Supporting Information to

Synthesis of labile all-*trans*-7,8,7',8'-bis-acetylenic carotenoids by bi-directional Horner-Wadsworth-Emmons condensation

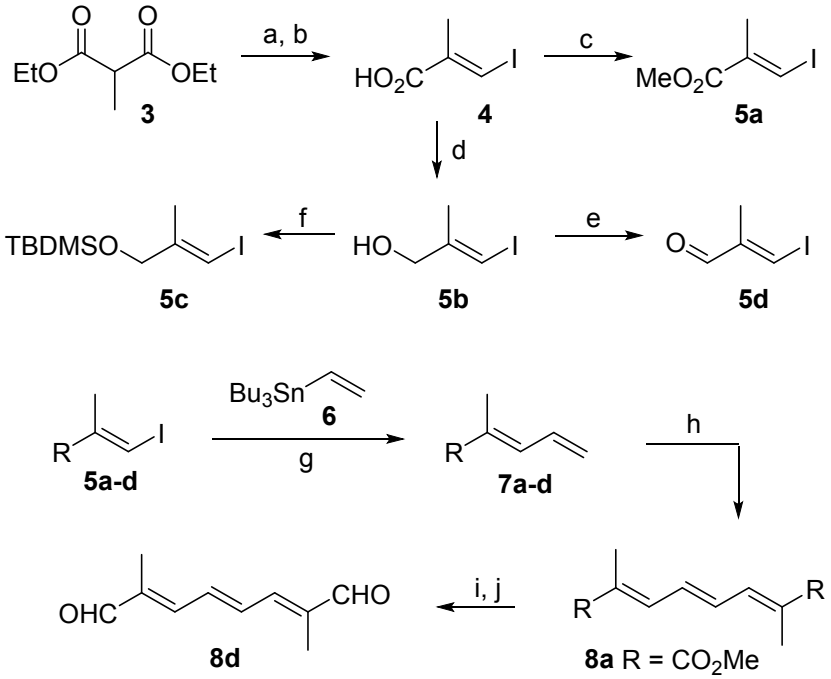
Belén Vaz,*[a] Noelia Fontán,[a] Marta Castiñeira,[a] Rosana Álvarez,*[a] and Ángel R. de Lera*[a]

Experimental section

General: Solvents were dried according to published methods and distilled before use except THF, CH_2Cl_2, CH_3CN, MeOH, Et_2O and DMF which were dried using a Puresolv™ solvent purification system. All other reagents were commercial compounds of the highest purity available. All reactions were carried out under an argon atmosphere and those not involving aqueous reagents were carried out in oven-dried glassware. All solvents and anhydrous solutions were transferred through syringes and cannulae, previously dried in the oven for at least 12 h and kept in a desiccator with KOH. Et_3N, acetone, *i*Pr_2NH, *N*,*N*-diisopropylethylamine (DIPEA), and pyridine were dried by distillation from CaH_2. Distillations were carried out in a Büchi GKR-50 Kügelrohr and in that case the boiling points indicate the external temperature. For fractional distillations a microstill was used with an internal thermometer in the distillation head. The *n*-BuLi concentration was determined by titration in triplicate with diphenylacetic acid or *N*-pivaloyl-*o*-toluidine in THF at 0 °C. For reactions at low temperature, ice/water or CO_2/acetone systems were used. For different temperatures, a HaaKe EK90 Immersion Cooler (-90 to -15 °C) was used. Analytical TLC was performed on aluminum plates with silica gel Merk Kiesegel $60F_{254}$ or in glass plates with silica gel 60 RP-18 F_{254}s or silica gel 60 CN F_{254}s and visualized by UV irradiation (254 nm) or 365 nm or by staining with a solution of phosphomolybdic acid, $KMnO_4$, DNP (2,4-dinitrophenylhydrazine) or anisaldehyde. Flash column chromatography was carried out using MercK Kieselgel 60 (230-400 mesh) or Silicycle SilicaFlash®P60 (230-400 mesh), Merck Preparative C_{18} (125 Å, 55-105 μm) or Redisep Rf CN (100 Å, 400-632 mesh) under pressure. Alternatively, an AnaLogix Intelliflash 310 HPFC Flash collector system was used. IR spectra were obtained with a JASCO FTIR 4200 spectrophotometer, from a thin film deposited onto NaCl glass. Specific rotations were measured on a JASCO P-1020 polarimeter with a Na lamp. HPLC (High Performance Liquid Chromatography) was performed using a Waters instrument by using a dual wave length detector and a 3.5x100 mm glass cell. UV-spectra were developed in a Cary C BIO spectrometer using methanol as solvent. HRMS (ESI^+) were measured with an Apex III FT ICR mass spectrometer (Bruker Daltonics). ^{1}H-NMR spectra and ^{13}C-NMR spectra were recorded in $CDCl_3$, C_6D_6, CD_3OD, and $(CD_3)_2CO$ at ambient temperature on a Bruker AMX-400 spectrometer operating at 400.16 MHz and 100.62 MHz with residual protic solvent as the internal reference ($CDCl_3$, δ = 7.26 ppm; C_6D_6, δ = 7.16 ppm; $(CD_3)_2CO$, δ = 2.05 ppm and $(CD)_3OD$, δ = 3.31 ppm) for the former and $CDCl_3$ (δ_C = 77.2 ppm), C_6D_6 (δ_C = 128.0 ppm), $(CD_3)_2CO$ (δ_C = 29.8 ppm) and

CD_3OD (δ_C = 49.0 ppm) as the internal reference for the last. Chemical shifts (δ) are given in parts per million (ppm) and coupling constants (*J*) are given in Hertz (Hz). The proton spectra are reported as follows: δ (multiplicity, coupling constant *J*, number of protons). Multiplicity in the ^{13}C-NMR spectral data refers to the attached hydrogens. A DEPT-135 pulse sequence was used to aid in the assignment of signals in the ^{13}C-NMR spectra.

Experimental procedures



Scheme 1. Reagents and conditions: a. CHI_3, NaH, THF, reflux, 20 h. b. KOH, EtOH/H_2O, reflux, 18 h, 56% combined yield. c. $TMSCHN_2$, MeOH, benzene, 25 ºC, 5 min, 89%. d. $LiAlH_4$, THF, 25 ºC, 4.5 h, 98%. e. MnO_2, CH_2Cl_2, 25 ºC, 1 h, 81%. f. TBDMSCl, imidazole, DMF, 25 ºC, 1 h, 77%. g. $Pd_2(dba)_3$, $AsPh_3$, NMP, 25 ºC, 2h, 81% **7a**, 97% **7b**, 76% **7c**, 50% **7d**. h. Hoveyda-Grubbs (15 mol%), CH_2Cl_2, 25 ºC, 8.5 h, 66%. i. DIBAL-H, THF, from -78 to -20 °C, 1 h. j. MnO_2, Na_2CO_3, acetone, 14 h, 97% (two steps).

(*E*)-3-Iodo-2-methylacrylic acid 4. In a three-necked flask equipped with a condenser and a dropping funnel, was introduced sodium hydride (60% in mineral oil; 5.0 g, 125.72 mmol) and ahydrous THF (110 mL). To the resulting suspension, diethyl methylmalonate neat (19.9 g, 114.29 mmol) was slowly added during 1 h while vigorous stirring and the resulting mixture was refluxed for further 2 h. Iodoform (45.0 g, 114.29 mmol) in THF (50 mL) was then added and the mixture refluxed overnight under argon. After being cooled to 0 ºC (ice-water bath), 10% aqueous HCl was added and the mixture stirred for 10 min. Et_2O was added and the aqueous layer extracted with Et_2O (2x). The combined organic layers were washed with saturated aqueous solution of $Na_2S_2O_3$ (3x), dried (Na_2SO_4) and concentrated. The residue was used in the next step without further purification.

A solution of the residue thus obtained and KOH (19.6 g, 349.65 mmol) in EtOH/H_2O (3:1, 160 mL) was refluxed for 18 h. After being cooled to room temperature, the EtOH

was removed under reduced pressure and the residue was extracted with hexane (300 mL, 1x). The hexane organic phase was washed with aqueous solution of $Na_2S_2O_3$ and the combined aqueous phases were acidified to pH 3 by the addition of 10% HCl, extracted with CH_2Cl_2 (4x). The combined organic layers were dried (Na_2SO_4) and concentrated to a white solid identified as (*E*)-3-iodo-2-methylacrylic acid **4** (13.6 g, 56% combined yield). **^{1}H NMR** (400.13 MHz, $CDCl_3$): δ 8.02 (q, *J* = 1.2 Hz, 1H, H3), 2.06 (d, *J* = 1.2 Hz, 3H, CH_3) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ 169.3 (s), 139.1 (s), 102.2 (d), 19.9 (c) ppm.

Methyl (*E*)-3-iodo-2-methylacrylate 5a. To a solution of (*E*)-3-iodo-2-methylacrylic acid **4** (1.00 g, 4.72 mmol) in benzene (26.2 mL) and methanol (7.6 mL) was added dropwise $TMSCHN_2$ (3.07 mL, 2M in hexane, 6.14 mmol) and the mixture was stirred for 5 minutes. The solvent was removed at reduced pressure to afford 0.952 g (89%) of a pale yellow oil identified as methyl (*E*)-3-iodo-2-methylacrylate **5a**. **^{1}H NMR** (400.13 MHz, $CDCl_3$): δ 7.79 (q, *J* = 1.3 Hz, 1H, H3), 3.75 (s, 3H, OCH_3), 2.05 (d, *J* = 1.3 Hz, 3H, CH_3) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ 164.4 (s), 139.6 (s), 98.9 (s), 52.5 (q), 20.4 (q) ppm.

(*E*)-3-Iodo-2-methylprop-2-en-1-ol 5b. To a cooled (0 ºC) suspension of $LiAlH_4$ (2.47 g, 64.17 mmol) in dry THF (60 mL), a solution of (*E*)-3-iodo-2-methylacrylic acid **4** (13.60 g, 64.17 mmol) in THF (40 mL) was slowly added via cannula while stirring. Then the mixture was warmed up to 25 ºC and stirred for further 4.5 h. Then, the reaction mixture was recooled to 0 ºC and the excess of hydride was quenched by careful addition of saturated aqueous NH_4Cl first followed by aqueous citric acid (1:1). The mixture was warmed up to 25 ºC and saturated with solid NaCl. After extraction with Et_2O (3x), the combined organic extracts were dried (Na_2SO_4) and the solvent removed under vacuum. Flash chromatography of the residue (silica gel, gradient from hexane to 70:30 hexane/EtOAc) afforded the alcohol **5b** (12.50 g, 98%) as a colorless oil. **^{1}H NMR** (400.13 MHz, $CDCl_3$): δ 6.28 (dd, *J* = 2.3, 1.2 Hz, 1H, H3), 4.13 (s, 2H, CH_2), 1.84 (s, 3H, CH_3) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ 147.3 (s), 77.5 (d), 67.3 (t), 21.5 (q) ppm.

(*E*)-*tert*-Butyl[(3-iodo-2-methylallyl)oxy]dimethylsilane 5c. To a solution of (*E*)-3-iodo-2-methylprop-2-en-1-ol **5b** (0.139 g, 0.700 mmol) and imidazole (0.114 g, 1.680 mmol) in anhydrous DMF (0.7 mL), was added TBDMSCl (0.158 g, 1.050 mmol) and the mixture was stirred at 25 ºC for 1 h under argon. Then, water was added and the solution was extracted with Et_2O (3x). The combined organic extracts were washed with water (7x), dried (Na_2SO_4) and concentrated. Flash chromatography (silica gel, hexane) of the residue gave the silane **5c** (0.219 g, 77%) as a colorless liquid. **^{1}H NMR** (400.13 MHz, $CDCl_3$): δ 6.20 (s, 1H, H3), 4.10 (s, 2H, CH_2), 1.78 (s, 3H, CH_3), 0.90 (s, 9H, 3xCH_3), 0.07 (s, 6H, 2xCH_3) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ 146.94 (s), 76.06 (d), 67.23 (t), 25.99 (q, 3x), 21.28 (q), 18.48 (s), -5.29 (q, 2x) ppm.

(*E*)-3-Iodo-2-methylacrylaldehyde 5d. Activated MnO_2 (2.01 g, 23.09 mmol) was added in one portion to a cooled (0 ºC) solution of the alcohol **5a** (0.254 g, 1.28 mmol) in dry CH_2Cl_2 (24.4 mL). After stirring the resulting mixture under argon for 1 h at 25 ºC, the solid was removed by filtration through a pad of Celite® and washed with CH_2Cl_2. The resulting yellow solution of the crude aldehyde was dried over Na_2SO_4 and concentrated to provide a pale yellow oil identified as (*E*)-3-iodo-2-methylacrylaldehyde **5d**. (0.203 g, 81%). **^{1}H NMR** (400.13 MHz, $CDCl_3$): δ 9.52 (s, 1H, CHO), 7.81 (q, *J* = 1.2 Hz, 1H, H3), 1.91 (d, *J* = 1.2 Hz, 3H, CH_3) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ 189.6 (d), 150.9 (s), 109.7 (d), 16.6 (q) ppm.

Methyl (*E*)-2-Methylpenta-2,4-dienoate 7a. General procedure for the Stille reaction. A solution of methyl (*E*)-3-iodo-2-methylacrylate **5a** (0.304 g, 1.345 mmol) in NMP (2.4 mL) was added to a mixture of Pd_2dba_3 (0.037 g, 0.040 mmol) and $AsPh_3$ (0.082 g, 0.269 mmol) in NMP (4.1 mL). After stirring for 10 min at 25 ºC, a solution of tributylvinylstannane **6** (0.472 mL, 0.512 g, 1.614 mmol) in NMP (2.4 mL) was added and the mixture was stirred for 1.5 h. A saturated aqueous solution of KF was added and the mixture was stirred for 5 min and then extracted with Et_2O (3x). The combined organic layers were washed with H_2O (3x), dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by column chromatography (silica gel, 99:1 hexane/Et_2O) to afford 0.137 g (81%) of a colorless oil identified as methyl (*E*)-2-methylpenta-2,4-dienoate **7a**. **^{1}H NMR** (400.13 MHz, C_6D_6): δ 7.32 (d, *J* = 11.4 Hz, 1H, H3), 6.36 (ddd, *J* = 16.8, 11.4, 10.1 Hz, 1H, H4), 5.19 (d, *J* = 16.8 Hz, 1H, H5), 5.07 (d, *J* = 10.1 Hz, 1H, H5), 3.41 (s, 3H, OCH_3), 1.83 (s, 3H, CH_3) ppm. **^{13}C NMR** (100.62 MHz, C_6D_6): δ 168.2 (s), 138.5 (d), 132.5 (d), 123.8 (t), 51.4 (q), 12.8 (q) ppm. **IR** (NaCl): ν 3089 (w, C-H), 2995 (w, C-H), 2952 (w, C-H), 1711 (s, C=O), 1436 (m), 1263 (s), 1250 (s), 1103 (m) cm^{-1}. **UV** (MeOH): λ_{max} 253 nm.

(*E*)-2-Methylpenta-2,4-dien-1-ol 7b. (Yield: 97%). Colorless oil. **^{1}H NMR** (400.13 MHz, C_6D_6): δ 6.54 (ddd, *J* = 16.8, 11.0, 10.2 Hz, 1H, H4), 6.05 (d, *J* = 11.0 Hz, 1H, H3), 5.16 (d, *J* = 16.8, 1H, H5-*E*), 5.10 (d, *J* = 10.2 Hz, 1H, H5-*Z*), 3.72 (s, 2H, CH_2), 1.52 (s, 3H, CH_3) ppm. **^{13}C NMR** (100.62 MHz, C_6D_6): δ 138.4 (s), 133.2 (d), 125.3 (d), 116.5 (t), 67.9 (t), 13.9 (q) ppm.

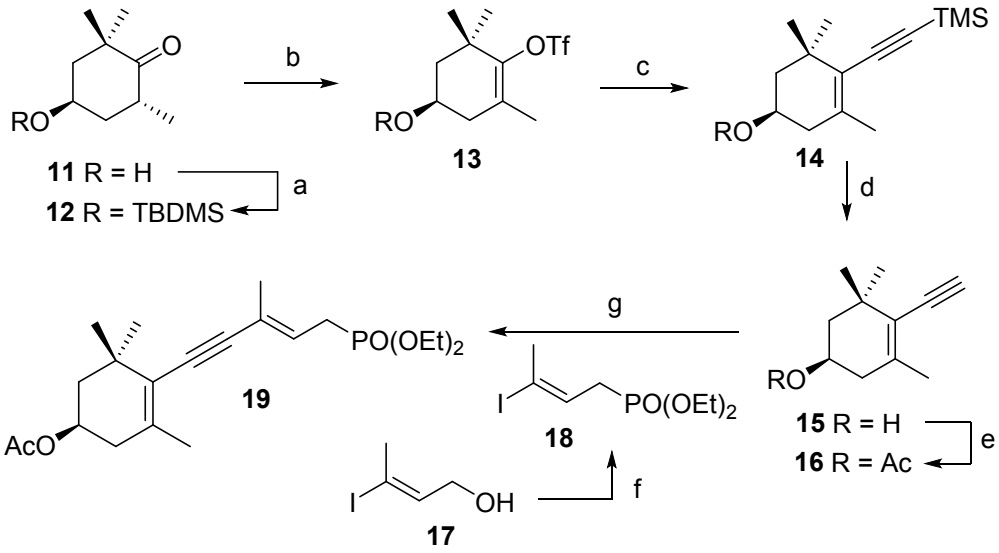
(*E*)-*tert*-Butyldimethyl[(2-methylpenta-2,4-dien-1-yl)oxy]silane 7c. (Yield: 76%). Colorless oil. **^{1}H NMR** (400.13 MHz, C_6D_6): δ 6.60 (ddd, *J* = 16.8, 11.0, 10.2 Hz, 1H, H4), 6.26 (d, *J* = 11.0 Hz, 1H, H3), 5.20 (d, *J* = 16.8 Hz, 1H, H5-*E*), 5.04 (d, *J* = 10.2 Hz, 1H, H5-*Z*), 3.96 (s, 2H, CH_2), 1.58 (s, 3H, CH_3), 0.98 (s, 9H, 3xCH_3), 0.05 (s, 6H, 2xCH_3) ppm. **^{13}C NMR** (101 MHz, C_6D_6): δ 137.9 (s), 133.2 (d), 124.9 (d), 116.4 (t), 68.2 (t), 26.1 (c, 3x), 18.6 (s), 13.9 (q), -5.2 (q, 2x) ppm.

(*E*)-2-methylpenta-2,4-dienal 7d. (Yield: 50 %). Colorless oil. **^{1}H NMR** (400.13 MHz, C_6D_6): δ 9.25 (s, 1H, CHO), 6.30 (ddd, *J* = 16.6, 11.2, 10.0 Hz, 1H, H4), 6.17 (d, *J* = 11.2 Hz, 1H, H3), 5.13 (d, *J* = 16.6 Hz, 1H, H5-*E*), 5.05 (d, *J* = 10.0 Hz, 1H, H5-*Z*), 1.63 (s, 3H) ppm. **^{13}C NMR** (101 MHz, C_6D_6): δ 193.9 (d), 147.1 (d), 138.7 (s), 132.2 (d), 124.9 (t), 9.4 (q) ppm.

Dimethyl (2*E*,4*E*,6*E*)-2,7-Dimethylocta-2,4,6-trienedioate 8a. General procedure for the metathesis reaction. A degassed solution of methyl (*E*)-2-methylpenta-2,4-dienoate **5a** (0.068 g, 0.054 mmol) in CH_2Cl_2 (10 mL) was prepared by three sequential freeze-thaw cycles under argon atmosphere, and Hoveyda-Grubbs catalyst (0.051 g, 0.081 mmol) was added. After stirring at 25 ºC for 8.5 h the solvent was evaporated and the residue was purified by column chromatography (silica gel, from 95:5 hexane/EtOAc to 90:10 hexane/EtOAc) to afford 0.040 g (66 %) of a white solid identified as dimethyl (2*E*,4*E*,6*E*)-2,7-dimethylocta-2,4,6-trienedioate **8a**. The spectroscopic data matched those previously reported.[1] **^{1}H NMR** (400.13 MHz, $CDCl_3$): δ 7.28 (ddd, *J* = 7.8, 2.9, 1.3 Hz, 2H, H3 + H6), 6.79 (dd, *J* = 7.8, 3.0 Hz, 2H, H4 + H5), 3.77 (s, 6H, 2x OCH_3), 2.00 (d, *J* = 1.2 Hz, 6H, 2x CH_3) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ 168.6 (s, 2x), 137.5 (d, 2x), 133.7 (d, 2x), 130.1 (s, 2x), 52.1 (q, 2x), 13.1 (q, 2x) ppm.

(2*E*,4*E*,6*E*)-2,7-Dimethylocta-2,4,6-trienedial 8d. A solution of diethyl (2*E*,4*E*,6*E*)-2,7-dimethylocta-2,4,6-trienedioate **8a** (0.59 g, 2.34 mmol) in THF (6 mL) was cooled to -78 °C and DIBAL-H (10.3 mL, 1M in hexane, 10.30 mmol) was added dropwise. The reaction mixture was stirred for 1 h and allowed to warm up to -20 °C. Then a mixture of SiO_2 (18.1 g) and H_2O (5.4 mL) was added and the reaction mixture was stirred for 1 h at 0 °C. K_2CO_3 and $MgSO_4$ were added and the mixture was filtered through a pad of Celite® washing with CH_2Cl_2 and a mixture of CH_2Cl_2-MeOH (80:20) to elute the product. The product obtained was used without further purification.

To a cooled (0 °C) solution of the reaction crude in acetone (2 mL), was added Na_2CO_3 (1.21 g, 11.4 mmol) and MnO_2 (0.99 g, 11.4 mmol), and the reaction mixture was stirred overnight at 25 °C. The reaction mixture was filtered through a pad of Celite® and washed with CH_2Cl_2 and a mixture of CH_2Cl_2-MeOH (80:20). The residue was purified by column chromatography (silica gel, from 90:10 to 80:20 hexane/EtOAc) to afford 0.1 g (97%) of a yellow solid identified as (2*E*,4*E*,6*E*)-2,7-dimethylocta-2,4,6-trienedial **8d**. The spectroscopic data matched those previously reported.[2] **^{1}H NMR** (400.13 MHz, $CDCl_3$): δ 9.54 (s, 2H, CHO), 7.08 (dd, *J* = 8.1, 3.1 Hz, 2H, H_3 + H_6), 7.05 - 6.95 (m, 2H, H_4 + H_5), 1.95 (s, 6H, 2xCH_3) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ 194.6 (d, 2x), 146.2 (d, 2x), 141.2 (s, 2x), 134.5 (d, 2x), 10.1 (q, 2x) ppm.



Scheme 2. Reagents and conditions: a TBDMSCl, imidazole, DMF, 25 ºC, 6 h, 98%. b. LDA, Tf_2NPh, THF, -78 to 0 ºC, 14 h, 87%. c. TMS-acetylene, K_2CO_3, $Pd(PPh_3)_4$, DMF, 60 ºC, 95%. d. *n*-Bu_4NF, THF, 25 ºC, 2.5 h, 99 %. e. Ac_2O, pyridine, 25 ºC, 14 h, 77%. f. ZnI_2, $P(OEt)_3$, THF, 85 ºC, 16 h, 84 %. g. $Pd(PPh_3)_4$, CuI, Et_3N, THF, 25 ºC, 4 h, 73%.

Alkyne **16** was prepared from available (-)-actinol **11** folowing previously described protocols:[3]

(4*R*,6*R*)-4-*tert*-Butyldimethylsilyloxy]-2,2,6-trimethylcyclohexanohexanone 12. To a cool solution (0 ºC) of (-)-actinol **11** (8.0 g, 51.21 mmol) and imidazole (8.7 g, 128.02 mmol) in anhydrous DMF (170 mL), was added via cannula a solution of TBDMSCl (11.6 g, 76.81 mmol) in DMF (70 mL). The resulting mixture was warmed up to 25 ºC and stirred for 2.5 h under argon. Then, water was added and the solution was extracted with hexane (4x). The combined organic extracts were washed with water (2x), dried (Na_2SO_4) and concentrated. Flash chromatography (silica gel, 95:5 hexane/EtOAc) of the residue gave the silane **12** (13.344 g, 96%) as a colorless oil.

(*R*)-4-(*tert*-butyldimethylsilyloxy)-2,6,6-trimethylcyclohex-1-en-1-yl trifluoromethanesulfonate 13. To a cool solution (-78 ºC) of diisopropylamine (1.55 mL, 11.10 mmol) in anhydrous THF (24 mL) was added *n*BuLi (7.35 mL, 1.51 M, 11.10 mmol) and the mixture was stirred for 30 min at the same temperature. To the LDA thus generated, a solution of (4*R*,6*R*)-4-*tert*-butyldimethylsilyloxy]-2,2,6-trimethylcyclohexanohexanone **12** (2.0 g, 7.40 mmol) in THF (24 mL) was added via cannula. Then, $(Tf)_2NPh$ (2.38 g, 7.92 mmol) was added and the resulting mixture was warmed up to 0 ºC and stirred for 14 h under argon. Then, brine was added and the solution was extracted with Et_2O (3x). The combined organic extracts were washed with 10% aqueous citric acid (3x) and a saturated aqueous solution of $NaHCO_3$ (3x). After that, the organic extract was dried (Na_2SO_4) and concentrated. Flash chromatography

(silica gel, gradient from hexane to 98:2 hexane/EtOAc) of the residue gave the triflate **13** (2.6 g, 87%) as a colorless oil.

***tert*-Butyldimethylsilyl (*R*)-3,5,5-Trimethyl-4-(trimethylsilylethynyl)cyclohex-3-en-1-yl Ether 14**. To a degassed solution (3 frezze-thaw cycles under argon atmosphere) of trifluoromethanesulfonate **13** (0.63 g, 1.55 mmol) in anhydrous DMF (19 mL) was added $Pd(PPh_3)_4$ (0.18 g, 0.16 mmol) followed by K_2CO_3 (0.64 g, 4.66 mmol) and TMS-acetylene (0.65 mL, 4.66 mmol). The resulting mixture was stirred for 6 h at 60 ºC. After this time, the reaction crude was cooled down to room temperature and diluted with Et_2O. After addition of water, the layers were separated and the aqueous solution was extracted with Et_2O (3x). The combined organic extracts were washed with water (3x), dried (Na_2SO_4) and concentrated. Flash chromatography (silica gel, 98:2 hexane/EtOAc) of the residue provided the expected *tert*-butyldimethylsilyl (*R*)-3,5,5-trimethyl-4-(trimethylsilylethynyl)cyclohex-3-en-1-yl ether **14** (0.52 g, 95%) as a colorless oil.

