Synthesis of the Bicyclic Butenolide Core of Pallamolide A: A Biomimetic Approach

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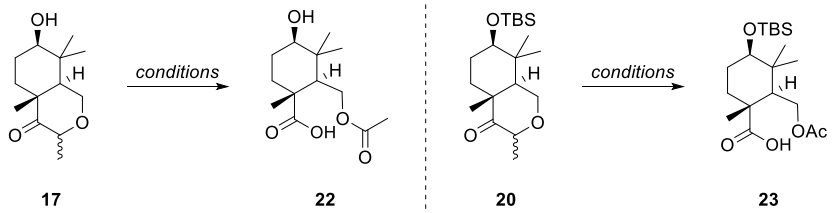
Supporting Information

Investigation of the autoxidation of keto-ether 17 and 20

Table **S1**. Investigation of the autoxidation of keto-ether **17** and **20**.



17 **22** **20** **23**

Entry	Substrate	Conditions	Results
1	**17**	Open to air, absence of light, rt, 5 d	inseparable mixture of **22** + other oxidation products
2		Open to air, absence of light, rt, 32 d	91%
3		O_2 (balloon), absence of light, rt, 1 d	no product observed by TLC analysis
4	**20**	Open to air, absence of light, rt, 5 d	1:0.067 **20**:**23**
5		Open to air, absence of light, rt, 32 d	86%
6		Open to air, cyclohexane, 50 °C, 1 d	no product observed by TLC analysis
7		Open to air, methanolic KOH, 1 d	no product observed by TLC analysis
8		O_2 (balloon), Cu_2O, hppH, MeCN, rt, 1h	inseparable mixture of **23** + other oxidation products

hppH = 1,3,4,6,7,8-hexahydro-2*H*-pyrimido[1,2-a]pyrimidine (hppH)

General Methods

Unless otherwise noted, all reactions were performed in oven-dried glassware under an oxygen-free atmosphere of nitrogen. Anhydrous solvents were either freshly distilled or dried using an LC Technology Solutions Inc. SP-1 solvent purification system (under an atmosphere of dry nitrogen). Tetrahydrofuran (THF) and diethyl ether (Et_2O) were freshly distilled over sodium/benzophenone ketyl. Dichloromethane (CH_2Cl_2) was freshly distilled from calcium hydride. Toluene was freshly distilled over sodium. Triethylamine and diisopropylamine were freshly distilled from calcium hydride and stored over molecular sieves (Linde type 4 Å). Commercially available starting materials and all other reagents were used as received unless otherwise noted.

Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. Reactions performed at low temperature were cooled either with an acetone/dry ice bath to reach −78 °C, acetonitrile/dry ice bath to reach −50 °C, a salt/ice bath to reach −20 °C or an ice/water bath to reach 0 °C. Reactions were monitored by thin-layer chromatography (TLC) carried out on E. Merck silica gel plates using UV light (254 and/or 360 nm) as visualizing agent and an ethanolic solution of vanillin or potassium permanganate and heat as developing agents. Kieselgel S 63-100 μm (Riedel-de-Hahn) silica gel was used for flash chromatography.

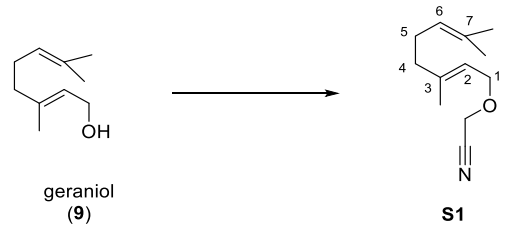
NMR spectra were recorded at room temperature in $CDCl_3$ solution on a Bruker DRX400 spectrometer operating at 400 MHz for ^{1}H nuclei and 100 MHz for ^{13}C nuclei. Chemical shifts are reported in parts per million (ppm) from tetramethylsilane (δ 0.00 ppm) and were measured relative to the solvent in which the sample was analysed ($CDCl_3$: δ_H 7.26 ppm or δ_H 0.00 ppm (TMS), δ_C 77.2 ppm). ^{1}H NMR data were reported as position (δ), multiplicity (s = singlet, br s = broad singlet, d = doublet, br d = broad doublet, dd = doublet of doublets, ddd = doublet of doublets of doublets, dq = doublet of quartets, t = triplet, dt = doublet of triplets, q = quartet, quin = quintet, ABq = AB quartet, m = multiplet), coupling constant (J, Hz), relative integral and structural assignment. ^{13}C NMR data were reported as position (δ), type (CH_3, CH_2, CH or C) and structural assignment. Assignments were achieved with the aid of DEPT 135, COSY, HSQC, HMBC and NOESY experiments where required. Where specified diastereomeric resonances are denoted by *, ** or † where specified.

Infrared (IR) spectra were recorded on a Perkin Elmer Spectrum 100 FT-IR spectrometer using a diamond ATR sampling accessory. Absorption maxima are expressed in wavenumbers

(cm^{-1}). High-resolution mass spectra (HRMS) were obtained using a VG70SE spectrometer or on a micrOTOF-Q II mass spectrometer.

Experimental Procedures and Characterisation Data

(*E*)-2-((3,7-Dimethylocta-2,6-dien-1-yl)oxy)acetonitrile (S1)



To a suspension of NaH (3.37 g, 84.3 mmol, 60% dispersion in mineral oil) in THF (50 mL) at rt was added geraniol (**9**) (5.6 mL, 32.4 mmol) dropwise. The reaction was heated to reflux for 2.5 h, then cooled to rt. To the yellow suspension was added bromoacetonitrile (4.0 mL, 58.3 mmol) dropwise over 2.5 h. The reaction was immediately quenched with MeOH (5 mL), then concentrated *in vacuo* onto Celite® (22 g). The resulting powder was filtered through a short plug of silica gel (5% EtOAc in pet. ether) to afford the *title compound* **S1** (4.60 g, 73%) as a colourless oil.

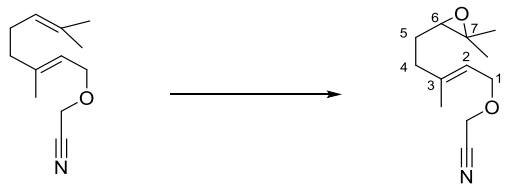
R_f : 0.88 (20% EtOAc in pet. ether);

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.30 – 5.26 (m, 1H, H-2), 5.09 – 5.04 (m, 1H, H-6), 4.20 (s, 2H, OCH_2CN), 4.14 (d, J = 7.2 Hz, 2H, H-1), 2.12 – 2.04 (m, 4H, H-4, H-5), 1.71 (s, 3H, 3-CH_3), 1.67 (s, 3H, 7-CH_{3a}), 1.59 (s, 3H, 7-CH_{3b});

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.9 (C, C-3), 132.0 (C, C-7), 123.7 (CH, C-6), 118.4 (CH, C-2), 116.3 (C, CN), 67.3 (CH_2, C-1), 54.4 (CH_2, O*C*H_2CN), 39.7 (CH_2, C-4), 26.3 (CH_2, C-5), 25.7 (CH_3, 7-CH_{3a}), 17.7 (CH_3, 7-CH_{3b}), 16.5 (CH_3, 3-CH_3).

Spectroscopic data obtained were in agreement with those reported in the literature.[16]

(*E*)-2-((5-(3,3-Dimethyloxiran-2-yl)-3-methylpent-2-en-1-yl)oxy)acetonitrile (18)



S1 **18**

To a solution of alkene **S1** (6.00 g, 31.0 mmol) in THF/H_2O (1.2 L, 2:1 *v/v*) at 0 °C was added recrystallised NBS (7.18 g, 40.4 mmol) in THF/H_2O (70 mL, 2:1 *v/v*) dropwise over 1 h. The reaction mixture was stirred at 0 °C for a further 1.3 h before the addition of sat. aq. $Na_2S_2O_3$ (20 mL). K_2CO_3 (21.5 g, 155 mmol) and MeOH (160 mL) were then added and the resulting mixture was allowed to warm to rt and stirred overnight. Most of the organic solvent was removed under reduced pressure and the residue was extracted with EtOAc (3 × 750 mL). The combined organic extracts were washed with brine (75 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude oil was purified by flash chromatography (10 → 45% EtOAc in pet. ether) to afford the *title compound* **18** (5.40 g, 83%) as a colourless oil.

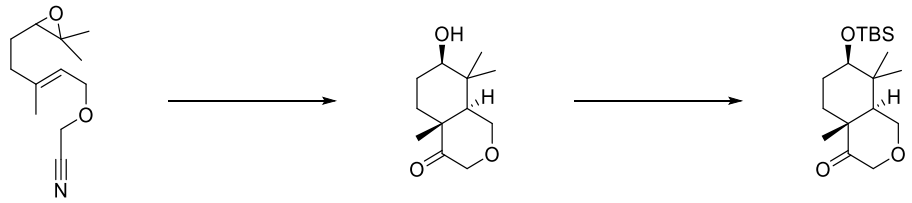
R_f : 0.58 (20% EtOAc in pet. ether);

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.35 – 5.31 (m, 1H, H-2), 4.20 (s, 2H, OCH_2CN), 4.12 (d, J = 7.0 Hz, 2H, H-1), 2.67 (t, J = 6.2 Hz, 1H, H-6), 2.26 – 2.11 (m, 2H, H-4), 1.71 (s, 3H, 3-CH_3), 1.69 – 1.57 (m, 2H, H-5), 1.27 (s, 3H, 7-CH_{3a}), 1.23 (s, 3H, 7-CH_{3b});

^{13}C NMR (100 MHz, $CDCl_3$): δ 142.8 (C, C-3), 119.0 (CH, C-2), 116.3 (C, CN), 67.4 (CH_2, C-1), 63.9 (CH, C-6), 58.3 (C, C-7), 54.7 (CH_2, O*C*H_2CN), 36.4 (CH_2, C-4), 27.1 (CH_2, C-5), 24.9 (CH_3, 7-CH_{3a}), 18.9 (CH_3, 7-CH_{3b}), 16.6 (CH_3, 3-CH_3).

Spectroscopic data obtained were in agreement with those reported in the literature.[16]

(±)-(4a*R*,7*R*,8a*R*)-7-((*Tert*-butyldimethylsilyl)oxy)-4a,8,8-trimethylhexahydro-1*H*-isochromen-4(3*H*)-one (S2)



18 19 S2

A mixture of Cp_2TiCl_2 (15.8 g, 27.6 mmol) and Zn dust (8.30 g, 127 mmol) in rigorously deoxygenated THF (110 mL) was stirred at rt for 20 min. The resulting green solution was then added dropwise over 1.3 h to a solution of epoxide **18** (5.77 g, 27.6 mmol) in deoxygenated THF (980 mL) at rt. The reaction was stirred at rt for 1.2 h, then quenched with sat. aq. KH_2PO_4 (60 mL) and stirred at rt overnight. The mixture was filtered over Celite®, concentrated to remove most of the organic solvent, and the residue was partitioned between EtOAc (250 mL) and water (100 mL). The organic phase was separated and the aqueous phase was extracted with EtOAc (2 × 150 mL). The combined organic extracts were washed with sat. aq. $NaHCO_3$ (50 mL) and brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to afford crude **19**. A sample of high purity for analysis could be obtained by flash chromatography (40% EtOAc in pet. ether) to afford the *title compound* **19** as a colourless oil that solidifies upon storage.

R_f : 0.42 (40% EtOAc in pet. ether);

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.00 (ABq, $\Delta\delta_{AB}$ = 0.2, J_{AB} = 16.6 Hz, 2H, H-3), 3.98 – 3.96 (m, 2H, H-1), 3.20 (dd, J = 11.4, 4.5 Hz, 1H, H-7), 1.80 (dt, J = 13.4, 3.3 Hz, 1H, H-5$_a$), 1.74 (dq, J = 13.0, 3.8, 1H, H-6$_a$), 1.67 – 1.59 (m, 2H, H-6$_b$, H-8a), 1.50 (dd, J = 14.4, 4.0, 1H, H-5$_b$), 1.27 (s, 3H, 4a-CH_3), 0.99 (s, 3H, 8-CH_{3a}), 0.94 (s, 3H, 8-CH_{3b});

^{13}C NMR (100 MHz, $CDCl_3$): δ 213.5 (C, C-4), 77.4 (CH, C-7), 69.9 (CH_2, C-3), 63.2 (CH_2, C-1), 46.7 (CH, C-8a), 45.5 (C, C-4a), 38.2 (C, C-8), 30.8 (CH_2, C-5), 27.2 (CH_3, 8-CH_{3a}), 26.2 (CH_2, C-6), 17.8 (CH_3, 4a-CH_3), 15.5 (CH_3, 8-CH_{3b}).

Spectroscopic data obtained were in agreement with those reported in the literature.[16]

To a solution of crude ketone **19** in CH_2Cl_2 (150 mL) at −50 °C was added 2,6-lutidine (7.7 mL, 66.1 mmol), then TBSOTf (7.1 mL, 33.1 mmol) dropwise. The resulting solution was stirred at this temperature for 40 mins then quenched with sat. aq. NH_4Cl (50 mL). The mixture was allowed to warm to rt and extracted with CH_2Cl_2 (2 × 100 mL). The combined organic extracts were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude mixture was purified by flash chromatography (5 → 10% EtOAc in pet. ether) to afford the *title compound* **S2** (3.13 g, 35%) as a white solid.

