Electronic Supplementary Information (ESI) for the manuscript:

Domino dehydration / intermolecular (enantioselective) ketone–ene reaction catalysed by a simple solid in batch and in flow

Miguel Espinosa and Antonio Leyva-Pérez*

Instituto de Tecnología Química (UPV-CSIC), Universitat Politècnica de València-Agencia Estatal Consejo Superior de Investigaciones Científicas, Avda. de los Naranjos s/n, 46022 Valencia, Spain

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General procedures

All catalytic reactions were carried out in 2 mL glass vials. Reactions were monitored by TLC analysis using Merck Silica Gel 60 F-254 thin layer plates. After elution, TLC plates were observed under UV light and chemically revealed using a solution prepared from $KMnO_4$ (1.5 g), K_2CO_3 (10 g) and 10% NaOH (1.25 mL) in water (200 mL). Alternatively, the reactions were followed by GC.

Flash column chromatography was performed on Merck silica gel 60, 0.040-0.063 mm.

Nuclear magnetic resonance (NMR)

NMR spectra were run in a Bruker Avance 300 DPX spectrometer (300 MHz for ^{1}H, 75 MHz for ^{13}C and 282 MHz for ^{19}F NMR) or in a Bruker Avance 400 spectrometer (400 MHz for ^{1}H, 101 MHz for ^{13}C and 282 MHz for ^{19}F NMR).

Samples were dissolved in deuterated solvents, using the residual non-deuterated solvent as an internal standard (δ 7.26 for ^{1}H NMR and δ 77.16 for ^{13}C NMR in the case of $CDCl_3$). For ^{19}F NMR experiments, $CFCl_3$ was used as an internal standard. Chemical shifts (δ values) are given in ppm. Coupling constants (*J*) are given in Hz. The carbon multiplicity was determined by DEPT experiments.

Gas chromatography-mass spectrometry

Gas chromatographic analyses were performed in a Shimadzu instrument equipped with a 25 cm capillary column of 5% phenylmethylsilicone. *N*-dodecane was used as an external standard. Gas chromatography-mass spectrometry analyses were performed on an Agilent spectrometer equipped with the same column as the GC and operated under the same conditions.

Chiral gas chromatography

Chiral gas chromatographic analyses were performed in a GC-2025 Shimadzu instrument equipped with aAOC-20i Plus auto injector.

The GC conditions used were: Tecknochroma Sapiens β-DEX20 column; film thickness (df) = 0.25 µm; 0.25 mm inner diameter (i.d.) × 30 m column length; carrier gas, He (flow 0.79 mL/min); injection temperature, 230 °C; initial column temperature, 100 °C; hold time, 2 min; progress rate, 5 °C·min^{-1}; final column temperature, 230 °C; detector temperature, 230 °C; tR (R) = 16.656 min; and tR (S) = 16.744 min.

The GC data was processed using the LabSolutions Lite software.

Mass spectrometry

ESI-HRMS (electro-spray ionization-high resolution mass spectrometry): Samples were diluted in methanol and analyzed by means of a Waters ACQUITY XevoQToF spectrometer (Waters Corp.) through direct infusion of the liquid sample in an ESI interface. The ESI source was operated in positive ionization mode with the capillary voltage at 1.5 kV. The temperature of the source and desolvation was set at 100 °C and 400 °C, respectively. The cone and desolvation gas flows were 100 and 800 L h^{-1}, respectively. All data collected in centroid mode were acquired by using the Masslynx software (Waters Corp.). Leucine-enkephalin was used as the lock mass generating an $[M+H]^+$ ion (m/z=556.2771) at a concentration of 2 ng mL^{-1} and flow rate of 50 µL min^{-1} to ensure accuracy during the MS analysis.

Polarimetry

Specific optical rotations were measured in a Jasco P-2000 polarimeter using sodium light (D line 589 nm) in a 1 dm cell. Concentrations (c) are given in g/100 mL.

HPLC analyses

Chiral HPLC analyses were performed in an Agilent 1100 series instrument equipped with a UV Detector - VWD, Standard flow cell using chiral stationary columns from Daicel. Variable mixtures of *n*-hexane and isopropanol were used as eluents. Retention times (t_r) are expressed in minutes.

Fourier Transformed Infrared (FT-IR) Spectroscopy

Attenuated total reflectance (ATR) Fourier transform infrared (FTIR) measurements of solid and liquid samples were recorded with 50 scans from 400 to 4000 cm^{-1} on a JASCO FT/IR 4700 series spectrophotometer.

X-ray photoelectron spectroscopy (XPS) measurements

Samples of $MgCl_2$, before and after reaction, were prepared by dropping the solids onto a molybdenum plat were measured on a SPECS spectrometer equipped with a Phoibos 150 MCD-9 analyzer using non-monochromatic Al KR (1486.61 eV), X-ray source working at 50 W. As an internal reference for the peak positions in the XPS spectra, the C1s peak has been set at 284.5 eV.

X-Ray diffraction spectra

X-Ray diffraction spectra were recorded in a CubiX PRO (PAN Analytical) spectrometer, with a Cu K(α) radiation source, 1.5406 Å wavelength.

Figures.

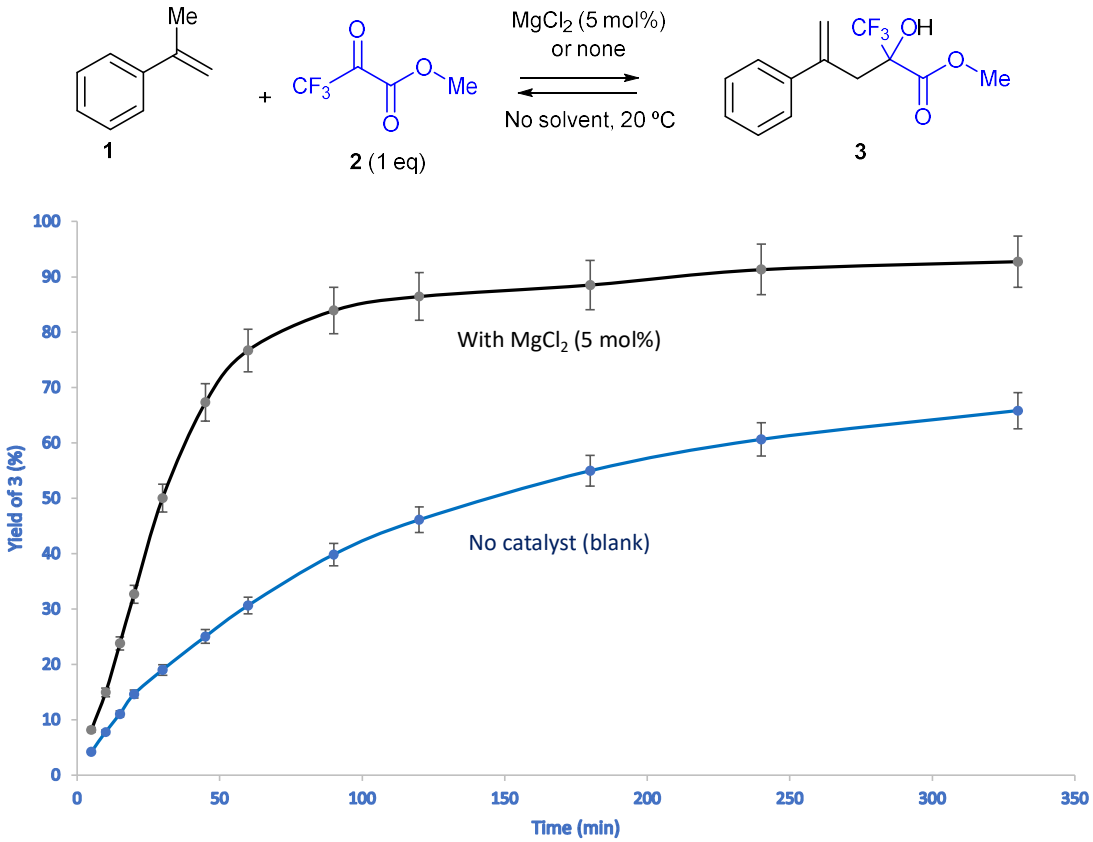


Figure S1. Kinetic plot for the intermolecular ketone-ene reaction between α-methyl styrene **1** and methyl pyruvate **2** (1 equivalent) catalyzed by $MgCl_2$ (5 mol%, black line) or none (blue line) without any solvent at room temperature. Lines are a guide to the eye. GC yields. Error bars account for a 5% uncertainty.

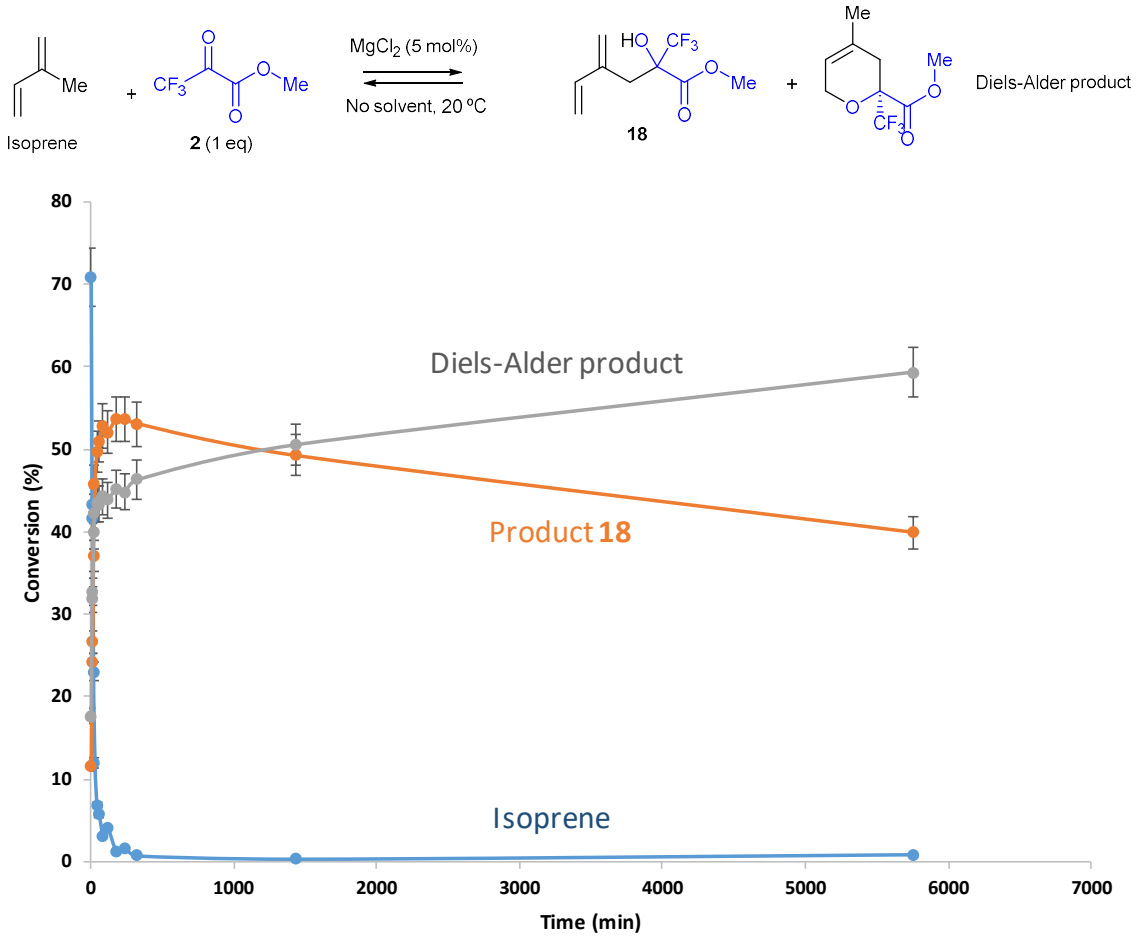


Figure S2. Kinetic plot for the intermolecular ketone-ene reaction between isoprene and methyl pyruvate **2** (1 equivalent) catalyzed by $MgCl_2$ without any solvent at room temperature. Lines are a guide to the eye. GC yields. Error bars account for a 5% uncertainty.

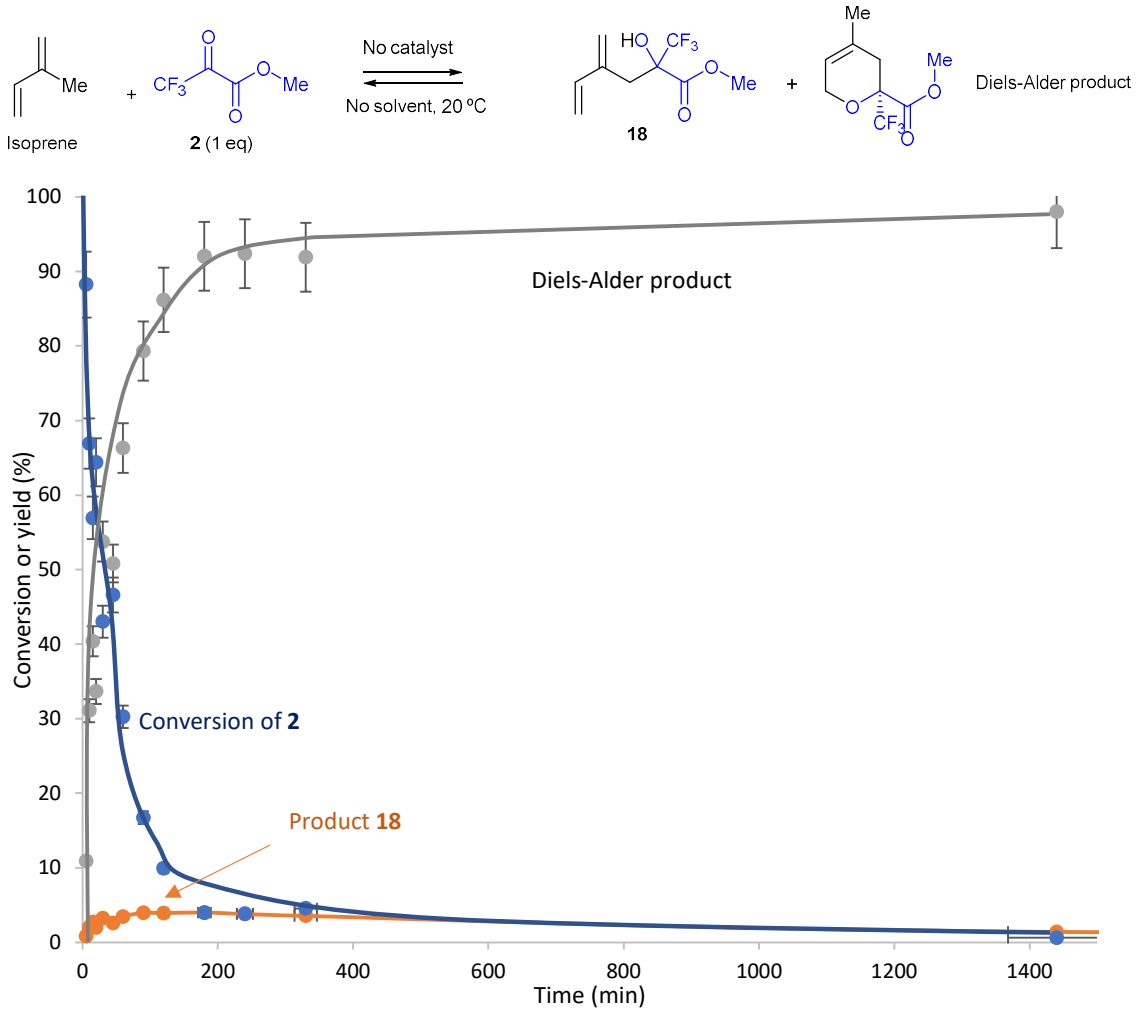


Figure S3. Kinetic plot for the intermolecular ketone-ene reaction between isoprene and methyl pyruvate **2** (1 equivalent), uncatalyzed and without any solvent, at room temperature. Lines are a guide to the eye. GC yields. Error bars account for a 5% uncertainty.

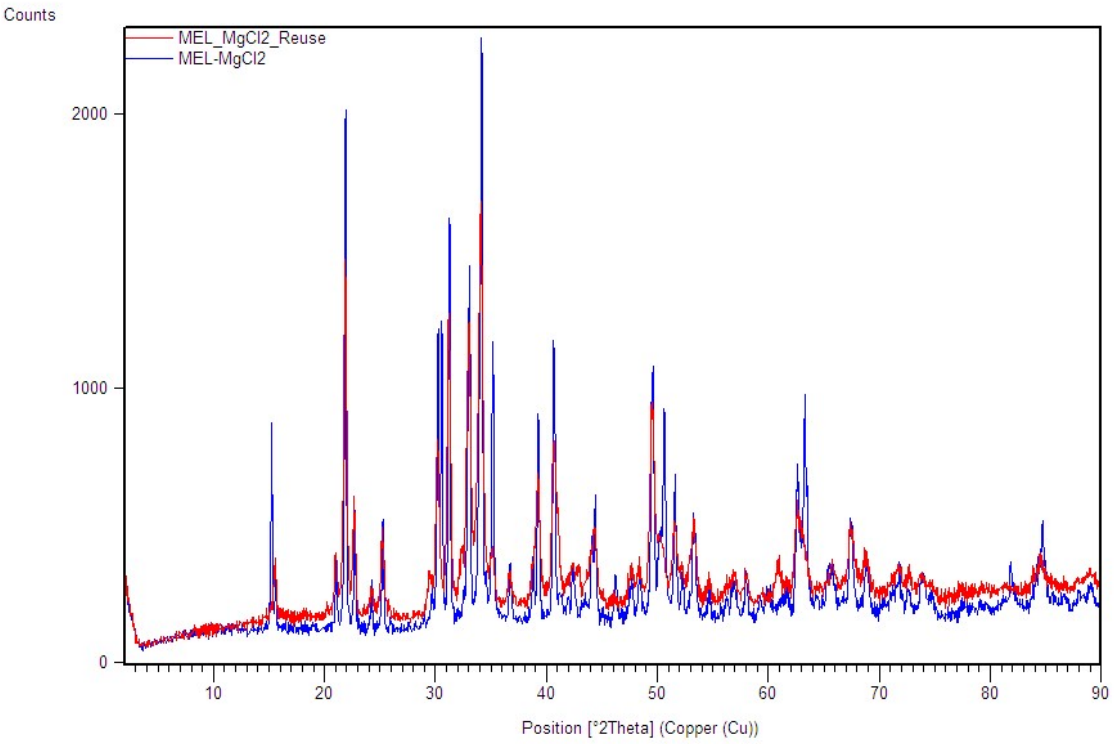


Figure S4. XRPD pattern of fresh $MgCl_2$ and $MgCl_2$ recovered after 10 reuses.

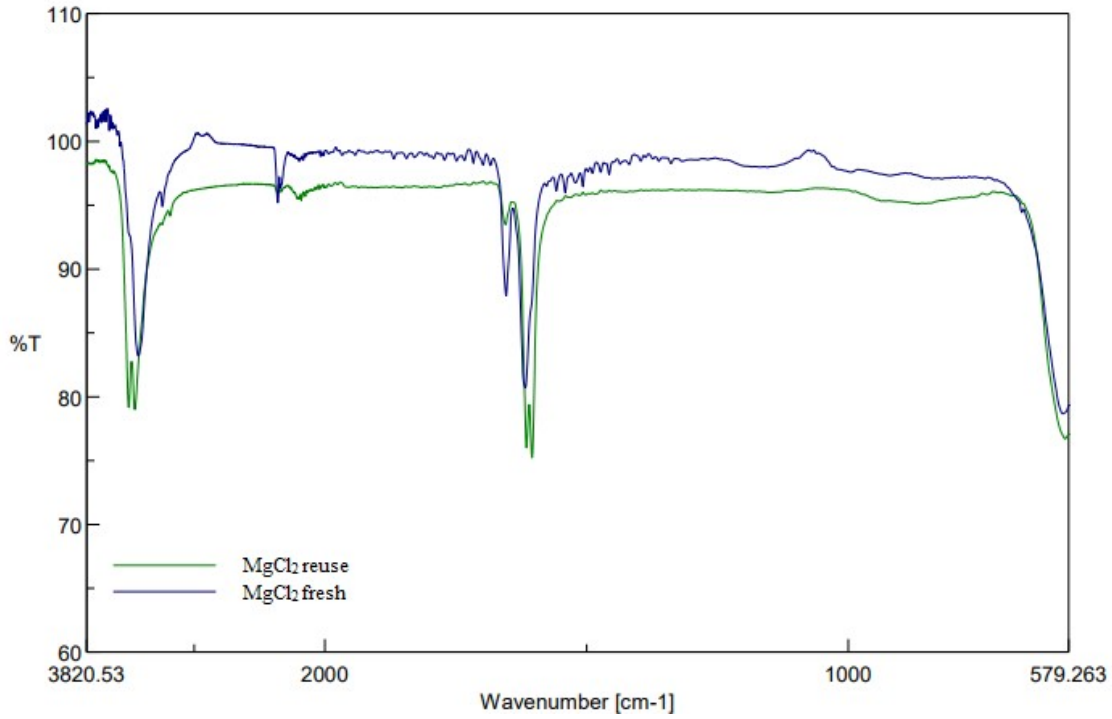


Figure S5. Comparison of the Fourier transform infrared spectra (FT-IR) for the fresh $MgCl_2$ and $MgCl_2$ recovered after 10 reuses.

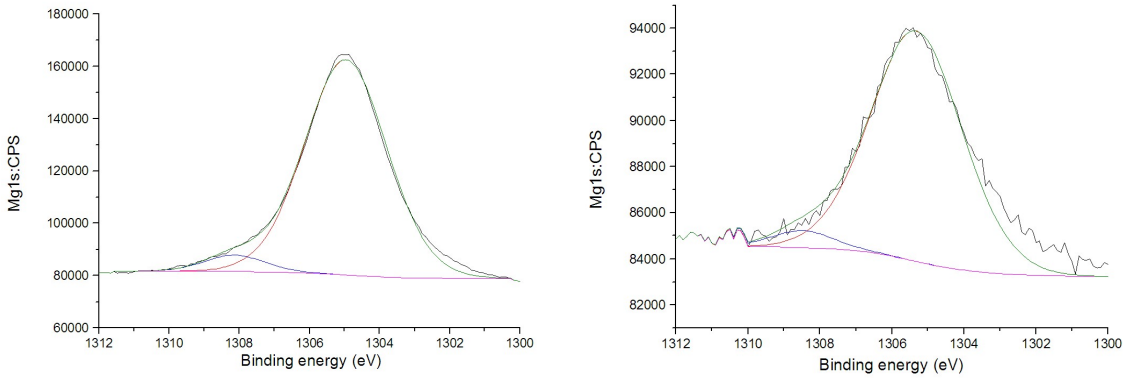


Figure S6. XPS spectra analysis (Mg 1s region) of fresh $MgCl_2$ (left) and recovered $MgCl_2$ after 10 reuses (right).

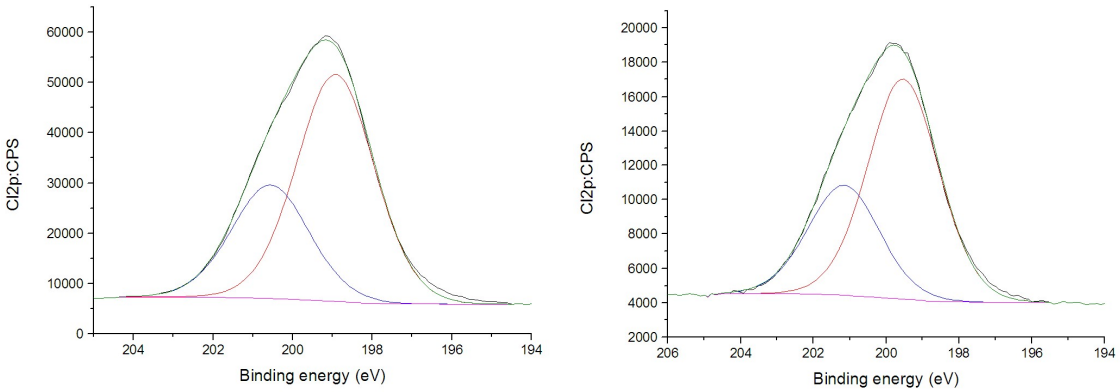


Figure S7. XPS spectra analysis (Cl 2p region) of fresh $MgCl_2$ (left) and recovered $MgCl_2$ after 10 reuses (right).

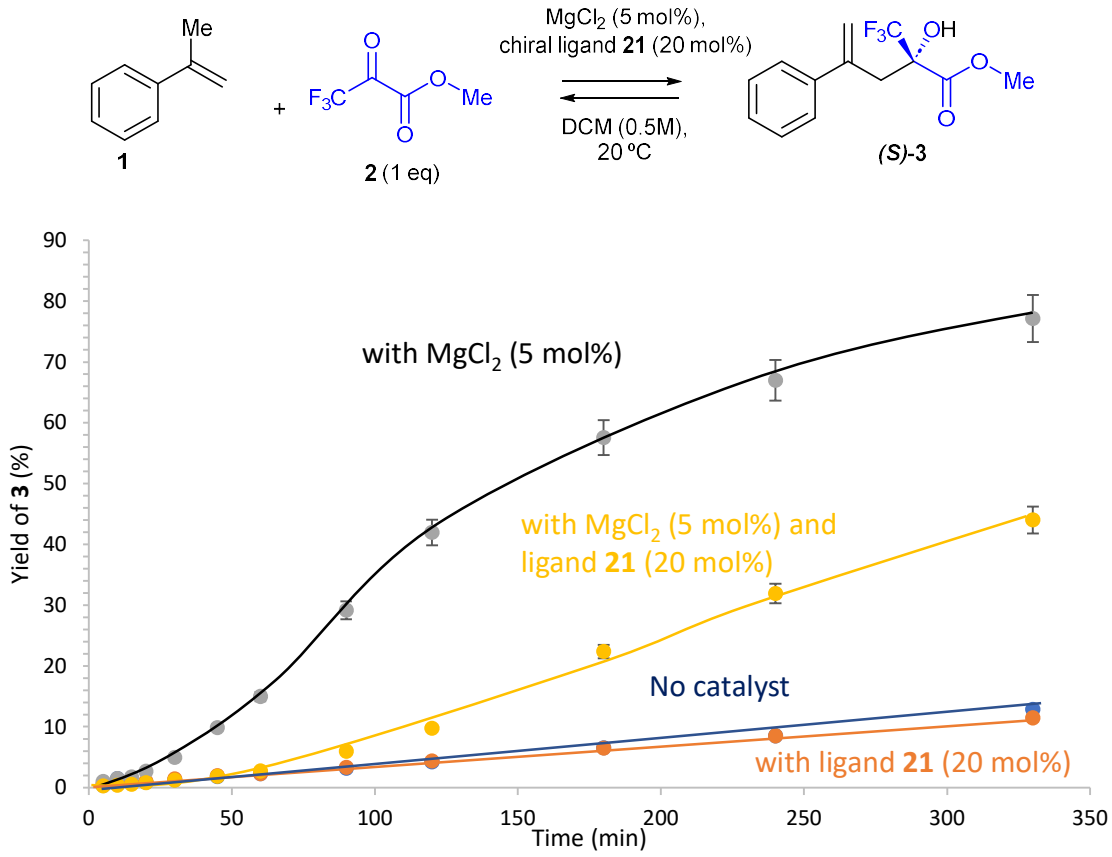


Figure S8. Kinetic plot for the intermolecular ketone-ene reaction between α-methyl styrene **1** and methyl pyruvate **2** (1 equivalent) in DCM (1M) at room temperature catalysed by either $MgCl_2$ (5 mol%, black line), $MgCl_2$ (5 mol%) + ligand **21** (20 mol%, yellow line), ligand **21** alone (20 mol%, orange line) or none (blue line). Lines are a guide to the eye. GC yields. Error bars account for a 5% uncertainty.

