General

Chemicals were purchased from Sigma Aldrich Chemie GmbH (Steinheim, Germany), Carbolution Chemicals GmbH (St. Ingbert, Germany), or Carl Roth (Karlsruhe, Germany) and used without purification. Solvents for column chromatography were purchased in p.a. grade and purified by distillation. Thin-layer chromatography was performed with 0.2 mm precoated plastic sheets Polygram Sil G/UV254 purchased from Machery-Nagel (Düren, Germany). Column chromatography was performed using silica gel 60 (0.040-0.060 nm) purchased from Merck (Darmstadt, Germany).

GC/MS

GC/MS analyses were carried out on a 7890B/5977A series gas chromatography/mass selective detector (Agilent, Santa Clara, CA, USA). The GC was equipped with an HP5-MS fused silica capillary column (30 m, 0.25 mm i. d., 0.50 µm film; Agilent) and operated using the settings: 1) inlet pressure: 77.1 kPa, He at 23.3 mL min^{-1}, 2) injection volume: 1 µL, 3) temperature program: 5 min at 50 °C then increasing 10 °C min^{-1} to 320 °C, 4) splitless or split ratio 50:1, 60 s valve time, and 5) carrier gas: He at 1 mL min^{-1}. The MS was operated with settings: 1) source: 230 °C, 2) transfer line: 250 °C, 3) quadrupole: 150 °C and 4) electron energy: 70 eV. Retention indices (*I*) were determined from a homologous series of *n*-alkanes (C_7-C_{40}).

Chiral GC

An Agilent GC 7820A GC equipped with an FID detector and an Agilent Cyclosil-B capillary column (30 m, 0.25 mm inner diameter, 0.25 µm film) was used for chiral GC analysis. For analysis of 2,3-dimethylbut-3-en-1-ol (**S4**), the GC was programmed as follows: starting from 50 °C, increasing with 2 °C/min to 120 °C, then further increasing with 40 °C/min to 245 °C while holding this temperature for 5 min. Inlet temperature: 250 °C, injection volume: 1 µL, carrier gas: H_2 at 2.3 mL/min.

NMR spectroscopy

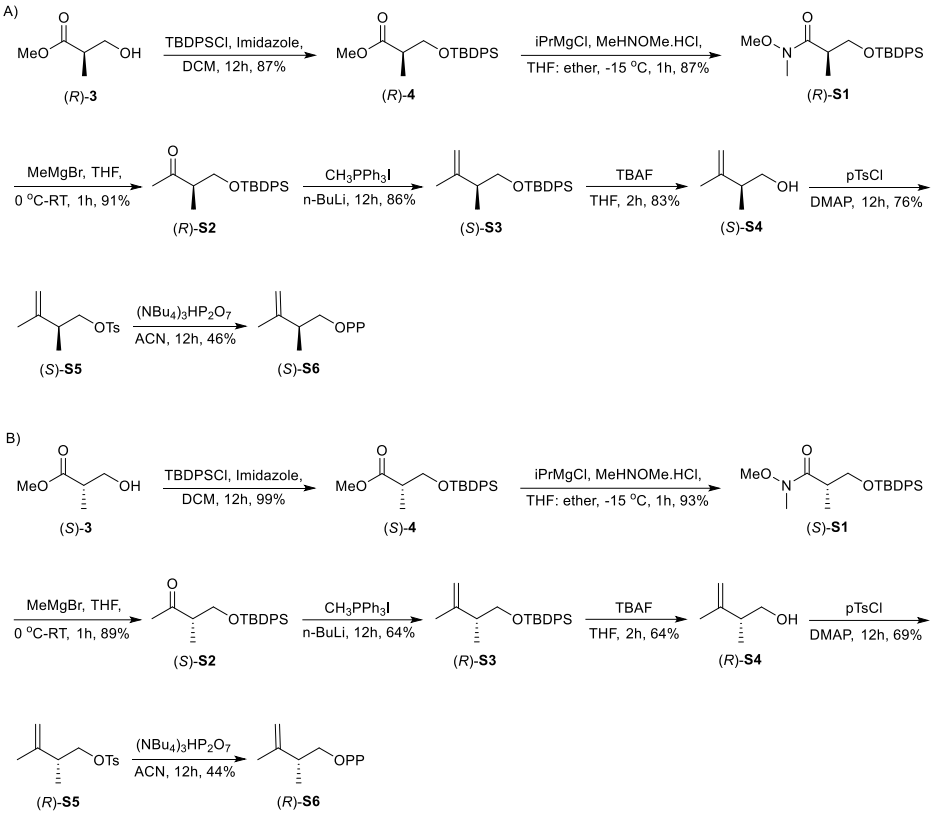
NMR spectra were recorded on a Bruker Avance I 500 MHz spectrometer and a Bruker Avance III HD 700 MHz Cryo spectrometer. Chemical shifts were referenced to the residual proton signal of C_6D_6 (δ = 7.16 ppm) for ^{1}H NMR and the ^{13}C signal of C_6D_6 (δ = 128.06 ppm) for ^{13}C NMR.[1]

HRMS

High resolution mass spectra were recorded with LTQ Orbitrap XL (Thermo Fisher Scientific, Waltham. Massachusetts, USA).

Optical rotations

Optical rotations were recorded on a Modular Compact Polarimeter MCP 100 (Anton Paar, Graz, Austria). The temperature setting was 25 °C; the wavelength of the light used was 589 nm (sodium D line); the path-length was 10 cm; the compound concentrations *c* are given in g 100 mL^{-1}.



Scheme S1. Synthesis of A) (*S*)-2-Me-IPP and B) (*R*)-2-Me-IPP.

Synthesis of (*R*)- and (*S*)-methyl 3-(*tert*-butyldiphenylsilyloxy)-2-methylpropanoate (4)

In a literature-known procedure,[2] the (*R*)-Roche ester ((*R*)-**3**, 2.00 g, 16.9 mmol, 1.0 eq., 99% *ee*) and imidazole (1.62 g, 23.8 mmol, 1.4 eq.) were dissolved in CH_2Cl_2 (100 mL) and the mixture was stirred at room temperature. TBDPSCl (5.67 g, 20.4 mmol, 1.2 eq.) was added dropwise and the reaction mixture was stirred overnight at room temperature. The reaction was quenched by adding H_2O (200 mL). The mixture was extracted three times with diethyl ether (3 x 200 mL). The combined organic layers were dried with $MgSO_4$ and the solvent was removed under reduced pressure. Column chromatography on silica gel [cyclohexane/ethyl acetate (20:1)] resulted in the silylated (*R*)-Roche ester (*R*)-**4** (5.25 g, 14.7 mmol, 87%) as colourless oil. The same procedure was used to convert (*S*)-Roche ester ((*S*)-**3**, 2.00 g, 16.9 mmol, 1.0 eq, 99% *ee*) into (*S*)-**4** (6.05 g, 16.9 mmol, 99%).

(*R*)-4: ^{1}H-NMR (500 MHz, C_6D_6): δ [ppm] = 7.80-7.74 (m, 4H, 4 x CH), 7.26-7.19 (m, 6H, 6 x CH), 3.86 (dd, *J* = 9.7, 7.0 Hz, 1H, 0.5 x CH_2), 3.72 (dd, *J* = 9.7, 5.5 Hz, 1H, 0.5 x CH_2), 3.39 (s, 3H, CH_3), 2.71-2.54 (m, 1H, CH), 1.15 (s, 9H, 3 x CH_3), 1.02 (d, *J* = 7.1 Hz, 3H, CH_3). ^{13}C-NMR (126 MHz, C_6D_6) δ [ppm] = 174.7 (C_q), 136.0 (2 x CH), 136.0 (2 x CH), 134.0 (C_q), 133.9 (C_q), 130.1 (2 x CH), 128.1 (2 x CH), 128.1 (2 x CH), 66.4 (CH_2), 51.2 (CH_3), 42.7 (CH), 27.0 (3 x CH_3), 19.5 (C_q), 13.6 (CH_3). TLC [cyclohexane/ethyl acetate (20:1)]: R_f = 0.36. GC (HP-5MS): *I* = 2243. MS (EI, 70 eV): *m*/*z* (%) = 325 (3), 299 (82), 269 (4), 237 (9), 213 (100), 199 (16), 197 (16), 183 (56), 181 (26), 153 (20), 135 (13), 105

(24), 91 (10), 77 (8), 57 (9), 41 (9). $[\alpha]_D^{20}$ = –17.2° (*c* 1.8, CH_2Cl_2). Lit: $[\alpha]_D^{20}$ = –13.6° (*c* 2.1, $CHCl_3$).[3]

(*S*)-4: $[\alpha]_D^{20}$ = +14.6° (*c* 1.5, CH_2Cl_2). Lit: $[\alpha]_D^{20}$ = +17.1° (*c* 1.1, $CHCl_3$).[4] Spectroscopic data as for the (*R*) enantiomer.

Synthesis of (*R*)- and (*S*)-3-(*tert*-butyldiphenylsilyloxy)-*N*-methoxy-*N*,2-dimethylpropanamide (S1)

Ester (*R*)-**4** (5.25 g, 14.7 mmol, 1.0 eq.) and *N*,*O*-dimethylhydroxylamine hydrochloride (4.28 g, 44.1 mmol, 3.0 eq.) were suspended in THF (65 mL) and cooled to –15 °C. A solution of *i*PrMgCl (2 M in Et_2O, 18.4 mL, 36.8 mmol, 2.5 eq.) was added dropwise and the reaction mixture was stirred at –15 °C for 1 h. After completion of the reaction (monitered by TLC), the reaction was quenched by addition of sat. aq. NH_4Cl (25 mL) at 0 °C. The mixture was extracted three times with EtOAc (3 x 60 mL). The combined organic layers were washed with sat. NaCl (40 mL), dried over $MgSO_4$, and concentrated in vacuo. Column chromatography on silica gel [cyclohexane/ethyl acetate (5:1)] gave the amide (*R*)-**S1** (4.92 g, 12.8 mmol, 87%) as white solid. The same procedure was used to convert ester (*S*)-**4** (6.05 g, 16.9 mmol, 1.0 eq.) into (*S*)-**S1** (6.05 g, 15.7 mmol, 93%).

(*R*)-S1: ^{1}H-NMR (500 MHz, C_6D_6): δ [ppm] = 7.89-7.85 (m, 2H, 2 x CH), 7.83-7.79 (m, 2H, 2 x CH), 7.29-7.19 (m, 6H, 6 x CH), 4.20 (dd, *J* = 9.5, 8.5 Hz, 1H, 0.5 x CH_2), 3.68 (dd, *J* = 9.4, 5.8 Hz, 1H, 0.5 x CH_2), 3.24 (m, 1H, CH), 3.16 (s, 3H, CH_3), 2.93 (s, 3H, CH_3), 1.18 (s, 9H, 3 x CH_3), 1.04 (d, *J* = 6.9 Hz, 3H, CH_3). ^{13}C-NMR (126 MHz, C_6D_6) δ [ppm] = 175.9 (C_q), 136.2 (2 x CH), 136.0 (2 x CH), 134.4 (C_q), 133.9 (C_q), 130.0 (CH), 130.0 (CH), 128.1 (2 x CH), 128.1 (2 x CH), 66.9 (CH_2), 61.1 (CH), 38.4 (CH_3), 32.1 (CH), 27.1 (3 x CH_3), 19.5 (C_q), 14.0 (CH_3). TLC [cyclohexane/ethyl acetate (5:1)]: R_f = 0.35. GC (HP-5MS): *I* = 2497. MS (EI, 70 eV): *m*/*z* (%) = 328 (100), 296 (6), 213 (6), 199 (26), 197 (16), 183 (12), 181 (11), 135 (14), 105 (9), 91 (4), 82 (4), 77 (6), 57 (7), 41 (6). $[\alpha]_D^{20}$ = –13.9° (*c* 1.8, CH_2Cl_2).

(*S*)-S1: $[\alpha]_D^{20}$ = +10.2° (*c* 1.6, CH_2Cl_2). Spectroscopic data as for the (*R*) enantiomer.

Synthesis of (*R*)- and (*S*)-4-(*tert*-butyldiphenylsilyloxy)-3-methylbutan-2-one (S2)

Amide (*R*)-**S1** (4.92 g, 12.8 mmol, 1.0 eq.) was dissolved in THF (50 mL) and the mixture was stirred at 0 °C until it dissolved. The MeMgBr (3 M in Et_2O,12.8 mL, 38.4 mmol, 3.0 eq.) was added dropwise and the reaction mixture was stirred at 0 °C for 1 h. After completion of the reaction (monitered by TLC), the reaction was quenched by addition of sat. aq. NH_4Cl (25 mL) at 0 °C. The mixture was extracted three times with EtOAc (3 x 80 mL). The combined organic layers were washed with sat. NaCl (20 mL), dried over $MgSO_4$, and concentrated in vacuo. Column chromatography on silica gel [cyclohexane/ethyl acetate (20:1)] gave the methyl ketone (*R*)-**S2** (3.94 g, 11.6 mmol, 91%) as as colourless oil. The same procedure was used to convert amide (*S*)-**S1** (6.05 g, 15.7 mmol, 1.0 eq.) into (*S*)-**S2** (4.75 g, 14.0 mmol, 89%).

(*R*)-S2: ^{1}H-NMR (500 MHz, C_6D_6): δ [ppm] = 7.78-7.70 (m, 4H, 4 x CH), 7.26-7.19 (m, 6H, 6 x CH), 3.78 (dd, *J* = 10.0, 7.3 Hz, 1H, 0.5 x CH_2), 3.60 (dd, *J* = 10.0, 5.3 Hz, 1H, 0.5 x

CH_2), 2.52-2.38 (m, 1H, CH), 1.85 (s, 3H, CH_3), 1.13 (s, 9H, 3 x CH_3), 0.82 (d, *J* = 7.0 Hz, 3H, CH_3).^{13}C-NMR (126 MHz, C_6D_6) δ [ppm] = 208.8 (C_q), 136.0 (2 x CH), 136.0 (2 x CH), 133.9 (C_q), 133.8 (C_q), 130.1 (2 x CH), 128.1 (4 x CH), 66.4 (CH_2), 49.2 (CH), 29.0 (CH_3), 27.0 (3 x CH_3), 19.5 (C_q), 12.9 (CH_3). TLC [cyclohexane/ethyl acetate (20:1)]: R_f = 0.26. GC (HP-5MS): *I* = 2239. MS (EI, 70 eV): *m*/*z* (%) = 283 (96), 253 (13), 239 (50), 205 (61), 199 (74), 197 (25), 187 (23), 183 (100), 181 (43), 175 (20), 135 (16), 123 (25), 105 (25), 77 (22), 43 (28). $[\alpha]_D^{20}$ = –18.0° (*c* 1.5, CH_2Cl_2).
(*S*)-S2: $[\alpha]_D^{20}$ = +20.9° (*c* 1.8, CH_2Cl_2). Spectroscopic data as for the (*R*) enantiomer.

