Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry

First Total Synthesis of (+)-Apotrisporin E and (+)-Apotrientriols A-B: A Cyclization Approach to Apocarotenoids

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Supporting Information

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General Experimental section:

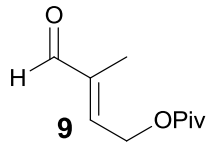
All NMR spectra (δ values, ppm) were recorded with a Varian Direct-Drive 600 (^{1}H 500 MHz/^{13}C 150 MHz), Varian Direct-Drive 500 (^{1}H 500 MHz/^{13}C 125 MHz), Varian Direct-Drive 400 (^{1}H 400 MHz/^{13}C 100 MHz) and Varian Inova Unity 300 (^{1}H 300 MHz/^{13}C 75 MHz) spectrometers. Tetramethylsilane (TMS) was used as an external reference for recording ^{1}H (of residual proton; δ = 7.26 ppm) and ^{13}C (δ = 77.0 ppm) spectra in $CDCl_3$. Chemical shift multiplicities are reported as s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and br = broad. The accurate mass determination was carried out with a mass spectometer equipped with a TOF, system Triwave® *WATERS* model *SYNAP G2* and an AutoSpec-Q mass spectrometer arranged in an EBE geometry (Micromass Instrument, Manchester, UK) and equipped with a FAB (LSIMS) source. The instrument was operated at 8 KV of accelerating voltage and Cs^{+} were used as primary ions. Optical rotations were measured on a Perkin-Elmer 141 polarimeter, using CH_2Cl_2 as the solvent. Reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as the visualizing agent and a solution of phosphomolybdic acid in ethanol and heat as developing agent. Silica gel SDS 60 (35-70 mm) was used for flash column chromatography. HPLC with UV and RI detection was used. Semi-preparative HPLC separations were carried out on a column (5 μm Silica, 10 x 250 mm) at a flow rate of 2.0 mL/min in an Agilent Series 1100 instrument. All air- and water-sensitive reactions were performed in flaks flame-dried under a positive flow of argon and conducted under an argon atmosphere. The solvents used were purified according to standard literature techniques and stored under argon. THF and toluene were freshly distilled immediately prior to use from sodium/benzophenone and strictly deoxygenated for 30 min under argon for each of the Cp_2TiCl_2/Mn or Zn reactions. Reagents were purchased at the higher commercial quality and used without further purification, unless otherwise stated.

Experimental Procedures

Strains and culture conditions: Strains of *Phycomyces blakesleeanus* Bgff: Strain NRRL1555, sexually (–), is the standard wild-type; Strain NRRL1554, (+) is a different natural isolate. Strain A56 is a (+) wild type derived from ten successive backcrosses into NRRL1555, and therefore largely consanguineous with this strain.[1] Standard culture media and handling were used.[2] Plates containing 25.0 mL minimal agar were inoculated with 10^4 heat-activated spores each and incubated in the dark at 22 ºC for five days. Growth on the same agar enriched with yeast extract (1.0 g/L) did not sensibly modify the results. Mated cultures were incubated with 5 x 10^3 spores of each sex.[3]

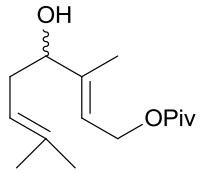
Extraction and isolation of natural compounds: For extraction and isolation of natural (+)-apotrisporin E and natural (+)-apotrientriols A-B see our previous works.[4] Starting from an extract (1.0 L) of mated cultures A56 × NRRL1555 (80 minimal agar plates) yielded 302 mg dry neutral and 258 mg dry acid extract. The neutral extract was fractionated by semi-preparative HPLC. (+)-Apotrisporin E was present in the fraction $21.9 < t_R < 23.5$ min (5.5 mg). $[\alpha]_D^{20}$ +7.8 (c 0.1, CH_2Cl_2). (+)-Apotrientriol A was present in the fraction $24.9 < t_R < 26.7$ min (3.4 mg). $[\alpha]_D^{20}$ = +5.9 (c 0.12, CH_2Cl_2) and (+)-apotrientriols A-B in the fraction $26.7 < t_R < 29.3$ min (7.8 mg). $[\alpha]_D^{20}$ = +4.3 (c 0.35, CH_2Cl_2)

[1] M. I. Alvarez and A. P. Eslava, *Genetics*, 1983, **105**, 873–879.
[2] E. Cerdá-Olmedo, in *Phycomyces*, ed. E. Cerdá-Olmedo and E. D. Lipson, Cold Spring Harbor Laboratory: Cold Spring Harbor, New York, USA, 1987, pp 337–339.
[3] E. Cerdá-Olmedo and A. Hüttermann, *Angew. Botan*., 1986, **60**, 59–70.
[4] (*a*) S. Polaino, M. M. Herrador, E. Cerdá-Olmedo and A. F. Barrero, *Org. Biomol. Chem*., 2010, **8**, 4229–4231; (*b*) S. Polaino, J. A. González-Delgado, P. Arteaga, M. M. Herrador, A. F. Barrero and E. Cerdá-Olmedo, *Org. Biomol. Chem*., 2012, **10**, 3002–3009.



9

(*E*)-3-methyl-4-oxobut-2-en-1-yl pivalate (9): A mixture of SeO_2 (1080 mg, 9.70 mmol), *t*-BuOOH (5.0–6.0 M in decane, 3.6 mL) and CH_2Cl_2 (21 mL) was stirred at 0 ºC for 7 hours, then prenyl pivalate[5] (5000 mg, 29.37 mmol) was added and the complete mixture stirred at the same temperature (TLC monitoring). The reaction was quenched by addition of CH_2Cl_2, washed with H_2O, dried over anhyd Na_2SO_4 and concd under reduced pressure. The resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 90:10) on silica gel to yield 61% of aldehyde **9** as a colorless oil.[6] TLC (hexane/*t*-BuOMe, 70:30) R_f: 0.18; ^{1}H NMR: δ_H (500 MHz; $CDCl_3$; Me_4Si) 5.48 (t, 1H, *J* = 5.5 Hz), 4.51 (d, 2H, *J* = 6.8 Hz), 3.90 (s, 2H), 1.60 (s, 3H), 1.08 (s, 9H); ^{13}C NMR: δ_C (125 MHz; $CDCl_3$; Me_4Si) 178.7, 140.5, 118.7, 67.3, 61.0, 38.8, 27.2 (3C), 13.8 ppm.

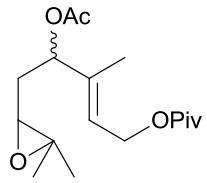


11

(*E*)-4-hydroxy-3,7-dimethylocta-2,6-dien-1-yl pivalate (11): *Method A*: To a –78 ºC solution of aldehyde **9** (3300 mg, 17.92 mmol) and prenyl stannane **10b** (12.8 mL, 38.2 mmol) in CH_2Cl_2 (150 mL) was added, rapidly, BCl_3 (1.0 M in CH_2Cl_2, 1.58 mL).[7] After 10 minutes, the reaction was poured into saturated aq $NaHCO_3$ and extracted with CH_2Cl_2. The combined organics layers were washed with saturated aq KF, dried over Na_2SO_4, filtered, concd and

[5] B. M. Smith, E. J. Skellam, S. J. Oxley and A. E. Graham, *Org. Biomol. Chem*., 2007, **5**, 1979–1982.
[6] A. F. Barrero, J. F. Quílez del Moral, M. M. Herrador, E. M. Sánchez and J. F. Arteaga, *J. Mex. Chem. Soc.*, 2006, **50**, 149–156.
[7] E. Schöttner, K. Simon, M. Friedel, P. G. Jones and T. Lindel, *Tetrahedron Lett*., 2008, **49**, 5580–5582.

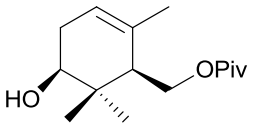
purified by silica gel column chromatography (hexane/*t*-BuOMe, 80:20) to yield 24% of α,α' product (790 mg, 4.30 mmol). *Method B*: A mixture of Cp_2TiCl_2 (1227 mg, 4.53 mmol) and Mn dust (865 mg, 15.75 mmol) in strictly deoxygenated THF (45 mL) was stirred at rt until the red solution turned green. Then, a solution of the aldehyde **9** (363 mg, 1.97 mmol) and prenyl bromide **10a** (0.45 mL, 3.94 mmol) in strictly deoxygenated THF (50 mL) was added to the solution of Cp_2TiCl. The reaction mixture was stirred until consumption of the starting material (20 min). The mixture was diluted with *t*-BuOMe, filtered through a Buchner, and washed with 2.0 N HCl and brine, and the resultant organic phase was dried over anhyd Na_2SO_4 and concd under reduced pressure. The resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 80:20) on silica gel to afford 180 mg (0.71 mmol, 36% overall yield) of **11** as a colorless oil. TLC (hexane/*t*-BuOMe, 70:30) R_f: 0.25; ^{1}H NMR: δ_H (500 MHz; $CDCl_3$; Me_4Si) 5.57 (t, 1H, *J* = 6.7 Hz), 5.08 (t, 1H, *J* = 8.9 Hz), 4.61 (d, 1H, *J* = 6.5 Hz), 4.02 (t, 2H, *J* = 6.5 Hz), 2.26 (t, 2H, *J* = 6.6 Hz), 1.72 (s, 3H), 1.70 (s, 3H), 1.19 (s, 9H); ^{13}C NMR: δ_C (125 MHz; $CDCl_3$; Me_4Si) 178.6, 142.4, 135.9, 119.9, 119.7, 76.3, 61.1, 38.9, 34.2, 27.3 (3C), 26.0, 18.1, 12.5 ppm; HRFABMS: calcd. for $C_{15}H_{26}O_3Na$ $[M+Na]^+$ 277.1780, found: 277.1783.



7

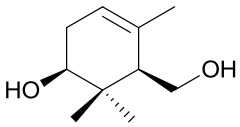
(***E*)-4-acetoxy-5-(3,3-dimethyloxiran-2-yl)-3-methylpent-2-en-1-yl pivalate (7):** 3–Chloroperoxybenzoic acid (802 mg, 4.66 mmol) in anhyd CH_2Cl_2 (7 mL) was added to a solution of acetylated derivate of **11** (1000 mg, 3.38 mmol) in anhyd CH_2Cl_2 (6 mL) under an argon atmosphere at 0 ºC, and the mixture was stirred for 3 hours. Then, CH_2Cl_2 (25 mL) was added and was successively washed with saturated aq $NaHCO_3$ solution and brine, dried with anhyd Na_2SO_4, filtered, and evaporated to give a crude residue which yielded 855 mg (2.74

mmol, 59% yield) of **7** after chromatography (hexane/*t*-BuOMe, 60:40) as a colorless oil. TLC (hexane/*t*-BuOMe, 50:50) R_f: 0.53; ^{1}H NMR: δ_H (400 MHz; $CDCl_3$; Me_4Si) 5.63 (t, 1H, *J* = 6.3 Hz), 5.33 (m, 1H), 4.61 (d, 2H, *J* = 6.3 Hz), 2.72 (dt, 1H, *J* = 10.4, 6.2 Hz), 2.07 (s, 3H), 1.88 (t, 2H, *J* = 6.8 Hz), 1.73 (s, 3H), 1.29 (s, 3H), 1.26 (s, 3H), 1.19 (s, 9H); ^{13}C NMR: δ_C (100 MHz; $CDCl_3$; Me_4Si) 178.5, 170.1, 138.3, 122.3, 75.9, 60.9, 60.7, 58.1, 38.9, 32.8, 27.3 (3C), 24.8, 21.3, 19.1, 13.0 ppm; TOFESMS: calcd. for $C_{17}H_{29}O_5$ $[M+H]^+$ 313.2015, found: 313.2008.



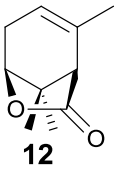
6b

((1*R*,5*S*)-5-hydroxy-2,6,6-trimethylcyclohex-2-en-1-yl)methyl pivalate (6b): Strictly deoxygenated THF (7.0 mL) was added to a mixture of Cp_2TiCl_2 (1920 mg, 7.69 mmol) and Mn dust (1130 mg, 20.50 mmol) under an Ar atmosphere and the suspension was stirred at rt until it turned green. Then, a solution of epoxide (800 mg, 2.56 mmol) in THF (7.0 mL) was added and the solution was stirred for 6 hours at 40 ºC. The reaction was then quenched with saturated aq $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4 and the solvent was removed. Product was purified by flash chromatography on silica gel (hexane/*t*-BuOMe, 65:35) to yield 436 mg (1.72 mmol, 67% yield) of monocycle **6b** as a colorless solid. TLC (hexane/*t*-BuOMe, 50:50) R_f: 0.43; $[\alpha]_D^{20}$ +23.1 (c 1.40, CH_2Cl_2); ^{1}H NMR: δ_H (500 MHz; $CDCl_3$; Me_4Si) 5.39 (br t, 1H), 4.46 (dd, 1H, *J* = 4.4 Hz), 4.11 (dd, 1H, *J* = 3.9 Hz), 3.46 (t, 1H, *J* = 6.3 Hz), 2.31 (m, 1H), 2.07 (m, 1H), 2.00 (br t, 1H), 1.70 (s, 3H), 1.55 (br s, 1H), 1.19 (s, 9H), 1.03 (s, 3H), 0.95 (s, 3H); ^{13}C NMR: δ_C (125 MHz; $CDCl_3$; Me_4Si) 178.5, 132.9, 120.5, 73.9, 63.2, 48.6, 38.9, 37.3, 31.9, 27.3 (3C), 26.5, 22.3, 18.9 ppm; HRFABMS: calcd. for $C_{15}H_{26}O_3Na$ $[M+Na]^+$ 277.1780, found: 277.1783.



6

(1*S*,5*R*)-5-(Hydroxymethyl)-4,6,6-trimethylcyclohex-3-enol (6): Solid $ZrCl_4$ (4920 mg, 21.15 mmol) was added to a solution of (*S*)-epoxygeraniol (**8**)[8] (1200 mg, 7.05 mmol) in freshly distilled CH_2Cl_2 (1000 mL) at rt. The resulting whitish suspension was stirred for 10 min, then 1.0 M HCl (150 mL) was added and the two layers were separated. The aq layer was extracted with CH_2Cl_2 (3 x 150 mL) and the combined organic layers were washed with saturated aq $NaHCO_3$ and brine, dried over Na_2SO_4, and concd under reduced pressure. The residue was purified by silica gel flash chromatography (hexane/*t*-BuOMe, 40:60) to yield 706 mg of **6** (4.16 mmol, 59% yield) as a colorless solid.[14b] TLC (*t*-BuOMe) R_f: 0.4; $[\alpha]_D^{20}$ +54.1 (c 1.63, CH_2Cl_2), lit. $[\alpha]_D^{20}$ +57.8 (c 2.00, CH_2Cl_2);[9] ^{1}H NMR: δ_H (400 MHz; $CDCl_3$; Me_4Si) 5.42 (bs, 1H), 4.65 (bs, 2H), 3.72 (s, 2H), 3.35 (d, 2H, J = 4.5 Hz), 2.34 (br dt, 1H, J = 2.3, 18.6 Hz), 2.10 (br dd, 1H, J = 18.5 Hz), 1.73 (s, 3H), 1.08 (s, 3H), 0.92 (s, 3H); ^{13}C NMR: δ_C (100 MHz; $CDCl_3$; Me_4Si) 131.6, 120.4, 71.3, 58.7, 51.1, 37.1, 32.2, 28.6, 24.4, 22.6 ppm; TOFESMS: calcd. for $C_{10}H_{19}O_2$ $[M+H]^+$ 171.1307, found: 171.1310.

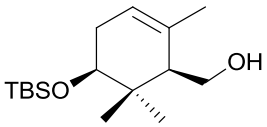


12

(1*R*,5*S*)-2,8,8-trimethyl-6-oxabicyclo[3.2.1]oct-2-en-7-one (12): A solution of diol **6** (170 mg, 1.00 mmol), TEMPO (15.6 mg, 0.10 mmol) and TBACl (27.7 mg, 0.10 mmol) in 10 mL of CH_2Cl_2 and 10 mL of an aq solution of $NaHCO_3$ (0.5 M) and K_2CO_3 (0.05 M) were vigorously stirred at rt. Solid *N*-Chlorosuccinimide (200 mg, 1.50 mmol) was then added. Stirring was

[8] M. Bovolenta, F. Castronovo, A. Vadalá, G. Zanoni and G. Vidari, *J. Org. Chem*., 2004, **69**, 8959–8962.
[9] S. Serra, F. G. Gatti and C. Fuganti, *Tetrahedron Asymm*., 2009, **20**, 1319–1329.