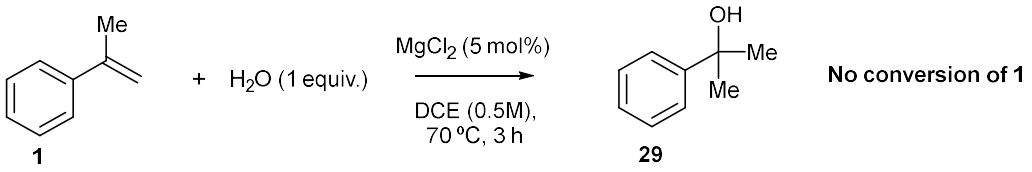


Figure S9. Lack of hydration reaction α–methyl styrene **1** with $MgCl_2$ (5 mol%) as a catalyst in dichloroethane (DCE, 0.5M), at 70 ºC for 3 h. GC conversion.

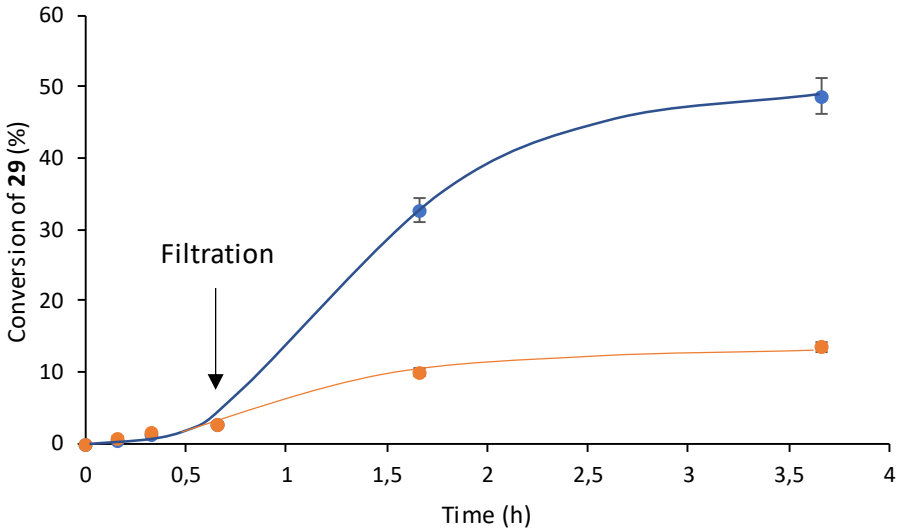
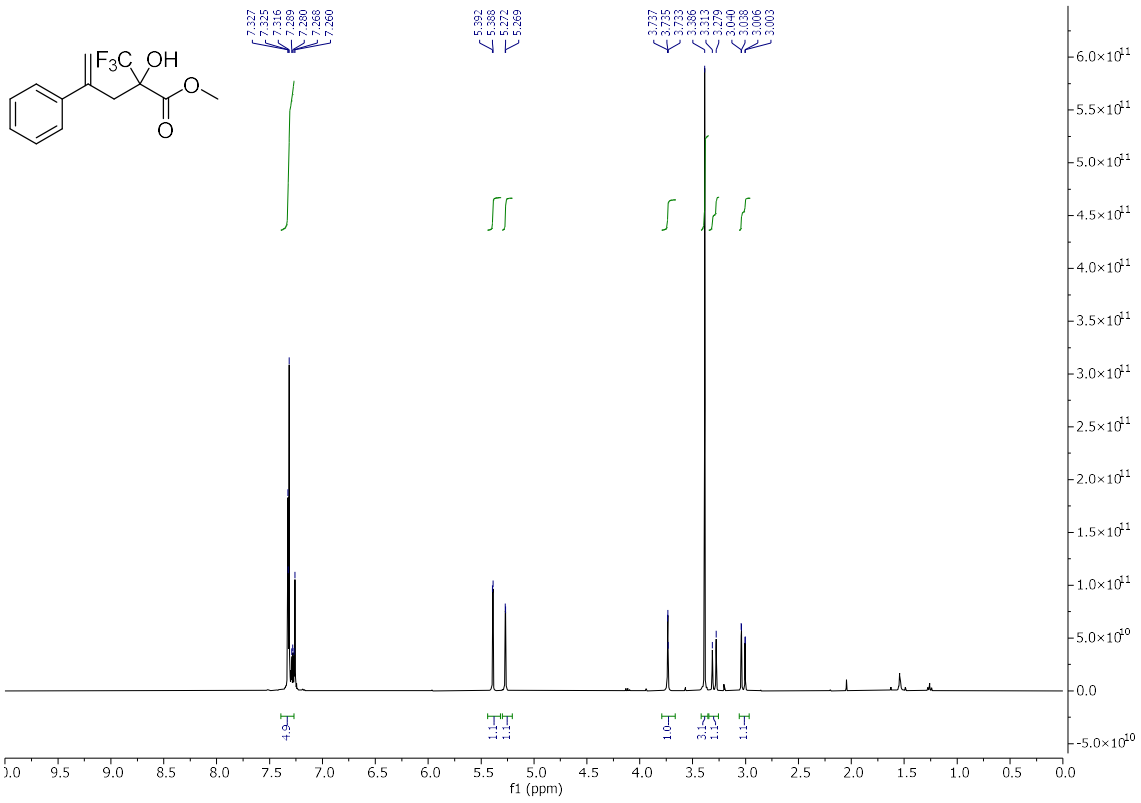
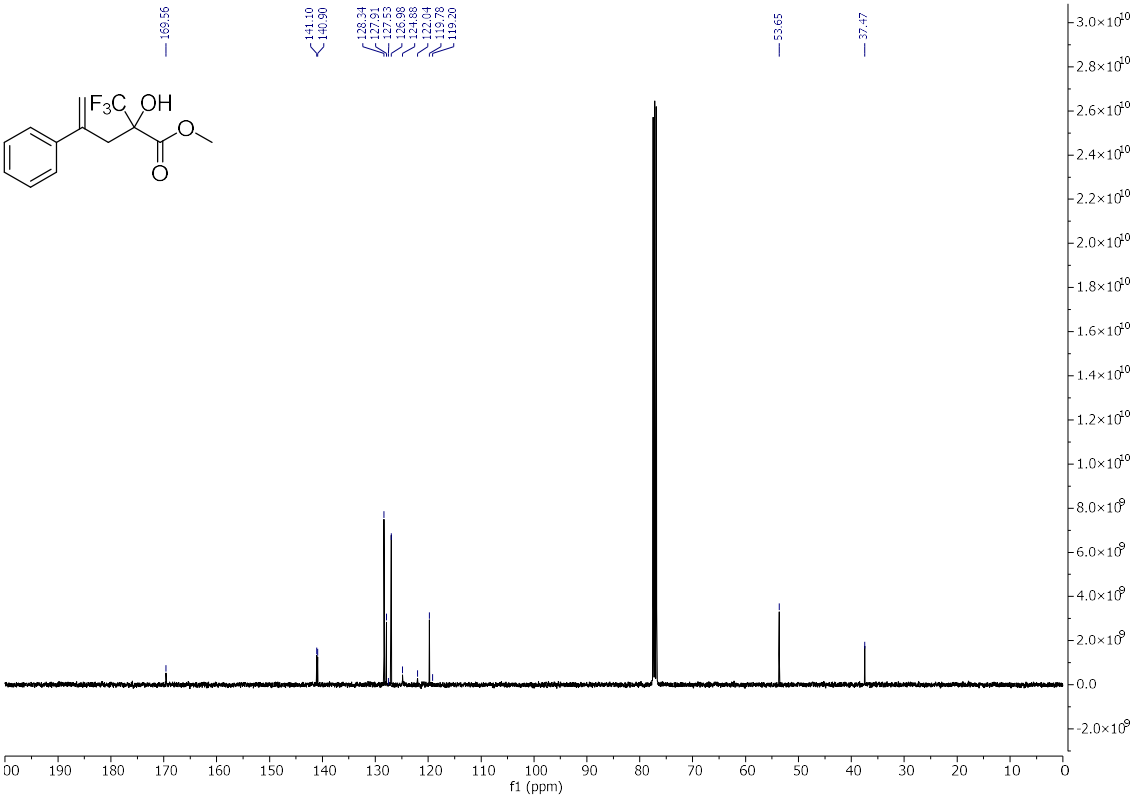


Figure S10. Hot filtration test for the domino dehydration / intermolecular carbonyl–ene reaction of alcohol **29** with methyl pyruvate **2** (1 equiv.) catalysed by $MgCl_2$ (5 mol%) in DCE (0.5M), at 50 ºC for 18 h. Lines are a guide to the eye. GC yields. Error bars account for a 5% uncertainty.


F3C
OH
O
O
7.327
7.325
7.316
7.289
7.280
7.268
7.260
5.392
5.388
5.272
5.269
3.737
3.735
3.733
3.386
3.313
3.279
3.040
3.038
3.006
3.003
4.9
1.1
1.1
1.0
3.1
1.1
1.1
f1 (ppm)


F3C
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O
O
169.56
141.10
140.90
128.34
127.91
127.53
126.98
124.88
122.04
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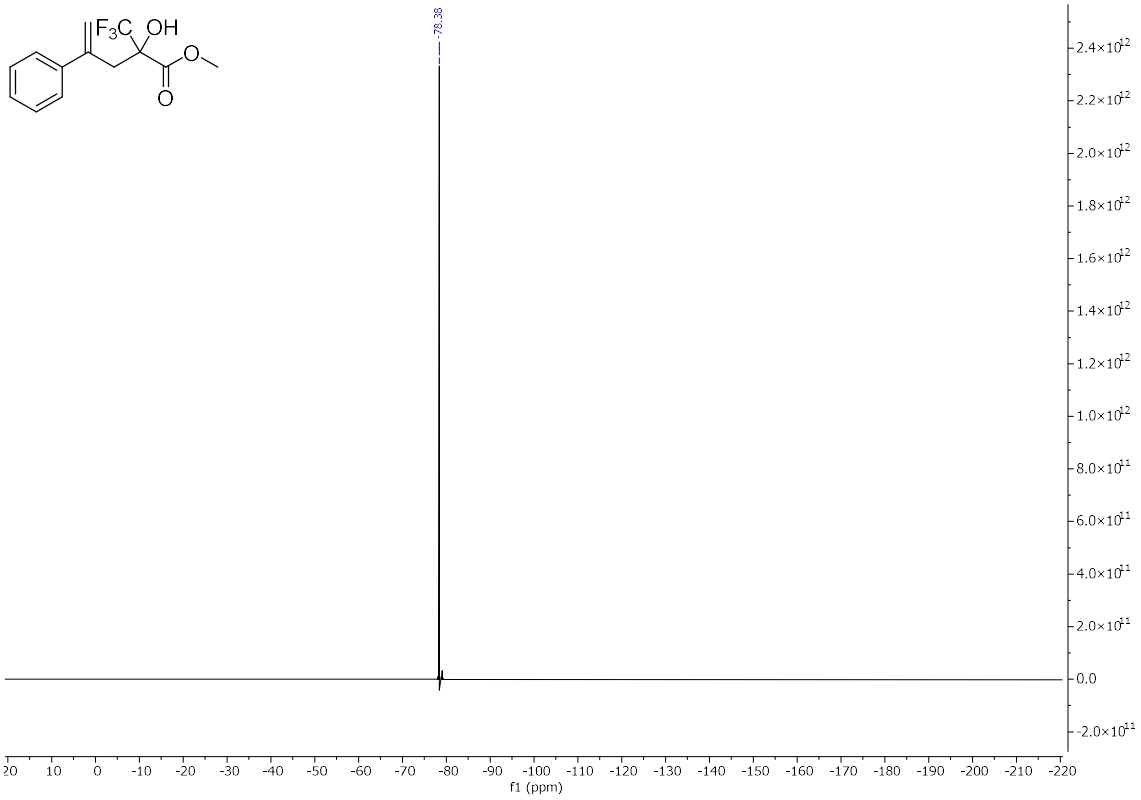
119.20
53.65
37.47
f1 (ppm)


F3C
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O
O
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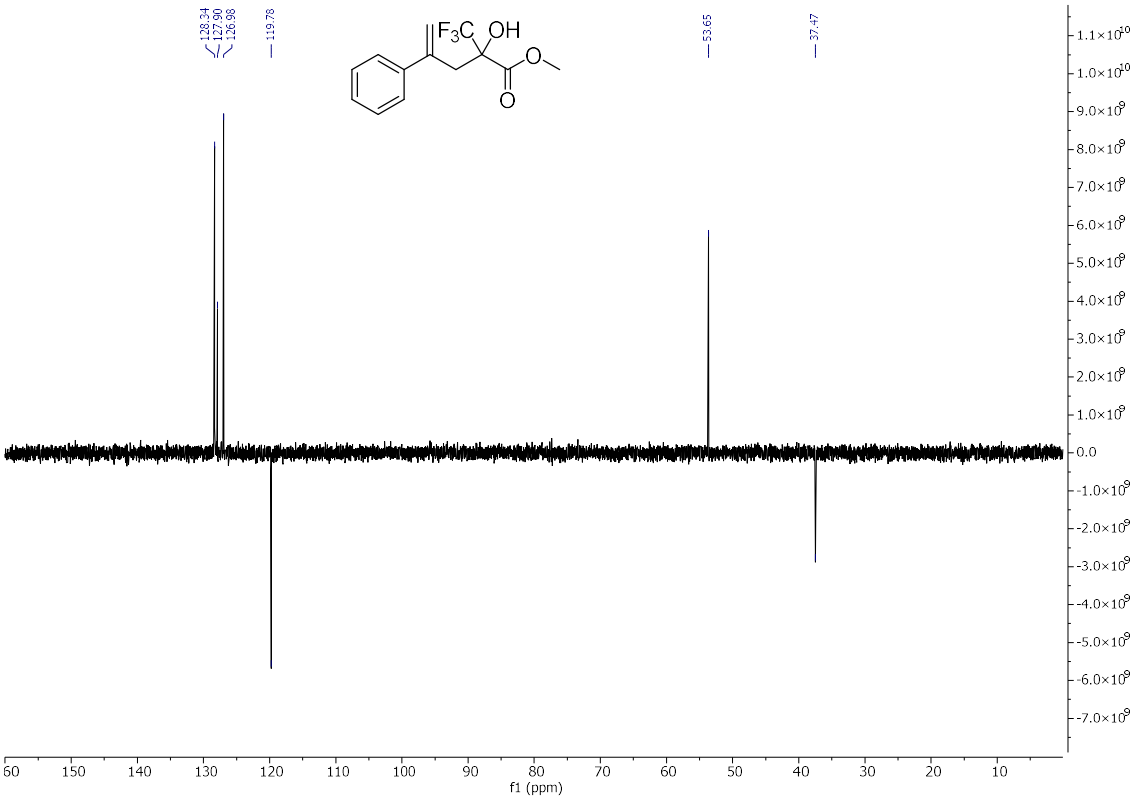
f1 (ppm)


128.34
127.90
126.98
119.78
53.65
37.47
F3C
OH
O
O
f1 (ppm)

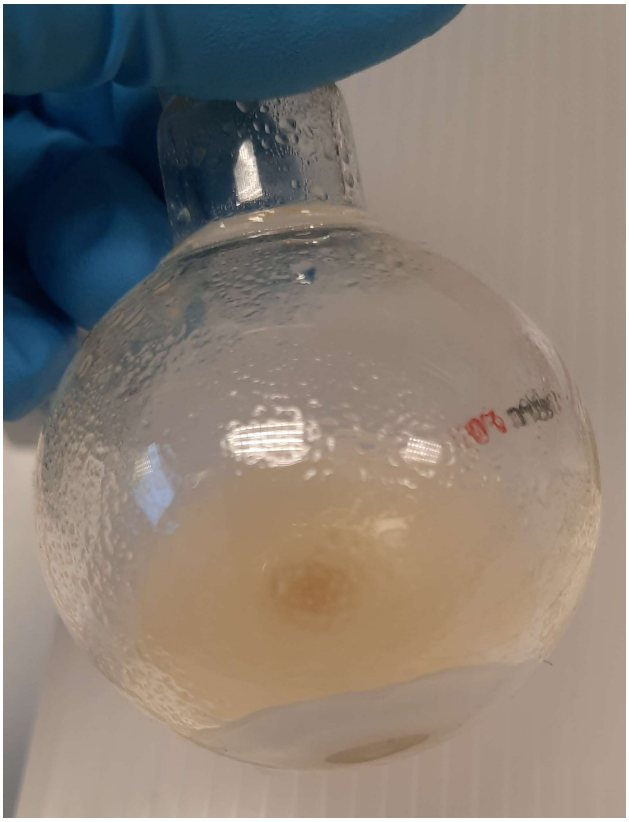


Figure S11. Top: ^{1}H, ^{13}C, ^{19}F and DEPT NMR spectra for the organic phase of the domino dehydration / intermolecular carbonyl–ene reaction of alcohol **29** with methyl pyruvate **2** (1.5 equiv.), at 9-grams scale (30 mmol of each reactant), catalysed by $MgCl_2$ (5 mol%) without any solvent, at 50 ºC for 18 h. [a] GC yields, mass balances are complete with unreacted starting material **29**. [b] GC, weight and ^{1}H NMR yield for an experiment. Bottom: A photograph of the reaction mixture at the end of the reaction, with the shows $MgCl_2$ solid easily separated from the liquid phase, and the water generated during reaction stuck as droplets on the round-bottomed flask walls.

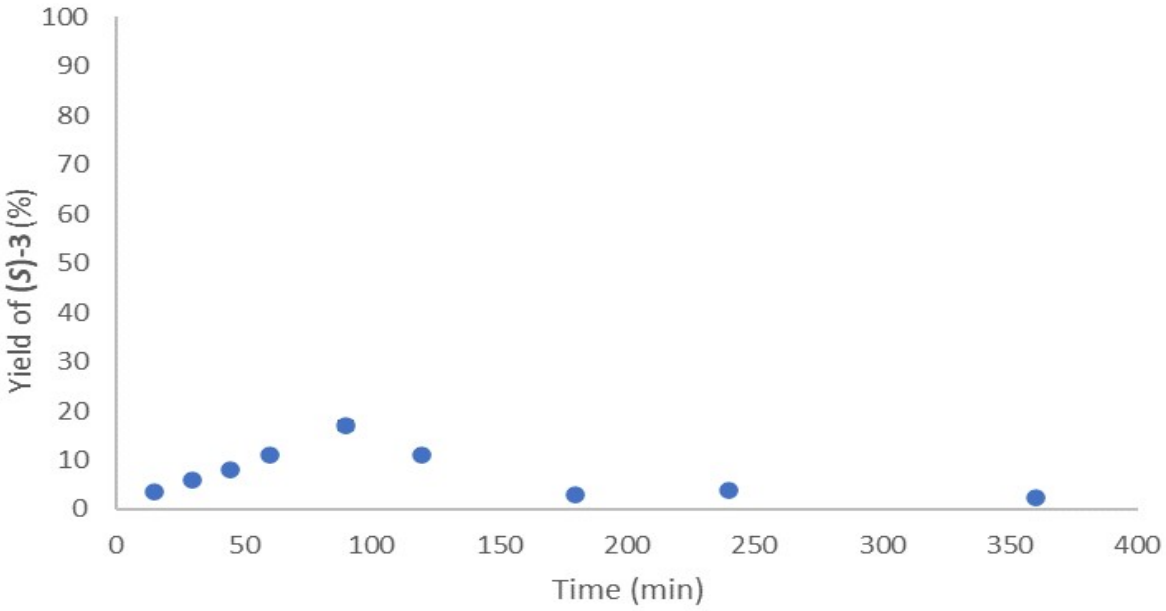


Figure S12. In–flow reaction with $MgCl_2$ + chiral ligand **21** as a catalyst (111 mg in total, 5:2 wt% ratio) for the domino reaction, in DCE (0.5M) at room temperature. Feed flow rate is 2.0 ml·h^{-1}. Error bars account for a 5% uncertainty.

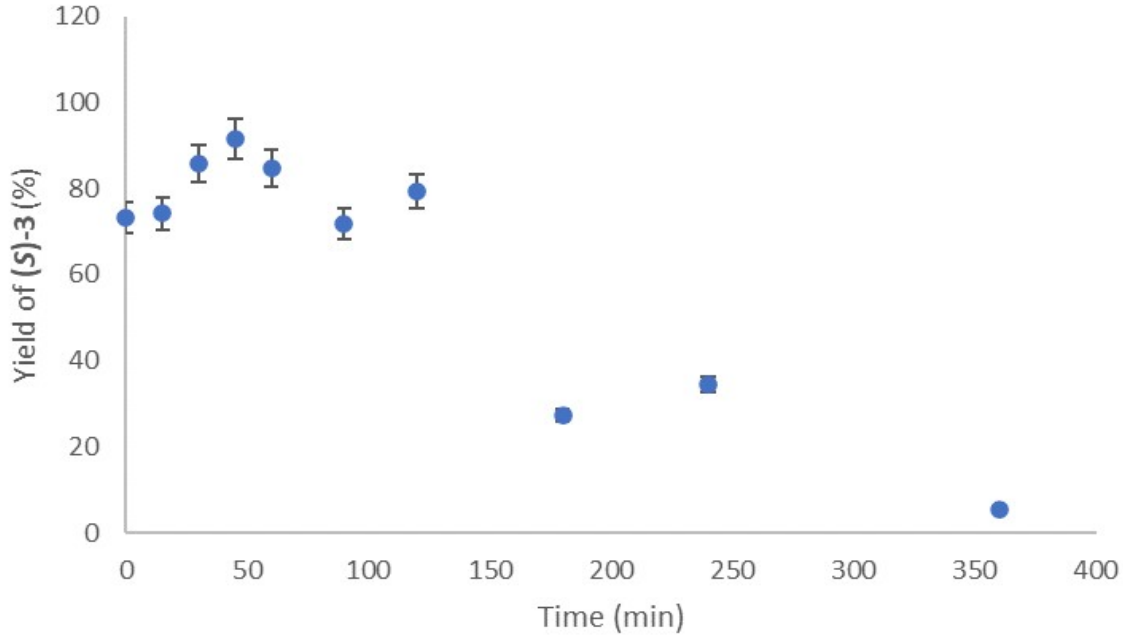
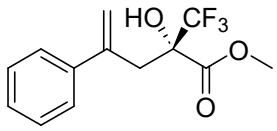


Figure S13. In–flow reaction with $MgCl_2$ + chiral ligand **21** as a catalyst (111 mg in total, 5:2 wt% ratio) for the domino reaction, in DCE (0.5M) at room temperature. Feed flow rate is 1.5 ml·h^{-1}. Error bars account for a 5% uncertainty.

Product characterization.

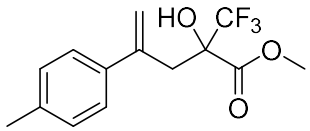
Methyl (*S*)-2-hydroxy-4-phenyl-2-(trifluoromethyl)pent-4-enoate (3)



Chiral HPLC analysis: Chiralpak AD-H, hexane-*i*PrOH 90:10, 1 mL/min: *major enantiomer* t_r = 4.50 min, *minor enantiomer* t_r = 4.72 min

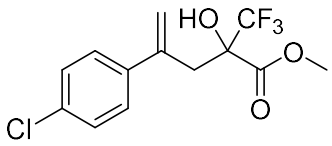
$[\alpha]_D$ -19 (c 1.01, $CHCl_3$, *ee* = 55%); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.33-7.26 (m, 5H), 5.39 (d, *J* = 0.9 Hz, 1H), 5.27 (d, *J* = 0.3 Hz, 1H), 3.74 (s, 1H), 3.39 (s, 3H), 3.30 (d, *J* = 10.2 Hz, 1H), 3.02 (dd, *J* = 10.5, 0.3 Hz, 1H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.5 (C), 141.1 (C), 140.9 (C), 128.3 (CH), 127.9 (CH), 127.7 (CH), 123.5 (C, q, $J_{C\text{-}F}$ = 284.0 Hz), 119.7 (CH_2), 77.2 (C, q, $J_{C\text{-}F}$ = 29.0 Hz), 53.6 (CH_3), 37.4 (CH_2); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −78.37 (s, CF_3); **HRMS (ESI)** 275.0890 $(M+H)^+$, $C_{13}H_{13}F_3O_3$ required 275.0906.

