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Fsp^3-Rich and Diverse Fragments Inspired by Natural Products as a Collection to Enhance Fragment-Based Drug Discovery

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SUPPORTING INFORMATION

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1. GENERAL EXPERIMENTAL PROCEDURES

Except as otherwise indicated, reactions were carried out in oven- or flame-dried glassware under nitrogen or argon with dry, freshly distilled solvents. Tetrahydrofuran was distilled from calcium hydride and $LiAlH_4$ in the presence of triphenyl methane. Diethyl ether was distilled from calcium hydride and $LiAlH_4$. CH_2Cl_2, MeOH, PhMe, MeCN and hexane were distilled from calcium hydride. All other reagents were used as supplied by commercial sources. Organic layers were dried over $MgSO_4$, unless otherwise stated. Yields refer to chromatographically and spectroscopically pure compounds. Thin layer chromatography was performed on glass plates coated with 60 F_{254} silica. Plates were visualised using UV light (254 nm) or 1% aq $KMnO_4$. Retention factors (R_f) are quoted to 0.01. Flash chromatography was carried out using slurry-packed Merck 9385 Kieselgel 60 silica gel. Melting points were obtained using a Büchi Melting Point B-545 melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Spectrum One spectrometer with internal referencing as neat films. Absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}) and the following abbreviations are used: w, weak; m, medium; s, strong; br, broad. Proton magnetic resonance spectra were recorded at 298 K using either a 400 MHz Bruker AVANCE III HD spectrometer equipped with a Smart probe, a 500 MHz Bruker AVANCE III HD spectrometer equipped with a DCH Cryoprobe, or a 600 MHz Bruker AVANCE III spectrometer equipped with a inverse broadband probe. Whilst all compounds were formed as racemates, stereochemistry is indicated to demonstrate relative relationships between multiple stereocentres. Chemical shifts (δ_H) are quoted in ppm to the nearest 0.01 ppm and are referenced to the residual non-deuterated solvent peak. Coupling constants (*J*) are reported in Hertz to the nearest 0.5 Hz. Data are reported as follows: chemical shift, integration, multiplicity [br, broad; s, singlet; d, doublet; t, triplet; q, quartet; qui, quintet; sept, septet; m, multiplet; or as a combination of these (e.g. dd, dt, etc.)] and coupling constant(s).

Carbon magnetic resonance spectra were recorded on Bruker Avance 400 QNP (101 MHz), Bruker DRX-400 (100 MHz), Bruker Avance 500 BB ATM (125 MHz) and Bruker Avance 500 Cryo Ultrashield (125 MHz) spectrometers. Chemical shifts (δ_C) are quoted in ppm to the nearest 0.01 ppm, and are referenced to the deuterated solvent.

High resolution mass spectrometry (HRMS) measurements were recorded on a Micromass QTOF mass spectrometer or a Waters LCT Premier Time of Flight mass spectrometer. Mass values are quoted within the error limits of ± 5 ppm mass units. ESI refers to the electrospray ionisation technique.

2. PROCEDURES AND ANALYTICAL DATA

General Procedure A

Propargyl bromide (1.0 equiv) was added to a stirred solution of the diketone (1.0 equiv) and NaOH (1.0 equiv) in H_2O (1.06 M) at rt. The resultant mixture was stirred at 60 °C for 16 h after which the aqueous layer was extracted with CH_2Cl_2 (3 ×) and the combined organic extracts were washed with brine, then dried and concentrated *in vacuo* to give a crude material.

General Procedure B

$NaBH_4$ (0.5 equiv) was added to a stirred solution of the α,α-disubstituted ketone (1.0 equiv) in DME (0.5 M) at rt. The resultant mixture was stirred at 60 °C for 24 h before 1 N HCl was added. The mixture was diluted with EtOAc, the phases were separated, and the aqueous phase was extracted with EtOAc (3 ×). The combined organic extracts were washed with brine, then dried and concentrated *in vacuo* to give a crude material.

General Procedure C

Imidazole (9.5 equiv) and *tert*-butyldimethylsilyl chloride (5.0 equiv) were added to a stirred solution of the alcohol (1.0 equiv) in DMF (0.1 M) at rt and the resultant mixture was stirred for 24 h. H_2O was added, and the aqueous phase was extracted with petroleum ether (3 ×). The combined organic extracts were dried and concentrated *in vacuo* to give a crude material.

General Procedure D

TBAF (1.0 M in THF, 2 equiv) was added to a stirred solution of the silyl ether (1 equiv) in anhydrous THF (0.05 M) at rt. The reaction mixture was stirred at rt until TLC showed complete consumption of the starting material. The mixture was concentrated *in vacuo* to give a crude material.

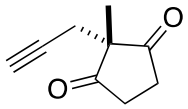
General Procedure E

10% Pd/C (20 mol%) was added to a stirred solution of the benzylamine (1.0 equiv) in EtOH (0.05 M), and the reaction mixture was stirred under an atmosphere of H_2 at 40 °C for 4 h. The mixture was filtered through a pad of celite and concentrated *in vacuo* to give the title compound.

General Procedure F

DCC (1.35 eq.) was added to a stirred solution of *syn*-**1** (1.0 equiv), the carboxylic acid (1.35 equiv), and DMAP (0.1 equiv) at 0 °C in anhydrous CH_2Cl_2 (0.1 M). The reaction mixture was stirred at rt for 16 h. Then, precipitate was filtered off and the mixture was concentrated *in vacuo* to give a crude material.

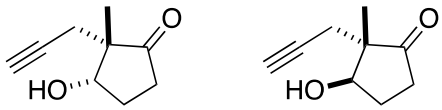
2-Methyl-2-(prop-2-yn-1-yl)cyclopentane-1,3-dione (3)



3

According to General Procedure A, propargyl bromide (10 mL, 106 mmol), 2-methylcyclopentane-1,3-dione (10 g, 106 mmol) and NaOH (3.6 g, 106 mmol) gave a crude material. Purification *via* flash column chromatography (eluent hexane/EtOAc, 10:2) gave **3** as an amorphous white solid (15.9 g, 93.3.0 mmol, 88%). $\mathbf{R_f}$ = 0.25 (eluent hexane/EtOAc, 80:20); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 2.90–2.75 (4H, m), 2.47 (2H, d, *J* 2.8), 1.98 (1H, t, *J* 2.5), 1.14 (3H, s); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 215.0, 78.8, 70.8, 55.1, 35.6, 24.0, 19.1; **IR** ν_{max}: 3280 (m, C≡C–H), 1749, 1723 (C=O). These characterisation data are in accordance with that previously reported in the literature.[1]

(2*S,3*S**)-3-Hydroxy-2-methyl-2-(prop-2-yn-1-yl)cyclopentan-1-one (*syn*-1) and (2*S**,3*R**)-3-hydroxy-2-methyl-2-(prop-2-yn-1-yl)cyclopentan-1-one (*anti*-1)**



syn-**1** *anti*-**1**

According to General Procedure B, $NaBH_4$ (630 mg, 16.5 mmol) and **3** (5.0 g, 33.3 mmol) gave a crude material. Purification *via* flash column chromatography (eluent hexane/EtOAc, 80:20) gave *syn*-**1** (1.78 g, 11.7 mmol, 35%) and *anti*-**1** (1.16 g, 7.66 mmol, 23%) both as colourless oils.

Data of *syn*-**1**:

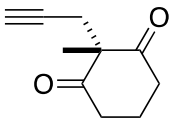
$\mathbf{R_f}$ = 0.19 (eluent hexane/EtOAc, 80:20); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 4.27 (1H, dd, *J* 4.6, 1.9), 2.56–2.32 (4H, m), 2.23 (1H, dddd, *J* 13.9, 10.3, 9.2, 4.5), 2.09–1.99 (2H, m), 1.96 (1H, br s), 1.12 (3H, s); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 219.7, 81.2, 77.0, 70.8, 53.3, 34.3, 27.6, 21.1, 20.1; **IR** ν_{max}: 3435 (br, O–H), 3289 (m, C≡C–H), 1729 (s, C=O).

Data of *anti*-**1**:

$\mathbf{R_f}$ = 0.17 (eluent hexane/EtOAc, 80:20); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 4.41 (1H, ddd, *J* 9.5, 6.4, 3.5), 2.59–2.24 (4H, m), 2.22–2.09 (2H, m), 2.05 (1H, t, *J* 2.7), 1.93–1.79 (1H, m), 1.06 (3H, s); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 218.4, 80.8, 75.7, 71.3, 51.8, 35.0, 27.3, 25.1, 15.2; **IR** ν_{max}: 3439 (br, O–H), 3287 (m, C≡C–H), 1731 (s, C=O).

These characterisation data are in accordance with that previously reported in the literature.[1]

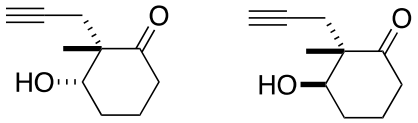
2-Methyl-2-(prop-2-yn-1-yl)cyclohexane-1,3-dione (6)



6

According to General Procedure A, propargyl bromide (6 mL, 53.5 mmol), 2-methylcyclohexane-1,3-dione (6.75 g, 53.5 mmol) and NaOH (2.14 g, 53.5 mmol) gave a crude material. Purification *via* flash column chromatography (eluent hexane/EtOAc, 10:2) gave **6** as a yellow oil (6.14 g, 37.5 mmol, 70%). $\mathbf{R_f}$ **=** 0.27 (eluent hexane/EtOAc, 80:20); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 2.73–2.52 (6H, m), 2.02–1.80 (3H, m), 1.24 (3H, s); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 208.8, 80.4, 70.5, 64.0, 38.1, 24.3, 22.3, 17.2; **IR** ν_{max}: 3276 (m, C≡C–H), 1728, 1694 (C=O). These characterisation data are in accordance with that previously reported in the literature.

(2*S,3*S**)-3-Hydroxy-2-methyl-2-(prop-2-yn-1-yl)cyclohexan-1-one (*syn*-8) and (2*S**,3*R**)-3-hydroxy-2-methyl-2-(prop-2-yn-1-yl)cyclohexan-1-one (*anti*-8)**



syn-**8** *anti*-**8**

According to General Procedure B, $NaBH_4$ (680 mg, 18.0 mmol) and **6** (5.88 g, 35.8 mmol) gave a crude material. Purification *via* flash column chromatography (eluent hexane/EtOAc, 80:20) gave *syn*-**8** (2.26 g, 13.6 mmol, 38%) and *anti*-**8** (1.84 g, 11.1 mmol, 31%) both as colourless oils.

Data of *syn*-**8**:

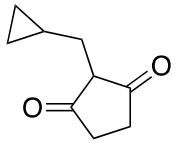
$\mathbf{R_f}$ **=** 0.19 (eluent hexane/EtOAc, 80:20); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 4.19 (1H, m), 2.69 (1H, dd, *J* 17.3, 2.7), 2.59–2.41 (2H, m), 2.37–2.29 (1H, m), 2.15–2.02 (2H, m), 2.01 (1H, t, *J* 2.7), 1.94 (1H, d, *J* 4.0), 1.92–1.76 (2H, m), 1.27 (3H, s); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 213.1, 81.2, 75.1, 71.3, 52.5, 37.8, 28.2, 23.0, 21.3, 20.7; **IR** ν_{max}: 3505 (br, O–H), 3393 (s, C≡C–H), 1696 (s, C=O).

Data of *anti*-**8**:

$\mathbf{R_f}$ **=** 0.16 (eluent hexane/EtOAc, 80:20); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 4.07 (1H, dd, *J* 10.3, 3.8), 2.60 (1H, d, *J* 16.8), 2.52–2.41 (2H, m), 2.33–2.26 (2H, m), 2.07–1.91 (3H, m), 1.91–1.79 (1H, m), 1.63–1.50 (1H, m), 1.24 (3H, s); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 211.9, 81.7, 74.7, 71.5, 54.4, 37.3, 29.2, 24.9, 20.16, 17.3; **IR** ν_{max}: 3448 (br, O–H), 3289 (s, C≡C–H), 1702 (s, C=O).

These characterisation data are in accordance with that previously reported in the literature.[1]

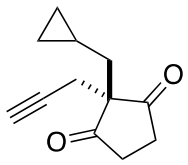
2-(Cyclopropylmethyl)cyclopentane-1,3-dione (5)



5

L-Proline (37.4 mg, 0.325 mmol) was added to a stirred suspension of cyclopentane-1,3-dione (638 mg, 6.50 mmol), cyclopropanecarboxaldehyde (1.46 mL, 19.5 mmol) and hantzsch ester (1.66 g, 6.57 mmol) in anhydrous CH_2Cl_2 (25 mL) at rt. The resultant mixture was stirred at rt for 24 h, the concentrated *in vacuo.* Purification *via* flash column chromatography (EtOAc/petroleum ether/AcOH, 90:10:2) gave **5** as a light orange solid (899 mg, 5.92 mmol, 91%). $\boldsymbol{R_f}$ = 0.38 (EtOAc/AcOH, 98:2); **^{1}H NMR** (400 MHz, DMSO-d_6): δ_H 11.45 (1H, s), 2.35 (4H, s), 1.93 (2H, d, *J* 6.6), 0.88–0.71 (1H, m), 0.35–0.19 (2H, m), 0.06– -0.02 (2H, m); **^{13}C NMR** (101 MHz, DMSO-d_6): δ_C 115.9, 25.0, 9.9, 4.2, 4 x C (cyclopentadione) not seen; **IR** ν_{max}: 2500 (br, O–H), 1673 (s, C=O); **HRMS** (ESI): $[M+H]^+$ calcd. for $C_9H_{13}O_2^+$**:** 153.0916, found**:** 153.0918.

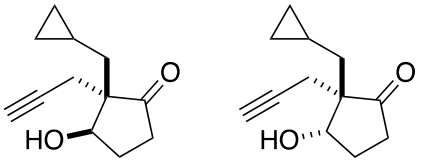
2-(Cyclopropylmethyl)-2-(prop-2-yn-1-yl)cyclopentane-1,3-dione (7)



7

According to General Procedure A, propargyl bromide (0.295 mL, 2.73 mmol), **3** (416 mg, 2.73 mmol) and NaOH (147 mg, 2.73 mmol) gave a crude material. Purification *via* flash column chromatography (eluent Petroleum ether/EtOAc, 86:14) gave **7** as a colourless oil (336 mg, 1.77 mmol, 65%). $\boldsymbol{R_f}$ = 0.32 (petroleum ether/EtOAc, 86:14); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 2.92–2.67 (4H, m), 2.41 (2H, d, *J* 2.6), 1.91 (1H, t, *J* 2.6), 1.55 (2H, d, *J* 7.1), 0.59–0.41 (1H, m), 0.42–0.32 (2H, m), 0.06– -0.05 (2H, m); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 216.5, 78.9, 70.7, 60.1, 40.5, 37.1, 23.9, 6.9, 4.9; **IR** ν_{max}: 3278 (s, C≡C–H), 1719 (s, C=O); **HRMS** (ESI): calcd. for $C_{12}H_{15}O_2$ $[M+H]^+$**:** 191.1072, found**:** 191.1071.

(2*S,3*R**)-2-(Cyclopropylmethyl)-3-hydroxy-2-(prop-2-yn-1-yl)cyclopentan-1-one (*anti*-9) and (2*S**,3*S**)-2-(cyclopropylmethyl)-3-hydroxy-2-(prop-2-yn-1-yl)cyclopentan-1-one (*syn*-9)**



anti-**9** *syn*-**9**

According to General Procedure B, $NaBH_4$ (35.0 mg, 0.925 mmol) and **7** (320 mg, 1.68 mmol) gave a crude material. Purification *via* flash column chromatography (CH_2Cl_2/EtOAc, 99:1 to 95:5) gave *anti*-**9** (174.2 mg, 0.91 mmol, 54%) and *syn*-**9** (62.6 mg, 0.32 mmol, 19%) both as colourless oils.

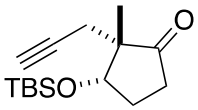
Data for *anti*-**9**

***R*f** = 0.41 (CH_2Cl_2/EtOAc, 9:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 4.42 (1H, ddd, *J* 9.8, 7.0, 3.0), 2.67 (1H, dd, *J* 17.0, 2.6), 2.51 (1H, ddd, *J* 19.3, 10.0, 2.6), 2.38–2.23 (3H, m), 2.23–2.08 (1H, m), 2.06 (1H, t, *J* 2.7), 1.97 (1H, dq, *J* 12.5, 9.8), 1.74 (1H, dd, *J* 14.7, 5.4), 1.40 (1H, dd, *J* 14.7, 8.3 Hz), 0.71 (1H, dtt, *J* 13.3, 8.3, 5.1), 0.56–0.36 (2H, m), 0.14 (1H, dtd, *J* 8.0, 4.8, 3.5), 0.06 (1H, d, *J* 3.2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 218.0, 81.3, 76.5, 71.5, 55.2, 35.1, 33.4, 27.1, 23.3, 5.9, 5.4, 4.8; **IR** ν_{max}: 3452 (br, O–H), 3287 (s, C≡C–H), 1729 (s, C=O); **HRMS** (ESI): $[M+H]^+$ calcd. for $C_{12}H_{17}O_2^+$**:** 193.1229, found**:** 193.1225.

Data for *syn*-**9**

***R*f** = 0.37 (CH_2Cl_2/EtOAc, 9:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 4.34 (1H, dq, *J* 5.0, 3.0), 2.70 (1H, dd, *J* 17.3, 2.7), 2.56–2.24 (4H, m), 2.12 (1H, d, *J* 3.6), 2.09–1.99 (2H, m), 1.58 (1H, dd, *J* 14.5, 5.9), 1.43 (1H, dd, *J* 14.5, 7.8), 0.65 (1 H, qq, *J* 7.9, 5.1), 0.55–0.39 (2H, m), 0.18 (1H, dtd, *J* 7.9, 4.8, 3.5), –0.01 (1 H, dtd, *J* 10.0, 4.8, 3.5); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C 219.0, 81.6, 75.5, 71.0, 57.4, 37.9, 35.0, 27.7, 19.0, 6.2, 5.0, 4.6; **IR** ν_{max}: 3453 (br, O–H), 3303 (s, C≡C–H), 1732 (s, C=O); **HRMS** (ESI): $[M+H]^+$ calcd. for $C_{12}H_{17}O_2^+$**:** 193.1229, found**:** 193.1224.

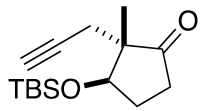
(2*S,3*S**)-3-((*tert*-Butyldimethylsilyl)oxy)-2-methyl-2-(prop-2-yn-1-yl)cyclopentan-1-one (*syn*-S1)**



syn-**S1**

According to General Procedure C, imidazole (811 mg, 11.9 mmol), *tert*-butyldimethylsilyl chloride (939 mg, 6.23 mmol) and *syn*-**1** (190 mg, 1.25 mmol) gave a crude material. Purification *via* flash column chromatography (eluent hexane/EtOAc, 90:10) gave *syn*-**S1** as a colourless oil (327 mg, 1.23 mmol, 98%). $\mathbf{R}_f$ = 0.42 (eluent hexane/EtOAc, 90:10); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 4.15 (1H, m), 2.49–2.30 (4H, m), 2.17 (1H, m), 1.95 (2H, m), 1.09 (3H, s), 0.87 (9H, s), 0.12 (3H, s) 0.11 (3H, s); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 219.5, 81.6, 76.8, 70.1, 53.7, 33.6, 28.1, 25.7, 20.6, 19.2, 18.0, –4.5, –5.0; **IR** ν_{max}: 3307 (s, C≡C–H), 2930 (m, C–H), 1744 (s, C=O); **HRMS** (ESI): $[M+H]^+$ calcd. for $C_{15}H_{27}O_2Si^+$: 267.1775, found: 267.1775.

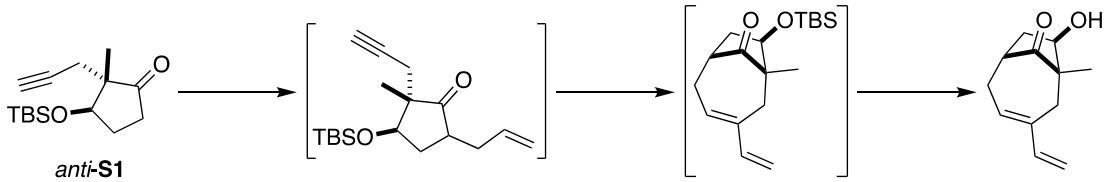
(2S*,3R*)-3-((*tert*-Butyldimethylsilyl)oxy)-2-methyl-2-(prop-2-yn-1-yl)cyclopentan-1-one (*anti*-S1)



anti-**S1**

According to General Procedure C, imidazole (427 mg, 6.23 mmol), *tert*-butyldimethylsilyl chloride (494 mg, 3.28 mmol) and *anti*-**1** (100 mg, 0.66 mmol) gave a crude material. Purification *via* flash column chromatography (eluent hexane/EtOAc, 90:10) gave *anti*-**S1** as a colourless oil (167 mg, 0.63 mmol, 95%). $\mathbf{R_f}$ = 0.42 (eluent hexane/EtOAc, 90:10); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 4.50–4.42 (1H, m), 2.53–2.35 (2H, m), 2.18–2.06 (3H, m), 1.95 (1H, t, *J* 2.6), 1.88–1.73 (1H, m), 0.96 (3H, s), 0.89 (9H, s), 0.10 (6H, 2 × s); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 218.6, 80.7, 74.4, 70.7, 53.0, 35.6, 28.5, 25.9, 24.5, 18.1, 16.2, –4.3, –4.8; **IR** ν_{max}: 3309 (s, C≡C–H), 2930 (s, C–H), 1747 (s, C=O); **HRMS** (ESI): $[M+H]^+$ calcd. for $C_{15}H_{27}O_2Si^+$: 267.1775, found: 267.1775.

(2*S,3*R**,5*R**)-5-Allyl-3-((*tert*-butyldimethylsilyl)oxy)-2-methyl-2-(prop-2-yn-1-yl)cyclopentan-1-one (10)**

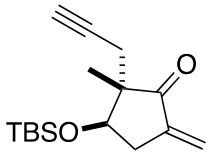


anti-**S1** **10**

To a solution of *anti*-**S1** (86 mg, 0.322 mmol) in anhydrous THF (6.6 mL) was added LiHMDS (1.0 M in PhMe, 0.39 mL, 0.39 mmol) at –78 °C and the mixture was stirred for 30 min. Then, cooling was removed and the mixture was allowed to warm to rt. After stirring 30 min at rt, the mixture was cooled to 0 °C and allyl bromide (33.6 µL, 0.39 mmol) was added. The reaction mixture was stirred at 0 °C for 1 h, then concentrated *in vacuo* and filtered through a short silica plug (eluent EtOAc/petroleum ether 2:98) to give a crude material as a mixture of diastereomers (76:24 *dr*).

Hoveyda-Grubbs 2nd generation catalyst (12.5 mg, 20.0 µmol) was added to a stirred solution of the crude product in anhydrous PhMe (40 mL) at rt. The reaction mixture was stirred under an ethylene atmosphere at reflux for 3 h. The mixture was concentrated *in vacuo* and filtered through a short plug of silica. TBAF (1.0 M in THF, 0.103 mL, 0.103 mmol) was added to a solution of the crude product in anhydrous THF (3 mL). The solution was stirred at rt for 2 h, then concentrated *in vacuo*. Purification *via* flash column chromatography (petroleum ether/EtOAc, 66:33) gave **10** as a colourless oil (8.0 mg, 41.7 µmol, 13% over three steps). $\mathbf{R_f}$ = 0.45 (petroleum ether/EtOAc, 50:50); **^{1}H NMR** (600 MHz, $CDCl_3$): δ_H 6.30 (1H, dd, J 17.5, 11.0), 5.69 (1H, dd, *J* 6.6, 3.2), 5.06 (1H, d, *J* 17.5), 4.93 (1H, d, *J* 11.0), 4.06 (1H, dd, *J* 6.9, 2.4), 2.77 (1H, dt, *J* 9.0, 4.0), 2.47 (1H, d, *J* 18.4), 2.43–2.32 (2H, m), 2.15 (ddd, *J* 14.5, 6.9, 4.0 Hz, 1H), 2.03–1.98 (1H, m), 1.96 (1H, ddd, *J* 14.5, 9.0, 2.5), 1.61 (1H, br s), 1.22 (3H, s); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C 206.3, 142.8, 135.7, 129.4, 110.9, 76.3, 53.3, 44.6, 37.3, 35.5, 33.3, 17.1; **IR** ν_{max}: 3397 (br., O–H), 1733 (s, C=O); **HRMS** (ESI): $[M+H]^+$ calcd. for $C_{12}H_{17}O_2^+$: 193.1223, found: 193.1232.

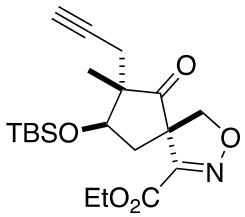
(2*S,3*R**)-3-((*tert*-Butyldimethylsilyl)oxy)-2-methyl-5-methylene-2-(prop-2-yn-1-yl)cyclopentan-1-one (11)**



11

CH_2Br_2 (0.868 mL, 12.4 mmol) and Et_2NH (2.56 mL, 24.8 mmol) were added to a stirred solution of *anti*-**S1** (550 mg, 2.06 mmol) in CH_2Cl_2 (10 mL). The mixture was heated under microwave irradiation at 125 °C for 20 min. The mixture was diluted with Et_2O (150 mL) and precipitate was removed by filtration, the filtrate was then concentrated *in vacuo*. Purification *via* flash column chromatography (petroleum ether/EtOAc, 97:3) gave **11** as a colourless oil (389 mg, 1.40 mmol, 68%). R_f = 0.20 (petroleum ether/EtOAc, 97:3); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 6.11 (1H, ddd, 3.1, 2.0, 1.1), 5.37 (1H, ddd, *J* 3.1, 2.0, 1.1), 4.46 (1H, dd, *J* 8.0, 6.9), 2.89 (1H, ddt, *J* 16.5, 6.9, 2.0), 2.60–2.49 (1H, m), 2.48 (1H, dd, *J* 16.9, 2.7), 2.23 (1H, dd, *J* 16.9, 2.7), 1.95 (1H, t, *J* 2.7), 1.02 (3H, s), 0.90 (9H, s), 0.11 (6H, app s); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 206.2, 142.2, 119.6, 80.7, 72.0, 70.8, 53.4, 36.4, 25.9, 24.3, 18.1, 16.4, –4.3, –4.8; **IR** ν_{max}: 3313, (m, C≡C–H), 1730 (s, C=O), 1641 (s, C=C), 1462 (m, $C=CH_2$); **HRMS** (ESI): $[M + H]^+$ calcd. for $C_{16}H_{27}O_2Si^+$: 279.1775, found 279.1767.

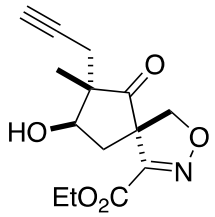
Ethyl (5*S,7*S**,8*R**)-8-((*tert*-butyldimethylsilyl)oxy)-7-methyl-6-oxo-7-(prop-2-yn-1-yl)-2-oxa-3-azaspiro[4.4]non-3-ene-4-carboxylate (S2)**



S2

1-Ethyl oxalyl chloride 2-oxime (56.2 mg, 0.371 mmol) in anhydrous CH_2Cl_2 (5 mL) was added dropwise over 1 h to a stirred solution of **11** (86.0 mg, 0.309 mmol) and Et_3N (52.0 µL, 0.371 mmol) in anhydrous CH_2Cl_2 (5 mL). The mixture was then concentrated *in vacuo*. Purification *via* flash column chromatography (petroleum ether/EtOAc, 90:10) gave **S2** as a colourless oil (85.0 mg, 0.216 mmol, 70%). R_f = 0.33 (petroleum ether/EtOAc, 90:10); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 4.55 (1H, t, *J* 5.5), 4.34 (2H, q, *J* 7.1), 3.49 (1H, d, *J* 18.0), 3.14 (1H, d, *J* 18.0), 2.61 (1H, dd, *J* 14.4, 5.5), 2.45 (1H, dd, *J* 17.1, 2.6), 2.28 (1H, dd, *J* 17.1, 2.6), 2.14–2.04 (2H, m), 1.36 (3H, t, *J* 7.1), 1.11 (3H, s), 0.89 (9H, s), 0.11 (6H, app s); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 213.3, 160.1, 150.7, 90.1, 79.1, 72.0, 71.8, 62.4, 52.7, 42.8, 42.6, 25.9, 25.1, 18.1, 16.7, 14.2, –4.4, –4.8; **IR** ν_{max}: 3297 (m, C≡C–H), 1752 (s, C=O), 1721 (s, C=O), 1597 (m, C=N); **HRMS** (ESI): $[M + H]^+$ calcd. for $C_{20}H_{32}NO_5Si^+$: 394.2044, found 394.2044.

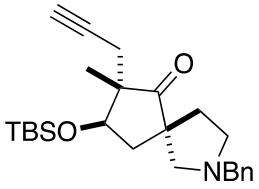
Ethyl (5*S,7*S**,8*R**)-8-hydroxy-7-methyl-6-oxo-7-(prop-2-yn-1-yl)-2-oxa-3-azaspiro[4.4]non-3-ene-4-carboxylate (12)**



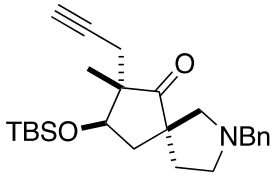
12

According to General Procedure D, **S2** (29.0 mg, 73.7 µmol) and TBAF (1.0 M in THF, 0.111 mL, 0.111 mmol) gave a crude material. Purification *via* flash column chromatography (EtOAc/petroleum ether 2:3) gave **12** as a colourless oil (9.0 mg, 32.4 µmol, 44%). R_f = 0.42 (EtOAc/petroleum ether 1:1); **^{1}H NMR** (600 MHz, $CDCl_3$): δ_H 4.60 (1H, ddd, *J* 8.1, 6.1, 3.3), 4.35 (2H, qd, *J* 7.2, 0.7), 3.53 (1H, d, *J* 18.0), 3.17 (1H, d, *J* 18.0), 2.70 (1H, dd, *J* 14.4, 6.1), 2.49–2.40 (2H, m), 2.12 (1H, t, *J* 2.7), 2.10 (1H, d, *J* 3.3), 2.08–2.03 (1H, m), 1.36 (3H, t, *J* 7.2), 1.18 (3H, s); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C 212.5, 160.0, 150.9, 90.1, 79.8, 73.0, 71.9, 62.5, 51.0, 41.1, 40.8, 25.9, 15.9, 14.3; **IR** ν_{max}: 3506 (br. O–H), 3281 (m, C≡C–H), 1752 (s, C=O), 1721 (s, C=O), 1598 (m, C=N); **HRMS** (ESI): $[M + Na]^+$ calcd. for $C_{14}H_{17}NO_5Na^+$: 302.0999, found 302.1002.

(5*S,7*S**,8*R**)-2-Benzyl-8-((*tert*-butyldimethylsilyl)oxy)-7-methyl-7-(prop-2-yn-1-yl)-2-azaspiro[4.4]nonan-6-one (S3a) and (5*R**,7*S**,8*R**)-2-benzyl-8-((*tert*-butyldimethylsilyl)oxy)-7-methyl-7-(prop-2-yn-1-yl)-2-azaspiro[4.4]nonan-6-one (S3b)**



S3a



S3b

N-(methoxymethyl)-*N*-(trimethylsilylmethyl)benzylamine (90%, 0.122 mL, 0.427 mmol) and TFA (0.1 M in CH_2Cl_2, 0.355 mL, 35.6 µmol) were added to a stirred solution of **11** (99.0 mg, 0.356 mmol) in CH_2Cl_2 (7 mL). The reaction mixture was stirred at 0 °C for 1 h, then concentrated *in vacuo* to give a mixture of diastereomers (66:43 *dr*). Purification *via* flash column chromatography (petroleum ether/EtOAc, 80:20) gave **S3a** (89.9 mg, 0.219 mmol, 61%) and **S3b** (47.5 mg, 0.116 mmol, 32%) both as yellow oils.

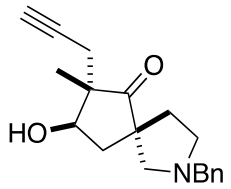
Data of **S3a**:

R_f = 0.54 (petroleum ether/EtOAc, 80:20); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.37–7.19 (5H, m), 4.37 (1H, dd, *J* 8.4, 6.1), 3.72–3.56 (2H, m), 2.85 (1H, td, *J* 8.4, 7.5, 4.2), 2.64–2.50 (3H, m), 2.39 (1H, dd, *J* 16.9, 2.7), 2.31 (1H, dd, *J* 13.0, 6.1), 2.22 (1H, ddd, *J* 12.5, 8.0, 4.2), 2.13 (1H, dd, *J* 16.9, 2.7), 1.90 (1H, dd, *J* 13.0, 8.4), 1.84–1.73 (2H, m), 0.98 (3H, s), 0.90 (9H, s), 0.10 (3H, s), 0.08 (3H, s); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 221.9, 139.1, 128.8, 128.4, 127.1, 80.9, 72.4, 70.8, 64.0, 59.8, 54.5, 54.4, 53.5, 44.5, 37.2, 25.9, 25.0, 18.2, 17.1, –4.3, –4.8; **IR** ν_{max}: 3311 (m, C≡C–H), 1737 (s, C=O); **HRMS** (ESI): $[M + H]^+$ calcd. for $C_{25}H_{38}NO_2Si^+$: 412.2667, found 412.2667.

Data of **S3b**:

***R*$_f$** = 0.36 (petroleum ether/EtOAc, 80:20); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.37–7.16 (5H, m), 4.44 (1H, dd, *J* 7.8, 5.9), 3.70 (1H, d, *J* 12.8), 3.58 (1H, d, *J* 12.8), 2.86 (1H, ddd, *J* 9.0, 7.3, 4.2), 2.68 (2H, d, *J* 2.4), 2.55 (1H, dt, *J* 9.0, 7.8), 2.42 (1H, dd, *J* 16.9, 2.7), 2.25–2.08 (3H, m), 2.02–1.92 (2H, m), 1.64 (1H, dt, *J* 12.6, 7.5), 0.94 (3H, s), 0.86 (9H, s), 0.08 (3H, s), 0.07 (3H, s); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 221.7, 139.1, 128.9, 128.4, 127.1, 81.0, 72.2, 70.9, 64.2, 60.2, 54.4, 54.1, 53.6, 44.6, 37.5, 25.9, 25.1, 18.1, 16.9, –4.3, –4.8; **IR** ν_{max}: 3311 (m, C≡C–H), 1737 (s, C=O); **HRMS** (ESI): $[M + H]^+$ calcd. for $C_{25}H_{38}NO_2Si^+$: 412.2667, found 412. 2666.

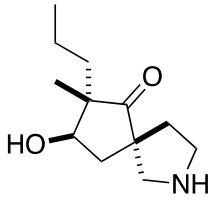
(5*S,7*S**,8*R**)-2-Benzyl-8-hydroxy-7-methyl-7-(prop-2-yn-1-yl)-2-azaspiro[4.4]nonan-6-one (S4a)**



S4a

According to General Procedure D, **S3a** (67.0 mg, 0.163 mmol) and TBAF (1.0 M in THF, 0.326 mL, 0.326 mmol) gave a crude material. Purification *via* flash column chromatography (EtOAc) gave **S4a** as a yellow oil (46.0 mg, 0.155 mmol, 95%). ***R*$_f$** = 0.28 (EtOAc); **^{1}H NMR** (600 MHz, $CDCl_3$): δ_H 7.35–7.19 (5H, m), 4.32 (1H, dd, *J* 9.9, 6.5), 3.65 (1H, d, *J* 13.0), 3.61 (1H, d, *J* 13.0), 2.93–2.85 (1H, m), 2.60–2.53 (2H, m), 2.46 (1H, dd, *J* 12.9, 6.5), 2.41 (1H, d, *J* 9.3), 2.38–2.27 (3H, m), 2.24 (1H, dt, *J* 8.2, 4.4), 1.93 (1H, t, *J* 2.6), 1.87 (1H, dd, *J* 12.9, 9.9), 1.79 (1H, dt, *J* 12.9, 7.7), 1.05 (3H, s); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 221.8, 154.6, 128.8, 128.4, 127.2, 81.0, 73.4, 71.2, 64.3, 59.8, 54.4, 54.4, 52.1, 43.4, 36.7, 25.6, 16.0; **IR** ν_{max}: 3370 (br s, O–H), 3291 (m, C≡C–H), 1735 (s, C=O); **HRMS** (ESI): $[M + H]^+$ calcd. for $C_{19}H_{24}NO_2^+$: 298.1802, found 298.1805.

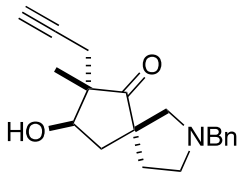
(5*S,7*S**,8*R**)-8-Hydroxy-7-methyl-7-propyl-2-azaspiro[4.4]nonan-6-one (13a)**



13a

According to General Procedure E, **S4a** (30.0 mg, 0.101 mmol) and 10% Pd/C (21.5 mg, 20.2 µmol) gave **13a** as an off-white amorphous solid (20.8 mg, 99.0 µmol, 98%). **^{1}H NMR** (400 MHz, CD_3OD): δ_H 4.15 (1H, dd, *J* 7.2, 5.9), 3.09 (1H, ddd, *J* 11.4, 8.3, 5.6), 3.00 (1H, dt, *J* 11.4, 7.4), 2.88 (1H, d, *J* 11.5), 2.76 (1H, d, *J* 11.5), 2.29 (1H, dd, *J* 13.2, 5.9), 2.12 (1H, ddd, *J* 13.0, 8.3, 6.9), 1.95 (1H, dd, *J* 13.2, 7.2), 1.83 (1H, ddd, *J* 13.0, 7.7, 5.6), 1.45–1.30 (4H, m), 1.24–1.14 (1H, m), 0.99 (3H, s), 0.91 (3H, t, *J* 7.0); **^{13}C NMR** (101 MHz, CD_3OD): δ_C 226.0, 73.8, 58.3, 56.4, 55.1, 47.7, 42.1, 39.9, 39.0, 18.5, 16.7, 15.0; **IR** ν_{max}: 3299 (br s, O–H), 1727 (s, C=O); **HRMS** (ESI): $[M + H]^+$ calcd. for $C_{12}H_{22}NO_2^+$: 212.1651, found 212.1648.

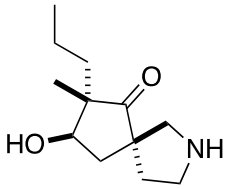
(5*R,7*S**,8*R**)-2-Benzyl-8-hydroxy-7-methyl-7-(prop-2-yn-1-yl)-2-azaspiro[4.4]nonan-6-one (S4b)**



S4b

According to General Procedure D, **S3b** (43.0 mg, 0.104 mmol) and TBAF (1.0 M in THF, 0.209 mL, 0.209 mmol) gave a crude material. Purification *via* flash column chromatography (EtOAc) **S4b** as a yellow oil (24.5 mg, 82.5 µmol, 79%). R_f = 0.22 (EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.36–7.28 (4H, m), 7.27–7.21 (1H, m), 4.43 (1H, dd, *J* 9.6, 6.4), 3.72–3.58 (2H, m), 2.83 (1H, ddd, *J* 9.2, 7.1, 4.5), 2.76 (1H, d, *J* 9.6), 2.66 (1H, d, *J* 9.6), 2.57 (1H, dt, *J* 9.2, 7.4), 2.39–2.31 (3H, m), 2.10 (1H, br s), 2.06–1.89 (3H, m), 1.68 (1H, dt, *J* 12.5, 7.4), 1.01 (3H, s); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 221.3, 139.1, 128.8, 128.4, 127.1, 81.1, 72.9, 71.3, 63.7, 60.1, 54.2, 54.0, 52.1, 43.5, 38.0, 25.7, 15.8; **IR** ν_{max}: 3331 (br s, O–H), 3285 (m, C≡C–H), 1735 (s, C=O); **HRMS** (ESI): $[M + H]^+$ calcd. for $C_{19}H_{25}NO_2^+$: 298.1802, found 298.1799.

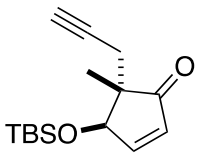
(5*R,7*S**,8*R**)-8-Hydroxy-7-methyl-7-propyl-2-azaspiro[4.4]nonan-6-one (13b)**



13b

According to General Procedure E, **S4b** (20.0 mg, 67.3 µmol) and 10% Pd/C (14.3 mg, 13.5 µmol) gave **13b** as an off-white amorphous solid (14.0 mg, 66.4 µmol, 99%). **^{1}H NMR** (400 MHz, CD_3OD) δ_H 4.19 (1H, t, *J* 5.4), 3.49–3.35 (3H, m), 3.26 (1H, d, *J* 12.1), 2.41 (1H, dd, *J* 13.6, 5.4), 2.19–1.97 (3H, m), 1.49–1.40 (2H, m), 1.38–1.20 (2H, m), 1.02 (3H, s), 0.92 (3H, t, *J* 7.2); **^{13}C NMR** (101 MHz, CD_3OD) δ_C 223.0, 73.9, 55.6, 55.0, 54.0, 46.3, 40.4, 39.0, 36.5, 18.5, 16.2, 14.9; **IR** ν_{max}: 3364 (br. s, O–H), 1733 (s, C=O); **HRMS** (ESI): $[M + H]^+$ calcd. for $C_{12}H_{22}NO_2^+$: 212.1651, found 212.1645.

(4*R,5*S**)-4-((*tert*-Butyldimethylsilyl)oxy)-5-methyl-5-(prop-2-yn-1-yl)cyclopent-2-en-1-one (14)**

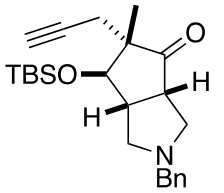


14

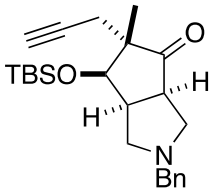
IBX (45% wt., 460 mg, 0.74 mmol) was added to a stirred solution of **S1** (100 mg, 0.37 mmol) in a mixture of fluorobenzene (1.70 mL) and DMSO (0.85 mL), and the resultant solution was stirred at 65 °C for 24 h. The reaction mixture was cooled to room temperature and diluted with ether (100 mL) and then washed successively with satd. $NaHCO_3$, H_2O and brine. The organic layer was then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (hexane/EtOAc, 99:1) gave **14** as a colourless oil (45 mg, 0.17 mmol, 45%). R_f = 0.15 (eluent hexane/EtOAc, 99:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.37 (1H, dd, *J* 5.9, 2.1), 6.17 (1H dd, *J* 5.9, 1.7), 4.94 (1H, app t, *J* 1.7), 2.48 (1H, dd, *J* 16.9, 2.7), 2.30 (dd, *J* 16.9, 2.7), 1.92 (t, *J* 2.7), 1.04 (3H, s), 0.93 (9H, s), 0.17

(3H, s), 0.16 (3H, s); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 209.5, 162.8, 132.2, 80.6, 76.6, 70.6, 51.9, 25.9, 25.2, 19.6, 18.2, –4.4, –4.6; **IR** ν_{max}: 1717 (s, C=O); **HRMS** (ESI): $[M+H]^+$ calcd. for $C_{15}H_{24}O_2NaSi^+$: 287.1438, found: 287.1424.

(3a*S*,5*S***,6*R***,6a*R***)-2-Benzyl-6-((*tert*-butyldimethylsilyl)oxy)-5-methyl-5-(prop-2-yn-1-yl)hexahydrocyclopenta[*c*]pyrrol-4(1*H*)-one (S5a) and (3a*R***,5*S***,6*R***,6a*S***)-2-benzyl-6-((*tert*-butyldimethylsilyl)oxy)-5-methyl-5-(prop-2-yn-1-yl)hexahydrocyclopenta[*c*]pyrrol-4(1*H*)-one (S5b)**



S5a



S5b

N-(methoxymethyl)-*N*-(trimethylsilylmethyl)benzylamine (90%, 51.6 µL, 0.181 mmol) and TFA (0.1 M in CH_2Cl_2, 0.151 mL, 15.1 µmol) were added to a stirred solution of **14** (40 mg, 0.151 mmol) in CH_2Cl_2 (3 mL). The reaction mixture was stirred at rt for 1 h, then concentrated *in vacuo* to give a mixture of diastereomers (55:54 *dr*). Purification *via* flash column chromatography (petroleum ether/EtOAc, 95:5) gave **S5a** (18.0 mg, 45.3 µmol, 30%) and **S5b** (15.0 mg, 37.7 µmol, 25%) both as yellow oils.

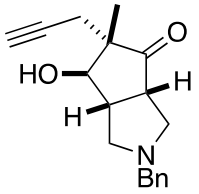
Data of **S5a**:

***R*$_f$** = 0.46 (petroleum ether/EtOAc, 90:10); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.33–7.15 (5H, m), 4.37 (1H, d, *J* 6.3), 3.69 (1H, d, *J* 13.4), 3.46 (1H, d, *J* 13.4), 3.19 (1H, d, *J* 9.2), 3.00 (2H, t, *J* 9.2), 2.90 (1H, d, *J* 9.2), 2.64–2.54 (2H, m), 2.31–2.23 (2H, m), 2.16 (1H, dd, *J* 16.9, 2.7), 2.01 (1H, t, *J* 2.7), 1.02 (3H, s), 0.88 (s, 9H), 0.07 (3H, s), –0.01 (3H, s); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 219.3, 139.3, 128.3, 128.3, 127.0, 81.1, 78.6, 70.5, 58.8, 58.5, 56.3, 55.3, 49.7, 46.0, 25.9, 23.5, 18.2, 17.5, –4.0, –4.5; **IR** ν_{max}: 3309 (m, C≡C–H), 1745 (s, C=O); **HRMS** (ESI): $[M + H]^+$ calcd. for $C_{24}H_{36}NO_2Si^+$: 398.2510, found 398.2526.

Data of **S5b**:

***R*$_f$** = 0.35 (petroleum ether/EtOAc, 90:10); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.37–7.21 (5H, m), 4.73 (1H, d, *J* 8.3), 3.66 (1H, d, *J* 13.2), 3.55 (1H, d, *J* 13.2), 3.41 (1H, dd, *J* 9.8, 2.6), 3.22 (1H, d, *J* 8.9), 3.06–2.94 (1H, m), 2.69 (1H, ddd, *J* 8.9, 6.2, 1.1), 2.54 (1H, dd, *J* 16.7, 2.6), 2.38 (1H, dd, *J* 8.9, 6.2), 2.31–2.17 (2H, m), 1.96 (1H, t, *J* 2.6), 1.19 (3H, s), 0.94 (9H, s), 0.16 (3H, s), 0.13 (3H, s); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 222.5, 139.0, 128.5, 128.3, 127.0, 81.4, 73.9, 70.4, 59.8, 58.3, 53.1, 53.0, 52.8, 43.4, 26.7, 25.9, 18.3, 18.2, –4.4, –4.8; **IR** ν_{max}: 3308 (m, C≡C–H), 1740 (s, C=O); **HRMS** (ESI): $[M + H]^+$ calcd. for $C_{24}H_{36}NO_2Si^+$: 398.2510, found 398.2528.

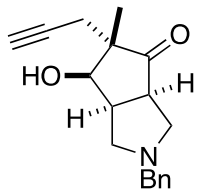
(3a*S,5*S**,6*R**,6a*R**)-2-Benzyl-6-hydroxy-5-methyl-5-(prop-2-yn-1-yl)hexahydrocyclopenta[*c*]pyrrol-4(1*H*)-one (15a)**



15a

According to General Procedure D, **S5a** (22.0 mg, 55.3 µmol) and TBAF (1.0 M in THF, 0.111 mL, 0.111 mmol) gave a crude material. Purification *via* flash column chromatography (petroleum ether/EtOAc/Et_3N, 65:35:1) gave **15a** as a colourless amorphous solid (13.4 mg, 49.77 µmol, 90%). R_f = 0.25 (petroleum ether/EtOAc/Et_3N, 65:35:1); **^{1}H NMR** (600 MHz, $CDCl_3$): δ_H 7.34–7.22 (5H, m), 4.12 (1H, d, *J* 6.8), 3.64 (1H, d, *J* 13.2), 3.52 (1H, d, *J* 13.2), 3.18 (1H, d, *J* 9.1), 3.05–3.00 (2H, m), 2.66 (1H, dt, *J* 10.5, 6.8), 2.46 (1H, dd, *J* 17.1, 2.7), 2.36 (1H, dd, *J* 17.1, 2.7), 2.30 (1H, dd, *J* 9.4, 5.9), 2.22 (1H, t, *J* 9.1), 2.11 (1H, t, *J* 2.7), 1.16 (3H, s); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C 219.1, 138.9, 128.5, 128.4, 127.1, 81.4, 80.6, 71.3, 59.2, 58.8, 56.1, 53.4, 48.7, 44.7, 24.3, 16.1; **IR** ν_{max}: 3470 (br s, O–H), 3293 (m, C≡C–H), 1739 (s, C=O); **HRMS** (ESI): $[M + H]^+$ calcd. for $C_{18}H_{22}NO_2^+$: 284.1645, found 284.1644.

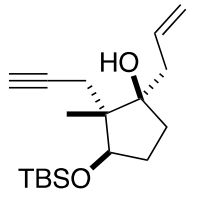
(3a*R,5*S**,6*R**,6a*S**)-2-Benzyl-6-hydroxy-5-methyl-5-(prop-2-yn-1-yl)hexahydrocyclopenta[*c*]pyrrol-4(1*H*)-one (15b)**



15b

According to General Procedure D, **S5b** (25.0 mg, 62.9 µmol) and TBAF (1.0 M in THF, 0.126 mL, 0.126 mmol) gave a crude material. Purification *via* flash column chromatography (petroleum ether/EtOAc/Et_3N, 65:35:1) gave **15b** as a (14.8 mg, 52.2 µmol, 83%). R_f = 0.25 (petroleum ether/EtOAc/Et_3N, 65:35:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.39–7.22 (5H, m), 5.27 (1H, s), 4.15 (1H, d, *J* 5.7), 3.71 (1H, d, *J* 12.8), 3.60 (1H, d, *J* 12.8), 3.27 (1H, d, *J* 9.5), 3.19 (1H, d, *J* 9.3), 3.12 (1H, dt, *J* 9.5, 5.7), 3.00 (1H, dd, *J* 10.6, 9.3), 2.42–2.33 (2H, m), 2.29 (2H, t, *J* 2.9), 2.10 (1H, t, *J* 2.9), 1.27 (3H, s); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 219.8, 137.4, 128.7 (x 2), 127.7, 79.2, 76.2, 71.7, 59.2, 57.5, 55.5, 55.3, 48.0, 40.2, 25.4, 14.7; **IR** ν_{max}: 3297 (br s, O–H), 3280 (m, C≡C–H), 1738 (s, C=O); **HRMS** (ESI): $[M + H]^+$ calcd. for $C_{18}H_{22}NO_2^+$: 284.1645, found 284.1644.

(1*R,2*S**,3*R**)-1-Allyl-3-((*tert*-butyldimethylsilyl)oxy)-2-methyl-2-(prop-2-yn-1-yl)cyclopentan-1-ol (16)**

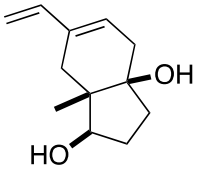


16

Allylmagnesium bromide (1.0 M in THF, 161 µL, 0.161 mmol) was added dropwise to stirred solution of *anti*-**S1** (43.0 mg, 0.161 mmol) in anhydrous THF (3 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h, then concentrated *in vacuo* to give a mixture of diastereomers (75:25 *dr*). Purification *via* flash column

chromatography (petroleum ether/EtOAc, 97:3) gave **16** (30.3 mg, 0.100 mmol, 62%) as a single diastereomer. R_f = 0.26 (petroleum ether/EtOAc, 97:3); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 5.99 (1H, ddt, *J* 17.4, 10.5, 7.1), 5.12–5.07 (1H, m), 5.07–5.05 (1H, m), 4.30 (1H, d, *J* 5.6), 4.05 (1H, d, *J* 1.9), 2.29 (1H, dd, *J* 13.7, 7.2), 2.16 (1H, dd, *J* 16.7, 2.7), 2.06–1.95 (4H, m), 1.87 (2H, ddt, *J* 13.0, 7.2, 3.4), 1.79–1.70 (1H, m), 1.17 (3H, s), 0.89 (9H, s), 0.08 (6H, s); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 134.9, 117.0, 83.8, 81.4, 81.3, 71.0, 51.8, 39.8, 36.3, 30.6, 25.9, 25.8, 18.0, 14.2, –4.7, –5.0; **IR** ν_{max}: 3511 (br, O–H), 3311 (s, C≡C–H), 1639 (s, C=C), 1462 (s, C=CH_2); **HRMS** (ESI): $[M + H]^+$ calcd. for $C_{18}H_{33}O_2Si^+$: 309.2245, found 309.2241.

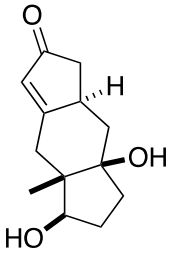
(1*R,3a*R**,7a*S**)-7a-Methyl-6-vinyl-1,2,3,4,7,7a-hexahydro-3a*H*-indene-1,3a-diol (17)**



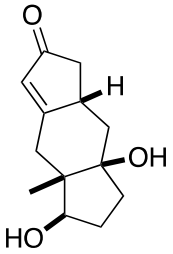
17

Grubbs 2nd generation catalyst (10.7 mg, 12.6 µmol) was added to a stirred solution of **16** (39.0 mg, 0.126 mmol) in anhydrous CH_2Cl_2 (25 mL). The reaction mixture was stirred under an ethylene atmosphere at rt for 4 h then concentrated *in vacuo*. TBAF (1.0 M in THF, 0.253 mL, 0.253 mmol) was added to a solution of the crude product in anhydrous THF (3 mL). The solution was stirred at rt for 2 h, then concentrated *in vacuo*. Purification *via* flash column chromatography (petroleum ether/EtOAc, 60:40) gave **17** as a white amorphous solid (16.0 mg, 82.8 µmol, 66%); R_f = 0.35 (petroleum ether/EtOAc, 60:40); **^{1}H NMR** (600 MHz, $CDCl_3$): δ_H 6.36 (1H, dd, *J* 17.5, 10.8), 5.60 (1H, dt, *J* 5.4, 2.6), 5.01 (1H, d, *J* 17.5), 4.92 (1H, d, *J* 10.8), 3.89 (1H, t, *J* 6.3), 2.58 (1H, d, *J* 7.2), 2.53 (1H, s), 2.45 (1H, ddd, *J* 18.8, 5.4, 2.1), 2.40–2.29 (1H, m), 2.26 (1H, d, *J* 18.8), 2.05 (1H, d, *J* 17.6), 1.87–1.78 (3H, m), 1.69 (1H, d, *J* 17.6), 1.07 (3H, s); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C 139.4, 133.2, 126.2, 110.9, 82.0, 81.9, 46.5, 36.1, 34.8, 34.5, 31.3, 14.7; **IR** ν_{max}: 3353 (br., O–H), 1647 (m, C=C), 1607 (m, C=C), 1460 (s, C=CH_2); **HRMS** (ESI): $[M - H]^-$ calcd. for $C_{12}H_{17}O_2^-$: 193.1234, found 193.1229.

