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Supporting Information

Total Synthesis of the Guangnanmycin A Alcohol

*K. Yahata, A. Fürstner**

SUPPORTING INFORMATION

Total Synthesis of the Guangnanmycin A Alcohol

Kenzo Yahata and Alois Fürstner*

Max-Planck-Institut für Kohlenforschung, 45470 Mülheim/Ruhr, Germany

Email: fuerstner@kofo.mpg.de

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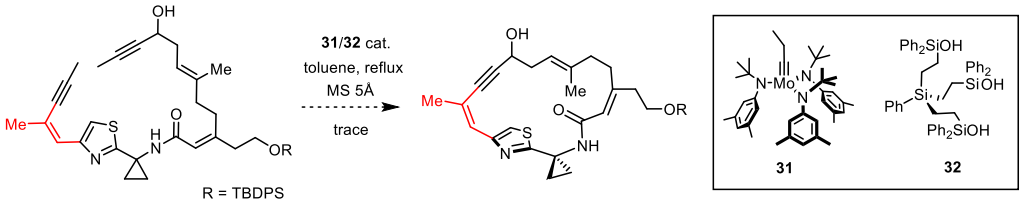
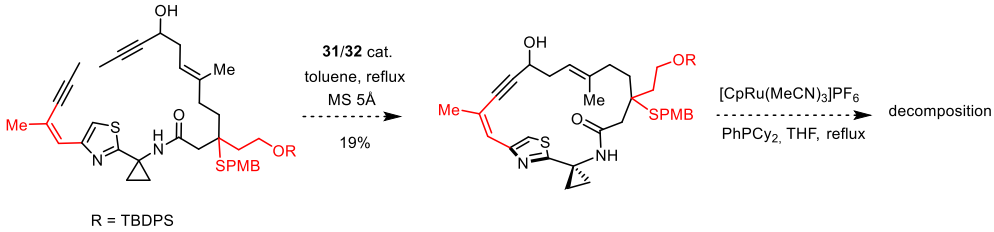
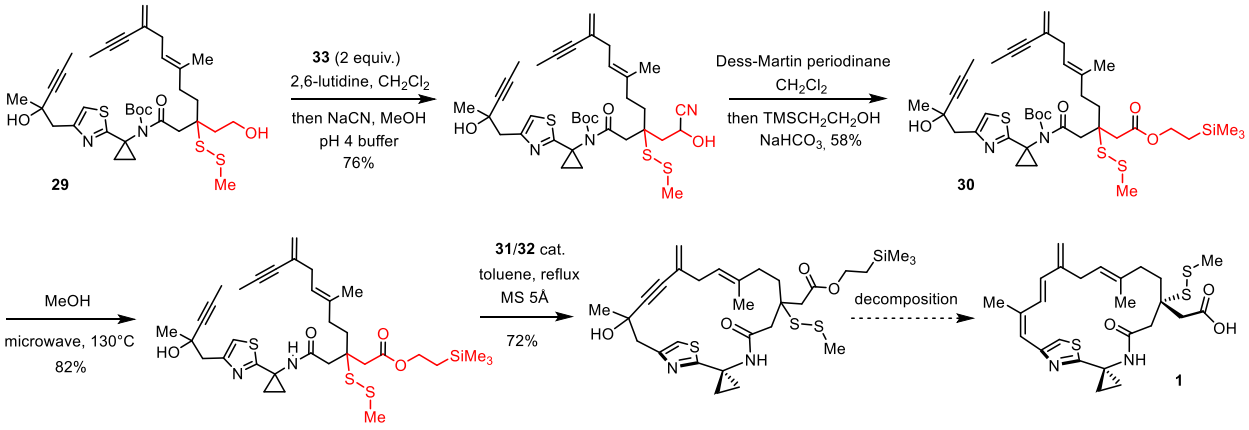
UNSUCCESSFUL FORAYS



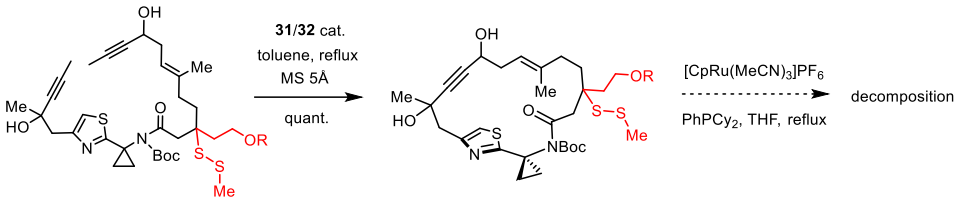
- RCAM essentially failed when the C2-C3 and the C12-C13 alkenes were both in place, likely because of overly high ring strain in the incipient macrocycle



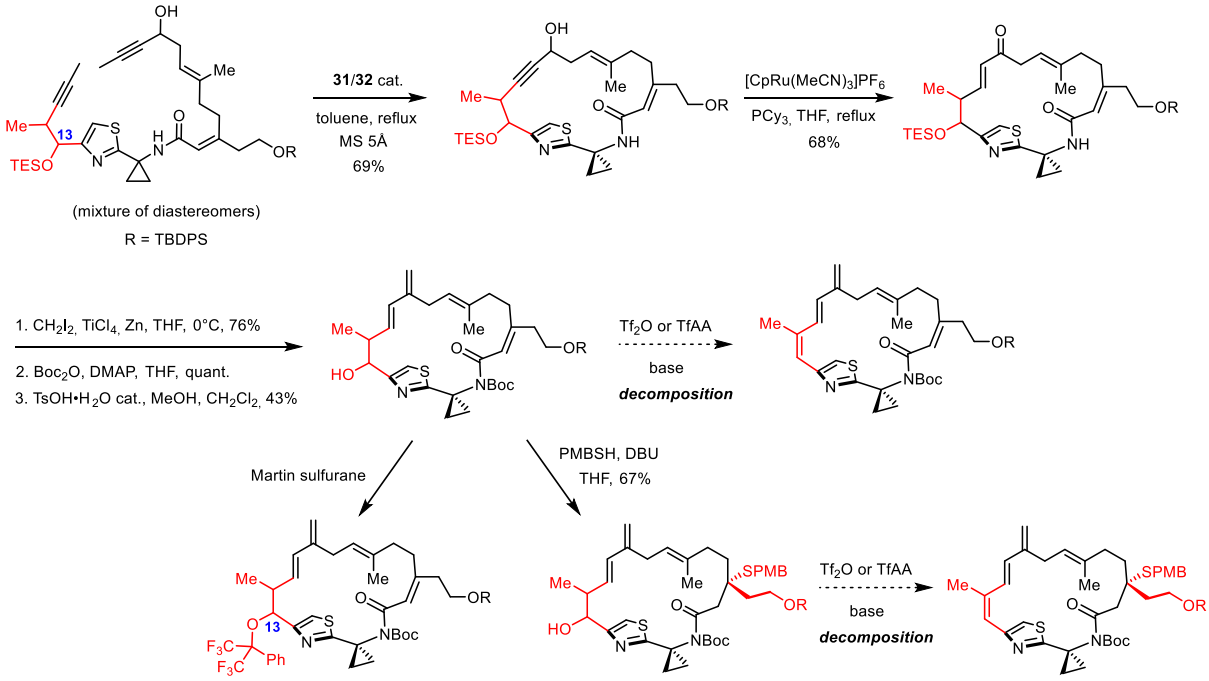
- likewise, RCAM proceeded very poorly with a substrate comprising the C12-C13 alkene and a thioether at C3 intoduced by a thia-Michael addition in the hope of relaxing the backbone
- attempted redox isomerization of the small available sample failed and led to instant decomposition



- two-step oxidation of the primary alcohol **29** to ester **30** was successful when performed prior to macrocyclization in the presence of the unsymmetrical disulfide
- RCAM was successful; the molybdenum catalyst is compatible with the disulfide
- attempted *trans*-reduction/dehydration resulted in decomposition



- RCAM was successful in the presence of the disulfide, confirming the compatibility of the molybdenum catalyst with this type of functional group
- attempted redox isomerization failed even when performed with (over)stoichiometric amounts of the ruthenium catalyst



- an alternative route used a substrate (mixture of diastereomers) in which the –OH group to be eliminated was relocated to the benzylic C13 position
- numerous attempts at eliminating this benzylic alcohol under different conditions met with failure, independent of whether the substrate contained the C2-C3 olefin or had a slightly more relaxed backbone after introduction of a C3-thioether group
- the exceptional reluctance to elimination is best illustrated by a reaction using Martin sulfurane ($Ph_2S[OC(CF_3)_2Ph]_2$): the only discrete product detectable in the crude reaction mixture was the corresponding ether, in which $Ph(F_3C)_2COH$ derived from the reagent had attacked the transient benzylic cation despite the very low nucleophilicity and steric hindrance of this alcohol

GENERAL INFORMATION

Unless stated otherwise, all reactions were carried out under argon in flame-dried glassware, ensuring rigorously inert conditions. The solvents were purified by distillation over the indicated drying agents and were stored and handled under argon: THF, Et_2O (Mg/anthracene); hexanes, toluene (Na/K); NEt_3, *N*,*N*-diisopropylethylamine, *N*,*N*,*N*',*N*'-tetramethylethylenediamine, 2,6-lutidine, pyridine, DBU, *tert*-butyl methyl ether, CH_2Cl_2 (CaH_2); MeOH (Mg, stored over MS 3Å); DMF, 1,4-dioxane, and CH_3CN were dried by an adsorption solvent purification system based on molecular sieves.

Thin layer chromatography (TLC): Macherey-Nagel precoated plates (POLYGRAM®SIL/UV254); Flash chromatography: Merck silica gel 60 (40-63 µm or 15-40 µm (referred to as "fine silica")) with pre-distilled or HPLC grade solvents.

NMR spectra were recorded on Bruker DPX 300, AMX 300, AV 400 or AV III 600 spectrometers in the solvents indicated; chemical shifts (δ) are given in ppm relative to TMS, coupling constants (*J*) in Hz. The solvent signals were used as references and the chemical shifts converted to the TMS scale ($CDCl_3$: δ_C = 77.16 ppm; residual $CHCl_3$: δ_H = 7.26 ppm; CD_2Cl_2: δ_C = 53.84 ppm; residual $CHDCl_2$: δ_H = 5.32 ppm; C_6D_6: δ_C = 128.06 ppm; residual C_6HD_5: δ_H = 7.16 ppm; CD_3OD: δ_C = 49.00 ppm; residual CHD_2OD: δ_H = 3.31 ppm; $D_3C(C{=}O)CD_3$: δ_C = 29.84 ppm; residual $D_3C(C{=}O)CHD_2$: δ_H = 2.05 ppm; $CD_3(SO)CD_3$: δ_C = 39.52 ppm; residual $CD_3(SO)CHD_2$: δ_H = 2.50 ppm).

IR: Alpha Platinum ATR (Bruker), wavenumbers ($\tilde{\nu}$) in cm^{-1}.

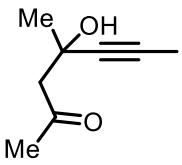
MS (EI): Finnigan MAT 8200 (70 eV), DI-MS (EI and CI): Finnigan MAT SSQ 7000, ESI-MS: ESQ 3000 (Bruker) or Thermo Scientific LTQ-FT or Thermo Scientific Exactive. HRMS: Bruker APEX III FT-MS (7 T magnet) or MAT 95 (Finnigan) or Thermo Scientific LTQ-FT or Thermo Scientific Exactive. GC-MS was measured on a Shimadzu GCMS-QP2010 Ultra instrument.

Unless stated otherwise, all commercially available compounds (abcr, Acros, TCI, Aldrich, Alfa Aesar) were used without further purification.

The following compounds were prepared according to the cited literature: molybdenum alkylidyne complex **31**,[1] trissilanol ligand **32**,[2] and $CpRu(MeCN)_3PF_6$.[3]

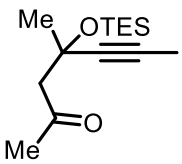
THE AMINE FRAGMENT

4-Hydroxy-4-methylhept-5-yn-2-one (6). A solution of acetylacetone (**5**) (13.7 mL, 133 mmol) in THF



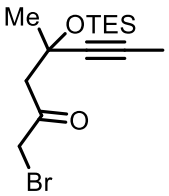
(70 mL) was added dropwise over 30 min to a solution of *i*-PrMgCl (2 M in Et_2O, 50 mL, 100 mmol) at 0 °C. The mixture was stirred for 30 min at 0 °C before 1-propynylmagnesium bromide (0.5 M in THF, 400 mL, 200 mmol) was added. The mixture was warmed to 50 °C. After stirring for 15 h at 50 °C, the solution was cooled to 0 °C and poured with vigorous stirring into pH 7 phosphate buffer (1 M, 200 mL) at 0 °C. The aqueous layer was saturated with NaCl and filtered through a pad of Celite, which was washed with EtOAc. After separating the two phases, the aqueous layer was extracted with EtOAc, and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified with flash chromatography (silica gel; *tert*-butyl methyl ether/hexanes = 1:2 to 1:1) to give the title compound as a yellow oil (8.47 g, 45%). ^{1}H NMR (400 MHz, C_6D_6) δ 4.45 (s, 1H), 2.42 (d, *J* = 16.7 Hz, 1H), 2.12 (d, *J* = 16.7 Hz, 1H), 1.61 (s, 3H), 1.45 (s, 3H), 1.42 (s, 3H). ^{13}C NMR (101 MHz, C_6D_6) δ 208.3, 83.4, 78.3, 65.6, 54.3, 30.9, 30.4, 3.2. IR (film) $\tilde{\nu}$ = 3445, 2982, 2922, 1700, 1360, 1265, 1174, 1131, 1080, 975, 935, 535 cm^{-1}. HRMS (CI) calcd. for $C_8H_{13}O_2$ $[M+H]^+$: 141.09101; found: 141.09108.

4-Methyl-4-((triethylsilyl)oxy)hept-5-yn-2-one (S1). Imidazole (5.50 g, 80.8 mmol) and TESCl (7.5 mL,



44.7 mmol) were added at room temperature to a solution of compound **6** (4.7 g, 33.5 mmol) in CH_2Cl_2 (90 mL). After stirring for 30 min, the reaction was quenched with H_2O. The two phases were separated and the aqueous layer was extracted with *tert*-butyl methyl ether. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel; EtOAc/hexanes = 1:10) to give the title compound as a yellow oil (8.45 g, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.71 (d, *J* = 12.8 Hz, 1H), 2.66 (d, *J* = 12.8 Hz, 1H), 2.22 (s, 3H), 1.80 (s, 3H), 1.48 (s, 3H), 0.94 (t, *J* = 7.9 Hz, 9H), 0.74 – 0.56 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.0, 82.8, 80.7, 67.3, 58.3, 32.2, 31.4, 7.1, 6.1, 3.5. IR (film) $\tilde{\nu}$ = 1954, 1711, 1355, 1154, 1098, 1005, 724, 544 cm^{-1}. HRMS (ESI) calcd. for $C_{14}H_{26}O_2NaSi$ $[M+Na]^+$: 277.15943; found: 277.15943.

1-Bromo-4-methyl-4-((triethylsilyl)oxy)hept-5-yn-2-one (7). Et_3N (17 mL, 122 mmol) and TBSOTf (17



mL, 74.0 mmol) were added at 0 °C to a solution of ketone **S1** (15.1 g, 59.3 mmol) in CH_2Cl_2 (170 mL). After stirring for 2 h, the reaction was quenched with sat. aq. $NaHCO_3$ The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The obtained crude enol silyl ether was subjected to the next reaction without further purification.

The obtained crude enol silyl ether was dissolved in THF (250 mL). $NaHCO_3$ (6.0 g, 71.4 mmol) and NBS (12.7 g, 71.4 mmol) were added at −78 °C to the solution. After stirring for 1 h, the mixture was warmed

to 0 °C and stirred for another 30 min before the reaction was quenched with sat. aq. $NaHCO_3$. After separation of the two phases, the aqueous layer was extracted with *tert*-butyl methyl ether, and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc/hexanes = 1:10) to give the title compound as a pale yellow oil (16.0 g, 81% for 2 steps).

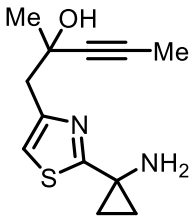
When carried out on a smaller scale (3.96 g of **S1**) under otherwise identical conditions, the yield was 92%.

^{1}H NMR (400 MHz, C_6D_6) δ 3.74 (d, *J* = 1.7 Hz, 2H), 2.75 (d, *J* = 13.2 Hz, 1H), 2.66 (d, *J* = 13.2 Hz, 1H), 1.48 (s, 3H), 1.35 (s, 3H), 1.02 (t, *J* = 7.9 Hz, 9H), 0.80 – 0.60 (m, 6H). ^{13}C NMR (101 MHz, C_6D_6) δ 197.2, 82.6, 81.4, 67.8, 54.1, 36.6, 31.4, 7.3, 6.4, 3.0. IR (film) $\tilde{\nu}$ = 2955, 2876, 1719, 1236, 1138, 1001, 725, 544 cm^{-1}. HRMS (ESI) calcd. for $C_{14}H_{25}{}^{79}BrO_2SiNa$ $[M+Na]^+$: 355.06995; found: 355.06987.

***tert*-Butyl (1-carbamoylcyclopropyl)carbamate (S2).** NH_4OH (25% *w/w*, 18.5 mL, 119 mmol) was added at room temperature to a mixture of 1-*tert*-butoxycarbonylamino-cyclopropanecarboxylic acid (**8**) (20.0 g, 99.4 mmol), di-*tert*-butyl dicarbonate (30.0 mL, 130 mmol) and pyridine (8.0 mL, 98.9 mmol) in MeCN (290 mL). The cloudy, colorless reaction mixture was stirred for 16 h and then concentrated under reduced pressure. The residue was absorbed on SiO_2 and purified by flash chromatography (EtOAc/hexanes = 1:1 to EtOAc to EtOAc/MeOH = 95:5) to give the title compound as a colorless solid (16.3 g, 82%). M.p. = 167-169 °C; ^{1}H NMR (400 MHz, [D_6]-DMSO) δ 7.34 (s(br), 1H), 7.01 (s(br), 1H), 6.97 (s(br), 1H), 1.38 (s, 9H), 1.22 – 1.13 (m, 2H), 0.86 – 0.77 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d6) δ 174.3, 155.5, 78.1, 34.5, 28.2, 16.1. IR (film) $\tilde{\nu}$ = 3486, 3230, 3123, 2974, 1701, 1657, 1600, 1407, 1363, 1309, 1258, 1153, 1063, 1006, 768, 723, 618, 510, 496 cm^{-1}. HRMS (ESI) calcd. for $C_9H_{16}N_2O_3Na$ $[M+Na]^+$: 223.10531; found: 223.10529.

***tert*-Butyl (1-carbamothioylcyclopropyl)carbamate (9).** Lawesson's reagent (8.20 g, 20.3 mmol) was added at room temperature to a suspension of amide **S2** (5.80 g, 29.0 mmol) in THF (90 mL). The pale yellow cloudy mixture was stirred for 3 h and then partitioned between EtOAc (80 mL) and aq. NaOH (0.5 M, 30 mL). The organic phase was washed with water and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was absorbed on SiO_2 and purified by flash chromatography (hexanes/EtOAc = 4:1 to 2:1 to 1:1) to give the title compound as a colorless solid (5.86 g, 94%). M. p. = 170-173 °C; ^{1}H NMR (600 MHz, MeOD) δ 1.92 (dd, *J* = 4.2, 4.2 Hz, 2H), 1.44 (s, 9H), 1.18 (dd, *J* = 4.2, 4.2 Hz, 2H). ^{13}C NMR (MeOD, 151 MHz): δ 210.6, 157.7, 81.0, 42.7, 28.6, 22.9. IR (film) $\tilde{\nu}$ = 3427, 3303, 1691, 1597, 1499, 1413, 1247, 1154, 1064, 1037, 916, 845, 597 cm^{-1}. HRMS (ESI) calcd. for $C_9H_{16}N_2O_2SK$ $[M+K]^+$: 255.05641; found: 255.05643.

1-(2-(1-Aminocyclopropyl)thiazol-4-yl)-2-methylpent-3-yn-2-ol (10). Thioamide **9** (5.50 g, 25.4 mmol) was added at room temperature to a solution of bromo ketone **7** (9.33 g, 28.0 mmol) in EtOH (120 mL). After stirring for 1 h at 70 °C, the solvent was removed under reduced pressure to give a crude thiazole, which was subjected to the next reaction without purification.



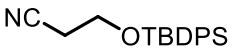
The crude material was dissolved in 1,4-dioxane (35 mL). HCl solution (4 M in 1,4-dioxane, 38 mL, 152 mmol) was added and the mixture was stirred at ambient temperature for 3 h. All volatile material were removed under reduced pressure. The residue was dissolved in NaOH (3 M, 60 mL) and the resulting solution was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc/hexanes = 1:1 to 2:1 to 3:1) to give the title compound as a red oil (3.68 g, 61% over two steps).

When carried out on a smaller scale (2.31 g of thioamide **9**) under otherwise identical conditions, the yield was 69%.

^{1}H NMR (400 MHz, MeOD) δ 7.10 (s, 1H), 3.00 (s, 2H), 1.75 (s, 3H), 1.40 (s, 3H), 1.35 – 1.29 (m, 2H), 1.23 – 1.18 (m, 2H). ^{13}C NMR (101 MHz, MeOD) δ 179.4, 153.6, 116.1, 83.9, 80.1, 68.5, 45.6, 37.4, 30.0, 21.0, 21.0, 3.1. IR (film) $\tilde{\nu}$ = 3379, 2980, 2919, 1733, 1519, 1409, 1371, 1246, 1073, 847, 730, 639 cm^{-1}. HRMS (ESI) calcd. for $C_{12}H_{17}N_2OS$ [M+H]$^+$: 237.10561; found: 237.10559.

THE CARBOXYLIC ACID FRAGMENT

3-((*tert*-Butyldiphenylsilyl)oxy)propanenitrile (12). TBDPSCl (27.0 mL, 104 mmol) was added to a solution of imidazole (20.0 g, 294 mmol) and 3-hydroxypropionitrile (**11**) (10.0 mL, 146 mmol) in CH_2Cl_2. After stirring for 12 h, the reaction was quenched with H_2O and the mixture diluted with EtOAc. After separating the two phases, the organic layer was washed with HCl (1 M), brine, sat. $NaHCO_3$ aq., and again brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the title compound as a colorless oil (32.0 g, quant.).



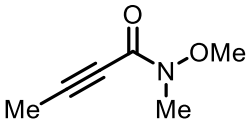
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 – 7.65 (m, 4H), 7.50 – 7.38 (m, 6H), 3.86 (t, *J* = 6.3 Hz, 2H), 2.55 (t, *J* = 6.3 Hz, 2H), 1.09 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.7, 132.8, 130.1, 128.0, 118.1, 59.2, 26.8, 21.6, 19.3. IR (film) $\tilde{\nu}$ = 2931, 2858, 1472, 1427, 1390, 1104, 915, 822, 734, 700, 613, 503, 487 cm^{-1}. HRMS (ESI) calcd. for $C_{19}H_{23}OSiNa$ [M+Na]$^+$: 332.14411; found: 332.14405.

The spectral data matched the literature.[5]

***tert*-Butyl 5-((*tert*-butyldiphenylsilyl)oxy)-3-oxopentanoate (13).** TMSCl (0.78 mL, 6.15 mmol) was added to a suspension of Zn powder (12.1 g, 185 mmol) in THF (140 mL). After stirring for 30 min at reflux temperature, the mixture was cooled to 60 °C. A solution of nitrile **12** (19.0 g, 61.4 mmol) and *tert*-butyl bromoacetate (17.9 mL, 123 mmol) in THF (50 mL) was added at such a rate as to maintain the reaction temperature between 60 and 65 °C. Once the addition was complete, stirring was continued for 19 h at 60 °C. After cooling to ambient temperature, the reaction was quenched with aqueous citric acid (20% *w/w*, 100 mL) and the resulting mixture was filtered through a pad of Celite, which was carefully washed with EtOAc. After removing the organic solvent under reduced pressure, the aqueous layer was extracted with EtOAc, and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc/hexanes = 1:15) to give the title compound as a colorless oil (23.5 g, 90%, ca. 1:4 mixture of tautomers). ^{1}H NMR (400 MHz, C_6D_6) δ 12.82 (s, 0.2H), 7.87 – 7.67 (m, 4H), 7.28 – 7.19 (m, 6H), 5.08 (s, 0.2H), 3.85 – 3.76 (m, 2H), 3.12 (s, 1.6H), 2.36 (t, *J* = 6.1 Hz, 1.6H), 2.21 (t, *J* = 6.4 Hz, 0.4H), 1.37 (s, 1.8H), 1.35 (s, 7.2H), 1.14 (s, 1.8H), 1.13 (s, 7.2H). ^{13}C NMR (101 MHz, C_6D_6) δ 200.8, 176.0, 173.2, 166.4, 136.0, 135.3, 134.0, 133.8, 130.1, 130.0, 130.0, 129.8, 128.1, 92.4, 81.1, 80.6, 60.9, 59.7, 51.2, 45.4, 38.7, 28.3, 28.0, 27.0, 19.5, 19.4. IR (film) $\tilde{\nu}$ = 2931, 2858, 1736, 1715, 1647, 1473, 1427, 1367, 1312, 1250, 1145, 1106, 957, 822, 737, 700, 612, 504, 489 cm^{-1}. HRMS (ESI) calcd. for $C_{25}H_{34}O_4SiNa$ [M+Na]$^+$: 449.21186; found: 449.21207.

***tert*-Butyl (*Z*)-5-((*tert*-butyldiphenylsilyl)oxy)-3-(((trifluoromethyl)-sulfonyl)oxy)pent-2-enoate (14).** LiOH solution (5 M in H_2O, 60 mL, 300 mmol) was added at 0 °C to a solution of ketoester **13** (17.6 g, 41.3 mmol) in toluene (175 mL). After stirring for 5 min, trifluoromethanesulfonic anhydride (14.0 mL, 83.2 mmol) was added over 40 min. The resulting mixture was diluted with H_2O and *tert*-butyl methyl ether, and the two phases were separated. The organic layer was washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc/hexanes = 1:20) to give the title compound as a colorless solid (22.9 g, 99%, *Z:E* > 20:1). M. p. = 51.0–52.4 °C; ^{1}H NMR (500 MHz, C_6D_6) δ 7.70 – 7.63 (m, 4H), 7.28 – 7.21 (m, 6H), 5.59 (t, *J* = 0.8 Hz, 1H), 3.48 (t, *J* = 5.9 Hz, 2H), 2.08 (td, *J* = 5.9, 0.8 Hz, 2H), 1.40 (s, 9H), 1.10 (s, 9H). ^{13}C NMR (126 MHz, C_6D_6) δ 161.5, 154.8, 135.9, 133.3, 130.3, 128.2, 119.0 (q, $^1J_{C\text{-}F}$ = 320.2 Hz), 115.8, 81.9, 59.5, 37.6, 28.0, 26.9, 19.4. ^{19}F NMR (470 MHz, C_6D_6) δ −75.0. IR (film) $\tilde{\nu}$ = 2927, 2855, 1724, 1679, 1438, 1335, 1255, 1224, 1207, 1151, 1083, 988, 915, 741, 701, 655, 614, 593, 500 cm^{-1}. HRMS (ESI) calcd. for $C_{26}H_{33}O_6F_3SiSNa$ [M+Na]$^+$: 581.16115; found: 581.16199.

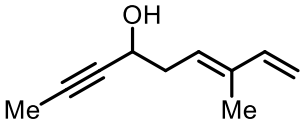
***N*-Methoxy-*N*-methylbut-2-ynamide (16).** Et_3N (79.0 mL, 567 mmol), DMAP (1.15 g, 9.41 mmol), and



N-ethyl-*N*'-(3-dimethylaminopropyl)carbodiimide hydrochloride (43.5 g, 227 mmol) were added at 0 °C to a solution of 2-butynoic acid (**15**) (15.9 g, 189 mmol) and *N,O*-dimethylhydroxyamine hydrochloride (22.1 g, 227 mmol) in CH_2Cl_2 (300 mL). The mixture was allowed to stir for 18 h while warming to room temperature. The mixture was diluted with EtOAc and water. The organic layer was washed with HCl (1 M), sat. $NaHCO_3$ aq., and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, hexanes/EtOAc = 2:1 to 1:1) to obtain the title compound as a colorless oil (20.3 g, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.71 (s, 3H), 3.17 (s(br), 3H), 1.97 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.3, 89.2, 72.2, 61.8, 32.0, 3.8. IR (film) $\tilde{\nu}$ = 2974, 2938, 2240, 1631, 1459, 1414, 1380, 1199, 1159, 1047, 975, 870, 722, 580 cm^{-1}. HRMS (EI) calcd. for $C_6H_9NO_2$ $[M]^+$: 127.06278; found: 127.06286.

The spectral data matched the literature.[4]

(*E*)-7-Methylnona-6,8-dien-2-yn-4-ol (S3). *sec*-BuLi solution (1.4 M in cyclohexane, 41 mL, 57.4 mmol)



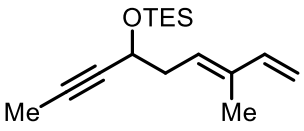
was added at −78 °C to a solution of 3-methyl-1,4-pentadiene (**17**) (7.3 mL, 60.0 mmol) in THF (200 mL). After removing the cooling bath, the mixture was stirred for 30 min and then re-cooled to −78 °C. A solution of Weinreb amide **16** (7.63 g, 60.0 mmol) in THF (50 mL) was added dropwise to the resulting solution. After stirring for 30 min, the mixture was warmed to ambient temperature and the reaction was quenched with sat. aq. NH_4Cl. The two phases were separated, and the aqueous layer was extracted with *tert*-butyl methyl ether. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a crude ynone, which was used in the next step without further purification.

A solution of Dibal-H (1 M in CH_2Cl_2, 120 mL, 120 mmol) was diluted with CH_2Cl_2 (200 mL) and cooled to −78 °C. To this solution was added dropwise a solution of the crude ynone in CH_2Cl_2 (50 mL). After stirring for 30 min, the reaction was quenched with sat. aq. Rochelle`s salt solution and the mixture was diluted with *tert*-butyl methyl ether. The resulting mixture was vigorously stirred for 2 h before the resulting two clear phases were separated. The aqueous layer was extracted with *tert*-butyl methyl ether, the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc/hexanes = 1:20 to 1:10) to give the title compound as a pale yellow oil (6.41 g, 74% for 2 steps, *E*/*Z* = >20:1).

NOTE: This compound tends to polymerize upon storage and should be used immediately after preparation.

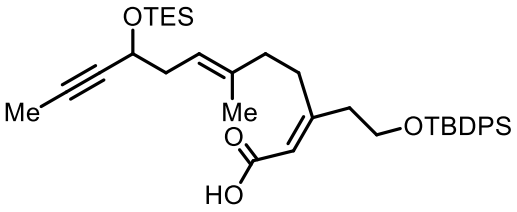
^{1}H NMR (400 MHz, CD_2Cl_2) δ 6.41 (dd, *J* = 17.4, 10.6 Hz, 1H), 5.58 (t, *J* = 7.4 Hz, 1H), 5.15 (d, *J* = 17.4 Hz, 1H), 4.98 (d, *J* = 10.7 Hz, 1H), 4.39 – 4.32 (m, 1H), 2.52 (t, *J* = 6.9 Hz, 2H), 1.88 (s(br), 1H), 1.83 (d, *J* = 2.1 Hz, 3H), 1.77 (s, 3H). ^{13}C NMR (CD_2Cl_2, 101 MHz) δ 141.6, 137.4, 127.5, 111.7, 81.3, 80.4, 62.5, 37.5, 12.2, 3.6. IR (film) $\tilde{\nu}$ = 3345, 2920, 1607, 1414, 1138, 1027, 989, 889, 533, 430 cm^{-1}. HRMS (ESI) calcd. for $C_{10}H_{14}O$ [M]$^+$: 150.10392; found: 150.10402.

