Biocatalytic approaches for a more sustainable synthesis of sandalwood fragrances

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General information

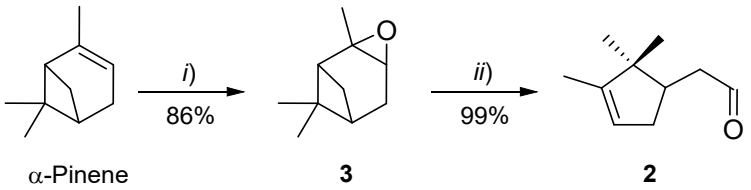
Chemicals and solvents were purchased from suppliers and used without further purification, while, where required, the solvents were dried over molecular sieves (4 Å). ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a 400 MHz spectrometer at 302 K in $CDCl_3$; chemical shifts (δ) are expressed in ppm relative to the TMS reference signal or to the signal of residual $CHCl_3$ (signal = 7.26 ppm for ^{1}H and signal = 77.16 ppm for ^{13}C) or to the signal of internal standard reference ppm for ^{19}F (C_6H_5F, signal= -112.96). The concentration of H_2O_2 was measured in a coaxial tube (5 mm), D_2O was used as external lock, and the chemical shift calibration was done on the HDO residual (signal = 4.71 ppm). The GC-MS analyses of all compounds were performed on a column with a low polarity stationary phase (30 m x 0.25 mm x 0.25 µm). Program temperature: 60 °C (1 min)/6 °C min^{-1}/150 °C (1 min)/12 °C min^{-1}/280 °C (5 min). For compounds **7c**-**d** was used a slightly modified program temperature: 60 °C (0 min)/2.5 °C min^{-1}/120 °C (9 min)/90 °C min^{-1}/280 °C (3 min). TLC analyses were performed on precoated silica gel 60 F_{254} plates, and spots were visualized either by UV light (254 nm) or by spraying with phosphomolybdic acid reagent. All chromatographic separations were carried out on silica gel columns (230-400 mesh). The distillations were performed on a bulb-to-bulb Kugelrohr like apparatus. Photoisomerization was carried out on a Rayonet photoreactor equipped with UV lamps (80 W). Before use, XAD-1180 resins were pre-conditioned in water until reaching a neutral pH, then washed with acetone. Optical rotations [α_D] were determined on a digital automatic polarimeter at 589 nm (sodium *D* line) and are given at 20 °C in ° cm^3 g^{-1} dm^{-1}. Chiral GC analyses were performed on a CP7502 Chirasil-DEX CB column (25 m x 0.25 mm x 0.25 µm). Program temperature: 80 °C (1 min)/5 °C min^{-1}/150 °C (1 min)/60 °C min^{-1}/200 °C (2 min).

Enzymes and strains

OYE1 (UniProtKB accession number Q02899) from *Saccharomyces pastorianus*, OYE2 (UniProtKB accession number Q03558) from *Saccharomyces cerevisiae*, OYE3 (UniProtKB accession number P41816) from *Saccharomyces cerevisiae*, NemA (UniProtKB accession number P77258) from *E. coli*, YqjM (UniProtKB accession number P54550) from *Bacillus subtilis*. GDH from *Bacillus megaterium*[1] (UniProtKB accession D5DB49) harboring a specific plasmid, according to standard molecular biology techniques.[2] Protein concentrations were determined according to the Bradford test, using Bovine Serum Albumin (BSA) as a standard. Evo270, Evo440 from an unspecified source were purchased from evoxx GmbH in the form of freeze-dried powder and used without further purifications. For Evo270 the activity was 15u/mg, test carried out on acetophenone as standard substrate. For Evo440 the activity was 1 u/mg, test carried out on cyclohexanone as standard substrate. Glucose Oxidase (GOX) from *Aspergillus niger* was purchased from Sigma-Aldrich in the form of lyophilized powder (Type II, 19˙290 units/g solid) and used without further purifications.

Synthesis of campholenic aldehyde from α-pinene (2 and 3)

Campholenic aldehyde **2** was prepared from commercially available α-pinene by a two-step sequence: *i*) Payne epoxidation, followed by *ii*) the $ZnBr_2$ catalysed Meinwald rearrangement (Scheme S1). Payne epoxidation proved to be the most performing procedure among a series of tested methodologies (Table S1). Both overall yield (85%) and chemoselectivity were more than satisfactory. After work-up, the pinene epoxide had a sufficiently high purity (89%) to be directly used the in the subsequent steps, rendering additional purification procedures unnecessary.

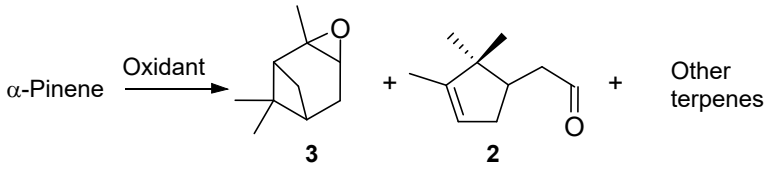


Scheme S1 Reaction conditions: *i*) H_2O_2, CCl_3CN, K_2HPO_4 buffer, CH_2Cl_2; *ii*) cat. $ZnBr_2$, toluene.

Screening of epoxidations methods for synthesis of α-pinene oxide (3)

Different oxidation protocols were tested, in the following we report the procedures according to Table S1.

Table S1 Screening of different epoxidation methods



Reaction conditions	Conv. [%][a]	Prod. Distribution [%][a]		
		3	**2**	Other terps
A) O_2,[b] 3 eq CH_3CHO, 0.1 eq NHPI, MeCN, 60 °C	62	55	17	28
B) 1.3 eq MCPBA, 1.0 eq $NaHCO_3$, CH_2Cl_2, 5-10 °C	91 (91)[c]	82	8	10
C) 1.2 eq H_2O_2,[d] 1.2 eq CCl_3CN, KPi (pH=7), CH_2Cl_2, rt	>99 (99)[c]	86	5	9
D) 1.1 eq H_2O_2,[d] 1.8 eq MeCN, MeOH, $KHCO_3$ buffer (pH=9), rt	-	-	-	-
E) 1.1 eq H_2O_2,[d] 13.3 eq MeCN, KPi (pH=7), 60 °C	18	64	7	29
F) 1.5 eq H_2O_2,[d] 6.6 eq PhCN, KPi (pH=7), 60 °C	-	-	-	-
G) *i*) O_2,[b] GOX, 3 eq glucose, KPi (pH=7), 30 °C; *ii*) 1.5 eq CCl_3CN, CH_2Cl_2, rt	65	68	17	15

a) Not isolated yield, by GC-MS; b) Bubbling; c) Yield of not isolated product; d) Concentration 30% w/v.

Procedures

A) NHPI catalyzed epoxidation with O_2/CH_3CHO

This procedure was slightly modified with respect to that reported in the literature.[3] To a solution of NHPI (163 mg) in MeCN (7 mL) heated at 60 °C was added acetaldehyde (1.32 g) and α-pinene (1.36 g). Then, pure O_2 was gently bubbled into the reaction solution for 2 hours. Product not isolated.

B) Epoxidation with MCPBA

This procedure was slightly modified with respect to that reported in the literature.[4] To an ice-cooled and mechanically stirred suspension of MCPBA (77% w/w, 22.0 g) and $NaHCO_3$ (11.0 g) in CH_2Cl_2 (250 mL) was added dropwise a solution of α-pinene (13.6 g) in CH_2Cl_2 (20 mL) at a rate such that the temperature was kept between 5-10 °C (usually over 30 minutes). After 2 hours the reaction mixture was quenched with an aq. solution of $NaHSO_3$ (1.0 M, 50 mL) and left to stir (30 minutes) at room temperature, then it was filtered. The white solid was washed with CH_2Cl_2 (2 x 25 mL). The organic phase was first washed with H_2O (50 mL) and then with an aq. solution of $NaHCO_3$ (sat., 100 mL). The combined aqueous phase was washed with CH_2Cl_2 (2 x 25 mL). Then, the combined organic phase was dried over anhydrous Na_2SO_4

and concentrated under *vacuum* affording **3** as a pale-yellow liquid. Yield 91% (14.0 g); tr= 9.2 min, 82% purity by GC-MS.

C) Payne epoxidation with CCl_3CN

Th following oxidation was adapted from Payne's seminal paper.[5] To a solution of α-pinene (20.4 g) in CH_2Cl_2 (350 mL) were added CCl_3CN (26.0 g) and an aq. solution of $K_2HPO_4 \cdot 3H_2O$ (1.3 M, 40 mL). Then, to the ice-cooled biphasic mixture was added dropwise (rate = 1 mL/min) a solution of H_2O_2 (30% w/v, 20.4 mL). After 1 hour the reaction mixture was left to stir for 12 hours at room temperature. Then, the organic phase was separated and washed with brine (sat., 50 mL). The combined aqueous phase was washed with CH_2Cl_2 (2 x 30 mL). The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated under *vacuum*. The mixture was diluted in *n*-hexane (150 mL), filtered and the cake was washed with *n*-hexane (3 x 20 mL). The by-product CCl_3CONH_2 was isolated as white solid (24.1 g). Then, the organic solution was concentrated under *vacuum* affording **3** of sufficient purity to be used in the next step.

Yield 99% (22.5 g) as a pale-yellow oil; tr= 9.2 min, 86% purity by GC-MS. **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 3.05 (dd, *J* = 4.2 and 1.5 Hz, 1H), 2.04-1.84 (m, 4H), 1.71 (m, 1H), 1.61 (d, *J* = 9.4 Hz, 1H), 1.33 (s, 3H), 1.28 (s, 3H), 0.93 (s, 3H); **^{13}C{^{1}H}-NMR** ($CDCl_3$, 101 MHz): δ 60.4, 57.0, 45.3, 40.7, 39.9, 27.8, 26.9, 26.0, 22.5, 20.3; GC-MS: m/z (%): 152 (M^+, 2), 137 (45), 109 (65), 67 (100). For oxidation of (–)-α-pinene (*ee* 82%, by chiral GC) $[\alpha]_D$ = –78.7 ($CHCl_3$, *c*= 1.3) *vs* litt. –103.9 ($CHCl_3$, *c*= 4.1),[6] for (+) enantiomer (*ee* 92%, by chiral GC) $[\alpha]_D$ = +80.7 ($CHCl_3$, *c*= 1.1) *vs* litt. +55 ($CHCl_3$, *c*= 0.2).[7]

D) Payne epoxidation with MeCN in MeOH

The procedure C was applied with the following exceptions: MeCN (14 mL) instead of CCl_3CN, $KHCO_3$ (2.6 g) instead of K_2HPO_4 solution, MeOH (80 mL) instead of CH_2Cl_2. Product not isolated.

E) Payne epoxidation with MeCN

The procedure C was applied with the following exceptions: MeCN (104 mL) instead of CCl_3CN and MeOH, T=60 °C. product not isolated.

F) Payne epoxidation with PhCN

The procedure C was applied with the following exceptions: PhCN (103 mL) instead of CCl_3CN and MeOH, T=60 °C. Product not isolated.

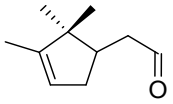
G) Payne epoxidation with CCl_3CN with *in situ* H_2O_2 generation

To an aqueous solution of anhydrous α-D-glucose (270 mg) and GOX (60 mg) in a phosphate buffer (pH=7, 50 mM, 3 mL) at 30 °C was gently bubbled pure O_2 for 12 hours. The formation of H_2O_2 was monitored by $^{13}C\{^1H\}$-NMR of the crude material in a coaxial tube with capillary filled with D_2O, the H_2O_2 concentration was evaluated 1.2% w/v (see NMR specra). Then, the solution was used in the Payne oxidation of α-pinene with CCl_3CN (C procedure). Product not isolated.

Recovery of CCl_3CN from CCl_3CONH_2

The amide CCl_3CONH_2 (24.1 g) was mechanically mixed with P_4O_{10} (42.0 g). Then, xylene (20 mL) was added, and the mixture was refluxed.[8] After 12 hours, the resulting mixture was distilled (Claisen type head distillation equipped with a 10 cm Vigreux column) affording crude CCl_3CN (b.p. 85-86 °C, 17.5 g). To obtain a higher purity, a rectification was required. Yield 65% (13.9 g); 96% purity by **^{13}C{^{1}H}-NMR** ($CDCl_3$, 101 MHz): δ=113.1, 70.2.[9]

Campholenic aldehyde (2)



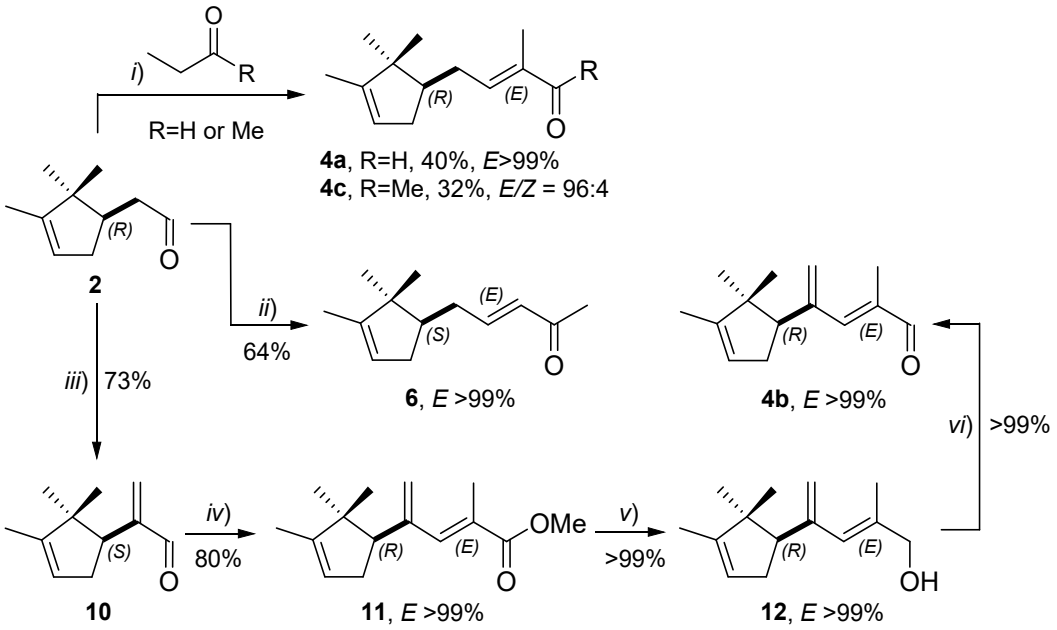
2

To a solution of **3** (22.5 g) in dry toluene (150 mL) was added anhydrous $ZnBr_2$ (1.7 g). The mixture was stirred at room temperature under an inert atmosphere (N_2). After 12 hours, the reaction mixture was quenched with an aq. solution of CH_3CO_2H (10% v/v, 30 mL) and left to stir at room temperature (10 min). The organic phase was washed with H_2O (50 mL) and then with a aq. solution of $NaHCO_3$ (sat., 50 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated under *vacuum* affording **2**.[10]

Yield 99% (22.3 g) as a pale-yellow oil; tr= 9.9 min, 89% purity by GC-MS; **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 9.79 (t, *J*=2.3 Hz, 1H), 5.23 (m, 1H), 2.52 (ddd, *J*=15.5, 4.3 and 2.0 Hz, 1H), 2.43-2.33 (m, 2H), 2.27 (m, 1H), 1.88 (ddt, *J*=15.5, 8.7 and 2.4 Hz, 1H), 1.61 (dt, 2.8 and 1.6 Hz, 3H), 0.99 (s, 3H), 0.78 (s, 3H); **^{13}C{^{1}H}-NMR** ($CDCl_3$, 101 MHz): δ 203.0, 148.1, 121.7, 47.1, 45.2, 44.4, 35.7, 25.8, 20.1, 12.7; GC-MS: m/z (%): 152 (M^+, 1), 108 (100), 95 (40), 93 (80). For rearrangement of (–)-α-pinene oxide (*ee* 82%) was obtained the (*R*)-campholenic aldehyde: $[\alpha]_D$ = +3.8 ($CHCl_3$, *c*= 1.1) *vs* litt. +3.0 ($CHCl_3$, *c*= 1.06);[11] for rearrangement of (+)-α-pinene oxide (*ee* 92%) was obtained the (*S*)-campholenic aldehyde: $[\alpha]_D$ = –4.1 ($CHCl_3$, *c*= 1.1) *vs* litt. –3.7 (neat).[12]

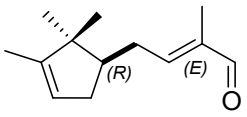
Synthesis of α,β-unsaturated carbonyl compounds for bioreductions (4a-c and 6)

Substrates **4a**-**c** and **6** were prepared following procedures reported in patent literature (Scheme S2). Yields and diastereoselectivity were consistent with those reported in the patents.



Scheme S2 Reaction conditions: *i*) with propanal, cat. MeONa, MeOH, with butan-2-one, cat. $NaOH_{(aq)}$, MeOH; *ii*) $Ph_3P{=}CHCOCH_3$, reflux. CH_2Cl_2; *iii*) $CH_2O_{(aq)}$, cat. pyrrolidine, cat. $CH_3CH_2CO_2H$, *i*-PrOH, 45 °C; *iv*) $Ph_3P{=}C(CH_3)CO_2Me$, reflux. CH_2Cl_2; *v*) $LiAlH_4$, THF; *vi*) MnO_2, reflux. $CHCl_3$.

(*R*,*E*)-2-methyl-4-(2,2,3-trimethylcyclopent-3-en-1-yl)but-2-enal (4a)

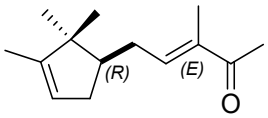


4a

To an ice-cooled and well stirred solution of MeONa (129 mg) in MeOH (5 mL) was added dropwise a mixture of (+)-**2** (3.0 g, 19.7 mmol) and propionaldehyde (3.8 g) at a rate such that the temperature was kept between 5-10 °C (usually over half an hour). After 4 hours the reaction was quenched with acetic acid until neutral pH. Then, Et_2O (50 mL) was added to the mixture, which was washed in sequence with an aq. solution of $NaHCO_3$ (sat., 50 mL), HCl (1 M, 50 mL) and brine (sat., 50 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under *vacuum* affording **4a** as pale-yellow liquid, which was purified by bulb-to-bulb distillation (105 °C, 0.2-0.3 mbar).[13]

Yield 40% (1.5 g) as a colourless oil; tr= 17.4 min, 91% purity (*E*>99%) by GC-MS; **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 9.39 (s, 1H), 6.53 (td, *J* = 7.5 and 1.5 Hz, 1H), 5.22 (m, 1H), 2.46 (m, 1H), 2.39-2.23 (m, 2H), 1.94-1.92 (m, 2H), 1.76 (m, 3H), 1.61 (m, 3H), 1.01 (s, 3H), 0.83 (s, 3H); **^{13}C{^{1}H}-NMR** ($CDCl_3$, 101 MHz): δ 195.4, 154.8, 148.5, 139.6, 121.6, 49.7, 47.1, 35.6, 30.0, 26.0, 19.9, 12.7, 9.4; GC-MS: m/z (%): 192 (M^+, 6), 121 (32), 108 (100), 93 (56); $[\alpha]_D$ = +3.6 ($CHCl_3$, *c*= 0.5).

(*R*,*E*)-3-methyl-5-(2,2,3-trimethylcyclopent-3-en-1-yl)pent-3-en-2-one (4c, Sandex®)



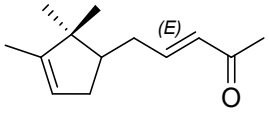
4c

To an ice-cooled and well stirred solution of butan-2-one (15.0 g) in MeOH (25 mL) was added an aq. solution of NaOH (12 M, 5 mL). Then, (+)-**2** (8.0 g) was added dropwise (rate = 0.5 mL/min) to the mixture. After 3 hours, the mixture was left to reach room temperature and then an aq. solution of HCl (1 M) was added dropwise until acidic pH was reached. The reaction mixture was kept under stirring overnight, and then diluted with CH_2Cl_2 (100 mL). The organic phase was

separated, and the aqueous phase was washed with CH_2Cl_2 (3 x 20 mL). The combined organic phase was washed with brine (sat., 40 mL), dried over anhydrous Na_2SO_4 and concentrated under *vacuum* to give the crude product, which was isolated by column chromatography in *n*-hexane/EtOAc (97:3) and by *vacuum* distillation (90 °C, 0.2-0.3 mbar), affording **4c**.[14]

Yield 32% (3.5 g) as an almost colourless liquid; tr=18.9 min, 96% purity (*E*/*Z*= 96:4) by GC-MS; **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 6.68 (tq, *J* = 7.3, 1.4 Hz, 1H), 5.23 (m, 1H), 2.37 (m, 1H), 2.30 (s, 3H), 2.23 (m, 1H), 1.98-1.81 (m, 2H), 1.79 (q, *J* = 1.1 Hz, 3H), 1.62 (m, 3H), 1.57 (s, 1H), 1.02 (s, 3H), 0.83 (s, 3H); **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ 199.9, 148.6, 143.6, 137.8, 121.6, 49.9, 47.1, 35.7, 30.1, 26.0, 25.5, 19.9, 12.7, 11.3; GC-MS: m/z (%): 206 (M^+, 12), 136 (64), 109 (72), 98 (100); $[\alpha]_D$ = +0.4 ($CHCl_3$, *c*= 1.0).

General procedure for the synthesis of (*S*) or (*R*) enantiomer of (*E*)-5-(2,2,3-trimethylcyclopent-3-en-1-yl)pent-3-en-2-one (6)

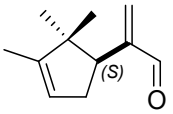


6

To a refluxing and well stirred solution of Ph_3P=$CHCOCH_3$ (25.0 g, 79 mmol) in CH_2Cl_2 (30 mL) was added the campholenic aldehyde (8.0 g). After 20 hours the reaction mixture was concentrated under *vacuum*, then the crude solid was triturated with a solvent mixture of *n*-hexane/Et_2O (9:1, 100 mL) and filtrated. The organic phase was concentrated under *vacuum* to give the crude product, which was purified by distillation under *vacuum* (110 °C, 0.2-0.3 mbar), affording **6**.[15]

Yield 64% (6.5 g) as an almost colourless liquid; tr=17.6 min, 92% purity by GC-MS; *E*>99% by ^{1}H-NMR; **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 6.81 (dt, *J* = 15.9, 7.3 Hz, 1H), 6.11 (dt, *J* = 15.9, 1.4 Hz, 1H), 5.22 (m, 1H), 2.38 (m, 1H), 2.24 (s, 3H), 2.17 (m, 1H), 1.96-182 (m, 2H), 1.61 (m, 3H), 1.58 (s, 1H), 1.00 (s, 3H), 0.81 (s, 3H); **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ 198.5, 148.39, 148.36, 131.8, 121.5, 49.4, 47.0, 35.5, 33.6, 26.9, 25.9, 19.8, 12.6; GC-MS: m/z (%): 192 (M^+, 3), 159 (35), 108 (100), 93 (87); for (*S*)-**6** (from (–)-pinene, *ee* 82%) $[\alpha]_D$ = –2.9 ($CHCl_3$, *c*= 1.1); for (*R*)-**6** (from (+)-pinene, *ee* 92% of pinene) $[\alpha]_D$ = +3.8 ($CHCl_3$, *c*= 1.2).

(*S*)-2-(2,2,3-trimethylcyclopent-3-en-1-yl)acrylaldehyde (10)

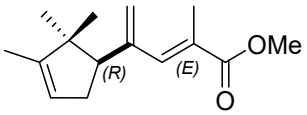


10

To a stirred solution of (+)-**2** (7.0 g) in *i*-PrOH (7 mL) at 45 °C was added an aqueous solution of formaldehyde (37% w/w, 6.8 mL), pyrrolidine (0.64 g), and propanoic acid (0.67 g). After 4 hours, Et_2O (100 mL) was added to the mixture, which was washed in sequence with an aq. solution of $NaHCO_3$ (sat., 50 mL), HCl (1 M, 50 mL) and brine (sat., 50 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated under *vacuum* affording **10** as a yellow liquid, which was purified by bulb-to-bulb-distillation (90 °C, 0.2-0.3 mbar).[16]

Yield 73% (5.5 g) as a colourless oil; tr= 11.3 min, 95% purity by GC-MS; **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 9.55 (s, 1H), 6.32 (s, 1H), 6.09 (s, 1H), 5.27 (m, 1H), 3.18 (tt, *J*= 8.2 and 0.9 Hz, 1H), 2.35-2.26 (m, 2H), 1.58 (m, 3H), 1.01 (s, 3H), 0.66 (s, 3H); **^{13}C{^{1}H}-NMR** ($CDCl_3$, 101 MHz): δ 195.2, 151.4, 147.4, 135.5, 121.5, 48.2, 46.6, 34.7, 26.6, 21.7, 12.8; GC-MS: m/z (%): 164 (M^+, 43), 149 (100), 107 (93), 93 (86); $[\alpha]_D$ = –124.0 ($CHCl_3$, *c*= 1.0) *vs* litt. –103.6 (neat).[17b]

Methyl (*R*,*E*)-2-methyl-4-(2,2,3-trimethylcyclopent-3-en-1-yl)penta-2,4-dienoate (11)

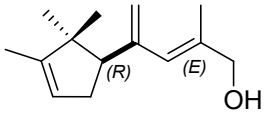


11

To a refluxing and well stirred solution of **10** (4.0 g) in CH_2Cl_2 (50 mL) was added $Ph_3P{=}C(CH_3)CO_2Me$ (17.0 g). After 8 hours the reaction mixture was concentrated under *vacuum*, then the crude solid was triturated with a solvent mixture of *n*-hexane/Et_2O (9:1, 50 mL) and filtrated. The organic phase was concentrated under *vacuum* affording **11** as a yellow liquid, which was purified by bulb-to-bulb distillation (120 °C, 0.2-0.3 mbar).

Yield 80% (4.5 g) as a colourless oil; tr= 19.9 min, 97% purity (*E*>99%) by GC-MS; **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 7.15 (t, *J* = 1.6 Hz, 1H), 5.29 (t, *J* = 1.6 Hz, 1H), 5.26 (m, 1H), 5.08 (t, *J* = 1.6 Hz, 1H), 3.75 (s, 3H), 2.63 (tt, *J* = 8.5 Hz and 0.9 Hz, 1H), 2.32-2.30 (m, 2H), 2.00 (d, *J*= 1.6 Hz, 3H), 1.58 (m, 3H), 1.02 (s, 3H), 0.71 (s, 3H); **^{13}C{^{1}H}-NMR** ($CDCl_3$, 101 MHz): δ 169.2, 147.7, 145.2, 141.7, 127.5, 121.3, 117.6, 57.0, 51.9, 48.1, 33.4, 26.5, 20.8, 14.4, 12.8; GC-MS: m/z (%): 234 (M^+, 11), 164 (57), 159 (100), 132 (45); $[\alpha]_D$ = +65.9 ($CHCl_3$, *c*= 1.0).

(*R*,*E*)-2-methyl-4-(2,2,3-trimethylcyclopent-3-en-1-yl)penta-2,4-dien-1-ol (12)

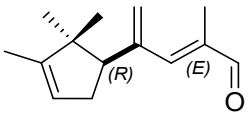


12

To an ice-cooled and well stirred solution of **11** (4.0 g) in dry THF (30 mL) was portion wise added $LiAlH_4$ (325 mg), usually over 30 minutes. Then, the mixture was left to reach room temperature and after 1 hours the reaction was ice-cooled and quenched with a Seignette solution (sat., 30 mL) and left to stir over 1 hour. Then, the mixture was washed with EtOAc (3 x 30 mL). The combined organic phase was washed with brine (sat., 30 mL), dried over anhydrous Na_2SO_4 and concentrated under *vacuum* affording **12** as a yellow liquid, the product was of sufficient purity to be used in the next step.

Yield > 99% (3.5 g) as a pale-yellow oil; tr= 18.9 min, 96% purity (*E*>99%) by GC-MS; **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 5.92 (m, 1H), 5.25 (m, 1H), 5.12 (m, 1H), 4.95 (t, *J* = 1.6 Hz, 1H), 4.07 (s, 2H), 2.57 (t, *J* = 8.5 Hz, 1H), 2.33 (m, 1H), 2.21 (m, 1H), 1.83 (m, 3H), 1.59 (m, 3H), 1.43 (bs, 1H), 1.03 (s, 3H), 0.72 (s, 3H); **^{13}C{^{1}H}-NMR** ($CDCl_3$, 101 MHz): δ 147.7, 145.7, 136.1, 127.8, 121.5, 114.9, 69.2, 57.3, 48.1, 33.6, 26.7, 20.9, 15.7, 12.9; GC-MS: m/z (%): 206 (M^+, 18), 175 (80), 105 (100), 91 (92); $[\alpha]_D$ = +40.5 ($CHCl_3$, *c*= 0.8).

(*R*,*E*)-2-methyl-4-(2,2,3-trimethylcyclopent-3-en-1-yl)penta-2,4-dienal (4b)



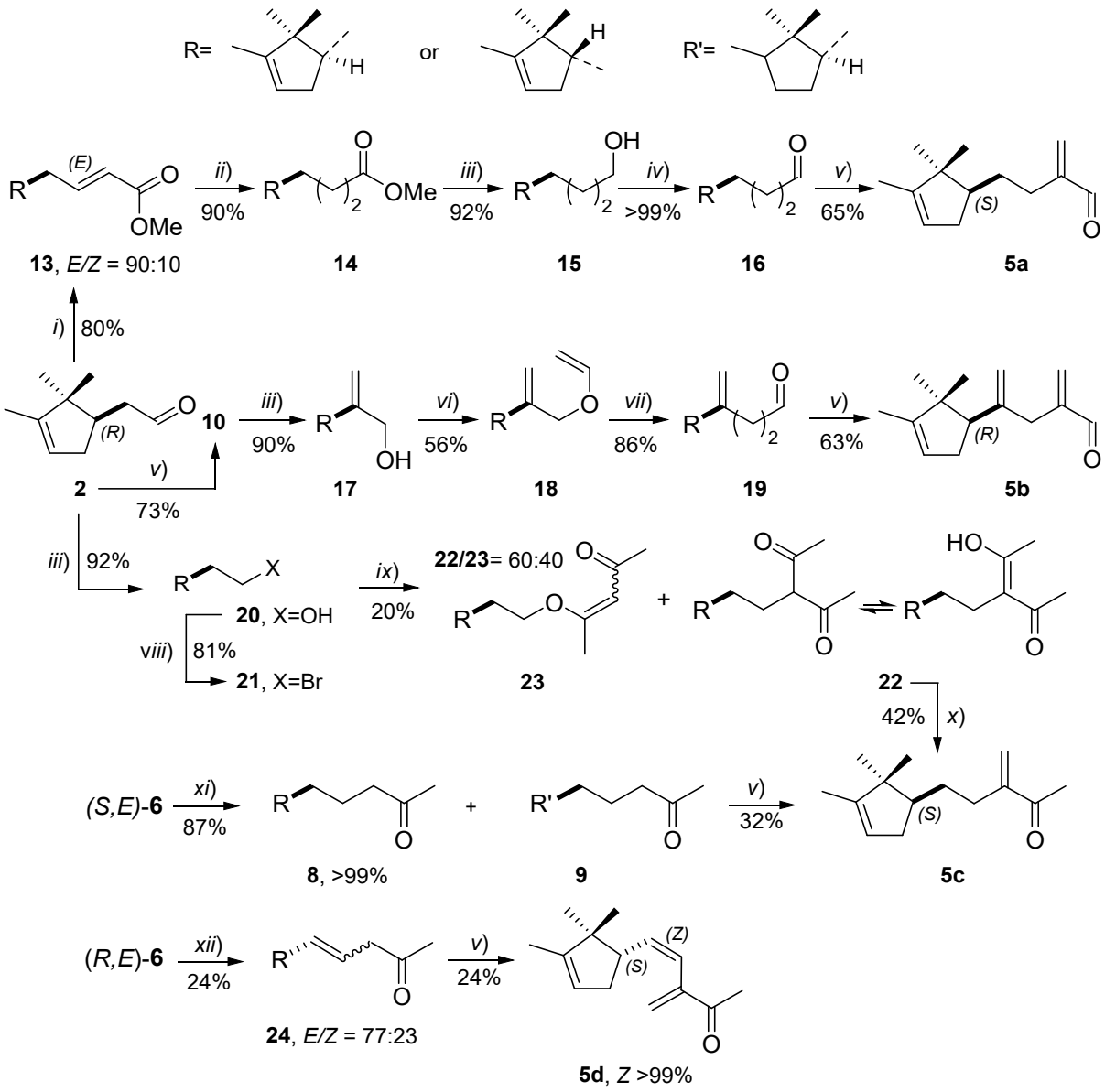
4b

To a refluxing and well stirred solution of **12** (3.4 g) in $CHCl_3$ (30 mL) was added MnO_2 (17.0 g). After 8 hours the reaction mixture was filtered on a celite pad, which washed with $CHCl_3$ (3 x 30 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated under *vacuum* affording **4b** as a yellow liquid, which was purified by bulb-to-bulb distillation (110 °C, 0.2-0.3 mbar).

Yield > 99% (3.4 g) as a colourless oil; tr= 18.5, >99% purity (*E*>99%) by GC-MS; **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 9.44 (s, 1H), 6.78 (m, 1H), 5.40 (t, *J* = 1.3 Hz, 1H), 5.26 (m, 1H), 5.23 (t, *J* = 1.3 Hz, 1H), 2.69 (td, *J* = 8.2 and 1.1 Hz, 1H), 2.34-2.31 (m, 2H), 1.89 (d, *J* = 1.5 Hz, 3H), 1.58 (m, 3H), 1.02 (s, 3H), 0.70 (s, 3H); **^{13}C{^{1}H}-NMR** ($CDCl_3$, 101 MHz): δ 195.7, 151.9, 147.6, 144.7, 138.5, 121.3, 119.3, 57.0, 48.2, 33.6, 26.7, 20.9, 12.7, 11.3; GC-MS: m/z (%): 204 (M^+, 14), 134 (72), 108 (100), 91 (88); $[\alpha]_D$ = +112.0 ($CHCl_3$, *c*= 1.1).

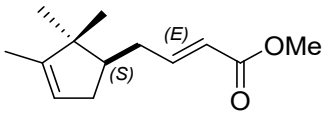
Synthesis of α-methylene carbonyl substrates for bioreductions (5a-d)

Unlike to the α,β-unsaturated substates **4a**-**c** and **6**, the preparation of α-methylene carbonyl compounds **5a**-**d** required a completely new synthetic route (Scheme S3). Our strategy was based on introducing the α methylene group in the last stage of the synthesis *via* Mannich homologation. The carbon skeleton of Mannich precursors, *i.e.* aldehydes and ketones **16**, **19**, **9** and **23**, was build-up from campholenic aldehyde **2** by Wittig reaction or Claisen rearrangement, followed by standard functional group transformations. This synthetic strategy demonstrated robustness, generality, and in most cases high yields. In contrast, attempts to synthesize the vinyl ketone **5c** by reacting the 1,3-diketone **22** with formaldehyde resulted in unsatisfactory yield, selectivity, and purity.



Scheme S3 Reaction conditions: *i*) $Ph_3P{=}CHCO_2Me$, CH_2Cl_2; *ii*) Mg, MeOH; *iii*) $LiAlH_4$, THF; *iv*) DMP, CH_2Cl_2; *v*) $CH_2O_{(aq)}$, pyrrolidine, $CH_3CH_2CO_2H$, *i*-PrOH, 45 °C; *vi*) $C_2H_5OCH{=}CH_2$, cat. $Hg(OAc)_2$; *vii*) 160 °C; *viii*) PPh_3, CBr_4, CH_2Cl_2; *ix*) 2,4-pentandione, cat. TBAI, K_2CO_3, acetone; *x*) $CH_2O_{(aq)}$, K_2CO_3, H_2O, 35 °C; *xi*) Different methods were tested (Table S2), the best chemoselectivity was achieved with: OYE2, GDH, glucose, NADPH, KPi buffer, 30 °C; *xii*) UV irradiation (λ= 350 nm), acetone.

Methyl (*S*,*E*)-4-(2,2,3-trimethylcyclopent-3-en-1-yl)but-2-enoate (13)

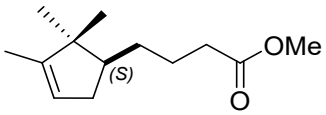


13

To a well stirred solution of (+)-**2** (4.0 g, 26.3 mmol) in CH_2Cl_2 (50 mL) was added $Ph_3P{=}CHCO_2Me$ (17.6 g, 52.6 mmol), the mixture was left to stir at room temperature. After 8 hours the reaction mixture was concentrated under *vacuum*, then the crude solid was triturated with a solvent mixture of *n*-hexane/Et_2O (9:1, 50 mL) and filtrated. The organic phase was concentrated under *vacuum* affording **13** as a yellow liquid, which was purified by bulb-to-bulb distillation (120 °C, 0.2-0.3 mbar).

Yield 80% (4.3 g) as a colourless oil; tr= 18.3 min, 87% purity (*E*/*Z*= 90:10) by GC-MS; **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 6.98 (dt, *J* = 15.1 and 7.8 Hz, 1H), 5.83 (dt, *J* = 15.1 and 1.6 Hz,1H), 5.20 (m, 1H), 3.71 (s, 3H), 2.38-2.21 (m, 2H), 2.13 (m, 1H), 1.93-1.79 (m, 2H), 1.59 (m, 3H), 0.98 (s, 3H), 0.78 (s, 3H); **^{13}C{^{1}H}-NMR** ($CDCl_3$, 101 MHz): δ 167.2, 149.6, 121.6, 121.4, 119.5, 51.4, 49.3, 47.1, 35.6, 33.4, 25.9, 19.9, 12.7; GC-MS: m/z (%): 208 (M^+, 16), 161 (67), 133 (100), 109 (77); $[\alpha]_D$ = −0.6 ($CHCl_3$, *c*= 1.0).

Methyl (*S*)-4-(2,2,3-trimethylcyclopent-3-en-1-yl)butanoate (14)

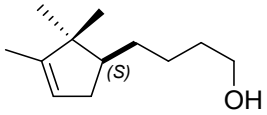


14

To an ice-cooled and well stirred solution of **13** (3.8 g) in dry MeOH (40 mL) were added magnesium cuttings (2.2 g), after the evolution of H_2 (10 min) the mixture was left to stir at room temperature. After 8 hours the reaction was ice-cooled and quenched with an aq. solution of HCl (3 N, 40 mL), then the mixture was washed with CH_2Cl_2 (3 x 40 mL). The combined organic phase was washed in sequence with an aq. solution of NH_4Cl (sat., 50 mL) and brine (sat., 50 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under *vacuum* affording **14** as pale-yellow oil, which was purified through silica gel column chromatography with *n*-hexane/EtOAc (95:5).[18]

Yield 90% (3.4 g) as pale yellow oil; tr= 17.1 min, 93% purity by GC-MS; **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 5.20 (m, 1H), 3.64 (s, 3H), 2.33-2.29 (m, 2H), 1.76-1.74 (m, 2H), 1.70-1.67 (m, 2H), 1.57 (m, 3H), 1.41 (m, 1H), 1.26-1.24 (m, 2H), 0.94 (s, 3H), 0.72 (s, 3H); **^{13}C{^{1}H}-NMR** ($CDCl_3$, 101 MHz): δ 174.3, 148.7, 121.7, 51.5, 50.2, 46.9, 35.7, 34.6, 29.7, 25.9, 24.4, 19.8, 12.7; GC-MS: m/z (%): 210 (M^+, 11), 195 (100), 163 (55), 121 (88); $[\alpha]_D$ = +9.25 ($CHCl_3$, *c*= 0.8).

(*S*)-4-(2,2,3-trimethylcyclopent-3-en-1-yl)butan-1-ol (15)

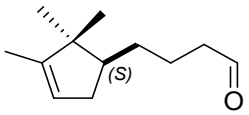


15

The same procedure used for the synthesis of **12** was adapted for the reduction of **14** (3.4 g).

Yield 92% (2.5 g) as a pale-yellow oil; tr= 14.6 min, 97% purity by GC-MS; **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 5.22 (m, 1H), 3.65 (t, *J* = 6.6 Hz, 2H), 2.30 (m, 1H), 1.84-1.68 (m, 3H), 1.60 (m, 3H), 1.48-1.39 (m, 2H), 1.34-1.23 (m, 3H), 0.97 (s, 3H), 0.75 (s, 3H); **^{13}C{^{1}H}-NMR** ($CDCl_3$, 101 MHz): δ 148.90, 121.8, 63.2, 50.6, 46.9, 35.8, 33.4, 29.9, 26.0, 25.1, 19.8, 12.7; GC-MS: m/z (%): 182 (M^+, 13), 180 (33), 147 (100), 121 (88); $[\alpha]_D$ = +8.5 ($CHCl_3$, *c*= 0.9).

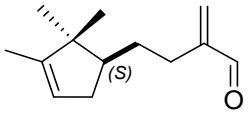
(*S*)-4-(2,2,3-trimethylcyclopent-3-en-1-yl)butanal (16)



16

To an ice-cooled and well stirred solution of **15** (2.5 g) in CH_2Cl_2 (30 mL) was added Dess-Martin reagent (DMP, 6.4 g), then the reaction mixture was left to reach room temperature. After 1 hours the mixture was filtered on a celite pad, which washed with CH_2Cl_2 (3 X 30 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated under *vacuum* affording **16** as a yellow liquid, the product was of sufficient purity to be used in the next step.
Yield > 99% (2.4 g) as a pale-yellow oil; tr= 15.1, 96% purity by GC-MS; **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 9.77 (t, *J* = 1.8 Hz, 1H), 5.22 (m, 1H), 2.50-2.38 (m, 2H), 2.29 (m, 1H), 1.84-1.66 (m, 3H), 1.61-1.55 (m, 3H+1H), 1.43 (m, 1H), 1.28 (m, 1H), 0.96 (s, 3H), 0.74 (s, 3H); **^{13}C{^{1}H}-NMR** ($CDCl_3$, 101 MHz): δ 202.8, 148.8, 121.7, 50.4, 46.9, 44.4, 35.7, 29.8, 25.9, 21.5, 19.8, 12.7; GC-MS: m/z (%): 180 (M^+, 24), 147 (68), 121 (100), 91 (39); $[\alpha]_D$ = +5.5 ($CHCl_3$, *c*= 0.7).

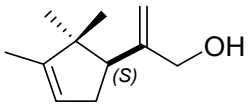
(*S*)-2-methylene-4-(2,2,3-trimethylcyclopent-3-en-1-yl)butanal (5a)



5a

The same procedure used for the synthesis of **10** was adapted for the Mannich homologation of **16** (2.0 g), but the product was purified by silica gel column chromatography purification with *n*-hexane/EtOAc (95:5).
Yield 65% (1.4) as a pale-yellow oil; tr= 16.4, 97% purity by GC-MS; **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 9.54 (s, 1H), 6.27 (td, *J* = 1.4 and 0.9 Hz, 1H), 5.99 (td, *J* = 1.4 and 0.9 Hz, 1H), 5.22 (m, 1H), 2.34-2.31 (m, 2H), 2.18 (m, 1H), 1.89-1.68 (m, 1H+2H), 1.59 (dt, *J* = 2.7 and 1.6 Hz, 3H), 1.40 (m, 1H), 0.96 (s, 3H), 0.75 (s, 3H); **^{13}C{^{1}H}-NMR** ($CDCl_3$, 101 MHz): δ 194.9, 150.9, 148.8, 133.9, 121.7, 50.1, 46.9, 35.6, 28.4, 27.1, 25.9, 19.9, 12.7; GC-MS: m/z (%): 192 (M^+, 18), 159 (36), 121 (100), 109 (54); $[\alpha]_D$ = +10.1 ($CHCl_3$, *c*= 0.8).

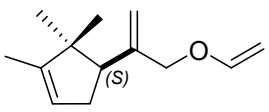
(*S*)-2-(2,2,3-trimethylcyclopent-3-en-1-yl)prop-2-en-1-ol (17)



17

The same procedure used for the synthesis of **12** was adapted for the reduction of **10** (3.3 g).
Yield 90% (3.0 g) as a pale-yellow oil; tr= 13.2 min, 98% purity by GC-MS; **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 5.28 (m, 1H), 5.22 (q, *J* = 1.6 Hz, 1H), 5.00 (quint, *J* = 1.2 Hz,1H), 4.20-4.02 (m, 2H), 2.59 (t, *J* = 8.7 Hz 1H), 2.34 (m, 1H), 2.26, (m, 1H), 1.60 (m, 3H), 1.07 (s, 3H), 0.76 (s, 3H); **^{13}C{^{1}H}-NMR** ($CDCl_3$, 101 MHz): δ 149.7, 147.6, 121.7, 110.7, 66.4, 53.9, 47.9, 34.0, 26.9, 21.1, 12.9; GC-MS: m/z (%): 166 (M^+, 30), 133 (100), 105 (80), 91 (60); $[\alpha]_D$ = –78.5 ($CHCl_3$, *c*= 0.8) *vs* litt. –68.0 (neat).[17a]

(*S*)-1,5,5-trimethyl-4-(3-(vinyloxy)prop-1-en-2-yl)cyclopent-1-ene (18)

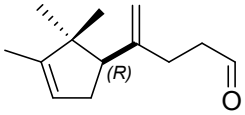


18

To a well stirred solution of **17** (2.2 g) in ethyl vinylether (19.1 mL) was added $Hg(AcO)_2$ (758 mg), the mixture was left to stir at room temperature. After 4 hours, a solvent mixture of *n*-hexane/Et_2O (1:1, 20 mL) was added to the reaction, which was washed with H_2O (3 x 20 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated under

vacuum affording **18** as a yellow liquid, which was purified through silica gel column chromatography with *n*-hexane/EtOAc (9:1).[17a]
Yield 56% (1.4 g) as a pale-yellow oil; tr= 13.3 min, 98% purity by GC-MS; **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 6.47 (dd, *J* = 14.3 and 6.7 Hz, 1H), 5.29 (m, 1H), 5.25 (qd, *J* = 1.6 and 0.3 Hz, 1H), 5.07 (quint, *J* = 1.6 Hz 1H), 4.23 (dd, *J* = 14.3 and 2.0 Hz, 1H), 4.19 (m, 2H), 4.02 (dd, *J* = 6.7 and 2.0 Hz, 1H), 2.64 (m, 1H), 2.42-2.21 (m, 2H), 1.60 (m, 3H), 1.08 (s, 3H), 0.79 (s, 3H); **^{13}C{^{1}H}-NMR** ($CDCl_3$, 101 MHz): δ 151.8, 147.5, 145.0, 121.7, 113.5, 87.2, 71.7, 53.8, 47.8, 33.9, 26.9, 21.1, 12.9; GC-MS: m/z (%): 192 (M^+, 8), 133 (92), 105 (86), 93 (100); $[\alpha]_D$ = –67.2 ($CHCl_3$, *c*= 0.8).

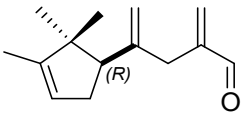
(*R*)-4-(2,2,3-trimethylcyclopent-3-en-1-yl)pent-4-enal (19)



19

Neat vinylether **18** (1.4 g) was left at 160 °C for 2 hours under to an inert atmosphere of Argon. After cooling, the crude product was purified through silica gel column chromatography with *n*-hexane/EtOAc (95:5).[17a]
Yield 86% (1.2 g) as a pale-yellow oil; tr= 16.2 min, 98% purity by GC-MS; **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 9.77 (m, 1H), 5.26 (m, 1H), 4.89 (m, 1H), 4.83 (m, 1H), 2.61-2.59 (m, 2H), 2.54 (m, 1H), 2.48-2.33 (m, 2H), 2.31-2.16 (m, 2H), 1.59 (m, 3H), 1.07 (s, 3H), 0.75 (s, 3H); **^{13}C{^{1}H}-NMR** ($CDCl_3$, 101 MHz): δ 202.3, 148.2, 147.4, 121.6, 111.2, 56.7, 48.1, 42.5, 34.0, 28.7, 27.0, 21.0, 12.9; GC-MS: m/z (%): 192 (M^+, 61), 133 (96), 105 (100), 91 (86); $[\alpha]_D$ = –76.0 ($CHCl_3$, *c*= 0.9).

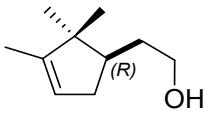
(*R*)-2-methylene-4-(2,2,3-trimethylcyclopent-3-en-1-yl)pent-4-enal (5b)



5b

The same procedure used for the synthesis of **10** was adapted for the Mannich homologation of **19** (1.2 g), the product was purified by silica gel column chromatography with *n*-hexane/EtOAc (95:5).
Yield 63% (800 mg) as a pale-yellow oil; tr= 17.2 min, 85% purity by GC-MS; **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 9.59 (s, 1H), 6.27 (m, 1H), 6.11 (m, 1H), 5.25 (m, 1H), 4.98 (m, 1H), 4.83 (m, 1H), 3.05-2.98 (m, 2H), 2.53 (m, 1H), 2.28 (m, 1H), 2.18 (m, 1H), 1.58 (m, 3H), 1.08 (s, 3H), 0.81 (s, 3H); **^{13}C{^{1}H}-NMR** ($CDCl_3$, 101 MHz): δ 194.2, 148.7, 147.5, 146.4, 135.5, 121.5, 113.7, 56.2, 48.1, 35.0, 34.4, 27.0, 21.2, 12.9; GC-MS: m/z (%): 204 (M^+, 50), 189 (83), 105 (77), 91 (100); $[\alpha]_D$ = –37.8 ($CHCl_3$, *c*= 0.6).

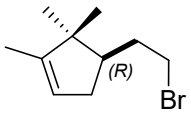
(*R*)-2-(2,2,3-trimethylcyclopent-3-en-1-yl)ethan-1-ol (20)



20

To a refluxing and stirred mixture of $LiAlH_4$ (760 mg) in dry Et_2O (140 mL), was added dropwise (rate = 0.5 mL/min) a solution of (+)-**2** (6.0 g) in Et_2O (40 mL). After completion of the addition, stirring was continued at room temperature for 1 hour. The reaction was ice-cooled and quenched with a Seignette solution (sat., 30 mL) and left to stir over 1 hour. Then, the mixture was washed with EtOAc (3 x 50 mL). The combined organic phase was washed with brine (sat., 50 mL), dried over anhydrous Na_2SO_4 and concentrated under *vacuum* to get a crude product, which was purified through distillation (145 °C, 10 mbar) affording **20**.
Yield 92% (5.6 g) as a colourless oil; tr=11.6 min, 98% purity by GC-MS; **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ=5.22 (m, 1H), 3.73 (m, 1H), 3.64 (m, 1H), 2.29 (m, 1H), 1.90-1.69 (m, 1H+2H), 1.61 (m, 3H), 1.52 (m, 1H), 1.34 (m, 1H), 0.98 (s, 3H), 0.78 (s, 3H); **^{13}C{^{1}H}-NMR** ($CDCl_3$, 101 MHz): δ=148.8, 121.7, 62.8, 47.0, 46.9, 35.7, 33.5, 25.9, 19.9, 12.7; GC-MS: m/z (%): 154 (M^+, 5), 139 (10), 121 (25), 95 (100); $[\alpha]_D$ = +1.34 ($CHCl_3$, *c*=1.1) *vs* litt. +5.4 ($CHCl_3$, *c*= 2.06).[19]

(*R*)-4-(2-bromoethyl)-1,5,5-trimethylcyclopent-1-ene (21)

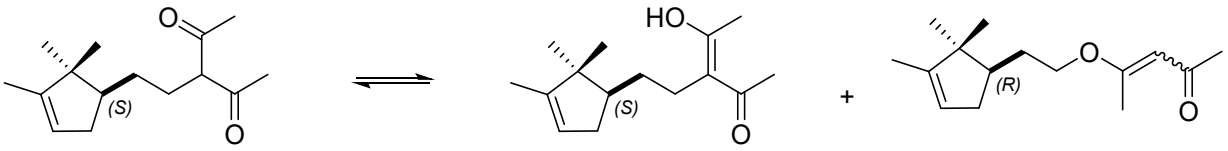


21

To an ice-cooled stirred solution of PPh_3 (22.4 g) in CH_2Cl_2 (200 mL) were added CBr_4 (28.4 g) and **20** (6.6 g). The reaction mixture was stirred at the same temperature under an inert atmosphere (N_2) for 30 min. The cooling bath was removed, the mixture was allowed to reach the room temperature and the stirring continued for 20 h. Then the crude solid was triturated with a solvent mixture of *n*-hexane/Et_2O (9:1, 100 mL) and filtrated. The organic phase was concentrated under *vacuum* to get the crude product, which was purified through silica gel column chromatography with *n*-hexane affording **21**.

Yield 81% (7.5 g) as a pale-yellow oil; tr=13.2 min, 83% purity by GC-MS; **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ=5.23 (m, 1H), 3.50 (ddd, *J* = 9.6, 8.6 and 4.7 Hz, 1H), 3.35 (dt, *J* = 9.6 and 7.9 Hz, 1H), 2.32 (m, 1H), 2.05-1.79 (m, 2H+2H), 1.61 (m, 3H), 1.00 (s, 3H), 0.78 (s, 3H); **^{13}C{^{1}H}-NMR** ($CDCl_3$, 101 MHz): δ= 148.8, 121.7, 62.8, 47.0, 46.9, 35.7, 33.5, 25.9, 19.9, 12.7; GC-MS: m/z (%): 217 (M^+, 2), 203 (98), 201 (100), 121 (15); $[\alpha]_D$ = +13.4 ($CHCl_3$, *c*=1.2) *vs* litt. +24 ($CHCl_3$, *c*= 0.69).[20]

(*S*)-3-(2-(2,2,3-trimethylcyclopent-3-en-1-yl)ethyl)pentane-2,4-dione (22) and (*R*)-4-(2-(2,2,3-trimethyl cyclopent-3-en-1-yl)ethoxy)pent-3-en-2-one (23)



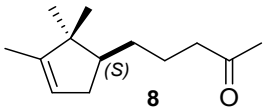
22 **23**

To a stirred mixture of **21** (2.0 g), TBAI (1.03 g), and K_2CO_3 (1.9 g) in acetone (20 mL) was added acetylacetone (0.92 g, 9.2 mmol). After 22 hours, the reaction mixture was diluted with brine (sat., 100 mL) and ice cooled. An aq. solution of HCl (1 M) was added until 5 to 6 pH was reached. The mixture was washed with EtOAc (3 x 20 mL), and the combined organic phase was washed with brine (sat., 20 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated under *vacuum* to get a crude product which was purified through silica gel column chromatography with *n*-hexane/EtOAc (95:5) affording **22** as a mixture of enol and diketone.[21]

Compound **22**. Yield 20% (440 mg) as a pale-yellow oil; tr=20.4 min, 68% purity by GC-MS; **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 16.64 (s, enol, 0.5H), 5.24 (m, diketone, 0.55H), 5.22 (m, enol, 0.45H), 3.62 (t, *J* = 7.2 Hz, diketone, 0.5H), 2.44-2.19 (m, diketone+enol, 2H), 2.18 (d, *J* = 2.0 Hz, enol, 2.7H), 2.14 (s, diketone, 3.3H), 1.97-1.66 (m, diketone+enol, 1H+2H), 1.62-1.58 (m, diketone+enol 3H), 1.40-1.13 (m, diketone+enol, 2H), 0.98 (s, diketone, 1.65H), 0.95 (s, enol, 1.35H), 0.76 (s, diketone, 1.65H), 0.72 (s, enol, 1.35H); **^{13}C{^{1}H}-NMR** ($CDCl_3$, 101 MHz): δ 204.6 (CO enol), 191.0 (CO diketone), 148.9, 148.8, 121.6, 121.5, 111.0 (C_q enol), 69.6 (CO<u>C</u>HCO diketone), 50.9, 50.4, 47.03 (C_q), 46.96 (C_q), 35.8, 35.6, 31.4, 29.2, 29.1, 28.1, 27.8, 27.3, 26.1, 26.0, 23.0, 19.82, 19.80, 12.72, 12.70. GC-MS: m/z (%): 218 ([M-18]$^+$, 1), 175 (29), 134 (100), 121 (51).

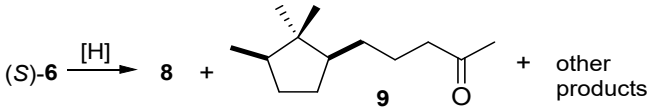
Compound **23**. Yield 16% (348 mg) as a pale-yellow oil; tr= 21.8 min, 43% purity by GC-MS. Due to the low purity of **23** we report only **^{13}C{^{1}H}-NMR** ($CDCl_3$, 101 MHz): δ 197.2, 172.4, 148.7, 121.6, 99.9, 68.0, 47.2, 47.1, 35.6, 32.0, 29.3, 25.8, 19.8, 12.7; GC-MS: m/z (%): 236 (M^+, 1), 121 (58), 108 (100), 93 (67).

(*S*)-5-(2,2,3-trimethylcyclopent-3-en-1-yl)pentan-2-one (8)



Different reductive methodologies were tested, in the following we report the procedures according to Table S2. The most performing procedure in terms of chemoselectivity resulted the OYE2 catalyzed bioreduction.

Table S2 Reduction of (*S*)-**6** with different methodologies



Reaction conditions [a]	Conv. [%][b]	Prod. Distribution [%][b]		
		8	**9**	Other prod.[c]
A) OYE2, GDH, 0.009 eq $NADP^+$, 3.9 eq glucose, pH 7.0 KPi/*i*-PrOH (99:1), 30 °C	96 (87)[d]	>99	-	-
B) 0.15 eq Pd/C,[e] NH_4HCO_2, MeOH, 30 °C	>99 (67)[d]	95	4	1
C) 0.2 eq Raney®-Ni, pyridine, EtOH, rt	90	28	72	-
D) 5 eq Mg, MeOH, rt	-[f]	-	-	-
E) 0.25 eq Lindlar cat., H_2,[g] MeOH, 50 °C	15	84	-	16
F) 0.1 eq Wilkinson cat., H_2,[g] CH_2Cl_2, 36 °C	-	-	-	-
G) 3 eq $NaBH_4$, 5 eq $NiCl_2{\cdot}6H_2O$, MeOH/H_2O, rt	93	97	2	1

[a] Catalyst/substrate ratio is in weight/weight. [b] Not isolated yield, by GC-MS. [c] By GC-MS. [c] Other products are allylic alcohol, saturated alcohol, positional isomers. [d] Isolated yield without column chromatography. [e] 5% w/w. [f] Decomposition. [g] Pressure 1 atm.