(4a*S,5*R**,7a*R**,8a*R**)-5,7a-Dihydroxy-4a-methyl-4,4a,5,6,7,7a,8,8a-octahydro-s-indacen-2(1*H*)-one (18a) and (4a*S**,5*R**,7a*R**,8a*S**)-5,7a-dihydroxy-4a-methyl-4,4a,5,6,7,7a,8,8a-octahydro-s-indacen-2(1*H*)-one (18b)**



18a



18b

A solution of $Co_2(CO)_8$ (68.0 mg, 0.195 mmol) in anhydrous CH_2Cl_2 (5 mL) was added to a stirred solution of **16** (50.0 mg, 0.162 mmol) in anhydrous CH_2Cl_2 (1 mL) at rt. The reaction mixture was stirred at rt for 2 h, then 4-methylmorpholine *N*-oxide (190 mg, 1.62 mmol) was added portion-wise and the mixture was stirred for a further 18 h. The violet Co precipitate was removed by filtration through a short plug of silica (washed with CH_2Cl_2/MeOH 19:1) and the filtrate was concentrated *in vacuo*. TBAF (1.0 M in THF, 0.325 mL, 0.324 mmol) was added to a solution of the crude product in anhydrous THF (3.5 mL). The solution was stirred at rt for 1 h, then concentrated *in vacuo* to give a mixture of diastereomers (71:29 *dr*). Purification *via* flash column

chromatography (EtOAc) gave **18a** (15.0 mg, 67.6 µmol, 42%) and **18b** (6.0 mg, 27.0 µmol, 17%) both as colourless oils.

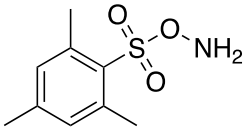
Data of **18a**:

***R*$_f$** = 0.29 (EtOAc); **^{1}H NMR** (600 MHz, $CDCl_3$): δ_H 5.93 (1H, t, *J* 1.8), 3.88 (1H, t, *J* 6.6), 2.81 (1H, dtt, *J* 12.8, 6.4, 1.8), 2.74 (1H, s), 2.65–2.58 (2H, m), 2.43 (1H, d, *J* 13.8), 2.40–2.32 (1H, m), 2.29–2.20 (2H, m), 2.07 (1H, ddd, *J* 18.7, 2.4, 0.9), 2.04–1.93 (3H, m), 1.38 (1H, t, *J* 12.8), 1.03 (3H, s); **^{13}C NMR** (151 MHz, $CDCl_3$) δ_C 208.5, 180.0, 130.1, 82.6, 82.3, 51.1, 42.2, 39.8, 38.7, 38.6, 34.9, 31.1, 14.2; **IR** ν_{max}: 3385 (br., O–H), 1704 (s, C=O), 1620 (s, C=C); **HRMS** (ESI): $[M + H]^+$ calcd. for $C_{13}H_{19}O_3^+$: 223.1329, found 223.1341.

Data of **18b**:

***R*$_f$** = 0.28 (EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 5.93 (1H, t, *J* 1.8), 3.88 (1H, q, *J* 8.0), 3.01 (1H, dt, *J* 12.0, 5.6), 2.78 (1H, d, *J* 14.6), 2.59 (1H, ddd, *J* 18.8, 6.6, 0.7), 2.31 (1H, d, *J* 14.7), 2.13–2.01 (2H, m), 1.97–1.84 (2H, m), 1.67–1.60 (1H, m), 1.55–1.48 (1H, m), 1.32 (1H, t, *J* 13.5), 1.06 (3H, s); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 208.8, 181.7, 128.9, 78.1, 73.6, 49.4, 44.3, 41.8, 37.1, 36.1, 34.9, 28.5, 15.8; **IR** ν_{max}: 3391 (br, O–H), 1704 (s, C=O), 1618 (s, C=C); **HRMS** (ESI): $[M + H]^+$ calcd. for $C_{13}H_{19}O_3^+$: 223.1329, found 223.1341.

***O*-Mesitylsulfonylhydroxylamine (S6)**

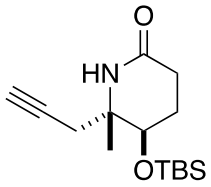


S6

Et_3N (1.5 mL, 10.8 mmol) was added to a stirred solution of Ethyl *N*-hydroxyacetamidate (1.18 g, 11.4 mmol) in DMF (6 mL) and the solution was cooled to 0 °C. 2-Mesitylensulfonylchloride (2.5 g, 11.4 mmol) was added in small portions and the mixture was stirred vigorously for 30 min. The reaction was diluted with Et_2O (100 mL) and washed with H_2O (5 × 50 mL). The organic layer was dried and concentrated in vacuo. Ethyl-*O*-(mesitylensulfonyl)acetohydroxamate (2.20 g) was obtained and used in the next step without further purification.

Perchloric acid (70%, 0.95 mL) was added dropwise to a stirred solution of Ethyl-*O*-(mesitylsulfonyl)-acetohydroxamate (2.20 g, 7.72 mmol) in dioxane (3 mL) at 0 °C. The reaction was stirred for 10 min, then transferred onto ice water (100 mL). The aqueous layer was extracted with Et_2O (3 × 30 mL) and the combined organic layers were washed with brine (2 × 50 mL) then dried/neutralized with K_2CO_3. After filtration, the solution was concentrated to a volume less than 10 mL and poured into 20 mL of ice-cold petroleum ether. After crystallization, **S6** was obtained (805 mg, 4.04 mmol, 37%) as a white crystalline solid. **R_f** = 0.32 (eluent hexane/EtOAc, 80:20); **m**.**p**. 93 ºC [Lit. 90-91 °C];[2] **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H (400 MHz, $CDCl_3$) 7.00 (2H, s), 2.65 (6H s), 2.33 (3H, s); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 143.9, 141.1, 131.9, 129.3, 22.9, 21.2; **IR** ν_{max}: 3469, 3198 (m, N–H stretch), 2980 (br, Ar C–H), 1603 (s, N–H bend), 1170 (s, S=O). These characterisation data are in accordance with that previously reported in the literature.[2]

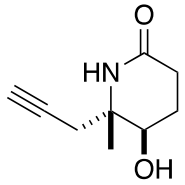
(5*R,6*S**)-5-((*tert*-Butyldimethylsilyl)oxy)-6-methyl-6-(prop-2-yn-1-yl)piperidin-2-one (19)**



19

S6 (636 mg, 2.95 mmol) was added to a stirred solution of *anti*-**S1** (432 mg, 1.62 mmol) in CH_2Cl_2 (5 ml) at 0 °C. After 20 min the temperature was raised to rt and the solution was stirred for a further 18 h. $BF_3{\cdot}Et_2O$ (0.63 ml, 5.1 mmol) was added, and the mixture was stirred at rt for 1 h. The reaction mixture was diluted with CH_2Cl_2 (50 ml) and washed with saturated aqueous $NaHCO_3$ (2 × 50 ml). The aqueous layers were re-extracted with Et_2O (3 × 50 ml), and the combined organic layers were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (hexane/EtOAc, 50:50) gave **19** as a white crystalline solid (300 mg, 1.07 mmol, 66%); $\mathbf{R_f}$ = 0.20 (hexane/EtOAc, 50:50); **m**.**p**. 125 ºC; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 5.95 (1H, br s), 3.84 (1H, dd, *J* 7.8, 4.9), 2.58–2.26 (4H, m), 2.11 (1H, t, *J* 2.7), 1.90 (2H, td, *J* 8.0, 5.1), 1.28 (3H, s), 0.89 (9H, s), 0.09 (6H, s); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 171.0, 79.3, 72.6, 70.7, 58.0, 31.7, 28.3, 25.8, 22.3, 18.1, –4.1, –4.9; **IR** ν_{max}: 3313 (s, C≡C–H), 1660 (s, C=O); **HRMS** (ESI): $[M+H]^+$ calcd. for $C_{15}H_{28}NO_2Si^+$: 282.1884, found: 282.1879.

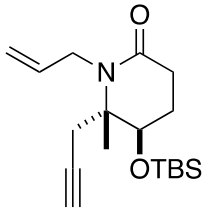
(5*R,6*S**)-5-Hydroxy-6-methyl-6-(prop-2-yn-1-yl)piperidin-2-one (20)**



20

According to General Procedure D, **19** (30 mg, 0.11 mmol) and TBAF (1.0 M in THF, 0.168 mL, 0.168 mmol) gave a crude material. Purification *via* flash column chromatography (EtOAc/MeOH, 95:5) gave **20** as a colourless oil (17 mg, 0.10 mmol, 94%). $\boldsymbol{R_f}$ = 0.21 (EtOAc/MeOH, 95:5); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 5.95 (1H, br s), 3.88 (1H, td, *J* 6.6, 3.4), 2.59–2.25 (6H, m), 2.14 (1H, t, *J* 2.7), 2.06–1.91 (2H, m), 1.34 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_c 171.0, 79.1, 72.8, 70.4, 57.5, 31.8, 28.3, 25.6, 21.7; **IR** ν_{max}: 3305 (m, N–H), 1638 (s, C=O); **HRMS** (ESI): $[M + H]^+$ calcd. for $C_9H_{14}NO_2^+$: 168.1019, found 168.1018.

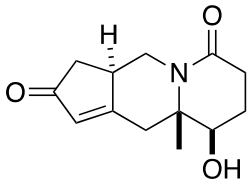
(5*R,6*S**)-1-Allyl-5-((*tert*-butyldimethylsilyl)oxy)-6-methyl-6-(prop-2-yn-1-yl)piperidin-2-one (S7)**



S7

NaH (60% in mineral oil, 33 mg, 2.29 mmol) was added to a stirred solution of **19** (190 mg, 0.66 mmol) in anhydrous DMF (7 mL) at 0 °C. The mixture was stirred at rt for 30 min, then allyl bromide (0.126 mL, 1.46 mmol) was added and the reaction mixture was stirred for another 2 h. The mixture was diluted with EtOAc (200 mL), washed with H_2O (2 × 150 mL) and brine (1 × 150 mL), and the organic extract was dried and concentrated *in vacuo*. Purification *via* flash column chromatography (petroleum ether/EtOAc, 80:20) gave **S7** as a colourless oil (161 mg, 0.50 mmol, 76%). R_f = 0.19 (petroleum ether/EtOAc, 80:20); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 5.88 (1H, dddd, *J* 17.3, 10.3, 5.9, 5.0), 5.19–5.05 (2H, m), 4.26 (1H, ddt, *J* 16.1, 5.1, 1.8), 4.09 (1H, dd, *J* 8.2, 3.0), 3.77 (1H, ddt, *J* 16.1, 5.9, 1.6), 2.66–2.55 (2H, m), 2.48–2.34 (2H, m), 2.06 (1H, t, *J* 2.7), 1.95 (1H, dtd, *J* 13.8, 6.9, 3.0), 1.83 (1H, dddd, *J* 13.7, 8.2, 7.3, 6.7), 1.29 (3H, s), 0.90 (9H, s), 0.12 (3H, s), 0.11 (3H, s); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C 170.0, 135.7, 115.8, 79.8, 72.3, 70.3, 63.6, 45.0, 28.8, 28.7, 25.9, 24.9, 21.7, 18.1, –4.1, –4.9; **IR** ν_{max}: 3314 (s, C≡C–H), 1639 (m, C=O); **HRMS** (ESI): $[M + H]^+$ calcd. for $C_{18}H_{32}NO_2Si^+$: 322.2197, found 322.2198.

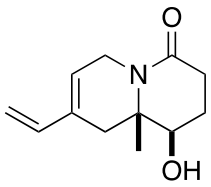
(3a*R,9*R**,9a*S**)-9-Hydroxy-9a-methyl-3a,4,8,9,9a,10-hexahydrocyclopenta[b]quinolizine-2,6(3H,7H)-dione (21)**



21

S7 (38.0 mg, 0.118 mmol) in CH_2Cl_2 (1.0 mL) was added to a stirred solution of $Co_2(CO)_8$ (50.5 mg, 0.147 mmol) in CH_2Cl_2 (4.25 mL) at rt. The reaction mixture was stirred at rt for 2 h, then 4-methylmorpholine *N*-oxide (138 mg, 1.18 mmol) was added portion-wise and the mixture was stirred for a further 18 h. The violet Co precipitate was removed by filtration through a short plug of silica (washed with CH_2Cl_2/MeOH 19:1) and the filtrate was concentrated *in vacuo*. TBAF (1.0 M in THF, 0.21 mL, 0.21 mmol) was added to a solution of the crude product in anhydrous THF (5.4 mL). The solution was stirred at rt for 2 h, then concentrated *in vacuo*. Purification *via* flash column chromatography (EtOAc/MeOH, 95:5) gave **21** as a colourless oil (21.1 mg, 89.8 µmol, 76%). R_f = 0.34 (EtOAc/MeOH, 90:10); **^{1}H NMR** (400 MHz, CD_3OD): δ_H 6.02 (1H, d, *J* 1.8), 5.05 (1H, dd, *J* 13.2, 6.6), 3.89 (1H, app p, *J* 7.5), 3.03 (1H, d, *J* 13.5), 2.78 (1H, dt, *J* 13.0, 6.7), 2.73–2.37 (5H, m), 2.10–2.02 (1H, m), 1.98 (2H, tt, *J* 8.5, 4.7), 1.24 (3H, s); **^{13}C NMR** (101 MHz, CD_3OD): δ_C 207.6, 177.5, 169.1, 130.1, 74.0, 61.2, 43.9, 41.9, 40.2, 39.0, 29.8, 25.5, 17.8; **IR** ν_{max}: 3361 (br., O–H), 1702 (s, C=O), 1673 (s, C=O), 1614 (s, C=C), 1407 (s. O–H); **HRMS** (ESI): $[M + H]^+$ calcd. for $C_{13}H_{18}NO_3^+$: 236.1281, found 236.1283.

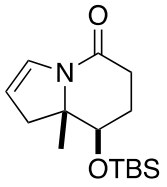
(1*R,9a*S**)-1-Hydroxy-9a-methyl-8-vinyl-1,2,3,6,9,9a-hexahydro-4H-quinolizin-4-one (22)**



22

Grubbs 2nd generation catalyst (12.0 mg, 14.2 µmol) was added to a stirred solution of **S7** (40 mg, 0.142 mmol) in anhydrous CH_2Cl_2 (25 mL). The reaction mixture was stirred under an ethylene atmosphere at rt for 4 h then concentrated *in vacuo*. TBAF (1.0 M in THF, 0.253 mL, 0.253 mmol) was added to a solution of the crude product in anhydrous THF (3 mL). The solution was stirred at rt for 2 h, then concentrated *in vacuo*. Purification *via* flash column chromatography (eluent EtOAc/MeOH, 98:2) gave **22** as a white amorphous solid (20.0 mg, 0.097 mmol, 69%). R_f = 0.39 (EtOAc/MeOH, 9:1); **^{1}H NMR** (400 MHz, CD_3OD): δ_H 6.49 (1H, dd, *J* 17.5, 10.8), 5.79 (1H, q, *J* 3.2), 5.22 (1H, d, *J* 17.5), 5.06 (1H, d, *J* 10.8), 4.70 (1H, dt, *J* 20.5, 3.6), 3.83 (1H, t, *J* 6.7), 3.68–3.57 (1H, m), 2.65–2.53 (2H, m), 2.53–2.42 (1H, m), 2.21 (1H, dd, *J* 16.7, 3.1), 2.07–1.87 (2H, m), 1.28 (3H, s); **^{13}C NMR** (101 MHz, CD_3OD): δ_C 171.8, 139.6, 133.7, 124.0, 112.4, 73.9, 59.8, 41.5, 36.7, 30.3, 25.6, 18.6; **IR** ν_{max}: 3370 (br., O–H), 1611 (s, C=O), 1600 (s, C=C), 1408 (s, O–H); **HRMS** (ESI): $[M + H]^+$ calcd. for $C_{12}H_{18}NO_2^+$ 208.1332, found 208.1328.

***Anti*-8-((*tert*-Butyldimethylsilyl)oxy)-8a-methyl-6,7,8,8a-tetrahydroindolizin-5(1*H*)-one (S8)**



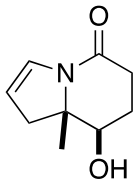
S8

$InCl_3$ (101 mg, 0.46 mmol) was introduced into 10 mL flask and heated with a heat gun (150 °C) under vacuum for 2 min. After being allowed to cool to room temperature, THF (1.2 mL) was added. The mixture was stirred at room temperature for 10 min and then cooled to −78 °C. DIBAL-H (1.0 M in hexane, 0.44 mL, 0.44 mmol) was added dropwise and the mixture was stirred at −78 °C for 40 min. **19** (83 mg, 0.30 mmol) was then added, followed by Et_3B (1.0 M in THF, 0.17 mL, 0.17 mmol) and the mixture was stirred at −78 °C for 4 hours. A solution of iodine (449 mg, 1.78 mmol) in THF (0.75 mL) was then added. After 40 minutes, the mixture was poured onto satd. $NaHCO_3$ (5 mL). $Na_2S_2O_3$ was added under stirring until complete decoloration and the aqueous layer was extracted with EtOAc (5 × 10 mL). The combined organic layers were washed with brine (50 mL), dried and concentrated *in vacuo*.

Cs_2CO_3 (115 mg, 0.35 mmol), CuI (23 mg, 0.12 mmol) and *N*,*N'*-dimethylethyl-1,2-diamine (25 µL, 0.24 mmol) were added to a stirred solution of the crude product in PhMe (2 mL) and the mixture was heated to 85 °C for 3 hours. H_2O (10 mL) was added and the reaction extracted with CH_2Cl_2 (5 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried and concentrated *in vacuo*. Purification *via* flash column chromatography (Petroleum ether/EtOAc, 60:40) gave **S8** as a white amorphous solid (53 mg, 0.19 mmol, 64%). R_f = 0.32 (Petroleum ether/EtOAc, 50:50); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 6.81 (1H, t, *J* 4.1), 5.19 (1H, dt, *J* 4.8, 2.6), 3.85 (1H, t, *J* 8.4), 2.70–2.51 (2H, m), 2.51–2.32 (2H, m), 1.87 (2H, td, *J* 7.9, 7.1, 5.3), 1.23 (3H, s), 0.87 (9H, s), 0.06 (6H, 2 ×

s); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 165.5, 128.0, 110.3, 73.4, 65.3, 44.8, 29.1, 26.5, 25.7, 19.5, 18.0, –3.9, –4.8; **IR** ν_{max}: 1664 (s, C=O), 1629 (s, C=C); **HRMS** (ESI): $[M+H]^+$ calcd. for $C_{15}H_{28}NO_2Si^+$: 282.1884, found: 282.1882.

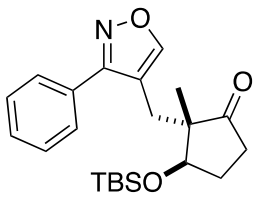
(8*R,8a*S**)-8-Hydroxy-8a-methyl-6,7,8,8a-tetrahydroindolizin-5(1H)-one (23)**



23

According to General Procedure D, **S8** (53 mg, 0.19 mmol) and TBAF (1.0 M in THF, 0.27 mL, 0.27 mmol) gave a crude material. Purification *via* flash column chromatography (EtOAc/MeOH, 95:5) gave **23** as a colourless oil (25 mg, 0.15 mmol, 79%). R_f = 0.36 (EtOAc/MeOH, 95:5); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 6.80 (1H, ddd, *J* 4.4, 2.9, 1.4), 5.28–5.21 (1H, m), 3.88 (1H, dd, *J* 11.6, 5.4), 2.78 (1H, dt, *J* 16.3, 2.5), 2.58 (1H, ddd, *J* 18.9, 9.3, 2.3), 2.52–2.41 (2H, m), 2.04–1.83 (2H, m), 1.25 (3H, s); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 165.8, 127.8, 111.0, 72.4, 65.1, 44.3, 29.1, 25.8, 19.2; **IR** ν_{max}: 1603 (m, C=O), 1440 (m, O-H); **HRMS** (ESI): $[M+H]^+$ calcd. for $C_9H_{14}NO_2^+$: 168.1019, found: 168.1025.

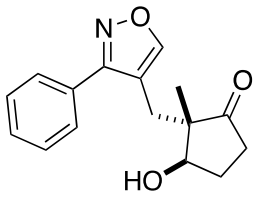
(2*S,3*R**)-3-((*tert*-Butyldimethylsilyl)oxy)-2-methyl-2-((3-phenylisoxazol-4-yl)methyl)cyclopentan-1-one (S9)**



S9

Cp*Ru(COD)Cl (10 mg, 0.028 mmol) and NEt_3 (80 µl, 0.57 mmol) were added to a degassed solution of α-chlorobenzaldoxime (200 mg, 1.3 mmol) and *anti*-**S1** (69 mg, 0.26 mmol) in DCE (5 mL). The mixture was stirred at 80 °C for 24 h before being concentrated *in vacuo*. Purification *via* flash column chromatography (eluent hexane/EtOAc, 93:7) gave **S9** (77 mg, 0.20 mmol, 77%) as a colourless oil. R_f = 0.28 (eluent hexane/EtOAc, 90:10); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 8.29 (1H, app s), 7.56–7.46 (5H, m), 3.87 (1H, t, *J* 5.8), 2.69 (1H, d, *J* 15.1), 2.58 (1H, d, *J* 15.1), 2.39 (1H, ddd, *J* 18.8, 9.6, 5.7), 1.98 (1H, ddd, *J* 18.8, 9.0, 7.2), 1.87 (1H, app ddt, *J* 12.9, 9.0, 5.7), 1.68 (dddd, *J* 12.9, 9.6, 7.2, 5.8), 0.90 (3H, s), 0.75 (9H, s), –0.08 (3H, s), –0.20 (3H, s); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 220.4, 162.7, 157.7, 129.6, 129.1, 129.0, 128.9, 113.6, 75.3, 54.4, 35.1, 28.4, 27.0, 25.7, 18.0, 16.3, –4.3, –5.1; **IR** ν_{max}: 3619 (br, O–H), 1739 (s, C=O); **HRMS** (ESI): $[M+H]^+$ calcd. for $C_{22}H_{32}O_3NSi^+$: 386.2146, found: 386.2154.

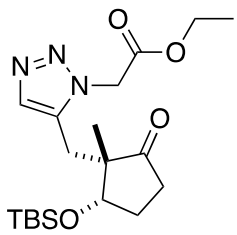
(2*S,3*R**)-3-Hydroxy-2-methyl-2-((3-phenylisoxazol-4-yl)methyl)cyclopentan-1-one (24)**



24

TBAF (1.0 M in THF, 2.0 mL, 2.0 mmol) was added to a stirred solution of **S9** (76 mg, 0.20 mmol) and AcOH (0.20 mL) in THF (7.8 mL) under argon. The reaction mixture was stirred at rt for 5 days, then concentrated *in vacuo*. The residue was treated with brine (4 mL) and satd. $NaHCO_3$ to adjust the pH to 7. The aqueous layer was extracted with Et_2O (3 × 10 mL), and the combined extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (petroleum ether/EtOAc, 55:45) gave **24** as a yellow oil (43 mg, 0.16 mmol, 80%). $\mathbf{R_f}$ = 0.24 (petroleum ether/EtOAc, 50:50); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 8.22 (1H, s), 7.58 (2H, dd, *J* 6.7, 3.0), 7.53–7.43 (3H, m), 3.82 (1H, dd, *J* 8.8, 6.5), 2.86 (1H, d, *J* 5.1), 2.65 (1H, d, *J* 15.1), 2.40 (1H, ddd, *J* 19.2, 9.3, 2.7), 2.00 (1H, dddd, *J* 11.9, 9.0, 6.3, 2.6), 1.89 (1H, dt, *J* 19.0, 9.3), 1.71 (1H, dq, *J* 12.0, 9.2), 1.37 (1H, br s), 0.93 (3H, s); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 219.2, 162.7, 158.0, 129.9, 129.2, 129.0, 128.8, 113.8, 73.4, 54.4, 35.5, 27.3, 26.3, 16.0; **IR** ν_{max}: 3422 (br, O–H), 1732 (s, C=O); **HRMS** (ESI): $[M+H]^+$ calcd. for $C_{16}H_{18}NO_3^+$: 272.1281, found: 272.1281.

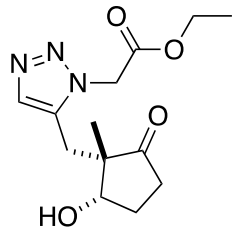
Ethyl 2-(5-(((1*S,2*S**)-2-((tert-butyldimethylsilyl)oxy)-1-methyl-5-oxocyclopentyl)methyl)-1H-1,2,3-triazol-1-yl)acetate (S10)**



S10

$[Cp^*RuCl]_4$ (59 mg, 0.054 mmol) was added to a degassed solution of *syn*-**S1** (130 mg, 0.49 mmol) and ethyl azidoacetate (114 mg, 0.88 mmol) in PhMe (8 mL) under argon. The reaction mixture was stirred at rt for 18 hours before being concentrated *in vacuo*. Purification *via* flash column chromatography (hexane/EtOAc, 60:40) gave **S10** as a yellow oil (160 mg, 0.42 mmol, 86%). $\mathbf{R_f}$ = 0.26 (hexane/EtOAc, 60:40); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.52 (1H, s), 5.19 (1H, d, *J* 17.7), 5.12 (1H, d, *J* 17.7), 4.27–4.16 (3H, m), 2.79 (2H, app s), 2.41–2.22 (2H, m), 2.15 (1H, m), 1.78 (1H, m), 1.27 (3H, t, *J* 7.1), 0.98 (3H, s), 0.84 (9H, s), 0.11 (3H, s), 0.03 (3H, s); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 219.6, 166.6, 134.9, 133.7, 78.1, 62.5, 53.7, 49.1, 33.9, 28.4, 25.9, 24.6, 20.0, 18.2, 14.3, –4.0, –4.8; **IR** ν_{max}: 1743 (s, C=O); **HRMS** (ESI): $[M+H]^+$ calcd. for $C_{19}H_{34}N_3O_4Si^+$: 396.2313, found: 396.2313.

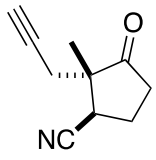
Ethyl 2-(5-(((1*S,2*S**)-2-hydroxy-1-methyl-5-oxocyclopentyl)methyl)-1H-1,2,3-triazol-1-yl)acetate (25)**



25

TBAF (3.3 mL, 1 M in THF, 3.3 mmol) was added to a stirred solution of **S10** (125 mg, 0.32 mmol) and AcOH (0.33 mL, 5.7 mmol) in THF (12.5 mL) under argon. The reaction mixture was stirred at rt for 5 days, then concentrated *in vacuo*. The residue was treated with brine (4 mL) and satd. $NaHCO_3$ to adjust the pH to 7. The aqueous layer was extracted with Et_2O (3 × 10 mL), and the combined extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent hexane/EtOAc, 70:30) gave **25** as a yellow oil (67 mg, 0.24 mmol, 76%). $\mathbf{R_f}$ = 0.09 (eluent hexane/EtOAc, 60:40); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.55 (1H, s), 5.30 (1H, d, *J* 17.6), 5.15 (1H, d, *J* 17.6), 4.22 (2H, q, *J* 7.1), 4.06 (1H, dd, *J* 4.1, 1.7), 2.93 (1H, d, *J* 15.6), 2.79 (1H, d, *J* 15.6), 2.50–2.34 (2H, m), 2.27–2.13 (1H, m), 1.97–1.88 (1H, m), 1.26 (3H, t, *J* 7.1), 1.00 (3H, s); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 220.1, 166.9, 135.4, 133.5, 75.5, 62.3, 53.7, 49.0, 33.4, 28.3, 24.2, 19.8, 14.0; **IR** ν_{max}: 3338 (br, O–H), 1741 (s, C=O); **HRMS** (ESI): $[M+H]^+$ calcd. for $C_{13}H_{20}N_3O_4^+$: 282.1448, found: 282.1445.

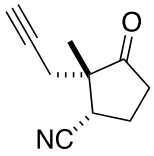
(1*R,2*S**)-2-Methyl-3-oxo-2-(prop-2-yn-1-yl)cyclopentane-1-carbonitrile (*anti*-26)**



anti-**26**

MsCl (76 μL, 0.99 mmol) was added to a stirred solution of *anti*-**1** (50 mg, 0.33 mmol) in pyridine (2.25 mL) at 0 °C, and the resultant mixture was stirred at rt for 24 h. After addition of 1 M HCl (20 mL), the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried and concentrated *in vacuo*. KCN (42 mg, 0.64 mmol) was added to a stirred solution of the crude material in DMSO (3 mL) at rt, and the resultant mixture was stirred for 5 days. After addition of aq. NaCl (20 mL), the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent hexane/EtOAc, 85:15) gave *anti*-**26** as an amorphous white solid (38 mg, 0.24 mmol, 72%). $\mathbf{R_f}$ = 0.16 (eluent hexane/EtOAc, 85:15); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 3.47 (1H, dd, *J* 11.0, 6.8), 2.63–2.52 (2H, m), 2.52–2.32 (1H, m), 2.36 (1H, dd, *J* 17.0, 2.7), 2.29–2.09 (2H, m), 2.07 (1H, t, *J* 2.7), 1.22 (3H, s); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 214.7, 119.0, 79.2, 72.5, 50.7, 36.2, 34.9, 25.7, 23.5, 19.5; **IR** ν_{max}: 3291 (C≡C–H), 2242 (m, C≡N), 1746 (s, C=O); **HRMS** (ESI): $[M+H]^+$ calcd. for $C_{10}H_{12}NO^+$: 162.0913, found: 162.0914.

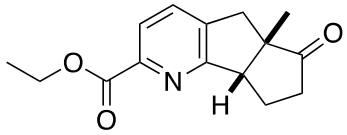
(1*S,2*S**)-2-Methyl-3-oxo-2-(prop-2-yn-1-yl)cyclopentane-1-carbonitrile (*syn*-26)**



syn-**26**

MsCl (95 µL, 1.23 mmol) was added to a stirred solution of *syn*-**1** (63 mg, 0.41 mmol) in pyridine (2.80 mL) at 0 °C, and the resultant mixture was stirred at rt for 24 h. After addition of 1 M HCl (20 mL), the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried and concentrated *in vacuo*. The crude mesylate was used in the next step without further purification. KCN (50 mg, 0.77 mmol) was added to a stirred solution of the crude material in DMSO (3.5 mL) at rt, and the resultant mixture was stirred for 5 days. After addition of aq. NaCl (20 mL), the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent hexane/EtOAc, 80:20) gave *syn*-**26** as an amorphous white solid (40 mg, 0.25 mmol, 60%). $\mathbf{R_f}$ = 0.19 (eluent hexane/EtOAc, 80:20); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 3.10–3.05 (1H, m), 2.65–2.27 (6H, m), 2.09 (1H, t, *J* 2.7), 1.24 (3H, s); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 215.2, 119.1, 78.8, 71.9, 50.6, 37.9, 35.5, 24.9, 23.6, 21.6; **IR** ν_{max}: 3291 (s, C≡C–H), 2242 (m, C≡N), 1744 (s, C=O); **HRMS** (ESI): $[M+H]^+$ calcd. for $C_{10}H_{12}NO^+$: 162.0913, found: 162.0914.

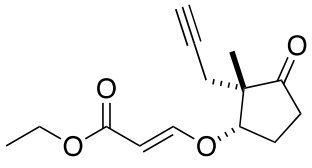
Ethyl (5a*S,8a*S**)-5a-methyl-6-oxo-5,5a,6,7,8,8a-hexahydropentaleno[1,2-b]pyridine-2-carboxylate (27)**



27

$CpCo(CO)_2$ (11 mg, 60 µmol) was added to a degassed solution of *syn*-**26** (20 mg, 120 µmol) and ethyl propiolate (62 µl, 600 µmol) in PhMe (1 mL) in a vial. The vial was sealed and the reaction mixture was stirred at 110 °C for 18 h. Upon completion, the reaction mixture was filtered through celite, washed with EtOAc (20 mL) and the filtrate concentrated *in vacuo*. Purification *via* flash column chromatography (hexane/EtOAc, 70:30) gave **27** as a yellow oil (3 mg, 0.012 mmol, 10%). $\mathbf{R_f}$ = 0.21 (hexane/EtOAc, 75:35); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.94 (1H, d, *J* 7.9), 7.55 (1H, d, *J* 7.9), 4.56–4.40 (2H, m), 3.66 (1H, d, *J* 6.7), 3.29 (1H, d, *J* 17.3), 2.88 (1H, d, *J* 17.3), 2.71–2.58 (1H, m), 2.49–2.30 (2H, m), 2.00–1.85 (1H, m), 1.44 (3H, t, *J* 7.1), 1.34 (3H, s); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 223.7, 165.7, 165.5, 148.0, 140.1, 132.9 124.1, 62.0, 54.8, 54.4, 40.6, 36.6, 23.9, 21.2, 14.5; **IR** ν_{max}: 1735 (m, C=O), 1447, 1410 (C=C); **HRMS** (ESI): $[M+H]^+$ calcd. for $C_{15}H_{18}NO_3^+$: 260.1281, found: 260.1280.

Ethyl (*E*)-3-(((1*S,2*S**)-2-methyl-3-oxo-2-(prop-2-yn-1-yl)cyclopentyl)oxy)acrylate (28)**

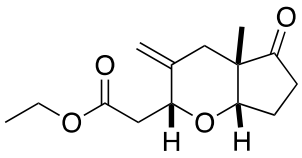


28

Ethyl propiolate (30 µl, 0.3 mmol) and NMM (30 mg, 0.3 mmol) were added to a stirred solution of *syn*-**1** (100 mg, 0.66 mmol) in CH_2Cl_2 (2 mL). The mixture was stirred at rt for 2 h then concentrated *in vacuo*. Purification *via*

flash column chromatography (hexane/EtOAc, 82:18) gave **28** as a colourless oil (153 mg, 0.61 mmol, 93%). $\mathbf{R_f}$ = 0.10 (hexane/EtOAc, 90:10); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.54 (1H, d, *J* 12.5), 5.29 (1H, d, *J* 12.5), 4.43 (1H, t, *J* 2.8), 4.17 (2H, q, *J* 7.1), 2.50–2.35 (4H, m), 2.29–2.17 (2H, m), 1.98 (1H, t, *J* 2.7), 1.27 (3H, t, *J* 7.1), 1.19 (3H, s); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 217.1, 167.8, 161.0, 98.6, 86.1, 80.3, 70.7, 60.1, 52.8, 33.7, 24.8, 20.8, 20.0, 14.5; **IR** ν_{max}: 1743 (s, C=O ketone), 1705 (s, C=O ester), 1643 (m, C=C), 1622 (m, C=C); **HRMS** (ESI): $[M+H]^+$ calcd. for $C_{14}H_{19}O_4^+$: 251.1283, found: 251.1279.

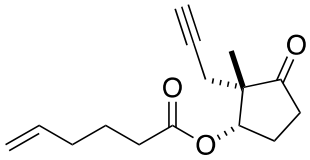
Ethyl 2-((2*R,4a*S**,7a*S**)-4a-methyl-3-methylene-5-oxooctahydrocyclopenta[*b*]pyran-2-yl)acetate (29)**



29

A degassed solution of Bu_3SnH (0.08 mL, 0.29 mmol) and AIBN (5.9 mg, 36.0 µmol) in PhMe (0.72 mL) was added dropwise over 5 h to a degassed solution of **28** (36 mg, 0.144 mmol) in PhMe (2.16 mL) at 80 °C. The reaction mixture was stirred for a further 12 h at 80 °C, then concentrated *in vacuo*. *p*-Toluenesulfonic acid monohydrate (15 mg, 76.5 µmol) was added to a stirred solution of the crude material in CH_2Cl_2 (0.3 mL) at rt. The mixture was stirred for 1.5 h, then poured into satd. $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (hexane/EtOAc, 90:10) gave **29** as a colourless oil (21.4 mg, 85.0 µmol, 59%). $\mathbf{R_f}$ = 0.18 (hexane/EtOAc, 90:10); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 4.87 (1H, d, *J* 1.7), 4.74 (d, *J* 1.6), 4.26 (1H, dd, *J* 8.2, 5.2), 4.16 (2H, qq, *J* 7.5, 3.7), 3.95 (1H, d, *J* 4.0), 2.70 (1H, d, *J* 14.0), 2.67–2.48 (2H, m), 2.47–2.24 (2H, m), 2.20–1.96 (3H, m), 1.26 (3H, t, *J* 7.1), 0.96 (3H, s); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 220.0, 171.4, 142.8, 108.9, 83.1, 74.2, 60.7, 51.5, 38.2, 37.8, 34.0, 25.7, 21.2, 14.3; **IR** ν_{max}: 1708 (br, C=O ketone); **HRMS** (ESI): $[M+H]^+$ calcd. for $C_{14}H_{20}O_4Na^+$: 275.1254, found: 275.1249.

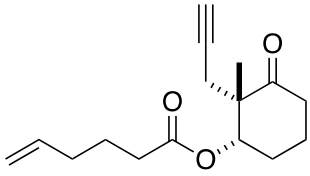
(1*S,2*S**)-2-Methyl-3-oxo-2-(prop-2-yn-1-yl)cyclopentyl hex-5-enoate (30)**



30

According to General Procedure F, *syn*-**1** (100 mg, 0.66 mmol), 5-hexenoic acid (0.11 mL, 0.891 mmol), DMAP (8 mg, 0.066 mmol) and DCC (184 mg, 0.891 mmol) gave a crude material. Purification *via* flash column chromatography (petroleum ether/EtOAc, 88:12) gave **30** as a colourless oil (149 mg, 0.60 mmol, 91%). $\mathbf{R_f}$ = 0.11 (eluent petroleum ether/EtOAc, 92:8); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 5.77 (1H, ddt, *J* 17.0, 10.2, 6.7), 5.25 (1H, dd, *J* 4.6, 1.8), 5.08–4.95 (2H, m), 2.48–2.36 (4H, m), 2.36–2.22 (3H, m), 2.08 (3H, m), 1.94 (1H, t, *J* 2.6), 1.73 (2H, p, *J* 7.4), 1.19 (3H, s); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 218.2, 172.6, 137.7, 115.7, 80.3, 78.2, 70.4, 51.9, 34.1, 33.8, 33.1, 25.7, 24.2, 21.3, 20.1; **IR** ν_{max}: 1733 (m, 2 × C=O), 1641 (m, C=C); **HRMS** (ESI): $[M+H]^+$ calcd. for $C_{15}H_{21}O_3^+$: 249.1485, found: 249.1487.

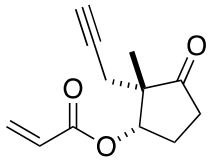
(1*S,2*S**)-2-Methyl-3-oxo-2-(prop-2-yn-1-yl)cyclohexyl hex-5-enoate (S11)**



S11

According to General Procedure F, *syn*-**8** (111 mg, 0.66 mmol), 5-hexenoic acid (0.11 mL, 0.891 mmol), DMAP (8 mg, 0.066 mmol) and DCC (184 mg, 0.891 mmol) gave a crude material. Purification *via* flash column chromatography (petroleum ether/EtOAc, 88:12) gave **S11** as a colourless oil (164 mg, 0.626 mmol, 95%). $\mathbf{R_f}$ = 0.11 (petroleum ether/EtOAc, 92:8); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 5.76 (1H, ddt, *J* 17.0, 10.2, 6.7), 5.25 (1H, t, *J* 3.4), 5.07–4.94 (2H, m), 2.63–2.22 (6H, m), 2.12–1.98 (4H, m), 1.96 (t, *J* 2.7), 1.93–1.84 (2H, m), 1.78–1.63 (2H, m), 1.33 (3H, s); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 211.9, 172.4, 137.7, 115.7, 80.1, 77.2, 71.4, 50.9, 37.6, 33.8, 33.1, 25.2, 24.2, 23.3, 21.3, 20.9; **IR** ν_{max}: 1733 (s, C=O), 1710 (s, C=O), 1640 (m, C=C); **HRMS** (ESI): $[M+H]^+$ calcd. for $C_{16}H_{23}O_3^+$: 263.1642, found: 263.1643.

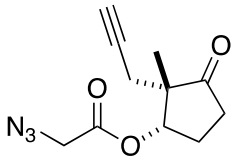
(1*S,2*S**)-2-Methyl-3-oxo-2-(prop-2-yn-1-yl)cyclopentyl acrylate (31)**



31

According to General Procedure F, *syn*-**1** (136 mg, 0.894 mmol), acrylic acid (82.8 µL, 1.21 mmol), DMAP (16.4 mg, 0.134 µmol) and DCC (249 mg, 1.21 mmol) gave a crude material. Purification *via* flash column chromatography (EtOAc/petroleum ether, 11:89) gave **31** as a colourless oil (93.7 mg, 0.455 mmol, 51%). $\boldsymbol{R_f}$ = 0.42 (EtOAc/petroleum ether, 20:80); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 6.39 (1H, dd, *J* 17.3, 1.4), 6.10 (1H, dd, *J* 17.3, 10.5), 5.86 (1H, dd, *J* 10.5, 1.4), 5.32 (1H, dd, *J* 4.5, 2.1), 2.49–2.38 (4H, m), 2.31 (1H, dddd, *J* 14.8, 10.5, 8.6, 4.5), 2.13 (1H, dddd, *J* 14.8, 7.5, 5.7, 2.1), 1.93 (1H, t, *J* 2.7), 1.20 (3H, s); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 218.0, 165.2, 131.5, 128.3, 80.1, 78.6, 70.4, 52.0, 34.1, 25.6, 21.3, 20.2; **IR** ν_{max}: 3279 (m, C≡C–H), 1743 (s, C=O), 1720 (s, C=O), 1636 (s, C=C); **HRMS** (ESI): $[M+H]^+$ calcd. for $C_{12}H_{14}O_3^+$: 207.1016, found: 207.1013.

(1*S,2*S**)-2-Methyl-3-oxo-2-(prop-2-yn-1-yl)cyclopentyl 2-azidoacetate (32)**

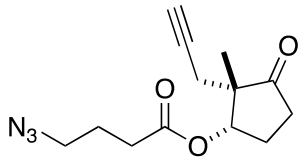


32

According to General Procedure F, *syn*-**1** (298 mg, 1.96 mmol), 2-azidoacetic (0.198 mL, 2.64 mmol), DMAP (35.9 mg, 0.294 mmol) and DCC (545 mg, 2.64 mmol) gave a crude material. Purification *via* flash column chromatography (petroleum ether/EtOAc, 83:17) gave **32** as a colourless oil (448 mg, 1.91 mmol, 97%). $\boldsymbol{R_f}$ = 0.26 (petroleum ether/EtOAc, 80:20); **^{1}H NMR** (600 MHz, $CDCl_3$): δ_H 5.38 (1H, dd, *J* 4.6, 2.0), 3.89 (2H, q, *J* 17.2), 2.50–2.42 (2H, m), 2.38 (2H, d, *J* 2.7), 2.38–2.28 (1H, m), 2.13 (1H, dddd, *J* 14.5, 8.1, 4.1, 2.0), 1.96 (1H, t, *J* 2.7), 1.21

(3H, s); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C 217.3, 167.5, 80.2, 80.0, 70.62, 52.0, 50.5, 34.1, 25.7, 21.5 20.3; **IR** ν_{max}: 3273 (s, C≡C–H), 2106 (s, N=N=N), 1735 (m, C=O); **HRMS** (ESI): $[M + H]^+$ calcd for $C_{11}H_{14}N_3O_3^+$: 236.1030, found 236.1030.

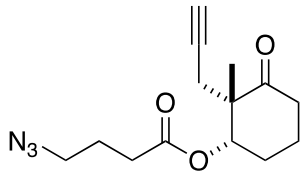
(1*S,2*S**)-2-methyl-3-oxo-2-(prop-2-yn-1-yl)cyclopentyl 4-azidobutanoate (33)**



33

According to General Procedure F, *syn*-**1** (100 mg, 0.66 mmol), 4-azidobutanoic acid (115 mg, 0.891 mmol), DMAP (8 mg, 0.066 mmol) and DCC (184 mg, 0.891 mmol) gave a crude material. Purification *via* flash column chromatography (hexane/EtOAc, 12:88) gave **33** as a colourless oil (145 mg, 0.55 mmol, 84%). $\mathbf{R_f}$ = 0.11 (hexane/EtOAc, 92:8); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 5.27 (1H, dd, *J* 4.6, 1.9), 3.36 (2H, t, *J* 6.7), 2.42 (4H, m), 2.38 (2H, d, *J* 2.7), 2.29 (1H, m), 2.12–2.03 (1H, m), 1.96–1.87 (3H, m), 1.19 (3H, s); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 217.9, 171.8, 80.3, 78.6, 70.4, 51.9, 50.7, 34.1, 31.4, 25.7, 24.4, 21.4, 20.2; **IR** ν_{max}: 2099 (s, N=N=N), 1732 (m, 2 × C=O); **HRMS** (ESI): $[M+H]^+$ calcd. for $C_{13}H_{18}N_3O_3^+$: 264.1343, found: 264.1343.

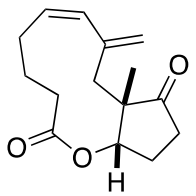
(1*S,2*S**)-2-Methyl-3-oxo-2-(prop-2-yn-1-yl)cyclohexyl 4-azidobutanoate (S12)**



S12

According to General Procedure F, *syn*-**8** (111 mg, 0.66 mmol), 4-azidobutanoic acid (115 mg, 0.891 mmol), DMAP (8 mg, 0.066 mmol) and DCC (184 mg, 0.891 mmol) gave a crude material. Purification *via* flash column chromatography (hexane/EtOAc, 88:12) gave **S12** as a colourless oil (155 mg, 0.56 mmol, 85%). $\mathbf{R_f}$ = 0.11 (hexane/EtOAc, 92:8); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 5.27 (1H, dd, *J* 4.1, 2.7), 3.34 (2H, td, *J* 6.7, 1.4), 2.67–2.30 (6H, m), 2.15–2.01 (2H, m), 1.97 (1H, t, *J* 2.7), 1.93–1.85 (4H, m), 1.33 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 211.7, 171.5, 80.1, 77.6, 71.4, 50.9, 50.7, 37.6, 31.4, 25.2, 24.4, 23.3, 21.4, 20.9; **IR** ν_{max}: 2097 (s, N=N=N), 1733 (s, C=O), 1709 (s, C=O); **HRMS** (ESI): $[M+H]^+$ calcd. for $C_{14}H_{20}O_3N_3^+$: 278.1499, found: 278.1488.

(9a*S,12a*S**,*Z**)-9a-methyl-8-methylene-4,5,8,9,9a,11,12,12a-octahydro-2*H*-cyclopenta[*b*][1]oxacycloundecine-2,10(3*H*)-dione (34)**

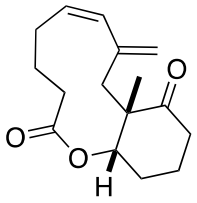


34

Grubbs 2nd generation catalyst (30 mg, 35.3 µmol) was added to a stirred solution of **30** (138 mg, 0.56 mmol) in PhMe (70 mL). The reaction mixture was stirred under an ethylene atmosphere at reflux for 4 h, then degassed

with N_2 and stirred for a further 16 h. The resultant mixture was filtered through celite then concentrated *in vacuo*. Purification *via* flash column chromatography (petroleum ether/EtOAc, 90:10) gave **34** as a white amorphous solid (117 mg, 0.47 mmol, 85%). R_f = 0.24 (Petroleum ether/EtOAc, 90:10); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 5.91 (1H, d, *J* 15.8), 5.63 (1H, dt, *J* 15.6, 7.7), 5.17–4.99 (2H, m), 4.84 (1H, d, *J* 2.0), 2.50–2.09 (8H, m), 2.08–1.80 (4H, m), 1.10 (3H, s); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 220.2, 175.1, 142.4, 136.5, 128.1, 116.3, 77.4, 53.4, 35.4, 34.4, 33.8, 31.4, 26.2, 24.8, 22.0; **IR** ν_{max}: 1729 (m, C=O); **HRMS** (ESI): $[M+H]^+$ calcd. for $C_{15}H_{21}O_3^+$: 249.1485, found: 249.1491.

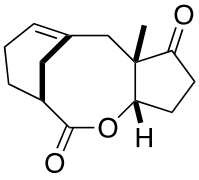
(9a*S,13a*S**,*Z**)-9a-Methyl-8-methylene-3,4,5,8,9,9a,11,12,13,13a-decahydrobenzo[*b*][1]oxacycloundecine-2,10-dione (S13)**



S13

Grubbs 2nd generation catalyst (9.5 mg, 11 µmol) was added to a stirred solution of **S11** (45 mg, 0.17 mmol) in PhMe (22 mL). The reaction mixture was stirred under an ethylene atmosphere at reflux for 4 h, then degassed with N_2 and stirred for a further 16 h. The resultant mixture was filtered through celite then concentrated *in vacuo*. Purification *via* flash column chromatography (petroleum ether/EtOAc, 90:10) gave **S13** as a white amorphous solid (37 mg, 0.14 mmol, 83%). R_f = 0.26 (petroleum ether/EtOAc, 90:10); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 5.93 (1H, d, *J* 15.9), 5.12 (1H, s), 4.84 (1H, t, *J* 1.5), 4.77– 4.70 (1H, m), 2.64 (1H, ddd, *J* 15.1, 12.7, 7.3), 2.38–2.14 (6H, m), 2.05–1.81 (7H, m), 1.31 (3H, s); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 213.9, 175.3, 142.2, 135.7, 116.2, 51.9, 37.7 (2C), 33.2, 29.8, 25.2, 24.7, 23.8, 20.8; **IR** ν_{max}: 1726 (s, C=O), 1706 (s, C=O); **HRMS** (ESI): $[M+H]^+$ calcd. for $C_{16}H_{22}O_3^+$: 263.1642, found: 263.1643.

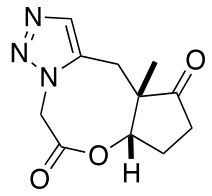
(3*R,8a*S**,11a*S**)-8a-Methyl-3,4,5,8,8a,10,11,11a-octahydro-3,7-methanocyclopenta[*b*]oxecine-2,9-dione (35)**



35

Hoveyda-Grubbs 2nd generation catalyst (11.6 mg, 18.4 µmol) was added to a stirred solution of **31** (38.0 mg, 0.184 mmol) in PhMe (37 mL). The reaction mixture was stirred under an ethylene atmosphere at reflux for 4 h, then concentrated *in vacuo*. Purification *via* flash column chromatography (petroleum ether/EtOAc, 89:11) gave **35** as a colourless oil (37.5 mg, 0.160 mmol, 87%). R_f = 0.42 (petroleum ether/EtOAc, 80:20); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 5.70 (1H, ddd, *J* 8.0, 3.8, 1.6), 5.08 (1H, t, *J* 2.9), 3.11 (1H, dt, *J* 14.2, 1.6), 2.99–2.90 (1H, m), 2.44–2.36 (2H, m), 2.35–2.15 (4H, m), 2.15–2.05 (1H, m), 1.88 (1H, d, *J* 14.2), 1.81–1.68 (2H, m), 1.55–1.45 (1H, m), 0.94 (3H, s); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 219.2, 178.9, 137.8, 126.5, 85.2, 57.9, 44.0, 39.7, 38.7, 34.7, 26.0, 23.6, 23.2, 22.5; **IR** ν_{max}: 1729 (s, C=O); **HRMS** (ESI): $[M+H]^+$ calcd. for $C_{14}H_{19}O_3^+$: 235.1329, found: 235.1334.

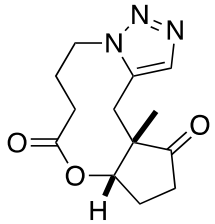
(7a*S,10a*S**)-10a-Methyl-8,9,10a,11-tetrahydrocyclopenta[*g*][1,2,3]triazolo[1,5-*d*][1,4]oxazocine-6,10(5*H*,7a*H*)-dione (36)**



36

Cp*RuCl(COD) (13.9 mg, 36.6 µmol) was added to a degassed solution of **32** (43.0 mg, 0.183 mmol) in PhMe (180 mL). The resultant solution heated under refluxed for 16 h before being cooled to rt. The crude mixture was filtered through celite and concentrated *in vacuo*. Purification *via* flash column chromatography (CH_2Cl_2/MeOH, 96:4) gave **36** as a colourless oil (38.0 mg, 0.162 mmol, 88%). R_f = 0.38 (CH_2Cl_2/MeOH, 95:5); **^{1}H NMR** (400 MHz, CD_3OD): δ_H 7.61 (1H, s), 5.44 (1H, d, *J* 17.8), 5.34 (1H, d, *J* 17.8), 3.92 (1H, dd, *J* 4.2, 2.3), 2.88 (1H, d, *J* 15.4), 2.80 (1H, d, *J* 15.4), 2.41–2.31 (2H, m), 2.25–2.13 (1H, m), 1.86 (1H, dddd, *J* 14.1, 7.6, 4.6, 2.3), 0.94 (3H, s); **^{13}C NMR** (101 MHz, CD_3OD): δ_C 221.9, 169.1, 137.2, 134.6, 76.7, 54.7, 49.8, 34.1, 28.8, 24.9, 19.9; **IR** ν_{max}: 1736 (m, C=O); **HRMS** (ESI): $[M-H]^-$ calcd. for $C_{11}H_{12}N_3O_3^-$: 234.0884, found 234.0879.

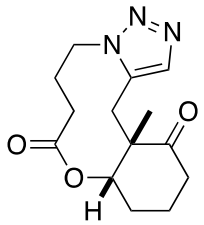
(9a*S,12a*S**)-12a-Methyl-6,7,10,11,12a,13-hexahydrocyclopenta[*b*][1,2,3]triazolo[5,1-*e*][1,6]oxazecine-8,12(5*H*,9a*H*)-dione (37)**



37

Cp*RuCl(COD) (17 mg, 45 µmol) was added to a degassed solution of **33** (82 mg, 0.31 mmol) in PhMe (120 mL). The resultant solution heated under refluxed for 16 h before being cooled to rt. The crude mixture was filtered through celite and concentrated *in vacuo*. Purification *via* flash column chromatography (CH_2Cl_2/MeOH, 97:3) gave **37** as an amorphous yellow solid (71 mg, 0.27 mmol, 87%). R_f = 0.24 (Hexane/EtOAc, 90:10); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.47 (1H, s), 4.27 (2H, app s), 3.01 (1H, app s), 2.85–2.29 (7H, m), 2.30–2.14 (2H, m), 2.02–1.91 (1H, m), 1.26 (3H, s); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 218.4, 170.8, 134.3, 132.8, 78.4, 52.9, 45.7, 34.4, 29.7, 29.3, 26.5, 25.8, 22.0; **IR** ν_{max}: 1736 (m, C=O); **HRMS** (ESI): $[M+H]^+$ calcd. for $C_{13}H_{18}N_3O_3^+$: 264.1343, found 264.1345.