Methyl 2-hydroxy-4-(*p*-tolyl)-2-(trifluoromethyl)pent-4-enoate (4)



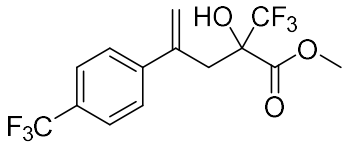
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.4 Hz, 2H), 7.14 (d, *J* = 8.0 Hz, 2H), 5.38 (d, *J* = 1.6 Hz, 1H), 5.23 (s, 1H), 3.75 (s, 1H), 3.44 (s, 3H), 3.29 (d, *J* = 14.0 Hz, 1H), 3.02 (dd, *J* = 14.0, 0.8 Hz, 1H), 2.35 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.6 (C), 141.0 (C), 138.0 (C), 137.7 (C), 129.0 (CH), 126.8 (CH), 123.5 (C, q, $J_{C\text{-}F}$ = 286.8 Hz), 118.8 (CH_2), 77.4 (C, q, $J_{C\text{-}F}$ = 26.6 Hz), 53.6 (CH_3), 37.4 (CH_2), 21.7 (CH_3); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −78.36 (s, CF_3); **HRMS (ESI)** 289.1066 $(M+H)^+$, $C_{14}H_{15}F_3O_3$ required 289.1046.

Methyl 4-(4-chlorophenyl)-2-hydroxy-2-(trifluoromethyl)pent-4-enoate (5)



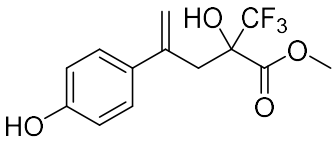
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.25 (m, 4H), 5.38 (s, 1H), 5.27 (s, 1H), 3.74 (s, 1H), 3.50 (s, 3H), 3.23 (d, *J* = 14.0 Hz, 1H), 3.02 (d, *J* = 14.0 Hz, 1H); **^{13}C NMR (75 MHz, $CDCl_3$)** δ 169.5 (C), 140.2 (C), 139.4 (C), 133.8 (C), 128.5 (CH), 128.2 (CH), 123.4 (C, q, J_{C-F} = 285.0 Hz), 120.1 (CH_2), 77.4 (C, q, J_{C-F} = 29.3 Hz), 53.8 (CH_3), 37.3 (CH_2); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −78.39 (s, CF_3); **HRMS (ESI)** 309.0504 $(M+H)^+$, $C_{13}H_{12}ClF_3O_3$ required 309.0500.

Methyl 2-hydroxy-2-(trifluoromethyl)-4-(4-(trifluoromethyl)phenyl)pent-4-enoate (6)



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.4 Hz, 2H), 7.44 (d, *J* = 8.4 Hz, 2H), 5.46 (s, 1H), 5.36 (s, 1H), 3.75 (s, 1H), 3.49 (s, 3H), 3.26 (d, *J* = 14.0 Hz, 1H), 3.08 (d, *J* = 14.0 Hz, 1H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.5 (C), 144.7 (C), 140.3 (C), 129.9 (C, q, J_{C-F} = 32.3 Hz), 127.6 (CH), 125.3 (CH, q, J_{C-F} = 4.0 Hz), 123.7 (C, J_{C-F} = 272.7 Hz), 123.0 (C, q, J_{C-F} = 286.9 Hz), 121.3 (CH_2), 77.5 (C, q, J_{C-F} = 29.3 Hz), 53.8 (CH_3), 37.2 (CH_2); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −62.66 (s, CF_3), -78.50 (s, CF_3); **HRMS (ESI)** 343.0751 $(M+H)^+$, $C_{14}H_{12}F_6O_3$ required 343.0763.

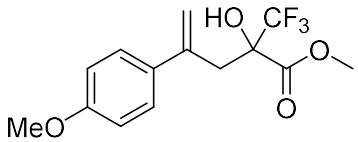
Methyl 2-hydroxy-4-(4-hydroxyphenyl)-2-(trifluoromethyl)pent-4-enoate (7)



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (dt, *J* = 8.4, 3.2 Hz, 2H), 6.77 (dt, *J* = 8.4, 3.2 Hz, 2H), 5.32 (d, *J* = 1.2 Hz, 1H), 5.17 (d, *J* = 0.8 Hz, 1H), 4.84 (bs, 1H), 3.73 (s, 1H), 3.47 (s, 3H), 3.25 (d, *J* = 13.6 Hz, 1H), 2.99 (dd, *J* = 13.6, 1.2 Hz, 1H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.6 (C), 155.4 (C), 140.4 (C), 133.5

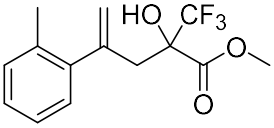
(C), 128.4 (CH), 123.5 (C, q, $J_{C\text{-}F}$ = 284.0 Hz), 118.4 (CH_2), 115.1 (CH), 77.6 (C, q, $J_{C\text{-}F}$ = 32.0 Hz), 53.7 (CH_3), 37.5 (CH_2); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −78.33 (s, CF_3); **HRMS (ESI)** 291,0841 $(M+H)^+$, $C_{13}H_{13}F_3O_4$ required 291,0839.

Methyl 2-hydroxy-4-(4-methoxyphenyl)-2-(trifluoromethyl)pent-4-enoate (8)



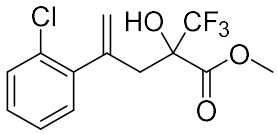
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (dd, *J* = 8.8, 2.8 Hz, 2H), 6.85 (dd, *J* = 8.8, 2.8 Hz, 2H), 5.33 (d, *J* = 1.6 Hz, 1H), 5.18 (d, *J* = 1.2 Hz, 1H), 3.81 (s, 3H), 3.74 (s, 1H), 3.46 (s, 3H), 3.26 (d, *J* = 13.8 Hz, 1H), 3.00 (dd, *J* = 13.8, 0.6 Hz, 1H); **^{13}C NMR (75 MHz, $CDCl_3$)** δ 169.6 (C), 159.5 (C), 140.5 (C), 133.2 (C), 128.1 (CH), 123.5 (C, q, $J_{C\text{-}F}$ = 284.3 Hz), 118.2 (CH_2), 113.7 (CH), 77.3 (C, q, $J_{C\text{-}F}$ = 24.8 Hz) 55.4 (CH_3), 53.7 (CH_3), 37.5 (CH_2); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −78.31 (s, CF_3); **HRMS (ESI)** 305.1010 $(M+H)^+$, $C_{14}H_{15}F_3O_4$ required 305.0995.

Methyl 2-hydroxy-4-(*o*-tolyl)-2-(trifluoromethyl)pent-4-enoate (9)



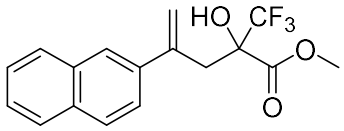
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17-7.03 (m, 4H), 5.42 (d, *J* = 1.6 Hz, 1H), 5.12 (d, *J* = 2.4 Hz, 1H), 3.78 (s, 1H), 3.34 (s, 3H), 3.22 (d, *J* = 18.4 Hz, 1H), 2.96 (dd, *J* = 18.8, 0.8 Hz, 1H), 2.31 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.6 (C), 141.4 (C), 140.9 (C), 135.4 (C), 130.4 (CH), 129.1 (CH), 127.6 (CH), 125.6 (CH), 123.5 (C, q, $J_{C\text{-}F}$ = 286.8 Hz), 121.7 (CH_2), 76.8 (C, q, $J_{C\text{-}F}$ = 29.3 Hz), 53.7 (CH_3), 39.0 (CH_2), 20.1 (CH_3); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −78.84 (s, CF_3); **HRMS (ESI)** 289.1063 $(M+H)^+$, $C_{14}H_{15}F_3O_3$ required 289.1046.

Methyl 4-(2-chlorophenyl)-2-hydroxy-2-(trifluoromethyl)pent-4-enoate (10)



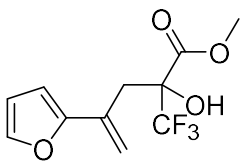
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.34 (m, 1H), 7.23-7.20 (m, 2H), 7.13-7.09 (m, 1H), 7.66 (d, *J* = 7.2 Hz, 2H), 5.45 (s, 1H), 5.23 (s, 1H), 3.75 (s, 1H), 3.45 (s, 3H), 3.40 (d, *J* = 14.1 Hz, 1H), 3.04 (d, *J* = 14.1 Hz, 1H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 173.6 (C), 140.4 (C), 132.4 (C), 131.2 (CH), 129.7 (CH), 129.0 (CH), 127.5 (C), 126.7 (CH), 124.2 (C, q, J_{C-F} = 284.0 Hz), 123.2 (CH_2), 77.1 (C, q, J_{C-F} = 38.0 Hz), 53.8 (CH_3), 38.0 (CH_2); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −78.70 (s, CF_3); **HRMS (ESI)** 309.0518 $(M+H)^+$, $C_{13}H_{12}ClF_3O_3$ required 309.0500.

Methyl 2-hydroxy-4-(naphthalen-2-yl)-2-(trifluoromethyl)pent-4-enoate (11)



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87-7.80 (m, 4H), 7.51-7.50 (m, 3H), 5.56 (s, 1H), 5.40 (s, 1H), 3.83 (s, 1H), 3.45 (d, *J* = 14.0 Hz, 1H), 3.29 (s, 3H), 3.17 (d, *J* = 14.0 Hz, 1H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.6 (C), 141.0 (C), 138.1 (C), 133.2 (C), 132.9 (C), 128.3 (CH), 127.9 (CH), 127.7 (CH), 126.5 (CH), 126.3 (CH), 125.7 (CH), 125.1 (CH), 123.5 (C, q, J_{C-F} = 284.0 Hz), 120.2 (CH_2), 77.4 (C, q, J_{C-F} = 29.0 Hz), 53.6 (CH_3), 37.4 (CH_2); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −78.26 (s, CF_3); HRMS (ESI) 325.1037 $(M+H)^+$, $C_{17}H_{15}F_3O_3$ required 325.1046.

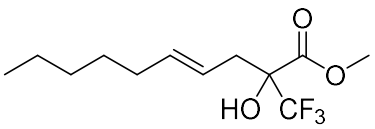
Methyl 4-(furan-2-yl)-2-hydroxy-2-(trifluoromethyl)pent-4-enoate (12)



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, *J* = 1.2 Hz, 1H), 6.37 (m, 2H), 5.68 (d, *J* =0.8 Hz, 1H), 5.11 (d, *J* = 1.2 Hz, 1H), 3.85 (s, 1H), 3.76 (s, 3H), 3.11 (d, *J* = 14.0 Hz, 1H), 2.92 (dd, *J* = 14.0, 1.2 Hz, 1H); **^{13}C**

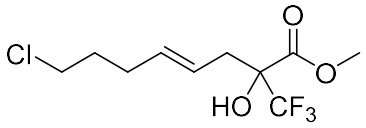
NMR (100 MHz, $CDCl_3$) δ 169.5 (C), 153.9 (C), 142.5 (CH), 129.8 (C), 123.4 (C, q, J_{C-F} = 284.0 Hz), 115.0 (CH_2), 111.4 (CH), 107.7 (CH), 77.9 (C, q, J_{C-F} = 29.0 Hz), 54.0 (CH_3), 35.0 (CH_2); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −78.38 (s, CF_3); **HRMS (ESI)** 279.0834 $(M+H)^+$, $C_{11}H_{11}F_3O_4$ required 279.0839.

Methyl (*E*)-2-hydroxy-2-(trifluoromethyl)dec-4-enoate (13)



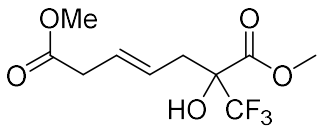
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.60 (dt, J = 15.2, 6.8 Hz, 1H), 5.30 (dt, *J* = 15.2, 6.8 Hz, 1H), 3.88 (s, 3H), 3.75 (s, 1H), 2.68-2.56 (m, 2H), 1.98 (q, *J* = 7.2 Hz, 2H), 1.32-1.28 (m, 6H), 0.88 (t, *J* = 6.8 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 170.1 (C), 137.6 (CH), 123.4 (C, q, J_{C-F} = 284 Hz), 120.4 (CH), 78.1 (C, q, J_{C-F} = 28 Hz), 54.2 (CH_3), 35.4 (CH_2), 32.7 (CH_2), 31.4 (CH_2), 29.1 (CH_2), 22.6 (CH_2), 14.2 (CH_3); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −78.33 (s, 1F); **HRMS (ESI)** 269.1367 $(M+H)^+$, $C_{12}H_{19}F_3O_3$ required 269.1359

Methyl (*E*)-8-chloro-2-hydroxy-2-(trifluoromethyl)oct-4-enoate (14)



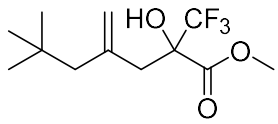
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.60 (dt, *J* = 15.2, 6.8 Hz, 1H), 5.30 (dt, *J* = 15.2, 6.8 Hz, 1H), 3.89 (s, 3H), 3.76 (s, 1H), 3.50 (t, *J* = 6.4 Hz, 2H), 2.70-2.58 (m, 2H), 2.16 (q, *J* = 6.8 Hz, 2H), 1.81 (dq, *J* = 6.8, 1.6 Hz, 2H); **^{13}C NMR (75 MHz, $CDCl_3$)** δ 169.0 (C), 135.2 (CH), 123.1 (C, q, J_{C-F} = 285.0 Hz), 122.2 (CH), 77.6 (C, q, J_{C-F} = 28.5 Hz), 54.3 (CH_3), 44.2 (CH_2), 35.3 (CH_2), 32.0 (CH_2), 29.9 (CH_2); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −78.24 (s, 1F); **HRMS (ESI)** 275.0659 $(M+H)^+$, $C_{10}H_{14}ClF_3O_3$ required 275.0656.

Dimethyl (*E*)-6-hydroxy-6-(trifluoromethyl)hept-3-enedioate (15)



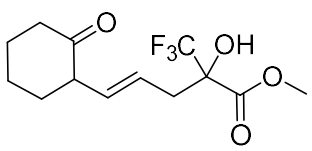
^{1}H NMR (300 MHz, $CDCl_3$) δ 5.73 (m, 1H), 5.47 (m, 1H), 3.90 (s, 3H), 3.81 (s, 1H), 3.68 (s, 3H), 3.07-3.04 (m, 2H), 2.74-2.61 (m, 2H); **^{13}C NMR (75 MHz, $CDCl_3$)** δ 171.9 (C), 169.9 (C), 128.4 (CH), 125.0 (CH), 123.3 (C, q, J_{C-F} = 285.0 Hz), 77.9 (C, q, J_{C-F} = 29.0 Hz), 54.4 (CH_3), 52.0 (CH_3), 37.8 (CH_2), 29.9 (CH_2); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −78.41 (s, CF_3); **HRMS (ESI)** 271.0786 $(M+H)^+$, $C_{10}H_{13}F_3O_5$ required 271.0788.

Methyl 2-hydroxy-5,5-dimethyl-4-methylene-2-(trifluoromethyl)hexanoate (16)



^{1}H NMR (300 MHz, $CDCl_3$) δ 4.99 (s, 1H), 4.88 (s, 1H), 3.88 (s, CH_3), 3.79 (s, 1H), 2.74 (d, *J* = 14.0 Hz, 1H), 2.64 (d, *J* = 14.0 Hz, 1H), 2.10 (d, *J* = 12.8 Hz, 1H), 1.86 (d, *J* = 12.8 Hz, 1H), 0.9 (s, 9H); **^{13}C NMR (75 MHz, $CDCl_3$)** δ 170.2 (C), 140.6 (C), 123.4 (C, q, J_{C-F} = 285.0 Hz), 118.5 (CH_2), 78.8 (C, q, J_{C-F} = 28.5 Hz), 54.0 (CH), 50.4 (CH_2), 38.7 (CH_2), 31.8 (C), 29.8 (CH_3); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −78.59 (s, CF_3); **HRMS (ESI)** 269.1380 $(M+H)^+$, $C_{11}H_{17}F_3O_3$ required 269.1359.

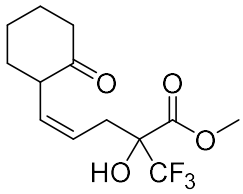
Methyl (*E*)-2-hydroxy-5-(2-oxocyclohexyl)-2-(trifluoromethyl)pent-4-enoate (*E*-17)



^{1}H NMR (300 MHz, $CDCl_3$) δ 5.72-5.59 (m, 1H), 4.97-4.95 (m, 1H), 4.92-4.90 (m, 1H), 3.88 (s, 1H), 3.76 (s, 3H), 3.25 (dd, *J* = 11.7, 6.0 Hz, 1H), 2.45-2.26 (m, 2H), 2.13-2.07 (m, 1H), 1.91-1.67 (m, 6H); **^{13}C NMR (75 MHz, $CDCl_3$)** δ 209.8 (C), 170.2 (C), 136.0 (CH), 123.4 (C, q, J_{C-F} = 286.5), 116.7 (CH), 77.2 (C, q, J_{C-F} = 30.0 Hz), 54.1 (CH_3), 53.8 (CH), 50.6 (CH_2), 33.6

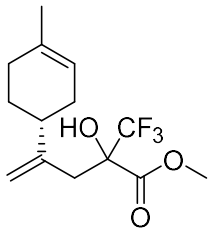
(CH_2), 33.3 (CH_2), 28.2 (CH_2), 24.6 (CH_2); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −74.62 (s, CF_3); **HRMS (ESI)** 295.1154 $(M+H)^+$, $C_{10}H_{13}F_3O_5$ required 295.1152.

Methyl (*Z*)-2-hydroxy-5-(2-oxocyclohexyl)-2-(trifluoromethyl)pent-4-enoate (*Z*-17)



^{1}H NMR (300 MHz, $CDCl_3$) δ 5.70-5.57 (m, 1H), 5.10-5.06 (m, 1H), 5.04-5.02 (m, 1H), 3.96 (s, 1H), 3.81 (s, 3H), 3.38 (dd, *J* = 12, 6.3 Hz, 1H), 2.49-2.42 (m, 2H), 2.30-2.23 (m, 2H), 1.91-1.77 (m, 5H); **^{13}C NMR (75 MHz, $CDCl_3$)** δ 210.4 (C), 168.9 (C), 133.6 (CH), 122.2 (C, q, $J_{C\text{-}F}$ = 286.5 Hz), 116.2 (CH), 76.4 (C, q, $J_{C\text{-}F}$ = 31.5 Hz), 52.9 (CH_3), 49.3 (CH), 48.9 (CH_2), 34.5 (CH_2), 28.7 (CH_2), 25.4 (CH_2), 18.5 (CH_2); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −74.33 (s, CF_3); HRMS (ESI) 295.1154 $(M+H)^+$, $C_{10}H_{13}F_3O_5$ required 295.1152.

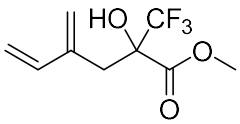
Methyl 2-hydroxy-4-((*R*)-4-methylcyclohex-3-en-1-yl)-2-(trifluoromethyl)pent-4-enoate (18)



Mixture of diastereoisomers in a 1:1 ratio; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 5.38 (m 2H), 4.93-4.89 (m, 4H), 3.87 (s, 3H), 3.86 (s, 3H), 3.81 (d, *J* = 0.8 Hz, 1H), 3.80 (d, *J* = 0.8 Hz, 1H), 2.72 (dt, *J* = 15.6, 14.0 Hz, 4H), 2.16-1.96 (m, 8H), 1.81-1.76 (m, 4H), 1.64 (s, 6H), 1.47-1.33 (m, 2H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 170.2 (C), 147.8 (C), 147.4 (C), 133.9 (C), 133.8 (C), 123.4 (C, q, $J_{C\text{-}F}$ = 285.0 Hz), 120.51 (CH), 150.49 (CH), 113.0 (CH_2), 112.8 (CH_2), 78.7 (C, q, $J_{C\text{-}F}$ = 29.0 Hz), 78.6 (C, q, $J_{C\text{-}F}$ = 29.0 Hz) 54.09 (CH_3), 54.07 (CH_3), 40.13 (CH), 40.10 (CH), 36.40 (CH_2), 36.36 (CH_2), 31.8 (CH_2), 31.1 (CH_2), 30.8 (CH_2), 30.7 (CH_2), 28.5 (CH_2), 28.2

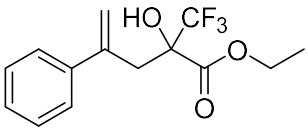
(CH_2), 23.51 (CH_3), 23.50 (CH_3); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −78.70 (s, 1F), −78.74 (s, 1F); HRMS (ESI) 293.1348 $(M+H)^+$, $C_{14}H_{19}F_3O_3$ required 293.1359.

Methyl 2-hydroxy-4-methylene-2-(trifluoromethyl)hex-5-enoate (19)



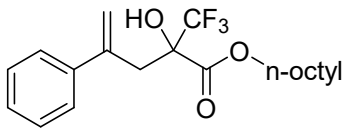
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.33 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.30 (d, *J* = 17.2 Hz, 1H), 5.23 (s, 1H), 5.13 (s, 1H), 5.10 (d, *J* = 11.2 Hz, 1H), 3.84 (s, 3H), 3.76 (s, 1H), 2.96 (d, *J* = 14.4 Hz, 1H), 2.78 (d, *J* = 14.4 Hz, 1H); **^{13}C NMR (75 MHz, $CDCl_3$)** δ 169.2 (C), 138.5 (C), 123.5 (C, q, $J_{C\text{-}F}$ = 28.5 Hz), 120.7 (CH_2), 118.75 (CH), 114.8 (CH_2), 77.9 (C, q, $J_{C\text{-}F}$ = 285.0 Hz), 54.0 (CH_3), 32.9 (CH_2); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −78.42 (s, 1F); HRMS (ESI) 225.027 $(M+H)^+$, $C_{14}H_{19}F_3O_3$ required 225.0733.

Ethyl 2-hydroxy-4-phenyl-2-(trifluoromethyl)pent-4-enoate (20)



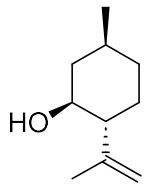
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.27 (m, 5H), 5.40 (s, 1H), 5.29 (s, 1H), 4.04 (dq, *J* = 10.8, 6.8 Hz, 1H), 3.81 (s, 1H), 3.64 (dq, *J* = 10.8, 6.8 Hz, 1H), 3.30 (d, *J* = 14.0 Hz, 1H), 3.05 (dd, *J* = 14.0, 0.8 Hz, 1H), 1.12 (t, *J* = 8.0 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.1 (C), 141.2 (C), 128.3 (CH), 127.9 (CH), 126.9 (CH), 123.5 (C, q, $J_{C\text{-}F}$ = 285.0 Hz), 119.5 (CH_2), 77.3 (C, q, $J_{C\text{-}F}$ = 28.0 Hz), 63.6 (CH_2), 37.2 (CH_2), 13.7 (CH_3); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −78.45 (s, CF_3); **HRMS (ESI)** 289.1057 $(M+H)^+$, $C_{14}H_{15}F_3O_3$ required 289.1046.

Octyl 2-hydroxy-4-phenyl-2-(trifluoromethyl)pent-4-enoate (21)



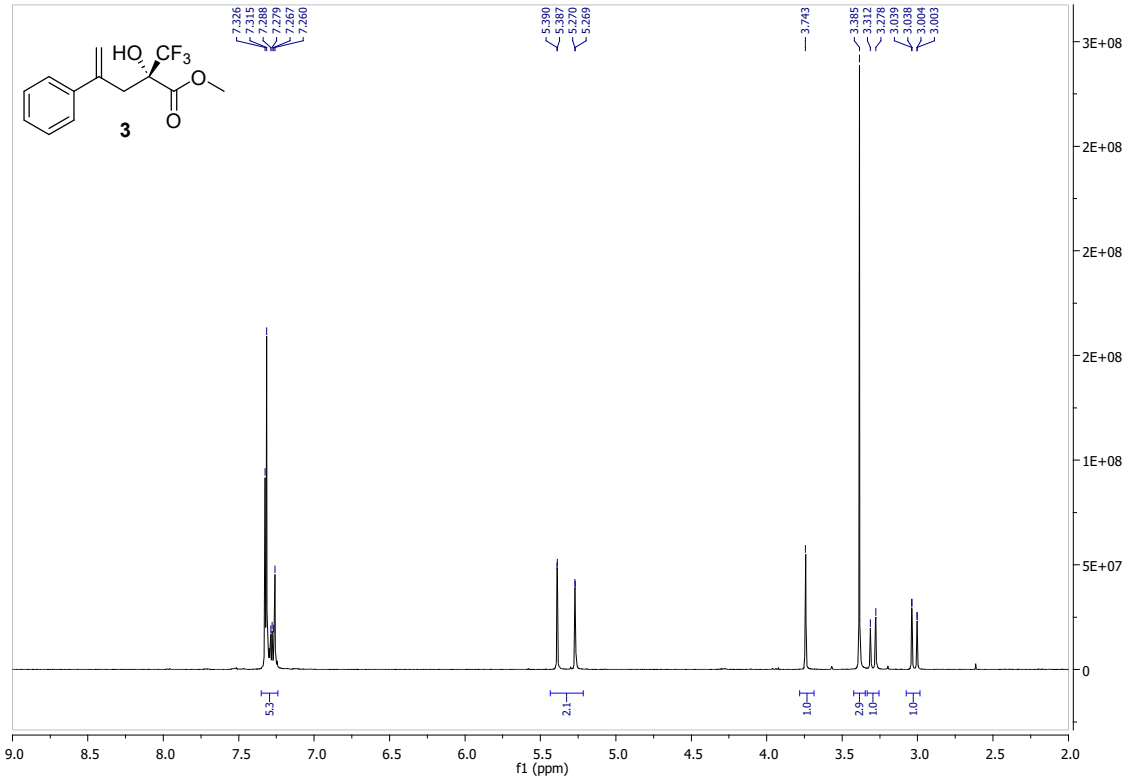
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.23 (m, 5H), 5.38 (d, *J* = 1.5 Hz, 1H), 5.28 (d, *J* = 0.9 Hz, 1H), 4.01 (dt, *J* = 10.8, 6.6 Hz, 1H), 3.77 (br s, 1H), 3.50 (dt, *J* = 10.5, 6.6 Hz, 1H), 3.28 (d, *J* = 14.1 Hz, 1H), 3.04 (dd, *J* = 14.1, 0.9 Hz, 1H), 1.48-1.44 (m, 2H), 1.31-1.25 (m, 10H), 0.89 (t, *J* = 6.6 Hz, 3H); **^{13}C NMR (75 MHz, $CDCl_3$)** δ 169.2 (C), 141.2 (C), 128.3 (CH), 127.8 (CH), 126.9 (CH), 123.6 (C, q, $J_{C\text{-}F}$ = 282.0 Hz), 119.5 (CH_2), 77.4 (C, q, $J_{C\text{-}F}$ = 28.5 Hz), 67.7 (CH_2), 37.2 (CH_2), 31.8 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 28.1 (CH_2), 25.6 (CH_2), 22.8 (CH_2), 14.2 (CH_3); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −78.36 (s, CF_3); **HRMS (ESI)** 373.1991 $(M+H)^+$, $C_{14}H_{15}F_3O_3$ required 373.1985.