Procedures

A) OYE2 catalysed reduction

A solution of (*S*)-**6** (576 mg) in *i*-PrOH (0.8 mL) was added to a KPi buffer solution (pH 7.0, 50 mM, 15 mL) containing OYE2 (≈3 mg/mL, 5 mL), GDH (200 U), glucose (2.1 g), $NADP^+$ (20 mg). The mixture was incubated for 10-12 hours in an orbital shaker (150 rpm, 30 °C). The reaction was monitored by TLC until complete conversion, eventually, more enzymes were added to increase the conversion. Then, XAD-1180 resins (5.0 g) were added to the reaction mixture and left to shaker for 30 minutes. The mixture was filtered into a porous filter (porosity 0) and the resins were washed several times with EtOAc (15 mL x 4). The combined organic phase was washed with water (10 mL), dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The crude material was submitted to bulb-to-bulb distillation affording **8** (90 °C, 0.2-0.3 mbar).

Yield 87% (512 mg) as a colourless oil; tr=16.4 min, 96% purity by GC-MS; **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ=5.16 (m, 1H), 2.40 (m, 2H), 2.24 (m, 1H), 2.08 (s, 3H), 1.80-1.57 (m, 1H+2H), 1.54 (m, 3H), 1.50-1.30 (m, 2H), 1.18 (m, 1H), 0.91 (s, 3H), 0.68 (s, 3H); **^{13}C{^{1}H}-NMR** ($CDCl_3$, 101 MHz): δ=209.0, 148.6, 121.7, 50.3, 46.8, 44.1, 35.6, 29.8, 29.6, 25.9, 23.1, 19.7, 12.6; GC-MS: m/z (%): 194 (M^+, 17), 161 (43), 121 (100), 109 (50); $[\alpha]_D$ = +6.6 ($CHCl_3$, *c*=0.9).

B) Reduction catalysed by Pd/C in presence of NH_4HCO_2

To a stirred mixture of (*S*)-**6** (5.5 g) and NH_4HCO_2 (10 g) in MeOH (200 mL) was added Pd/C (5% w/w, 890 mg). The reaction mixture was stirred at 30 °C for 4 hours. Then, the reaction mixture was filtered on a celite pad and washed with MeOH (5 x 10 mL). The solvent was removed under *vacuum* and the crude material was diluted with *n*-hexane (100 mL) and filtered. The organic solution was washed with brine (sat., 20 mL), dried over anhydrous Na_2SO_4, and the solvent

was removed under reduced pressure. Finally, the crude material was submitted to bulb-to-bulb distillation affording **8** (90 °C, 0.2-0.3 mbar).[22]
Yield 67% (3.7 g) as colourless oil; tr=16.4 min, 91% purity by GC-MS.

C) Reduction catalysed by Pd/C in presence of NH_4HCO_2

To a stirred mixture of Raney®-Ni (40 mg) and pyridine (47.4 mg) in EtOH (5 mL) was added a solution of (*S*)-**6** (192 mg) in EtOH (5 mL). The reaction mixture was stirred at room temperature for 5 hours. Product not isolated.

D) Reduction with Mg/MeOH

The same procedure used for the synthesis of **14** was adapted for the reduction of (*S*)-**6** (192 mg). Product not isolated.

E) Hydrogenation catalyzed by Lindlar catalyst

To a stirred solution of (*S*)-**6** (100 mg) in MeOH (5 mL) was added the Lindlar catalyst (25 mg), the reaction was left under an H_2 atmosphere (1 atm) at 50 °C for 24 hours. Product not isolated.

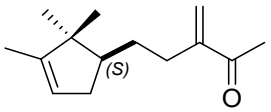
F) Hydrogenation catalyzed by Wilkinson catalyst

To a stirred mixture of Wilkinson catalyst (10 mg) in dry CH_2Cl_2 (2 mL), under H_2 atmosphere (1 atm), was added a solution of (*S*)-**6** (100 mg) in CH_2Cl_2 (3 mL). The reaction mixture was stirred at 36 °C for 24 hours. Product not isolated.[23]

G) Reduction with $NiCl_2/NaBH_4$

To a stirred mixture of (*S*)-**6** (100 mg), $NiCl_2 \cdot 6H_2O$ (600 mg), H_2O (1 mL) in MeOH (6 mL) was added $NaBH_4$ (60 mg). The reaction mixture was stirred at room temperature for 5 hours. Product not isolated.[24]

(*S*)-3-methylene-5-(2,2,3-trimethylcyclopent-3-en-1-yl)pentan-2-one (5c)



5c

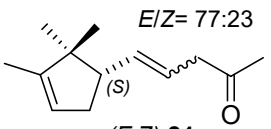
Route A: Deacylation/methylenation of 22

To a stirred mixture of **22** (440 mg) and K_2CO_3 (700 mg) in H_2O (0.2 mL) was added an aq. of formaldehyde (37% w/w, 0.5 mL) at 35 °C, and left to stir for 18 hours. Then, it was quenched with an aq. solution of HCl (1 M) until pH 7. The mixture was washed with EtOAc (3 x 10 mL) and the combined organic phase was washed with brine (sat., 10 mL), dried over anhydrous Na_2SO_4 and concentrated under *vacuum* to get a crude product. The latter was purified through silica gel column chromatography with *n*-hexane/EtOAc (95:5) affording **5c**.[25]
Yield 42% (160 mg) as a pale-yellow oil; tr=17.7 min, 96% purity by GC-MS.

Route B: Mannich of 8

To a stirred solution of **8** (4.9 g) in *i*-PrOH (9 mL) were added an aqueous solution of formaldehyde (37% w/w, 10.3 mL), pyrrolidine (1.6 g) and propanoic acid (2.0 g) at 45 °C. After 24 hours, *n*-hexane (50 mL) was added to the mixture, which was washed in sequence with aq. solution of HCl (1 M, 30 mL), an aq. solution of $NaHCO_3$ (sat., 30 mL) and brine (sat., 30 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated under *vacuum* affording **5c** as a yellow liquid, which was purified through silica gel column chromatography with *n*-hexane/EtOAc (98:2).
Yield 32% (1.65 g) as a colourless oil; tr=17.7 min, 98% purity by GC-MS; **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ=5.95 (s, 1H), 5.73 (s, 1H), 5.17 (m, 1H), 2.29 (m, 1+3H), 2.14 (m, 1H), 1.79 (m, 1H), 1.68 (m, 1H), 1.55 (m, 3H), 1.53-1.46 (m, 1H), 1.49 (m, 2H), 0.92 (s, 3H), 0.71 (s, 3H); **^{13}C{^{1}H}-NMR** ($CDCl_3$, 101 MHz): δ=199.7, 149.7, 148.6, 124.5, 121.7, 50.1, 46.8, 35.6, 29.8, 29.0, 26.0, 25.9, 19.7, 12.6; GC-MS: m/z (%): 206 (M^+, 30), 173 (40), 122 (100), 107 (75); $[\alpha]_D$ = +14.0 ($CHCl_3$, *c*=1.1).

(*S*,*E*,*Z*)-5-(2,2,3-trimethylcyclopent-3-en-1-yl)pent-4-en-2-one (24)

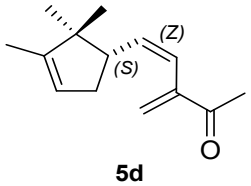


(E,Z)-**24**

The O_2 of a solution of (*R*)-**6** (250 mg) in acetone (100 mL) in a quartz tube was purged by bubbling N_2 (5 min). Then, the solution was irradiated in a Rayonet photoreactor (λ = 350 nm) for 18 hours. The solution was concentrated under *vacuum* to get the crude product, which was purified through silica gel column chromatography with *n*-hexane/EtOAc (9:1) affording **24**.[26]

Yield 24% (60 mg) as a pale-yellow liquid; tr=16.0 min, 82% purity by GC-MS; *E*/*Z*= 77:23 by ^{13}C-NMR; **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ=5.69-5.48 (m, *E*+*Z*, 2H), 5.21 (m, *E*+*Z*, 1H), 3.29-3.3.11 (m, *E*+*Z*, 2H), 2.68 (q, *J* = 8.8 Hz, *Z*, 0.23H), 2.40 (dd, *J* = 9.4 and 7.6 Hz, *E*, 0.77H), 2.30-1.96 (m, *E*+*Z* , 2H+3H), 1.59 (m, *E*+*Z*, 3H), 0.95 (s, *E*, 2.31H), 0.94 (s, *Z*, 0.69H), 0.80 (s, *Z*, 0.69H), 0.74 (s, *E*, 2.31H); **^{13}C{^{1}H}-NMR** ($CDCl_3$, 101 MHz) (*E*)-**24**: δ=207.5, 148.1, 136.3, 122.6, 121.5, 54.2, 48.8, 48.0, 35.4, 31.4, 25.5, 20.6, 12.8; (*Z*)-**24**: δ=207.0, 148.2, 135.0, 121.7, 121.6, 50.5, 48.4, 48.3, 36.1, 31.4, 26.0, 20.4, 12.7; GC-MS: m/z (%): 192 (M^+, 33), 134 (100), 119 (92), 93 (58); $[\alpha]_D$ = +58.3 ($CHCl_3$, *c*=0.9).

(*S*,*Z*)-3-methylene-5-(2,2,3-trimethylcyclopent-3-en-1-yl)pent-4-en-2-one (5d)



5d

To a stirred solution of **23** (1.60 g, 8.3 mmol) in *i*-PrOH (3 mL) were added an aqueous solution of formaldehyde (37% w/w, 3.4 mL, 45.6 mmol), pyrrolidine (540 mg, 7.6 mmol) and propanoic acid (700 mg, 9.5 mmol) at 45 °C. After 6 hours, *n*-hexane (20 mL) was added to the mixture, which was washed in sequence with HCl (1 M, 10 mL), an aqueous solution of $NaHCO_3$ (sat., 10 mL) and brine (sat., 10 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated under *vacuum* affording **5d** as a yellow liquid, which was purified through silica gel column chromatography with *n*-hexane/EtOAc (98:2).[16]

Yield 24% (400 mg) as a pale-yellow liquid; tr=17.4 min, 47% purity by GC-MS; *Z*>99% by ^{1}H-NMR; **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 6.21 (dt, *J* = 11.4 and 1.1 Hz, 1H), 6.08 (m, 1H), 5.80 (t, *J* = 11.4 Hz, 1H), 5.75 (m, 1H), 5.22 (m, 1H), 2.81 (dt, *J* = 11.1 and 8.3 Hz, 1H), 2.34 (s, 3H), 1.60 (m, 2H+3H), 0.90 (s, 3H), 0.85 (s, 3H); **^{13}C{^{1}H}-NMR** ($CDCl_3$, 101 MHz): δ 199.7, 148.3, 144.8, 136.3, 125.5, 125.4, 121.5, 48.9, 48.7, 36.5, 26.6, 26.0, 20.6, 12.6; GC-MS: m/z (%): 204 (M^+, 21), 161 (50), 108 (100), 91 (67); $[\alpha]_D$ = +24.0 ($CHCl_3$, *c*= 0.9).

Evaluation of ER stereoselectivity from the diastereomeric excess by mass balance

To quantify the ER stereoselectivity (enantioselectivity, *Sel*) from the diastereomeric ratio of products, determined either by means of ^{13}C-NMR spectroscopy (Brahmanol® and Firsantol® and Ebanol®) or of GC-MS (Sandalore®), a mass balance analysis was carried out (Fig. S1). The reduction of the C=C double bond of enantiomerically enriched substrates like **4a-c** or **5a-d** leads always to the formation of a couple of diastereoisomers. However, if the reduction occurs with complete enantioselectivity (100%), the proportion between the product diastereoisomers must be equal to the initial proportion between the enantiomers. If the initial enantiomeric excess of pinene (ee_{pinene}) is retained during all synthesis, and that ER selectivity is not influenced by stereochemistry of precursor, it is possible to establish a relationship between the area of peaks ($\%Pk_1$ or $\%Pk_2$) and the ER enantioselectivity (*Sel*). The following demonstration outlines such relationship.

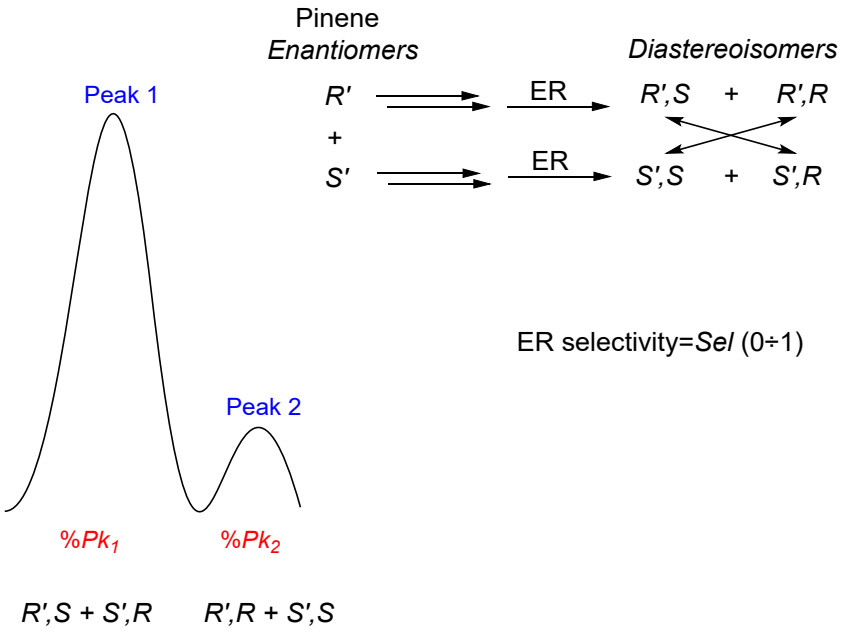


Figure S1 Example of GC chromatogram of a mixture of two diastereoisomers.

$$\%Pk_1 = \frac{[R',S] + [S',R]}{[R',S] + [S',R] + [R',R] + [S',S]}100 = \frac{\%R' \cdot Sel + \%S'(1 - Sel)}{\%R' \cdot Sel + \%S'(1 - Sel) + \%R'(1 - Sel) + \%S' \cdot Sel}100$$

Where $\%R'$ and $\%S'$ represent the molar percentages of (*R'*)-α-pinene and (*S'*)-α-pinene in the starting α-pinene. Given that $\%R' + \%S' = 100$ and after some manipulation of the above eq., *Sel* can be determined from the following equation:

$$Sel = \frac{\%Pk_1 - 100 + \%R'}{2 \cdot \%R' - 100}$$

Considering that $ee_{pinene} = \%R' - \%S'$, ant that $\%R' = 0.5\ (ee_{pinene} + 100)$, *Sel* can be expressed as:

$$Sel = \frac{2 \cdot \%Pk_1 + ee_{pinene} - 100}{2 \cdot ee_{pinene}}$$

General procedure for the screening of the ER catalyzed reduction of 4c and 5c

To a solution of substrate (**4c** or **5c**)in DMSO (10 µL, 500 mM) in KPi buffer solution (1.0 mL, 50 mM, pH 7.0) containing glucose (3.6 mg, 20 µmol), $NADP^+$ (0.1 µmol), GDH (4 U), was added an ene-reductase (80-120 µg mL^{-1}) according to Table S3 and S4. The mixture was incubated for 24 h in an orbital shaker (150 rpm, 30 °C). The solution was extracted with EtOAc (2x250 µL), centrifuging after each extraction (15000 *g*, 1.5 min), and the combined organic solutions were dried over Na_2SO_4, and submitted to GC-MS analysis. Conversion and selectivity are summarized in Table S3 and S4.

Table S3 Reduction of **4c**

Enzyme	**I° Peak** 31.4 min (%)	**II° Peak** 31.6 min (%)	**Sel *pro-S vs pro-R***	**Conversion** (%)
OYE 1	83	17	90:10	91
OYE 2	86	14	94:6	100
OYE 3	85	15	93:7	92
YqjM	57	43	58:42	85
NemA	18	82	11:89	47

Table S4 Reduction of **5c**

Enzyme	**I° Peak** 31.4 min (%)	**II° Peak** 31.6 min (%)	**Sel *pro-S vs pro-R***	**Conversion** (%)
OYE 1	15	85	7:93	84
OYE 2	14	86	6:94	100
OYE 3	10	90	1:99	72
YqjM	9	91	1:99	45
NemA	19	81	12:88	53

Bioreductions at preparative scale

General procedure for the enzymatic cascade reduction

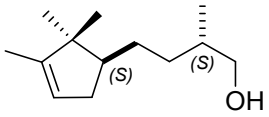
A solution of substrate (3.0 mmol) in *i*-PrOH (0.8 mL) was added to a KPi buffer solution (pH 7.0, 50 mM, 15 mL) containing OYE2 (≈3 mg/mL, 5 mL), GDH (200 U), glucose (4.2 g), $NADP^+$ (20 mg). The mixture was incubated for 10-12 hours in an orbital shaker (150 rpm, 30 °C). The reaction was monitored by TLC until complete conversion. Eventually, more enzymes were added to increase the conversion. After 10-12 hours ADH (Evo270 or Evo440, 30-40 mg) and $NADP^+$ (10 mg) were added to the reaction mixture. After 10-12 hours XAD-1180 resins (5.0 g) were added to the reaction mixture and left to shaker for 30 minutes. The mixture was filtered into a porous filter (porosity 0) and the resins were washed several times with EtOAc (15 mL x 4). The combined organic phase was washed with water (10 mL), dried over Na_2SO_4, and the solvent was removed under reduced pressure. The crude material was submitted to silica gel column chromatography purification and then distilled by bulb-to-bulb apparatus affording alcohol **1**. In Table S5 are reported diastereomeric ratio (*dr*) and OYE2 selectivity.

Table S5 OYE2 stereoselectivity

Substrate	α–Pinene %*S*':%*R*' or *ee* (%)	Product	*dr*	Selectivity OYE2
4a		(2*S*,*S*')-**1a**	90:10 [a]	99(*S*):1(*R*)
5a		(2*R*,*S*')-**1a**	87:13 [a]	95(*R*):5(*S*)
4b	91(*S'*):9(*R'*)	(2*S*,*R*')-**1b**	92:8 [a]	>99(*S*)
5b	82	(2*R*,*R*')-**1b**	91:9 [a]	>99(*R*)
4c		(3*S*,*S*')-**7c**	86:14 [b]	94(*S*):6(*R*)
5c		(3*R*,*S*')-**7c**	86:14 [b]	94(*R*):6(*S*)
5d	4(*S'*):96(*R'*) 92	(3*R*,*S*',*Z*)-**7d**	96:4 [c]	>99(*R*)

[a] By ratio of ^{13}C-NMR signal integrations C(1) for **1a**-**b**. [b] By GC-MS. [c] By ^{13}C-NMR signal integration CH_2.

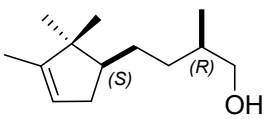
(*S*)-2-methyl-4-((*S*)-2,2,3-trimethylcyclopent-3-en-1-yl)butan-1-ol (2*S*,*S*'-1a)



(2*S*,*S*')-**1a**

Yield 84% (494 mg) as a colourless oil; tr= 17.3 min, >99% purity by GC-MS; *dr*= 90:10 by ^{13}C-NMR; **^{1}H-NMR ($CDCl_3$, 400 MHz):** δ 5.21 (m, 1H), 3.52 (dd, *J* = 10.4 and 5.6, 1H), 3.41 (dd, *J* = 10.4 and 6.6 Hz, 1H), 2.28 (m, 1H), 1.80 (m, 1H), 1.72-1.63 (m, 2H), 1.59 (m, 3H), 1.54-1.42 (m, 2H), 1.18 (m, 1H), 1.05 (m, 1H), 0.96 (s, 3H), 0.93 (d, J = 6.7 Hz, 3H), 0.75 (s, 3H); **^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz):** δ 148.7, 121.8, 68.5, 50.6, 46.8, 36.1, 35.7, 32.3, 27.3, 25.9, 19.8, 16.6, 12.6; GC-MS: m/z (%): 196 (M^+, 21), 181 (100), 107 (79), 95 (42); $[\alpha]_D$ = +2.5 ($CHCl_3$, *c*= 0.65)

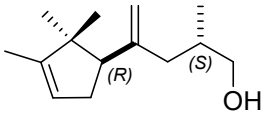
(*R*)-2-methyl-4-((*S*)-2,2,3-trimethylcyclopent-3-en-1-yl)butan-1-ol (2*R*,*S*'-1a)



(2*R*,*S*')-**1a**

Yield 82% (482 mg) as a colourless oil; tr= 17.3 min, >99% purity by GC-MS; *dr*= 87:13 by ^{13}C-NMR; **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 5.22 (m, 1H), 3.51 (dd, *J* = 10.4 and 5.9 Hz, 1H), 3.43 (dd, *J* = 10.4 and 6.4 Hz, 1H), 2.27 (m, 1H), 1.82-1.63 (m, 1H + 2H), 1.60 (m, 3H), 1.53-1.38 (m, 2H), 1.28 (m, 1H), 1.16 (m, 1H), 0.97 (s, 3H), 0.92 (d, J = 6.8 Hz, 3H), 0.75 (s, 3H); **^{13}C{^{1}H}-NMR** ($CDCl_3$, 101 MHz): δ 148.7, 121.7, 68.4, 50.5, 46.8, 36.1, 35.7, 32.2, 27.3, 25.9, 19.7, 16.5, 12.6; GC-MS: m/z (%): 196 (M^+, 16), 181 (100), 107 (75), 95 (41); $[\alpha]_D$ = +17.0 ($CHCl_3$, *c*= 0.8)

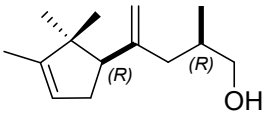
(*S*)-2-methyl-4-((*R*)-2,2,3-trimethylcyclopent-3-en-1-yl)pent-4-en-1-ol (2*S*,*R*'-1b)



(2*S*,*R*')-**1b**

Yield 81% (505 mg) as a colourless oil; tr= 18.5 min, 92% purity by GC-MS; *dr*= 92:8 by ^{13}C-NMR; **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 5.28 (m, 1H), 4.91 (m, 2H), 3.53 (dd, *J* = 10.5 and 5.6 Hz, 1H), 3.47 (dd, *J* = 10.5 and 5.9 Hz, 1H), 2.53 (m, 1H), 2.39-2.12 (m, 3H), 1.98-1.79 (m, 2H), 1.60 (m, 3H), 1.10 (s, 3H), 0.88 (d, J = 6.3 Hz, 3H), 0.76 (s, 3H); **^{13}C{^{1}H}**-NMR ($CDCl_3$, 101 MHz): δ 148.07, 147.55, 121.71, 112.28, 68.74, 55.30, 47.89, 41.53, 34.41, 34.35, 27.19, 21.15, 16.48, 12.96; GC-MS: m/z (%): 208 (M^+, 63), 135 (100), 107 (95), 91 (82); $[\alpha]_D$ = −79.3 ($CHCl_3$, *c*= 1.1) *vs* litt. –73.1 (CCl_4, *c*= 0.6).[17a]

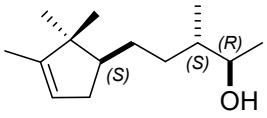
(*R*)-2-methyl-4-((*R*)-2,2,3-trimethylcyclopent-3-en-1-yl)pent-4-en-1-ol (2*R*,*R*'-1b)



(2*R*,*R*')-**1b**

Yield 80% (500 mg) as a colourless oil; tr= 18.4 min, 91% purity by GC-MS; *dr*= 91:9 by ^{13}C-NMR; **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 5.27 (m, 1H), 4.93 (m, 1H), 4.91 (m, 1H), 3.53 (dd, *J* = 10.7 and 5.4 Hz, 1H), 3.42 (dd, *J* = 10.7 and 5.9 Hz, 1H), 2.56 (m, 1H), 2.34 (m, 1H), 2.25-2.09 (m, 2H), 2.01-1.84 (m, 2H), 1.59 (m, 3H), 1.09 (s, 3H), 0.95 (d, J = 6.5 Hz, 3H), 0.75 (s, 3H); **^{13}C{^{1}H}-NMR** ($CDCl_3$, 101 MHz): δ 148.8, 147.5, 121.7, 112.1, 68.3, 55.7, 47.9, 42.0, 34.3, 34.3, 27.1, 21.1, 17.5, 12.9; GC-MS: m/z (%): 208 (M^+, 60), 135 (100), 107 (82), 91 (57); $[\alpha]_D$ = −57.6 ($CHCl_3$, *c*= 1.1) *vs* litt. –60.8 (CCl_4, *c*= 0.9).[17a]

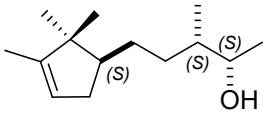
(2*R*,3*S*)-3-methyl-5-((*S*)-2,2,3-trimethylcyclopent-3-en-1-yl)pentan-2-ol (2*R*,3*S*,*S*'-1c)



(2*R*,3*S*,*S*')-**1c**

A sample of rection mixture was analyzed by GC-MS before ADH reduction: tr= 31.4 min (3*S*,*S*') and 31.6 min (3*R*,*S*'); *dr*= 86:14. Yield 73% (460 mg) as a colourless oil; tr= 18.1 min, 98% purity by GC-MS; *dr*= 91:5:4 by ^{13}C-NMR; **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 5.23 (m, 1H), 3.69 (quint, *J* = 6.3 Hz, 1H), 2.31 (m, 1H), 1.80 (m, 1H), 1.69 (m, 1H), 1.60 (m, 3H), 1.57-1.47 (m, 1H + 2H), 1.31 (m, 1H), 1.18 (m, 1H), 1.13 (d, *J* = 6.3 Hz, 3H), 1.05 (m, 1H), 0.98 (s, 3H), 0.90 (d, *J* = 6.7 Hz, 3H), 0.76 (s, 3H); **^{13}C{^{1}H}-NMR** ($CDCl_3$, 101 MHz): δ 148.9, 121.8, 71.7, 51.1, 46.9, 40.8, 36.0, 32.1, 27.9, 26.1, 19.8, 19.3, 14.8, 12.7; GC-MS: m/z (%): 210 (M^+, 17), 177 (78), 121 (72), 107 (100); $[\alpha]_D$ = −4.4 ($CHCl_3$, *c*= 1.0).

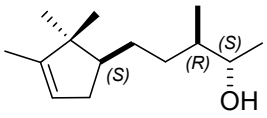
(2*S*,3*S*)-3-methyl-5-((*S*)-2,2,3-trimethylcyclopent-3-en-1-yl)pentan-2-ol (2*S*,3*S*,*S*'-1c)



(2*S*,3*S*,*S*')-**1c**

A sample of rection mixture was analyzed by GC-MS before ADH reduction: tr= 31.4 min (3*S*,*S*') and 31.6 min (3*R*,*S*'); *dr*= 86:14. Yield 71% (447 mg) as a colourless oil; tr= 18.1 min, 98% purity by GC-MS; *dr*= 82:10:8 by ^{13}C-NMR; **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 5.22 (m, 1H), 3.71 (qd, *J* = 6.3 and 4.2 Hz, 1H), 2.29 (m, 1H), 1.81 (m, 1H), 1.68 (m, 1H), 1.60 (m, 3H), 1.54-1.39 (m, 1H + 2H), 1.36-1.18 (m, 2H), 1.13 (d, *J* = 6.4 Hz, 3H), 1.05 (m, 1H), 0.98 (s, 3H), 0.90 (d, *J* = 6.7 Hz, 3H), 0.76 (s, 3H); **^{13}C{^{1}H}-NMR** ($CDCl_3$, 101 MHz): δ 148.6, 121.8, 71.1, 51.0, 46.8, 40.4, 35.9, 32.0, 27.9, 26.0, 20.3, 19.7, 14.4, 12.6; GC-MS: m/z (%): 210 (M^+, 15), 177 (70), 121 (70), 107 (100); $[\alpha]_D$ = −3.0 ($CHCl_3$, *c*= 1.0).

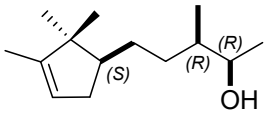
(2*S*,3*R*)-3-methyl-5-((*S*)-2,2,3-trimethylcyclopent-3-en-1-yl)pentan-2-ol (2*S*,3*R*,*S*'-1c)



(2*S*,3*R*,*S*')-**1c**

A sample of rection mixture was analyzed by GC-MS before ADH reduction: tr= 31.6 min (3*R*,*S*') and 31.4 min (3*S*,*S*'); *dr*= 86:14. Yield 72% (454 mg) as a colourless oil; tr= 18.2 min, >99% purity by GC-MS; *dr*= 91:9 by ^{13}C-NMR; **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 5.23 (m, 1H), 3.67 (quint, *J* = 6.2 Hz, 1H), 2.29 (m, 1H), 1.82-1.68 (m, 2H), 1.60 (m, 3H), 1.56 (m, 1H), 1.48-1.25 (m, 1H + 2H + 2H), 1.14 (d, *J* = 6.3 Hz, 3H), 0.97 (s, 3H), 0.89 (d, *J* = 6.7 Hz, 3H), 0.76 (s, 3H); **^{13}C{^{1}H}-NMR** ($CDCl_3$, 101 MHz): δ 148.9, 121.9, 72.1, 50.6, 46.9, 40.5, 35.8, 31.5, 27.6, 26.0, 29.9, 19.7, 14.8, 12.8; GC-MS: m/z (%): 210 (M^+, 19), 177 (80), 121 (67), 107 (100); $[\alpha]_D$ = +30.3 ($CHCl_3$, *c*= 0.9).

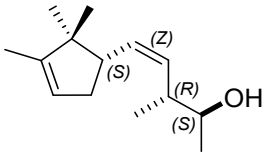
(2*R*,3*R*)-3-methyl-5-((*S*)-2,2,3-trimethylcyclopent-3-en-1-yl)pentan-2-ol (2*R*,3*R*,*S*'-1c)



(2*R*,3*R*,*S*')-**1c**

A sample of rection mixture was analyzed by GC-MS before ADH reduction: tr= 31.6 min (3*R*,*S*') and 31.4 min (3*S*,*S*'); *dr*= 86:14. Yield 70% (441 mg) as a colourless oil; tr= 18.2 min, >99% purity by GC-MS; *dr*= 87:13 by ^{13}C-NMR; **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 5.23 (m, 1H), 3.71 (bm, 1H), 2.29 (m, 1H), 1.79 (m, 1H), 1.69 (m, 1H), 1.60 (m, 3H), 1.58 (s, 1H), 1.52-1.22 (m, 1H + 2H + 2H), 1.16 (d, *J* = 6.4 Hz, 3H), 0.97 (s, 3H), 0.90 (d, *J* = 6.7 Hz, 3H), 0.76 (s, 3H); **^{13}C{^{1}H}-NMR** ($CDCl_3$, 101 MHz): δ 148.9, 121.8, 71.8, 50.6, 46.9, 40.2, 35.8, 31.8, 27.7, 26.0, 20.5, 19.9, 14.3, 12.8; GC-MS: m/z (%): 210 (M^+, 17), 177 (78), 121 (72), 107 (100); $[\alpha]_D$ = +27.0 ($CHCl_3$, *c*= 1.1).

(2*S*,3*R*,*Z*)-3-methyl-5-((*S*)-2,2,3-trimethylcyclopent-3-en-1-yl)pent-4-en-2-ol (*Z*,2*S*,3*R*,*S*'-1d)



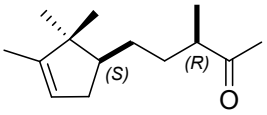
(*Z*,2*S*,3*R*,*S*'-**1d**)

Yield 49% (306 mg) as a colourless oil; tr= 16.8 min, 96% purity by GC-MS; *Z*>99% by ^{13}C-NMR, *dr*= 96:4 by ^{13}C-NMR; **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 5.61 (dd, *J* = 10.8 and 1.0 Hz, 1H), 5.33 (ddd, *J* = 10.8, 9.8 and 0.9 Hz, 1H), 5.22 (m, 1H), 3.56 (quint, *J* = 6.3 Hz, 1H), 2.77 (dt, *J* = 10.5 and 8.5 Hz, 1H), 2.48 (m, 1H), 2.24 (dddt, *J* = 15.7, 7.9, 3.2 and 1.6 Hz,1H), 2.00 (m, 1H), 1.63 (bs, 1H), 1.60 (m, 3H), 1.18 (d, *J* = 6.2 Hz, 3H), 0.98 (s, 3H), 0.94 (d, *J* = 6.9 Hz, 3H), 0.83 (s, 3H); **^{13}C{^{1}H}-NMR** ($CDCl_3$, 101 MHz): δ 148.4, 133.4, 132.5, 121.6, 71.7, 48.7, 48.3, 40.1, 36.8, 26.1, 20.7, 20.3, 17.7, 12.8; GC-MS: m/z (%): 208 (M^+, 17), 149 (83), 121 (100), 107 (83); $[\alpha]_D$ = +106.0 ($CHCl_3$, *c*= 0.8).

General procedure for bioreduction with OYE2 at preparative scale

According to Scheme 4 of the article, the same procedure used for the synthesis of **8** was adapted for the reduction of **5c** (634 mg) and **5d** (79 mg). The crude material was submitted to silica gel column chromatography purification affording **7c** and **7d**.

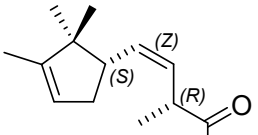
(*R*)-3-methyl-5-((*S*)-2,2,3-trimethylcyclopent-3-en-1-yl)pentan-2-one (3*R*,*S*'-7c)



(3*R*,*S*')-**7c**

Yield 89% (570 mg) as a pale-yellow oil; tr= 31.6 min (3*R*,*S*') and 31.4 min (3*S*,*S*'), *dr*= 86:14, 97% purity by GC-MS; **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 5.16 (m, 1H), 2.47 (m, 1H), 2.24 (m, 1H), 2.09 (s, 3H), 1.79-1.56 (m, 1H+2H), 1.60 (m, 3H), 1.41-1.28 (m, 2H), 1.18 (m, 1H), 1.04 (d, *J* = 7.0 Hz, 3H), 0.91 (s, 3H), 0.69 (s, 3H); **^{13}C{^{1}H}-NMR** ($CDCl_3$, 101 MHz): δ 212.7, 148.7, 121.6, 50.4, 47.5, 46.8, 35.6, 32.0, 28.0, 27.5, 25.9, 19.7, 16.1, 12.6; GC-MS: m/z (%): 208 (M^+, 10), 121 (100), 109 (42), 93 (23); $[\alpha]_D$ = −3.3 ($CHCl_3$, *c*= 1.1).

(*R*,*Z*)-3-methyl-5-((*S*)-2,2,3-trimethylcyclopent-3-en-1-yl)pent-4-en-2-one (*Z*,3*R*,*S*'-7d)

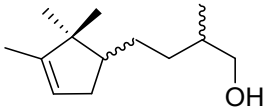


(*Z*,3*R*,*S*'-**7d**)

Yield 81% (65 mg) as a pale-yellow oil; tr= 16.5 min, 88% purity by GC-MS; *Z*>99% by ^{13}C-NMR, *dr*= 96:4 by ^{13}C-NMR; **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 5.60 (dd, *J* = 10.8 and 1.0 Hz, 1H), 5.40 (ddd, *J* = 10.8, 9.8 and 0.9 Hz, 1H), 5.22 (m, 1H), 3.48 (dq, *J* = 10.0 and 6.9 Hz, 1H), 2.76 (dt, *J* = 10.8 and 8.5 Hz, 1H), 2.23 (dddt, *J* = 15.7, 7.8, 3.2 and 1.6 Hz,1H), 2.13 (s, 3H), 2.00 (m, 1H), 1.60 (m, 3H), 1.11 (d, *J* = 6.9 Hz, 3H), 0.96 (s, 3H), 0.82 (s, 3H); **^{13}C{^{1}H}-NMR** ($CDCl_3$, 101 MHz): δ 210.3, 148.2, 133.5, 129.5, 121.6, 48.7, 48.6, 46.4, 36.5, 28.1, 26.2, 20.6, 17.6, 12.7; GC-MS: m/z (%): 206 (M^+, 33), 134 (67), 107 (100), 93 (72); $[\alpha]_D$ = −116.8 ($CHCl_3$, *c*= 1.1).

Characterization of commercial sandalwood fragrances

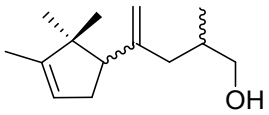
1a, Brahmanol®



1a, Brahmanol®

tr= 17.3 min by GC-MS; *dr*= 54:46 by ^{13}C-NMR; **^{1}H-NMR ($CDCl_3$, 400 MHz):** δ 5.26-5.18 (m, 1H), 3.55-3.49 (m, 1H), 3.45-3.40 (m, 1H), 2.32-2.25 (m, 1H), 1.82-1.74 (m, 1H), 1.73-1.61 (m, 2H), 1.60-1.59 (m, 3H), 1.51-1.42 (m, 2H), 1.23-1.14 (m, 1H), 1.09-1.05 (m, 1H), 0.98-0.96 (m, 3H), 0.95-0.91 (m, 3H), 0.78-0.73 (m, 3H); **^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz):** δ 148.9, 121.84, 121.82, 68.7, 68.4, 51.0, 50.7, 46.93, 46.91, 36.4, 36.2, 35.9, 35.8, 32.6, 32.3, 27.6, 27.4, 26.1, 26.0, 19.9, 19.8, 17.0, 16.2, 12.7; GC-MS: m/z (%): 196 (M^+, 16), 181 (100), 107 (75), 95 (46); $[\alpha]_D$ = +8.9 ($CHCl_3$, *c*= 1.6).

1b, Firsantol®

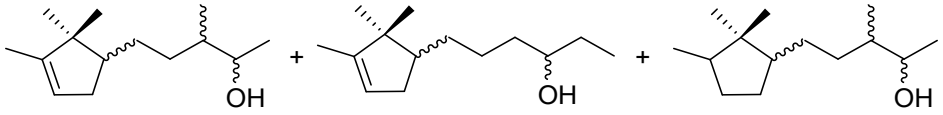


1b, Firsantol®

tr= 18.4 min (2*SR*,*S*'*R*') and 18.5 min (2*RS*,*S*'*R*') by GC-MS; *dr*= 42:58 by GC-MS and ^{13}C-NMR; **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 5.26-5.25 (m, 1H), 4.93-4.88 (m, 2H), 3.55-3.48 (m, 1H), 3.47-3.37 (m, 1H), 2.60-2.49 (m, 1H), 2.41-2.29 (m, 1H), 2.28-2.09 (m, 2H), 1.91-1.78 (m, 2H), 1.61-1.56 (m, 3H), 1.11-1.06 (m, 3H), 0.97-0.84 (m, 3H), 0.77-0.71 (m, 3H); **^{13}C{^{1}H}-NMR** ($CDCl_3$, 101 MHz): δ 148.7, 148.0, 147.5, 147.4, 121.7, 112.2, 112.0, 68.6, 68.2, 57.8, 55.2, 47.9, 47.8 42.0, 41.5, 34.4, 34.32, 34.27, 34.2, 27.1, 27.0, 21.10, 21.06, 17.4, 16.4, 12.9; GC-MS (2*SR*,*S*'*R*'): m/z (%): 208 (M^+, 71), 135 (100), 107 (83), 91 (64); GC-MS (2*RS*,*S*'*R*'): m/z (%): 208 (M^+, 78), 135 (100), 107 (90), 91 (73); $[\alpha]_D$ = –57.4 ($CHCl_3$, *c*= 1.2).

1c, Sandalore®

1c/regioisomer/dihydro-Sandalore® = 84:13.4:2.6

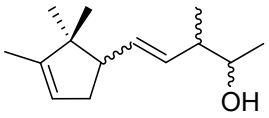


1c, Sandalore® regioisomer dihydro-Sandalore®

tr= 18.16-18.26 min (**1c**, Sandalore®), tr= 18.8 min (regioisomer) and tr= 18.6 (dihydro-Sandalore®), 84:13.4:2.6 by GC-MS; *dr*= 31:31:20:18 by ^{13}C-NMR; **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 5.24-5.18 (m, 1H), 3.81-3.58 (m, 1H), 3.56-3.46 (m, regioisomer, 0.15H) 2.33-2.21 (m, 1H), 1.86-1.61 (m, 2H), 1.61-1.56 (m, 3H), 1.56-1.29 (m, 5H), 1.16-1.09 (m, 3H), 1.52-1.22 (m, 2H), 1.16-1.09 (m, 3H), 0.97-0.94 (m, 3H), 0.93-0.85 (m, 3H), 0.75-0.72 (m, 3H); **^{13}C{^{1}H}-NMR** ($CDCl_3$, 101 MHz): δ 148.83, 148.81, 121.85, 121.83, 121.80, 73.43, 73.36, 71.97, 71.67, 71.62, 71.24, 51.04, 50.57, 50.52, 46.90, 46.87, 40.75, 40.45, 40.39, 40.18, 37.44, 35.98, 35.95, 35.81, 35.77, 35.73, 32.09, 32.06, 31.71, 31.52, 30.33, 30.26, 30.15, 27.95, 27.90, 27.64, 27.56, 26.06, 26.04, 25.98, 25.04, 24.93, 20.45, 20.40, 19.84, 19.80, 19.61, 19.27, 14.77, 14.71, 14.41, 14.29, 12.70; GC-MS: m/z (%): 210 (M^+, 20), 177 (83), 121 (67), 107 (100); GC-MS: m/z (%): 210 (M^+, 5), 177 (100), 121 (81), 107 (88); $[\alpha]_D$ = –1.2 ($CHCl_3$, *c*= 1.0).

1d, Ebanol®

E/*Z*= 90:10



1d, Ebanol®

tr= 16.9 min and 17.2 min (*E*); 16.7 min and 16.8 min (*Z*), *E*/*Z*= 92:8 by GC-MS; *E*/*Z*= 90:10 by ^{13}C-NMR, *dr*= 25:25:25:25 by ^{13}C-NMR; **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 5.65-5.45 (m, 1H), 5.41-5.24 (m, 1H), 5.24-5.19 (m, 1H), 3.69-3.39 (m, 1H), 2.43-2.30 (m, 1H), 2.29-2.00 (m, 3H), 1.87-1.62 (m,1H), 1.62-1.53 (m, 3H), 1.18-1.10 (m, 3H), 1.04-0.97 (m, 3H), 0.96-0.92 (m, 3H), 0.77-0.71 (m, 3H); **^{13}C{^{1}H}-NMR** ($CDCl_3$, 101 MHz): δ 148.10, 148.05, 133.86, 132.82, 132.77, 132.72, 132.57, 121.60, 121.57, 121.55, 71.34, 71.31, 71.12, 71.08, 54.42, 54.37, 54.26, 54.14, 48.16, 48.08, 48.05, 45.41, 45.39, 45.34, 44.39, 44.15, 35.60, 35.54, 35.50, 35.48, 25.60, 25.56, 25.50, 25.46, 20.69, 20.64, 20.60, 20.58, 20.31, 20.20, 20.10, 20.07, 16.03, 12.79; GC-MS (*E*): m/z (%): 208 (M^+, 1), 164 (64), 149 (100), 121 (100); GC-MS (*Z*): m/z (%): 208 (M^+, 12), 149 (75), 121 (100), 107 (88); $[\alpha]_D$ = +1.1 ($CHCl_3$, *c*= 1.0).

Stacked ^{13}C-NMR spectra of sandalwood fragrances

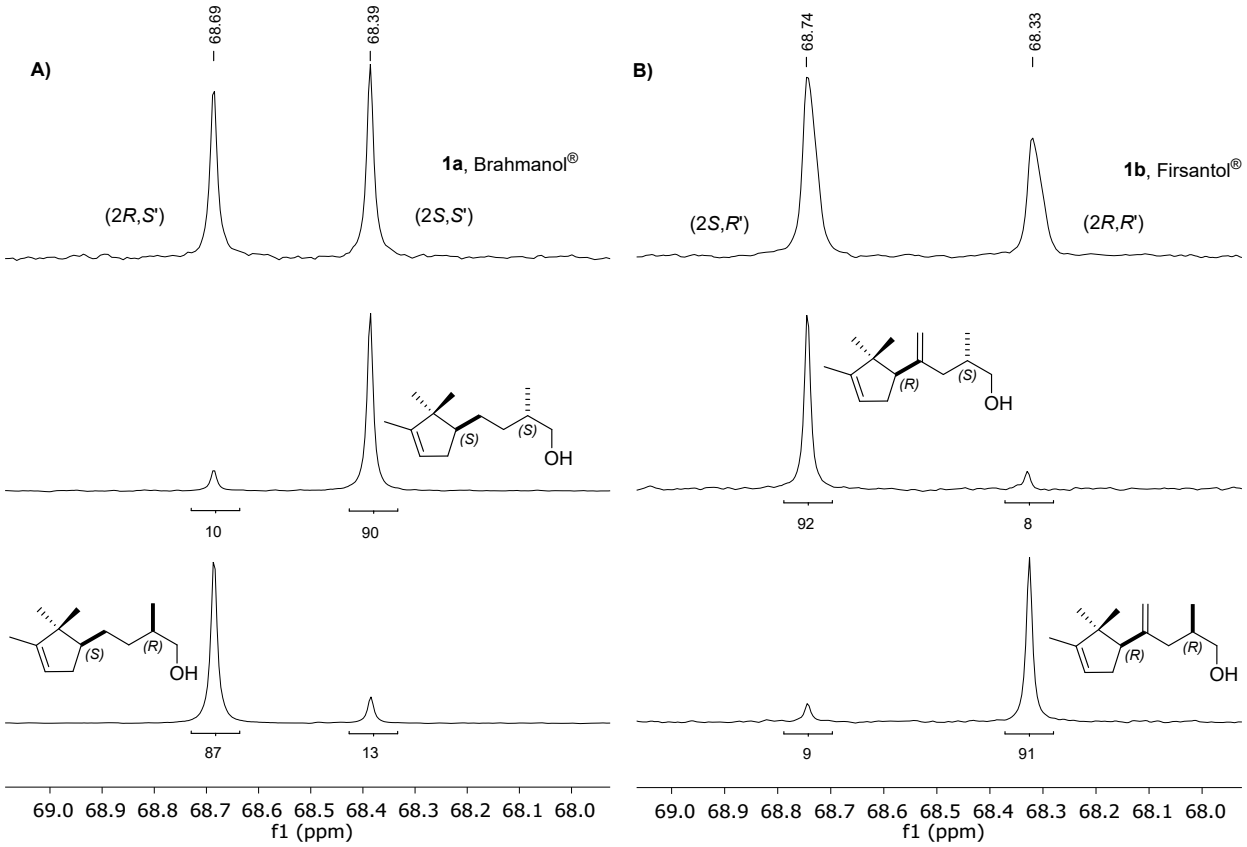


Figure S2 ^{13}C NMR spectra ($CDCl_3$, 100 MHz, 302 K), C1 signal expanded regions: **A)** Brahamnol® isomers; **B)** Firsantol® isomers.

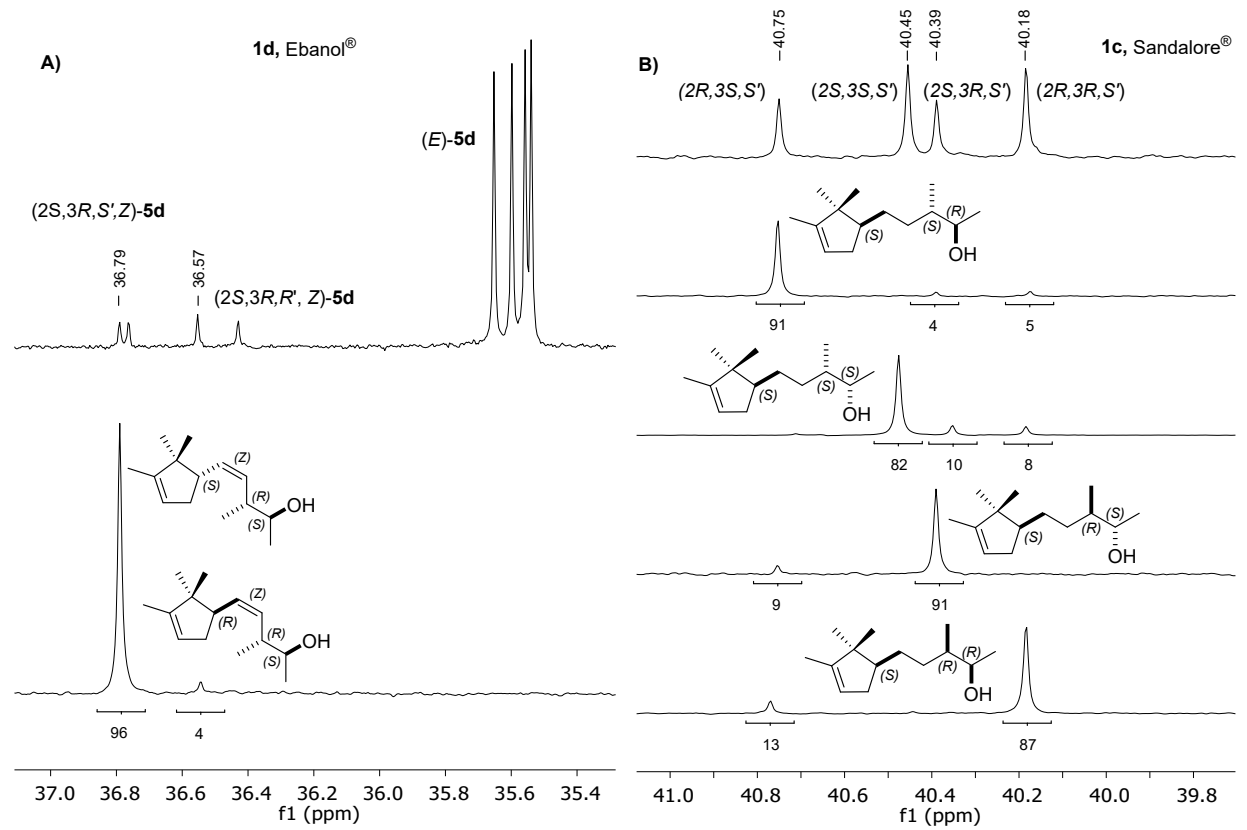


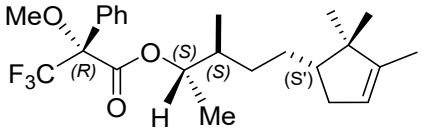
Figure S3 ^{13}C NMR spectra ($CDCl_3$, 100 MHz, 302 K) expanded regions: **A)** C(3)-*Me* signal for Ebanol® isomers; **B)** C(3) signal for Sandalore® isomers.

General procure for the preparation of the Mosher's esters of 1c

To a freshly prepared and an ice-cold solution of α-methoxy-α-(trifluoromethyl)phenylacetic acid chloride (0.2 mmol) in dry CH_2Cl_2 was added a solution of alcohol **1c** (21 mg) in CH_2Cl_2 (0.2 mL) in the presence of DMAP (10 mg) under a N_2 atmosphere. After 12 h a room temperature, the reaction mixture was quenched with few drops of water and the solvent was removed under reduced pressure. The crude material was submitted to column chromatographic purification with *n*-hexane/EtOAc (95:5), affording the corresponding MTPA ester. The acid chloride was prepared by reaction of α-methoxy-α-(trifluoromethyl)phenylacetic acid (0.2 mmol) with oxalyl chloride (2.0 mmol) and a catalytic amount of DMF (5 µL) in *n*-hexane (2 mL) at room temperature. After 1 day, the solvent was removed under reduced pressure affording the acid chloride of a sufficient purity to be used without further purifications.[27]

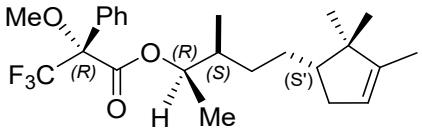
The MTPA-esters were prepared from the couple of alcohols **1c** obtained from the reduction of **4c** with OYE2 and Evo440 or Evo270:

(*R*)-MTPA-Evo440



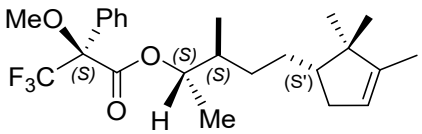
Yield 82% (35 mg) as a pale-yellow oil; **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 7.58-7.51 (m, 1H+1H), 7.43-7.36 (m, 1H+1H+1H), 5.21 (m, 1H), 5.15 (qd, *J* = 6.5 and 4.0 Hz, 1H), 3.57 (m, 3H), 2.20 (dddt, *J* = 14.8, 7.3, 2.9 and 1.6 Hz, 1H), 1.74-1.61 (m, 2H), 1.60 (m, 3H), 1.56 (m, 1H), 1.48-1.34 (m, 1H+1H), 1.31 (d, J = 6.4 Hz, 3H), 1.18-0.98 (m, 2H), 0.95 (s, 3H), 0.89 (d, *J* = 6.8 Hz, 3H), 0.73 (s, 3H); **^{13}C{^{1}H}-NMR** ($CDCl_3$, 101 MHz): δ 166.2, 148.8, 132.8, 129.6, 128.5, 127.43, 127.41, 125.1, 122.2, 121.8, 76.9, 55.5, 50.9, 50.5, 46.9, 38.4, 35.8, 31.9, 27.3, 26.0, 19.8, 17.0, 14.7, 12.7; **^{19}F{^{1}H}-NMR** ($CDCl_3$, 377 MHz): δ −71.19; $[\alpha]_D$ = +37.7 ($CHCl_3$, *c*= 0.7).

(*R*)-MTPA-Evo270



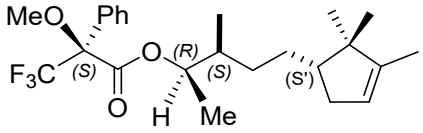
Yield 92% (39 mg) as a pale-yellow oil; **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 7.58-7.51 (m, 1H+1H), 7.43-7.36 (m, 1H+1H+1H), 5.22 (m, 1H), 5.10 (quint, *J* = 6.3 Hz, 1H), 3.54 (m, 3H), 2.25 (dddt, *J* = 15.0, 7.4, 3.0 and 1.4 Hz, 1H), 1.84-1.71 (m, 2H), 1.67 (m, 1H), 1.60 (m, 3H), 1.56-1.42 (m, 1H+1H), 1.20 (d, J = 6.4 Hz, 3H), 1.17-1.00 (m, 2H), 0.97 (s, 3H), 0.93 (d, *J* = 6.8 Hz, 3H), 0.76 (s, 3H); **^{13}C{^{1}H}-NMR** ($CDCl_3$, 101 MHz): δ 166.3, 148.9, 132.6, 129.6, 128.5, 127.6, 125.0, 122.1, 121.7, 77.5, 55.44, 55.43, 50.9, 50.5, 46.9, 37.9, 35.9, 32.0, 27.6, 26.0, 19.8, 15.4, 14.9, 12.7; **^{19}F{^{1}H}-NMR** ($CDCl_3$, 377 MHz): δ −71.28; $[\alpha]_D$ = +19.5 ($CHCl_3$, *c*= 0.7).

(*S*)-MTPA-Evo440



Yield 92% (39 mg) as a pale-yellow oil; **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 7.58-7.50 (m, 1H+1H), 7.43-7.36 (m, 1H+1H+1H), 5.22 (m, 1H), 5.11 (qd, *J* = 6.4 and 4.1 Hz, 1H), 3.53 (m, 3H), 2.20 (dddt, *J* = 14.8, 7.2, 2.9 and 1.5 Hz, 1H), 1.75 (m, 1H), 1.70-1.62 (m, 2H), 1.60 (m, 3H), 1.55 (m, 1H), 1.48 (m, 1H), 1.25 (d, J = 6.4 Hz, 3H), 1.20-1.04 (m, 2H), 0.97 (s, 3H), 0.94 (d, *J* = 6.9 Hz, 3H), 0.75 (s, 3H); **^{13}C{^{1}H}-NMR** ($CDCl_3$, 101 MHz): δ 166.4, 148.9, 132.6, 129.6, 128.5, 127.69, 127.68, 125.0, 122.2, 121.8, 77.1, 55.4, 51.0, 50.5, 46.9, 38.4, 35.9, 32.1, 27.8, 26.0, 19.8, 16.7, 14.8, 12.7; **^{19}F{^{1}H}-NMR** ($CDCl_3$, 377 MHz): δ −71.23; $[\alpha]_D$ = −17.0 ($CHCl_3$, *c*= 0.7).

(*S*)-MTPA-Evo270



Yield 89% (38 mg) as a pale-yellow oil; **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 7.58-7.51 (m, 1H+1H), 7.43-7.36 (m, 1H+1H+1H), 5.21 (m, 1H), 5.10 (quint, *J* = 6.2 Hz, 1H), 3.57 (q, *J* = 1.2 Hz, 3H), 2.20 (dddt, *J* = 14.9, 7.3, 2.9 and 1.5 Hz, 1H), 1.78-1.68 (m, 2H), 1.64 (m, 1H), 1.60 (m, 3H), 1.56 (s, 1H), 1.28 (d, J = 6.4 Hz, 3H), 1.26 (m, 1H), 1.18-1.01 (m, 2H), 0.96 (s, 3H), 0.85 (d, *J* = 6.9 Hz, 3H), 0.74 (s, 3H); **^{13}C{^{1}H}-NMR** ($CDCl_3$, 101 MHz): δ 166.2, 148.9, 132.8, 129.6, 128.5, 127.44, 127.42, 125.0, 122.2, 121.8, 77.4, 55.59, 55.48, 50.9, 46.9, 37.8, 35.9, 31.7, 27.5, 26.0, 19.8, 15.8, 14.7, 12.7; **^{19}F{^{1}H}-**NMR ($CDCl_3$, 377 MHz): δ −71.25; $[\alpha]_D$ = −36.9 ($CHCl_3$, *c*= 0.7).

