Supporting Information for

Stereoselective Synthesis of Dihydropyrone Containing Marine Natural Products. Total Synthesis and Structural Elucidation of (–)-Membrenone-C

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General Experimental

^{1}H NMR (nuclear magnetic resonace) spectra were recorded on Fourier transform instruments: Varian Gemini (300 MHz) and Varian Unity Inova (600 MHz). ^{13}C NMR was recorded in the same manner on Fourier transform instrument: Varian Gemini (75.5 MHz). All 2D spectra were recorded on Fourier transform instrument: Varian Unity Inova (151 MHz). All spectra were recorded using an internal deuterium lock for the appropriate reference at ambient probe temperatures. All data that appears in the experimental are presented as follows: 1) chemical shift (in ppm, referenced to δ $CHCl_3$ = 7.26, however if the compound contains overlapping signals at that region, the spectra was referenced to δ TMS = 0); 2) Intergration; 3) Multiplicity (s = singlet, d= doublet, t = triplet, q = quartet, m = multiplet, br = broad); 4) coupling constant (Hz); 5) interpretation of signal where possible.

Infrared spectra were recorded on a Perkin Elmer 1600 FT-Infrared spectrophotometer employing 5 mm fused sodium chloride plates. Oil products were analysed neat by liquid film. Major absorbances are quoted in cm^{-1} followed by an abbreviation: vs = very sharp and strong; s = sharp and strong; m = medium; w = weak; br = broad.

Electron Impact mass spectra were recorded using a Kratos MS25RF time of flight spectrometer. The molecular formula is presented followed by the molecular ion (M^+), calculated mass and accurate mass.

Optical rotations were measured on a PolA AR 21 polarimeter using the sodium D line (589 nm) and all rotations were measured at 20°C and are presented as follows: $[\alpha]_D^{20}$, concentration (c in g/100 ml) and solvent.

Melting points were determined employing a Reichert melting point hot stage.

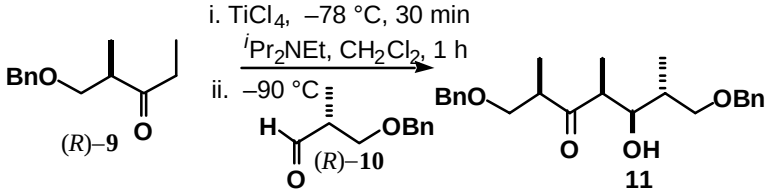
All reagents and solvents were dried and purified by standard means. Solvents such as dichloromethane, toluene, acetonitrile, cyclohexane were distilled from calcium hydride and used immediately or stored under an atmosphere of nitrogen over 4Å molecular sieves. Diethyl ether and tetrahydrofuran were distilled from sodium wire/benzophenone and used immediately after distilled. Ethanol was dried by distilling it from its ethoxide (prepared by heating ethanol under reflux in the presence of magnesium turnings). Dry ethanol was stored over molecular sieves (4Å) under an atmosphere of nitrogen. All solvents used in extractions during product isolation procedures or chromatography were pre-distilled prior to use. Methacrolein, triethylamine, and 2,6-lutidine were freshly distilled over anhydrous calcium chloride prior to use. DMSO, di-*iso*-propylethylamine, oxalyl chloride (Aldrich, Supa seal anhydrous) were all used as received. Acetic acid was dried (before use as a solvent) by adding a small quantity of acetic anhydride and CrO_3 heating under reflux followed by fractional distillation.

Experiments were conducted under anhydrous conditions in an atmosphere of nitrogen except where stated employing oven dried glassware. All moisture sensitive reagents were handled under nitrogen using standard techniques.

Thin layer chromatography (TLC) was employed to monitor the progress of a reaction or alternatively to monitor contents of eluted fractions from column chromatography. TLC plates used were Merck Kieselgel 60 F_{254} silica. with visualisation by ultra-violet light or anisaldehyde dip. All compounds were visualised employing anisaldehyde dip, those viewed by ultra-violet light are specified in the text. Column chromatography performed using Merck Kieselgel 60 (particle size 0.040-0.063 mm) 230-400 mesh silica. All R_f values reported are for silica gel medium, except where stated otherwise in the text.

Isomer *ent*-3 membrenone-C synthesis:

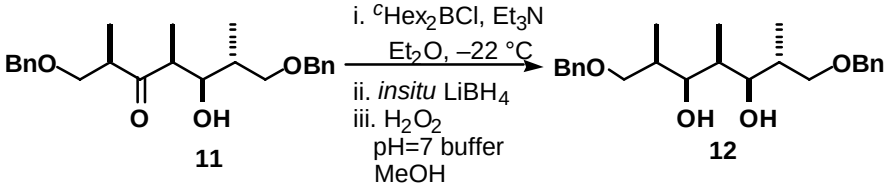
(2*R*, 4*S*, 5*R*, 6*R*)-1,7-Dibenzyloxy-5-hydroxy-2,4,6-trimethyl-heptan-3-one, 11



To a stirred solution of (*R*)-1-Benzyloxy-2-methylpentan-3-one **9** (0.7519 g, 3.65 mmol) in dry CH_2Cl_2 (7 ml) was added $TiCl_4$ (1.0M in CH_2Cl_2, 3.65 ml, 3.65 mmol) at –78°C and the mixture was stirred for 30 minutes at –78°C. Di-*iso*-propylethylamine ($^iPr_2NEt$) (0.634 ml, 3.65 mmol) was added and the mixture was stirred for one hour at –78°C. The reaction was cooled to –90°C and (*R*)-3-Benzyloxy-2-methylpropanal **10** (crude

>95% pure) (0.5297 g, 2.97 mmol) was added *via* cannula (2 × 5 ml dry CH_2Cl_2). The mixture was warmed slowly to –78°C and was stirred for 2 hours. The reaction was allowed to warm up slowly to –10°C, stirred for 5 minutes and quenched by the addition of pH=7 buffer (50 ml). The mixture was stirred until it reached RT and extracted with CH_2Cl_2 (3 × 50 ml). Combined organic extracts were washed with brine (saturated aqueous, 30 ml), dried (anhydrous $MgSO_4$) and concentrated *in vacuo* to give an oil. The product **11** (>95% ds, determined by ^1H and ^{13}C NMR analysis of the crude product) was purified by column chromatography (5%Et_2O/CH_2Cl_2). (0.789 g, 70%). R_f = 0.5 (5%Et_2O/CH_2Cl_2); $[\alpha]_D^{20}$ = –3.57° (c0.56, $CHCl_3$); IR (liquid film) 3494 (br), 2859 (s), 1709 (s), 1495 (s), 1454 (s), 1096 (m); ^1H NMR δ (300 MHz, $CDCl_3$) 7.37-7.25 (10H, m, 2 × Ph), 4.49 & 4.45 (2H, ABq, *J* = 12 Hz, CH_XH_YPh), 4.46 & 4.42 (2H, ABq, *J* = 12 Hz, CH_AH_BPh), 3.93 (1H, ddd, *J* = 8.7, 3.6, 3 Hz, C*H*OH), 3.65 (1H, t, *J* = 8.7 Hz, C$H_A$$H_B$OBn), 3.55 (1H, dd, J = 9, 4.5 Hz, C$H_X$$H_Y$OBn), 3.51 (1H, dd, *J* = 9, 5.4 Hz, CH$_X$$H_Y$OBn), 3.45 (1H, dd, *J* = 8.7, 5.1 Hz, CH$_A$$H_B$OBn), 3.27 (1H, d, *J* = 3.6 Hz, O*H*), 3.18 (1H, dqd, *J* = 8.7, 7.2, 5.1 Hz, BnOCH$_2$C*H*), 2.79 (1H, qd, *J* = 6.9, 3 Hz, O=CC*H*CH$_3$CHOH), 1.92-1.79 (1H, m, HOCHC*H*CH$_3$CH$_2$OBn), 1.10 (3H, d, *J* = 7.2 Hz, CHCH_3), 1.04 (3H, d, *J* = 6.9 Hz, CHCH_3), 0.92 (3H, d, *J* = 6.9 Hz, CHCH_3); ^{13}C NMR δ (75.5 MHz, $CDCl_3$); 217.6, 138.5, 137.8, 128.5, 128.4, 127.9, 127.8, 127.7, 127.6, 73.5, 73.4, 73.3, 73.2, 72.7, 48.7, 44.2, 35.8, 13.9, 13.8, 8.2;

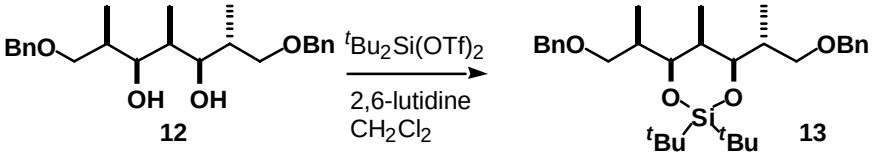
(2*R*, 3*S*, 4*R*, 5*R*, 6*R*)-1,7-Dibenzyloxy-2,4,6-trimethyheptan-3,5-diol



To a stirred solution of fresh dicyclohexylboron chloride (*c*-$C_6H_{11}BCl$) (0.388 g, 1.82 mmol) in dry Et_2O (3 ml) was added triethylamine (Et_3N) (0.272 ml, 1.96 mmol) at –23°C and the mixture was stirred for 5 minutes. β-hydroxyketone **11** (0.5395 g, 1.4 mmol) was added *via* cannula (2 × 3 ml dry Et_2O) and the reaction was stirred for 2 hours at –23°C. The reaction was cooled to –90°C and $LiBH_4$ (2.0 M in THF, 2.81 ml, 5.612 mmol) was added dropwise and the mixture was stirred for 2 hours at –78°C. The reaction was quenched with NH_4Cl (saturated aqueous, 60 ml), extracted with Et_2O (3 × 40 ml) and combined Et_2O extracts were concentrated *in vacuo*. The residue was suspended in MeOH (24 ml) and 10% NaOH (9 ml). H_2O_2 (30% aqueous, 12 ml) was added dropwise at 0°C (ice/salt bath) and the mixture was stirred at RT for 2 hours. The mixture was diluted with water (40 ml) and extracted with CH_2Cl_2 (4 × 30 ml). Combined organic extracts were washed with brine (saturated aqueous, 30 ml), dried (anhydrous $MgSO_4$) and concentrated *in vacuo* to give an oil. The product **12** (>95% ds, determined by ^1H and ^{13}C NMR analysis of the crude product) was purified by column chromatography (10%Et_2O/CH_2Cl_2). (0.4744 g, 88%). R_f = 0.25 (10%Et_2O/CH_2Cl_2);

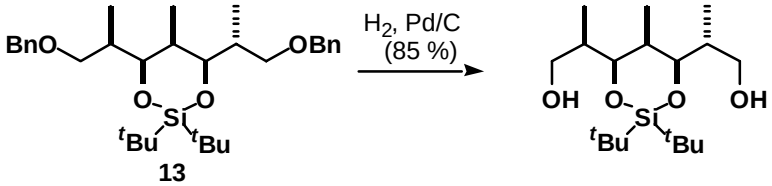
$[\alpha]_D^{20} = -26.3°$ (c0.266, $CHCl_3$); IR (liquid film) 3435 (br), 2860 (s), 1453 (s), 1361 (s), 1074 (s), 1028 (s); ^{1}H NMR δ (300 MHz, $CDCl_3$) 7.38-7.26 (10H, m, 2 × Ph), 4.52 (2H, s, CH_XH_YPh), 4.50 & 4.46 (2H, ABq, J = 12 Hz, CH_AH_BPh), 4.17 (1H, s, O*H*), 3.74 (1H, ddd, J = 6.9, 3.6, 1.5 Hz, C*H*OH), 3.62 (1H, d, J = 1.5 Hz, O*H*), 3.64 (1H, dd, J = 9, 2.1 Hz, C*H*OH), 3.59 (1H, dd, J = 9, 4.05 Hz, CH_AH_BOBn), 3.46 (1H, t, J = 9 Hz, CH_AH$_B$OBn), 3.42 (2H, d, J = 5.1 Hz, CH_XH_YOBn), 2.07-1.91 (2H, m, 2 × C*H*CH_3), 1.82-1.73 (1H, m, C*H*CH_3), 1.07 (3H, d, J = 6.9 Hz, CHCH_3), 0.94 (3H, d, J = 6.9 Hz, CHCH_3), 0.72 (3H, d, J = 6.9 Hz, CHCH_3); ^{13}C NMR δ (75.5 MHz, $CDCl_3$); 138.5, 137.5, 128.6, 128.4, 128.0, 127.8, 127.6, 127.56, 81.4, 78.5, 76.8, 74.3, 73.6, 73.2, 36.4, 36.2, 35.8, 13.2, 12.9, 5.6; EIMS: Calculated for $C_{24}H_{34}O_4$ (M^+) 386.24567. Found 386.2416.

(2*R*, 3*S*, 4*R*, 5*R*, 6*R*)-1,7-Dibenzyloxy-2,4,6-trimethyl-3,5-[[bis(1,1-dimethylethyl)-silylene]dioxy]-heptane



Diol **12** was azeotrophically dried by addition of toluene (2 × 1 ml) and concentration *in vacuo*. To a solution of diol **12** (0.3648 g, 0.944 mmol) in CH_2Cl_2 (1 ml) was added 2,6-lutidine (0.385 ml, 3.3 mmol) and di-*tert*-butylsilyl bis(trifluoromethanesulfonate) (0.688 ml, 1.89 mmol). The reaction was stirred for 6 hours at 65°C. The mixture was diluted with CH_2Cl_2 (10 ml), washed with $NaHCO_3$ (saturated aqueous, 3 ml), $NaHSO_4$ (0.3M, 2 × 3 ml), NaCl (saturated aqueous, 3 ml), dried (anhydrous $MgSO_4$) and concentrated *in vacuo*. The crude product was filtered through a column (plugged with cotton wool) with freshly distilled pentane, pentane extracts were combined and concentrated *in vacuo* to give an oil. The protected diol **13** was purified by column chromatography (CH_2Cl_2). (0.497 g, 72%). R_f = 0.9 (CH_2Cl_2); $[\alpha]_D^{20} = +6.66°$ (c0.3, $CHCl_3$); IR (liquid film) 2964 (s), 1476 (s), 1097 (m); ^{1}H NMR δ (300 MHz, $CDCl_3$) 7.35-7.26 (10H, m, 2 × Ph), 4.54 & 4.50 (2H, ABq, J = 12.3 Hz, CH_XH_YPh), 4.53 & 4.43 (2H, ABq, J = 12.3 Hz, CH_AH_BPh), 4.03 (1H, br m, C*H*OSi), 4.00 (1H, br m, C*H*OSi), 3.68 (1H, dd, J = 8.7, 3 Hz, CH_AH_BOBn), 3.55 (1H, dd, J = 8.7, 6.3 Hz, CH_AH$_B$OBn), 3.33 (1H, dd, J = 9.2, 4.8 Hz, CH_XH_YOBn), 3.26 (1H, dd, J = 9.2, 5.4 Hz, CH_XH$_Y$OBn), 1.96-1.70 (3H, m, 3 × C*H*CH_3), 1.10 (3H, d, J = 6.9 Hz, CHCH_3), 1.04 (9H, s, ^{t}Bu), 1.01 (9H, s, ^{t}Bu), 0.90 (3H, d, J = 6.9 Hz, CHCH_3), 0.87 (3H, d, J = 6.9 Hz, CHCH_3); ^{13}C NMR δ (75.5 MHz, $CDCl_3$) 139.1, 138.7, 128.4, 128.3, 127.64, 127.57, 127.4, 80.1, 78.6, 73.2 (×2), 72.8, 72.5, 37.8, 38.78, 35.1, 28.8, 27.6, 23.4, 20.4, 14.5, 13.2, 4.9;

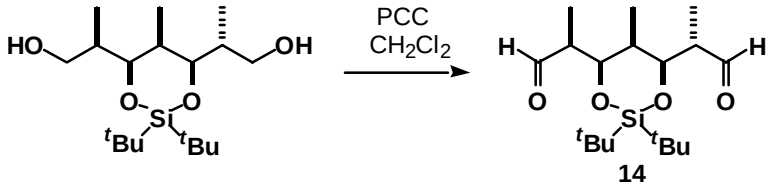
(2*R*, 3*S*, 4*R*, 5*R*, 6*R*)-2,4,6-Trimethyl-3,5-[[bis(1,1-dimethylethyl)-silylene]dioxy]-heptan-1,7-diol



13

To a stirred solution of benzyl ether **13** (0.3585 g, 0.681 mmol) in dry EtOH (6 ml) was added 10% Pd/C (0.13g) and the reaction was under an atmosphere of hydrogen for 4 hours. The mixture was diluted with dry Et_2O and filtered through a column of celite (pre-wet with dry Et_2O). Combined Et_2O extracts were concentrated *in vacuo*. The diol was purified by column chromatography (20% Et_2O/ CH_2Cl_2). (0.1997 g, 85%). R_f = 0.35 (20%Et_2O/CH_2Cl_2); $[\alpha]_D^{20} = -9.58°$ (c0.313, $CHCl_3$); IR (liquid film) 3381 (br), 2935 (s), 1475 (s), 1391 (s), 1000 (m); ^{1}H NMR δ (300 MHz, $CDCl_3$) 4.11 (1H, dd, *J* = 9.6, 2.1 Hz, C*H*OSi), 4.07 (1H, dd, *J* = 8.4, 2.1 Hz, C*H*OSi), 3.70 (1H, dd, J = 10.8, 8.7 Hz, CH_AH$_B$OH), 3.60-3.46 (3H, m, CH$_A$$H_B$OH & C$H_X$$H_Y$OH), 2.30 (2H, br m, 1 × O*H*), 2.03-1.91 (1H, m, C*H*CH$_3$), 1.86-1.76 (2H, m, 2 × C*H*CH$_3$), 1.08 (3H, d, *J* = 6.6 Hz, CHCH_3), 1.08 (9H, s, ^{t}Bu), 1.01 (9H, s, ^{t}Bu), 0.99 (3H, d, *J* = 7.2 Hz, CHCH_3), 0.72 (3H, d, *J* = 6.9 Hz, CHCH_3); ^{13}C NMR δ (75.5 MHz, $CDCl_3$) 85.9, 79.6, 69.6, 64.8, 39.4, 37.9, 35.7, 28.7, 27.5, 23.3, 20.4, 13.6, 12.7, 5.2. EIMS: Calculated for $C_{18}H_{38}O_4Si$ (M^+) 346.25392. Found 346.2574.

