Hz, 1H), 2.40–2.31 (m, 1H), 1.79 (d, *J* = 1.5 Hz, 3H), 1.55 (s, 1H), 0.97 (d, *J* = 6.9 Hz, 3H) ppm.

¹³C NMR (100 MHz, CDCl₃): δ 140.9, 140.6, 117.1, 103.4, 74.1, 42.8, 17.2, 15.9 ppm.

FTIR (ATR): 3423 (m), 3077 (w), 2970 (m), 2920 (m), 2161 (w), 1637 (m), 1436 (m), 1375 (m), 1292 (m), 1008 (vs), 915 (s), 725 (s) cm⁻¹.

HRMS (CI): Calcd. for C₈H₁₄OBr (MH): 205.0228; Found: 205.0225.

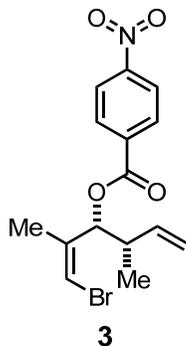
GC: (Cyclosil-B: Initial temperature: 50 °C (3 min hold), final temperature: 200 °C; rate: 10 K/min):

(Z)-*anti*-diastereoisomer: *t*_{major} = 13.4 min, *t*_{minor} = 13.5 min

(Z)-*syn*-diastereoisomer: *t*_{major} = 13.6 min; (*E*)-diastereoisomer: *t* = 14.1 min

ee = 94%, *dr* = 12:1

(3*R*,4*S*,*Z*)-1-Bromo-2,4-dimethylhexa-1,5-dien-3-yl 4-nitrobenzoate (3)



Diisopropyl azodicarboxylate (0.23 mL, 1.2 mmol, 220 mol %) was added dropwise to a solution of compound **2** (110 mg, 0.54 mmol, 100 mol %), PPh₃ (281 mg, 1.07 mmol, 200 mol %), ethyldiisopropylamine (0.18 mL, 1.1 mmol, 200 mol %) and 4-nitrobenzoic acid (179 mg, 1.07 mmol, 200 mol %) in THF (35 mL, 0.015 M) at 0 °C under an atmosphere of argon. The reaction mixture was stirred at 0 °C for 3 h. The crude reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography (SiO₂, 10% EtOAc/hexanes) to furnish the title compound **3** (150 mg, 0.42 mmol) in 79% yield as a colorless solid.

R_f = 0.43 (SiO₂, hexanes/EtOAc = 5 : 1).

MP: 49–50 °C (*rac*), 62–63 °C.

[α]_D²⁶ = +139° (c = 1.03, CHCl₃ 96% *ee*).

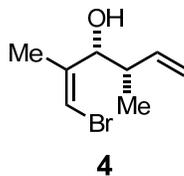
¹H NMR (400 MHz, CDCl₃): δ 8.33–8.29 (m, 2H), 8.25–8.22 (m, 2H), 6.16–6.13 (m, 1H), 5.89 (d, *J* = 8.8 Hz, 1H), 5.78 (ddd, *J* = 17.1 Hz, 10.3 Hz, 8.1 Hz, 1H), 5.14 (dt, *J* = 17.1 Hz, 1.2 Hz, 1H), 5.08 (ddd, *J* = 10.3 Hz, 1.5 Hz, 0.5 Hz, 1H), 2.88–2.79 (m, 1H), 1.80 (d, *J* = 1.5 Hz, 3H), 1.19 (d, *J* = 6.7 Hz, 3H) ppm.

¹³C NMR (100 MHz, CDCl₃): δ 163.6, 150.6, 137.8, 137.4, 135.4, 130.7, 123.7, 116.1, 105.4, 78.6, 40.5, 18.4, 16.5 ppm.

FTIR (ATR): 3111 (w), 3080 (w), 2975 (m), 2922 (m), 2854 (w), 1727 (s), 1527 (s), 1319 (m), 1270 (vs), 1101 (s), 952 (m), 719 (s) cm⁻¹.

HRMS (CI): Calcd. for C₁₅H₁₇NO₄Br (MH⁺): 354.0341; Found: 354.0343.

(Z,3R,4S)-1-Bromo-2,4-dimethyl-3-hydroxyhexa-1,5-diene (4)



Ester **3** (3.77 g, 10.6 mmol, 100 mol %) was dissolved in a mixture of THF, MeOH and water (71 mL, 0.15 M, 5:1:1 volume ratios, respectively) at 25 °C. LiOH•H₂O (3.57 g, 85.1 mmol, 800 mol %) was added and the reaction mixture was stirred at 25 °C for 2 h. The reaction mixture was transferred to a separatory funnel and the organic layer was washed with brine (70 mL). The aqueous layer was extracted with Et₂O (3 x 70 mL), and the combined organic extracts were dried (Na₂SO₄), filtered, and evaporated under reduced pressure. The residue was purified by column chromatography (SiO₂, 10–20% EtOAc/hexanes) to furnish the title compound **4** (2.15 g, 10.5 mmol) in 99% yield as a light yellow oil.

R_f = 0.38 (SiO₂, hexanes/EtOAc = 5 : 1).

[α]₂₈^D = +30.9° (c = 1.25, CHCl₃ 96% *ee*).

¹H NMR (400 MHz, CDCl₃): δ 5.97–5.95 (m, 1H), 5.71 (ddd, *J* = 17.2 Hz, 10.3 Hz, 7.9 Hz, 1H), 5.06 (ddd, *J* = 17.2 Hz, 1.7 Hz, 1.2 Hz, 1H), 5.01 (ddd, *J* = 10.4 Hz, 1.8 Hz, 0.9 Hz, 1H), 4.56 (d, *J* = 8.4 Hz, 1H), 2.52–2.42 (m, 1H), 1.85 (s, 1H), 1.79 (d, *J* = 1.5 Hz, 3H), 1.16 (d, *J* = 6.7 Hz, 3H) ppm.

¹³C NMR (100 MHz, CDCl₃): δ 142.0, 139.4, 115.1, 102.4, 74.9, 41.9, 17.7, 16.2 ppm.

FTIR (ATR): 3371 (m), 3076 (w), 2975 (m), 2922 (m), 1641 (m), 1436 (m), 1374 (m), 1292 (m), 1008 (vs), 915 (s), 716 (s) cm⁻¹.

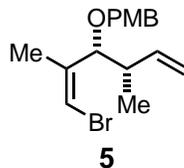
GC: (Cyclosil-B: Initial temperature: 50 °C (3 min hold), final temperature: 200 °C; rate: 10 K/min):

(*Z*)-*anti*-diastereoisomer: *t*_{major} = 13.5 min,

(*Z*)-*syn*-diastereoisomer: *t*_{major} = 13.8 min; *t*_{minor} = 13.7 min

ee = 93%, *dr* = 17 : 1

(Z,3R,4S)-1-Bromo-3-(4-methoxybenzyloxy)-2,4-dimethylhexa-1,5-diene (5)



NaH (807 mg, 20.2 mmol, 60% in mineral oil, 300 mol %) was added portion wise to a solution of alcohol **4** (1.38 g, 6.73 mmol, 100 mol %) at 0 °C. *p*-Methoxybenzyl chloride (1.58 g, 10.1 mmol, 150 mol %) was added as a solution in THF–DMSO (34 mL, 0.2 M, 5:1, volume ratio, respectively). The cooling bath was removed and the reaction mixture was allowed to stir 2 h. A saturated solution of NaHCO₃ (30 mL) was carefully added and the reaction mixture transferred to a separatory funnel. The aqueous layer was extracted with Et₂O (3 x 30 mL), the combined organic extracts were dried (Na₂SO₄), filtered and the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO₂, 0–5% EtOAc/hexanes) to furnish the title compound **5** (1.75 g, 5.38 mmol) in 80% yield as a light yellow oil.

R_f = 0.57 (SiO₂, hexanes/EtOAc = 5 : 1).

[α]₂₆^D = +32° (c = 1.3, CHCl₃ 94% *ee*).

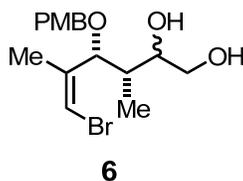
¹H NMR (400 MHz, CDCl₃): δ 7.29–7.24 (m, 2H), 6.89–6.85 (m, 2H), 6.13 (qd, *J* = 1.4 Hz, 0.5 Hz, 1H), 5.63 (dddd, *J* = 17.2 Hz, 10.2 Hz, 8.4 Hz, 0.5 Hz, 1H), 5.03–4.98 (m, 1H), 4.93 (ddt, *J* = 10.3 Hz, 1.8 Hz, 0.8 Hz, 1H), 4.41 (d, *J* = 11.3 Hz, 1H), 4.22 (d, *J* = 9.4 Hz, 1H), 4.21 (d, *J* = 11.3 Hz, 1H), 3.83 (s, 3H), 2.43 (tq, *J* = 8.5 Hz, 6.6 Hz, 1H), 1.75 (dd, *J* = 1.5 Hz, 0.6 Hz, 3H), 1.13 (d, *J* = 6.6 Hz, 3H) ppm.

¹³C NMR (100 MHz, CDCl₃): δ 159.1, 139.9, 139.3, 130.4, 129.6, 114.6, 113.6, 104.7, 81.5, 70.3, 55.2, 41.2, 17.4, 17.4 ppm.

FTIR (ATR): 3072 (w), 2959 (m), 2929 (m), 2835 (w), 1641 (m), 1513 (s), 1246 (vs), 1172 (m), 1109 (s), 1064 (s) cm⁻¹.

HRMS (CI): Calcd. for C₁₆H₂₀BrO₂ (M–H⁺): 323.0647; Found: 323.0651.

(3*S*,4*R*,5*Z*)-6-Bromo-4-(4-methoxybenzyloxy)-3,5-dimethylhex-5-ene-1,2-diol (6)



NMO (144 mg, 1.23 mmol, 200 mol %) was added to a solution of olefin **5** (200 mg, 0.615 mmol, 100 mol %) and osmium tetroxide (3 mg, 0.01 mmol, 2 mol %) in DCM (6.0 mL, 0.1 M) at 25 °C. Water (22 mg, 1.2 mmol, 200 mol %) was added and the solution was allowed to stir for 4 h at 25 °C. The reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography (SiO₂, 30–50% EtOAc/hexanes) to furnish the title compound **6** (214 mg, 0.595 mmol) in 97% yield as a highly viscous colorless oil.

R_f = 0.24 (SiO₂, hexanes/EtOAc = 1 : 1).

[α]₂₅^D = +26° (c = 0.80, 94% *ee* CHCl₃).

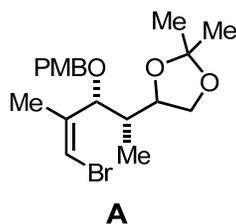
¹H NMR (400 MHz, CDCl₃): major diastereoisomer, *dr* = 4:1 (NMR) δ 7.28–7.25 (m, 2H), 6.92–6.87 (m, 2H), 6.19 (s, br, 1H), 4.60 (d, *J* = 5.3 Hz, 1H), 4.45 (d, *J* = 11.4 Hz, 1H), 4.19 (d, *J* = 11.3 Hz, 1H), 3.81 (s, 3H), 3.68–3.60 (m, 2H), 3.52–3.46 (m, 1H), 2.89 (s, br, 2H), 2.11–2.03 (m, 1H), 1.90–1.88 (m, 3H), 0.99 (d, *J* = 7.1 Hz, 3H) ppm.

¹³C NMR (100 MHz, CDCl₃): δ 159.4, 140.7, 129.7, 129.5, 113.9, 104.4, 79.2, 74.3, 70.8, 64.7, 55.2, 39.2, 18.9, 11.7 ppm.

FTIR (ATR): 3404 (m), 3069 (w), 2922 (m), 2882 (m), 2836 (w), 1612 (m), 1513 (m), 1246 (s), 1033 (s) cm⁻¹.

HRMS (CI): Calcd. for C₁₆H₂₂BrO₄ (M–H⁺): 357.0701; Found: 357.0699.

4-[(2*R*,3*R*,4*Z*)-5-Bromo-3-(4-methoxybenzyloxy)-4-methylpent-4-en-2-yl]-2,2-dimethyl-1,3-dioxolane (A)



2,2-Dimethoxypropane (812 mg, 7.79 mmol, 1000 mol %) was added to a solution of diol **6** (280 mg, 0.779 mmol, 100 mol %) in DCM (8.0 mL, 0.1 M) under nitrogen at 25 °C. Then pyridinium *p*-toluenesulfonate (10 mg, 0.04 mmol, 5 mol %) was added and the solution was allowed to stir at 25 °C for 17 h. After completion of the reaction the solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO₂, 10–20% EtOAc/hexanes) to furnish the title compound **A** (308 mg, 7.71 mmol) in 99% yield as a viscous colorless oil.

R_f = 0.54 (SiO₂, hexanes/EtOAc = 5 : 1).

$[\alpha]_{26}^D = -1.4^\circ$ (c = 1.38, CHCl₃ 94% *ee*).

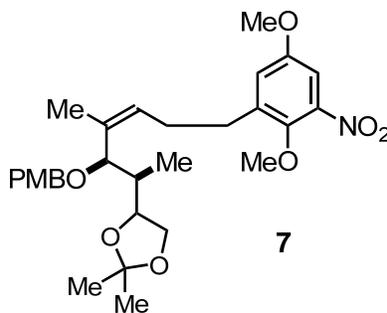
¹H NMR (400 MHz, CDCl₃): major diastereoisomer, *dr* = 3:1 δ 7.27–7.25 (m, 2H), 6.89–6.86 (m, 2H), 6.13 (qd, *J* = 1.4 Hz, 0.7 Hz, 1H), 4.39 (d, *J* = 11.2 Hz, 1H), 4.31 (dd, *J* = 7.2 Hz, 0.7 Hz, 1H), 4.22 (d, *J* = 11.3 Hz, 1H), 4.01–3.91 (m, 2H), 3.80 (s, 3H), 3.69–3.60 (m, 1H), 2.14 (dq, *J* = 7.2 Hz, 6.8 Hz, 5.8 Hz, 1H), 1.82 (d, *J* = 1.5 Hz, 3H), 1.40 (s, 3H), 1.32 (s, 3H), 0.96 (d, *J* = 6.8 Hz, 3H) ppm.

¹³C NMR (100 MHz, CDCl₃): δ 159.1, 140.9, 130.3, 129.5, 113.6, 108.2, 103.9, 79.5, 76.3, 70.6, 66.3, 55.2, 38.8, 26.4, 25.3, 18.4, 10.2 ppm.

FTIR (ATR): 3064 (w), 2982 (m), 2934 (m), 2857 (w), 1612 (m), 1513 (s), 1369 (m), 1246 (s), 1036 (vs) cm⁻¹.

HRMS (CI): Calcd. for C₁₉H₂₆BrO₄ (M–H⁺): 397.1014; Found: 397.1018.

4-[(2R,3R,4Z)-7-(2,5-Dimethoxy-3-nitrophenyl)-3-[(4-methoxybenzyloxy)-4-methyl-hept-4-en-2-yl]-2,2-dimethyl-1,3-dioxolane (7)



Fragment **A** (110 mg, 0.275 mmol, 100 mol %) and fragment **B** (139 mg, 0.413 mmol, 150 mol %) were added to a resealable pressure tube (13 x 100 mm) and dissolved in THF (1.05 mL, 0.26 M). Degassed NaOH solution (0.1 mL, 0.825 mmol, 300 mol %, 3 M) was added and after additional degassing of the reaction mixture, Pd(dppf)Cl₂•DCM (23 mg, 0.028 mmol, 10 mol %) was added. The mixture was stirred under argon at 50°C for 25 h. The black reaction mixture was transferred to a separatory funnel diluted with DCM (3 mL) and aqueous saturated NaHCO₃ solution (3 mL) was added. The layers were separated and the aqueous layer was extracted with DCM (3 x 3 mL), the combined organic extracts were dried (MgSO₄), filtered and the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO₂, 10–20% EtOAc/hexanes) to furnish the title compound **7** (109 mg, 0.206 mmol) in 75% yield as a yellow oil.

R_f = 0.32 (SiO₂, hexanes/EtOAc = 5 : 1).

[α]₂₇^D = +17.5° (c = 1.55, CHCl₃ 92% *ee*).

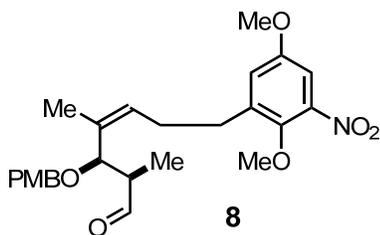
¹H NMR (400 MHz, CDCl₃): major diastereoisomer, *dr* = 5 : 1, δ 7.21–7.19 (m, 2H), 7.15 (d, *J* = 3.2 Hz, 1H), 6.93 (d, *J* = 3.1 Hz, 1H), 6.86–6.84 (m, 2H), 5.43 (t, *J* = 7.2 Hz, 1H), 4.30 (d, *J* = 11.3 Hz, 1H), 4.11 (d, *J* = 5.6 Hz, 1H), 4.05 (d, *J* = 11.2 Hz, 1H), 4.04–3.95 (m, 1H), 3.86–3.83 (m, 1H), 3.83 (s, 3H), 3.79 (s, 3H), 3.77 (s, 3H), 3.58 (t, *J* = 7.9 Hz, 1H), 2.78–2.64 (m, 2H), 2.46–2.36 (m, 1H), 2.30–2.20 (m, 1H), 1.91 (dq, *J* = 6.9 Hz, 5.9 Hz, 6.7 Hz, 1H), 1.73 (d, *J* = 0.7 Hz, 3H), 1.35 (s, 3H), 1.30 (s, 3H), 0.92 (d, *J* = 6.9 Hz, 3H) ppm.

¹³C NMR (100 MHz, CDCl₃): δ 158.9, 154.8, 145.4, 143.9, 139.0, 135.8, 130.6, 129.0, 127.9, 121.6, 113.6, 108.0, 106.6, 77.5, 76.6, 70.0, 66.5, 62.6, 55.7, 55.1, 40.5, 30.0, 28.0, 26.4, 25.3, 19.5, 10.0 ppm.

FTIR (ATR): 2982 (m), 2936 (m), 1613 (m), 1531 (s), 1456 (s), 1368 (m), 1235 (s), 1052 (vs) cm⁻¹.

HRMS (CI): Calcd. for C₂₉H₄₀NO₈ (MH⁺): 530.2754; Found: 530.2745.

(2*R*,3*R*,4*Z*)-7-(2,5-Dimethoxy-3-nitrophenyl)-3-(4-methoxybenzyloxy)-2,4-dimethyl-hept-4-enal
(8)



Acetonide **7** (1.52 g, 2.87 mmol, 100 mol %) was dissolved in EtOAc (78 mL, 0.04 M). This solution was added to a suspension of H₅IO₆ (1.31 g, 5.74 mmol, 200 mol %) in EtOAc (78 mL, 0.04 M) at 25 °C. The reaction mixture was stirred for 40 min (color change) at 25 °C, then Na₂S₂O₃ (one spatula) was added and the resulting mixture was stirred for a further 5 min at 25 °C. The suspension was filtered through a plug of Celite:SiO₂ (4:1) and the filtrate was concentrated under reduced pressure to furnish aldehyde **8** (1.30 g, 2.84 mmol) in 99% yield as a yellow oil. (Note: Aldehyde **8** is highly unstable and epimerizes easily at elevated temperatures and/or catalytic amounts of acid)

R_f = 0.26 (SiO₂, hexanes/EtOAc = 5 : 1).

[α]₂₆^D = +16° (c = 0.83, CHCl₃ 95% *ee*).

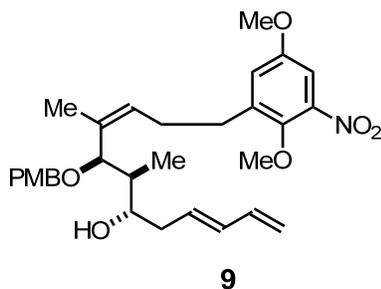
¹H NMR (400 MHz, CDCl₃): δ 9.56 (d, *J* = 2.1 Hz, 1H), 7.21–7.18 (m, 2H), 7.16 (d, *J* = 3.1 Hz, 1H), 6.94 (d, *J* = 3.2 Hz, 1H), 6.88–6.85 (m, 2H), 5.53 (t, *J* = 7.2 Hz, 1H), 4.34 (d, *J* = 11.3 Hz, 1H), 4.29 (d, *J* = 8.4 Hz, 1H), 4.06 (d, *J* = 11.3 Hz, 1H), 3.84 (s, 3H), 3.79 (s, 3H), 3.78 (s, 3H), 2.74–2.64 (m, 3H), 2.41–2.32 (m, 1H), 2.30–2.22 (m, 1H), 1.73 (d, *J* = 1.0 Hz, 3H), 1.14 (d, *J* = 6.8 Hz, 3H) ppm.

¹³C NMR (100 MHz, CDCl₃): δ 203.1, 159.2, 154.0, 145.5, 143.0, 138.9, 133.6, 130.1, 129.0, 129.3, 121.6, 113.7, 106.9, 75.8, 69.4, 62.7, 55.8, 55.2, 49.6, 30.1, 28.2, 18.5, 10.7 ppm.

FTIR (ATR): 2939 (m), 2838 (m), 1723 (m), 1531 (s), 1514 (s), 1368 (m), 1236 (s), 1053 (s) cm⁻¹.

HRMS (CI): Calcd. for C₂₅H₃₁NO₇ (M⁺): 457.2101; Found: 457.2094.

(3E,6R,7S,8R,9Z)-12-(2,5-dimethoxy-3-nitrophenyl)-8-(4-methoxybenzyloxy)-7,9-dimethyldodeca-1,3,9-trien-6-ol (9)



A solution of Me_2AlCl in hexanes (5.7 mL, 5.7 mmol, 250 mol %, 1.0 M) was added dropwise (over glass wall) at $-78\text{ }^\circ\text{C}$ to a stirred solution of aldehyde **8** (1.05 g, 2.29 mmol, 100 mol %) in DCM (11.5 mL, 0.2 M). After 10 min penta-1,3-dienyltrimethyl silane⁴ (964 mg, 6.87 mmol, 300 mol %) was added dropwise (over glass wall) at $-78\text{ }^\circ\text{C}$ and the dark orange solution was stirred for a further 5 h at this temperature. Phosphate buffer (15 mL, 0.05 M, pH = 7) was added followed by a concentrated citric acid solution (20 mL). The reaction mixture was added to a separatory funnel and was extracted with Et_2O (3 x 30 mL). The combined organic fractions were dried (Na_2SO_4), filtered, concentrated under reduced pressure and purified column chromatography (SiO_2 , 10–20% EtOAc /hexanes) to furnish the title compound **9** (635 mg, 1.209 mmol, $dr = >10:1$) in 53% yield as a yellow oil.

$R_f = 0.46$ (SiO_2 , hexanes/ $\text{EtOAc} = 2 : 1$).

$[\alpha]_{25}^D = +95.4^\circ$ ($c = 1.00$, CHCl_3 92% *ee*).

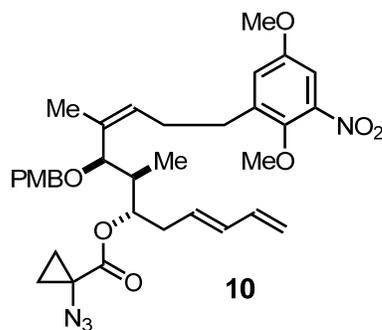
$^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.21–7.19 (m, 2H), 7.15 (d, $J = 3.2$ Hz, 1H), 6.93 (d, $J = 3.2$ Hz, 1H), 6.88–6.85 (m, 2H), 6.27 (dt, $J = 17.0$ Hz, 10.4 Hz, 1H), 6.05 (dd, $J = 15.0$ Hz, 10.4 Hz, 1H), 5.67 (dt, $J = 15.2$ Hz, 7.4 Hz, 1H), 5.45 (t, $J = 7.2$ Hz, 1H), 5.07 (dd, $J = 17.0$ Hz, 1.1 Hz, 1H), 4.96 (dd, $J = 10.3$ Hz, 1.5 Hz, 1H), 4.32 (d, $J = 11.3$ Hz, 1H), 4.26 (d, $J = 5.4$ Hz, 1H), 4.04 (d, $J = 11.3$ Hz, 1H), 3.84 (s, 3H), 3.80 (s, 3H), 3.78 (s, 3H), 3.55 (ddt, $J = 7.4$ Hz, 5.4 Hz, 5.3 Hz, 1H), 2.76–2.68 (m, 2H), 2.64 (d, $J = 5.2$ Hz, 1H), 2.41 (sext, $J = 7.7$ Hz, 1H), 2.30–2.22 (m, 1H), 2.18–2.12 (m, 2H), 1.82–1.74 (m, 1H), 1.76 (d, $J = 1.0$ Hz, 3H), 0.98 (d, $J = 7.0$ Hz, 3H) ppm.

$^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 159.2, 154.9, 145.4, 144.0, 138.9, 136.8, 135.2, 133.4, 131.2, 130.0, 129.4, 128.7, 121.6, 115.5, 113.7, 106.7, 77.7, 73.4, 69.0, 62.6, 55.7, 55.1, 41.7, 37.6, 30.1, 28.2, 19.7, 12.0 ppm.

FTIR (ATR): 3476 (OH, br), 3083 (w), 2939 (m), 2837 (m), 1613 (m), 1531 (vs), 1514 (s), 1236 (s), 1053 (s) cm^{-1} .

HRMS (CI): Calcd. for $\text{C}_{30}\text{H}_{39}\text{NO}_7$ (M^+): 525.2727; Found: 525.2717.

(3*E*,6*R*,7*S*,8*R*,9*Z*)-12-(2,5-Dimethoxy-3-nitrophenyl)-8-(4-methoxybenzyloxy)-7,9-dimethyl-dodeca-1,3,9-trien-6-yl 1-azidocyclopropane-1-carboxylate (10)



Oxalylchloride (119 mg, 0.936 mmol, 240 mol %) was added at 0 °C to a solution of 1-azidocyclopropane-1-carboxylic acid (**d**) (149 mg, 1.17 mmol, 300 mol %), DMF (9 mg, 0.1 mmol, 30 mol%) in toluene (1.3 mL, 0.9 M). The mixture was stirred for 1 h at 25 °C. In a separate reaction vessel DMAP (14 mg, 0.12 mmol, 30 mol %) was added to a solution of Et₃N (237 mg, 2.34 mmol, 600 mol %) and alcohol **9** (200 mg, 0.380 mmol, 100 mol %) in DCM (1.3 mL, 0.3 M) at 25 °C. The acid chloride solution was then transferred to the alcohol **9** solution at 0 °C and the mixture was stirred for 1 h at 0 °C. Phosphate buffer (3 mL, 0.05 M, pH = 7) was added and the aqueous layer was extracted with EtOAc (3 x 3 mL). The combined organic extracts were washed with brine (3 mL), dried (Na₂SO₄), filtered, the solvent was removed under reduced pressure, and purified by column chromatography (SiO₂, 5–10% EtOAc/hexanes) to furnish the title compound **10** (214 mg, 0.337 mmol) in 89% yield as a yellow oil.

R_f = 0.29 (SiO₂, hexanes : EtOAc = 5 : 1).

[α]₂₇^D = +53.5° (c = 1.17, CHCl₃ 90% *ee*).