Synthesis of (*S*)- and (*R*)-*tert*-butyl((2,3-dimethylbut-3-en-1-yl)oxy)diphenylsilane (S3)

CH_3PPh_3I (8.44 g, 20.9 mmol, 1.8 eq.) was suspended in THF (100 mL) and cooled to 0 °C. The *n*-BuLi (1.6 M in hexane, 13.0 mL, 20.8 mmol, 1.8 eq.) was added dropwise and the mixture was stirred at 0 °C for 1 h. After cooling to the mixture to –78 °C, the ketone (*R*)-**S2** (3.94 g, 11.6 mmol, 1.0 eq.) was added dropwise and the reaction mixture was stirred at room temperature overnight. The reaction was quenched by pouring ice-water mixture (200 mL). The mixture was extracted three times with diethyl ether (3 x 200 mL). The combined organic layers were washed with sat. NaCl (20 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Column chromatography on silica gel [cyclohexane/ethyl acetate (100:1)] gave the olefin (*S*)-**S3** (3.38 g, 10.0 mmol, 86%) as colourless oil. The same procedure was used to convert ketone (*S*)-**S2** (4.75 g, 14.0 mmol, 1.0 eq.) into (*R*)-**S3** (3.03 g, 8.95 mmol, 64%).
(*S*)-S3: ^{1}H-NMR (500 MHz, C_6D_6): δ [ppm] = 7.84-7.73 (m, 4H, 4 x CH), 7.27-7.20 (m, 6H, 6 x CH), 4.83-4.79 (m, 2H, CH_2), 3.70 (dd, *J* = 9.9, 6.3 Hz, 1H, 0.5 x CH_2), 3.57 (dd, *J* = 9.9, 6.8 Hz, 1H, 0.5 x CH_2), 2.44-2.32 (m, 1H, CH), 1.57 (t, *J* = 1.2 Hz, 3H, CH_3), 1.19 (s, 9H, 3 x CH_3), 1.03 (d, *J* = 7.0 Hz, 3H, CH_3). ^{13}C-NMR (126 MHz, C_6D_6) δ [ppm] = 147.7 (C_q), 136.1 (2 x CH), 136.1 (2 x CH), 134.4 (C_q), 134.4 (C_q), 130.0 (2 x CH), 128.1 (4 x CH), 111.0 (CH_2), 68.0 (CH_2), 43.8 (CH), 27.2 (3 x CH_3), 20.6 (CH_3), 19.6 (C_q), 16.3 (CH_3). TLC [cyclohexane/ethyl acetate (100:1)]: R_f = 0.40. GC (HP-5MS): *I* = 2122. MS (EI, 70 eV): *m*/*z* (%) = 281 (37), 239 (100), 211 (8), 203 (10), 199 (15), 197 (13), 135 (16), 121 (8), 105 (14), 77 (8), 57 (10), 41 (15). $[\alpha]_D^{20}$ = –0.1° (*c* 1.8, CH_2Cl_2).
(*R*)-S3: $[\alpha]_D^{20}$ = +0.2° (*c* 1.3, CH_2Cl_2). Spectroscopic data as for the (*S*) enantiomer.

Synthesis of (*S*)- and (*R*)-2,3-dimethylbut-3-en-1-ol (S4)

Olefin (*S*)-**S3** (3.38 g, 10.0 mmol, 1.0 eq.) was suspended in THF (45 mL) and the solution was cooled to 0 °C. TBAF (1 M in THF, 12.0 mL, 12.0 mmol, 1.2 eq.) was added dropwise and the reaction mixture was stirred at room temperature for 2 h. The reaction was quenched by addition of water (50 mL). The mixture was extracted three times with diethyl ether (3 x 100 mL). The combined organic layers were washed with sat. NaCl (10 mL), dried over $MgSO_4$, and concentrated under reduced pressure (700 mbar, 40 °C, 20 min). Column chromatography on silica gel [*n*-pentane/diethyl ether (1:1)] gave the alcohol (*S*)-**S4** (0.83 g, 8.3 mmol, 83%) as colourless oil in high enantiomeric purity (99% *ee*, Figure

S1). The same procedure was used to convert olefin (*R*)-**S3** (3.03 g, 8.95 mmol, 1.0 eq.) into (*R*)-**S4** (0.57 g, 5.69 mmol, 64%, 99% *ee*).

(*S*)-S4: ^{1}H-NMR (500 MHz, C_6D_6): δ [ppm] = 4.79-4.74 (m, 1H, CH), 4.73- 4.70 (m, 1H, CH), 3.35-3.29 (m, 1H, 0.5 x CH_2), 3.29-3.24 (m, 1H, 0.5 x CH_2), 2.19-2.08 (m, 1H, CH), 1.51 (t, *J* = 1.2 Hz, 3H, CH_3), 0.87 (d, *J* = 6.9 Hz, 3H, CH_3). ^{13}C-NMR (126 MHz, C_6D_6) δ [ppm] = 147.3 (C_q), 111.4 (CH_2), 65.7 (CH_2), 43.9 (CH), 19.9 (CH_3), 15.8 (CH_3). TLC [*n*-pentane/diethyl ether (1:1)]: R_f = 0.50. GC (HP-5MS): *I* < 800. MS (EI, 70 eV): *m*/*z* (%) = 100 (5), 82 (11), 70 (37), 69 (37), 67 (36), 55 (43), 53 (18), 41 (100), 39 (41). $[\alpha]_D^{20}$ = –9.0° (*c* 0.67, CH_2Cl_2).

(*R*)-S4: $[\alpha]_D^{20}$ = +10.5° (c = 0.6, CH_2Cl_2). Lit: $[\alpha]_D^{22}$ = +9.0° (*c* 3.0, $CHCl_3$).[5] Spectroscopic data as for the (*S*) enantiomer.

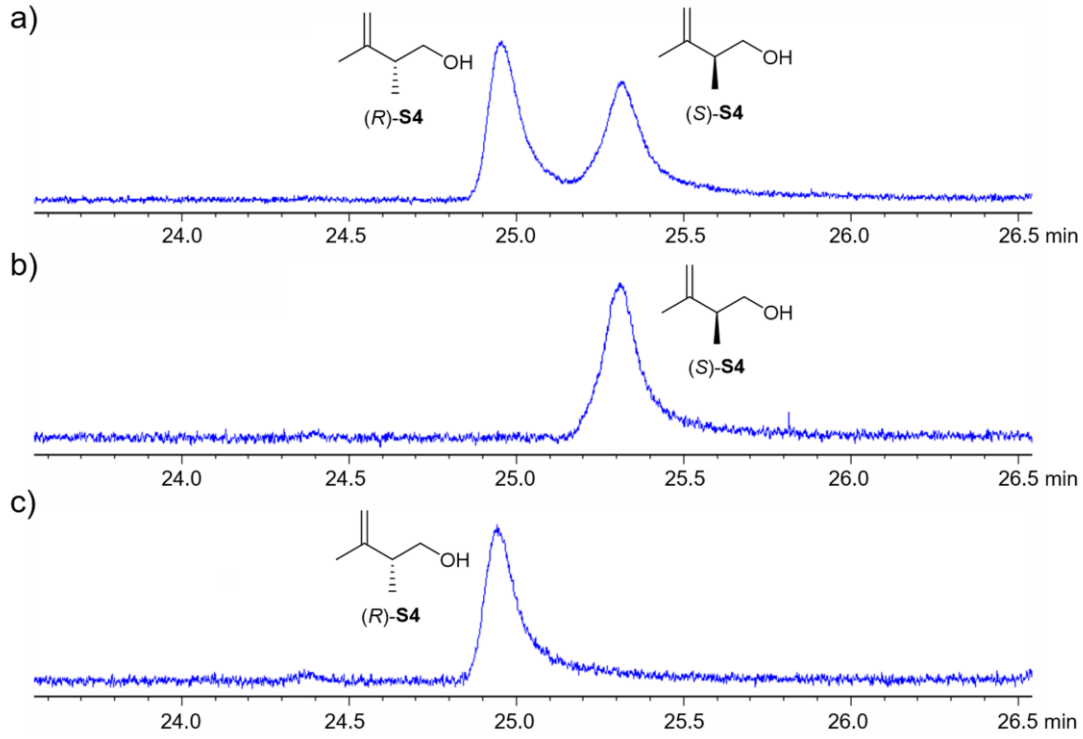


Figure S1. Chiral GC analysis of 2-Me-IPP precursors. a) Mixture of (*S*)- and (*R*)-2,3-dimethylbut-3-en-1-ol, b) (*S*)-2,3-dimethylbut-3-en-1-ol, and c) (*R*)-2,3-dimethylbut-3-en-1-ol.

Synthesis of (*S*)- and (*R*)-2,3-dimethylbut-3-en-1-yl 4-methylbenzenesulfonate (S5)

Alcohol (*S*)-**S4** (0.83 g, 8.3 mmol, 1.0 eq.) was suspended in CH_2Cl_2 (80 mL) and the solution was cooled to 0 °C. After adding of DMAP (3.35 g, 27.4 mmol, 3.3 eq.), *p*-TsCl (partially dissolved in 10 mL CH_2Cl_2, 3.96 g, 20.8 mmol, 2.5 eq.) was added dropwise to the solution and the reaction mixture was stirred at room temperature overnight. The reaction was quenched by addition of sat. NH_4Cl (100 mL). The mixture was extracted three times with diethyl ether (3 x 100 mL). The combined organic layers were washed with

sat. NaCl (10 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Column chromatography on silica gel [cyclohexane/ethyl acetate (10:1)] gave the tosylate (*S*)-**S5** (1.60 g, 6.29 mmol, 76%) as colourless oil. The same procedure was used to convert alcohol (*R*)-**S4** (0.57 g, 5.69 mmol, 1.0 eq.) into (*R*)-**S5** (1.00 g, 3.93 mmol, 69%).

(*S*)-S5: ^{1}H-NMR (500 MHz, C_6D_6): δ [ppm] = 7.76 (d, J = 8.3 Hz, 2H, 2 x CH), 6.69 (d, J = 8.0, 0.7 Hz, 2H, 2 x CH), 4.69-4.64 (m, 1H, 0.5 x CH_2), 4.62-4.57 (m, 1H, 0.5 x CH_2), 3.91 (dd, J = 9.6, 6.7 Hz, 1H, CH), 3.79 (dd, J = 9.6, 6.9 Hz, 1H, CH), 2.29-2.17 (m, 1H, CH), 1.82 (s, 3H, CH_3), 1.37 (dd, J = 1.5, 0.8 Hz, 3H, CH_3), 0.76 (d, J = 7.0 Hz, 3H, CH_3). ^{13}C-NMR (126 MHz, C_6D_6) δ [ppm] = 145.3 (C_q), 144.2 (C_q), 134.5 (C_q), 129.8 (2 x CH), 128.2 (2 x CH), 112.1 (CH_2), 72.9 (CH_2), 40.4 (CH), 21.1 (CH_3), 20.0 (CH_3), 15.8 (CH_3). TLC [cyclohexane/ethyl acetate (10:1)]: R_f = 0.38. GC (HP-5MS): I = 1879. MS (EI, 70 eV): m/z (%) = 173 (6), 155 (58), 91 (100), 82 (90), 69 (28), 67 (39), 65 (40), 41 (41), 39 (23). $[\alpha]_D^{20}$ = +7.0° (c = 1.0, CH_2Cl_2). Lit: $[\alpha]_D^{27}$ = +7.4° (*c* 0.91, $CHCl_3$).[6]

(*R*)-S5: $[\alpha]_D^{20}$ = –6.5° (*c* 0.8, CH_2Cl_2). Lit: $[\alpha]_D^{25}$ = –6.1° (*c* 5.5, $CHCl_3$).[7] Spectroscopic data as for the (*S*) enantiomer.

Synthesis of (*S*)- and (*R*)-2,3-dimethylbut-3-en-1-yl diphosphate (S6)

Following a known pyrophosphorylation method,[8] (^{n}NBu$_4$)$_3$HP$_2$O$_7$ (8.52 g, 9.44 mmol, 1.5 eq.) was added to acetonitrile (2 mL), followed by the dropwise addition of the tosylate (*S*)-**S5** (1.60 g, 6.29 mmol,1.0 eq., in 6 mL acetonitrile). The reaction mixture was stirred overnight, and the solvent was removed under reduced pressure. The residue was loaded onto an ion exchange resin column (DOWEX® 50W-X8, 100-200 mesh, NH_4^+ form), followed by elution with two column volumes of elution buffer (25 mM NH_4HCO_3 in 2% ^{i}PrOH/H_2O). The eluate was lyophilized, the residue was dissolved in NH_4HCO_3 solution (0.1 M, 8 mL) and mixed with 1:1 MeCN/^{i}PrOH (20 mL). The precipitate was separated by centrifugation (2000 x g, 5 min) and the liquid phase containing the target compound was collected. The procedure of dissolving the precipitate in NH_4HCO_3 solution (0.1 M, 8 mL) and mixing with 1:1 MeCN/^{i}PrOH (20 mL) followed by centrifugation was repeated three times, before the pooled liquid fractions were concentrated under reduced pressure. The residue was taken up in water (6 mL) and lyophilized again to yield the diphosphate (*S*)-**S6** as an inseparable 1:1.7 mixture (by NMR peak integration) with ammonium tosylate as a white solid (0.90 g, 2.89 mmol, 46%). The same procedure was used to convert tosylate (*R*)-**S5** (1.00 g, 3.93 mmol, 69%) into the (*R*)-**S6** as an inseparable 1:1.7 mixture (by NMR peak integration) with ammonium tosylate as a white solid (0.54 g, 1.73 mmol, 44%).

(*S*)-S6: ^{1}H-NMR (500 MHz, D_2O): δ [ppm] = 4.86-4.83 (m, 2H, CH_2), 3.93-3.87 (m, 1H, 0.5 x CH_2), 3.87-3.80 (m, 1H, 0.5 x CH_2), 2.59-2.45 (m, 1H, CH), 1.74 (s, 3H, CH_3), 1.04 (dd, J = 6.9, 1.4 Hz, 3H, CH_3). ^{13}C-NMR (126 MHz, D_2O) δ [ppm] = 148.9 (C_q), 110.6 (CH_2), 68.9 (d, $^2J_{C,P}$ = 6.0 Hz, CH_2), 41.2 (d, $^3J_{C,P}$ = 7.6 Hz, CH), 19.2 (CH_3), 15.5 (CH_3). ^{31}P-NMR (202 MHz, D_2O): δ [ppm] = –7.32 (d, $^2J_{P,P}$ = 21.3 Hz, 1P), –10.47 (d, $^2J_{P,P}$ = 21.3 Hz, 1P). HRMS (TOF): m/z = 259.0146 (calc. for $[C_6H_{13}O_7P_2]^-$ 259.0142).

(*R*)-S6: HRMS (TOF): m/z = 259.0145 (calc. for $[C_6H_{13}O_7P_2]^-$ 259.0142). Spectroscopic data as for the (*S*) enantiomer.

Strain and culture condition

Streptomyces coelicolor A3(2) DSM 40783 was obtained from Deutsche Sammlung von Mikroorganismen und Zellkulturen (Braunschweig, Germany). This strain was cultivated in 65. GYM medium (4.0 g glucose, 4.0 g yeast extract, 10.0 g malt extract, dissolved in 1 L distilled water, pH 7.2) at 28 °C.

Isolation of genomic DNA

Streptomyces coelicolor A3(2) DSM 40783 cells from a 65. GYM liquid culture (100 mL) were harvested by centrifugation, resuspended in SET buffer (5 mL, 75 mM NaCl, 25 mM EDTA, 20 mM Tris/HCl, pH 8.0) and incubated with lysozyme solution (1 mg/mL) for 30 min at 37 °C. Proteinase K solution (100 µL, 1 mg/mL) was added and the solution was mixed. It was incubated for 1 h at 55 °C after addition of 10% SDS (600 µL) and mixing by inversion. Phenol/chloroform (5 mL) was added and the solution was mixed by inversion before centrifugation for 5 min at 14000 g. The aqueous layer was transferred to a fresh tube and ice-cold ethanol (60%-70% vol.) was added for precipitation of DNA. After centrifugation and washing with 70% ethanol the DNA was redissolved in TE buffer (100 µL, 10 mM Tris/HCl, 1 mM EDTA, pH 8.0).

Gene cloning

The target gene of 2MIBS[9] from *S. coelicolor* A3(2) (NP_733742) was amplified from gDNA by PCR using Q5 High-fidelity DNA polymerase (New England Biolabs, Ipswich, MA, USA) and primer pair in Table S1 named after the accession number. Yeast homologous recombination of the PCR product with the linearized pYE-Express shuttle vector[10] was carried out through the standard protocol using LiOAc, polyethylene glycol and salmon sperm DNA.[11] After yeast transformation culture was grown on SM-URA agar (425 mg yeast nitrogen base, 1.25 g ammonium sulphate, 5 g glucose, 192.5 mg nutritional supplement minus uracil, 5 g agar, 250 mL water) at 28 °C for 3 days. The recombinant plasmid was isolated from grown yeast colonies using the Zymoprep Yeast Plasmid Miniprep II kit (Zymo Research, Irvine, CA, USA) and subsequently used for transformation of *E. coli* BL21(DE3) electrocompetent cells. Cells were plated on LB agar plates with Kanamycin (50 µg mL^{-1}) followed by incubation at 37 °C overnight. Single colonies were selected and used to inoculate LB medium (6 mL) liquid cultures with kanamycin (6 µL; 50 mg mL^{-1}). After 24 h growth plasmid DNA was isolated and checked for correct insertion of the desired gene by PCR amplifying the DNA sequence, containing the target gene, using T7 primer pair and by sequencing. The obtained plasmid was named pYE-NP_733742. The pYE-Express plasmid containing the gene for farnesyl diphosphate synthase (FPPS) from *S. coelicolor* A3(2) was constructed as reported before using the same method (pYE-WP_01103116) and stored in the lab refrigerator.[12]

Table S1. Primers used in this study.