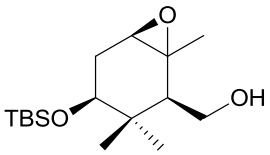
maintained and the reaction monitored by TLC. After 1 hour the organic layer was separated, and the aq phase was extracted with CH_2Cl_2 (2 x 10 mL). The dichloromethane extracts were washed with brine (2 x 10 mL), dried, and evaporated. The residue was purified by silica gel flash chromatography (hexane/*t*-BuOMe, 50:50) to yield 123 mg of lactone **12** (0.74 mmol, 74% yield) as a colorless solid. TLC (*t*-BuOMe) R_f: 0.5; $[\alpha]_D^{20}$ +46.3 (c 1.30, CH_2Cl_2); ^{1}H NMR: δ_H (400 MHz; $CDCl_3$; Me_4Si) 5.41 (bs, 1H), 4.15 (bs, 1H), 2.41 (s, 1H), 2.34 (m, 2H), 1.82 (s, 3H), 1.17 (s, 3H), 1.05 (s, 3H); ^{13}C NMR: δ_C (100 MHz; $CDCl_3$; Me_4Si) 176.4, 132.5, 119.4, 83.1, 54.5, 39.5, 29.6, 25.1, 22.9, 17.9 ppm; HRFABMS: calcd. for $C_{10}H_{14}O_2Na$ $[M+Na]^+$ 189.0886, found: 189.0891.



13

((1*R*,5*S*)-5-((tert-butyldimethylsilyl)oxy)-2,6,6-trimethylcyclohex-2-en-1-yl)methanol (13): Benzoylated derivated of **13** (1200 mg, 3.09 mmol) was added to a solution of NaOH (865 mg, 21.60 mmol) in MeOH (129 ml) and the resulting mixture was stirred at rt overnight. After evaporation of MeOH under reduced pressure and addition of water, the resulting solid crude was extracted with *t*-BuOMe. The organic extract was washed with water, dried over Na_2SO_4 and the solvent was removed. The residue was purified by silica gel flash chromatography (hexane/*t*-BuOMe, 85:15) to yield 598 mg of alcohol **13** (2.10 mmol, 68% yield) as a colorless oil. TLC (hexane/*t*-BuOMe, 65:35) R_f: 0.48; $[\alpha]_D^{20}$ +34.1 (c 1.03, CH_2Cl_2); ^{1}H NMR: δ_H (600 MHz; $CDCl_3$; Me_4Si) 5.39 (bs, 1H), 4.26 (d, 1H, J = 10.0 Hz), 3.75 (dd, 2H, J = 13.0, 1.2 Hz), 3.68 (td, 1H, J = 11.7, 11.0, 3.8 Hz), 3.47 (d, 1H, J = 4.8 Hz), 2.35 (ddq, 1H, J = 18.5, 4.9, 2.4 Hz), 2.07 (m, 1H), 1.76 (s, 3H), 1.05 (s, 3H), 0.95 (s, 3H), 0.91 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H); ^{13}C NMR: δ_C (150 MHz; $CDCl_3$; Me_4Si) 132.5, 118.9, 73.8, 59.0, 51.4, 37.6, 31.9, 28.7

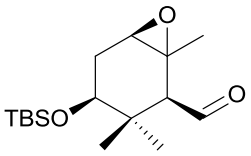
(3C), 26.0, 24.9, 22.7, 18.3, -4.4, -4.7 ppm; TOFESMS: calcd. for $C_{16}H_{33}O_2Si$ $[M+H]^+$ 285.2247, found: 285.2250.



14

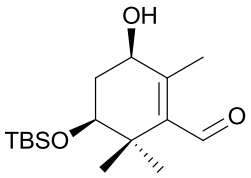
((1*S*,2*R*,4*S*,6*R*)-4-((tert-butyldimethylsilyl)oxy)-1,3,3-trimethyl-7-oxabicyclo[4.1.0]heptan-2-yl) methanol (14): 3–Chloroperoxybenzoic acid (435 mg, 2.52 mmol) in anhyd CH_2Cl_2 (14 mL) was added to a solution of **13** (598 mg, 2.10 mmol) in anhyd CH_2Cl_2 (9 mL) under an argon atmosphere at rt, and the mixture was stirred for 3 hours. Then, CH_2Cl_2 (50 mL) was added and was successively washed with saturated aq $NaHCO_3$ solution and brine, dried over anhyd Na_2SO_4, filtered, and evaporated to give a crude which yielded 537 mg of **14** after silica gel chromatography (hexane/*t*-BuOMe, 60:40) as a colorless oil.[10] (hexane/*t*-BuOMe, 50:50) R_f: 0.25; $[\alpha]_D^{20}$ +14.1 (c 0.96, CH_2Cl_2); ^{1}H NMR: δ_H (400 MHz; $CDCl_3$; Me_4Si) 4.04 (dd, 1H, *J* = 11.1, 5.8 Hz), 3.93 (dd, 1H, *J* = 11.1, 3.4 Hz), 3.30 (t, 1H, *J* = 5.2 Hz), 2.91 (d, 1H, *J* = 3.3 Hz), 2.03 (m, 2H), 1.67 (t, 1H, *J* = 4.1 Hz), 1.41 (s, 3H), 0.95 (s, 3H), 0.92 (s, 3H), 0.89 (s, 9H), 0.06 (s, 3H), 0.02 (s, 3H); ^{13}C NMR: δ_C (100 MHz; $CDCl_3$; Me_4Si) 73.9, 61.2, 58.5, 57.8, 49.2, 36.9, 30.3, 28.5, 25.9 (3C), 24.8, 21.1, 18.1, –4.2, –4.8 ppm; HRFABMS: calcd. for $C_{16}H_{32}O_3SiNa$ $[M+Na]^+$ 300.2121, found: 300.2119.

[10] L. Alcaraz, J. J. Harnett, C. Mioskowski, T. Le Gall, S. Dong-Soo and J. R. Falck, *J. Org. Chem*., 1995, **60**, 7209–7214



5

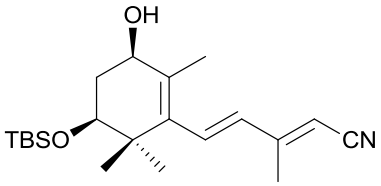
(1*S*,2*S*,4*S*,6*R*)-4-((tert-butyldimethylsilyl)oxy)-1,3,3-trimethyl-7-oxabicyclo[4.1.0]heptane-2-carbaldehyde (5): Dess-Martin periodinane (938 mg, 2.21 mmol) was added to a solution of alcohol **14** (537 mg, 1.79 mmol) in anhyd CH_2Cl_2 (10 mL) at rt. After 15 min of stirring at rt, the reaction was quenched by addition of a saturated aq 1:1 mixture of $NaHCO_3$ and $Na_2S_2O_3$ and stirring was continued until two clear layers were obtained (10 min). The aq phase was extracted with CH_2Cl_2 (3 x 15 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, and concd under reduced pressure. The crude product was purified by silica gel flash chromatography (hexane/*t*-BuOMe, 60:40) to yield 453 mg of epoxyaldehyde **5** (1.88 mmol, 85% yield) as a white solid.[3] TLC (hexane/*t*-BuOMe, 50:50) R_f: 0.63; $[\alpha]_D^{20}$ –40.4 (c 0.73, CH_2Cl_2); ^{1}H NMR: δ_H (400 MHz; $CDCl_3$; Me_4Si) 9.90 (d, J = 4.3 Hz, 1H), 3.35 (t, J = 5.7 Hz, 1H), 3.01 (dd, J = 3.3, 1.8 Hz, 1H), 2.17 (d, J = 4.2 Hz, 1H), 2.09 (m, 2H), 1.31 (s, 3H), 0.98 (s, 3H), 0.93 (s, 3H), 0.88 (s, 9H), 0.07 (s, 3H), 0.02 (s, 3H); ^{13}C NMR: δ_C (100 MHz; $CDCl_3$; Me_4Si) 205.4, 73.0, 60.2, 56.5, 56.4, 38.0, 30.3, 27.1, 25.9 (3C), 24.3, 20.5, 18.1, –4.1, –4.8 ppm.



15

(3*R*,5*S*)-5-((tert-butyldimethylsilyl)oxy)-3-hydroxy-2,6,6-trimethylcyclohex-1-enecarbaldehyde (15): To a solution of **5** (453 mg, 1.52 mmol) in Et_2O (91 mL) was added freshly distilled pyrrolidine (0.28 mL, 3.37 mmol) at rt, and the reaction was stirred overnight.

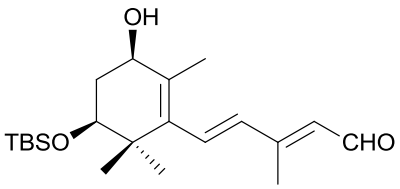
Once the reaction was finished (TLC monitoring), water (25 mL) was added. The mixture was extracted with *t*-BuOMe (3 x 20 mL), the organic layer washed successively with brine, dried over Na_2SO_4, concd in vacuo, and purified by silica gel column chromatography (hexane/*t*-BuOMe, 75:25) to give 408 mg of **15** (1.37 mmol, 90% yield) as a white solid.[16] TLC (hexane/*t*-BuOMe, 50:50) R_f: 0.3; $[\alpha]_D^{20}$ +27.7 (c 1.11, CH_2Cl_2); ^{1}H NMR: δ_H (400 MHz; $CDCl_3$; Me_4Si) 10.2, (s, 1H), 3.90 (m, 1H), 3.64 (t, 1H, *J* = 2.7 Hz), 2.24 (s, 3H), 2.06 (q, 2H, *J* = 4.2 Hz), 1.24 (s, 3H), 1.14 (s, 3H), 0.90 (s, 9H), 0.16 (s, 3H), 0.11 (s, 3H); ^{13}C NMR: δ_C (100 MHz; $CDCl_3$; Me_4Si) 193.8, 152.5, 137.7, 77.3, 70.0, 38.9, 33.1, 26.5, 26.1 (3C), 23.4, 18.2, 16.5, –4.0, –4.6 ppm.



4

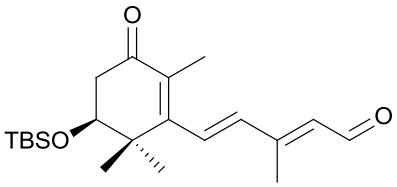
(2*E*,4*E*)-5-((3*R*,5*S*)-5-((tert-butyldimethylsilyl)oxy)-3-hydroxy-2,6,6-trimethylcyclohex-1-en-1-yl)-3-methylpenta-2,4-dienenitrile (4): In a flame-dried flask, *n*-BuLi (1.6 M in hexane, 0.30 mL) was added to a solution of diethyl (cyanomethylallyl)phosphonate (367 mg, 1.69 mmol) in dry THF (7.0 mL), and the mixture stirred at rt for 30 min. The solution was then cooled to 0 °C and **15** (408 mg, 1.37 mmol) in dry THF (10.0 mL) was added dropwise. After 2 hours of stirring at rt, the reaction was quenched by adding saturated aq NH_4Cl and the mixture was extracted with *t*-BuOMe (3 x 25 mL). The combined organic layers were washed with brine, dried with Na_2SO_4 and concd in vacuo. After purification on a silica gel column (hexane/*t*-BuOMe, 80:20), **4** (286 mg, 0.79 mmol, 58% yield) was obtained as a colorless oil. TLC (hexane/*t*-BuOMe, 50:50) R_f: 0.35; $[\alpha]_D^{20}$ +49.8 (c 0.66, CH_2Cl_2); ^{1}H NMR: δ_H (400 MHz; $CDCl_3$; Me_4Si) 6.48 (d, 1H, *J* = 16.1 Hz), 6.15 (d, 1H, *J* = 16.1 Hz), 5.20 (s, 1H), 3.90 (t, 1H, *J* = 4.4 Hz), 3.68 (dd, 1H, *J* = 6.0, 2.2 Hz), 2.21 (s, 3H), 2.06 (m, 1H), 2.00 (m, 1H), 1.82 (s, 3H),

1.01 (s, 3H), 0.98 (s, 3H), 0.90 (s, 9H), 0.13 (s, 3H), 0.08 (s, 3H); ^{13}C NMR: δ_C (100 MHz; $CDCl_3$; Me_4Si) 156.8, 136.4, 135.0, 134.2, 132.5, 117.8, 97.5, 75.9, 69.5, 40.2, 34.3, 27.1, 26.1 (3C), 24.5, 18.7, 18.2, 16.7, –4.0, –4.7 ppm; HRFABMS: calcd. for $C_{21}H_{35}NO_2SiNa$ $[M+Na]^+$ 384.2344, found: 384.2335.



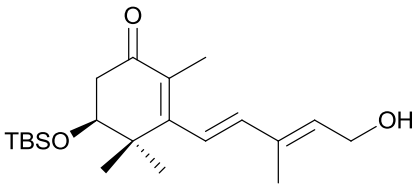
16

(2*E*,4*E*)-5-((3*R*,5*S*)-5-((tert-butyldimethylsilyl)oxy)-3-hydroxy-2,6,6-trimethylcyclohex-1-en-1-yl)-3-methylpenta-2,4-dienal (16): A solution of **4** (286 mg, 0.79 mmol) in dry toluene (6.0 mL) was cooled to –20 °C and DIBALH (1.82 mL, 1.82 mmol) was added. The solution was allowed to warm to rt and stirred for 6 h (TLC monitoring). The reaction was then quenched by adding H_2O and the mixture was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were washed with saturated aq NaCl, dried over Na_2SO_4 and concd in vacuo. After purification on a silica gel column (hexane/*t*-BuOMe, 30:70), 205 mg of **16** (0.56 mmol, 71% yield) were obtained as a colorless oil. TLC (hexane/*t*-BuOMe, 50:50) R_f: 0.30; $[\alpha]_D^{20}$ +21.1 (c 0.70, CH_2Cl_2); ^{1}H NMR: δ_H (400 MHz; $CDCl_3$; Me_4Si) 10.14 (d, 1H, J = 8.1 Hz), 6.65 (d, 1H, J = 16.2 Hz), 6.22 (d, 1H, J = 16.1 Hz), 5.96 (d, 1H, J = 8.1 Hz), 3.92 (t, 1H, J = 4.3 Hz), 3.70 (dd, 1H, J = 5.9, 2.2 Hz), 2.32 (s, 3H), 2.00 (m, 2H), 1.85 (s, 3H), 1.04 (s, 3H), 1.00 (s, 3H), 0.91 (s, 9H), 0.14 (s, 3H), 0.09 (s, 3H); ^{13}C NMR: δ_C (100 MHz; $CDCl_3$; Me_4Si) 191.5, 154.3, 137.2, 136.7, 134.9, 132.5, 129.5, 76.0, 69.5, 40.3, 34.3, 27.2, 26.1 (3C), 24.5, 18.7, 18.2, 13.1, –4.0, –4.7 ppm; TOFESMS: calcd. for $C_{21}H_{37}O_3Si$ $[M+H]^+$ 365.2526, found: 365.2512.



17

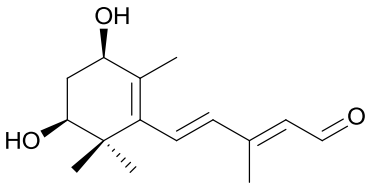
(2*E*,4*E*)-5-((S)-5-((tert-butyldimethylsilyl)oxy)-2,6,6-trimethyl-3-oxocyclohex-1-en-1-yl)-3-methylpenta-2,4-dienal (17): Dess-Martin periodinane (295 mg, 0.70 mmol) was added to a solution of **16** (205 mg, 0.56 mmol) in anhyd CH_2Cl_2 (3.3 mL) and stirred at rt for 15 min. At this point, the reaction was quenched by addition of a saturated aq 1:1 mixture of $NaHCO_3$ and $Na_2S_2O_3$ and stirring was continued until two clear layers were obtained (10 min). The aq phase was extracted with CH_2Cl_2 (3 x 15 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, and concd under reduced pressure. The crude product was purified by silica gel flash chromatography (hexane/*t*-BuOMe, 70:30) to yield 171 mg of **17** (0.47 mmol, 84% yield) as a colorless oil. TLC (hexane/*t*-BuOMe, 35:65) R_f: 0.59; $[\alpha]_D^{20}$ +24.6 (c 0.58, CH_2Cl_2); ^{1}H NMR: δ_H (400 MHz; $CDCl_3$; Me_4Si) 10.17 (d, 1H, *J* = 8.0 Hz), 6.74 (d, 1H, *J* = 16.3 Hz), 6.29 (d, 1H, *J* = 16.3 Hz), 6.01 (d, 1H, *J* = 7.6 Hz), 3.84 (m, 1H), 2.63 (m, 2H), 2.35 (s, 3H), 1.81 (s, 3H), 1.16 (s, 3H), 1.14 (s, 3H), 0.89 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); ^{13}C NMR: δ_C (100 MHz; $CDCl_3$; Me_4Si) 197.8, 191.3, 159.7, 152.9, 138.4, 132.8, 131.3, 130.9, 74.2, 43.5, 42.0, 30.3, 29.8 (2C), 25.9 (3C), 13.7, 13.1, –4.0, –4.8 ppm; TOFESMS: calcd. for $C_{21}H_{35}O_3Si$ $[M+H]^+$ 363.2355, found: 363.2362.



