Supporting Information

Catalysis-Enabled Concise and Stereoselective Total Synthesis of the Tricyclic Prostaglandin D_2 Metabolite Methyl Ester

Hunter S. Sims,[a] Pedro de Andrade Horn,[a] Ryota Isshiki,[a][c] Melissa Lim,[a]Yan Xu,[b] Robert H. Grubbs,[b] and Mingji Dai*[a]

[a] Department of Chemistry and Center for Cancer Research
Purdue University, West Lafayette, IN 47907 (USA)

[b] The Arnold and Mabel Beckman Laboratory of Chemical Synthesis
Division of Chemistry and Chemical Engineering
California Institute of Technology, Pasadena, CA 91125 (USA)

[c] Department of Applied Chemistry
Waseda University, Shinjuku, Tokyo 162-0041 (Japan)

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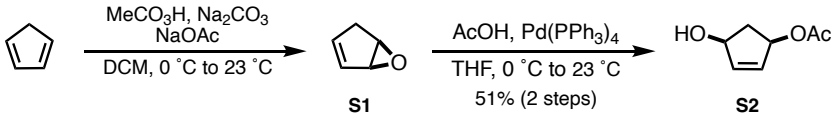
Part 1. Experimental procedure and spectra data

General methods

NMR spectra were recorded on Bruker spectrometers (^{1}H at 500 MHz, and ^{13}C at 125 MHz MHz). Chemical shifts (δ) are given in ppm with reference to residual protiated solvent as the internal standard [^{1}H NMR: $CDCl_3$ (^{1}H, 7.26 ppm), $(CD_3)_2CO$ (^{1}H, 2.05), C_6D_6 (^{1}H, 7.16); ^{13}C NMR: $CDCl_3$ (77.2), $(CD_3)_2CO$ (29.8, 206.3), C_6H_D (128.1)]. High-resolution mass measurements were carried out using a Waters SYNAPT G2-Si system with QuanTof analyzer on an Agilent 6550 QTOF system. Column chromatography was performed on silica gel. All reactions sensitive to air or moisture were conducted under argon atmosphere in dry SPS (Solvent Purification System- Cabinet Mount SPS from Pure Process Technology) or freshly distilled (THF over sodium benzophenone and all other over CaH_2 unless otherwise noted) solvents. All other solvents and reagents were used as obtained from commercial sources without further purification unless otherwise noted. Room temperature (rt) is around 23 ºC.

Experimental Procedures and Data



Compound **S1**: This compound was prepared with slight modifications to the known procedure.[1] To a rapidly stirring solution of freshly cracked cyclopentadiene (23 mL, 273 mmol, 1.0 eq.) in anhydrous DCM (160 mL) under an argon atmosphere was added anhydrous sodium carbonate (46 g, 438 mmol, 1.6 eq.) (Note 1). The solution was cooled to 0 ˚C in an ice bath, and then a solution of sodium acetate (1.76 g, 21.4 mmol, 0.03 eq.) in peracetic acid (32% in AcOH, 28.8 mL, 136.5 mmol, 0.5 eq.) was added dropwise over a 35 min period. The solution was left to stir at 0 ˚C for another 10 min, and then to room temperature for 1 h. After this time, the reaction mixture was filtered through a fritted filter with DCM (200 mL), and then the filtrate was carefully concentrated

under reduced pressure at 0 ˚C to give around 125 mL of a solution of product epoxide **S1** in DCM (Note 2). The amount of product was estimated to be 8.19 g (0.2 M in DCM) based on H-NMR integration. The analytical data is in agreement with the referenced procedure.

Note 1: The sodium carbonate should be added slow enough to maintain stirring (if it is added too quickly the stir bar can stop moving). Although one was not used, a mechanical stirrer would likely work best for this reaction.

Note 2: Distillation of the crude is advised against, as it has been reported that (especially on larger scales) the epoxide can explosively decompose at elevated temperatures.

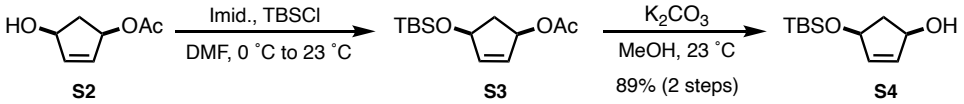
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.14 (m, 1H), 5.98 (dd, *J* = 5.8, 2.2 Hz, 1H), 3.90 (dd, *J* = 5.8, 3.0 Hz, 1H), 3.81 (m, 1H), 2.62 (ddd, *J* = 19.2, 4.2, 2.2 Hz, 1H), 2.38 (ddt, *J* = 19.1, 3.5, 2.1 Hz, 1H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 137.9, 131.3, 59.2, 56.9, 35.6.

Compound **S2**: This compound was prepared with slight modifications to the known procedure.[1] In a flame dried 250 mL flask, $Pd(PPh_3)_4$ (230 mg, 0.199 mmol, 0.002 eq.) was combined with anhydrous THF (50 mL) to give a clear, yellow solution. The solution was cooled in an ice bath to 0 ˚C, and then glacial acetic acid (5.7 mL, 100 mmol, 1.0 eq.) was added all at once. To the solution, the DCM solution of epoxide **S1** (approx. 8.19 g, 100 mmol, 0.2 M in DCM) was then added dropwise via a cannula over a 20-min period. The solution was left to stir at 0 ˚C for another 1 h, and then to room temperature until the solution changed to dark orange (1 h). The crude reaction mixture was concentrated under reduced pressure, filtered through a short silica plug followed by ether (500 mL), and then concentrated again under reduced pressure to give a dark orange oil. This oil was purified by flash chromatography (3:1 to 1:1 hexanes/EtOAc) to give mono-acetylated diol **S2** (9.91 g, 51% over 2 steps (based on mol of peracetic acid)) as an oil, which solidified in the fridge to a yellow solid. The analytical data is in agreement with the referenced procedure.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.10 (m, 1H), 5.97 (m, 1H), 5.48 (m, 1H), 4.71 (m, 1H), 2.79 (dt, *J* = 14.6, 7.4 Hz, 1H), 2.04 (s, 3H), 1.64 (dt, *J* = 14.5, 3.9 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 138.5, 132.6, 77.1, 74.9, 40.5, 21.2.



Compound **S3**: Following the known procedure,[2] in a flame dried 250 mL round bottom flask, mono-acetylated diol **S2** (4.41 g, 31 mmol, 1.0 eq.) was combined with anhydrous DMF (40 mL) and imidazole (3.17 g, 46.5 mmol, 1.5 eq.) under an argon atmosphere. The solution was cooled to 0 ˚C, and then TBSCl (5.61 g. 37 mmol, 1.2 eq.) in anhydrous DMF (20 mL) was added over a 30-min period. The solution was left to slowly stir to room temperature overnight (20 h), and then was cooled again to 0 ˚C and quenched with 10 mL of water. The reaction mixture was diluted with DI water (200 mL) and extracted with ether (3 x 100 mL), and then the combined organic phases were back extracted with DI water (100 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a crude yellow oil. This oil was purified by flash chromatography (95:5 hexanes/EtOAc) to give acetylated-TBS diol **S3** as a colorless oil. The analytical data is in agreement with the referenced procedure.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.97 (m, 1H), 5.88 (m, 1H), 5.45 (m, 1H), 4.71 (m, 1H), 2.80 (dt, J = 13.8, 7.4 Hz, 1H), 2.04 (s, 3H), 1.60 (dt, J = 13.8, 5.1 Hz, 1H), 0.89 (s, 9H), 0.08 (s, 6H).

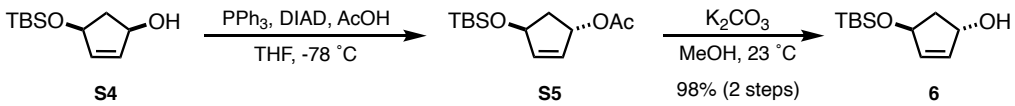
^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 138.9, 131.2, 77.0, 74.9, 41.2, 25.9, 21.2, 18.2, -4.6.

Compound **S4**: Following the known procedure,[2] in a 250 mL round bottom flask, acetylated-TBS diol **S3** (7.95 g, 31.0 mmol, 1.0 eq.) was combined with MeOH (160 mL) and K_2CO_3 (4.71 g, 34.1 mmol, 1.1 eq.). After stirring at room temperature for 4.5 h, the reaction mixture was concentrated under reduced pressure, and diluted with DI water (100 mL) and ether (150 mL). The organic phase was collected, and then the aq. phase was washed with more ether (2 x 100 mL). The combined organic phases were then dried over magnesium sulfate, filtered, concentrated under reduced pressure, and purified by flash chromatography (8:1 to 4:1 hexanes/EtOAc) to give mono-TBS diol

S4 (5.94 g, 89%, over 2 steps) as a clear, colorless oil. The analytical data is in agreement with the referenced procedure.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.94 (m, 1H), 5.89 (m, 1H), 4.66 (m, 1H), 4.59 (m, 1H), 2.68 (dt, *J* = 13.8, 6.9 Hz, 1H), 1.50 (dt, *J* = 13.8, 4.6 Hz, 1H), 0.89 (s, 9H), 0.08 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 137.1, 135.6, 75.2, 75.1, 44.8, 25.9, 18.2, -4.6.



S4 **S5** **6**

Compound **S5**: Following a slight variation of the known procedure,[3] in a flame dried 250 mL flask mono-TBS diol **S4** (5.94 g, 27.7 mmol, 1.0 eq.) was combined with anhydrous THF (140 mL) and PPh_3 (14.54 g, 55.4 mmol, 2.0 eq.) under an argon atmosphere. The solution was cooled to -78 ˚C, and then glacial acetic acid (3.2 mL, 55.4 mmol, 2.0 eq.) was added all at once, followed by the dropwise addition of DIAD (10.9 mL, 55.4 mmol, 2.0 eq.) over a 30-min period. The solution was left to stir at -78 ˚C for 6 h, and was then quenched with 45 mL of 10% $NaHCO_3$ and left to warm to room temperature. The reaction mixture was extracted with ether (2 x 140 mL), and then the combined organic phases were dried over magnesium sulfate, filtered, and concentrated under reduced pressure to give a yellow solid. This solid was sonicated with 30 mL of 95:5 pentanes/EtOAc to give a white suspension, which was filtered through a silica plug (moistened with 95:5 pentanes/EtOAc) followed by another 400 mL of 95:5 pentanes/EtOAc. The resulting filtrate was concentrated to give 7.0 g of fairly pure acetylated-TBS diol **S5** as a yellow oil which was used directly in the next step without further purification.

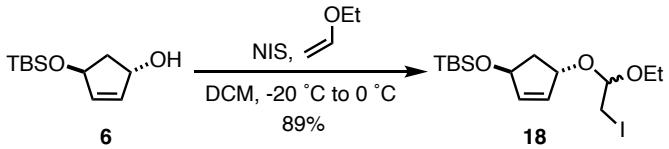
Compound **6**: Following the known procedure,[2] in a 250 mL round bottom flask acetylated-TBS diol **S5** (7.0 g, approx. 27.3 mmol, 1 eq.) was combined with MeOH (140 mL) and K_2CO_3 (4.15 g, 30 mmol, 1.1 eq.). After stirring at room temperature for 3 h, the reaction mixture was concentrated, and diluted with ether (150 mL) and DI water (100 mL). The organic phase was collected, and then

the aq. phase was washed with more ether (2 x 100 mL). The combined organic phases were then dried over magnesium sulfate, filtered, and concentrated to give pure mono-TBS diol **6** (5.85 g, 98% over 2 steps) as a colorless oil (no chromatography required).

Using the above procedure, we prepared more than decagram of compound **6**.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.94 (m, 2H), 5.09 (m, 1H), 5.01 (m, 1H), 2.04 (m, 2H), 0.89 (s, 9H), 0.08 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 138.3, 135.6, 76.6, 76.2, 44.4, 25.9, 18.2, -4.6.



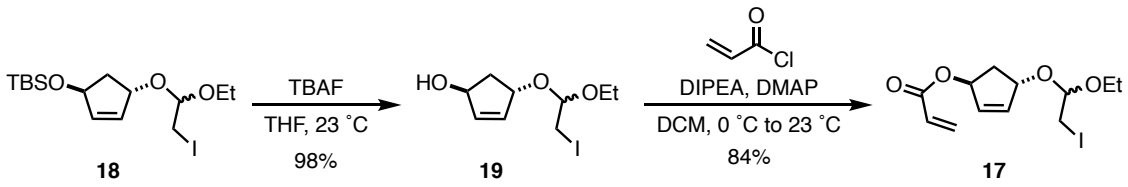
Compound **18**: In a flame dried 250 flask, mono-TBS diol **6** (5.85 g, 27.3 mmol, 1.0 eq.) was combined with anhydrous DCM (175 mL) and NIS (6.75 g, 30.0 mmol, 1.1 eq.) under argon, and then cooled to -20 ˚C. To the solution, ethyl vinyl ether (5.2 mL, 54.6 mmol, 2.0 eq.) was then added over a 30-min period (solution changed from pink to light yellow). After the addition, the solution was left to stir at -20 ˚C for another 30 min, and then to 0 ˚C for 4 h. After this time, the solution was quenched with 15 mL $Na_2S_2O_3$, left to warm to room temperature, and diluted with DCM (50 mL) and DI water (50 mL). The organic phase was collected and the aq. phase was washed with more DCM (50 mL). The combined organic phases were then dried over magnesium sulfate, filtered, and concentrated under reduced pressure to give a cloudy yellow oil, which was filtered through a short silica plug with 150 mL of 95:5 hexanes/EtOAc. The resulting filtrate was then concentrated under reduced pressure, and purified by flash chromatography (96:4 hexanes/Et_2O) to give iodo-acetal **18** (9.97 g, 89%) as a colorless oil and inconsequential mixture of acetal diastereomers.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.96 (m, 2H), 5.06 (m, 1H), 4.91 (m, 1H), 4.68 (m, 1H), 3.71-3.51 (m, 2H), 3.2 (m, 2H), 2.19 (m, 1H), 1.95 (m, 1H), 1.23 (m, 3H), 0.88 (s, 9H), 0.08 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 139.3, 139.2, 133.4, 133.0, 101.6, 101.5, 81.2, 80.8, 76.4, 76.3, 62.0, 61.3, 42.2, 41.5, 25.9, 18.2, 15.2, 15.1, 6.0, 5.9, -4.6.