Primer	Sequence[a]
NP_733742_F	GGCAGCCATATGGCTAGCATGACTGGTGGAatgcccgactccgggacctc
NP_733742_R	TCTCAGTGGTGGTGGTGGTGGTGCTCGAGTGctaccagaagtcgggcaggctgtagc

[a] The sequences of capital letters are homology arms for recombination in yeast which match the terminal sequences of linearized pYE-Express (HindIII and EcoRI digestion).

Gene expression and protein purification

precultures of *E. coli* BL21(DE3) transformed with pYE-WP_01103116 (FPPS) and pYE-NP_733742 (2MIBS) were grown in LB medium with kanamycin (50 µg mL^{-1}) overnight with shaking at 37 °C. Gene expression cultures were inoculated with the precultures (2/100) and grown in LB medium containing kanamycin (50 µg mL^{-1}) with shacking at 37 °C until OD_{600} = 0.4 – 0.6 was reached. After cooling the cultures to 18 °C enzyme expression was induced by the addition of aqueous IPTG solution (400 mM, 1/1000). The cultures were shaken at 18 °C overnight. The cells were harvested via centrifugation (10000 g, 5 min, 4 °C), resuspended in binding buffer (10 mL L^{-1} culture; 20 mM Na_2HPO_4, 500 Mm NaCl, 20 mM imidazole, 1 mM $MgCl_2$, pH 7.4, 4 °C) and lysed by ultrasonication (8x 1 min) on ice. The cell debris was removed by centrifugation (14600 g, 10 min, 4 °C) and the soluble protein fractions were loaded onto Ni^{2+}-NTA superflow affinity chromatography columns (Qiagen, Venlo, Netherlands) equilibrated with binding buffer. The columns were washed with wash buffer (2x 10 mL L^{-1} culture; 20 mM Na_2HPO_4, 500 Mm NaCl, 50 mM imidazole, 1 mM $MgCl_2$, pH 7.4, 4 °C) and the desired proteins were eluted with elution buffer (2x 6.25 mL L^{-1} culture; 20 mM Na_2HPO_4, 500 Mm NaCl, 500 mM imidazole, 1 mM $MgCl_2$, pH 7.4, 4 °C). The protein concentrations were determined by Bradford assay.[13] Typical yields were: FPPS (1.7 mg mL^{-1}) and 2MIBS (1.8 mg mL^{-1}).

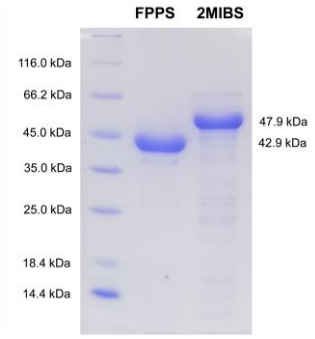


Figure S2. SDS-PAGE analysis of recombinant FPPS and 2MIBS.

Incubation of DMAPP and (*S*)-2-Me-IPP (or (*R*)-2-Me-IPP) with FPPS and 2MIBS

Culture conditions, protein expressions and protein purifications were performed as described above. The soluble enzyme fractions were checked for purity by SDS-PAGE. The incubations were performed with 0.3 mg DMAPP and 0.3 mg (*S*)-2-Me-IPP (or (*R*)-2-Me-IPP) dissolved respectively in substrate buffer (50 µL; 25 mM NH_4HCO_3) and diluted with incubation buffer (700 µL; 50 mM Tris/HCl, 10 mM $MgCl_2$, 10% glycerol, pH = 8.2). FPPS and 2MIBS protein solutions (100 µL) obtained respectively from 100 mL expression culture were added to the mixture, followed by incubation with shaking at 30 °C overnight. The crude product was extracted with hexane (500 µL), the extract was tried with $MgSO_4$ and directly analysed by GC/MS (Figure S2).

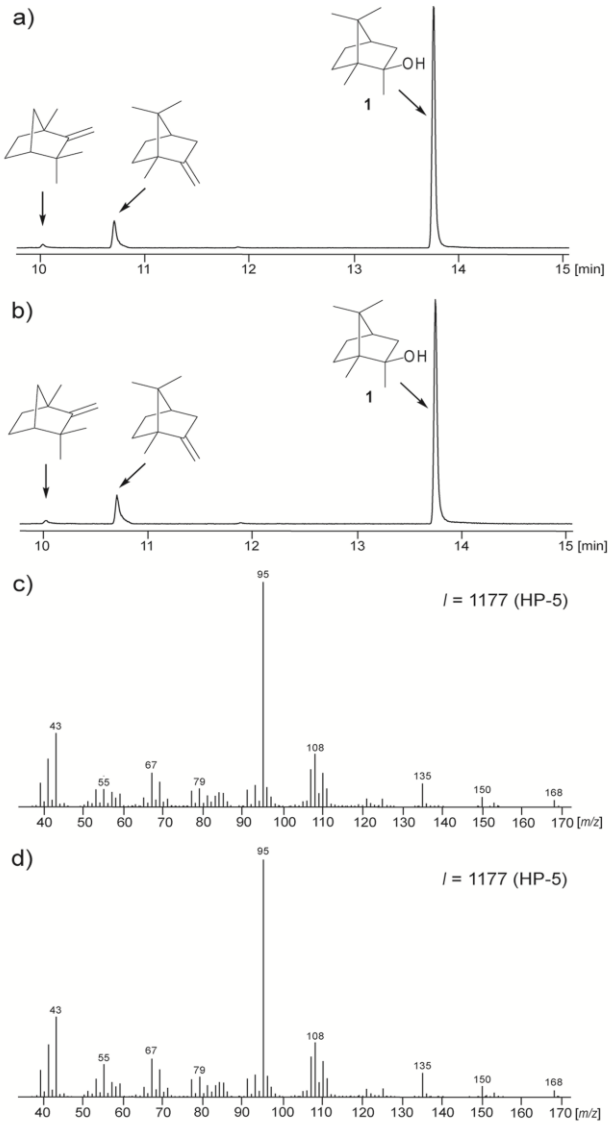


Figure S3. Total ion chromatogram (TIC) of products obtained by incubations of a) DMAPP and (*S*)-2-Me-IPP with FPPS and 2MIBS and of b) DMAPP and (*R*)-2-Me-IPP with FPPS and 2MIBS, and c) EI-MS spectrum of main product 2-methylisoborneol (**1**) from TIC a) and d) EI-MS spectrum of main product 2-methylisoborneol (**1**) from TIC b). Retention indices (*I*) were determined from a homologous series of *n*-alkanes (C_7-C_{40}).

Enzyme incubation of DMAPP and (*S*)-2-Me-IPP (or (*R*)-2-Me-IPP) with FPPS and then dephosphorylation with calf intestinal phosphatase

Culture conditions, protein expressions and protein purifications were performed as described above. The soluble enzyme fractions were checked for purity by SDS-PAGE. The incubations were performed with 0.3 mg DMAPP and 0.3 mg (*S*)-2-Me-IPP (or (*R*)-2-Me-IPP) dissolved respectively in substrate buffer (50 µL; 25 mM NH_4HCO_3) and diluted with incubation buffer (800 µL; 50 mM Tris/HCl, 10 mM $MgCl_2$, 10% glycerol, pH = 8.2). FPPS protein solution (100 µL) obtained from 100 mL expression culture was added to the mixture, followed by incubation with shaking for 3 h at 30 °C. Then calf intestinal phosphate (CIP, New England Biolabs, 10 units) and CutSmart Buffer (10 µL) were added and the mixture was incubated for 1 h at 37 °C. The mixture was extracted with hexane (500 µL), the extracts were dried and subjected to GC/MS (Figure S3).

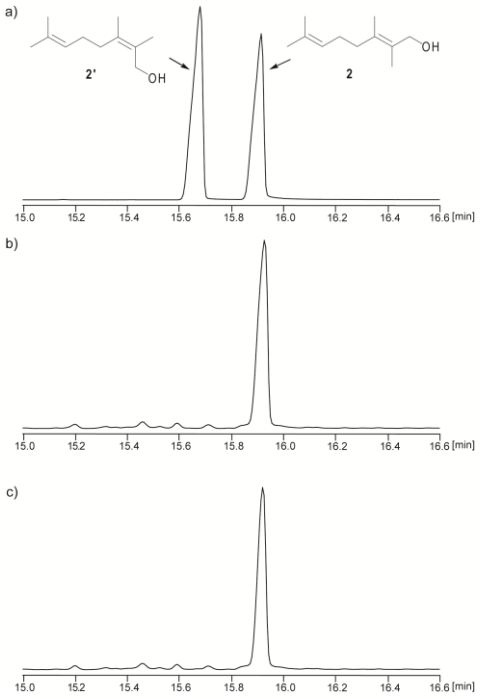


Figure S4. Total ion chromatogram of a) a mixed reference compounds 2-methylgeraniol (**2**) and 2-methylnerol (**2'**) and of products obtained by incubations of b) DMAPP and (*S*)-2-Me-IPP with FPPS and CIP and of c) DMAPP and (*R*)-2-Me-IPP with FPPS and CIP. Compounds **2** and **2'** were synthesized as reported before.[14]

Synthesis of (*R*)- and (*S*)-methyl 3-(*tert*-butyldiphenylsilyloxy)-2-methylpropanoate (4)

As described above, the (*R*)-Roche ester ((*R*)-**3**, 3.30 g, 28.0 mmol, 1.0 eq.) was transformed into the silylated (*R*)-Roche ester (*R*)-**4** (9.80 g, 27.5 mmol, 99%) as colourless oil and the (*S*)-Roche ester ((*S*)-**3**, 2.36 g, 20.0 mmol, 1.0 eq) was transformed into (*S*)-**4** (7.00 g, 19.8 mmol, 99%). Spectroscopic data of (*R*)- and (*S*)-**4** are the same as described above.

Synthesis of (*S*)- and (*R*)-3-(*tert*-butyldiphenylsilyloxy)-2-methylpropan-1-ol (5)

According to a reported procedure,[15] ester (*R*)-**4** (9.80 g, 27.5 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (60 mL) and the mixture was cooled to –78 °C. DIBAL-H (1 M in hexane, 57.8 mL, 57.8 mmol, 2.1 eq.) was added dropwise and the reaction mixture was stirred at –78 °C for 1.5 h. The reaction was quenched by adding saturated aqueous Rochelle's salt (sodium potassium tartrate). After stirring for 1 h, the mixture was extracted three times with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Column chromatography on silica gel [cyclohexane/ethyl acetate (5:1)] gave the alcohol (*S*)-**5** (8.06 g, 24.6 mmol, 89%) as colourless oil. The same procedure was used to convert ester (*S*)-**4** (7.00 g, 19.8 mmol, 1.0 eq.) into (*R*)-**5** (5.20 g, 15.9 mmol, 80%).

(*S*)-5: ^{1}H-NMR (400 MHz, C_6D_6): δ [ppm] = 7.82-7.71 (m, 4H, 4 x CH), 7.26-7.20 (m, 6H, 6 x CH), 3.67-3.55 (m, 2H, CH_2), 3.54-3.46 (m, 2H, CH_2), 1.86-1.75 (m, 1H, CH), 1.60 (brt, J = 5.4 Hz, 1H, CH), 1.15 (s, 9H, 3 x CH_3), 0.73 (d, J = 6.9 Hz, 3H, CH_3). ^{13}C-NMR (101 MHz, C_6D_6) δ [ppm] = 136.0 (2 x CH), 136.0 (2 x CH), 134.0 (2 x C_q), 130.1 (2 x CH), 128.1 (4 x CH), 67.8 (CH_2), 66.3 (CH_2), 38.2 (CH), 27.1 (3 x CH_3), 19.5 (C_q), 13.5 (CH_3). TLC [cyclohexane/ethyl acetate (5:1)]: R_f = 0.37. GC (HP-5MS): I = 2241. MS (EI, 70 eV): m/z (%) = 271 (32), 229 (16), 199 (100), 197 (22), 193 (52), 181 (34), 139 (54), 135 (13), 121 (11), 105 (14), 91 (11), 77 (20), 57 (14), 41 (11). $[\alpha]_D^{20}$ = –4.4° (*c* 2.0, CH_2Cl_2). Lit: $[\alpha]_D^{20}$ = –4.3° (*c* 1.2, $CHCl_3$).[16]

(*R*)-5: $[\alpha]_D^{20}$ = +4.3° (*c* 1.6, CH_2Cl_2). Lit: $[\alpha]_D^{23}$ = +6.0° (*c* 1.2, $CHCl_3$).[17] Spectroscopic data as for the (*S*) enantiomer.

Synthesis of (*R*)- and (*S*)-3-(*tert*-butyldiphenylsilyloxy)-2-methylpropanal (6)

According to a reported procedure,[15] oxalyl chloride (6.88 g, 54.2 mmol, 2.2 eq.) was dissolved in CH_2Cl_2 (300 mL) and the mixture was cooled to –78 °C. DMSO (5.40 g, 69.1 mmol, 2.8 eq.) was added dropwise, and the mixture was stirred at –78 °C for 30 min. At this point, alcohol (*S*)-**5** (dissolved in 30 mL CH_2Cl_2, 8.06 g, 24.6 mmol, 1.0 eq.) was added dropwise. After stirring the mixture at –78 °C for 20 min, Et_3N (11.76 g, 116.2 mmol, 4.7 eq.) was added. The reaction mixture was stirred at –78 °C for 15 min, then at 0 °C for 10 min. The reaction mixture was quenched by addition of saturated aqueous NaCl and extracted with EtOAc. The organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography [cyclohexane/ethyl acetate (10:1)] to give pure aldehyde (*R*)-**6** (7.20 g,

22.1 mmol, 90%) as colourless oil. The same procedure was used to convert alcohol (*R*)-**5** (5.20 g, 15.9 mmol, 1.0 eq.) into (*S*)-**6** (4.80 g, 14.7 mmol, 92%).

(*R*)-6: ^{1}H-NMR (400 MHz, C_6D_6): δ [ppm] = 9.49 (d, *J* = 1.4 Hz, 1H, CH), 7.73-7.66 (m, 4H, 4 x CH), 7.25-7.19 (m, 6H, 6 x CH), 3.65 (dd, *J* = 10.3, 4.8 Hz, 1H, 0.5 x CH_2), 3.59 (dd, *J* = 10.3, 6.1 Hz, 1H, 0.5 x CH_2), 2.11-2.02 (m, 1H, CH), 1.10 (s, 9H, 3 x CH_3), 0.82 (d, *J* = 7.0 Hz, 3H, CH_3). ^{13}C-NMR (101 MHz, C_6D_6) δ [ppm] = 202.4 (C_q), 136.0 (4 x CH), 133.7 (2 x C_q), 130.2 (CH), 130.1 (CH), 128.2 (2 x CH), 128.2 (2 x CH), 64.3 (CH_2), 48.9 (CH), 27.0 (3 x CH_3), 19.5 (C_q), 10.2 (CH_3). TLC [cyclohexane/ethyl acetate (10:1)]: R_f = 0.43. GC (HP-5MS): *I* = 2176. MS (EI, 70 eV): *m*/*z* (%) = 269 (53), 239 (64), 211 (23), 199 (31), 197(14), 191 (92), 183 (100), 181 (37), 161(17), 117 (15), 105 (21), 77 (15), 57 (15), 41 (14). $[\alpha]_D^{20}$ = –21.5° (*c* 1.7, CH_2Cl_2). Lit: $[\alpha]_D^{20}$ = –21.5° (*c* 1.4, $CHCl_3$).[18]

(*S*)-6: $[\alpha]_D^{20}$ = +19.9° (*c* 2.0, CH_2Cl_2). Lit: $[\alpha]_D^{20}$ = +22.2° (*c* 3.7, $CHCl_3$).[19] Spectroscopic data as for the (*R*) enantiomer.