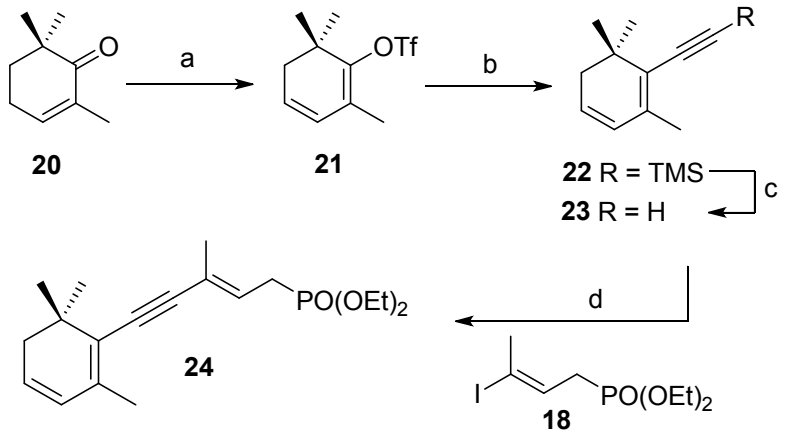
(*R*)-4-Ethynyl-3,5,5-trimethylcyclohex-3-enol 15. To a solution of silane **14** (0.094 g, 0.27 mmol) in anhydrous THF (2 mL), was added (nBu)$_4$NF (0.81 mL, 1.0 M in THF, 0.81 mmol) and the reaction mixture was stirred for 2 h at 25 ºC. Then, the mixture was poured over a saturated solution of $NaHCO_3$ and the solution was extracted with Et_2O (3x). The combined organic extracts were dried (Na_2SO_4) and concentrated. Flash chromatography (silica gel, 80:20 hexane/EtOAc) of the residue gave the alkyne **15** (0.040 g, 99%) as a white solid.

(*R*)-4-Ethynyl-3,5,5-trimethylcyclohex-3-en-1-yl Acetate 16. To a solution of (*R*)-4-ethynyl-3,5,5-trimethylcyclohex-3-enol **15** (0.150 g, 0.91 mmol) in pyridine (3 mL) was added Ac_2O (0.171 mL, 1.83 mmol) and the reaction mixture was stirred for 3 h at 25 ºC. Then, the mixture was diluted with Et_2O and washed with a saturated aqueous solution of $CuSO_4$ (2x). The organic extract was dried (Na_2SO_4) and concentrated. Flash chromatography (silica gel, 95:5 hexane/EtOAc) of the residue afforded 0.146 g (77%) of the expected (*R*)-4-ethynyl-3,5,5-trimethylcyclohex-3-en-1-yl acetate **16** as a colorless oil.

(*E*)-Diethyl (3-iodobut-2-en-1-yl)phosphonate 18. To a solution of ZnI_2 (1.03 g, 3.23 mmol) in THF (1.6 mL) was added triethyl phosphite (1 mL, 6.45 mmol), and a solution of (*E*)-3-iodobut-2-en-1-ol **17** (0.43 g, 2.15 mmol) in THF (1.8 mL) via cannula. After stirring overnight at 85 °C, the solvent was evaporated and the reaction mixture was washed with a 2M aqueous solution of NaOH (3x). The aqueous layer was extracted with Et_2O (3x) and the combined organic layers were dried (Na_2SO_4) and the solvent removed. Purification by column chromatography (C-18 silica gel, 55:45 CH_3CN/H_2O) afforded 0.58 g (84%) of a colorless oil identified as diethyl (*E*)-(3-iodobut-2-en-1-yl)phosphonate **18**. **^{1}H NMR** (400.13 MHz, $CDCl_3$): δ 6.11 (dtq, J = 6.5, 1.4 Hz, $^3J_{H\text{-}P}$ = 8.0, 1H, H2), 4.14 – 3.96 (m, 4H, 2x $CO_2\underline{CH_2}CH_3$), 2.49 (ddd, J = 8.0, 1.0 Hz, $^2J_{H\text{-}P}$ = 21.9 Hz, 2H, 2H1), 2.34 (d, $^5J_{H\text{-}P}$ = 4.4 Hz, 3H, CH_3), 1.26 (t, J = 7.1 Hz, 6H, 2x $CO_2CH_2\underline{CH_3}$) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ 129.1, (d, $^2J_{P\text{-}C}$ = 10.8 Hz), 97.6 (s,

$^{3}J_{P\text{-}C}$ = 17.7 Hz), 62.1 (t, $^{2}J_{P\text{-}C}$ = 6.8 Hz, 2x), 28.9 (t, $^{1}J_{P\text{-}C}$ = 141.0 Hz), 27.7 (q, $^{4}J_{P\text{-}C}$ = 2.5 Hz), 16.5 (q, $^{3}J_{P\text{-}C}$ = 6.0 Hz, 2x) ppm. **HRMS** (ESI^{+}): Calcd. for $C_8H_{17}IO_3P$ ([M+H]$^{+}$), 318.9954; found,318.9958. **IR** (NaCl): ν 2980 (m, C-H), 2919 (w, C-H), 1390 (w), 1253 (s) cm^{-1}.

(*R*,*E*)-4-[5´-(Diethoxyphosphoryl)-3´-methylpent-3´-en-1-ynyl]-3,5,5-trimethylcyclohex-3-enyl Acetate 19. To a degassed solution of $Pd(PPh_3)_4$ (3.9 mg, 0.003 mmol) in THF (0.5 mL) was added CuI (1.9 mg, 0.010 mmol). To this reaction mixture were added a degassed solution of diethyl (*E*)-3-iodobut-2-enylphosphonate **18** (0.032 g, 0.112 mmol) in THF (1.0 mL), freshly distilled Et_3N (0.039 mL, 0.280 mmol) and a solution of (*R*)-4-ethynyl-3,5,5- trimethylcyclohex-3-enyl acetate **16** (0.030 g, 0.145 mmol) in THF (1.0 mL). The mixture was stirred for 4 h at 25 ºC, then the mixture was filtered through a pad of Celite® and the solvent was evaporated. The residue was purified by column chromatography (silica gel-NH_2, from 90:10 hexane/CH_2Cl_2 to CH_2Cl_2) to afford 0.03 g (73%) of an oil identified as (*R*,*E*)-4-[5-(diethoxyphosphoryl)-3-methylpent-3-en-1-ynyl]-3,5,5-trimethylcyclohex-3-enyl acetate **19**. **^{1}H NMR** (400.13 MHz, C_6D_6): δ 6.03 (q, *J* = 8.2 Hz, $^{3}J_{H\text{-}P}$ = 1.5 Hz, 1H, H4´), 5.19-5.11 (m, 1H, H1), 3.95-3.84 (m, 4H, 2 x OCH_2CH_3), 2.47 (d, *J* = 8.2 Hz, $^{2}J_{H\text{-}P}$ = 23.0 Hz, 2H, H2´), 2.29 (dd, *J* = 17.6, 5.6 Hz, 1H, H2), 1.97 (dd, *J* = 17.6, 9.1 Hz, 1H, H2), 1.83-1.78 (m, 7H, H6 + 2 x CH_3), 1.71 (s, 3H, CH_3), 1.51 (t, *J* = 11.9 Hz, 1H, H6), 1.23 (s, 3H, CH_3), 1.19 (s, 3H, CH_3), 1.01 (t, *J* = 7.1 Hz, 6H, OCH_2CH_3) ppm. **^{13}C NMR** (100.62 MHz, C_6D_6): δ 169.7 (s), 136.7 (s, $^{6}J_{C\text{-}P}$ = 1.4 Hz), 125.2 (d, $^{2}J_{C\text{-}P}$ = 12.7 Hz), 124.6 (s, $^{5}J_{C\text{-}P}$ = 3.3 Hz), 122.8 (s, $^{2}J_{C\text{-}P}$ = 15.4 Hz), 96.9 (s, $^{4}J_{C\text{-}P}$ = 6.5 Hz), 86.2 (s, $^{7}J_{C\text{-}P}$ = 1.3 Hz), 67.8 (d), 61.8 (t, $^{3}J_{C\text{-}P}$ = 6.7 Hz, 2x), 42.7 (t), 37.6 (t), 36.3 (s), 30.4 (q), 28.8 (q), 27.9 (t, $^{1}J_{C\text{-}P}$ = 140.0 Hz), 22.4 (q), 21.0 (q), 17.9 (q, $^{4}J_{C\text{-}P}$ = 2.9 Hz), 16.5 (q, $^{3}J_{C\text{-}P}$ = 5.7 Hz, 2x) ppm. **MS** (EI): *m/z* (%). **HRMS** (ESI^{+}): Calcd. for $C_{21}H_{34}O_5P$ ([M+H]$^{+}$), 397.2152; found, 397.2132. **IR** (NaCl): ν 2965 (m, C-H), 2927 (m, C-H), 1736 (s, C=O), 1442 (w), 1365 (m), 1241 (s), 1027 (s) cm-1. $[\alpha]_D^{26}$ – 39.5 (*c* 0.895, MeOH).



Scheme 3. Reagents and reaction conditions: a. *i*Pr_2NH, *n*BuLi, HMPA, Tf_2NPh, THF, 3 h, -78 ºC, 66%. b. TMS-acetylene, K_2CO_3, CuI, $Pd(PPh_3)_4$, DMF, 60 °C, 5 h, 93%. c. TBAF, 25 °C, 40 min, 79%. d. $Pd(PPh_3)_4$, CuI, Et_3N, THF, 25 °C, 2.5 h, 66%.

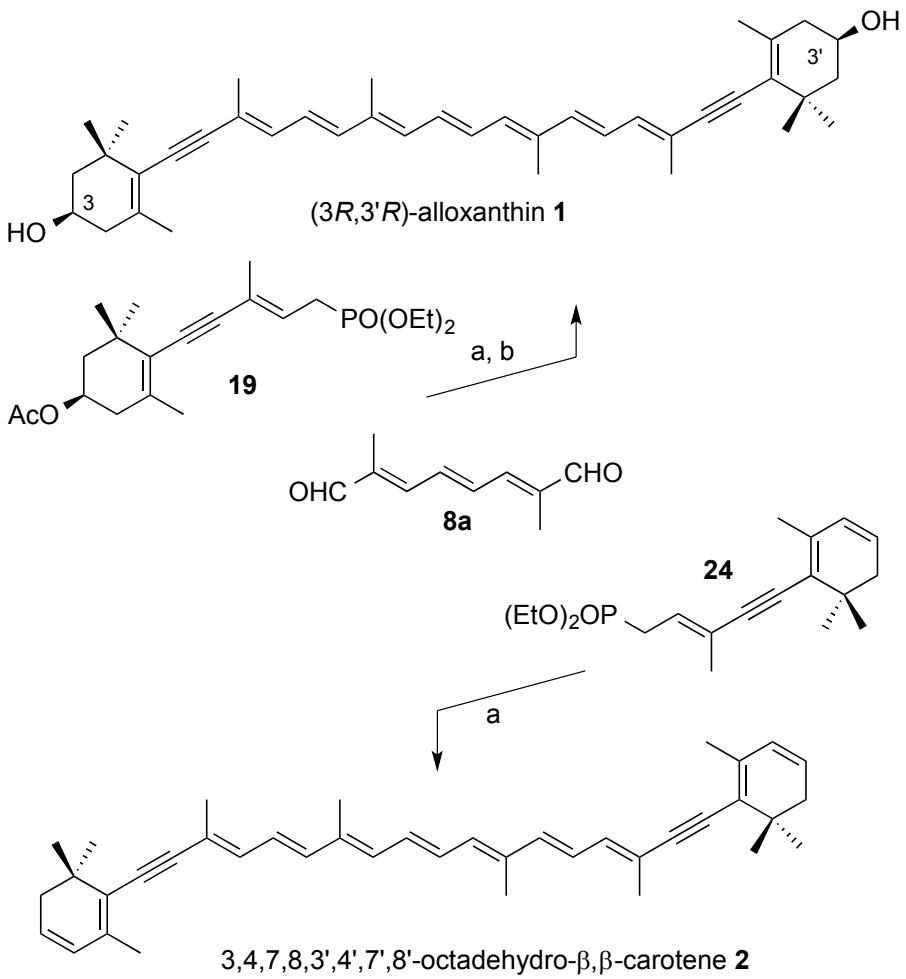
1-(Trifluoromethanesulfonyl)oxy-2,6,6-trimethylcyclohexa-1,3-diene 21. A cooled (0 °C) solution of diisopropylamine (0.92 mL, 0.72 mmol) in THF (8 mL) was treated with *n*BuLi (3.14 mL, 2.0M in hexane, 6.37 mmol) and stirred for 30 min. The mixture was cooled down to -78 °C and a solution of 2,2,6-trimethylcyclohex-2-en-1-one **20** (0.80 g, 5.79 mmol) in THF (8 mL) was added. After stirring for 1 h, HMPA (6.0 mL, 34.76 mmol) and a solution of *N*-phenyltriflimide (2.21 g, 6.20 mmol) in THF (8 mL) were added. The resulting mixture was stirred for 3 h at -78 °C and then a saturated aqueous solution of NaCl was added. The reaction mixture was extracted with Et_2O (3x) and the combined organic layers were washed with a 10% aqueous solution of citric acid (3x) and a saturated aqueous solution of $NaHCO_3$ (3x). The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by column chromatography (silica gel, from 98:2 to 95:5 hexane/EtOAc) to afford 1.6 g (66%) of a pale yellow oil identified as 1-(trifluoromethanesulfonyl)oxy-2,6,6-trimethylcyclohexa-1,3-diene **21**. The spectroscopic data matched those previously reported.[43] **^{1}H NMR** (400.13 MHz, $CDCl_3$): δ 5.8-5.7 (m, 2H, H3 + H4), 2.30 (d, *J* = 2.6 Hz, 2H, 2H5), 1.83 (s, 3H, CH_3), 1.13 (s, 6H, 2xCH_3) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ 150.5 (s), 127.2 (d), 126.1 (d), 122.9 (s), 118.8 (s, $^1J_{F\text{-}C}$ = 320.0 Hz, CF_3), 41.9 (t), 35.1 (s), 24.5 (q, 2x), 16.0 (q).

Trimethyl[(2,6,6-trimethylcyclohexa-1,3-dien-1-yl)ethynyl]silane 22. To a degassed solution of 1-[(trifluoromethanesulfonyl)oxy]-2,6,6-trimethylcyclohexa-1,3-diene **21** (0.7 g, 2.59 mmol) in DMF (31.2 mL) was added $Pd(PPh_3)_4$ (299 mg, 0.26 mmol) followed by anhydrous K_2CO_3 (1.07 g, 7.78 mmol), and trimethylsilylacetylene (1.1 mL, 7.78 mmol). After stirring for 5 h at 60 °C, Et_2O was added and the organic layer was washed with H_2O (3x). The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by column chromatography (silica gel, hexane) to afford 0.57 g (93%) of a pale yellow oil identified as trimethyl[(2,6,6-trimethylcyclohexa-1,3-dien-1-yl)ethynyl]silane **22**. **^{1}H NMR** (400.13 MHz, $CDCl_3$): δ 5.86 (dt, *J* = 9.6, 1.5 Hz, 1H, H_3), 5.80 (dt, *J* = 9.6, 4.2 Hz, 1H, H_4), 2.09 (dd, *J* = 4.2, 1.5 Hz, 2H, $2H_5$), 1.95 (s, 3H, CH_3), 1.07 (s, 6H, 2xCH_3), 0.21 (s, 9H, 3xCH_3). **^{13}C NMR** (100.62 MHz, $CDCl_3$): δ 137.6 (s), 127.7 (d), 126.8 (d), 123.6 (s), 103.8 (s), 101.7 (s), 38.2 (t), 32.4 (s), 27.0 (q, 2x), 20.7 (q), 0.2 (q, 3x). **IR (NaCl):** ν 2958 (s, C-H), 2128 (s, C≡C), 859 (s, Si-C), 842 (s, Si-C) cm^{-1}. **HRMS** (ESI^+): Calcd. for $C_{14}H_{23}Si$ ($[M+H]^+$), 219.1564; found, 219.1569.

1-Ethynyl-2,6,6-trimethylcyclohexa-1,3-diene 23. To a solution of trimethyl[(2,6,6-trimethylcyclohexa-1,3-dien-1-yl)ethynyl]silane **22** (0.53 g, 2.42 mmol) in THF (24 mL) was added TBAF (3.63 mL, 1M in hexane, 3.63 mmol). After stirring for 40 min at 25 °C the reaction mixture was poured over a saturated aqueous $NaHCO_3$ solution and

extracted with Et_2O (3x). The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated. Purification by column chromatography (silica gel, hexane) afforded 0.28 g (79%) of a yellow oil identified as 1-ethynyl-2,6,6-trimethylcyclohexa-1,3-diene **23**. **^{1}H NMR** (400.13 MHz, $CDCl_3$): δ 5.87 (dt, *J* = 9.6, 1.4 Hz, 1H, H_3), 5.83 (dt, *J* = 9.6, 4.0 Hz, 1H, H_4), 3.32 (s, 1H), 2.11 (dd, *J* = 4.0, 1.4 Hz, 2H, $2H_5$), 1.96 (s, 3H, C_2-CH_3), 1.09 (s, 6H, 2xC_6-CH_3). **^{13}C NMR** (100.62 MHz, $CDCl_3$): δ 138.1 (s), 127.6 (d), 126.9 (d), 122.6 (s), 110.0 (s), 84.1 (d), 38.1 (t), 32.4 (s), 26.9 (q, 2x), 20.5 (q). **IR (NaCl):** ν 3306 (s, C≡C-H), 2958 (s, C-H), 2920 (s, C-H), 2859 (s, C-H), 2080 (w, C≡C) cm^{-1}.

Diethyl (*E*)-[3-methyl-5-(2,6,6-trimethylcyclohexa-1,3-dien-1-yl]pent-2-en-4-yn-1-yl)phosphonate (C_{15} -alkynylphosphonate) 24. To a degassed solution of $Pd(PPh_3)_4$ (14.0 mg, 0.01 mmol) in THF (1.4 mL) was added CuI (6.8 mg, 0.036 mmol) and a solution of **18** (127.0 mg, 0.40 mmol) in THF (2.8 mL) via cannula. To the described mixture was added Et_3N (0.14 mL, 1.00 mmol) and a solution of 1-ethynyl-2,6,6-trimethylcyclohexa-1,3-diene **23** (87.6 mg, 0.60 mmol) in THF (2.8 mL). The reaction mixture was stirred for 2 h 30 min at 25 °C. Then it was filtered with AcOEt through a pad of Celite® and the solvent was evaporated. The residue was purified by column chromatography (C-18 silica gel, from 65:35 to 100:0 CH_3CN/H_2O) to afford 88.8 mg (66%) of a pale yellow oil identified as diethyl (*E*)-[3-methyl-5-(2,6,6-trimethylcyclohexa-1,3-dien-1-yl]pent-2-en-4-yn-1-yl)phosphonate **24**. **^{1}H NMR** (400.13 MHz, C_6D_6): δ 6.12-6.00 (m, 1H, $H_{4'}$), 5.79 (dt, *J* = 9.5, 1.7 Hz, 1H, $H_{3'}$), 5.63 (dt, *J* = 9.3, 4.5 Hz, 1H, H_2), 3.97-3.83 (m, 4H, 2xO$\underline{CH_2}CH_3$), 2.49 (dd, *J* = 23.6, 8.3 Hz, 2H, $2H_1$), 1.98 (dd, J = 4.5, 1.7 Hz, 2H, $2H_{5'}$), 1.96 (s, 3H, $C_{2'}$-CH_3), 1.82 (d, *J* = 4.5 Hz, 3H, C_3-CH_3), 1.18 (s, 6H, 2xC_6-CH_3), 1.01 (t, *J* = 6.9 Hz, 6H, 2xOCH$_2\underline{CH_3}$) ppm. **^{13}C NMR** (100.62 MHz, C_6D_6): δ 136.3 (s, $J_{P\text{-}C}$ = 2.0 Hz), 127.9 (d), 126.5 (d), 125.2 (d, $^2J_{P\text{-}C}$ = 12.8 Hz), 124.6 (s, $J_{P\text{-}C}$ = 2.1 Hz), 123.0 (s, $J_{P\text{-}C}$ = 15.9 Hz), 100.4 (s, $J_{P\text{-}C}$ = 6.5 Hz), 87.2 (s, $J_{P\text{-}C}$ = 3.6 Hz), 61.7 (t, $J_{P\text{-}C}$ = 6.4 Hz), 38.5 (t), 33.2 (s), 27.9 (t, $^1J_{P\text{-}C}$ = 139.3 Hz), 20.4 (q, 2x), 17.9 (q, $J_{P\text{-}C}$ = 2.8 Hz), 16.5 (q, $J_{P\text{-}C}$ = 5.5 Hz, 2x) ppm. **IR (NaCl):** ν 2966 (s, C-H), 2912 (s, C-H), 2865 (s, C-H), 1251 (m, P=O), 1050-1027 (s, P-O-C) cm^{-1}. **HRMS** (ESI^+): Calcd. for $C_{19}H_{29}NaO_3P$ ($[M+H]^+$), 359.1747; found, 359.1745.



Scheme 4. Reagents and conditions: a. NaHMDS, THF, -78 ºC, 2 h, 47% **2**. b. MeLi, Et_2O, -15 ºC, 30 min, 78 % **1** (two steps).

(3*R*,3'*R*)-Alloxanthin 1.

To a cooled (-78 ºC) solution of (*R*,*E*)-4-[5-(diethoxyphosphoryl)-3-methylpent-3-en-1-ynyl]-3,5,5-trimethylcyclohex-3-enyl acetate **19** (28 mg, 0.070 mmol) in THF (0.9 mL) was added NaHMDS (0.08 mL, 1 M in hexane, 0.08 mmol). After stirring for 30 min, a solution of (2*E*,4*E*,6*E*)-2,7-dimethylocta-2,4,6-triene-1,8-dial **8d** (5.2 mg, 0.032 mmol) in THF (1.1 mL) was added. After being stirred for 2 h at the same temperature a saturated aqueous solution of NH_4Cl was added and the mixture was extracted with a 90:10 EtOAc/CH_2Cl_2 mixture. The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$, dried (Na_2SO_4) and the solvent was evaporated. The residue was used in the next reaction without further purification. To a cooled (-15 ºC) solution of alloxanthin acetate (0.021 g, 0.032 mmol) in Et_2O (0.5 mL) was added MeLi (0.1 mL, 1.6 M, 0.16 mmol) and the mixture was stirred for 30 min at the same temperature. Then the mixture was warmed to 25 ºC and a solution of saturated aqueous

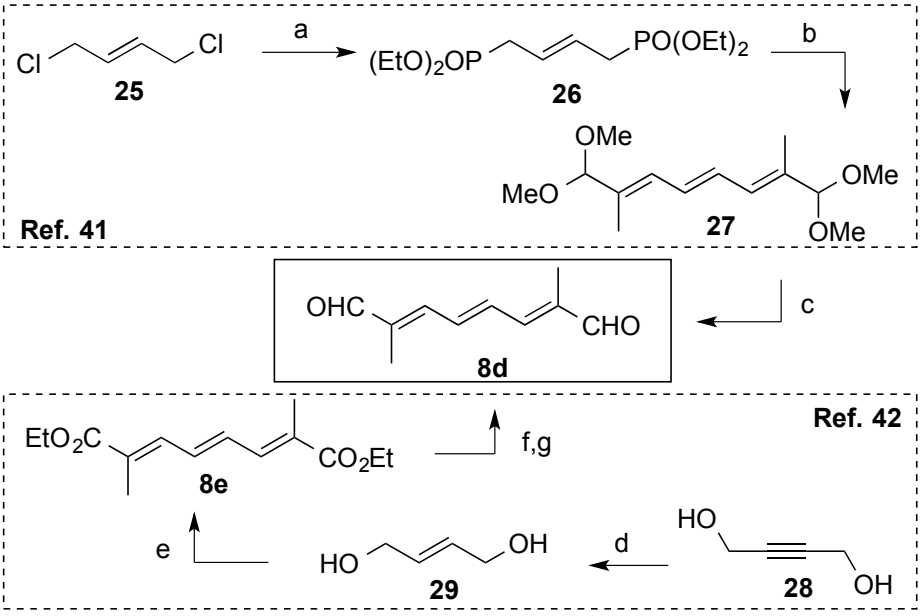
solution of $NaHCO_3$ was added. The mixture was extracted with a 90:10 EtOAc/CH_2Cl_2 mixture, dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by column chromatography (C18 silica gel, CH_3CN) to afford 14 mg (78%) of a red solid identified as (3*R*,3'*R*)-alloxanthin **1**. **^{1}H NMR** (400.13 MHz, C_6D_6): δ 6.79 (d, *J* = 11.4 Hz, 2H, 2H10), 6.64-6.55 (m, 4H, 2H11 + 2H14), 6.36 (d, *J* = 14.8 Hz, 2H, 2H12), 6.27-6.24 (m, 2H, 2H15), 3.75-3.68 (m, 2H, 2H3), 2.16 (dd, *J* = 18.2, 5.1 Hz, 2H, 2H4), 1.98 (s, 6H, 2 x CH_3), 1.92 (s, 6H, 2 x CH_3), 1.88 (dd, *J* = 18.2, 8.3 Hz, 2H, 2H4), 1.79 (s, 6H, 2 x CH_3), 1.65 (ddd, *J* = 12.2, 3.2, 1.7 Hz, 2H, 2H2), 1.39 (d, *J* = 12.0 Hz, 2H, 2H2), 1.35 (s, 6H, 2 x CH_3), 1.23 (s, 6H, 2 x CH_3) ppm. **^{13}C NMR** (100.62 MHz, C_6D_6): δ 138.5 (d, 2x), 137.8 (s, 2x), 136.7 (s, 2x), 135.7 (d, 2x), 134.1 (d, 2x), 130.9 (d, 2x), 124.8 (s, 2x), 124.7 (d, 2x), 119.7 (s, 2x), 99.2 (s, 2x), 90.2 (s, 2x), 64.5 (d, 2x), 47.0 (t, 2x), 41.7 (t, 2x), 36.8 (s, 2x), 30.9 (q, 2x), 29.0 (q, 2x), 22.7 (q, 2x), 18.3 (q, 2x), 12.9 (q, 2x) ppm. **HRMS** (ESI$^+$): Calcd. for $C_{40}H_{53}O_2$ ([M+H]$^+$), 565.4040; found, 565.4039. $[\alpha]_D^{24}$ − 106.0 (*c* 0.01, $CHCl_3$).