IR (ATR): 2935, 2928, 2884, 2856, 2162, 2035, 2017, 1970, 1471, 1462, 1414, 1366, 1251, 1177, 1102, 1050, 1030, 1002 cm^{-1}.

HRMS (ESI): *m/z* Calc. for $C_{15}H_{29}IO_3SiNa$ $[M+Na]^+$: 453.0823, found: 435.0821.



Compound **19**: In a flame dried 20 mL vial, iodo-acetal **18** (200 mg, 0.48 mmol, 1.0 eq.) was combined with anhydrous THF (8 mL) under argon, and then TBAF (1.0 M solution in THF, 0.53 mL, 0.53 mmol, 1.0 eq.) was added all at once. The solution was left to stir at room temperature for 1 h, and then was concentrated under reduced pressure and purified directly by flash chromatography (2:1 hexanes/EtOAc) to give deprotected iodo-acetal **19** (142 mg, 98%) as a clear, colorless oil and inconsequential mixture of acetal diastereomers.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.04 (m, 2H), 5.03 (m, 1H), 4.96 (m, 1H), 4.68 (m, 1H), 3.70-3.50 (m, 2H), 3.23-3.13 (m, 2H), 2.26-2.19 (m, 1H), 2.07-1.96 (m, 1H), 1.73 (bs, 1H), 1.26-1.20 (m, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 138.1, 138.0, 135.2, 134.8, 101.7, 101.5, 81.0, 80.7, 76.0, 75.9, 62.0, 61.4, 42.0, 41.3, 15.2, 15.1, 5.8.

IR (ATR): 3371, 3060, 2974, 2923, 2851, 1481, 1416, 1350, 1316, 1272, 1177, 1102, 1040, 1000 cm^{-1}.

HRMS (ESI): *m/z* Calc. for $C_9H_{15}IO_3Na$ $[M+Na]^+$: 320.9958, found: 320.9957.

Compound **17:** In a flame dried 2-dram vial, deprotected iodo-acetal **19** (100.0 mg, 0.335 mmol, 1.0 eq.) was combined with anhydrous DCM (1 mL), DMAP (7.5 mg, 0.061 mmol, 0.18 eq.) and

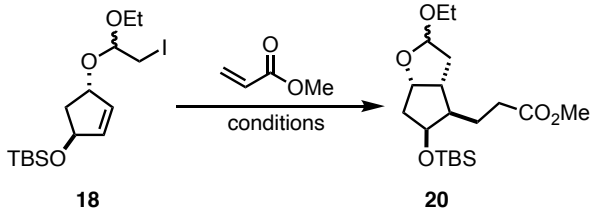
DIPEA (0.18 mL, 1.01 mmol, 3.0 eq.) under an argon atmosphere. The solution was cooled to 0 ˚C, and then a solution of acryloyl chloride (0.07 mL, 0.839 mmol, 2.5 eq.) in DCM (1 mL) was added slowly over a 5-min period (solution turned yellow). The solution was left to stir at 0 ˚C for another 15 min, and then to room temperature for 45 min. The solution was then quenched with DI water (1 mL), diluted with 30 mL EtOAc (30 mL), and washed with DI water (10 mL) and brine (10 mL). The organic phase was collected, dried over sodium sulfate, filtered and concentrated under reduced pressure to give a yellow oil, which was purified by flash chromatography (10:1 hexanes/EtOAc) to give acrylate tethered iodo-acetal **17** (100 mg, 84%) as a colorless oil and inconsequential mixture of acetal diastereomers.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.38-6.31 (m, 2H), 6.13 (m, 1H), 6.09-6.00 (m, 2H), 5.83 (m, 1H), 5.78 (m, 1H), 4.95 (m, 1H), 4.68 (m, 1H), 3.68-3.49 (m, 2H), 3.22-3.14 (m, 2H), 2.29-2.13 (m, 2H), 1.26-1.15 (m, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 166.0, 138.0, 137.6, 133.5, 130.9, 128.5, 101.7, 101.6, 80.4, 80.2, 78.8, 78.7, 61.9, 61.4, 38.6, 38.0, 15.2, 15.1, 5.6, 5.5.

IR (ATR): 3066, 3037, 2976, 2890, 1717, 1635, 1619, 1405, 1369, 1339, 1293, 1268, 1184, 1121, 1102, 1027 cm^{-1}.

HRMS (ESI): *m/z* Calc. for $C_{12}H_{17}IO_4Na$ $[M+Na]^+$: 375.0063, found: 375.0064.



18 **20**

a. Stork radical cascade
AIBN (0.1 eq.), *n*Bu_3SnCl (0.1 eq.)
$NaCNBH_3$ (1.5 eq.), MA (5.0 eq)
*t*BuOH (0.04 M), 85 ˚C, 72 h
61% (10.0 g scale)

b. nickel catalysis
$NiCl_2$•glyme (10 mol%)
neo (12 mol%), Zn (3 eq.), MA (1.5 eq.)
MeOH (0.2 M), 40 ˚C, 1 h
59% (0.25 g scale)
46% (3.2 g scale)

MA= methyl acrylate neo= neocuproine

Compound **20:**

(a) Stork radical cascade: Stork and colleagues performed tandem radical cyclizations on similar substrates, however, their reported conditions were unsuccessful for our case.[4] Our modified procedure is as follows: to iodo-acetal **18** (9.97 g, 24.2 mmol 1.0 eq) in a flame dried 1-L flask under argon were added the following reagents: AIBN (397 mg, 2.4 mmol, 0.1 eq.), $NaCNBH_3$ (2.28 g, 36.3 mmol, 1.5 eq.), 590 mL *t*BuOH (ACS grade), methyl acrylate (10.9 mL, 120.9 mmol, 5.0 eq.) (filtered neat through basic alumina before use) and nBu$_3$SnCl (0.73 mL, 2.4 mmol, 0.1 eq., Oakwood 90% purity). The solution was then heated to 85 ˚C. After stirring at this temperature for 72 h, the reaction was cooled to room temperature, and then concentrated with benzene three times to remove the *t*BuOH. The crude mixture was then dissolved in EtOAc (150 mL) and washed with DI water (50 mL) and brine (50 mL). The combined aqueous phases were washed with more EtOAc (2 x 100 mL), and then the combined organic phases were dried over magnesium sulfate, filtered and concentrated under reduced pressure to give a crude, orange oil. This oil was filtered through a silica plug with 1:1 hexanes/EtOAc (300 mL), and then the filtrate was concentrated to give a yellow oil. Purification was then performed using flash chromatography (pure hexanes to 9:1 hexanes/EtOAc) to give cyclized product **20** (5.47 g, 61%) (viscous, colorless oil) only as the desired diastereomer at the ester side chain (ester side chain on convex face of the molecule; still inconsequential mixture of acetal diastereomers). For stereochemical confirmation see the x-ray analysis of cyclopropanol **15** (Part 2). The other diastereomer (ester on the concave face of the molecule) was not found/able to be fully characterized after column. For smaller scale reactions (<1 g), anhydrous *t*BuOH (from Sigma-Aldrich, Sure/Seal) was used, the reaction was stirred for 24 hours, and no aqueous workup was performed (directly filtered through silica plug with 1:1 hexanes/EtOAc).

(b) Nickel conditions: To a flame dried 2-dram vial containing iodo-acetal **18** (250 mg, 0.61 mmol, 1.0 eq.), $NiCl_2$•glyme (13.3 mg, 0.061, 0.1 eq.) (weighed in glovebox) in 1.3 mL MeOH (HPLC grade) and neocuproine (15.2 mg, 0.073 mmol, 0.12 eq.) in 1.8 mL MeOH were added consecutively and all at once. The reaction mixture was stirred at room temperature for 10 min

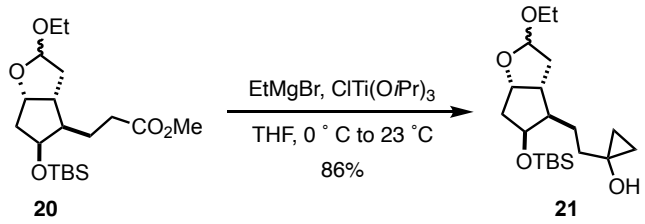
(reaction turned light green), and then to 40 ˚C for 10 min. After this time, Zn nanopowder (119 mg, 1.82 mmol, 3.0 eq.) and methyl acrylate (82 uL, 0.91 mmol, 1.5 eq.) (filtered neat through basic alumina before using) were added consecutively and all at once, and then the reaction was left to stir at 40 ˚C for another 1 h. After cooling to room temperature for 5 min, the reaction was filtered through a short celite pad followed by EtOAc (100 mL). The crude filtrate was then concentrated to give an orange solid, which was purified by flash chromatography (pure hexanes to 9:1 hexanes/EtOAc) to give cyclized product **20** (135 mg, 59%) only as the desired diastereomer at the ester side chain.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.20-5.10 (m, 1H), 4.78-4.62 (m, 1H), 4.27 (m, 1H), 3.71-3.64 (m, 4H), 3.43-3.31 (m, 1H), 2.59-2.25 (m, 3H), 2.15-1.48 (m, 7H), 1.20-1.10 (m, 3H), 0.86 (m, 9H), 0.03 (m, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 174.2, 174.1, 106.2, 106.0, 85.2, 82.5, 76.2, 75.8, 62.4, 62.3, 51.5, 51.4, 51.3, 50.4, 45.8, 45.3. 43.9, 41.5, 39.2, 37.9, 32.8, 32.6, 25.8, 24.6, 23.9, 18.0, 15.2, 15.1, -4.4, -4.5, -5.0.

IR (ATR): 2951, 2930, 2898, 2857, 1740, 1472, 1463, 1436, 1361, 1334, 1291, 1252 cm^{-1}.

HRMS (ESI): *m/z* Calc. for $C_{19}H_{36}O_5SiNa$ $[M+Na]^+$: 395.2224, found: 395.2227.



Compound **21**: The reaction was low yielding using the traditional protocol.[5] The reaction was successful using stoichiometric amounts of $ClTi(OiPr)_3$ as follows.[6] In a flame dried 250 mL flask, cyclized product **20** (3.72 g, 9.98 mmol, 1.0 eq.), was combined with $ClTi(OiPr)_3$ (0.46 M solution made from anhydrous THF, 104 mL, 48 mmol, 4.8 eq.) under argon. The solution was cooled to 0 ˚C, and then EtMgBr (1.0 M in THF, 96 mL, 96 mmol, 9.6 eq.) was added dropwise over a 1.5-h

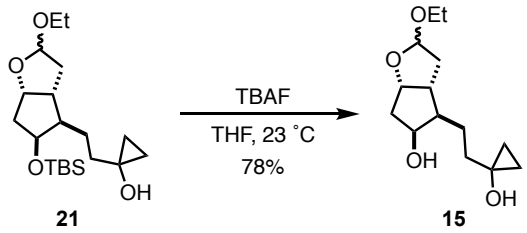
period (solution became dark brown/black). The solution was left to stir at 0 ˚C for another 1 h, and then to room temperature for 30 min. The reaction was then quenched by the addition EtOAc (15 mL) followed by sat. aqueous NH_4Cl (15 mL). The solution was then filtered through a celite pad, followed by EtOAc (250 mL), and then the filtrate was concentrated under reduced pressure, and diluted with EtOAc (150 mL) and brine (100 mL). The organic phase was collected, and then the aq. phase was washed with more EtOAc (100 mL). The combined organic phases were dried over magnesium sulfate, filtered, concentrated under reduced pressure, and purified by column (4:1 hexanes/EtOAc) to give cyclopropanol **21** (3.19 g, 86%) as a colorless oil and inconsequential mixture of acetal diastereomers.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.20-5.10 (m, 1H), 4.79-4.61 (m, 1H), 4.28 (m, 1H), 3.74-3.64 (m, 1H), 3.44-3.33 (m, 1H), 2.61-2.37 (m, 1H), 2.15-1.96 (m, 2H), 1.85-1.37 (m, 8H), 1.21-1.11 (m, 3H), 0.86 (m, 9H), 0.73 (m, 2H), 0.43 (m, 2H), 0.05-0.00 (m, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 106.1 105.9, 85.3, 82.3, 76.0, 75.9, 62.5, 62.3, 56.0, 55.9, 52.1, 50.9, 46.1, 45.5, 43.9, 41.4, 39.4, 37.9, 36.9, 36.7, 25.8, 25.1, 24.6, 18.0, 15.3, 15.2, 13.6, 13.5, 13.4, 13.3, -4.3, -4.4, -4.9.

IR (ATR): 3427, 2953, 2929, 2856, 1714, 1462, 1403, 1375, 1362, 1287, 1253, 1155, 1108, 1090, 1055, 1006 cm^{-1}.

HRMS (ESI): *m/z* Calc. for $C_{20}H_{38}O_4SiNa$ $[M+Na]^+$: 393.2431, found: 393.2431.