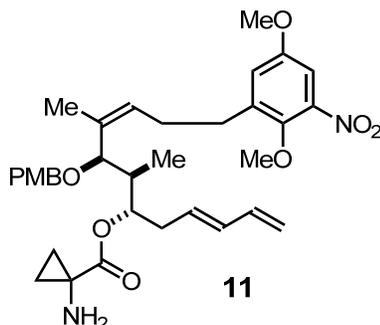
¹H NMR (400 MHz, CDCl₃): δ 7.19–7.17 (m, 2H), 7.14 (d, *J* = 3.2 Hz, 1H), 6.94 (d, *J* = 3.2 Hz, 1H), 6.86–6.84 (m, 2H), 6.25 (dt, *J* = 17.0 Hz, 10.3 Hz, 1H), 6.00 (dd, *J* = 15.0 Hz, 10.3 Hz, 1H), 5.55–5.46 (m, 2H), 5.08 (d, *J* = 16.8 Hz, 1H), 4.99 (d, *J* = 10.8 Hz, 1H), 4.89 (ddd, *J* = 9.3 Hz, 5.1 Hz, 2.7 Hz, 1H), 4.23 (d, *J* = 11.1 Hz, 1H), 3.97 (d, *J* = 11.0 Hz, 1H), 3.93 (d, *J* = 8.0 Hz, 1H), 3.83 (s, 3H), 3.79 (s, 3H), 3.76 (s, 3H), 2.78–2.66 (m, 2H), 2.48–2.38 (m, 1H), 2.37–2.08 (m, 4H), 1.78 (s, 3H), 1.35–1.33 (m, 2H), 1.13–1.10 (m, 2H), 1.04 (d, *J* = 6.9 Hz, 3H) ppm.

¹³C NMR (100 MHz, CDCl₃): δ 170.5, 159.0, 154.9, 145.4, 144.0, 138.9, 136.4, 134.7, 133.9, 130.4, 129.3, 129.2, 121.5, 116.1, 113.6, 106.7, 77.2, 75.7, 69.6, 62.6, 55.7, 55.1, 42.6, 39.4, 33.1, 30.2, 28.2, 18.7, 16.6, 16.4, 10.9 ppm.

FTIR (ATR): 3083 (w), 2939 (m), 2104 (m), 1728 (s), 1612 (m), 1532 (s), 1513 (s), 1362 (m), 1236 (vs), 1052 (s) cm⁻¹.

HRMS (CI): Calcd. for C₃₄H₄₃N₂O₈ (M+H⁺-N₂): 607.3019; Found: 607.3016.

(3E,6R,7S,8R,9Z)-12-(2,5-Dimethoxy-3-nitrophenyl)-8-(4-methoxybenzyloxy)-7,9-dimethyl-dodeca-1,3,9-trien-6-yl 1-aminocyclopropane-1-carboxylate (11)



1,3-Propanedithiol (4.7 mL, 5.1 g, 47 mmol, 5000 mol %) was added to a solution of azide **10** (599 mg, 0.944 mmol, 100 mol %), Et₃N (4.77 g, 47.2 mmol, 5000 mol %) in MeOH (24 mL, 0.04 M) at 25 °C. The mixture was stirred at 25 °C for 22 h. The solvent was removed under reduced pressure, phosphate buffer solution (25 mL, 0.05 M, pH = 7) was added and the mixture was transferred to a separatory funnel. The aqueous layer was extracted with CHCl₃ (3 x 25 mL). The combined organic extracts were washed with brine (25 mL), dried (MgSO₄), filtered and the solvent was removed under reduced pressure. Flash column chromatography (SiO₂, 30–50% EtOAc/hexanes) furnished the amino carboxylate **11** (511 mg, 0.839 mmol) in 89% yield as a yellow oil.

R_f = 0.19 (SiO₂, hexanes/EtOAc = 2 : 1).

$[\alpha]_{26}^D = +43^\circ$ (c = 1.5, CHCl₃ 90% *ee*).

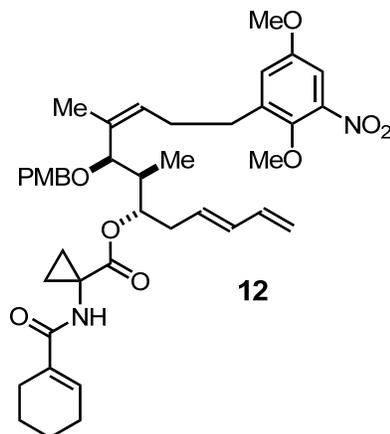
¹H NMR (400 MHz, CDCl₃): δ 7.19–7.17 (m, 2H), 7.15 (d, *J* = 3.1 Hz, 1H), 6.94 (d, *J* = 3.1 Hz, 1H), 6.86–6.84 (m, 2H), 6.24 (dt, *J* = 17.1 Hz, 10.3 Hz, 1H), 5.97 (dd, *J* = 15.3 Hz, 10.2 Hz, 1H), 5.51 (t, *J* = 7.1 Hz, 1H), 5.51–5.44 (m, 1H), 5.08 (d, *J* = 17.2 Hz, 1H), 4.98 (d, *J* = 10.1 Hz, 1H), 4.78 (ddd, *J* = 9.6 Hz, 5.2 Hz, 2.8 Hz, 1H), 4.23 (d, *J* = 11.1 Hz, 1H), 3.96 (d, *J* = 11.2 Hz, 1H), 3.88 (d, *J* = 8.0 Hz, 1H), 3.83 (s, 3H), 3.79 (s, 3H), 3.77 (s, 3H), 2.76 (ddd, *J* = 14.0 Hz, 9.3 Hz, 6.4 Hz, 1H), 2.69 (ddd, *J* = 14.0 Hz, 9.3 Hz, 6.8 Hz, 1H), 2.41 (sext, *J* = 7.8 Hz, 1H), 2.28–2.20 (m, 2H), 2.14–2.08 (m, 1H), 2.06–2.02 (m, 1H), 1.80 (s, 3H), 1.60 (s, br, 2H), 1.17–1.14 (m, 2H), 0.99 (d, *J* = 6.9 Hz, 3H), 0.93–0.90 (m, 2H) ppm.

¹³C NMR (100 MHz, CDCl₃): δ 175.7, 159.0, 154.9, 145.4, 144.0, 138.9, 136.5, 134.8, 133.6, 130.4, 129.6, 129.2, 129.1, 121.6, 115.9, 113.6, 106.7, 77.1, 74.4, 69.5, 62.6, 55.8, 55.1, 39.3, 35.6, 32.8, 30.3, 28.3, 18.7, 17.2, 10.8 ppm.

FTIR (ATR): 3090 (w), 2936 (m), 2835 (w), 1716 (s), 1612 (m), 1531 (s), 1513 (s), 1302 (m), 1236 (vs), 1053 (s) cm⁻¹.

HRMS (CI): Calcd. for C₃₄H₄₅N₂O₈ (M+H⁺): 609.3176; Found: 609.3180.

(3E,6R,7S,8R,9Z)-12-(2,5-dimethoxy-3-nitrophenyl)-8-(4-methoxybenzyloxy]-7,9-dimethylododeca-1,3,9-trien-6-yl 1-[(cyclohex-1-ene)amido]cyclopropane-1-carboxylate (12)



A solution of cyclohexene-1-carboxylic acid (93 mg, 0.74 mmol, 300 mol %) in DCM (2 mL) was added to a solution of amino cyclopropyl carboxylate **11** (150 mg, 0.246 mmol, 100 mol %) and DMAP (241 mg, 1.97 mmol, 800 mol %) in DCM (3 mL) at 25 °C. Then EDCI · HCl (189 mg, 0.984 mmol, 400 mol %) was added and the mixture was stirred under inert conditions for 24 h. Saturated NaHCO₃ solution (10 mL) was added, the layers separated and the aqueous layer was extracted with chloroform (3 x 10 mL). The combined organic extracts were washed with brine (2 x 10 mL), dried (MgSO₄) and the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO₂, 20–50% EtOAc/hexanes) to furnish the title compound **12** (148 mg, 0.206 mmol) in 84% yield as a yellow oil.

R_f = 0.20 (SiO₂, hexanes/EtOAc = 2 : 1).

$[\alpha]_{26}^D = +53.3^\circ$ (c = 1.17, CHCl₃ 90% ee).

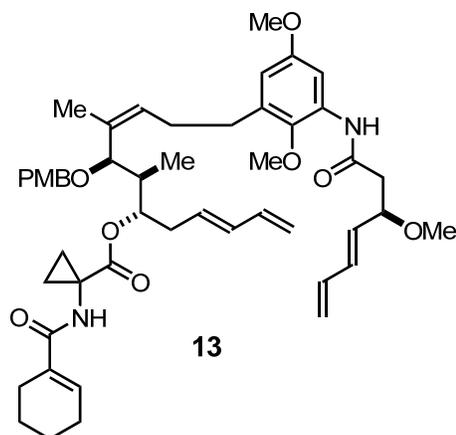
¹H NMR (400 MHz, CDCl₃): δ 7.19–7.17 (m, 2H), 7.15 (d, *J* = 3.1 Hz, 1H), 6.95 (d, *J* = 3.1 Hz, 1H), 6.86–6.83 (m, 2H), 6.58–6.55 (m, 1H), 6.25 (dt, *J* = 17.0 Hz, 10.4 Hz, 1H), 6.17 (s, 1H), 5.97 (dd, *J* = 15.6 Hz, 10.3 Hz, 1H), 5.55–5.49 (m, 1H), 5.48 (t, *J* = 8.4 Hz, 1H), 5.07 (d, *J* = 17.0 Hz, 1H), 4.97 (d, *J* = 10.4 Hz, 1H), 4.81 (ddd, *J* = 8.5 Hz, 5.1 Hz, 3.1 Hz, 1H), 4.22 (d, *J* = 11.1 Hz, 1H), 3.98 (d, *J* = 11.1 Hz, 1H), 3.90 (d, *J* = 7.7 Hz, 1H), 3.83 (s, 3H), 3.79 (s, 3H), 3.77 (s, 3H), 2.75–2.70 (m, 2H), 2.45–2.35 (m, 1H), 2.25–2.05 (m, 8H), 1.76 (s, 3H), 1.65–1.55 (m, 4H), 1.48–1.45 (m, 2H), 1.13–1.10 (m, 2H), 0.97 (d, *J* = 6.9 Hz, 3H) ppm.

¹³C NMR (100 MHz, CDCl₃): δ = 171.7, 169.2, 158.9, 154.9, 145.4, 143.9, 139.0, 136.7, 135.0, 133.7, 133.5, 133.1, 130.6, 129.8, 129.2, 128.8, 121.6, 115.7, 113.6, 106.8, 77.3, 75.0, 69.6, 62.7, 55.8, 55.1, 39.3, 33.7, 33.0, 30.3, 28.2, 25.3, 24.1, 22.0, 21.4, 18.9, 17.2, 10.8 ppm.

FTIR (ATR): 3359 (w, br), 2935 (m), 1724 (m), 1665 (m), 1531 (s), 1513 (s), 1337 (m), 1236 (s), 1173 (s) cm⁻¹.

HRMS (ESI): Calcd. for C₄₁H₅₂N₂O₉Na (M+Na⁺): 739.3565; Found: 739.3566.

(3*E*,6*S*,7*S*,8*R*,9*Z*)-12-{2,5-dimethoxy-3-[(3*R*,4*E*)-3-methoxyhepta-4,6-dienamido]phe-nyl}-8-(4-methoxybenzyloxy)-7,9-dimethyldodeca-1,3,9-trien-6-yl1-[(cyclohex-1-ene)amido]cyclopropane-1-carboxylate (13)



Sulfur (156 mg, 4.88 mmol, 3500 mol %) and NaBH₄ (105 mg, 2.78 mmol, 2000 mol %) were added at 25 °C to a stirred solution of nitroarene **12** (100 mg, 0.139 mmol, 100 mol %) in THF (14 mL, 0.01 M). This solution was stirred under inert conditions for a further 1 h at 50 °C. After cooling to 25 °C saturated NaHCO₃ solution (15 mL) was slowly added, the layers separated and the aqueous layer was extracted with chloroform (3 x 15 mL). The combined organic extracts were washed with brine (15 mL), dried (MgSO₄) and filtered. Then the solvent was removed in vacuo and the crude solid residue was used in the next step.

Freshly distilled ethyldiisopropylamine (898 mg, 6.95 mmol, 5000 mol %) was added to a solution of the solid residue in toluene (14 mL, 0.01 M) at 25 °C. This solution was added at 25 °C to a stirred solution of Fragment **D** (109 mg, 0.698 mmol, 500 mol %) and BOPCl (212 mg, 0.834 mmol, 600 mol%) in THF (23 mL, 0.03 M with respect to Fragment **D**). After addition of powdered molecular sieves (4 Å, 2 spatulas) the reaction mixture was stirred for further 21 h at 25 °C under an argon atmosphere. The reaction mixture was transferred to a separatory funnel and saturated NaHCO₃ solution (45 mL) was added. The layers separated and the aqueous layer was extracted with chloroform (3 x 45 mL). The combined organic extracts were dried (MgSO₄), filtered, and the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO₂, toluene/EtOAc/hexanes = 3:1:1) to furnish the title compound **13** (79 mg, 0.096 mmol) in 69% yield as a yellow oil.

R_f = 0.10 (SiO₂, toluene/EtOAc/hexanes = 3 : 1 : 1).

[α]₂₆^D = +34.1° (c = 1.00, CHCl₃, 90% ee).

¹H NMR (400 MHz, CDCl₃): δ 8.94 (s, 1H), 7.92 (d, *J* = 3.0 Hz, 1H), 7.21–7.19 (m, 2H), 6.85–6.83 (m, 2H), 6.57–6.55 (m, 1H), 6.43 (d, *J* = 3.0 Hz, 1H), 6.33 (dt, *J* = 16.4 Hz, 10.4 Hz, 1H), 6.30 (dd, *J* = 21.2 Hz, 10.8 Hz, 1H), 6.24 (dt, *J* = 17.0 Hz, 10.2 Hz, 1H), 6.17 (s, 1H), 5.98 (dd, *J* = 15.2 Hz,

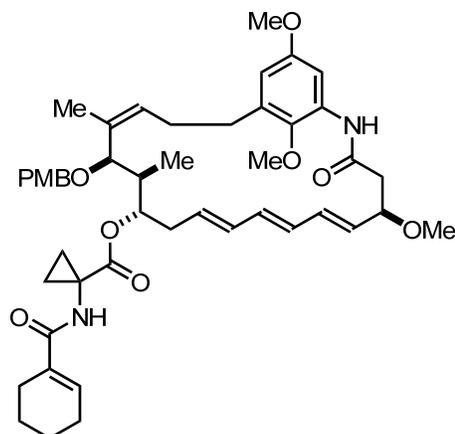
10.3 Hz, 1H), 5.56 (ddd, $J = 20.3$ Hz, 14.3 Hz, 8.0 Hz, 1H), 5.55–5.48 (m, 2H), 5.28 (d, $J = 16.7$ Hz, 1H), 5.17 (d, $J = 9.6$ Hz, 1H), 5.06 (d, $J = 17.0$ Hz, 1H), 4.96 (d, $J = 10.1$ Hz, 1H), 4.80 (ddd, $J = 8.9$ Hz, 4.8 Hz, 3.0 Hz, 1H), 4.28 (d, $J = 11.3$ Hz, 1H), 4.07 (td, $J = 7.9$ Hz, 3.9 Hz, 1H), 4.01 (d, $J = 11.3$ Hz, 1H), 3.91 (d, $J = 8.1$ Hz, 1H), 3.79 (s, 3H), 3.75 (s, 3H), 3.68 (s, 3H), 3.37 (s, 3H), 2.69–2.60 (m, 4H), 2.43–2.35 (m, 1H), 2.30–2.05 (m, 8H), 1.76 (s, 4H), 1.67–1.60 (m, 2H), 1.59–1.54 (m, 2H), 1.50–1.47 (m, 2H), 1.14–1.10 (m, 2H), 0.98 (d, $J = 6.8$ Hz, 3H) ppm.

^{13}C NMR (125 MHz, CDCl_3): $\delta = 171.7, 169.2, 168.8, 159.0, 156.0, 140.8, 136.9, 135.7, 134.7, 134.4, 134.3, 133.8, 133.5, 133.3, 132.4, 131.3, 131.0, 130.1, 129.8, 129.2, 118.9, 115.6, 113.7, 110.6, 103.3, 78.7, 77.5, 75.1, 69.6, 61.2, 56.4, 55.5, 55.2, 44.2, 39.2, 33.9, 33.0, 30.1, 28.6, 25.4, 24.2, 22.1, 21.5, 18.8, 17.2, 11.0$ ppm.

FTIR (ATR): 3311 (w, br), 2936 (m), 2245 (w), 1724 (m), 1667 (m), 1529 (m), 1513 (s), 1420 (m), 1171 (s), 1083 (s) cm^{-1} .

HRMS (CI): Calcd. for $\text{C}_{49}\text{H}_{65}\text{N}_2\text{O}_9$ ($\text{M}+\text{H}^+$): 825.4690; Found: 825.4695.

Cytotrienin A Core



Indinylidene Grubbs-I derivative⁵ (18 mg, 0.02 mmol, 20 mol %) was added to a solution of bisdiene **13** (79 mg, 0.096 mmol, 100 mol %) in DCM (60 mL, 1.6 mM) at 25 °C. The solution was then stirred at 40 °C under inert conditions in the dark. After 16 h additional ruthenium complex (9 mg, 0.01 mmol, 10 mol %) was added, the mixture was sparged with argon, and stirred for 3 h at 40 °C. The solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO₂, 30–50% EtOAc/hexanes) to furnish the cytotrienin A core (33 mg, 0.041 mmol) in 43% yield as a yellow oil.

$R_f = 0.22$ (SiO₂, EtOAc/hexanes = 1 : 1).

$[\alpha]_{27}^D = +51^\circ$ (c = 1.00, CHCl₃ 90% *ee*).

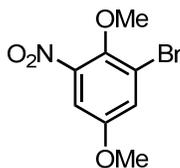
¹H NMR (500 MHz, CDCl₃): δ 8.19 (s, 1H), 7.84 (d, $J = 3.1$ Hz, 1H), 7.19–7.17 (m, 2H), 6.85–6.83 (m, 2H), 6.59–6.56 (m, 1H), 6.38–6.31 (m, 1H), 6.33 (d, $J = 3.1$ Hz, 1H), 6.11 (s, 1H), 6.03–5.98 (m, 2H), 5.55 (dd, $J = 15.6$ Hz, 5.5 Hz, 1H), 5.49–5.46 (m, 2H), 4.81 (td, $J = 6.9$ Hz, 3.0 Hz, 1H), 4.31 (d, $J = 11.2$ Hz, 1H), 4.15–4.12 (m, 1H), 4.00 (d, $J = 5.5$ Hz, 1H), 3.97 (d, $J = 11.2$ Hz, 1H), 3.80 (s, 3H), 3.69 (s, 3H), 3.66 (s, 3H), 3.44 (s, 3H), 2.85–2.80 (m, 1H), 2.75–2.70 (m, 1H), 2.50–2.44 (m, 1H), 2.39–2.33 (m, 1H), 2.24–2.10 (m, 8H), 1.89–1.85 (m, 1H), 1.78 (d, $J = 1.1$ Hz, 3H), 1.66–1.63 (m, 3H), 1.59–1.57 (m, 3H), 1.30–1.20 (m, 3H), 0.98 (d, $J = 6.9$ Hz, 3H) ppm.

¹³C NMR (125 MHz, CDCl₃): δ 171.1, 169.3, 168.2, 158.9, 155.7, 140.6, 134.8, 134.2, 133.9, 133.5, 133.2, 133.0, 132.2, 131.0, 129.5, 129.3, 129.3, 129.2, 129.1, 113.7, 110.5, 103.1, 77.9, 75.3, 74.8, 70.1, 61.0, 56.9, 55.4, 55.3, 43.6, 39.7, 33.9, 32.5, 31.2, 28.8, 25.4, 24.2, 22.1, 21.5, 19.3, 17.3, 17.1, 10.6 ppm.

FTIR (ATR): 3346 (w, br), 2934 (m), 1724 (m), 1667 (m), 1613 (m), 1514 (s), 1465 (m), 1247 (m), 1173 (s) cm⁻¹.

HRMS (ESI): Calcd. for C₄₇H₆₀N₂O₉Na (M+Na⁺): 819.4197; Found: 819.4187.

1-Bromo-2,5-dimethoxy-3-nitrobenzene



Dimethylsulfate (3.05 g, 34.2 mmol, 200 mol %) was added at 25 °C to a stirred suspension of K_2CO_3 (5.02 g, 36.3 mmol, 300 mol %) and bromomethoxynitrophenol (3.00 g, 12.1 mmol, 100 mol %) in acetone (60 mL, 0.2 M). After stirring the mixture at reflux for 16 h, the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2 , 10–20% EtOAc/hexanes) to furnish the title compound 1-bromo-2,5-dimethoxy-3-nitrobenzene (3.02 g, 11.5 mmol) in 95% yield as a yellow solid.

R_f = 0.45 (SiO_2 , hexanes/EtOAc = 5 : 1).

MP: 100–101°C. (Lit.: 98–98.5 °C)⁶

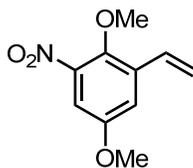
1H NMR (400 MHz, $CDCl_3$): δ 7.34 (d, J = 3.1 Hz, 1H), 7.28 (d, J = 3.1 Hz, 1H), 3.96 (s, 3H), 3.83 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.5, 145.0, 144.4, 123.8, 120.1, 109.2, 62.7, 56.2 ppm.

FTIR (ATR): 3102 (w), 2946 (w), 2840 (w), 1524 (s), 1475 (m), 1341 (m), 1229 (m), 1042 (m) cm^{-1} .

HRMS (CI): Calcd. for $C_8H_8NO_4Br$ (M): 260.9637; Found: 260.9635.

2,5-Dimethoxy-1-nitro-3-vinylbenzene



1-Bromo-2,5-dimethoxy-3-nitrobenzene (131 mg, 0.500 mmol, 100 mol %), triphenylphosphine (10.5 mg, 0.040 mmol, 8 mol %), PdCl₂(PPh₃)₂ (7 mg, 0.01 mmol, 2 mol %), Cs₂CO₃ (489 mg, 1.50 mmol, 300 mol %), and potassium vinyltrifluoroborate (67 mg, 0.50 mmol, 100 mol %) were added to a resealable pressure tube (13 x 100 mm). THF (2.1 mL, 2 M) and H₂O (0.2 mL) were added in oxygen free conditions and the mixture was stirred under argon at 85 °C for 2 d. Saturated NH₄Cl solution (2 mL) was added, the layers were separated and the aqueous layer was extracted with DCM (3 x 2 mL). The combined organic extracts were dried (MgSO₄), filtered, and the solvent removed under reduced pressure. The residue was purified by column chromatography (SiO₂, 10–20% EtOAc/hexanes) to furnish the title compound 2,5-dimethoxy-1-nitro-3-vinylbenzene (96 mg, 0.46 mmol) in 92% yield as a yellow solid.

R_f = 0.39 (SiO₂, hexanes/EtOAc = 5 : 1).

MP: 54–55 °C.

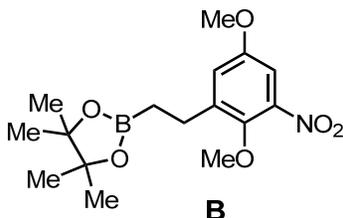
¹H NMR (400 MHz, CDCl₃): δ 7.26 (d, *J* = 3.2 Hz, 1H), 7.24 (d, *J* = 3.2 Hz, 1H), 6.97 (dd, *J* = 17.7 Hz, 11.1 Hz, 1H), 5.82 (dd, *J* = 17.7 Hz, 0.9 Hz, 1H), 5.47 (dd, *J* = 11.1 Hz, 1.1 Hz, 1H), 3.85 (s, 3H), 3.84 (s, 3H) ppm.

¹³C NMR (100 MHz, CDCl₃): δ 155.1, 144.6, 144.6, 134.9, 129.9, 117.8, 116.9, 108.6, 63.1, 56.0 ppm.

FTIR (ATR): 3090 (w), 2941 (w), 2837 (w), 1528 (s), 1477 (m), 1414 (m), 1352 (m), 1230 (m), 1071 (w), 994 (s) cm⁻¹.

HRMS (CI): Calcd. for C₁₀H₁₁NO₄ (M): 209.0688; Found: 209.0692.

2-(2,5-dimethoxy-3-nitrophenethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



To a stirred solution of $[\text{Ir}(\text{cod})\text{Cl}]_2$ (88 mg, 0.13 mmol, 2.5 mol %), 1,2-bis(diphenylphosphino)ethane (171 mg, 0.274 mmol, 5.2 mol %), toluene (4.5 mL), 1,2-dichloroethane (0.5 mL) under argon at 25 °C was added 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.89 mL, 13 mmol, 250 mol %) followed by 2,5-dimethoxy-1-nitro-3-vinylbenzene (1.1 g, 5.2 mmol, 100 mol %). The resulting solution was stirred for 14 hours. The reaction mixture was added to a separatory funnel containing Et_2O (50 mL) and methanol (3 mL) was added slowly. After gas evolution ceased, brine (10 mL) was added and the organic layer was washed, dried (Na_2SO_4), filtered, concentrated, and purified by column chromatography (SiO_2 , 20-100% DCM/hexanes) to furnish the title compound (1.56 g, 4.63 mmol) in 88 % yield as a yellow solid.

R_f = 0.2 (SiO_2 , hexanes/DCM = 1 : 1).

MP: 36–37 °C.

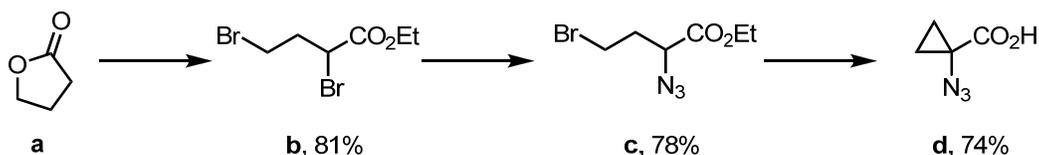
$^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.14 (d, J = 3.2 Hz, 1H), 7.04 (d, J = 3.2 Hz, 1H), 3.84 (s, 3H), 3.79 (s, 3H), 2.78 (t, J = 8.1 Hz, 2H), 1.22 (s, 12H), 1.12 (t, J = 8.1 Hz, 2H) ppm.

$^{13}\text{C NMR}$ (100 MHz, CDCl_3 , C attached to quadrupole B not observed): δ 156.8, 147.1, 145.8, 143.6, 122.6, 108.5, 85.1, 64.5, 57.7, 26.6, 25.8 ppm.

FTIR (ATR): λ^{-1} 2977, 1530, 1369, 1319, 1229, 1141, 1050 cm^{-1} .

HRMS (ESI): Calcd. for $\text{C}_{16}\text{H}_{24}\text{NBO}_6$ ($\text{M}+\text{Na}^+$): 360.1594, found 360.1592.

Preparation of 1-azidocyclopropane-1-carboxylic acid (d)



Ethyl 2,4-dibromobutanoate (b)

Freshly distilled γ -butyrolactone (a) (16.0 g, 186 mmol, 100 mol %) and PBr_3 (0.3 mL) were combined at 100 °C. The reaction vessel was heated to 110 °C and bromine (9.55 mL, 29.7 g, 186 mmol, 100 mol %) was added dropwise to the stirred solution. PBr_3 (0.2 mL) was added and the solution was stirred for 2 h at 110 °C. After cooling to 25 °C, the flask was sparged with nitrogen, absolute EtOH (35 mL, 28 g, 600 mmol, 320 mol %) and *p*-toluenesulfonic acid (1.77 g, 9.31 mmol, 5 mol %) were added and the reaction mixture was stirred at 50 °C for 21 h.

