

# Synthesis of the C(18)-C(34) Fragment of Amphidinolide C and the C(18)-C(29) Fragment of Amphidinolide F

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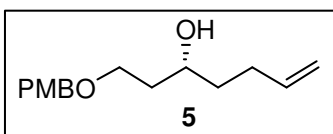
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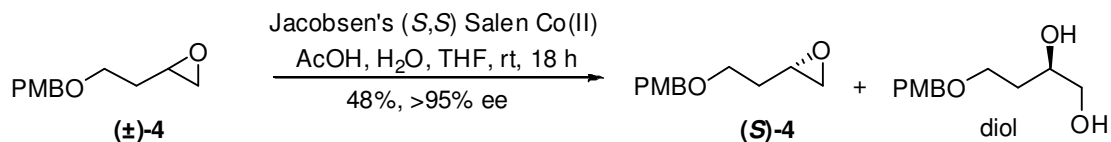
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## General Experimental

NMR spectra were recorded in  $\text{CDCl}_3$  at 300 or 500 ( $^1\text{H}$ ), 75 or 125 ( $^{13}\text{C}$ ) and 121 ( $^{31}\text{P}$ ) MHz, respectively.  $^1\text{H}$  NMR spectra were referenced to residual  $\text{CHCl}_3$  (7.27 ppm),  $^{13}\text{C}$  NMR spectra were referenced to the center line of  $\text{CDCl}_3$  (77.23 ppm), and  $^{31}\text{P}$  NMR spectra were referenced to external 85%  $\text{H}_3\text{PO}_4$  (0 ppm). Coupling constants,  $J$ , are reported in Hz. All reactions were carried out in oven dried glassware under an atmosphere of argon unless otherwise noted. Tetrahydrofuran (THF) and diethyl ether ( $\text{Et}_2\text{O}$ ) were dried by passing through activated alumina columns and then refluxed over Na/benzophenone. Toluene ( $\text{PhCH}_3$ ), methylene chloride ( $\text{CH}_2\text{Cl}_2$ ), and acetonitrile ( $\text{CH}_3\text{CN}$ ) were dried over calcium hydride ( $\text{CaH}_2$ ). Methanol ( $\text{CH}_3\text{OH}$ ) and isopropanol ( $\text{C}_3\text{H}_7\text{OH}$ ) were dried over magnesium. Reagent grade DMF was used without further purification. Commercial reagents of high purity were purchased and used without further purification, unless otherwise noted. Bis(pinacolato)diboron was stored cold in a glove box and used within 6 months of purchase. Reactions were monitored by thin-layer chromatography (TLC) using TLC silica gel 60 Å 254 nm plates and visualizing with UV light or  $\text{KMnO}_4$  stain. Silica gel (230-400 mesh) was used for flash column chromatography.

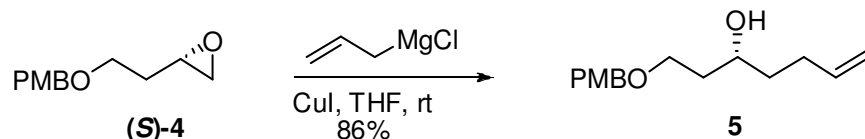
### Synthesis of the alkenol 5.





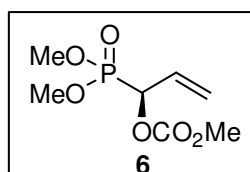
**(S)-epoxide (S)-4.** To the racemic epoxide (±)-**4** (10.07 g, 48.38 mmol, 1 eq.) at room temp., was added the (*S,S*) salen Co(II) catalyst (0.146 g, 0.24 mmol, 0.5 mol%), AcOH (55 μL, 0.96 mmol, 2 mol%) and THF (13 mL). The reaction mixture was cooled down to 0 °C and H<sub>2</sub>O (0.48 mL, 26.60 mmol, 0.55 eq.) was added in one portion. The reaction mixture was warmed up to room temperature and stirred for 18 h under an atmosphere of oxygen (2 balloons). After the completion of the reaction, the THF was concentrated under reduced pressure and the residue purified by column chromatography (SiO<sub>2</sub>, 20% EtOAc/hexanes) to give epoxide (**S**)-**4** as light brown oil (4.95 g, 48%). TLC: R<sub>f</sub> = 0.48 (20% EtOAc/hexanes); [α]<sup>26</sup><sub>D</sub> = -13.9 (c 1, CHCl<sub>3</sub>); IR (neat, NaCl) 3046, 2997, 2925, 2860, 1613 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.27 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 4.47 (s, 2H), 3.81 (s, 3H), 3.62 (t, *J* = 5.6 Hz, 2H), 3.06 (m, 1H), 2.79 (t, *J* = 4.5, 1H), 2.52 (m, 1H) 1.90 (m, 1H), 1.76 (m, 1H).

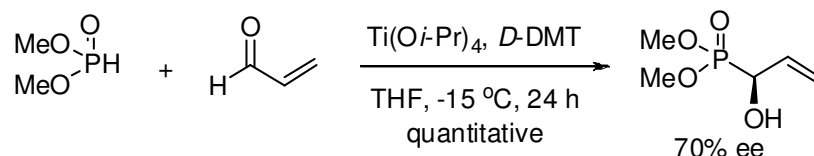
Note: The Specific rotation reported by Marshall and co-workers<sup>1</sup> for the (*R*)-epoxide formed via HKR is [α]<sup>26</sup><sub>D</sub> = -12.3 (c 1, CHCl<sub>3</sub>). Whereas, Ley and co-workers<sup>2</sup> report [α]<sup>25</sup><sub>D</sub> -13.1 (c 0.58, CHCl<sub>3</sub>) for the (*S*)-epoxide. Since Ley formed the (*S*)-epoxide from malic acid, we have assumed that the negative rotation is correct for the (*S*)-epoxide.



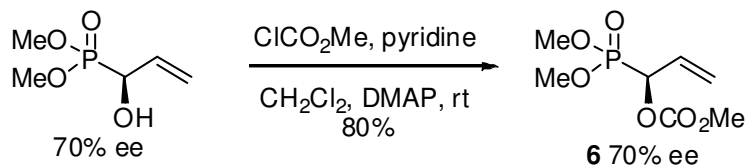
**Alkenol 5.** To a suspension of CuI (33 mg, 0.17 mmol, 0.12 eq.) in THF (8 mL) at -30 °C, was added allylmagnesium bromide (0.870 mL, 2 M solution in THF, 1.75 mmol, 1.4 eq.) drop wise over 15 min time period. The reaction mixture was stirred for an additional 5 min., after which a solution of **(S)-4** (0.216 g, 1.25 mmol, 1 eq.) in 1.5 mL THF was added drop wise over a period of 15 min. The reaction mixture was warmed to 0 °C and stirred for an additional 30 min. The reaction was quenched with aqueous NH<sub>4</sub>Cl/NaOH (9:1) and extracted with Et<sub>2</sub>O (x3). The combined organic layers were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The residue was purified by column chromatography (SiO<sub>2</sub>, 10% EtOAc/hexanes) to give the alkenol **5** as colorless oil (0.270 g, 86%). TLC: R<sub>f</sub> = 0.35 (10% EtOAc/hexanes); [α]<sup>26</sup><sub>D</sub> = +12.7 (c 1, CHCl<sub>3</sub>); IR (neat, NaCl): 3441, 2999, 2935, 2860, 1640, 1613 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.25 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 5.84 (m, 1H), 5.01 (m, 2H), 4.46 (s, 2H), 3.81 (s, 3H), 3.66 (m, 2H), 2.94 (d, *J* = 2.9 Hz, 1H), 2.15 (m, 2H), 1.75 (m, 2H), 1.55 (m, 2H).

### Synthesis of the (S)-carbonate 6.

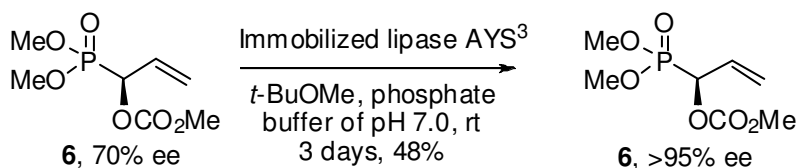




**Hydroxy phosphonate.** To a solution of dry *D*-dimethyl tartrate (3.18 g, 89.3 mmol, 20 mol%) in dry THF (135 mL) at -15 °C under argon was added freshly distilled  $\text{Ti}(\text{O}i\text{-Pr})_4$  (5.23 mL, 17.8 mmol, 20 mol%) and the resulting mixture was stirred for 0.5 h. Freshly distilled dimethyl phosphate (16.36 mL, 178.6 mmol, 2 eq.) was added followed, after 10 min, by the addition of acrolein (5.95 mL, 89.3 mmol, 1 eq.). The flask containing the reaction mixture was placed in a freezer at a temperature of -15 °C for a period of 24 h. The reaction was quenched by drop wise addition of  $\text{H}_2\text{O}$  to precipitate the  $\text{TiO}_2$ , which was removed by filtration through celite. The organic solution was washed with brine and the aqueous layer re-extracted with  $\text{CH}_2\text{Cl}_2$  (x2). The combined organic layers were dried over anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. The residue was purified by column chromatography ( $\text{SiO}_2$ , 50% EtOAc/hexanes) to give the hydroxy phosphonate as colorless oil (10.15 g, 100%) with 70% e.e. (measured by  $^{31}\text{P}$  NMR after the addition of quinine, chemical shift reagent). TLC:  $R_f = 0.25$  (100% EtOAc); IR (neat, NaCl): 3298, 2959, 2855, 1638  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ) 5.99 (m, 1H), 5.53 (m, 1H), 5.36 (m, 1H), 4.55 (m, 1H), 3.82 (d,  $J_{\text{HP}} = 11.3$  Hz, 6H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  24.2.



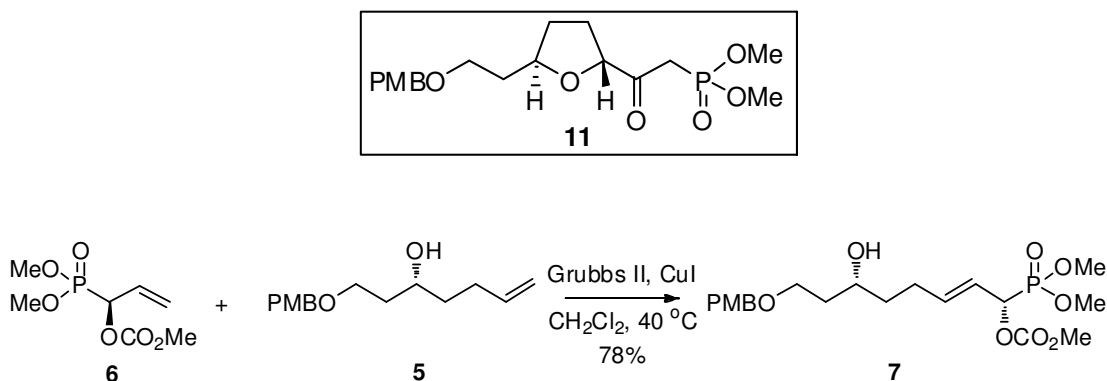
**(S)-Carbonate 6.** To a solution of hydroxy phosphonate (1.86 g, 16.05 mmol, 1 eq.) in  $\text{CH}_2\text{Cl}_2$  (15.6 mL) was added DMAP (4-dimethylaminopyridine) (0.392 g, 3.21 mmol, 20 mol%) followed by pyridine (1.94 mL, 24.1 mmol, 1.5 eq.) at 0 °C. The reaction mixture was allowed to warm to room temperature and was stirred for 16 h. The reaction was quenched with 1N HCl and the aqueous layer was re-extracted with  $\text{CH}_2\text{Cl}_2$  (x2). The combined organic layers were dried over anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. The residue was purified by column chromatography ( $\text{SiO}_2$ , 50% EtOAc/hexanes) to give the carbonate **6** as colorless oil (2.87 g, 80%) yield. TLC:  $R_f = 0.58$  (100% EtOAc); IR (neat, NaCl): 2960, 2856, 1757, 1642  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ) 5.95 (m, 1H), 5.54 (m, 2H), 5.43 (m, 1H), 3.85 (s, 3H), 3.83 (d,  $J_{\text{HP}} = 10.5$  Hz, 6H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  19.48.



**(S)-Carbonate 6.** To the (S)-carbonate **6** (3.09 g, 70% e.e.) was added *t*-BuOMe (61 mL) and pH 7.0 phosphate buffer (61 mL), followed by the immobilized lipase  $\text{AYS}^3$  (4.43 g). The reaction mixture was stirred using a rotary shaker for 24 h, after which another batch of immobilized lipase (4.43 g) was added. The reaction mixture was stirred for an additional 48 h and then filtered through a pad of celite.

After the addition of brine, the aqueous mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (x2). The combined organic layers were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The residue was purified by column chromatography (SiO<sub>2</sub>, 50% EtOAc/hexanes) to give the carbonate **6** as colorless oil (1.29 g, 42%, >95% ee). [ $\alpha$ ]<sub>D</sub><sup>26</sup> = +16.7 (c 1, CHCl<sub>3</sub>). The enantiomeric excess (e.e.) was measured indirectly by first converting **6** to a UV active phosphonate by a Grubbs cross metathesis reaction with styrene. The e.e. of the resulting phosphonate was measured by HPLC using Whelk-O chiral column, 20% EtOH/hexanes, 254 nm and flow rate = 1 mL/min.).

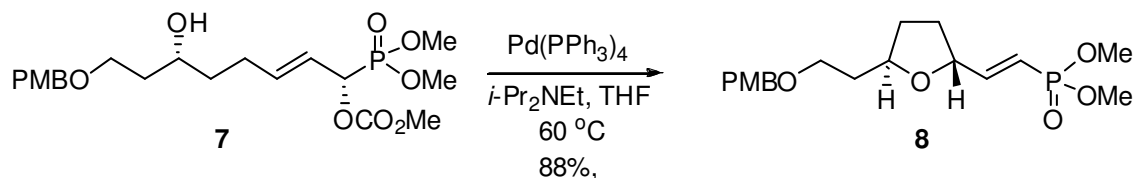
### Synthesis of the northern fragment **11**.



**Phosphono allylic carbonate 7.** To a solution of (*S*)-carbonate **6** (0.23 g, 1.03 mmol, 1 eq.) and alkenol **2** (0.250 g, 1.03 mmol, 1 eq.) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) was added Grubbs second generation catalyst (0.044 g, 0.051 mmol, 5 mol %) and CuI (0.019 g, 0.10 mmol, 10 mol %). The resulting mixture was heated at reflux for 3h. The reaction was monitored by <sup>31</sup>P NMR until complete conversion. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (SiO<sub>2</sub>, 100% EtOAc) to give the phosphono allylic

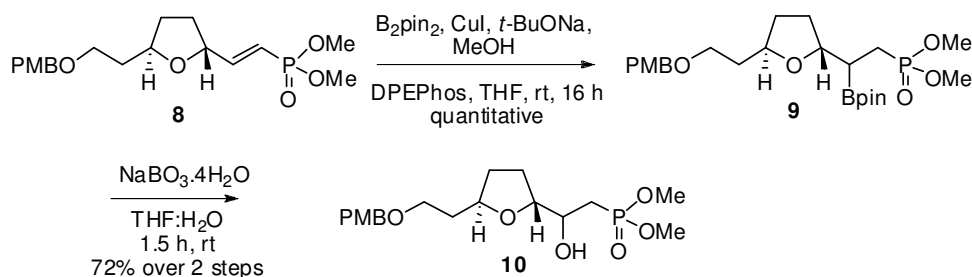


carbonate **7** as a  $\geq 9:1$  mixture of the *E* and *Z* isomers (0.35 g, 78% yield). TLC:  $R_f = 0.23$  (100% EtOAc);  $[\alpha]_D^{26} = -13.4$  ( $c$  1,  $\text{CHCl}_3$ ); IR (neat, NaCl): 3440, 2956, 2853, 1755, 1613,  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.25 (d,  $J = 8.4$  Hz, 2H), 6.68 (d,  $J = 8.3$  Hz, 2H), 5.97 (m, 1H), 5.60 (m, 1H), 5.45 (m, 1H), 4.45 (s, 2H), 3.80 (m, 9H), 3.60 (m, 2H), 2.13 (m, 2H), 1.97 (s, 1H), 1.53 (m, 4H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  159.5 154.9 (d,  $J_{\text{CP}} = 9.8$  Hz), 138.6 (d,  $J_{\text{CP}} = 12.5$  Hz), 130.1, 129.5, 120.7 (d,  $J_{\text{CP}} = 3.8$  Hz), 114.0, 73.1 (d,  $J_{\text{CP}} = 170$  Hz), 73.2, 70.9, 55.5, 55.4, 54.0 (d,  $J_{\text{CP}} = 7.0$  Hz), 53.8 (d,  $J_{\text{CP}} = 6.4$  Hz), 36.5, 36.3 (d,  $J_{\text{CP}} = 2.3$  Hz), 28.7;  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  20.4; HRMS (FAB,  $\text{MH}^+$ ) calculated for  $\text{C}_{20}\text{H}_{31}\text{O}_9\text{P}$  446.1783. Found 446.1772.



**Vinyl phosphonate 8.** To a solution of carbonate **7** (1.44 g, 3.23 mmol, 1 eq.) in THF (8 mL), was added  $\text{Pd(PPh}_3)_4$  (186 mg, 0.160 mmol, 5 mol%) followed by Hunig's base (2.25 mL, 12.9 mmol, 4 eq.) drop wise. The reaction mixture was stirred at  $60\text{ }^\circ\text{C}$  for 3 h. THF was evaporated under reduced pressure and the residue was purified by column chromatography ( $\text{SiO}_2$ , 100% EtOAc) to give the vinyl phosphonate **8** as a light brown oil (1.05 g, 88%) as a mixture of 95:5 to 92:8 mixture of *trans* and *cis* diastereomers. TLC:  $R_f = 0.25$  (100% EtOAc);  $[\alpha]_D^{24} = -8.2$  ( $c$  1,  $\text{CHCl}_3$ ); IR (neat, NaCl): 2953, 2852, 1710, 1611  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.23 (d,  $J = 8.5$  Hz, 2H), 6.85 (d,  $J = 8.6$  Hz, 1H), 6.76 (m, 1H),

5.87 (m, 2H), 4.55 (m, 1H), 4.41 (s, 2H), 4.11 (m, 2H), 3.77 (s, 3H), 3.69 (d,  $J = 11.0$  Hz, 6H), 3.53 (t,  $J = 6.4$  Hz, 2H), 2.16 (m, 1H), 2.02 (m, 1H), 1.78 (m, 2H), 1.62 (m, 2H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  159.3, 154.5 (d,  $J_{\text{CP}} = 5.1$  Hz), 130.6, 129.4, 113.9, 113.4 (d,  $J_{\text{CP}} = 189$  Hz), 78.1 (d,  $J_{\text{CP}} = 21.6$  Hz), 72.8, 67.4, 55.4, 52.5 (d,  $J_{\text{CP}} = 5.6$  Hz), 52.4 (d,  $J_{\text{CP}} = 5.6$  Hz), 36.0, 31.9, 31.8 (d,  $J_{\text{CP}} = 2.0$  Hz);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  22.47; HRMS (FAB,  $\text{MH}^+$ ) calculated for  $\text{C}_{20}\text{H}_{27}\text{O}_6\text{P}$  371.1623. Found 371.1631.



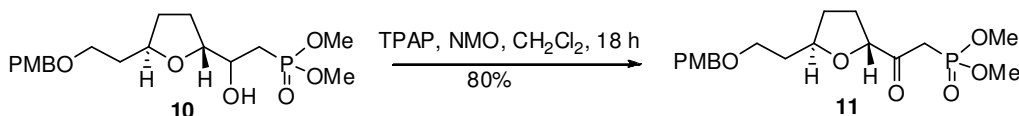
**$\beta$ -Hydroxy phosphonate 10.**  $\text{CuI}$  (1.5 mg, 0.008 mmol, 3 mol%),  $t\text{-BuONa}$  (2.4 mg, 0.024 mmol, 9 mol%) and  $\text{DPEphos}$  (4.4 mg, 0.008 mmol, 3 mol%) was weighed out in glove box and placed in a schlenk flask. The schlenk flask was then transferred into a fume hood and attached to the schlenk line.  $\text{THF}$  (0.2 mL) was added and the mixture stirred for 30 min. A yellowish brown coloration of the reaction mixture was observed. During this time, a solution of  $\text{B}_2\text{pin}_2$  (76 mg, 0.33 mmol, 1.2 eq.) in  $\text{THF}$  (0.16 mL) was also prepared in a glove box and was added to the reaction mixture. Stirring was continued for 10 min. At this point the reaction mixture's color was changed to greenish grey. A solution of vinyl phosphonate, **4** (102 mg, 0.27 mol, 1 eq.) in  $\text{THF}$  (0.16 mL) was added, followed by the final addition of  $\text{MeOH}$  (22  $\mu\text{L}$ , 0.55 mmol, 2 eq.). The grey colored

reaction mixture was stirred for 18 h at room temp. Quantitative conversion to the  $\beta$ -borylated product **9** was observed by  $^{31}\text{P}$  NMR. The reaction mixture was then filtered through a short plug of celite and concentrated under reduced pressure to furnish the crude product **9** (143 mg, 100%) which was used for the subsequent  $\text{NaBO}_3$  oxidation step without any further purification.  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  36.16, 36.00.

Note: Success of this reaction was highly dependent on the high purity of the reagents and their storage conditions.  $\text{B}_2\text{pin}_2$ ,  $\text{NaOt-Bu}$  and anhydrous  $\text{CuI}$  of high purity were stored in glove box. Amongst them  $\text{B}_2\text{pin}_2$  was stored cold and used within 6 months after opening the bottle. Also, the  $\beta$ -borylated product, **9** was found to be column sensitive.  $\beta$ -elimination was observed under column chromatography conditions and also upon standing.

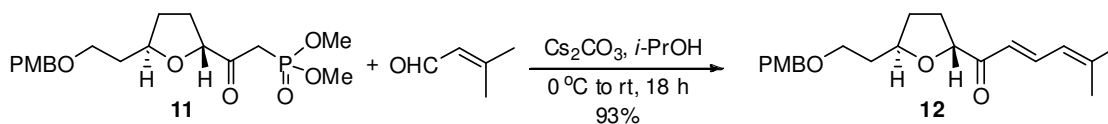
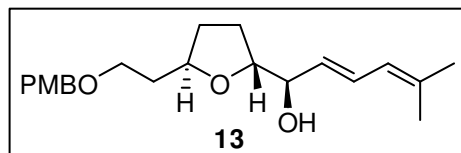
To the boronate **9** (143 mg, 0.28 mmol, 1 eq.) was added THF: $\text{H}_2\text{O}$  (1.3 mL, 1:1 ratio) followed by  $\text{NaBO}_3 \cdot 4\text{H}_2\text{O}$  (220 mg, 1.43 mmol, 5 eq.). The reaction mixture was stirred at room temp. for 1.5 h and monitored by  $^{31}\text{P}$  NMR. After complete conversion, the reaction mixture was diluted with brine and extracted with  $\text{CH}_2\text{Cl}_2$  (x3). The combined organic extracts were dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. The crude product was purified by column chromatography ( $\text{SiO}_2$ , 100% EtOAc) to give a 1:1 diastereomeric mixture of the hydroxy phosphonate **10** as colorless oil (78 mg, 72%). TLC:  $R_f$  = 0.61 (20% EtOH/EtOAc); IR (neat, NaCl) 3374, 2954, 2855, 1613  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.23 (d,  $J$  = 8.4 Hz, 2H), 6.85 (d,  $J$  = 8.4 Hz, 2H), 4.40 (s, 2H), 4.02 (m,

1H), 3.85 (m, 2H), 3.78 (s, 3H), 3.74 (d,  $J_{HP} = 10.9$  Hz, 6H), 3.51 (t,  $J = 6.5$  Hz, 2H), 3.25 (d, br, 1H), 1.80 (m, 8H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  33.84, 33.26; HRMS (FAB,  $\text{MH}^+$ ) calculated for  $\text{C}_{18}\text{H}_{29}\text{O}_7\text{P}$  389.1729. Found 389.1742.