R_f : 0.75 (10% EtOAc in pet. ether); 0.33 (10% Et_2O in pet. ether);

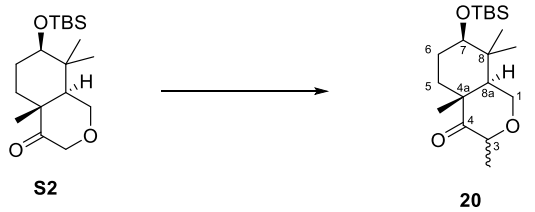
IR ν_{max} (neat): 2929, 2885, 1780, 1096, 832 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.01 (ABq, $\Delta\delta_{AB}$ = 0.2, J_{AB} = 16.6 Hz, 2H, H-3), 3.99 – 3.96 (m, 2H, H-1), 3.17 (dd, J = 8.9, 6.6 Hz, 1H, H-7), 1.78 (dt, J = 13.8, 3.4 Hz, 1H, H-5$_a$), 1.68 – 1.60 (m, 3H, H-6, H-8a), 1.50 – 1.43 (m, 1H, H-5$_b$), 1.28 (s, 3H, 4a-CH_3), 0.93 (s, 3H, 8-CH_{3a}), 0.92 (s, 3H, 8-CH_{3b}), 0.89 (s, 9H, TBS), 0.05 (s, 3H, TBS), 0.03 (s, 3H, TBS);

^{13}C NMR (100 MHz, $CDCl_3$): δ 213.8 (C, C-4), 78.6 (CH, C-7), 70.3 (CH_2, C-3), 63.8 (CH_3, C-1), 47.1 (CH, C-8a), 45.8 (C, C-4a), 39.1 (C, C-8), 31.0 (CH_2, C-5), 28.0 (CH_3, 8-CH_{3a}), 27.2 (CH_2, C-6), 26.0 (CH_3, 3 × TBS), 18.2 (C, TBS), 18.1 (CH_3, 4a-CH_3), 16.2 (CH_3, 8-CH_{3b}), −3.7 (CH_3, TBS), −4.8 (CH_3, TBS);

HRMS *m/z* (ESI/Q-TOF) $[M + Na]^+$ calcd for $C_{18}H_{34}NaO_3Si$, 349.2169; found, 349.2160.

(±)-(4a*R*,7*R*,8a*R*)-7-((*Tert*-butyldimethylsilyl)oxy)-3,4a,8,8-tetramethylhexahydro-1*H*-isochromen-4(3*H*)-one (20)



To a solution of *n*BuLi (0.50 mL, 0.92 mmol, 1.9 M in cyclohexane) in THF (3.0 mL) at −78 °C was added diisopropylamine (0.12 mL, 0.92 mmol), and the reaction was stirred at this temperature for 5 min. To the reaction mixture was added ketone **S2** (100 mg, 0.306 mmol) in THF (0.65 mL). The reaction was warmed to rt, stirred for 45 min, then cooled to −78 °C and MeI (0.07 mL, 1.53 mmol) was added dropwise. The reaction mixture was warmed to rt and stirred for 1.5 h, then quenched with sat. aq. NH_4Cl (1.75 mL) and stirred for 5 min. The reaction mixture was extracted with Et_2O (3 × 4 mL), and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude mixture was purified by flash chromatography (1 → 10% Et_2O in pet. ether) to afford the *title compound* **20** (52 mg, 50%, in a 1:0.6 diastereomeric ratio) as a white solid.

R_f : 0.52 (10% Et_2O in pet. ether);

IR ν_{max} (neat): 2938, 2858, 1722, 1107, 836 cm^{-1};

m.p 40 – 42 °C;

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.20 (q, J = 6.5 Hz, 0.4H, H-3**), 4.02 – 3.98 (m, 2H, H-1†), 3.94 (q, J = 6.8 Hz, 0.6H, H-3*), 3.20 – 3.12 (m, 1H, H-7†), 1.80 – 1.53 (m, 4.4H, H-5$_a^\dagger$, H-5$_b$**, H-6†, H-8a†), 1.44 – 1.37 (m, 0.6H, H-5$_b$*), 1.31 (d, J = 6.6 Hz, 1.8H, 3-CH_3*), 1.27 (s, 1.2H, 4a-CH_3**), 1.26 (s, 1.8H, 4a-CH_3*), 1.23 (d, J = 6.5 Hz, 1.2H, 3-CH_3**), 0.99 (s, 1.8H, 8-CH_{3a}*), 0.97 (s, 1.2H, 8-CH_{3b}**), 0.89 (s, 9H, TBS†), 0.87 (s, 3H, 8-CH_{3b}* & 8-CH_{3a}**), 0.05 (s, 1.2H, TBS**), 0.04 (s, 1.8H, TBS*), 0.03 (s, 1.2H, TBS**), 0.02 (s, 1.8H, TBS*);

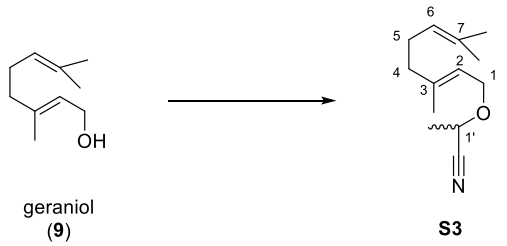
^{13}C NMR (100 MHz, $CDCl_3$): δ 217.2* & 212.0** (C, C-4), 78.9* & 78.4** (CH, C-7), 75.1* & 74.3** (CH, C-3), 63.7* & 63.4** (CH_2, C-1), 51.9 (CH, C-8a**), 46.9** & 44.6* (C, C-4a), 44.5 (CH, C-8a*), 39.5* & 38.8** (C, C-8) , 31.8* & 31.0** (CH_2, C-5), 28.3** & 27.6* (CH_3,

8-CH_{3b}), 27.3** & 27.2* (CH_2, C-6), 26.0 (CH_3, 3 × TBS†), 18.5 (C, TBS†), 18.2* & 18.1** (CH_3, 4a-CH_3), 17.3 (CH_3, 3-CH_3*), 16.9 (8-CH_{3a}**), 15.6 (CH_3, 3-CH_3** or 8-CH_{3a}*), 15.5 (CH_3, 8-CH_{3a}* or 3-CH_3**), −3.7** & −3.8* (CH_3, TBS), −4.8 (CH_3, TBS†);

HRMS *m/z* (ESI/Q-TOF) $[M + Na]^+$ calcd for $C_{19}H_{36}O_3SiNa$, 363.2326; found, 363.2321.

*denotes peaks arising from major diastereomer **denotes peak arising from minor diastereomer †denotes peaks arising from both diastereomers

(*E*)-2-((3,7-Dimethylocta-2,6-dien-1-yl)oxy)propanenitrile (S3)



geraniol (**9**) → **S3**

To a suspension of NaH (340 mg, 8.43 mmol, 60% dispersion in mineral oil) in THF (5 mL) at rt was added geraniol (**9**) (0.56 mL, 3.24 mmol) dropwise. The reaction was heated to reflux for 2.5 h, then cooled to rt. To the resulting yellow mixture was added 2-bromopropionitrile (0.50 mL, 5.83 mmol) dropwise over 2.5 h, then the reaction was left to stir for 48 h. The reaction was quenched with MeOH (0.5 mL), then filtered over silica gel. The solid residue was washed with pet. ether (2 × 3 mL) and EtOAc (2 × 3 mL), and the filtrate was concentrated *in vacuo*. The resultant crude oil was purified by flash chromatography (5% EtOAc in pet. ether) to afford the *title compound* **S3** (322 mg, 48%) as a yellow oil.

R_f : 0.77 (20% EtOAc in pet. ether);

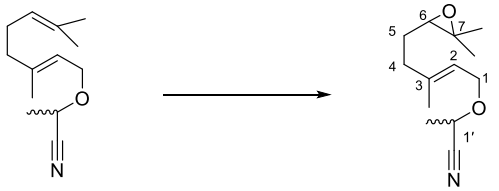
IR ν_{max} (neat): 3343, 2941, 2833, 1111, 1024, 735 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.33 – 5.29 (m, 1H, H-2), 5.09 – 5.06 (m, 1H, H-6), 4.29 – 4.24 (m, 2H, H-1_a, H-1′), 4.09 (dd, J = 11.5, 7.7 Hz, H-1_b), 2.15 – 2.05 (m, 4H, H-5, H-4), 1.71 (s, 3H, 3-CH_3), 1.68 (s, 3H, 7-CH_{3a}), 1.60 (s, 3H, 7-CH_{3b}), 1.55 (d, J = 6.6 Hz, 3H, 1′-CH_3);

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.3 (C, C-3), 132.1 (C, C-7), 123.9 (CH, C-6), 119.3 (C, CN), 118.8 (CH, C-2), 66.7 (CH_2, C-1), 63.0 (CH, C-1′), 39.7 (CH_2, C-4), 26.6 (CH_2, C-5), 25.8 (CH_3, 7-CH_{3a}), 20.0 (CH_3, 1′-CH_3), 17.8 (CH_3, 7-CH_{3b}), 16.7 (CH_3, 3-CH_3);

HRMS *m/z* (ESI/Q-TOF) $[M + Na]^+$ calcd for $C_{13}H_{21}NNaO$, 230.1515; found, 230.1512.

(*E*)-2-((5-(3,3-Dimethyloxiran-2-yl)-3-methylpent-2-en-1-yl)oxy)propanenitrile (21)



S3 **21**

To a solution of alkene **S3** (1.00 g, 4.83 mmol) in THF/H_2O (200 mL, 2:1 *v/v*) at 0 °C was added recrystallised NBS (1.11 g, 6.28 mmol) in THF/H_2O (12 mL, 2:1 *v/v*) dropwise over 1 h. The reaction mixture was stirred at 0 °C for a further 1 h before the addition of sat. aq. $Na_2S_2O_3$ (14 mL). K_2CO_3 (3.33 g, 24.1 mmol) and MeOH (25 mL) were then added and the resulting mixture was allowed to warm to rt and stirred overnight. Most of the organic solvent was removed under reduced pressure and the residue was extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude oil was purified by flash chromatography (10% EtOAc in pet. ether) to afford the *title compound* **21** (0.684 g, 63%) as a colourless oil.

R_f : 0.69 (20% EtOAc in pet. ether);

IR ν_{max} (neat): 2963, 1451, 1378, 1110, 1063, 733 cm^{-1};

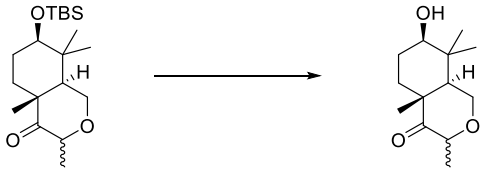
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.32 (t, J = 6.9 Hz, 1H, H-2), 4.25 – 4.19 (m, 2H, H-1_a, H-1′), 4.03 (dd, J = 11.4, 7.5 Hz, 1H, H-1_b), 2.64 (t, J = 6.2 Hz, 1H, H-6), 2.23 – 2.08 (m, 2H, H-4), 1.69 (s, 3H, 3-CH_3), 1.65 – 1.59 (m, 2H, H-5), 1.50 (d, J = 6.9 Hz, 3H, 1′-CH_3), 1.25 (s, 3H, 7-CH_{3a}), 1.21 (s, 3H, 7-CH_{3b});

^{13}C NMR (100 MHz, $CDCl_3$): δ 142.2 (C, C-3), 119.5 (CH, C-2 or C, CN), 119.4 (C, CN or CH, C-2), 66.7 (CH_2, C-1), 64.0 (CH, C-6), 63.3 (CH, C-1′), 58.5 (C, C-7), 36.4 (CH_2, C-4), 27.2 (CH_2, C-5), 25.0 (CH_3, 7-CH_{3a}), 23.8 (CH_3, 1′-CH_3), 18.9 (CH_3, 7-CH_{3b}), 16.7 (CH_3, 3-CH_3);

HRMS *m/z* (ESI/Q-TOF) $[M + Na]^+$ calcd for $C_{13}H_{21}NNaO_2$, 246.1464; found, 246.1463.

(±)-(4a*R*,7*R*,8a*R*)-7-Hydroxy-3,4a,8,8-tetramethylhexahydro-1*H*-isochromen-4(3*H*)-one (17)

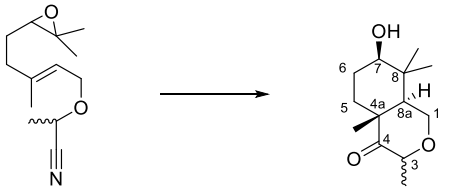
Method A:



20 **17**

To a solution of ketone **20** (1.0 g, 2.94 mmol) in THF (10 mL) was added TBAF (7.4 mL, 7.4 mmol, 1.0 M in THF), and the resulting solution was stirred at rt for 1 h, then 40 °C for 4.5 h. The reaction mixture was cooled to rt and quenched with sat. aq. $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude mixture was purified by flash chromatography (25 → 60% EtOAc in pet. ether) to afford the *title compound* **17** (0.54 g, 81%) as a colourless oil.

Method B:



21 **17**

A mixture of Cp_2TiCl_2 (1.90 g, 7.61 mmol) and Zn dust (1.00 g, 15.2 mmol) in rigorously deoxygenated THF (12.5 mL) was stirred at rt for 15 min. The resulting green solution was then added dropwise over 1.5 h to a solution of epoxide **21** (0.5 g, 2.23 mmol) in deoxygenated THF (113 mL) at 60 °C. The reaction was stirred at this temperature for 1 h, then cooled to rt, quenched with sat. aq. KH_2PO_4 (30 mL) and stirred at rt for 30 mins. The resulting mixture was diluted with Et_2O (60 mL), then the organic phase was separated and the aqueous phase was extracted with Et_2O (3 × 40 mL). The combined organic phases were washed with sat. aq. $NaHCO_3$ (15 mL) and brine (15 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude mixture was purified by flash chromatography (10 → 40% EtOAc in pet. ether) to afford the *title compound* **17** (0.1 g, 20%, in a 1:0.5 diastereomeric ratio) as a colourless oil.

