Supplementary Information

Sesquiterpene Cyclisations Catalysed inside the Supramolecular Resorcinarene Capsule and Application in the Short Synthesis of Isolongifolene and Isolongifolenone

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Supplementary Methods

General information

Experimental. Reactions were carried out under an atmosphere of argon unless otherwise indicated. For the cyclisation reactions, no precaution against air and moisture was taken. Analytical thin-layer chromatography (TLC) was performed on Merck silica gel 60 F_{254} glass-baked plates, which were analysed after exposure to standard staining solutions (CAM: cerium ammonium molybdate or basic $KMnO_4$). All NMR experiments were performed on a Bruker Avance III NMR spectrometers operating at 400 MHz and a Bruker Avance Neo NMR spectrometer operating at 500 MHz proton frequency. The instruments were equipped with a direct observe 5-mm BBFO smart probe or a direct observe 5-mm BBFO FB probe with a self-shielded z-gradient (500 MHz). The experiments were performed at 295 K and 298 K (500 MHz) and the temperature was calibrated using a methanol standard showing accuracy within +/- 0.2 K. Chemical shifts of ^{1}H NMR and ^{13}C NMR are given in ppm by using $CHCl_3$ and $CDCl_3$ (7.26 ppm and 77.16 ppm, respectively). Coupling constants (*J*) are reported in Hertz (Hz). Standard abbreviations indicating multiplicity were used as follows: s (singlet), d (doublet), t (triplet), dd (doublet of doublets), m (multiplet). GC-analyses were done on two Agilent GC5890 instruments equipped with a FID detector and a HP-5 capillary column (length = 29.5 m or 30 m) and a Shimadzu GC-2010 Plus instrument equipped with a FID detector and an Rtx-5 capillary column (length = 30 m). Hydrogen was used as the carrier gas and the constant-flow mode (flow rate = 1.8 mL/min for the Agilent instrument and 40 mL/min for the Shimadzu instrument) with a split ratio of 1:20 was used. The following temperature-program was used: 60 °C for 3 min, 15 °C/min to 250 °C, and 250 °C for 5 min. The cyclisation reactions of farnesols (**FOH**) and farnesyl acetates (**FOAc**) were monitored with the Agilent GC instrument. The cyclisation reactions of cyclofarnesols (**cycloFOH**) and cyclofarnesyl acetates (**cycloFOAc**) were monitored with the Shimadzu GC instrument. For GC/MS analysis, an Agilent 7890B GC fitted with a HP5-MS fused silica capillary column (30 m, 0.25 mm i. d., 0.50 μm film), which was connected to a 5977A mass detector was used. GC parameters were 1) inlet pressure: 77.1 kPa, He at 23.3 mL min^{-1}, 2) injection volume: 2 μL, 3) inlet temperature: 250 °C, 4) temperature program: 5 min at 50 °C increasing at 5 °C min^{-1} or 10 °C min^{-1} to 320 °C, 5) 60 s valve time, 6) carrier gas: He at 1.2 mL

min^{-1}. MS parameters were 1) source: 230 °C, 2) transfer line: 250 °C, 3) quadrupole: 150 °C and 4) electron energy: 70 eV. Retention indices (*I*) were determined against a homologous series of *n*-alkanes (C_7-C_{40}).

Sources of chemicals. Anhydrous dichloromethane (CH_2Cl_2), diethyl ether (Et_2O) and tetrahydrofuran (THF) were taken from a solvent drying system (Pure Solv). Deuterated chloroform ($CDCl_3$, 99.8%) was purchased from Deutero GmbH and Cambridge Isotope Laboratories (stabilized over silver foil). Anhydrous acetone, anhydrous acetonitrile, aluminum oxide (activated, basic, Brockmann I), anhydrous benzene, α-cedrene, chromium(0) hexacarbonyl ($Cr(CO)_6$), ethanol (99.9%), dihydro-β-ionone, 4-(dimethylamino)pyridine (DMAP), ethyl acetoacetate, *n*-hexane (HPLC grade), isolongifolene, methanol, phenol red, phosphorus tribromide, sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al, 60% in toluene), tetrabutylammonium bromide, triethylamine and (1-^{13}C)triethyl phosphonoacetate were purchased from Sigma-Aldrich. Acetic anhydride, *n*-butyl lithium (1.6 M solution in hexane), potassium carbonate (anhydrous), diisobutylaluminium hydride (1 M solution in THF), triethyl phosphonoacetate and pyridine were purchased from Acros Organics. Silica gel (0.040-0.063 mm, 230-400 mesh ASTM) and sodium hydride (60% suspension in paraffin oil) were purchased from Merck KGaA. Chloroform (stabilized with amylene), dodecanal, geraniol, nerol and resorcinol were purchased from Alfa Aesar. *n*-Hexane (HPLC grade), potassium hydroxide, sodium chloride and sulfuric acid (98%) were purchased from VWR. Hydroperoxide (70% in water) was purchased from TCI. *n*-Decane, hydrochloric acid (37%) (TraceSELECT) and diisopropyl amine were purchased from Fluka. All chemicals were used as received. Transfer of liquids with a volume ranging from 1 to 10 µL or from 10 to 100 µL was performed with a microman M1 pipette (Gilson, systematic error: 1.40% - 1.60%) equipped with 10 µL or 100 µL pipette tips, respectively.

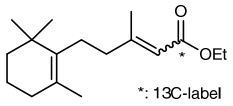
Synthesis of catalyst and cyclisation substrates

Synthesis of resorcinarene 7: To a stirred solution of 99.9% ethanol (57 mL) and 37% aqueous HCl (19 mL), resorcinol (15.0 g, 136 mmol, 1.0 eq) was added. After the solution was cooled to 0 °C, a solution of dodecanal (30.0 mL, 136 mmol, 1.0 eq) in 99.9% ethanol (38 mL) was added slowly into the reaction mixture over 15min. The resulting solution was allowed to warm to 25 °C slowly and was then refluxed at 110 °C for 23h. Afterwards, the reaction mixture was cooled to room temperature and MeOH (150 mL) was added. The precipitate was filtered, washed with MeOH (150 mL) and air was drawn through the precipitate for 20 min (aspirator). The solid (29.6 g) was recrystallized from methanol (95 mL) and air was drawn through the precipitate for 20 min (aspirator). The obtained crystalline material was then dried with stirring under vacuum (0.3 Torr), until the residual MeOH was removed. Compound **7** (26.1 g, 69%) was obtained as yellow powder. After dissolving **7** (11.1 mg) in $CDCl_3$ (0.5 mL), a water content of 10–12 eq H_2O/hexamer **I** was obtained (measured by ^1H NMR).

Synthesis of cyclisation substrates: (2*E*,6*E*)-Farnesyl acetate[1], (2*E*,6*Z*)-Farnesol[1], (2*E*,6*Z*)-Farnesyl acetate[1], (2*Z*,6*Z*)-Farnesol[1], (2*Z*,6*Z*)-Farnesyl acetate[1], (2*Z*,6*E*)-Farnesol[1], (2*Z*,6*E*)-Farnesyl acetate[1], (*E*)-cyclofarnesol[2], (*E*)-cyclofarnesyl acetate[1], (*Z*)-cyclofarnesol[2] and (*Z*)-cyclofarnesyl acetate[1] were synthesized according to literature procedures. (2*E*,6*E*)-Farnesol was purchased from Sigma Aldrich.

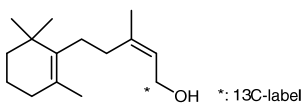
Synthesis of the ^{13}C-labelled substrate for mechanistic investigations: (2*Z*)-(1-^{13}C)-cyclofarnesyl acetate (**20**) was synthesized according to a literature known route used for the synthesis of labelled farnesols[3]. The ^{13}C-label was introduced by utilizing (1-^{13}C)-triethyl phosphonoacetate in the corresponding Horner-Wadsworth-Emmons reaction. The esters were reduced by DIBAL-H and stereoisomers were separated to obtain (2*Z*)-(1-^{13}C)cyclofarnesol, which was converted to the acetate.

Ethyl (1-^{13}C)-3-methyl-5-(2,6,6-trimethylcyclohex-1-en-1-yl)pent-2-enoate (**30**)



To a solution of diisopropyl amine (106 mg, 1.05 mmol, 1.05 eq.) in dry THF (4 mL) stirred at 0 °C was slowly added a solution of *n*BuLi (0.66 mL; 1.6 M in hexane, 1.05 mmol, 1.05 eq.). The reaction mixture was stirred for 1 h at the same temperature, before (1-^{13}C)-triethyl phosphonoacetate (225 mg, 1.00 mmol, 1.00 eq.) was added dropwise. After further stirring for 2 h at 0 °C, dihydro-β-ionone (**19**) (194 mg, 1.00 mmol, 1.00 eq.) was added and the reaction mixture was stirred overnight at room temperature. Water (5 mL) was added, the mixture was extracted with Et_2O (3x 5 mL), the combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel [petrol ether/EtOAc (50:1)] to yield a mixture of (2*E* and 2*Z*) stereoisomers of the title compound as a colorless oil (176 mg, 0.71 mmol, 71%). GC/MS data indicated an (*E*)/(*Z*) ratio of 33:1. (2*E*) Stereoisomer: TLC [petrol ether/EtOAc (10:1)]: R_f = 0.60. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.71-5.68 (m, 1H, CH), 4.15 (qd, $^3J_{H,H}$ = 7.2 Hz, $^3J_{H,C}$ = 3.0 Hz, 2H, CH_2), 2.20 (s, 3H, CH_3), 2.19-2.09 (m, 4H, 2x CH_2), 1.91 (t, $^3J_{H,H}$ = 6.2 Hz, 2H, CH_2), 1.60 (s, 3H, CH_3), 1.60-1.53 (m, 2H, CH_2), 1.44-1.40 (m, 2H, CH_2), 1.28 (t, $^3J_{H,H}$ = 7.1 Hz, 3H, CH_3), 0.99 (s, 6H, 2x CH_3) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 167.1* (C_q), 160.8 (d, $^2J_{C,C}$ = 2.0 Hz, C_q), 136.3 (C_q), 128.0 (C_q), 115.2 (d, $^1J_{C,C}$ = 75.7 Hz, CH), 59.6 (d, $^2J_{C,C}$ = 2.3 Hz, CH_2), 41.6 (d, $^3J_{C,C}$ = 7.0 Hz, CH_2), 39.9 (CH_2), 35.2 (C_q), 32.9 (CH_2), 28.7 (2x CH_3), 27.2 (CH_2), 19.9 (CH_3), 19.6 (CH_2), 19.0 (d, $^3J_{C,C}$ = 1.5 Hz, CH_3), 14.5 (d, $^3J_{C,C}$ = 2.2 Hz, CH_3) ppm. GC: *I* = 1864 (HP-5MS). MS (EI, 70 eV): *m*/*z* (%) = 265 (2), 250 (1), 220 (6), 176 (10), 137 (100), 129 (84), 123 (6), 121 (12), 109 (7), 107 (8), 101 (12), 95 (60), 93 (12), 91 (10), 81 (45), 79 (12), 69 (12), 67 (11), 55 (10), 41 (11). (2*Z*)-Stereoisomer: TLC [petrol ether/EtOAc (10:1)]: R_f = 0.65. Because of the low quantity of this isomer within the mixture, NMR data were not resolved. GC: *I* = 1826 (HP-5MS). MS (EI, 70 eV): *m*/*z* (%) = 265 (9), 250 (4), 220 (14), 176 (13), 175 (10), 137 (100), 136 (9), 129 (74), 123 (13), 121 (15), 109 (11), 107 (11), 101 (15), 95 (46), 93 (14), 91 (11), 81 (33), 79 (10), 69 (10), 55 (9), 41 (7).

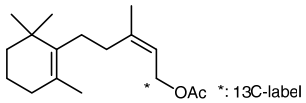
(2*Z*)-(1-^{13}C)-3-Methyl-5-(2,6,6-trimethylcyclohex-1-en-1-yl)pent-2-en-1-ol



A solution of DIBAL-H (1.46 mL; 1 M in THF, 1.46 mmol, 2.2 eq.) was added to a stirred solution

of the isomeric ester mixture (176 mg, 0.66 mmol, 1.0 eq) in THF (6.6 mL) at -78 °C. The reaction mixture was allowed to warm up to room temperature within 2 h, before it was quenched by adding a saturated Na-K-tartrate solution (10 mL). The mixture was extracted with Et_2O (3x 5 mL), the combined extracts were dried with $MgSO_4$, concentrated under reduced pressure und subjected to column chromatography on silica gel [petrol ether/EtOAc (10:1)] to yield the (2*E*)-alcohol (116 mg, 0.52 mmol, 78%) and the (2*Z*)-alcohol (10 mg, 0.04 mmol, 7%), each as a colorless liquid. (2*E*)-Stereoisomer: TLC [petrol ether/EtOAc (3:1)]: R_f = 0.53. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 5.46-5.41 (m, 1H, CH), 4.16 (dd, $^1J_{H,C}$ = 141.7 Hz, $^3J_{H,H}$ = 6.8 Hz, 2H, CH_2), 2.12-2.02 (m, 4H, 2x CH_2), 1.91 (t, $^3J_{H,H}$ = 6.3 Hz, 2H, CH_2), 1.72 (s, 3H, CH_3), 1.60 (s, 3H, CH_3), 1.59-1.53 (m, 2H, CH_2), 1.44-1.39 (m, 2H, CH_2), 0.99 (s, 6H, 2x CH_3) ppm. ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 140.9 (d, $^2J_{C,C}$ = 1.3 Hz, C_q), 136.9 (C_q), 127.4 (C_q), 122.8 (d, $^1J_{C,C}$ = 47.5 Hz, CH), 59.6* (CH_2), 40.2 (d, $^3J_{C,C}$ = 6.7 Hz, CH_2), 39.9 (CH_2), 35.1 (C_q), 32.9 (CH_2), 28.7 (2x CH_3), 27.6 (CH_2), 20.0 (CH_3), 19.7 (CH_2), 16.5 (d, $^3J_{C,C}$ = 4.3 Hz, CH_3) ppm. GC: *I* = 1740 (HP-5MS). MS (EI, 70 eV): *m*/*z* (%) = 223 (2), 205 (3), 191 (5), 137 (100), 136 (38), 123 (10), 121 (20), 109 (10), 107 (10), 95 (86), 93 (16), 91 (11), 81 (62), 79 (14), 69 (20), 67 (14), 57 (10), 55 (13), 41 (17). (2*Z*)-Stereoisomer: TLC [petrol ether/EtOAc (3:1)]: R_f = 0.62. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 5.43-5.36 (m, 1H, CH), 4.16 (dd, $^1J_{H,C}$ = 141.6 Hz, $^3J_{H,H}$ = 7.0 Hz, 2H, CH_2), 2.14-2.00 (m, 4H, 2x CH_2), 1.92 (t, $^3J_{H,H}$ = 6.3 Hz, 2H, CH_2), 1.80 (s, 3H, CH_3), 1.63 (s, 3H, CH_3), 1.61-1.54 (m, 2H, CH_2), 1.44-1.40 (m, 2H, CH_2), 1.00 (s, 6H, 2x CH_3) ppm. ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 141.1 (d, $^2J_{C,C}$ = 1.6 Hz, C_q), 137.0 (C_q), 127.7 (C_q), 123.8 (d, $^1J_{C,C}$ = 47.4 Hz, CH), 59.4* (CH_2), 39.9 (CH_2), 35.1 (C_q), 32.9 (CH_2), 28.8 (2x CH_3), 27.8 (CH_2), 27.1 (CH_2), 23.6 (d, $^3J_{C,C}$ = 5.1 Hz, CH_3), 20.0 (CH_3), 19.6 (CH_2) ppm. GC: *I* = 1715 (HP-5MS). MS (EI, 70 eV): *m*/*z* (%) = 223 (4), 205 (7), 190 (7), 162 (4), 149 (3), 137 (100), 136 (46), 123 (18), 121 (33), 109 (12), 107 (15), 95 (81), 93 (21), 91 (13), 85 (22), 81 (54), 79 (14), 69 (17), 67 (12), 55 (10), 41 (11).

