SUPPORTING INFORMATION

Cyclopropane Compatibility with Oxidative Carbocation Formation: Total Synthesis of Clavosolide A

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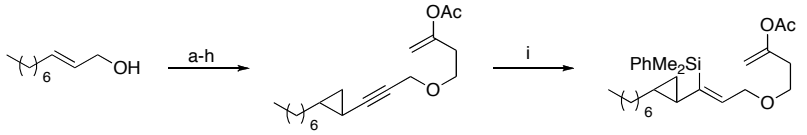
General Experimental:

Proton (^{1}H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded on a Bruker Avance 300 spectrometer at 300 MHz and 75 MHz, a Bruker Avance 400 spectrometer at 400 MHz and 100 MHz, a Bruker Avance 500 spectrometer at 500 MHz, a Bruker Avance 600 spectrometer at 600 MHz if specified. The chemical shifts are reported in parts per million (ppm) on the delta (δ) scale. The solvent peak was used as a reference value, for ^{1}H NMR: $CDCl_3$ = 7.26 ppm, DMSO = 2.50, for ^{13}C NMR: $CDCl_3$ = 77.23, DMSO = 39.52. Data are reported as follows: (s = singlet; d = doublet; t = triplet; q = quartet; sept = septet; dd = doublet of doublets; ddd = doublet of doublet of doublets; dddd = doublet of doublet of doublet of doublet; td = triplet of doublets; dtd = doublet of triplet of doublets; br = broad). High resolution and low resolution mass spectra were recorded on a VG 7070 spectrometer. Infrared (IR) spectra were collected on a Mattson Cygnus 100 spectrometer. Samples for IR were prepared as a thin film on a NaCl plate by dissolving the compound in CH_2Cl_2 and then evaporating the CH_2Cl_2. Tetrahydrofuran and diethyl ether were distilled from sodium and benzophenone. Methylene chloride and *t*BuOMe were distilled from CaH_2 under a N_2 atmosphere prior to use. CuI was purchased from Avacado Chemical research Ltd. (*R*)-TolBINAP was purchased from Strem chemical Inc. Grignard reagent (MeMgBr) was purchased from Sigma-Aldrich. Analytical TLC was performed on E. Merck pre-coated (25 mm) silica gel 60F-254 plates. Visualization was done under UV (254 nm). Flash chromatography was done using ICN SiliTech 32-63 60 Å silica gel. Reagent grade ethyl acetate, diethyl ether, toluene and hexanes (commercial mixture) were purchased from EM Science and used as is for chromatography. All reactions were performed using oven or flame-dried glassware under N_2 with magnetic stirring unless otherwise noted.

General procedure for DDQ cyclization reactions

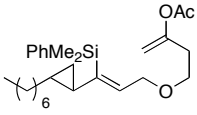
The substrate (1 equiv), 2,6-dichloropyridine (2 equiv) and 4 Å molecular sieves (200 wt%) were dissolved in anhydrous 1,2-dichloroethane (~0.1 M). The mixture was stirred at room temperature for 15 min, followed by the addition of $LiClO_4$ (0.2 equiv). After 5 min, DDQ (4 equiv) was added. The reaction was monitored by TLC at rt or 45 °C unless otherwise specified and, upon starting material consumption, was quenched with 5% aqueous $NaHCO_3$. The mixture was extracted with CH_2Cl_2 (3x), and the combined organic layers were dried over $NaHCO_3$. The filtrate was concentrated in vacuo and purified by flash column chromatography to give the desired product.



Reagents and conditions

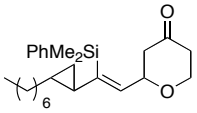
a) Et_2Zn, CH_2I_2, CH_2Cl_2, 0 °C to rt, 85%. b) PCC, CH_2Cl_2, 94%. c) CBr_4, Zn, Ph_3P, CH_2Cl_2, 87%. d) *n*-BuLi, THF, –78 °C, then CH_2O, rt, 82%. e) KOH, 2-chloropyridine, 18-C-6, PhMe, reflux, 89%. f) MeOTf, PhMe. g) 3-Butyn-1-ol, MgO, $PhCF_3$, 85 °C, 71% (two steps). h) HOAc, $[(p\text{-cymene})RuCl_2]_2$, Fur_3P, Na_2CO_3, PhMe, 80 °C, 41%. i) $PhMe_2SiH$, $[Cp^*Ru(NCCH_3)_3]PF_6$, acetone, 66%.

Scheme 1. Synthesis of **4**.



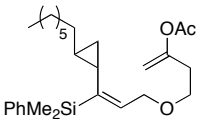
(*Z*)-4-(3-(Dimethyl(phenyl)silyl-3-(2-heptylcyclopropyl)allyloxy)but-1-en-2-yl acetate (4)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.50 (m, 2H), 7.36 – 7.32 (m, 3H), 5.97 (td, *J* = 6.6, 1.4 Hz, 1H), 4.75 (d, *J* = 1.5 Hz, 1H), 4.71 (d, *J* = 1.5 Hz, 1H), 3.80 (dd, *J* = 6.6, 0.9 Hz, 2H), 3.26 (t, *J* = 6.7 Hz, 2H), 2.36 (t, *J* = 6.5 Hz, 1H), 2.11 (s, 3H), 1.47 – 1.38 (m, 1H), 1.37 – 1.21 (m, 10H), 1.18 – 1.12 (m, 1H), 1.11 – 1.01 (m, 1H), 0.88 (t, *J* = 6.9 Hz, 3H), 0.81 – 0.71 (m, 1H), 0.70 – 0.64 (m, 1H), 0.45 – 0.41 (m, 6H), 0.41 – 0.35 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.3, 153.6, 143.1, 139.4, 136.3, 133.9, 129.1, 128.0, 103.0, 70.1, 67.1, 34.4, 34.0, 32.1, 29.7, 29.5, 25.4, 22.9, 21.7, 21.2, 14.3, 13.6, –0.80, –0.8; IR (thin film neat) 2957, 2924, 2854, 1759, 1667, 1428, 1368, 1250, 1214, 1185, 1109, 1020, 834, 816, 772, 732 cm^{-1}; HRMS (ESI) calcd for $C_{27}H_{42}NaO_3Si$, $[M+Na]^+$ 465.2801, found 465.2794.



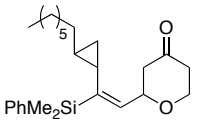
(*Z*)-2-(2-(dimethyl(phenyl)silyl)-2-(2-heptylcyclopropyl)vinyl)-tetrahydropyran-4-one (6)

The general oxidative cyclization reaction procedure was followed with **4** (21 mg, 0.047 mmol), 2,6-dichloropyridine (14 mg, 0.094 mmol), 4 Å molecular sieves (42 mg), 1,2 dichloroethane (0.7 mL), $LiClO_4$ (1.5 mg, 0.014 mmol), and DDQ (32 mg, 0.14 mmol). The reaction was stirred at 45 °C for 8 h, then was quenched with 5% aqueous $NaHCO_3$. The crude mixture was extracted with CH_2Cl_2, concentrated, and purified by flash chromatography (5%-15% EtOAc in hexane) to give the desired product (11 mg, 54%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.48 (m, 2H), 7.35 (dd, *J* = 5.5, 1.7 Hz, 3H), 5.80 (ddd, *J* = 8.8, 3.5, 1.4 Hz, 1H), 4.12 – 4.03 (m, *J* = 11.5, 7.3, 1.0 Hz, 1H), 3.99 – 3.91 (m, 1H), 3.17 – 3.07 (m, 1H), 2.53 – 2.40 (m, 1H), 2.30 – 2.20 (m, 1H), 2.18 – 2.05 (m, 1H), 1.35 – 1.17 (m, 13H), 1.15 – 1.00 (m, 1H), 0.94 – 0.79 (m, 4H), 0.74 – 0.64 (m, 1H), 0.46 – 0.45 (m, 3H), 0.43 – 0.42 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.5, 145.7, 139.0, 137.3, 137.2, 133.9, 129.4, 128.2, 76.7, 66.1, 48.3, 48.2, 42.1, 34.4, 34.4, 32.1, 29.9, 29.5, 25.3, 25.2, 22.9, 22.4, 21.9, 14.3, 14.1, 13.7, -0.7, -0.7, -0.9; IR (thin film neat) 2955, 2923, 2853, 1721, 1462, 1427, 1374, 1249, 1154, 1111, 1080, 832 cm^{-1}; HRMS (EI) calcd for $C_{25}H_{37}O_2Si$ $[M–H]^+$: 397.2563, found: 397.2549.



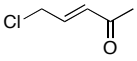
(*E*)-4-((3-(Dimethyl(phenyl)silyl)-3-(2-heptylcyclopropyl)allyl)oxy)but-1-en-2-yl acetate (7)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 – 7.46 (m, 2H), 7.34 – 7.30 (m, 3H), 5.96 (td, *J* = 5.5, 1.7 Hz, 1H), 4.81 (t, *J* = 1.8 Hz, 2H), 4.28 (ddd, *J* = 5.3, 1.7, 1.0 Hz, 2H), 3.59 (t, *J* = 6.6 Hz, 2H), 2.54 (t, *J* = 6.6 Hz, 2H), 2.13 (s, 3H), 1.33 – 1.15 (m, 12H), 1.12 – 0.95 (m, 2H), 0.70 – 0.59 (m, 1H), 0.46 – 0.37 (m, 1H), 0.35 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.4, 153.7, 142.8, 140.8, 139.3, 134.0, 129.0, 127.9, 103.1, 69.0, 67.7, 34.7, 34.2, 32.1, 29.7, 29.5, 29.4, 22.9, 21.3, 20.6, 19.9, 14.3, 13.7, –1.7, –1.7; IR (thin film, neat) 2955, 2924, 2854, 1722, 1674, 1462, 1372, 1250, 1181, 1120, 815 cm^{-1}; HRMS (ESI) calcd for $C_{27}H_{42}NaO_3Si$ $[M+Na]^+$: 465.2801, found: 465.2794.



(*E*)-2-(2-(dimethyl(phenyl)silyl)-2-(2-heptylcyclopropyl)vinyl)dihydro-2H-pyran-4(3H)-one (8)

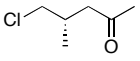
The general cyclization reaction procedure was followed with **7** (10 mg, 0.023 mmol), 2,6-dichloropyridine (21 mg, 0.14 mmol), 4 Å molecular sieves (21 mg), 1,2 dichloroethane (0.5 mL), $LiClO_4$ (0.7 mg, 0.007 mmol), and DDQ (16 mg, 0.069 mmol). The reaction was stirred at 45 °C for 4 h, then was quenched with 5% aqueous $NaHCO_3$. The crude mixture was extracted with CH_2Cl_2, concentrated, and purified by flash chromatography (5%-15% EtOAc in hexane) to give the desired product as a 3.6:1 mixture of diastereomers (5.1 mg, 56%). Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.43 (m, 2H), 7.37 – 7.30 (m, 3H), 5.87 (dt, *J* = 7.2, 1.3 Hz, 1H), 4.80 – 4.72 (m, 1H), 4.37 – 4.31 (m, 1H), 3.75 (tt, *J* = 11.9, 2.7 Hz, 1H), 2.64 (ddd, *J* = 13.8, 12.6, 7.4 Hz, 1H), 2.54 – 2.31 (m, 3H), 1.25 (s, br, 12H), 0.92 – 0.84 (m, 5H), 0.68 – 0.60 (m, 1H), 0.51 (dt, *J* = 8.3, 4.9 Hz, 1H), 0.36 (s, br, 6H). For the mixture of inseparable diastereomers: ^{13}C NMR (126 MHz, $CDCl_3$) δ 206.83, 206.78, 144.4, 144.2, 141.7, 141.6, 138.7, 134.0, 133.9, 129.4, 129.2, 128.2, 128.0, 75.6, 75.4, 66.9, 66.1, 48.0, 47.8, 42.5, 34.63, 34.58, 32.1, 29.6, 29.5, 29.4, 29.3, 22.88, 22.9, 20.8, 20.5, 20.2, 20.0, 14.34, 14.29, 14.1, 13.8, -0.7, -0.8, -1.68, -1.72; IR (thin film neat) 2955.8, 2923.7, 2853.6, 1759.2, 1666.4, 1611.9, 1462.3, 1427.5, 1368.4, 1246.3, 1212.5, 1184.3, 1109.3, 1019.19, 814.9, 832.6 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{39}O_2Si$ $[M+H]^+$: 399.2735, found: 399.2735.



***(E)*-5-Chloropent-3-en-2-one (14)**

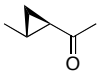
To a stirred solution of acetyl chloride (6.9 mL, 100 mmol) and allyl chloride (16.3 mL, 200 mmol) in CH_2Cl_2 was added $AlCl_3$ (16 g, 120 mmol, 1.2 equiv.) in portions over 20 min. The mixture was stirred for 2 h at 0 °C and for 1 h at rt. The reaction was quenched by pouring the mixture onto crushed ice (100 g). The organic layer was separated, dried with Na_2SO_4, and filtered. Triethylamine (21 mL, 150 mmol, 1.5 equiv.) was added, then the mixture was refluxed for 2 h, cooled to rt and washed successively with HCl (2 x 100 mL), $NaHCO_3$ (2 x 100 mL), H_2O (1 x 200 mL) and brine (1 x 200 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated. Purification by flash chromatography (10:90 EtOAc: hexane) yielded the desired product (4.03 g, 34%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.79 (dt, *J* = 15.7, 6.1 Hz, 1H), 6.31 (d, *J* = 15.7 Hz, 1H), 4.19 (dd, *J* = 6.1, 1.4 Hz, 2H), 2.30 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.8, 140.4, 132.5, 42.9, 27.6. IR (thin film, neat) 1700.5, 1680.3, 1636.3, 1424.0, 1362.1, 1254.3, 977.1 cm^{-1}. *These data are consistent with literature values.*[1]

[1] Kulinkovich, O. G.; Tischenko, I. G.; Sorokin, V. L. *Synthesis* **1985,** 1058.



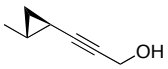
(*S*)-5-Chloro-4-methylpentan-2-one (15)

The catalyst was prepared by stirring CuI (76 mg, 0.40 mmol,) and (*R*)-TolBINAP (407 mg, 0.60 mmol) in anhydrous *t*BuOMe (320 mL) for 1 h to give a clear yellow solution. The mixture was cooled to −78 °C and MeMgBr (2.7 M solution in Et_2O, 17 mL, 46 mmol) was added. After stirring for 10 min, a solution of **14** (4.74 g, 40 mmol) in anhydrous CH_2Cl_2 (320 mL) was added over 2 h with a syringe pump. The mixture was stirred for 4 h (including addition time) at −78 °C. The reaction was quenched at −78 °C with EtOH (16 mL, 0.4 mL/mmol substrate), followed by a 1 M aq. NH_4Cl-solution (80 mL, 2 mL/mmol substrate), and was allowed to warm to room temperature. A 1 M aq. NH_4Cl-solution (200 mL, 5 mL/mmol substrate) and Et_2O (100 mL, 2.5 mL/mmol substrate) were added and the layers were separated. After extraction with Et_2O (2 x 200 mL, 5 mL/mmol substrate), the combined organic extracts were dried and carefully concentrated to a yellow oil. Purification by flash chromatography (10:90 EtOAc: hexane) yielded the desired product (3.9 g, 72%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.56 (dd, *J* = 10.8, 4.8 Hz, 1H), 3.47 (dd, *J* = 10.8, 5.4 Hz, 1H), 2.69 (dd, *J* = 17.1, 5.8 Hz, 1H), 2.43 (td, *J* = 11.9, 5.5 Hz, 1H), 2.35 (dd, *J* = 17.1, 7.1 Hz, 1H), 2.16 (s, 3H), 1.03 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 207.5, 50.6, 47.2, 31.1, 30.6, 17.9. $[\alpha]_D^{20}$ +4.7 (*c* 0.95, $CHCl_3$); IR (thin film, neat) 2962, 1714, 1459, 1440, 1408, 1366, 1299, 1159 cm^{-1}.



1-((1*R*,2*R*)-2-Methylcyclopropyl)ethanone (15)[2]

To a solution of NaOH (3.54 g, 0.088 mmol) in of H_2O (4.4 mL) was added the chloro ketone (7.9 g, 59 mmol) over 20 min with a 10 mL syringe. The reaction mixture was stirred for 1 h (including addition time) at 80 °C. H_2O (8.7 mL) was added slowly to the reaction mixture over a 20 min period, and the mixture heated under reflux for an additional hour. Upon cooling to rt, the reaction mixture was extracted with Et_2O (2 x 15 mL). The aqueous layer of the extraction was saturated with K_2CO_3 and extracted with additional Et_2O (15 mL). The combined organic layers were dried over Na_2SO_4 and concentrated at 0 °C under reduced pressure (168 mm Hg) to yield the desired compound (5.55 g, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.22 (s, 3H), 1.67 (ddd app dt, *J* = 8.1, 4.2, 4.2 Hz, 1H), 1.46-1.36 (m, 1H), 1.23 (ddd, *J* = 8.5, 4.5, 3.8 Hz, 1H), 1.11 (d, *J* = 6.0 Hz, 3H), 0.72 (ddd, *J* = 7.9, 6.5, 3.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.7, 30.6, 30.5, 20.3, 19.6, 18.3. IR (thin film neat) 2923, 1706, 1601, 1451, 1195, 1114, 808 cm^{-1} $[\alpha]_D^{20}$ –125.7 (*c* 0.82, $CHCl_3$).

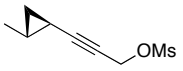


3-((1*R*,2*R*)-2-Methylcyclopropyl)prop-2-yn-1-ol[9]

To a solution of LDA prepared at 0 °C from diisopropylamine (2.98 mL, 21.2 mmol) and *n*-butyllithium in hexane (1.56M, 13.6 mL, 21.2 mmol) in dry THF (40 mL) at −78 °C was added **15** (1.98 g, 20.2 mmol) in THF (25 mL). The solution was stirred for 1 h, then diethyl chlorophosphate (3.51 mL, 24.2 mmol) was added. The mixture was allowed to warm to rt slowly over 2-3 h, then was added dropwise over 45 min to a solution of LDA in THF (46.5 mmol) prepared at 0 °C as described above. The reaction was allowed to stir at 0 °C for 30 min, producing a brown-black color and a precipitate. HMPA (13 mL, 71 mmol) was added and the mixture was warmed to 5 °C. Paraformaldehyde (1.87 g, 61 mmol, 3.0 equiv.) was added and the mixture was refluxed for 1 h. The reaction was quenched with saturated NH_4Cl (100 mL) and EtOAc (100 mL). After extraction with EtOAc (2x 75 mL), the combined yellow-orange organic extracts were dried and concentrated. Purification by flash chromatography (15% EtOAc in hexane) yielded the desired product (1.36 g, 61%). ^{1}H

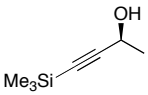
[2] Cannon, G. W.; Ellis, R. C.; Leal, J. R., *Organic Synth*. **1963,** *4,* 597.

NMR (500 MHz, $CDCl_3$) δ 4.22 (s, 2H), 1.51 (s, br, 1H), 1.11 – 1.04 (m, 4H), 0.93 (dddd, , *J* = 8.6, 4.9, 2.0, 2.0 Hz, 1H), 0.85 – 0.81 (m, 1H), 0.54 (ddd, *J* = 7.0, 4.4, 4.4 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 89.7, 74.1, 51.7, 18.5, 17.0, 16.7, 7.7. $[\alpha]_D^{20}$ –117.8 (*c* 0.93, $CHCl_3$); IR (thin film, neat) 3333, 3055, 2955, 2929, 2868, 2227, 1444, 1377, 1308, 1068, 1013, 965, 908, 848, 775 cm^{-1}; HRMS (EI) calcd for $C_7H_{10}O$ $[M]^+$: 110.0732, found: 110.0699 cm^{-1}.



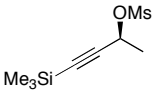
3-((1*R*,2*R*)-2-Methylcyclopropyl)prop-2-ynyl methanesulfonate (16)

To the cyclopropyl homopropargylic alcohol (50 mg, 0.45 mmol) in CH_2Cl_2 (1 mL) at 0 °C followed by Et_3N (130 μL, 0.91 mmol) and of methanesulfonyl chloride (45 μL, 0.55 mmol). The reaction was stirred for 1 h then was quenched with sat. aq. $NaHCO_3$ solution. The mixture was allowed to warm to room temperature, then was concentrated in vacuo and diluted with H_2O (5 mL) and Et_2O (10 mL). The organic layer was separated, dried ($MgSO_4$), filtered and concentrated to yield the desired product (63 mg, 73%), which was used without further purification. *Characterization was not performed on this intermediate due to its instability and volatility.*



(*S*)-4-Trimethylsilyl-3-butyn-2-ol

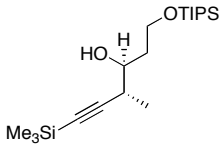
To 4-(trimethylsilyl)-3-butyn-2-one (3.12 g, 22.2 mmol) in CH_2Cl_2 (65 mL) was added (*S*,*S*)-Noyori-TsDPEN catalyst (280 mg, 0.445 mmol) in CH_2Cl_2 (3 mL) and NEt_3 (9.4 mL, 68 mmol). The mixture was cooled to 10 °C and formic acid (6 mL, 155 mmol) was added dropwise over 2 h. The reaction was stirred at rt overnight. CH_2Cl_2 was partially removed under reduced pressure. The mixture was diluted with 80 mL of pentane, and K_2CO_3 (13g) and $MgSO_4$ (8g) were added. The slurry was stirred vigorously for 2 h at rt, then was filtered through a plug of silica gel and concentrated under reduced pressure to yield the desired product (3.04 g, 96%). ^1H NMR (300 MHz, $CDCl_3$) δ 4.52 (dt, *J* = 13.0, 6.6 Hz, 1H), 1.79 (d, *J* = 5.2 Hz, 1H), 1.45 (d, *J* = 6.6 Hz, 3H), 0.17 (s, 9H). $[\alpha]_D^{20}$ -23.8 (*c* 0.93, $CHCl_3$). The dr of the (*R*)-Mosher ester of this material was found to be > 95:5 by ^{19}F NMR analysis. [δ –72.02 (major) and δ –71.66 (minor), in $CDCl_3$]. *These data are consistent with literature values.*[3]



(*S*)-3-Butyn-2-yl Mesylate (17)

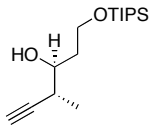
To (*S*)-4-trimethylsilyl-3-butyn-2-ol (1.84 g, 12.9 mmol) in CH_2Cl_2 (155 mL) at −78 °C was added Et_3N (3.7 mL, 26.1 mmol) and methanesulfonyl chloride (1.6 mL, 19.8 mmol). The solution was stirred at −78 °C for 1 h then was quenched with sat. aq. $NaHCO_3$ solution. The mixture was allowed to warm to room temperature, concentrated in vacuo and then diluted with H_2O (100 mL) and Et_2O (50 mL). The organic layer was separated, dried over $MgSO_4$, filtered and concentrated to the desired product (2.65 g, 93%), which was used without further purification. ^1H NMR (400 MHz, $CDCl_3$) δ 5.24 (q, *J* = 6.7 Hz, 1H), 3.10 (s, 3H), 1.61 (d, *J* = 6.7 Hz, 3H), 0.19 – 0.15 (m, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 101.4, 93.8, 68.7, 39.3, 22.6, -0.3. $[\alpha]_D^{20}$ –109.3 (*c* 1.18, $CHCl_3$); lit $[\alpha]_D^{20}$ –113.5 (*c* 1.18, $CHCl_3$); er > 90:10 based on optical rotation. *These data are consistent with literature values.*[3]

[3] Marshall, J. A.; Chobanian, H. R.; Yanik, M. M. *Org. Lett.* **2001,** *3*, 3369.



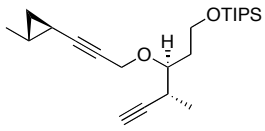
(3*S*,4*R*)-4-Methyl-1-(triisopropylsilyloxy)-6-(trimethylsilyl)hex-5-yn-3-ol (19)

To a solution of $Pd(OAc)_2$ (107 mg, 0.48 mmol) in THF (67 mL) at −78 °C was added PPh_3 (125 mg, 0.48 mmol). Mesylate **17** (3.48 g, 11.4 mmol) and aldehyde **18** (2.20 g, 9.52 mmol) were added, followed by Et_2Zn (1M in hexane, 28.6 mL, 28.6 mmol, added dropwise over 15 min). The resulting yellow solution was immediately warmed to −20 °C and stirred for 16 h. The reaction was quenched by pouring into a rapidly stirring solution of sat. aq. NH_4Cl (50 mL). After 15 min the phases were separated and the aqueous layer was extracted with (2 x 50 mL) Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Purification by flash chromatography (10% EtOAc in hexane) provided the desired product (3.08 g, 82%) as an inseparable 8:1 mixture with the *syn*-diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.01 – 3.87 (m, 2H), 3.78 (dt, *J* = 7.5, 3.5 Hz, 1H), 3.14 (s, 1H), 2.62 (qd, *J* = 7.0, 4.3 Hz, 1H), 1.86 – 1.69 (m, 2H), 1.21 (d, *J* = 7.1 Hz, 3H), 1.06 (dd, *J* = 6.4, 3.7 Hz, 21H), 0.15 (d, *J* = 3.5 Hz, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 108.5, 86.8, 73.7, 62.7, 36.2, 34.0, 18.2, 16.5, 12.0, 0.4. $[\alpha]_D^{20}$ +6.6 (*c* 1.11, $CHCl_3$); IR (thin film, neat) 3502, 2944, 2893, 2867, 2165, 1463, 1385, 1249, 1100, 1012, 994, 921, 843, 759 cm^{-1}; HRMS (ASAP+) calcd for $C_{19}H_{39}OSi_2$ $[M–OH]^+$: 339.2539, found: 339.2546.



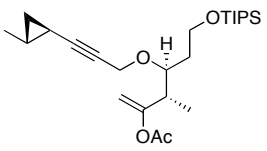
(3*S*,4*R*)-4-Methyl-1-((triisopropylsilyl)oxy)hex-5-yn-3-ol

For analytical purpose of determining e.r., (20 mg, 0.056 mmol, 1.0 equiv.) of **19** was dissolved in 0.5 mL of MeOH and (24 mg, 0.056 mmol, 1.0 equiv) of K_2CO_3 was added at rt. After 1.5 h, the reaction was quenched with 1 mL of sat. NH_4Cl and extracted with (3 x 5 mL) of Et_2O. The combined extracts were washed with H_2O (2 x 5 mL) and dried over $MgSO_4$. Purification by flash column chromatography (10% Et_2O in hexane) to yield a clear oil (12 mg, 75%) of the major desilylated *anti*-homopropargylic alcohol. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.03 (ddd, *J* = 9.4, 5.4, 1.5 Hz, 1H), 3.95-3.90 (m, 1H), 3.86 (s, *J* = 2.3 Hz, 1H), 3.74 – 3.69 (m, 1H), 2.56 – 2.49 (m, 1H), 2.06 (dd, *J* = 2.4, 1.7 Hz, 1H), 1.95 (ddd, *J* = 6.5, 3.3, 1.7 Hz, 1H), 1.92 (ddd, *J* = 6.5, 3.3, 1.7 Hz, 1H), 1.79 (dddd, *J* = 10.9, 9.3, 4.2, 1.6 Hz, 1H), 1.23 (d, *J* = 7.0 Hz, 3H), 1.06-1.00 (m, 21 H). The ee of this material was found to be 87% by ^{19}F NMR analysis. [δ –71.49 (minor) and δ –71.60 (major), in $CDCl_3$] of the (*R*)-Mosher ester.



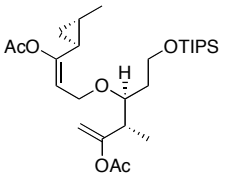
Triisopropyl((3*S*,4*R*)-4-methyl-3-(3-((1*R*,2*R*)-2-methylcyclopropyl)prop-2-ynyloxy)hex-5-ynyloxy)silane

To the homopropargylic alcohol (660 mg, 1.84 mmol) and mesylate **17** (289 mg, 1.54 mmol) in THF (4 mL) at 0 °C was added 15-crown-5 (425 μL, 2.15 mmol). The reaction stirred for 15 min, then NaH (85 mg, 2.1 mmol) was added portion wise (17 mg/5 mins). The reaction was warmed to rt and stirred overnight. The reaction was quenched with brine (3 mL) and extracted with Et_2O (3 x 5mL). The combined organic extracts were dried and the solvent was concentrated in vacuo. Purification by flash chromatography (5% EtOAc in hexane) provided the desired product (414 mg, 63%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.18 (d, *J* = 2.0 Hz, 2H), 3.81 (dd, *J* = 7.1, 5.5 Hz, 2H), 3.68 (dt, *J* = 8.3, 4.2 Hz, 1H), 2.80 (dtd, *J* = 6.9, 4.4, 1.4 Hz, 1H), 2.06 (d, *J* = 2.5 Hz, 1H), 1.93 – 1.83 (m, 1H), 1.81 – 1.71 (m, 1H), 1.21 (d, *J* = 7.0 Hz, 3H), 1.09 – 1.04 (m, 25H), 0.95 – 0.87 (m, 1H), 0.85 – 0.77 (m, 1H), 0.54 – 0.48 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 89.5, 86.2, 78.2, 72.2, 69.9, 60.3, 58.3, 34.6, 29.5, 18.5, 18.2, 16.8, 16.6, 16.0, 12.2, 7.8; $[\alpha]_D^{20}$ –37.2 (*c* 0.90, $CHCl_3$); IR (thin film, neat) 3311, 2943, 2866, 2239, 1462, 1379, 1250, 1100, 1060, 882, 847 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{40}O_2Si$ $[M+H]^+$: 377.2876, found: 377.2881.