18

(*S*)-5-((tert-butyldimethylsilyl)oxy)-3-((1E,3E)-5-hydroxy-3-methylpenta-1,3-dien-1-yl)-2,4,4-trimethylcyclohex-2-enone (18): A solution of **17** (171 mg, 0.47 mmol) and zinc

borohydride (45 mg, 0.47 mmol, prepared from sodium borohydride and zinc chloride),[11] in THF (5.0 mL) was stirred at –40 ºC for 2 h. The reaction was then quenched by careful dropwise addition of water. The THF layer was separated and the aq phase was extracted with *t*-BuOMe (3 x 20 mL). The combined THF and ether extract was washed with brine, dried over Na_2SO_4 and concd under reduced pressure. The resulting crude was purified by silica gel flash chromatography (hexane/*t*-BuOMe, 30:70) to yield 139 mg of **18** (0.38 mmol, 81% yield) as a colorless oil. TLC (hexane/*t*-BuOMe, 35:65) R_f: 0.35; $[\alpha]_D^{20}$ +11.2 (c 0.50, CH_2Cl_2); ^{1}H NMR: δ_H (500 MHz; $CDCl_3$; Me_4Si) 6.20 (s, 2H), 5.75 (t, 1H, J = 6.8 Hz), 4.34 (d, 2H, J = 6.9 Hz), 3.82 (dd, 1H, J = 10.4, 4.6 Hz), 2.60 (m, 2H), 1.88 (s, 3H), 1.82 (s, 3H), 1.14 (s, 3H), 1.12 (s, 3H), 0.89 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H); ^{13}C NMR: δ_C (125 MHz; $CDCl_3$; Me_4Si) 198.2, 160.5, 140.0, 135.8, 132.4, 130.3, 125.0, 74.2, 59.6, 43.6, 42.1, 25.9 (3C), 25.6, 21.1, 18.2, 13.8, 12.6, –3.9, –4.8 ppm; TOFESMS: calcd. for $C_{21}H_{37}O_3Si$ $[M+H]^+$ 365.2497, found: 365.2512.

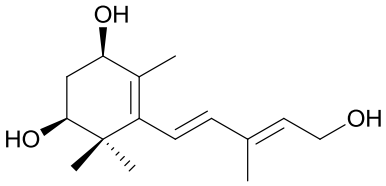


19

(2*E*,4*E*)-5-((3*R*,5*S*)-3,5-dihydroxy-2,6,6-trimethylcyclohex-1-en-1-yl)-3-methylpenta-2,4-dienal (19): To a solution of **16** (90 mg, 0.25 mmol) in anhyd THF (3.4 mL) at rt, was added 1.0 M TBAF in THF (0.12 mL, 0.12 mmol) and the mixture stirred for 30 min at the same temperature. Solvent was then removed under reduced pressure and the crude extracted with EtOAc. Organic extracts were washed with brine, dried over anhyd Na_2SO_4 and concd under reduced pressure. The resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 5:95) on silica gel yielding 46 mg of **19** (0.19 mmol, 74% yield) as a colorless oil. TLC (EtOAc) R_f: 0.35; $[\alpha]_D^{20}$ +10.1 (c 0.52, CH_2Cl_2); ^{1}H NMR: δ_H (500 MHz; $CDCl_3$; Me_4Si) 10.14

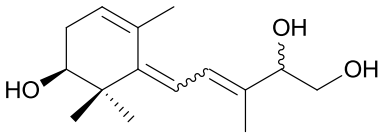
[11] S. Narasimhan and R. Balakumar, *Aldrichimica Acta*, 1998, **31**, 19–26.

(d, 1H, *J* = 8.1 Hz), 6.66 (d, 1H, *J* = 16.2 Hz), 6.25 (d, 1H, *J* = 16.2 Hz), 5.96 (d, 1H, *J* = 8.0 Hz), 4.01 (t, 1H, *J* = 3.6 Hz), 3.73 (m, 1H), 2.33 (s, 3H), 2.17–2.04 (m, 2H), 1.88 (s, 3H), 1.14 (s, 3H), 1.03 (s, 3H); ^{13}C NMR: δ_H (125 MHz; $CDCl_3$; Me_4Si) 191.5, 154.2, 137.4, 136.7, 134.4, 131.9, 129.6, 75.5, 69.2, 39.8, 33.4, 27.0, 24.3, 19.0, 13.1 ppm; TOFESMS: calcd. for $C_{15}H_{23}O_3$ $[M+H]^+$ 251.1640, found: 251.1647.



20

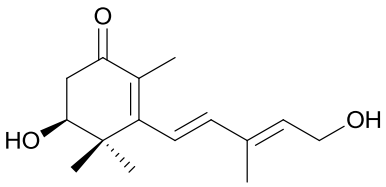
(1*S*,3*R*)-5-((1*E*,3*E*)-5-hydroxy-3-methylpenta-1,3-dien-1-yl)-4,6,6-trimethylcyclohex-4-ene-1,3-diol (20): In a similar DIBALH reduction to the one described earlier, **19** (46 mg, 0.18 mmol) was reduced with DIBALH (0.04 mL, 0.04 mmol) in dry toluene (1.0 mL). After column purification (hexane/EtOAc, 5:95), 38 mg of compound **20** (0.15 mmol, 82% yield) were obtained as a colorless oil. TLC (EtOAc) R_f: 0.23; $[\alpha]_D^{20}$ +15.7 (c 0.63, CH_2Cl_2); ^{1}H NMR: δ_H (500 MHz; $CDCl_3$; Me_4Si) 6.09 (s, 2H), 5.66 (t, 1H, *J* = 7.3 Hz), 4.32 (d, 2H, *J* = 6.9 Hz), 4.00 (t, 1H, *J* = 3.8 Hz), 3.72 (dd, 1H, *J* = 4.9, 2.4 Hz), 2.00 (m, 2H), 1.85 (s, 6H), 1.11 (s, 3H), 1.00 (s, 3H); ^{13}C NMR: δ_C (125 MHz; $CDCl_3$; Me_4Si) 138.5, 137.6, 136.5, 129.8, 129.5, 125.9, 75.7, 69.5, 59.6, 39.8, 33.5, 26.9, 24.2, 18.9, 12.6 ppm; HRFABMS: calcd. for $C_{15}H_{24}O_3Na$ $[M+Na]^+$ 275.1629, found: 275.1623.



(+)-apotrientriols **(2)** 6*E*
(3) 6*Z*

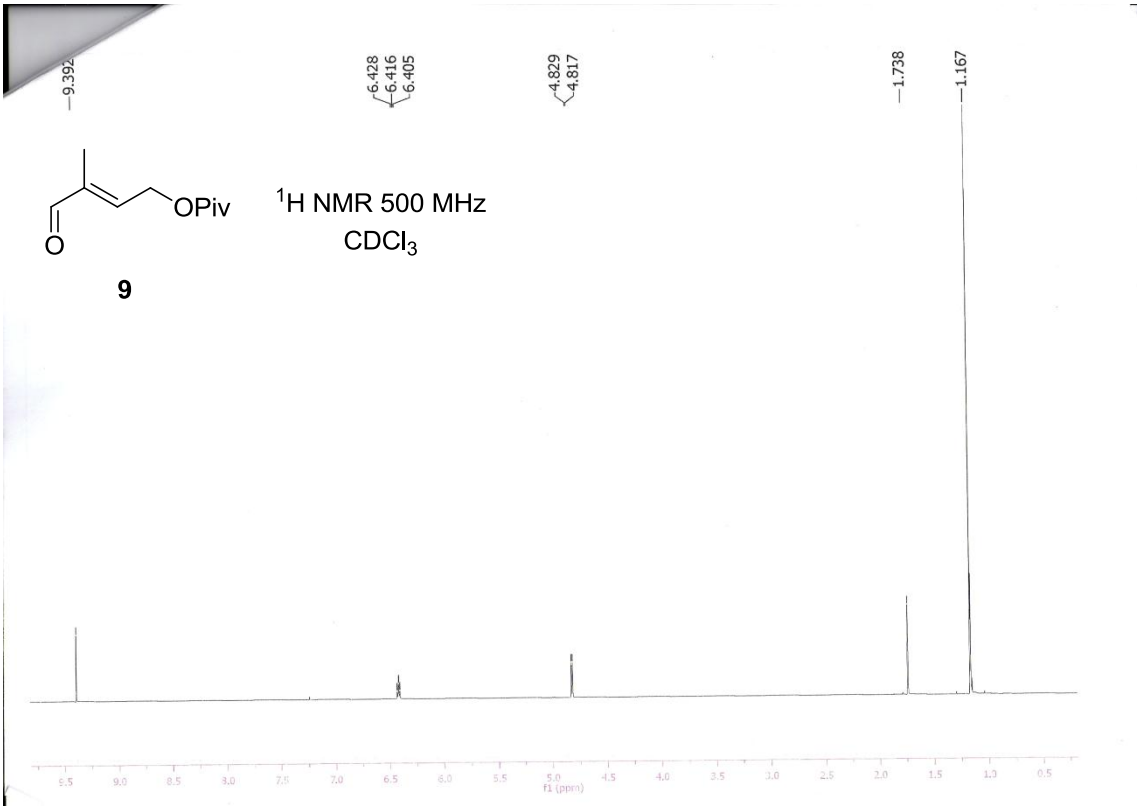
(+)-Apotrientriols A-B (2–3): To a solution of **20** (30 mg, 0.12 mmol) in THF:H_2O (1:1 v/v, 1.0 mL) at rt, was added FSO_3H (0.001 mmol) and the mixture stirred for 3 min at rt, quenched with saturated aq $NaHCO_3$ and extracted with EtOAc. Organic extracts were washed with brine, dried over anhyd Na_2SO_4 and concd under reduced pressure. The resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 5:95) on silica gel yielding 65% of **2-3** (20 mg, 0.08 mmol) as a colorless syrup. For semi-preparative normal-phase HPLC, aliquots (0.5 mL) of the crude dissolved in *t*-BuOMe were injected into a column (10 by 250 mm, 5 μm silica particles); with a 15 mm refillable guard pre-column filled with the same material in a Series 1100 liquid chromatograph (Agilent). The column was eluted at room temperature at a flow rate of 2 mL min^{-1} for 25 min with hexane/*t*-BuOMe (5:95, v/v). and monitored with a refractometer. Compound **2** was present in the fraction 25.9 < t_R < 27.4 min (3.9 mg) and compounds **2-3** in the fraction 27.4 < t_R < 29.0 min (7.8 mg). Compound **2**: TLC (EtOAc) R_f: 0.18; $[\alpha]_D^{20}$ = +5.1 (c 0.09, CH_2Cl_2); ^{1}H NMR: δ_H (500 MHz; $(CD_3)_2CO$; Me_4Si) 6.67 (d, 1H, *J* = 11.3 Hz), 6.26 (d, 1H, *J* = 11.3 Hz), 5.48 (br t, 1H), 4.10 (m, 1H), 3.86 (t, 1H, *J* = 3.6 Hz), 3.51-3.43 (m, 2H), 2.75 (s, 2H), 2.43-2.39 (m, 1H), 1.76 (s, 3H), 1.13 (s, 3H), 1.03 (s, 3H); ^{13}C NMR: δ_C (125 MHz; $(CD_3)_2CO$; Me_4Si) 138.8, 133.2, 127.0, 124.4, 121.0, 78.5, 74.3, 66.4, 42.8, 34.2, 25.6, 25.5, 22.2, 13.1 ppm; HRFABMS: calcd. for $C_{15}H_{24}O_3Na$ $[M+Na]^+$ 275.1623, found: 275.1625. Compounds **2–3**: TLC (EtOAc) R_f: 0.18; $[\alpha]_D^{20}$ +4.3 (c 0.42, CH_2Cl_2); ^{1}H NMR (500 MHz, $(CD_3)_2CO$, Me_4Si): δ 6.84 (d, 1H, *J* = 11.8 Hz), 6.31 (d, 1H, *J* = 11.8 Hz), 5.56 (br t, 1H), 4.15 (m, 1H), 3.94 (t, 1H, *J* = 3.6 Hz), 3.55-3.52 (m, 3H), 2.33-2.29 (m, 1H), 2.03 (s, 3H), 1.86 (s, 3H), 1.35 (s, 3H), 1.21 (s, 3H); ^{13}C NMR (125 MHz, $(CD_3)_2CO$, Me_4Si): δ 144.8, 135.0, 124.5, 124.0 123.8, 122.3, 75.8, 66.5, 41.2, 32.3, 27.1, 22.0, 13.2 ppm;[†] HRFABMS: calcd. for $C_{15}H_{24}O_3Na$ $[M+Na]^+$ 275.1623, found: 275.1627.

‡ Signals corresponding to compound **2**, † Signals corresponding to compound **3**