The reaction mixture was transferred to a separatory funnel containing Et_2O (100 mL) and was washed with saturated NaHCO_3 solution (50 mL), and brine (50 mL). The organic extract was dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure. The yellow residue was purified by fractional vacuum distillation (0.1 Torr) to furnish the title compound **b** (41.2 g, 151 mmol) in 81% yield as a colorless oil. The data for the title compound was consistent with reported values.⁷

BP: 112–120 °C.

¹H NMR (400 MHz, CDCl_3): δ 4.51 (dd, $J = 8.2$ Hz, 6.1 Hz, 1H), 4.28 (ABX₃, $J = 10.8$ Hz, 7.1 Hz, 1H), 4.24 (ABX₃, $J = 10.8$ Hz, 7.1 Hz, 1H), 3.55 (dd, $J = 6.5$ Hz, 5.8 Hz, 2H), 2.53 (ABMX₂, $J = 15.3$ Hz, 6.6 Hz, 5.9 Hz, 1H), 2.51 (ABMX₂, $J = 15.3$ Hz, 8.1 Hz, 5.7 Hz, 1H), 1.32 (t, $J = 7.1$ Hz, 3H) ppm.

¹³C NMR (100 MHz, CDCl_3): δ 169.1, 62.3, 43.8, 36.8, 29.8, 13.9 ppm.

Ethyl 2-azido-4-bromobutanoate (c)

Sodium azide (4.19 g, 64.4 mmol, 110 mol %) was added to a stirred solution of dibromobutanoate **b** (16.1 g, 58.6 mmol, 100 mol %) in acetone–water (290 mL, 1:3, 0.2 M) at 25 °C and the reaction was stirred for 21 h. DCM (500 mL) was added and the organic layer was washed with water (3 x 150 mL), dried (MgSO₄), filtered and the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO₂, 5–10% EtOAc/hexanes) to furnish the title compound **c** (10.8 g, 45.7 mmol) in 78% yield as a colorless oil. This procedure is a variation of a previous report, the data for the title compound was consistent with reported values.⁸

R_f = 0.48 (SiO₂, EtOAc/hexanes = 1 : 5).

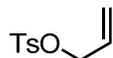
¹H NMR (400 MHz, CDCl₃): δ 4.28 (q, J = 7.1 Hz, 2H), 4.20 (dd, J = 9.5 Hz, 4.5 Hz, 1H), 3.53 (ABXX', J = 13.9 Hz, 8.7 Hz, 5.3 Hz, 1H), 3.49 (ABXX', J = 13.9 Hz, 6.5 Hz, 5.4 Hz, 1H), 2.34 (dddd, J = 14.8 Hz, 8.7 Hz, 6.6 Hz, 4.5 Hz, 1H), 2.18 (ddt, J = 14.7 Hz, 9.5 Hz, 5.3 Hz, 1H), 1.34 (t, J = 7.2 Hz, 3H) ppm.

1-Azidocyclopropane-1-carboxylic acid (d)

A solution of bromide **c** (6.74 g, 28.4 mmol, 100 mol %) in DMF (56 mL, 0.5 M) was treated with potassium *tert*-butoxide (3.83 g, 34.1 mmol, 120 mol %) at 25 °C. The reaction mixture was stirred for 1 h then KOH (3.18 g, 56.8 mmol, 200 mol %) was added, followed by water (20 mL). This mixture was stirred for 5 h at 25 °C. Water (100 mL) was added and the mixture was added to a separatory funnel. The aqueous layer was washed with DCM (3 x 50 mL) and Et₂O (50 mL), acidified with HCl to pH 2 (by pH paper), and extracted with Et₂O (5 x 100 mL). The combined organic extracts were washed with brine (5 x 100 mL), dried (MgSO₄), filtered and the solvent was removed under reduced pressure to furnish the title compound **d** (2.81 g, 22.1 mmol) in 74 % yield as a light yellow solid. The data for the title compound was consistent with reported values.⁹

¹H NMR (400 MHz, CDCl₃): δ 8.30 (br, s, 1H), 1.56 (AA'BB', 2H), 1.31 (AA'BB', 2H) ppm.

Allyl 4-methylbenzenesulfonate



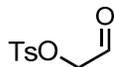
To a suspension of sodium hydride (60% in mineral oil, 2.5 g, 65 mmol, 150 mol %) and Et₂O (65 mL) under an atmosphere of argon was added allyl alcohol (2.9 mL, 43 mmol, 100 mol %) at 25 °C. After gas evolution ceased the reaction mixture was cooled to 0 °C. *p*-Toluenesulfonyl chloride (8.1 g, 43 mmol, 100 mol %) was dissolved in Et₂O (100 mL) and resulting solution was added slowly to reaction mixture. After the addition was complete the reaction mixture was warmed to 25 °C and allowed to stir for 1 hour. The reaction mixture was added to a saturated solution of ammonium chloride (100 mL) in a separatory funnel. The mixture was extracted with Et₂O (3 x 50 mL), dried (Na₂SO₄), filtered, and concentrated under reduced pressure. The resulting oil was washed with hexanes (2 x 20 mL) and concentrated under reduced pressure to furnish the title compound allyl 4-methylbenzenesulfonate (9.0 g, 42 mmol) in 98% yield as a clear oil. The data for the compound was consistent with reported values.¹⁰

R_f = 0.6 (SiO₂, hexanes/EtOAc = 9 : 1).

¹H NMR (400 MHz, CDCl₃): δ 7.75 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 7.9 Hz, 2H), 5.78 (ddt, *J* = 17.1 Hz, 10.4 Hz, 5.9 Hz, 1H), 5.31–5.19 (m, 2H), 4.49 (ddd, *J* = 5.9 Hz, 1.5 Hz, 1.2 Hz, 2H), 2.41 (s, 3H) ppm.

¹³C NMR (100 MHz, CDCl₃): δ 144.9, 133.1, 130.2, 129.9, 127.8, 120.2, 70.8, 21.6 ppm.

2-Oxoethyl 4-methylbenzenesulfonate

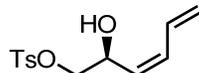


A solution of allyl 4-methylbenzenesulfonate (3.1 g, 15 mmol, 100 mol %) in DCM (140 mL) at -78 °C was sparged with ozone until the reaction mixture was pale blue. Ozone was removed and the reaction was sparged with argon for 5 minutes. Dimethyl sulfide (10.0 mL, 142 mmol, 1000 mol %) was added at -78 °C and reaction was allowed to warm to 25 °C with stirring for 12 hours. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (SiO_2 , 30% to 70% ethyl acetate/hexanes, gradient elution) to furnish the title compound 2-oxoethyl 4-methylbenzenesulfonate (2.25 g, 8.20 mmol) in 72 % yield as a light yellow oil. Due to the rapid decomposition of the title compound, it was stored as a 0.2 M solution in toluene at -20 °C. The data for the title compound was consistent with reported values.¹¹

$R_f = 0.2$ (SiO_2 , hexanes/EtOAc = 1 : 2)

$^1\text{H NMR}$ (400 MHz, CDCl_3): δ 9.60 (s, 1H), 7.82–7.79 (m, 2H), 7.38–7.35 (m, 2H), 4.50 (s, 2H), 2.45 (s, 3H) ppm.

(*S,Z*)-2-Hydroxyhexa-3,5-dienyl 4-methylbenzenesulfonate



To a solution of [Rh(COD)₂]BARF (155 mg, 0.13 mmol, 5 mol %), (*S*)-MeO-BIPHEP (72 mg, 0.13 mmol, 5 mol %), 3-nitrobenzoic acid (39 mg, 0.20 mmol, 7.5 mol %), and Na₂SO₄ (1.85 g, 13.1 mmol, 400 mol %) in 1,2-dichloroethane (11 mL) and toluene (11 mL) under an atmosphere of hydrogen and acetylene gas (approximately 1:1 by volume) was added a solution of 2-oxoethyl 4-methylbenzenesulfonate (700 mg, 3.27 mmol, 100 mol %) in 1,2-dichloroethane (3.5 mL) and toluene (3.5 mL). The resulting mixture was stirred at 25 °C for 16 hours. The crude reaction mixture was filtered, concentrated under reduced pressure, and purified by column chromatography (SiO₂, 30% ethyl acetate/hexanes) to furnish the title compound (*S,Z*)-2-hydroxyhexa-3,5-dienyl 4-methylbenzenesulfonate (729 mg, 2.71 mmol) in 83% yield as a colorless oil. The resulting compound was not stable as a neat oil at -20 °C.

R_f = 0.5 (SiO₂, hexanes/EtOAc = 1 : 2).

[α]₂₄^D = +106° (*c* = 0.65, CHCl₃, 85% *ee*).

¹H NMR (400 MHz, CDCl₃): δ 7.73 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 6.49–6.39 (m, 1H), 6.02 (t, *J* = 11.1 Hz, 1H), 5.26–5.12 (m, 3H), 4.75 (s, 1H), 3.90 (dd, *J* = 8.0 Hz, 5.7 Hz, 2H), 3.18 (s, 1H), 2.37 (s, 3H) ppm.

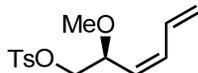
¹³C NMR (100 MHz, CDCl₃): δ 145.1, 133.0, 132.5, 131.2, 129.9, 127.9, 120.7, 72.9, 66.0, 21.6 ppm.

FTIR (ATR): 1354, 1172, 1095 cm⁻¹.

HRMS (CI): Calcd. for C₁₃H₁₆O₄S (M): 268.0769, found 268.0765.

HPLC (Chiralcel OD-H column, 3% *i*-PrOH/hexanes, 1 mL/min, 230 nm), *t*_{minor} = 11.1 min, *t*_{major} = 13.3 min; *ee* = 85%.

(*S,Z*)-2-Methoxyhexa-3,5-dienyl 4-methylbenzenesulfonate



To a solution of (*S,Z*)-2-hydroxyhexa-3,5-dienyl 4-methylbenzenesulfonate (330 mg, 1.23 mmol, 100 mol %) in DCM (25 mL) at 25 °C under an atmosphere of argon was added trimethyloxonium tetrafluoroborate (455 mg, 3.08 mmol, 250 mol %) and 1,8-bis(dimethylamino)naphthalene (791 mg, 3.69 mmol, 300 mol %). The resulting mixture was stirred for 2 hours at 25 °C. The crude reaction mixture was filtered, concentrated under reduced pressure, and purified by column chromatography (SiO₂, 10% ethyl acetate/hexanes) to furnish the title compound (*S,Z*)-2-methoxyhexa-3,5-dienyl 4-methylbenzenesulfonate (330 mg, 1.17 mmol) in 95% yield as a clear oil.

R_f = 0.8 (SiO₂, hexanes/EtOAc = 1 : 2).

[α]₂₆^D = +78° (*c* = 1.0, CHCl₃, 85% *ee*).

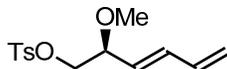
¹H NMR (400 MHz, CDCl₃): δ 7.89–7.30 (m, 2H), 7.46–7.30 (m, 2H), 6.54 (dt, *J* = 16.8 Hz, 10.5 Hz, 1H), 6.23 (t, *J* = 11.3 Hz, 1H), 5.30–5.26 (m, 2H), 5.16 (t, *J* = 10.0 Hz, 1H), 4.33 (dt, *J* = 9.0 Hz, 5.7 Hz, 1H), 4.00–3.98 (m, 2H), 3.24 (s, 3H), 2.44 (s, 3H) ppm.

¹³C NMR (100 MHz, CDCl₃): δ 144.8, 134.9, 132.9, 131.0, 129.8, 127.9, 126.2, 121.0, 74.6, 56.5, 21.6 ppm.

FTIR (ATR): 1359, 1188, 1174, 1096 cm⁻¹.

HRMS (CI): Calcd. for C₁₄H₁₈O₄S (M): 282.0926, found 282.0924.

(*S,E*)-2-Methoxyhexa-3,5-dienyl 4-methylbenzenesulfonate



To a solution of (*S,Z*)-2-methoxyhexa-3,5-dienyl 4-methylbenzenesulfonate (512 mg, 1.82 mmol, 100 mol %) in DCM (3.6 mL) under an atmosphere of argon was added PdCl₂(MeCN)₂ (55 mg, 0.36 mmol, 20 mol %), the resulting mixture was stirred for 5 days at 25 °C. The crude reaction mixture was diluted with Et₂O (30 mol), filtered, concentrated under reduced pressure, and purified by column chromatography (SiO₂, 10–30% Et₂O/hexanes) to furnish the title compound (*S,E*)-2-methoxyhexa-3,5-dienyl 4-methylbenzenesulfonate (398 mg, 1.41 mmol, 15:1, *E:Z*) in 78% yield as a light yellow oil.

R_f = 0.8 (SiO₂, hexanes/EtOAc = 1 : 2).

[α]₂₅^D = +118° (*c* = 1.50, CHCl₃, 85% *ee*).

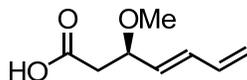
¹H NMR (400 MHz, CDCl₃): δ 7.79–7.77 (m, 2H), 7.42–7.32 (m, 2H), 6.30–6.23 (m, 2H), 5.43 (dd, *J* = 14.0 Hz, 7.6 Hz, 1H), 5.29–5.22 (m, 1H), 5.17–5.14 (m, 1H), 4.01–3.95 (m, 2H), 3.88–3.79 (m, 1H), 3.25 (s, 3H), 2.44 (s, 3H) ppm.

¹³C NMR (100 MHz, CDCl₃): δ 145.1, 135.9, 135.6, 133.1, 130.0, 128.4, 128.1, 119.2, 79.3, 71.6, 56.9, 21.8 ppm.

FTIR (ATR): 1359, 1189, 1175 cm⁻¹.

HRMS (CI): Calcd. for C₁₄H₁₉O₄S (M+H⁺): 283.1001, found 283.1004.

(*R,E*)-3-Methoxyhepta-4,6-dienoic acid (Fragment D)

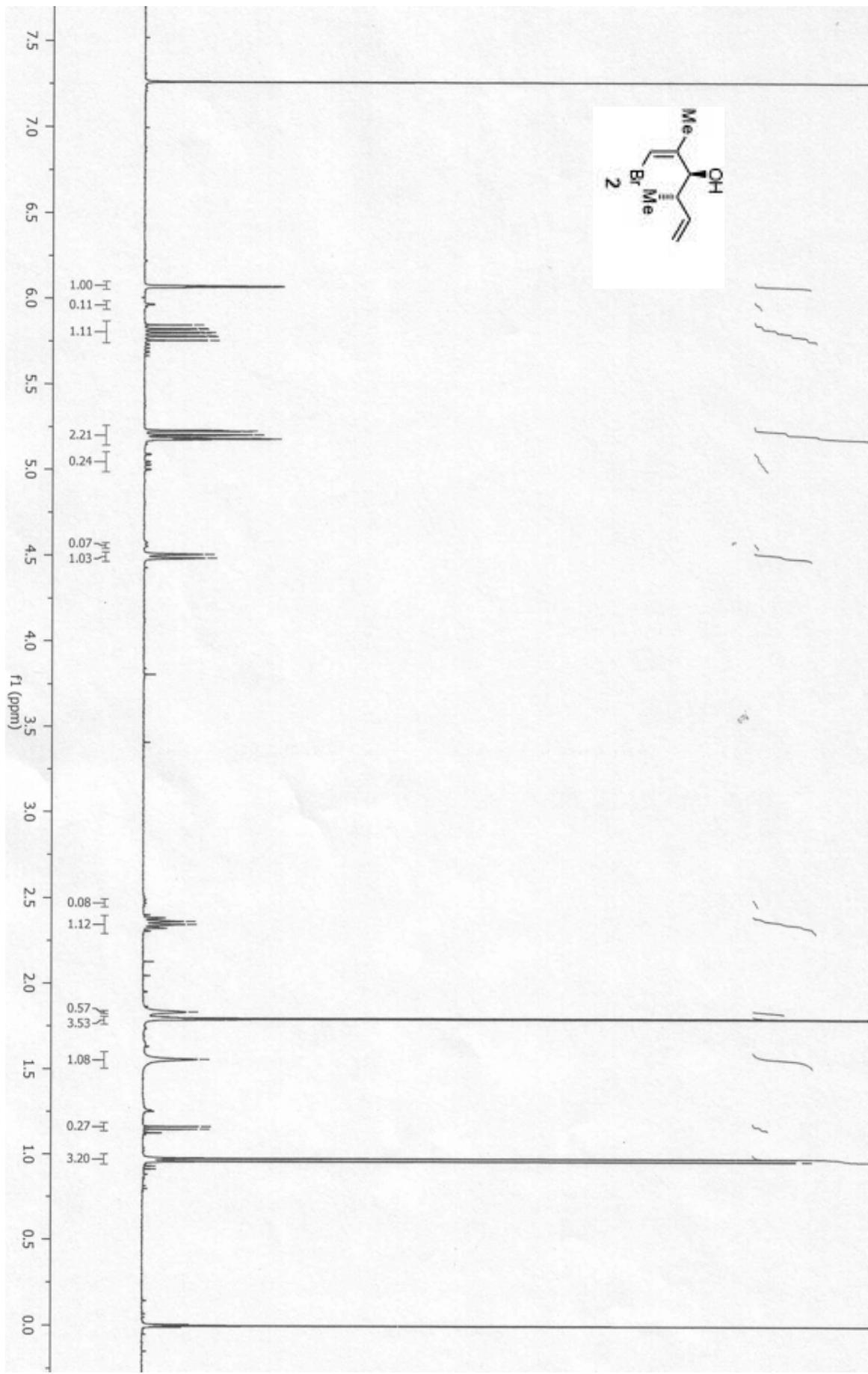
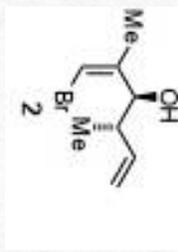


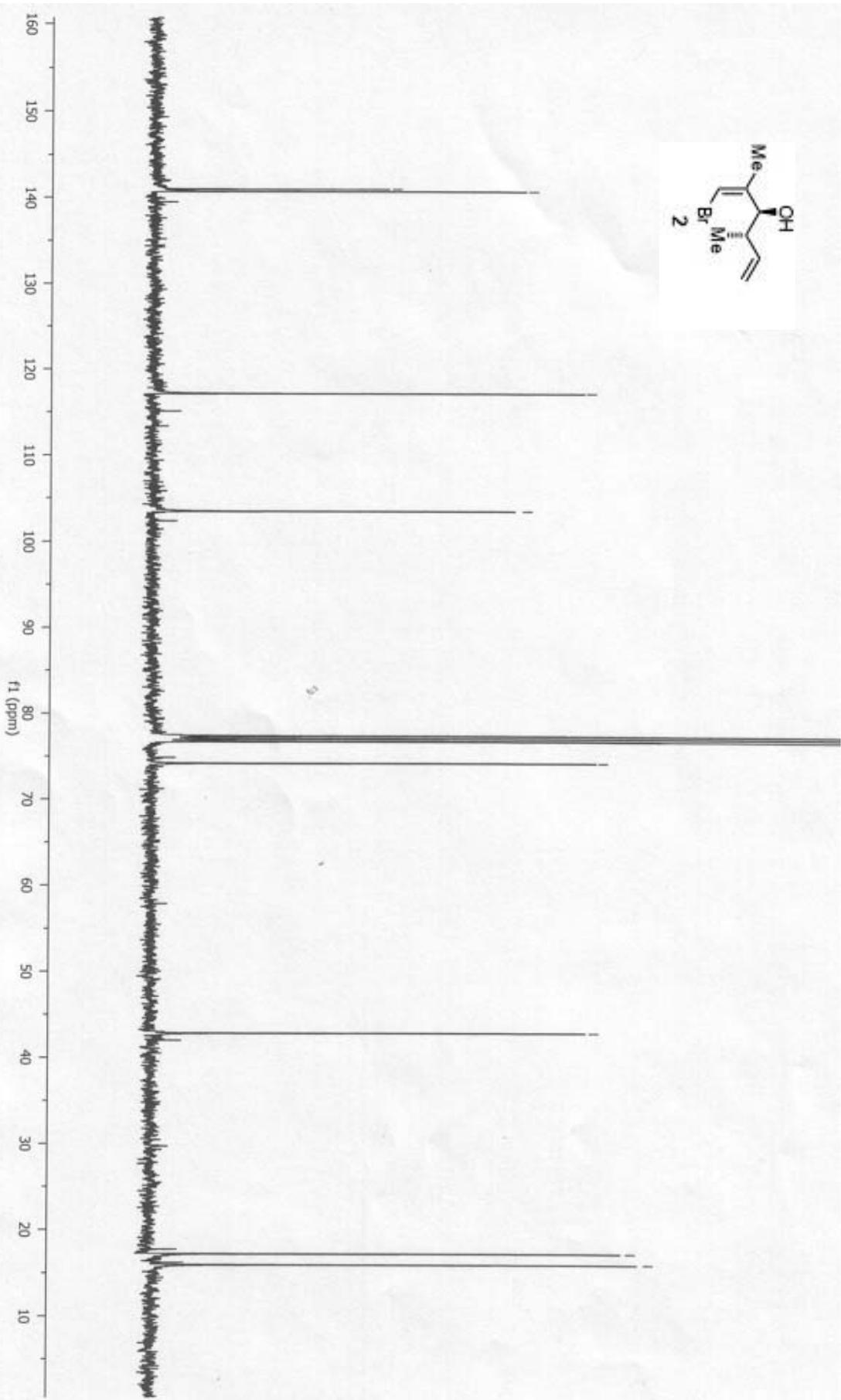
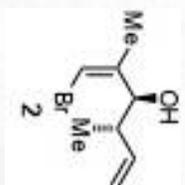
To a solution of (*S,E*)-2-methoxyhexa-3,5-dienyl 4-methylbenzenesulfonate (340 mg, 1.38 mmol, 100 mol %), [18]-crown-6 (360 mg, 1.40 mmol, 100 mol %), tetrabutylammonium iodide (100 mg, 0.28 mmol, 20 mol %) in dimethyl sulfoxide (1.3 mL) was added potassium cyanide (270 mg, 4.14 mmol, 300 mol%) and stirred at 45 °C for 2 hours. The crude reaction mixture was added to a separatory funnel containing Et₂O (10 mL). Water (30 mL) was added. The resulting mixture was extracted with Et₂O (3 x 30 mL). The organic extracts were combined and filtered through a plug of celite. The filtrate was concentrated under reduced pressure and diluted with ethanol (6 mL). Hydrogen peroxide (6 mL, 30 % solution) and LiOH•H₂O (283 mg, 11.9 mmol, 400 mol %) were added at 25 °C. The resulting solution was stirred for 24 hours. The reaction mixture was added to a separatory funnel containing brine (10 mL), the aqueous layer was washed with Et₂O (2 x 20 mL), citric acid (2.5 g, 12 mmol, 300 mol %) was added. The resulting mixture was extracted with Et₂O (3 x 30 mL), the combined organic extracts were washed with brine (10 mL), dried (Na₂SO₄), filtered, and concentrated under reduced pressure to furnish Fragment **D** (135 mg, 0.12 mmol) in 72% yield as a clear oil. To corroborate the assignment of absolute stereochemistry, the optical rotation was correlated with a known compound.¹²

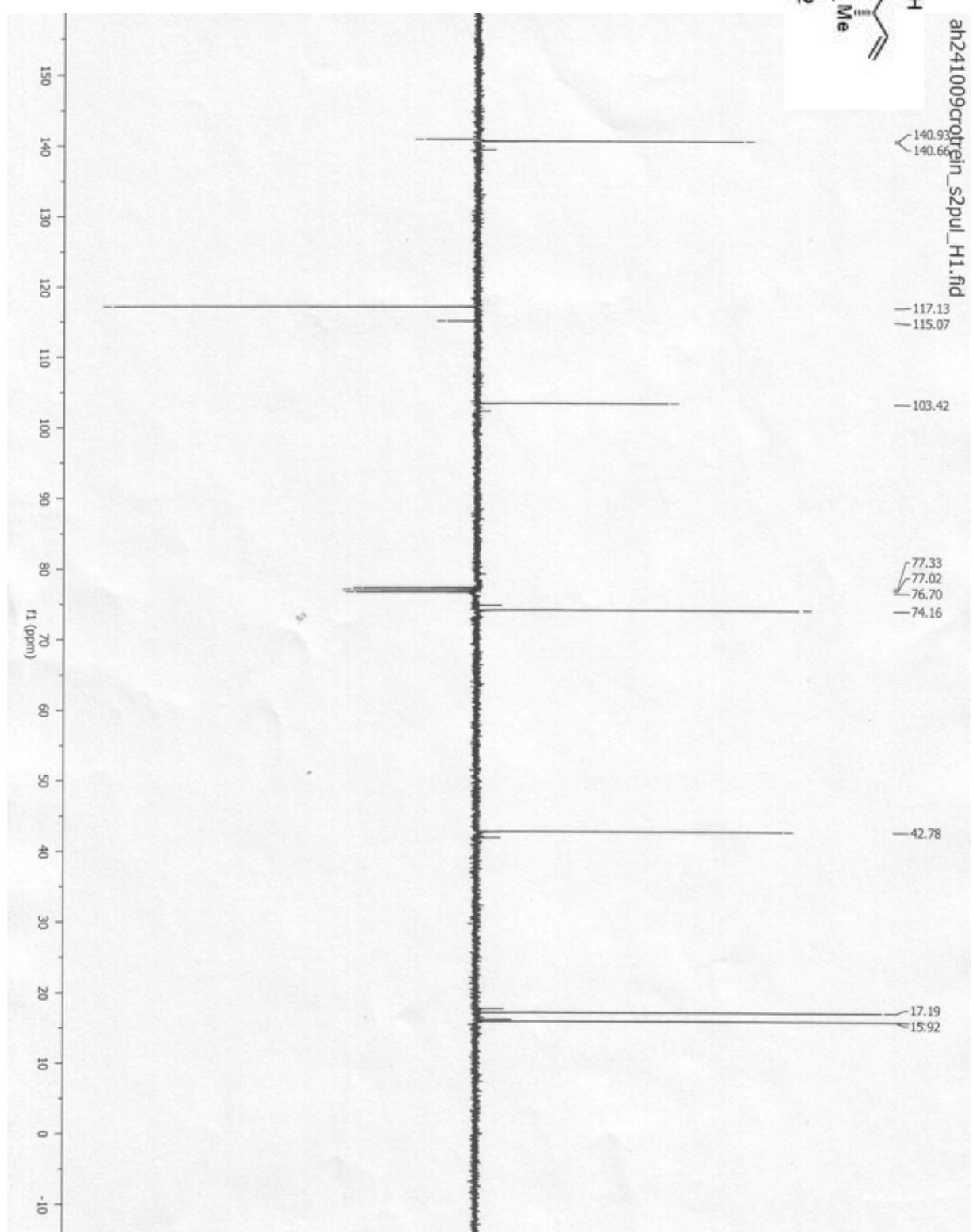
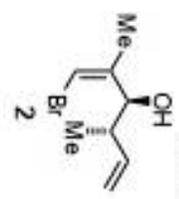
$[\alpha]_{26}^D = +6.5^\circ$ ($c = 0.61$, CHCl₃, 85% *ee*)

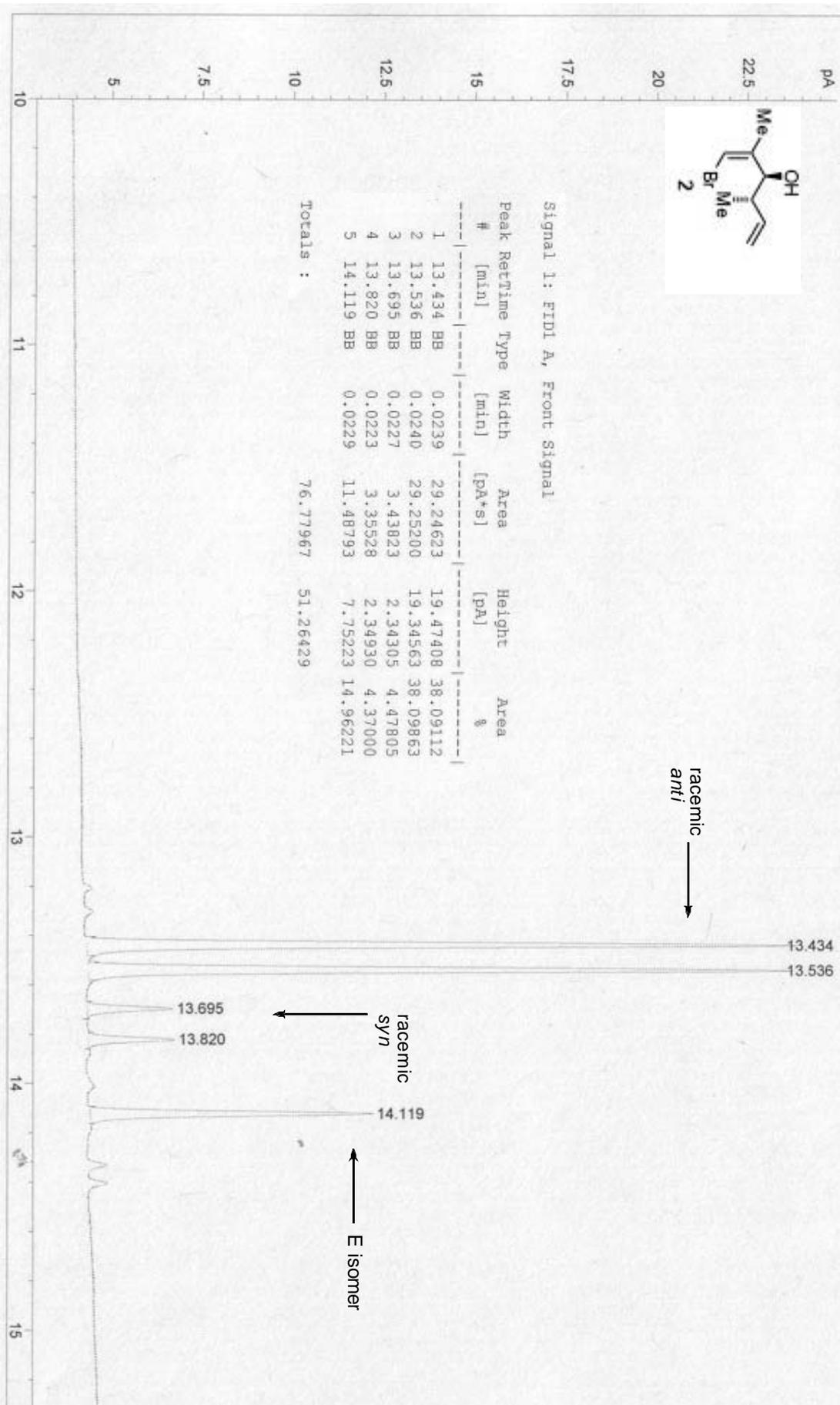
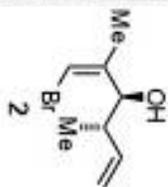
Lit. $[\alpha]_{26}^D = +7.8^\circ$ ($c = 0.61$, CHCl₃, 98% *ee*)¹²

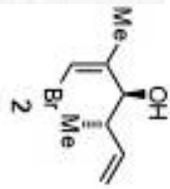
¹H NMR (400 MHz, CDCl₃): δ 6.38–6.24 (m, 2H), 5.55 (dd, $J = 14.5$ Hz, 8.0 Hz, 1H), 5.26 (dd, $J = 15.9$ Hz, 1.9 Hz, 1H) 5.15 (dd, $J = 9.7$ Hz, 1.9 Hz, 1H), 4.10–4.05 (m, 1H), 3.30 (s, 3H), 2.68–2.51 (m, 2H) ppm.