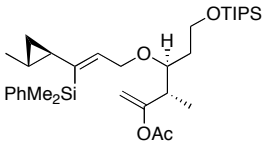
(3*S*,4*S*)-3-Methyl-4-(3-((1R,2R)-2-methylcyclopropyl)prop-2-ynyloxy)-6-(triisopropylsilyloxy)hex-1-en-2-yl acetate (20)

A mixture of Na_2CO_3 (13 mg, 0.12 mmol), [(*p*-cymene)$RuCl_2$]$_2$ (20 mg, 0.033 mmol), tri(2-furyl)phosphine (0.08 equiv), acetic acid (190 μL, 3.3 mmol), and 1-decyne (300 μL, 1.67 mmol) in toluene (1 mL) was heated to 80 °C and stirred for 1 h. The alkyne substrate (311 mg, 0.83 mmol) was dissolved in toluene (1 mL) and added to the mixture. The reaction was stirred at 80 °C for 6 h. The crude mixture was concentrated and purified by flash chromatography (5% EtOAc in hexane) to give the desired product (357 mg, 55%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.78 (s, br, 2H), 4.11 – 4.05 (m, 2H), 3.73 (dd, *J* = 7.5, 4.8 Hz, 3H), 2.70 (dd, *J* = 6.8, 4.7 Hz, 1H), 2.09 (s, 3H), 1.68 – 1.61 (m, 1H), 1.57 – 1.50 (m, 1H), 1.10 – 0.94 (m, 27H), 0.89 – 0.83 (m, 1H), 0.79 – 0.73 (m, 1H), 0.49 – 0.44 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2, 157.5, 102.5, 89.4, 76.2, 72.2, 60.2, 58.0, 40.3, 33.4, 21.3, 18.5, 18.3, 16.9, 16.6, 12.2, 7.8; $[\alpha]_D^{20}$ –24.4 (*c* 0.8, $CHCl_3$); IR (thin film, neat) 2943, 2866, 1762, 1661, 1463, 1368, 1220, 1180, 1097, 1057, 882 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{44}NaO_4Si$ $[M+Na]^+$: 459.2907, found: 459.2948.



(3*S*,4*S*)-4-(((*E*)-3-Acetoxy-3-((1*S*,2*S*)-2-methylcyclopropyl)allyl)oxy)-3-methyl-6-((triisopropylsilyl)oxy)hex-1-en-2-yl acetate (21)

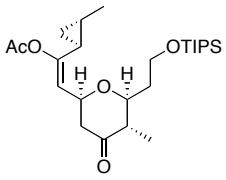
A mixture of Na_2CO_3 (40 mg, 0.36 mmol), [(*p*-cymene)$RuCl_2$]$_2$ (52 mg, 0.085 mmol), tri(2-furyl)phosphine (40 mg, 0.17 mmol), acetic acid (495 μL, 8.54 mmol), and 1-decyne (610 μL, 2.85 mmol) was stirred at 80 °C for 1 h. The ether (536 mg, 1.42 mmol) was added and the reaction was stirred for 12 h at 80 °C. The mixture was purified by flash chromatography (20% EtOAc in hexane) to give the desired product (487 mg, 69%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.30 (t, *J* = 7.3 Hz, 1H), 4.84 (app d, *J* = 4.9 Hz, 1H), 4.23 (dd, *J* = 11.6, 7.3 Hz, 1H), 4.15 – 4.10 (m, 1H), 3.83 – 3.75 (m, 2H), 3.73 (ddd, *J* = 9.6, 4.8, 2.6 Hz, 1H), 2.79 – 2.73 (m, 1H), 2.13 (s, 3H), 2.08 (s, 3H), 1.74 – 1.67 (m, 1H), 1.59 – 1.52 (m, 1H), 1.44 – 1.39 (m, 1H), 1.14 – 1.03 (m, 27H), 1.02 – 0.94 (m, 1H), 0.77 – 0.73 (m, 1H), 0.48 (dt, *J* = 8.7, 5.1 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.4, 169.3, 157.6, 151.4, 114.9, 102.5, 76.3, 64.9, 60.1, 40.3, 33.6, 21.3, 21.0, 19.1, 18.6, 18.3, 13.7, 13.6, 12.2, 12.1; $[\alpha]_D^{20}$ –21.3 (*c* 0.31, $CHCl_3$); IR (thin film, neat) 2943, 2866, 1761, 1663, 1463, 1369, 1218, 1178, 1098, 1068, 882 cm^{-1}; HRMS (ESI) calcd for $C_{27}H_{48}O_6Si$ $[M+Na]^+$: 519.3118, found: 519.3097.



(3*S*,4*S*)-4-(((*Z*)-3-(Dimethyl(phenyl)silyl)-3-((1*R*,2*R*)-2-methylcyclopropyl)allyl)oxy)-3-methyl-6-((triisopropylsilyl)oxy)hex-1-en-2-yl acetate (22)

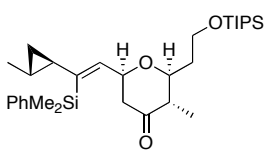
To a solution of with enol acetate ether **20** (8 mg, 0.02 mmol) and dimethylphenylsilane (5 μL, 0.02 mmol) in acetone (0.5 mL) was added [Cp*Ru(MeCN)$_3$]PF_6 (0.2 mg, 0.0004 mmol). The mixture was stirred for 3 h then was purified by flash column chromatography (5% ether in hexane) to provide the desired product (7.4 mg, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.48 (m, 2H), 7.35 – 7.31 (m, 3H), 5.98 (td, *J* = 6.6, 1.6 Hz, 1H), 4.77 (s, 2H), 3.91 (dd, *J* = 12.1, 6.9 Hz, 1H), 3.77 – 3.74 (m, 1H), 3.71 (dd, *J* = 7.6, 4.4 Hz, 2H), 3.48 (ddd, *J* = 9.6, 4.6, 2.6 Hz, 1H), 2.48 (qd, *J* = 6.9, 4.4 Hz, 1H), 2.06 (s, 3H), 1.61 (dtd, *J* = 10.3, 7.7, 2.6 Hz, 1H), 1.55 – 1.43 (m, 1H), 1.04 (s, 24H), 0.93 (d, *J* = 7.0 Hz, 3H), 0.90 (dd, *J* = 6.9, 4.1 Hz, 1H), 0.77 – 0.70 (m, 1H), 0.69 – 0.63 (m, 1H), 0.43 (s, 3H), 0.42 (s, 3H), 0.35 – 0.29 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.1, 157.5, 141.4, 139.3, 137.2, 133.9, 129.1, 128.1, 102.4, 69.5, 60.2, 40.2, 33.5, 26.9, 21.3, 19.3,

18.3, 15.6, 14.0, 12.2, 11.9, –0.8, –0.9; $[\alpha]_D^{20}$ –11.4 (*c* 0.74, $CHCl_3$); IR (thin film, neat) 2944, 2866, 1761, 1462, 1368, 1220, 1179, 1098, 834 cm^{-1}; HRMS (ESI) calcd for $C_{33}H_{57}O_4Si_2$ $[M+H]^+$: 573.3795, found: 573.3810.



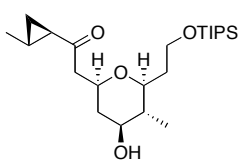
(*E*)-2-((2*S*,5*S*,6*S*)-5-Methyl-4-oxo-6-(2-((triisopropylsilyl)oxy)ethyl)tetrahydro-2H-pyran-2-yl)-1-((1*S*,2*S*)-2-methylcyclopropyl)vinyl acetate (23)

The general cyclization reaction procedure was followed with **21** (90 mg, 0.18 mmol), 2,6-dichloropyridine (54 mg, 0.36 mmol), 4 Å molecular sieves (180 mg), 1,2 dichloroethane (5 mL), $LiClO_4$ (6 mg, 0.05 mmol), and DDQ (165 mg, 0.73 mmol). The reaction was stirred at rt for 1.5 h, then was quenched with 5% aqueous $NaHCO_3$. The crude mixture was extracted with CH_2Cl_2, concentrated, and purified by flash chromatography (5% EtOAc in hexane) to give the desired product (81 mg, 62%).^{1}H NMR (400 MHz, $CDCl_3$) δ 5.25 (d, *J* = 8.3 Hz, 2H), 4.51 (ddd, *J* = 10.0, 8.2, 4.1 Hz, 1H), 3.95 – 3.84 (m, 2H), 3.58 – 3.51 (m, 1H), 2.55 – 2.50 (m, 2H), 2.40 (dq, *J* = 12.6, 6.4 Hz, 1H), 2.11 (s, 3H), 2.01 (dddd, *J* = 14.6, 8.5, 6.1, 2.1 Hz, 1H), 1.76 (app dq, dddd, *J* = 8.9, 8.9, 8.9, 4.4 Hz, 1H), 1.39 – 1.34 (m, 1H), 1.09 (d, *J* = 2.4 Hz, 3H), 1.07 (s, 24H), 1.00 – 0.89 (m, 1H), 0.87 – 0.81 (m, 1H), 0.51 (dt, *J* = 8.6, 5.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.4, 169.0, 151.3, 117.8, 79.6, 73.5, 59.5, 50.2, 48.5, 37.6, 21.0, 19.4, 18.6, 18.2, 13.9, 13.8, 12.2, 9.5; $[\alpha]_D^{20}$ –31.8 (*c* 0.63, $CHCl_3$); IR (thin film, neat) 2943, 2867, 1762, 1717, 1462, 1369, 1209, 1098, 1067, 883 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{44}NaO_5Si$ $[M+Na]^+$: 475.2856, found: 475.2855.



(2*S*,3*S*)-6-((*Z*)-2-(Dimethyl(phenyl)silyl)-2-((1*R*,2*R*)-2-methylcyclopropyl)vinyl)-3-methyl-2-(2-((triisopropylsilyl)oxy)ethyl)dihydro-2H-pyran-4(3H)-one (24)

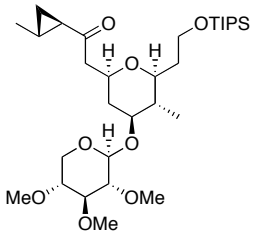
The general cyclization reaction procedure was followed with **22** (7.4 mg, 0.013 mmol), 2,6-dichloropyridine (16 mg, 0.11 mmol), 4 Å molecular sieves (21 mg), 1,2 dichloroethane (0.5 mL), $LiClO_4$ (1 mg, 0.01 mmol), and DDQ (12 mg, 0.052 mmol). The reaction was stirred at 45 °C for 4 h, then was quenched with 5% aqueous $NaHCO_3$. The crude mixture was extracted with CH_2Cl_2, concentrated, and purified by flash chromatography (5%-15% ether in hexane) to give the desired product (3.5 mg, 51%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.45 (m, 2H), 7.35 – 7.31 (m, 3H), 5.81 (dd, *J* = 8.9, 1.5 Hz, 1H), 4.05 (ddd, *J* = 11.4, 9.0, 2.6 Hz, 1H), 3.84 (ddd, *J* = 9.7, 6.8, 4.9 Hz, 1H), 3.74 (ddd, *J* = 10.0, 7.7, 6.0 Hz, 1H), 3.07 (ddd, *J* = 10.5, 8.5, 2.4 Hz, 1H), 2.30 – 2.21 (m, 2H), 2.06 (dd, *J* = 14.0, 2.6 Hz, 1H), 1.87 (dtd, *J* = 9.7, 7.4, 2.4 Hz, 1H), 1.72 (ddt, *J* = 14.1, 8.5, 5.5 Hz, 1H), 1.36 – 1.24 (m, 1H), 1.13 – 1.02 (m, 24H), 0.92 (d, *J* = 6.6 Hz, 1H), 0.90 – 0.83 (m, 1H), 0.82 – 0.76 (m, 1H), 0.68 – 0.56 (m, 1H), 0.44 (s, 3H), 0.42 (s, 3H), 0.35 (dt, *J* = 8.1, 4.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.3, 144.1, 138.9, 138.1, 133.9, 129.3, 128.2, 79.5, 76.2, 60.0, 49.9, 48.0, 37.6, 26.7, 19.2, 18.3, 16.2, 14.2, 12.2, 9.5, –0.6, –0.8. $[\alpha]_D^{20}$ –47.8 (*c* 0.32, $CHCl_3$); IR (thin film, neat) 2944, 2865, 1717, 1462, 1250, 1096, 835, 771, 732 cm^{-1}; HRMS (ASAP+) calcd for $C_{31}H_{52}O_3Si_2$ $[M+H]^+$: 529.3533, found: 529.3541.



2-((2S,4S,5R,6S)-6-(2-(tert-butyldimethylsilyloxy)ethyl)-4-hydroxy-5-methyl-tetrahydro-2H-pyran-2-yl)-1-((1R,2R)-2-methylcyclopropyl)ethanone

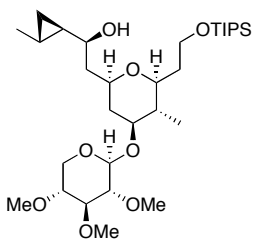
To a solution of **23** (7.3 mg, 0.018 mmol) in MeOH (0.8 mL) at –10 °C was added $NaBH_4$ (0.5 mg, 0.01 mmol, 0.7 equiv.) in one portion. The

mixture was stirred at –10 °C for 15 min, then was quenched with H_2O. After concentration, the crude product was used directly in the next step without further purification. To a solution of the ketone in MeOH (0.5 mL) at 0 °C was added K_2CO_3 (13 mg, 0.09 mmol) in one portion. The mixture was stirred for 30 min at 0 °C, then was quenched with NH_4Cl (5 mL) and extracted with Et_2O (2 x 10 mL). The combined organic layers were dried over $MgSO_4$ and purified by flash chromatography (15% to 25% EtOAc in hexane) to afford the desired product (6.1 mg, 81%, two steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.85 – 3.72 (m, 3H), 3.37 (td, *J* = 10.4, 4.7 Hz, 1H), 3.14 (td, *J* = 9.6, 2.2 Hz, 1H), 2.80 (dd, *J* = 15.6, 6.7 Hz, 1H), 2.55 (dd, *J* = 15.6, 6.0 Hz, 1H), 2.03 – 1.99 (m, 1H), 1.95 – 1.88 (m, 1H), 1.69 (dt, *J* = 8.3, 4.3 Hz, 1H), 1.61 – 1.51 (m, 1H), 1.43 – 1.36 (m, 1H), 1.28 – 1.22 (m, 4H), 1.11 (d, *J* = 6.0 Hz, 3H), 1.06 (s, br, 21H), 0.98 (d, *J* = 6.5 Hz, 3H), 0.71 (td, *J* = 7.2, 3.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.3, 78.1, 73.5, 71.8, 60.2, 49.7, 43.8, 41.2, 36.5, 30.5, 20.4, 19.6, 18.3, 18.2, 13.1, 12.2; $[\alpha]_D^{20}$ –45.0 (*c* 2.54, $CHCl_3$); IR (thin film, neat) 3443, 2942, 2866, 1693, 1463, 1404, 1381, 1094 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{45}O_4Si$ $[M+H]^+$: 413.3087, found: 413.3091.



2-((2*S*,4*S*,5*S*,6*S*)-5-Methyl-6-(2-((triisopropylsilyl)oxy)ethyl)-4-(((2*S*,3*R*,4*S*,5*R*)-3,4,5-trimethoxytetrahydro-2H-pyran-2-yl)oxy)tetrahydro-2H-pyran-2-yl)-1-((1*R*,2*R*)-2-methylcyclopropyl)ethanone (26)

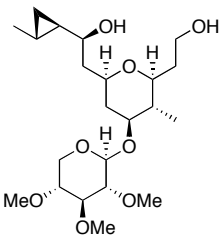
To a solution of the keto alcohol (199 mg, 0.484 mmol) in CH_2Cl_2 (13 mL) were added trichloroacetimidate **25** (0.5 M solution in CH_2Cl_2, 1.45 mL, 0.726 mmol) and 4Å MS (300 mg). The mixture was stirred for 30 min at rt then was cooled to –20 °C. TMSOTf (1.0 M solution in CH_2Cl_2, 65 μL, 0.063 mmol) was added dropwise. The reaction was stirred at –20 °C for 30 min then was warmed to rt slowly over 1 h. The reaction was quenched with Et_3N (5 drops) and purified by flash chromatography (25% EtOAc in hexane) to yield the desired product (148 mg, 52%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.29 (d, *J* = 7.7 Hz, 1H), 3.97 (dd, *J* = 11.6, 5.2 Hz, 1H), 3.85 – 3.73 (m, 3H), 3.63 (s, 3H), 3.61 (s, 3H), 3.48 (s, 3H), 3.31 – 3.23 (m, 2H), 3.17 (td, *J* = 9.6, 2.2 Hz, 1H), 3.13 – 3.06 (m, 2H), 2.98 (dd, *J* = 9.1, 7.6 Hz, 1H), 2.79 (dd, *J* = 15.7, 6.9 Hz, 1H), 2.55 (dd, *J* = 15.7, 5.7 Hz, 1H), 2.16 (ddd, *J* = 12.5, 4.9, 1.9 Hz, 1H), 1.93 (dtd, *J* = 13.8, 7.6, 2.2 Hz, 1H), 1.70 (dt, *J* = 8.2, 4.2 Hz, 1H), 1.61 – 1.54 (m, 1H), 1.45 – 1.37 (m, 2H), 1.29 – 1.23 (m, 2H), 1.12 (d, *J* = 6.0 Hz, 3H), 1.06 (s, br, 21H), 1.02 (d, *J* = 6.4 Hz, 3H), 0.72 (ddd, *J* = 7.8, 6.4, 3.6 Hz, 1H); ^{13}C NMR (126 MHz, CDCl3) δ 208.3, 105.7, 85.7, 84.0, 83.6, 79.6, 78.3, 71.8, 63.4, 60.9, 60.2, 58.9, 49.7, 42.3, 40.4, 36.6, 30.5, 20.3, 19.5, 18.3, 18.2, 13.0, 12.2; $[\alpha]_D^{20}$ –23.8 (*c* 0.66, $CHCl_3$); IR (thin film, neat) 3373, 3246, 2927, 2865, 1693, 1614, 1462, 1381, 1106, 834 cm^{-1}; HRMS (ESI) calcd for $C_{31}H_{59}O_8Si$ $[M+H]^+$: 587.3979 found: 587.3990.



(*S*)-2-((2*R*,4*S*,5*S*,6*S*)-5-Methyl-6-(2-((triisopropylsilyl)oxy)ethyl)-4-(((2*S*,3*R*,4*S*,5*R*)-3,4,5-trimethoxytetrahydro-2H-pyran-2-yl)oxy)tetrahydro-2H-pyran-2-yl)-1-((1*R*,2*R*)-2-methylcyclopropyl)ethanol

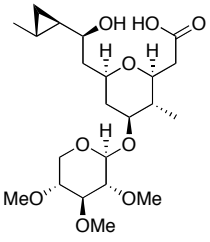
A solution of catalyst **27** (1M in toluene, 125 μL, 0.049 mmol) was dried on a high vacuum pump for 1 h. The catalyst was dissolved in THF (3.5 mL) the resulting solution was cooled to −20 °C. A solution of BH_3•SMe_2 in THF (1M, 495 μL, 0.495 mmol) was added. The mixture was stirred for 30 min at –20 °C, then the ketone (144 mg, 0.245 mmol) in THF (1 mL) was added dropwise over 10 min. The reaction was stirred at −20 °C for 12h then was quenched with MeOH (5

mL, dropwise). Saturated NH_4Cl (15 mL) and EtOAc (20 mL) were added. After extraction with EtOAc (2 x 20 mL), the combined organic extracts were dried and concentrated. Purification by flash chromatography (20% EtOAc in hexane) provided the desired product (113 mg, 78%) and its diastereomer (13 mg, 9%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.30 (d, *J* = 7.6 Hz, 1H), 3.97 (dd, *J* = 11.6, 5.2 Hz, 1H), 3.85 – 3.74 (m, 3H), 3.64 (s, 3H), 3.62 (s, *J* = 1.6 Hz, 3H), 3.49 (s, 3H), 3.29 – 3.23 (m, 4H), 3.15 – 3.09 (m, 2H), 3.00 (dd, *J* = 9.1, 7.6 Hz, 1H), 2.12 – 2.07 (m, 1H), 1.94 (tdd, *J* = 8.7, 6.6, 2.5 Hz, 1H), 1.84 – 1.74 (m, 1H), 1.74 – 1.66 (m, 1H), 1.64 – 1.56 (m, 1H), 1.53 – 1.44 (m, 2H), 1.08 (s br, 24H), 1.04 (d, *J* = 6.5 Hz, 3H), 0.81 – 0.71 (m, 1H), 0.61 (tt, *J* = 8.6, 4.4 Hz, 1H), 0.37 – 0.28 (m, 1H), 0.20 (dt, *J* = 8.4, 4.8 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 105.9, 85.8, 84.1, 83.5, 79.6, 78.4, 76.0, 75.9, 63.4, 61.0, 61.0, 59.8, 59.0, 42.9, 42.2, 41.0, 36.4, 26.4, 18.9, 18.3, , 13.1, 12.2, 11.3, 10.5. $[\alpha]_D^{20}$ –19.6 (*c* 1.14, $CHCl_3$); IR (thin film, neat) 3490, 2942, 2866, 1731, 1463, 1369, 1162, 1095, 989, 884 cm^{-1}; HRMS (ESI) calcd for $C_{31}H_{60}O_8NaSi$ $[M+Na]^+$: 611.3955 found: 611.3951.



(*S*)-2-((2*R*,4*S*,5*S*,6*S*)-6-(2-Hydroxyethyl)-5-methyl-4-(((2*S*,3*R*,4*S*,5*R*)-3,4,5-trimethoxytetrahydro-2H-pyran-2-yl)oxy)tetrahydro-2H-pyran-2-yl)-1-((1*R*,2*R*)-2-methylcyclopropyl)ethanol

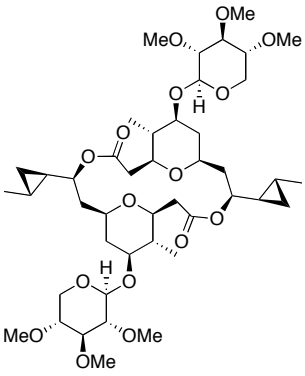
To a solution of the silyl ether (108 mg, 0.184 mmol) in EtOH (6.4 mL) was added 1% HCl (1.95 mL). The solution was stirred at rt for 5h. The reaction was quenched with saturated $NaHCO_3$ (5 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and purified by flash chromatography (35% to 20% hexane in EtOAc) to afford the desired product (80 mg, 100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.27 (d, *J* = 7.6 Hz, 1H), 3.95 (dd, *J* = 11.5, 5.2 Hz, 1H), 3.79 – 3.72 (m, 2H), 3.61 (s, *J* = 2.5 Hz, 3H), 3.59 (s, 3H), 3.47 (s, *J* = 2.7 Hz, 3H), 3.28 – 3.20 (m, 3H), 3.12 – 3.04 (m, 3H), 2.97 (dd, *J* = 9.1, 7.6 Hz, 1H), 2.09 (ddd, *J* = 12.7, 4.8, 2.0 Hz, 1H), 1.99 – 1.88 (m, 1H), 1.81 (dt, *J* = 14.4, 9.1 Hz, 1H), 1.72 – 1.58 (m, 2H), 1.53 – 1.35 (m, 2H), 1.05 (d, *J* = 5.9 Hz, 3H), 1.00 (d, *J* = 6.5 Hz, 3H), 0.79 – 0.69 (m, 1H), 0.64 – 0.57 (m, 1H), 0.31 (dt, *J* = 8.4, 4.7 Hz, 1H), 0.22 (dt, *J* = 8.3, 4.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 105.8, 85.8, 84.0, 83.2, 81.1, 79.6, 76.0, 75.7, 63.5, 61.1, 61.0, 60.6, 59.1, 42.8, 42.5, 35.2, 26.9, 18.9, 14.4, 13.0, 11.4, 10.8; $[\alpha]_D^{20}$ –20.5 (*c* 0.57, $CHCl_3$); IR (thin film, neat) 3427, 2930, 1455, 1372, 1326, 1162, 1090, 988 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{40}NaO_8$ $[M+Na]^+$: 455.2621 found: 455.2620.



2-((2*S*,3*S*,4*S*,6*R*)-6-((*S*)-2-Hydroxy-2-((1*R*,2*R*)-2-methylcyclopropyl)ethyl)-3-methyl-4-(((2*S*,3*R*,4*S*,5*R*)-3,4,5-trimethoxytetrahydro-2H-pyran-2-yl)oxy)tetrahydro-2H-pyran-2-yl)acetic acid (28)

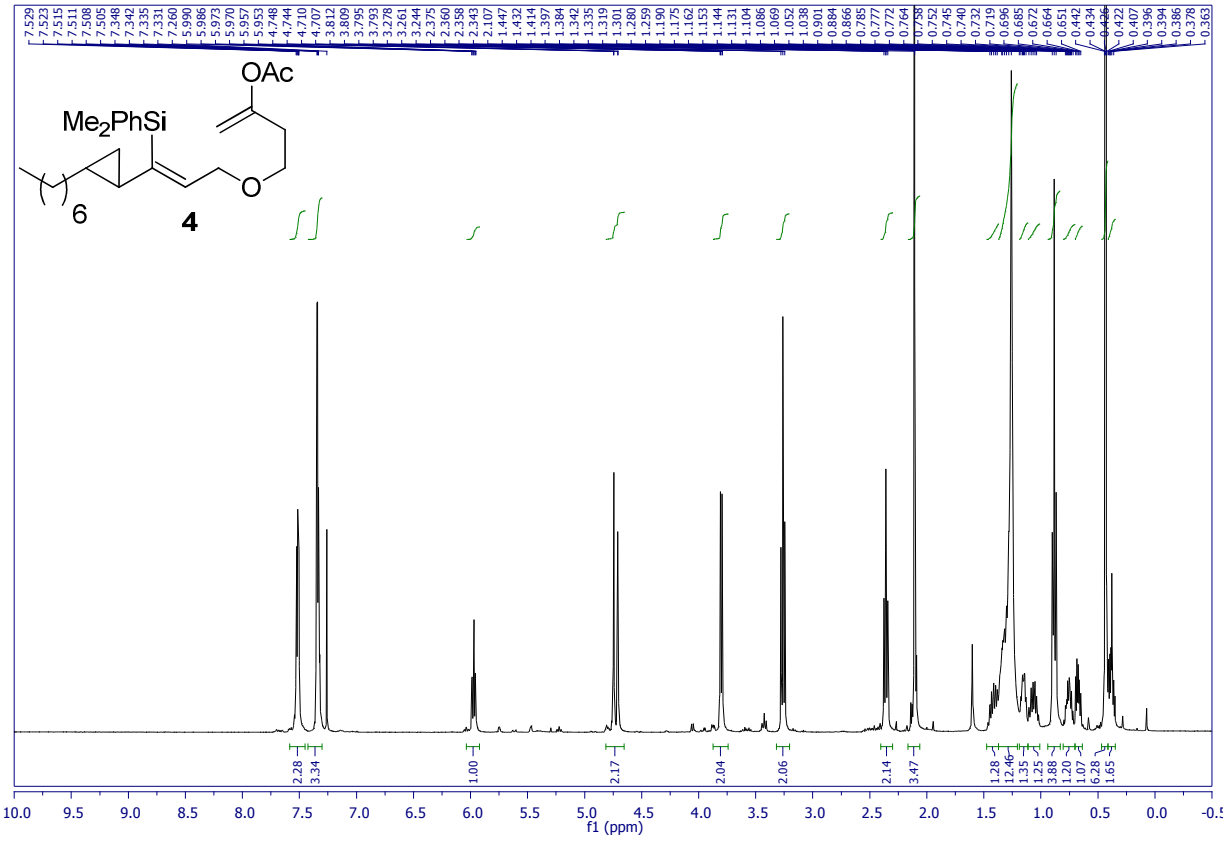
To a solution of the diol (10 mg, 0.024 mmol) in CH_2Cl_2 (110 μL) was added TEMPO (0.2 mg, 0.001 mmol) and saturated $NaHCO_3$ (60 μL). KBr (5 μL, 0.002 mmol, 0.5M aq. stock solution) and Bu_4NCl (25 μL, 0.0017 mmol, 0.08M aq stock solution) were added subsequently and the mixture was cooled to 0 °C. To the vigorously stirring biphasic solution was added a stock solution of sat. $NaHCO_3$ (35 μL), brine (65 μL) and bleach (95 μL, 0.065 mmol, 0.7 M) dropwise over 45 min. The mixture was allowed to stir for an additional 30 min at 0 °C upon completion of the addition. The solution was then diluted with H_2O (5 mL) and EtOAc (5 mL). The diluted mixture was acidified with 10% citric acid (4 drops) to pH 3-4. The aqueous layer was extracted with EtOAc (3 x 5mL). The combined organic extracts were dried over $MgSO_4$. The crude colorless oil (8 mg, 78%) was determined pure by ^{1}H NMR and used without further

purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.26 (d, *J* = 7.6 Hz, 1H), 3.94 (dd, *J* = 11.5, 5.1 Hz, 1H), 3.61 (s, 3H), 3.58 (s, 3H), 3.46 (s, 3H), 3.30 – 3.20 (m, 3H), 3.13 – 3.07 (m, 3H), 2.97 (dt, *J* = 9.0, 4.8 Hz, 1H), 2.67 (d, br, *J* = 14.7 Hz, 1H), 2.40 (m, 1H), 2.14 – 2.02 (m, 1H), 1.78 (dt, *J* = 15.0, 9.8 Hz, 1H), 1.72 – 1.65 (m, 1H), 1.55 – 1.40 (m, 2H), 1.01 (d, *J* = 6.6 Hz, 3H), 1.00 (d, *J* = 5.8 Hz, 3H), 0.92 – 0.79 (m, 1H), 0.78 – 0.68 (m, 1H), 0.57 (tt, *J* = 8.7, 4.5 Hz, 1H), 0.28 – 0.20 (m, 1H), 0.16 (dt, *J* = 8.7, 4.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.7, 105.7, 85.7, 83.9, 82.6, 79.5, 78.4, 77.63, 76.9, 63.4, 61.0, 61.0, 59.0, 42.1, 41.8, 40.7, 38.7, 25.8, 18.7, 12.8, 12.0, 10.4; $[\alpha]_D^{20}$ –24 (*c* 2.1, $CHCl_3$); IR (thin film, neat) 3455, 2926, 1731, 1457, 1373, 1327, 1257, 1162, 1091 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{38}NaO_9$ $[M+Na]^+$: 469.2414 found: 469.2436.