In order to check the stability of alloxanthin **1** in $CDCl_3$, a NMR sample was prepared using freshly filtered $CDCl_3$ through a pad of basic alumina. Immediate NMR acquisition provided a clean ^{1}H-spectrum. In order to investigate photochemical conditions, the same sample was exposed to light for 48 h and systematic ^{1}H-NMR were acquired to monitor photoinduced or acid catalyzed conformational changes. However no changes were observed in the 48 h monitoring at 25 ºC.

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 6.64 (dd, *J* = 8.0, 2.9 Hz, 2H, H15+H15'), 6.52 (dd, *J* = 14.1, 11.5 Hz, 2H, H11+ H11'), 6.45 (dd, *J* = 11.4, 1.0 Hz, 2H, H10+H10'), 6.35 (d, *J* = 14.2 Hz, 2H, H12+H12'), 6.27 (dd, *J* = 7.9, 2.0 Hz, 2H, H14+H14'), 4.05-3.94 (m, 2H, H3+H3'), 2.43 (dd, *J* = 17.7, 5.3 Hz, 2H, H4+H4'), 2.06 (dd, *J* = 17.7, 9.5 Hz, 2H, H4+H4'), 2.00 (s, 6H, C9-CH_3+C9'-CH_3), 1.96 (s, 6H, C13-CH_3+C13'-CH_3), 1.92 (s, 6H, C5-CH_3+C5'-CH_3), 1.83 (ddd, *J* = 12.3, 3.6, 2.0 Hz, 2H, H2+H2'), 1.45 (t, *J* = 12.1 Hz, 2H, H2+H2'), 1.20 (s, 6H, C1-CH_3+C1'-CH_3), 1.14 (s, 6H, C1-CH_3+C1'-CH_3) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ 138.2 (d, 2x), 137.5 (s, 2x), 136.6 (s, 2x), 135.3 (d, 2x), 133.6 (d, 2x), 130.5 (d, 2x), 124.4 (s, 2x), 124.3 (d, 2x), 119.2 (s, 2x), 98.8 (s, 2x), 89.2 (s, 2x), 65.0 (d, 2x), 46.8 (t, 2x), 41.6 (t, 2x), 36.8 (s, 2x), 30.7 (q, 2x), 28.9 (q, 2x), 22.6 (q, 2x), 18.2 (q, 2x), 12.9 (q, 2x) ppm.

Octadehydro-β,β-carotene 2. To a cooled (-78 °C) solution of diethyl (*E*)-[3-methyl-5-(2,6,6-trimethylcyclohexa-1,3-dien-1-yl]pent-2-en-4-yn-1-yl)phosphonate (C_{15}-alkynylphosphonate) **24** (24.5 mg, 0.07 mmol) in THF (1 mL) was added NaHMDS (0.083 mL, 1M in hexane, 0.08 mmol). After stirring for 30 min, a solution of (2*E*,4*E*,6*E*)-2,7-dimethylocta-2,4,6-triene-1,8-dial **8d** (5.4 mg, 0.03 mmol) in THF (1 mL) was added. The mixture was stirred at -78 °C for 1.5 h. Then, a saturated aqueous solution of NH_4Cl was added at -78 °C and the mixture was allowed to reach room temperature and extracted with 90:10 EtOAc/CH_2Cl_2. The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$, dried (Na_2SO_4) and the solvent was evaporated. The crude was purified by column chromatography (silicagel-

CN, from 100:0 to 90:10 hexane/EtOAc) afforded 8.2 mg (47%) of an orange solid identified as octadehydro-β,β-carotene **2**. **^{1}H NMR** (400.13 MHz, C_6D_6): δ 6.81 (d, *J* = 11.4 Hz, 2H, $H_{10} + H_{10'}$), 6.63 (dd, *J* = 8.0, 2.9 Hz, 2H, $H_{14} + H_{14'}$), 6.60 (dd, *J* = 14.9, 11.4 Hz, 2H, $H_{11} + H_{11'}$), 6.37 (d, *J* = 14.9 Hz, 2H, $H_{12} + H_{12'}$), 6.26 (dd, *J* = 8.0, 2.0 Hz, 2H, $H_{15} + H_{15'}$), 5.86 (dt, *J* = 9.5, 1.9 Hz, 2H, $H_4 + H_{4'}$), 5.67 (dt, *J* = 9.5, 4.5 Hz, 2H, $H_3 + H_{3'}$), 2.07 (s, 3H, CH_3), 2.03 (dd, *J* = 4.5, 1.9 Hz, 4H, $2H_2 + 2H_{2'}$), 1.99 (d, *J* = 2.0 Hz, 6H, 2xCH_3), 1.79 (s, 6H, 2xCH_3), 1.28 (s, 12H, 4xCH_3). **^{13}C NMR** (100.62 MHz, C_6D_6): δ 138.6 (d, 2x), 136.8 (s, 2x), 136.4 (s, 2x), 135.9 (d, 2x), 134.2 (d, 2x), 131.0 (d, 2x), 128.7 (d, 2x), 126.7 (d, 2x), 125.1 (s, 2x), 124.8 (d, 2x), 119.8 (s, 2x), 103.3 (s, 2x), 91.2 (s, 2x), 38.6 (t, 2x), 33.4 (s, 2x), 27.5 (q, 4x), 20.9 (q, 2x), 18.2 (q, 2x), 12.8 (q, 2x)ppm. **IR (NaCl):** ν 3031 (w, C-H), 2956 (s, C-H), 2919 (s, C-H), 2857 (w, C-H), 2148 (w, C≡C) cm^{-1}. **UV** (MeOH)(ε$M^{-1}cm^{-1}$): λ_{max} 380 (547000); 470 (453000). **HRMS** (ESI^+): Calcd. for $C_{40}H_{48}$ ($[M+H]^+$), 528.3750; found, 528.3749



Scheme 5. Reagents and reaction conditions: a. $P(OEt)_3$, from 25 to 180 °C, 97%. b. Methyl glyoxal dimethyl acetal, *t*BuOK, THF-DMSO, 56%. c. Acid-catalyzed acetal removal (see article text). d. $LiAlH_4$, THF, 85 °C, 87%. e. MnO_2, ethyl 2-(triphenyl-λ^5-phosphanylidene)propanoate, Na_2CO_3, CH_2Cl_2, from 0 to 25 °C, 74%. f. DIBAL-H, THF, from -78 to -20 ºC. g. MnO_2, Na_2CO_3, acetone.

Following the procedure described by Azim et al.,[5] bis-phosphonate **26** was prepared from (*E*)-1,4-dichlorobut-2-ene **25** and condensed with methyl glyoxal dimethylacetal to obtain the corresponding bis(dimethylacetal) compound **27**:

(*E*)-1,4-bis(triethoxy-λ^4-phosphanyl)but-2-ene 26. A solution of (*E*)-1,4-dichlorobut-2-ene **25** (12.0 g, 96.0 mmol) in $P(OEt)_3$ (15.6 mL, 88.90 mmol) was added dropwise to a flask containing $P(OEt)_3$ (27.0 mL, 148.32 mmol) at 140 °C, and the reaction mixture was stirred for 12 h at the same temperature. During this time, the ethyl chloride generated was continuously distilled off of the reaction. After that, the reaction temperature was risen to 180 °C so that the excess of $P(OEt)_3$ could be eliminated from the reaction mixture. The residue was purified via fractional distillation under reduced pressure and then by column chromatography (silica gel, 95:5 CH_2Cl_2/MeOH) to afford 30.56 g (97%) of a colorless oil identified as (*E*)-1,4-bis(triethoxy-λ^4-phosphanyl)but-2-ene **27**. The spectroscopic data matched those previously reported. **^{1}H NMR** (400.16 MHz, $CDCl_3$) 5.61 – 5.55 (s, 2H, H2 + H3), 4.14 – 3.99 (m, 8H, 4x CH_2), 2.57 (td, J = 1.5 Hz, $^2J_{H\text{-}P}$ = 17.1 Hz, 4H, 2H1 + 2H4), 1.28 (t, J = 7.1 Hz, 12H, 4 x CH_3) ppm. The ^{13}C NMR spectra showed non-first order multiplicities due to coupling to the phosphorous nuclei. Only the multiplicities due to ^{1}H splitting are given, together with the value of the large $^nJ_{P\text{-}C}$ coupling constants: **^{13}C NMR** (101 MHz, $CDCl_3$): δ 124.4 (d, $^3J_{P\text{-}C}$ = 21.1 Hz, 2x), 62.0 (t, $^2J_{P\text{-}C}$ = 3.2 Hz, 4x), 30.7 (t, $^1J_{P\text{-}C}$ = 142.0 Hz, $^4J_{P\text{-}C}$ = 4.3 Hz, 2x), 16.5 (q, $^3J_{P\text{-}C}$ = 3.0 Hz, 4x) ppm

(2*E*,4*E*,6*E*)-1,1,8,8-tetramethoxy-2,7-dimethylocta-2,4,6-triene 27. To a solution of (*E*)-1,4-bis(triethoxy-λ^4-phosphanyl)but-2-ene **26** (16.25 g, 49.50mmol) and 1,1-dimethoxypropan-2-one (13.1 mL, 107.87mmol) in THF/DMSO (12:1, 169 mL) was added potasium *tert*-butoxide (11.33 g, 97.97 mmol) at 5°C. The reaction mixture was stirred for 5 min at the same temperature and then 7 h at r.t. The reaction mixture was diluted with Et_2O/pentane 1:1 and the organic layer was washed with a 10% NaCl aqueous solution (3x). The combined organic layers were dried (Na_2SO_4) and the solvent removed by evaporation. Purification by column chromatography (silica gel, from 100:0 to 80:20 hexane/EtOAc) afforded 7.13 g (56 %) of an oil identified as (2*E*,4*E*,6*E*)-1,1,8,8-tetramethoxy-2,7-dimethylocta-2,4,6-triene **27**. The spectroscopic data matched those previously reported. **^{1}H NMR** (400.16 MHz, $CDCl_3$): δ 6.51 (dd, J = 7.5, 3.0 Hz, 2H, H4+H5), 6.27 (d, J = 7.5 Hz, 2H, H3+H6), 4.56 (s, 2H, H1+H9), 3.29 (s, 12H, 2x OCH_3), 1.74 (s, 12H, 2x CH_3) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ 134.5 (s, 2x), 129.3 (d, 2x), 128.2 (d, 2x), 106.8 (d, 2x), 53.5 (q, 4x), 12.3 (q, 2x).

Alternatively, the large scale synthesis of bisaldehyde **8d** was performed following the procedure reported by Lugtenburg[2] based on a double Wittig reaction of the symmetrical C_4-(*E*)-but-2-ene-dial with the phosphorane ethyl 2-(triphenyl-λ^5-phosphanylidene)propanoate:

(*E*)-But-2-ene-1,4-diol 29. To a cooled (0 °C) suspension of $LiAlH_4$ (0.46 g, 12.14 mmol) in THF (16 mL) was added dropwise a solution of but-2-yn-1,4-diol **28** (0.5 g, 5.81 mmol) in THF (25 mL). The reaction mixture was allowed to warm up to room temperature, and then heated under reflux for 2 h. The reaction mixture was cooled down to 0 °C and treated dropwise with a 3M NaOH aqueous solution until effervescence stopped. Then, the pH was adjusted to neutral with a 3M aqueous solution

of HCl. Et_2O and silica gel were added to the mixture and the solvent was evaporated. The residue was purified by column chromatography (silica gel, from 100:0 to 90:10 EtOAc/acetone) to afford 0.44 g (87 %) of a yellow oil corresponding to (*E*)-but-2-ene-1,4-diol **29**. The spectroscopic data matched those previously reported.[2] **^{1}H NMR** (400.13 MHz, $CDCl_3$): δ 5.90 (t, *J* = 2.5 Hz, 2H, H2 + H3), 4.19 (s, 4H, 2x$\underline{CH_2}$OH) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ 130.6 (d), 62.9 (t).

Diethyl (2*E*,4*E*,6*E*)-2,7-Dimethylocta-2,4,6-trienedioate 8e. A solution of (*E*)-but-2-ene-1,4-diol **29** (0.025 g, 0.29 mmol) in CH_2Cl_2 (0.5 mL) was added to a suspension of MnO_2 (0.446 mg, 5.13 mmol) and Na_2CO_3 (0.544 g, 5.13 mmol) in CH_2Cl_2 (1.1 mL) at 0 °C. Then, a solution of (1-ethoxyethylidene)triphenyl-λ^5-phosphane (0.3 g, 0.68 mmol) in CH_2Cl_2 (0.3 mL) was added and the reaction mixture was allowed to reach 25 °C. After 14 h, the reaction mixture was filtered over a pad of Celite® and washed with CH_2Cl_2 and a mixture of CH_2Cl_2-MeOH (90:10). The residue obtained was purified by column chromatography (silica gel, from 90:10 to 40:60 hexane/EtOAc) to afford 0.054 g (74%) of a white solid identified as diethyl (2*E*,4*E*,6*E*)-2,7-dimethylocta-2,4,6-trienedioate **8e**. The spectroscopic data matched those previously reported.[2] **^{1}H NMR** (400.13 MHz, $CDCl_3$): δ 7.28 (ddd, *J* = 7.8, 3.1, 1.3 Hz, 2H, H3 + H6), 6.79 (dd, *J* = 7.8, 3.1 Hz, 2H, H4 + H5), 4.22 (q, *J* = 7.1 Hz, 4H, 2xO$\underline{CH_2}$$CH_3$), 2.00 (d, *J* = 1.3 Hz, 6H, 2xCH_3), 1.31 (t, *J* = 7.1 Hz, 6H, 2xO$CH_2\underline{CH_3}$) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ 168.2 (s, 2x), 137.2 (d, 2x), 133.7 (d, 2x), 130.3 (s, 2x), 60.9 (t, 2x), 14.4 (q, 2x), 13.1 (q, 2x) ppm.

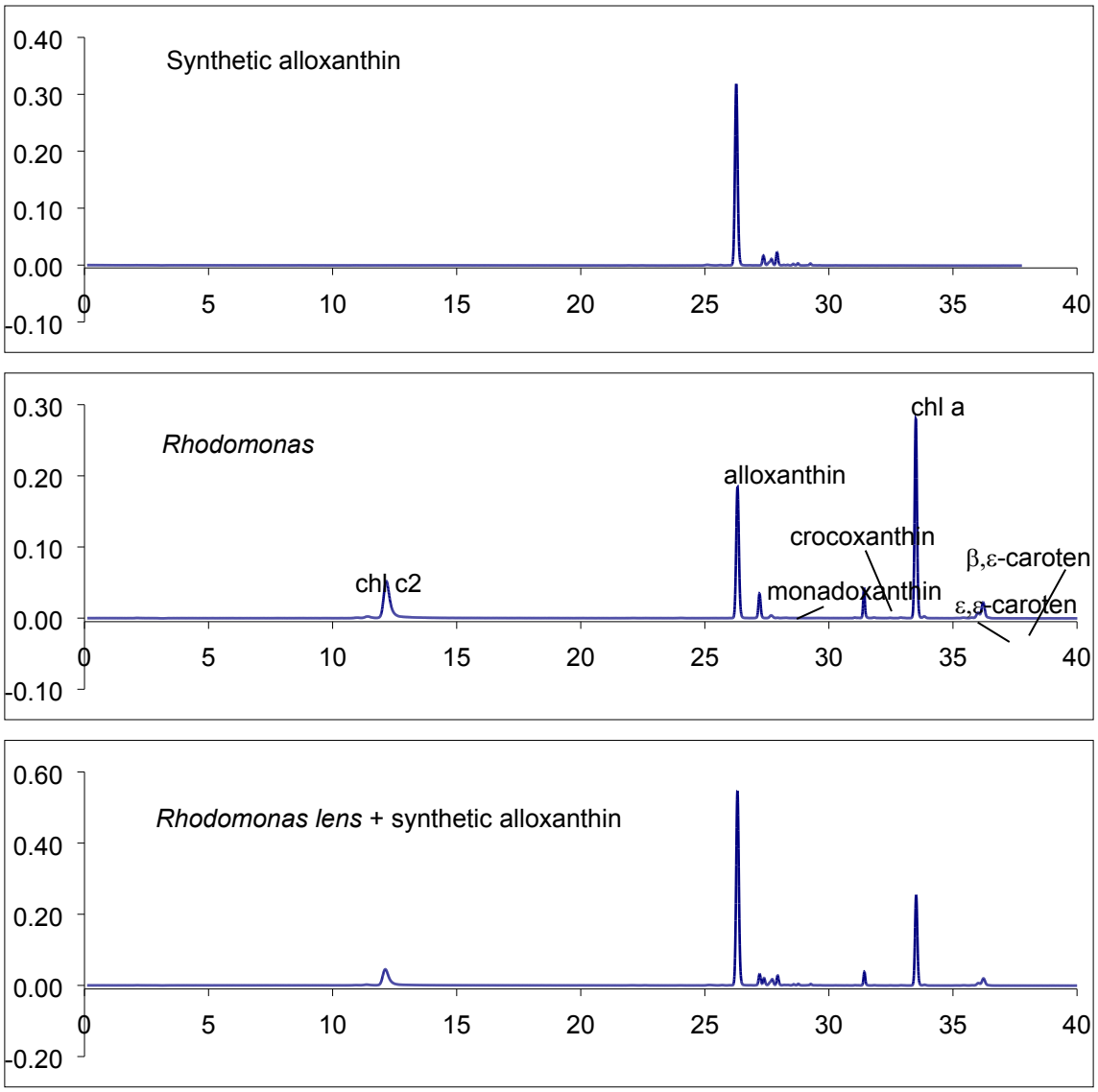
The transformation of diethyl diester **8e** into final dialdehyde **8d** was performed analogously to the transformation of dimethyl diester **8a** into **8d**, described in page 7.

HPLC comparison: Natural and synthetic alloxanthin.

Elution of pigments was perfomed using the method developed by Zapata *et al.* on a reversed phase C_8 column and pyridine containing mobile phase. See reference for further details.[6]

Column: Waters Symmetry C_8 column (150 x 4.6 mm, 3.5 µm particle size, 100 Å pore size).

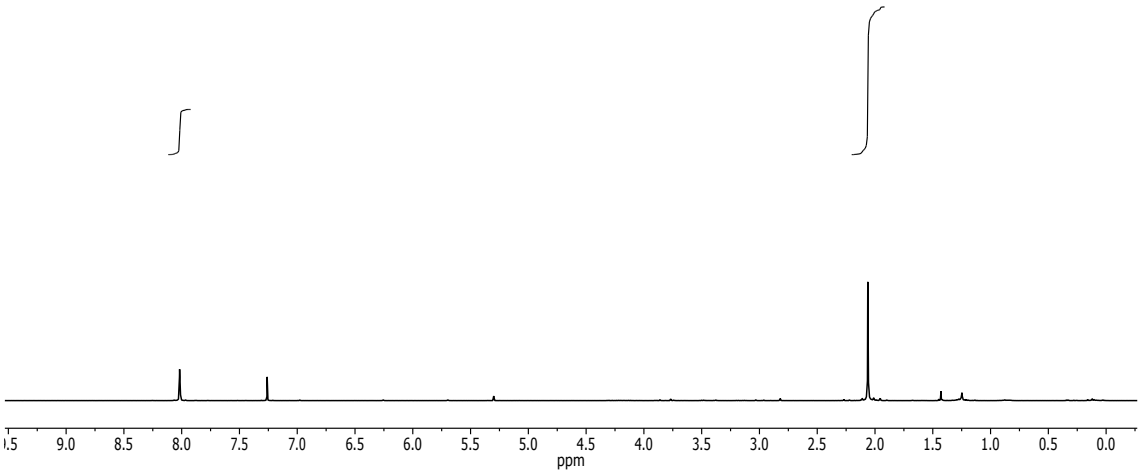
Mobile Phase: Eluent A: MeOH / CH_3CN / 0.25 M Pyridine(aq) (50:25:25 v:v:v). Eluent B: CH3CN / Acetone (80:20 v:v:v). Flow: 1 mL/min



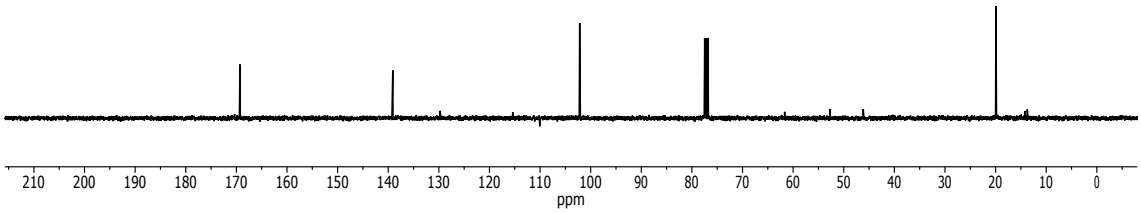
Spectroscopic data

(*E*)-3-Iodo-2-methylacrylic acid 4.

^{1}H NMR (400.13 MHz, $CDCl_3$)

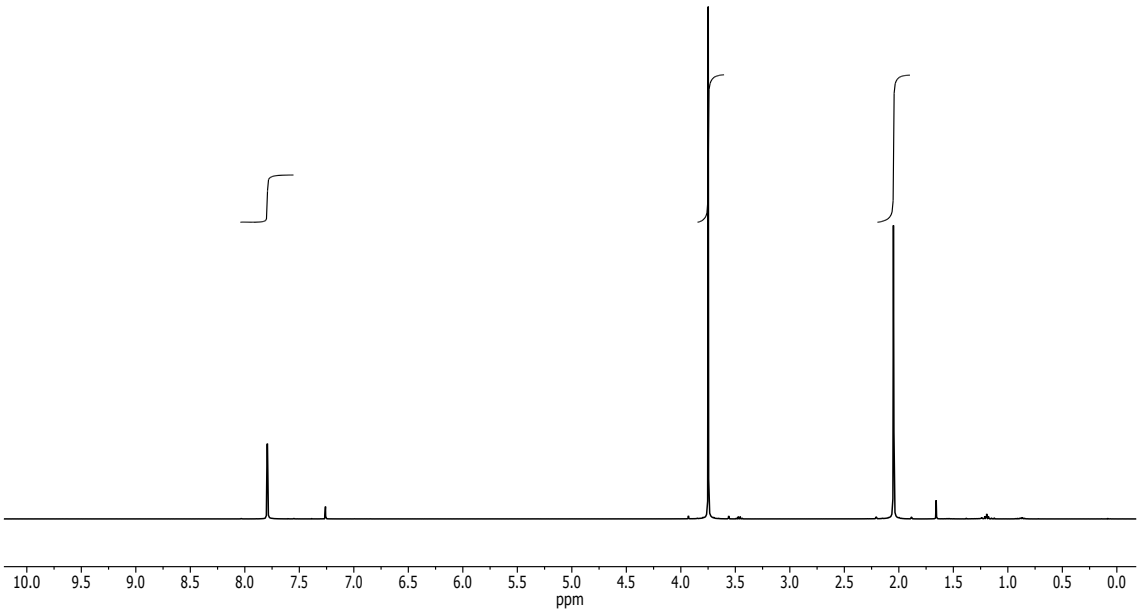


^{13}C NMR (101 MHz, $CDCl_3$)

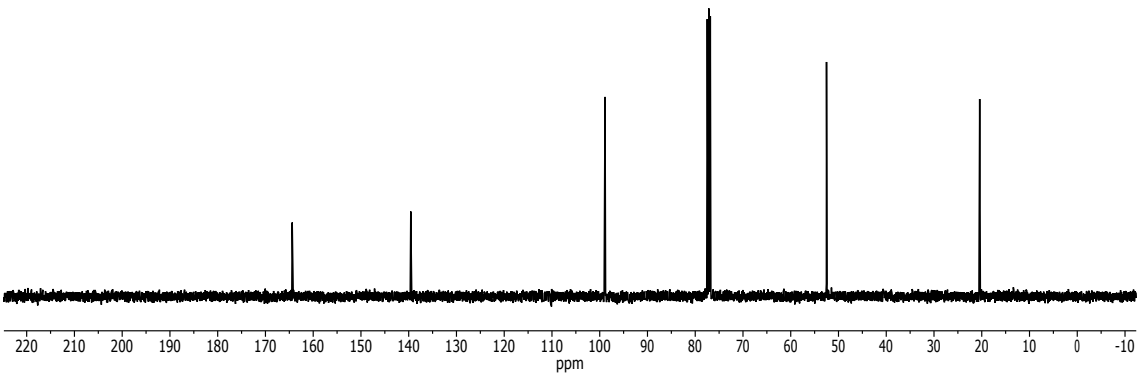


Methyl (*E*)-3-iodo-2-methylacrylate 5a.