(2*Z*)-(1-^{13}C)-3-Methyl-5-(2,6,6-trimethylcyclohex-1-en-1-yl)pent-2-en-1-yl acetate



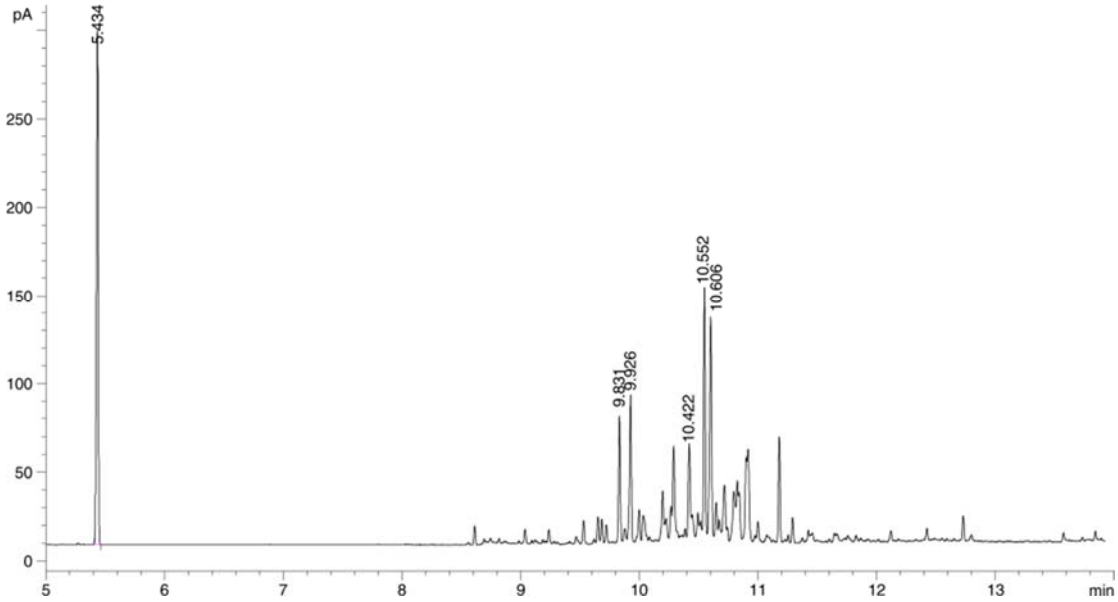
To a solution of (*Z*)-(1-^{13}C)-cyclofarnesol (10 mg, 0.045 mmol, 1 eq.) in pyridine (0.2 mL) was

added acetic anhydride (18 mg, 0.180 mmol, 4 eq.) at room temperature. The reaction mixture was stirred for 2 h at room temperature, before a HCl solution (0.5 mL; 0.1 M) was added. The mixture was extracted with Et_2O (3x 0.5 mL), the organic layers were dried with $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography using silica gel [cyclohexane/EtOAc (30:1)] to yield the desired acetate as a pale yellow oil (6 mg, 0.023 mmol, 50%). TLC [petrol ether/EtOAc (10:1)]: R_f = 0.60. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 5.37-5.31 (m, 1H, CH), 4.58 (dd, $^1J_{H,C}$ = 146.7 Hz, $^3J_{H,H}$ = 7.5 Hz, 2H, CH_2), 2.17-2.02 (m, 4H, 2x CH_2), 2.05 (s, 3H, CH_3), 1.91 (t, $^3J_{H,H}$ = 6.2 Hz, 2H, CH_2), 1.82 (s, 3H, CH_3), 1.64 (s, 3H, CH_3), 1.61-1.54 (m, 2H, CH_2), 1.45-1.40 (m, 2H, CH_2), 1.00 (s, 6H, 2x CH_3) ppm. ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 171.2 (d, $^3J_{C,C}$ = 2.4 Hz, C_q), 144.0 (d, $^2J_{C,C}$ = 2.0 Hz, C_q), 136.8 (C_q), 127.7 (C_q), 118.6 (d, $^1J_{C,C}$ = 50.0 Hz, CH), 61.2* (CH_2), 39.9 (CH_2), 35.1 (C_q), 32.9 (d, $^3J_{C,C}$ = 3.8 Hz, CH_2), 32.9 (CH_2), 28.7 (2x CH_3), 27.7 (CH_2), 23.6 (d, $^3J_{C,C}$ = 5.3 Hz, CH_3), 21.2 (CH_3), 20.0 (CH_3), 19.6 (CH_2) ppm. GC: I = 1829 (HP-5MS). MS (EI, 70 eV): m/z (%) = 265 (1), 205 (22), 190 (15), 176 (2), 162 (6), 137 (100), 136 (77), 134 (9), 123 (12), 121 (33), 120 (11), 109 (12), 107 (14), 95 (65), 93 (17), 81 (39), 79 (10), 69 (16), 67 (8), 55 (7), 43 (9), 41 (7).

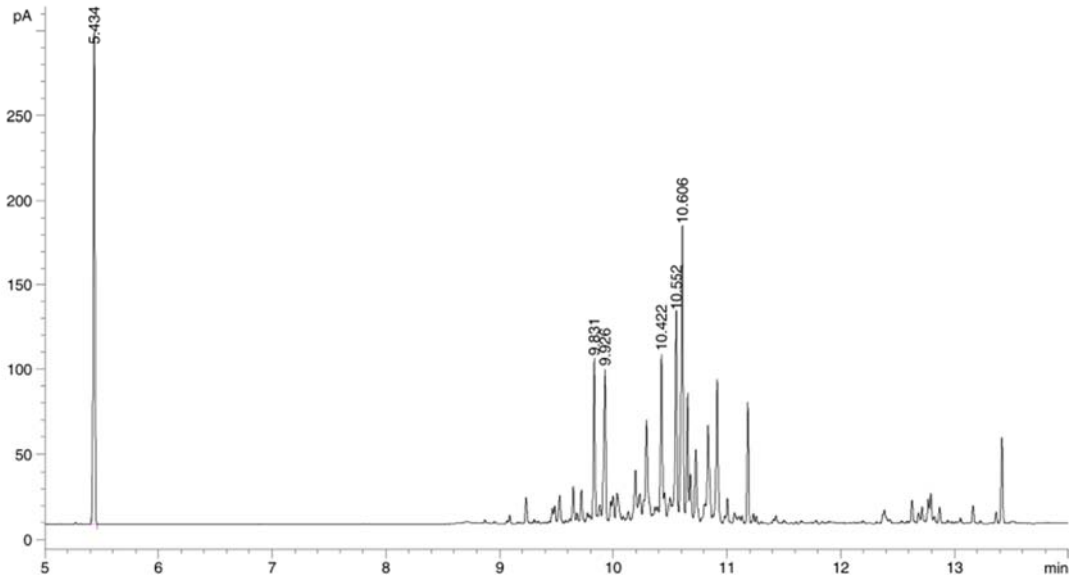
Supplementary Discussion

Cyclisation of farnesyl substrates

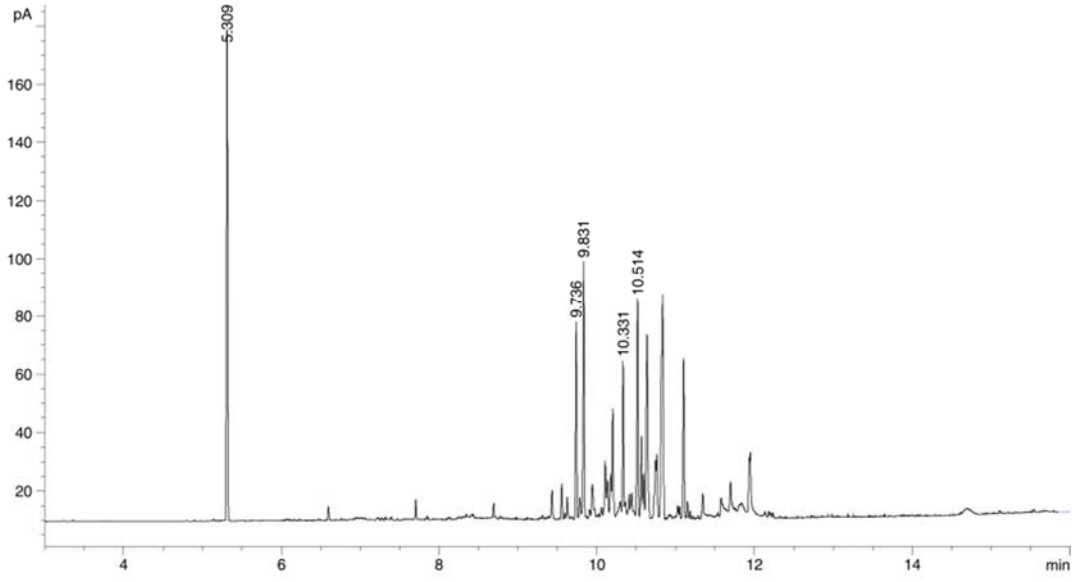
Product analysis via gas chromatography (GC): The samples were measured with two Agilent GC-instruments, which differ in the length of the column. Consequently, the retention times of the same compound differ by 0.09-0.10 min. The peak at 5.31 min(GC1)/5.43 min(GC2) is attributed to *n*-decane, which is used as the internal standard for GC-measurements. The retention times of compound **B**, **C**, **D**, **E** and **F** are 9.74 min(GC1)/9.83 min(GC2), 9.83 min(GC1)/9.93 min(GC2), 10.33 min(GC1)/10.42 min(GC2), 10.55 min(GC2) and 10.51 min(GC1)/10.61 min(GC2), respectively.



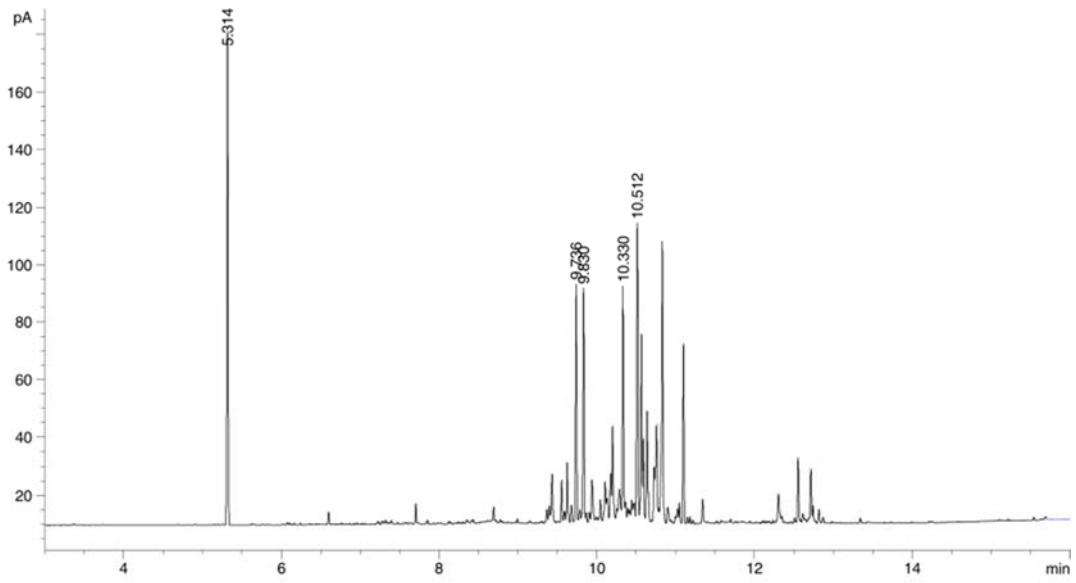
Supplementary Figure 1: GC-trace of the cyclisation reaction of (2*E*,6*E*)-farnesol at full conversion (4d)



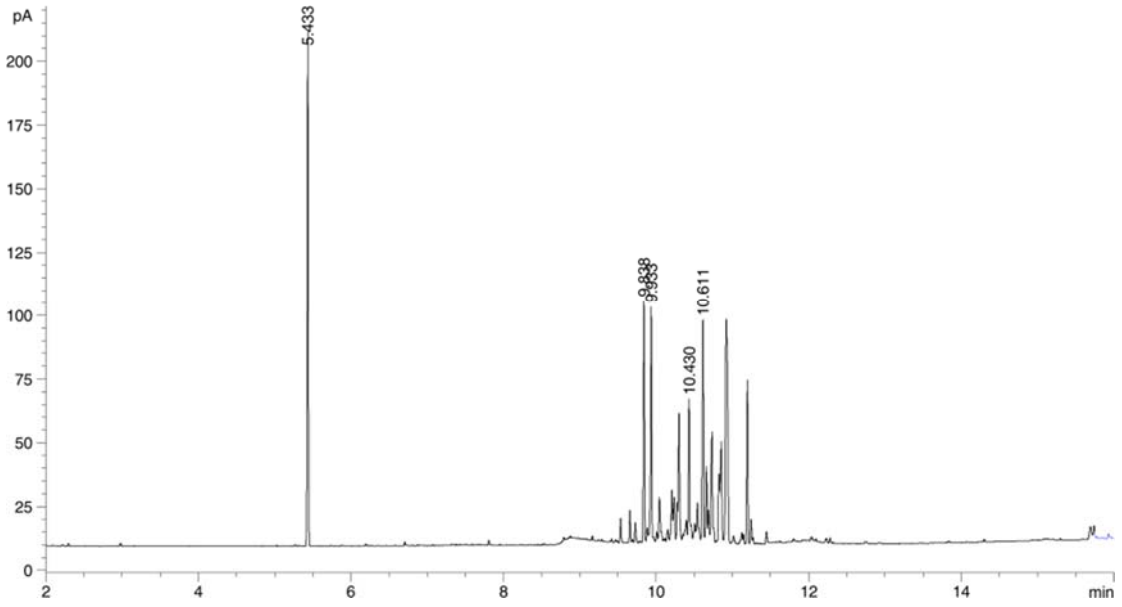
Supplementary Figure 2: GC-trace of the cyclisation reaction of (2*E*,6*E*)-farnesyl acetate at full conversion (5d)