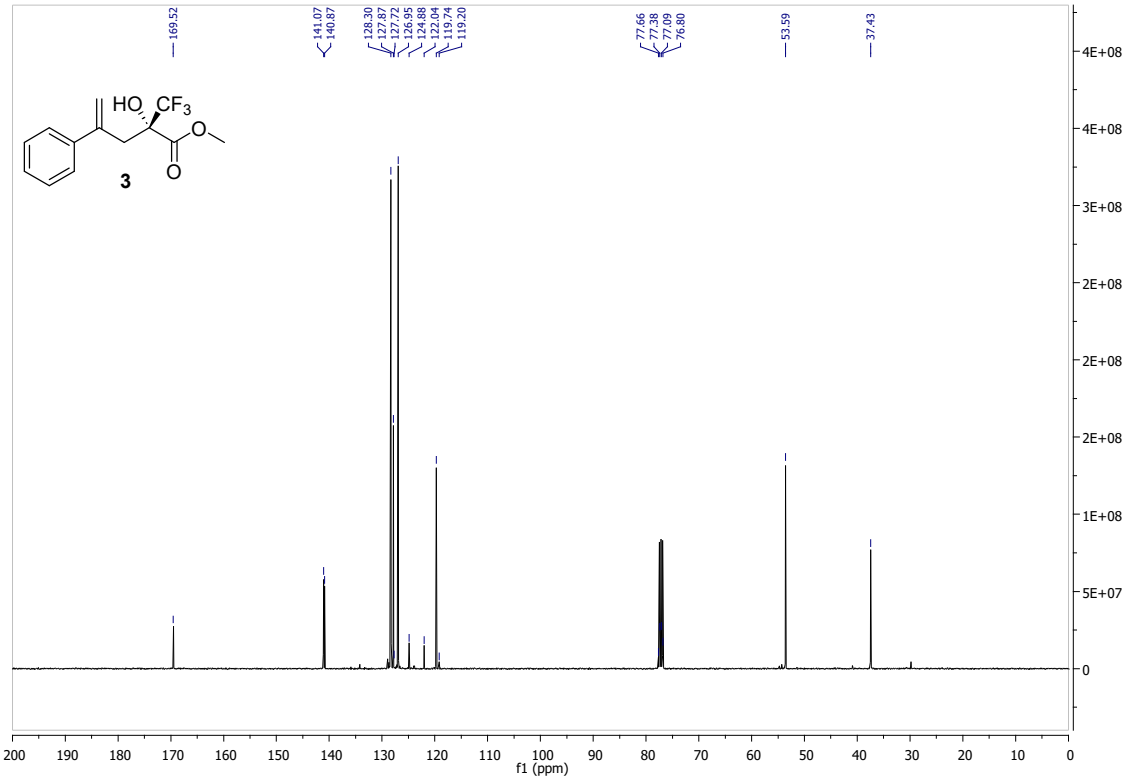
(1*S*,2*R*,5*S*)-5-methyl-2-(prop-1-en-2-yl)cyclohexan-1-ol (neo-isoisopulegol) (28)

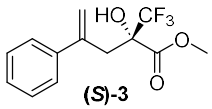


^{1}H NMR (400 MHz, $CDCl_3$) δ 4.90 (s, 1H), 4.86 (s, 1H), 3.46 (dt, *J* = 10.4, 4.4 Hz, 1H), 2.07-2.01 (m, 1H), 1.92-1.85 (m, 2H), 1.71 (s, 3H), 1.70-1.65 (m, 2H), 1.52-1.49 (m, 1H), 1.38-1.30 (m, 2H), 0.94 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 146.8 (C), 113.0 (CH_2), 70.5 (CH), 54.3 (CH), 42.8 (CH_2), 34.5 (CH_2), 31.6 (CH), 29.8 (CH_2), 22.4 (CH_3), 19.3 (CH_3); **HRMS (ESI)** 155.1433 $(M+H)^+$, $C_{14}H_{15}F_3O_3$ required 155.1430.

NMR and HPLC copies.

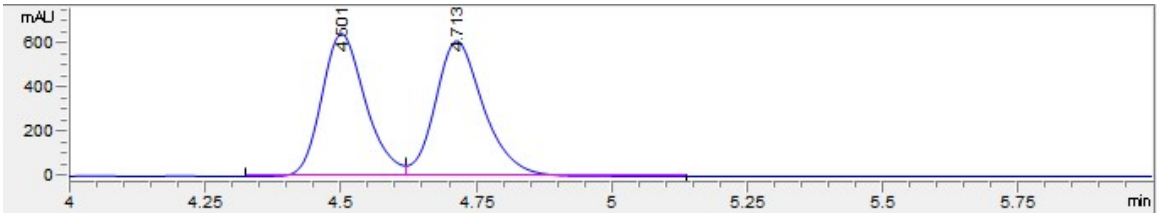




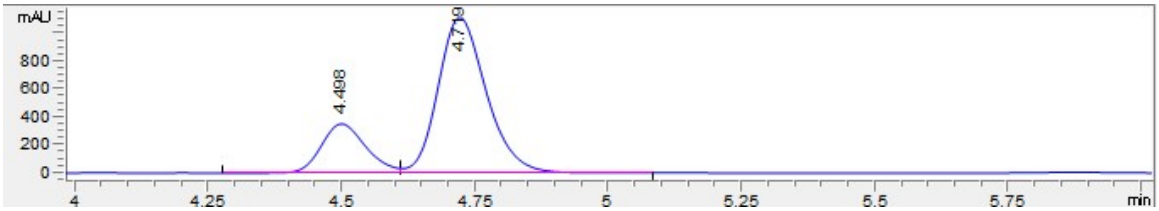


(*S*)-3

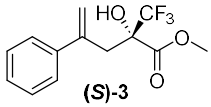
Results for the enantioselective synthesis of **3** *via* ene-carbonyl reaction without sustraction of the blank reaction (Table 3, entry **6**).



#	Time	Area	Height	Width	Area%	Symmetry
1	4.501	3577	636.5	0.0856	48.801	0.779
2	4.713	3752.8	604.2	0.0945	51.199	0.752

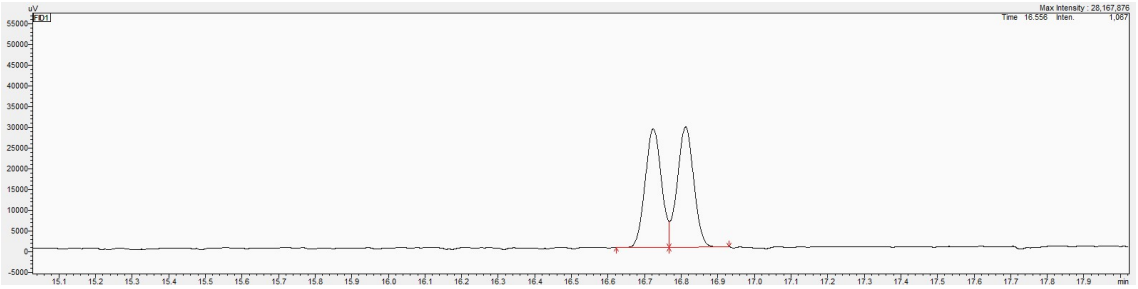


#	Time	Area	Height	Width	Area%	Symmetry
1	4.498	2048.7	354.8	0.0894	22.578	0.792
2	4.719	7025.1	1125.2	0.0968	77.422	0.765



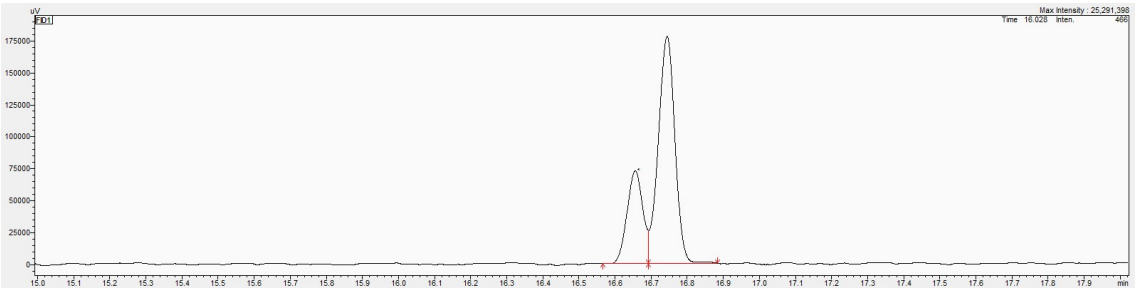
(*S*)-3

Results for the enantioselective synthesis of **3** *via* domino dehydration / intermolecular carbonyl–ene reaction (Table 7, entry **2**).



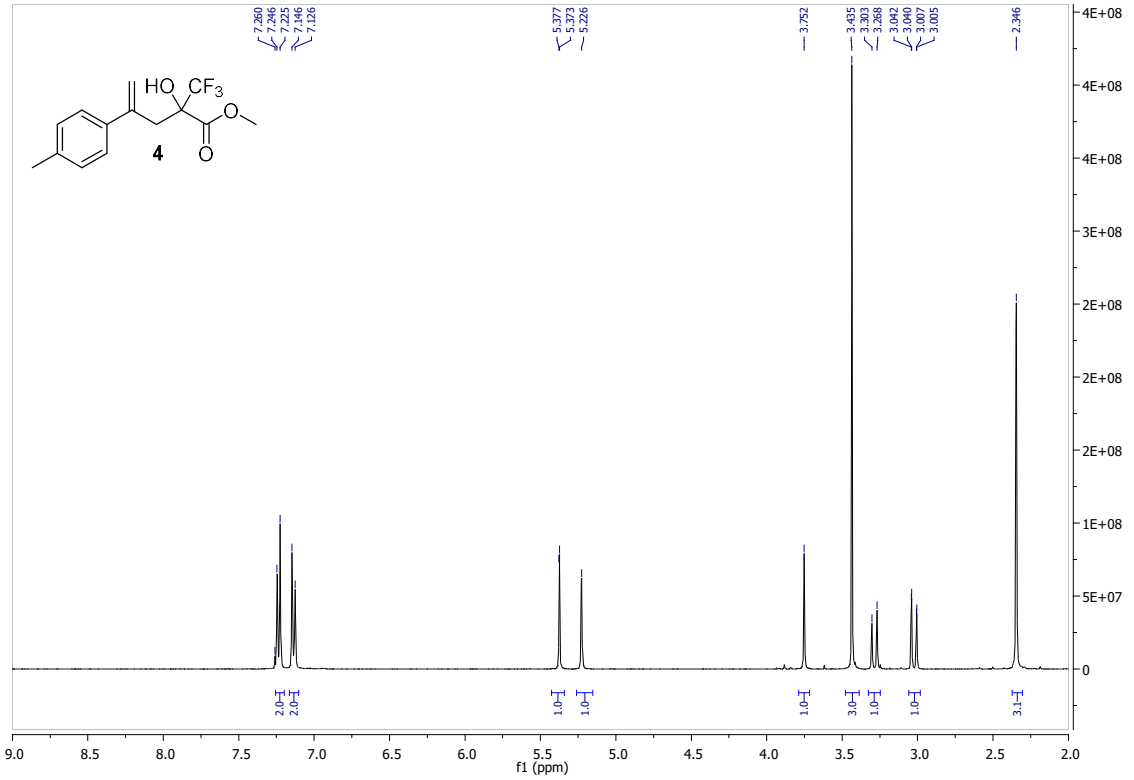
Peak Table | Compound | Group | Calibration Curve

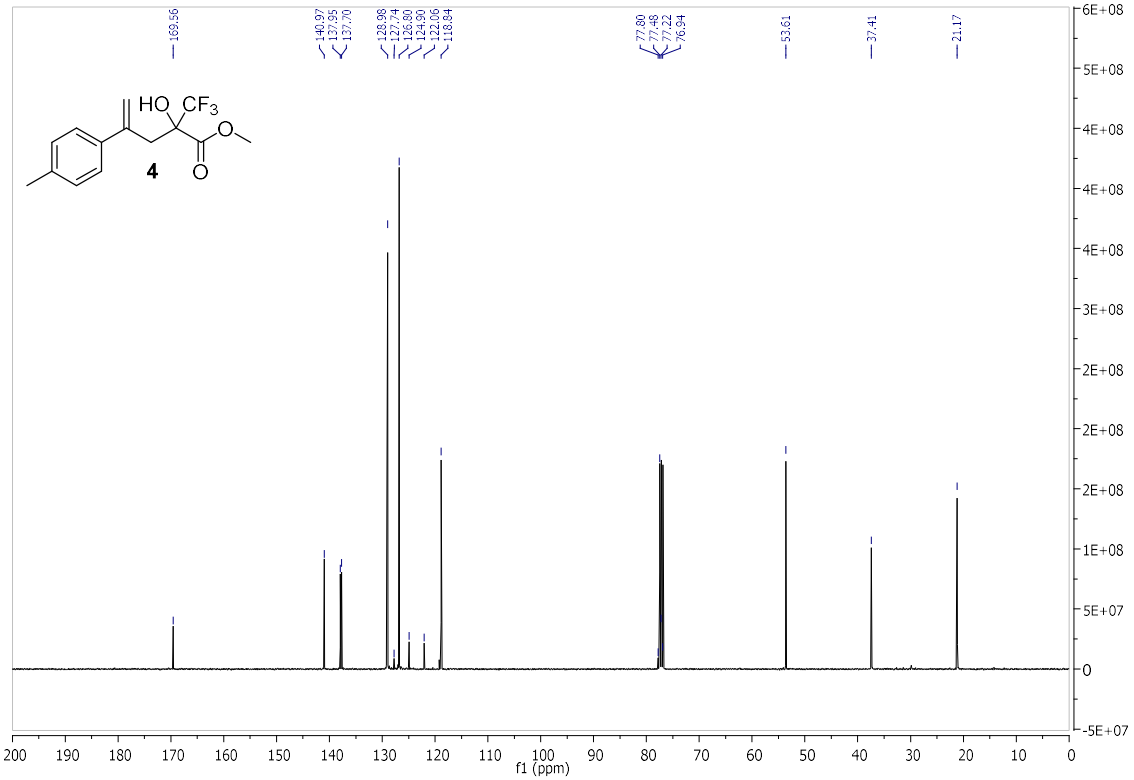
Peak	Ret. Time	Area	Height	Conc.	Area%
1	16.724	88508	28520	49.408	49.408
2	16.812	90628	28939	50.592	50.592
Total		179136	57459	100.000	100.000

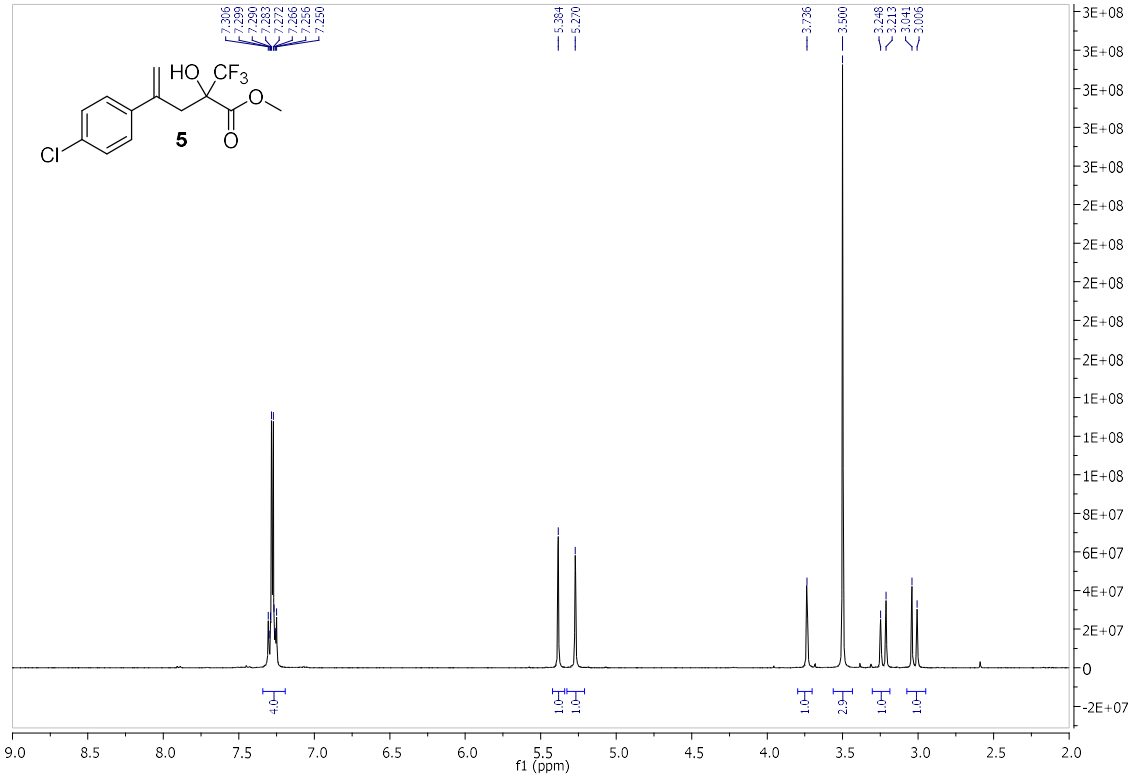


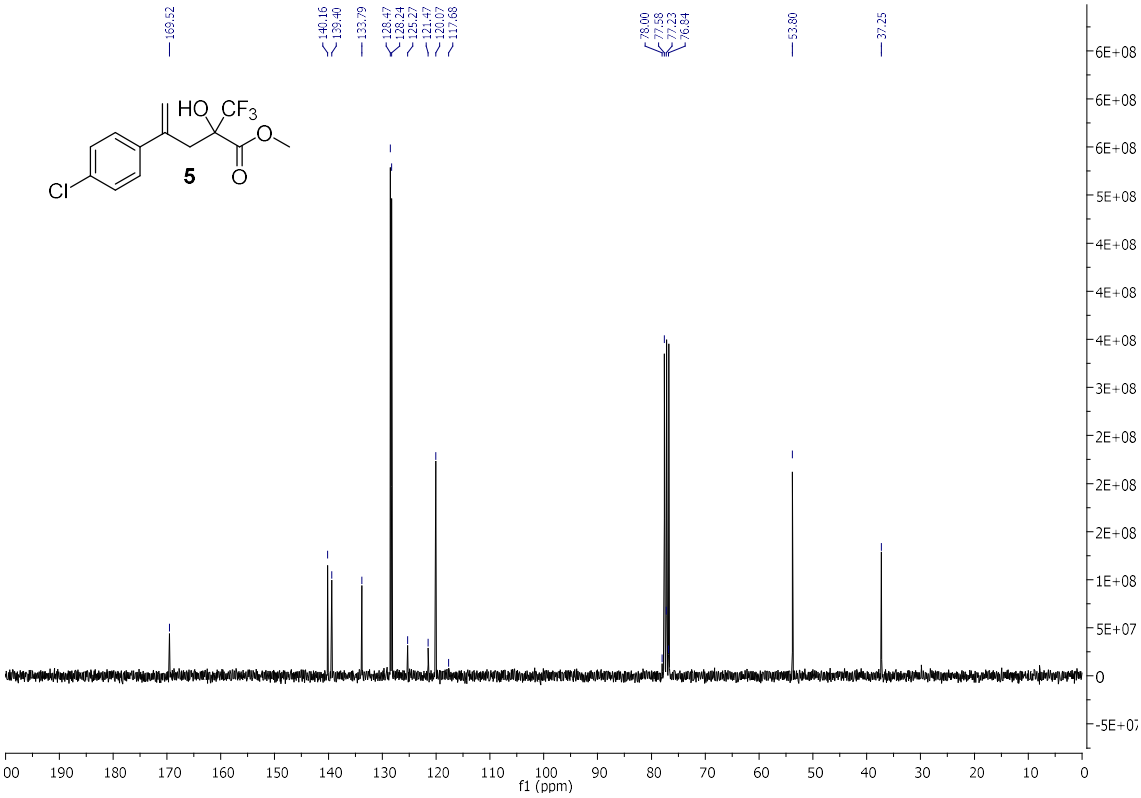
Peak Table | Compound | Group | Calibration Curve

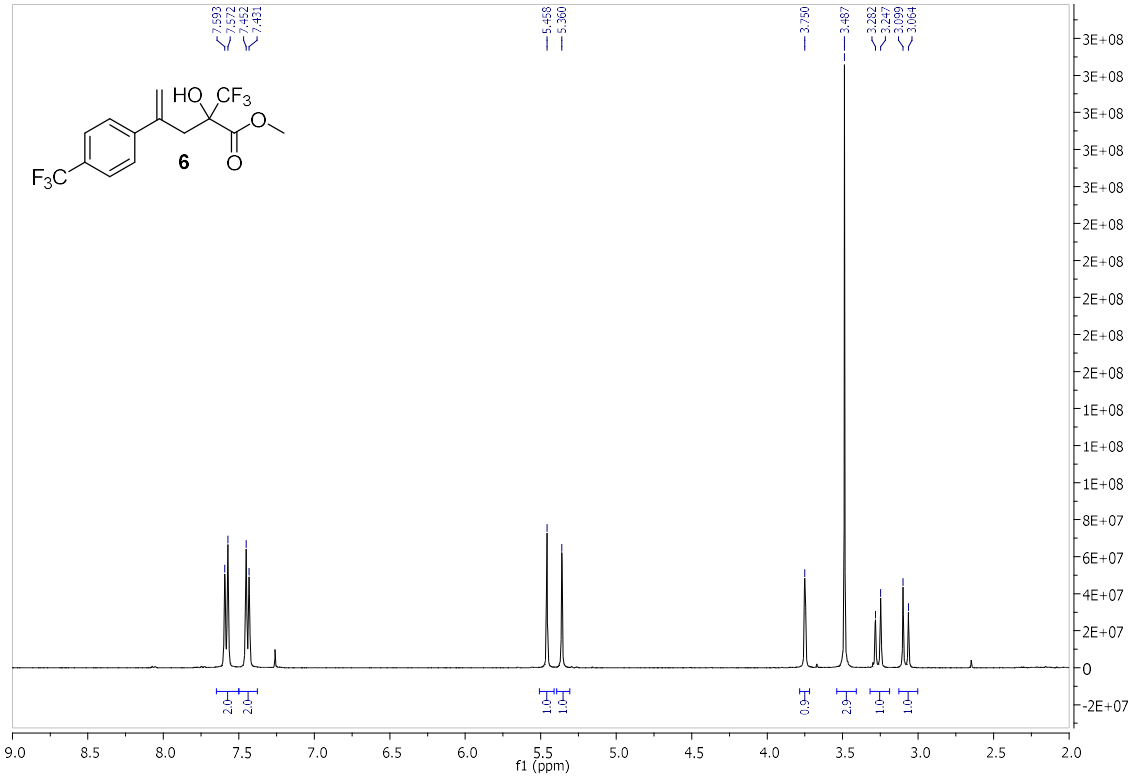
Peak	Ret. Time	Area	Height	Conc.	Area%
1	16.656	221022	71731	28.050	28.050
2	16.744	566923	176490	71.950	71.950
Total		787946	248222	100.000	100.000

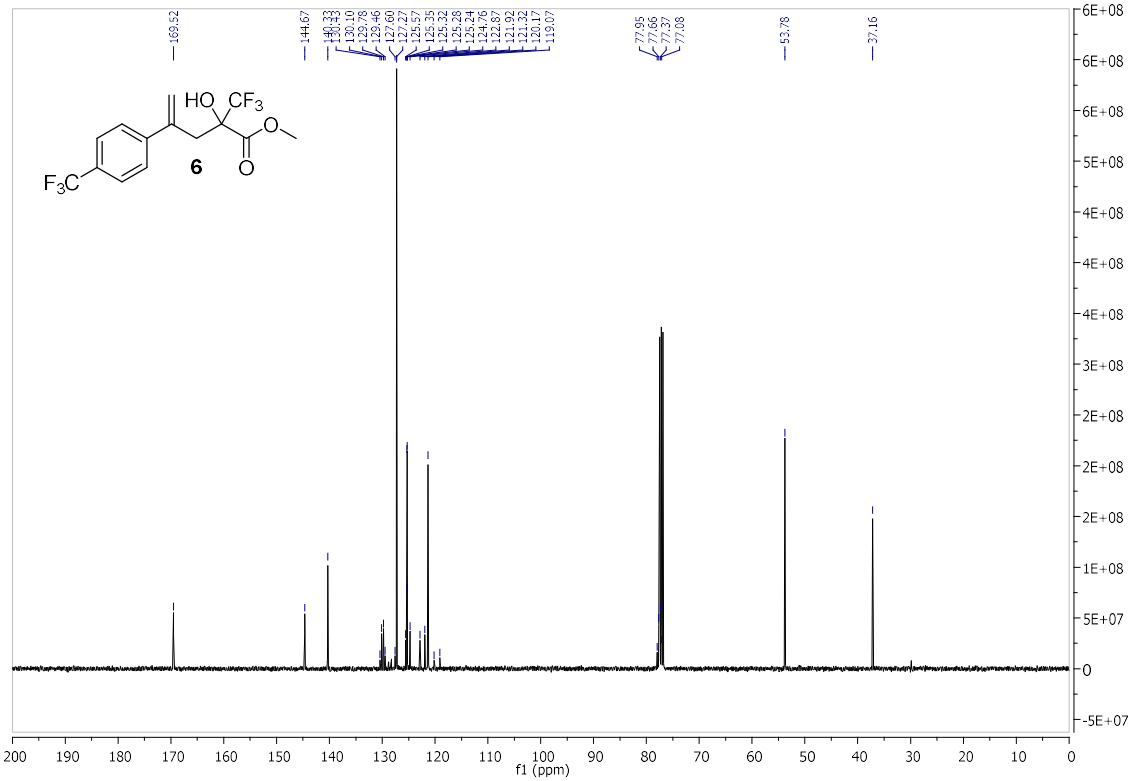

7.260
7.246
7.225
7.146
7.126
5.377
5.373
5.226
3.752
3.435
3.303
3.268
3.042
3.040
3.007
3.005
2.346
HO
CF3
O
4
O
f1 (ppm)