21 **15**

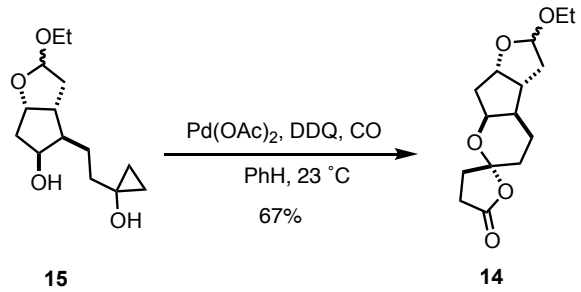
Compound **15**: In a flame dried 250 mL flask, cyclopropanol **21** (2.7 g, 7.3 mmol, 1.0 eq.) was combined with anhydrous THF (115 mL) under an argon atmosphere and cooled to 0 ˚C. To the solution, TBAF (1 M solution in THF, 7.3 mL, 7.3 mmol, 1.0 eq.) was added dropwise over a 30-min period, and then the solution was left to slowly warm to room temperature. After stirring for 43 h at room temperature, the reaction mixture was concentrated and diluted with EtOAc (50 mL) and DI water (50 mL). The organic phase was collected, and then the aq. phase was washed with more EtOAc (2 x 50 mL). The combined organic phases were then dried over sodium sulfate, filtered, concentrated under reduced pressure, and purified by flash chromatography (3:1 EtOAc/hexanes) to give deprotected cyclopropanol **15** (1.46 g, 78%) as a white solid. On smaller scale (<1 g) the reaction was done in less time (<1 day) and gave slightly higher yields (80-85%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.22-5.13 (m, 1H), 4.88-4.67 (m, 1H), 4.42 (m, 1H), 3.76-3.65 (m, 1H), 3.45-3.33 (m, 1H), 2.59-2.40 (m, 1H), 2.27-2.06 (m, 3H), 1.98-1.82 (m, 2H), 1.80-1.50 (m, 6H), 1.17 (m, 3H), 0.76 (m, 2H), 0.47 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 106.1, 105.8, 85.2, 82.4, 75.8, 75.7, 62.5, 62.4, 55.5, 55.4, 51.6, 50.6, 46.4, 46.1, 43.7, 41.1, 39.0, 37.8, 36.8, 36.6, 24.9, 21.1, 15.2, 15.1, 14.3, 14.2, 13.3, 13.2.

IR (ATR): 3352, 3083, 2972, 2936, 1647, 1444, 1417, 1405, 1373, 1333, 1290, 1253, 1209, 1184, 1163, 1106, 1083, 1052, 1007 cm^{-1}.

HRMS (ESI): *m/z* Calc. for $C_{14}H_{24}O_4Na$ $[M+Na]^+$: 279.1567, found: 279.1569.



15 **14**

Compound **14**: Following our reported conditions for synthesizing bicyclic lactones,[7] in a flame dried 100 mL flask, cyclopropanol **15** (68 mg, 0.265 mmol, 1.0 eq.) was combined with anhydrous

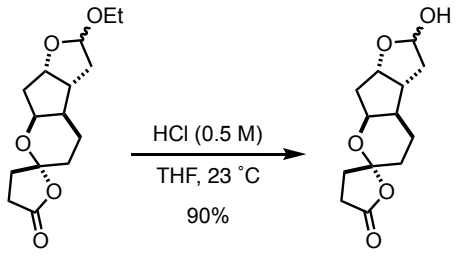
benzene (26 mL) to give a 0.01 M solution. To the solution, DDQ (120 mg, 0.530 mmol, 2.0 eq.) was added (solution turned bright orange) and then the flask was evacuated/backfilled with CO three times. $Pd(OAc)_2$ (6 mg, 0.027 mmol, 0.1 eq) was added all at once, and then the solution was left to stir at room temperature for 20 h (with CO balloon). The reaction was filtered through a celite pad with DCM, and then the filtrate was concentrated under reduced pressure and purified by flash chromatography (3:1 hexanes/EtOAc) to give oxaspirolactone **14** (50 mg, 67%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.26-5.15 (m, 1H), 4.85-4.68 (m, 1H), 4.41-4.34 (m, 1H), 3.76-3.67 (m, 1H), 3.46-3.34 (m, 1H), 2.80-2.60 (m, 2H), 2.52-2.42 (m, 1H), 2.35-1.96 (m, 6H), 1.93-1.63 (m, 5H), 1.22-1.12 (m, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 176.6, 176.5, 107.8, 107.7, 106.2, 106.1, 86.0, 83.5, 78.7, 78.2, 62.7, 62.6, 43.6, 42.8, 42.4, 42.2, 42.1, 39.7, 38.3, 37.5, 34.7, 34.6, 28.2, 28.1, 27.9, 19.3, 18.9, 15.3, 15.2.

IR (ATR): 2971, 2931, 2867, 1775, 1447, 1420, 1378, 1334, 1287, 1267, 1245, 1205, 1193, 1159, 1117, 1103, 1084, 1044, 1024, 1002 cm^{-1}.

HRMS (ESI): *m/z* Calc. for $C_{15}H_{22}O_5Na$ $[M+Na]^+$: 305.1360, found: 305.1361.



Compound **23**: In a 2-dram vial, oxaspirolactone **14** (13.9 mg, 0.049 mmol) was combined with THF (0.4 mL) and 0.5 M aq. HCl (0.6 mL). After stirring for 6 h, the reaction mixture was diluted with EtOAc (10 mL) and DI water (1 mL). The organic phase was collected, and the aqueous phase was washed with more EtOAc (2 x 10 mL). The combined organic phases were dried over sodium

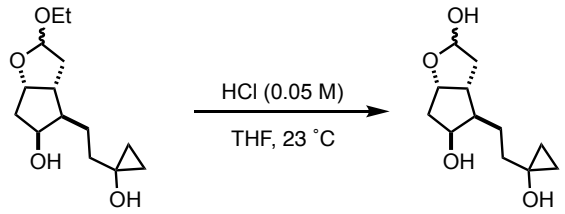
sulfate, concentrated under reduced pressure, and filtered through a pipette silica column followed by around another 15 mL of EtOAc. The filtrate was then concentrated under reduced pressure to give hemiacetal **23** (12 mg, 90%) which was used immediately in the next step (hemi-acetal **23** was freshly prepared each time for the olefination and alkynylation experiments).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.68-5.58 (m, 1H), 4.88-4.77 (m, 1H), 4.39 (m, 1H), 2.81-2.65 (m, 3H), 2.51-2.44 (m, 1H), 2.40-1.64 (m, 11H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 176.7, 176.6, 107.8, 107.7, 101.3, 100.8, 86.5, 83.9, 78.5, 78.3, 43.4, 42.8, 42.7, 42.6, 42.4, 39.8, 39.0, 37.9, 34.7, 28.2, 28.1, 27.8, 19.1, 18.9.

IR (ATR): 3424, 2927, 2856, 1771, 1552, 1449, 1379, 1327, 1286, 1266, 1246, 1203, 1121, 1108, 1070, 1043, 1021, 1001 cm^{-1}.

HRMS (ESI): *m/z* Calc. for $C_{13}H_{18}O_5Na$ $[M+Na]^+$: 277.1046, found: 277.1048.



15 **25**

Compound **25**: In a 50 mL flask, cyclopropanol **15** (498 mg, 1.94 mmol) was combined with THF (13 mL) (Note 1) and 0.05 M aqueous HCl (19 mL). After stirring for 2 h, the reaction mixture was quenched with K_2CO_3 (134 mg, 0.97 mmol) (Note 2), left to stir for 5 min, and then extracted with EtOAc (5 x 100 mL). The combined organic phases were then dried over sodium sulfate, filtered, concentrated under reduced pressure, and then concentrated an additional three times with DCM (Note 3) to give hemi-acetal **25** as a sticky solid which was briefly put under high vacuum, placed under argon atmosphere, and used directly in the next step (Wittig olefination) within one hour. Hemi-acetal **25** can be purified quickly by flash chromatography (pure EtOAc) and the purified product seems to be more stable (could be stored in fridge overnight under argon without

appreciable degradation) relative to the crude, however, we found that using the crude directly in the Wittig olefination gives a higher yield over 2 steps.

Note 1: Solvent purification system (SPS) or freshly distilled THF works best for the reaction. Directly using HPLC THF should be avoided, as with some (especially older) bottles a significant byproduct formed within 10 min of starting the reaction.

Note 2: The reaction should be quenched just when the starting material spot becomes faint by TLC (there will be 5-10% of SM remaining in the crude NMR). It is better to stop the reaction at this point because if left to stir for too long the product begins to rapidly degrade. Reaction times are usually slightly shorter for smaller scale reactions.

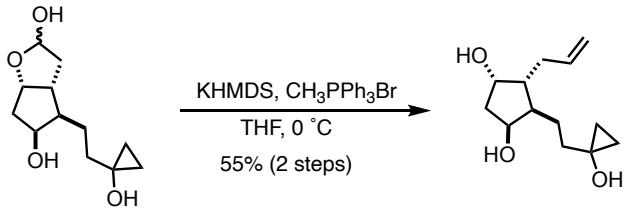
Note 3: Concentrating several times with DCM seemed to help slow the degradation of the product.

^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 5.52-5.43 (m, 1H), 4.86-4.62 (m, 2H), 4.31-4.02 (m, 2H), 3.54-3.42 (m, 1H), 2.56-2.32 (m, 1H), 2.15-1.91 (m, 3H), 1.82-1.47 (m, 6H), 0.63-0.54 (m, 2H), 0.44-0.31 (m, 2H).

^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ 100.6, 100.1, 84.7, 82.1, 74.9, 54.5, 54.4, 51.7, 51.1, 46.7, 46.1, 44.3, 41.6, 40.1, 38.7, 37.0, 25.0, 24.5, 13.0, 12.9.

IR (ATR): 3332, 3089, 3001, 2927, 2857, 1648, 1564, 1453, 1358, 1316, 1252, 1211, 1150, 1113, 1068, 1011 cm^{-1}.

HRMS (ESI): *m/z* Calc. for $C_{12}H_{20}O_4Na$ $[M+Na]^+$: 251.1254, found: 251.1255.



25 **26**

Compound **26**: In a flame dried 50 mL flask, CH_3PPh_3Br (2.6 g, 7.28 mmol, 3.75 eq.) was combined with anhydrous THF (50 mL) under argon, and then KHMDS (1 M solution in THF, 6.8 mL, 6.8

mmol, 3.5 eq.) (Note 1) was added all at once to give a bright yellow solution. The solution was left to stir at room temperature for 1 h, and then to 0 ˚C for another 1 h. After this time, hemi-acetal **25** (443 mg, 1.94 mmol, 1.0 eq., based on theoretical yield of the previous step) was combined with THF (4.7 mL) and added to the cooled ylide solution over an 8.5 min, followed by another THF (2 mL) wash of the hemi-acetal vial added over another 2 min period. After stirring at 0 ˚C for another 37 min (Note 2), the solution was quenched with saturated aq NH_4Cl (15 mL), diluted with DI water (10 mL), and extracted with EtOAc (5 x 100 mL). The combined organic phases were then dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a crude solid. This solid was purified by flash chromatography (pure DCM to 95:5 DCM/MeOH) to give olefin **26** (263 mg, 55%, over 2 steps) as a clear, sticky oil.

Note 1: The quality of the KHMDS can greatly impact the rate of the reaction. In general, for older bottles (< 1 M) the rate is slower. Regardless, the reaction should be tracked very closely by TLC as described in note 2.

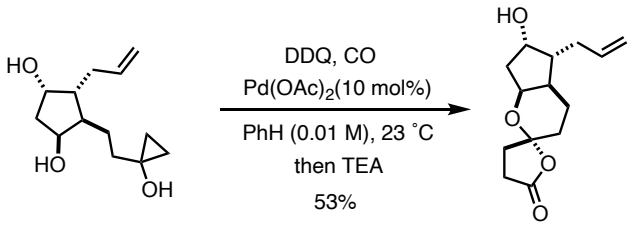
Note 2: The reaction should be monitored around every 5 min by TLC. Once the notable byproduct (pure EtOAc, rf = 0.3 for product, rf = 0.6 for byproduct) begins to form, the reaction should be stopped.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.92 (m, 1H), 5.14 (dd, *J* = 17.2, 1.5 Hz, 1H), 5.05 (dd, *J* = 10.2, 0.7 Hz, 1H), 4.45 (q, *J* = 4.2 Hz, 1H), 4.37 (q, *J* = 4.8 Hz, 1H), 2.30 (dt, *J* = 14.6, 4.9 Hz, 1H), 2.15 (m, 1H), 2.02 (t, *J* = 4.4 Hz, 2H), 1.84 (m, 1H), 1.78-1.55 (m, 6H), 0.74 (m, 2H), 0.44 (m, 2H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 138.2, 115.6, 72.4, 72.1, 55.4, 47.4, 46.6, 44.2, 36.9, 32.2, 22.8, 14.4, 13.2.

IR (ATR): 3270, 3077, 3005, 2973, 2926, 2907, 2861, 1641, 1454, 1437, 1415, 1379, 1345, 1328, 1285, 1219, 1202 cm^{-1}.

HRMS (ESI): *m/z* Calc. for $C_{13}H_{22}O_3Na$ $[M+Na]^+$: 249.1461, found: 249.1463.