(*E*)-Triethyl((7-methylnona-6,8-dien-2-yn-4-yl)oxy)silane (18). Imidazole (4.90 g, 72.0 mmol) and



TESCl (7.3 mL, 43.5 mmol) were added to a solution of alcohol **S3** (5.41 g, 36.0 mmol) in CH_2Cl_2 (100 mL). After stirring for 30 min, the mixture was diluted with hexanes and washed with H_2O and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, *tert*-butyl methyl ether/hexanes = 1:40) to give the title compound as a colorless oil (8.76 g, 92%). ^{1}H NMR (400 MHz, C_6D_6) δ 6.48 (dd, *J* = 17.4, 10.7 Hz, 1H), 5.75 (t, *J* = 7.1 Hz, 1H), 5.10 (d, *J* = 17.4 Hz, 1H), 4.93 (d, *J* = 11.2 Hz, 1H), 4.46 (tq, *J* = 6.6, 2.2 Hz, 1H), 2.72 – 2.57 (m, 2H), 1.69 (dd, *J* = 1.4, 0.8 Hz, 3H), 1.47 (d, *J* = 2.1 Hz, 3H), 1.07 (t, *J* = 7.9 Hz, 9H), 0.81 – 0.62 (m, 6H). ^{13}C NMR (101 MHz, C_6D_6) δ 141.9, 136.3, 128.6, 111.2, 81.5, 80.3, 63.2, 38.6, 12.1, 7.1, 5.4, 3.2. IR (film) $\tilde{\nu}$ = 2954, 2876, 1608, 1459, 1414, 1238, 1076, 1004, 893, 725 cm^{-1}. HRMS (ESI) calcd. for $C_{16}H_{28}OSi$ [M]$^+$: 264.19039; found: 264.19032.

(2*E*,6*E*)-3-(2-((*tert*-Butyldiphenylsilyl)oxy)ethyl)-6-methyl-9-((triethylsilyl)oxy)dodeca-2,6-dien-10-

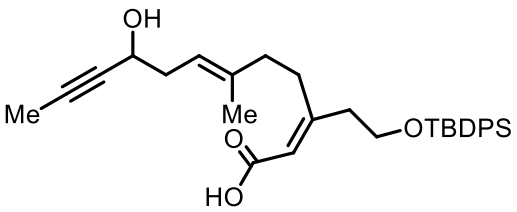


ynoic acid (19). A solution of 9-H-9-BBN (0.5 M in THF, 13.9 mL, 6.84 mmol) was added at ambient temperature to compound **18** (1.81 g, 6.84 mmol). After stirring overnight, degassed H_2O (10 mL) was introduced and the resulting mixture was stirred for 30 min. To this solution were added triflate **14** (1.91 g, 3.42 mmol), Cs_2CO_3 (3.34 g, 10.3 mmol), and $PdCl_2(PPh_3)_2$ (120 mg, 0.171 mmol) and the resulting mixture was stirred for 2 h before it was diluted with brine and hexanes. After separating the two phases, the aqueous layer was extracted with hexanes. The combined organic layers were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was subjected to flash chromatography (silica gel, EtOAc/hexanes = 1:40) to give an inseparable mixture of the coupling product and unreacted **18**.

2,6-Lutidine (3.2 mL, 27.4 mmol) and TMSOTf (2.5 mL, 13.7 mmol) were added at 0 °C to a solution of this crude material in CH_2Cl_2 (50 mL). After stirring for 1 h at this temperature, the reaction was quenched with pH 4 citrate buffer (20 mL) and diluted with Et_2O (20 mL). After stirring for 1 h, the two phases were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was

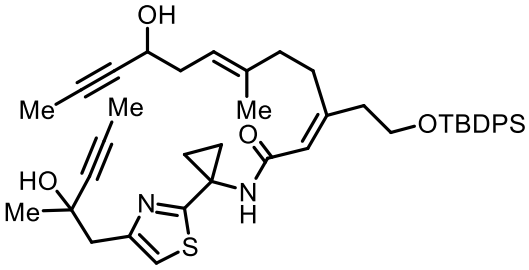
purified by flash chromatography (silica gel, EtOAc/hexanes = 1: 20 to 1:10 to 1:4) to give the title compound as a colorless oil (1.40 g, 66% for 2 steps). ^{1}H NMR (400 MHz, C_6D_6) δ 11.8 (brs, 1H), 7.78 – 7.68 (m, 4H), 7.31 – 7.20 (m, 6H), 5.82 (s, 1H), 5.49 (t, *J* = 6.5 Hz, 1H), 4.49 (ddq, *J* = 6.4, 6.4, 2.1 Hz, 1H), 3.64 (t, *J* = 6.4 Hz, 2H), 2.85 – 2.71 (m, 2H), 2.60 (ddd, *J* = 7.3, 7.1, 7.1 Hz, 2H), 2.20 – 2.11 (m, 4H), 1.68 (s, 3H), 1.54 (d, *J* = 2.1 Hz, 3H), 1.15 (s, 9H), 1.11 (t, *J* = 7.9 Hz, 9H), 0.85 – 0.66 (m, 6H). ^{13}C NMR (101 MHz, C_6D_6) δ 171.9, 164.2, 137.2, 136.0, 134.0, 130.1, 128.2, 121.1, 117.3, 81.8, 80.0, 63.6, 62.3, 41.7, 38.9, 38.5, 31.6, 27.1, 19.4, 16.3, 7.2, 5.4, 3.3. IR (film) $\tilde{\nu}$ = 2954, 1688, 1635, 1427, 1247, 1082, 1005, 822, 736, 700, 613, 503 cm^{-1}. HRMS (ESI) calcd. for $C_{37}H_{53}O_4Si_2$ [M-H]$^-$: 617.34879; found: 617.34903.

(2*E*,6*E*)-3-(2-((*tert*-Butyldiphenylsilyl)oxy)ethyl)-9-hydroxy-6-methyldodeca-2,6-dien-10-ynoic acid (20). Amberlyst 15 (H$^+$-form, 800 mg) was added to a solution of carboxylic acid **19** (1.33 g, 2.15 mmol) in MeOH (14 mL). After stirring for 4 h, the mixture was filtered through a pad of Celite, which was washed with a 1:1 mixture of EtOAc/hexanes. The organic solvent was removed under reduced pressure and the residue was purified by flash chromatography (silica gel, EtOAc/hexanes = 1:5 to 1:3 to 1:2 to 2:3 to 1:1) to give the title compound as a colorless oil (1.00 g, 92%). ^{1}H NMR (400 MHz, MeOD) δ 7.70 – 7.61 (m, 4H), 7.48 – 7.33 (m, 6H), 5.70 (s, 1H), 5.21 (tq, *J* = 7.2, 1.3 Hz, 1H), 4.19 (tq, *J* = 6.5, 2.2 Hz, 1H), 3.80 (t, *J* = 6.3 Hz, 2H), 2.66 (ddd, *J* = 9.9, 6.0, 1.6 Hz, 2H), 2.37 (t, *J* = 6.3 Hz, 2H), 2.34 – 2.26 (m, 2H), 2.09 (dd, *J* = 8.8, 7.1 Hz, 2H), 1.77 (d, *J* = 2.1 Hz, 3H), 1.63 (s, 3H), 1.03 (s, 9H). ^{13}C NMR (101 MHz, MeOD) δ 169.6, 162.2, 138.5, 136.7, 134.6, 130.9, 128.8, 121.1, 118.9, 81.5, 80.8, 63.3, 63.1, 42.3, 39.5, 38.0, 31.9, 27.4, 20.0, 16.4, 3.2. IR (film) $\tilde{\nu}$ = 3399, 2972, 1931, 2858, 1689, 1638, 1427, 1364, 1247, 1200, 1106, 1083, 848, 823, 738, 701, 613, 503 cm^{-1}. HRMS (ESI$^-$) calcd. for $C_{31}H_{39}O_4Si$ [M-H]$^-$: 503.26231; found: 503.26291.



GUNAGNANMYCIN A ALCOHOL

(2*E*,6*E*)-3-(2-((*tert*-Butyldiphenylsilyl)oxy)ethyl)-9-hydroxy-*N*-(1-(4-(2-hydroxy-2-methylpent-3-yn-1-yl)thiazol-2-yl)cyclopropyl)-6-methyldodeca-2,6-dien-10-ynamide (21). *N*,*N*-Diisopropylethylamine (3.9 mL, 22.4 mmol) and HATU (5.05 g, 13.3 mmol) were added at ambient temperature to a solution of carboxylic acid **20** (5.59 g, 11.1 mmol) and amine **10** (3.55 g, 15.0 mmol) in DMF (22 mL). After stirring for 3 h, the mixture was diluted with H_2O (50 mL) and extracted with *tert*-butyl methyl ether. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue



was purified by flash chromatography (silica gel, *tert*-butyl methyl ether/hexanes = 1:1 to 3:2) to give the title compound as a colorless amorphous solid (6.00 g, 75%). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.72 – 7.62 (m, 4H), 7.50 – 7.34 (m, 6H), 6.86 (t, *J* = 0.8 Hz, 1H), 6.10 (s, 1H), 5.57 (s, 1H), 5.20 (tt, *J* = 7.4, 1.3 Hz, 1H), 4.70 (s, 1H), 4.26 (s, 1H), 3.82 (t, *J* = 6.5 Hz, 2H), 2.98 (d, *J* = 15.0 Hz, 1H), 2.90 (dd, *J* = 14.4, 1.1 Hz, 1H), 2.65 (dd, *J* = 9.3, 6.7 Hz, 2H), 2.38 (td, *J* = 6.5, 1.1 Hz, 2H), 2.34 (t, *J* = 6.9 Hz, 2H), 2.12 (t, *J* = 7.7 Hz, 2H), 1.97 (s(br), 1H), 1.81 (d, *J* = 2.2 Hz, 3H), 1.72 (s, 3H), 1.69 – 1.58 (m, 5H), 1.43 (s, 3H), 1.36 – 1.29 (m, 2H), 1.05 (s, 9H). ^{13}C NMR (151 MHz, CD_2Cl_2) δ 175.2, 166.9, 157.3, 153.1, 139.4, 136.0, 134.1, 130.1, 128.1, 119.7, 119.5, 114.8, 83.3, 80.8, 80.7, 79.0, 67.9, 62.6, 62.5, 44.7, 41.1, 38.8, 37.4, 35.2, 30.9, 30.3, 27.0, 21.0, 20.9, 19.5, 16.6, 3.6, 3.5. IR (film) $\tilde{\nu}$ = 3292, 2929, 2857, 1663, 1635, 1518, 1427, 1301, 1254, 1185, 1109, 1082, 823, 738, 703, 613, 505 cm^{-1}. HRMS (ESI) calcd. for $C_{43}H_{54}N_2O_4SiSNa$ [M+Na]$^{+}$: 745.34658; found: 745.34747.

Compound 22. A suspension of diyne **21** (1.40 g, 1.94 mmol) and activated molecular sieves 5Å (powder, 15 g) in toluene (700 mL) was stirred at ambient temperature for 30 min before it was heated to reflux. In a separate flask, the molybdenum alkylidyne complex **31** (515 mg, 0.774 mmol) and the tris-silanol ligand **32** (610 mg, 0.775 mmol) were dissolved in toluene (5.0 mL) at room temperature. The resulting catalyst solution was added dropwise to the solution of **21** at reflux temperature. After stirring for 10 min, the mixture was cooled to ambient temperature and a slurry of Celite (30 g) in CH_2Cl_2/EtOAc (1:1, 200 mL) was added. The suspension was then filtered through a pad of Celite, the filtrate was evaporated under reduced pressure, and the residue was purified by flash chromatography (silica gel, *tert*-butyl methyl ether/hexanes/CH_2Cl_2 = 4:2:1 to *tert*-butyl methyl ether/CH_2Cl_2 = 10:1) to give the title compound as a pale yellow amorphous solid (868 mg, 67%, 1:1 mixture of diastereomers). ^{1}H NMR (400 MHz, MeOD) δ 7.74 – 7.58 (m, 4H), 7.50 – 7.34 (m, 6H), 7.17 (s, 0.5H), 7.13 (s, 0.5H), 5.75 (s, 1H), 4.25 (dd, *J* = 7.9, 4.1 Hz, 0.5H), 4.15 (dd, *J* = 9.9, 3.8 Hz, 0.5H), 3.86 – 3.78 (m, 2H), 3.01 – 2.73 (m, 3H), 2.38 (t, *J* = 6.5 Hz, 2H), 2.35 – 1.72 (m, 7H), 1.58 (s, 3H), 1.50 (s, 3H), 1.44 – 1.22 (m, 2H), 1.22 – 1.11 (m, 1H), 1.04 (s, 9H). ^{13}C NMR (101 MHz, MeOD) δ 176.0, 175.9, 170.8, 170.7, 158.0, 157.6, 153.0, 153.0, 138.6, 138.4, 136.7, 134.7, 134.7, 130.9, 128.9, 128.8, 120.9, 120.8, 120.5, 120.4, 117.4, 117.2, 88.1, 87.9, 86.3, 86.1, 69.5, 63.3, 63.3, 62.9, 62.6, 45.8, 45.7, 43.4, 43.3, 42.4, 42.4, 37.5, 37.1, 35.9, 35.8, 32.6, 32.4, 30.6, 30.5, 28.9, 27.5, 27.4, 27.2, 20.0, 18.2, 18.1, 17.9, 17.7, 16.0, 15.9. IR (film) $\tilde{\nu}$ = 3292, 2973, 2931, 2858, 1662, 1635, 1516, 1427, 1364, 1295, 1246, 1201, 1109, 1078, 849, 823, 738, 702, 613, 505 cm^{-1}. HRMS (ESI) calcd. for $C_{39}H_{48}N_2O_4SiSNa$ [M+Na]$^{+}$: 691.29963; found: 691.29978.

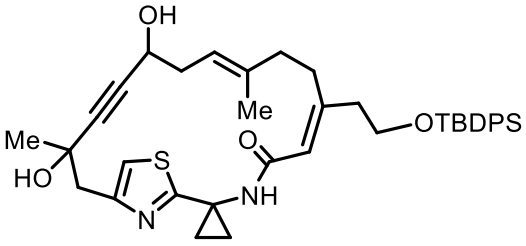
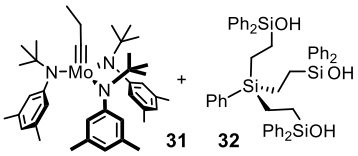
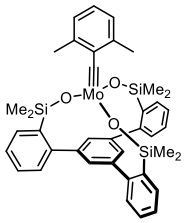
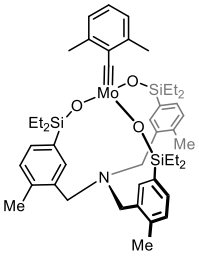
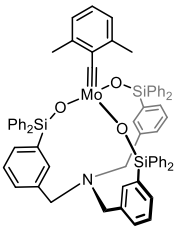
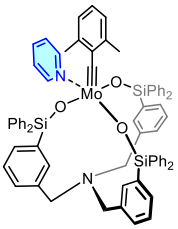
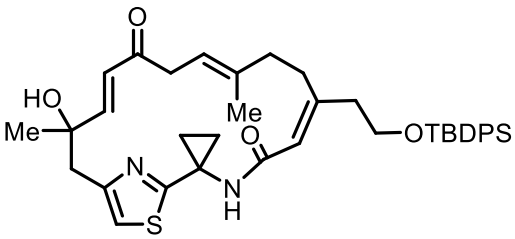


Table S1. Comparison of the Performance of Different Catalysts in the RCAM Reaction of Diyne **21** with Formation of Cycloalkyne **22**.[a]

Nr	Catalyst	Ref.	Loading / Scale	t (min)	22
1	 **31** **32**	2	20 mol% [≈100 mg scale]	10	67%
2			40 mol% [1.4 g scale]	10	67%
3		6	40 mol% [≈100 mg scale]	120	42%
4		7	20 mol% [≈100 mg scale]	180	62%
			40 mol% [≈100 mg scale]	90	54%
5		7	40 mol% [≈100 mg scale]	90	45%
6		7	40 mol% [≈100 mg scale][b]	180	39%

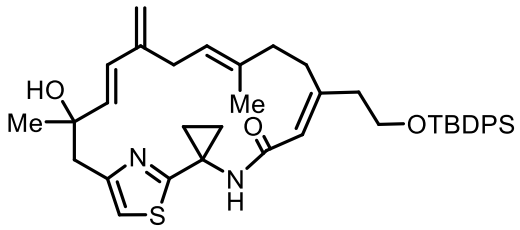
[a] All reactions were carried out in toluene at reflux temperature in the presence of powdered MS 5Å; [b] the pyridine adduct shown in entry 6 is air-stable when kept in a desiccator, see ref. 7

Compound 23. **[**$CpRu(MeCN)_3]PF_6$ (112 mg, 0.258 mmol) and tricyclohexylphosphine (72.7 mg, 0.259 mmol) were dissolved in THF (6.0 mL) and the resulting mixture was stirred for 10 min at ambient temperature to form the active catalyst. In a separate flask, compound **22** (868 mg, 1.30 mmol) and NH_4PF_6 (42.3 mg, 0.260 mmol) were dissolved in THF (20 mL), and the resulting mixture was stirred at reflux temperature. The catalyst solution was added dropwise to the



hot solution of the substrate. Stirring was continued at reflux temperature for 14 h before the mixture was cooled to rt, diluted with *tert*-butyl methyl ether/hexanes/CH_2Cl_2 (10 mL each), and filtered through a pad of silica gel, which was carefully washed with *tert*-butyl methyl ether. After removing the organic solvent under reduced pressure, the residue was purified by flash chromatography (silica gel, *tert*-butyl methyl ether/hexanes = 1:2 to 2:3) to give the title compound as a pale yellow amorphous solid (701 mg, 81%). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.75 – 7.63 (m, 4H), 7.48 – 7.34 (m, 6H), 6.77 (d, *J* = 1.0 Hz, 1H), 6.71 (d, *J* = 15.6 Hz, 1H), 6.30 (s, 1H), 6.16 (d, *J* = 15.6 Hz, 1H), 5.58 (s, 1H), 5.00 – 4.91 (m, 2H), 3.80 (t, *J* = 6.6 Hz, 2H), 3.06 – 2.87 (m, 4H), 2.70 (td, *J* = 11.4, 4.4 Hz, 1H), 2.35 (t, *J* = 6.7 Hz, 2H), 2.27 (td, *J* = 11.5, 6.3 Hz, 1H), 2.09 – 1.87 (m, 2H), 1.52 (s, 3H), 1.39 (s, 3H), 1.34 – 1.13 (m, 4H), 1.06 (s, 9H). ^{13}C NMR (101 MHz, CD_2Cl_2) δ 198.5, 175.7, 167.5, 156.3, 152.3, 151.8, 139.1, 136.0, 134.2, 134.1, 130.1, 128.1, 126.4, 119.7, 116.7, 115.3, 73.7, 62.5, 43.3, 42.7, 41.8, 40.1, 35.2, 32.0, 28.6, 27.0, 19.5, 19.3, 17.4, 16.4. IR (film) $\tilde{\nu}$ = 3399, 2930, 2857, 1660, 1633, 1500, 1427, 1374, 1290, 1246, 1185, 1106, 1080, 840, 737, 701, 612, 557, 504, 487 cm^{-1}. HRMS (ESI) calcd. for $C_{39}H_{48}N_2O_4SiSNa$ $[M+Na]^+$: 691.29963; found: 691.29960.

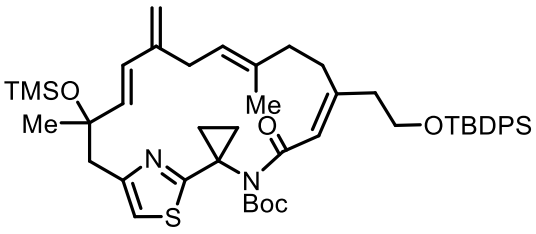
Compound 24. A suspension of anhydrous $CeCl_3$ (2.0 g, 8.11 mmol) in THF (20 mL) was stirred for 2 h at ambient temperature before it was cooled to −78 °C. A solution of $TMSCH_2Li$ (0.7 M in hexane, 9.7 mL, 6.79 mmol) was added dropwise with vigorous stirring. After stirring for 30 min, a solution of enone **23** (701 mg, 1.05 mmol) in THF (10 mL) was added and stirring was continued for another 30 min. *N*,*N*,*N*′,*N*′-Tetramethyl-ethylenediamine (1.4 mL, 9.34 mmol) was introduced and the resulting mixture was stirred for 15 min before it was diluted with pre-cooled *tert*-butyl methyl ether (−78 °C, 30 mL). The mixture was poured into sat. $NaHCO_3$ aq. After separating the two phases, the aqueous layer was extracted with *tert*-butyl methyl ether. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was subjected to the next step without further purification.



A solution of KHMDS (0.5 M in toluene, 5.0 mL, 2.50 mmol) was added at 0 °C to a solution of the crude material in THF (40 mL). After stirring for 30 min, the reaction was quenched with sat. aq. NH_4Cl and the aqueous layer was extracted with *tert*-butyl methyl ether. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, *tert*-butyl methyl ether/hexanes = 1:1) to give the title compound as a pale yellow amorphous solid (472 mg, 68% over 2 steps, ca. 3:2 mixture of rotamers). ^{1}H NMR (600 MHz, C_6D_6, 283 K) δ 7.85 – 7.75 (m, 4H), 7.36 – 7.20 (m, 6H), 6.68 (s(br), 0.4H), 6.48 – 6.42 (m, 1H), 6.19 (d, *J* = 1.2 Hz, 0.6H), 6.15 (s, 0.4H), 6.08 (s, 0.4H), 5.84 (d, *J* = 16.0 Hz, 0.6H), 5.58 (d, *J* = 15.9 Hz, 0.4H), 5.39

(s, 0.6H), 5.23 (s, 0.6H), 5.20 (s(br), 0.6H), 5.01 (t, *J* = 7.0 Hz, 0.6H), 4.96 (d, *J* = 2.3 Hz, 0.6H), 4.90 (d, *J* = 2.3 Hz, 0.6H), 4.85 (d, *J* = 2.1 Hz, 0.4H), 4.81 (d, *J* = 2.1 Hz, 0.4H), 4.64 – 4.60 (m, 0.8H), 4.34 (dt, *J* = 12.6, 4.7 Hz, 0.4H), 3.79 – 3.73 (m, 1.6H), 3.68 (ddd, *J* = 10.3, 7.2, 6.1 Hz, 0.4H), 3.00 (dd, *J* = 14.2, 1.3 Hz, 0.6H), 2.94 – 2.82 (m, 2.6H), 2.77 (dd, *J* = 13.8, 5.9 Hz, 0.4H), 2.55 (d, *J* = 14.2 Hz, 0.6H), 2.54 – 2.46 (m, 0.6H), 2.36 (d, *J* = 13.8 Hz, 0.4H), 2.26 (t, *J* = 6.8 Hz, 1.2H), 2.24 – 2.16 (m, 1.2H), 2.15 – 2.00 (m, 1.6H), 1.97 (ddd, *J* = 10.3, 7.5, 4.3 Hz, 0.4H), 1.84 (dt, *J* = 12.0, 7.2 Hz, 0.4H), 1.74 – 1.68 (m, 0.6H), 1.53 (s, 1.8H), 1.50 (s, 1.8H), 1.47 (s, 1.2H), 1.43 (s, 1.2H), 1.19 (s, 5.4H), 1.17 (s, 3.6H), 1.07 – 1.00 (m, 0.6H), 0.96 – 0.91 (m, 0.4H), 0.88 – 0.76 (m, 1.6H), 0.75 – 0.69 (m, 0.4H). ^{13}C NMR (151 MHz, C_6D_6, 283 K) δ 177.8, 174.8, 166.6, 161.4, 155.9, 154.1, 153.9, 153.2, 146.4, 145.5, 138.1, 136.1, 136.0, 136.0, 134.1, 134.0, 134.0, 133.9, 133.8, 133.7, 130.2, 130.1, 130.1, 129.9, 129.5, 128.2, 124.1, 123.3, 119.5, 117.0, 114.8, 114.7, 114.6, 114.4, 73.4, 72.8, 62.9, 62.5, 44.4, 44.2, 44.1, 42.5, 41.1, 40.4, 36.7, 34.6, 33.2, 32.9, 31.4, 29.8, 29.8, 28.1, 27.1, 27.1, 22.0, 19.7, 19.5, 19.4, 18.2, 16.9, 15.9, 15.3. IR (film) $\tilde{\nu}$ = 3286, 2930, 2857, 1662, 1632, 1517, 1472, 1427, 1389, 1291, 1265, 1184, 1107, 1077, 967, 881, 845, 823, 736, 702, 613, 504 cm^{-1}. HRMS (ESI) calcd. for $C_{40}H_{50}N_2O_3SiSNa$ [M+Na]$^+$: 689.32036; found: 689.32049.

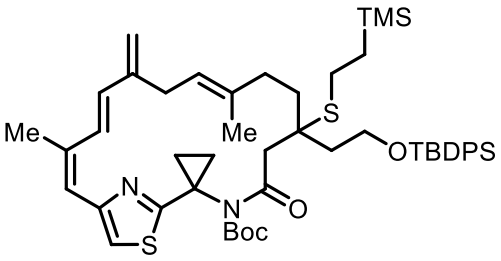
Compound 25. Imidazole (145 mg, 2.13 mmol) and TMSCl (0.14 mL, 1.10 mmol) were added at 0 °C to a solution of compound **24** (472 mg, 0.708 mmol) in CH_2Cl_2 (8.0 mL). After stirring for 30 min, the reaction was quenched with sat. aq. $NaHCO_3$ and the aqueous layer was extracted with *tert*-butyl methyl ether. The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude material was used in the next step without further purification.



Di-*tert*-butyl dicarbonate (0.49 mL, 0.450 mmol) and DMAP (86.4 mg, 0.707 mmol) were added at room temperature to a solution of the crude material in THF (5.0 mL). After stirring for 2 h, the mixture was diluted with hexanes and filtered through a pad of silica gel, which was carefully rinsed with *tert*-butyl methyl ether/hexanes (1:4). The filtrate was evaporated under reduced pressure, and the residue was purified by flash chromatography (silica gel, *tert*-butyl methyl ether/hexanes = 1:10) to give the title compound as a colorless amorphous solid (488 mg, 82% for 2 steps). ^{1}H NMR (400 MHz, C_6D_6) δ 7.80 – 7.73 (m, 4H), 7.31 – 7.18 (m, 6H), 6.93 (s(br), 1H), 6.66 (s, 1H), 6.35 (d, *J* = 15.8 Hz, 1H), 5.81 (d, *J* = 14.4 Hz, 1H), 5.12 (s(br), 1H), 5.02 (d, *J* = 2.3 Hz, 1H), 4.93 (d, *J* = 2.3 Hz, 1H), 3.80 (t, *J* = 6.8 Hz, 2H), 3.27 – 3.01 (m, 2H), 3.00 – 2.81 (m, 2H), 2.67 (s(br), 1H), 2.33 (t, *J* = 6.7 Hz, 2H), 2.29 – 1.98 (m, 3H), 1.53 (s, 6H), 1.34 (s, 9H), 1.32 – 1.20 (m, 4H), 1.18 (s, 9H), 0.19 (s, 9H). ^{13}C NMR (101 MHz, C_6D_6) δ 171.9, 167.8, 157.4, 153.6, 152.5, 146.0, 137.1, 136.0, 134.7, 134.1, 134.1, 130.0, 129.9, 128.1, 123.4, 121.2, 114.8, 82.4, 76.3, 62.8, 46.9, 42.5, 40.1, 39.7, 33.7, 32.2, 29.5, 28.0, 27.2, 22.7, 21.4, 19.5, 16.2, 2.7. IR (film)

$\tilde{\nu}$ = 1735, 1690, 1624, 1458, 1428, 1370, 1298, 1277, 1251, 1156, 1114, 1072, 1010, 841, 740, 703, 613, 505 cm^{-1}. HRMS (ESI) calcd. for $C_{48}H_{66}N_2O_5Si_2SNa$ $[M+Na]^+$: 861.41232; found: 861.41215.

Compound 27. 2-(Trimethylsilyl)ethanethiol (225 mg, 1.68 mmol) and DBU (0.20 mL, 1.34 mmol) were added at ambient temperature to a solution of compound **25** (470 mg, 0.560 mmol) in THF (2.2 mL). After stirring for 3 h, the mixture was diluted with hexanes (4.0 mL) and then filtered through a pad of SiO_2, which was carefully rinsed with a mixture of *tert*-butyl methyl ether/hexanes (1:3). After removing the organic solvent, the resulting crude sulfide was used in the next step without further purification.



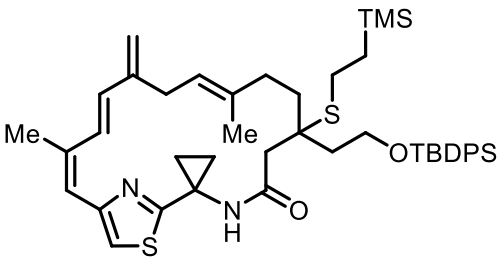
PPTS (3.5 mg, 13.9 µmol) was added at ambient temperature to a solution of the crude sulfide in MeOH (3.5 mL) and CH_2Cl_2 (3.5 mL). After stirring for 30 min, the reaction was quenched with sat. aq. $NaHCO_3$ and the mixture was diluted with brine (10 mL) and *tert*-butyl methyl ether (10 mL). After separating the two phases, the aqueous layer was extracted with *tert*-butyl methyl ether. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude alcohol **26** was used in the next step without further purification.

To a solution of the crude alcohol **26** in CH_2Cl_2 (7.0 mL) was added Et_3N (0.35 mL, 2.51 mmol). MsCl (0.10 mL, 1.29 mmol) was then added dropwise over 10 min at ambient temperature. After stirring for 10 min, the reaction was quenched with sat. aq. $NaHCO_3$. After separating the two phases, the aqueous layer was extracted with *tert*-butyl methyl ether. The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude mixture was purified by flash chromatography (fine silica gel, *tert*-butyl methyl ether/hexanes = 1:20 to 1:1) to give the title compound **27** (161.6 mg) as a colorless amorphous and recovered unreacted alcohol **26** (158 mg).

The recovered alcohol **26** was dissolved in CH_2Cl_2 (5.0 mL). Et_3N (0.10 mL, 0.718 mmol) and MsCl (30 µL, 0.388 mmol) were then successively added over 10 min. After stirring for 10 min, the workup was conducted as above. This operation was repeated twice to give additional crops of the title compound In total, product **27** was obtained as a colorless amorphous solid (255 mg, 52% over 3 steps, 3:2 mixture of rotamers). ^{1}H NMR (600 MHz, CD_2Cl_2, 233 K) δ 7.70 – 7.57 (m, 4H), 7.45 – 7.32 (m, 6H), 7.03 (d, *J* = 1.0 Hz, 0.6H), 6.99 (d, *J* = 15.9 Hz, 0.6H), 6.97 (d, *J* = 1.0 Hz, 0.4H), 6.85 (d, *J* = 16.0 Hz, 0.4H), 6.43 (d, *J* = 17.4 Hz, 0.4H), 6.40 (d, *J* = 16.6 Hz, 0.6H), 6.33 (s, 0.4H), 6.25 (s, 0.6H), 5.08 (s, 1.2H), 5.06 (s, 0.8H), 4.88 (d, *J* = 8.3 Hz, 0.6H), 4.79 (d, *J* = 10.3 Hz, 0.4H), 3.95 – 3.85 (m, 1H), 3.74 – 3.65 (m, 1H), 3.25 (d, *J* = 16.3 Hz, 0.6H), 3.15 (dd, *J* = 16.5, 8.6 Hz, 0.6H), 3.07 (dd, *J* = 16.1, 7.6 Hz, 0.4H), 3.02 (d, *J* = 17.5 Hz, 0.4H), 2.90 (d, *J* = 17.5 Hz, 0.4H), 2.83 (d, *J* = 13.8 Hz, 0.6H), 2.81 (d, *J* = 14.1 Hz, 0.4H), 2.67 – 2.53 (m, 1H), 2.48 (d, *J* = 16.2 Hz, 0.6H), 2.44 – 2.38 (m, 0.6H), 2.31 – 2.23 (m, 1.2H), 2.07 (td, *J* = 10.8, 6.1 Hz,

0.6H), 2.03 – 2.00 (m, 0.6H), 1.99 (d, *J* = 1.5 Hz, 1.2H), 1.95 (dd, *J* = 14.9, 5.0 Hz, 0.4H), 1.92 (d, *J* = 1.4 Hz, 1.8H), 1.87 (ddd, *J* = 16.9, 11.7, 5.8 Hz, 1.2H), 1.81 – 1.71 (m, 0.4H), 1.69 – 1.60 (m, 1H), 1.58 (s, 1.2H), 1.57 (s, 3.6H), 1.56 (s, 1.8H), 1.53 (s, 5.4H), 1.53 – 1.50 (m, 0.6H), 1.46 – 1.30 (m, 2.2H), 1.23 – 0.97 (m, 1.2H), 1.00 – 0.97 (m, 0.4H), 0.96 (s, 5.4H), 0.93 (s, 3.6H), 0.68 – 0.62 (m, 0.8H), 0.57 – 0.45 (m, 1.2H), −0.05 (s, 5.4H), −0.07 (s, 3.6H), −0.22 (s(br), 0.6H). ^{13}C NMR (151 MHz, CD_2Cl_2, 233 K) δ 171.9, 171.3, 171.0, 170.2, 153.6, 152.3, 150.4, 149.7, 146.3, 146.3, 137.8, 136.9, 135.9, 135.5, 135.5, 135.5, 135.4, 134.9, 133.6, 133.5, 133.5, 133.3, 132.8, 132.7, 129.6, 129.6, 129.5, 129.5, 127.8, 127.7, 127.6, 127.6, 127.6, 124.2, 124.1, 123.9, 122.2, 118.4, 118.3, 117.4, 116.4, 84.1, 84.0, 61.0, 61.0, 51.1, 50.0, 43.3, 42.3, 40.9, 38.5, 38.2, 38.1, 36.6, 34.2, 34.1, 33.4, 33.2, 32.9, 27.7, 27.6, 26.4, 26.3, 22.7, 22.0, 21.7, 21.0, 20.4, 20.1, 18.9, 18.9, 18.1, 17.0, 16.5, 15.4, 14.9, −2.2. IR (film) $\tilde{\nu}$ = 2932, 1774, 1735, 1424, 1368, 1300, 1249, 1155, 1112, 1071, 1000, 853, 740, 703, 614, 505 cm^{-1}. HRMS (ESI) calcd. for $C_{50}H_{70}N_2O_4Si_2S_2Na$ $[M+Na]^+$: 905.42078; found: 905.42119.