Clavosolide A (9)

To the seco acid **28** (6.0 mg, 0.014 mmol) in THF (0.8 mL) was added Et_3N (40 μL, 0.28 mmol) and 2,4,6-trichlorobenzoyl chloride (25 μL, 0.14 mmol) dropwise. The reaction was allowed to stir for 2.5 h at rt and the Et_3N•HCl salt was removed by flitration. The filtrate was diluted with toluene (0.8 mL) and added dropwise over 5 h to a stirred solution of DMAP (16 mg, 0.132 mmol) in toluene (13 mL) at 90°C via a syringe pump. The reaction was cooled to rt and allowed to stir for another 12h. The reaction mixture was quenched with aq. NH_4Cl (5 mL), extracted with EtOAc (2 x 5mL) and concentrated under vacuum. Purification by flash chromatography (45% to 35% hexanes in EtOAc) provided the natural product as a white solid (2.6 mg, 44%). ^{1}H NMR (601 MHz, $CDCl_3$) δ 4.42 (td, *J* = 8.9, 2.0 Hz, 1H), 4.26 (d, *J* = 7.6 Hz, 1H), 3.95 (dd, *J* = 11.6, 5.2 Hz, 1H), 3.61 (s, 3H), 3.58 (s, 3H), 3.46 (s, 3H), 3.44 (qd, *J* = 4.3, 1.4 Hz, 2H), 3.27 – 3.21 (m, 1H), 3.09 (ddd, *J* = 10.1, 7.9, 3.2 Hz, 2H), 2.96 (dd, *J* = 9.1, 7.6 Hz, 1H), 2.54 (dd, *J* = 17.4, 3.6 Hz, 1H), 2.41 (dd, *J* = 17.3, 6.6 Hz, 1H), 2.04 (ddd, *J* = 12.7, 4.8, 1.8 Hz, 1H), 1.89 (dt, *J* = 15.0, 9.0 Hz, 1H), 1.68 (ddd, *J* = 15.1, 3.5, 2.1 Hz, 1H), 1.41 – 1.34 (m, 2H), 0.97 (d, *J* = 5.1 Hz, 3H), 0.85 – 0.78 (m, 1H), 0.71 (tt, *J* = 8.8, 4.6 Hz, 1H), 0.34 (dt, *J* = 8.4, 4.7 Hz, 1H), 0.22 (dt, *J* = 8.3, 4.9 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.3, 105.7, 85.8, 84.1, 83.4, 79.6, 77.5, 77.3, 75.1, 63.5, 61.0, 61.0, 59.0, 42.8, 41.5, 40.9, 39.5, 25.0, 18.7, 12.8, 12.1, 11.1; $[\alpha]_D^{20}$ –41.3 (*c* 0.1, $CHCl_3$); IR (thin film, neat) 2945, 1734, 1165, 1089 cm^{-1}; HRMS (ESI) calcd for $C_{44}H_{72}NaO_{16}$ $[M+Na]^+$: 879.4716 found: 879.4739; m.p: 249-252 °C.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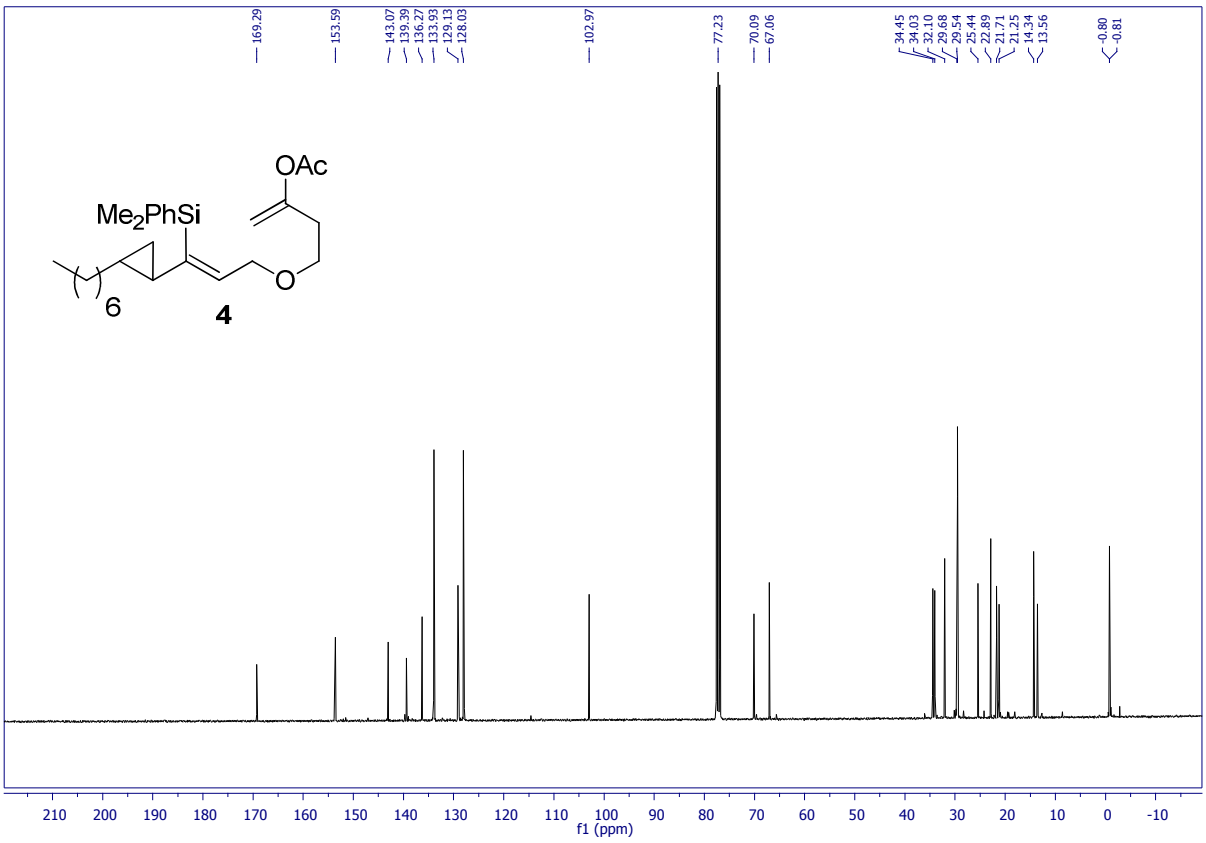
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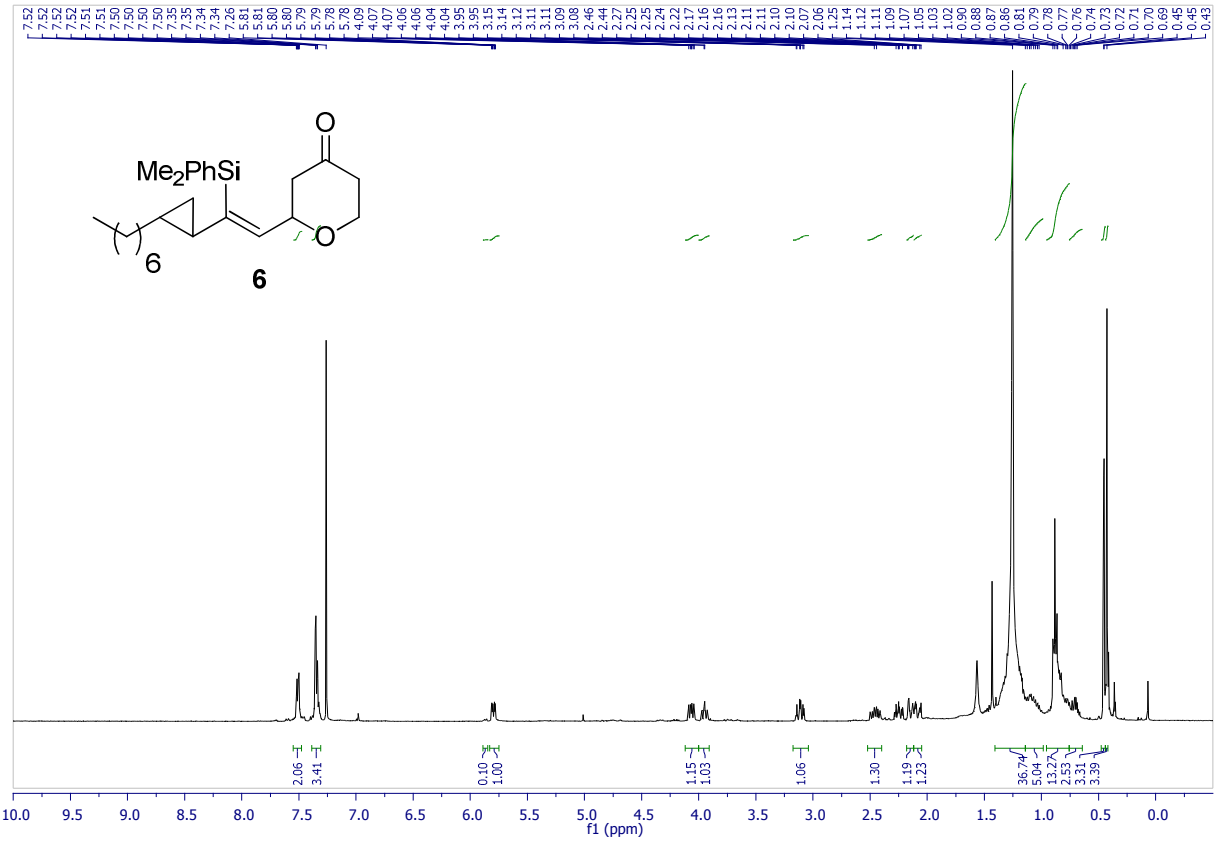
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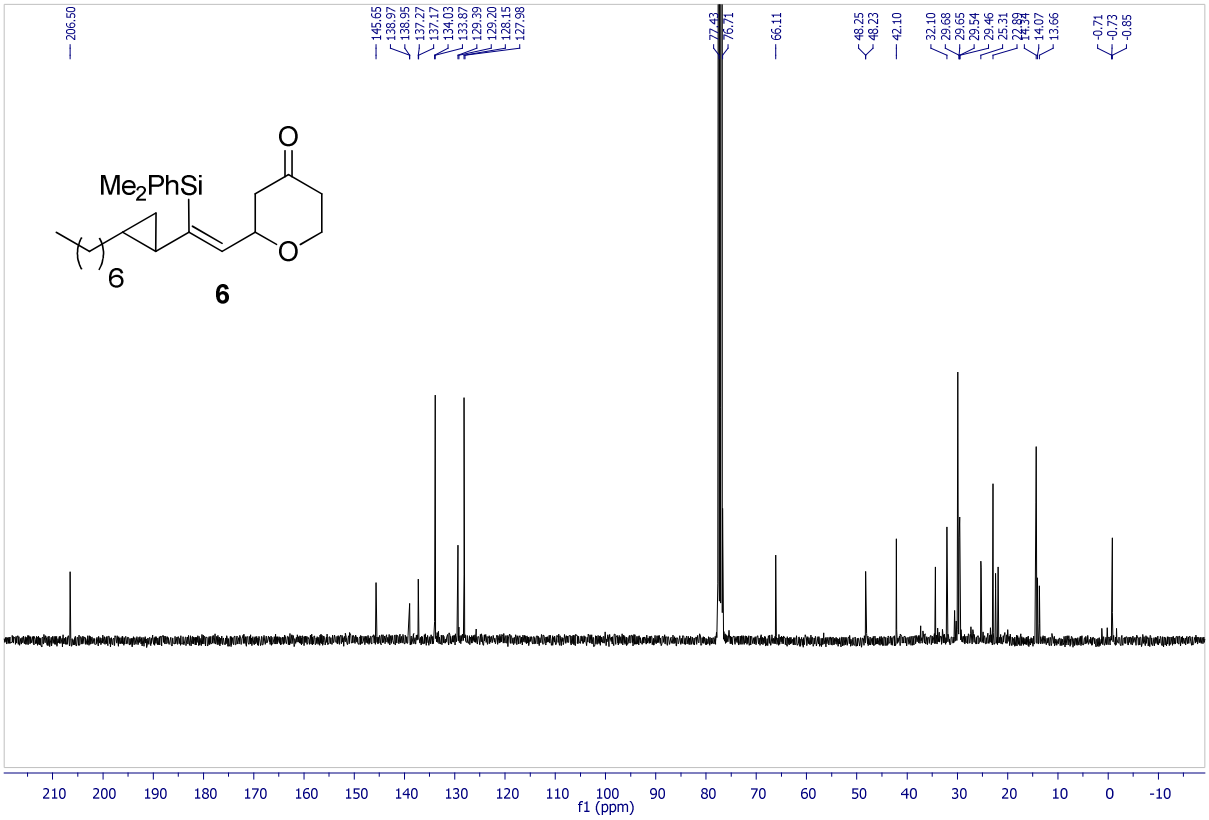
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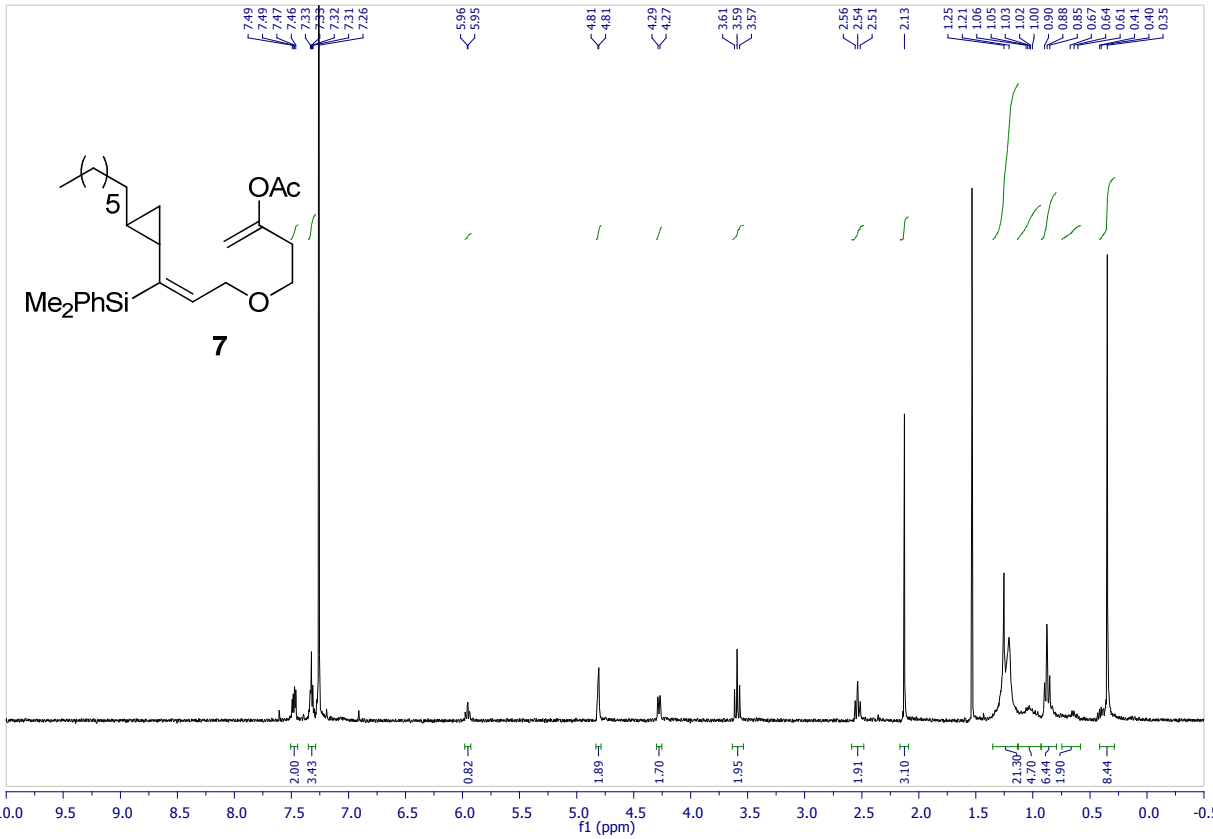
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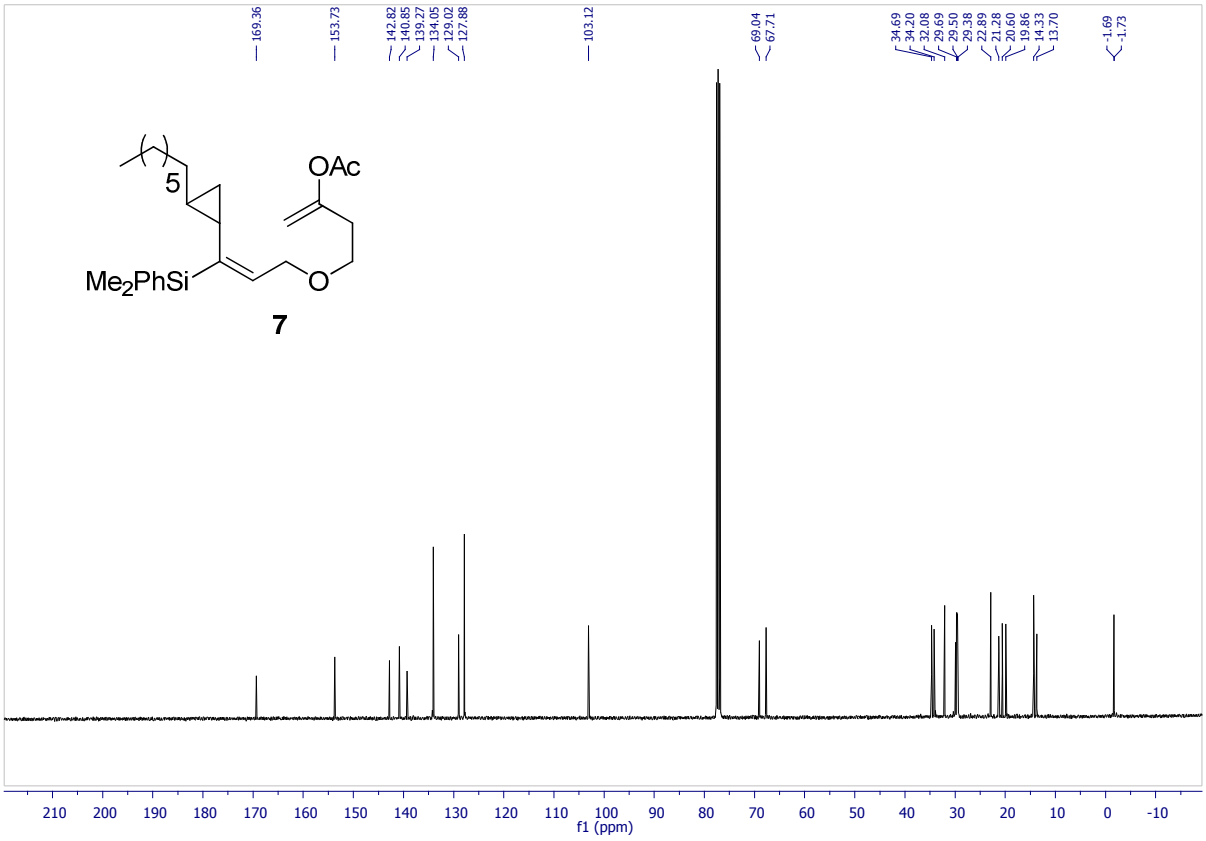
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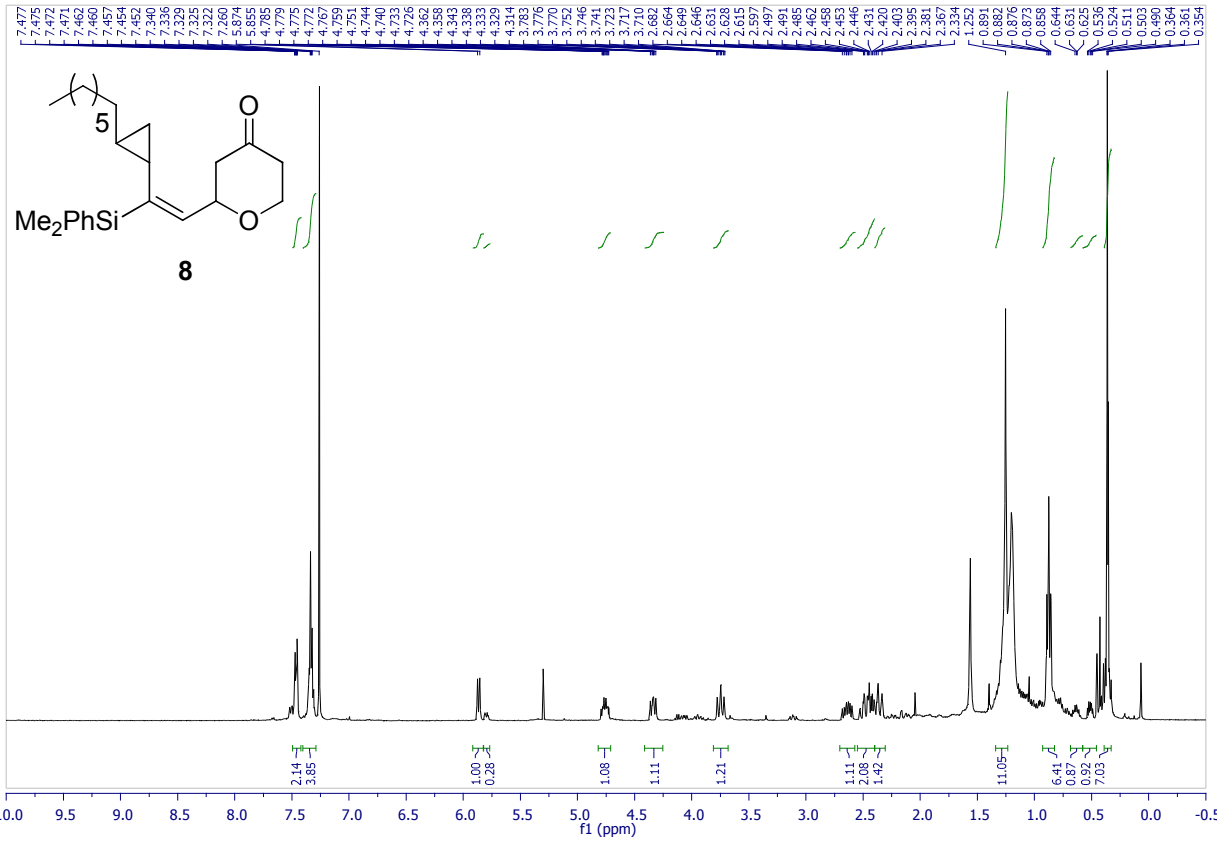
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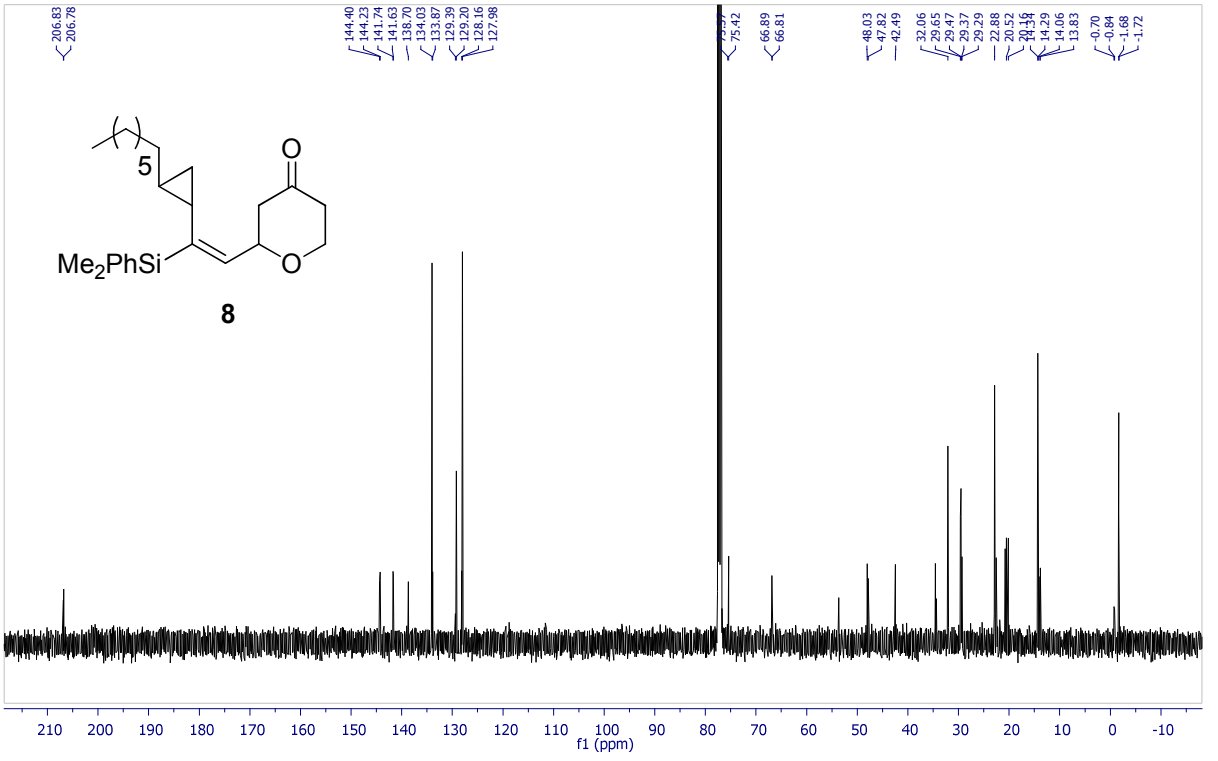
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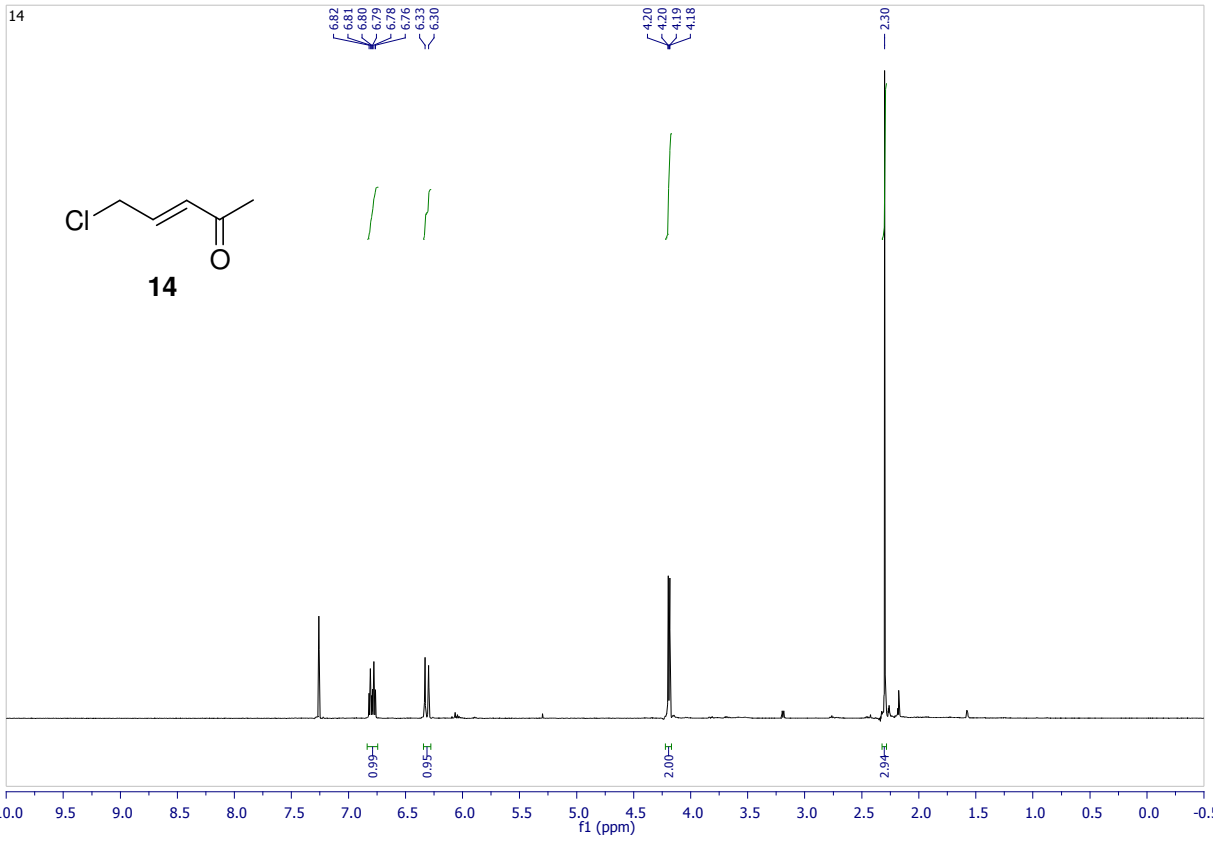
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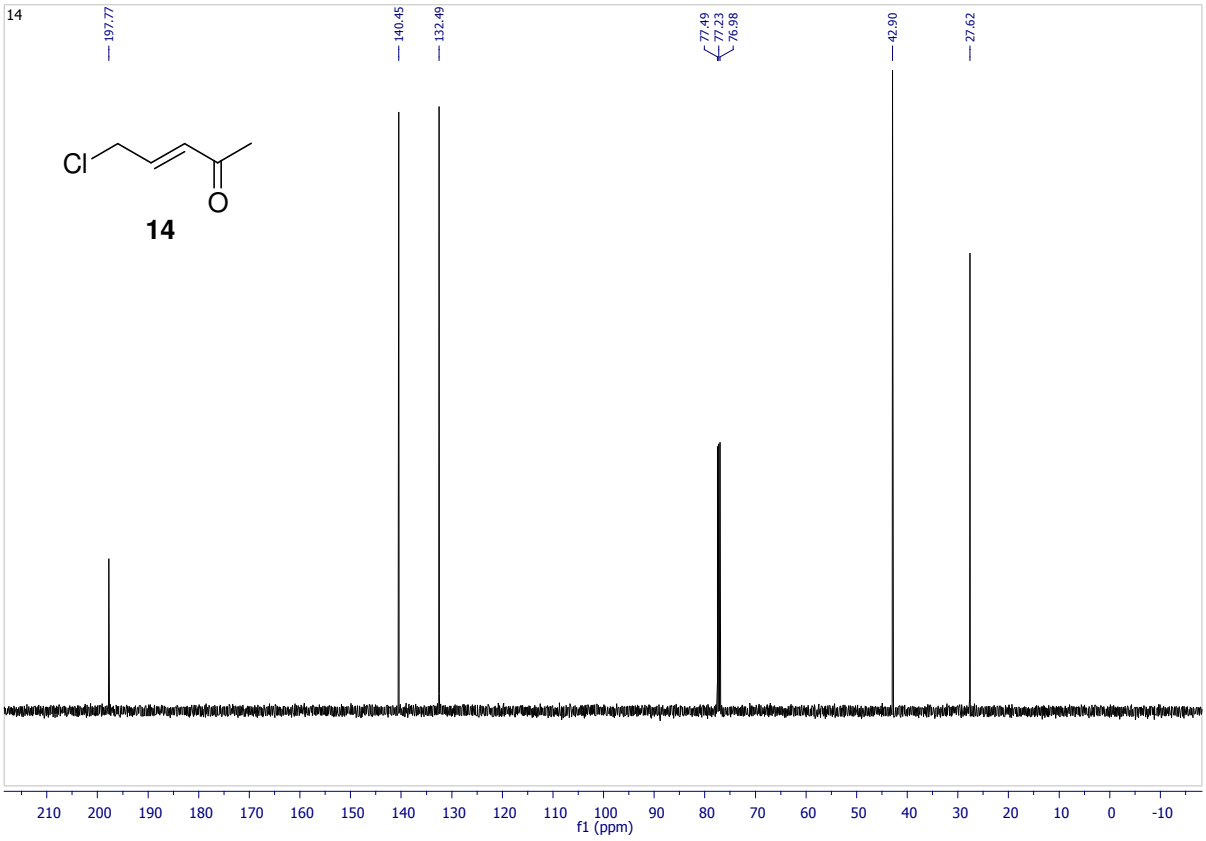
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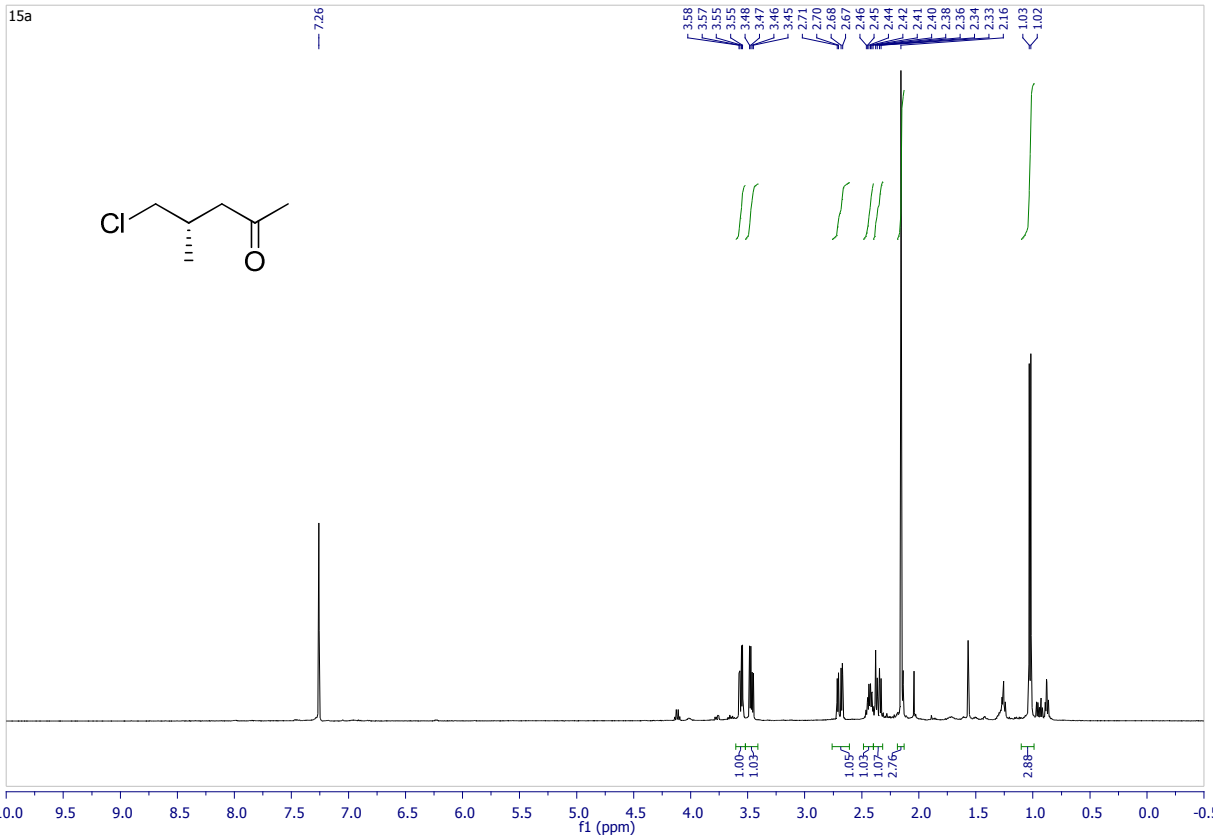
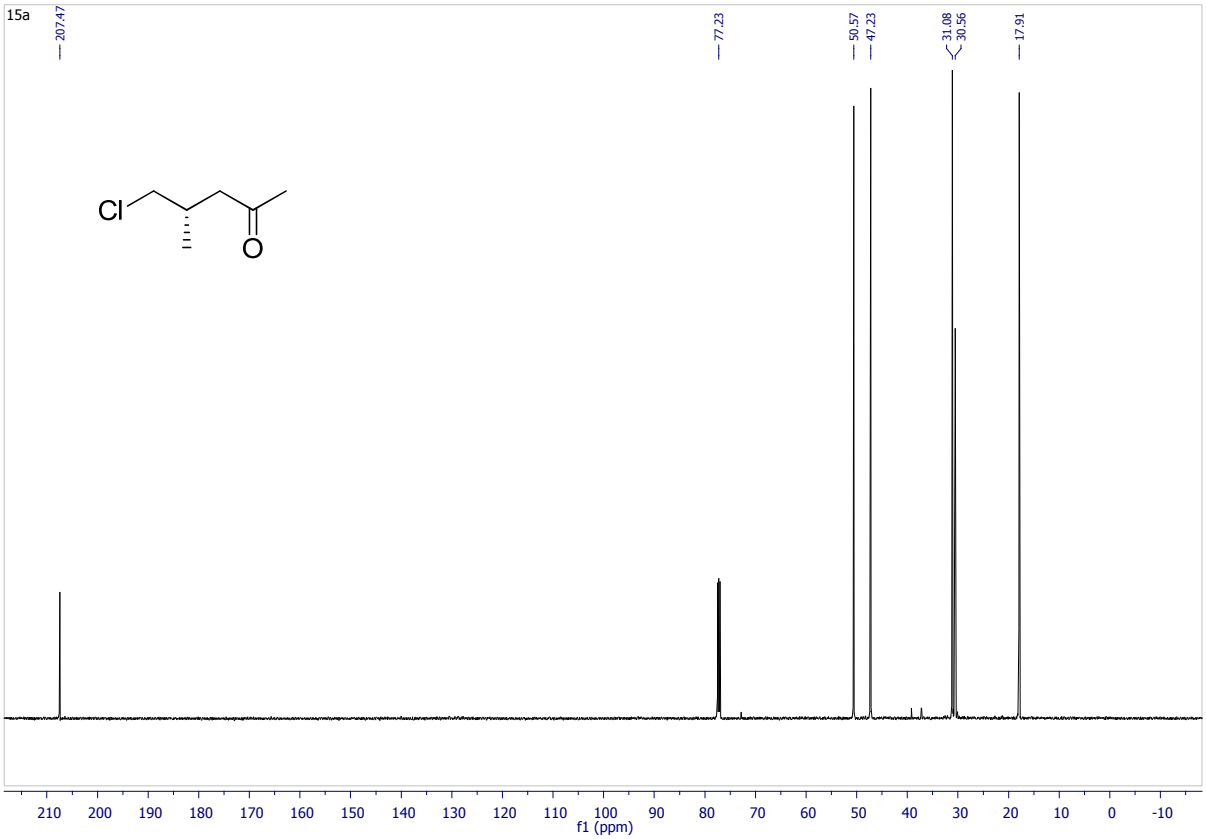
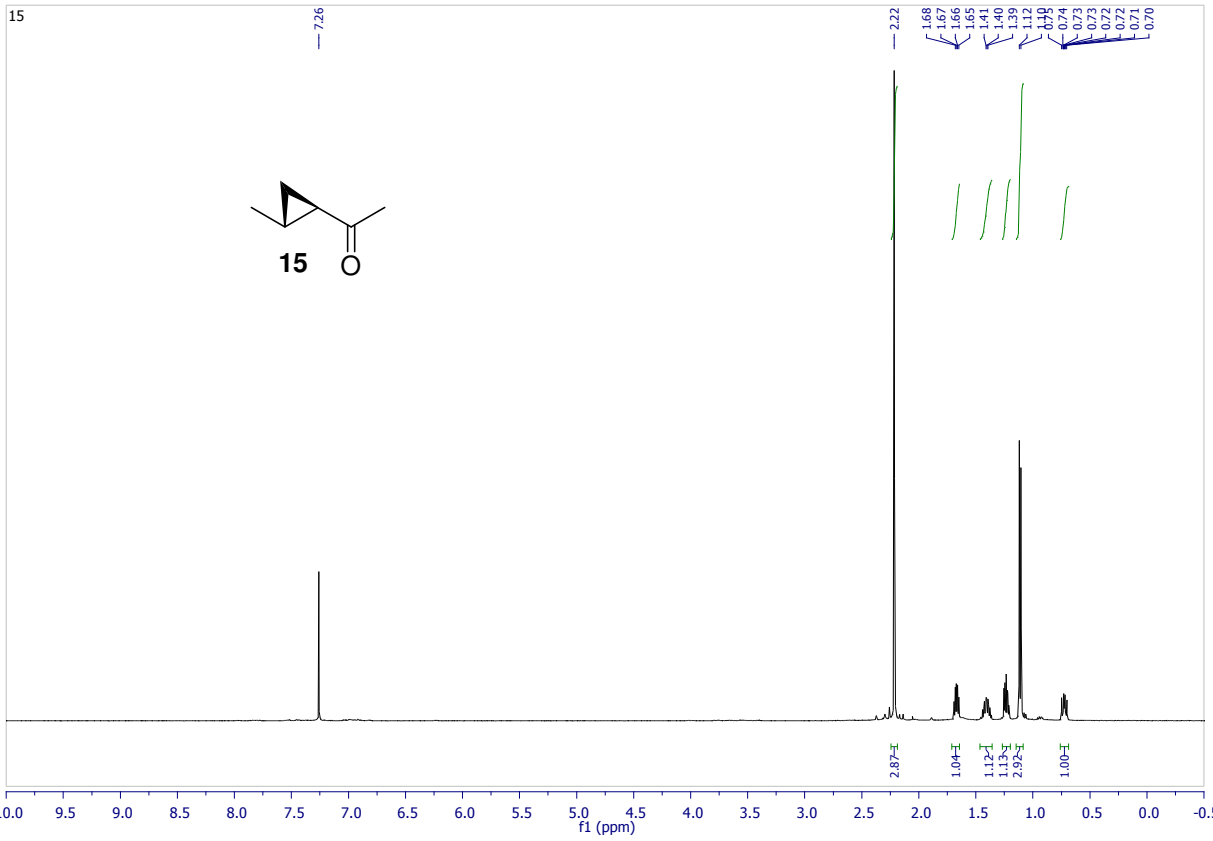
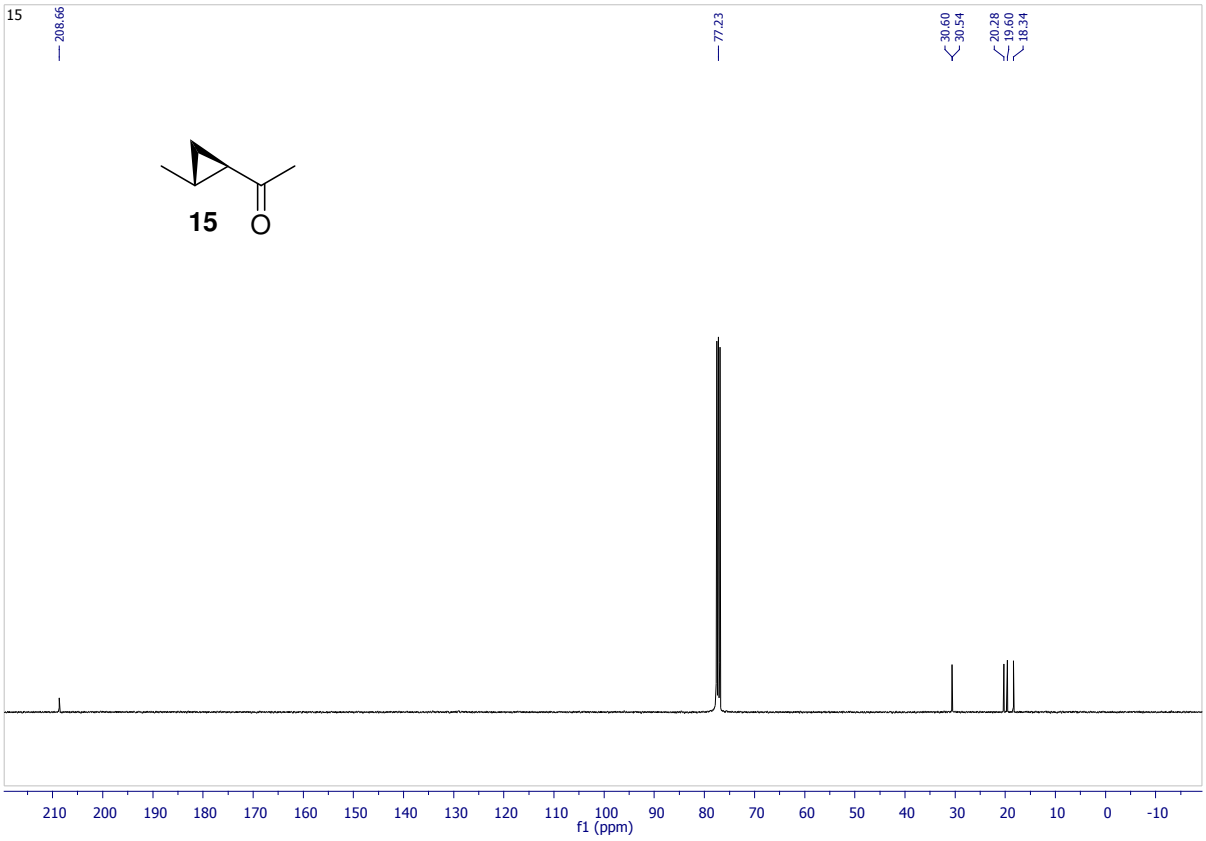
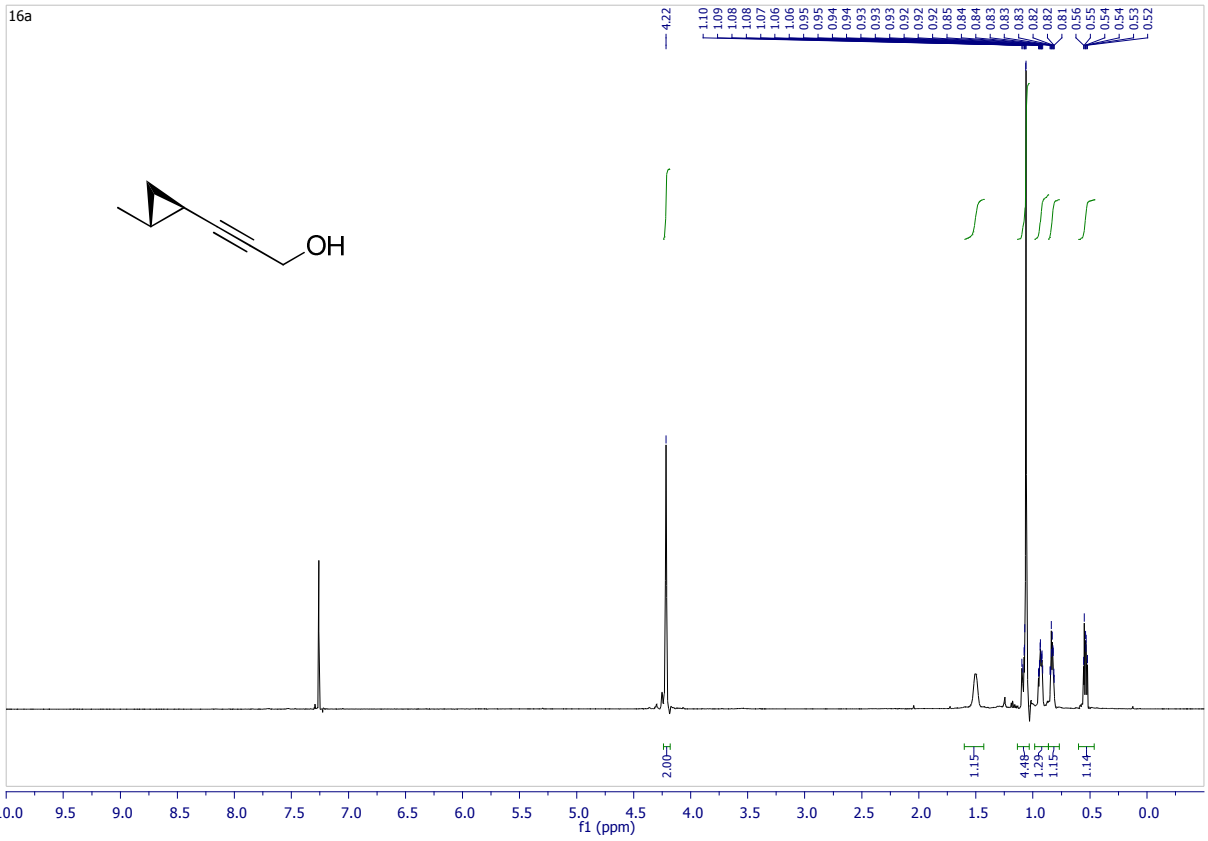
76.98
42.90
27.62
Cl
O
14
f1 (ppm)