(+)-apotrisporin E **(1)**

(+)-Apotrisporin E (1): In a similar deprotection to the one described earlier, **18** (90 mg, 0.25 mmol) in anhyd THF (3.4 mL) was reacted with 1.0 M TBAF in THF (0.12 mL, 0.12 mmol) and the mixture stirred for 30 min at rt. Solvent was then removed under reduced pressure and the crude extracted with EtOAc. Organic extracts were washed with brine, dried over anhyd Na_2SO_4 and concd under reduced pressure. The resulting crude was purified by column chromatography (hexane/EtOAc, 10:90) on silica gel yielding 70% of (+)-apotrisporin E (44 mg, 0.18 mmol) as a colorless oil. TLC (*t*-BuOMe) R_f: 0.23; IR: ν_{max}/cm^{-1} 3407, 2958, 2926, 2871, 1735, 1719, 1648, 1012, 736; $[\alpha]_D^{20}$ +7.1 (c 0.80, CH_2Cl_2); ^1H NMR: δ_H (500 MHz; $CDCl_3$; Me_4Si) 6.22 (s, 2H), 5.76 (t, 1H, *J* = 6.7 Hz), 4.35 (d, 2H, *J* = 6.7 Hz), 3.88 (dd, 1H, *J* = 9.1, 4.2), 2.78 (dd, 1H, *J* = 16.9, 4.2 Hz), 2.60 (dd, 1H, *J* = 16.9, 9.1 Hz), 1.88 (s, 3H), 1.84 (s, 3H), 1.18 (s, 6H); ^{13}C NMR: δ_C (125 MHz; $CDCl_3$; Me_4Si) 197.3, 159.4, 140.5, 135.6, 132.7, 130.5, 124.5, 74.3, 55.6, 42.8, 41.4, 25.7, 21.5, 13.8, 12.6 ppm; TOFESMS: calcd. for $C_{15}H_{23}O_3$ $[M+H]^+$ 251.1647, found: 251.1644.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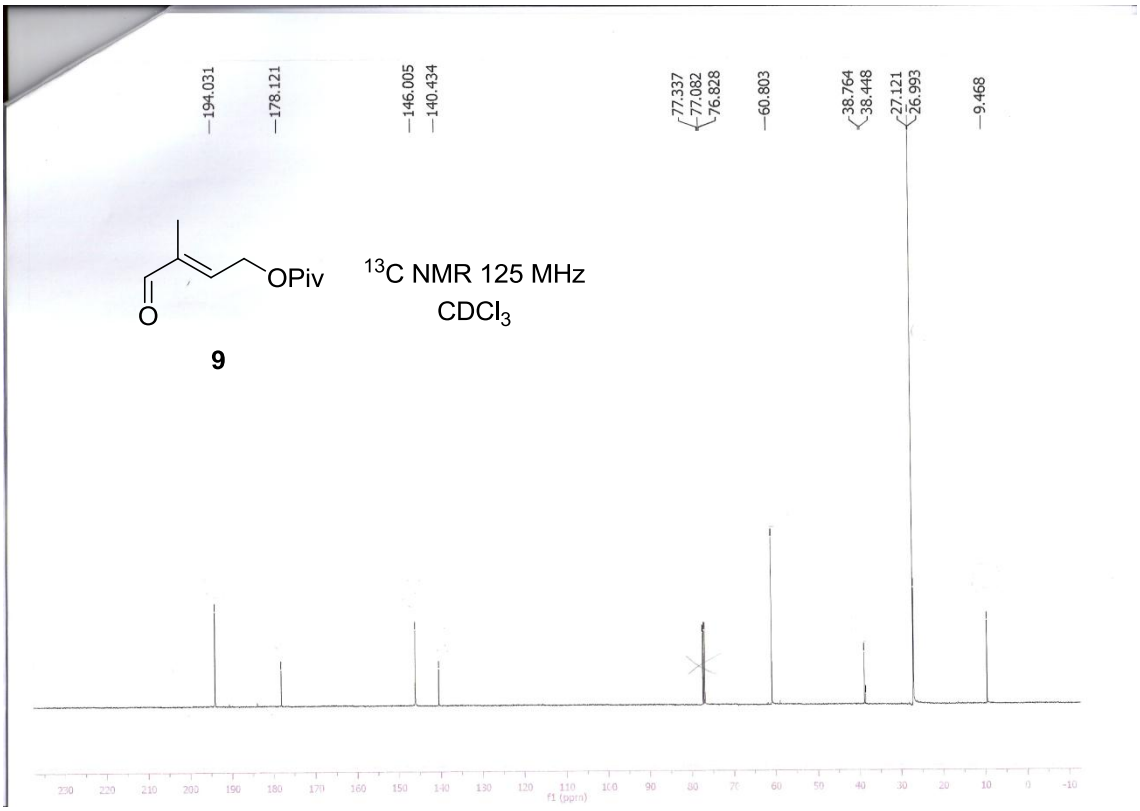
9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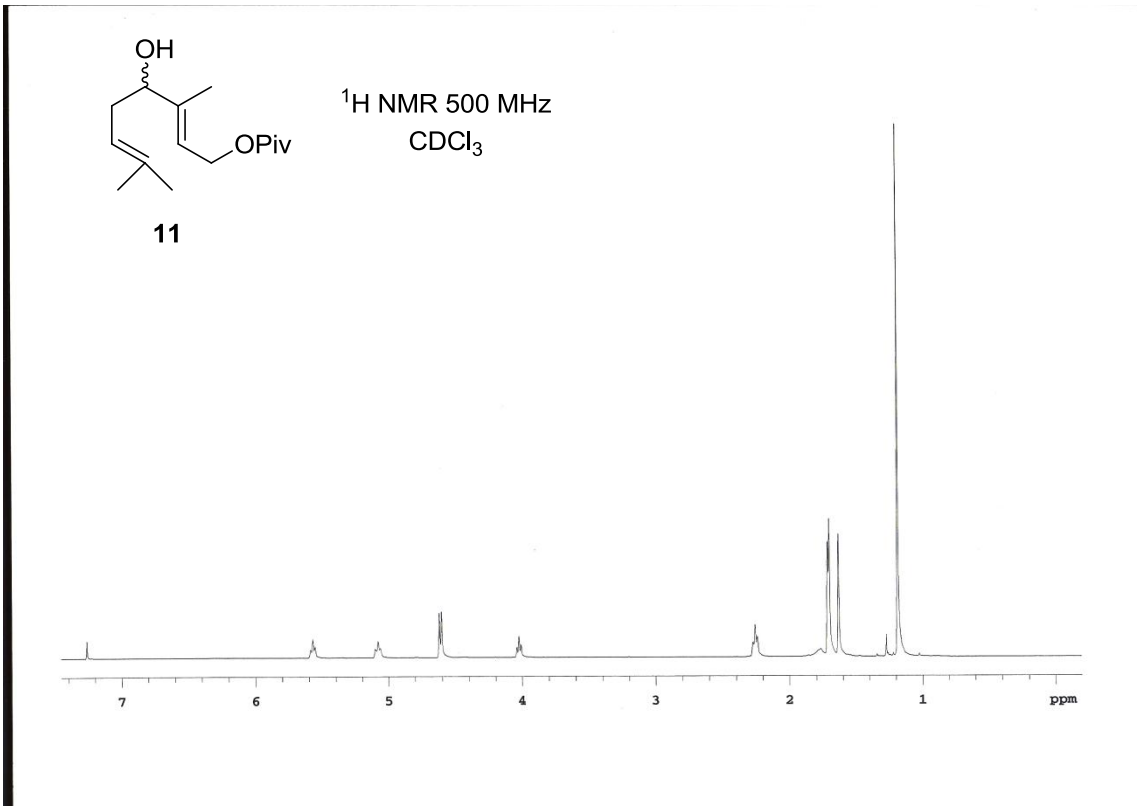
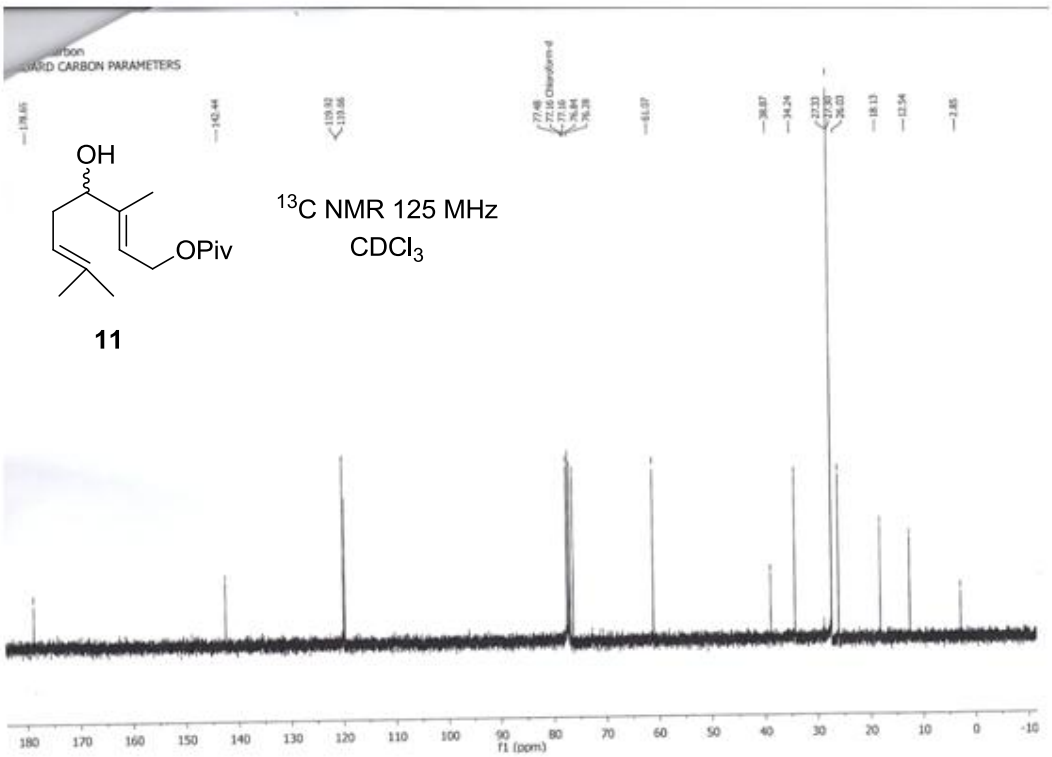
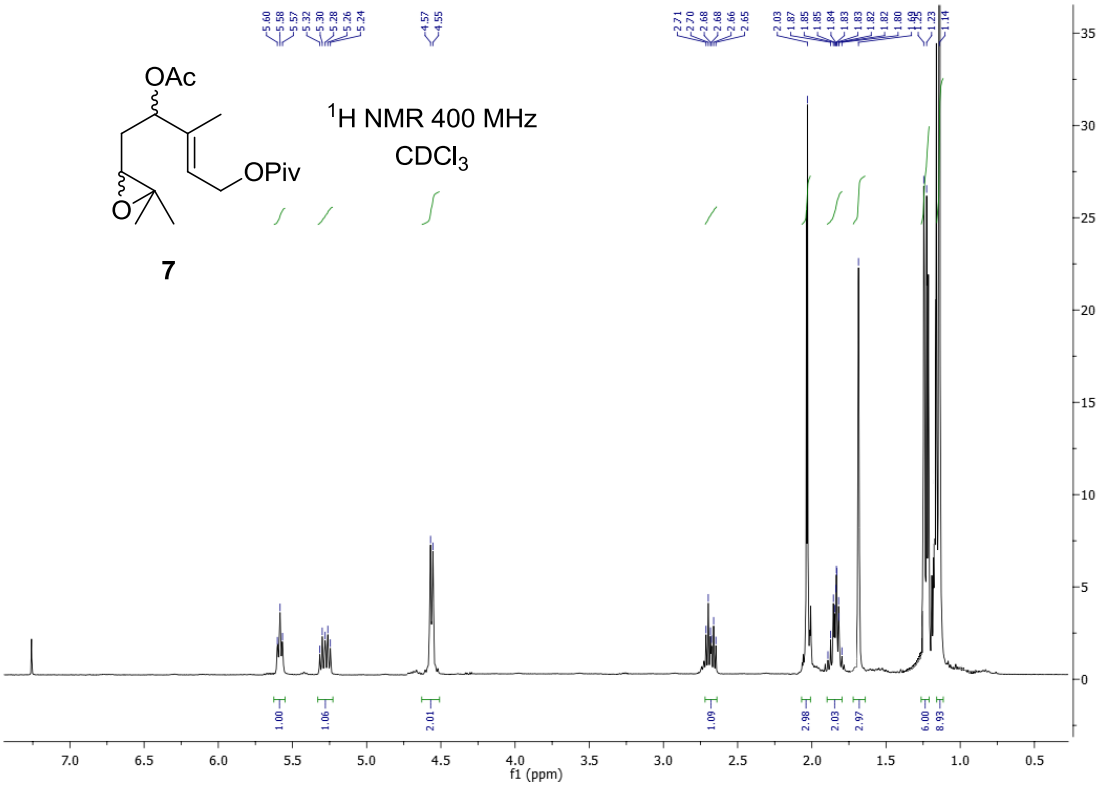
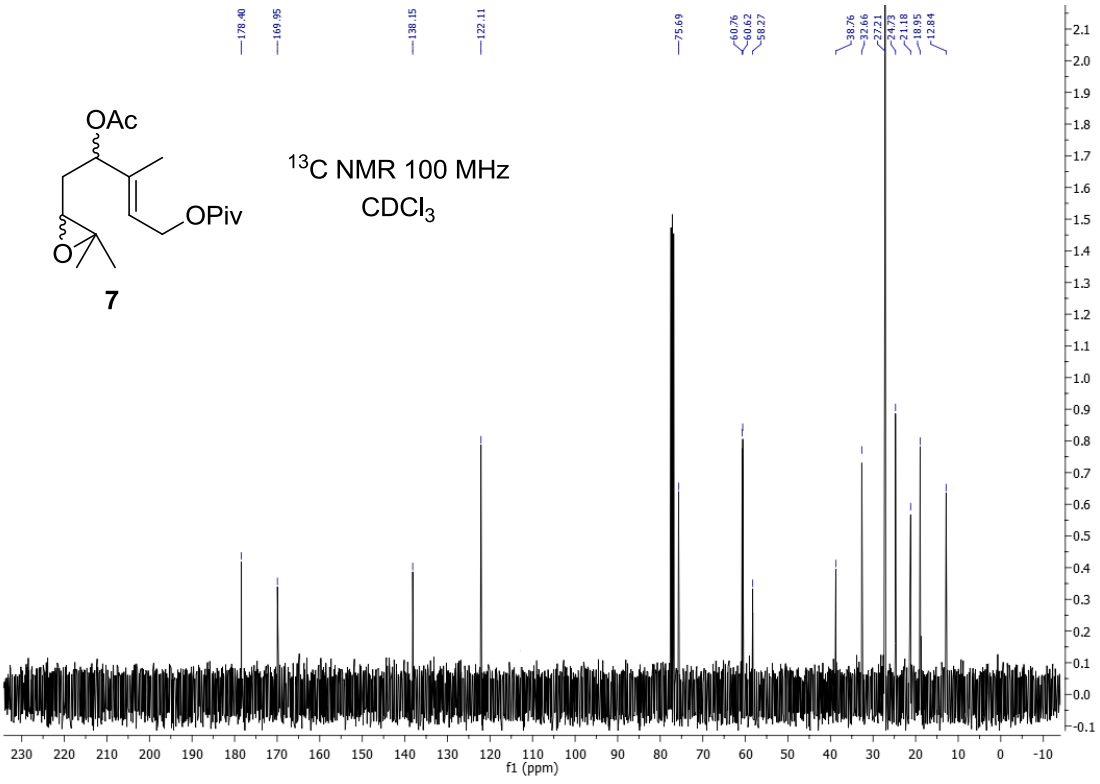
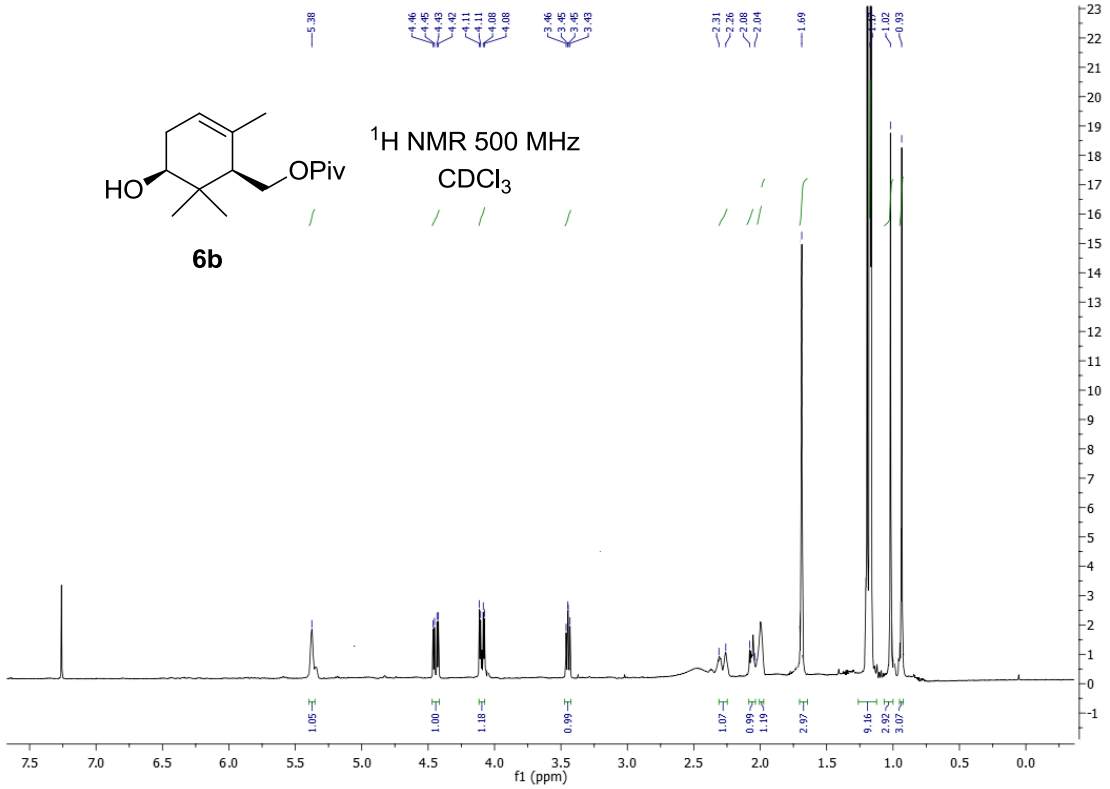
9