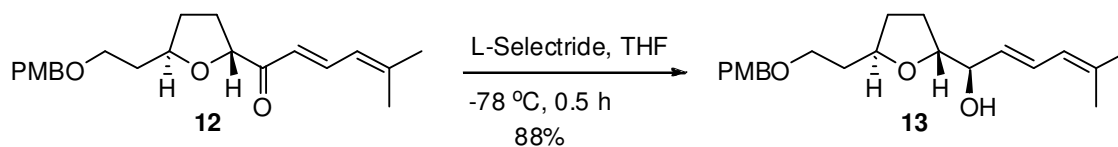
**$\beta$ -Ketophosphonate 11.** To a solution of the hydroxy phosphonate **10** (107 mg, 0.27 mmol, 1 eq.) in  $\text{CH}_2\text{Cl}_2$  (3.2 mL) was added 4 Å MS (321 mg), and NMO (64 mg, 0.55 mmol, 2 eq.) and the resulting mixture was stirred for 15-20 min. Finally, TPAP (5 mg, 0.027 mmol, 10 mol%) was added and the resultant black colored reaction mixture was stirred at room temp for 18 h. The reaction was monitored by  $^{31}\text{P}$  NMR. After complete conversion, the reaction mixture was filtered through a short plug of celite, concentrated under reduced pressure and purified by column chromatography ( $\text{SiO}_2$ , 100% EtOAc) to give the pure  $\beta$ -ketophosphonate **11** as a colorless oil (85 mg, 80%). TLC:  $R_f = 0.67$  (20% EtOH/EtOAc);  $[\alpha]_D^{24} = +8.1$  ( $c$  0.95,  $\text{CHCl}_3$ ); IR (neat, NaCl) 2955, 2855, 1718, 1612  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.25 (d,  $J = 8.3$  Hz, 2H), 6.88 (d,  $J = 8.3$  Hz, 2H), 4.44 (s, 2H), 4.44 (m, 1H), 4.15 (m, 1H), 3.80 (s, 3H), 3.79 (d,  $J = 11.4$  Hz, 6H), 3.56 (t,  $J = 6.5$  Hz, 2H), 3.29 (m, 2H), 2.21 (m, 1H), 2.05 (m, 2H), 1.85 (m, 2H), 1.54 (m, 1H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ) 204.8 (d,  $J_{CP} = 6.8$  Hz), 159.3, 130.6, 129.4, 114.0, 83.2 (d,  $J_{CP} = 2.2$  Hz), 78.5, 72.9, 67.2, 55.4, 53.2 (d,  $J_{CP} = 6.2$  Hz), 53.2 (d,  $J_{CP} = 6.2$  Hz), 36.2 (d,  $J_{CP} = 131$  Hz), 35.7, 31.8, 28.6;  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  23.57; HRMS (FAB,  $\text{MNa}^+$ ) calculated for  $\text{C}_{18}\text{H}_{27}\text{O}_7\text{PNa}$  409.1392. Found 409.1386.

## Synthesis of the C(18)-C(29) fragment of amphidinolide F 13



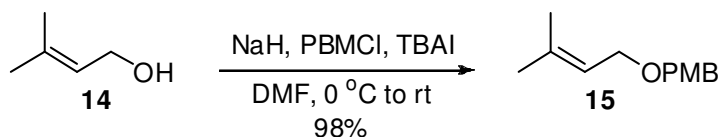
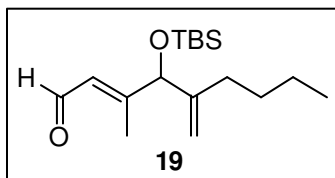
**1,3-Dienone 12.** To a solution of  $\beta$ -ketophosphonate **11** (20 mg, 0.050 mmol, 1.2 eq.) in *i*-PrOH (0.4 mL) was added  $\text{Cs}_2\text{CO}_3$  (14 mg, 0.040 mmol, 1 eq.). The reaction mixture was stirred for 2.5 h at 0 °C and then 3-methyl-2-butenal (4.2  $\mu\text{L}$ , 0.04 mmol, 1 eq.) was added drop wise. The resulting mixture was warmed to room temperature and stirred for an additional 18 h. The reaction was monitored by TLC. After the reaction was complete, it was quenched with 5% aqueous citric acid solution and extracted with  $\text{CH}_2\text{Cl}_2$  (x3), dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. The residue was purified by column chromatography ( $\text{SiO}_2$ , 20% EtOAc/hexanes) to give the dienone **12** as a colorless oil (14 mg, 93%). TLC:  $R_f = 0.27$  (20% EtOAc/hexanes); IR (neat, NaCl): 2934, 2862, 1679, 1626, 1613  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.63 (dd,  $J = 15.1, 11.7$  Hz, 1H), 7.27 (d,  $J = 8.5$  Hz, 2H), 6.88 (d,  $J = 8.3$  Hz, 2H), 6.42 (d,  $J = 15.1$  Hz, 1H), 6.03 (d,  $J = 11.7$  Hz, 1H), 4.52 (t,  $J = 7.3$  Hz, 2H), 4.46 (s, 2H), 4.18 (m, 1H), 3.81 (s, 3H), 3.59 (t,  $J = 6.5$  Hz, 2H), 2.55 (m, 1H), 2.02 (m, 3H), 1.92 (s, 3H), 1.90 (s, 3H), 1.84 (m, 1H), 1.57 (m, 1H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ) 202.0, 159.3, 149.1, 140.6, 130.8, 129.4, 124.8, 122.1, 114.0, 82.7, 78.4, 72.9,

67.5, 55.5, 35.9, 31.8, 29.8, 27.0, 19.4; HRMS (FAB, MNa<sup>+</sup>) calculated for C<sub>21</sub>H<sub>28</sub>O<sub>4</sub>Na 367.1885. Found 367.1880.

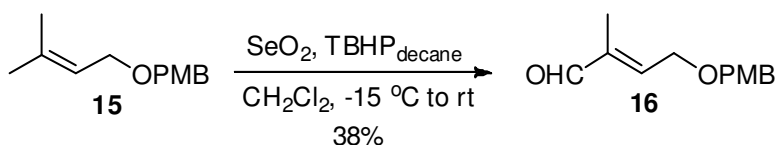


**C(18)-C(29) unit of amphidinolide F 13.** To a cooled (-78 °C) solution of 1,3-dienone **12** (8 mg, 0.02 mmol, 1 eq.) in THF (0.6 mL) was added L-selectride (1 M in THF, 46  $\mu$ L, 0.04 mmol, 2 eq.) and the resulting reaction mixture was stirred for 30 min. at -78 °C. The reaction was monitored by TLC. After the reaction was complete, it was quenched with 3N NaOH (2 mL) and H<sub>2</sub>O<sub>2</sub> (4 mL) at 0 °C. After 30 min. the reaction mixture was diluted with water, extracted with CH<sub>2</sub>Cl<sub>2</sub> (x3), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The residue was purified by column chromatography (SiO<sub>2</sub>, 20% EtOAc/hexanes) to give the alcohol **13** as colorless oil (7 mg, 88%). TLC: R<sub>f</sub> = 0.43 (30% EtOAc/hexanes); IR (neat, NaCl): 3438, 2962, 2919, 2851, 1612 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.26 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 6.52 (dd, *J* = 15.0, 11.0 Hz, 1H), 5.82 (d, *J* = 11.0 Hz, 1H), 5.46 (dd, *J* = 15.1, 6.9 Hz, 1H), 4.44 (s, 2H), 4.08 (m, 1H), 3.94 (brt, *J* = 6.9 Hz, 1H), 3.85 (m, 1H), 3.81 (s, 3H), 3.55 (t, *J* = 6.4 Hz, 2H), 2.56 (brs, 1H), 2.04 (m, 1H), 1.93 (m, 1H), 1.86 (m, 1H), 1.79 (m, 1H), 1.78 (s, 3H), 1.77 (s, 3H), 1.63 (m, 1H), 1.57 (m, 1H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) 159.4, 136.7, 130.8, 129.5, 129.5, 128.4, 124.6, 114.0, 82.1, 76.8, 75.8, 72.9, 67.5, 55.5, 35.9, 32.5, 28.2, 26.2, 18.6; HRMS (FAB, MNa<sup>+</sup>) calculated for C<sub>21</sub>H<sub>30</sub>O<sub>4</sub>Na 369.2042. Found 369.2050.

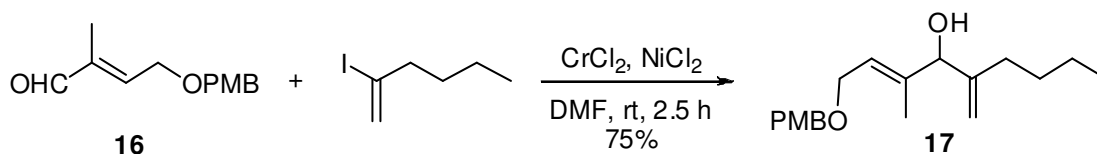
## Synthesis of the side chain aldehyde of amphidinolide C 19



**Alkene 15.**<sup>4</sup> A solution of prenil **15** (0.83 mL, 9.7 mmol, 1 eq.) in DMF (30 mL) was cooled to 0 °C and NaH (1.164 g, 60% w/w, 29.12 mmol, 3 eq.) was added in small batches. The reaction mixture was stirred for 1 h at 0 °C and then PMBCl (1.98 ml, 14.6 mmol, 1.5 eq.) and tetrabutylammonium iodide (358 mg, 0.97 mmol, 0.1 eq.) were added. The resulting reaction mixture was stirred at 0 °C for 1 h and then warmed to room temperature and stirred for an additional 18 h. The reaction was quenched by the slow addition of brine and was extracted with Et<sub>2</sub>O (x3). The combined organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The residue was purified by column chromatography (SiO<sub>2</sub>, 10% EtOAc/hexanes) to give alkene **15** as colorless oil (4.69 g, 98%). TLC: R<sub>f</sub> = 0.82 (10% EtOAc/hexanes); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.28 (d, *J* = 8.5 Hz, 2H), 6.93 (d, *J* = 8.5 Hz, 2H), 5.39 (m, 1H), 4.44 (s, 2H), 3.98 (d, *J* = 6.8 Hz, 2H), 3.81 (s, 3H), 1.76 (s, 3H), 1.66 (s, 3H).



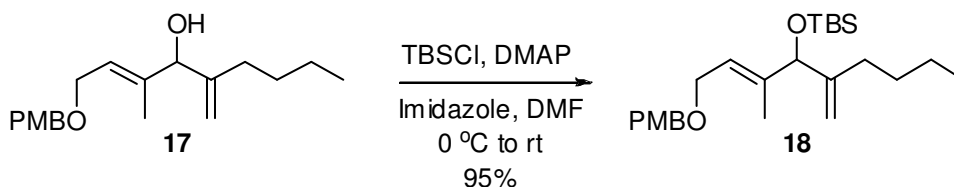
**Aldehyde 16.**<sup>5</sup> SeO<sub>2</sub> (156 mg, 1.48 mmol, 0.5 eq.) and *t*-BuOOH (1.02 mL of 5-6 M solution in decane, 5.63 mmol, 2 eq.) were dissolved in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) and the resulting solution was cooled to -15 °C and stirred for 30 min. The alkene **15** (581 mg, 2.81 mmol, 1 eq.) in CH<sub>2</sub>Cl<sub>2</sub> (3 mL) was added to the solution over a period of 10 min. The resulting reaction mixture was stirred at room temperature for 36 h and then portioned with brine. The aqueous layer was re-extracted with CH<sub>2</sub>Cl<sub>2</sub> (x3). The combined organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The residue was purified by column chromatography (SiO<sub>2</sub>, 20% EtOAc/hexanes) to give aldehyde **16** as a colorless oil (0.235 g, 38%). TLC: R<sub>f</sub> = 0.53 (30% EtOAc/hexanes); IR (neat, NaCl): 2996, 2934, 2837, 1689, 1653, 1613 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 9.43 (s, 1H), 7.28 (d, *J* = 8.7 Hz, 2H), 6.9 (d, *J* = 8.7 Hz, 2H), 6.59 (m, 1H), 4.51 (s, 2H), 4.32 (d, *J* = 5.6 Hz, 2H), 3.80 (s, 3H), 1.72 (d, *J* = 1.1 Hz, 3H). 20-30% of the *Z*-isomer was also isolated.



**Alkenol 17.** To a solution of CrCl<sub>2</sub> (515 mg, 4.19 mmol, 4 eq.) and NiCl<sub>2</sub> (2 mg, 0.02 mmol, 2 mol%) in DMF (10 mL) was added the vinyl iodide<sup>6</sup> (440 mg, 2.097 mmol, 2 eq.) dissolved in DMF (5 mL) and the resulting mixture was stirred for 15-20 min at room temperature. The aldehyde **16** (231 mg, 1.04 mmol, 1 eq.) dissolved in DMF (5 mL) was added to the above solution and the reaction mixture was stirred for an additional 2.5 h at room temperature. Reaction progress was monitored by TLC analysis. The reaction mixture was quenched

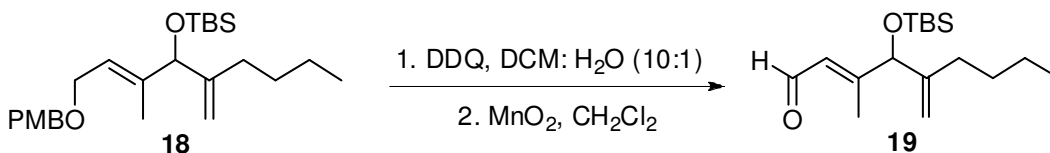


with saturated aqueous  $\text{NH}_4\text{Cl}$  solution and extracted with  $\text{CH}_2\text{Cl}_2$  (x3). The combined organic extracts were dried over anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. The residue was purified by column chromatography ( $\text{SiO}_2$ , 30% EtOAc/hexanes) to give alkenol **17** as a colorless liquid (0.533 g, 75%). TLC:  $R_f = 0.32$  (20% EtOAc/hexanes); IR (neat, NaCl): 3429, 2956, 2930, 2859, 1646, 1613  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.27 (d,  $J = 8.6$  Hz, 2H), 6.88 (d,  $J = 8.6$  Hz, 2H), 5.74 (t,  $J = 6.3$  Hz, 1H), 5.14 (s, 1H), 4.95 (s, 1H), 4.48 (s, 1H), 4.45 (s, 2H), 4.08 (d,  $J = 6.4$  Hz, 2H), 3.81 (s, 3H), 1.92 (m, 2H), 1.54 (s, 3H), 1.43 (m, 2H), 1.30 (m, 2H), 0.90 (t,  $J = 7.1$  Hz, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ) 159.4, 149.2, 139.4, 130.6, 129.6, 124.2, 114.0, 110.1, 79.8, 72.0, 66.3, 55.5, 31.8, 30.2, 22.7, 14.2, 12.1; HRMS (FAB,  $\text{MNa}^+$ ) calculated for  $\text{C}_{19}\text{H}_{28}\text{O}_3\text{Na}$  327.1936. Found 327.1937.



**TBS-protected alkenol 18.** A solution of alkenol **17** (89 mg, 0.29 mmol, 1 eq.) in DMF (0.3 mL) was cooled to 0 °C and imidazole (220 mg, 1.46 mmol, 5 eq.), DMAP (7 mg, 0.05 mmol, 20 mol%) and TBSCl (49 mg, 0.73 mmol, 2.5 eq.) were added. The reaction mixture was warmed to room temperature and was stirred overnight. Reaction progress was monitored by TLC analysis. After the reaction was complete, the reaction mixture was cooled to 0 °C, quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  solution and extracted with  $\text{CH}_2\text{Cl}_2$  (x3). The combined organic extracts were dried over anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated under reduced

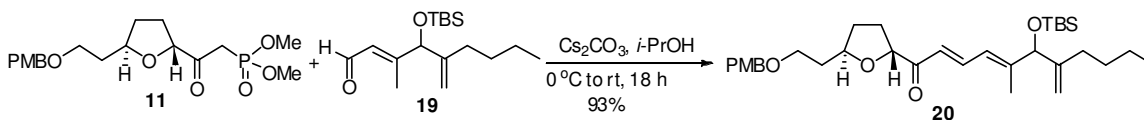
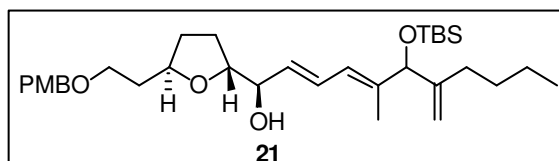
pressure. The residue was purified by column chromatography (SiO<sub>2</sub>, 10% Et<sub>2</sub>O/hexanes) to give the pure TBS ether **18** as colorless oil (0.110 g, 95%). TLC: R<sub>f</sub> = 0.66 (10% Et<sub>2</sub>O/hexanes); IR (neat, NaCl): 2956, 2930, 2857, 1613 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.27 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 5.66 (m, 1H), 5.13 (s, 1H), 4.87 (s, 1H), 4.43 (s, 2H), 4.42 (s, 1H), 4.07 (d, *J* = 6.5 Hz, 2H), 3.81 (s, 3H), 1.87 (m, 2H), 1.48 (s, 3H), 1.41 (m, 2H), 1.32 (m, 2H), 0.91 (m, 9H), 0.90 (t, *J* = 7.1 Hz, 3H), 0.04 (m, 6H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) 159.3, 149.6, 140.1, 130.8, 129.6, 123.1, 114.0, 110.0, 80.7, 71.6, 66.4, 55.5, 31.1, 30.3, 26.0, 22.8, 18.5, 14.3, 11.8, -4.7, -4.8; HRMS (FAB, MNa<sup>+</sup>) calculated for C<sub>25</sub>H<sub>42</sub>O<sub>3</sub>SiNa 441.2800. Found 441.2805.



**Side chain aldehyde 19.** To a solution of TBS-protected alkenol **18** (324 mg, 0.770 mmol, 1 eq.) in CH<sub>2</sub>Cl<sub>2</sub> (8 mL) and H<sub>2</sub>O (0.8 mL) was added DDQ (263 mg, 1.16 mmol, 1.5 eq.). The resulting reaction mixture was stirred at room temperature for 50 min. The reaction was quenched with a saturated solution of NaHCO<sub>3</sub> and the layers were separated. The aqueous layer was re-extracted with CH<sub>2</sub>Cl<sub>2</sub> (x3). The combined organic extracts were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude product then was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (8 mL) and MnO<sub>2</sub> (1.39 g, 20 eq.) was added. The reaction mixture was stirred at room temperature for 1.5 h and then the solids were

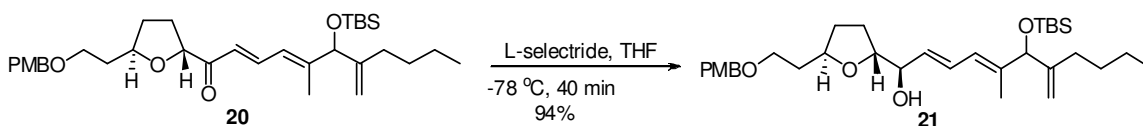
removed by filtration through a short plug of celite. The solvent was evaporated under reduced pressure to give the aldehyde **19** (0.213 g, 93%) as a mixture of E:Z (9:1) isomers. Separation using column chromatography (SiO<sub>2</sub>, 30:1 Et<sub>2</sub>O/hexanes) gave the pure aldehyde **19** in 70% isolated yield. R<sub>f</sub> = 0.82 (10% EtOAc/hexanes); IR (neat, NaCl): 2957, 2930, 2858, 1680, 1637, 1611 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 10.05 (d, *J* = 8.1 Hz, 1H), 6.19 (dt, *J* = 8.1, 1.0 Hz, 1H), 5.15 (s, 1H), 4.97 (m, 1H), 4.51 (s, 1H), 2.08 (s, 3H), 1.92 (m, 1H), 1.77 (m, 1H), 1.42 (m, 2H), 1.28 (m, 2H), 0.90 (m, 9H), 0.89 (t, *J* = 7.1 Hz, 3H), 0.04 (s, 6H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 191.1, 162.9, 148.3, 126.5, 112.4, 80.8, 30.1, 30.0, 25.9, 22.7, 18.5, 14.2, 13.3, -4.8, -4.9; HRMS (FAB) calculated for C<sub>17</sub>H<sub>32</sub>O<sub>2</sub>SiNa 319.2069. Found 319.2071.

### Synthesis of the C(18)-C(34) unit of amphidinolide C **21**.



**1,3-Dienone 20.** To a solution of  $\beta$ -ketophosphonate **11** (15 mg, 39  $\mu$ mol, 1 eq.) in *i*-PrOH (0.1 mL) at 0 °C was added Cs<sub>2</sub>CO<sub>3</sub> (12 mg, 38.82  $\mu$ mol, 1 eq.). The resulting mixture was stirred for 2 h at 0 °C, then a solution of aldehyde **19** (11 mg, 39  $\mu$ mol, 1 eq.) in *i*-PrOH (0.15 mL) was added drop wise. The resulting mixture was warmed to room temperature and was stirred for 18 h. The reaction

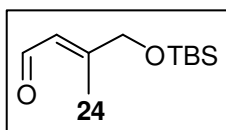
was monitored by TLC. After the reaction was complete, it was quenched with 5% aqueous citric acid solution and the layers were separated. The aqueous layer was re-extracted with CH<sub>2</sub>Cl<sub>2</sub> (x3), and the combined organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The residue was purified by column chromatography (SiO<sub>2</sub>, 20% EtOAc/hexanes) to give the dienone **20** as colorless oil (20 mg, 93%). TLC: R<sub>f</sub> = 0.62 (20% EtOAc/hexanes); IR (neat, NaCl): 2955, 2930, 2857, 1682, 1615 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.64 (dd, *J* = 15.1 Hz, 11.7 Hz, 1H), 7.27 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 6.51 (dd, *J* = 15.2 Hz, 4.8 Hz, 1H), 6.32 (d, *J* = 11.6 Hz, 1H), 5.12 (s, 1H), 4.90 (s, 1H), 4.54 (m, 1H), 4.48 (s, 1H), 4.45 (ABq, *J* = 11.5 Hz, Δ*v* = 0.036 ppm, 2H), 4.23 (m, 1H), 3.80 (s, 3H), 3.59 (t, *J* = 6.5 Hz, 2H), 2.27 (m, 1H), 2.04 (m, 1H), 1.97 (m, 2H), 1.91 (m, 1H), 1.82 (m, 1H), 1.77 (s, 3H), 1.60 (m, 2H), 1.38 (m, 2H), 1.29 (m, 2H), 0.90 (m, 9H), 0.88 (t, *J* = 7.1 Hz, 3H), 0.04 (m, 6H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) 201.7, 159.4, 151.8, 149.1, 140.1, 130.7, 129.5, 124.0, 124.0, 114.0, 111.1, 82.7, 81.0, 78.5, 73.0, 67.5, 55.5, 35.9, 31.8, 30.5, 30.2, 29.8, 26.0, 22.7, 18.5, 14.2, 13.4, -4.8, -4.9; HRMS (FAB, MNa<sup>+</sup>) calculated for C<sub>33</sub>H<sub>52</sub>O<sub>5</sub>SiNa 579.3482. Found 579.3474.