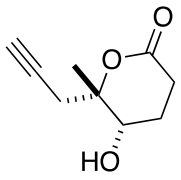
(9a*S,13a*S**)-13a-Methyl-6,7,9a,10,11,12,13a,14-octahydro-13*H*-benzo[*b*][1,2,3]triazolo[5,1-*e*][1,6]oxazecine-8,13(5*H*)-dione (S14)**



S14

$[RuCp^*Cl]_4$ (42 mg, 38.6 µmol) was added to a degassed solution of **S12** (92 mg, 0.33 mmol) in PhMe (134 mL). The resultant solution heated under refluxed for 24 h before being cooled to rt. The crude mixture was filtered through celite and concentrated *in vacuo*. Purification *via* flash column chromatography gave **S14** as an amorphous yellow solid (78 mg, 0.28 mmol, 85%). $\mathbf{R_f}$ = 0.20 (Hexane/EtOAc, 90:10); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.52 (1H, s), 4.42 (2H, m), 4.29–4.17 (1H, m), 3.36 (1H, d, *J* 15.6), 2.86–2.55 (3H, m), 2.47–2.29 (4H, m), 2.02–1.79 (4H, m), 1.46 (3H, s); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 212.8, 171.0, 133.4, 132.4, 77.4, 50.9, 46.8, 37.6, 33.8, 27.5, 26.9, 25.4, 23.2, 20.9; **IR** ν_{max}: 1735 (s, C=O), 1703 (s, C=O); **HRMS** (ESI): $[M+H]^+$ calcd. for $C_{14}H_{20}N_3O_3^+$: 278.1499, found 278.1499.

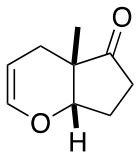
(5*S,6*S**)-5-Hydroxy-6-methyl-6-(prop-2-yn-1-yl)tetrahydro-2H-pyran-2-one (38)**



38

$KHCO_3$ (82.7 mg, 0.826 mmol) and *m*CPBA (<77%, 1.02 g, 4.13 mmol) were added to a solution of *syn*-**1** (110 mg, 0.413 mmol) in anhydrous CH_2Cl_2 and the reaction mixture was stirred at reflux for 40 h. The mixture was concentrated *in vacuo* and filtered through a short plug of silica. TBAF (1.0 M in THF, 0.657 mL, 0.657 mmol) was added to a solution of the crude Baeyer–Villiger oxidation product in anhydrous THF (5 mL). The mixture was stirred at rt for 2 h, then concentrated *in vacuo*. Purification *via* flash column chromatography (petroleum ether/EtOAc/AcOH, 49:49:2) gave **38** as a colourless oil (20.2 mg, 0.120 mmol, 29%); $\boldsymbol{R_f}$ = 0.36 (petroleum ether/EtOAc, 50:50); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 4.56 (1H, dd, *J* 7.9, 7.2), 2.64–2.50 (4H, m), 2.29 (2H, dddd, *J* 12.9, 9.9, 9.2, 7.9), 2.18 (1H, dddd, *J* 12.9, 9.9, 7.2, 4.5), 2.08 (1H, t, *J* 2.7), 1.27 (3H, s); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 177.2, 83.6, 79.8, 72.4, 71.6, 30.2, 29.0, 22.1, 21.7; **IR** ν_{max}: 3452 (br., O–H), 3285 (s, C≡C–H), 1754 (s, C=O); **HRMS** (ESI): $[M+H]^+$ calcd. for $C_9H_{13}O_3^+$: 169.0859, found 169.0859.

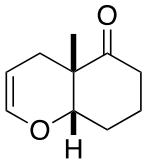
(4a*S*,7a*S***)-4a-Methyl-4a,6,7,7a-tetrahydrocyclopenta[b]pyran-5(4H)-one (39)**



39

$CpRu(PPh_3)_2Cl$ (57 mg, 0.079 mmol) and PPh_3 (42 mg, 0.16 mmol) were added to a degassed solution of *N*-hydroxy succinimide (45 mg, 0.40 mmol), NBu_4PF_6 (40 mg, 0.1 mmol), $NaHCO_3$ (34 mg, 0.40 mmol) and *syn*-**1** (120 mg, 0.79 mmol) in DMF (8 mL). The reaction was degassed once more and then sealed in a vial. The resultant mixture was stirred at 80 °C for 18 hours. Further $CpRu(PPh_3)_2Cl$ (57 mg, 0.079 mmol) was added and the reaction was stirred at 80 °C for 38 hours. Upon completion, the reaction was filtered through celite and partitioned between EtOAc (20 mL) and brine (20 mL). The organic layer was separated, dried and concentrated *in vacuo*. Purification *via* flash column chromatography (hexane/EtOAc, 90:10) gave **39** as a colourless oil (78 mg, 0.51 mmol, 65%). $\mathbf{R_f}$ = 0.30 (hexane/EtOAc, 90:10); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 6.32 (1H, dt, *J* 6.3, 2.1), 4.62 (1H, ddd, *J* 6.3, 4.3, 3.2), 4.17 (1H, t, *J* 3.7), 2.48–2.30 (3H, m), 2.28–2.19 (1H, m), 2.13–2.06 (1H, m), 1.82–1.77 (1H, m), 1.07 (3H, s); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 218.0, 142.6, 98.4, 79.7, 47.5, 33.0, 25.8, 24.6, 21.8; **IR** ν_{max}: 1742 (s, C=O), 1659 (m, C=C); **HRMS** (ESI): $[M+H]^+$ calcd. for $C_9H_{13}O_2^+$: 153.0910, found: 153.0910.

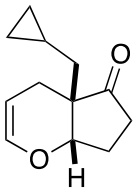
(4a*S*,8a*S***)-4a-Methyl-4,4a,6,7,8,8a-hexahydro-5H-chromen-5-one (S15)**



S15

$CpRu(PPh_3)_2Cl$ (61 mg, 0.084 mmol) and PPh_3 (45 mg, 0.17 mmol) were added to a degassed solution of *N*-hydroxy succinimide (48 mg, 0.43 mmol), NBu_4PF_6 (43 mg, 0.11 mmol), $NaHCO_3$ (36 mg, 0.43 mmol) and *syn*-**8** (140 mg, 0.84 mmol) in DMF (8.5 mL). The reaction was degassed once more and then sealed in a vial. The resultant mixture was stirred at 80 °C for 18 hours. Further $CpRu(PPh_3)_2Cl$ (61 mg, 0.084 mmol) was added and the reaction was stirred at 80 °C for 38 hours. Upon completion, the reaction was filtered through celite and partitioned between EtOAc (20 mL) and brine (20 mL). The organic layer was separated, dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent hexane/EtOAc, 90:10) gave **S15** as a colourless oil (88 mg, 0.53 mmol, 63%). $\mathbf{R_f}$ = 0.30 (eluent hexane/EtOAc, 90:10); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 6.26 (1H, dt, *J* 6.2, 2.0), 4.63 (1H, ddd, *J* 6.2, 4.5, 3.0), 3.96 (1H, dd, *J* 5.5, 2.2), 2.61–2.44 (2H, m), 2.41–2.30 (1H, m), 2.15–2.00 (2H, m), 1.99–1.87 (1H, m), 1.85–1.72 (1H, m), 1.60 (1H, dt, *J* 17.2, 2.6), 1.20 (3H, s); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 212.20, 142.4, 98.8, 80.0, 47.6, 36.9, 27.7, 25.8, 23.0, 20.0; **IR** ν_{max}: 1708 (s, C=O), 1661 (m, C=C); **HRMS** (ESI): $[M+H]^+$ calcd. for $C_{10}H_{15}O_2^+$: 167.1067, found: 167.1066.

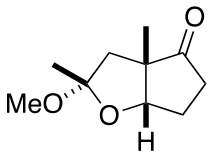
(4a*S,7a*S**)-4a-(Cyclopropylmethyl)-4a,6,7,7a-tetrahydrocyclopenta[*b*]pyran-5(4*H*)-one (S16)**



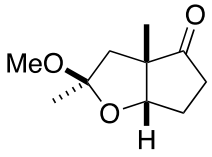
S16

$CpRu(PPh_3)_2Cl$ (32.3 mg, 40.6 μmol) and PPh_3 (10.6 mg, 40.6 μmol) were added to a degassed solution of *N*-hydroxy succinimide (11.7 mg, 0.101 mmol), NBu_4PF_6 (10.2 mg, 26.4 μmol), $NaHCO_3$ (8.5 mg, 0.101 mmol) and *syn*-**9** (39.0 mg, 0.203 mmol) in DMF (4 mL). The reaction was degassed once more and then sealed in a vial. The resultant mixture was stirred at 80 °C for 18 hours. The reaction was filtered through celite and partitioned between EtOAc (20 mL) and brine (20 mL). The organic layer was separated, dried and concentrated *in vacuo*. Purification *via* flash column chromatography (petroleum ether/EtOAc, 90:10) gave **S16** as a colourless oil (19.1 mg, 0.099 mmol, 49%). R_f = 0.46 (petroleum ether/EtOAc, 90:10); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.31 (1H, dt, *J* 6.3, 2.1), 4.64 (1H, dt, *J* 6.3, 3.7), 4.48 (1H, t, *J* 4.0), 2.45 (1H, ddd, *J* 18.1, 9.2, 6.7), 2.37–2.18 (3H, m), 2.11–2.01 (1H, m), 1.95 (1H, dddd, *J* 17.7, 4.0, 2.1, 0.7), 1.40 (2H, d, *J* 6.7), 0.67 (1H, dddt, *J* 14.3, 8.4, 6.9, 4.9), 0.52–0.40 (2H, m), 0.10– –0.04 (2H, m); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 217.3, 142.3, 98.2, 77.6, 51.5, 39.1, 33.5, 25.7, 22.8, 6.1, 4.9, 4.8; **IR** ν_{max}: 3066 (m, C=C–H), 1740 (s, C=O), 1660 (s, C=C), 1236 (s, C=C–O–C), 1063 (s, C=C–O–C); **HRMS** (ESI): [M+H]+ calcd. for $C_{12}H_{17}O_2$ $[M + H]^+$ 193.1223, found 193.1232.

(2*S,3a*S**,6a*S**)-2-Methoxy-2,3a-dimethylhexahydro-4*H*-cyclopenta[*b*]furan-4-one (40a) and (2*R**,3a*S**,6a*S**)-2-methoxy-2,3a-dimethylhexahydro-4*H*-cyclopenta[*b*]furan-4-one (40b)**



40a



40b

$[Ir(cod)Cl]_2$ (4 mg, 0.005 mmol) was added to a stirred solution of *syn*-**1** (33 mg, 0.22 mmol) in MeOH (0.6 mL). The resultant mixture was stirred at rt for 4 hours. Upon completion, the reaction was filtered through celite and concentrated *in vacuo* to give a mixture of diastereomers (22:78 *dr*). Purification *via* flash column chromatography (hexane/EtOAc, 90:10) gave **40a** (7 mg, 18%) and **40b** (23 mg, 58%) both as colourless oils.

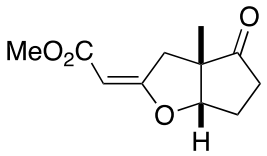
Data of **40a**:

R_f = 0.24 (hexane/EtOAc, 90:10); **^{1}H NMR** (400 MHz, $CDCl_3$): 4.35 (1H, app d, *J* 4.3), 3.21 (3H, s), 2.54–2.42 (1H, m), 2.37–2.27 (1H, m), 2.25–2.13 (2H, m), 2.04–1.94 (2H, m), 1.33 (3H, s), 1.15 (3H, s); **^{13}C NMR** (126 MHz, $CDCl_3$): δ_C 222.9, 108.3, 86.6, 56.5, 50.8, 48.7, 34.6, 24.0, 21.5, 18.6; **IR** ν_{max}: 1738 (s, C=O); **HRMS** (ESI): $[M+Na]^+$ calcd. for $C_{10}H_{16}O_3Na^+$: 207.0992, found: 207.0993.

Data of **40b**:

R_f = 0.13 (hexane/EtOAc, 90:10); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 4.47 (1H, app d, *J* 5.1), 3.13 (3H, s), 2.59–2.41 (2H, m), 2.37–2.23 (1H, m), 2.20–2.01 (2H, m), 1.79 (1H, d, *J* 12.7), 1.39 (3H, s), 1.12 (3H, s); **^{13}C NMR** (126 MHz, $CDCl_3$): δ_C 221.9, 107.7, 88.8, 55.5, 50.8, 48.4, 35.3, 26.2, 20.9, 19.4; **IR** ν_{max}: 1739 (s, C=O); **HRMS** (ESI): $[M+H]^+$ calcd. for $C_{10}H_{16}O_3Na^+$: 207.0992, found: 207.0998.

Methyl (*E*)-2-((3a*S,6a*S**)-3a-Methyl-4-oxohexahydro-2*H*-cyclopenta[*b*]furan-2-ylidene)acetate (41)**



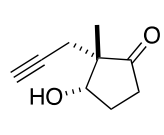
41

A CO atmosphere was introduced to a stirred solution of $Pd(CH_3CN)_2Cl_2$ (30.2 mg, 0.117 mmol) and *p*-benzoquinone (277 mg, 2.57 mmol) in anhydrous MeOH (30 mL). The mixture was cooled to 50 °C and then added dropwise a solution of *syn*-**1** (355 mg, 2.33 mmol) in anhydrous MeOH (15 mL). The reaction mixture was stirred under a CO atmosphere at –50 °C for 16 h. The mixture was allowed to warm to 22 °C then diluted with CH_2Cl_2 (200 mL). The mixture was washed with 1 M NaOH (1 × 200 mL), dried and concentrated *in vacuo*. Purification *via* flash column chromatography (petroleum ether/EtOAc, 80:20) gave **41** as a colourless oil (160 mg, 0.762 mmol, 33%). R_f = 0.40 (petroleum ether/EtOAc, 70:30); **^{1}H NMR** (600 MHz, $CDCl_3$) δ_H 5.26 (1H, dd, *J* 2.3, 1.5), 4.72 (1H, dd, *J* 4.2, 1.0), 3.67–3.62 (4H, m), 2.86 (1H, dd, *J* 18.9, 2.3), 2.43–2.34 (3H, m), 2.18–2.10 (1H, m), 1.22 (3H, s); **^{13}C NMR** (151 MHz, $CDCl_3$) δ_C 219.4, 174.0, 168.4, 91.0, 90.6, 54.2, 51.0, 42.0, 34.5, 25.0, 18.0; **IR** ν_{max}: 1741 (s, C=O), 1701 (s, C=O), 1637 (s, C=C); **HRMS** (ESI): $[M + H]^+$ calcd. for $C_{11}H_{15}O_4^+$: 211.0965, found 211.0972.

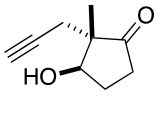
3. COMPUTATIONAL ANALYSIS

A) Compound Collections Analysed

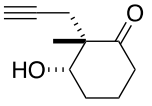
Collection 1: This Work.
Only final compounds in their fully deprotected forms were analysed. The relevant structures are shown in Fig. 1.



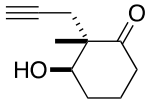
syn-**1**



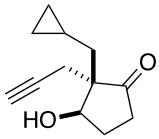
anti-**1**



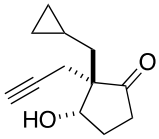
syn-**8**



anti-**8**



syn-**9**



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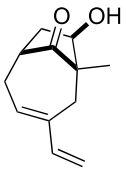

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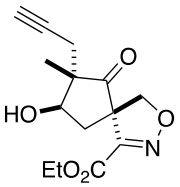

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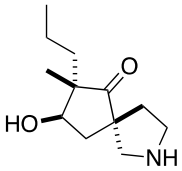

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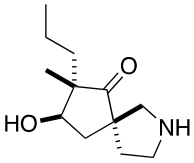

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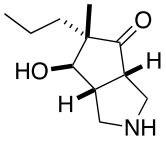

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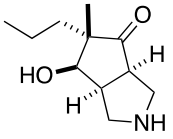

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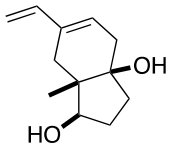

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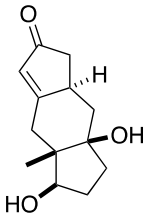

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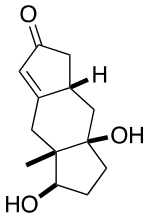

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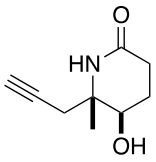

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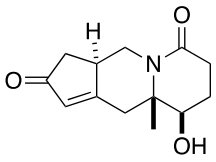

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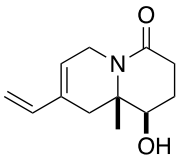

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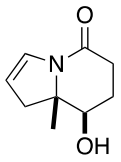

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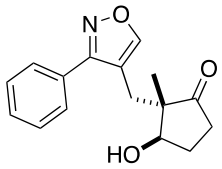

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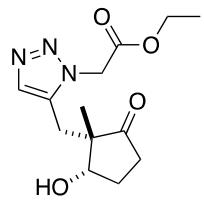

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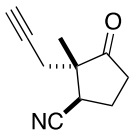

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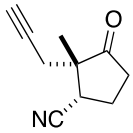

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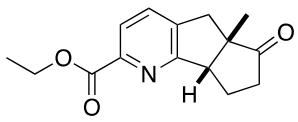

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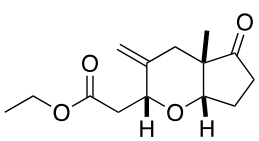

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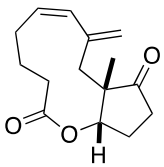

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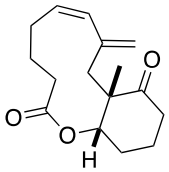

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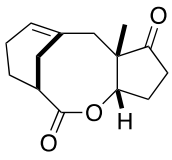

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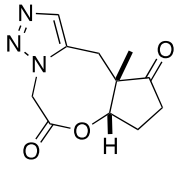

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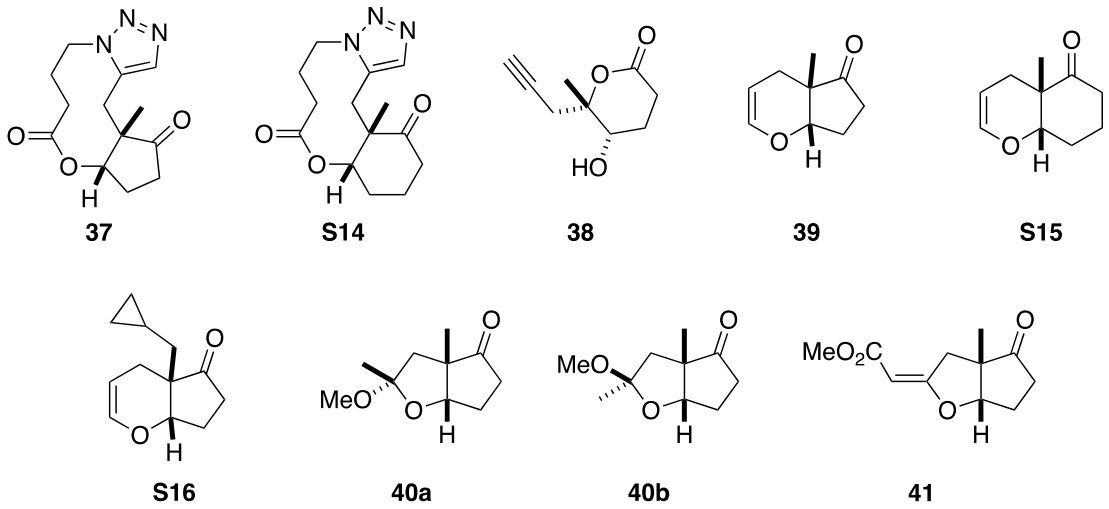

Fig. 1: The structures of the analysed final compounds. When applicable protecting groups were virtually removed.

Collection 2: Maybridge 'Ro3' Diversity Set 1 Fragment Collection

This library is based on the Maybridge 'Ro3' Diversity Set 1 within the Maybridge Fragment collection. Details of the library (including SMILES and SDF) are available from 'http://www.maybridge.com/' under the Fragment collection 'Maybridge Ro3 Diversity Sets' section.

Collection 3: Life Chemicals 3D Fragment Library

This library is based on the 3D Fragment library within the Life chemicals Fragment collection. Details of the library (including SMILES and SDF) are available from 'http://www.lifechemicals.com/' under the Fragment libraries '3D fragment library' section.

B) Calculation of Physicochemical Properties

Calculation of the physicochemical properties of library members was carried out using a Molecular Operating Environment (MOE) software package version 2012.10 from the Chemical Computing Group. Merck molecular force field Amber 10 EHT, an all-atom force field parameterised for small organic molecules with the Generalised Born solvation model, was used to minimise the energy potential. A LowModeMD search was employed for conformation generation. Detailed settings for conformational search are listed below.

Conformation Search Settings	
Rejection Limit	100
RMS Gradient	0.005
Iteration Limit	10000
MM Iteration Limit	500
RMSD Limit	0.15
Energy Window	3
Conformation Limit	100

Our library compounds were analysed for the following properties: SlogP, molecular weight (MW), number of hydrogen-bond acceptors (HBA), number of hydrogen-bond donors (HBD), number of chiral centres and fraction aromatic (the number of aromatic atoms expressed as a fraction of the total number of heavy atoms). Fraction sp^3 (the number of sp^3 hybridised carbon atoms expressed as a fraction of the total number of carbon atoms) was calculated using the LLAMA web tool. The distribution of these data and the mean values are displayed in a series of histograms in Fig 2.

By means of comparison with existing libraries, the percentage of the library complying with the fragment 'rule of three' properties is shown alongside those of two popular commercially available fragment libraries, Maybridge Diversity Set 1 and Life Chemicals 3D, in Table 1.

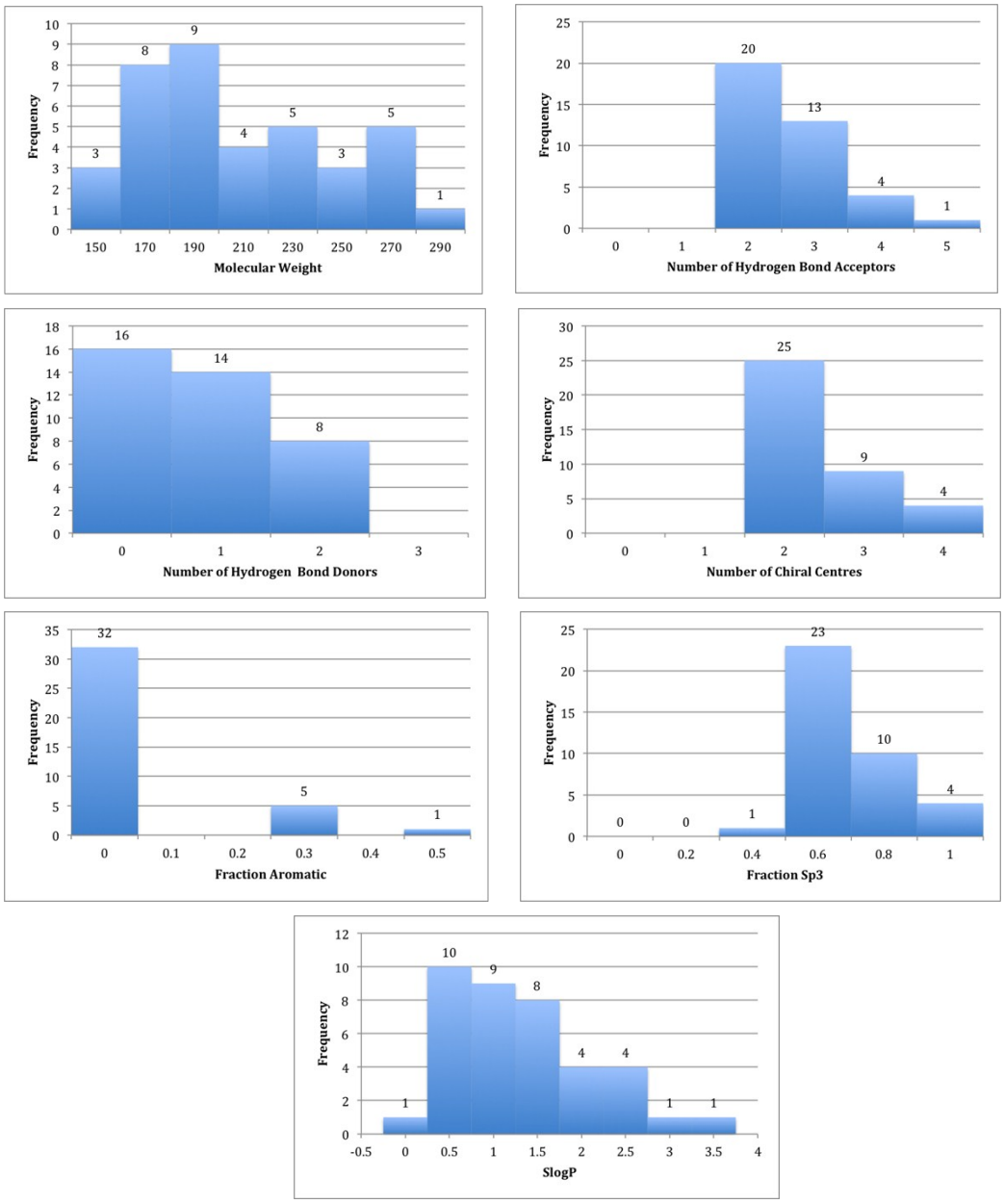

Fig. 2: Histograms showing the distribution of physicochemical properties amongst the compounds in Fig. 1.

Table 1. Percentage of each library complying with the fragment 'rule of three'.

Property[a]	This Work	Maybridge Diversity Set 1	Life Chemicals 3D	Ideal Value[b]
MW	68%	87%	25%	≤230
SlogP	97%	91%	92%	≤3
HBA	87%	100%	78%	≤3
HBD	100%	100%	100%	≤3

[a] MW = molecular weight, HBA = number of hydrogen bond acceptors, HBD = number of hydrogen bond donors. [b] Ideal range based on guidelines of 'rule of three'.[3, 4]

C) Principal Moment of Inertia

The principal moments of inertia (PMI) of the lowest energy conformations of the virtual library was performed using the LLAMA web tool and the data replotted in excel.[5]

Table 2. Normalised PMI ratio values of conformers of fig. 1 compounds with the lowest energy.

Compound	Canonical SMILES	PMI x (npr1)	PMI y (npr2)
syn-**1**	O[C@H]([C@@]1(CC#C)C)CCC1=O	0.48903	0.7995
anti-**1**	O[C@@H]([C@@]1(CC#C)C)CCC1=O	0.44513	0.76579
syn-**8**	O[C@H]([C@@]1(CC#C)C)CCCC1=O	0.56362	0.80854
anti-**8**	O[C@@H]([C@@]1(CC#C)C)CCCC1=O	0.42554	0.75246
syn-**9**	O[C@@H]([C@@]1(CC#C)CC2CC2)CCC1=O	0.58255	0.78519
anti-**9**	O[C@H]([C@@]1(CC#C)CC2CC2)CCC1=O	0.54026	0.78265
10	O[C@@H]([C@@]1(CC(C=C)=CC2)C)C[C@@H]2C1=O	0.50541	0.88669
12	O[C@@H]([C@@]1(CC#C)C)C[C@]2(CON=C2C(OCC)=O)C1=O	0.50782	0.70959
13a	O[C@@H]([C@@]1(CCC)C)C[C@]2(CCNC2)C1=O	0.31222	0.94676
13b	O[C@@H]([C@@]1(CCC)C)C[C@]2(CNCC2)C1=O	0.30808	0.94576
S17a	O[C@@H]([C@@]1(CCC)C)[C@](CNC2)([H])[C@]2([H])C1=O	0.39961	0.88123
S17b	O[C@@H]([C@@]1(CCC)C)[C@@](CNC2)([H])[C@@]2([H])C1=O	0.31094	0.84209
17	O[C@@H]1CC[C@]2(O)[C@]1(CC(C=C)=CC2)C	0.40534	0.8956
18b	O[C@@H]1CC[C@@](O)(C[C@@]2([H])C3)[C@]1(CC2=CC3=O)C	0.381	0.88754
18a	O[C@@H]1CC[C@@](O)(C[C@]2([H])C3)[C@]1(CC2=CC3=O)C	0.27281	0.93321
20	O=C1CC[C@@H](O)[C@@](CC#C)(C)N1	0.62855	0.77882
21	O=C1CC[C@@H](O)[C@@](C2)(C)N1C[C@@]3([H])C2=CC(C3)=O	0.2911	0.79301
22	O=C1CC[C@@H](O)[C@@]2(C)N1CC=C(C=C)C2	0.37601	0.73635
23	O=C1CC[C@@H](O)[C@@]2(C)N1C=CC2	0.56255	0.639
24	O=C1CC[C@@H](O)[C@@]1(CC2=CON=C2C3=CC=CC=C3)C	0.48685	0.75436
25	O[C@H]([C@@]1(CC2=CN=NN2CC(OCC)=O)C)CCC1=O	0.18636	0.90693
syn-**26**	O=C1CC[C@H](C#N)[C@@]1(CC#C)C	0.67563	0.88966
anti-**26**	O=C1CC[C@@H](C#N)[C@@]1(CC#C)C	0.48064	0.70721
27	O=C1CC[C@@]2([H])[C@]1(C)CC3=C2N=C(C(OCC)=O)C=C3	0.15122	0.94161
29	O=C1CC[C@@](O[C@]2([H])CC(OCC)=O)([H])[C@@]1(CC2=C)C	0.4243	0.97837
34	O=C1CC[C@@](OC(CCC/C=C\2)=O)([H])[C@@]1(CC2=C)C	0.4175	0.74513

S13	O=C1CCC[C@@](OC(CCC/C=C\2)=O)([H])[C@@]1(CC2=C)C	0.49196	0.69301
35	O=C1CC[C@@](OC2=O)([H])[C@@]1(CC3=CCC[C@H]2C3)C	0.50253	0.87337
36	O=C1CC[C@@](OC2=O)([H])[C@@]1(CC3=CN=NN3C2)C	0.41922	0.74743
37	O=C1CC[C@@](OC2=O)([H])[C@@]1(CC3=CN=NN3CCC2)C	0.54235	0.70377
S14	O=C1CCC[C@@](OC2=O)([H])[C@@]1(CC3=CN=NN3CCC2)C	0.47444	0.72708
38	O=C(O1)CC[C@H](O)[C@@]1(CC#C)C	0.53357	0.6862
39	O=C1CC[C@@]2(OC=CC[C@]12C)[H]	0.48472	0.8194
S15	O=C1CCC[C@@]2(OC=CC[C@]12C)[H]	0.65594	0.87239
S16	O=C1CC[C@@]2(OC=CC[C@]12CC3CC3)[H]	0.48683	0.79487
40a	C[C@]12[C@](O[C@](C)(OC)C2)([H])CCC1=O	0.56959	0.91568
40b	C[C@]12[C@](O[C@@](C)(OC)C2)([H])CCC1=O	0.43335	0.97777
41	C[C@]12[C@](O/C(C2)=C/C(OC)=O)([H])CCC1=O	0.26256	0.91833

D) Natural Product-Likeness

The natural product-likeness of molecules was calculated using the open-source and open-data "Natural-Product-Likeness Scorer" based on a previously developed algorithm.[6,7] This Bayesian measure evaluates how similar a molecule is to the structural space covered by natural products. The algorithm removes small disconnected fragments (e.g. counter ions and metals) and divides each compound into smaller substructures, which are compared to two training sets consisting of: 1) 113,425 synthetic lead-like compounds selected from the ZINC database[8] and 2) 58,018 natural products derived from the Traditional Chinese Medicinal Database @ Taiwan[9] and the ChEMBL database (only *Journal of Natural Products* structures selected).[10] On a logarithmic scale, each molecule is assigned a score (typically in the range of −3 to 3) based on the resemblance of its substructures to the two training sets. Positive values indicate higher resemblance to natural products and negative values indicate a more synthetic character. For full experimental details see references.[5,6] The NuBBE database of 2712 natural products was used as the source for natural products.[11]

4. REFERENCES

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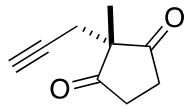
5. NMR SPECTRA



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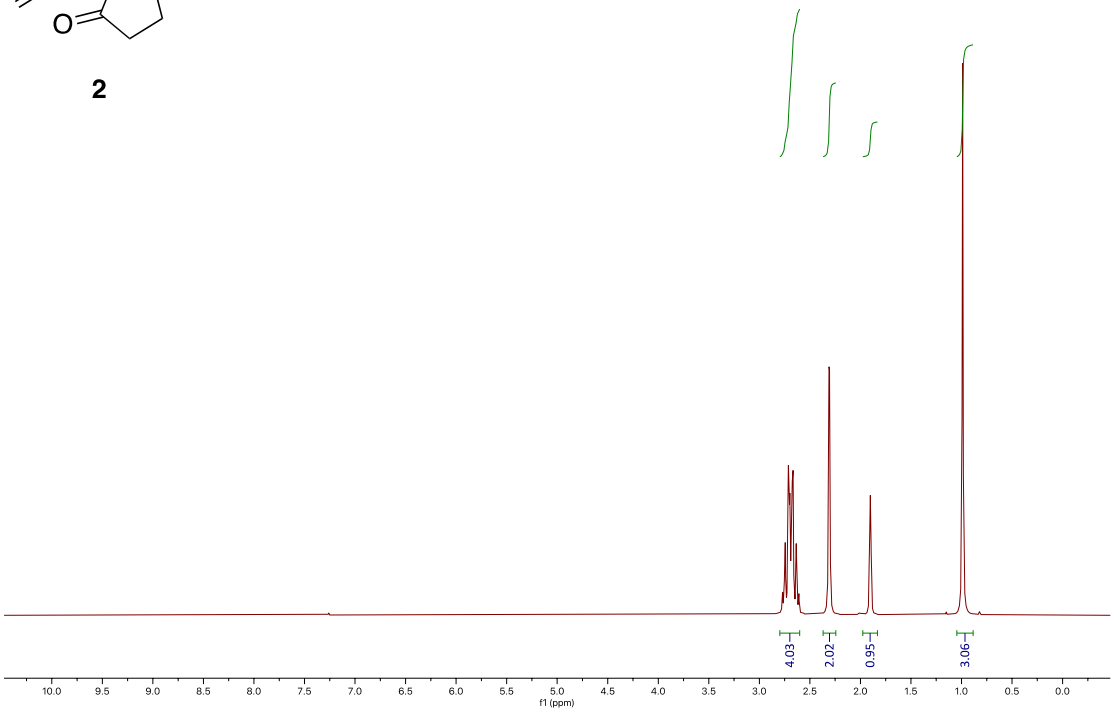

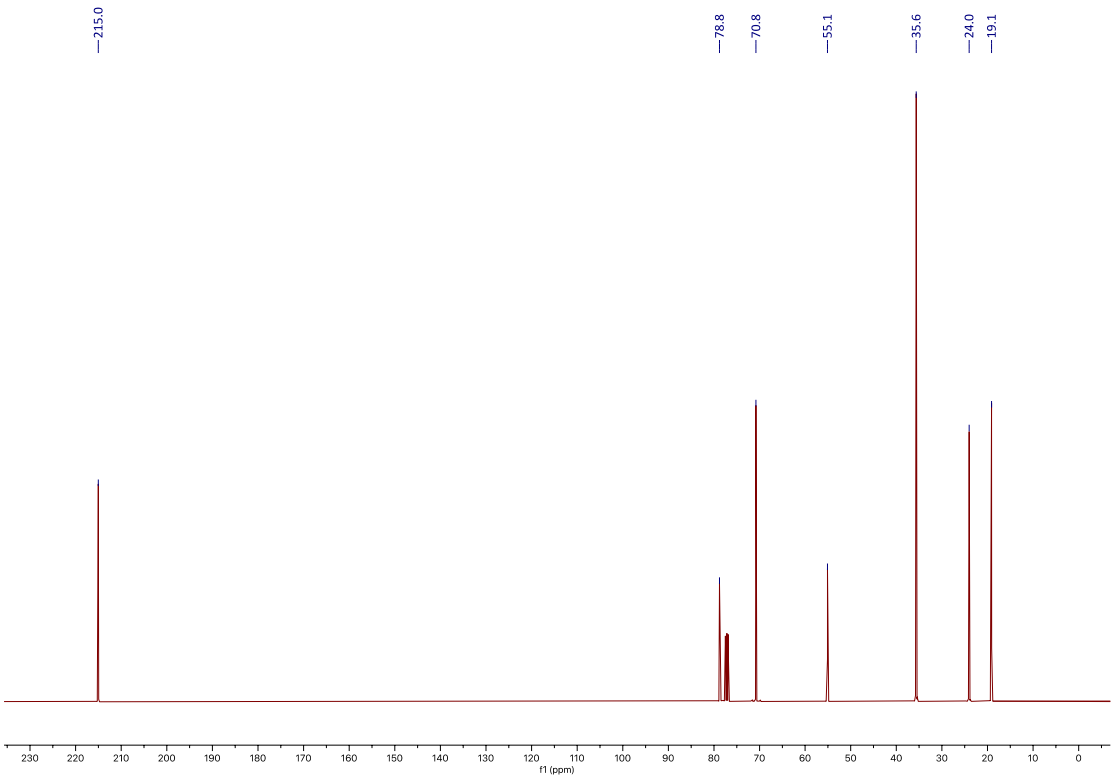

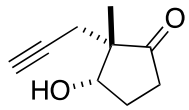
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HO

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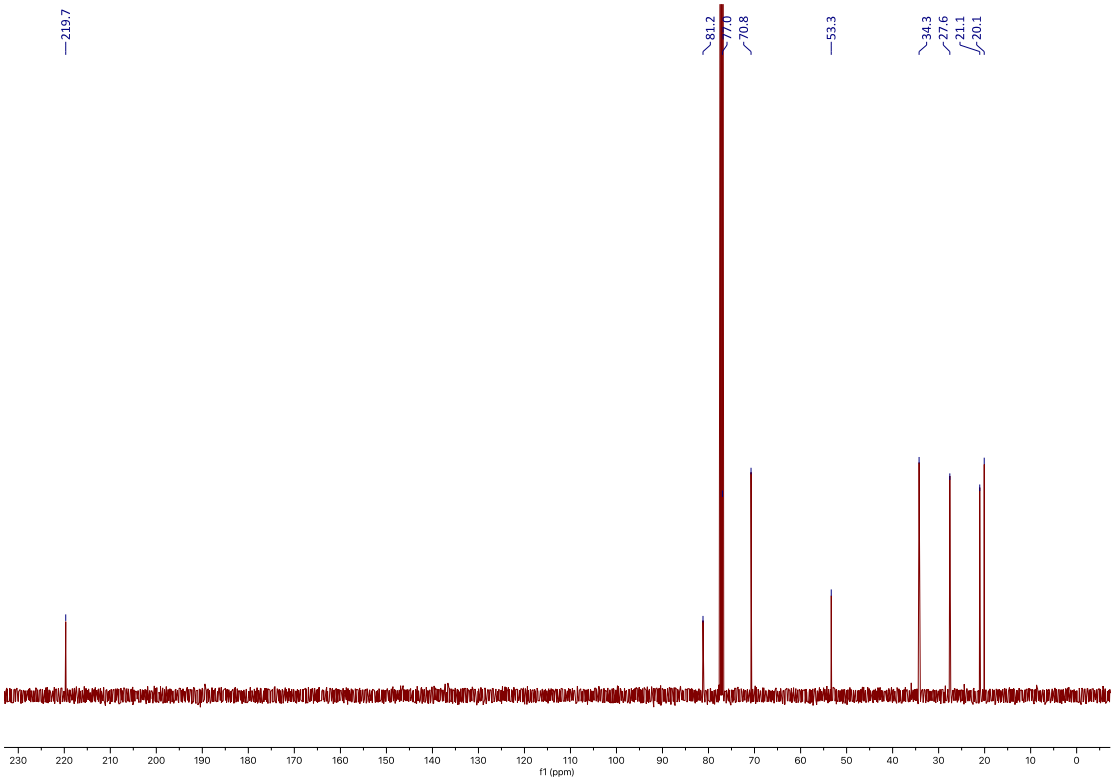
2.03
1.16
2.96
f1 (ppm)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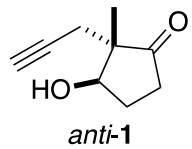
27.6
21.1
20.1
f1 (ppm)


O
HO

anti-**1**

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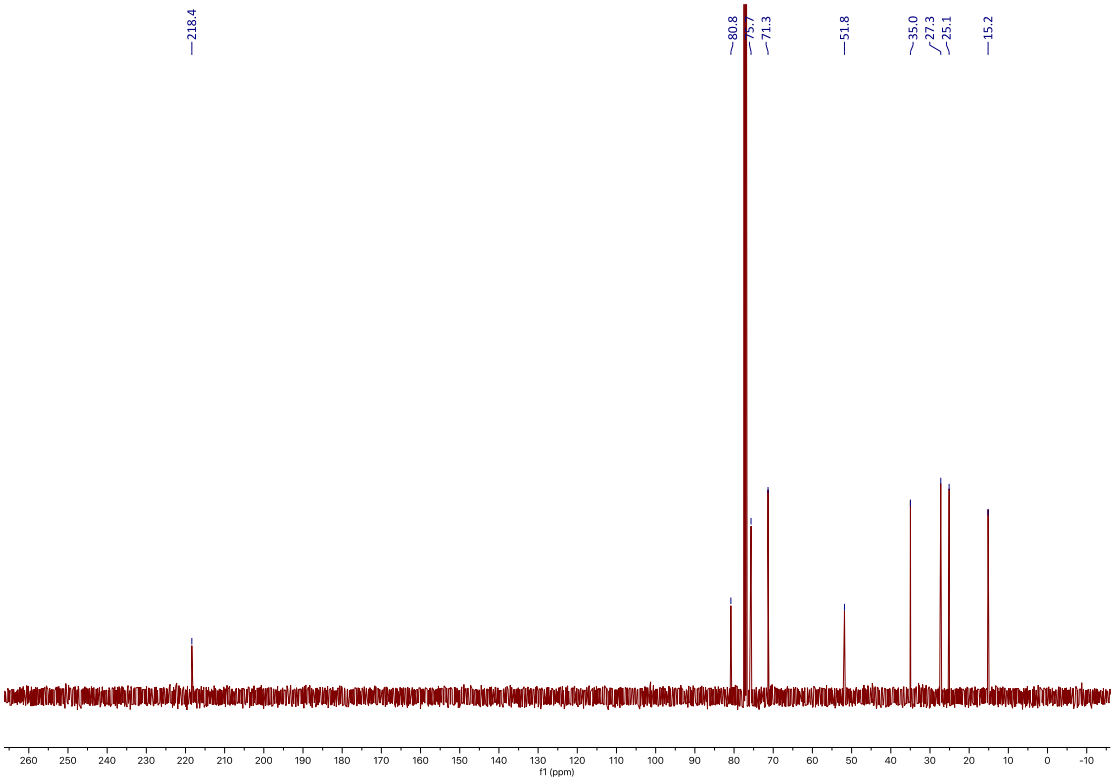
2.00
0.97
1.00
2.87
f1 (ppm)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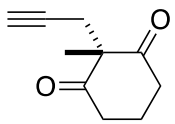
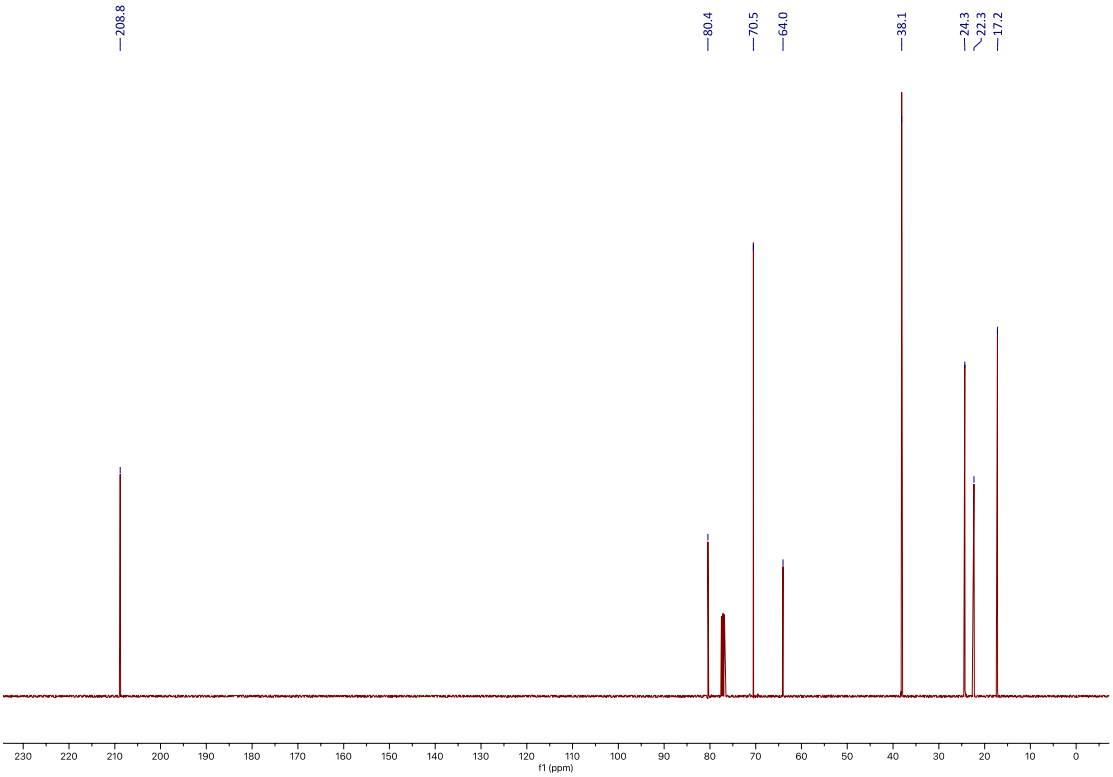
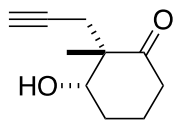
15.2
f1 (ppm)


O
O

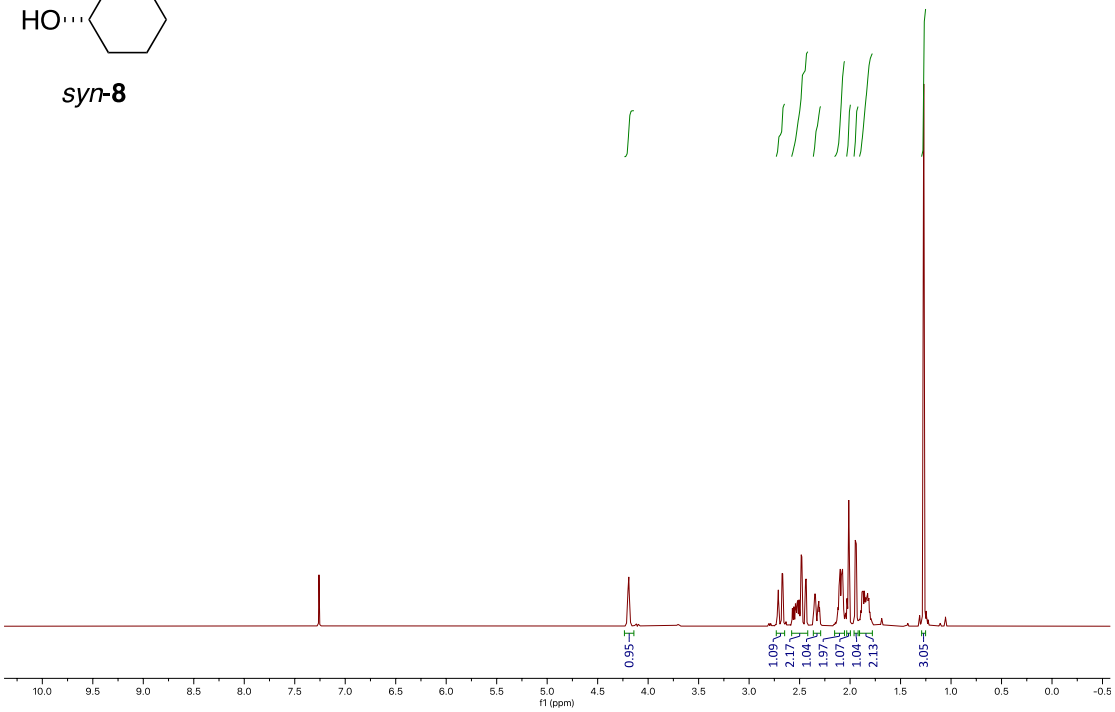
6

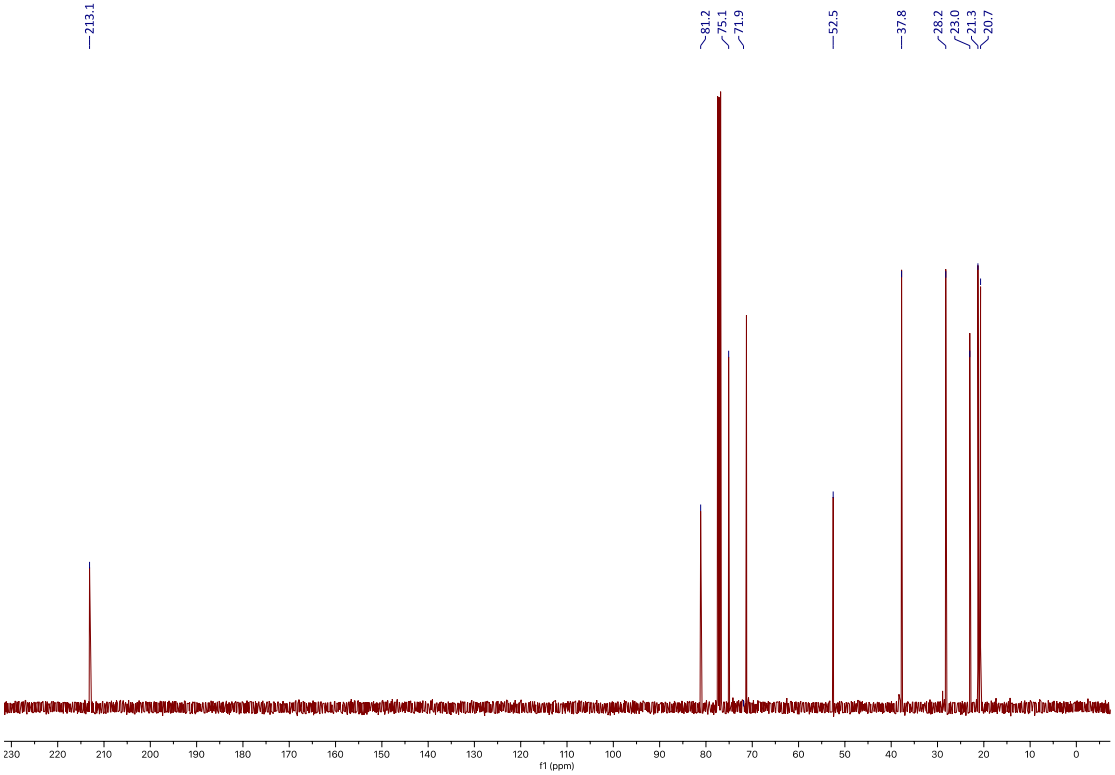
5.95
2.93
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

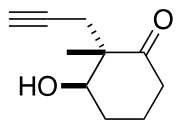

208.8
80.4
70.5
64.0
38.1
24.3
22.3
17.2
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O
HO

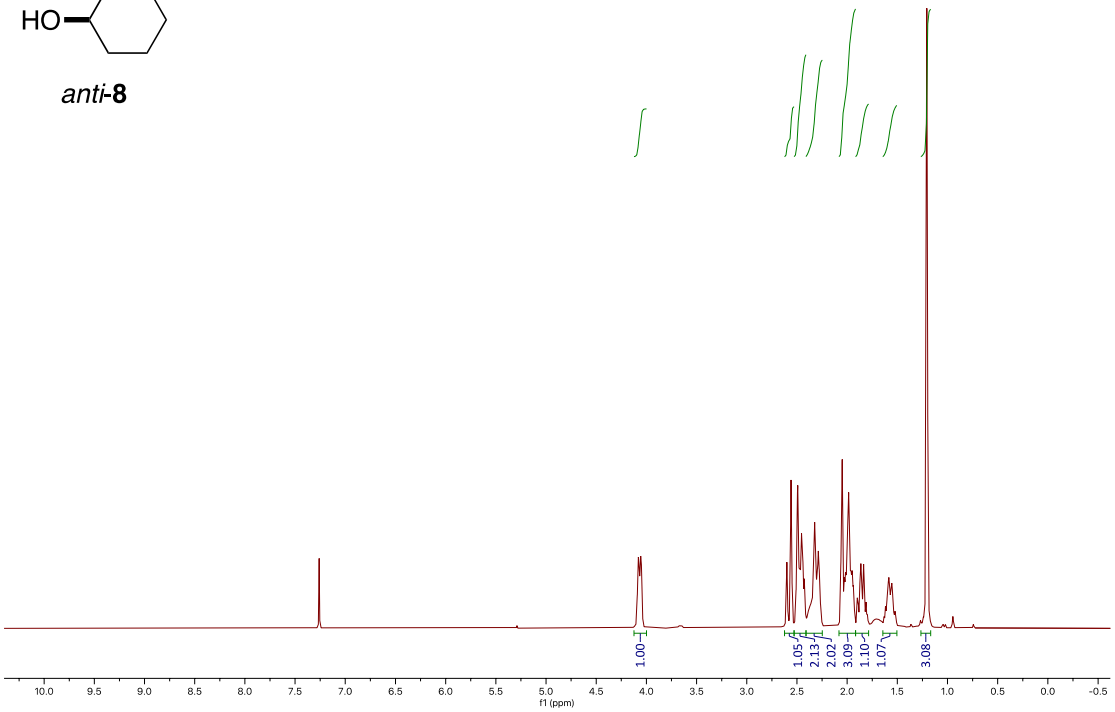
syn-**8**

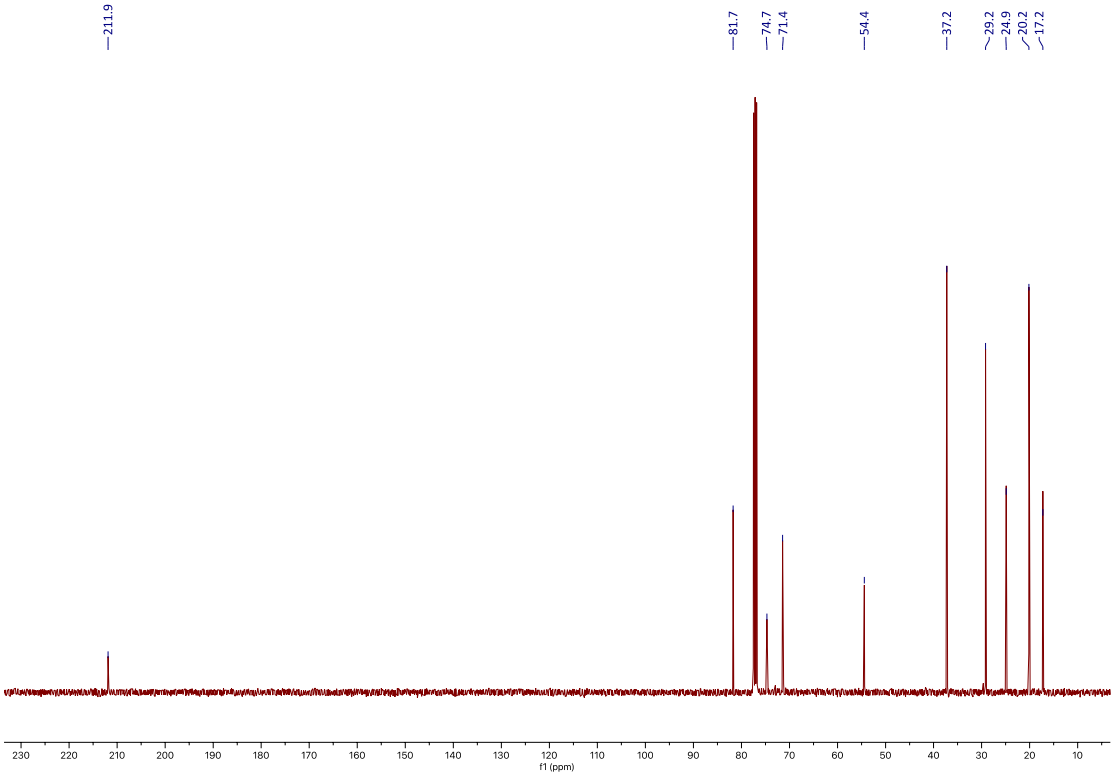

0.95
1.09
2.17
1.04
1.97
1.07
1.04
2.13
3.05
f1 (ppm)