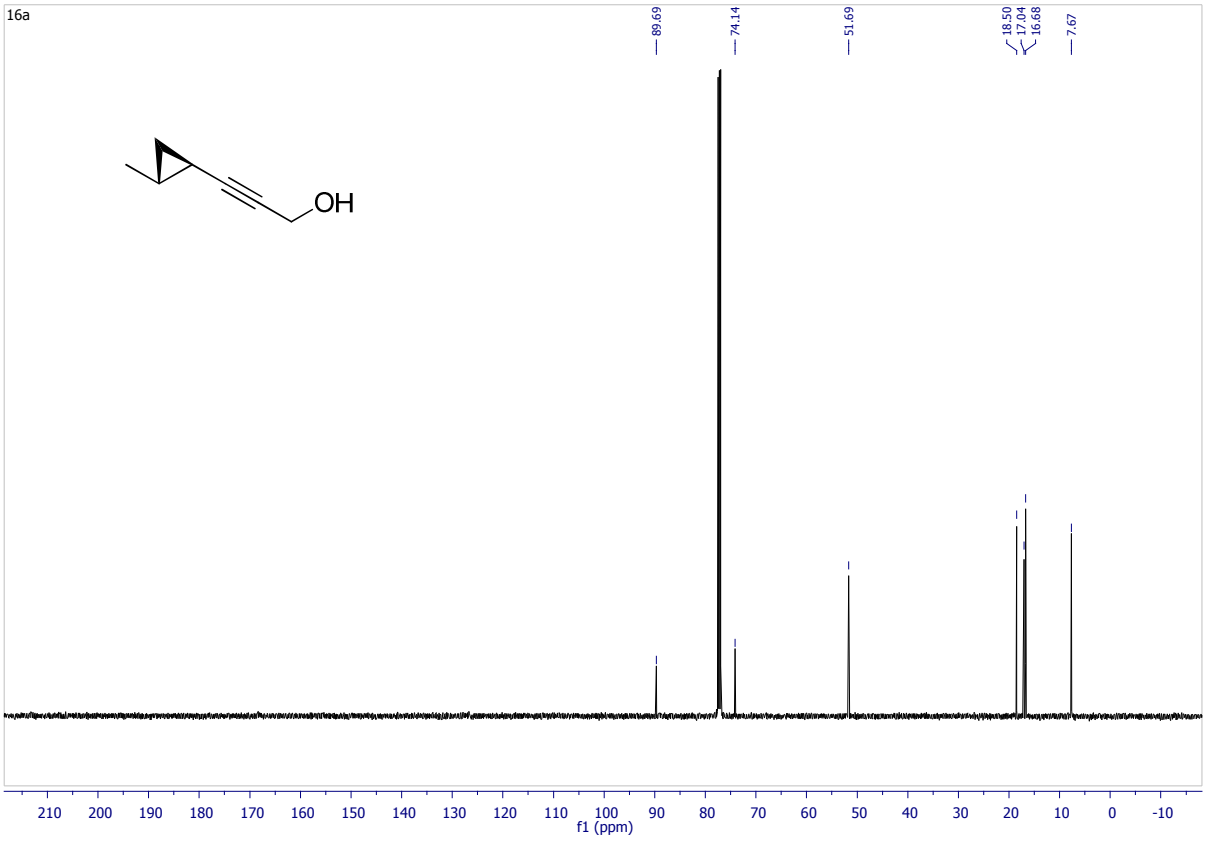

15a
7.26
3.58
3.57
3.55
3.55
3.48
3.47
3.46
3.45
2.71
2.70
2.68
2.67
2.46
2.45
2.44
2.42
2.41
2.40
2.38
2.36
2.34
2.33
2.16
1.03
1.02
Cl
O
1.00
1.03
1.05
1.03
1.07
2.76
2.88
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

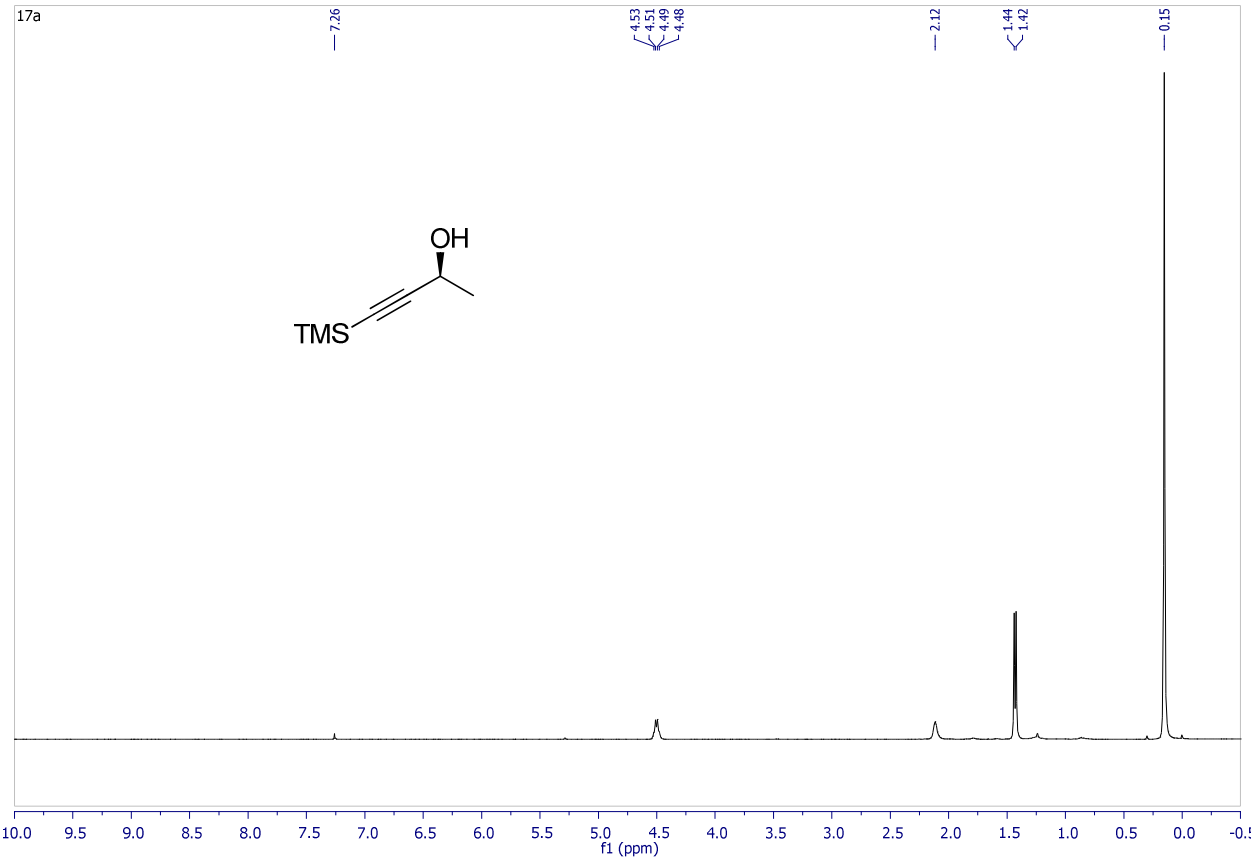

15a
207.47
77.23
50.57
47.23
31.08
30.56
17.91
Cl
O
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

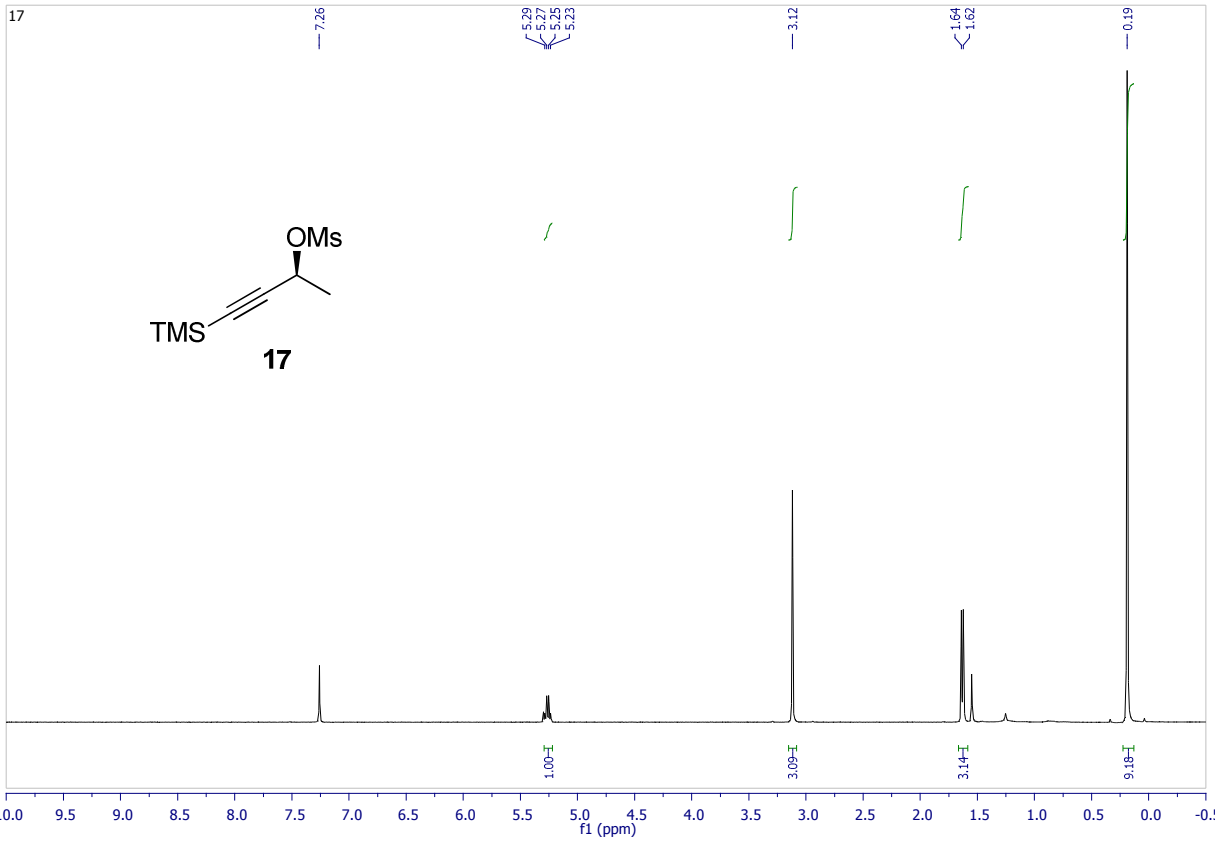

15
7.26
2.22
1.68
1.67
1.66
1.65
1.41
1.40
1.39
1.12
0.74
0.73
0.72
0.71
0.70
15
O
2.87
1.04
1.12
1.13
2.92
1.00
f1 (ppm)