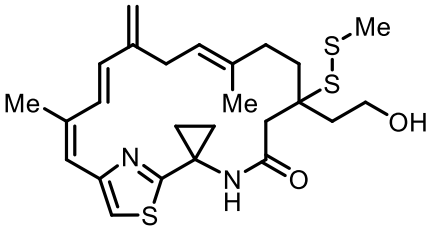
Compound S4. 2,6-Lutidine (0.35 mL, 3.01 mmol) and TMSOTf (0.25 mL, 1.38 mmol) were added at 0 °C to a solution of compound **27** (188 mg, 0.213 mmol) in CH_2Cl_2 (10 mL). After stirring for 24 h at ambient temperature, the reaction was quenched with sat. aq. $NaHCO_3$ and the aqueous layer was extracted with *tert*-butyl methyl ether. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (fine silica gel, *tert*-butyl methyl ether/hexanes = 1:4 to 1:3) to give the title compound as a colorless oil (96.8 mg, 58%, 7:3 mixture of rotamers). ^{1}H NMR (600 MHz, MeOD, 233 K) δ 7.77 – 7.61 (m, 4H), 7.51 – 7.38 (m, 6H), 7.36 (s, 0.3H), 7.30 (s, 0.7H), 7.10 (d, *J* = 16.0 Hz, 0.3H), 6.87 (d, *J* = 16.1 Hz, 0.7H), 6.49 – 6.44 (m, 1H), 6.36 (s, 0.7H), 6.31 (s, 0.3H), 5.14 – 5.07 (m, 2H), 4.89 – 4.80 (m, 1H), 4.05 – 3.98 (m, 1H), 3.81 – 3.71 (m, 1H), 3.31 – 3.26 (m, 0.3H), 3.15 (d, *J* = 15.3 Hz, 0.3H), 3.02 (dd, *J* = 15.5, 6.5 Hz, 0.7H), 2.95 (dd, *J* = 15.7, 5.5 Hz, 0.7H), 2.85 (d, *J* = 16.3 Hz, 0.3H), 2.63 – 2.57 (m, 1H), 2.38 – 2.34 (m, 2.4H), 2.30 – 2.24 (m, 0.7H), 2.17 – 2.09 (m, 0.3H), 2.09 – 2.00 (m, 2.4H), 1.98 (s, 0.9H), 1.97 – 1.91 (m, 0.3H), 1.90 – 1.75 (m, 2.4H), 1.68 – 1.58 (m, 1.5H), 1.54 (s, 2.1H), 1.45 – 1.11 (m, 4.7H), 1.02 (s, 6.3H), 1.00 – 0.96 (m, 3.4H), 0.68 (t, *J* = 8.7 Hz, 1.4H), 0.62 – 0.48 (m, 0.6H), 0.01 (s, 6.3H), −0.02 (s, 2.7H), −0.03 – −0.07 (m, 0.3H). ^{13}C NMR (151 MHz, MeOD, 233 K) δ 177.2, 175.4, 173.1, 172.2, 152.2, 151.9, 147.9, 147.8, 139.4, 138.3, 137.0, 136.7, 136.7, 136.7, 136.3, 134.5, 134.5, 134.1, 134.1, 133.8, 131.1, 131.1, 130.9, 130.8, 129.1, 129.1, 129.0, 129.0, 128.9, 125.9, 125.3, 124.8, 124.3, 119.2, 119.1, 119.0, 62.2, 62.0, 51.1, 50.9, 44.3, 41.3, 40.1, 39.7, 38.6, 36.7, 35.6, 34.6, 34.3, 34.1, 33.5, 33.3, 27.3, 27.1, 23.3, 23.1, 20.8, 20.5, 20.0, 19.9, 17.0, 16.9, 16.4, 16.1, 15.2, 15.1, −1.5, −1.6. IR (film) $\tilde{\nu}$ = 3243, 2927, 2855, 1737, 1673, 1506, 1428,



1389, 1290, 1249, 1111, 1081, 857, 840, 739, 703, 613, 506 cm^{-1}. HRMS (ESI) calcd. for $C_{45}H_{62}N_2O_2Si_2S_2Na$ $[M+Na]^+$: 805.36835; found: 805.36953.

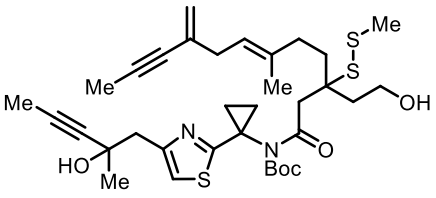
Compound S5. A solution of dimethyl(methylthio)-sulfonium tetrafluoroborate (3.3 mg, 16.8 µmol) in MeCN (0.50 mL) was added dropwise over 5 min at 0 °C to a solution of compound **S4** (12 mg, 15.3 µmol) and dimethyl disulfide (27 µL, 0.305 mmol) in THF (1.0 mL) and MeCN (0.50 mL). After stirring for 10 min, the reaction was quenched with sat. $NaHCO_3$ aq. After separation of the two phases, the aqueous layer was extracted with *tert*-butyl methyl ether, and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified with flash chromatography (silica gel, *tert*-butyl methyl ether/hexanes = 1:3 to 1:2) to give unreacted starting material **S4** (2.6 mg) and the title compound **S5** as a colorless oil (3.0 mg, 34% based on the recovered starting material, 7:3 mixture of rotamers). ^{1}H NMR (600 MHz, MeOD) δ 7.71 – 7.59 (m, 4H), 7.46 – 7.33 (m, 6H), 7.25 (d, *J* = 1.0 Hz, 0.3H), 7.16 (d, *J* = 1.1 Hz, 0.7H), 7.07 (d, *J* = 16.0 Hz, 0.3H), 6.91 (d, *J* = 16.4 Hz, 0.7H), 6.48 – 6.38 (m, 1H), 6.33 (s, 1H), 5.10 – 5.07 (m, 0.6H), 5.07 – 5.03 (m, 1.4H), 4.89 (t, *J* = 3.6 Hz, 0.7H), 4.85 – 4.81 (m, 0.3H), 4.00 (td, *J* = 9.3, 5.9 Hz, 0.3H), 3.94 (dt, *J* = 10.3, 6.8 Hz, 0.7H), 3.84 – 3.75 (m, 1H), 3.37 (d, *J* = 15.4 Hz, 0.3H), 3.23 (dd, *J* = 16.2, 8.2 Hz, 0.3H), 2.97 (dd, *J* = 15.5, 6.4 Hz, 0.7H), 2.92 (dd, *J* = 15.6, 6.1 Hz, 0.7H), 2.85 (d, *J* = 16.0 Hz, 0.3H), 2.58 (d, *J* = 14.4 Hz, 0.7H), 2.55 – 2.49 (m, 0.3H), 2.46 (d, *J* = 14.4 Hz, 0.7H), 2.30 (s, 2.1H), 2.29 – 2.21 (m, 1H), 2.10 (s, 0.9H), 2.06 – 2.02 (m, 0.3H), 2.01 (d, *J* = 1.4 Hz, 2.1H), 1.97 (d, *J* = 1.4 Hz, 0.9H), 1.97 – 1.93 (m, 0.7H), 1.82 (dt, *J* = 10.4, 5.4 Hz, 1.4H), 1.80 – 1.71 (m, 0.3H), 1.69 – 1.63 (m, 0.3H), 1.63 (s, 0.9H), 1.52 (d, *J* = 1.3 Hz, 2.1H), 1.53 – 1.45 (m, 1H), 1.44 – 1.25 (m, 1.7H), 1.24 – 1.08 (m, 3H), 1.03 (s, 6.3H), 1.01 (s, 2.7H), 0.41 (t, *J* = 13.3 Hz, 0.3H). ^{13}C NMR (151 MHz, MeOD) δ 177.2, 175.4, 172.5, 172.5, 152.8, 152.2, 147.9, 147.9, 139.3, 138.5, 136.8, 136.7, 136.7, 136.4, 136.2, 134.8, 134.5, 134.0, 133.6, 130.9, 130.8, 130.7, 129.3, 129.2, 128.9, 128.8, 128.7, 126.1, 124.7, 124.7, 124.4, 118.9, 118.7, 118.6, 62.1, 62.0, 56.4, 56.3, 43.5, 40.9, 40.2, 38.9, 38.7, 36.4, 35.2, 34.5, 34.4, 34.2, 33.9, 27.4, 27.4, 25.0, 24.8, 20.3, 20.2, 20.0, 19.9, 16.9, 16.8, 15.7, 15.5. IR (film) $\tilde{\nu}$ = 3309, 3071, 2929, 2856, 1673, 1503, 1427, 1390, 1289, 1251, 1110, 1079, 823, 738, 703, 614, 506 cm^{-1}. HRMS (ESI) calcd. for $C_{41}H_{53}N_2O_2SiS_3$ $[M+H]^+$: 729.30329; found: 729.30384.

Compound 28. Pyridine (180 µL, 2.23 mmol) was added to a solution of HF·pyridine (hydrogen fluoride



≈70 % *w/w*, 60 µL, ca. 0.466 mmol) in MeCN (0.40 mL) at 0 °C. This mixture was then added to a solution of compound **S5** (15.0 mg, 20.6 µmol) in THF (0.50 mL) and MeCN (0.50 mL) at ambient temperature. After stirring for 2 h, the reaction was quenched with sat. aq. $NaHCO_3$, the two phases were separated, and the aqueous layer was extracted with *tert*-butyl methyl ether. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, *tert*-butyl methyl ether/hexanes = 2:1 to 3:1) to give the title compound as a colorless oil (7.2 mg, 71%, 7:3 mixture of rotamers). ^{1}H NMR (600 MHz, MeOD) δ 7.29 (d, *J* = 1.0 Hz, 0.3H), 7.19 (d, *J* = 1.1 Hz, 0.7H), 7.07 (dd, *J* = 16.1, 0.9 Hz, 0.3H), 6.91 (dd, *J* = 16.1, 0.8 Hz, 0.7H), 6.46 (d, *J* = 16.0 Hz, 0.3H), 6.44 (d, *J* = 16.1 Hz, 0.7H), 6.36 (s, 0.3H), 6.35 (s, 0.7H), 5.11 – 5.07 (m, 0.6H), 5.08 – 5.06 (m, 1.4H), 4.93 (tq, *J* = 6.7, 1.3 Hz, 0.7H), 4.87 – 4.85 (m, 0.3H), 3.86 (ddd, *J* = 10.4, 8.5, 6.6 Hz, 0.3H), 3.83 (ddd, *J* = 10.8, 7.5, 6.1 Hz, 0.7H), 3.69 (ddd, *J* = 10.7, 6.6, 5.3 Hz, 0.7H), 3.65 (ddd, *J* = 10.4, 9.2, 5.0 Hz, 0.3H), 3.53 (d, *J* = 15.2 Hz, 0.3H), 3.25 (dd, *J* = 16.1, 8.5 Hz, 0.3H), 3.03 (dd, *J* = 16.0, 7.0 Hz, 0.7H), 2.91 (dd, *J* = 15.8, 5.3 Hz, 0.7H), 2.84 (d, *J* = 16.3 Hz, 0.3H), 2.59 (d, *J* = 13.7 Hz, 0.7H), 2.46 (dd, *J* = 13.8, 0.9 Hz, 0.7H), 2.42 – 2.37 (m, 0.3H), 2.38 (d, *J* = 15.3 Hz, 0.3H), 2.37 (s, 2.1H), 2.13 (s, 0.9H), 2.12 – 2.06 (m, 1H), 2.03 (d, *J* = 1.4 Hz, 2.1H), 1.99 (d, *J* = 1.4 Hz, 0.9H), 1.97 (td, *J* = 12.4, 4.3 Hz, 0.7H), 1.93 – 1.84 (m, 1.4H), 1.84 – 1.77 (m, 0.3H), 1.64 (t, *J* = 1.5 Hz, 0.9H), 1.62 – 1.56 (m, 0.6H), 1.58 (q, *J* = 1.1 Hz, 2.1H), 1.51 (ddd, *J* = 14.4, 12.4, 4.7 Hz, 0.7H), 1.43 – 1.40 (m, 2H), 1.32 – 1.23 (m, 2H), 1.19 (ddd, *J* = 14.1, 12.4, 4.5 Hz, 0.7H), 0.38 (td, *J* = 13.4, 2.9 Hz, 0.3H). ^{13}C NMR (151 MHz, MeOD) δ 177.6, 175.3, 172.8, 172.4, 152.7, 152.2, 147.9, 147.9, 139.3, 138.6, 136.5, 136.3, 134.0, 133.6, 129.2, 129.2, 126.3, 124.8, 124.7, 124.3, 118.9, 118.8, 118.8, 118.6, 59.7, 59.1, 56.4, 56.3, 43.2, 40.8, 39.8, 39.1, 38.6, 37.5, 35.3, 34.5, 34.4, 34.2, 33.9, 25.0, 24.7, 20.3, 20.2, 16.9, 16.8, 15.6, 15.3. IR (film) $\tilde{\nu}$ = 3264, 2921, 2853, 1658, 1504, 1446, 1379, 1289, 1193, 1065, 1029, 968, 735 cm^{-1}. HRMS (ESI) calcd. for $C_{25}H_{35}N_2O_2S_3$ $[M+H]^+$: 491.18552; found: 491.18581.

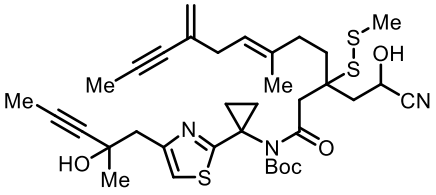
Compound 29. The compound (mixture of diastereomers and rotamers) analyzed as follows: ^{1}H NMR



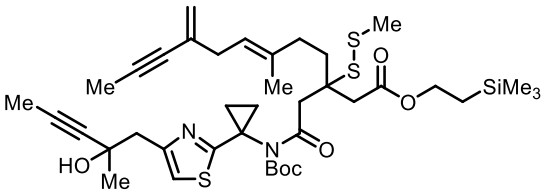
(400 MHz, MeOD) δ 7.08 (s, 1H), 5.28 – 5.19 (m, 1H), 5.15 – 5.07 (m, 2H), 3.73 (t, *J* = 7.1 Hz, 2H), 3.30 – 3.17 (m, 2H), 2.99 (s, 2H), 2.80 (d, *J* = 7.2 Hz, 2H), 2.43 (s, 3H), 2.24 – 1.94 (m, 5H), 1.90 (s, 3H), 1.88 – 1.85 (m, 1H), 1.84 – 1.76 (m, 2H), 1.75 (s, 3H), 1.63 (d, *J* = 1.4 Hz, 3H), 1.58 – 1.46 (m, 2H), 1.46 (s, 9H), 1.40 (s, 3H). ^{13}C NMR (101 MHz, MeOD) δ 174.6, 174.0, 154.5, 153.1, 138.2, 132.6, 122.3, 119.4, 115.9, 86.2, 84.8, 83.8, 81.3, 80.11, 80.09, 68.66, 68.64, 59.2, 56.8, 45.6, 44.0, 41.4, 36.9, 35.0, 29.95, 29.93, 28.2, 24.9,

24.2, 16.5, 3.8, 3.1. IR (film) $\tilde{\nu}$ = 3393, 2976, 2918, 1734, 1369, 1285, 1255, 1156, 1120, 1077, 895, 848, 772 cm^{-1}. HRMS (ESI) calcd. for $C_{34}H_{49}N_2O_5S_3$ $[M+H]^+$: 661.27981; found: 661.28059.

Compound S6. A buffer solution was prepared by mixing MeOH (3.0 mL), H_2O (0.40 mL), HOAc (0.20 mL), and NaOAc (286 mg). In a separate flask, AZADO-BF_4 **33** (25.3 mg, 0.106 mmol)[8] was added to a solution of compound **29** (35.0 mg, 53.0 µmol) and 2,6-lutidine (12 µL, 0.106 mmol) in CH_2Cl_2 (3.0 mL) at ambient temperature. After 5 min, the buffer solution (1.6 mL) was added, followed by NaCN (13.0 mg, 0.265 mmol). After stirring for 4.5 h, sat. aq. $NaHCO_3$ was introduced and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (fine silica, EtOAc/hexanes = 1:3) to give the title compound as a colorless oil (27.7 mg, 76 %). Because the product contains four diastereomers and their rotamers, no detailed analysis of the NMR spectra was carried out; rather the product was directly used in the next step. HRMS (ESI) calcd. for $C_{35}H_{47}N_3O_5S_3Na$ $[M+Na]^+$: 708.25701; found: 708.25704.



Compound 30. Dess-Martin periodinane (51.44 mg, 0.121 mmol) was added to a solution of compound **S6** (27.7 mg, 40.4 µmol) in CH_2Cl_2 (2.0 mL) at ambinent temperature. After stirring for 30 min, 2-(trimethylsilyl)ethanol (0.12 mL, 0.808 mmol) and $NaHCO_3$ (33.9 mg, 0.404 mmol) were added, and stirring was continued for 1 h. The reaction was quenched with sat. aq. $NaHCO_3$ and the aqueous phase was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified with flash chromatography (silica gel, EtOAc/hexanes = 1:5) to give the title compound as a colorless amorphous solid (18.0 mg, 58%, ca. 1:1:1:1 mixture of rotamers of two diastereomers). ^{1}H NMR (600 MHz, CD_2Cl_2, 233 K) δ 6.88 – 6.82 (m, 1H), 5.43 (d, *J* = 2.0 Hz, 0.5H), 5.24 – 5.20 (m, 0.5H), 5.20 – 5.15 (m, 1H), 5.15 – 5.11 (m, 1H), 5.10 – 5.06 (m, 1H), 4.13 – 4.01 (m, 2H), 3.62 (d, *J* = 18.3 Hz, 0.25H), 3.59 (d, *J* = 18.3 Hz, 0.25H), 3.47 (d, *J* = 18.1 Hz, 0.25H), 3.44 (d, *J* = 18.1 Hz, 0.25H), 3.29 (d, *J* = 18.0 Hz, 0.25H), 3.24 (d, *J* = 18.0 Hz, 0.25H), 3.16 (d, *J* = 18.3 Hz, 0.25H), 3.15 (d, *J* = 18.4 Hz, 0.25H), 2.97 – 2.71 (m, 6H), 2.44 – 2.36 (m, 3H), 2.17 – 1.70 (m, 10H), 1.70 – 1.59 (m, 3H), 1.59 – 1.53 (m, 3H), 1.49 – 1.31 (m, 13H), 0.98 – 0.88 (m, 2H), −0.01 (s, 9H). ^{13}C NMR (151 MHz, CD_2Cl_2, 233 K) δ 173.93, 173.88, 173.8, 173.7, 173.4, 173.2, 172.8, 172.7, 170.59, 170.56, 170.53, 152.71, 152.68, 152.66, 152.62, 152.3, 152.2, 152.0, 151.9, 137.15, 137.14, 137.05, 137.03, 130.80, 130.79, 130.77, 120.51, 120.47, 120.44, 119.2, 114.2, 114.1, 113.9, 85.60, 85.58, 85.57, 83.7, 83.6, 83.5, 83.4, 82.6, 82. 5, 80.1,

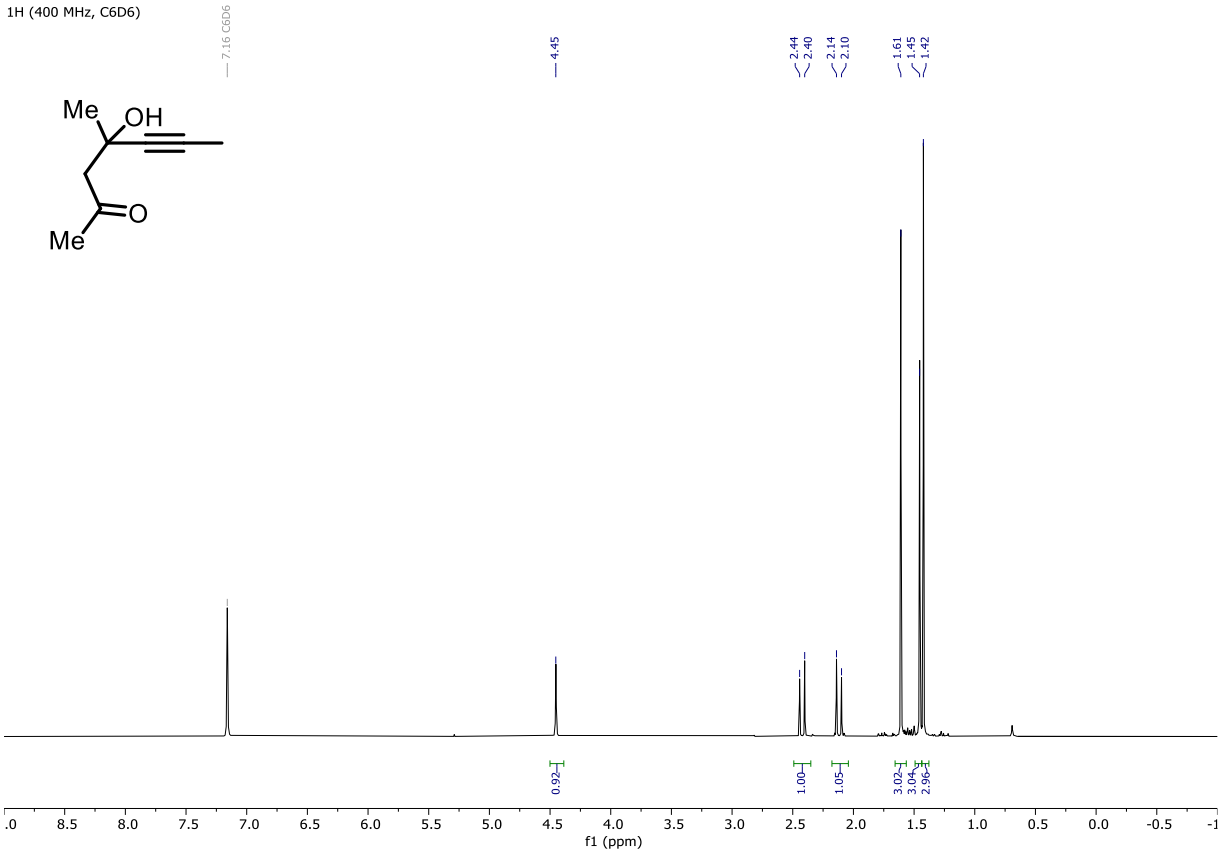


80.0, 78.50, 78.48, 78.2, 67.5, 67.4, 67.3, 62.8, 62.7, 54.29, 54.27, 53.92, 53.89, 43.7, 43.6, 41.9, 41.8, 41.7, 40.8, 40.7, 40.2, 40.06, 40.05, 40.02, 39.99, 39.92, 39.86, 35.7, 34.64, 34.55, 34.41, 34.36, 33.6, 33.4, 29.89, 29.86, 29.79, 27.5, 27.4, 24.5, 24.41, 24.39, 24.26, 24.17, 23.9, 23.7, 23.6, 23.5, 23.4, 23.3, 17.08, 17.06, 17.02, 17.01, 16.2, 16.1, 4.2, 3.39, 3.36, 3.27, 3.26, −1.87, −1.88. IR (film) $\tilde{\nu}$ = 3410, 2977, 2953, 2919, 1734, 1369, 1287, 1252, 1157, 1121, 1078, 857, 839, 772 cm^{-1}. HRMS (ESI) calcd. for $C_{39}H_{58}N_2O_6S_3SiNa$ $[M+Na]^+$: 797.31185; found: 797.31260.

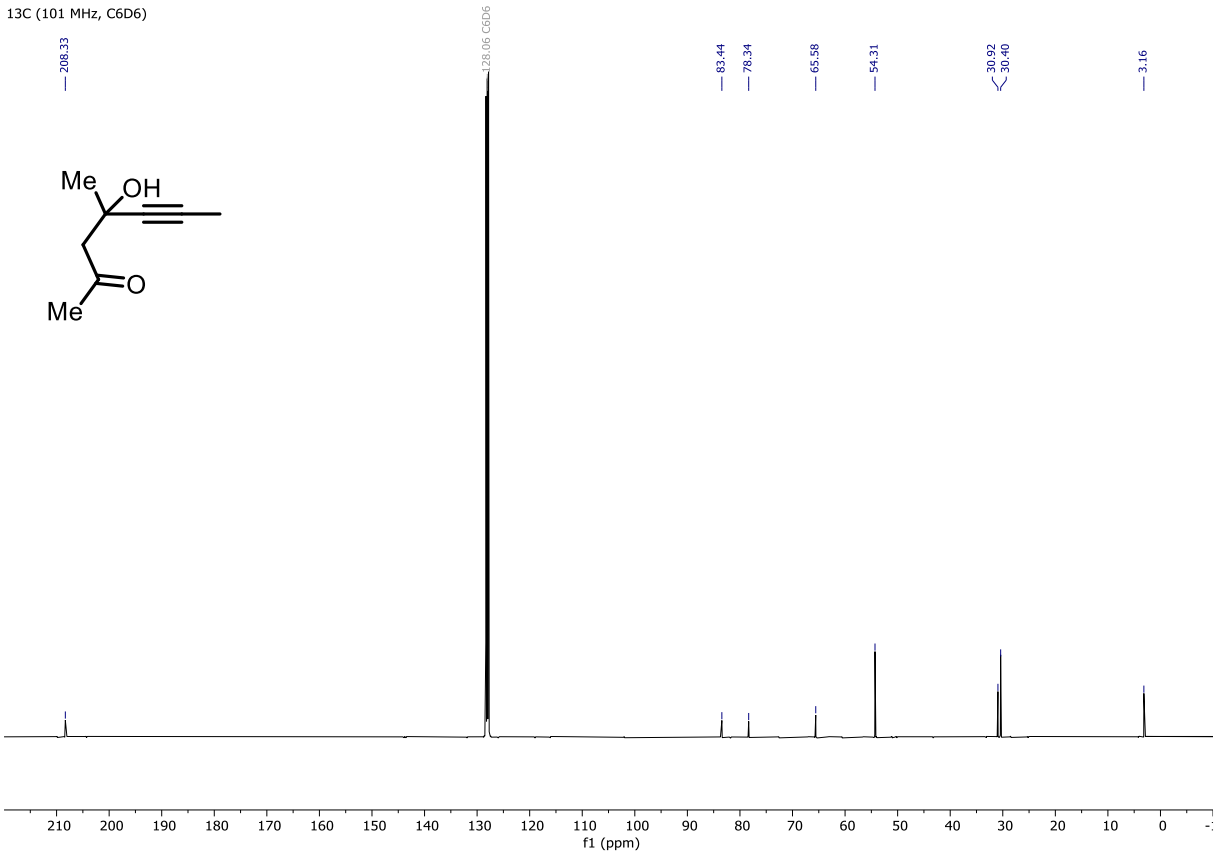
COPIES OF SPECTRA

Compound **6**

1H (400 MHz, C6D6)

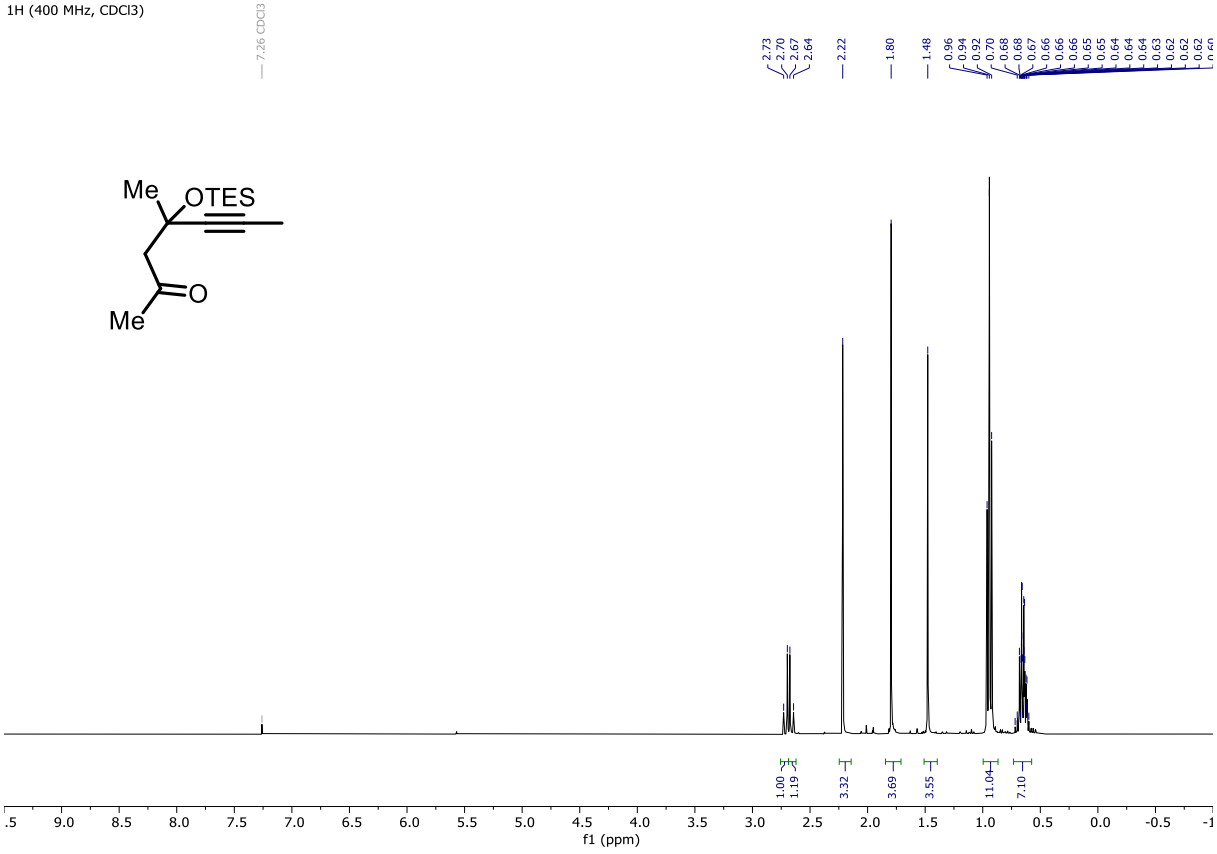


13C (101 MHz, C6D6)