26 **12**

Compound **12**: Following our reported conditions for synthesizing bicyclic lactones,[7] in a flame dried 100 mL flask, olefin **26** (194 mg, 0.86 mmol, 1.0 eq.) was combined with 80 mL of anhydrous PhH (80 mL) (Note 1) and then DDQ (390 mg, 1.7 mmol, 2.0 eq.) (Note 2) was added all at once to give a bright orange solution. The mixture was evacuated/backfilled with CO three times, and then $Pd(OAc)_2$ (0.013 M solution in PhH, 6.4 mL, 0.086 mmol, 0.1 eq.) (Note 3) was added all at once (no initial color change). After rapid stirring for 1 h at room temperature (with CO balloon) (mixture looked dark orange), the reaction was quenched with 2 mL of TEA (solution turned black) and was left to stir for an additional 30 min (Note 4). After this time, the mixture was filtered through a short celite pad with around EtOAc (150 mL), and then the filtrate was concentrated under reduced pressure, and then filtered through a short silica plug (Note 5) followed by EtOAc (200 mL). The filtrate was then concentrated under reduced pressure to give a dark green oil, which was purified by flash chromatography (first deactivated column with excess 95:5 hexanes/TEA, then ran 9:1 to 3:1 hexanes/EtOAc to purify product) to give oxaspirolactone **12** (115 mg, 53%) as a colorless oil (Note 6 and 7). The analytical data for this intermediate is consistent with the Sulikowski synthesis.[8] The product was purified twice to insure high purity for the next step (*Z*-selective metathesis).

Note 1: THF also worked for the reaction but gave a slightly lower yield.

Note 2: Other oxidants such as BQ or O_2 gave little to no product for the reaction.

Note 3: $Pd(TFA)_2$ or higher catalyst loadings of $Pd(OAc)_2$(0.25 eq.) gave slightly lower yields for the reaction.

Note 4: The purification steps following should be done immediately after this time (the product is not stable in the crude mixture).

Note 5: The silica plug was first deactivated with 200 mL of 95:5 EtOAc/TEA; the product seems to be acid sensitive.

Note 6: $CDCl_3$ for NMR should be neutralized with K_2CO_3.

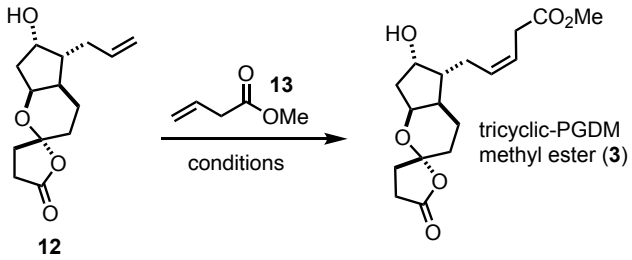
Note 7: If the product is exposed to acid during the workup or purification, a byproduct with a very similar rf to the product (difficult to remove by column) will form. If the above procedure is followed carefully the amount of byproduct stays <5% in the NMR, even after prolonged storage in the fridge.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.90 (m, 1H), 5.12 (dd, *J* = 17.1, 1.5 Hz, 1H), 5.03 (dd, *J* = 10.2, 0.8 Hz, 1H), 4.35 (m, 2H), 2.72 (dt, *J* = 17.7, 9.9 Hz, 1H), 2.45 (ddd, *J* = 17.7, 9.5, 2.7 Hz, 1H), 2.20-2.10 (m, 4H), 2.05-1.95 (m, 3H), 1.90-1.60 (m, 5H), 1.53 (bs, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 176.6, 137.8, 115.9, 108.1, 74.9, 72.6, 42.8, 42.1, 39.7, 34.8, 31.8, 28.6, 28.3, 18.5.

IR (ATR): 3447, 3074, 2933, 1764, 1639, 1452, 1418, 1380, 1287, 1242, 1195, 1120, 1097, 1035 cm^{-1}.

HRMS (ESI): *m/z* Calc. for $C_{14}H_{20}O_4Na$ $[M+Na]^+$: 275.1254, found: 275.1255.



Tricyclic-PGDM methyl ester **3**:

Overview: The "Metathesis Reaction Parameters" outlined in Part 1(c) were implemented herein. Table S1 provides the screened metathesis conditions for the synthesis of tricyclic-PGDM methyl

ester **3**. Entries 1-12 were on small scale (5 mg scale **12**), entry 13 corresponds to a "medium scale" (16 mg scale **12**) reaction using the best condition from entries 1-12, and entry 14 is a "large scale" (100 mg scale **12**) using the "Optimized *Z*-Selective Metathesis General Procedure" outlined in Part 1(c).

Exemplary Procedure: In a N_2 filled glovebox, oxaspirolactone **12** (16 mg, 0.063 mmol, 1.0 eq.) was combined with DCE (0.33 mL) and methyl 3-butenoate **13** (54 uL, 0.51 mmol, 8.0 eq.) in a Biotage (0.5-2 mL) microwave vial (Figure S1(b)). To the vial, the Grubbs *Z*-selective (DIPP) catalyst (6.4 mg, 0.0095 mmol, 0.15 eq.) was then added all at once in DCE (0.3 mL) to give a final concentration of 0.1 M (solution looks light purple). As soon as the catalyst was added, the microwave vial (open to the atmosphere of the glovebox, no cap, see Figure S1(b)) was placed in a sand bath to 40 ˚C. After stirring at this temperature for 2 h, the reaction mixture (looks brown) was removed from the glovebox, concentrated, and purified by column (slow gradient, pure hexanes to 3:2 hexanes/EtOAc) to give tricyclic-PGDM methyl ester **3** (10.7 mg, 52%, >95% *Z*) as a colorless oil. The analytical data is in agreement with the reported syntheses.[8,9]

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.67 (td, *J* = 10.3, 4.9, 1H), 5.59-5.52 (m, 1H), 4.40 (td, *J* = 5.1, 1.5 Hz, 1H), 4.33-4.27 (m, 1H), 3.69 (s, 3H), 3.27 (dd, *J* = 15.9, 8.9 Hz, 1H), 3.03 (dd, *J* = 15.9, 6.1 Hz, 1H), 2.75 (dt, *J* = 17.6, 9.9 Hz, 1H), 2.57-2.51 (m, 1H), 2.47 (ddd, *J* = 17.6, 9.5, 2.7 Hz, 1H), 2.31 (dt, *J* = 14.5, 10.2 Hz, 1H), 2.24-1.57 (m, 11H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 176.6, 173.1, 132.9, 121.6, 108.1, 74.9, 71.9, 52.2, 43.7, 42.2, 39.3, 34.8, 32.9, 28.7, 28.3, 25.0, 18.4.

IR (ATR): 3485, 3022, 2930, 1769, 1735, 1650, 1437, 1380, 1330, 1287, 1272, 1242, 1193, 1170, 1120, 1100, 1079, 1035, 1007 cm^{-1}.

HRMS (ESI): *m/z* Calc. for $C_{17}H_{24}O_6Na$ $[M+Na]^+$: 347.1465, found: 347.1464.

Table S1: *Z*-Selective metathesis condition screening for the total synthesis of tricyclic-PGDM methyl ester **(3)**

Entry	Solvent (0.1 M)	Me-Ester (equiv.)	*Z*-Ru cat. (mol%)	Temp (˚C)	Time (h)	Yield (isolated)	Recovered SM	% *Z*
1	DCE	10	Mes (20)[1]	53	2	10-15%	NA	90
2	DCE	8	Mes (20)	53	2	35%	40%	90
3	DCE	8	DIPP (20)	53	2	42%	45%[2]	94
4	DCE	8	DIPP (20)	40	2	50%	44%	>95
5	DCE	8	DIPP (20)	30	2[3]	38%	58%	>95
6	DCE	8	DIPP (10)	40	2	33%	51%	>95
7	DCE	8	DIPP (5)	40	2	22%	78%	>95
8	DCE	2	DIPP (20)	40	2[3]	35%	45%[2]	94
9	THF	8	DIPP (20)	40	2	7%	65%	>95
10	THF	8	Mes (20)	40	2	4%	70%	95
11	DCE	8[4]	DIPP (20)	40	2	32%	39%	>95
12	DCE	8	DIPP (20)[5]	40	2[3]	35%	39%	>95
13[6]	DCE	8	DIPP (15)	40	2	52%	35%	>95
14[7]	DCE	5	DIPP (5)	30	12	38%	52%[2]	>95

Typical Procedure: In a glovebox, combined **12** (5 mg, 0.02 mmol) with 0.1 mL DCE and methyl 3-butenoate **(13)** in 0.2-0.5 mL Biotage vial (see Figure S1(b)), add catalyst in 0.1 mL DCE all at once, and then heat to appropriate temperature with stirring (reaction open to glovebox atmosphere; see Figure S1(b)). In general, after 2 h the reaction mixture changed from light purple to brown.

[1]Exemplary result using Ru-Mes catalyst directly from Sigma without purification. Around 20 conditions were tried using this impure catalyst but they were inconsistent. The remaining entries for this catalyst use the re-purified Ru-Mes catalyst (see "Metathesis Reaction Parameters" in Part 1(c))
[2]The recovered starting material contained an impurity that was inseparable by chromatography.
[3]Reaction still looked slightly red/purple
[4]Added 1.0 eq. of methyl 3-butenoate **(13)** at the beginning and then 1.0 eq. every 15 min
[5]Added 5 mol% Ru-cat at beginning (initial conc. 0.15 M of substrate), and then 5 mol% (25 uL, 0.04 M in DCE) every 30 min (final conc. 0.1 M)
[6]Reaction performed on 16 mg scale **(12)** in 0.5-2.0 mL Biotage microwave vial (Figure S1(b))
[7]Reaction performed on 100 mg scale **(12)** in VWR vial (Figure S1(b)) following "Optimized *Z*-Selective Metathesis General Procedure" (Part 1(c))

Z-Selective Metathesis

Metathesis Reaction Parameters: All solvents (DCE, THF, PhH, pentanes) were freshly distilled over CaH_2 (or Na/benzophenone for THF) and degassed by freeze pump thaw. Deuterated benzene for NMR monitoring was degassed by freeze pump thaw. The *Z*-selective (DIPP) catalyst was graciously sent by Professor Grubbs, and the *Z*-selective (Mes) catalyst was purchased from Sigma-Aldrich and repurified as follows: in a N_2 filled glovebox, the *Z*-selective (Mes) catalyst (80 mg) (looks dark brown/black) was combined with 1 mL of pentane, and then filtered through a 1 mL syringe (clogged with a small piece of cotton) filled to the 0.5 mL mark with celite (celite briefly

dried in oven before putting in glovebox) and pre-moistened with pentane. The above catalyst solution was then filtered followed by 2 mL of PhH to give a dark purple solution. The resulting filtrate was then concentrated under reduced pressure (in the glovebox) to give a dark purple/black solid (see Figure S1 (a) for catalyst descriptions). Methyl 3-butenoate **13** (purchased from Sigma-Aldrich) and all commercial olefins were filtered neat through neutral alumina in the glovebox before use.

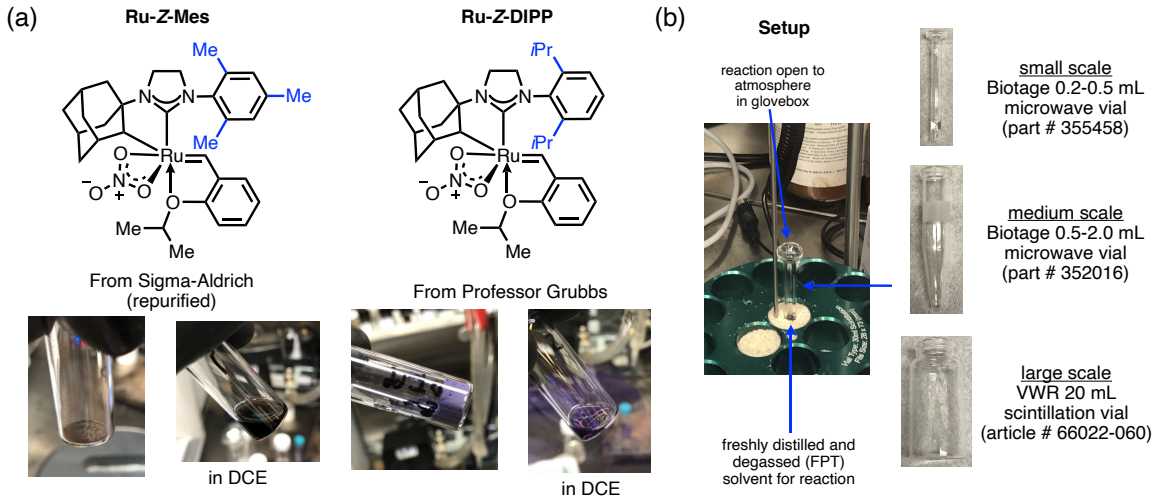
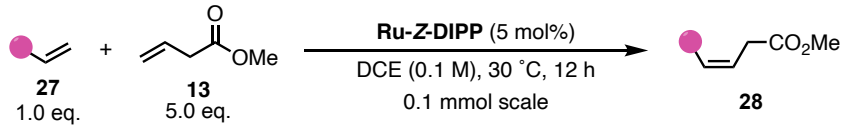


Figure S1: (a) Catalyst desciption and (b) reaction setup

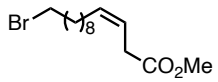
Z-selective Metathesis Optimization NMR Studies: In a 0.5-2 mL Biotage microwave vial (see Figure S1 (b)), 11-Bromo-1-undecene (23.3 mg, 0.1 mmol, 1.0 eq.) was combined with DCE (0.5 mL) and methyl 3-butenoate **13** (54 uL, 0.5 mmol, 5.0 eq.). To the solution, the Grubbs *Z*-selective (DIPP) catalyst (3.4 mg, 0.005 mmol, 0.05 eq.) in 0.5 mL DCE was then added all at once to give a final concentration of 0.1 M (solution looks light purple). The mixture (reaction ran open to the atmosphere of the glovebox (no cap); see Figure S1 (b)) was then heated to 30 ˚C and monitored by H-NMR (Note 1) to track the quantity of the ruthenium catalyst remaining. To track the *Z/E* ratio, each NMR sample was immediately concentrated under reduced pressure and reanalyzed in C_6D_6.

Note 1: For sampling, 200 uL of the reaction mixture was combined with 400 uL of C_6D_6 containing anthracene as an internal standard (combined in NMR tube in glovebox and sealed cap with parafilm) and immediately analyzed. After each addition, a line was marked on the side of the microwave vial and DCE was intermittently added to account for evaporation.