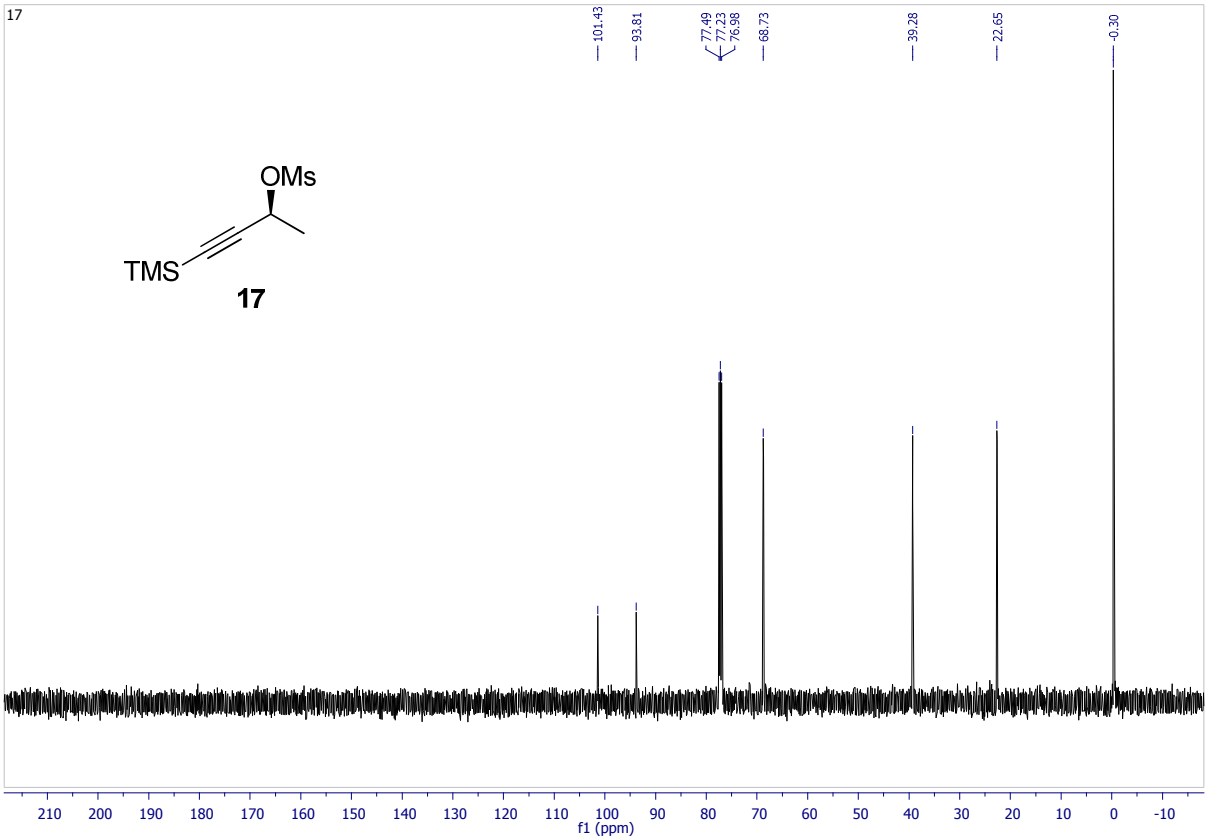

15
208.66
77.23
30.60
30.54
20.28
19.60
18.34
15
O
f1 (ppm)

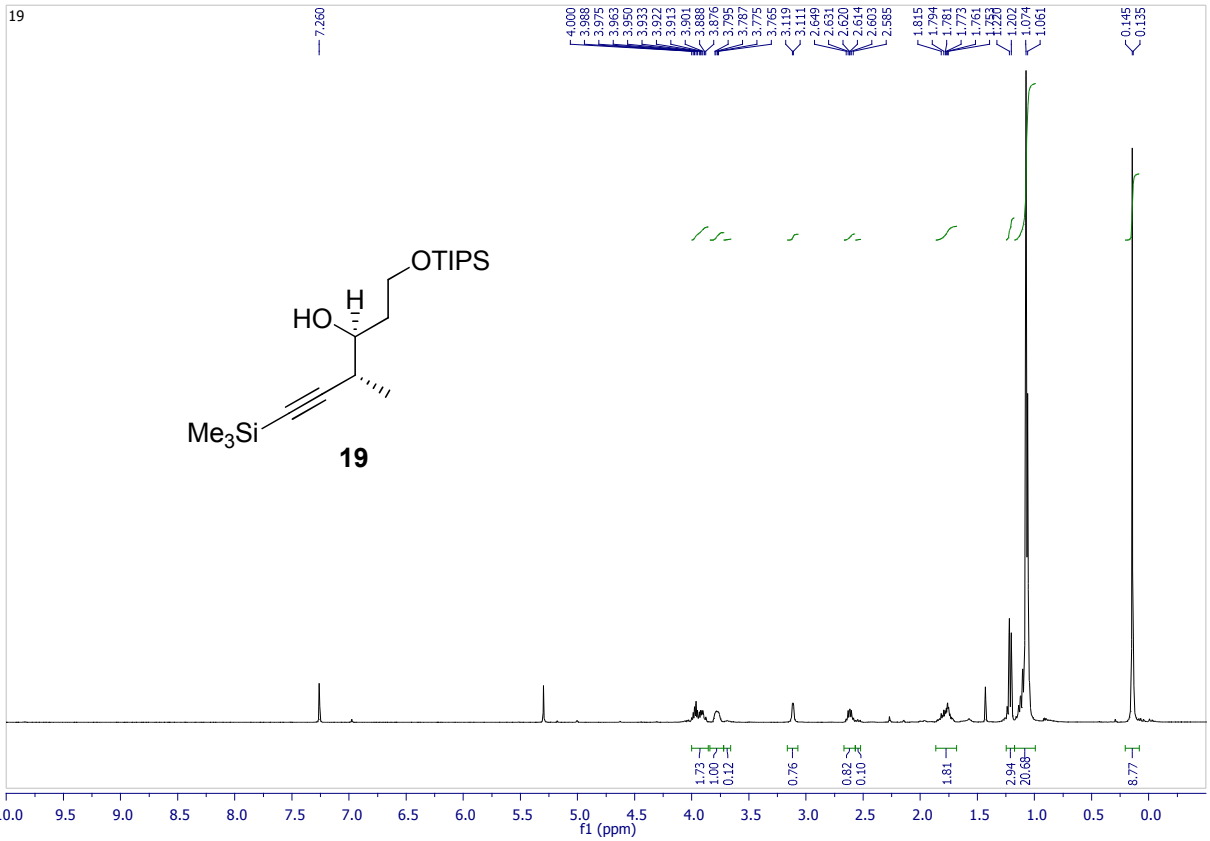

16a
OH
f1 (ppm)

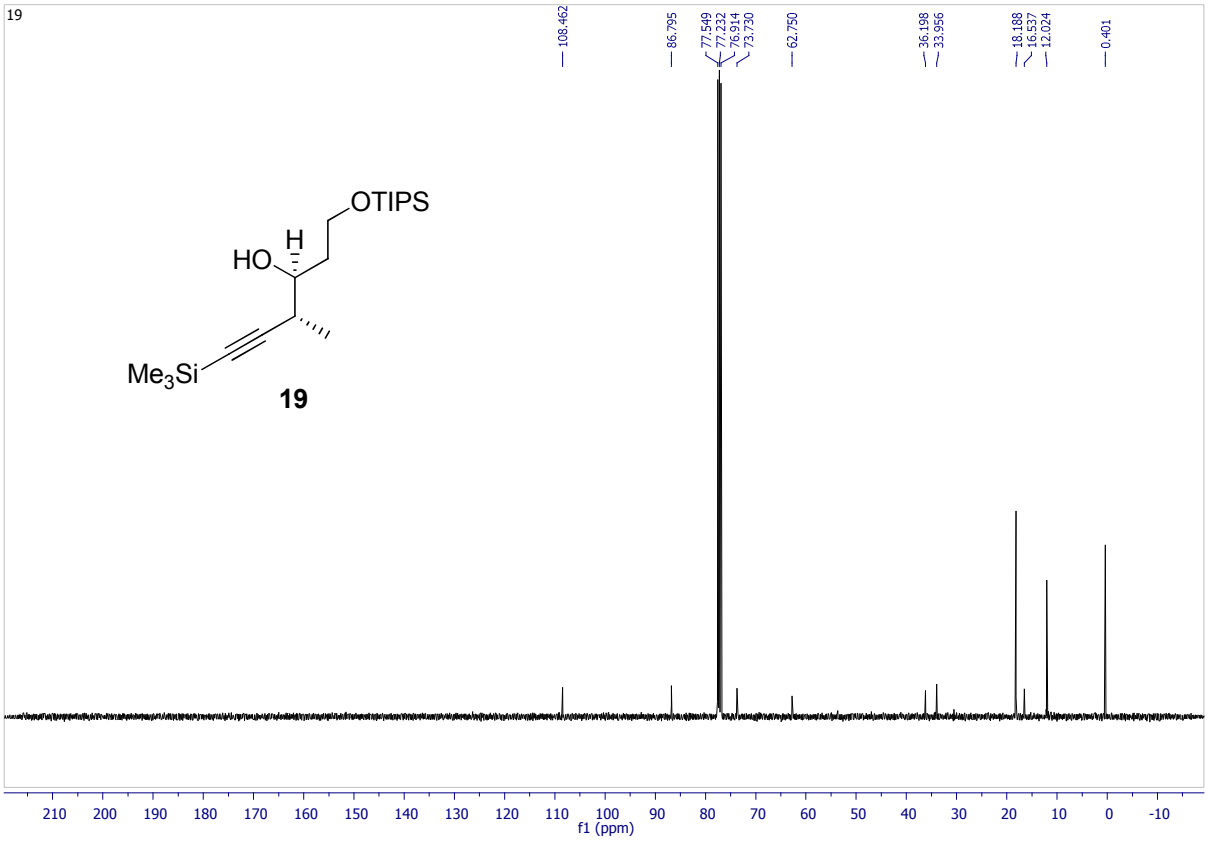

16a
OH
f1 (ppm)

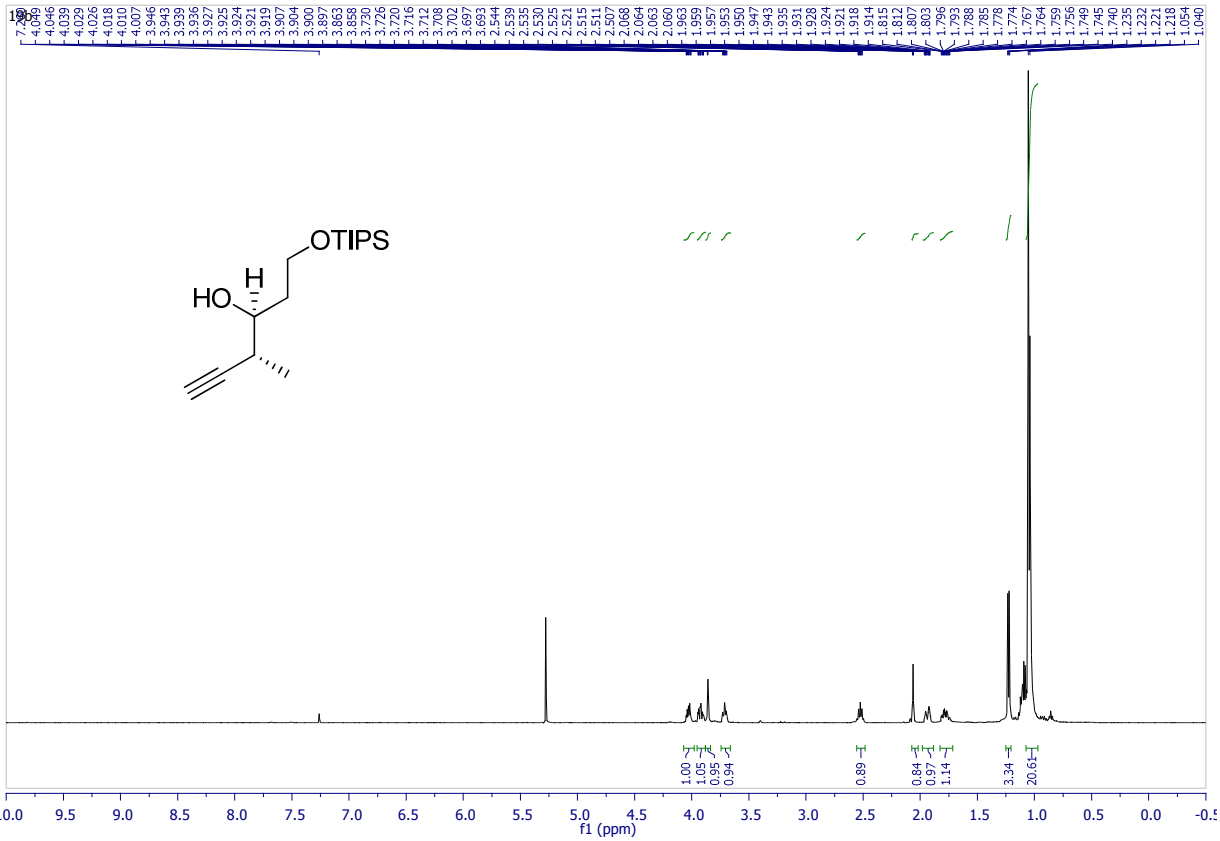

17a
7.26
4.53
4.51
4.49
4.48
2.12
1.44
1.42
0.15
OH
TMS
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

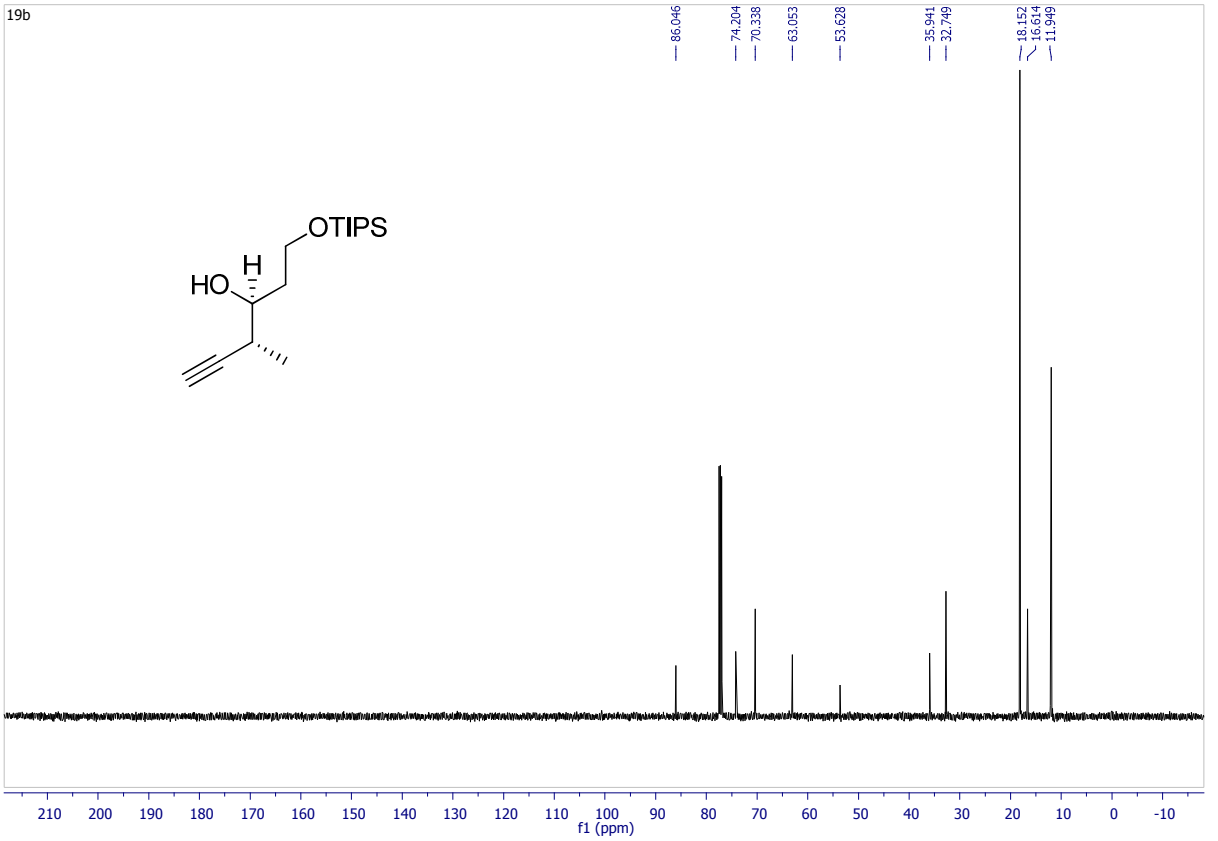

17
7.26
5.29
5.27
5.25
5.23
3.12
1.64
1.62
0.19
OMs
TMS
17
1.00
3.09
3.14
9.18
f1 (ppm)

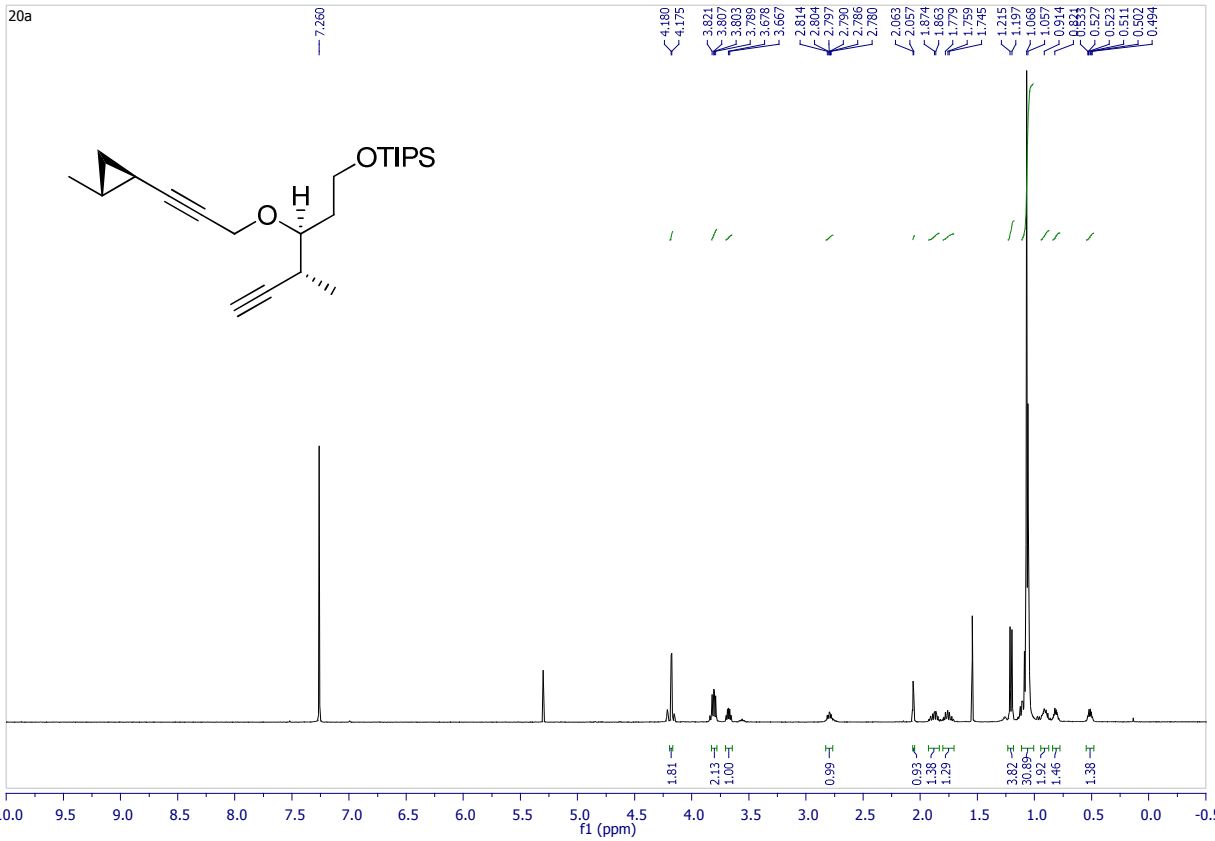

17
101.43
93.81
77.49
77.23
76.98
68.73
39.28
22.65
-0.30
OMs
TMS
17
f1 (ppm)

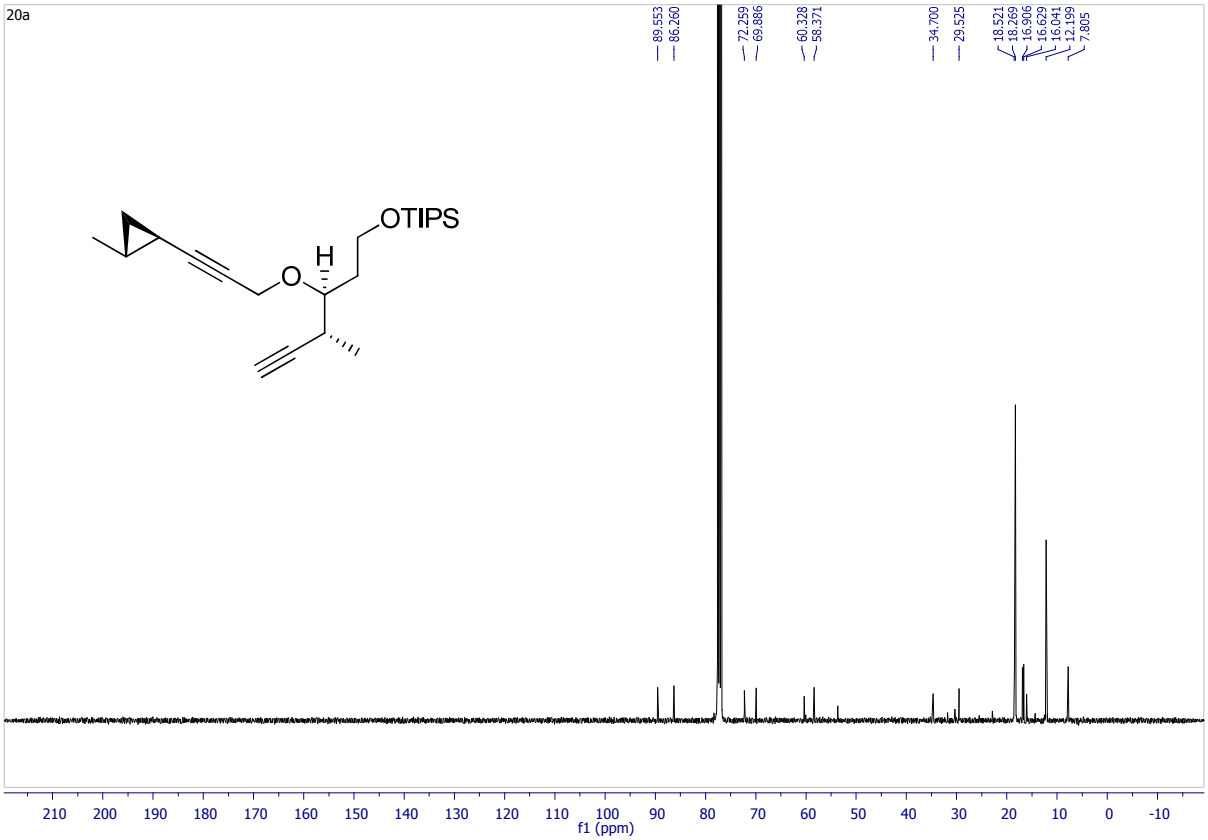

19
OTIPS
H
HO
Me3Si
19
f1 (ppm)

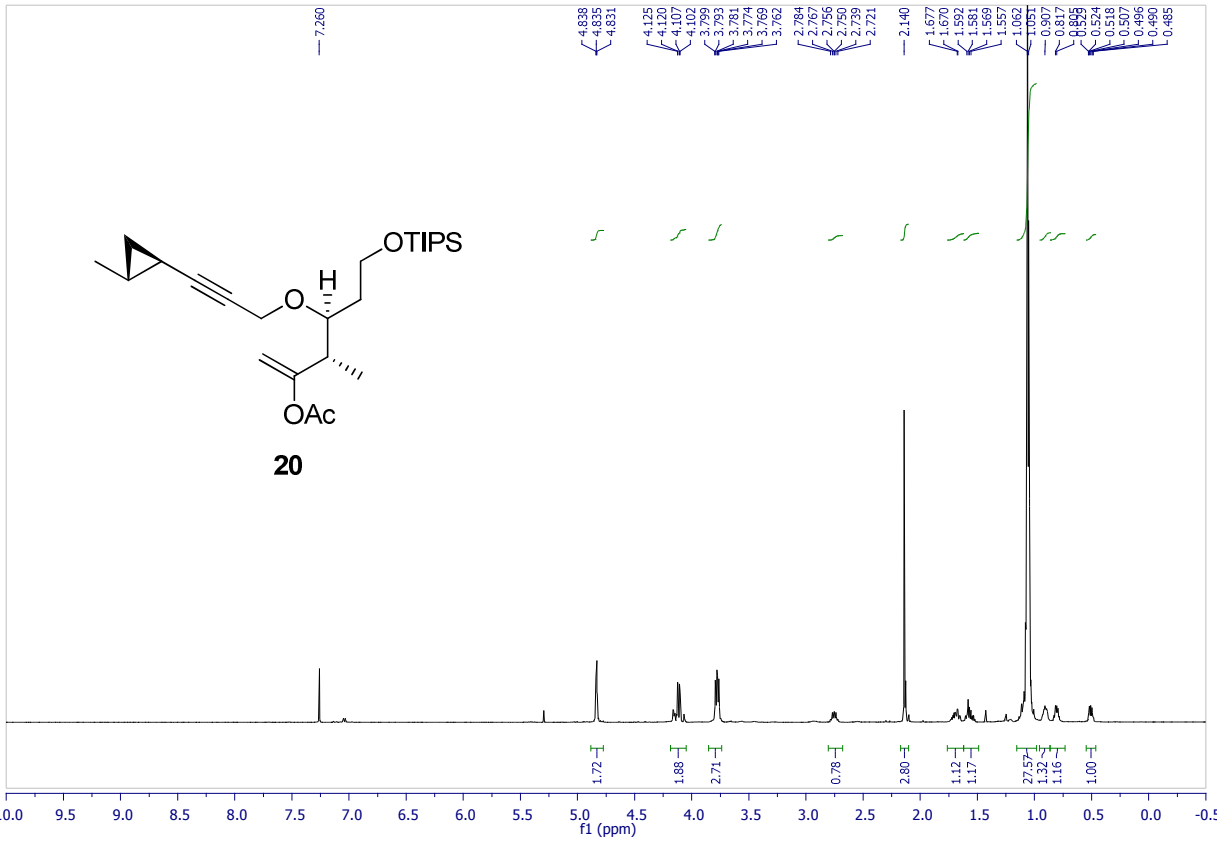

19
OTIPS
H
HO
Me3Si
19
f1 (ppm)

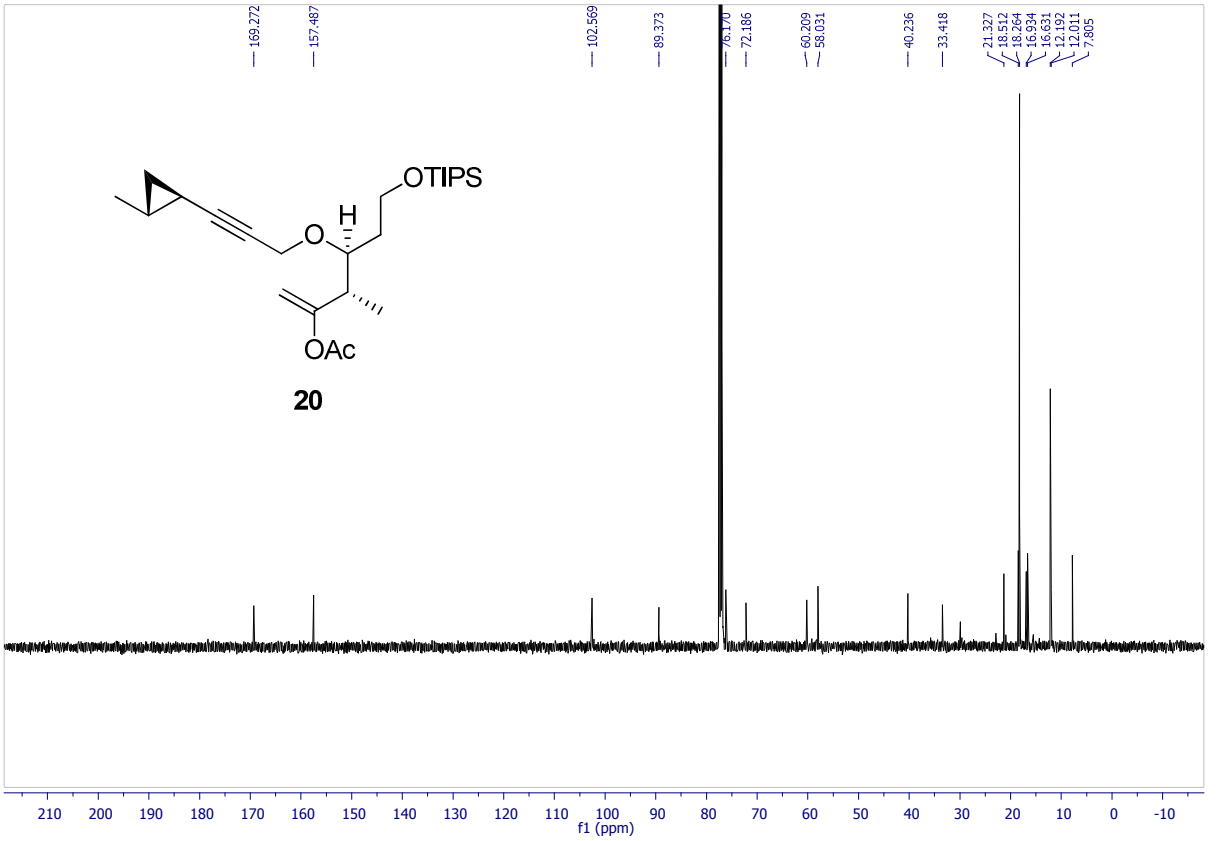

19b
OTIPS
H
HO
1.00
1.05
0.95
0.94
0.89
0.84
0.97
1.14
3.34
20.61
f1 (ppm)