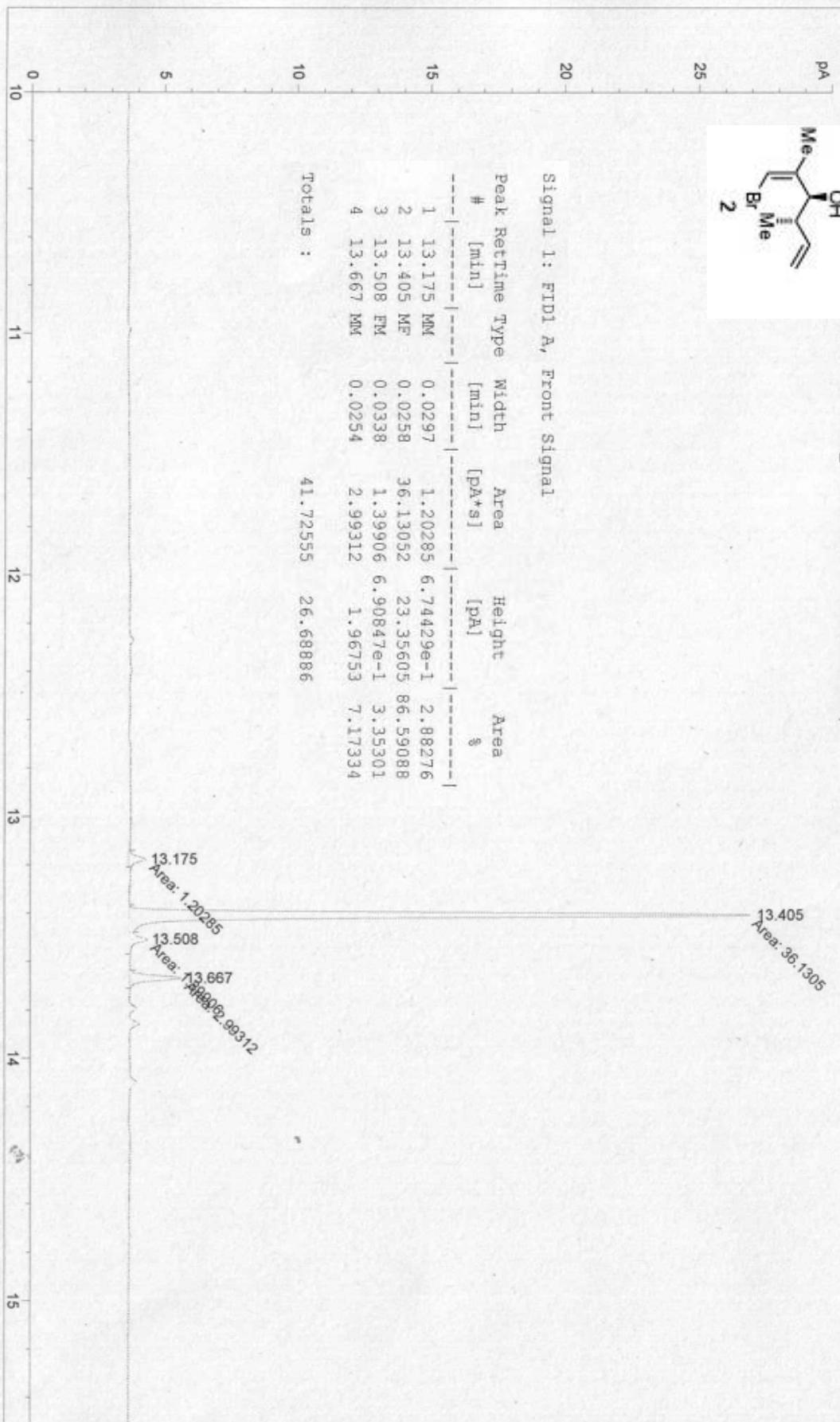


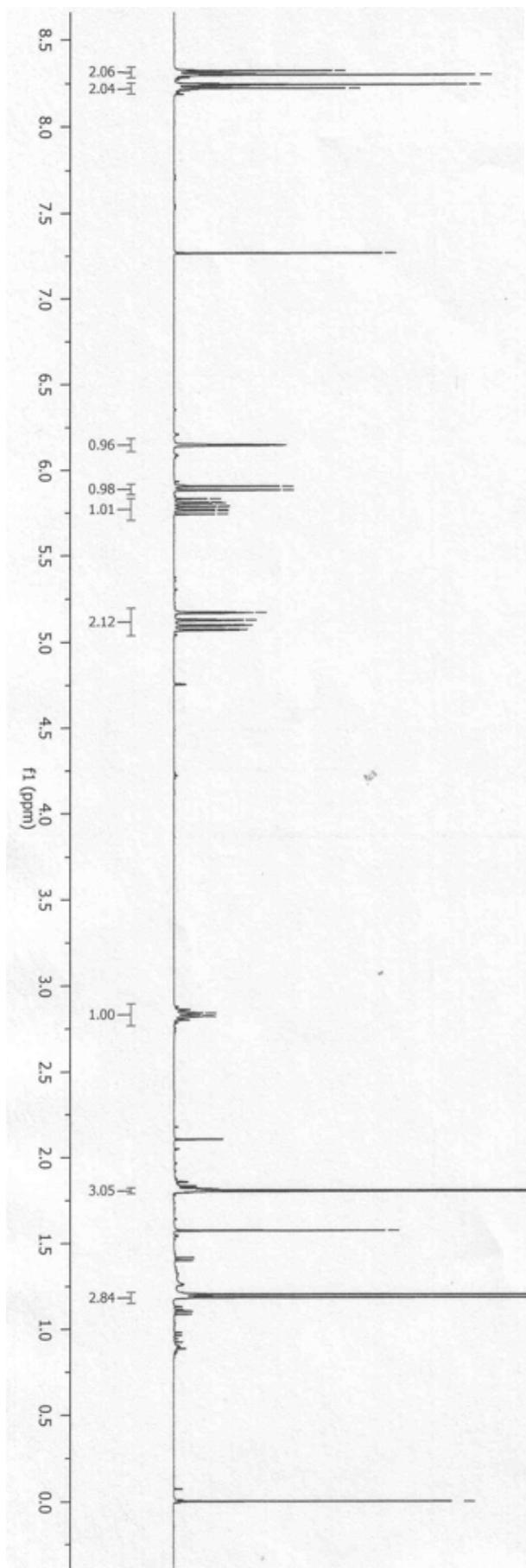
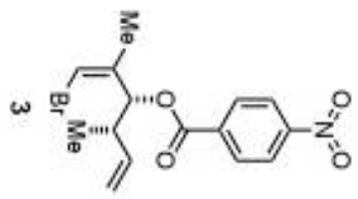


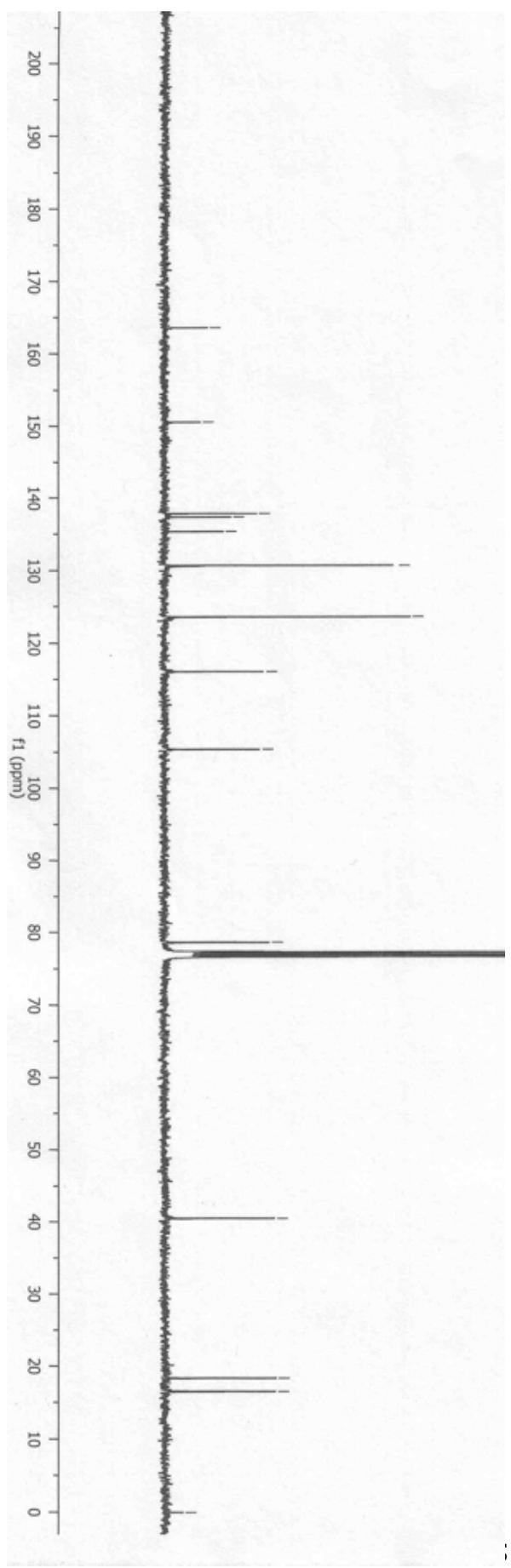
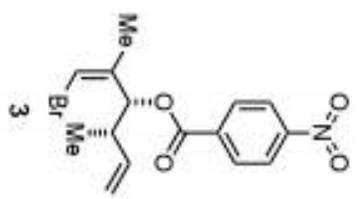


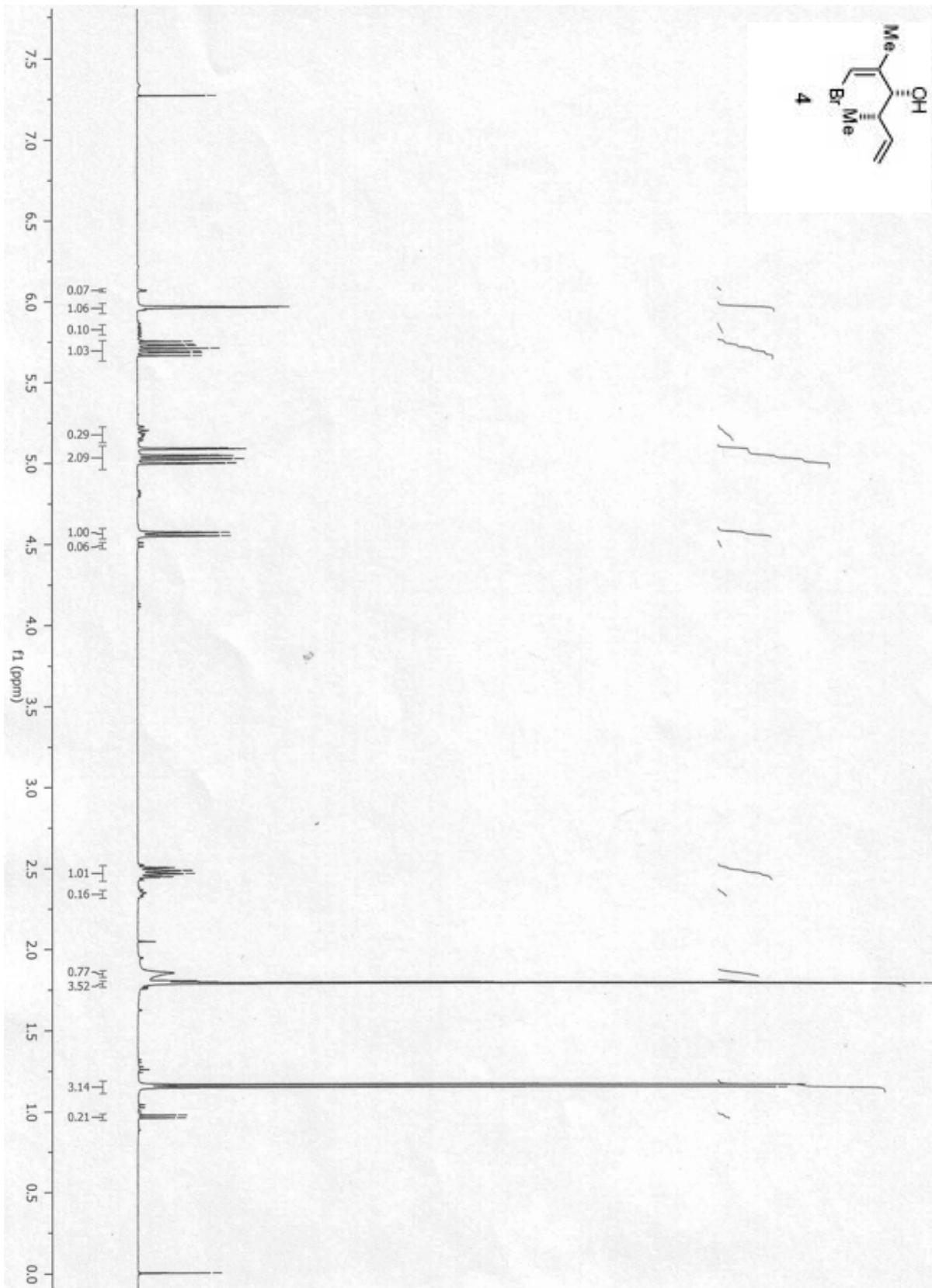
Signal 1: FID1 A, Front Signal

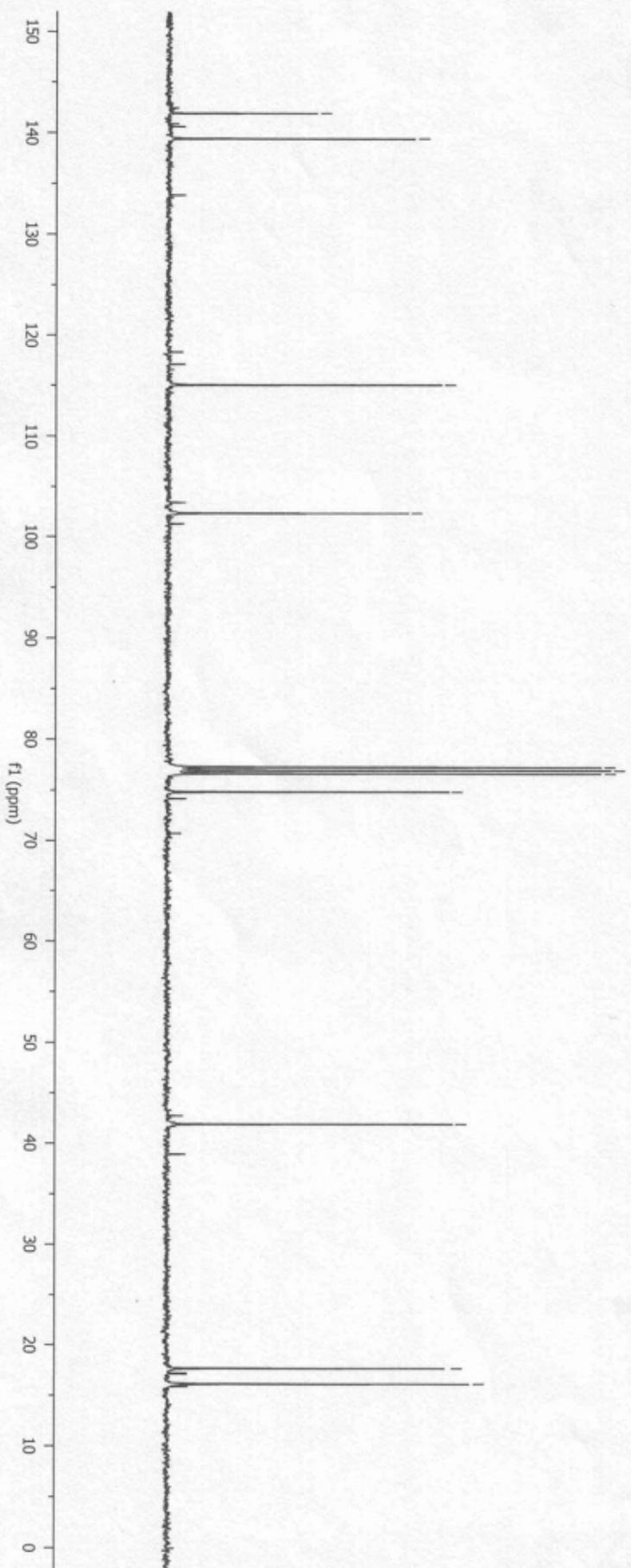
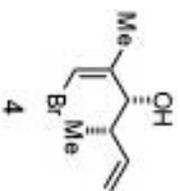
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	13.175	MM	0.0297	1.20285	6.74429e-1	2.88276
2	13.405	MF	0.0258	36.13052	23.35605	86.59088
3	13.508	FM	0.0338	1.39906	6.90847e-1	3.35301
4	13.667	MM	0.0254	2.99312	1.96753	7.17334
Totals :				41.72555	26.68886	

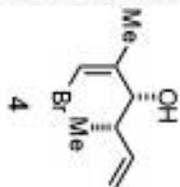








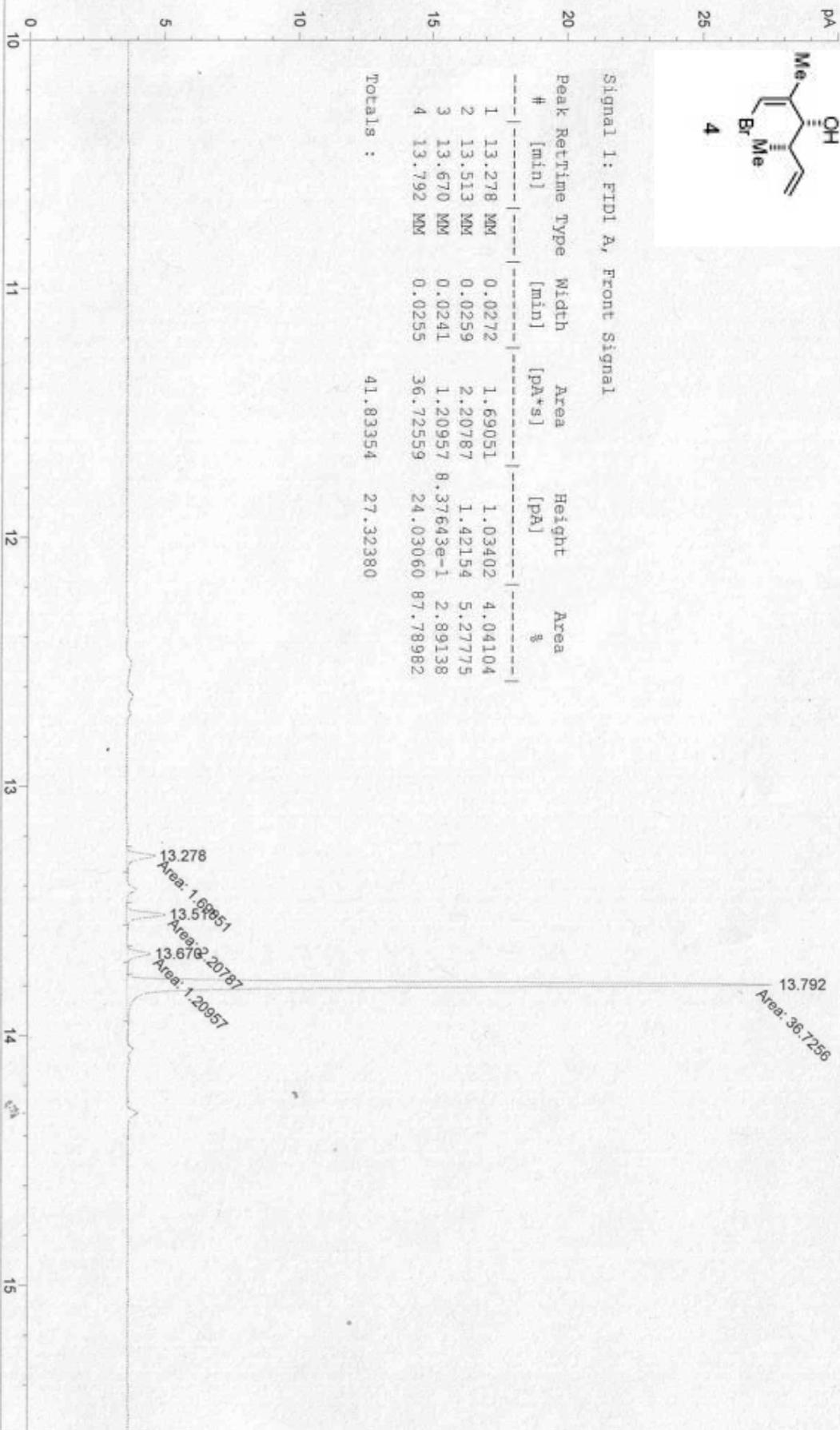




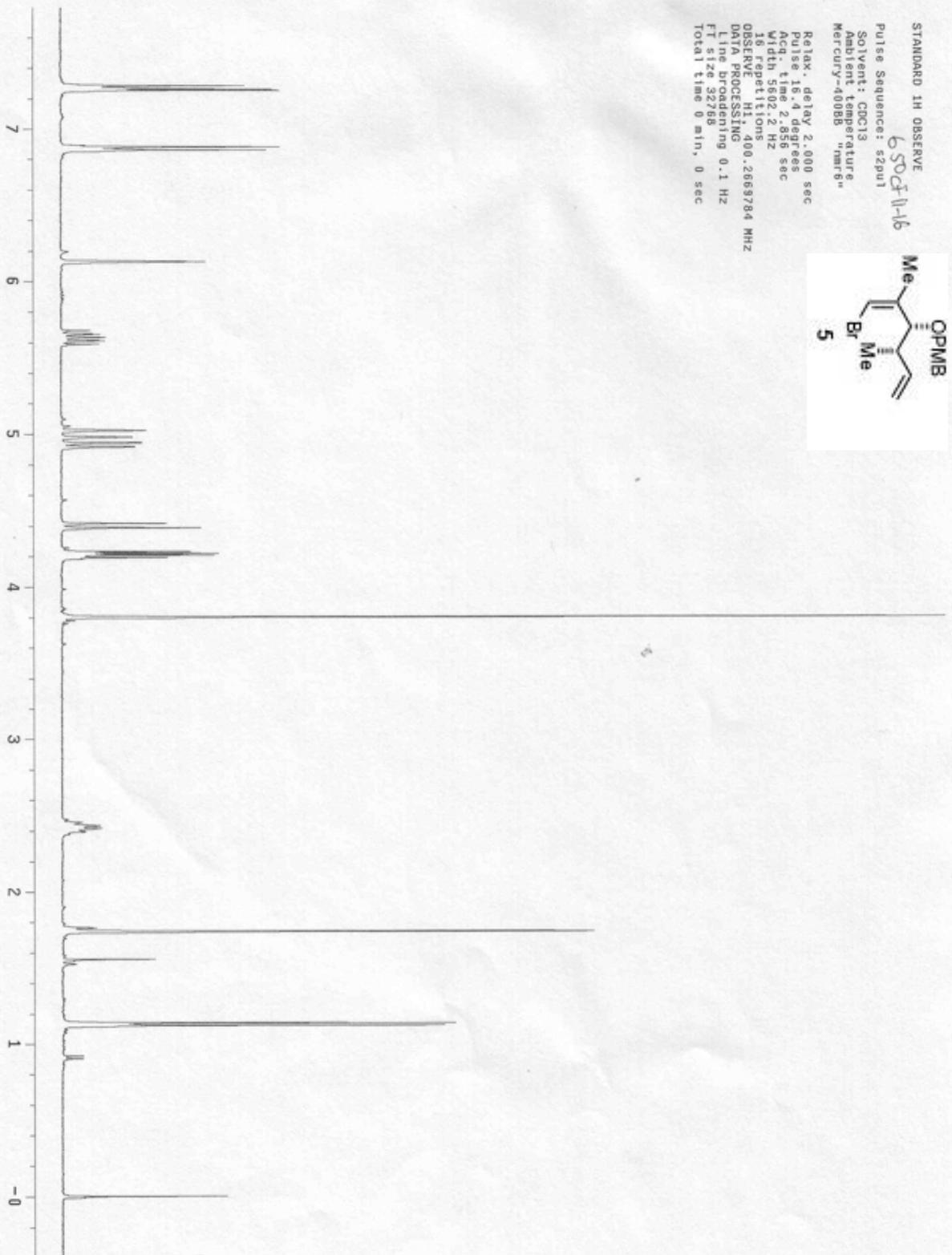
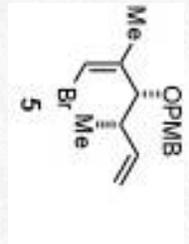
Signal 1: FID1 A, Front Signal