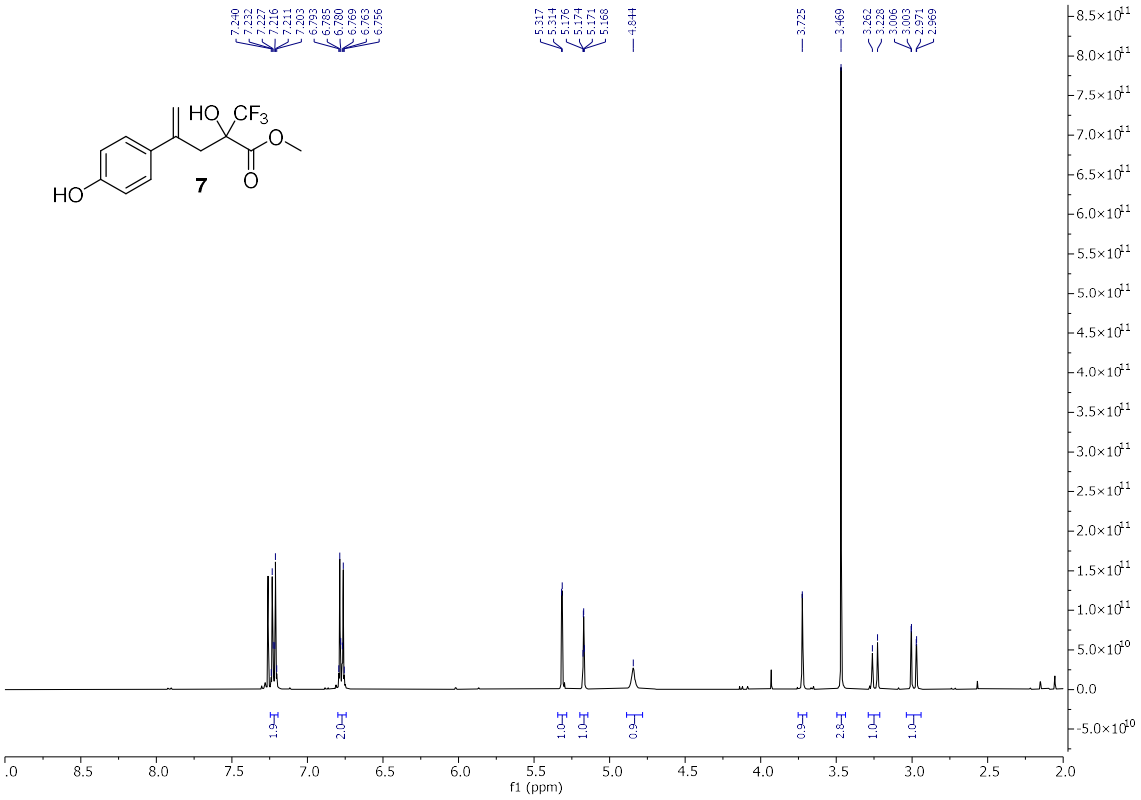

169.56
140.97
137.95
137.70
128.98
127.74
126.80
124.90
122.06
118.84
77.80
77.46
77.22
76.94
53.61
37.41
21.17
HO
CF3
O
4
O
f1 (ppm)

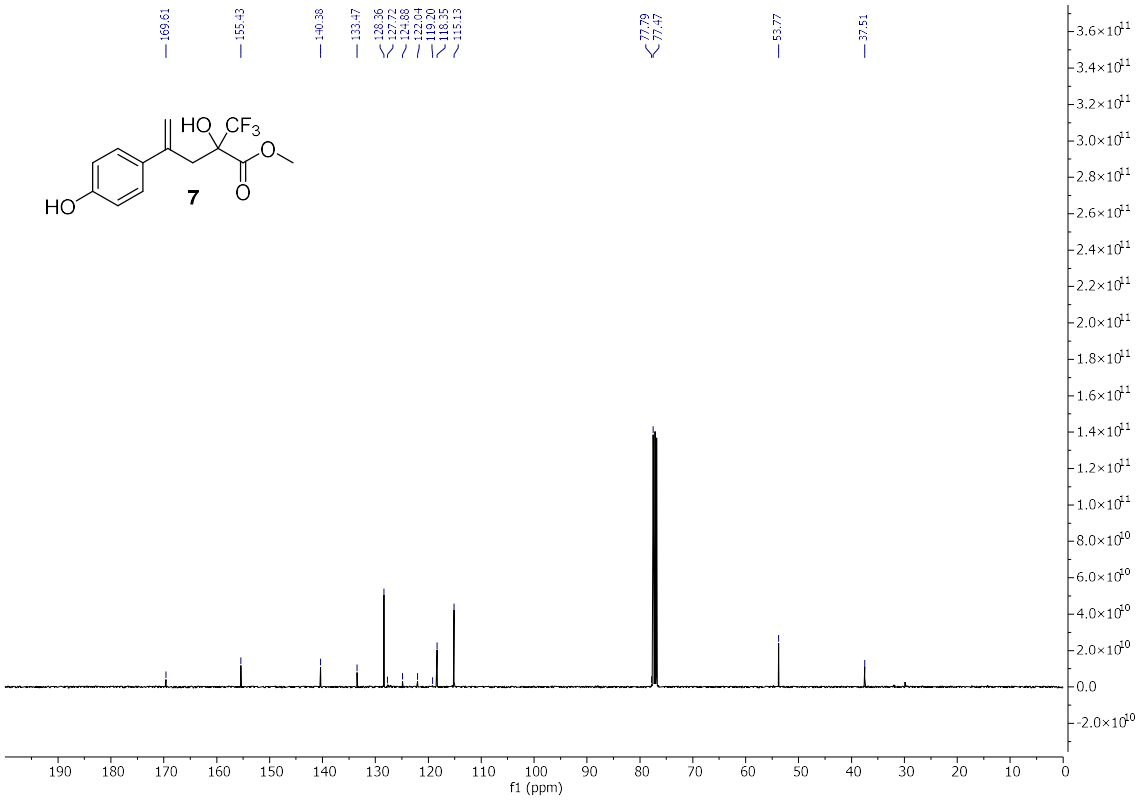

HO
CF3
O
Cl
5
O
7.306
7.299
7.290
7.283
7.272
7.266
7.256
7.250
5.384
5.270
3.736
3.500
3.248
3.213
3.041
3.006
f1 (ppm)

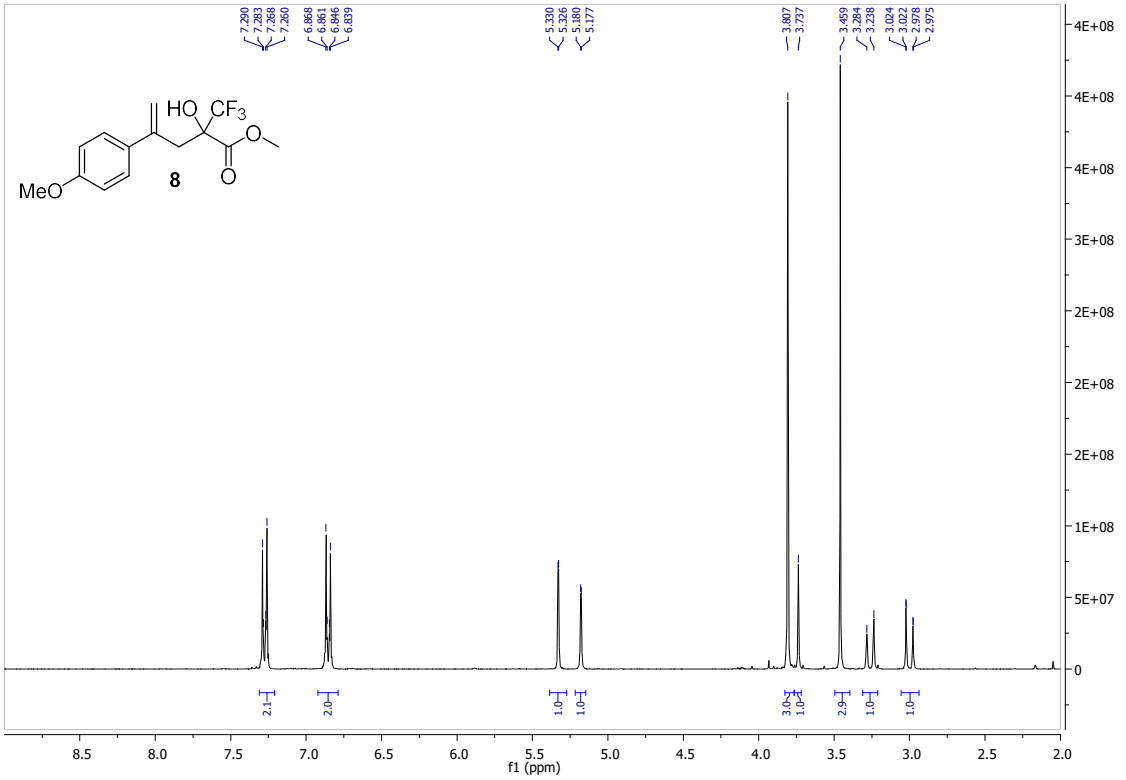

HO
CF3
O
Cl
5
O
169.52
140.16
139.40
133.79
128.47
128.24
125.27
121.47
120.07
117.68
78.00
77.58
77.23
76.84
53.80
37.25
f1 (ppm)

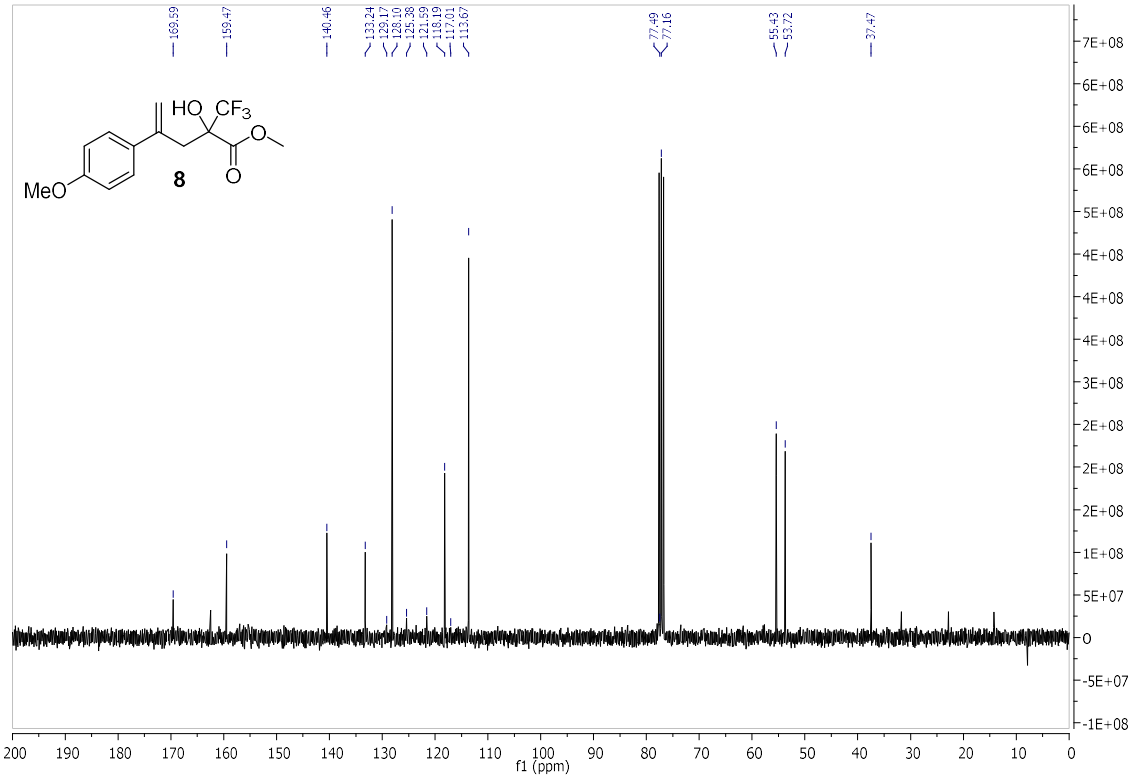

7.593
7.572
7.452
7.431
5.458
5.360
3.750
3.487
3.282
3.247
3.099
3.064
HO
CF3
O
F3C
6
O
f1 (ppm)

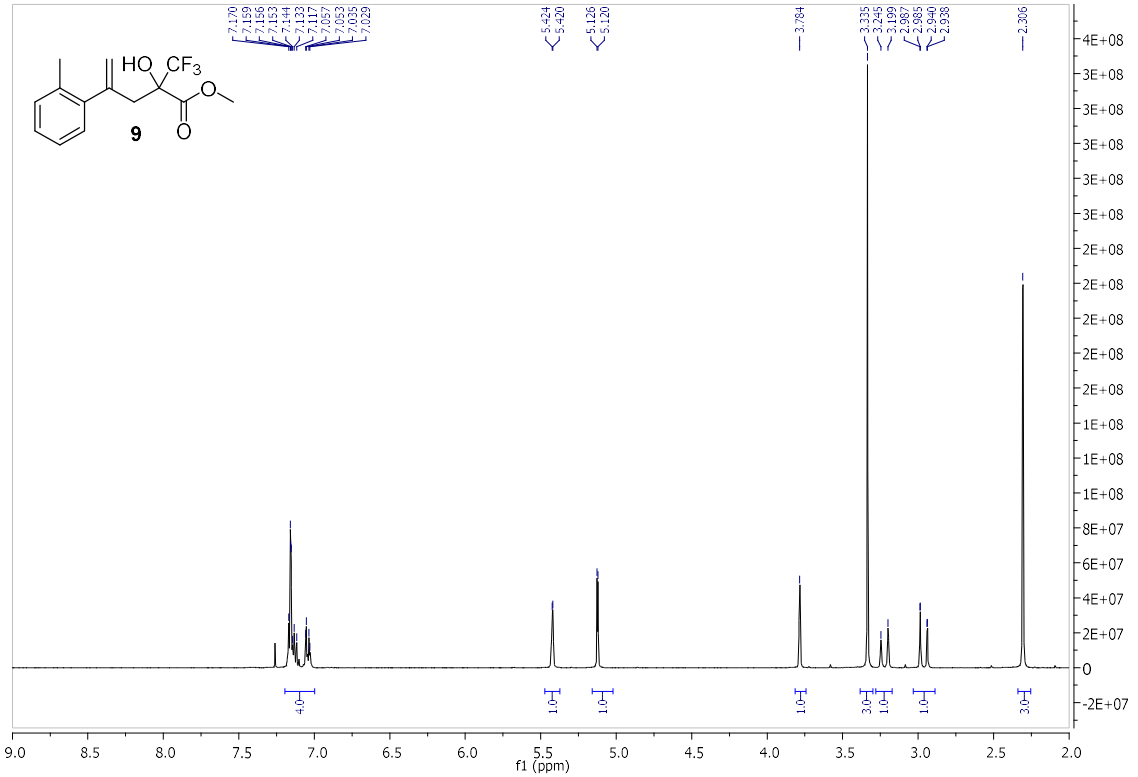

169.52
144.67
140.33
130.10
128.78
128.46
127.60
127.27
125.57
125.35
125.32
125.28
125.24
124.76
122.87
121.92
121.32
120.17
119.07
77.95
77.66
77.37
77.08
53.78
37.16
HO
CF3
O
F3C
6
O
f1 (ppm)

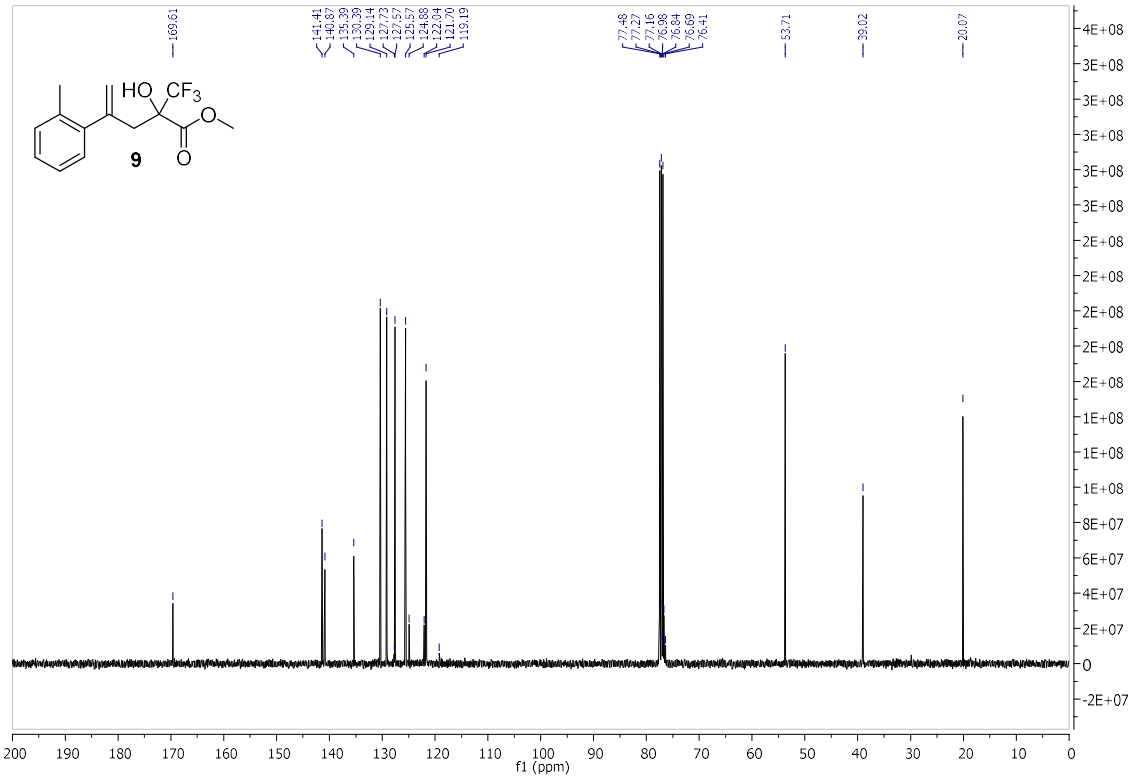

7.240
7.232
7.227
7.216
7.211
7.203
6.793
6.785
6.780
6.769
6.763
6.756
5.317
5.314
5.176
5.174
5.171
5.168
4.844
3.725
3.469
3.262
3.238
3.006
3.003
2.971
2.969
HO
CF3
O
O
HO
7
1.9
2.0
1.0
1.0
0.9
0.9
2.8
1.0
1.0
f1 (ppm)

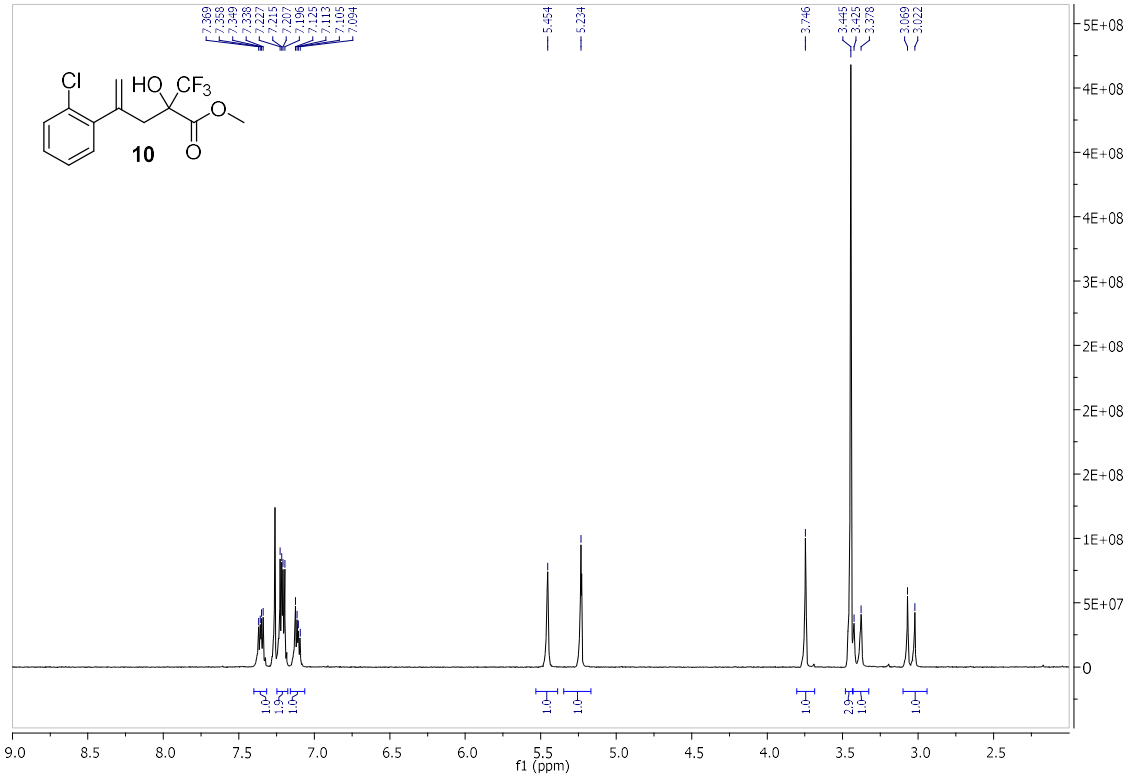

169.61
155.43
140.38
133.47
128.36
127.72
124.88
122.04
119.20
118.35
115.13
77.79
77.47
53.77
37.51
HO
CF3
O
O
HO
7
f1 (ppm)

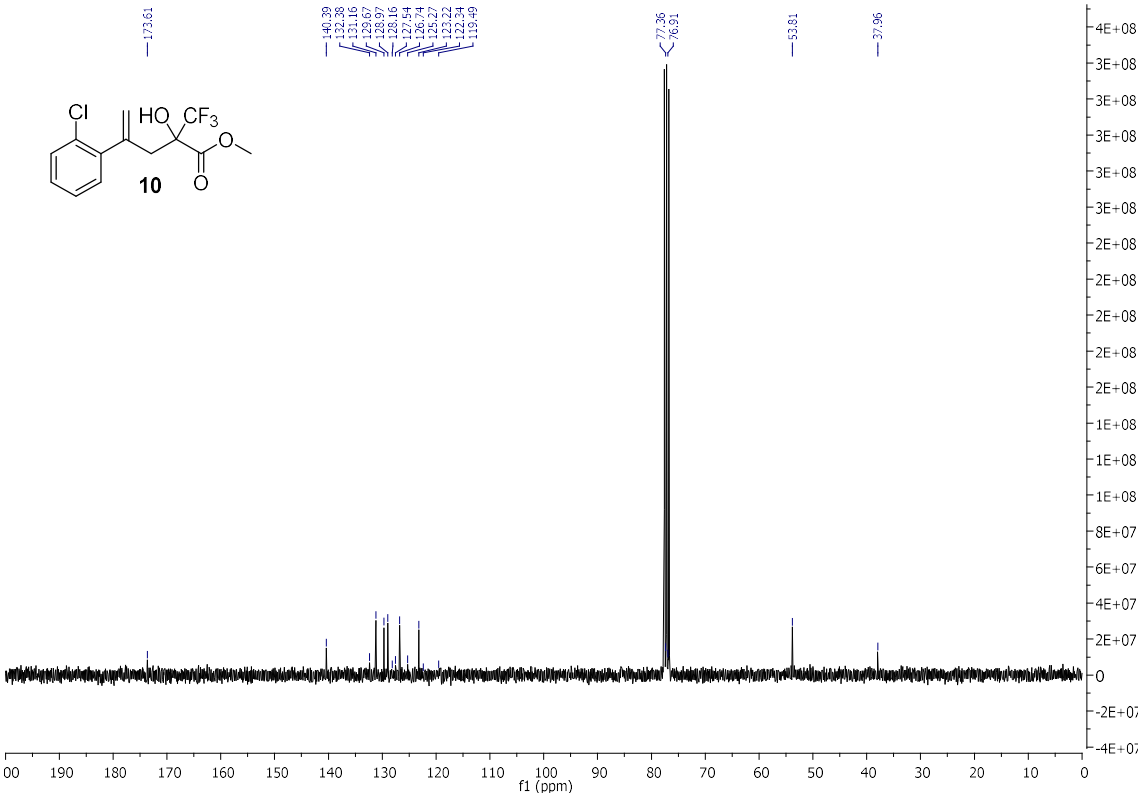

HO
CF3
O
MeO
8
O
7.290
7.283
7.268
7.260
6.868
6.861
6.846
6.839
5.330
5.326
5.180
5.177
3.807
3.737
3.459
3.284
3.238
3.024
3.022
2.978
2.975
2.1
2.0
1.0
1.0
3.0
1.0
2.9
1.0
1.0
f1 (ppm)