Assignment of absolute stereochemical configuration of C(2) stereogenic center of Sandalore® alcohols through analysis of NMR chemical shift of Mosher's esters

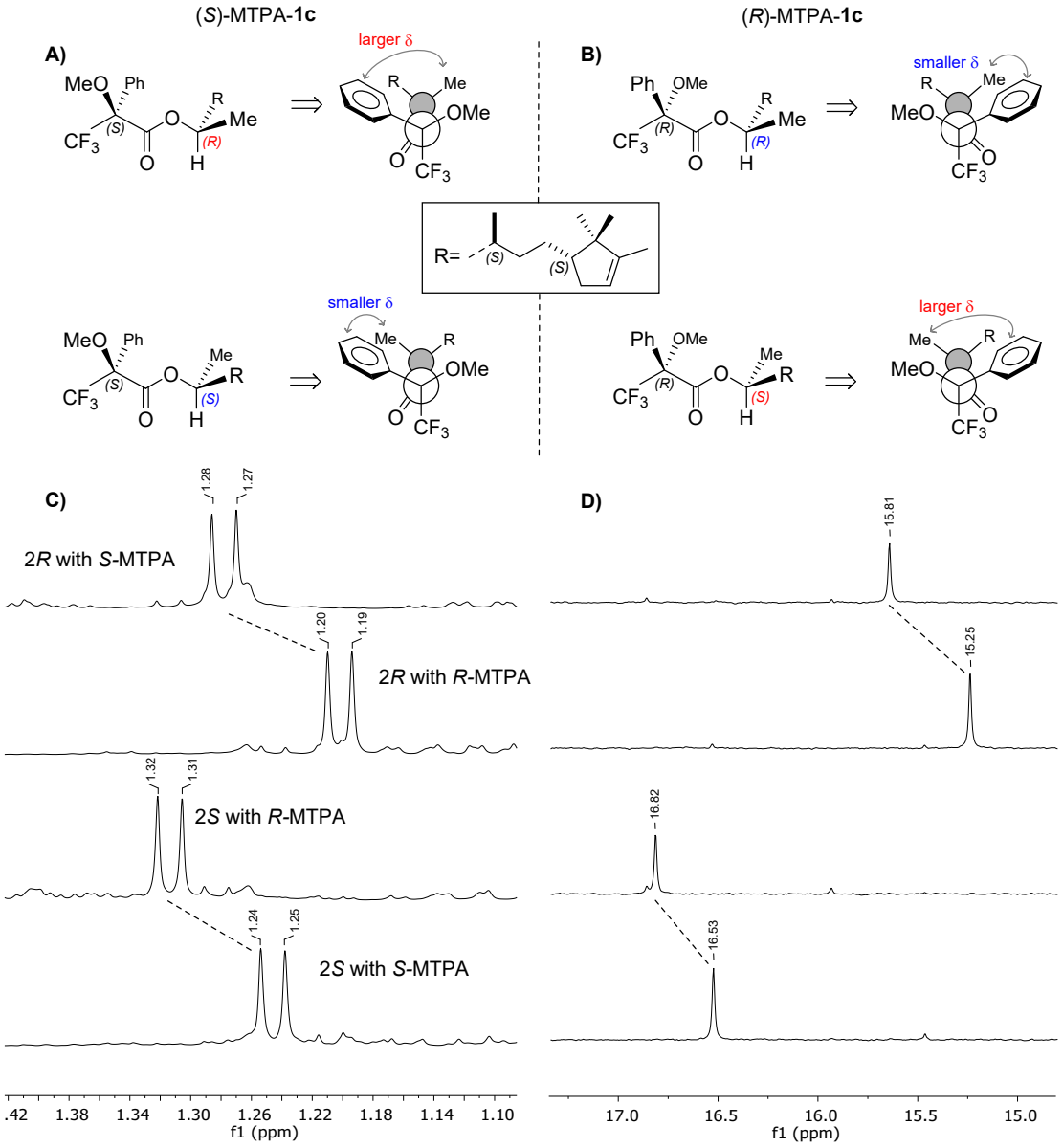


Figure S4 A) Preferred conformers of (*S*)-MTPA esters of **1c**: the conformations are elucidated based on Mosher's model (CF_3 group eclipsed to CO carbonyl). The analyzed alcohols **1c** were obtained from the reduction of the α,β-unsaturated ketone **4c** using OYE2 coupled with a *pro* (*R*) (Evo270) or a *pro* (*S*) (Evo440) ADH. **B)** Preferred conformers of (*R*)-MTPA derivatives obtained from the same couple of alcohols. **C)** Expanded ^{1}H-NMR (400 MHz) region relative to C(1) methyl signal of Mosher's esters ($CDCl_3$ at 302 K). When the methyl group lies closer to the shielding region of phenyl ring, its chemical shift is up-field, conversely if it is distanced from the aromatic ring its protons are less deshielded, resulting in a downfield chemical shift. **D)** A trend similar to that of C) is observed for the C(1) signal of the ^{13}C-NMR spectrum (100 MHz, $CDCl_3$ at 302 K), but for the ^{13}C the differential chemical shifts ($\Delta\delta^{S,R}$) are more pronounced than those observed for ^{1}H (0.07 ppm *vs* 0.3÷0.5 ppm). The signals were assigned by means of ^{13}C pendant experiments combined with HMBC-(^{1}H-^{13}C)-NMR (see pag. S81, S83, S85, S87).

Assignment of absolute stereochemical configuration of C(2) stereogenic center of ketone 7d through 2D NOESY experiment and DFT computation

NOESY experiment

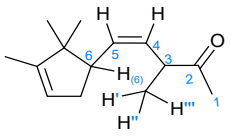
The NMR sample was prepared in a 5 mm tubes with 0.5 ml $CDCl_3$ and ~14 mg of **7d**, without degassing. NMR data were collected on a 400 MHz spectrometer (Bruker Avance II). Acquisition parameters of 2D-NOESY spectra: TD: F2=1 k, F1=256 experiments; d8= 400/600/800/1000 ms mixing time; d1= 4 s relaxation delay; ns= 2 scans. NOESY sequence is based on *noesygpphzs* pulse program of Bruker Top-spin experiment library software (phase sensitive; with gradient/rf spoil pulse in mixing time).[28] NOE build-up curve was obtained with mixing times up to 800 ms. The integration values are referenced to H4-H5 contact, which distance is estimated 2.33 Å. According to the following equation, $r_{H6\text{-}Me}$= 3.07 Å.

$$r_{H6-Me} = r_{H4-H5}\left(\frac{I_{H4-H5}}{I_{H6-Me}}\right)^{1/6}$$

DFT calculations

Density functional theory (DFT) calculations were performed with Gaussian 16.6 software.[29] Molecular geometry optimizations were performed using the B3LYP functional,[30] augmented with Grimme's D3 empirical dispersion term,[31] using the 6-31+G(d,p) basis set in *vacuum*.[32] Single point frequency calculations were performed with the Truhlar's implicit solvent model, SCRF=SMD (solvent= $CHCl_3$, 298.15 K).[33] 3D rendering of optimized structures was generated using CYLview software.[34]

Table S6 Energies and geometric parameters of conformers.



Comp.	Conf.	H (au)	G (au)	ΔG [a] (kcal mol^{-1})	Pop. [b] (%)	Dihedral angle C4-C3-C(Me)-H' (°)	Avg Dist. [c] H6-(CHCH_3) (Å)	WAvg Dist. [d] (Å)
(*Z,3R,S'*)-**7d**	**Conf1**	-621.707749	-621.769502	0.39	66	-13.22	3.97	3.70
	Conf2	-621.705232	-621.768883		34	167.27	3.20	
(*Z,3S,S'*)-**7d**	**Conf1**	-621.705800	-621.769803	5.88	>99	-37.86	4.63	4.63
	Conf2	-621.699848	-621.760434		-	125.81	2.70	

a) Gibbs energy difference between the most stable and less stable conformer. *b*) Population is calculated as *Boltzman* distribution at 298.15 K. *c*) Average distance between H6 and the three protons of CH_3 (H', H'', and H'''). *d*) Weighted average distance.

Coordinates

Conf1 of (*Z,3R,S'*)-**7d**
Energy (RB3LYP)= -622.053184 Hartree

C	-0.80508	0.71593	0.10392
C	-1.74974	1.94563	0.12081
C	-3.02304	1.38747	-0.46024
C	-3.04254	0.05064	-0.45915
C	-1.77001	-0.52216	0.16831
H	-1.33247	2.78400	-0.44806
H	-1.90887	2.31671	1.14471
H	-3.84113	2.01474	-0.80288
H	-0.34914	0.68746	-0.89124
C	-1.18932	-1.70943	-0.60844
H	-0.23096	-2.01319	-0.17665
H	-1.85668	-2.57679	-0.57396
H	-1.02374	-1.45125	-1.65993
C	-2.06962	-0.95826	1.61655
H	-2.83449	-1.74108	1.63209
H	-1.17276	-1.35934	2.09942
H	-2.43825	-0.12096	2.21685
C	-4.16025	-0.82970	-0.92554
H	-5.01346	-0.23934	-1.26987
H	-3.84135	-1.47806	-1.75058
H	-4.50929	-1.49282	-0.12422
C	0.26697	0.76643	1.14800
H	-0.08602	0.92153	2.16689
C	1.59038	0.68411	0.96786
H	2.23491	0.78672	1.84115
C	2.33399	0.51941	-0.33932
H	1.61856	0.23863	-1.12197
C	3.32647	-0.64642	-0.21183
O	4.52878	-0.46717	-0.24338
C	2.73053	-2.02871	-0.03066
H	2.07935	-2.04682	0.84884
H	2.10607	-2.28554	-0.89377
H	3.52793	-2.7644	0.07788
C	3.05134	1.81536	-0.73577
H	2.32390	2.61909	-0.87595
H	3.75838	2.11618	0.04133
H	3.61888	1.67999	1.66009

Conf2 of (*Z,3R,S'*)-**7d**
Energy= -622.051871 Hartree

C	0.36045	0.14532	-0.37843
C	0.70136	1.62610	-0.69440
C	2.01015	1.81772	0.02647
C	2.58129	0.65813	0.36717
C	1.75224	-0.53365	-0.11784
H	-0.09202	2.29866	-0.34984
H	0.81008	1.79715	-1.77636
H	2.44311	2.79608	0.21489
H	-0.15440	0.14918	0.58432
C	1.62876	-1.65374	0.92216
H	0.93368	-2.42355	0.57115
H	2.59383	-2.13711	1.10726
H	1.25433	-1.26718	1.87564
C	2.39282	-1.09885	-1.40167
H	3.41921	-1.42445	-1.20531
H	1.83753	-1.96586	-1.77364
H	2.43002	-0.34575	-2.19496
C	3.89204	0.47712	1.06767
H	4.37315	1.43892	1.26417
H	3.76368	-0.03983	2.02625
H	4.58458	-0.13254	0.47396
C	-0.50083	-0.51068	-1.41377
H	-0.03720	-0.64564	-2.38997
C	-1.77077	-0.91591	-1.28806
H	-2.24399	-1.36438	-2.15926
C	-2.64719	-0.82203	-0.04647
H	-3.67415	-1.03214	-0.37795
C	-2.69502	0.60940	0.50884
O	-2.32293	0.87560	1.63643
C	-3.25107	1.67457	-0.41654
H	-2.71281	1.67050	-1.36826
H	-4.30309	1.46138	-0.63945
H	-3.17253	2.65296	0.05845
C	-2.27517	-1.84082	1.03788
H	-2.28677	-2.85285	0.62419
H	-1.27811	-1.64205	1.43237
H	-2.97914	-1.79229	1.87283

Conf1 of (*Z,3S,S'*)-**7d**
Energy (RB3LYP)= -622.052469 Hartree

C	0.57376	-0.24136	0.36648
C	1.11052	-1.59321	0.90097
C	2.44813	-1.70075	0.2143
C	2.85815	-0.53511	-0.29647
C	1.8587	0.58349	0.00453
H	0.42411	-2.41309	0.66398
H	1.22496	-1.58416	1.99599
H	3.01873	-2.62442	0.17415
H	0.07658	-0.46829	-0.57963
C	1.58570	1.50502	-1.19047
H	0.77278	2.19999	-0.95212
H	2.46643	2.10211	-1.44990
H	1.29264	0.92814	-2.07364
C	2.37952	1.42249	1.18873
H	3.34252	1.88057	0.94137
H	1.68216	2.22910	1.43704
H	2.52444	0.80535	2.08086
C	4.14536	-0.27323	-1.01498
H	4.75994	-1.17568	-1.07116
H	3.96667	0.07955	-2.03795
H	4.73359	0.50597	-0.51417
C	-0.38894	0.44393	1.28516
H	-0.03725	0.61665	2.30161
C	-1.62459	0.85721	0.97949
H	-2.22782	1.32393	1.75757
C	-2.30617	0.69055	-0.36728
H	-1.57906	0.83389	-1.17084
C	-2.7587	-0.77133	-0.48805
O	-2.14679	-1.55859	-1.1866
C	-3.96452	-1.20238	0.3242
H	-3.89703	-0.82771	1.35033
H	-4.87892	-0.78728	-0.11441
H	-4.03278	-2.29058	0.32454
C	-3.45506	1.69285	-0.54251
H	-3.96997	1.54846	-1.49715
H	-4.19365	1.60218	0.26044
H	-3.06597	2.71499	-0.51881

Conf2 of (*Z,3S,S'*)-**7d**
Energy (RB3LYP)= -622.045758 Hartree

C	0.81551	-0.78818	0.06662
C	1.85941	-1.93363	0.12432
C	3.11302	-1.25994	-0.36996
C	3.01959	0.07348	-0.347
C	1.66831	0.52604	0.2106
H	1.54992	-2.79304	-0.48125
H	1.98848	-2.31062	1.15036
H	4.00002	-1.8095	-0.67236
H	0.4246	-0.776	-0.94953
C	1.03989	1.67622	-0.58505
H	0.03218	1.88978	-0.21556

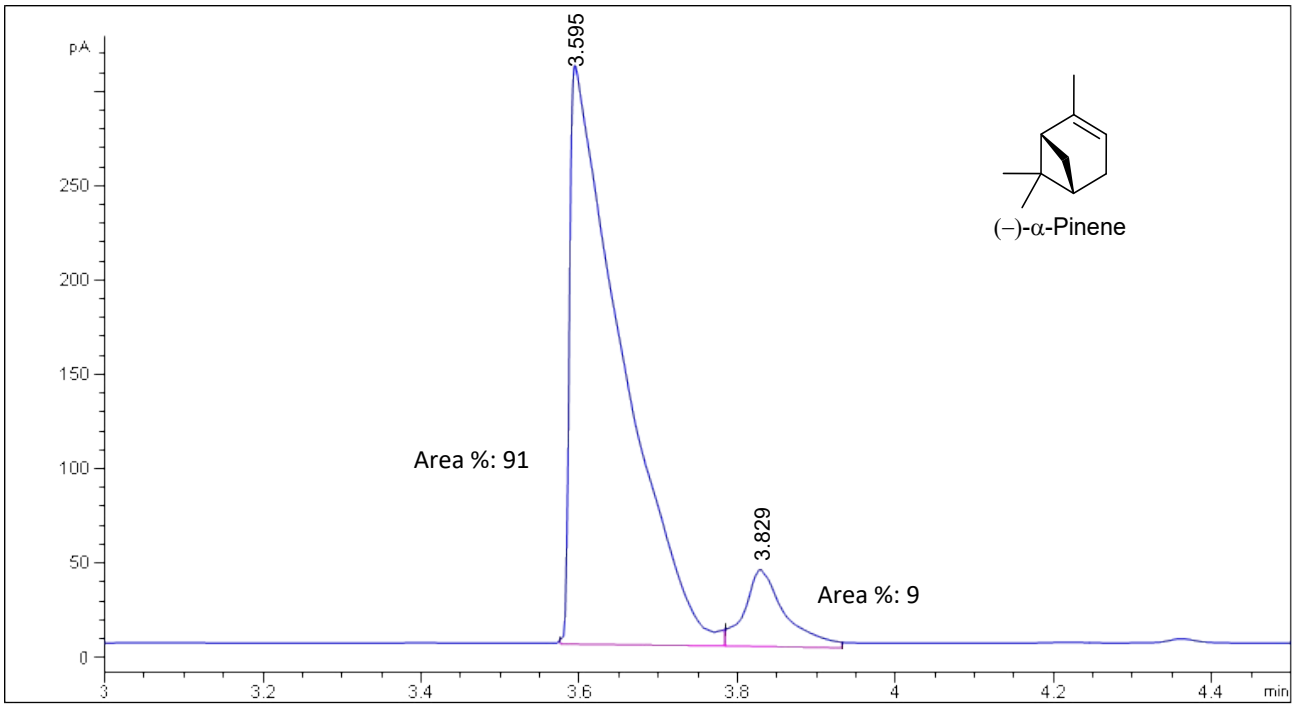
H	1.62681	2.59584	-0.49154
H	0.96844	1.42867	-1.64959
C	1.84517	0.96109	1.679
H	2.53702	1.80646	1.74843
H	0.89072	1.27512	2.1134
H	2.24999	0.1489	2.29028
C	4.08514	1.05252	-0.73202
H	5.00313	0.54145	-1.03396
H	3.76208	1.68921	-1.56451
H	4.33067	1.72552	0.09886
C	-0.29338	-0.94784	1.06216
H	0.06195	-1.09106	2.08301
C	-1.6256	-0.97237	0.91953
H	-2.19088	-1.1255	1.83999
C	-2.54963	-0.8367	-0.27131
H	-3.20112	-1.71948	-0.26877
C	-3.52652	0.33051	-0.01688
O	-4.7225	0.13236	0.07346
C	-2.93651	1.7211	0.1151
H	-2.19165	1.73783	0.91644
H	-2.42002	2.00943	-0.8065
H	-3.73192	2.43648	0.32486
C	-1.93686	-0.71161	-1.67393
H	-2.73668	-0.64261	-2.41792
H	-1.30368	0.1721	-1.77639
H	-1.33528	-1.59207	-1.91266

Table S7 Olfactory evaluation

Fragrance	Olfactory description	Leffingwell odour evaluation [35]
1a-(2*S*,*S*')	Much more pungent and unpleasant than **1a**-(2*R*,*S*'). The head impact is 7/10, but over time it loses a lot in tenacity. Within 2 hours it reaches around 2.5/10.	Weak and less preferred enantiomer. Odour Threshold = 166.0 ppb.[36]
1a-(2*R*,*S*')	Round smell and closest to commercial Brahmanol®. It is creamy, sandalwood without the earthy-amber component, making it more pleasant. Head Impact is slightly stronger than commercial Brahmanol® (**6.5/10**) and over time maintains its olfactory note and tenacity well (**6.5/10**).	Peculiar sandalwood's strongly excellent smell. Odour Threshold = 14.5 ppb.[36]
1b-(2*S*,*R*')	Impact 6.5/10. Olfactory profile a little creamier than commercial Firsantol®. Tenacity: 6.5/10 (more tenacious than commercial Firsantol®).	Sandalwood note is not as powerful as the **1b**-(2*R*,*R*')-isomer but is accompanied of a more marked woody-cedar character. Odour Threshold = NA.[17a]
1b-(2*R*,*R*')	Impact: **8.5/10**. It has a very impactful note on the head, but unpleasant and pungent. Tends to lose the unpleasant note over time. Loses tenacity over time (**6**/10).	Elegant and powerful sandalwood note. Preferred of the four isomers. Odour Threshold = NA.[17a]
1c-(2*R*,3*S*,*S*')	It has the amber-woody component of Sandalore® and slightly less of the creamy component. It also has a tobacco note that is pleasant. After the first few minutes the impact seems to be stronger than the commercial Sandalore® (7.5/10). Very tenacious, holds the note well over time (7.5/10).	-
1c-(2*S*,3*S*,*S*')	It has an unpleasant head impact (7/10). After a few minutes, although remaining unpleasant, the intensity of the note drops significantly compared to the **1c**-(2*R*,3*S*,*S*'), (3.5/10).	-
1c-(2*S*,3*R*,*S*')	Impact **8/10**. It has the creamy appearance of sandalwood. Very tenacious even over time **9/10** (the most tenacious of all diastereoisomers).	-
1c-(2*R*,3*R*,*S*')	Impact 7/10. Olfactory similar to **1c**-(2*R*,3*S*,*S*'), but slightly creamier and less dry. Less tenacious than **1c**-(2*R*,3*S*,*S*'): tenacity approximately 3/10.	-

Copies of α-pinene chiral GC chromatograms

The *ee* of (–) and (+)-α-pinene were evaluated by chiral GC analysis on a CP7502 Chirasil-DEX CB column (25 m x 0.25 mm x 0.25 µm). Program temperature: 80 °C (1 min)/5 °C min^{-1}/150 °C (1 min)/60 °C min^{-1}/200 °C (2 min).



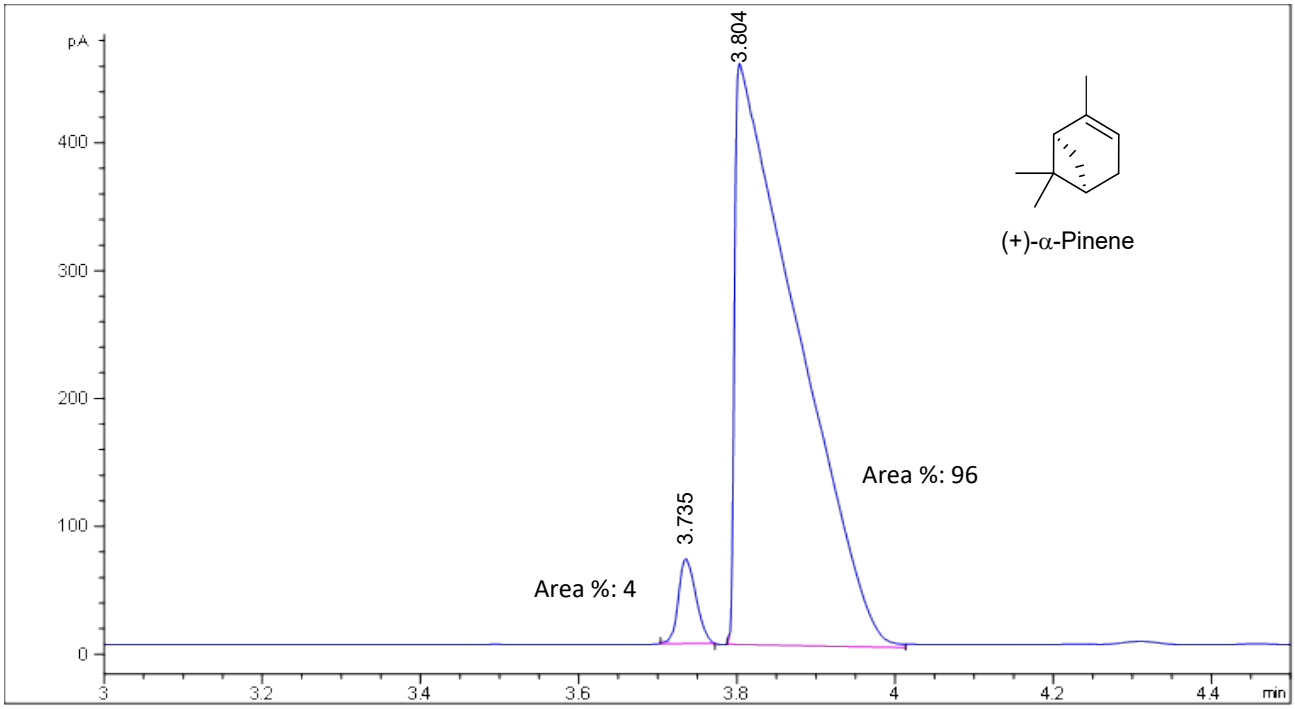


Table S8 Simplified Environmental factor (sEF) analysis

	Chemo reductive process				Bio reductive process	
	$LiAlH_4$ [ref. 38]		H_2 [ref. 36]		OYE2+Evo440	
	Materials	Mass (g)	Materials	Mass (g)	Materials	Mass (g)
Reagents	**4a**	96.00	Allylic alcohol	5.00	**4a**	0.58
	$LiAlH_4$	7.50	Ru cat.	0.02	OYE2	0.02
		103.50	H_2 [a]	0.99	Evo440	0.04
				6.01	GDH	0.08
					$NADP^+$	0.03
					Glucose	4.20
						4.94
Product	Allylic alcohol	**82.60**	(*S',S*)-**1a**	**4.30**		**0.49**
Waste		**20.90**		**1.72**		**4.44**
sEF		**0.25**		**0.40**		**8.99**

a) Autoclave hydrogenation volume of 0.3 L assuming an ideal behavior of H_2.

Table S9 Complete Environmental factor (cEF) analysis

	Chemo reductive process								Bio reductive process			
	$LiAlH_4$ [a]				H_2 [ref. 36]				OYE2+Evo440			
	Materials	V (mL)	d (g/mL)	Mass (g)	Materials	V (mL)	d (g/mL)	g	Materials	V (mL)	d (g/mL)	g
Reagents	**4a**			2.00	Allylic alcohol			5.00	**4a**			0.58
	$LiAlH_4$			0.16	Ru cat.			0.02	OYE2			0.02
				2.16	H_2 [b]			0.99	Evo440			0.04
								6.01	GDH			0.08
									$NADP^+$			0.03
									Glucose			4.20
												4.94
Product	Allylic alcohol			**1.70**	(*S',S*)-**1a**			**4.30**				**0.49**
Solvents	Et_2O	120	0.71	85.56	MeOH	20	0.79	15.84	KPi Buffer	15		15.00
	Seignette sol.	30	1.0	30.00					*i*-PrOH	0.80	0.79	0.63
	Brine	30	1.0	30.00					AcOEt	60	0.90	54.12
				145.56					Water	10		10.00
									Resin			5.00
												84.75
Waste				**146.02**				**17.56**				**89.19**
cEF				**85.89**				**4.08**				**180.55**

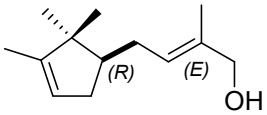
a) The reduction of **4a** was replicated based on a patent procedure [ref. 38], see below ; b) Autoclave hydrogenation volume of 0.3 L assuming an ideal behavior of H_2.

Table S10 Semi-quantitative ECOScale analysis [37]

Parameters	Chemo reductive process				Bio reductive process	
	$LiAlH_4$ [a]		H_2 [ref. 36]		OYE2+Evo440	
	Issue	Penalty	Issue	Penalty	Issue	Penalty
Stereoselectivity [b]	-	-	88:12	12	99:1	1
Work-up/purification	Simple filtration	0	Simple filtration	-	Solid phase extract.	2
	Water wash	3	Water wash	-	Water wash	3
	Distillation	3	Distillation	3	Distillation	3
Risk and hazards	$LiAlH_4$	5	Ru cat.	5	OYE2	0
	Et_2O	10	H_2	10	Evo440	0
	Seignette sol.	0	MeOH	5	GDH	0
	Brine	0			$NADP^+$	0
					Glucose	0
					KPi Buffer	0
					i-PrOH	5
					AcOEt	3
Temp. and time	0 °C, 1 h	4	80 °C, 24 h	3	30 °C, 24 h	1
Technical set-up	Inert atm.	1	High pressure	3	Common	0
	No pot economy	2.5	No pot economy	2.5	Pot economy	0
Nature of waste	Non-biodegradable	3	Non-biodegradable	3	Biodegradable	0
	Heavy metals	-	Heavy metals	3	Heavy metals	-
Resource depletion	-	0	Ru cat.	5	-	0
ECOScale		**68.5**		**45.5**		**82**
Average EcoScale			**57**		**82**	

a) The reduction of **4a** was replicated based on a patent procedure [ref. 38], see below; b) Penalty = [100-*ee*]/2.

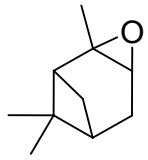
(*R*,*E*)-2-methyl-4-(2,2,3-trimethylcyclopent-3-en-1-yl)but-2-en-1-ol



To an ice-cooled and well stirred solution of **4a** (2.0 g) in dry Et_2O (30 mL) was portion wise added $LiAlH_4$ (158.3 mg), usually over 15 minutes. Then, the mixture was left to reach room temperature and after 1 hours the reaction was ice-cooled and quenched with a Seignette solution (sat., 30 mL) and left to stir over 1 hour. Then the mixture was washed with Et_2O (3 x 30 mL). The combined organic phase was washed with brine (sat., 30 mL), dried over anhydrous Na_2SO_4 and concentrated under *vacuum* affording the product as a yellow liquid, which was purified by distillation.
Yield 85% (1.7 g) as a pale-yellow oil; tr= 18.0 min, 94% purity by GC-MS; **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 5.42 (m, 1H), 5.20 (m, 1H), 3.97 (s, 2H), 2.32-2.10 (m, 2H), 2.01-1.93 (m, 1H), 1.86-1.73 (m, 2H), 1.66 (s, 3H), 1.58 (m, 3H), 0.98 (s, 3H), 0.78 (s, 3H); **^{13}C{^{1}H}-NMR** ($CDCl_3$, 101 MHz): δ 148.6, 134.8, 126.0, 121.8, 69.1, 50.5, 46.8, 35.7, 28.3, 26.0, 19.8, 13.8, 12.7; GC-MS: m/z (%): 194 (M^+, 28), 121 (100), 108 (93), 95 (87).

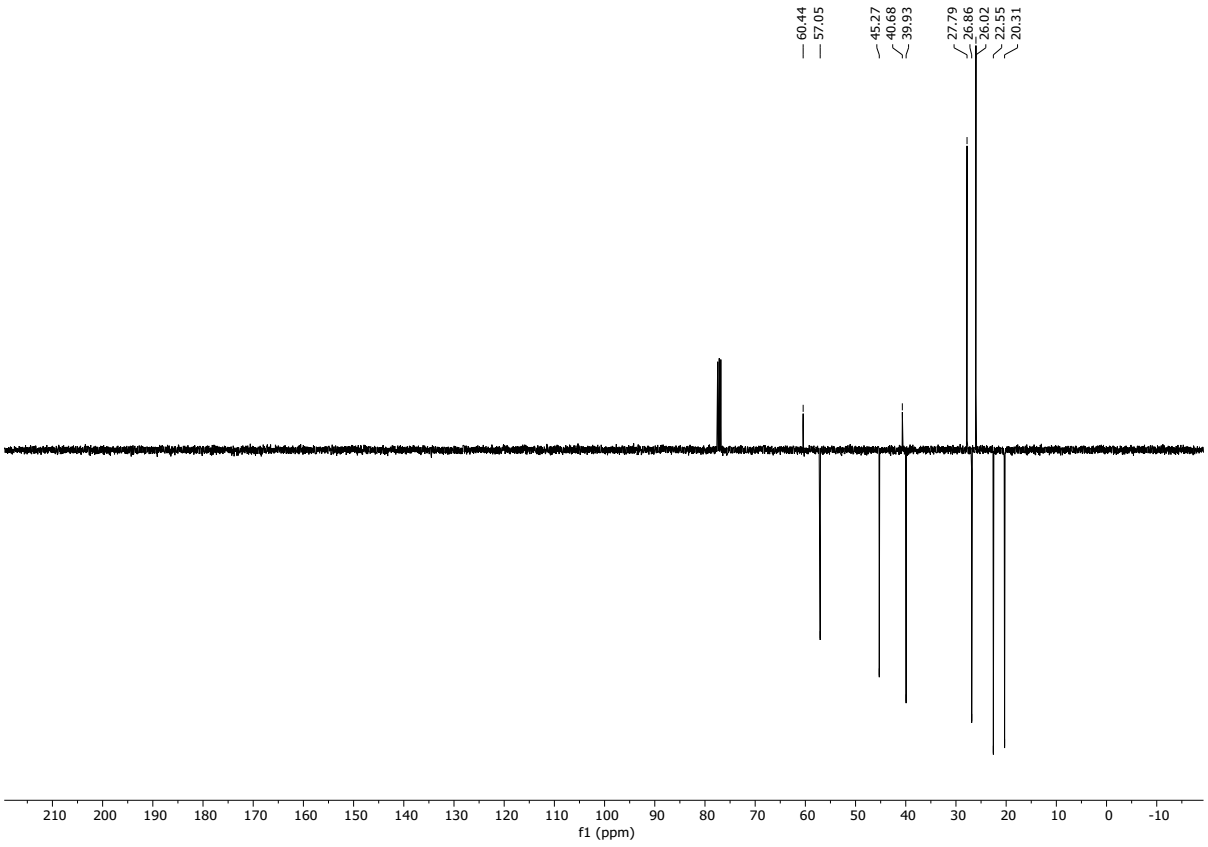
Copies of ^{1}H, ^{13}C and ^{19}F NMR spectra

3 ^{1}H-NMR ($CDCl_3$, 400 MHz)



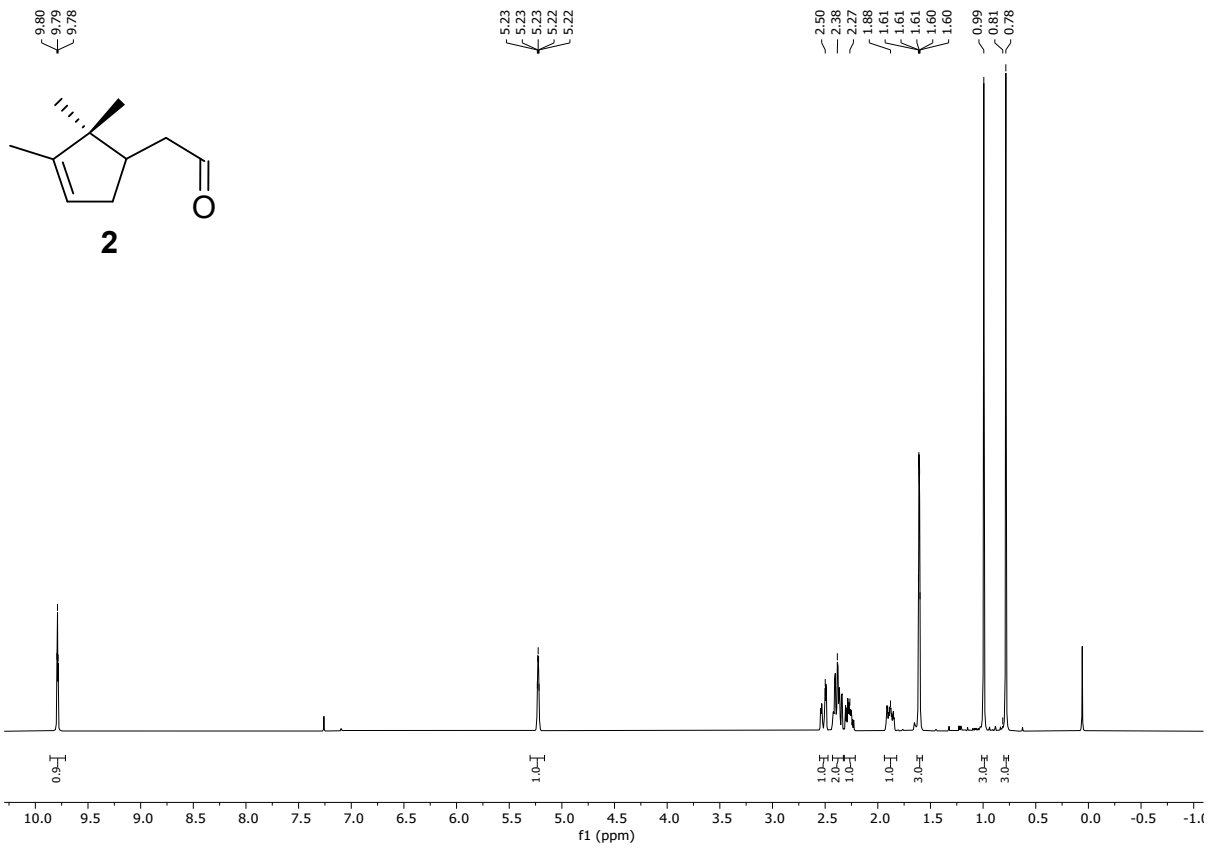
3

^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz)

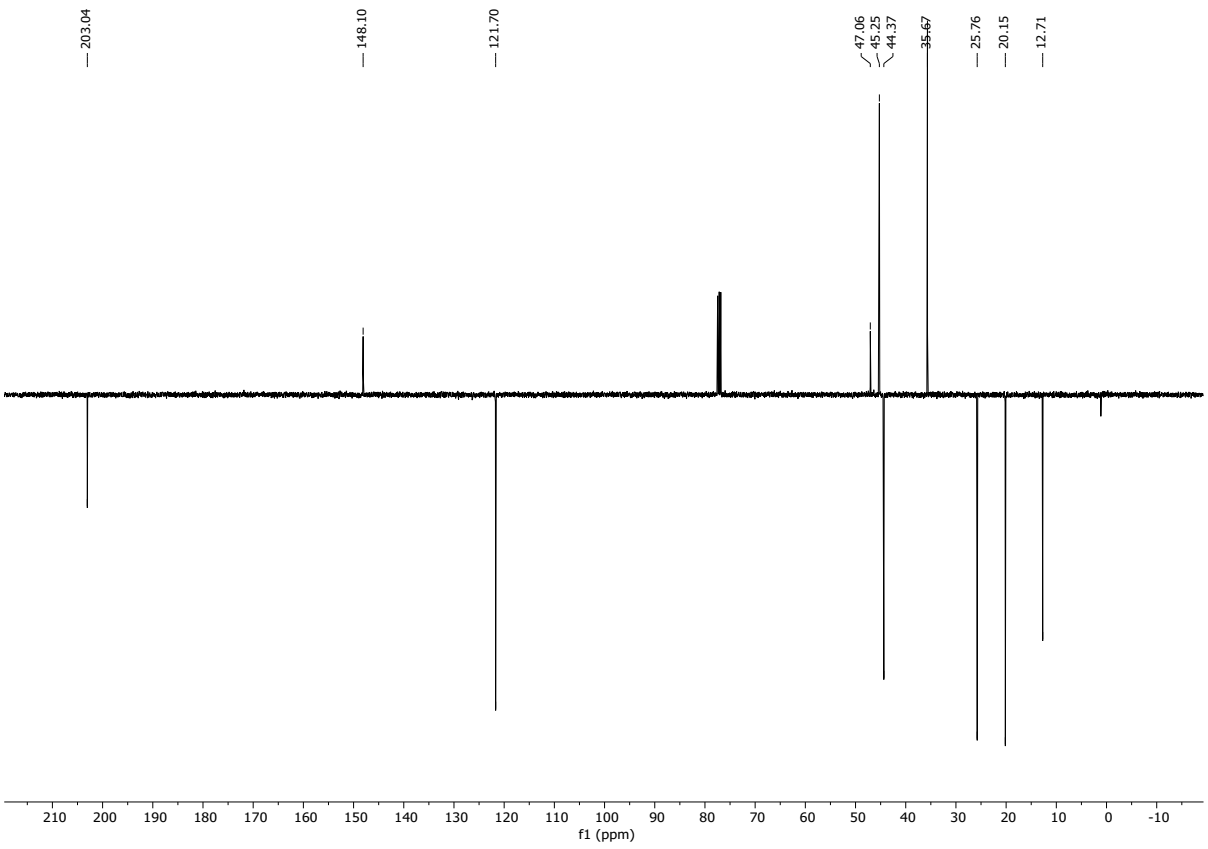


2

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

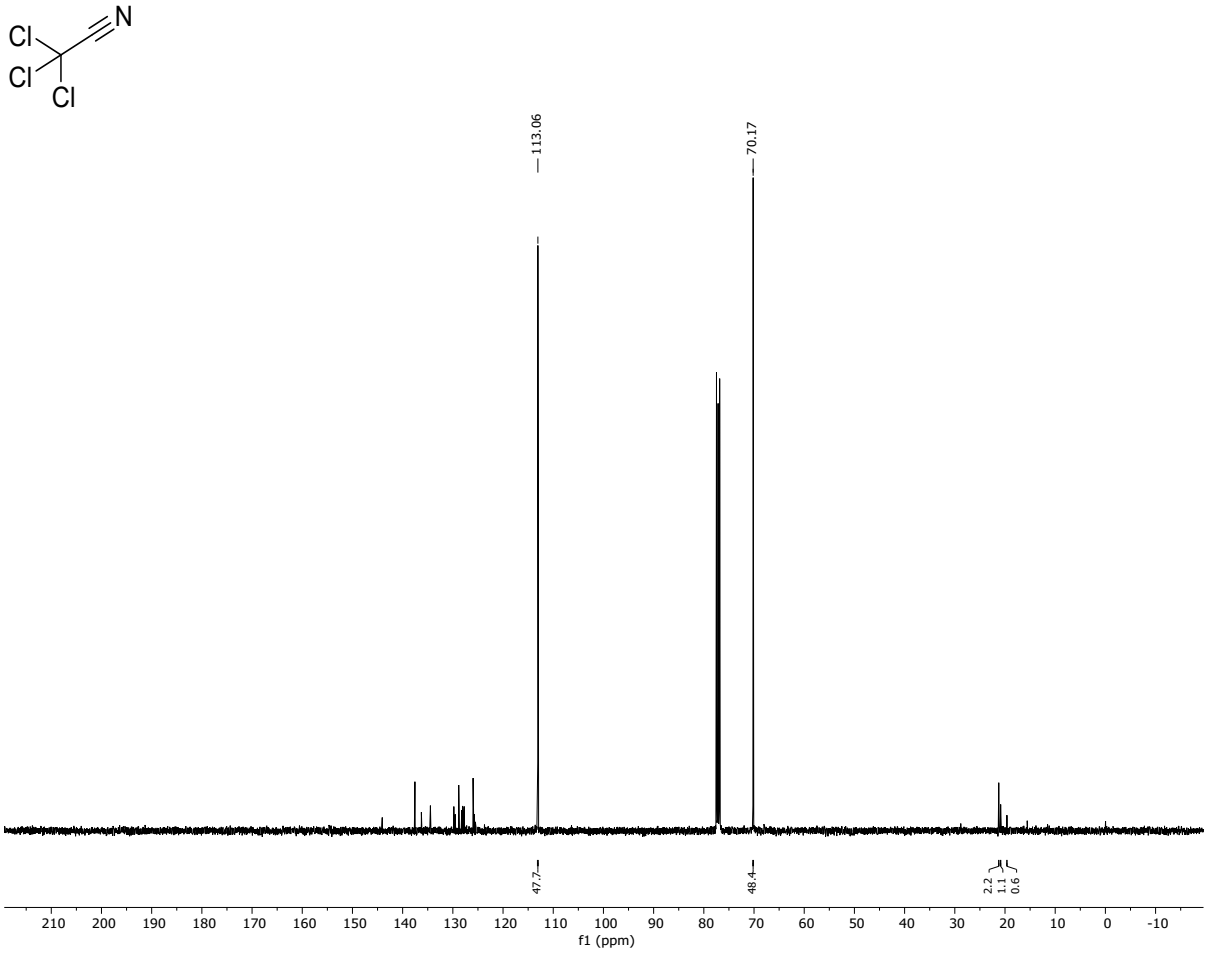


^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz)



Trichloroacetonitrile

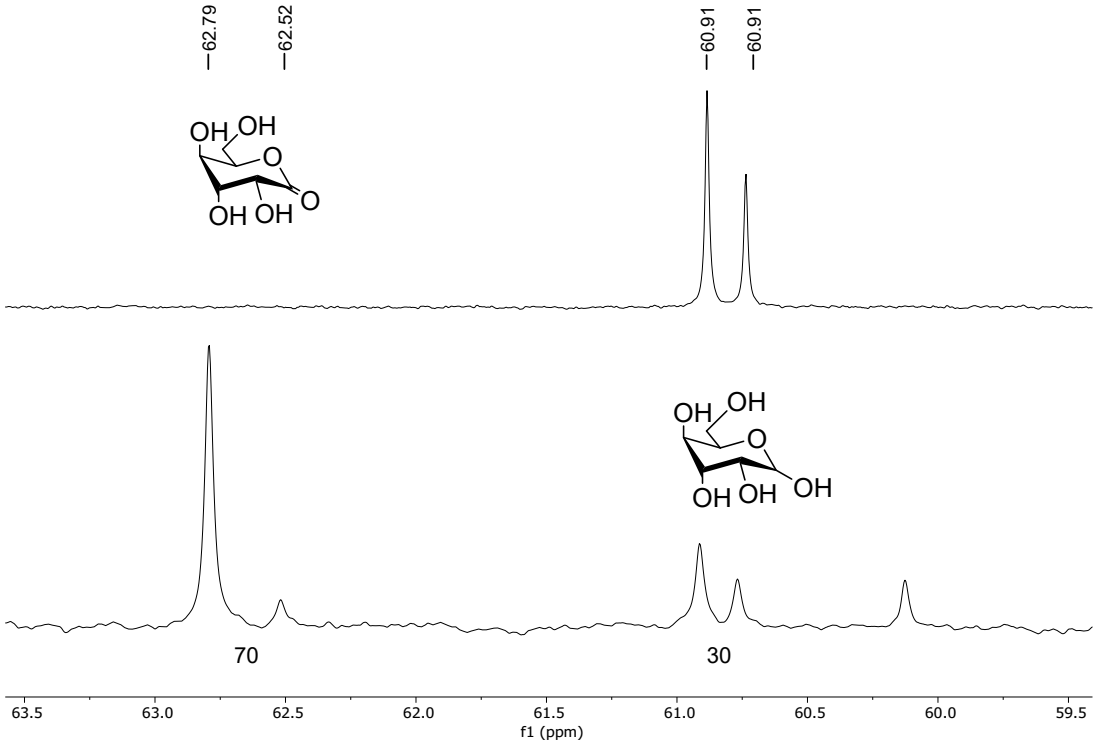
$^{13}C\{^{1}H\}$-NMR ($CDCl_3$, 101 MHz)



Integration of $\underline{C}Cl_3\underline{C}N$ signals *versus* xylenes methyl group signals enables the determination of CCl_3CN purity (97.1% w/w).

Glucose and H_2O_2

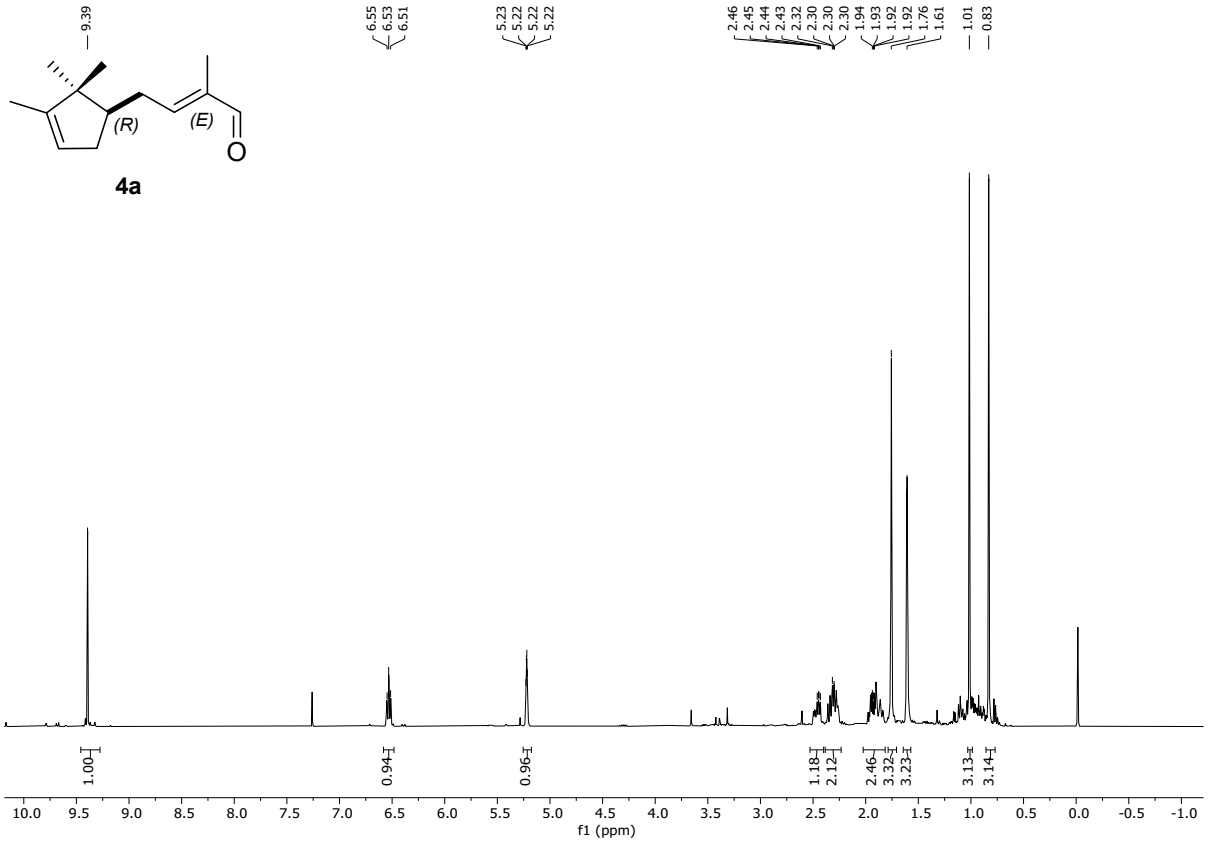
$^{13}C\{^1H\}$-NMR ($CDCl_3$, 101 MHz)



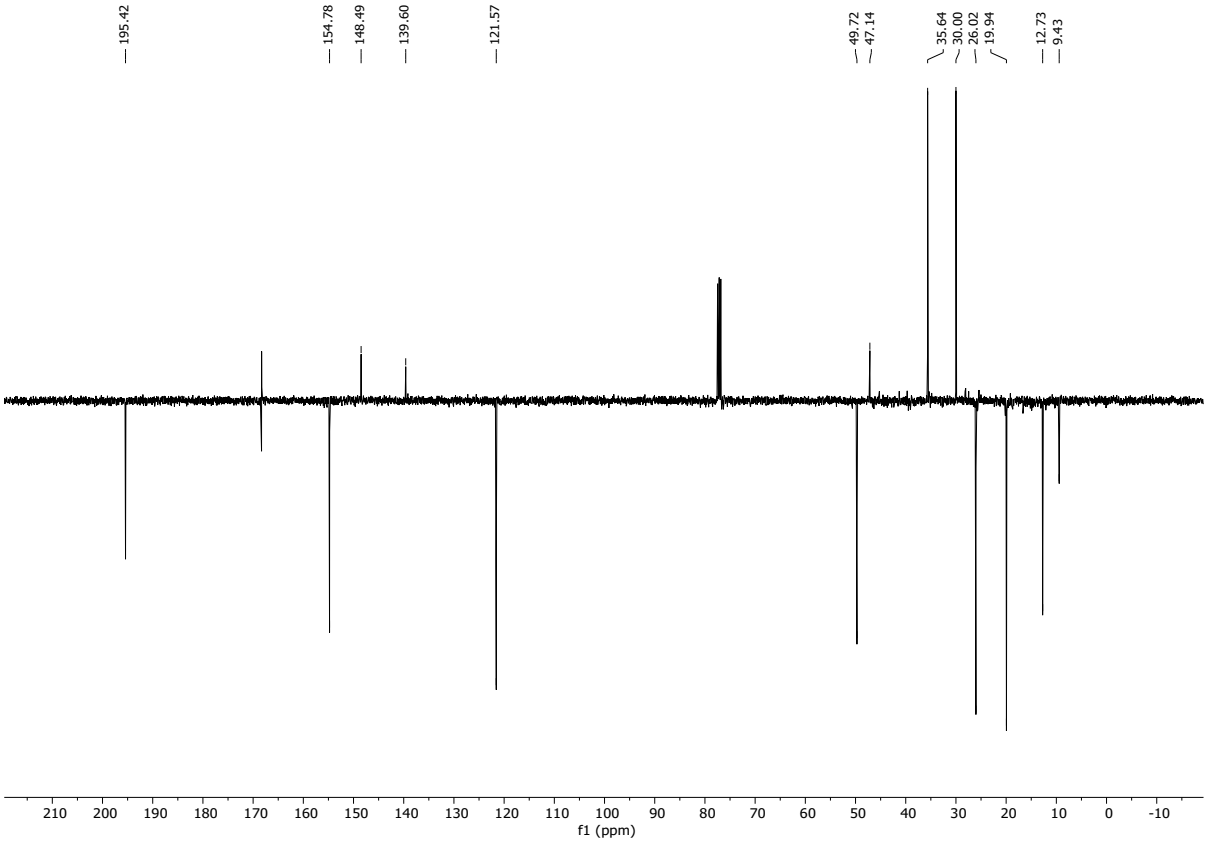
An aliquot of reaction mixture (400 uL) was analyzed by ^{13}C-NMR with a coaxial tube capillary filled with D_2O. Integration of $\underline{C}H_2OH$ signal of α-D-glucose *versus* $\underline{C}H_2OH$ signal of α-D-gluconolactone gave a conversion of 70%, which corresponds to a 1.2% w/v concentration of H_2O_2.