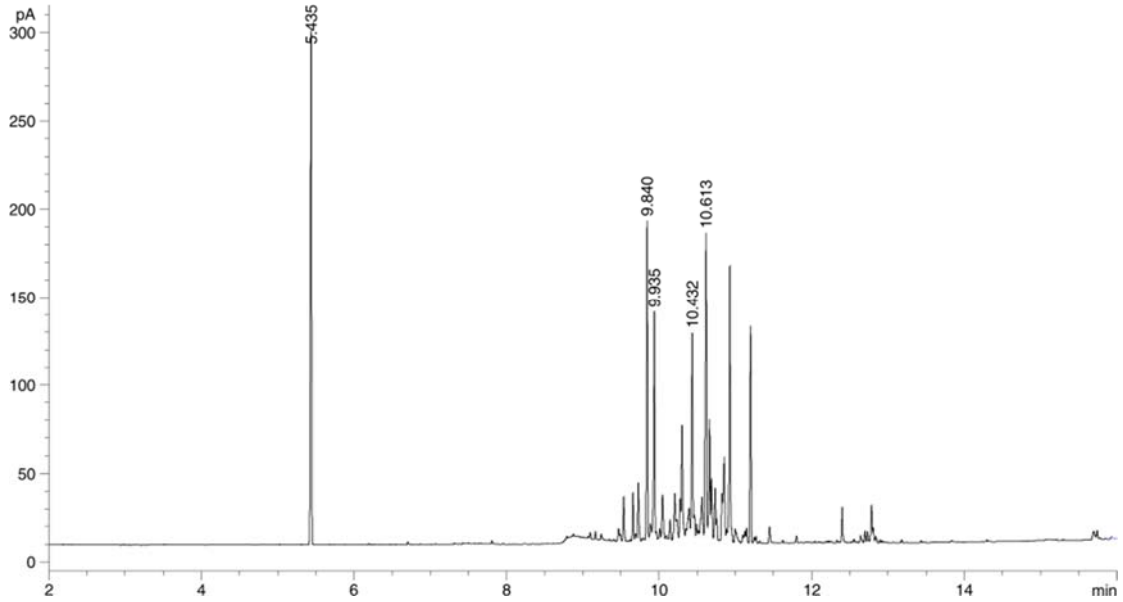
Supplementary Figure 3: GC-trace of the cyclisation reaction of (2*Z*,6*E*)-farnesol at full conversion (5d)



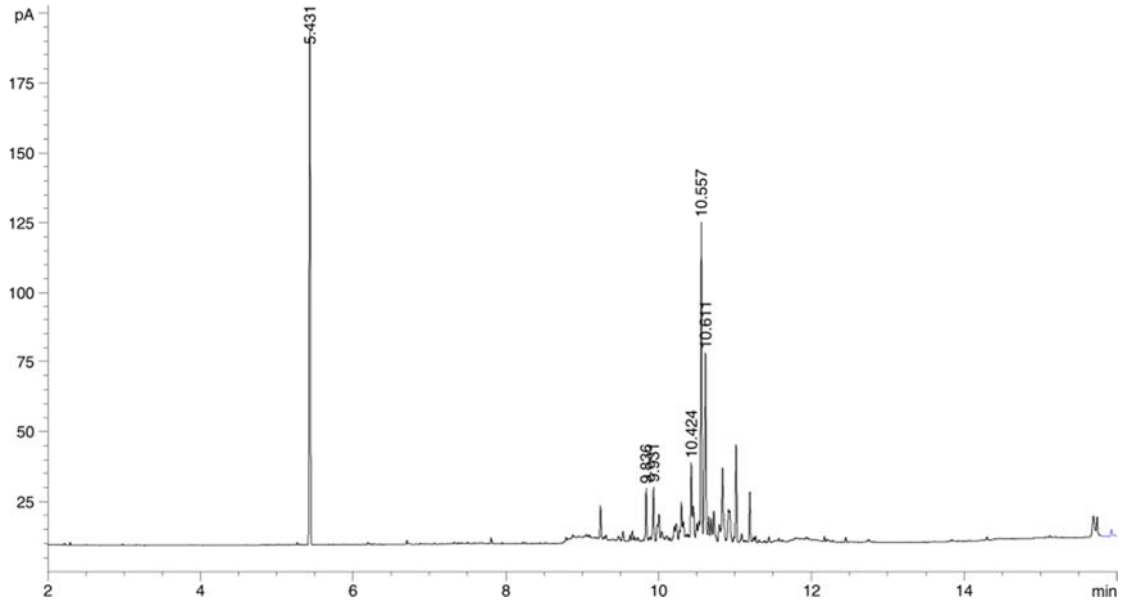
Supplementary Figure 4: GC-trace of the cyclisation reaction of (2*Z*,6*E*)-farnesyl acetate at full conversion (5d)



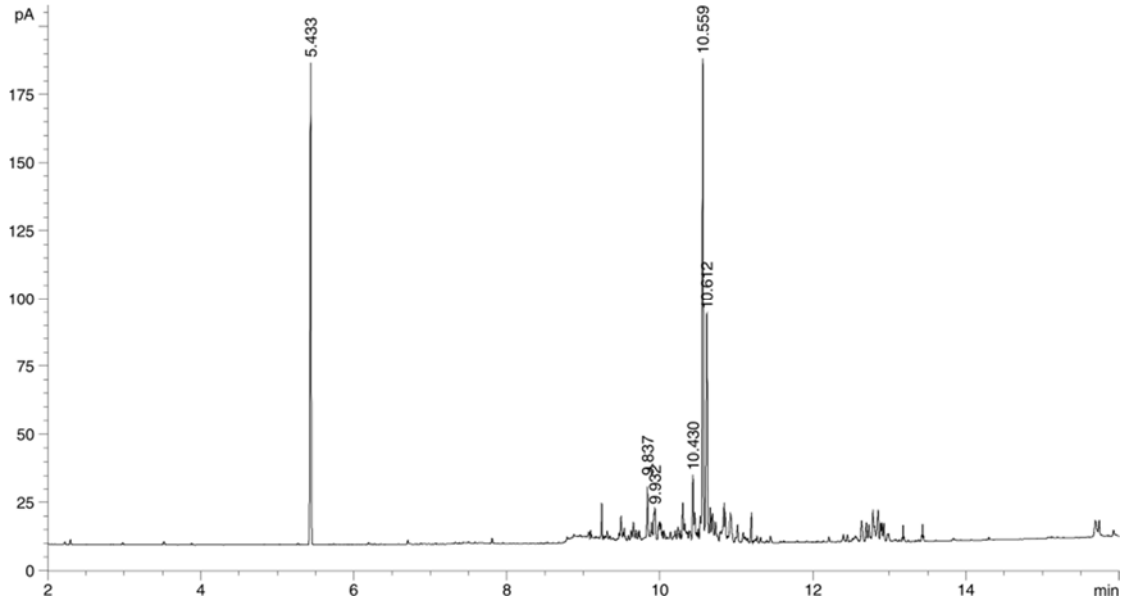
Supplementary Figure 5: GC-trace of the cyclisation reaction of (2*Z*,6*Z*)-farnesol at full conversion (5d)



Supplementary Figure 6: GC-trace of the cyclisation reaction of (2*Z*,6*Z*)-farnesyl acetate at full conversion (5d)

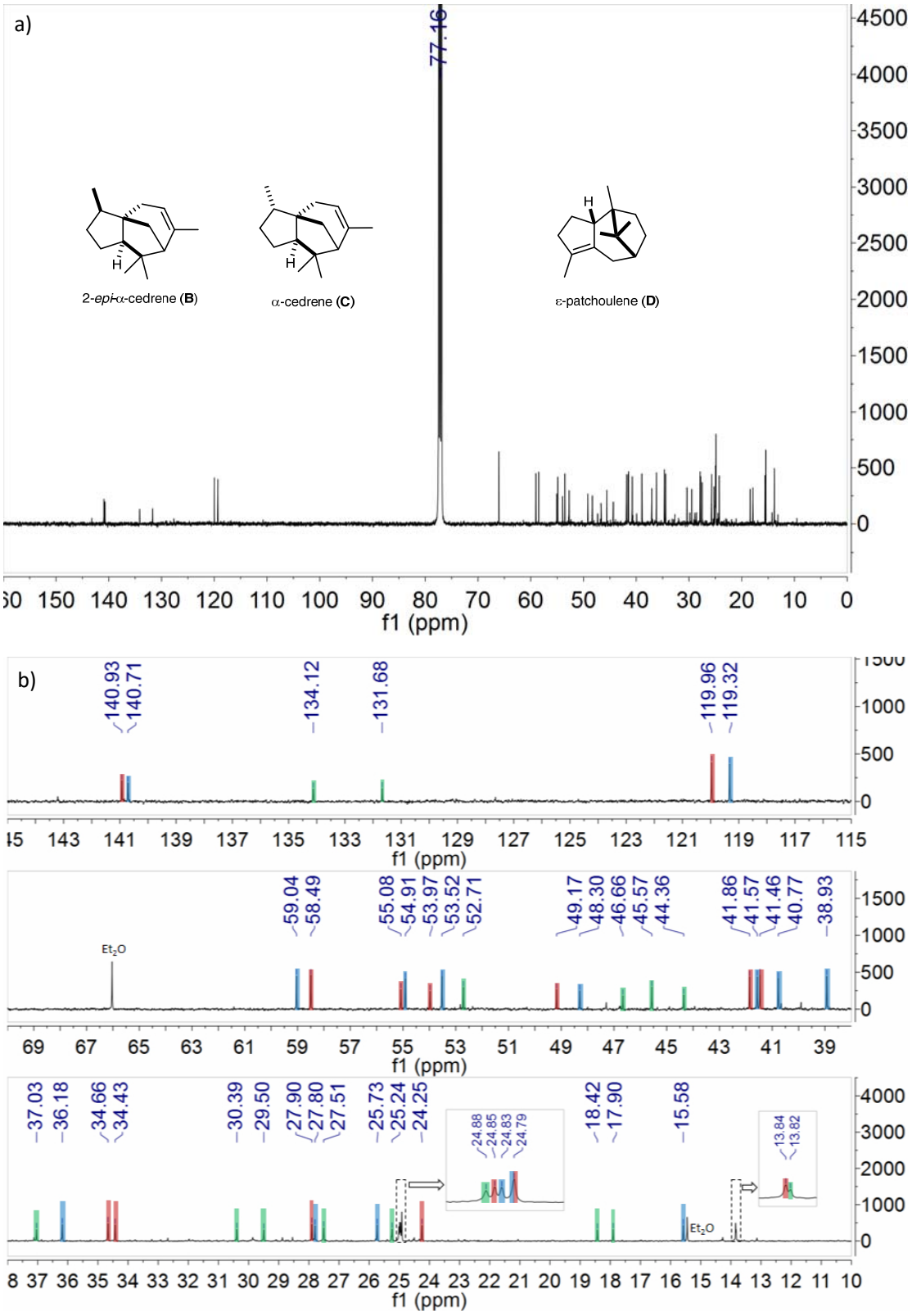


Supplementary Figure 7: GC-trace of the cyclisation reaction of (2*E*,6*Z*)-farnesol at full conversion (8d)

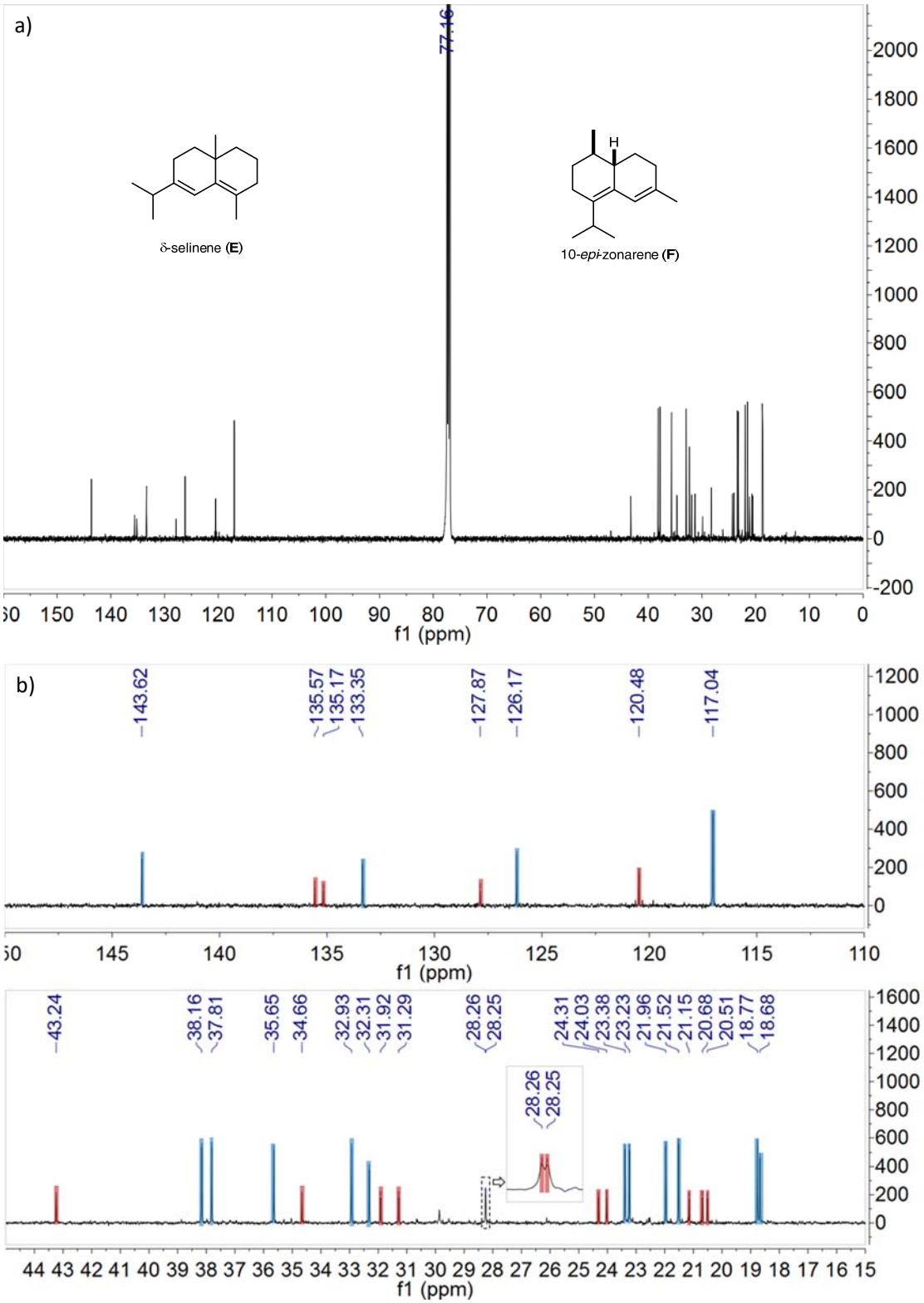


Supplementary Figure 8: GC-trace of the cyclisation reaction of (2*E*,6*Z*)-farnesyl acetate at full conversion (8d)

Product analysis via NMR spectroscopy: To identify the cyclisation products, the cyclisation reaction were performed in large scale (227 µmol (2*Z*,6*Z*)-farnesol and (2*E*,6*Z*)-farnesyl acetate, respectively). After the completion of the cyclisation reaction, the reaction mixture was subjected to column chromatography (40 mL silica gel, eluted with pentane) to remove the resorcinarene. The product mixture displayed two spots on the TLC-plate, with an R_f-value of 0.91 and 0.88 (eluted with pentane, stained with basic $KMnO_4$), respectively. Repeated column chromatography with pentane as the eluent enabled the complete separation of the fractions corresponding to the two different spots. Subsequent GC-analysis revealed that the less polar fraction (R_f = 0.91) mainly contained compound **B** (9.83 min), **C** (9.93 min) and **D** (10.42 min) (retention time at GC2). Compound **E** (10.55 min) and **F** (10.61 min) (retention time at GC2) were found in the more polar fraction (R_f = 0.88). Based on NMR analysis, compound **B** (9.83 min), **C** (9.93 min), **D** (10.42 min), **E** (10.55 min) and **F** (10.61 min) (retention time at GC2) were identified as 2-*epi*-α-cedrene, α-cedrene, ε-patchoulene, δ-selinene and 10-*epi*-zonarene. The comparison of the ^{13}C-NMR data of the isolated compounds with the reported values are tabulated in Supplementary Table 1 and 2. The GC-yields of the cyclisation products were reported in Supplementary Table 5.