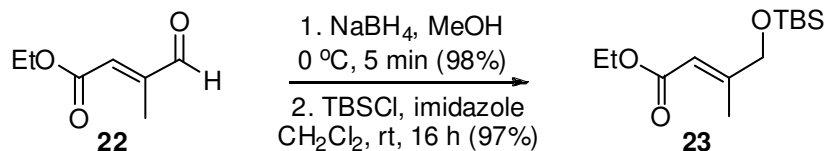


**C(18)-C(34) unit of amphidinolide C 21.** A solution of 1,3-dienone **20** (16 mg, 29 μmol, 1 eq.) in THF (0.7 mL) was cooled to -78 °C and L-selectride (1 M in THF, 57 μL, 57 μmol, 2 eq.) was added. The resulting reaction mixture was

stirred for 40 min at  $-78\text{ }^{\circ}\text{C}$ . The reaction progress was monitored by TLC analysis. After the reaction was complete, it was quenched by the addition of 3N NaOH (2 mL) and  $\text{H}_2\text{O}_2$  (4 mL) at  $0\text{ }^{\circ}\text{C}$  and stirring was continued for an additional 30 min. The reaction mixture was partitioned with water and the layers were separated. The aqueous layer was re-extracted with  $\text{CH}_2\text{Cl}_2$  (x3) and the combined organic extracts were dried over anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. The residue was purified by column chromatography ( $\text{SiO}_2$ , 20% EtOAc/hexanes) to give dienol **21** as colorless oil (15 mg, 94%). TLC:  $R_f = 0.44$  (20% EtOAc/hexanes); IR (neat, NaCl): 3431, 2955, 2928, 2857, 1612  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.26 (d,  $J = 8.5$  Hz, 2H), 6.88 (d,  $J = 8.5$  Hz, 2H), 6.54 (dd,  $J = 15$  Hz, 11 Hz, 1H), 6.07 (d,  $J = 11$  Hz, 1H), 5.58 (dd,  $J = 15$  Hz, 6.9 Hz, 1H), 5.20 (s, 1H), 4.85 (s, 1H), 4.44 (s, 2H), 4.37 (s, 1H), 4.10 (m, 1H), 3.96 (m, 1H), 3.87 (q,  $J = 7.2$  Hz, 1H), 3.81 (s, 3H), 3.55 (t,  $J = 6.2$  Hz, 2H), 2.69 (brd, 1H), 2.05 (m, 1H), 1.97 (m, 1H), 1.88 (m, 2H), 1.79 (m, 2H), 1.65 (m, 1H), 1.60 (s, 3H), 1.56 (m, 1H), 1.38 (m, 2H), 1.29 (m, 2H), 0.89 (s, 9H), 0.88 (t,  $J = 7.2$  Hz, 3H), 0.02 (s, 3H), 0.01 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ) 159.4, 149.8, 139.9, 130.7, 130.5, 129.5, 129.1, 124.9, 114.0, 110.0, 82.0, 80.8, 76.8, 75.8, 72.9, 67.4, 55.5, 35.9, 32.5, 30.9, 30.2, 28.3, 26.0, 22.8, 18.5, 14.3, 12.3, -4.8, -4.8; HRMS (FAB,  $\text{MNa}^+$ ) calculated for  $\text{C}_{33}\text{H}_{54}\text{O}_5\text{SiNa}$  581.3638. Found 581.3631.

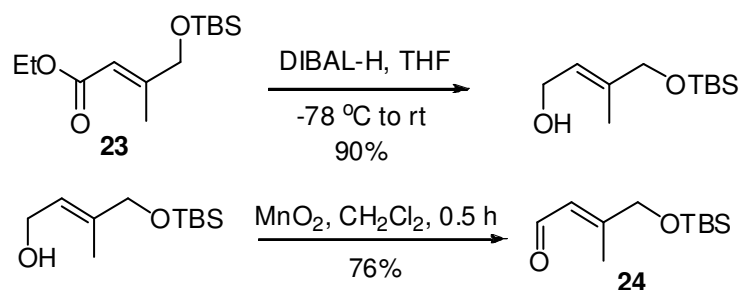
#### Synthesis of the side chain aldehyde of synthetic analog **24**.





**TBS-protected ester 23.** To a solution of aldehyde **22** (1.91 mL, 14.0 mmol, 1 eq.) in MeOH (20 mL) at 0 °C was added NaBH<sub>4</sub> (0.532 g, 14.0 mmol, 1 eq.). The reaction mixture was stirred for 10 min and then quenched by the addition of H<sub>2</sub>O. The aqueous mixture was extracted with Et<sub>2</sub>O (x3), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to furnish the product as colorless liquid (1.97 g, 98%). TLC: R<sub>f</sub> = 0.58 (50% EtOAc/hexanes). The product was used in the next reaction without further purification

To the crude reduction product (2.66g, 18.5 mmol, 1 eq.) in CH<sub>2</sub>Cl<sub>2</sub> (90 mL) was added TBSCl (4.17 g, 27.7 mmol, 1.5 eq.) followed by imidazole (3.14 g, 46.1 mmol, 2.5 eq.) under argon. The reaction mixture was stirred for 16 h and was quenched with saturated NH<sub>4</sub>Cl solution. The layers were separated and the aqueous layer was re-extracted with CH<sub>2</sub>Cl<sub>2</sub> (x3). The combined organic extracts were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The residue was purified by column chromatography (SiO<sub>2</sub>, 30% EtOAc/hexanes) to give the TBS ether **23** as a colorless liquid (4.62 g, 97%). TLC: R<sub>f</sub> = 0.66 (5% EtOAc/hexanes); IR (neat, NaCl): 2956, 2931, 2899, 2856, 1717, 1662 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 5.98 (d, *J* = 0.8 Hz, 1H), 4.16 Hz (q, *J* = 7.1 Hz, 2H), 4.10 (d, *J* = 0.6 Hz, 2H), 2.04 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H), 0.92 (s, 9H), 0.08 (s, 6H).

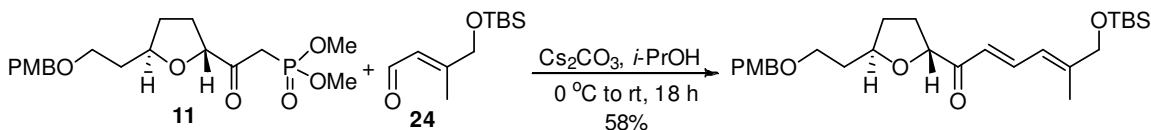
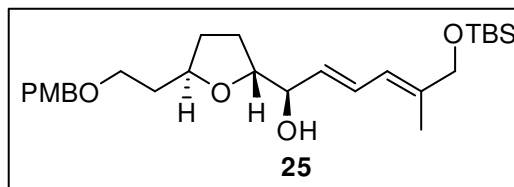


**TBS-protected Aldehyde 24.** To a solution of TBS-protected ester **23** (1.00 g, 3.86 mmol, 1 eq.) in THF (2.6 mL) at -78 °C was added DIBAL-H (1 M in hexane, 15.47 mL, 15.47 mmol, 4 eq.). The reaction mixture was stirred at -78 °C for 30 min and at 0 °C for 2.5 h, and then it was cooled to -78 °C and quenched with MeOH (3 mL), followed by saturated Rochelle's salt solution (20 mL), EtOAc (20 mL) and Et<sub>2</sub>O (20 mL). The mixture was stirred for 5-6 h till 2 layers separated out. The aqueous layer was re-extracted with Et<sub>2</sub>O (x2) and finally with EtOAc (x1). The combined organic extracts were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The residue was purified by column chromatography (SiO<sub>2</sub>, 30% EtOAc/hexanes) to give the alcohol as colorless liquid (0.75 g, 90%). TLC: R<sub>f</sub> = 0.62 (30% EtOAc/hexanes); IR (neat, NaCl): 3313, 2956, 2929, 2886, 2857 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 5.69 (m, 1H), 4.22 (t, *J* = 5.1 Hz, 2H), 4.04 (s, 3H), 1.65 (d, *J* = 0.4 Hz, 3H), 1.22 (br, 1H), 0.92 (s, 9H), 0.08 (s, 6H).

To a solution of alcohol (100 mg, 0.46 mmol, 1 eq.) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) was added MnO<sub>2</sub> (1.0 g, 12 mmol, 25 eq.). The reaction mixture was stirred at rt. for 1 h and then the solids were removed by filtration through a pad of celite to and the solvent was evaporated under reduced pressure to give the aldehyde **24** (75 mg, 76%) as colorless oil. TLC: R<sub>f</sub> = 0.67 (20% EtOAc/hexanes); IR (neat, NaCl):

2956, 2930, 2857, 1683 $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  10.07 (d,  $J = 8.1$  Hz, 1H), 6.21 (dq,  $J = 8.1, 1.4$  Hz, 1H), 4.18 (d,  $J = 0.9$  Hz, 2H), 2.08 (s, 3H), 0.92 (s, 9H), 0.09 (s, 6H).

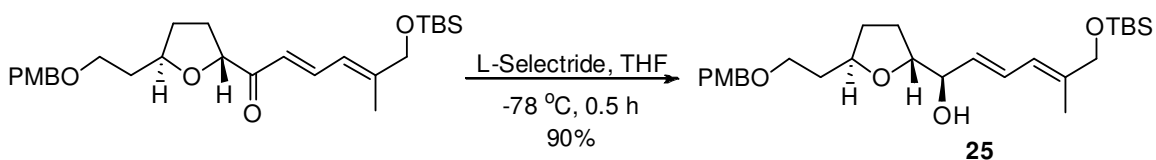
### Synthesis of the synthetic analog **25**.



**1,3-Dienone.** To a solution of  $\beta$ -ketophosphonate **11** (15 mg, 39  $\mu\text{mol}$ , 1 eq.) in *i*-PrOH (0.1 mL) at 0  $^\circ\text{C}$  was added  $\text{Cs}_2\text{CO}_3$  (12 mg, 39  $\mu\text{mol}$ , 1 eq.). The reaction mixture was stirred for 2h at 0  $^\circ\text{C}$  and a solution of aldehyde **24** (8 mg, 38.82  $\mu\text{mol}$ , 1 eq.) in *i*-PrOH (0.15 mL) was added drop wise. The resulting mixture was warmed to room temperature and was stirred for 18 h. The reaction progress was monitored by TLC analysis. After the reaction was complete, it was quenched with 5% aqueous citric acid solution and the layers were separated. The aqueous layer was re-extracted with  $\text{CH}_2\text{Cl}_2$  (x3), and the combined organic extracts were dried over anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. The residue was purified by column chromatography ( $\text{SiO}_2$ , 20% EtOAc/hexanes) to give the dienone as colorless oil (10 mg, 58%). TLC:  $R_f = 0.69$  (20% EtOAc/hexanes); IR (neat, NaCl): 2953, 2928, 2856, 1682, 1633, 1613  $\text{cm}^{-1}$ ;  $^1\text{H}$



NMR (500 MHz, CDCl<sub>3</sub>) δ 7.67 (dd, *J* = 15.1 Hz, 11.8 Hz, 1H), 7.26 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 6.49 (d, *J* = 15.2 Hz, 1H), 6.21 (d, *J* = 11.8 Hz, 1H), 4.54 (app t, *J* = 7.5 Hz, 1H), 4.45 (ABq, *J* = 11.5 Hz, Δ*v* = 0.035 ppm, 2H), 4.20 (m, 1H), 4.14 (s, 2H), 3.80 (s, 3H), 3.59 (t, *J* = 6.6 Hz, 2H), 2.26 (m, 1H), 2.03 (m, 1H), 1.96 (m, 2H), 1.85 (s, 3H), 1.82 (m, 1H), 1.55 (m, 1H), 0.93 (s, 9H), 0.08 (s, 6H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) 201.8, 159.4, 150.2, 139.8, 130.7, 129.5, 123.6, 121.8, 114.0, 82.7, 78.4, 73.0, 67.6, 67.5, 55.5, 35.9, 31.8, 29.8, 29.8, 26.1, 18.6, 14.8, -5.2; HRMS (FAB, MNa<sup>+</sup>) calculated for C<sub>27</sub>H<sub>42</sub>O<sub>5</sub>SiNa 497.299. Found 497.2691.



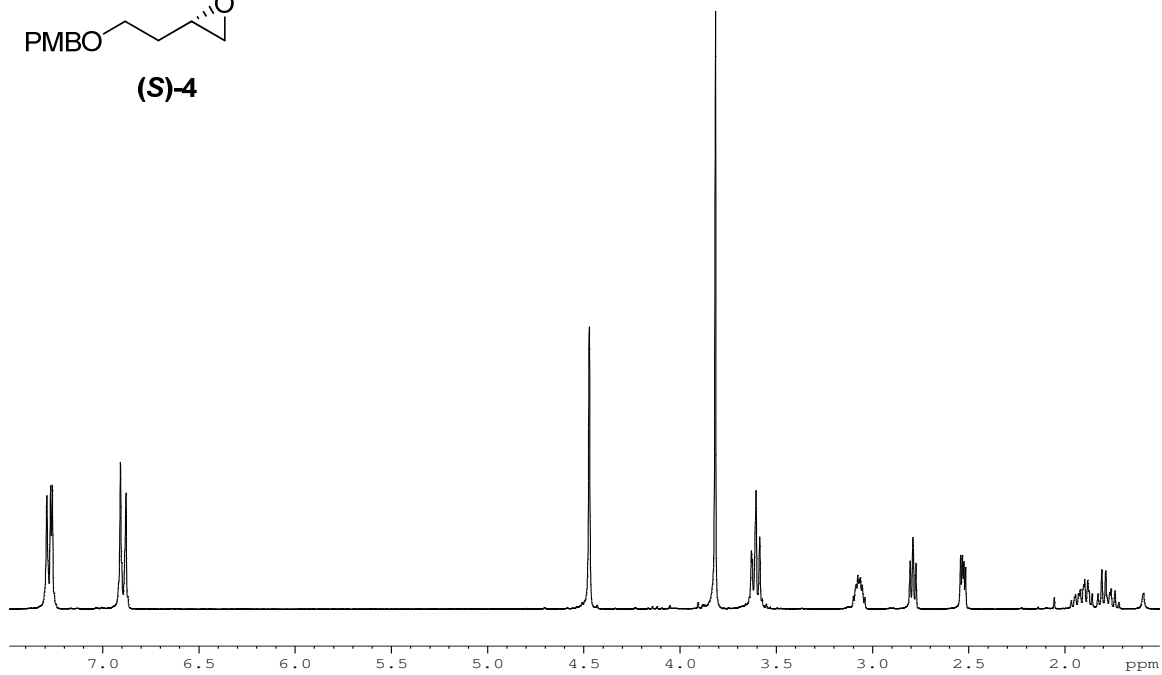
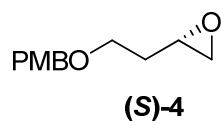
**Synthetic analog 25.** To a solution of 1,3-dienone (10 mg, 21 μmol, 1 eq.) in THF (0.5 mL) at -78 °C was added L-selectride (1 M in THF, 42 μL, 42 μmol, 2 eq.) and the resulting reaction mixture was stirred for 30 min at -78 °C. The reaction progress was monitored by TLC analysis. After the reaction was complete, it was quenched by the addition of 3N NaOH (2 mL) solution and H<sub>2</sub>O<sub>2</sub> (4 mL) at 0 °C and stirring was continued for an additional 30 min. The reaction mixture was partitioned with water and the layers were separated. The aqueous layer was re-extracted with CH<sub>2</sub>Cl<sub>2</sub> (x3) and the combined organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The residue was purified by column chromatography (SiO<sub>2</sub>, 20% EtOAc/hexanes) to give the dienol **25** as colorless oil (9 mg, 90%). TLC: R<sub>f</sub> = 0.15 (20% EtOAc/hexanes); IR

(neat, NaCl): 3444, 2955, 2928, 2856, 1613  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.26 (d,  $J = 8.5$  Hz, 2H), 6.88 (d,  $J = 8.5$  Hz, 2H), 6.56 (dd,  $J = 15.2, 10.9$  Hz, 1H), 6.07 (d,  $J = 10.9$  Hz, 1H), 5.53 (dd,  $J = 15.1, 6.7$  Hz, 1H), 4.44 (s, 2H), 4.10 (m, 1H), 4.07 (s, 2H), 3.97 (m, 1H), 3.85 (m, 1H), 3.81 (s, 3H), 3.55 (t,  $J = 6.1$  Hz, 2H), 2.57 (brd, 1H), 2.04 (m, 1H), 1.93 (m, 1H), 1.86 (m, 1H), 1.79 (m, 1H), 1.78 (s, 3H), 1.73 (s, 3H), 1.63 (m, 1H), 1.57 (m, 1H), 0.92 (s, 9H), 0.07 (s, 6H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ) 159.4, 138.4, 130.7, 130.4, 129.5, 128.8, 123.0, 114.0, 82.0, 76.8, 75.8, 72.9, 68.1, 67.5, 55.5, 35.9, 32.5, 28.2, 26.1, 18.6, 14.2, -5.1; HRMS (FAB,  $\text{MNa}^+$ ) calculated for  $\text{C}_{27}\text{H}_{44}\text{O}_5\text{SiNa}$  499.2855. Found 499.2845.

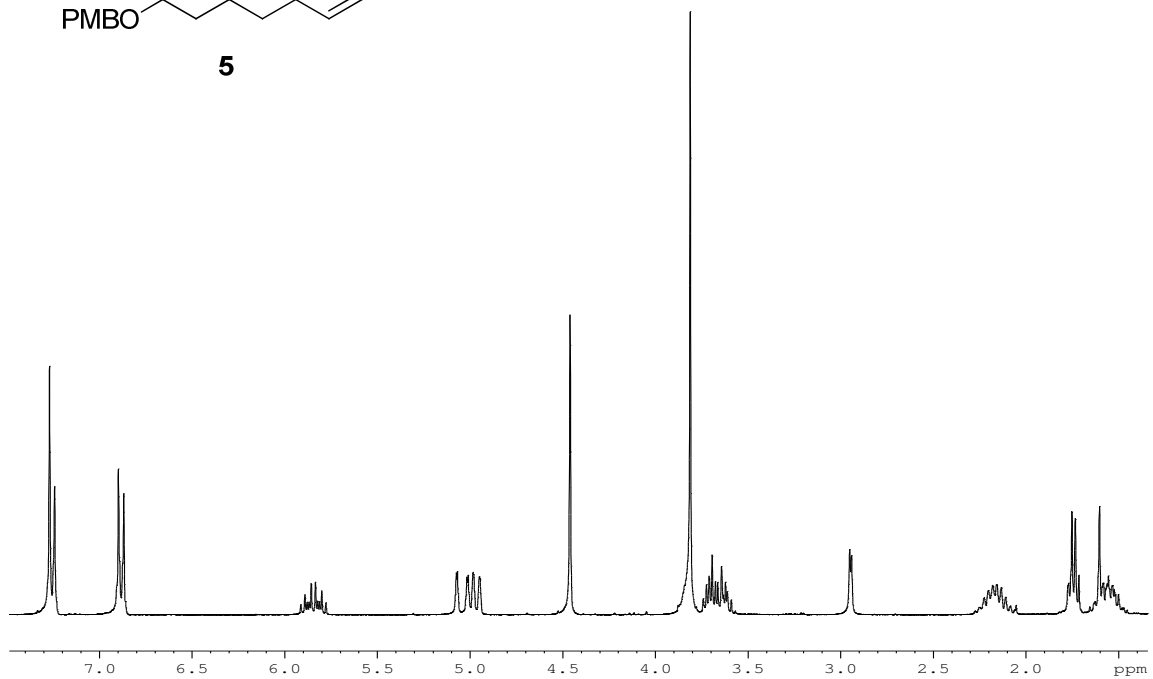
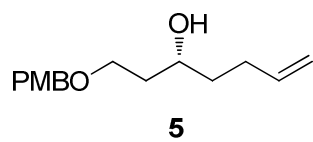
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<sup>1</sup>H NMR

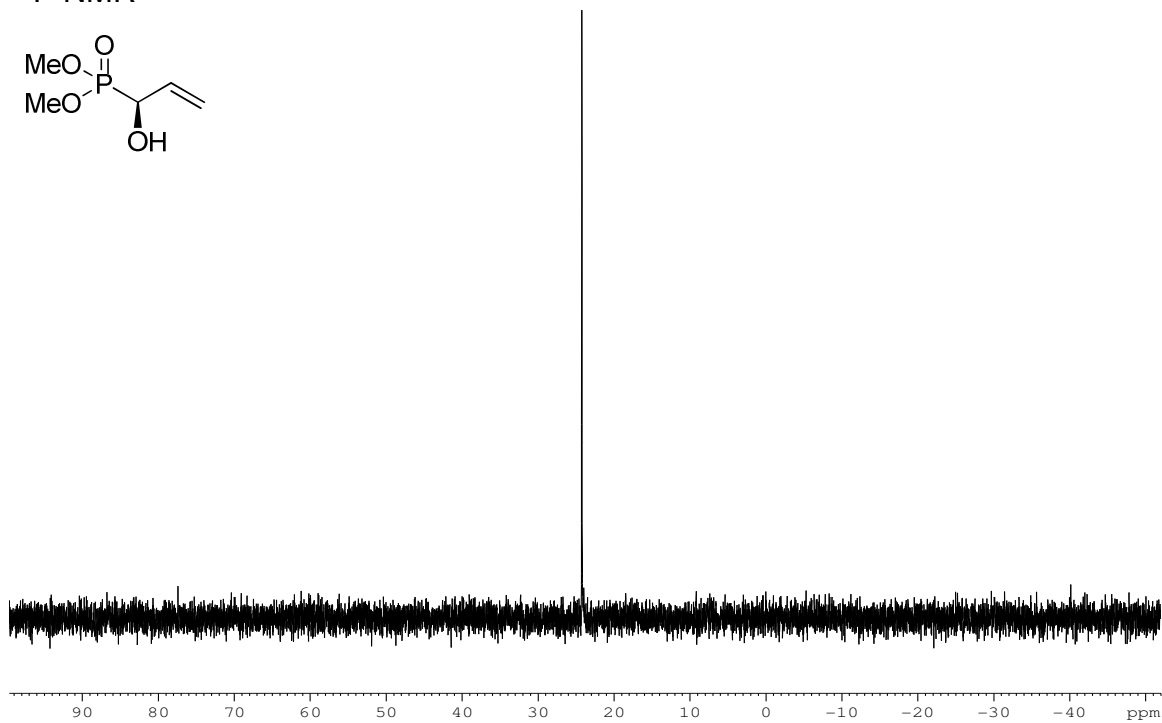
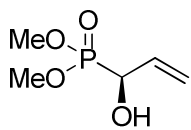