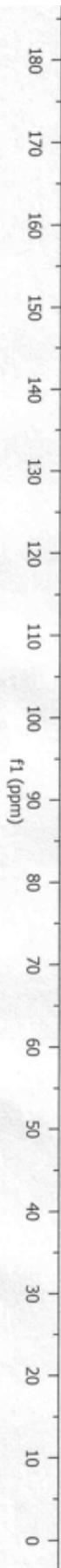
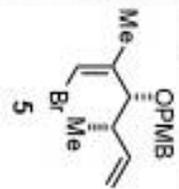
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	13.278	NM	0.0272	1.69051	1.03402	4.04104
2	13.513	NM	0.0259	2.20787	1.42154	5.27775
3	13.670	NM	0.0241	1.20957	8.37643e-1	2.89138
4	13.792	NM	0.0255	36.72559	24.03060	87.78982

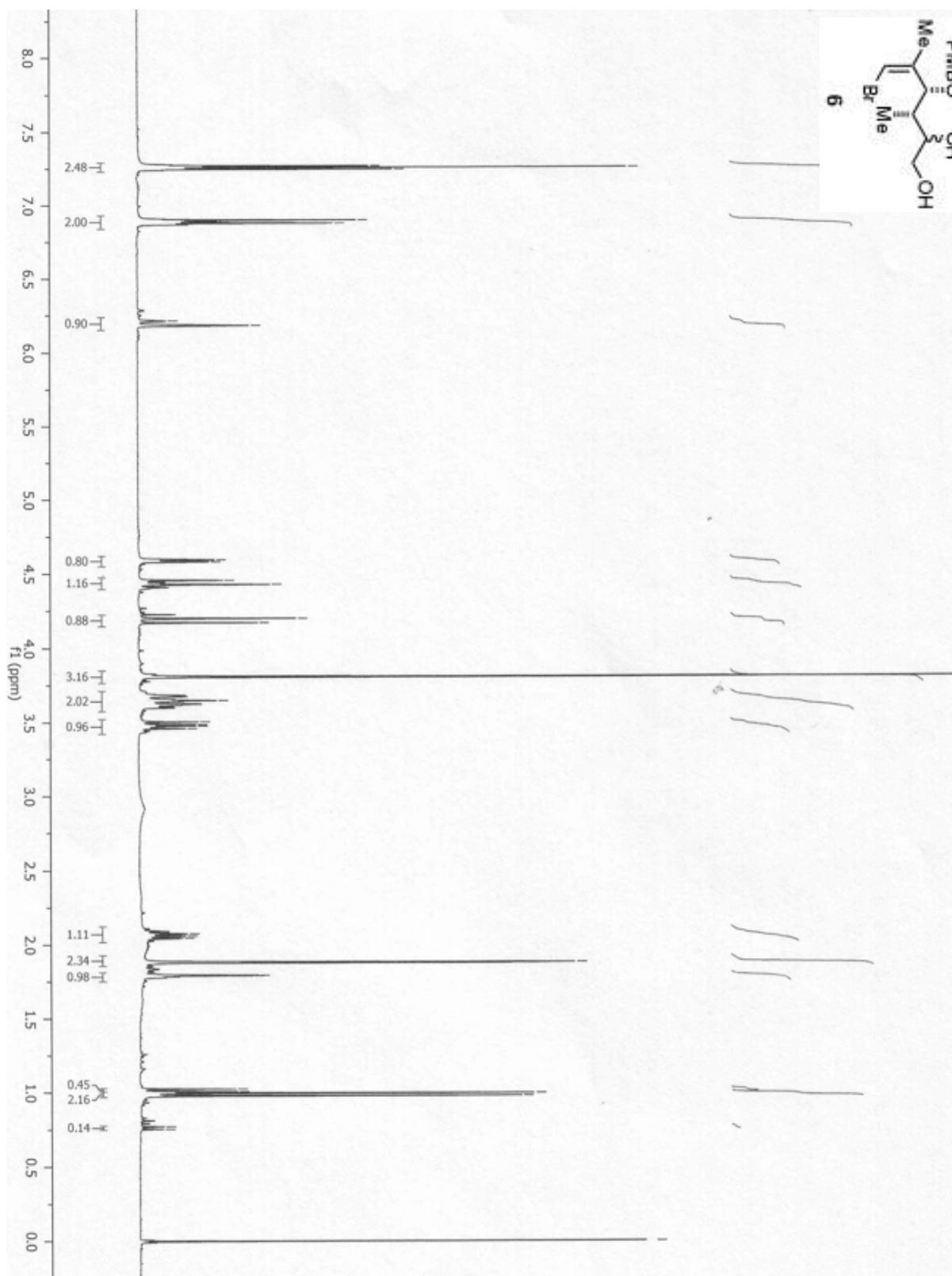
Totals : 41.83354 27.32380

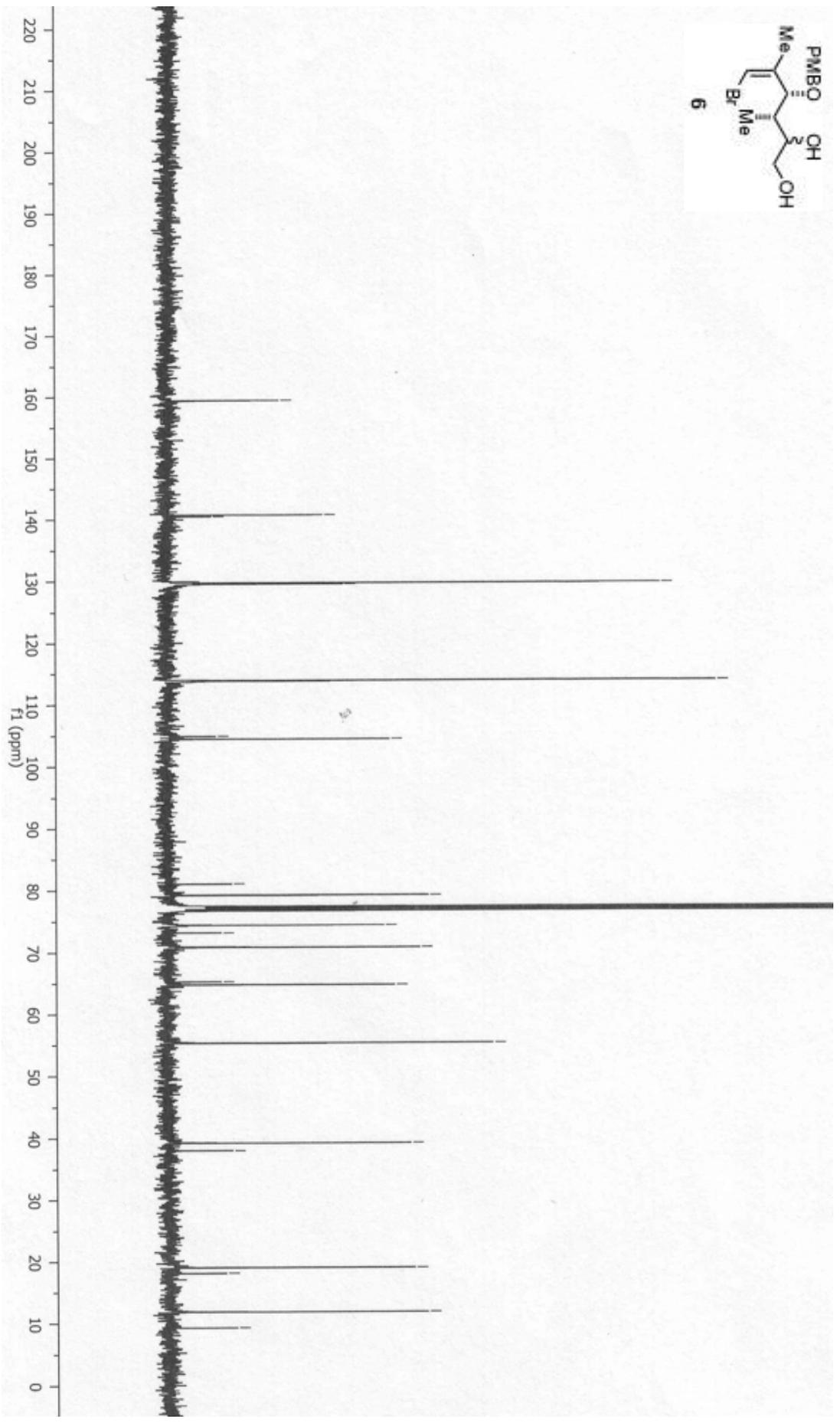
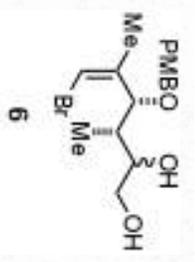


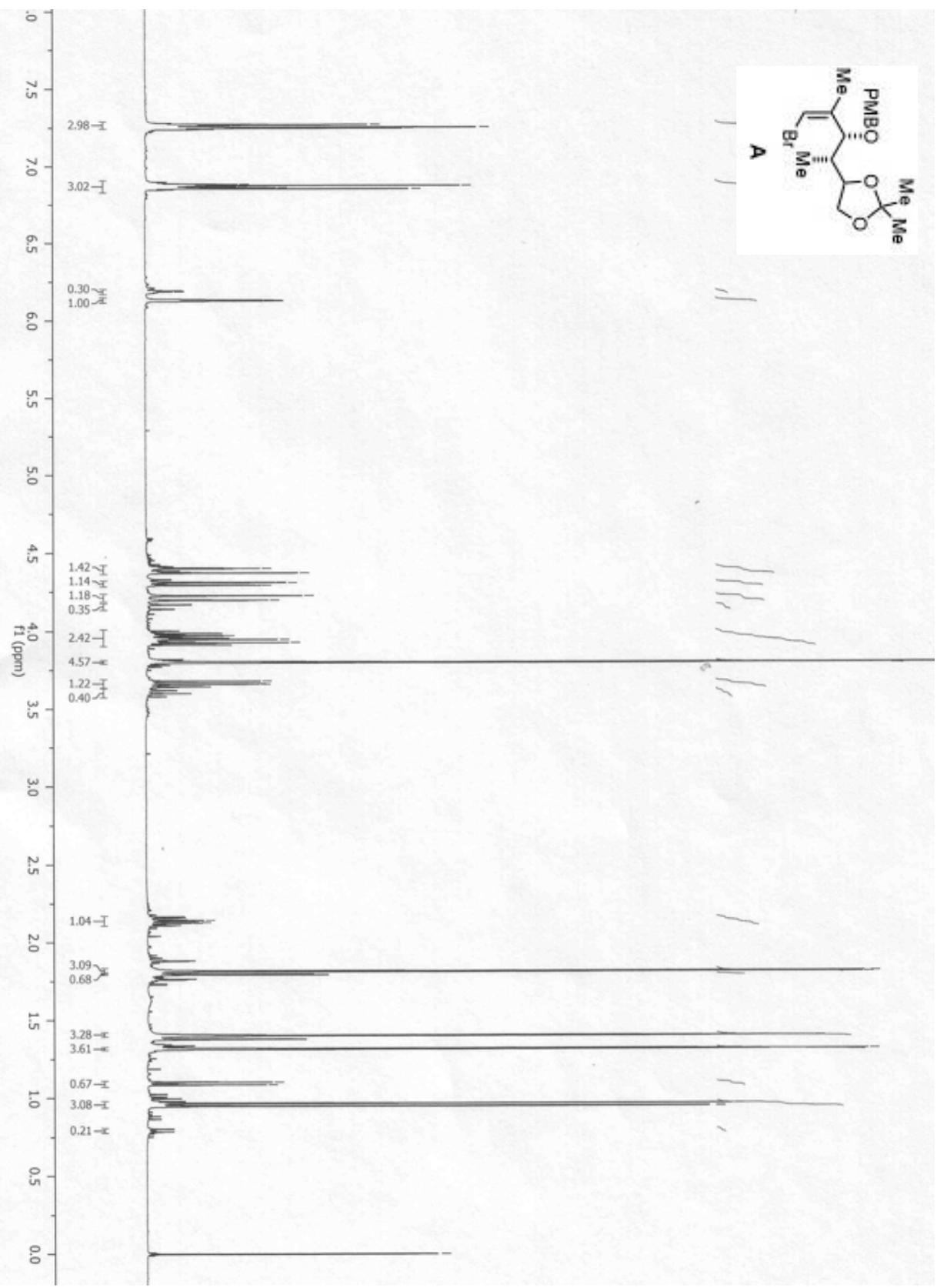
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650CF-11-16
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-400BB "nmr6"
Relax. delay 2.000 sec
Pulse 16.4 degrees
Acq. time 2.856 sec
Width 5602.2 Hz
16 repetitions
OBSERVE H1, 400.2663784 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 32768
Total time 0 min, 0 sec

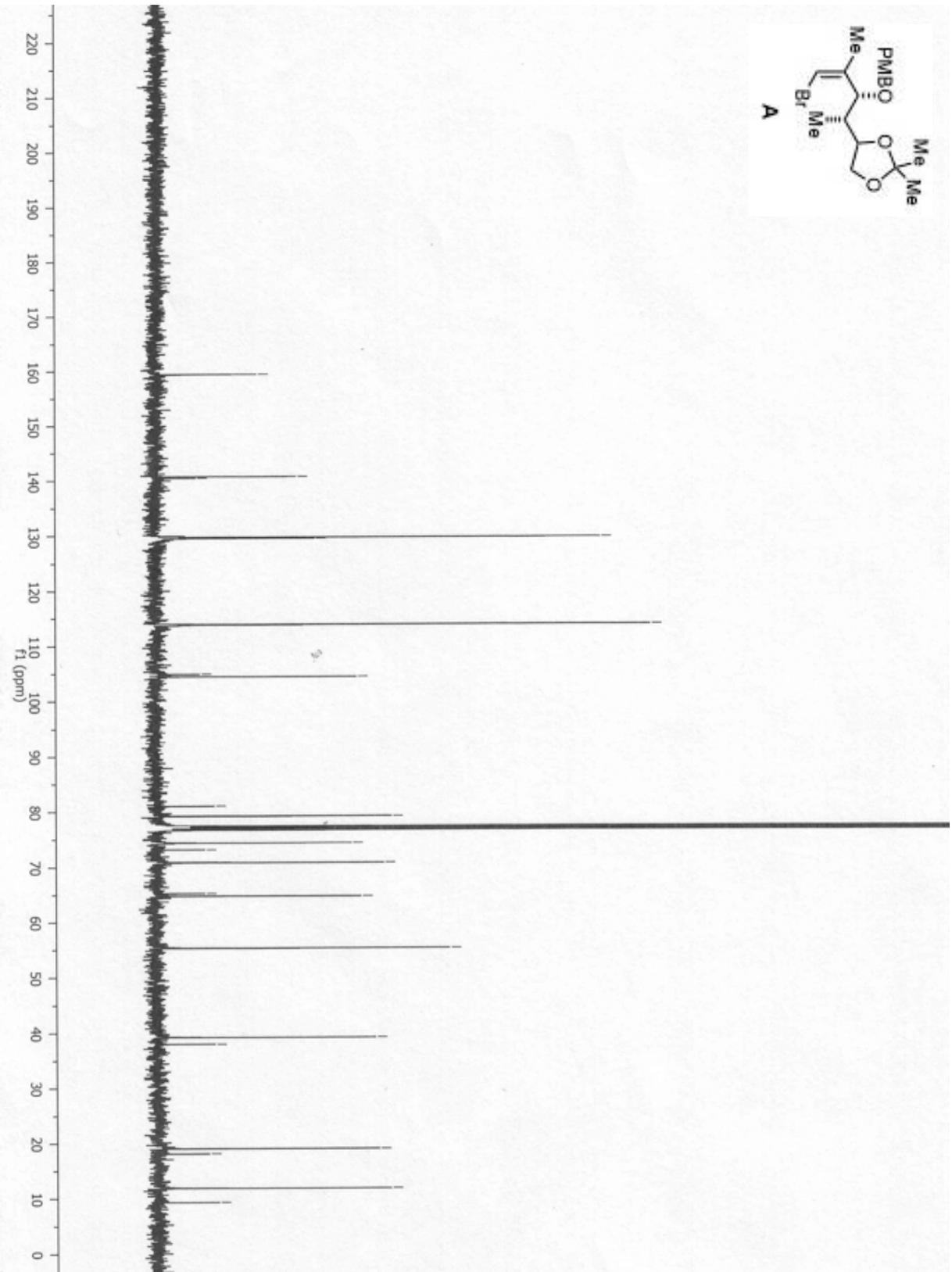




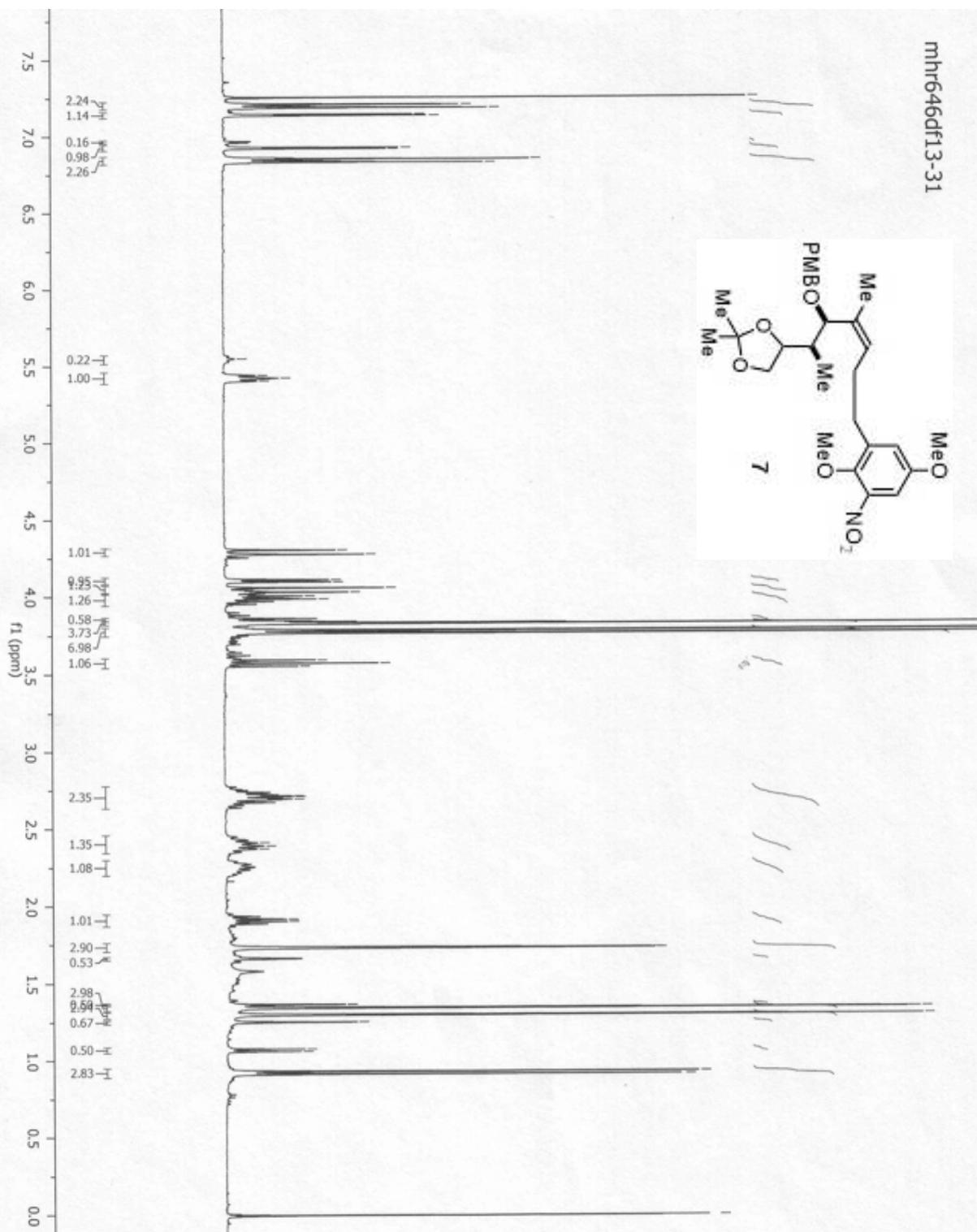
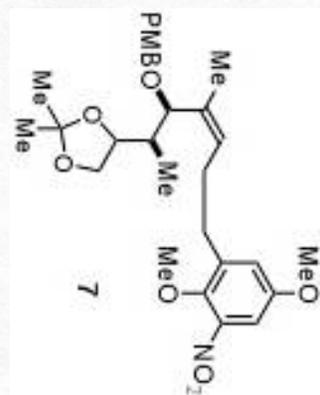