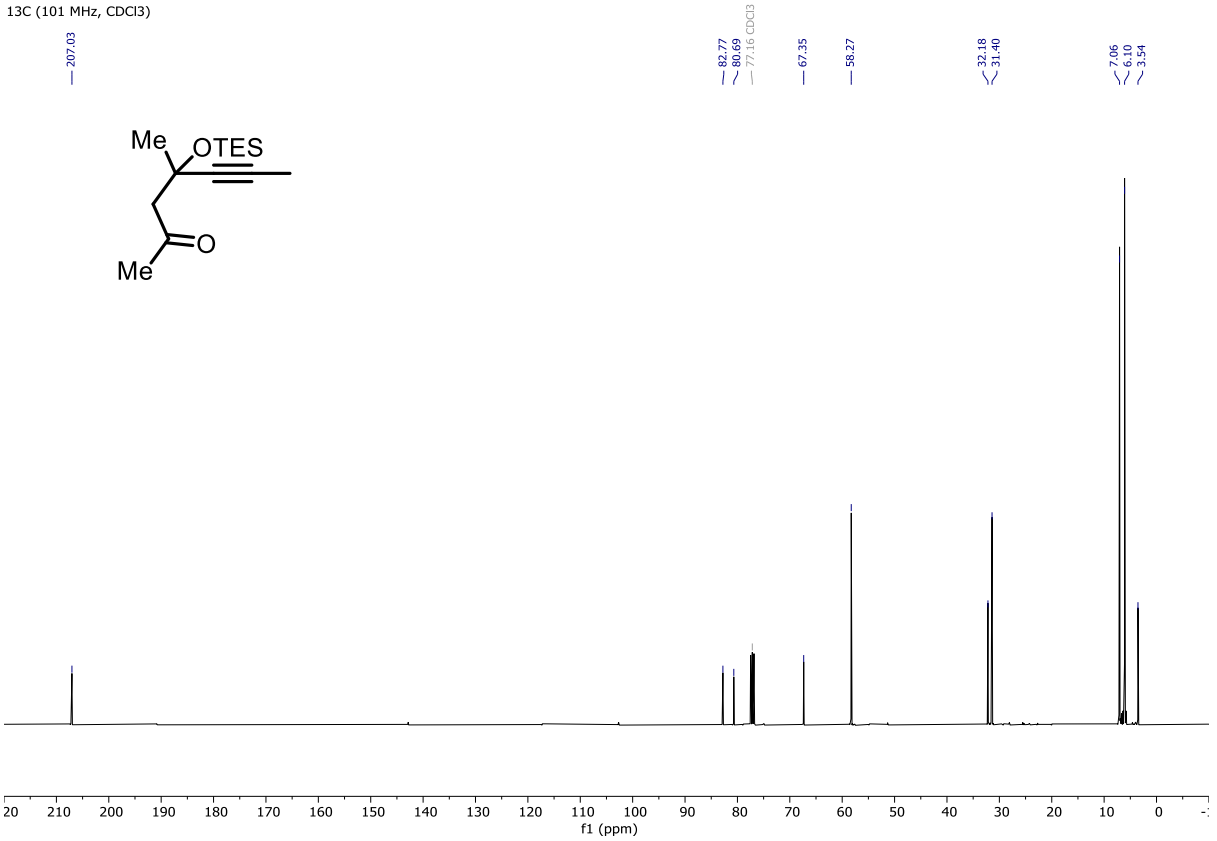


Compound **S1**

1H (400 MHz, CDCl3)

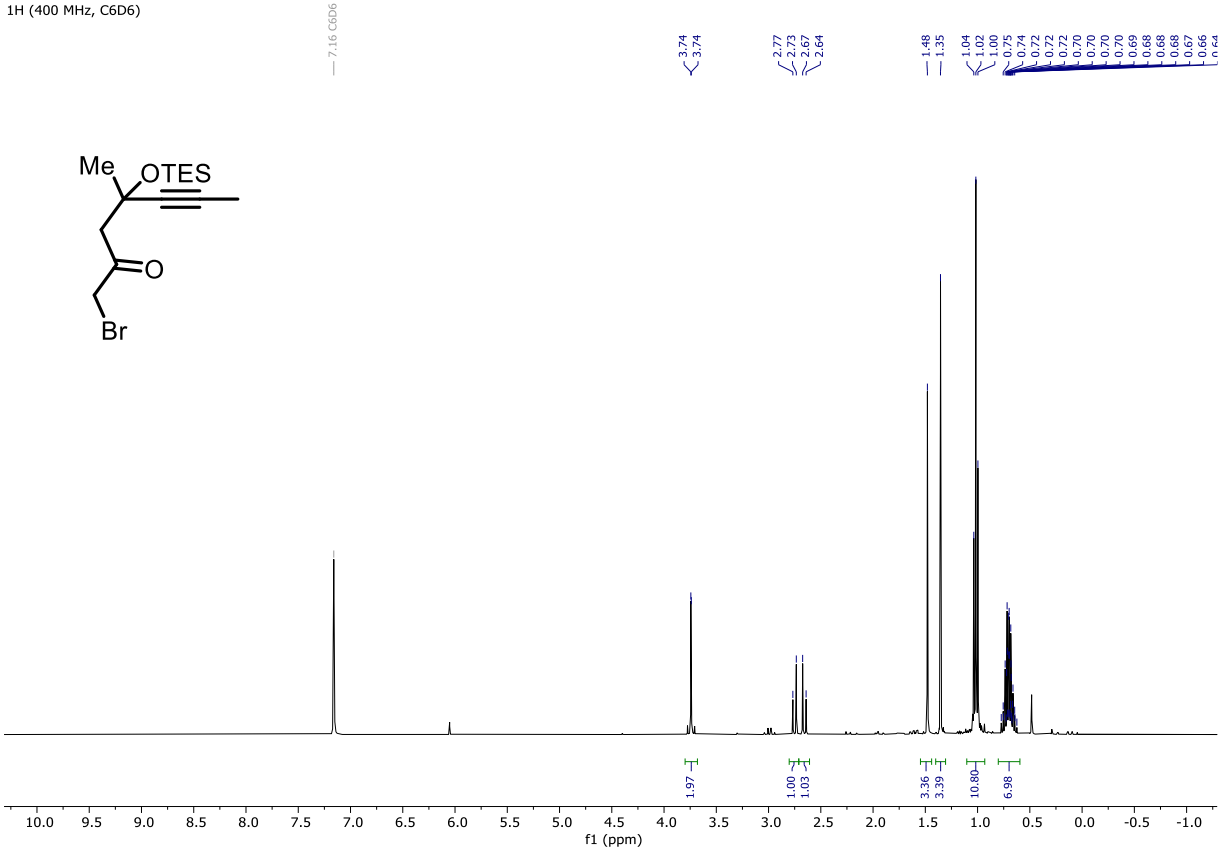


13C (101 MHz, CDCl3)

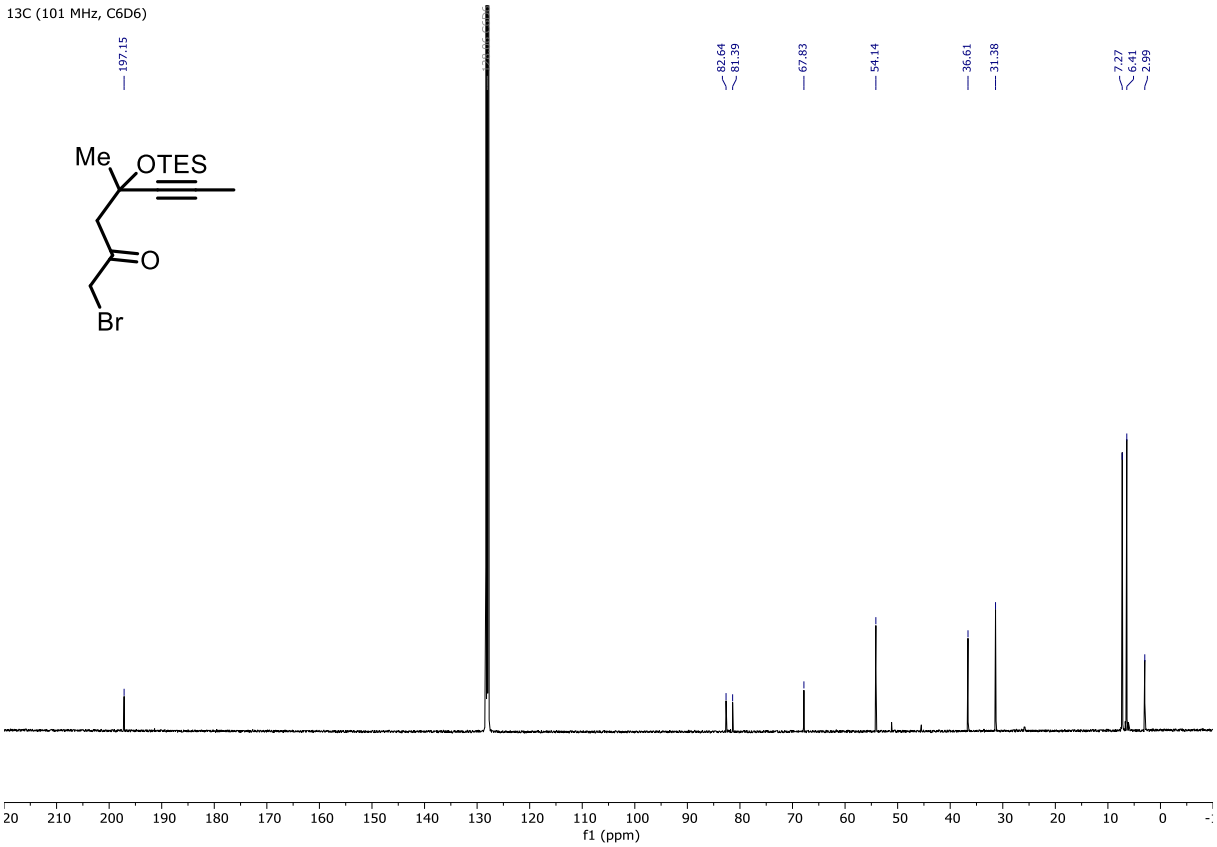


Compound **7**

1H (400 MHz, C6D6)

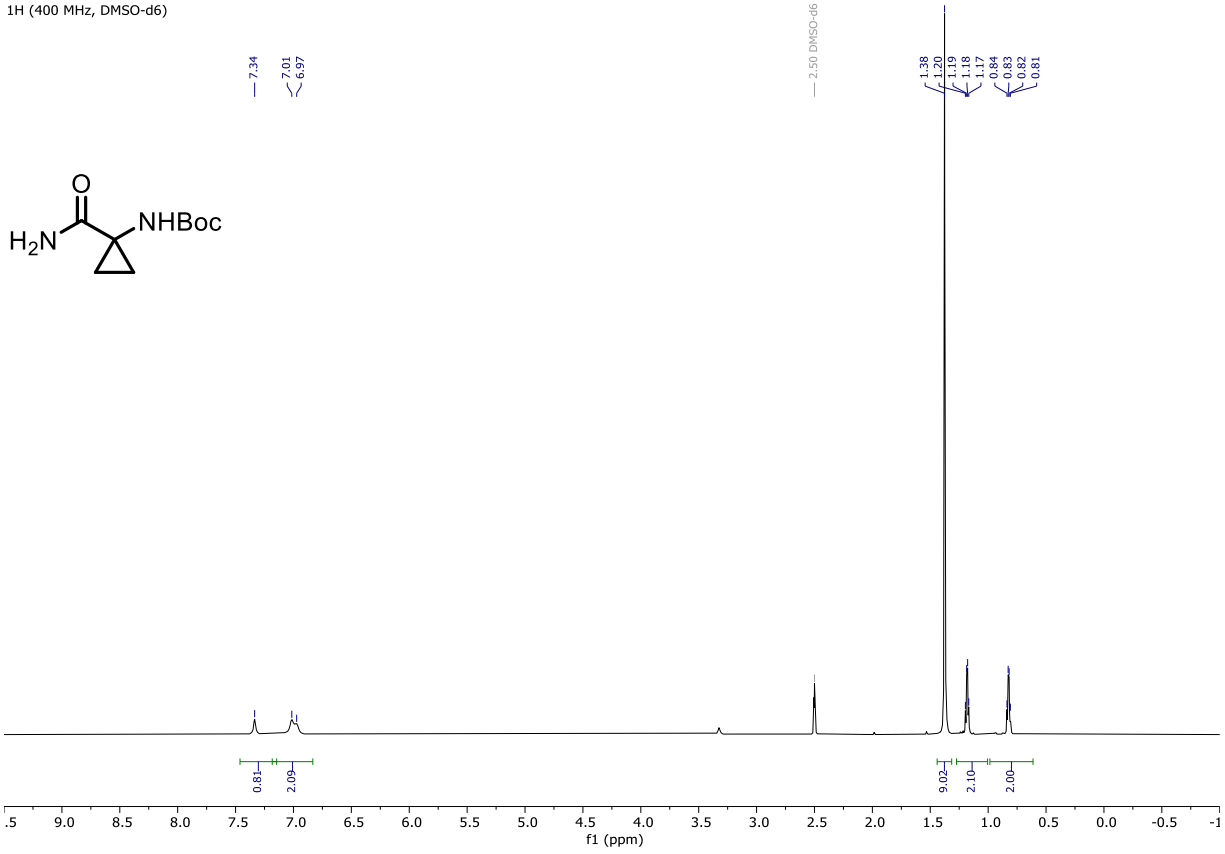


13C (101 MHz, C6D6)

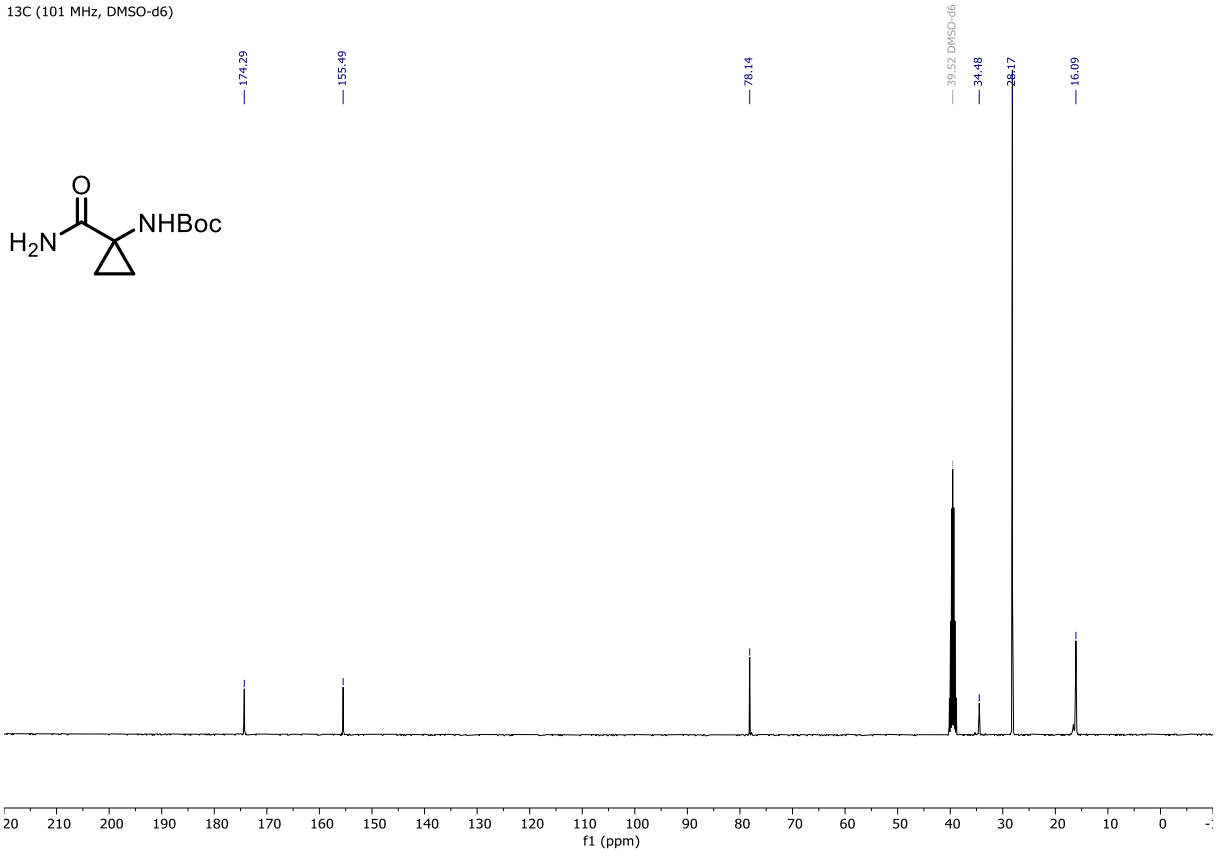


Compound **S2**

1H (400 MHz, DMSO-d6)

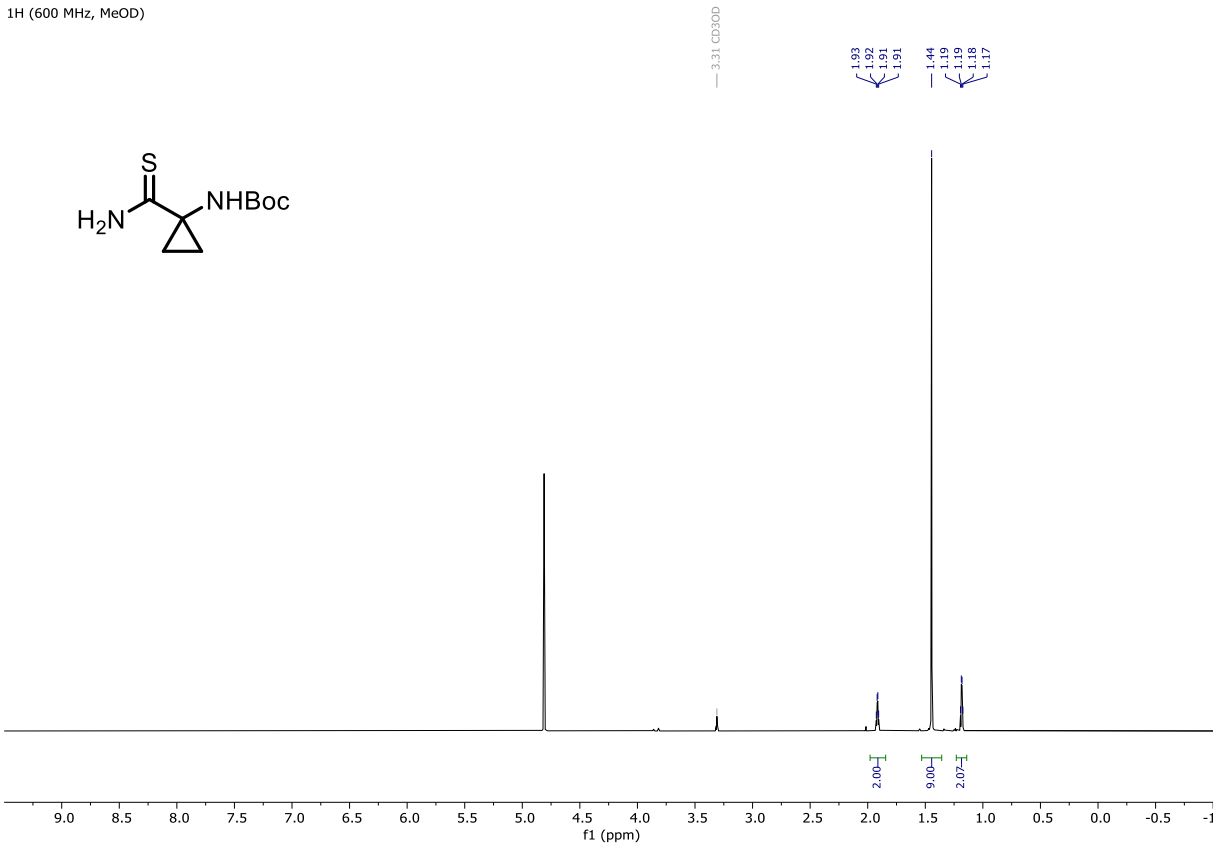


13C (101 MHz, DMSO-d6)

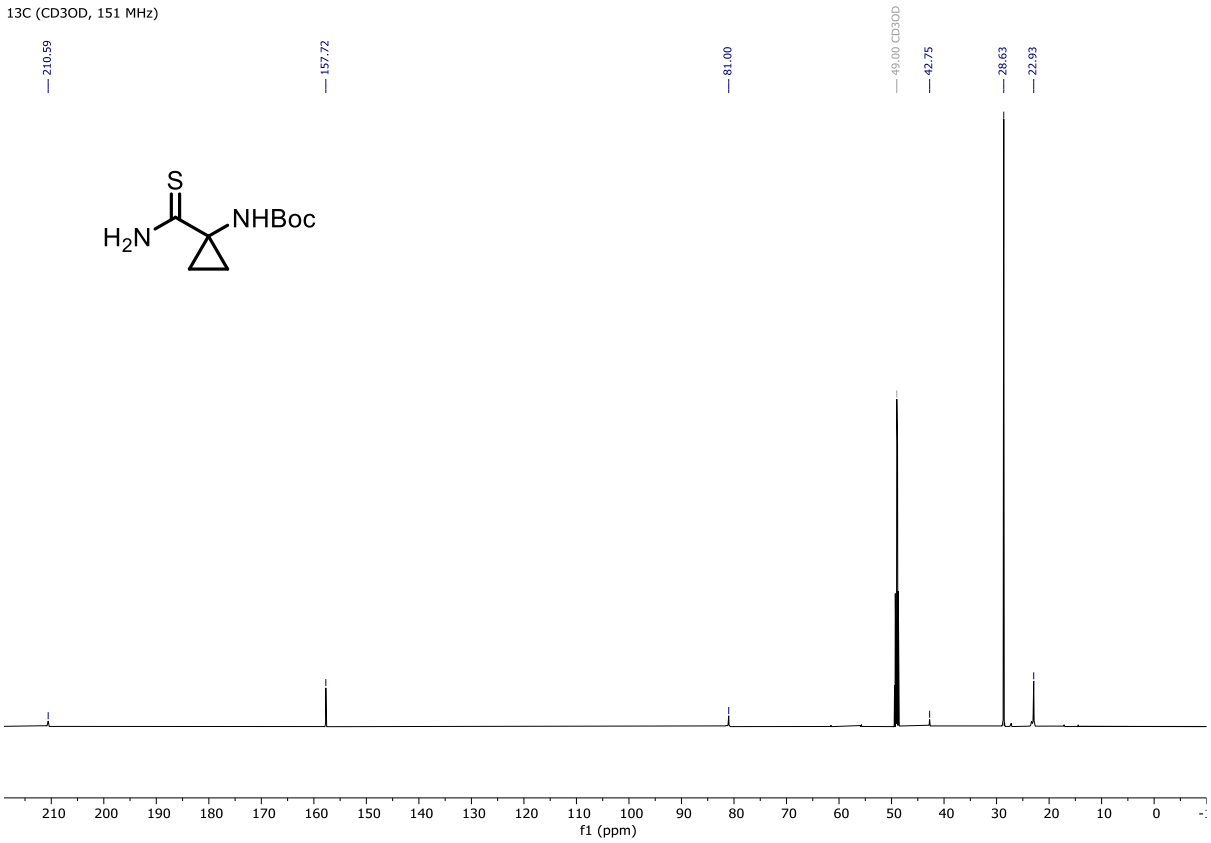


Compound **9**

1H (600 MHz, MeOD)

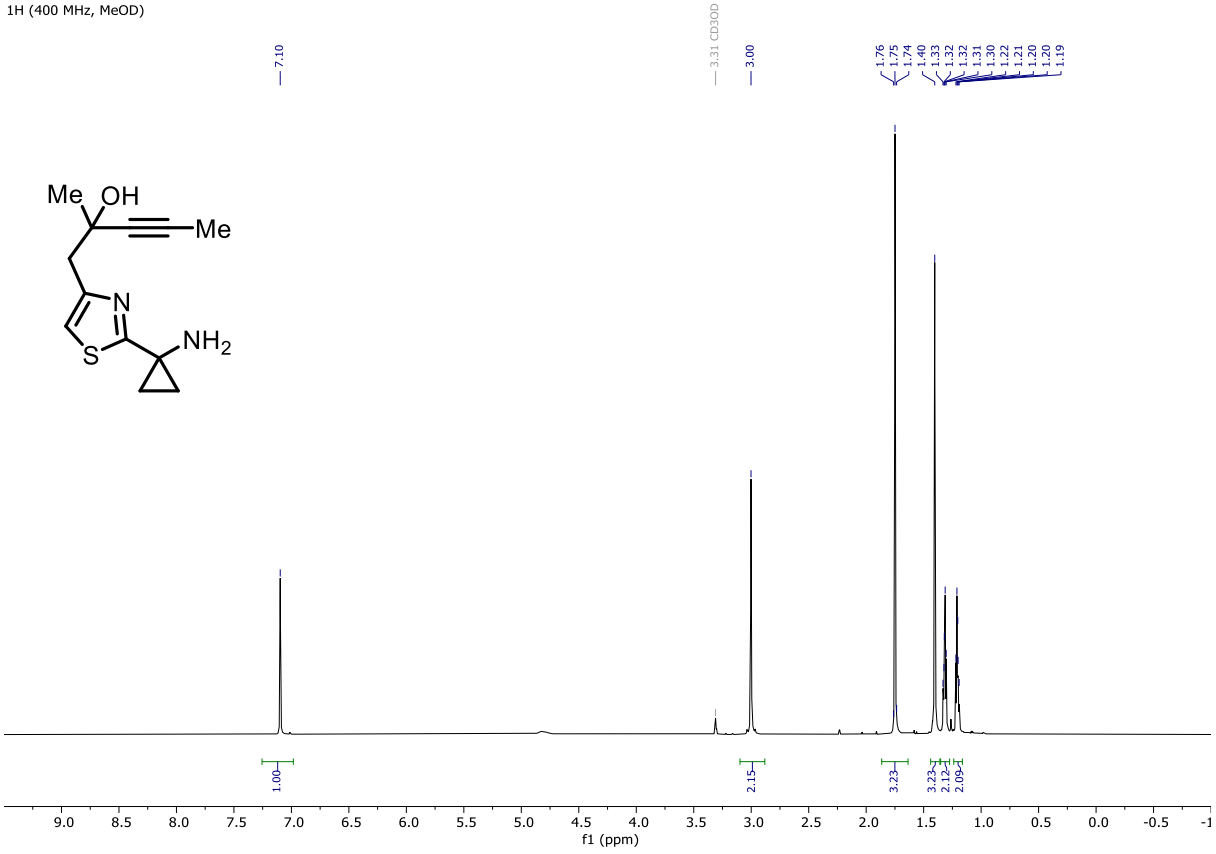


13C (CD3OD, 151 MHz)

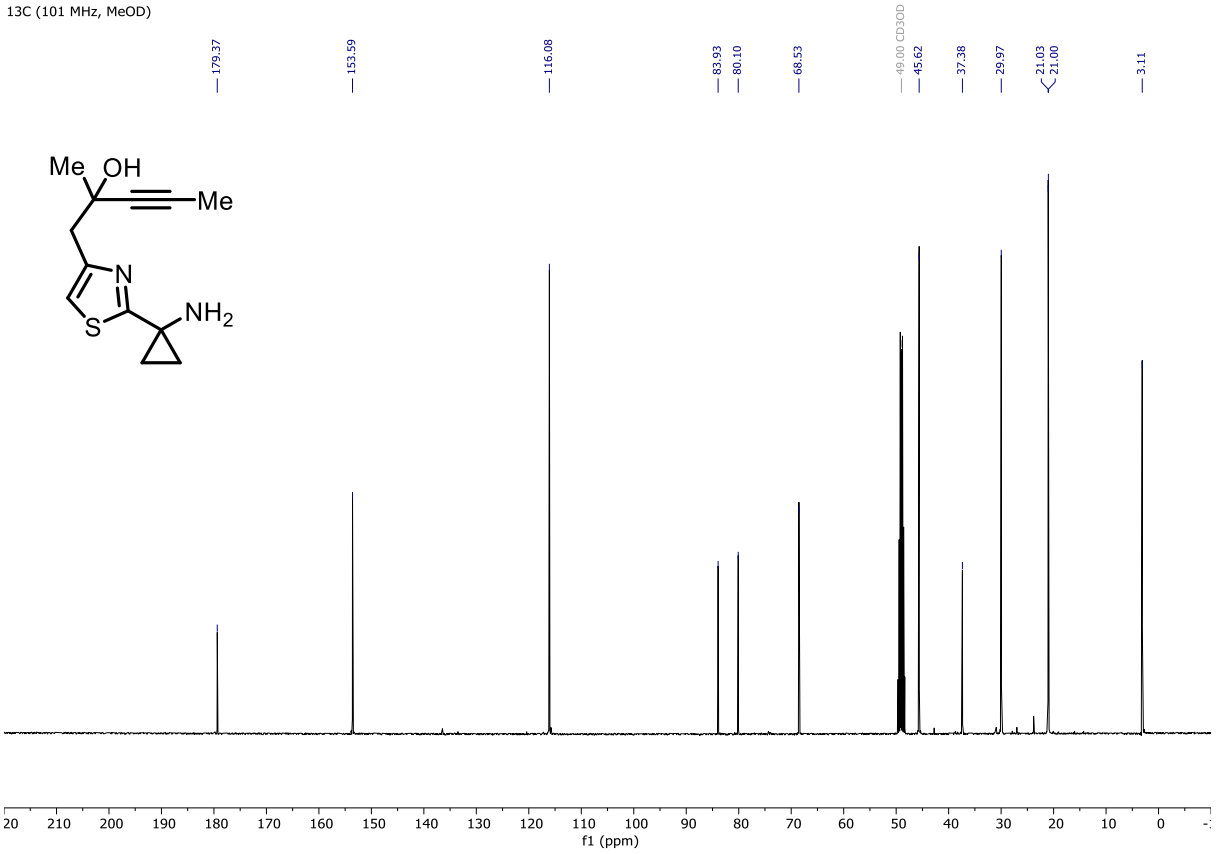


Compound **10**

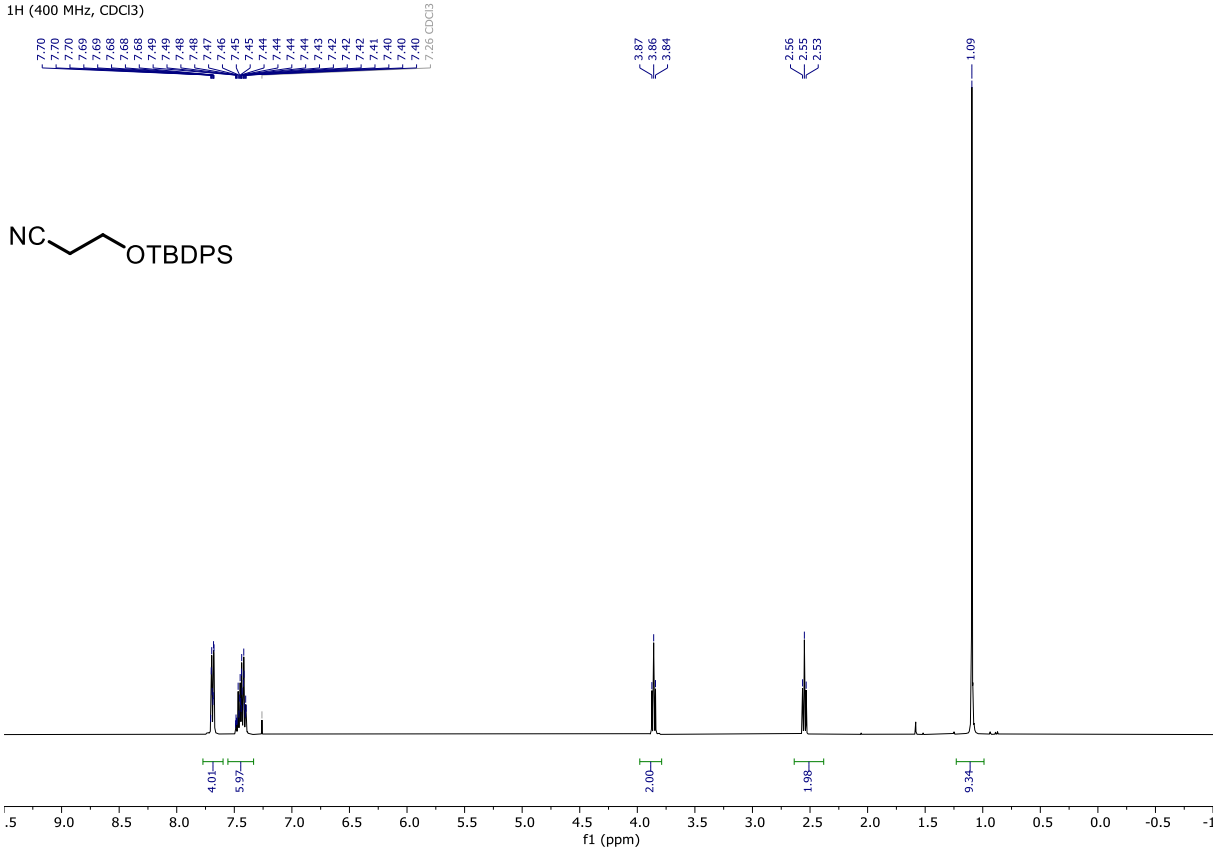
1H (400 MHz, MeOD)