Optimized *Z*-Selective Metathesis General Procedure: In a 0.5-2 mL Biotage microwave vial (see Figure S1 (b)), the olefin substrate **27** (0.1 mmol, 1.0 eq.) was combined with DCE (0.5 mL) and methyl 3-butenoate **13** (53 uL, 0.5 mmol, 5.0 eq.). The Grubbs Z-selective DIPP catalyst (3.4 mg, 0.005 mmol, 0.05 eq.) was then combined with DCE (0.5 mL) and added all at once to the microwave vial (solution looks light purple). The reaction mixture (open to atmosphere of the glovebox (no cap); see Figure S1 (b)) was left to stir at 30 ˚C for 12 h (for all substrates reaction looked brown after this time), and was then removed from the glovebox, concentrated under reduced pressure, and purified by flash chromatography to give the metathesis products **28**.

Metathesis Experimental Data



28a
54% (95% *Z*)

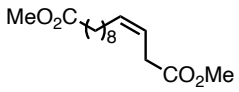
Compound **28a**: 11-Bromo-1-undecene and methyl 3-butenoate were reacted following the general procedure. Flash chromatography (pure hexanes to 3% EtOAc) gave product **28a** (16.6 mg, 54% yield, 95% *Z*) as a colorless oil.

^{1}H NMR (500 MHz, C_6D_6) δ 5.71-5.65 (dtt, *J* = 10.5, 7.2, 1.6 Hz, 1H), 5.51-5.44 (dtt, *J* = 10.9, 7.3, 1.8 Hz, 1H), 3.29 (s, 3H), 2.96-2.91 (m, 4H), 1.89 (q, *J* = 7.4 Hz, 2H), 1.48 (m, 2H), 1.26-1.18 (m, 2H), 1.17-0.98 (m, 10H).

^{13}C NMR (125 MHz, C_6D_6) δ 171.2, 132.9, 121.4, 50.9, 33.4, 32.7, 32.6, 29.4, 29.3, 29.2, 29.1, 28.7, 28.0, 27.3.

IR (ATR): 3021, 2925, 2854, 1740, 1458, 1435, 1402, 1329, 1287, 1251, 1194 cm^{-1}.

HRMS (ESI): *m/z* Calc. for $C_{14}H_{26}BrO_2$ $[M+H]^+$: 305.1111/305.1093, found: 305.1111/305.1091.



28b
60%, (>95% *Z*)

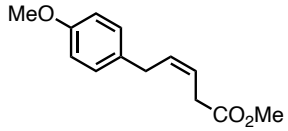
Compound **28b**: Methyl 10-undecenoate and methyl 3-butenoate were reacted following the general procedure. Flash chromatography (pure hexanes to 3% EtOAc) gave product **28b** (16.3 mg, 60%, >95% *Z*) as a colorless oil.

^{1}H NMR (500 MHz, C_6D_6) δ 5.66 (dtt, *J* = 10.5, 7.2, 1.6 Hz, 1H), 5.45 (dtt, *J* = 10.9, 7.4, 1.8 Hz, 1H), 3.34 (s, 3H), 3.29 (s, 3H), 2.92 (dd, *J* = 7.3, 1.8 Hz, 2H), 2.08 (t, *J* = 7.4 Hz, 2H), 1.86 (q, *J* = 7.0 Hz, 2H), 1.55-1.47 (m, 2H), 1.35-1.07 (m, 10H).

^{13}C NMR (125 MHz, C_6D_6) δ 173.0, 171.2, 132.9, 121.3, 50.9, 50.6, 33.8, 32.6, 29.3, 29.2, 29.1, 29.0, 27.3, 24.9.

IR (ATR): 3023, 2926, 2854, 1737, 1457, 1436, 1401, 1363, 1329, 1252, 1194 cm^{-1}.

HRMS (ESI): *m/z* Calc. for $C_{13}H_{27}O_3$ $[M+H]^+$: 271.1904, found: 271.1904.



28c
59% (>95% *Z*)

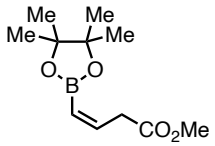
Compound **28c**: 4-Allylanisole and methyl 3-butenoate were reacted following the general procedure. Flash chromatography (pure hexanes to 1% EtOAc) gave product **28c** (13.0 mg, 59% yield, >95% *Z*) as a colorless oil.

^{1}H NMR (500 MHz, C_6D_6) δ 6.94 (d, *J* = 8.6 Hz, 2H), 6.74 (d, *J* = 8.6 Hz, 2H), 5.74-5.65 (dtt, *J* = 10.7, 7.1, 1.5 Hz, 1H), 5.64-5.57 (dtt, *J* = 10.6, 7.4, 1.5 Hz, 1H), 3.29 (m, 6H), 3.11 (dd, *J* = 7.3, 1.6 Hz, 2H), 2.92 (dd, *J* = 7.1, 1.7 Hz, 2H).

^{13}C NMR (125 MHz, C_6D_6) δ 171.1, 158.4, 132.0, 131.8, 129.3, 121.7, 114.0, 54.4, 51.0, 32.6, 32.5.

IR (ATR): 3029, 2998, 2951, 2926, 2853, 2041, 1736, 1611, 1584, 1510, 1464, 1436, 1398, 1330, 1301, 1243, 1194 cm^{-1}.

HRMS (ESI): *m/z* Calc. for $C_{13}H_{17}O_3$ $[M+H]^+$: 221.1172, found: 221.1172.



28d
35% (>95% *Z*)

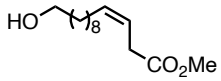
Compound **28d**: Vinylboronic acid pinacol ester and methyl 3-butenoate were reacted following the general procedure. Flash chromatography (pure hexanes to 15% EtOAc) gave product **28d** (8.5 mg, 35% yield, >95% *Z*) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.57 (dt, *J* = 13.7, 7.0 Hz, 1H), 5.55 (dt, 13.5, 1.7 Hz, 1H), 3.69 (s, 3H), 3.53 (dd, *J* = 7.1, 1.7 Hz, 2H), 1.26 (s, 12H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4, 144.9, 83.2, 51.8, 37.1, 24.9.

IR (ATR): 2979, 2953, 2928, 2855, 1740, 1634, 1436, 1424, 1391, 1380, 1372, 1321, 1283, 1263, 1214, 1198 cm^{-1}.

HRMS (ESI): *m/z* Calc. for $C_{11}H_{20}BO_4$ $[M+H]^+$: 227.1452, found: 227.1451.



28e
68% (>95% *Z*)

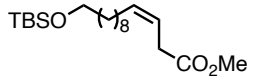
Compound **28e**: 10-Undecen-1-ol and methyl 3-butenoate were reacted following the general procedure. Flash chromatography (pure hexanes to 15% EtOAc) gave product **28e** (16.5 mg, 68% yield, >95% *Z*) as a colorless oil.

^{1}H NMR (500 MHz, C_6D_6) δ 5.70-5.62 (dtt, *J* = 10.5, 7.2, 1.6 Hz, 1H), 5.51-5.42 (dtt, *J* = 10.8, 7.3, 1.7 Hz, 1H), 3.37 (t, *J* = 6.5 Hz, 2H), 3.29 (s, 3H), 2.92 (dd, *J* = 7.3, 1.9 Hz, 2H), 1.89 (q, *J* = 7.2 Hz, 2H), 1.38 (m, 2H), 1.26-1.12 (m, 13H).

^{13}C NMR (125 MHz, C_6D_6) δ 171.3, 133.0, 121.3, 62.4, 50.9, 32.9, 32.6, 29.6, 29.5, 29.3, 29.2, 27.3, 25.8.

IR (ATR): 3363, 3024, 2924, 2853, 1741, 1462, 1436, 1400, 1329, 1294, 1256, 1195 cm^{-1}.

HRMS (ESI): *m/z* Calc. for $C_{14}H_{27}O_3$ $[M+H]^+$: 243.1957, found: 243.1955.



28f
57% (>95% *Z*)

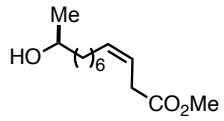
Compound **28f:** TBS protected 10-Undecen-1-ol[10] and methyl 3-butenoate were reacted following the general procedure. Flash chromatography (pure hexanes to 1% EtOAc) gave product **28f** (20.4 mg, 57% yield, >95% *Z*) as a colorless oil.

^{1}H NMR (500 MHz, C_6D_6) δ 5.70-5.63 (dtt, *J* = 10.6, 7.2, 1.6 Hz, 1H), 5.50-5.42 (dtt, *J* = 10.8, 7.3, 1.8 Hz, 1H), 3.55 (t, *J* = 6.4 Hz, 2H), 3.29 (s, 3H), 2.92 (dd, *J* = 7.2, 1.8 Hz, 2H), 1.88 (q, *J* = 7.0 Hz, 2H), 1.51 (m, 2H), 1.37-1.30 (m, 2H), 1.26-1.14 (m, 10H), 0.96 (s, 9H), 0.05 (s, 6H).

^{13}C-NMR (125 MHz, C_6D_6) δ 171.2, 132.9, 121.3, 63.0, 50.9, 33.0, 32.6, 29.7, 29.5, 29.4, 29.3, 29.2, 27.3, 26.0, 25.8, 18.2, -5.5.

IR (ATR): 3024, 2927, 2855, 1744, 1463, 1435, 1402, 1387, 1361, 1328, 1253, 1193 cm^{-1}.

HRMS (ESI): *m/z* Calc. for $C_{20}H_{41}O_3Si$ $[M+H]^+$: 357.2819, found: 357.2820.



28g
69% (>95% *Z*)

Compound **28g**: Dec-9-en-2-ol[11] and methyl 3-butenoate were reacted following the general procedure. Flash chromatography (pure hexanes to 10% EtOAc) gave product **28g** (15.8 mg, 69%, >95% *Z*) as a colorless oil.

^{1}H NMR (500 MHz, C_6D_6) δ 5.65 (dtt, *J* = 10.5, 7.2, 1.6 Hz, 1H), 5.46 (dtt, *J* = 10.8, 7.4, 1.7 Hz, 1H), 3.55-3.48 (m, 1H), 3.29 (s, 3H), 2.92 (dd, *J* = 7.2, 1.9 Hz, 2H), 1.87 (q, *J* = 7.2 Hz, 2H), 1.34-1.12 (m, 11H), 0.99 (d, *J* = 6.2 Hz, 3H).

^{13}C NMR (125 MHz, C_6D_6) δ 171.3, 133.0, 121.3, 67.3, 50.9, 39.4, 32.6, 29.5, 29.2, 29.1, 27.3, 25.7, 23.5.

IR (ATR): 3397, 3024, 2925, 2854, 1740, 1657, 1457, 1436, 1328, 1257, 1195 cm^{-1}.

HRMS (ESI): *m/z* Calc. for $C_{13}H_{24}O_3Na$ $[M+Na]^+$: 251.1620, found: 251.1618.

References:

1) M. E. Jung, J. A. Berliner, D. Angst, D. Yue, L. Koroniak, A. D. Watson, R. Li, *Org. Lett*., **2005**, *7*, 3933.
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Part 2. X-Ray structure and analysis data

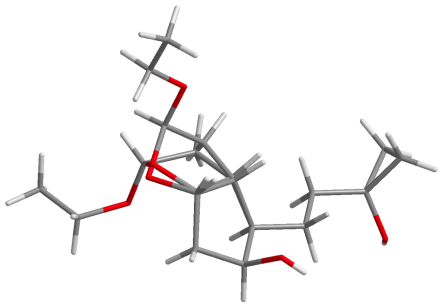


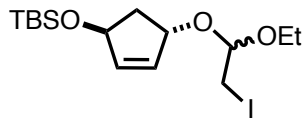
Figure S2: X-Ray Structure of **15**

Solid Structure of **15**: Vapor diffusion crystallization (DCE/hexanes: dissolved compound **15** in DCE in inner chamber and placed hexanes in outer chamber) afforded small white crystals of **15** for X-ray diffraction. The data were collected at 150 K on a Bruker AXS D8 Quest CMOS diffractometer with Mo sealed tube and curved triumph monochromator with a 10 cm x 10 cm Photon-100 detector and fixed chi angle. The supplementary crystallographic data was deposited in The Cambridge Crystallographic Data Centre (CCDC 2089935). X-ray analysis data of **15** (Figure S2 and S3).