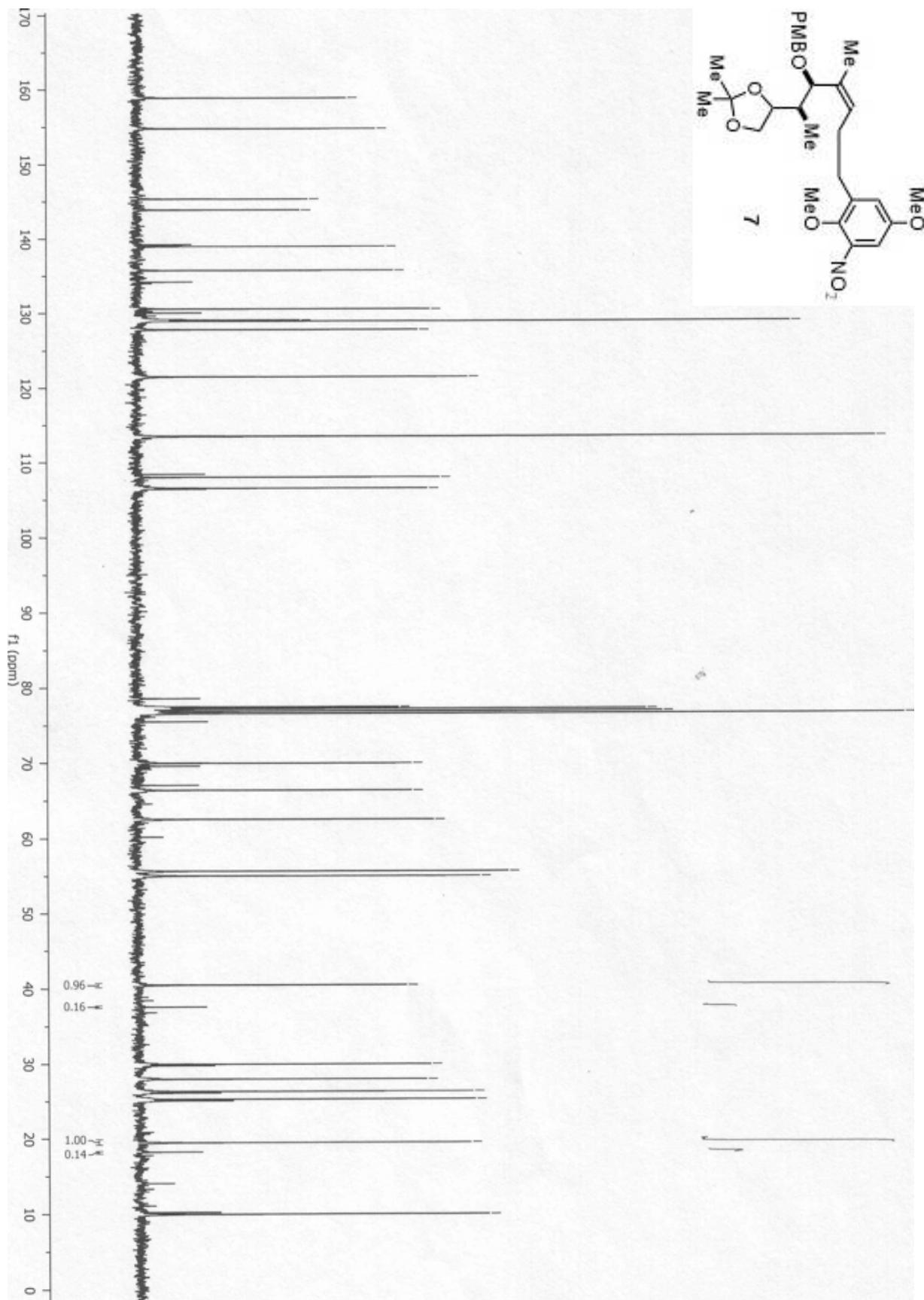


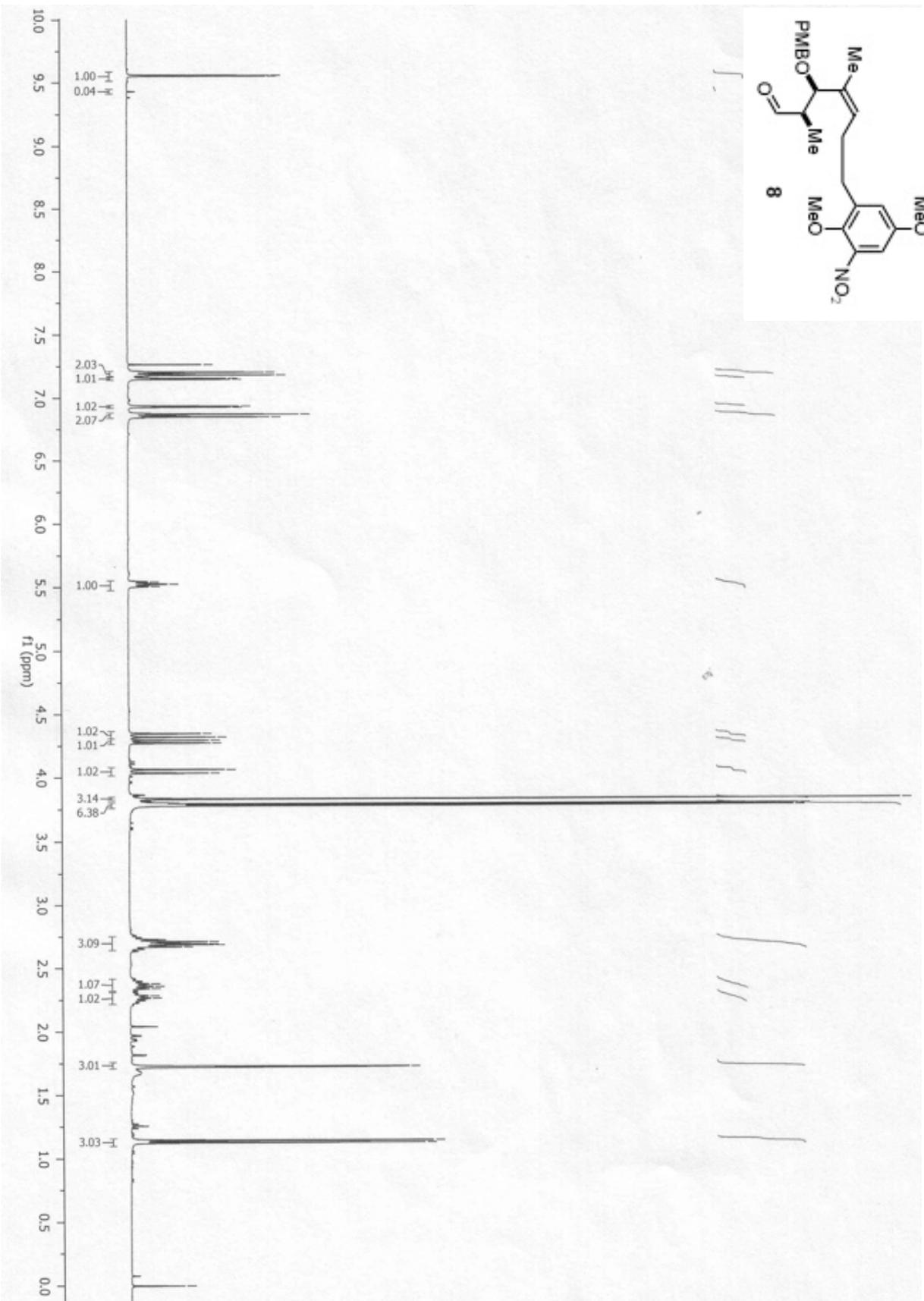


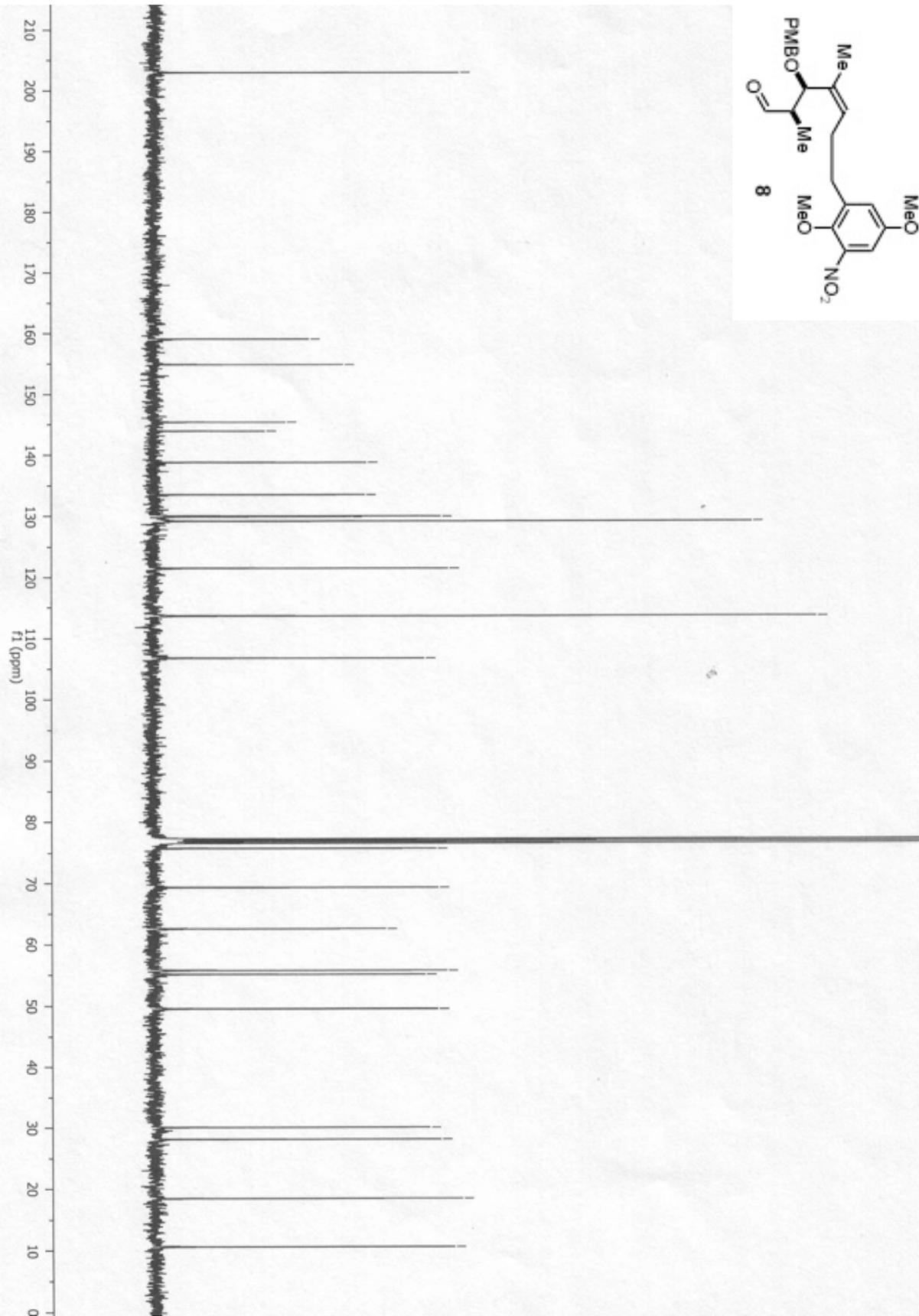


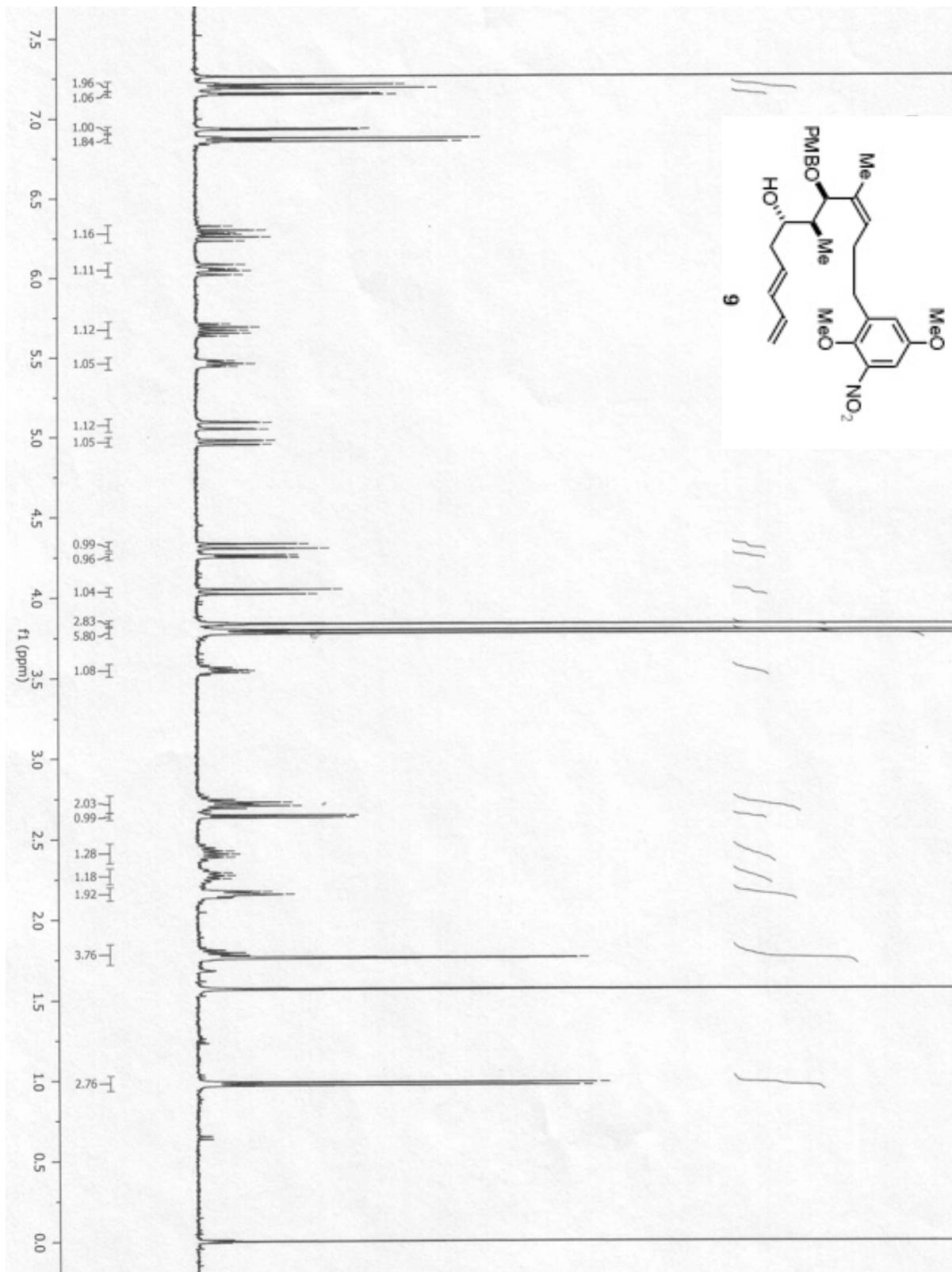
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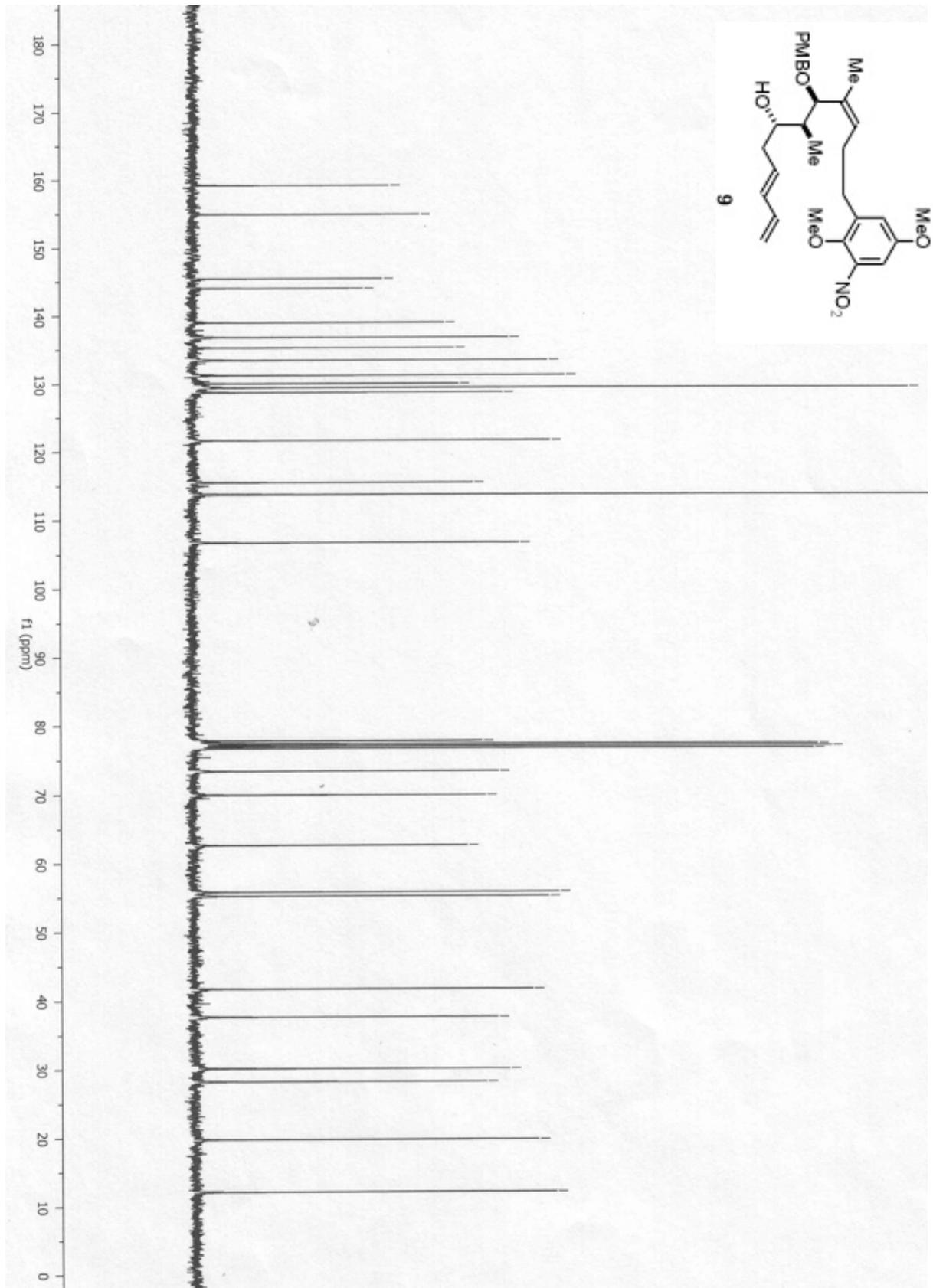


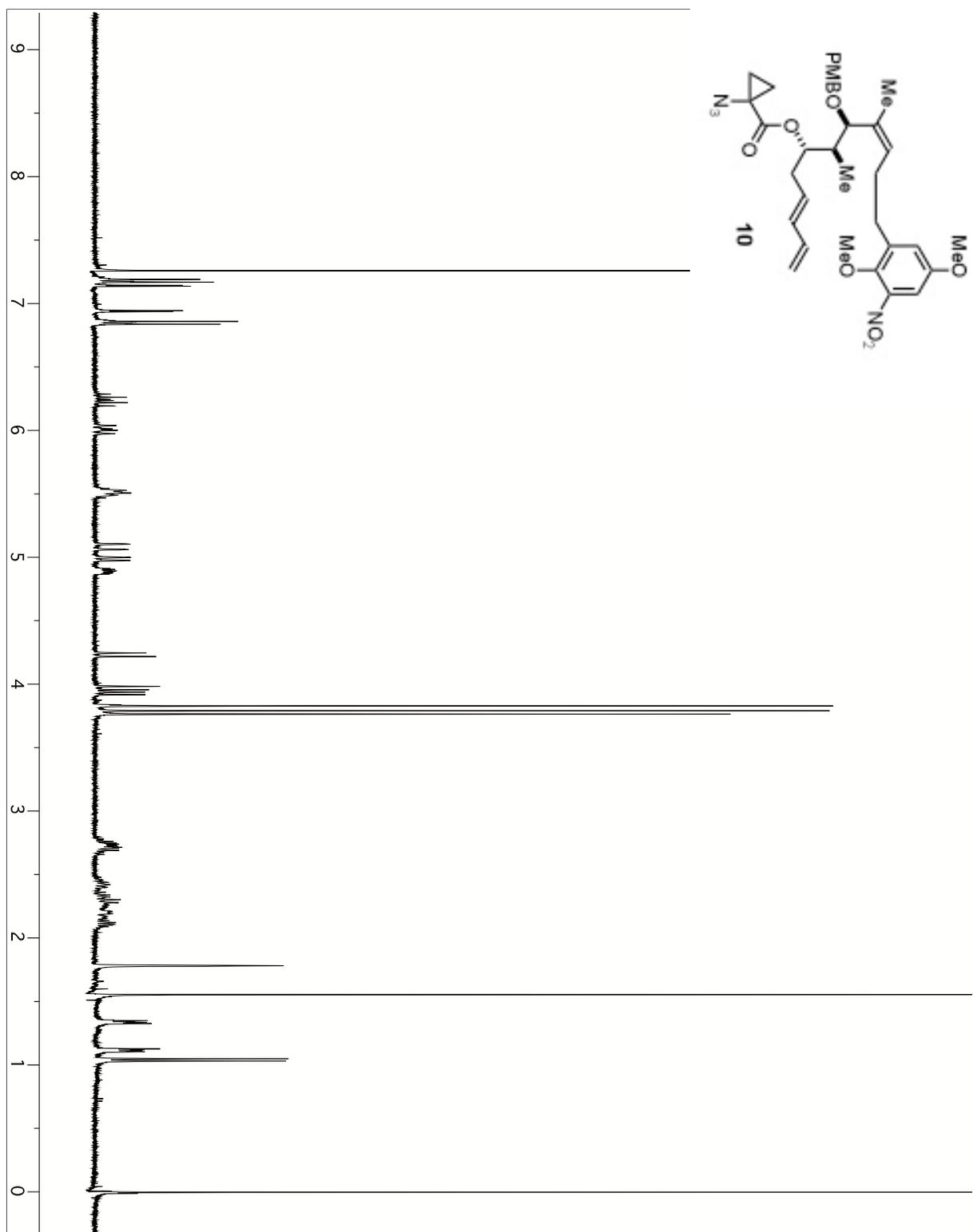
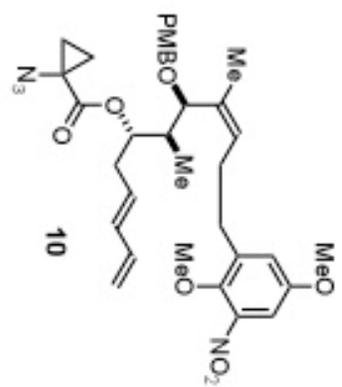


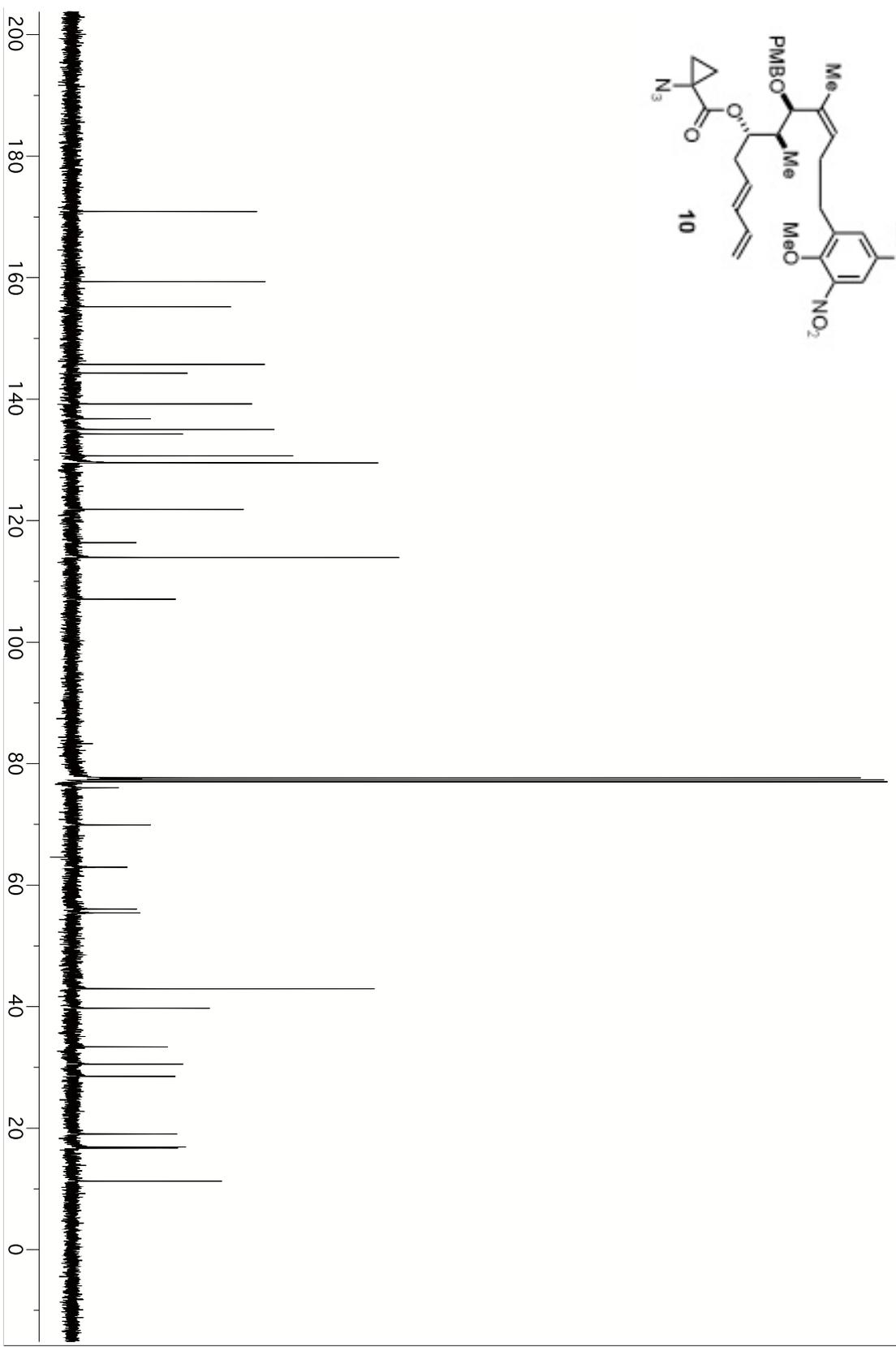
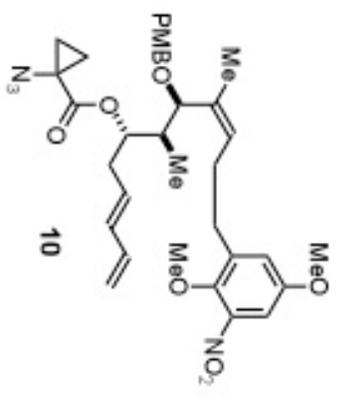


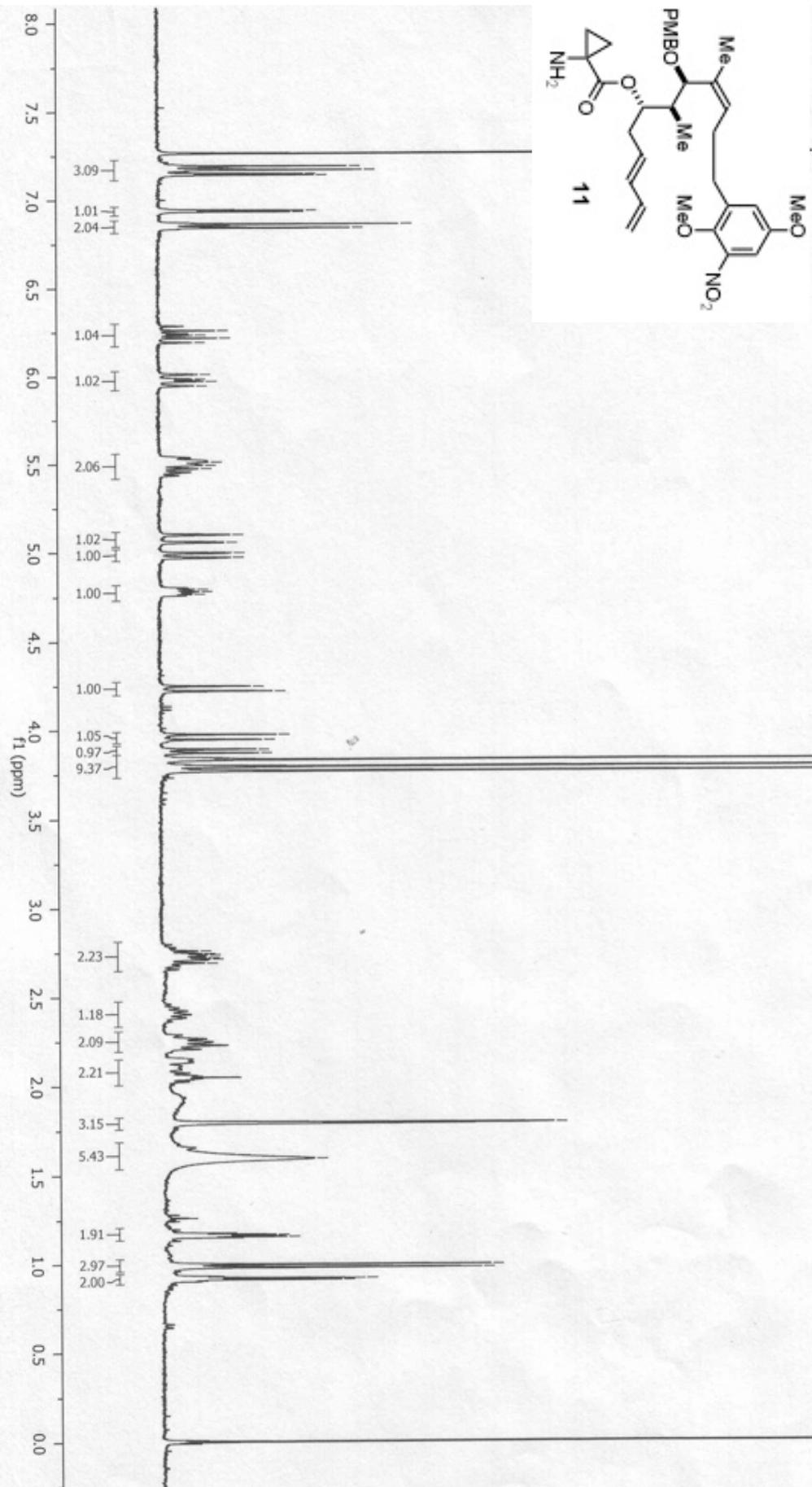


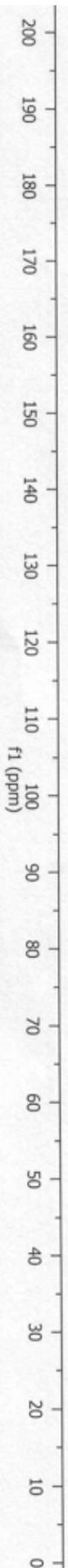
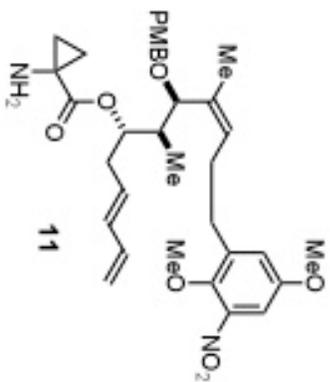