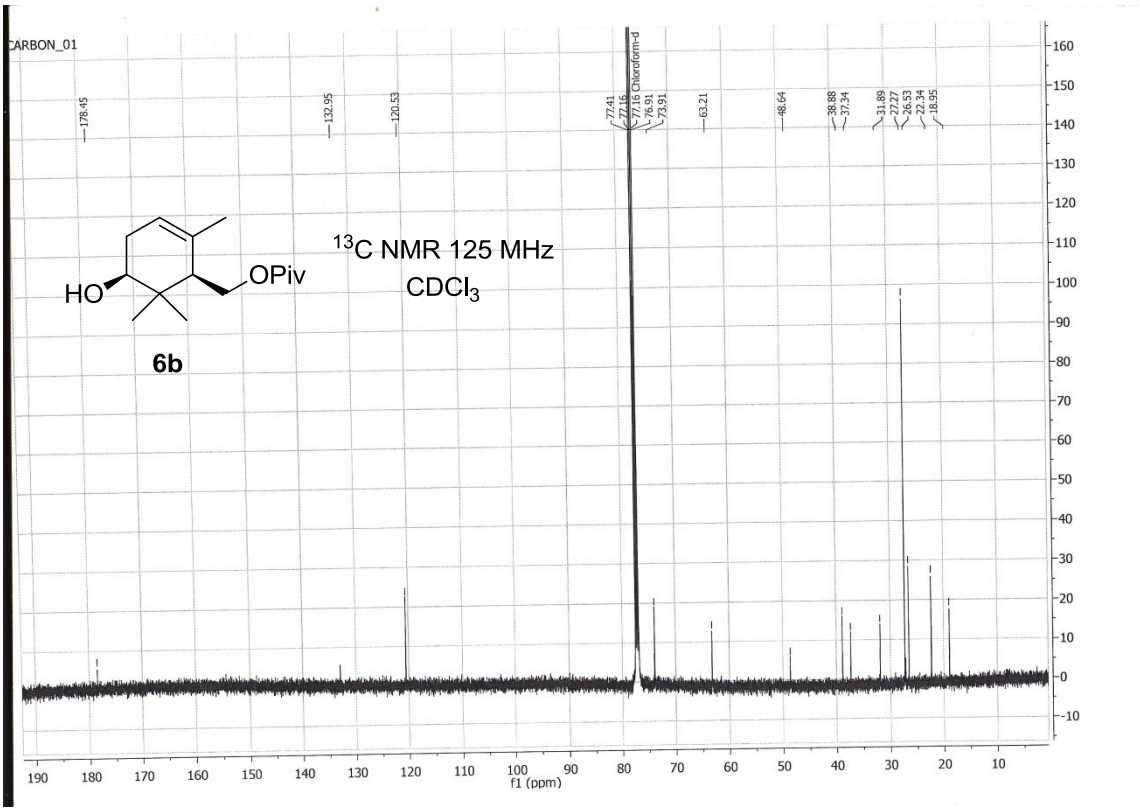












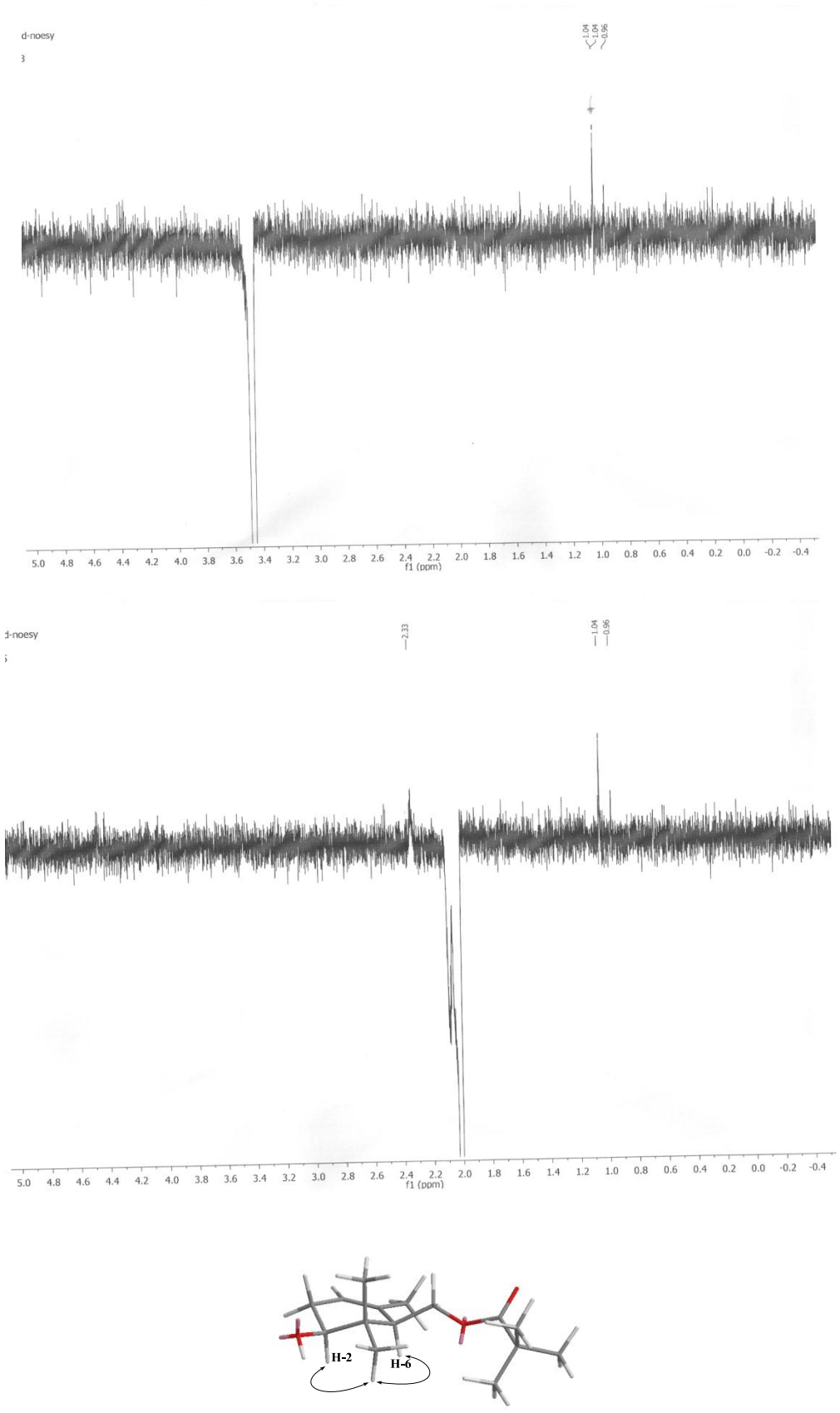
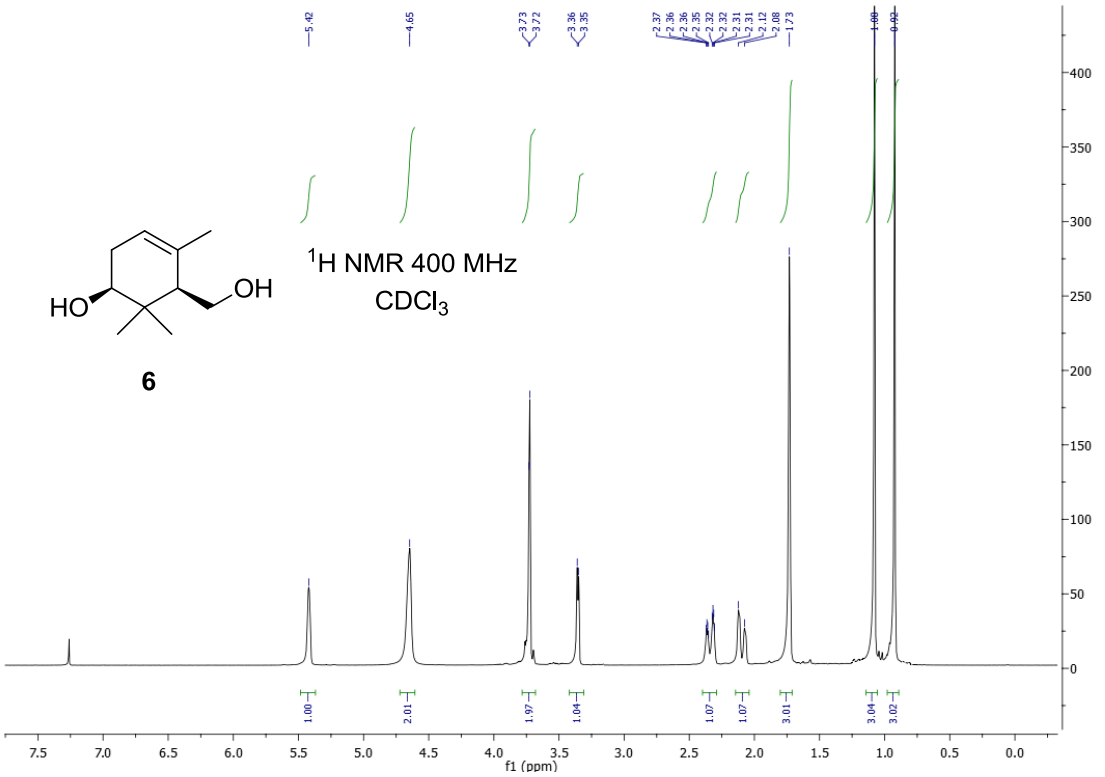
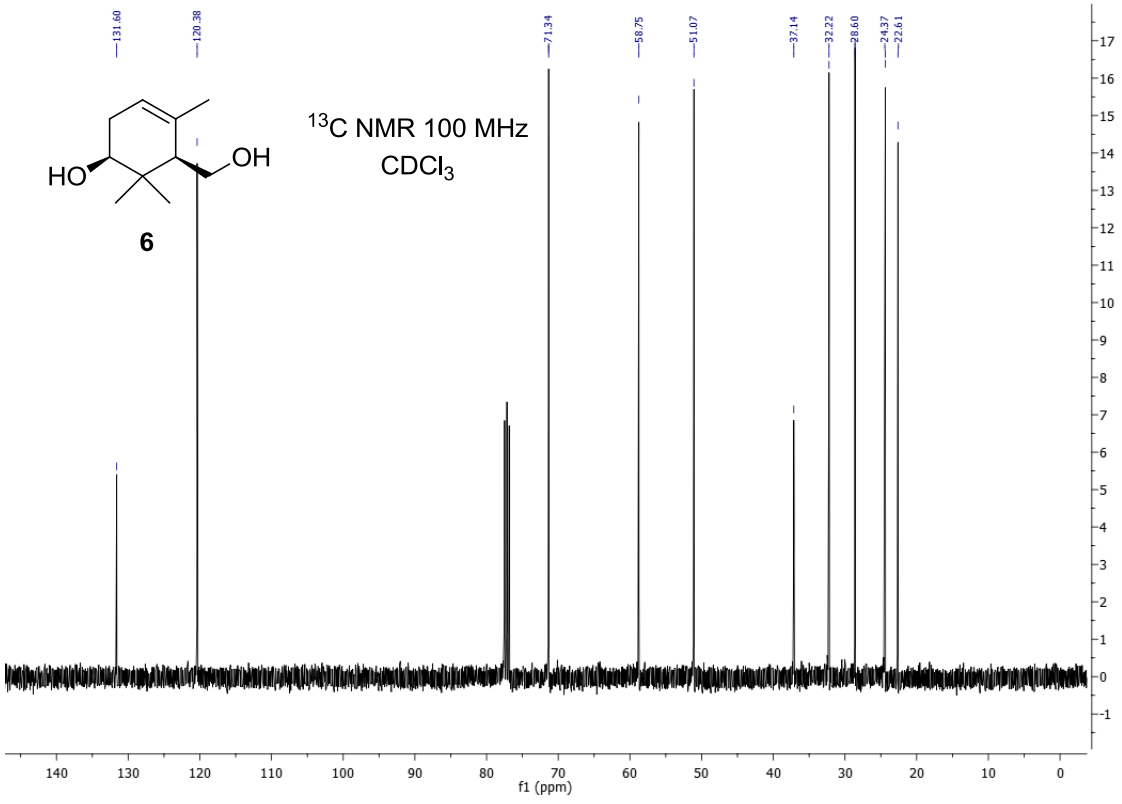
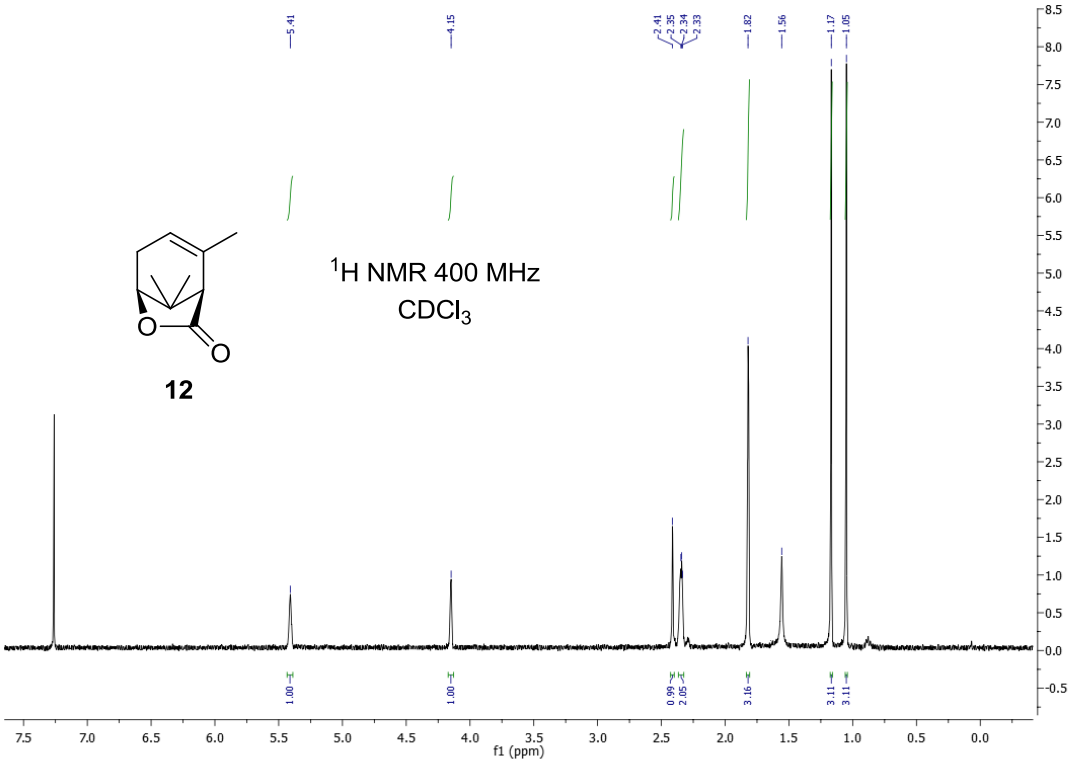
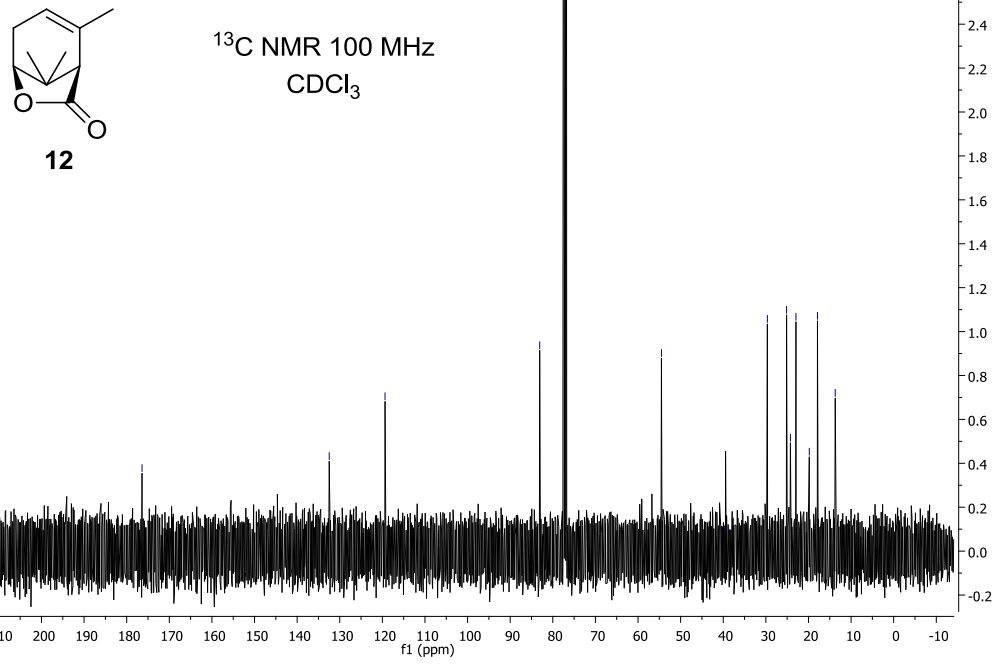


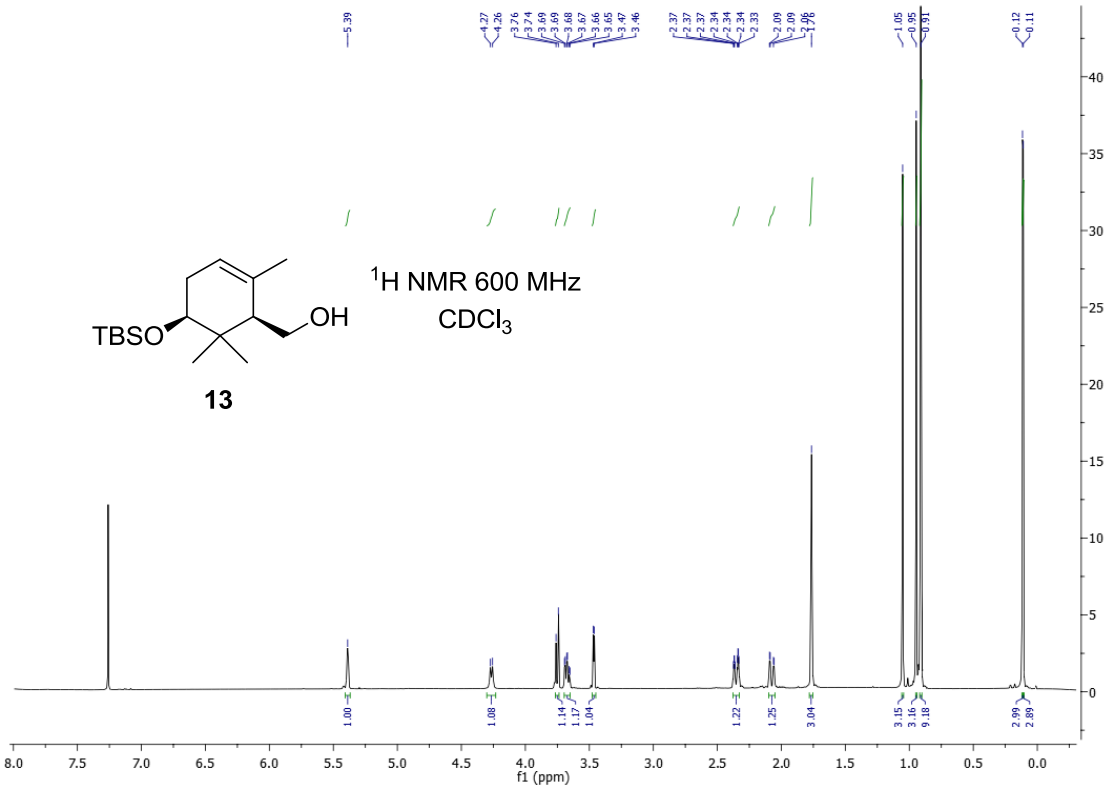
Fig. 1 NOE experiments to establish the stereochemistry of **6b**.