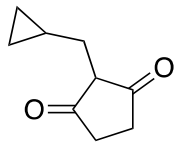

213.1
81.2
75.1
71.9
52.5
37.8
28.2
23.0
21.3
20.7
f1 (ppm)


O
HO

anti-**8**

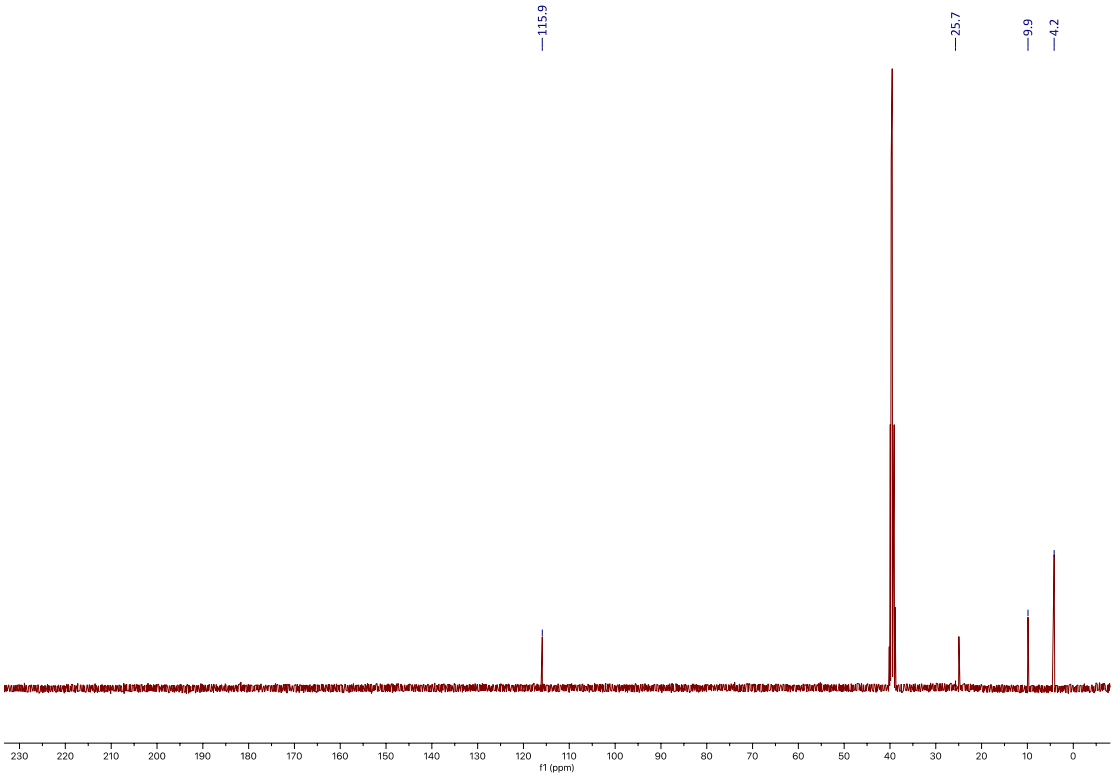

1.00
1.05
2.13
2.02
3.09
1.10
1.07
3.08
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

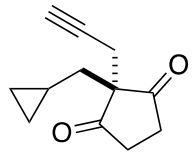

211.9
81.7
74.7
71.4
54.4
37.2
29.2
24.9
20.2
17.2
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


O
O

5

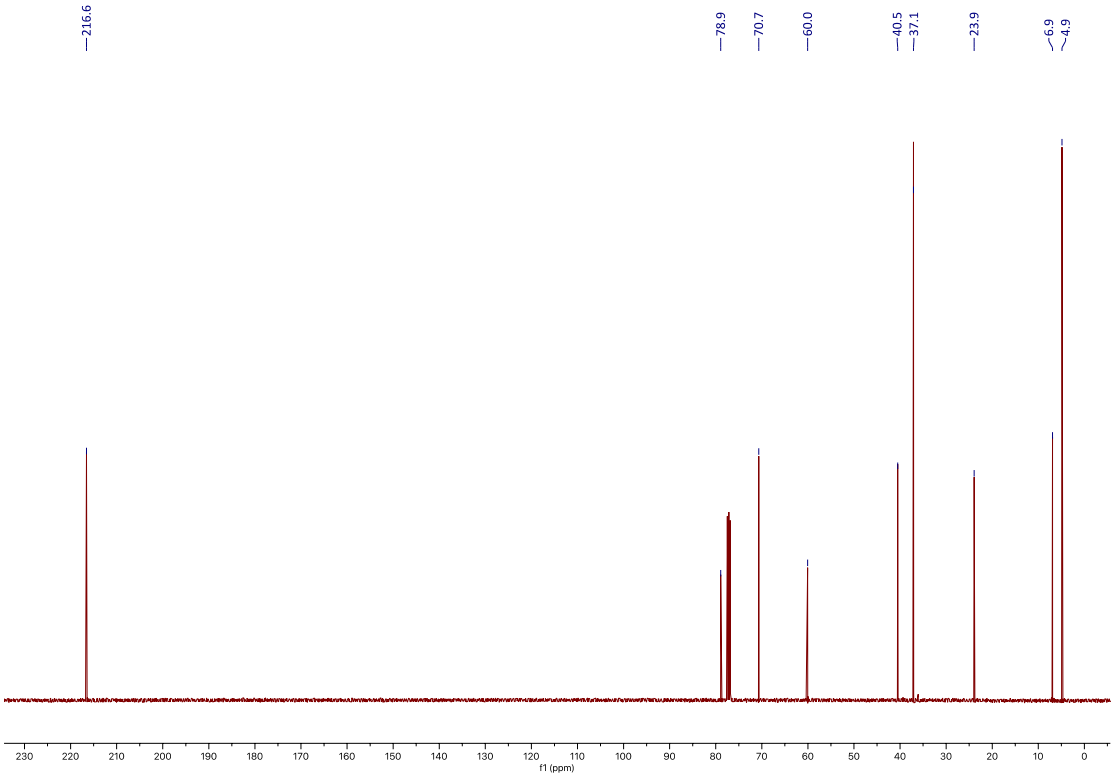
4.00
2.19
1.07
2.11
2.13
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

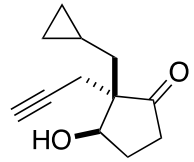

115.9
25.7
9.9
4.2
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O
O

7

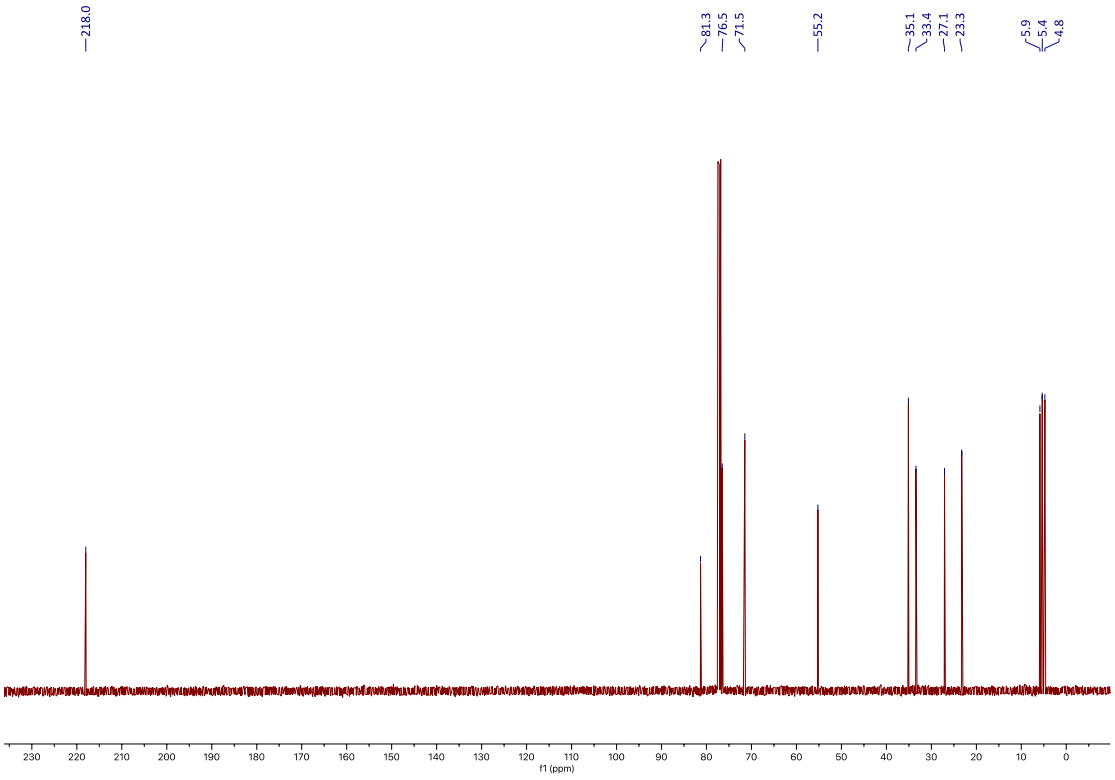
4.08
1.96
0.90
1.99
0.99
1.98
1.98
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

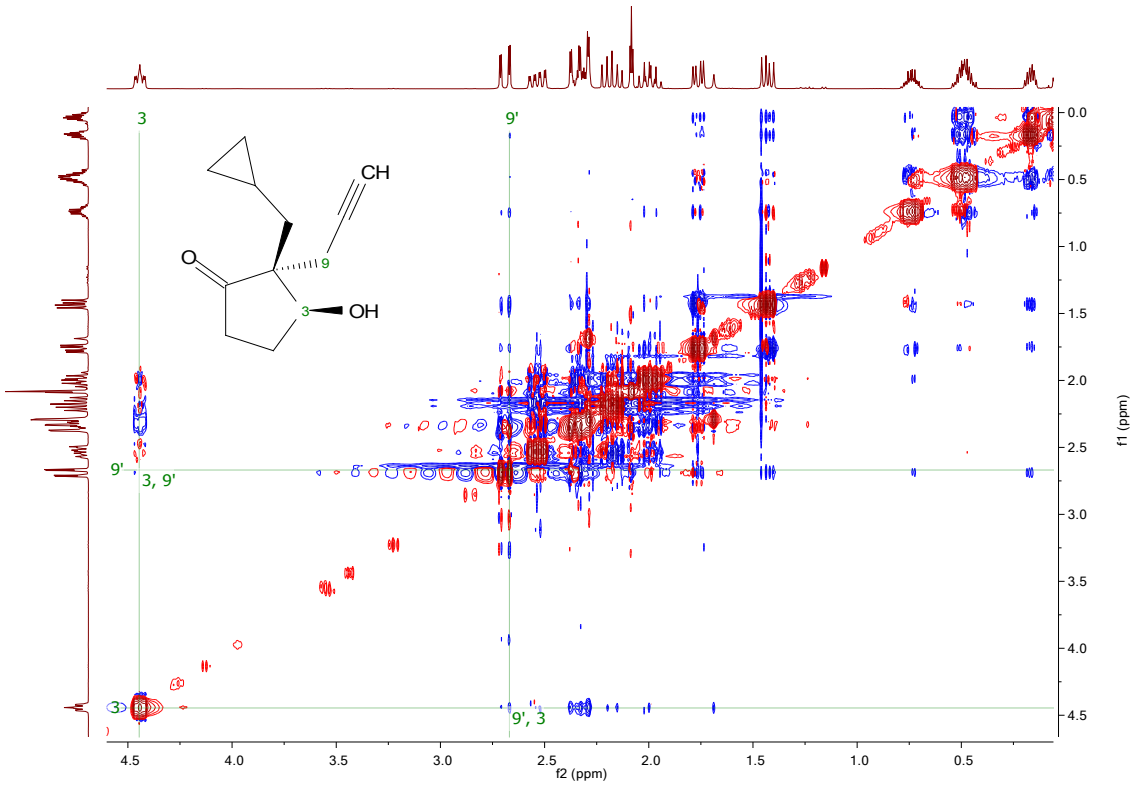

216.6
78.9
70.7
60.0
40.5
37.1
23.9
6.9
4.9
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

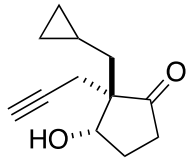

O
HO

anti-**9**

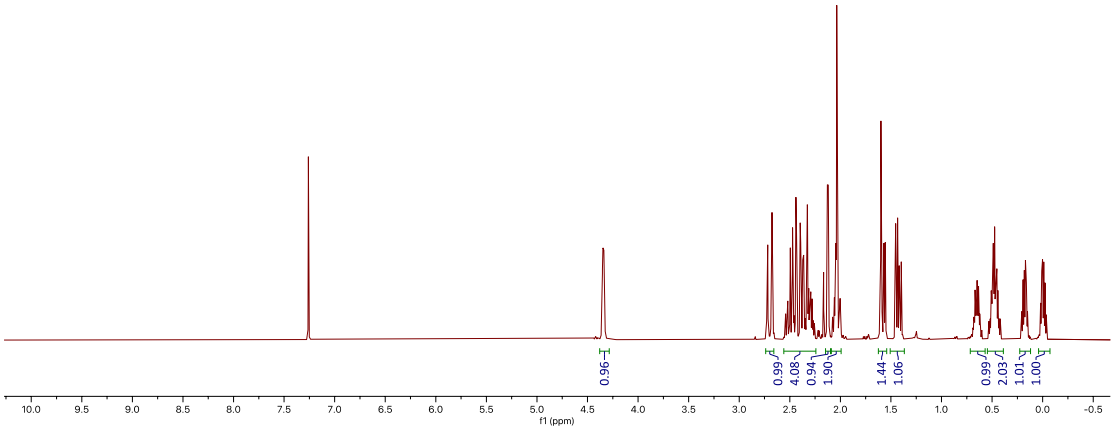
1.00
1.00
1.04
3.01
1.07
0.91
1.09
1.01
1.03
0.99
2.04
1.00
1.02
f1 (ppm)

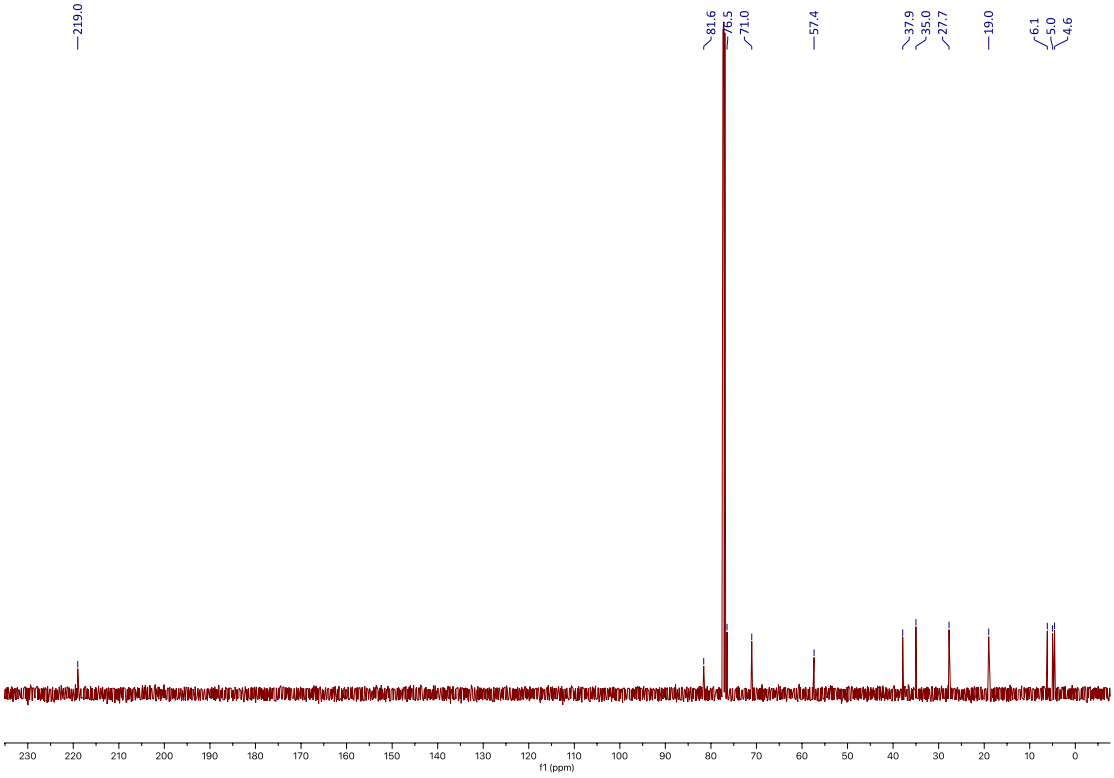

218.0
81.3
76.5
71.5
55.2
35.1
33.4
27.1
23.3
5.9
5.4
4.8
f1 (ppm)

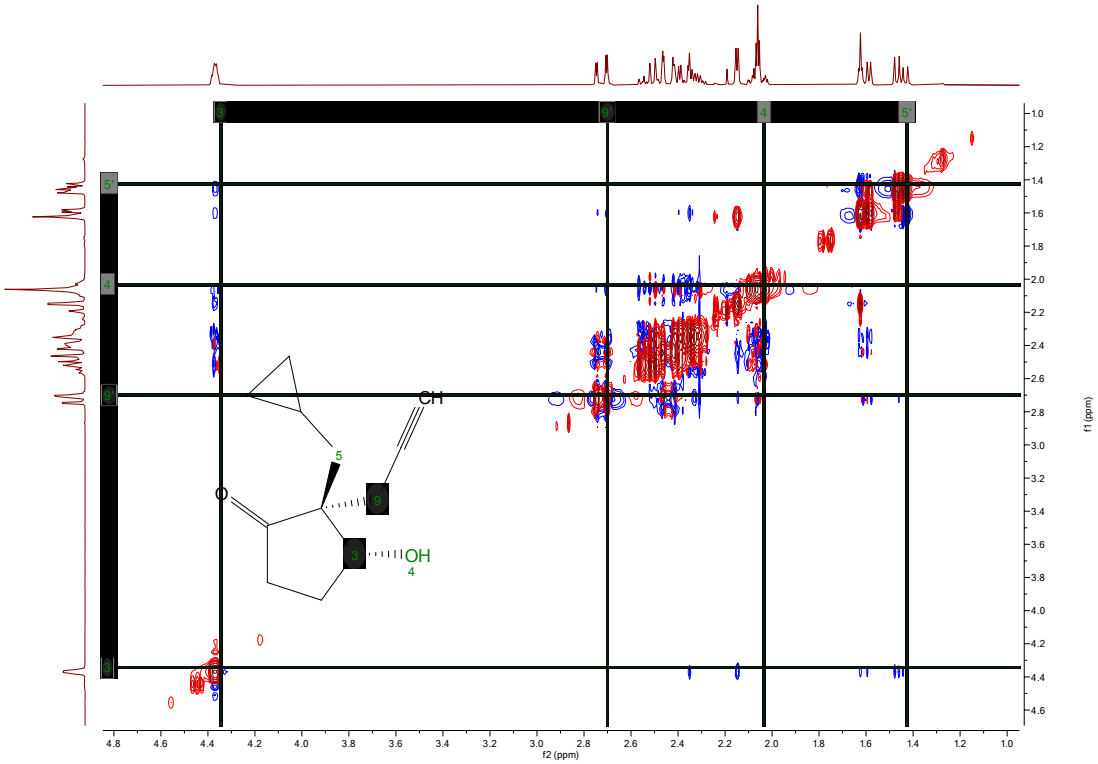

3
9'
CH
O
9
3
OH
9'
3, 9'
3
9', 3
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f2 (ppm)
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
f1 (ppm)

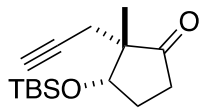

O
HO

syn-**9**


0.96
0.99
4.08
0.94
1.90
1.44
1.06
0.99
2.03
1.01
1.00
f1 (ppm)

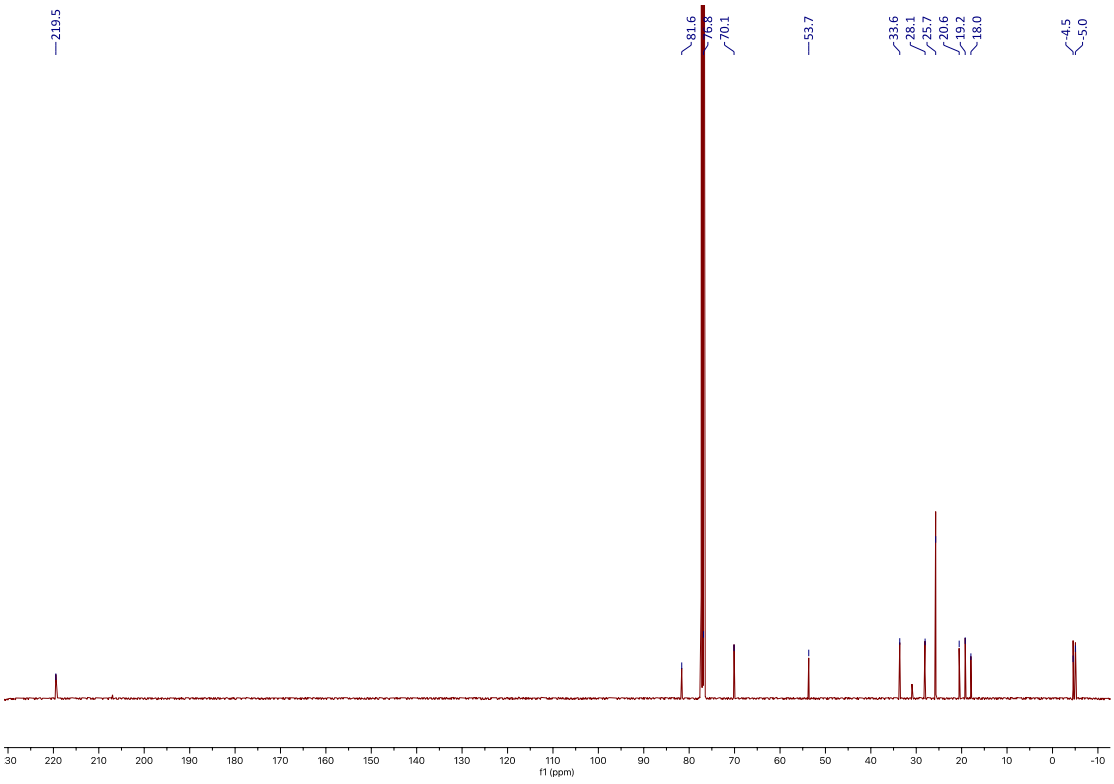

219.0
81.6
76.5
71.0
57.4
37.9
35.0
27.7
19.0
6.1
5.0
4.6
f1 (ppm)

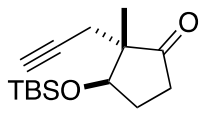

CH
5
O
3
OH
4
f2 (ppm)
f1 (ppm)


O
TBSO

syn-**S1**

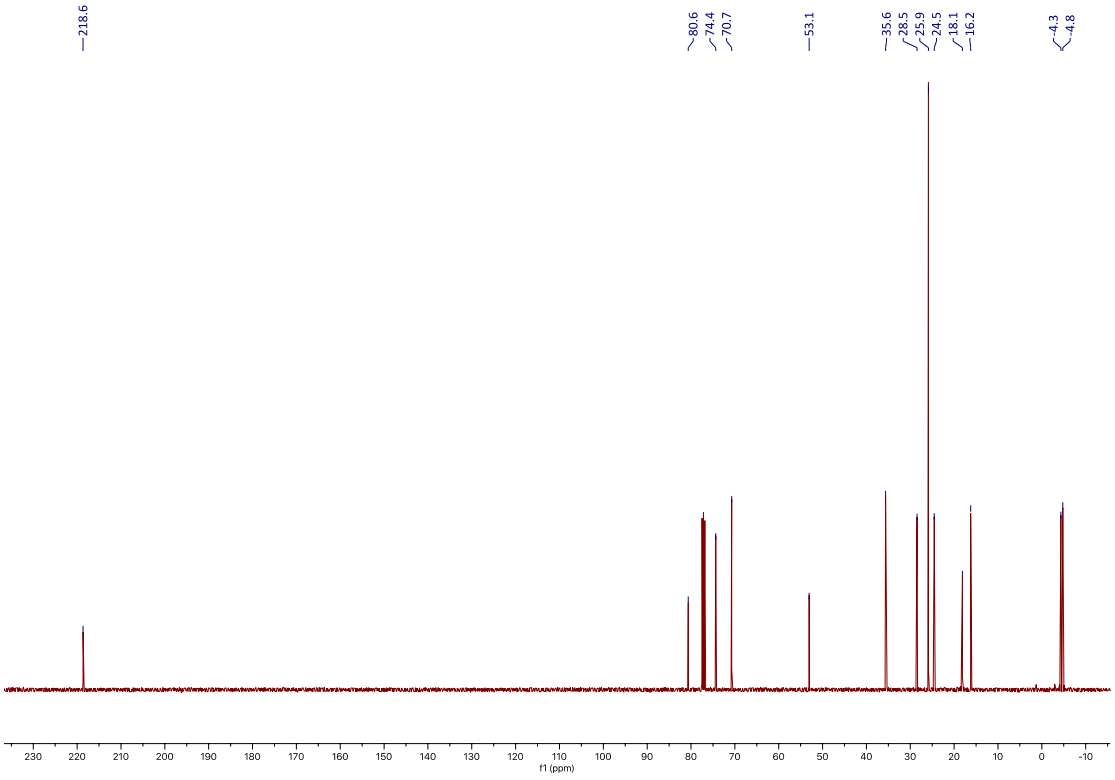
0.96
4.04
1.05
1.92
2.93
9.04
2.91
2.86
f1 (ppm)

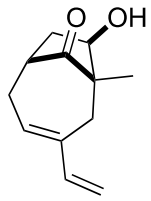

219.5
81.6
76.8
70.1
53.7
33.6
28.1
25.7
20.6
19.2
18.0
-4.5
-5.0
f1 (ppm)


O
TBSO

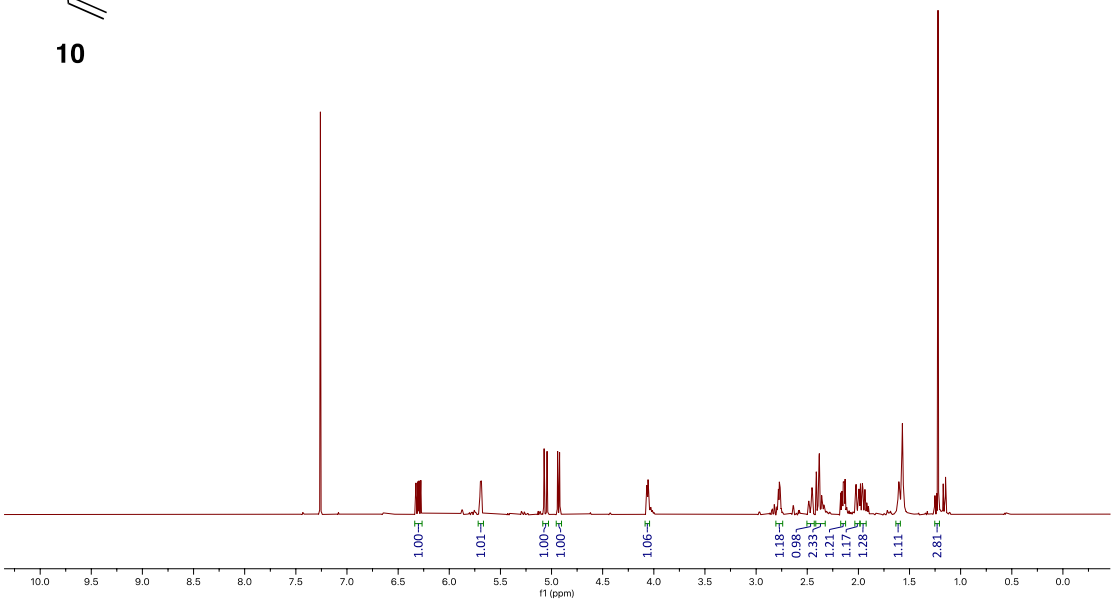
anti-**S1**

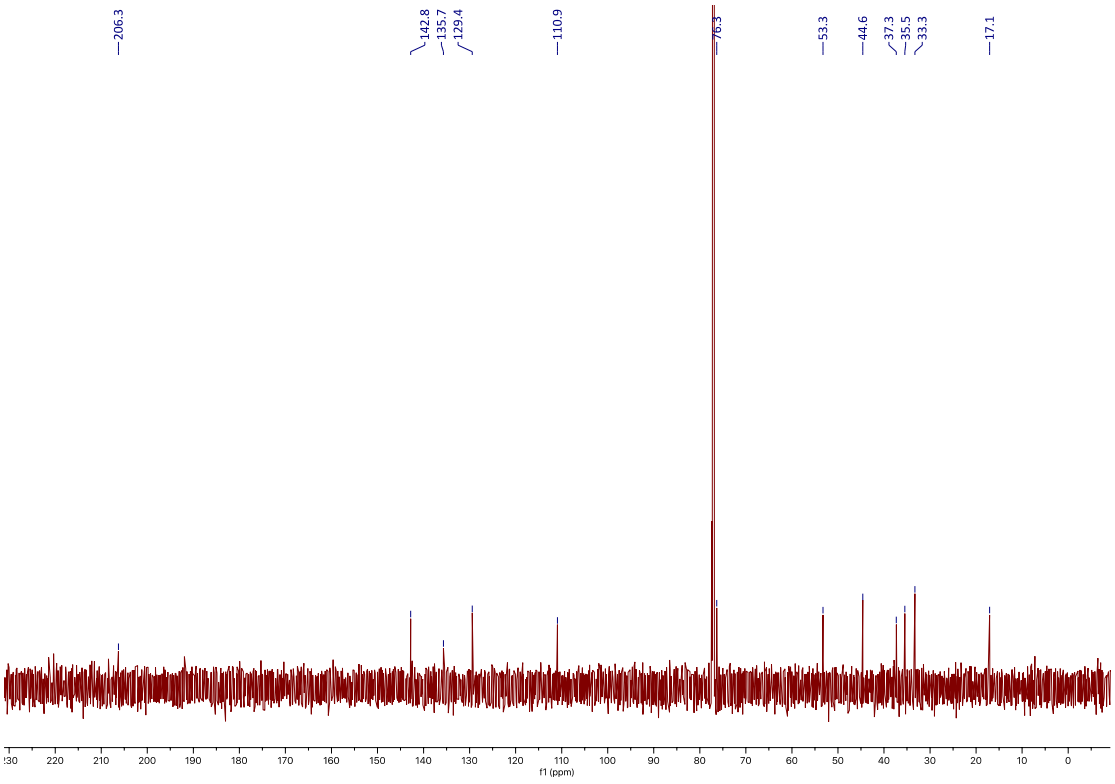
1.01
2.15
1.67
1.28
0.99
1.07
3.14
9.10
3.01
2.82
f1 (ppm)

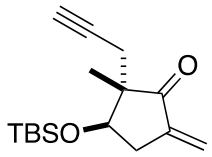

218.6
80.6
74.4
70.7
53.1
35.6
28.5
25.9
24.5
18.1
16.2
-4.3
-4.8
f1 (ppm)


O
OH

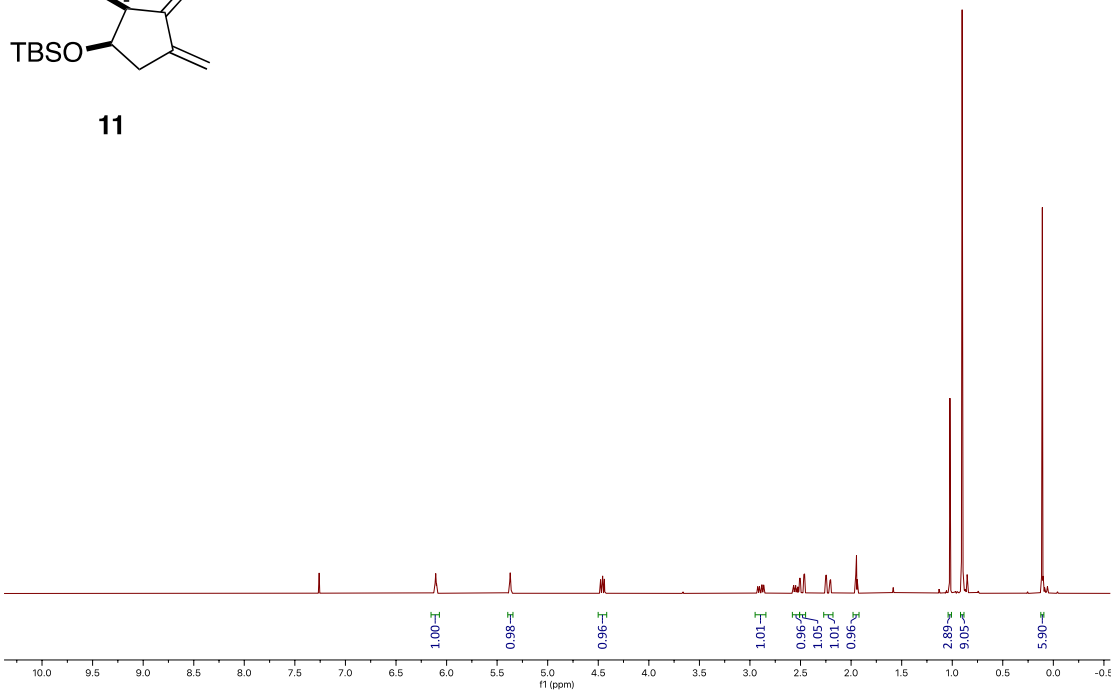
10

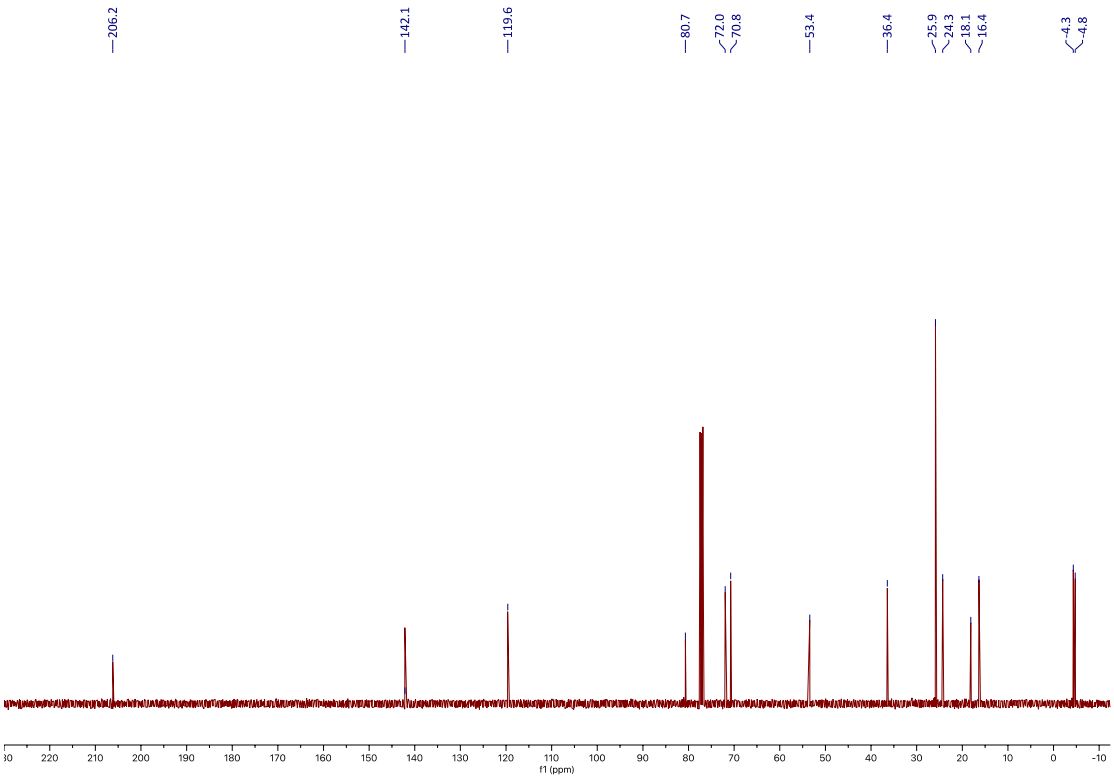

1.00
1.01
1.00
1.00
1.06
1.18
0.98
2.33
1.21
1.17
1.28
1.11
2.81
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

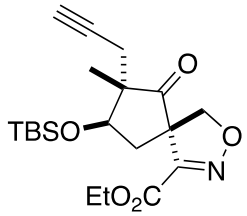

206.3
142.8
135.7
129.4
110.9
76.3
53.3
44.6
37.3
35.5
33.3
17.1
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O
TBSO

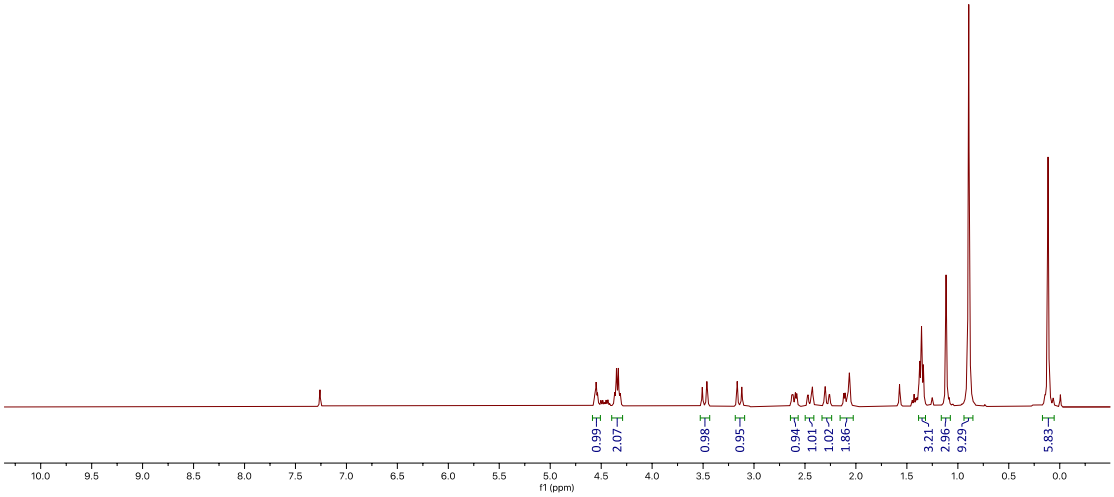
11

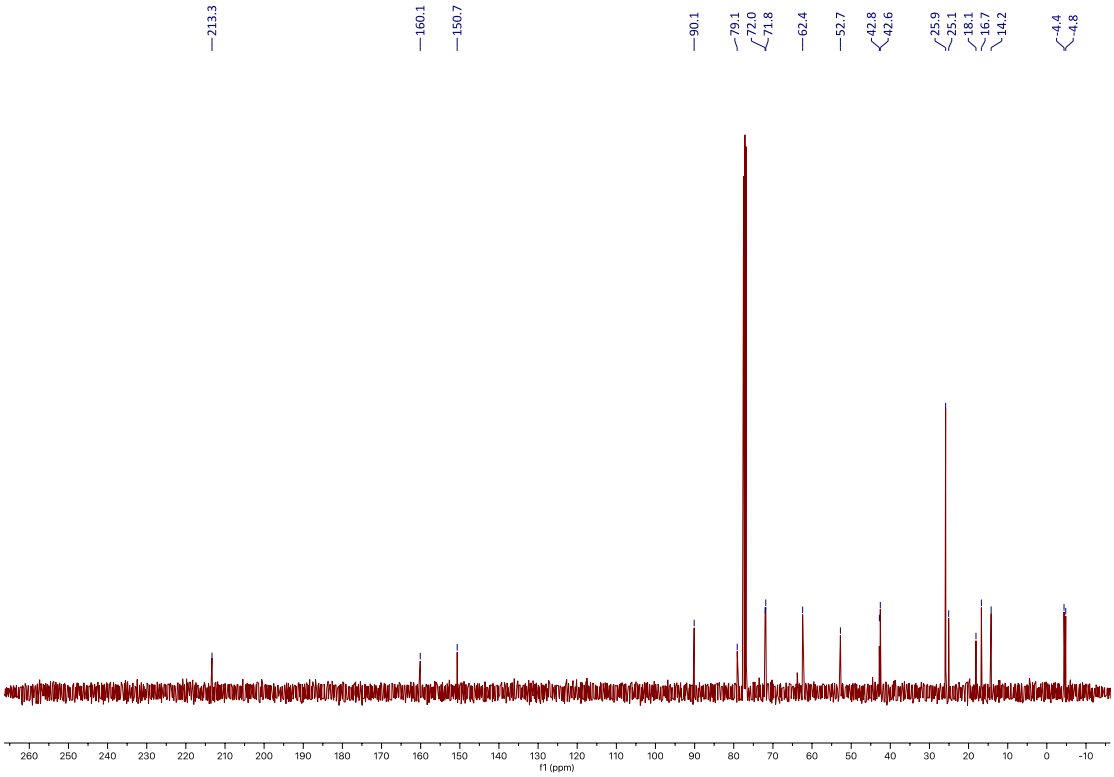

1.00
0.98
0.96
1.01
0.96
1.05
1.01
0.96
2.89
9.05
5.90
f1 (ppm)

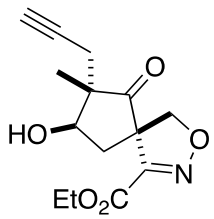

206.2
142.1
119.6
80.7
72.0
70.8
53.4
36.4
25.9
24.3
18.1
16.4
-4.3
-4.8
f1 (ppm)


O
TBSO
O
N
EtO2C

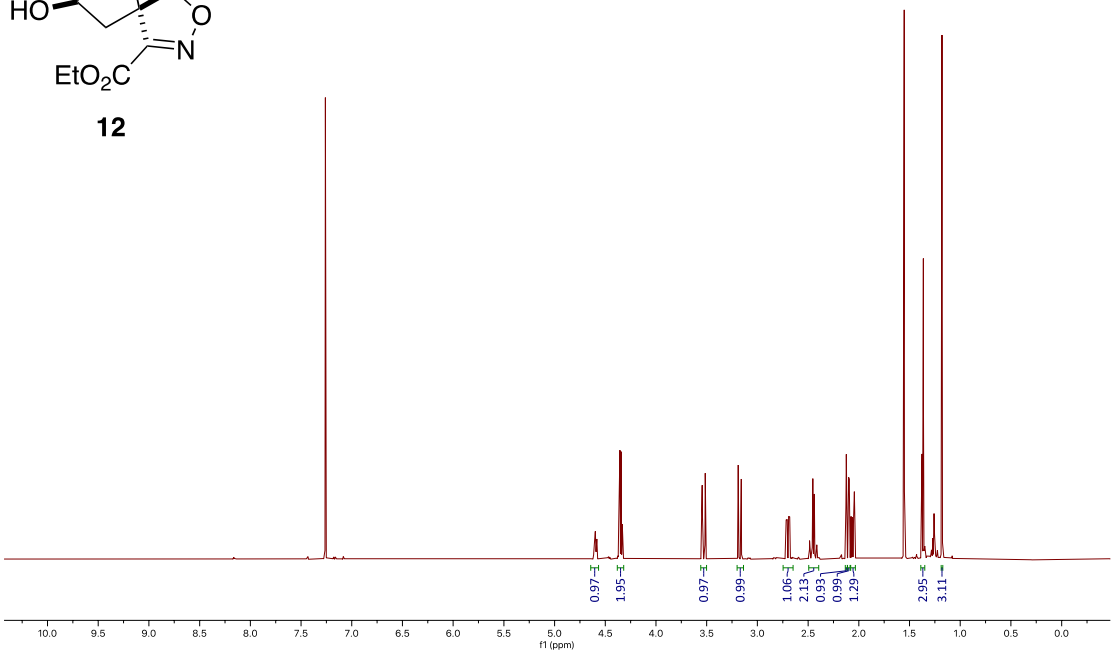
S2

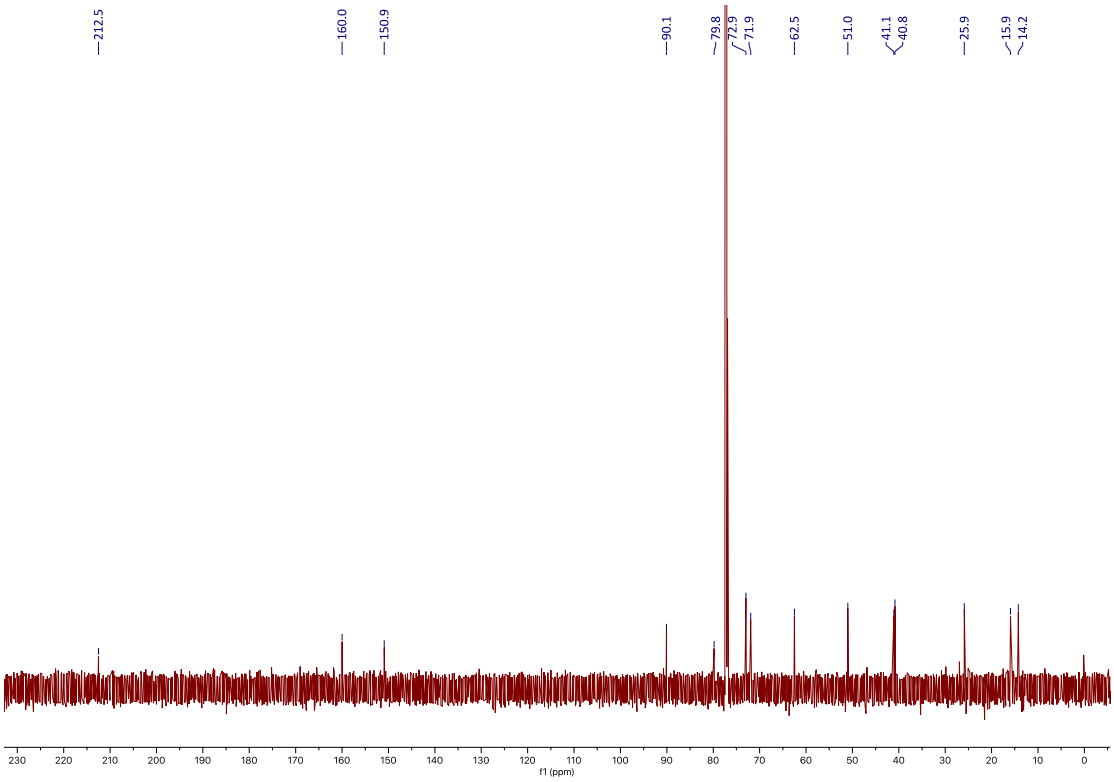

0.99
2.07
0.98
0.95
0.94
1.01
1.02
1.86
3.21
2.96
9.29
5.83
f1 (ppm)

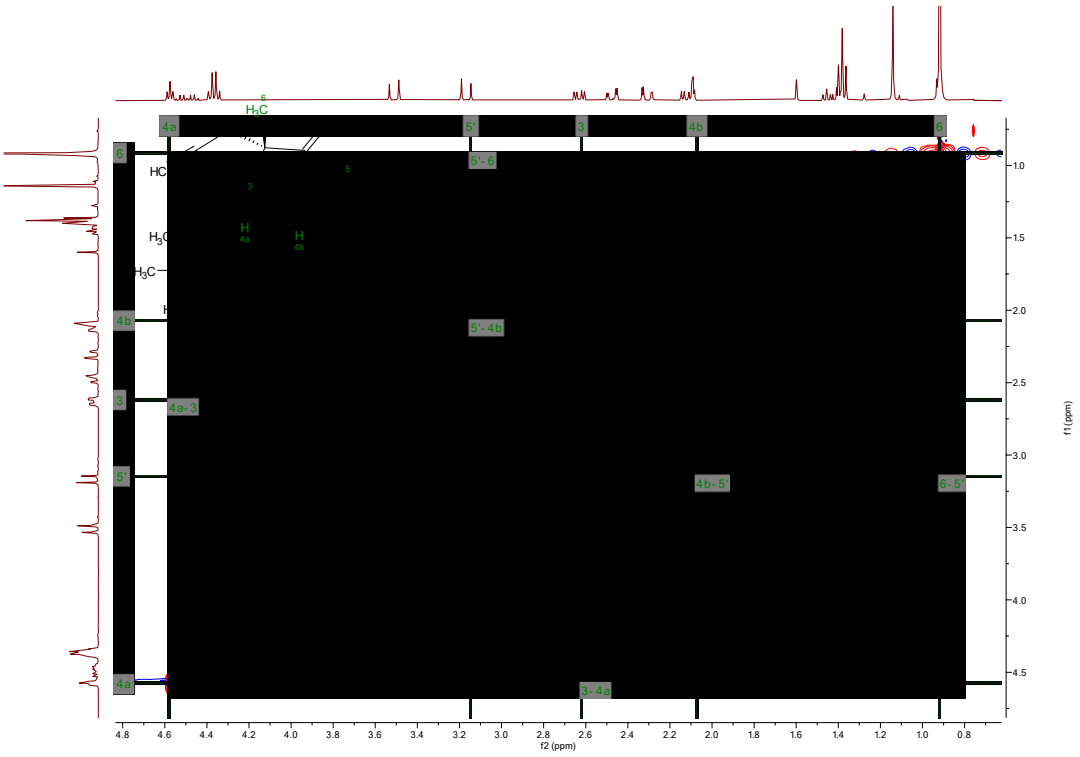

213.3
160.1
150.7
90.1
79.1
72.0
71.8
62.4
52.7
42.8
42.6
25.9
25.1
18.1
16.7
14.2
-4.4
-4.8
f1 (ppm)

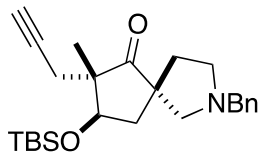

O
HO
O
N
EtO2C

12


0.97
1.95
0.97
0.99
1.06
2.13
0.93
0.99
1.29
2.95
3.11
f1 (ppm)

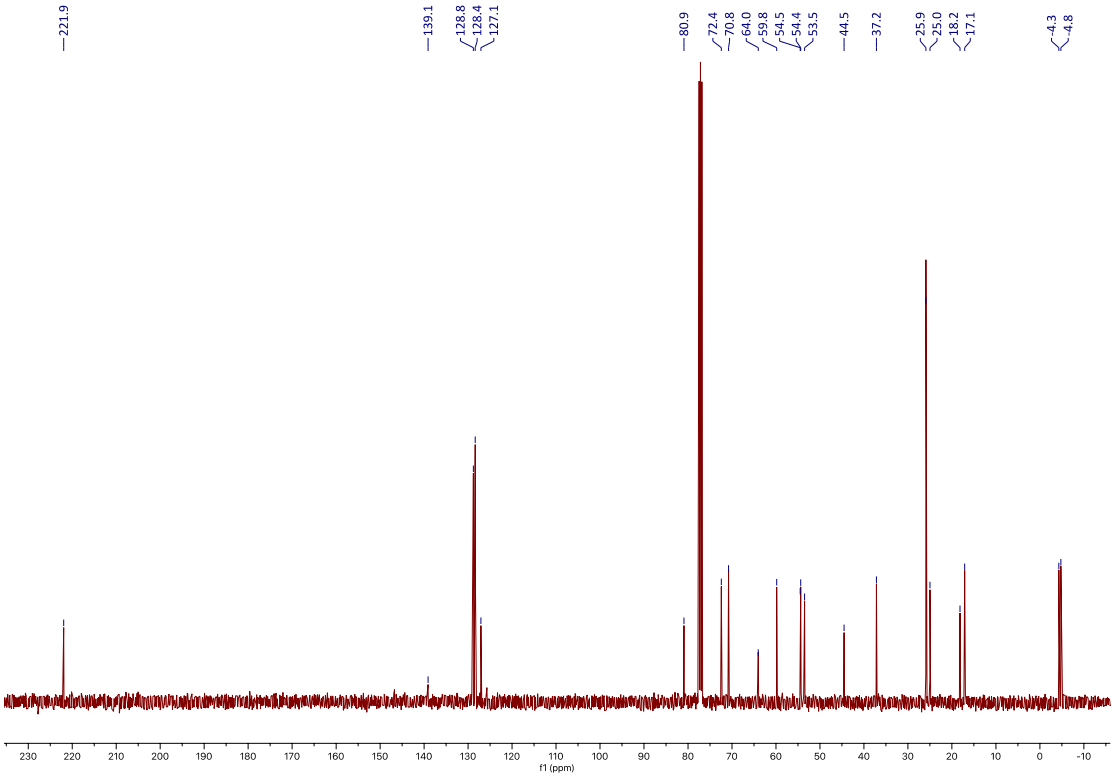

212.5
160.0
150.9
90.1
79.8
72.9
71.9
62.5
51.0
41.1
40.8
25.9
15.9
14.2
f1 (ppm)