Synthesis of (*S*)- and (*R*)-*tert*-butyl((4,4-dibromo-2-methylbut-3-en-1-yl)oxy)diphenylsilane (7)

According to a reported procedure,[20] 3 g of (*R*)-**6** (3.00 g, 9.2 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (60 mL) and the mixture was cooled to 0 °C. To the solution, PPh_3 (9.70 g, 36.8 mmol, 4.0 eq.) was added, before CBr_4 (6.10 g, 18.4 mmol, 2.0 eq.) was added in small portions. The solution was stirred for 1 h at room temperature, diluted with cyclohexane (180 mL) and passed through a plug of celite. After washing with cyclohexane (3 x 20 mL), the combined cyclohexane eluent was concentrated under reduced pressure and purified by column chromatography on silica gel [cyclohexane/ethyl acetate (50:1)] to yield dibromide (*S*)-**7** (4.25 g, 8.8 mmol, 96%) as colourless oil. The same procedure was used to convert (*S*)-**6** (3.00 g, 9.2 mmol, 1.0 eq.) into (*R*)-**7** (4.20 g, 8.7 mmol, 95%).

(*S*)-7: ^{1}H-NMR (500 MHz, C_6D_6): δ [ppm] = 7.77-7.68 (m, 4H, 4 x CH), 7.27-7.21 (m, 6H, 6 x CH), 6.07 (d, *J* = 9.3 Hz, 1H, CH), 3.42-3.29 (m, 2H, CH_2), 2.73-2.54 (m, 1H, CH), 1.15 (s, 9H, 3 x CH_3), 0.74 (d, *J* = 6.8 Hz, 3H, CH_3). ^{13}C-NMR (126 MHz, C_6D_6) δ [ppm] = 141.8 (CH), 136.1 (2 x CH), 136.0 (2 x CH), 134.0 (C_q), 133.9 (C_q), 130.1 (CH), 130.1 (CH), 128.2 (4 x CH), 89.4 (C_q), 66.9 (CH_2), 41.3 (CH), 27.1 (3 x CH_3), 19.5 (C_q), 15.3 (CH_3). TLC [cyclohexane/ethyl acetate (50:1)]: R_f = 0.45. GC (HP-5MS): *I* = 2576. MS (EI, 70 eV): *m*/*z* (%) = 425 (23), 423 (15), 263 (100), 261 (91), 211 (16), 199 (25), 197 (18), 181 (44), 135 (24), 105 (26), 91 (16), 83 (71), 77 (17), 57 (16), 41 (13). $[\alpha]_D^{20}$ = +12.4° (*c* 1.6, CH_2Cl_2).

(*R*)-7: $[\alpha]_D^{20}$ = –11.6° (*c* 1.7, CH_2Cl_2). Lit: $[\alpha]_D^{25}$ = –14.3° (*c* 0.5, $CHCl_3$).[21] Spectroscopic data as for the (*S*) enantiomer.

Synthesis of (S)- and (*R*)-*tert*-butyl((2-methylbut-3-yn-1-yl)oxy)diphenylsilane (8a) and (S)- and (*R*)-*tert*-butyl(((4-^{2}H)-2-methylbut-3-yn-1-yl)oxy)diphenylsilane (8b)

Dibromide (*S*)-**7** (2.00 g, 4.2 mmol, 1.0 eq.) was dissolved in THF (30 mL) and the mixture was cooled to 0 °C. A solution of *n*-BuLi (1.6 M in hexane, 5.80 mL, 9.2 mmol, 2.2 eq.) was added dropwise and the reaction mixture was stirred for 2 h at room temperature, before quenching with H_2O (15 mL) for the synthesis of (*S*)-**8a** or with D_2O for the synthesis of

(*S*)-**8b**. The mixture was extracted with Et_2O (3 x 40 mL), the combined organic layers were dried with $MgSO_4$, concentrated under reduced pressure and the crude product was purified by column chromatography on silica gel [cyclohexane/ethyl acetate (50:1)] to yield alkyne (*S*)-**8a** (1.25 g, 3.9 mmol, 93%) or (*S*)-**8b** (1.30 g, 4.0 mmol, 95%) as a colourless oil. The same procedure was used to convert (*R*)-**7** (2.00 g, 4.2 mmol, 1.0 eq.) into (*R*)-**8a** (1.20 g, 3.7 mmol, 88%) or (*R*)-**8b** (1.21 g, 3.7 mmol, 88%).

(*S*)-8a: ^{1}H-NMR (500 MHz, C_6D_6): δ [ppm] = 7.80-7.72 (m, 4H, 4 x CH), 7.25-7.19 (m, 6H, 6 x CH), 3.74 (dd, *J* = 9.6, 5.9 Hz, 1H, 0.5 x CH_2), 3.56 (dd, *J* = 9.6, 7.1 Hz, 1H, 0.5 x CH_2), 2.64-2.51 (m, 1H, CH), 1.81 (d, *J* = 2.4 Hz, 1H, CH), 1.17 (s, 9H, 3 x CH_3), 1.11 (d, *J* = 6.9 Hz, 3H, CH_3). ^{13}C-NMR (126 MHz, C_6D_6) δ [ppm] = 136.1 (4 x CH), 134.0 (C_q), 134.0 (C_q), 130.0 (2 x CH), 128.1 (4 x CH), 86.5 (C_q), 69.8 (CH), 68.0 (CH_2), 29.3 (CH), 27.1 (3 x CH_3), 19.6 (C_q), 17.5 (CH_3). TLC [cyclohexane/ethyl acetate (50:1)]: R_f = 0.28. GC (HP-5MS): *I* = 2052. MS (EI, 70 eV): *m*/*z* (%) = 265 (94), 247 (18), 235 (100), 211 (19), 207 (84), 197 (22), 187 (89), 181 (48), 143 (25), 135 (29), 129 (36), 105 (45), 57 (23), 41 (18). $[\alpha]_D^{20}$ = –5.8° (*c* 1.8, CH_2Cl_2). Lit: $[\alpha]_D^{26}$ = –5.3° (*c* 4.1, $CHCl_3$).[2]

(*R*)-8a: $[\alpha]_D^{20}$ = +6.9° (*c* 1.4, CH_2Cl_2). Lit: $[\alpha]_D^{25}$ = +5.6° (*c* 1.0, $CHCl_3$).[22] Spectroscopic data as for the (*S*) enantiomer.

(*S*)-8b: ^{1}H-NMR (500 MHz, C_6D_6): δ [ppm] = 7.81-7.70 (m, 4H, 4 x CH), 7.25-7.18 (m, 6H, 6 x CH), 3.74 (dd, *J* = 9.6, 5.9 Hz, 1H, 0.5 x CH_2), 3.56 (dd, *J* = 9.6, 7.1 Hz, 1H, 0.5 x CH_2), 2.63-2.52 (m, 1H, CH), 1.17 (s, 9H, 3 x CH_3), 1.11 (d, *J* = 6.9 Hz, 3H, CH_3). ^{13}C-NMR (126 MHz, C_6D_6) δ [ppm] = 136.1 (4 x CH), 134.0 (C_q), 134.0 (C_q), 130.0 (2 x CH), 128.1 (4 x CH), 86.0 (t, *J* = 7.5 Hz, C_q), 69.5 (t, *J* = 38.0 Hz, CH), 68.0 (CH_2), 29.3 (CH), 27.1 (3 x CH_3), 19.6 (C_q), 17.5 (CH_3). TLC [cyclohexane/ethyl acetate (50:1)]: R_f = 0.28. GC (HP-5MS): *I* = 2049. MS (EI, 70 eV): *m*/*z* (%) = 266 (98), 236 (100), 208 (76), 197 (27), 188 (91), 181 (52), 144 (23), 135 (30), 130 (50), 105 (59), 77 (16), 57 (24), 41 (22). $[\alpha]_D^{20}$ = –5.9° (*c* 1.8, CH_2Cl_2).

(*R*)-8b: $[\alpha]_D^{20}$ = +5.4° (*c* 1.2, CH_2Cl_2). Spectroscopic data as for the (*S*) enantiomer.

Synthesis of (*S*,*E*)- and (*R*,*E*)-*tert*-butyl(((4-^{2}H)-2,3-dimethylbut-3-en-1-yl)oxy)diphenylsilane (9a) and (*S*,*Z*)- and (*R*,*Z*)-*tert*-butyl(((4-^{2}H)-2,3-dimethylbut-3-en-1-yl)oxy)diphenylsilane (9b)

Following a known procedure,[20] Cp_2ZrCl_2 (340 mg, 1.16 mmol, 0.3 eq.) was dissolved in 1,2-dichloroethane (12 mL), before a solution of $AlMe_3$ (5.8 mL, 2 M in hexane, 11.6 mmol, 3.0 eq.) was added dropwise. The suspension was cooled to 0 °C and a solution of alkyne (*S*)-**8a** (1.25 g, 3.88 mmol, 1.0 eq.) in 1,2-dichloroethane (1.2 mL) was added dropwise. The reaction was stirred at room temperature overnight and quenched by addition of acetic acid-d_1 (5.0 mL, 1 M in D_2O). The mixture was concentrated under reduced pressure and the residue was extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with $NaHCO_3$ solution (10 mL) and water (10 mL), dried with $MgSO_4$ and concentrated under reduced pressure. Purification was done by column chromatography on silica gel [cyclohexane/ethyl acetate (50:1)] to yield silane (*S*)-**9a** (890 mg, 2.62 mmol, 68%) as colourless oil. (*S*)-**8b** (1.30 g, 4.02 mmol, 1.0 eq.) was converted into (*S*)-**9b** (930 mg, 2.74 mmol, 68%) by the same procedure except that the reaction mixture was

quenched by addition of acetic acid (5.0 mL, 1 M in H_2O). The same procedure was used to convert (*R*)-**8a** (1.20 g, 3.7 mmol, 1.0 eq.) into (*R*)-**9a** (830 mg, 2.44 mmol, 66%) or convert (*R*)-**8b** (1.21 g, 3.7 mmol, 1.0 eq.) into (*R*)-**9b** (920 mg, 2.71 mmol, 73%).
(*S*)-9a: ^{1}H-NMR (500 MHz, C_6D_6): δ [ppm] = 7.83-7.74 (m, 4H, 4 x CH), 7.27-7.20 (m, 6H, 6 x CH), 4.86-4.72 (m, 1H, CH), 3.70 (dd, *J* = 9.9, 6.3 Hz, 1H, 0.5 x CH_2), 3.57 (dd, *J* = 9.9, 6.8 Hz, 1H, 0.5 x CH_2), 2.44-2.33 (m, 1H, CH), 1.57 (d, *J* = 0.8 Hz, 3H, CH_3), 1.19 (s, 9H, 3 x CH_3), 1.03 (d, *J* = 6.9 Hz, 3H, CH_3). ^{13}C-NMR (126 MHz, C_6D_6) δ [ppm] = 147.6 (C_q), 136.1 (2 x CH), 136.1 (2 x CH), 134.4 (C_q), 134.4 (C_q), 130.0 (2 x CH), 128.1 (4 x CH), 110.7 (t, *J* = 23.8 Hz, CH), 68.0 (CH_2), 43.8 (CH), 27.2 (3 x CH_3), 20.6 (CH_3), 19.6 (C_q), 16.3 (CH_3). TLC [cyclohexane/ethyl acetate (50:1)]: R_f = 0.43. GC (HP-5MS): *I* = 2123. MS (EI, 70 eV): *m*/*z* (%) = 282 (41), 239 (100), 211 (10), 199 (12), 197 (11), 183 (39), 181 (25), 135 (11), 105 (13), 57 (14), 41 (13). $[\alpha]_D^{20}$ = –0.1° (*c* 1.6, CH_2Cl_2).
(*R*)-9a: $[\alpha]_D^{20}$ = +0.1° (*c* 1.6, CH_2Cl_2). Spectroscopic data as for the (*S*) enantiomer.
(*S*)-9b: ^{1}H-NMR (500 MHz, C_6D_6): δ [ppm] = 7.86-7.71 (m, 4H, 4 x CH), 7.26-7.20 (m, 6H, 6 x CH), 4.80 (q, *J* = 1.5 Hz, 1H, CH), 3.70 (dd, *J* = 9.9, 6.3 Hz, 1H, 0.5 x CH_2), 3.57 (dd, *J* = 9.9, 6.8 Hz, 1H, 0.5 x CH_2), 2.44-2.32 (m, 1H, CH), 1.57 (d, *J* = 1.5 Hz, 3H, CH_3), 1.19 (s, 9H, 3 x CH_3), 1.03 (d, *J* = 6.9 Hz, 3H, CH_3). ^{13}C-NMR (126 MHz, C_6D_6) δ [ppm] = 147.6 (C_q), 136.1 (2 x CH), 136.1 (2 x CH), 134.4 (C_q), 134.4 (C_q), 130.0 (2 x CH), 128.1 (2 x CH), 128.1 (2 x CH), 110.7 (t, *J* = 23.7 Hz, CH), 68.0 (CH_2), 43.8 (CH), 27.2 (3 x CH_3), 20.6(CH_3), 19.6 (C_q), 16.3 (CH_3). TLC [cyclohexane/ethyl acetate (50:1)]: R_f = 0.43. GC (HP-5MS): *I* = 2124. MS (EI, 70 eV): *m*/*z* (%) = 282 (31), 239 (100), 199 (10), 197 (10), 183 (38), 181 (23), 135 (11), 105 (11), 57 (12), 41 (12). $[\alpha]_D^{20}$ = –0.5° (*c* 2.0, CH_2Cl_2).
(*R*)-9b: $[\alpha]_D^{20}$ = +0.3° (*c* 1.5, CH_2Cl_2). Spectroscopic data as for the (*S*) enantiomer.

Synthesis of (*S*,*E*)- and (*R*,*E*)-(4-^{2}H)-2,3-dimethylbut-3-en-1-yl 4-methylbenzenesulfonate (10a) and (*S*,*Z*)- and (*R*,*Z*)-(4-^{2}H)-2,3-dimethylbut-3-en-1-yl 4-methylbenzenesulfonate (10b)
Silane (*S*)-**9a** (890 mg, 2.62 mmol, 1.0 eq.) was dissolved in THF (15 mL). After cooling to 0 °C, a solution of TBAF (3.2 mL, 1 M in THF, 3.20 mmol, 1.2 eq.) was added dropwise. The reaction was stirred for 2 h at room temperature and quenched with water (20 mL). The mixture was extracted with Et_2O (3 x 30 mL), the combined organic layers were dried with $MgSO_4$ and carefully concentrated under reduced pressure (700 mbar, 40 °C, 20 min) to acquire the residue. The concentrated residue was dissolved in CH_2Cl_2 (30 mL) and the solution was cooled to 0 °C. After adding of DMAP (1.06 g, 8.68 mmol, 3.3 eq.), *p*-TsCl (partially dissolved in 10 mL CH_2Cl_2, 1.25 g, 6.56 mmol, 2.5 eq.) was added dropwise to the solution and the reaction mixture was stirred at room temperature overnight. The reaction was quenched by addition of sat. NH_4Cl (50 mL). The mixture was extracted three times with Et_2O (3 x 50 mL). The combined organic layers were washed with sat. NaCl (10 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Column chromatography on silica gel [cyclohexane/ethyl acetate (15:1)] gave the tosylate (*S*)-**10a** (290 mg, 1.14 mmol, 43%) as colourless oil. The same procedure was used to convert (*S*)-**9b** (930 mg, 2.74 mmol, 1.0 eq.) into (*S*)-**10b** (540 mg, 2.11 mmol, 77%), (*R*)-**9a** (830 mg, 2.44 mmol, 1.0 eq.) into (*R*)-**10a** (450 mg, 1.76 mmol, 72%), and (*R*)-**9b** (920 mg, 2.71

mmol, 1.0 eq.) into (*R*)-**10b** (510 mg, 2.00 mmol, 74%).