R_f : 0.43 (40% EtOAc in pet. ether);

IR ν_{max} (neat): 3412, 2938, 2873, 1716, 1113, 1026 cm^{-1};

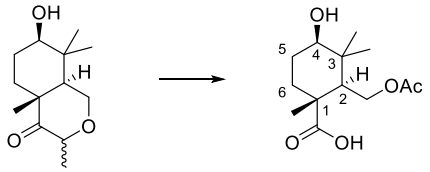
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.21 (q, J = 6.5 Hz, 0.5H, H-3**), 4.04 – 4.00 (m, 2H, H-1†), 3.96 (q, J = 6.8 Hz, 0.5H, H-3*), 3.25 – 3.20 (m, 1H, H-7†), 1.86 – 1.59 (m, 4.5H, H-5_a**, H-5_b†, H-6†, H-8a†), 1.45 – 1.44 (m, 0.5H, H-5_a*), 1.32 (d, J = 7.0 Hz, 1.5H, 3-CH_3*), 1.283 (s, 1.5H, 4a-CH_3**), 1.276 (s, 1.5H, 4a-CH_3*), 1.24 (d, J = 6.5 Hz, 1.5H, 3-CH_3**) 1.07 (s, 1.5H, 8-CH_{3a}**), 1.02 (s, 1.5H, 8-CH_{3b}*), 0.97 (s, 1.5H, 8-CH_{3a}*), 0.92 (s, 1.5H, 8-CH_{3b}**);

^{13}C NMR (100 MHz, $CDCl_3$): δ 216.9* & 211.9** (C, C-4), 78.3* & 77.7** (CH, C-7), 75.1* & 74.3** (CH, C-3), 63.5* & 63.3** (CH_2, C-1), 51.9 (CH, C-8a**), 46.9** & 44.3* (C, C-4a), 44.4 (CH, C-8a*), 38.9* & 38.2** (C, C-3), 31.8* & 31.0** (CH_2, C-5), 27.9** & 27.2* (CH_3, 8-CH_{3a}), 26.9* & 26.8** (CH_2 C-6), 18.5** & 18.2* (CH_3, 4-CH_3), 17.3 (CH_3, 3-CH_3*), 16.5 (CH_3, 8-CH_{3b}**), 15.5 (CH_3, 3-CH_3**), 15.1 (CH_3, 8-CH_{3b}*);

HRMS *m/z* (ESI/Q-TOF) $[M + Na]^+$ calcd for $C_{13}H_{22}NaO_3$, 249.1461; found, 249.1455.

†denotes peaks arising from both diastereomers *denotes peaks arising from one diastereomer **denotes peak arising from other diastereomer

(±)-(1*R*,2*R*,4*R*)-2-(Acetoxymethyl)-4-hydroxy-1,3,3-trimethylcyclohexane-1-carboxylic acid (22)



17 **22**

On a crystallization dish, ketone **17** (0.5 g, 2.21 mmol) was spread out in as thin film as possible, and left to stand open to air for 32 d. The residue was dissolved in CH_2Cl_2 and concentrated *in vacuo* to afford *title compound* **22** (0.519 g, 91%) as a white crystalline solid, which can be submitted directly to the next step without further purification. A sample of high purity for analysis could be obtained by flash chromatography (60% EtOAc in pet. ether).

R_f : 0.2 (50% EtOAc in pet. ether);

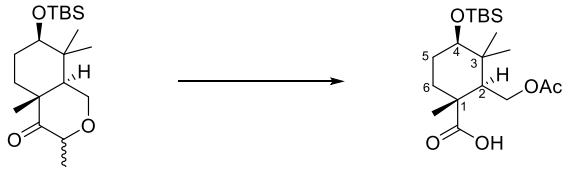
IR ν_{max} (neat): 3539, 3372, 2947, 1726, 1692, 1237, 1027 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.37 (dd, J = 11.6, 4.4 Hz, 1H, 2-CH_{2a}), 4.07 (dd, J = 11.6, 9.6 Hz, 1H, 2-CH_{2b}), 3.41 (dd, J = 11.2, 4.0 Hz, 1H, H-4), 2.34 (dd, J = 9.6, 4.4 Hz, 1H, H-2), 1.95 – 1.88 (m, 4H, H-6_a, Ac), 1.75 – 1.59 (m, 3H, H-5, H-6_b), 1.25 (s, 3H, 1-CH_3), 1.15 (s, 3H, 3-CH_{3a}), 0.91 (s, 3H, 3-CH_{3b});

^{13}C NMR (100 MHz, $CDCl_3$): δ 184.5 (C, CO_2H), 170.8 (C, Ac), 77.4 (CH, C-4), 62.7 (CH_2, 2-CH_2), 47.6 (CH, C-2), 45.0 (C, C-1), 38.3 (C, C-3), 35.3 (CH_2, C-6), 28.3 (CH_3, 3-CH_{3a}), 26.6 (CH_2, C-5), 20.8 (CH_3, Ac), 17.0 (CH_3, 1-CH_3), 16.0 (CH_3, 3-CH_{3b});

HRMS *m/z* (ESI/Q-TOF) $[M + Na]^+$ calcd for $C_{13}H_{22}NaO_5$, 218.1359; found, 281.1359.

(±)-(1*R*,2*R*,4*R*)-2-(Acetoxymethyl)-4-((*tert*-butyldimethylsilyl)oxy)-1,3,3-trimethylcyclohexane-1-carboxylic acid (23)



20 **23**

On a crystallization dish, ketone **20** (0.54 g, 1.59 mmol) was spread out in as thin film as possible, and left to stand open to air for 32 d. The residue was dissolved in CH_2Cl_2 and concentrated *in vacuo* to afford *title compound* **23** (0.509 g, 86%) as a white crystalline solid, which can be submitted directly to the next step without further purification. A sample of high purity for analysis could be obtained by flash chromatography (40% EtOAc in pet. ether).

R_f : 0.59 (50% EtOAc in pet. ether);

IR ν_{max} (neat): 3451, 2928, 1743, 1696, 1104, 834, 773 cm^{-1};

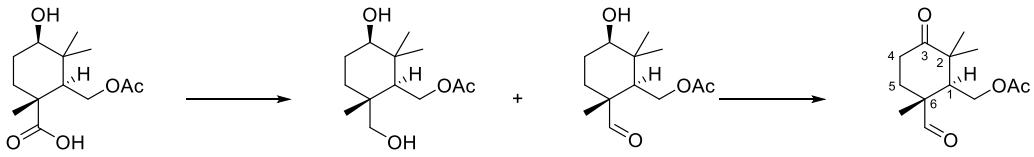
m.p 92 – 94°C;

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.37 (dd, J = 11.6, 4.1 Hz, 1H, 2-CH_{2a}), 4.06 (dd, J = 11.4, 10.1 Hz, 1H, 2-CH_{2b}), 3.37 – 3.33 (m, 1H, H-4), 2.32 (dd, J = 9.9, 4.2 Hz, 1H, H-2), 1.95 (s, 3H, Ac), 1.88 – 1.83 (m, 1H, H-6_a), 1.64 – 1.60 (m, 3H, H-5, H-6_b), 1.24 (s, 3H, 1-CH_3), 1.06 (s, CH_3, 3-CH_{3a}), 0.89 (s, 9H, TBS), 0.88 (s, 3H, 3-CH_{3b}), 0.05 (s, 6H, TBS);

^{13}C NMR (100 MHz, $CDCl_3$): δ 184.4 (C, CO_2H), 170.9 (C, Ac), 78.0 (CH, C-4), 63.0 (CH_3, 2-CH_2), 47.6 (CH, C-2), 44.9 (C, C-1), 38.8 (C, C-3), 34.9 (CH_2, C-6), 28.8 (CH_3, 3-CH_{3a}), 27.0 (CH_2, C-5), 26.0 (CH_3, 3 × TBS), 20.9 (CH_3, Ac), 18.2 (C, TBS), 17.5 (CH_3, 1-CH_3), 17.0 (CH_3, 3-CH_{3b}), −3.8 (CH_3, TBS), −4.8 (CH_3, TBS);

HRMS *m/z* (ESI/Q-TOF) $[M + Na]^+$ calcd for $C_{19}H_{36}O_5SiNa$, 359.2224; found, 395.2220.

(±)-((1*S*,6*R*)-6-Formyl-2,2,6-trimethyl-3-oxocyclohexyl)methyl acetate (24)



To a solution of acid **22** (99.6 mg, 0.39 mmol) in THF (5. mL) at 0 °C was added BH_3·DMS (0.05 mL, 0.53 mmol) dropwise slowly. The resulting mixture was allowed to gradually warm to rt, then stirred for 20 h. The reaction mixture was cooled to 0 °C then quenched with sat. aq. NH_4Cl (4 mL) and extracted with Et_2O (3 × 5 mL). The combined organic extracts were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to afford crude **S4** (R_f: 0.26, 60% EtOAc in pet. ether, *blue stain in vanillin*) or a mixture of **S4** and **S5** (R_f: 0.47, 60% EtOAc in pet. ether, *grey/green stain in vanillin*).

To a solution of the previous crude reaction in CH_2Cl_2 (4.0 mL) was added DMP (390 mg, 0.92 mmol). The resulting solution was stirred at rt for 1.5 h, quenched with sat. aq. $NaHCO_3$ (2 mL) and sat. aq. $Na_2S_2O_3$ (2 mL), then extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude mixture was purified by flash chromatography (40% EtOAc, 0.5% Et_3N in pet. ether) to afford the *title compound* **24** (35.9 mg, 39%) as a colourless oil.

R_f : 0.69 (40% EtOAc in pet. ether);

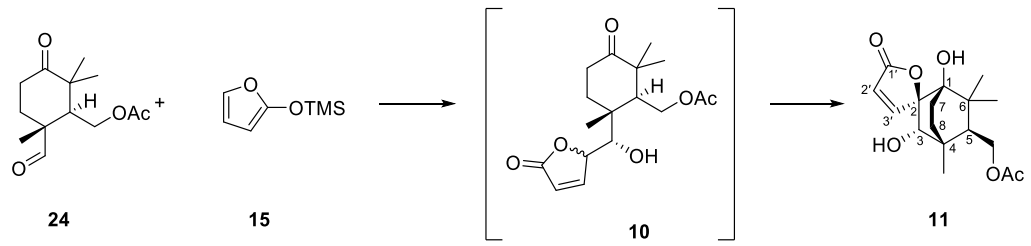
IR ν_{max} (neat): 2979, 1708, 1227, 732 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.41 (s, 1H, CHO), 4.25 – 4.18 (m, 2H, 1-H_2), 2.59 – 2.45 (m, 2H, H-4), 2.42 (dd, J = 7.6, 4.9 Hz, 1H, H-1), 2.09 – 2.01 (m, 1H, H-5$_a$), 1.97 (s, 3H, Ac), 1.69 – 1.63 (m, 1H, H-5$_b$), 1.27 (s, 3H, 6-CH_3), 1.22 (s, 3H, 2-CH_{3a}), 1.14 (s, 3H, 2-CH_{3b});

^{13}C NMR (100 MHz, $CDCl_3$): δ 213.0 (C, C-3), 203.2 (CH, CHO), 170.5 (C, Ac), 61.9 (CH_2, 1-CH_2), 47.9 (CH, C-1), 47.8 (C, C-6), 46.4 (C, C-2), 33.5 (CH_2, C-4), 30.8 (CH_2, C-5), 26.2 (CH_3, 2-CH_{3a}), 22.8 (CH_3, 2-CH_{3b}), 20.9 (CH_3, Ac), 16.7 (CH_3, 6-CH_3);

HRMS *m/z* (ESI/Q-TOF) $[M + Na]^+$ calcd for $C_{13}H_{20}NaO_4$, 263.1254; found, 263.1254.

(±)-((1*R*,2*R*,3*S*,4*R*,5*S*)-1,3-Dihydroxy-4,6,6-trimethyl-5'-oxo-5'*H*-spiro[bicyclo[2.2.2]octane-2,2'-furan]-5-yl)methyl acetate (11)



24 **15** **10** **11**

To a solution of ketoaldehyde **24** (21.3 mg, 88.0 μmol) in CH_2Cl_2 (1.2 mL) at −20 °C was added $TiCl_4$ (0.10 mL, 0.10 mmol, 1 M in CH_2Cl_2) dropwise. The reaction was stirred at this temperature for 10 min, then (trimethylsiloxy)furan (**15**) (21.0 μL, 0.12 mmol) was added dropwise. The resulting dark orange mixture was stirred at this temperature for 3 h, then quenched with sat. aq. NH_4Cl (1 mL), diluted with H_2O (3 mL), and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude mixture was purified by flash chromatography (60% EtOAc in pet. ether) to afford the *title compound* **11** (7.3 mg, 31%, 49% BRSM) as a white solid.

R_f : 0.43 (60% EtOAc in pet. ether);

IR ν_{max} (neat): 3435, 2966, 1702, 1247, 1016 cm^{-1};

m.p 100 – 105 °C;

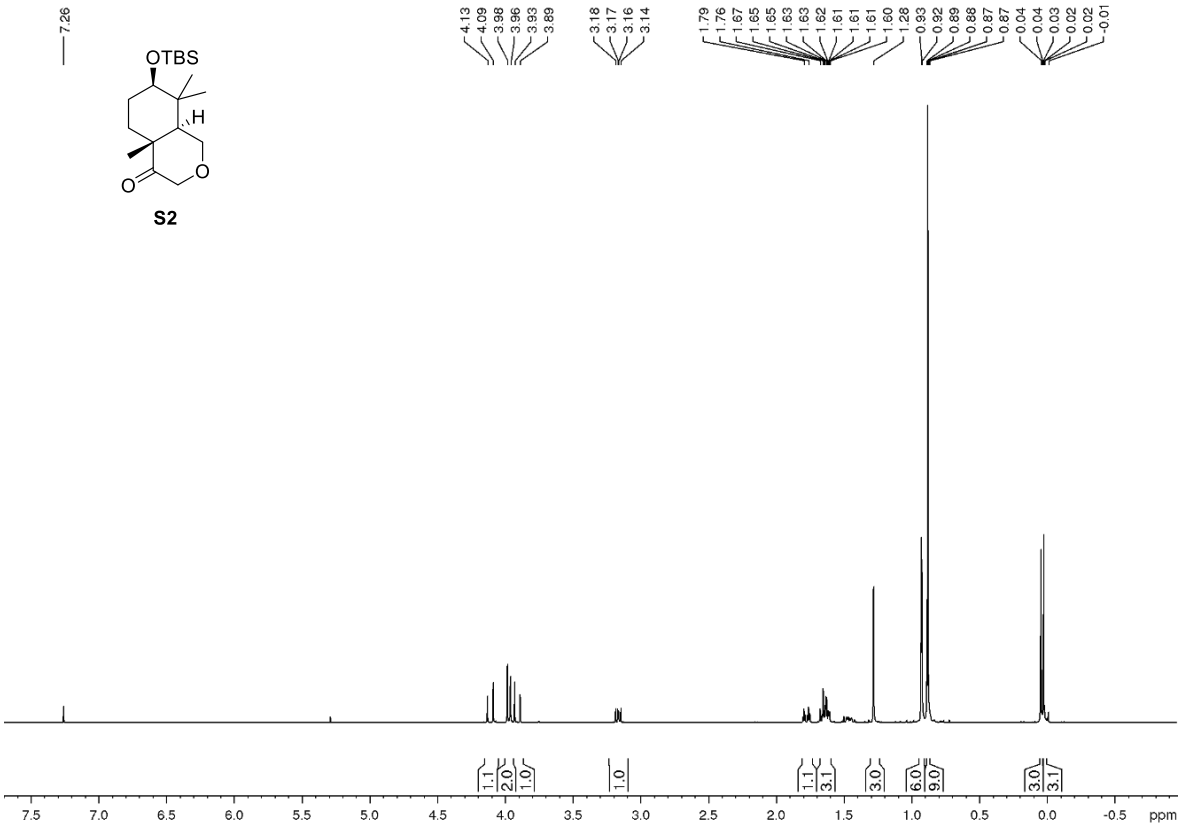
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, J = 6.0 Hz, 1H, H-3′), 6.10 (d, J = 6.0 Hz, 1H, H-2′), 4.27 – 4.16 (m, 2H, 5-CH_2), 3.84 (d, J = 4.3 Hz, 1H, 3-H), 2.20 (ddd, J = 7.3, 5.4, 1.8 Hz, 1H, H-5), 2.08 (s, 3H, Ac), 2.06 – 2.01 (m, 1H, H-7_a), 1.94 – 1.88 (m, 1H, H-8_a), 1.75 (ddd, J = 12.9, 11.5, 3.0 Hz, 1H, H-7_b), 1.44 – 1.37 (m, 1H, H-8_b), 1.18 (s, 3H, 6-CH_{3a}), 1.14 (s, 3H, 6-CH_{3b}), 0.94 (s, 3H, 4-CH_3);