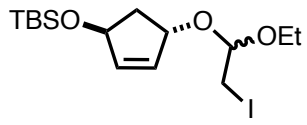
```
Bond precision:        C-C = 0.0046 A                  Wavelength=1.54178
Cell:        a=15.137(3)       b=7.8516(11)      c=11.998(2)
             alpha=90          beta=103.523(13)  gamma=90
Temperature: 150 K
                     Calculated                          Reported
Volume               1386.4(4)                           1386.5(4)
Space group          P 21/c                              P 21/c
Hall group           -P 2ybc                             -P 2ybc
Moiety formula       C14 H24 O4                          ?
Sum formula          C14 H24 O4                          C14 H24 O4
Mr                   256.33                              256.33
Dx,g cm-3            1.228                               1.228
Z                    4                                   4
Mu (mm-1)            0.718                               0.718
F000                 560.0                               560.0
F000'                561.74
h,k,lmax             19,10,15                            19,9,15
Nref                 3018                                2898
Tmin,Tmax            0.891,0.986                         0.589,0.754
Tmin'                0.891
Correction method= # Reported T Limits: Tmin=0.589 Tmax=0.754
AbsCorr = MULTI-SCAN
Data completeness= 0.960           Theta(max)= 79.868
R(reflections)= 0.0832( 1643)          wR2(reflections)= 0.2642( 2898)
S = 1.071               Npar= 242
```

Figure S3: X-ray analysis data for **15**

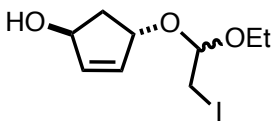
Part 3. ^{1}H and ^{13}C NMR spectra



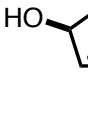
^{1}H-NMR (500 MHz, $CDCl_3$)



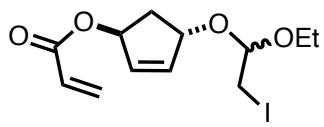
^{13}C-NMR (125 MHz, $CDCl_3$)



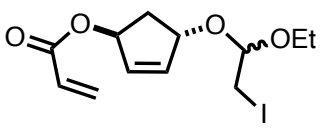
^{1}H-NMR (500 MHz, $CDCl_3$)



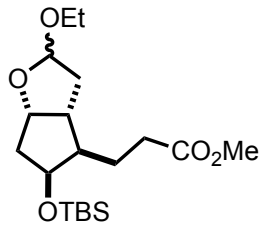
^{13}C-NMR (125 MHz, $CDCl_3$)



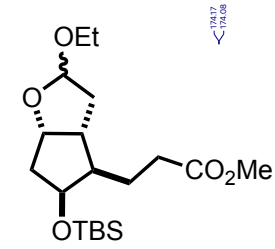
^{1}H-NMR (500 MHz, $CDCl_3$)



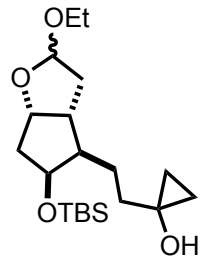
^{13}C-NMR (125 MHz, $CDCl_3$)



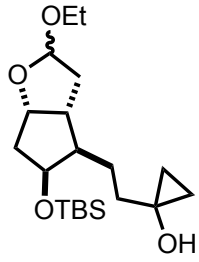
^{1}H-NMR (500 MHz, $CDCl_3$)



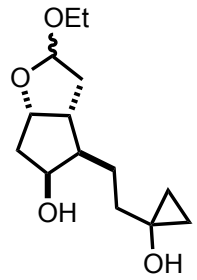
^{13}C-NMR (125 MHz, $CDCl_3$)



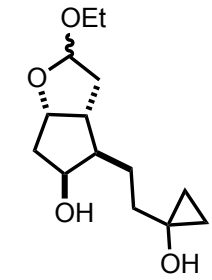
^{1}H-NMR (500 MHz, $CDCl_3$)



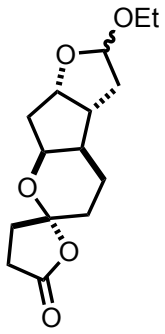
^{13}C-NMR (125 MHz, $CDCl_3$)



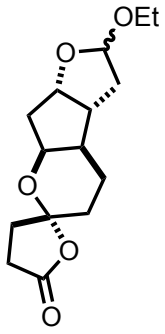
^{1}H-NMR (500 MHz, $CDCl_3$)



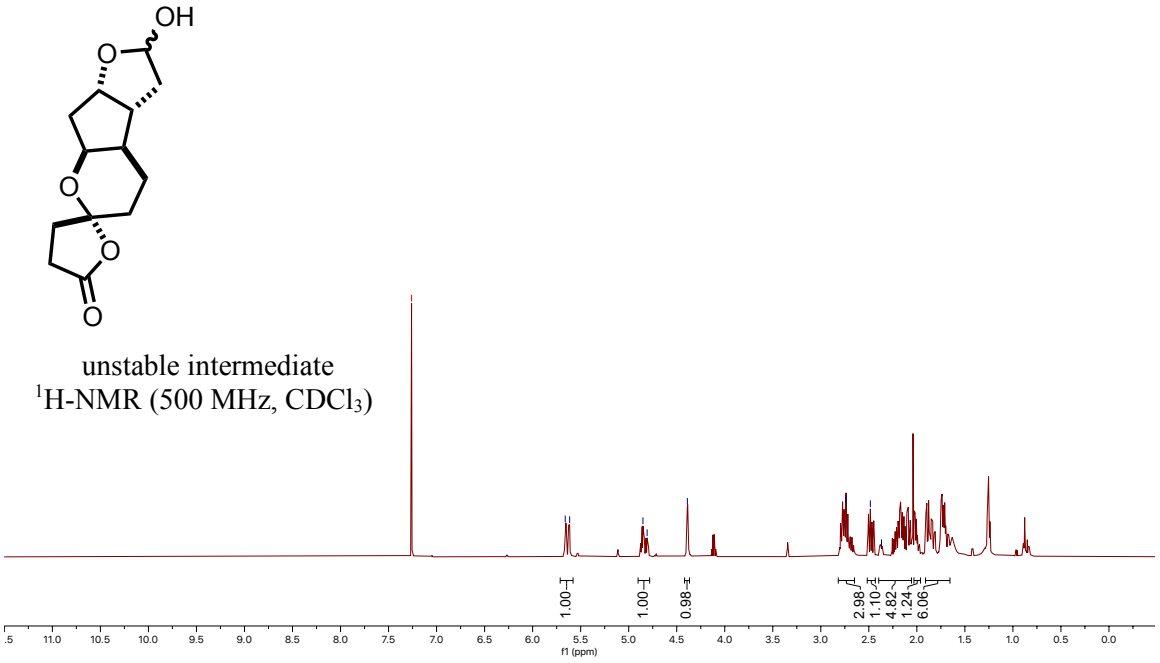
^{13}C-NMR (125 MHz, $CDCl_3$)



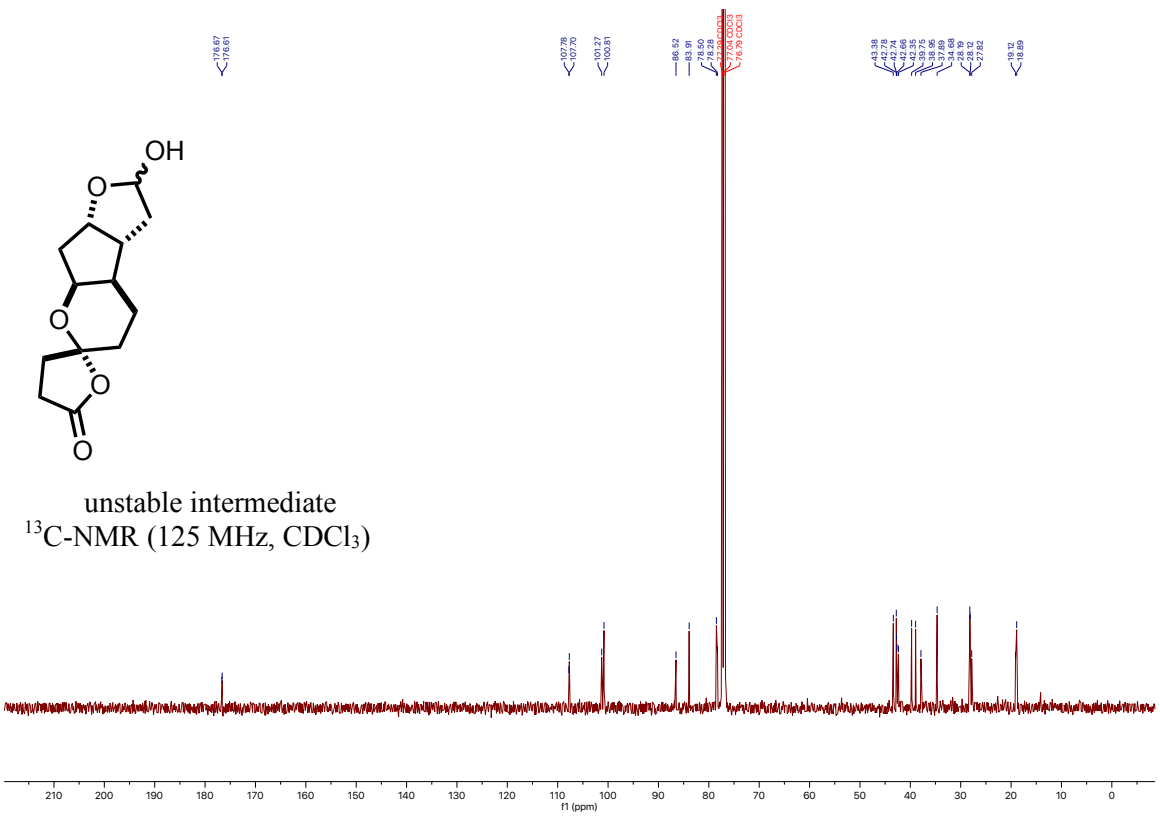
^{1}H-NMR (500 MHz, $CDCl_3$)



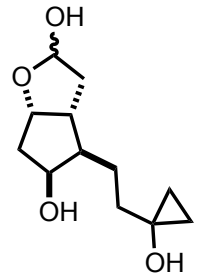
^{13}C-NMR (125 MHz, $CDCl_3$)



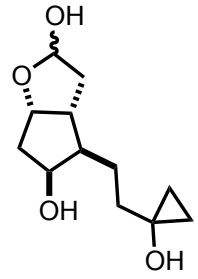
unstable intermediate
^{1}H-NMR (500 MHz, $CDCl_3$)



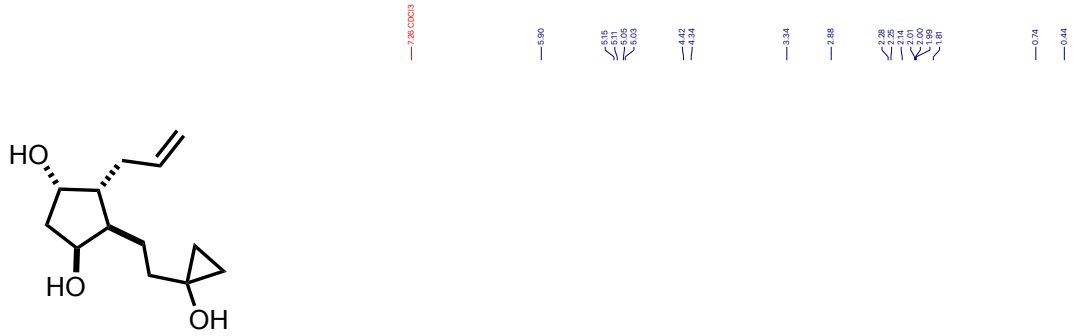
unstable intermediate
^{13}C-NMR (125 MHz, $CDCl_3$)



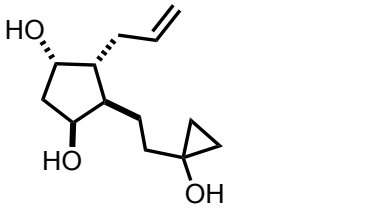
unstable intermediate
^{1}H-NMR (500 MHz, $(CD_3)_2CO$)



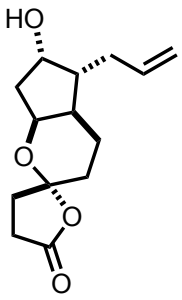
unstable intermediate
^{13}C-NMR (125 MHz, $(CD_3)_2CO$)



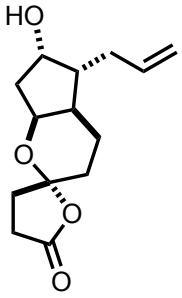
^{1}H-NMR (500 MHz, $CDCl_3$)



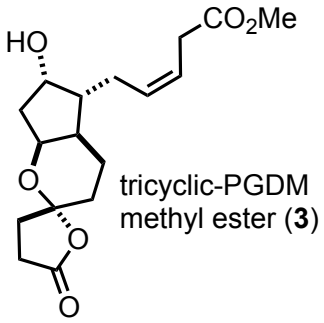
^{13}C-NMR (125 MHz, $CDCl_3$)



^{1}H-NMR (500 MHz, $CDCl_3$)

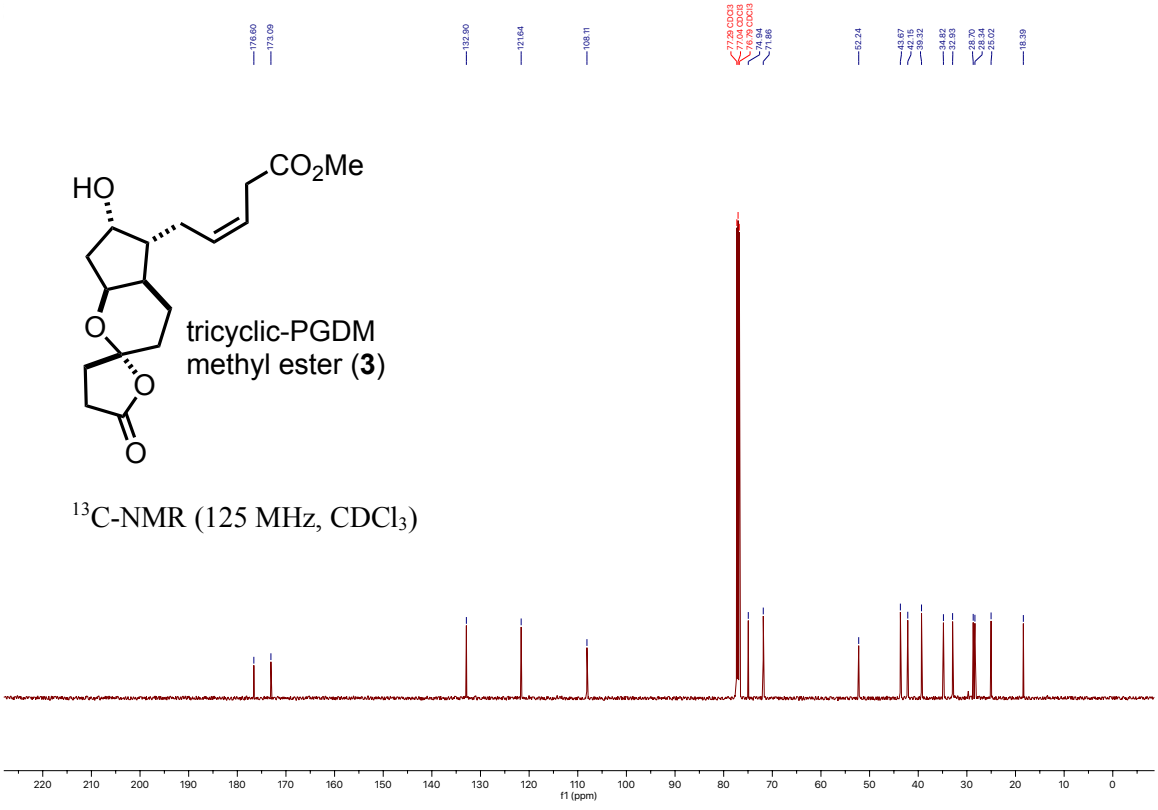


^{13}C-NMR (125 MHz, $CDCl_3$)