4a

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

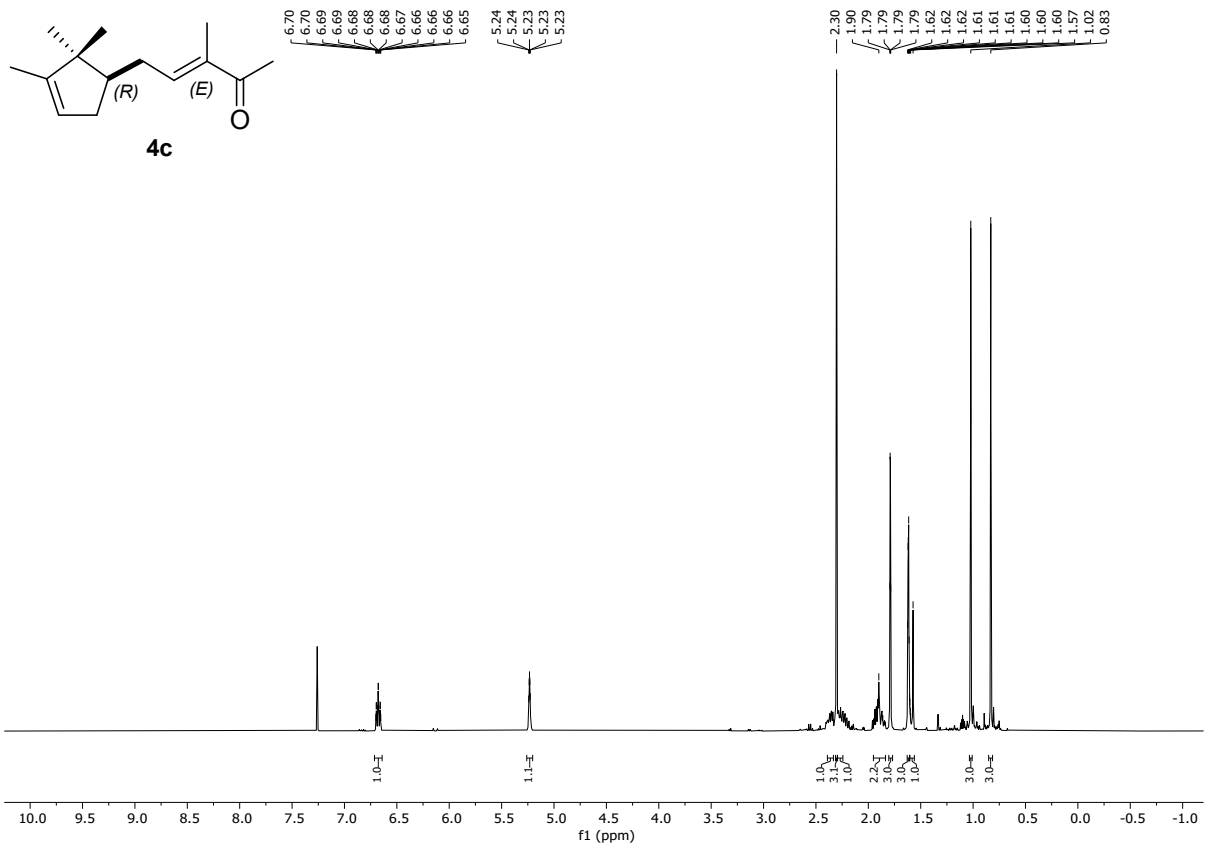


^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz)

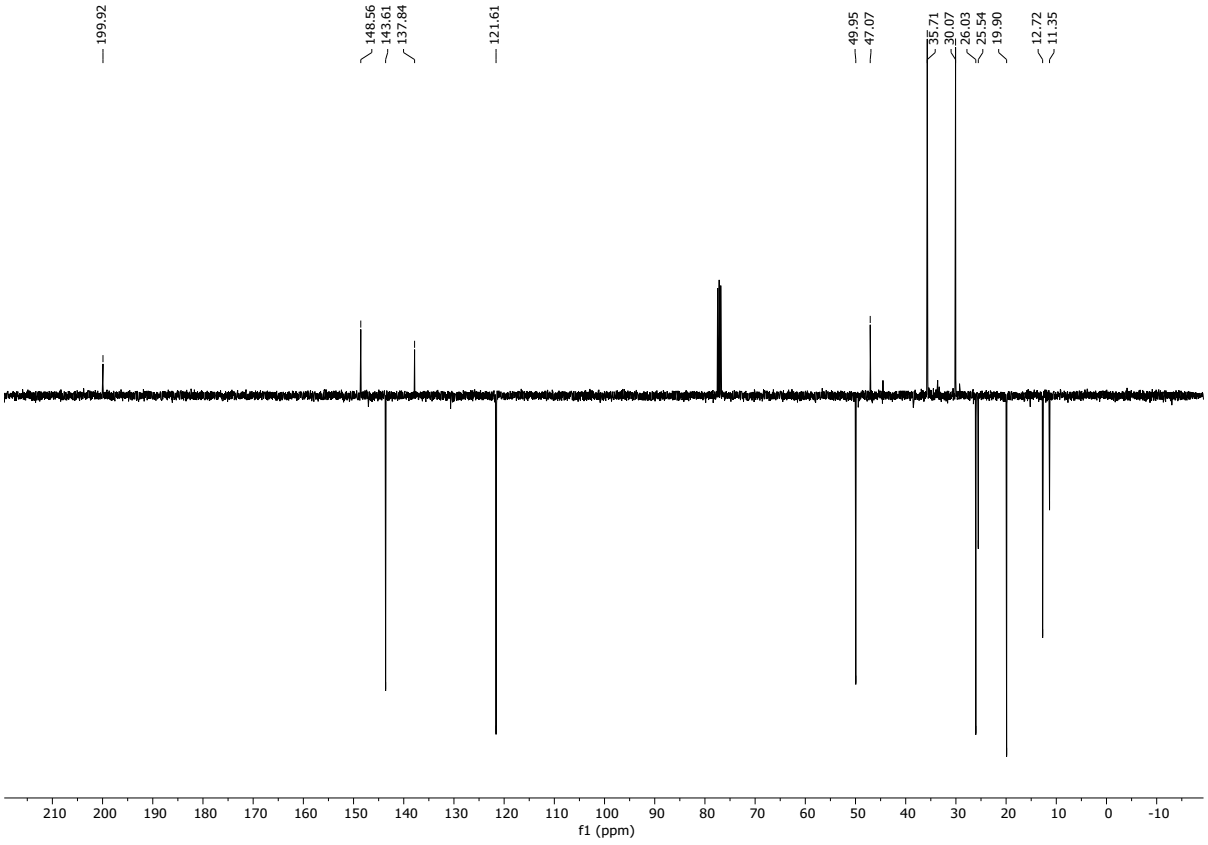


4c

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

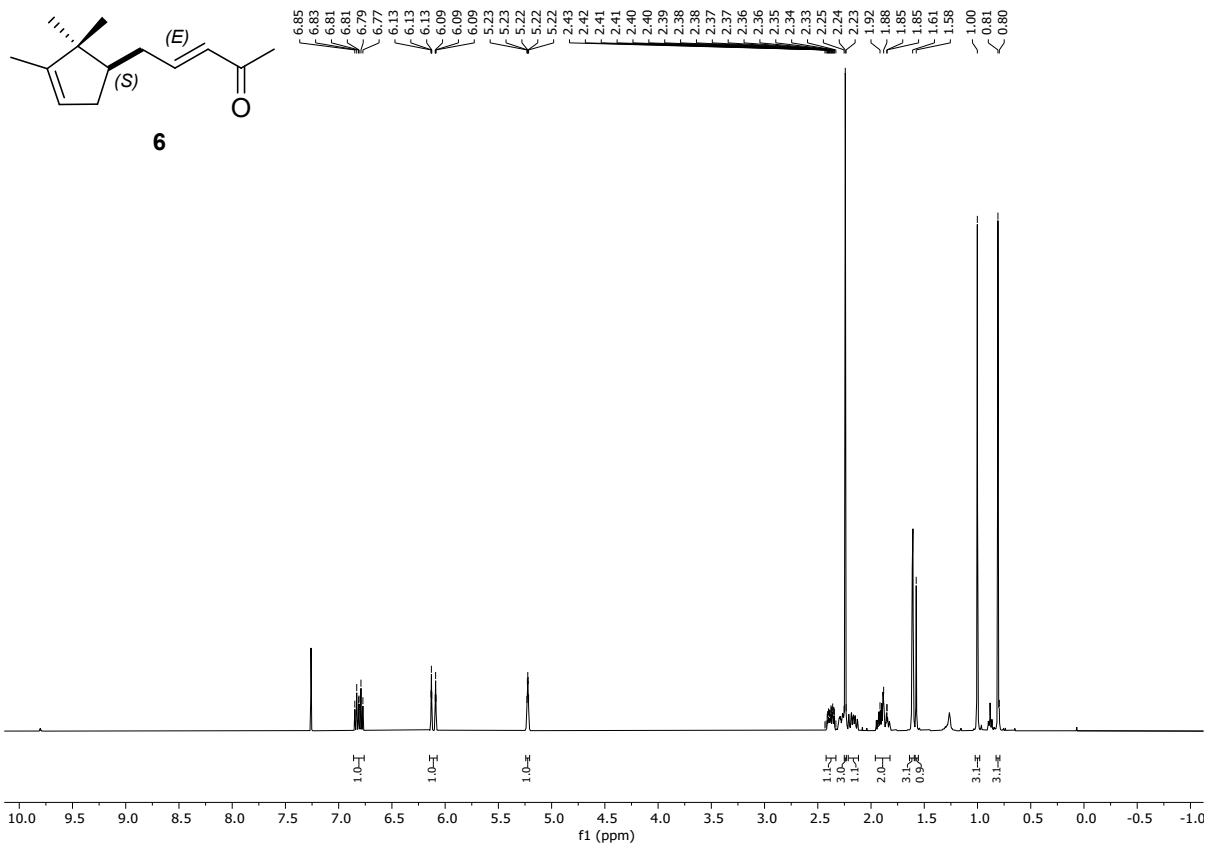


^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz)

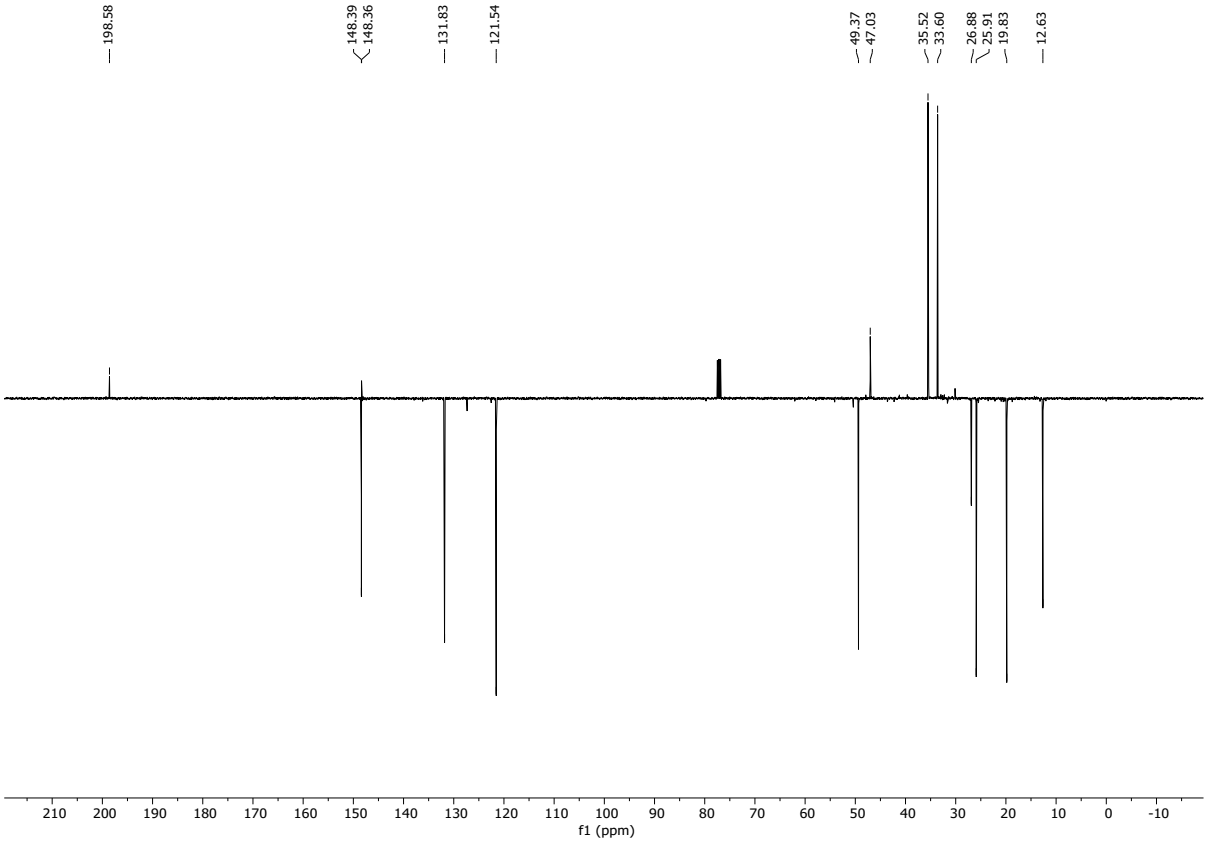


6

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

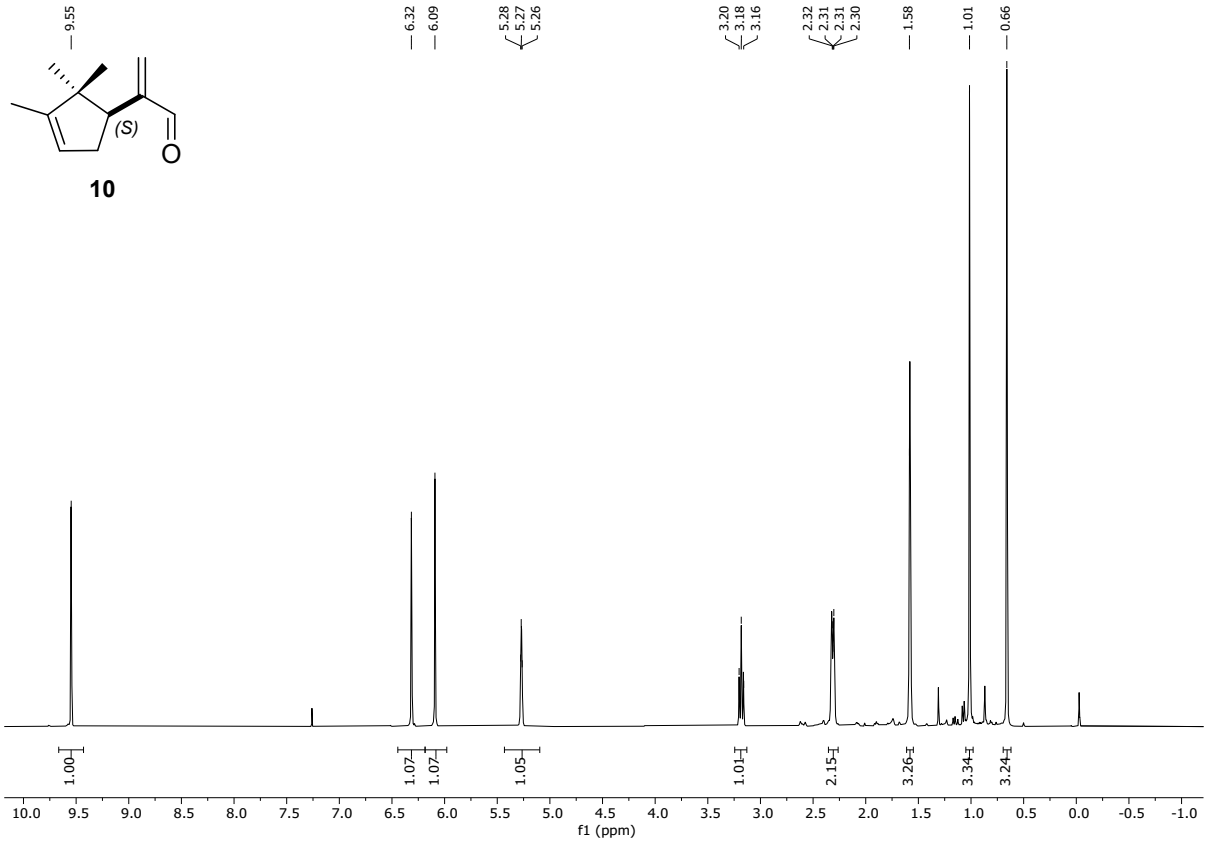


^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz)

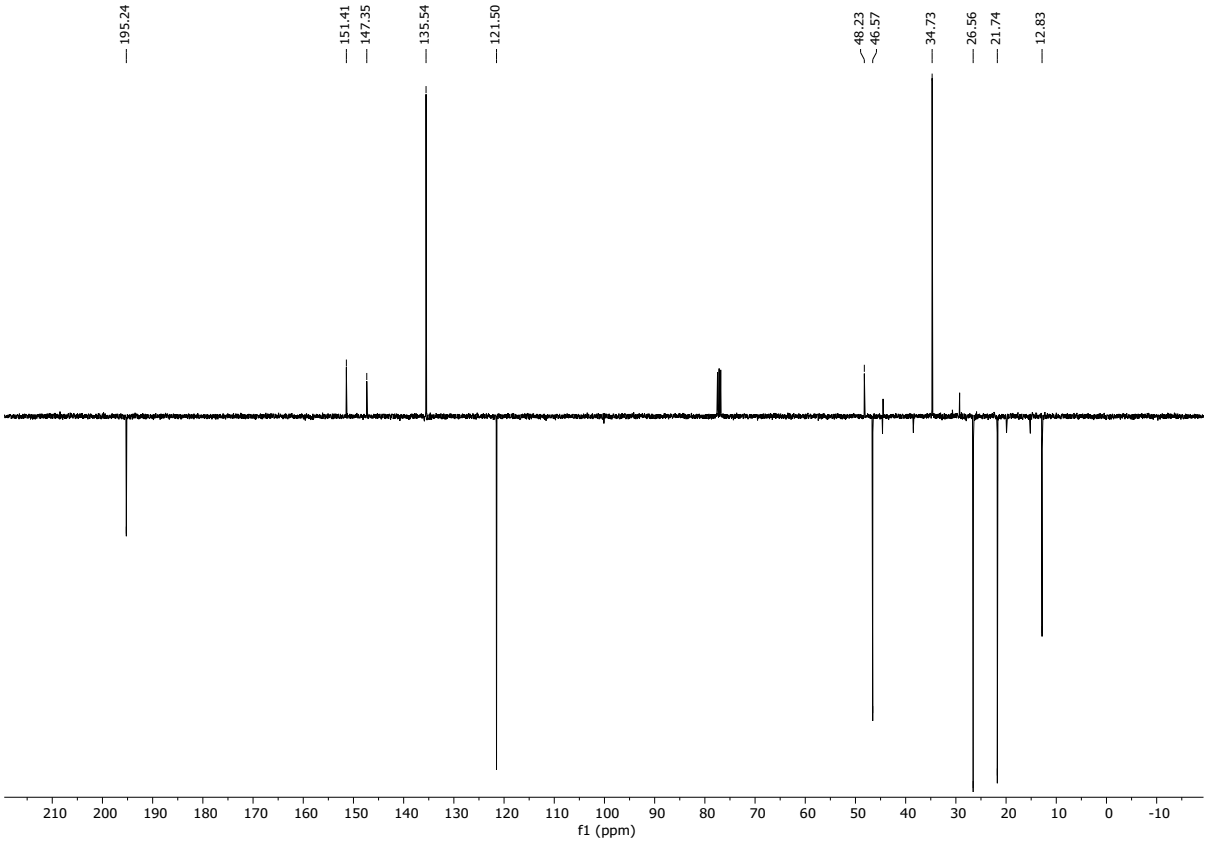


10

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



^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz)



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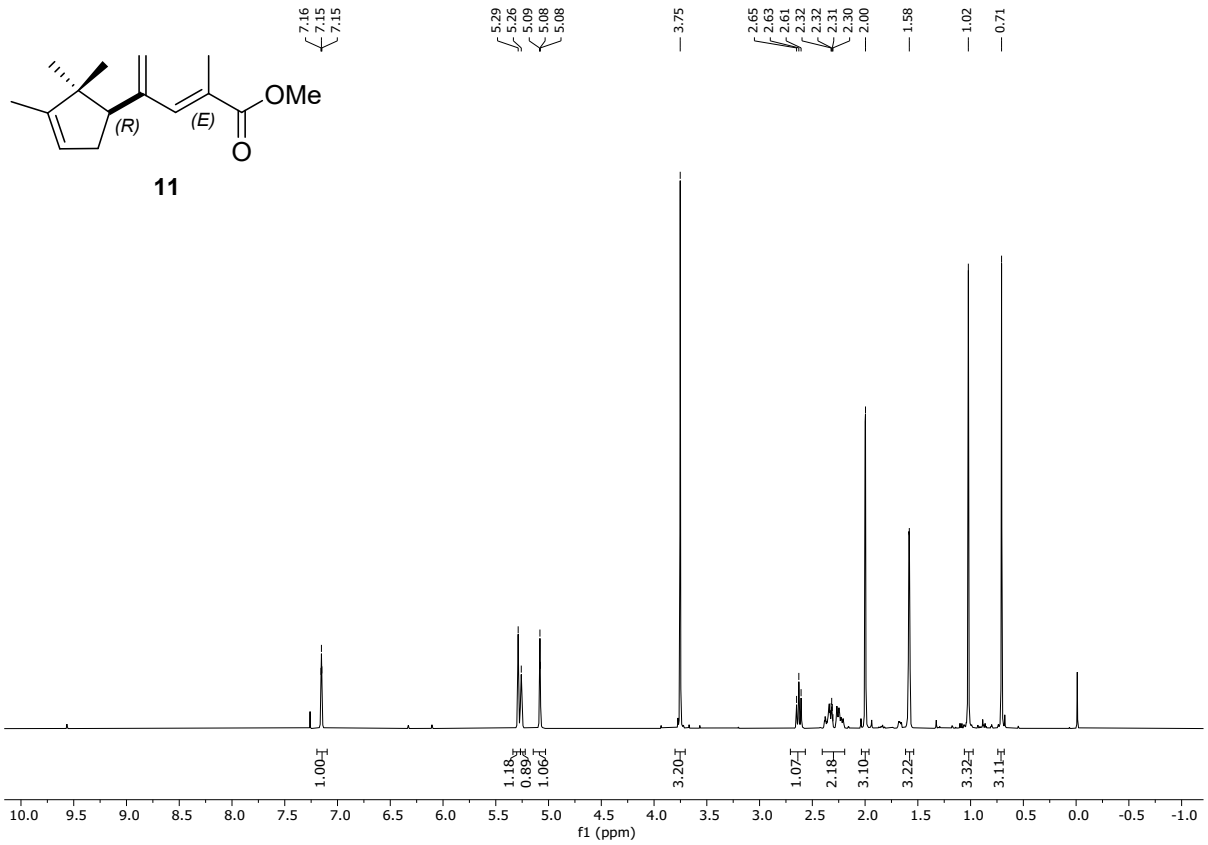
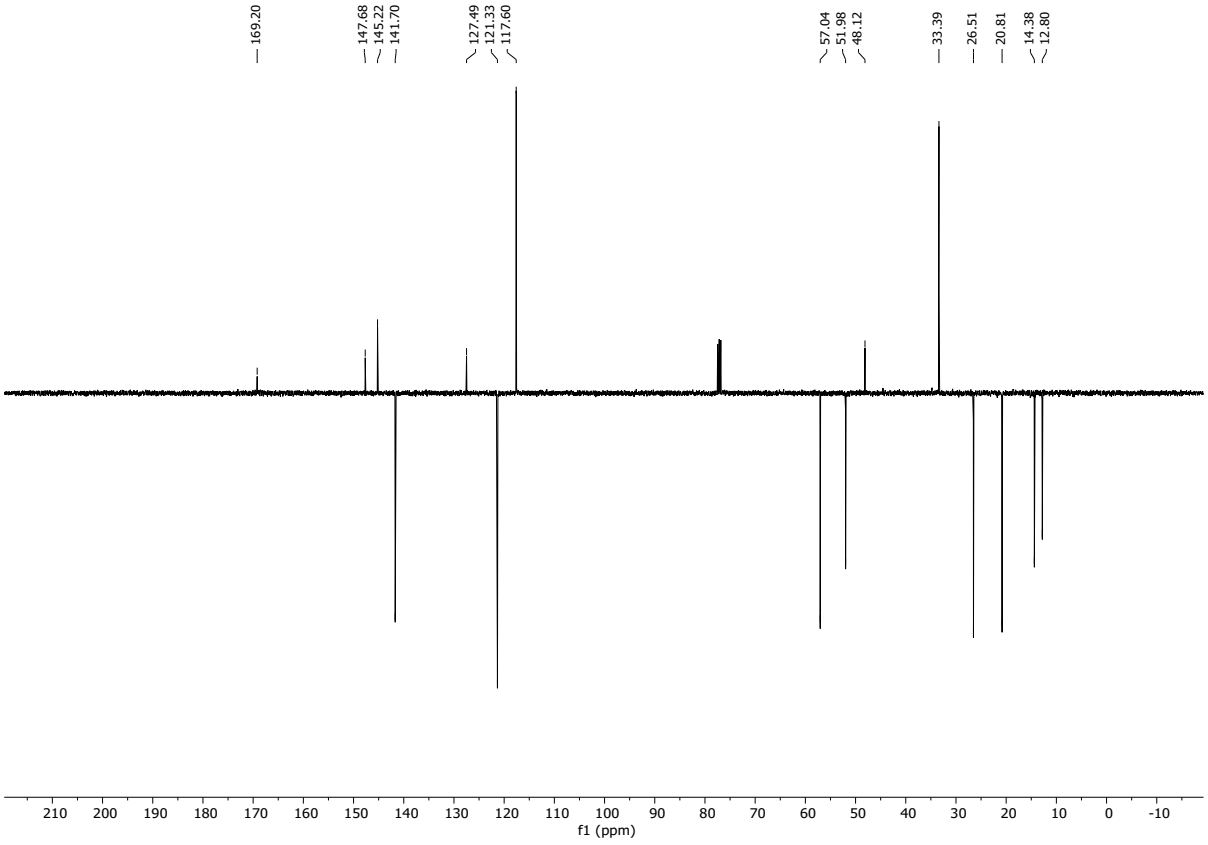
^{1}H-NMR ($CDCl_3$, 400 MHz)

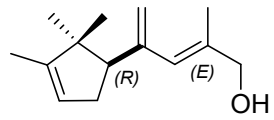


^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz)



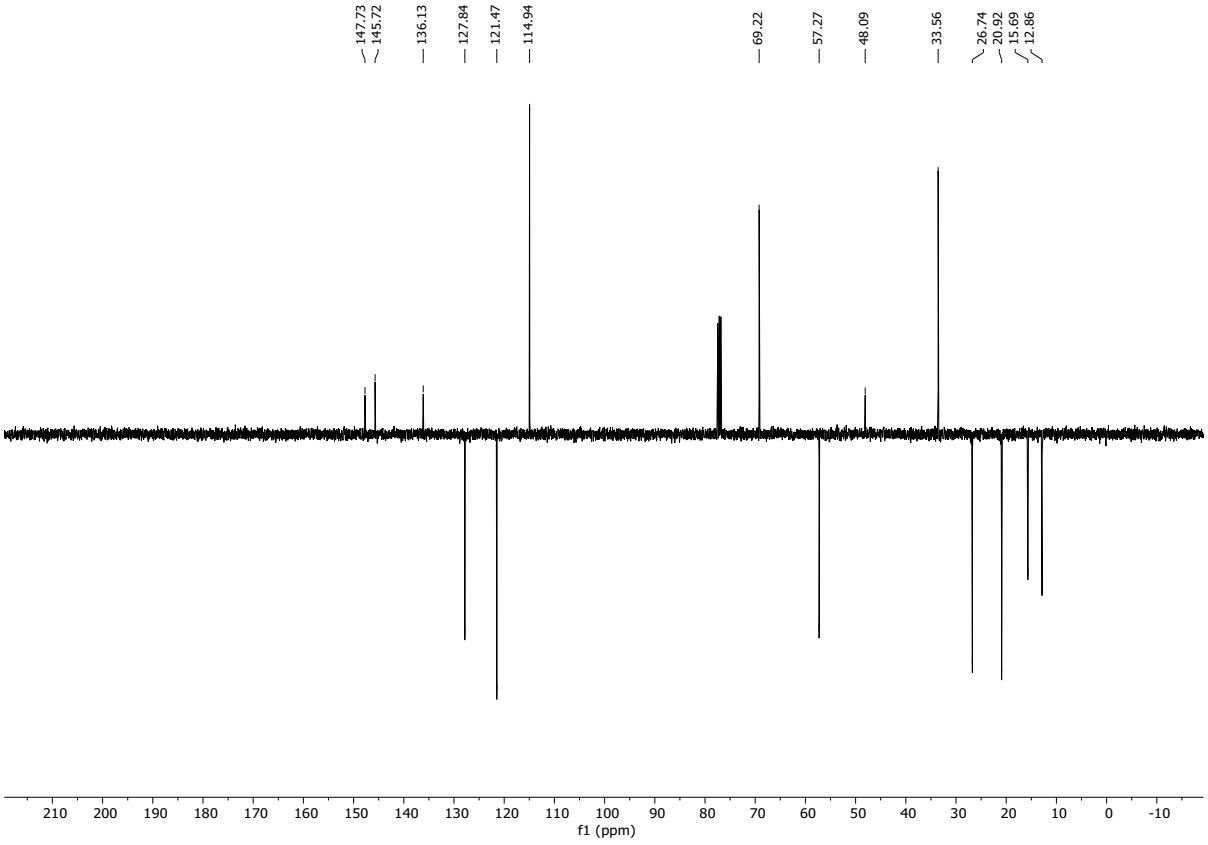
12

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



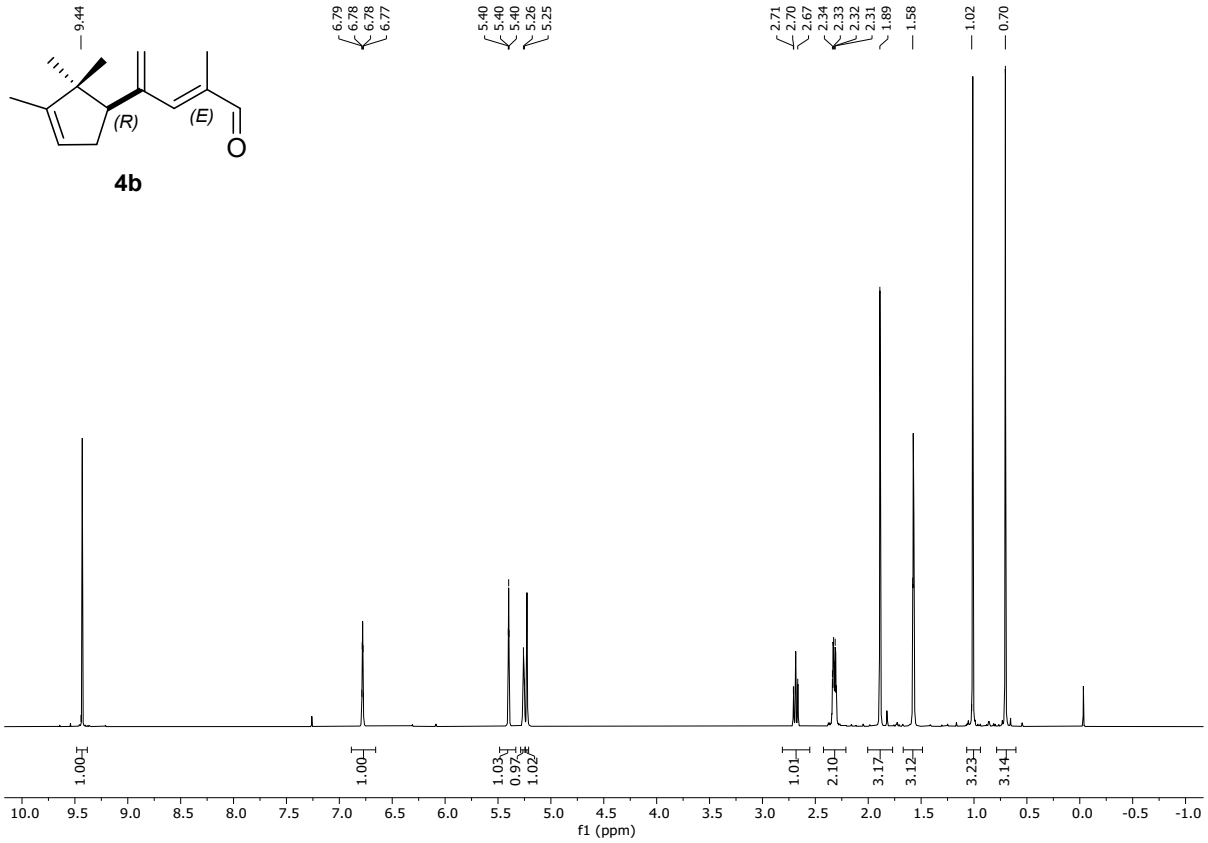
12

^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz)

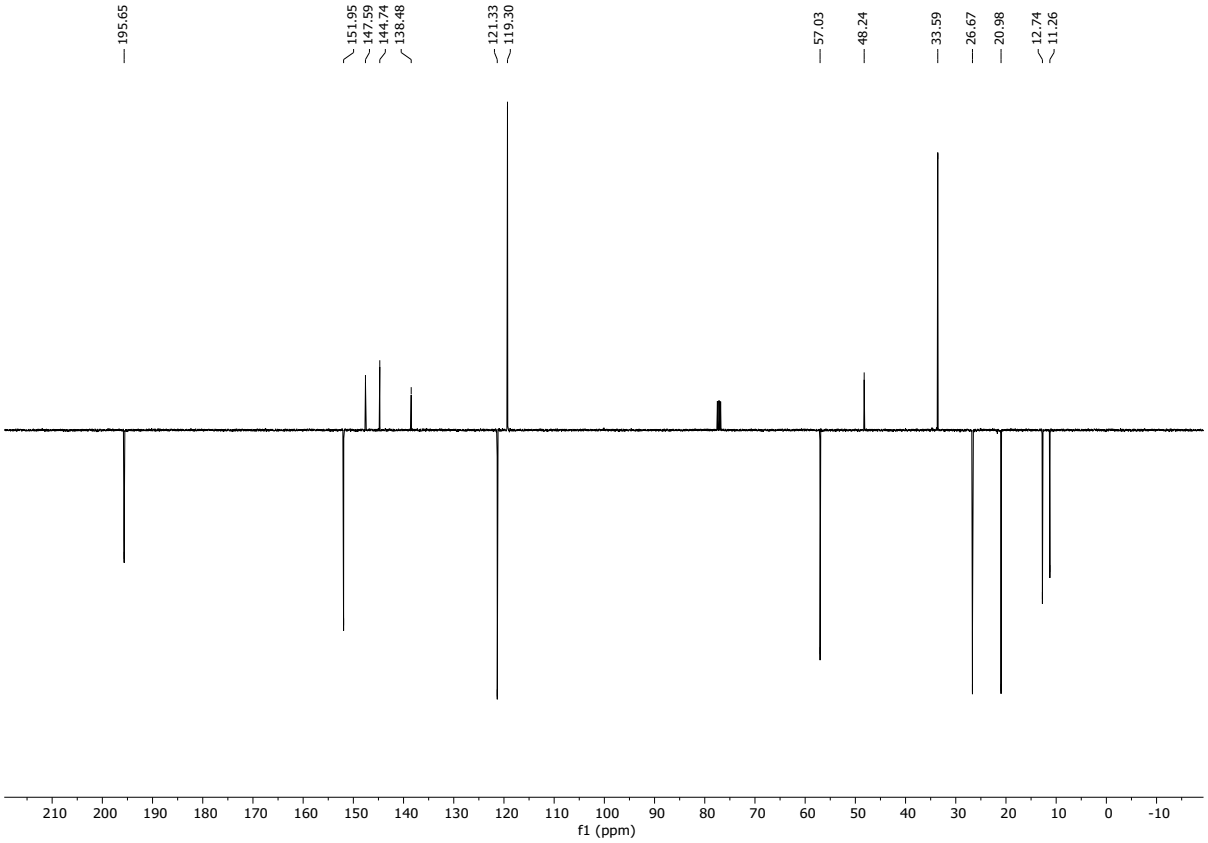


4b

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

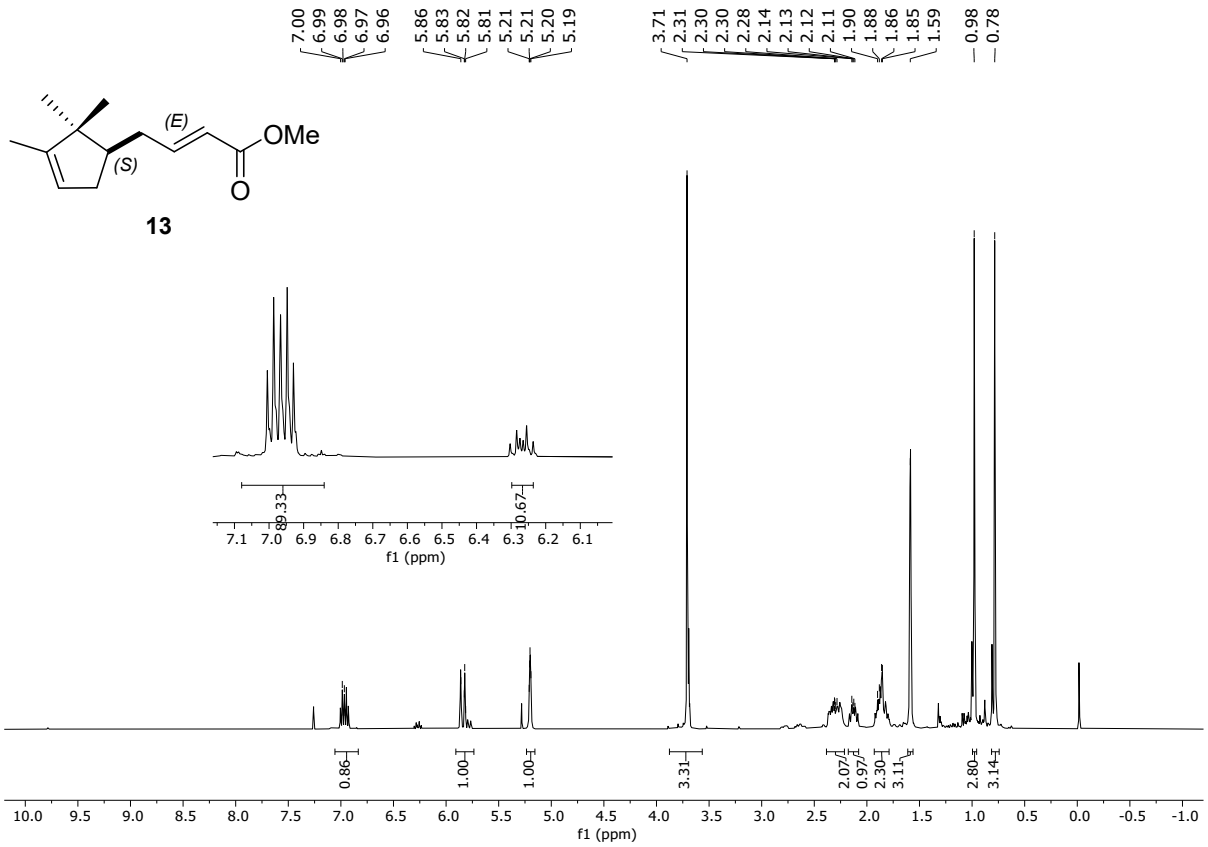


^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz)

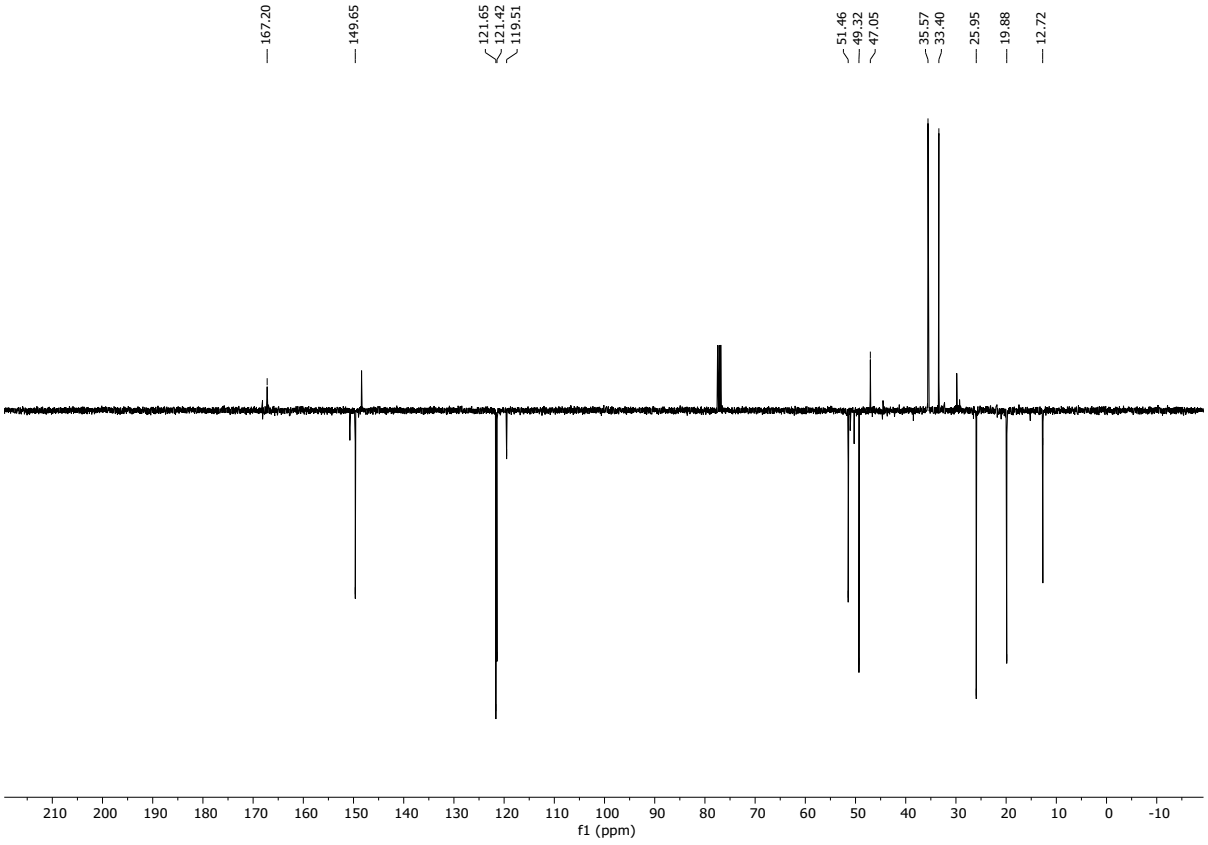


13

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

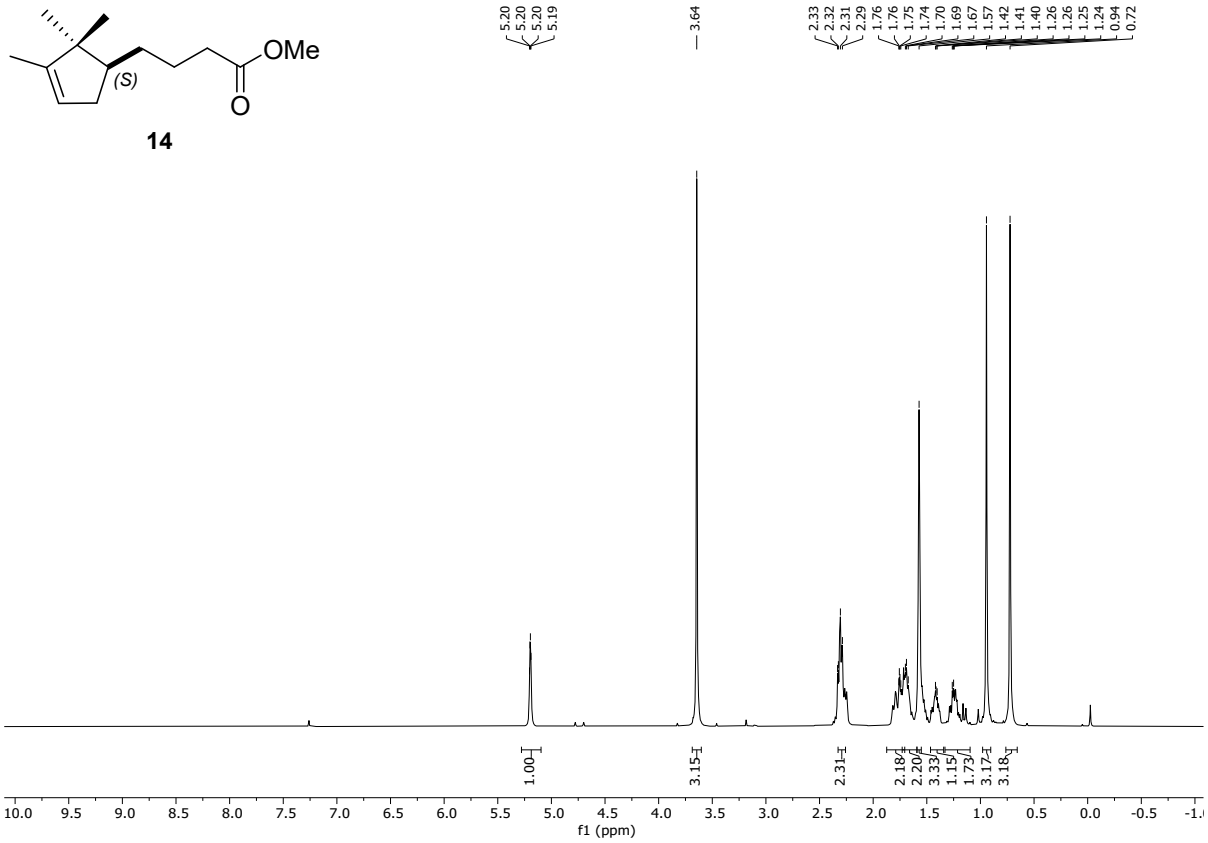


^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz)

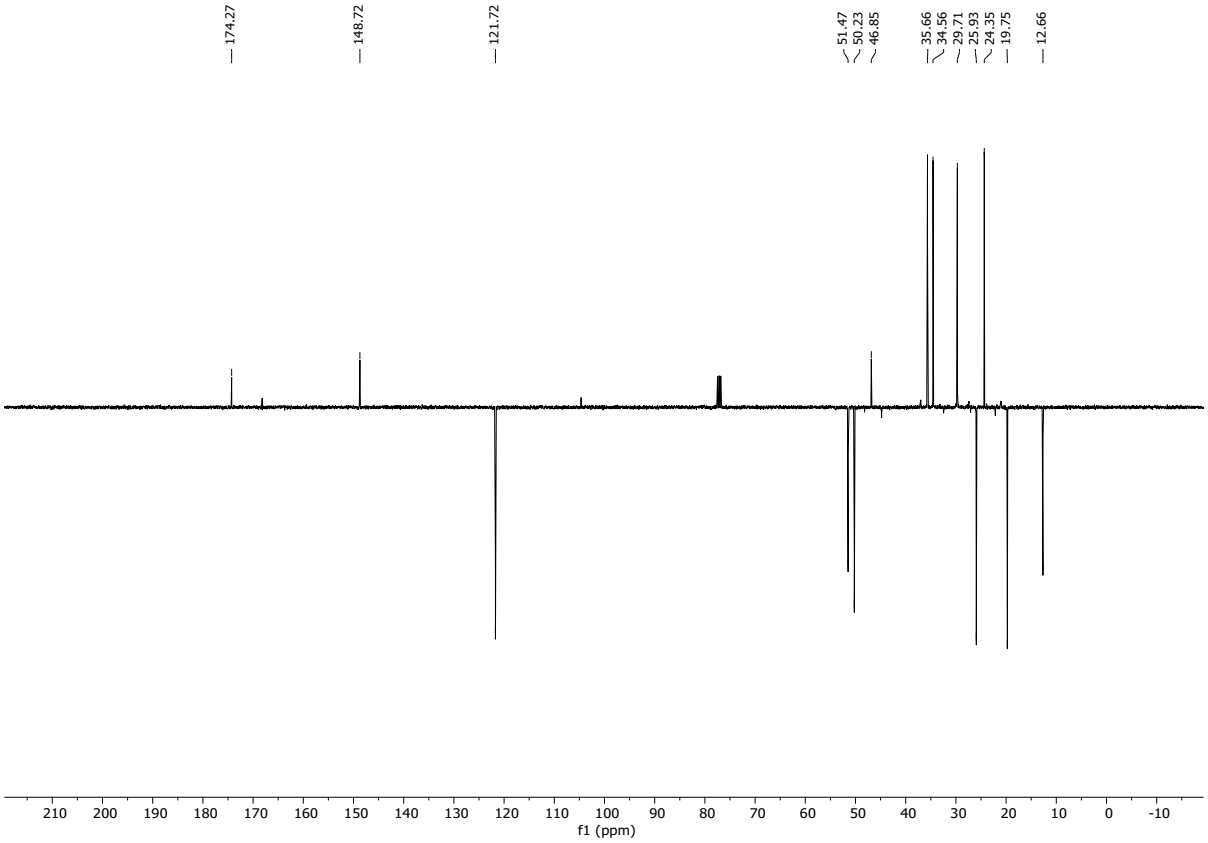


14

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

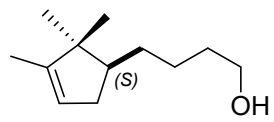


^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz)



15

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



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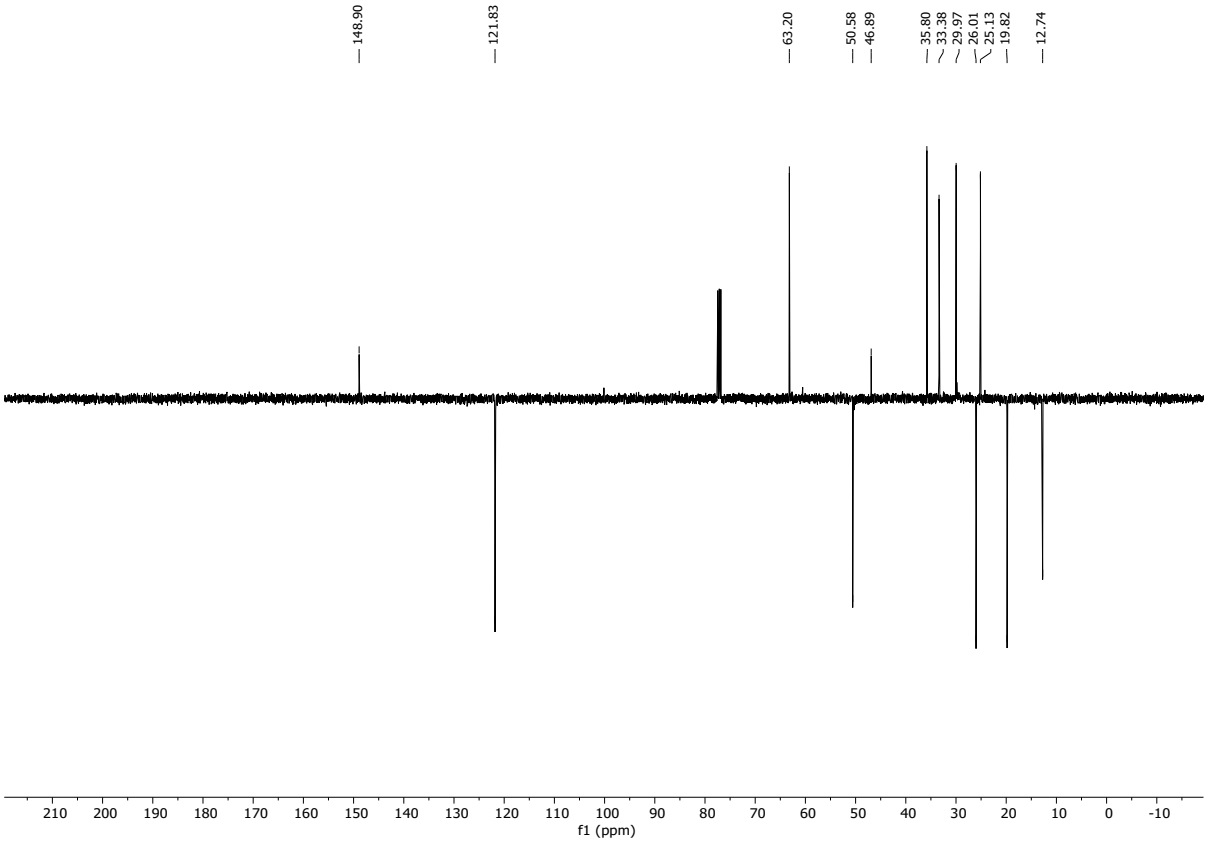
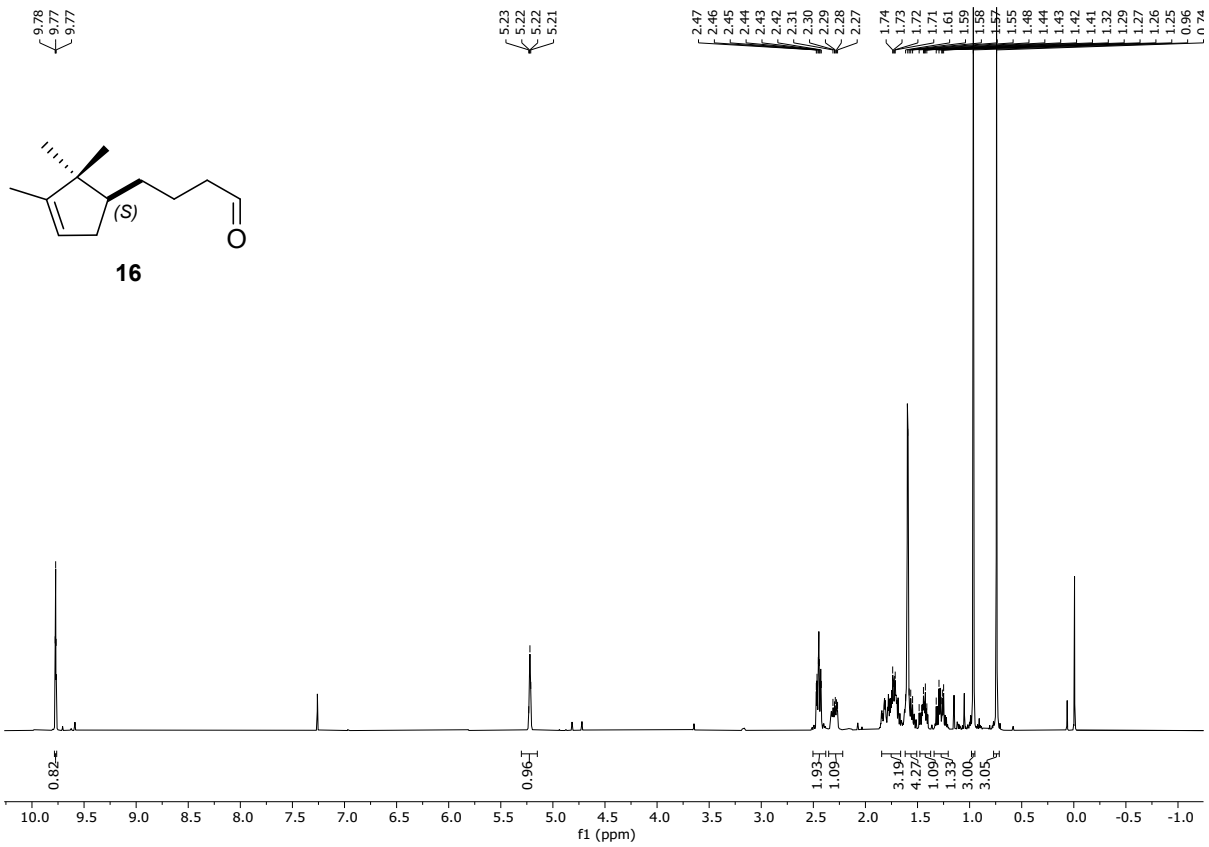
^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz)

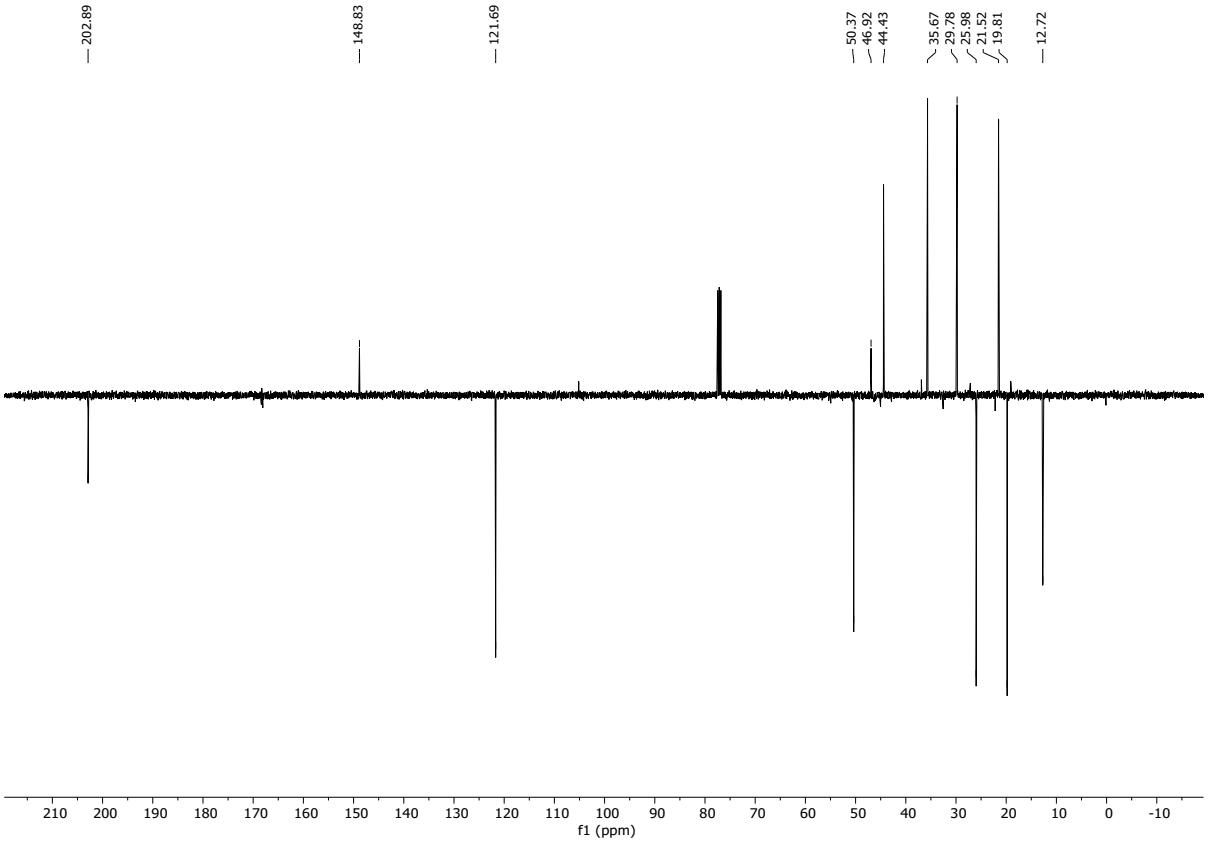


16

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

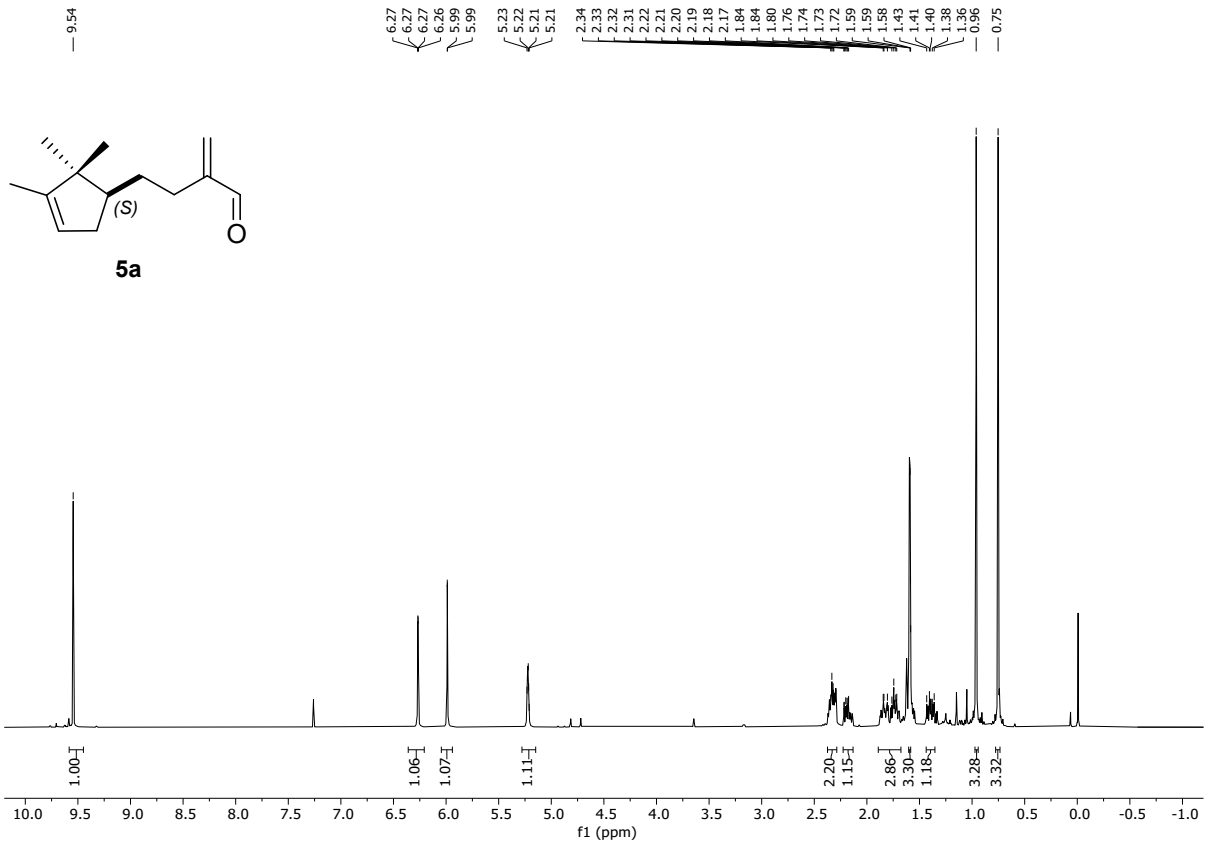


^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz)

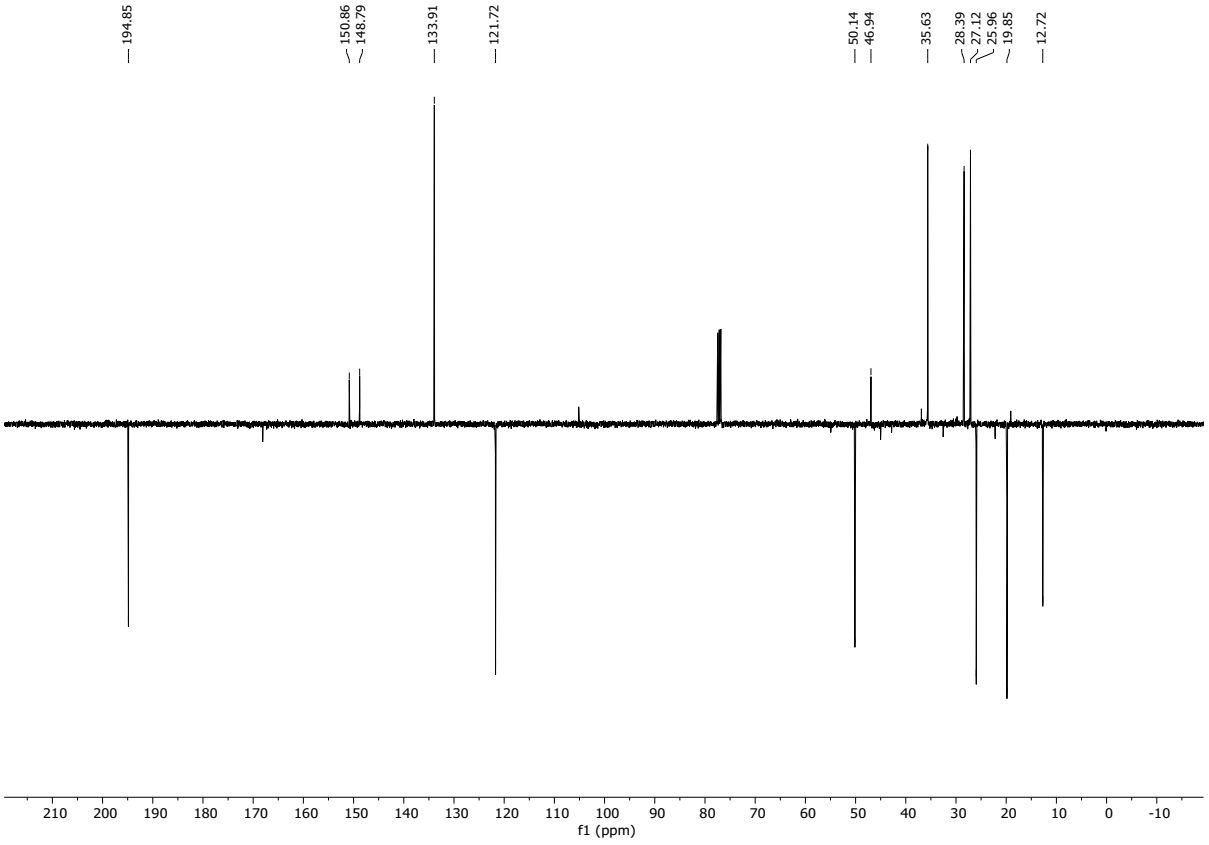


5a

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

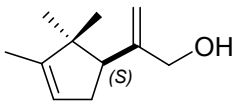


^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz)