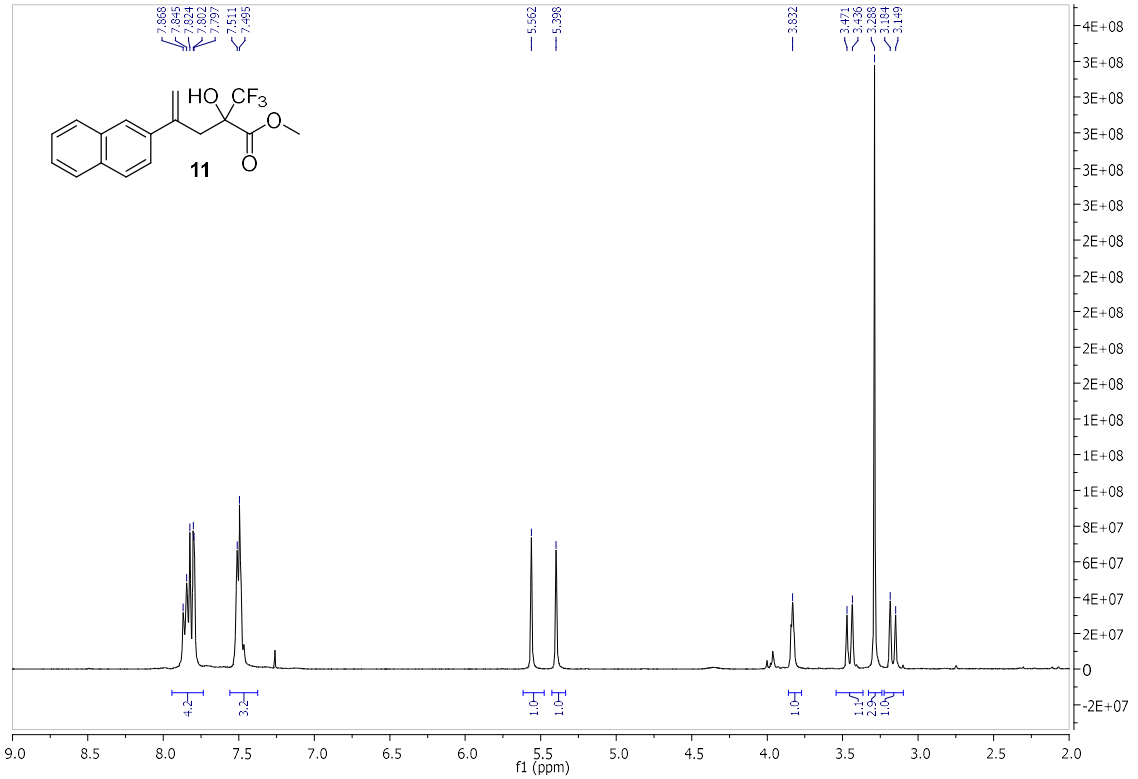

HO
CF3
O
MeO
8
O
169.59
159.47
140.46
133.24
129.17
128.10
125.38
121.59
118.19
117.01
113.67
77.49
77.16
55.43
53.72
37.47
f1 (ppm)

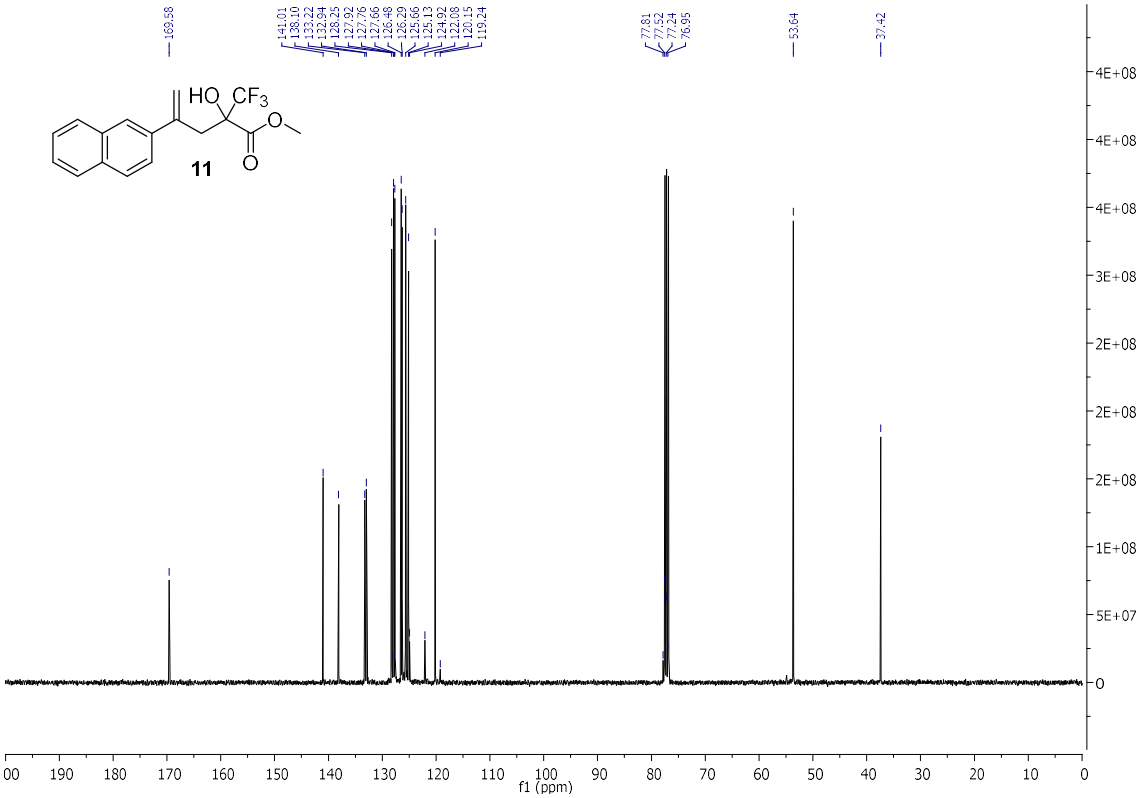

HO
CF3
O
O
9
7.170
7.159
7.156
7.153
7.144
7.133
7.117
7.057
7.053
7.035
7.029
5.424
5.420
5.126
5.120
3.784
3.335
3.245
3.199
2.987
2.985
2.940
2.938
2.306
f1 (ppm)

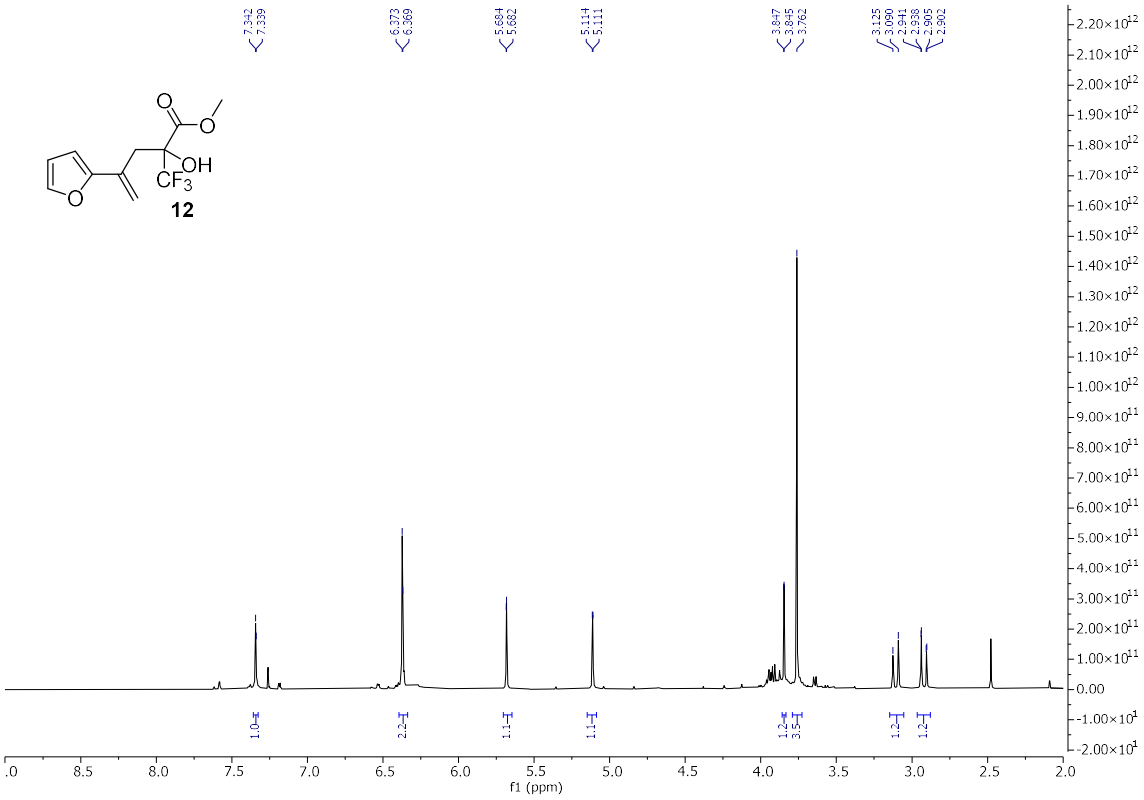

HO
CF3
O
O
9
169.61
141.41
140.87
135.39
130.39
129.14
127.73
127.57
125.57
124.88
122.04
121.70
119.19
77.48
77.27
77.16
76.98
76.84
76.69
76.41
53.71
39.02
20.07
f1 (ppm)

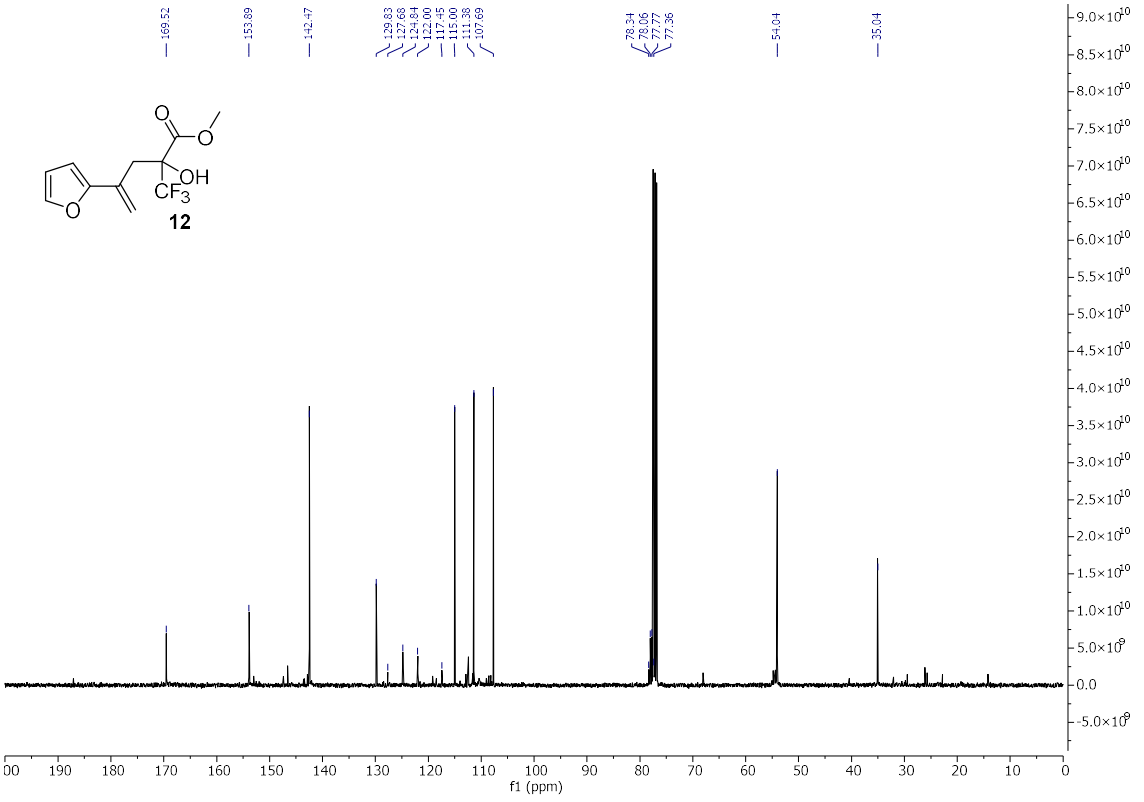

7.369
7.358
7.349
7.338
7.227
7.215
7.207
7.196
7.125
7.113
7.105
7.094
5.454
5.234
3.746
3.445
3.425
3.378
3.069
3.022
Cl
HO
CF3
O
O
10
f1 (ppm)

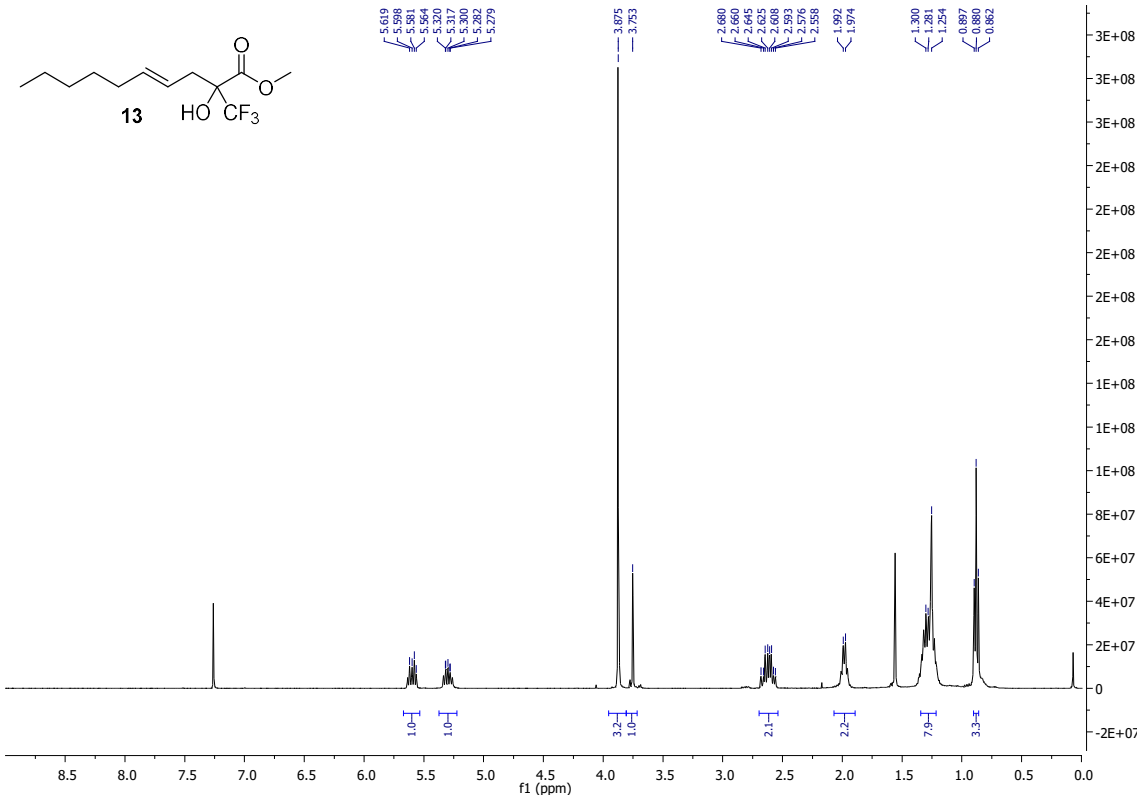

173.61
140.39
132.38
131.16
128.67
128.07
128.16
127.54
126.74
125.27
123.22
122.34
119.49
77.36
76.91
53.81
37.96
Cl
HO
CF3
O
O
10
f1 (ppm)

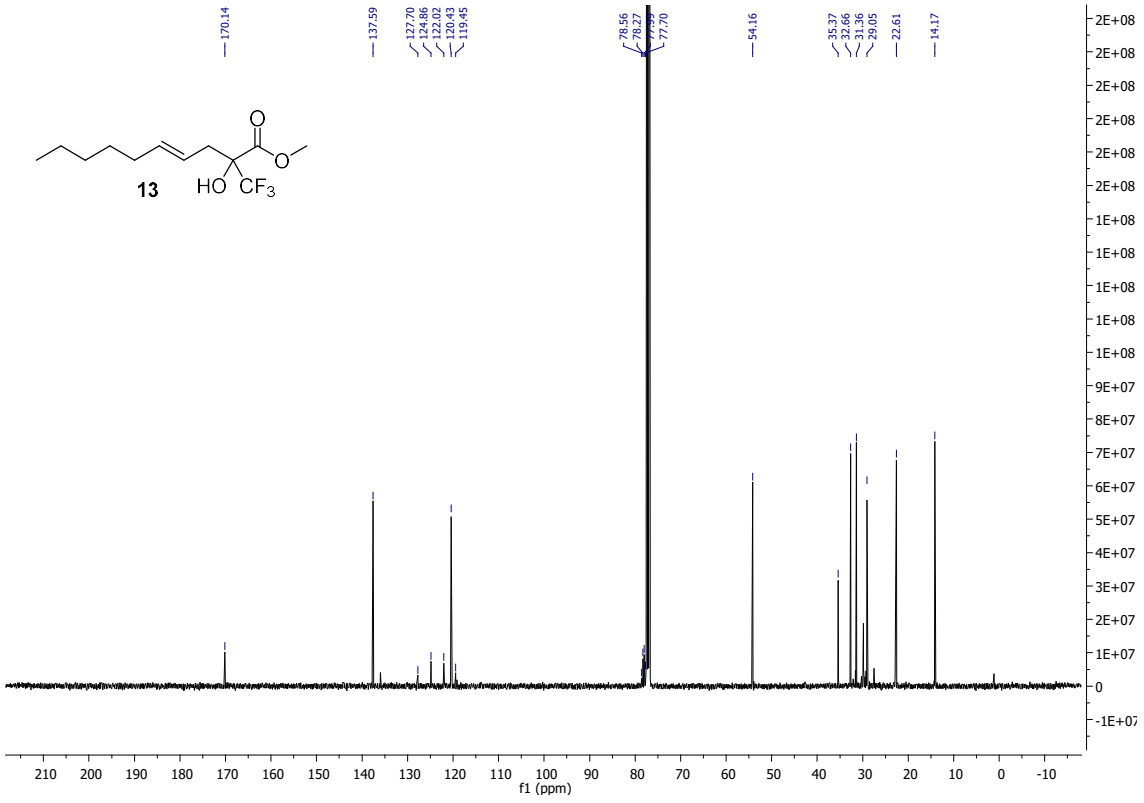

7.868
7.845
7.824
7.802
7.797
7.511
7.495
5.562
5.398
3.832
3.471
3.436
3.288
3.194
3.149
HO
CF3
O
O
11
4.2
3.2
1.0
1.0
1.0
1.1
2.9
1.0
f1 (ppm)

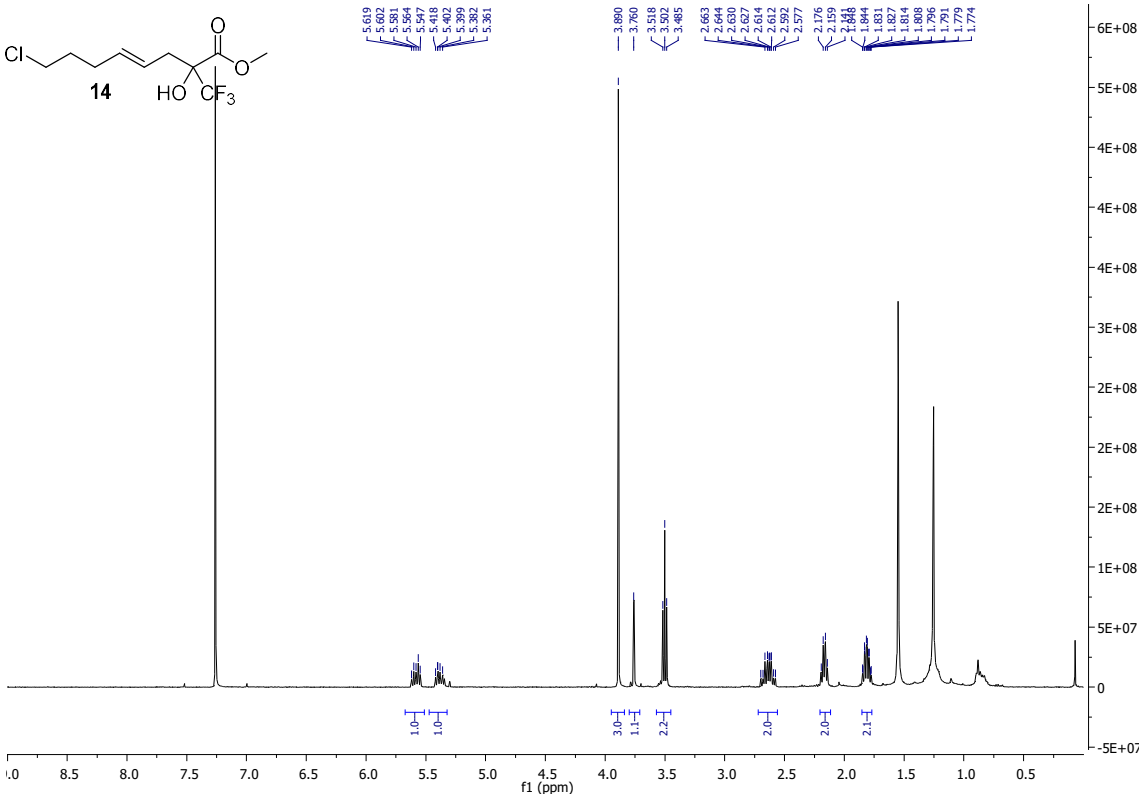

169.58
141.01
138.10
133.22
132.94
128.25
127.92
127.76
127.66
126.48
126.29
125.66
125.13
124.92
122.08
120.15
119.24
77.81
77.52
77.24
76.95
53.64
37.42
HO
CF3
O
O
11
f1 (ppm)

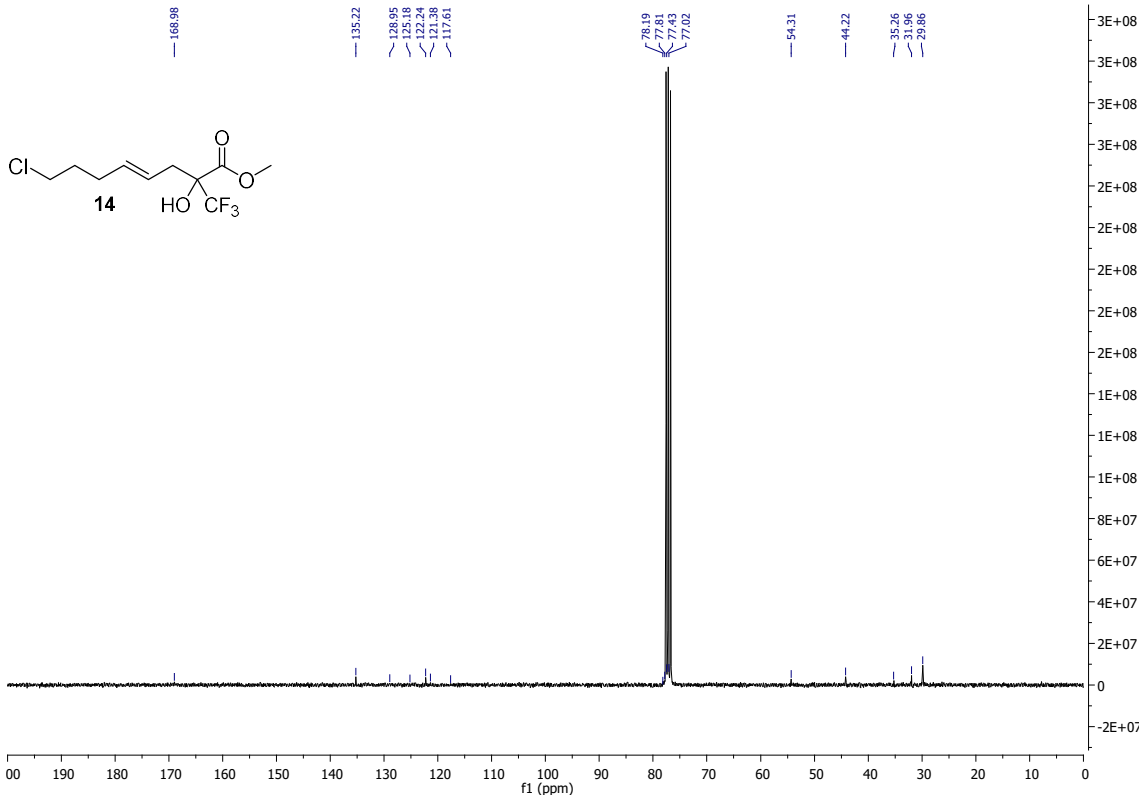

7.342
7.339
6.373
6.369
5.684
5.682
5.114
5.111
3.847
3.845
3.762
3.125
3.090
2.941
2.938
2.905
2.902
O
O
OH
CF3
12
1.0
2.2
1.1
1.1
1.2
3.5
1.2
1.2
f1 (ppm)

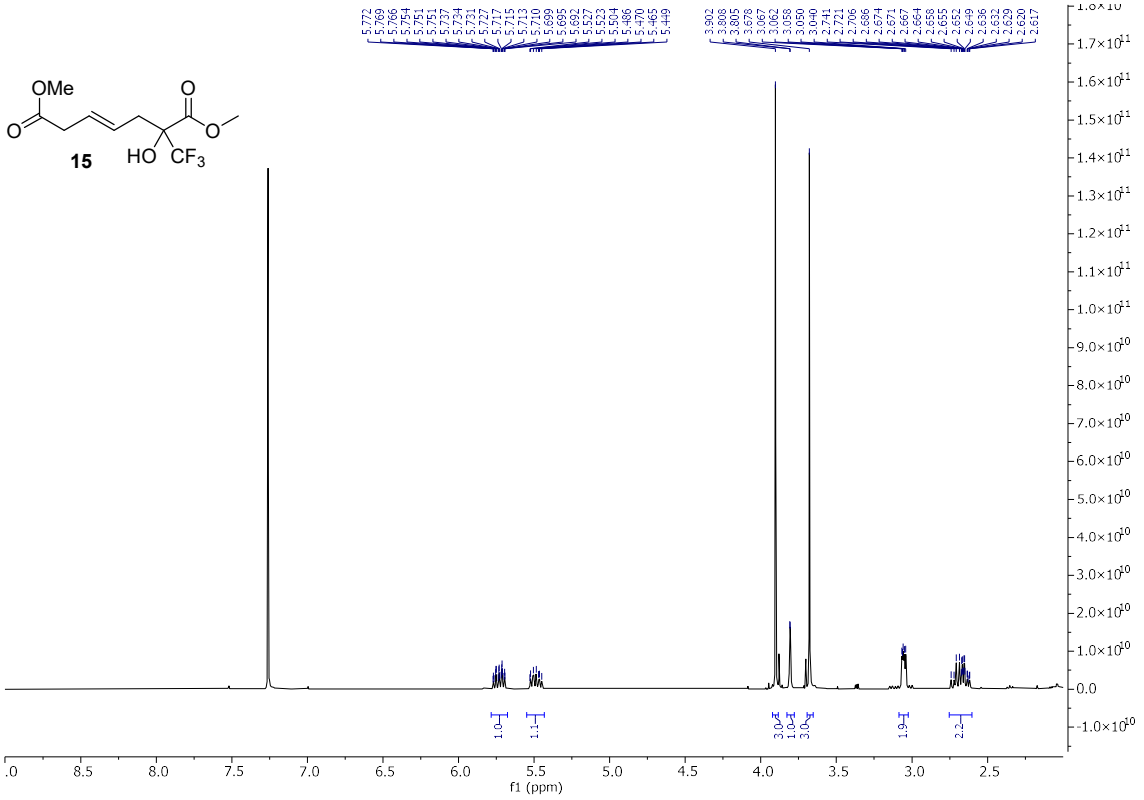

169.52
153.89
142.47
129.83
127.68
124.84
122.00
117.45
115.00
111.38
107.69
78.34
78.06
77.77
77.36
54.04
35.04
O
O
OH
CF3
12
f1 (ppm)