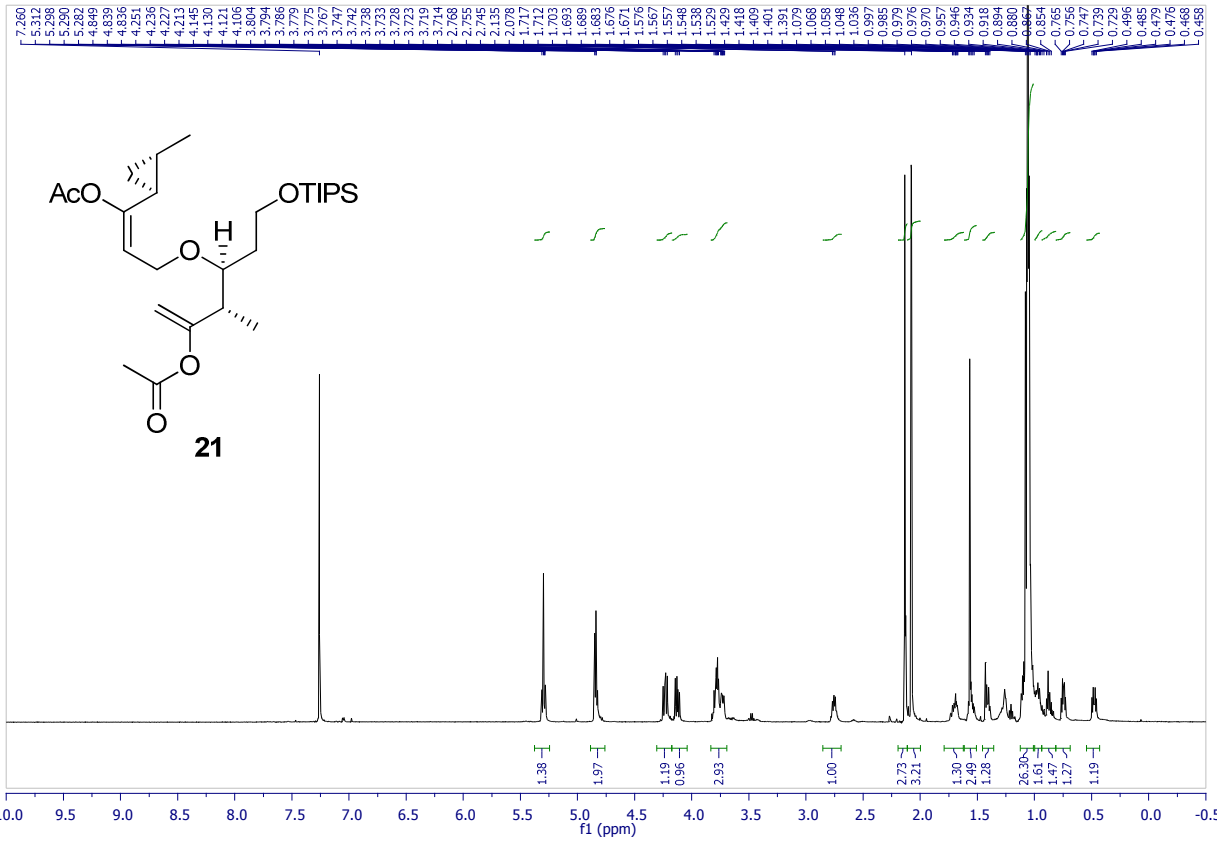

19b
86.046
74.204
70.338
63.053
53.628
35.941
32.749
18.152
16.614
11.949
OTIPS
H
HO
f1 (ppm)

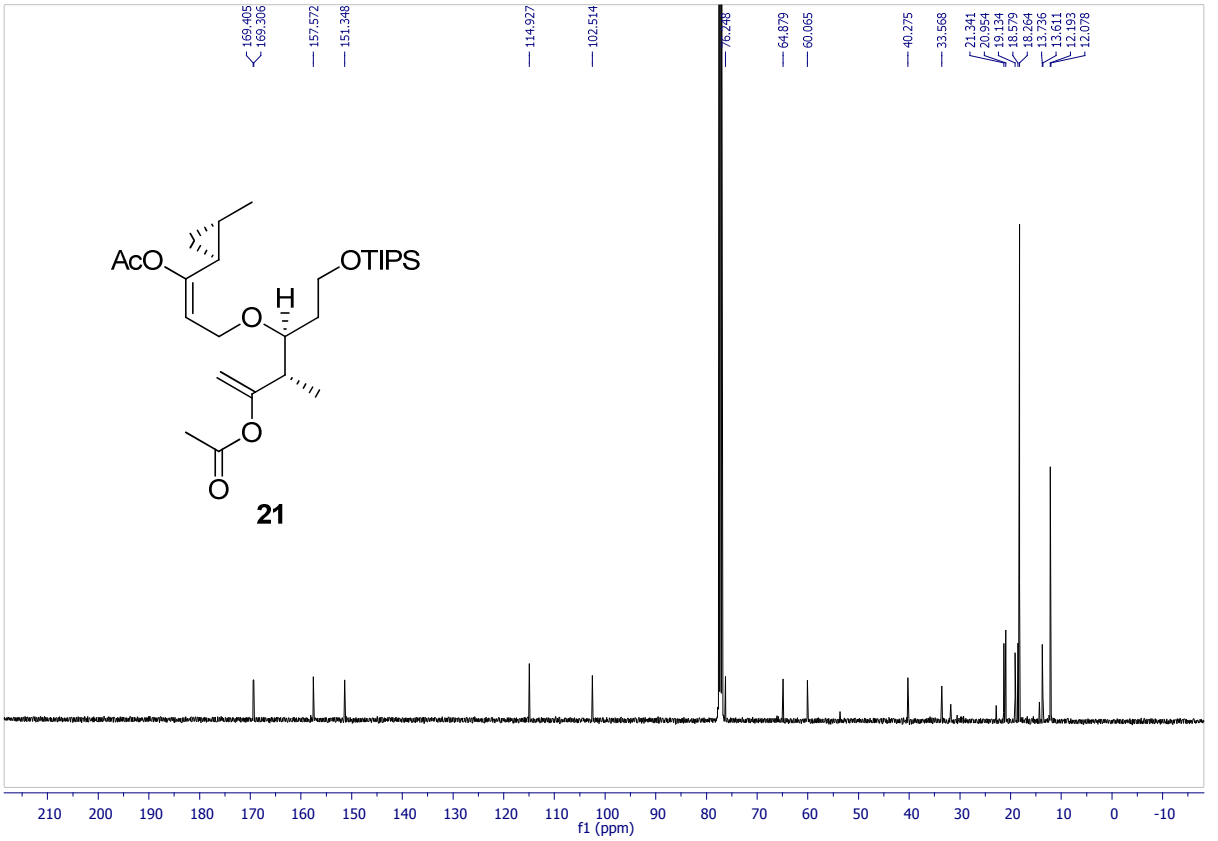

20a
OTIPS
H
O
f1 (ppm)

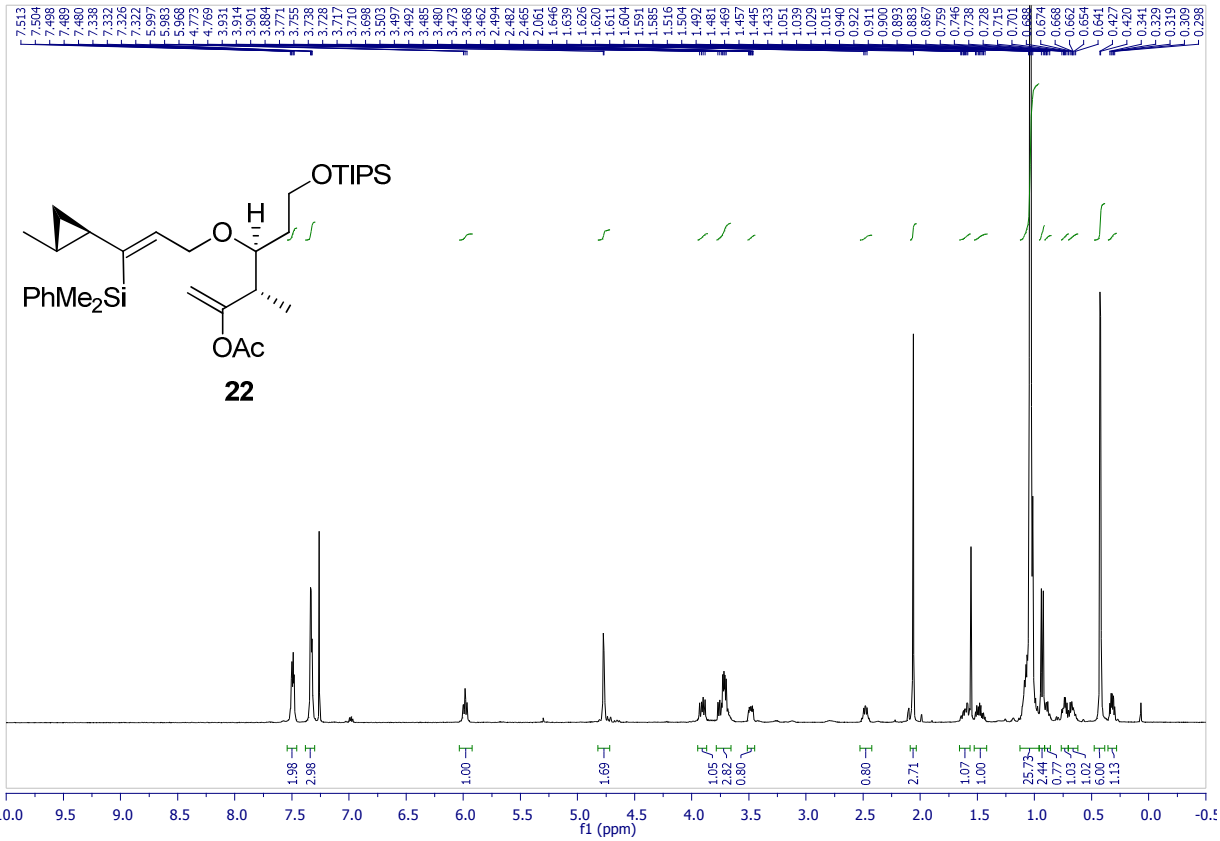

20a
OTIPS
H
O
f1 (ppm)

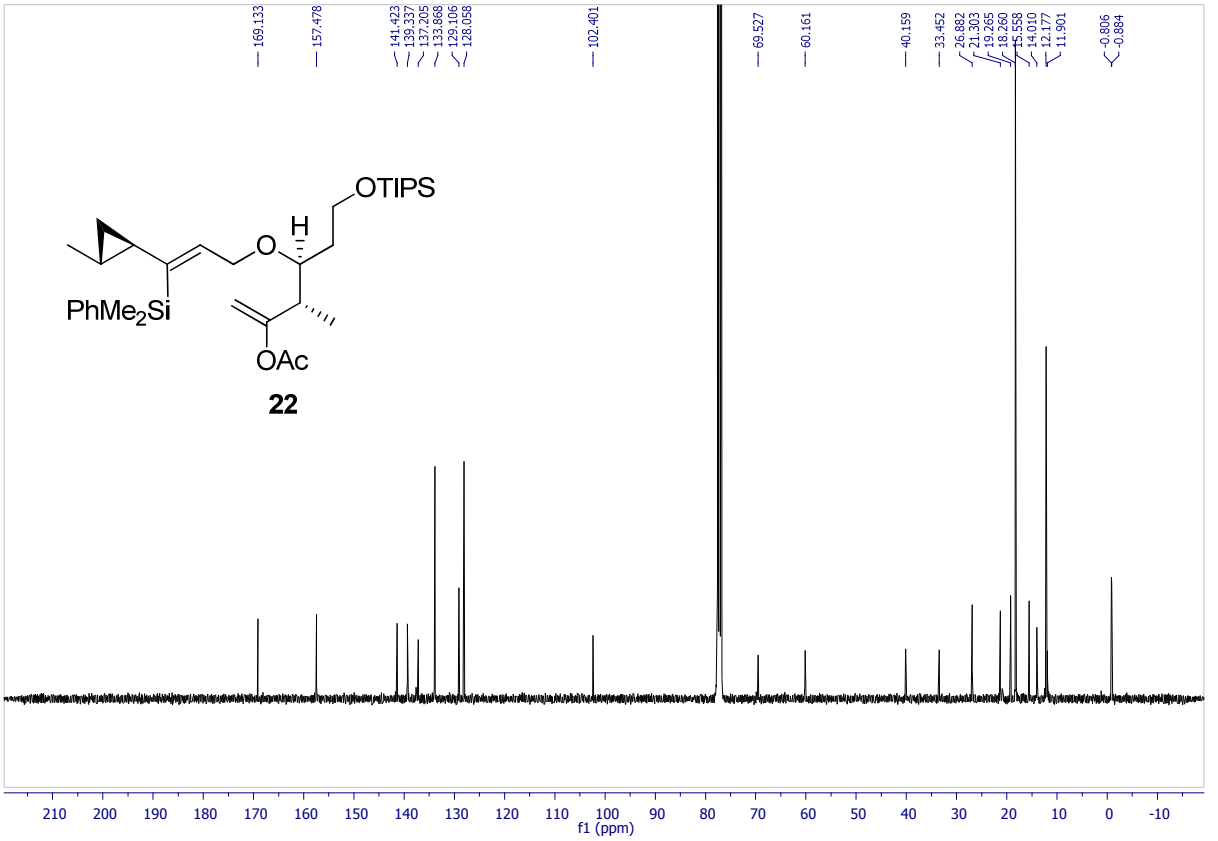

OTIPS
H
O
OAc
20
f1 (ppm)

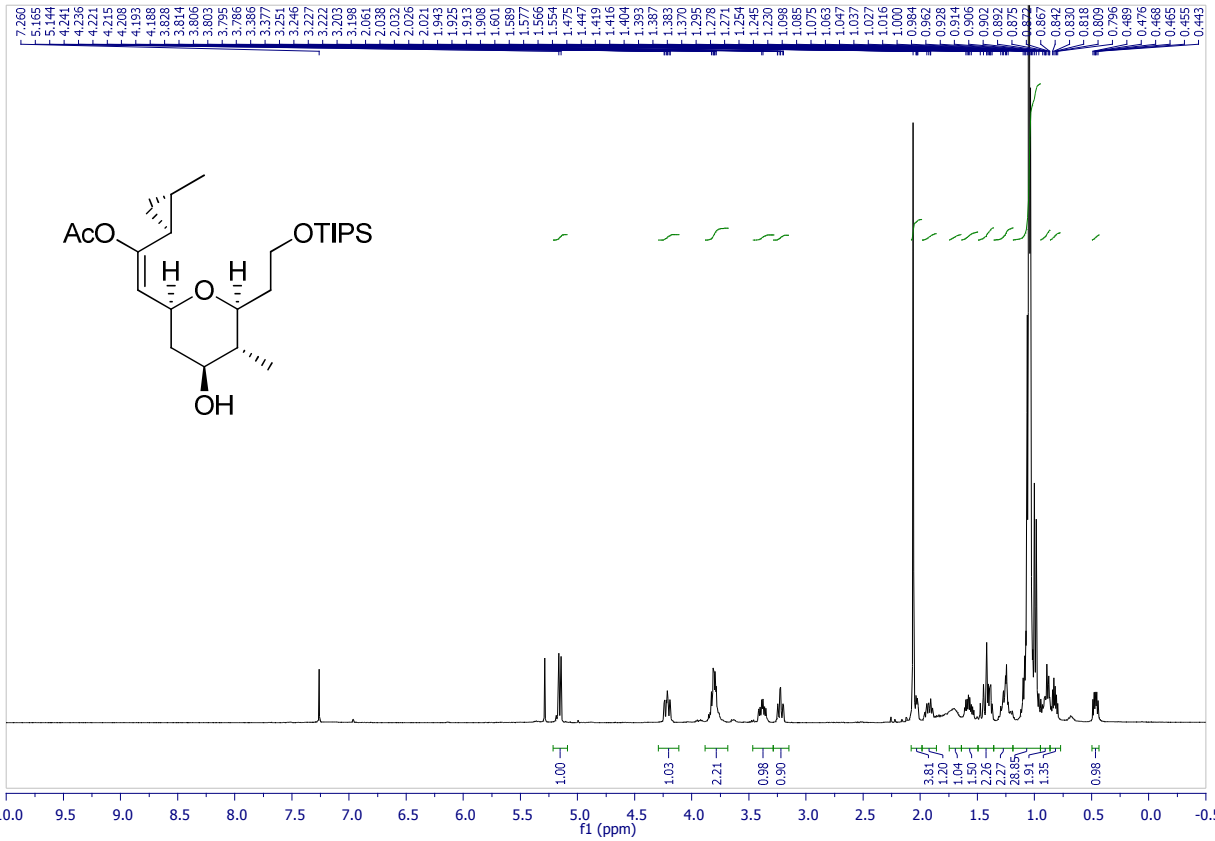

OTIPS
H
O
OAc
20
f1 (ppm)

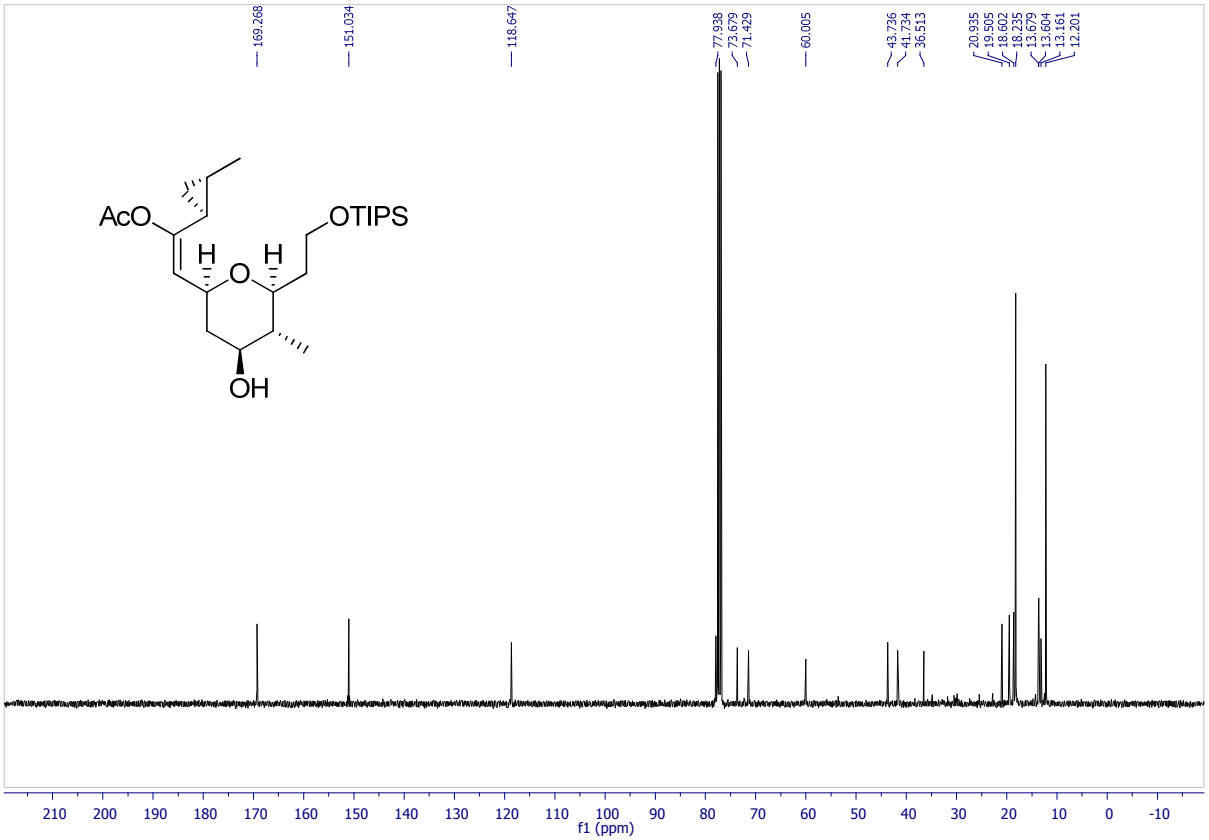

AcO
OTIPS
H
O
O
O
21
f1 (ppm)

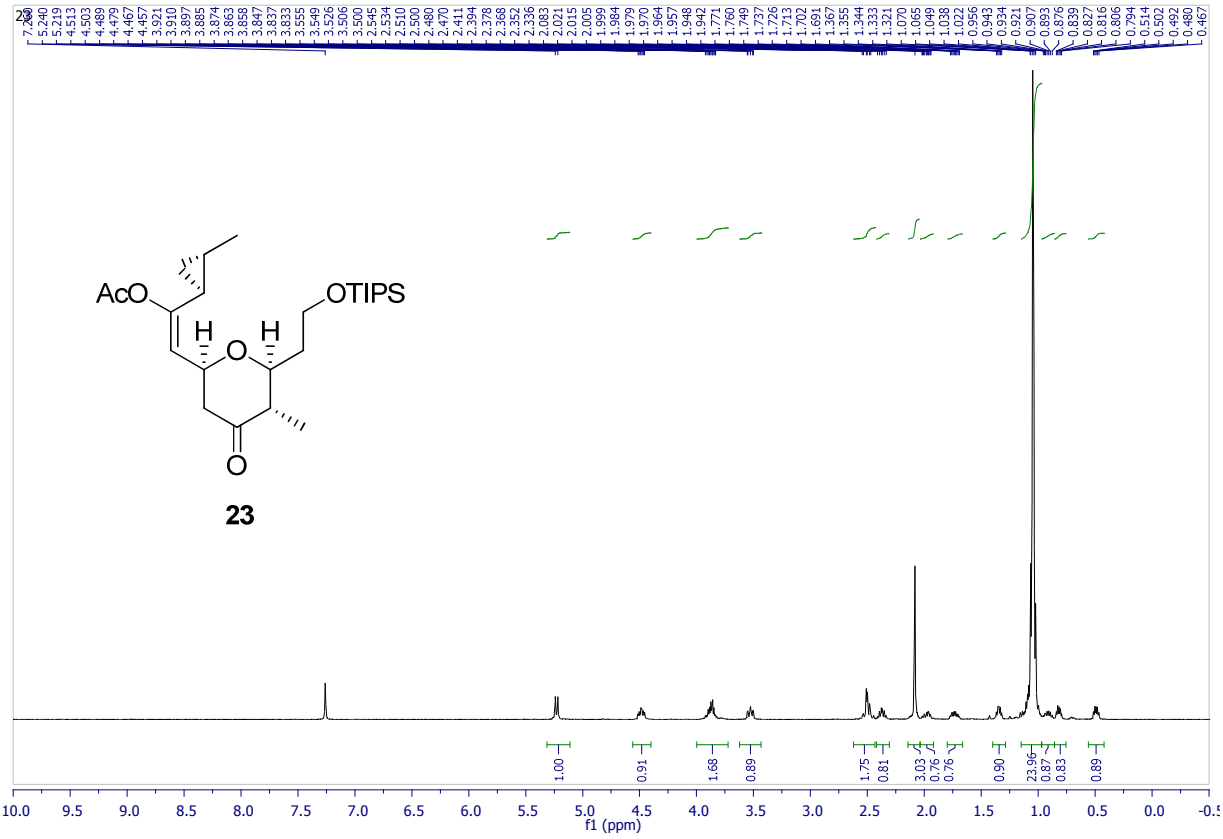

AcO
OTIPS
H
O
O
O
21
f1 (ppm)

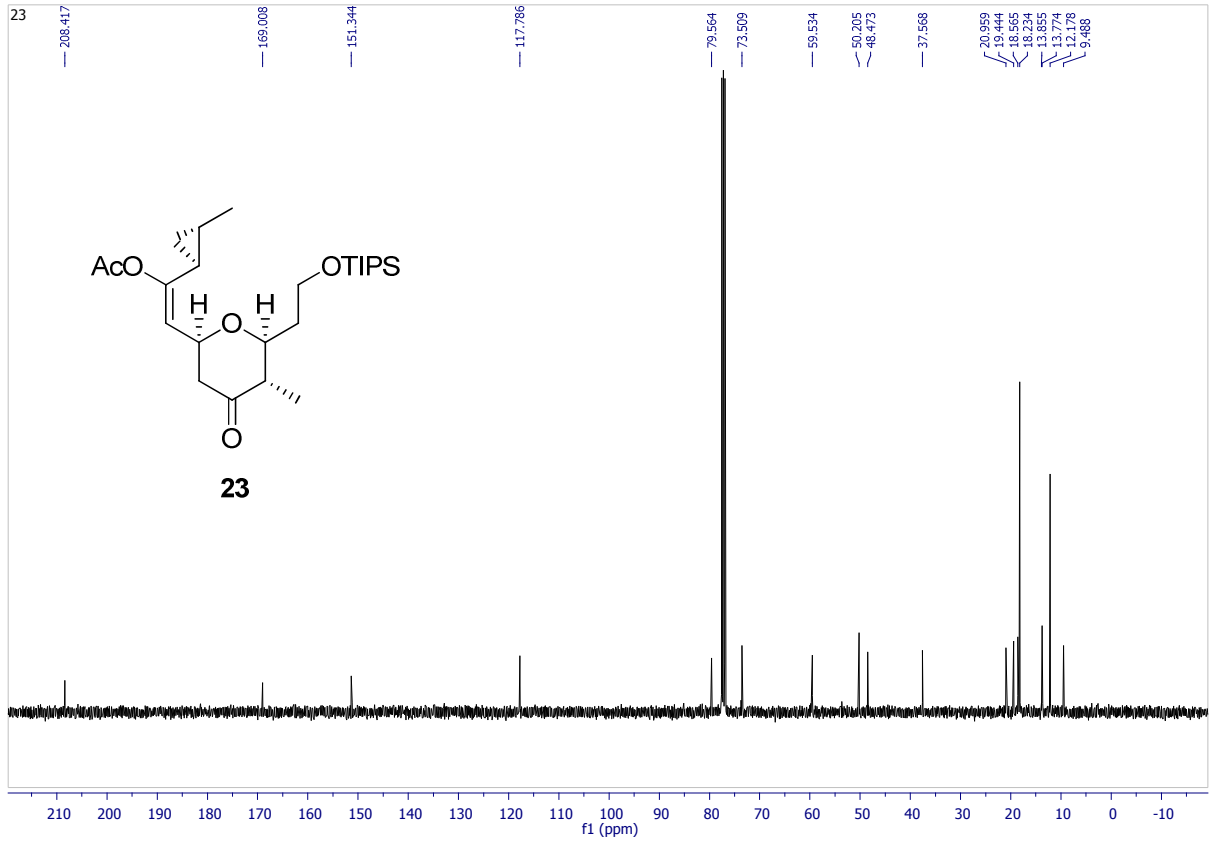

OTIPS
H
O
PhMe2Si
OAc
22
f1 (ppm)