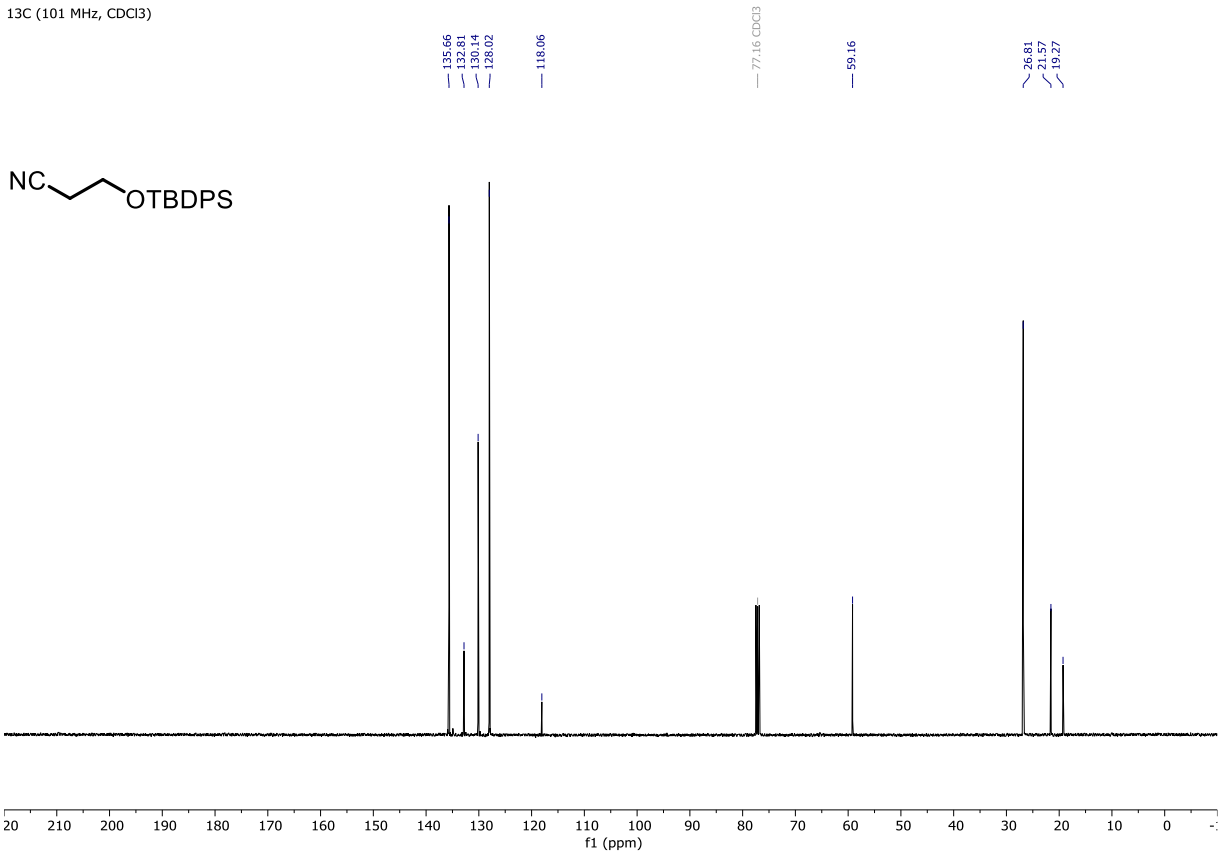


13C (101 MHz, MeOD)

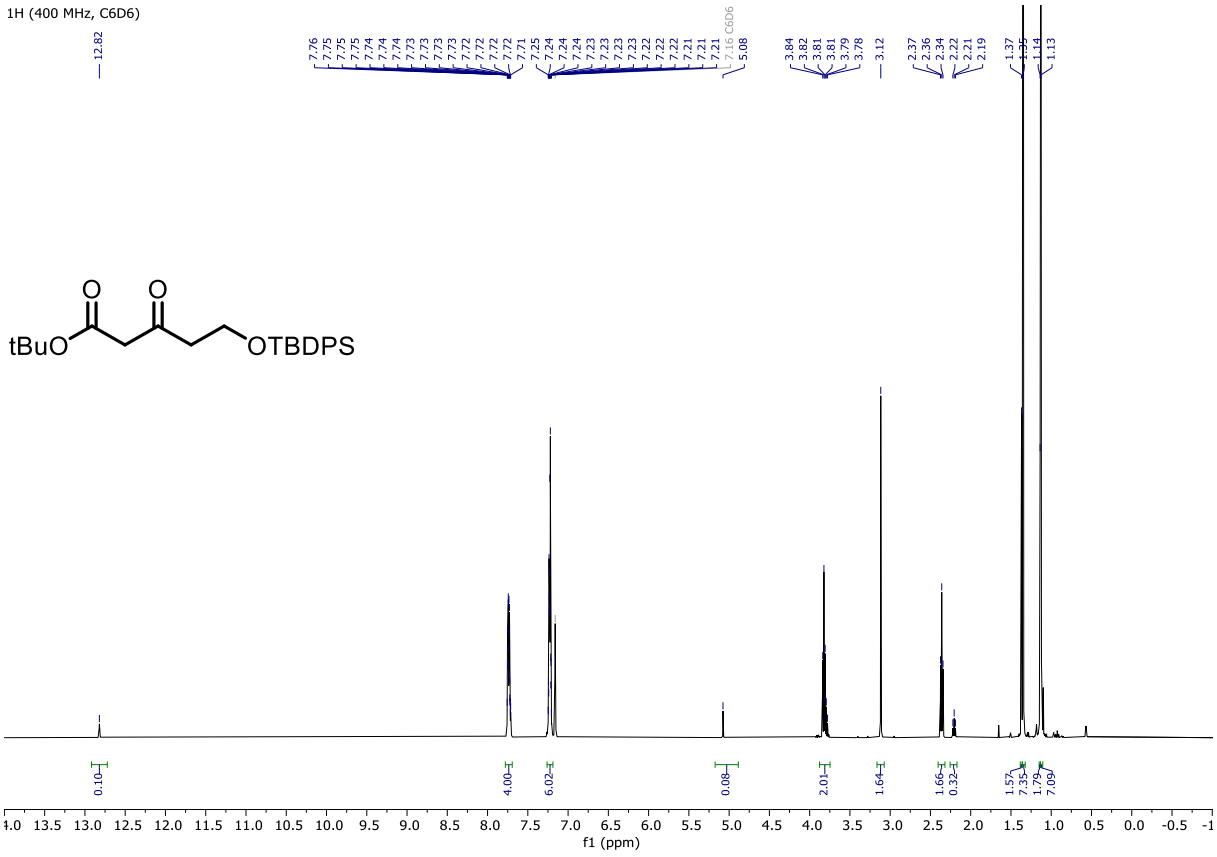


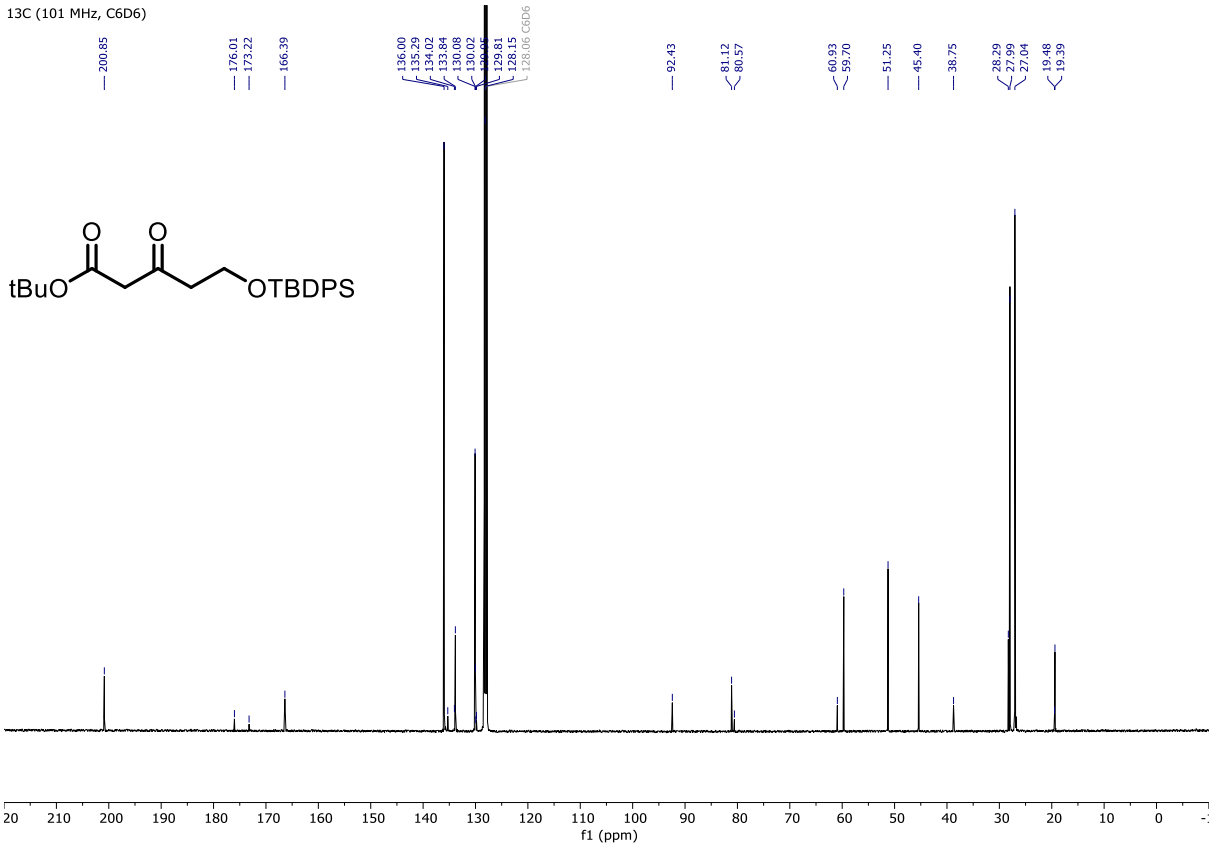
Compound **12**


1H (400 MHz, CDCl3)
7.70
7.70
7.70
7.69
7.69
7.68
7.68
7.68
7.49
7.49
7.48
7.48
7.47
7.46
7.45
7.45
7.44
7.44
7.44
7.43
7.43
7.42
7.42
7.41
7.40
7.40
7.40
7.26 CDCl3
3.87
3.86
3.84
2.56
2.55
2.53
1.09
NC
OTBDPS
4.01
5.97
2.00
1.98
9.34
f1 (ppm)


13C (101 MHz, CDCl3)
135.66
132.81
130.14
128.02
118.06
77.16 CDCl3
59.16
26.81
21.57
19.27
NC
OTBDPS
f1 (ppm)

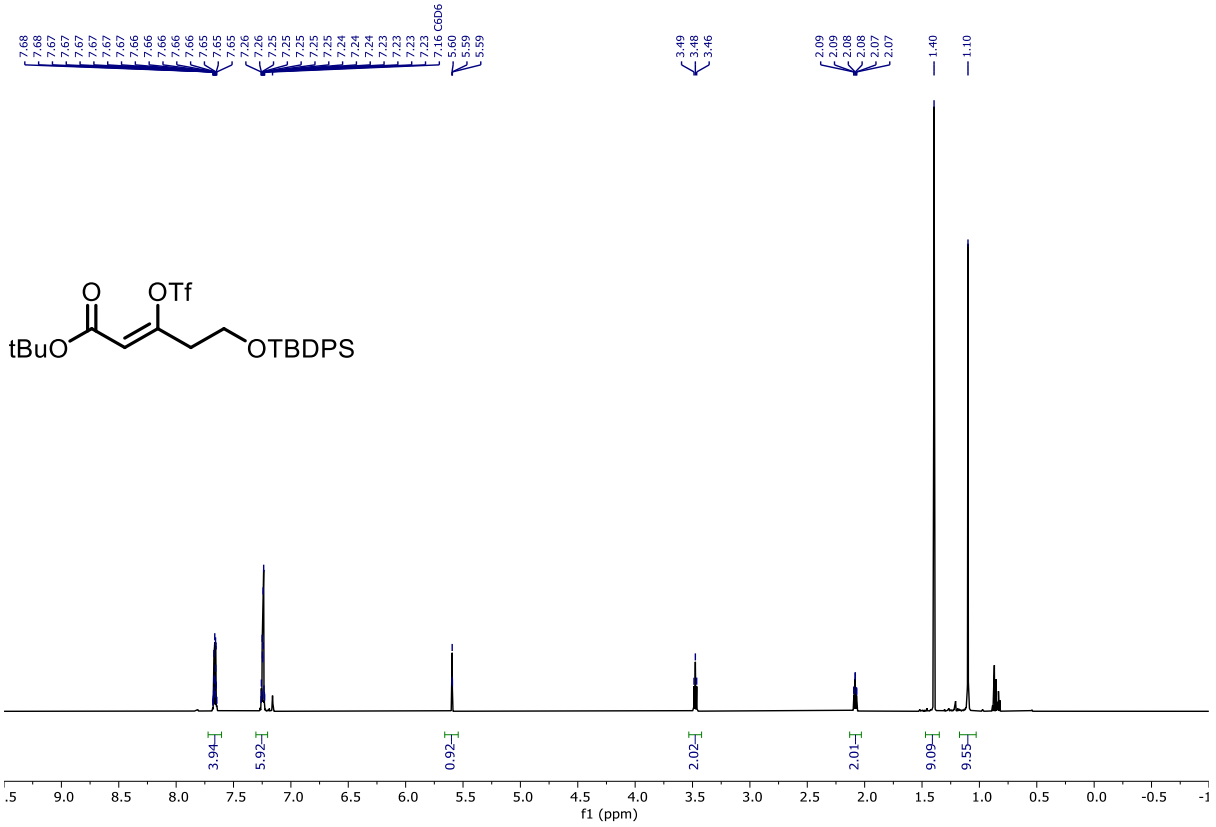
Compound **13**


1H (400 MHz, C6D6)
tBuO
OTBDPS
f1 (ppm)

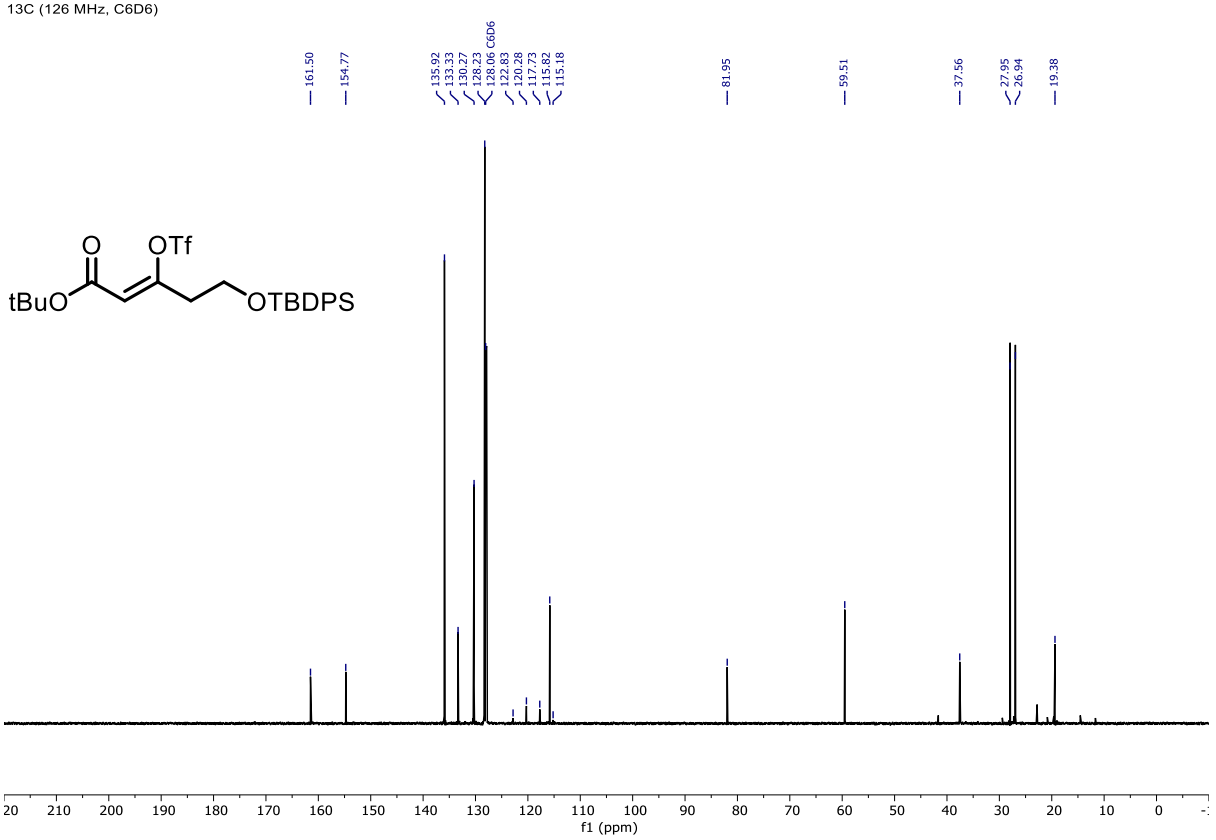

13C (101 MHz, C6D6)
tBuO
OTBDPS
f1 (ppm)

Compound **14**

1H (500 MHz, C6D6)

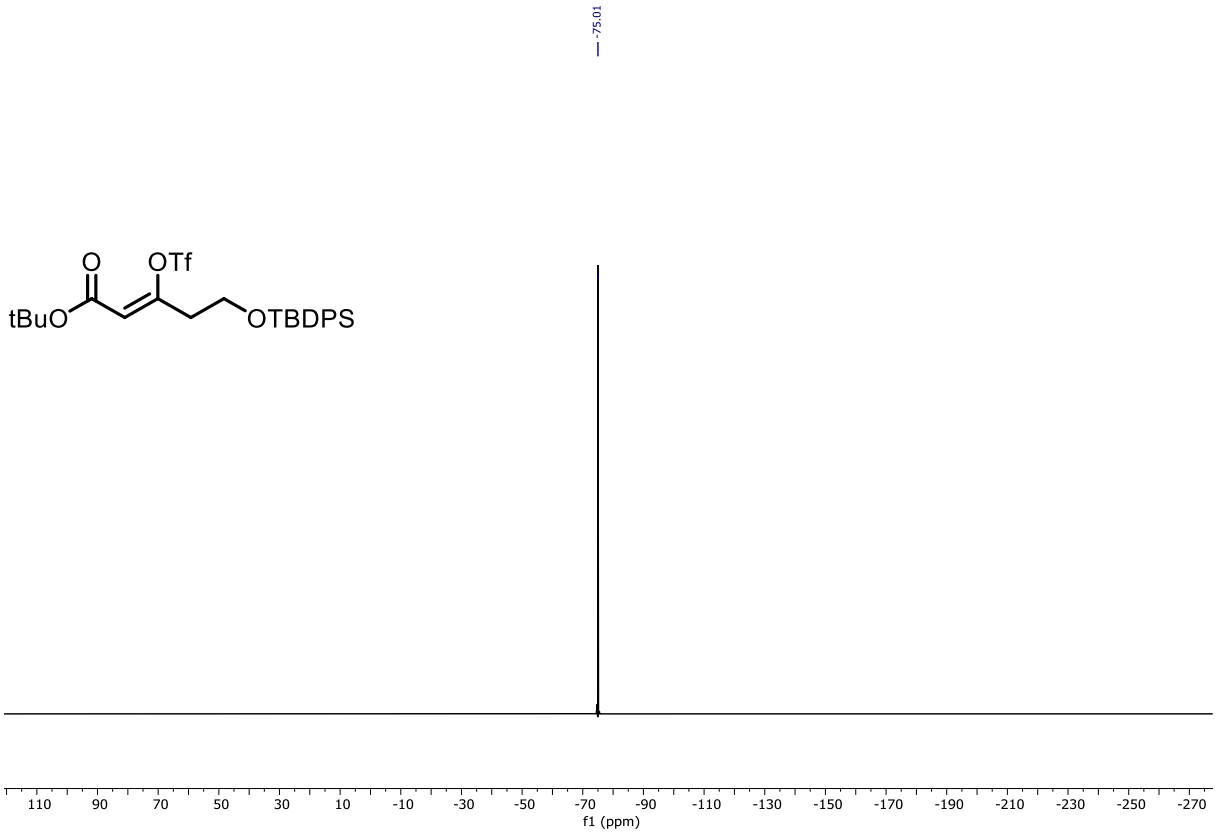


13C (126 MHz, C6D6)



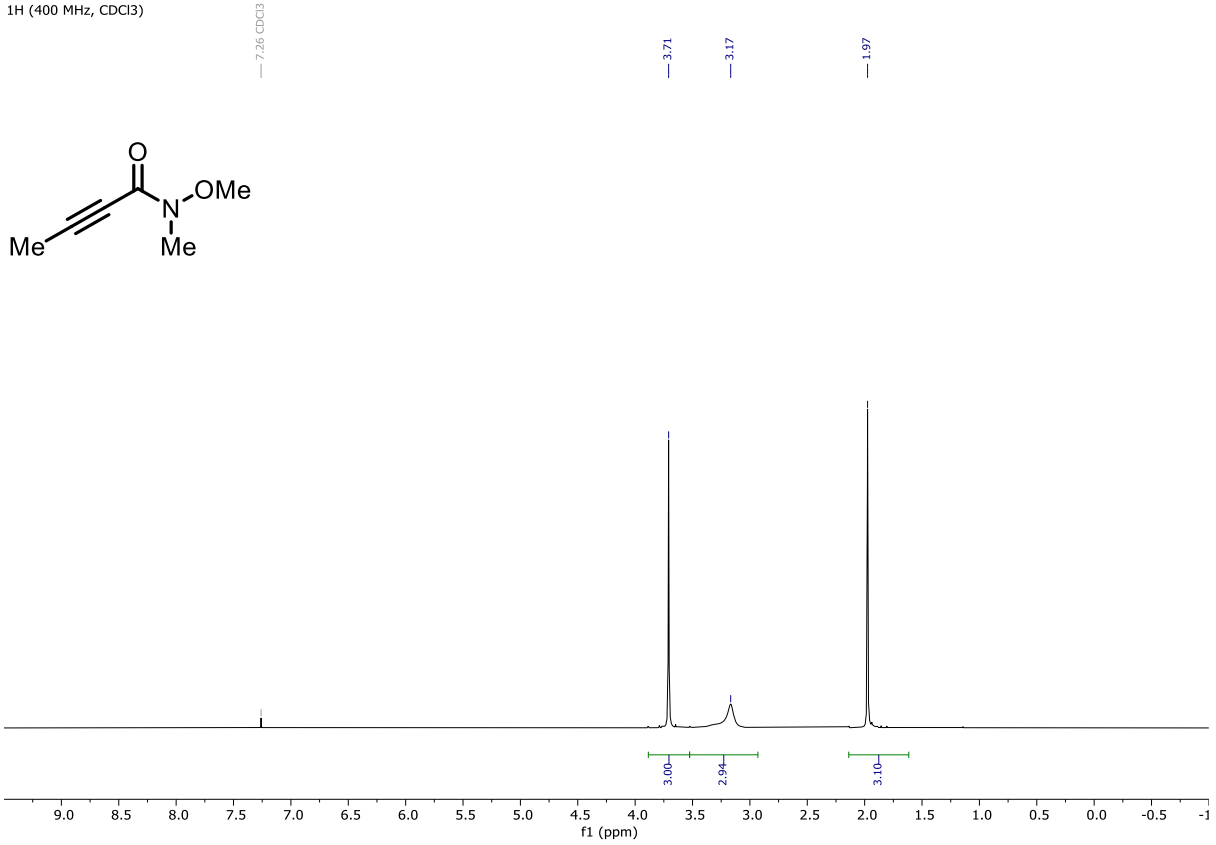
Compound **14**

19F (470 MHz, C6D6)

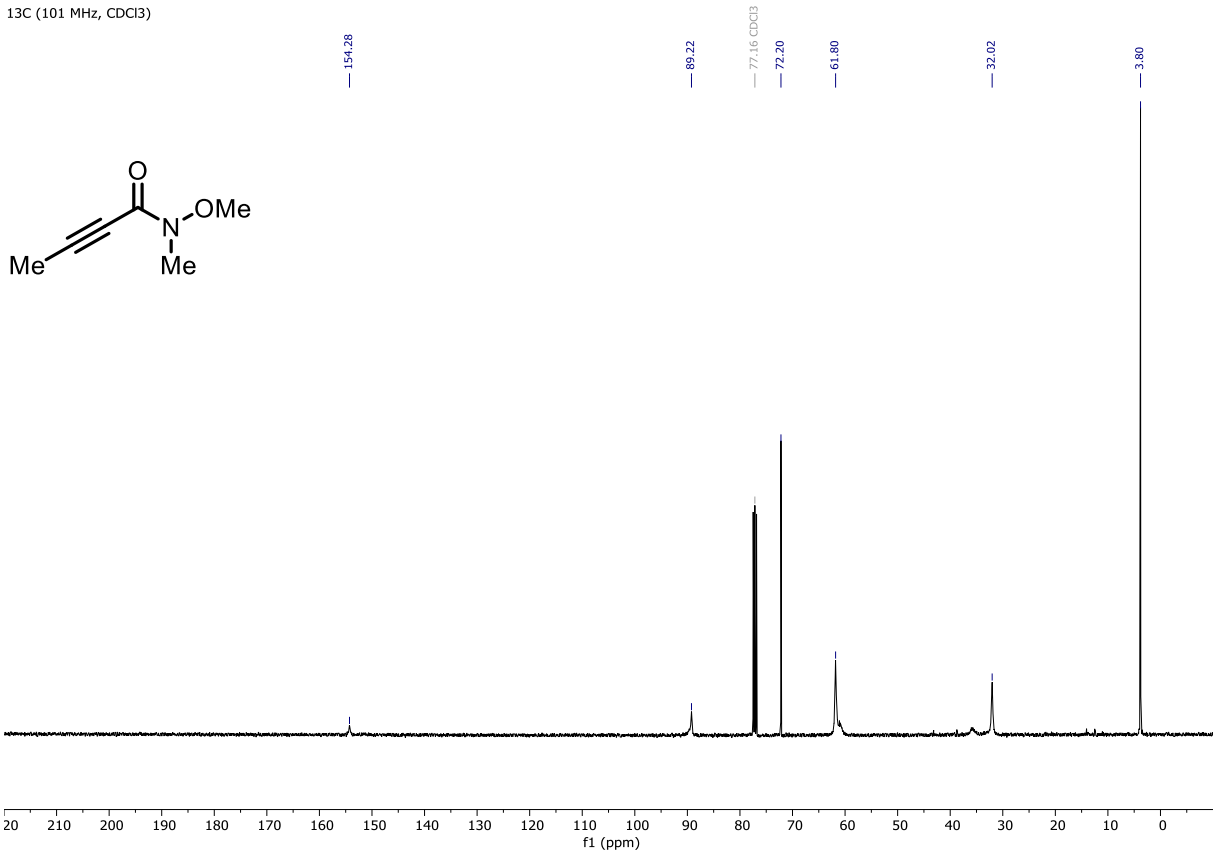


Compound **16**

1H (400 MHz, CDCl3)

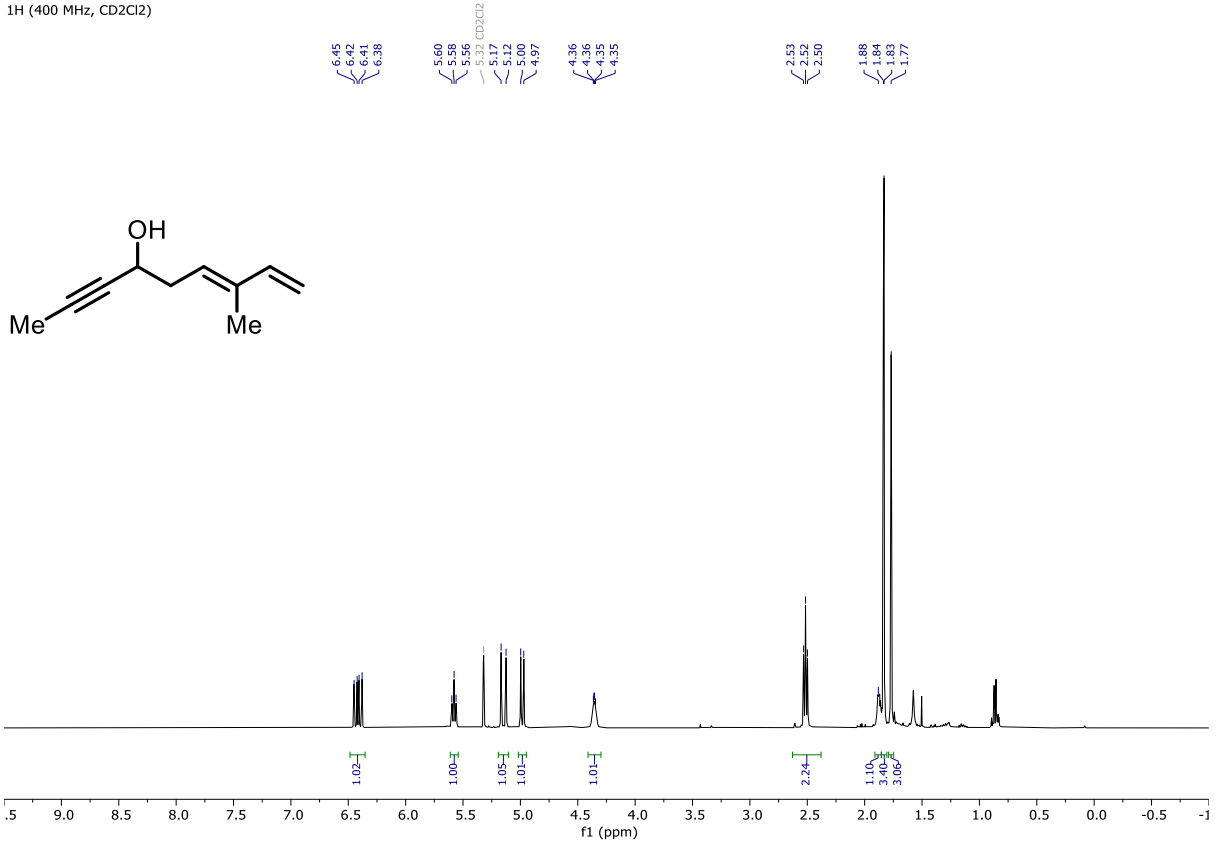


13C (101 MHz, CDCl3)