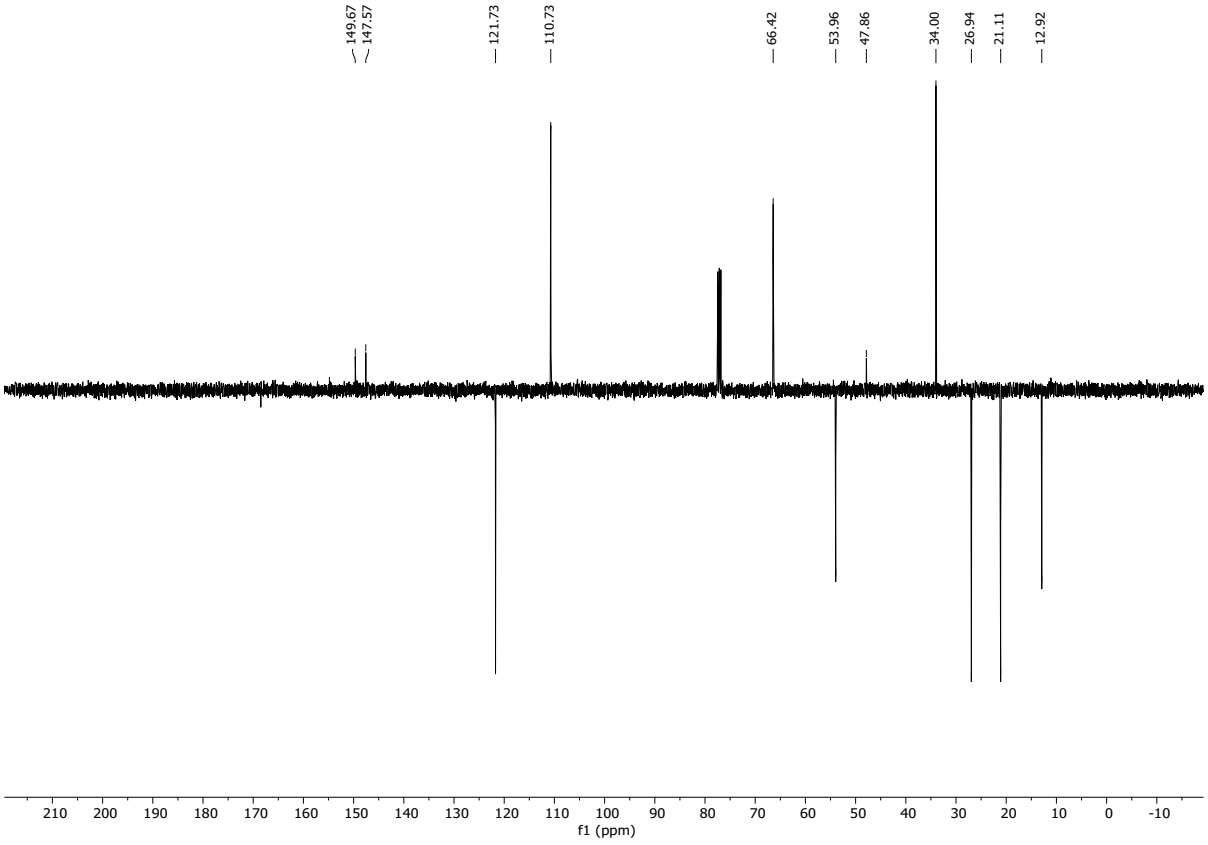
17

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



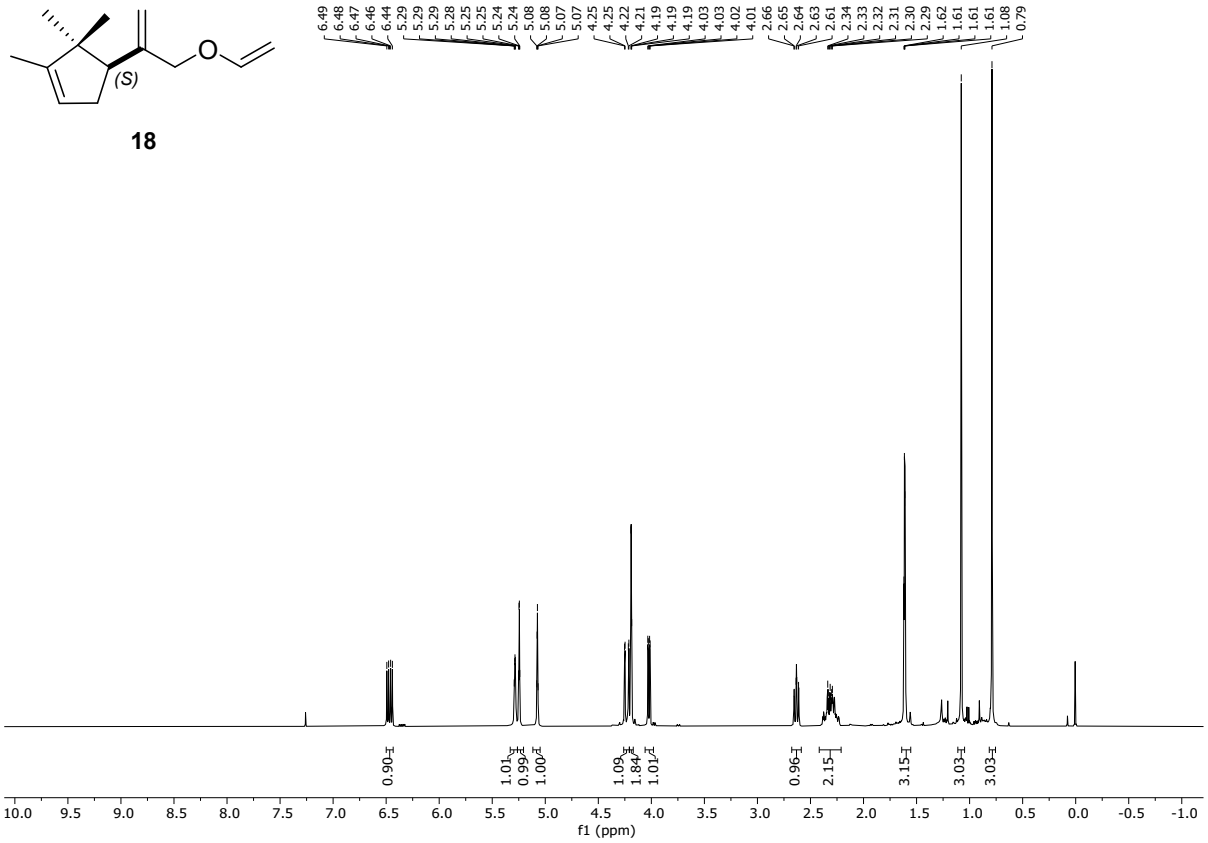
17

^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz)

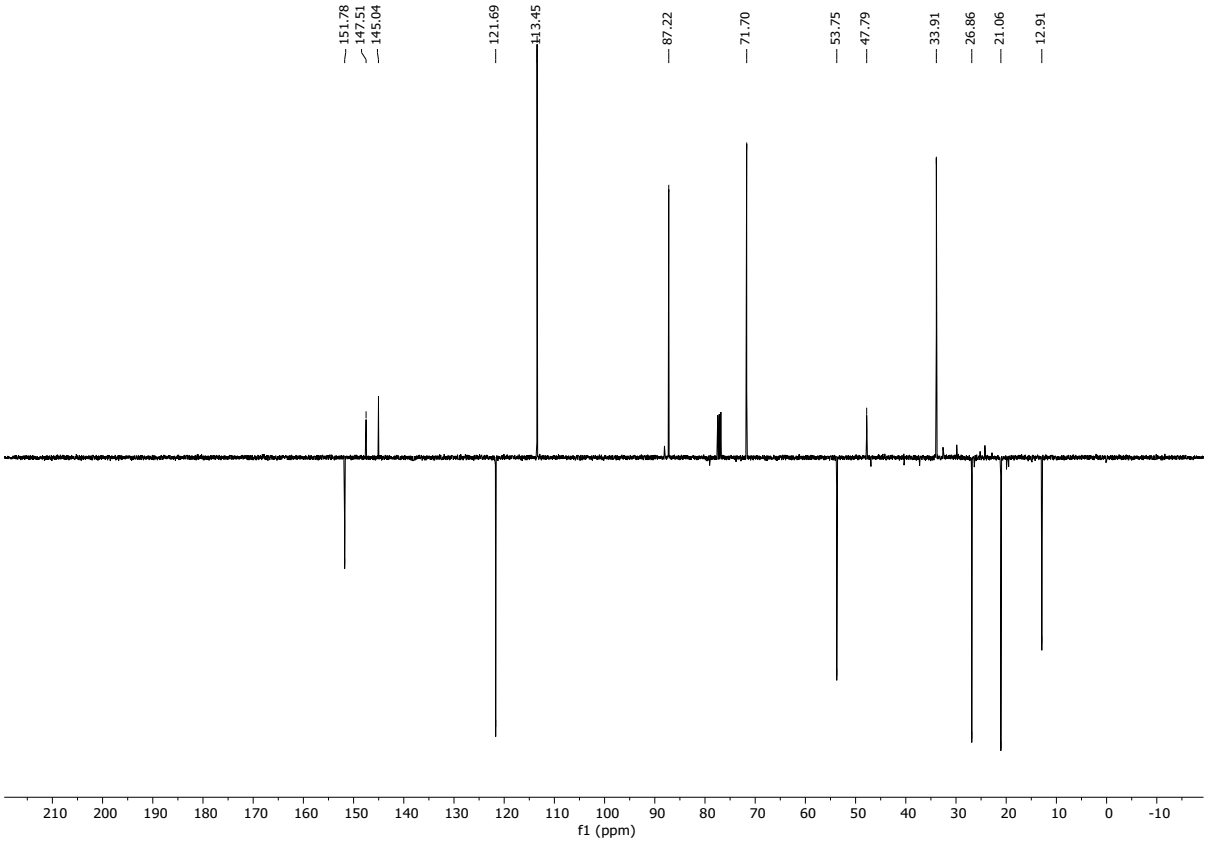


18

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

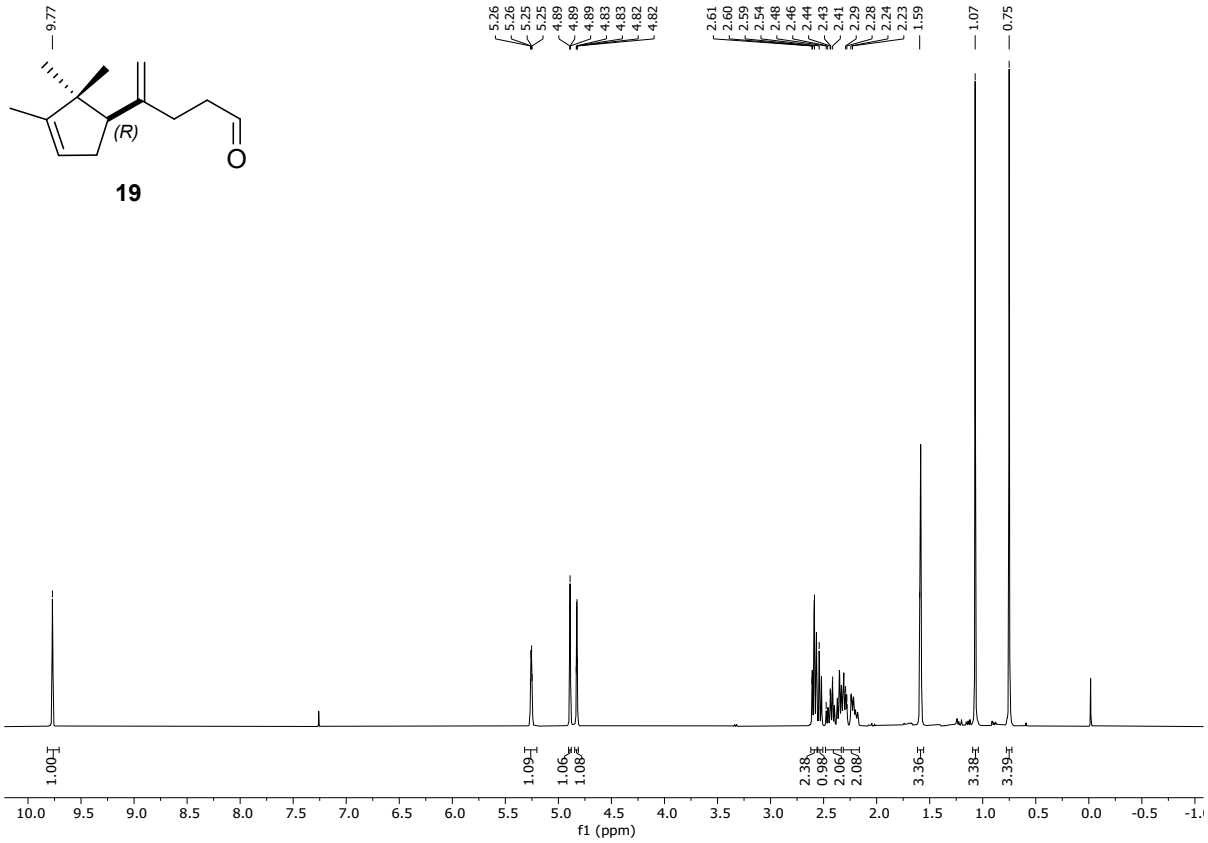


^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz)

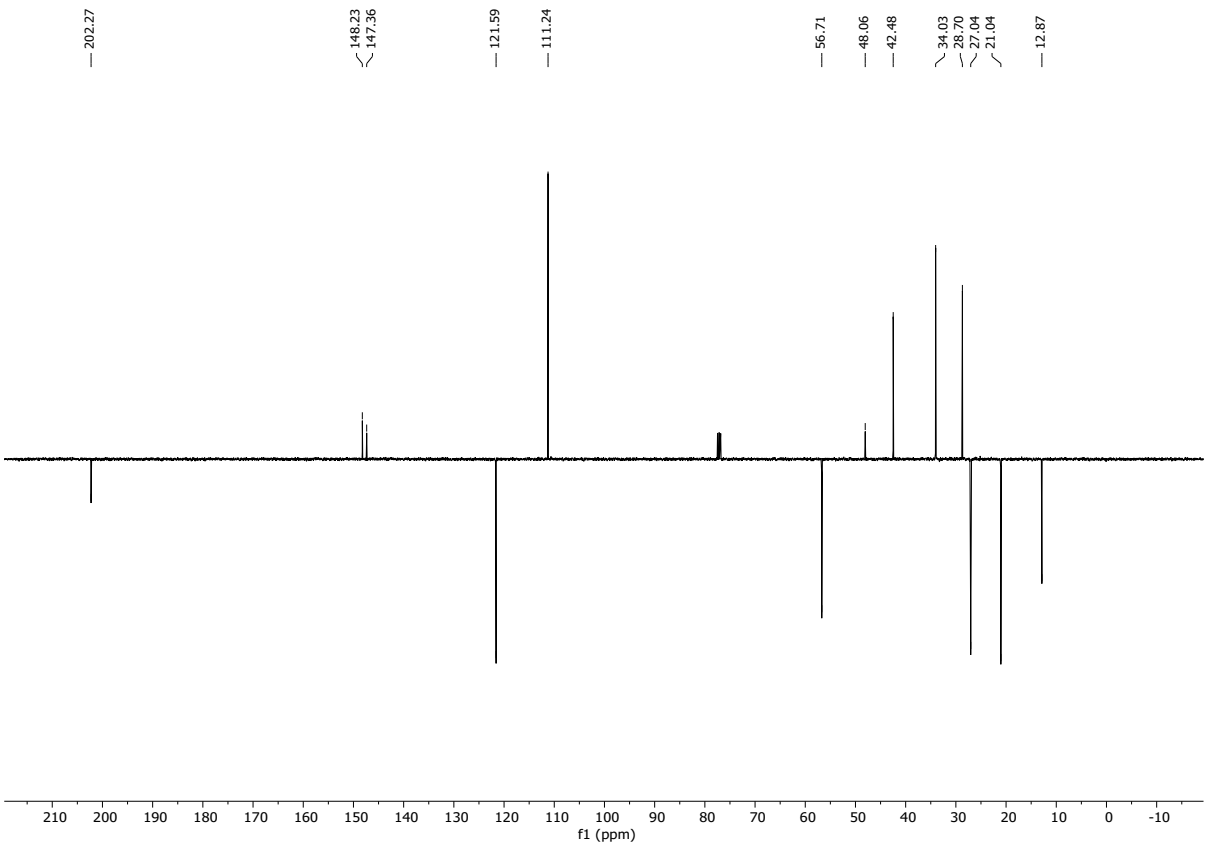


19

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

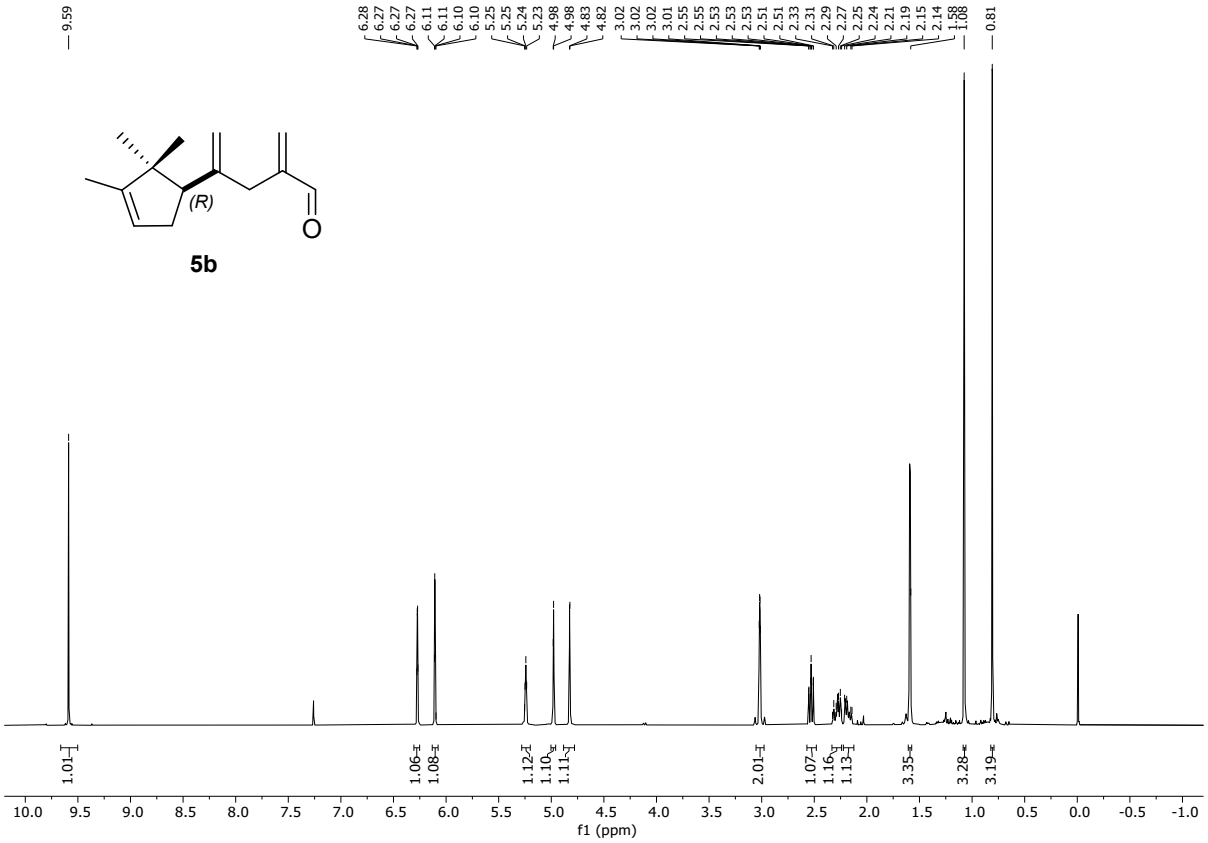


^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz)

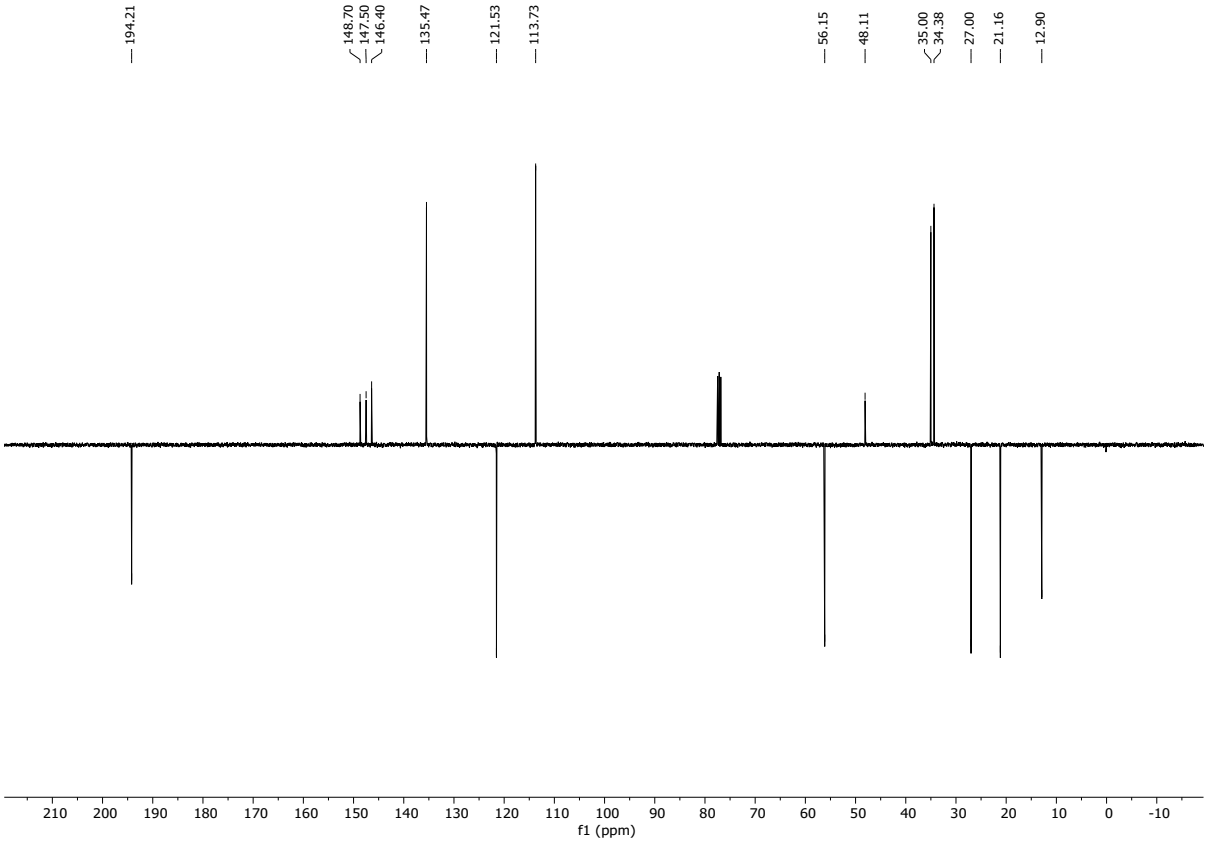


5b

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

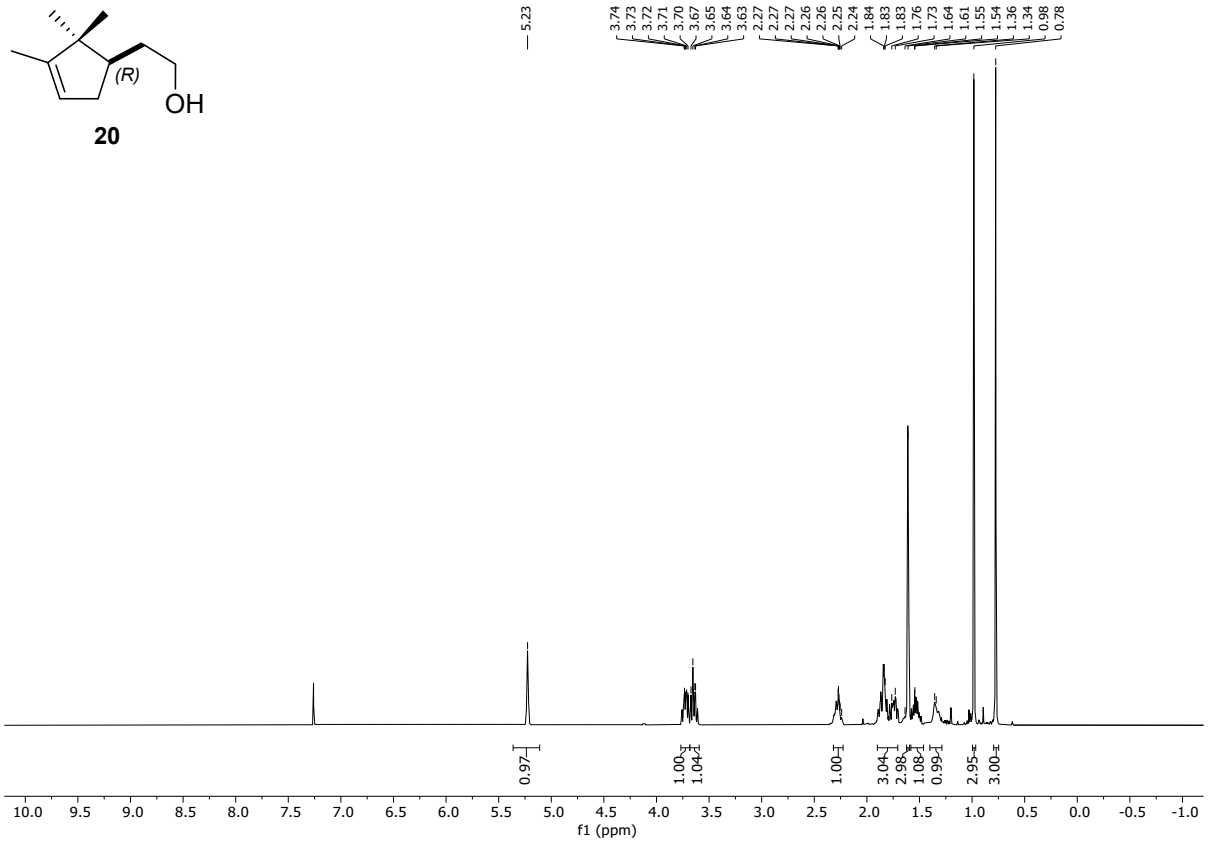


^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz)

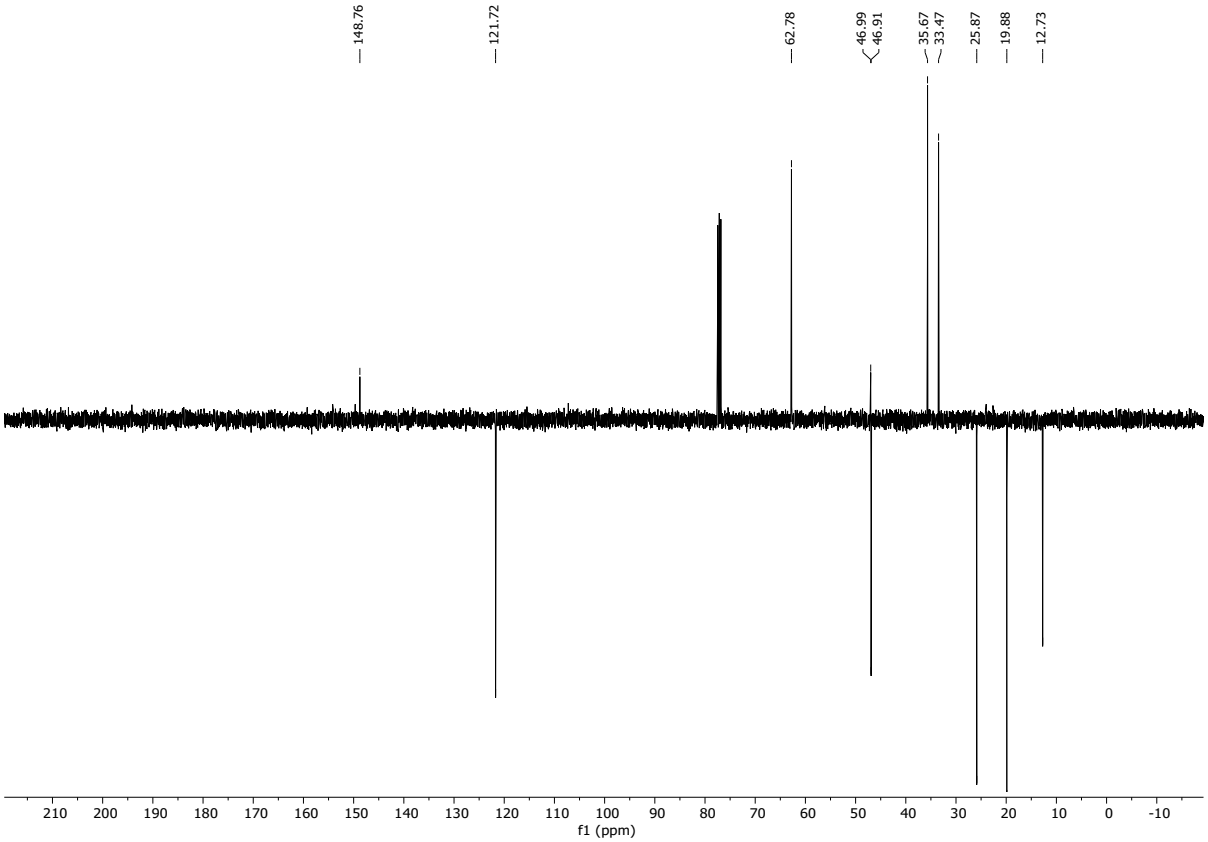


20

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

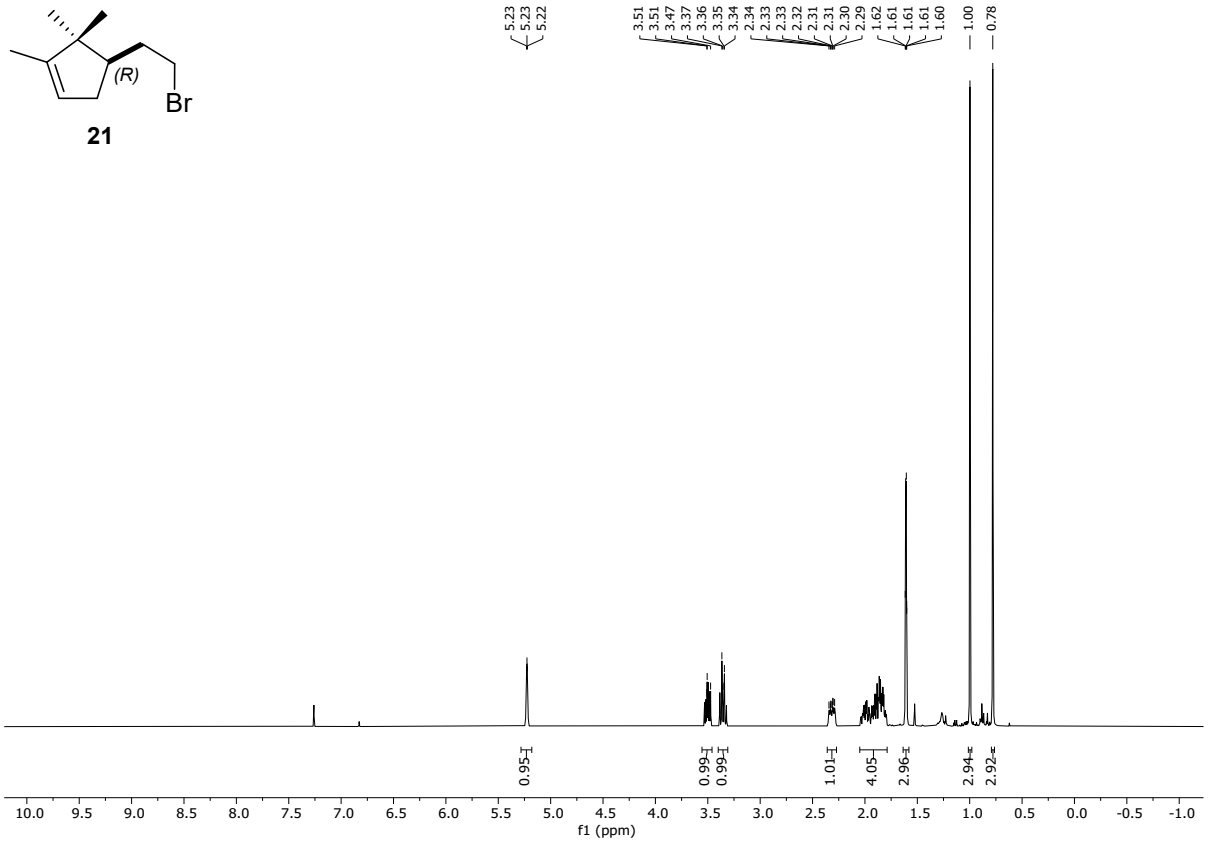


^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz)

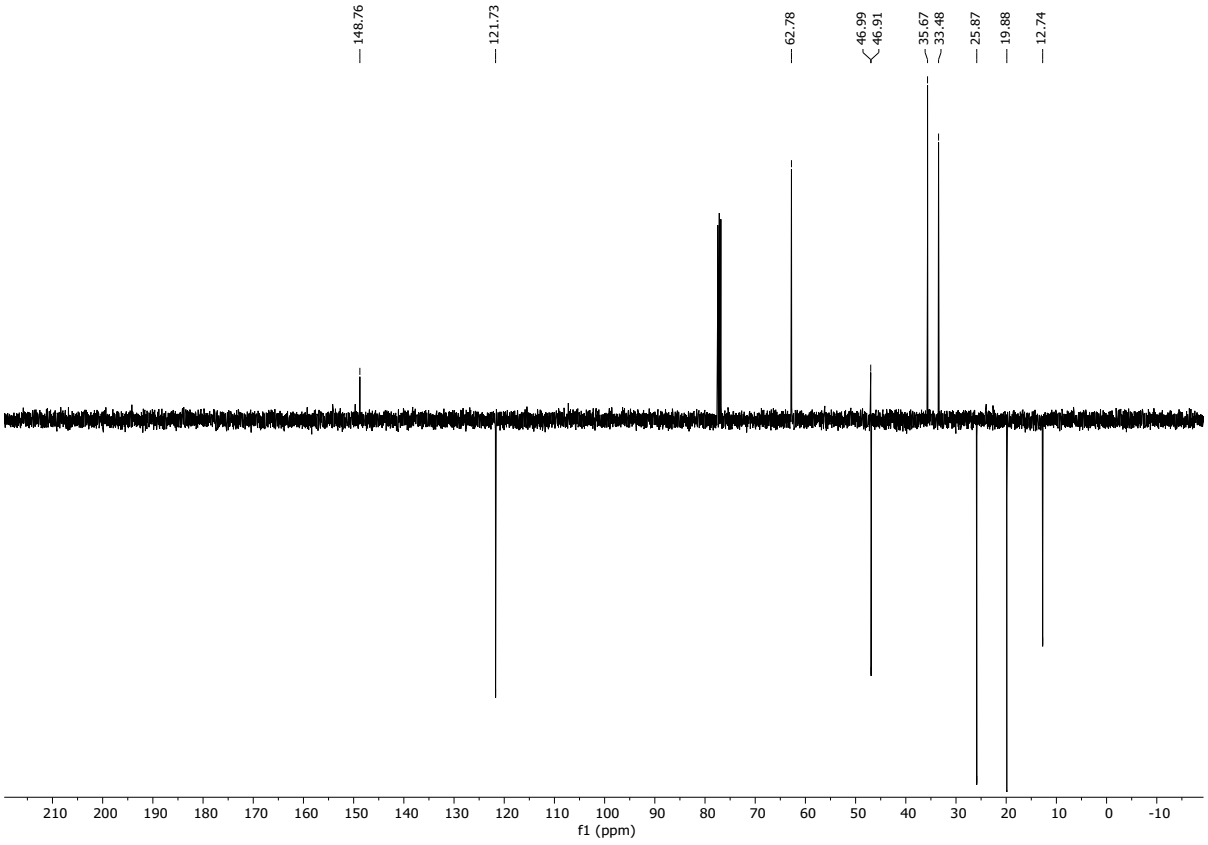


21

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

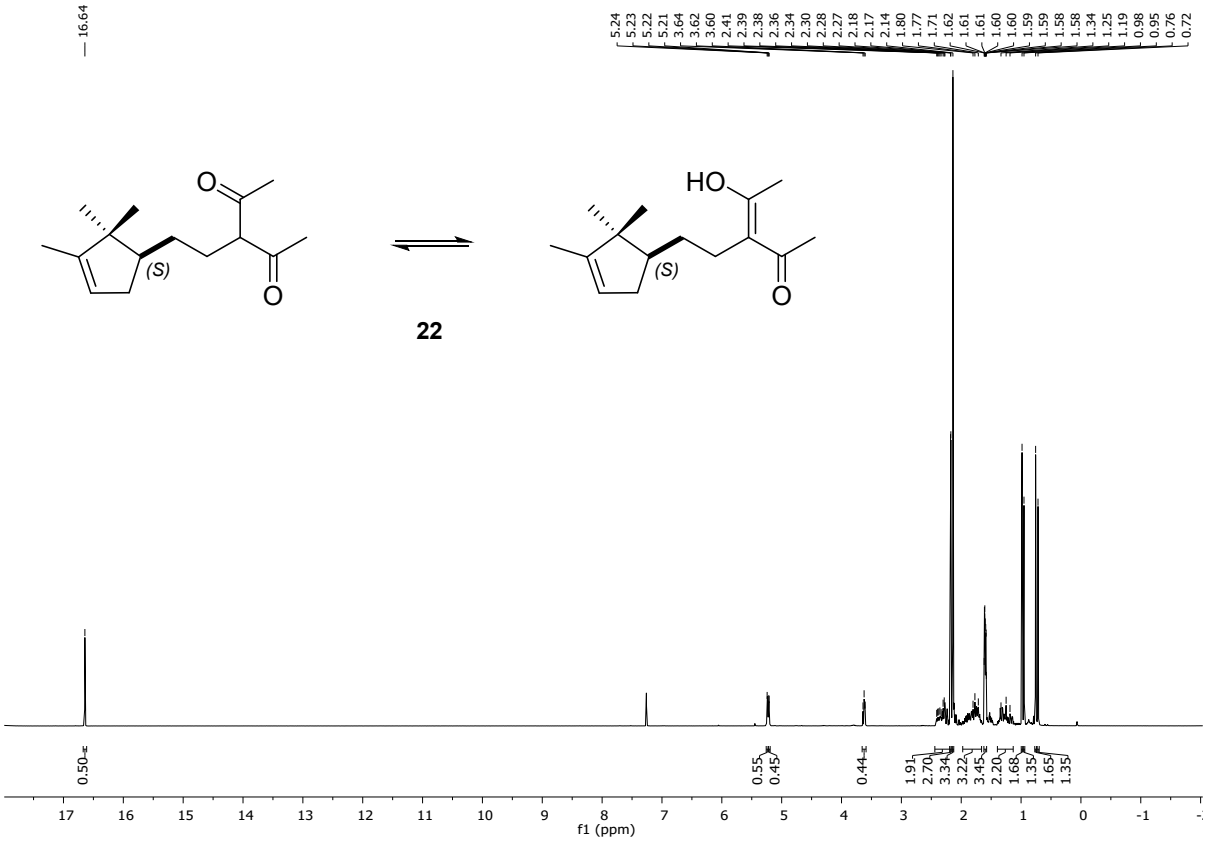


^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz)

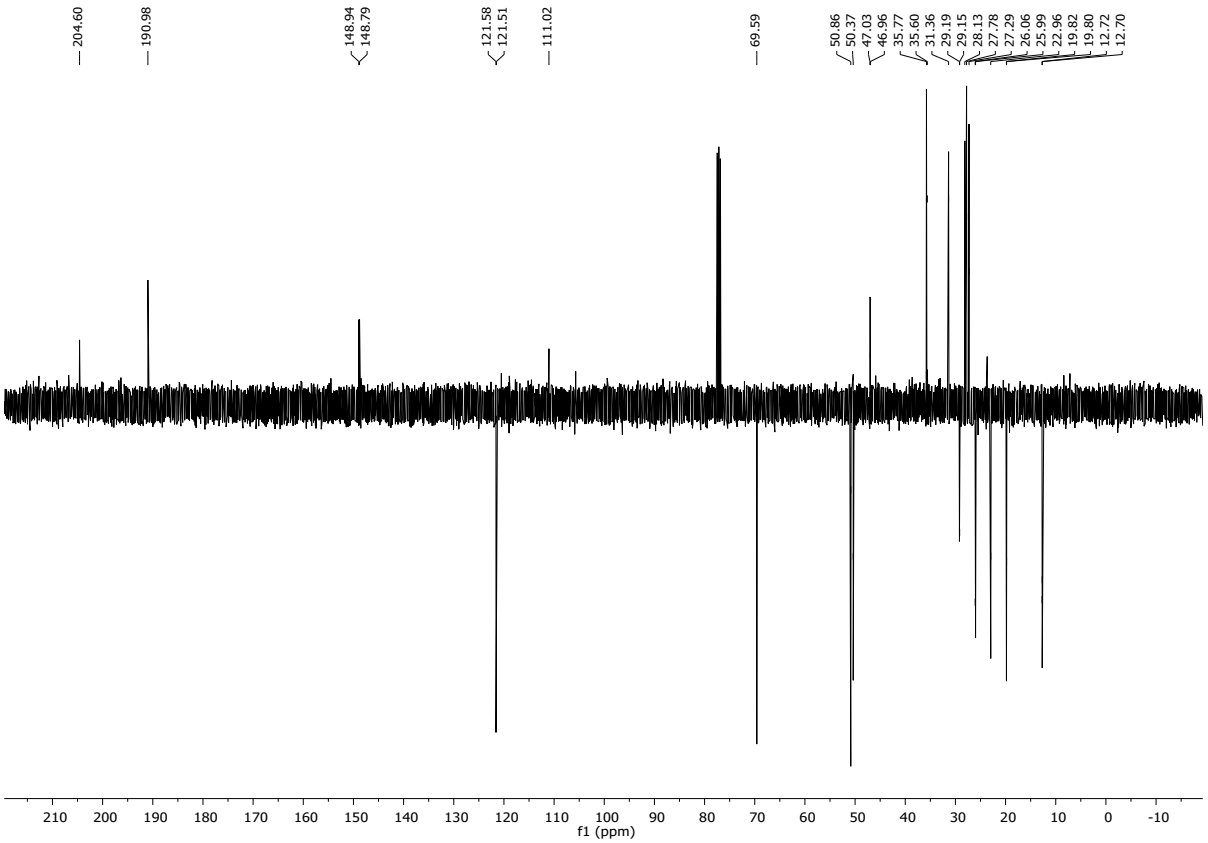


22

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

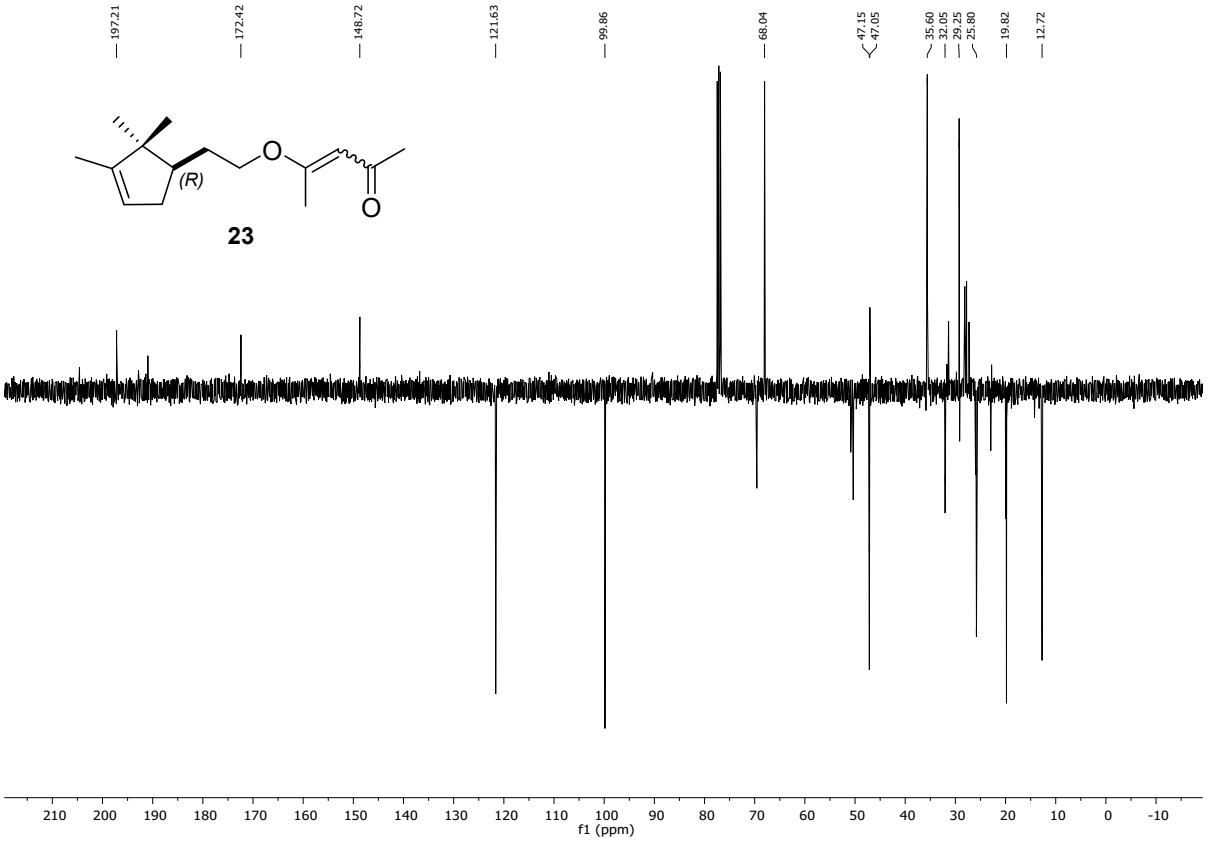


^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz)



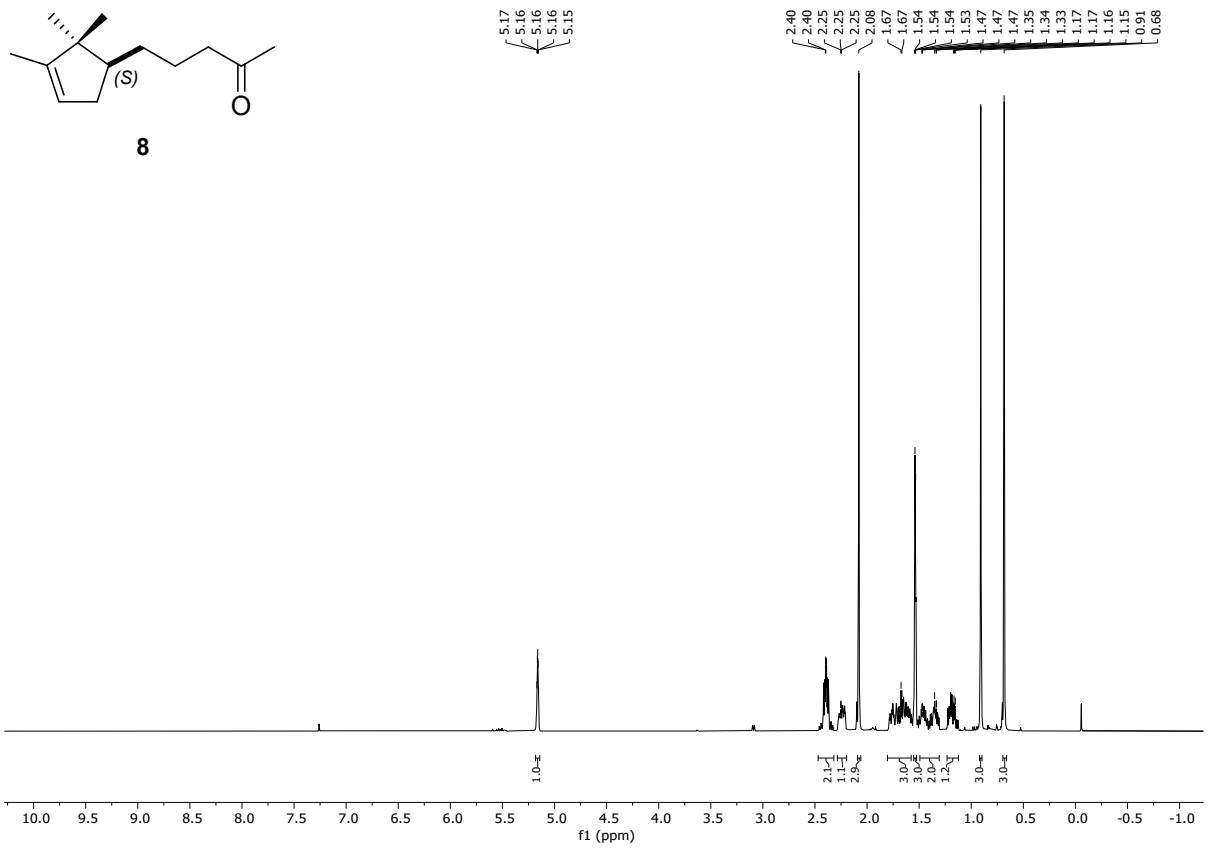
23

$^{13}C\{^{1}H\}$-NMR ($CDCl_3$, 101 MHz)

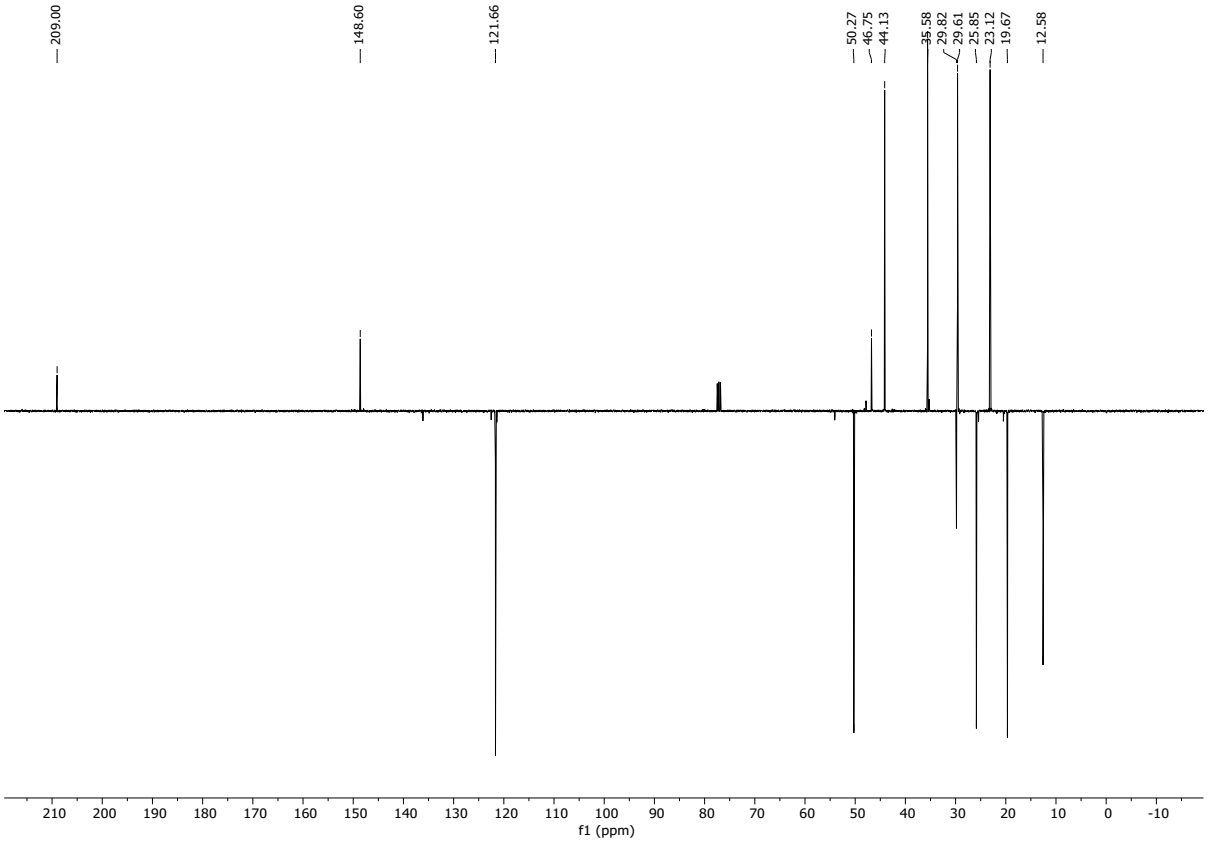


8

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

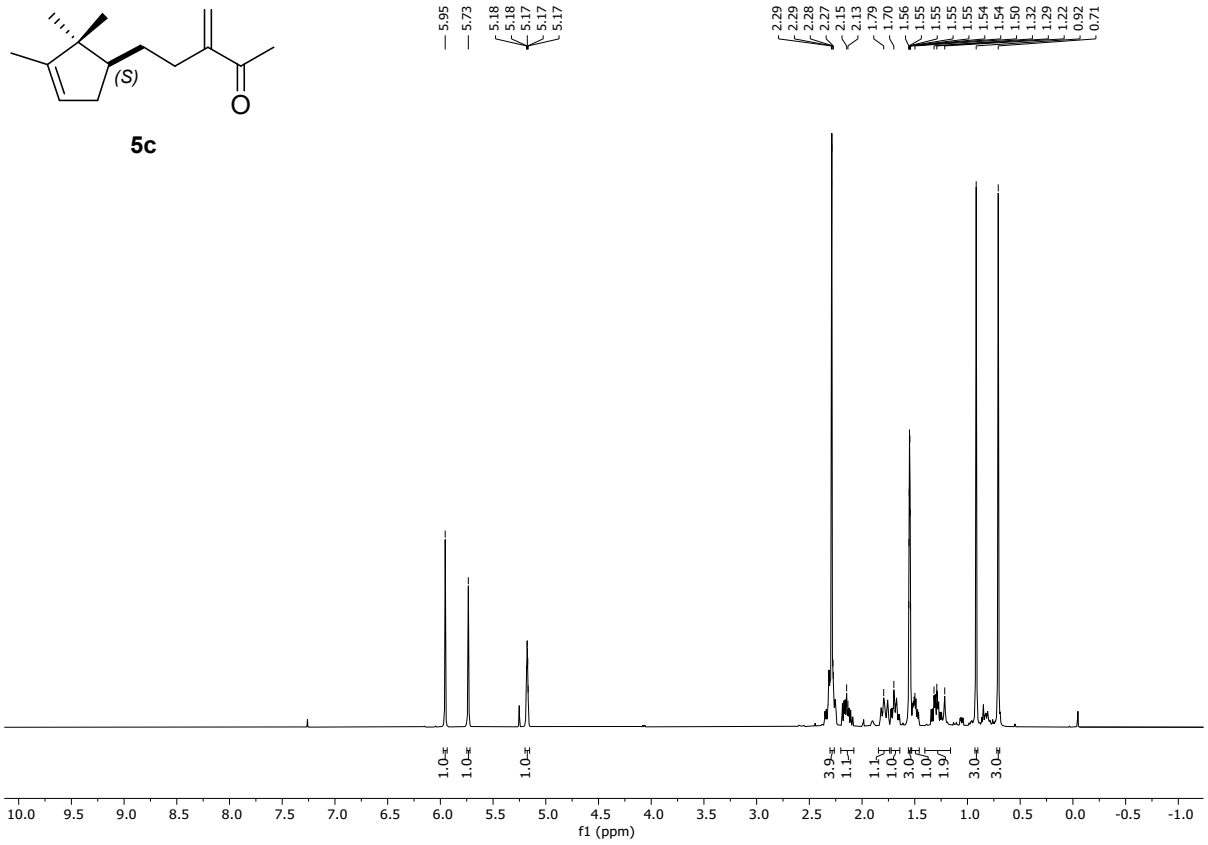


^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz)