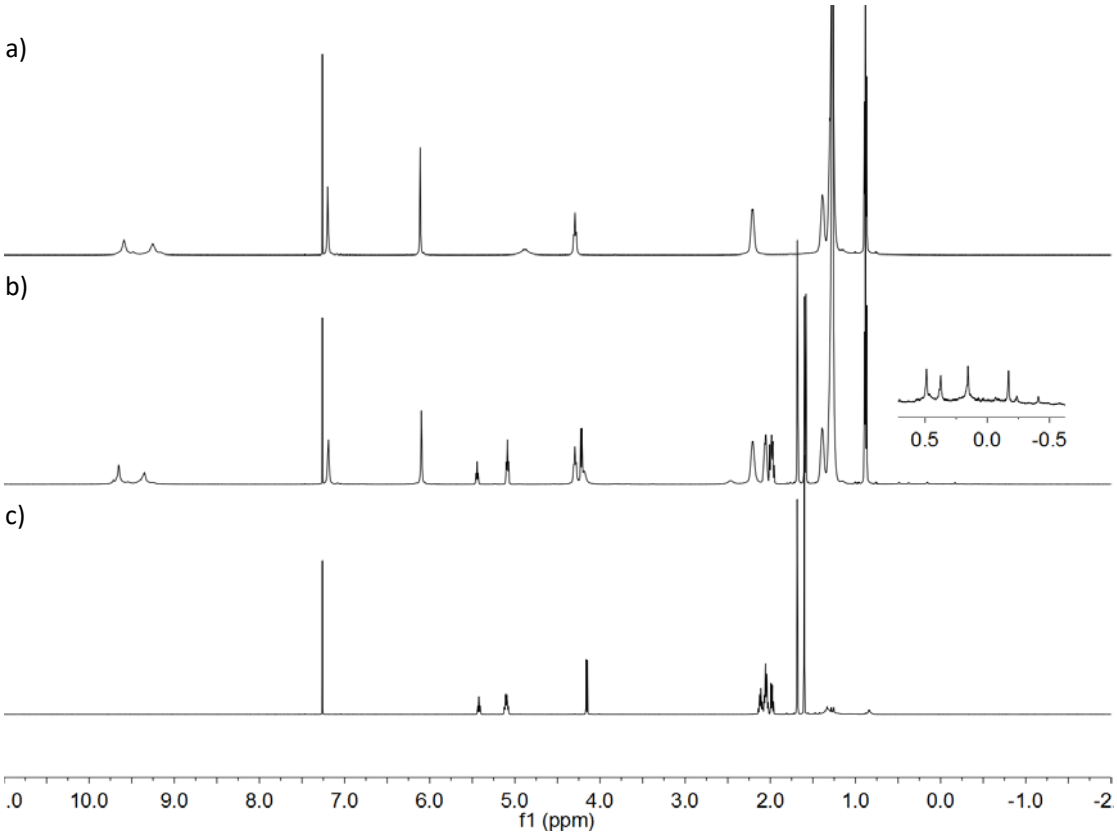


Supplementary Figure 9: ^{13}C-NMR spectra of 2-*epi*-α-cedrene (**B**, red), α-cedrene (**C**, blue) and ε-patchoulene (**D**, green). a) Full spectrum; b) Partial spectra with peak assignment.



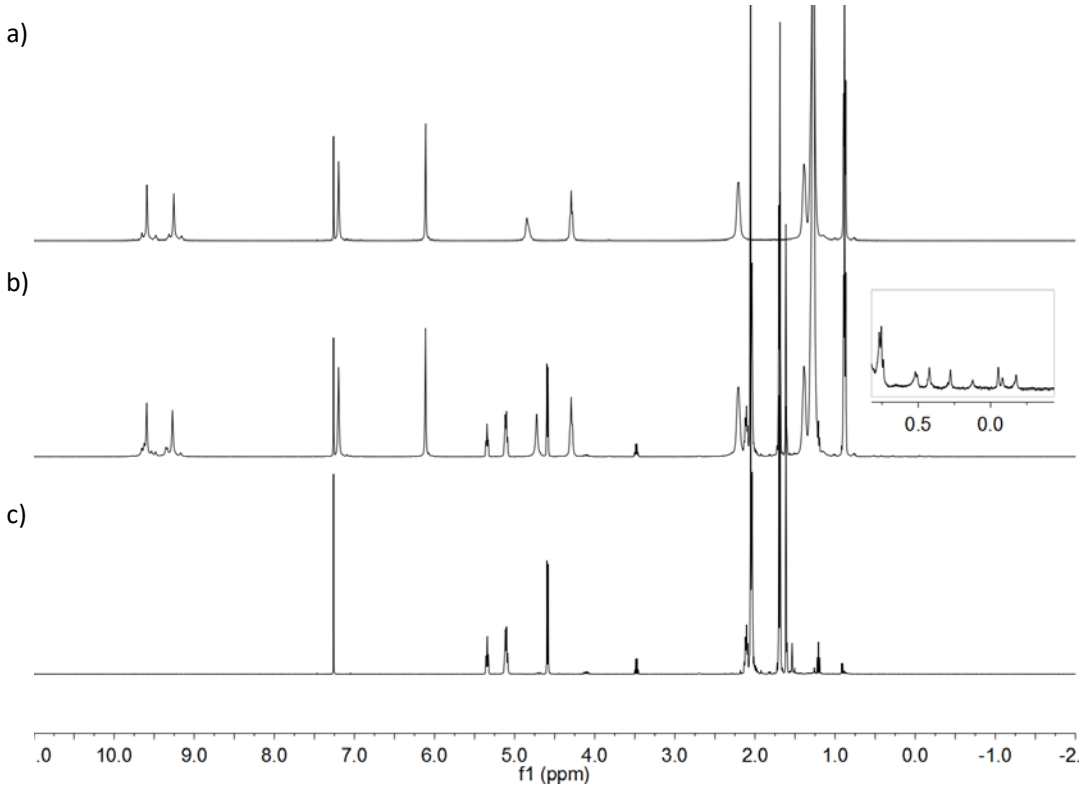
Supplementary Figure 10: ^{13}C-NMR spectra of δ-selinene (**E**, blue) and 10-*epi*-zonarene (**F**, red). a) Full spectrum; b) Partial spectra with peak assignment.

Control experiments: Different control experiments were performed to probe the origin of the catalytic activity of the presented system. First, the cyclisation reactions were run with 3 mol% HCl as the only catalyst. Not surprisingly, no conversion of substrate ((2*E*,6*E*)-, (2*Z*,6*E*)-, (2*Z*,6*Z*)- and (2*E*,6*Z*)-**FOAc**) was observed at 30 °C after 8d, whereas all these substrates were completely converted under the standard reaction conditions (10 mol% capsule **I** and 3 mol% HCl, 30 °C) after the same reaction time. Second, when HCl was omitted, capsule **I** (10 mol%) also failed to effect any detectable formation of cyclisation products, although the uptake of substrate by capsule **I** was clearly demonstrated by ^{1}H NMR spectroscopy (**Supplementary Figure 11** and **12**). Third, cyclisation reactions were probed with capsule **I** blocked by a strong binding inhibitor (nBu$_4$Br) in the presence of 3 mol% HCl. Under these conditions, 4% to 6% substrates were consumed after 8d, but only trace amounts (less than 0.22%) of cyclisation products (**B**, **C**, **D**, **E** and **F**) were detected (**Supplementary Table 6**). Taken together, these control experiments provided strong evidence that the cyclisation reaction occurs inside the cavity of capsule **I** and the catalytic activity relied on the synergistic interplay between capsule **I** and HCl.

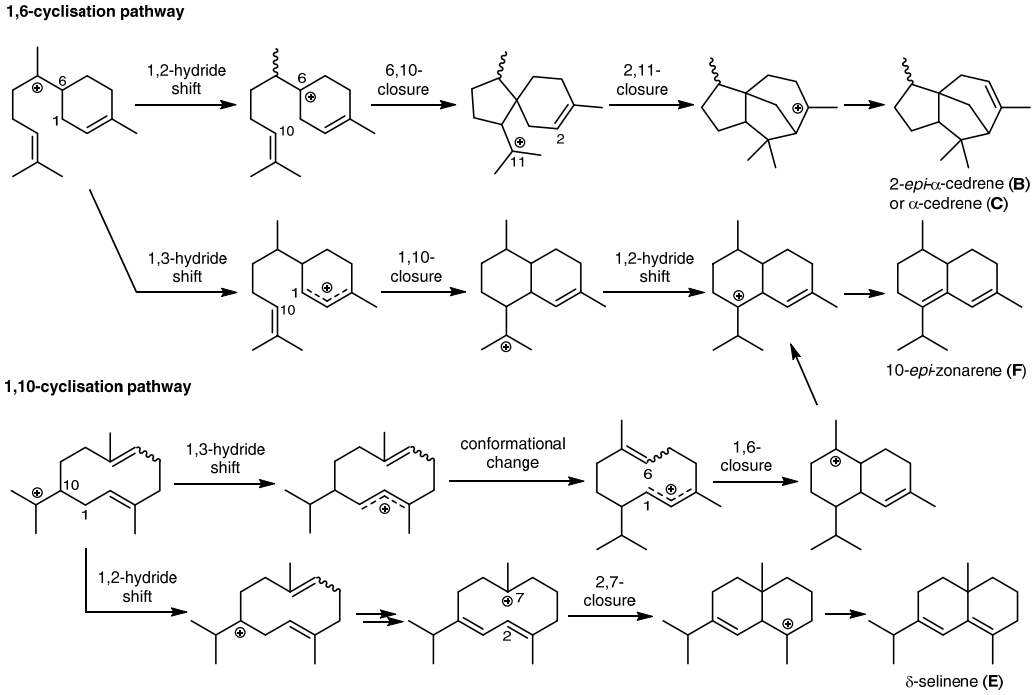


Supplementary Figure 11: ^{1}H-NMR spectra of the encapsulation study with (2*E*,6*E*)-farnesol. Solvent: $CDCl_3$ filtered through basic Al_2O_3. a) capsule **I** (3.33 mM); b) a mixture of capsule **I** (3.33 mM) and (2*E*,6*E*)-farnesol (33.3 mM); c) (2*E*,6*E*)-farnesol. The encapsulation of substrate is indicated by the appearance of new signals

between 0.7 and -0.5 ppm.



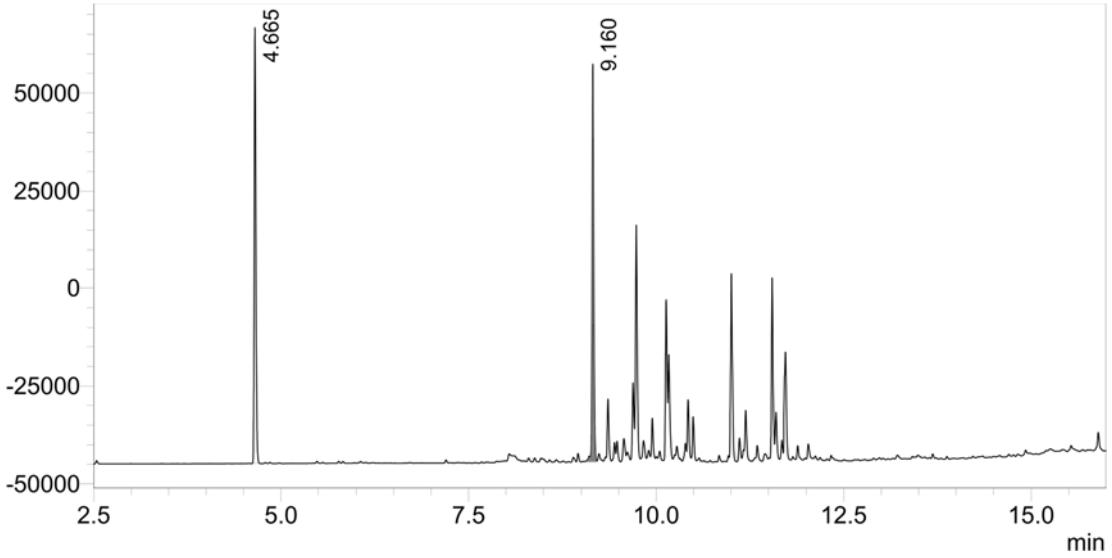
Supplementary Figure 12: ^{1}H-NMR spectra of the encapsulation study with (2*E*,6*Z*)-farnesyl acetate. Solvent: $CDCl_3$ filtered through basic Al_2O_3. a) capsule **I** (3.33 mM); b) a mixture of capsule **I** (3.33 mM) and (2*E*,6*Z*)-farnesyl acetate (33.3 mM); c) (2*E*,6*Z*)-farnesyl acetate. The encapsulation of substrate is indicated by the appearance of new signals between 0.7 and -0.3 ppm.



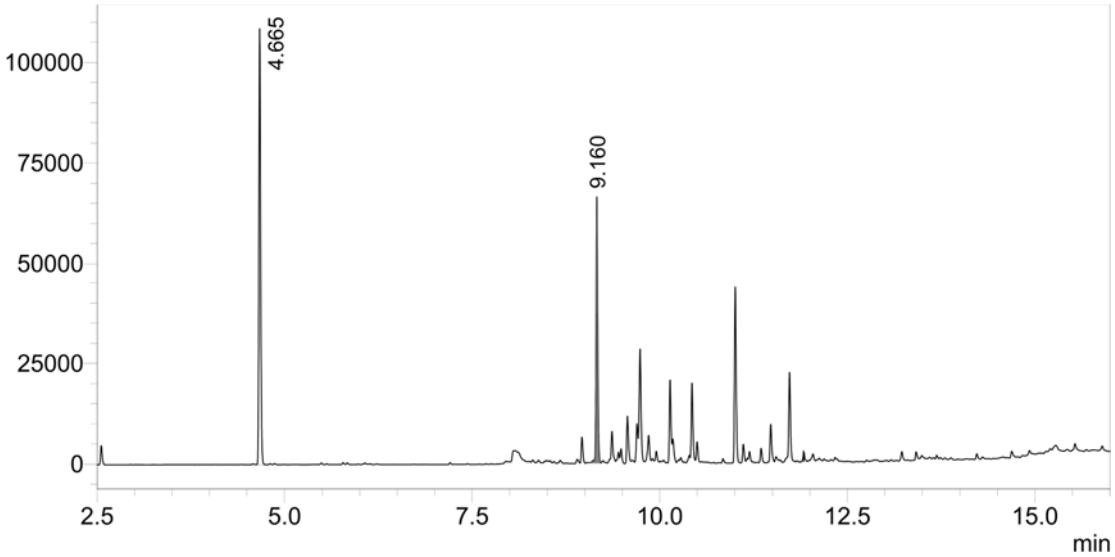
Supplementary Figure 13: Proposed mechanism for the cyclisation of farnesyl substrates

Cyclisation of cyclofarnesyl substrates

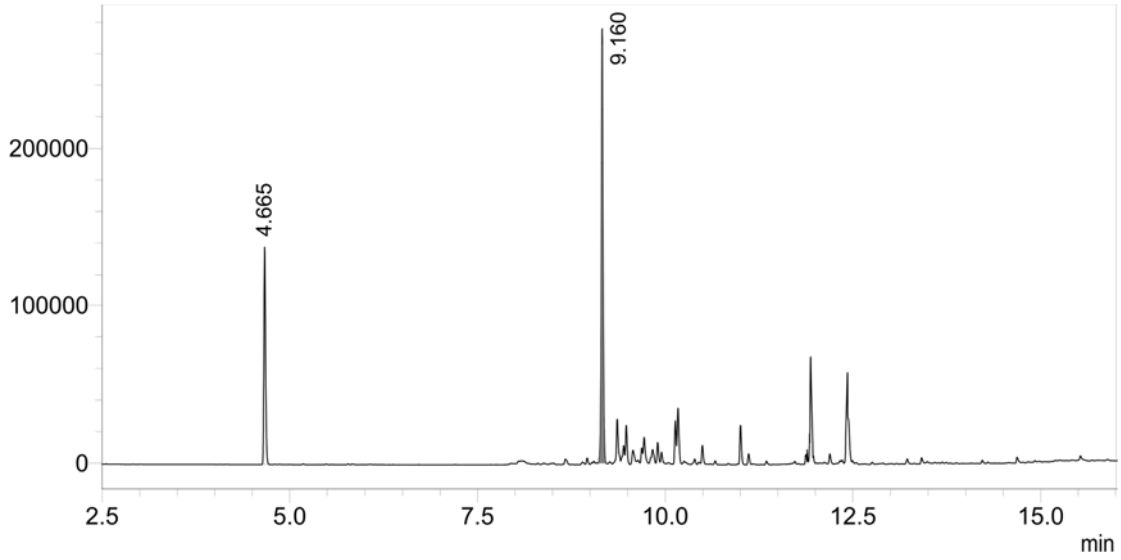
Product analysis via gas chromatography (GC): The peak at 4.67 min is attributed to *n*-decane, which is used as the internal standard for GC-measurements.