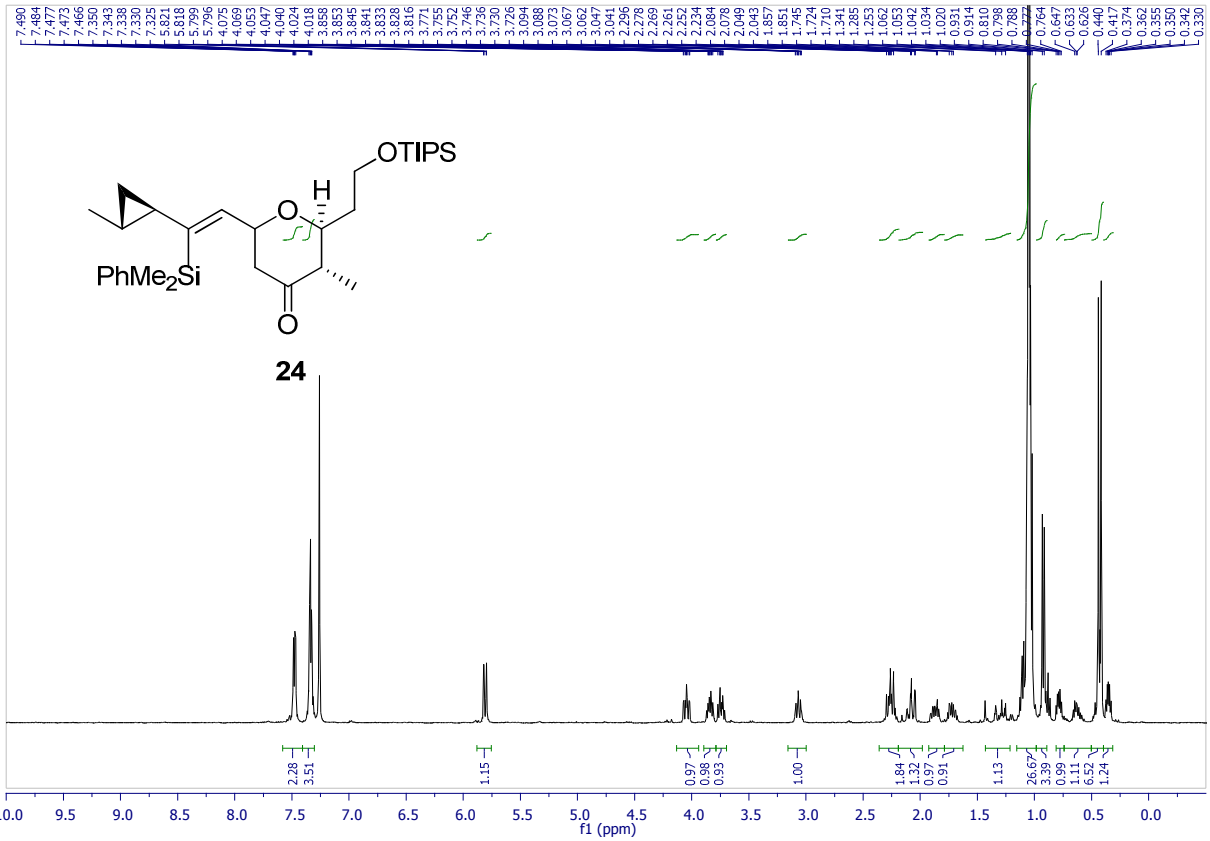

OTIPS
H
O
PhMe2Si
OAc
22
f1 (ppm)

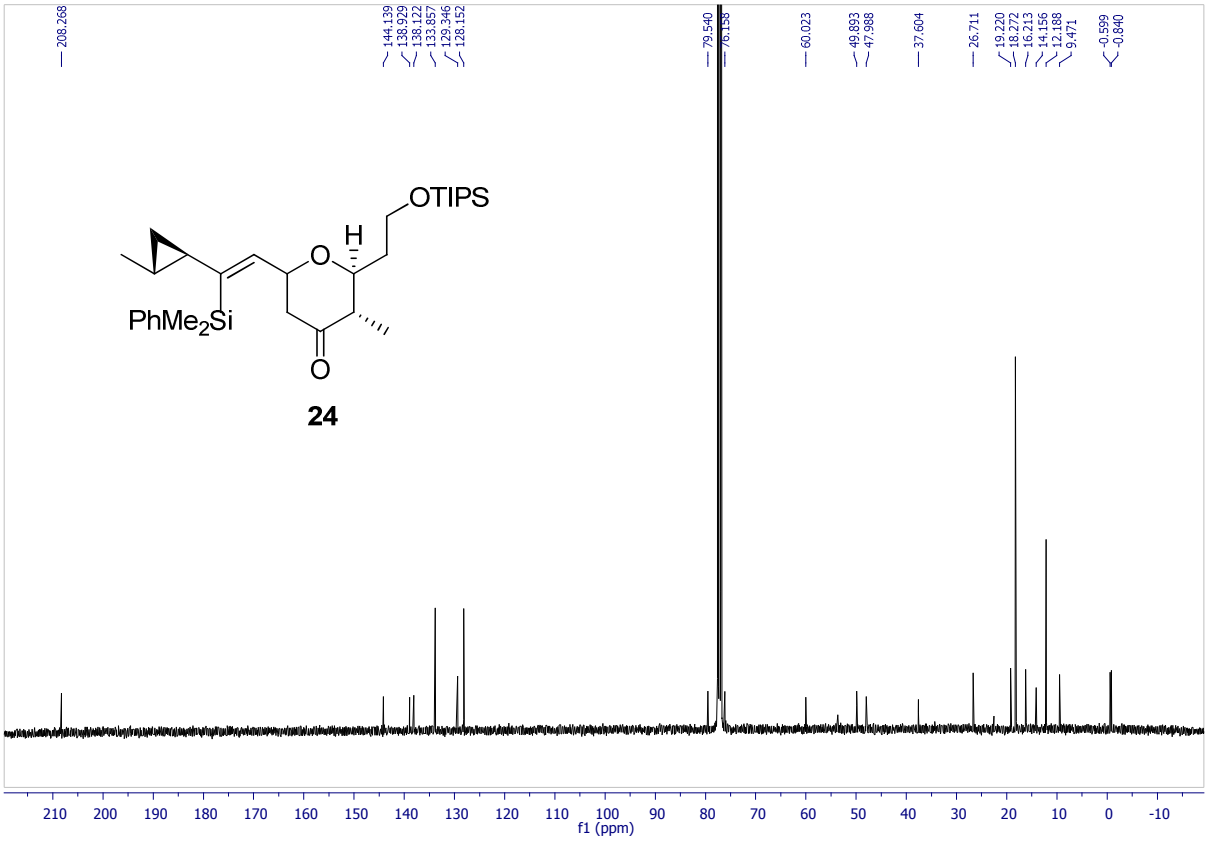

AcO
OTIPS
H
O
H
OH
f1 (ppm)

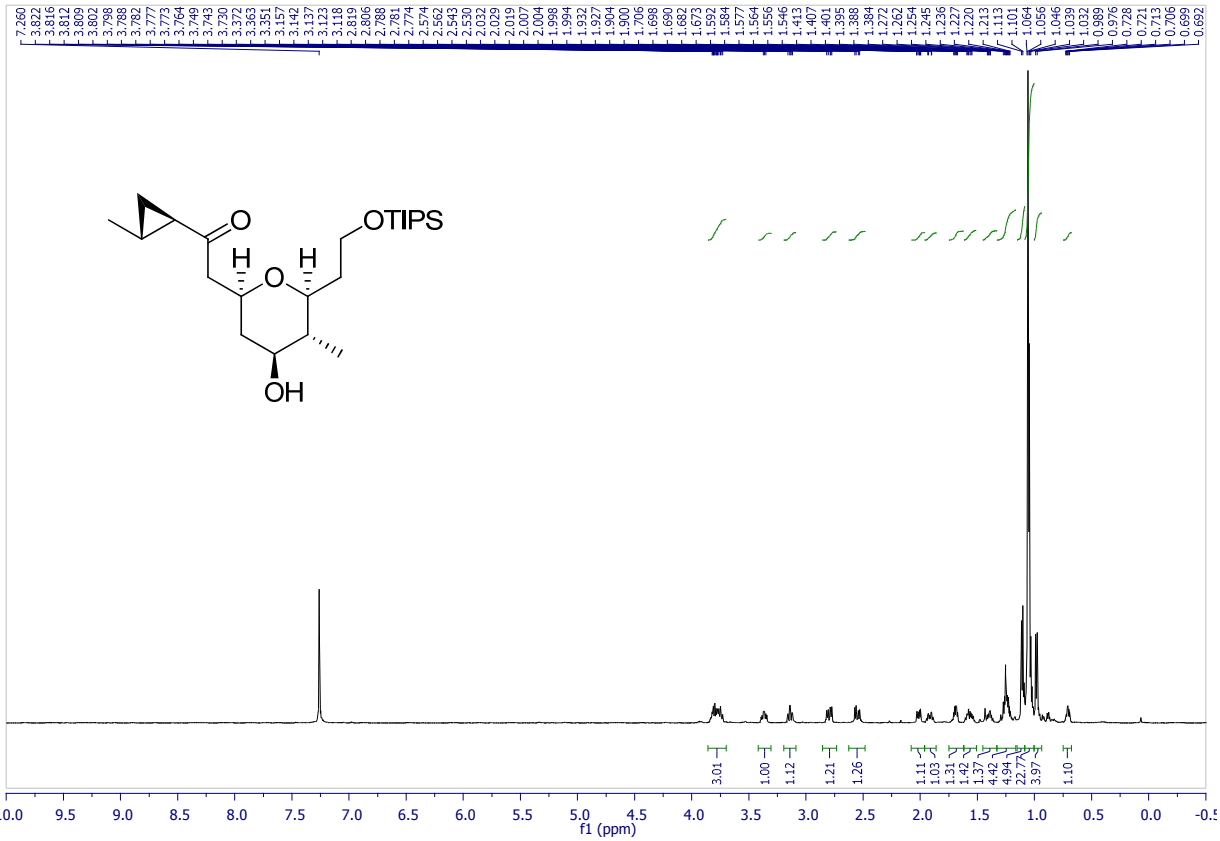

AcO
OTIPS
H
O
H
OH
f1 (ppm)

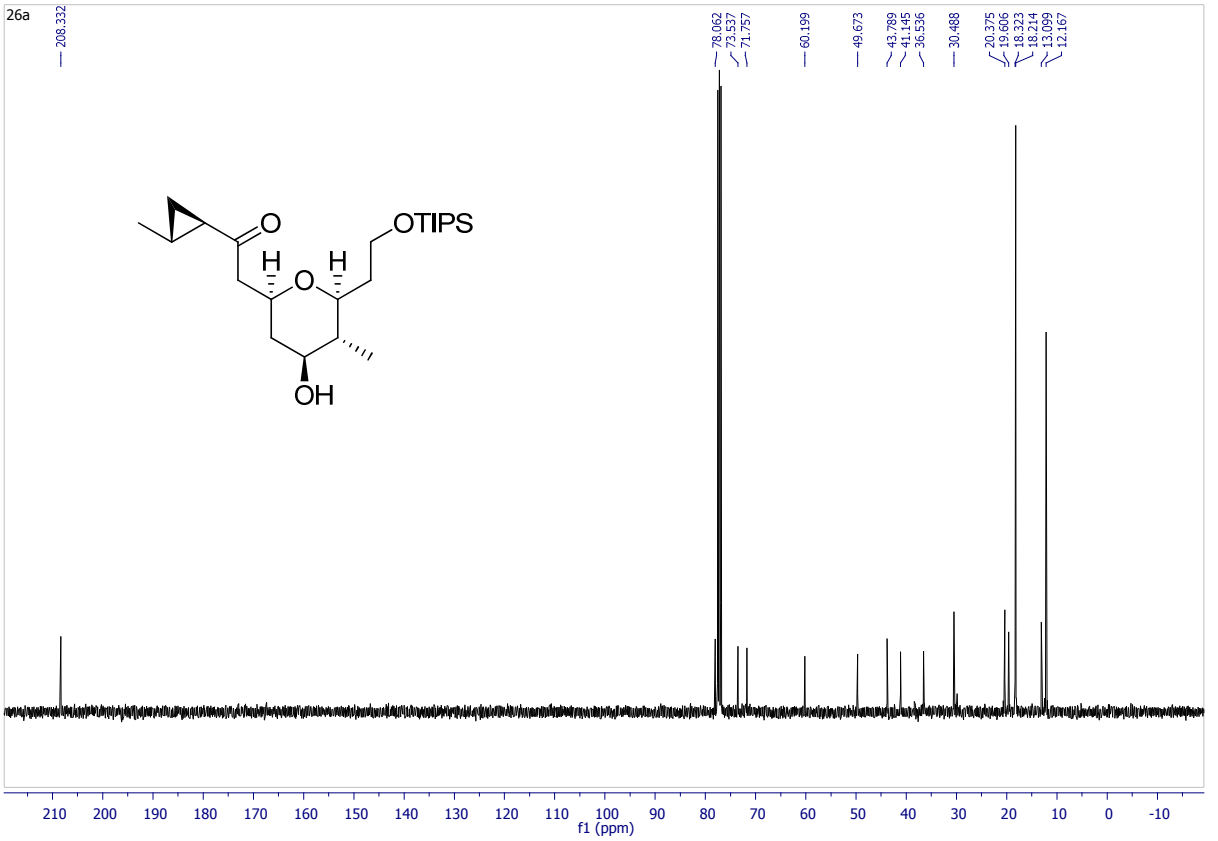

AcO
OTIPS
H
O
H
O
23
1.00
0.91
1.68
0.89
1.75
0.81
3.03
0.76
0.76
0.90
23.96
0.87
0.83
0.89
f1 (ppm)

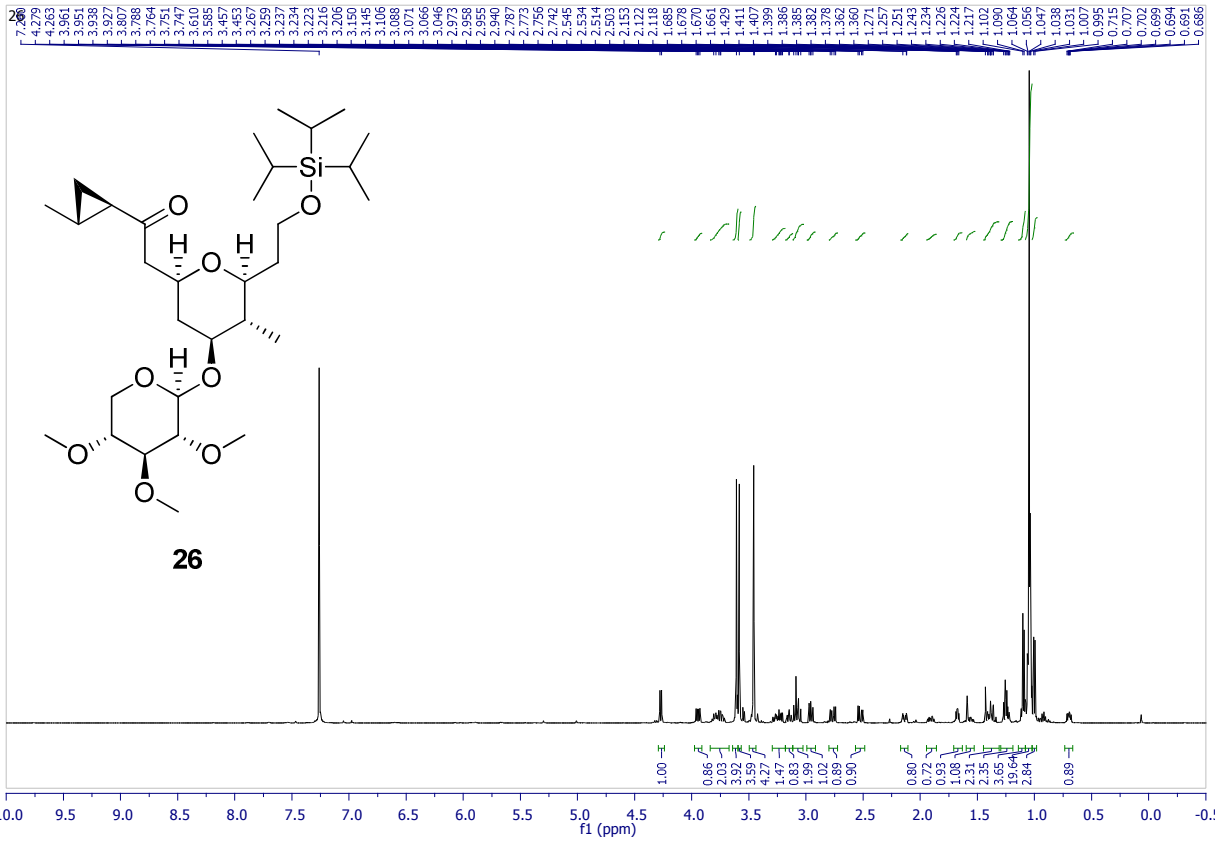

23
208.417
169.008
151.344
117.786
79.564
73.509
59.534
50.205
48.473
37.568
20.959
19.444
18.565
18.234
13.855
13.774
12.178
9.488
AcO
OTIPS
H
O
H
O
23
f1 (ppm)

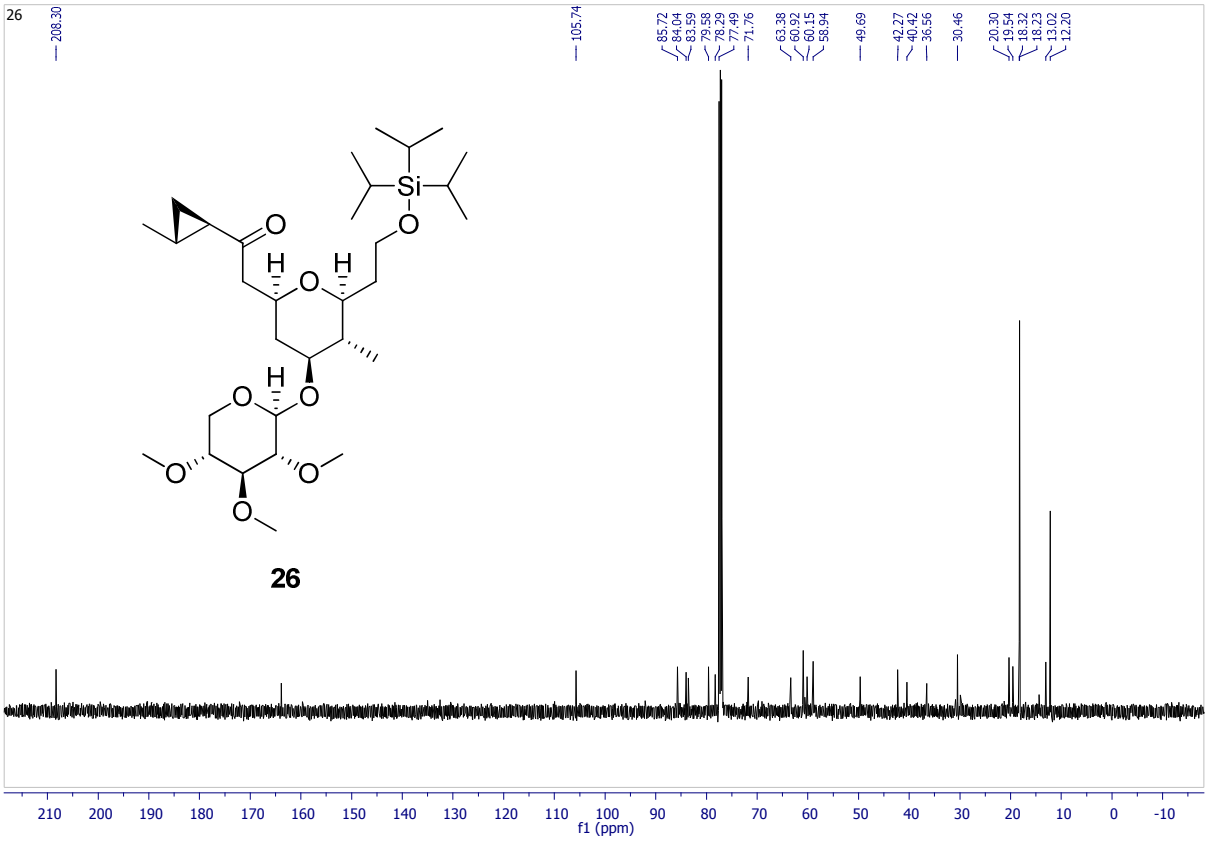

OTIPS
H
O
PhMe2Si
O
24
f1 (ppm)

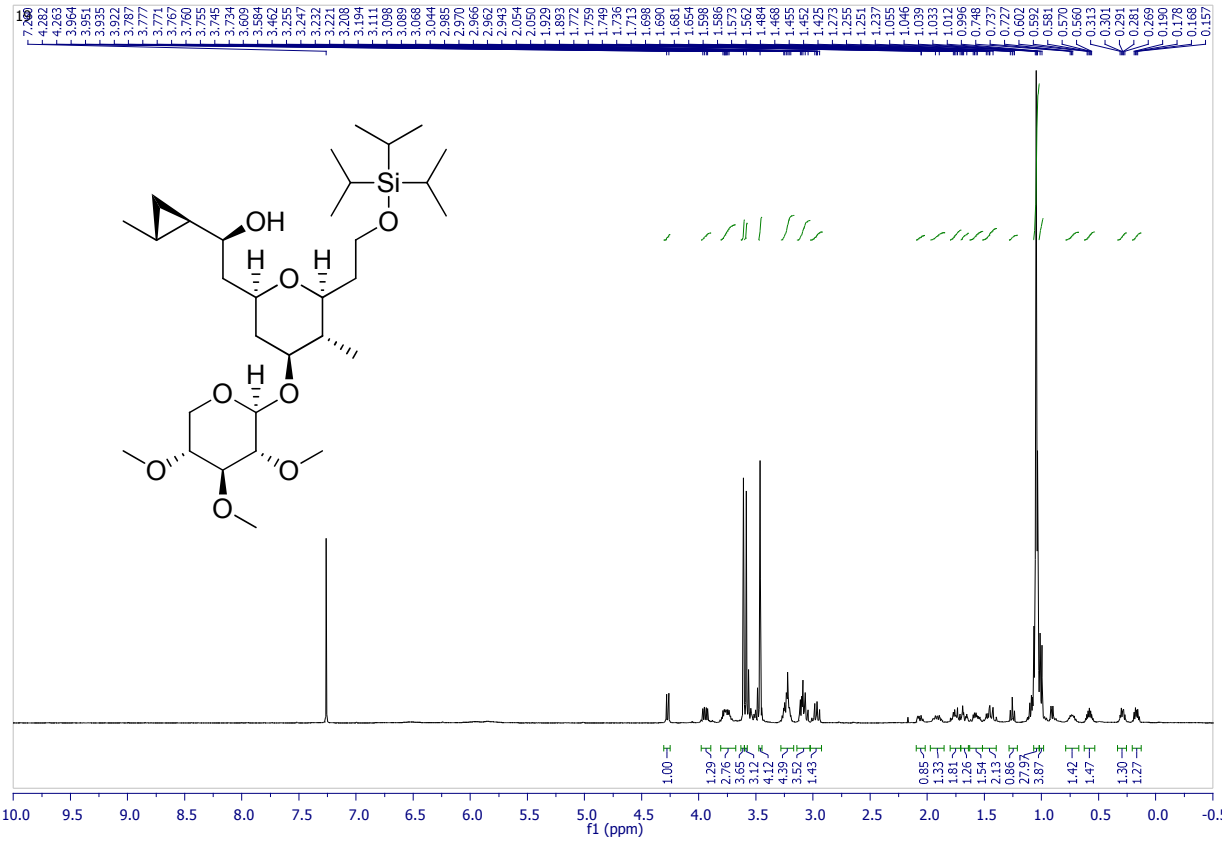

OTIPS
H
O
PhMe2Si
O
24
f1 (ppm)

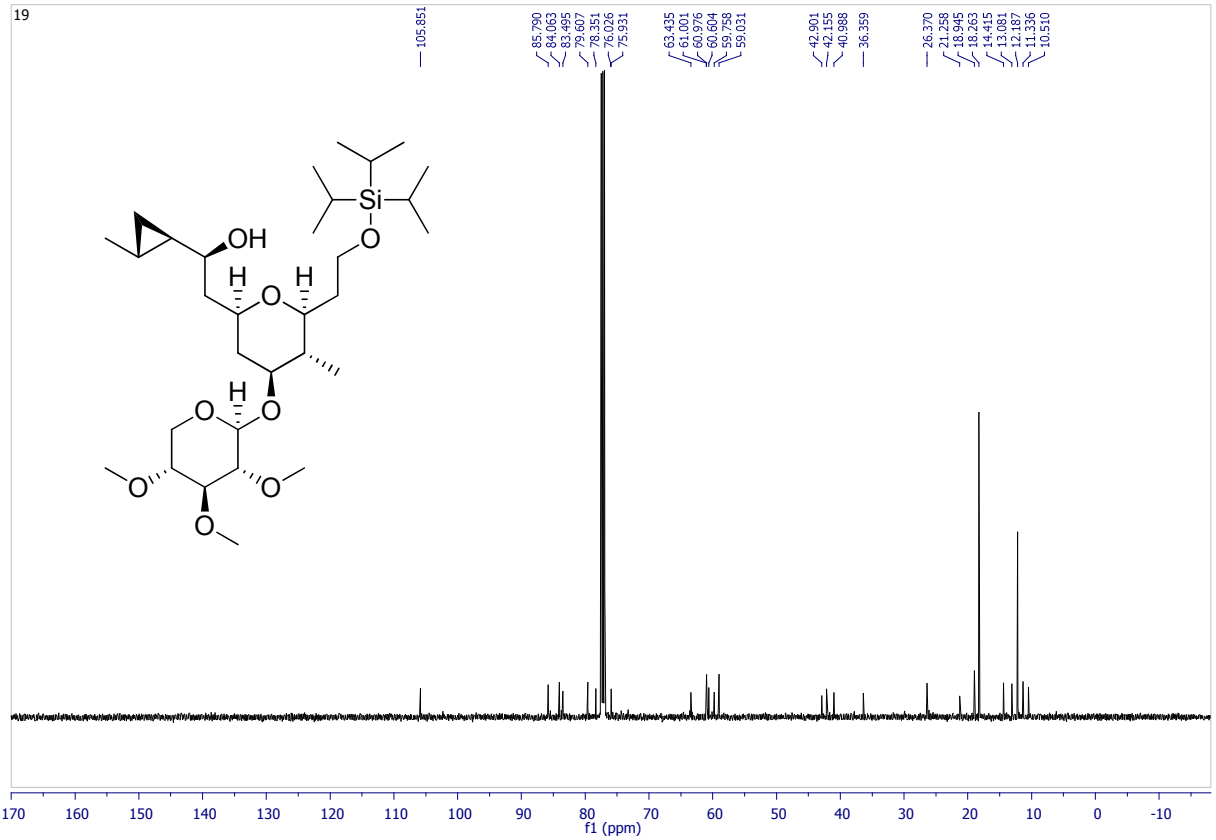

O
OTIPS
H
H
O
OH
f1 (ppm)

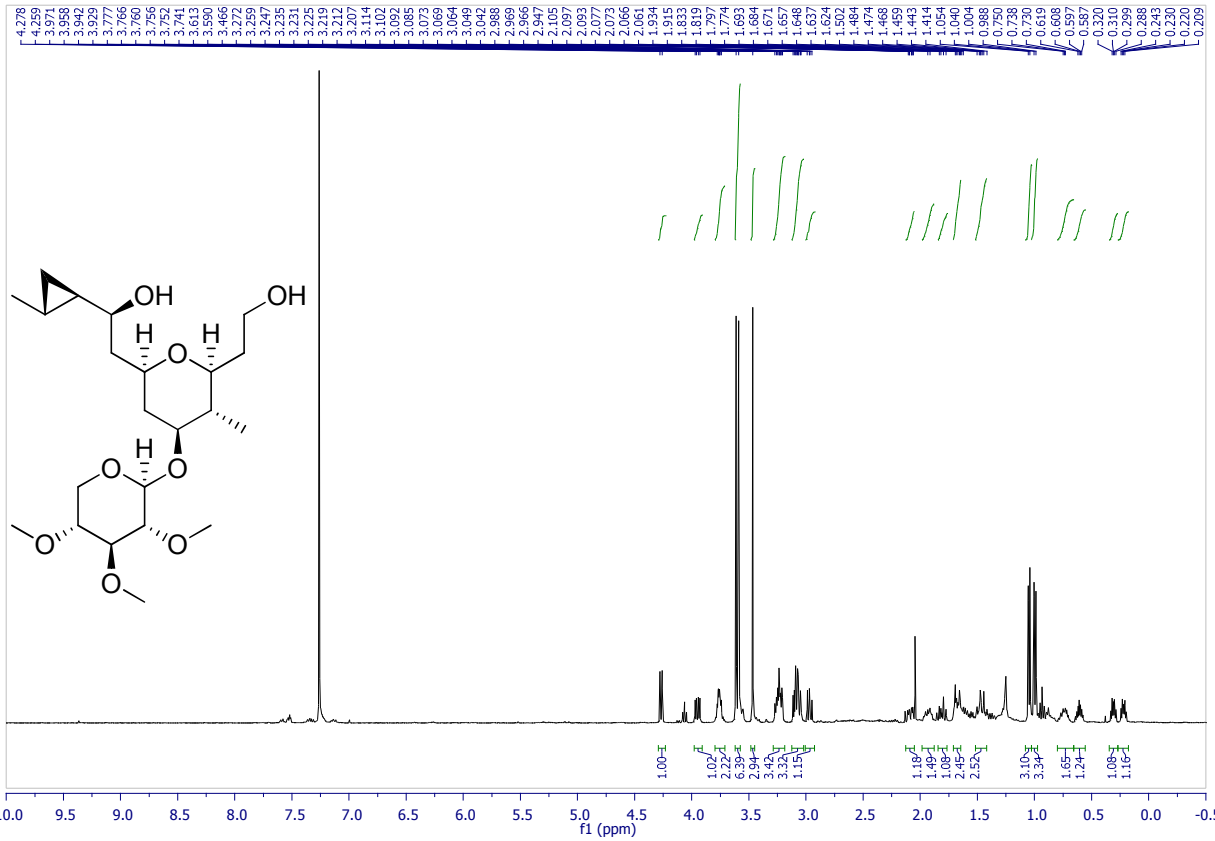

26a
O
OTIPS
H
H
O
OH
f1 (ppm)