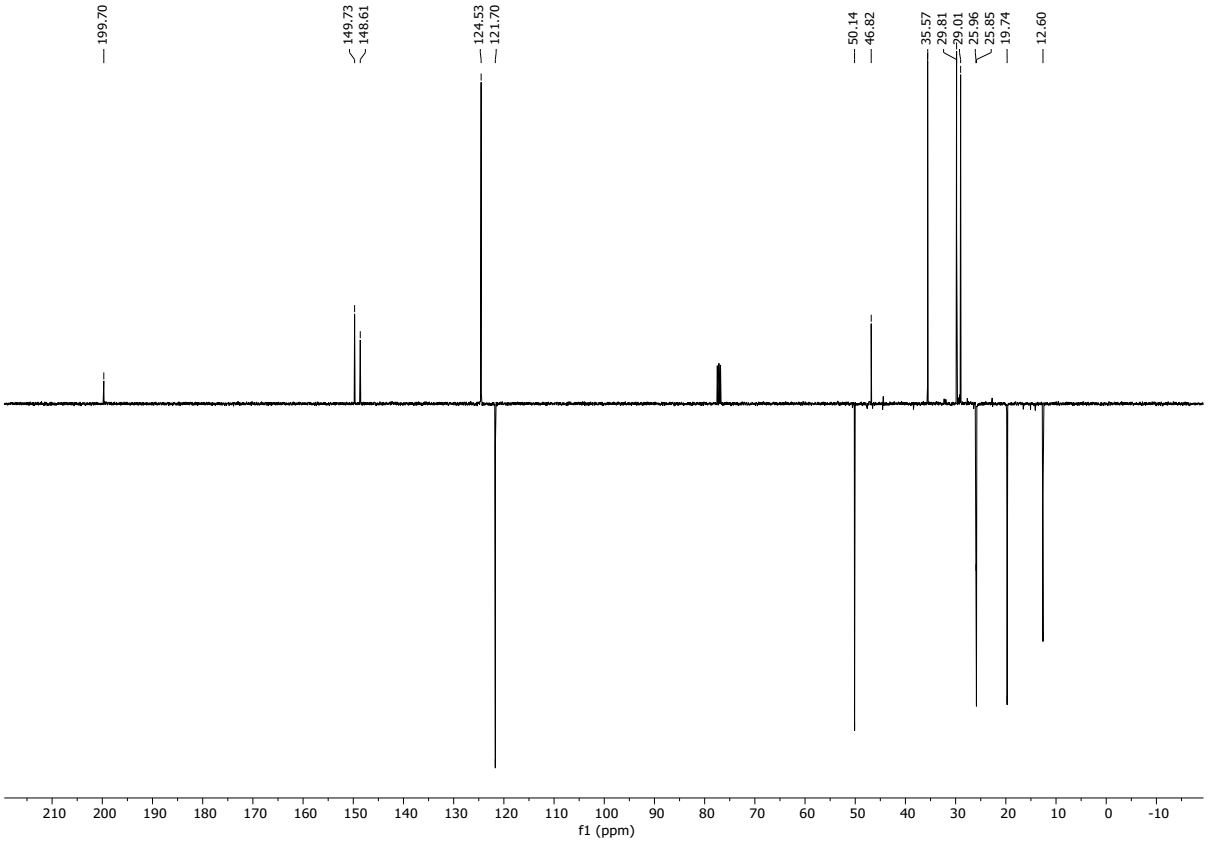


5c

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

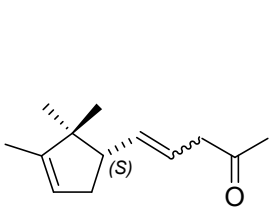


^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz)



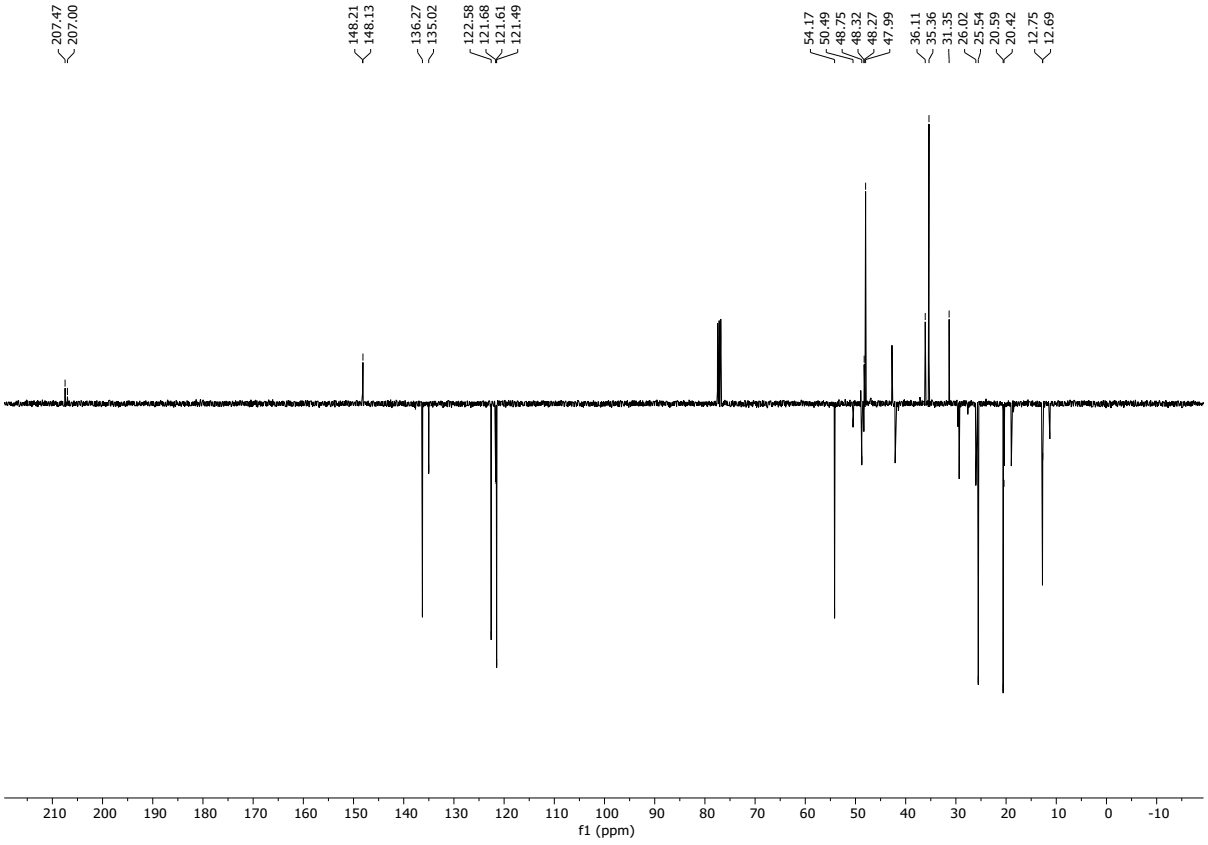
24

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



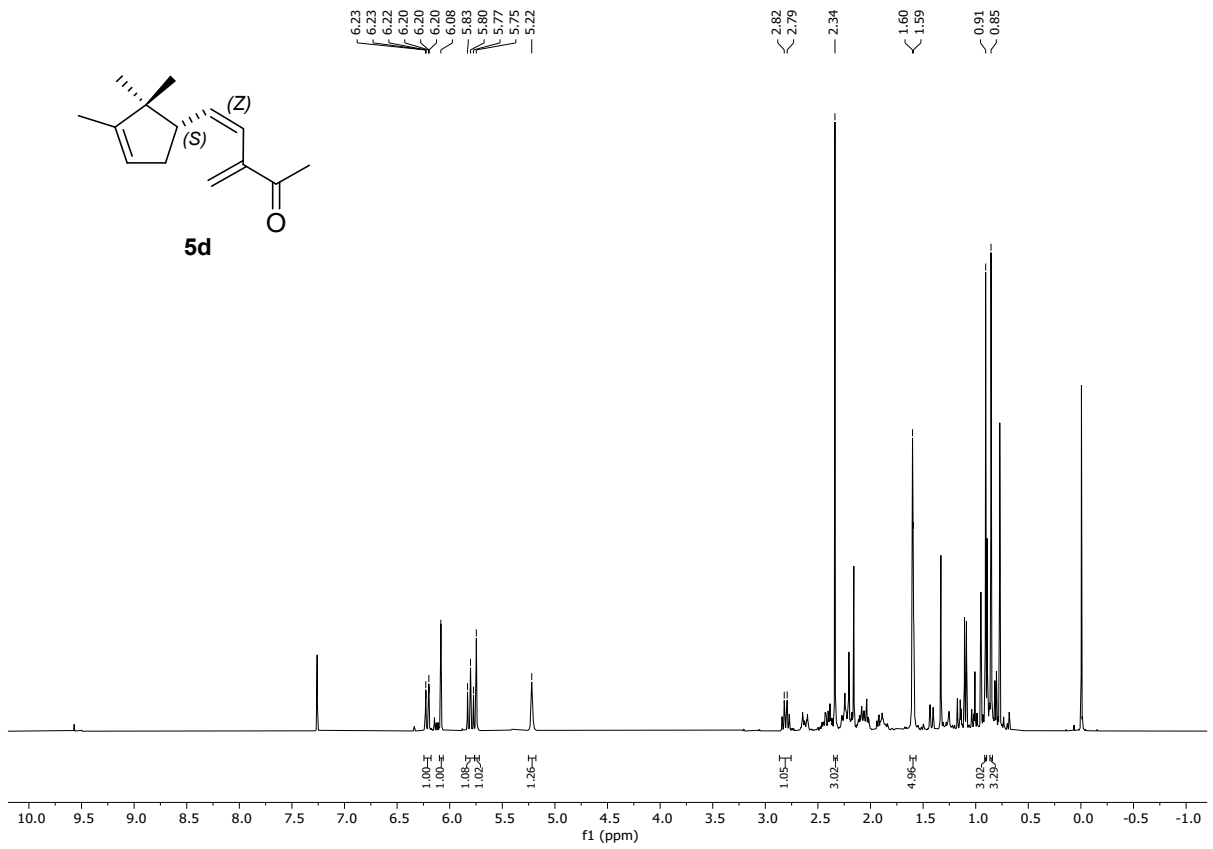
24, *E/Z* = 23:77

^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz)

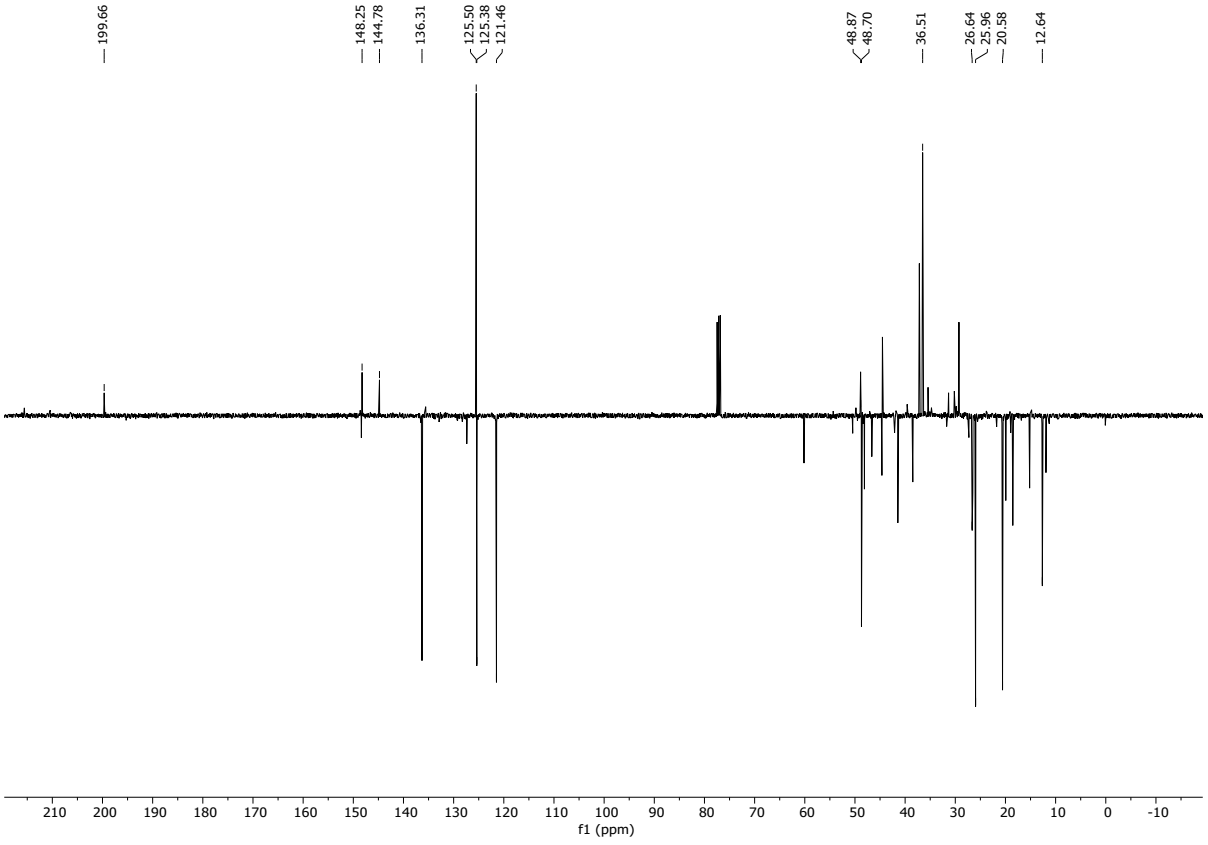


5d

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

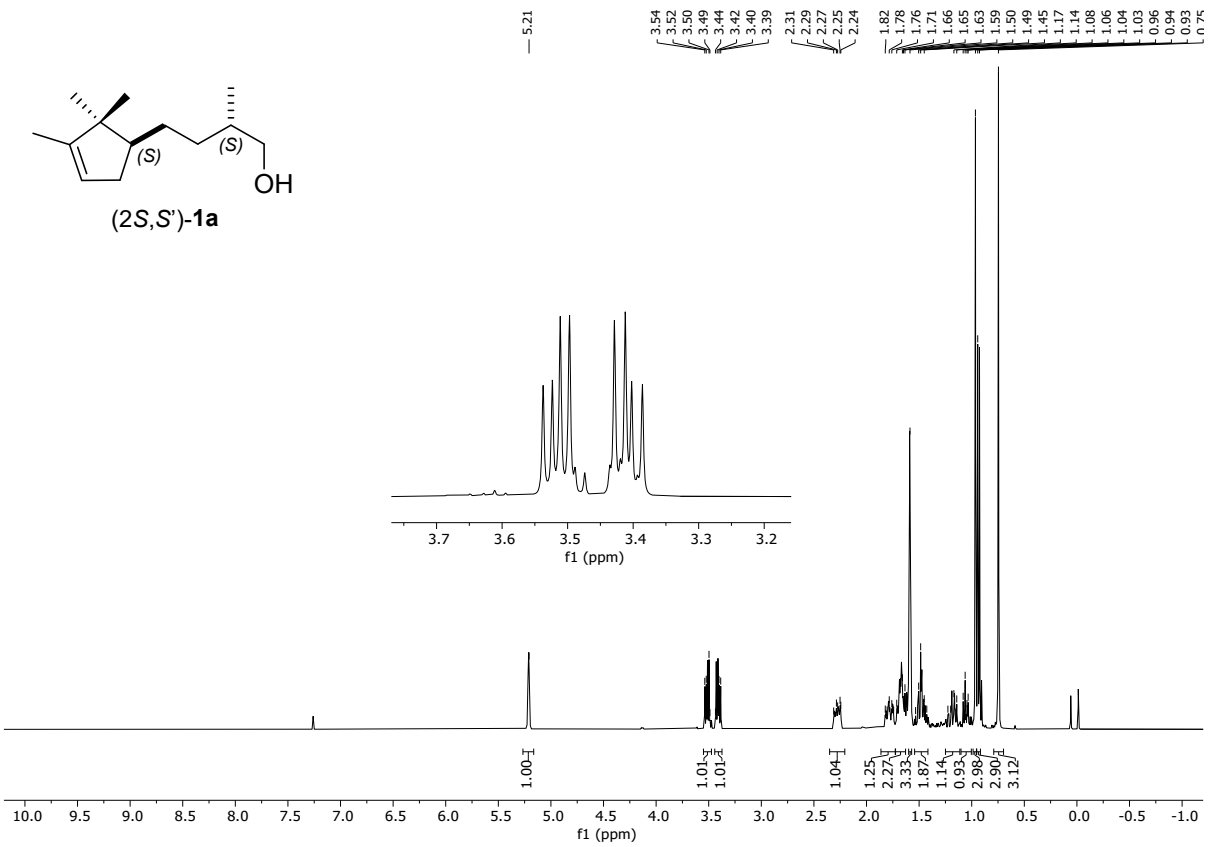


^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz)

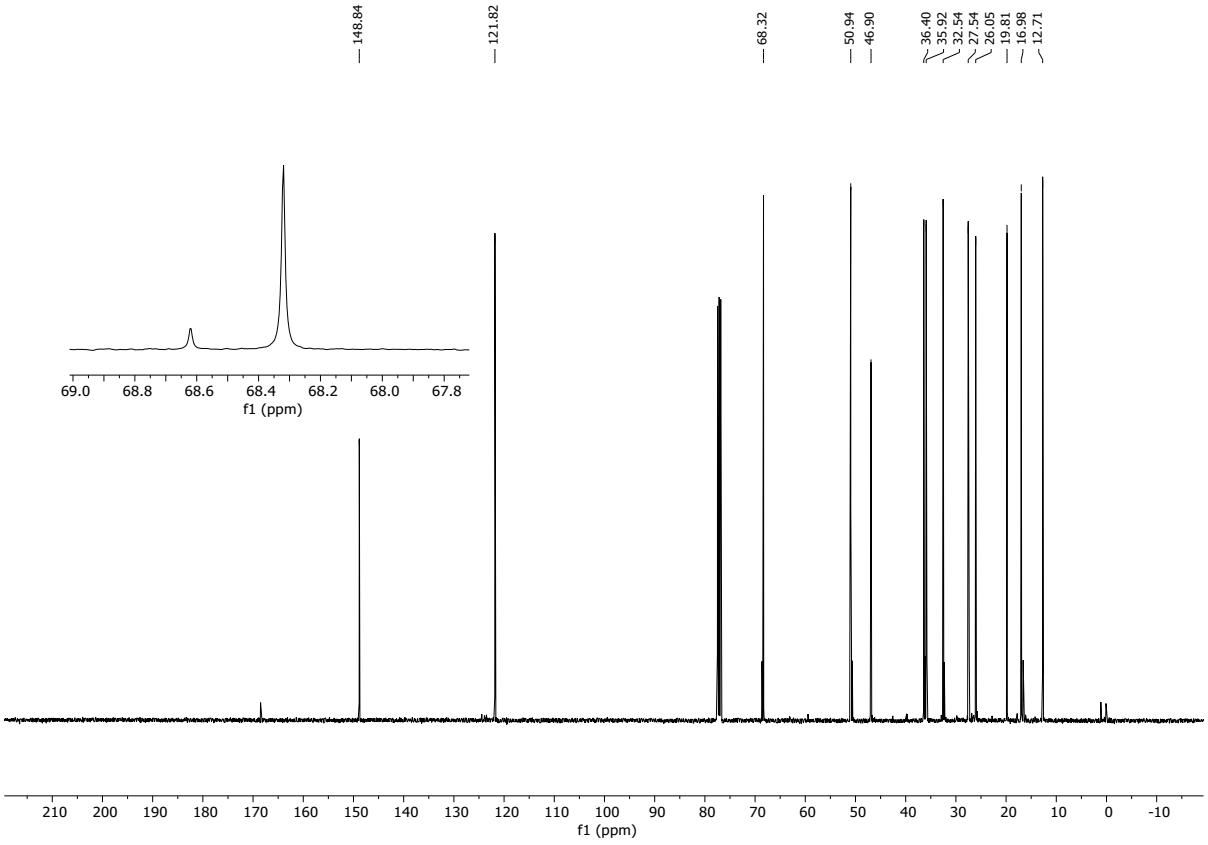


(2*S*,*S*')-**1a**

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

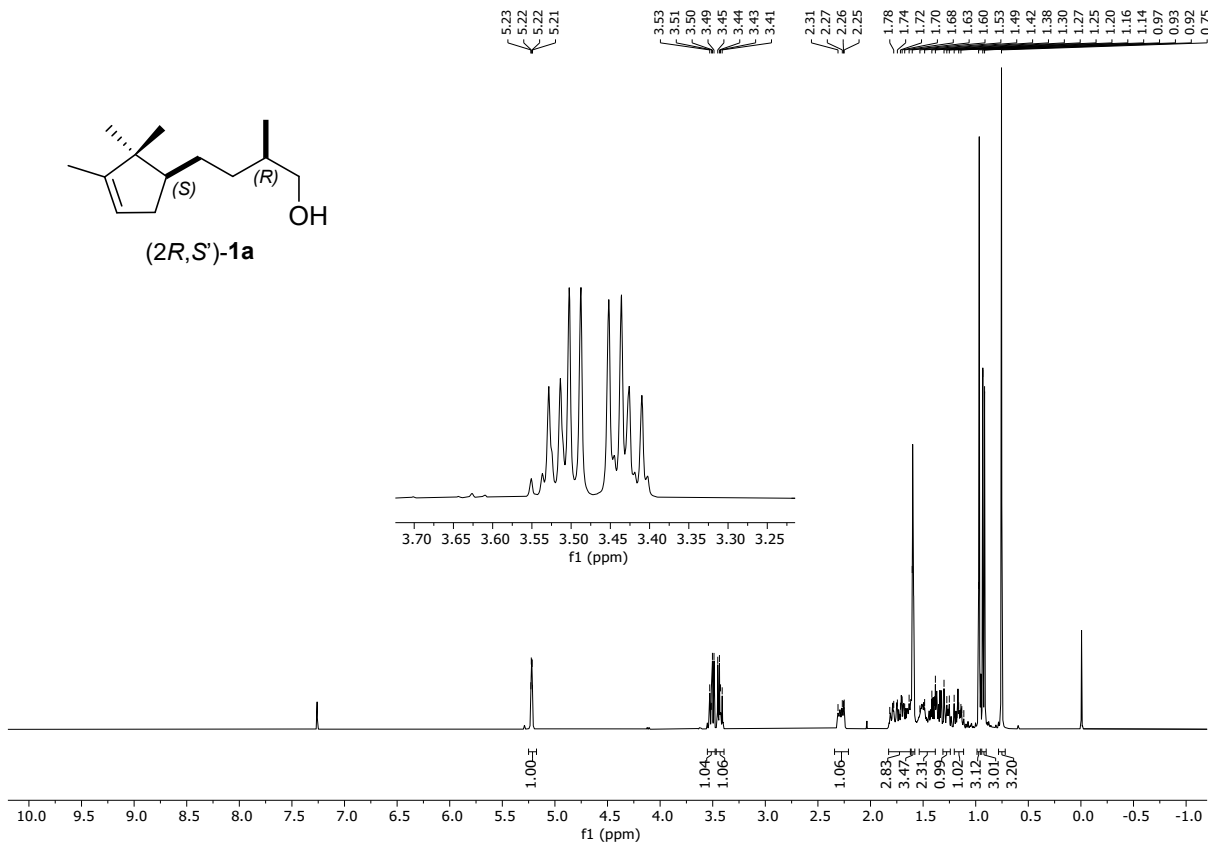


^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz)

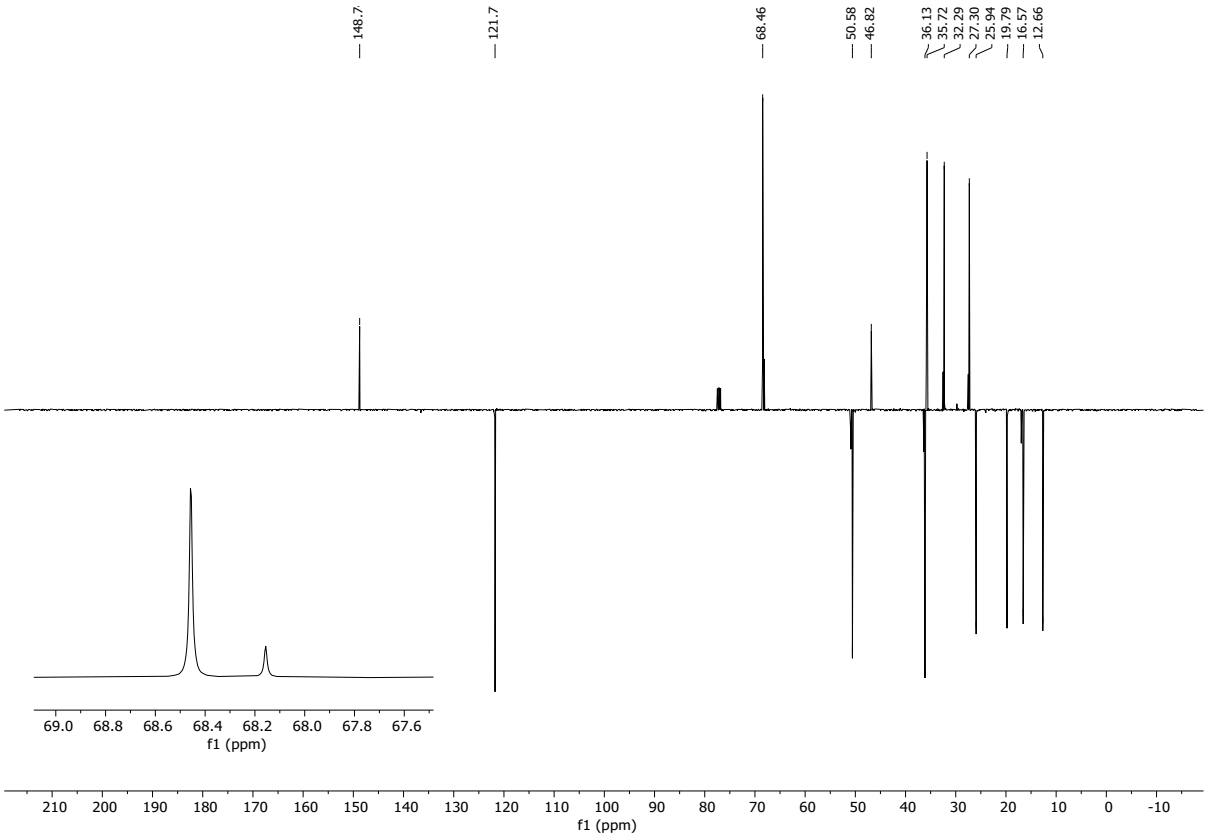


(2*R*,*S*')-**1a**

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

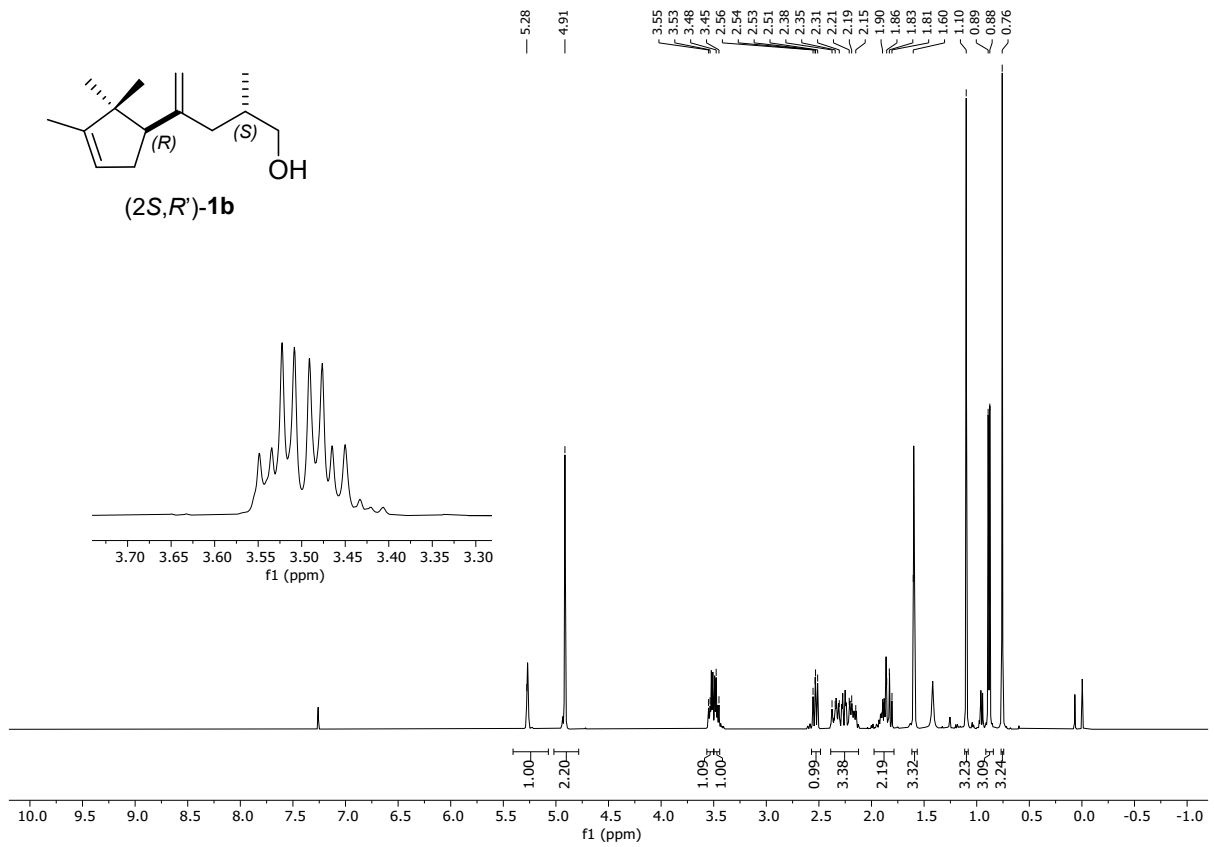


^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz)

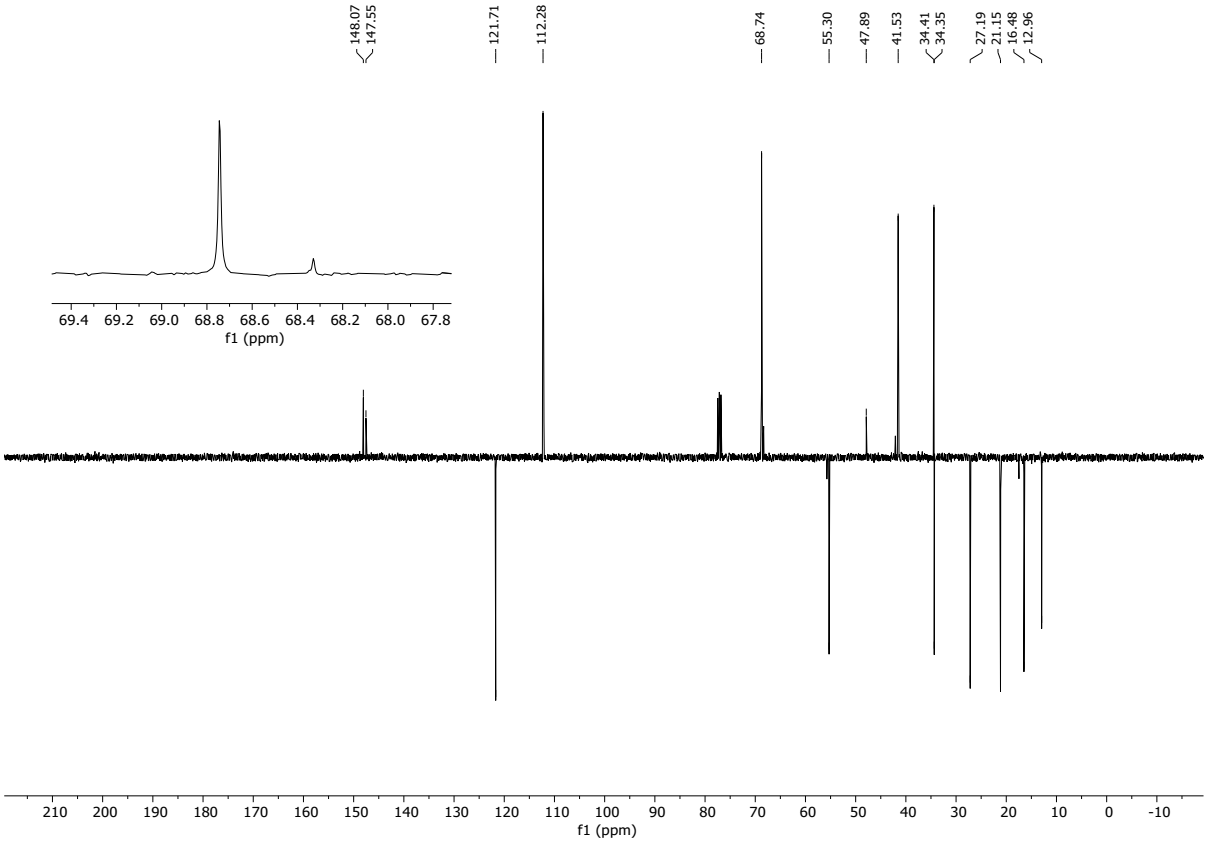


(2*S*,*R*')-**1b**

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

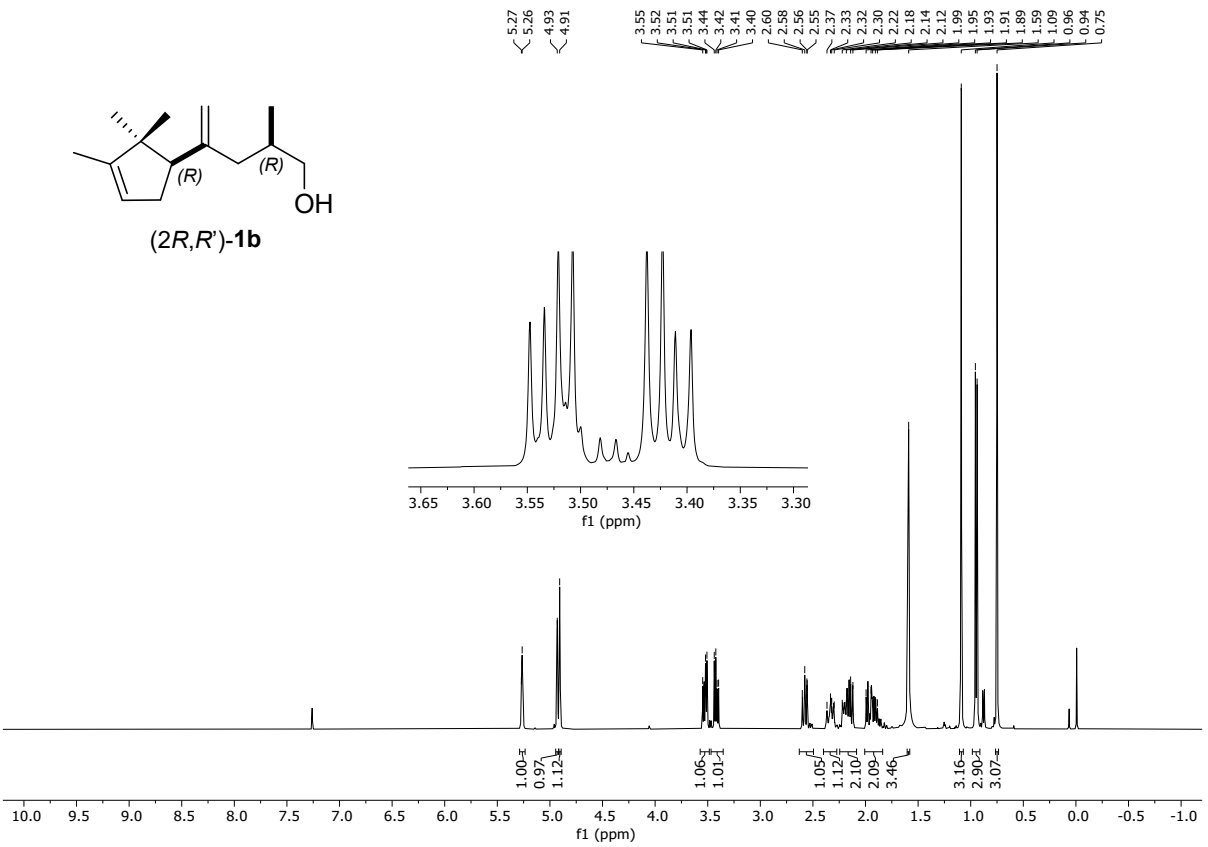


^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz)

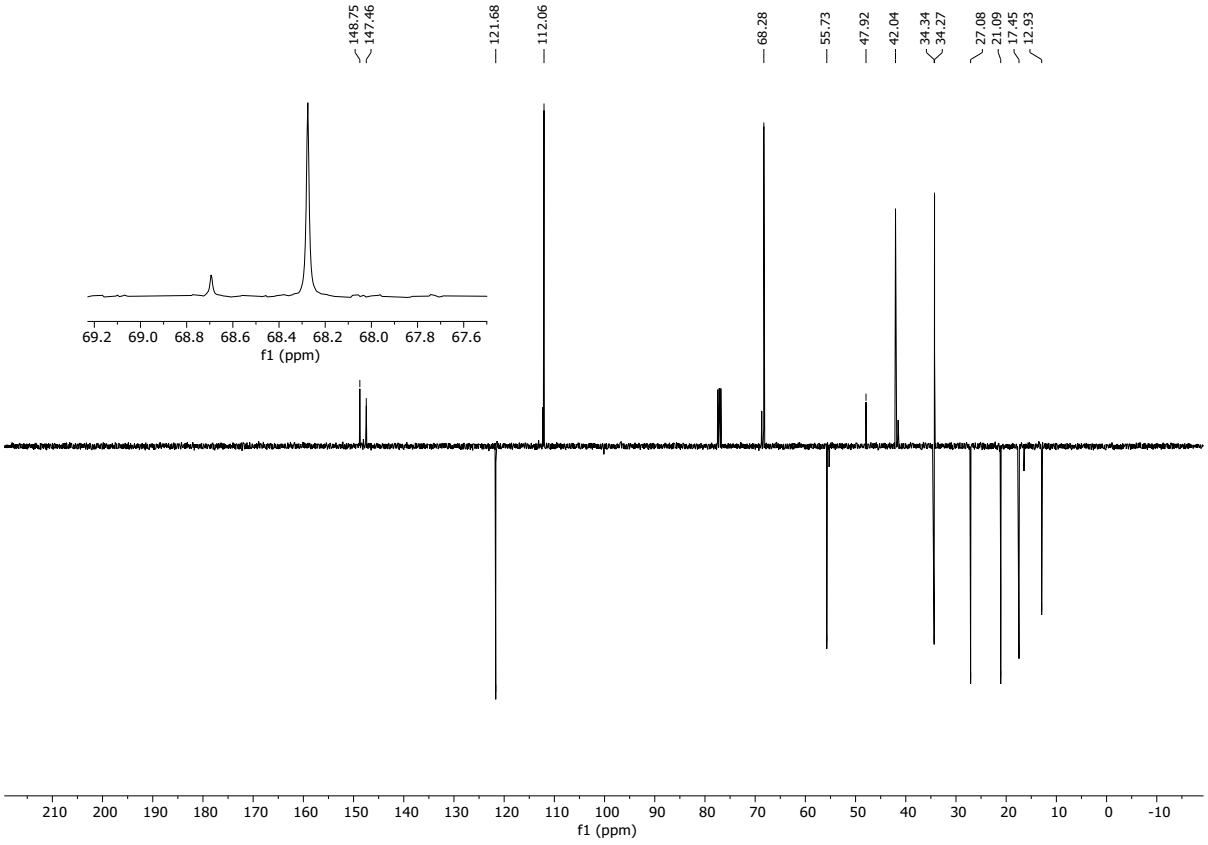


(2*R*,*R*')-**1b**

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

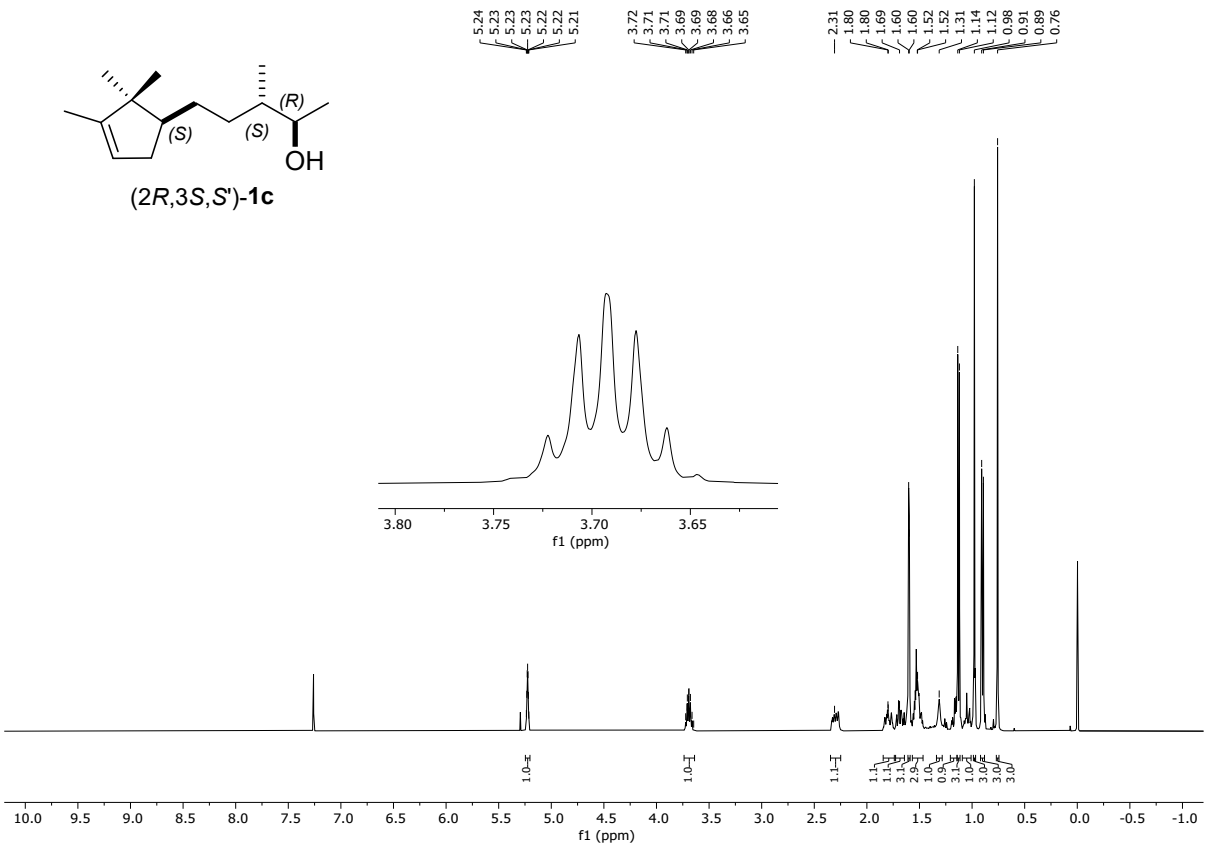


^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz)

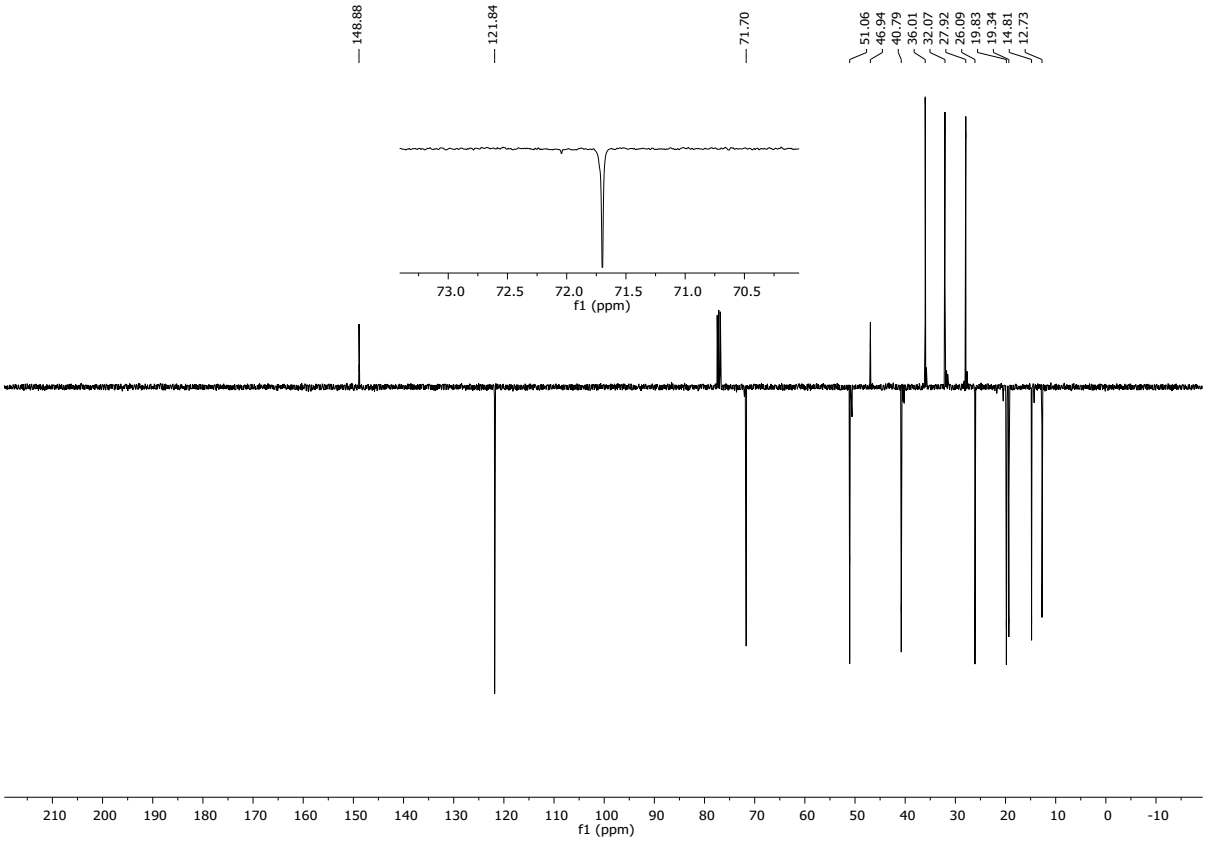


(2*R*,3*S*,*S*')-**1c**

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

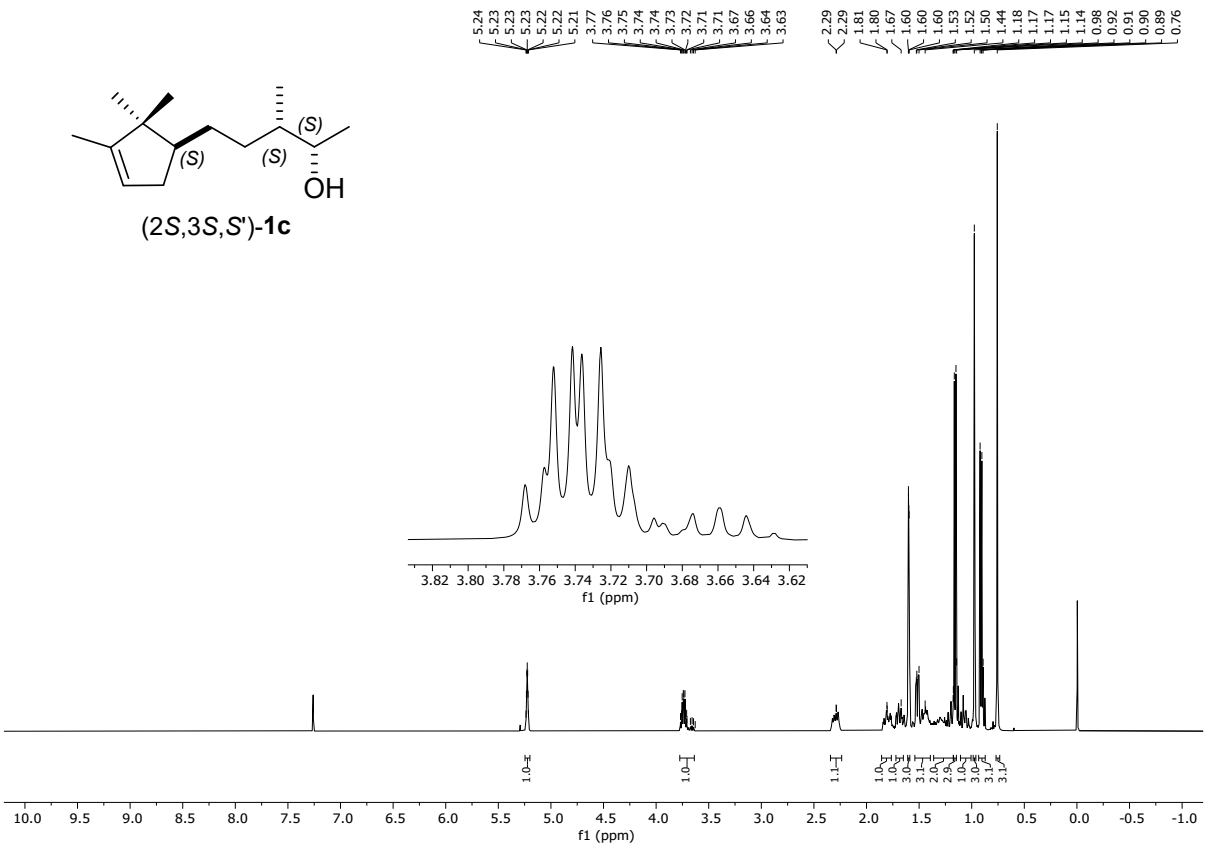


^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz)

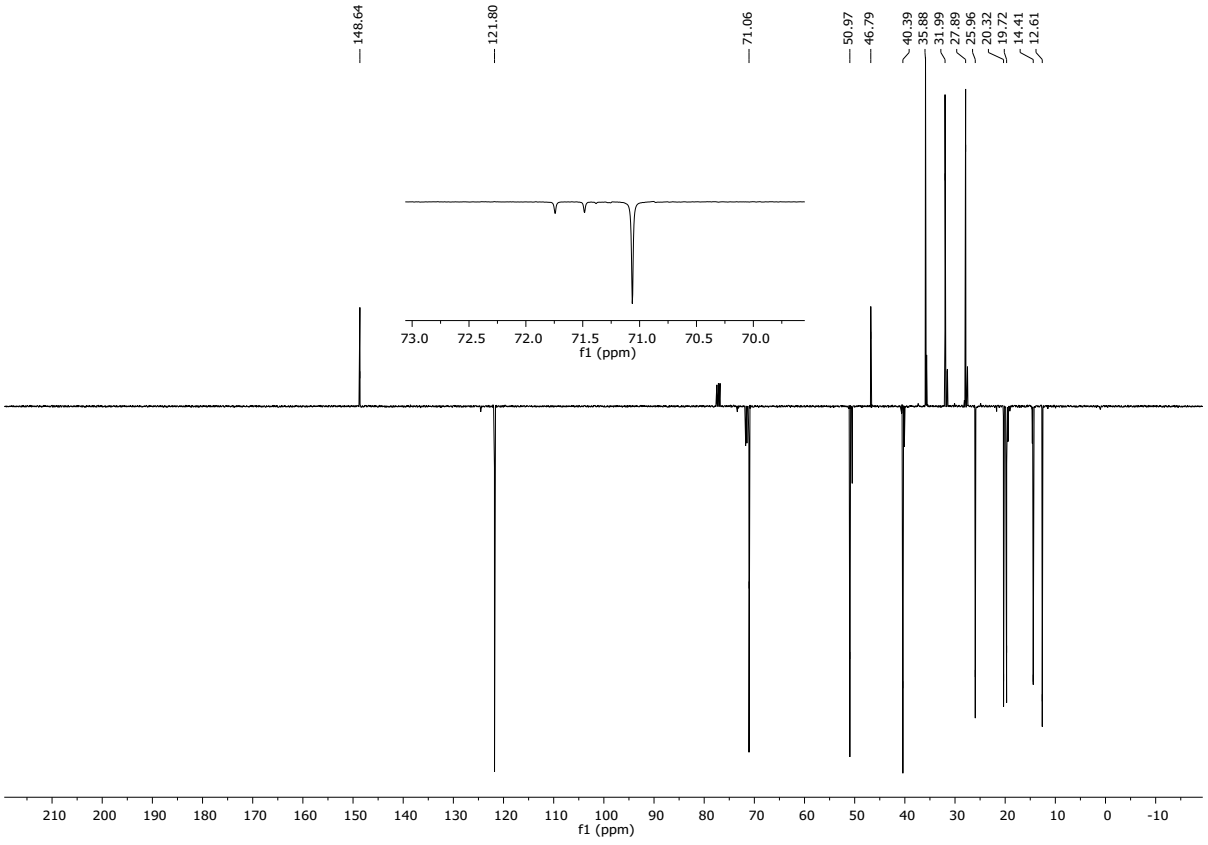


(2*S*,3*S*,*S*')-**1c**

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

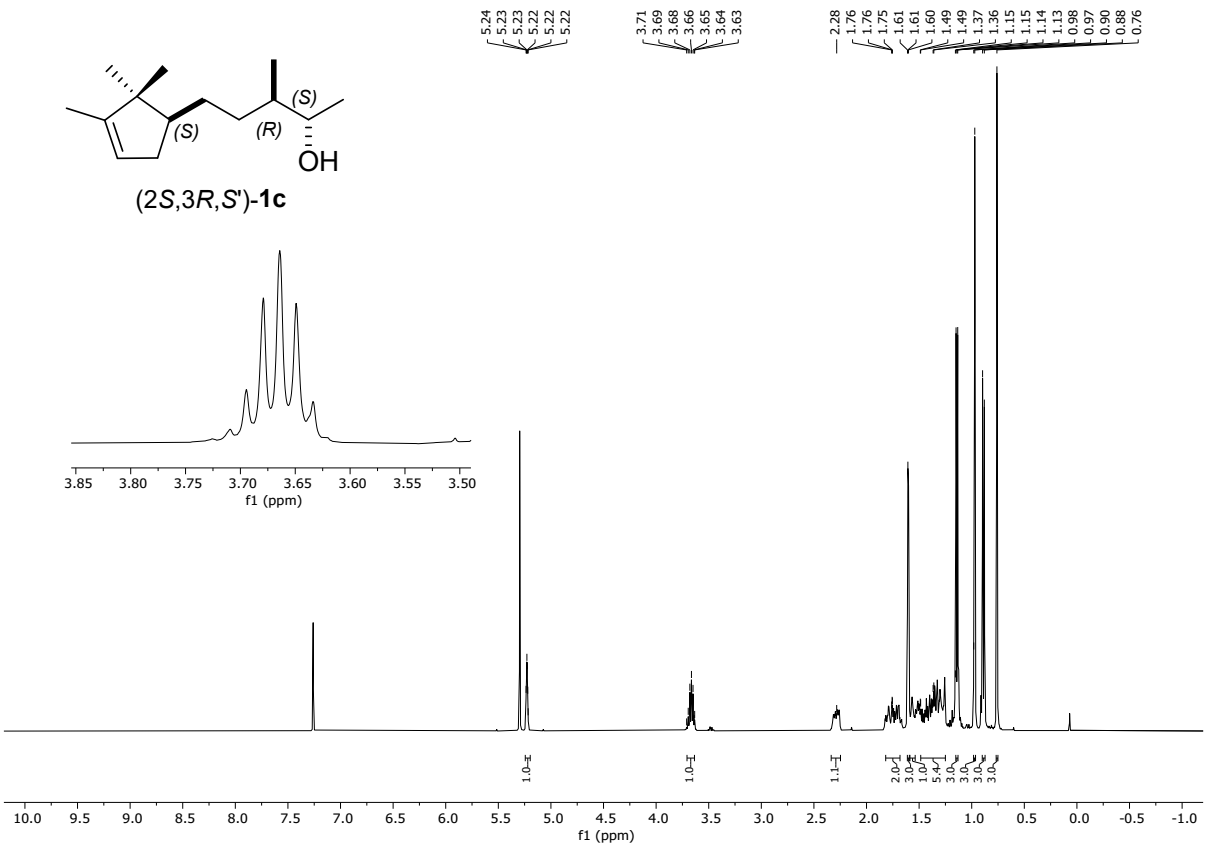


^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz)

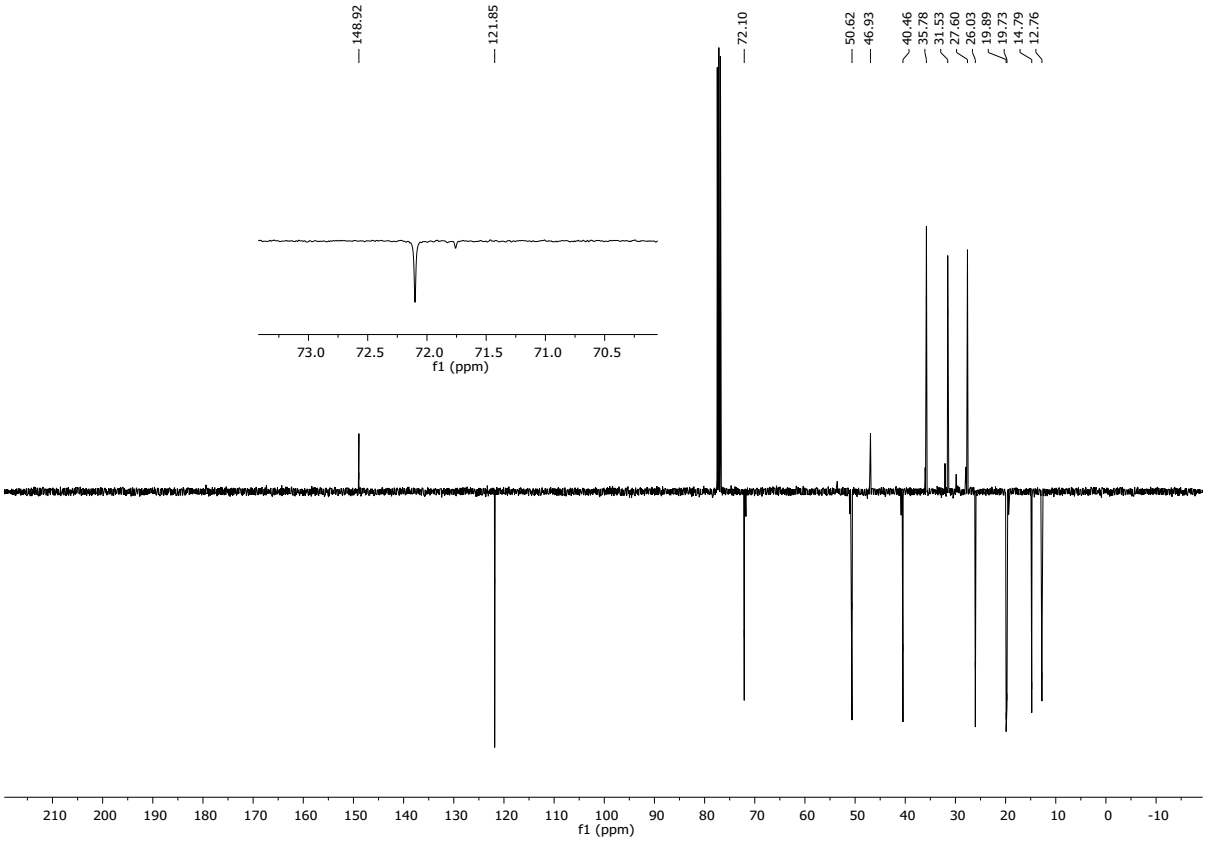


(2*S*,3*R*,*S*')-**1c**

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

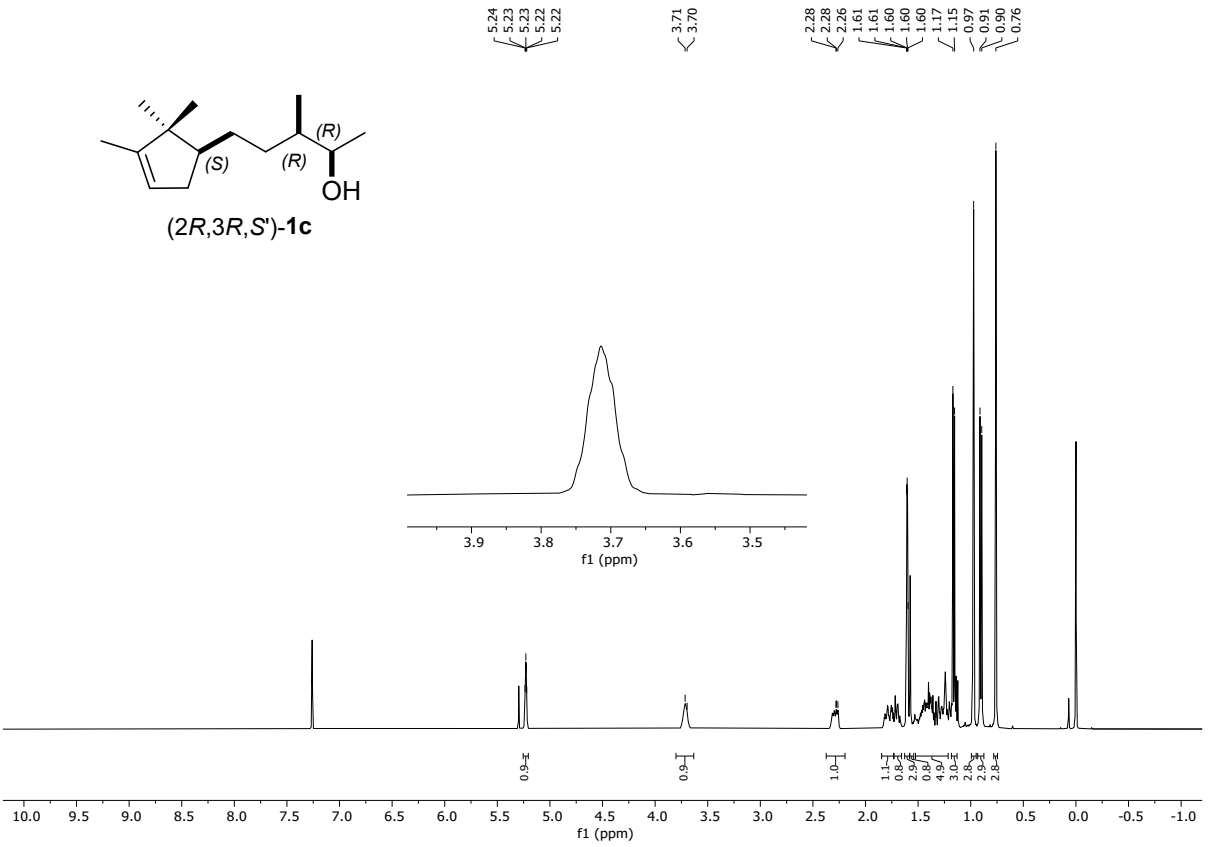


^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz)