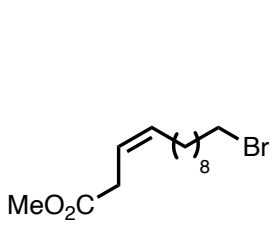
tricyclic-PGDM
methyl ester (**3**)

^{1}H-NMR (500 MHz, $CDCl_3$)

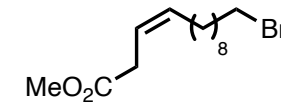


tricyclic-PGDM
methyl ester (**3**)

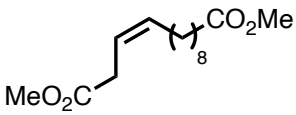
^{13}C-NMR (125 MHz, $CDCl_3$)



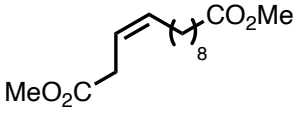
^{1}H-NMR (500 MHz, C_6D_6)



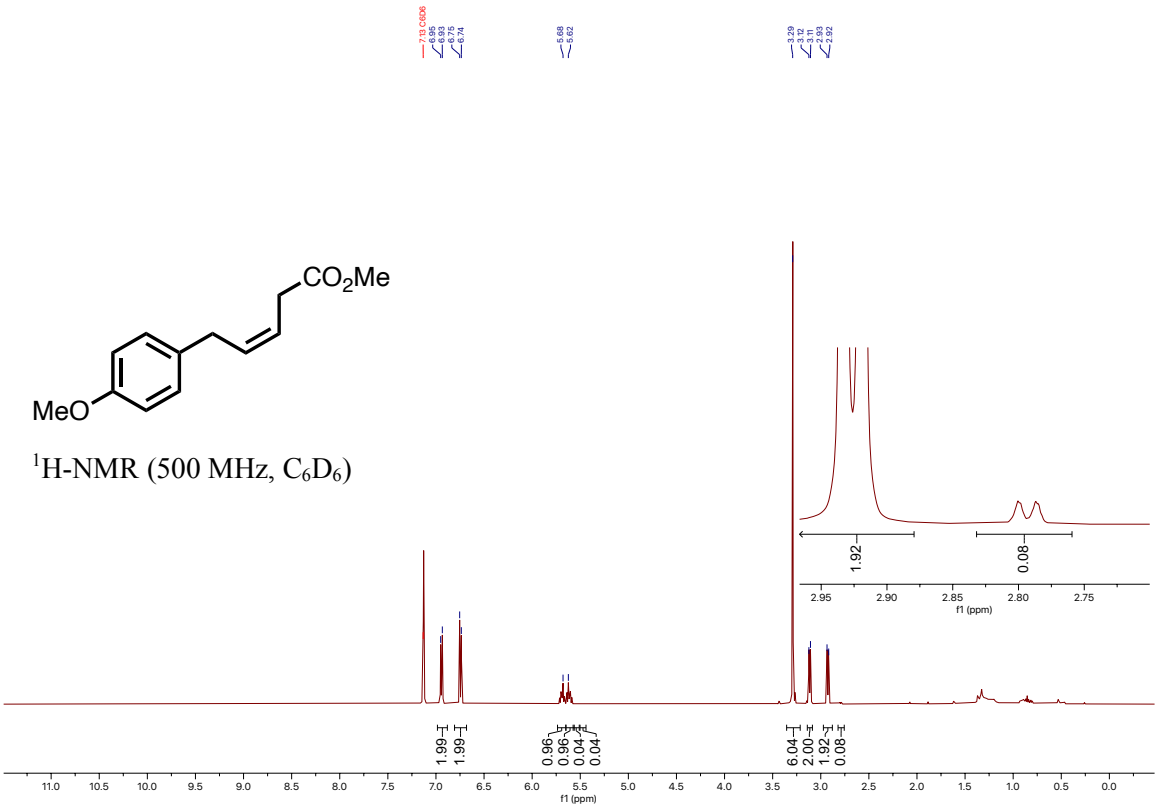
^{13}C-NMR (125 MHz, C_6D_6)

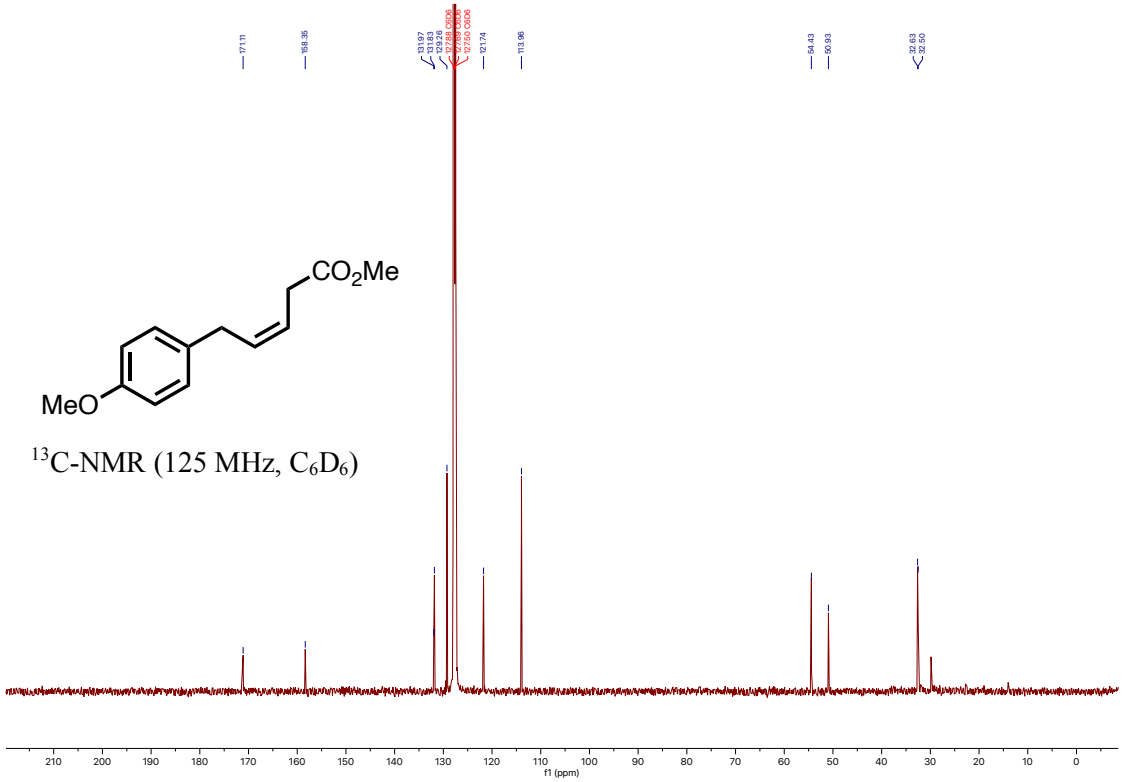


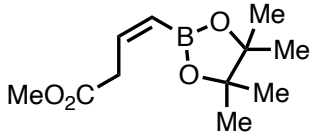
^{1}H-NMR (500 MHz, C_6D_6)



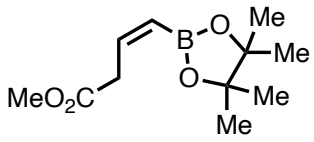
^{13}C-NMR (125 MHz, C_6D_6)


CO2Me
MeO
1H-NMR (500 MHz, C6D6)
7.15 C6D6
6.95
6.93
6.75
6.74
5.68
5.62
3.29
3.12
3.11
2.93
2.92
1.92
0.08
f1 (ppm)

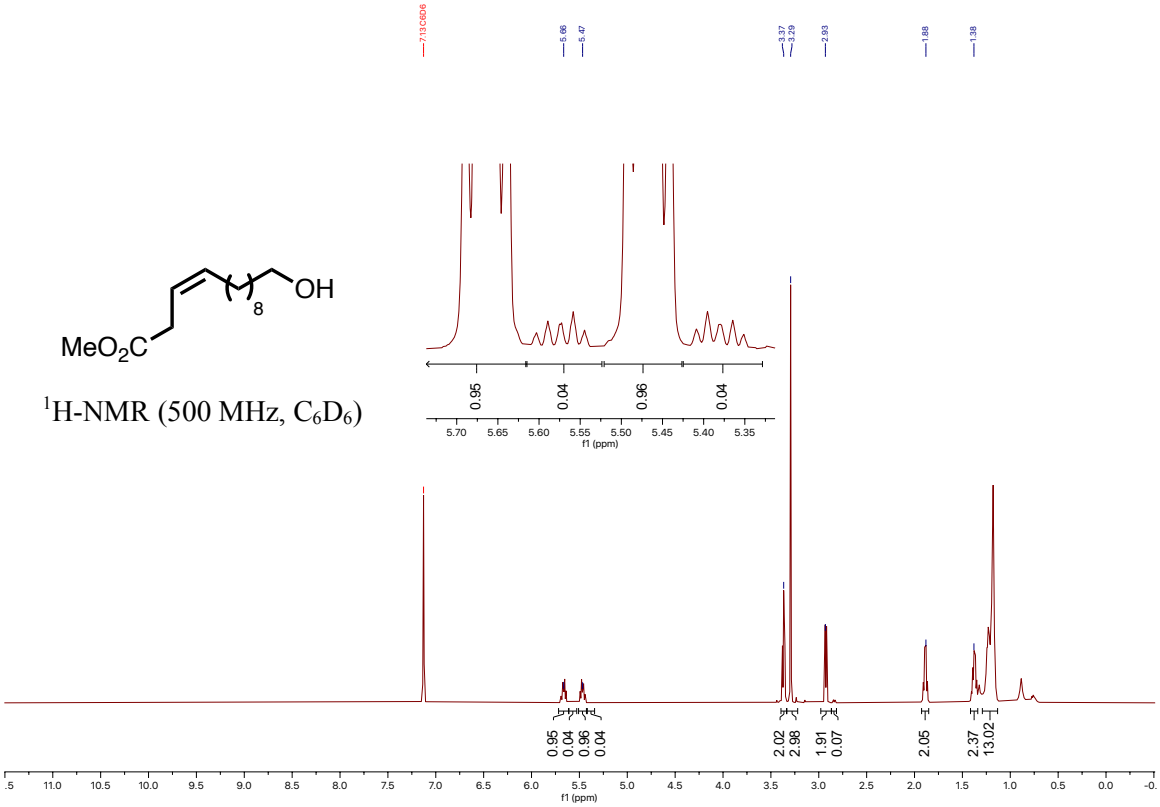

CO2Me
MeO
13C-NMR (125 MHz, C6D6)
171.11
158.35
131.97
131.93
129.26
128.00 C6D6
121.74
113.96
54.43
50.93
32.63
32.50
f1 (ppm)



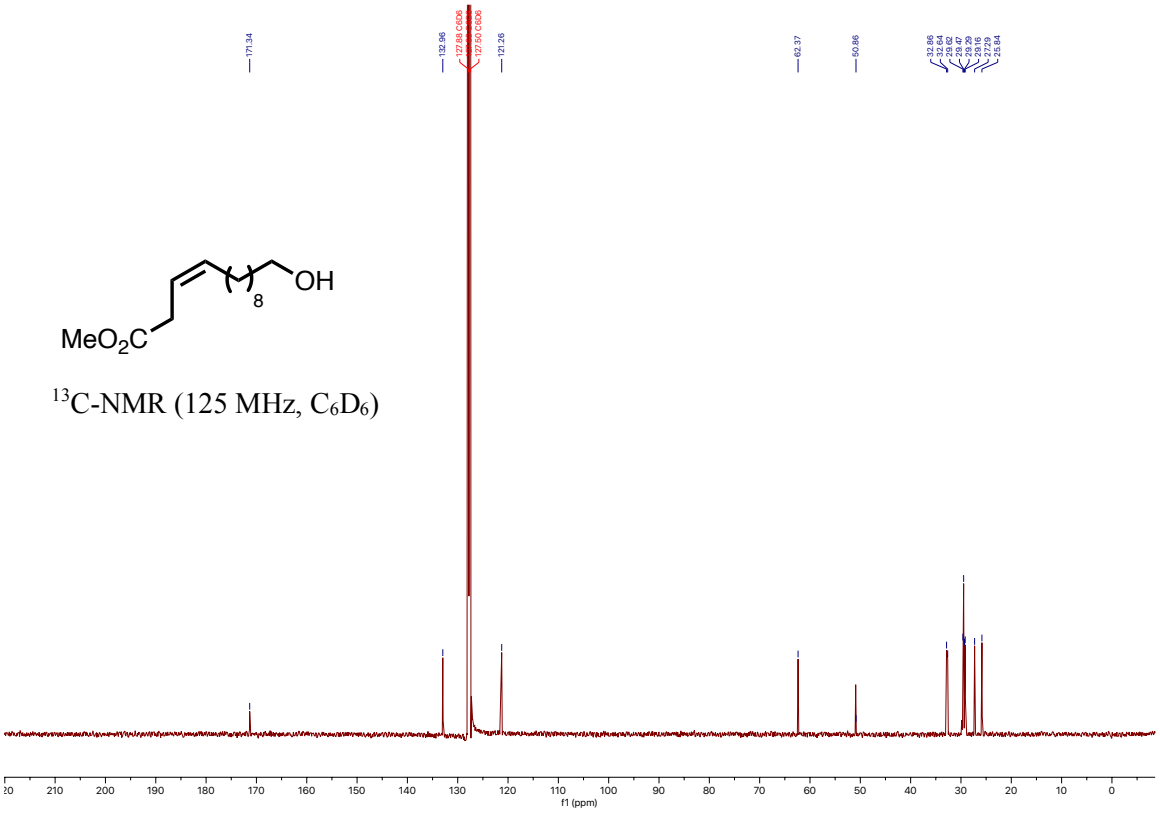
^{1}H-NMR (500 MHz, $CDCl_3$)