^{1}H NMR (400.13 MHz, $CDCl_3$

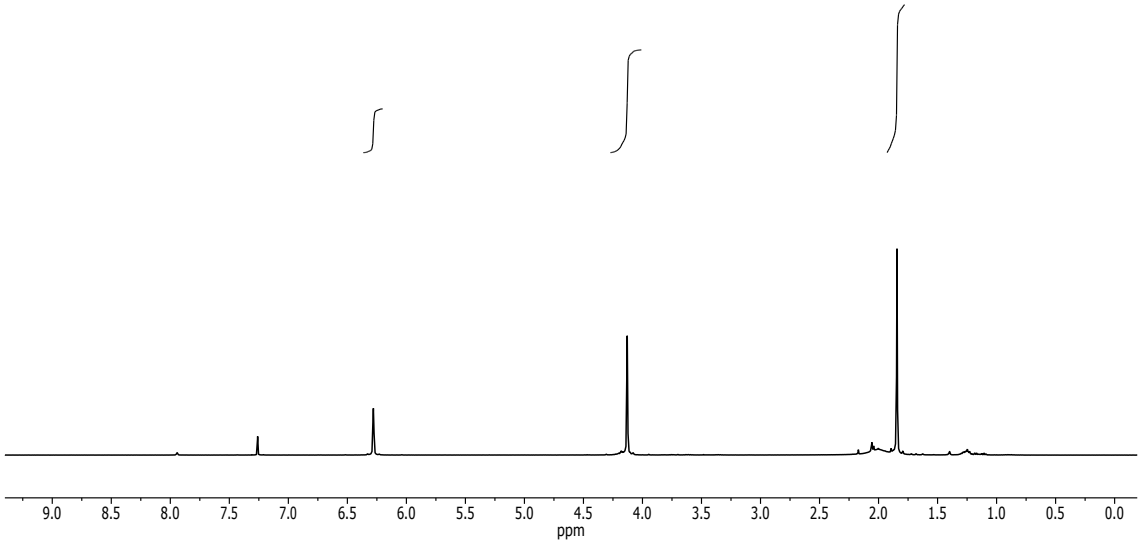


^{13}C NMR (101 MHz, $CDCl_3$)

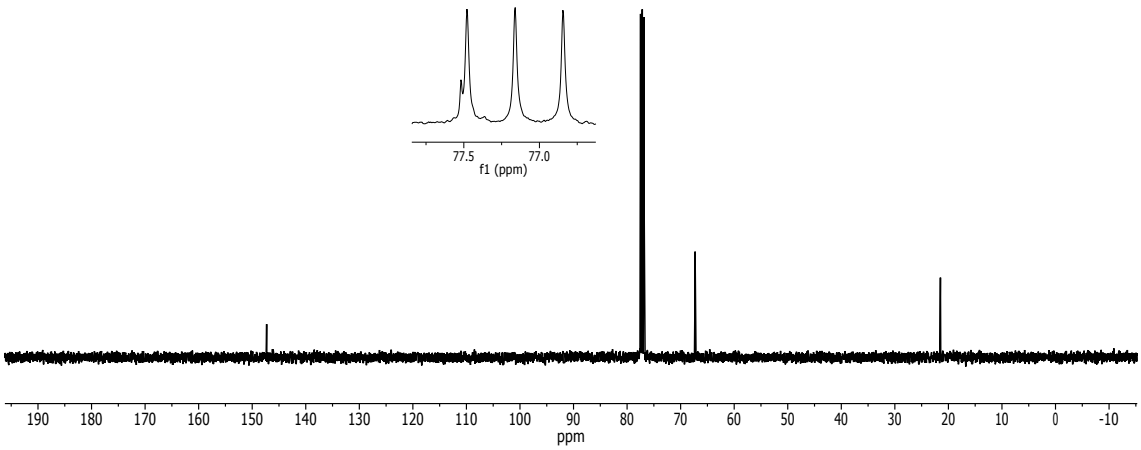


(*E*)-3-Iodo-2-methylprop-2-en-1-ol 5b.

^{1}H NMR (400.13 MHz, $CDCl_3$

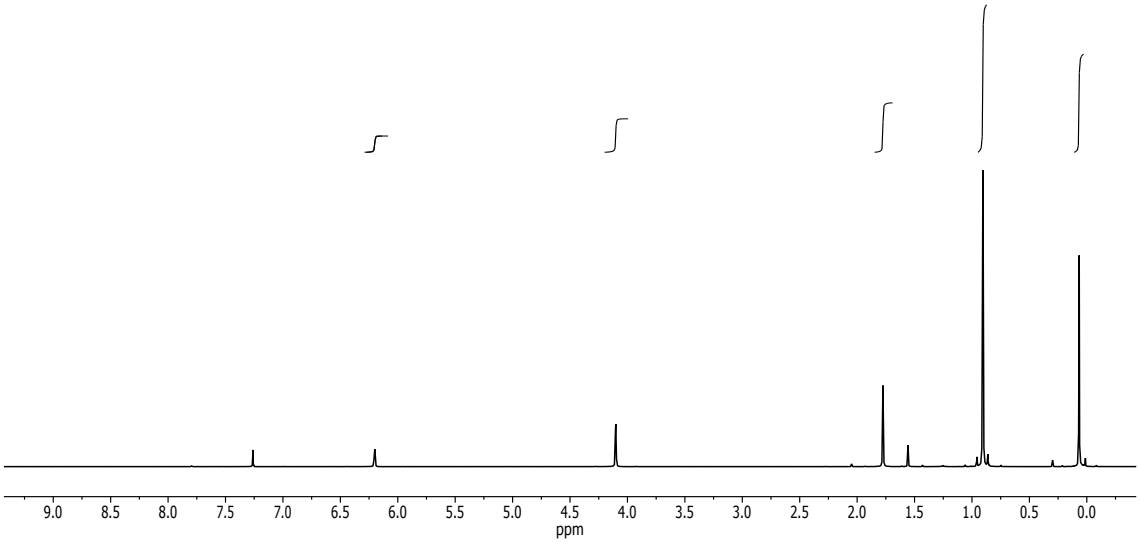


^{13}C NMR (101 MHz, $CDCl_3$)

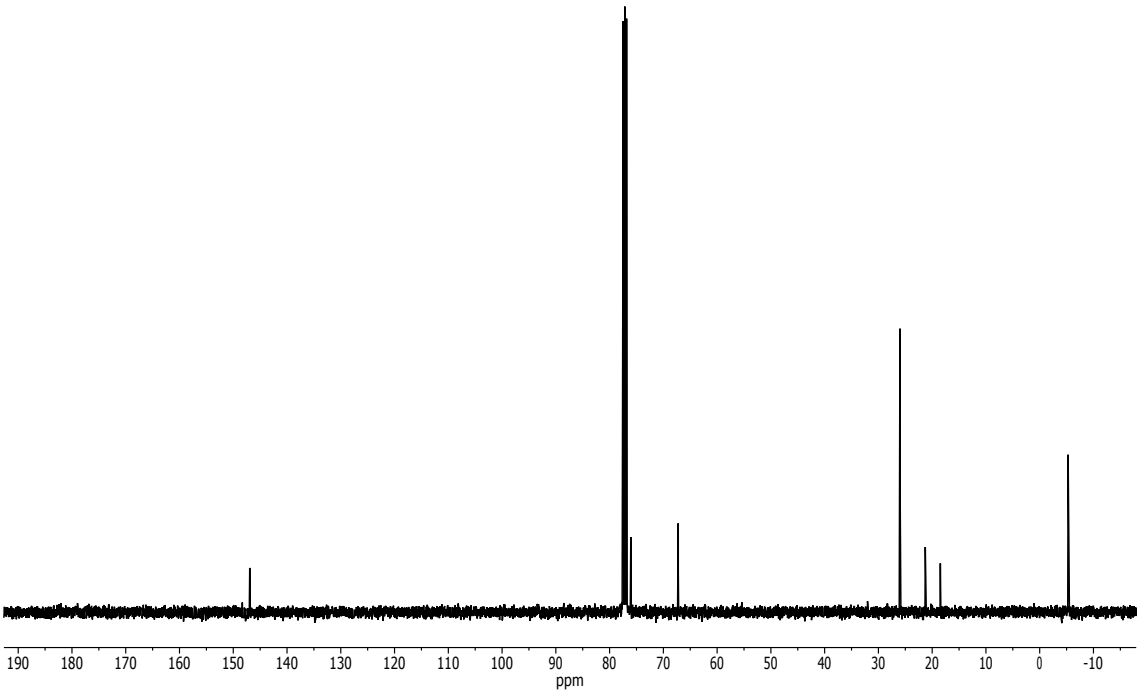


(*E*)-*tert*-Butyl[(3-iodo-2-methylallyl)oxy]dimethylsilane 5c.

^{1}H NMR (400.13 MHz, $CDCl_3$)

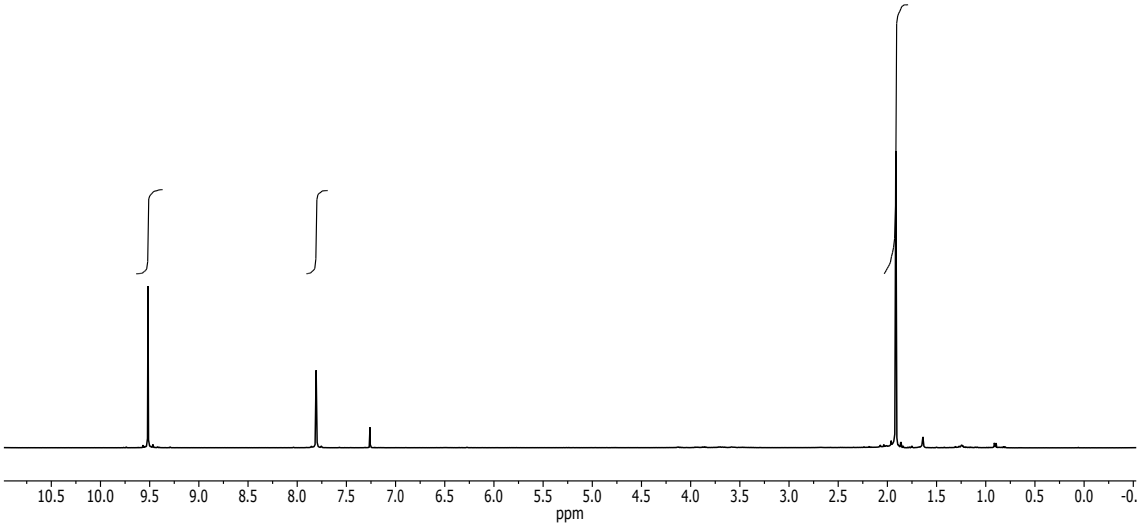


^{13}C NMR (101 MHz, $CDCl_3$)

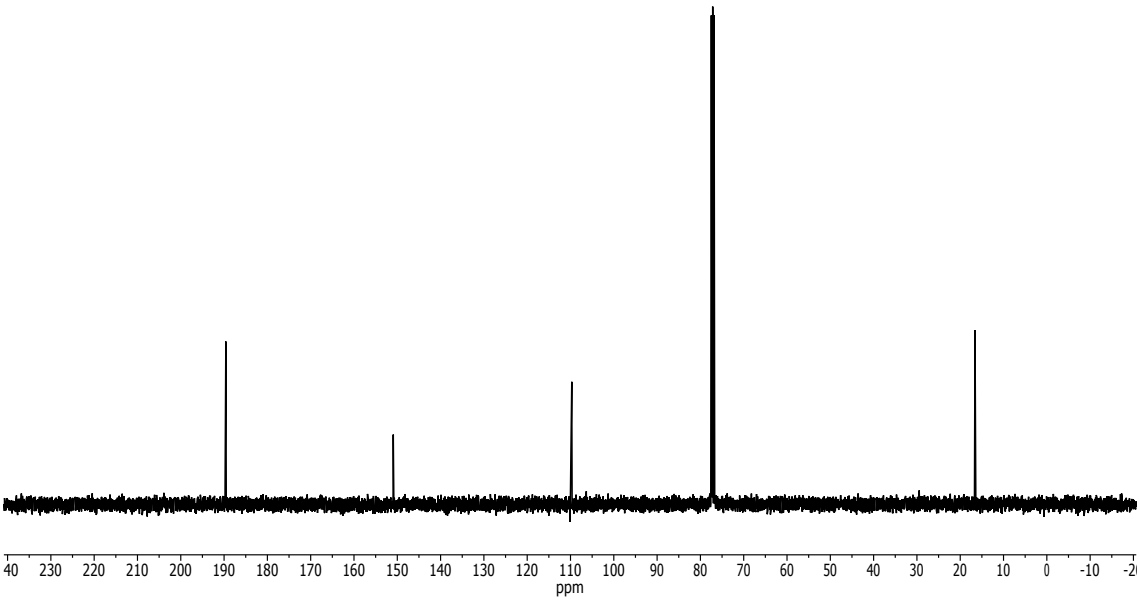


(*E*)-3-Iodo-2-methylacrylaldehyde 5d.

^{1}H NMR (400.13 MHz, $CDCl_3$)

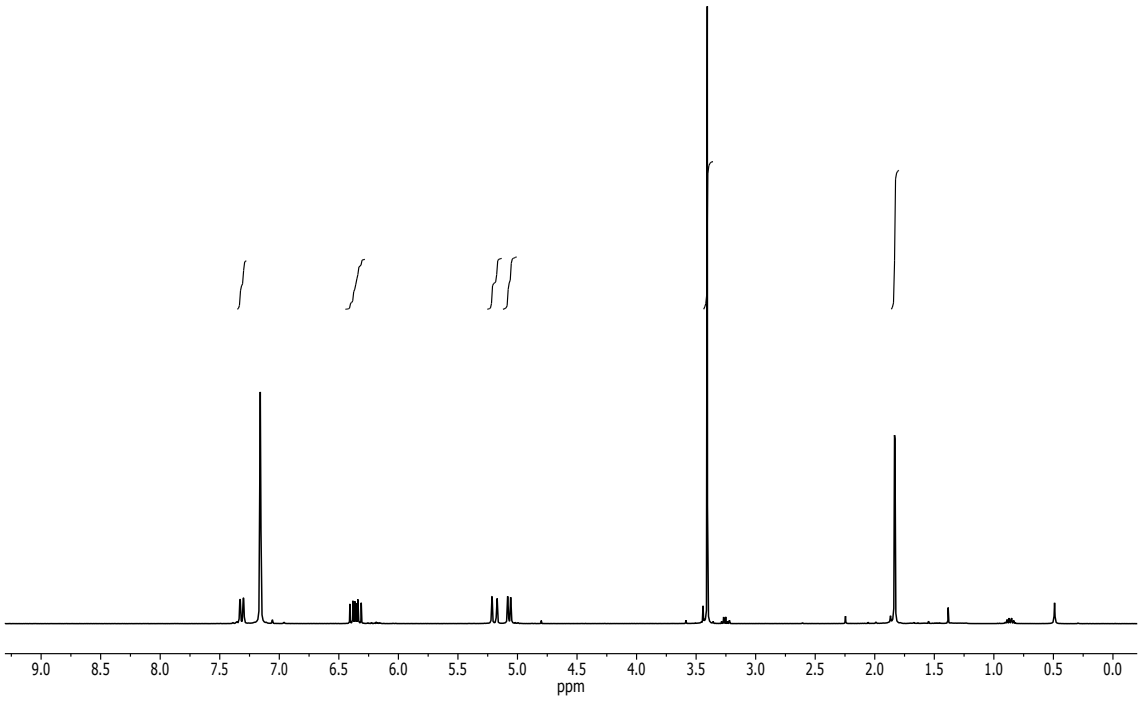


^{13}C NMR (101 MHz, $CDCl_3$)

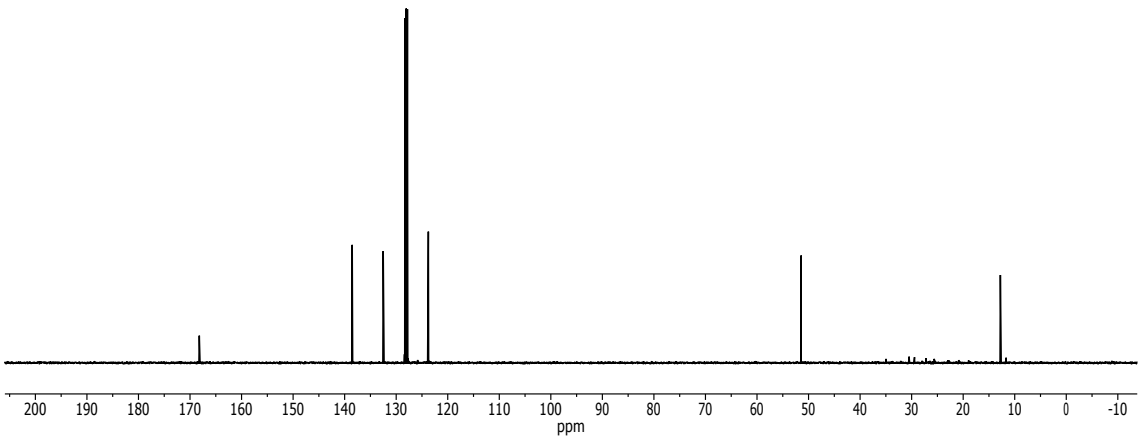


Methyl (*E*)-2-Methylpenta-2,4-dienoate 7a.

^{1}H-NMR (400.13 MHz, C_6D_6)

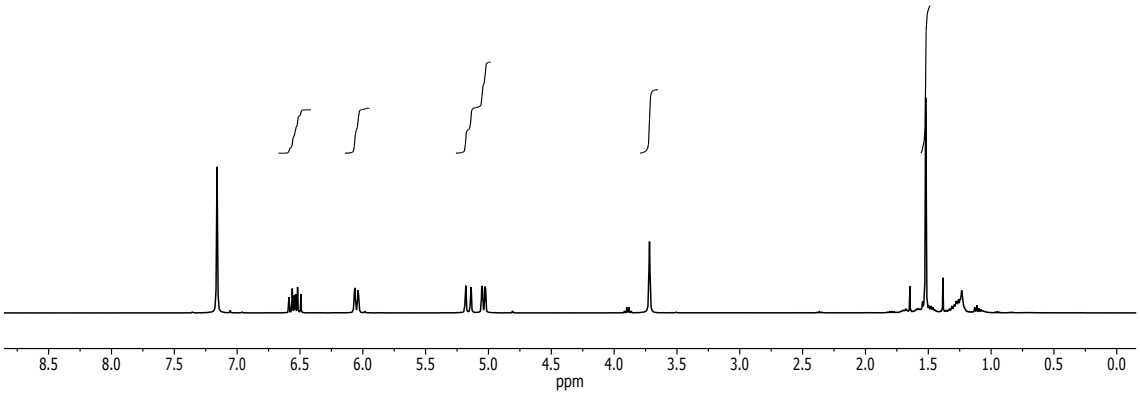


^{13}C-NMR (100.62 MHz, C_6D_6)

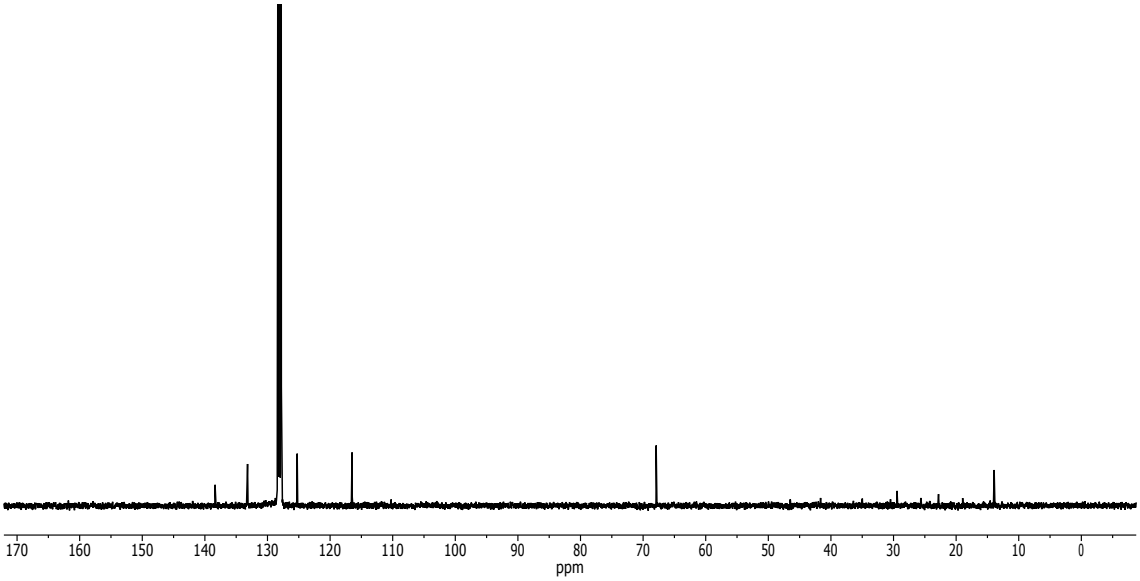


(*E*)-2-Methylpenta-2,4-dien-1-ol 7b.

^{1}H-NMR (400.13 MHz, C_6D_6)

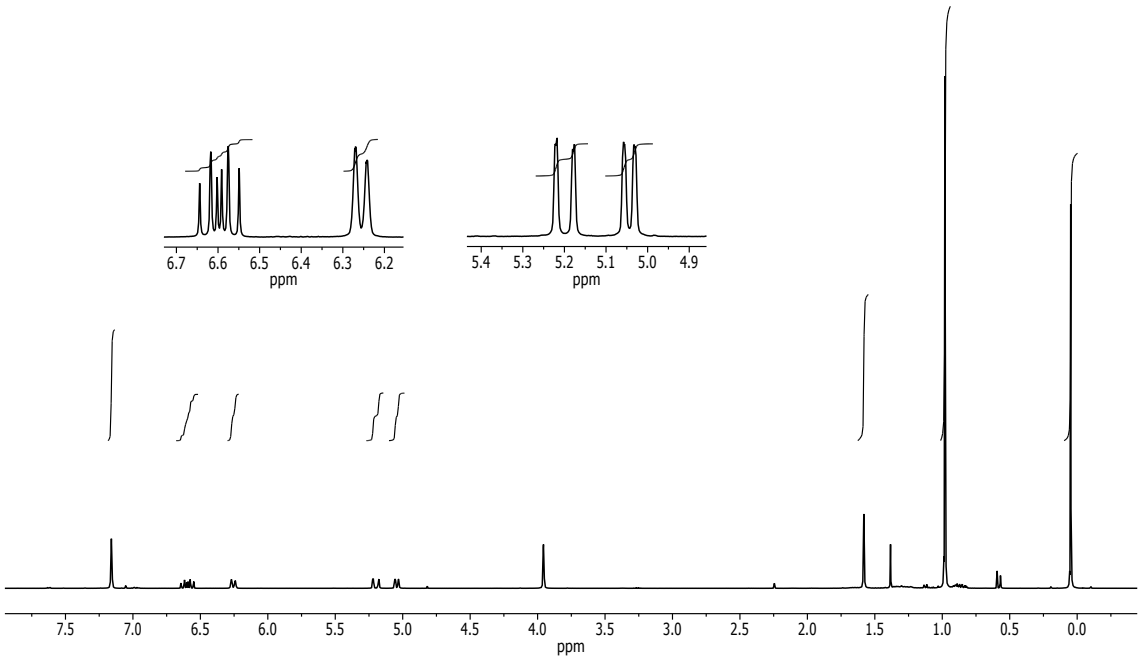


^{13}C-NMR (100.62 MHz, C_6D_6)

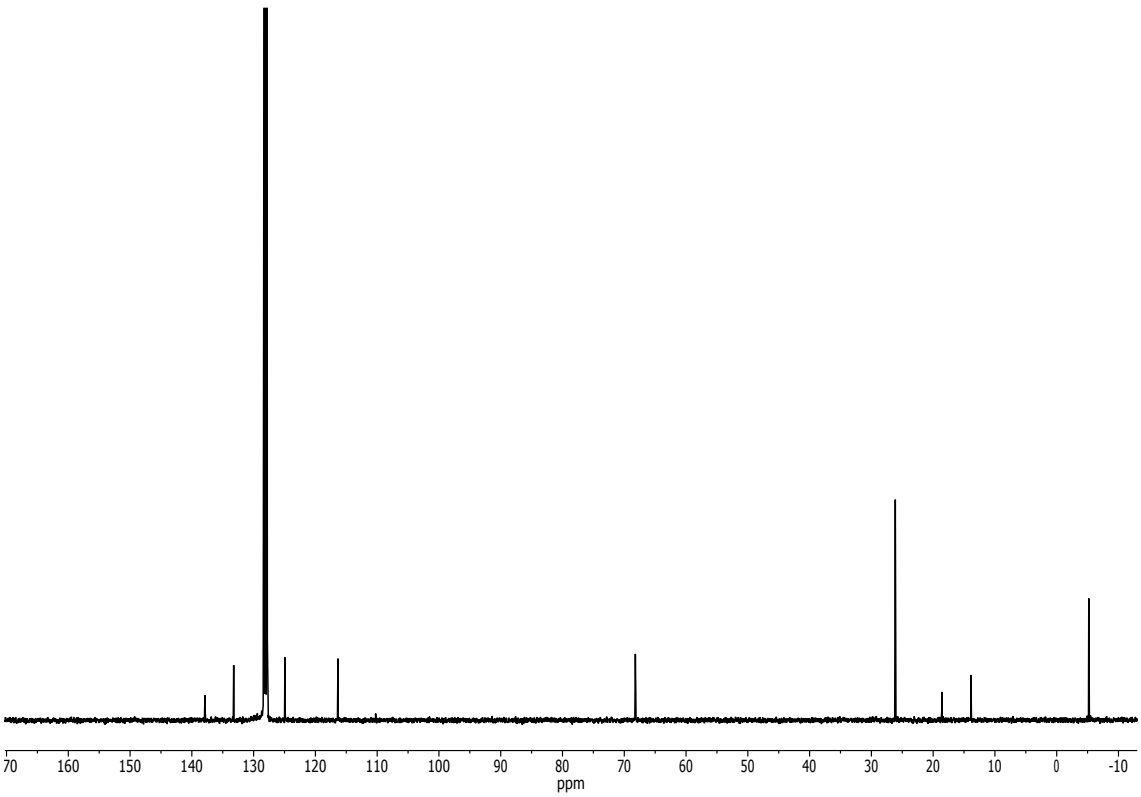


(*E*)-*tert*-Butyldimethyl[(2-methylpenta-2,4-dien-1-yl)oxy]silane 7c.