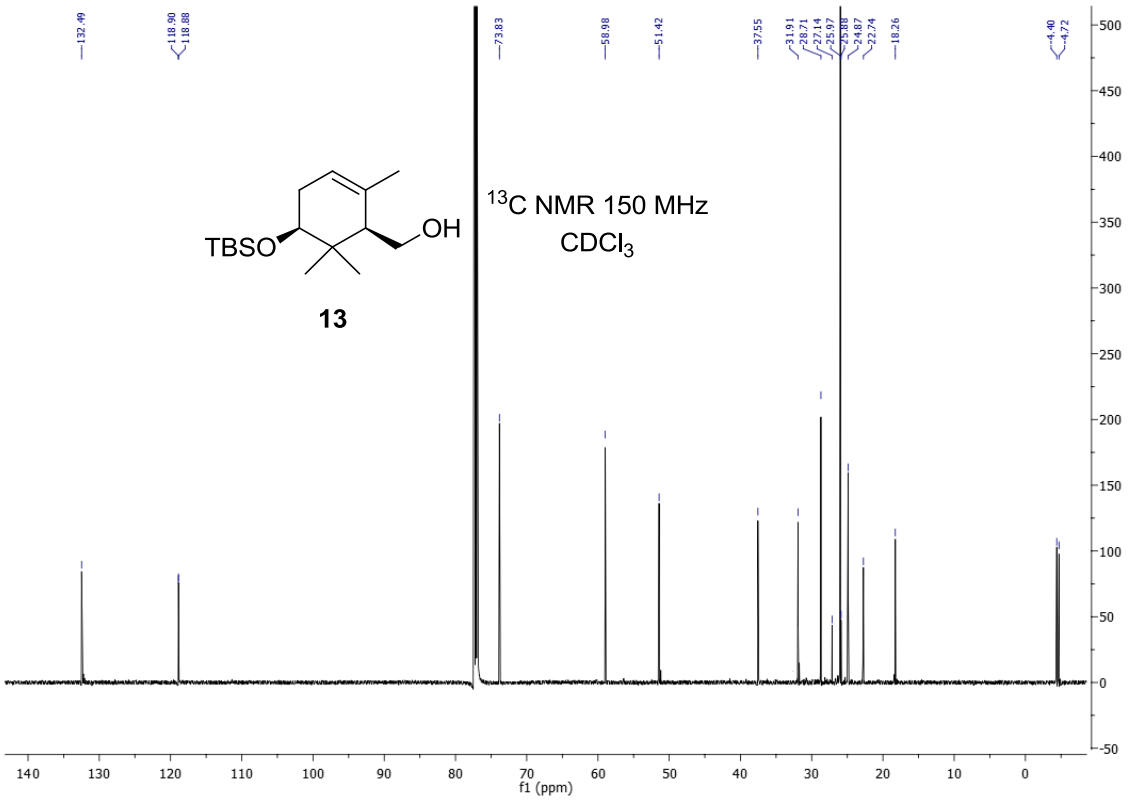


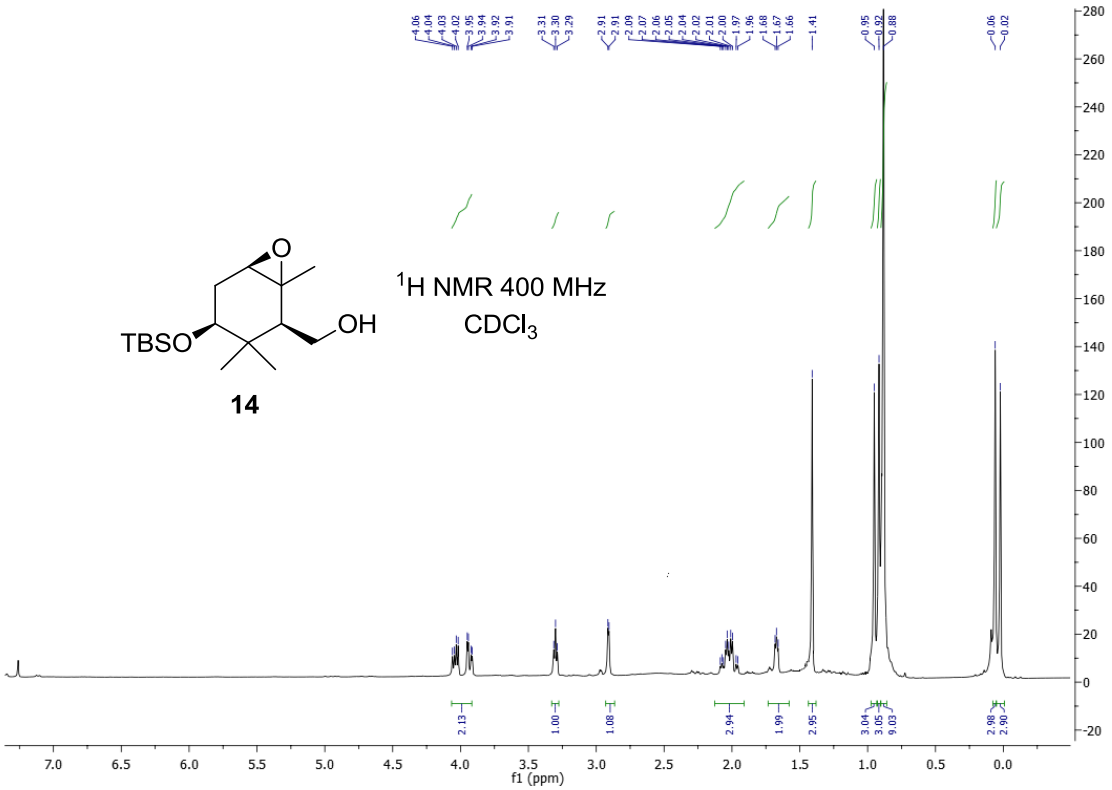


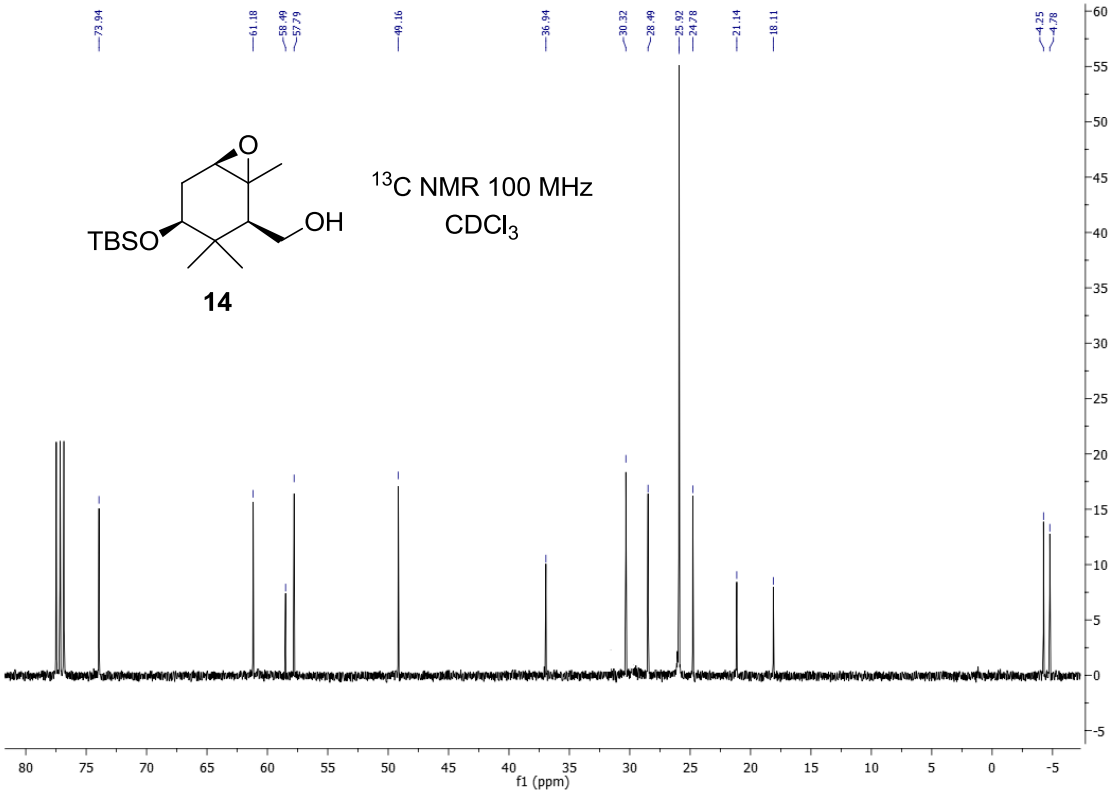


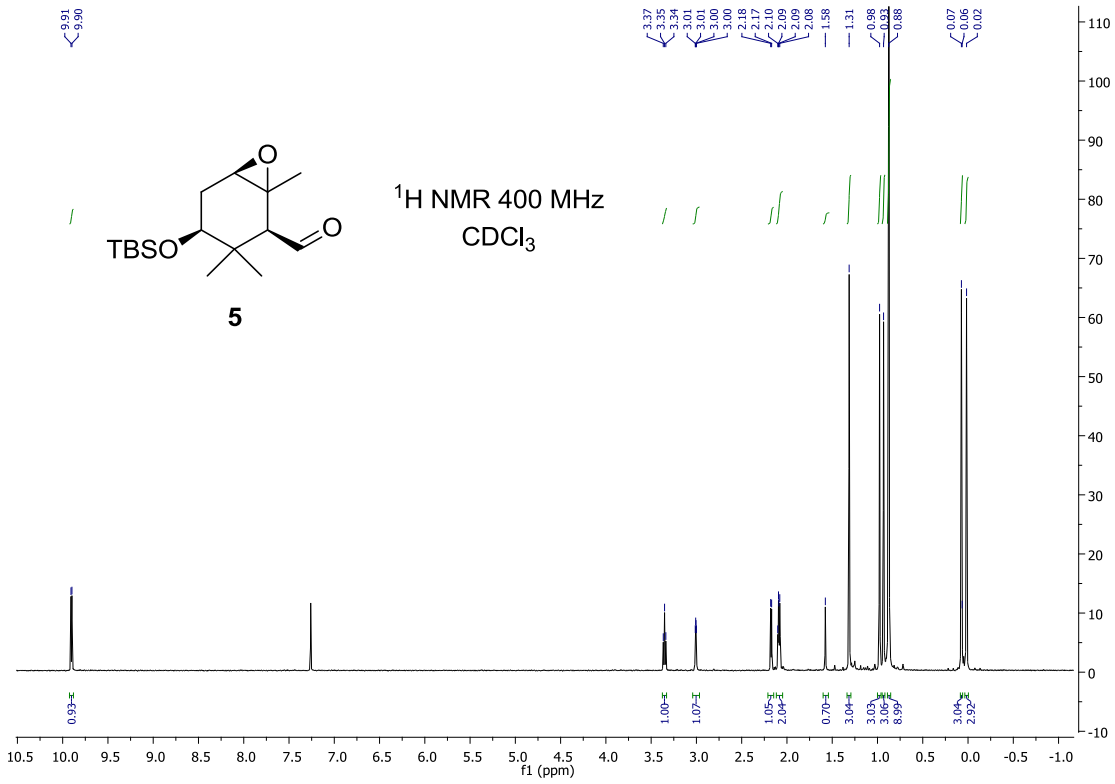


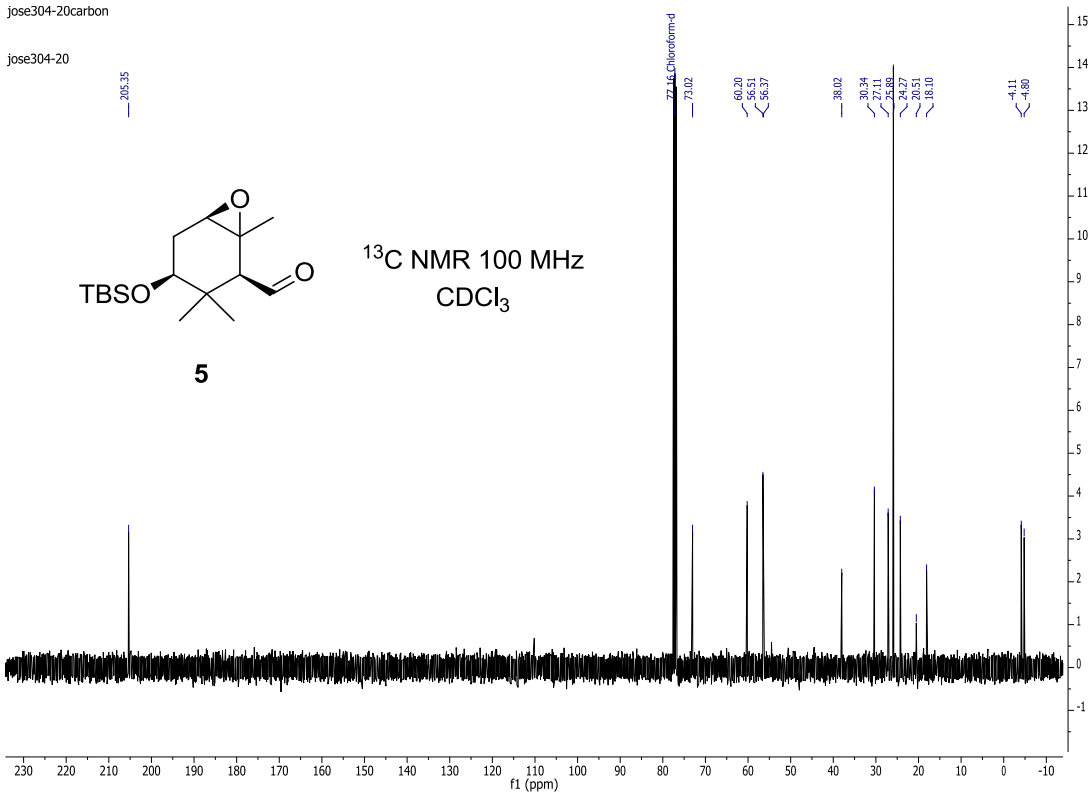

TBSO
OH
13
^{1}H NMR 600 MHz
$CDCl_3$
f1 (ppm)

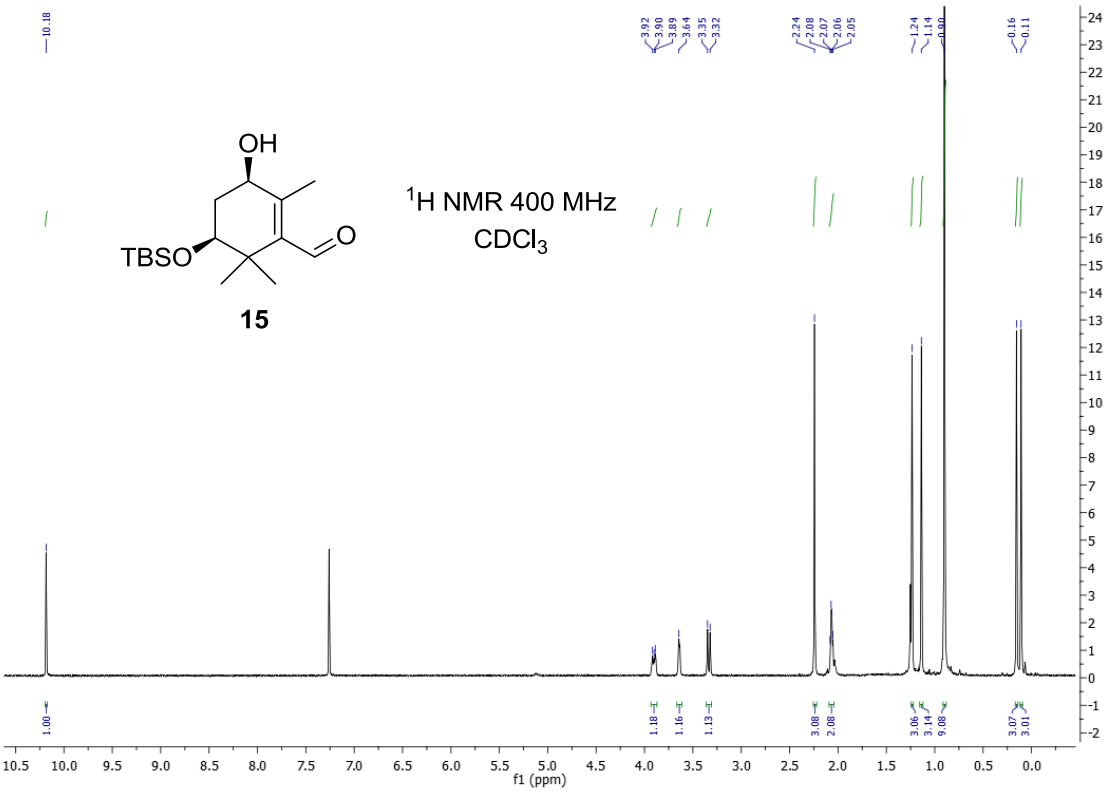

TBSO
OH
13
^{13}C NMR 150 MHz
$CDCl_3$
f1 (ppm)