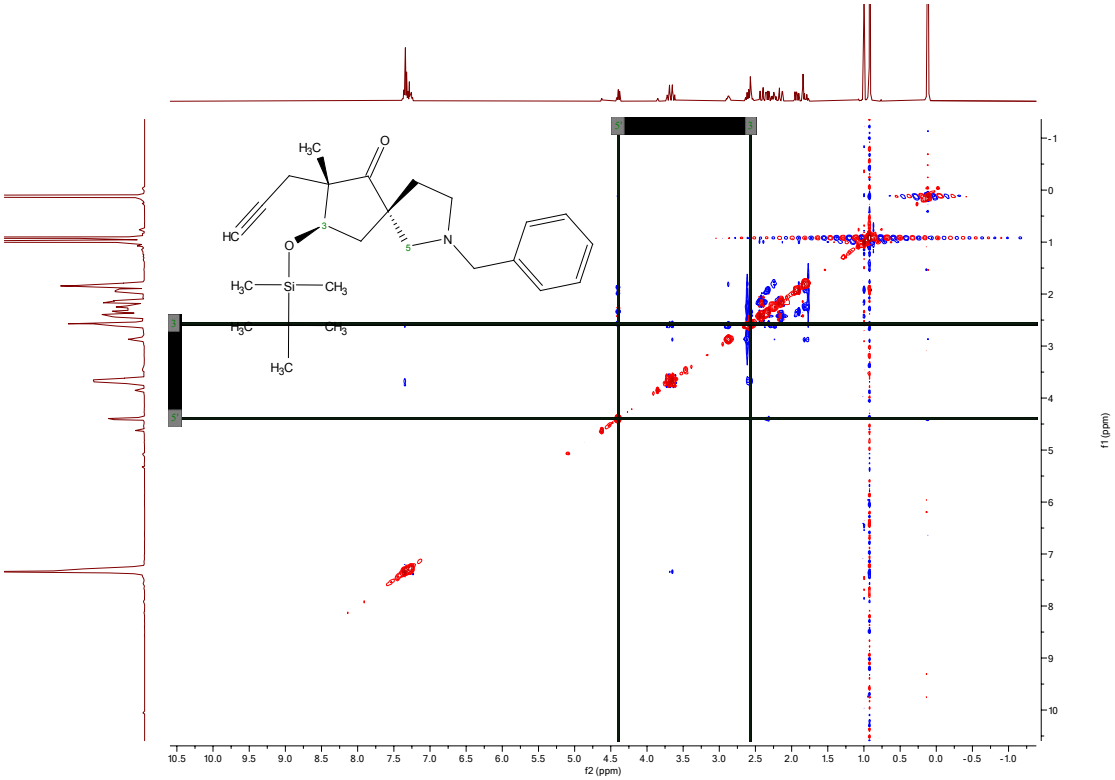

4a
5'
3
4b
6
5'-6
5'-4b
4a-3
4b-5'
6-5'
3-4a
4b
3
5'
4a
f2 (ppm)
f1 (ppm)

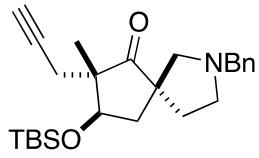

O
NBn
TBSO

S3a

5.98
1.01
2.00
1.06
2.97
1.11
1.07
1.11
1.11
1.02
1.95
2.86
9.16
3.12
3.01
f1 (ppm)

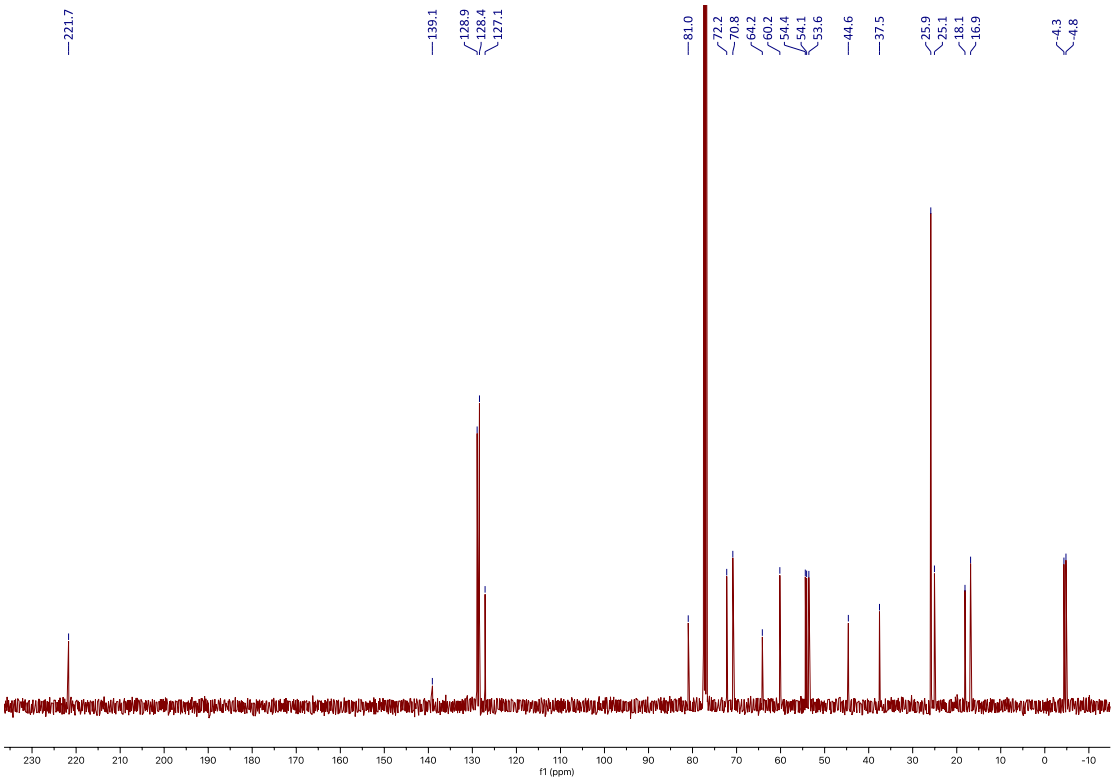

221.9
139.1
128.8
128.4
127.1
80.9
72.4
70.8
64.0
59.8
54.5
54.4
53.5
44.5
37.2
25.9
25.0
18.2
17.1
-4.3
-4.8
f1 (ppm)

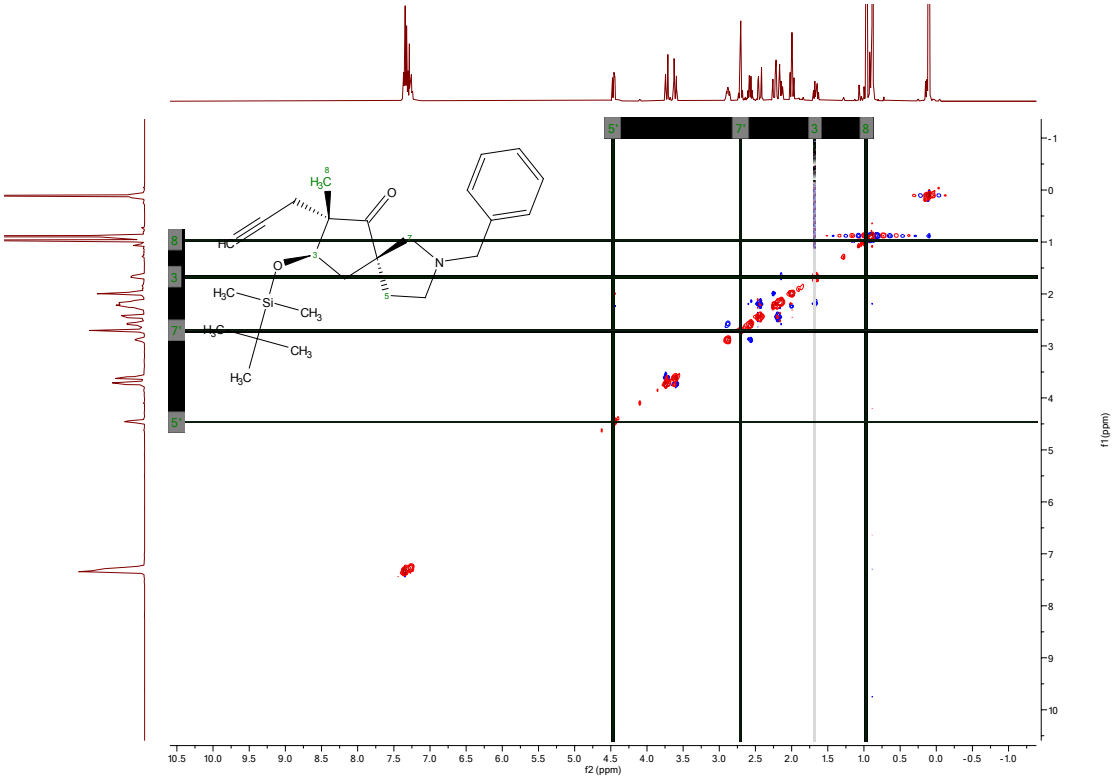

H3C
O
HC
O
Si
CH3
H3C
CH3
H3C
N
f2 (ppm)
f1 (ppm)

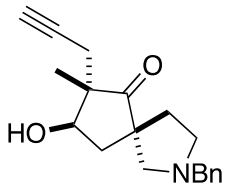

O
NBn
TBSO

S3b

6.76
0.99
1.07
1.06
1.13
2.06
1.19
1.10
3.34
2.14
1.10
3.00
9.09
2.96
3.15
f1 (ppm)

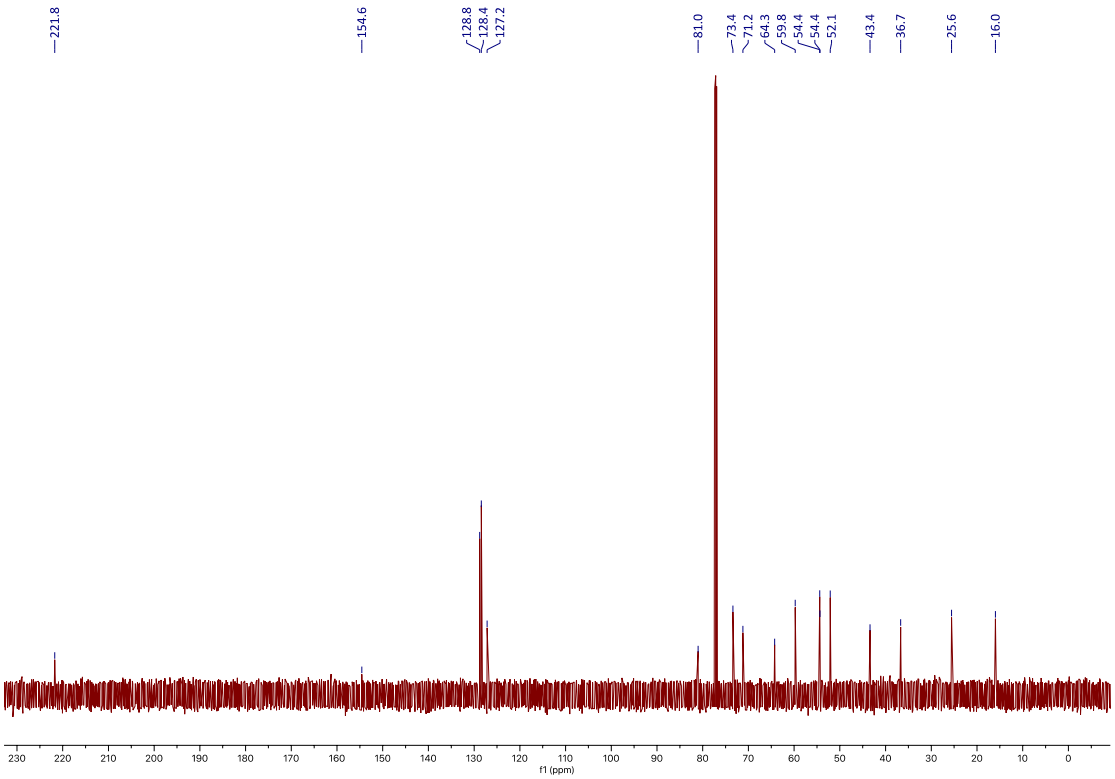

221.7
139.1
128.9
128.4
127.1
81.0
72.2
70.8
64.2
60.2
54.4
54.1
53.6
44.6
37.5
25.9
25.1
18.1
16.9
-4.3
-4.8
f1 (ppm)

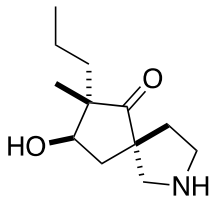

5'
7'
3
8
H3C
O
HC
O
N
H3C
Si
CH3
H3C
CH3
H3C
f2 (ppm)
f1 (ppm)


O
HO
NBn

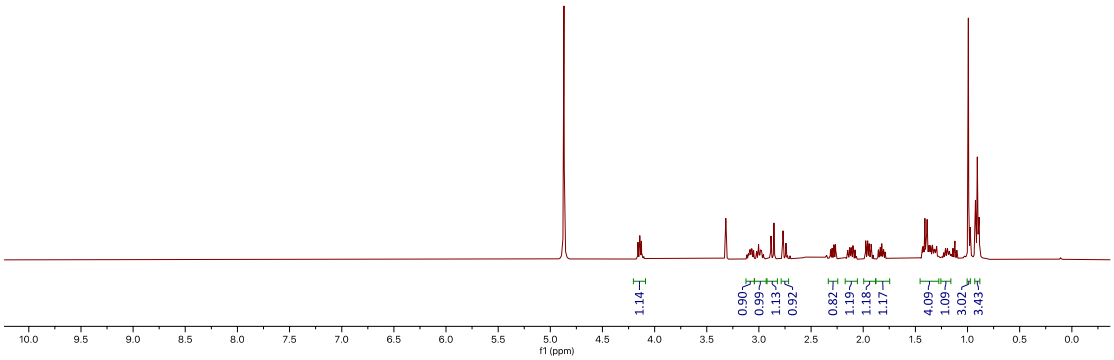
S4a

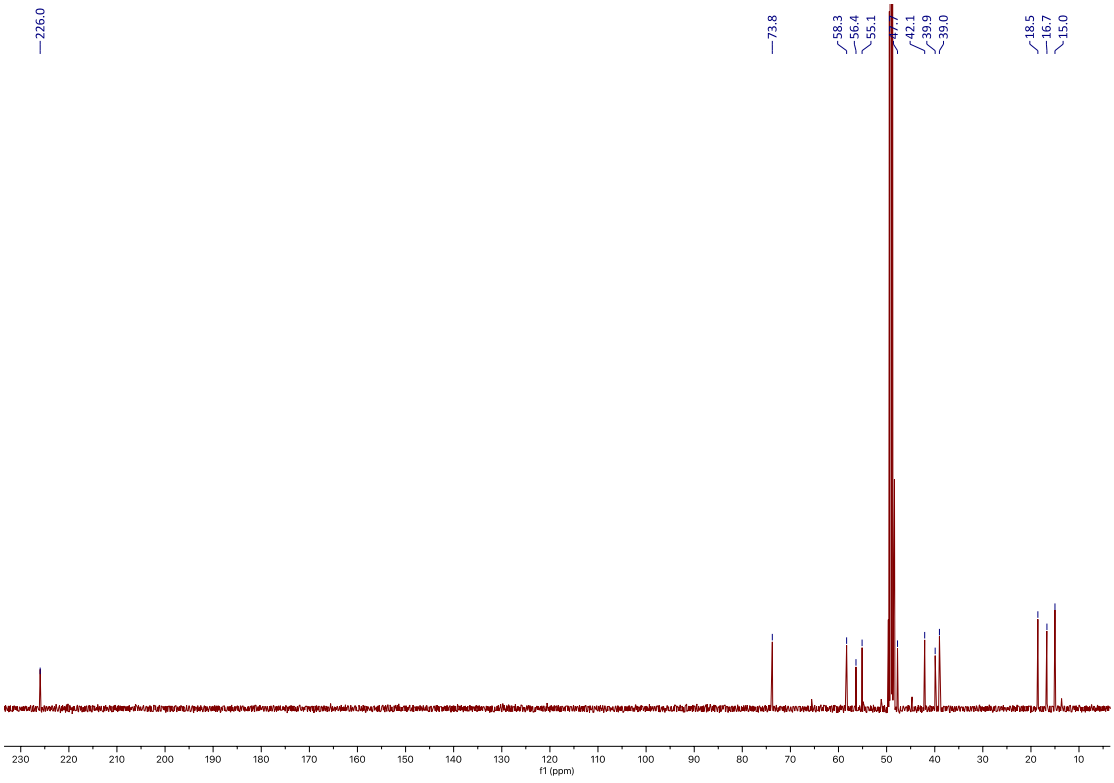
4.42
1.00
1.02
1.01
1.02
1.01
2.05
1.12
1.14
2.98
0.94
0.85
1.02
1.04
3.21
f1 (ppm)

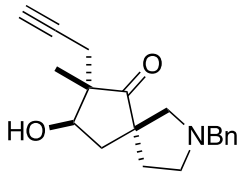

221.8
154.6
128.8
128.4
127.2
81.0
73.4
71.2
64.3
59.8
54.4
54.4
52.1
43.4
36.7
25.6
16.0
f1 (ppm)


O
HO
NH

13a

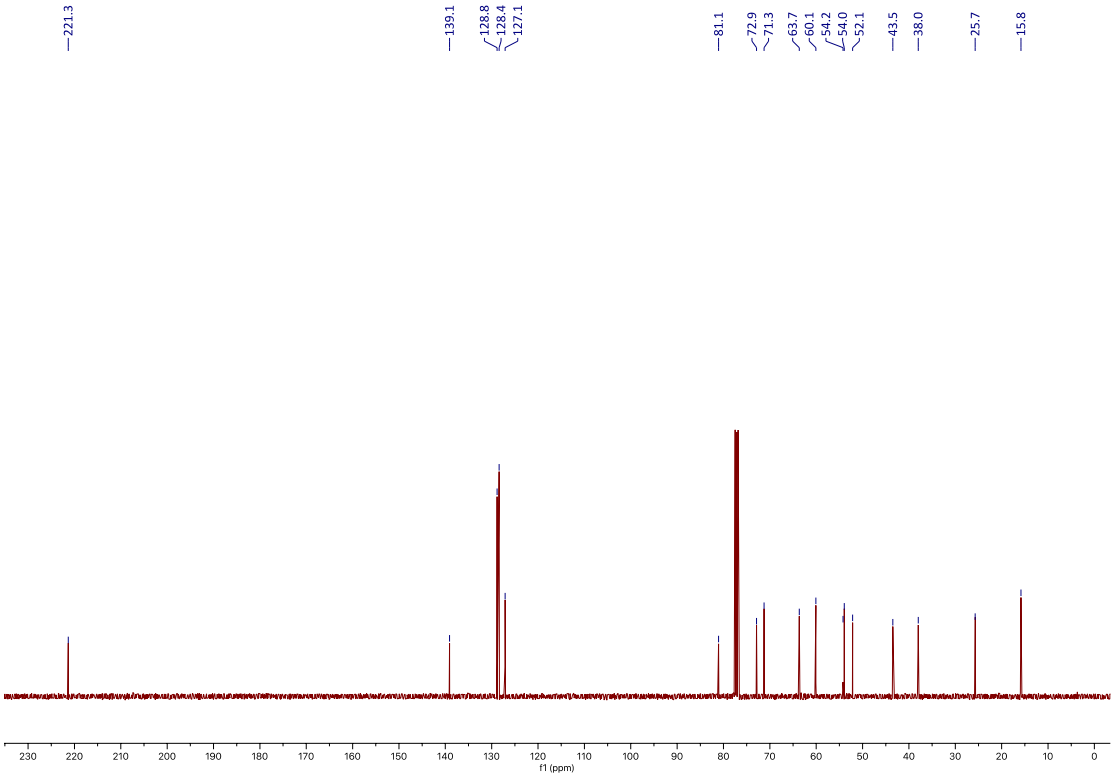

1.14
0.90
0.99
1.13
0.92
0.82
1.19
1.18
1.17
4.09
1.09
3.02
3.43
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

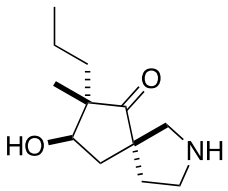

226.0
73.8
58.3
56.4
55.1
47.7
42.1
39.9
39.0
18.5
16.7
15.0
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


O
HO
NBn

S4b

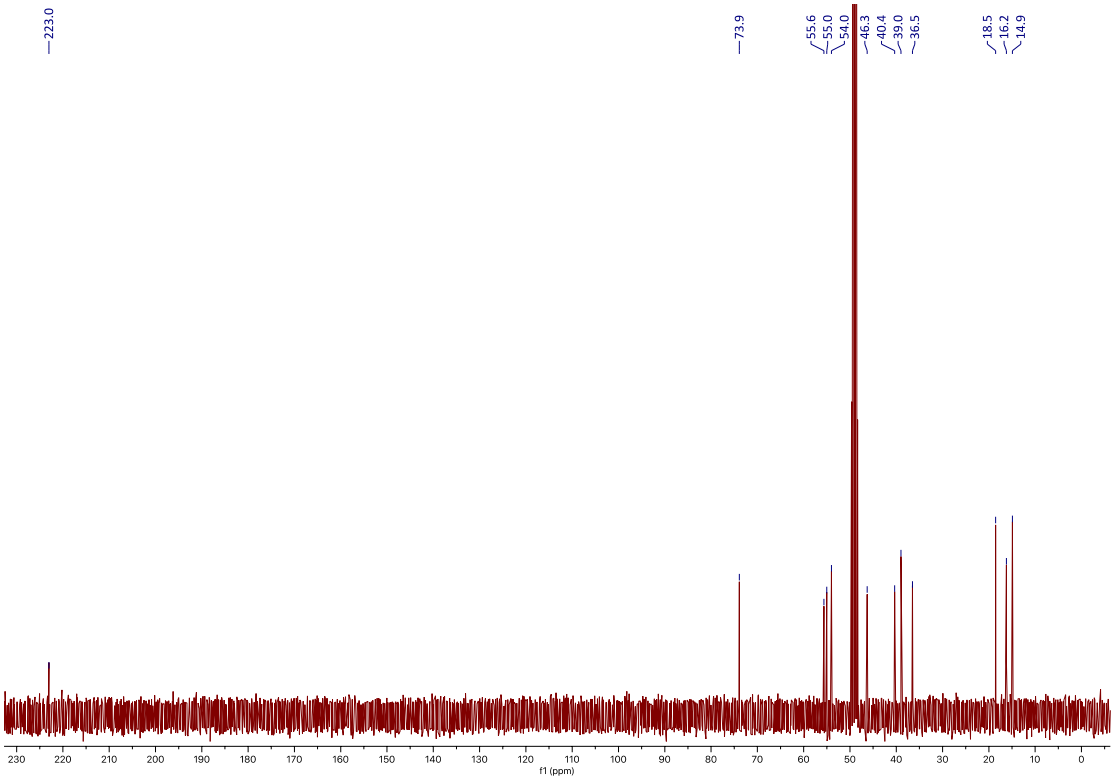
4.11
1.18
1.01
2.12
1.07
1.01
1.02
1.10
2.98
1.29
3.18
1.01
3.00
f1 (ppm)

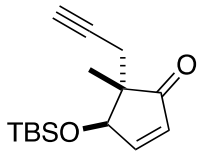

221.3
139.1
128.8
128.4
127.1
81.1
72.9
71.3
63.7
60.1
54.2
54.0
52.1
43.5
38.0
25.7
15.8
f1 (ppm)


O
HO
NH

13b

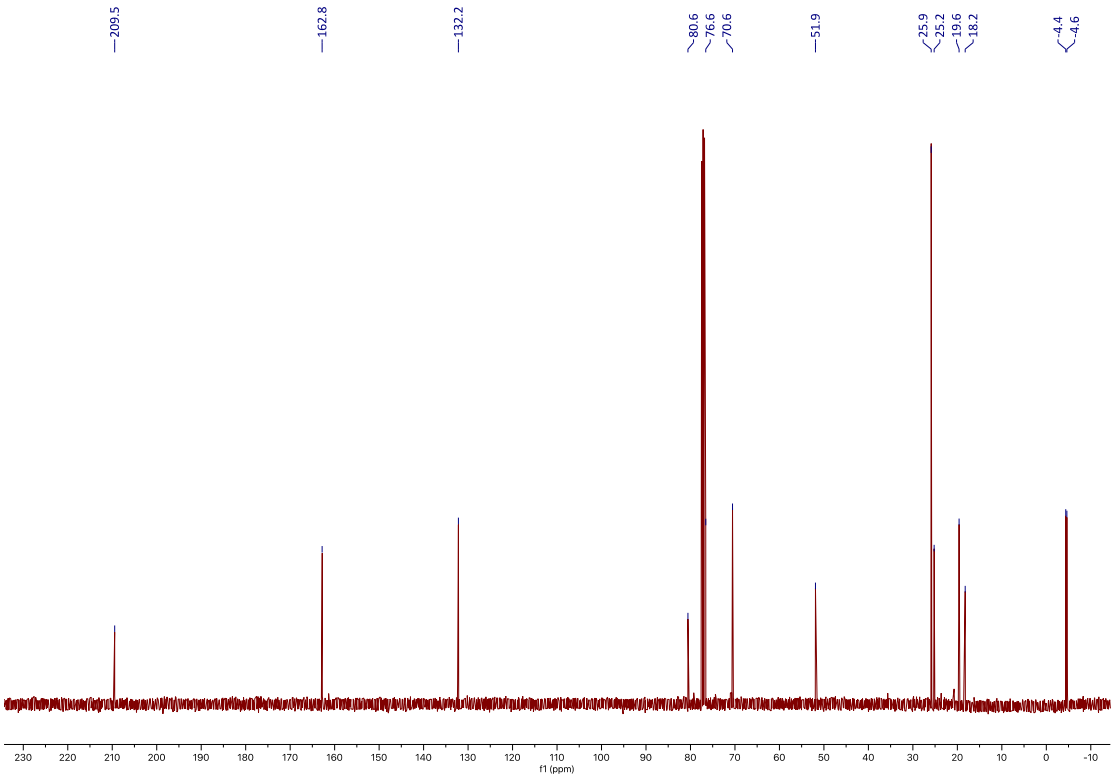
1.00
3.04
1.06
1.01
3.09
2.02
2.27
2.94
3.07
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

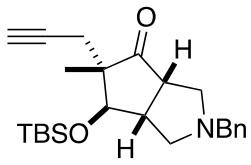

223.0
73.9
55.6
55.0
54.0
46.3
40.4
39.0
36.5
18.5
16.2
14.9
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O
TBSO

14

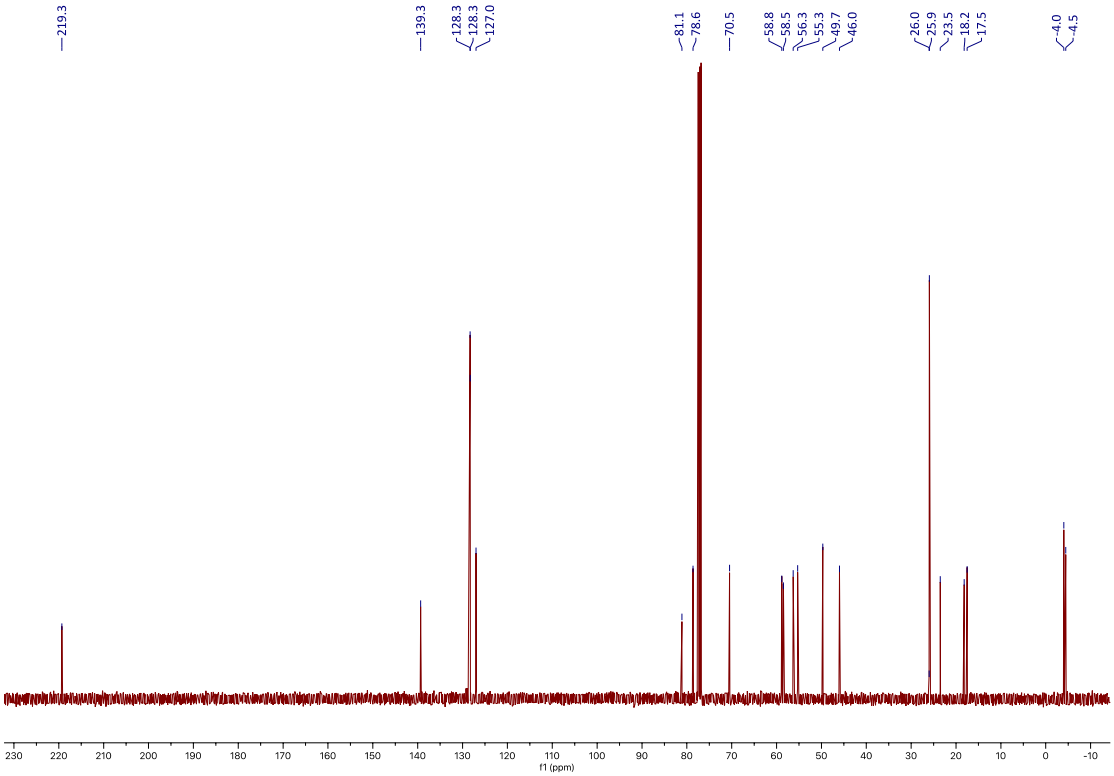
0.99
0.96
0.90
1.01
1.07
0.83
2.92
9.28
2.82
3.17
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

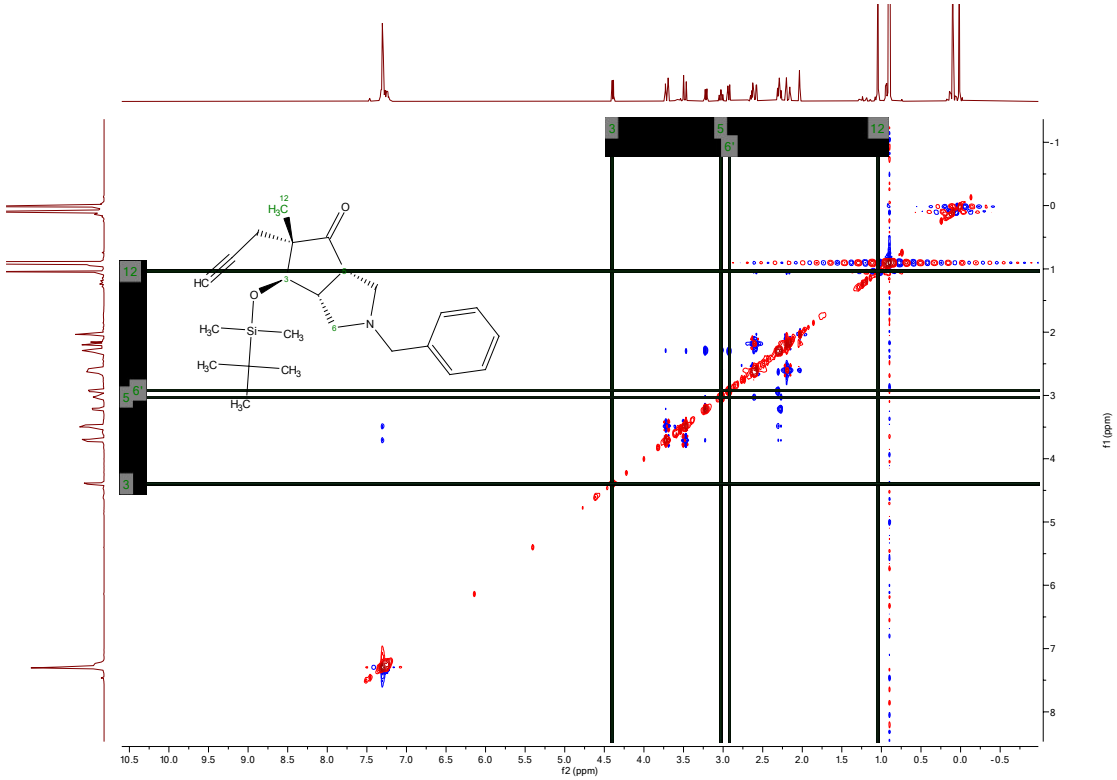

209.5
162.8
132.2
80.6
76.6
70.6
51.9
25.9
25.2
19.6
18.2
-4.4
-4.6
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

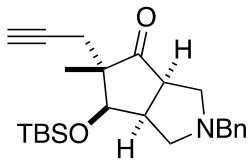

O
H
TBSO
NBn
H

S5a

6.62
1.00
1.03
1.08
1.02
1.09
1.05
2.19
2.18
1.35
0.96
3.26
9.03
3.15
3.04
f1 (ppm)

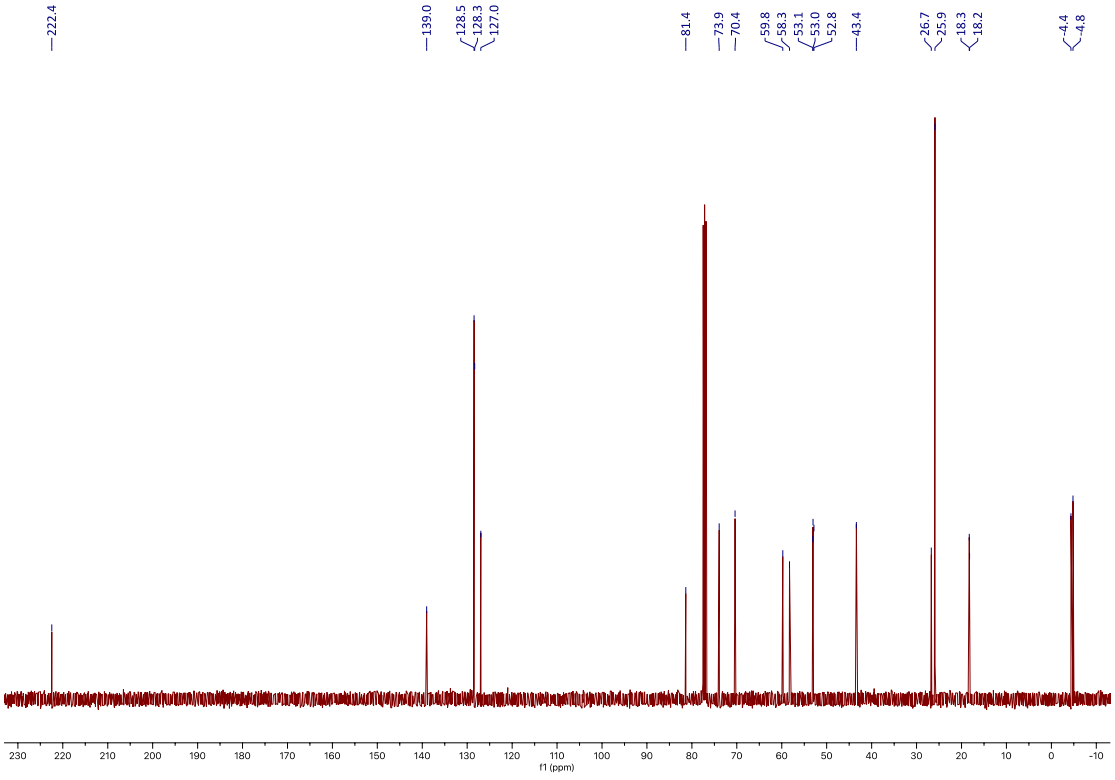

219.3
139.3
128.3
128.3
127.0
81.1
78.6
70.5
58.8
58.5
56.3
55.3
49.7
46.0
26.0
25.9
23.5
18.2
17.5
-4.0
-4.5
f1 (ppm)

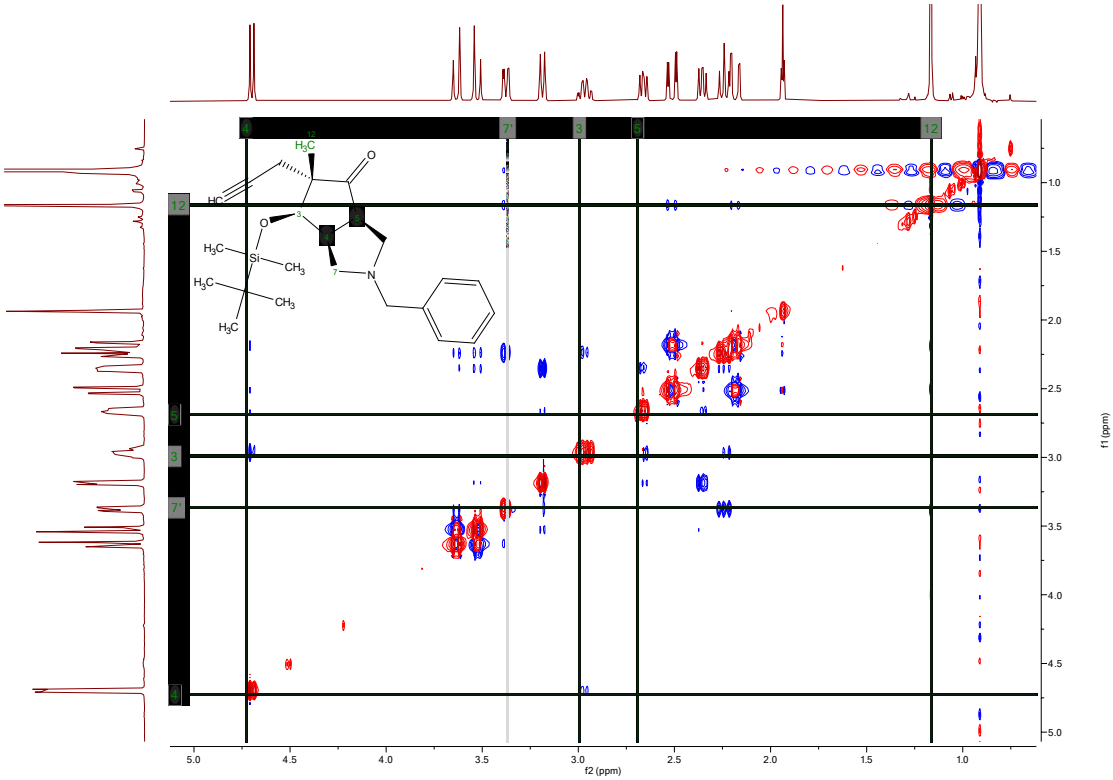

12
3
5
6'
f2 (ppm)
f1 (ppm)

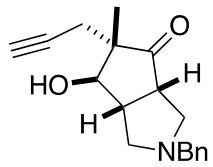

O
H
TBSO
NBn
H

S5b

5.26
0.96
1.01
1.03
1.02
0.98
1.01
1.02
1.06
1.02
2.06
0.92
2.92
9.12
3.05
3.00
f1 (ppm)

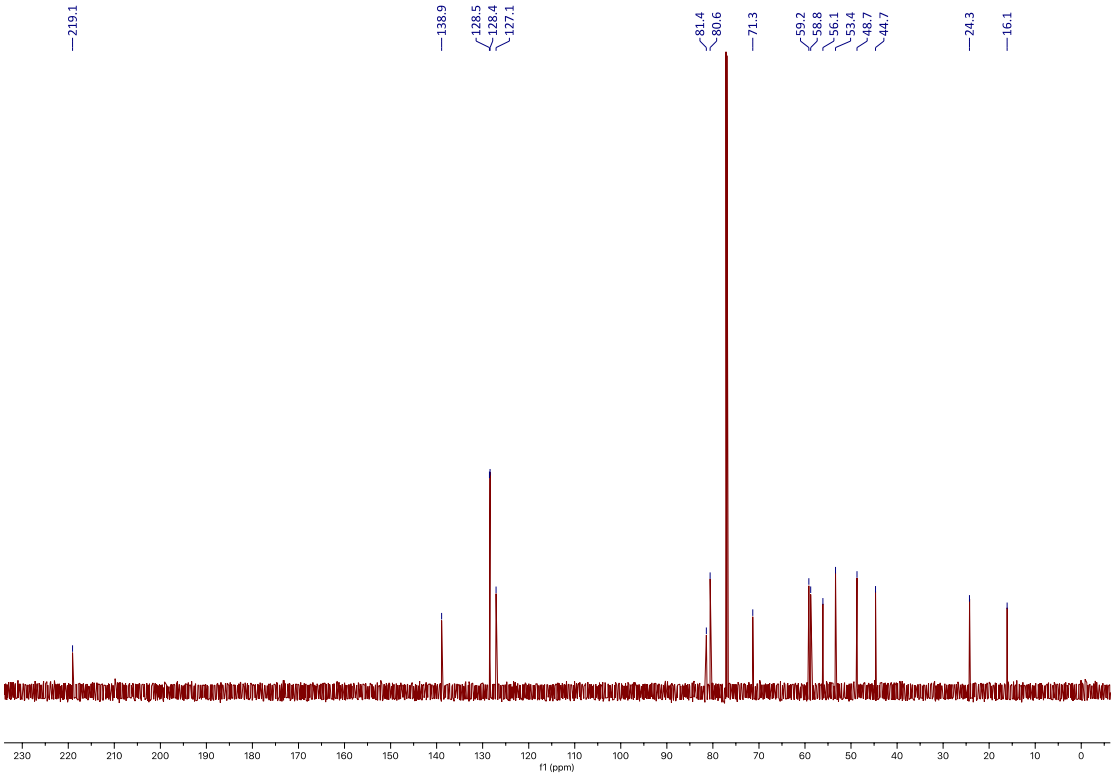

222.4
139.0
128.5
128.3
127.0
81.4
73.9
70.4
59.8
58.3
53.1
53.0
52.8
43.4
26.7
25.9
18.3
18.2
-4.4
-4.8
f1 (ppm)

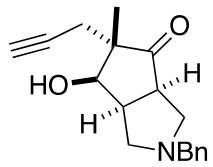

4
12
7'
3
5
12
5
3
7'
4
f2 (ppm)
f1 (ppm)


O
HO
H
H
NBn

15a

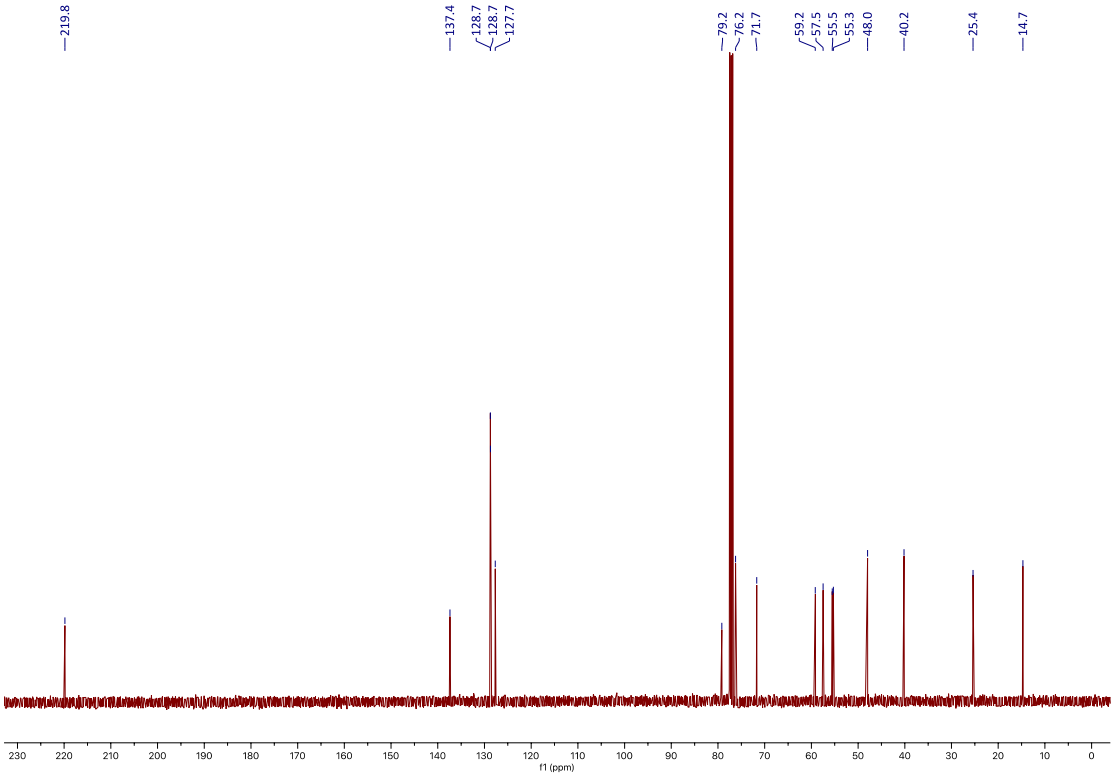
5.36
0.97
0.98
1.00
1.15
1.93
0.95
1.01
1.12
1.10
1.09
0.99
2.90
f1 (ppm)

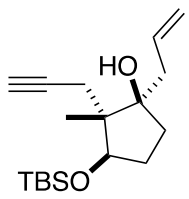

219.1
138.9
128.5
128.4
127.1
81.4
80.6
71.3
59.2
58.8
56.1
53.4
48.7
44.7
24.3
16.1
f1 (ppm)


O
HO
H
H
NBn

15b

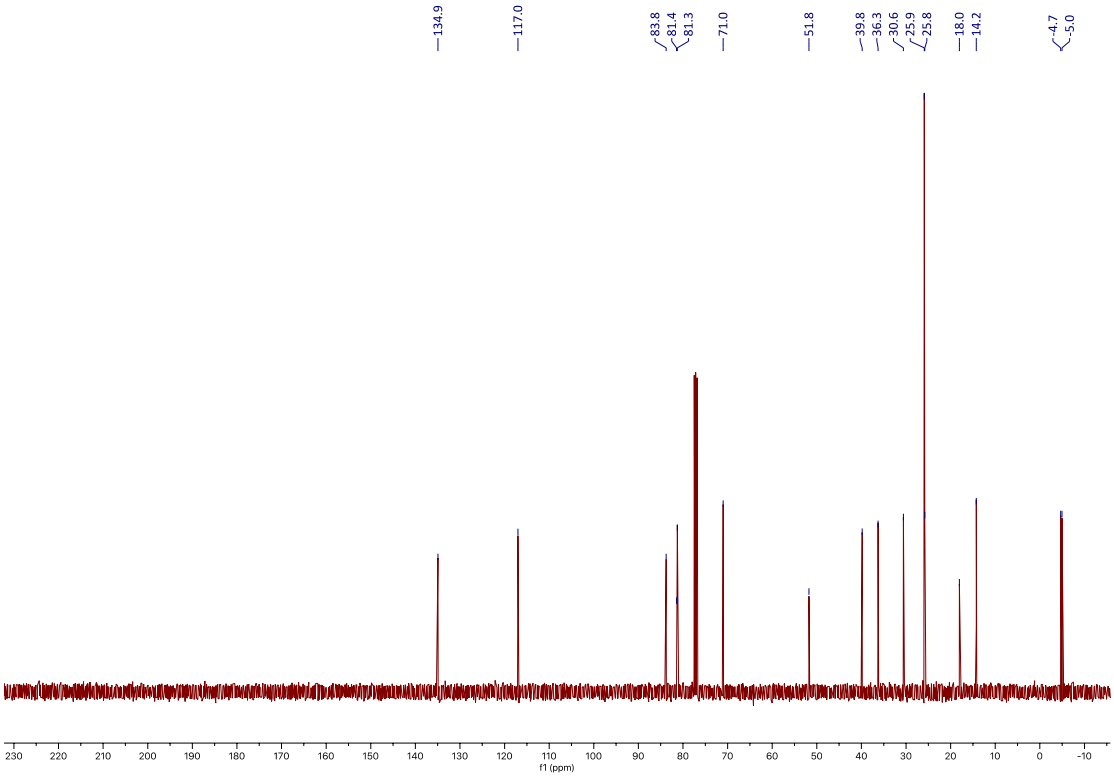
5.17
0.84
1.00
1.02
1.03
1.03
1.00
1.03
1.02
2.03
1.97
0.95
3.02
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
f1 (ppm)

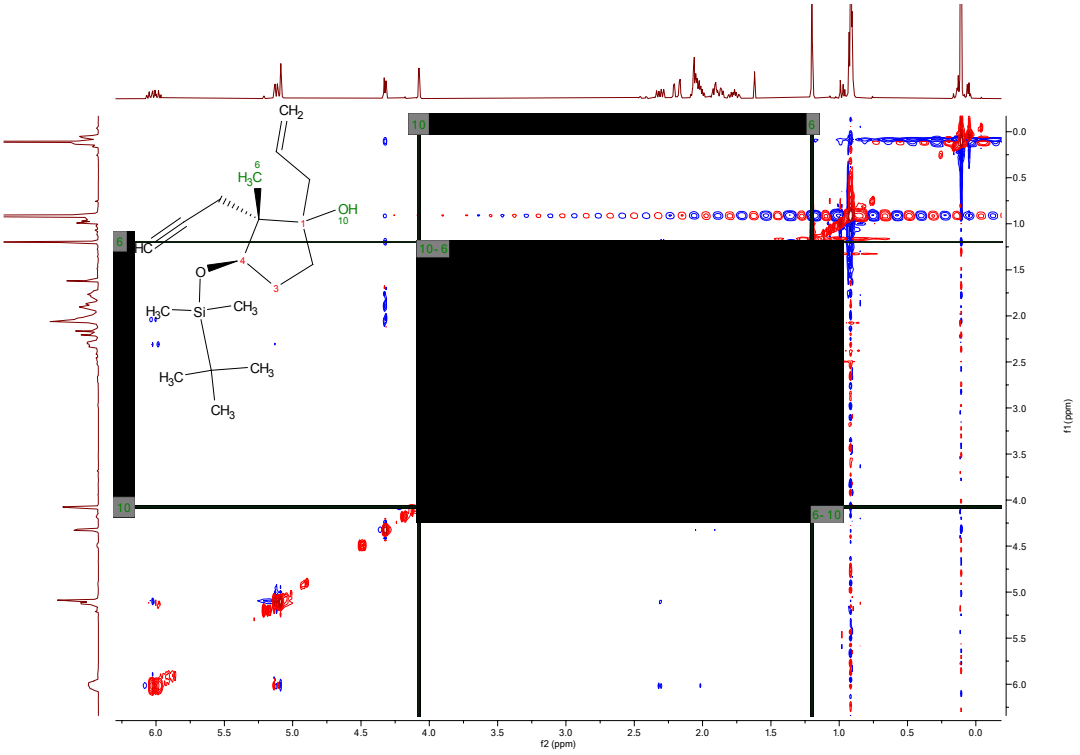

219.8
137.4
128.7
128.7
127.7
79.2
76.2
71.7
59.2
57.5
55.5
55.3
48.0
40.2
25.4
14.7
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

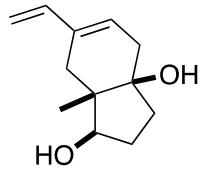

HO
TBSO

16

0.96
1.01
0.90
0.92
0.91
1.01
1.18
3.96
2.10
1.02
2.83
9.17
5.82
f1 (ppm)

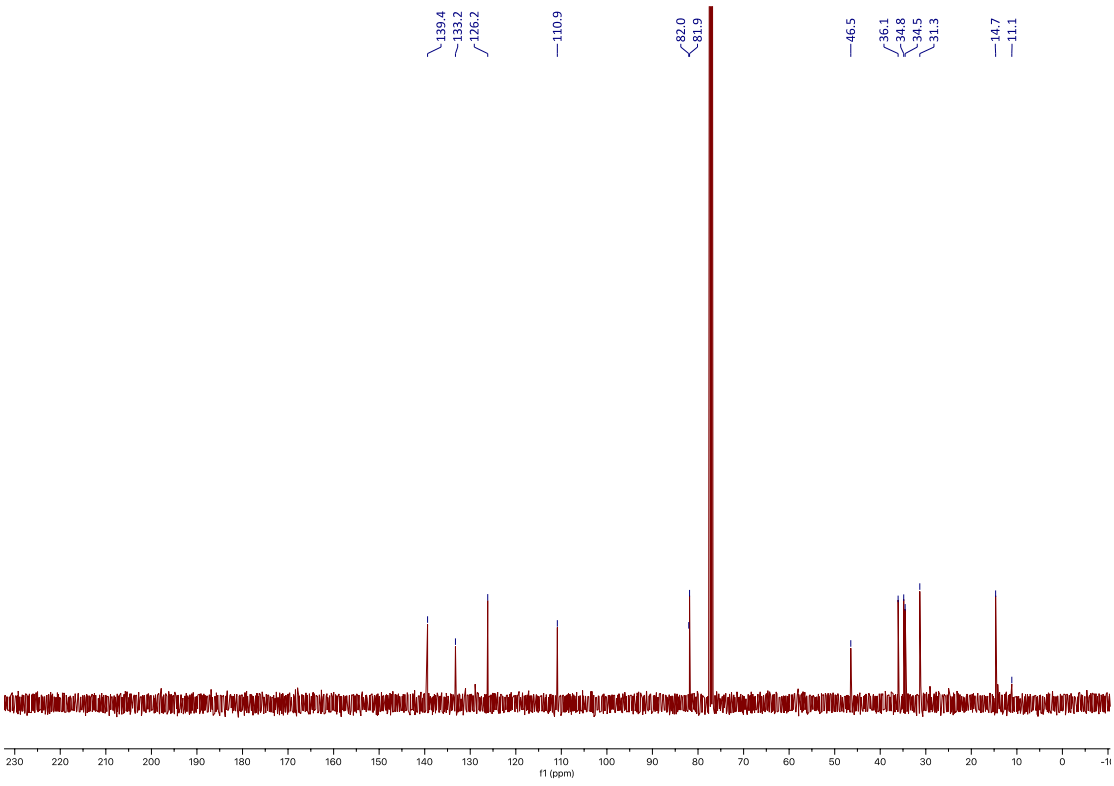

134.9
117.0
83.8
81.4
81.3
71.0
51.8
39.8
36.3
30.6
25.9
25.8
18.0
14.2
-4.7
-5.0
f1 (ppm)

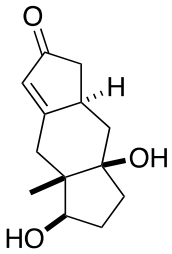

CH2
6
H3C
OH
10
1
HC
6
4
3
O
H3C
Si
CH3
H3C
CH3
CH3
10
6
10 - 6
6 - 10
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f2 (ppm)
f1 (ppm)