^{13}C NMR (100 MHz, $CDCl_3$): δ 172.5 (C, C-1′), 171.1 (C, Ac), 156.8 (CH, C-3′), 121.1 (CH, C-2′), 97.2 (C, C-2), 81.7 (CH, C-3), 77.4 (C, C-1), 62.7 (CH_2, 5-CH_2), 42.9 (CH, C-5), 38.4 (C, C-6), 36.9 (C, C-4), 28.0 (CH_2, C-8), 27.4 (CH_3, 6-CH_{3a}), 27.2 (CH_2, C-7), 21.3 (2 × CH_3, 4-CH_3, Ac), 21.1 (CH_3, 6-CH_{3b});

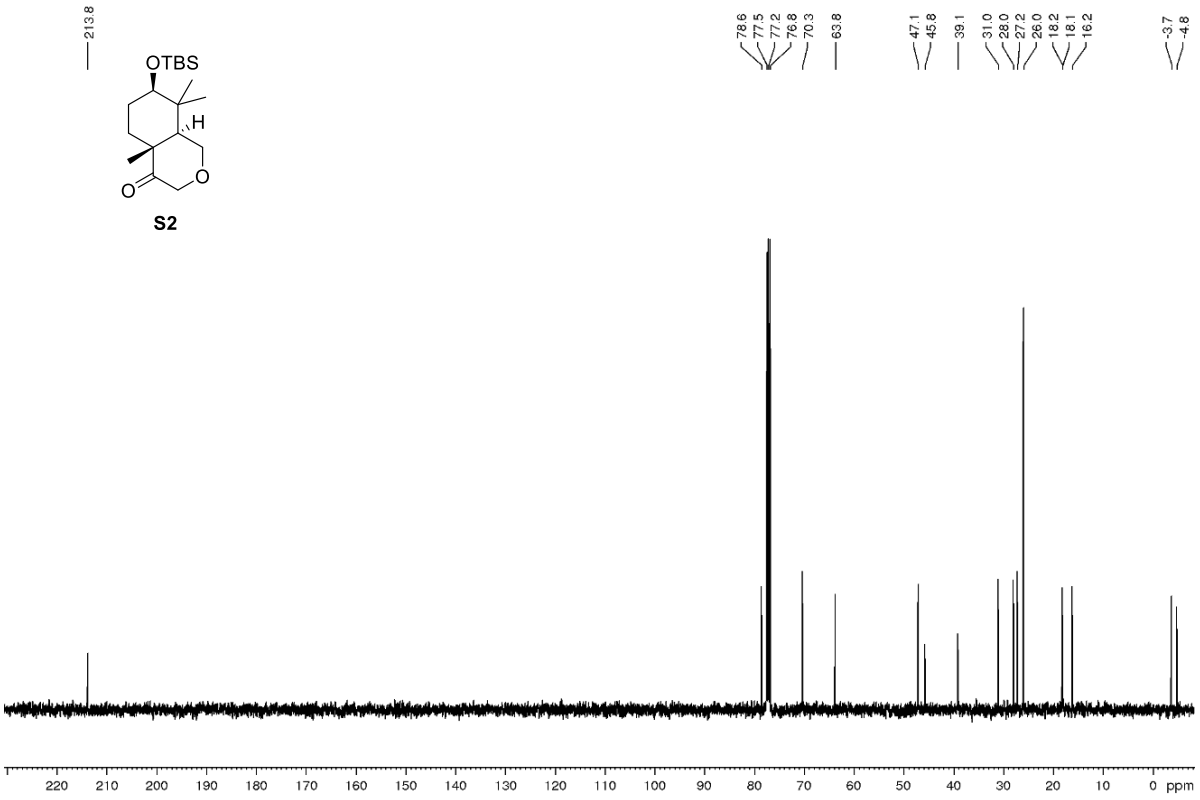
HRMS *m/z* (ESI/Q-TOF) $[M + Na]^+$ calcd for $C_{17}H_{24}NaO_6$, 347.1466; found, 347.1465.

Experimental Spectra

^{1}H NMR (400 MHz, $CDCl_3$)

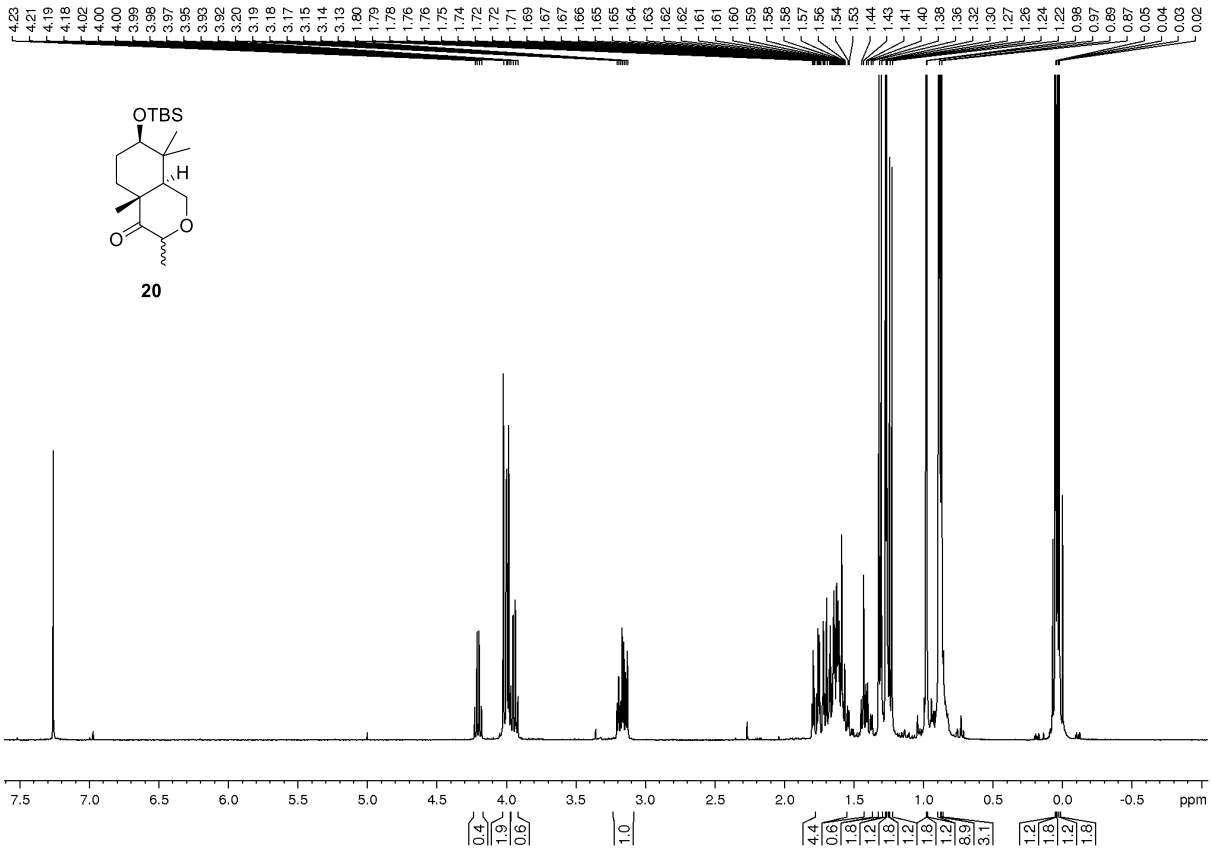


^{13}C NMR (100 MHz, $CDCl_3$)

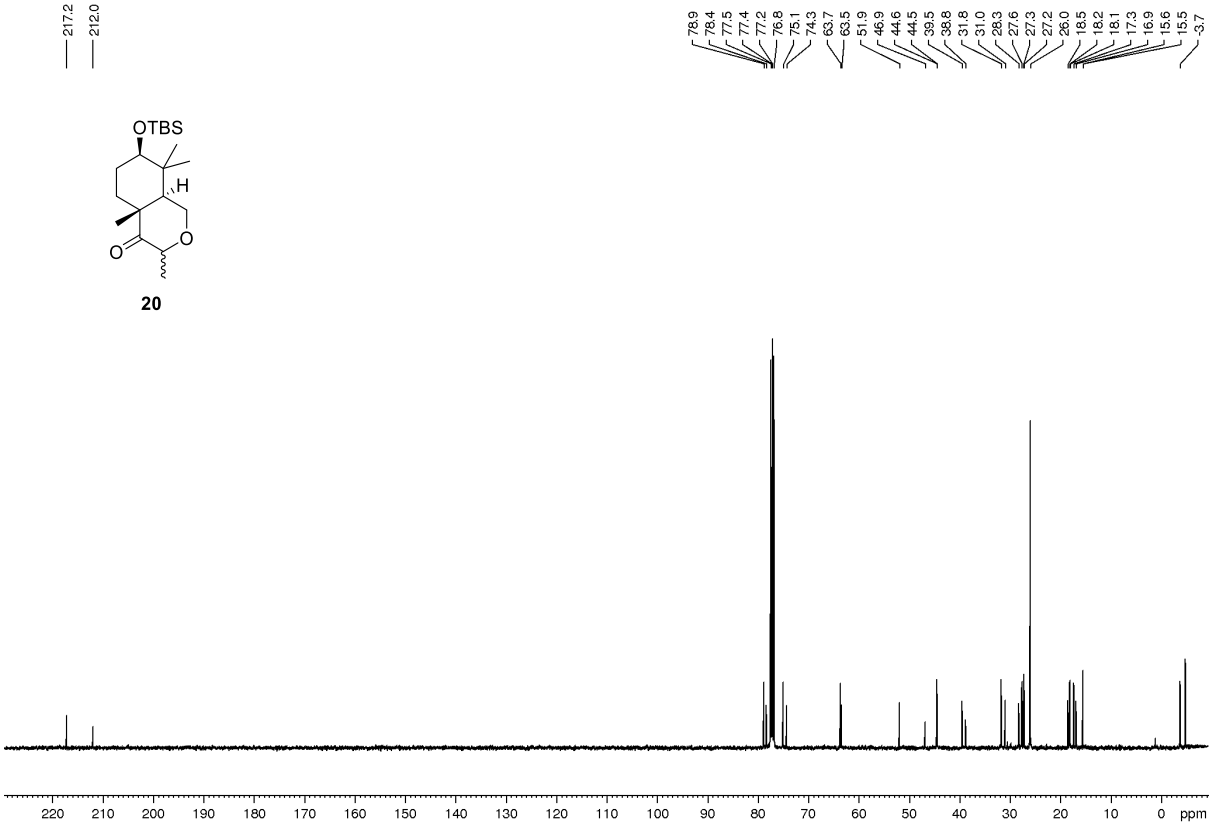

213.8
78.6
77.5
77.2
76.8
70.3
63.8
47.1
45.8
39.1
31.0
28.0
27.2
26.0
18.2
18.1
16.2
-3.7
-4.8
OTBS
H
O
O
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

S2

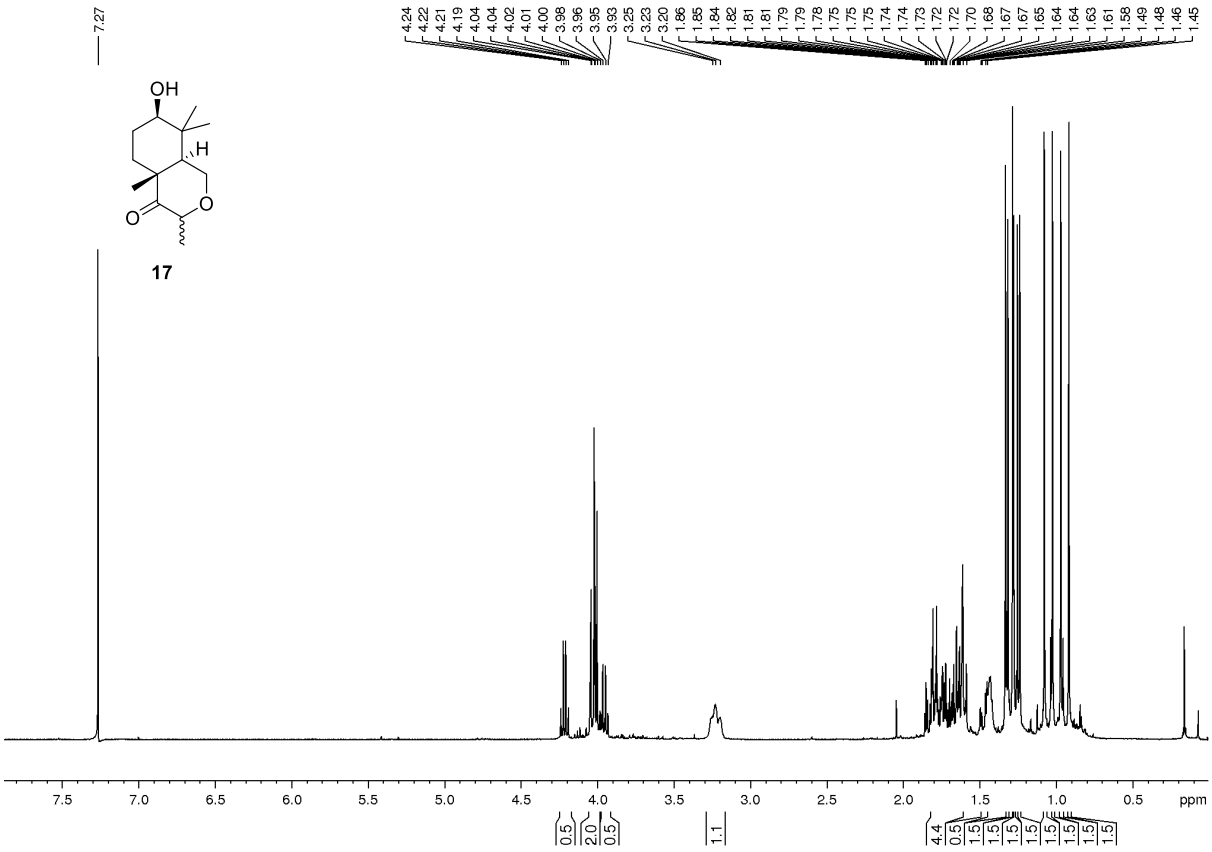
^{1}H NMR (400 MHz, $CDCl_3$)