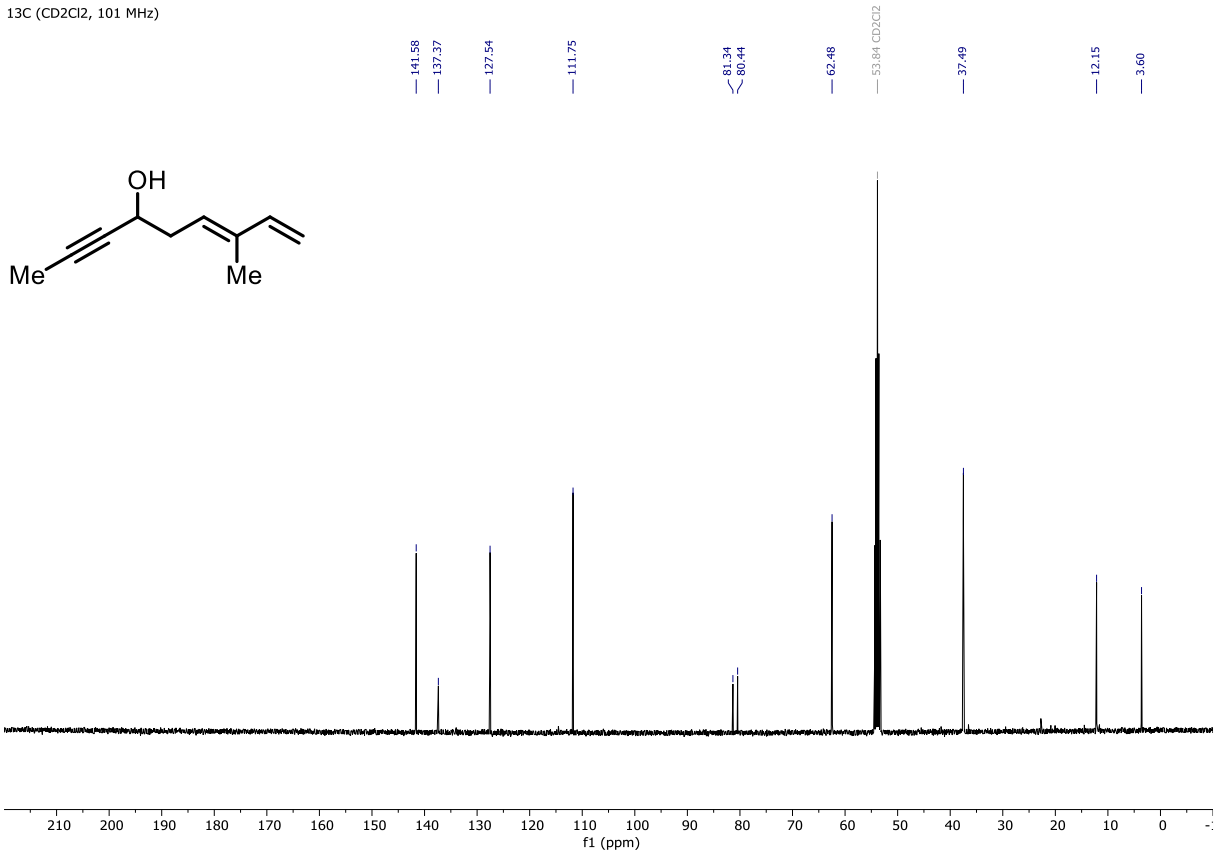


Compound **S3**

1H (400 MHz, CD2Cl2)

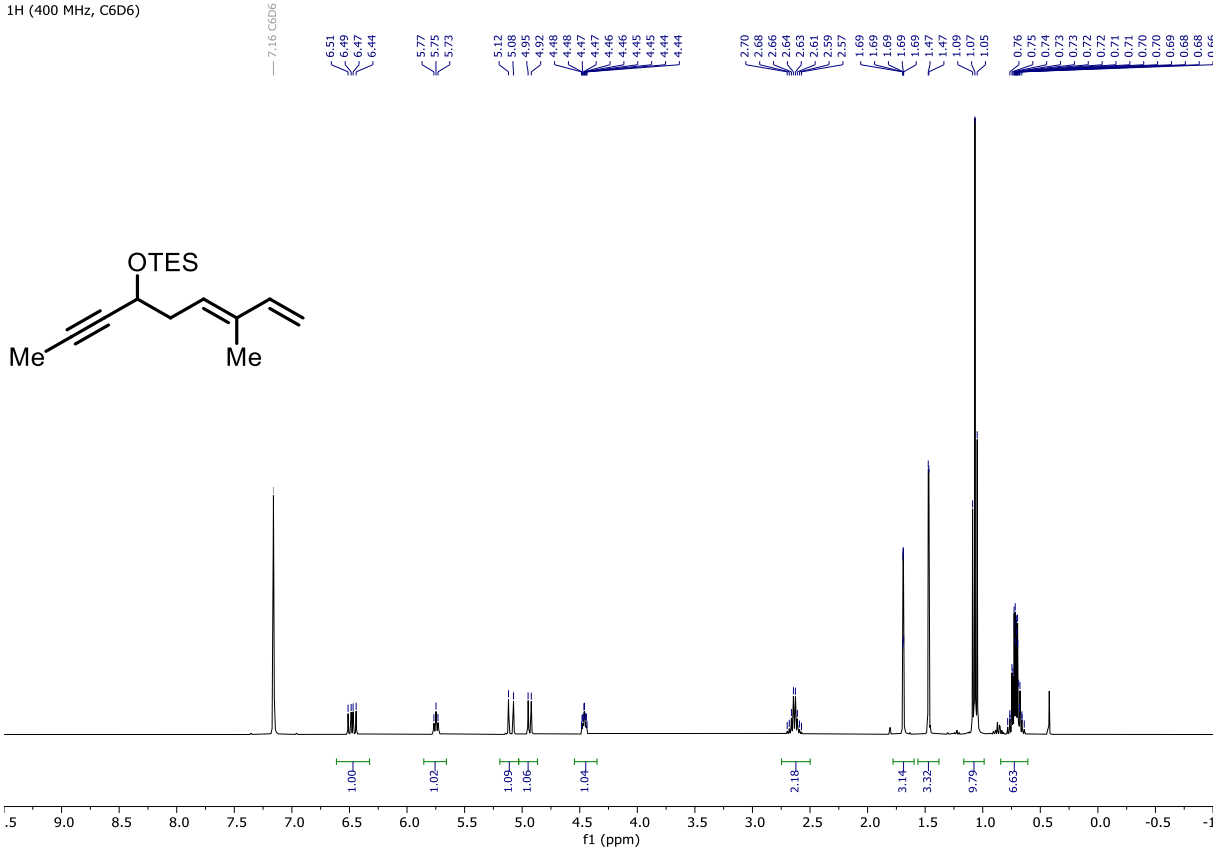


13C (CD2Cl2, 101 MHz)

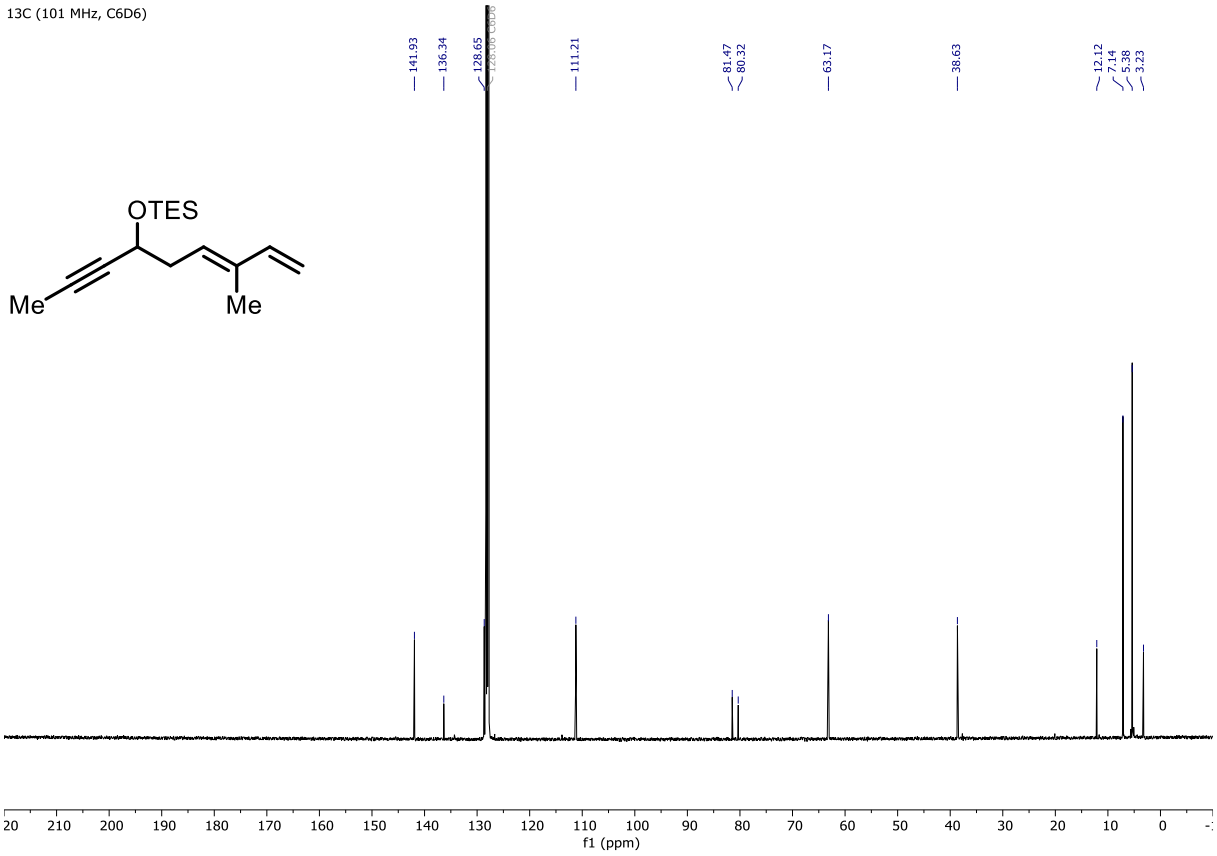


Compound **18**

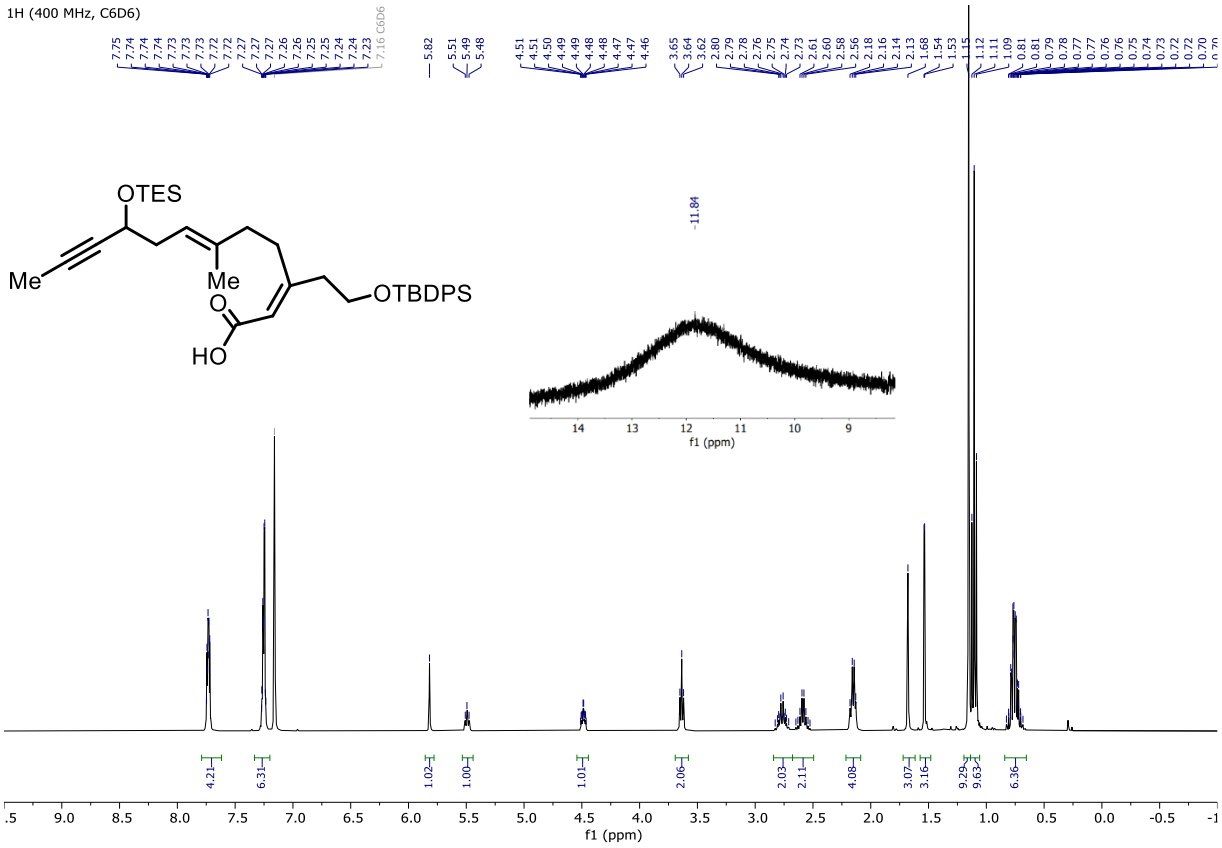
1H (400 MHz, C6D6)

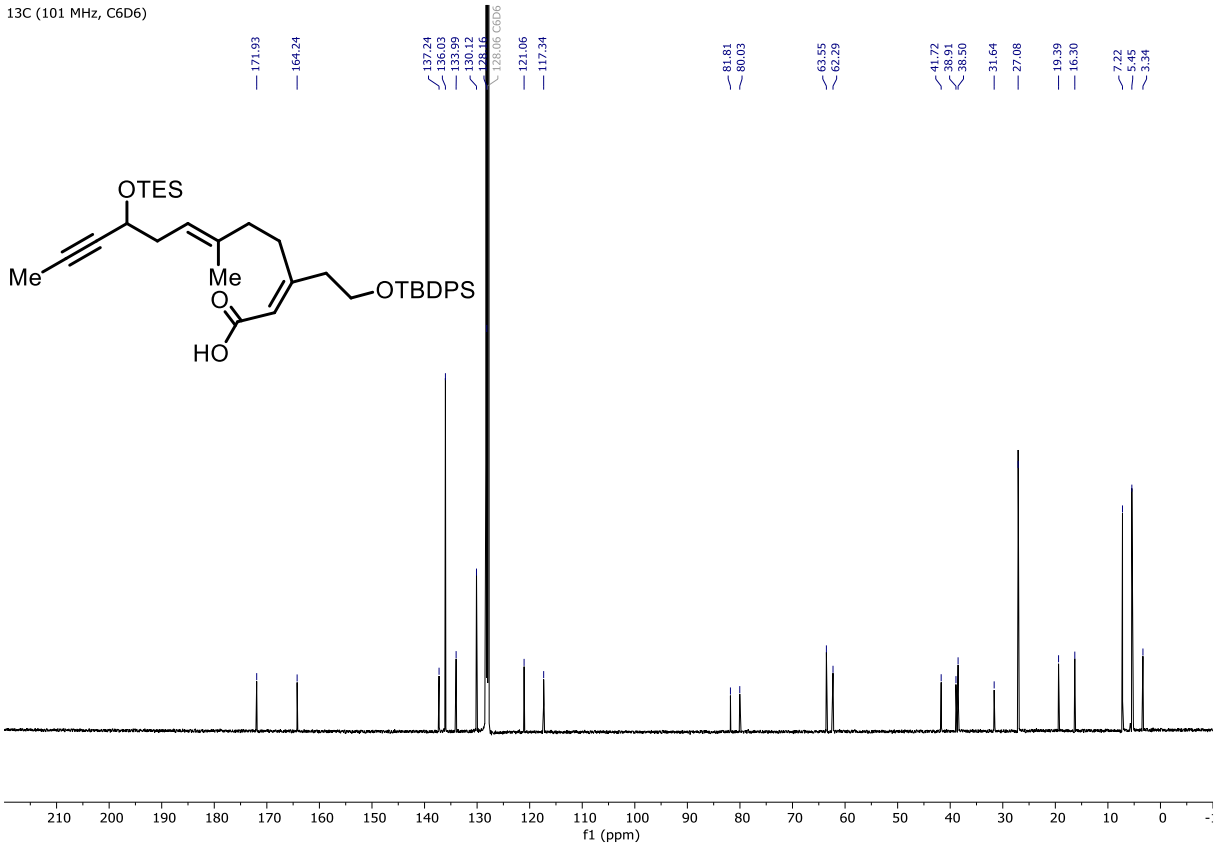


13C (101 MHz, C6D6)

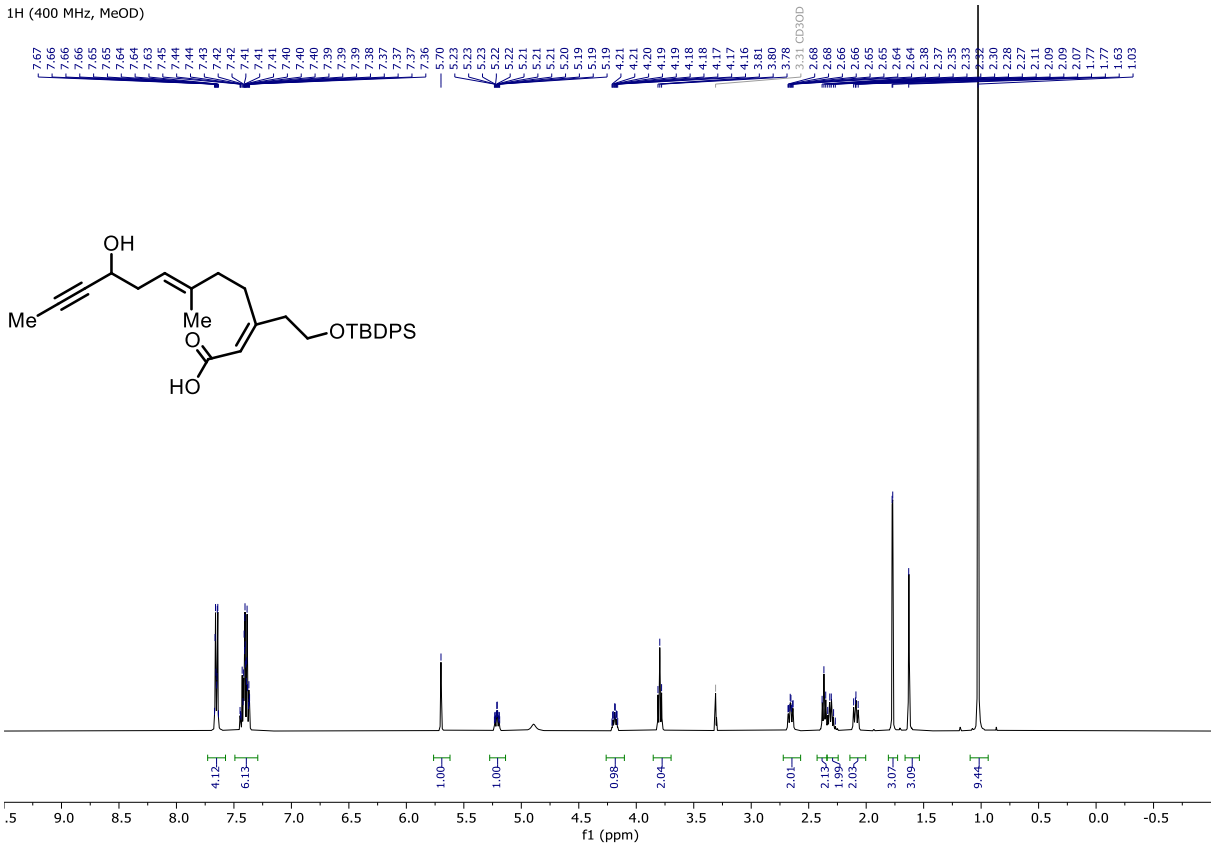


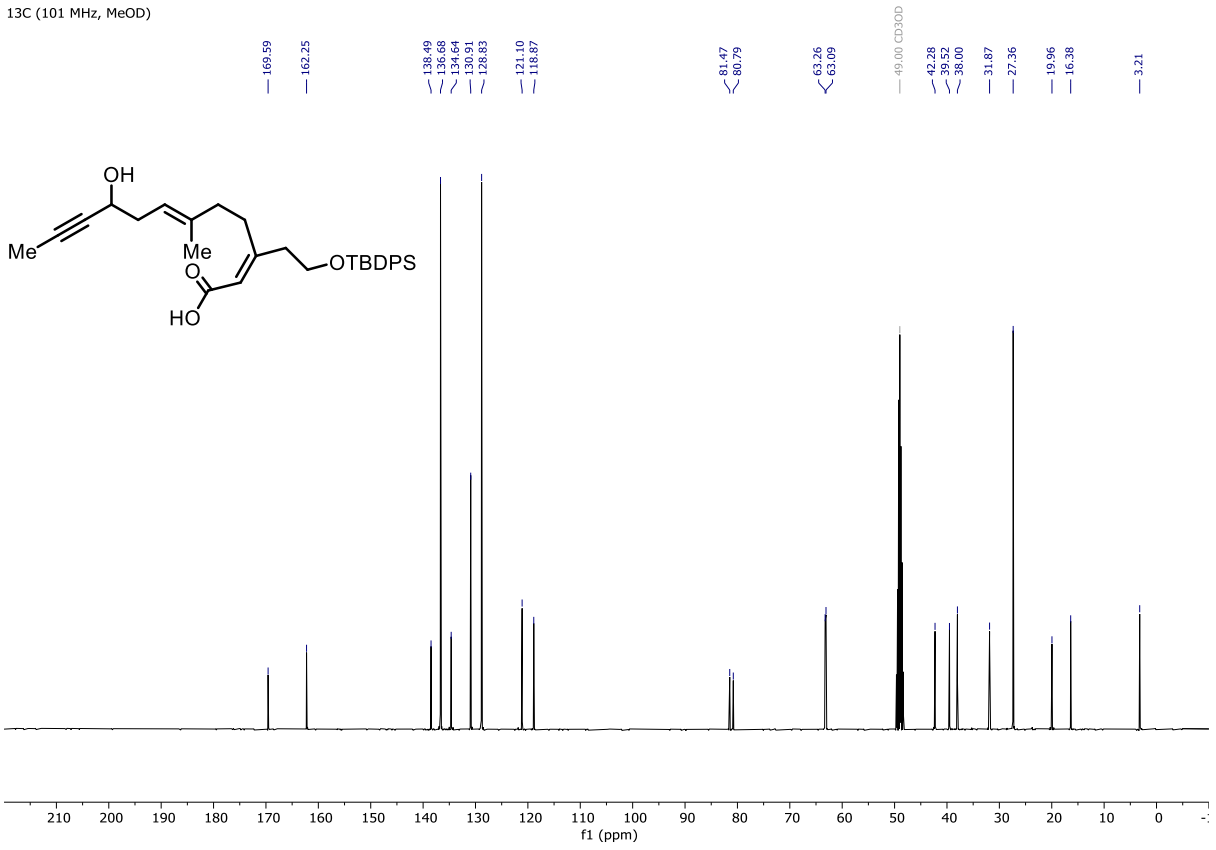
Compound **19**


1H (400 MHz, C6D6)
OTES
Me
Me
O
HO
OTBDPS
f1 (ppm)

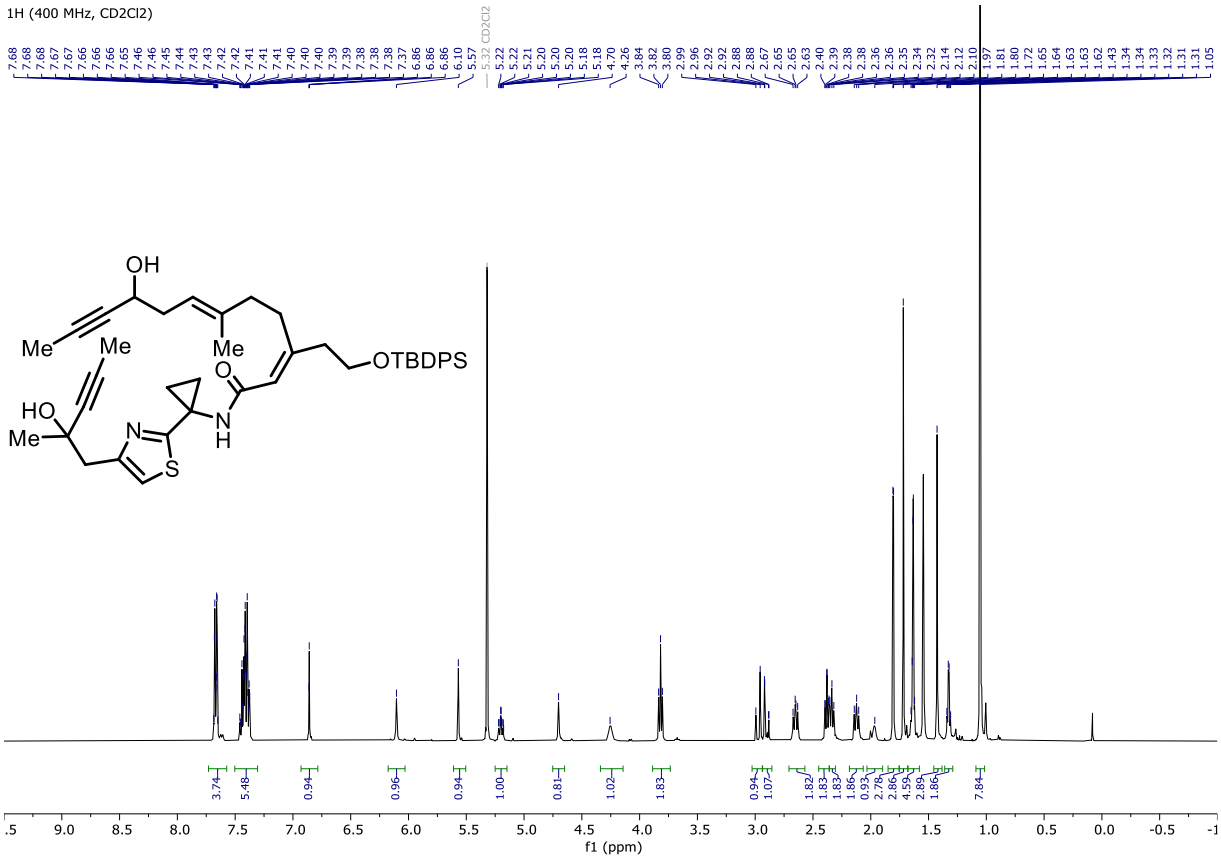

13C (101 MHz, C6D6)
OTES
Me
Me
O
HO
OTBDPS
f1 (ppm)

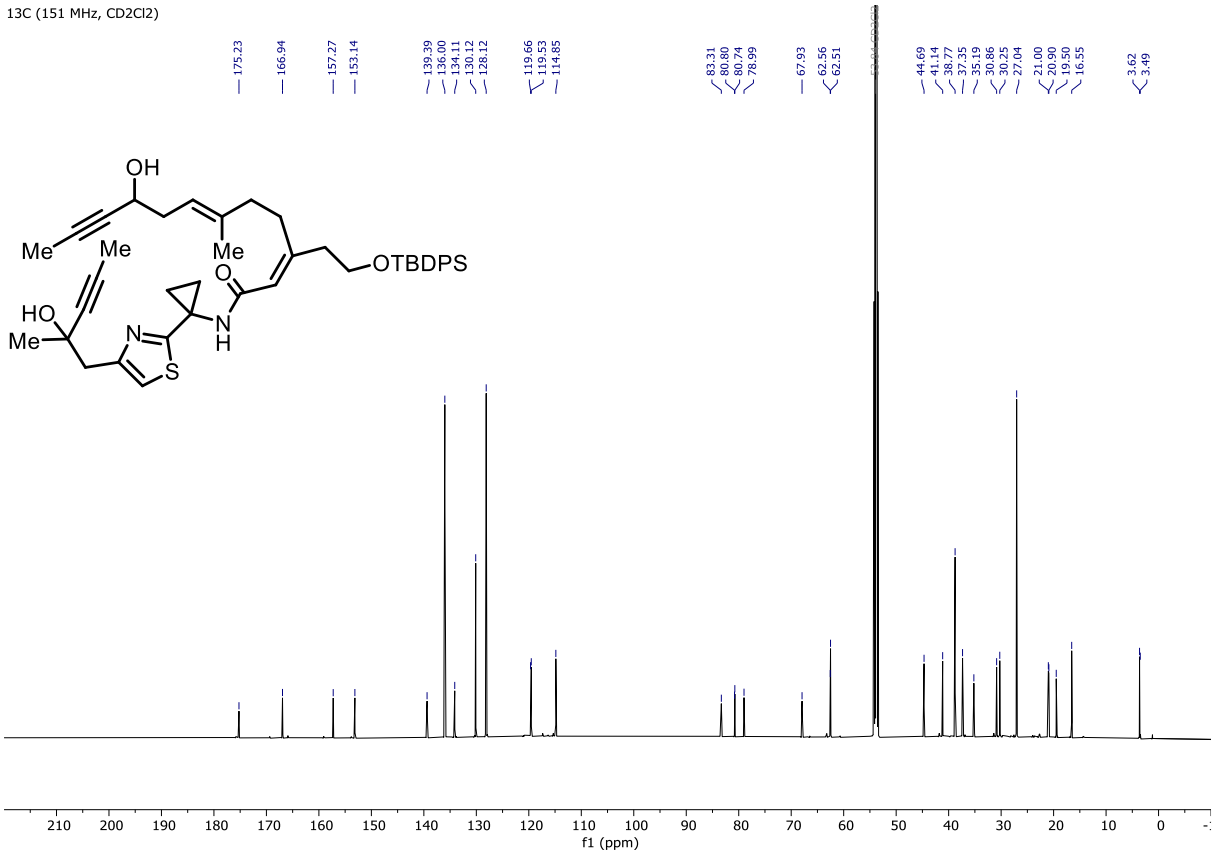
Compound **20**


1H (400 MHz, MeOD)
OH
Me
Me
O
HO
OTBDPS
f1 (ppm)

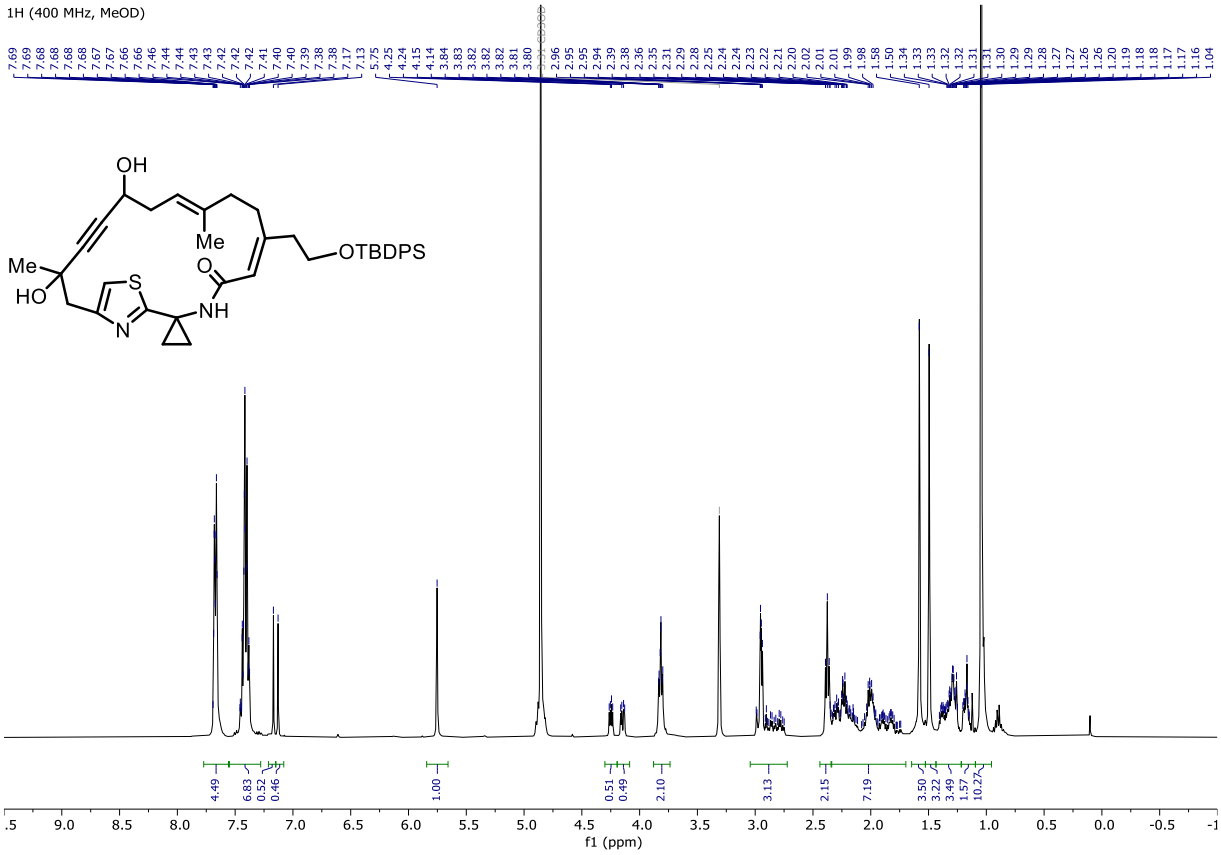

13C (101 MHz, MeOD)
OH
Me
Me
O
HO
OTBDPS
f1 (ppm)