(2*S*, 3*R*, 4*S*, 5*S*, 6*S*)-2,4,6-Trimethyl-3,5-[[bis(1,1-dimethylethyl)-silylene]dioxy]-heptan-1,7-dial 14

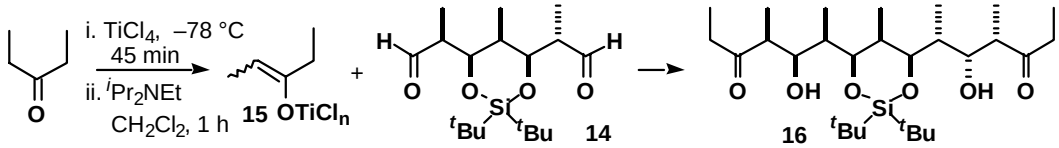


14

To a stirred solution of pyridinium chlorochromate (PCC) (0.93 g, 4.32 mmol) in dry CH_2Cl_2 (5 ml) was added the above diol (0.1872 g, 0.54 mmol) *via* cannula (2 × 3 ml CH_2Cl_2). The reaction stirred for 3 hours at RT. The mixture was triturated with dry Et_2O and filtered through a column of florisil (pre-wet with dry Et_2O) until the resulting black gum became a granular solid. Combined Et_2O extracts were concentrated *in vacuo*. The dialdehyde **14** was purified by column chromatography (CH_2Cl_2). (0.1130 g, 61%). R_f = 0.68 (CH_2Cl_2); $[\alpha]_D^{20} = +30.8°$ (c0.26, $CHCl_3$); ^{1}H NMR δ (300 MHz,

$CDCl_3$) 9.865 (1H, d, *J* = 2.4 Hz, O=C*H*), 9.73 (1H, d, *J* = 2.4 Hz, O=C*H*), 4.44 (1H, dd, *J* = 8.7, 2.1 Hz, C*H*OSi), 4.41 (1H, dd, *J* = 9.9, 2.4 Hz, C*H*OSi), 2.69 (1H, dqd, *J* = 8.7, 7.2, 2.4 Hz, HC=OC*H*CH_3), 2.55 (1H, dqd, *J* = 9.9, 7.2, 2.4 Hz, HC=OC*H*CH_3), 1.79 (1H, qdd, *J* = 7.2, 2.4, 2.1 Hz, CHC*H*CH_3CH), 1.23 (3H, d, *J* = 7.2 Hz, CHC*H*$_3$), 1.06 (9H, s, ^{t}Bu), 1.01 (9H, s, ^{t}Bu), 0.97 (3H, d, *J* = 7.2 Hz, CHC*H*$_3$), 0.91 (3H, d, *J* = 7.2 Hz, CHC*H*$_3$); ^{13}C NMR δ (75.5 MHz, $CDCl_3$) 205.2, 203.7, 78.6, 77.4, 50.96, 49.96, 35.5, 28.6, 27.4, 23.4, 20.4, 10.9, 9.6, 5.2;

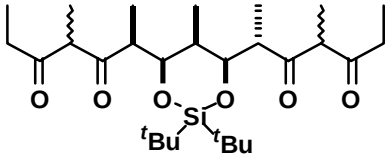
(4*RS*, 5*RS*, 6*R*, 7*S*, 8*R*, 9*R*, 10*R*, 11*R*, 12*S*)-5,11-Dihydroxy-4,6,8,10,12-pentamethyl-7,9-[[bis(1,1dimethylethyl)-silylene]dioxy]-pentadec-3,13-dione 16



To a stirred solution of pentan-3-one (0.348 ml, 3.296 mmol) in dry CH_2Cl_2 (4 ml) was added $TiCl_4$ (1.0M in CH_2Cl_2, 2.96 ml, 2.96 mmol) at –78°C and the solution was stirred for 30 minutes at –78°C. Di-*iso*-propylethylamine (^{i}Pr$_2$NEt) (0.516 ml, 2.96 mmol) was added dropwise and the enolate was stirred for one hour at –78°C. The reaction was cooled to –90°C and dialdehyde **14** (0.1129 g, 0.3296 mmol) was added *via* cannula (2 × 1.5 ml dry CH_2Cl_2). The mixture warmed up slowly to –78°C and stirred for 2 hours. The reaction was allowed warm up slowly until it reached –5°C and quenched by the addition of pH=7 buffer (50 ml). The mixture was stirred until it reached RT and extracted with Et_2O (3 × 50 ml). Combined organic extracts were washed with brine (saturated aqueous, 40 ml), dried (anhydrous $MgSO_4$) and concentrated *in vacuo*. The predominating double aldol product **16** (>90% ds, determined by ^{1}H and ^{13}C NMR analysis of the crude product) was purified by column chromatography (10%Et_2O/CH_2Cl_2). (0.1525 g, 89.9%). $[\alpha]_D^{20} = +12.5°$ (c0.16, $CHCl_3$); IR (liquid film) 3483 (br), 2973 (s) 1701 (s), 1476 (s); R_f = 0.15 (10%Et_2O/CH_2Cl_2); ^{1}H NMR δ (300 MHz, $CDCl_3$) 4.54 (1H, dd, *J* = 3, 2.4 Hz, C*H*O), 4.19 (1H, dd, *J* = 9.6, 2.1 Hz, C*H*O), 4.15 (1H, dd, *J* = 8.1, 2.7 Hz, C*H*O), 3.81 1H, ddd, *J* = 8.7, 2.4, 2.4 Hz, C*H*O), 3.31 (1H, d, *J* = 2.4 Hz, O*H*), 2.88 (1H, dq, *J* = 7.5, 6.9 Hz, O=CC*H*CH_3), 2.71 (1H, qd, *J* = 7.2, 2.4 Hz, O=CC*H*CH_3), 2.65-2.38 (5H, m, 2 × C*H*$_2$$CH_3$, 1 × O*H*), 1.82-1.75 (1H, m, C*H*CH_3), 1.70-1.60 (2H, m, 2 × C*H*CH_3), 1.22 (3H, d, *J* = 7.2 Hz, CHC*H*$_3$), 1.12 (3H, d, *J* = 7.2 Hz, CHC*H*$_3$), 1.08 (9H, s, ^{t}Bu), 1.07-1.00 (6H, m, 2 × CH_2C*H*$_3$),1.02 (9H, s, ^{t}Bu), 0.98 (3H, d, *J* = 7.2 Hz, CHC*H*$_3$), 0.89 (3H, d, *J* = 6.9 Hz, CHC*H*$_3$), 0.74 (3H, d, *J* = 6.9 Hz, CHC*H*$_3$); ^{13}C NMR δ (75.5 MHz, $CDCl_3$) 217.5, 215.25, 80.5, 77.7, 73.0, 72.7, 50.6, 46.7, 40.2, 39.7, 39.0, 34.7, 33.9, 28.7, 27.7, 23.4, 20.7, 13.8, 11.5, 10.1, 9.1, 7.5 (×2), 5.99; On the first attempt, a minor diastereomer (<10%) was observed. It was found that the colder the temperature (–90°C) upon the addition of the dialdehyde the higher the selectivity of the predominating double aldol **16** product. Minor double aldol product: R_f = 0.20 (10%Et_2O/CH_2Cl_2); ^{1}H NMR δ (300

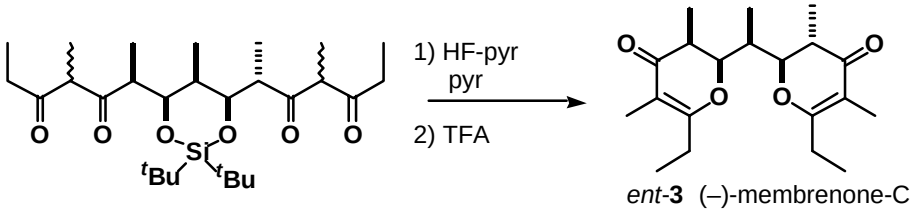
MHz, $CDCl_3$) 4.55 (1H, dd, *J* = 3.3, 2.4 Hz, C*H*O), 4.28 (1H, dd, *J* = 9.6, 2.1 Hz, C*H*O), 4.24 (1H, dd, *J* = 9, 2.4 Hz, C*H*O), 3.83 1H, dd, *J* = 8.7, 2.7 Hz, C*H*O), 2.81-2.43 (8H, m, 2 × O=CC*H*CH_3, 2 × C*H*$_2$$CH_3$, 2 × O*H*), 1.87-1.61 (3H, m, 3 × C*H*CH_3), 1.14 (3H, d, *J* = 7.2 Hz, CHC*H*$_3$), 1.03-0.99 (12H, m, 2 × CHC*H*$_3$, 2 × CH_2C*H*$_3$), 1.08 (9H, s, ^{t}Bu), 1.02 (9H, s, ^{t}Bu), 0.92 (3H, d, *J* = 6.9 Hz, CHC*H*$_3$), 0.76 (3H, d, *J* = 6.9 Hz, CHC*H*$_3$); ^{13}C NMR δ (75.5 MHz, $CDCl_3$) 217.4, 215.5, 78.9, 78.0, 73.3, 72.1, 49.3, 46.2, 40.2, 38.8, 38.1, 35.6, 34.7, 28.7, 27.7, 23.4, 20.7, 13.7, 11.7, 9.3, 8.6, 7.5, 7.4, 6.1;

(4*RS*, 6*S*, 7*R*, 8*S*, 9*S*, 10*S*, 12*RS*)-4,6,8,10,12-pentamethyl-7,9-[[bis(1,1dimethylethyl)-silylene]dioxy]-pentadecan-3,4,11,13-tetraone



To a stirred solution of oxalyl chloride (2.0 M in dry CH_2Cl_2, 1.149 ml, 2.2998 mmol) in dry CH_2Cl_2 (5 ml) at –78°C was added anhydrous methyl sulfoxide (DMSO) (Aldrich, 0.319 ml, 4.499 mmol) *via* cannula (2 × 1 ml CH_2Cl_2). The solution was stirred for 5 minutes at –78°C and double aldol product **16** (0.148 g, 0.2875 mmol) was added at –78°C *via* cannula (2 × 2 ml CH_2Cl_2) and stirring continued for 45 minutes. Triethylamine (Et_3N) (1.03 ml, 7.412 mmol) was added dropwise and the mixture was stirred for 20 minutes at –78°C. The reaction was allowed to warm up slowly to –5°C and quenched by the addition of NH_4Cl (saturated aqueous, 20 ml). The mixture was stirred until it reached RT and extracted with CH_2Cl_2 (3 × 30 ml). Combined organic extracts were dried (anhydrous $MgSO_4$) and concentrated *in vacuo*. The resulting residue was triturated with freshly distilled pentane (10 ml), filtered to remove the insoluble Et_3NH•Cl and concentrated *in vacuo* to give the crude product. (Assumed 0.1468 g, 100%); ^{1}H NMR δ (300 MHz, $CDCl_3$) diastereomeric and enol forms 4.49-4.12 (1.625H, m), 4.05-3.96 (0.55H, m), 3.89-3.65 (1.33H, m), 3.48-3.19 (2.11H, m), 3.12-2.84 (1.24H, m), 2.78-2.37 (3.397H, m), 2.30-2.05 (2.21H, m), 1.88-1.52 (3.51H, m), 1.49-0.79 (34.028H, m); ^{13}C NMR δ (75.5 MHz, $CDCl_3$) 211.3, 210.4, 209.3, 208.8, 207.7, 207.6, 207.5, 199.8, 190.4, 130.9, 128.8, 125.7, 125.5, 81.0, 80.9, 80.3, 80.0, 79.9, 79.8, 79.7, 79.6, 78.9, 78.8, 78.2. 78.1. 77.8, 77.7, 77.5, 72.9, 62.7, 62.6, 61.6, 59.9, 59.8, 59.5, 59.4, 49.9, 49.8, 49.4, 49.3, 49.2, 48.4, 48.3, 48.2, 46.6, 45.8, 41.8, 40.8, 34.8, 34.7, 34.6, 34.5, 34.3, 34.2, 34.0, 33.95, 33.9, 33.8, 33.7, 31.7, 31.6, 31.3, 30.4, 30.1, 29.5, 28.5, 27.5, 27.4, 25.6, 25.1, 24.2, 23.3, 22.5, 22.1, 20.3, 16.5, 16.1, 15.7, 14.9, 14.8, 14.7, 13.9, 13.0, 12.97, 12.8, 12.82, 12.3, 12.08, 12.07, 11.9, 11.5, 9.1, 8.5, 8.1, 8.0, 7.5, 7.4, 7.3, 5.0, 4.9, 4.8;

(–)-Membrenone-C



ent-**3** (–)-membrenone-C

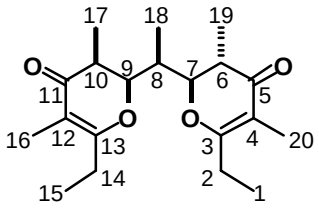
To the tetraone shown above (0.1468 g, 0.2875 mmol) was added buffered pyridinium hydrogen fluoride (3 ml of a stock solution prepared from dry THF (10 ml), pyridine (5 ml) and pyridinium hydrogen fluoride (Aldrich, 2.1 g)). The reaction was stirred at RT for 3 hours, diluted with CH_2Cl_2 (20 ml) and successively washed with $CuSO_4$ (saturated aqueous, 2 × 10 ml), $NaHCO_3$ (saturated aqueous, 10 ml), brine (saturated aqueous, 10 ml), dried (anhydrous $MgSO_4$) and concentrated *in vacuo*. Crude ^{1}H NMR suggested that cyclisation and dehydration was not complete giving a complex mixture of isomers. To a stirred solution of crude mixture in CH_2Cl_2 (4 ml) was added and trifluoroacetic acid (0.1 ml). The formation of a double γ-dihydropyrone ring system was monitored by TLC (UV active: R_f = 0.3 (10%Et_2O/CH_2Cl_2)). Upon completion of cyclisation/dehydration the mixture was diluted with CH_2Cl_2 (10 ml), washed with $NaHCO_3$ (saturated aqueous, 5 ml), brine (saturated aqueous, 5 ml), dried (anhydrous $MgSO_4$) and concentrated *in vacuo* to give an oil. The oil was purified by column chromatography (10%Et_2O/CH_2Cl_2) to give *ent*-**3** (–)-Membrenone-C as a white solid (mp 98-100°C). (0.0506g, 52%). (Overall Yield over 8 steps: 10.75%). R_f = 0.3 (10%Et_2O/CH_2Cl_2); $[\alpha]_D^{20} = -28.2°$ (c0.46, $CHCl_3$); ^{1}H NMR δ (600 MHz, $CDCl_3$) 4.24 (1H, dd, *J* = 10.2, 3 Hz, C*H*O *syn*-ring), 3.89 (1H, dd, *J* = 13.8, 2.1 Hz, C*H*O *anti*-ring), 2.51 (1H, dq, *J* = 13.8, 7.2 Hz, O=CC*H*CH_3, *anti*-ring), 2.46-2.22 (5H, m, 1 × O=CC*H*CH_3 & 2 × C*H*$_2$$CH_3$), 2.20 (1H, dqd, *J* = 10.2, 6.6, 2.1 Hz, CHC*H*CH_3CH), 1.733 (3H, s, vinyl C*H*$_3$), 1.704 (3H, s, vinyl C*H*$_3$), 1.19 (3H, d, *J* = 6.6 Hz, CHC*H*$_3$), 1.165 (3H, t, *J* = 7.5 Hz, CH_2C*H*$_3$), 1.08 (3H, d, *J* = 7.2 Hz, CHC*H*$_3$), 1.06 (3H, t, *J* = 7.5 Hz, CH_2C*H*$_3$), 1.01 (3H, d, *J* = 7.2 Hz, CHC*H*$_3$); ^{13}C NMR δ (151 MHz, $CDCl_3$) 197.11, 194.57, 173.73, 172.48, 108.65, 107.70, 81.69, 80.93, 40.43, 39.91, 34.67, 25.449, 25.431, 10.915, 10.817, 9.79, 9.328, 9.258, 9.113, 9.098; EIMS: Calculated for $C_{20}H_{30}O_4$ (M^+) 334.2144. Found 334.21484.