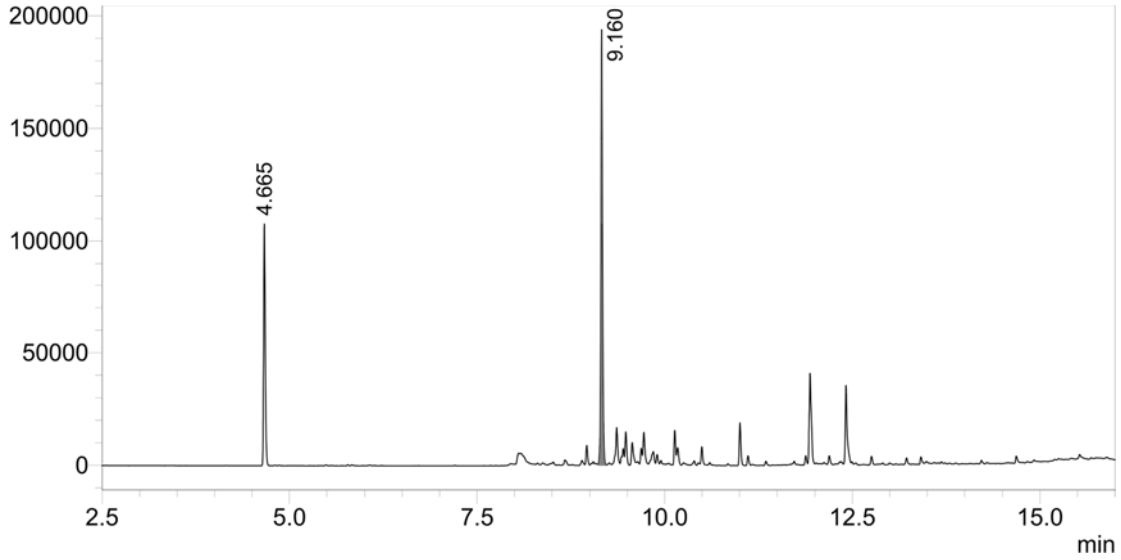
Supplementary Figure 14: GC-trace of the cyclisation reaction of (2*Z*)-cyclofarnesol at full conversion (8d)



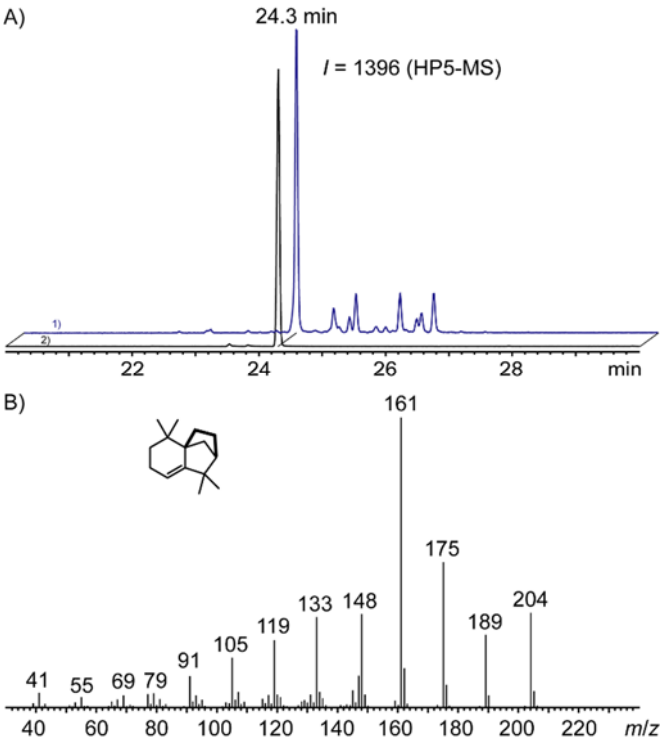
Supplementary Figure 15: GC-trace of the cyclisation reaction of (2*E*)-cyclofarnesol at full conversion (8d)



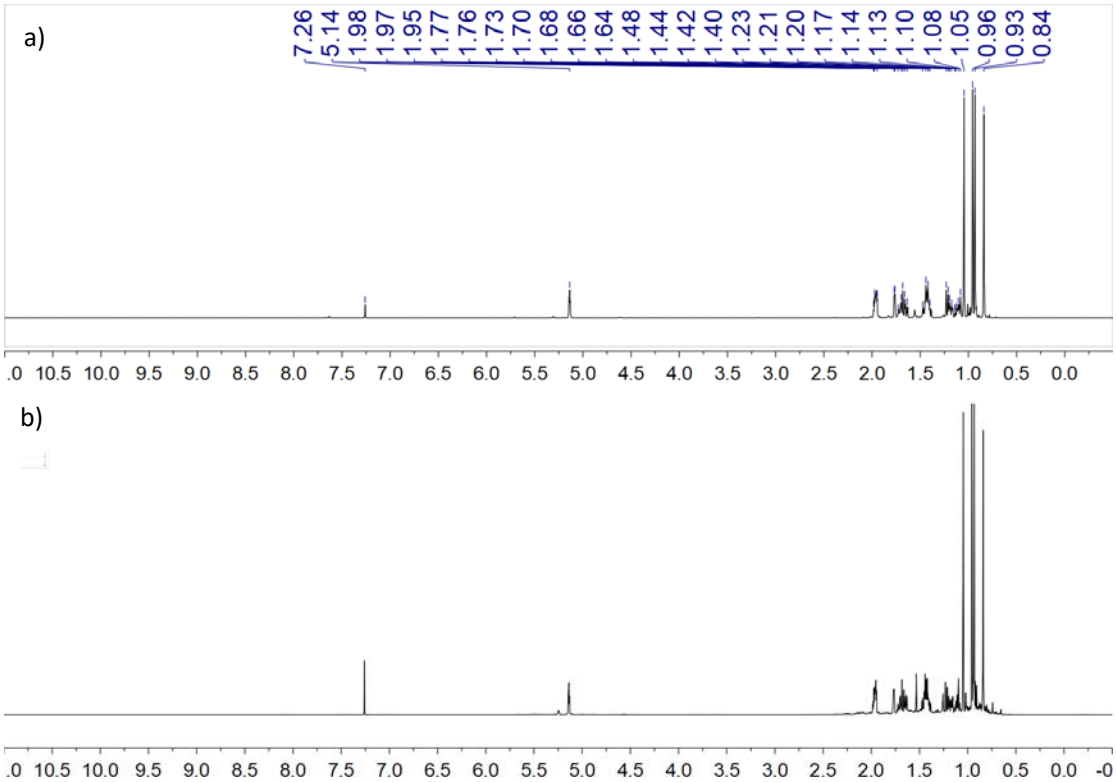
Supplementary Figure 16: GC-trace of the cyclisation reaction of (2*Z*)-cyclofarnesyl acetate at full conversion (9d)



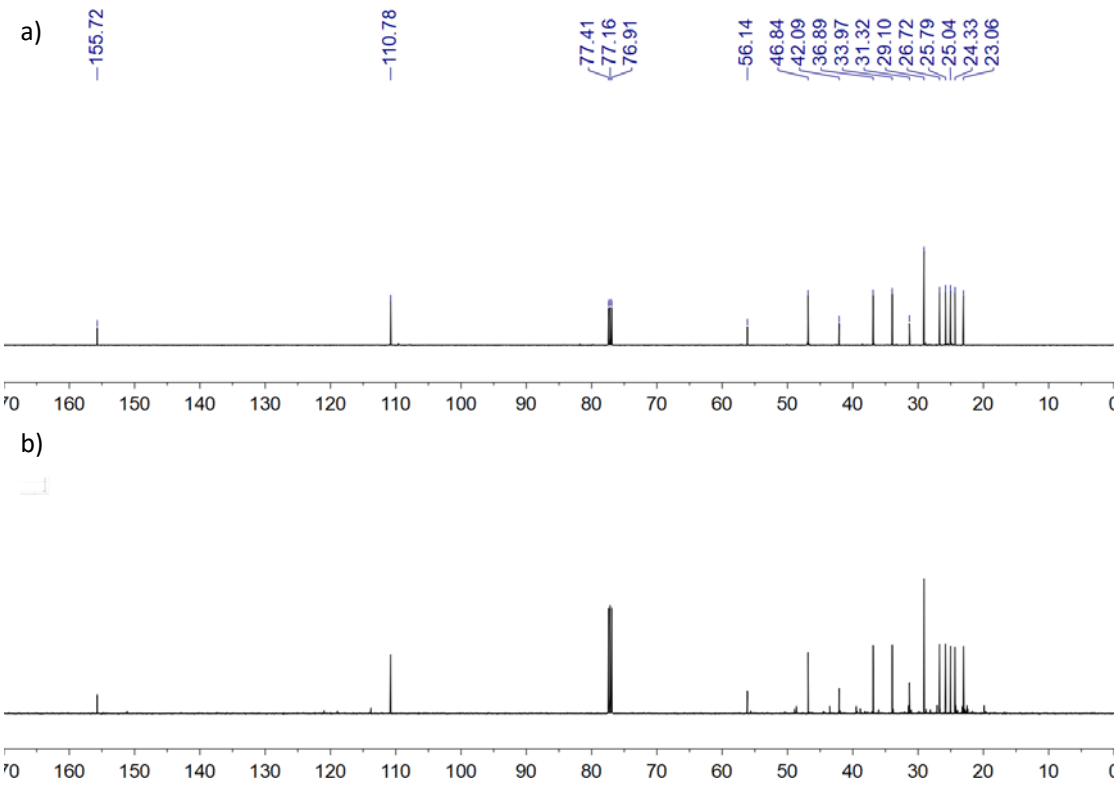
Supplementary Figure 17: GC-trace of the cyclisation reaction of (2*E*)-cyclofarnesyl acetate at full conversion (9d)



Supplementary Figure 18: Identification of the cyclisation product via GC-MS. A) Total ion chromatogram of 1) cyclisation products of (2*Z*)-cyclofarnesyl acetate and 2) an authentic isolongifolene **A** sample. B) EI-MS spectrum of isolongifolene.



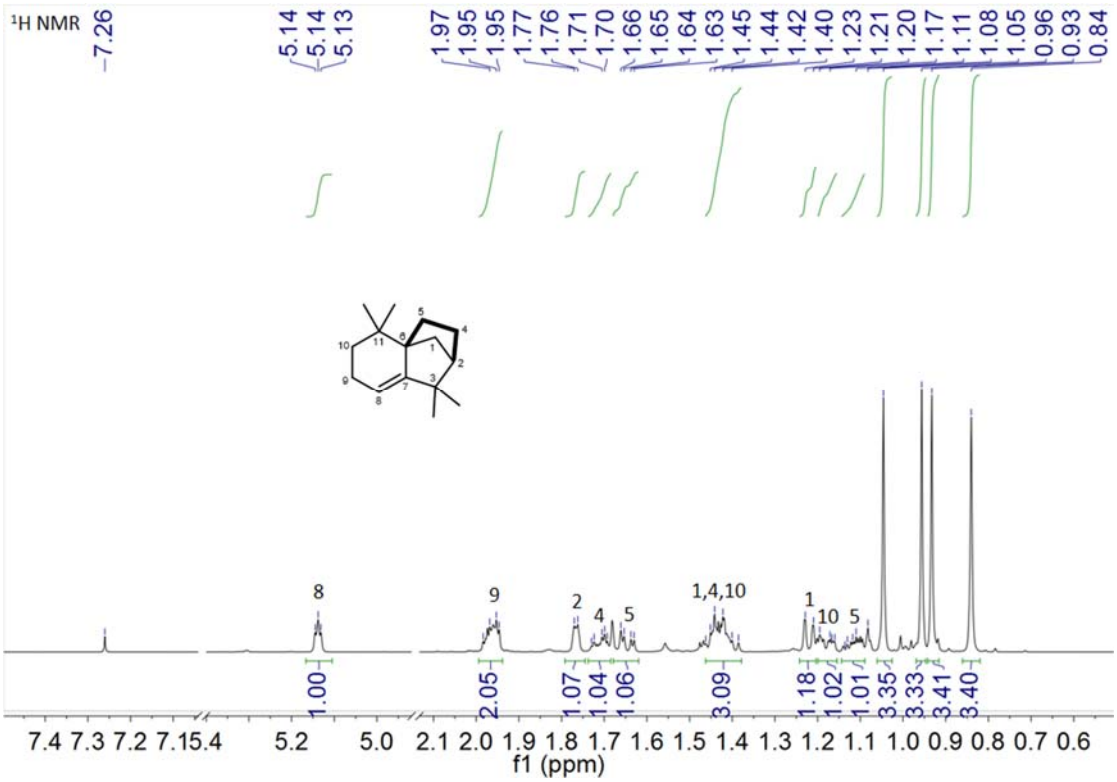
Supplementary Figure 19: Comparison of the ^{1}H-NMR spectrum of the isolated isolongifolene (b) with that of an authentic isolongifolene sample (a).