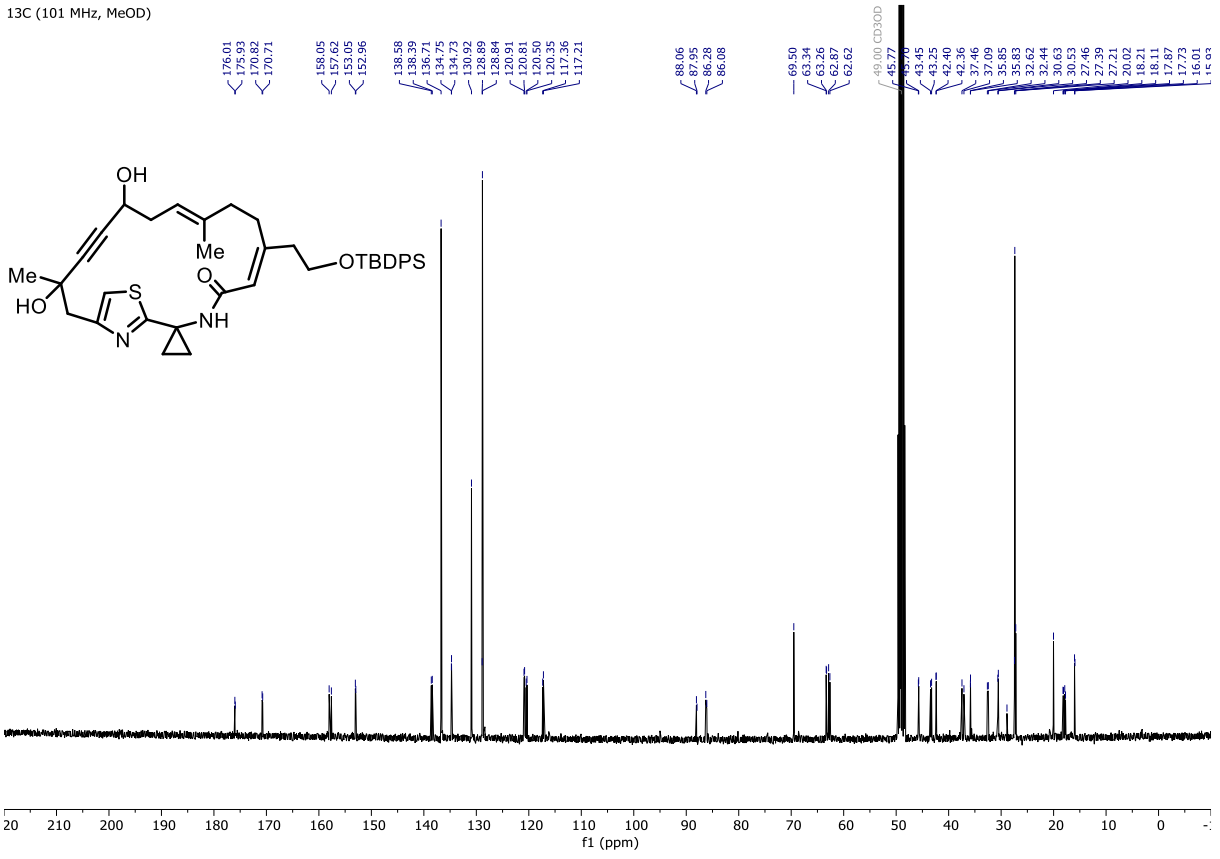
Compound **21**


1H (400 MHz, CD2Cl2)
OH
Me
Me
Me
O
OTBDPS
HO
Me
N
H
S
f1 (ppm)


13C (151 MHz, CD2Cl2)
OH
Me
Me
Me
O
OTBDPS
HO
Me
N
H
S
f1 (ppm)

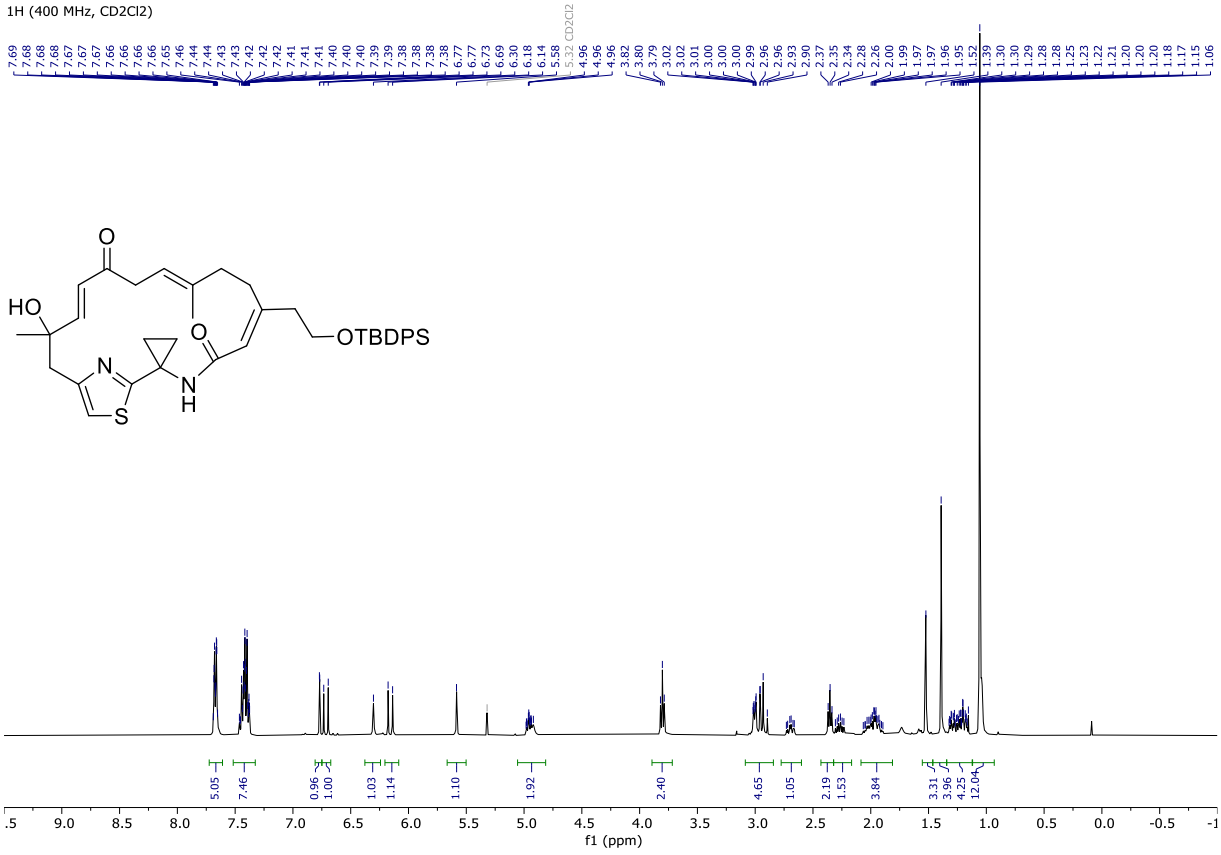
Compound **22** (≈1:1 mixture of diastereomers)



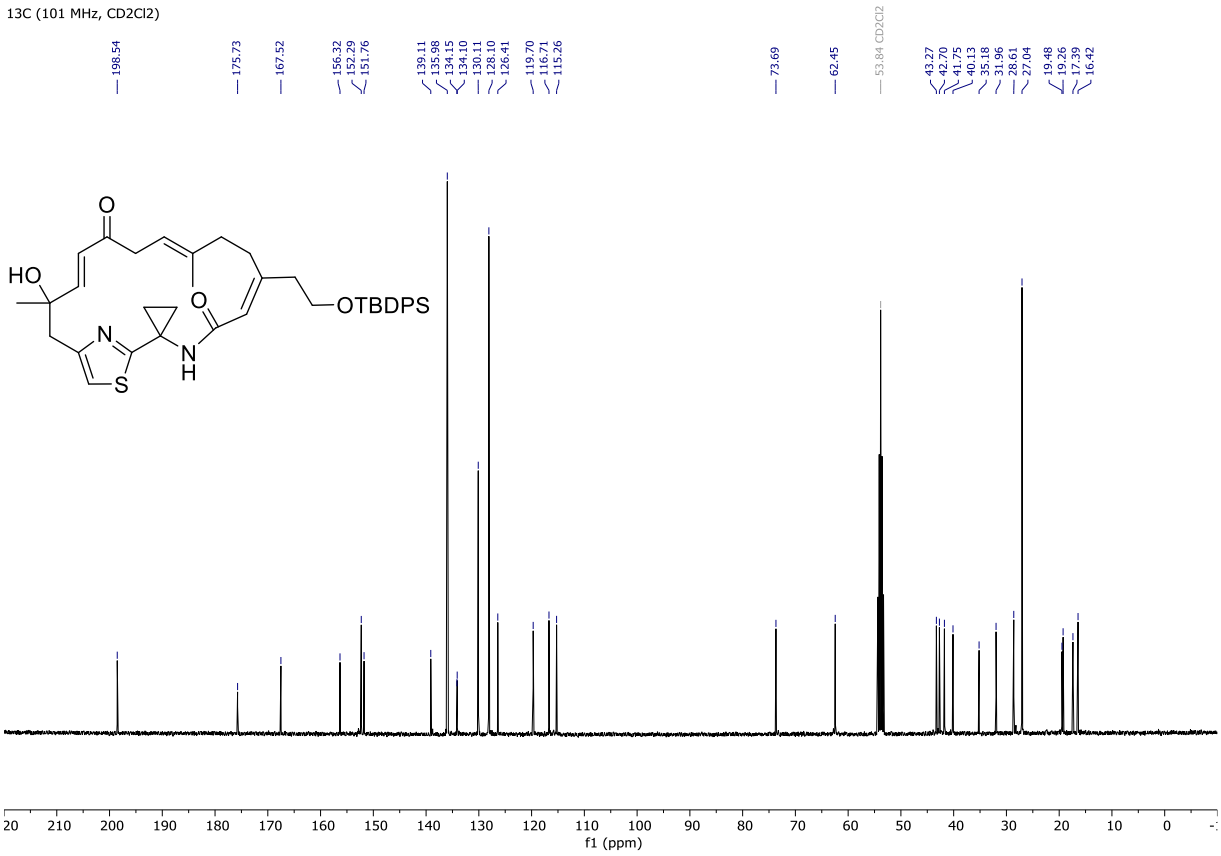


Compound **23**

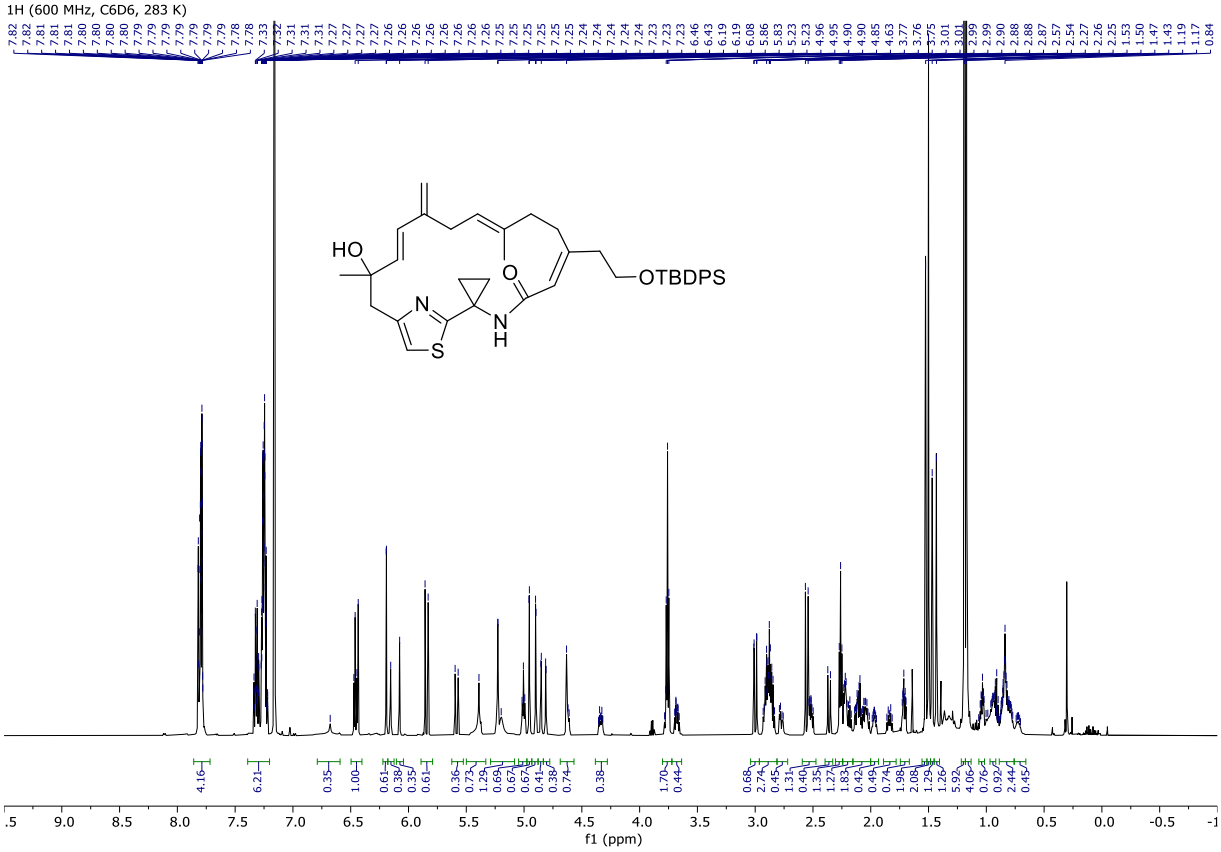
1H (400 MHz, CD2Cl2)

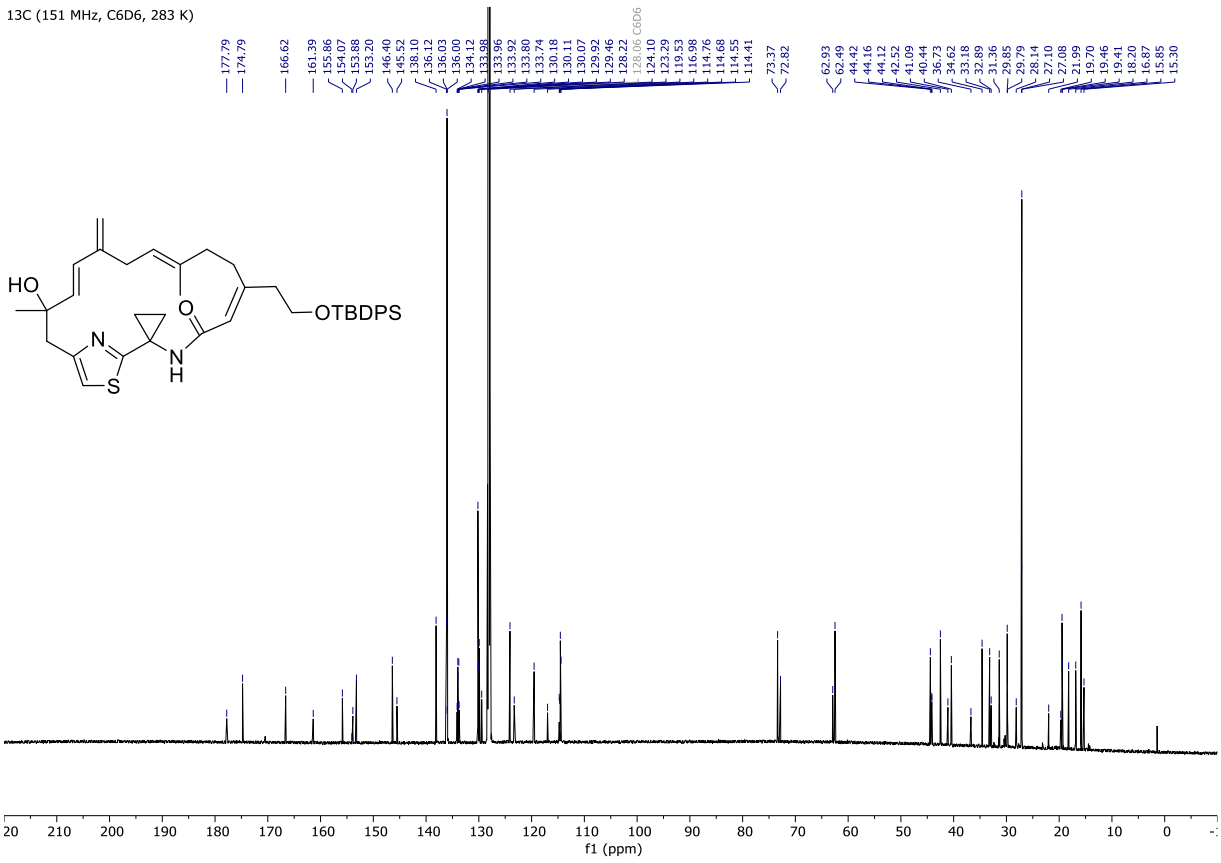


13C (101 MHz, CD2Cl2)

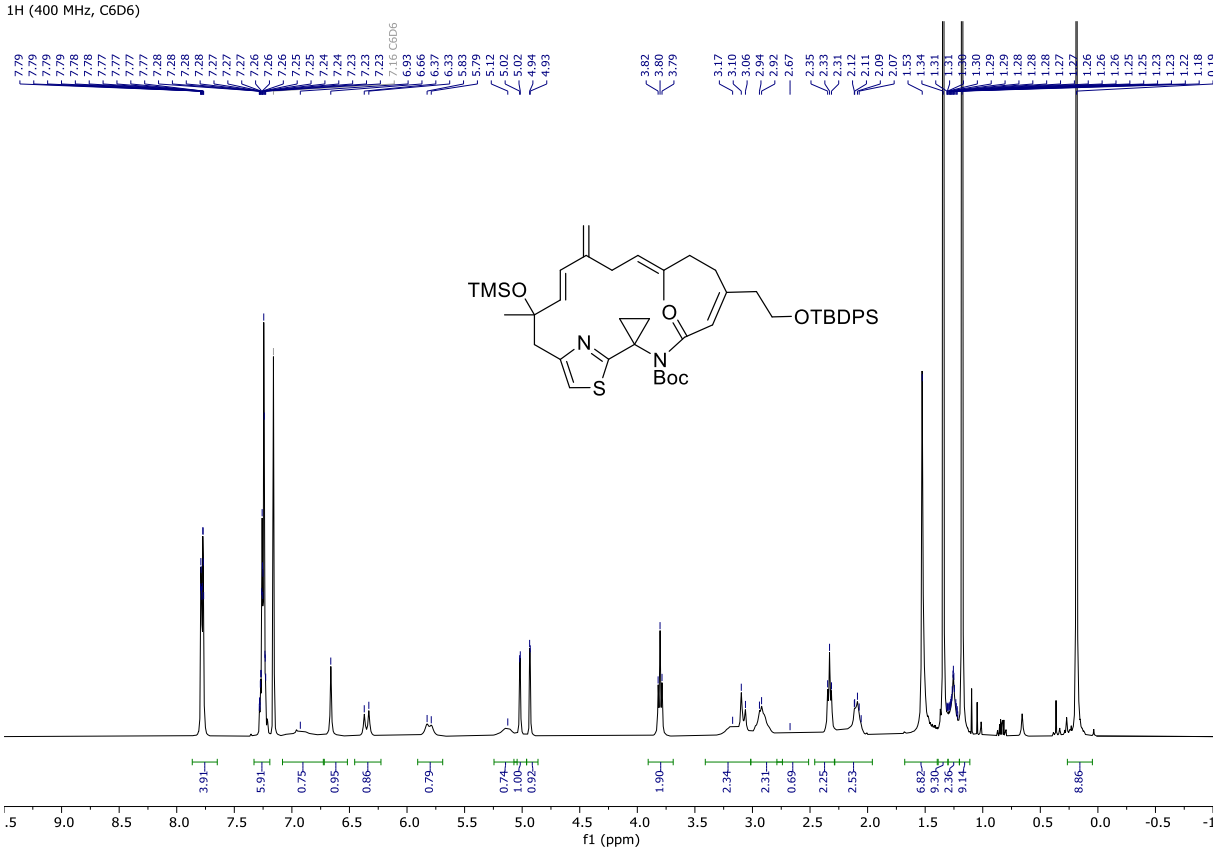


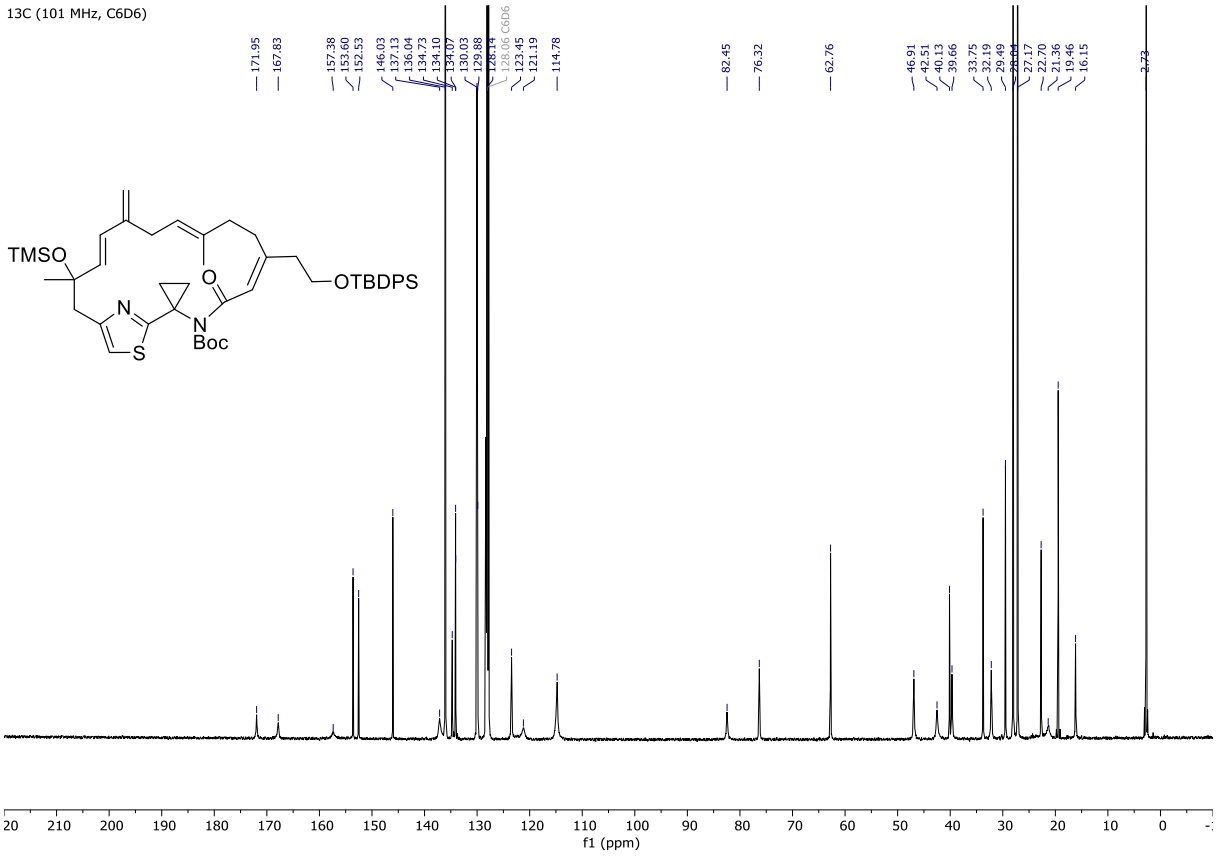
Compound **24** (≈3:2 mixture of rotamers)





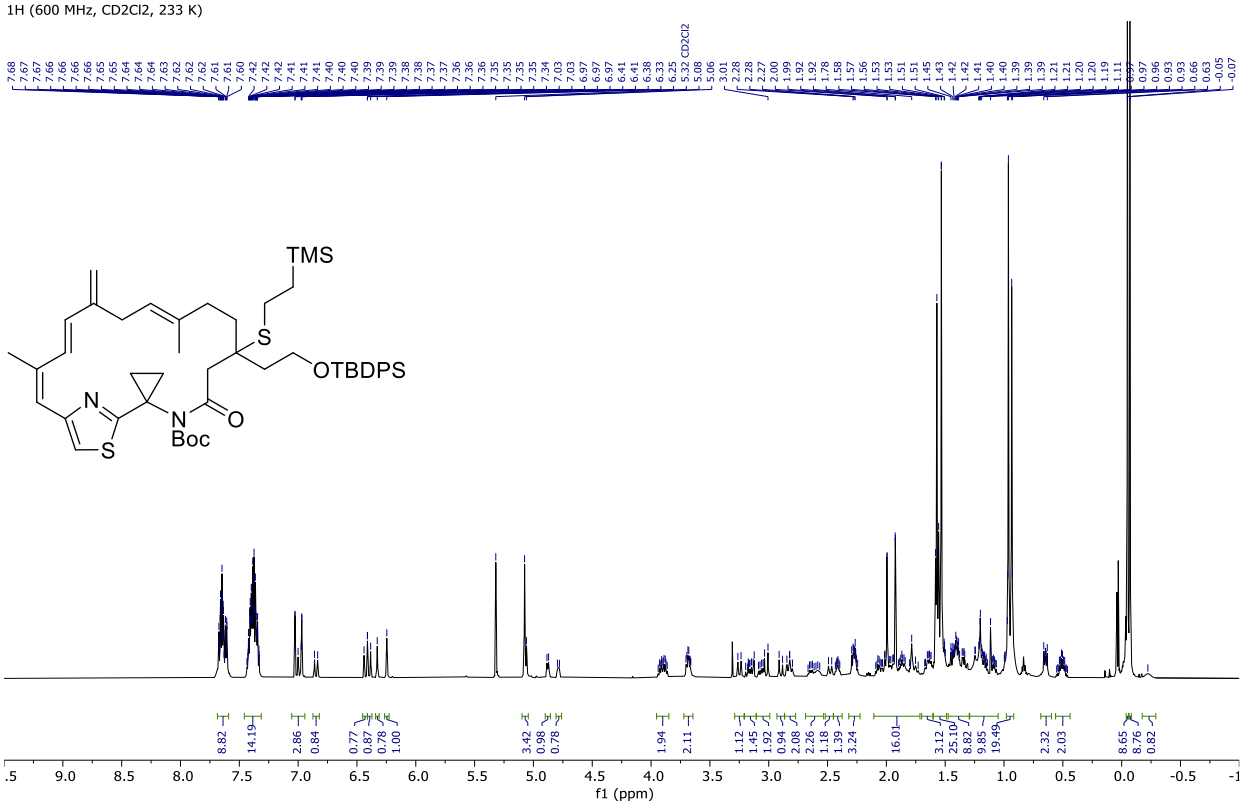
Compound **25**


1H (400 MHz, C6D6)
TMSO
OTBDPS
N
O
N
Boc
S
f1 (ppm)

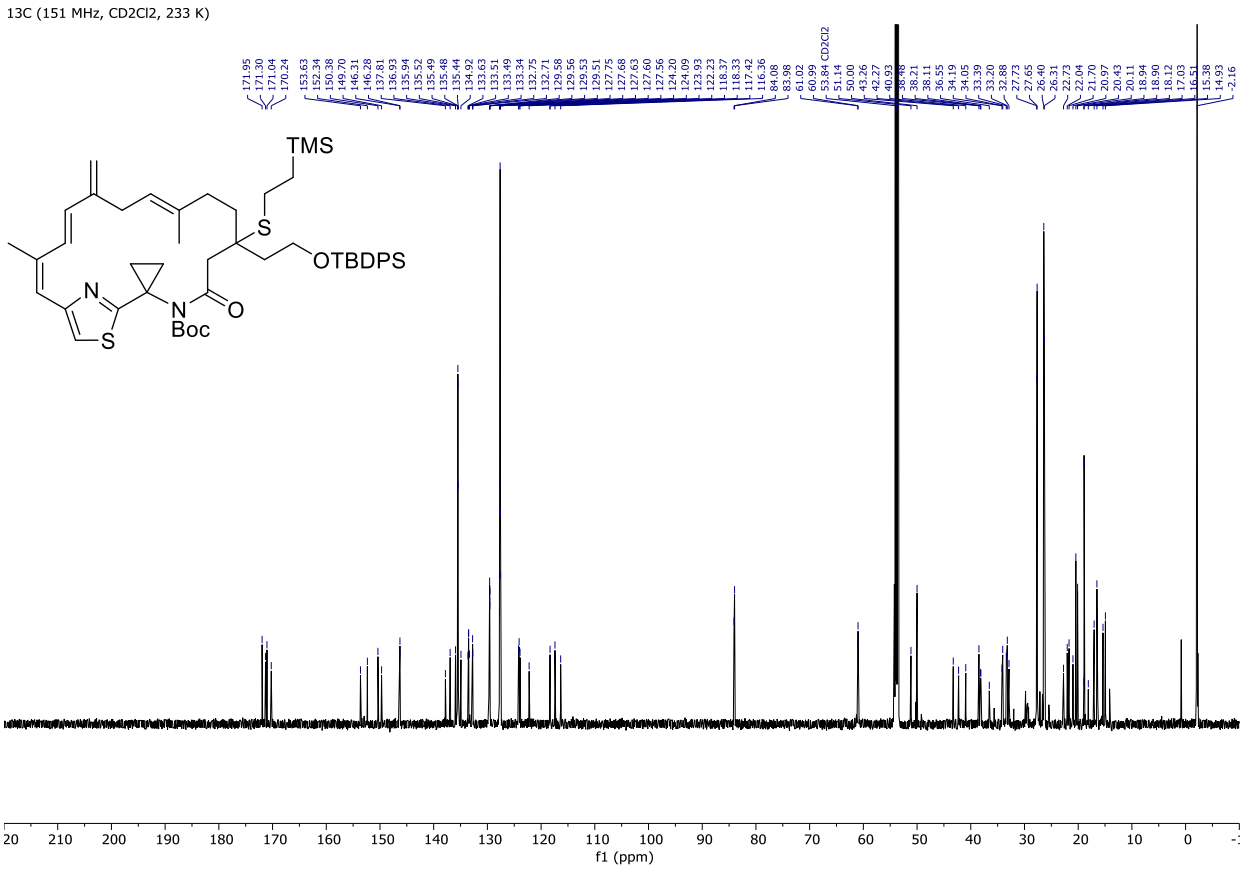

13C (101 MHz, C6D6)
TMSO
OTBDPS
N
O
N
Boc
S
f1 (ppm)

Compound **27** (≈3:2 mixture of rotamers)

1H (600 MHz, CD2Cl2, 233 K)