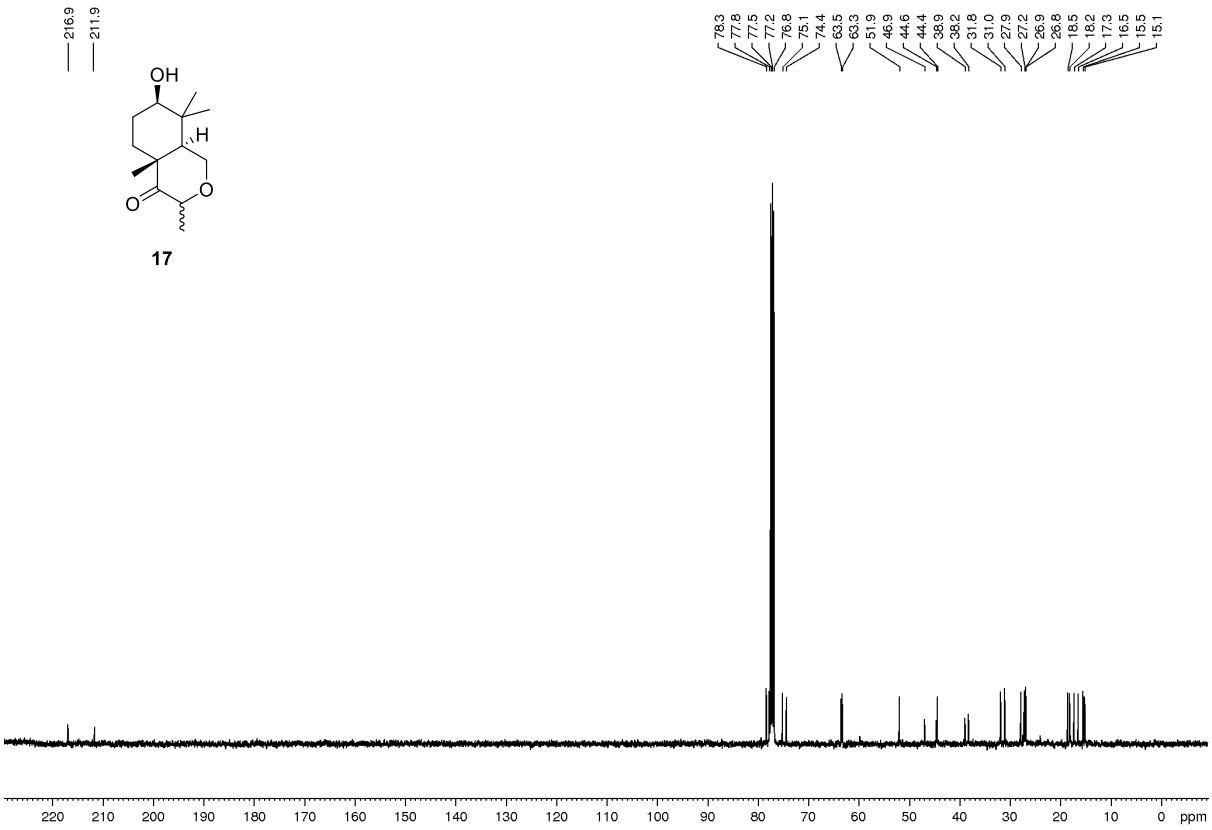
^{13}C NMR (100 MHz, $CDCl_3$)



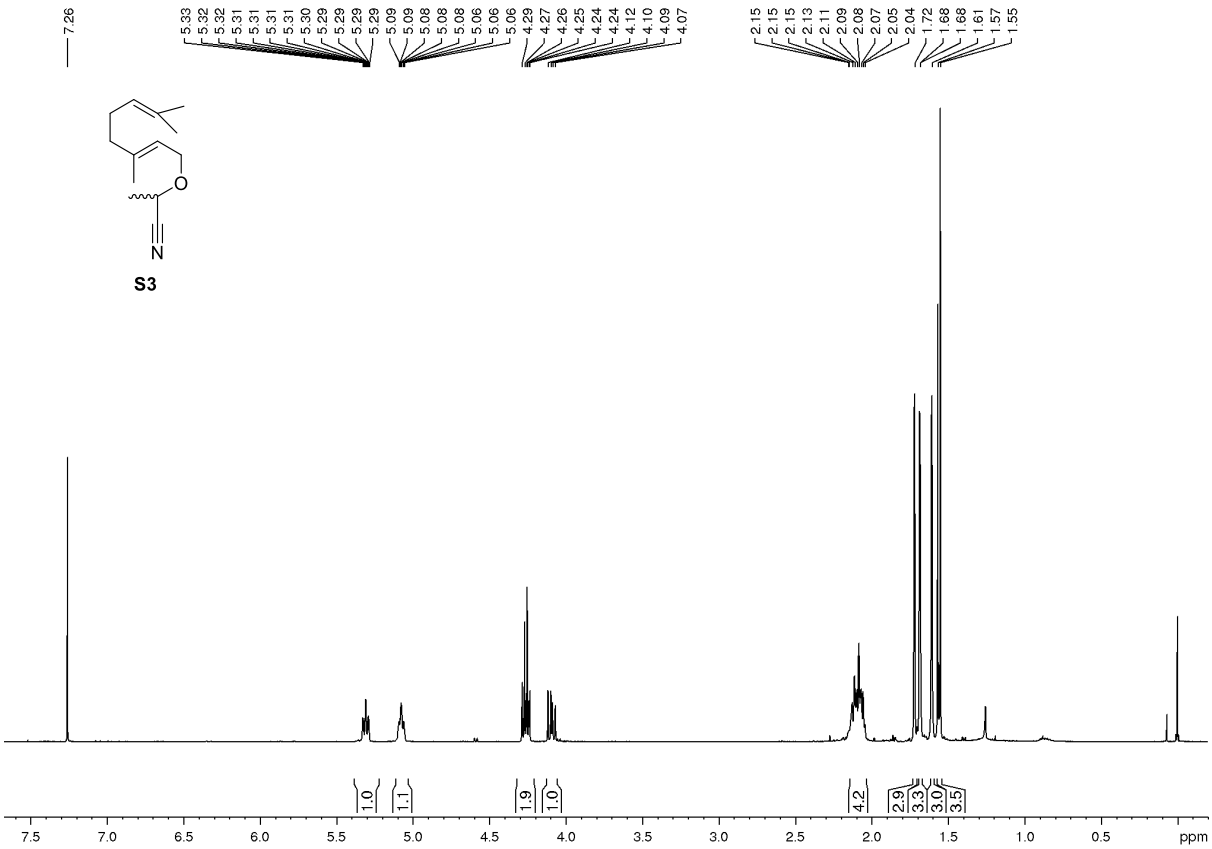
^{1}H NMR (400 MHz, $CDCl_3$)



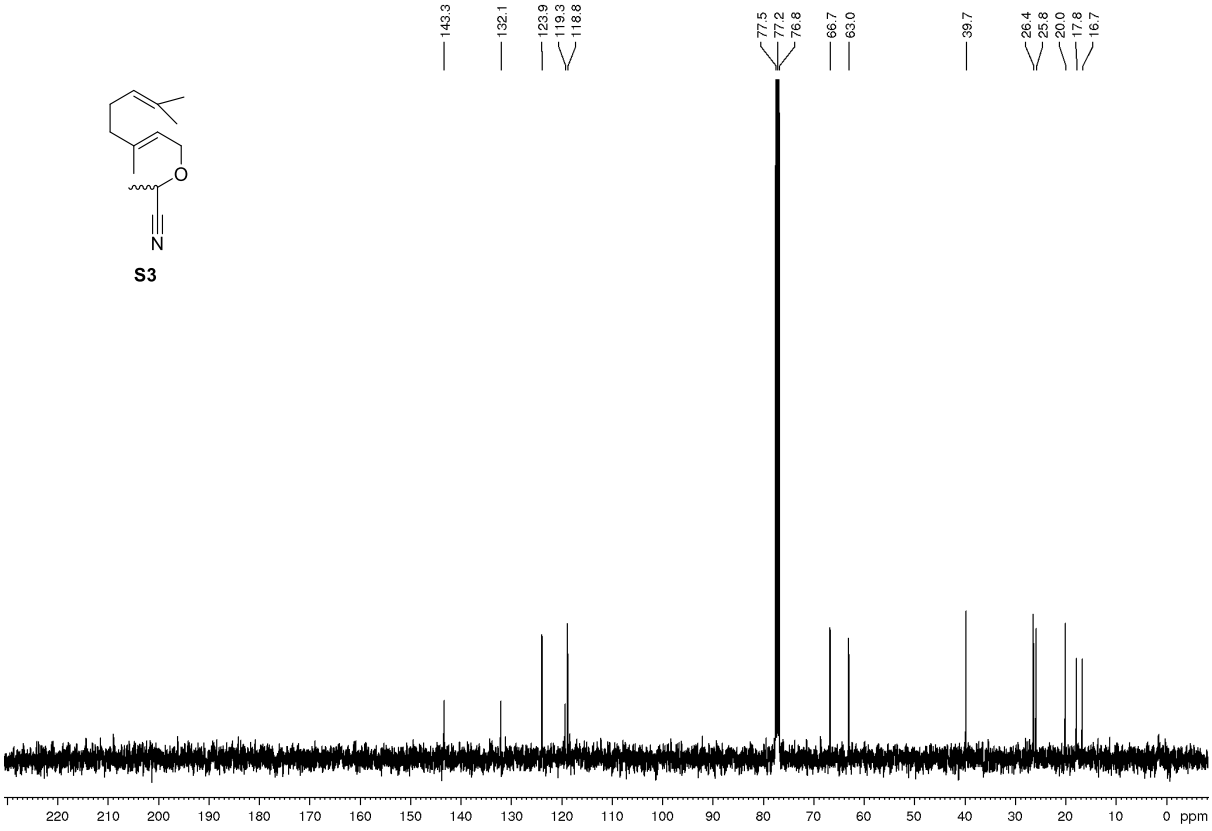
^{13}C NMR (100 MHz, $CDCl_3$)



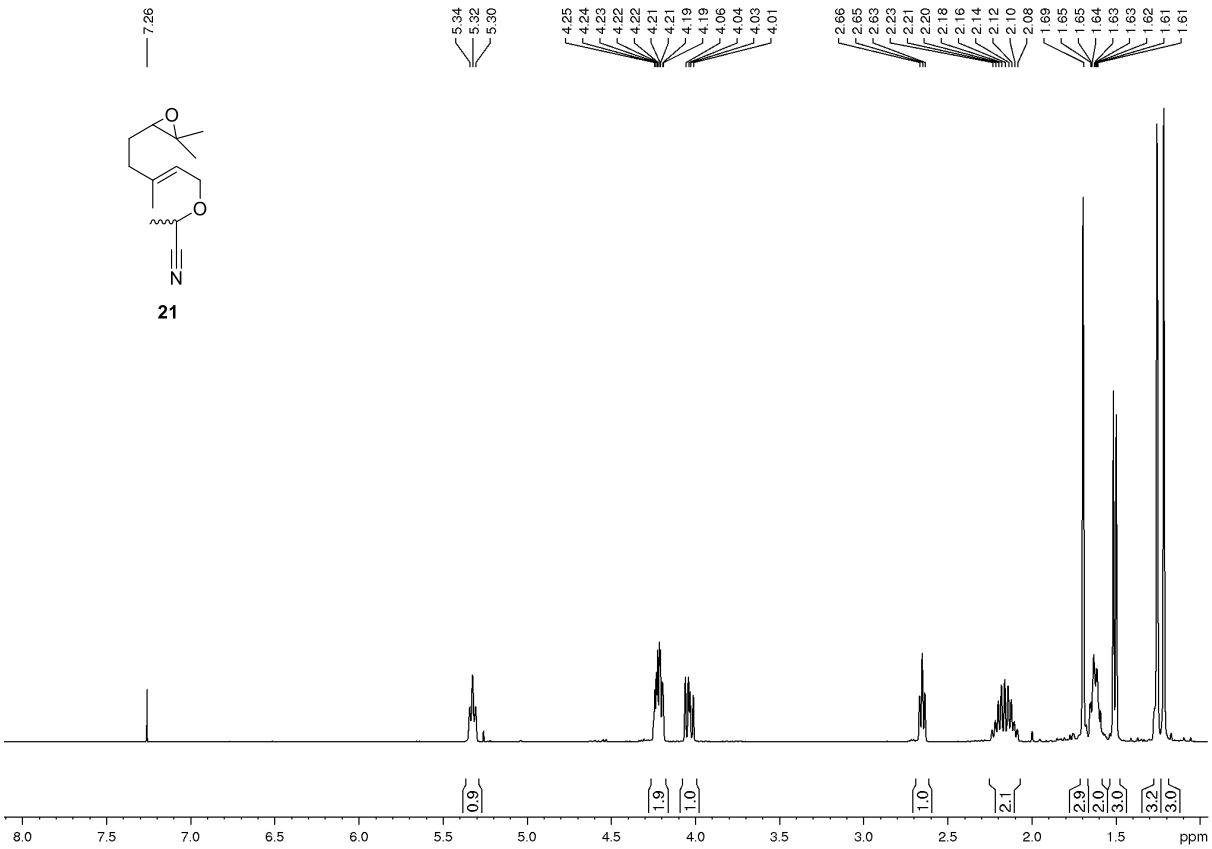
^{1}H NMR (400 MHz, $CDCl_3$)