(*S*)-10a: ^{1}H-NMR (500 MHz, C_6D_6): δ [ppm] = 7.76 (d, *J* = 8.2 Hz, 2H, 2 x CH), 6.69 (d, *J* = 8.2 Hz, 2H, 2 x CH), 4.60-4.57 (m, 1H, CH), 3.91 (dd, *J* = 9.6, 6.7 Hz, 1H, 0.5 x CH_2), 3.79 (dd, *J* = 9.6, 6.9 Hz, 1H, 0.5 x CH_2), 2.28-2.17 (m, 1H, CH), 1.82 (s, 3H, CH_3), 1.37 (d, *J* = 0.9 Hz, 3H, CH_3), 0.76 (d, *J* = 7.0 Hz, 3H, CH_3). ^{13}C-NMR (126 MHz, C_6D_6) δ [ppm] = 145.2 (C_q), 144.2 (C_q), 134.5 (C_q), 129.8 (2 x CH), 128.2 (2 x CH), 111.8 (t, *J* = 23.9 Hz, CH), 72.9 (CH_2), 40.4 (CH), 21.1 (CH_3), 19.9 (CH_3), 15.8 (CH_3). TLC [cyclohexane/ethyl acetate (15:1)]: R_f = 0.22. GC (HP-5MS): *I* = 1878. MS (EI, 70 eV): *m*/*z* (%) = 155 (60), 91 (100), 89 (17), 83 (63), 70 (23), 68 (27), 65 (47), 42 (28), 41 (23), 39 (20). $[\alpha]_D^{20}$ = +4.9° (*c* 1.4, CH_2Cl_2).

(*R*)-10a: $[\alpha]_D^{20}$ = –5.2° (*c* 1.3, CH_2Cl_2). Spectroscopic data as for the (*S*) enantiomer.

(*S*)-10b: ^{1}H-NMR (500 MHz, C_6D_6): δ [ppm] = 7.76 (d, *J* = 8.2 Hz, 2H, 2 x CH), 6.69 (d, *J* = 8.2 Hz, 2H, 2 x CH), 4.65 (q, *J* = 1.5 Hz, 1H, CH), 3.91 (dd, *J* = 9.6, 6.7 Hz, 1H, 0.5 x CH_2), 3.79 (dd, *J* = 9.6, 6.9 Hz, 1H, 0.5 x CH_2), 2.28-2.17 (m, 1H, CH), 1.82 (s, 3H, CH_3), 1.37 (d, *J* = 1.5 Hz, 3H, CH_3), 0.76 (d, *J* = 7.0 Hz, 3H, CH_3). ^{13}C-NMR (126 MHz, C_6D_6) δ [ppm] = 145.2 (C_q), 144.2 (C_q), 134.5 (C_q), 129.8 (2 x CH), 128.2 (2 x CH), 111.8 (t, *J* = 23.8 Hz, CH), 72.9 (CH_2), 40.4 (CH), 21.1 (CH_3), 19.9 (t, *J* = 1.7 Hz, CH_3), 15.8 (CH_3). TLC [cyclohexane/ethyl acetate (15:1)]: R_f = 0.22. GC (HP-5MS): *I* = 1876. MS (EI, 70 eV): *m*/*z* (%) = 155 (59), 91 (100), 89 (17), 83 (65), 70 (24), 68 (28), 65 (44), 42 (28), 41 (23), 39 (20). $[\alpha]_D^{20}$ = +5.5° (*c* 1.1, CH_2Cl_2).

(*R*)-10b: $[\alpha]_D^{20}$ = –5.3° (*c* 1.1, CH_2Cl_2). Spectroscopic data as for the (*S*) enantiomer.

Synthesis of (*S*,*E*)- and (*R*,*E*)-(4-^{2}H)-2-Me-IPP and (*S*,*Z*)- and (*R*,*Z*)-(4-^{2}H)-2-Me-IPP

In the same procedure as described above, tosylate (*S*)-**10a** (290 mg, 1.14 mmol, 1.0 eq.) was converted to the corresponding IPP with (^{n}NBu$_4$)$_3$HP$_2$O$_7$ (1.54 g, 1.71 mmol, 1.5 eq.) in MeCN (3.0 mL) to yield (*S*,*E*)-(4-^{2}H)-2-Me-IPP as an inseparable 1:1.9 mixture (by NMR peak integration) with ammonium tosylate as a white solid (0.54 g, 0.43 mmol, 37%). The same procedure was used to convert (*S*)-**10b** (540, 2.11 mmol, 1.0 eq.) into (*S*,*Z*)-(4-^{2}H)-2-Me-IPP as an inseparable 1:2.1 mixture with ammonium tosylate as a white solid (1.03 g, 0.85 mmol, 40%), (*R*)-**10a** (450 mg, 1.76 mmol, 1.0 eq.) into (*R*,*E*)-(4-^{2}H)-2-Me-IPP as an inseparable 1:2.0 mixture with ammonium tosylate as a white solid (880 mg, 0.70 mmol, 39%), and (*R*)-**10b** (510 mg, 2.00 mmol, 1.0 eq.) into (*R*,*Z*)-(4-^{2}H)-2-Me-IPP as an inseparable 1:2.1 mixture with ammonium tosylate as a white solid (1.10 g, 0.93 mmol, 46%).

(*S*,*E*)-(4-^{2}H)-2-Me-IPP: ^{1}H-NMR (500 MHz, D_2O): δ [ppm] = 4.83-4.82 (m, 1H, CH), 3.93-3.86 (m, 1H, 0.5 x CH_2), 3.86-3.80 (m, 1H, 0.5 x CH_2), 2.57-2.46 (m, 1H, CH), 1.74 (d, *J* = 1.4 Hz, 3H, CH_3), 1.03 (dd, *J* = 7.0, 1.4 Hz, 3H, CH_3). ^{13}C-NMR (126 MHz, D_2O) δ [ppm] = 148.8 (C_q), 110.2 (t, *J* = 22.9 Hz, CH), 68.7 (d, $^{2}J_{C,P}$ = 5.8 Hz, CH_2), 41.1 (d, $^{3}J_{C,P}$ = 7.9 Hz, CH), 19.1 (CH_3), 15.4 (CH_3). ^{31}P-NMR (202 MHz, D_2O): δ [ppm] = –6.69 (d, $^{2}J_{P,P}$ = 21.6 Hz, 1P), –10.49 (d, $^{2}J_{P,P}$ = 21.6 Hz, 1P). HRMS (TOF): *m*/*z* = 260.0208 (calc. for $[C_6H_{12}DO_7P_2]^-$ 260.0205).

(*R*,*E*)-(4-^{2}H)-2-Me-IPP: HRMS (TOF): *m*/*z* = 260.0207 (calc. for $[C_6H_{12}DO_7P_2]^-$ 260.0205). Spectroscopic data as for the (*S*) enantiomer.

(*S*,*Z*)-(4-^{2}H)-2-Me-IPP: ^{1}H-NMR (500 MHz, D_2O): δ [ppm] = 4.83-4.82 (m, 1H, CH), 3.93-3.87 (m, 1H, 0.5 x CH_2), 3.86-3.79 (m, 1H. 0.5 x CH_2), 2.56-2.47 (m, 1H, CH), 1.74-1.72 (m, 3H, CH_3), 1.03 (dd, J = 7.6, 3.0 Hz, 3H, CH_3). ^{13}C-NMR (126 MHz, D_2O) δ [ppm] = 148.7 (C_q), 110.2 (t, J = 23.5 Hz, CH), 68.8 (d, $^2J_{C,P}$ = 5.8 Hz, CH_2), 41.0 (d, $^3J_{C,P}$ = 7.6 Hz, CH),19.1 (CH_3), 15.4 (CH_3). ^{31}P-NMR (202 MHz, D_2O): δ [ppm] = –7.28 (d, $^2J_{P,P}$ = 21.2 Hz, 1P), –10.53 (d, $^2J_{P,P}$ = 21.3 Hz, 1P). HRMS (TOF): m/z = 260.0207 (calc. for $[C_6H_{12}DO_7P_2]^-$ 260.0205).

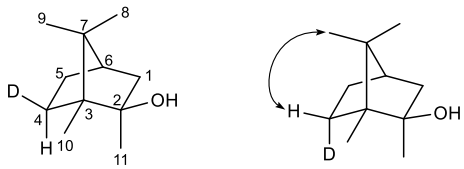
(*R*,*Z*)-(4-^{2}H)-2-Me-IPP: HRMS (TOF): m/z = 260.0208 (calc. for $[C_6H_{12}DO_7P_2]^-$ 260.0205). Spectroscopic data as for the (*S*) enantiomer.

Enzyme incubation of DMAPP and (*S*,*E*)-(4-^{2}H)-2-Me-IPP (or (*S*,*Z*)-(4-^{2}H)-2-Me-IPP, (*R*,*E*)-(4-^{2}H)-2-Me-IPP, (*R*,*Z*)-(4-^{2}H)-2-Me-IPP) with FPPS and 2MIBS

Culture conditions, protein expressions and protein purifications were performed as described above. The soluble enzyme fractions were checked for purity by SDS-PAGE. The test incubations were performed with 0.3 mg DMAPP and 0.3 mg (*S*,*E*)-(4-^{2}H)-2-Me-IPP (or (*S*,*Z*)-(4-^{2}H)-2-Me-IPP, (*R*,*E*)-(4-^{2}H)-2-Me-IPP, (*R*,*Z*)-(4-^{2}H)-2-Me-IPP) dissolved respectively in substrate buffer (50 µL; 25 mM NH_4HCO_3) and diluted with incubation buffer (700 µL; 50 mM Tris/HCl, 10 mM $MgCl_2$, 10% glycerol, pH = 8.2). FPPS and 2MIBS protein solutions (100 µL) obtained respectively from 100 mL expression culture were added to the mixture, followed by incubation with shaking at 30 °C overnight. The crude product was extracted with hexane (500 µL), the extract was tried with $MgSO_4$ and directly analysed by GC/MS. Large scale preparations were done by dissolving 30 mg DMAPP and 40 mg (*S*,*E*)-(4-^{2}H)-2-Me-IPP (or (*S*,*Z*)-(4-^{2}H)-2-Me-IPP, (*R*,*E*)-(4-^{2}H)-2-Me-IPP, (*R*,*Z*)-(4-^{2}H)-2-Me-IPP) in substrate buffer (25 mL). These solutions were added into reaction mixture of FPPS (25 mL; from 8 L expression culture, 2.1 mg mL^{-1}) and 2MIBS (25 mL; from 8 L expression culture, 2.3 mg mL^{-1}) protein preparations and incubation buffer (150 mL). The reaction mixture was stirred overnight at 30 °C. The reaction was extracted *n*-pentane (3x 200 mL), and the extracts were dried with $MgSO_4$ and concentrated in vacuo (600 mbar, 35 °C). Column chromatography on silica gel [*n*-pentane/Et_2O (2:1)] yield pure (*S*)-(4-^{2}H)-**1** and (*R*)-(4-^{2}H)-**1**.

(*S*)-(4-^{2}H)-1. TLC [*n*-pentane/Et_2O (2:1)]: R_f = 0.59. GC (HP5-MS): *I* = 1196. NMR data are given in Table S2.

(*R*)-(4-^{2}H)-1. TLC [*n*-pentane/Et_2O (2:1)]: R_f = 0.59. GC (HP5-MS): *I* = 1196. NMR data are given in Table S2.



(*S*)-(4-^{2}H)-**1** (*R*)-(4-^{2}H)-**1**

Figure S5. Carbon numbering and structure determination for (*S*)-(4-^{2}H)-**1** and (*R*)-(4-^{2}H)-**1.** Double headed arrow: key NOESY correlation.

Table S2. NMR data of (*S*)-(4-^{2}H)-**1** and (*R*)-(4-^{2}H)-**1** in C_6D_6 recorded at 298 K.

		(*S*)-(4-^{2}H)-**1**		(*R*)-(4-^{2}H)-**1**	
C[a]	type	^{13}C[b]	^{1}H[b]	^{13}C[b]	^{1}H[b]
1	CH_2	47.8	2.10 (ddd, *J* = 12.9, 4.4, 3.2) 1.22 (d, *J* = 12.9)	47.8	2.10 (ddd, *J* = 12.9, 4.4, 3.2) 1.22 (d, *J* = 12.9)
2	C_q	78.9		79.0	
3	C_q	52.0		52.0	
4	CH	31.2 (t, *J* = 19.8)	1.21 (m)	31.2 (t, *J* = 20.1)	1.27 (m)
5	CH_2	27.2	1.59 (m) 0.88 (dd, *J* = 12.3, 9.4)	27.2	1.59 (m) 0.89 (m)
6	CH	45.9	1.62 (m)	45.9	1.62 (m)
7	C_q	49.2		49.2	
8	CH_3	21.9	1.25 (s)	21.8	1.25 (s)
9	CH_3	21.4	0.82 (s)	21.4	0.83 (s)
10	CH_3	10.1	0.78 (s)	10.1	0.78 (s)
11	CH_3	27.1	0.99 (s)	27.1	0.98 (s)
	2-OH		0.74 (br s)		0.73 (br s)

[a] Carbon numbering and colour code for hydrogens as shown in Figure S5. [b] Chemical shifts δ in ppm; multiplicity: s = singlet, d = doublet, t = triplet, m = multiplet, br = broad; coupling constants *J* are given in Hertz.

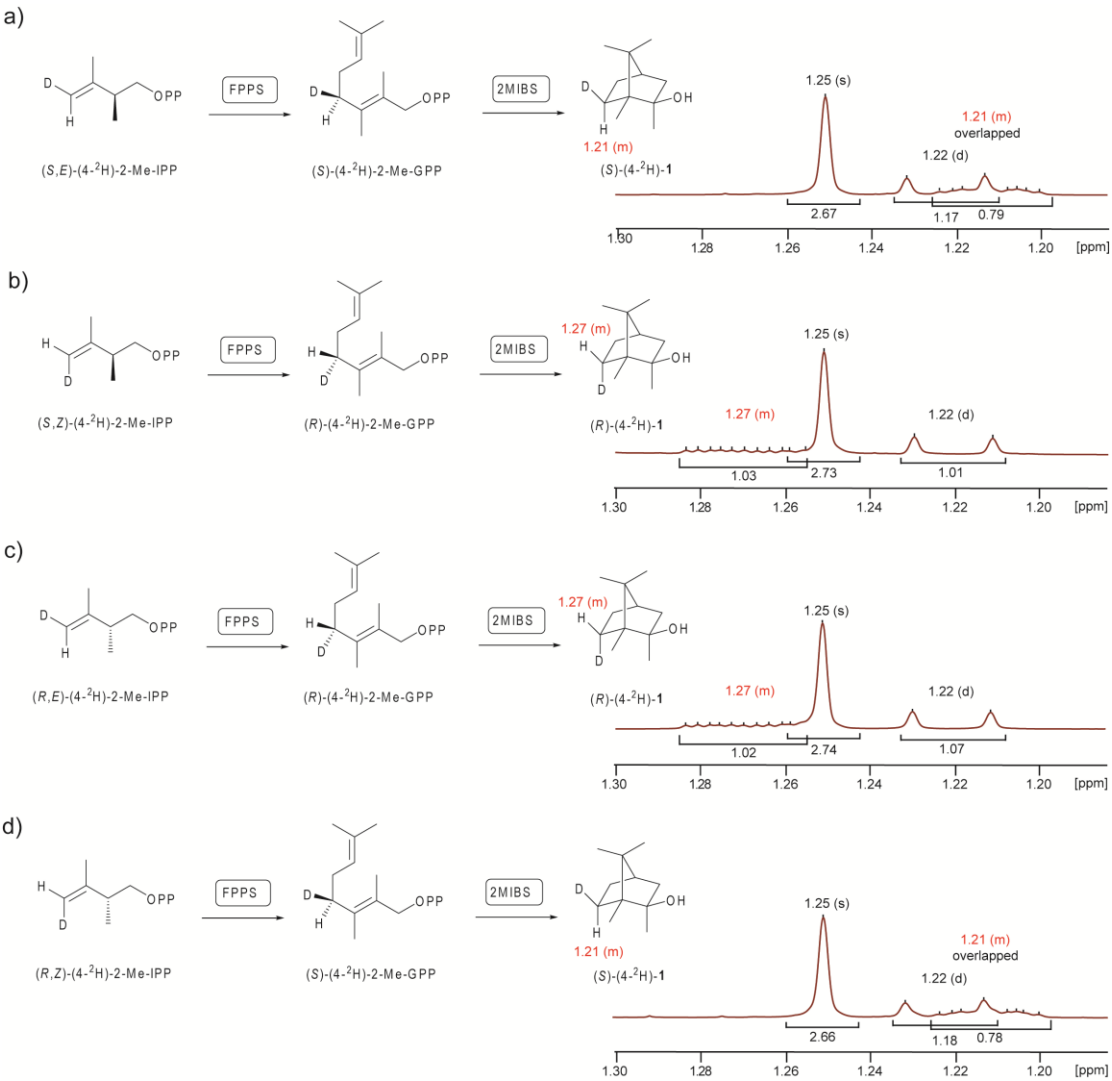


Figure S6. Partial enlarged ^{1}H-NMR spectra (700 MHz, C_6D_6) for the correspondingly purified compounds from large scale enzyme catalytic reactions of a) DMAPP and (*S*,*E*)-(4-^{2}H)-2-Me-IPP with FPPS and 2MIBS ((*S*)-(4-^{2}H)-**1**), of b) DMAPP and (*S*,*Z*)-(4-^{2}H)-2-Me-IPP with FPPS and 2MIBS ((*R*)-(4-^{2}H)-**1**), of c) DMAPP and (*R*,*E*)-(4-^{2}H)-2-Me-IPP with FPPS and 2MIBS ((*R*)-(4-^{2}H)-**1**), and of d) DMAPP and (*R*,*Z*)-(4-^{2}H)-2-Me-IPP with FPPS and 2MIBS ((*S*)-(4-^{2}H)-**1**). The C_4-H chemical shifts of product compounds are highlighted in red. The peak integrals for the diastereotopic hydrogens at C4 indicate a high enantiomeric purity for the four deuterated isotopomers of the precursor 2-Me-IPP (>98% *ee*).