<sup>1</sup>H NMR

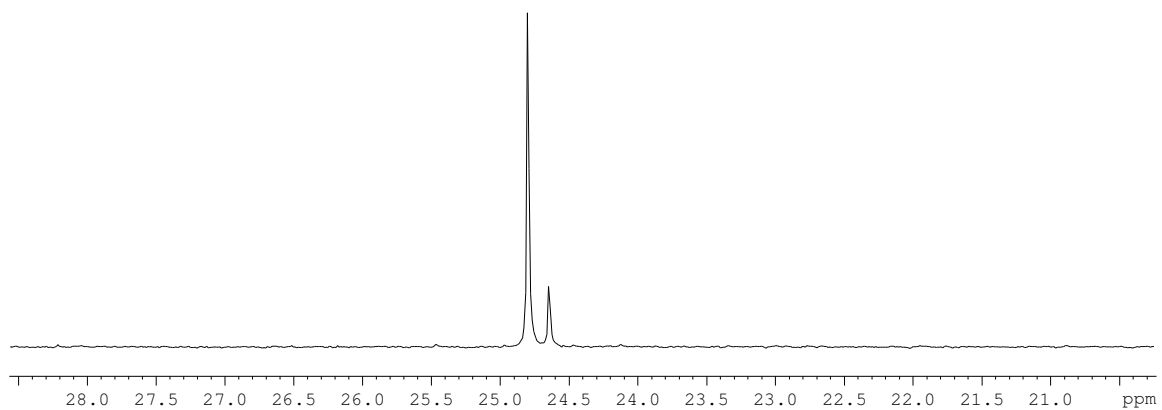
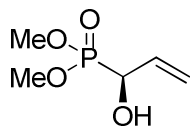


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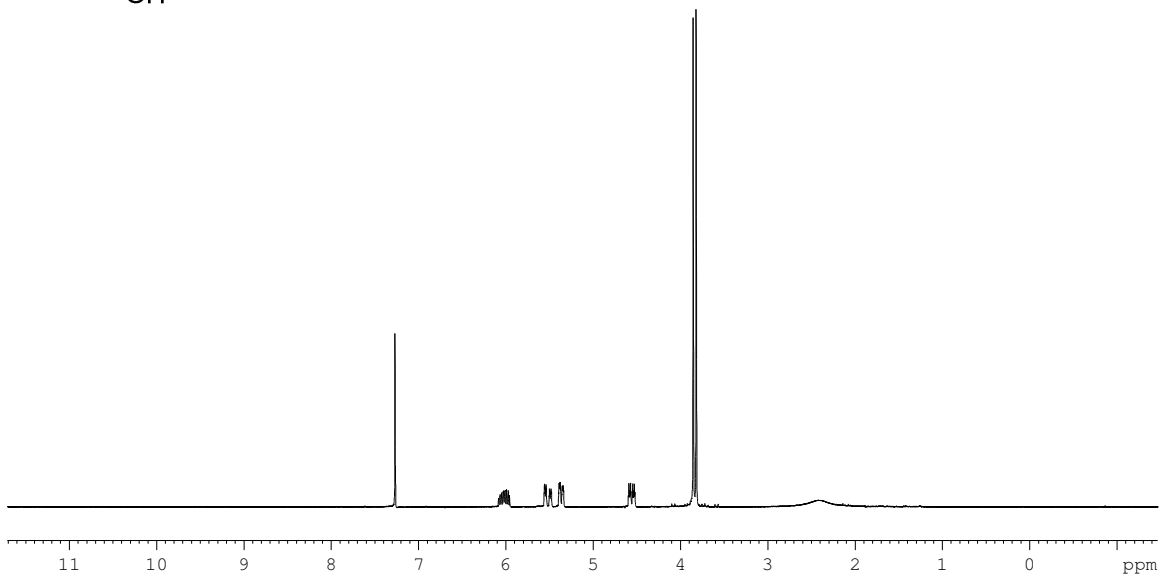
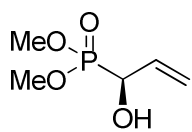
$^{31}\text{P}$  NMR



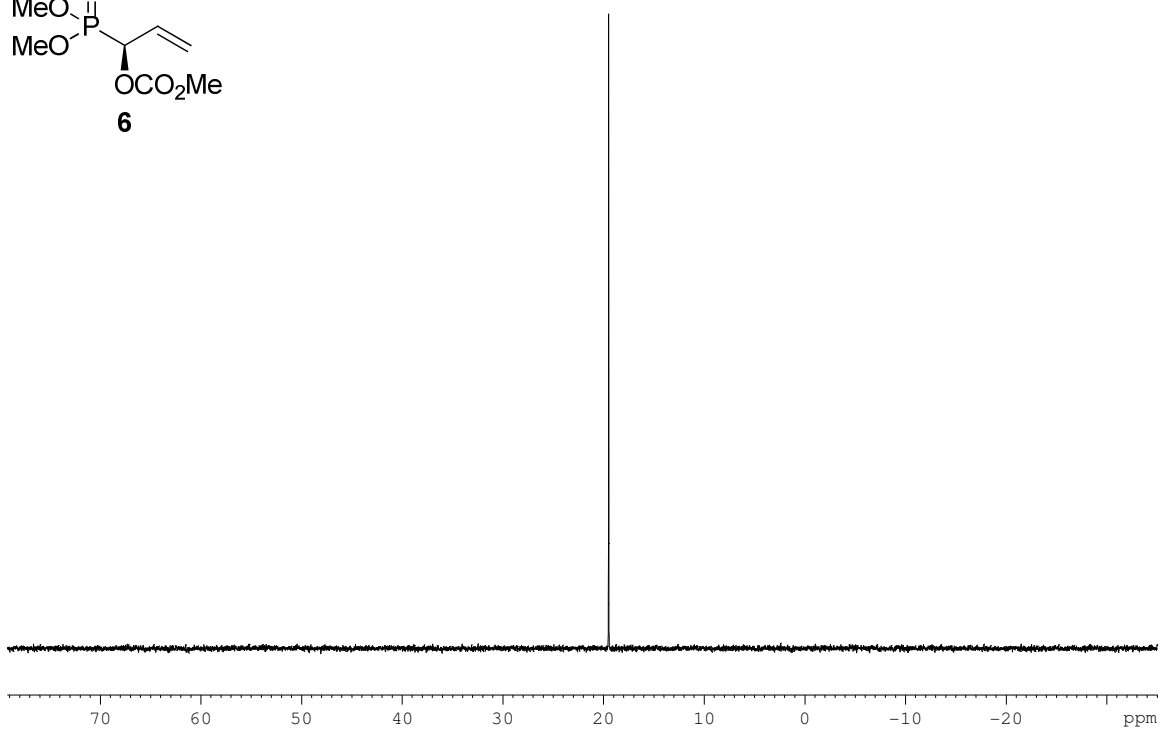
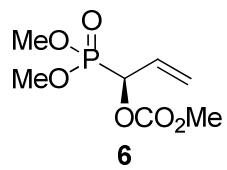
$^{31}\text{P}$  NMR, after addition quinine



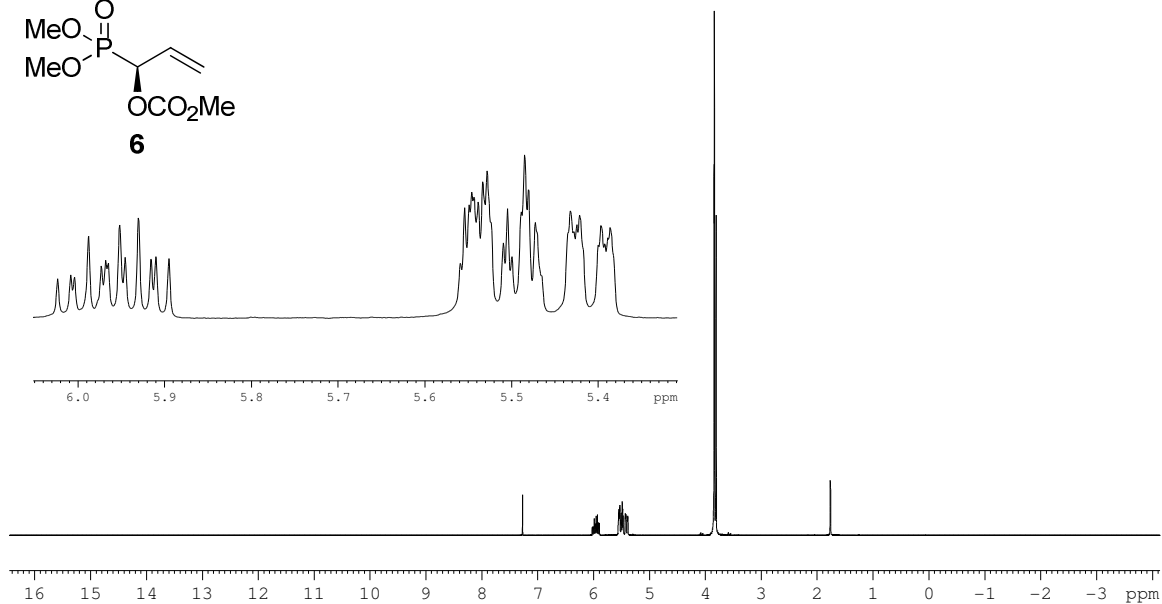
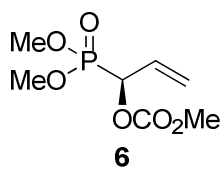
$^1\text{H}$  NMR



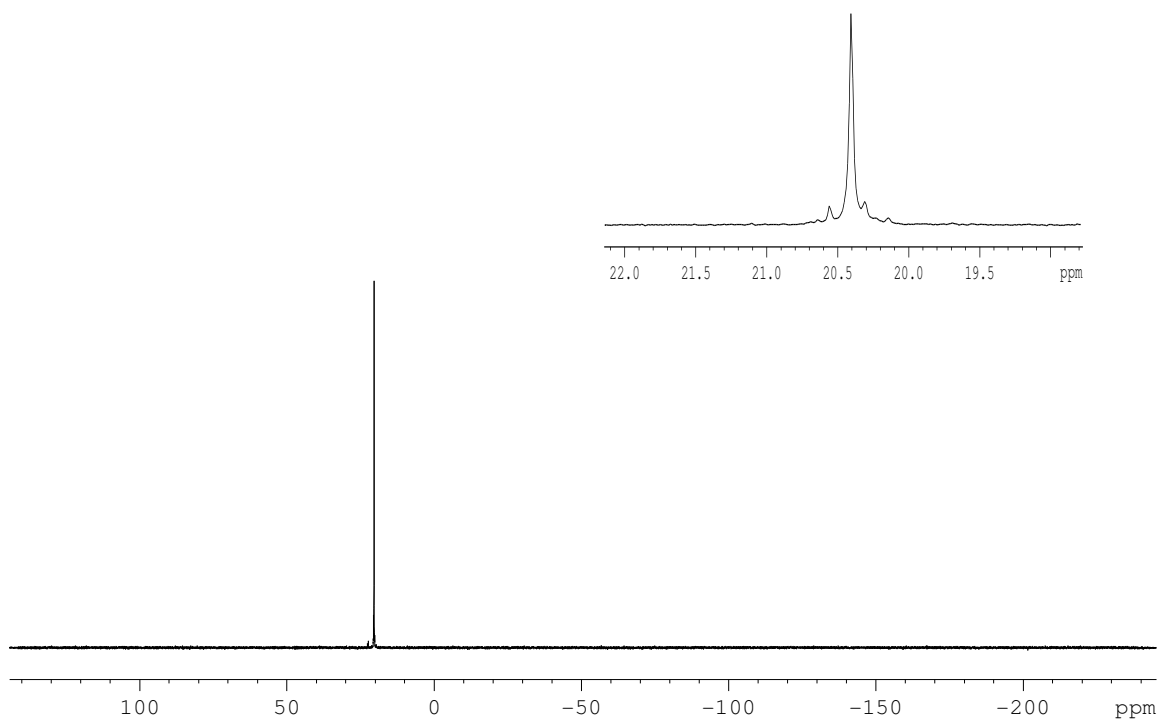
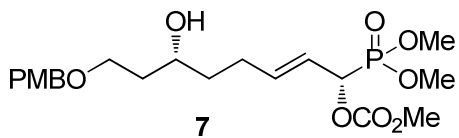
$^{31}\text{P}$  NMR



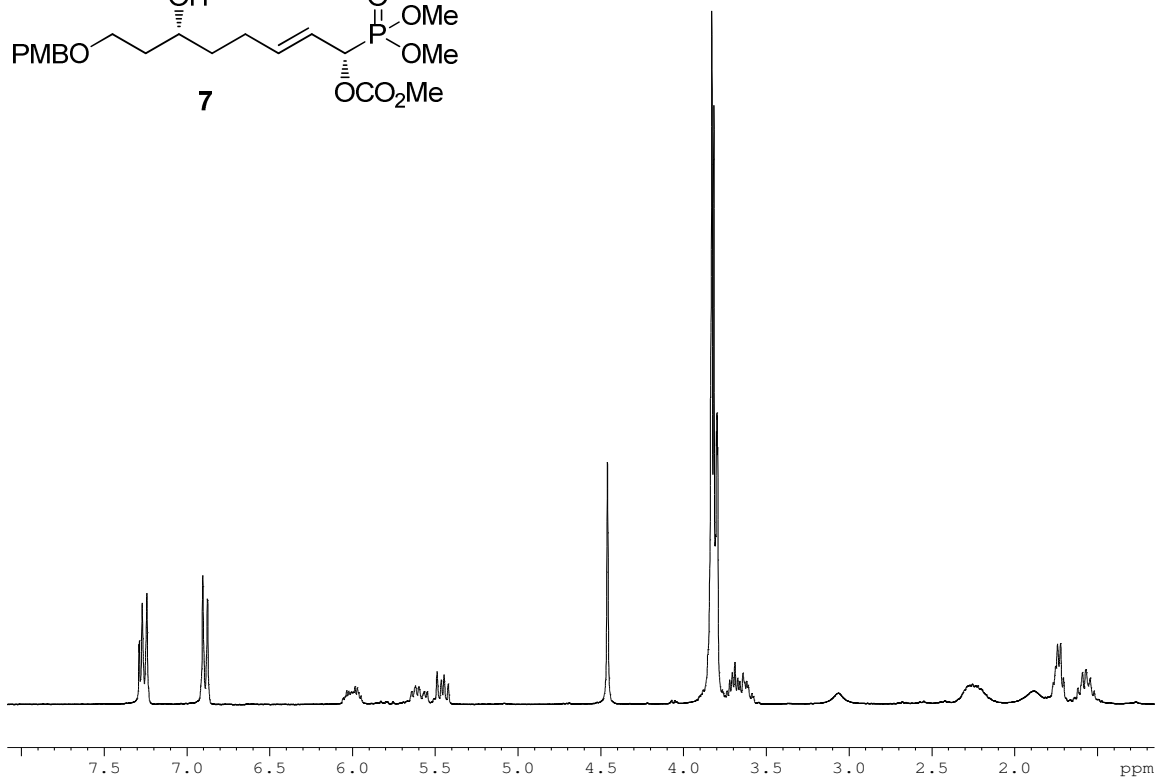
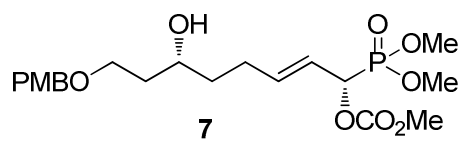
$^1\text{H}$  NMR



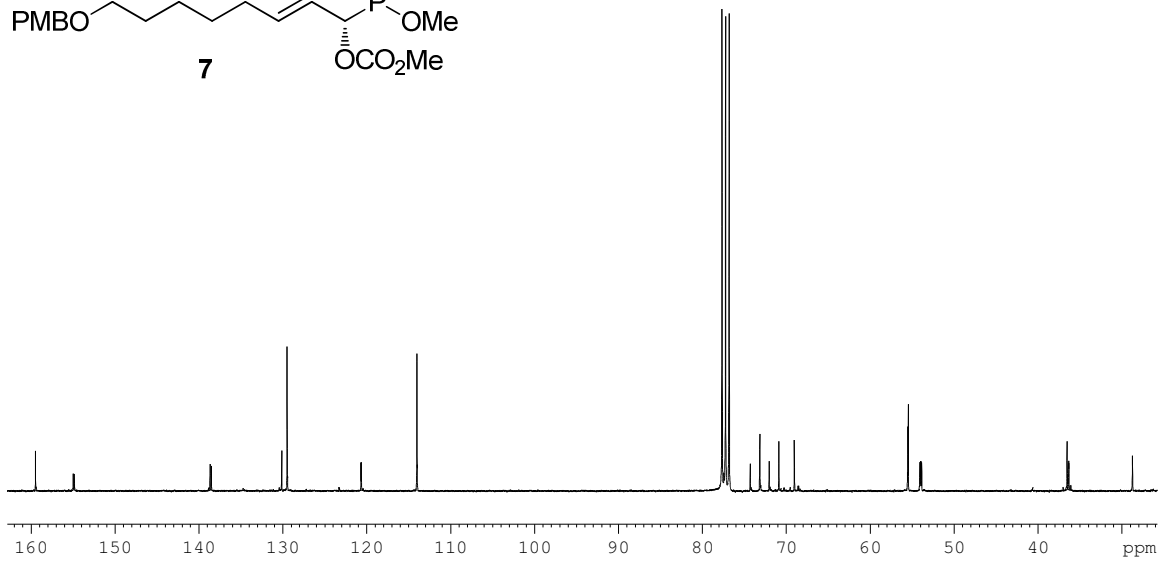
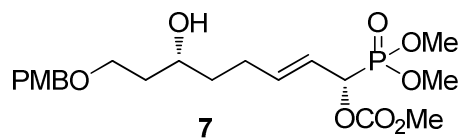
$^{31}\text{P}$  NMR



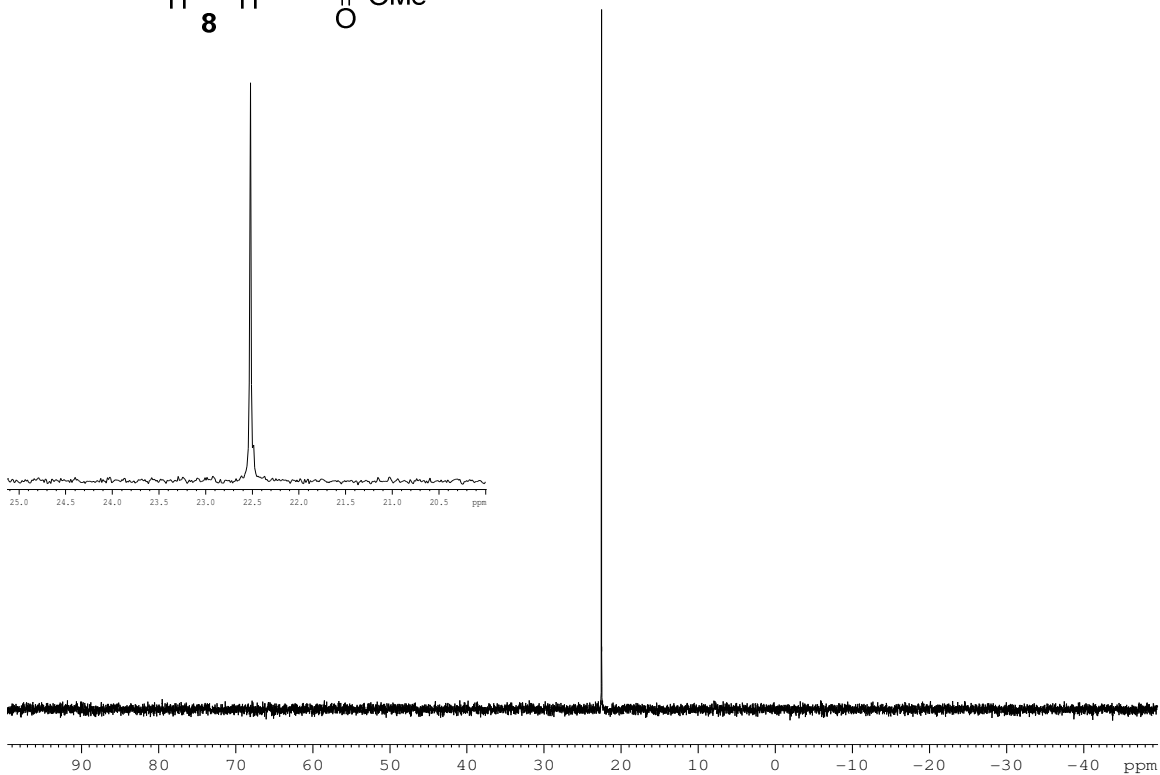
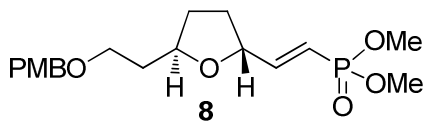
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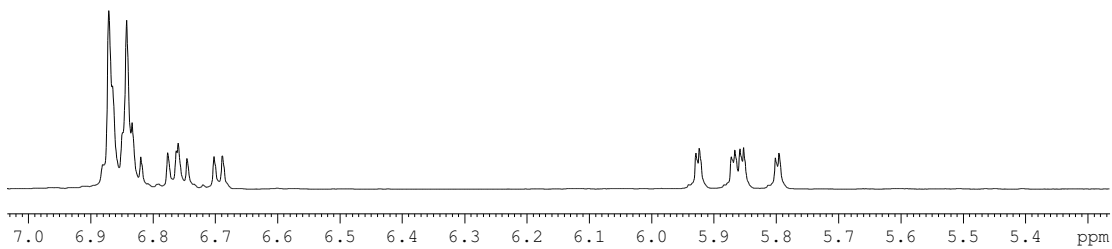
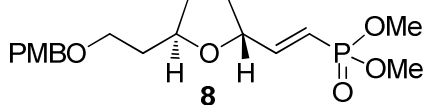
$^{13}\text{C}$  NMR