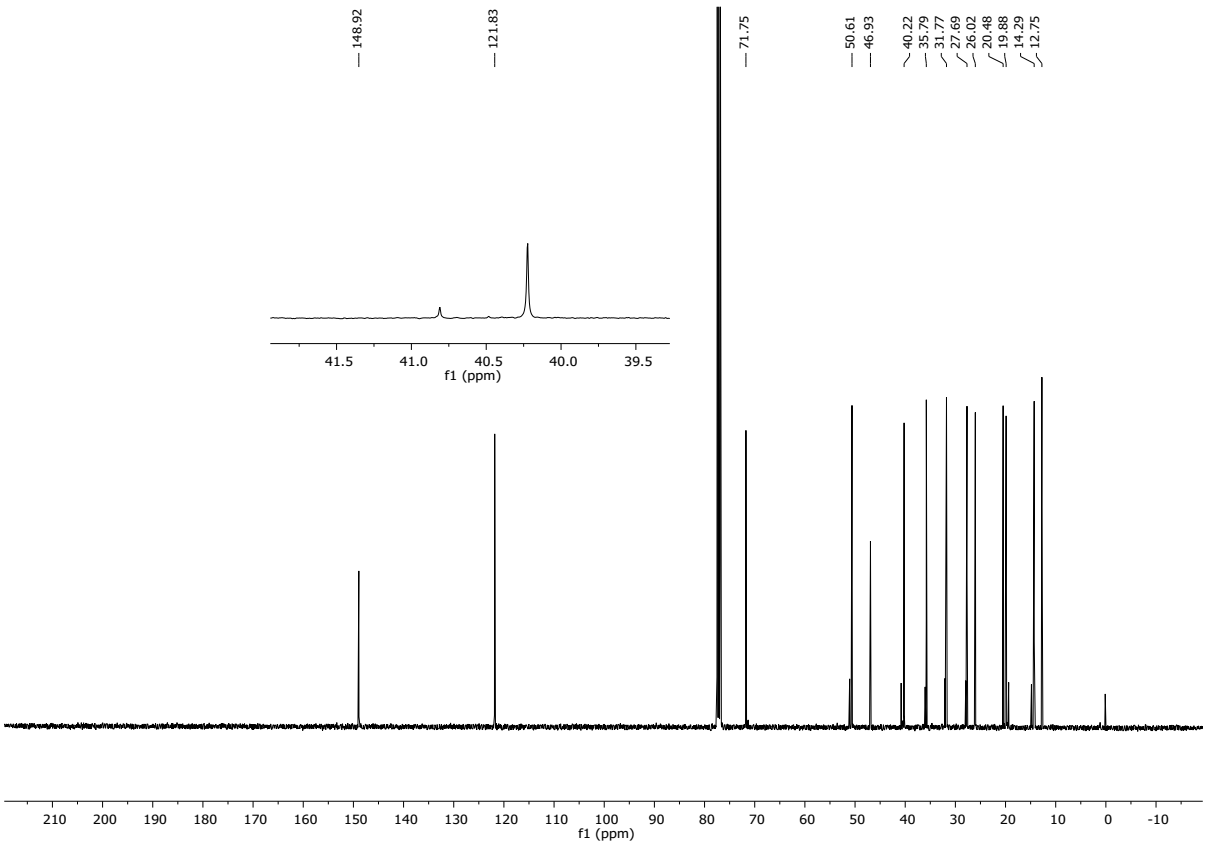


(2*R*,3*R*,*S*')-**1c**

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

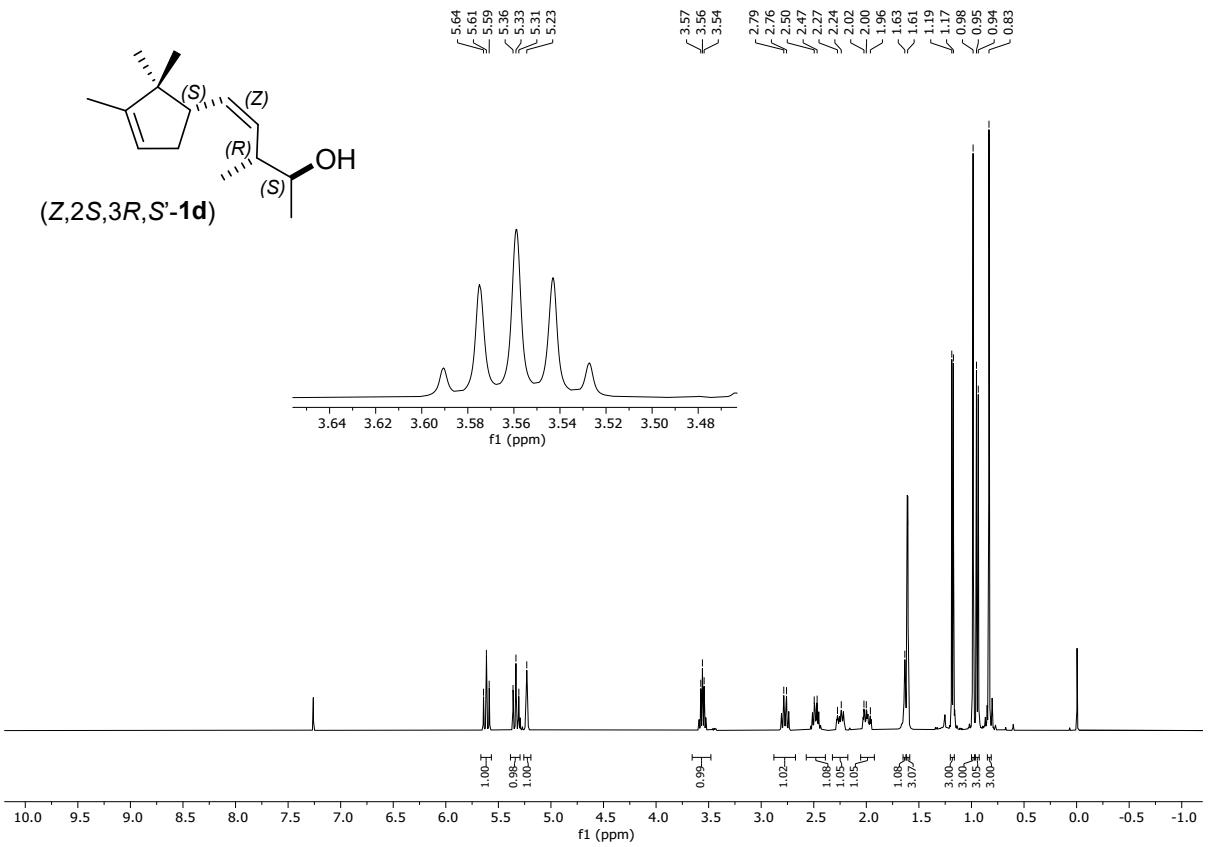


^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz)

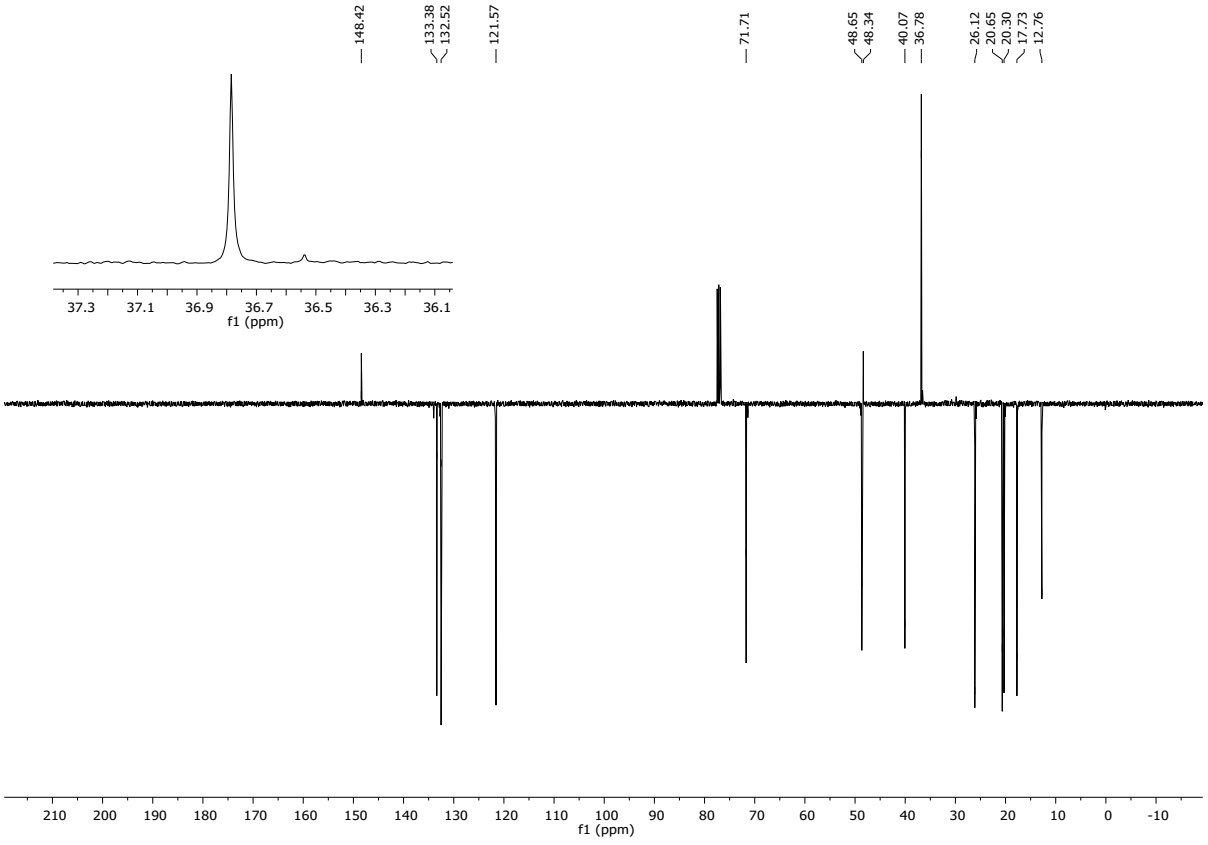


(*Z*,2*S*,3*R*,*S*')-**1d**

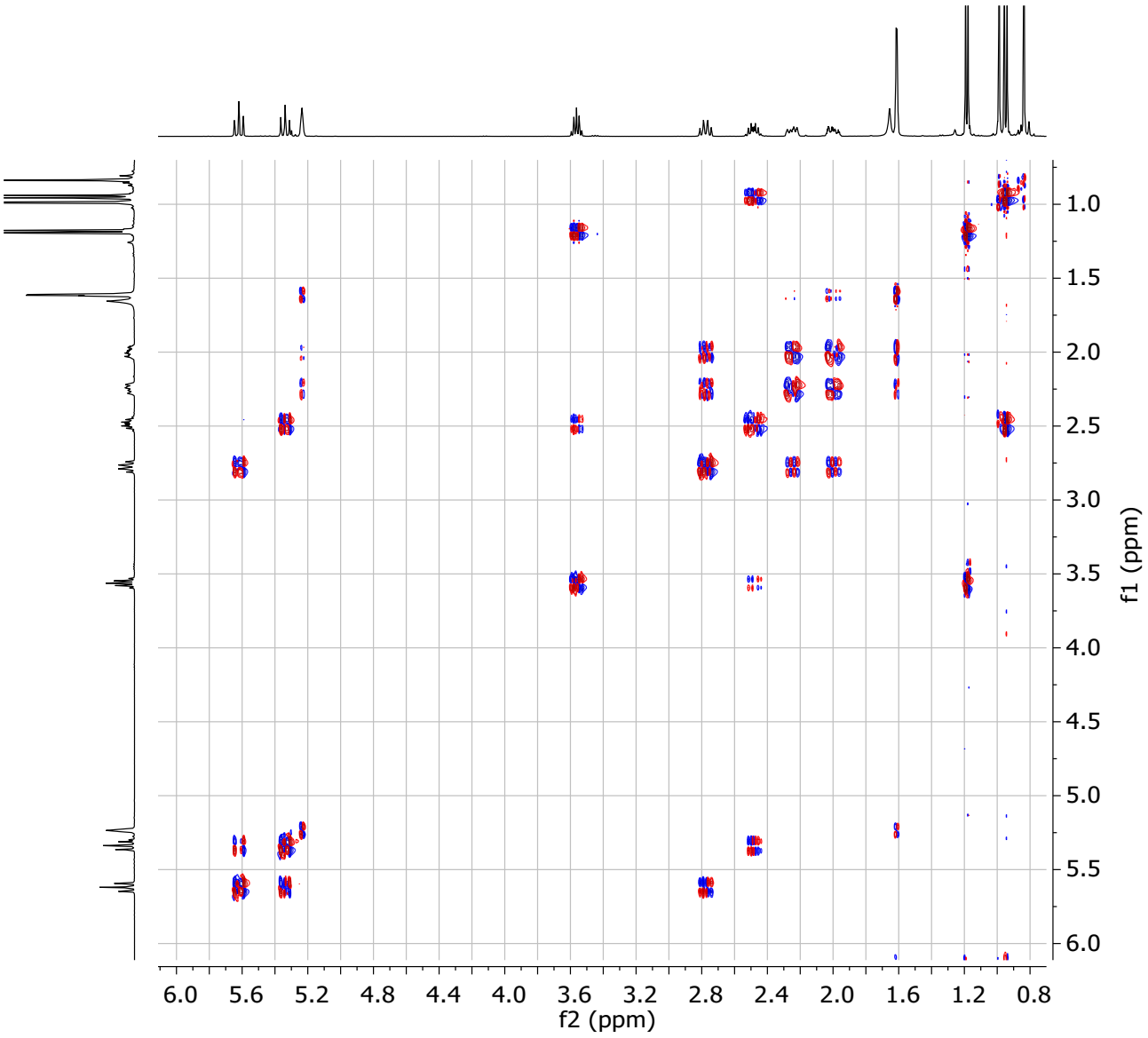
^{1}H-NMR ($CDCl_3$, 400 MHz)



^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz)

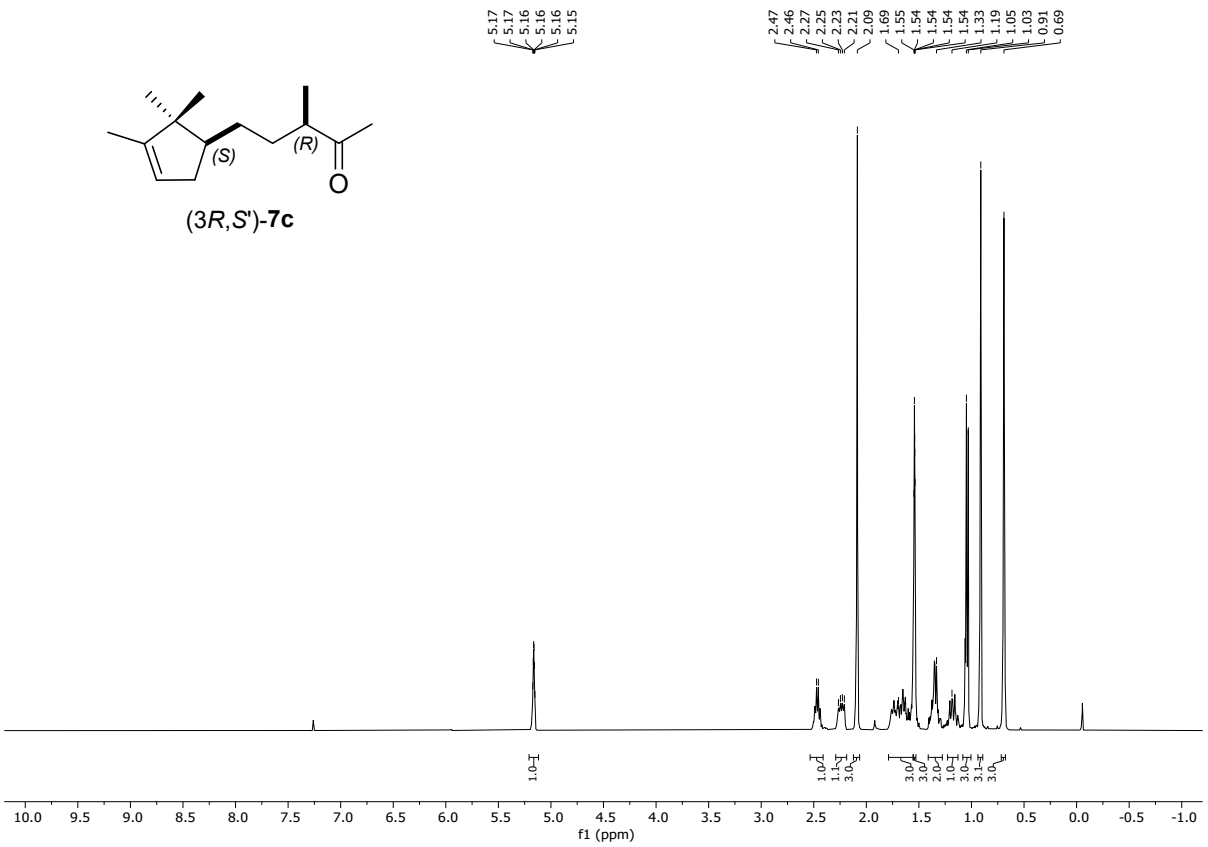


^{1}H-^{1}H COSY (phase sensitive) ($CDCl_3$, 400 MHz)

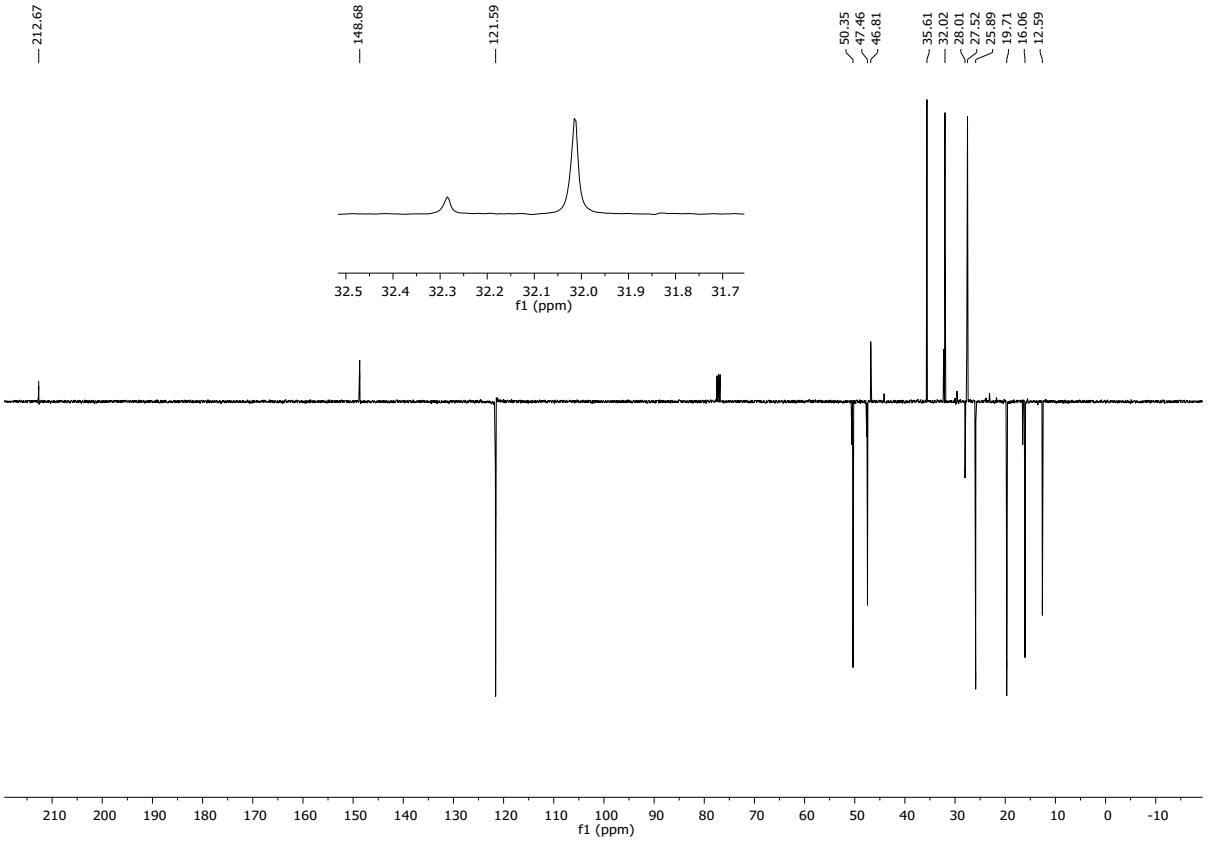


(3*R*,*S*')-**7c**

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

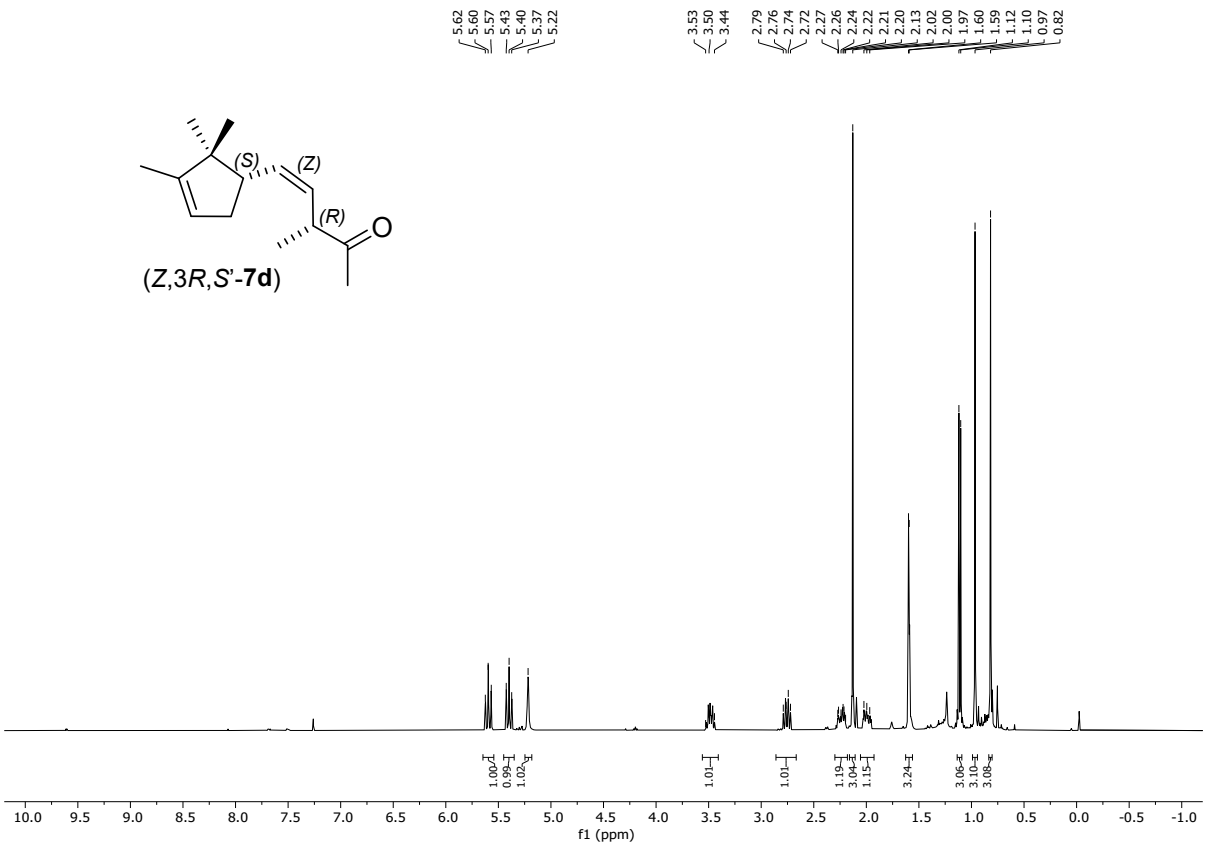


^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz)

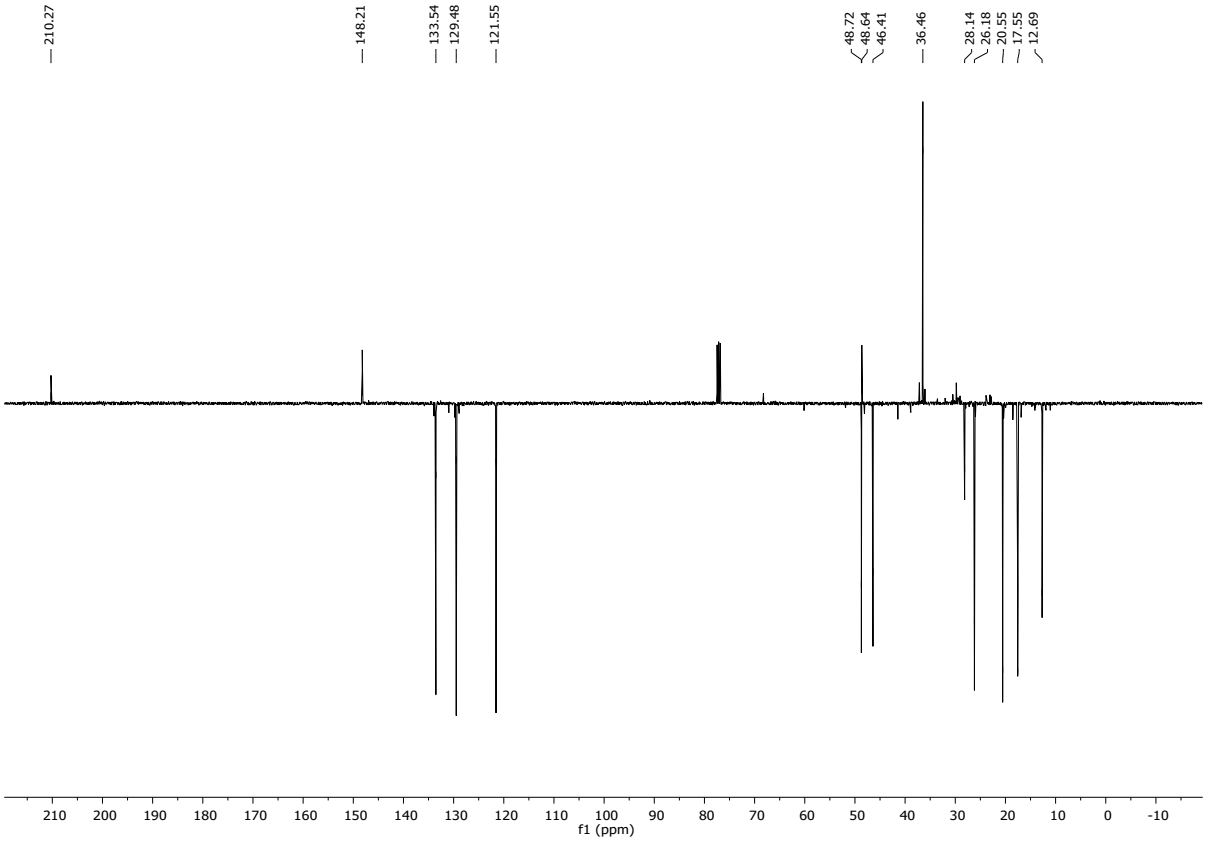


(*Z*,3*R*,*S*')-**7d**

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

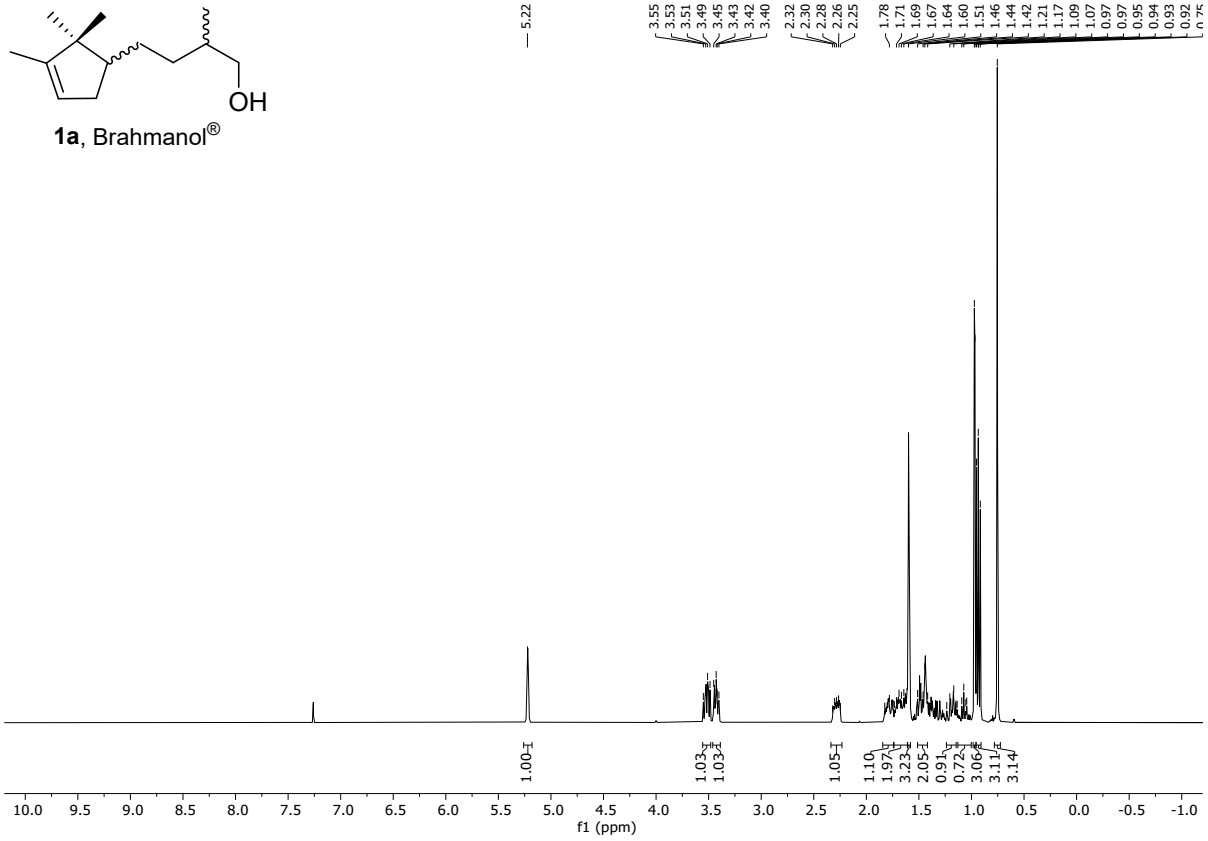


^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz)

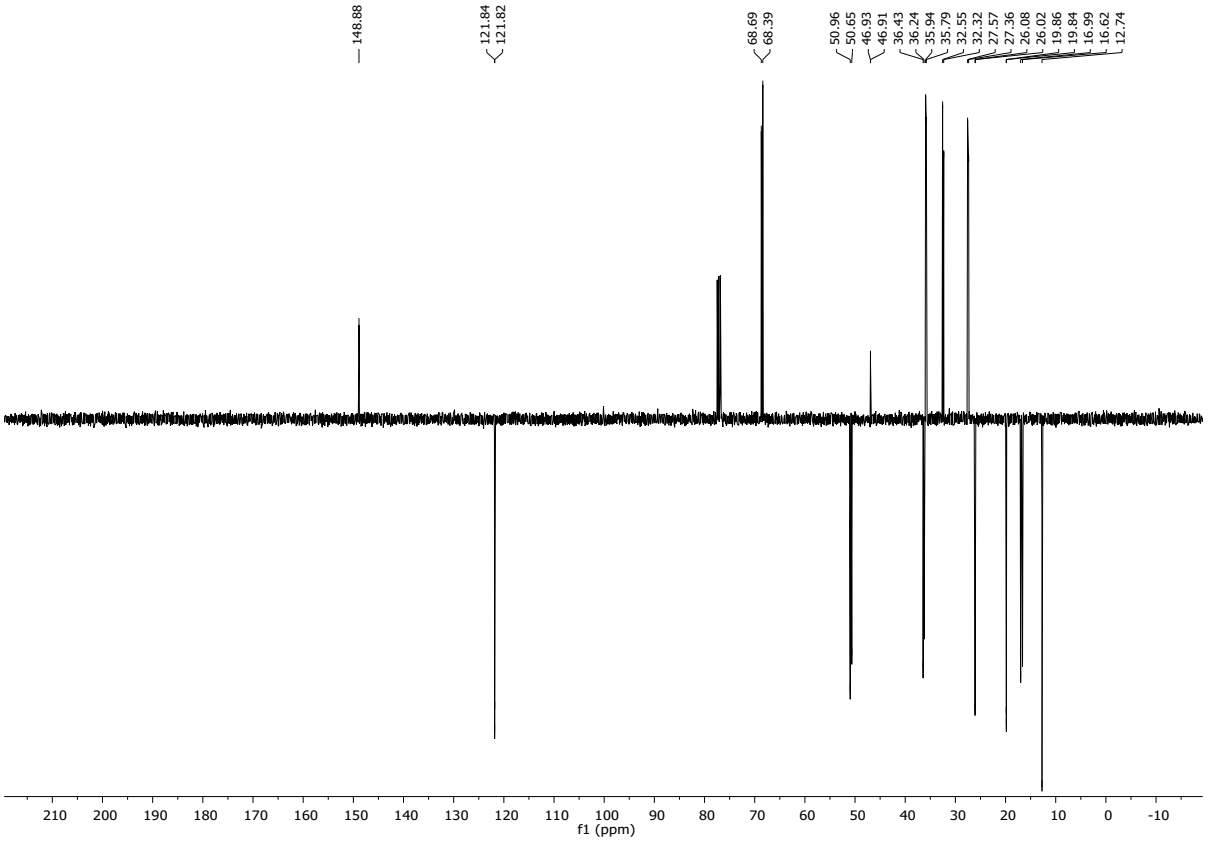


1a, Brahmanol®

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

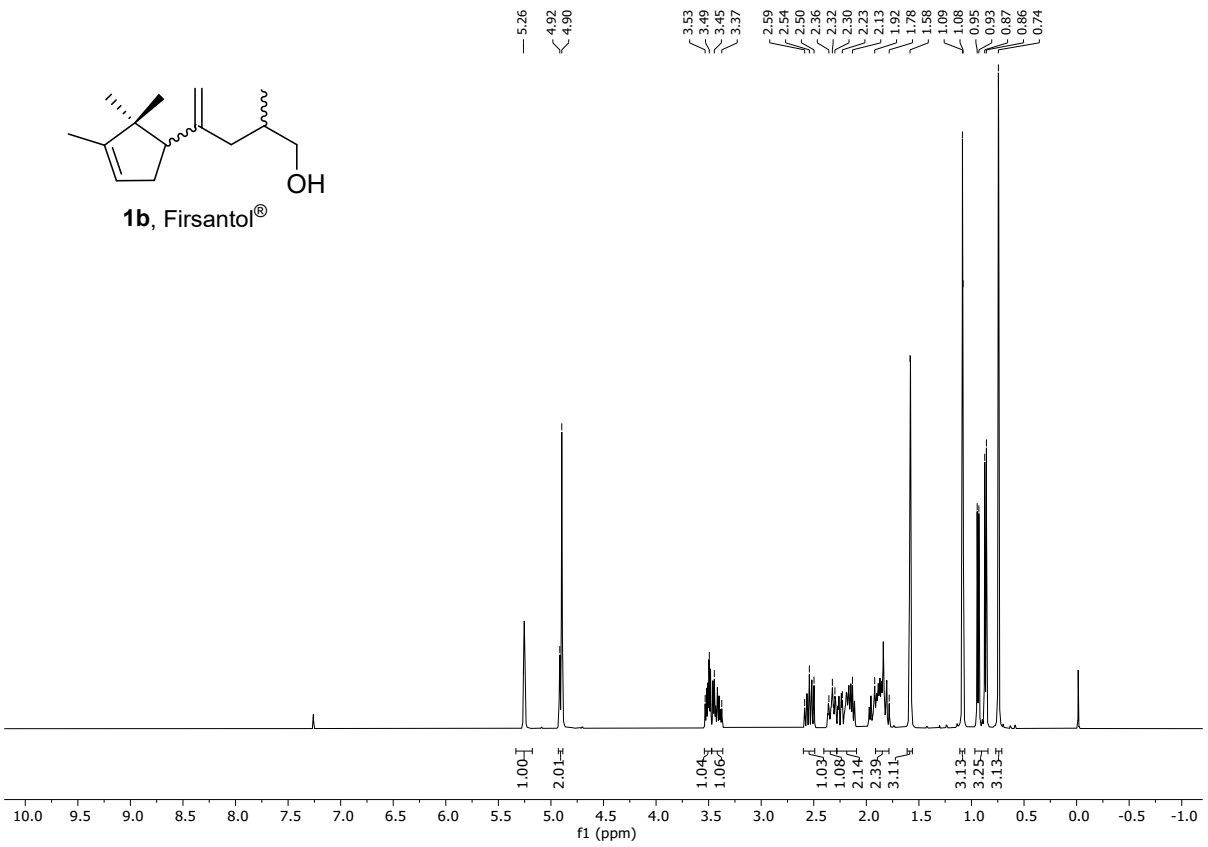


^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz)

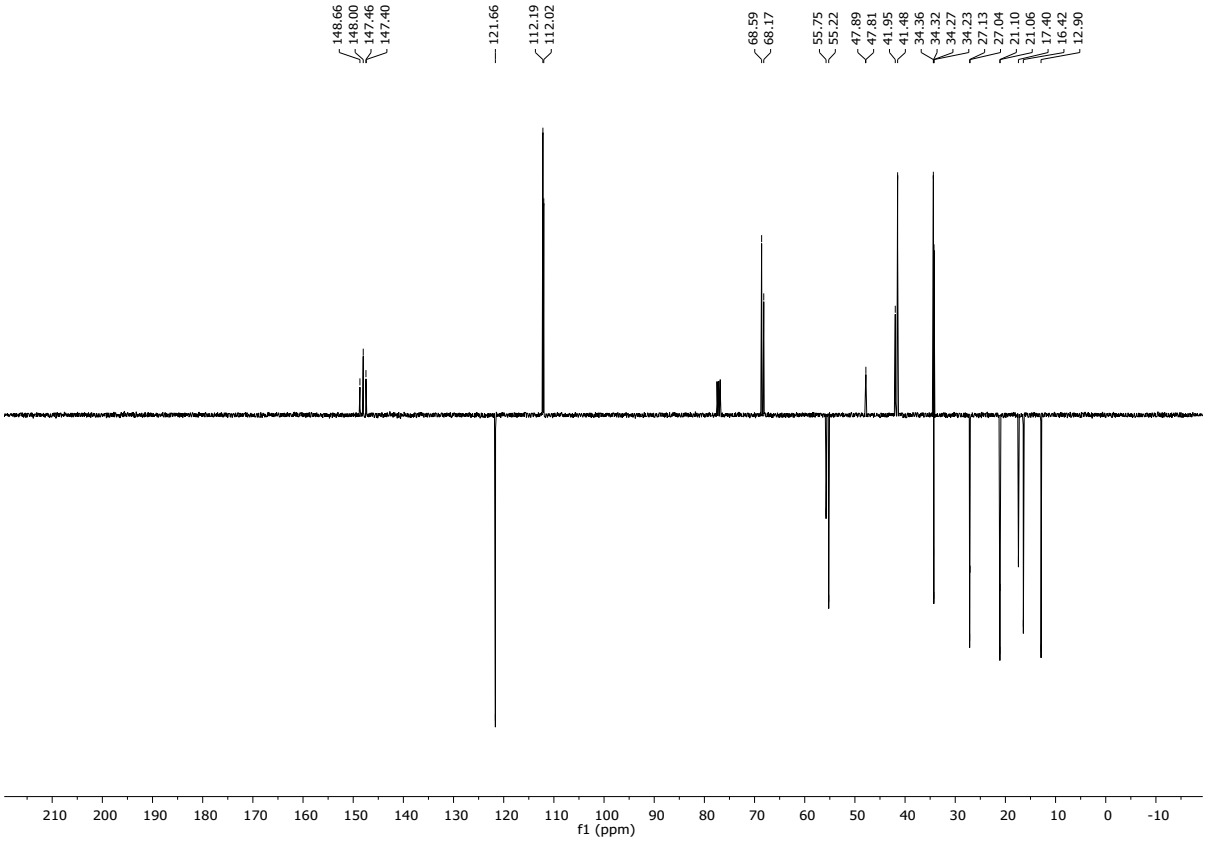


1b, Firsantol®

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

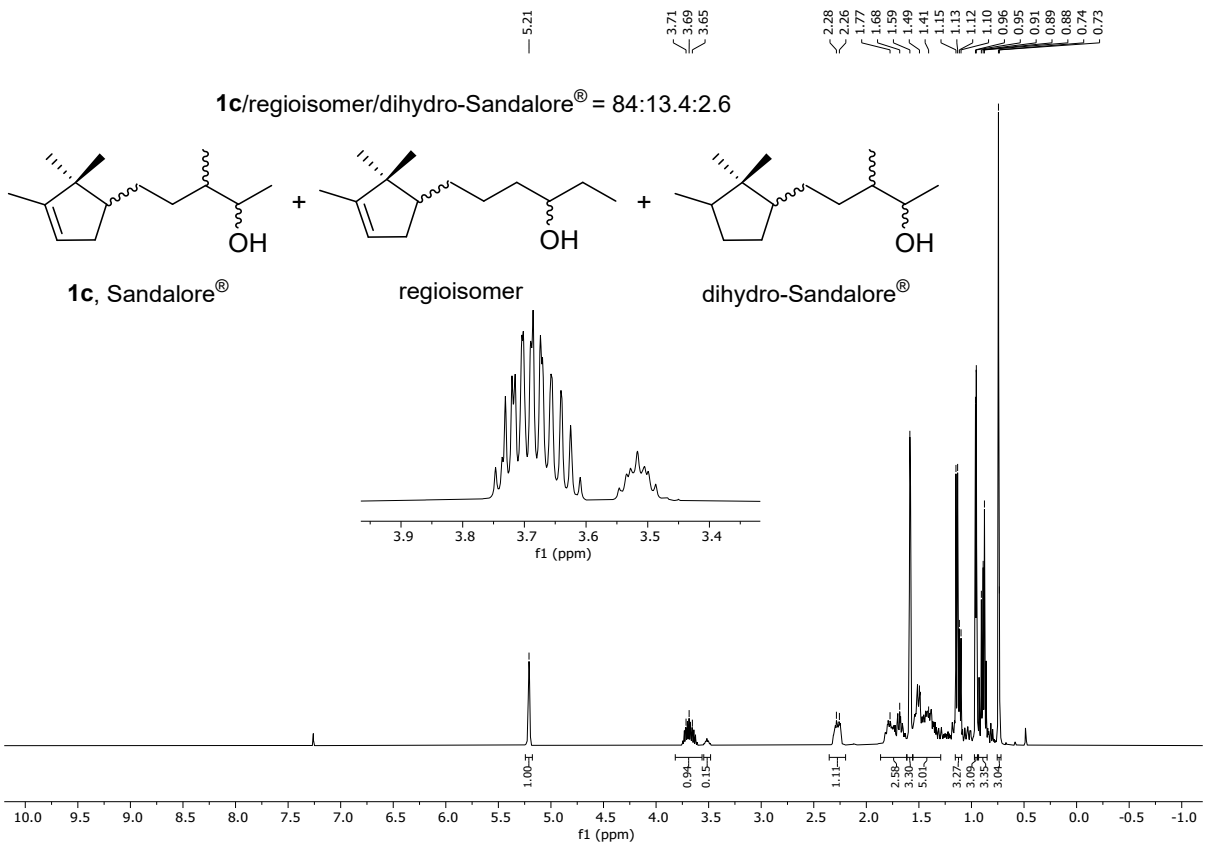


^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz)

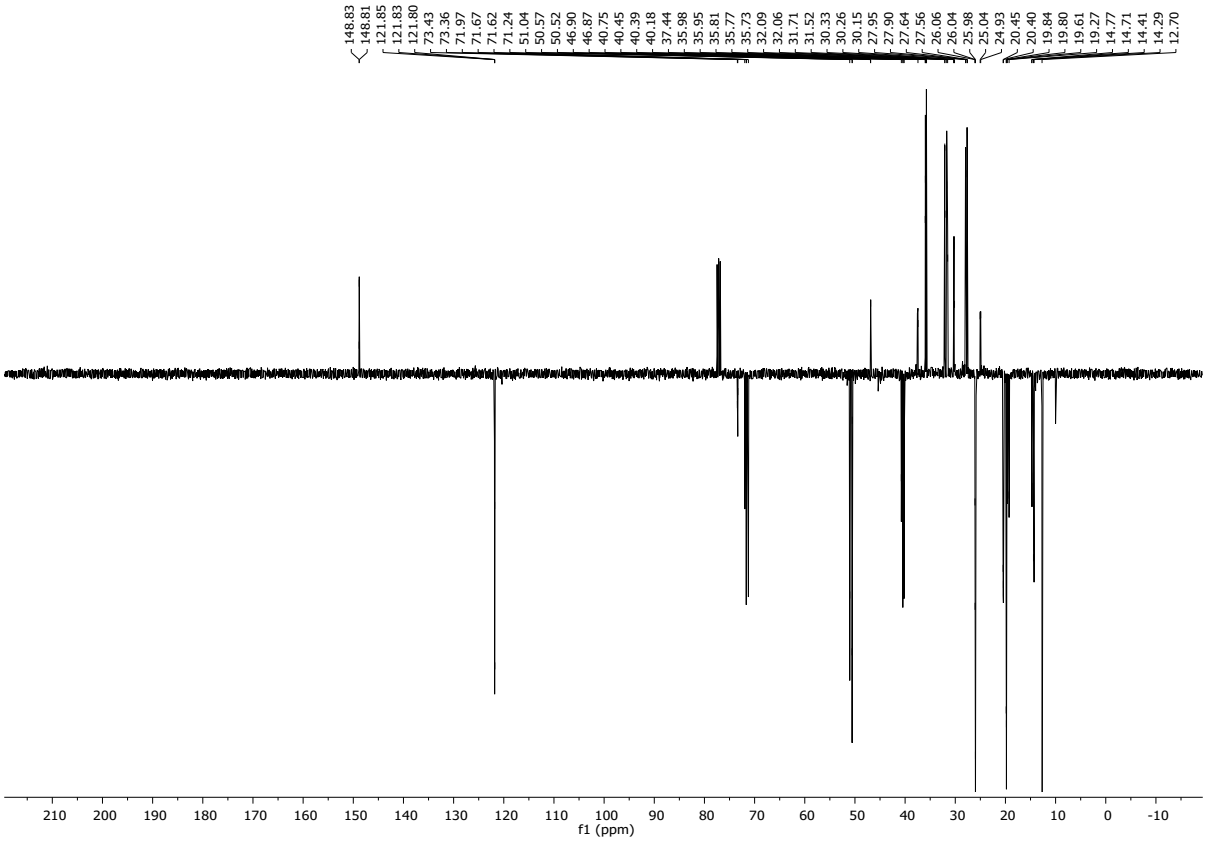


1c, Sandalore®

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

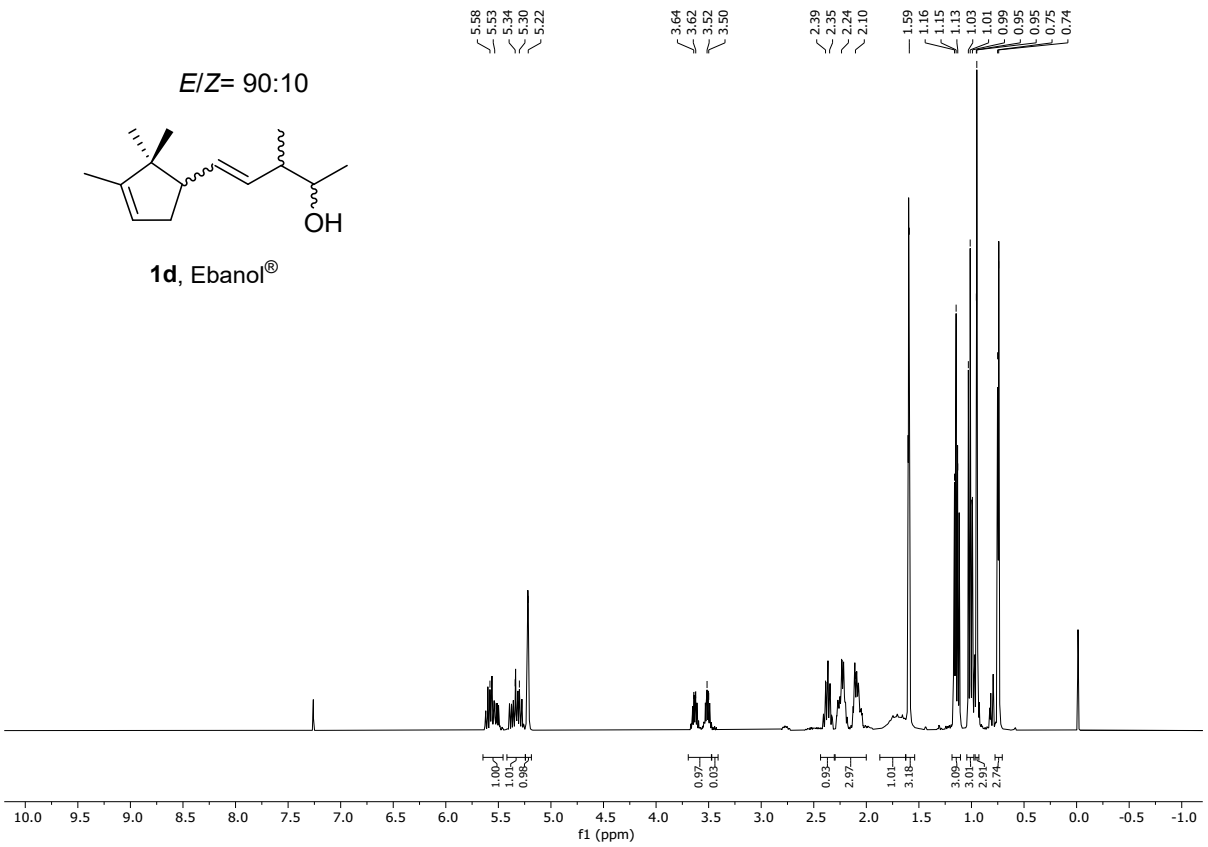


^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz)

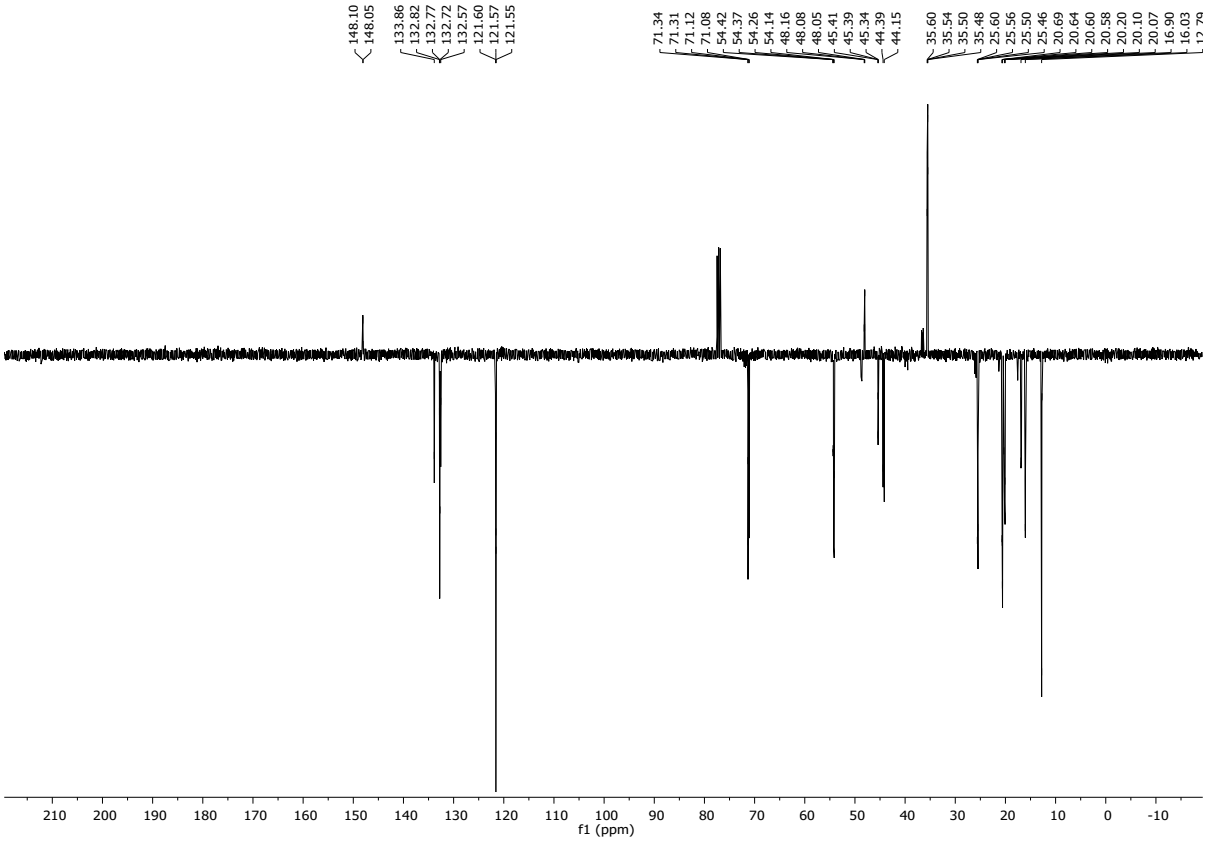


1d, Ebanol®

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

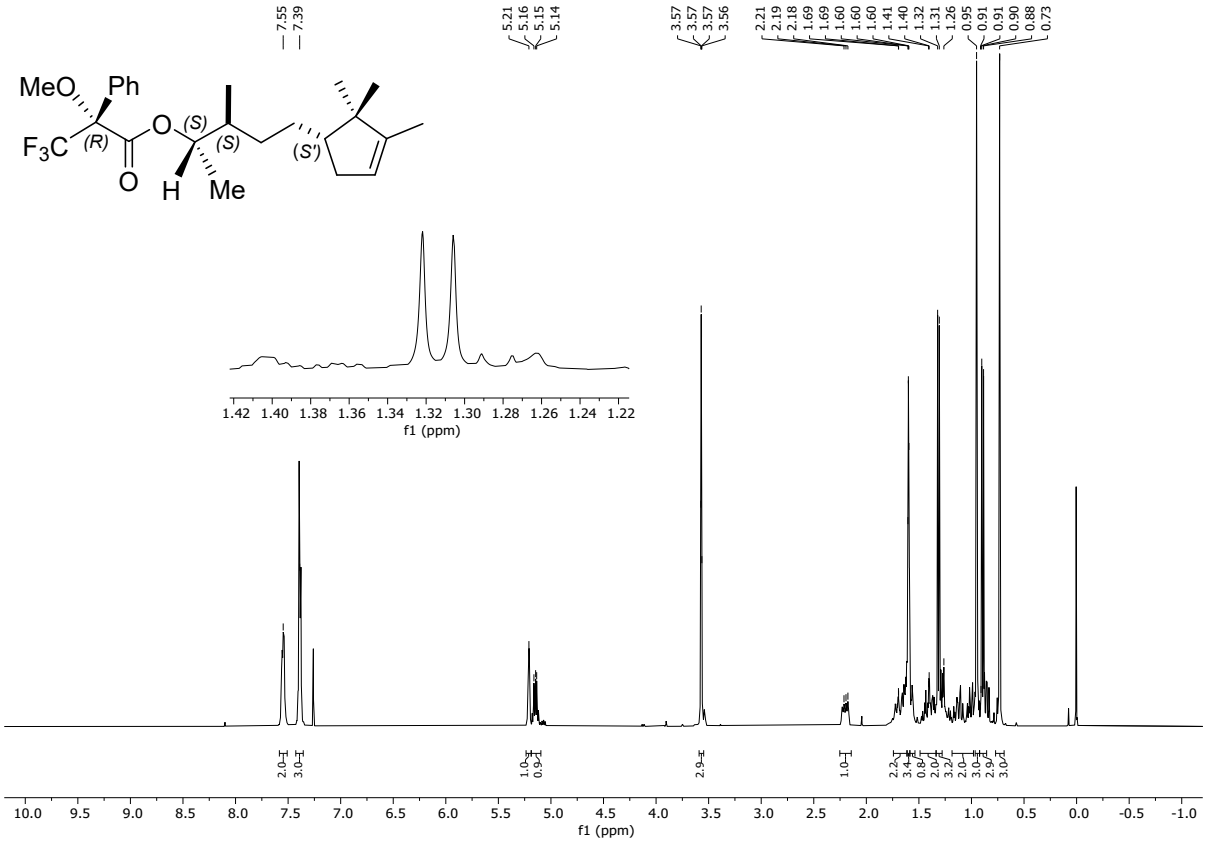


^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz)