^{1}H-NMR (400.13 MHz, C_6D_6)

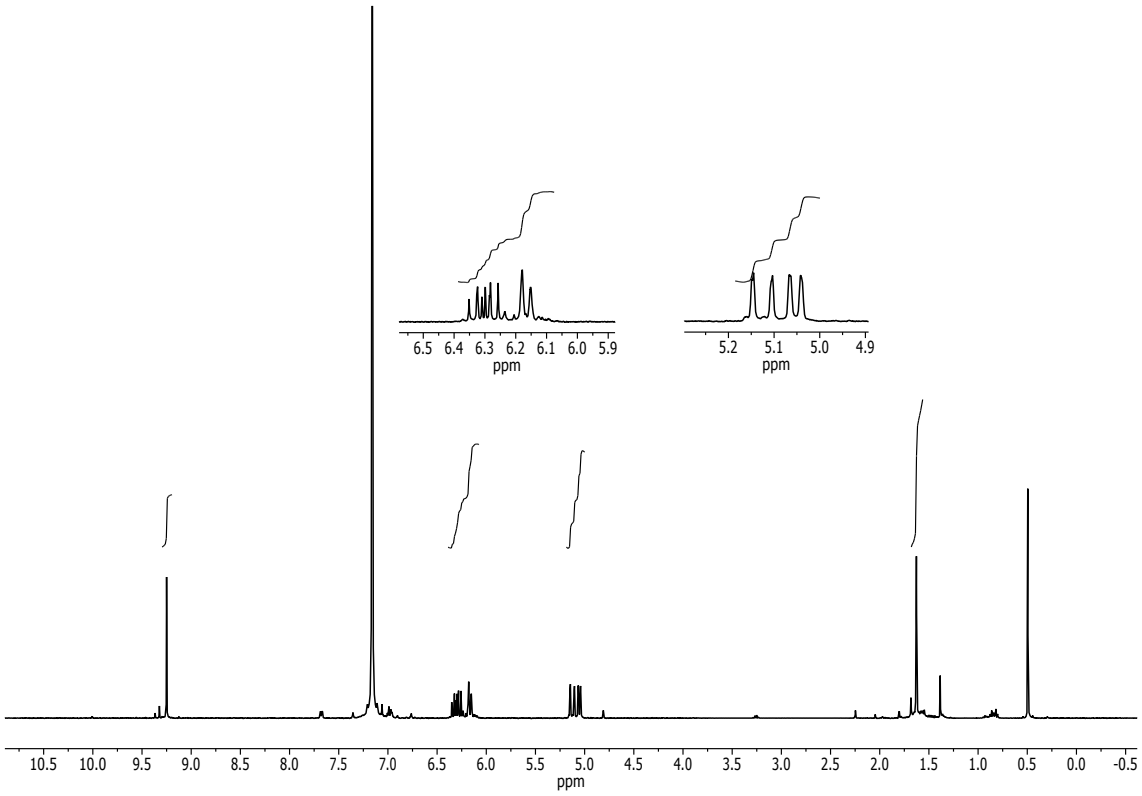


^{13}C NMR (101 MHz, C_6D_6)

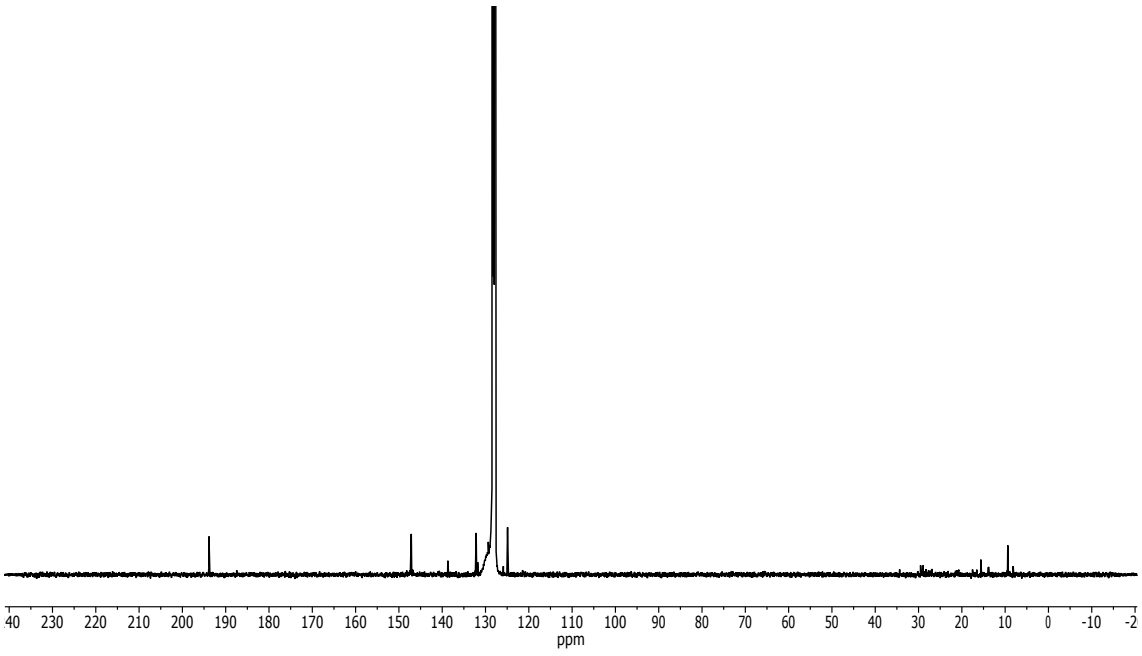


(*E*)-2-methylpenta-2,4-dienal 7d.

^{1}H-NMR (400.13 MHz, C_6D_6

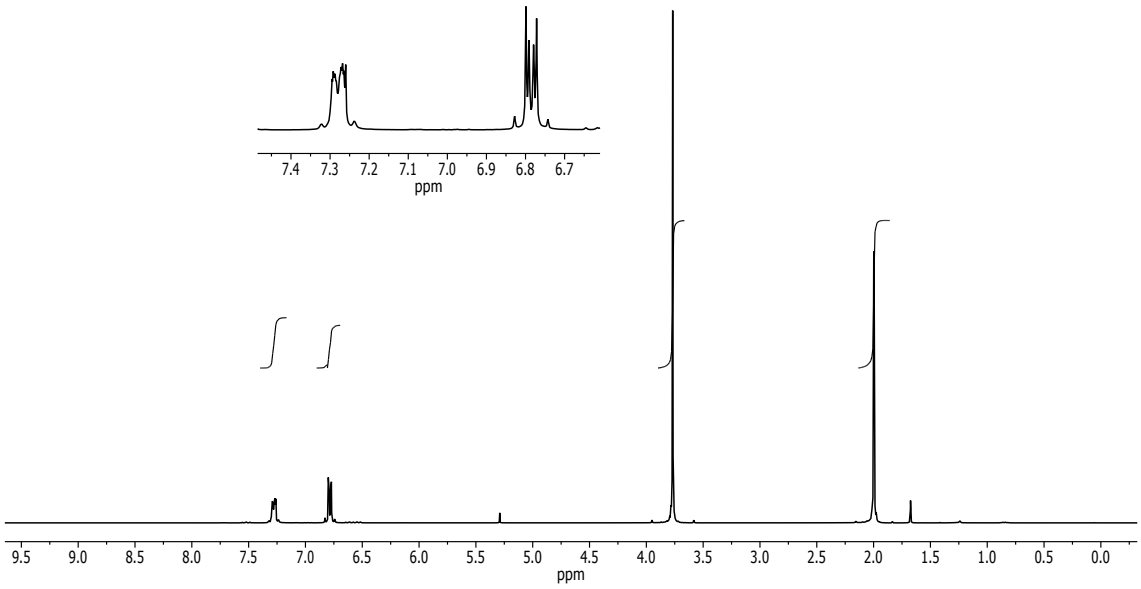


^{13}C NMR (101 MHz, C_6D_6)

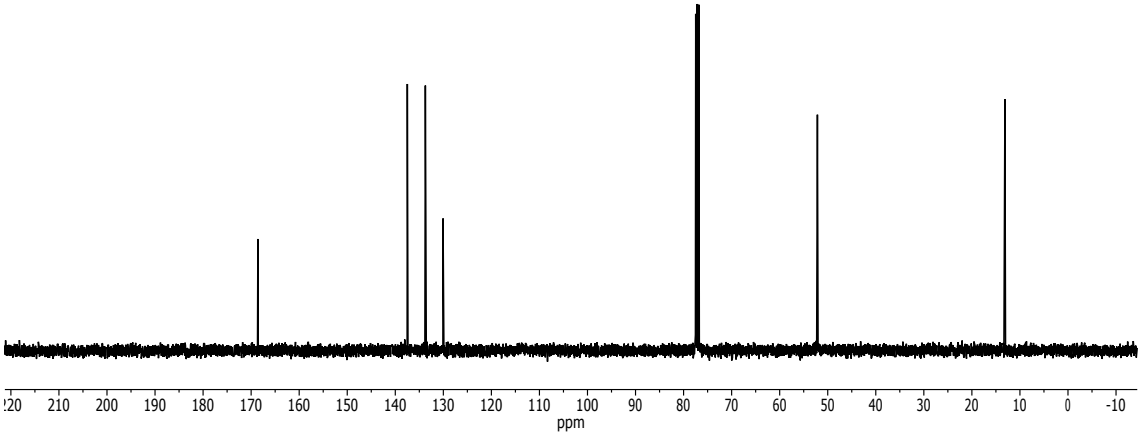


Dimethyl (2*E*,4*E*,6*E*)-2,7-Dimethylocta-2,4,6-trienedioate 8a.

^{1}H-NMR (400.13 MHz, $CDCl_3$)

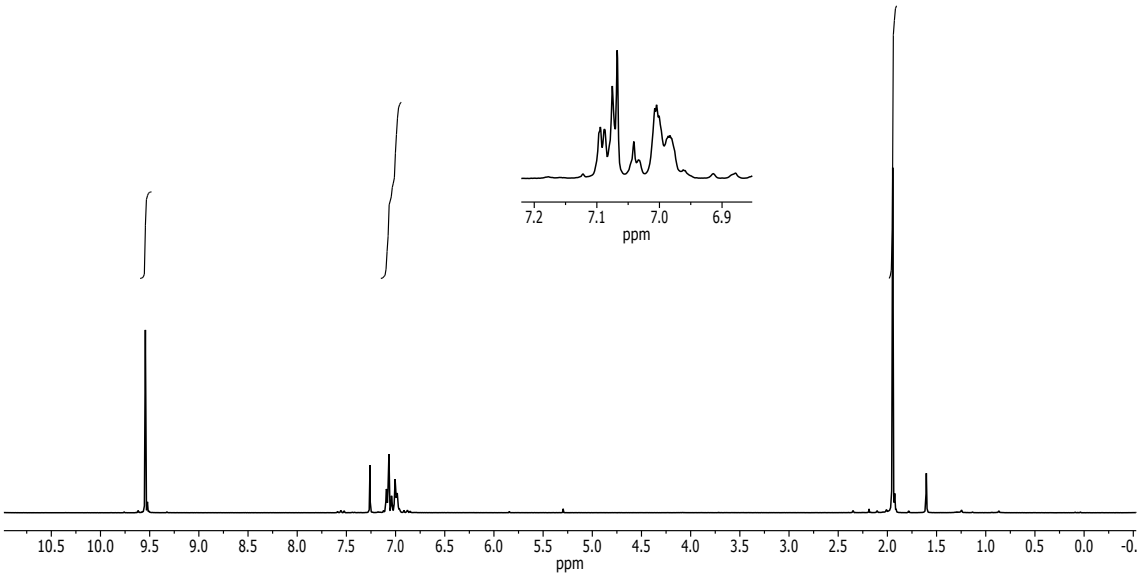


^{13}C NMR (101 MHz, $CDCl_3$)

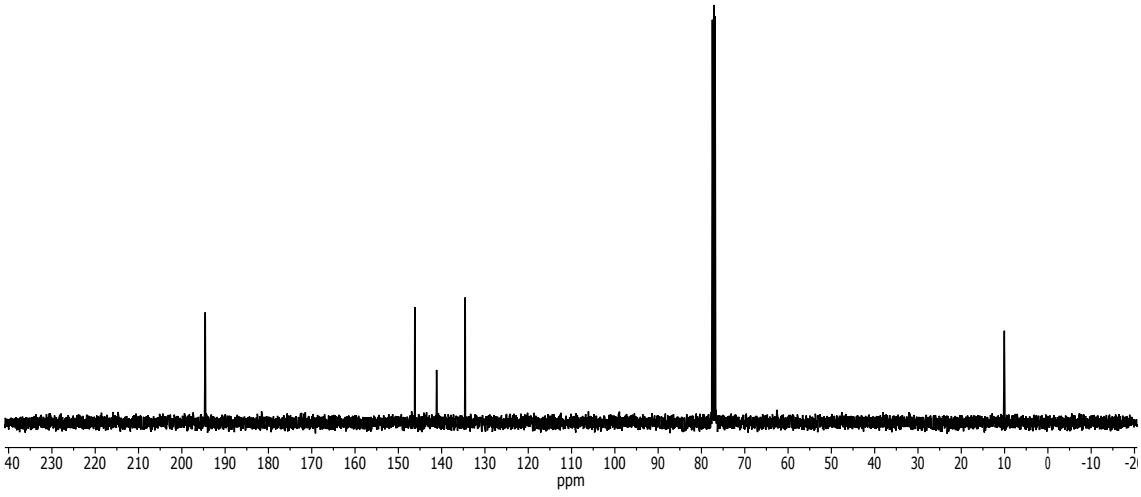


(2*E*,4*E*,6*E*)-2,7-Dimethylocta-2,4,6-trienedial 8d.

^{1}H-NMR (400.13 MHz, $CDCl_3$)

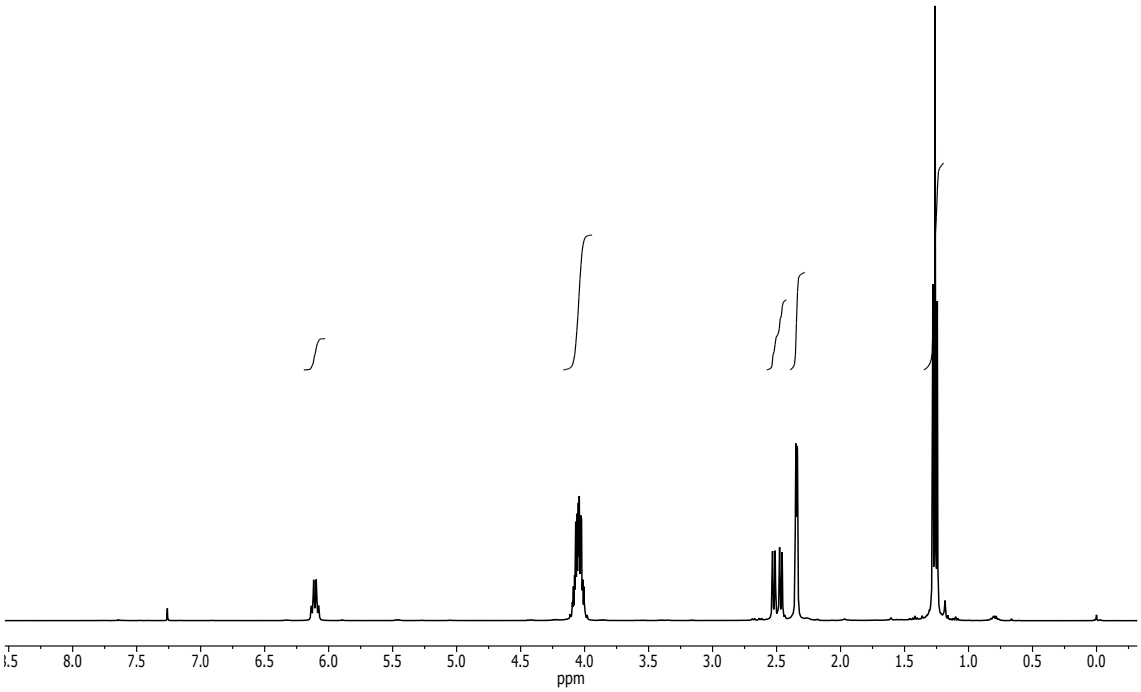


^{13}C NMR (101 MHz, $CDCl_3$)

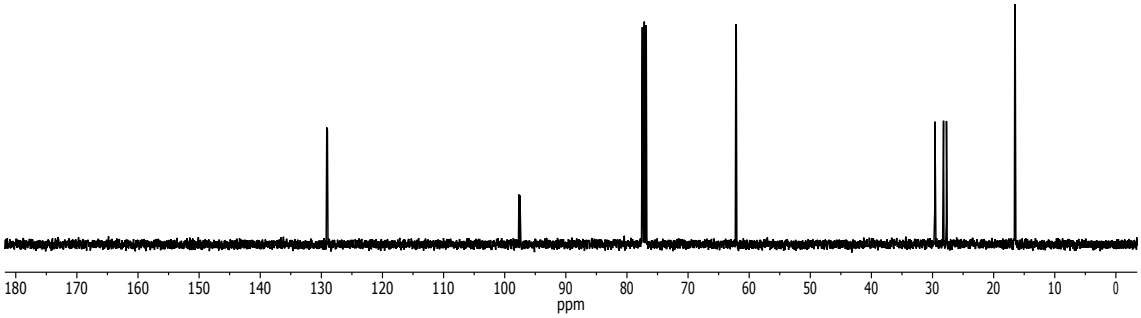


(*E*)-Diethyl (3-iodobut-2-en-1-yl)phosphonate 18.

^{1}H NMR (400.13 MHz, $CDCl_3$)

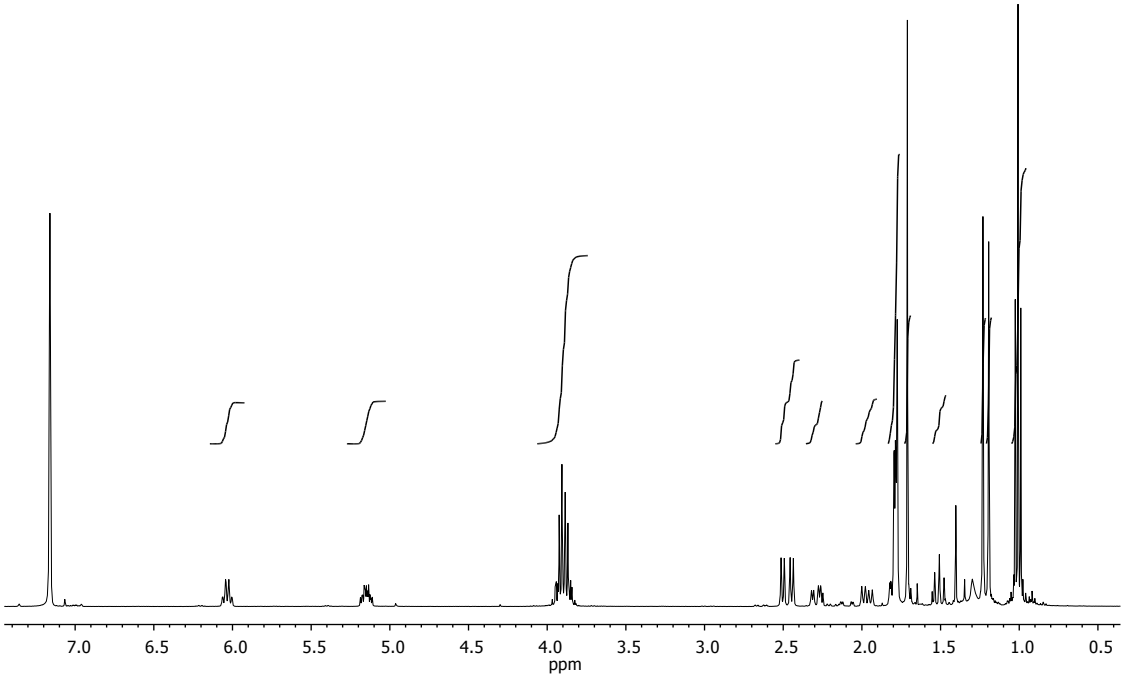


^{13}C NMR (101 MHz, $CDCl_3$)

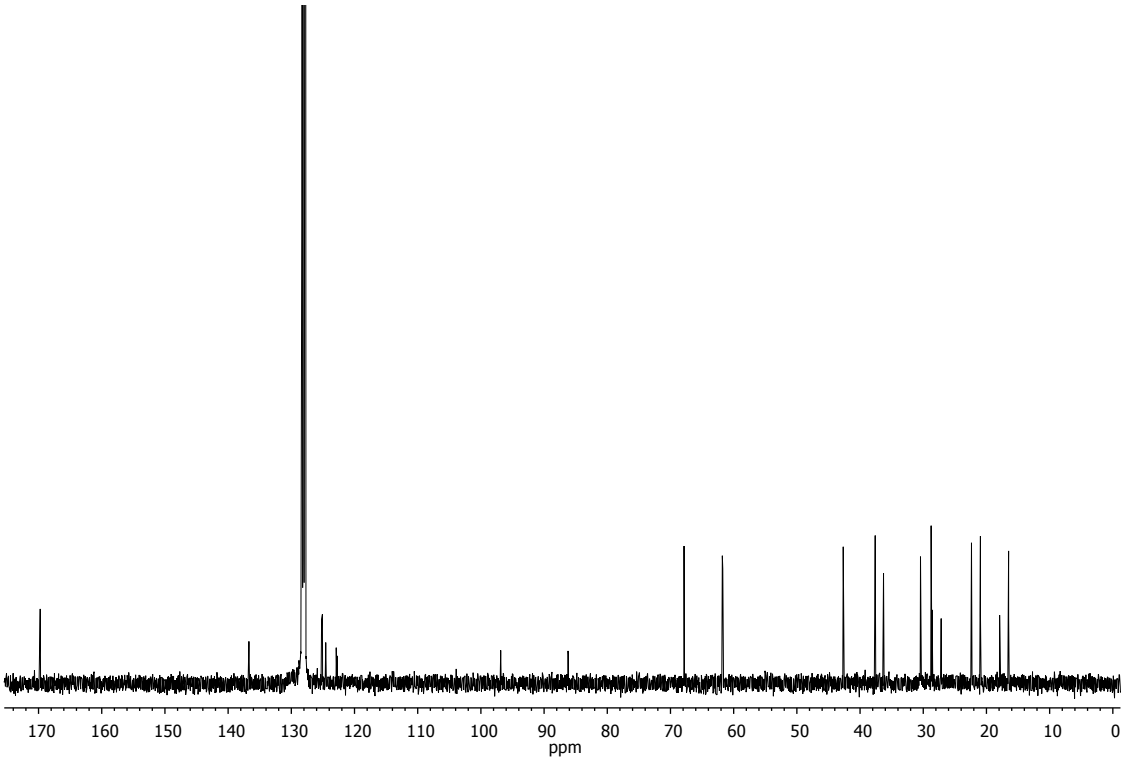


(*R*,*E*)-4-[5´-(Diethoxyphosphoryl)-3´-methylpent-3´-en-1-ynyl]-3,5,5-trimethylcyclohex-3-enyl Acetate 19

^{1}H-NMR (400.13 MHz, C_6D_6):

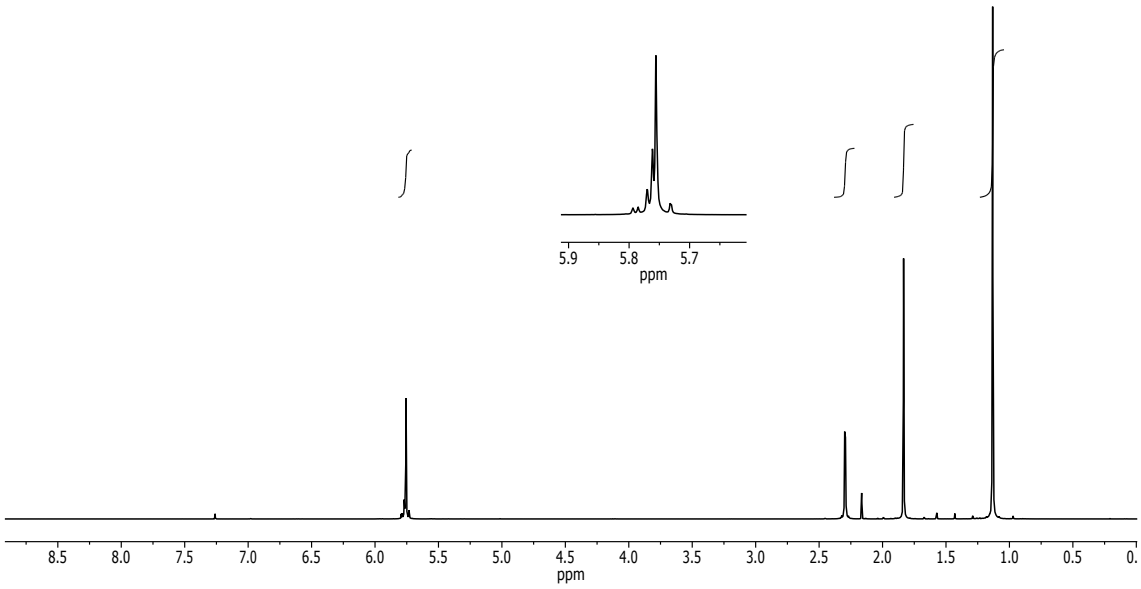


^{13}C-NMR (100.62 MHz, C_6D_6):

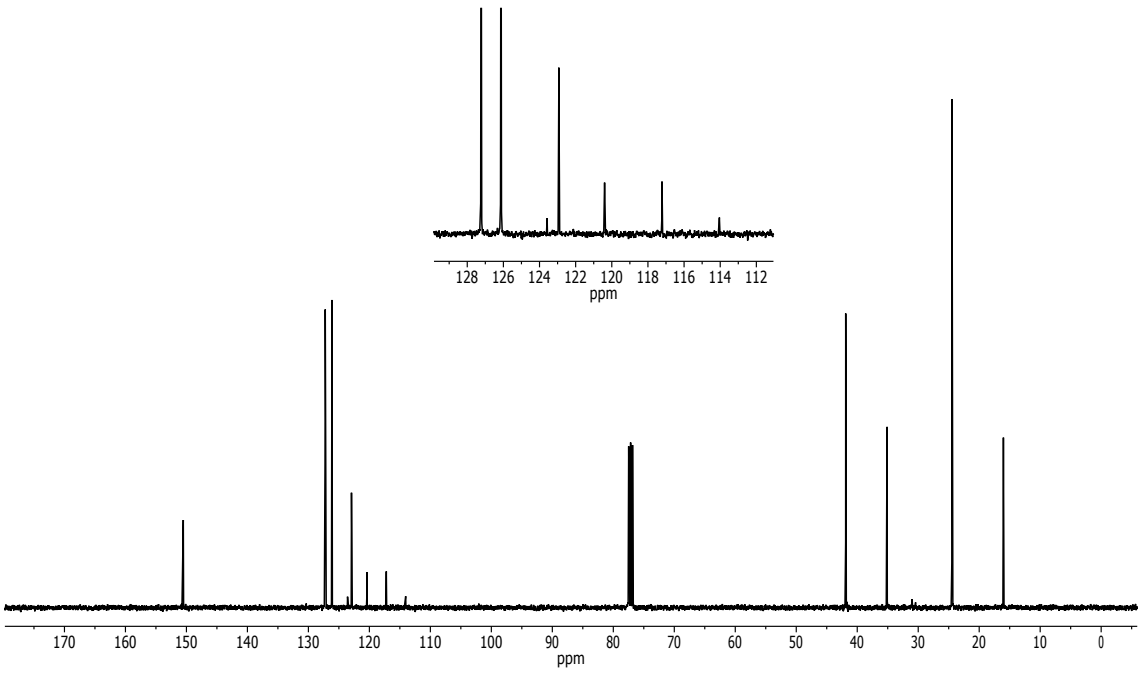


1-(Trifluoromethanesulfonyl)oxy-2,6,6-trimethylcyclohexa-1,3-diene 21.