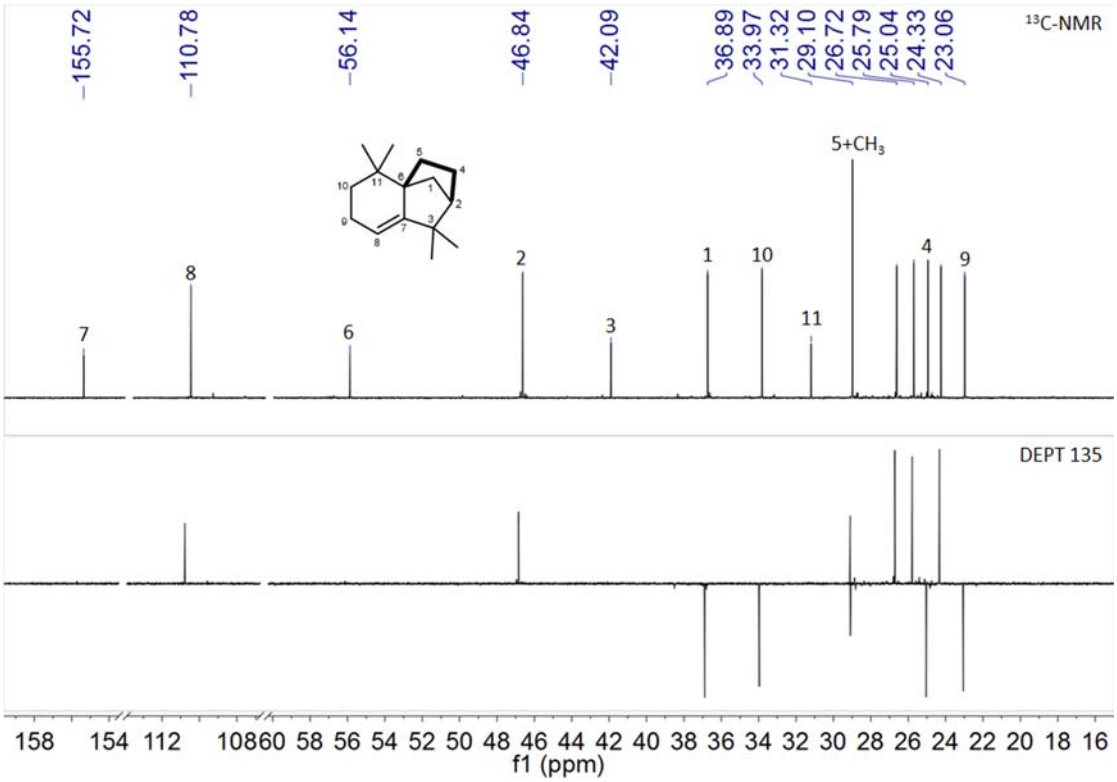
Supplementary Figure 20: Comparison of the ^{13}C-NMR spectrum of the isolated isolongifolene (b) with that of an authentic isolongifolene sample (a).

Mechanistic investigations: Two mechanisms for the formation of isolongifolene were considered. To differentiate between the two possibilities, a cyclisation reaction was performed with the 1-^{13}C-labelled substrate **20** (for the synthesis of **20**, see Supplementary Method). In order to identify the position of the ^{13}C-label, all carbon atoms in isolongifolene had to be assigned at first.

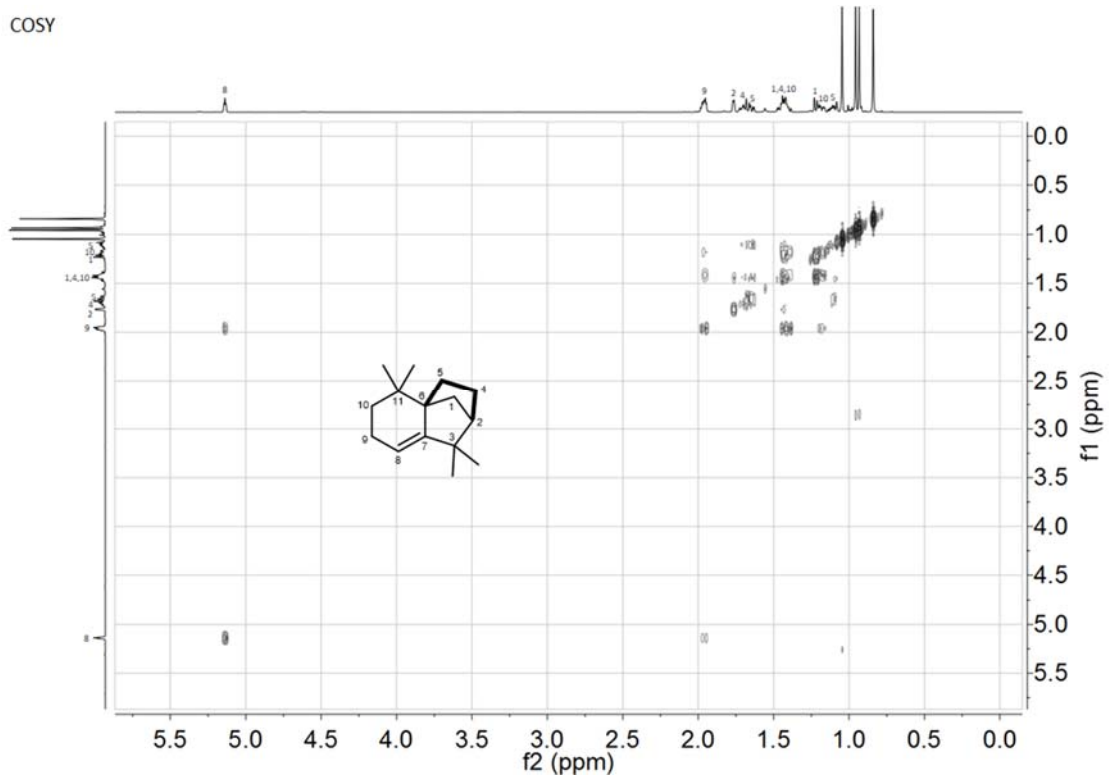
The signals in the ^{1}H (Supplementary Figure 21) and ^{13}C NMR spectra (Supplementary Figure 22) of isolongifolene were assigned based on the DEPT135 (Supplementary Figure 22), COSY (Supplementary Figure 23), HSQC (Supplementary Figure 24) and HMBC spectra (Supplementary Figure 25) recorded with an authentic sample of isolongifolene. The numbering of the carbon atoms corresponds to that of cyclofarnesyl acetate.



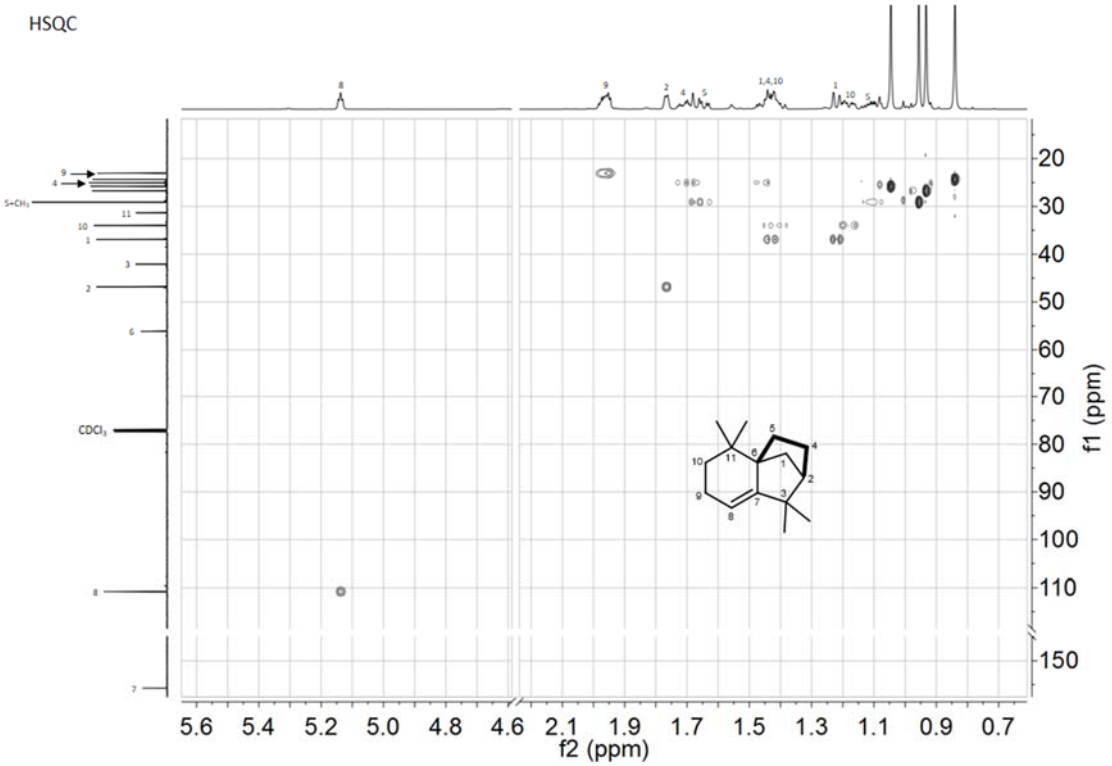
Supplementary Figure 21: [1]H NMR spectrum of an authentic sample of isolongifolene.



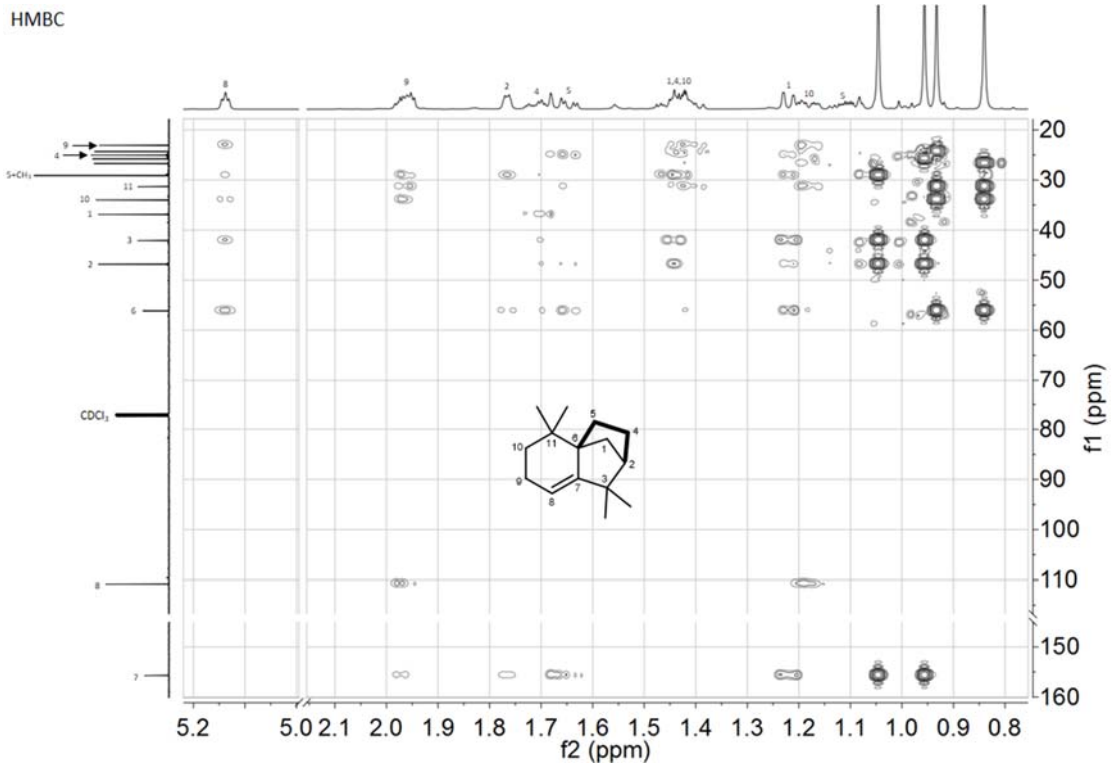
Supplementary Figure 22: [13]C NMR and DEPT 135 spectra of an authentic sample of isolongifolene.



Supplementary Figure 23: COSY spectrum of an authentic sample of isolongifolene.

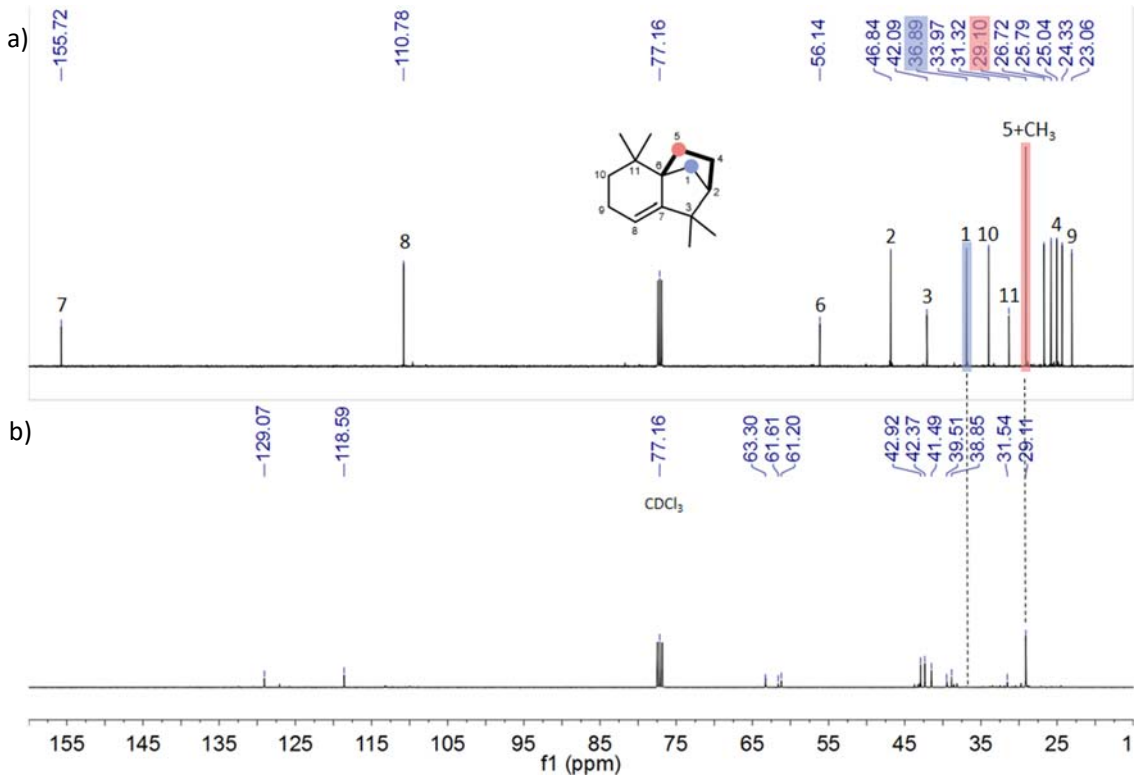


Supplementary Figure 24: HSQC spectrum of an authentic sample of isolongifolene.



Supplementary Figure 25: HMBC spectrum of an authentic sample of isolongifolene.