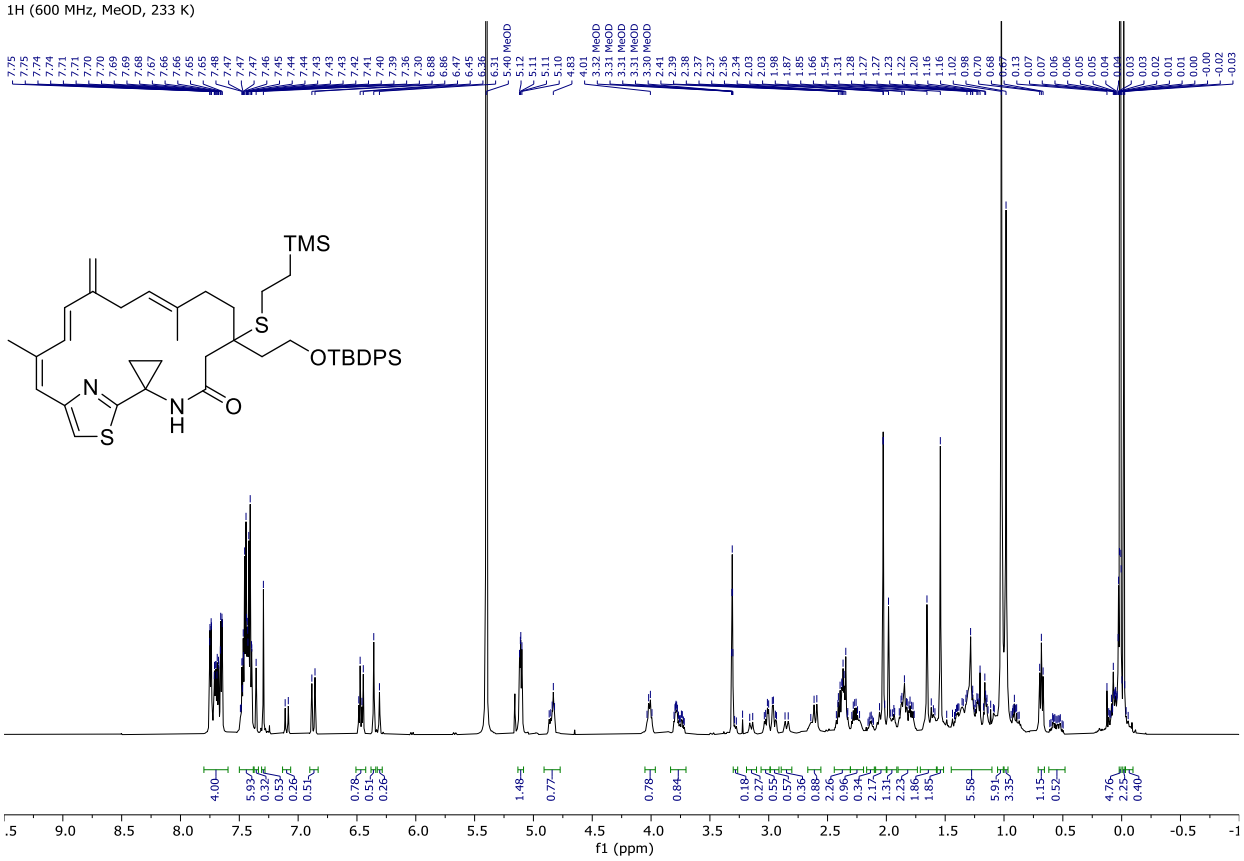


13C (151 MHz, CD2Cl2, 233 K)

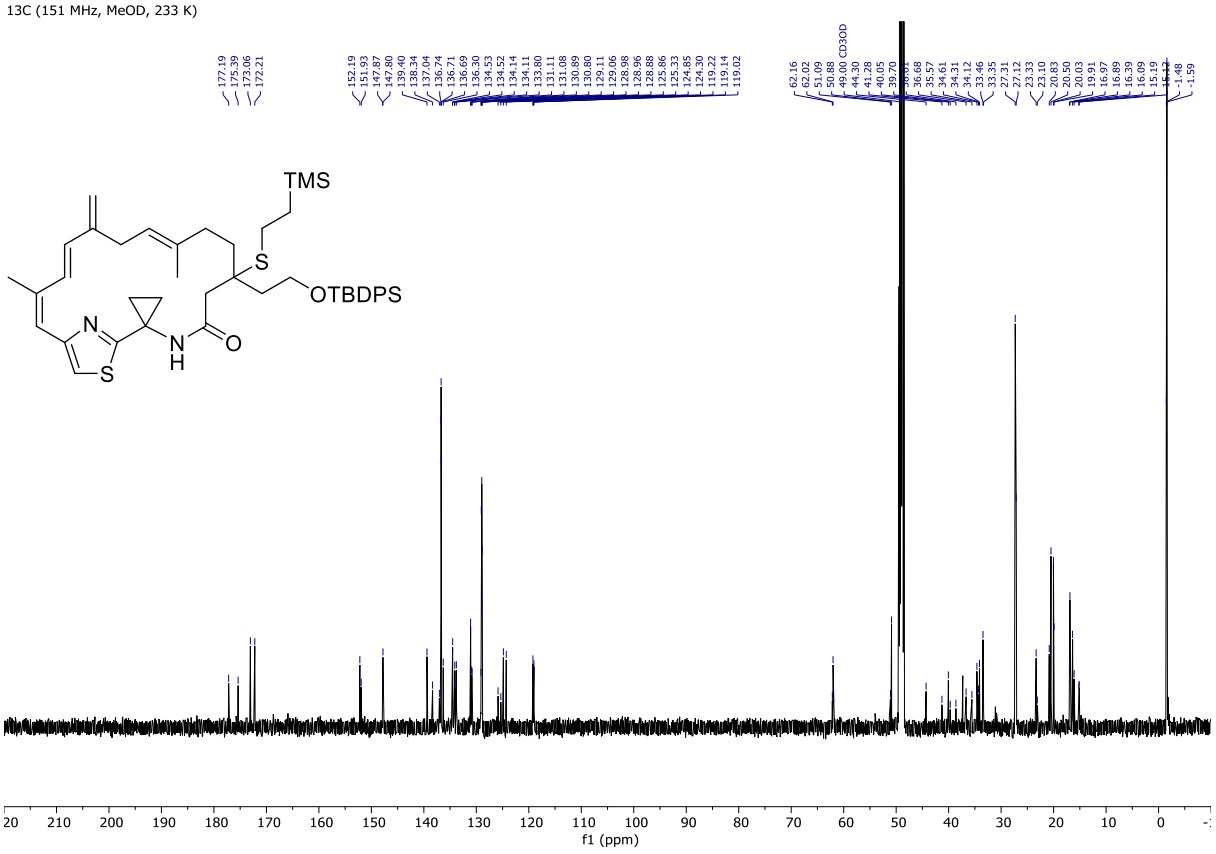


Compound **S4** (≈7:3 mixture of rotamers)

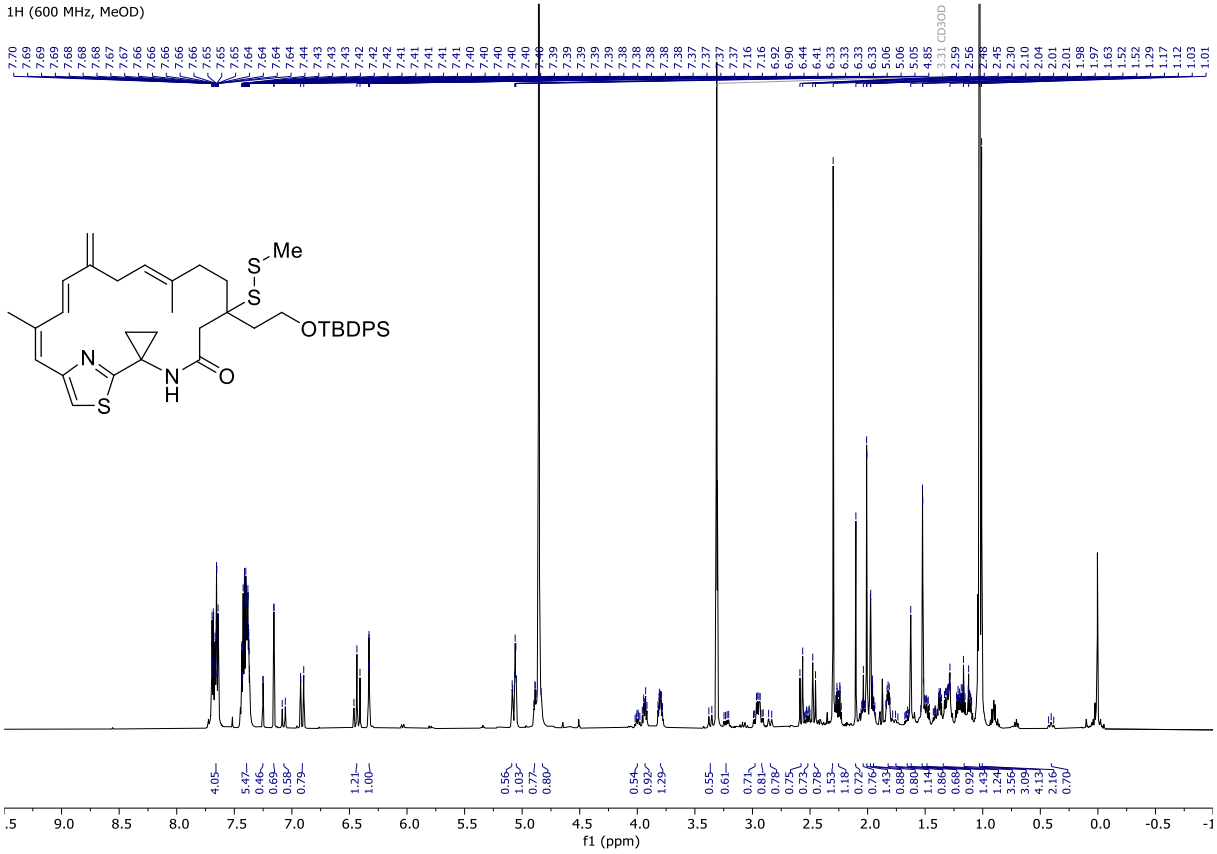
1H (600 MHz, MeOD, 233 K)

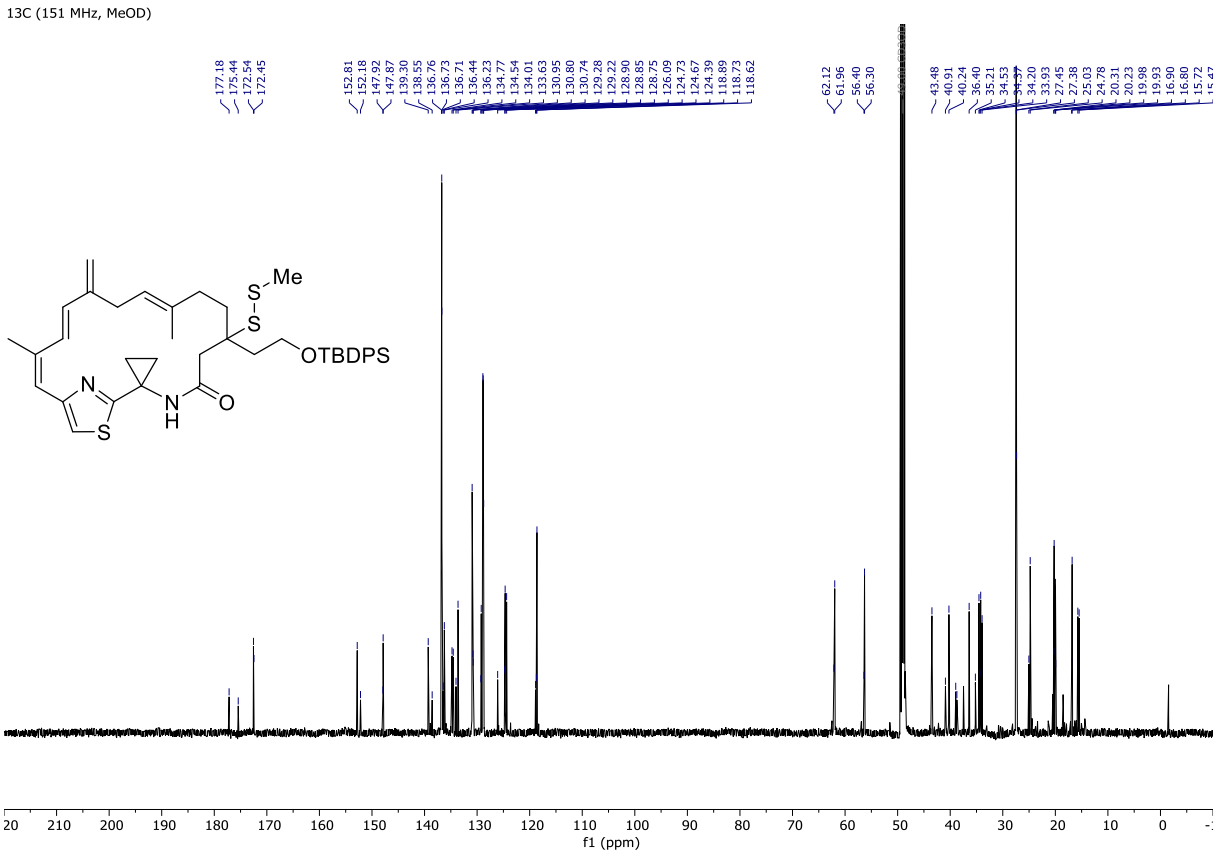


13C (151 MHz, MeOD, 233 K)

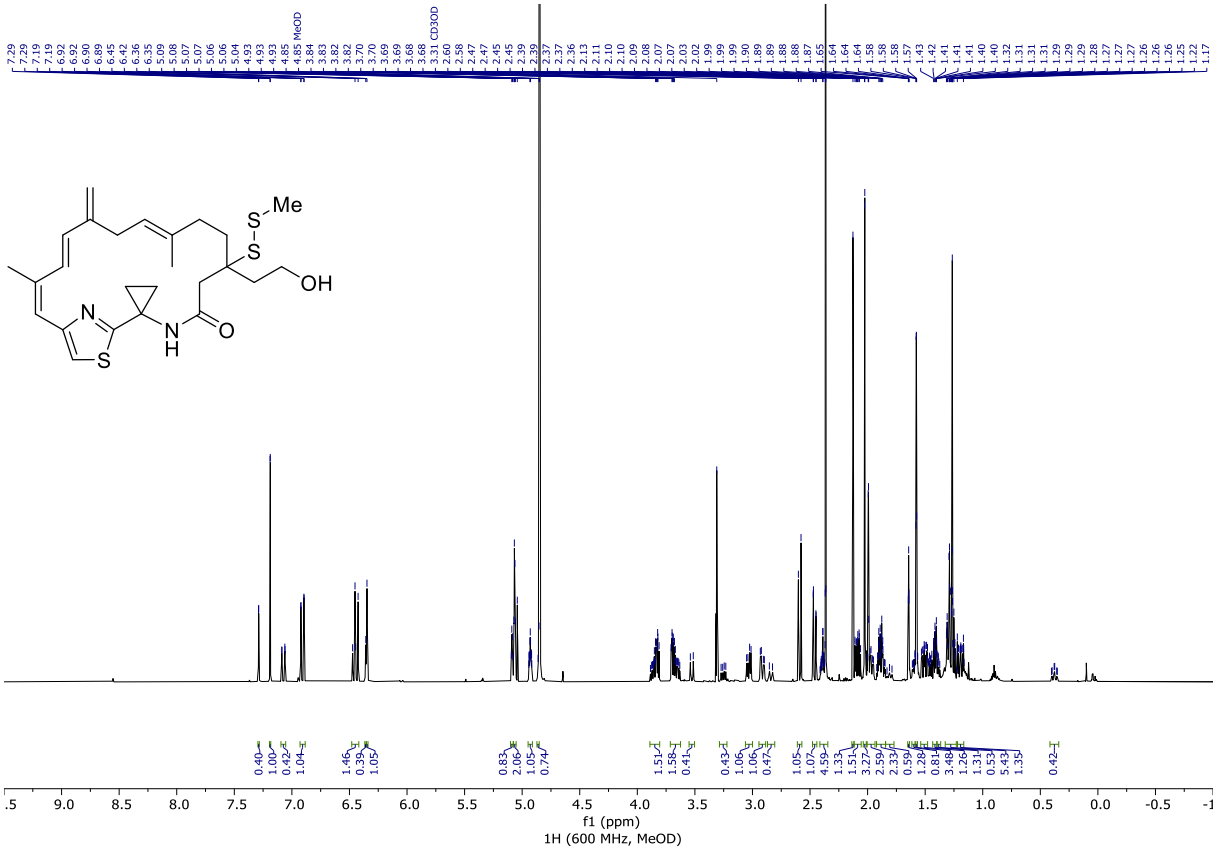


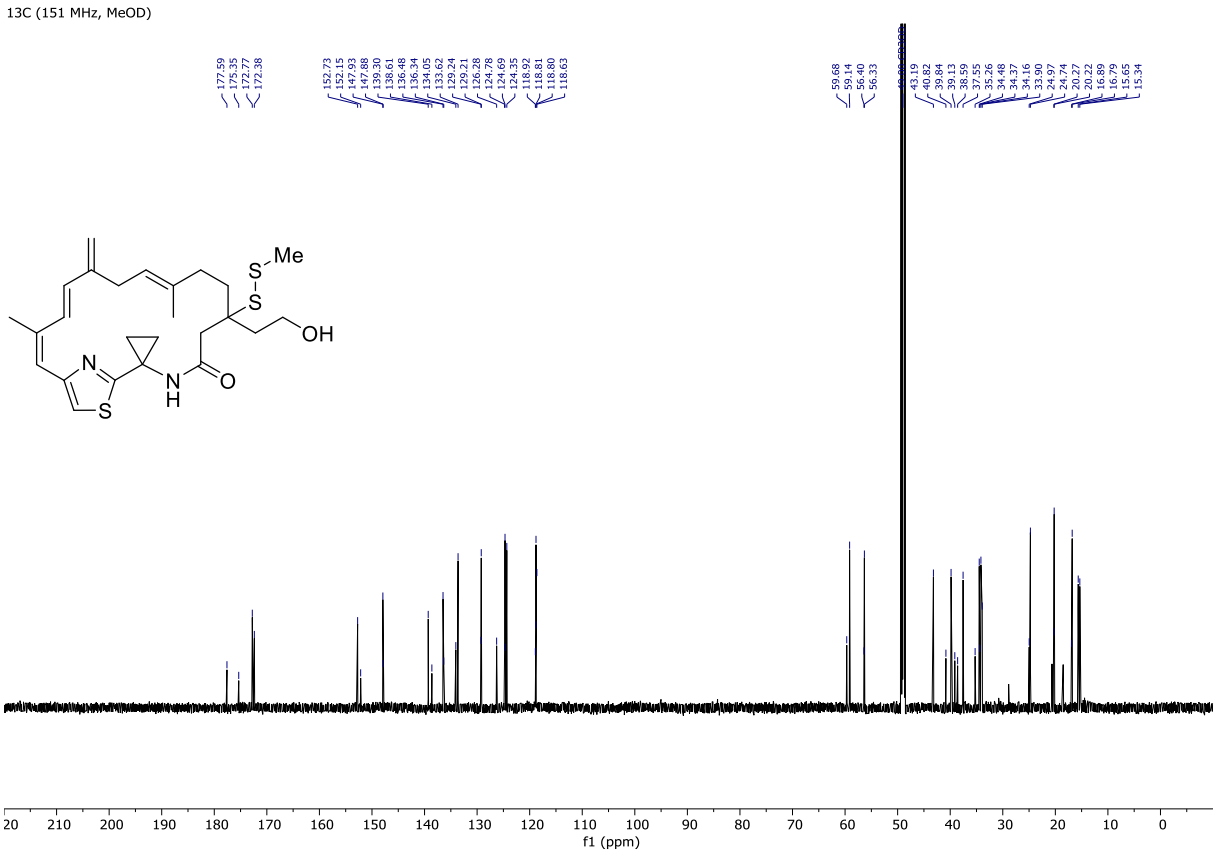
Compound **S5** (≈7:3 mixture of rotamers)



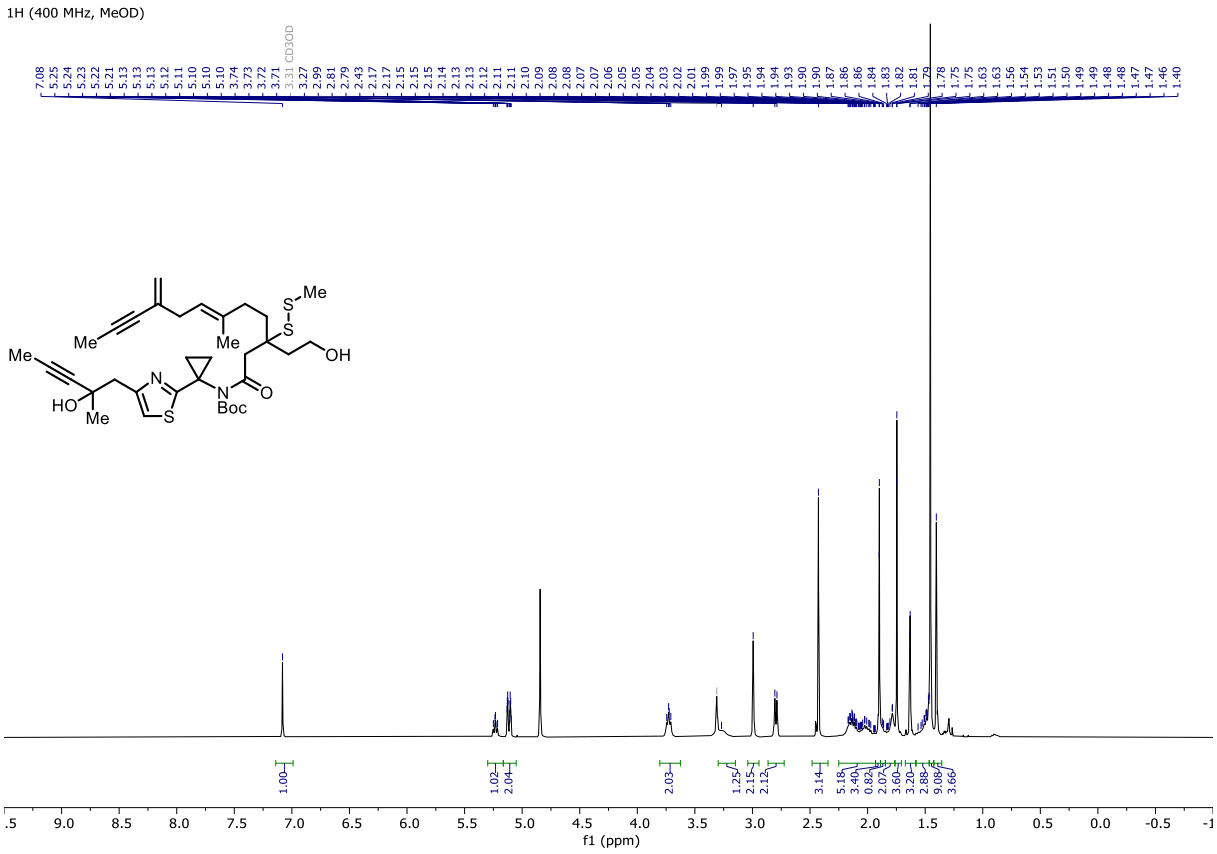


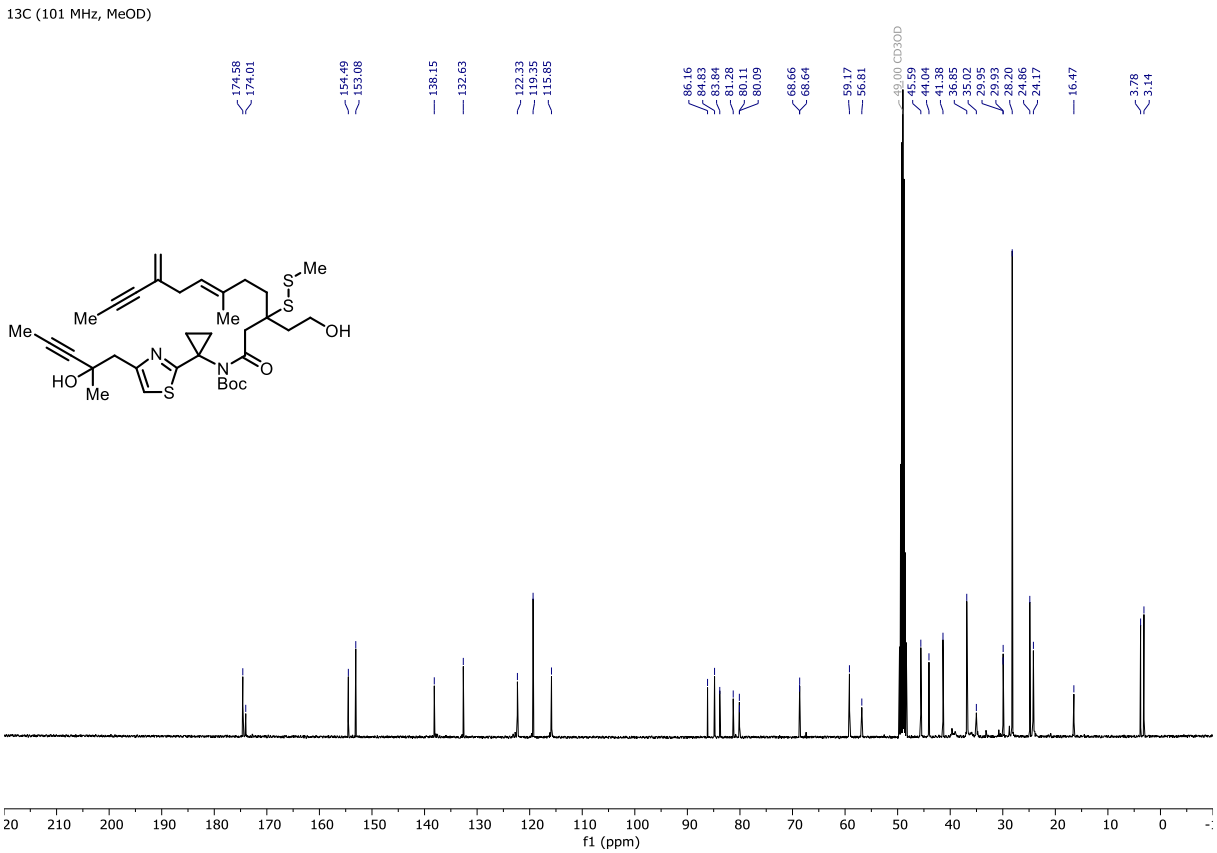
Compound **28** (≈7:3 mixture of rotamers)





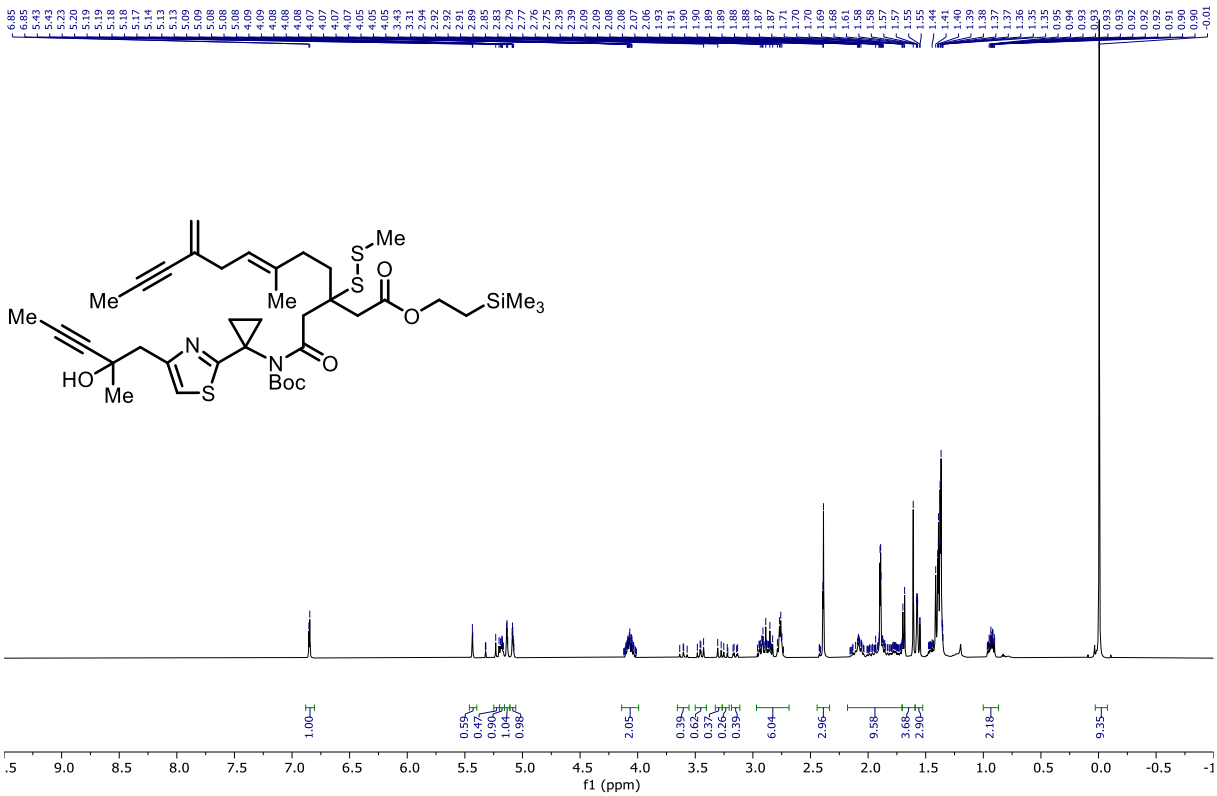
Compound **29** (mixture of diastereomers and rotamers)



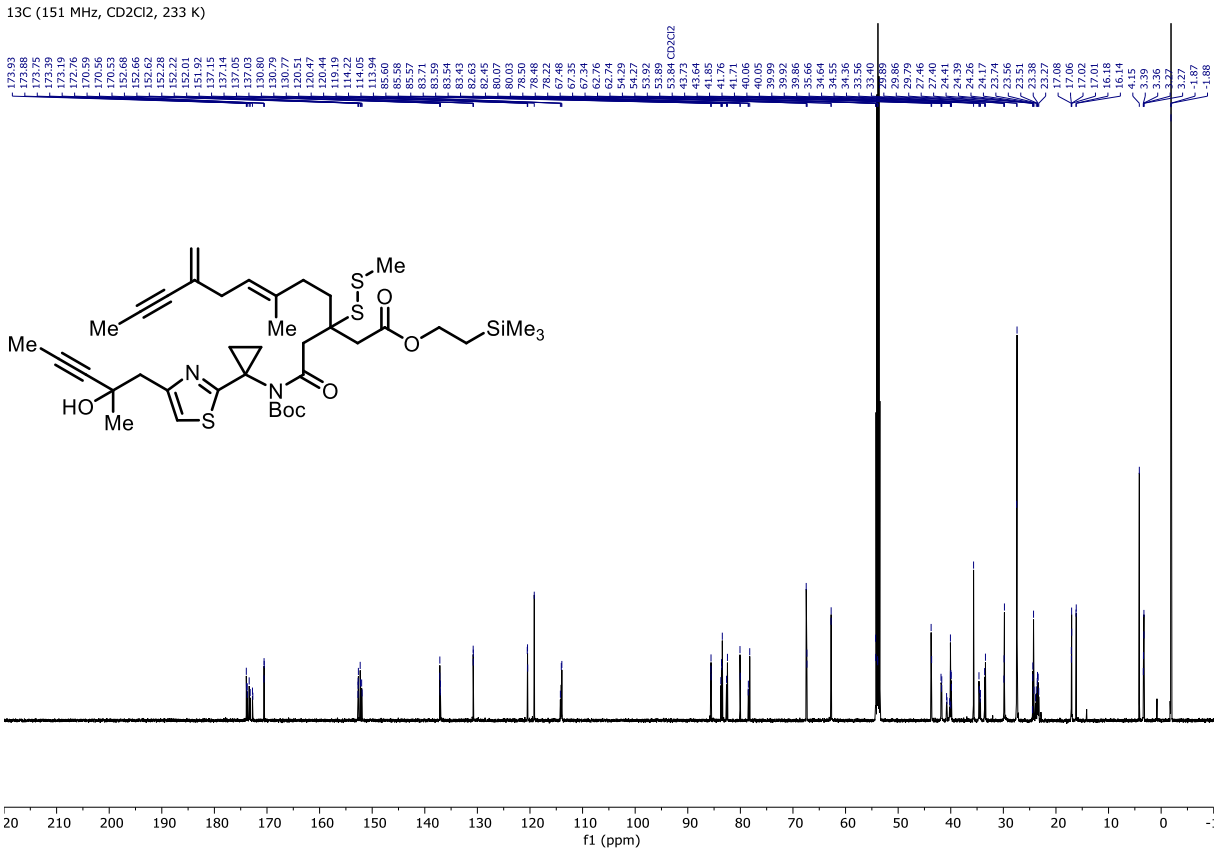


Compound **30** (mixture of diastereomers and rotamers)

1H (600 MHz, CD2Cl2, 233 K)



13C (151 MHz, CD2Cl2, 233 K)



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