OH
HO

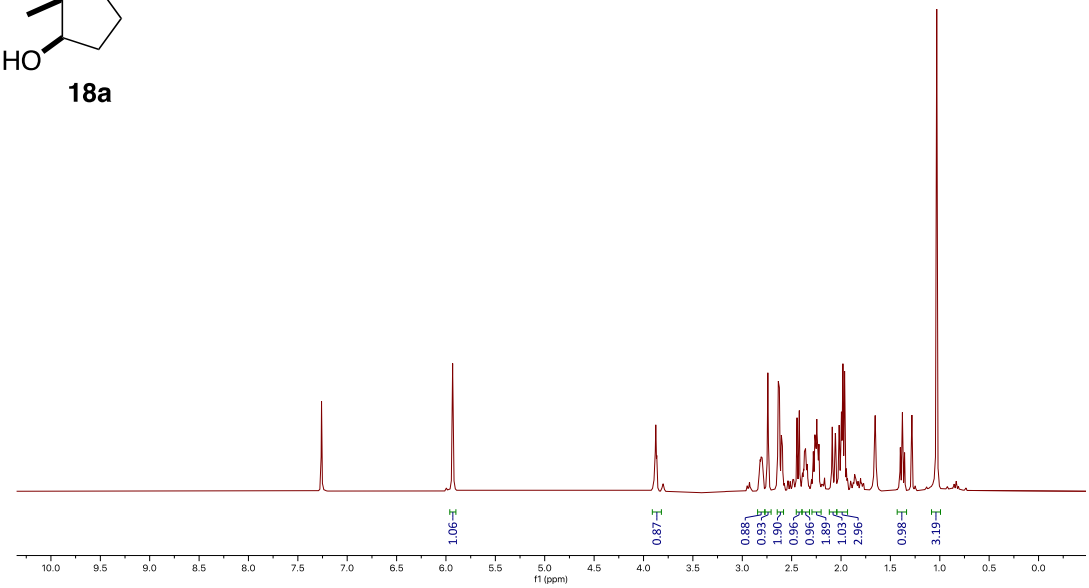
17

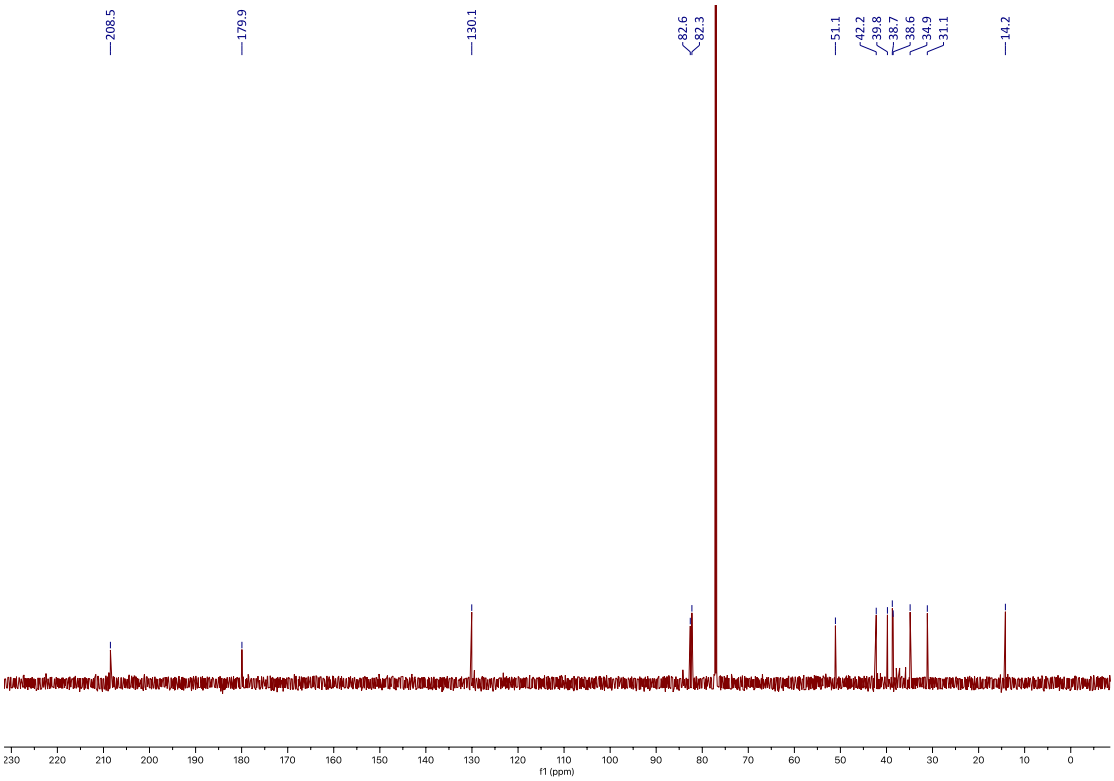
1.00
1.03
1.08
1.06
1.05
1.02
1.00
1.11
1.18
1.10
1.09
3.27
1.14
3.24
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

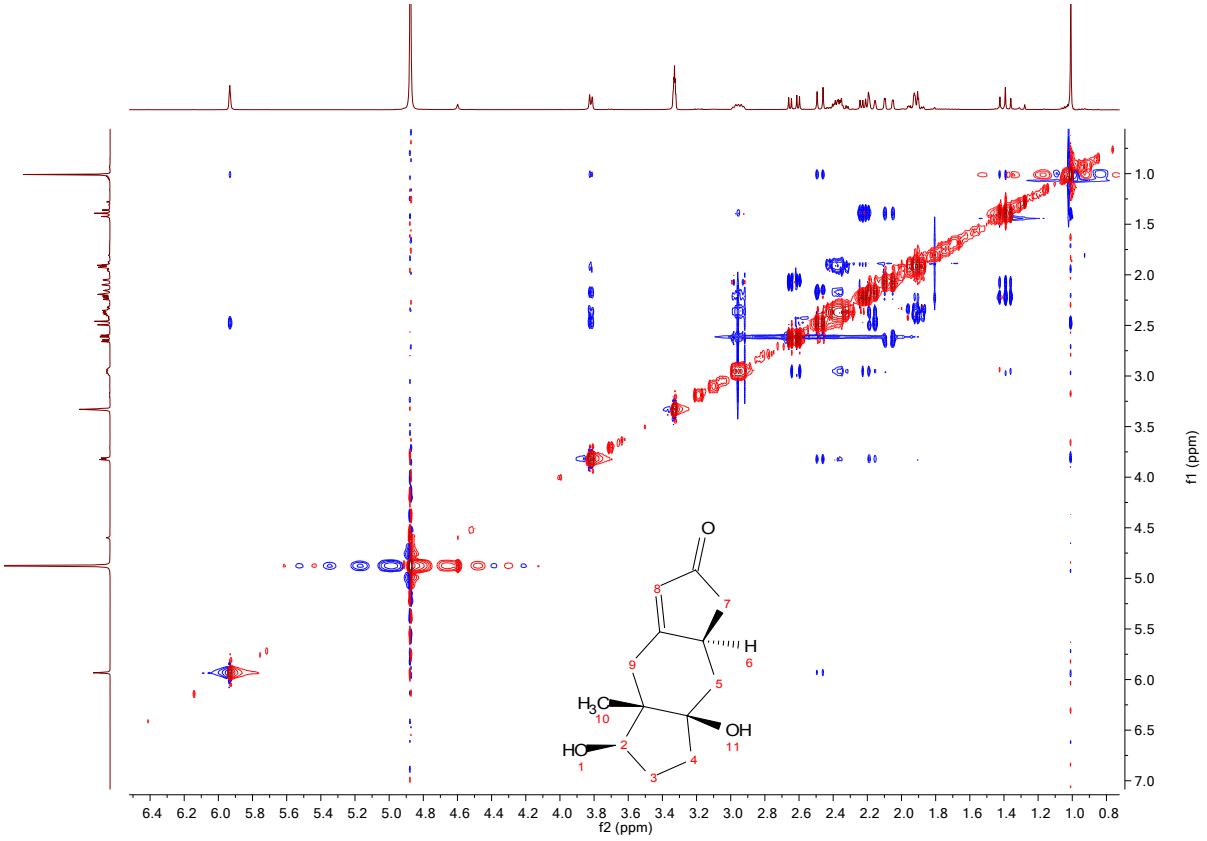

139.4
133.2
126.2
110.9
82.0
81.9
46.5
36.1
34.8
34.5
31.3
14.7
11.1
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

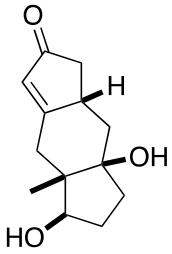

O
H
OH
HO

18a

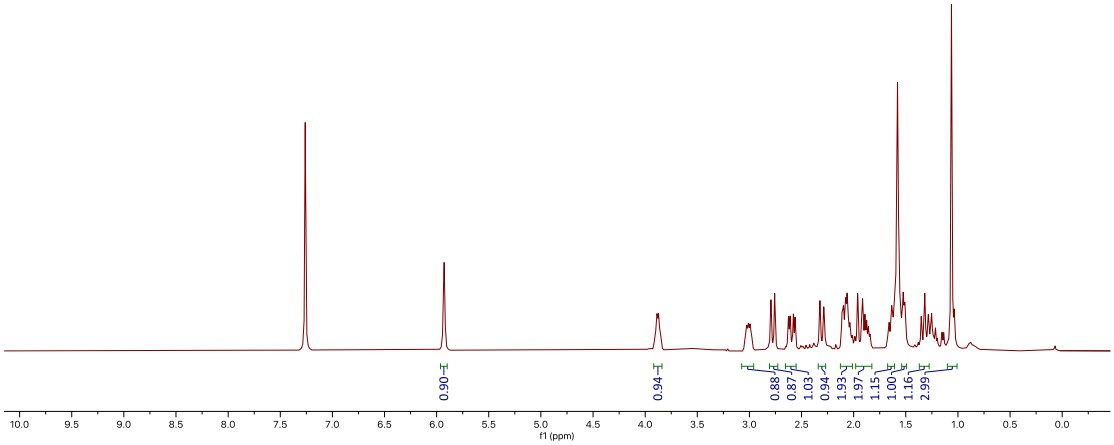

1.06
0.87
0.88
0.93
1.90
0.96
0.96
1.89
1.03
2.96
0.98
3.19
f1 (ppm)

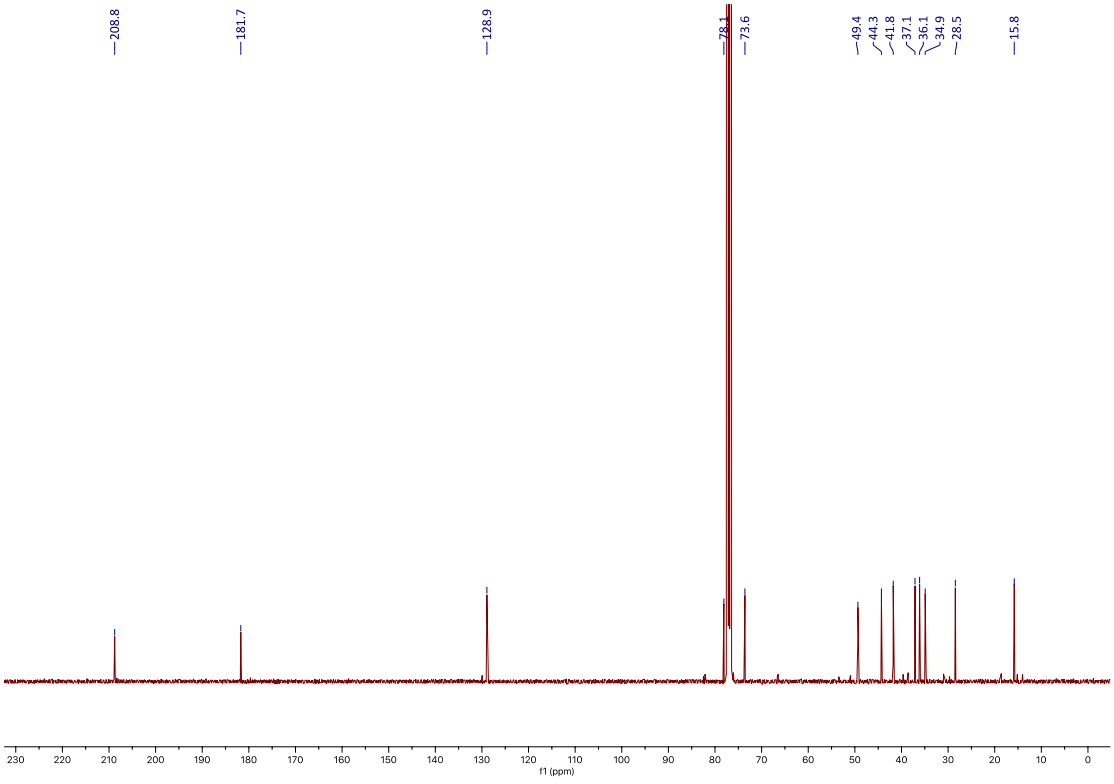

208.5
179.9
130.1
82.6
82.3
51.1
42.2
39.8
38.7
38.6
34.9
31.1
14.2
f1 (ppm)

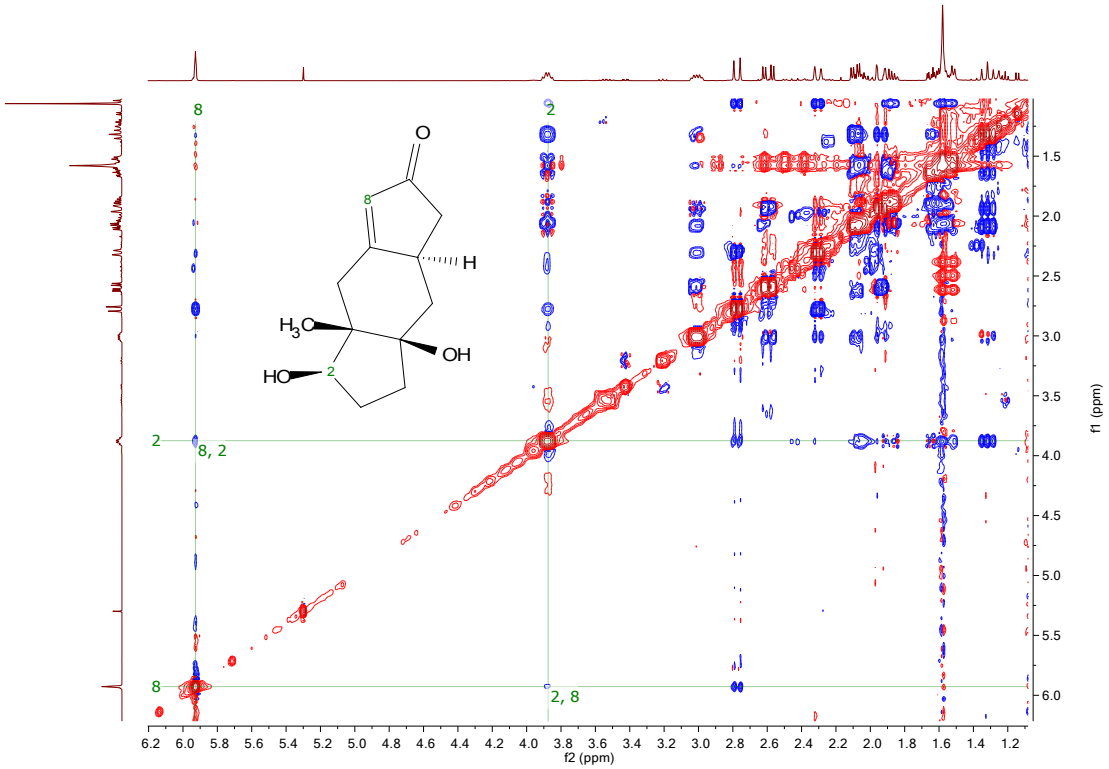

f2 (ppm)
f1 (ppm)
O
H
6
OH
11
HO
1
H3C
10

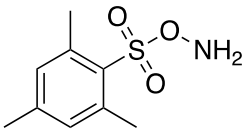

O
H
OH
HO

18b

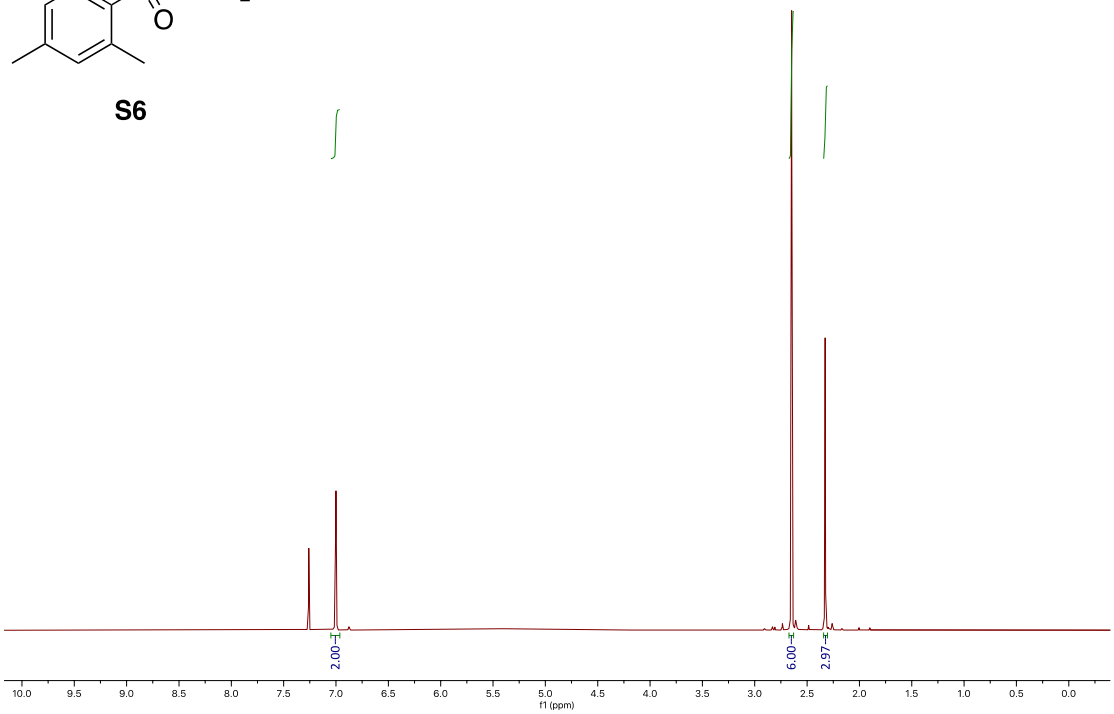

0.90
0.94
0.88
0.87
1.03
0.94
1.93
1.97
1.15
1.00
1.16
2.99
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

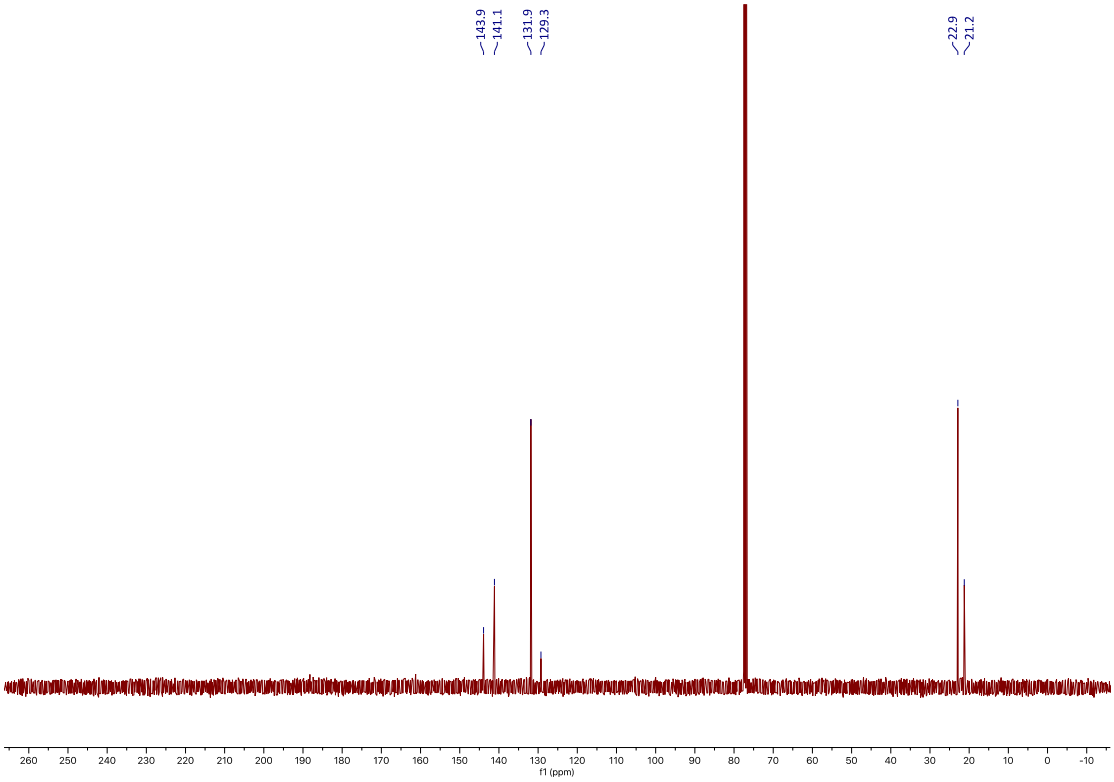

208.8
181.7
128.9
78.1
73.6
49.4
44.3
41.8
37.1
36.1
34.9
28.5
15.8
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

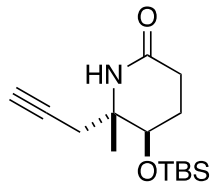

8
2
O
H
H3O
OH
HO
2
8, 2
2, 8
f2 (ppm)
f1 (ppm)


O
S
O
O
NH2

S6

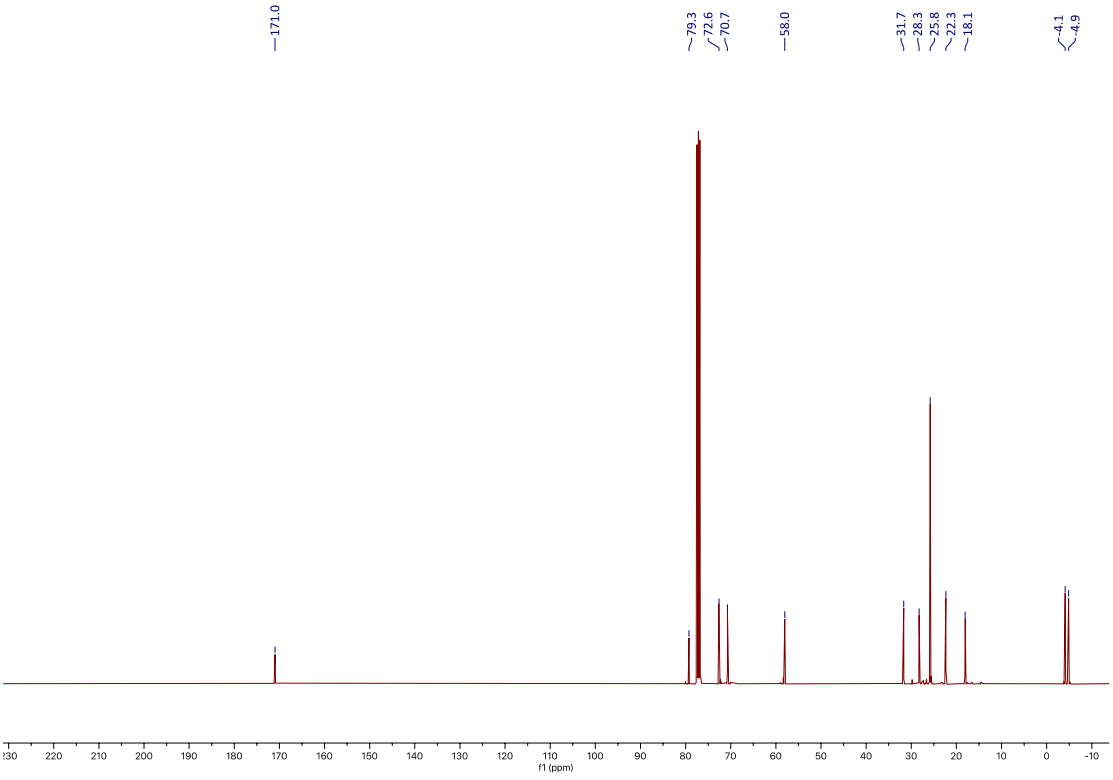

2.00
6.00
2.97
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

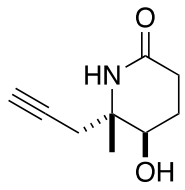

143.9
141.1
131.9
129.3
22.9
21.2
260
250
240
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


O
HN
OTBS

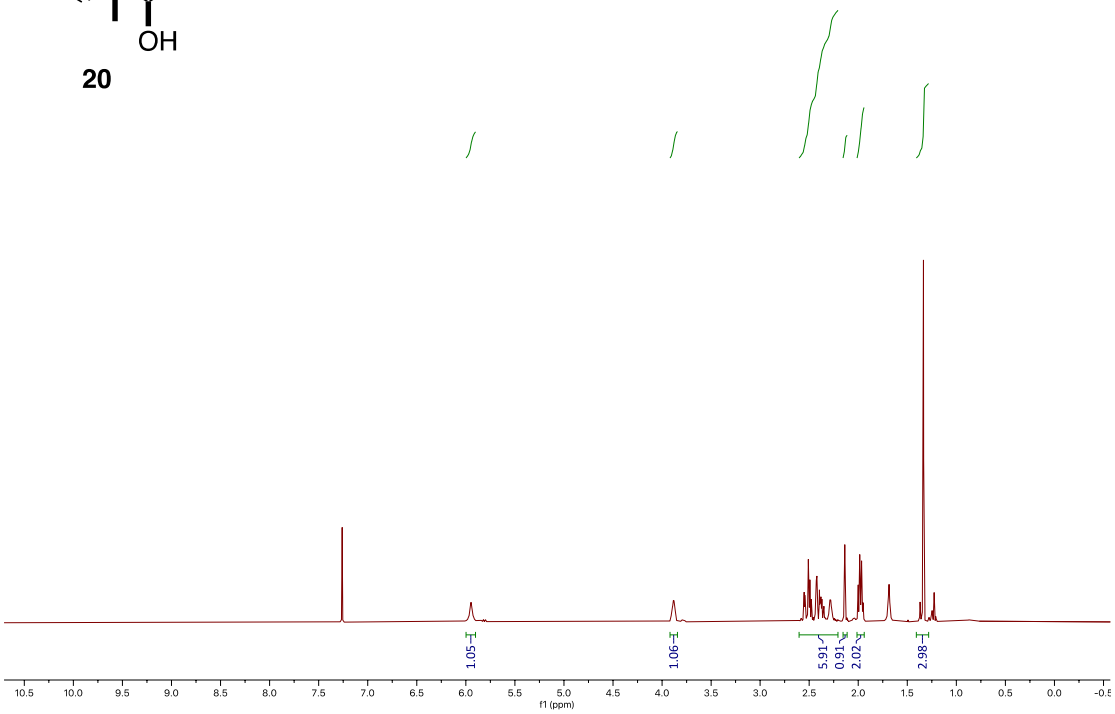
19

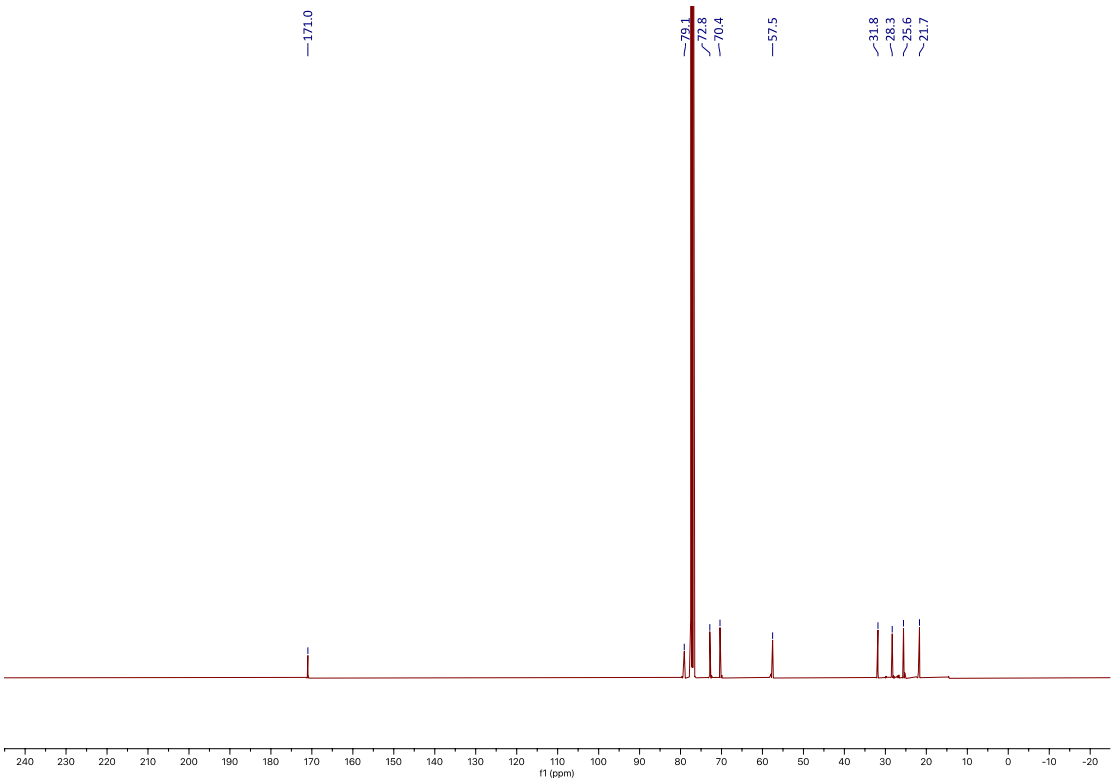
0.94
1.00
4.21
0.97
2.07
2.87
9.00
6.10
f1 (ppm)

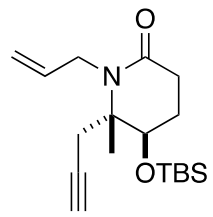

171.0
79.3
72.6
70.7
58.0
31.7
28.3
25.8
22.3
18.1
-4.1
-4.9
f1 (ppm)


O
HN
OH

20

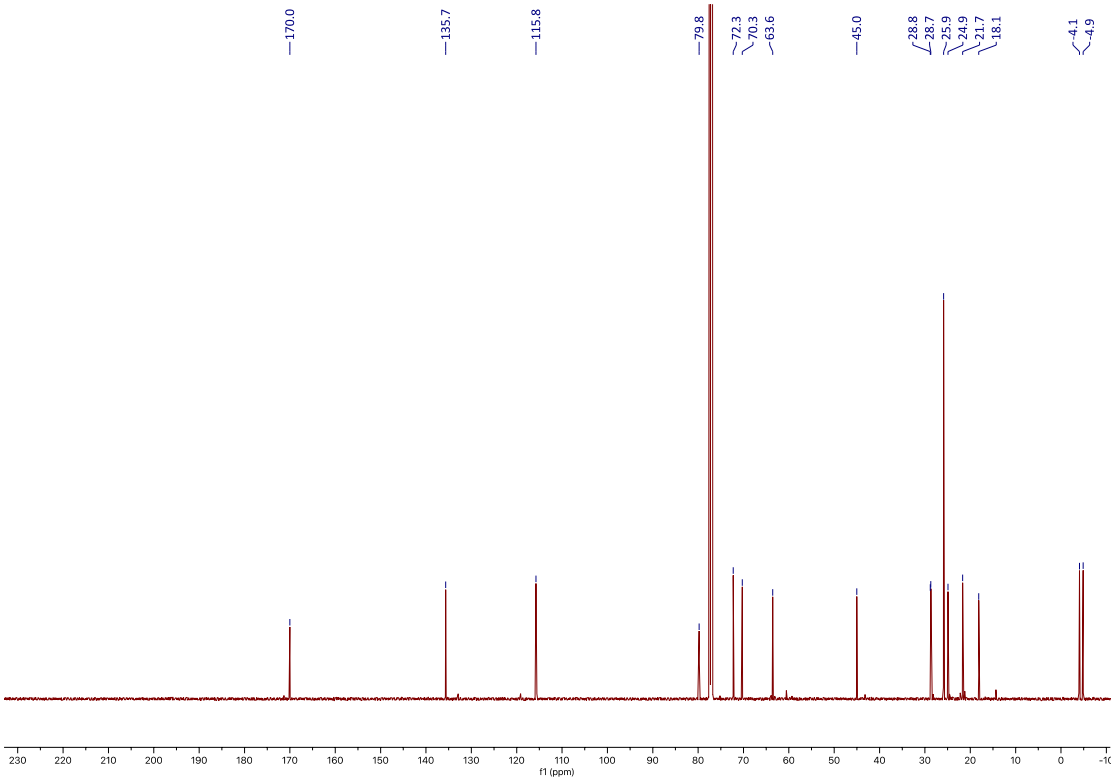

1.05
1.06
5.91
0.91
2.02
2.98
f1 (ppm)

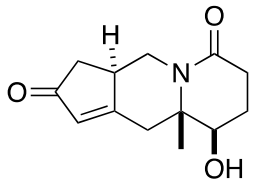

171.0
79.1
72.8
70.4
57.5
31.8
28.3
25.6
21.7
f1 (ppm)


O
N
OTBS

S7

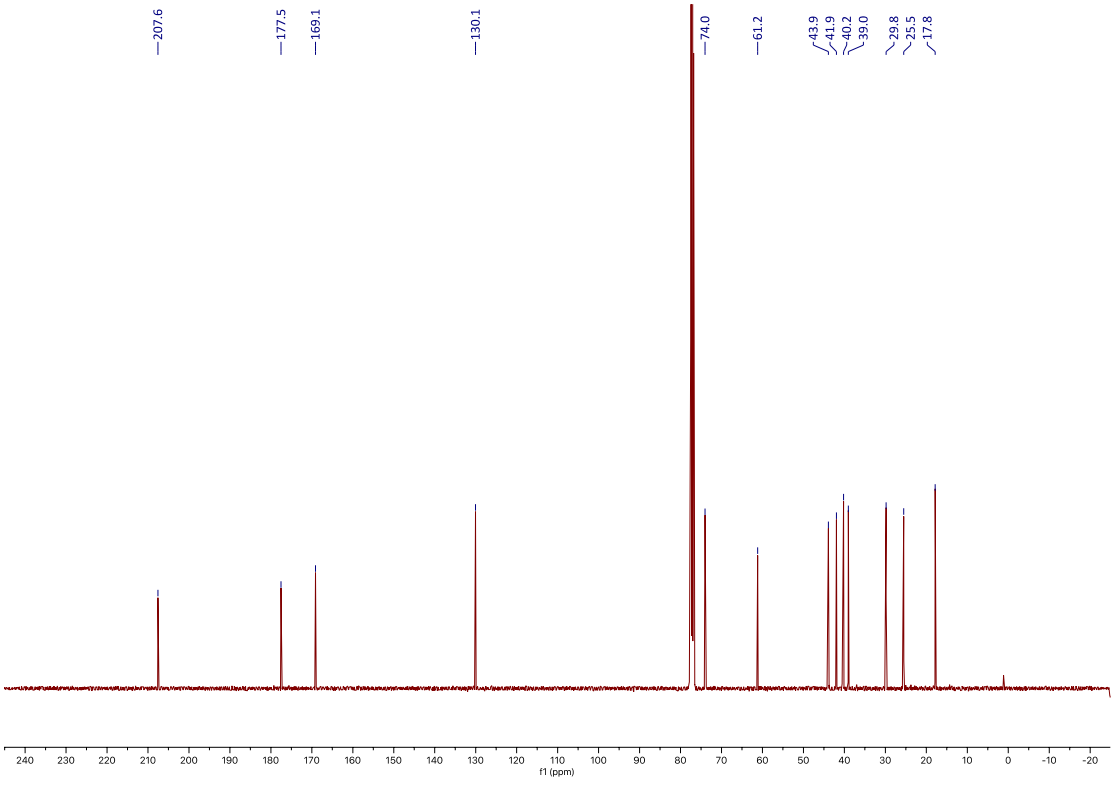
1.09
2.16
1.06
1.02
1.07
2.05
2.19
0.95
1.07
0.99
2.90
9.02
6.04
f1 (ppm)

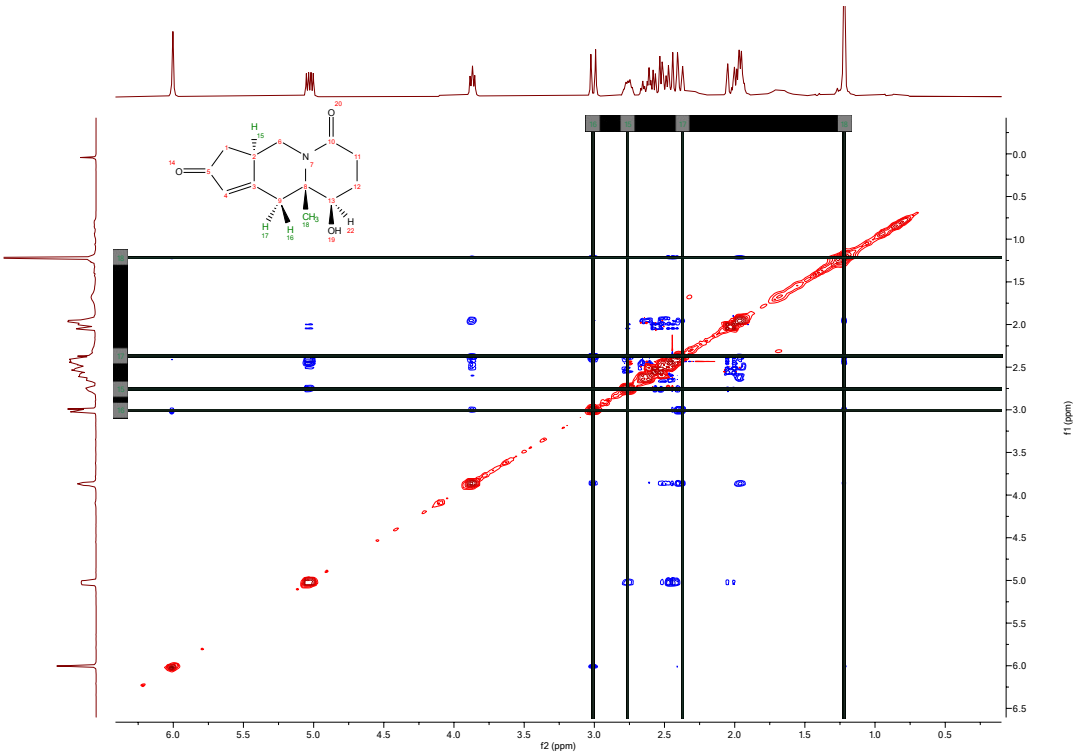

170.0
135.7
115.8
79.8
72.3
70.3
63.6
45.0
28.8
28.7
25.9
24.9
21.7
18.1
-4.1
-4.9
f1 (ppm)

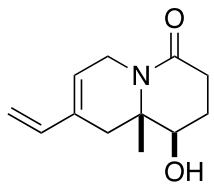

H
O
N
O
OH

21

0.89
1.02
1.03
0.94
1.06
5.04
0.90
2.02
2.94
f1 (ppm)

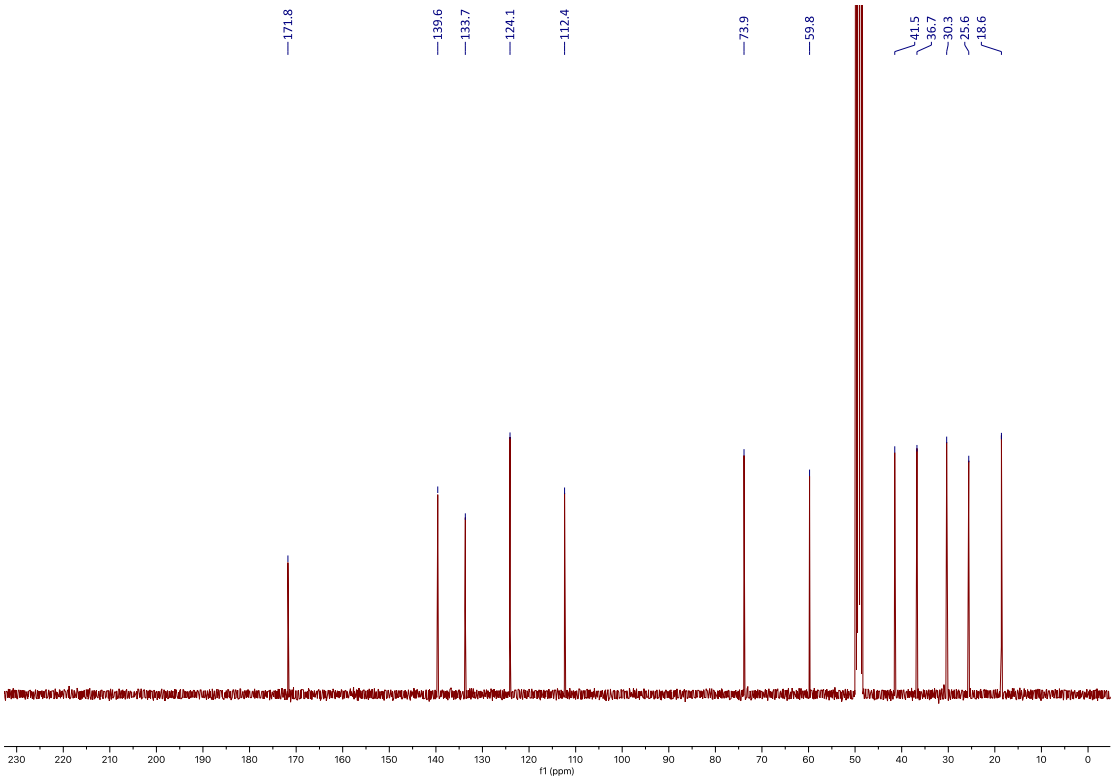

207.6
177.5
169.1
130.1
74.0
61.2
43.9
41.9
40.2
39.0
29.8
25.5
17.8
f1 (ppm)

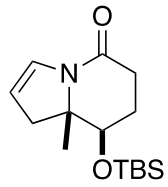

f2 (ppm)
f1 (ppm)


O
N
OH

22

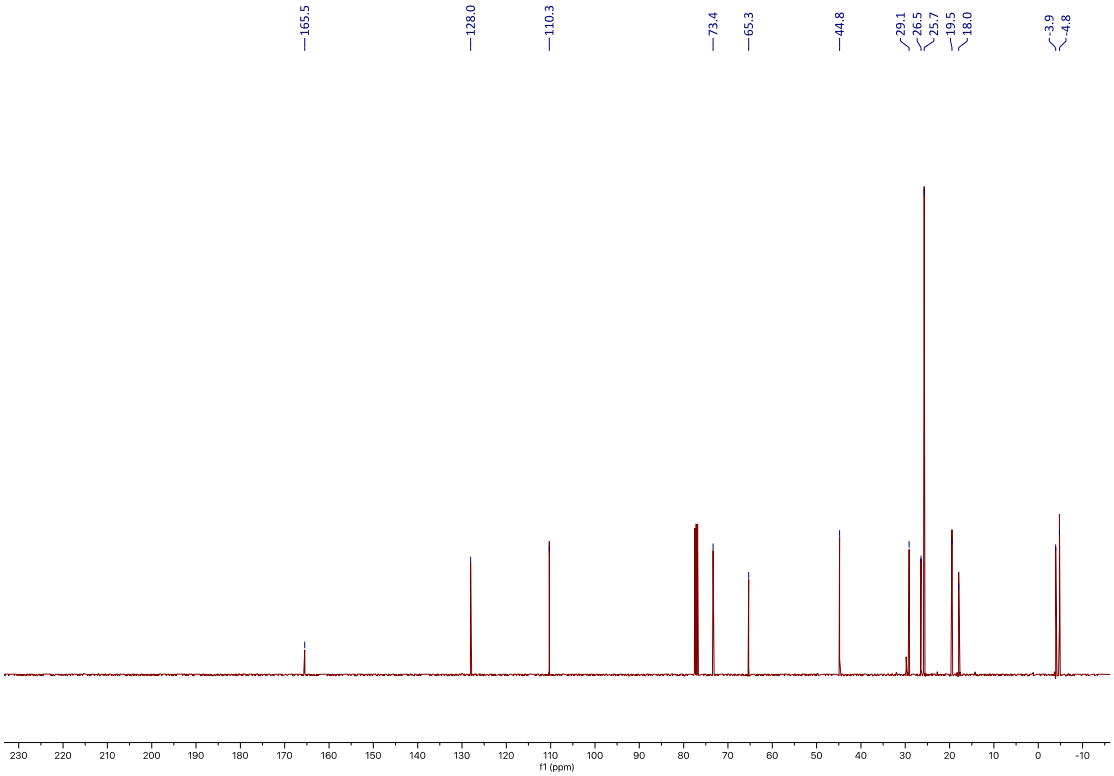
1.06
0.90
1.00
0.97
1.01
0.96
1.04
1.97
1.12
1.03
2.03
3.00
f1 (ppm)

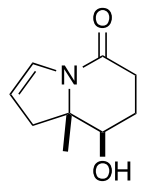

171.8
139.6
133.7
124.1
112.4
73.9
59.8
41.5
36.7
30.3
25.6
18.6
f1 (ppm)


O
N
OTBS

S8

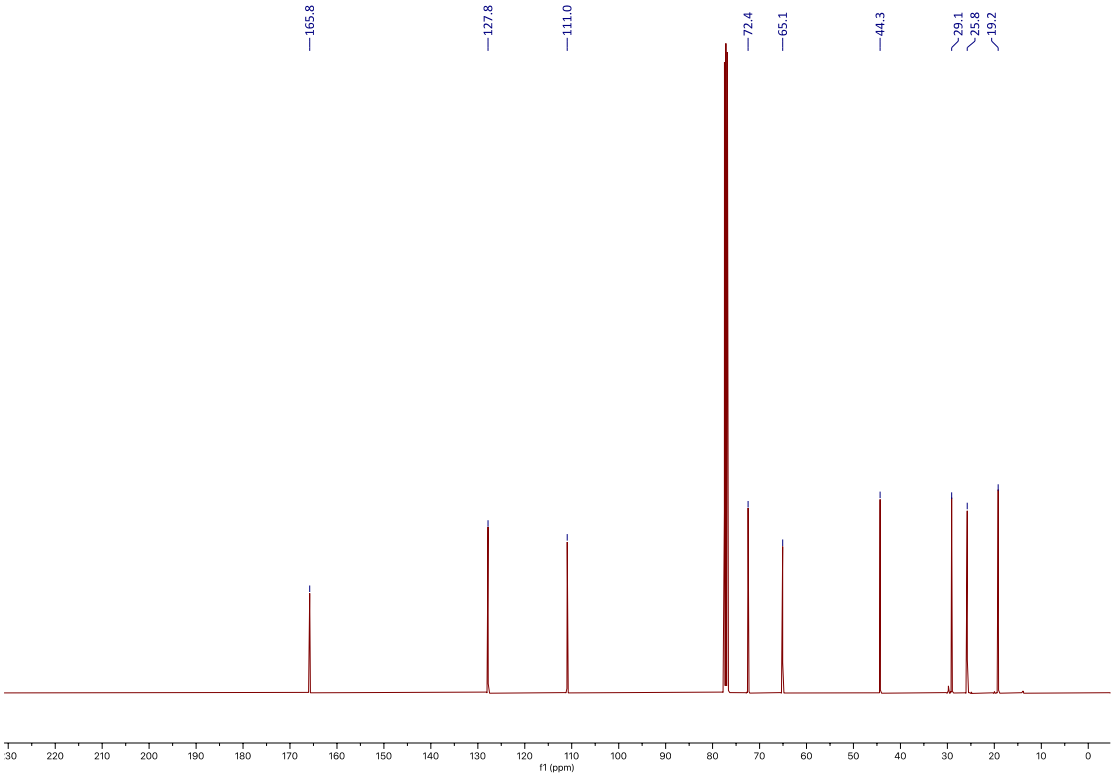
0.95
0.96
0.97
2.00
1.97
1.97
3.16
9.12
6.07
f1 (ppm)

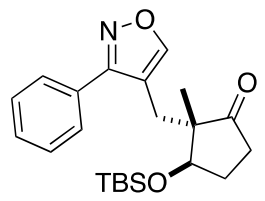

165.5
128.0
110.3
73.4
65.3
44.8
29.1
26.5
25.7
19.5
18.0
-3.9
-4.8
f1 (ppm)


O
N
OH

23

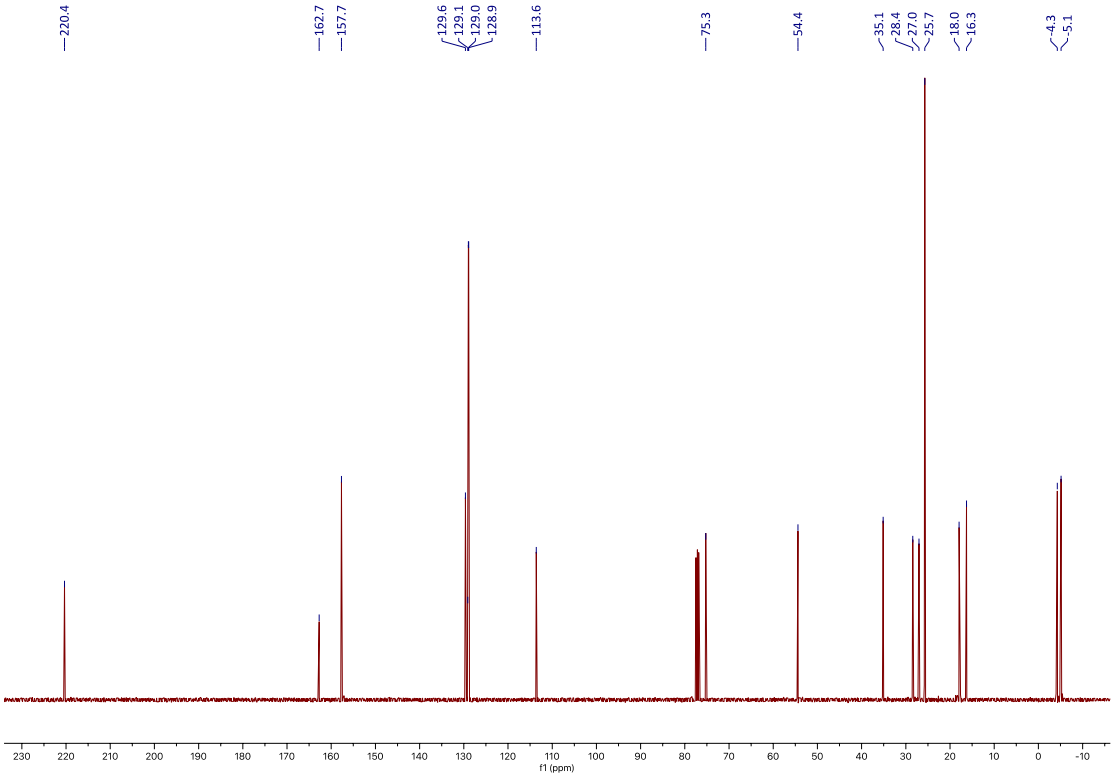
0.97
0.98
1.01
1.03
1.06
2.02
2.16
3.03
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

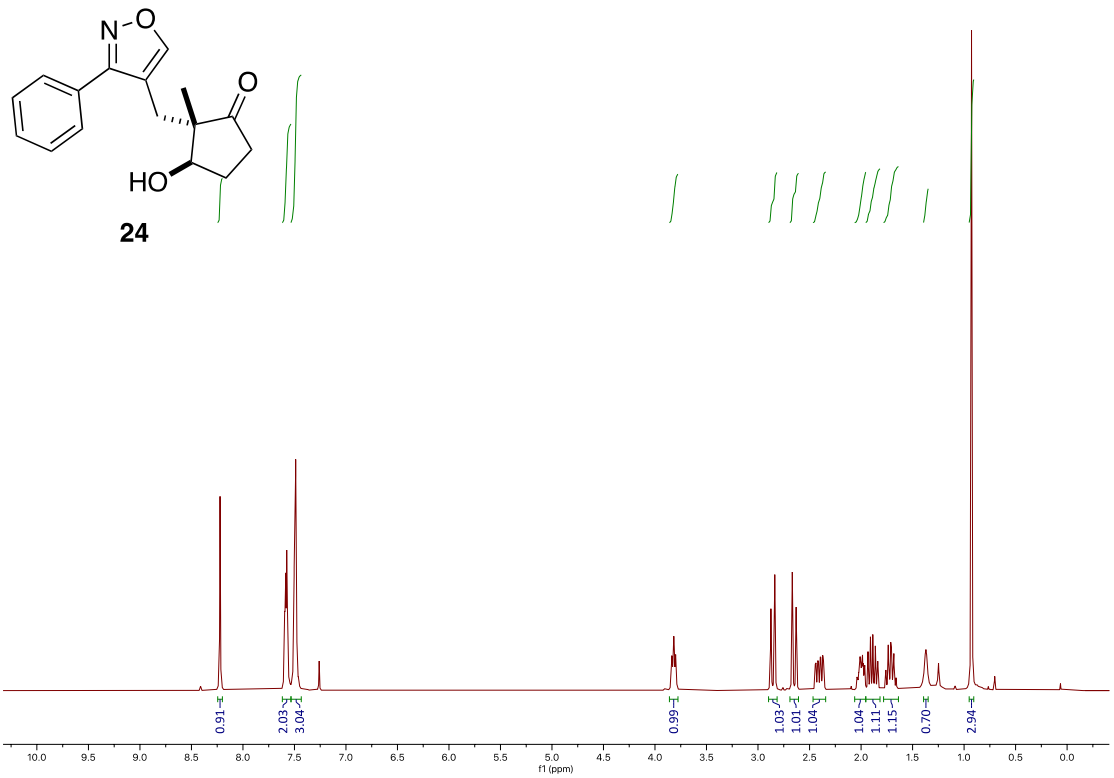

165.8
127.8
111.0
72.4
65.1
44.3
29.1
25.8
19.2
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

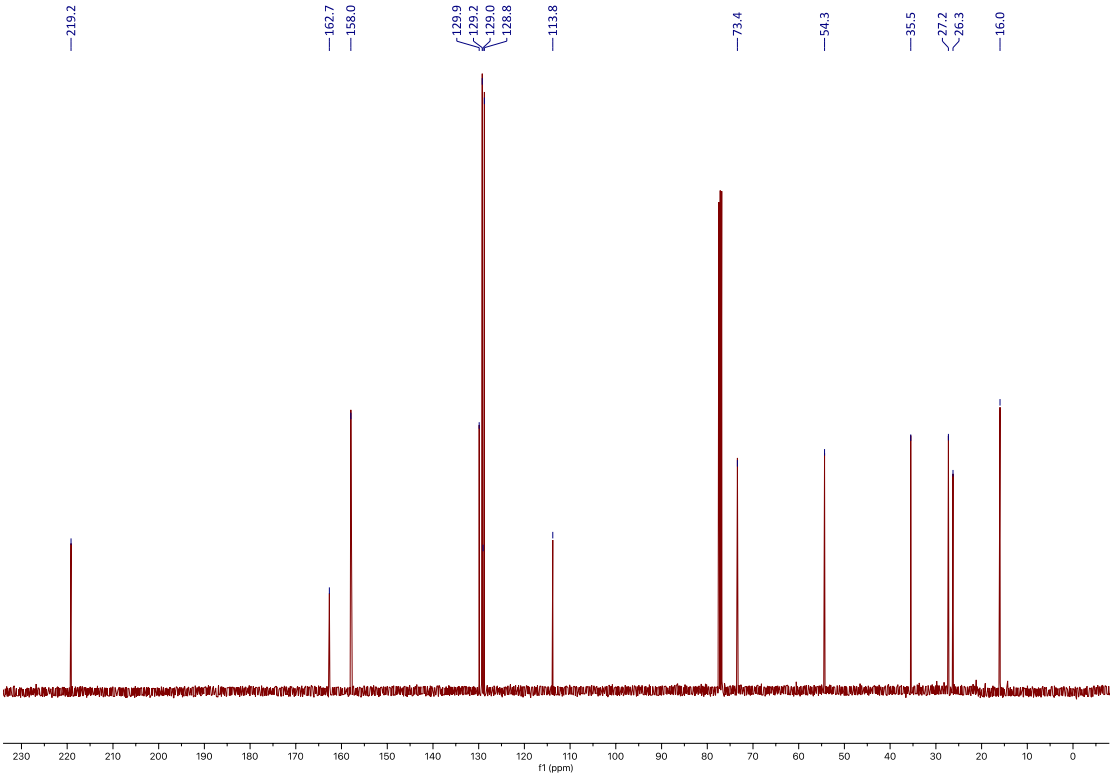

N
O
O
TBSO

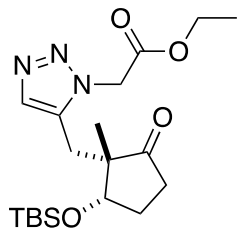
S9

0.88
1.95
3.02
0.99
1.01
1.01
1.02
2.11
1.07
3.10
9.00
2.93
2.91
f1 (ppm)


220.4
162.7
157.7
129.6
129.1
129.0
128.9
113.6
75.3
54.4
35.1
28.4
27.0
25.7
18.0
16.3
-4.3
-5.1
f1 (ppm)