^{1}H NMR (400.13 MHz, $CDCl_3$)

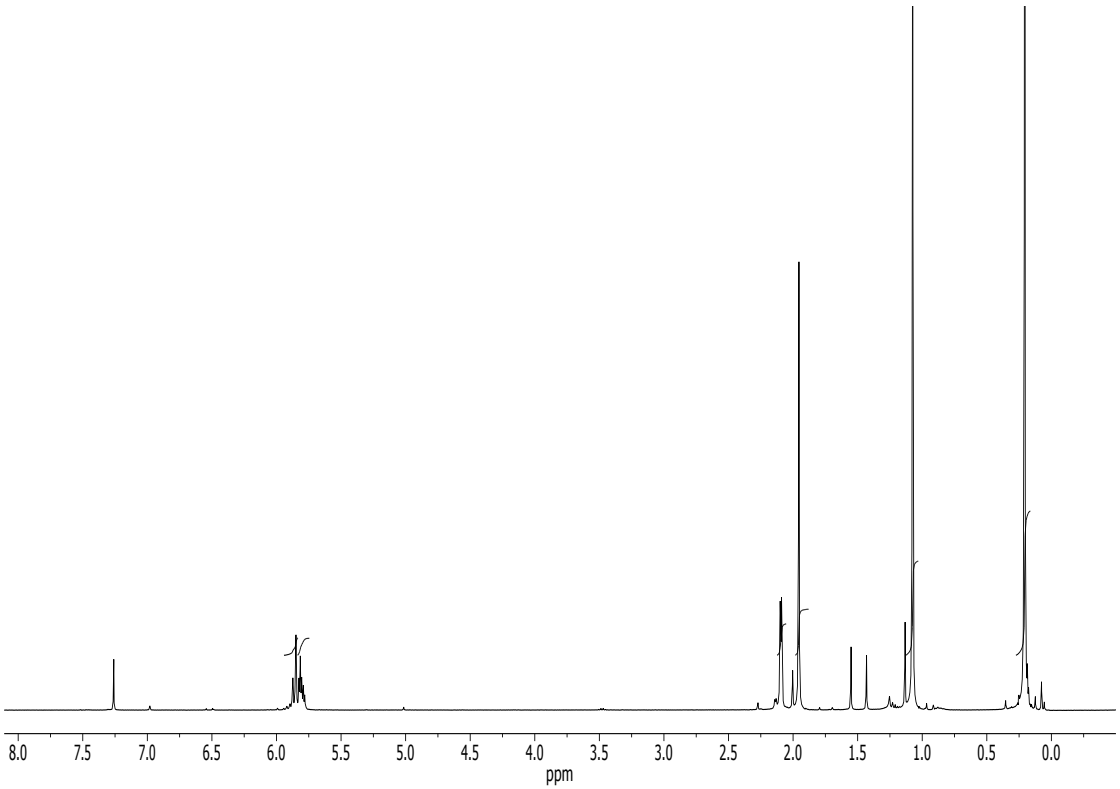


^{13}C NMR (101 MHz, $CDCl_3$)

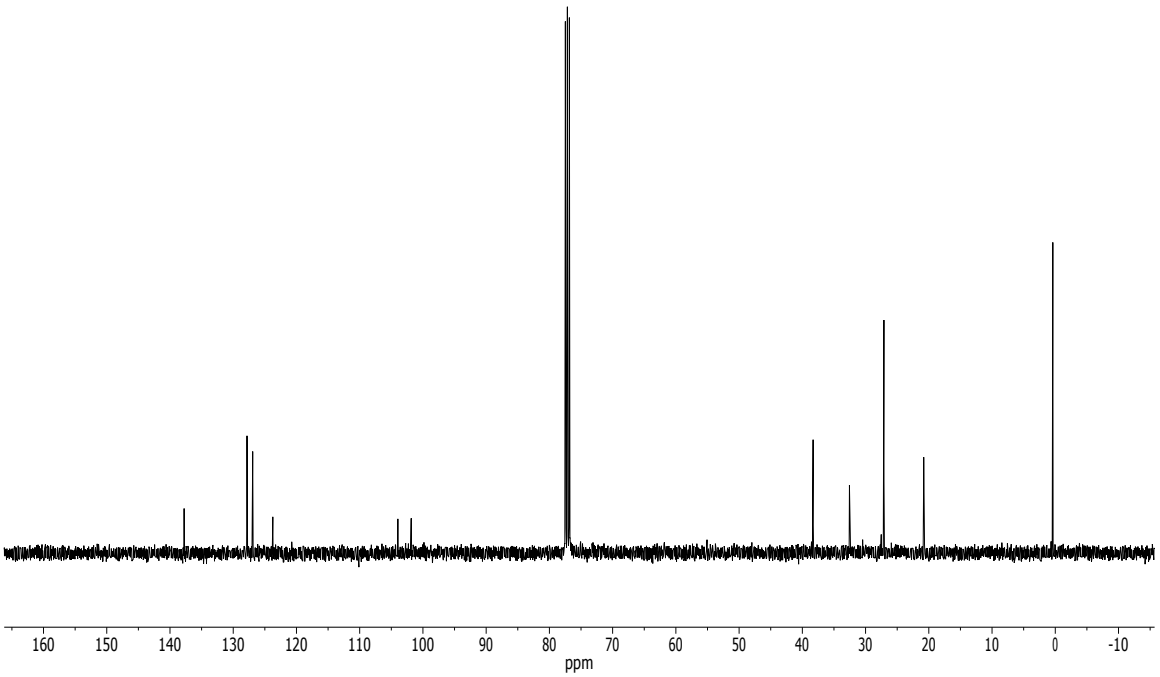


Trimethyl[(2,6,6-trimethylcyclohexa-1,3-dien-1-yl)ethynyl]silane 22.

^{1}H-NMR (400.13 MHz, $CDCl_3$)

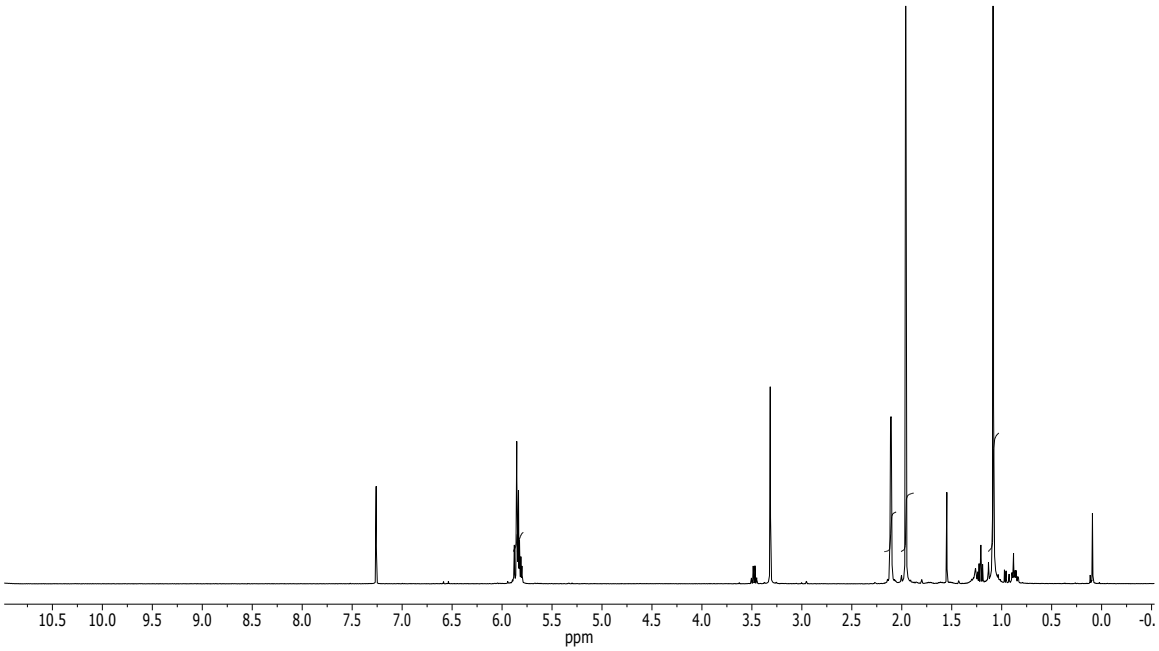


^{13}C NMR (100.62 MHz, $CDCl_3$)

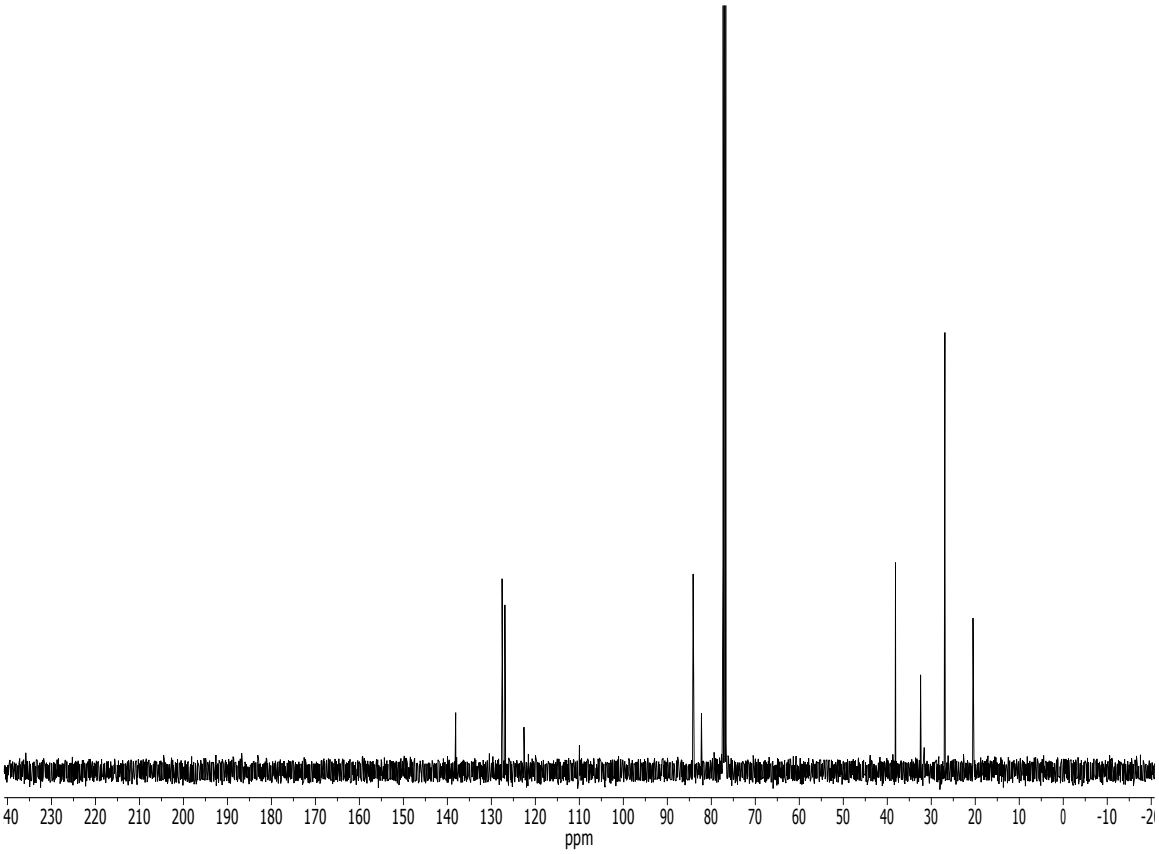


1-Ethynyl-2,6,6-trimethylcyclohexa-1,3-diene 23

^{1}H-NMR (400.13 MHz, $CDCl_3$)

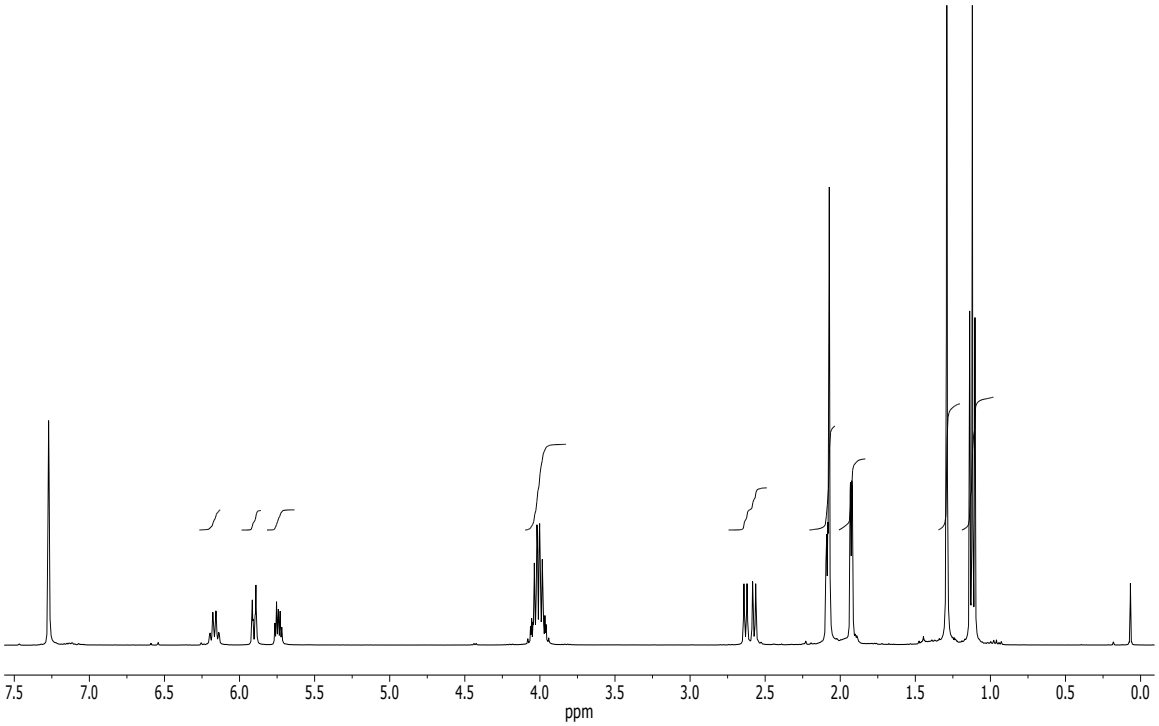


^{13}C NMR (100.62 MHz, $CDCl_3$)

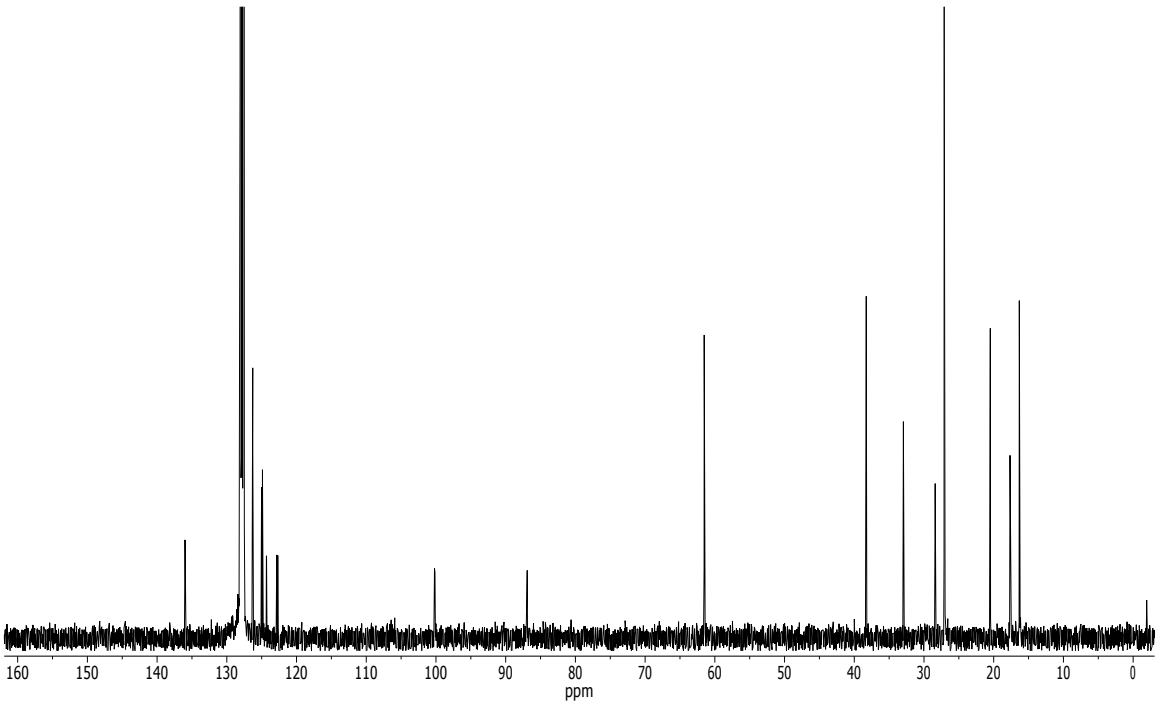


Diethyl (*E*)-[3-methyl-5-(2,6,6-trimethylcyclohexa-1,3-dien-1-yl]pent-2-en-4-yn-1-yl)phosphonate (C_{15}-alkynylphosphonate) 24

^{1}H NMR (400.13 MHz, C_6D_6)

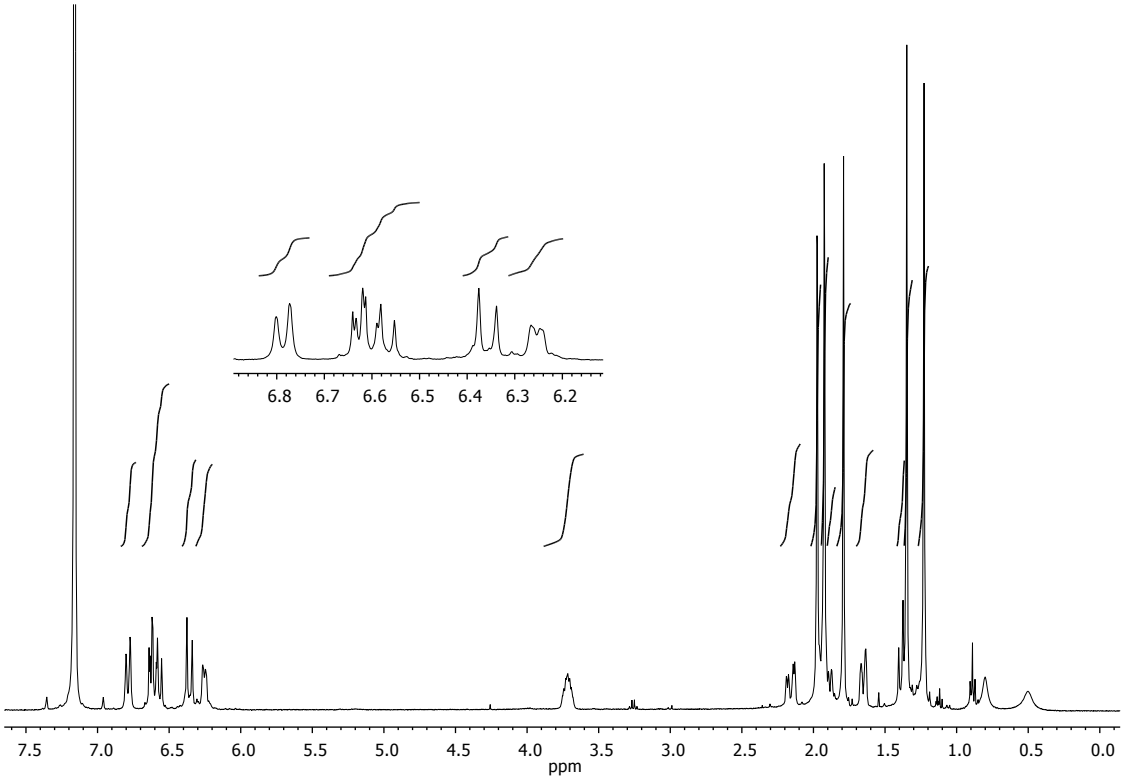


^{13}C NMR (100.62 MHz, C_6D_6)

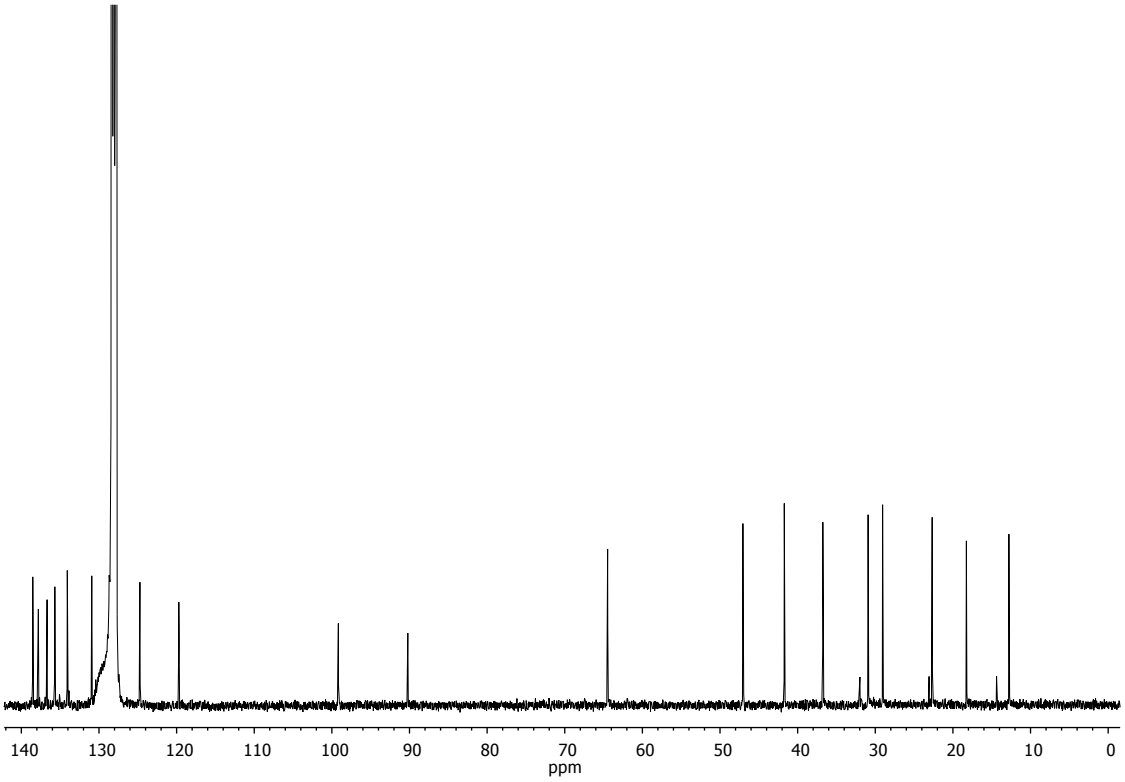


Alloxanthin 1

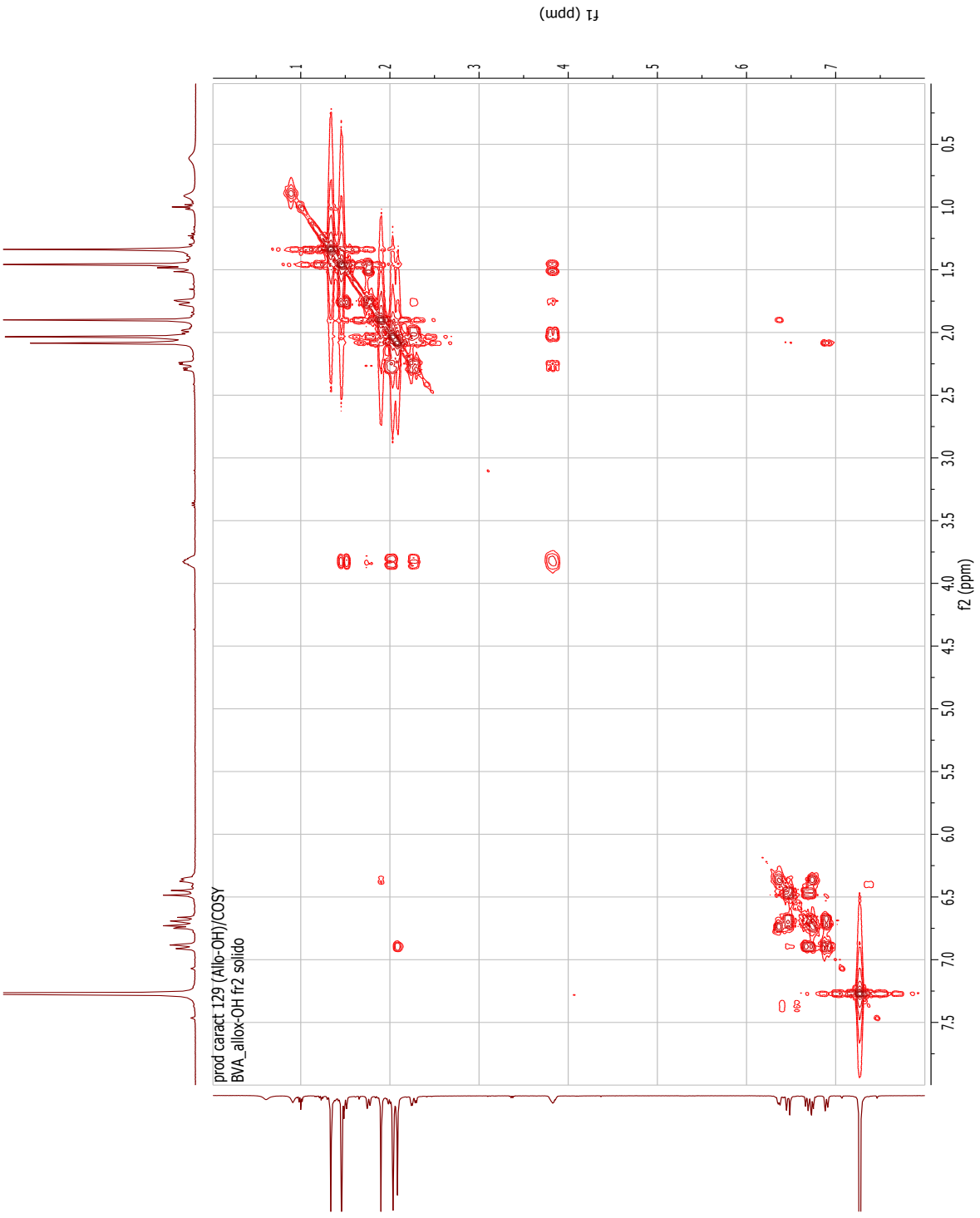
^{1}H-NMR (400.13 MHz, C_6D_6):