The cyclisation/dehydration step to (–)-Membrenone-C was also achieved on small scale in an NMR tube and its formation monitored by ^{1}H NMR after addition of trifluoroacetic acid (see methods for cyclisation/dehydration of Isomer 1 and 2 of Membrenone-C). Before adding trifluoroacetic acid, initial ^{1}H NMR revealed a complex mixture of

products. The cyclisation/dehydration process was complete within 20 minutes of adding the acid catalyst and the initial mixture of complex products had dramatically simplified to one compound that was observed to be >95% pure. Attempts to purify (–)-Membrenone-C (and related synthesised isomers 1,2 & 4) using silica gel chromatography would give ~50% yield. This suggests that the double γ-dihydropyrone ring system may be sensitive to these purification conditions.

In later cyclisation/dehydration experiments *para*-toluenesulphonate (*p*-TsOH) was found successful in catalysing the cyclisation/dehydration to form the double γ-dihydropyrone system. To the crude tetraone shown above (0.0285 g, 0.0557 mmol) was added buffered pyridinium hydrogen fluoride (0.5 ml of a stock solution prepared from dry THF (10 ml), pyridine (5 ml) and pyridinium hydrogen fluoride (Aldrich, 2.1 g)). The reaction was stirred at RT for 3 hours, diluted with CH_2Cl_2 (10 ml) and successively washed with $CuSO_4$ (saturated aqueous, 2 × 3 ml), $NaHCO_3$ (saturated aqueous, 3 ml), brine (saturated aqueous, 3 ml), dried (anhydrous $MgSO_4$) and concentrated *in vacuo*. Initial ^1H NMR of the crude product revealed a complex mixture of products. A large rice grain of *p*-TsOH was added to the NMR tube and cyclisation/dehydration was monitored by ^1H NMR. Crude ^1H NMR revealed two singlets at ~1.7 ppm for the vinyl methyl groups after 15 minutes. The NMR tube was left to sit for 2 days and the two dd at 4.2 and 3.98 ppm became defined compared with the initial ^1H NMR. The crude ^1H NMR also revealed that the cyclisation/dehydration employing *p*-TsOH was not as efficient compared with trifluoroacetic acid catalysed cyclisation/dehydration. The contents of the NMR tube were diluted with CH_2Cl_2 (6 ml), washed with $NaHCO_3$ (saturated aqueous, 3 ml), brine (saturated aqueous, 3 ml), dried (anhydrous $MgSO_4$) and concentrated *in vacuo*. The product was purified by column chromatography (10%Et_2O/CH_2Cl_2). (0.0027g, 15%).

Table 1: 600 MHz NMR data of (–)-Membrenone-C ***ent*-3**.[a,b,c]



C	$\delta^{13}C$ (ppm)	$\delta^{1}H$ (ppm)	m	^{3}J (Hz)	C's related to H (HMBC)	H's related to H (COSY)	NOE (Rosey)
16	9.098	1.733	s				
20	9.113	1.704	s				
18	9.258	1.19	d	6.6	C18 → H7, H8, H9	H18 → H8	H18 → H6, H9
19	9.328	1.08	d	7.2	C19 → H6, H7	H19 → H6	H19 → H7, H8
17	9.79	1.01	d	7.2	C17 → H9, H10	H17 → H10	H17 → H7, H8
15	10.817	1.165	t	7.5	C15 → H14	H15 → H14	
1	10.915	1.06	t	7.5	C1 → H2	H1 → H2	
2	25.431 #	2.36-2.22	m		C2 → H1	H2 → H1	
14	25.449 #	2.46-2.32	m		C14 → H15	H14 → H15	H8 → H17, H19
8	34.67	2.20	dq d	10.2, 6.6, 2.1	C8 → H6, H7, H9, H18	H8 → H7, H9, H18	
6	39.91	2.51	dq	13.8, 7.2	C6 → H7, H19	H6 → H7, H19	H6 → H18
10	40.43	2.40	m		C10 → H17	H10 → H9, H17	H10 → H7
7	80.93	3.89	dd	13.8, 2.1	C7 → H18, H19	H7 → H6, H8	H7 → H10, H17, H19
9	81.69	4.24	dd	10.2, 3	C9 → H7, H8, H17, H18	H9→ H8, H10	H9 → H18
12	107.70				C12 → H14, H16		
4	108.65				C4 → H2, H20		
3	172.48				C3 → H1, H2, H20		
13	173.73				C13 → H14, H15, H16		
5	194.57				C5 → H6, H7, H19, H20		
11	197.11				C11 → H9, H10, H16, H17		

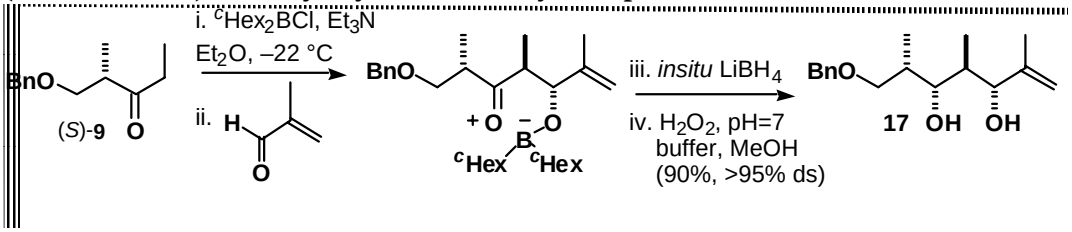
a) Varian Unity Inova 600 MHz NMR Spectrometer. Chemical shifts referenced to C<u>H</u>Cl_3 at 7.26 ppm and to <u>C</u>DCl_3 at 77.0 ppm.

b) Assigments assisted by ^{1}H-^{13}C HMBC, HSQC, ^{1}H-^{1}H COSY.

c) # indicates a tentative assignment and may be interchangeable.

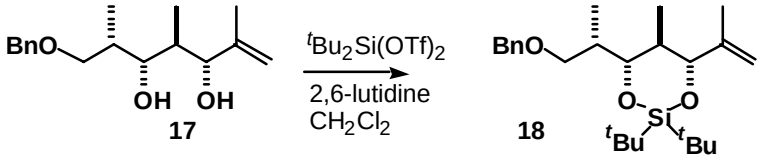
Isomer 1 membrenone-C synthesis:

(3*R*, 4*R*, 5*R*, 6*S*)-7-Benzyloxy-2,4,6-trimethyl-1-heptene-3,5-diol, 17



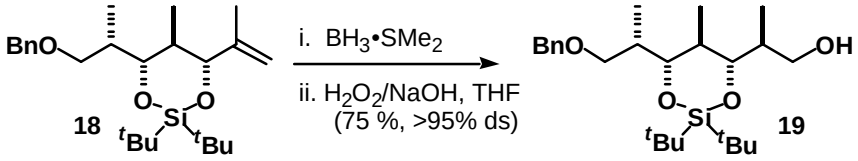
To a stirred solution of dicyclohexylboron chloride (0.308 g, 1.45 mmol) in dry Et_2O (3 ml) was added triethylamine (Et_3N) (0.201 ml, 1.45 mmol) at –22°C. (*S*)-1-Benzyloxy-2-methylpentan-3-one **9** (0.2990 g, 1.45 mmol) was added *via* cannula (2 × 1 ml dry Et_2O) and the mixture was stirred for 2 hours at –22°C. Methacrolein (0.143 ml, 2.9 mmol) was added *via* cannula (2 × 1 ml dry Et_2O) at –22°C and the mixture was stirred for 2 hours at –22°C. The reaction was cooled to –90°C and $LiBH_4$ (2.0 M in THF, 2.54 ml, 5.07 mmol) was added dropwise. The mixture was warmed slowly to –78°C and stirred at this temperature for 2 hours. The reaction was quenched by the addition of NH_4Cl (saturated aqueous, 40 ml) and extracted with Et_2O (3 × 25 ml). Organic extracts were combined and washed with NaCl (saturated aqueous, 20 ml) and concentrated *in vacuo*. The residue was suspended in MeOH (6 ml) and 10% NaOH (3 ml) and cooled to 0°C (ice/salt bath). H_2O_2 (30% aqueous, 4 ml) was added dropwise and stirring continued at RT for 3 hours. The mixture was diluted with H_2O (40 ml) and extracted with CH_2Cl_2 (3 × 30 ml). Combined organic extracts were washed with $NaHCO_3$ (saturated aqueous 20 ml), $NaHSO_3$ (saturated aqueous, 2 × 20 ml), NaCl (saturated aqueous, 20 ml), dried (anhydrous $MgSO_4$) and concentrated *in vacuo*. The diol **17** was purified by column chromatography (10%Et_2O/CH_2Cl_2). (0.3658g, 90%). R_f = 0.46 (10%Et_2O/CH_2Cl_2); $[\alpha]_D^{20}$ = –3.63° (c0.826, $CHCl_3$); IR (neat) 3340 (br), 2973 (vs), 2929 (s), 1106 (m), 1013 (s); ^{1}H NMR δ (300 MHz, $CDCl_3$) 7.38-7.25 (5H, m, Ph), 4.88 (1H, br m, olfinic), 4.86 (1H, br m, olfinic), 4.55 & 4.51 (2H, ABq, *J* = 12.3 Hz, CH_AH_BPh), 4.38 (1H, s, O*H*), 4.01 (1H, d, *J* = 9.3 Hz, C*H*OH), 3.99 (1H, s, O*H*), 3.85 (1H, br d, *J* = 9.6 Hz, HOC*H*); 3.62 (1H, dd, *J* = 9, 4.5 Hz, CH_AH$_B$OBn), 3.57 (1H, dd, *J* = 9, 4.5 Hz, CH$_A$$H_B$OBn), 1.97-1.90 (1H, m, C*H*CH$_3$), 1.79-1.70 (1H, m, C*H*CH$_3$), 1.73 (3H, s, vinyl CH_3), 0.99 (3H, d, *J* = 7.2 Hz, CHCH_3), 0.63 (3H, d, *J* = 6.6 Hz, CHCH_3); ^{13}C NMR δ (75.5 MHz, $CDCl_3$) 146.0, 138.0, 128.6, 127.9, 127.7, 114.0, 83.3, 80.0, 75.7, 73.6, 37.8, 35.2, 16.2, 13.1, 9.2;

(3*R*, 4*R*, 5*R*, 6*S*)-7-Benzyloxy-2,4,6-trimethyl-3,5-[[bis(1,1-dimethylethyl)-silylene]dioxy]-1-heptene, 18



To a stirred solution of *syn*-diol **17** (0.2993g, 1.075 mmol) in CH_2Cl_2 (0.5 ml) was added 2,6-lutidine (0.438 ml, 3.76 mmol) and di-*tert*-butylsilyl bis(trifluoromethanesulfonate) (0.784 ml, 2.15 mmol). The mixture was stirred at RT for 19 hours, diluted with CH_2Cl_2 (20 ml) and washed with $NaHCO_3$ (saturated aqueous, 10 ml), $NaHSO_4$ (0.3M, 2 × 10 ml), NaCl (saturated aqueous, 10 ml), dried (anhydrous $MgSO_4$) and concentrated *in vacuo*. The crude product was filtered through a column (plugged with cotton wool) with freshly distilled pentane, pentane extracts were combined and concentrated *in vacuo*. The product **18** was purified by column chromatography (CH_2Cl_2). (0.3688 g, 82%). R_f = 0.85 (CH_2Cl_2); $[\alpha]_D^{20}$ = +14.5° (c0.62, $CHCl_3$); IR (liquid film) 2856 (s), 1048 (s); ^{1}H NMR δ (300 MHz, $CDCl_3$) 7.36-7.25 (5H, m, Ph), 4.87 (1H, m, olefinic), 4.865 (1H, m, olefinic); 4.56 & 4.48 (2H, ABq, *J* = 12.3 Hz, C*H*$_A$*H*$_B$Ph), 4.17 (1H, d, *J* = 9.9 Hz, C*H*OSi), 4.07 (1H, dd, *J* = 9.9, 2.1 Hz, C*H*OSi), 3.60 (1H, t, *J* = 8.7 Hz, C*H*$_A$H$_B$OBn), 3.36 (1H, dd, *J* = 8.7, 5.7 Hz, CH$_A$*H*$_B$OBn), 2.14-2.00 (1H, m, C*H*CH$_3$), 1.84-1.71 (1H, m, C*H*CH$_3$), 1.75 (3H, s, vinyl C*H*$_3$), 1.04 (9H, s, ^{t}Bu), 1.02 (9H, s, ^{t}Bu), 0.87 (3H, d, *J* = 6.6 Hz, CHC*H*$_3$); 0.63 (3H, d, *J* = 6.9 Hz, CHC*H*$_3$); ^{13}C NMR δ (75.5 MHz, $CDCl_3$) 145.8, 138.8, 128.4, 127.8, 127.5, 114.0, 85.6, 77.8, 73.4, 73.3, 37.1, 36.0, 27.7, 27.2, 23.0, 20.2, 16.3, 12.4, 9.0; EIMS: Calculated for $C_{25}H_{42}O_3Si$ (M^+) 418.2903. Found 418.2916.

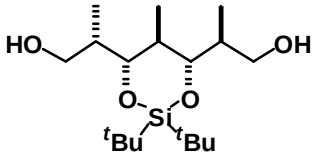
(2*S*, 3*R*, 4*S*, 5*S*, 6*S*)-1-Benzyloxy-2,4,6-trimethyl-3,5-[[bis(1,1-dimethylethyl)-silylene]dioxy]-heptan-7-ol, 19



To a stirred solution of alkene **18** (0.3632 g, 0.8674 mmol) in dry THF (4 ml) was added BH_3•SMe_2 (10 M, 0.346 ml, 3.46 mmol) and the solution was stirred for 16 hours at RT. The reaction was cooled to 0°C (ice/salt bath) and H_2O_2 (30%, 4 ml) (NB: care taken as peroxide addition to excess BH_3 is very exothermic) was added dropwise followed by 10% NaOH (4 ml). The mixture was warmed slowly to RT and stirred for 2 hours. The mixture was diluted with H_2O (50 ml) and extracted with EtOAc (4 × 25 ml). Organic extracts were washed with $NaHCO_3$ (saturated aqueous, 20ml), $NaHSO_3$ (saturated aqueous, 20 ml), NaCl (saturated aqueous, 20 ml) and concentrated *in vacuo*. The residue was suspended in THF/10%NaOH (1:1, 8 ml) and stirred for 24 hours. The mixture was diluted with H_2O (40 ml), extracted with EtOAc (3 × 20 ml) and combined

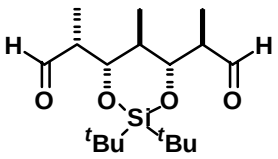
organic extracts were dried (anhydrous $MgSO_4$) and concentrated *in vacuo*. The product **19** was purified by column chromatography (5%Et_2O/CH_2Cl_2). (0.2828g, 75%). R_f = 0.6 (5%Et_2O/CH_2Cl_2); $[\alpha]_D^{20}$ = +10.65° (c1.127, $CHCl_3$); IR (liquid film) 3417 (br), 2932 (s), 1473 (s), 1363 (s); ^{1}H NMR δ (300 MHz, $CDCl_3$) 7.37-7.26 (5H, m, Ph), 4.54 & 4.48 (2H, ABq, *J* =11.5 Hz, CH_AH_BPh), 4.03 (1H, dd, *J* = 9.9, 2.1 Hz, C*H*OSi), 3.89-3.83 (2H, m, CH_AH$_B$O & C*H*OSi), 3.63 (1H, dd, *J* = 10.8, 4.2 Hz, CH$_A$$H_B$O), 3.59 (1H, t, *J* = 8.7 Hz, CH_XH$_Y$O), 3.36 (1H, dd, *J* = 8.7, 5.7 Hz, CH$_X$$H_Y$O), 2.27 (1H, m O*H*), 2.15-2.04 (1H, m, C*H*CH$_3$), 2.00-1.87 (2H, m, 2 × C*H*CH$_3$), 1.18 (3H, d, *J* = 6.9 Hz, CHCH_3), 1.03 (9H, s, ^{t}Bu), 0.99 (9H, s, ^{t}Bu), 0.87 (3H, d, *J* = 6.6 Hz, CHCH_3), 0.74 (3H, d, *J* = 6.9 Hz, CHCH_3); ^{13}C NMR δ (75.5 MHz, $CDCl_3$) 138.8, 128.4, 127.8, 127.5, 84.9, 78.7, 73.3(× 2), 63.4, 38.3, 36.0, 35.8, 27.8, 27.1, 23.0, 20.0, 15.4, 12.0, 9.1;

(2*S*, 3*R*, 4*S*, 5*S*, 6*S*)-2,4,6-Trimethyl-3,5-[[bis(1,1-dimethylethyl)-silylene]dioxy]-heptan-1,7-diol