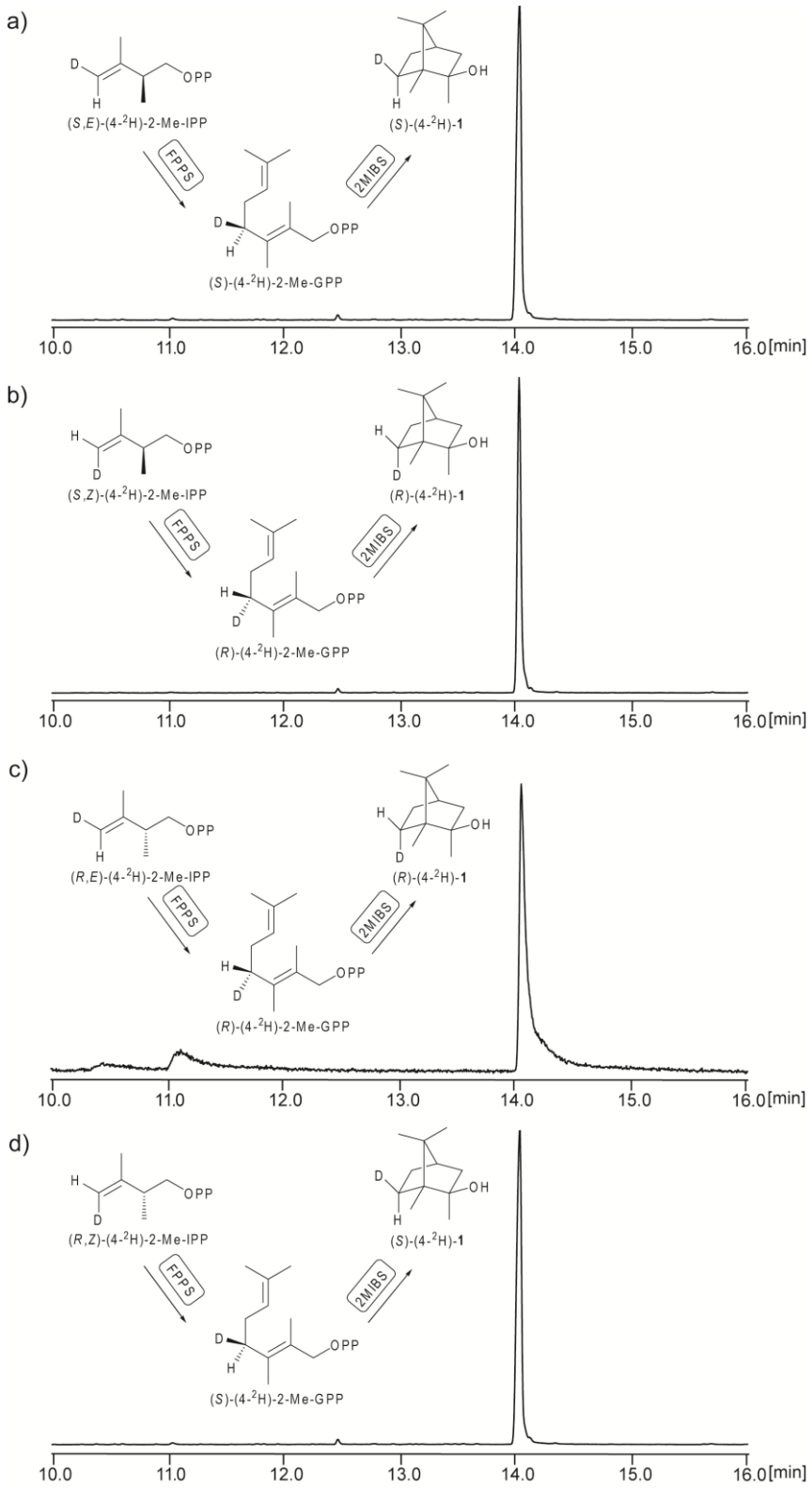


Figure S7. Total ion chromatograms of an extract from the incubation of a) DMAPP and (*S*,*E*)-(4-^{2}H)-2-Me-IPP with FPPS and 2MIBS, of b) DMAPP and (*S*,*Z*)-(4-^{2}H)-2-Me-IPP with FPPS and 2MIBS, of c) DMAPP and (*R*,*E*)-(4-^{2}H)-2-Me-IPP with FPPS and 2MIBS, and of d) DMAPP and (*R*,*Z*)-(4-^{2}H)-2-Me-IPP with FPPS and 2MIBS.

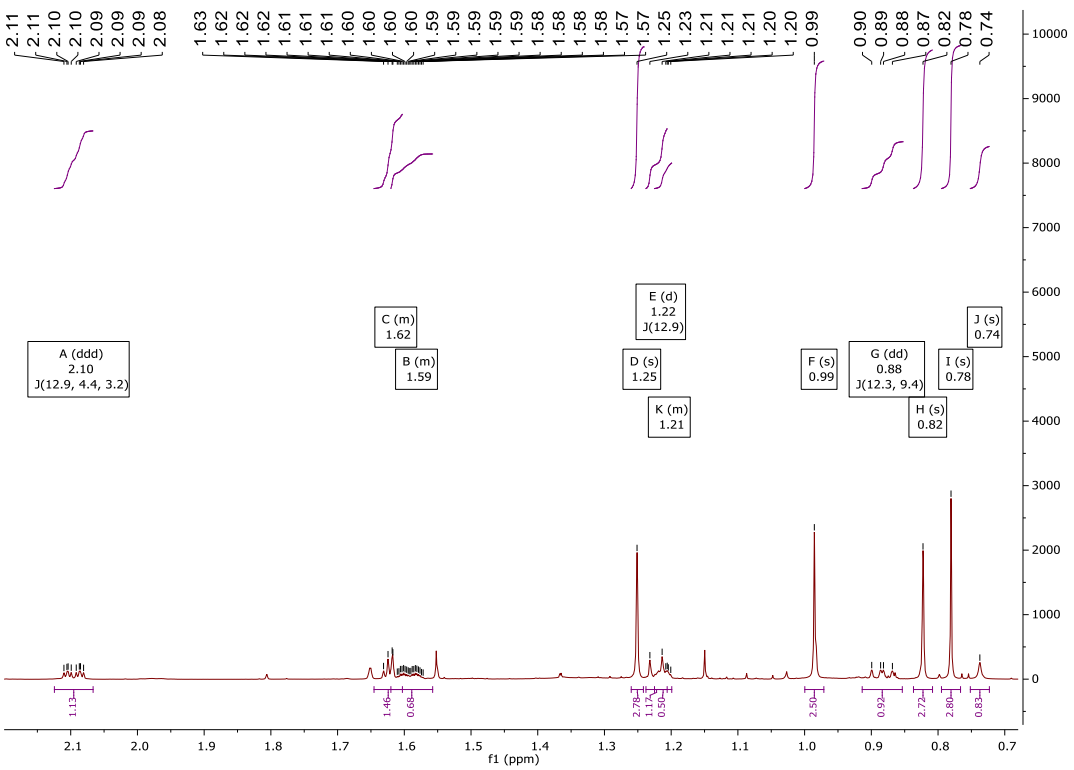


Figure S8. ^{1}H-NMR (700 MHz, C_6D_6) of (*S*)-(4-^{2}H)-**1**.

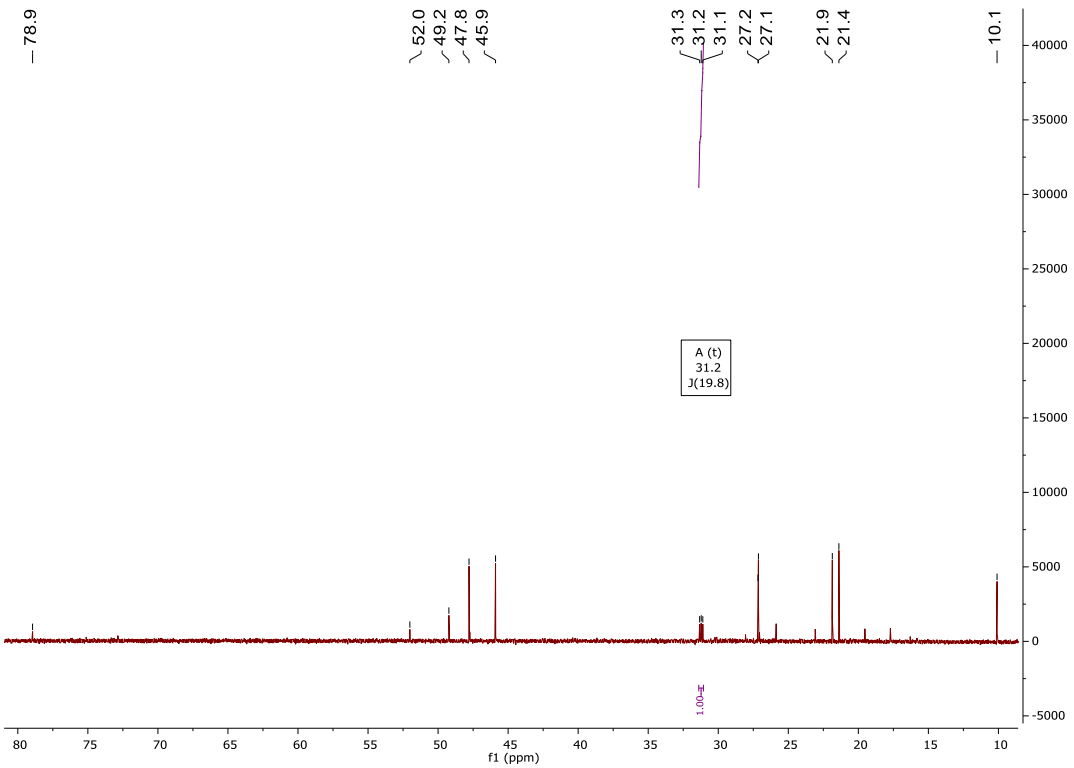


Figure S9. ^{13}C-NMR (176 MHz, C_6D_6) of (*S*)-(4-^{2}H)-**1**.

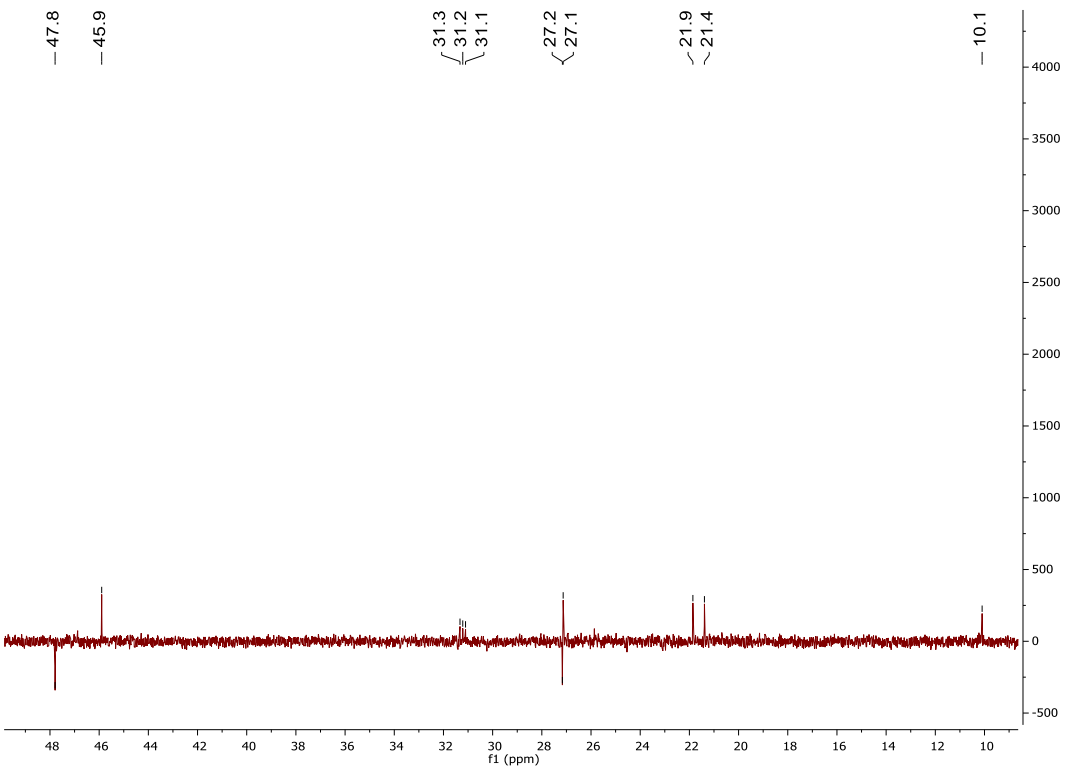


Figure S10. DEPT135 (176 MHz, C_6D_6) of (*S*)-(4-^{2}H)-**1**.

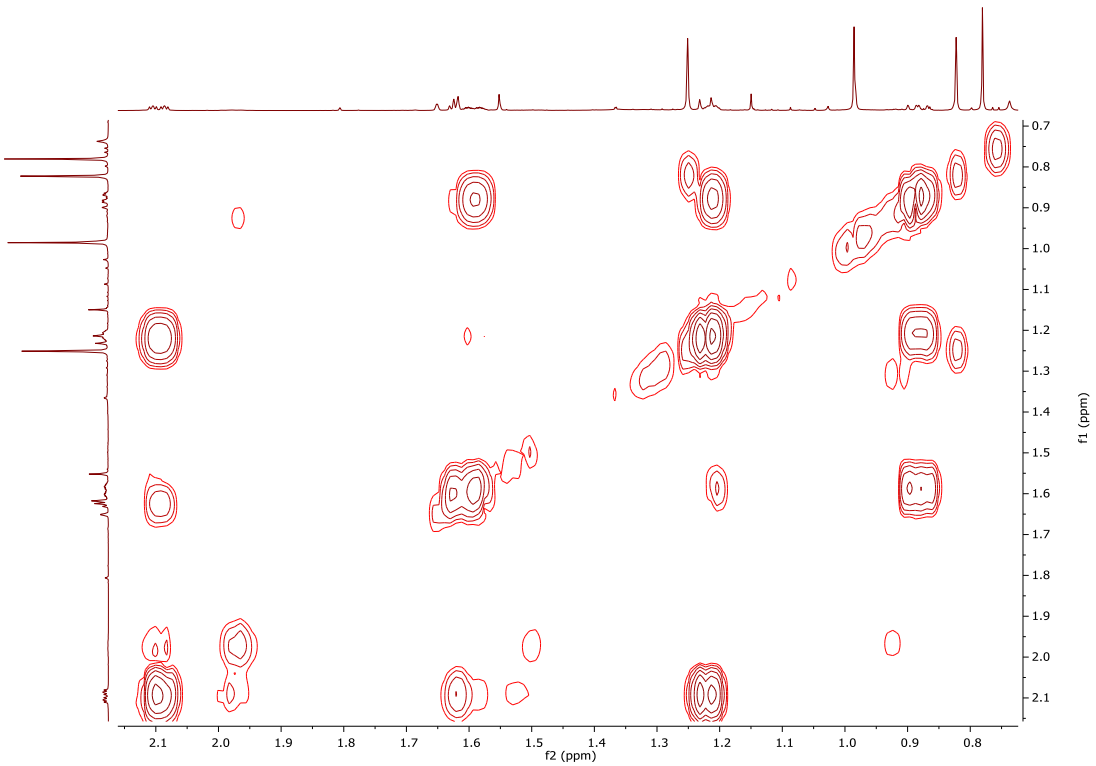


Figure S11. ^{1}H-^{1}H COSY (700 MHz, C_6D_6) of (*S*)-(4-^{2}H)-**1**.