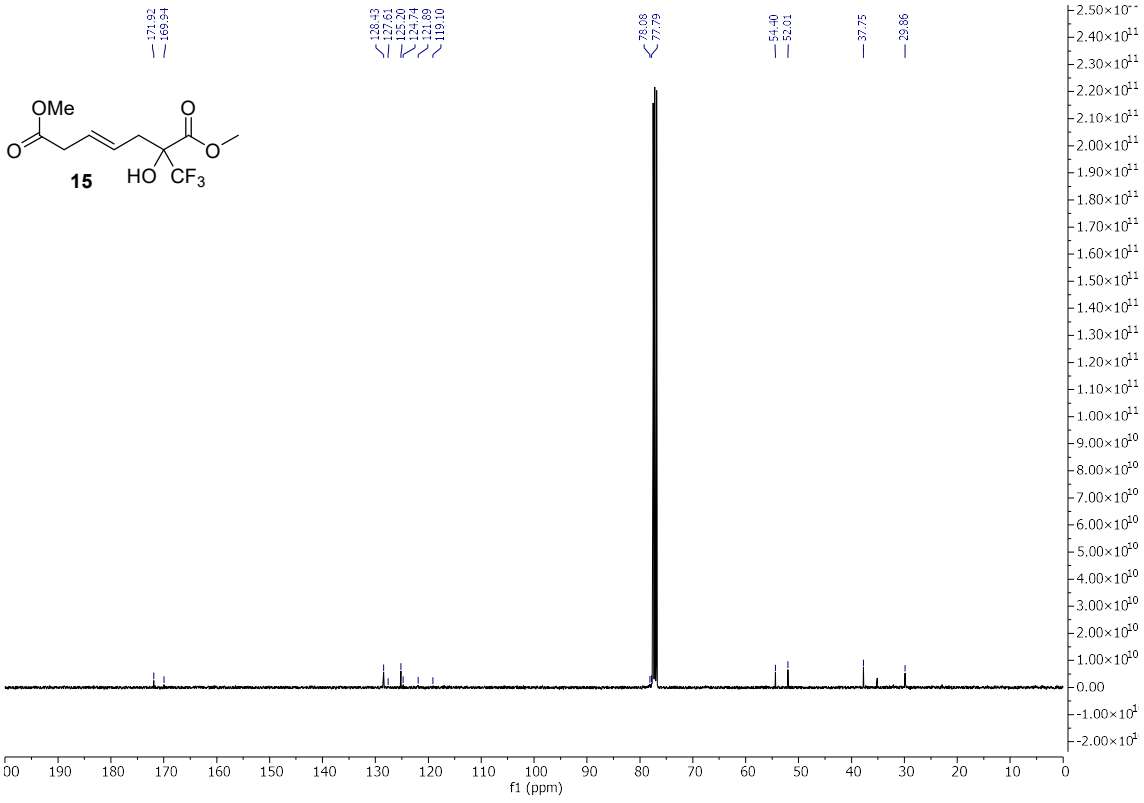

13
HO CF3
5.619
5.598
5.581
5.564
5.320
5.317
5.300
5.282
5.279
3.875
3.753
2.680
2.660
2.645
2.625
2.608
2.593
2.576
2.558
1.992
1.974
1.300
1.281
1.254
0.897
0.880
0.862
1.0
1.0
3.3
1.0
2.1
2.2
7.9
3.3
f1 (ppm)

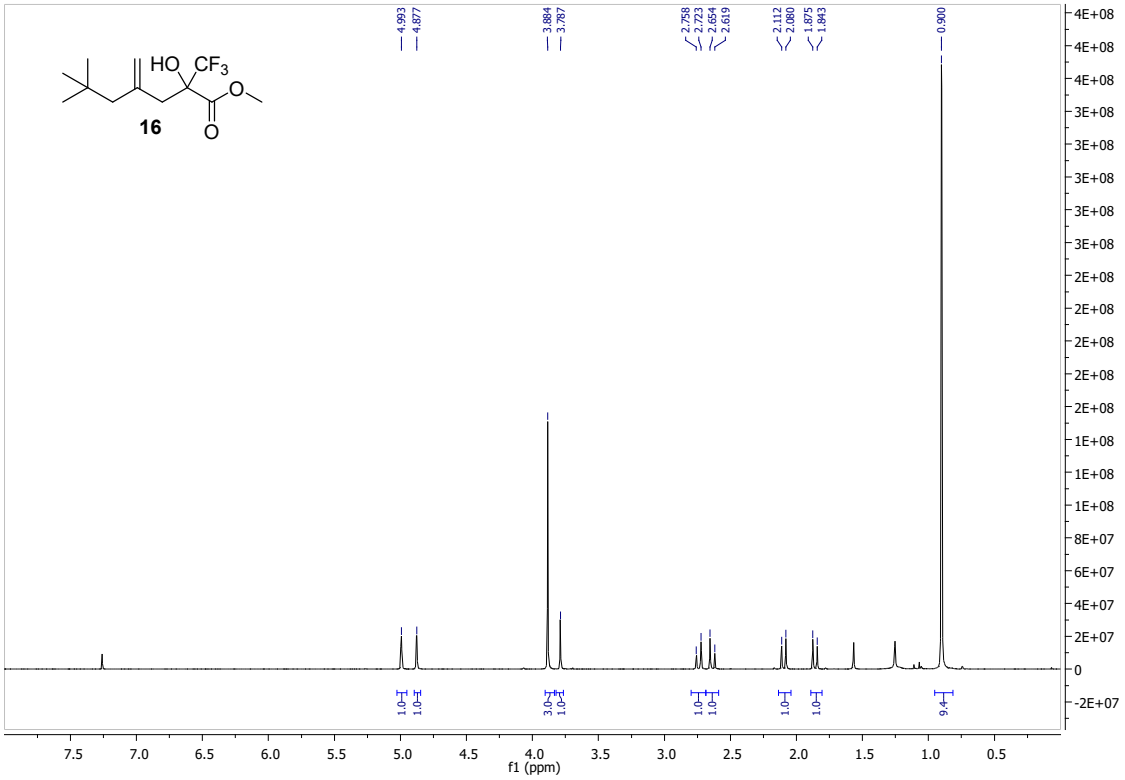

13
HO CF3
170.14
137.59
127.70
124.86
122.02
120.43
119.45
78.56
78.27
77.70
54.16
35.37
32.66
31.36
29.05
22.61
14.17
f1 (ppm)

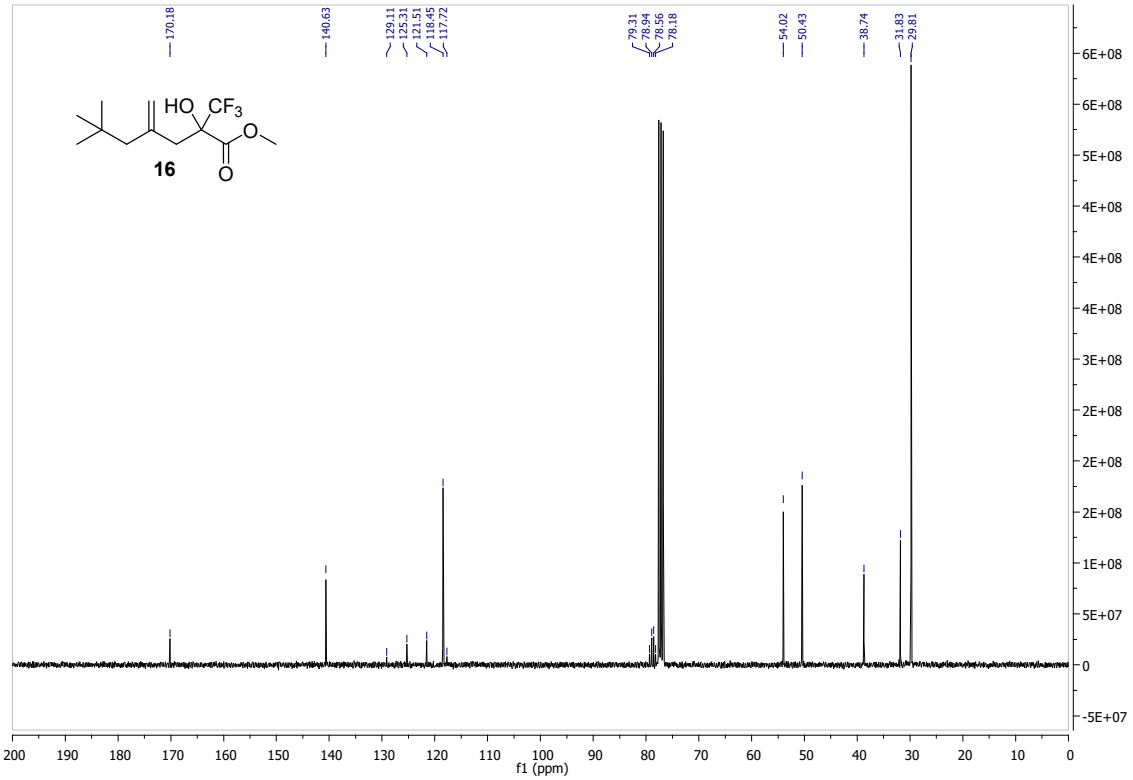

Cl
O
O
14
HO
CF3
5.619
5.602
5.581
5.564
5.547
5.418
5.402
5.399
5.382
5.361
3.890
3.760
3.518
3.502
3.485
2.663
2.644
2.630
2.627
2.614
2.612
2.592
2.577
2.176
2.159
1.844
1.831
1.827
1.814
1.808
1.796
1.791
1.779
1.774
1.0
1.0
3.0
1.1
2.2
2.0
2.0
2.1
f1 (ppm)

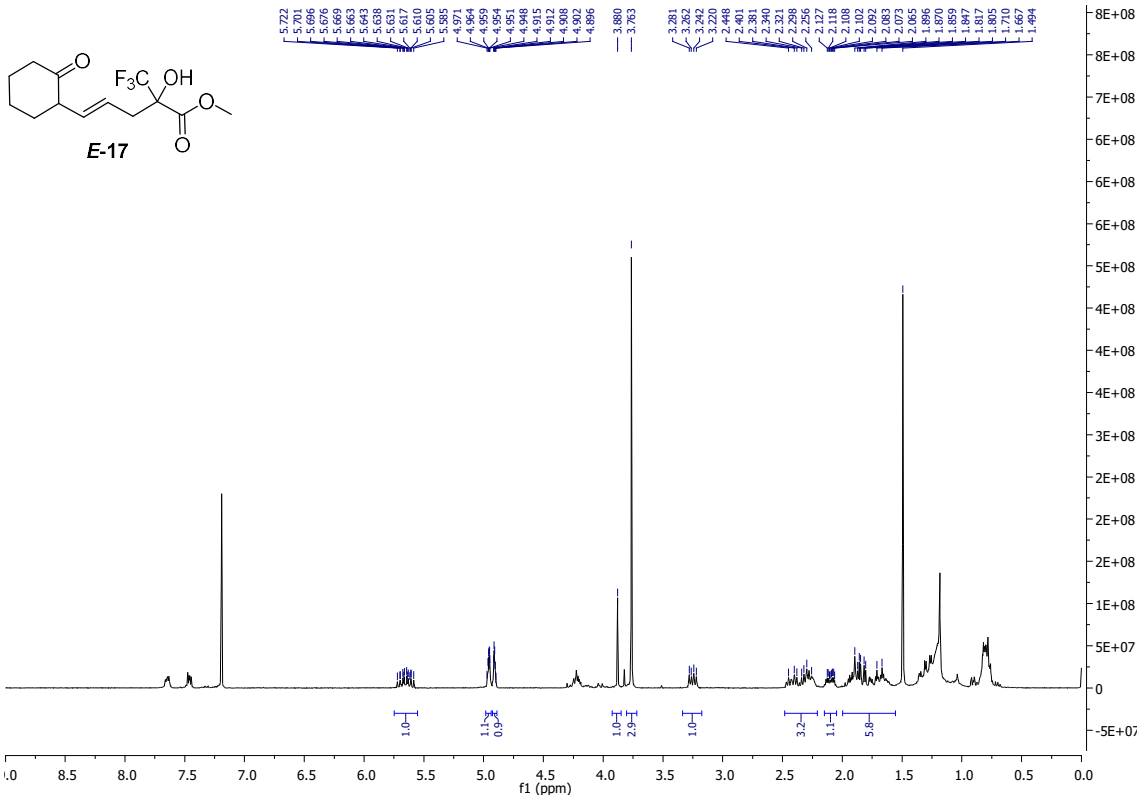

Cl
O
O
14
HO
CF3
168.98
135.22
128.95
125.18
122.24
121.38
117.61
78.19
77.81
77.43
77.02
54.31
44.22
35.26
31.96
29.86
f1 (ppm)

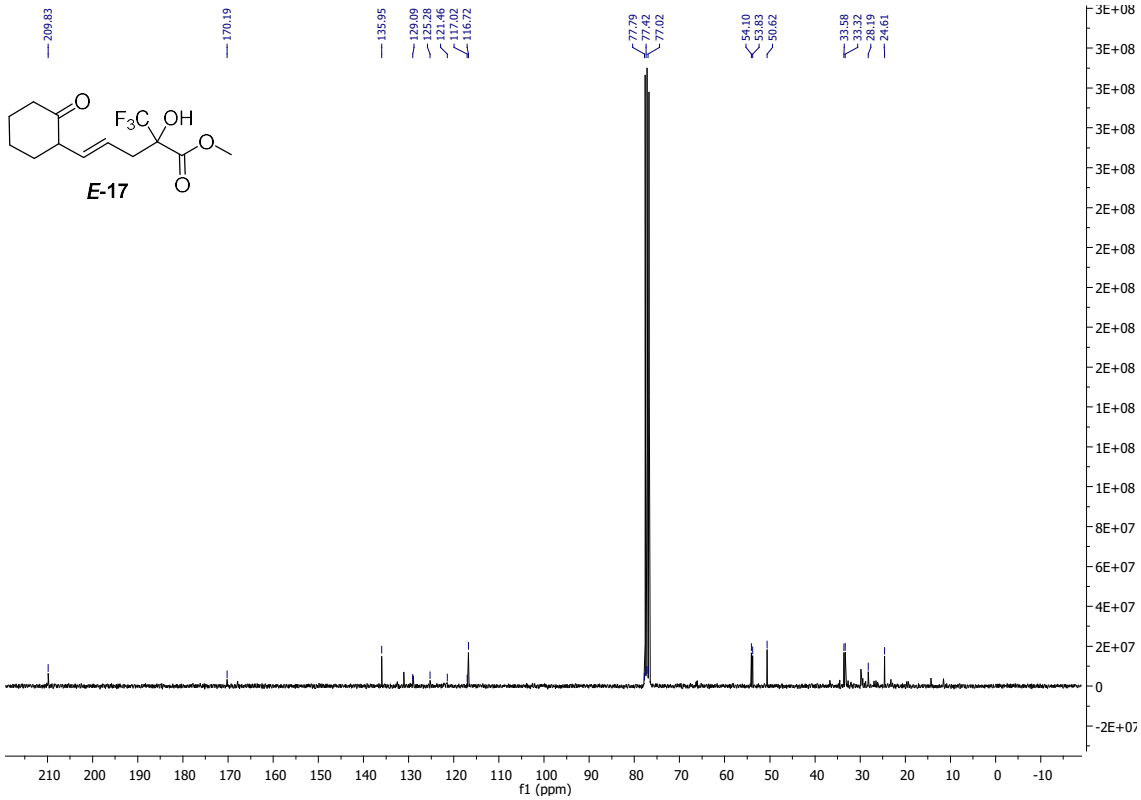

OMe
O
O
O
HO
CF3
15
f1 (ppm)

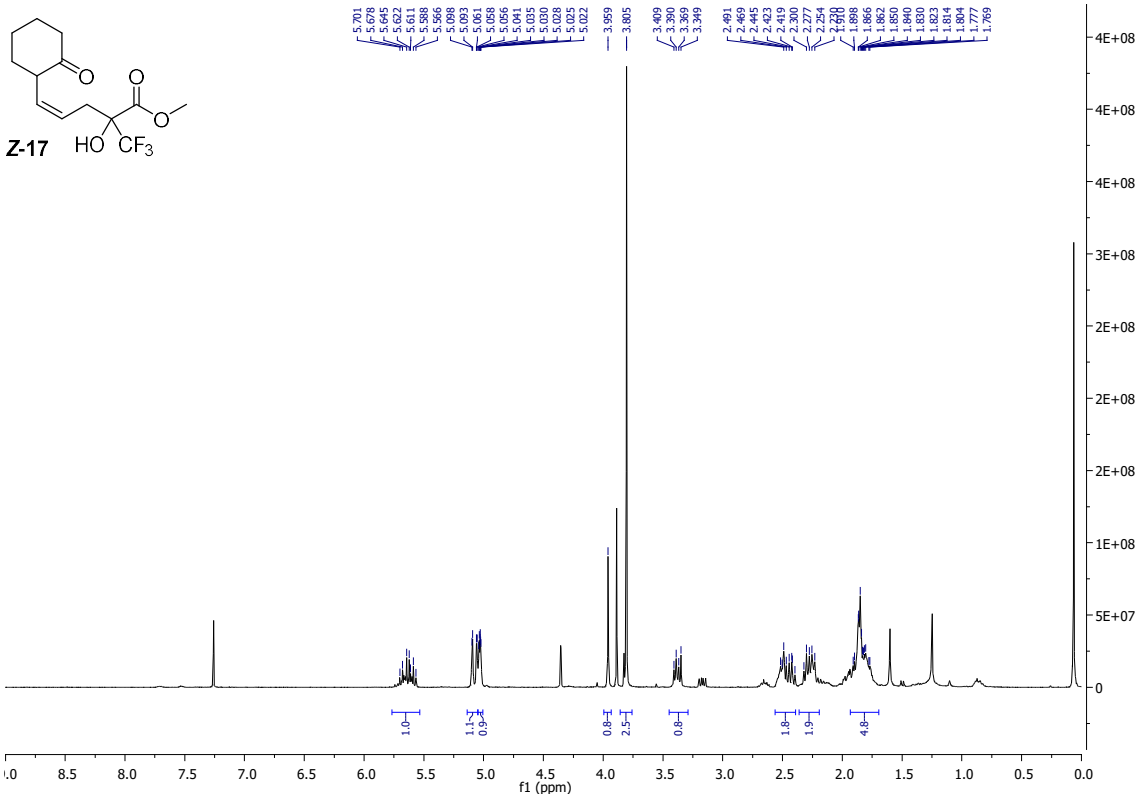

OMe
O
O
O
HO
CF3
15
f1 (ppm)

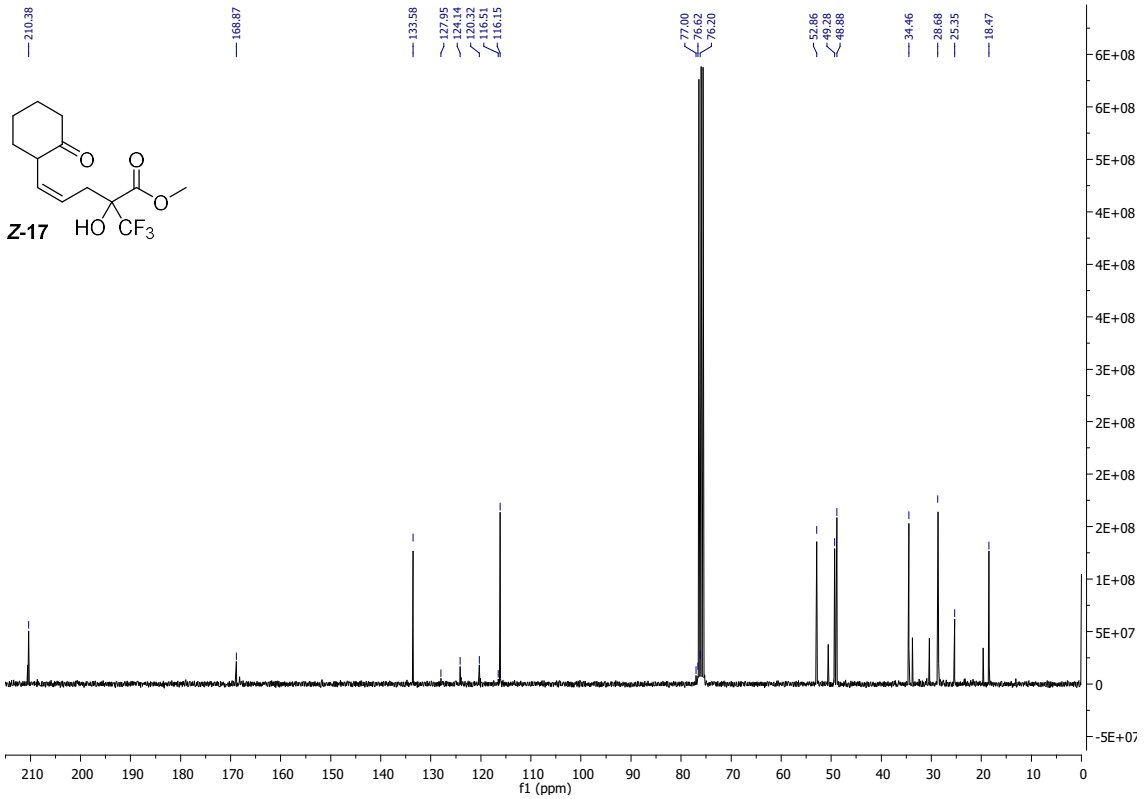

4.993
4.877
3.884
3.787
2.758
2.723
2.654
2.619
2.112
2.060
1.875
1.843
0.900
HO
CF3
O
O
16
1.0
1.0
3.0
1.0
1.0
1.0
1.0
1.0
9.4
f1 (ppm)

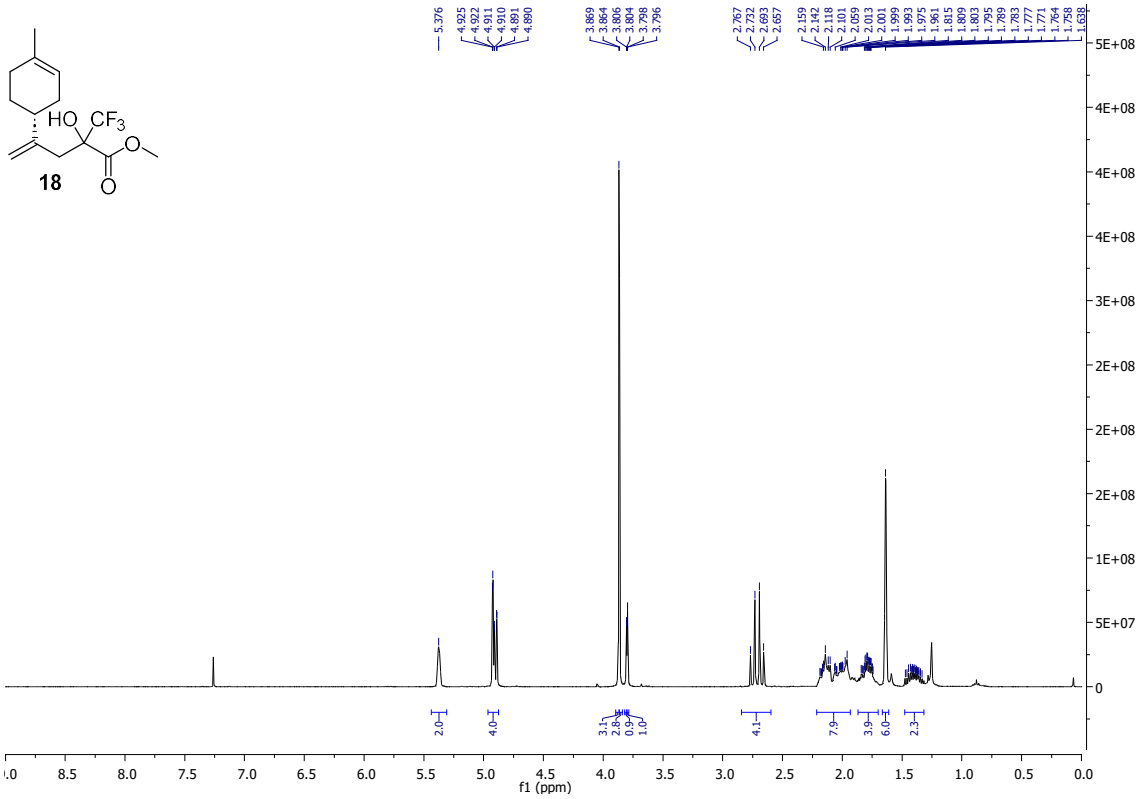

170.18
140.63
129.11
125.31
121.51
118.45
117.72
79.31
78.94
78.56
78.18
54.02
50.43
38.74
31.83
29.81
HO
CF3
O
O
16
f1 (ppm)