To a stirred solution of benzyl ether **19** (0.2669 g, 0.6111 mmol) in dry EtOH (5 ml) was added 10%Pd/C (0.03 g) and the reaction was stirred under an atmosphere of hydrogen for 4 hours at RT. The mixture was diluted with dry Et_2O and filtered through a column of celite (pre-wet with dry Et_2O) to remove the catalyst. Et_2O extracts were combined and concentrated *in vacuo*. The diol was purified by column chromatography (20%Et_2O/CH_2Cl_2) to give a fine white crystalline solid. (0.1837 g, 87%). R_f = 0.45 (20%Et_2O/CH_2Cl_2); $[\alpha]_D^{20}$ = +1.63° (c0.613, $CHCl_3$); IR (liquid film) 3417 (br), 2932 (s), 1473 (s), 1363 (vs); ^{1}H NMR δ (300 MHz, $CDCl_3$) 4.06 (1H, dd, *J* = 9.9, 2.1 Hz, C*H*OSi), 3.87-3.62 (5H, m, 1 × C*H*OSi & 2 × CH_2OH), 2.52 (1H, dd, *J* = 8.4, 3.0 Hz, O*H*), 2.26 (1H, dd, *J* = 7.5, 2.7 Hz, O*H*), 2.01-1.86 (3H, m, 3 × C*H*CH$_3$), 1.17 (3H, d, *J* = 6.9 Hz, CHCH_3), 1.04 (9H, s, ^{t}Bu), 1.00 (3H, d, *J* = 6.9 Hz, CHCH_3), 0.997 (9H, s, ^{t}Bu), 0.76 (3H, d, *J* = 6.9 Hz, CHCH_3); ^{13}C NMR δ (75.5 MHz, $CDCl_3$) 84.4, 83.2, 67.8, 63.3, 38.4, 36.5, 36.2, 27.8, 27.0, 23.0, 20.0, 15.3, 12.1, 8.6;

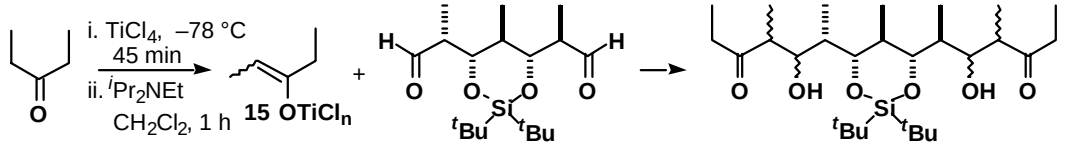
(2*R*, 3*S*, 4*R*, 5*R*, 6*R*)-2,4,6-Trimethyl-3,5-[[bis(1,1-dimethylethyl)-silylene]dioxy]-heptan-1,7-dial



To a stirred solution of pyridinium chlorochromate (PCC) (0.34 g, 1.57 mmol) in dry CH_2Cl_2 (5 ml) was added the above diol (0.1068 g, 0.3081 mmol) *via* cannula (2 × 1.5

ml CH_2Cl_2). The reaction was stirred for 3 hours at RT. The mixture was triturated with dry Et_2O and filtered through a column of florisil (pre-wet with Et_2O) until the resulting black gum became a granular solid. Combined Et_2O extracts were concentrated *in vacuo*. The dialdehyde was purified by column chromatography (CH_2Cl_2). (0.083 g, 79%). R_f = 0.56 (CH_2Cl_2); $[\alpha]_D^{20} = -21.1°$ (c0.473, $CHCl_3$); IR (liquid film) 2933 (s), 1699 (m), 1475 (s); ^{1}H NMR δ (300 MHz, $CDCl_3$) 9.817 (1H, d, *J* = 3 Hz, *H*C=O), 9.73 (1H, s, *H*C=O), 4.45 (1H, dd, *J* = 9.9, 2.4 Hz, C*H*OSi), 4.02 (1H, dd, *J* = 9.9, 2.1 Hz, C*H*OSi), 2.63 (1H, dqd, *J* = 9.9, 6.9, 3 Hz, HC=OC*H*CH_3), 2.50 (1H, dq, *J* = 6.9, 2.4 Hz, HC=OC*H*CH_3), 1.97 (1H, dqd, *J* = 9.9, 6.6, 2.1 Hz, CHC*H*CH_3CH), 1.31 (3H, d, *J* = 6.9 Hz, CHC*H*$_3$), 1.14 (3H, d, *J* = 6.9 Hz, CHC*H*$_3$), 1.02 (9H, s, ^{t}Bu), 0.93 (9H, s, ^{t}Bu), 0.84 (3H, d, *J* = 6.6 Hz, CHC*H*$_3$); ^{13}C NMR δ (75.5 MHz, $CDCl_3$) 205.3, 204.5, 81.9, 78.5, 49.2, 49.0, 38.1, 27.6, 26.9, 23.0, 20.1, 12.1, 11.7, 5.8;

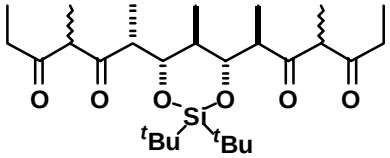
(4*RS*, 5*RS*, 6*S*, 7*R*, 8*S*, 9*S*, 10*S*, 11*RS*, 12*RS*)-5,11-Dihydroxy-4,6,8,10,12-pentamethyl-7,9-[[bis(1,1dimethylethyl)-silylene]dioxy]-pentadec-3,13-dione



To a stirred solution of pentan-3-one (0.437 ml, 4.134 mmol) in dry CH_2Cl_2 (3 ml) was added $TiCl_4$ (1.0M in CH_2Cl_2, 3.72 ml, 3.72 mmol) at –78°C and the mixture was stirred for 30 minutes at –78°C. Di-*iso*-propylethylamine (^{i}Pr$_2$NEt) (0.648 ml, 3.72 mmol) was added dropwise at –78°C and the enolate was stirred for one hour this temperature. The reaction was cooled to –90°C and the above dialdehyde (0.0708 g, 2.06 mmol) was added *via* cannula (2 × 1 ml dry CH_2Cl_2). The solution was warmed slowly to –78°C and stirred for 2 hours. The reaction was warmed up slowly to –5°C stirred for 5 minutes, quenched by the addition of pH=7 buffer (30 ml) and extracted with Et_2O (3 × 30 ml). Combined organic extracts were washed in brine (saturated aqueous, 20 ml), dried (anhydrous $MgSO_4$) and concentrated *in vacuo*. The double aldol products were purified by column chromatography (5%Et_2O/CH_2Cl_2). (0.0826 g, 78%). R_f = 0.15 (5%Et_2O/CH_2Cl_2); ^{1}H NMR δ (300 MHz, $CDCl_3$) Mixture of Double-Aldol products A,B & C: 4.31-3.97 (2.13H, m (4.14 (dd, *J* = 9.9, 2.1 Hz, C*H*OSi), 4.08 (dd, *J* = 10.2, 2.1 Hz C*H*OSi)), 3.92-3.63 (2.2H, m), 3.49-3.41 (0.29H, m), 2.97-2.74 (1.66H, m), 2.65-2.35 (5.85H, m), 2.17 & 2.63 (0.69H, 2 × s), 2.00-1.87 (1.14H, m), 1.79-1.61 (1.07H, m), 1.58-1.42 (1.11H, m), 1.23-1.17 (2.23H, m (1.19 (t, *J* = 6.6Hz, CH_2CH_3), 1.19 (d, *J* = 6.9 Hz, CHC*H*$_3$)), 1.142-0.915 (30.97H, m (1.06 (s, ^{t}Bu), 1.03 (s, ^{t}Bu), 0.999 (s, ^{t}Bu), 0.991 (s, ^{t}Bu)), 0.847 (2H, t, *J* = 7.2 Hz, CHC*H*$_3$), 0.76-0.69 (2.66H, m (0.75 (d, *J* = 6.6 Hz, CHC*H*$_3$), 0.71 (d, *J* = 6.6 Hz, CHC*H*$_3$), 0.70 (d, *J* = 6.6Hz, CHC*H*$_3$)); Mixture of Double-Aldol products A & B: 4.25-4.09 (1.40H, m (4.14 (dd, *J* = 9.9, 2.1 Hz, C*H*OSi)), 4.02-3.73 (2.84H, m (4.00 (dd, *J* = 8.1, 2.4 Hz, C*H*OSi)), 2.90-2.71 (1.71H, m), 2.66-2.36 (6H, m), 2.17 (1.5H, m), 1.99-1.90 (0.99H, m), 1.78-1.41

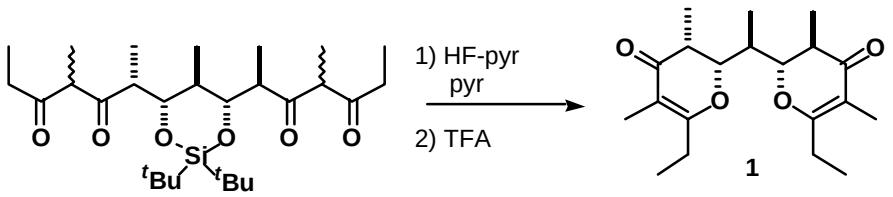
(2.68H, m), 1.22-1.18 (1.96H, m), 1.14-1.11(3.1H, m), 1.08-0.92 (29.02H, m), 0.89-0.69 (2.8H, m (0.72 (d, J = 6.6Hz, CHCH_3), 0.71 (d, J = 6.3 Hz, CHCH_3)); ^{13}C NMR δ (75.5 MHz, $CDCl_3$) ; Double-Aldol product A: 217.48, 215.37, 86.5, 85.1, 76.8, 69.7, 49.1, 47.1, 39.3, 36.9, 36.6, 35.6, 34.6, 27.7, 27.1, 23.0, 22.2, 16.1, 13.6, 12.4, 8.5, 7.6 (×2), 5.5; Double-Aldol product B: 217.4, 216.1. 85.4, 80.5, 78.9, 69.9, 49.5, 47.2, 39.2, 37.0, 36.3, 34.5, 34.45, 27.62, 27.16, 23.0, 20.2, 16.2, 12.3, 12.1, 9.9, 8.5, 7.6, 7.55; Double-Aldol product C: 217.52, 215.48, 85.2, 81.72, 79.15, 69.8, 49.7, 47.0, 39.14, 37.0, 36.6, 34.6, 34.4, 27.6, 27.1, 23.0, 20.3, 16.06, 13.8, 12.4, 10.6, 8.5, 7.8, 7.3;

(4*RS*, 6*R*, 7*S*, 8*R*, 9*R*, 10*R*, 12*RS*)-4,6,8,10,12-pentamethyl-7,9-[[bis(1,1dimethylethyl)-silylene]dioxy]-pentadecan-3,5,11,13-tetraone



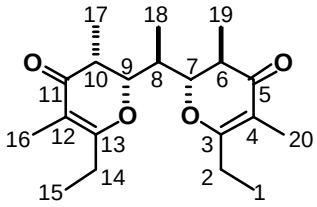
To a stirred solution of oxalyl chloride (2.0 M solution in CH_2Cl_2, 0.78 ml, 1.563 mmol) in dry CH_2Cl_2 (2 ml) at –78°C was added anhydrous methyl sulfoxide (DMSO) (Aldrich, 0.217 ml, 3.05 mmol in 1 ml CH_2Cl_2) *via* cannula. The solution was stirred for 5 minutes at –78°C and combined double aldol products (0.0805 g, 0.1563 mmol) were added *via* cannula (2 × 1 ml CH_2Cl_2) and stirring continued at –78°C for 45 minutes. Triethylamine (Et_3N) (0.696 ml, 5.027 mmol) was added dropwise and the solution was stirred for 20 minutes at –78°C. The mixture was allowed to warm up slowly to –5°C and quenched by the addition of NH_4Cl (saturated aqueous, 40 ml). The solution was stirred until it reached RT and extracted with CH_2Cl_2 (3 × 25 ml). Combined organic extracts were dried (anhydrous $MgSO_4$) and concentrated *in vacuo*. The resulting residue was triturated with freshly distilled pentane (10 ml) and filtered to remove the insoluble Et_3NH•Cl and concentrated *in vacuo*. (Assumed crude product 0.0798 g, 100%); ^{1}H NMR δ (300 MHz, $CDCl_3$) Crude mixture of diastereomeric and enol forms: 4.43-4.26 (0.58H, m), 4.07-3.76 (1.95H, m), 2.88-2.26 (8.09H, m), 2.09-1.7 (1.76H, m), 1.155-1.4 (0.92H, m), 1.31-0.7 (36.7H, m); ^{13}C NMR δ (75.5 MHz, $CDCl_3$) 210.4, 210.34, 208.6, 208.4, 208.3, 208.25, 207.8, 206.99, 206.85, 81.9, 81.16, 81.06, 80.6, 80.5, 80.4, 79.6, 79.4, 61.1, 60.0, 58.7, 57.4, 56.9, 53.3, 51.8, 50.8, 49.7, 49.6, 49.8, 48.7, 48.5, 40.9, 39.6, 39.5, 38.8, 38.6, 34.4, 34.0, 33.7, 33.3, 33.2, 27.6, 27.57, 27.43, 27.38, 26.94, 26.9, 22.9, 22.89, 22.88, 22.83, 22.82, 22.78, 22.2, 19.9, 19.8, 19.4, 13.9, 13.8, 13.7, 13.55, 13.5, 12.9, 12.7, 12.66, 12.4, 12.3, 11.9, 11.85, 8.7, 7.67, 7.65, 7.52, 7.5, 7.48, 7.43, 7.39;

Isomer 1 of Membrenone-C



To the above tetraone (0.0798 g, 0.1563 mmol) was added buffered pyridinium hydrogen fluoride (2 ml of a stock solution prepared from dry THF (10 ml), pyridine (5 ml) and pyridinium hydrogen fluoride (Aldrich, 2.1 g)). The reaction was stirred at RT for 3 hours, diluted with CH_2Cl_2 (20 ml) and successively washed with $CuSO_4$ (saturated aqueous, 2 × 5 ml), $NaHCO_3$ (saturated aqueous, 5 ml), brine (saturated aqueous, 5 ml), dried (anhydrous $MgSO_4$) and concentrated *in vacuo*. Crude ^1H NMR suggested that dehydration was not complete giving a complex mixture of isomers. Trifluoroacetic acid (0.08 ml) was added to the NMR tube and the formation of the double γ-dihydropyrone ring system was monitored by ^1H NMR. ^1H NMR (after adding the acid) had dramatically simplified to a single compound (>95% pure). The contents of the NMR tube were diluted with CH_2Cl_2 (15 ml), washed with $NaHCO_3$ (saturated aqueous, 5 ml), brine (saturated aqueous, 5 ml), dried (anhydrous $MgSO_4$) and concentrated *in vacuo*. The product **1** was purified by column chromatography (10%Et_2O/CH_2Cl_2). (0.028 g, 54%). (Overall Yield over 8 steps: 16.02%). R_f = 0.3 (10%Et_2O/CH_2Cl_2); $[\alpha]_D^{20}$ = +54.5° (c0.733, $CHCl_3$); ^1H NMR δ (600 MHz, $CDCl_3$) 4.48 (1H, dd, *J* = 10.2, 2.4 Hz, C*H*O *syn*-ring), 3.96 (1H, dd, *J* = 13.8, 1.8 Hz, C*H*O *anti*-ring), 2.86 (1H, dq, *J* = 13.8, 6.6 Hz, O=CC*H*CH_3), 2.42 (1H, dqd, *J* = 10.2, 7.2, 1.8 Hz, CHC*H*CH_3CH), 2.36 (1H, qd, *J* = 7.2, 2.4 Hz, O=CC*H*CH_3), 2.42-2.37 (1H, m, $CH_3CH_AH_B$), 2.37-2.26 (3H, m, $CH_3CH_AH_B$ & $CH_3CH_XH_Y$), 1.731 (3H, s, vinyl CH_3), 1.722 (3H, s, vinyl CH_3), 1.2015 (3H, d, *J* = 6.6 Hz, CHC*H*$_3$), 1.12 (3H, t, *J* = 7.2 Hz, CH_2CH_3), 1.085 (3H, t, *J* = 7.2 Hz, CH_2CH_3), 1.0785 (3H, d, *J* = 7.2 Hz, CHC*H*$_3$), 1.065 (3H, d, *J* = 7.2 Hz, CHC*H*$_3$); ^{13}C NMR δ (151 MHz, $CDCl_3$) 197.53, 195.51, 173.19, 172.76, 108.39, 107.97, 86.03, 80.10, 42.47, 41.25, 34.55, 25.5, 25.5, 14.115, 11.173, 10.83, 10.339, 9.308, 9.308, 9.061; ^1H NMR δ (300 MHz, D_6 Benzene) 4.31 (1H, dd, *J* = 10.2, 2.7 Hz, C*H*O *syn*-ring), 3.64 (1H, dd, *J* = 13.65, 1.35 Hz, C*H*O *anti*-ring), 2.84 (1H, dq, *J* = 13.65, 6.9 Hz, C*H*CH_3C=O), 2.28 (1H, dq, *J* = 7.2, 2.7 Hz, O=CC*H*CH_3), 2.09-1.85 (5H, m, 1 × CHC*H*CH_3CH, 2 × C$H_2$$CH_3$), 1.796 (3H, s, vinyl CH_3), 1.71 (3H, s, vinyl CH_3), 1.20 (3H, d, *J* = 6.9 Hz, CHC*H*$_3$), 0.90 (3H, d, *J* = 7.5 Hz, CHC*H*$_3$), 0.84 (3H, t, *J* = 7.5 Hz, CH_2CH_3), 0.73 (3H, t, *J* = 7.6 Hz, CH_2CH_3), 0.60 (3H, d, *J* = 7.2 Hz, CHC*H*$_3$); ^{13}C NMR δ (75.5 MHz, D_6 Benzene) 195.8, 194.0, 171.8, 171.5, 108.6, 108.2, 86.1, 80.3, 42.7, 41.4, 34.7, 25.3, 25.1, 13.56, 10.88, 10.79, 10.48, 9.45, 9.09, 9.03; EIMS: Calculated for $C_{20}H_{30}O_4$ (M^+) 334.2144. Found 334.2151.