$^{31}\text{P}$  NMR

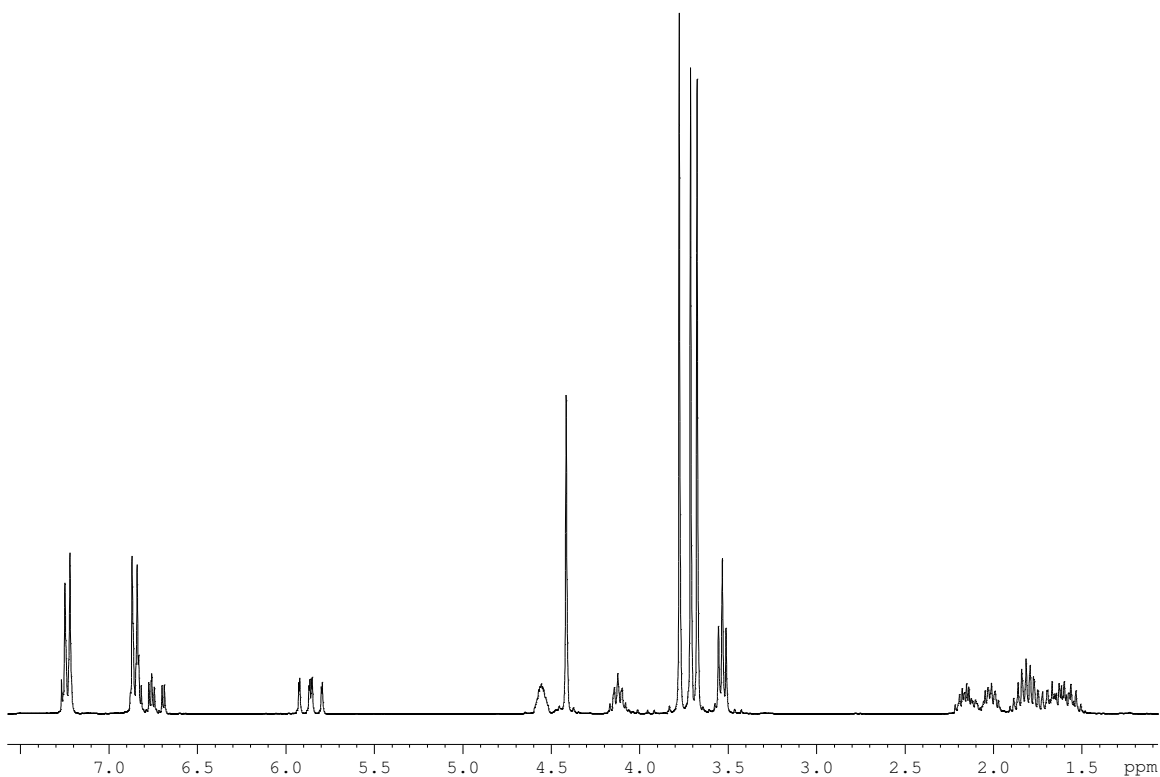


$^1\text{H}$  NMR

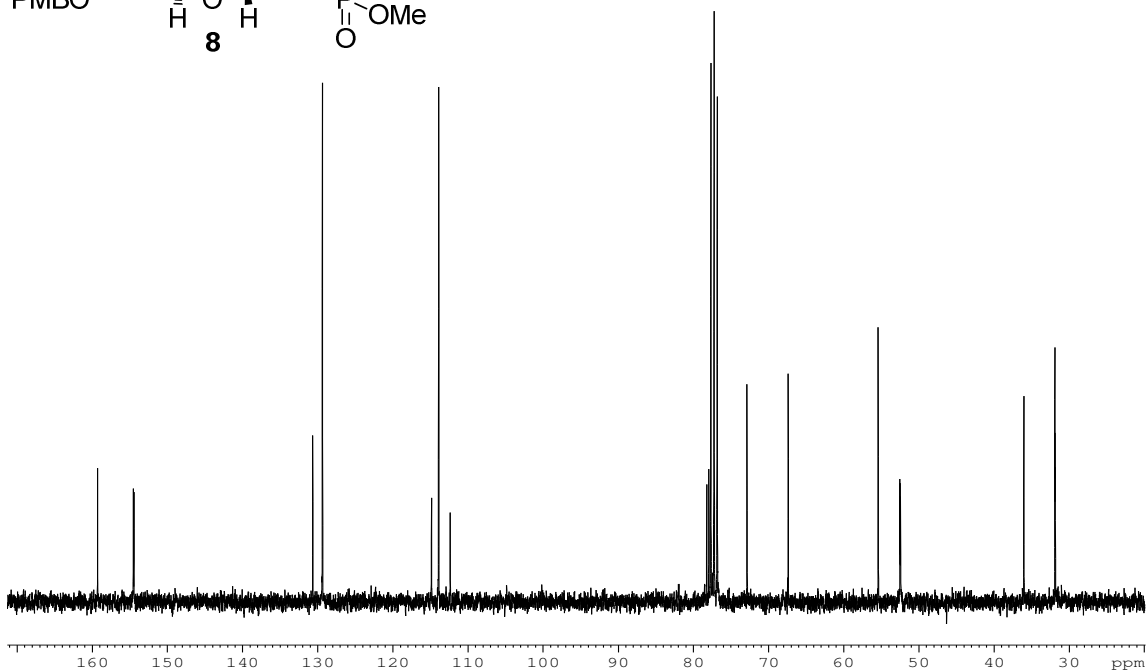
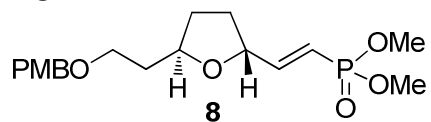




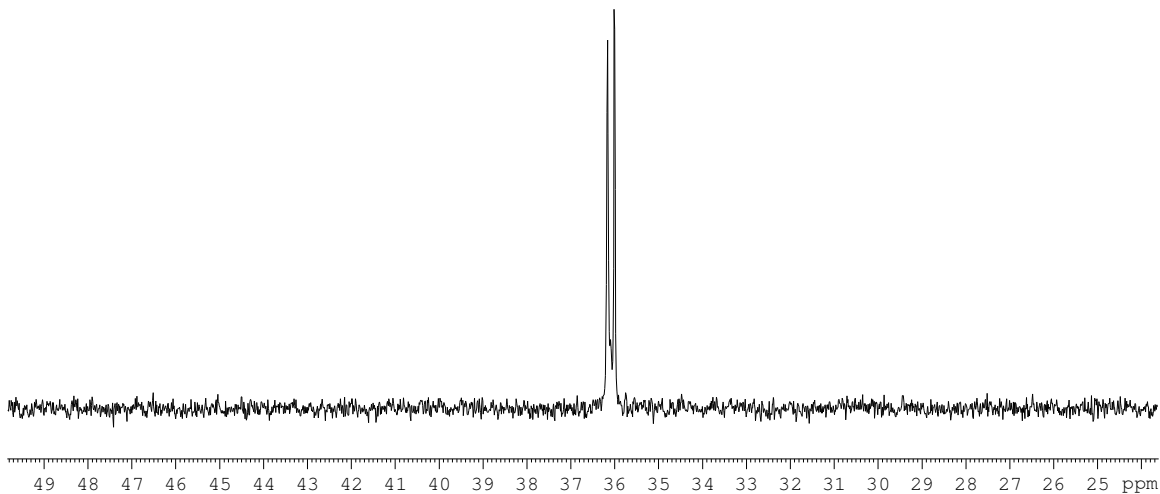
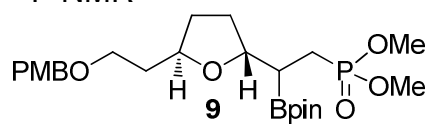
$^1\text{H}$  NMR (continued)



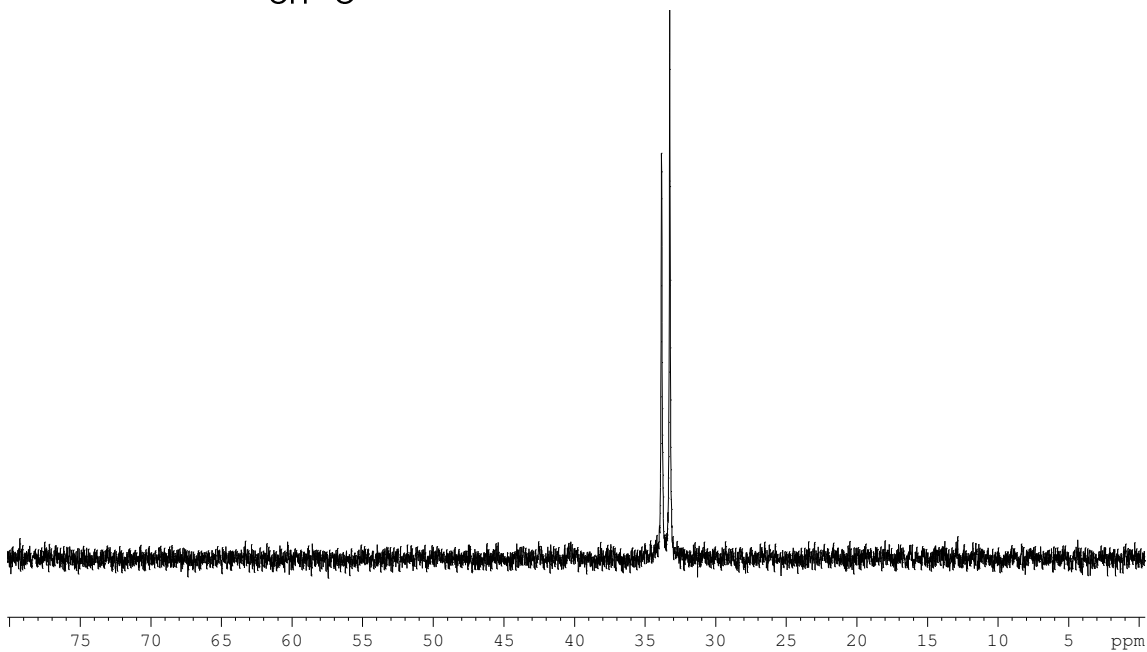
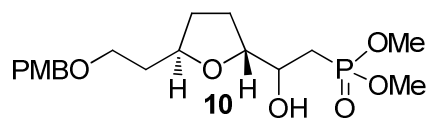
$^{13}\text{C}$  NMR



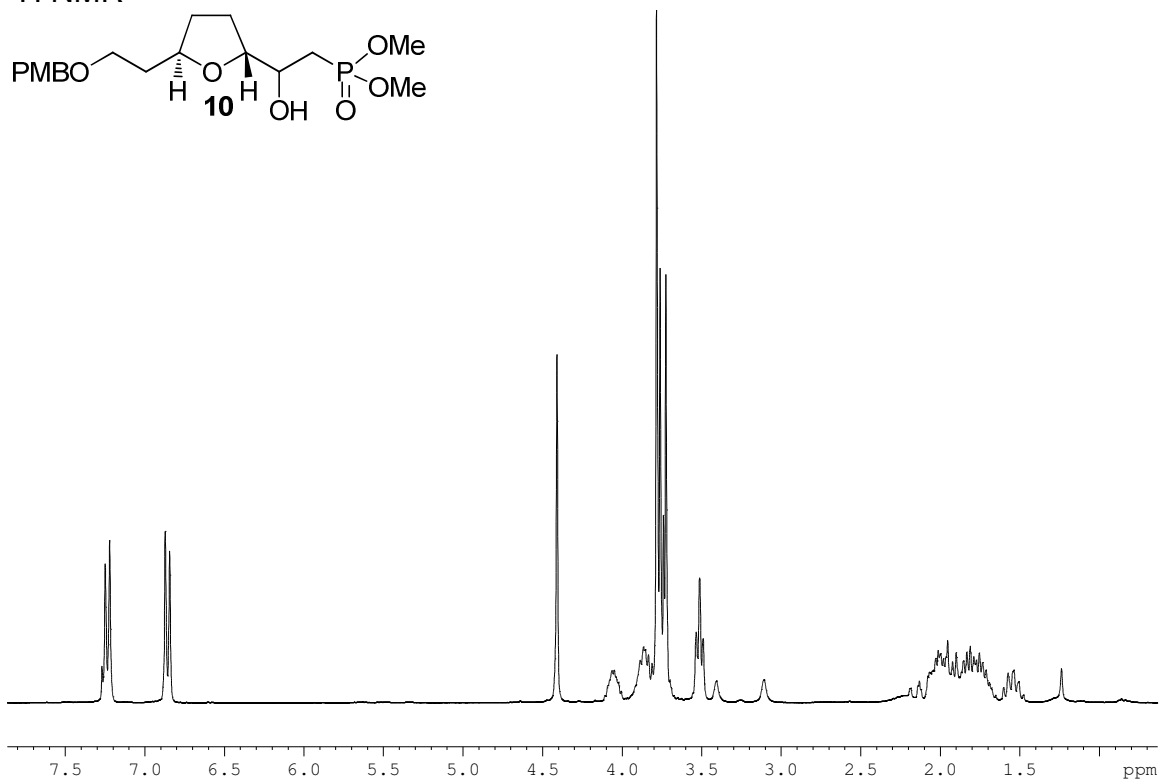
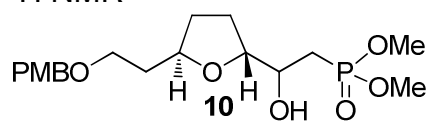
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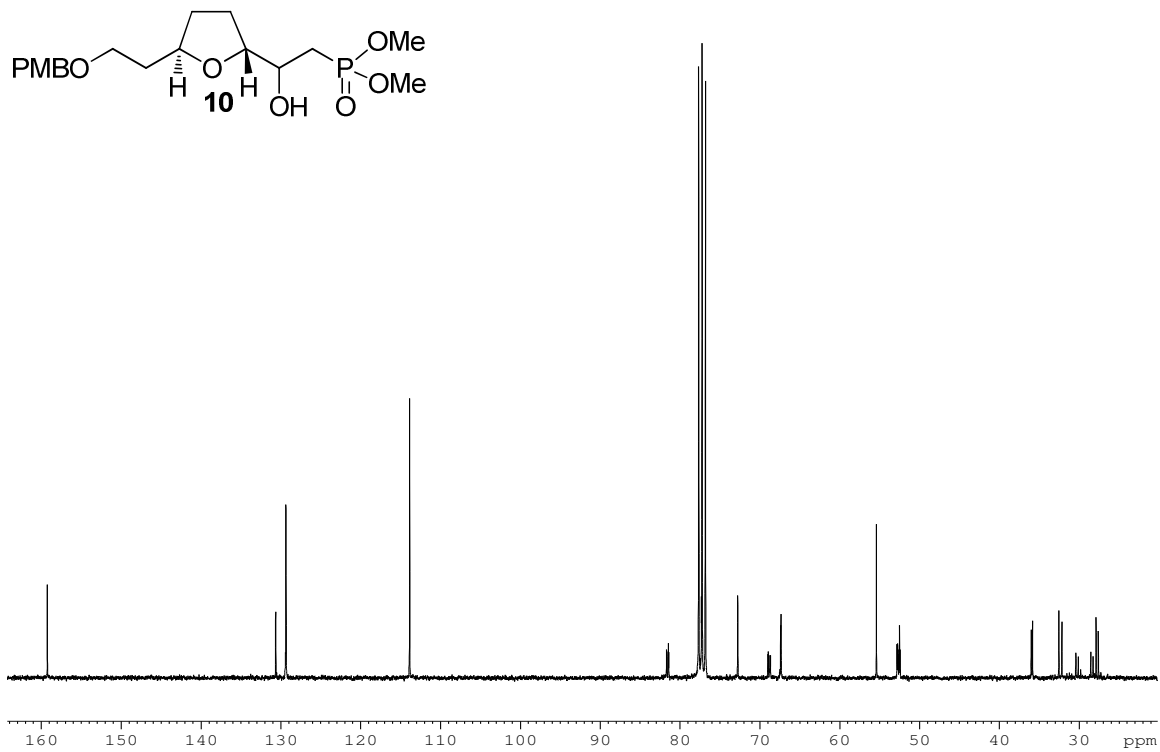
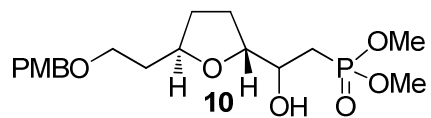
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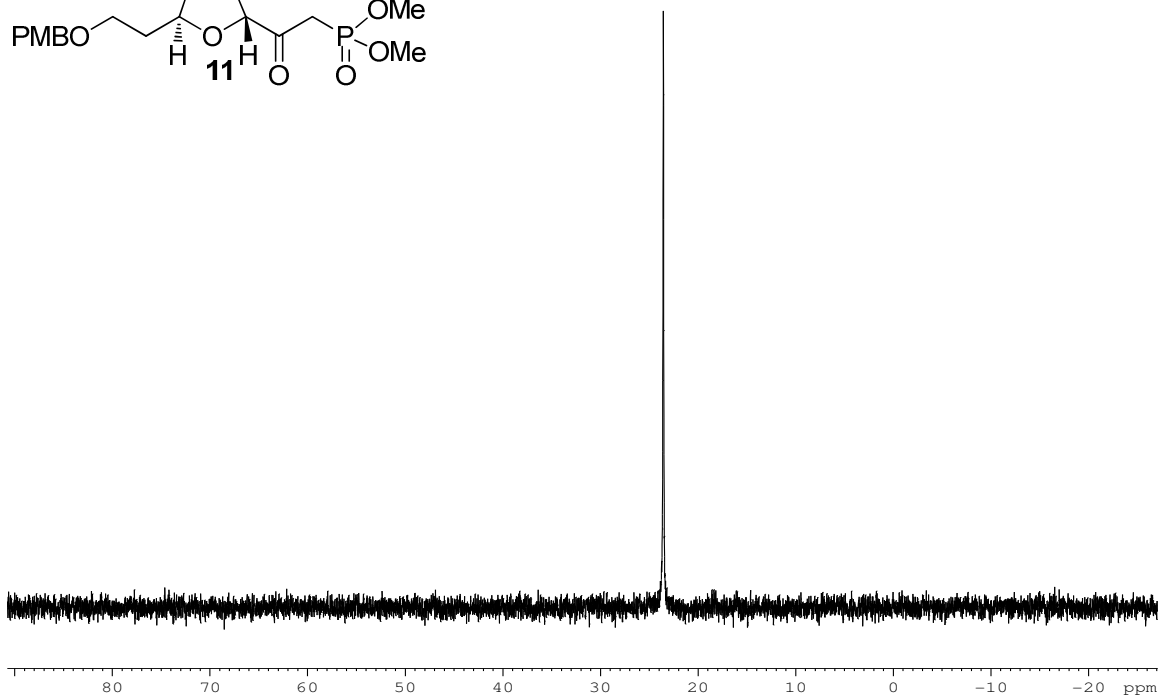
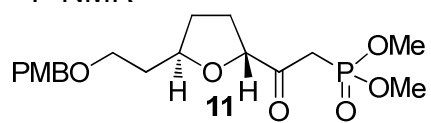
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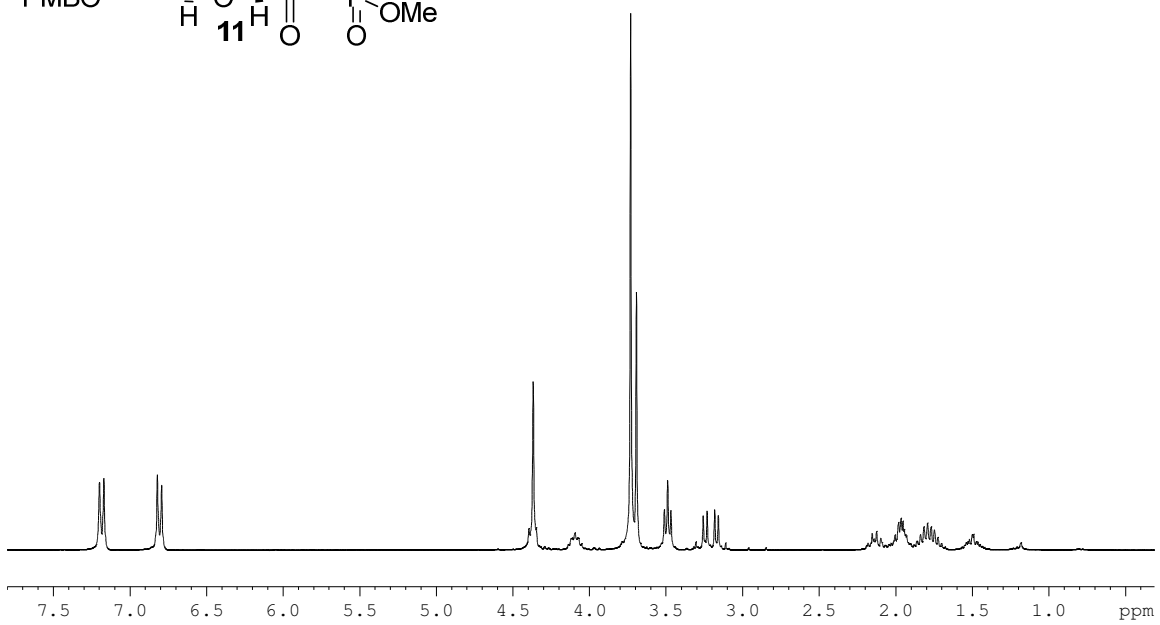
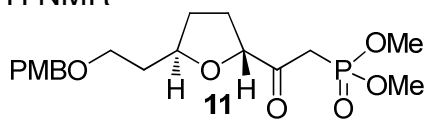
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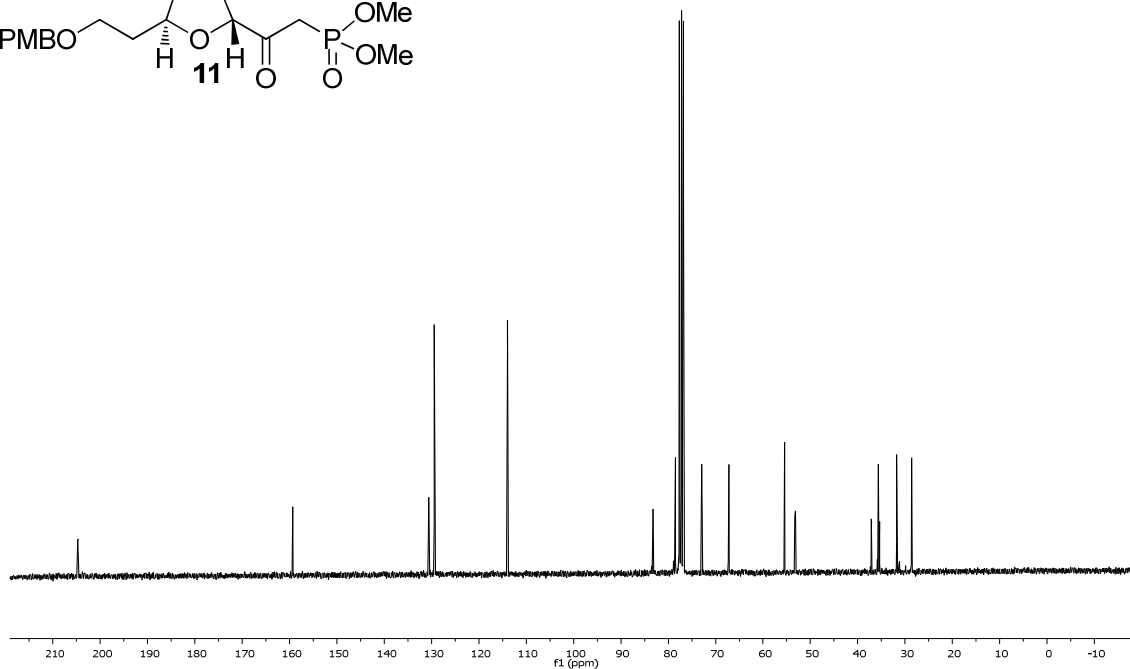
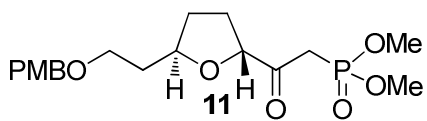
$^{31}\text{P}$  NMR



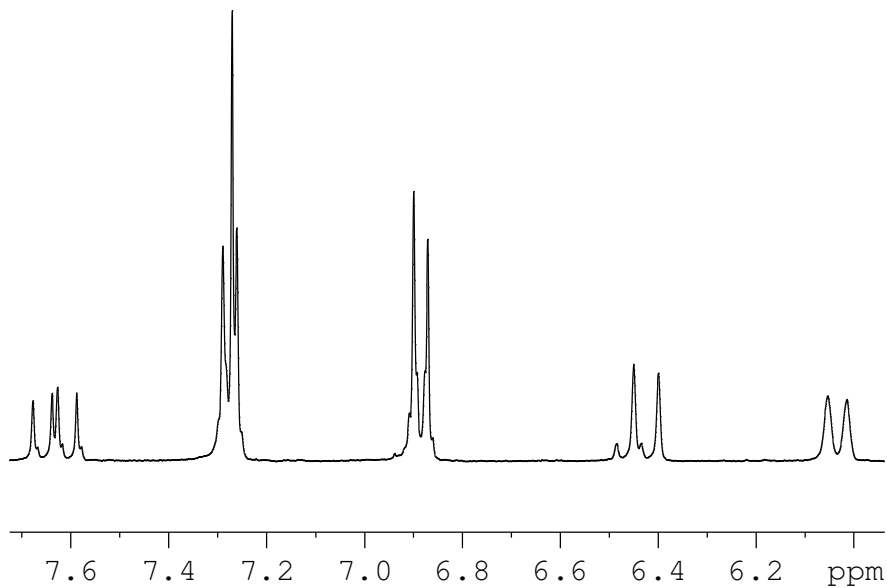
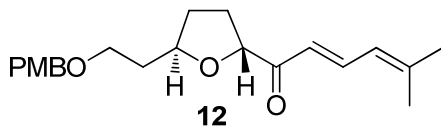
$^1\text{H}$  NMR