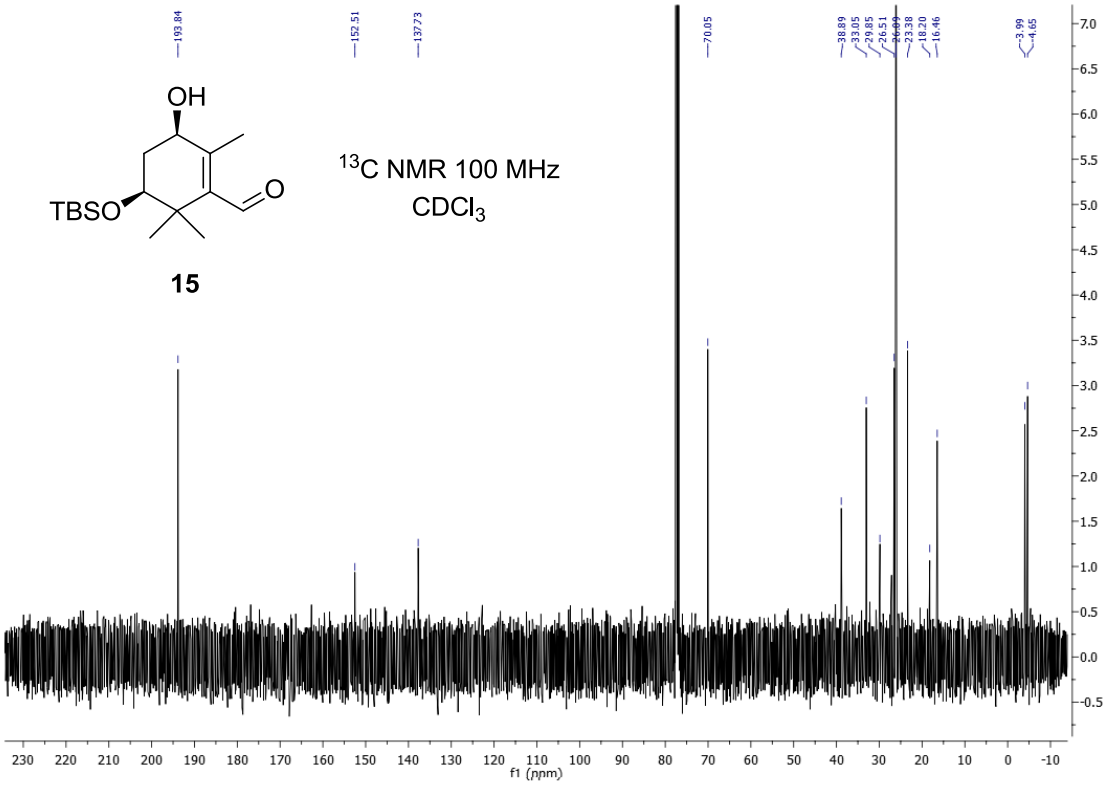


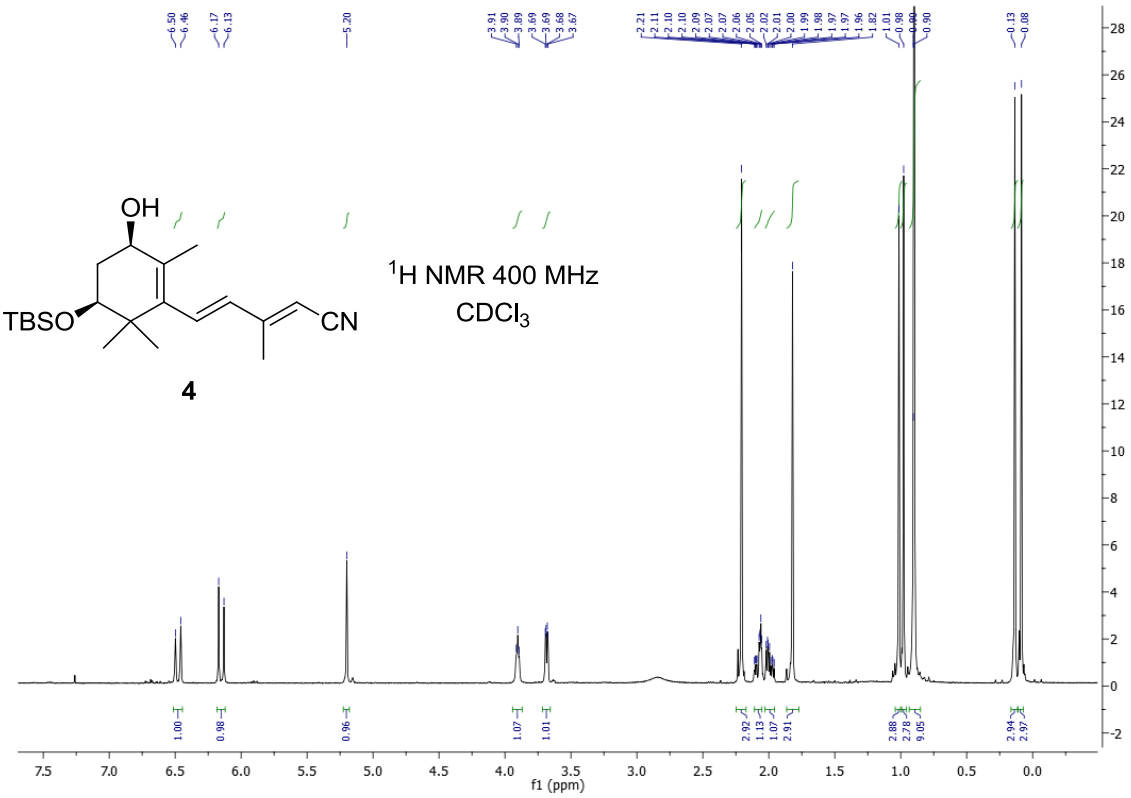


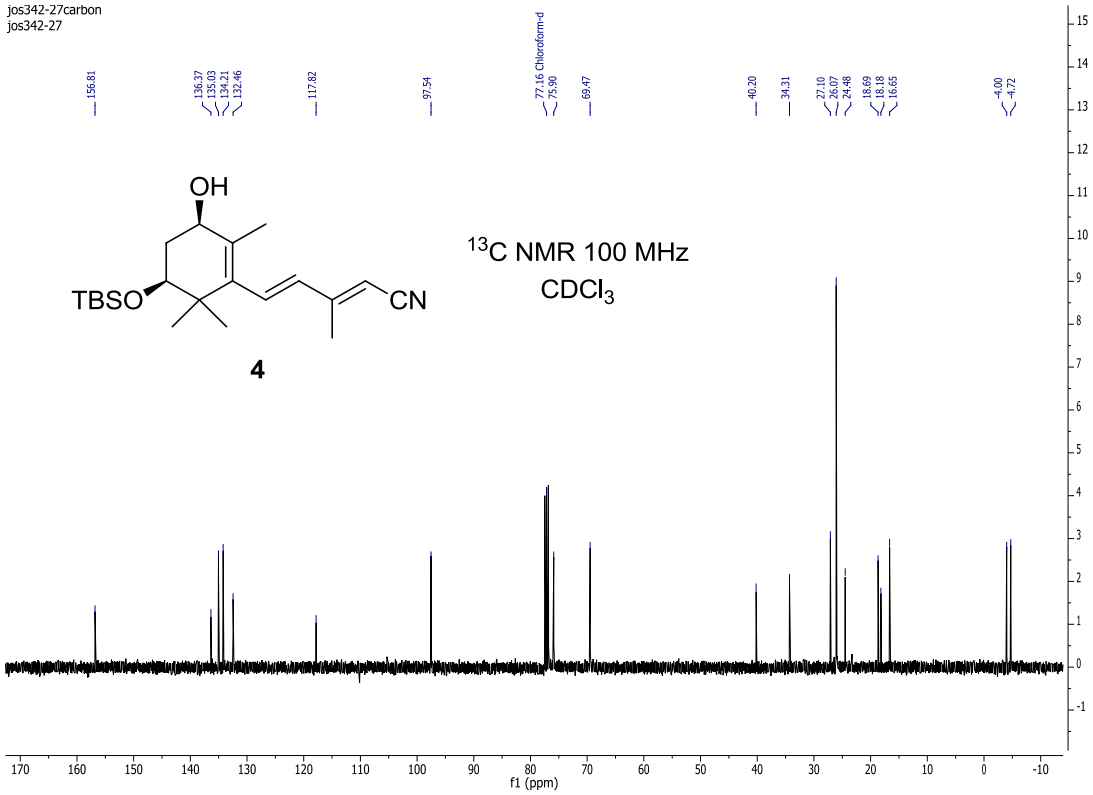

TBSO
O
O
5
^{1}H NMR 400 MHz
$CDCl_3$
f1 (ppm)

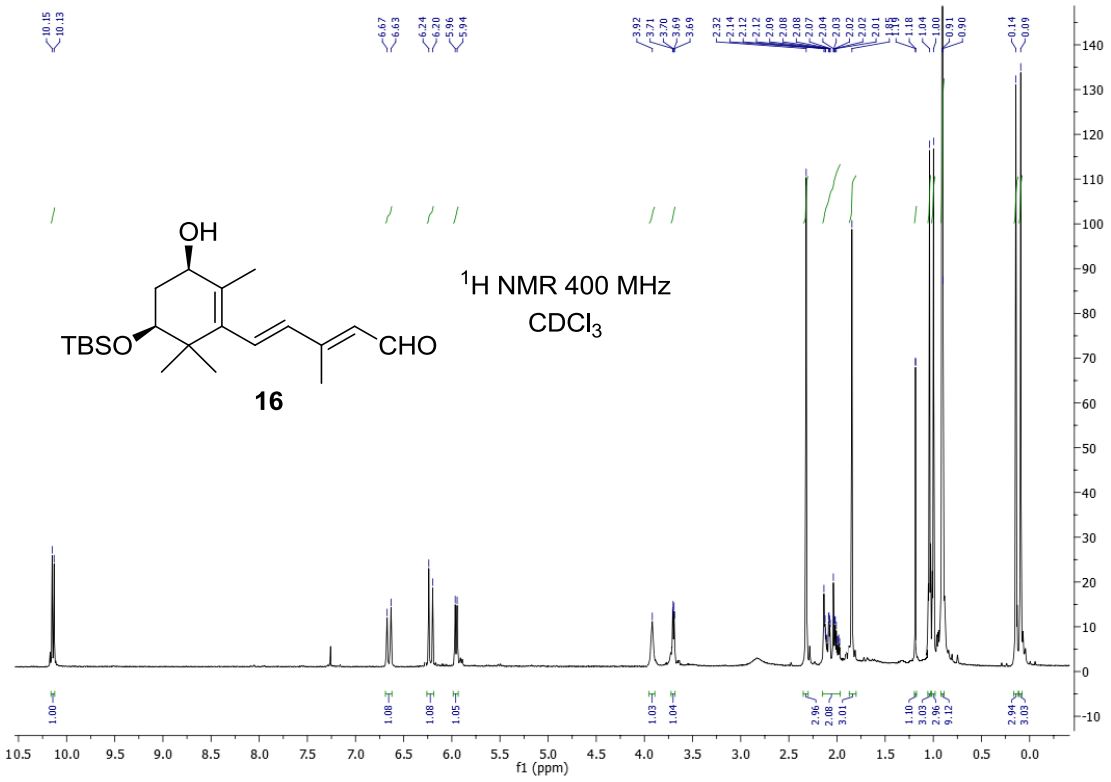

jose304-20carbon
jose304-20
TBSO
O
O
5
^{13}C NMR 100 MHz
$CDCl_3$
f1 (ppm)

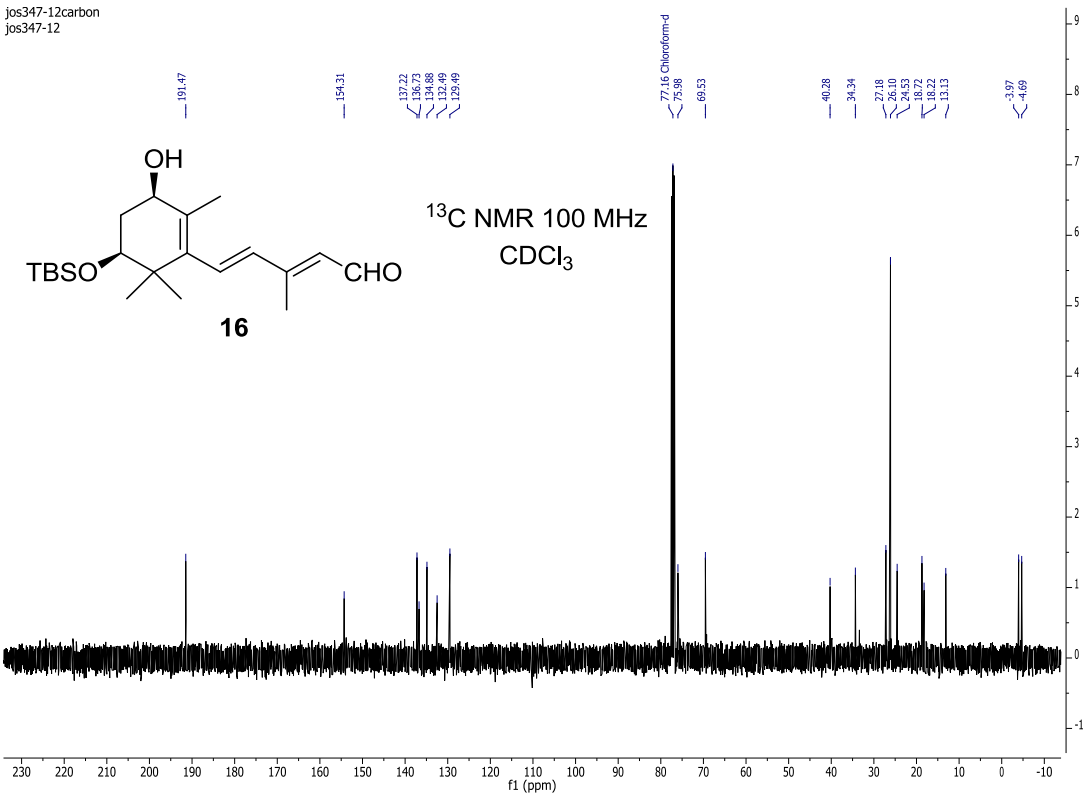

OH
TBSO
O
15
^{1}H NMR 400 MHz
$CDCl_3$
f1 (ppm)