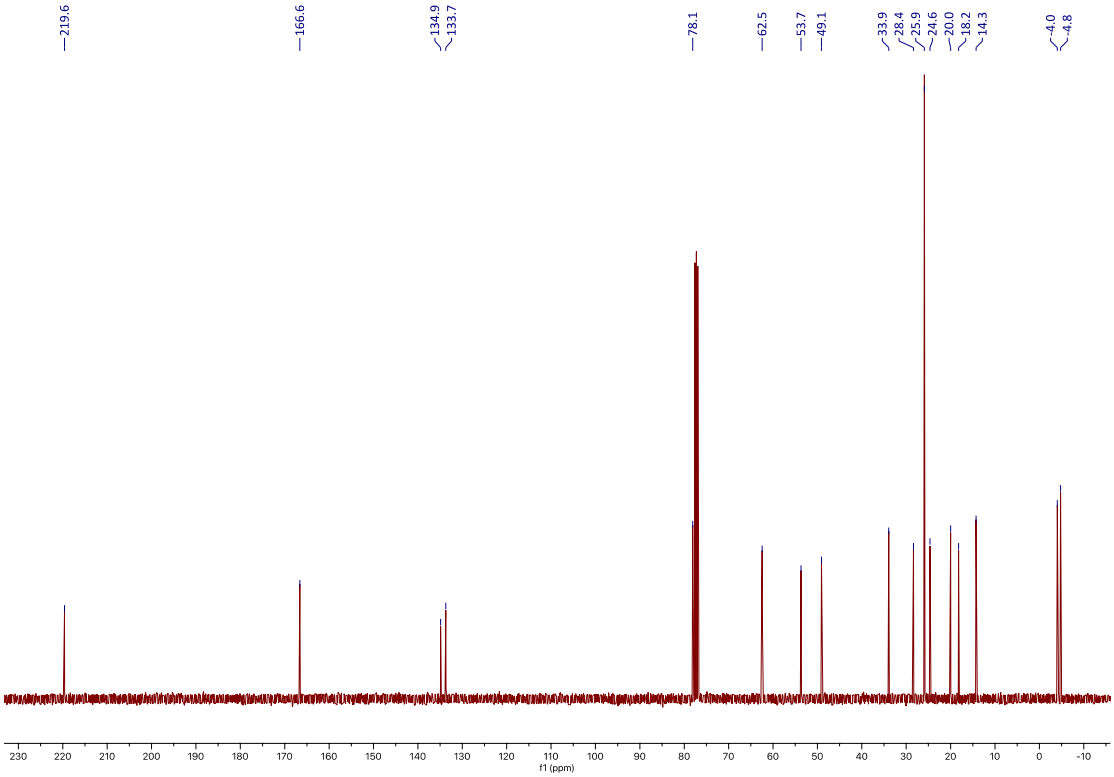

N
O
O
HO
24
0.91
2.03
3.04
0.99
1.03
1.01
1.04
1.04
1.11
1.15
0.70
2.94
f1 (ppm)

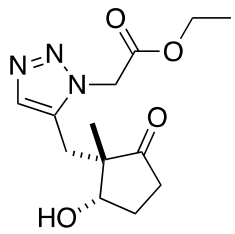

219.2
162.7
158.0
129.9
129.2
129.0
128.8
113.8
73.4
54.3
35.5
27.2
26.3
16.0
f1 (ppm)


O
O
N
N
N
O
TBSO

S10

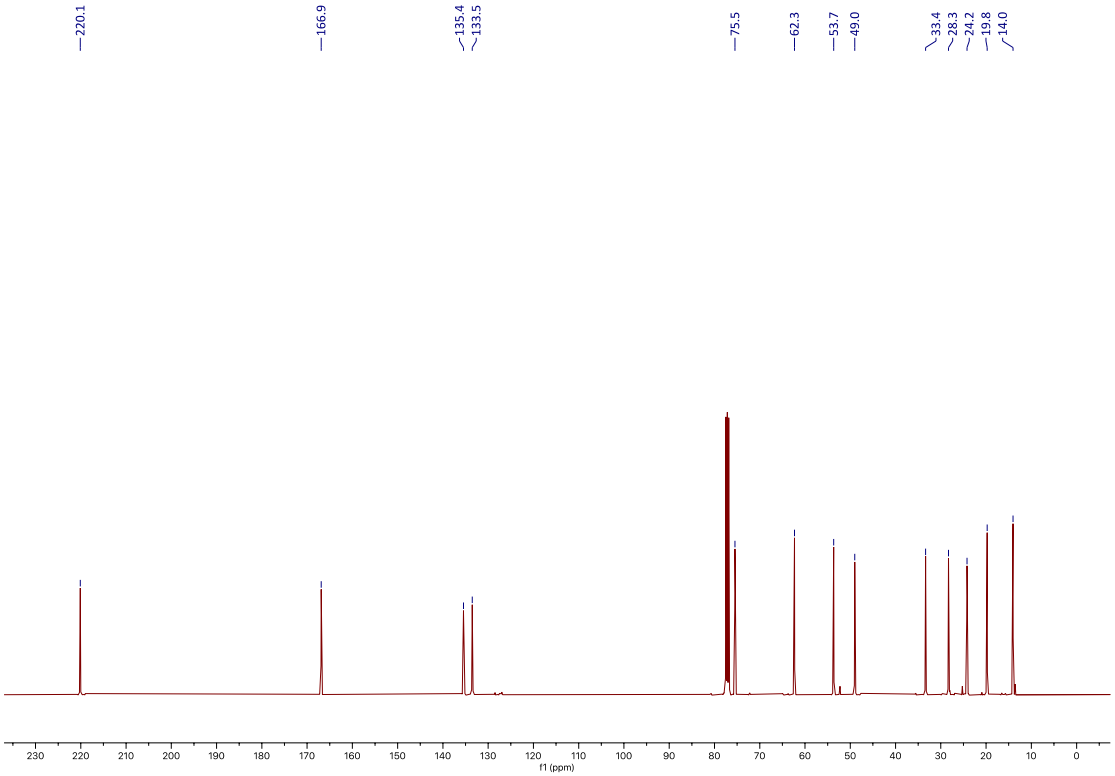
0.96
1.99
3.05
1.99
2.07
1.04
1.04
3.21
2.97
9.02
3.00
3.02
f1 (ppm)

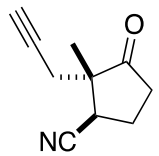

219.6
166.6
134.9
133.7
78.1
62.5
53.7
49.1
33.9
28.4
25.9
24.6
20.0
18.2
14.3
-4.0
-4.8
f1 (ppm)


O
O
N
N
N
O
HO

25

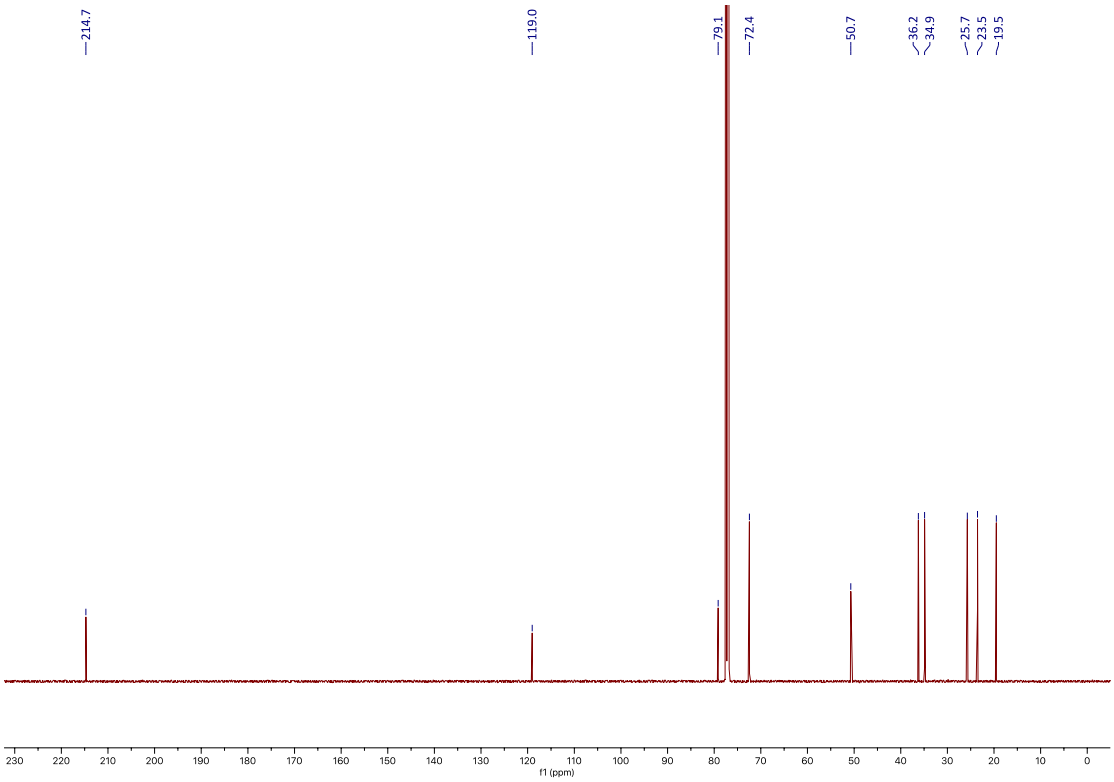
1.01
1.06
1.05
1.96
1.00
1.04
1.04
2.23
1.36
1.02
3.06
2.80
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

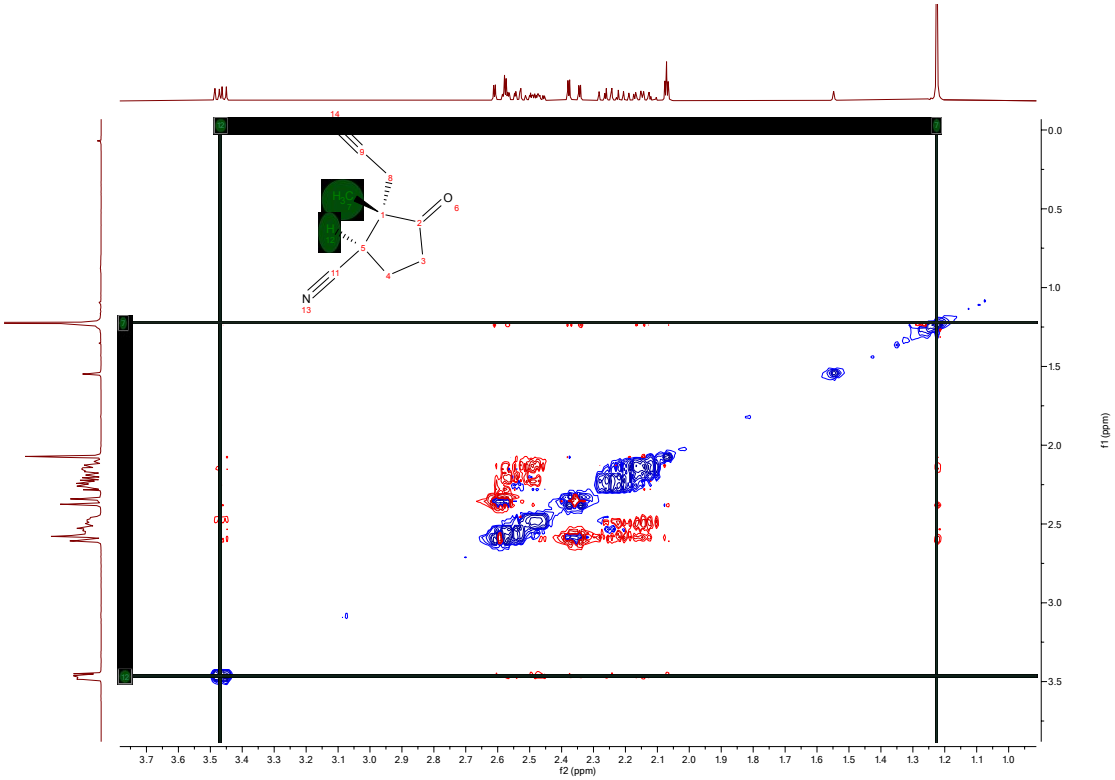

220.1
166.9
135.4
133.5
75.5
62.3
53.7
49.0
33.4
28.3
24.2
19.8
14.0
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

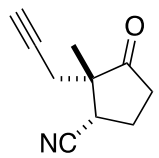

O
NC

anti-**26**

0.95
2.02
1.13
1.02
2.18
0.91
2.92
f1 (ppm)

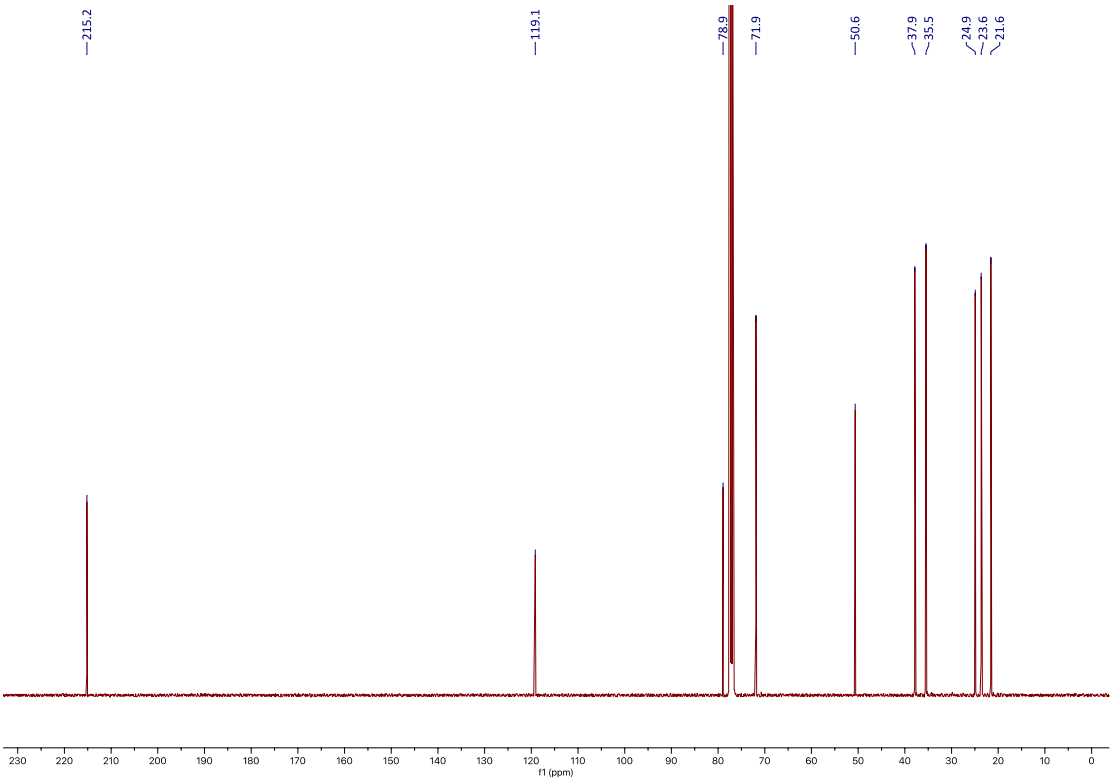

214.7
119.0
79.1
72.4
50.7
36.2
34.9
25.7
23.5
19.5
f1 (ppm)

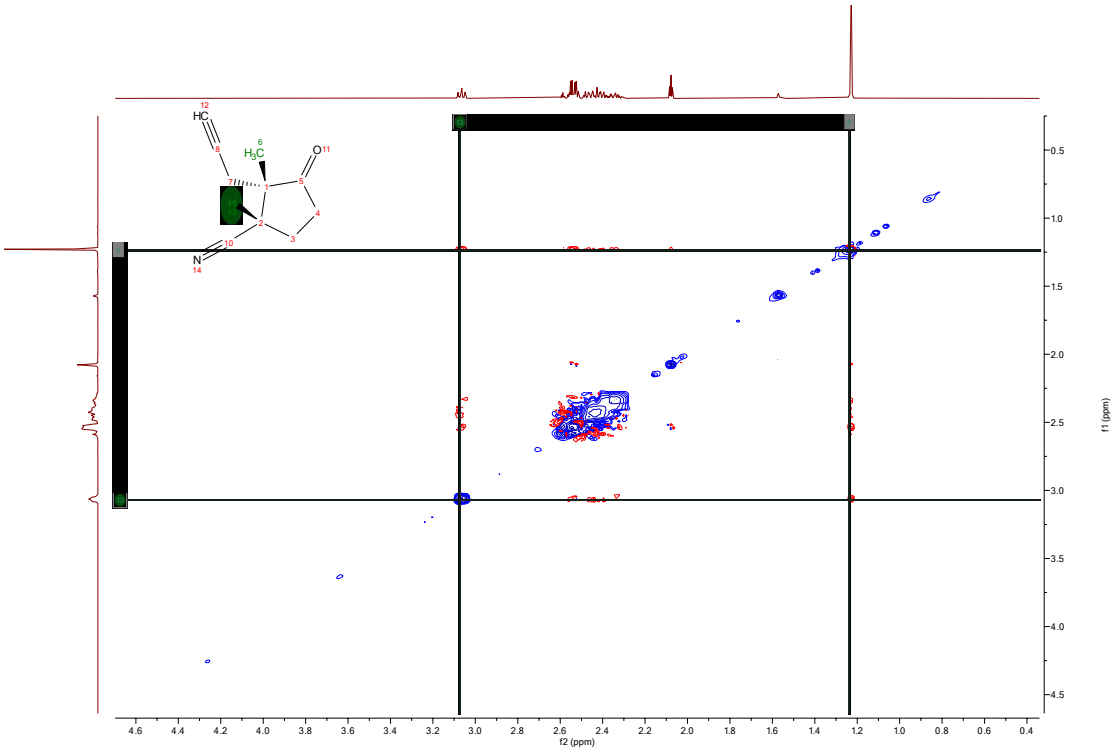

f2 (ppm)
f1 (ppm)

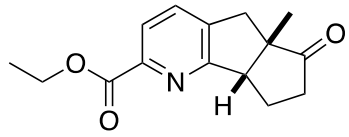

O
NC

syn-**26**

1.04
6.09
0.96
2.80
f1 (ppm)

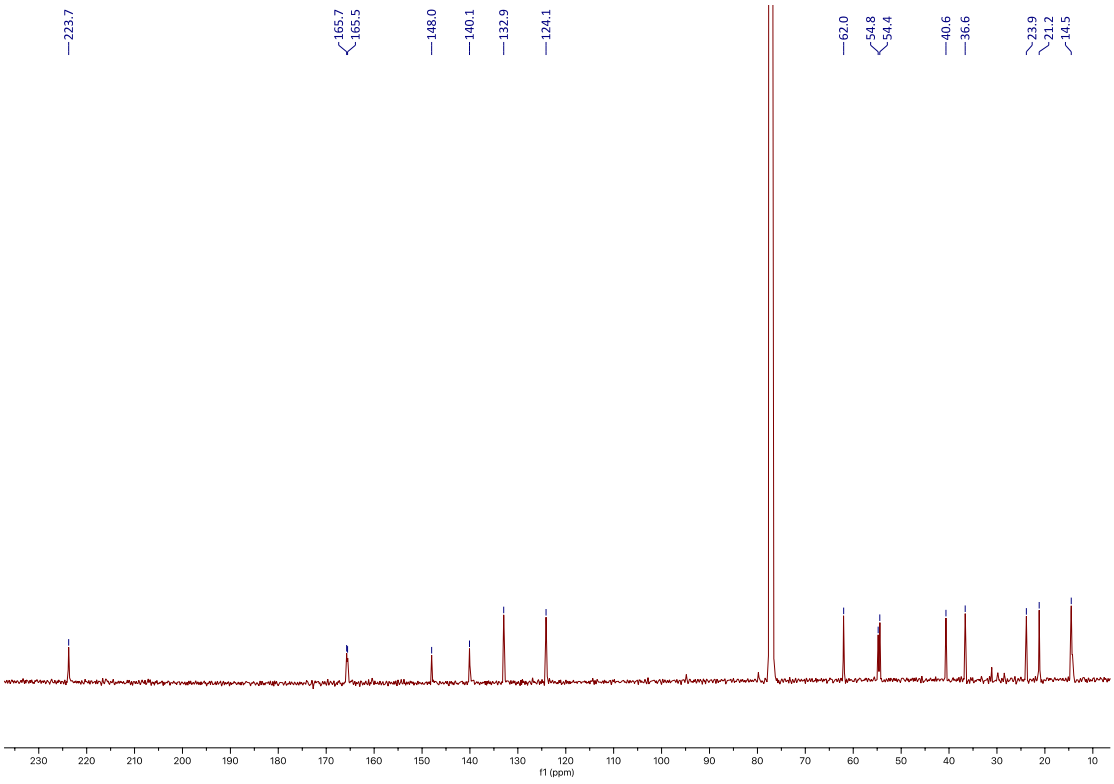

215.2
119.1
78.9
71.9
50.6
37.9
35.5
24.9
23.6
21.6
f1 (ppm)

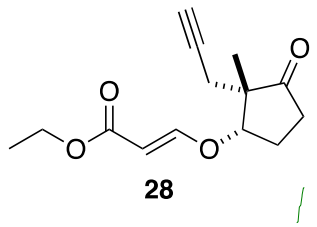

HC
12
8
H3C
6
O
11
7
1
5
2
4
3
10
N
14
f2 (ppm)
f1 (ppm)


O
O
N
H
O

27

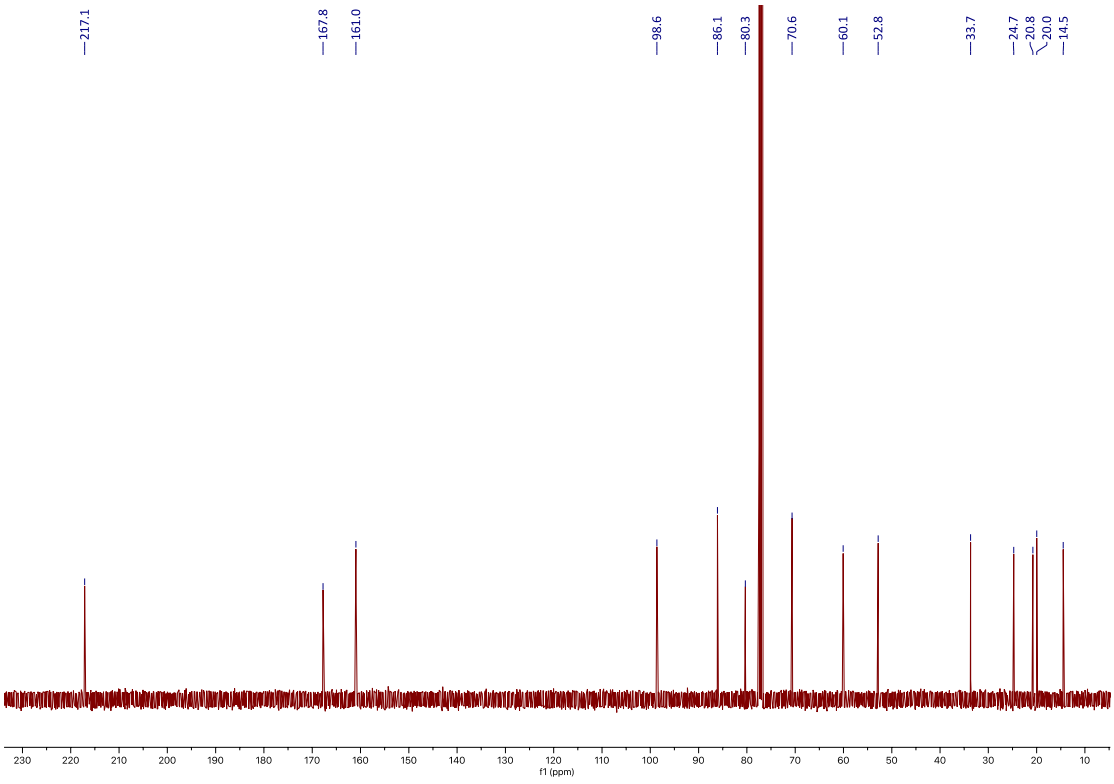
0.99
1.02
2.10
1.04
1.01
1.02
1.00
2.03
0.91
3.29
2.98
f1 (ppm)

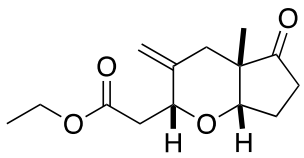

223.7
165.7
165.5
148.0
140.1
132.9
124.1
62.0
54.8
54.4
40.6
36.6
23.9
21.2
14.5
f1 (ppm)



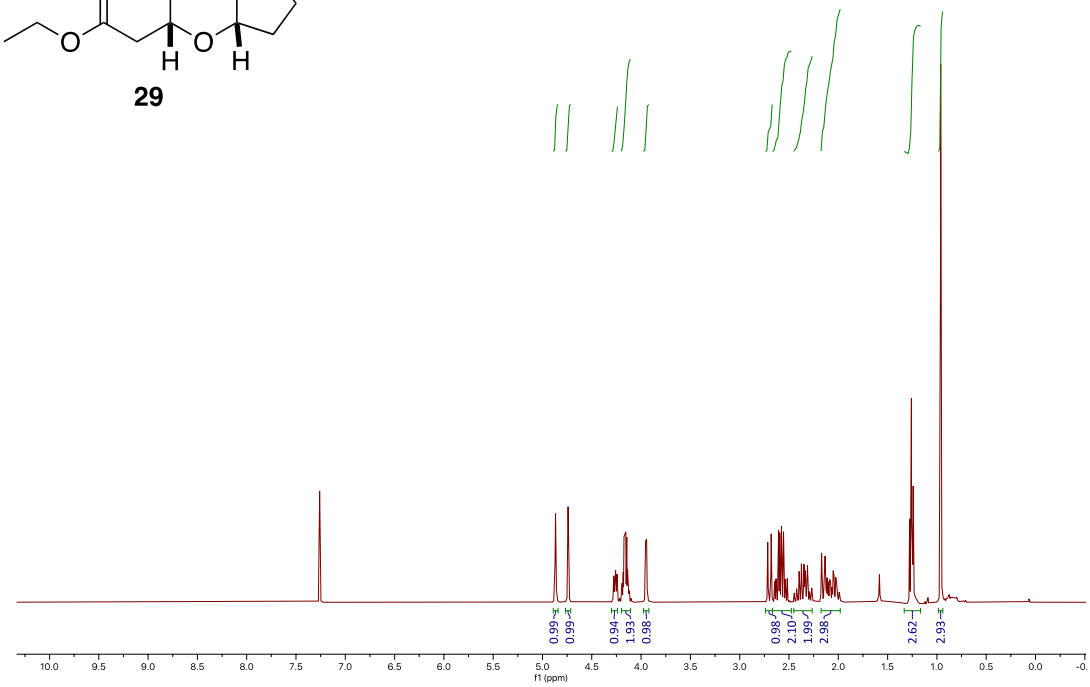
28

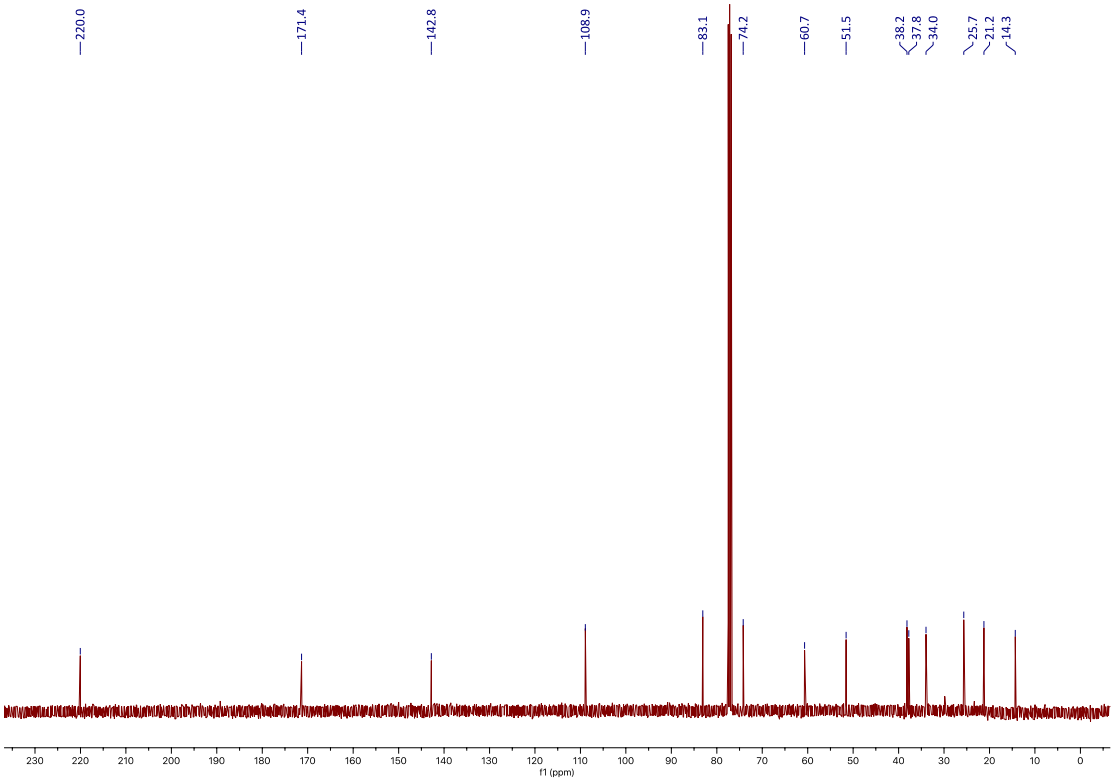
0.95
0.95
0.99
1.97
4.02
1.96
0.89
3.27
2.91
f1 (ppm)

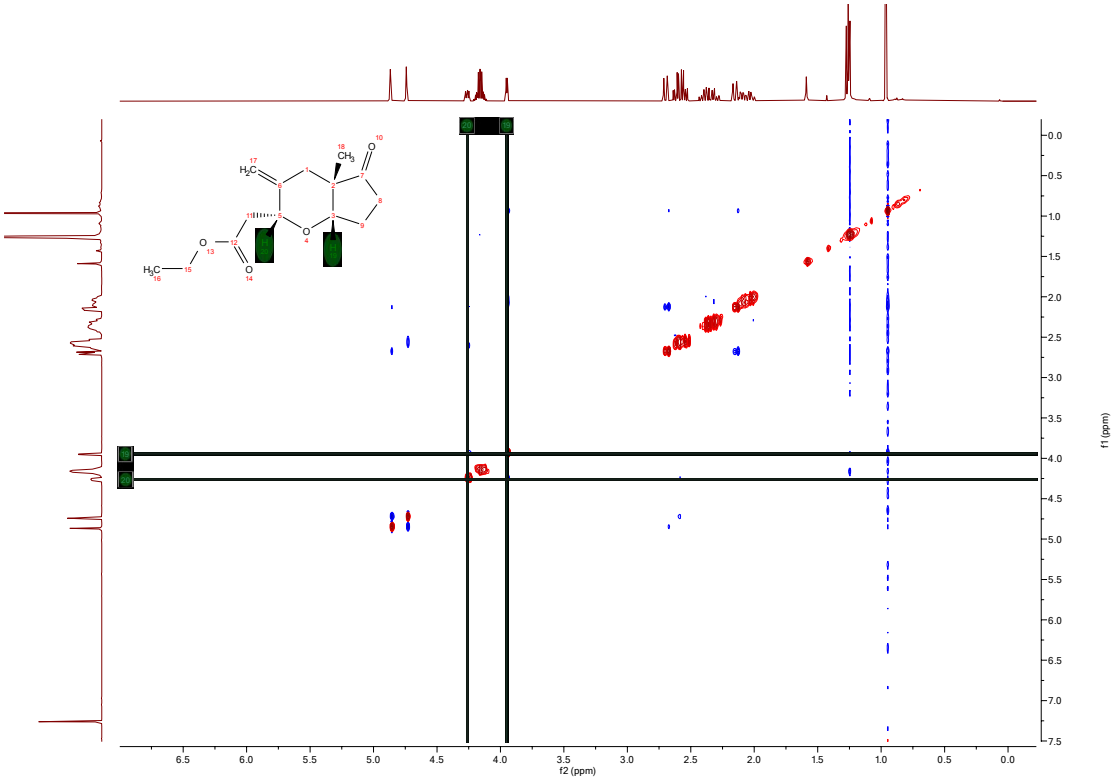

217.1
167.8
161.0
98.6
86.1
80.3
70.6
60.1
52.8
33.7
24.7
20.8
20.0
14.5
f1 (ppm)

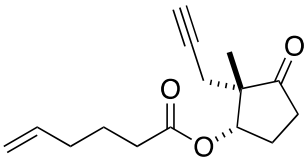


29

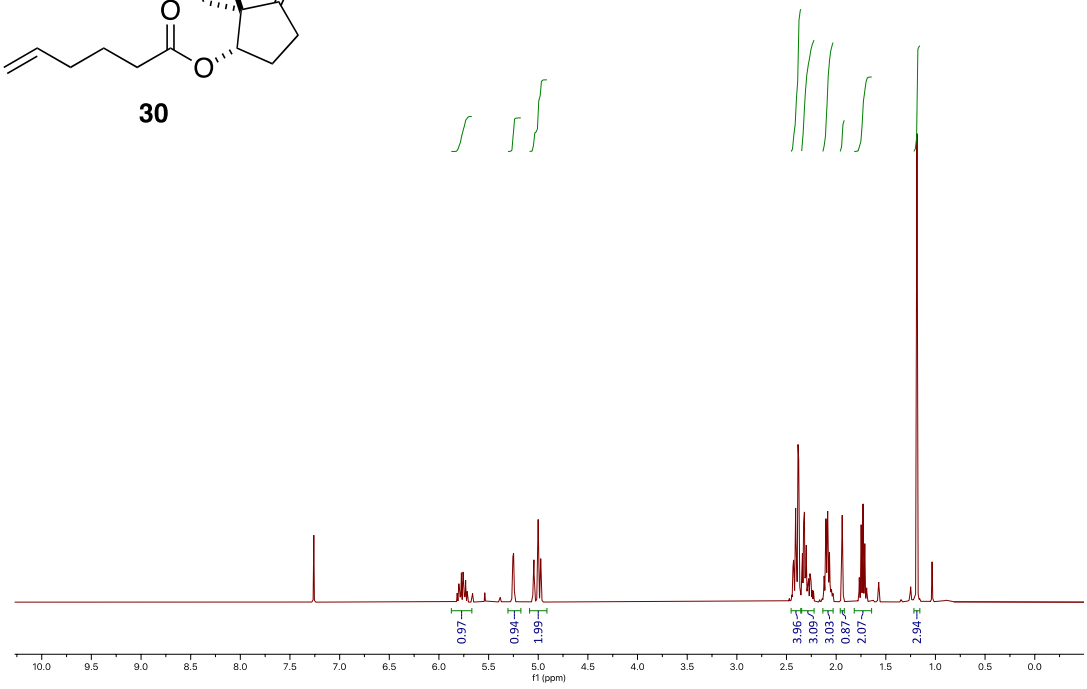

0.99
0.99
0.94
1.93
0.98
0.98
2.10
1.99
2.98
2.62
2.93
f1 (ppm)

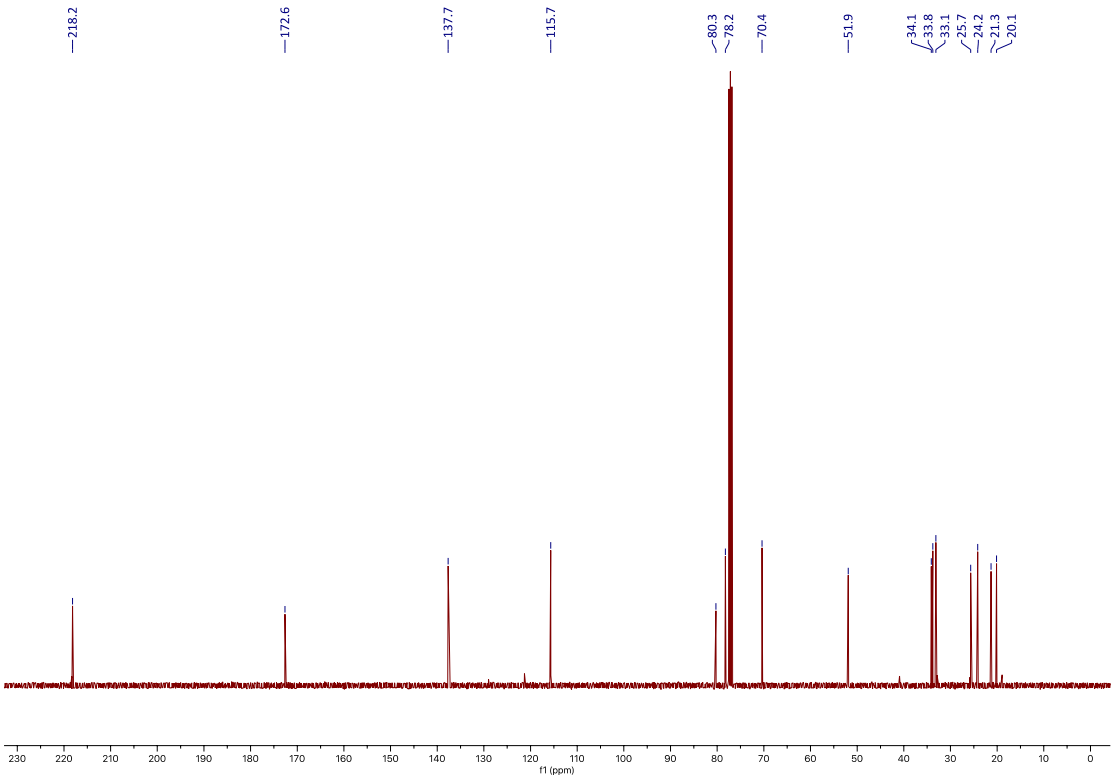

220.0
171.4
142.8
108.9
83.1
74.2
60.7
51.5
38.2
37.8
34.0
25.7
21.2
14.3
f1 (ppm)

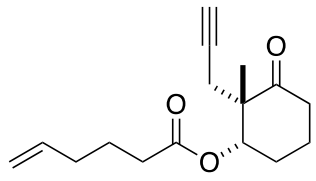

f2 (ppm)
f1 (ppm)



30

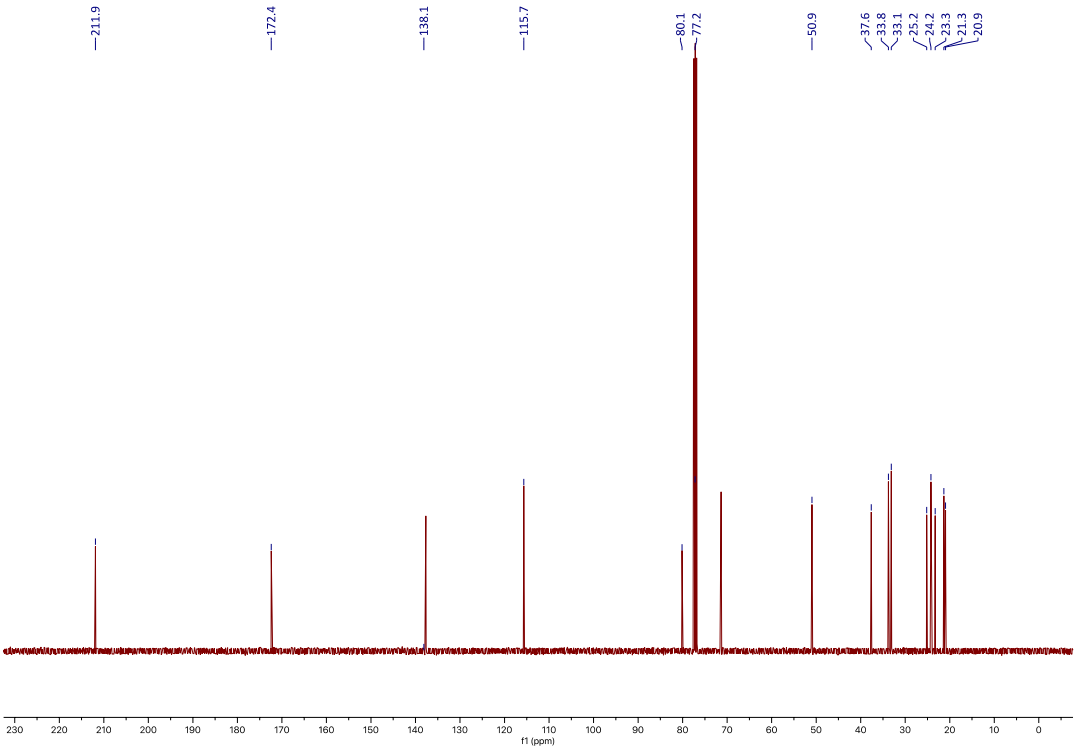

0.97
0.94
1.99
3.96
3.09
3.03
0.87
2.07
2.94
f1 (ppm)

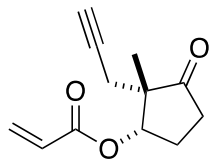

218.2
172.6
137.7
115.7
80.3
78.2
70.4
51.9
34.1
33.8
33.1
25.7
24.2
21.3
20.1
f1 (ppm)



S11

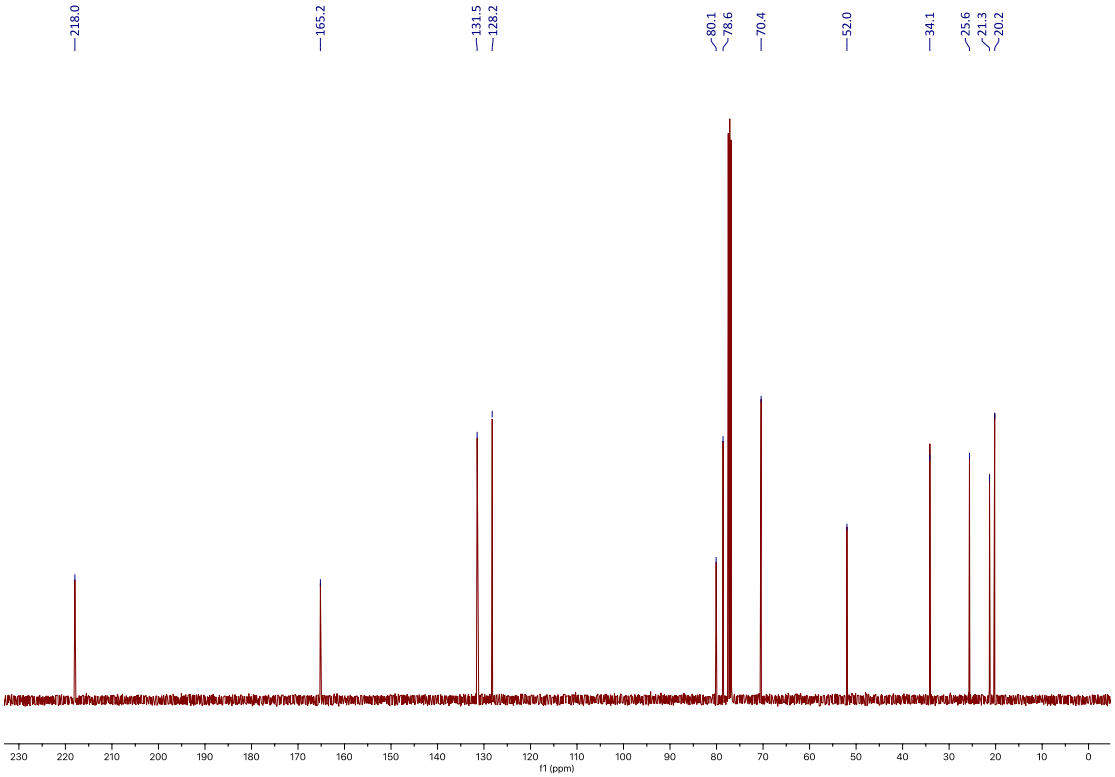
0.95
1.01
1.93
6.13
4.03
1.00
2.00
2.00
3.01
f1 (ppm)

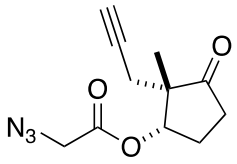

211.9
172.4
138.1
115.7
80.1
77.2
50.9
37.6
33.8
33.1
25.2
24.2
23.3
21.3
20.9
f1 (ppm)


O
O
O

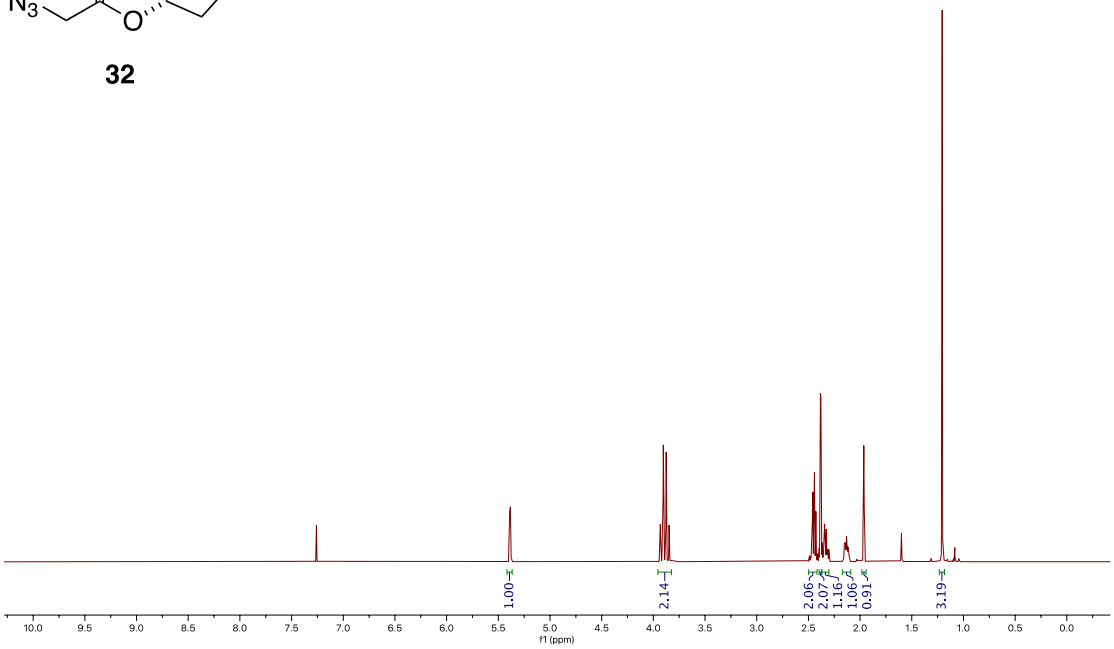
31

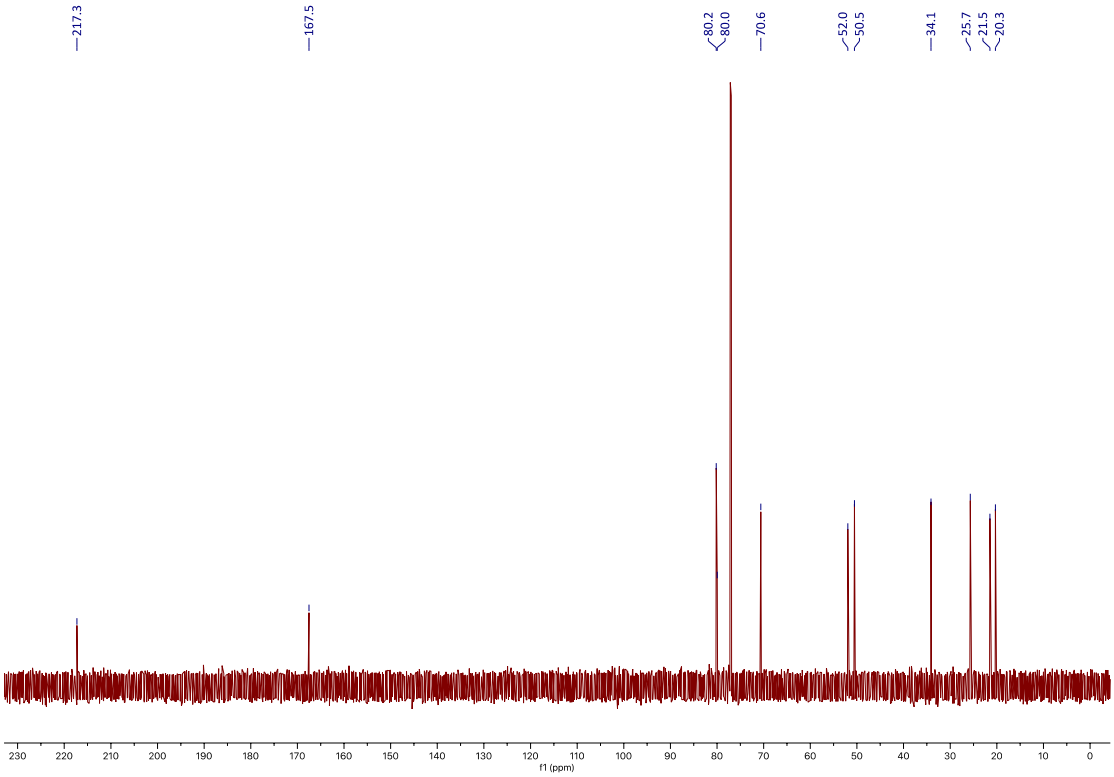
1.00
0.95
1.00
0.96
3.97
1.10
1.04
0.95
3.01
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

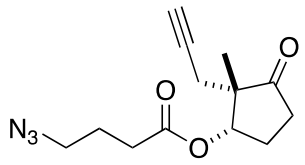

218.0
165.2
131.5
128.2
80.1
78.6
70.4
52.0
34.1
25.6
21.3
20.2
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O
O
N3
O

32

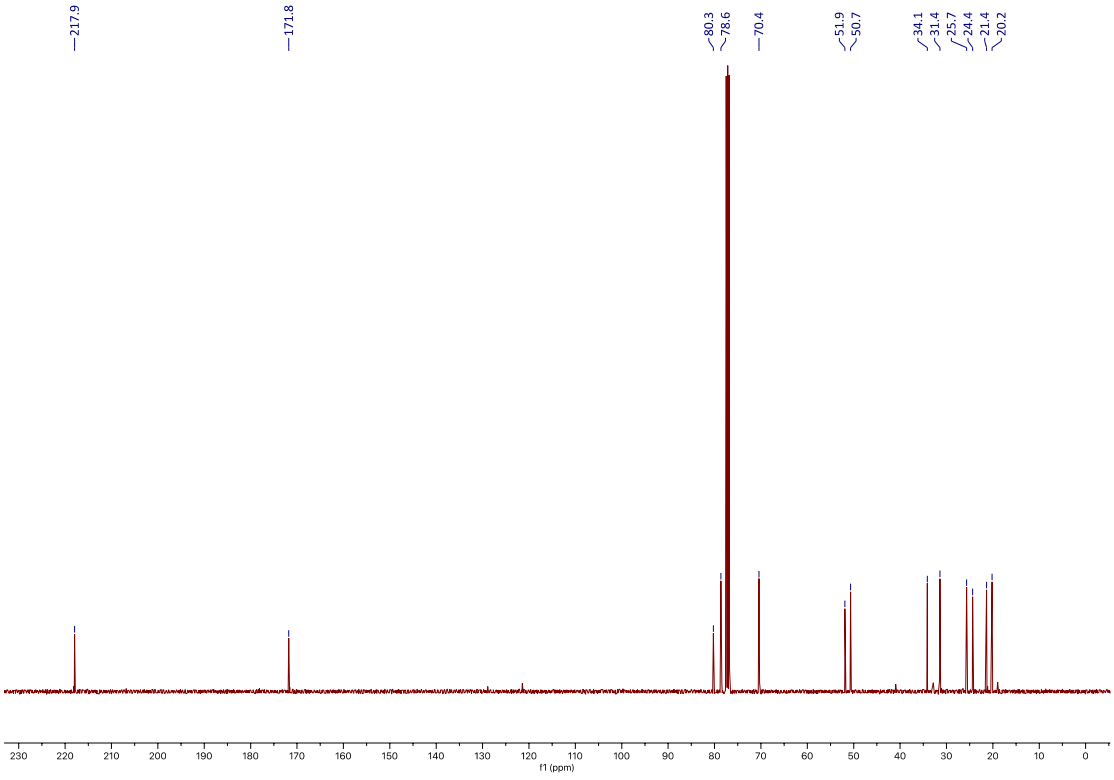

1.00
2.14
2.06
2.07
1.16
1.06
0.91
3.19
f1 (ppm)

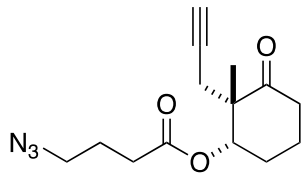

217.3
167.5
80.2
80.0
70.6
52.0
50.5
34.1
25.7
21.5
20.3
f1 (ppm)


N3
O
O
O

33

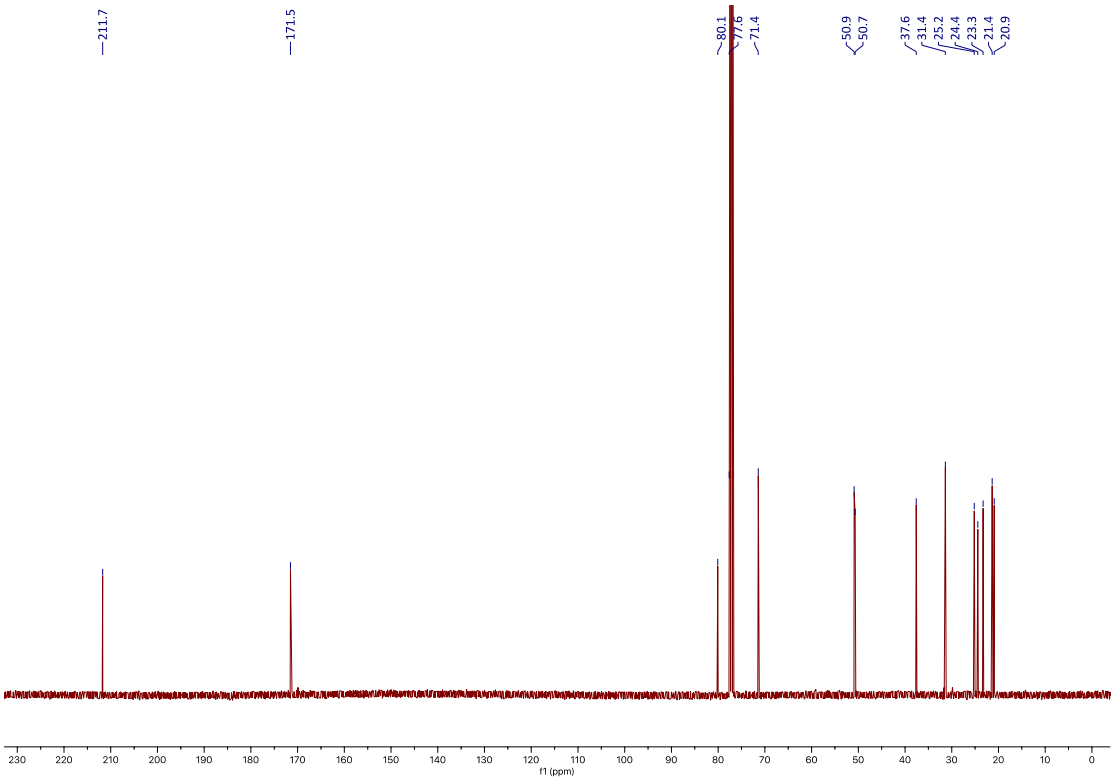
1.00
1.93
3.82
2.10
1.08
1.15
2.91
3.09
f1 (ppm)