Table 2: 600 MHz NMR data of Isomer **1** of Membrenone-C.[a,b,c]



C	$\delta^{13}C$ (ppm)	$\delta^{1}H$ (ppm)	m	^{3}J (Hz)	C's related to H (HMBC)	H's related to H (COSY)	NOE (Rosey)
20	9.061#	1.731	s				
16	9.308#	1.722	s				
17	9.308	1.0785	d	7.2	C17 → H9, H10	H17 → H10	H17 → H6
19	10.339	1.2015	d	6.6	C19 → H6, H7	H19 → H6	H19 → H7, H8 H19 → H9 (small)
15	10.830 *	1.085	t	7.2	C15 → H14	H15 → H14	
1	11.173 *	1.12	t	7.2	C1 → H2	H1 → H2	
18	14.115	1.065	d	7.2	C18 → H7, H8	H18 → H8	H18 → H7, H9, H10
14	25.50	2.37-2.26	m		C14 → H15	H14 → H15	
2	25.50	2.42-2.37 2.37-2.26	m		C2 → H1	H2 → H1	
8	34.55	2.42	dq d	10.2, 7.2, 1.8	C8 → H6, H7, H9, H18	H8 → H9, H18	H8 → H19
10	41.25	2.36	qd	7.2, 2.4	C10 → H17	H10 → H9, H17	H10 → H18
6	42.47	2.865	dq	13.8, 6.6	C6 → H7, H19	H6 → H7, H19	H6 → H17
9	80.10	4.48	dd	10.2, 2.4	C9 → H7, H8, H10, H17, H18	H9→ H8, H10	H9 → H18 H9 → H19 (small)
7	86.03	3.96	dd	13.8, 1.8	C7 → H9, H18, H19	H7→ H6	H7 → H18, H19
12	107.97				C12 → H14, H16		
4	108.39				C4 → H2, H20		
3	172.76				C3 → H1, H2, H20		
13	173.19				C13 → H14, H15, H16		
5	195.51				C5 → H6, H7, H19, H20		
11	197.53				C11 → H10, H16, H17		

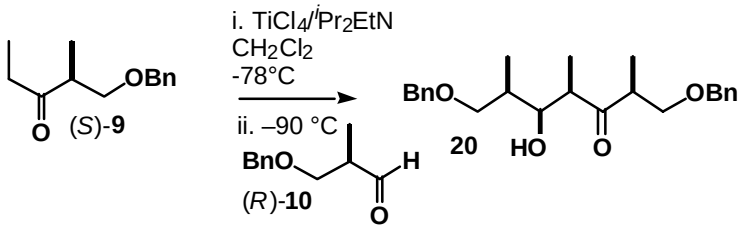
a) Varian Unity Inova 600 MHz NMR Spectrometer. Chemical shifts referenced to C<u>H</u>Cl_3 at 7.26 ppm and to <u>C</u>DCl_3 at 77.0 ppm.

b) Assigments assisted by ^{1}H-^{13}C HMBC, HSQC, ^{1}H-^{1}H COSY.

c) # and * indicate a tentative assignment and may be interchangeable.

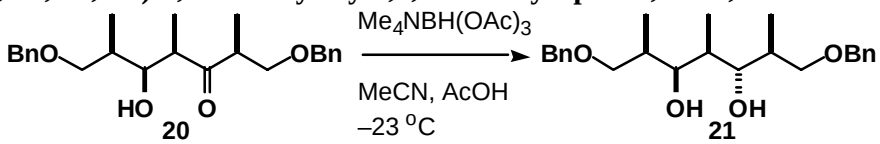
Isomer 2 membrenone-C synthesis:

(2*S*, 4*R*, 5*S*, 6*R*)-1,7-Dibenzyloxy-5-hydroxy-2,4,6-trimethyl-heptan-3-one, 20



To a stirred solution of (*S*)-1-Benzyloxy-2-methylpentan-3-one (*S*)-**9** (0.2611 g, 1.26 mmol) in dry CH_2Cl_2 (5 ml) at –78°C was added $TiCl_4$ (1.0M in CH_2Cl_2, 1.26 ml, 1.26 mmol) and the solution was stirred for 30 minutes at –78°C. Di-*iso*-propylethylamine ($^iPr_2NEt$) (0.219 ml, 1.26 mmol) was added dropwise and the enolate was stirred for one hour at –78°C. The reaction was cooled to –90°C and (*R*)-3-Benzyloxy-2-methylpropanal (*R*)-**10** (0.189 g, 1.06 mmol) (crude >95% pure) was added *via* cannula (2 × 3 ml CH_2Cl_2). The solution was warmed to –78°C and stirred for 2 hours. The mixture was allowed to warm up slowly to –5°C and stirred at this temperature for 5 minutes. The reaction was quenched by the addition of pH=7 buffer (50 ml) and extracted with Et_2O (3 × 70 ml). The combined organic extracts were washed with brine (saturated aqueous, 50 ml), dried (anhydrous $MgSO_4$) and concentrated *in vacuo*. The aldol product **20** (>95% ds, determined by ^1H and ^{13}C NMR analysis of the crude product) was purified by column chromatography ($7^1/_2$%Et_2O/CH_2Cl_2). (0.2833 g, 70%). R_f = 0.53 ($7^1/_2$%Et_2O/CH_2Cl_2); $[\alpha]_D^{20}$ = +8.94° (c1.006, $CHCl_3$); IR (liquid film) 3504 (br), 2876 (s), 1708 (s), 1455 (vs), 1100 (m); ^1H NMR δ (300 MHz, $CDCl_3$) 7.38-7.24 (10H, m. 2 × Ph), 4.47 & 4.43 (2H, m, ABq, *J* = 12 Hz, CH_AH_BPh), 4.45 & 4.41 (2H, m, ABq, *J* = 12 Hz, CH_XH_YPh), 3.98 (1H, ddd, *J* = 5.7, 5.4, 3 Hz, C*H*OH), 3.62 (1H, t, *J* = 8.7 Hz, CH_AH$_B$OBn), 3.45-3.41 (2H, m, CH_XH_YOBn), 3.35 (1H, dd, *J* = 8.7, 4.8 Hz, CH$_A$$H_B$OBn), 3.09 (1H, dqd, *J* = 8.7, 6.9, 4.8 Hz, BnOCH$_2$C*H*CH$_3$C=O), 2.985 (1H, d, *J* = 3 Hz, CHO*H*), 2.89 (1H, qd, *J* = 7.2, 5.4 Hz, O=CC*H*CH$_3$CHOH), 1.89-1.78 (1H, m, HOCHC*H*CH$_3$CH$_2$OBn), 1.13 (3H, d, *J* = 7.2 Hz, CHCH_3), 1.03 (3H, d, *J* = 7.2 Hz, CHCH_3), 0.99 (3H, d, *J* = 6.9 Hz, CHCH_3); ^{13}C NMR δ (75.5 MHz, $CDCl_3$) 217.6, 138.3, 137.8, 128.4, 127.8, 127.7, 127.67, 127.6, 74.3, 73.4, 73.3, 73.2, 72.95, 49.1, 45.0, 35.6, 13.6, 12.6, 10.8;

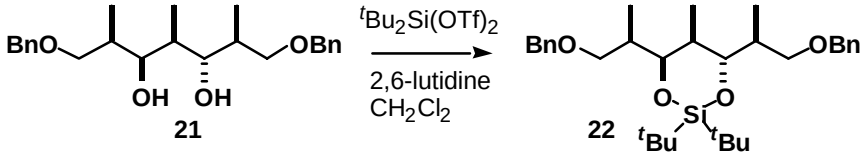
(2*S*, 3*S*, 4*S*, 5*S*, 6*R*)-1,7-Dibenzyloxy-2,4,6-trimethyheptan-3,5-diol, 21



To a stirred solution of tetramethylammonium triacetoxyborohydride (1.28 g, 4.865 mmol) in dry acetonitrile (5 ml) was added glacial acetic acid (5 ml) with resulting effervescence. The mixture was stirred for 1.5 hours at RT. The mixture was cooled to –23°C and β-hydroxyketone **20** (0.1001 g, 0.2603 mmol) was added *via* cannula (2 ×

1.5 ml acetonitrile). The reaction was stirred at –23°C for 2 hours and placed in the freezer for 96 hours. The mixture was diluted with CH_2Cl_2 (50 ml) and added *via* cannula to a potassium sodium tartrate solution (0.5 N, 50 ml) and stirred vigorously for 1 hour. The layers were separated and the tartrate layer was extracted with CH_2Cl_2 (3 × 50 ml). Combined organic extracts were washed with $NaHCO_3$ (sat. aqueous, 50 ml), brine (saturated aqueous, 50 ml), dried (anhydrous $MgSO_4$) and concentrated *in vacuo*. The *anti*-diol **21** was purified by column chromatography ($7^1/_2$%Et_2O/CH_2Cl_2). (0.0885 g, 87.9%). R_f = 0.35 ($7^1/_2$%Et_2O/CH_2Cl_2); $[\alpha]_D^{20}$ = –2.73° (c0.367, $CHCl_3$); IR (liquid film) 3432 (br), 2966 (s), 1455 (s), 1096 (m); ^{1}H NMR δ (300 MHz, $CDCl_3$) 7.38-7.24 (10H, m, 2 × Ph), 4.57 (1H, m, O*H*), 4.52 (2H, m, CH_AH_BPh), 4.48 & 4.42 (2H, ABq, *J* = 12 Hz, CH_XH_YPh), 3.97 (1H, d, *J* = 0.9 Hz, CHO*H*), 3.865 (1H, br d, *J* = 8.4 Hz, C*H*OH), 3.63 (1H, dd, *J* = 9, 3.9 Hz, CH_AH_BOBn), 3.57 (1H, m, C*H*OH), 3.46 (1H, t, *J* = 9 Hz, CH_AH$_B$OBn), 3.37 (2H, d, *J* = 5.1 Hz, CH_XH_YOBn), 2.25-2.11 (1H, m, C*H*CH_3), 1.95-1.85 (2H, m, 2 × C*H*CH_3), 1.12 (3H, d, *J* = 6.9 Hz, CHCH_3), 1.08 (3H, d, *J* = 7.2 Hz, CHCH_3), 0.73 (3H, d, *J* = 6.9 Hz, CHCH_3); ^{13}C NMR δ (75.5 MHz, $CDCl_3$) 138.5, 137.4, 128.6, 128.4, 128.0, 127.8, 127.6, 83.3, 76.8, 73.6, 73.3, 73.2, 72.97, 36.9, 35.7, 35.2, 14.6, 13.0, 11.2;

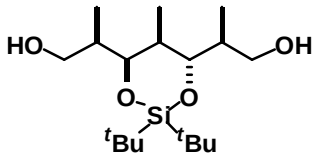
(2*S*, 3*S*, 4*S*, 5*S*, 6*R*)-1,7-Dibenzyloxy-2,4,6-trimethyl-3,5-[[bis(1,1-dimethylethyl)-silylene]dioxy]-heptane, 22



To a solution of diol **21** (0.0772 g, 0.1997 mmol) in CH_2Cl_2 (2 ml) was added 2,6-lutidine (0.0816 ml, 0.7009 mmol) and di-*tert*-butylsilyl bis(trifluoromethanesulfonate) (0.161 ml, 0.4407 mmol) and the reaction was stirred for 24 hours at RT. The mixture was diluted with CH_2Cl_2 (15 ml) and washed with $NaHCO_3$ (saturated aqueous, 5 ml), $NaHSO_4$ (0.3M, 2 × 5 ml), NaCl (saturated aqueous, 5 ml), dried (anhydrous $MgSO_4$) and concentrated *in vacuo*. The crude product was filtered through a column (plugged with cotton wool) with freshly distilled pentane, pentane extracts were combined and concentrated *in vacuo*. The product **22** was purified by column chromatography (CH_2Cl_2). (0.0744 g, 71%). R_f = 0.77 (CH_2Cl_2); $[\alpha]_D^{20}$ = –24.69° (c0.486, $CHCl_3$); IR (liquid film) 2859 (s), 1476 (s), 1097 (m); ^{1}H NMR δ (300 MHz, $CDCl_3$) 7.36-7.26 (10H, m, 2 × Ph), 4.52-4.48 (2H, ABq, *J* = 12.3 Hz, CH_AH_BPh), 4.49 (2H, m, CH_XH_YPh), 4.11 (1H, dd, *J* = 7.2, 3.9 Hz, C*H*OSi), 3.78 (1H, dd, *J* = 5.4, 4.8 Hz, C*H*OSi), 3.70 (1H, dd, *J* = 9, 4.5 Hz, CH_AH_BOBn), 3.46-3.40 (2H, m, CH_XH_YOBn), 3.285 (1H, dd, *J* = 9, 6 Hz, CH_AH$_B$OBn), 2.15-2.05 (1H, m, C*H*CH_3), 2.05-1.93 (2H, m, 2 × C*H*CH_3), 1.12 (3H, d, *J* = 6.6 Hz, CHCH_3), 1.06 (9H, s, ^{t}Bu), 1.045 (9H, s, ^{t}Bu), 1.05-1.02 (6H, m, 2 × CHCH_3); ^{13}C NMR δ (75.5 MHz, $CDCl_3$) 138.9, 138.8, 128.4,

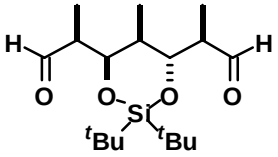
128.3, 127.6, 127.5, 127.4, 80.5, 73.9, 73.12, 73.09, 73.0, 71.98, 36.99, 36.81, 36.8, 28.0, 27.7, 21.9, 21.7, 14.7, 14.1, 13.9;

(2*S*, 3*S*, 4*S*, 5*S*, 6*R*)-2,4,6-Trimethyl-3,5-[[bis(1,1-dimethylethyl)-silylene]dioxy]-heptan-1,7-diol



To a stirred solution of benzyl ether **22** (0.0649 g, 0.123 mmol) in dry EtOH (4 ml) was added 10%Pd/C (0.03 g) and the reaction was stirred under an atmosphere of hydrogen for 4 hours at RT. The mixture was diluted with dry Et_2O and filtered through a column of celite (pre-wet with dry Et_2O) to remove the catalyst. Et_2O extracts were combined and concentrated *in vacuo*. The product shown above was purified by column chromatography (20%Et_2O/CH_2Cl_2). (0.0398 g, 93%). R_f = 0.25 (20%Et_2O/CH_2Cl_2); $[\alpha]_D^{20} = -38.78°$ (c0.593, $CHCl_3$); IR (liquid film) 3226 (br), 2861 (s), 1475 (s); ^{1}H NMR δ (300 MHz, $CDCl_3$) 4.26 (1H, dd, *J* = 5.7, 5.4 Hz, C*H*OSi), 3.90 (1H, dd, J = 6, 5.7 Hz, C*H*OSi), 3.79 (1H, dd, J = 11.1, 3.6 Hz, CH_AH$_B$OH), 3.66-3.60 (3H, m, CH$_A$$H_B$OH & 2 × C$H_X$$H_Y$OH), 2.46 (2H, br m, O*H*), 2.305-2.18 (1H, m, C*H*CH$_3$), 1.89-1.85 (2H, m, 2 × C*H*CH$_3$), 1.11 (3H, d, *J* = 6.9 Hz, CHCH_3), 1.05 (9H, s, ^{t}Bu), 1.04 (9H, s, ^{t}Bu), 1.03 (3H, d, *J* = 6.9 Hz, CHCH_3), 0.99 (3H, d, *J* = 7.2 Hz, CHCH_3); ^{13}C NMR δ (75.5 MHz, $CDCl_3$) 82.8, 75.6, 66.7, 65.7, 39.0 (× 2), 38.0, 27.9, 27.6, 22.0, 21.7, 14.6, 13.7, 12.9;

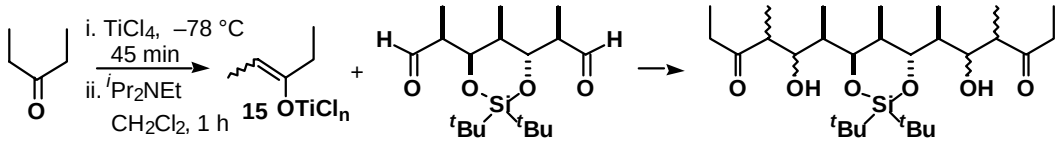
(2*R*, 3*R*, 4*R*, 5*R*, 6*S*)-2,4,6-Trimethyl-3,5-[[bis(1,1-dimethylethyl)-silylene]dioxy]-heptan-1,7-dial