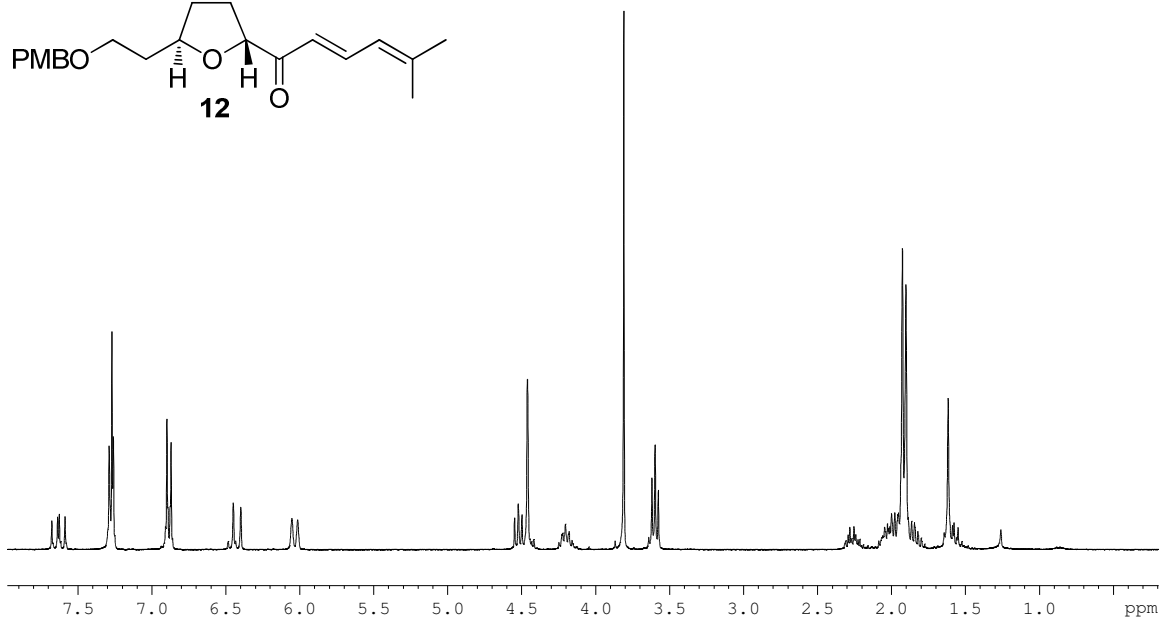
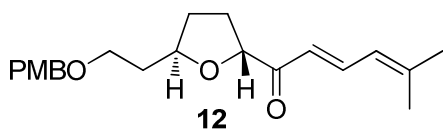
<sup>13</sup>C NMR



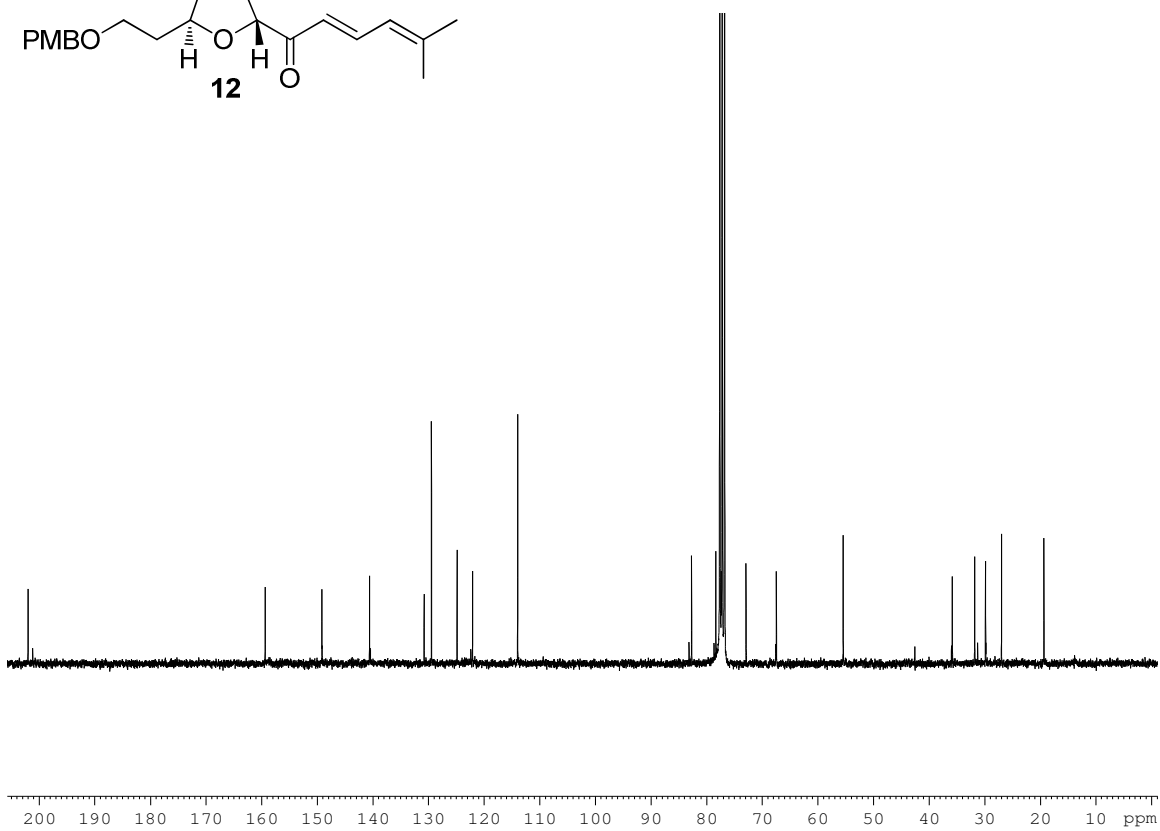
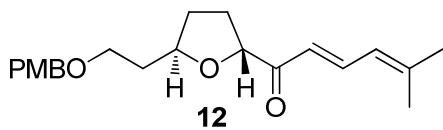
<sup>1</sup>H NMR



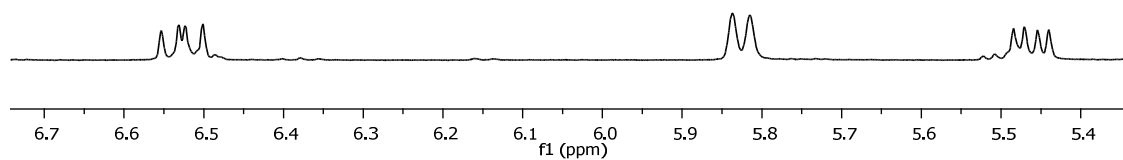
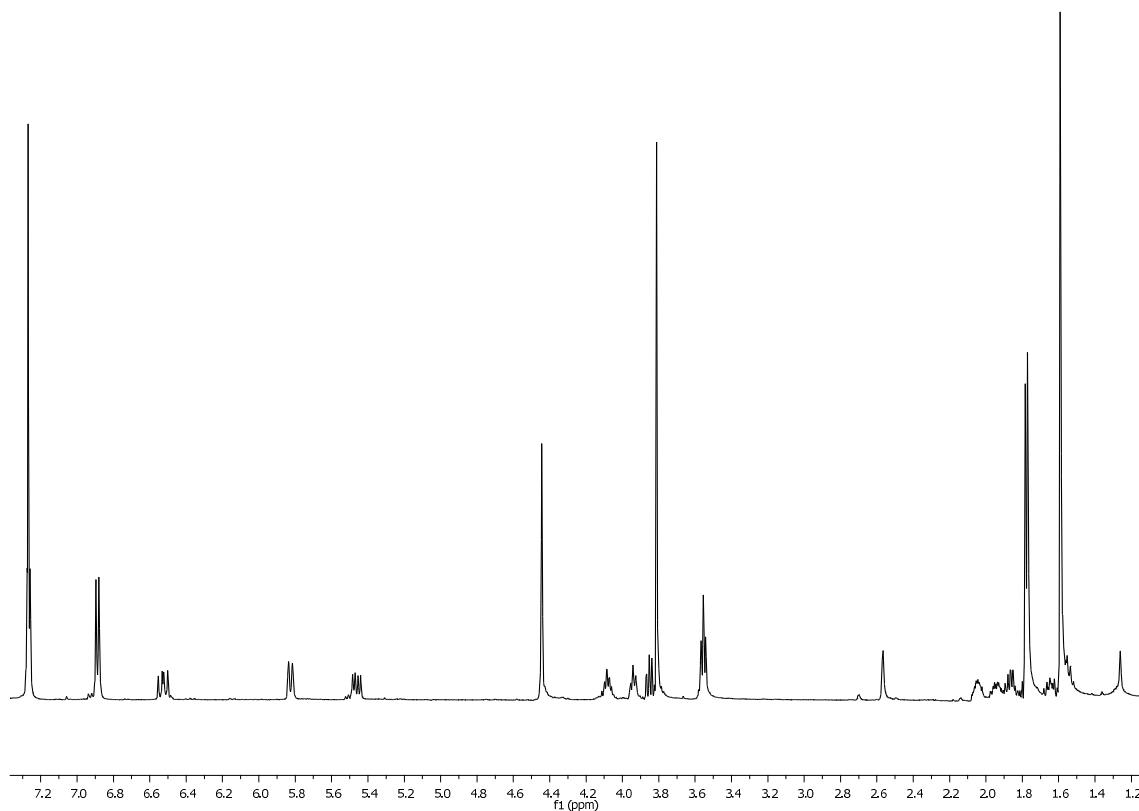
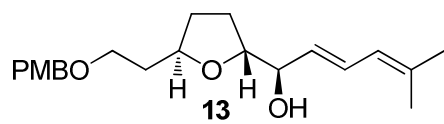
$^1\text{H}$  NMR (continued)



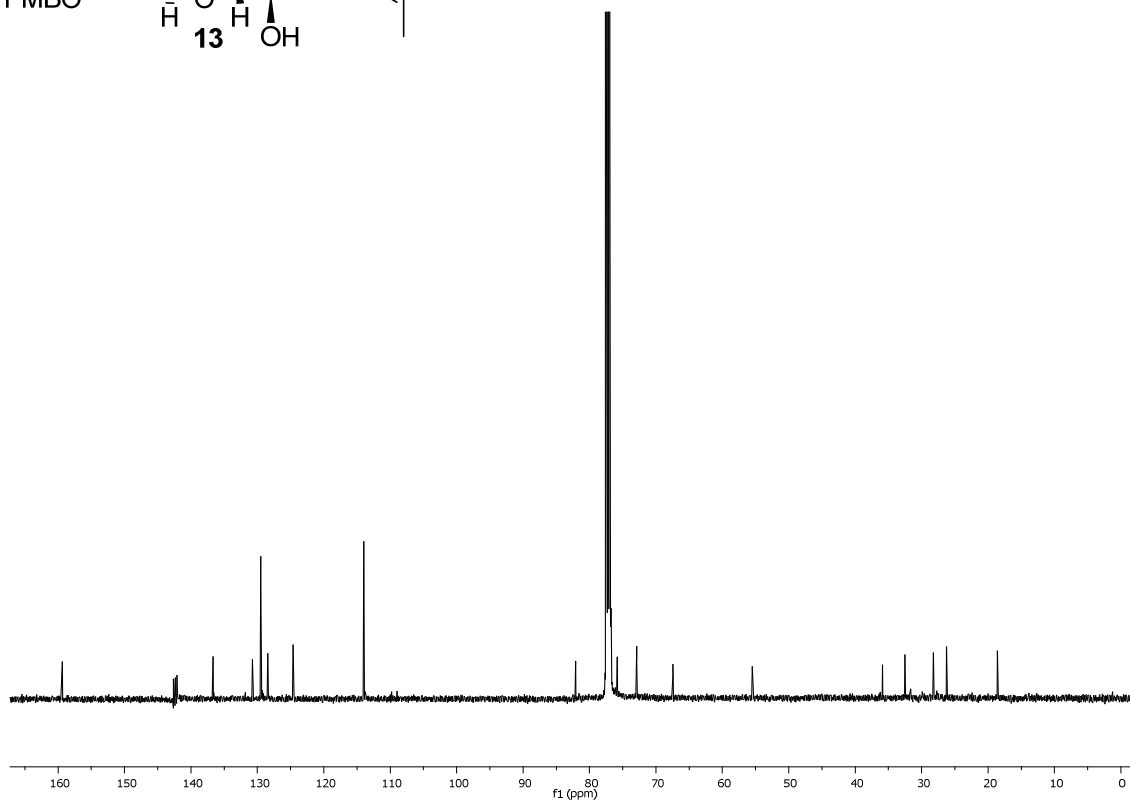
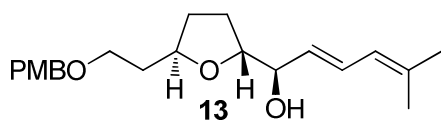
$^{13}\text{C}$  NMR



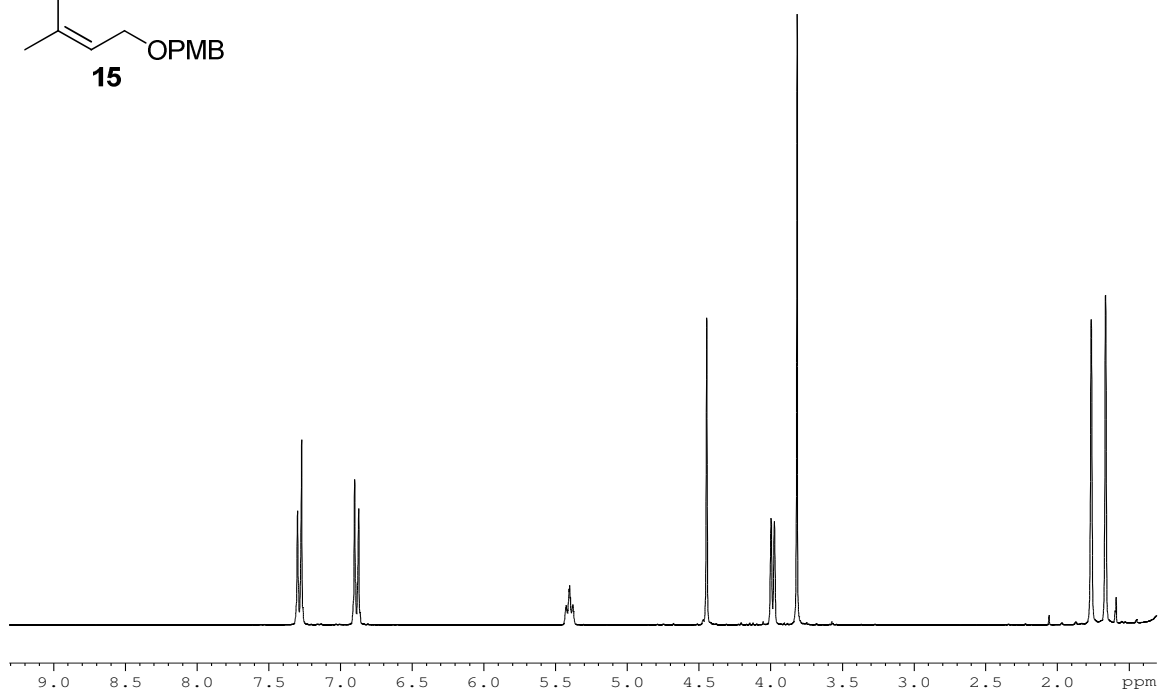
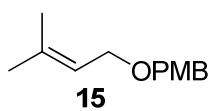
$^1\text{H}$  NMR



<sup>13</sup>C NMR

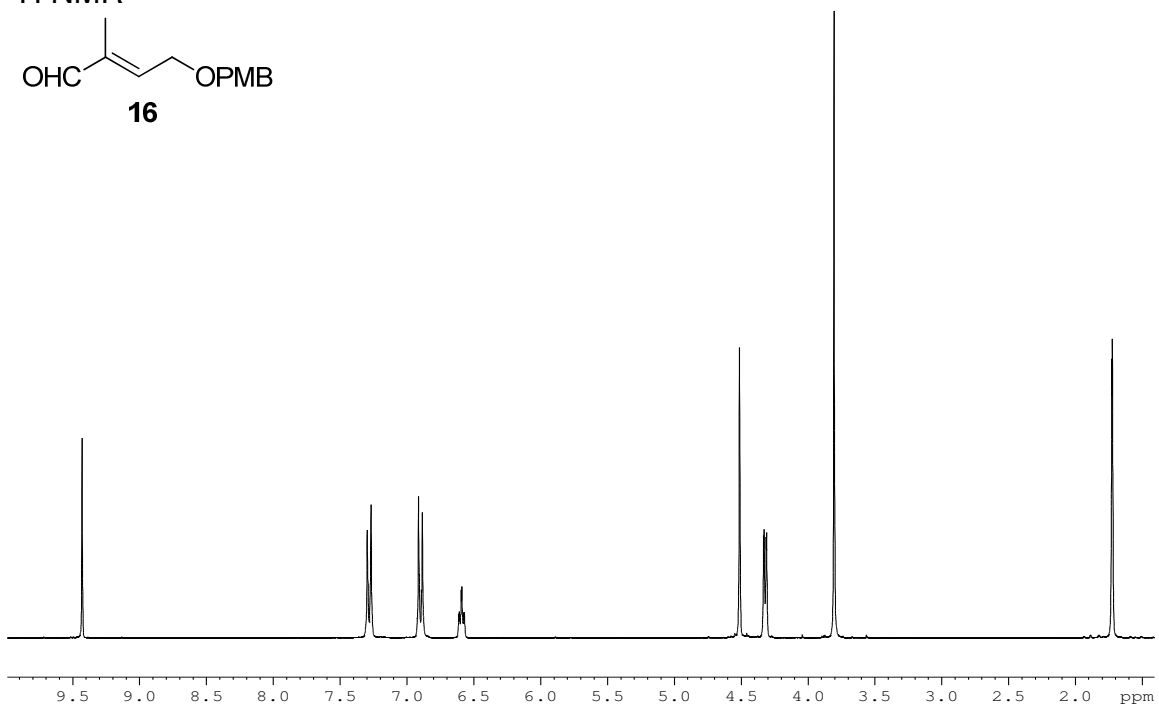
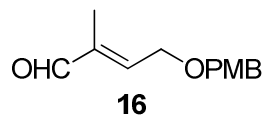


<sup>1</sup>H NMR

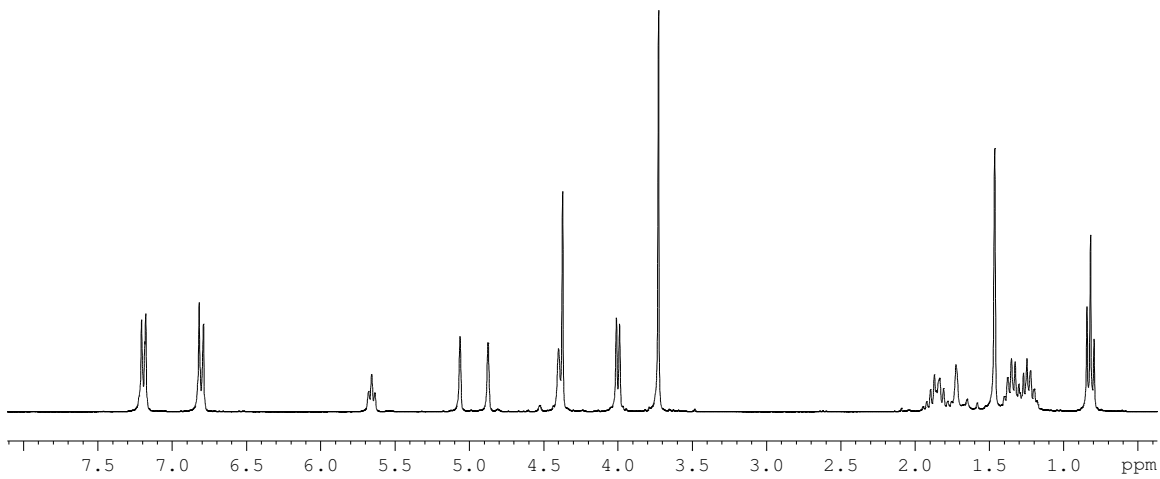
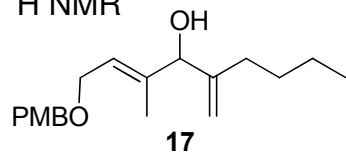




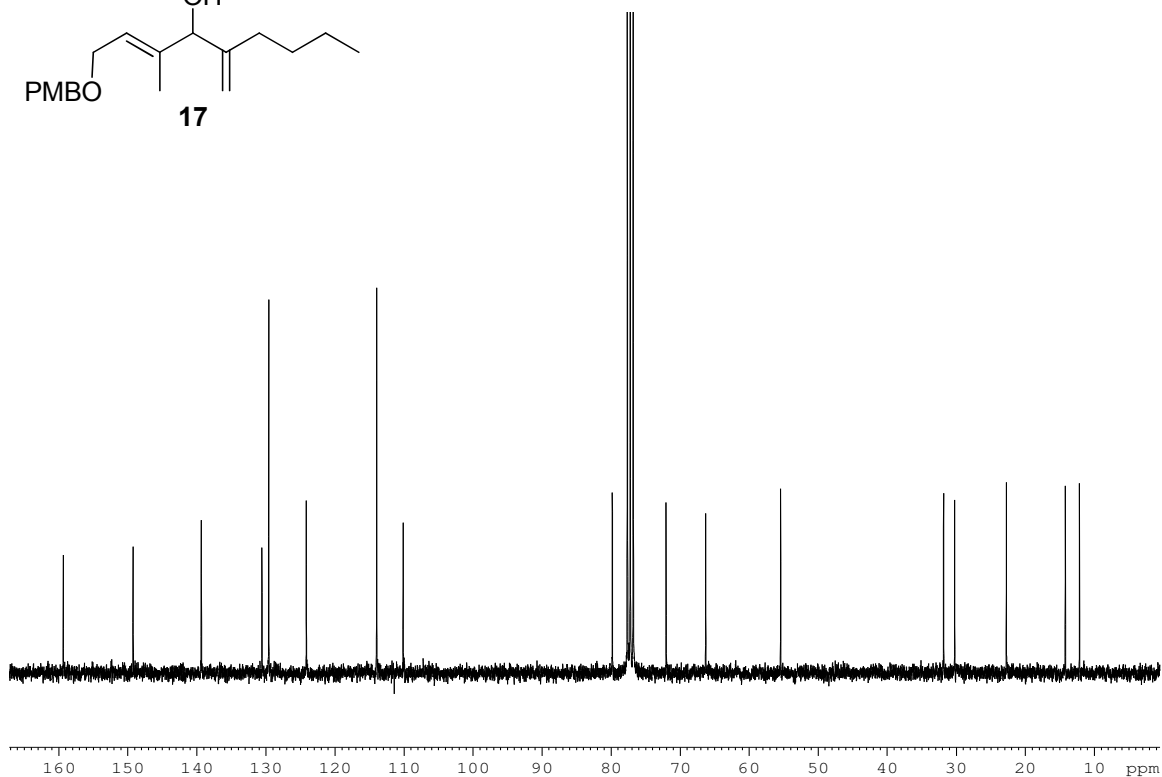
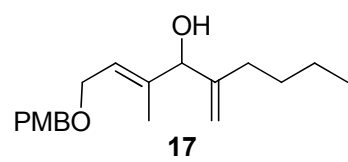
<sup>1</sup>H NMR