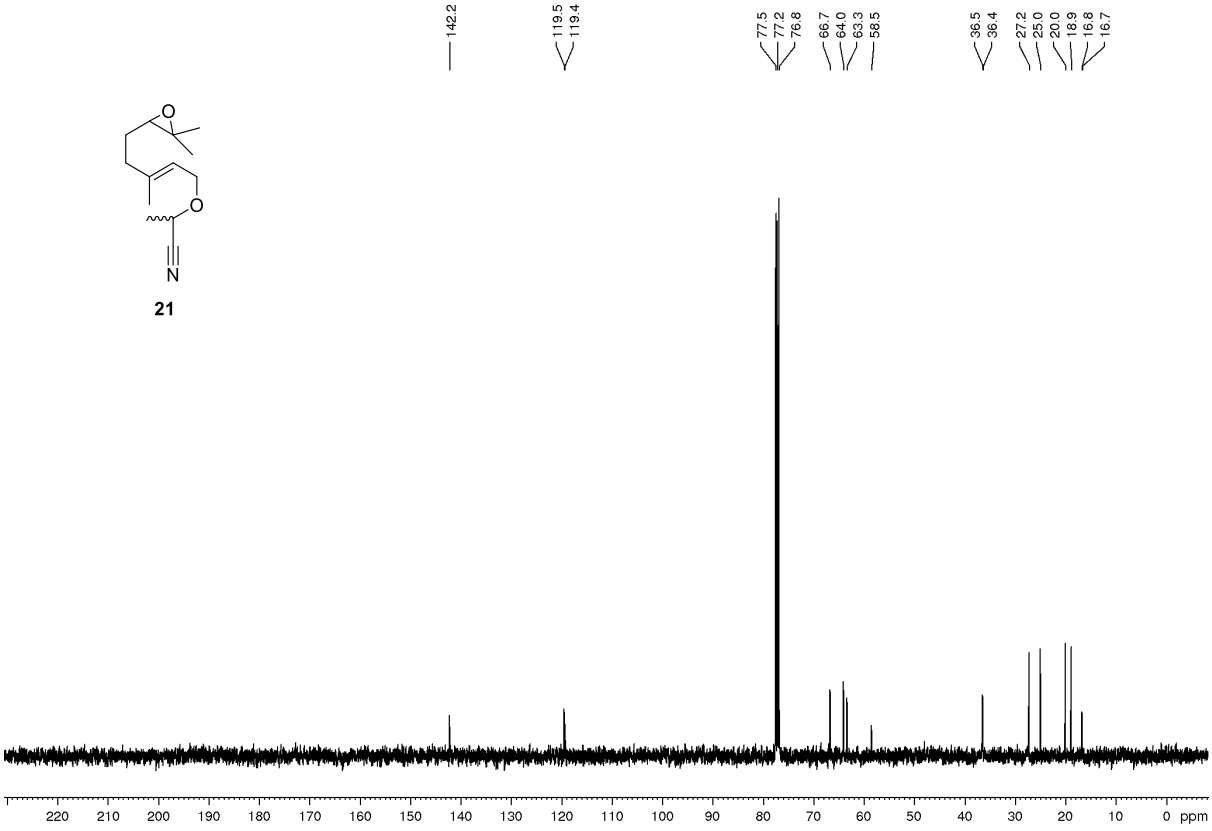
^{13}C NMR (100 MHz, $CDCl_3$)



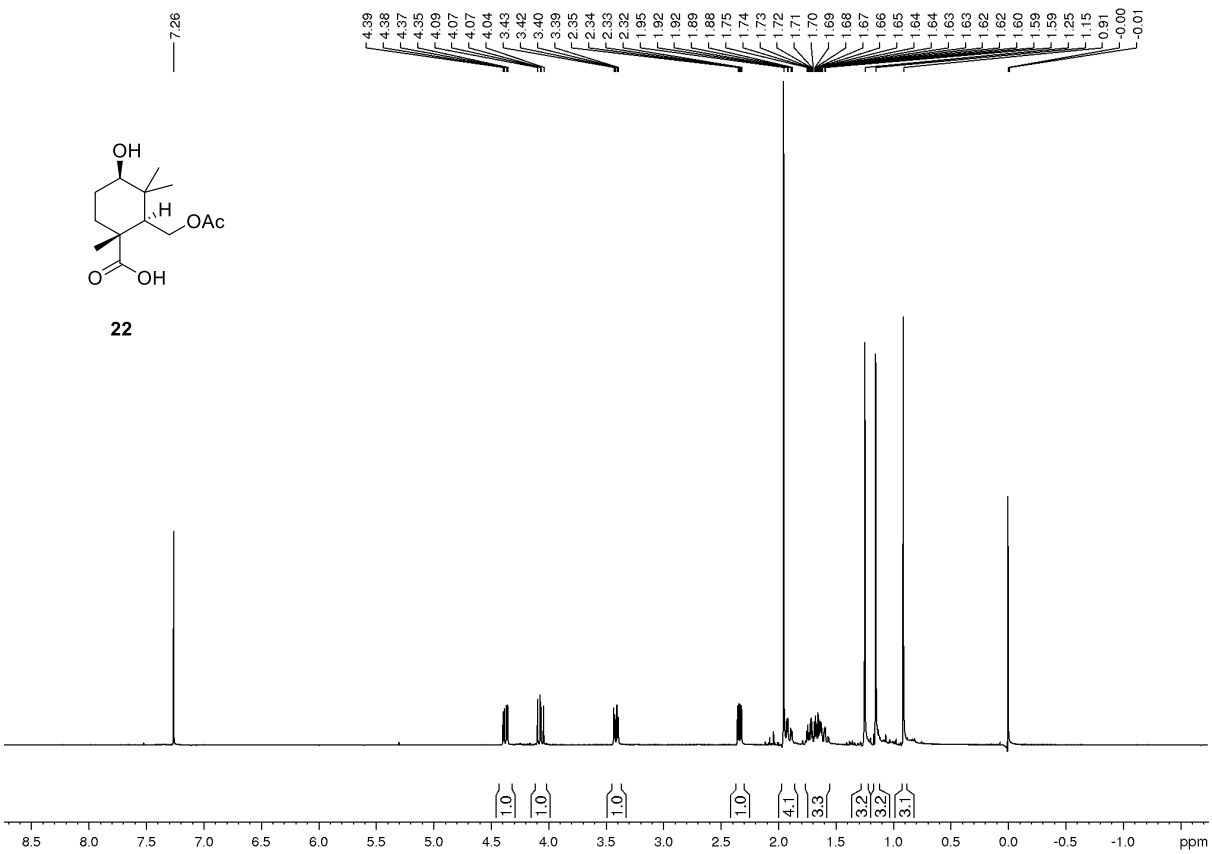
(^{1}H NMR (400 MHz, $CDCl_3$)



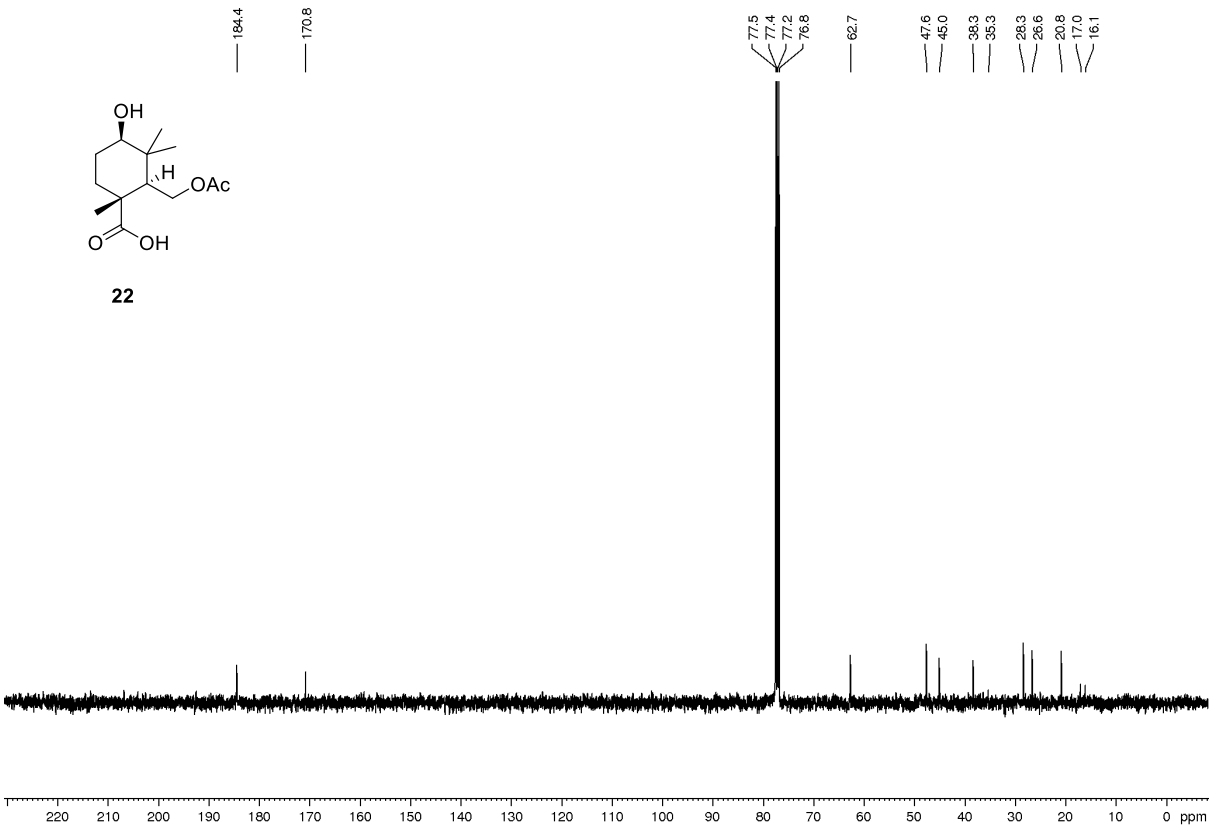
^{13}C NMR (100 MHz, $CDCl_3$)



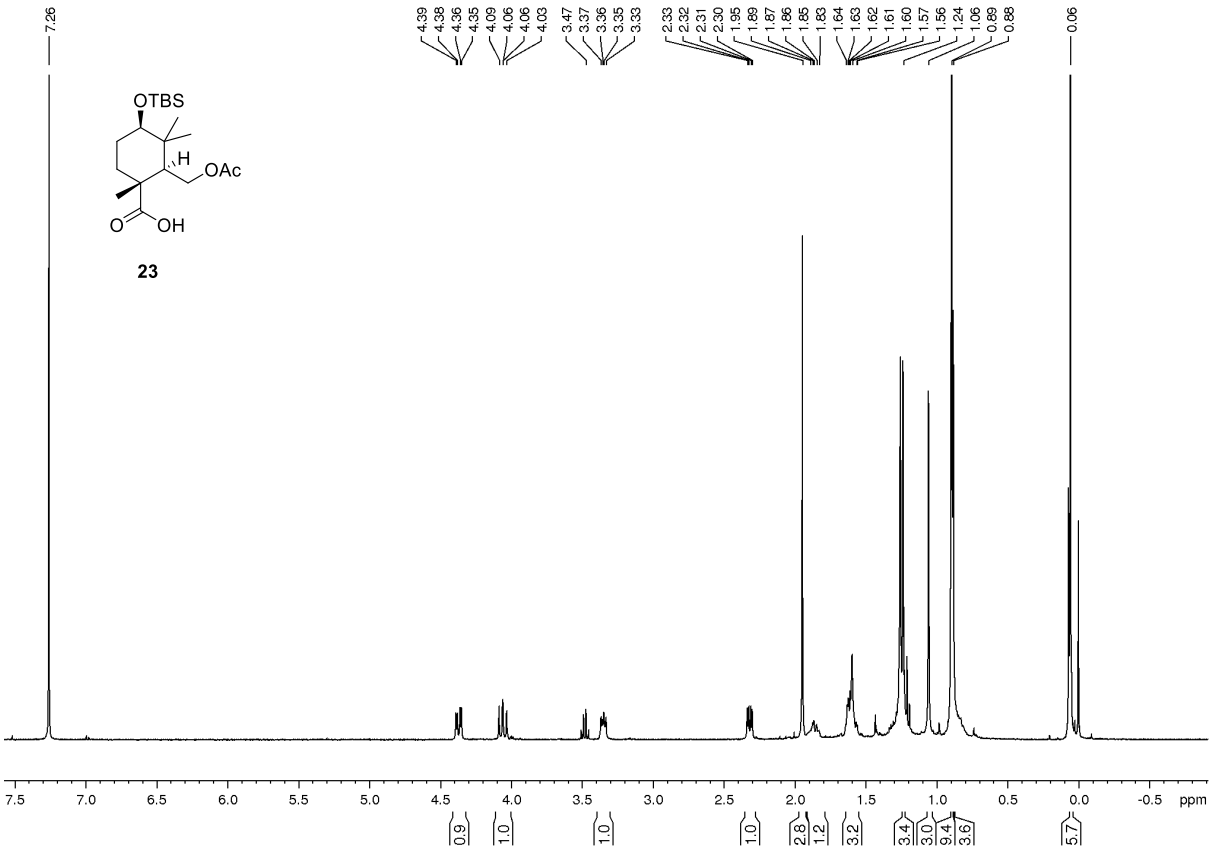
^{1}H NMR (400 MHz, $CDCl_3$)