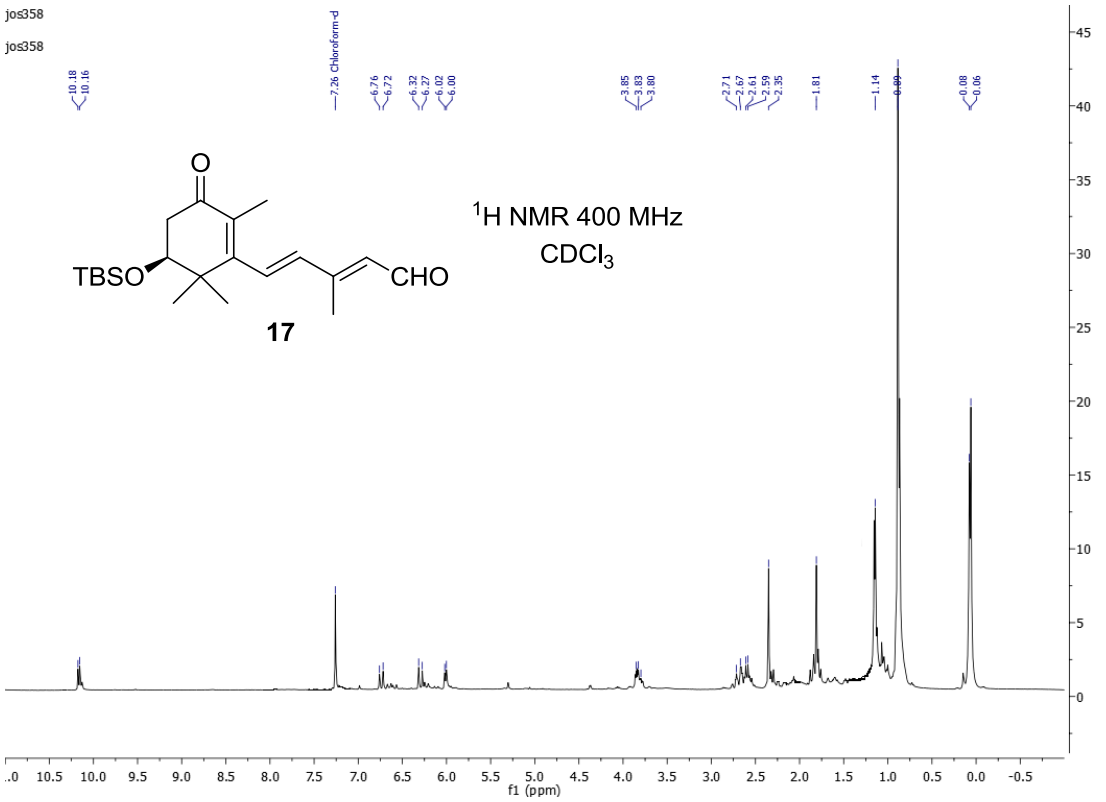

OH
TBSO
O
15
^{13}C NMR 100 MHz
$CDCl_3$
f1 (ppm)

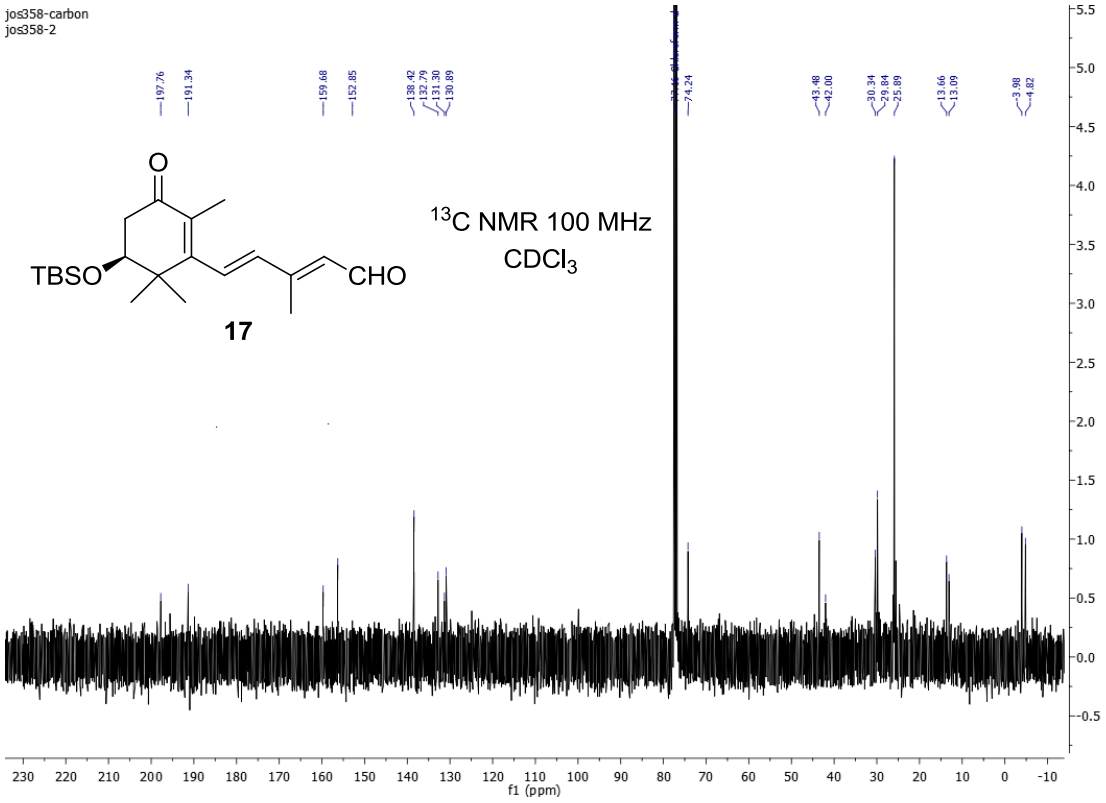

OH
TBSO
CN
4
^{1}H NMR 400 MHz
$CDCl_3$
f1 (ppm)

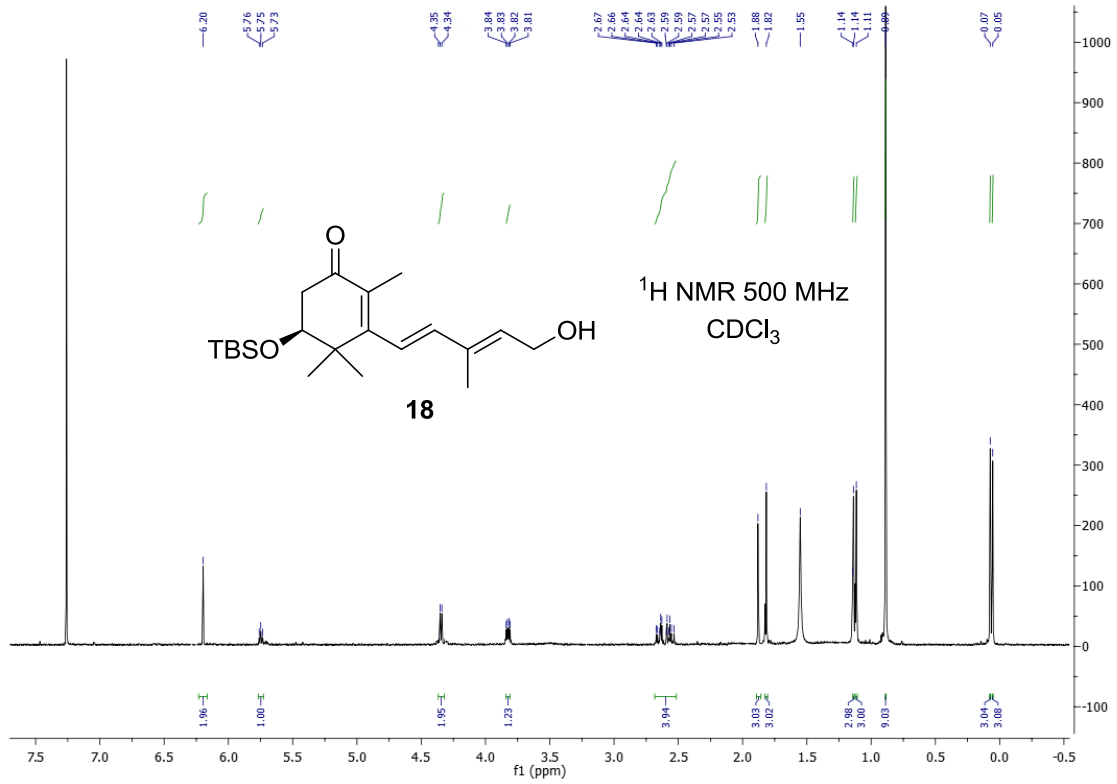

jos342-27carbon
jos342-27
OH
TBSO
CN
4
^{13}C NMR 100 MHz
$CDCl_3$
f1 (ppm)

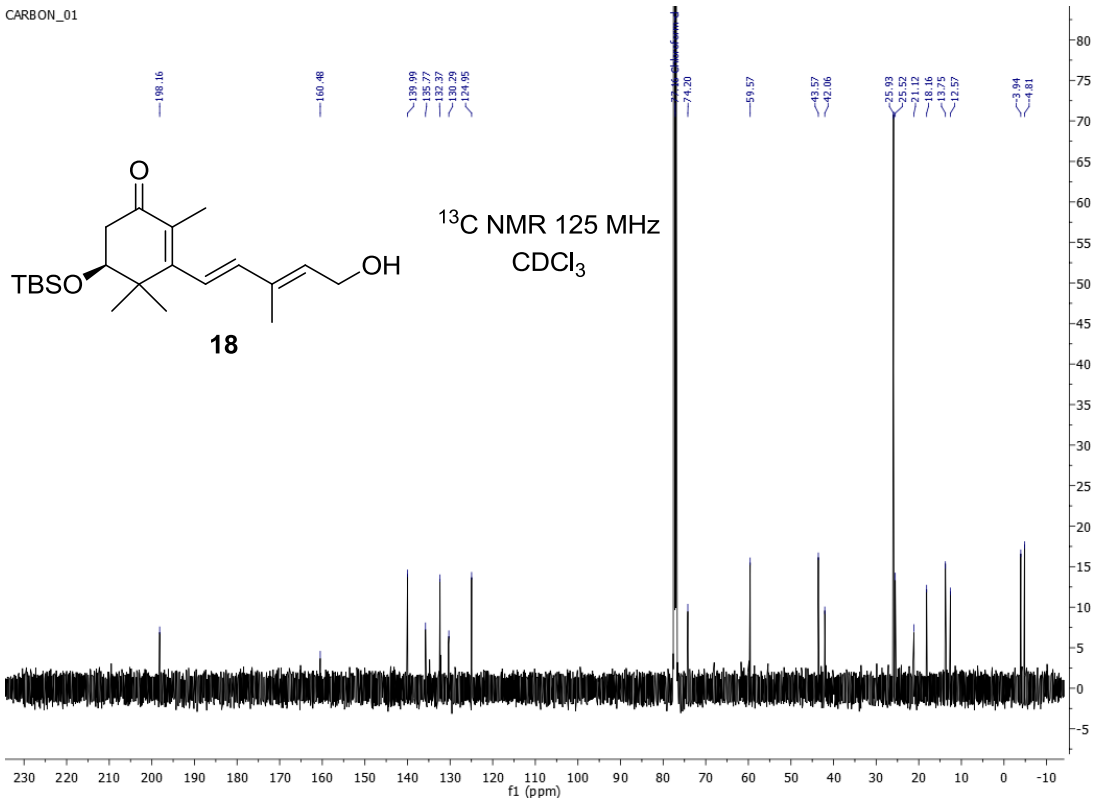


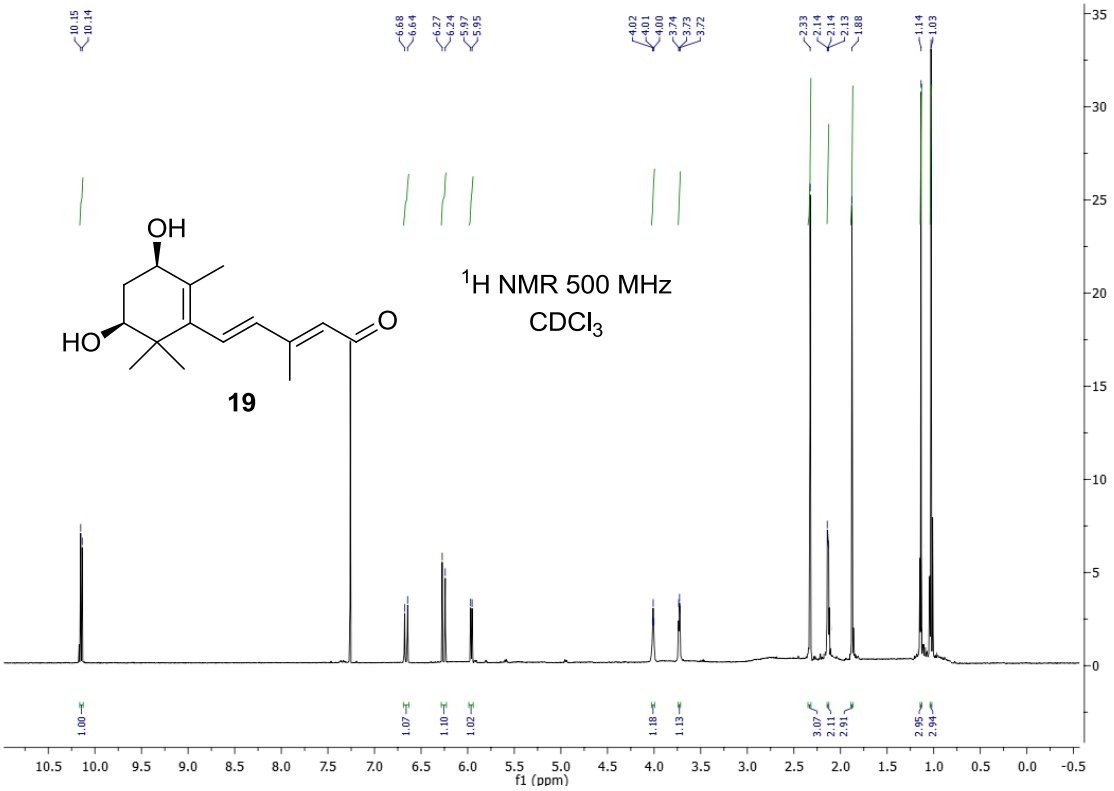


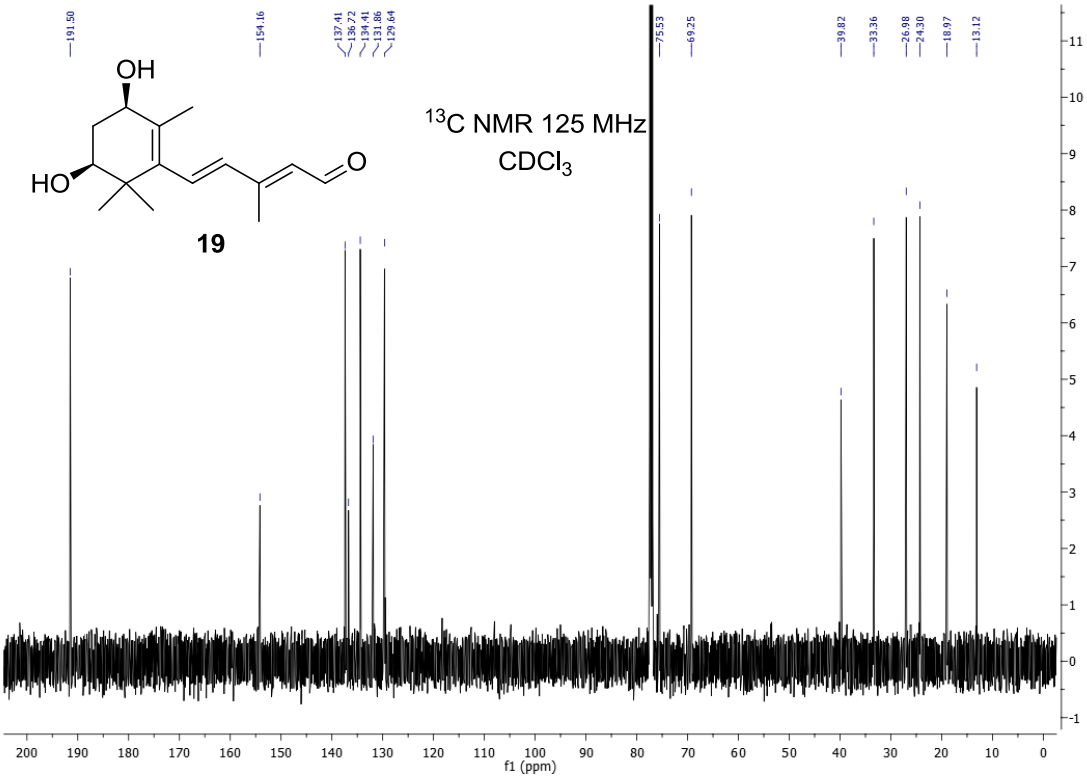

jos358
jos358
10.18
10.16
7.26 Chloroform-d
6.76
6.72
6.32
6.27
6.02
6.00
3.85
3.83
3.80
2.71
2.67
2.61
2.59
2.35
1.81
1.14
0.89
0.08
0.06
O
TBSO
CHO
17
1H NMR 400 MHz
CDCl3
f1 (ppm)


jos358-carbon
jos358-2
197.76
191.34
159.68
152.85
138.42
132.79
131.30
130.89
77.16
77.00
76.84
74.24
43.48
42.00
30.34
29.84
25.89
13.66
13.09
3.98
4.82
O
TBSO
CHO
17
13C NMR 100 MHz
CDCl3
f1 (ppm)


TBSO
OH
O
18
^{1}H NMR 500 MHz
$CDCl_3$
f1 (ppm)


CARBON_01
TBSO
OH
O
18
^{13}C NMR 125 MHz
$CDCl_3$
f1 (ppm)


OH
HO
O
19
^{1}H NMR 500 MHz
$CDCl_3$
f1 (ppm)


OH
HO
O
19
^{13}C NMR 125 MHz
$CDCl_3$
f1 (ppm)