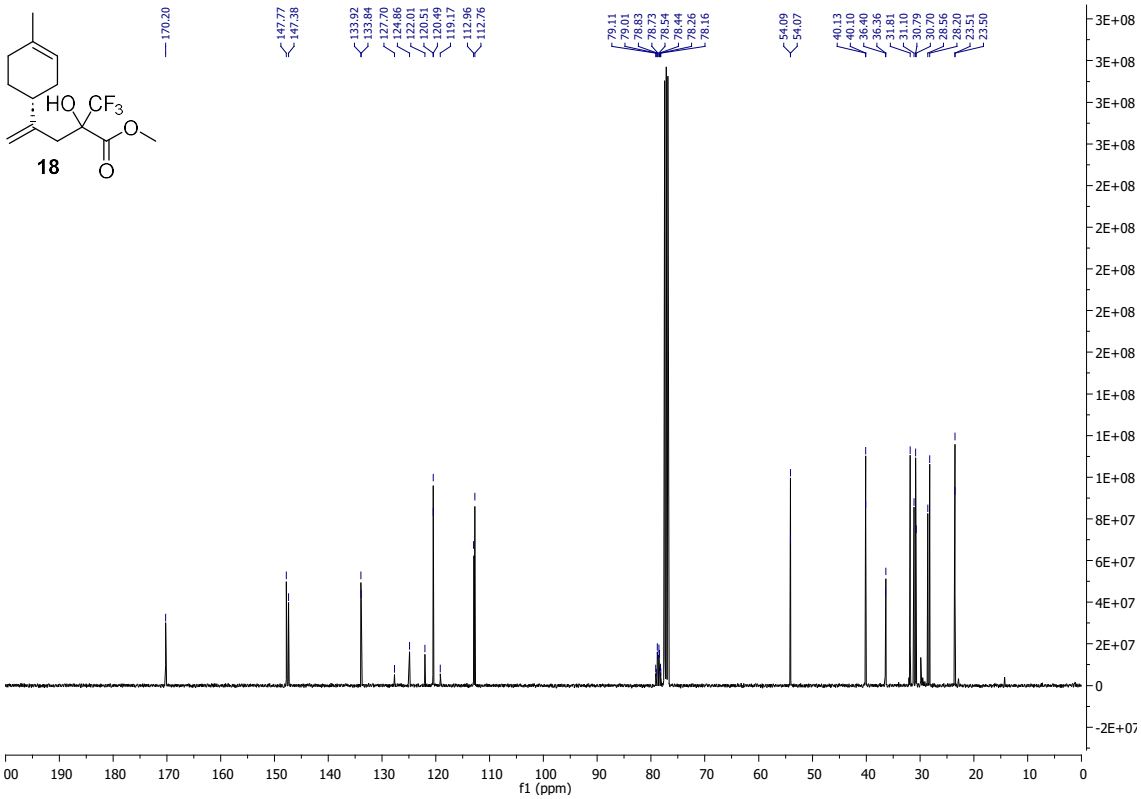

E-17
f1 (ppm)

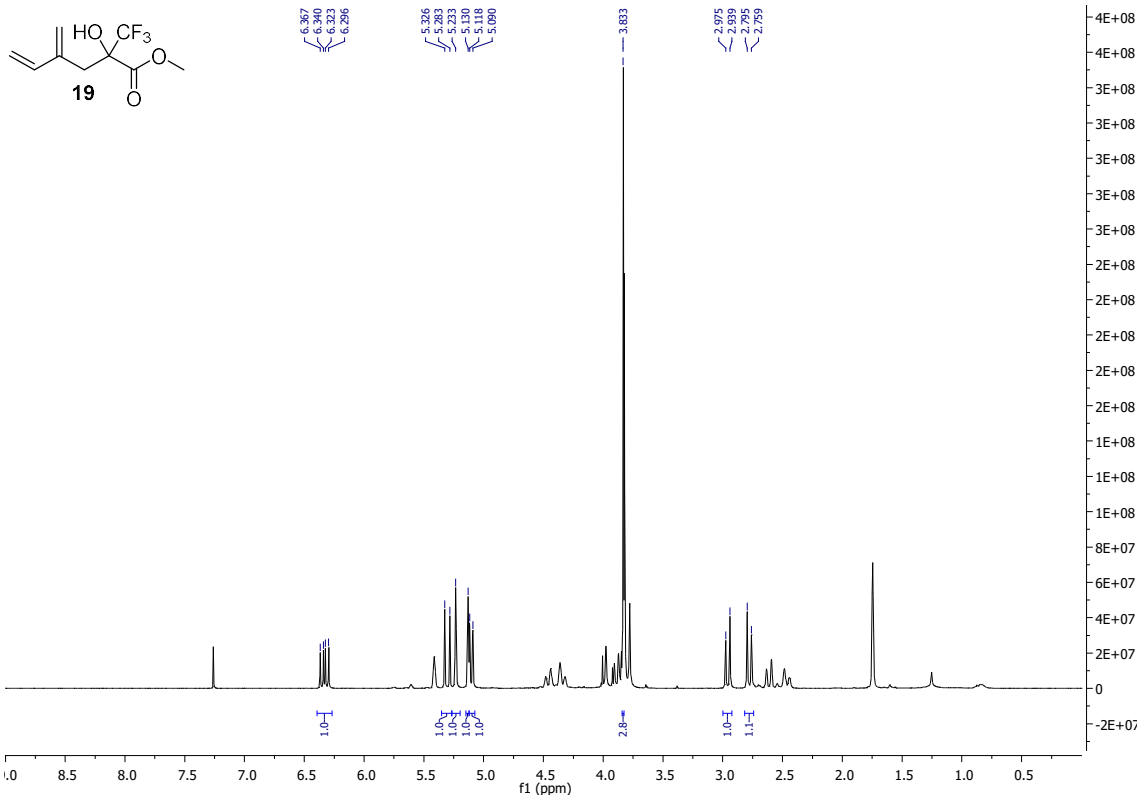

E-17
f1 (ppm)

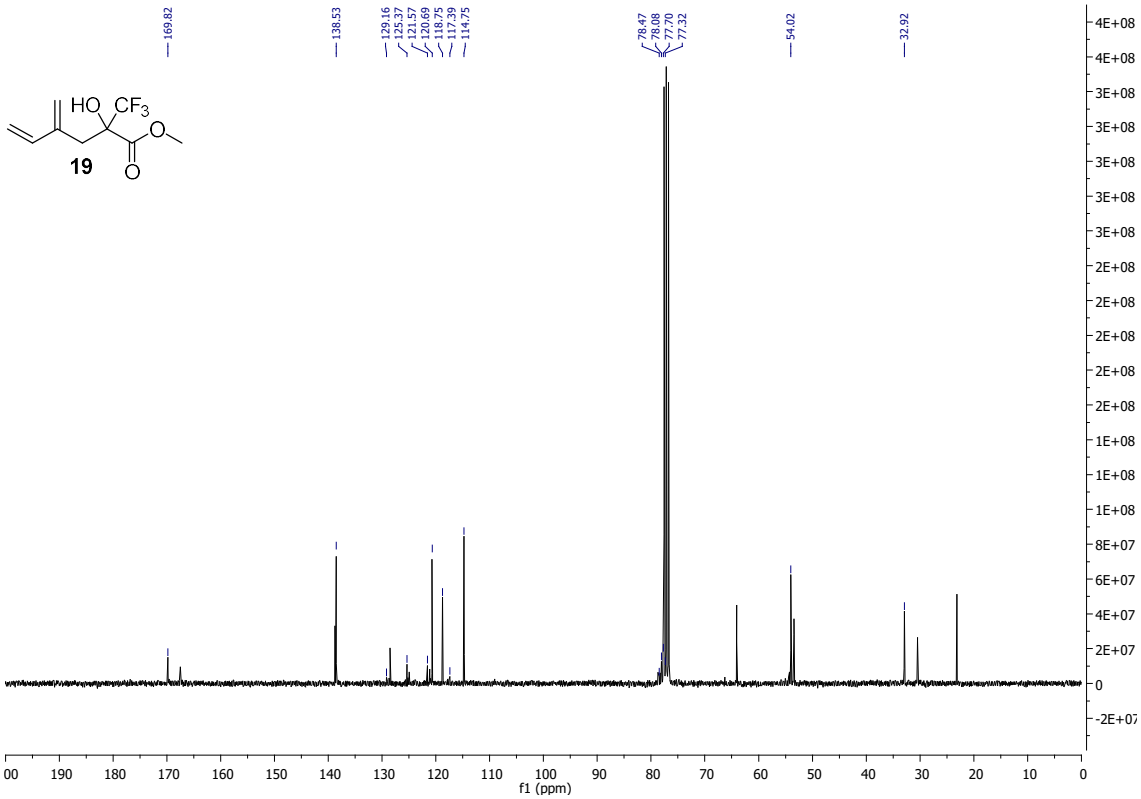

Z-17
HO CF3
f1 (ppm)

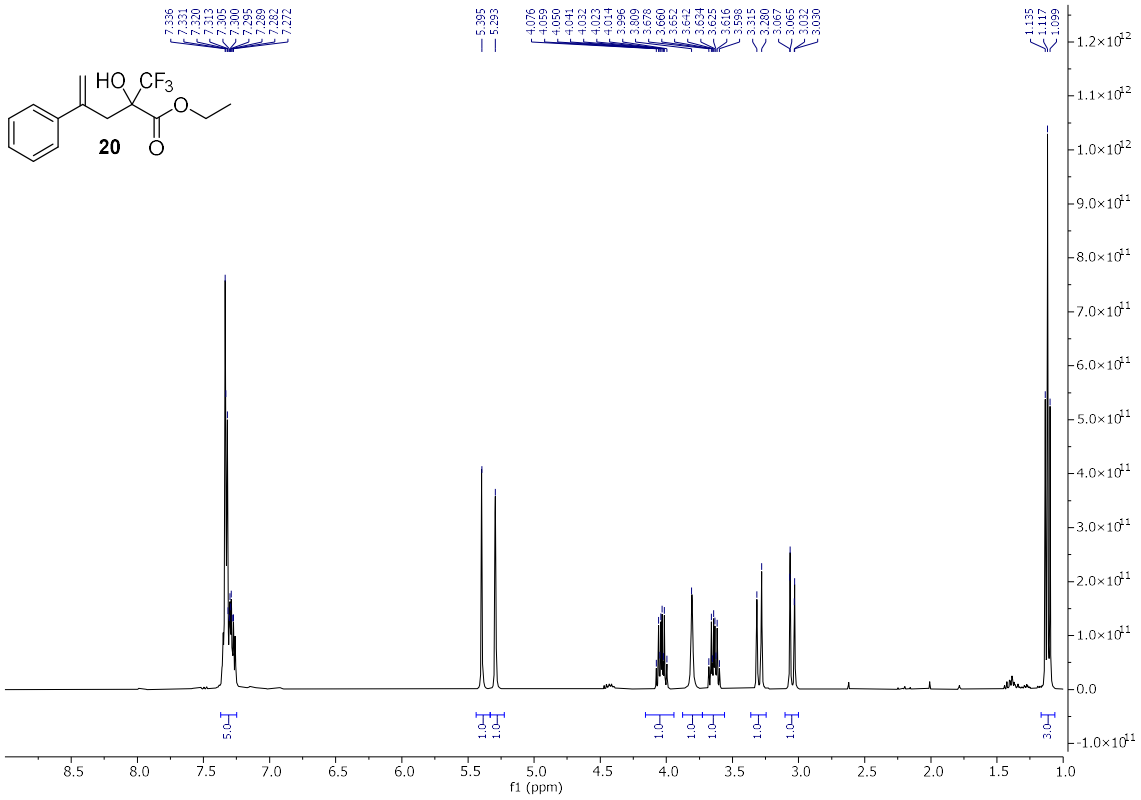

Z-17
HO CF3
f1 (ppm)

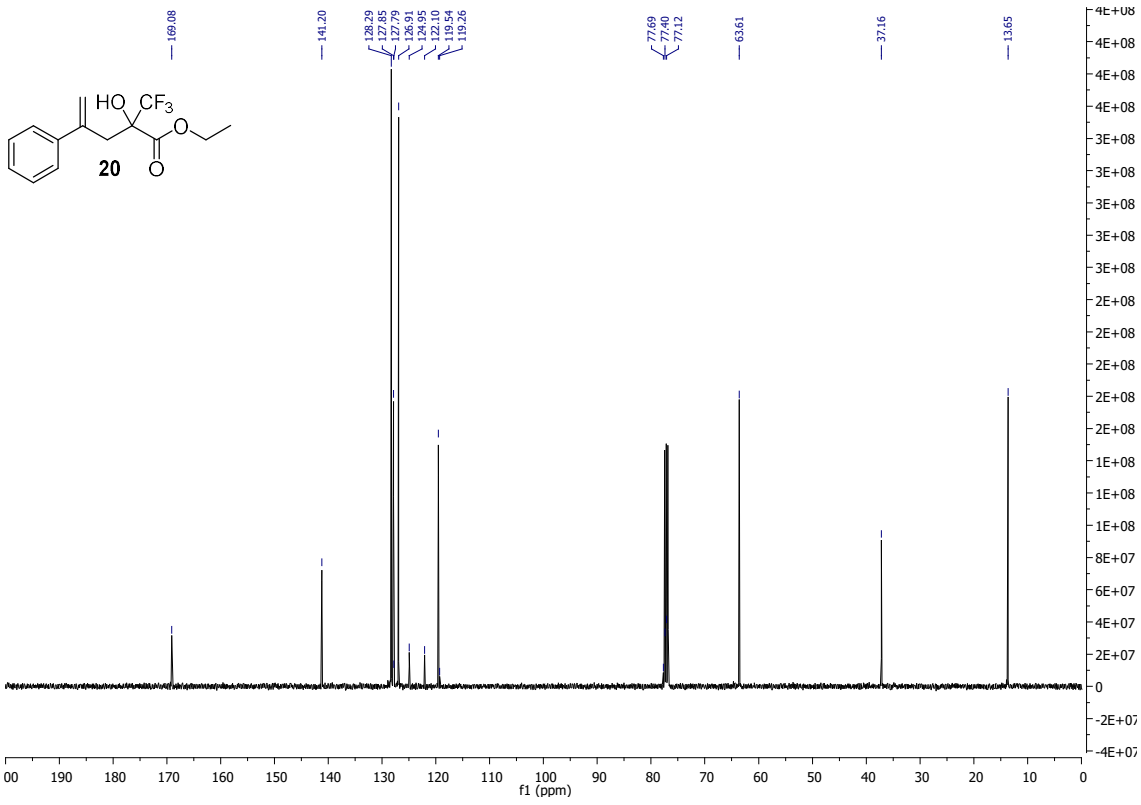

HO
CF3
O
O
18
f1 (ppm)

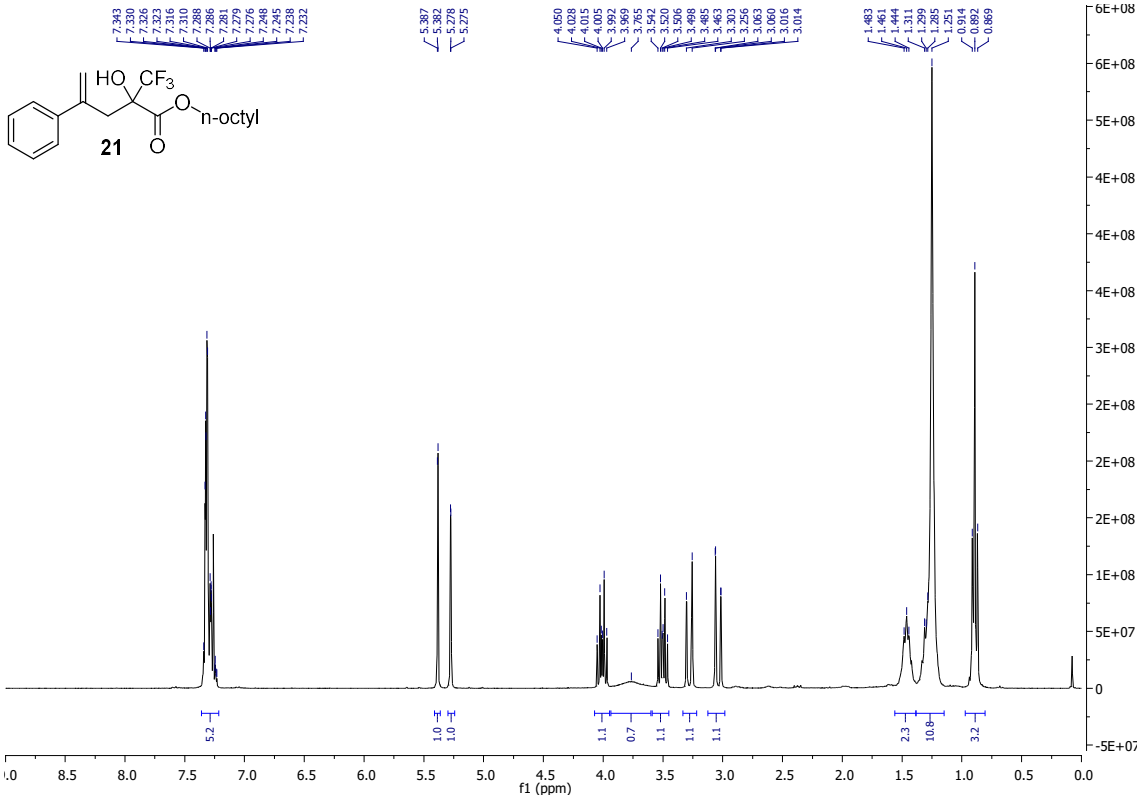

HO
CF3
O
O
18
f1 (ppm)

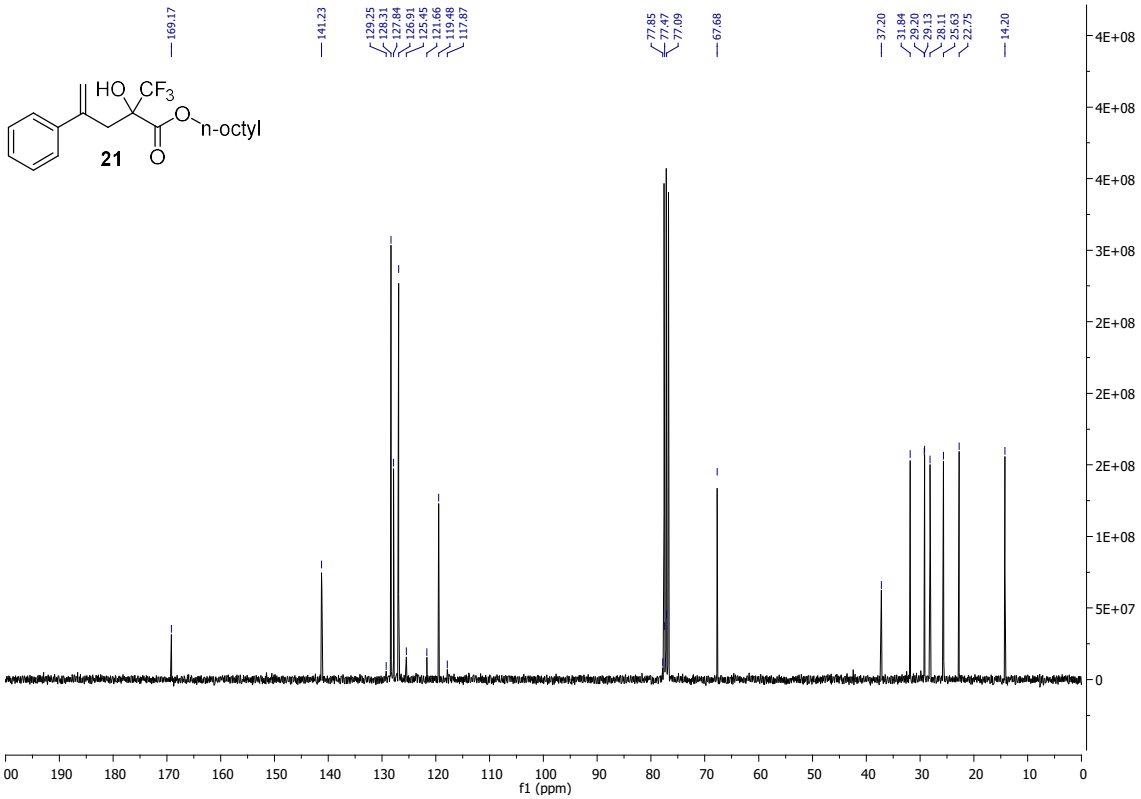

HO
CF3
O
O
19
6.367
6.340
6.323
6.296
5.326
5.283
5.233
5.130
5.118
5.090
3.833
2.975
2.959
2.795
2.759
1.0
1.0
1.0
1.0
2.8
1.0
1.1
f1 (ppm)

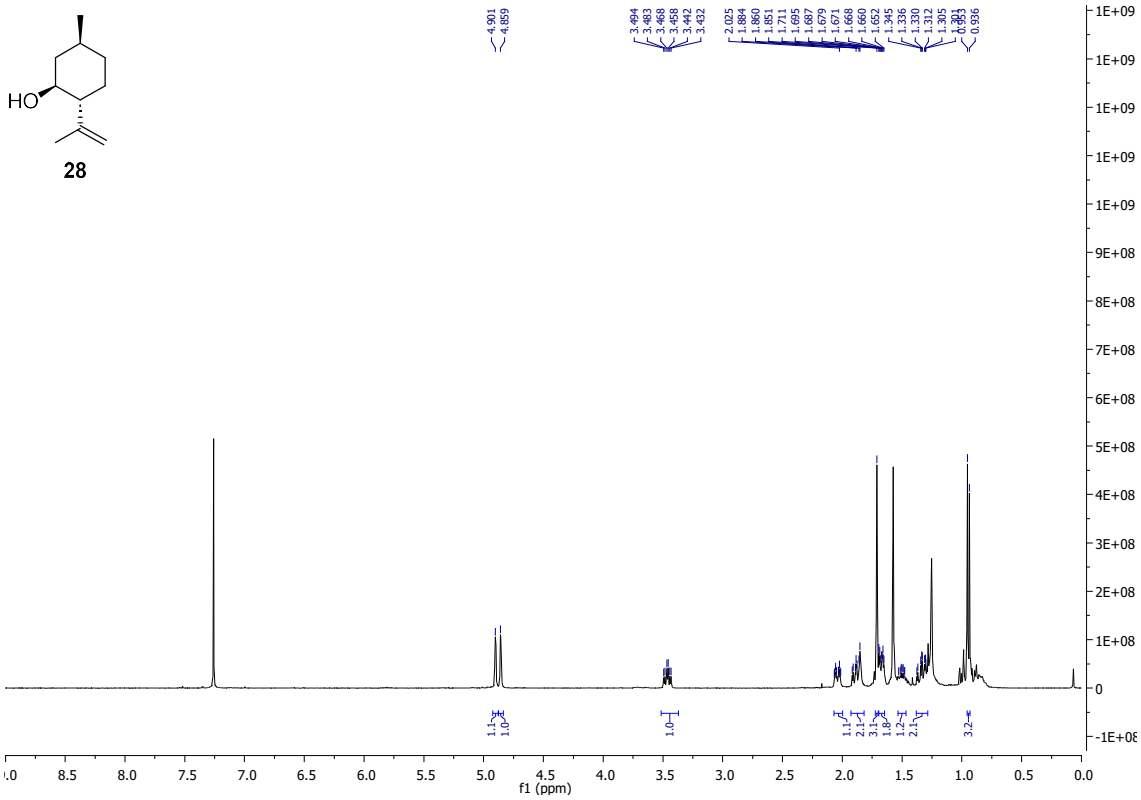

HO
CF3
O
O
19
169.82
138.53
129.16
125.37
121.57
120.69
118.75
117.39
114.75
78.47
78.08
77.70
77.32
54.02
32.92
f1 (ppm)

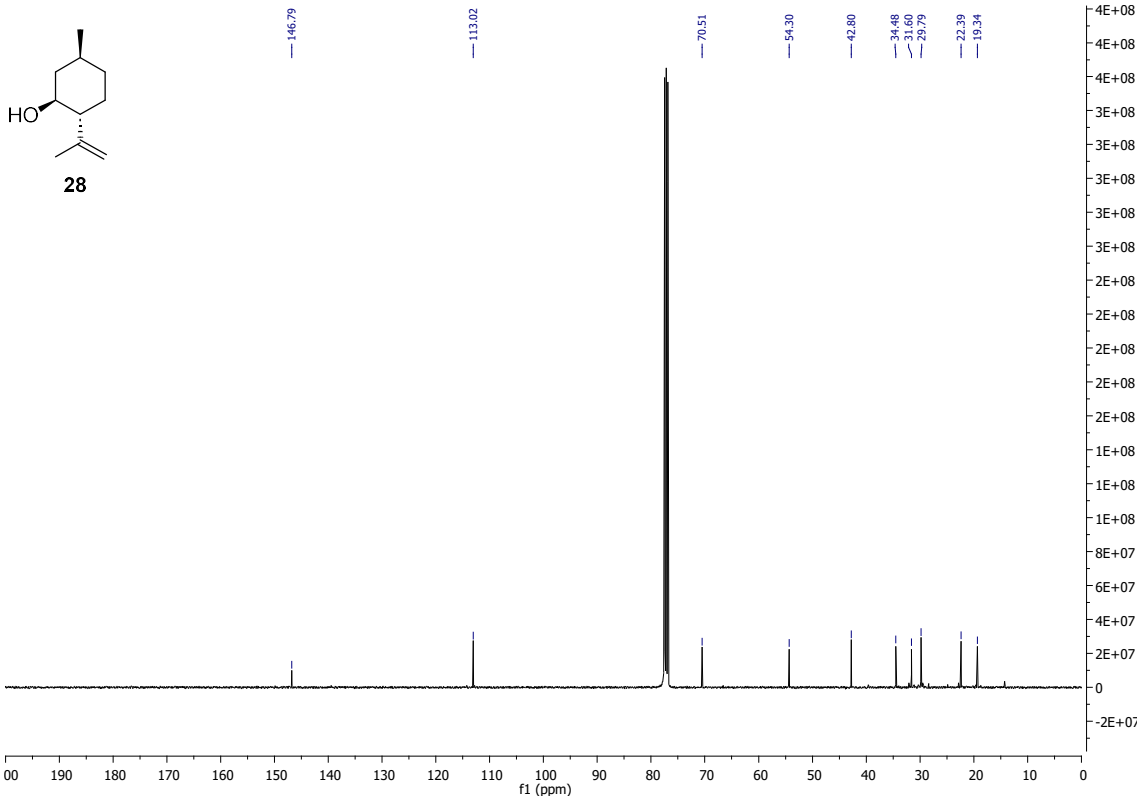

HO
CF3
O
O
20
f1 (ppm)


HO
CF3
O
O
20
f1 (ppm)


HO
CF3
O
n-octyl
O
21
f1 (ppm)


HO
CF3
O
n-octyl
O
21
f1 (ppm)


HO
28
4.901
4.859
3.494
3.483
3.468
3.458
3.442
3.432
2.025
1.884
1.860
1.851
1.711
1.695
1.687
1.679
1.671
1.668
1.660
1.652
1.345
1.336
1.330
1.312
1.305
0.936
f1 (ppm)


HO
28
146.79
113.02
70.51
54.30
42.80
34.48
31.60
29.79
22.39
19.34
f1 (ppm)