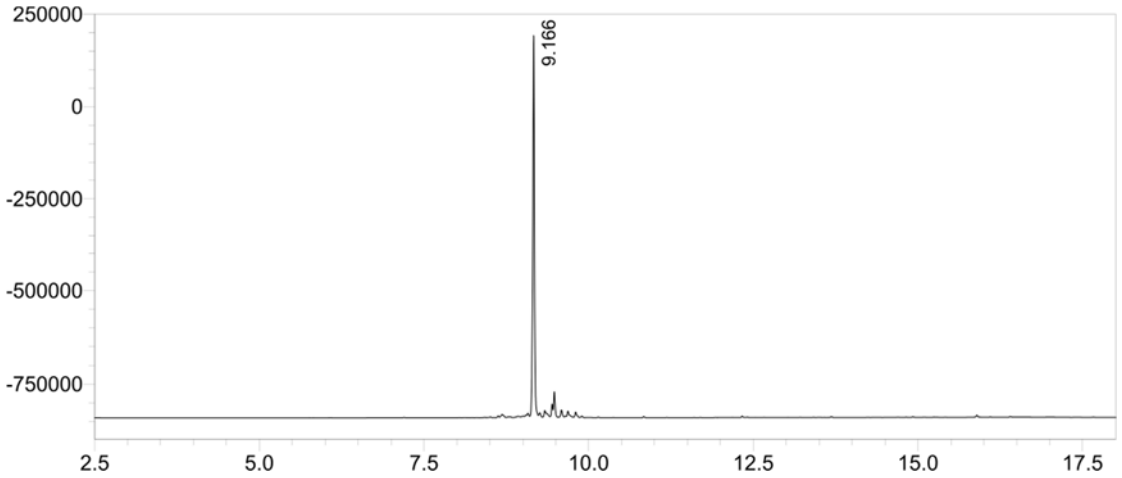
The ^{13}C-labelled cyclofarnesyl acetate (**20**) was converted according to the general procedure of the cyclisation reaction. Upon complete conversion, resorcinarene was removed via column chromatography (eluted with pentane), and the product mixture was subjected to ^{13}C NMR measurement. In the NMR spectrum (Supplementary Figure 26), each signal corresponds to a product carrying the ^{13}C-label on a specific carbon atom. The only signal corresponding to isolongifolene is the peak at 29.1 ppm (analysis with the DEPT135 spectrum reveals that this peak is attributed to a CH_2 group), which matches the chemical shift of the C5-atom of isolongifolene (**A**). This indicates that the mechanism with the additional 1,3-hydride shift step is likely operational in the cyclisation of cyclofarnesyl acetate.



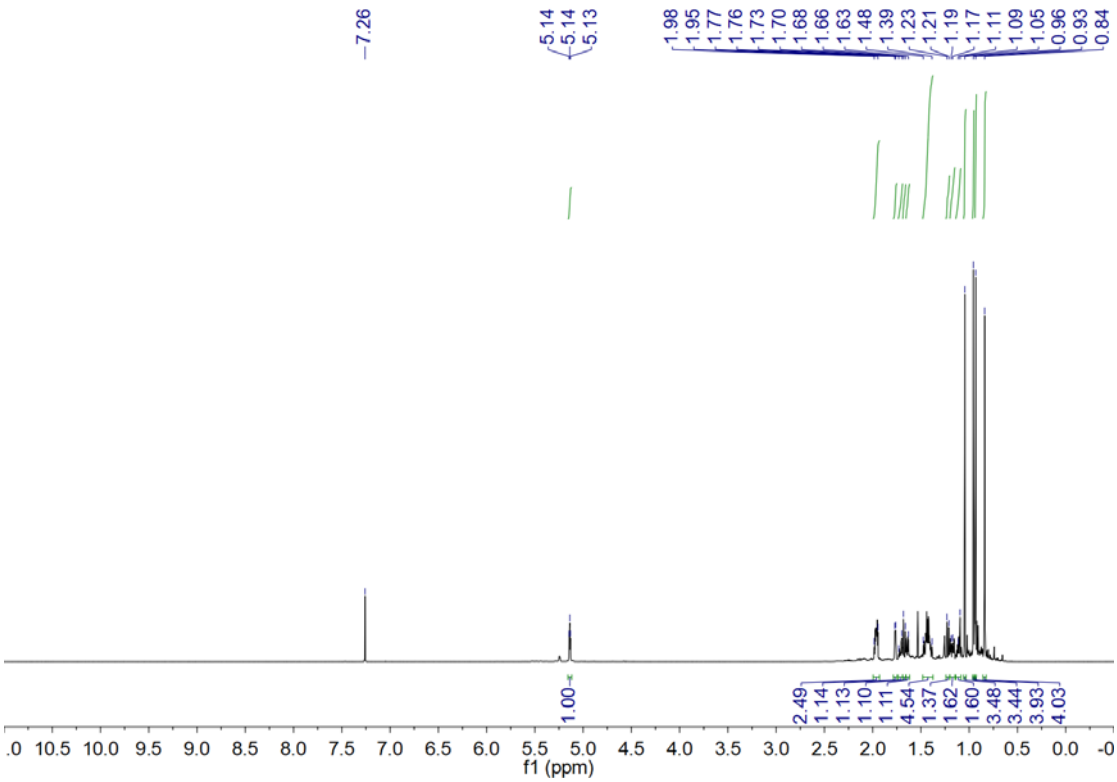
Supplementary Figure 26: Comparison of the ^{13}C NMR spectrum of isolongifolene **A** (a) with that of the product mixture (b) from (2*Z*)-(1-^{13}C)-cyclofarnesyl acetate (**20**).

Isolation and derivatisation of the cyclisation product: To determine the isolated yield of isolongifolene, a large scale cyclisation reaction of cyclofarnesyl acetate was performed. To a solution of capsule **I** (533 mg, 80.3 µmol, 0.10 eq) in $CHCl_3$ (24 mL, containing 100-200 ppm amylene as stabilizer) was added successively a stock solution of HCl (24.l µmol, 0.03 eq) in $CHCl_3$ (0.45 mL) and cyclofarnesyl acetate (*E*/*Z*-ratio = 6/1, 212 mg, 803 µmol). The reaction mixture was stirred at 30 °C. After the completion of the reaction (11d, monitored by GC), the reaction mixture was subjected to column chromatography (250 mL silica gel, pentane as the eluent) to remove resorcinarene. The crude cyclisation product mixture was purified by a second column (40 mL silica gel, pentane as the eluent, **elution without additionally applied pressure**). The pure fractions were collected and the impure fractions were further purified by column chromatography. After two additional columns, the pure fractions were combined. Isolongifolene is volatile under reduced pressure (**Supplementary Table 10**). To avoid the loss due to evaporation, the combined fractions were concentrated in an open flask **at 40 °C and under atmospheric pressure**, which afforded isolongifolene (28 mg, 17%) as a colourless oil.

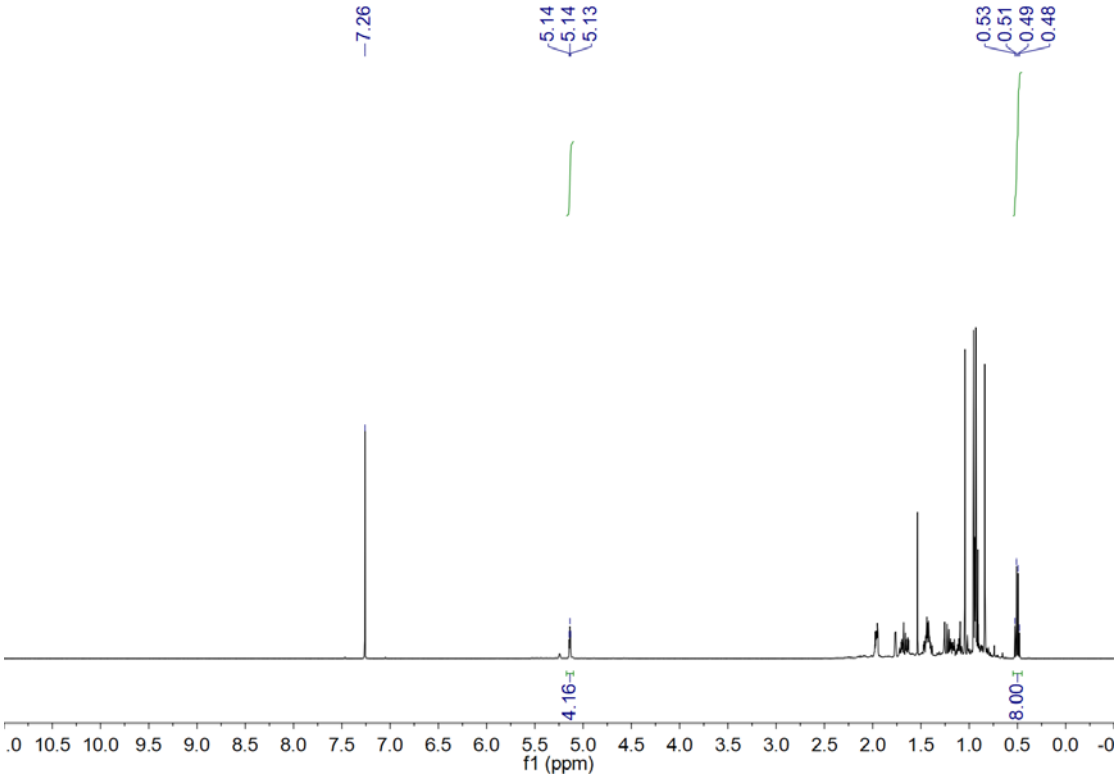
The GC-trace and the ^{1}H NMR spectrum of the isolated isolongifolene are shown in Supplementary Figure 27 and 28. The GC-analysis revealed that the isolated isolongifolene is 85% pure. The purity of the isolated isolongifolene was also determined with ^{1}H NMR spectroscopy (Supplementary Figure 29). A sample containing 2.92 mg (14.3 µmol if the material is 100% pure, 1.0 eq) isolated isolongifolene and tetraethylsilane (2.86 µmol, 0.2 eq) was prepared and subjected to ^{1}H NMR. The triplet of isolongifolene at 5.14 ppm (corresponding to 1 proton) and the quartet of tetraethylsilane (TES) at 0.50 ppm (corresponding to 8 protons) have no overlap with other signals and are therefore used for the calculation. The ^{1}H NMR spectrum revealed a ratio between isolongifolene and TES of 4.16:1, which corresponds to an 83% purity of isolongifolene.



Supplementary Figure 27: GC-trace of the isolongifolene isolated from the large scale cyclisation reaction of cyclofarnesyl acetate.

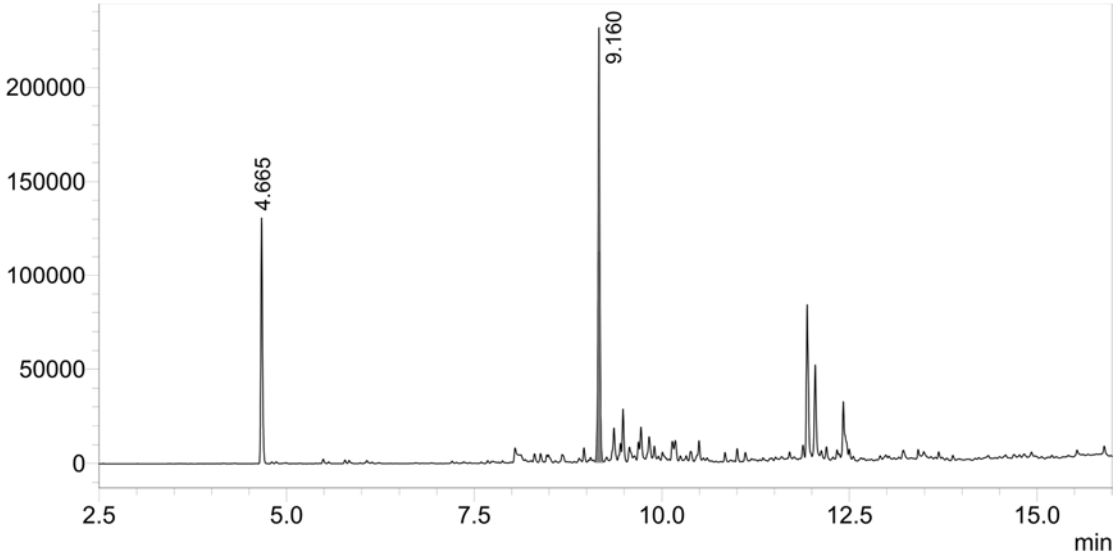


Supplementary Figure 28: ^{1}H NMR spectrum of isolongifolene isolated from the large scale cyclisation reaction of cyclofarnesyl acetate.

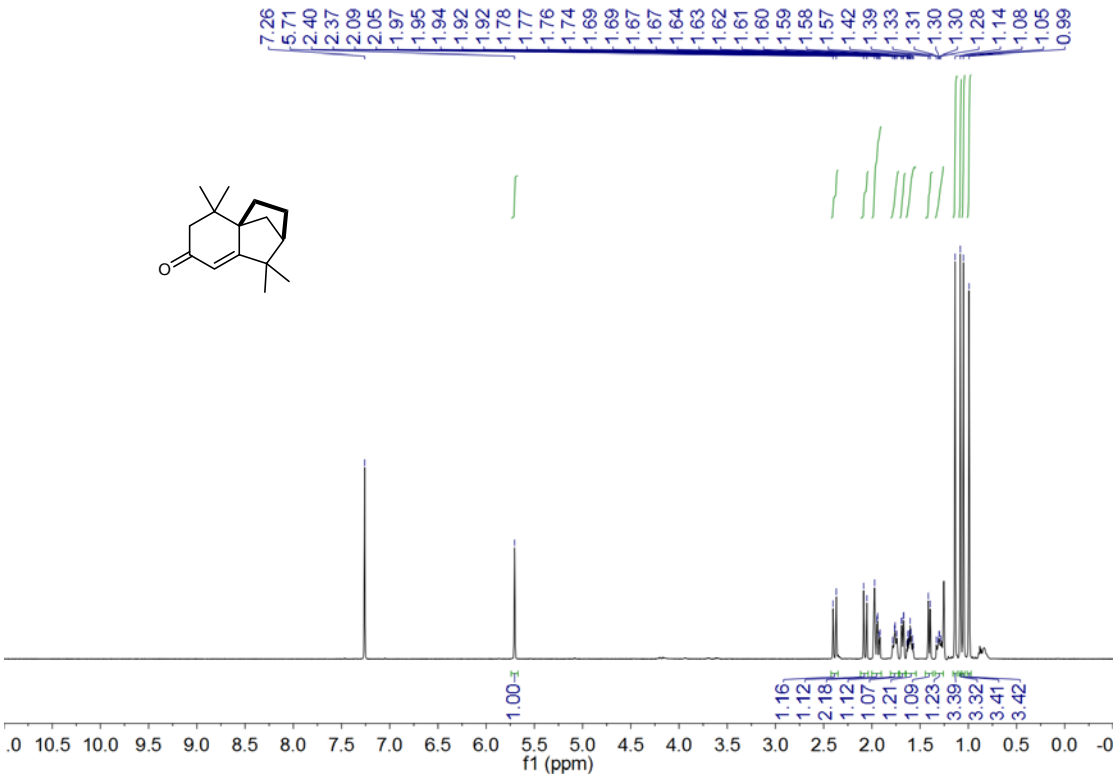


Supplementary Figure 29: Determination of the purity of the isolated isolongifolene with ^{1}H NMR spectroscopy.