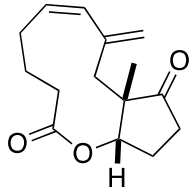

217.9
171.8
80.3
78.6
70.4
51.9
50.7
34.1
31.4
25.7
24.4
21.4
20.2
f1 (ppm)


O
O
N3
O

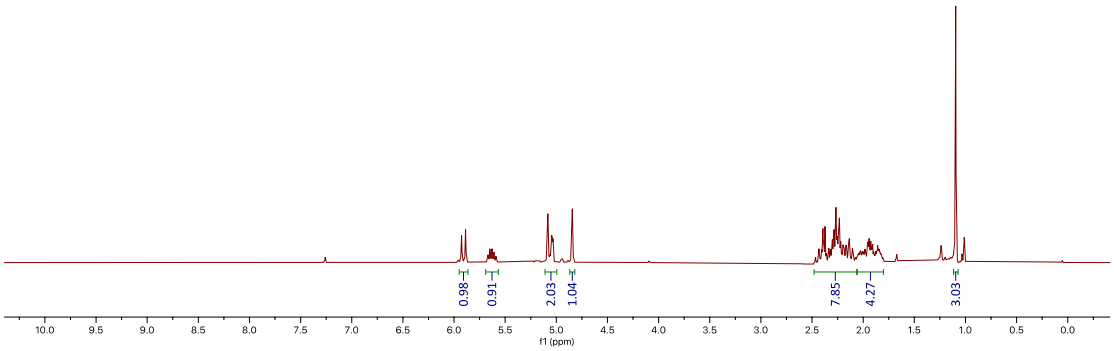
S12

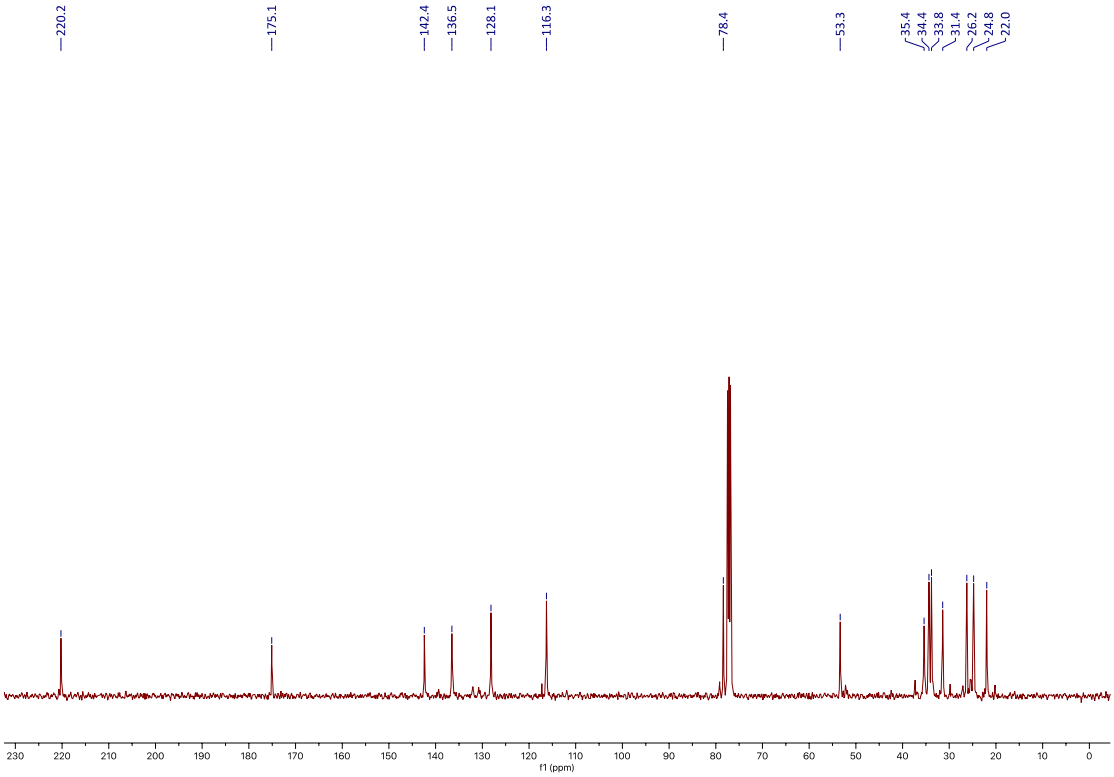
0.97
1.93
6.00
2.09
0.99
3.90
3.01
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

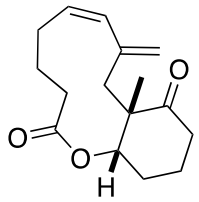

211.7
171.5
80.1
77.6
71.4
50.9
50.7
37.6
31.4
25.2
24.4
23.3
21.4
20.9
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O
O
O
H

34

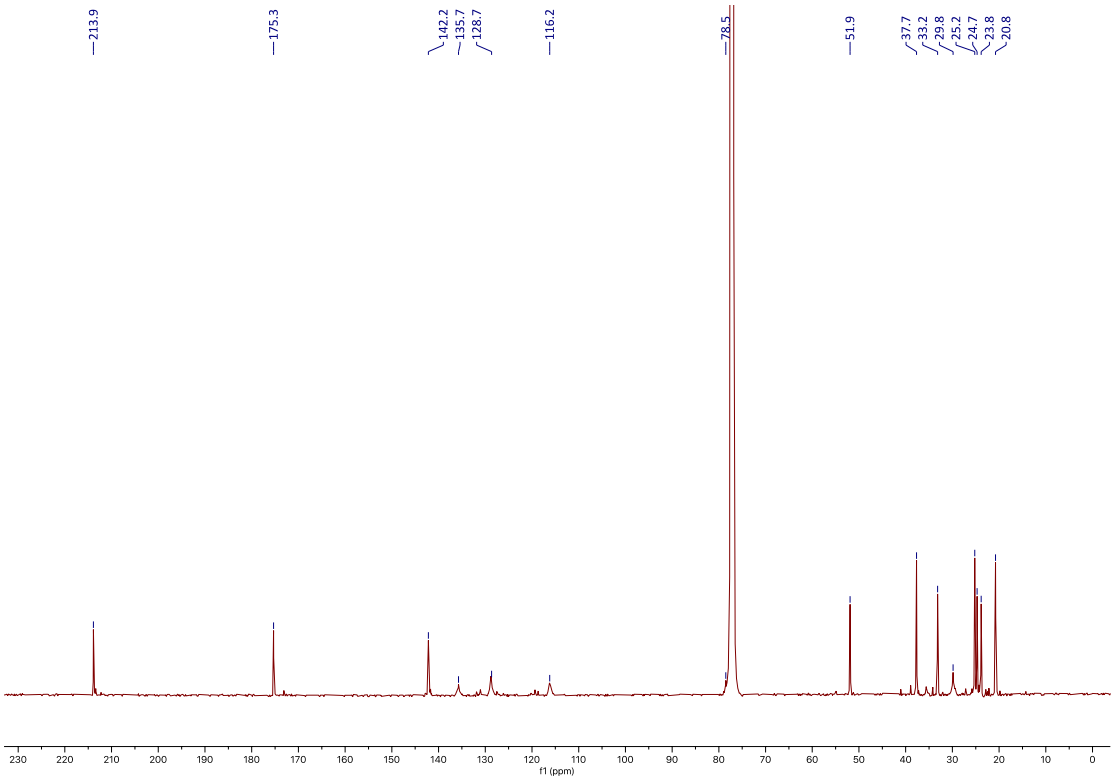

0.98
0.91
2.03
1.04
7.85
4.27
3.03
f1 (ppm)

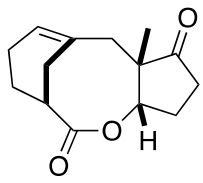

220.2
175.1
142.4
136.5
128.1
116.3
78.4
53.3
35.4
34.4
33.8
31.4
26.2
24.8
22.0
f1 (ppm)


O
O
O
H

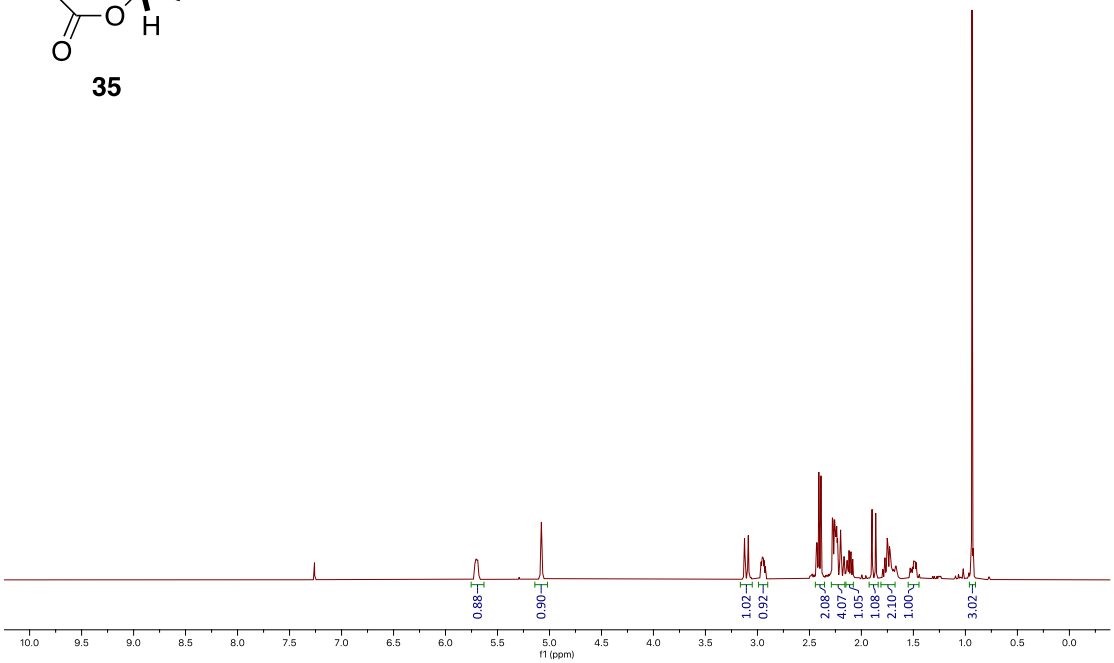
S13

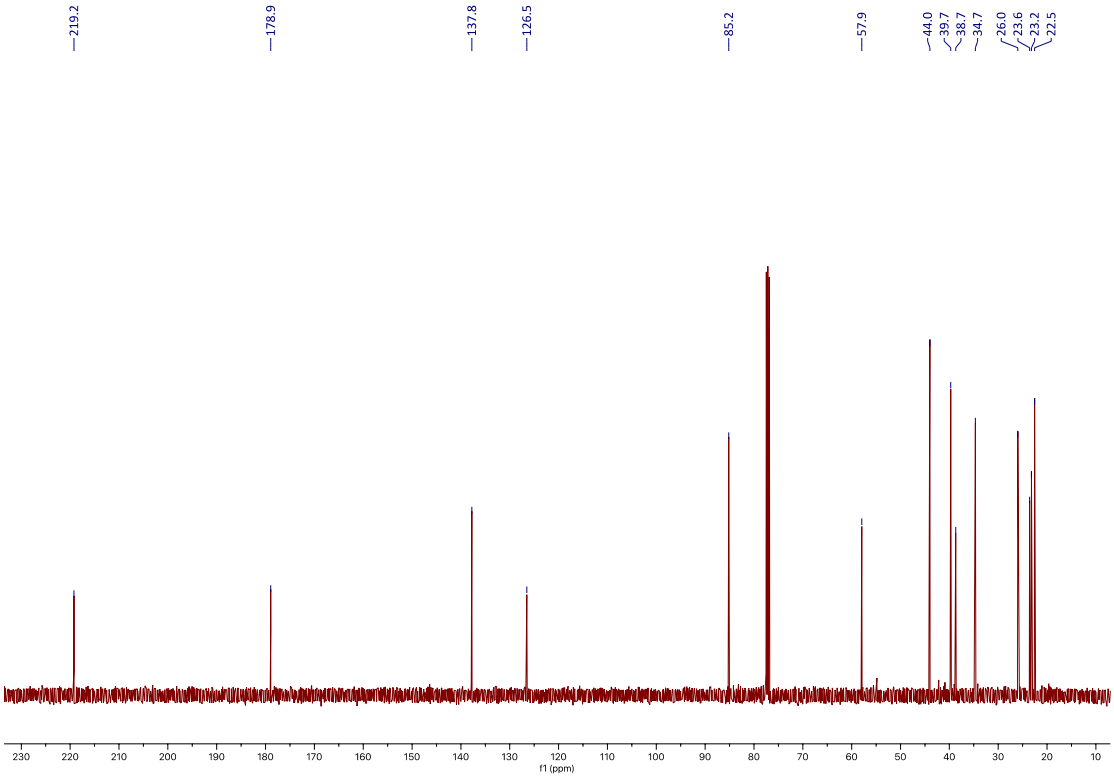
1.04
0.84
0.98
1.01
1.07
1.07
6.25
7.12
2.89
f1 (ppm)

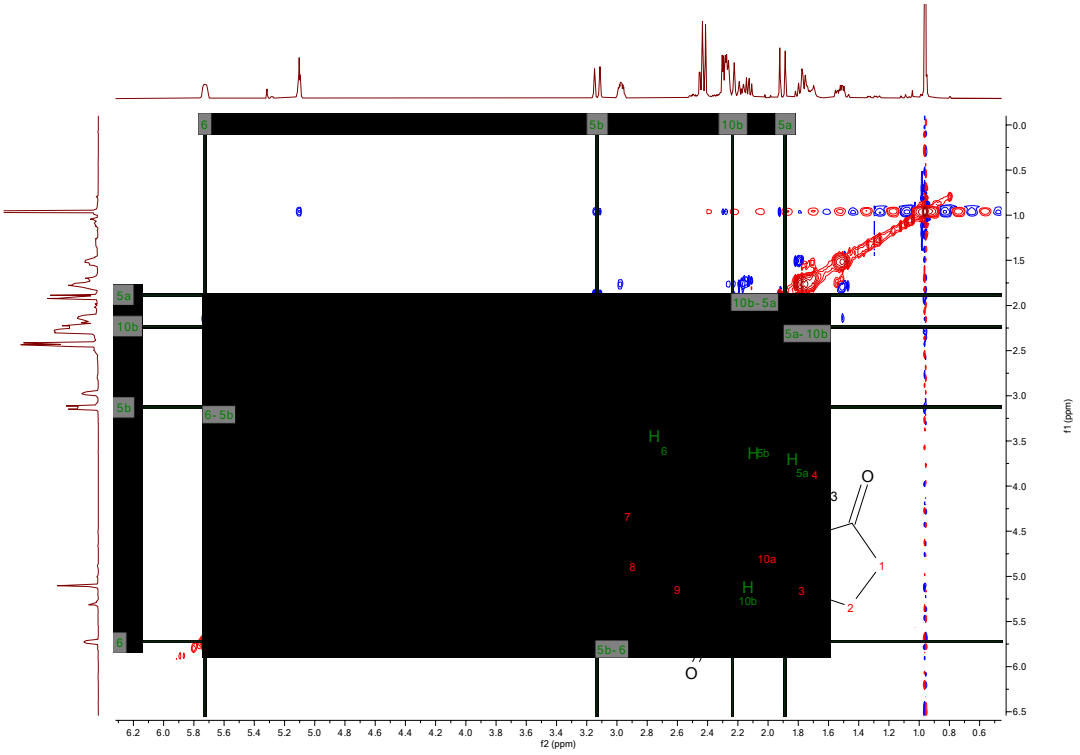

213.9
175.3
142.2
135.7
128.7
116.2
78.5
51.9
37.7
33.2
29.8
25.2
24.7
23.8
20.8
f1 (ppm)

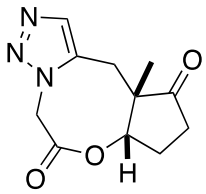

O
O
O
H

35


0.88
0.90
1.02
0.92
2.08
4.07
1.05
1.08
2.10
1.00
3.02
f1 (ppm)

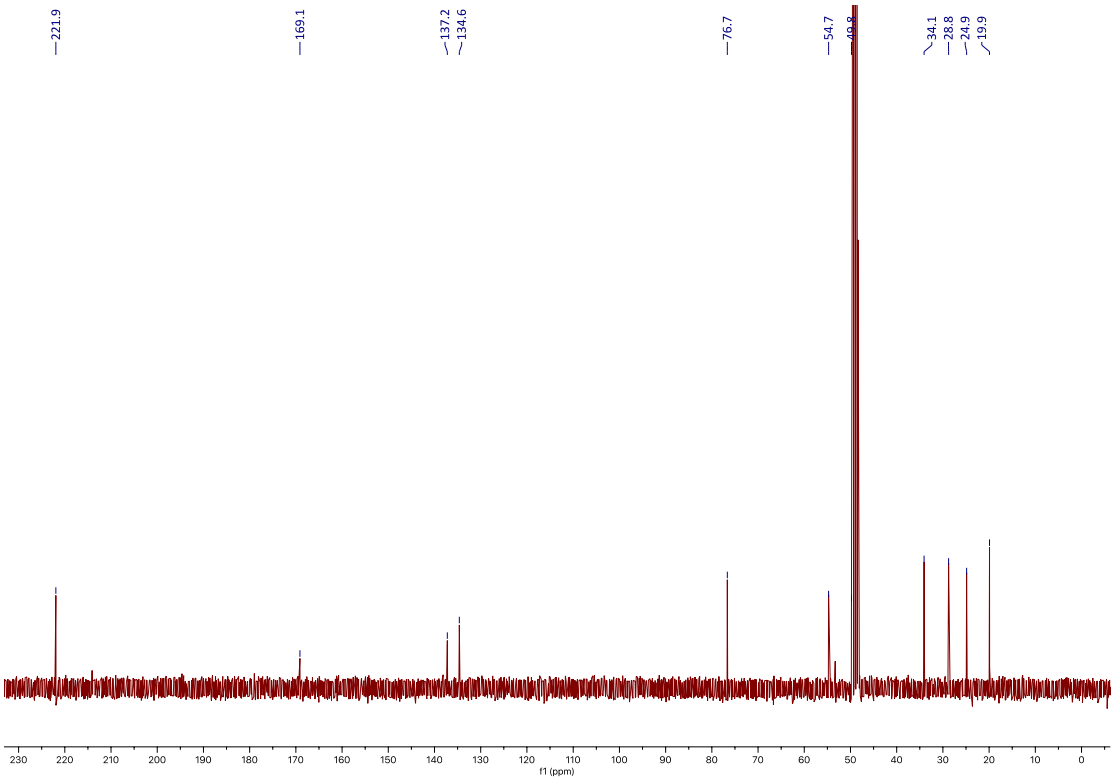

219.2
178.9
137.8
126.5
85.2
57.9
44.0
39.7
38.7
34.7
26.0
23.6
23.2
22.5
f1 (ppm)

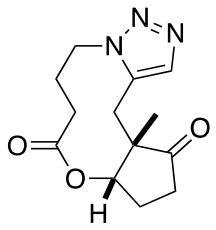

6
5b
10b
5a
5a
10b
5b
6
10b- 5a
5a- 10b
6- 5b
5b- 6
H 6
H 5b
H 5a
4
3
O
7
8
9
10a
H 10b
1
2
O
f2 (ppm)
f1 (ppm)



36

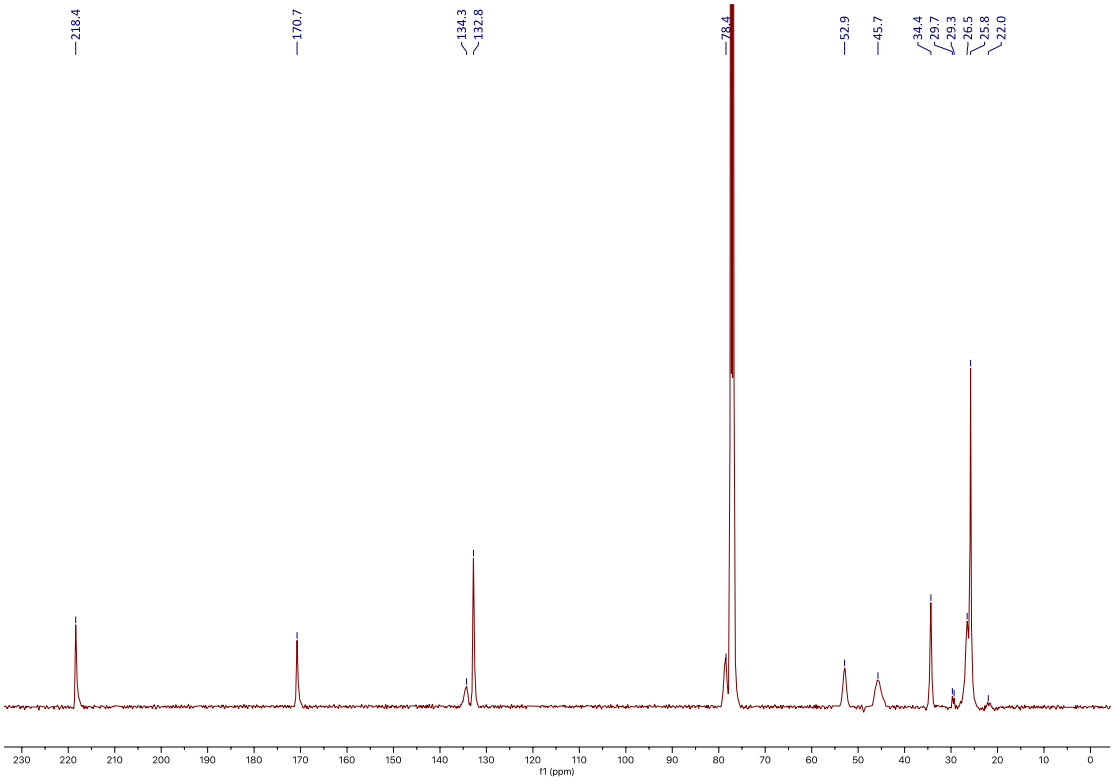
0.94
0.99
1.00
0.97
1.00
0.98
1.91
1.10
1.04
3.01
f1 (ppm)

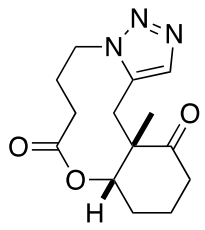

221.9
169.1
137.2
134.6
76.7
54.7
49.8
34.1
28.8
24.9
19.9
f1 (ppm)


N
N
N
O
O
O
H

37

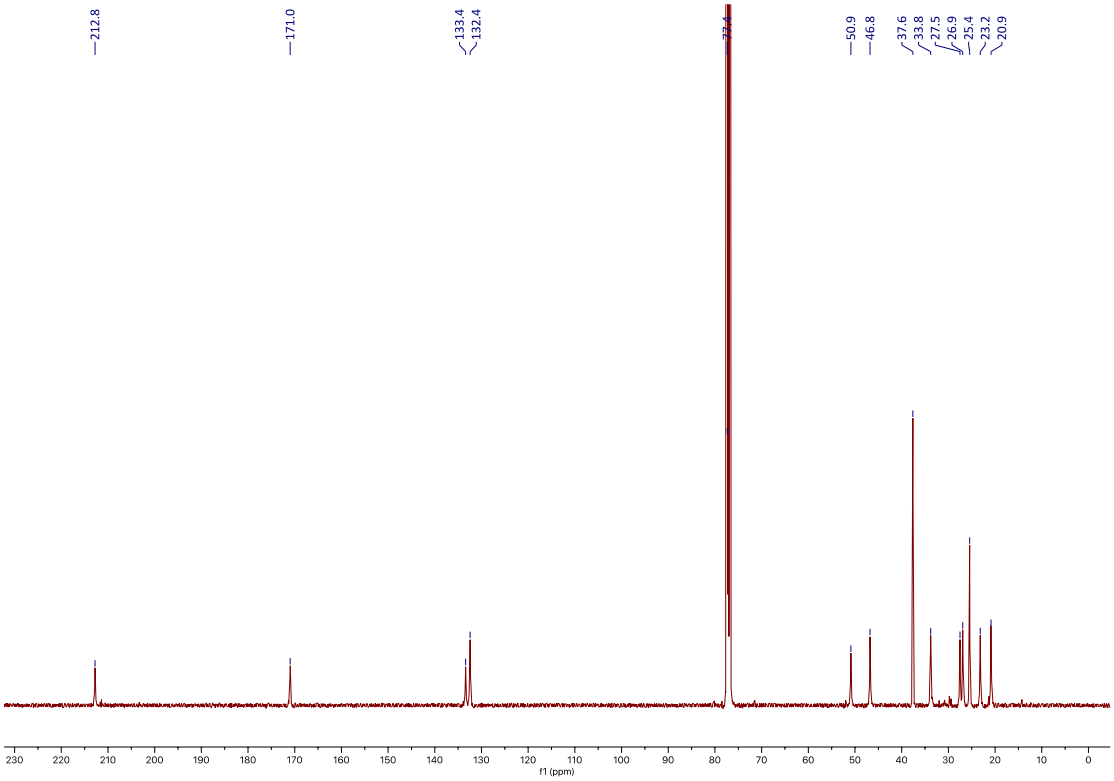
1.00
2.07
1.08
6.99
1.91
1.18
3.37
f1 (ppm)

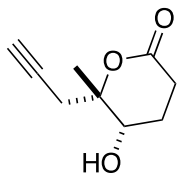

218.4
170.7
134.3
132.8
78.4
52.9
45.7
34.4
29.7
29.3
26.5
25.8
22.0
f1 (ppm)



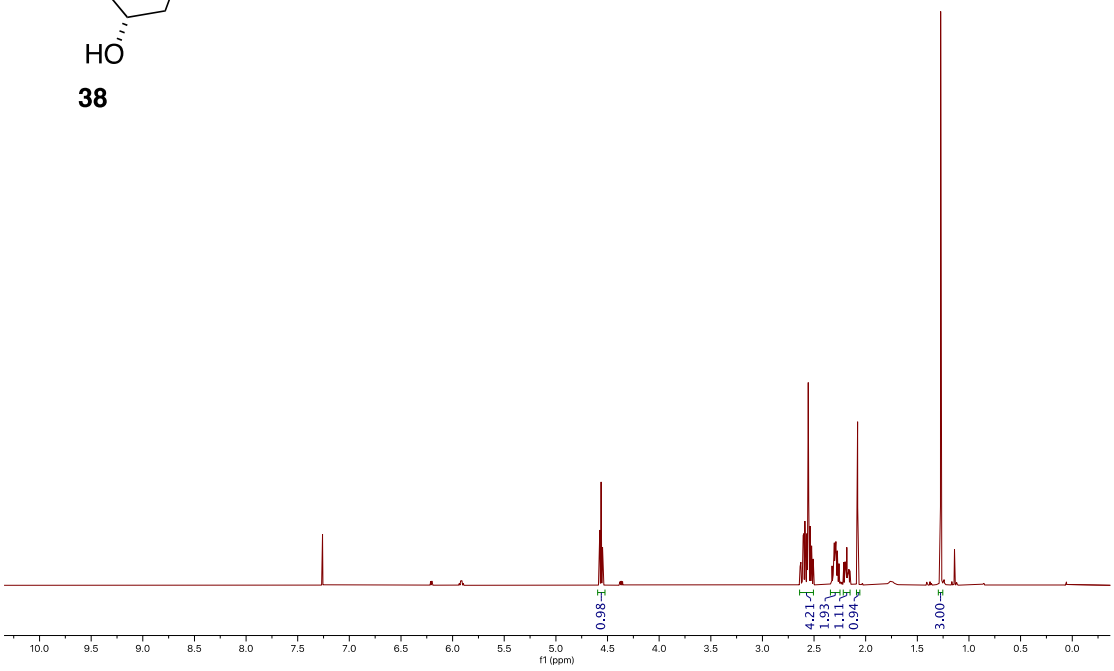
S14

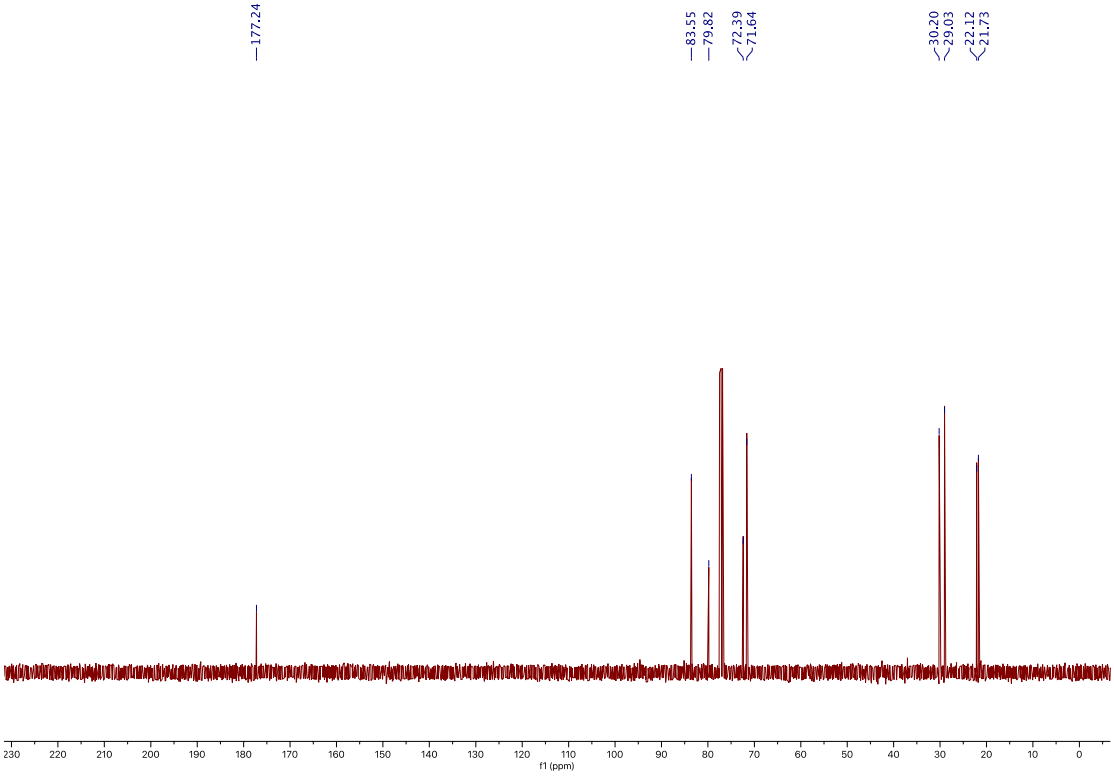
0.98
1.79
1.04
1.02
2.97
3.96
4.13
3.00
f1 (ppm)

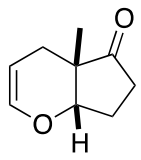

212.8
171.0
133.4
132.4
77.4
50.9
46.8
37.6
33.8
27.5
26.9
25.4
23.2
20.9
f1 (ppm)


O
O
HO

38

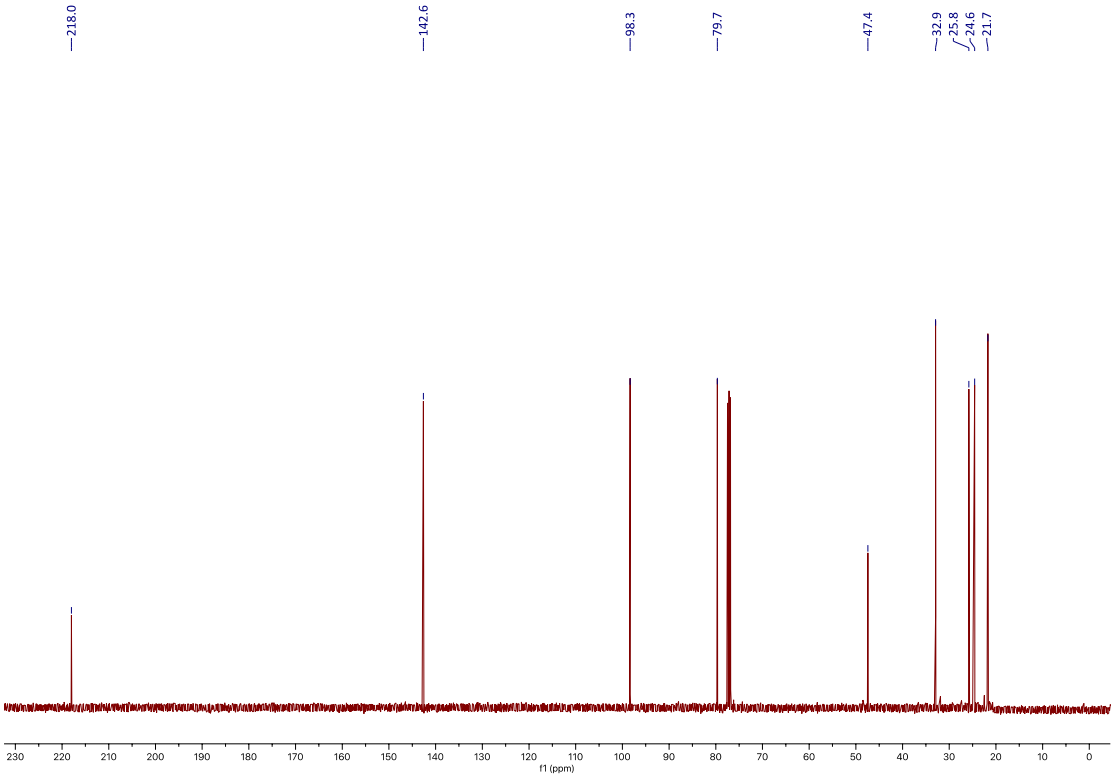

0.98
4.21
1.93
1.11
0.94
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

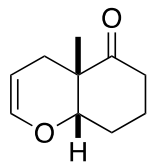

177.24
83.55
79.82
72.39
71.64
30.20
29.03
22.12
21.73
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O
O
H

39

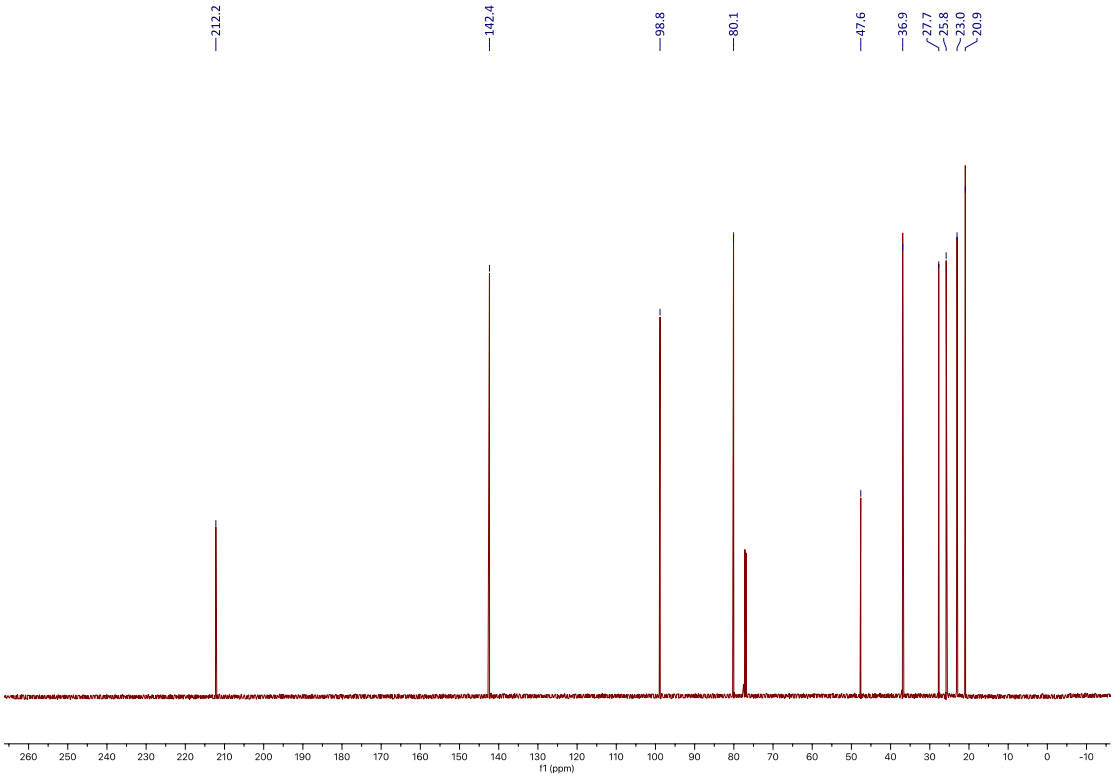
0.80
0.96
1.00
3.07
0.95
1.39
1.23
1.11
2.97
f1 (ppm)

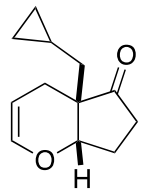

218.0
142.6
98.3
79.7
47.4
32.9
25.8
24.6
21.7
f1 (ppm)


O
O
H

S15

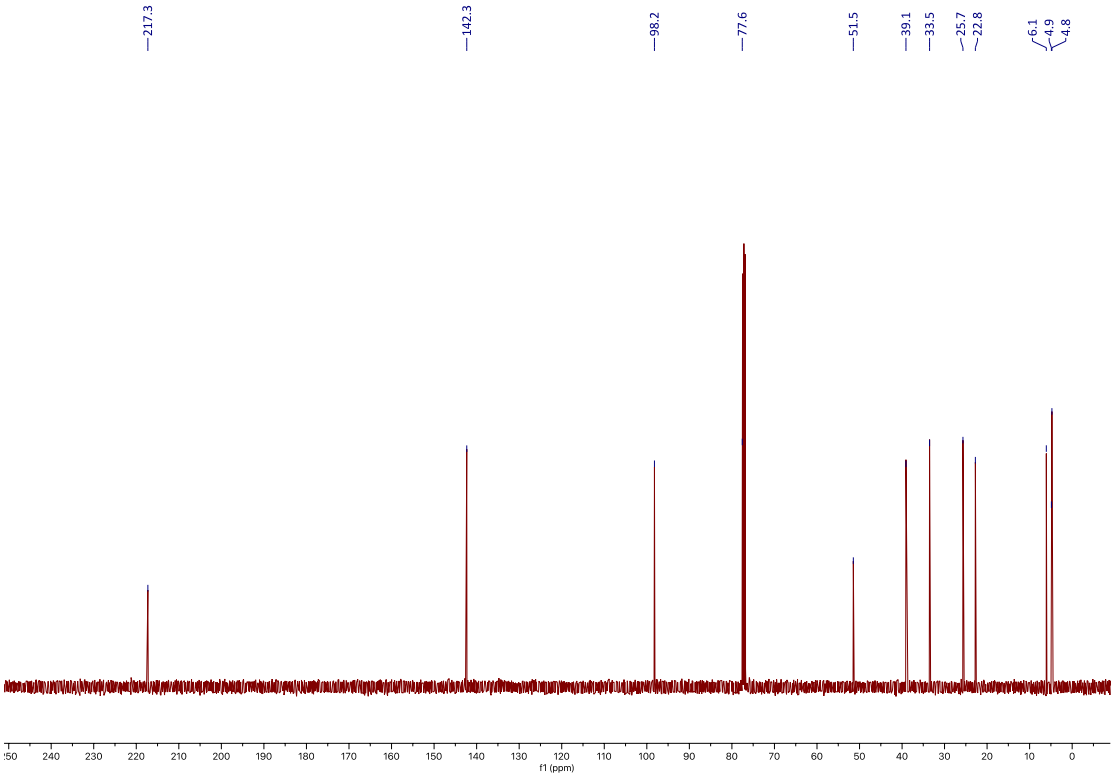
0.70
0.85
0.89
2.10
1.04
2.13
1.08
1.11
1.05
3.09
f1 (ppm)

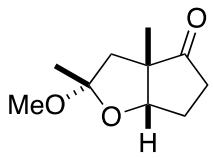

212.2
142.4
98.8
80.1
47.6
36.9
27.7
25.8
23.0
20.9
f1 (ppm)


O
O
H

S16

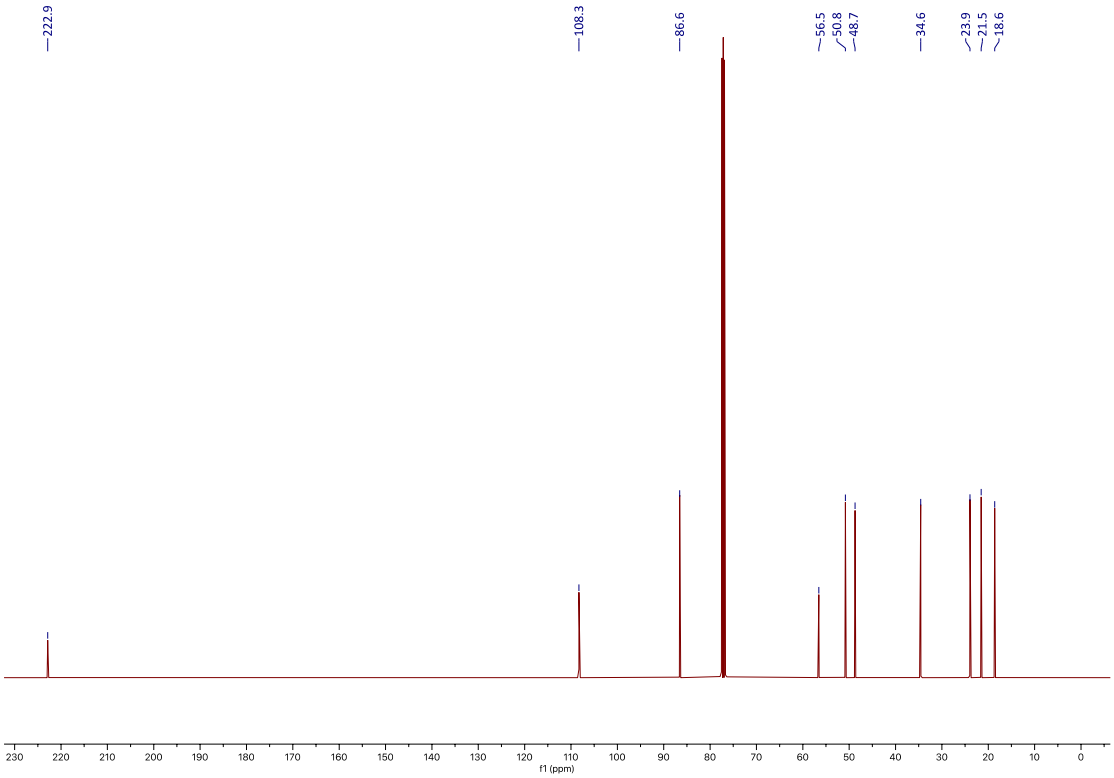
0.94
0.97
0.97
1.04
3.08
1.04
1.01
1.99
1.00
2.02
2.01
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

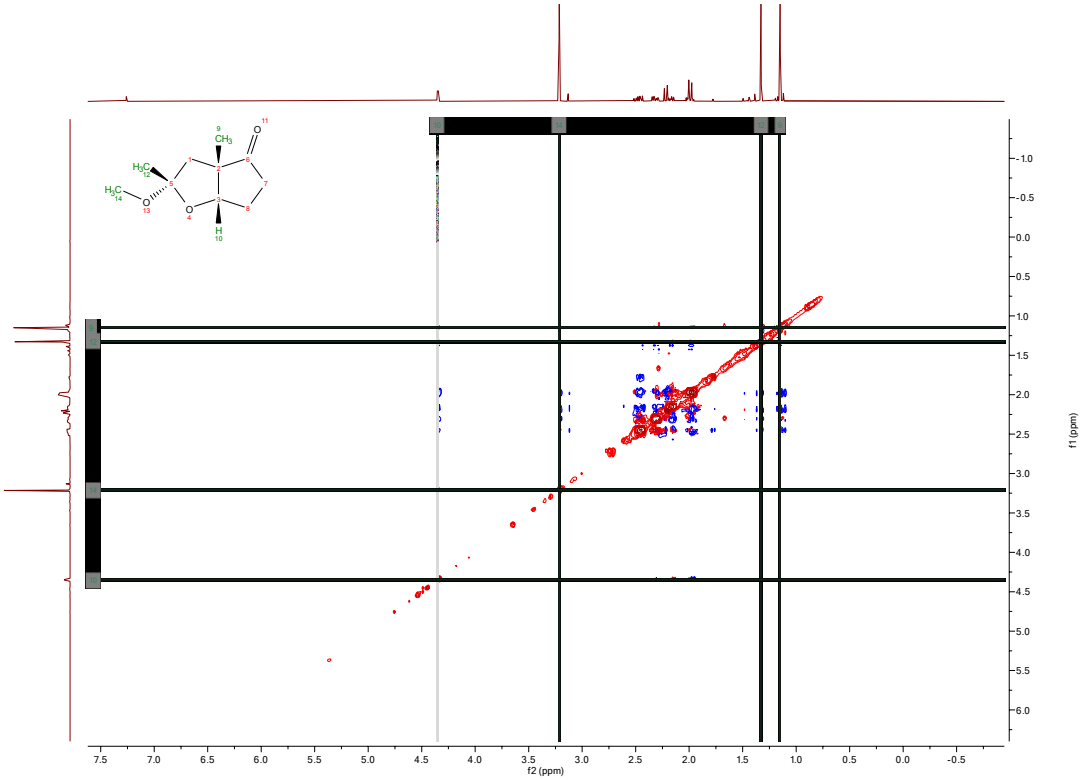

217.3
142.3
98.2
77.6
51.5
39.1
33.5
25.7
22.8
6.1
4.9
4.8
240
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

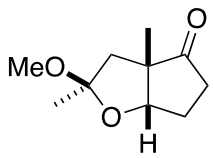

MeO
O
O
H

40a

0.98
3.00
1.08
1.17
2.16
2.13
3.17
3.27
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)

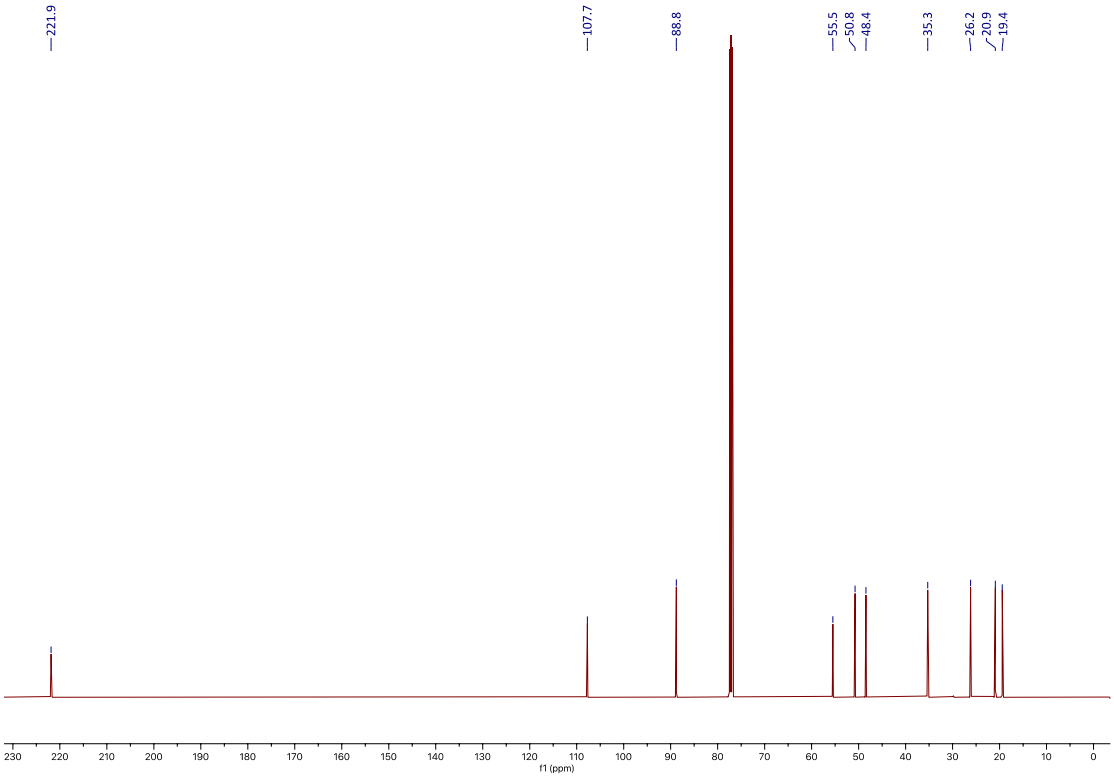

222.9
108.3
86.6
56.5
50.8
48.7
34.6
23.9
21.5
18.6
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

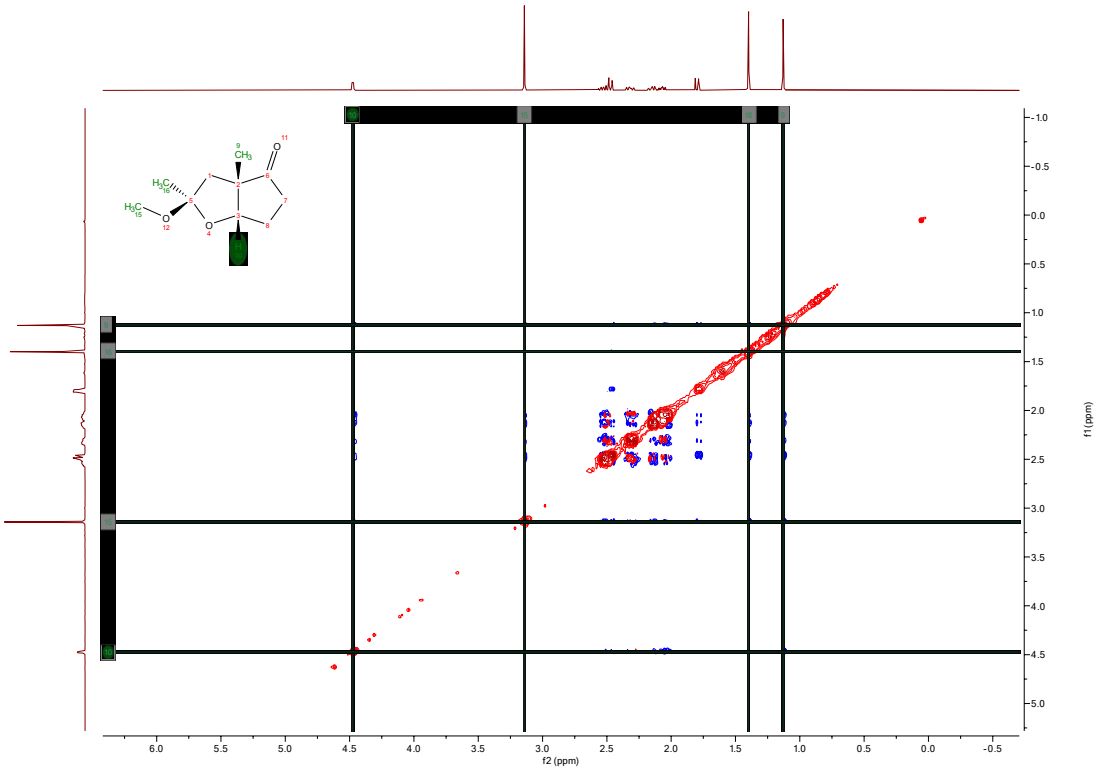

f2 (ppm)
f1 (ppm)

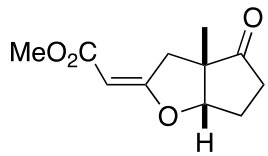

MeO
O
O
H

40b

1.00
3.08
2.07
1.06
2.14
1.01
3.15
3.16
f1 (ppm)

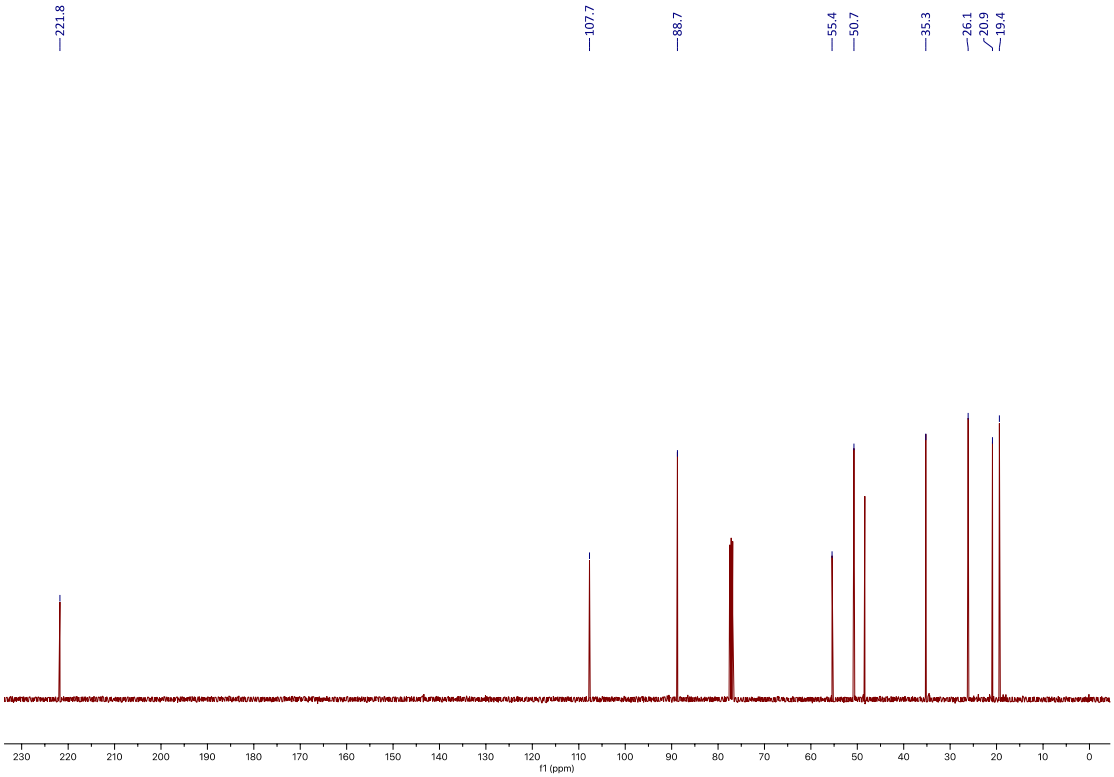

221.9
107.7
88.8
55.5
50.8
48.4
35.3
26.2
20.9
19.4
f1 (ppm)


f2 (ppm)
f1 (ppm)


MeO2C
O
O
H

41

0.97
3.02
2.08
1.06
1.08
1.07
1.12
3.01
3.05
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)


221.8
107.7
88.7
55.4
50.7
35.3
26.1
20.9
19.4
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)