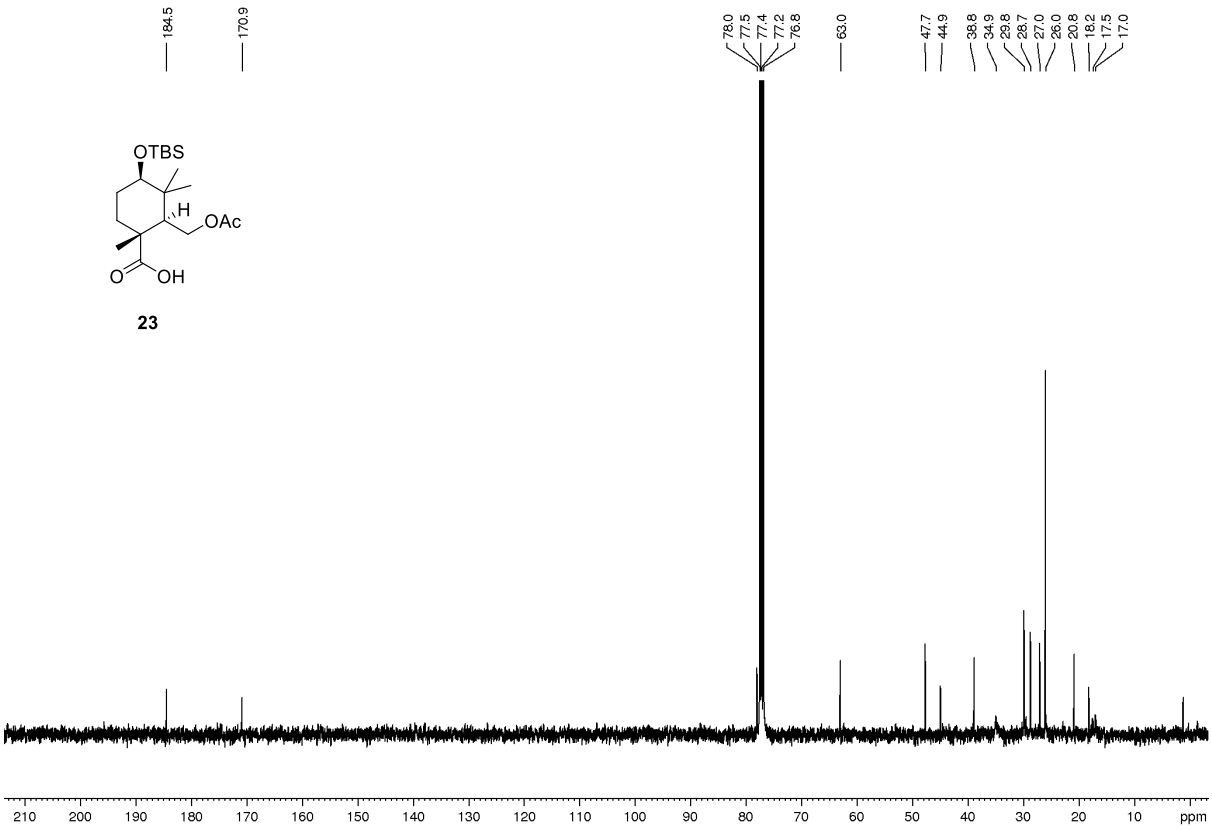
^{13}C NMR (100 MHz, $CDCl_3$)



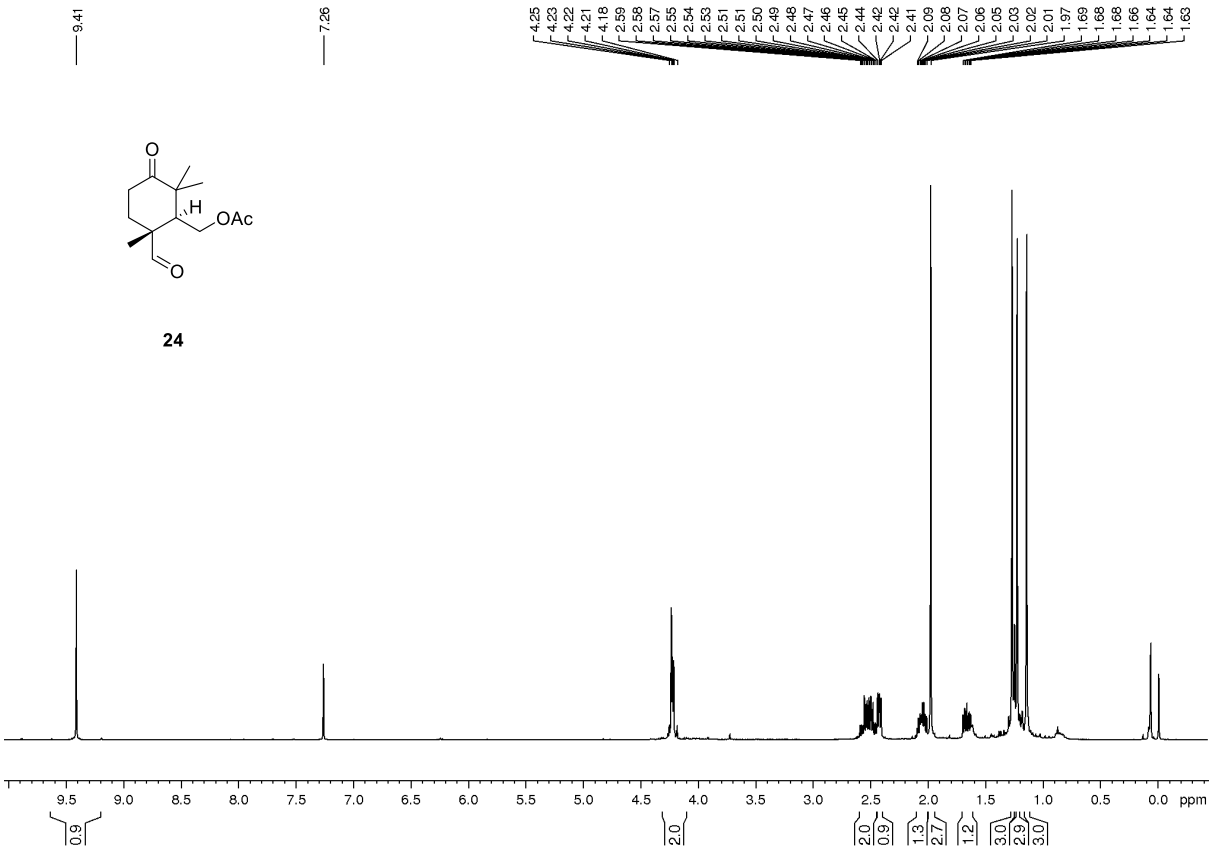
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)

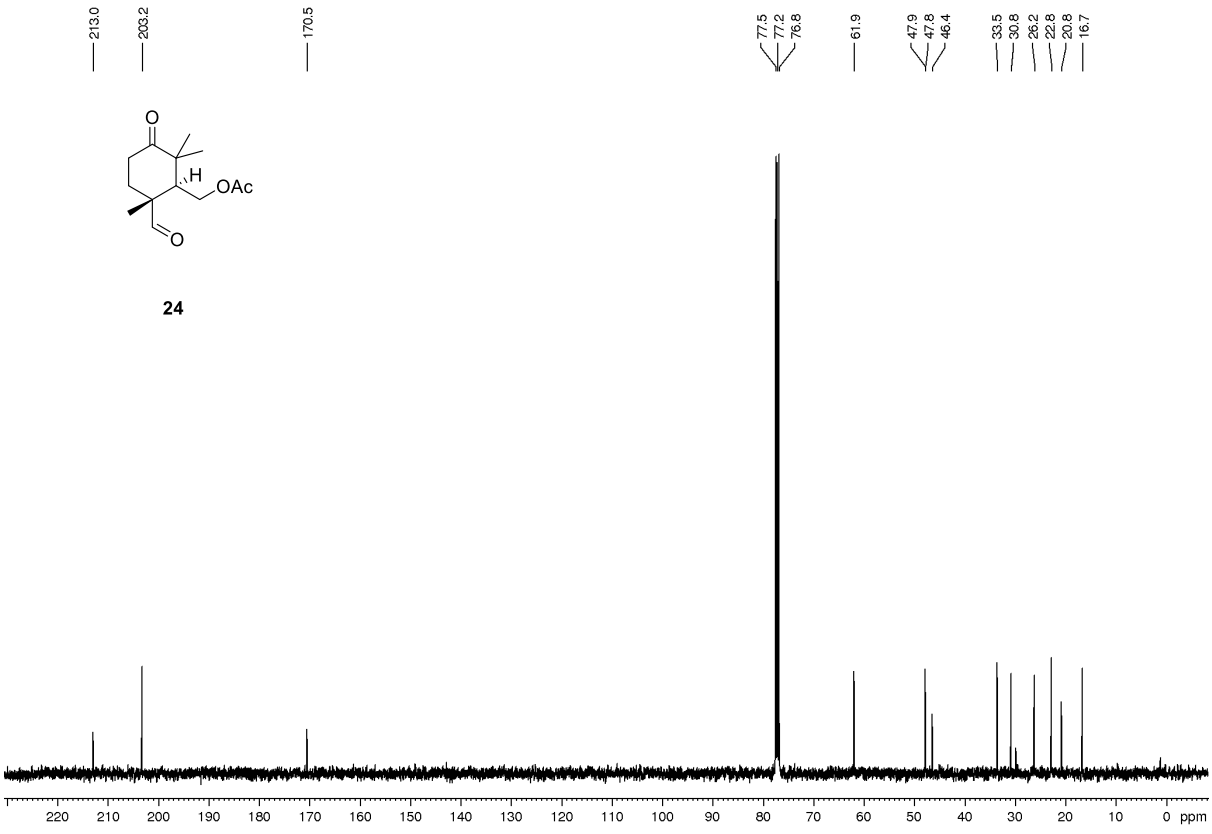


^{1}H NMR (400 MHz, $CDCl_3$)



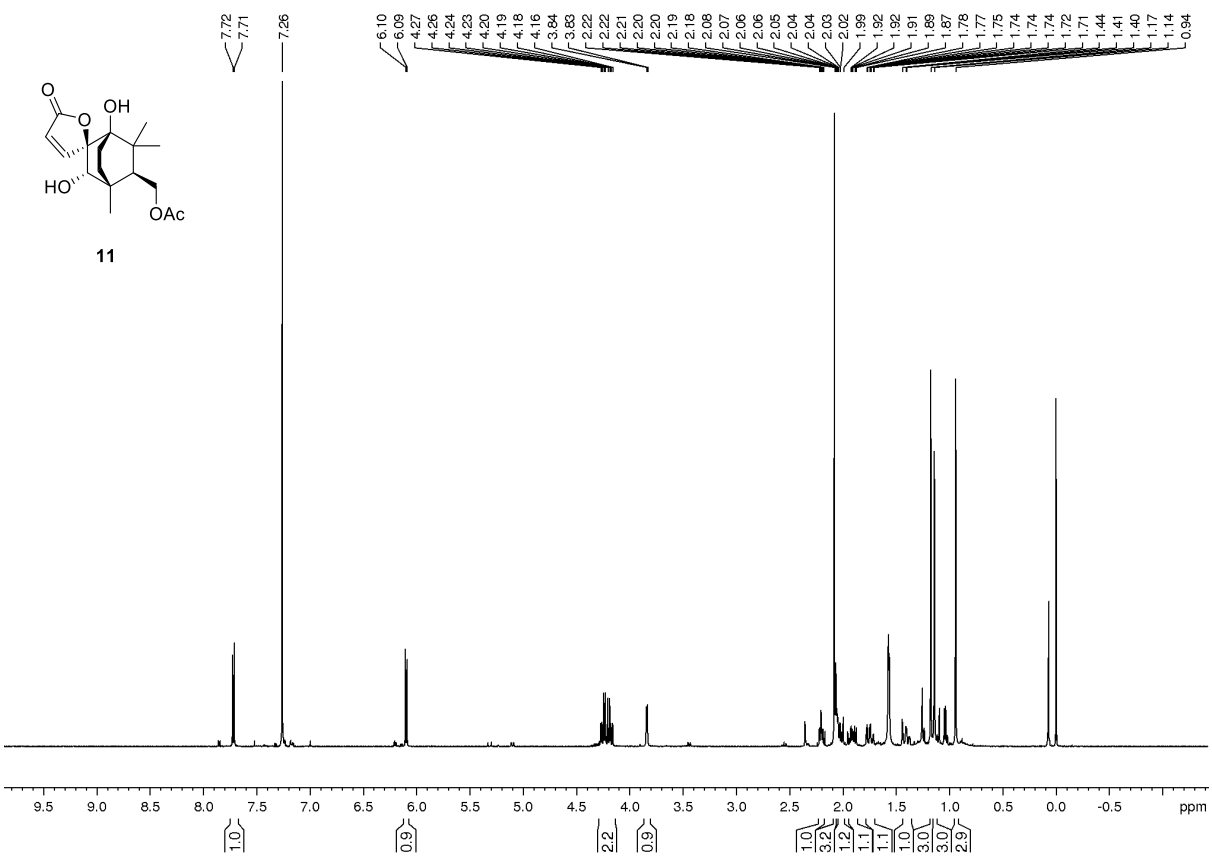
24

^{13}C NMR (100 MHz, $CDCl_3$)