The isolation yield of isolongifolene (17%, 83% NMR-purity) is significantly lower than the corresponding GC-yield (24% from cyclofarnesyl acetate of an *E*/*Z*-ratio of 6/1), which is probably due to the loss occurring during the repeated purification with column chromatography. Purification attempts with $AgNO_3$-coated silica also failed to improve the purity of the isolated isolongifolene. To avoid the loss and to eliminate the minor impurities in the isolated isolongifolene, an allylic oxidation reaction was performed with the product mixture (after the removal of the resorcinarene) according to a literature procedure[4]. To simplify the calculation of stoichiometry, it was assumed that the substrate (cyclofarnesyl acetate, *E*/*Z*-ratio = 6/1, 26.4 mg, 0.10 mmol, 1.00 eq) was quantitatively converted to isolongifolene. A solution of the obtained crude product in a mixture of MeCN (0.30 mL) and benzene (30.0 µL) was treated with $Cr(CO)_6$ (10.8 mg, 0.05 mmol, 0.50 eq) and *t*BuOOH (70% aqueous solution, 41.7 µL, 0.30 mmol, 3.00 eq). The reaction mixture was then stirred at 80 ºC. Complete conversion of isolongifolene was reached after 2h, as indicated by GC. Afterwards, the reaction mixture was allowed to cool down to room temperature, and subjected to column chromatography (15 mL silica gel, pentane/Et_2O = 3/1). Isolongifolenone (**29**) was isolated as a colourless oil with an overall yield of 20 % (4.4 mg) over two steps from cylcofarnesyl acetate. The allylic oxidation was also performed with an authentic sample of isolongifolene (10 mg), which afforded isolongifolenone in 94% yield.



Supplementary Figure 30: GC-trace of the cyclisation reaction of cyclofarnesyl acetate (*E*/*Z* = 6/1) at full conversion (9d). The peak at 4.67 min and 9.16 min are attributed to *n*-decane (internal standard) and isolongifolene, respectively.



Supplementary Figure 31: ^{1}H NMR spectrum of isolongifolenone (**29**) isolated from the cyclisation/oxidation sequence.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.71 (s, 1H), 2.39 (d, J = 16.2 Hz, 1H), 2.07 (d, J = 16.2 Hz, 1H), 1.99–1.91 (m, 2H), 1.80–1.71 (m, 1H), 1.68 (dd, J = 10.0 Hz, J = 1.1 Hz, 1H), 1.64–1.56 (m, 1H), 1.40 (d, J = 10.0 Hz, 1H), 1.34–1.27 (m, 1H), 1.14 (s, 3H), 1.08 (s, 3H), 1.05 (s, 3H), 0.99 (s, 3H)

The ^{1}H NMR spectrum is consistent with that reported in literature.[5]

Supplementary Tables

Supplementary Table 1: Comparison of ^{13}C NMR data of isolated 2-*epi*-α-cedrene (**B**), α-cedrene (**C**) and ε-patchoulene (**D**) with literature values

2-*epi*-α-cedrene (**B**)			α-cedrene (**C**)			ε-patchoulene (**D**)		
Isolated	Literature[6]	Δ	Isolated	Literature[7]	Δ	Isolated	Literature[8]	Δ
140.9	140.8	0.1	140.7	140.6	0.1	134.1	133.9	0.2
120.0	119.9	0.1	119.3	119.3	0	131.7	131.4	0.3
58.5	58.5	0	59.0	59.0	0	52.7	52.5	0.2
55.1	55.0	0.1	54.9	55.0	-0.1	46.7	46.4	0.3
53.5	53.6	-0.1	53.9	53.9	0	45.6	45.4	0.2
49.2	49.1	0.1	48.3	48.2	0	44.4	44.1	0.3
41.9	41.8	0.1	41.6	41.6	0	37.0	36.8	0.2
41.5	41.4	0.1	40.7	40.7	0	30.4	30.2	0.2
34.7	34.6	0.1	38.9	38.8	0.1	29.5	29.3	0.2
34.4	34.3	0.1	36.2	36.2	0	27.5	27.3	0.2
27.9	27.8	0.1	27.8	27.7	0.1	25.2	25.0	0.2
24.9	24.9	0	25.7	25.6	0.1	24.9	24.8	0.1
24.8	24.8	0	24.8	24.9	-0.1	18.4	18.2	0.2
24.3	24.1	0.2	24.8	24.8	0	17.9	17.6	0.3
13.8	13.7	0.1	15.6	15.5	0.1	13.8	13.5	0.3

Supplementary Table 2: Comparison of ^{13}C NMR data of isolated δ-selinene (**E**) and 10-*epi*-zonarene (**F**) with literature values

δ-selinene (**E**)			10-*epi*-zonarene (**F**)		
Isolated	Literature[9]	Δ	Isolated	Literature[10]	Δ
143.6	--	--	135.6	135.3	0.3
133.4	--	--	135.2	135.0	0.2
126.2	--	--	127.9	127.9	0
117.0	117.0	0	120.5	120.4	0.1
38.2	38.1	0.1	43.2	43.2	0
37.8	37.7	0.1	34.7	34.6	0.1
35.7	35.6	0.1	31.9	31.8	0.1
32.9	32.8	0.1	31.3	31.2	0.1
32.3	--	--	28.3	28.2	0.1
23.4	23.3	0.1	28.3	28.1	0.2
23.2	--	--	24.3	24.1	0.2
22.0	21.9	0.1	24.0	23.9	0.1
21.5	21.4	0.1	21.1	21.0	0
18.8	18.7	0.1	20.7	20.5	0.2
18.7	--	--	20.5	20.4	0.1

Supplementary Table 3: Determination of the response factor of (2*E*,6*Z*)-farnesyl acetate. *n*-Decane was used as the internal standard. Other cyclisation substrates were assumed to have the same response factor as (2*E*,6*Z*)-farnesyl acetate.

Entry	Ratio ((2*E*,6*Z*)-**FOAc** to IS)		Response factor
	Theoretical	Determined	
1	4.42	6.98	1.58
2	1.64	2.57	1.57
3	0.56	0.89	1.59
Mean value			1.58

Supplementary Table 4: Determination of the response factor of commercially α-cedrene. *n*-Decane was used as the internal standard. As the cyclic products have the same chemical composition ($C_{15}H_{24}$), other cyclisation products were assumed to have the same response factor as α-cedrene.

Entry	Ratio (α-cedrene to IS)		Response factor
	Theoretical	Determined	
1	4	5.95	1.49
2	2	2.88	1.44
3	1	1.48	1.48
Mean value			1.47

Supplementary Table 5: GC-yields of 2-*epi*-α-cedrene (**B**), α-cedrene (**C**), ε-patchoulene (**D**), δ-selinene (**E**) and 10-*epi*-zonarene (**F**) under the standard reaction conditions from different cyclisation precursors.

Substrate	GC-yield				
	B	**C**	**D**	**E**	**F**
(2*E*,6*E*)-FOAc	5%	6%	6%	8%	12%
(2*Z*,6*E*)-FOAc	7%	7%	7%	0%	11%
(2*Z*,6*Z*)-FOAc	9%	7%	8%	0%	11%
(2*E*,6*Z*)-FOAc	4%	3%	3%	18%	10%

Supplementary Table 6: GC-yields of 2-*epi*-α-cedrene (**B**), α-cedrene (**C**), ε-patchoulene (**D**), δ-selinene (**E**) and 10-*epi*-zonarene (**F**) with capsule **I** blocked by nBu$_4$NBr . Conditions: substrate (33.3 mM, 1.00 eq), capsule **I** (3.33 mM, 0.10 eq), HCl (1.00 mM, 0.03 eq), nBu$_4$NBr (5.00 mM, 0.15 eq), solvent: $CDCl_3$ filtered through basic Al_2O_3.

Substrate	conversion (8d)	GC-yield				
		B	**C**	**D**	**E**	**F**
(2*E*,6*E*)-FOAc	4.4%	0.07%	0.08%	0.04%	0.04%	0.06%
(2*Z*,6*E*)-FOAc	5.3%	0.09%	0.12%	0.09%	0%	0.18%
(2*Z*,6*Z*)-FOAc	6.1%	0.19%	0.21%	0.15%	0%	0.22%
(2*E*,6*Z*)-FOAc	3.9%	0.06%	0.05%	0.07%	0.10%	0.05%

The GC response factors of (2*Z*)-cyclofarnesyl acetate (Supplementary Table 7) and isolongifolene (Supplementary Table 8) were determined to be 1.64 and 1.55. Accordingly, the GC yield of isolongifolene in the cyclisation reaction of (*Z*)- and (*E*)-cyclofarnesyl acetate was calculated to be 29 % and 23%, respectively.

Supplementary Table 7: Determination of the response factor of (2*Z*)-cyclofarnesyl acetate. *n*-Decane was used as the internal standard.

	Ratio ((2*Z*)-**cycloFOAc** to IS)		Response factor
Entry	Theoretical	Determined	
1	0.95	1.56	1.64
2	2.61	4.61	1.76
3	3.62	5.49	1.52
Mean value			1.64

Supplementary Table 8: Determination of the response factor of isolongifolene (**A**). *n*-Decane was used as the internal standard.

	Ratio (**A** to IS)		Response factor
Entry	Theoretical	Determined	
1	4.00	6.13	1.53
2	2.00	3.31	1.55
3	1.00	1.56	1.56
Mean value			1.55

Supplementary Table 9. Computed energies (mPW1PW91/6-311+G(d,p)//B3LYP/6-311+G(d,p)-GD3BJ, ZPE unscaled)[11-13] of carbocations and of transition structures yielding isolongifolene. a) Species with number (and value, cm^{-1}) of imaginary frequencies. b) Electronic energy mPW1PW91/6-311+G(d,p)//B3LYP/6-311+G(d,p)-GD3BJ (H), with unscaled ZPE-correction, H. c) in parentheses: Electronic energy (mPW1PW91) and unscaled zero point energy (B3LYP/6-311+G(d,p)-GD3BJ, H. d) Free energy B3LYP/6-311+G(d,p)-GD3BJ (H) and electronic energy mPW1PW91/6-311+G(d,p)//B3LYP/6-311+G(d,p)-GD3BJ with unscaled ZPE-correction, H. e) relative electronic energy (with ZPE correction) with respect to the most stable, corresponding structure, kcal/mol.

Species [a]	E (mPW1PW91[b] + B3LYP-ZPE)[c]	Gibbs and Electronic(+ZPE) B3LYP energies[d]	ΔE (mPW1PW91+ZPE)[e] E_{rel}	ΔE (mPW1PW91+ZPE)[e] E_a	Profile E_{rel}[e]
15a (0) eq	**-586.0246448** (-586.3903278 + 0.365683)	-586.283390 -586.24257	+1.3		
15b (0) ax	**-586.0267041** (-586.3932161 +0.366512)	-586.286822 -586.245877	0.0		0.0
15c (0) ax	**-586.0170537** (-586.3837807 +0.366727)	-586.277426 -586.236646	+ 6.1		
15d (0) eq	**-586.0250513** (-586.3911183 +0.366067)	-586.283677 -586.243189	+1.0		
TS1a (1, -313)	**-586.0122159** (-586.3792839 +0.367068)	-586.264145 -586.225971	0.0	+9.1 (vs. **15b**)	
TS1b (1, -310)	**-586.0081944** (-586.3755184 +0.367324)	-586.260437 -586.222395	2.5 (vs **TS1a**)	+11.6 (vs. **15b**)	
16 (0) (Me *cis* to ethylene, *endo*-Me)	**-586.0440958** (-586.4127168 +0.368621)	-586.295380 -586.255921	0.0		-10.9
18/*ent*-**18** (0) (Me *trans* to	**-586.0347617** (-586.4034247 +0.368663)	-586.285222 -586.245881	+5.8 (vs **13**)		-5.1

ethylene, *exo*-Me)					
TS2a (1, -505)	**-586.0188735** (-586.3856615 +0.366788)	-586.260580 -586.222925		+15.8 (vs **16**) +10.0 (vs **18**/*ent*-**18**)	+4.9
TS2b (1, -367) shift of *endo*-Me	**-586.0127508** (-586.3809128 +0.368162)	-586.258839 -586.220770	+3.8 (vs **TS2a**) +10.7 (vs **TS3**)	+19.6 (vs **16**)	+8.7
TS3 (1, -328) shift of *exo*-Me	**-586.0299305** (-586.3983455 +0.368415)	-586.276287 -586.238224	0.0	+3.1 (vs **18**/*ent*-**18**)	-2.0
19 (0)	**-586.0507617** (-586.4192297 +0.368468)	-586.300084 -586.260959		-15.1 (vs. **15b**)	-15.1

Supplementary Table 10: volatility tests of isolongifolene. The tests were performed with 20 mg authentic isolongifolene. a: Residual pentane detected in ^{1}H NMR. b: No residual pentane detected in ^{1}H NMR.

Temperature	Treatment	Loss
40 °C	30 min at 480 mbar	5.4%
40 °C	1h at 700 mbar	3.2%
40 °C	dissolved in 15 mL pentane, then 1h at 700 mbar	4.7%[a]
40 °C	dissolved in 3 mL pentane, then 3h at atmospheric pressure	<1%[b]

Supplementary References

1 Snyder, S. A., Treitler, D. S. & Brucks, A. P. Simple Reagents for Direct Halonium-Induced Polyene Cyclizations. *J. Am. Chem. Soc.* **132**, 14303-14314, (2010).

2 Fráter, G., Müller, U. & Kraft, P. Synthesis of Tricyclic Ketones with Sesquiterpene Skeletons by Acid-Catalyzed Rearrangement of β-Monocyclofarnesol. *Helv. Chim. Acta* **82**, 522-530, (1999).

3 Citron, C. A., Rabe, P., Barra, L., Nakano, C., Hoshino, T. & Dickschat, J. S. Synthesis of Isotopically Labelled Oligoprenyl Diphosphates and Their Application in Mechanistic Investigations of Terpene Cyclases. *Eur. J. Org. Chem.* **2014**, 7684-7691, (2014).

4 Wang, S. & Zhang, A. Facile and efficient synthesis of isolongifolennone. *Org. Prep. Proced. Int.* **40**, 405-410, (2008).

5 Robles-Dutenhefner, P. A., da Silva Rocha, K. A., Sousa, E. M. B. & Gusevskaya, E. V. Cobalt-catalyzed oxidation of terpenes: Co-MCM-41 as an efficient shape-selective heterogeneous catalyst for aerobic oxidation of isolongifolene under solvent-free conditions. *J. Catal.* **265**, 72-79, (2009).

6 Horton, M. & Pattenden, G. Bicyclo[3.3.0]octenones in synthesis. A new synthesis of (±)-cedrene using sequential inter- and intra-molecular Michael reactions. *J. Chem. Soc., Perkin Trans. 1*, 811-817, (1984).

7 Brown, G. D., Liang, G.-Y. & Sy, L.-K. Terpenoids from the seeds of Artemisia annua. *Phytochemistry* **64**, 303-323, (2003).

8 Polovinka, M. P. *et al.* Molecular Rearrangements of (-)-α-Cedrene in Superacids. *Tetrahedron Lett.* **36**, 8093-8096, (1995).

9 Sun, H. H. & Erickson, K. L. Sesquiterpenoids from the Hawaiian marine alga Laurencia nidifica. 7. (+)-Selina-4,7(11)-diene. *J. Org. Chem.* **43**, 1613-1614, (1978).

10 Sy, L.-K. & Brown, G. D. The role of the 12-carboxylic acid group in the spontaneous autoxidation of dihydroartemisinic acid. *Tetrahedron* **58**, 909-923, (2002).

11 Frisch, M. I. *et al*, Gaussian 16, Wallingford, CT, 2016.

12 Matsuda, S. P. T., Wilson, W. K. & Xiong, Q. Mechanistic insights into triterpene synthesis from quantum mechanical calculations. Detection of systematic errors in B3LYP cyclization energies. *Org. Biomol. Chem.* **4**, 530-543, (2006).

13 Tantillo, D. J. Biosynthesis via carbocations: Theoretical studies on terpene formation. *Nat. Prod. Rep.* **28**, 1035-1053, (2011).