To a stirred solution of diol from above (0.0398, 0.1148 mmol) in dry CH_2Cl_2 (4 ml) was added pyridinium chlorochromate (PCC) (0.098 g, 0.4592 mmol). The reaction was stirred for 3 hours at RT. The mixture was triturated with dry Et_2O and filtered through a column of florisil (pre-wet with dry Et_2O) until the resulting black gum became a granular solid. Combined Et_2O extracts were concentrated *in vacuo*. The dialdehyde was purified by column chromatography (CH_2Cl_2). (0.0204 g, 52%). R_f = 0.62 (CH_2Cl_2); $[\alpha]_D^{20} = -46.6°$ (c0.3, $CHCl_3$); IR (liquid film) 2937 (s), 1731 (s), 1476 (s); ^{1}H NMR δ (300 MHz, $CDCl_3$) 9.77 (1H, d, *J* = 3.3 Hz, O=C*H*), 9.676 (1H, d, *J* = 2.4 Hz, O=C*H*), 4.495 (1H, dd, *J* = 7.8, 4.8 Hz, C*H*OSi), 4.06 (1H, dd, *J* = 5.7, 5.7 Hz, C*H*OSi), 2.63 (1H, dqd, *J* = 7.8, 6.9, 2.4 Hz, HC=OC*H*CH$_3$), 2.53 (1H, qdd, *J* = 6.9, 5.7, 3.3 Hz, HC=OC*H*CH$_3$), 2.25 (1H, qdd, *J* = 6.9, 5.7, 4.8 Hz, CHC*H*CH$_3$CH), 1.23 (3H, d, *J* = 6.9 Hz, CHCH_3), 1.18 (3H, d, *J* = 6.9 Hz, CHCH_3), 1.02 (9H, s, ^{t}Bu), 1.00 (9H, s, ^{t}Bu),

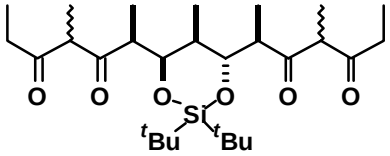
0.99 (3H, d, J = 6.9 Hz, CHCH_3); ^{13}C NMR δ (75.5 MHz, $CDCl_3$) 205.0, 203.45, 78.9, 72.97, 50.7, 49.95, 38.4, 27.5, 27.4, 21.7, 21.6, 12.8, 11.2, 10.7;

(4*RS*, 5*RS*, 6*S*, 7*S*, 8*S*, 9*S*, 10*R*, 11*RS*, 12*RS*)-5,11-Dihydroxy-4,6,8,10,12-pentamethyl-7,9-[[bis(1,1dimethylethyl)-silylene]dioxy]-pentadec-3,13-dione



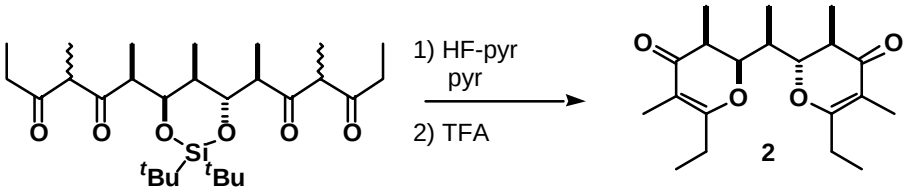
To a stirred solution of pentan-3-one (0.126 ml, 1.19 mmol) in dry CH_2Cl_2 (2 ml) was added $TiCl_4$ (1.0M in CH_2Cl_2, 1.07 ml, 1.072 mmol) at –78°C and the mixture was stirred for 30 minutes at –78°C. Di-*iso*-propylethylamine (^{i}Pr$_2$NEt) (0.187 ml, 1.072 mmol) was added dropwise and the enolate was stirred for 1 hour at –78°C. The reaction was cooled to –90°C and dialdehyde from above (0.0204 g, 0.0595 mmol) was added *via* cannula (2 × 1 ml CH_2Cl_2). The reaction was warmed slowly to –78°C and stirred for 2 hours at this temperature. The mixture was warmed slowly to –5°C and stirred for 5 minutes. The reaction was quenched at –5°C by the addition of pH=7 buffer (30 ml) and extracted with Et_2O (3 × 30 ml). Combined Et_2O extracts were washed with brine (saturated aqueous, 30 ml), dried (anhydrous $MgSO_4$) and concentrated *in vacuo*. The double aldol products were purified by column chromatography (5% Et_2O/ CH_2Cl_2). (combined diastereomers: 0.0285g, 93%). Double Aldol product A: (0.01852 g, 60%). R_f = 0.2 (5% Et_2O/ CH_2Cl_2); IR (liquid film) 3482 (br), 1699 (s), 1455 (s); ^{1}H NMR δ (300 MHz, $CDCl_3$) 4.51 (1H, dd, J = 4.8, 3.3 Hz, C*H*O), 4.06 (1H, ddd, J = 9.6, 4.5, 2.1 Hz, C*H*O), 4.01 (1H, t, J = 5.7 Hz, C*H*O), 3.85-3.80 (1H, m, C*H*O), 3.76 (1H, d, J = 2.1 Hz, O*H*), 3.45 (1H, d, J = 4.5 Hz, O*H*), 2.77-2.30 (6H, m, 2 × C*H*C=O, 2 × CH_2C=O), 1.90-1.82 (2H, m, 2 × C*H*CH$_3$), 1.77-1.71 (1H, m, C*H*CH$_3$), 1.16 (3H, d, J = 7.2 Hz, CHCH_3), 1.13 (3H, d, J = 7.2Hz, CHCH_3), 1.08-1.03 (27H, m, 1 × CHCH_3, 2 × CH$_2$CH_3, 2 × ^{t}Bu), 0.99 (3H, d, J = 7.2 Hz, CHCH_3), 0.87 (3H, d, J = 6.9 Hz, CHCH_3); ^{13}C NMR δ (75.5 MHz, $CDCl_3$) 216.4. 216, 81.9, 74.4, 73.6, 73.0, 48.0, 47.9, 40.5, 40.4, 38.0, 34.7, 34.3, 27.9, 27.6, 22.1, 21.8, 14.7, 13.6, 12.2, 10.5, 8.6, 7.8, 7.7; Double Aldol product B + trace amounts of another diastereomer: (0.0099 g, 32%). R_f = 0.12 (5% Et_2O/ CH_2Cl_2); IR (liquid film) 3458 (br), 1699 (s), 1456 (s); ^{1}H NMR δ (300 MHz, $CDCl_3$) 4.24 (1H, dd, J = 6.3, 4.8 Hz, C*H*O), 4.12 (1H, ddd, J = 8.7, 2.4 Hz, C*H*O), 3.99 (1H, dd, J = 5.7, 4.2 Hz, C*H*O), 3.87 (1H, dd, J = 9.3, 2.4 Hz, C*H*O), 2.86-2.35 (8H, m, 2 × C*H*C=O, 2 × CH_2C=O, 2 × O*H*), 1.87-1.56 (3H, m, 3 × C*H*CH$_3$), 1.19 (3H, d, J = 7.2 Hz, CHCH_3), 1.14 (3H, d, J = 7.2Hz, CHCH_3), 1.09-0.99 (30H, m, 2 × CHCH_3, 2 × CH$_2$CH_3, 2 × ^{t}Bu), 0.90 (3H, d, J = 6.9 Hz, CHCH_3); ^{13}C NMR δ (75.5 MHz, $CDCl_3$) 216.5, 214.6, 82.1, 77.2, 74.2, 72.5, 49.2, 47.7, 40.7, 38.5, 38.2, 35.8, 34.3, 28.1, 27.7, 22.0, 21.9, 14.7, 14.5, 13.9, 8.8, 8.77, 7.8, 7.6;

(4*RS*, 6*R*, 7*R*, 8*R*, 9*R*, 10*S*, 12*RS*)-4,6,8,10,12-pentamethyl-7,9-[[bis(1,1dimethylethyl)-silylene]dioxy]-pentadecan-3,5,11,13-tetraone



To a stirred solution of oxalyl chloride (2.0 M in CH_2Cl_2, 0.22 ml, 0.4424 mmol) in dry CH_2Cl_2 (0.5 ml) at −78°C was added anhydrous methyl sulfoxide (DMSO) (0.062 ml, 0.866 mmol) *via* cannula (2 × 0.5 ml CH_2Cl_2). The solution was stirred for 5 minutes at −78°C and combined double aldol products from above (0.0285 g, 0.0553 mmol) were added *via* cannula (2 × 1 ml CH_2Cl_2) and stirring continued at −78°C for 45 minutes. Triethylamine (Et_3N) (0.198 ml, 1.43 mmol) was added dropwise at −78°C and the mixture was stirred for 20 minutes at −78°C. The mixture warmed slowly to −5°C and quenched by the addition of NH_4Cl (saturated aqueous, 15 ml). The mixture was stirred until it reached RT and extracted with CH_2Cl_2 (3 × 20 ml). Combined organic extracts were dried (anhydrous $MgSO_4$) and concentrated *in vacuo*. The resulting residue was triturated with freshly distilled pentane (10 ml), filtered to remove the insoluble Et_3NH•Cl and concentrated *in vacuo*. (Assumed crude product 0.0282 g, 100%). ^1H NMR δ (300 MHz, $CDCl_3$) diastereomeric and enol forms: 4.43-4.39 (0.46H, m, C*H*OSi), 4.23-4.16 (0.415H, m, C*H*OSi), 4.09-3.84 (1.204H, m, C*H*OSi), 3.58-3.42 (0.503H, m, C*H*OSi), 2.96-2.7 (3.425H, m), 2.10-1.50 (4.695H, m), 1.44-1.25 (12.807H, m), 1.133-0.85 (26.491H, m); ^{13}C NMR δ (75.5 MHz, $CDCl_3$) 219.4, 214.0, 210.0, 207.9, 202.2, 130.86, 128.8, 82.6, 82.3, 82.0, 80.1, 75.9, 72.4, 72.3, 68.2, 61.4, 61.3, 59.5, 53.3, 53.2, 52.8, 52.7, 45.2, 45.1, 45.1, 38.7, 36.5, 36.4, 36.1, 34.3, 31.9, 31.6, 31.4, 30.4, 29.6, 29.4, 28.2, 28.0, 27.8, 27.7, 25.6, 24.9, 23.8, 23.0, 22.7, 21.0, 21.7, 16.4, 16.0, 14.6, 14.3, 14.1, 14.0, 13.1, 12.0, 12.89, 12.6, 12.1, 10.9, 8.3, 7.64;

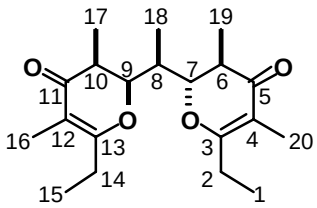
Isomer 2 of Membrenone-C



To the tetraone shown above (0.0282 g, 0.0553 mmol) was added buffered pyridinium hydrogen fluoride (1 ml of a stock solution prepared from dry THF (10 ml), pyridine (5 ml) and pyridinium hydrogen fluoride (Aldrich, 2.1 g)). The reaction was stirred at RT for 3 hours, diluted with CH_2Cl_2 (15 ml) and successively washed with $CuSO_4$ (saturated aqueous, 2 × 5 ml), $NaHCO_3$ (saturated aqueous, 5 ml), brine (saturated aqueous, 5 ml), dried (anhydrous $MgSO_4$) and concentrated *in vacuo*. An initial crude ^1H NMR suggested that dehydration was not complete giving a complex mixture of isomers. Trifluoroacetic acid (0.06 ml) was added to the NMR tube and the formation of

the double γ-dihydropyrone ring system was monitored by ^{1}H NMR. The complex mixture of products dramatically simplified (after adding the acid) to a single isomer containing two γ-dihydropyrone rings (>95% pure). The contents of the NMR tube were diluted with CH_2Cl_2 (10 ml), washed with $NaHCO_3$ (saturated aqueous, 5 ml), brine (saturated aqueous, 5 ml), dried (anhydrous $MgSO_4$) and concentrated *in vacuo*. The product was purified by column chromatography (10%Et_2O/CH_2Cl_2). (0.009 g, 49%). (Overall Yield over 8 steps: 9.6%). R_f = 0.3 (10%Et_2O/CH_2Cl_2); $[\alpha]_D^{20}$ = +100° (c0.2, $CHCl_3$);^{1}H NMR δ (600 MHz, $CDCl_3$) 4.34 (1H, dd, *J* = 6.9, 3.3 Hz, C*H*O *syn*-ring), 3.94 (1H, dd, *J* = 10.2, 3.6 Hz, C*H*O *anti*-ring), 2.47 (1H, dq, *J* = 10.2, 7.2 Hz, O=CC*H*CH_3 *anti*-ring), 2.44-2.26 (6H, m, 2 × C*H*$_2$$CH_3$, O=CC*H*$CH_3$ *syn*-ring, CHC*H*CH_3CH), 1.723 (3H, s, vinyl C*H*$_3$), 1.716 (3H, s, vinyl C*H*$_3$), 1.22 (3H, d, *J* = 6.6 Hz, CHC*H*$_3$), 1.15 (3H, t, *J* = 7.5 Hz, CH_2C*H*$_3$), 1.14 (3H, d, *J* = 7.2 Hz, CHC*H*$_3$), 1.12 (3H, t, *J* = 7.8 Hz, CH_2C*H*$_3$), 1.08 (3H, d, *J* = 7.2 Hz, CHC*H*$_3$); ^{13}C NMR δ (151 MHz, $CDCl_3$) 197.08, 194.60, 173.29, 171.95, 108.13, 107.67, 84.36, 80.12, 43.36, 40.66, 36.20, 25.58, 25.43, 13.255, 12.486, 10.84, 10.785, 10.414, 9.176, 9.101; EIMS: Calculated for $C_{20}H_{30}O_4$ (M^+) 334.2144. Found 334.2141

Table 3: 600 MHz NMR data of Isomer **2** of Membrenone-C.[a,b,c]



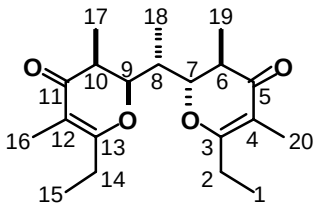
C	$\delta^{13}C$ (ppm)	$\delta^{1}H$ (ppm)	m	^{3}J (Hz)	C's related to H (HMBC)	H's related to H (COSY)	NOE (Rosey)
20	9.101#	1.716	s				
16	9.176#	1.723	s				
17	10.414	1.08	d	7.2	C17 → H9, H10	H17 → H10	H17 → H8
1	10.785 *	1.12	t	7.8	C1 → H2	H1 → H2	H1 → H6
15	10.840 *	1.15	t	7.5	C15 → H14	H15 → H14	
19	12.486	1.14	d	7.2	C19 → H6, H7	H19 → H6	H19 → H9
18	13.255	1.22	d	6.6	C18 → H7, H8, H9	H18 → H8	H18 → H6
14	25.43	2.44-2.33	m		C14 → H15	H14 → H15	
2	25.58	2.40-2.26	m		C2 → H1	H2 → H1	
8	36.20	2.33	m		C8 → H6, H7, H8, H9, H18	H8 → H7, H9, H18	H8 → H17
6	40.66	2.47	dq	10.2, 7.2	C6 → H7, H19	H6 → H7, H19	H6 → H1, H18 H6 → H9 (slight)
10	43.36	2.37	m		C10 → H17	H10 → H9, H17	H10 → H7 (slight)
9	80.12	4.34	dd	6.9, 3.3	C9 → H7, H8, H17, H18	H9→ H8, H10	H9 → H19 H9 → H6 (slight)
7	84.36	3.94	dd	10.2, 3.6	C7 → H9, H18, H19	H7→ H6, H8	H7 → H10 (slight)
12	107.67				C12 → H14, H16		
4	108.13				C4 → H2, H20		
3	171.95				C3 → H1, H2, H7, H20		
13	173.29				C13 → H14, H15, H16		
5	194.60				C5 → H6, H7, H19, H20		
11	197.08				C11 → H9, H10, H16, H17		

a) Varian Unity Inova 600 MHz NMR Spectrometer. Chemical shifts referenced to $C\underline{H}Cl_3$ at 7.26 ppm and to $\underline{C}DCl_3$ at 77.0 ppm.

b) Assigments assisted by ^{1}H-^{13}C HMBC, HSQC, ^{1}H-^{1}H COSY.

c) # and * indicate a tentative assignment and may be interchangeable.