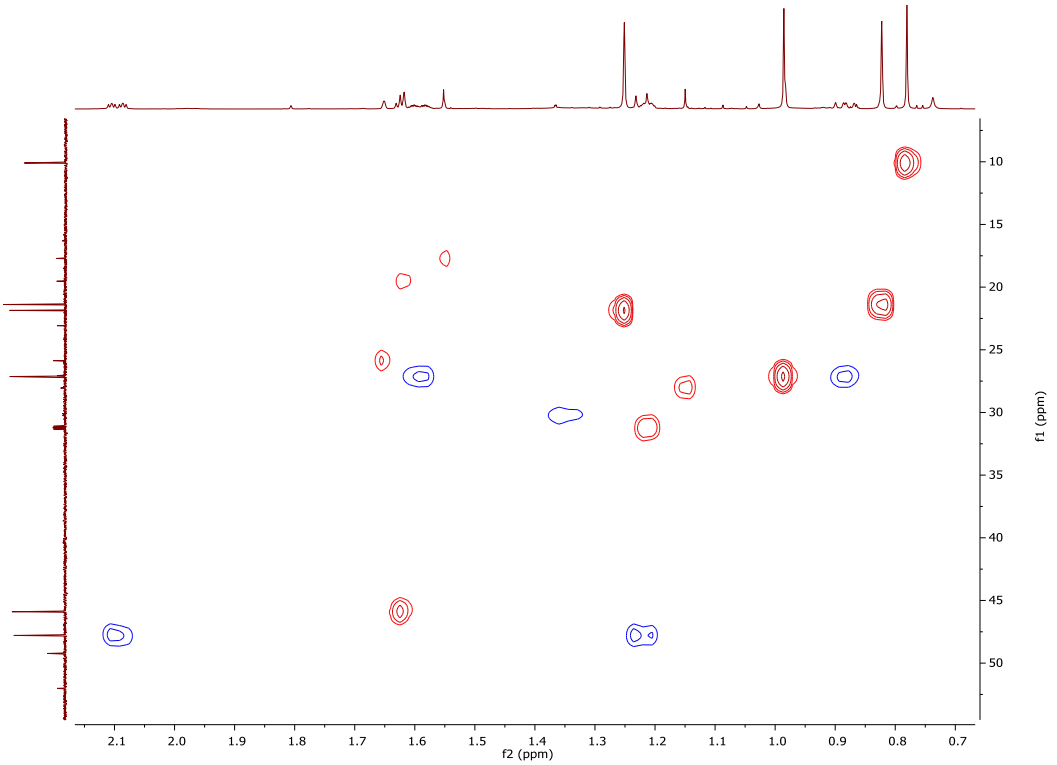


Figure S12. HSQC (700 MHz, C_6D_6) of (*S*)-(4-^{2}H)-**1**.

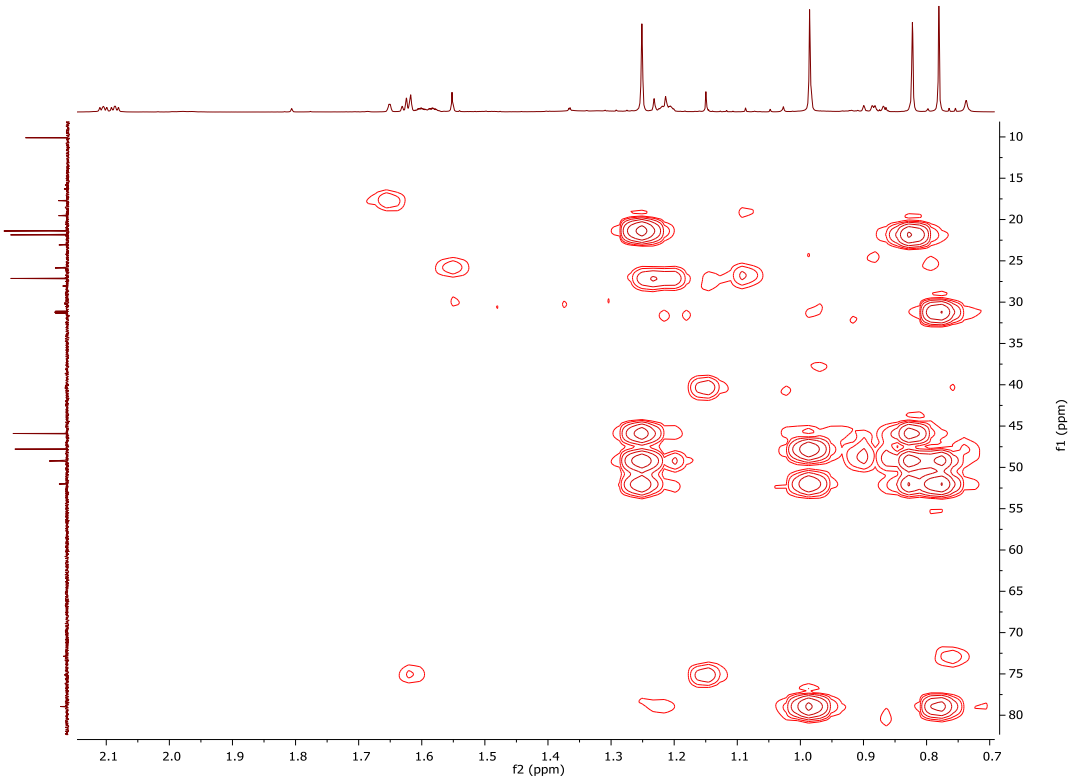


Figure S13. HMBC (700 MHz, C_6D_6) of (*S*)-(4-^{2}H)-**1**.

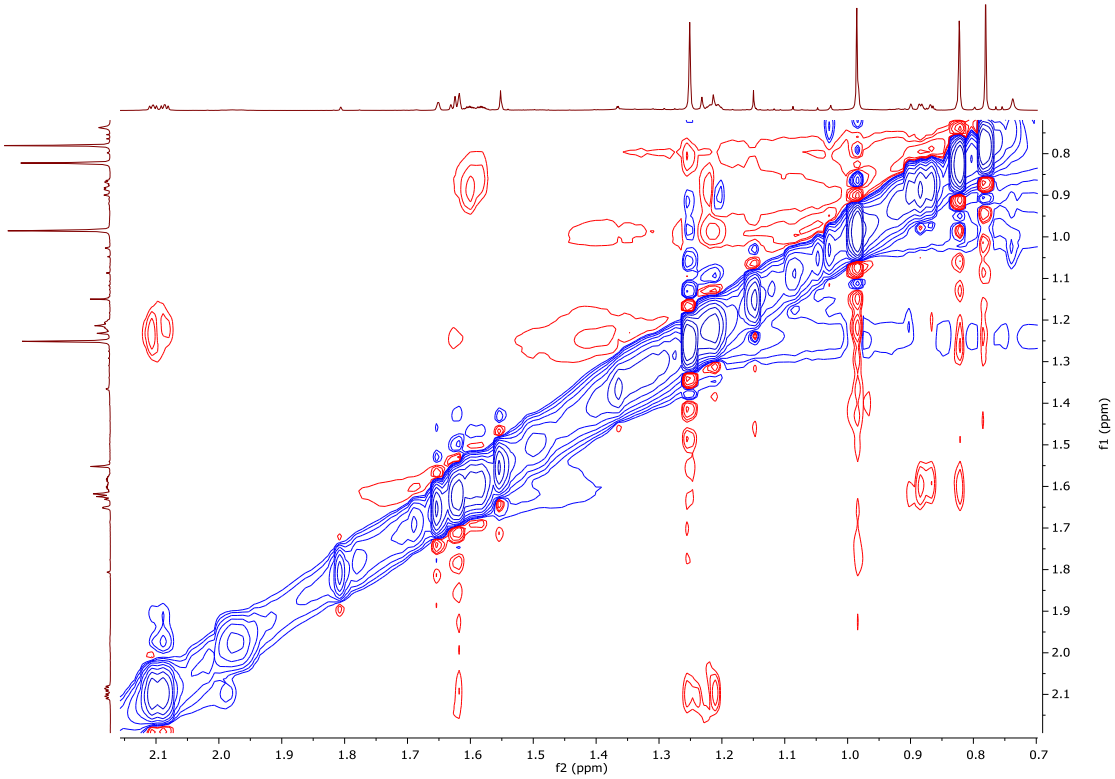


Figure S14. NOESY (700 MHz, C_6D_6) of (*S*)-(4-^{2}H)-**1**.

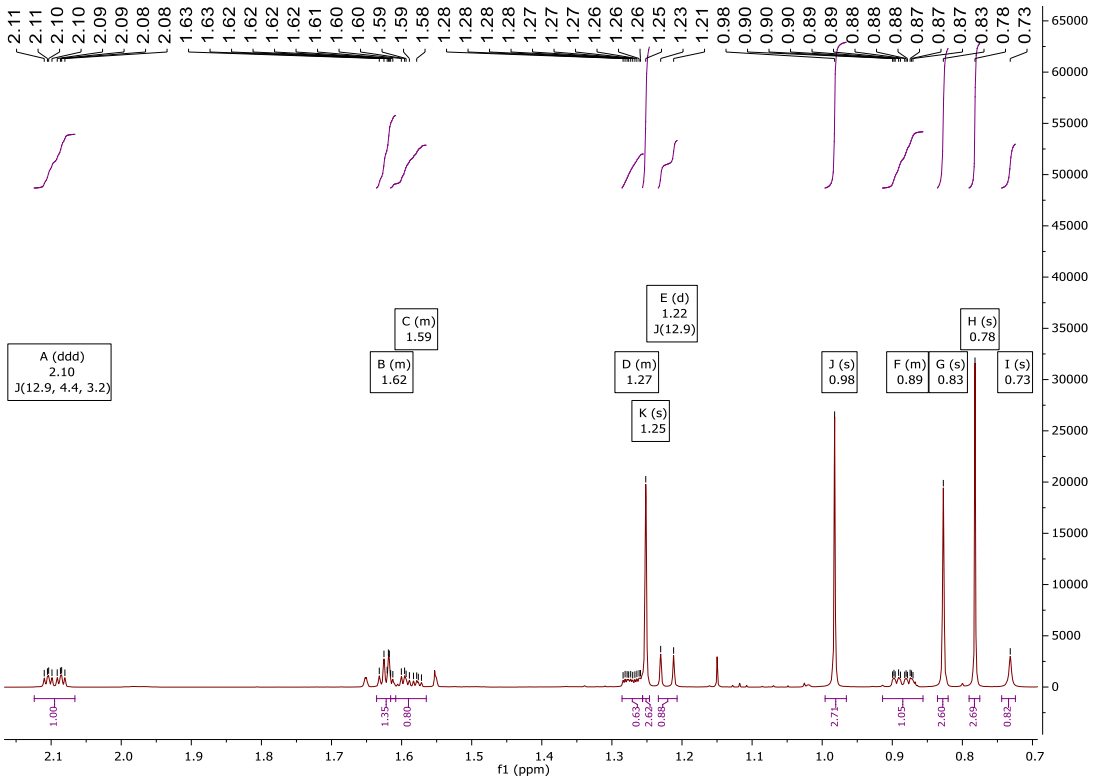


Figure S15. ^{1}H-NMR (700 MHz, C_6D_6) of (*R*)-(4-^{2}H)-**1**.

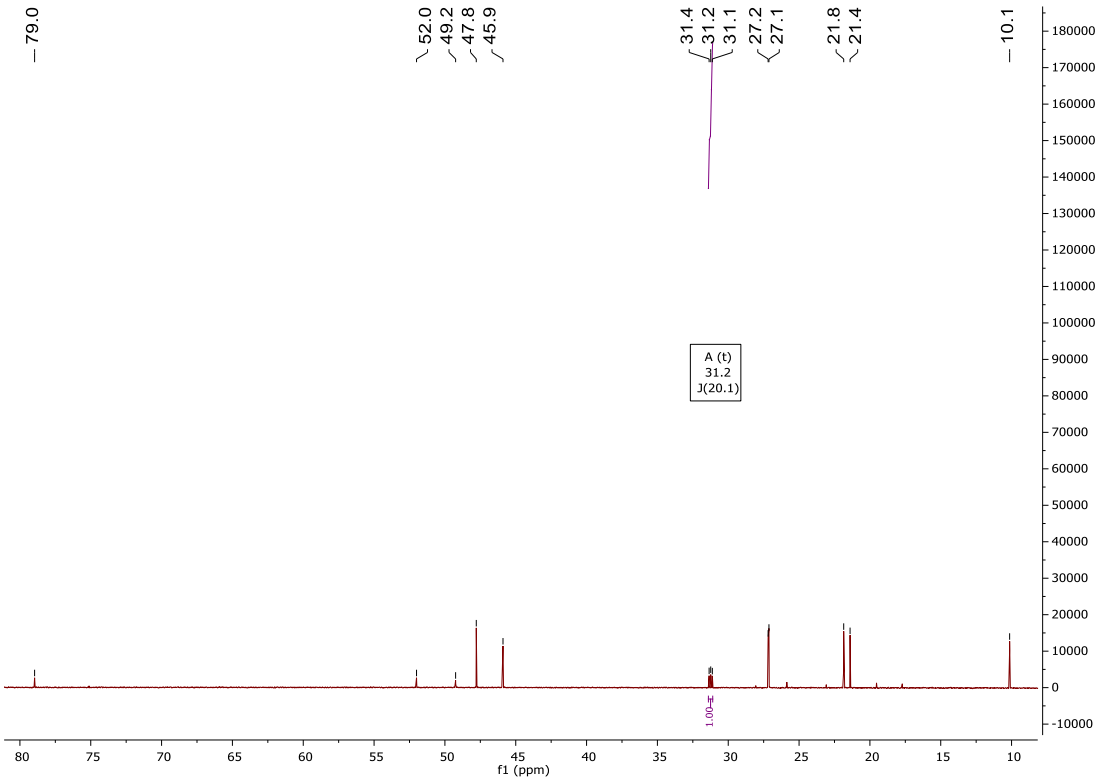


Figure S16. ^{13}C-NMR (176 MHz, C_6D_6) of (*R*)-(4-^{2}H)-**1**.

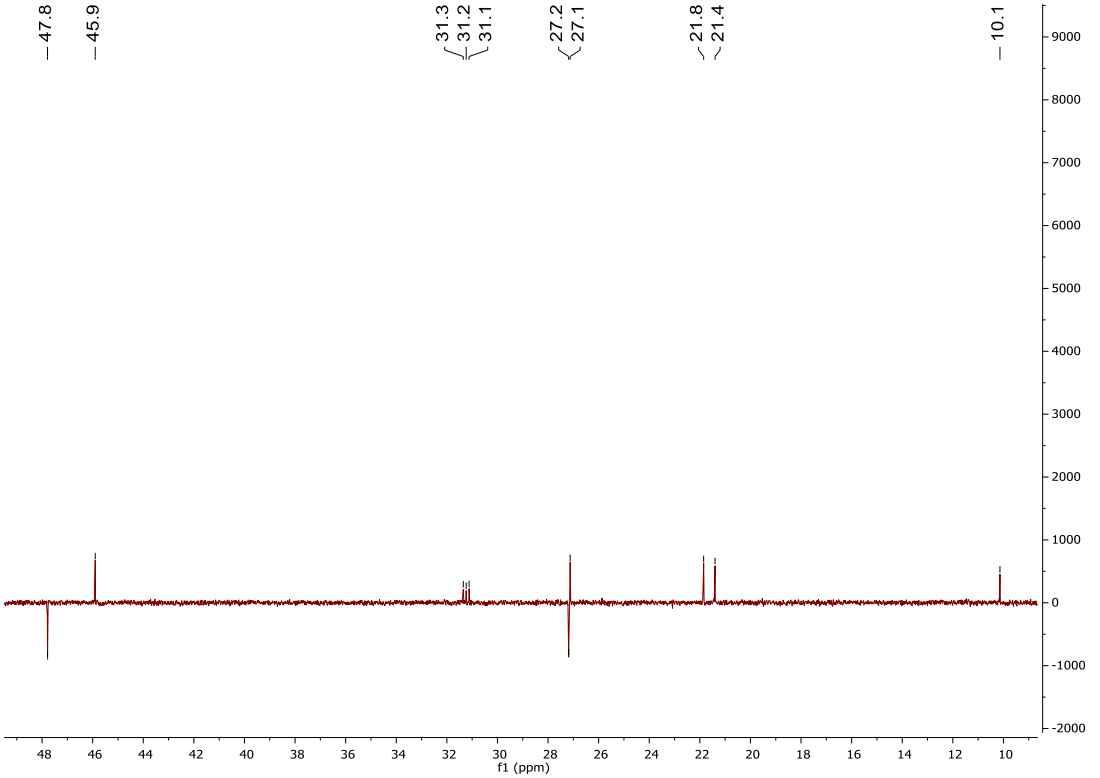


Figure S17. DEPT135 (176 MHz, C_6D_6) of (*R*)-(4-^{2}H)-**1**.