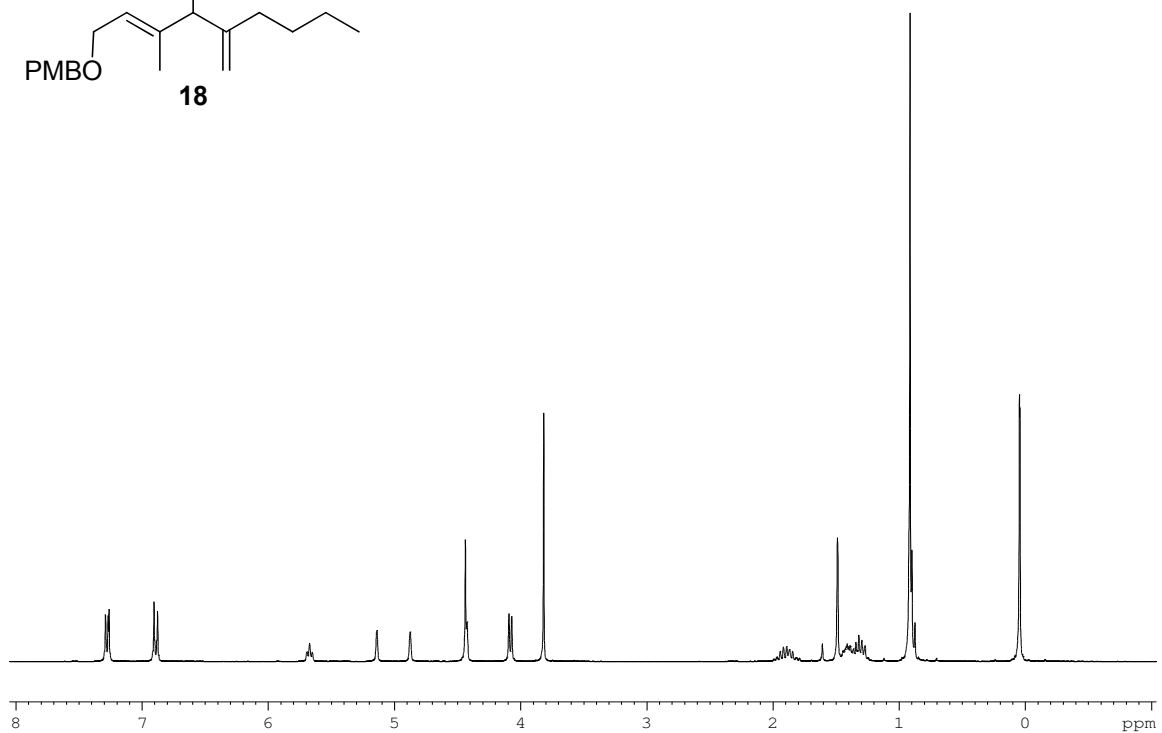
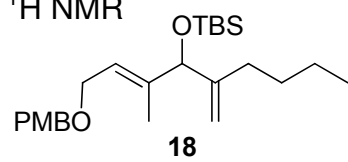
<sup>1</sup>H NMR



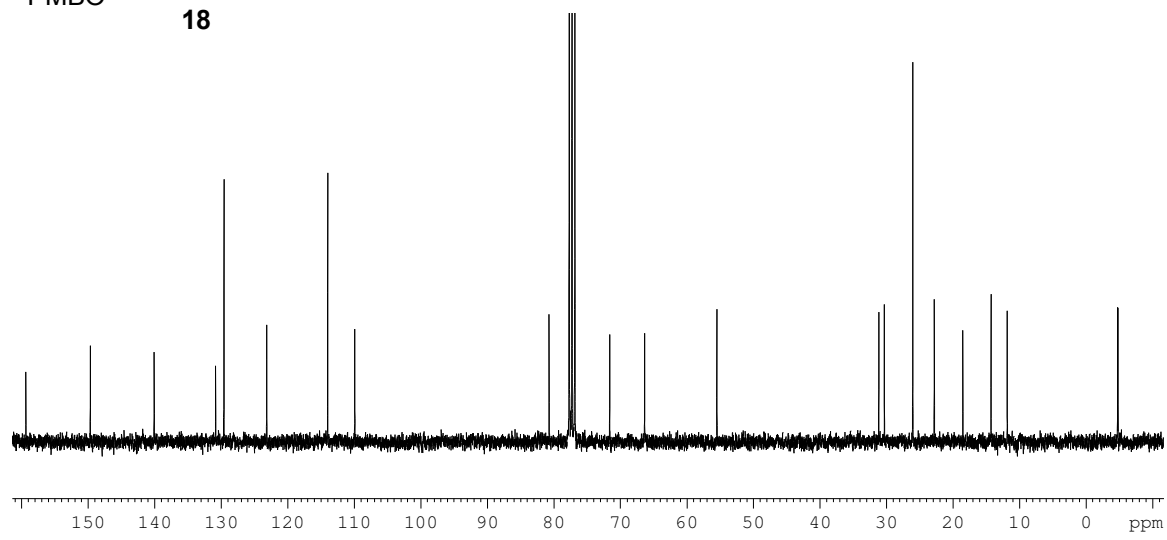
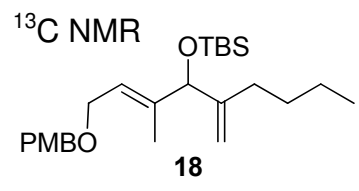
$^{13}\text{C}$  NMR



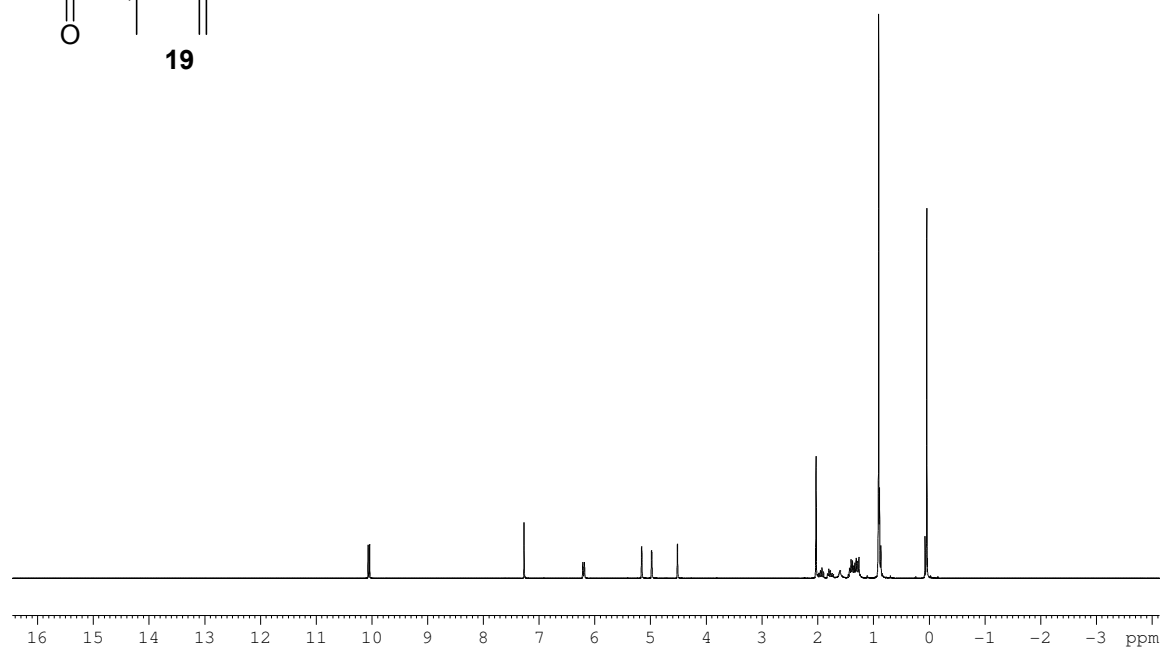
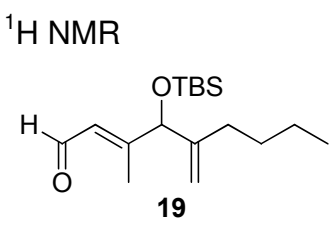
$^1\text{H}$  NMR



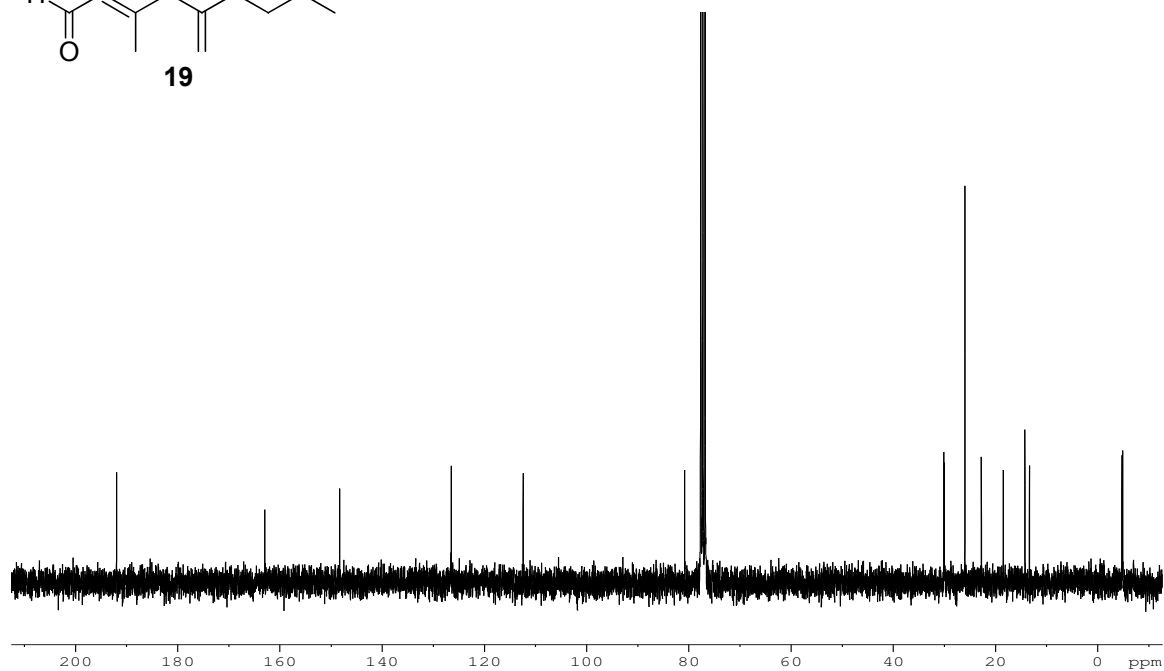
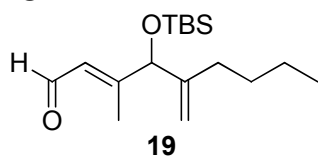
<sup>13</sup>C NMR



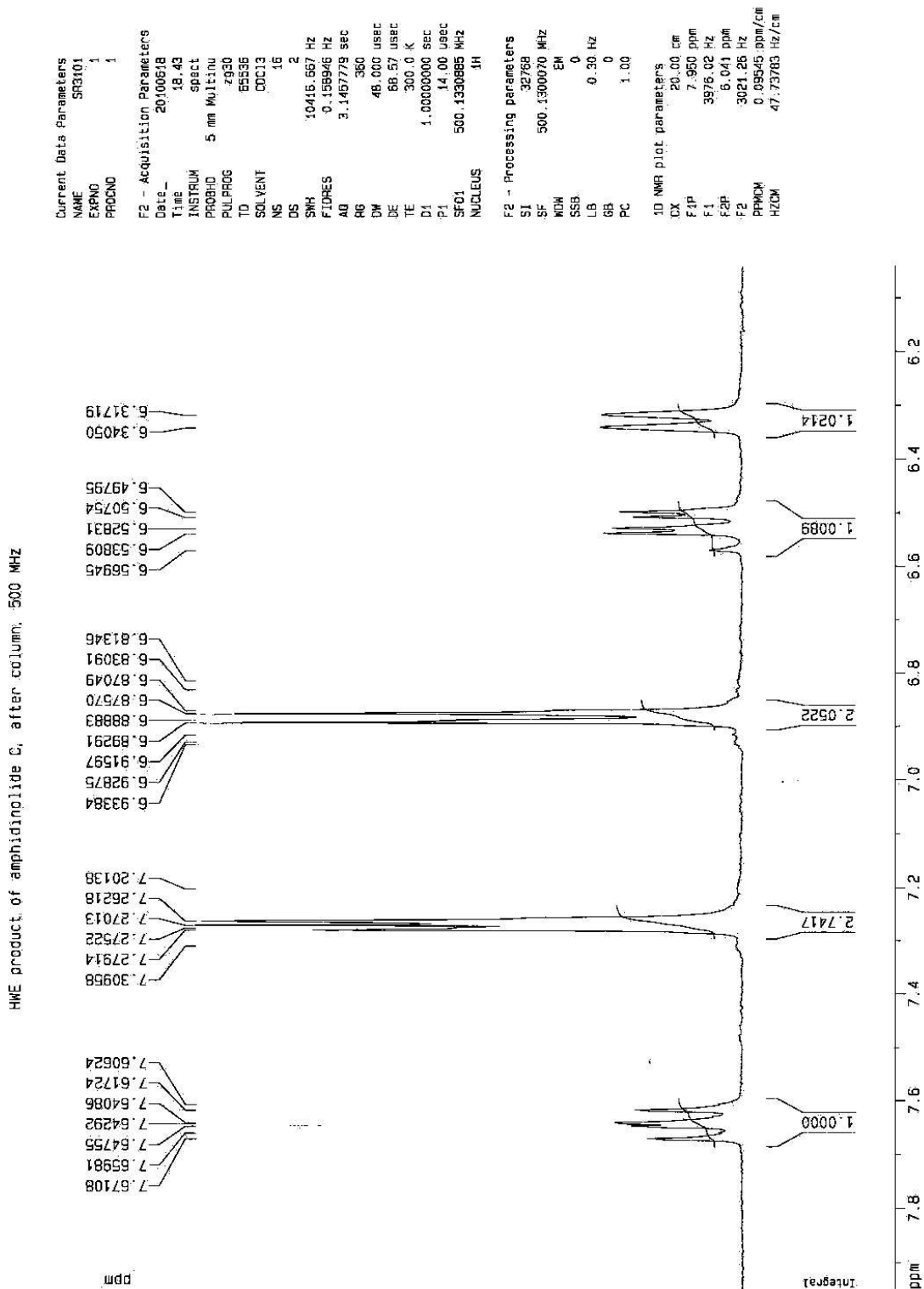
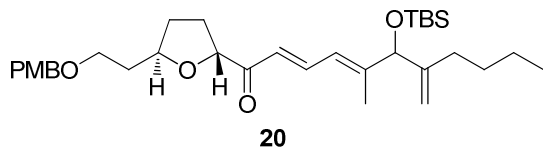
<sup>1</sup>H NMR

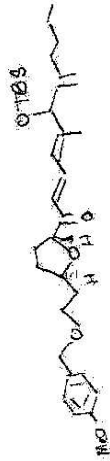


<sup>13</sup>C NMR



<sup>1</sup>H NMR





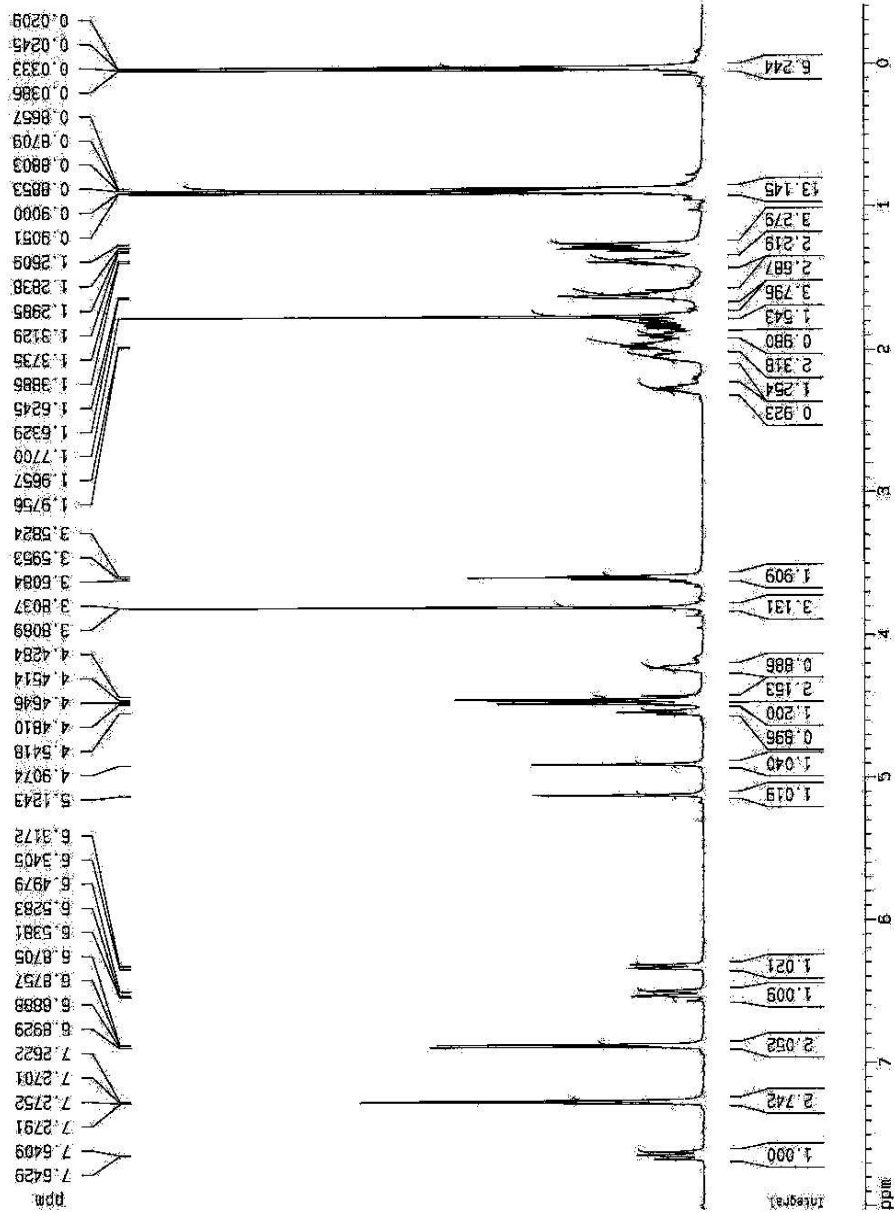
HWE product of amphetamine, c. after column, 500 MHz

Current Data Parameters  
 NAME: SR3101  
 EXPNO: 1  
 PROCNO: 1

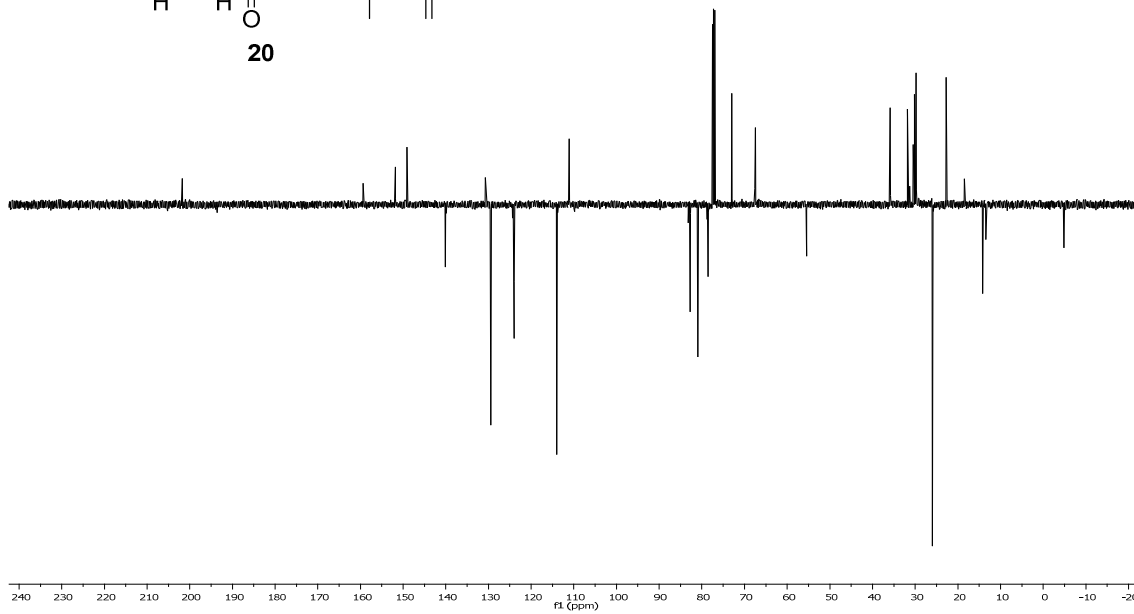
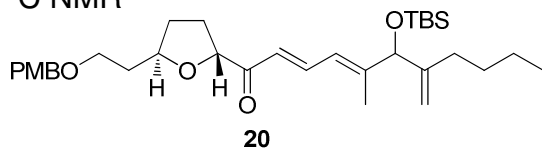
F2 - Acquisition Parameters  
 Date\_: 20100818  
 Time: 18.43  
 INSTRUM: spect  
 PROBHD: 5 mm NuiTnu  
 PULPROG: zg30  
 TO: gssg36  
 SOLVENT: CDCl3  
 NS: 36  
 DS: 4  
 SWH: 10415.867 Hz  
 FIDRES: 0.1168946 Hz  
 AQ: 3.1457778 sec  
 RG: 360  
 DW: 48.000 usec  
 DE: 68.57 usec  
 TE: 300.0 K  
 D1: 1.00000000 sec  
 P1: 14.00 usec  
 SFO1: 500.1320866 MHz  
 NUCLEUS: 1H

F2 - Processing parameters  
 SI: 32768  
 SF: 500.1300070 MHz  
 MDW: EM  
 SSB: 0  
 LB: 0.30 Hz  
 GB: 0  
 PC: 1.00

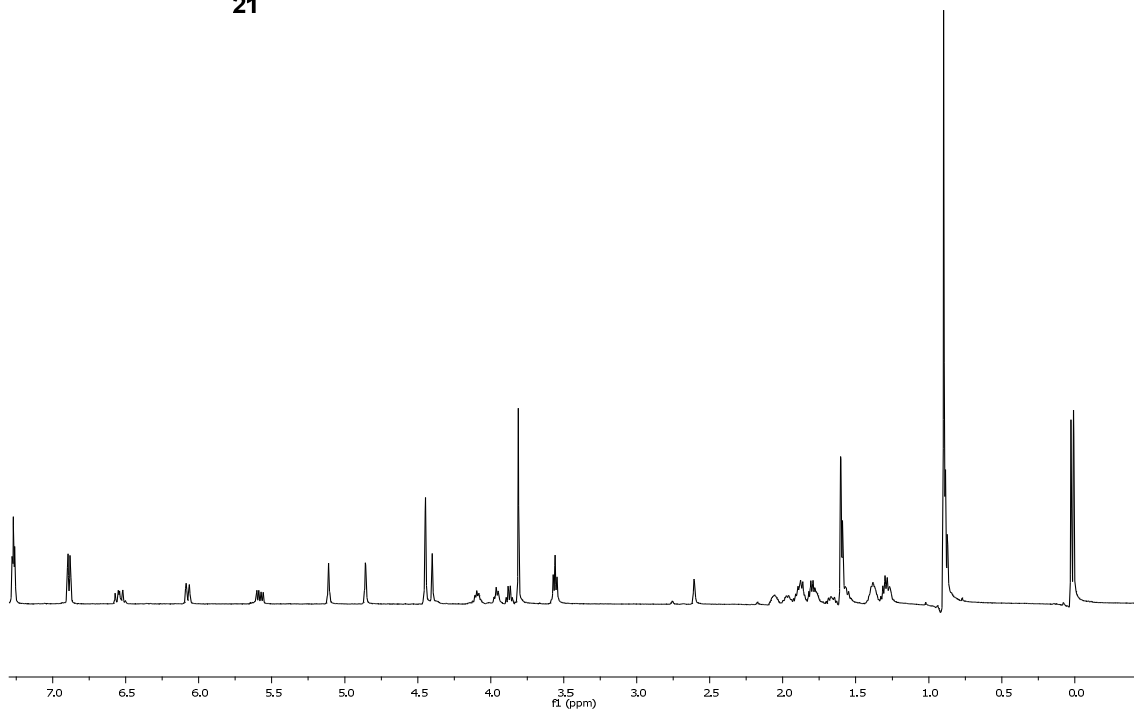
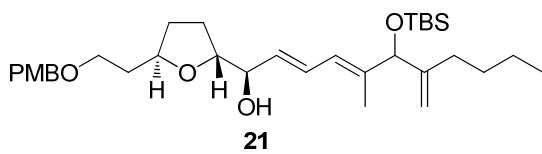
1D NMR plot parameters:  
 CX: 20.00 cm  
 F1A: 8.028 ppm  
 F1: 4035.53 Hz  
 F2P: -0.408 ppm  
 F2: -263.88 Hz  
 PHC1M: 9.42183 ppm/cm  
 HZCM: 210.57046 Hz/cm