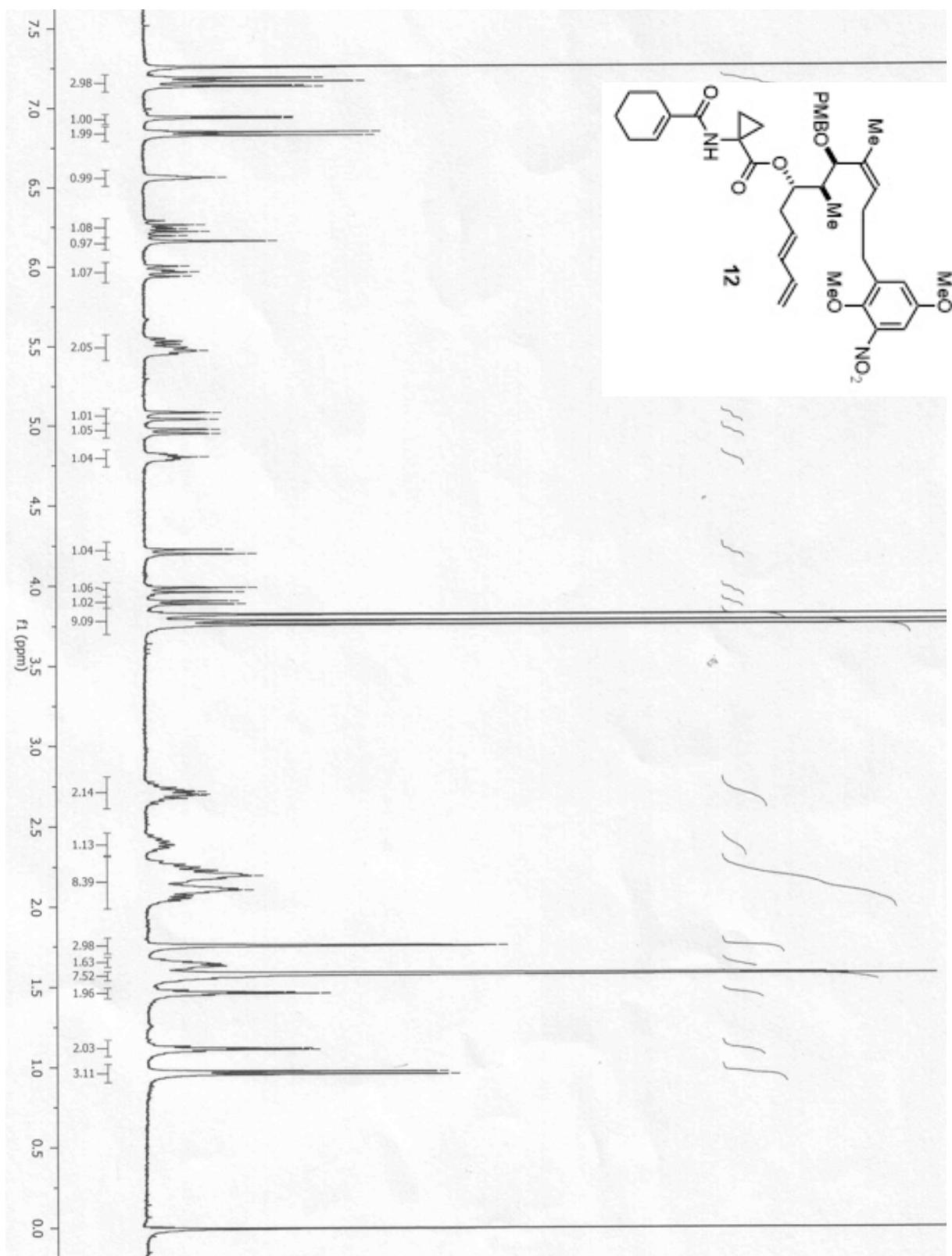


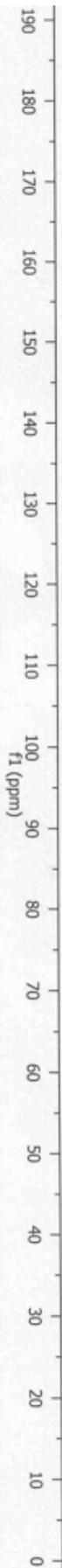
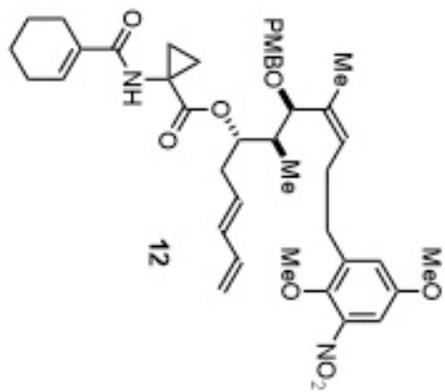


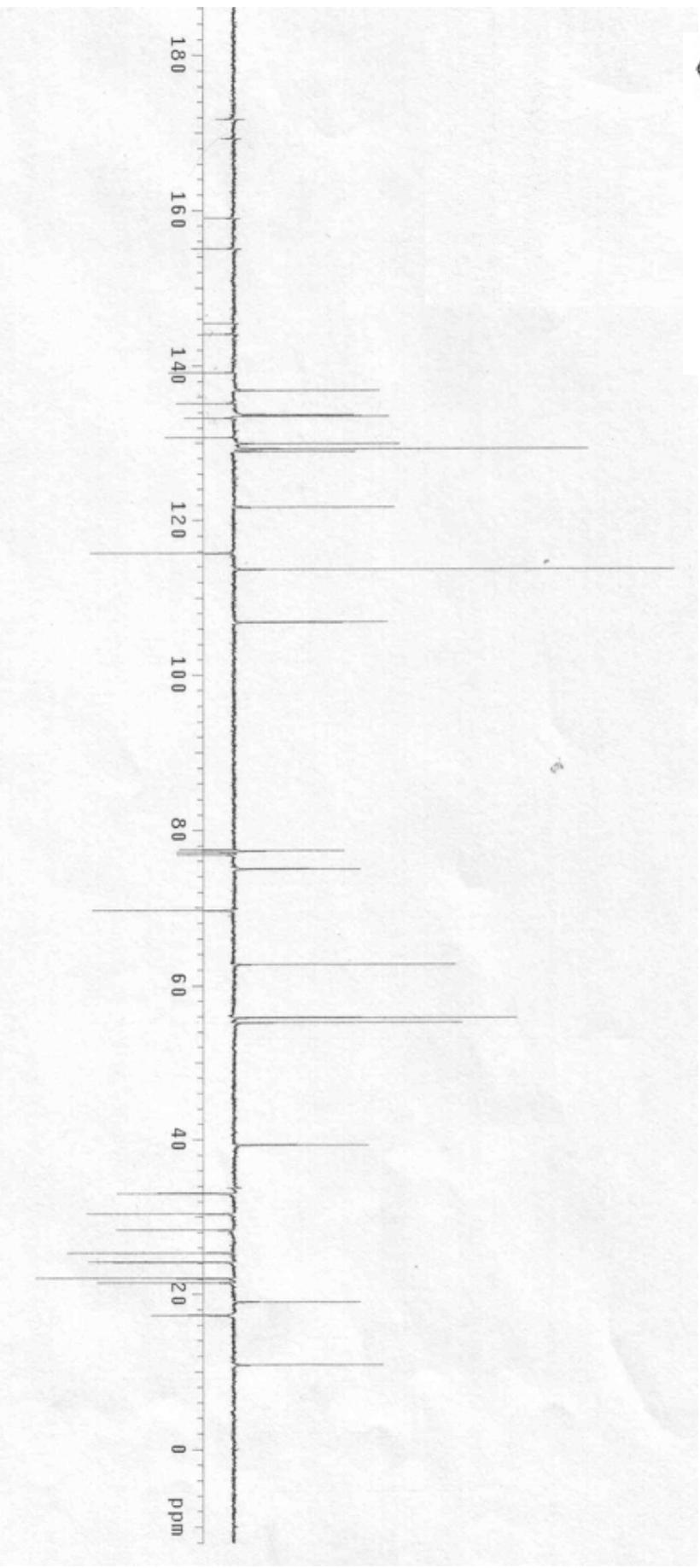
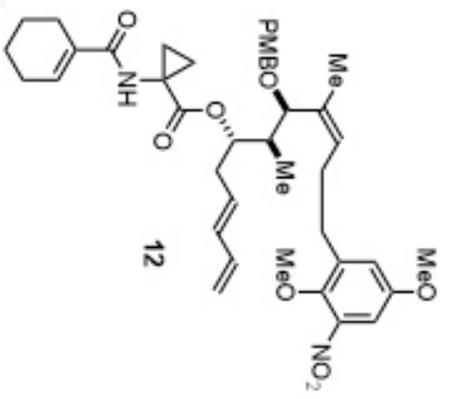


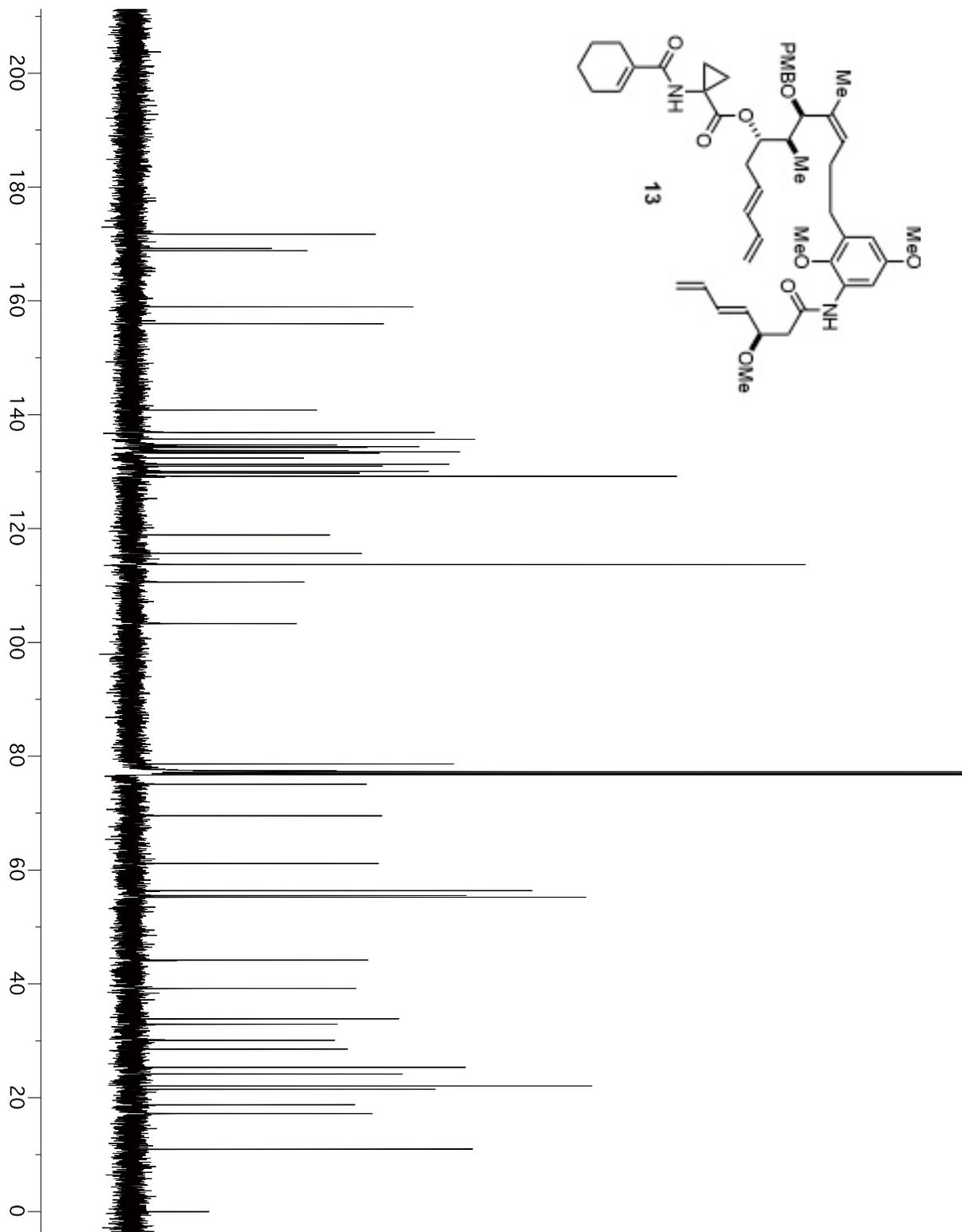
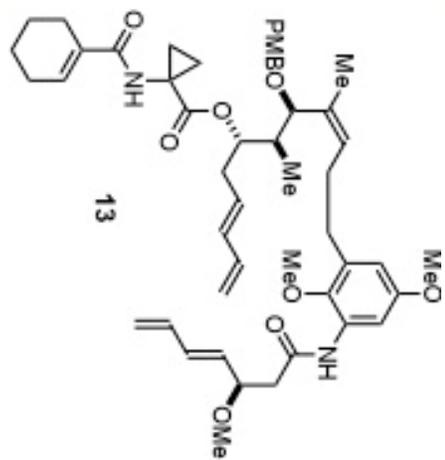


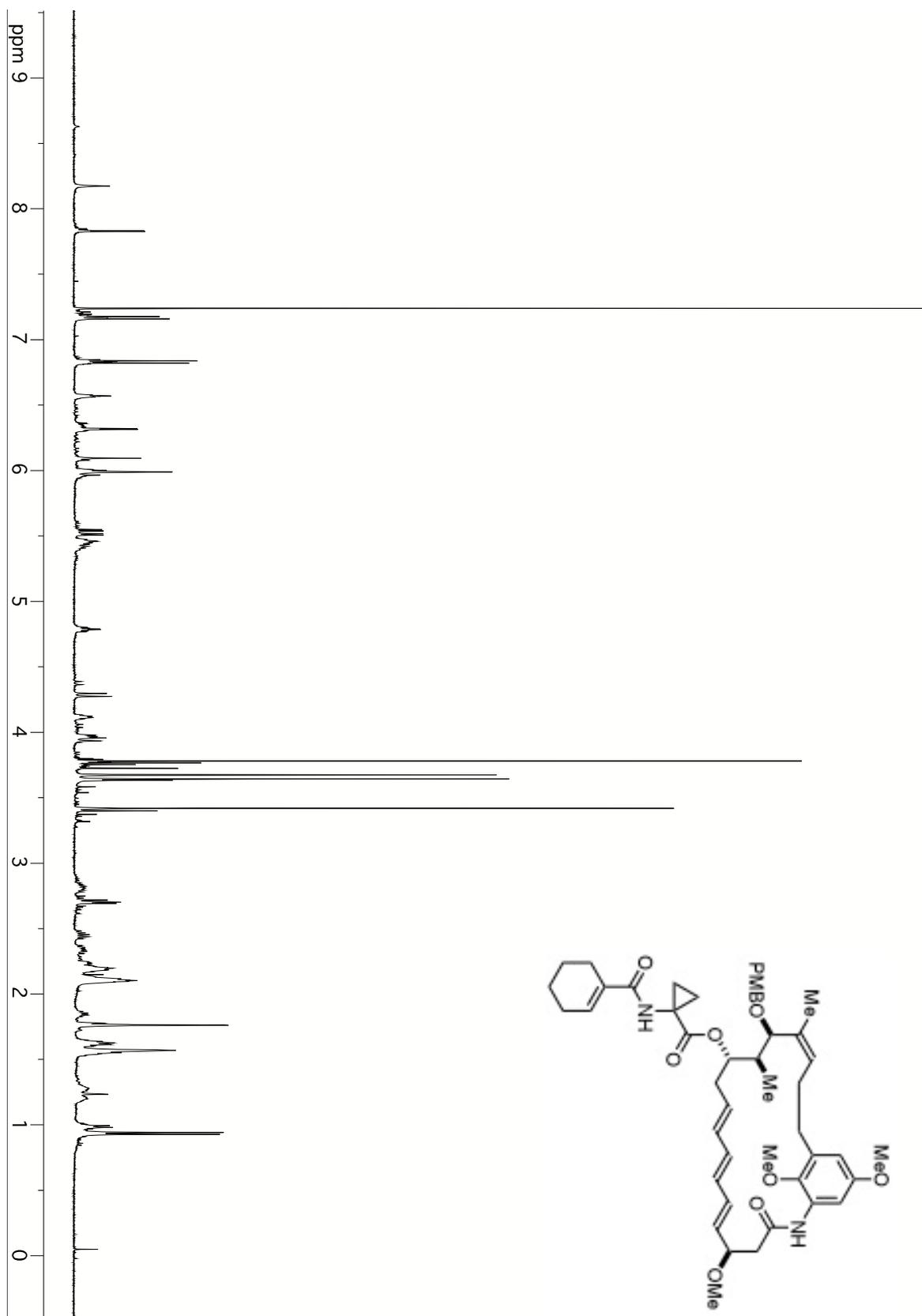
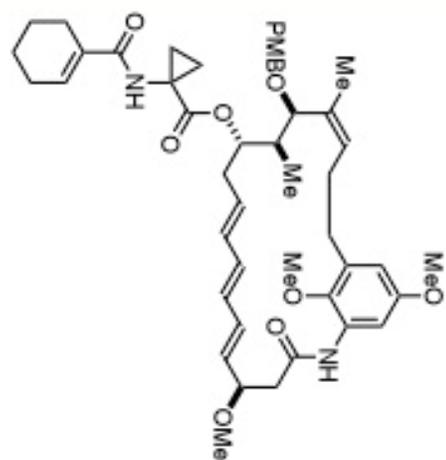


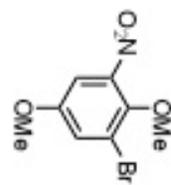


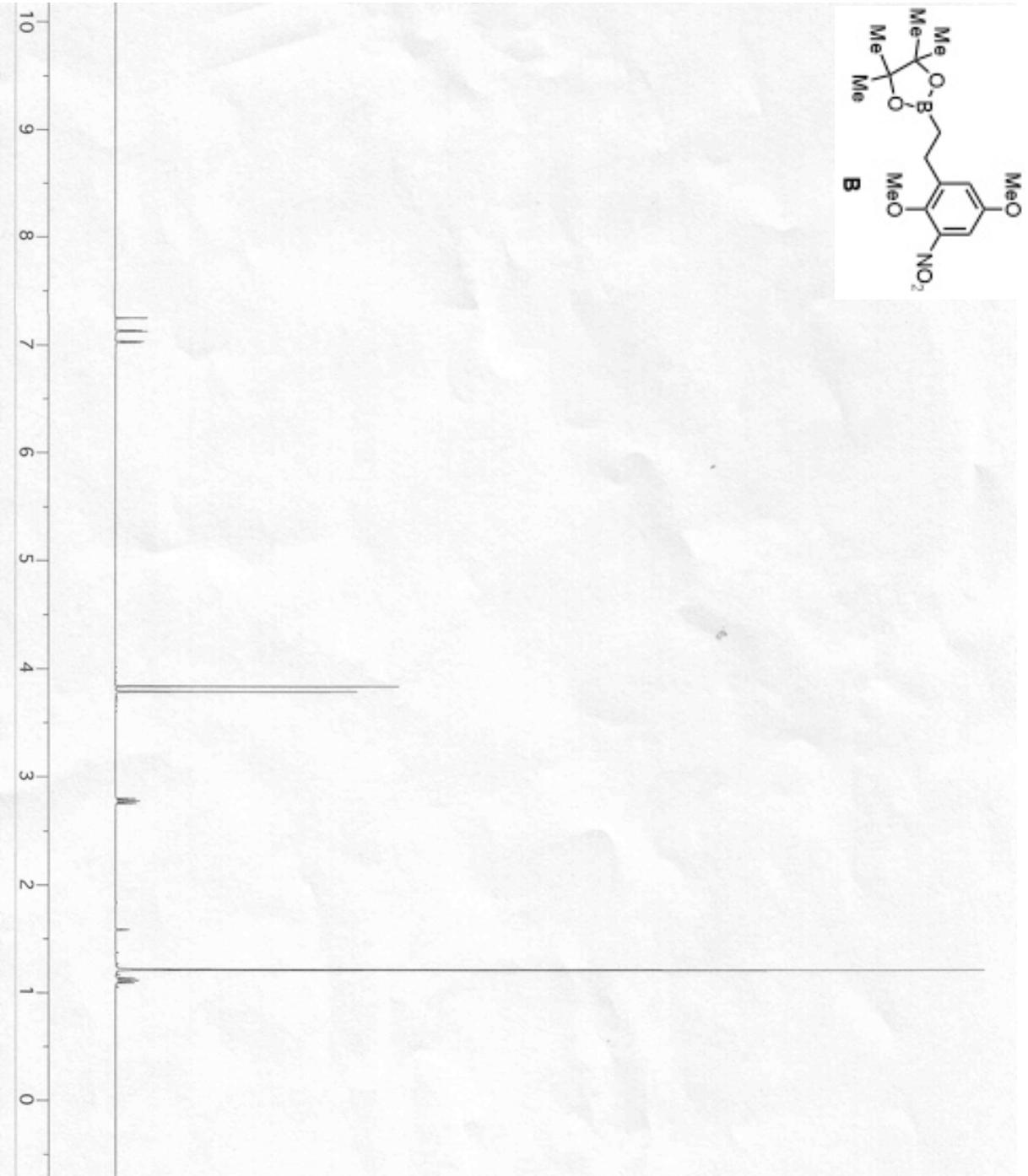


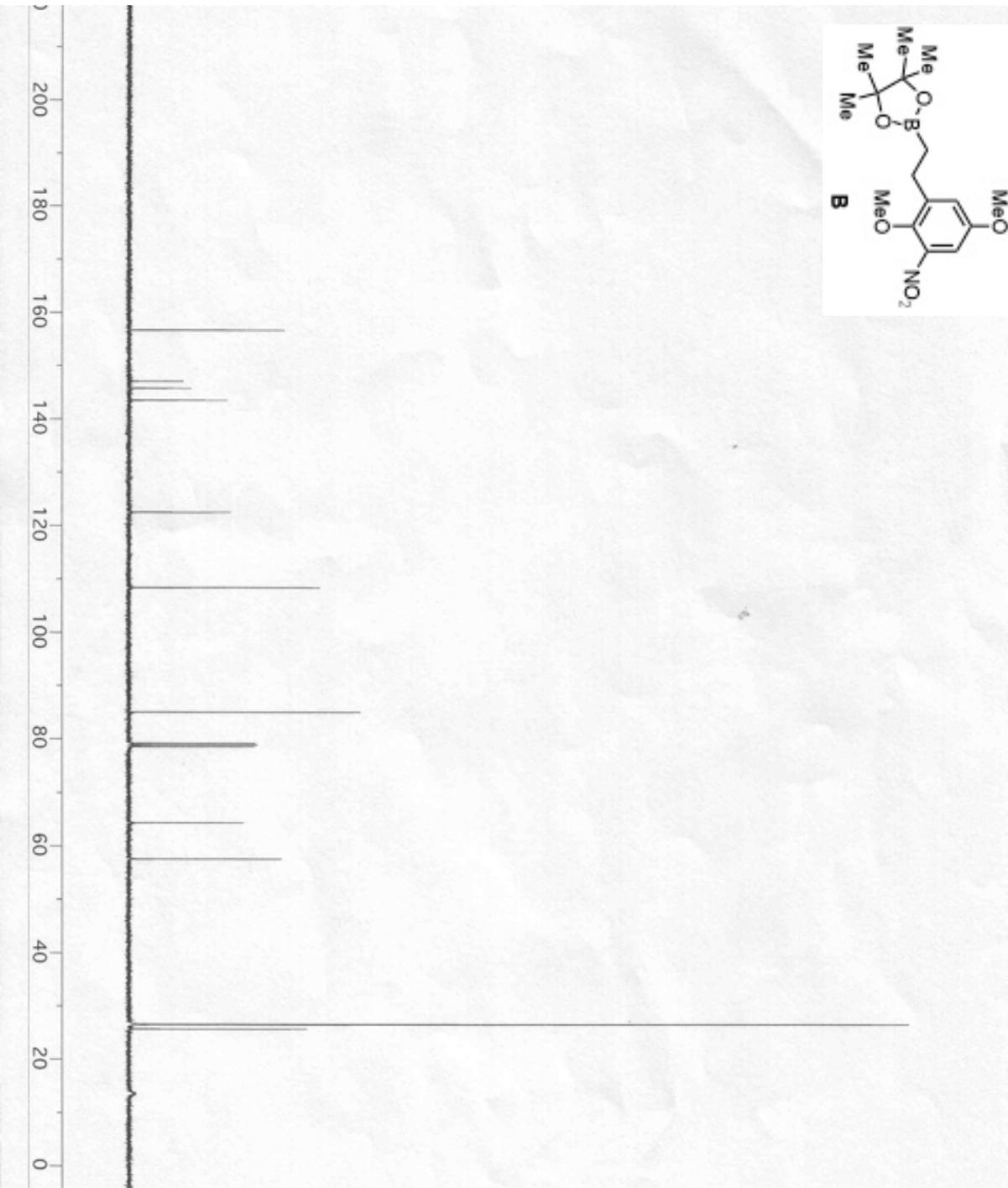


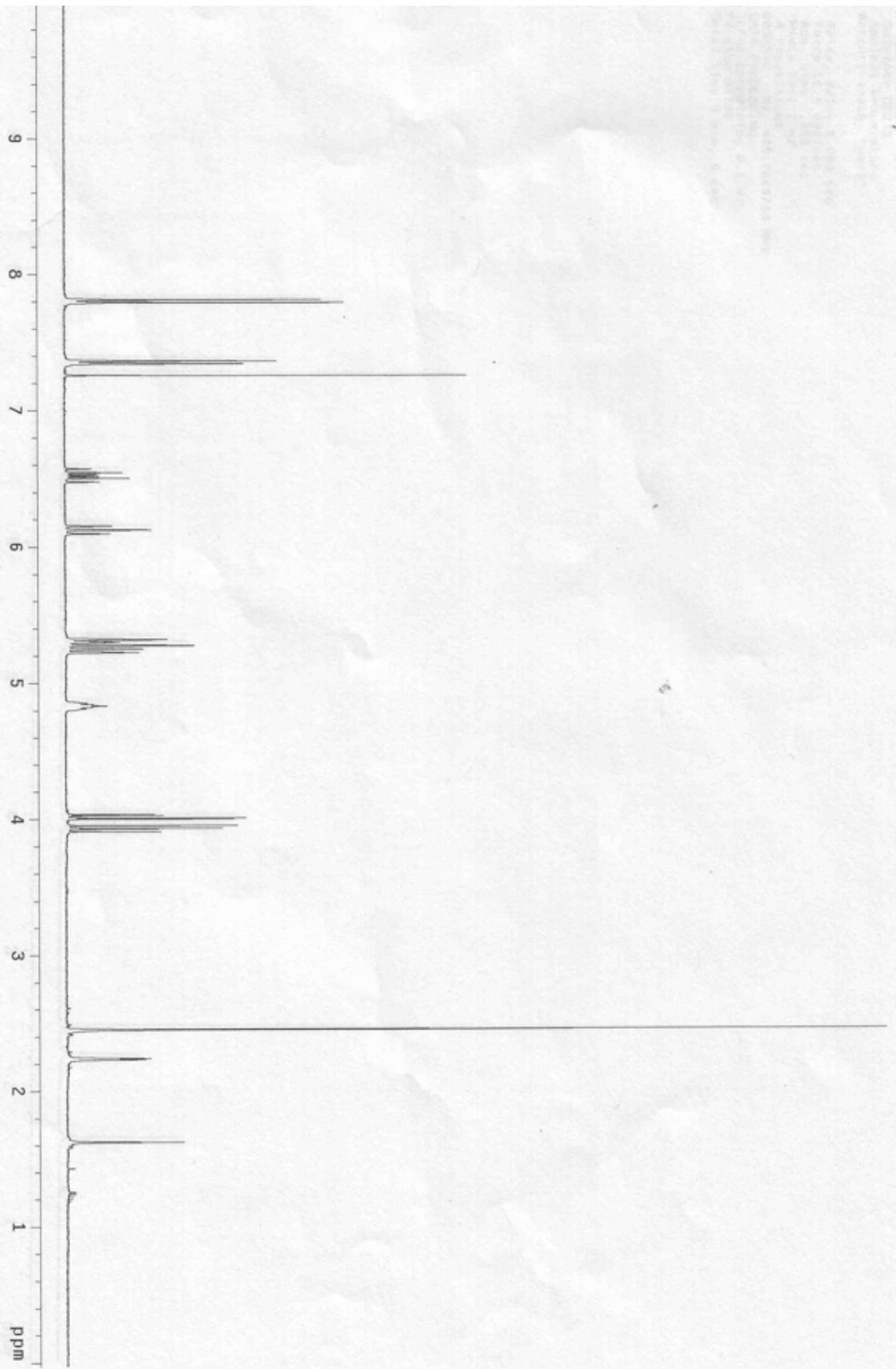
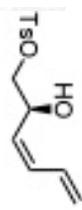