Table 4: 600 MHz NMR data of Isomer **4** of Membrenone-C.[a,b,c]



C	$\delta^{13}C$ (ppm)	$\delta^{1}H$ (ppm)	m	^{3}J (Hz)	C's related to H (HMBC)	H's related to H (COSY)	NOE (Rosey)
18	7.556	0.92	d	7.2	C18 → H7, H8, H9	H18 → H8	H18 → H6, H10
17	9.125	1.04	d	7.2	C17 → H9, H10	H17 → H10	H17 → H8
20	9.125*	1.736	s				
16	9.358*	1.735	s				
19	9.445	1.10	d	7.2	C19 → H6, H7	H19 → H6	H19 → H8
15	10.916 #	1.07	t	7.2	C15 → H14	H15 → H14	
1	10.953 #	1.06	t	7.2	C1 → H2	H1 → H2	
14	25.28^	2.40-2.31 2.33-2.23	m		C14 → H15	H14 → H15	
2	25.44^	2.41-2.35 2.32-2.24	m		C2 → H1	H2 → H1	
8	34.70	2.17	dq d	10.2, 7.2, 1.8	C8 → H6, H7, H18	H8 → H7, H9, H18	H8 → H17, H19
6	39.85	2.50	dq	13.8, 7.2	C6 → H19	H6 → H7, H19	H6 → H18
10	40.82	2.42	qd	7.2, 3.0	C10 → H17	H10 → H9, H17	H10 → H18
9	79.08	4.345	dd	10.2, 3.0	C9 → H8, H17, H18	H9 → H8, H10	
7	79.91	4.37	dd	13.8, 1.8	C7 → H6, H18, H19	H7 → H6, H8	
12	107.87				C12 → H14, H16		
4	108.29				C4 → H2, H20		
3	172.57				C3 → H1, H2, H20		
13	173.02				C13 → H14, H15, H16		
5	195.22				C5 → H6, H19, H20		
11	197.61				C11 → H10, H16, H17		

a) Varian Unity Inova 600 MHz NMR Spectrometer. Chemical shifts referenced to C<u>H</u>Cl_3 at 7.26 ppm and to <u>C</u>DCl_3 at 77.0 ppm.

b) Assigments assisted by ^{1}H-^{13}C HMBC, HSQC, ^{1}H-^{1}H COSY.

c) #, * and ^ indicate a tentative assignment and may be interchangeable.

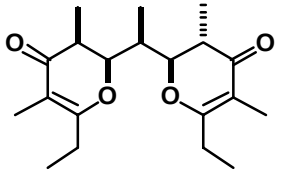
Table 4: Comparion of 600 MHz NMR data of all Isomers **1**, **2**, *ent*-**3** & **4** with (–)-Membrenone-C.[a,b,c]

C	(–)-Membrenone-C				Isomer *ent*-3				Isomer 1				Isomer 2				Isomer 4			
	$\delta^{13}C$ (ppm)	$\delta^{1}H$ (ppm)	m	^{3}J (Hz)	$\delta^{13}C$ (ppm)	$\delta^{1}H$ (ppm)	m	^{3}J (Hz)	$\delta^{13}C$ (ppm)	$\delta^{1}H$ (ppm)	m	^{3}J (Hz)	$\delta^{13}C$ (ppm)	$\delta^{1}H$ (ppm)	m	^{3}J (Hz)	$\delta^{13}C$ (ppm)	$\delta^{1}H$ (ppm)	m	^{3}J (Hz)
1	10.9	1.06	t	7.6	10.92	1.06	t	7.5	11.17*	1.12	t	7.2	10.79*	1.12	t	7.8	10.95#	1.06	t	7.2
2	25.16	2.35	m		25.43#	2.36 - 2.22	m		25.50	2.42 - 2.37 & 2.37 - 2.26	m		25.58	2.40 - 2.26	m		25.44*	2.414 - 2.35 & 2.326- 2.247	m	
3	172.5				172.48				172.76				171.95				172.57			
4	108.4				108.65				108.39				108.13				108.29			
5	194.51				194.57				195.51				194.60				195.22			
6	39.93	2.51	dq	13.7, 6.9	39.91	2.51	dq	13.8, 7.2	42.47	2.865	dq	13.8, 6.6	40.66	2.47	dq	10.2, 7.2	39.85	2.50	dq	13.8, 7.2
7	81.74	3.90	dd	13.7, 2.1	80.93	3.89	dd	13.8, 2.1	86.03	3.96	dd	13.8, 1.8	84.36	3.94	dd	10.2, 3.6	79.91	4.37	dd	13.8, 1.8
8	34.68	2.20	m		34.67	2.20	dqd	10.2, 6.6, 2.1	34.55	2.42	dq d	10.2,7.2, 1.8	36.20	2.33	m		34.70	2.17	dqd	10.2, 7.2, 1.8
9	83.05	4.25	dd	10, 2.6	81.69	4.24	dd	10.2, 3	80.10	4.48	dd	10.2, 2.4	80.12	4.34	dd	6.9, 3.3	79.08	4.345	dd	10.2, 3
10	40.25	2.40	m		40.43	2.40	m		41.25	2.36	qd	7.2, 2.4	43.36	2.37	m		40.82	2.42	qd	7.2, 3
11	197.41				197.11				197.53				197.08				197.61			
12	107.48				107.70				107.97				107.67				107.87			
13	173.81				173.73				173.19				173.29				173.02			
14	25.16	2.40	m		25.45#	2.46 - 2.32	m		25.50	2.37 - 2.26	m		25.43	2.44 - 2.33	m		25.28*	2.401 - 2.31 & 2.336 - 2.235	m	
15	10.8	1.17	t	7.6	10.82	1.165	t	7.5	10.83*	1.085	t	7.2	10.84*	1.15	t	7.5	10.92#	1.07	t	7.2
16	9.11	1.74	s		9.098	1.733	s		9.308#	1.722	s		9.176#	1.723	s		9.358^	1.735	s	
17	9.77	1.02	d	7.3	9.790	1.01	d	7.2	9.308	1.08	d	7.2	10.41	1.08	d	7.2	9.125	1.04	d	7.2
18	9.11	1.19	d	6.8	9.258	1.19	d	6.6	14.115	1.065	d	7.2	13.255	1.22	d	6.6	7.566	0.92	d	7.2
19	9.33	1.09	d	6.9	9.328	1.08	d	7.2	10.339	1.20	d	6.6	12.486	1.14	d	7.2	9.445	1.10	d	7.2
20	9.11	1.71	s		9.113	1.704	s		9.061#	1.731	s		9.101#	1.716	s		9.125^	1.736	s	

a) Varian Unity Inova 600 MHz NMR Spectrometer. Chemical shifts referenced to $C\underline{H}Cl_3$ at 7.26 ppm and to $\underline{C}DCl_3$ at 77.0 ppm.

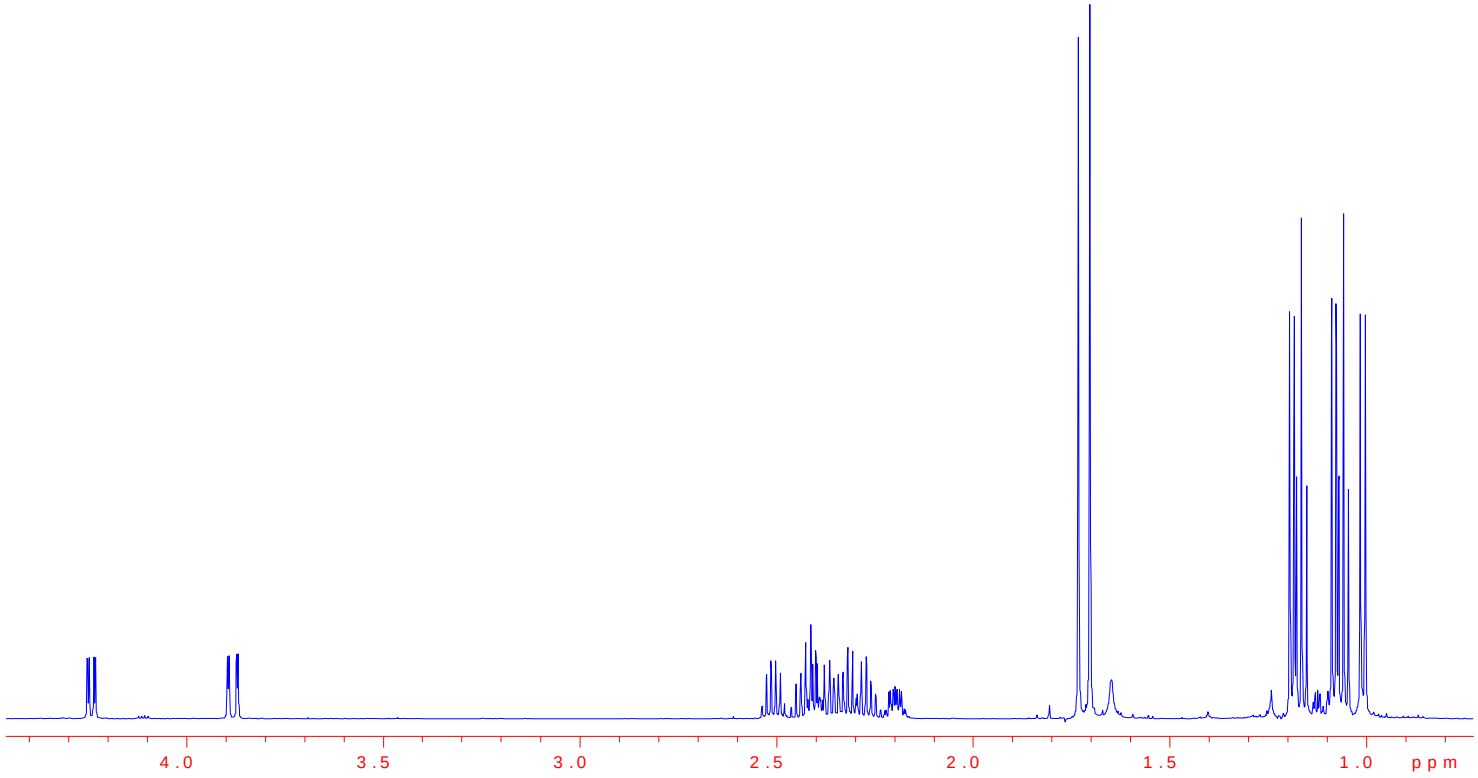
b) Assigments assisted by ^{1}H-^{13}C HMBC, HSQC, ^{1}H-^{1}H COSY.

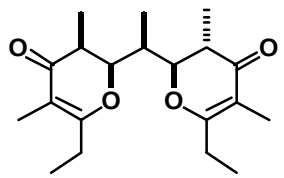
c) #, * and ^ indicate a tentative assignment and may be interchangeable.



ent-**3** (–)-membrenone-C

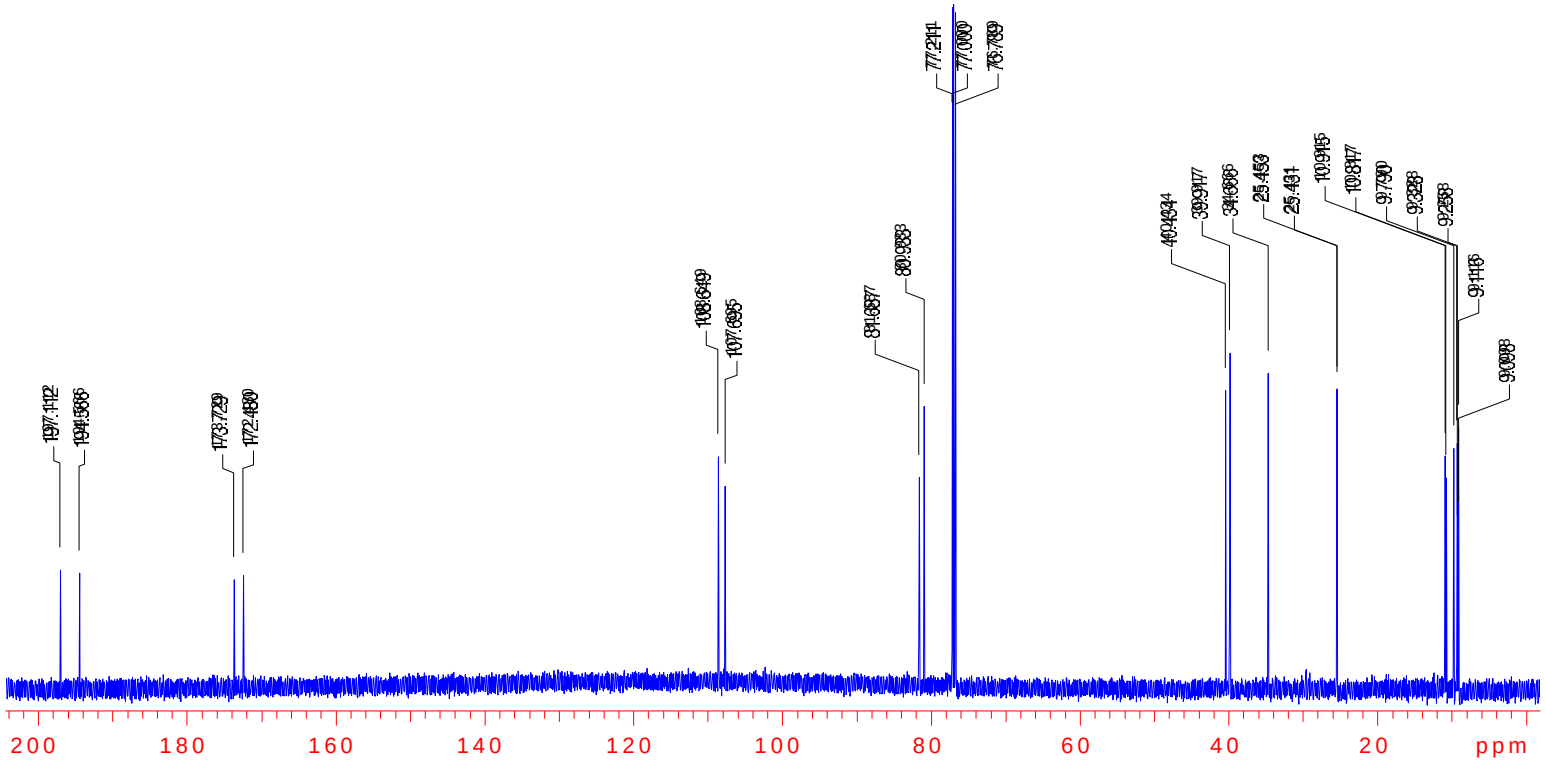
Figure 1: ^{1}H NMR (600 MHz) spectrum of Isomer ent-**3** (–)-Membrenone-C.





ent-**3** (–)-membrenone-C

Figure 2: ^{13}C NMR (151 MHz) spectrum of Isomer ent-**3** (–)-Membrenone-C.



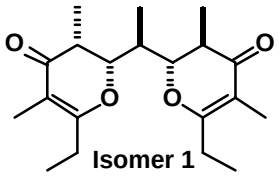
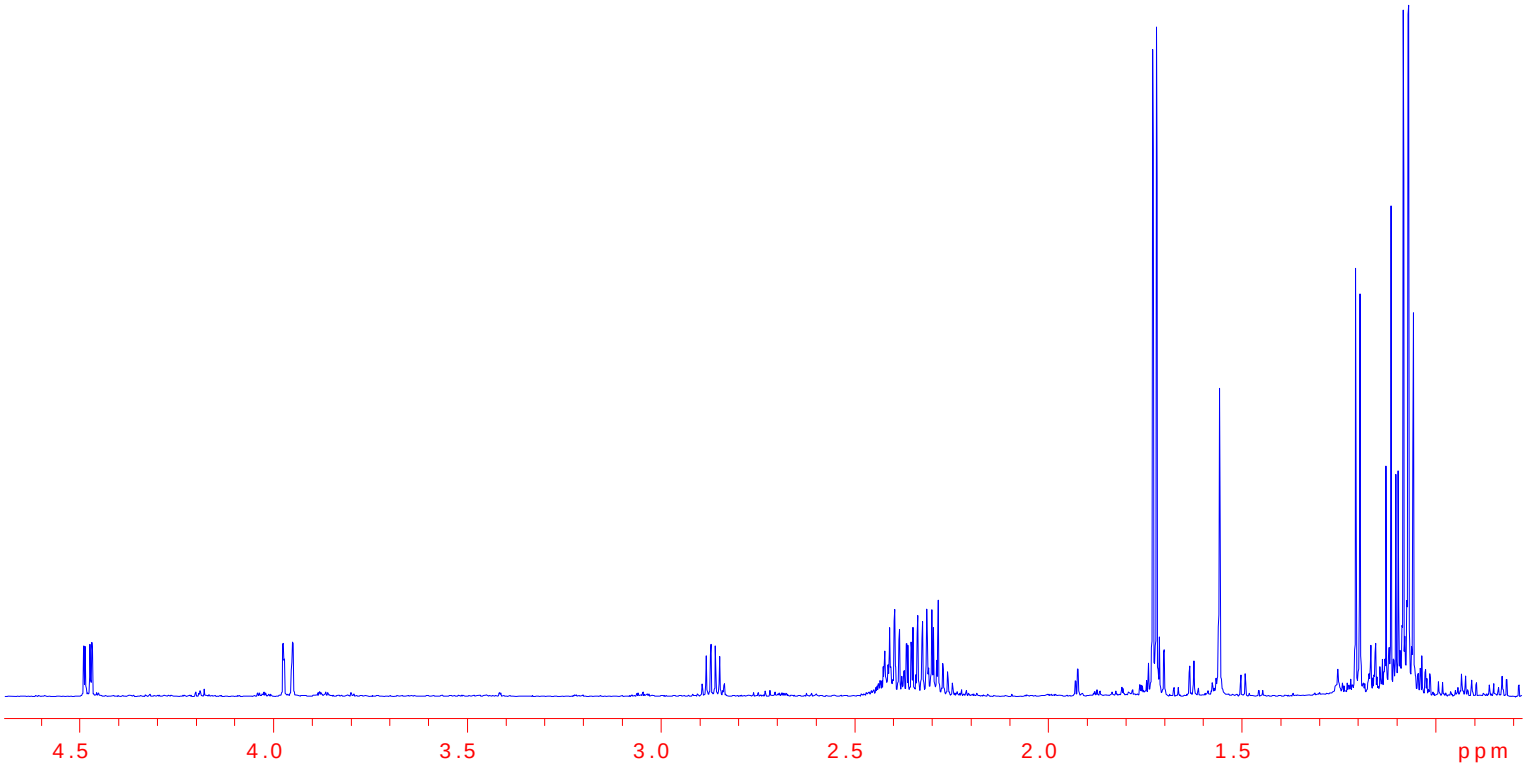