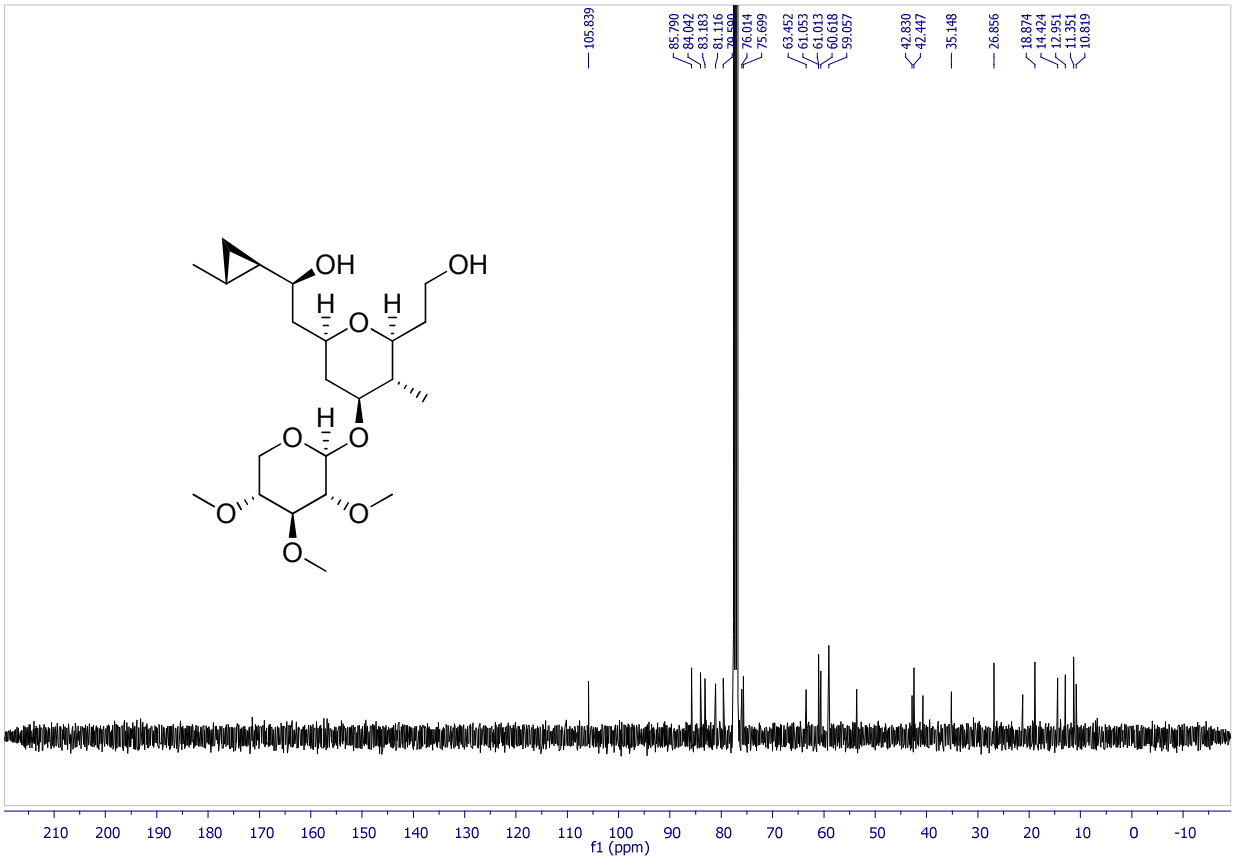

26
26
f1 (ppm)

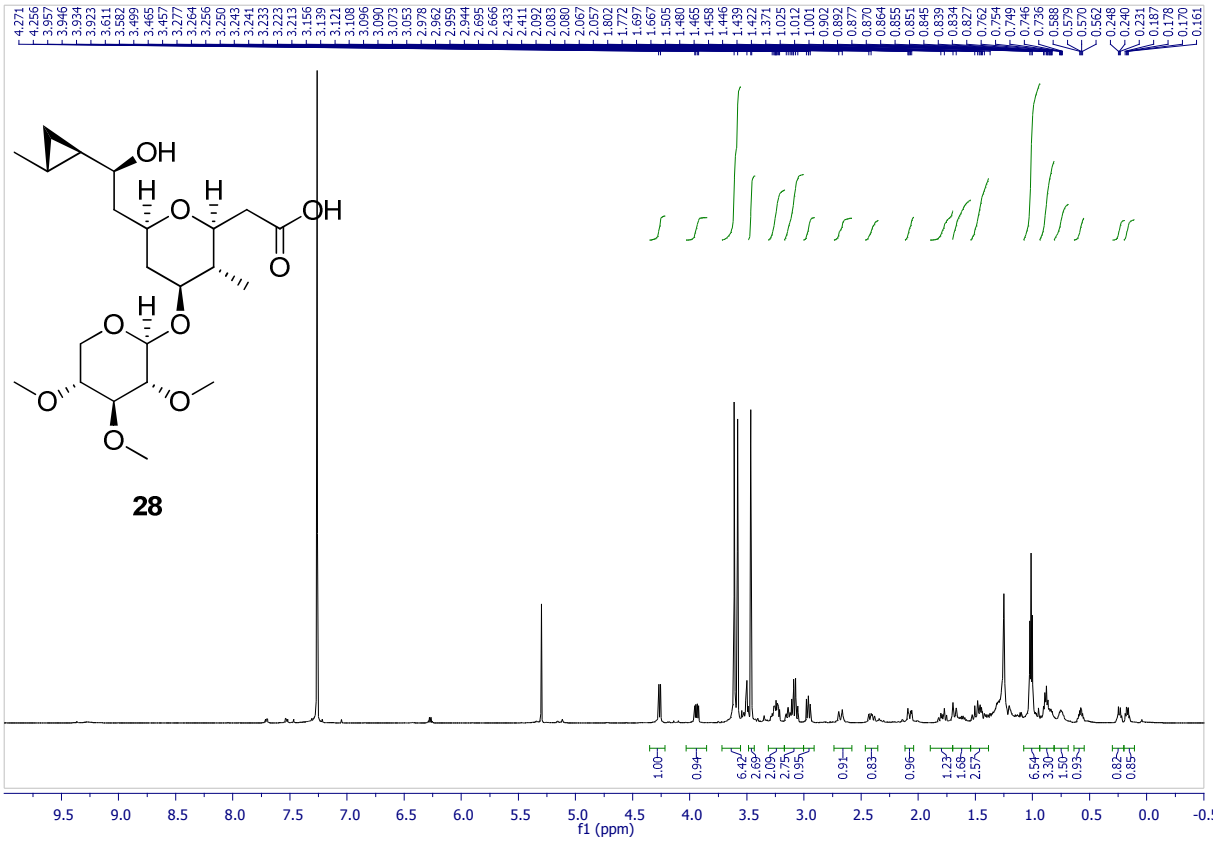

26
26
f1 (ppm)

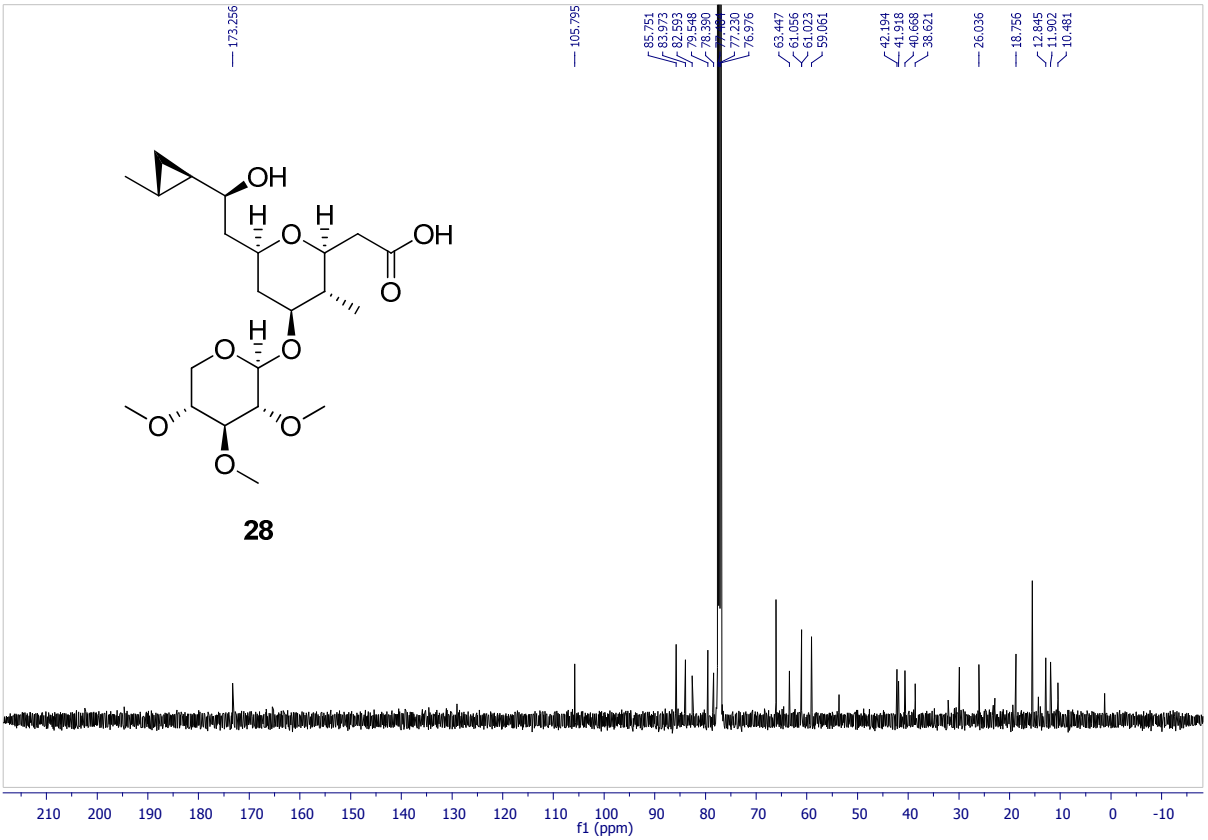

19
OH
Si
O
H
O
H
O
O
O
O
O
f1 (ppm)

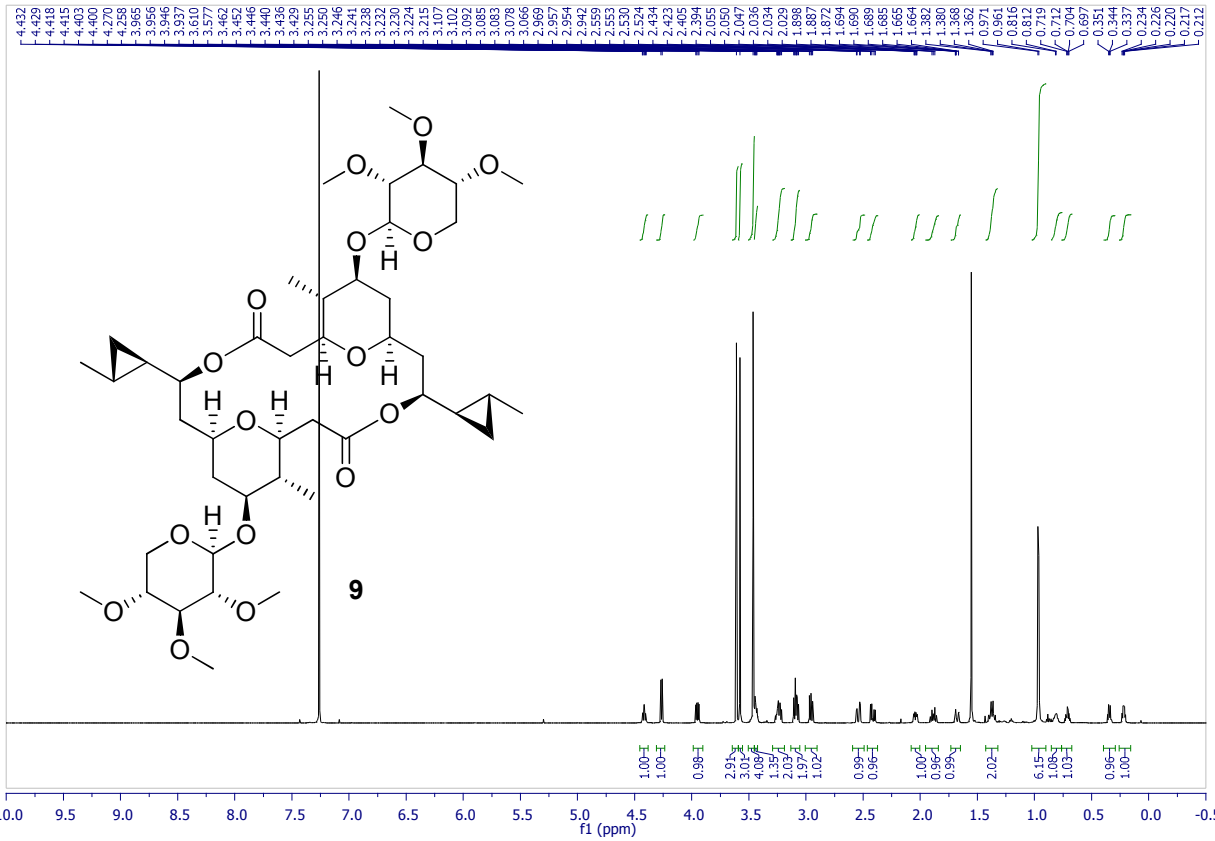

19
OH
Si
O
H
O
H
O
O
O
O
O
f1 (ppm)


OH
OH
H
H
O
H
O
O
O
O
O
O
f1 (ppm)


OH
OH
H
H
O
H
O
O
O
O
O
f1 (ppm)


OH
H
H
O
OH
O
H
O
O
O
O
O
28
f1 (ppm)


OH
H
H
O
OH
O
H
O
O
O
O
28
f1 (ppm)


9
f1 (ppm)

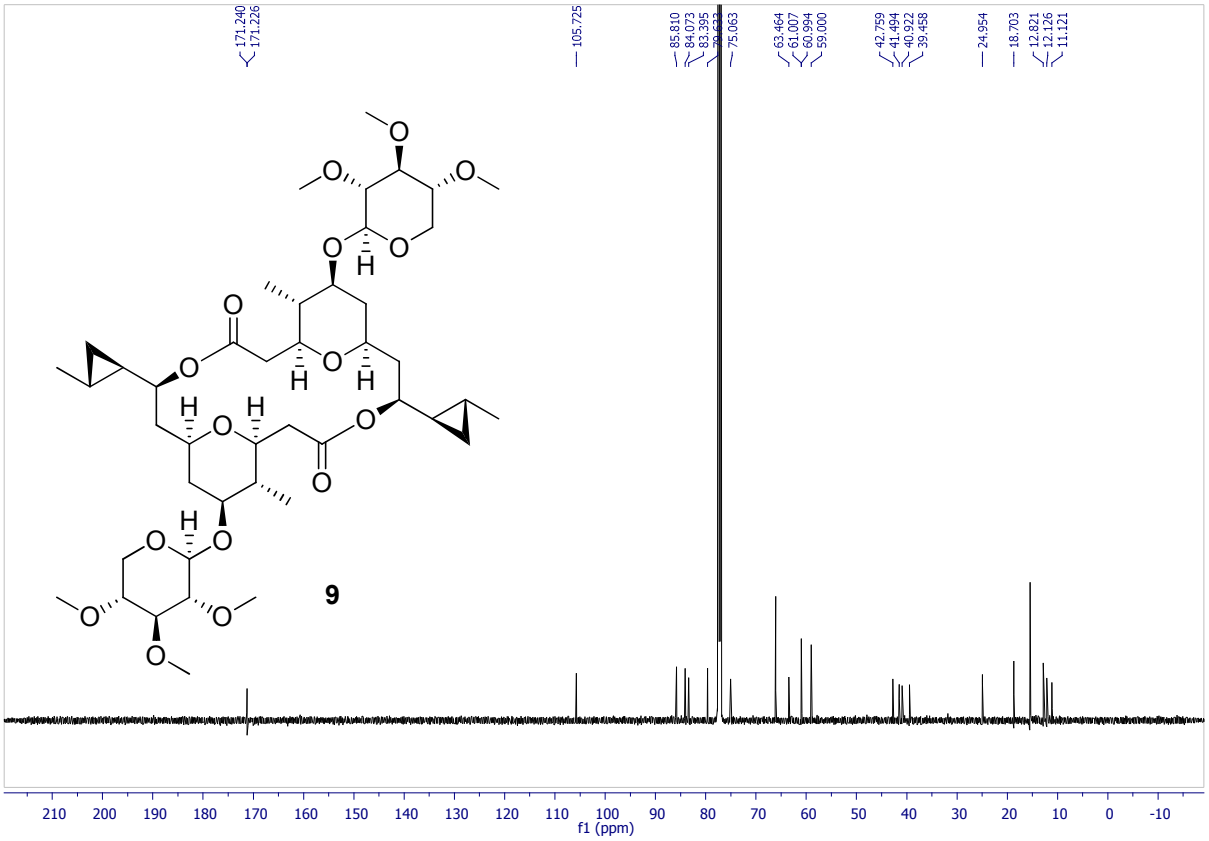
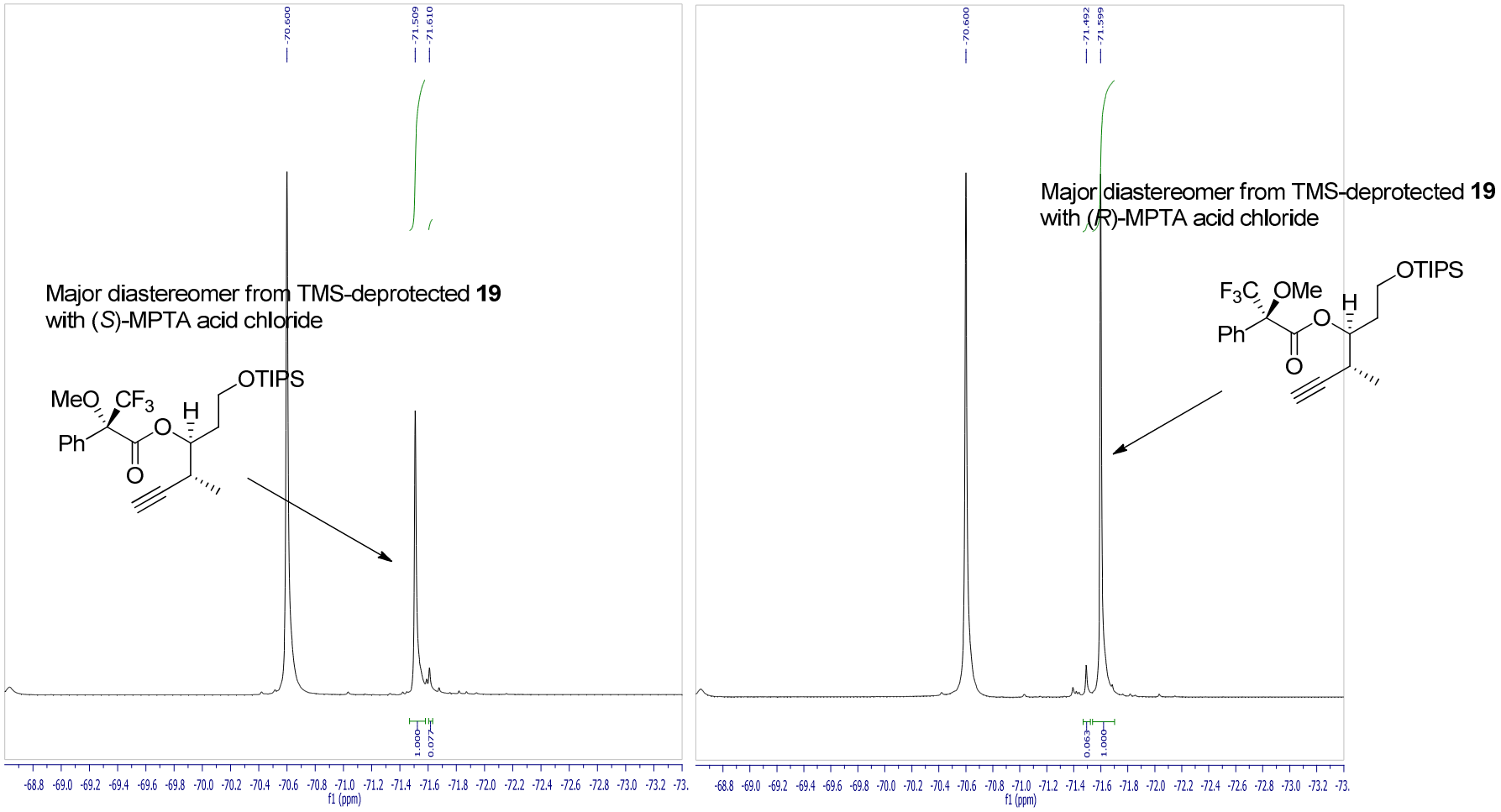

9
f1 (ppm)

Fig 1. HPLC traces for conjugate addition product of 14: Enantioenriched sample (pink) and racemic mixture (black)

Ee was determined to be >90% by chiral HPLC analysis using a Phenomenex Lux 5µ Cellulose-3 column (250 x 4.60 mm) with isopropanol/Hexane (0.5/95.5, v/v); 25 °C over 30 min; 0.7mL/ min; retention times (min): 10.2 min (*S*-addition product), 10.5 min (*R*-addition product).



The e.r. of this material was found to be > 85:15 by ^{19}F NMR analysis. [δ-71.49 (minor) and δ-71.60 (major), in $CDCl_3$] of the (*R*)-Mosher ester of TMS-deprotected **19**.

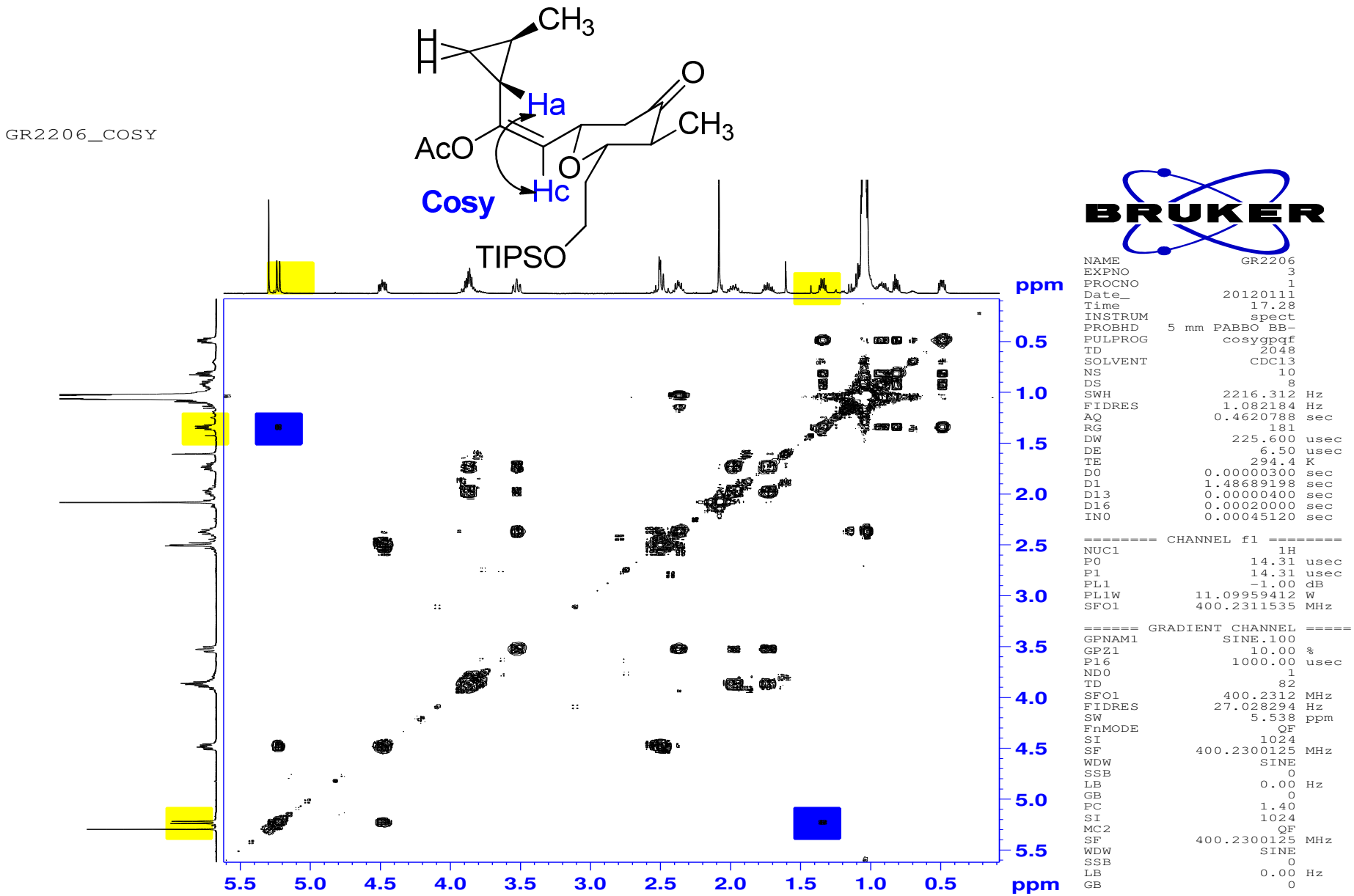


Fig 1: Allylic coupling between vinyl-Hc and cyclopropyl proton- Ha pinpoints the exact Ha proton for the nOesy experiment

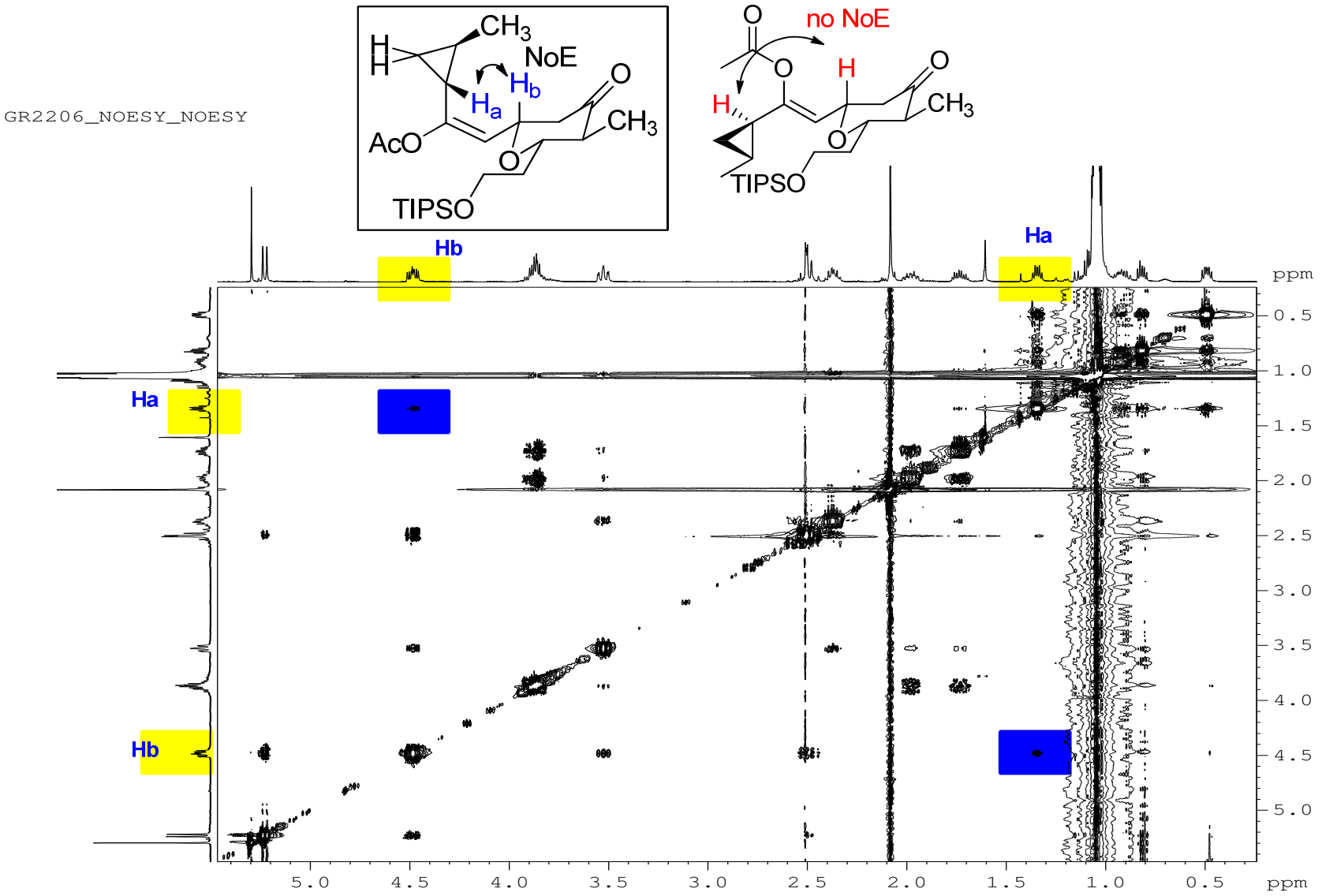


Fig 2: A subtle nOe coupling between the cyclopropane Ha and the Hb of the THP ring