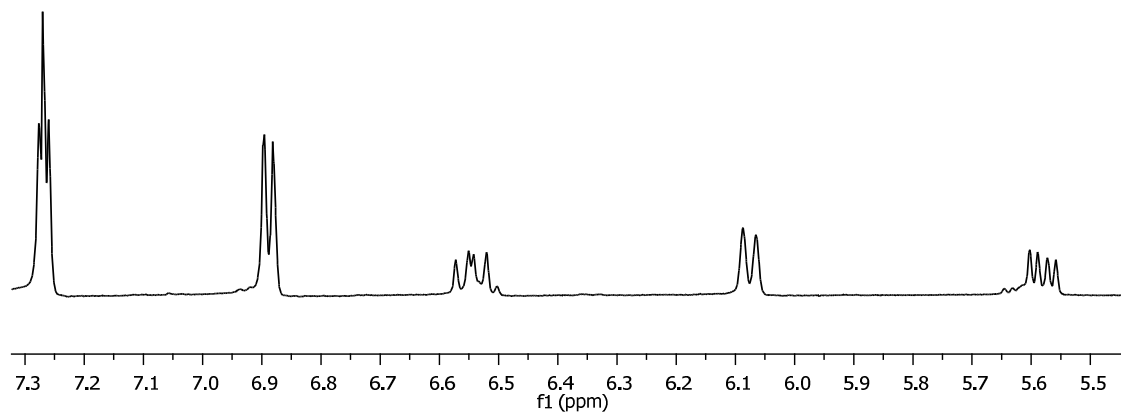
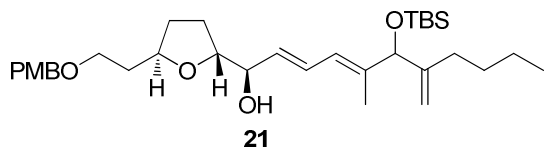


<sup>13</sup>C NMR

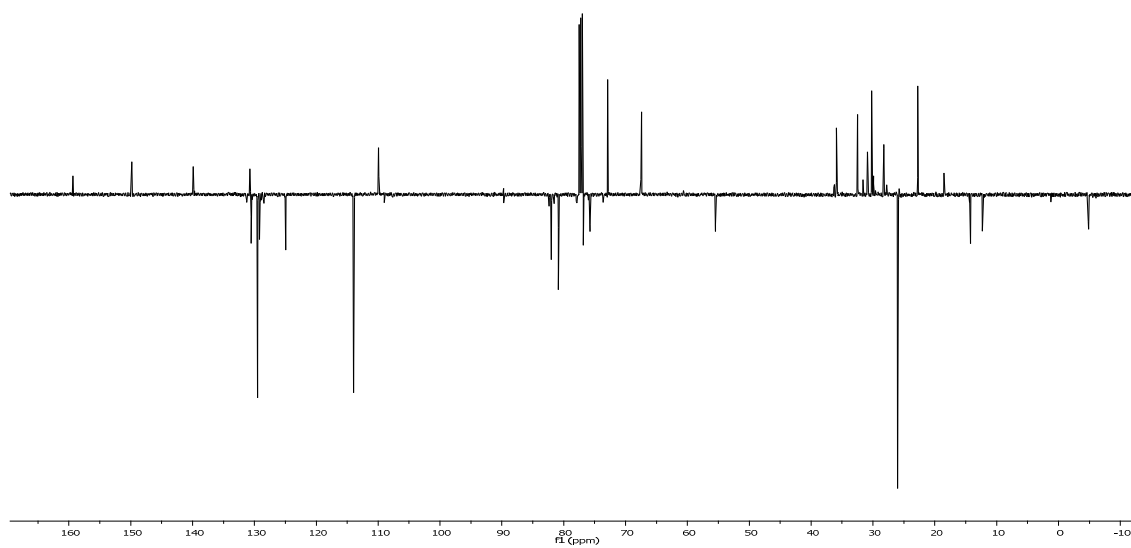
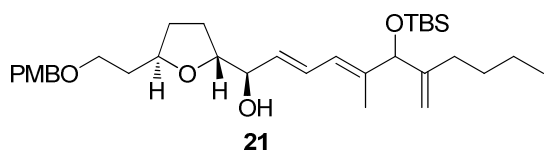


<sup>1</sup>H NMR



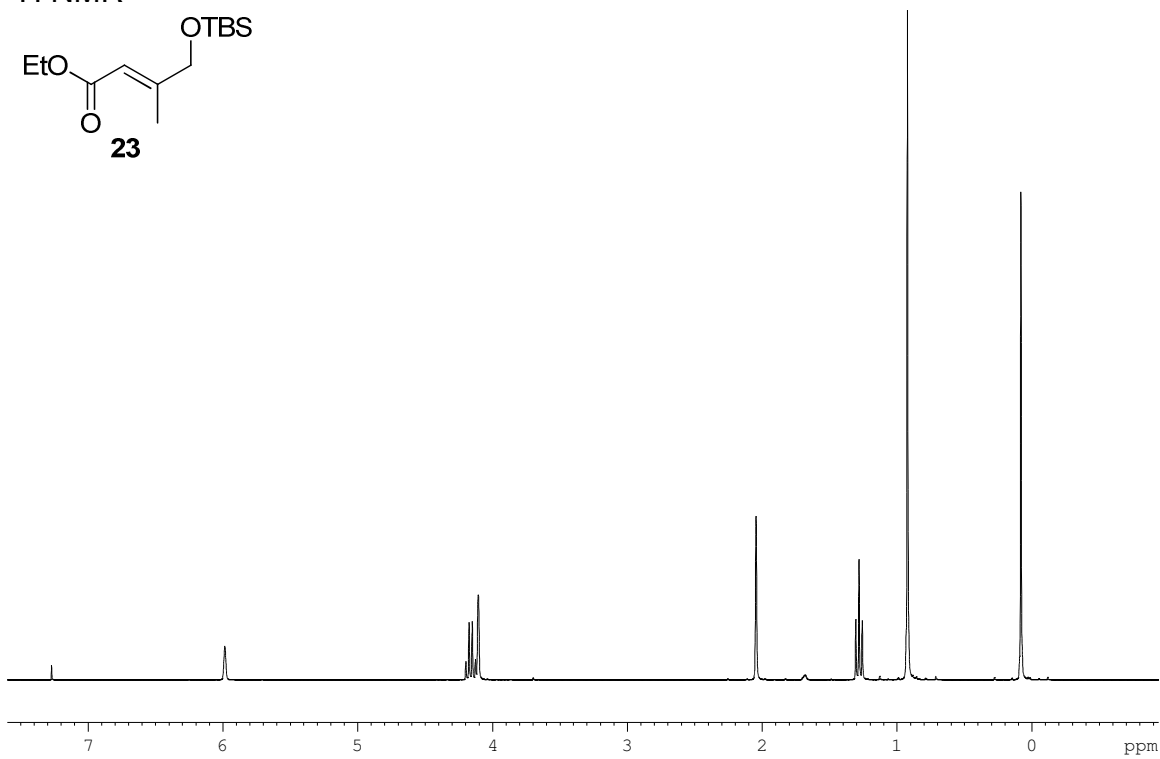
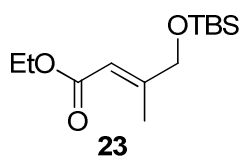


$^{13}\text{C}$  NMR

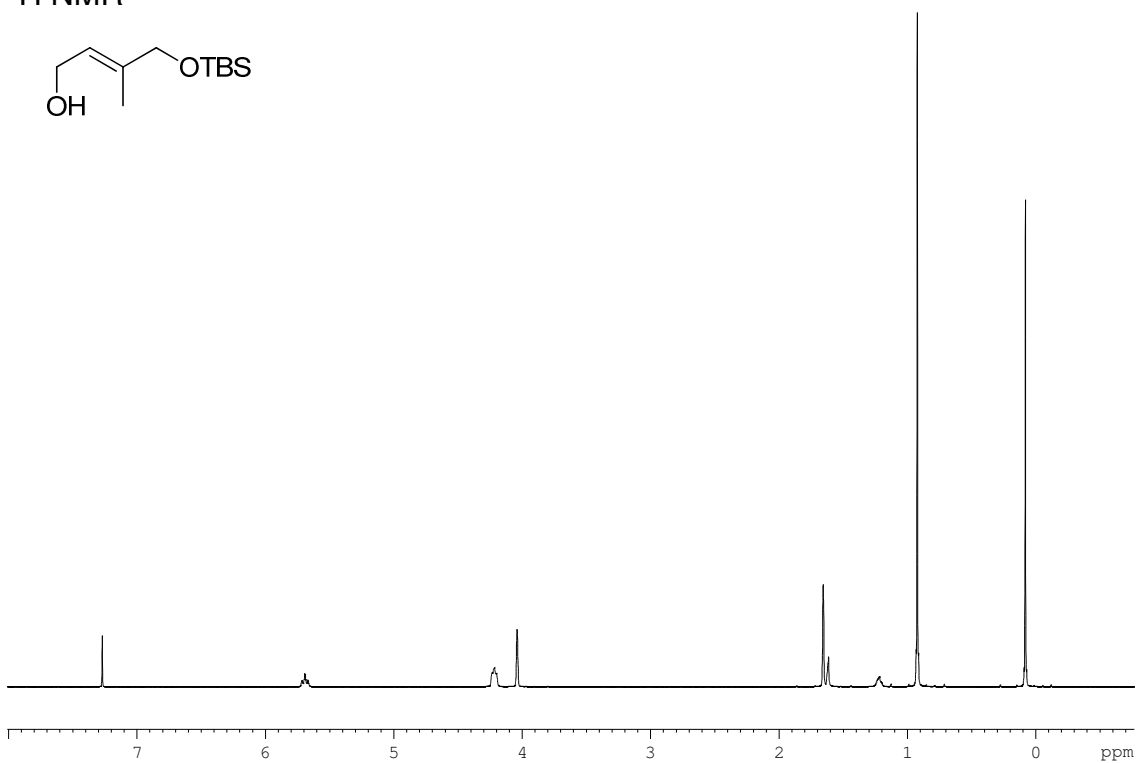
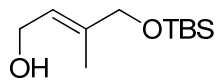




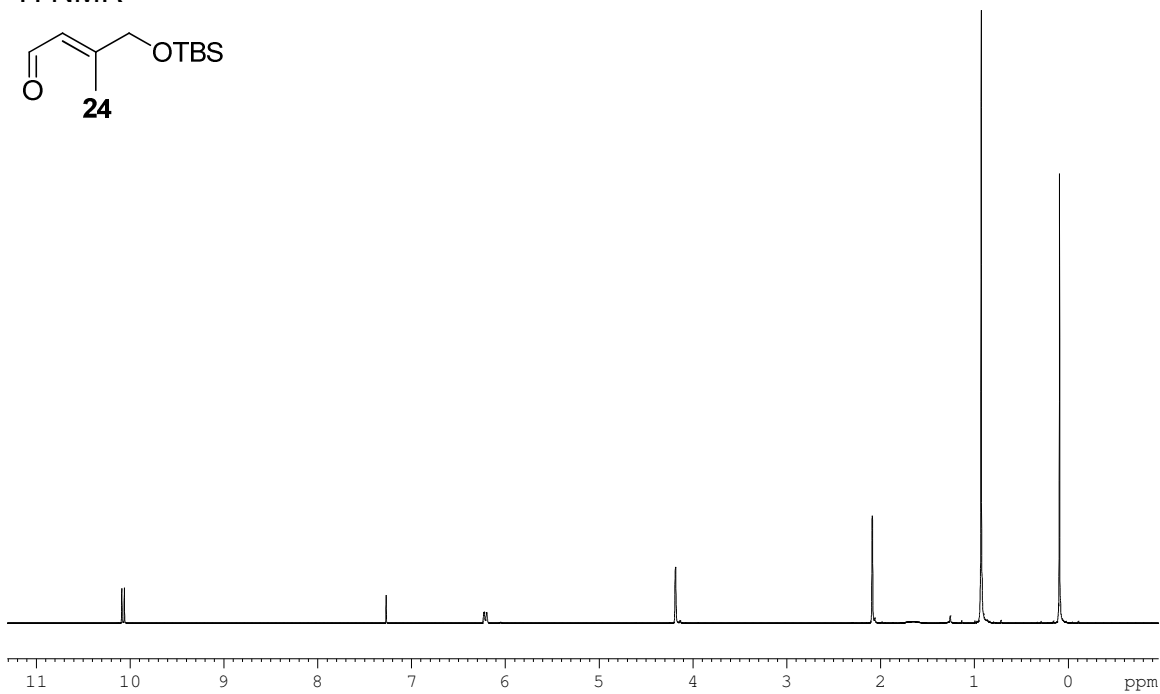
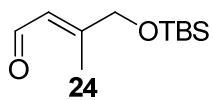
<sup>1</sup>H NMR



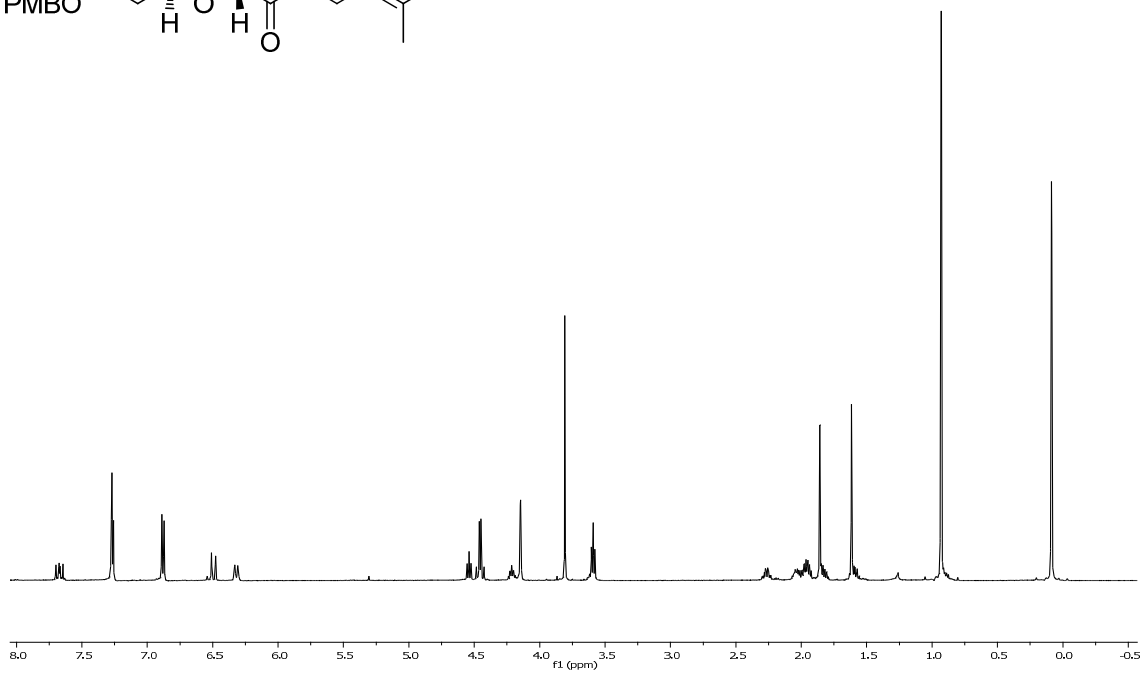
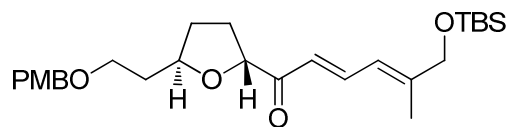
<sup>1</sup>H NMR



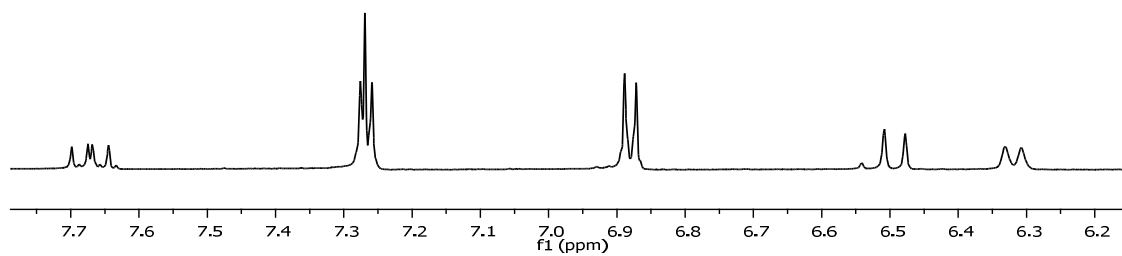
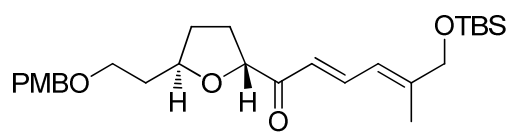
$^1\text{H}$  NMR



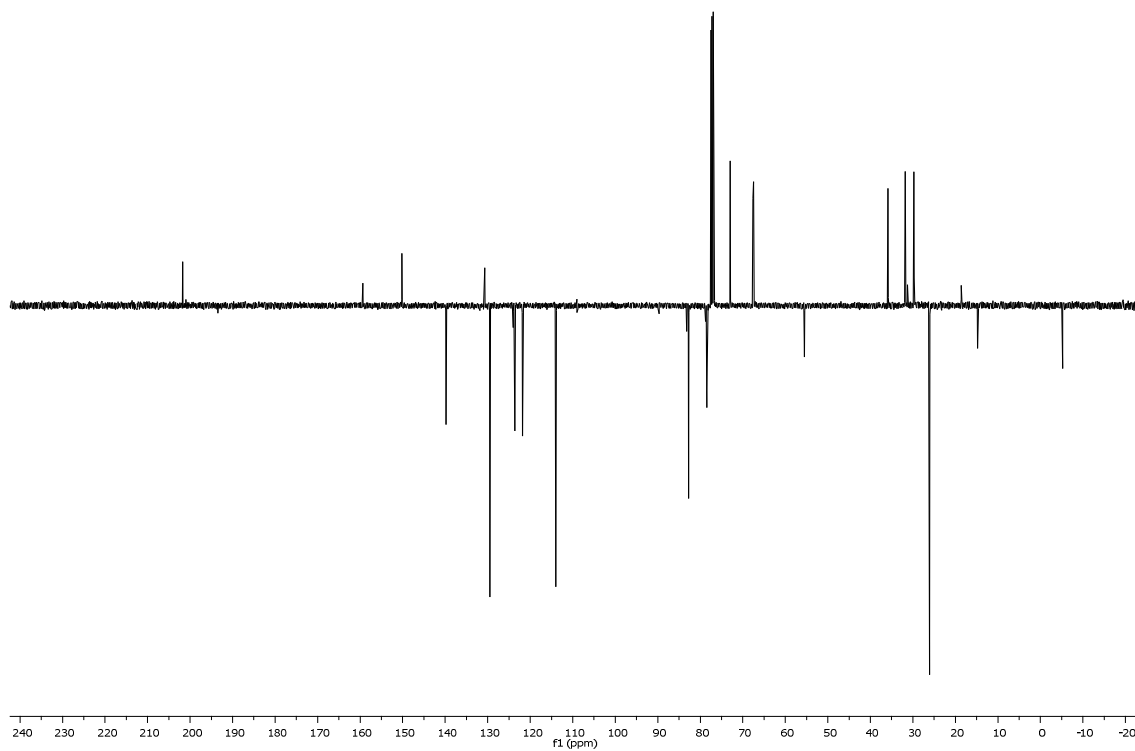
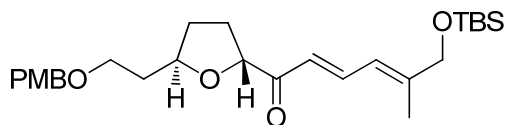
$^1\text{H}$  NMR



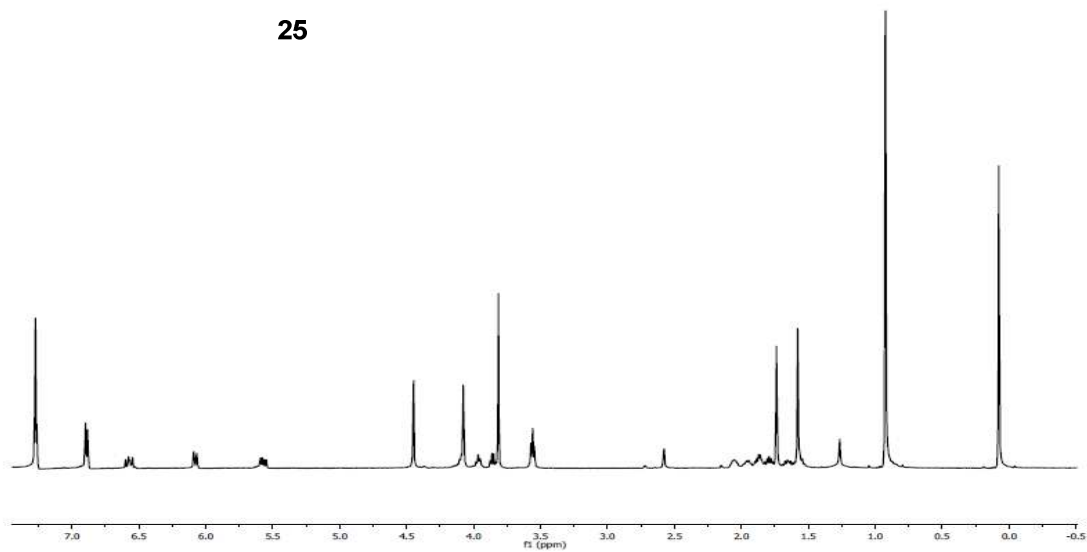
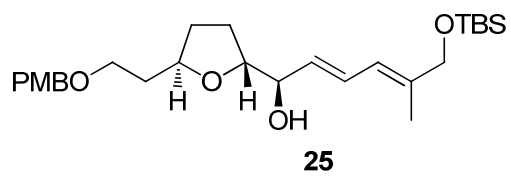
$^1\text{H}$  NMR (continued)



$^{13}\text{C}$  NMR



$^1\text{H}$  NMR



$^{13}\text{C}$  NMR