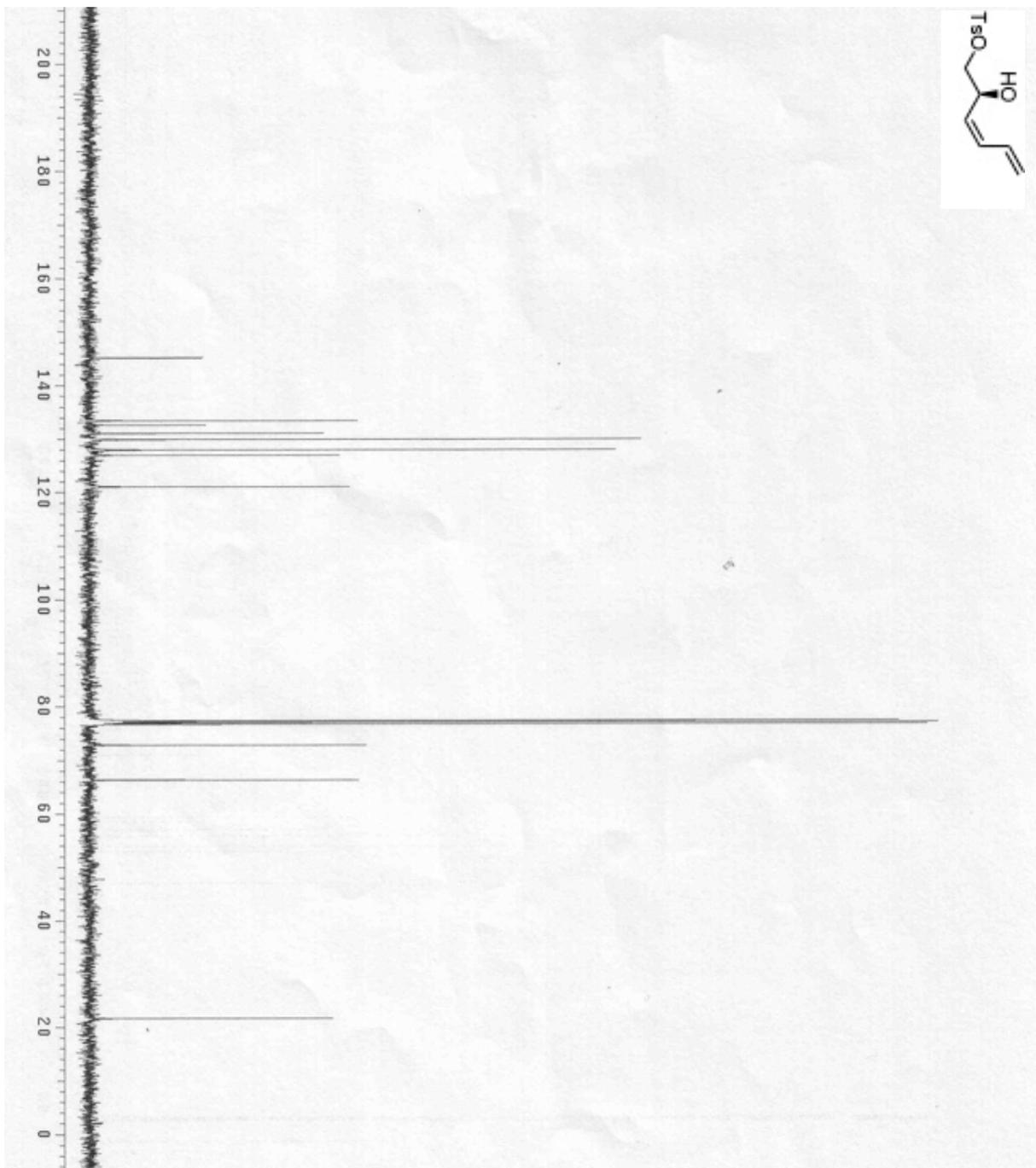
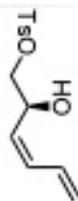


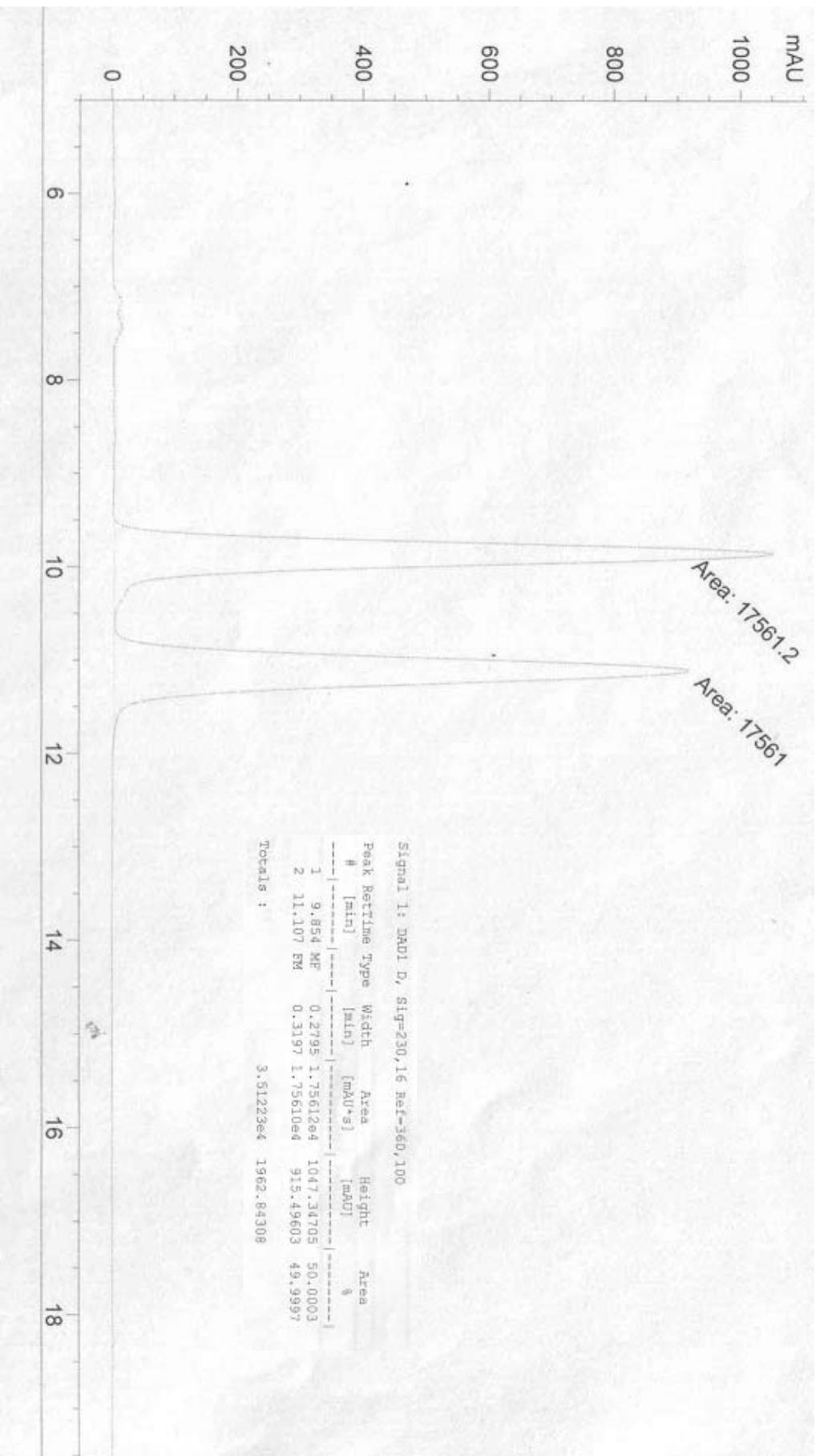
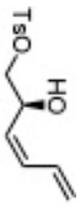


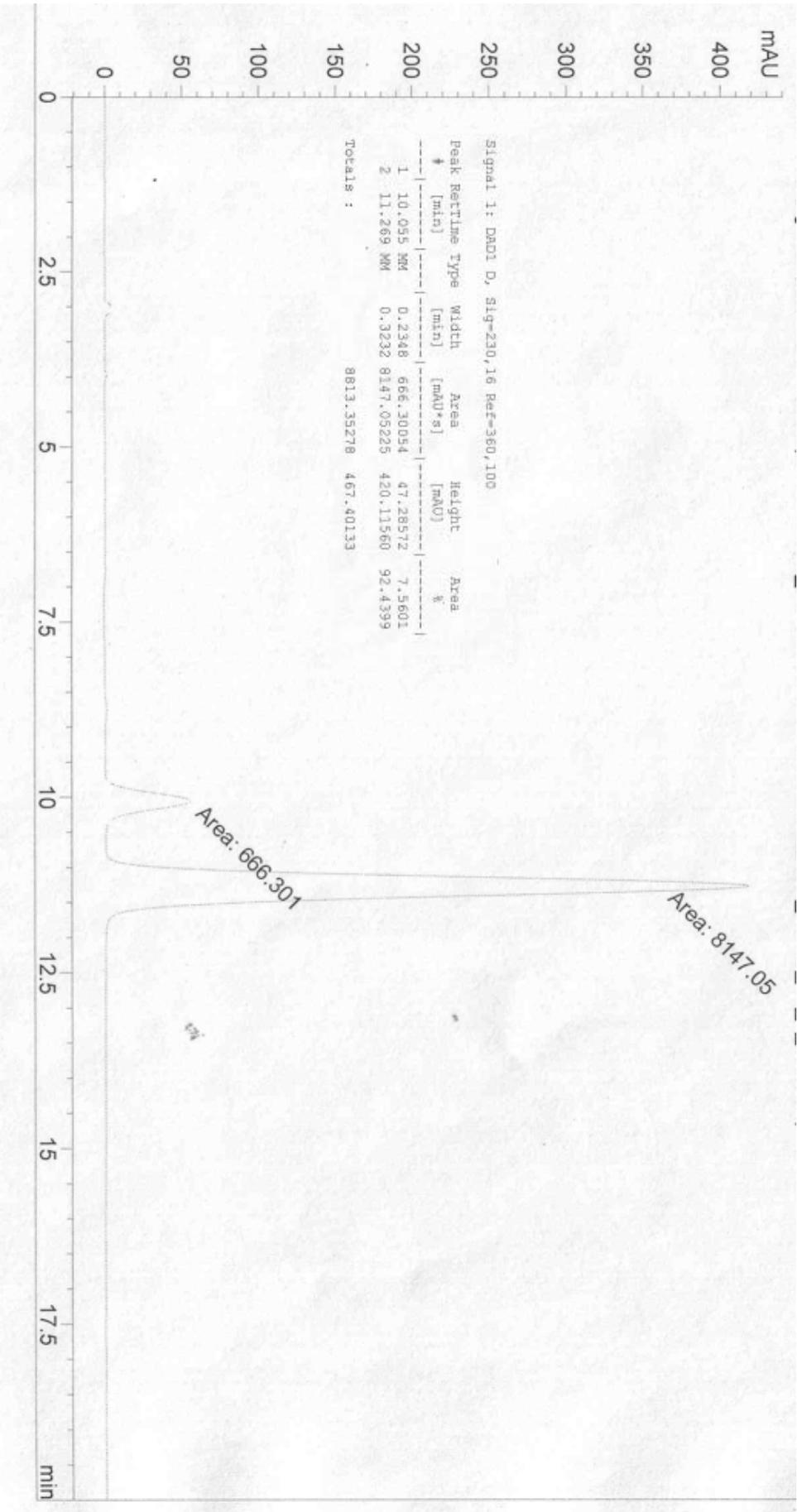
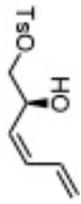


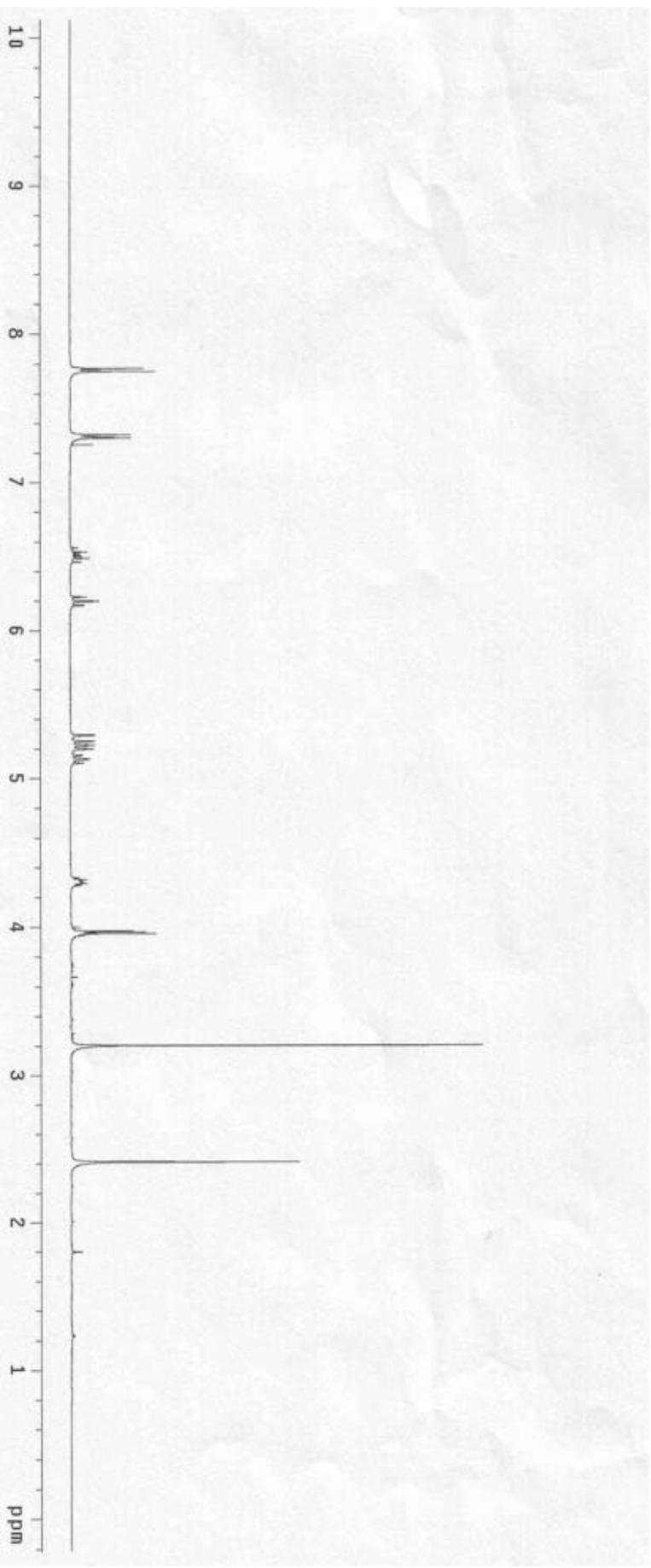
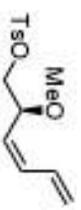


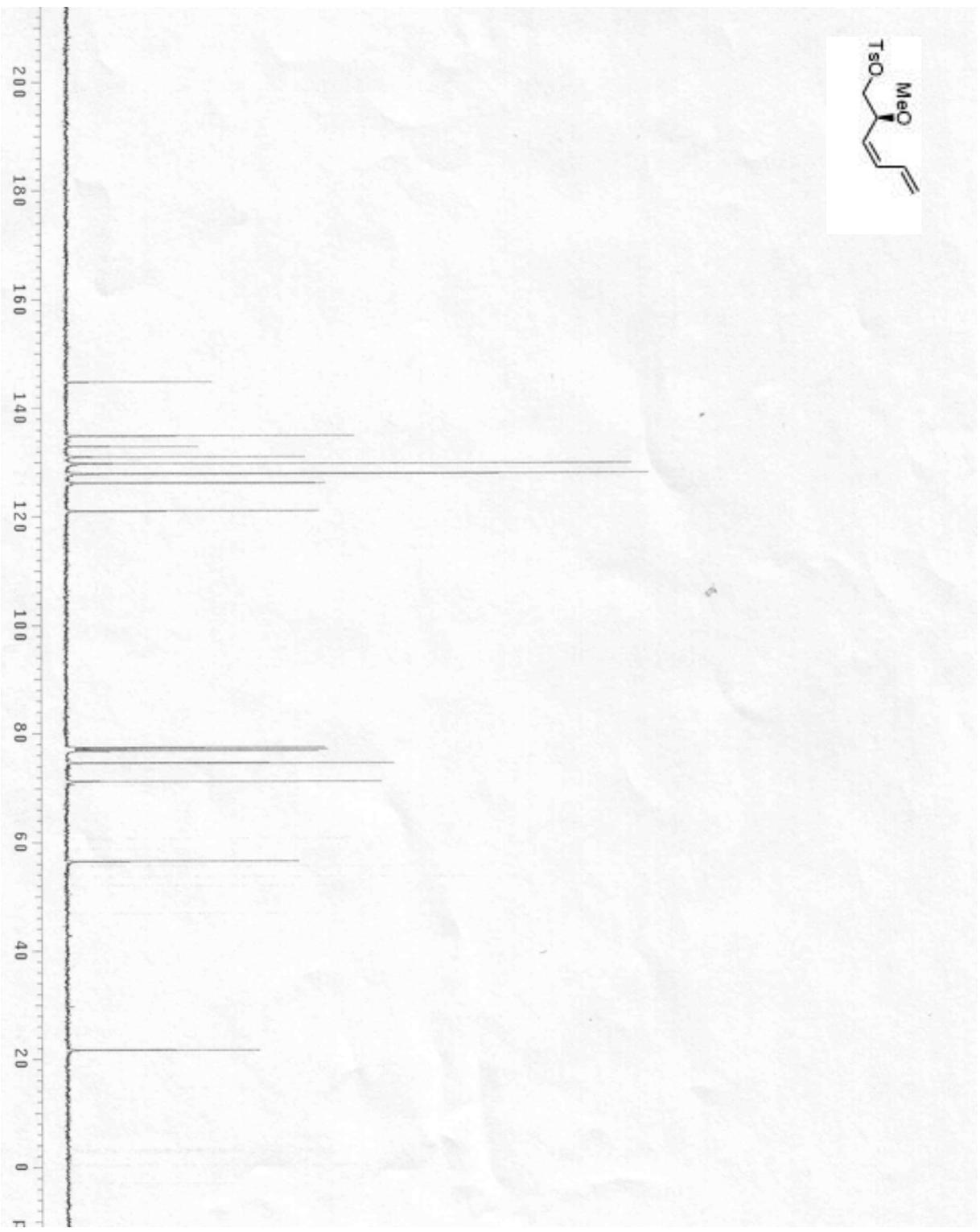


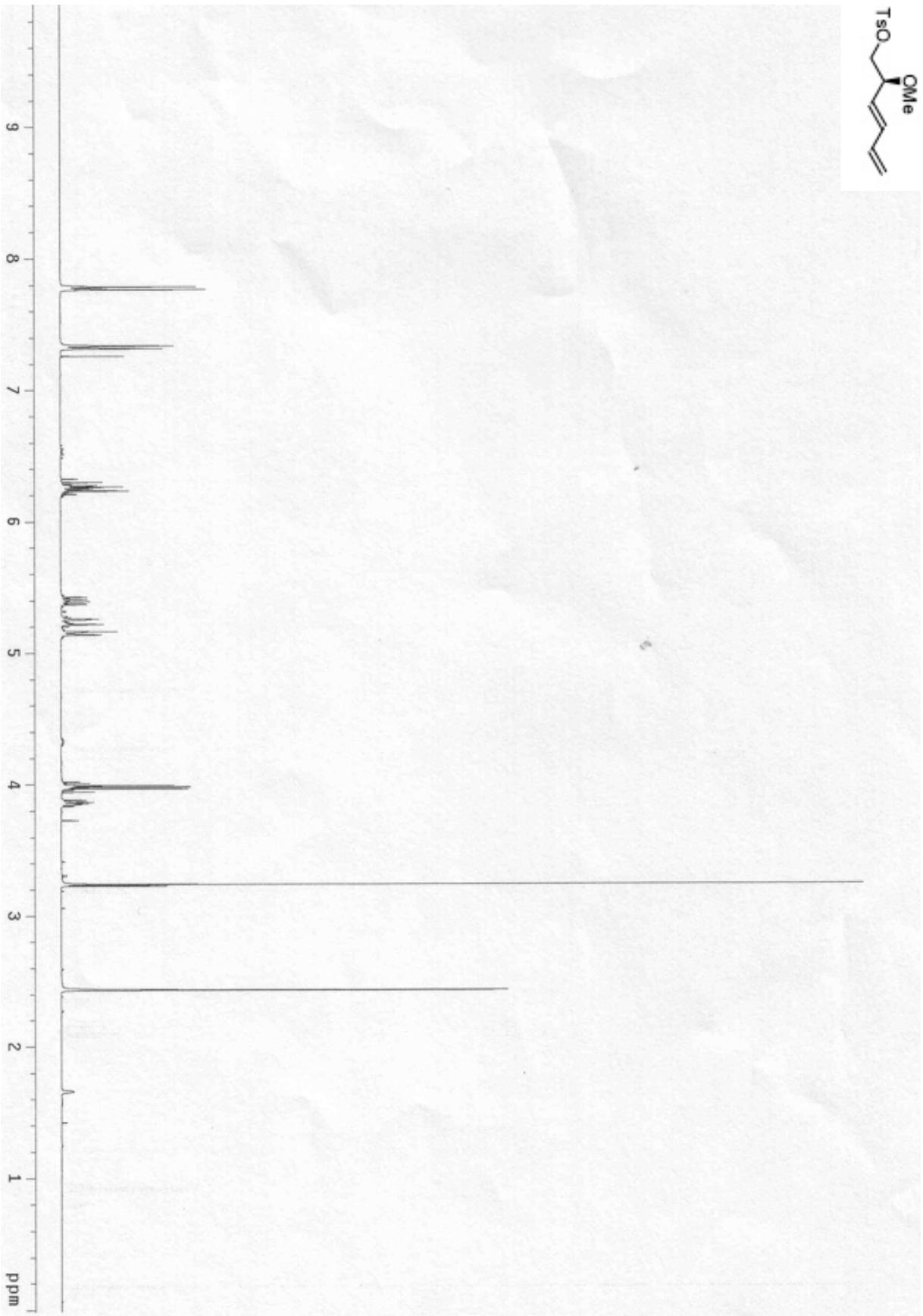


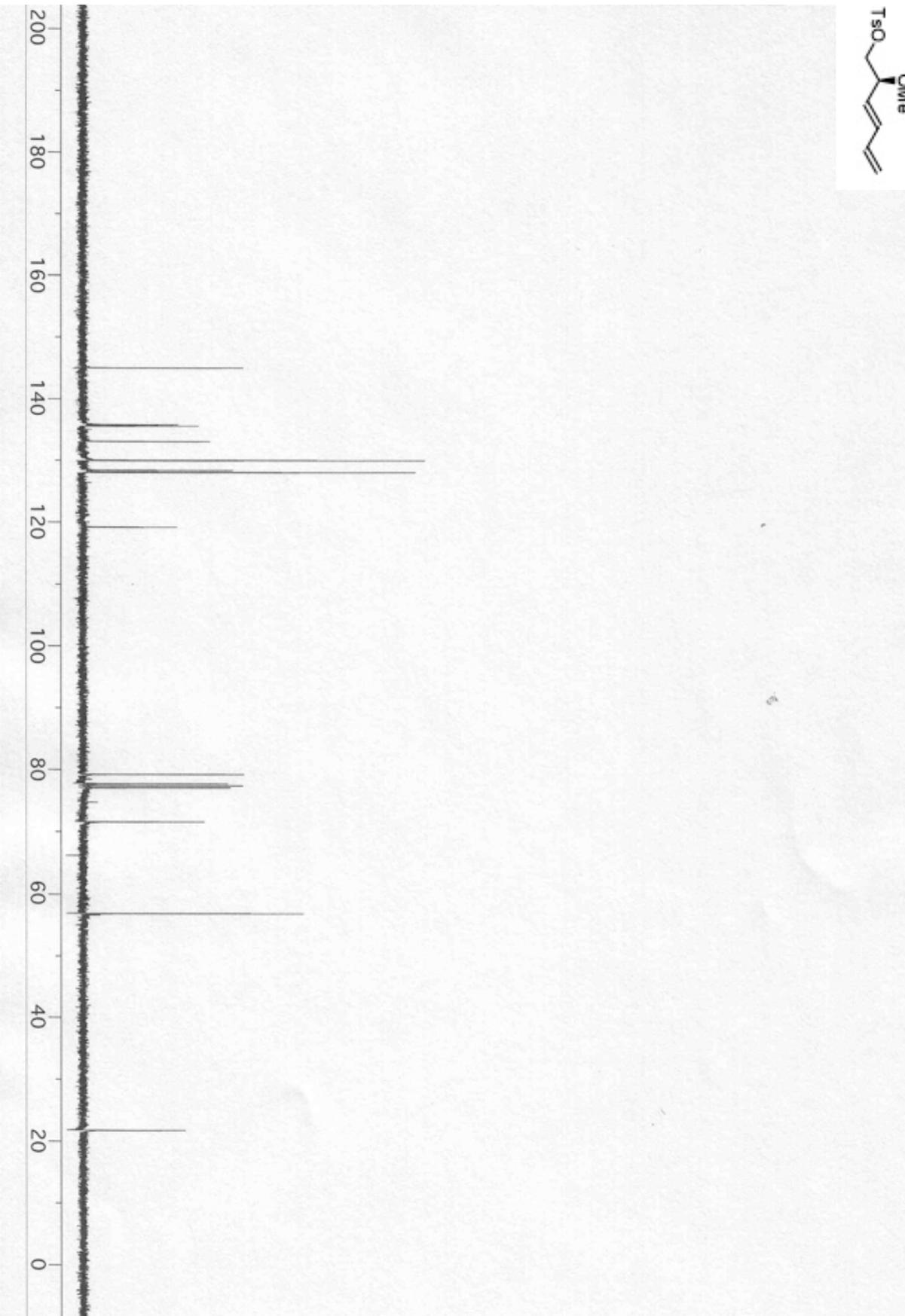
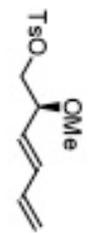












References:

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- ¹ Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
 - ² Jung, P.; Lutz, W.; Stoller, A.; Zambach, W.; Maienfisch, P.; Godfrey, C. R. A. SYNGENTA PARTICIPATIONS AG Patent: WO2008/74427 A1, **2008**
 - ³ Fischetti, William; Mak, K. Tim; Stakem, F. Gregory; Kim, Jin-II; Rheingold, Arnold L.; Heck, Richard F. *J. Org. Chem.* **1983**, *48*, 948.
 - ⁴ Seyferth, D.; Pornet, J.; Weinstein, R. M. *Organometallics* **1982**, *1*, 1651.
 - ⁵ Fürstner, A.; Grabowski, J.; Lehmann, C. W. *J. Org. Chem.* **1999**, *64*, 8275.
 - ⁶ Guay, V.; Brassard, P. *J. Het. Chem.*, **1987**, *24*, 1649.
 - ⁷ Wasserman, H. H.; Lipshutz, B. H.; Tremper, A. W.; Wu, J. S. *J. Org. Chem.* **1981**, *46*, 2991.
 - ⁸ DuBois, G. E.; Crosby, G. A.; McGarraugh, G. V.; Ng, S. Y.-W.; Stephenson, R. A.; Wang, P. C.; Wingard, R. E. *J. Org. Chem.* **1982**, *47*, 1319.
 - ⁹ Pirrung, M. C.; McGeehan, G. M. *J. Org. Chem.* **1983**, *48*, 5143.
 - ¹⁰ MacDowell, D. W. H.; Purpura, J. M. *J. Org. Chem.* **1986**, *51*, 183.
 - ¹¹ Maguire, R. J.; Thomas, E. J. *J. Chem. Soc. Perkin Trans. 1* **1995**, 2477.
 - ¹² Hayashi, Y.; Shoji, M.; Ishikawa, H.; Yamaguchi, J.; Tamaru, T.; Imai, H.; Nishigaya, Y.; Takabe, K.; Kakeya, H.; Osada, H. *Angew. Chem. Int. Ed.* **2008**, *47*, 6657.