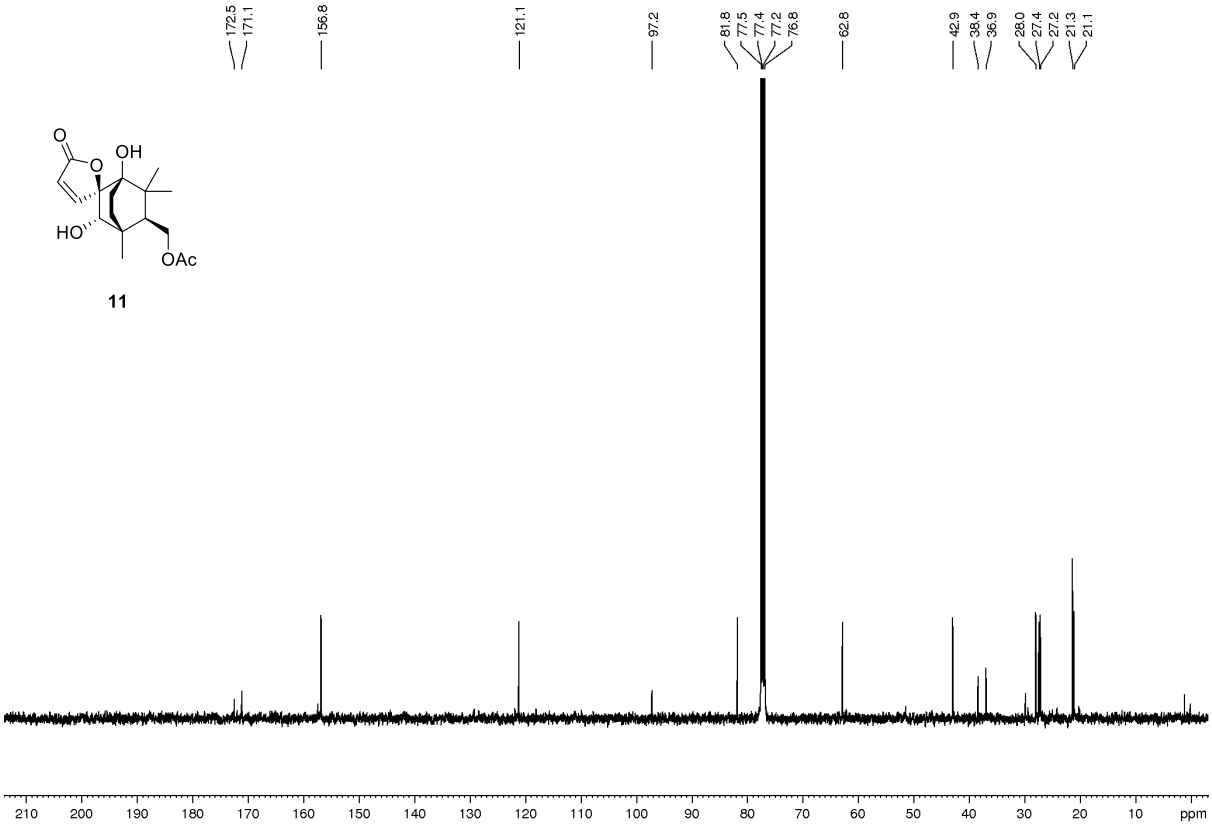


24

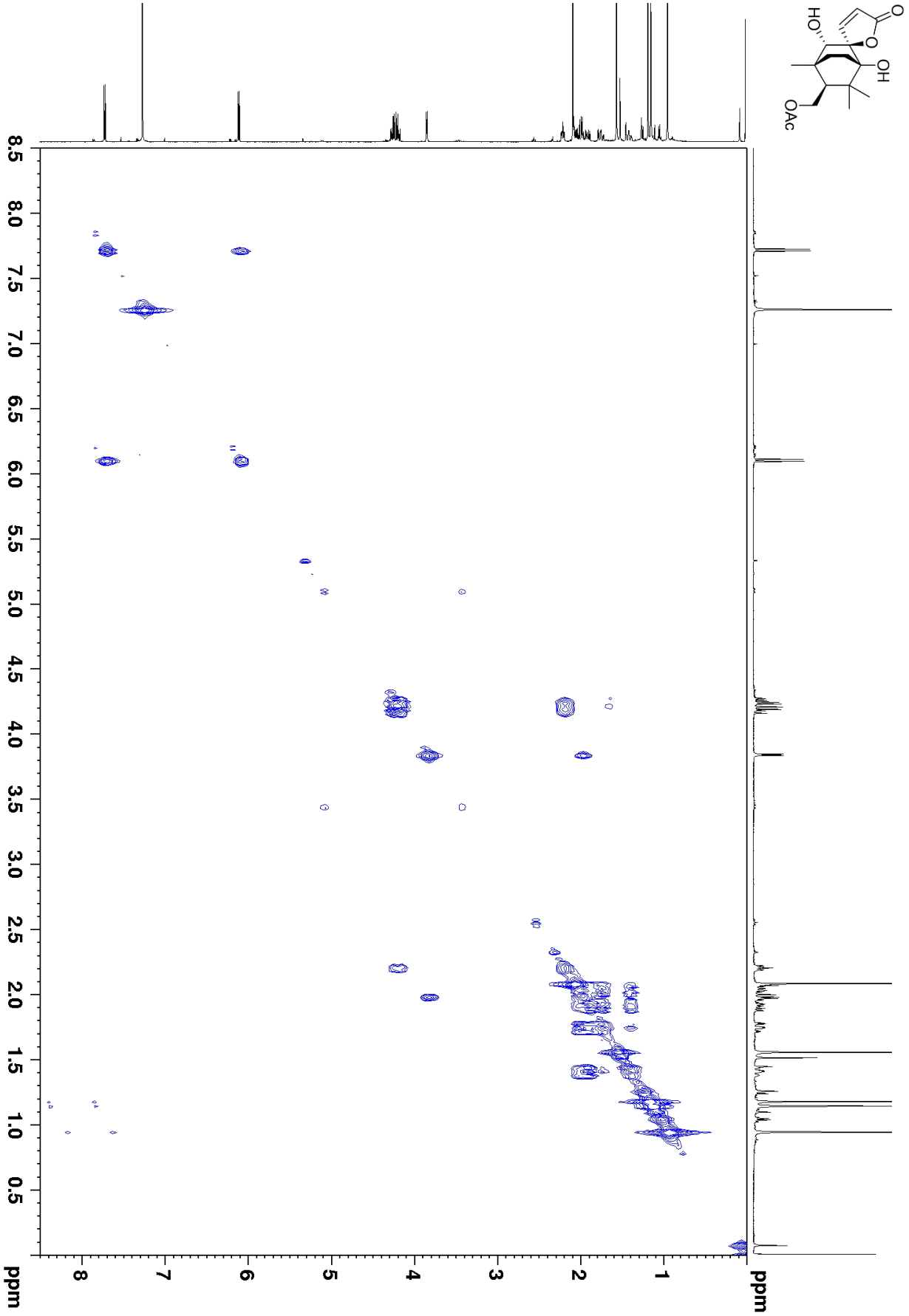
^{1}H NMR (400 MHz, $CDCl_3$)



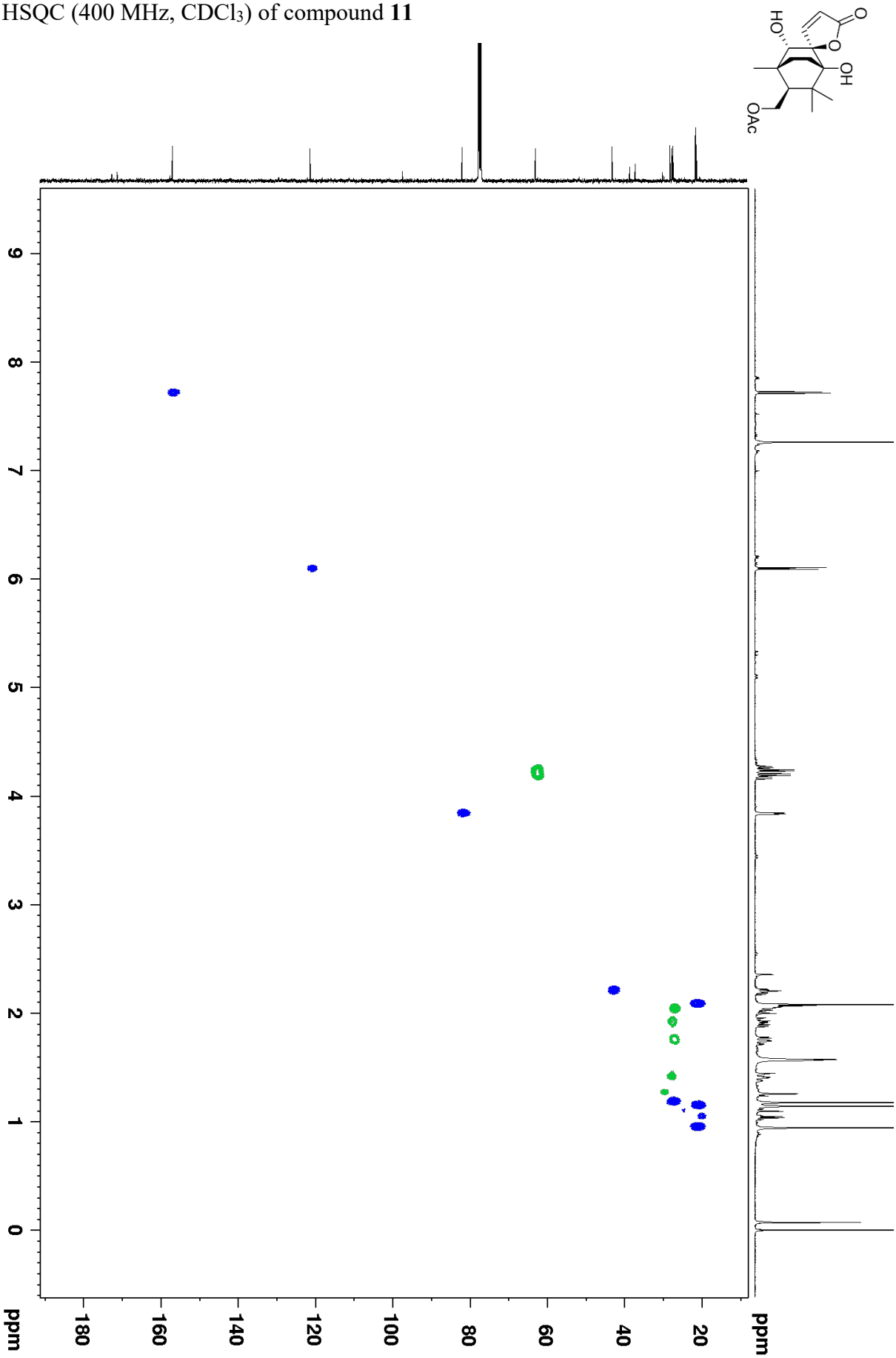
^{13}C NMR (100 MHz, $CDCl_3$)



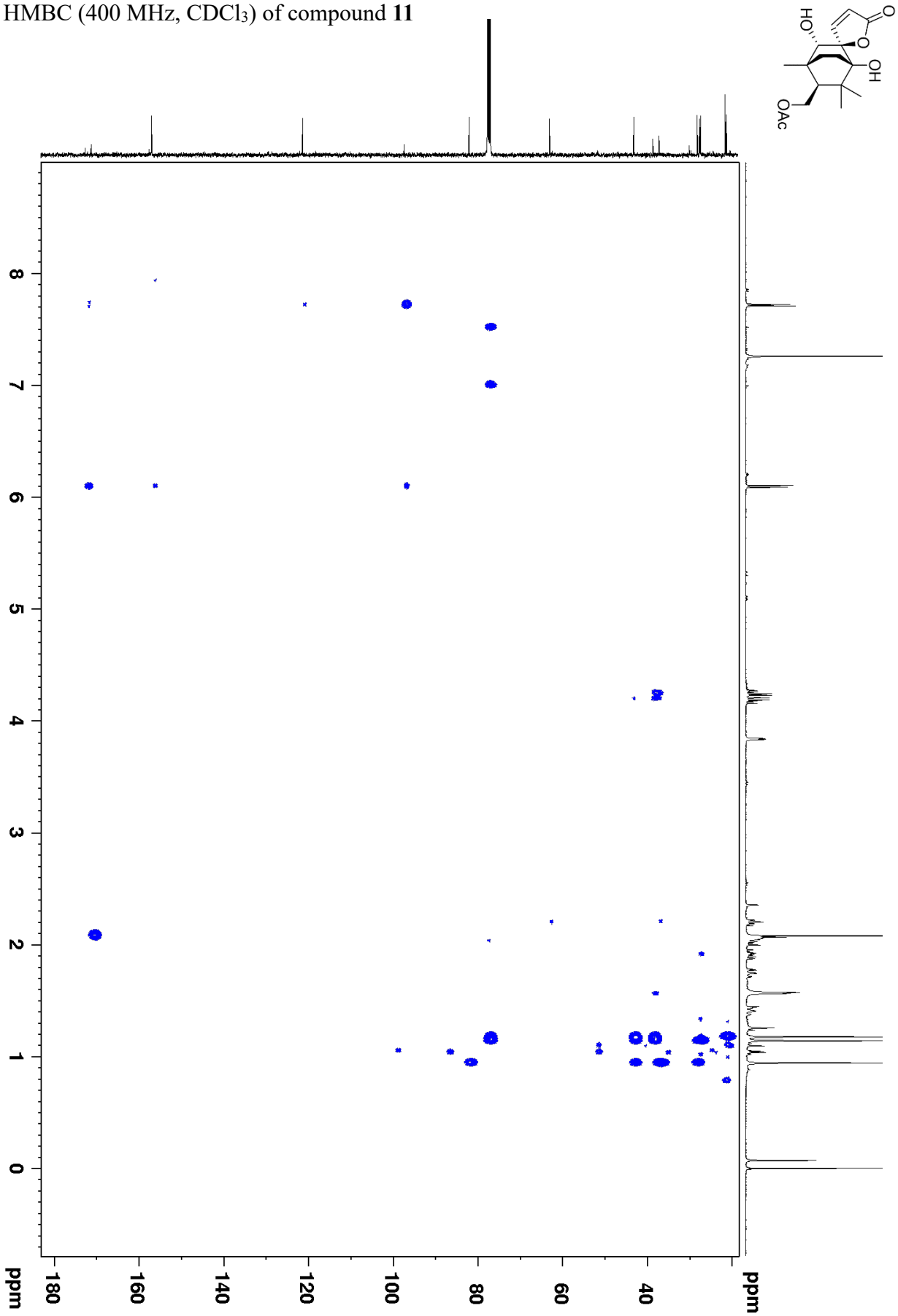
COSY (400 MHz, $CDCl_3$) of compound **11**



HSQC (400 MHz, $CDCl_3$) of compound **11**



HMBC (400 MHz, $CDCl_3$) of compound **11**



NOESY (400 MHz, $CDCl_3$) of compound **11**