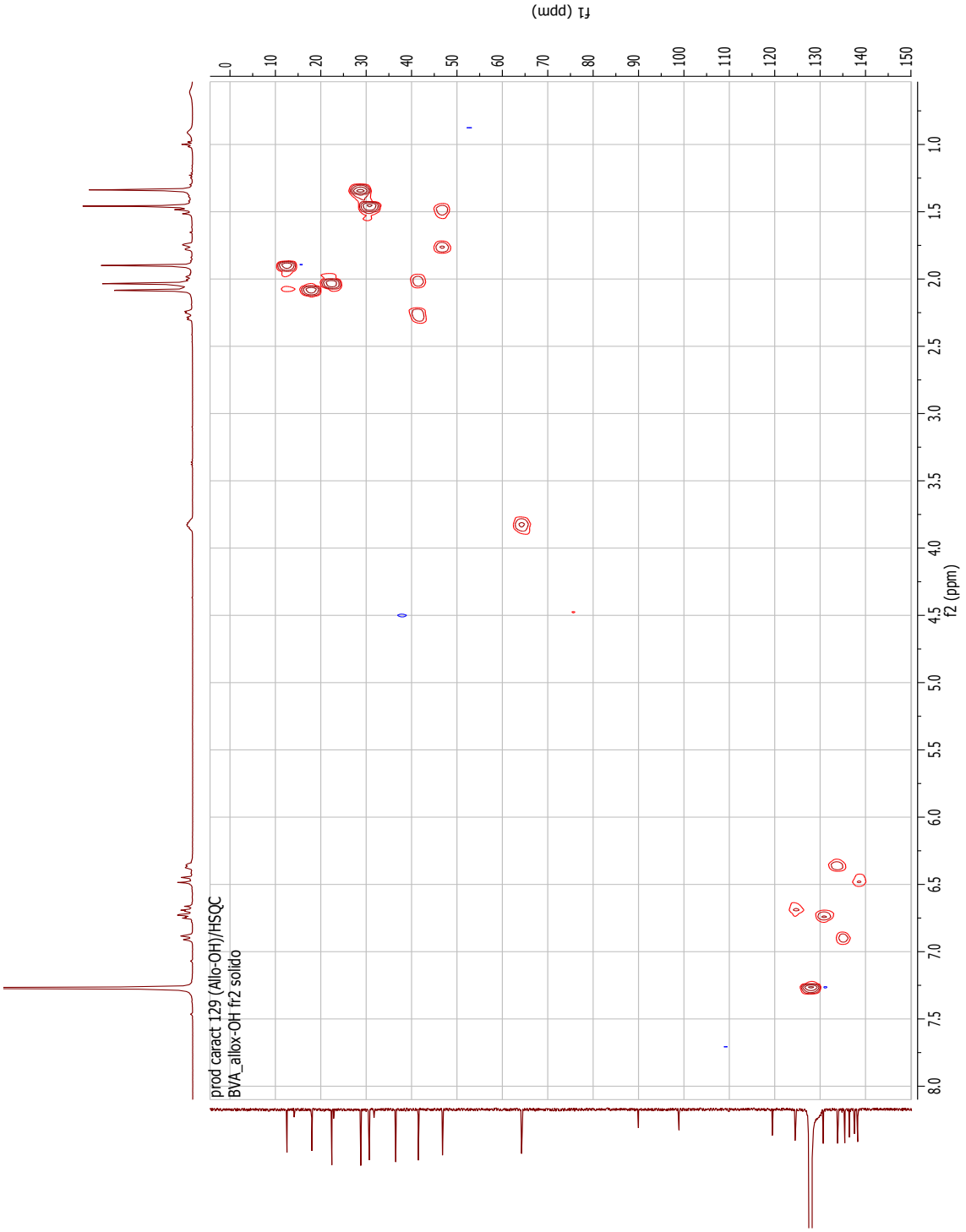
^{13}C-NMR (100.62 MHz, C_6D_6):



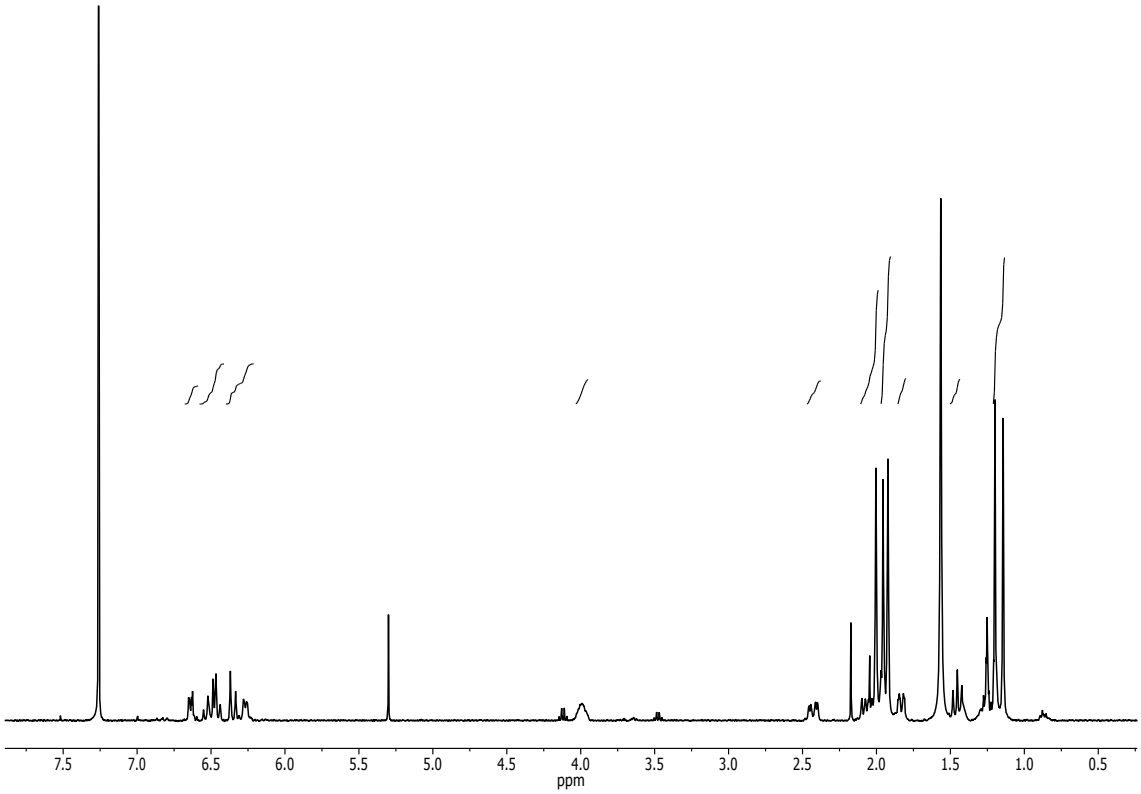
COSY (C_6D_6)


f1 (ppm)
f2 (ppm)
prod caract 129 (Allo-OH)/COSY
BVA_allox-OH fr2 solido

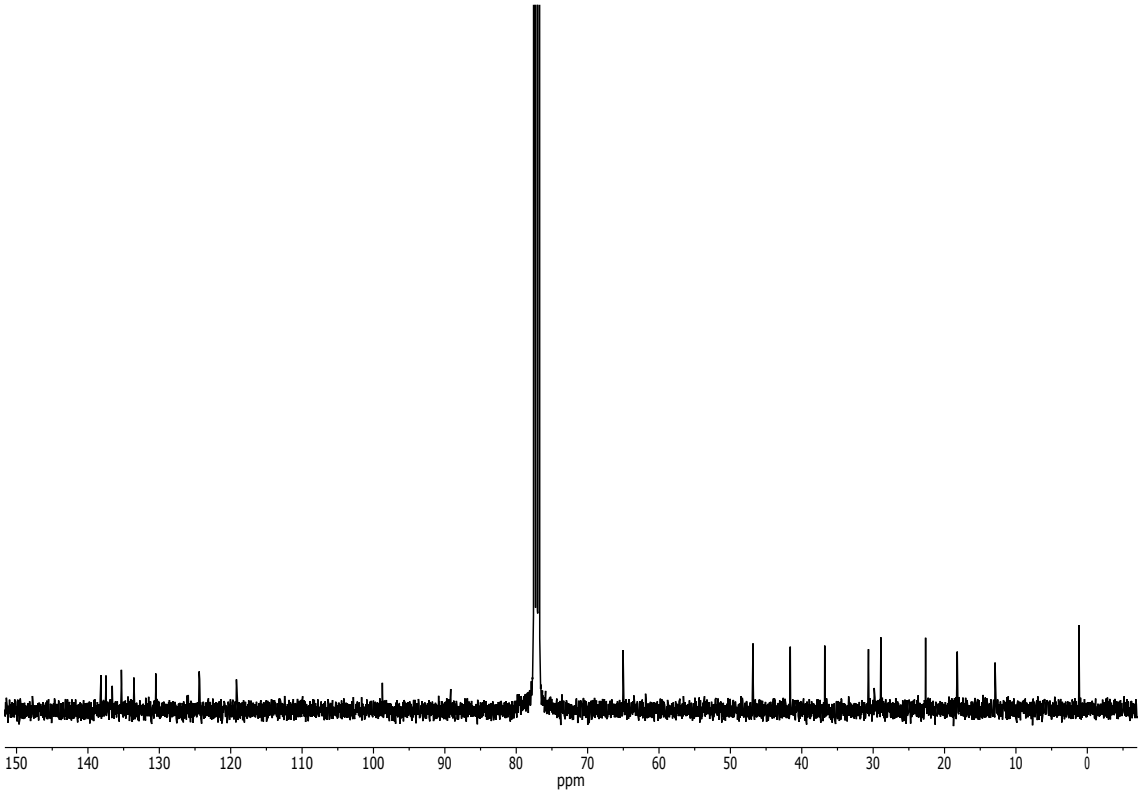
HSQC (C_6D_6)


f1 (ppm)
f2 (ppm)
prod caract 129 (Allo-OH)/HSQC
BVA_allox-OH fr2 solido

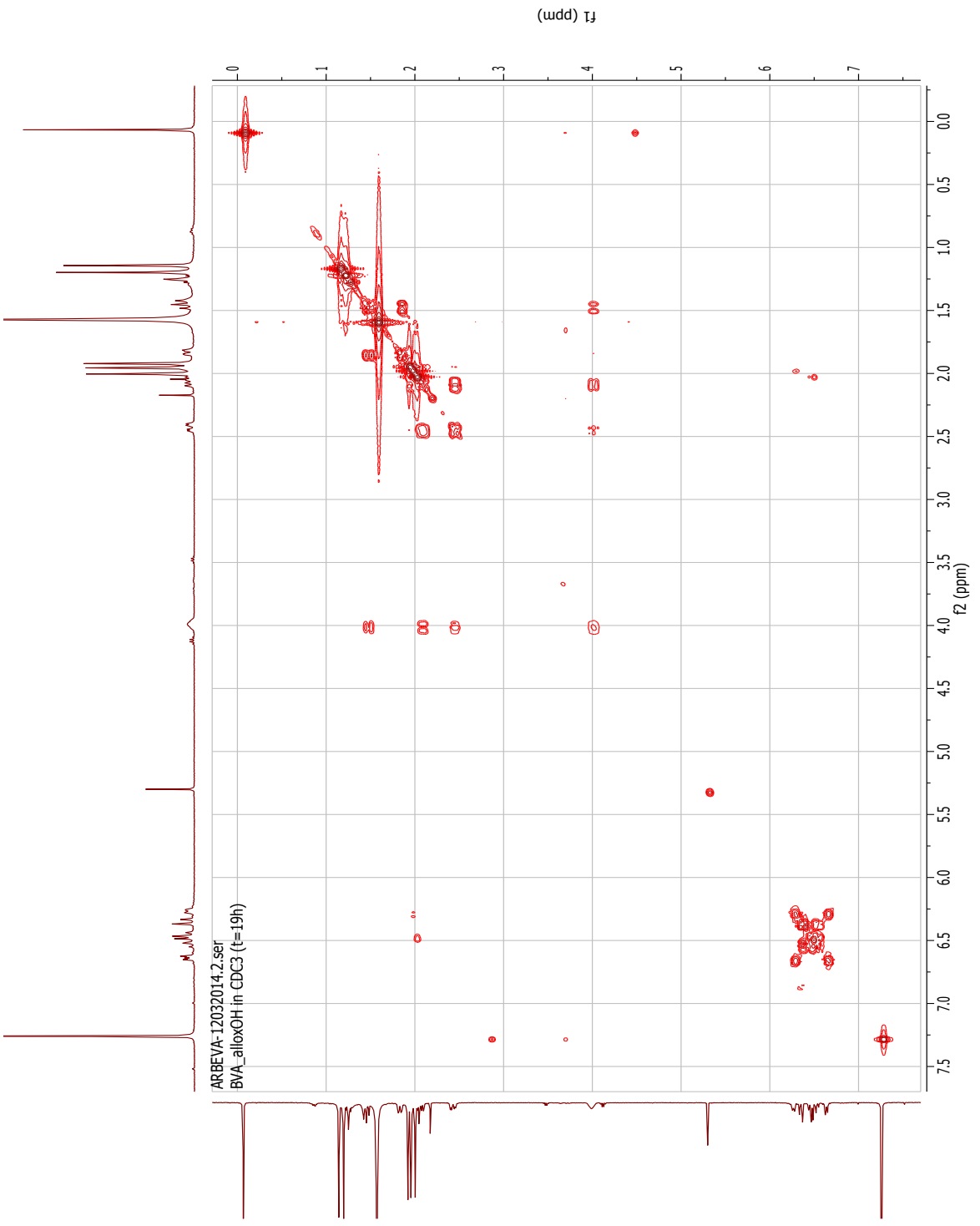
^{1}H-NMR (400.13 MHz, $CDCl_3$)



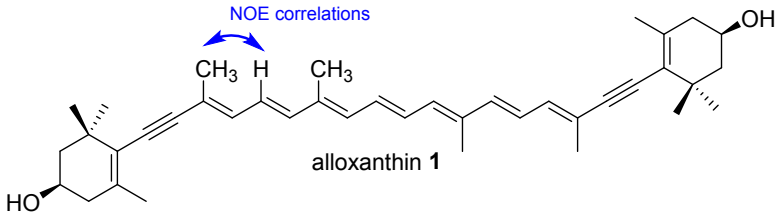
^{13}C-NMR (100.62 MHz, $CDCl_3$)

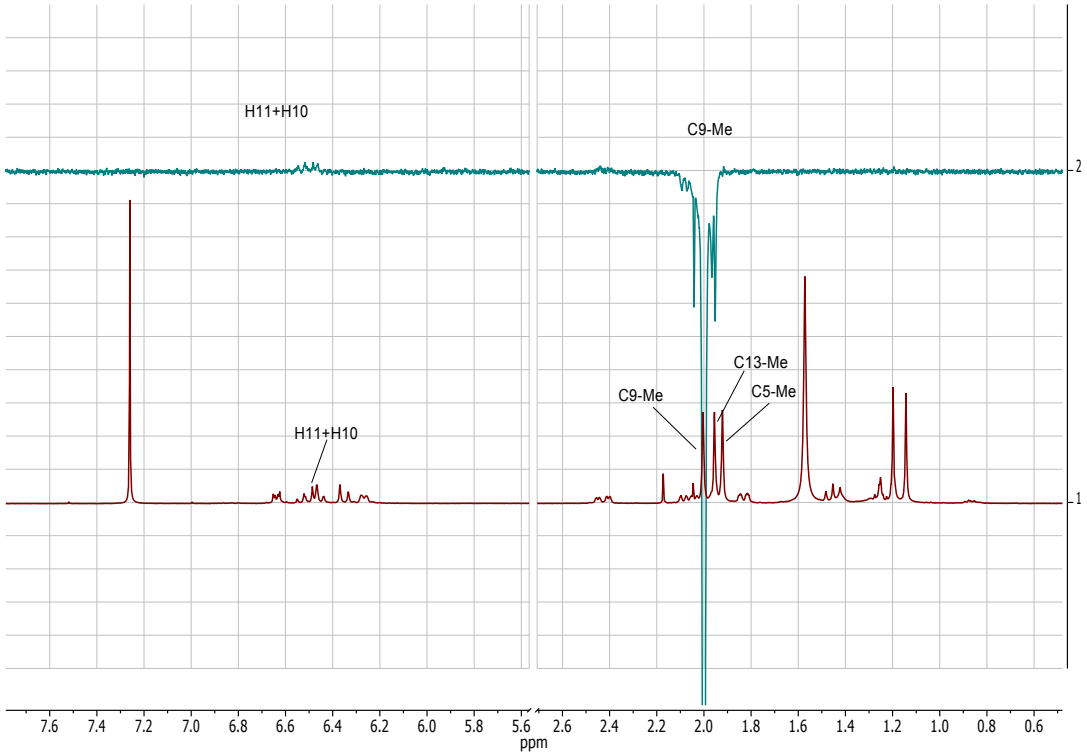


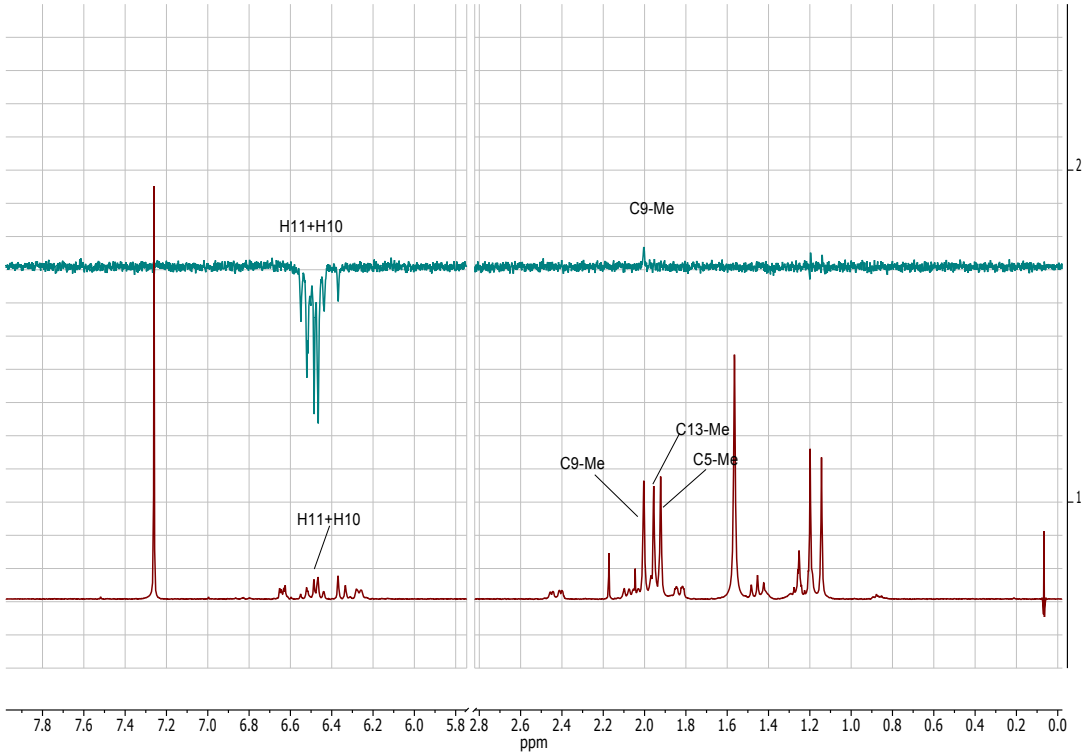
COSY-1d NMR ($CDCl_3$)



NOESY-1d NMR ($CDCl_3$)

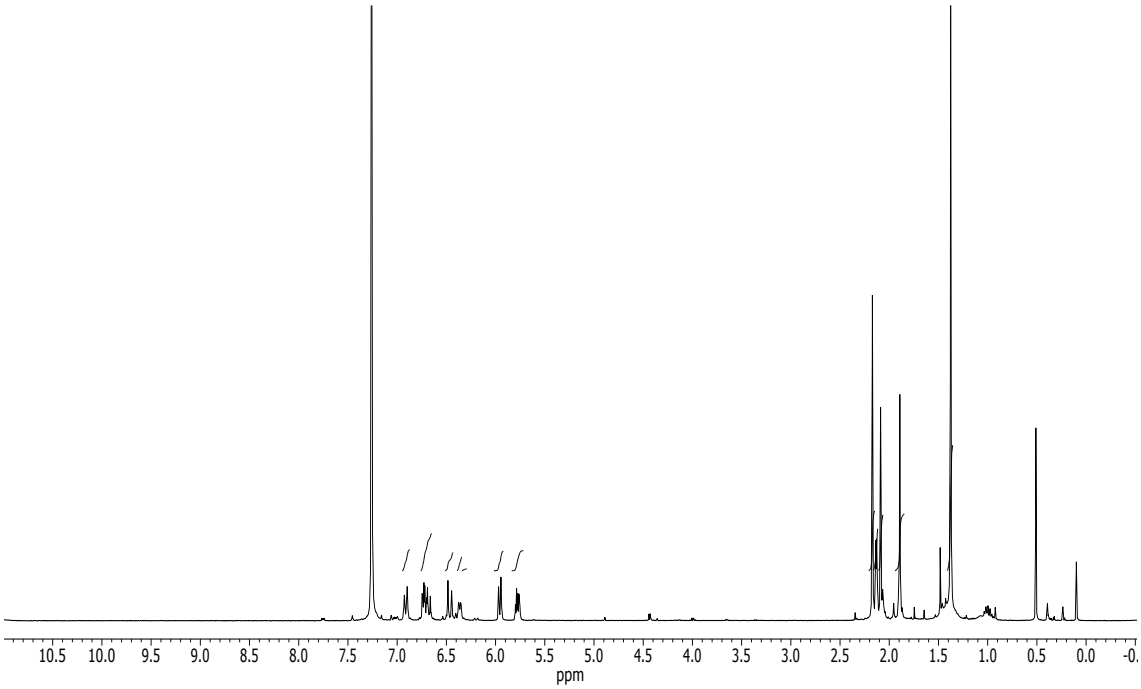




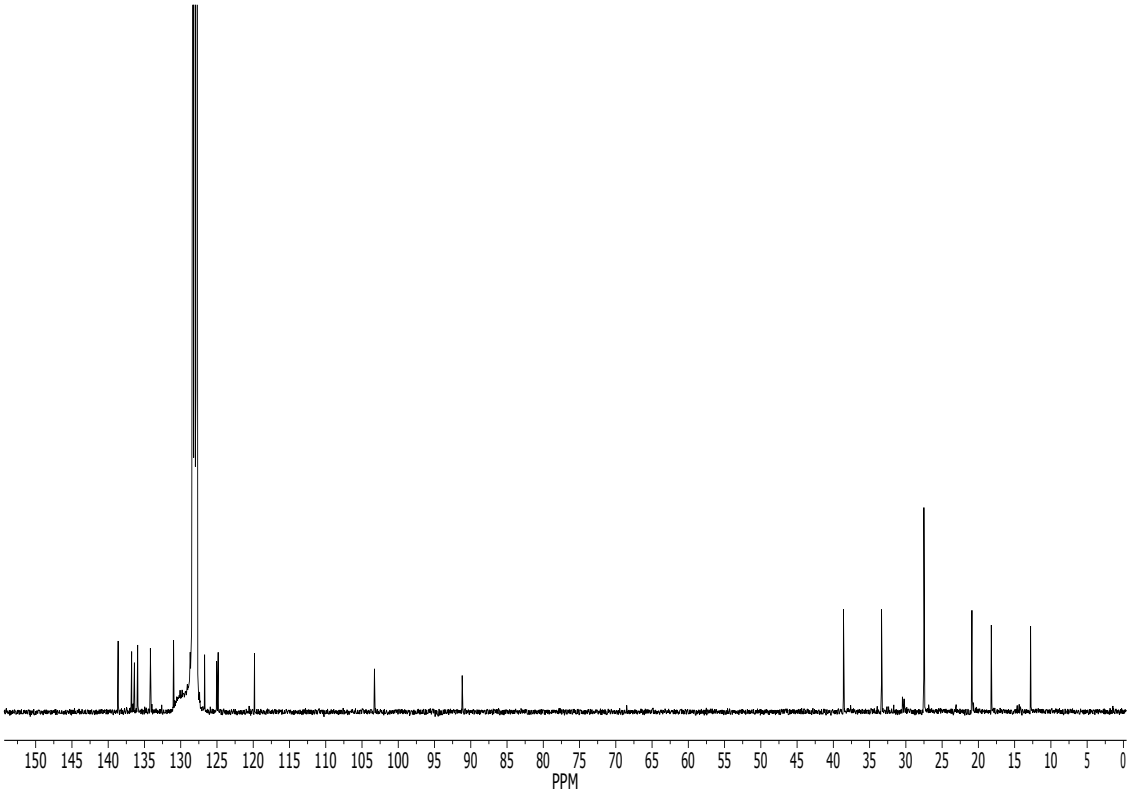


Octadehydro-β,β-carotene 2

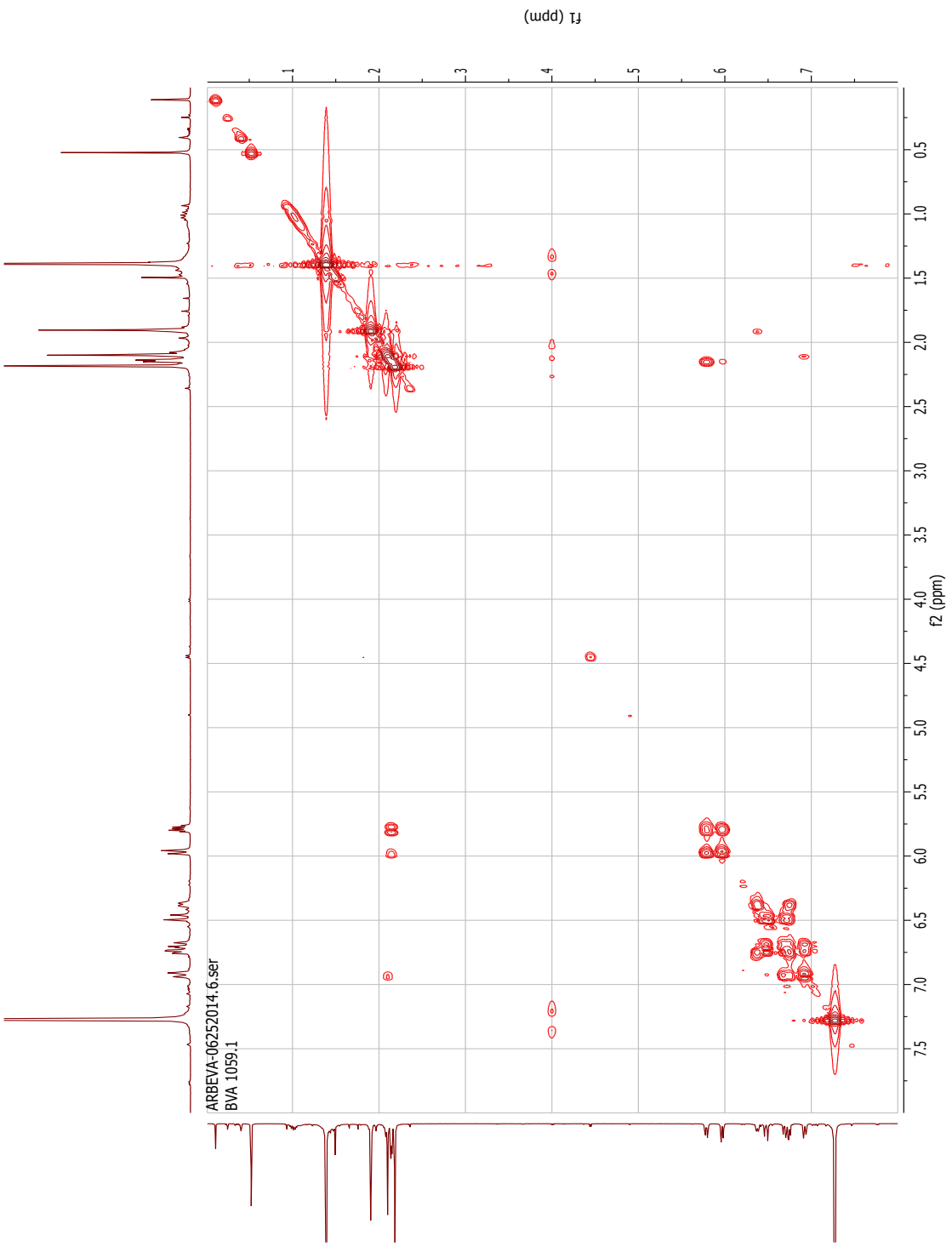
^{1}H-NMR (400.13 MHz, C_6D_6)