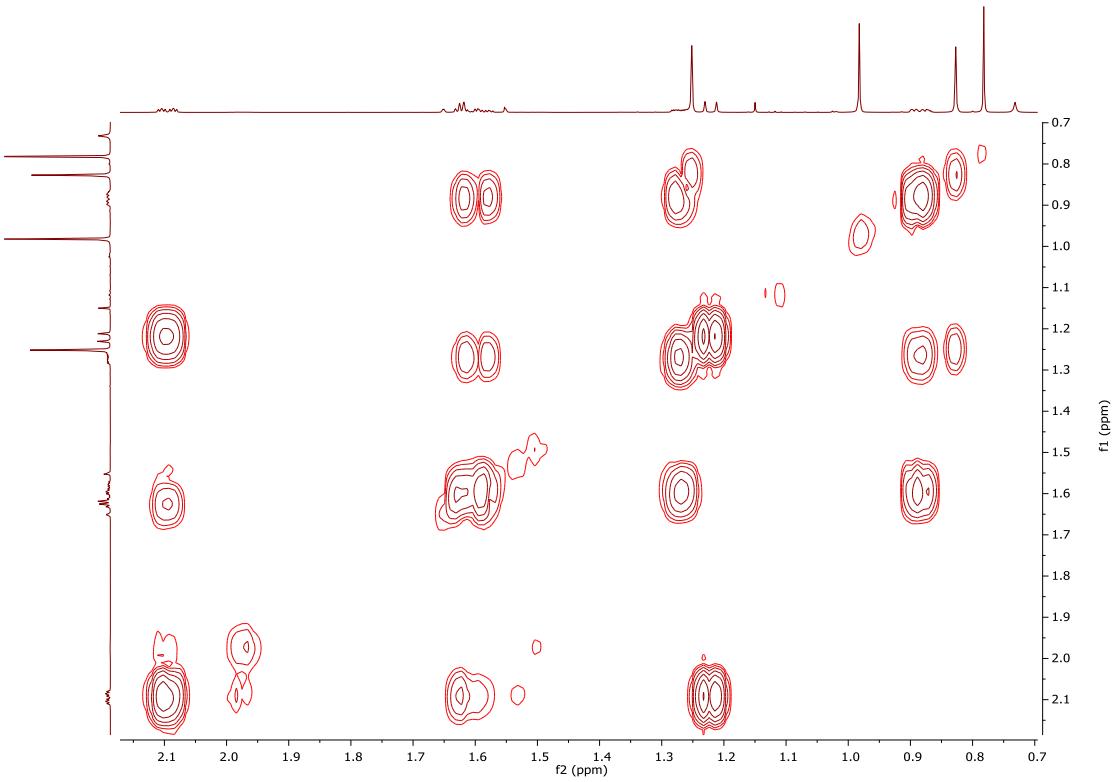


Figure S18. ^{1}H-^{1}H COSY (700 MHz, C_6D_6) of (*R*)-(4-^{2}H)-**1**.

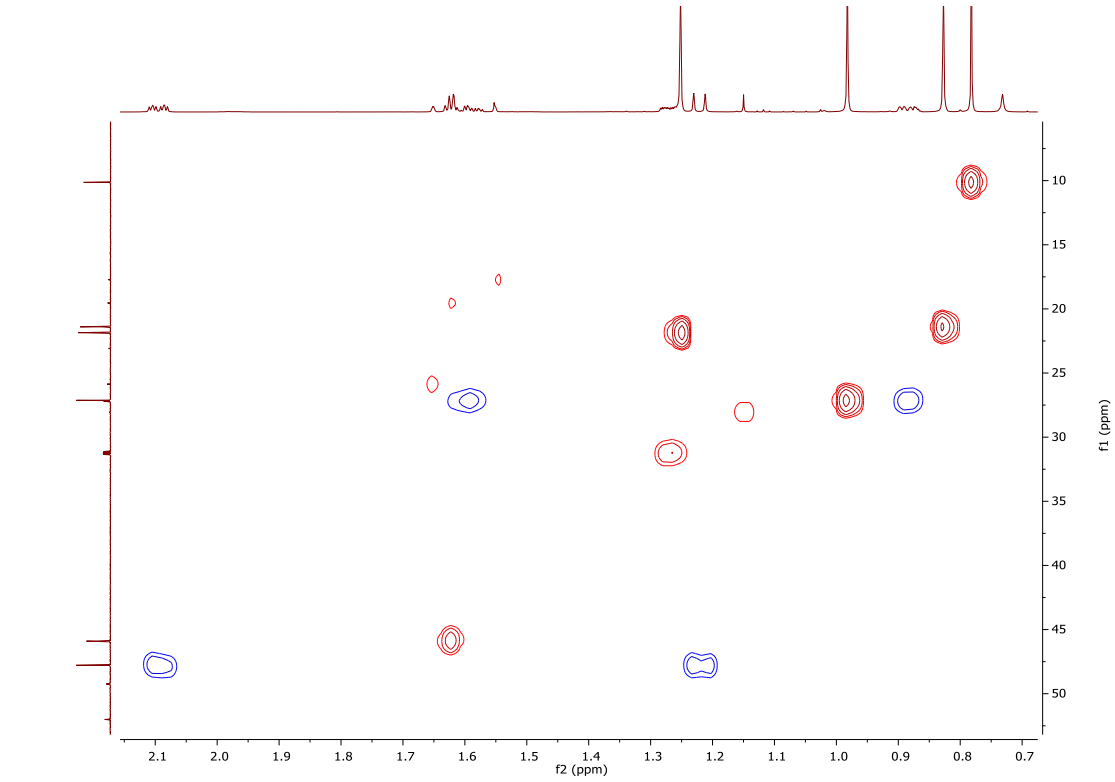


Figure S19. HSQC (700 MHz, C_6D_6) of (*R*)-(4-^{2}H)-**1**.

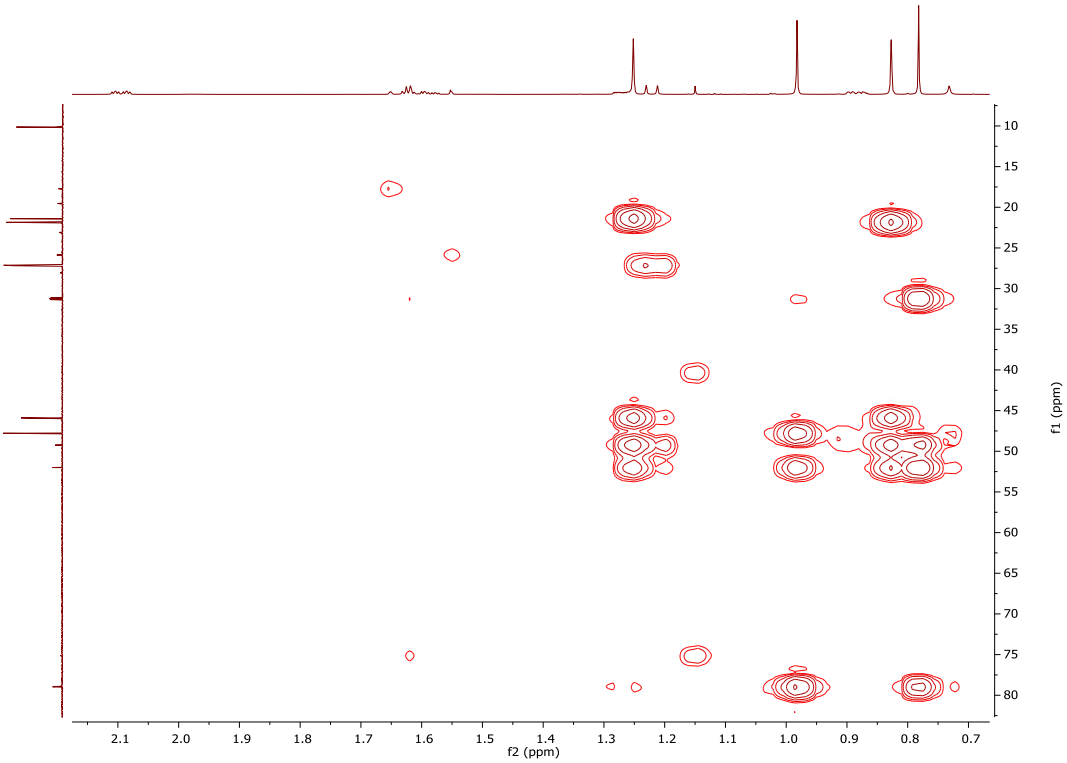


Figure S20. HMBC (700 MHz, C_6D_6) of (*R*)-(4-^{2}H)-**1**.

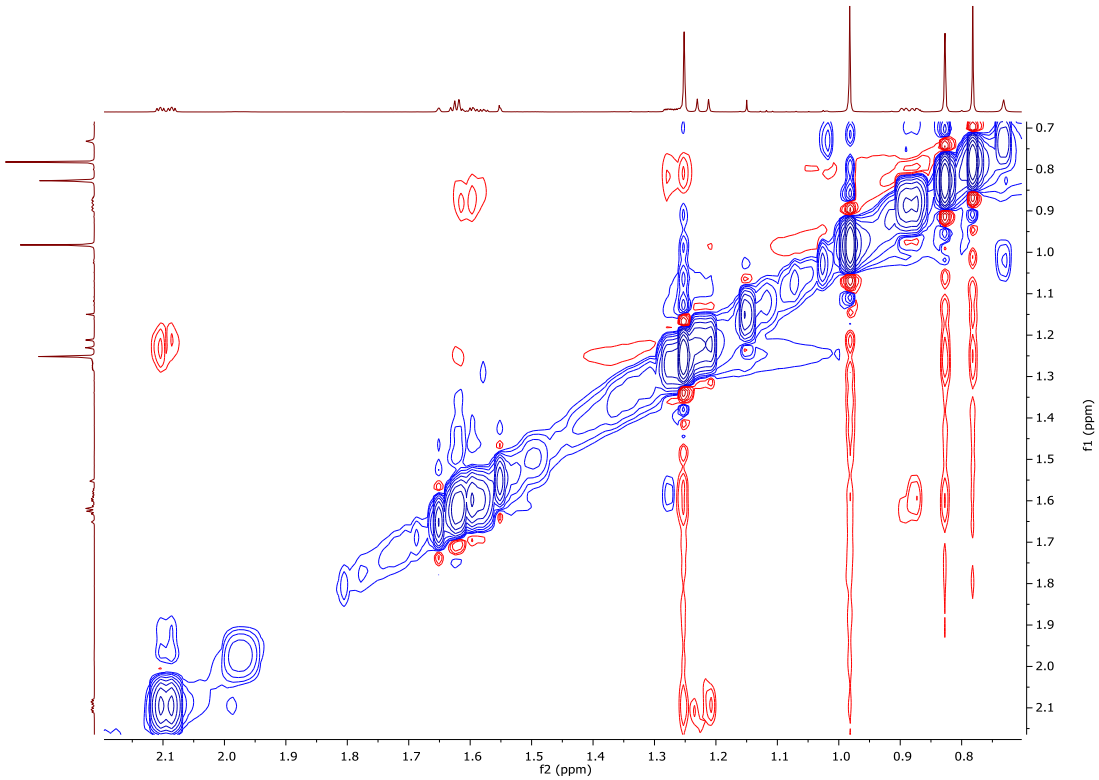


Figure S21. NOESY (700 MHz, C_6D_6) of (*R*)-(4-^{2}H)-**1**.

References

1. G. R. Fulmer, A. J. M. Miller, N. H. Sherden, H. E. Gottlieb, A. Nudelman, B. M. Stoltz, J. E. Bercaw and K. I. Goldberg, *Organometallics*, 2010, **29**, 2176–2179.
2. B. M. Trost and J. P. N. Papillon, *J. Am. Chem. Soc.*, 2004, **126**, 13618–13619.
3. S. Canova, V. Bellosta, A. Bigot, P. Mailliet, S. Mignani and J. Cossy, *Org. Lett.*, 2007, **9**, 145–148.
4. Y. Guan, J. Wu, L. Sun and W.-M. Dai, *J. Org. Chem.*, 2007, **72**, 4953–4960.
5. J. D. White, G. N. Reddy and G. O. Spessard, *J. Am. Chem. Soc.*, 1988, **110**, 1624–1626.
6. S. Sasaki, S. Samejima, T. Uruga, K. Anzai, N. Nishi, E. Kawakita, K. Takao and K. *J.* Tadano, *Antibiot. (Tokyo)*, 2013, **66**, 147–154.
7. J. D. White, G. N. Reddy and G. O. Spessard, *J. Chem. Soc. Perkin Trans. 1*, 1991, 759–767.
8. V. J. Davisson, A. B. Woodside, T. R. Neal, K. E. Stremler, M. Muehlbacher and C. D. Poulter, *J. Org. Chem.*, 1986, **51**, 4768–4779.
9. C.-M. Wang and D. E. Cane, *J. Am. Chem. Soc.*, 2008, **130**, 8908–8909.
10. J. S. Dickschat, K. A. K. Pahirulzaman, P. Rabe and T. A. Klapschinski, *ChemBioChem*, 2014, **15**, 810–814.
11. R. D. Giets and R. H. Schiestl, *Nat. Protoc.*, 2007, 2, 31–34.
12. P. Rabe, J. Rinkel, B. Nubbemeyer, T. G. Köllner, F. Chen and J. S. Dickschat, *Angew. Chem. Int. Ed.*, 2016, **55**, 15420–15423.
13. M. M. Bradford, *Anal. Biochem.*, 1976, **72**, 248–254.
14. J. S. Dickschat, T. Nawrath, V. Thiel, B. Kunze, R. Müller and S. Schulz, *Angew. Chem. Int. Ed.*, 2007, **46**, 8287–8290.
15. J. Cossy, D. Bauer and V, Bellosta, *Tetrahedron*, 2002, **58**, 5909–5922.
16. J. M. Clough, H. Dube, B. J. Martin, G. Pattenden, K. S. Reddy and I. R. Waldron, *Org. Biomol. Chem.*, 2006, **4**, 2906–2911.
17. S. Chandrasekhar, S. R. Yaragorla, L. Sreelakshmi and C. R. Reddy, *Tetrahedron*, 2008, **64**, 5174–5183.
18. A. Fürstner, E. Kattnig and O. Lepage, *J. Am. Chem. Soc.*, 2006, **128**, 9194–9204.
19. G. Pelletier, W. S. Bechara and A. B. Charette, *J. Am. Chem. Soc.*, 2010, **132**, 12817–12819.
20. J. Rinkel, L. Lauterbach, P. Rabe and J. S. Dickschat, *Angew. Chem. Int. Ed.*, 2018, **57**, 3238–3241.
21. P. Wipf and J. Xiao, *Org. Lett.*, 2005, **7**, 103–106.
22. C. H. Kim, H. J. An, W. K. Shin, W. Yu, S. K. Woo, S. K. Jung and E. Lee, *Angew. Chem. Int. Ed.*, 2006, **45**, 8019–8021.