Figure 3: ^{1}H NMR (600 MHz) spectrum of Isomer **1.**



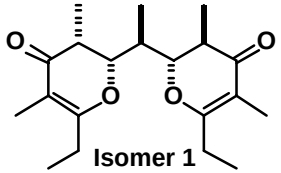
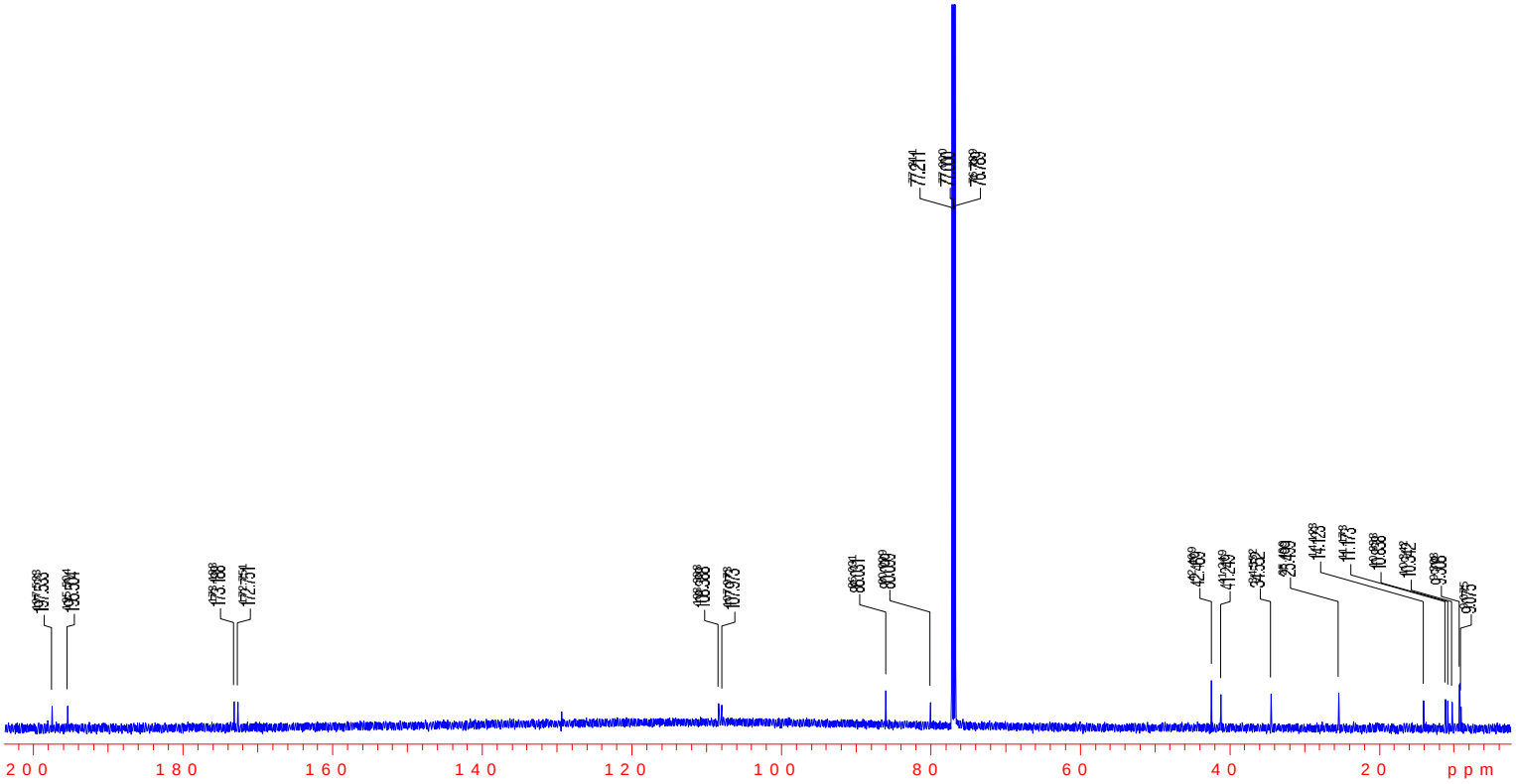


Figure 4: ^{13}C NMR (151 MHz) spectrum of Isomer **1.**



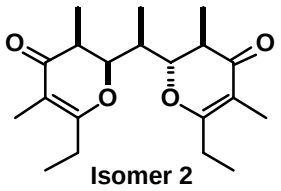
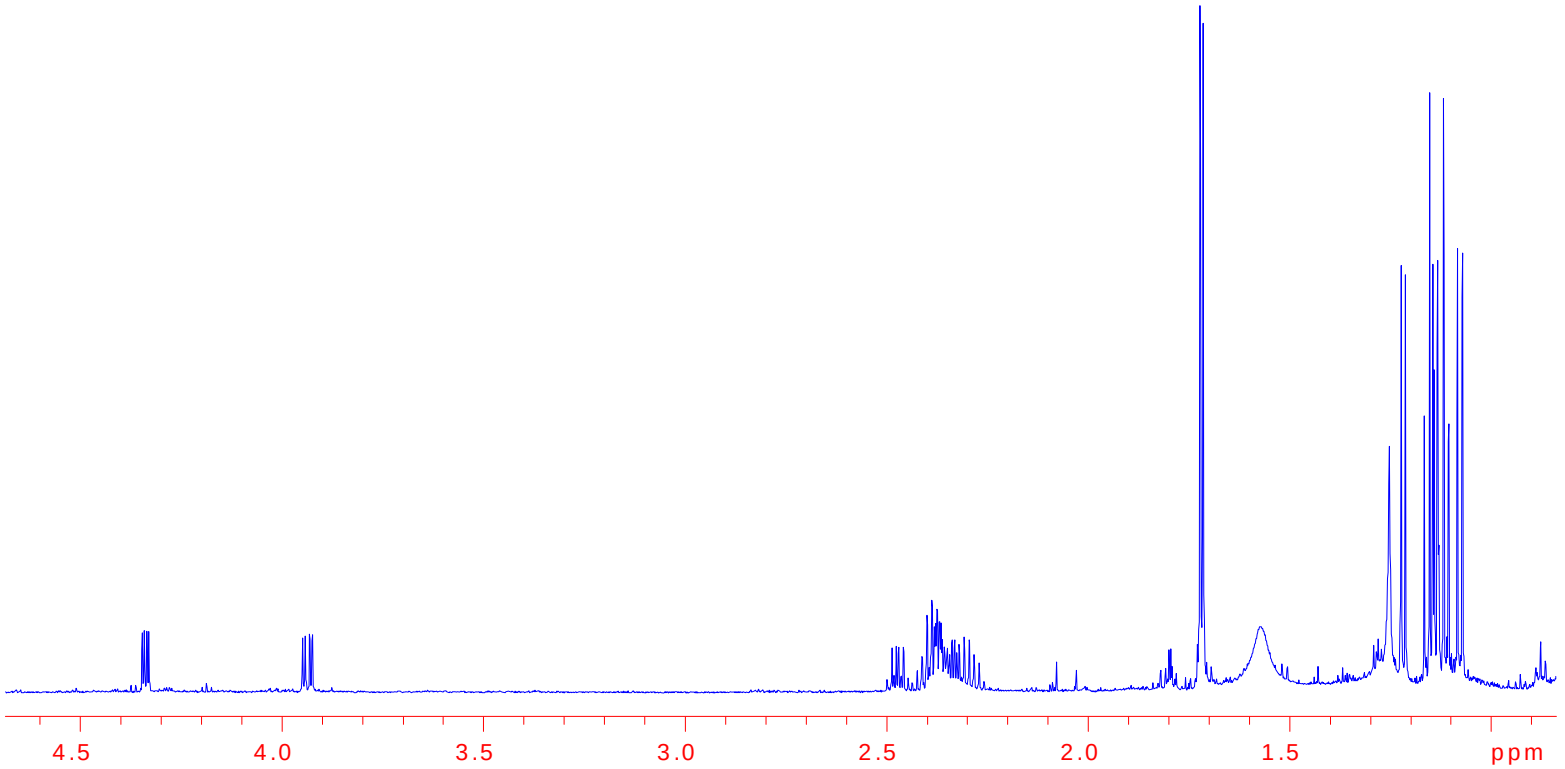


Figure 5: ^{1}H NMR (600 MHz) spectrum of Isomer **2.**



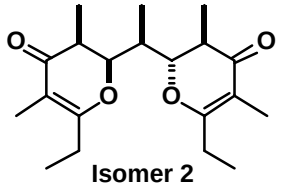
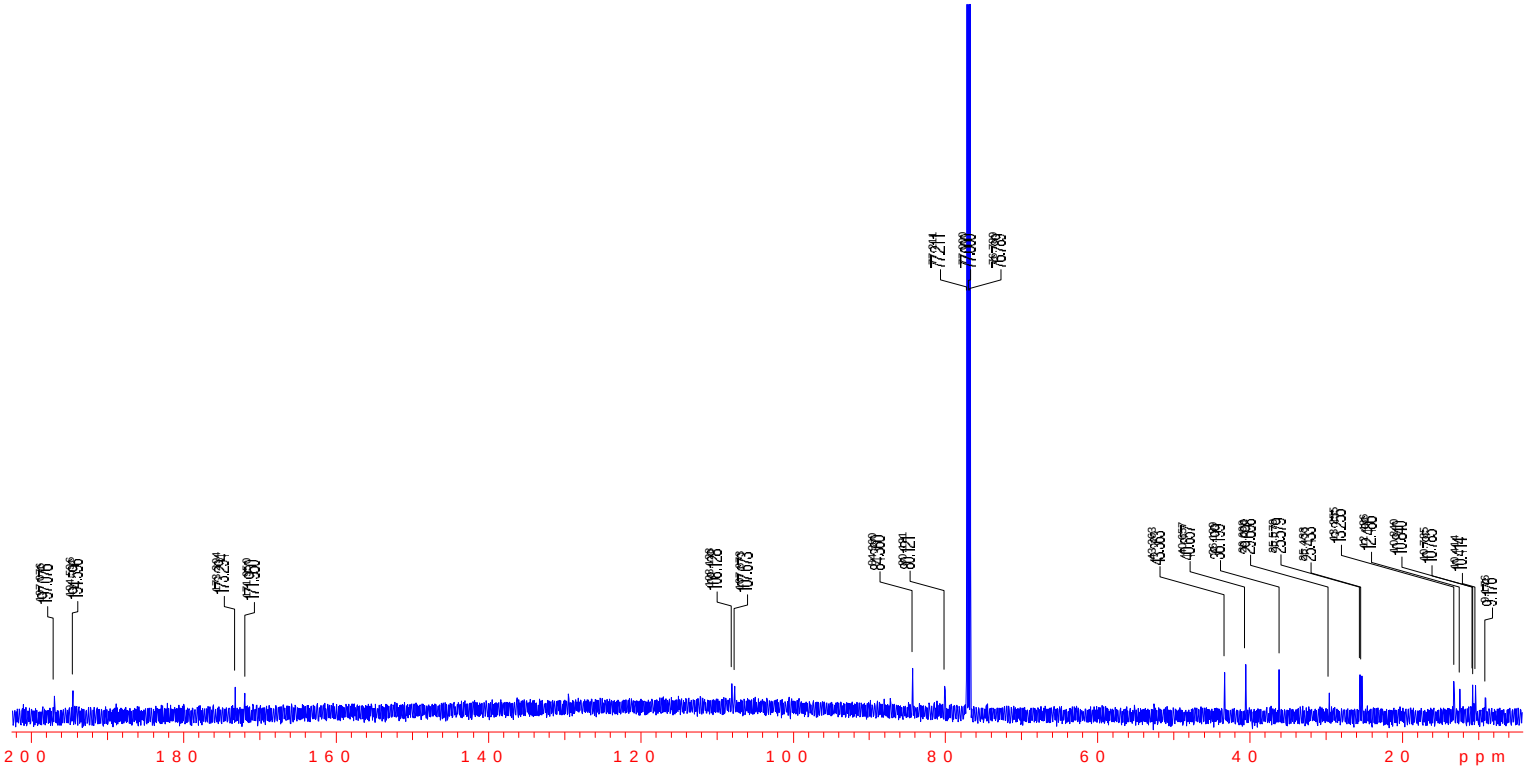


Figure 6: ^{13}C NMR (151 MHz) spectrum of Isomer **2.**



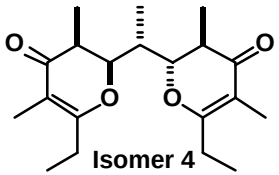
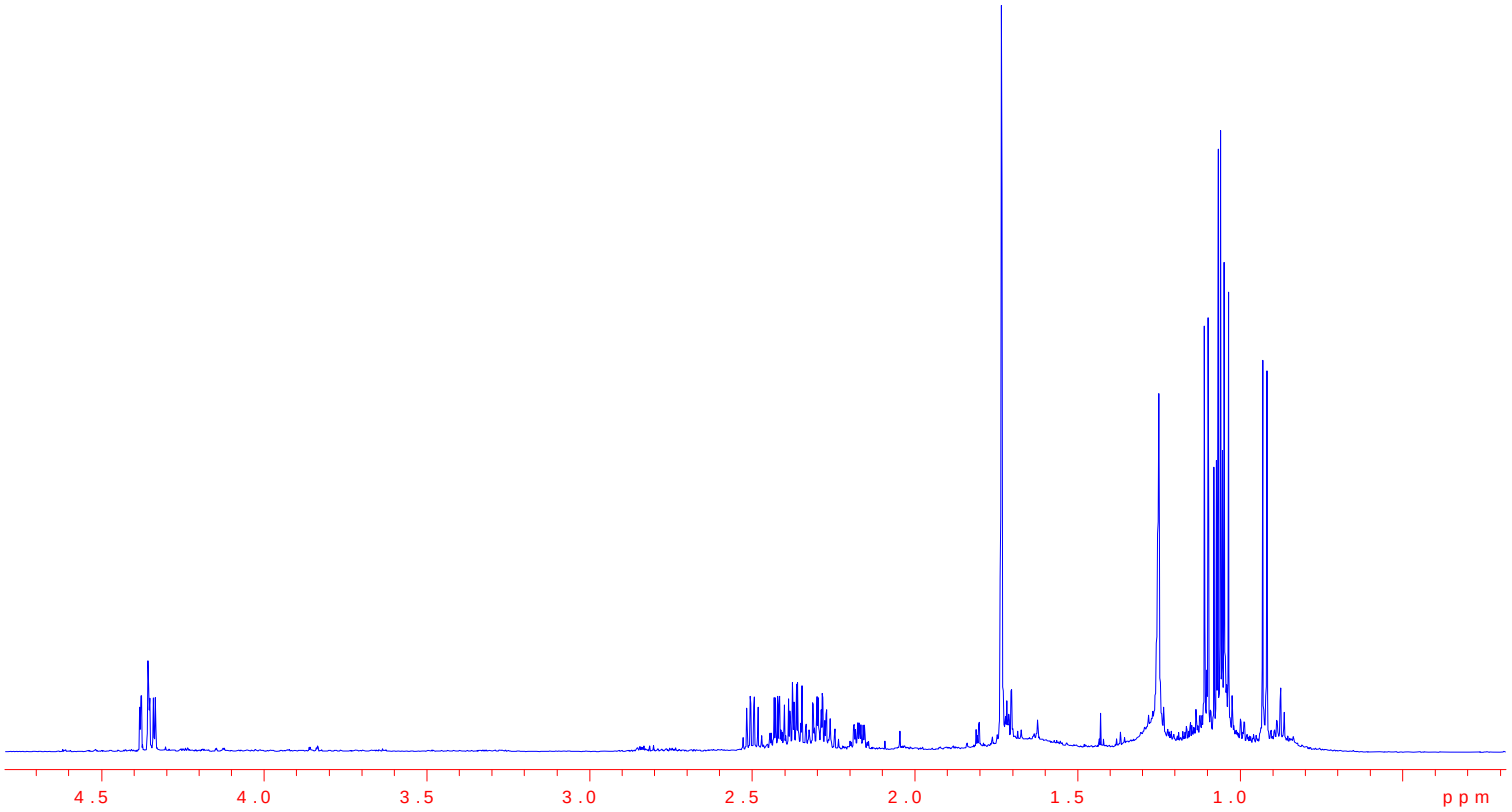


Figure 7: ^{1}H NMR (600 MHz) spectrum of Isomer **4.**



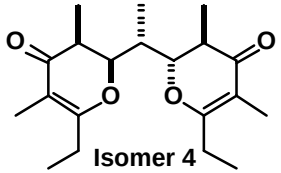


Figure 8: ^{13}C NMR (151 MHz) spectrum of Isomer **4.**