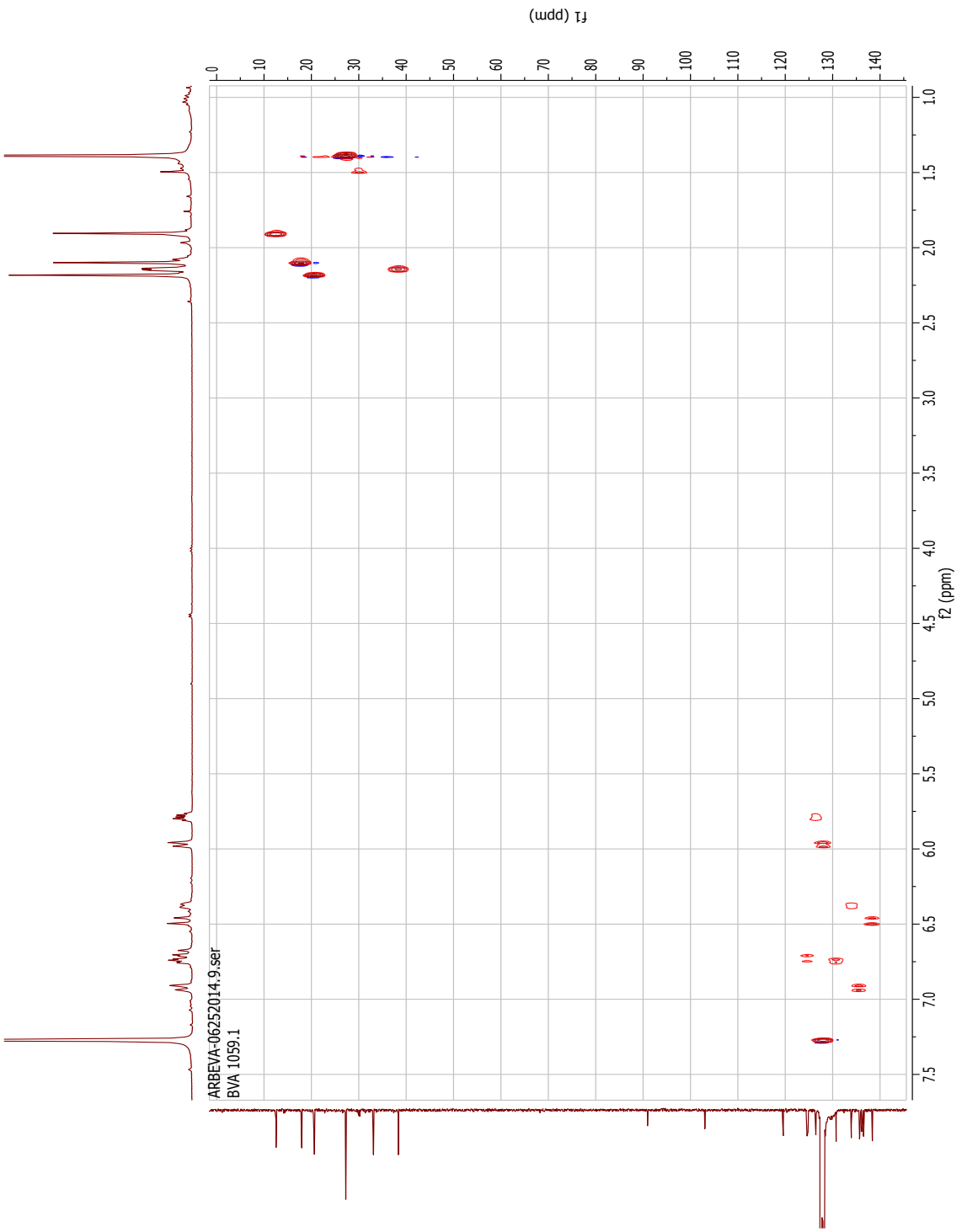
^{13}C NMR (100.62 MHz, C_6D_6)



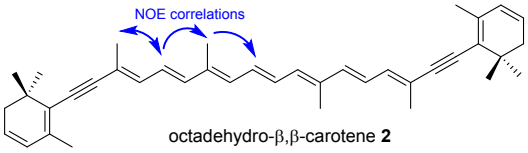
COSY (C_6D_6)



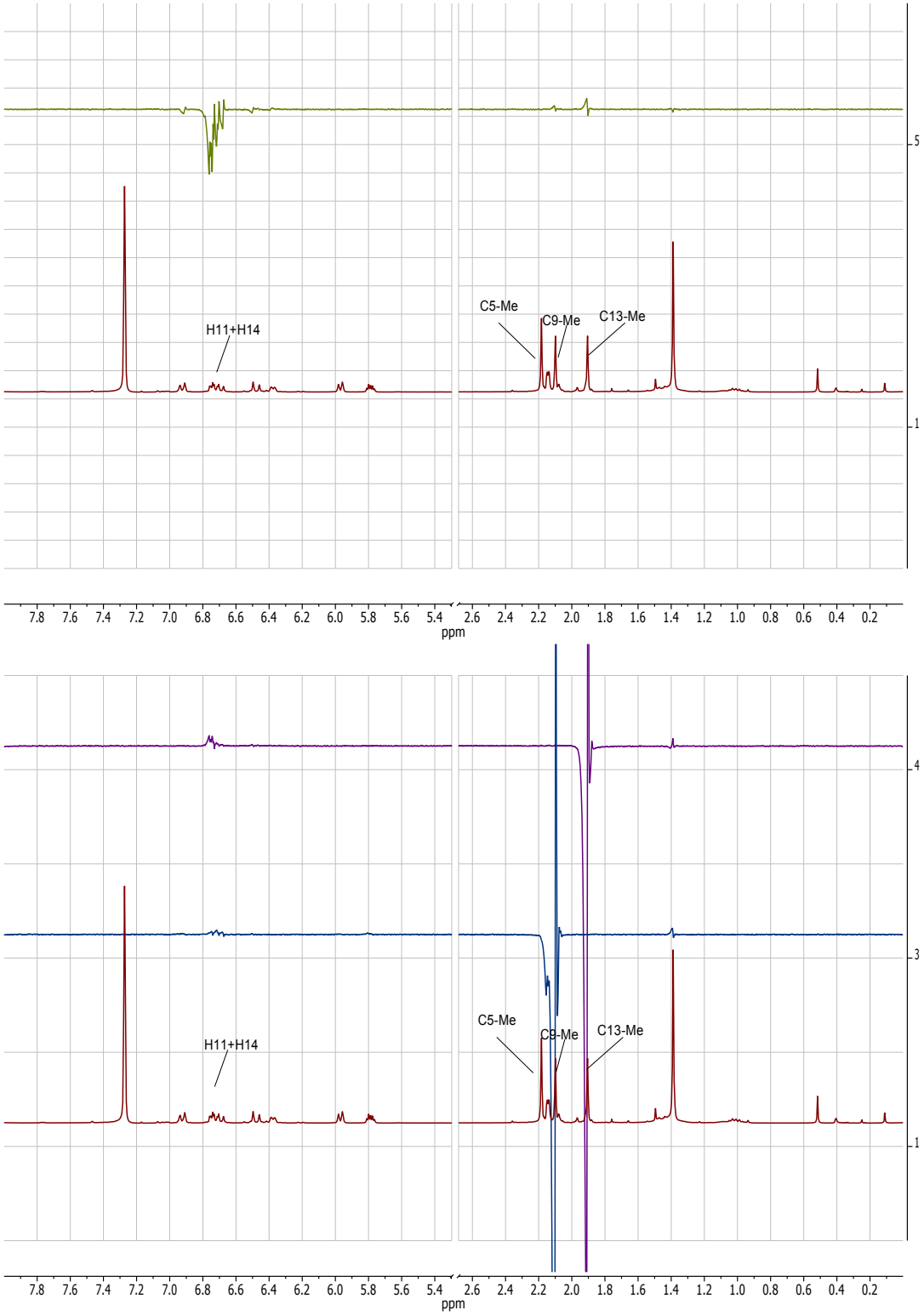
HSQC (C_6D_6)



NOESY-1d NMR (C_6D_6)

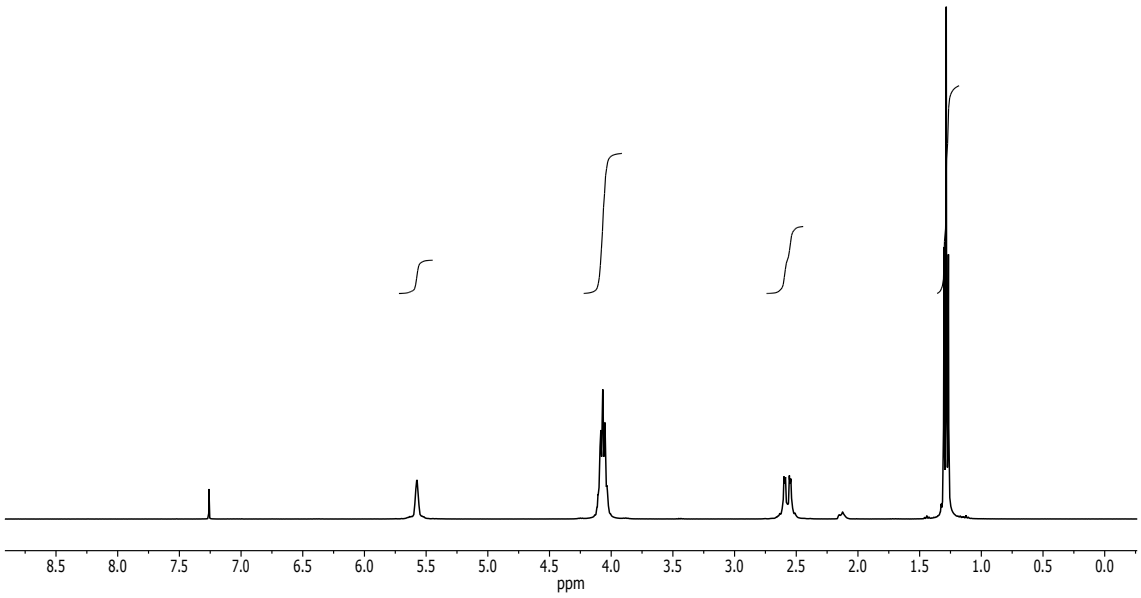


octadehydro-β,β-carotene **2**

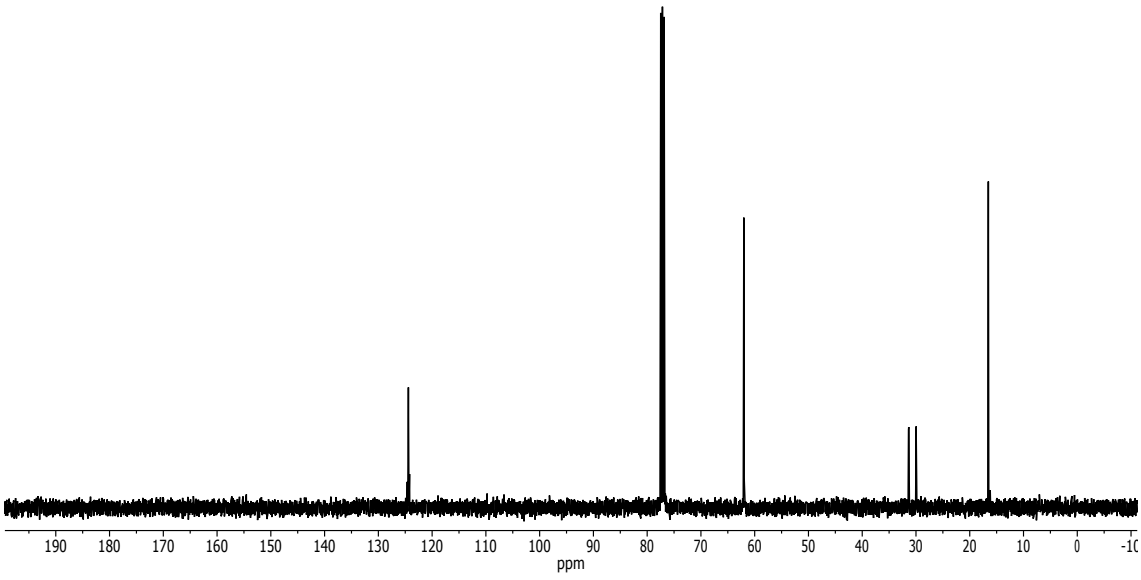


(*E*)-1,4-bis(triethoxy-λ^4-phosphanyl)but-2-ene 27.

^{1}H NMR (400.16 MHz, $CDCl_3$)

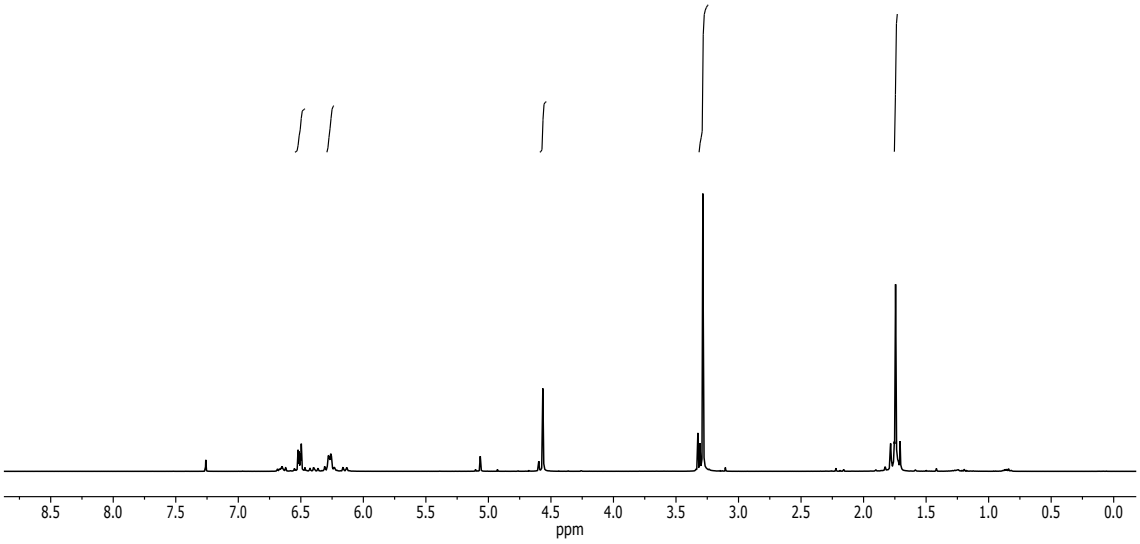


^{13}C NMR (101 MHz, $CDCl_3$)

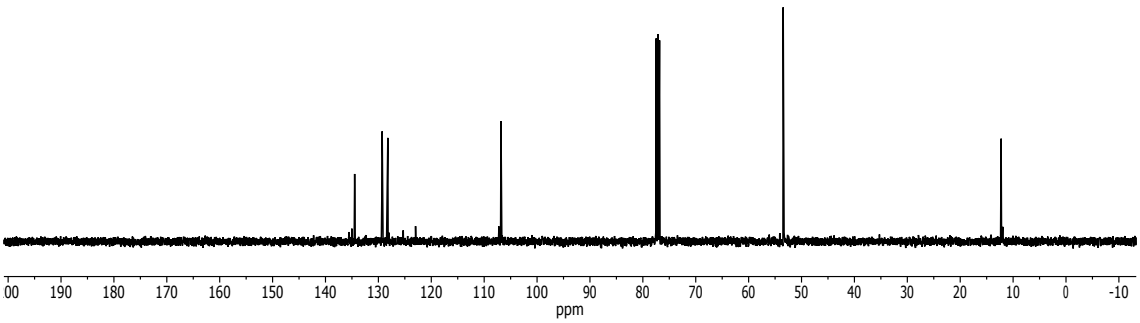


(2*E*,4*E*,6*E*)-1,1,8,8-tetramethoxy-2,7-dimethylocta-2,4,6-triene 28.

^{1}H NMR (400.16 MHz, $CDCl_3$)

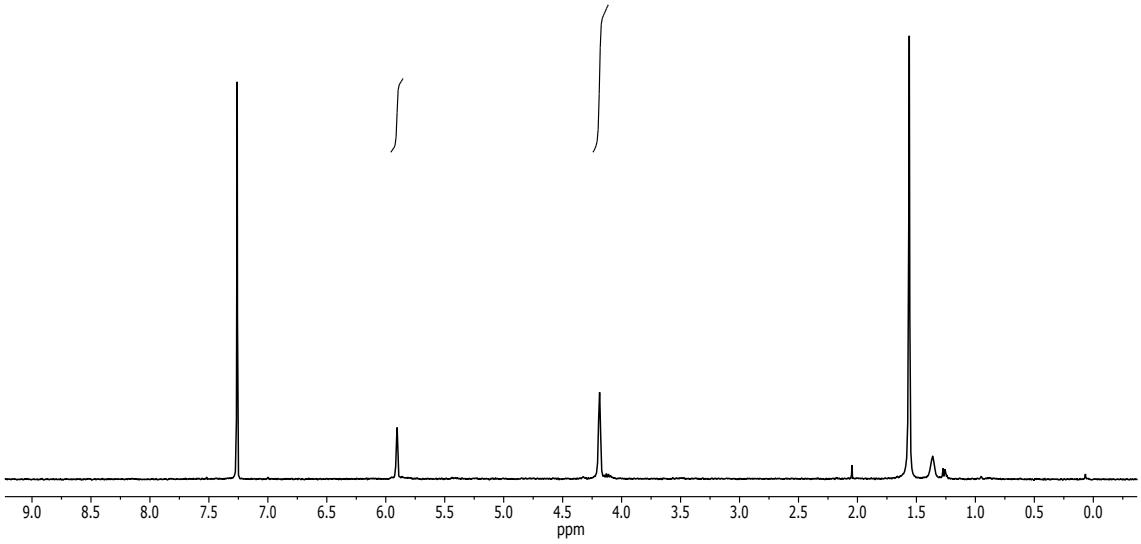


^{13}C NMR (101 MHz, $CDCl_3$)

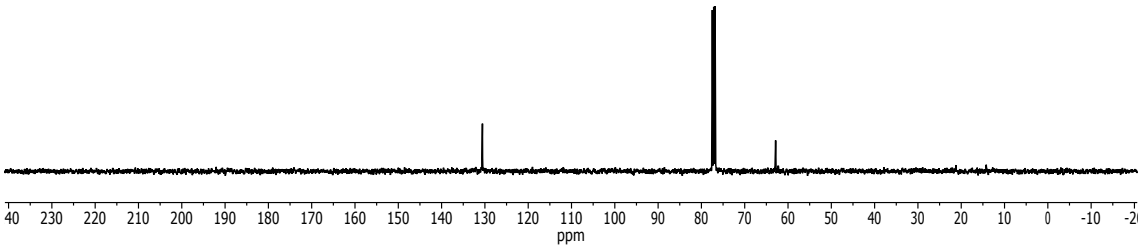


(*E*)-But-2-ene-1,4-diol 30.

^{1}H-NMR (400.13 MHz, $CDCl_3$)

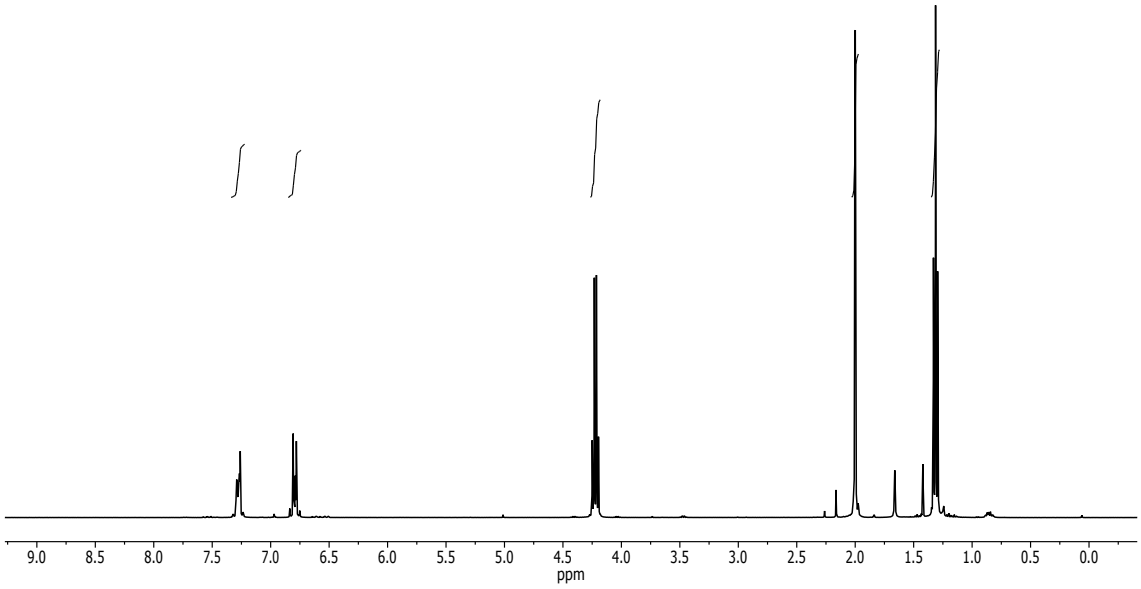


^{13}C NMR (101 MHz, $CDCl_3$)

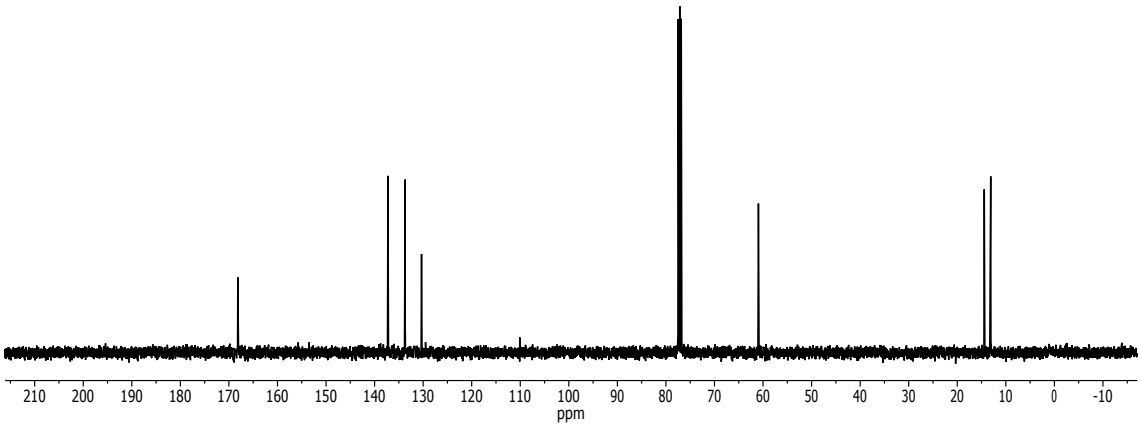


Diethyl (2*E*,4*E*,6*E*)-2,7-Dimethylocta-2,4,6-trienedioate 8e

^{1}H NMR (400.13 MHz, $CDCl_3$)



^{13}C NMR (101 MHz, $CDCl_3$)



References

[1] D. Federico, P. M. Donate, M. G. Constantino, E. S. Bronze, M. I. Sairre, *J. Org. Chem.* **2003**, *68*, 9126-9128.

[2] A. A. C. van Wijk and J. Lugtenburg, *Eur.J.Org. Chem.*, **2002**, 4217-4221

[3] Y. Yamano, M. V. Chary and A. Wada, *Org. Biomol. Chem.*, **2012**, *10*, 4103

[4] M. Domínguez, R. Alvarez, S. Martras, J. Farrés, X. Parés and A. R. de Lera, *Org. Biomol. Chem.*, **2004**, *2*, 3368-3373.

[5] E.-M. Azim, P. Auzeloux, J.-C. Maurizis, V. Braesco, P. Grolier, A. Veyre and J.-C. Madelmont, *J. Labelled Compd. Radiopharm.*, **1996**, *38*, 441-451.

[6] M. Zapata, F. Rodríguez, J. L. Garrido, *Mar. Ecol. Prog. Ser.* **2000**, *195*, 29-45.