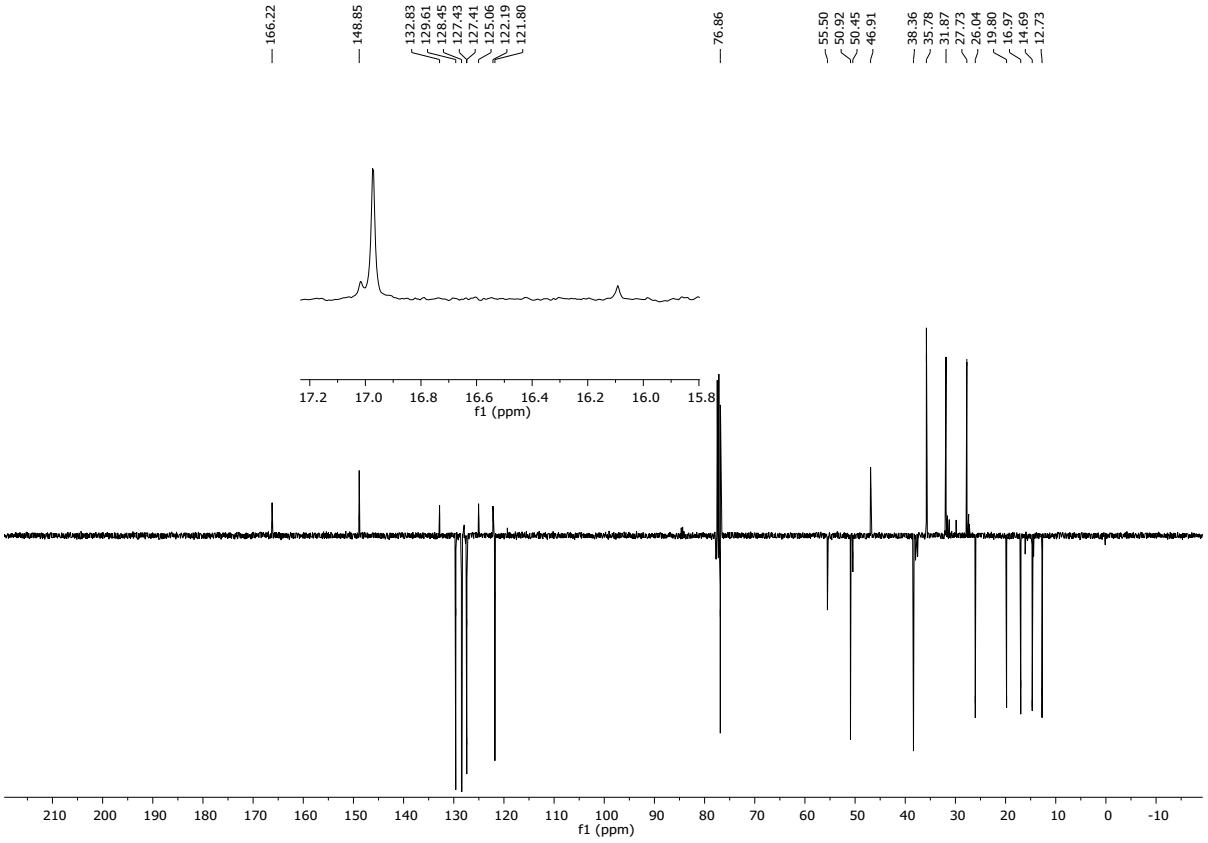


(*R*)-MTPA-Evo440

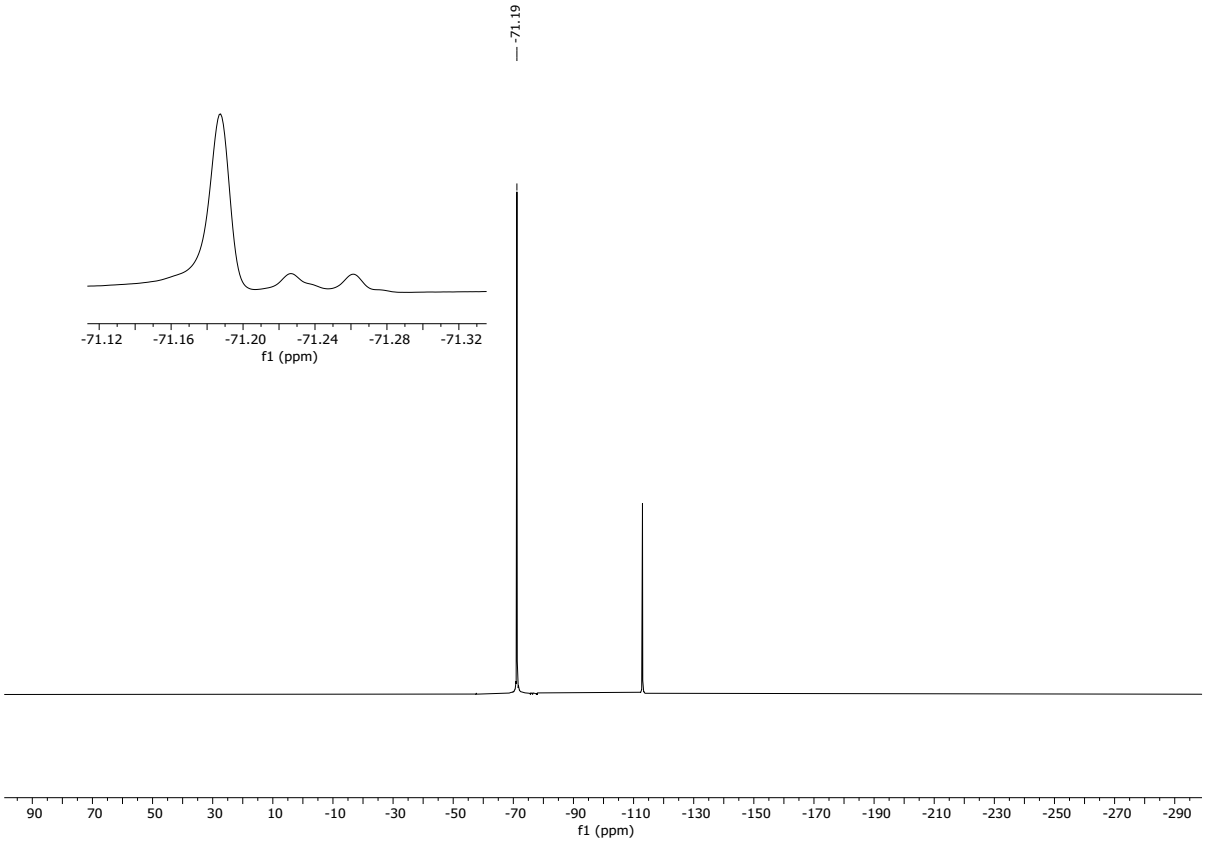
^{1}H-NMR ($CDCl_3$, 400 MHz)



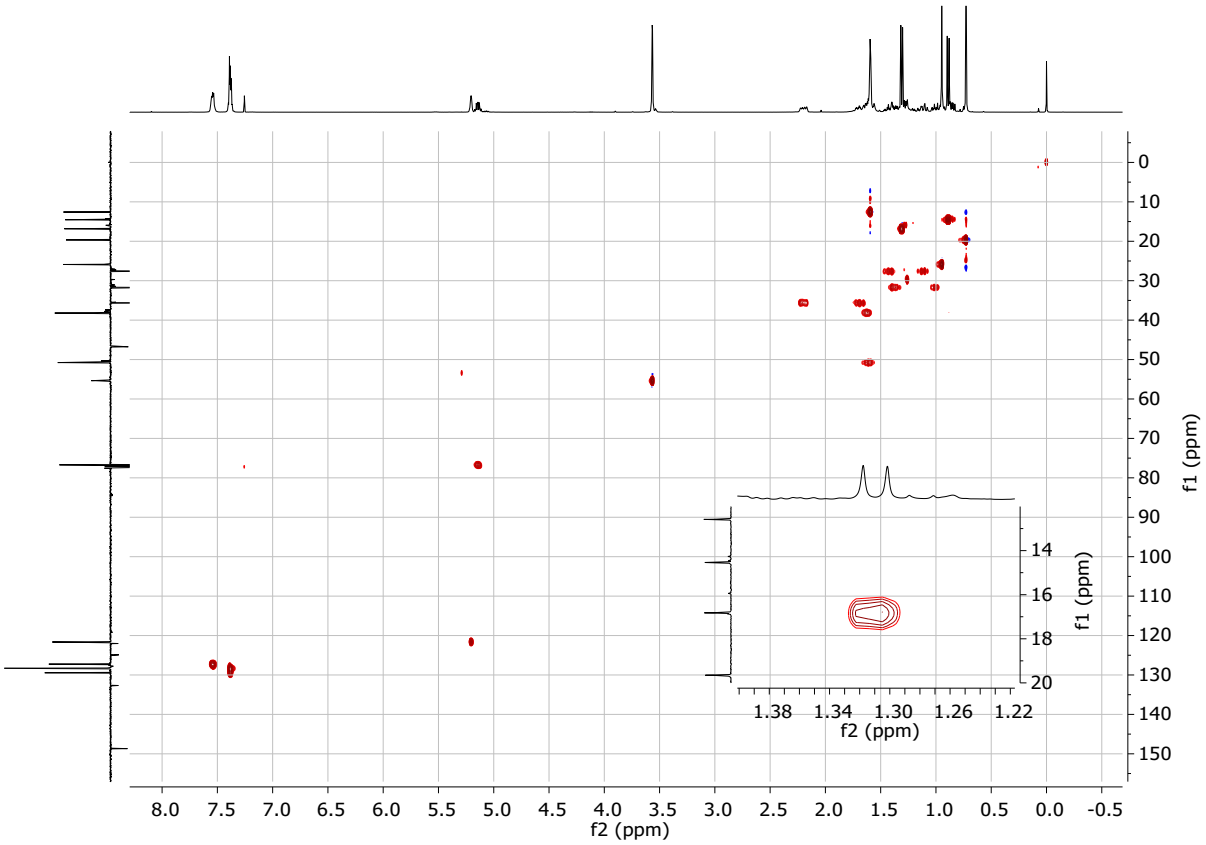
^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz)



$^{19}F\{^{1}H\}$-NMR ($CDCl_3$, 376.56 MHz)

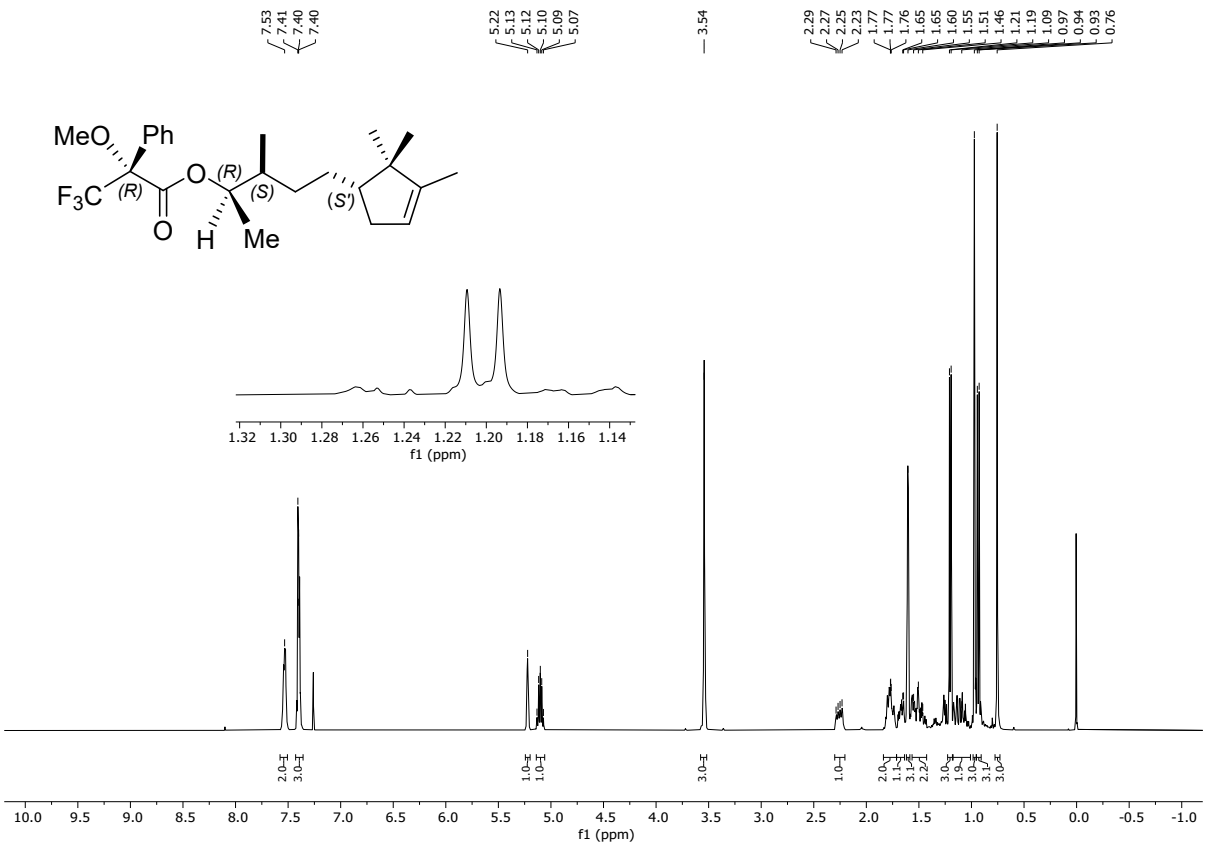


HSQC-(^{1}H-^{13}C)-NMR ($CDCl_3$, 400 MHz)

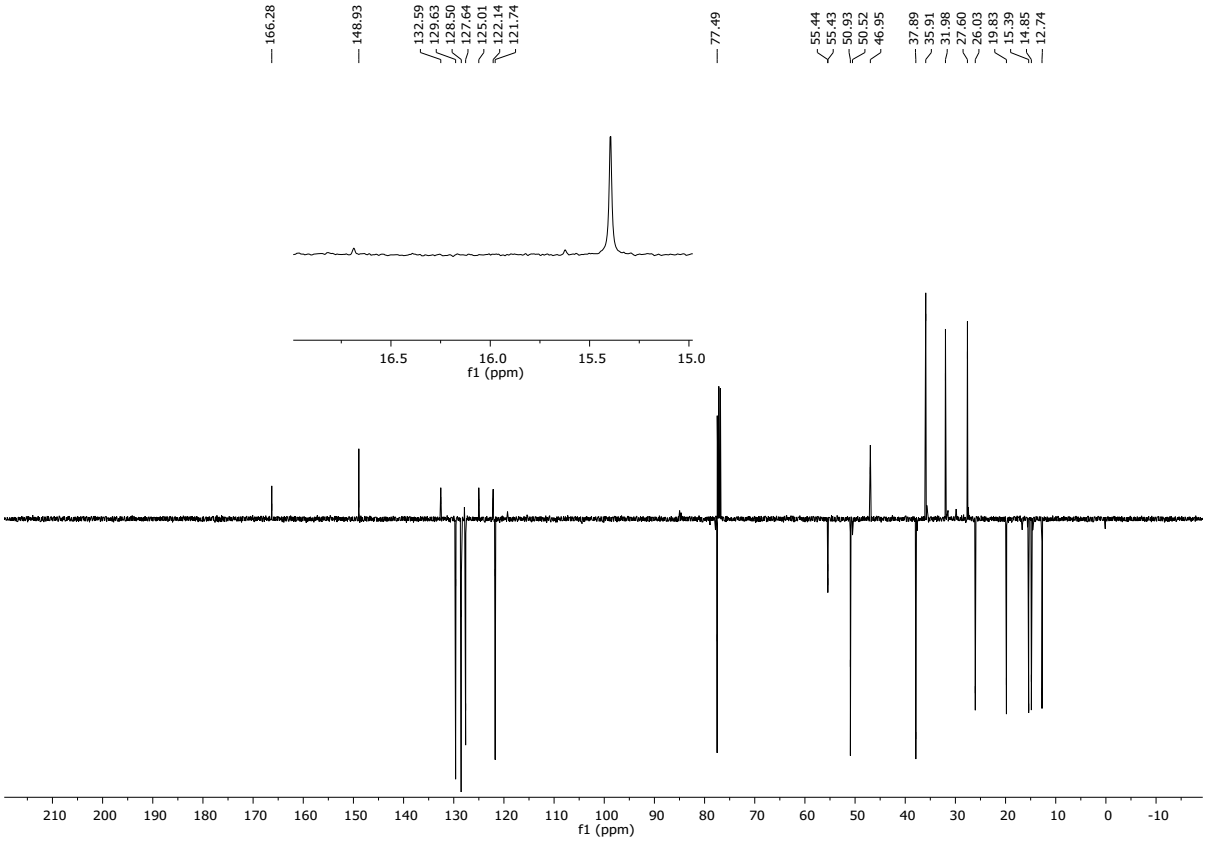


(*R*)-MTPA-Evo270

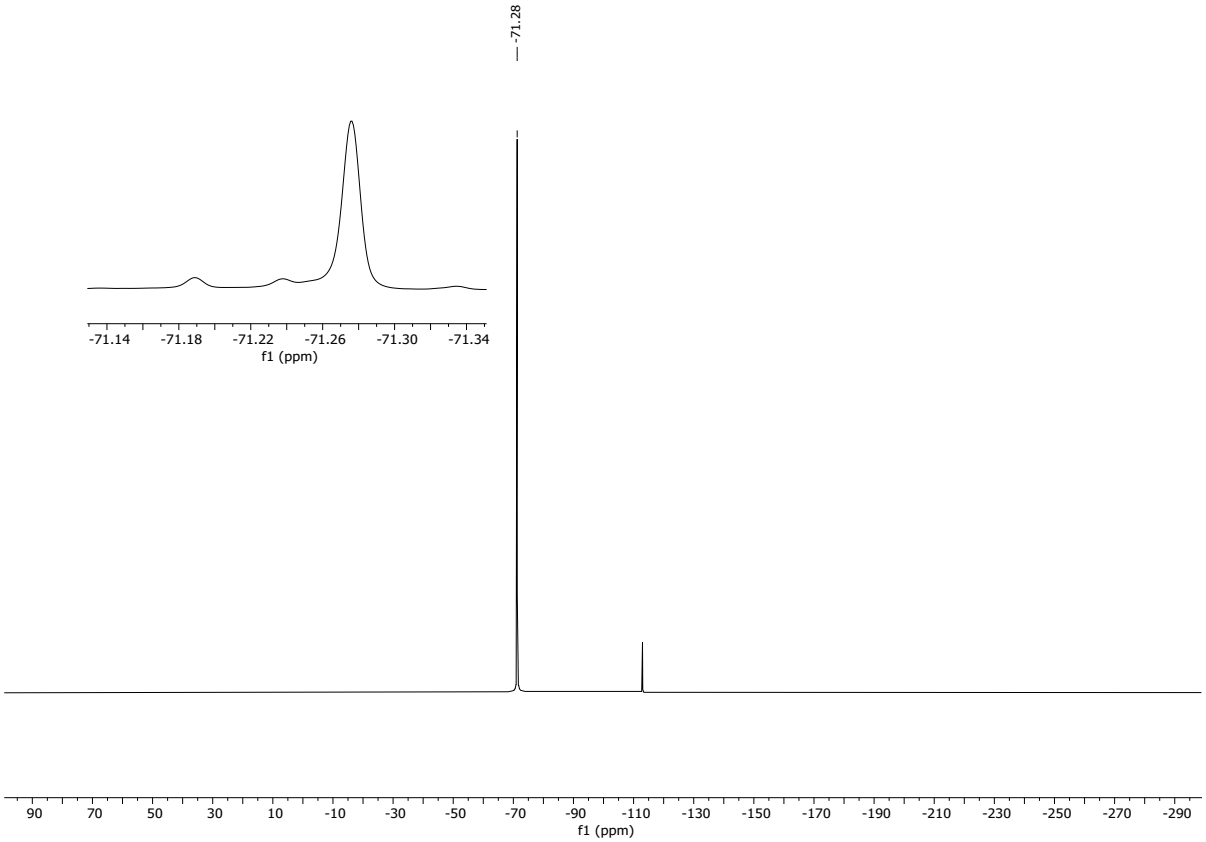
^{1}H-NMR ($CDCl_3$, 400 MHz)



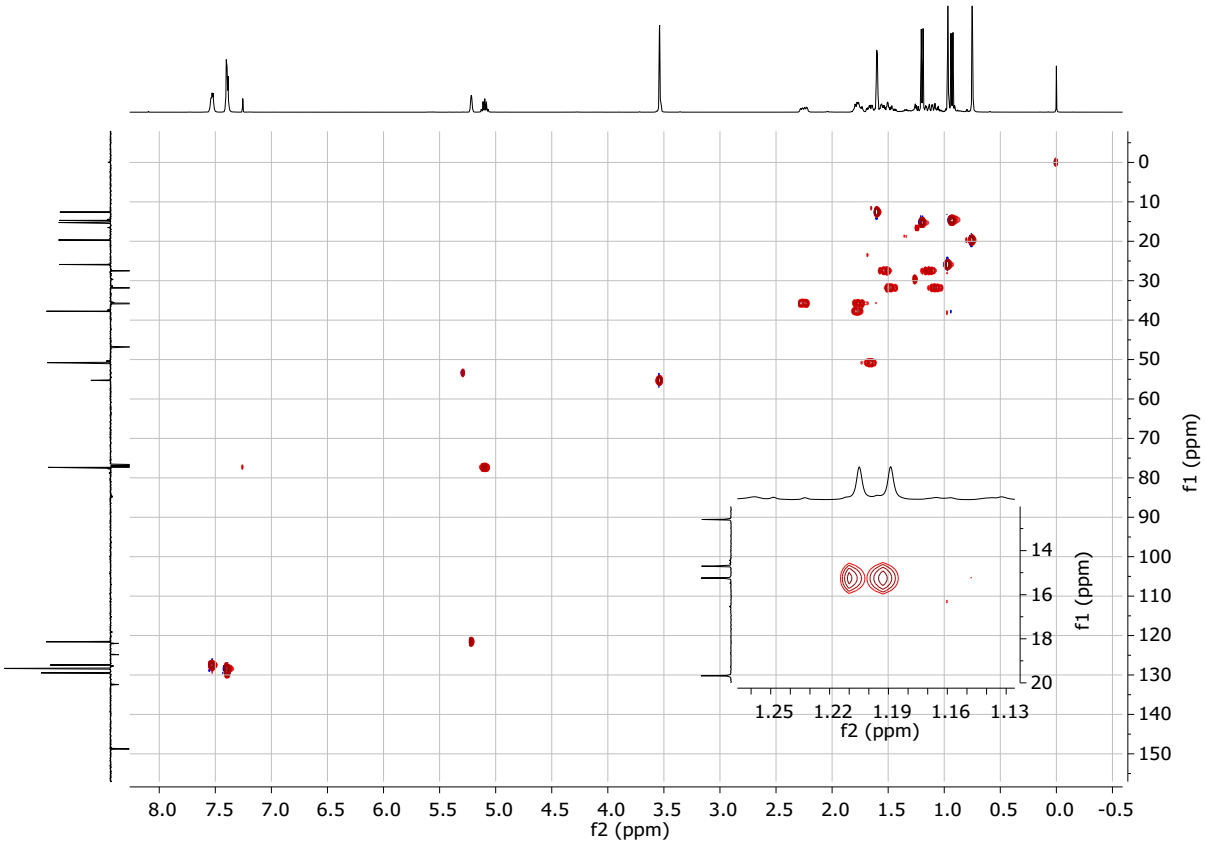
^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz)



$^{19}F\{^{1}H\}$-NMR ($CDCl_3$, 376.56 MHz)

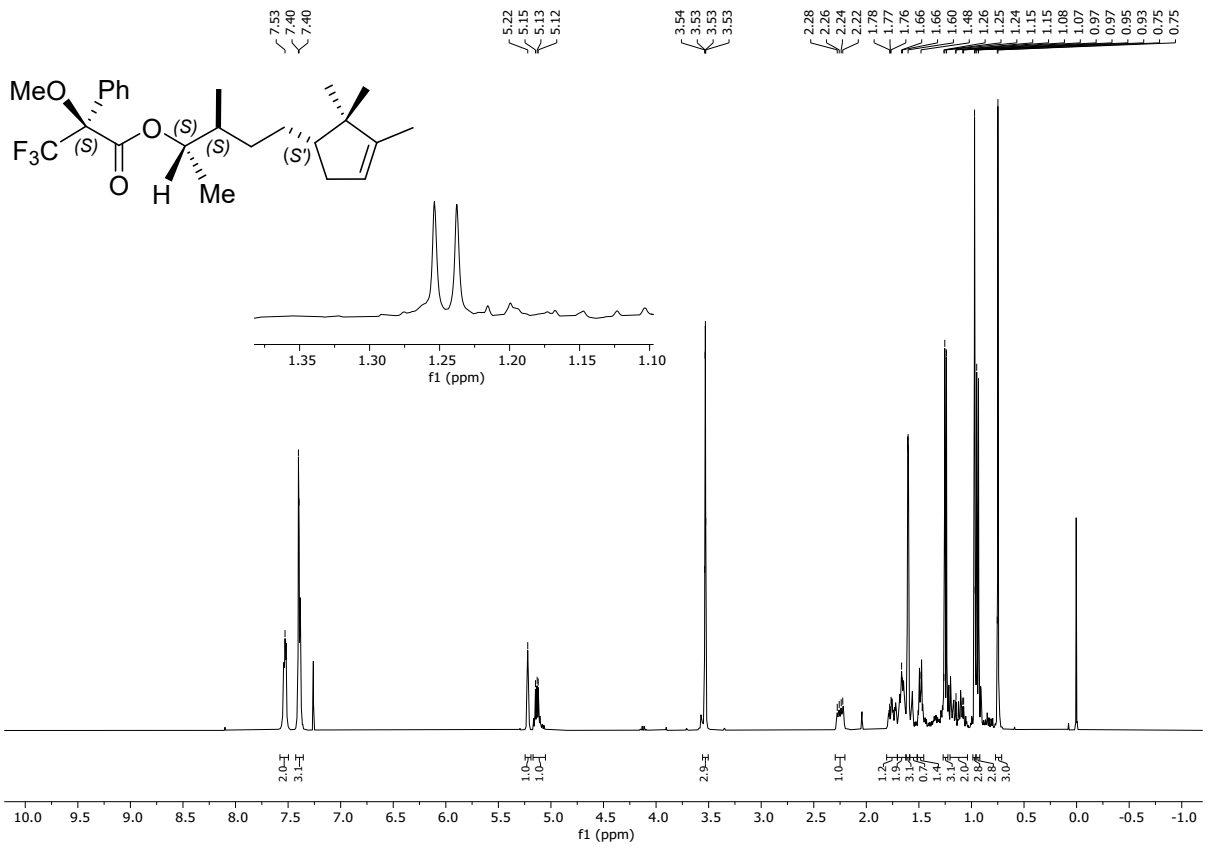


HSQC-(^{1}H-^{13}C)-NMR ($CDCl_3$, 400 MHz)

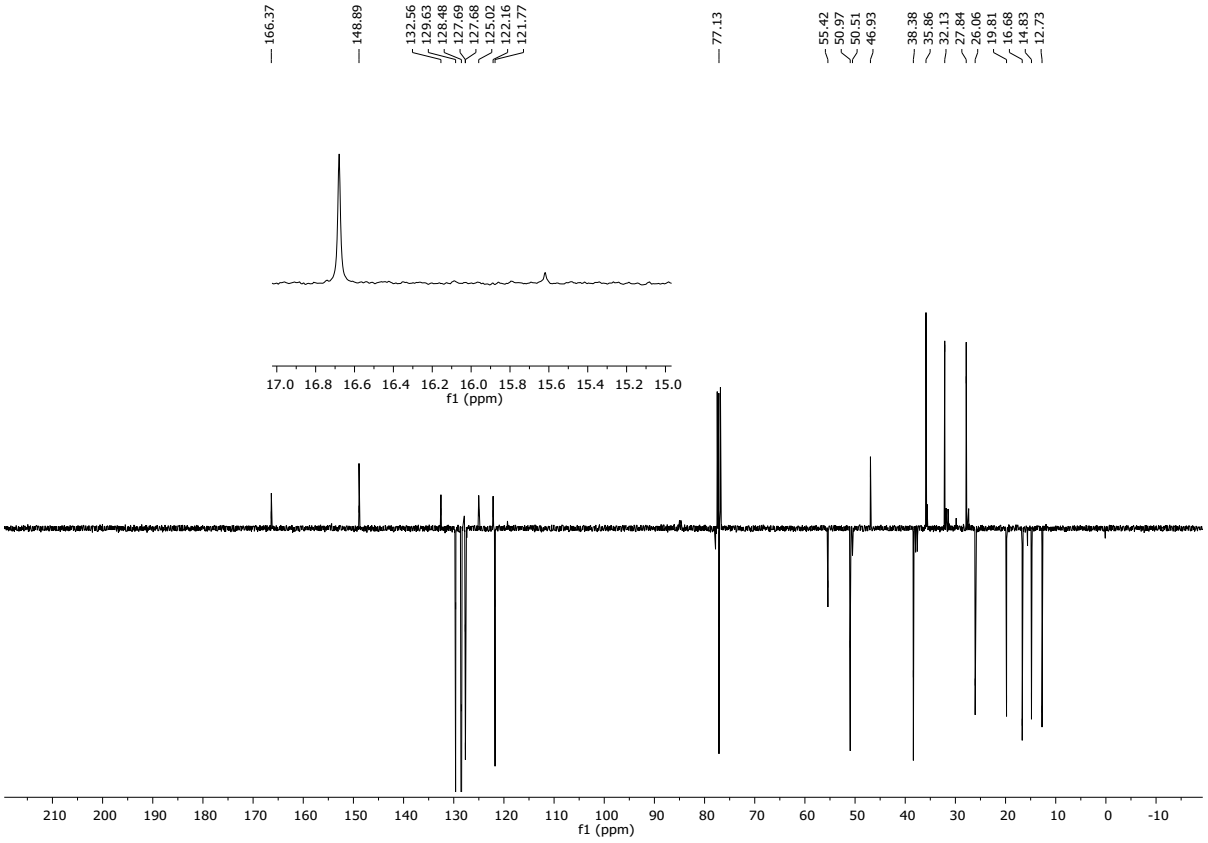


(*S*)-MTPA-Evo440

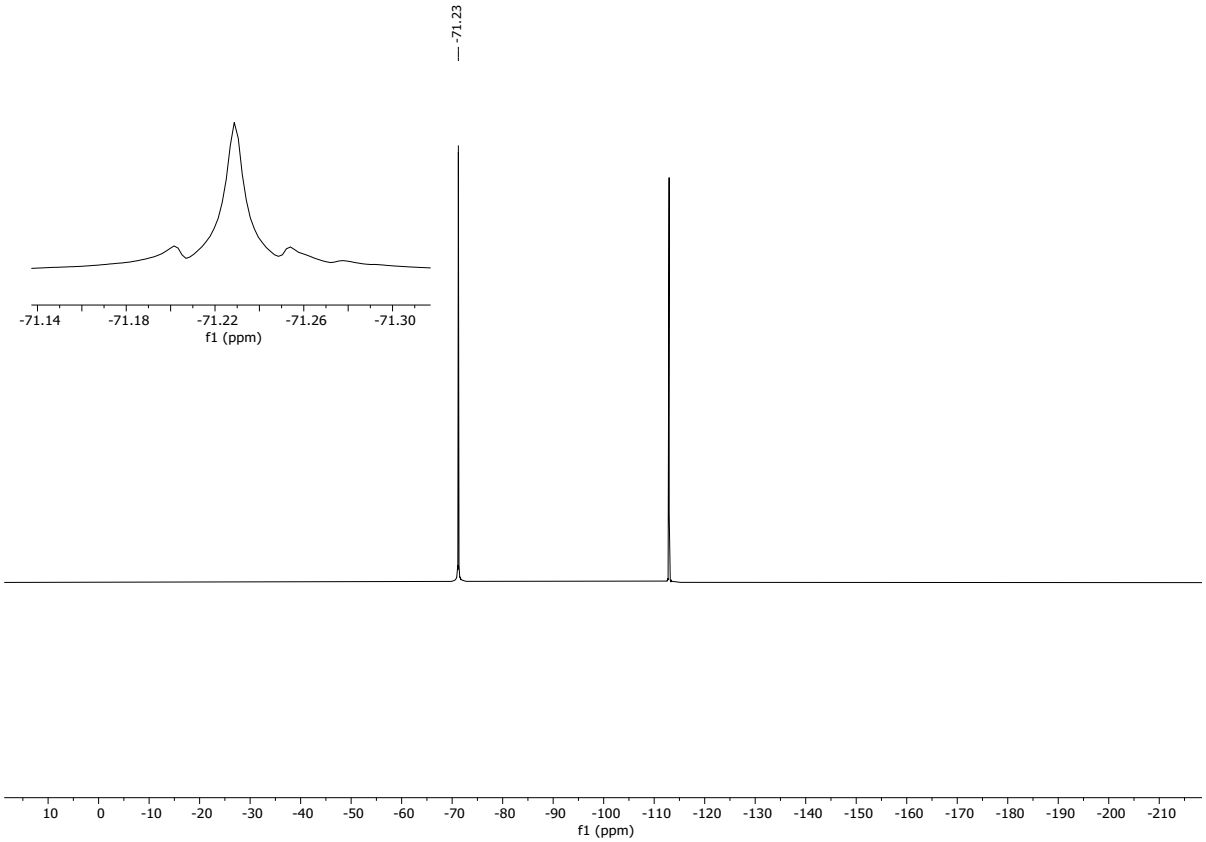
^{1}H-NMR ($CDCl_3$, 400 MHz)



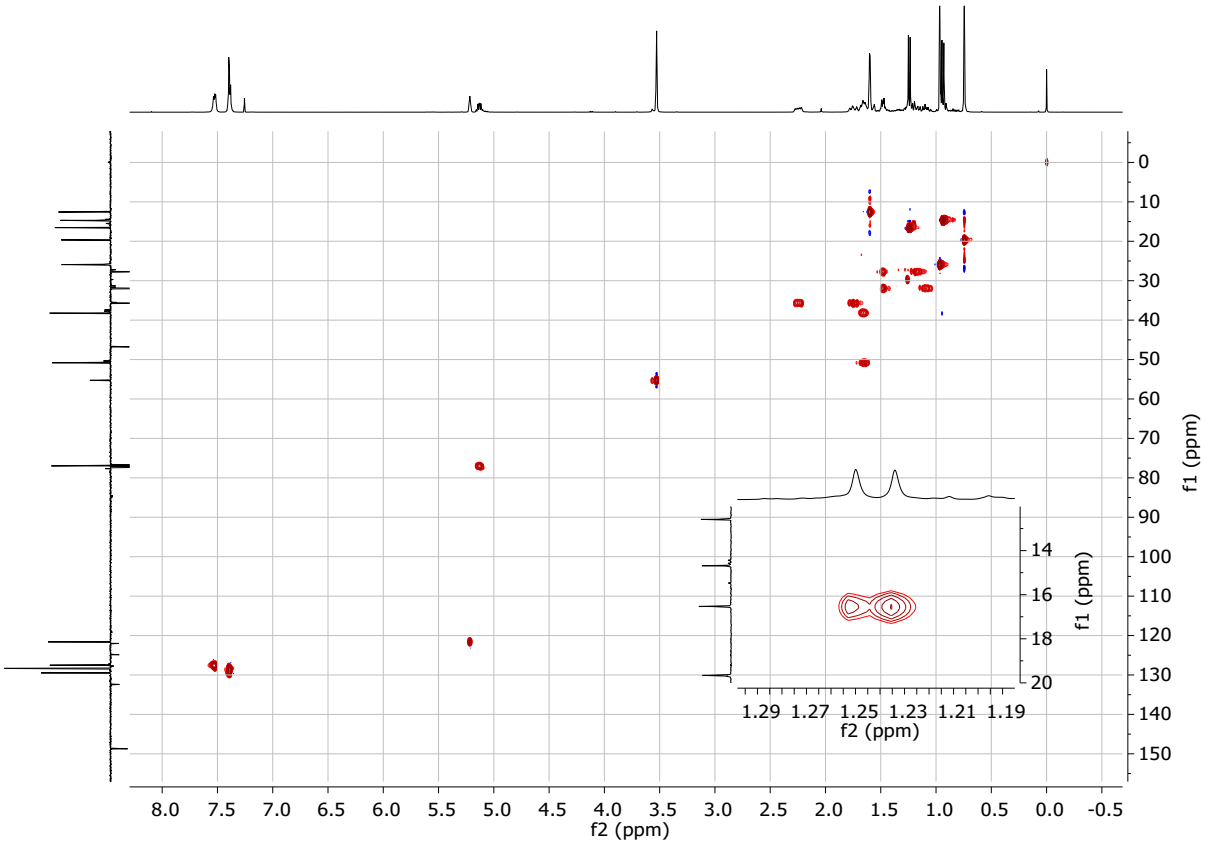
^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz)



$^{19}F\{^{1}H\}$-NMR ($CDCl_3$, 376.56 MHz)

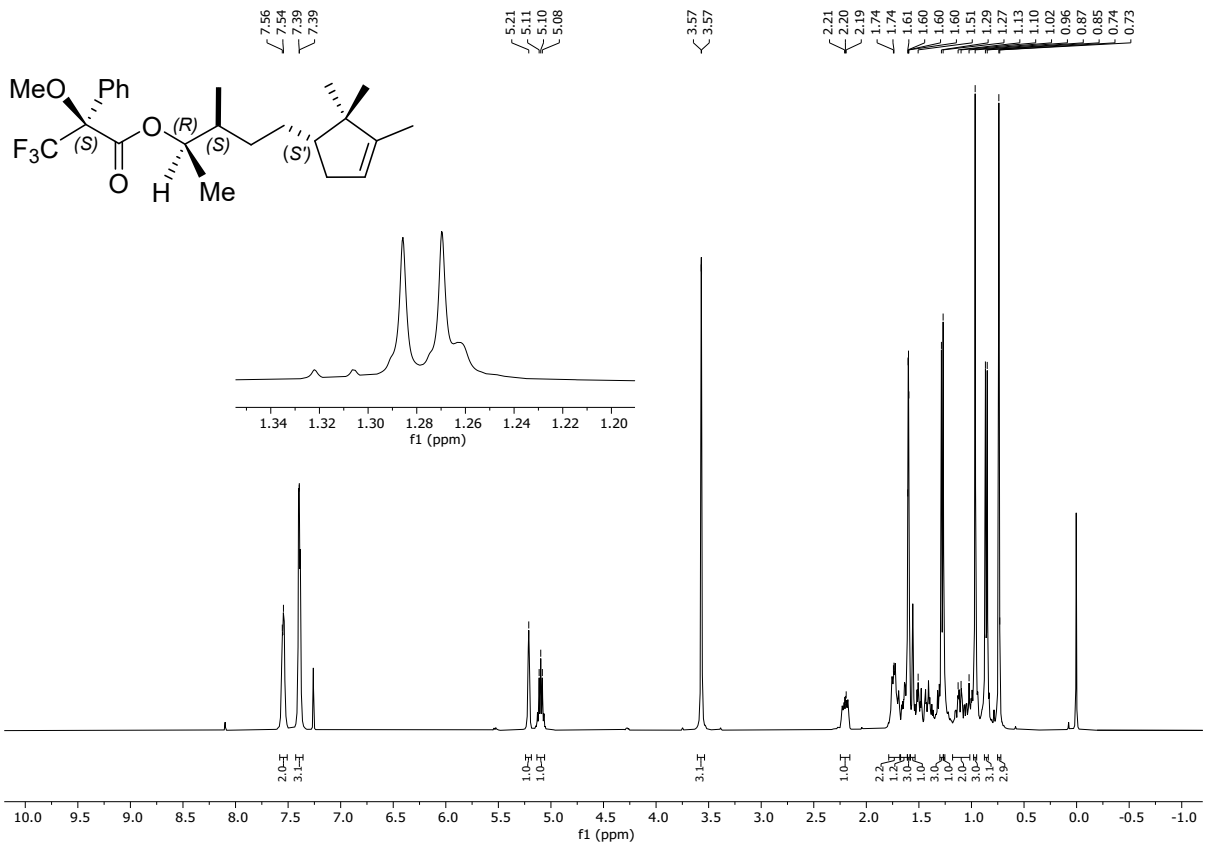


HSQC-(^{1}H-^{13}C)-NMR ($CDCl_3$, 400 MHz)

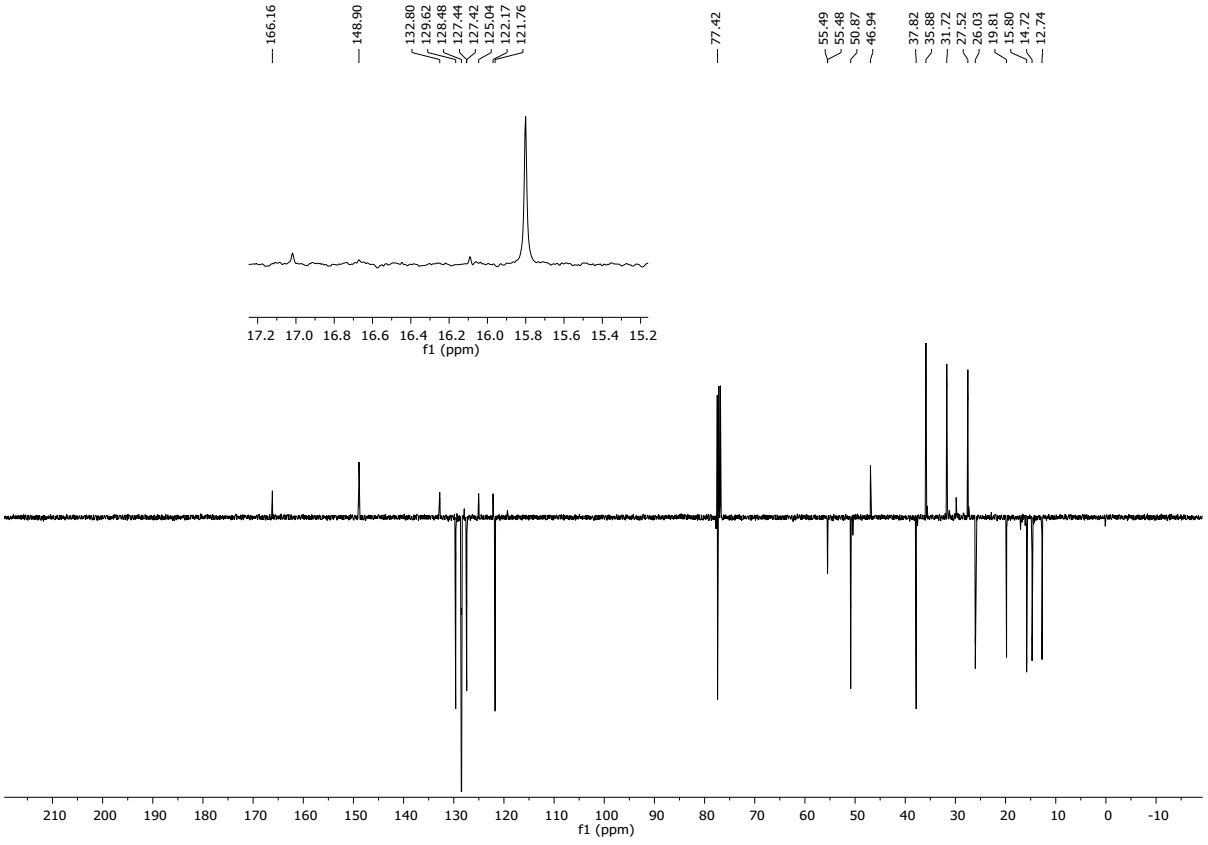


(*S*)-MTPA-Evo270

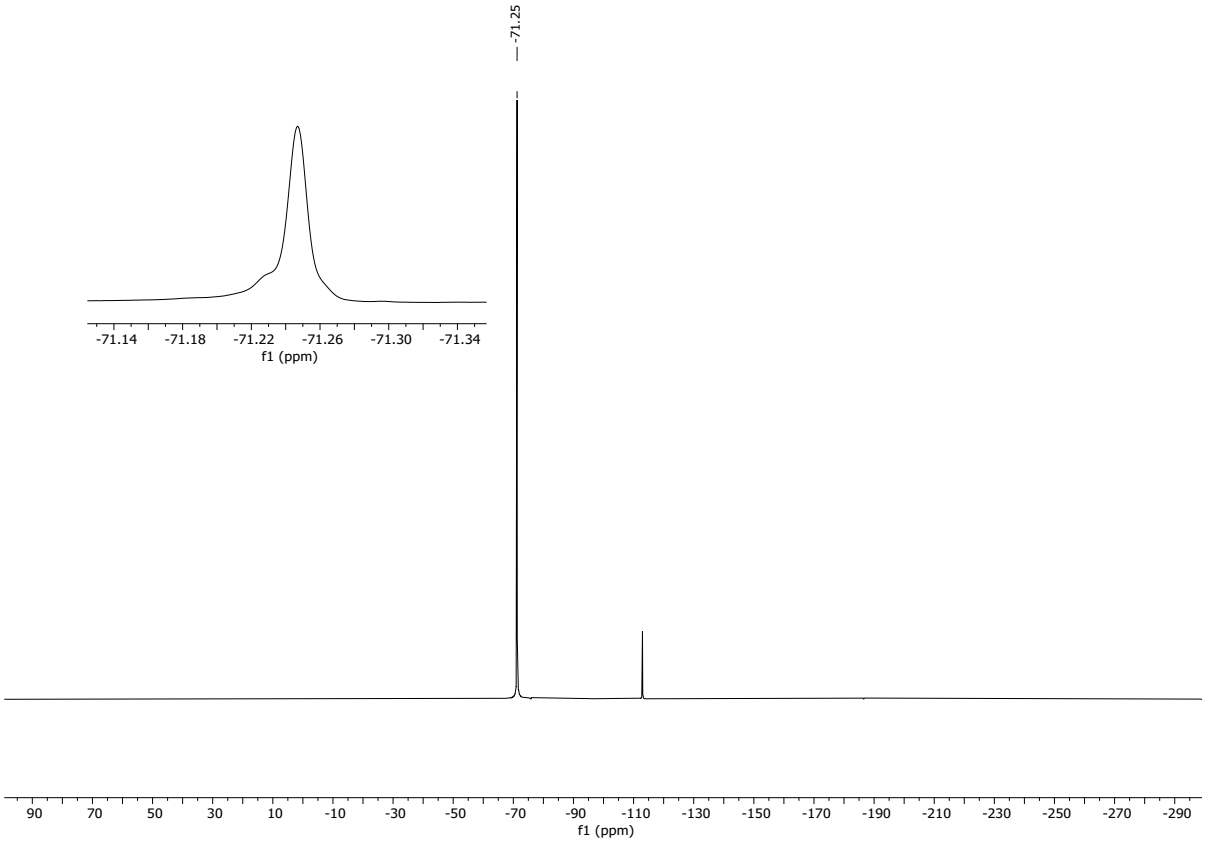
^{1}H-NMR ($CDCl_3$, 400 MHz)



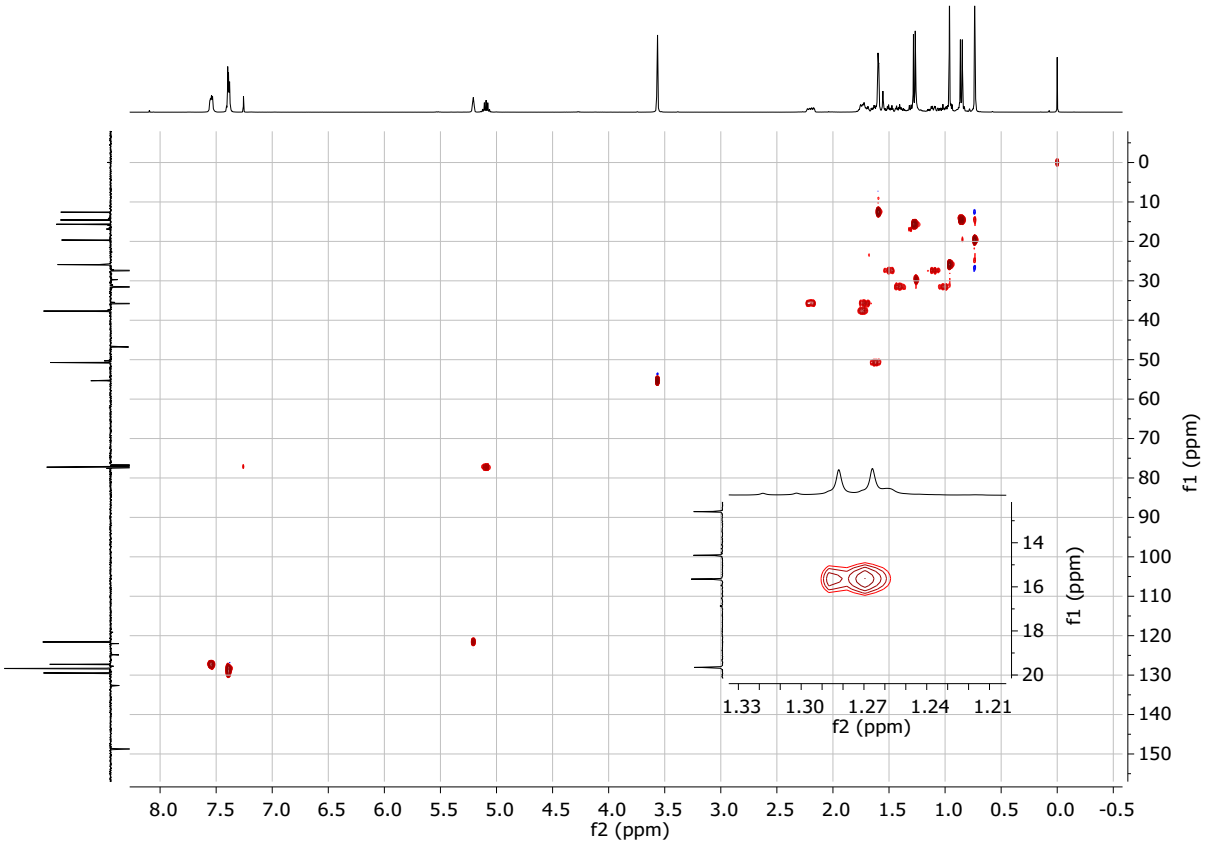
^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz)



$^{19}F\{^{1}H\}$-NMR ($CDCl_3$, 376.56 MHz)

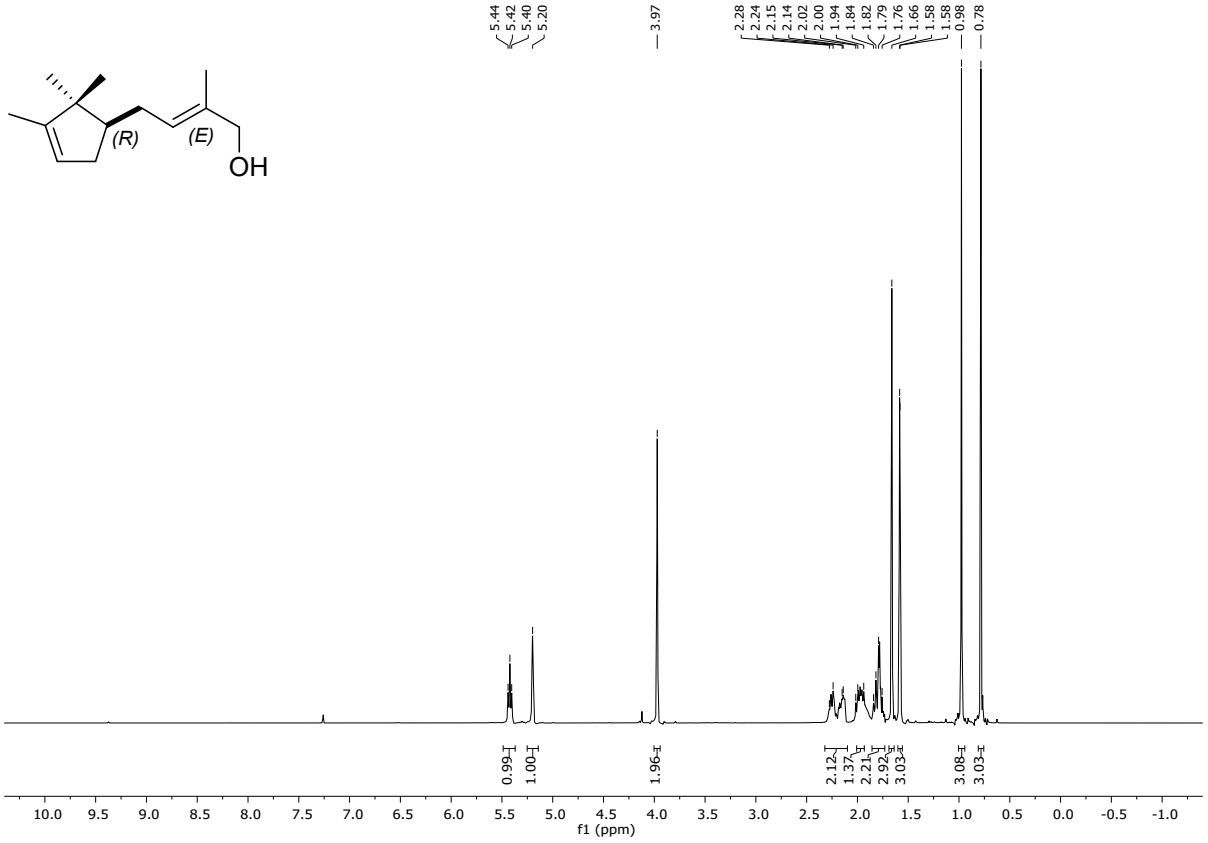


HSQC-(^{1}H-^{13}C)-NMR ($CDCl_3$, 400 MHz)

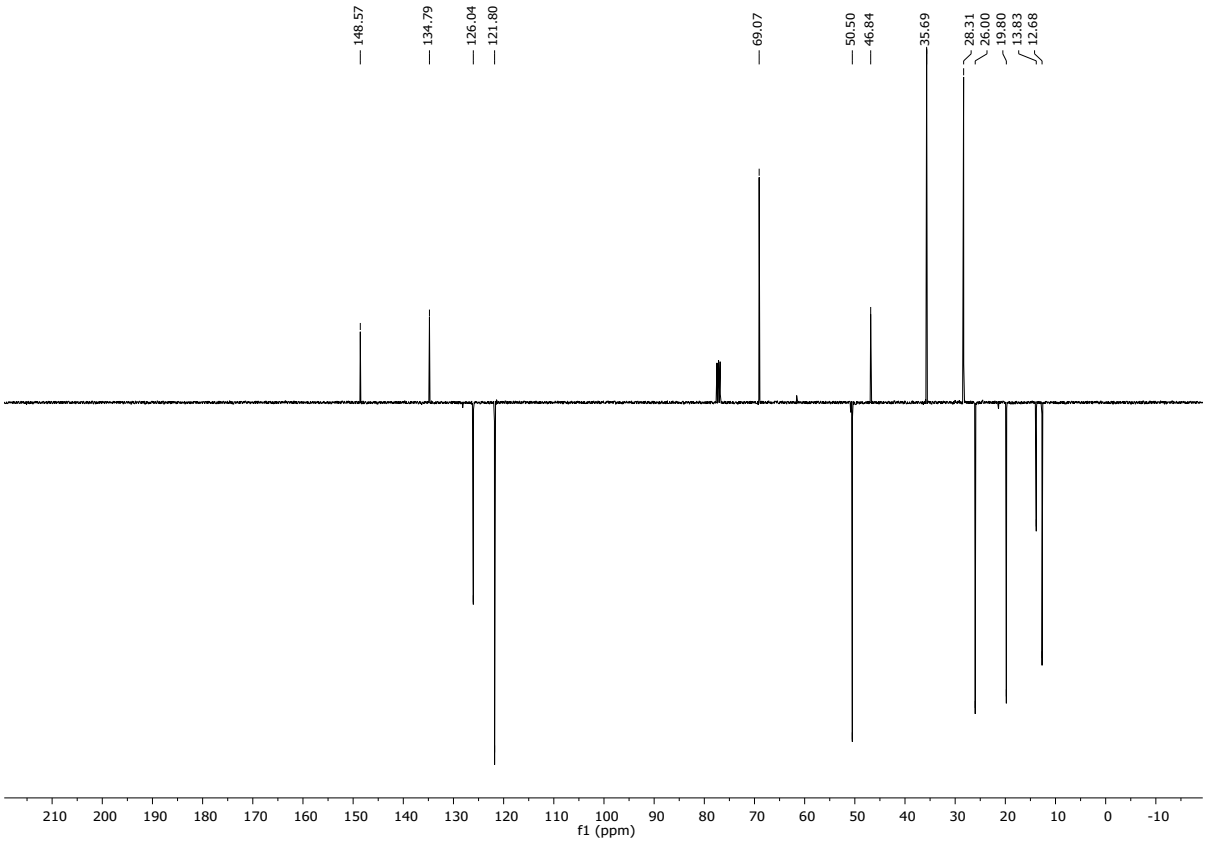


(*R*,*E*)-2-methyl-4-(2,2,3-trimethylcyclopent-3-en-1-yl)but-2-en-1-ol

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



^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz)



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