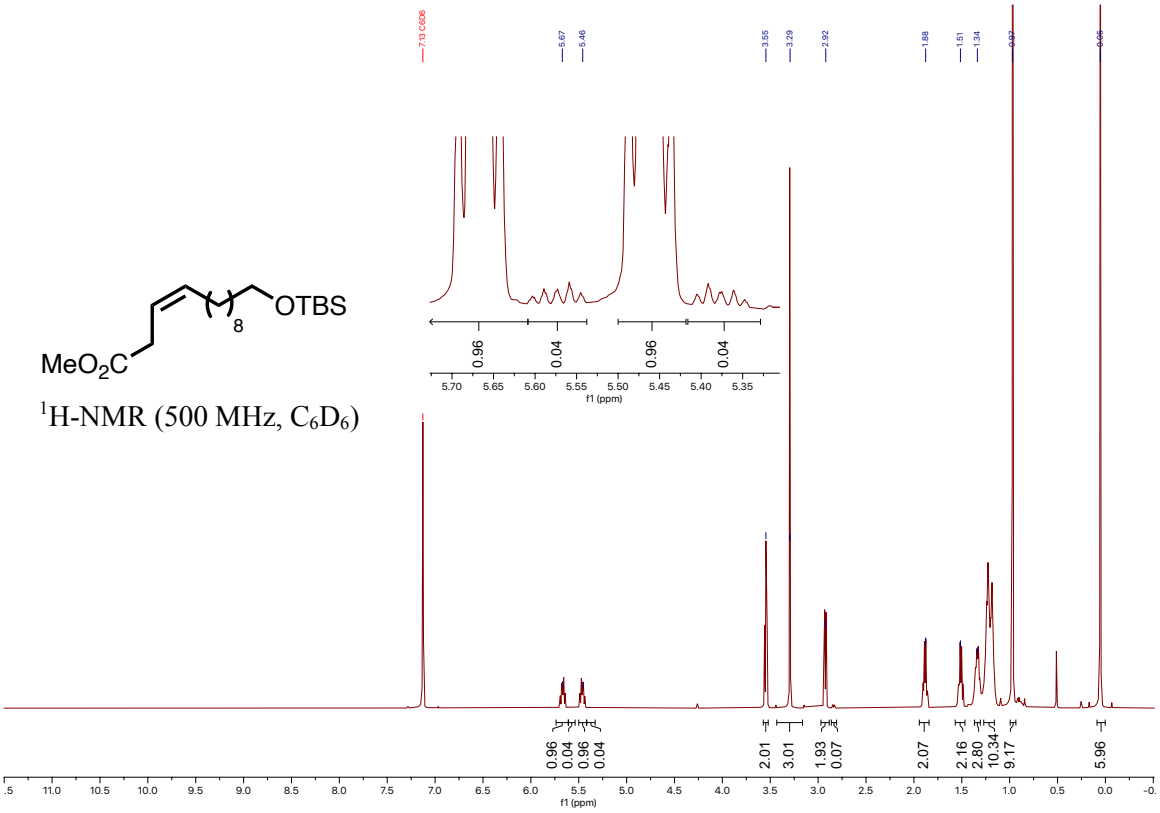
^{13}C-NMR (125 MHz, $CDCl_3$)



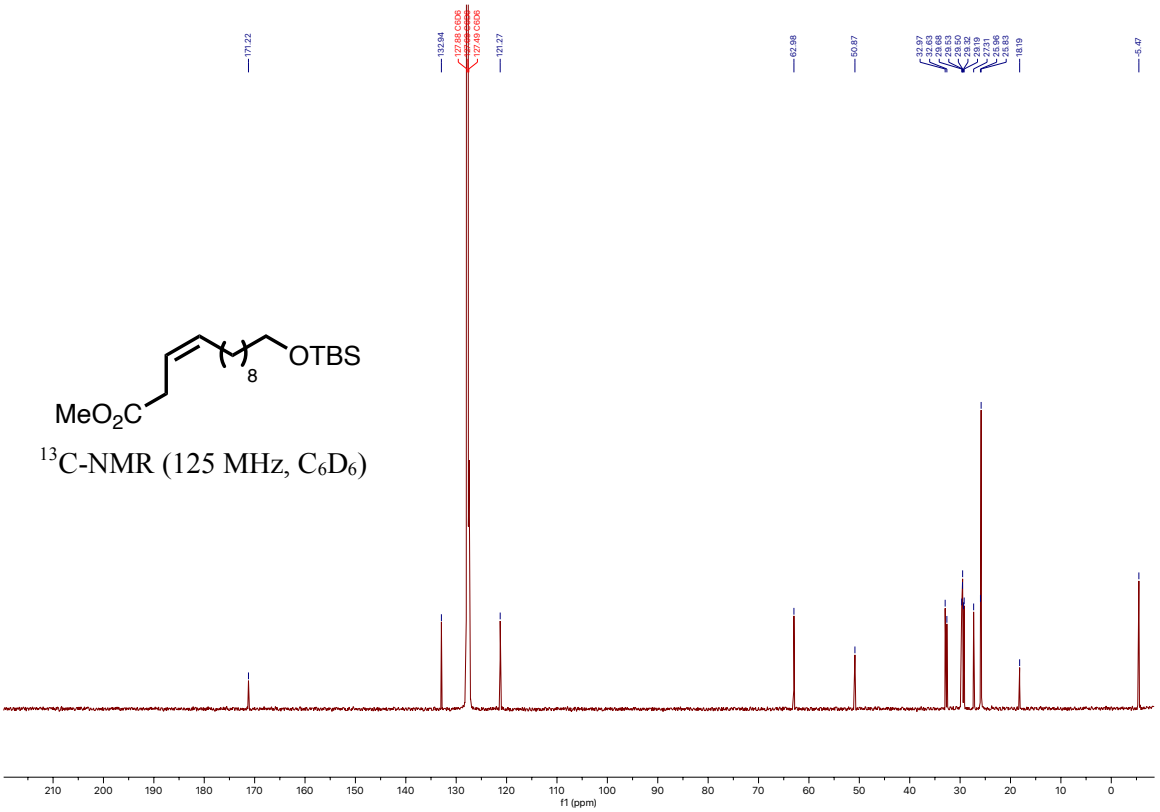
^{1}H-NMR (500 MHz, C_6D_6)



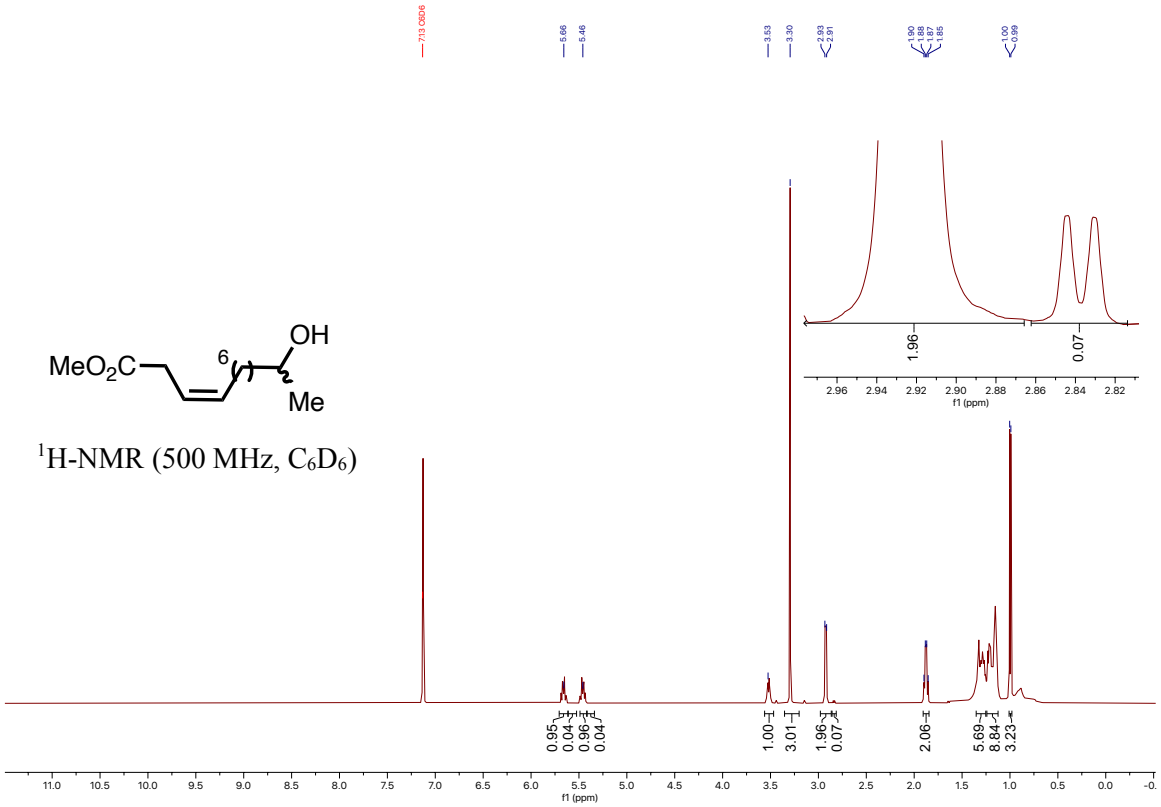
^{13}C-NMR (125 MHz, C_6D_6)



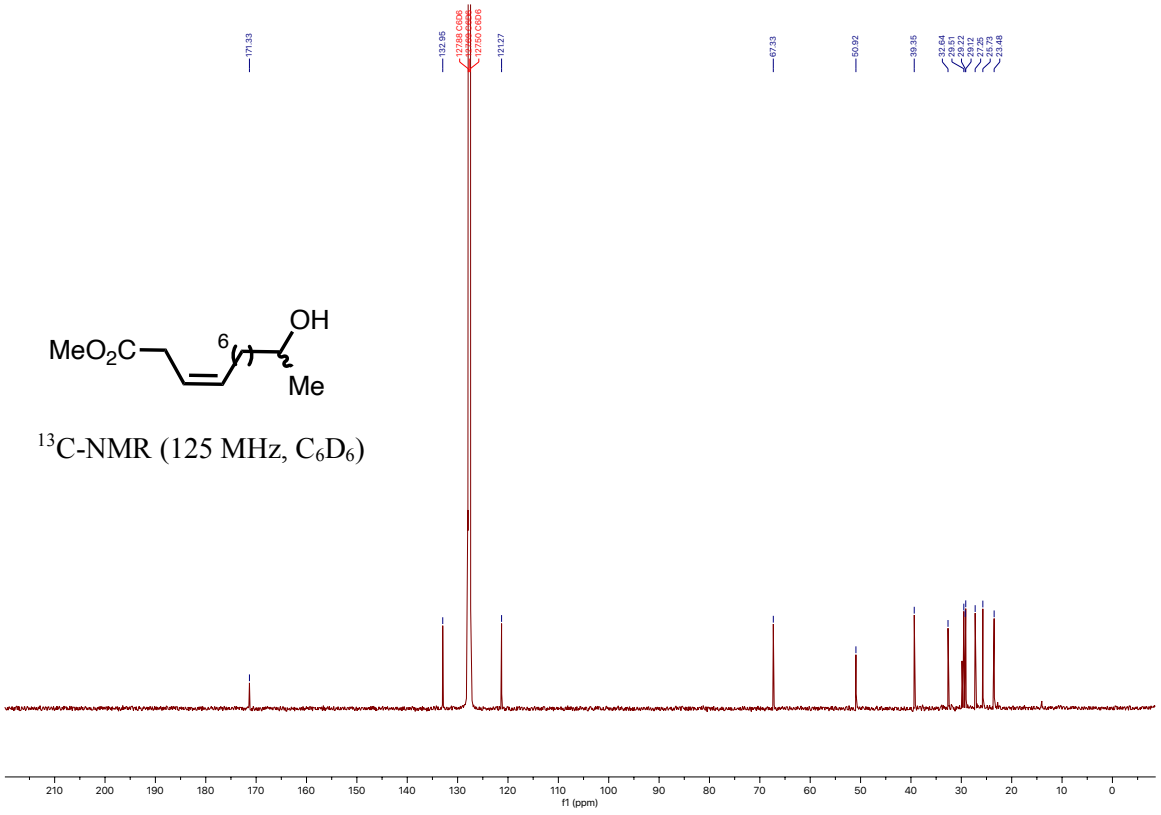
^{1}H-NMR (500 MHz, C_6D_6)



^{13}C-NMR (125 MHz, C_6D_6)



^{1}H-NMR (500 MHz, C_6D_6)



^{13}C-NMR (125 MHz, C_6D_6)